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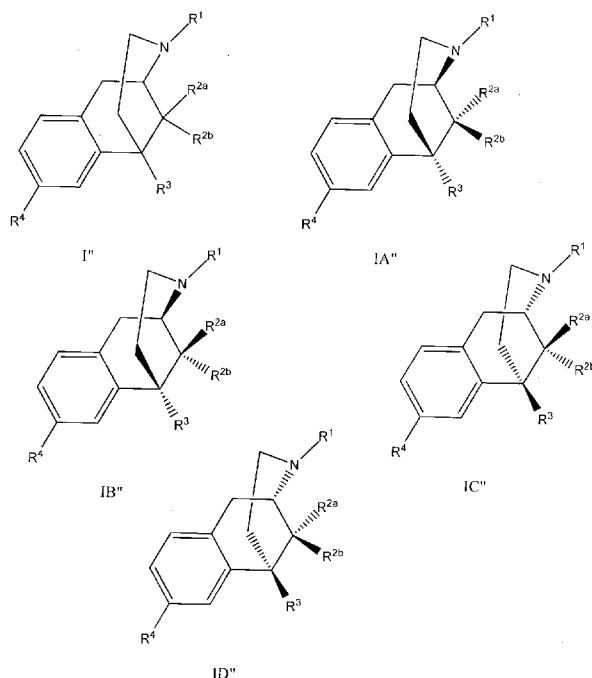
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[Continued on next page]

(54) Title: BENZOMORPHAN ANALOGS AND THE USE THEREOF

(57) Abstract: The present invention is directed to Benzo-morphan Analog compounds of the Formula I'', Formula IA'', Formula IB'', Formula IC'', or Formula ID'' as shown below; and related Formula I', Formula IA', Formula IB', Formula IC', or Formula ID'; Formula I, Formula IA, Formula IB, Formula IC, or Formula ID; wherein R¹, R^{2a}, R^{2b}, R³ and R⁴ are as defined herein. Compounds of the Invention are useful for treating pain, constipation, and other conditions modulated by activity of opioid and ORL-1 receptors.



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BENZOMORPHAN ANALOGS AND THE USE THEREOF

FIELD OF THE INVENTION

5 The invention is in the field of medicinal chemistry. It relates to novel benzomorphan analogs having activity as opioid receptor agonists and/or antagonists. In certain embodiments compounds of the invention have dual activity as opioid agonists and ORL-1 receptor antagonists.

BACKGROUND OF THE INVENTION

10 Pain is the most common symptom for which patients seek medical advice and treatment. While acute pain is usually self-limited, chronic pain can persist for 3 months or longer and lead to significant changes in a patient's personality, lifestyle, functional ability and overall quality of life (K.M. Foley, Pain, in *Cecil Textbook of Medicine* 100-107, J.C. Bennett and F. Plum eds., 20th ed. 1996).

15 Pain has traditionally been managed by administering either a non-opioid analgesic (such as acetylsalicylic acid, choline magnesium trisalicylate, acetaminophen, ibuprofen, fenoprofen, diflunisal or naproxen), or an opioid analgesic (such as morphine, hydromorphone, methadone, levorphanol, fentanyl, oxycodone or oxymorphone).

20 Although the term "narcotic" is often used to refer to opioids, the term is not specifically applicable to opioids. The term "narcotic", derived from the Greek word for "stupor", originally referred to any drug that induced sleep, only later being associated with opioids (Gutstein, Howard B., Akil, Huda, "Chapter 21. Opioid Analgesics" (Chapter 21), Brunton, LL, Lazo, JS, Parker, KI: Goodman & Gilman's The Pharmacological Basis of Therapeutics, 11th Edition: <http://www.accessmedicine.com/content.aspx?aID=940653>). In the legal context, the term "narcotic" refers to a variety of mechanistically unrelated substances with abuse or addictive potential (Gutstein, Howard B., Akil, Huda, "Chapter 21. Opioid Analgesics" (Chapter 21), Brunton LL, Lazo JS, Parker KI: Goodman & Gilman's The Pharmacological Basis of Therapeutics, 11th Edition:

<http://www.accessmedicine.com/content.aspx?aID=940653>). Thus, the term “narcotic” not only refers to opioids, but also refers to such drugs as cocaine, methamphetamine, ecstasy, etc., which exert their pharmacological effects via different receptors than opioids. Furthermore, because the term “narcotic” refers to
5 such a wide variety of unrelated drugs, many of which do not possess analgesic properties, it cannot be assumed that a drug that has “narcotic” properties is necessarily analgesic. For example, drugs such as ecstasy and methamphetamine are not analgesic, and are not used to treat pain.

Until recently, there was evidence of three major classes of opioid receptors in
10 the central nervous system (CNS), with each class having subtype receptors. These receptor classes are known as μ , δ and κ . As opiates have a high affinity to these receptors while not being endogenous to the body, research followed in order to identify and isolate the endogenous ligands to these receptors. These ligands were identified as endorphins, enkephalins, and dynorphins, respectively. Additional
15 experimentation has led to the identification of the opioid receptor-like (ORL-1) receptor, which has a high degree of homology to the known opioid receptor classes. This newly discovered receptor was classified as an opioid receptor based only on structural grounds, as the receptor did not exhibit pharmacological homology. It was initially demonstrated that non-selective ligands having a high affinity for μ , δ and κ
20 receptors had low affinity for the ORL-1 receptor. This characteristic, along with the fact that an endogenous ligand had not yet been discovered, led to the ORL-1 receptor being designated as an “orphan receptor”.

Subsequent research led to the isolation and structure of the endogenous ligand of the ORL-1 receptor. This ligand, nociceptin (also known as orphanin FQ (OFQ)), is
25 a seventeen amino acid peptide structurally similar to members of the opioid peptide family. (C. Altier et al., “ORL-1 receptor-mediated internalization of *N*-type calcium channels.” *Nature Neuroscience*, 2005, 9:31).

The discovery of the ORL-1 receptor and its endogenous ligand, presents an opportunity for the discovery of novel compounds that can be administered for pain
30 management or other syndromes influenced by this receptor.

Many publications in the ORL-1/nociceptin field provide evidence that activation of ORL-1 receptors in the brain can inhibit opioid-mediated analgesia (*e.g.*, D. Barlocco et al., "The opioid-receptor-like 1 (ORL-1) as a potential target for new analgesics." *Eur. J. Med. Chem.*, 2000, 35:275; J.S. Mogil et al., "Orphanin FQ is a functional anti-opioid peptide." *Neurosci.*, 1996, 75:333; K. Lutfy et al., "Tolerance develops to the inhibitory effect of orphanin FQ on morphine-induced antinociception in the rat." *NeuroReport*, 1999, 10:103; M.M. Morgan et al., "Antinociception mediated by the periaqueductal gray is attenuated by orphanin FQ." *NeuroReport*, 1997, 8:3431; and J. Tian et al., "Involvement of endogenous Orphanin FQ in electroacupuncture-induced analgesia." *NeuroReport*, 1997, 8:497).

A growing body of evidence supports a more generalized regulatory role for ORL-1 against the actions of the μ receptor, possibly contributing to the development of μ -agonist tolerance in patients being treated with classical opiates (*e.g.*, J. Tian et al., "Functional studies using antibodies against orphanin FQ/nociceptin." *Peptides*, 2000, 21:1047; and H. Ueda et al., "Enhanced Spinal Nociceptin Receptor Expression Develops Morphine Tolerance and Dependence." *J. Neurosci.*, 2000, 20:7640). Moreover, ORL-1 activation appears to have an inhibitory effect on the rewarding properties of several drugs of abuse, including μ agonists.

Use of opioid analgesics often leads to constipation as a side effect. Constipation associated with the use of opioid analgesics is presumed to occur primarily and mechanistically as a result of the action of μ opioid agonists directly upon μ opioid receptors located in the bowel (Wood & Galligan (2004), Function of opioids in the enteric nervous system. *Neurogastroenterology & Motility* 16(Suppl.2): 17-28.). Stimulation of the μ opioid receptors in the bowel causes inhibition of normal gastrointestinal (GI) motility, leading to constipation. The effect of μ opioid agonism on μ opioid receptors in the bowel can be observed via the action of loperamide (Imodium™) in treating diarrhea. Loperamide is a potent μ opioid agonist that is administered orally, but which has little to no absorption into the blood stream. As a result, loperamide exerts its action locally upon the μ opioid receptors in the bowel, and this results in inhibition of GI motility, which treats diarrhea.

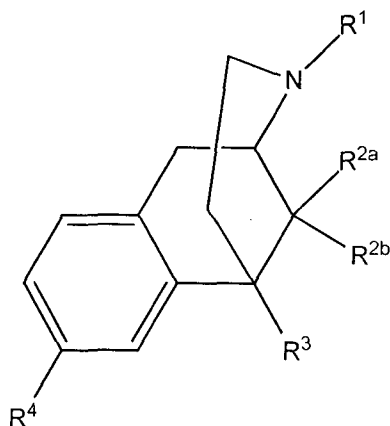
There has been recent interest in developing combinations of μ receptor agonists and antagonists having defined biodistribution properties that might serve to limit opioid-induced constipation. For example, the co-administration of an orally bio-available μ opioid receptor agonist (such as morphine, codeine, oxycodone or hydromorphone) together with a potent μ opioid receptor antagonist (such as N-methylnaloxone or N-methylnaltrexone) that is not orally bio-available may serve to prevent or reduce the constipation otherwise associated with mu opioid receptor agonist therapy. The rationale is that the agonist component will be absorbed and distributed throughout the periphery and the central nervous system (CNS), resulting in the desired analgesia, while the antagonist component will remain in the bowel where it will prevent or reduce any agonist-induced constipation that might otherwise occur.

Benzomorphan analog compounds, such as 3,11,11-trimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[d]azocine-6,8-diol and 8-methoxy-3,11,11-trimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[d]azocin-6-ol, having analgesic activity have been described (*see, e.g.* US 4,425,353; US 4,406,904; and US 4,366,325).

BRIEF SUMMARY OF THE INVENTION

The present invention provides novel benzomorphan analog compounds useful for treating a variety of conditions, including pain, in particular chronic pain, and constipation. More specifically, the present invention provides compounds of Formula I', Formula I'', and Formula I, below, and the pharmaceutically acceptable salts, prodrugs and solvates thereof, that exhibit affinity for one or more of the ORL-1, μ , δ , and κ opioid receptors. Such compounds, salts, prodrugs and solvates are collectively referred to hereinafter as "Compounds of the Invention" (each is individually referred to hereinafter as a "Compound of the Invention").

The present invention provides novel compounds of Formula I'':



I''

5 wherein

R¹ is selected from the group consisting of $-(C_1-C_{10})$ alkyl, $-(C_2-C_{10})$ alkenyl, $-(C_2-C_{10})$ alkynyl, $-(C_3-C_{12})$ cycloalkyl, (C_3-C_{12}) cycloalkyl- (C_1-C_6) alkyl-, $-(C_3-C_{12})$ cycloalkenyl, (C_3-C_{12}) cycloalkenyl- (C_1-C_6) alkyl-, $-(6- \text{ to } 14\text{-membered})$ aryl, $((6- \text{ to } 14\text{-membered})$ aryl)- (C_1-C_6) alkyl-, diphenyl- (C_1-C_6) alkyl-, $-(3- \text{ to } 12\text{-membered})$ heterocycle, $((3- \text{ to } 12 \text{ membered})$ heterocycle)- (C_1-C_6) alkyl-, $-(OCH_2CH_2)_s-O-(C_1-C_6)$ alkyl, $-(CH_2CH_2O)_s-(C_1-C_6)$ alkyl, (C_1-C_{10}) alkoxy, $C(\text{halo})_3$, $CH(\text{halo})_2$, $CH_2(\text{halo})$, $C(O)R^5$, $-C(O)O-(C_1-C_{10})$ alkyl, and $-(CH_2)_n-N(R^6)_2$, each of which is optionally substituted by 1, 2 or 3 independently selected R⁹ groups;

R^{2a} is hydrogen, OH, or absent;

R^{2b} is

- a) $((6- \text{ to } 14\text{-membered})$ aryl), $-((5- \text{ to } 12\text{-membered})$ heteroaryl), or $((3- \text{ to } 12\text{-membered})$ heterocycle), each of which is optionally substituted with one, two, or three independently selected R³⁰ groups; or
- b) $-Z-G-R^{10}$, provided that $-Z-G-R^{10}$ is other than hydrogen;

or R^{2a} and R^{2b} together form $=O$;

Z is absent or $-(CH_2)_m-$, optionally, substituted with 1 or 2 $-(C_1-C_6)$ alkyl;

G is selected from the group consisting of:

- 5 a) a bond, $-(C_1-C_6)$ alkylene, $-(C_2-C_6)$ alkenylene;
- b) O, $-OCO-$, $-C(=O)$, $=CH$;
- c) NR^8 , $=N-O$, $=N-NH$;
- d) S, SO, SO_2 ; and
- 10 e) $-NH-SO_2$;

and when Z is absent and G is $=CH$, $=N-O$, or $=N-NH$, then R^{2a} is absent;

- R^{10} is selected from the group consisting of hydrogen, $-(C_1-C_{10})$ alkyl, $-(C_2-C_{12})$ alkenyl, $-C(=O)$, $-C(=O)-(C_1-C_6)$ alkyl, $-C(=O)-(C_2-C_6)$ alkenyl, $-C(=O)-(6- to 14-$
- 15 membered)aryl, $-C(=O)-(C_1-C_6)$ alkyl-(6- to 14-membered)aryl, $-(C_2-C_{12})$ alkynyl, $-(C_1-C_{10})$ alkoxy, $-(OCH_2CH_2)_5-O(C_1-C_6)$ alkyl, $-(CH_2CH_2O)_5-(C_1-C_6)$ alkyl, $-NH_2$, $-NH(C_1-C_6)$ alkyl, CN, NR^5R^6 , $-(C_1-C_6)$ alkyl- NR^5R^6 , $-CONR^5R^6$, $-(C_1-C_6)$ alkyl-CO- NR^5R^6 , $-COOR^7$, $-(C_1-C_6)$ alkyl-CO- OR^7 , $-(C_1-C_6)$ alkoxy-COOR⁷, $-CO-(CH_2)_n$ -COOR⁷, $-CO-(CH_2)_n$ -CO- NR^5R^6 , $-(C_3-C_{12})$ cycloalkyl, $((C_3-C_{12})$ cycloalkyl)- $(C_1-$
 - 20 $C_6)$ alkyl-, $-(C_4-C_{12})$ cycloalkenyl, $((C_4-C_{12})$ cycloalkenyl)- (C_1-C_6) alkyl-, $-(C_6-C_{14})$ bicycloalkyl, $((C_6-C_{14})$ bicycloalkyl)- (C_1-C_6) alkyl-, $-(C_8-C_{20})$ tricycloalkyl, $((C_8-C_{20})$ tricycloalkyl)- (C_1-C_6) alkyl-, $-(C_7-C_{14})$ bicycloalkenyl, $((C_7-C_{14})$ bicycloalkenyl)- (C_1-C_6) alkyl-, $-(C_8-C_{20})$ tricycloalkenyl, $((C_8-C_{20})$ tricycloalkenyl)- (C_1-C_6) alkyl-, $-(6- to 14-membered)$ aryl, $((6- to 14-membered)$ aryl)- (C_1-C_6) alkyl-, $-SO_2-(C_1-C_6)$ alkyl, $-SO_2-((C_3-C_{12})$ cycloalkyl), $-SO_2-((C_3-C_{12})$ cycloalkyl)- (C_1-C_6) alkyl, $-SO_2-((5- to 12-membered)$ heteroaryl), $-SO_2-((5- to 12-membered)$ heteroaryl)- (C_1-C_6) alkyl, $-C(=O)-NH-((5- to 12-membered)$ heteroaryl), $-C(=O)-NH-((5- to 12-membered)$ heteroaryl)- (C_1-C_6) alkyl, $-C(=O)-NH-((3- to 12-membered)$ heterocycle), $-C(=O)-NH-((3- to 12-membered)$ heterocycle)- (C_1-C_6) alkyl, $-SO_2-((6- to 14-membered)$ aryl), $-SO_2-((6- to 14-$
 - 25 membered)aryl)- (C_1-C_6) alkyl, $-(7- to 12-membered)$ bicyclic ring system, $((7- to 12-membered)$ bicyclic ring system)- (C_1-C_6) alkyl-, $-(7- to 12-membered)$ bicyclic aryl, $((7-$
 - 30 membered)bicyclic ring system)- (C_1-C_6) alkyl-, $-(7- to 12-membered)$ bicyclic aryl, $((7-$

to 12-membered)bicyclic aryl)-(C₁-C₆)alkyl-, -(5- to 12-membered)heteroaryl, ((5- to 12-membered)heteroaryl)-(C₁-C₆)alkyl-, -(3- to 12-membered)heterocycle, ((3- to 12-membered)heterocycle)-(C₁-C₆)alkyl-, -(7- to 12-membered)bicycloheterocycle, ((7- to 12-membered)bicycloheterocycle)-(C₁-C₆)alkyl-, phenyl, benzyl and naphthyl; each of which is optionally substituted with one, two, or three substituents independently selected from the group consisting of -OH, (=O), halo, -C(halo)₃, -CH(halo)₂, -CH₂(halo), -(C₁-C₆)alkyl, halo(C₁-C₆)alkyl-, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, hydroxy(C₁-C₆)alkyl-, dihydroxy(C₁-C₆)alkyl-, -(C₁-C₆)alkoxy, ((C₁-C₆)alkoxy)CO(C₁-C₆)alkoxy-, phenyl, benzyl, -NH₂, -NH(C₁-C₆)alkyl, -(C₁-C₆)alkyl-NH(C₁-C₆)alkyl-R¹⁴, -CN, -SH, -OR¹¹, -CONR⁵R⁶, -(C₁-C₆)alkyl-CO-NR⁵R⁶, -COOR⁷, -(C₁-C₆)alkyl-CO-OR⁷, -(C₁-C₆)alkoxy-COOR⁷, -(OCH₂CH₂)_s-O(C₁-C₆)alkyl, -(CH₂CH₂O)_s-(C₁-C₆)alkyl, -SO₂-NR^{5a}R^{6a}, (C₁-C₆)alkyl)sulfonyl, ((C₁-C₆)alkyl)sulfonyl(C₁-C₆)alkyl-, -NH-SO₂(C₁-C₆)alkyl, NH₂-SO₂(C₁-C₆)alkyl-, -N(SO₂(C₁-C₆)alkyl)₂, -C(=NH)NH₂, -NH-CO-(C₁-C₆)alkyl, -NH-CO-NH₂, -NH-C(=O)-NH-(C₁-C₆)alkyl, -NH-C(=O)-(6- to 14- membered)aryl, -NH-C(=O)-(C₁-C₆)alkyl-(6- to 14- membered)aryl, -NH-(C₁-C₆)alkyl-CO-OR⁷, -NH-C(=O)-(C₁-C₆)alkyl-CO-OR⁷, -NH-C(=O)-CH(NH₂)-(C₁-C₆)alkyl-CO-OR⁷, -(C₃-C₁₂)cycloalkyl, ((C₃-C₁₂)cycloalkyl)-(C₁-C₆)alkyl-, -(6- to 14-membered)aryl, -(6- to 14-membered)aryloxy, -(C₁-C₆)alkoxy-C(O)NR⁵R⁶, -NH-(C₁-C₆)alkyl-C(O)-NR⁵R⁶, -C(O)NH-(C₁-C₆)alkyl-COOR⁷, ((6- to 14-membered)aryl)-(C₁-C₆)alkyl-, -(5- to 12-membered)heteroaryl, ((5- to 12-membered)heteroaryl)-(C₁-C₆)alkyl-, -(3- to 12-membered)heterocycle, ((3- to 12-membered)heterocycle)-(C₁-C₆)alkyl-, -(7- to 12-membered)bicycloheterocycle, and ((7- to 12-membered)bicycloheterocycle)-(C₁-C₆)alkyl-;

25

R³ is selected from:

- a) -H; or
- b) -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, or -(C₂-C₆)alkynyl;

30 R⁴ is selected from

- a) -H, -OH, halo, -C(halo)₃, -CH(halo)₂, -CH₂(halo), COOH, or CONH₂; or

- b) $-(C_1-C_5)\text{alkyl}$, $-(C_2-C_5)\text{alkenyl}$, $-(C_2-C_5)\text{alkynyl}$, $-(CH_2)_n-O-(CH_2)_n-CH_3$, or $-(C_1-C_5)\text{alkoxy}$, each of which is optionally substituted with 1, 2, or 3 independently selected R^9 groups;
- 5 R^5 and R^6 are each independently selected from
- a) hydrogen, $-OH$, halo, $-C(\text{halo})_3$, $-CH(\text{halo})_2$, $-CH_2(\text{halo})$;
- b) $-(C_1-C_6)\text{alkyl}$, $-(C_2-C_5)\text{alkenyl}$, $-(C_2-C_5)\text{alkynyl}$, $-(CH_2)_n-O-(CH_2)_n-CH_3$, $-(C_1-C_6)\text{alkoxy}$, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from $-OH$, halo, $-(C_1-C_{10})\text{alkyl}$, $-(C_2-C_{10})\text{alkenyl}$, $-(C_2-C_{10})\text{alkynyl}$, $-(C_1-C_{10})\text{alkoxy}$, $-(C_3-C_{12})\text{cycloalkyl}$, $-CHO$, $-C(O)OH$, $-C(\text{halo})_3$, $-CH(\text{halo})_2$, $CH_2(\text{halo})$, $-(CH_2)_n-O-(CH_2)_n-CH_3$, phenyl, or $CONR^{5a}R^{6a}$;
- 10 c) $-(C_3-C_8)\text{cycloalkyl}$, $((C_3-C_8)\text{cycloalkyl})-(C_1-C_6)\text{alkyl}$ -, $-COOR^7$, $-(C_1-C_6)\text{alkyl}-COOR^7$, $-CONH_2$, or $(C_1-C_6)\text{alkyl}-CONH$ -;
- d) ((6- to 14-membered)aryl) optionally substituted with 1, 2, or 3 independently selected R^{30} groups;
- 15 e) $-((5\text{- to }12\text{-membered})\text{heteroaryl})$ optionally substituted with 1, 2, or 3 independently selected R^{30} groups; or
- f) R^5 and R^6 together with the nitrogen atom to which they are attached form a (3- to 12-membered)heterocycle optionally substituted with 1, 2, or 3
- 20 independently selected R^{30} groups;

R^{5a} and R^{6a} are each independently selected from the group consisting of:

- a) hydrogen, $-OH$, halo, $-C(\text{halo})_3$, $-CH(\text{halo})_2$, and $-CH_2(\text{halo})$;
- b) $-(C_1-C_6)\text{alkyl}$, $-(C_2-C_6)\text{alkenyl}$, $-(C_2-C_6)\text{alkynyl}$, $-(CH_2)_n-O-(CH_2)_n-CH_3$, and $-(C_1-C_6)\text{alkoxy}$, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from $-OH$, halo, $-(C_1-C_{10})\text{alkyl}$, $-(C_2-C_{12})\text{alkenyl}$, $-(C_2-C_{12})\text{alkynyl}$, $-(C_1-C_{10})\text{alkoxy}$, $-(C_3-C_{12})\text{cycloalkyl}$, $-CHO$, $-COOH$, $-C(\text{halo})_3$, $-CH(\text{halo})_2$, $CH_2(\text{halo})$, $-(CH_2)_n-O-(CH_2)_n-CH_3$, and phenyl;
- 25 c) $-(C_3-C_8)\text{cycloalkyl}$, $((C_3-C_8)\text{cycloalkyl})-(C_1-C_6)\text{alkyl}$ -, $-COOR^7$, $-(C_1-C_6)\text{alkyl}-COOR^7$, $-CONH_2$, and $(C_1-C_6)\text{alkyl}-CONH$ -;
- 30

- d) -(6- to 14-membered)aryl optionally substituted with 1, 2, or 3 independently selected R^{30} groups;
- e) -((5- to 12-membered)heteroaryl) optionally substituted with 1, 2, or 3 independently selected R^{30} groups; or
- 5 f) R^{5a} and R^{6a} together with the nitrogen atom to which they are attached form a (3- to 12-membered)heterocycle optionally substituted with 1, 2, or 3 independently selected R^{30} groups;

each R^7 is independently selected from the group consisting of hydrogen, -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₃-C₁₂)cycloalkyl, -(C₄-C₁₂)cycloalkenyl, 10 ((C₃-C₁₂)cycloalkyl)-(C₁-C₆)alkyl-, and ((C₄-C₁₂)cycloalkenyl)-(C₁-C₆)alkyl-;

each R^8 is independently selected from H, -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₁-C₁₀)alkoxy, -(C₃-C₁₂)cycloalkyl, -(C₃-C₁₂)cycloalkenyl, ((C₃-C₁₂)cycloalkyl)-(C₁-C₆)alkyl-, ((C₃-C₁₂)cycloalkenyl)-(C₁-C₆)alkyl-, -C(=O)(C₁-C₆)alkyl or SO₂(C₁-C₆)alkyl; 15

each R^9 is independently selected from -OH, halo, -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₁-C₁₀)alkoxy, -(C₃-C₁₂)cycloalkyl, -CHO, -C(O)OH, -C(halo)₃, -CH(halo)₂, CH₂(halo), -(CH₂)_n-O-(CH₂)_n-CH₃, phenyl, or CONR^{5a}R^{6a}; 20

each R^{11} is independently selected from -C(halo)₃, -CH(halo)₂, -CH₂(halo), -(C₂-C₅)alkenyl, -(C₂-C₅)alkynyl, -(CH₂)_n-O-(CH₂)_n-CH₃, (6- to 14-membered)aryl, ((6- to 14-membered)aryl)-(C₁-C₆)alkyl-, or (5- to 12-membered)heteroaryl, ((5- to 12-membered)heteroaryl)-(C₁-C₆)alkyl-, each of which is optionally substituted with 1, 2, or 3 independently selected R^9 groups; 25

each R^{14} is independently selected from -COOR⁷, -(C₁-C₆)alkyl-COOR⁷, -C(=O)-(C₁-C₆)alkyl-COOR⁷, -(C₁-C₆)alkyl-C(=O)-(C₁-C₆)alkyl-COOR⁷, CONH₂, or -(C₁-C₆)alkyl-CONH; 30

each R^{30} is independently selected from COOR^7 , $\text{CONR}^{5a}\text{R}^{6a}$, $-(\text{C}_1\text{-C}_6)\text{alkyl}$, $-\text{C}(=\text{O})$, CN , $-(3\text{- to }12\text{-membered})\text{heteroaryl}$, $((3\text{- to }12\text{-membered})\text{heteroaryl})-(\text{C}_1\text{-C}_6)\text{alkyl}$ -, NH_2 , halo, and $((6\text{- to }14\text{-membered})\text{aryl})-(\text{C}_1\text{-C}_6)\text{alkoxy}$ -;

- 5 m is an integer 1, 2, 3, 4, 5, or 6;
 n is an integer 0, 1, 2, 3, 4, 5, or 6;
 s is an integer 1, 2, 3, 4, 5, or 6;

provided that when R^4 is $-(\text{C}_1\text{-C}_5)\text{alkoxy}$ then:

- 10 a) R^{2a} and R^{2b} cannot be taken together to form $=\text{O}$; or
 b) R^{2a} cannot be OH when R^{2b} is $-\text{Z-G-R}^{10}$, and $-\text{Z-G-R}^{10}$ is either:
 a. OH ;
 b. $-(\text{C}_1\text{-C}_6)\text{alkyl}$;
 c. 2-propenyl;
 15 d. 2-propynyl; or
 c) R^{2a} cannot be H when the combination $-\text{Z-G-R}^{10}$ is either:
 a. OH ;
 b. $-\text{O-C}(=\text{O})-(\text{C}_1\text{-C}_6)\text{alkyl}$; or
 c. $-\text{O-C}(=\text{O})-(\text{C}_2\text{-C}_6)\text{alkenyl}$;

20

and provided that when R^4 is OH then:

- a) R^{2a} cannot be OH when R^{2b} is $-\text{Z-G-R}^{10}$, and $-\text{Z-G-R}^{10}$ is:
 a. methyl;
 b. ethyl;
 25 c. 2-propenyl; or
 d. 2-propynyl;
 b) R^{2a} cannot be H when R^{2b} is $-\text{Z-G-R}^{10}$, and $-\text{Z-G-R}^{10}$ is either:
 a. OH ;
 b. $-\text{O-C}(=\text{O})-(\text{C}_1\text{-C}_6)\text{alkyl}$; or
 30 c. $-\text{O-C}(=\text{O})-(\text{C}_2\text{-C}_6)\text{alkenyl}$;

and provided that when R^3 is (C_1-C_6) alkyl or (C_2-C_6) alkenyl, and R^4 is H, OH, or (C_1-C_5) alkoxy, then R^{2b} is not:

- a) optionally substituted (5- to 12-membered)heteroaryl;
- b) optionally substituted (3- to 12-membered)heterocycle; or
- 5 c) unsubstituted phenyl or phenyl substituted with F or Cl, methyl, CF_3 , hydroxy, methoxy, (3- to 12-membered)heterocycle, or NH_2 ;

and provided that when R^4 is OH and R^1 is (C_1-C_{10}) alkyl, then R^{2a} and R^{2b} cannot be together selected =O;

10

and provided that when R^4 is hydrogen and when R^1 and R^3 are both methyl, then:

- a) R^{2a} and R^{2b} cannot together form =O or =N-OH; or
- b) R^{2b} may not be NH_2 or $NHC(O)CH_3$ if R^{2a} is hydrogen;

15 and provided that when R^{2a} is H, then R^{2b} may not be $-Z-G-R^{10}$, wherein $-Z-G-R^{10}$ is:

- a) $-CH_2-CHR^{20}-C(=O)R^{21}$, wherein
 R^{20} is H, or $-(C_1-C_6)$ alkyl, and
 R^{21} is selected from the group consisting of H, $-(C_1-C_{10})$ alkyl,
 $-(C_3-C_{12})$ cycloalkyl, $((C_3-C_{12})$ cycloalkyl)- (C_1-C_6) alkyl-, phenyl, and
 20 phenyl- (C_1-C_6) alkyl; or

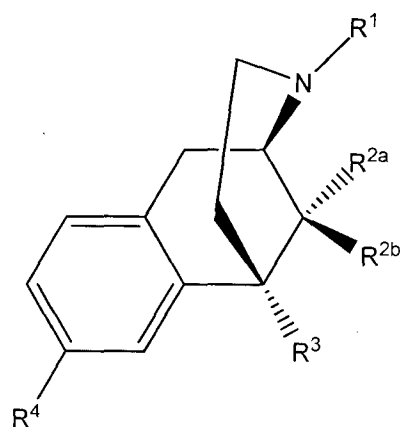
- b) $-CH_2-CHR^{20}-CR^{22}R^{23}OH$, wherein
 R^{20} is defined as above, and
 R^{22} and R^{23} are each independently selected from the group consisting of H,
 $-(C_1-C_{10})$ alkyl, $((C_3-C_{12})$ cycloalkyl)- (C_1-C_6) alkyl-, phenyl, and
 25 phenyl- (C_1-C_6) alkyl; or

- c) $-CH_2-CR^{20}=CR^{23}R^{24}$, wherein
 R^{20} and R^{23} are defined as above, and
 R^{24} is selected from the group consisting of H, and $-(C_1-C_6)$ alkyl;

30

and the pharmaceutically acceptable salts and solvates thereof.

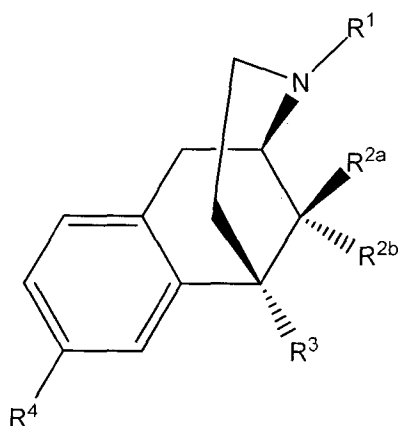
In one embodiment, the present invention provides novel compounds of Formula IA'':



IA''

wherein R¹, R^{2a}, R^{2b}, R³ and R⁴ are as defined above for Formula I'', and the pharmaceutically acceptable salts and solvates thereof.

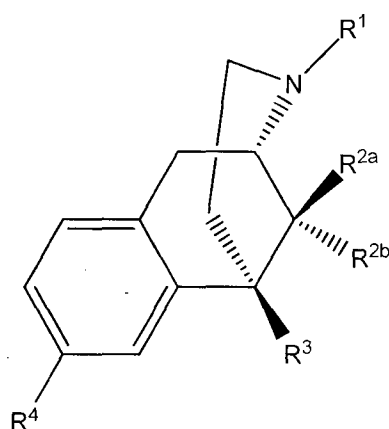
In another embodiment, the present invention provides novel compounds of Formula IB'':



IB''

wherein R^1 , R^{2a} , R^{2b} , R^3 and R^4 are as defined above for Formula I", and the pharmaceutically acceptable salts and solvates thereof.

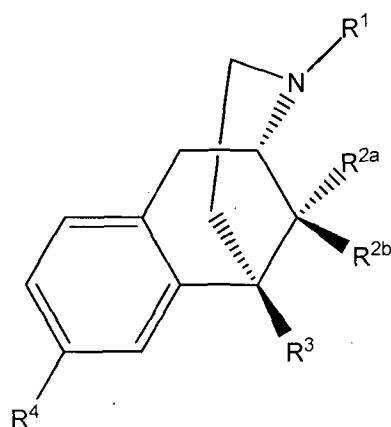
- 5 In another embodiment, the present invention provides novel compounds of Formula IC":



IC"

- 10 wherein R^1 , R^{2a} , R^{2b} , R^3 and R^4 are as defined above for Formula I", and the pharmaceutically acceptable salts and solvates thereof.

In another embodiment, the present invention provides novel compounds of Formula ID^{''}:

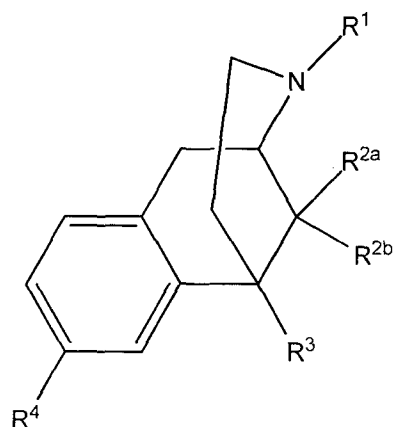
ID^{''}

5

wherein R¹, R^{2a}, R^{2b}, R³ and R⁴ are as defined above for Formula I^{''}, and the pharmaceutically acceptable salts and solvates thereof.

In one embodiment, the present invention provides novel compounds of Formula I^{''}:

10

I^{''}

wherein

R¹ is selected from the group consisting of $-(C_1-C_{10})$ alkyl, $-(C_2-C_{10})$ alkenyl, $-(C_2-C_{10})$ alkynyl, $-(C_3-C_{12})$ cycloalkyl, (C_3-C_{12}) cycloalkyl- $-(C_1-C_6)$ alkyl-, $-(C_3-C_{12})$ cycloalkenyl, (C_3-C_{12}) cycloalkenyl- $-(C_1-C_6)$ alkyl-, $-(6- \text{ to } 14\text{-membered})$ aryl, $((6- \text{ to } 14\text{-membered})$ aryl)- $-(C_1-C_6)$ alkyl-, diphenyl- $-(C_1-C_6)$ alkyl-, $-(3- \text{ to } 12\text{-membered})$ heterocycle, $((3- \text{ to } 12 \text{ membered})$ heterocycle)- $-(C_1-C_6)$ alkyl-, $-(OCH_2CH_2)_s-O-(C_1-C_6)$ alkyl, $-(CH_2CH_2O)_s-(C_1-C_6)$ alkyl, (C_1-C_{10}) alkoxy, $C(\text{halo})_3$, $CH(\text{halo})_2$, $CH_2(\text{halo})$, $C(O)R^5$, $-C(O)O-(C_1-C_{10})$ alkyl, and $-(CH_2)_n-N(R^6)_2$, each of which is optionally substituted by 1, 2 or 3 independently selected R⁹ groups;

10

R^{2a} is hydrogen, OH, or absent;

R^{2b} is

- a) $((6- \text{ to } 14\text{-membered})$ aryl), $-(5- \text{ to } 12\text{-membered})$ heteroaryl), or $((3- \text{ to } 12\text{-membered})$ heterocycle), each of which is optionally substituted with one, two, or three independently selected R³⁰ groups; or
 - b) $-Z-G-R^{10}$, provided that $-Z-G-R^{10}$ is other than hydrogen;
- or R^{2a} and R^{2b} together form =O;

15

Z is absent or $-(CH_2)_m-$, optionally substituted with 1 or 2 $-(C_1-C_6)$ alkyl;

20

G is selected from the group consisting of:

- a) a bond, $-(C_1-C_6)$ alkylene, $-(C_2-C_6)$ alkenylene;
- b) O, $-OCO-$, $-C(=O)$, $=CH$;
- c) NR^8 , $=N-O$, $=N-NH$;
- d) S, SO, SO₂; and
- e) $-NH-SO_2$;

25

and when Z is absent and G is $=CH$, $=N-O$, or $=N-NH$, then R^{2a} is absent;

R¹⁰ is selected from the group consisting of hydrogen, $-(C_1-C_{10})$ alkyl, $-(C_2-C_{12})$ alkenyl, $-C(=O)$, $-C(=O)-(C_1-C_6)$ alkyl, $-C(=O)-(C_2-C_6)$ alkenyl, $-C(=O)-(6- \text{ to } 14-$

30

membered)aryl, -C(=O)-(C₁-C₆)alkyl-(6- to 14-membered)aryl, -(C₂-C₁₂)alkynyl, -(C₁-C₁₀)alkoxy, -(OCH₂CH₂)_s-O(C₁-C₆)alkyl, -(CH₂CH₂O)_s-(C₁-C₆)alkyl, -NH₂, -NH(C₁-C₆)alkyl, CN, NR⁵R⁶, -(C₁-C₆)alkyl-NR⁵R⁶, -CONR⁵R⁶, -(C₁-C₆)alkyl-CO-NR⁵R⁶, -COOR⁷, -(C₁-C₆)alkyl-CO-OR⁷, -(C₁-C₆)alkoxy-COOR⁷, -CO-(CH₂)_n-COOR⁷, -CO-(CH₂)_n-CO-NR⁵R⁶, -(C₃-C₁₂)cycloalkyl, ((C₃-C₁₂)cycloalkyl)-(C₁-C₆)alkyl-, -(C₄-C₁₂)cycloalkenyl, ((C₄-C₁₂)cycloalkenyl)-(C₁-C₆)alkyl-, -(C₆-C₁₄)bicycloalkyl, ((C₆-C₁₄)bicycloalkyl)-(C₁-C₆)alkyl-, -(C₈-C₂₀)tricycloalkyl, ((C₈-C₂₀)tricycloalkyl)-(C₁-C₆)alkyl-, -(C₇-C₁₄)bicycloalkenyl, ((C₇-C₁₄)bicycloalkenyl)-(C₁-C₆)alkyl-, -(C₈-C₂₀)tricycloalkenyl, ((C₈-C₂₀)tricycloalkenyl)-(C₁-C₆)alkyl-, -(6- to 14-membered)aryl, ((6- to 14-membered)aryl)-(C₁-C₆)alkyl-, -SO₂-(C₁-C₆)alkyl-, -SO₂-((C₃-C₁₂)cycloalkyl), -SO₂-((C₃-C₁₂)cycloalkyl)-(C₁-C₆)alkyl-, -SO₂-((5- to 12-membered)heteroaryl), -SO₂-((5- to 12-membered)heteroaryl)-(C₁-C₆)alkyl-, -C(=O)-NH-((5- to 12-membered)heteroaryl), -C(=O)-NH-((5- to 12-membered)heteroaryl)-(C₁-C₆)alkyl-, -C(=O)-NH-((3- to 12-membered)heterocycle), -C(=O)-NH-((3- to 12-membered)heterocycle)-(C₁-C₆)alkyl, SO₂-((6- to 14-membered)aryl), SO₂-((6- to 14-membered)aryl)-(C₁-C₆)alkyl-, -(7- to 12-membered)bicyclic ring system, ((7- to 12-membered)bicyclic ring system)-(C₁-C₆)alkyl-, -(7- to 12-membered)bicyclic aryl, ((7- to 12-membered)bicyclic aryl)-(C₁-C₆)alkyl-, -(5- to 12-membered)heteroaryl, ((5- to 12-membered)heteroaryl)-(C₁-C₆)alkyl-, -(3- to 12-membered)heterocycle, ((3- to 12-membered)heterocycle)-(C₁-C₆)alkyl-, -(7- to 12-membered)bicycloheterocycle, ((7- to 12-membered)bicycloheterocycle)-(C₁-C₆)alkyl-, phenyl, benzyl and naphthyl; each of which is optionally substituted with one, two, or three substituents independently selected from the group consisting of -OH, (=O), halo, -C(halo)₃, -CH(halo)₂, -CH₂(halo), -(C₁-C₆)alkyl, halo(C₁-C₆)alkyl-, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, hydroxy(C₁-C₆)alkyl-, dihydroxy(C₁-C₆)alkyl-, -(C₁-C₆)alkoxy, ((C₁-C₆)alkoxy)CO(C₁-C₆)alkoxy-, phenyl, benzyl, -NH₂, -NH(C₁-C₆)alkyl, -(C₁-C₆)alkyl-NH(C₁-C₆)alkyl-R¹⁴, -CN, -SH, -OR¹¹, -CONR⁵R⁶, -(C₁-C₆)alkyl-CO-NR⁵R⁶, -COOR⁷, -(C₁-C₆)alkyl-CO-OR⁷, -(C₁-C₆)alkoxy-COOR⁷, -(OCH₂CH₂)_s-O(C₁-C₆)alkyl, -(CH₂CH₂O)_s-(C₁-C₆)alkyl, -SO₂-NR^{5a}R^{6a}, (C₁-C₆)alkyl)sulfonyl, ((C₁-C₆)alkyl)sulfonyl(C₁-C₆)alkyl-, -NH-SO₂(C₁-C₆)alkyl, NH₂-SO₂(C₁-C₆)alkyl-, -N(SO₂(C₁-C₆)alkyl)₂, -C(=NH)NH₂, -NH-CO-(C₁-C₆)alkyl, -NH-CO-NH₂, -NH-

C(=O)-NH-(C₁-C₆)alkyl, -NH-C(=O)-(6- to 14- membered)aryl, -NH-C(=O)-(C₁-C₆)alkyl-(6- to 14- membered)aryl, -NH-(C₁-C₆)alkyl-CO-OR⁷, -NH-C(=O)-(C₁-C₆)alkyl-CO-OR⁷, -NH-C(=O)-CH(NH₂)-(C₁-C₆)alkyl-CO-OR⁷, -(C₃-C₁₂)cycloalkyl, ((C₃-C₁₂)cycloalkyl)-(C₁-C₆)alkyl-, -(6- to 14-membered)aryl, -(6- to 14-
 5 membered)aryloxy, -(C₁-C₆)alkoxy-C(O)NR⁵R⁶, -NH-(C₁-C₆)alkyl-C(O)-NR⁵R⁶, -C(O)NH-(C₁-C₆)alkyl-COOR⁷, ((6- to 14-membered)aryl)-(C₁-C₆)alkyl-, -(5- to 12-membered)heteroaryl, ((5- to 12-membered)heteroaryl)-(C₁-C₆)alkyl-, -(3- to 12-membered)heterocycle, ((3- to 12-membered)heterocycle)-(C₁-C₆)alkyl-, -(7- to 12-membered)bicycloheterocycle, and ((7- to 12-membered)bicycloheterocycle)-(C₁-
 10 C₆)alkyl-;

R³ is selected from:

- a) -H; or
- b) -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, or -(C₂-C₆)alkynyl;

15

R⁴ is selected from

- a) -H, -OH, halo, -C(halo)₃, -CH(halo)₂, -CH₂(halo), COOH, or CONH₂; or
- b) -(C₁-C₅)alkyl, -(C₂-C₅)alkenyl, -(C₂-C₅)alkynyl, -(CH₂)_n-O-(CH₂)_n-CH₃, or -(C₁-C₅)alkoxy, each of which is optionally substituted with 1, 2, or 3 independently
 20 selected R⁹ groups;

20

R⁵ and R⁶ are each independently selected from

- a) hydrogen, -OH, halo, -C(halo)₃, -CH(halo)₂, -CH₂(halo);
- b) -(C₁-C₆)alkyl, -(C₂-C₅)alkenyl, -(C₂-C₅)alkynyl, -(CH₂)_n-O-(CH₂)_n-CH₃, -(C₁-C₆)alkoxy, each of which is optionally substituted with 1, 2, or 3 substituents
 25 independently selected from -OH, halo, -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₁-C₁₀)alkoxy, -(C₃-C₁₂)cycloalkyl, -CHO, -C(O)OH, -C(halo)₃, -CH(halo)₂, CH₂(halo), -(CH₂)_n-O-(CH₂)_n-CH₃, phenyl, or CONR^{5a}R^{6a};
- c) -(C₃-C₈)cycloalkyl, ((C₃-C₈)cycloalkyl)-(C₁-C₆)alkyl-, -COOR⁷, -(C₁-C₆)alkyl-
 30 COOR⁷, -CONH₂, or (C₁-C₆)alkyl-CONH-;

30

- d) ((6- to 14-membered)aryl) optionally substituted with 1, 2, or 3 independently selected R^{30} groups;
- e) -((5- to 12-membered)heteroaryl) optionally substituted with 1, 2, or 3 independently selected R^{30} groups; or
- 5 f) R^5 and R^6 together with the nitrogen atom to which they are attached form a (3- to 12-membered)heterocycle optionally substituted with 1, 2, or 3 independently selected R^{30} groups;

R^{5a} and R^{6a} are each independently selected from the group consisting of:

- 10 a) hydrogen, -OH, halo, -C(halo)₃, -CH(halo)₂, and -CH₂(halo);
- b) -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(CH₂)_n-O-(CH₂)_n-CH₃, and -(C₁-C₆)alkoxy, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from -OH, halo, -(C₁-C₁₀)alkyl, -(C₂-C₁₂)alkenyl, -(C₂-C₁₂)alkynyl, -(C₁-C₁₀)alkoxy, -(C₃-C₁₂)cycloalkyl, -CHO, -
- 15 COOH, -C(halo)₃, -CH(halo)₂, CH₂(halo), -(CH₂)_n-O-(CH₂)_n-CH₃, and phenyl;
- c) -(C₃-C₈)cycloalkyl, ((C₃-C₈)cycloalkyl)-(C₁-C₆)alkyl-, -COOR⁷, -(C₁-C₆)alkyl-COOR⁷, -CONH₂, and (C₁-C₆)alkyl-CONH-;
- d) -(6- to 14-membered)aryl optionally substituted with 1, 2, or 3 independently selected R^{30} groups;
- 20 e) -((5- to 12-membered)heteroaryl) optionally substituted with 1, 2, or 3 independently selected R^{30} groups; or
- f) R^{5a} and R^{6a} together with the nitrogen atom to which they are attached form a (3- to 12-membered)heterocycle optionally substituted with 1, 2, or 3 independently selected R^{30} groups;

25

each R^7 is independently selected from the group consisting of hydrogen, -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₃-C₁₂)cycloalkyl, -(C₄-C₁₂)cycloalkenyl, ((C₃-C₁₂)cycloalkyl)-(C₁-C₆)alkyl-, and ((C₄-C₁₂)cycloalkenyl)-(C₁-C₆)alkyl-;

- 30 each R^8 is independently selected from H, -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₁-C₁₀)alkoxy, -(C₃-C₁₂)cycloalkyl, -(C₃-C₁₂)cycloalkenyl, ((C₃-

(C₁₂)cycloalkyl)-(C₁-C₆)alkyl-, ((C₃-C₁₂)cycloalkenyl)-(C₁-C₆)alkyl-, -C(=O)(C₁-C₆)alkyl or SO₂(C₁-C₆)alkyl;

each R⁹ is independently selected from -OH, halo, -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -
 5 (C₂-C₁₀)alkynyl, -(C₁-C₁₀)alkoxy, -(C₃-C₁₂)cycloalkyl, -CHO, -C(O)OH, -C(halo)₃, -CH(halo)₂, CH₂(halo), -(CH₂)_n-O-(CH₂)_n-CH₃, phenyl, or CONR^{5a}R^{6a};

each R¹¹ is independently selected from -C(halo)₃, -CH(halo)₂, -CH₂(halo), -(C₂-C₅)alkenyl, -(C₂-C₅)alkynyl, -(CH₂)_n-O-(CH₂)_n-CH₃, (6- to 14-membered)aryl, ((6- to
 10 14-membered)aryl)-(C₁-C₆)alkyl-, or (5- to 12-membered)heteroaryl, ((5- to 12-membered)heteroaryl)-(C₁-C₆)alkyl-, each of which is optionally substituted with 1, 2, or 3 independently selected R⁹ groups;

each R¹⁴ is independently selected from -COOR⁷, -(C₁-C₆)alkyl-COOR⁷, -C(=O)-(C₁-C₆)alkyl-COOR⁷, -(C₁-C₆)alkyl-C(=O)-(C₁-C₆)alkyl-COOR⁷, CONH₂, or -(C₁-C₆)alkyl-CONH;

each R³⁰ is independently selected from COOR⁷, CONR^{5a}R^{6a}, -(C₁-C₆)alkyl, -C(=O), CN, -(3- to 12-membered)heteroaryl, ((3- to 12-membered)heteroaryl)-(C₁-C₆)alkyl-,
 20 NH₂, halo, and ((6- to 14-membered)aryl)-(C₁-C₆)alkoxy-;

m is an integer 1, 2, 3, 4, 5, or 6;

n is an integer 0, 1, 2, 3, 4, 5, or 6;

s is an integer 1, 2, 3, 4, 5, or 6;

25

provided that when R⁴ is -(C₁-C₅)alkoxy then:

a) R^{2a} and R^{2b} cannot be taken together to form =O; or

b) R^{2a} cannot be OH when R^{2b} is -Z-G-R¹⁰, and -Z-G-R¹⁰ is either:

a. OH;

30 b. -(C₁-C₆)alkyl;

c. -(C₂-C₆)alkenyl; or

- d. $-(C_2-C_6)$ alkynyl; or
- c) R^{2a} cannot be H when the combination $-Z-G-R^{10}$ is either:
 - a. OH;
 - b. $-O-C(=O)-(C_1-C_6)$ alkyl; or
 - 5 c. $-O-C(=O)-(C_2-C_6)$ alkenyl;

and provided that when R^4 is OH then:

- a) R^{2a} cannot be OH when R^{2b} is $-Z-G-R^{10}$, and $-Z-G-R^{10}$ is:
 - a. $-(C_1-C_6)$ alkyl;
 - b. $-(C_2-C_6)$ alkenyl;
 - 10 c. or $-(C_2-C_6)$ alkynyl;
- b) R^{2a} cannot be H when R^{2b} is $-Z-G-R^{10}$, and $-Z-G-R^{10}$ is:
 - a. OH
 - b. $-O-C(=O)-(C_1-C_6)$ alkyl; or
 - c. $-O-C(=O)-(C_2-C_6)$ alkenyl;

15

and provided that when R^3 is (C_1-C_6) alkyl or (C_2-C_6) alkenyl, and R^4 is H, OH, or (C_1-C_5) alkoxy, then R^{2b} is not

- a) optionally substituted (5- to 12-membered)heteroaryl,
- b) optionally substituted (3- to 12-membered)heterocycle, or
- 20 c) unsubstituted phenyl or phenyl substituted with halo, (C_1-C_6) alkyl, $C(\text{halo})_3$, hydroxy, (C_1-C_6) alkoxy, (3- to 12-membered)heterocycle, or NH_2

and provided that when R^4 is OH and R^1 is (C_1-C_{10}) alkyl, then R^{2a} and R^{2b} cannot be together selected =O.

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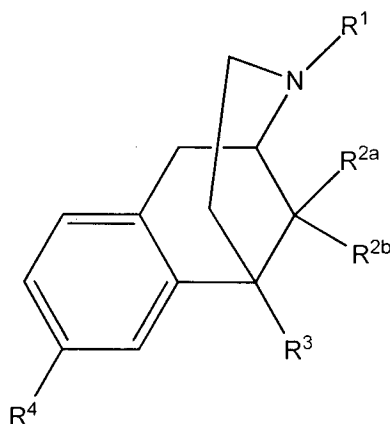
and provided that when R^4 is hydrogen and when R^1 and R^3 are both methyl, then

- a) R^{2a} and R^{2b} cannot together form =O or =N-OH; or
- b) R^{2b} may not be NH_2 or $NHC(O)CH_3$ if R^{2a} is hydrogen.

30 and provided that when R^{2a} is H, then R^{2b} may not be $-Z-G-R^{10}$, wherein $-Z-G-R^{10}$ is:

- a) $-\text{CH}_2-\text{CHR}^{20}-\text{C}(=\text{O})\text{R}^{21}$, wherein
 R^{20} is H, or $-(\text{C}_1-\text{C}_6)\text{alkyl}$, and
 R^{21} is selected from the group consisting of H, $-(\text{C}_1-\text{C}_{10})\text{alkyl}$,
 $-(\text{C}_3-\text{C}_{12})\text{cycloalkyl}$, $((\text{C}_3-\text{C}_{12})\text{cycloalkyl})-(\text{C}_1-\text{C}_6)\text{alkyl}$ -, $-(6\text{- to }14\text{-membered})\text{aryl}$, and $((6\text{- to }14\text{-membered})\text{aryl})-(\text{C}_1-\text{C}_6)\text{alkyl}$ -, or
- b) $-\text{CH}_2-\text{CHR}^{20}-\text{CR}^{22}\text{R}^{23}\text{OH}$, wherein
 R^{20} is defined as above, and
 R^{22} and R^{23} are each independently selected from the group consisting of H,
 $-(\text{C}_1-\text{C}_{10})\text{alkyl}$, $((\text{C}_3-\text{C}_{12})\text{cycloalkyl})-(\text{C}_1-\text{C}_6)\text{alkyl}$ -, $-(6\text{- to }14\text{-membered})\text{aryl}$,
and $((6\text{- to }14\text{-membered})\text{aryl})-(\text{C}_1-\text{C}_6)\text{alkyl}$ -, or
- c) $-\text{CH}_2-\text{CR}^{20}=\text{CR}^{23}\text{R}^{24}$, wherein
 R^{20} and R^{23} are defined as above, and
 R^{24} is selected from the group consisting of H, and $-(\text{C}_1-\text{C}_6)\text{alkyl}$.
- and the pharmaceutically acceptable salts and solvates thereof.

In another aspect, the present invention provides novel compounds of Formula I':



I'

wherein

R^1 is selected from the group consisting of $-(C_1-C_{10})$ alkyl, $-(C_2-C_{10})$ alkenyl, $-(C_2-C_{10})$ alkynyl, $-(C_3-C_{12})$ cycloalkyl, (C_3-C_{12}) cycloalkyl- (C_1-C_6) alkyl-, $-(C_3-C_{12})$ cycloalkenyl, (C_3-C_{12}) cycloalkenyl- (C_1-C_6) alkyl-, $-(6- \text{ to } 14\text{-membered})$ aryl, $((6- \text{ to } 14\text{-membered})$ aryl)- (C_1-C_6) alkyl-, diphenyl- (C_1-C_6) alkyl-, $-(3- \text{ to } 12\text{-membered})$ heterocycle, $((3- \text{ to } 12 \text{ membered})$ heterocycle)- (C_1-C_6) alkyl-, $-(OCH_2CH_2)_5-O-(C_1-C_6)$ alkyl, $-(CH_2CH_2O)_5-(C_1-C_6)$ alkyl, (C_1-C_{10}) alkoxy, $C(\text{halo})_3$, $CH(\text{halo})_2$, $CH_2(\text{halo})$, $C(O)R^5$, $-C(O)O-(C_1-C_{10})$ alkyl, and $-(CH_2)_n-N(R^6)_2$, each of which is optionally substituted by 1, 2 or 3 independently selected R^9 groups;

10

R^{2a} is absent or OH;

R^{2b} is

- a) $((6- \text{ to } 14\text{-membered})$ aryl) or $((3- \text{ to } 12\text{-membered})$ heterocycle), each of which is optionally substituted with one, two, or three independently selected R^{30} groups; or
- b) $-Z-G-R^{10}$, provided that $-Z-G-R^{10}$ is other than hydrogen;
- or R^{2a} and R^{2b} together form $=O$;

15

Z is absent or $-(CH_2)_m-$, optionally substituted with 1 or 2 $-(C_1-C_6)$ alkyl;

20

G is selected from the group consisting of:

- a) a bond, $-(C_1-C_6)$ alkylene, $-(C_2-C_6)$ alkenylene;
- b) O, $-OCO-$, $-C(=O)$, $=CH$;
- c) NR^8 , $=N-O$, $=N-NH$;
- d) S, SO, and SO_2 ;

25

R^{10} is selected from the group consisting of hydrogen, $-(C_1-C_{10})$ alkyl, $-(C_2-C_{12})$ alkenyl, $-C(=O)$, $-C(=O)-(C_1-C_6)$ alkyl, $-C(=O)-(C_2-C_6)$ alkenyl, $-C(=O)-(6- \text{ to } 14\text{-membered})$ aryl, $-C(=O)-(C_1-C_6)$ alkyl- $(6- \text{ to } 14\text{-membered})$ aryl, $-(C_2-C_{12})$ alkynyl, $-(C_1-C_{10})$ alkoxy, $-(OCH_2CH_2)_5-O-(C_1-C_6)$ alkyl, $-(CH_2CH_2O)_5-(C_1-C_6)$ alkyl, $-NH_2$, $-NH(C_1-C_6)$ alkyl, CN, NR^5R^6 , $-(C_1-C_6)$ alkyl- NR^5R^6 , $-CONR^5R^6$, $-(C_1-C_6)$ alkyl-CO-

30

NR^5R^6 , $-\text{COOR}^7$, $-(\text{C}_1-\text{C}_6)\text{alkyl}-\text{CO}-\text{OR}^7$, $-(\text{C}_1-\text{C}_6)\text{alkoxy}-\text{COOR}^7$, $-\text{CO}-(\text{CH}_2)_n-$
 COOR^7 , $-\text{CO}-(\text{CH}_2)_n-\text{CO}-\text{NR}^5\text{R}^6$, $-(\text{C}_3-\text{C}_{12})\text{cycloalkyl}$, $((\text{C}_3-\text{C}_{12})\text{cycloalkyl})-(\text{C}_1-$
 $\text{C}_6)\text{alkyl}$ -, $-(\text{C}_4-\text{C}_{12})\text{cycloalkenyl}$, $((\text{C}_4-\text{C}_{12})\text{cycloalkenyl})-(\text{C}_1-\text{C}_6)\text{alkyl}$ -, $-(\text{C}_6-$
 $\text{C}_{14})\text{bicycloalkyl}$, $((\text{C}_6-\text{C}_{14})\text{bicycloalkyl})-(\text{C}_1-\text{C}_6)\text{alkyl}$ -, $-(\text{C}_8-\text{C}_{20})\text{tricycloalkyl}$, $((\text{C}_8-$
5 $\text{C}_{20})\text{tricycloalkyl})-(\text{C}_1-\text{C}_6)\text{alkyl}$ -, $-(\text{C}_7-\text{C}_{14})\text{bicycloalkenyl}$, $((\text{C}_7-\text{C}_{14})\text{bicycloalkenyl})-$
 $(\text{C}_1-\text{C}_6)\text{alkyl}$ -, $-(\text{C}_8-\text{C}_{20})\text{tricycloalkenyl}$, $((\text{C}_8-\text{C}_{20})\text{tricycloalkenyl})-(\text{C}_1-\text{C}_6)\text{alkyl}$ -, $-(6-$
to 14-membered)aryl, $((6-$ to 14-membered)aryl) $-(\text{C}_1-\text{C}_6)\text{alkyl}$ -, $-(7-$ to 12-
membered)bicyclic ring system, $((7-$ to 12-membered)bicyclic ring system) $-(\text{C}_1-$
 $\text{C}_6)\text{alkyl}$ -, $-(7-$ to 12-membered)bicyclic aryl, $((7-$ to 12-membered)bicyclic aryl) $-(\text{C}_1-$
10 $\text{C}_6)\text{alkyl}$ -, $-(5-$ to 12-membered)heteroaryl, $((5-$ to 12-membered)heteroaryl) $-(\text{C}_1-$
 $\text{C}_6)\text{alkyl}$ -, $-(3-$ to 12-membered)heterocycle, $((3-$ to 12 membered)heterocycle) $-(\text{C}_1-$
 $\text{C}_6)\text{alkyl}$ -, $-(7-$ to 12-membered)bicycloheterocycle, $((7-$ to 12-
membered)bicycloheterocycle) $-(\text{C}_1-\text{C}_6)\text{alkyl}$ -, phenyl, benzyl and naphthyl; each of
which is optionally substituted with one, two, or three substituents independently
15 selected from the group consisting of $-\text{OH}$, $(=\text{O})$, halo, $-\text{C}(\text{halo})_3$, $-\text{CH}(\text{halo})_2$,
 $-\text{CH}_2(\text{halo})$, $-(\text{C}_1-\text{C}_6)\text{alkyl}$, halo $(\text{C}_1-\text{C}_6)\text{alkyl}$ -, $-(\text{C}_2-\text{C}_6)\text{alkenyl}$, $-(\text{C}_2-\text{C}_6)\text{alkynyl}$,
hydroxy $(\text{C}_1-\text{C}_6)\text{alkyl}$ -, dihydroxy $(\text{C}_1-\text{C}_6)\text{alkyl}$ -, $-(\text{C}_1-\text{C}_6)\text{alkoxy}$, $((\text{C}_1-$
 $\text{C}_6)\text{alkoxy})\text{CO}(\text{C}_1-\text{C}_6)\text{alkoxy}$ -, phenyl, benzyl, $-\text{NH}_2$, $-\text{NH}(\text{C}_1-\text{C}_6)\text{alkyl}$,
 $-(\text{C}_1-\text{C}_6)\text{alkyl}-\text{NH}(\text{C}_1-\text{C}_6)\text{alkyl}-\text{R}^{14}$, $-\text{CN}$, $-\text{SH}$, $-\text{OR}^{11}$, $-\text{CONR}^5\text{R}^6$, $-(\text{C}_1-\text{C}_6\text{alkyl})-\text{CO}-$
20 NR^5R^6 , $-\text{COOR}^7$, $-(\text{C}_1-\text{C}_6)\text{alkyl}-\text{CO}-\text{OR}^7$, $-(\text{C}_1-\text{C}_6)\text{alkoxy}-\text{COOR}^7$, $-(\text{OCH}_2\text{CH}_2)_s-$
 $\text{O}(\text{C}_1-\text{C}_6)\text{alkyl}$, $-(\text{CH}_2\text{CH}_2\text{O})_s-(\text{C}_1-\text{C}_6)\text{alkyl}$, $(\text{C}_1-\text{C}_6)\text{alkyl})\text{sulfonyl}$, $((\text{C}_1-$
 $\text{C}_6)\text{alkyl})\text{sulfonyl}(\text{C}_1-\text{C}_6)\text{alkyl}$ -, $-\text{NH}-\text{SO}_2(\text{C}_1-\text{C}_6)\text{alkyl}$, $\text{NH}_2-\text{SO}_2(\text{C}_1-\text{C}_6)\text{alkyl}$ -, $-$
 $\text{N}(\text{SO}_2(\text{C}_1-\text{C}_6)\text{alkyl})_2$, $-\text{C}(=\text{NH})\text{NH}_2$, $-\text{NH}-\text{CO}-(\text{C}_1-\text{C}_6)\text{alkyl}$, $-\text{NH}-\text{CO}-\text{NH}_2$, $-\text{NH}-$
 $\text{C}(=\text{O})-\text{NH}-(\text{C}_1-\text{C}_6)\text{alkyl}$, $-\text{NH}-\text{C}(=\text{O})-(6-$ to 14- membered)aryl, $-\text{NH}-\text{C}(=\text{O})-(\text{C}_1-$
25 $\text{C}_6)\text{alkyl}-(6-$ to 14- membered)aryl, $-\text{NH}-(\text{C}_1-\text{C}_6)\text{alkyl}-\text{CO}-\text{OR}^7$, $-\text{NH}-\text{C}(=\text{O})-(\text{C}_1-$
 $\text{C}_6)\text{alkyl}-\text{CO}-\text{OR}^7$, $-\text{NH}-\text{C}(=\text{O})-\text{CH}(\text{NH}_2)-(\text{C}_1-\text{C}_6)\text{alkyl}-\text{CO}-\text{OR}^7$, $-(\text{C}_3-\text{C}_{12})\text{cycloalkyl}$,
 $((\text{C}_3-\text{C}_{12})\text{cycloalkyl})-(\text{C}_1-\text{C}_6)\text{alkyl}$ -, $-(6-$ to 14-membered)aryl, $-(6-$ to 14-
membered)aryloxy, $-(\text{C}_1-\text{C}_6)\text{alkoxy}-\text{C}(\text{O})\text{NR}^5\text{R}^6$, $-\text{NH}-(\text{C}_1-\text{C}_6)\text{alkyl}-\text{C}(\text{O})-\text{NR}^5\text{R}^6$, $-$
 $\text{C}(\text{O})\text{NH}-(\text{C}_1-\text{C}_6)\text{alkyl}-\text{COOR}^7$, $((6-$ to 14-membered)aryl) $-(\text{C}_1-\text{C}_6)\text{alkyl}$ -, $-(5-$ to 12-
30 membered)heteroaryl, $((5-$ to 12-membered)heteroaryl) $-(\text{C}_1-\text{C}_6)\text{alkyl}$ -, $-(3-$ to 12-
membered)heterocycle, $((3-$ to 12-membered)heterocycle) $-(\text{C}_1-\text{C}_6)\text{alkyl}$ -, $-(7-$ to 12-

membered)bicycloheterocycle, and ((7- to 12-membered)bicycloheterocycle)-(C₁-C₆)alkyl-;

R³ is selected from:

- 5 a) -H; or
 b) -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, or -(C₂-C₆)alkynyl;

R⁴ is selected from

- a) -H, -OH, halo, -C(halo)₃, -CH(halo)₂, -CH₂(halo), COOH, or CONH₂; or
 10 b) -(C₁-C₅)alkyl, -(C₂-C₅)alkenyl, -(C₂-C₅)alkynyl, -(CH₂)_n-O-(CH₂)_n-CH₃, or -(C₁-C₅)alkoxy, each of which is optionally substituted with 1, 2, or 3 independently selected R⁹ groups;

R⁵ and R⁶ are each independently selected from

- 15 a) hydrogen, -OH, halo, -C(halo)₃, -CH(halo)₂, -CH₂(halo);
 b) -(C₁-C₆)alkyl, -(C₂-C₅)alkenyl, -(C₂-C₅)alkynyl, -(CH₂)_n-O-(CH₂)_n-CH₃, -(C₁-C₆)alkoxy, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from -OH, halo, -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₁-C₁₀)alkoxy, -(C₃-C₁₂)cycloalkyl, -CHO, -C(O)OH, -C(halo)₃,
 20 -CH(halo)₂, CH₂(halo), -(CH₂)_n-O-(CH₂)_n-CH₃, phenyl, or CONR⁵R⁶;
 c) -(C₃-C₈)cycloalkyl, ((C₃-C₈)cycloalkyl)-(C₁-C₆)alkyl-, -COOR⁷, -(C₁-C₆)alkyl-COOR⁷, -CONH₂, or (C₁-C₆)alkyl-CONH-;
 d) ((6- to 14-membered)aryl) optionally substituted with 1, 2, or 3 independently selected R³⁰ groups; or
 25 e) R⁵ and R⁶ together with the nitrogen atom to which they are attached form a (4- to 8-membered)heterocycle optionally substituted with 1, 2, or 3 independently selected R³⁰ groups;

R^{5a} and R^{6a} are each independently selected from the group consisting of:

- 30 a) hydrogen, -OH, halo, -C(halo)₃, -CH(halo)₂, and -CH₂(halo);

- b) $-(C_1-C_6)alkyl$, $-(C_2-C_6)alkenyl$, $-(C_2-C_6)alkynyl$, $-(CH_2)_n-O-(CH_2)_n-CH_3$, and $-(C_1-C_6)alkoxy$, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from $-OH$, halo, $-(C_1-C_{10})alkyl$, $-(C_2-C_{12})alkenyl$, $-(C_2-C_{12})alkynyl$, $-(C_1-C_{10})alkoxy$, $-(C_3-C_{12})cycloalkyl$, $-CHO$, $-COOH$, $-C(halo)_3$, $-CH(halo)_2$, $CH_2(halo)$, $-(CH_2)_n-O-(CH_2)_n-CH_3$, and phenyl;
- c) $-(C_3-C_8)cycloalkyl$, $((C_3-C_8)cycloalkyl)-(C_1-C_6)alkyl-$, $-COOR^7$, $-(C_1-C_6)alkyl-COOR^7$, $-CONH_2$, and $(C_1-C_6)alkyl-CONH-$;
- d) $-(6\text{ to }14\text{-membered})aryl$ optionally substituted with 1, 2, or 3 independently selected R^{30} groups; or
- e) R^{5a} and R^{6a} together with the nitrogen atom to which they are attached form a $(4\text{ to }8\text{-membered})heterocycle$ optionally substituted with 1, 2, or 3 independently selected R^{30} groups;

each R^7 is independently selected from the group consisting of hydrogen, $-(C_1-C_6)alkyl$, $-(C_2-C_6)alkenyl$, $-(C_2-C_6)alkynyl$, $-(C_3-C_{12})cycloalkyl$, $-(C_4-C_{12})cycloalkenyl$, $((C_3-C_{12})cycloalkyl)-(C_1-C_6)alkyl-$, and $((C_4-C_{12})cycloalkenyl)-(C_1-C_6)alkyl-$;

each R^8 is independently selected from H, $-(C_1-C_6)alkyl$, $-(C_2-C_6)alkenyl$, $-(C_2-C_6)alkynyl$, $-(C_1-C_{10})alkoxy$, $-(C_3-C_{12})cycloalkyl$, $-(C_3-C_{12})cycloalkenyl$, $((C_3-C_{12})cycloalkyl)-(C_1-C_6)alkyl-$, $((C_3-C_{12})cycloalkenyl)-(C_1-C_6)alkyl-$, $-C(=O)(C_1-C_6)alkyl$ or $SO_2(C_1-C_6)alkyl$;

each R^9 is independently selected from $-OH$, halo, $-(C_1-C_{10})alkyl$, $-(C_2-C_{10})alkenyl$, $-(C_2-C_{10})alkynyl$, $-(C_1-C_{10})alkoxy$, $-(C_3-C_{12})cycloalkyl$, $-CHO$, $-C(O)OH$, $-C(halo)_3$, $-CH(halo)_2$, $CH_2(halo)$, $-(CH_2)_n-O-(CH_2)_n-CH_3$, phenyl, or $CONR^{5a}R^{6a}$;

each R^{11} is independently selected from $-C(halo)_3$, $-CH(halo)_2$, $-CH_2(halo)$, $-(C_2-C_5)alkenyl$, $-(C_2-C_5)alkynyl$, $-(CH_2)_n-O-(CH_2)_n-CH_3$, $(6\text{ to }14\text{-membered})aryl$, $((6\text{ to }14\text{-membered})aryl)-(C_1-C_6)alkyl-$, or $(5\text{ to }12\text{-membered})heteroaryl$, $((5\text{ to }12\text{-membered})heteroaryl)-(C_1-C_6)alkyl-$, each of which is optionally substituted with 1, 2, or 3 independently selected R^9 groups;

each R^{14} is independently selected from $-\text{COOR}^7$, $-(\text{C}_1\text{-C}_6)\text{alkyl-COOR}^7$, $-\text{C}(=\text{O})-(\text{C}_1\text{-C}_6)\text{alkyl-COOR}^7$, $-(\text{C}_1\text{-C}_6)\text{alkyl-C}(=\text{O})-(\text{C}_1\text{-C}_6)\text{alkyl-COOR}^7$, CONH_2 , or $-(\text{C}_1\text{-C}_6)\text{alkyl-CONH}$;

5

each R^{30} is independently selected from COOR^7 , $\text{CONR}^{5a}\text{R}^{6a}$, $-(\text{C}_1\text{-C}_6)\text{alkyl}$, $-\text{C}(=\text{O})$, CN , $-(3\text{- to }12\text{-membered})\text{heteroaryl}$, $((3\text{- to }12\text{-membered})\text{heteroaryl})-(\text{C}_1\text{-C}_6)\text{alkyl}$, NH_2 , halo, and $((6\text{- to }14\text{-membered})\text{aryl})-(\text{C}_1\text{-C}_6)\text{alkoxy}$;

10 m is an integer 1, 2, 3, 4, 5, or 6;

n is an integer 0, 1, 2, 3, 4, 5, or 6;

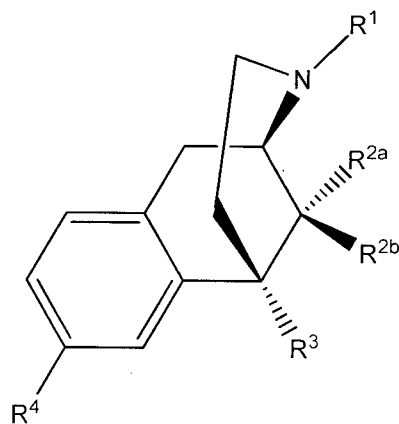
s is an integer 1, 2, 3, 4, 5, or 6;

provided that when R^4 is $-(\text{C}_1\text{-C}_5)\text{alkoxy}$ then:

- a) R^{2a} and R^{2b} cannot be taken together to form $=\text{O}$; or
- 15 b) R^{2a} cannot be OH when R^{2b} is $-\text{Z-G-R}^{10}$, and $-\text{Z-G-R}^{10}$ is either:
 - a. OH ; or
 - b. $-(\text{C}_1\text{-C}_6)\text{alkyl}$; or
 - c) R^{2a} cannot be H when the combination $-\text{Z-G-R}^{10}$ is OH ;

20 and the pharmaceutically acceptable salts and solvates thereof.

In one embodiment, the present invention provides novel compounds of Formula IA':



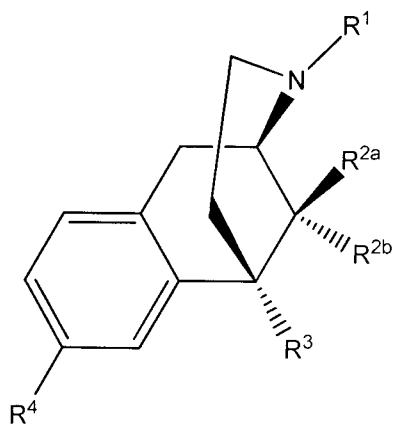
IA'

5

wherein R¹, R^{2a}, R^{2b}, R³ and R⁴ are as defined above for Formula I', and the pharmaceutically acceptable salts and solvates thereof.

In another embodiment, the present invention provides novel compounds of Formula IB':

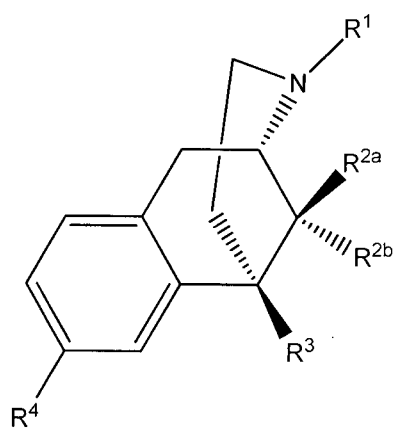
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IB'

wherein R^1 , R^{2a} , R^{2b} , R^3 and R^4 are as defined above for Formula I', and the pharmaceutically acceptable salts and solvates thereof.

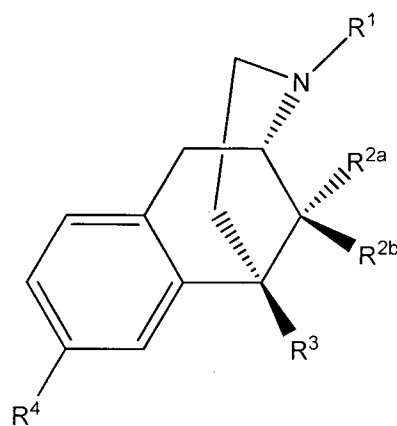
In another embodiment, the present invention provides novel compounds of
5 Formula IC':



IC'

wherein R^1 , R^{2a} , R^{2b} , R^3 and R^4 are as defined above for Formula I', and the
10 pharmaceutically acceptable salts and solvates thereof.

In another embodiment, the present invention provides novel compounds of Formula ID':



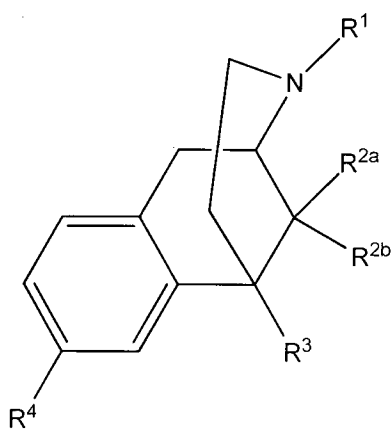
ID'

5

wherein R¹, R^{2a}, R^{2b}, R³ and R⁴ are as defined above for Formula I', and the pharmaceutically acceptable salts and solvates thereof.

The present invention further provides novel compounds of Formula I:

10



I

wherein

R^1 is selected from the group consisting of $-(C_1-C_{10})$ alkyl, $-(C_2-C_{10})$ alkenyl, $-(C_2-C_{10})$ alkynyl, $-(C_3-C_{12})$ cycloalkyl, (C_3-C_{12}) cycloalkyl- $-(C_1-C_6)$ alkyl-, $-(C_3-C_{12})$ cycloalkenyl, (C_3-C_{12}) cycloalkenyl- $-(C_1-C_6)$ alkyl-, $-(6- \text{ to } 14\text{-membered})$ aryl, $((6- \text{ to } 14\text{-membered})\text{aryl})\text{-}(C_1-C_6)\text{alkyl-}$, diphenyl $(C_1-C_6)\text{alkyl-}$, $-(OCH_2CH_2)_s\text{-O-}(C_1-C_6)\text{alkyl}$, $-(CH_2CH_2O)_s\text{-}(C_1-C_6)\text{alkyl}$, (C_1-C_{10}) alkoxy, $C(\text{halo})_3$, $CH(\text{halo})_2$, $CH_2(\text{halo})$, $C(O)R^5$, $-C(O)O\text{-}(C_1-C_{10})\text{alkyl}$, and $-(CH_2)_n\text{-N}(R^6)_2$, each of which is optionally substituted by 1, 2 or 3 independently selected R^9 groups;

R^{2a} is hydrogen or OH;

10 R^{2b} is

a) $((6- \text{ to } 14\text{-membered})\text{aryl})$ or $((3- \text{ to } 12\text{-membered})\text{heterocycle})$, each of which is optionally substituted with one, two, or three independently selected R^{30} groups; or

b) $-Z\text{-G-}R^{10}$, provided that $-Z\text{-G-}R^{10}$ is other than hydrogen;

15 or R^{2a} and R^{2b} together form $=O$;

Z is absent or $-(CH_2)_m\text{-}$, optionally substituted with 1 or 2 $-(C_1-C_6)\text{alkyl}$;

G is selected from the group consisting of:

- a) a bond, $-(C_1-C_6)\text{alkylene}$, $-(C_2-C_6)\text{alkenylene}$;
- 20 b) O, $-OCO\text{-}$, $-C(=O)$, $=CH$;
- c) NR^8 , $=N\text{-O}$, $=N\text{-NH}$;
- d) S, SO, and SO_2 ;

R^{10} is selected from the group consisting of hydrogen, $-(C_1-C_{10})$ alkyl, $-(C_2-C_{12})$ alkenyl, $-(C_2-C_{12})$ alkynyl, $-(C_3-C_{12})$ cycloalkyl, (C_3-C_{12}) cycloalkyl- $-(C_1-C_6)$ alkyl-, $-(6- \text{ to } 14\text{-membered})$ aryl, $-(C_1-C_6)\text{alkyl-}(6- \text{ to } 14\text{-membered})\text{aryl}$, $-(C_2-C_{12})$ alkynyl, $-(C_1-C_{10})$ alkoxy, $-(OCH_2CH_2)_s\text{-O}(C_1-C_6)\text{alkyl}$, $-(CH_2CH_2O)_s\text{-}(C_1-C_6)\text{alkyl}$, $-NH_2$, $-NH(C_1-C_6)\text{alkyl}$, CN, NR^5R^6 , $-(C_1-C_6)\text{alkyl-}NR^5R^6$, $-CONR^5R^6$, $-(C_1-C_6)\text{alkyl-CO-}NR^5R^6$, $-COOR^7$, $-(C_1-C_6)\text{alkyl-CO-OR}^7$, $-(C_1-C_6)\text{alkoxy-COOR}^7$, $-\text{CO-}(CH_2)_n\text{-COOR}^7$, $-\text{CO-}(CH_2)_n\text{-CO-}NR^5R^6$, $-(C_3-C_{12})$ cycloalkyl, $((C_3-C_{12})\text{cycloalkyl})\text{-}(C_1-C_6)\text{alkyl-}$, $-(C_4-C_{12})$ cycloalkenyl, $((C_4-C_{12})\text{cycloalkenyl})\text{-}(C_1-C_6)\text{alkyl-}$, $-(C_6-$

- C₁₄)bicycloalkyl, ((C₆-C₁₄)bicycloalkyl)-(C₁-C₆)alkyl-, -(C₈-C₂₀)tricycloalkyl, ((C₈-C₂₀)tricycloalkyl)-(C₁-C₆)alkyl-, -(C₇-C₁₄)bicycloalkenyl, ((C₇-C₁₄)bicycloalkenyl)-(C₁-C₆)alkyl-, -(C₈-C₂₀)tricycloalkenyl, ((C₈-C₂₀)tricycloalkenyl)-(C₁-C₆)alkyl-, -(6- to 14-membered)aryl, ((6- to 14-membered)aryl)-(C₁-C₆)alkyl-, -(7- to 12-
 5 membered)bicyclic ring system, ((7- to 12-membered)bicyclic ring system)-(C₁-C₆)alkyl-, -(7- to 12-membered)bicyclic aryl, ((7- to 12-membered)bicyclic aryl)-(C₁-C₆)alkyl-, -(5- to 12-membered)heteroaryl, ((5- to 12-membered)heteroaryl)-(C₁-C₆)alkyl-, -(3- to 12-membered)heterocycle, ((3- to 12 membered)heterocycle)-(C₁-C₆)alkyl-, -(7- to 12-membered)bicycloheterocycle, ((7- to 12-
 10 membered)bicycloheterocycle)-(C₁-C₆)alkyl-, phenyl, benzyl and naphthyl; each of which is optionally substituted with one, two, or three substituents independently selected from the group consisting of -OH, (=O), halo, -C(halo)₃, -CH(halo)₂, -CH₂(halo), -(C₁-C₆)alkyl, halo(C₁-C₆)alkyl-, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, hydroxy(C₁-C₆)alkyl-, dihydroxy(C₁-C₆)alkyl-, -(C₁-C₆)alkoxy, ((C₁-
 15 C₆)alkoxy)CO(C₁-C₆)alkoxy-, phenyl, benzyl, -NH₂, -NH(C₁-C₆)alkyl, -(C₁-C₆)alkyl-NH(C₁-C₆)alkyl-R¹⁴, -CN, -SH, -OR¹¹, -CONR⁵R⁶, -(C₁-C₆)alkyl-CO-NR⁵R⁶, -COOR⁷, -(C₁-C₆)alkyl-CO-OR⁷, -(C₁-C₆)alkoxy-COOR⁷, -(OCH₂CH₂)_s-O(C₁-C₆)alkyl, -(CH₂CH₂O)_s-(C₁-C₆)alkyl, (C₁-C₆)alkyl)sulfonyl, ((C₁-C₆)alkyl)sulfonyl(C₁-C₆)alkyl-, -NH-SO₂(C₁-C₆)alkyl, NH₂-SO₂(C₁-C₆)alkyl-, -
 20 N(SO₂(C₁-C₆)alkyl)₂, -C(=NH)NH₂, -NH-CO-(C₁-C₆)alkyl, -NH-CO-NH₂, -NH-C(=O)-NH-(C₁-C₆)alkyl, -NH-C(=O)-(6- to 14- membered)aryl, -NH-C(=O)-(C₁-C₆)alkyl-(6- to 14- membered)aryl, -NH-(C₁-C₆)alkyl-CO-OR⁷, -NH-C(=O)-(C₁-C₆)alkyl-CO-OR⁷, -NH-C(=O)-CH(NH₂)-(C₁-C₆)alkyl-CO-OR⁷, -(C₃-C₁₂)cycloalkyl, ((C₃-C₁₂)cycloalkyl)-(C₁-C₆)alkyl-, -(6- to 14-membered)aryl, -(6- to 14-
 25 membered)aryloxy, -(C₁-C₆)alkoxy-C(O)NR⁵R⁶, -NH-(C₁-C₆)alkyl-C(O)-NR⁵R⁶, -C(O)NH-(C₁-C₆)alkyl-COOR⁷, ((6- to 14-membered)aryl)-(C₁-C₆)alkyl-, -(5- to 12-membered)heteroaryl, ((5- to 12-membered)heteroaryl)-(C₁-C₆)alkyl-, -(3- to 12-membered)heterocycle, ((3- to 12-membered)heterocycle)-(C₁-C₆)alkyl-, -(7- to 12-membered)bicycloheterocycle, and ((7- to 12-membered)bicycloheterocycle)-(C₁-
 30 C₆)alkyl-;

R³ is selected from:

- a) -H; or
- b) -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, or -(C₂-C₆)alkynyl;

5 R⁴ is selected from

- a) -H, -OH, halo, -C(halo)₃, -CH(halo)₂, -CH₂(halo), COOH, or CONH₂; or
- b) -(C₁-C₅)alkyl, -(C₂-C₅)alkenyl, -(C₂-C₅)alkynyl, -(CH₂)_n-O-(CH₂)_n-CH₃, or -(C₁-C₅)alkoxy, each of which is optionally substituted with 1, 2, or 3 independently selected R⁹ groups;

10

R⁵ and R⁶ are each independently selected from

- a) hydrogen, -OH, halo, -C(halo)₃, -CH(halo)₂, -CH₂(halo);
- b) -(C₁-C₆)alkyl, -(C₂-C₅)alkenyl, -(C₂-C₅)alkynyl, -(CH₂)_n-O-(CH₂)_n-CH₃, -(C₁-C₆)alkoxy, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from -OH, halo, -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₁-C₁₀)alkoxy, -(C₃-C₁₂)cycloalkyl, -CHO, -C(O)OH, -C(halo)₃, -CH(halo)₂, CH₂(halo), -(CH₂)_n-O-(CH₂)_n-CH₃, phenyl, or CONR⁵R⁶;
- c) -(C₃-C₈)cycloalkyl, ((C₃-C₈)cycloalkyl)-(C₁-C₆)alkyl-, -COOR⁷, -(C₁-C₆)alkyl-COOR⁷, -CONH₂, or (C₁-C₆)alkyl-CONH-;
- d) ((6- to 14-membered)aryl) optionally substituted with 1, 2, or 3 independently selected R³⁰ groups; or
- e) R⁵ and R⁶ together with the nitrogen atom to which they are attached form a (4- to 8-membered)heterocycle optionally substituted with 1, 2, or 3 independently selected R³⁰ groups;

25

each R⁷ is independently selected from the group consisting of hydrogen, -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₃-C₁₂)cycloalkyl, -(C₄-C₁₂)cycloalkenyl, ((C₃-C₁₂)cycloalkyl)-(C₁-C₆)alkyl-, and ((C₄-C₁₂)cycloalkenyl)-(C₁-C₆)alkyl-;

30 each R⁸ is independently selected from H, -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₁-C₁₀)alkoxy, -(C₃-C₁₂)cycloalkyl, -(C₃-C₁₂)cycloalkenyl, ((C₃-

C₁₂)cycloalkyl)-(C₁-C₆)alkyl-, ((C₃-C₁₂)cycloalkenyl)-(C₁-C₆)alkyl-, -C(=O)(C₁-C₆)alkyl or SO₂(C₁-C₆)alkyl;

each R⁹ is independently selected from -OH, halo, -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -
 5 (C₂-C₁₀)alkynyl, -(C₁-C₁₀)alkoxy, -(C₃-C₁₂)cycloalkyl, -CHO, -C(O)OH, -C(halo)₃, -CH(halo)₂, CH₂(halo), -(CH₂)_n-O-(CH₂)_n-CH₃, phenyl, or CONR⁵R⁶;

each R¹¹ is independently selected from -C(halo)₃, -CH(halo)₂, -CH₂(halo), -(C₂-C₅)alkenyl, -(C₂-C₅)alkynyl, -(CH₂)_n-O-(CH₂)_n-CH₃, (6- to 14-membered)aryl, ((6- to
 10 14-membered)aryl)-(C₁-C₆)alkyl-, or (5- to 12-membered)heteroaryl, ((5- to 12-membered)heteroaryl)-(C₁-C₆)alkyl-, each of which is optionally substituted with 1, 2, or 3 independently selected R⁹ groups;

each R¹⁴ is independently selected from -COOR⁷, -(C₁-C₆)alkyl-COOR⁷, -C(=O)-(C₁-C₆)alkyl-COOR⁷, -(C₁-C₆)alkyl-C(=O)-(C₁-C₆)alkyl-COOR⁷, CONH₂, or -(C₁-C₆)alkyl-CONH;

each R³⁰ is independently selected from COOR⁷, CONR⁵R⁶, -(C₁-C₆)alkyl, CN, -(3- to 12-membered)heteroaryl, ((3- to 12-membered)heteroaryl)-(C₁-C₆)alkyl-, NH₂, halo,
 20 and ((6- to 14-membered)aryl)-(C₁-C₆)alkoxy-;

m is an integer 1, 2, 3, 4, 5, or 6;

n is an integer 0, 1, 2, 3, 4, 5, or 6;

s is an integer 1, 2, 3, 4, 5, or 6;

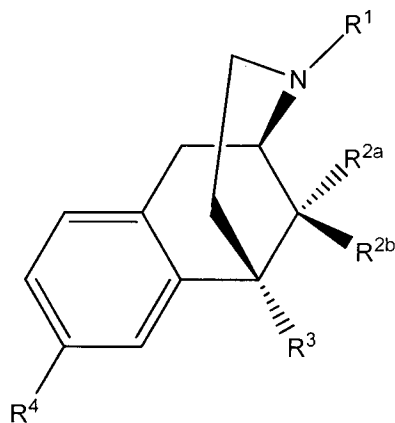
25 provided that when R⁴ is -(C₁-C₅)alkoxy then:

- a) R^{2a} and R^{2b} cannot be taken together to form =O; or
- b) R^{2a} cannot be OH when R^{2b} is -Z-G-R¹⁰, and -Z-G-R¹⁰ is either:
 - a. OH; or
 - b. -(C₁-C₆)alkyl; or
- 30 c) R^{2a} cannot be H when the combination -Z-G-R¹⁰ is OH;

and the pharmaceutically acceptable salts, prodrugs and solvates thereof.

In one embodiment, the present invention provides novel compounds of
Formula IA:

5

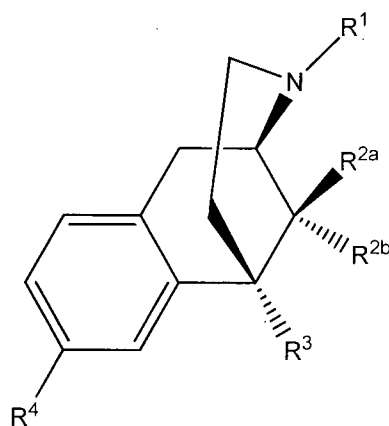


IA

wherein R¹, R^{2a}, R^{2b}, R³ and R⁴ are as defined above for Formula I, and the
pharmaceutically acceptable salts, prodrugs and solvates thereof.

10

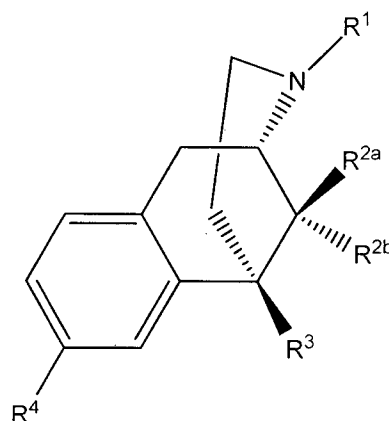
In another embodiment, the present invention provides novel compounds of
Formula IB:



IB

wherein R^1 , R^{2a} , R^{2b} , R^3 and R^4 are as defined above for Formula I, and the pharmaceutically acceptable salts, prodrugs and solvates thereof.

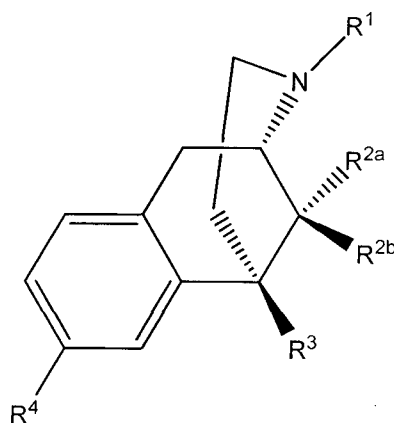
- 5 In another embodiment, the present invention provides novel compounds of Formula IC:



IC

- 10 wherein R^1 , R^{2a} , R^{2b} , R^3 and R^4 are as defined above for Formula I, and the pharmaceutically acceptable salts, prodrugs and solvates thereof.

In another embodiment, the present invention provides novel compounds of Formula ID:



ID

5

wherein R^1 , R^{2a} , R^{2b} , R^3 and R^4 are as defined above for Formula I, and the pharmaceutically acceptable salts, prodrugs and solvates thereof.

It is an object of certain embodiments of the present invention to provide new
 10 Compounds of the Invention that have antagonist activity at the ORL-1 receptor which is greater than compounds currently available, *e.g.*, JTC-801 (described in WO 99/48492; and Shinkai et al., "4-aminoquinolines: Novel nociceptin antagonists with analgesic activity", *J. Med. Chem.*, 2000, 43:4667-4677) and J-113397 (described in WO 98/54168; and Kawamoto et al., "Discovery of the first potent and selective small
 15 molecule opioid receptor-like (ORL-1) antagonist: 1-[(3R,4R)-1-cyclooctylmethyl-3-hydroxymethyl-4-piperidyl]-3-ethyl-1,3-dihydro-2H-benzimidazol-2-one (J-113397)", *J. Med. Chem.*, 1999, 42:5061-6063).

Certain Compounds of the Invention have agonist activity at the μ , δ and/or κ receptors which is greater than currently available compounds, *e.g.*, morphine.

20 Certain Compounds of the Invention have both: (i) antagonist activity at the ORL-1 receptor; and (ii) agonist activity at one or more of the μ , δ and/or κ opioid receptors. Certain Compounds of the Invention have both: (i) antagonist activity at

the ORL-1 receptor; and (ii) agonist activity at the μ opioid receptor. Certain compounds of the invention have both: (i) antagonist activity at the μ opioid receptor; and (ii) agonist activity at the κ opioid receptor. Certain compounds of the invention have: (i) antagonist activity at the ORL-1 receptor; (ii) antagonist activity at the μ opioid receptor; and (iii) agonist activity at the κ opioid receptor. Certain compounds of the invention have: (i) antagonist activity at the μ opioid receptor; (ii) agonist activity at the κ opioid receptor; and (iii) antagonist activity at the δ opioid receptor.

Compounds of the Invention may be useful as analgesics; anti-inflammatories; diuretics; anesthetics; neuroprotective agents; anti-hypertensives; anxiolytics; agents for appetite control; hearing regulators; anti-tussives; anti-asthmatics; anti-epileptics; anti-convulsants; modulators of locomotor activity; modulators of learning and memory; regulators of neurotransmitter release; modulators of hormone release; kidney function modulators; anti-depressants; agents to treat memory loss due to Alzheimer's disease or other dementias; agents to treat withdrawal from alcohol and/or drugs of addiction; agents to control water balance or sodium excretion; agents to treat arterial blood pressure disorders, or any of the following: UI, ulcers, IBD, IBS, diarrhea, constipation, addictive disorders, Parkinson's disease, parkinsonism, anxiety, epilepsy, stroke, a seizure, pruritic conditions, psychosis, cognitive disorders, memory deficits, restricted brain function, Huntington's chorea, ALS, dementia, retinopathy, muscle spasms, migraines, vomiting, dyskinesia, and/or depression (each being a "Condition").

The present invention further provides methods for treating a Condition, comprising administering to a subject in need thereof a therapeutically effective amount of a Compound of the Invention. In certain embodiments, the Condition is pain (chronic or acute pain). The Compounds of the Invention are particularly useful for treating chronic pain. In certain embodiments, the Compound of the Invention is an ORL-1 receptor antagonist. In other embodiments, the Compound of the Invention is an agonist at one or more of the μ , δ and/or κ opioid receptors. In other embodiments, the Compound of the Invention is both an ORL-1 receptor antagonist and an agonist at one or more of the μ , δ and/or κ opioid receptors. In other embodiments, the Compound of the Invention is both an ORL-1 receptor antagonist

and an agonist at the μ opioid receptor. In certain non-limiting embodiments, the Compound of the Invention produces fewer side effects and/or less severe side effects than currently available analgesic opioid compounds when administered at doses producing equivalent levels of analgesia and/or anti-hyperalgesia.

5 In certain non-limiting embodiments, the Compound of the Invention exhibits a substantially linear dose response curve, such that the bell-shaped dose response curve observed for most opioid analgesics (i.e. low and high doses do not produce significant analgesia, whereas mid-range doses produce analgesia) is not observed for the Compound of the Invention. It is expected, therefore, that it will be easier to titrate to
10 an effective dose of the Compound of the Invention in a patient than it is for conventional opioid analgesics. It is further expected that the Compound of the Invention will produce effective analgesia and/or anti-hyperalgesia in a patient who has become tolerant to conventional opioids, and for whom a conventional opioid is no longer an effective treatment. It is further expected that a Compound of the Invention
15 will produce effective analgesia and/or anti-hyperalgesia at doses that do not induce side effects such as respiratory depression in patients for whom a dose of a conventional opioid that is high enough to be an effective treatment also induces significant side effects such as respiratory depression.

 The present invention further provides methods for preventing a Condition,
20 comprising administering to a subject in need thereof a Condition-preventing effective amount of a Compound of the Invention.

 Another object of the invention is to provide benzomorphan analog compounds useful for treating or preventing constipation, preferably μ opioid receptor-induced constipation. More specifically, the present invention provides Compounds of the
25 Invention having activity as μ opioid receptor antagonists. In certain embodiments, Compounds of the Invention are expected to have dual activity as both μ opioid receptor antagonists and κ opioid receptor agonists. In other embodiments, Compounds of the Invention are expected to be μ opioid receptor antagonists, κ opioid receptor agonists, δ opioid receptor antagonists, and inactive at ORL-1 receptors. In
30 yet other embodiments, certain Compounds of the Invention are expected to be μ opioid receptor antagonists, κ opioid receptor agonists, δ opioid receptor antagonists,

and ORL-1 receptor antagonists. In other embodiments, certain Compounds of the Invention are expected to be μ opioid receptor antagonists, κ opioid receptor agonists, δ opioid receptor antagonists, and ORL-1 receptor partial agonists. In certain embodiments, Compounds of the Invention will be inactive at δ opioid receptors.

- 5 Certain Compounds of the Invention are expected to be substantially restricted to the GI tract.

Compounds of the Invention that have μ opioid receptor antagonist activity and are substantially restricted to the GI tract will significantly reduce or prevent constipation that would otherwise occur in a patient as a result of treatment with a μ opioid receptor agonist. In one embodiment, the reduction or prevention of constipation is obtained without reducing the desired analgesic effect of the μ agonist. Compounds of the Invention that also exhibit κ opioid receptor agonist activity should additionally stimulate GI motility via a non- μ receptor mediated mechanism.

The present invention provides a method for treating or preventing a Condition in a subject. In certain embodiments, the Condition treated will be pain (acute or chronic pain). The present invention further provides a method for treating or preventing constipation, preferably constipation associated with μ -opioid agonist therapy, by administering an effective amount of a Compound of the Invention to a patient in need of such treatment or prevention. In one embodiment, the Compound of the Invention is a μ antagonist that is substantially restricted to the GI tract. In another embodiment, the Compound of the Invention is both a μ antagonist and a κ agonist, and is substantially restricted to the GI tract. In another embodiment, the method comprises co-administering to a patient both an effective amount of a Compound of the Invention that is a μ antagonist and is substantially restricted to the GI tract, and an analgesically effective amount of a μ agonist. In another embodiment, the method comprises co-administration to a patient of both an effective amount of a Compound of the Invention that is both a μ antagonist and a κ agonist, and which is substantially restricted to the GI tract, and an analgesically effective amount of a μ agonist.

The present invention further provides pharmaceutical compositions comprising a therapeutically effective amount of a Compound of the Invention admixed with a pharmaceutically acceptable carrier or excipient. Such compositions

are useful for treating or preventing a Condition in a subject. The pharmaceutical compositions of the present invention may be formulated as immediate release formulations, or as controlled or sustained release formulations. Pharmaceutical compositions of the present invention may be formulated for administration by any of
5 a number of different routes known in the art, including but not limited to, oral, intradermal, intramuscular, intraperitoneal, parenteral, intravenous, subcutaneous, intranasal, epidural, sublingual, intracerebral, intravaginal, transdermal, transmucosal, rectal, by inhalation, or topical (particularly to the ears, nose, eyes, or skin).

The present invention further provides methods for preparing a composition,
10 comprising the step of admixing a Compound of the Invention and a pharmaceutically acceptable carrier or excipient to form a pharmaceutical composition.

The present invention further provides the use of a Compound of the Invention in the manufacturing of a medicament useful to treat or prevent a Condition in a subject.

15 The invention still further relates to a kit comprising a container (preferably sterile) containing an effective amount of a Compound of the Invention.

DETAILED DESCRIPTION OF THE INVENTION

20

The Compounds of the Invention are novel benzomorphan analogs. They are useful for treating or preventing one or more Conditions, such as pain or constipation. Compounds of the Invention may provide a reduced liability for developing analgesic tolerance and physical dependence.

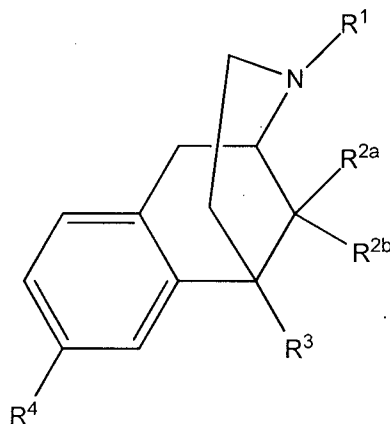
25 Compounds of the Invention are useful for modulating a pharmacodynamic response from ORL-1 receptors either centrally or peripherally, or both. Compounds of the Invention may also be useful for modulating a pharmacodynamic response from one or more opioid receptors (μ , δ , κ) either centrally or peripherally, or both. The pharmacodynamic response may be attributed to the compound stimulating
30 (agonizing) or inhibiting (antagonizing) the one or more receptors. Certain Compounds of the Invention may inhibit (or antagonize) the ORL-1 receptor, while

also stimulating (or agonizing) one or more other opioid receptors (*e.g.* as a μ , δ and/or κ agonist). Compounds of the Invention having agonist activity may be either full or partial agonists.

In certain embodiments, Compounds of the Invention can be used in combination with at least one other therapeutic agent. The other therapeutic agent can be, but is not limited to, a μ -opioid agonist, a non-opioid analgesic, a non-steroidal anti-inflammatory agent, a Cox-II inhibitor, an anti-emetic, a β -adrenergic blocker, an anticonvulsant, an antidepressant, a Ca^{2+} -channel blocker, an anticancer agent, or a mixture thereof.

10 Various objects and advantages of the present invention will become apparent from the following detailed description.

The present invention provides novel compounds of Formula I”:



I''

wherein

20 R¹ is selected from the group consisting of -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-C₁₂)cycloalkyl, (C₃-C₁₂)cycloalkyl-(C₁-C₆)alkyl-, -(C₃-C₁₂)cycloalkenyl, (C₃-C₁₂)cycloalkenyl-(C₁-C₆)alkyl-, -(6- to 14-membered)aryl, ((6-

to 14-membered)aryl)-(C₁-C₆)alkyl-, diphenyl(C₁-C₆)alkyl-, -(3- to 12-membered)heterocycle, ((3- to 12 membered)heterocycle)-(C₁-C₆)alkyl-, -(OCH₂CH₂)₅-O-(C₁-C₆)alkyl, -(CH₂CH₂O)₅-(C₁-C₆)alkyl, (C₁-C₁₀)alkoxy, C(halo)₃, CH(halo)₂, CH₂(halo), C(O)R⁵, -C(O)O-(C₁-C₁₀)alkyl, and -(CH₂)_n-N(R⁶)₂, each of which is optionally substituted by 1, 2 or 3 independently selected R⁹ groups;

R^{2a} is hydrogen, OH, or absent;

R^{2b} is

- a) ((6- to 14-membered)aryl), -((5- to 12-membered)heteroaryl), or ((3- to 12-membered)heterocycle), each of which is optionally substituted with one, two, or three independently selected R³⁰ groups; or
- b) -Z-G-R¹⁰, provided that -Z-G-R¹⁰ is other than hydrogen;

or R^{2a} and R^{2b} together form =O;

Z is absent or -(CH₂)_m-, optionally substituted with 1 or 2 -(C₁-C₆)alkyl;

G is selected from the group consisting of:

- a) a bond, -(C₁-C₆)alkylene, -(C₂-C₆)alkenylene;
- b) O, -OCO-, -C(=O), =CH;
- c) NR⁸, =N-O, =N-NH;
- d) S, SO, SO₂; and
- e) -NH-SO₂;

and when Z is absent and G is =CH, =N-O, or =N-NH, then R^{2a} is absent;

- R¹⁰ is selected from the group consisting of hydrogen, -(C₁-C₁₀)alkyl, -(C₂-C₁₂)alkenyl, -C(=O), -C(=O)-(C₁-C₆)alkyl, -C(=O)-(C₂-C₆)alkenyl, -C(=O)-(6- to 14-membered)aryl, -C(=O)-(C₁-C₆)alkyl-(6- to 14-membered)aryl, -(C₂-C₁₂)alkynyl, -(C₁-C₁₀)alkoxy, -(OCH₂CH₂)₅-O(C₁-C₆)alkyl, -(CH₂CH₂O)₅-(C₁-C₆)alkyl, -NH₂, -NH(C₁-C₆)alkyl, CN, NR⁵R⁶, -(C₁-C₆)alkyl-NR⁵R⁶, -CONR⁵R⁶, -(C₁-C₆)alkyl-CO-NR⁵R⁶, -COOR⁷, -(C₁-C₆)alkyl-CO-OR⁷, -(C₁-C₆)alkoxy-COOR⁷, -CO-(CH₂)_n-COOR⁷, -CO-(CH₂)_n-CO-NR⁵R⁶, -(C₃-C₁₂)cycloalkyl, ((C₃-C₁₂)cycloalkyl)-(C₁-

C₆)alkyl-, -(C₄-C₁₂)cycloalkenyl, ((C₄-C₁₂)cycloalkenyl)-(C₁-C₆)alkyl-, -(C₆-
 C₁₄)bicycloalkyl, ((C₆-C₁₄)bicycloalkyl)-(C₁-C₆)alkyl-, -(C₈-C₂₀)tricycloalkyl, ((C₈-
 C₂₀)tricycloalkyl)-(C₁-C₆)alkyl-, -(C₇-C₁₄)bicycloalkenyl, ((C₇-C₁₄)bicycloalkenyl)-
 (C₁-C₆)alkyl-, -(C₈-C₂₀)tricycloalkenyl, ((C₈-C₂₀)tricycloalkenyl)-(C₁-C₆)alkyl-, -(6-
 5 to 14-membered)aryl, ((6- to 14-membered)aryl)-(C₁-C₆)alkyl-, -SO₂-(C₁-C₆)alkyl, -
 SO₂-((C₃-C₁₂)cycloalkyl), -SO₂-((C₃-C₁₂)cycloalkyl)-(C₁-C₆)alkyl, -SO₂-((5- to 12-
 membered)heteroaryl), -SO₂-((5- to 12-membered)heteroaryl)-(C₁-C₆)alkyl, -C(=O)-
 NH-((5- to 12-membered)heteroaryl), -C(=O)-NH-((5- to 12-membered)heteroaryl)-
 (C₁-C₆)alkyl, -C(=O)-NH-((3- to 12-membered)heterocycle), -C(=O)-NH-((3- to 12-
 10 membered)heterocycle)-(C₁-C₆)alkyl, SO₂-((6- to 14-membered)aryl), SO₂-((6- to 14
 membered)aryl)-(C₁-C₆)alkyl, -(7- to 12-membered)bicyclic ring system, ((7- to 12-
 membered)bicyclic ring system)-(C₁-C₆)alkyl-, -(7- to 12-membered)bicyclic aryl, ((7-
 to 12-membered)bicyclic aryl)-(C₁-C₆)alkyl-, -(5- to 12-membered)heteroaryl, ((5- to
 12-membered)heteroaryl)-(C₁-C₆)alkyl-, -(3- to 12-membered)heterocycle, ((3- to 12
 15 membered)heterocycle)-(C₁-C₆)alkyl-, -(7- to 12-membered)bicycloheterocycle, ((7- to
 12-membered)bicycloheterocycle)-(C₁-C₆)alkyl-, phenyl, benzyl and naphthyl; each of
 which is optionally substituted with one, two, or three substituents independently
 selected from the group consisting of -OH, (=O), halo, -C(halo)₃, -CH(halo)₂,
 -CH₂(halo), -(C₁-C₆)alkyl, halo(C₁-C₆)alkyl-, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl,
 20 hydroxy(C₁-C₆)alkyl-, dihydroxy(C₁-C₆)alkyl-, -(C₁-C₆)alkoxy, ((C₁-
 C₆)alkoxy)CO(C₁-C₆)alkoxy-, phenyl, benzyl, -NH₂, -NH(C₁-C₆)alkyl,
 -(C₁-C₆)alkyl-NH(C₁-C₆)alkyl-R¹⁴, -CN, -SH, -OR¹¹, -CONR⁵R⁶, -(C₁-C₆)alkyl-CO-
 NR⁵R⁶, -COOR⁷, -(C₁-C₆)alkyl-CO-OR⁷, -(C₁-C₆)alkoxy-COOR⁷, -(OCH₂CH₂)_s-
 O(C₁-C₆)alkyl, -(CH₂CH₂O)_s-(C₁-C₆)alkyl, -SO₂-NR^{5a}R^{6a}, (C₁-C₆)alkyl)sulfonyl,
 25 ((C₁-C₆)alkyl)sulfonyl(C₁-C₆)alkyl-, -NH-SO₂(C₁-C₆)alkyl, NH₂-SO₂(C₁-C₆)alkyl-, -
 N(SO₂(C₁-C₆)alkyl)₂, -C(=NH)NH₂, -NH-CO-(C₁-C₆)alkyl, -NH-CO-NH₂, -NH-
 C(=O)-NH-(C₁-C₆)alkyl, -NH-C(=O)-(6- to 14- membered)aryl, -NH-C(=O)-(C₁-
 C₆)alkyl-(6- to 14- membered)aryl, -NH-(C₁-C₆)alkyl-CO-OR⁷, -NH-C(=O)-(C₁-
 C₆)alkyl-CO-OR⁷, -NH-C(=O)-CH(NH₂)-(C₁-C₆)alkyl-CO-OR⁷, -(C₃-C₁₂)cycloalkyl,
 30 ((C₃-C₁₂)cycloalkyl)-(C₁-C₆)alkyl-, -(6- to 14-membered)aryl, -(6- to 14-
 membered)aryloxy, -(C₁-C₆)alkoxy-C(O)NR⁵R⁶, -NH-(C₁-C₆)alkyl-C(O)-NR⁵R⁶, -

C(O)NH-(C₁-C₆)alkyl-COOR⁷, ((6- to 14-membered)aryl)-(C₁-C₆)alkyl-, -(5- to 12-membered)heteroaryl, ((5- to 12-membered)heteroaryl)-(C₁-C₆)alkyl-, -(3- to 12-membered)heterocycle, ((3- to 12-membered)heterocycle)-(C₁-C₆)alkyl-, -(7- to 12-membered)bicycloheterocycle, and ((7- to 12-membered)bicycloheterocycle)-(C₁-
 5 C₆)alkyl-;

R³ is selected from:

- a) -H; or
- b) -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, or -(C₂-C₆)alkynyl;

10

R⁴ is selected from

- a) -H, -OH, halo, -C(halo)₃, -CH(halo)₂, -CH₂(halo), COOH, or CONH₂; or
- b) -(C₁-C₅)alkyl, -(C₂-C₅)alkenyl, -(C₂-C₅)alkynyl, -(CH₂)_n-O-(CH₂)_n-CH₃, or -(C₁-C₅)alkoxy, each of which is optionally substituted with 1, 2, or 3 independently
 15 selected R⁹ groups;

R⁵ and R⁶ are each independently selected from

- a) hydrogen, -OH, halo, -C(halo)₃, -CH(halo)₂, -CH₂(halo);
- b) -(C₁-C₆)alkyl, -(C₂-C₅)alkenyl, -(C₂-C₅)alkynyl, -(CH₂)_n-O-(CH₂)_n-CH₃, -(C₁-C₆)alkoxy, each of which is optionally substituted with 1, 2, or 3 substituents
 20 independently selected from -OH, halo, -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₁-C₁₀)alkoxy, -(C₃-C₁₂)cycloalkyl, -CHO, -C(O)OH, -C(halo)₃, -CH(halo)₂, CH₂(halo), -(CH₂)_n-O-(CH₂)_n-CH₃, phenyl, or CONR^{5a}R^{6a};
- c) -(C₃-C₈)cycloalkyl, ((C₃-C₈)cycloalkyl)-(C₁-C₆)alkyl-, -COOR⁷, -(C₁-C₆)alkyl-COOR⁷, -CONH₂, or (C₁-C₆)alkyl-CONH-;
 25
- d) ((6- to 14-membered)aryl) optionally substituted with 1, 2, or 3 independently selected R³⁰ groups;
- e) -((5- to 12-membered)heteroaryl) optionally substituted with 1, 2, or 3 independently selected R³⁰ groups; or

- f) R^5 and R^6 together with the nitrogen atom to which they are attached form a (3- to 12-membered)heterocycle optionally substituted with 1, 2, or 3 independently selected R^{30} groups;
- 5 R^{5a} and R^{6a} are each independently selected from the group consisting of:
- hydrogen, -OH, halo, -C(halo)₃, -CH(halo)₂, and -CH₂(halo);
 - (C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(CH₂)_n-O-(CH₂)_n-CH₃, and -(C₁-C₆)alkoxy, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from -OH, halo, -(C₁-C₁₀)alkyl, -(C₂-C₁₂)alkenyl, -(C₂-C₁₂)alkynyl, -(C₁-C₁₀)alkoxy, -(C₃-C₁₂)cycloalkyl, -CHO, -COOH, -C(halo)₃, -CH(halo)₂, CH₂(halo), -(CH₂)_n-O-(CH₂)_n-CH₃, and phenyl;
 - (C₃-C₈)cycloalkyl, ((C₃-C₈)cycloalkyl)-(C₁-C₆)alkyl-, -COOR⁷, -(C₁-C₆)alkyl-COOR⁷, -CONH₂, and (C₁-C₆)alkyl-CONH-;
 - (6- to 14-membered)aryl optionally substituted with 1, 2, or 3 independently selected R^{30} groups;
 - (5- to 12-membered)heteroaryl optionally substituted with 1, 2, or 3 independently selected R^{30} groups; or
 - R^{5a} and R^{6a} together with the nitrogen atom to which they are attached form a (3- to 12-membered)heterocycle optionally substituted with 1, 2, or 3 independently selected R^{30} groups;

each R^7 is independently selected from the group consisting of hydrogen, -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₃-C₁₂)cycloalkyl, -(C₄-C₁₂)cycloalkenyl, ((C₃-C₁₂)cycloalkyl)-(C₁-C₆)alkyl-, and ((C₄-C₁₂)cycloalkenyl)-(C₁-C₆)alkyl-;

each R^8 is independently selected from H, -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₁-C₁₀)alkoxy, -(C₃-C₁₂)cycloalkyl, -(C₃-C₁₂)cycloalkenyl, ((C₃-C₁₂)cycloalkyl)-(C₁-C₆)alkyl-, ((C₃-C₁₂)cycloalkenyl)-(C₁-C₆)alkyl-, -C(=O)(C₁-C₆)alkyl or SO₂(C₁-C₆)alkyl;

- each R^9 is independently selected from -OH, halo, $-(C_1-C_{10})$ alkyl, $-(C_2-C_{10})$ alkenyl, $-(C_2-C_{10})$ alkynyl, $-(C_1-C_{10})$ alkoxy, $-(C_3-C_{12})$ cycloalkyl, -CHO, $-C(O)OH$, $-C(halo)_3$, $-CH(halo)_2$, $CH_2(halo)$, $-(CH_2)_n-O-(CH_2)_n-CH_3$, phenyl, or $CONR^{5a}R^{6a}$;
- 5 each R^{11} is independently selected from $-C(halo)_3$, $-CH(halo)_2$, $-CH_2(halo)$, $-(C_2-C_5)$ alkenyl, $-(C_2-C_5)$ alkynyl, $-(CH_2)_n-O-(CH_2)_n-CH_3$, (6- to 14-membered)aryl, ((6- to 14-membered)aryl)- (C_1-C_6) alkyl-, or (5- to 12-membered)heteroaryl, ((5- to 12-membered)heteroaryl)- (C_1-C_6) alkyl-, each of which is optionally substituted with 1, 2, or 3 independently selected R^9 groups;
- 10 each R^{14} is independently selected from $-COOR^7$, $-(C_1-C_6)$ alkyl- $COOR^7$, $-C(=O)-(C_1-C_6)$ alkyl- $COOR^7$, $-(C_1-C_6)$ alkyl- $C(=O)-(C_1-C_6)$ alkyl- $COOR^7$, $CONH_2$, or $-(C_1-C_6)$ alkyl- $CONH$;
- 15 each R^{30} is independently selected from $COOR^7$, $CONR^{5a}R^{6a}$, $-(C_1-C_6)$ alkyl, $-C(=O)$, CN, $-(3- \text{ to } 12\text{-membered})$ heteroaryl, $((3- \text{ to } 12\text{-membered})$ heteroaryl)- (C_1-C_6) alkyl-, NH_2 , halo, and $((6- \text{ to } 14\text{-membered})$ aryl)- (C_1-C_6) alkoxy-;
- m is an integer 1, 2, 3, 4, 5, or 6;
- 20 n is an integer 0, 1, 2, 3, 4, 5, or 6;
- s is an integer 1, 2, 3, 4, 5, or 6;
- provided that when R^4 is $-(C_1-C_5)$ alkoxy then:
- a) R^{2a} and R^{2b} cannot be taken together to form $=O$; or
- b) R^{2a} cannot be OH when R^{2b} is $-Z-G-R^{10}$, and $-Z-G-R^{10}$ is either:
- 25 a. OH;
- b. $-(C_1-C_6)$ alkyl;
- c. 2-propenyl;
- d. 2-propynyl; or
- c) R^{2a} cannot be H when the combination $-Z-G-R^{10}$ is either:
- 30 a. OH;
- b. $-O-C(=O)-(C_1-C_6)$ alkyl; or

c. $-\text{O}-\text{C}(=\text{O})-(\text{C}_2-\text{C}_6)\text{alkenyl}$;

and provided that when R^4 is OH then:

a) R^{2a} cannot be OH when R^{2b} is $-\text{Z}-\text{G}-\text{R}^{10}$, and $-\text{Z}-\text{G}-\text{R}^{10}$ is:

- 5 e. methyl;
f. ethyl;
g. 2-propenyl; or
h. 2-propynyl;

b) R^{2a} cannot be H when R^{2b} is $-\text{Z}-\text{G}-\text{R}^{10}$, and $-\text{Z}-\text{G}-\text{R}^{10}$ is either:

- 10 a. OH;
b. $-\text{O}-\text{C}(=\text{O})-(\text{C}_1-\text{C}_6)\text{alkyl}$; or
c. $-\text{O}-\text{C}(=\text{O})-(\text{C}_2-\text{C}_6)\text{alkenyl}$;

and provided that when R^3 is $(\text{C}_1-\text{C}_6)\text{alkyl}$ or $(\text{C}_2-\text{C}_6)\text{alkenyl}$, and R^4 is H, OH, or $(\text{C}_1-$

15 $\text{C}_5)\text{alkoxy}$, then R^{2b} is not:

- a) optionally substituted (5- to 12-membered)heteroaryl;
b) optionally substituted (3- to 12-membered)heterocycle; or
c) unsubstituted phenyl or phenyl substituted with F or Cl, methyl, CF_3 , hydroxy, methoxy, (3- to 12-membered)heterocycle, or NH_2 ;

20

and provided that when R^4 is OH and R^1 is $(\text{C}_1-\text{C}_{10})\text{alkyl}$, then R^{2a} and R^{2b} cannot be together selected $=\text{O}$;

and provided that when R^4 is hydrogen and when R^1 and R^3 are both methyl, then:

- 25 a) R^{2a} and R^{2b} cannot together form $=\text{O}$ or $=\text{N}-\text{OH}$; or
b) R^{2b} may not be NH_2 or $\text{NHC}(\text{O})\text{CH}_3$ if R^{2a} is hydrogen;

and provided that when R^{2a} is H, then R^{2b} may not be $-\text{Z}-\text{G}-\text{R}^{10}$, wherein $-\text{Z}-\text{G}-\text{R}^{10}$ is:

a) $-\text{CH}_2-\text{CHR}^{20}-\text{C}(=\text{O})\text{R}^{21}$, wherein

30 R^{20} is H, or $-(\text{C}_1-\text{C}_6)\text{alkyl}$, and

R^{21} is selected from the group consisting of H, $-(\text{C}_1-\text{C}_{10})\text{alkyl}$,

-(C₃-C₁₂)cycloalkyl, ((C₃-C₁₂)cycloalkyl)-(C₁-C₆)alkyl-, phenyl, and phenyl-(C₁-C₆)alkyl; or

b) $-\text{CH}_2\text{-CHR}^{20}\text{-CR}^{22}\text{R}^{23}\text{OH}$, wherein

R^{20} is defined as above, and

5 R^{22} and R^{23} are each independently selected from the group consisting of H, -(C₁-C₁₀)alkyl, ((C₃-C₁₂)cycloalkyl)-(C₁-C₆)alkyl-, phenyl, and phenyl-(C₁-C₆)alkyl; or

c) $-\text{CH}_2\text{-CR}^{20}=\text{CR}^{23}\text{R}^{24}$, wherein

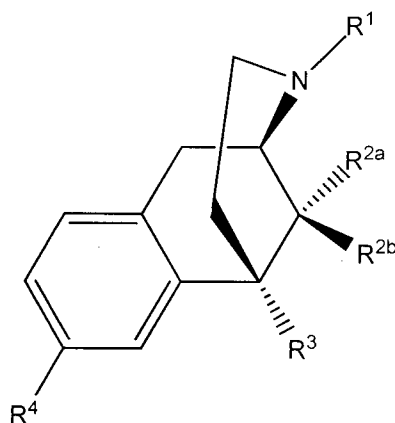
R^{20} and R^{23} are defined as above, and

10 R^{24} is selected from the group consisting of H, and -(C₁-C₆)alkyl;

and the pharmaceutically acceptable salts and solvates thereof.

In one embodiment, the present invention provides novel compounds of

15 Formula IA'':

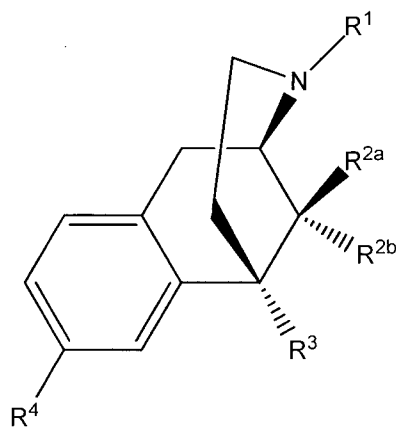


IA''

wherein R^1 , R^{2a} , R^{2b} , R^3 and R^4 are as defined above for Formula I'', and the

20 pharmaceutically acceptable salts and solvates thereof.

In another embodiment, the present invention provides novel compounds of Formula IB'':



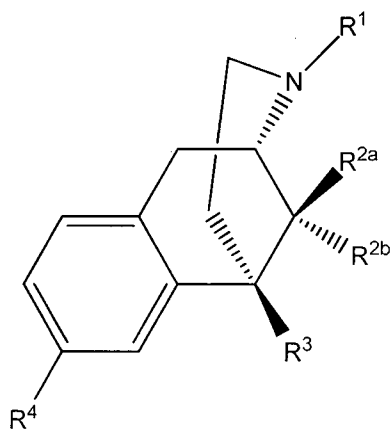
IB''

5

wherein R¹, R^{2a}, R^{2b}, R³ and R⁴ are as defined above for Formula I'', and the pharmaceutically acceptable salts and solvates thereof.

In another embodiment, the present invention provides novel compounds of Formula IC'':

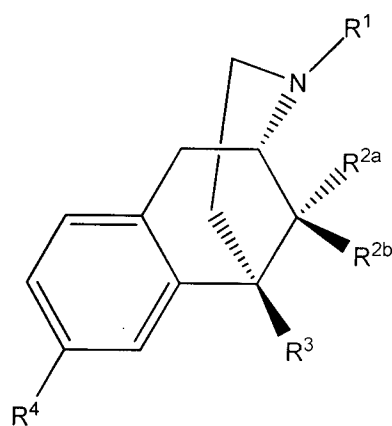
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IC''

wherein R^1 , R^{2a} , R^{2b} , R^3 and R^4 are as defined above for Formula I'', and the pharmaceutically acceptable salts and solvates thereof.

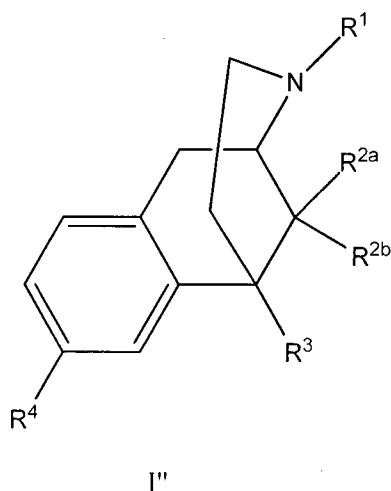
In another embodiment, the present invention provides novel compounds of
5 Formula ID'':



ID''

wherein R^1 , R^{2a} , R^{2b} , R^3 and R^4 are as defined above for Formula I'', and the
10 pharmaceutically acceptable salts and solvates thereof.

In one embodiment, the present invention provides novel compounds of Formula I'':



5

wherein

R¹ is selected from the group consisting of $-(C_1-C_{10})$ alkyl, $-(C_2-C_{10})$ alkenyl, $-(C_2-C_{10})$ alkynyl, $-(C_3-C_{12})$ cycloalkyl, (C_3-C_{12}) cycloalkyl- (C_1-C_6) alkyl-, $-(C_3-C_{12})$ cycloalkenyl, (C_3-C_{12}) cycloalkenyl- (C_1-C_6) alkyl-, $-(6- \text{ to } 14\text{-membered})$ aryl, $((6- \text{ to } 14\text{-membered})$ aryl)- (C_1-C_6) alkyl-, diphenyl- (C_1-C_6) alkyl-, $-(3- \text{ to } 12\text{-membered})$ heterocycle, $((3- \text{ to } 12 \text{ membered})$ heterocycle)- (C_1-C_6) alkyl-, $-(OCH_2CH_2)_s-O-(C_1-C_6)$ alkyl, $-(CH_2CH_2O)_s-(C_1-C_6)$ alkyl, (C_1-C_{10}) alkoxy, $C(\text{halo})_3$, $CH(\text{halo})_2$, $CH_2(\text{halo})$, $C(O)R^5$, $-C(O)O-(C_1-C_{10})$ alkyl, and $-(CH_2)_n-N(R^6)_2$, each of which is optionally substituted by 1, 2 or 3 independently selected R⁹ groups;

15

R^{2a} is hydrogen, OH, or absent;

R^{2b} is

- a) $((6- \text{ to } 14\text{-membered})$ aryl), $-(5- \text{ to } 12\text{-membered})$ heteroaryl, or $((3- \text{ to } 12\text{-membered})$ heterocycle), each of which is optionally substituted with one, two, or three independently selected R³⁰ groups; or
- b) $-Z-G-R^{10}$, provided that $-Z-G-R^{10}$ is other than hydrogen;

20

or R^{2a} and R^{2b} together form =O;

Z is absent or $-(CH_2)_m-$, optionally substituted with 1 or 2 $-(C_1-C_6)$ alkyl;

5 G is selected from the group consisting of:

- a) a bond, $-(C_1-C_6)$ alkylene, $-(C_2-C_6)$ alkenylene;
- b) O, $-OCO-$, $-C(=O)$, $=CH$;
- c) NR^8 , $=N-O$, $=N-NH$;
- d) S, SO, SO₂; and
- 10 e) $-NH-SO_2$;

and when Z is absent and G is $=CH$, $=N-O$, or $=N-NH$, then R^{2a} is absent;

R¹⁰ is selected from the group consisting of hydrogen, $-(C_1-C_{10})$ alkyl, $-(C_2-C_{12})$ alkenyl,
 15 $-C(=O)$, $-C(=O)-(C_1-C_6)$ alkyl, $-C(=O)-(C_2-C_6)$ alkenyl, $-C(=O)-(6- to 14-$
 $membered)$ aryl, $-C(=O)-(C_1-C_6)$ alkyl-(6- to 14-membered)aryl, $-(C_2-C_{12})$ alkynyl, $-(C_1-$
 $C_{10})$ alkoxy, $-(OCH_2CH_2)_s-O(C_1-C_6)$ alkyl, $-(CH_2CH_2O)_s-(C_1-C_6)$ alkyl, $-NH_2$, $-$
 $NH(C_1-C_6)$ alkyl, CN, NR^5R^6 , $-(C_1-C_6)$ alkyl- NR^5R^6 , $-CONR^5R^6$, $-(C_1-C_6)$ alkyl-CO-
 NR^5R^6 , $-COOR^7$, $-(C_1-C_6)$ alkyl-CO-OR⁷, $-(C_1-C_6)$ alkoxy-COOR⁷, $-CO-(CH_2)_n-$
 20 COOR⁷, $-CO-(CH_2)_n-CO-NR^5R^6$, $-(C_3-C_{12})$ cycloalkyl, $((C_3-C_{12})$ cycloalkyl)- $(C_1-$
 $C_6)$ alkyl-, $-(C_4-C_{12})$ cycloalkenyl, $((C_4-C_{12})$ cycloalkenyl)- (C_1-C_6) alkyl-, $-(C_6-$
 $C_{14})$ bicycloalkyl, $((C_6-C_{14})$ bicycloalkyl)- (C_1-C_6) alkyl-, $-(C_8-C_{20})$ tricycloalkyl, $((C_8-$
 $C_{20})$ tricycloalkyl)- (C_1-C_6) alkyl-, $-(C_7-C_{14})$ bicycloalkenyl, $((C_7-C_{14})$ bicycloalkenyl)-
 (C_1-C_6) alkyl-, $-(C_8-C_{20})$ tricycloalkenyl, $((C_8-C_{20})$ tricycloalkenyl)- (C_1-C_6) alkyl-, $-(6-$
 25 to 14-membered)aryl, $((6- to 14-membered)$ aryl)- (C_1-C_6) alkyl-, $-SO_2-(C_1-C_6)$ alkyl, $-$
 $SO_2-((C_3-C_{12})$ cycloalkyl), $-SO_2-((C_3-C_{12})$ cycloalkyl)- (C_1-C_6) alkyl, $-SO_2-((5- to 12-$
 $membered)$ heteroaryl), $-SO_2-((5- to 12-membered)$ heteroaryl)- (C_1-C_6) alkyl, $-C(=O)-$
 $NH-((5- to 12-membered)$ heteroaryl), $-C(=O)-NH-((5- to 12-membered)$ heteroaryl)-
 (C_1-C_6) alkyl, $-C(=O)-NH-((3- to 12-membered)$ heterocycle), $-C(=O)-NH-((3- to 12-$
 30 membered)heterocycle)- (C_1-C_6) alkyl, $SO_2-((6- to 14-membered)$ aryl), $SO_2-((6- to 14$
 membered)aryl)- (C_1-C_6) alkyl, $-(7- to 12-membered)$ bicyclic ring system, $((7- to 12-$

membered)bicyclic ring system)-(C₁-C₆)alkyl-, -(7- to 12-membered)bicyclic aryl, ((7-
 to 12-membered)bicyclic aryl)-(C₁-C₆)alkyl-, -(5- to 12-membered)heteroaryl, ((5- to
 12-membered)heteroaryl)-(C₁-C₆)alkyl-, -(3- to 12-membered)heterocycle, ((3- to 12
 membered)heterocycle)-(C₁-C₆)alkyl-, -(7- to 12-membered)bicycloheterocycle, ((7- to
 5 12-membered)bicycloheterocycle)-(C₁-C₆)alkyl-, phenyl, benzyl and naphthyl; each of
 which is optionally substituted with one, two, or three substituents independently
 selected from the group consisting of -OH, (=O), halo, -C(halo)₃, -CH(halo)₂,
 -CH₂(halo), -(C₁-C₆)alkyl, halo(C₁-C₆)alkyl-, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl,
 hydroxy(C₁-C₆)alkyl-, dihydroxy(C₁-C₆)alkyl-, -(C₁-C₆)alkoxy, ((C₁-
 10 C₆)alkoxy)CO(C₁-C₆)alkoxy-, phenyl, benzyl, -NH₂, -NH(C₁-C₆)alkyl,
 -(C₁-C₆)alkyl-NH(C₁-C₆)alkyl-R¹⁴, -CN, -SH, -OR¹¹, -CONR^{5R6}, -(C₁-C₆)alkyl-CO-
 NR^{5R6}, -COOR⁷, -(C₁-C₆)alkyl-CO-OR⁷, -(C₁-C₆)alkoxy-COOR⁷, -(OCH₂CH₂)_s-
 O(C₁-C₆)alkyl, -(CH₂CH₂O)_s-(C₁-C₆)alkyl, -SO₂-NR^{5aR6a}, (C₁-C₆)alkyl)sulfonyl,
 ((C₁-C₆)alkyl)sulfonyl(C₁-C₆)alkyl-, -NH-SO₂(C₁-C₆)alkyl, NH₂-SO₂(C₁-C₆)alkyl-, -
 15 N(SO₂(C₁-C₆)alkyl)₂, -C(=NH)NH₂, -NH-CO-(C₁-C₆)alkyl, -NH-CO-NH₂, -NH-
 C(=O)-NH-(C₁-C₆)alkyl, -NH-C(=O)-(6- to 14- membered)aryl, -NH-C(=O)-(C₁-
 C₆)alkyl-(6- to 14- membered)aryl, -NH-(C₁-C₆)alkyl-CO-OR⁷, -NH-C(=O)-(C₁-
 C₆)alkyl-CO-OR⁷, -NH-C(=O)-CH(NH₂)-(C₁-C₆)alkyl-CO-OR⁷, -(C₃-C₁₂)cycloalkyl,
 ((C₃-C₁₂)cycloalkyl)-(C₁-C₆)alkyl-, -(6- to 14-membered)aryl, -(6- to 14-
 20 membered)aryloxy, -(C₁-C₆)alkoxy-C(O)NR^{5R6}, -NH-(C₁-C₆)alkyl-C(O)-NR^{5R6}, -
 C(O)NH-(C₁-C₆)alkyl-COOR⁷, ((6- to 14-membered)aryl)-(C₁-C₆)alkyl-, -(5- to 12-
 membered)heteroaryl, ((5- to 12-membered)heteroaryl)-(C₁-C₆)alkyl-, -(3- to 12-
 membered)heterocycle, ((3- to 12-membered)heterocycle)-(C₁-C₆)alkyl-, -(7- to 12-
 membered)bicycloheterocycle, and ((7- to 12-membered)bicycloheterocycle)-(C₁-
 25 C₆)alkyl-;

R³ is selected from:

- a) -H; or
- b) -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, or -(C₂-C₆)alkynyl;

30

R⁴ is selected from

- a) -H, -OH, halo, -C(halo)₃, -CH(halo)₂, -CH₂(halo), COOH, or CONH₂; or
- b) -(C₁-C₅)alkyl, -(C₂-C₅)alkenyl, -(C₂-C₅)alkynyl, -(CH₂)_n-O-(CH₂)_n-CH₃, or -(C₁-C₅)alkoxy, each of which is optionally substituted with 1, 2, or 3 independently selected R⁹ groups;

5

R⁵ and R⁶ are each independently selected from

- a) hydrogen, -OH, halo, -C(halo)₃, -CH(halo)₂, -CH₂(halo);
- b) -(C₁-C₆)alkyl, -(C₂-C₅)alkenyl, -(C₂-C₅)alkynyl, -(CH₂)_n-O-(CH₂)_n-CH₃, -(C₁-C₆)alkoxy, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from -OH, halo, -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₁-C₁₀)alkoxy, -(C₃-C₁₂)cycloalkyl, -CHO, -C(O)OH, -C(halo)₃, -CH(halo)₂, CH₂(halo), -(CH₂)_n-O-(CH₂)_n-CH₃, phenyl, or CONR^{5a}R^{6a};
- c) -(C₃-C₈)cycloalkyl, ((C₃-C₈)cycloalkyl)-(C₁-C₆)alkyl-, -COOR⁷, -(C₁-C₆)alkyl-COOR⁷, -CONH₂, or (C₁-C₆)alkyl-CONH-;
- d) ((6- to 14-membered)aryl) optionally substituted with 1, 2, or 3 independently selected R³⁰ groups;
- e) -((5- to 12-membered)heteroaryl) optionally substituted with 1, 2, or 3 independently selected R³⁰ groups; or
- f) R⁵ and R⁶ together with the nitrogen atom to which they are attached form a (3- to 12-membered)heterocycle optionally substituted with 1, 2, or 3 independently selected R³⁰ groups;

20

R^{5a} and R^{6a} are each independently selected from the group consisting of:

- a) hydrogen, -OH, halo, -C(halo)₃, -CH(halo)₂, and -CH₂(halo);
- b) -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(CH₂)_n-O-(CH₂)_n-CH₃, and -(C₁-C₆)alkoxy, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from -OH, halo, -(C₁-C₁₀)alkyl, -(C₂-C₁₂)alkenyl, -(C₂-C₁₂)alkynyl, -(C₁-C₁₀)alkoxy, -(C₃-C₁₂)cycloalkyl, -CHO, -COOH, -C(halo)₃, -CH(halo)₂, CH₂(halo), -(CH₂)_n-O-(CH₂)_n-CH₃, and phenyl;
- c) -(C₃-C₈)cycloalkyl, ((C₃-C₈)cycloalkyl)-(C₁-C₆)alkyl-, -COOR⁷, -(C₁-C₆)alkyl-COOR⁷, -CONH₂, and (C₁-C₆)alkyl-CONH-;

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- d) -(6- to 14-membered)aryl optionally substituted with 1, 2, or 3 independently selected R^{30} groups;
- e) -((5- to 12-membered)heteroaryl) optionally substituted with 1, 2, or 3 independently selected R^{30} groups; or
- 5 f) R^{5a} and R^{6a} together with the nitrogen atom to which they are attached form a (3- to 12-membered)heterocycle optionally substituted with 1, 2, or 3 independently selected R^{30} groups;

each R^7 is independently selected from the group consisting of hydrogen, -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₃-C₁₂)cycloalkyl, -(C₄-C₁₂)cycloalkenyl, 10 ((C₃-C₁₂)cycloalkyl)-(C₁-C₆)alkyl-, and ((C₄-C₁₂)cycloalkenyl)-(C₁-C₆)alkyl-;

each R^8 is independently selected from H, -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₁-C₁₀)alkoxy, -(C₃-C₁₂)cycloalkyl, -(C₃-C₁₂)cycloalkenyl, ((C₃-C₁₂)cycloalkyl)-(C₁-C₆)alkyl-, ((C₃-C₁₂)cycloalkenyl)-(C₁-C₆)alkyl-, -C(=O)(C₁-C₆)alkyl or SO₂(C₁-C₆)alkyl; 15

each R^9 is independently selected from -OH, halo, -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₁-C₁₀)alkoxy, -(C₃-C₁₂)cycloalkyl, -CHO, -C(O)OH, -C(halo)₃, -CH(halo)₂, CH₂(halo), -(CH₂)_n-O-(CH₂)_n-CH₃, phenyl, or CONR^{5a}R^{6a}; 20

each R^{11} is independently selected from -C(halo)₃, -CH(halo)₂, -CH₂(halo), -(C₂-C₅)alkenyl, -(C₂-C₅)alkynyl, -(CH₂)_n-O-(CH₂)_n-CH₃, (6- to 14-membered)aryl, ((6- to 14-membered)aryl)-(C₁-C₆)alkyl-, or (5- to 12-membered)heteroaryl, ((5- to 12-membered)heteroaryl)-(C₁-C₆)alkyl-, each of which is optionally substituted with 1, 2, or 3 independently selected R^9 groups; 25

each R^{14} is independently selected from -COOR⁷, -(C₁-C₆)alkyl-COOR⁷, -C(=O)-(C₁-C₆)alkyl-COOR⁷, -(C₁-C₆)alkyl-C(=O)-(C₁-C₆)alkyl-COOR⁷, CONH₂, or -(C₁-C₆)alkyl-CONH; 30

each R^{30} is independently selected from COOR^7 , $\text{CONR}^{5a}\text{R}^{6a}$, $-(\text{C}_1\text{-C}_6)\text{alkyl}$, $-\text{C}(=\text{O})$, CN , $-(3\text{- to }12\text{-membered})\text{heteroaryl}$, $((3\text{- to }12\text{-membered})\text{heteroaryl})-(\text{C}_1\text{-C}_6)\text{alkyl}$, NH_2 , halo, and $((6\text{- to }14\text{-membered})\text{aryl})-(\text{C}_1\text{-C}_6)\text{alkoxy}$;

- 5 m is an integer 1, 2, 3, 4, 5, or 6;
 n is an integer 0, 1, 2, 3, 4, 5, or 6;
 s is an integer 1, 2, 3, 4, 5, or 6;

provided that when R^4 is $-(\text{C}_1\text{-C}_5)\text{alkoxy}$ then:

- 10 a) R^{2a} and R^{2b} cannot be taken together to form $=\text{O}$; or
 b) R^{2a} cannot be OH when R^{2b} is $-\text{Z-G-R}^{10}$, and $-\text{Z-G-R}^{10}$ is either:
 a. OH ;
 b. $-(\text{C}_1\text{-C}_6)\text{alkyl}$;
 c. $-(\text{C}_2\text{-C}_6)\text{alkenyl}$; or
 15 d. $-(\text{C}_2\text{-C}_6)\text{alkynyl}$; or
 c) R^{2a} cannot be H when the combination $-\text{Z-G-R}^{10}$ is either:
 a. OH ;
 b. $-\text{O-C}(=\text{O})-(\text{C}_1\text{-C}_6)\text{alkyl}$; or
 c. $-\text{O-C}(=\text{O})-(\text{C}_2\text{-C}_6)\text{alkenyl}$;
 20 and provided that when R^4 is OH then:
 a) R^{2a} cannot be OH when R^{2b} is $-\text{Z-G-R}^{10}$, and $-\text{Z-G-R}^{10}$ is:
 a. $-(\text{C}_1\text{-C}_6)\text{alkyl}$;
 b. $-(\text{C}_2\text{-C}_6)\text{alkenyl}$;
 c. or $-(\text{C}_2\text{-C}_6)\text{alkynyl}$;
 25 b) R^{2a} cannot be H when R^{2b} is $-\text{Z-G-R}^{10}$, and $-\text{Z-G-R}^{10}$ is
 a. OH
 b. $-\text{O-C}(=\text{O})-(\text{C}_1\text{-C}_6)\text{alkyl}$; or
 c. $-\text{O-C}(=\text{O})-(\text{C}_2\text{-C}_6)\text{alkenyl}$;

- 30 and provided that when R^3 is $(\text{C}_1\text{-C}_6)\text{alkyl}$ or $(\text{C}_2\text{-C}_6)\text{alkenyl}$, and R^4 is H , OH , or $(\text{C}_1\text{-C}_5)\text{alkoxy}$, then R^{2b} is not:

- a) optionally substituted (5- to 12-membered)heteroaryl,
- b) optionally substituted (3- to 12-membered)heterocycle; or
- c) unsubstituted phenyl or phenyl substituted with halo, (C₁-C₆)alkyl, C(halo)₃, hydroxy, (C₁-C₆)alkoxy, (3- to 12-membered)heterocycle, or NH₂;

5

and provided that when R⁴ is OH and R¹ is (C₁-C₁₀)alkyl, then R^{2a} and R^{2b} cannot be together selected =O;

and provided that when R⁴ is hydrogen and when R¹ and R³ are both methyl, then:

- 10 a) R^{2a} and R^{2b} cannot together form =O or =N-OH; or
- b) R^{2b} may not be NH₂ or NHC(O)CH₃ if R^{2a} is hydrogen.

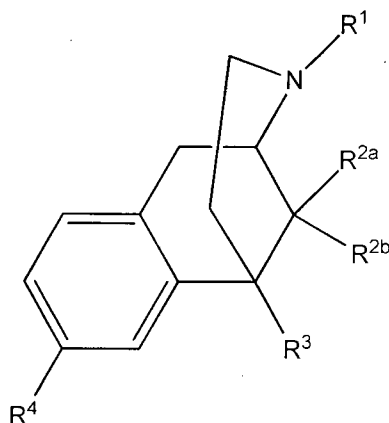
and provided that when R^{2a} is H, then R^{2b} may not be -Z-G-R¹⁰, wherein -Z-G-R¹⁰ is:

- 15 a) -CH₂-CHR²⁰-C(=O)R²¹, wherein
R²⁰ is H, or -(C₁-C₆)alkyl, and
R²¹ is selected from the group consisting of H, -(C₁-C₁₀)alkyl,
-(C₃-C₁₂)cycloalkyl, ((C₃-C₁₂)cycloalkyl)-(C₁-C₆)alkyl-, -(6- to 14-
membered)aryl, and ((6- to 14-membered)aryl)-(C₁-C₆)alkyl-; or
- b) -CH₂-CHR²⁰-CR²²R²³OH, wherein
20 R²⁰ is defined as above, and
R²² and R²³ are each independently selected from the group consisting of H,
-(C₁-C₁₀)alkyl, ((C₃-C₁₂)cycloalkyl)-(C₁-C₆)alkyl-, -(6- to 14-membered)aryl,
and ((6- to 14-membered)aryl)-(C₁-C₆)alkyl-; or
- c) -CH₂-CR²⁰=CR²³R²⁴, wherein
25 R²⁰ and R²³ are defined as above, and
R²⁴ is selected from the group consisting of H, and -(C₁-C₆)alkyl;

and the pharmaceutically acceptable salts and solvates thereof.

30

The present invention provides novel compounds of Formula I':



I'

5 wherein

R¹ is selected from the group consisting of $-(C_1-C_{10})$ alkyl, $-(C_2-C_{10})$ alkenyl, $-(C_2-C_{10})$ alkynyl, $-(C_3-C_{12})$ cycloalkyl, (C_3-C_{12}) cycloalkyl- (C_1-C_6) alkyl-, $-(C_3-C_{12})$ cycloalkenyl, (C_3-C_{12}) cycloalkenyl- (C_1-C_6) alkyl-, $-(6- \text{ to } 14\text{-membered})$ aryl, $((6- \text{ to } 14\text{-membered})$ aryl)- (C_1-C_6) alkyl-, diphenyl- (C_1-C_6) alkyl-, $-(3- \text{ to } 12\text{-membered})$ heterocycle, $((3- \text{ to } 12 \text{ membered})$ heterocycle)- (C_1-C_6) alkyl-, $-(OCH_2CH_2)_3-O-(C_1-C_6)$ alkyl, $-(CH_2CH_2O)_3-(C_1-C_6)$ alkyl, (C_1-C_{10}) alkoxy, $C(\text{halo})_3$, $CH(\text{halo})_2$, $CH_2(\text{halo})$, $C(O)R^5$, $-C(O)O-(C_1-C_{10})$ alkyl, and $-(CH_2)_n-N(R^6)_2$, each of which is optionally substituted by 1, 2 or 3 independently selected R⁹ groups;

15

R^{2a} is absent or OH;

R^{2b} is

- a) $((6- \text{ to } 14\text{-membered})$ aryl) or $((3- \text{ to } 12\text{-membered})$ heterocycle), each of which is optionally substituted with one, two, or three independently selected R³⁰ groups; or
- 20 b) $-Z-G-R^{10}$, provided that $-Z-G-R^{10}$ is other than hydrogen;
- or R^{2a} and R^{2b} together form =O;

Z is absent or $-(CH_2)_m-$, optionally substituted with 1 or 2 $-(C_1-C_6)$ alkyl;

G is selected from the group consisting of:

- a) a bond, $-(C_1-C_6)$ alkylene, $-(C_2-C_6)$ alkenylene;
- 5 b) O, $-OCO-$, $-C(=O)$, $=CH$;
- c) NR^8 , $=N-O$, $=N-NH$;
- d) S, SO, and SO_2 ;

R^{10} is selected from the group consisting of hydrogen, $-(C_1-C_{10})$ alkyl, $-(C_2-C_{12})$ alkenyl, $-C(=O)$, $-C(=O)-(C_1-C_6)$ alkyl, $-C(=O)-(C_2-C_6)$ alkenyl, $-C(=O)-(6- to 14-$
 10 $membered)$ aryl, $-C(=O)-(C_1-C_6)$ alkyl-(6- to 14-membered)aryl, $-(C_2-C_{12})$ alkynyl, $-(C_1-C_{10})$ alkoxy, $-(OCH_2CH_2)_5-O(C_1-C_6)$ alkyl, $-(CH_2CH_2O)_5-(C_1-C_6)$ alkyl, $-NH_2$, $-NH(C_1-C_6)$ alkyl, CN, NR^5R^6 , $-(C_1-C_6)$ alkyl- NR^5R^6 , $-CONR^5R^6$, $-(C_1-C_6)$ alkyl-CO- NR^5R^6 , $-COOR^7$, $-(C_1-C_6)$ alkyl-CO- OR^7 , $-(C_1-C_6)$ alkoxy-COOR⁷, $-CO-(CH_2)_n-$
 15 $COOR^7$, $-CO-(CH_2)_n-CO-NR^5R^6$, $-(C_3-C_{12})$ cycloalkyl, $((C_3-C_{12})$ cycloalkyl)- (C_1-C_6) alkyl-, $-(C_4-C_{12})$ cycloalkenyl, $((C_4-C_{12})$ cycloalkenyl)- (C_1-C_6) alkyl-, $-(C_6-C_{14})$ bicycloalkyl, $((C_6-C_{14})$ bicycloalkyl)- (C_1-C_6) alkyl-, $-(C_8-C_{20})$ tricycloalkyl, $((C_8-C_{20})$ tricycloalkyl)- (C_1-C_6) alkyl-, $-(C_7-C_{14})$ bicycloalkenyl, $((C_7-C_{14})$ bicycloalkenyl)- (C_1-C_6) alkyl-, $-(C_8-C_{20})$ tricycloalkenyl, $((C_8-C_{20})$ tricycloalkenyl)- (C_1-C_6) alkyl-, $-(6-$
 20 $to 14-membered)$ aryl, $((6- to 14-membered)$ aryl)- (C_1-C_6) alkyl-, $-(7- to 12-membered)$ bicyclic ring system, $((7- to 12-membered)$ bicyclic ring system)- (C_1-C_6) alkyl-, $-(7- to 12-membered)$ bicyclic aryl, $((7- to 12-membered)$ bicyclic aryl)- (C_1-C_6) alkyl-, $-(5- to 12-membered)$ heteroaryl, $((5- to 12-membered)$ heteroaryl)- (C_1-C_6) alkyl-, $-(3- to 12-membered)$ heterocycle, $((3- to 12 membered)$ heterocycle)- $(C_1-$
 25 $C_6)$ alkyl-, $-(7- to 12-membered)$ bicycloheterocycle, $((7- to 12-membered)$ bicycloheterocycle)- (C_1-C_6) alkyl-, phenyl, benzyl and naphthyl; each of which is optionally substituted with one, two, or three substituents independently selected from the group consisting of $-OH$, $(=O)$, halo, $-C(halo)_3$, $-CH(halo)_2$, $-CH_2(halo)$, $-(C_1-C_6)$ alkyl, halo (C_1-C_6) alkyl-, $-(C_2-C_6)$ alkenyl, $-(C_2-C_6)$ alkynyl,
 30 hydroxy (C_1-C_6) alkyl-, dihydroxy (C_1-C_6) alkyl-, $-(C_1-C_6)$ alkoxy, $((C_1-C_6)$ alkoxy)CO (C_1-C_6) alkoxy-, phenyl, benzyl, $-NH_2$, $-NH(C_1-C_6)$ alkyl,

-(C₁-C₆)alkyl-NH(C₁-C₆)alkyl-R¹⁴, -CN, -SH, -OR¹¹, -CONR⁵R⁶, -(C₁-C₆alkyl)-CO-
 NR⁵R⁶, -COOR⁷, -(C₁-C₆)alkyl-CO-OR⁷, -(C₁-C₆)alkoxy-COOR⁷, -(OCH₂CH₂)_s-
 O(C₁-C₆)alkyl, -(CH₂CH₂O)_s-(C₁-C₆)alkyl, (C₁-C₆)alkyl)sulfonyl, ((C₁-
 C₆)alkyl)sulfonyl(C₁-C₆)alkyl-, -NH-SO₂(C₁-C₆)alkyl, NH₂-SO₂(C₁-C₆)alkyl-, -
 5 N(SO₂(C₁-C₆)alkyl)₂, -C(=NH)NH₂, -NH-CO-(C₁-C₆)alkyl, -NH-CO-NH₂, -NH-
 C(=O)-NH-(C₁-C₆)alkyl, -NH-C(=O)-(6- to 14- membered)aryl, -NH-C(=O)-(C₁-
 C₆)alkyl-(6- to 14- membered)aryl, -NH-(C₁-C₆)alkyl-CO-OR⁷, -NH-C(=O)-(C₁-
 C₆)alkyl-CO-OR⁷, -NH-C(=O)-CH(NH₂)-(C₁-C₆)alkyl-CO-OR⁷, -(C₃-C₁₂)cycloalkyl,
 ((C₃-C₁₂)cycloalkyl)-(C₁-C₆)alkyl-, -(6- to 14-membered)aryl, -(6- to 14-
 10 membered)aryloxy, -(C₁-C₆)alkoxy-C(O)NR⁵R⁶, -NH-(C₁-C₆)alkyl-C(O)-NR⁵R⁶, -
 C(O)NH-(C₁-C₆)alkyl-COOR⁷, ((6- to 14-membered)aryl)-(C₁-C₆)alkyl-, -(5- to 12-
 membered)heteroaryl, ((5- to 12-membered)heteroaryl)-(C₁-C₆)alkyl-, -(3- to 12-
 membered)heterocycle, ((3- to 12-membered)heterocycle)-(C₁-C₆)alkyl-, -(7- to 12-
 membered)bicycloheterocycle, and ((7- to 12-membered)bicycloheterocycle)-(C₁-
 15 C₆)alkyl-;

R³ is selected from:

- a) -H; or
- b) -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, or -(C₂-C₆)alkynyl;

20

R⁴ is selected from

- a) -H, -OH, halo, -C(halo)₃, -CH(halo)₂, -CH₂(halo), COOH, or CONH₂; or
- b) -(C₁-C₅)alkyl, -(C₂-C₅)alkenyl, -(C₂-C₅)alkynyl, -(CH₂)_n-O-(CH₂)_n-CH₃, or -(C₁-
 C₅)alkoxy, each of which is optionally substituted with 1, 2, or 3 independently
 25 selected R⁹ groups;

25

R⁵ and R⁶ are each independently selected from

- a) hydrogen, -OH, halo, -C(halo)₃, -CH(halo)₂, -CH₂(halo);
- b) -(C₁-C₆)alkyl, -(C₂-C₅)alkenyl, -(C₂-C₅)alkynyl, -(CH₂)_n-O-(CH₂)_n-CH₃, -(C₁-
 30 C₆)alkoxy, each of which is optionally substituted with 1, 2, or 3 substituents
 independently selected from -OH, halo, -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-

- C_{10})alkynyl, $-(C_1-C_{10})$ alkoxy, $-(C_3-C_{12})$ cycloalkyl, $-\text{CHO}$, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{halo})_3$, $-\text{CH}(\text{halo})_2$, $\text{CH}_2(\text{halo})$, $-(\text{CH}_2)_n\text{-O}-(\text{CH}_2)_n\text{-CH}_3$, phenyl, or CONR^5R^6 ;
- c) $-(C_3-C_8)$ cycloalkyl, $((C_3-C_8)\text{cycloalkyl})-(C_1-C_6)\text{alkyl-}$, $-\text{COOR}^7$, $-(C_1-C_6)\text{alkyl-}$
 COOR^7 , $-\text{CONH}_2$, or $(C_1-C_6)\text{alkyl-CONH-}$;
- 5 d) ((6- to 14-membered)aryl) optionally substituted with 1, 2, or 3 independently selected R^{30} groups; or
- e) R^5 and R^6 together with the nitrogen atom to which they are attached form a (4- to 8-membered)heterocycle optionally substituted with 1, 2, or 3 independently selected R^{30} groups;

10

R^{5a} and R^{6a} are each independently selected from the group consisting of:

- a) hydrogen, $-\text{OH}$, halo, $-\text{C}(\text{halo})_3$, $-\text{CH}(\text{halo})_2$, and $-\text{CH}_2(\text{halo})$;
- b) $-(C_1-C_6)\text{alkyl-}$, $-(C_2-C_6)\text{alkenyl-}$, $-(C_2-C_6)\text{alkynyl-}$, $-(\text{CH}_2)_n\text{-O}-(\text{CH}_2)_n\text{-CH}_3$, and $-(C_1-C_6)\text{alkoxy}$, each of which is optionally substituted with 1, 2, or 3
- 15 substituents independently selected from $-\text{OH}$, halo, $-(C_1-C_{10})\text{alkyl-}$, $-(C_2-C_{12})\text{alkenyl-}$, $-(C_2-C_{12})\text{alkynyl-}$, $-(C_1-C_{10})\text{alkoxy}$, $-(C_3-C_{12})\text{cycloalkyl-}$, $-\text{CHO}$, $-\text{COOH}$, $-\text{C}(\text{halo})_3$, $-\text{CH}(\text{halo})_2$, $\text{CH}_2(\text{halo})$, $-(\text{CH}_2)_n\text{-O}-(\text{CH}_2)_n\text{-CH}_3$, and phenyl;
- c) $-(C_3-C_8)\text{cycloalkyl-}$, $((C_3-C_8)\text{cycloalkyl})-(C_1-C_6)\text{alkyl-}$, $-\text{COOR}^7$, $-(C_1-C_6)\text{alkyl-}$
 COOR^7 , $-\text{CONH}_2$, and $(C_1-C_6)\text{alkyl-CONH-}$;
- 20 d) $-(6\text{- to }14\text{-membered})\text{aryl}$ optionally substituted with 1, 2, or 3 independently selected R^{30} groups; or
- e) R^{5a} and R^{6a} together with the nitrogen atom to which they are attached form a (4- to 8-membered)heterocycle optionally substituted with 1, 2, or 3 independently selected R^{30} groups;

25

each R^7 is independently selected from the group consisting of hydrogen, $-(C_1-C_6)\text{alkyl-}$, $-(C_2-C_6)\text{alkenyl-}$, $-(C_2-C_6)\text{alkynyl-}$, $-(C_3-C_{12})\text{cycloalkyl-}$, $-(C_4-C_{12})\text{cycloalkenyl-}$, $((C_3-C_{12})\text{cycloalkyl})-(C_1-C_6)\text{alkyl-}$, and $((C_4-C_{12})\text{cycloalkenyl})-(C_1-C_6)\text{alkyl-}$;

30

each R^8 is independently selected from H, $-(C_1-C_6)\text{alkyl-}$, $-(C_2-C_6)\text{alkenyl-}$, $-(C_2-C_6)\text{alkynyl-}$, $-(C_1-C_{10})\text{alkoxy}$, $-(C_3-C_{12})\text{cycloalkyl-}$, $-(C_3-C_{12})\text{cycloalkenyl-}$, $((C_3-$

C₁₂)cycloalkyl)-(C₁-C₆)alkyl-, ((C₃-C₁₂)cycloalkenyl)-(C₁-C₆)alkyl-, -C(=O)(C₁-C₆)alkyl or SO₂(C₁-C₆)alkyl;

each R⁹ is independently selected from -OH, halo, -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -
 5 (C₂-C₁₀)alkynyl, -(C₁-C₁₀)alkoxy, -(C₃-C₁₂)cycloalkyl, -CHO, -C(O)OH, -C(halo)₃, -CH(halo)₂, CH₂(halo), -(CH₂)_n-O-(CH₂)_n-CH₃, phenyl, or CONR^{5a}R^{6a};

each R¹¹ is independently selected from -C(halo)₃, -CH(halo)₂, -CH₂(halo), -(C₂-C₅)alkenyl, -(C₂-C₅)alkynyl, -(CH₂)_n-O-(CH₂)_n-CH₃, (6- to 14-membered)aryl, ((6- to
 10 14-membered)aryl)-(C₁-C₆)alkyl-, or (5- to 12-membered)heteroaryl, ((5- to 12-membered)heteroaryl)-(C₁-C₆)alkyl-, each of which is optionally substituted with 1, 2, or 3 independently selected R⁹ groups;

each R¹⁴ is independently selected from -COOR⁷, -(C₁-C₆)alkyl-COOR⁷, -C(=O)-(C₁-C₆)alkyl-COOR⁷, -(C₁-C₆)alkyl-C(=O)-(C₁-C₆)alkyl-COOR⁷, CONH₂, or -(C₁-C₆)alkyl-CONH;

each R³⁰ is independently selected from COOR⁷, CONR^{5a}R^{6a}, -(C₁-C₆)alkyl, -C(=O), CN, -(3- to 12-membered)heteroaryl, ((3- to 12-membered)heteroaryl)-(C₁-C₆)alkyl-,
 20 NH₂, halo, and ((6- to 14-membered)aryl)-(C₁-C₆)alkoxy-;

m is an integer 1, 2, 3, 4, 5, or 6;

n is an integer 0, 1, 2, 3, 4, 5, or 6;

s is an integer 1, 2, 3, 4, 5, or 6;

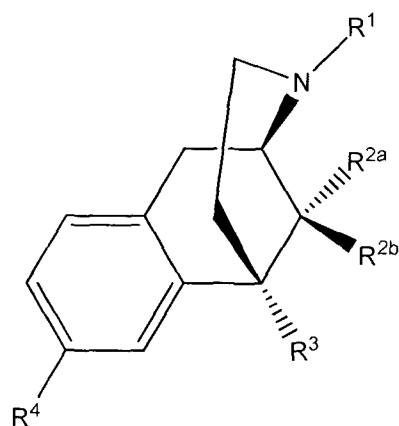
25 provided that when R⁴ is -(C₁-C₅)alkoxy then:

- a) R^{2a} and R^{2b} cannot be taken together to form =O; or
- b) R^{2a} cannot be OH when R^{2b} is -Z-G-R¹⁰, and -Z-G-R¹⁰ is either:
 - a. OH; or
 - b. -(C₁-C₆)alkyl; or
- 30 c) R^{2a} cannot be H when the combination -Z-G-R¹⁰ is OH;

and the pharmaceutically acceptable salts and solvates thereof.

In one embodiment, the present invention provides novel compounds of Formula IA':

5

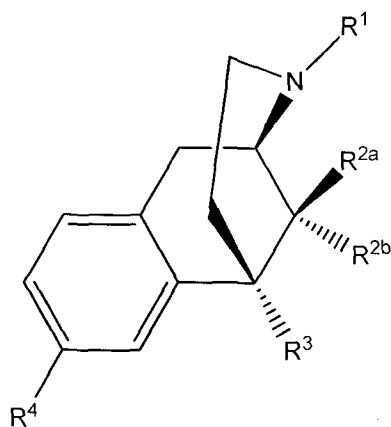


IA'

wherein R¹, R^{2a}, R^{2b}, R³ and R⁴ are as defined above for Formula I', and the pharmaceutically acceptable salts and solvates thereof.

10

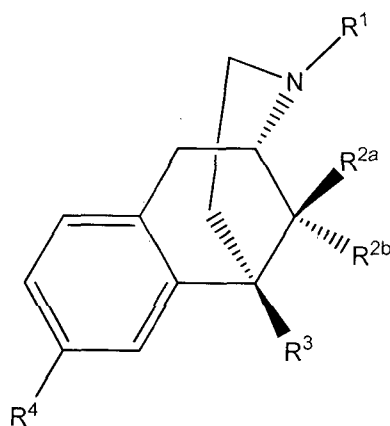
In another embodiment, the present invention provides novel compounds of Formula IB':



IB'

wherein R^1 , R^{2a} , R^{2b} , R^3 and R^4 are as defined above for Formula I', and the pharmaceutically acceptable salts and solvates thereof.

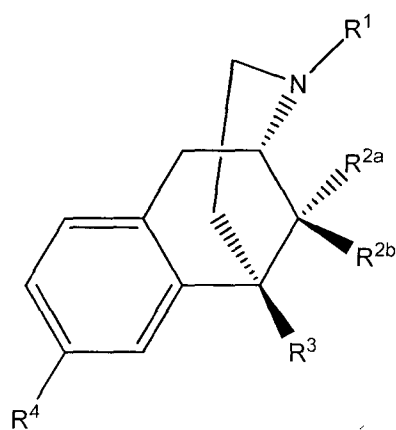
- 5 In another embodiment, the present invention provides novel compounds of Formula IC':



IC'

- 10 wherein R^1 , R^{2a} , R^{2b} , R^3 and R^4 are as defined above for Formula I', and the pharmaceutically acceptable salts and solvates thereof.

In another embodiment, the present invention provides novel compounds of Formula ID':



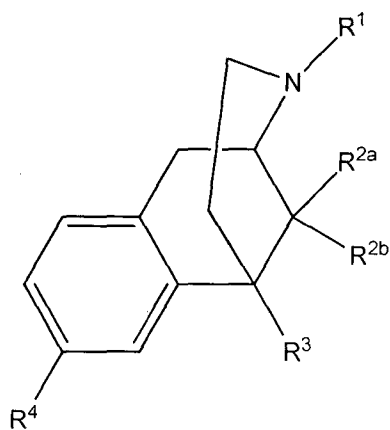
ID'

5

wherein R¹, R^{2a}, R^{2b}, R³ and R⁴ are as defined above for Formula I', and the pharmaceutically acceptable salts and solvates thereof.

10

The present invention further provides novel compounds of Formula I:



I

wherein

R^1 is selected from the group consisting of $-(C_1-C_{10})$ alkyl, $-(C_2-C_{10})$ alkenyl, $-(C_2-C_{10})$ alkynyl, $-(C_3-C_{12})$ cycloalkyl, (C_3-C_{12}) cycloalkyl- $-(C_1-C_6)$ alkyl-, $-(C_3-C_{12})$ cycloalkenyl, (C_3-C_{12}) cycloalkenyl- $-(C_1-C_6)$ alkyl-, $-(6- \text{ to } 14\text{-membered})$ aryl, $((6- \text{ to } 14\text{-membered})$ aryl)- $-(C_1-C_6)$ alkyl-, diphenyl- (C_1-C_6) alkyl-, $-(OCH_2CH_2)_5-O-(C_1-C_6)$ alkyl, $-(CH_2CH_2O)_5-(C_1-C_6)$ alkyl, (C_1-C_{10}) alkoxy, $C(\text{halo})_3$, $CH(\text{halo})_2$, $CH_2(\text{halo})$, $C(O)R^5$, $-C(O)O-(C_1-C_{10})$ alkyl, and $-(CH_2)_n-N(R^6)_2$, each of which is optionally substituted by 1, 2 or 3 independently selected R^9 groups;

R^{2a} is hydrogen or OH;

10 R^{2b} is

a) $((6- \text{ to } 14\text{-membered})$ aryl) or $((3- \text{ to } 12\text{-membered})$ heterocycle), each of which is optionally substituted with one, two, or three independently selected R^{30} groups; or

b) $-Z-G-R^{10}$, provided that $-Z-G-R^{10}$ is other than hydrogen;

15 or R^{2a} and R^{2b} together form $=O$;

Z is absent or $-(CH_2)_m-$, optionally substituted with 1 or 2 $-(C_1-C_6)$ alkyl;

G is selected from the group consisting of:

a) a bond, $-(C_1-C_6)$ alkylene, $-(C_2-C_6)$ alkenylene;

b) O, $-OCO-$, $-C(=O)$, $=CH$;

20 c) NR^8 , $=N-O$, $=N-NH$;

d) S, SO, and SO_2 ;

R^{10} is selected from the group consisting of hydrogen, $-(C_1-C_{10})$ alkyl, $-(C_2-C_{12})$ alkenyl, $-C(=O)$, $-C(=O)-(C_1-C_6)$ alkyl, $-C(=O)-(C_2-C_6)$ alkenyl, $-C(=O)-(6- \text{ to } 14\text{-membered})$ aryl, $-C(=O)-(C_1-C_6)$ alkyl- $(6- \text{ to } 14\text{-membered})$ aryl, $-(C_2-C_{12})$ alkynyl, $-(C_1-C_{10})$ alkoxy, $-(OCH_2CH_2)_5-O(C_1-C_6)$ alkyl, $-(CH_2CH_2O)_5-(C_1-C_6)$ alkyl, $-NH_2$, $-NH(C_1-C_6)$ alkyl, CN, NR^5R^6 , $-(C_1-C_6)$ alkyl- NR^5R^6 , $-CONR^5R^6$, $-(C_1-C_6)$ alkyl-CO- NR^5R^6 , $-COOR^7$, $-(C_1-C_6)$ alkyl-CO- OR^7 , $-(C_1-C_6)$ alkoxy-COOR⁷, $-CO-(CH_2)_n$ -COOR⁷, $-CO-(CH_2)_n$ -CO- NR^5R^6 , $-(C_3-C_{12})$ cycloalkyl, $((C_3-C_{12})$ cycloalkyl)- (C_1-C_6) alkyl-, $-(C_4-C_{12})$ cycloalkenyl, $((C_4-C_{12})$ cycloalkenyl)- (C_1-C_6) alkyl-, $-(C_6-C_{14})$ bicycloalkyl, $((C_6-C_{14})$ bicycloalkyl)- (C_1-C_6) alkyl-, $-(C_8-C_{20})$ tricycloalkyl, $((C_8-$

C₂₀)tricycloalkyl)-(C₁-C₆)alkyl-, -(C₇-C₁₄)bicycloalkenyl, ((C₇-C₁₄)bicycloalkenyl)-
 (C₁-C₆)alkyl-, -(C₈-C₂₀)tricycloalkenyl, ((C₈-C₂₀)tricycloalkenyl)-(C₁-C₆)alkyl-, -(6-
 to 14-membered)aryl, ((6- to 14-membered)aryl)-(C₁-C₆)alkyl-, -(7- to 12-
 membered)bicyclic ring system, ((7- to 12-membered)bicyclic ring system)-(C₁-
 5 C₆)alkyl-, -(7- to 12-membered)bicyclic aryl, ((7- to 12-membered)bicyclic aryl)-(C₁-
 C₆)alkyl-, -(5- to 12-membered)heteroaryl, ((5- to 12-membered)heteroaryl)-(C₁-
 C₆)alkyl-, -(3- to 12-membered)heterocycle, ((3- to 12 membered)heterocycle)-(C₁-
 C₆)alkyl-, -(7- to 12-membered)bicycloheterocycle, ((7- to 12-
 membered)bicycloheterocycle)-(C₁-C₆)alkyl-, phenyl, benzyl and naphthyl; each of
 10 which is optionally substituted with one, two, or three substituents independently
 selected from the group consisting of -OH, (=O), halo, -C(halo)₃, -CH(halo)₂,
 -CH₂(halo), -(C₁-C₆)alkyl, halo(C₁-C₆)alkyl-, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl,
 hydroxy(C₁-C₆)alkyl-, dihydroxy(C₁-C₆)alkyl-, -(C₁-C₆)alkoxy, ((C₁-
 C₆)alkoxy)CO(C₁-C₆)alkoxy-, phenyl, benzyl, -NH₂, -NH(C₁-C₆)alkyl,
 15 -(C₁-C₆)alkyl-NH(C₁-C₆)alkyl-R¹⁴, -CN, -SH, -OR¹¹, -CONR⁵R⁶, -(C₁-C₆)alkyl-CO-
 NR⁵R⁶, -COOR⁷, -(C₁-C₆)alkyl-CO-OR⁷, -(C₁-C₆)alkoxy-COOR⁷, -(OCH₂CH₂)_s-
 O(C₁-C₆)alkyl, -(CH₂CH₂O)_s-(C₁-C₆)alkyl, (C₁-C₆)alkyl)sulfonyl, ((C₁-
 C₆)alkyl)sulfonyl(C₁-C₆)alkyl-, -NH-SO₂(C₁-C₆)alkyl, NH₂-SO₂(C₁-C₆)alkyl-, -
 N(SO₂(C₁-C₆)alkyl)₂, -C(=NH)NH₂, -NH-CO-(C₁-C₆)alkyl, -NH-CO-NH₂, -NH-
 20 C(=O)-NH-(C₁-C₆)alkyl, -NH-C(=O)-(6- to 14- membered)aryl, -NH-C(=O)-(C₁-
 C₆)alkyl-(6- to 14- membered)aryl, -NH-(C₁-C₆)alkyl-CO-OR⁷, -NH-C(=O)-(C₁-
 C₆)alkyl-CO-OR⁷, -NH-C(=O)-CH(NH₂)-(C₁-C₆)alkyl-CO-OR⁷, -(C₃-C₁₂)cycloalkyl,
 ((C₃-C₁₂)cycloalkyl)-(C₁-C₆)alkyl-, -(6- to 14-membered)aryl, -(6- to 14-
 membered)aryloxy, -(C₁-C₆)alkoxy-C(O)NR⁵R⁶, -NH-(C₁-C₆)alkyl-C(O)-NR⁵R⁶, -
 25 C(O)NH-(C₁-C₆)alkyl-COOR⁷, ((6- to 14-membered)aryl)-(C₁-C₆)alkyl-, -(5- to 12-
 membered)heteroaryl, ((5- to 12-membered)heteroaryl)-(C₁-C₆)alkyl-, -(3- to 12-
 membered)heterocycle, ((3- to 12-membered)heterocycle)-(C₁-C₆)alkyl-, -(7- to 12-
 membered)bicycloheterocycle, and ((7- to 12-membered)bicycloheterocycle)-(C₁-
 C₆)alkyl-;

30

R³ is selected from:

(a) -H; or

(b) -(C₁-C₅)alkyl, -(C₂-C₅)alkenyl, or -(C₂-C₅)alkynyl;

R⁴ is selected from

- 5 a) -H, -OH, halo, -C(halo)₃, -CH(halo)₂, -CH₂(halo), COOH, or CONH₂; or
 b) -(C₁-C₅)alkyl, -(C₂-C₅)alkenyl, -(C₂-C₅)alkynyl, -(CH₂)_n-O-(CH₂)_n-CH₃, or -(C₁-C₅)alkoxy, each of which is optionally substituted with 1, 2, or 3 independently selected R⁹ groups;

10 R⁵ and R⁶ are each independently selected from

- a) hydrogen, -OH, halo, -C(halo)₃, -CH(halo)₂, -CH₂(halo);
 b) -(C₁-C₆)alkyl, -(C₂-C₅)alkenyl, -(C₂-C₅)alkynyl, -(CH₂)_n-O-(CH₂)_n-CH₃, -(C₁-C₆)alkoxy, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from -OH, halo, -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₁-C₁₀)alkoxy, -(C₃-C₁₂)cycloalkyl, -CHO, -C(O)OH, -C(halo)₃, -CH(halo)₂, CH₂(halo), -(CH₂)_n-O-(CH₂)_n-CH₃, phenyl, or CONR⁵R⁶;
 15 c) -(C₃-C₈)cycloalkyl, ((C₃-C₈)cycloalkyl)-(C₁-C₆)alkyl-, -COOR⁷, -(C₁-C₆)alkyl-COOR⁷, -CONH₂, or (C₁-C₆)alkyl-CONH-;
 d) ((6- to 14-membered)aryl) optionally substituted with 1, 2, or 3 independently
 20 selected R³⁰ groups; or
 e) R⁵ and R⁶ together with the nitrogen atom to which they are attached form a (4- to 8-membered)heterocycle optionally substituted with 1, 2, or 3 independently selected R³⁰ groups;

25 each R⁷ is independently selected from the group consisting of hydrogen, -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₃-C₁₂)cycloalkyl, -(C₄-C₁₂)cycloalkenyl, ((C₃-C₁₂)cycloalkyl)-(C₁-C₆)alkyl-, and ((C₄-C₁₂)cycloalkenyl)-(C₁-C₆)alkyl-;

 each R⁸ is independently selected from H, -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₁-C₁₀)alkoxy, -(C₃-C₁₂)cycloalkyl, -(C₃-C₁₂)cycloalkenyl, ((C₃-

30

(C₁₂)cycloalkyl)-(C₁-C₆)alkyl-, ((C₃-C₁₂)cycloalkenyl)-(C₁-C₆)alkyl-, -C(=O)(C₁-C₆)alkyl or SO₂(C₁-C₆)alkyl;

each R⁹ is independently selected from -OH, halo, -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -
 5 (C₂-C₁₀)alkynyl, -(C₁-C₁₀)alkoxy, -(C₃-C₁₂)cycloalkyl, -CHO, -C(O)OH, -C(halo)₃, -CH(halo)₂, CH₂(halo), -(CH₂)_n-O-(CH₂)_n-CH₃, phenyl, or CONR⁵R⁶;

each R¹¹ is independently selected from -C(halo)₃, -CH(halo)₂, -CH₂(halo), -(C₂-C₅)alkenyl, -(C₂-C₅)alkynyl, -(CH₂)_n-O-(CH₂)_n-CH₃, (6- to 14-membered)aryl, ((6- to
 10 14-membered)aryl)-(C₁-C₆)alkyl-, (5- to 12-membered)heteroaryl, or ((5- to 12-membered)heteroaryl)-(C₁-C₆)alkyl, each of which is optionally substituted with 1, 2, or 3 independently selected R⁹ groups;

each R¹⁴ is independently selected from -COOR⁷, -(C₁-C₆)alkyl-COOR⁷, -C(=O)-(C₁-C₆)alkyl-COOR⁷, -(C₁-C₆)alkyl-C(=O)-(C₁-C₆)alkyl-COOR⁷, CONH₂, or -(C₁-C₆)alkyl-CONH;

each R³⁰ is independently selected from COOR⁷, CONR⁵R⁶, -(C₁-C₆)alkyl, CN, -(3- to 12-membered)heteroaryl, ((3- to 12-membered)heteroaryl)-(C₁-C₆)alkyl-, NH₂, halo,
 20 and ((6- to 14-membered)aryl)-(C₁-C₆)alkoxy-;

m is an integer 1, 2, 3, 4, 5, or 6;

n is an integer 0, 1, 2, 3, 4, 5, or 6;

s is an integer 1, 2, 3, 4, 5, or 6;

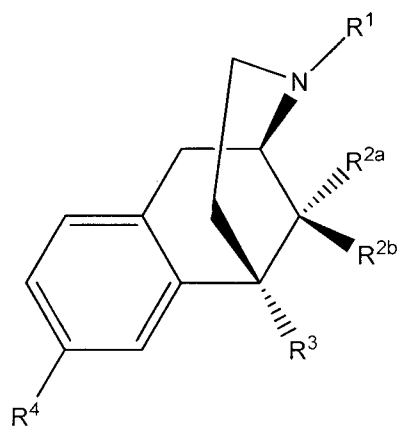
25 provided that when R⁴ is -(C₁-C₅)alkoxy then:

- a) R^{2a} and R^{2b} cannot be taken together to form =O; or
- b) R^{2a} cannot be OH when R^{2b} is -Z-G-R¹⁰, and -Z-G-R¹⁰ is either:
 - a. OH; or
 - b. -(C₁-C₆)alkyl; or

30 c) R^{2a} cannot be H when the combination -Z-G-R¹⁰ is OH;

and the pharmaceutically acceptable salts, prodrugs and solvates thereof.

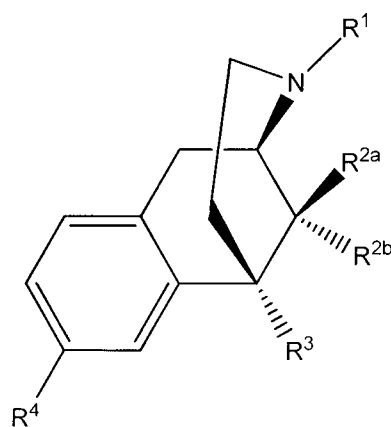
In one embodiment, the present invention provides novel compounds of Formula IA:



IA

- 5 wherein R¹, R^{2a}, R^{2b}, R³ and R⁴ are as defined above for Formula I, and the pharmaceutically acceptable salts, prodrugs, and solvates thereof.

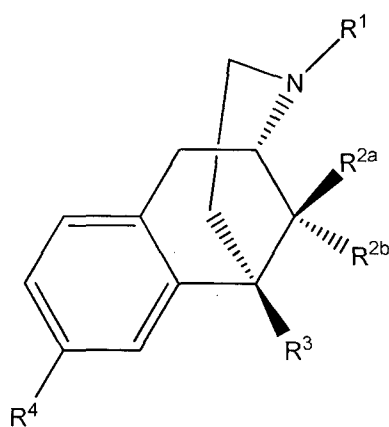
In another embodiment, the present invention provides novel compounds of Formula IB:



IB

wherein R¹, R^{2a}, R^{2b}, R³ and R⁴ are as defined above for Formula I, and the pharmaceutically acceptable salts, prodrugs and solvates thereof.

In another embodiment, the present invention provides novel compounds of Formula IC:



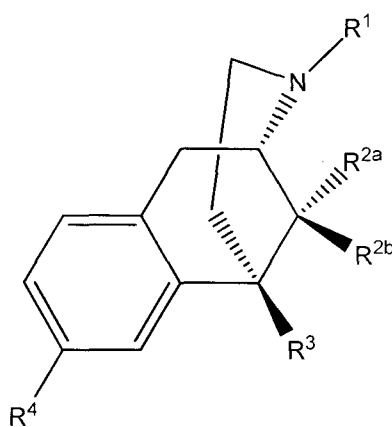
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IC

wherein R¹, R^{2a}, R^{2b}, R³ and R⁴ are as defined above for Formula I, and the pharmaceutically acceptable salts, prodrugs and solvates thereof.

10

In another embodiment, the present invention provides novel compounds of Formula ID:



ID

wherein R^1 , R^{2a} , R^{2b} , R^3 and R^4 are as defined above for Formula I, and the pharmaceutically acceptable salts, prodrugs and solvates thereof.

5 The following embodiments may be selected for any of the formulae shown above

Item 1. In certain embodiments, R^{2a} is absent.

Item 2. In certain embodiments, R^{2a} is hydrogen.

Item 3. In certain embodiments, R^{2a} is OH.

Item 4. In certain embodiments R^{2a} and R^{2b} together form =O.

10 Item 5. In certain embodiments of any one of Items 1 to 3, R^{2b} is ((6- to 14-membered)aryl) or ((3- to 12-membered)heterocycle), each of which is optionally substituted with one or more R^{30} .

Item 6. In certain embodiments of any one of Items 1 to 3, R^{2b} is -Z-G- R^{10} , provided that -Z-G- R^{10} is other than hydrogen.

15 Item 7. In certain embodiments of any one of Items 1 to 6, Z is absent.

Item 8. In certain embodiments, of any one of Items 1 to 3, or 6 Z is CH_2 .

Item 9. In certain embodiments of any one of Items 1 to 3, or 6 to 7, G is NR^8 .

Item 10. In certain embodiments of Item 9, G is NR^8 , wherein R^8 is hydrogen.

20 Item 11. In other embodiments of Item 9, G is NR^8 , wherein R^8 is (C_1 - C_6)alkyl.

Item 12. In other embodiments of Item 11, G is NR^8 , wherein R^8 is methyl or ethyl.

Item 13. In certain embodiments of any one of Items 1 to 3, or 6 to 8, G is a bond.

25 Item 14. In certain embodiments of any one of Items 1 to 3, or 6 to 8, G is O.

Item 15. In certain embodiments of any one of Items 1 to 3, or 6 to 8, G is -OCO-.

Item 16. In certain embodiments of any one of Items 1 to 3, or 6 to 8, G is -C(=O).

30 Item 17. In certain embodiments of any one of Items 1 to 3, or 6 to 8, G is =CH.

Item 18. In certain embodiments of any one of Items 1 to 3, or 6 to 8, G is =N-O.

Item 19. In certain embodiments of any one of Items 1 to 3, or 6 to 8, G is S.

Item 20. In certain embodiments of any one of Items 1 to 3, or 6 to 8, G is SO.

5 Item 21. In certain embodiments of any one of Items 1 to 3, or 6 to 8, G is SO₂.

Item 22. In certain embodiments of any of Items 1 to 3, or 6 to 21, R¹⁰ is a -(6- to 14-membered)aryl or ((6- to 14-membered)aryl)-(C₁-C₆)alkyl-, optionally substituted with one, two or three substituents independently selected from -(C₁-C₆)alkyl, halo, C(halo)₃, CH(halo)₂, CH₂(halo), -(C₁-C₆)alkyl-CO-NR⁵R⁶, NH₂-SO₂(C₁-C₆)alkyl-, or -SO₂-NR^{5a}R^{6a}. In certain embodiments, R¹⁰ is substituted with -(C₁-C₆)alkyl.

Item 23. In certain embodiments of Item 22, R¹⁰ is substituted with -SO₂-NR^{5a}R^{6a}.

15 Item 24. In certain embodiments of Item 23, at least one of R^{5a} or R^{6a} is hydrogen.

Item 25. In certain embodiments of any of Items 22 or 23, both R^{5a} and R^{6a} are hydrogen.

Item 26. In certain embodiments of Item 22, R¹⁰ is optionally substituted phenyl or benzyl.

Item 27. In certain embodiments, R¹⁰ is -(5- to 12-membered)heteroaryl, ((5- to 12-membered)heteroaryl)-(C₁-C₆)alkyl-, -(3- to 12-membered)heterocycle, ((3- to 12-membered)heterocycle)-(C₁-C₆)alkyl-, (7- to 12-membered)bicycloheterocycle, or ((7- to 12-membered)bicycloheterocycle)-(C₁-C₆)alkyl-, each of which is optionally substituted.

Item 28. In certain embodiments of Item 27, R¹⁰ is optionally substituted with one, two or three substituents independently selected from the group consisting of -(C₁-C₆)alkyl, -(C₃-12)cycloalkyl, -(6- to 14-membered)aryl, and -(5- to 12-membered)heteroaryl.

30 Item 29. In certain embodiments of Item 27, R¹⁰ is substituted with COOR⁷.

Item 30. In certain embodiments of Item 27, R⁷ is -(C₁-C₆)alkyl.

Item 31. In certain embodiments of Item 27, R¹⁰ is piperidinyl optionally substituted with COOR⁷ or NH₂.

Item 32. In certain embodiments of Item 27, R¹⁰ is pyrrolidinyl.

Item 33. In certain embodiments of Item 27, R¹⁰ is optionally substituted
5 pyridinyl.

Item 34. In other embodiments of Item 27, R¹⁰ is furanyl.

Item 35. In certain embodiments, R¹⁰ is optionally substituted -C(=O)-((6- to 14-membered)aryl).

Item 36. In certain embodiments, R¹⁰ is optionally substituted -C(=O)-NH-(4-
10 to 12-membered)heteroaryl.

Item 37. In other embodiments, R¹⁰ is -C(=O) or -C(=O)-(C₂-C₆)alkenyl, optionally substituted with -(C₃-C₁₂)cycloalkyl, -(6- to 14-membered)aryl or -(5- to 12-membered)heteroaryl.

Item 38. In certain embodiments of Item 37, R¹⁰ is substituted with -(C₃-
15 C₁₂)cycloalkyl.

Item 39. In certain embodiments, R¹⁰ is -C(=O)-(C₁-C₆)alkyl-(6- to 14-membered)aryl, optionally substituted with halo.

Item 40. In certain embodiments, R¹⁰ is NR⁵R⁶ or -(C₁-C₆)alkyl-NR⁵NR⁶, each of which is optionally substituted.

Item 41. In certain embodiments of Item 40, at least one of R⁵ or R⁶ is
20 hydrogen.

Item 42. In certain embodiments of any one of Items 40 or 41, at least one of R⁵ or R⁶ is -(C₁-C₆)alkyl.

Item 43. In certain embodiments of Item 40, at least one of R⁵ or R⁶ is -(6- to
25 14-membered)aryl.

Item 44. In certain embodiments of Item 40, at least one of R⁵ or R⁶ is -(5- to 12-membered)heteroaryl.

Item 45. In other embodiments of any one of Items 40 or 41, at least one of R⁵ or R⁶ is hydrogen, and the other is -(C₁-C₆)alkyl-COOR⁷.

Item 46. In certain embodiments of Item 45, R⁷ is hydrogen.

Item 47. In certain embodiments of Item 45, R⁷ is -(C₁-C₆)alkyl.

Item 48. In certain embodiments, R^{10} is CONR^5R^6 .

Item 49. In certain embodiments of Item 48, at least one of R^5 or R^6 is optionally substituted $-(\text{C}_1\text{-C}_6)\text{alkyl}$.

Item 50. In certain embodiments of any one of Items 48 or 49, at least one of
5 R^5 or R^6 is substituted with phenyl.

Item 51. In other embodiments of Item 48, at least one of R^5 or R^6 is $-(6\text{- to } 14\text{-membered})\text{aryl}$ optionally substituted with one, two or three independently selected R^{30} groups.

Item 52. In other embodiments of Item 48, at least one of R^5 or R^6 is $-(6\text{- to } 14\text{-membered})\text{aryl}$ substituted with one R^{30} group.
10

Item 53. In certain embodiments of Item 52, R^{30} is $-(\text{C}_1\text{-C}_6)\text{alkyl}$.

Item 54. In certain embodiments of Item 52, R^{30} is COOR^7 .

Item 55. In other embodiments of Item 54, R^7 is hydrogen.

Item 56. In certain embodiments of Item 48, at least one of R^5 or R^6 is $-(5\text{- to } 15\text{-membered})\text{heteroaryl}$ or $-(3\text{- to } 12\text{-membered})\text{heterocycle}$.

Item 57. In certain embodiments of Item 48, R^5 and R^6 together with the nitrogen to which they are attached, form an optionally substituted $-(3\text{- to } 12\text{-membered})\text{heterocycle}$.

Item 58. In certain embodiments of Item 57, the $-(3\text{- to } 12\text{-membered})\text{heterocycle}$ is substituted with one, two or three independently selected halo, $\text{C}(\text{halo})_3$, $\text{CH}(\text{halo})_2$, or $\text{CH}_2(\text{halo})$.
20

Item 59. In certain embodiments, R^{10} is optionally substituted $-\text{SO}_2-(\text{C}_1\text{-C}_6)\text{alkyl}$.

Item 60. In certain embodiments, R^{10} is optionally substituted $-\text{SO}_2-(\text{C}_3\text{-C}_{12})\text{cycloalkyl}$.
25

Item 61. In certain embodiments, R^{10} is optionally substituted $-\text{SO}_2-(5\text{- to } 12\text{-membered})\text{heteroaryl}$.

Item 62. In certain embodiments, R^{10} is optionally substituted $-\text{SO}_2-((6\text{- to } 14\text{-membered})\text{aryl})$ or $-\text{SO}_2-((6\text{- to } 14\text{-membered})\text{aryl})-(\text{C}_1\text{-C}_6)\text{alkyl}$.
30

Item 63. In certain embodiments of Item 60, R^{10} is substituted with one, two or three independently selected halo, $\text{C}(\text{halo})_3$, $\text{CH}(\text{halo})_2$, or $\text{CH}_2(\text{halo})$.

Item 64. In certain embodiments, R^{10} is optionally substituted $-(C_1-C_6)alkyl-NR^5R^6$.

Item 65. In certain embodiments of Item 64, at least one of R^5 and R^6 is hydrogen.

5 Item 66. In certain embodiments of any one of Items 64 or 65, at least one of R^5 and R^6 is $COOR^7$.

Item 67. In certain embodiments of Item 66, R^7 is $-(C_1-C_6)alkyl$.

Item 68. In certain embodiments, R^{2a} is hydrogen, and R^{2b} is $-Z-G-R^{10}$, wherein Z is absent, G is NR^8 where R^8 is hydrogen, and R^{10} is $-C(=O)-(C_2-C_6)alkenyl$
 10 substituted with a $-(5- \text{ to } 12\text{-membered})heteroaryl$.

Item 69. In other embodiments, R^{2a} is hydrogen, and R^{2b} is $-Z-G-R^{10}$, wherein Z is absent, G is NR^8 wherein R^8 is $(C_1-C_6)alkyl$, and R^{10} is $((6- \text{ to } 14\text{-membered})aryl)-(C_1-C_6)alkyl$.

Item 70. In other embodiments, R^{2a} is hydrogen, and R^{2b} is $-Z-G-R^{10}$, wherein
 15 Z is CH_2 , G is a bond, and R^{10} is $CONR^5R^6$, wherein one of R^5 or R^6 is hydrogen, and the other is $(6- \text{ to } 14\text{-membered})aryl$ substituted with one R^{30} wherein R^{30} is $COOR^7$ wherein R^7 is hydrogen.

Item 71. In other embodiments, R^{2a} is hydrogen, and R^{2b} is $-Z-G-R^{10}$, wherein Z is absent, G is NR^8 wherein R^8 is $(C_1-C_6)alkyl$, and R^{10} is $-C(=O)$ substituted with a
 20 $(6- \text{ to } 14\text{-membered})aryl$.

Item 72. In certain embodiments, R^{2a} is hydrogen, and R^{2b} is $-Z-G-R^{10}$, wherein Z is CH_2 , G is O, and R^{10} is $(6- \text{ to } 14\text{-membered})aryl$ substituted with a $-(C_1-C_6)alkyl-CO-NR^5R^6$, wherein R^5 and R^6 are both hydrogen.

Item 73. In other embodiments, R^{2a} is hydrogen, and R^{2b} is $-Z-G-R^{10}$, wherein
 25 Z is absent, G is NR^8 wherein R^8 is hydrogen, and R^{10} is $(6- \text{ to } 14\text{-membered})aryl$ substituted with $NH_2-SO_2(C_1-C_6)alkyl$.

Item 74. In other embodiments, R^{2a} is hydrogen, and R^{2b} is $-Z-G-R^{10}$, wherein Z is absent, G is NR^8 wherein R^8 is $(C_1-C_6)alkyl$, and R^{10} is $-(6- \text{ to } 14\text{-membered})aryl$ substituted with $NH_2-SO_2(C_1-C_6)alkyl$.

Item 75. In other embodiments, R^{2a} is hydrogen, and R^{2b} is $-Z-G-R^{10}$, wherein Z is absent, G is NR^8 wherein R^8 is (C_1-C_6) alkyl, and R^{10} is $-C(=O)-(C_2-C_6)$ alkenyl substituted with $-(5- \text{ to } 12\text{-membered})$ heteroaryl or $-(3- \text{ to } 12\text{-membered})$ heterocycle.

Item 76. In other embodiments, R^{2a} is hydrogen, and R^{2b} is $-Z-G-R^{10}$, wherein
 5 Z is absent, G is NR^8 wherein R^8 is hydrogen, and R^{10} is $-(6- \text{ to } 14\text{-membered})$ aryl substituted with $NH_2-SO_2(C_1-C_6)$ alkyl-.

Item 77. In other embodiments, R^{2a} is hydrogen, and R^{2b} is $-Z-G-R^{10}$, wherein Z is absent, G is NR^8 wherein R^8 is (C_1-C_6) alkyl, and R^{10} is $CONR^5R^6$ wherein one of R^5 or R^6 is hydrogen and the other is $-(C_1-C_6)$ alkyl-COOR⁷.

10 Item 78. In other embodiments, R^{2a} is hydrogen, and R^{2b} is $-Z-G-R^{10}$, wherein Z is absent, G is a bond, and R^{10} is $-(3- \text{ to } 12\text{-membered})$ heterocycle substituted with $-COOR^7$ wherein R^7 is hydrogen.

Item 79. In other embodiments, R^{2a} is hydrogen, and R^{2b} is $-Z-G-R^{10}$, wherein Z is CH_2 , G is NR^8 wherein R^8 is hydrogen, and R^{10} is $-C(=O)-(C_1-C_6)$ alkyl- $(6- \text{ to } 14\text{-membered})$ aryl substituted with two halo.
 15

Item 80. In other embodiments, R^{2a} is hydrogen, and R^{2b} is $-Z-G-R^{10}$, wherein Z is absent, G is NR^8 wherein R^8 is (C_1-C_6) alkyl, and R^{10} is $CONR^5R^6$ wherein one of R^5 or R^6 is hydrogen and the other is $-(C_1-C_6)$ alkyl-COOR⁷.

Item 81. In other embodiments, R^{2a} is hydrogen, and R^{2b} is $-Z-G-R^{10}$, wherein
 20 Z is absent, G is NR^8 wherein R^8 is (C_1-C_6) alkyl, and R^{10} is $-C(=O)-(C_2-C_6)$ alkenyl substituted with $-(3- \text{ to } 12\text{-membered})$ heterocycle.

Item 82. In one embodiment, R^{2a} is hydrogen, and R^{2b} is $-Z-G-R^{10}$, wherein Z is absent, G is NR^8 wherein R^8 is $-(C_1-C_6)$ alkyl, and R^{10} is $((3- \text{ to } 12\text{-membered})$ heterocycle)- (C_1-C_6) alkyl- substituted with COOR⁷.

25 Item 83. In one embodiment of Item 82, R^7 is $-(C_1-C_6)$ alkyl.

Item 84. In certain embodiments, R^{2a} is hydrogen, and R^{2b} is $-Z-G-R^{10}$, wherein Z is absent, G is NR^8 where R^8 is hydrogen, and R^{10} is optionally substituted $-SO_2-((6- \text{ to } 14\text{-membered})$ aryl).

Item 85. In certain embodiments, R^{2a} is hydrogen, and R^{2b} is $-Z-G-R^{10}$,
 30 wherein Z is absent, G is $-N-SO_2$, and R^{10} is $-(6- \text{ to } 14\text{-membred})$ aryl or $((6- \text{ to } 14\text{-membered})$ aryl)- (C_1-C_6) alkyl-, each of which is optionally substituted.

Item 86. In certain embodiments, R^{2a} is hydrogen, and R^{2b} is $-Z-G-R^{10}$, wherein Z is absent, G is NR^8 where R^8 is $-(C_1-C_6)\text{alkyl}$, and R^{10} is $-(6\text{- to }14\text{-membered})\text{aryl}$ substituted with $-SO_2-NR^{5a}R^{6a}$.

Item 87. In one embodiment, R^{2a} is hydrogen, and R^{2b} is $-Z-G-R^{10}$, wherein Z is absent, G is NR^8 where R^8 is hydrogen, and R^{10} is $-(C_1-C_6)\text{alkyl}-NR^5R^6$.

Item 88. In one embodiment of Item 87, at least one of R^5 and R^6 is hydrogen.

Item 89. In one embodiment of any one of Items 87 or 88 at least one of R^5 and R^6 is $-COOR^7$.

Item 90. In one embodiment of Item 89, R^7 is $-(C_1-C_6)\text{alkyl}$.

Item 91. In one embodiment, R^{2a} is hydrogen, and R^{2b} is $-Z-G-R^{10}$, wherein Z is absent, G is NR^8 where R^8 is $-(C_1-C_6)\text{alkyl}$, and R^{10} is $CONR^5R^6$.

Item 92. In one embodiment of Item 91, R^5 and R^6 taken together with the nitrogen atom to which they are attached form an optionally substituted $-(3\text{- to }12\text{-membered})\text{heterocycle}$.

Item 93. In one embodiment of Item 92, the $-(3\text{- to }12\text{-membered})\text{ heterocycle}$ is substituted with one R^{30} group.

Item 94. In one embodiment of Item 93, R^{30} is selected from the group consisting of halo, $C(\text{halo})_3$, $CH(\text{halo})_2$, and $CH_2(\text{halo})$.

Item 95. In one embodiment, R^{2a} is hydrogen, and R^{2b} is $-Z-G-R^{10}$, wherein Z is absent, G is NR^8 where R^8 is hydrogen, and R^{10} is optionally substituted $-SO_2-((6\text{- to }14\text{-membered})\text{aryl})$.

Item 96. In one embodiment of Item 95, R^{10} is substituted with one, two or three substituents independently selected from the group consisting of halo, $C(\text{halo})_3$, $CH(\text{halo})_2$, and $CH_2(\text{halo})$.

Item 97. In one embodiment, R^{2a} is hydrogen, and R^{2b} is $-Z-G-R^{10}$, wherein Z is absent, G is $-N-SO_2$, and R^{10} is optionally substituted $-(6\text{- to }14\text{-membered})\text{aryl}$.

Item 98. In one embodiment of Item 97, R^{10} is optionally substituted with one, two or three substituents independently selected from the group consisting of halo, $C(\text{halo})_3$, $CH(\text{halo})_2$, and $CH_2(\text{halo})$.

Item 99. In one embodiment, R^{2a} is hydrogen, and R^{2b} is $-Z-G-R^{10}$, wherein Z is absent, G is NR^8 , and R^{10} is $-CONR^5R^6$.

Item 100. In one embodiment of Item 99, R^8 is $-(C_1-C_6)\text{alkyl}$.

Item 101. In one embodiment of any one of Items 99 or 100 at least one of R^5 and R^6 is hydrogen.

Item 102. In one embodiment of any one of Items 99 to 101, at least one of R^5 and R^6 is optionally substituted $-(6\text{- to }14\text{-membered})\text{aryl}$.

Item 103. In one embodiment of Item 102, the $-(6\text{ to }14\text{-membered})\text{aryl}$ is substituted with one R^{30} group.

Item 104. In one embodiment of Item 103, R^{30} is $-(C_1-C_6)\text{alkyl}$.

Item 105. In one embodiment, R^{2a} is hydrogen, and R^{2b} is $-Z-G-R^{10}$, wherein Z is absent, G is NR^8 , and R^{10} is optionally substituted $((6\text{- to }14\text{-membered})\text{aryl})-(C_1-C_6)\text{alkyl}$.

Item 106. In one embodiment of Item 105, R^8 is hydrogen.

Item 107. In one embodiment of any one of Items 105 or 106, R^{10} is substituted with $-(C_1-C_6)\text{alkyl}$.

Item 108. In one embodiment, R^{2a} is hydrogen, and R^{2b} is $-Z-G-R^{10}$, wherein Z is absent, G is NR^8 , and R^{10} is $-(3\text{- to }12\text{-membered})\text{heterocycle}$, $((3\text{- to }12\text{-membered})\text{heterocycle})-(C_1-C_6)\text{alkyl}$, $(7\text{- to }12\text{-membered})\text{bicycloheterocycle}$, or $((7\text{- to }12\text{-membered})\text{bicycloheterocycle})-(C_1-C_6)\text{alkyl}$, each of which is optionally substituted.

Item 109. In one embodiment of Item 108, R^8 is hydrogen.

Item 110. In one embodiment of any one of Items 108 or 109, R^{10} is substituted with $-\text{COOR}^7$.

Item 111. In one embodiment of Item 110, R^7 is $-(C_1-C_6)\text{alkyl}$.

Item 112. In one embodiment, R^{2a} is hydrogen, and R^{2b} is $-Z-G-R^{10}$, wherein Z is absent, G is NR^8 , and R^{10} is optionally substituted $-C(=O)-\text{NH}-((3\text{- to }12\text{-membered})\text{heterocycle})$.

Item 113. In one embodiment of Item 112, R^8 is $-(C_1-C_6)\text{alkyl}$.

Item 114. In one embodiment of any one of Items 112 or 113, R^{10} is substituted with one, two or three independently selected halo, $\text{C}(\text{halo})_3$, $\text{CH}(\text{halo})_2$, and $\text{CH}_2(\text{halo})$.

Item 115. In one embodiment, R^{2a} is hydrogen, and R^{2b} is $-Z-G-R^{10}$, wherein Z is absent, G is NR^8 , and R^{10} is optionally substituted ((6- to 14-membered)aryl)-(C₁-C₆)alkyl-.

Item 116. In one embodiment of Item 115, R^8 is hydrogen.

5 Item 117. In one embodiment of any one of Items 115 or 116, R^{10} is substituted with $-SO_2-NR^{5a}R^{6a}$.

Item 118. In one embodiment of Item 117, at least one of R^{5a} and R^{6a} is hydrogen.

10 Item 119. In one embodiment of any one of Items 117 or 118, both R^{5a} and R^{6a} are hydrogen.

Item 120. In one embodiment, R^{2a} is hydrogen, and R^{2b} is $-Z-G-R^{10}$, wherein Z is absent, G is NR^8 , and R^{10} is optionally substituted $-C(=O)$.

Item 121. In one embodiment of Item 120, R^8 is $-(C_1-C_6)alkyl$.

15 Item 122. In one embodiment of any one of Items 120 or 121, R^{10} is substituted with $-(6- to 14-membered)aryl$.

Item 123. In one embodiment of Item 122, R^{10} is substituted with phenyl or benzyl.

Item 124. In any one of Items 120 or 121, R^{10} is substituted with $-(3- to 12-membered)heterocycle$ or $(5- to 12-membered)heteraryl$.

20 Item 125. In one embodiment, R^{2a} is hydrogen, and R^{2b} is $-Z-G-R^{10}$, wherein Z is absent, G is NR^8 , and R^{10} is (6- to 14-membered)aryl or ((6- to 14-membered)aryl)-(C₁-C₆)alkyl-, each of which is optionally substituted.

Item 126. In one embodiment of Item 125, R^8 is hydrogen.

25 Item 127. In one embodiment of any one of Items 125 or 126, R^{10} is substituted by one, two or three independently selected halo, C(halo)₃, CH(halo)₂, or CH₂(halo).

Item 128. In one embodiment, R^{2a} is hydrogen, and R^{2b} is $-Z-G-R^{10}$, wherein Z is absent, G is NR^8 , and R^{10} is optionally substituted $-C(=O)-(C_1-C_6)alkyl$.

30 Item 129. In one embodiment, R^{2a} is hydrogen, and R^{2b} is $-Z-G-R^{10}$, wherein Z is absent, G is NR^8 , and R^{10} is NR^5R^6 .

Item 130. In one embodiment of Item 129, R^8 is hydrogen.

Item 131. In any one of Items 129 or 130, at least one of R^5 or R^6 is hydrogen.

Item 132. In any one of Items 129 to 131, at least one of R^5 or R^6 is $-\text{COOR}^7$.

Item 133. In one embodiment of Item 132, R^7 is $-(\text{C}_1\text{-C}_6)\text{alkyl}$.

Item 134. In one embodiment R^{2a} is hydrogen, and R^{2b} is $-\text{Z-G-R}^{10}$, wherein Z is absent, G is NR^8 , and R^{10} is optionally substituted $-\text{SO}_2-((6\text{- to }14\text{-membered})\text{aryl})$.

Item 135. In one embodiment of Item 134, R^8 is hydrogen.

Item 136. In one embodiment of any one of Items 134 or 135, R^{10} is substituted with one, two or three independently selected halo, $\text{C}(\text{halo})_3$, $\text{CH}(\text{halo})_2$, or $\text{CH}_2(\text{halo})$.

Item 137. In one embodiment, R^{2a} is hydrogen, and R^{2b} is $-\text{Z-G-R}^{10}$, wherein Z is absent, G is NR^8 , and R^{10} is optionally substituted $((6\text{- to }14\text{-membered})\text{aryl})-(\text{C}_1\text{-C}_6)\text{alkyl}$.

Item 138. In one embodiment of Item 137, R^8 is $-(\text{C}_1\text{-C}_6)\text{alkyl}$.

Item 139. In one embodiment of any one of Items 137 or 138, R^{10} is substituted with $-\text{SO}_2\text{-NR}^{5a}\text{R}^{6a}$.

Item 140. In one embodiment of Item 139, at least one of R^{5a} and R^{6a} is hydrogen.

Item 141. In one embodiment of any one of Items 139 or 140, both R^{5a} and R^{6a} are hydrogen.

Item 142. In one embodiment, R^{2a} is hydrogen, and R^{2b} is $-\text{Z-G-R}^{10}$, wherein Z is absent, G is NR^8 , and R^{10} is optionally substituted $-(\text{C}_1\text{-C}_6)\text{alkyl-NR}^5\text{R}^6$.

Item 143. In one embodiment of Item 142, at least one of R^5 and R^6 is hydrogen.

Item 144. In one embodiment of any one of Items 142 or 143, at least one of R^5 and R^6 is $-\text{COOR}^7$.

Item 145. In one embodiment of Item 144, R^7 is $-(\text{C}_1\text{-C}_6)\text{alkyl}$.

Specific Compounds of the Invention include:

2-(((8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[d]azocin-11-ylidene)amino)oxy)acetic acid (**Compound 1**);

- 8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-one oxime (**Compound 2**);
- 2-(((6*R*,11*R*)-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)oxy)acetamide (**Compound 3**);
- 5 2-(((6*R*,11*S*)-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)oxy)acetamide (**Compound 4**);
- 8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-one-*O*-(2-(diethylamino)ethyl) oxime (**Compound 5**);
- 8-methoxy-3,6-dimethyl-11-propylidene-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocine (**Compound 6**);
- 10 4-(11,11-dihydroxy-8-methoxy-6-methyl-1,2,5,6-tetrahydro-2,6-methanobenzo[*d*]azocin-3(4*H*)-yl)-*N,N*-dimethyl-2,2-diphenylbutanamide (**Compound 7**);
- (6*R*,11*S*)-8-methoxy-*N*,3,6-trimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-amine (**Compound 8**);
- 15 (6*R*,11*R*)-8-methoxy-*N*,3,6-trimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-amine (**Compound 9**);
- 3-(cyclopropylmethyl)-8-methoxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-one *O*-methyl oxime (**Compound 10**);
- 20 ((6*S*,11*R*)-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)methanol (**Compound 11**);
- (*Z*)-ethyl 2-(8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-ylidene)acetate (**Compound 12**);
- (*Z*)-2-(8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-ylidene)acetic acid (**Compound 13**);
- 25 ethyl 2-(((6*S*,11*R*)-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)acetate (**Compound 14**);
- 2-(((6*S*,11*R*)-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)acetic acid (**Compound 15**);
- 30 (*E*)-3-(furan-3-yl)-*N*-(((6*R*,11*R*)-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-*N*-methylacrylamide (**Compound 16**);

4-((6*R*,11*S*)-11-hydroxy-8-methoxy-6-methyl-1,2,5,6-tetrahydro-2,6-methanobenzo[*d*]azocin-3(4*H*)-yl)-*N,N*-dimethyl-2,2-diphenylbutanamide
(**Compound 17**);

8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-one oxime (**Compound 18**);

4-(11-(hydroxyimino)-8-methoxy-6-methyl-1,2,5,6-tetrahydro-2,6-methanobenzo[*d*]azocin-3(4*H*)-yl)-*N,N*-dimethyl-2,2-diphenylbutanamide
(**Compound 19**);

(*E*)-3-(furan-3-yl)-*N*-((6*R*,11*S*)-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-*N*-methylacrylamide (**Compound 20**);

4-((6*R*,11*R*)-8,11-dihydroxy-6-methyl-1,2,5,6-tetrahydro-2,6-methanobenzo[*d*]azocin-3(4*H*)-yl)-*N,N*-dimethyl-2,2-diphenylbutanamide
(**Compound 21**);

4-((6*R*,11*S*)-8,11-dihydroxy-6-methyl-1,2,5,6-tetrahydro-2,6-methanobenzo[*d*]azocin-3(4*H*)-yl)-*N,N*-dimethyl-2,2-diphenylbutanamide
(**Compound 22**);

(*E*)-3-(furan-3-yl)-*N*-((2*R*,6*R*,11*S*)-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)acrylamide (**Compound 23**);

(*E*)-3-(furan-3-yl)-*N*-((2*R*,6*R*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-*N*-methylacrylamide (**Compound 24**);

(*E*)-*N*-ethyl-3-(furan-3-yl)-*N*-((2*R*,6*R*,11*S*)-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)acrylamide (**Compound 25**);

4-fluoro-*N'*-((2*S*,6*R*)-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-ylidene)benzohydrazide (**Compound 26**);

N-((2*R*,6*R*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-*N*-methyl-2-(4-(methylsulfonyl)phenyl)acetamide
(**Compound 27**);

4-(((2*R*,6*R*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)(methyl)amino)-4-oxobutanoic acid (**Compound 28**);

(2*R*,6*R*,11*S*)-3,6-dimethyl-11-(methyl(phenethyl)amino)-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-8-ol (**Compound 29**);

tert-butyl 4-((((2*R*,6*S*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)amino)methyl)piperidine-1-carboxylate (**Compound 30**);

tert-butyl 4-((((2*R*,6*S*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)(methyl)amino)methyl)piperidine-1-carboxylate (**Compound 31**);

4-(2-(((6*S*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)acetamido)benzoic acid (**Compound 32**);

5-(((2*R*,6*S*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)methoxy)nicotinic acid (**Compound 33**);

5-(((6*S*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)methoxy)nicotinic acid (**Compound 34**);

2-(2-(((6*S*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)acetamido)benzoic acid (**Compound 35**);

3-(((6*S*,11*R*)-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)benzonitrile (**Compound 36**);

3-(((6*R*,11*S*)-11-hydroxy-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)benzonitrile (**Compound 37**);

3-(((6*S*,11*R*)-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)benzoic acid (**Compound 38**);

N-(((2*R*,6*R*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-*N*-methylbenzamide (**Compound 39**);

3-(((6*S*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)methoxy)benzoic acid (**Compound 40**);

3-(((2*R*,6*S*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)methoxy)benzoic acid (**Compound 41**);

(6*S*,11*R*)-11-(3-(1*H*-tetrazol-5-yl)phenyl)-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocine (**Compound 42**);

(1*S*)-1-(5-chloro-6-(((6*S*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)methoxy)pyridin-3-yl)ethane-1,2-diol (**Compound 43**);

- 4-(((6*S*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)methoxy)benzamide (**Compound 44**);
- 4-(3-(((2*R*,6*R*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-3-methylureido)benzoic acid (**Compound 45**);
- 5 4-(3-(((2*R*,6*R*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-3-methylureido)benzoic acid (**Compound 46**);
- 3-(((2*R*,6*R*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)(methyl)carbamoyl)benzoic acid (**Compound 47**);
- 3-(((2*R*,6*R*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)(methyl)carbamoyl)benzoic acid (**Compound 48**);
- 10 2-(((2*R*,6*R*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)(methyl)carbamoyl)benzoic acid (**Compound 49**);
- 2-(4-(((2*R*,6*R*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)amino)phenyl)ethanesulfonamide (**Compound 50**);
- 15 2-(4-(((2*R*,6*R*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)(methyl)amino)phenyl)ethanesulfonamide (**Compound 51**);
- 4-(((6*S*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocine-11-carboxamido)benzoic acid (**Compound 52**);
- 20 2-(((6*S*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)methoxy)isonicotinamide (**Compound 53**);
- 3-(((6*S*,11*R*)-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)benzamide (**Compound 54**);
- (2*S*)-1-(2-(((6*S*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)acetyl)pyrrolidine-2-carboxylic acid (**Compound 55**);
- 25 (2*R*,6*R*,11*S*)-3-(cyclopropylmethyl)-8-methoxy-*N*,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-amine (**Compound 56**);
- (*E*)-*N*-((2*R*,6*R*,11*S*)-3-(cyclopropylmethyl)-8-methoxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-3-(furan-3-yl)-*N*-methylacrylamide
- 30 (**Compound 57**);

- 2-(4-(((2*R*,6*R*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)amino)phenyl)ethanesulfonamide (**Compound 58**);
- 4-(((2*R*,6*R*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)(methyl)carbamoyl)benzoic acid (**Compound 59**);
- 5 3-((6*R*,11*R*)-11-hydroxy-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)benzonitrile (**Compound 60**);
- (6*S*,11*R*)-11-(3-(benzyloxy)phenyl)-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocine (**Compound 61**);
- methyl 3-((6*R*,11*R*)-11-hydroxy-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)benzoate (**Compound 62**);
- 10 3-((6*R*,11*S*)-11-hydroxy-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)benzamide (**Compound 63**);
- methyl 3-((6*R*,11*S*)-11-hydroxy-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)benzoate (**Compound 64**);
- 15 (6*R*,11*R*)-11-(3-(1*H*-tetrazol-5-yl)phenyl)-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-ol (**Compound 65**);
- (6*R*,11*S*)-11-(3-(1*H*-tetrazol-5-yl)phenyl)-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-ol (**Compound 66**);
- 3-((6*R*,11*R*)-11-hydroxy-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)benzamide (**Compound 67**);
- 20 3-(3-((2*R*,6*R*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-3-methylureido)propanoic acid (**Compound 68**);
- (6*R*)-8-methoxy-3,6-dimethyl-11-(pyrrolidin-1-yl)-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocine (**Compound 69**);
- 25 1-((6*R*)-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)piperidin-4-amine (**Compound 70**);
- 3-((6*R*,11*S*)-11-hydroxy-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)benzoic acid (**Compound 71**);
- 1-(2-((6*S*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)acetyl)piperidine-4-carboxylic acid (**Compound 72**);
- 30

- 2-(((2*R*,6*R*,11*S*)-3-(cyclopropylmethyl)-8-methoxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)(methyl)amino)acetic acid (**Compound 73**);
- 1-((6*R*)-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)piperidine-3-carboxylic acid (**Compound 74**);
- 2-(3,4-dichlorophenyl)-*N*-(((6*S*,11*S*)-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)methyl)acetamide (**Compound 75**);
- 2-(3-(((2*R*,6*S*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-3-methylureido)-4-methylpentanoic acid (**Compound 76**);
- (*E*)-*N*-((2*R*,6*R*,11*S*)-3-(cyclopropylmethyl)-8-hydroxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-3-(furan-3-yl)-*N*-methylacrylamide (**Compound 77**);
- 3-(4-cyanophenyl)-1-((2*R*,6*R*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-1-methylurea (**Compound 78**);
- 3-(4-cyanophenyl)-1-((2*R*,6*R*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-1-methylurea (**Compound 79**); and
- the pharmaceutically acceptable salts and solvates thereof.
- Preferred Compounds of the Invention include:
- (*E*)-3-(furan-3-yl)-*N*-((2*R*,6*R*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-*N*-methylacrylamide (**Compound 24**);
- (2*R*,6*R*,11*S*)-3,6-dimethyl-11-(methyl(phenethyl)amino)-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-8-ol (**Compound 29**);
- 4-(2-(((6*S*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)acetamido)benzoic acid (**Compound 32**);
- N*-((2*R*,6*R*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-*N*-methylbenzamide (**Compound 39**);
- 4-(((6*S*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)methoxy)benzamide (**Compound 44**);

2-(4-(((2*R*,6*R*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)amino)phenyl)ethanesulfonamide (**Compound 50**);

2-(4-(((2*R*,6*R*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)(methyl)amino)phenyl)ethanesulfonamide (**Compound 51**);

(*E*)-*N*-((2*R*,6*R*,11*S*)-3-(cyclopropylmethyl)-8-methoxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-3-(furan-3-yl)-*N*-methylacrylamide (**Compound 57**);

2-(4-(((2*R*,6*R*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)amino)phenyl)ethanesulfonamide (**Compound 58**);

3-(3-((2*R*,6*R*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-3-methylureido)propanoic acid (**Compound 68**);

1-((6*R*)-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)piperidine-3-carboxylic acid (**Compound 74**);

2-(3,4-dichlorophenyl)-*N*-(((6*S*,11*S*)-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)methyl)acetamide (**Compound 75**);

2-(3-((2*R*,6*S*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-3-methylureido)-4-methylpentanoic acid (**Compound 76**);

(*E*)-*N*-((2*R*,6*R*,11*S*)-3-(cyclopropylmethyl)-8-hydroxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-3-(furan-3-yl)-*N*-methylacrylamide (**Compound 77**);

3-(4-cyanophenyl)-1-((2*R*,6*R*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-1-methylurea (**Compound 78**);

3-(4-cyanophenyl)-1-((2*R*,6*R*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-1-methylurea (**Compound 79**);
and the pharmaceutically acceptable salts and solvates thereof.

Specific Compounds of the Invention also include:

3-(4-cyanophenyl)-1-((6*R*,11*R*)-3-(cyclopropylmethyl)-8-hydroxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-1-methylurea (**Compound 80**);

5 3-(4-cyanophenyl)-1-((6*R*,11*S*)-3-(cyclopropylmethyl)-8-hydroxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-1-methylurea (**Compound 81**);

4-(3-((6*R*,11*S*)-3-(cyclopropylmethyl)-8-methoxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-3-methylureido)benzamide (**Compound 82**);

10 (*E*)-*N*-((6*R*,11*R*)-3-(cyclopropylmethyl)-8-hydroxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-3-(furan-3-yl)-*N*-methylacrylamide (**Compound 83**);

15 4-((2*R*,6*R*,11*S*)-11-(3-(4-cyanophenyl)-1-methylureido)-8-hydroxy-6-methyl-1,2,5,6-tetrahydro-2,6-methanobenzo[*d*]azocin-3(4*H*)-yl)-*N,N*-dimethyl-2,2-diphenylbutanamide (**Compound 84**);

(*E*)-*N*-((2*R*,6*R*,11*S*)-3-(cyclopropylmethyl)-8-methoxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-3-(furan-3-yl)-*N*-methylacrylamide (**Compound 85**);

20 (*Z*)-*N*-((2*R*,6*R*,11*S*)-3-(cyclopropylmethyl)-8-methoxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-3-(furan-3-yl)-*N*-methylacrylamide (**Compound 86**);

3-(4-cyanophenyl)-1-((2*R*,6*R*,11*S*)-8-hydroxy-6-methyl-3-phenethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-1-methylurea (**Compound 87**);

25 3-(4-cyanophenyl)-1-((6*R*,11*R*)-3-(cyclobutylmethyl)-8-hydroxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-1-methylurea (**Compound 88**);

30 3-(4-cyanophenyl)-1-((6*R*,11*R*)-3-(2,3-difluorobenzyl)-8-hydroxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-1-methylurea (**Compound 89**);

3-(4-cyanophenyl)-1-((2*R*,6*R*,11*S*)-3-(furan-3-ylmethyl)-8-hydroxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-1-methylurea (**Compound 90**);

3-((2*R*,6*R*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-3,4-dihydroquinazolin-2(1*H*)-one (**Compound 91**);
and the pharmaceutically acceptable salts and solvates thereof.

Specific Compounds of the Invention further include:

4-(2-(((2*R*,6*S*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)amino)ethyl)benzenesulfonamide (**Compound 92**);

10 4-(2-(((2*S*,6*R*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)amino)ethyl)benzenesulfonamide (**Compound 93**);

4-(2-(((2*R*,6*S*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)amino)ethyl)benzenesulfonamide (**Compound 94**);

15 4-(2-(((2*S*,6*R*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)amino)ethyl)benzenesulfonamide (**Compound 95**);

4-(2-(((2*R*,6*S*,11*R*)-3-(cyclopropylmethyl)-8-hydroxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)amino)ethyl)benzenesulfonamide (**Compound 96**);

20 4-(2-(((2*R*,6*S*,11*S*)-3-(cyclopropylmethyl)-8-hydroxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)amino)ethyl)benzenesulfonamide (**Compound 97**);

(2*R*,6*S*,11*R*)-11-((3,4-dichlorophenethyl)amino)-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-8-ol (**Compound 98**);

25 (2*R*,6*S*,11*S*)-11-((3,4-dichlorophenethyl)amino)-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-8-ol (**Compound 99**);

(2*R*,6*S*,11*R*)-11-((4-methoxyphenethyl)amino)-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-8-ol (**Compound 100**);

(2*R*,6*S*,11*R*)-11-((4-fluorophenethyl)amino)-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-8-ol (**Compound 101**);

- (2*R*,6*S*,11*S*)-3-(cyclopropylmethyl)-6-methyl-11-((piperidin-4-ylmethyl)amino)-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-8-ol (**Compound 102**);
- (2*R*,6*S*,11*S*)-3,6-dimethyl-11-((2-(pyridin-4-yl)ethyl)amino)-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-8-ol (**Compound 103**);
- (2*R*,6*S*,11*R*)-3,6-dimethyl-11-((2-(thiophen-2-yl)ethyl)amino)-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-8-ol (**Compound 104**);
- (2*R*,6*S*,11*S*)-11-((4-(*tert*-butyl)phenethyl)amino)-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-8-ol (**Compound 105**);
- tert*-butyl 4-((((2*R*,6*S*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)amino)methyl)piperidine-1-carboxylate (**Compound 106**);
- tert*-butyl 4-((((2*R*,6*S*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)amino)methyl)piperidine-1-carboxylate (**Compound 107**);
- tert*-butyl 4-((((2*R*,6*S*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)(methyl)amino)methyl)piperidine-1-carboxylate (**Compound 108**);
- 4-(2-((((2*R*,6*S*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)(methyl)amino)ethyl)benzenesulfonamide (**Compound 109**);
- (2*R*,6*S*,11*S*)-11-((2-(1*H*-indol-3-yl)ethyl)amino)-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-8-ol (**Compound 110**);
- tert*-butyl (3-((((2*R*,6*S*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)amino)propyl)carbamate (**Compound 111**);
- tert*-butyl (2-((((2*R*,6*S*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)amino)ethyl)carbamate (**Compound 112**);
- N*-((2*R*,6*S*,11*S*)-3-(cyclopropylmethyl)-8-hydroxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)thiophene-3-carboxamide (**Compound 113**);

N-((2*R*,6*S*,11*S*)-3-(cyclopropylmethyl)-8-hydroxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-*N*-methylthiophene-3-carboxamide (**Compound 114**);

N-((2*R*,6*S*,11*S*)-3-(cyclopropylmethyl)-8-hydroxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-*N*-methylbenzamide (**Compound 115**);

N-((2*R*,6*S*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-*N*,4-dimethylpentanamide (**Compound 116**);

N-((2*R*,6*S*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-*N*-methyl-2-phenylacetamide (**Compound 117**);

N-((2*R*,6*S*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-*N*-methyl-2-phenylacetamide (**Compound 118**);

N-((2*R*,6*S*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-*N*-methylbenzamide (**Compound 119**);

N-((2*R*,6*S*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-*N*-methylcyclohexanecarboxamide (**Compound 120**);

N-((2*R*,6*S*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-*N*-methylcyclohexanecarboxamide (**Compound 121**);

(*E*)-*N*-((2*R*,6*S*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-*N*-methyl-3-(pyridin-3-yl)acrylamide (**Compound 122**);

N-((2*R*,6*S*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-*N*-methyl-2-(thiophen-3-yl)acetamide (**Compound 123**);

N-((2*R*,6*S*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-*N*-methylthiophene-3-carboxamide (**Compound 124**);

N-((2*R*,6*S*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-*N*-methylthiophene-3-carboxamide (**Compound 125**);

N-((2*R*,6*S*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-*N*-methyl-5-(trifluoromethyl)picolinamide (**Compound 126**);

N-((2*R*,6*S*,11*R*)-3-(cyclopropylmethyl)-8-hydroxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)thiophene-3-carboxamide (**Compound 127**);

5 *N*-((2*R*,6*S*,11*S*)-3-(cyclopropylmethyl)-8-hydroxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-3-(trifluoromethyl)benzenesulfonamide (**Compound 128**);

N-((2*R*,6*S*,11*R*)-3-(cyclopropylmethyl)-8-hydroxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-3-(trifluoromethyl)benzenesulfonamide (**Compound 129**);

10 *N*-((2*R*,6*S*,11*S*)-3-(cyclopropylmethyl)-8-hydroxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-*N*-methyl-3-(trifluoromethyl)benzenesulfonamide (**Compound 130**);

N-((2*R*,6*S*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-*N*-methyl-3-(trifluoromethyl)benzenesulfonamide (**Compound 131**);

15 *N*-((2*R*,6*S*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-*N*-methyl-3-(trifluoromethyl)benzenesulfonamide (**Compound 132**);

20 3-(4-(*tert*-butyl)phenyl)-1-((2*R*,6*S*,11*S*)-3-(cyclopropylmethyl)-8-hydroxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-1-methylurea (**Compound 133**);

1-((2*R*,6*S*,11*S*)-3-(cyclopropylmethyl)-8-hydroxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-3-(5-fluorobenzo[*d*]thiazol-2-yl)-1-methylurea (**Compound 134**);

25 1-((6*R*,11*R*)-6-allyl-8-methoxy-3-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-3-(4-cyanophenyl)-1-methylurea (**Compound 135**);

3-(4-cyanophenyl)-1-((6*R*,11*R*)-8-methoxy-3-methyl-6-propyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-1-methylurea (**Compound 136**);

30 3-(4-cyanophenyl)-1-((6*R*,11*S*)-8-hydroxy-3-methyl-6-propyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-1-methylurea (**Compound 137**);

3-(4-(aminomethyl)phenyl)-1-((6*R*,11*S*)-8-methoxy-3-methyl-6-propyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-1-methylurea (**Compound 138**);

1-(5-fluorobenzo[*d*]thiazol-2-yl)-3-((2*R*,6*S*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)urea (**Compound 139**);

3-(5-fluorobenzo[*d*]thiazol-2-yl)-1-((2*R*,6*S*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-1-methylurea (**Compound 140**);

and the pharmaceutically acceptable salts and solvates thereof.

10

As used herein, the term “-(C₁-C₁₀)alkyl” refers to straight-chain and branched non-cyclic saturated hydrocarbons having from 1 to 10 carbon atoms. Representative straight chain -(C₁-C₁₀) alkyl groups include methyl, -ethyl, -n-propyl, -n-butyl, -n-pentyl, -n-hexyl, n-heptyl, n-octyl, n-nonyl and n-decyl. Representative branched –

15 (C₁-C₁₀)alkyl groups include isopropyl, sec-butyl, isobutyl, tert-butyl, isopentyl, neopentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1-ethylbutyl, 2-ethylbutyl, 3-ethylbutyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 5-

20 methylhexyl, 6-methylheptyl, and the like.

As used herein, the term “-(C₁-C₆)alkyl” refers to straight-chain and branched non-cyclic saturated hydrocarbons having from 1 to 6 carbon atoms. Representative straight chain -(C₁-C₆)alkyl groups include methyl, -ethyl, -n-propyl, -n-butyl, -n-pentyl, and -n-hexyl. Representative branched-chain -(C₁-C₆)alkyl groups include

25 isopropyl, sec-butyl, isobutyl, tert-butyl, isopentyl, neopentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1,1-dimethylpropyl, and 1,2-dimethylpropyl, methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1-ethylbutyl, 2-ethylbutyl, 3-ethylbutyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, and the like.

30 As used herein, the term “-(C₂-C₁₀)alkenyl” refers to straight chain and branched non-cyclic hydrocarbons having from 2 to 10 carbon atoms and including at

least one carbon-carbon double bond. Representative straight chain and branched -
(C₂-C₁₀)alkenyl groups include -vinyl, allyl, -1-butenyl, -2-butenyl, -isobutylenyl, -1-
pentenyl, -2-pentenyl, -3-methyl-1-butenyl, -2-methyl-2-butenyl, -2,3-dimethyl-2-
butenyl, -1-hexenyl, -2-hexenyl, 3-hexenyl, and the like.

5 As used herein, the term “-(C₂-C₆)alkenyl” refers to straight chain and
branched non-cyclic hydrocarbons having from 2 to 6 carbon atoms and including at
least one carbon-carbon double bond. Representative straight chain and branched –
(C₂-C₆)alkenyl groups include -vinyl, allyl, -1-butenyl, -2-butenyl, -isobutylenyl, -1-
pentenyl, -2-pentenyl, -3-methyl-1-butenyl, -2-methyl-2-butenyl, and the like.

10 As used herein, the term “-(C₂-C₁₀)alkynyl” refers to straight chain and
branched non-cyclic hydrocarbons having from 2 to 10 carbon atoms and including at
least one carbon-carbon triple bond. Representative straight chain and branched –(C₂-
C₁₀)alkynyl groups include -acetylenyl, -propynyl, -1 butynyl, -2-butynyl, -1-
pentynyl, -2-pentynyl, -3-methyl-1-butynyl, -4-pentynyl, -1-hexynyl, -2-hexynyl, -5-
15 hexynyl, and the like.

 As used herein, the term “-(C₂-C₆)alkynyl” refers to straight chain and
branched non-cyclic hydrocarbons having from 2 to 6 carbon atoms and including at
least one carbon-carbon triple bond. Representative straight chain and branched –(C₂-
C₆)alkynyl groups include -acetylenyl, -propynyl, -1 butynyl, -2-butynyl, -1-pentynyl,
20 -2-pentynyl, -3-methyl-1-butynyl, -4-pentynyl, and the like.

 As used herein, “-(C₁-C₁₀)alkoxy” means a straight chain or branched
non-cyclic hydrocarbon having one or more ether groups and from 1 to 10 carbon
atoms. Representative straight chain and branched (C₁-C₁₀)alkoxys include -methoxy,
-ethoxy, -propoxy, -butoxy, -pentyloxy, -hexyloxy, -heptyloxy, -methoxymethyl, -2-
25 methoxyethyl, -5-methoxypentyl, -3-ethoxybutyl and the like.

 As used herein, “-(C₁-C₆)alkoxy” means a straight chain or branched
non-cyclic hydrocarbon having one or more ether groups and from 1 to 6 carbon
atoms. Representative straight chain and branched (C₁-C₅)alkoxys include -methoxy, -
ethoxy, -propoxy, -butoxy, -pentyloxy, -hexyloxy, -methoxymethyl, -2-
30 methoxyethyl, -5-methoxypentyl, -3-ethoxybutyl and the like.

As used herein, “-(C₁-C₅)alkoxy” means a straight chain or branched non-cyclic hydrocarbon having one or more ether groups and from 1 to 5 carbon atoms. Representative straight chain and branched (C₁-C₅)alkoxys include -methoxy, -ethoxy, -propoxy, -butoxy, -pentyloxy, -methoxymethyl, -2-methoxyethyl, -5-methoxypentyl, -3-ethoxybutyl and the like.

As used herein, the term “-(C₃-C₁₂)cycloalkyl” refers to a cyclic saturated hydrocarbon having from 3 to 12 carbon atoms. Representative (C₃-C₁₂)cycloalkyls include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and cyclononyl, cyclodecyl, cycloundecyl, cyclododecyl, and the like.

As used herein, “-(C₆-C₁₄)bicycloalkyl” means a bicyclic hydrocarbon ring system having from 6 to 14 carbon atoms and at least one saturated cyclic alkyl ring. Representative -(C₆-C₁₄)bicycloalkyls include -indanyl, -norbornyl, -1,2,3,4-tetrahydronaphthalenyl, -5,6,7,8-tetrahydronaphthalenyl, -perhydronaphthalenyl, and the like.

As used herein, “-(C₈-C₂₀)tricycloalkyl” means a tricyclic hydrocarbon ring system having from 8 to 20 carbon atoms and at least one saturated cyclic alkyl ring. Representative -(C₈-C₂₀)tricycloalkyls include -pyrenyl, -adamantyl, -1,2,3,4-tetrahydroanthracenyl, -perhydroanthracenyl -aceanthrenyl, -1,2,3,4-tetrahydropenanthrenyl, -5,6,7,8-tetrahydrophenanthrenyl, -perhydrophenanthrenyl, tetradecahydro-1*H*-cyclohepta[*a*]naphthalenyl, tetradecahydro-1*H*-cycloocta[*e*]indenyl, tetradecahydro-1*H*-cyclohepta[*e*]azulenyl, hexadecahydrocycloocta[*b*]naphthalenyl, hexadecahydrocyclohepta[*a*]heptalenyl, tricyclo-pentadecanyl, tricyclo-octadecanyl, tricyclo-nonadecanyl, tricyclo-icosanyl, and the like.

As used herein, the term “-(C₄-C₁₂)cycloalkenyl” refers to a cyclic hydrocarbon having from 4 to 12 carbon atoms, and including at least one carbon-carbon double bond. Representative -(C₄-C₁₂)cycloalkenyls include -cyclobutenyl, -cyclopentenyl, -cyclopentadienyl, -cyclohexenyl, -cyclohexadienyl, -cycloheptenyl, -cycloheptadienyl, -cycloheptatrienyl, -cyclooctenyl, -cyclooctadienyl, -cyclooctatrienyl, -cyclooctatetraenyl, -cyclononenyl, -cyclononadienyl, -cyclodecenyl, -cyclodecadienyl, -norbornenyl, and the like.

As used herein, " $-(C_7-C_{14})$ bicycloalkenyl" means a bi-cyclic hydrocarbon ring system having at least one carbon-carbon double bond in at least one of the rings and from 7 to 14 carbon atoms. Representative $-(C_7-C_{14})$ bicycloalkenyls include -bicyclo[3.2.0]hept-2-enyl, -indenyl, -pentalenyl, -naphthalenyl, -azulenyl, -heptalenyl,
 5 -1,2,7,8-tetrahydronaphthalenyl, and the like.

As used herein, " $-(C_8-C_{20})$ tricycloalkenyl" means a tri-cyclic hydrocarbon ring system having at least one carbon-carbon double bond in one of the rings and from 8 to 20 carbon atoms. Representative $-(C_8-C_{20})$ tricycloalkenyls include -anthracenyl, -phenanthrenyl, -phenalenyl, -acenaphthalenyl, as-indacenyl, s-indacenyl,
 10 2,3,6,7,8,9,10,11-octahydro-1*H*-cycloocta[*e*]indenyl, 2,3,4,7,8,9,10,11-octahydro-1*H*-cyclohepta[*a*]naphthalenyl, 8,9,10,11-tetrahydro-7*H*-cyclohepta[*a*]naphthalenyl, 2,3,4,5,6,7,8,9,10,11,12,13-dodecahydro-1*H*-cyclohepta[*a*]heptalenyl, 1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-dicyclohepta[*a,c*]cyclooctenyl, 2,3,4,5,6,7,8,9,10,11,12,13-dodecahydro-1*H*-dibenzo[*a,d*]cyclononenyl, and the like.

15 As used herein, " $-(3- \text{ to } 12\text{-membered})$ heterocycle" or " $-(3- \text{ to } 12\text{-membered})$ heterocyclo" means a 3- to 12-membered monocyclic heterocyclic ring which is either saturated, or partially saturated, or non-aromatic. A 3-membered heterocycle can contain up to 1 heteroatom; a 4-membered heterocycle can contain up to 2 heteroatoms; a 5-membered heterocycle can contain up to 4 heteroatoms; a 6-
 20 membered heterocycle can contain up to 4 heteroatoms; and a 7-membered heterocycle can contain up to 5 heteroatoms. Each heteroatom is independently selected from nitrogen (which can be quaternized), oxygen, and sulfur (including sulfoxide and sulfone). The $-(3- \text{ to } 12\text{-membered})$ heterocycle can be attached via a nitrogen or carbon atom. Representative $-(3- \text{ to } 12\text{-membered})$ heterocycles include aziridinyl,
 25 thiazolidinyl, morpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, piperazinyl, 2,3-dihydrofuranyl, dihydropyranyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, dihydropyridinyl, tetrahydropyridinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, oxepanyl, thiopiny, 3,4,5,6-tetrahydro-2*H*-azepinyl, 1,4-thiazepinyl, azocinyl, thiocanyl, and the
 30 like.

As used herein, "-(5- to 12-membered)heterocycle" or "-(5- to 12-membered)heterocyclo" means a 5- to 12-membered monocyclic heterocyclic ring which is either saturated, or unsaturated, or non-aromatic. A 5-membered heterocycle can contain up to 4 heteroatoms; a 6-membered heterocycle can contain up to 4
5 heteroatoms; and a 7-membered heterocycle can contain up to 5 heteroatoms. Representative (5- to 12-membered)heterocycles include thiazolidinyl, morpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, piperazinyl, 2,3-dihydrofuranyl, dihydropyranyl, hydantoinyl, valerolactamyl, tetrahydrofuranyl, tetrahydropyranyl, dihydropyridinyl, tetrahydropyridinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl,
10 tetrahydrothiopyranyl, oxepanyl, thiepinyl, 3,4,5,6-tetrahydro-2*H*-azepinyl, 1,4-thiazepinyl, azocinyl, thiocanyl, and the like.

As used herein, "-(4- to 8-membered)heterocycle" or "-(4- to 8-membered)heterocyclo" means a 4- to 8-membered monocyclic heterocyclic ring which is either saturated or unsaturated, or non-aromatic. A 4-membered heterocycle
15 can contain up to 2 heteroatoms; a 5-membered heterocycle can contain up to 4 heteroatoms; a 6-membered heterocycle can contain up to 4 heteroatoms; and a 7-membered heterocycle can contain up to 5 heteroatoms. Each heteroatom is independently selected from nitrogen (which can be quaternized), oxygen, and sulfur (including sulfoxide and sulfone). The -(4- to 8-membered)heterocycle can be
20 attached via a nitrogen or carbon atom. Representative -(4- to 8-membered)heterocycles include morpholinyl, piperidinyl, piperazinyl, 2,3-dihydrofuranyl, dihydropyranyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, dihydropyridinyl, tetrahydropyridinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, and the like.

25 As used herein, "-(7- to 12-membered)bicycloheterocycle" or "-(7- to 12-membered)bicycloheterocyclo" means a 7- to 12-membered bicyclic, heterocyclic ring which is either saturated, unsaturated, or non-aromatic. At least one ring of the bicycloheterocycle contains at least one heteroatom. A -(7- to 12-membered)bicycloheterocycle contains from 1 to 4 heteroatoms independently selected
30 from nitrogen (which can be quaternized), oxygen, and sulfur (including sulfoxide and sulfone). The -(7- to 12-membered)bicycloheterocycle can be attached via a nitrogen

or carbon atom. Representative -(7- to 10-membered)bicycloheterocycles include -quinolinyl, -isoquinolinyl, -chromonyl, -coumarinyl, -indolyl, -indolizinyl, -benzo[b]furanyl, -benzo[b]thiophenyl, -benzo[d][1,3]dioxolyl, -indazolyl, -purinyl, -4H-quinolizinyl, -isoquinolyl, -quinolyl, -phthalazinyl, -naphthyridinyl, -carbazolyl, -
 5 β -carbolinyl, -indolinyl, isoindolinyl, -1,2,3,4-tetrahydroquinolinyl, -1,2,3,4-tetrahydroisoquinolinyl, pyrrolopyrrolyl and the like.

As used herein a "-(6- to 14- membered)aryl" means an aromatic carbocyclic ring containing 6 to 14 carbon atoms, including both mono- and bicyclic ring systems. Representative -(5- to 14-membered)aryl groups include -indenyl, -phenyl, -naphthyl,
 10 and the like.

As used herein a "-(7- to 12- membered)bicyclic aryl" means an bicyclic aromatic carbocyclic ring containing 7 to 12 carbon atoms. Representative -(7- to 12-membered) bicyclic aryl groups include -indenyl, -naphthyl, and the like.

As used herein a "-(6- to 14- membered)aryloxy" means an oxygen substituted
 15 by an aromatic carbocyclic ring containing 6 to 14 carbon atoms, including both mono- and bicyclic ring systems. Representative -(6- to 14-membered)aryloxy groups include phenoxy and 4-fluorophenoxy, and the like.

As used herein a "hydroxy(C₁-C₆)alkyl" means any of the above-mentioned C₁-
 6 alkyl groups substituted by one or more hydroxy groups. Representative hydroxy(C₁-
 20 C₆)alkyl groups include hydroxymethyl, hydroxyethyl, hydroxypropyl and hydroxybutyl groups, and especially hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 1,2-dihydroxyethyl, 2-hydroxypropyl, 3-hydroxypropyl, 3-hydroxybutyl, 4-hydroxybutyl, 2-hydroxy-1-methylpropyl, and 1,3-dihydroxyprop-2-yl.

As used herein a "dihydroxy(C₁-C₆)alkyl" means any of the above-mentioned
 25 C₁₋₆ alkyl groups substituted by two hydroxy groups. Representative dihydroxy(C₁-C₆)alkyl groups include dihydroxyethyl, dihydroxypropyl and dihydroxybutyl groups, and especially 1,2-dihydroxyethyl, 1,3-dihydroxypropyl, 2,3-dihydroxypropyl, 1,3-dihydroxybutyl, 1,4-dihydroxybutyl, and 1,3-dihydroxyprop-2-yl.

As used herein a "-(5- to 12- membered)carbocyclic ring" means a mono- or
 30 bicyclic hydrocarbon ring system having from 5 to 12 carbon atoms, which is either saturated, unsaturated, non-aromatic or aromatic. Representative -(5- to 12-

membered)carbocyclic rings include cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cycloundecyl, cyclododecyl, -indanyl, -norbornyl, -1,2,3,4-tetrahydronaphthalenyl, -5,6,7,8-tetrahydronaphthalenyl, -perhydronaphthalenyl, adamantyl, cyclopentenyl, -cyclopentadienyl, -cyclohexenyl, -cyclohexadienyl, -cycloheptenyl, -cycloheptadienyl, -cycloheptatrienyl, -cyclooctenyl, -cyclooctadienyl, -cyclooctatrienyl, -cyclooctatetraenyl, -cyclononenyl, -cyclononadienyl, -cyclodecenyl, -cyclodecadienyl, -norbornenyl, heptalenyl, and the like.

As used herein a "-(7- to 12- membered)bicyclic ring system" means a 7- to 12-membered carbocyclic or heterocyclic ring, which may be either unsaturated, saturated, non-aromatic or aromatic. Representative -(7- to 12-membered)bicyclic ring systems include azulenyl, -norbornyl, -1,2,3,4-tetrahydronaphthalenyl, -5,6,7,8-tetrahydronaphthalenyl, -perhydronaphthalenyl, bicyclo[3.2.0]hept-2-enyl, -indenyl, naphthyl, -pentalenyl, -naphthalenyl, -azulenyl, -heptalenyl, -1,2,7,8-tetrahydronaphthalenyl, -quinolinyl, -isoquinolinyl, -chromonyl, -coumarinyl, -indolyl, -indoliziny, -benzo[b]furanyl, -benzo[b]thiophenyl, -benzo[d][1,3]dioxolyl, -indazolyl, -purinyl, -4H-quinoliziny, -isoquinolyl, -quinolyl, -phthalazinyl, -naphthyridinyl, -carbazolyl, - β -carbolinyl, -indolinyl, isoindolinyl, -1,2,3,4-tetrahydroquinolinyl, -1,2,3,4-tetrahydroisoquinolinyl, pyrrolopyrrolyl, and the like.

As used herein, "-(5- to 12-membered)heteroaryl" means an aromatic heterocycle ring of 5 to 12 members, including both mono- and bicyclic ring systems, where at least one carbon atom (of one or both of the rings) is replaced with a heteroatom independently selected from nitrogen, oxygen, and sulfur, or at least two carbon atoms of one or both of the rings are replaced with a heteroatom independently selected from nitrogen, oxygen, and sulfur. In one embodiment, one of the bicyclic -(5- to 12-membered)heteroaryl rings contains at least one carbon atom. In another embodiment, both of the bicyclic -(5- to 12-membered)heteroaryl rings contain at least one carbon atom. Representative -(5- to 12-membered)heteroaryls include pyridyl, furyl, benzofuranyl, thiophenyl, benzothiophenyl, quinolinyl, isoquinolinyl, pyrrolyl, indolyl, oxazolyl, benzoxazolyl, imidazolyl, benzimidazolyl, thiazolyl, benzothiazolyl, isoxazolyl, oxadiazolyl, pyrazolyl, isothiazolyl, pyridazinyl, pyrimidyl, pyrimidinyl,

pyrazinyl, thiadiazolyl, triazinyl, thienyl, thiadiazolyl, cinnolinyl, phthalazinyl, quinazolinyl, and the like.

As used herein, the terms “halo” and “halogen” refer to fluoro, chloro, bromo or iodo.

5 As used herein, “-CH₂(halo)” means a methyl group where one of the hydrogens of the methyl group has been replaced with a halogen. Representative -CH₂(halo) groups include -CH₂F, -CH₂Cl, -CH₂Br, and -CH₂I.

As used herein, “-CH(halo)₂” means a methyl group where two of the hydrogens of the methyl group have been replaced with a halogen. Representative -CH(halo)₂ groups include -CHF₂, -CHCl₂, -CHBr₂, -CHBrCl, -CHClI, and -CHI₂.

10 As used herein, “-C(halo)₃” means a methyl group where each of the hydrogens of the methyl group has been replaced with a halogen. Representative -C(halo)₃ groups include -CF₃, -CCl₃, -CBr₃, and -CI₃.

As used herein, the term “optionally substituted” refers to a group that is either
15 unsubstituted or substituted.

Optional substituents on optionally substituted groups, when not otherwise indicated, include 1, 2, or 3 groups each independently selected from the group consisting of -(C₁-C₆)alkyl, OH, halo, -C(halo)₃, -CH(halo)₂, -CH₂(halo), NH₂, -NH(C₁-C₆)alkyl, CN, SH, -(5- to 12-membered)carbocyclic ring, -(5- to 12-membered)heterocycle, phenyl, benzyl, (=O), halo(C₁-C₆)alkyl-, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, hydroxy(C₁-C₆)alkyl-, OR^{4a} (such as -OC(halo)₃ and -O(C₁-C₆)alkyl), -CONR^{5b}R^{6b}, and -COOR^{7a}; where R^{4a} is selected from the group consisting of -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -C(halo)₃, hydroxy(C₁-C₆)alkyl-, -(C₃-C₁₂)cycloalkyl, -(C₆-C₁₄)bicycloalkyl, -(C₈-C₂₀)tricycloalkyl, -(C₄-C₁₂)cycloalkenyl, -(C₇-C₁₄)bicycloalkenyl, -(C₈-C₂₀)tricycloalkenyl, -(5- to 12-membered)aryl, -(5- to 12-membered)heteroaryl, -(3- to 12-membered)heterocycle, and -(7- to 12-membered)bicycloheterocycle; R^{5b} and R^{6b} are each independently selected from the group consisting of -(C₁-C₆)alkyl, -(C₃-C₈)cycloalkyl, ((C₃-C₈)cycloalkyl)-(C₁-C₆)alkyl-, or together with the nitrogen atom to which they may both be attached form
20 a (4- to 8- membered)heterocycle; and R^{7a} is selected from the group consisting of hydrogen, -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₃-C₁₂)cycloalkyl, -(C₄-
25

C₁₂)cycloalkenyl, ((C₃-C₁₂)cycloalkyl)-(C₁-C₆)alkyl-, ((C₄-C₁₂)cycloalkenyl)-(C₁-C₆)alkyl-, -(C₁-C₆)alkoxy-COOR⁷, -NH-C(=O)-NH-(C₁-C₆)alkyl-, -NH-C(=O)-(5- to 12- membered)aryl, -NH-C(=O)-(C₁-C₆)alkyl-(5- to 12- membered)aryl, -NH-(C₁-C₆)alkyl-COOR⁷, -NH-C(=O)-(C₁-C₆)alkyl-COOR⁷, -NH-C(=O)-CH(NH₂)-(C₁-C₆)alkyl-COOR⁷, -(C₃-C₁₂)cycloalkyl, -(5- to 12-membered)aryl, -(5- to 12-membered)aryloxy, -(C₁-C₆)alkoxy-CONR⁵R⁶, -NH-(C₁-C₆)alkyl-CONR⁵R⁶, -C(O)NH-(C₁-C₆)alkyl-COOR⁷, -(C₁-C₆)alkyl-C(=O)-(C₁-C₆)alkoxy, -(C₁-C₆)alkoxy-C(=O)-(C₁-C₆)alkyl, -(C₁-C₆)alkyl-CN, -(C₁-C₆)alkyl-COOR⁷, -(C₁-C₆)alkoxy-COOR⁷, -(C₃-C₁₂)cycloalkyl, ((C₃-C₁₂)cycloalkyl)-(C₁-C₆)alkyl-, ((C₃-C₁₂)cycloalkyl)-(C₁-C₆)alkoxy-, ((C₃-C₁₂)cycloalkyl)-(C₁-C₆)alkoxy-(C₁-C₆)alkyl-, -(C₄-C₁₂)cycloalkenyl, ((C₄-C₁₂)cycloalkenyl)-(C₁-C₆)alkyl-, ((C₄-C₁₂)cycloalkenyl)-(C₁-C₆)alkoxy-, ((C₄-C₁₂)cycloalkenyl)-(C₁-C₆)alkoxy-(C₁-C₆)alkyl-, -(5- to 12-membered)aryl, ((5- to 12-membered)aryl)-(C₁-C₆)alkyl-, ((5- to 12-membered)aryl)-(C₁-C₆)alkoxy-, ((5- to 12-membered)aryl)-(C₁-C₆)alkoxy-(C₁-C₆)alkyl-, -(5- to 12-membered)heteroaryl, ((5- to 12-membered)heteroaryl)-(C₁-C₆)alkyl-, ((5- to 12-membered)heteroaryl)-(C₁-C₆)alkoxy-, ((5- to 12-membered)heteroaryl)-(C₁-C₆)alkoxy-(C₁-C₆)alkyl-, -(3- to 12-membered)heterocycle, ((3- to 12-membered)heterocycle)-(C₁-C₆)alkyl-, ((3- to 12 membered)heterocycle)-(C₁-C₆)alkoxy-, and ((3- to 12 membered)heterocycle)-(C₁-C₆)alkoxy-(C₁-C₆)alkyl-;

20 wherein R⁵, R⁶, and R⁷ are as defined above for Formula I.

As used herein, the term "Z is unsubstituted" means that Z is "-(CH₂)_m-" and m is selected from 1, 2, 3, 4, 5, or 6.

As used herein, the term "Z is substituted" means that Z is "-(CH₂)_m-" and m is selected from 1, 2, 3, 4, 5, or 6 and one or two of the hydrogen atoms has been

25 independently replaced by a -(C₁-C₆)alkyl group.

As used herein, compounds that bind to receptors and mimic the regulatory effects of endogenous ligands are defined as "agonists". Compounds that bind to receptors and are only partly effective as agonists are defined as "partial agonists". Compounds that bind to receptors but produce no regulatory effect, but rather block

30 the binding of ligands to the receptors are defined as "antagonists". (Ross and Kenakin, "Ch. 2: Pharmacodynamics: Mechanisms of Drug Action and the

Relationship Between Drug Concentration and Effect", pp. 31-32, in *Goodman & Gilman's the Pharmacological Basis of Therapeutics*, 10th Ed. (J.G. Hardman, L.E. Limbird and A. Goodman-Gilman eds., 2001).

Compounds of the Invention can be in the form of prodrugs of the compounds of Formula I", Formula IA", Formula IB", Formula IC", Formula ID"; Formula I', Formula IA', Formula IB', Formula IC', or Formula ID'; Formula I, Formula IA, Formula IB, Formula IC, or Formula ID. Prodrugs are covalently bonded carrier molecules that release an active compound of Formula I", Formula IA", Formula IB", Formula IC", Formula ID"; Formula I', Formula IA', Formula IB', Formula IC', or Formula ID'; Formula I, Formula IA, Formula IB, Formula IC, or Formula ID *in vivo*. Non-limiting examples of prodrugs will typically include esters of the Compounds of the Invention that can be metabolized to the active compound by the action of enzymes in the body. Such prodrugs may be prepared by reacting a compound of Formula I", Formula IA", Formula IB", Formula IC", Formula ID"; Formula I', Formula IA', Formula IB', Formula IC', or Formula ID'; Formula I, Formula IA, Formula IB, Formula IC, or Formula ID, with an anhydride such as succinic anhydride.

Compounds of the Invention can be isotopically-labeled (*i.e.*, radio-labeled). Examples of isotopes that can be incorporated into the disclosed compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ²H, ³H, ¹¹C, ¹³C, ¹⁴C, ¹⁵N, ¹⁸O, ¹⁷O, ³¹P, ³²P, ³⁵S, ¹⁸F and ³⁶Cl, respectively, and preferably ³H, ¹¹C, and ¹⁴C. Isotopically-labeled Compounds of the Invention can be prepared by methods known in the art in view of this disclosure. For example, tritiated Compounds of the Invention can be prepared by introducing tritium into the particular compound by catalytic dehalogenation with tritium. This method may include reacting a suitable halogen-substituted precursor of a Compound of the Invention with tritium gas in the presence of an appropriate catalyst such as Pd/C in the presence of a base. Other suitable methods for preparing tritiated compounds are generally described in Filer, *Isotopes in the Physical and Biomedical Sciences*, Vol. 1, Labeled Compounds (Part A), Chapter 6 (1987). ¹⁴C-labeled compounds can be prepared by employing starting materials having a ¹⁴C carbon.

Isotopically labeled Compounds of the Invention, as well as the pharmaceutically acceptable salts, prodrugs and solvates thereof, can be used as radioligands to test for the binding of compounds to an opioid or ORL-1 receptor. For example, a radio-labeled Compound of the Invention can be used to characterize
5 specific binding of a test or candidate compound to the receptor. Binding assays utilizing such radio-labeled compounds can provide an alternative to animal testing for the evaluation of chemical structure-activity relationships. In a non-limiting embodiment, the present invention provides a method for screening a candidate compound for the ability to bind to an opioid or ORL-1 receptor, comprising the steps
10 of: a) introducing a fixed concentration of the radio-labeled compound to the receptor under conditions that permit binding of the radio-labeled compound to the receptor to form a complex; b) titrating the complex with a candidate compound; and c) determining the binding of the candidate compound to said receptor.

Compounds of the Invention disclosed herein may contain one or more
15 asymmetric centers, thus giving rise to enantiomers, diastereomers, and other stereoisomeric forms. The present invention encompasses all such possible forms, as well as their racemic and resolved forms and mixtures thereof, and the uses thereof. The individual enantiomers may be separated according to methods known to those of ordinary skill in the art in view of the present disclosure. When the compounds
20 described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, they include both E and Z geometric isomers. All tautomers are intended to be encompassed by the present invention as well.

As used herein, the term "stereoisomer" is a general term for all isomers of
25 individual molecules that differ only in the orientation of their atoms in space. It includes enantiomers and isomers of compounds with more than one chiral center that are not mirror images of one another (diastereoisomers).

The term "chiral center" refers to a carbon atom to which four different groups are attached.

30 The terms "enantiomer" and "enantiomeric" refer to a molecule that cannot be superimposed on its mirror image and hence is optically active such that the

enantiomer rotates the plane of polarized light in one direction and its mirror image compound rotates the plane of polarized light in the opposite direction.

The term “racemic” refers to a mixture of equal parts of enantiomers and which mixture is optically inactive. Racemic compounds can be separated into their
5 enantiomers by chiral chromatography.

The term “resolution” refers to the separation or concentration or depletion of one of the two enantiomeric forms of a molecule.

The terms “a” and “an” refer to one or more.

Compounds of the Invention encompass all salts of the disclosed compounds of
10 Formula I”, Formula IA”, Formula IB”, Formula IC”, Formula ID”; Formula I’, Formula IA’, Formula IB’, Formula IC’, or Formula ID’; Formula I, Formula IA, Formula IB, Formula IC, or Formula ID. The present invention preferably includes any and all non-toxic, pharmaceutically acceptable salts of the disclosed compounds. Examples of pharmaceutically acceptable salts include inorganic and organic acid
15 addition salts and basic salts. The pharmaceutically acceptable salts include, but are not limited to, metal salts such as sodium salt, potassium salt, cesium salt, and the like; alkaline earth metals such as calcium salt, magnesium salt and the like; organic amine salts such as triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N’-dibenzylethylenediamine salt and
20 the like; inorganic acid salts such as hydrochloride, hydrobromide, phosphate, sulphate and the like; organic acid salts such as citrate, lactate, tartrate, maleate, fumarate, mandelate, acetate, dichloroacetate, trifluoroacetate, oxalate, formate and the like; sulfonates such as methanesulfonate, benzenesulfonate, p-toluenesulfonate and the like; and amino acid salts such as arginate, glutamate and the like.

25 Acid addition salts can be formed by mixing a solution of the particular compound of the present invention with a solution of a pharmaceutically acceptable non-toxic acid such as hydrochloric acid, fumaric acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid, phosphoric acid, oxalic acid, dichloroacetic acid, and the like. Basic salts can be formed by mixing a solution of the
30 particular compound of the present invention and a pharmaceutically acceptable non-

toxic base such as sodium hydroxide, potassium hydroxide, choline hydroxide, sodium carbonate and the like.

Compounds of the Invention also encompass solvates of the disclosed compounds of Formula I^{''}, Formula IA^{''}, Formula IB^{''}, Formula IC^{''}, Formula ID^{''}; Formula I', Formula IA', Formula IB', Formula IC', or Formula ID'; Formula I, Formula IA, Formula IB, Formula IC, or Formula ID. The term "solvate" as used herein is a combination, physical association and/or solvation of a compound of Formula I^{''}, Formula IA^{''}, Formula IB^{''}, Formula IC^{''}, Formula ID^{''}; Formula I', Formula IA', Formula IB', Formula IC', or Formula ID'; Formula I, Formula IA, Formula IB, Formula IC, or Formula ID with a solvent molecule such as, e.g. a disolvate, monosolvate or hemisolvate, where the ratio of solvent molecule to compound of Formula I^{''}, Formula IA^{''}, Formula IB^{''}, Formula IC^{''}, Formula ID^{''}; Formula I', Formula IA', Formula IB', Formula IC', or Formula ID'; Formula I, Formula IA, Formula IB, Formula IC, or Formula ID is 2:1, 1:1 or 1:2, respectively.

This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances, the solvate can be isolated, such as when one or more solvent molecules are incorporated into the crystal lattice of a crystalline solid. Thus, "solvate" encompasses both solution-phase and isolatable solvates. A compound of Formula I^{''}, Formula IA^{''}, Formula IB^{''}, Formula IC^{''}, Formula ID^{''}; Formula I', Formula IA', Formula IB', Formula IC', or Formula ID'; Formula I, Formula IA, Formula IB, Formula IC, or Formula ID or may be present as a solvated form with a pharmaceutically acceptable solvent, such as water, methanol, ethanol, and the like, and it is intended that the invention include both solvated and unsolvated forms of Formula I^{''}, Formula IA^{''}, Formula IB^{''}, Formula IC^{''}, Formula ID^{''}; Formula I', Formula IA', Formula IB', Formula IC', or Formula ID'; Formula I, Formula IA, Formula IB, Formula IC, or Formula ID compounds. One type of solvate is a hydrate. A "hydrate" relates to a particular subgroup of solvates where the solvent molecule is water. Solvates typically can function as pharmacological equivalents. Preparation of solvates is known in the art. See, for example, M. Caira *et al*, *J. Pharmaceut. Sci.*, 93(3):601-611 (2004), which describes the preparation of solvates of fluconazole with ethyl acetate and with water. Similar preparation of solvates,

hemisolvates, hydrates, and the like are described by E.C. van Tonder et al., *AAPS Pharm. Sci. Tech.*, 5(1):Article 12 (2004), and A.L. Bingham et al., *Chem. Commun.*, 603-604 (2001). A typical, non-limiting, process of preparing a solvate would involve dissolving a compound of Formula I", Formula IA", Formula IB", Formula IC",
 5 Formula ID"; Formula I', Formula IA', Formula IB', Formula IC', or Formula ID'; Formula I, Formula IA, Formula IB, Formula IC, or Formula ID in a desired solvent (organic, water, or a mixture thereof) at temperatures above about 20°C to about 25°C, then cooling the solution at a rate sufficient to form crystals, and isolating the crystals by known methods, e.g., filtration. Analytical techniques such as infrared
 10 spectroscopy can be used to confirm the presence of the solvent in a crystal of the solvate.

The present invention also provides the use of a Compound of the Invention in the manufacture of a medicament for treating or preventing a Condition. In one embodiment, the Condition is pain, such as acute or chronic pain. In one embodiment,
 15 a Compound of the Invention has agonist activity at the μ , δ and/or κ receptors. In another embodiment a Compound of the Invention has agonist activity at the μ receptor. In another embodiment, a Compound of the Invention has antagonist activity at the ORL-1 receptor. In another embodiment, certain Compounds of the invention can stimulate one receptor (e.g., a μ , δ and/or κ agonist) and inhibit a different receptor
 20 (e.g., an ORL-1 antagonist). In another embodiment, the Compound of the Invention is an agonist at the μ receptor, and an antagonist at the ORL-1 receptor. In another embodiment, the Compound of the Invention is an antagonist at the μ receptor, and an agonist at the κ receptor.

25 List of abbreviations;

ACN	acetonitrile
AcOH	acetic acid
AIBN	2,2-azobisisobutyronitrile
30 Alloc	allyloxycarbonyl
aq.	aqueous

	atm	atmosphere(s)
	Bn	benzyl
	Boc	<i>tert</i> -butoxycarbonyl
	Boc ₂ O	di- <i>tert</i> -butyl dicarbonate
5	Bz	benzoyl
	°C	degrees Celcius
	CAN	ceric ammonium nitrate
	Cbz	benzyloxycarbonyl
	CSA	10-camphorsulfonic acid
10	d	day(s)
	DABCO	1,4-diazabicyclo[2.2.2]octane
	DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
	DCM	dichloromethane
	DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
15	DEAD	diethyl azodicarboxylate
	DIAD	diisopropyl azodicarboxylate
	DIBAL	diisobutylaluminum hydride
	DIPEA	diisopropylethylamine
	DMAC	dimethylacetamide
20	DMAP	4-dimethylaminopyridine
	DME	1,2-dimethoxyethane
	DMF	dimethylformamide
	DMPU	N,N-dimethylpropyleneurea
	DMSO	dimethylsulfoxide
25	EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide)
	Et ₂ O	diethyl ether
	EtOAc	ethyl acetate
	EtOH	ethanol
	Fmoc	9-fluorenylmethyloxycarbonyl
30	h	hour(s)

	HATU	2-(7-aza-1H-benzotriazole -1-yl)-1,1,3,3- tetramethyluronium hexafluorophosphate
	HPLC	high pressure liquid chromatography
	i-PrOH	<i>iso</i> -propanol
5	LAH	lithium aluminum hydride
	LDA	lithium diisopropylamide
	mCPBA	<i>meta</i> -chloroperoxybenzoic acid
	MEM	β -methoxyethoxymethyl
	MeOH	methanol
10	min	minute(s)
	MOM	methoxymethyl
	MPLC	medium pressure liquid chromatography
	Ms	methanesulfonyl
	MsCl	methanesulfonyl chloride
15	NaHMDS	sodium hexamethyldisilazide
	NBS	N-bromosuccinimide
	NMO	N-methylmorpholine N-oxide
	NMP	N-methyl-2-pyrrolidone
	PCC	pyridinium chlorochromate
20	Pd/C	palladium on carbon
	Pd(dppf)Cl ₂	[1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)
	Pd(Ph ₃ P) ₂ Cl ₂	bis(triphenylphosphine)palladium(II) dichloride
	(Ph) ₃ P	triphenylphosphine
	Piv	pivaloyl
25	PMB	p-methoxybenzyl
	PTSA	p-toluenesulfonic acid
	PyBOP	benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate
	RT	room temperature
30	TBAF	tetrabutylammonium fluoride
	TBDMS	<i>tert</i> -butyldimethylsilyl

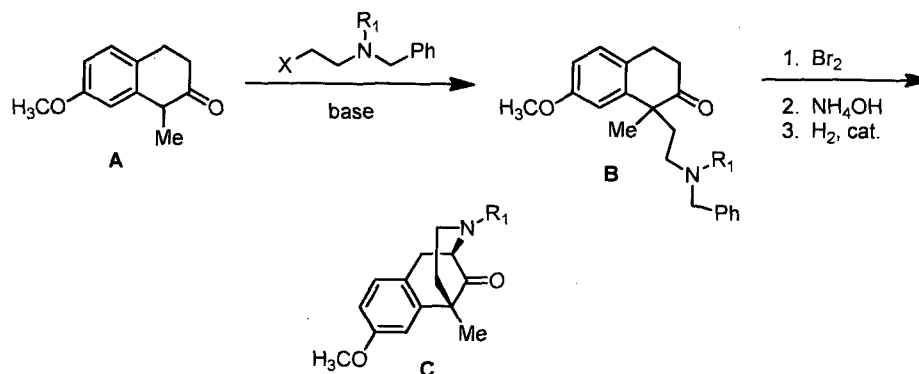
t-BuOH	<i>tert</i> -butyl alcohol
TEA	triethylamine
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
5 TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
THP	2-tetrahydropyranyl
TMS	trimethylsilyl
TMEDA	<i>N,N,N',N'</i> -tetramethylethylenediamine

10

Synthesis of Compounds

Compounds of Formula I'', I' and I can be made using conventional organic synthesis in view of this disclosure, or by the illustrative methods shown in the schemes below.

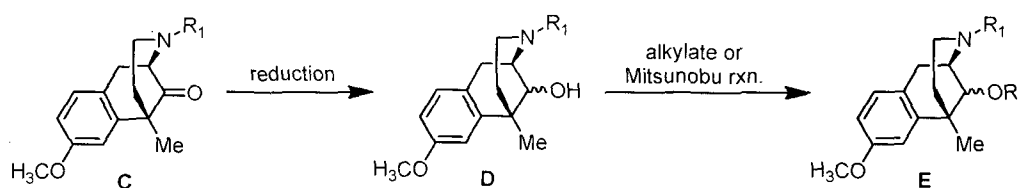
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Scheme A

- 20 Ketone C is prepared as generally described in US Patent 3956336A. Compound A [J. Amer. Chem. Soc., 1961, 83, 1492] is alkylated with a haloethyl amine in the presence of a base such as sodium hydride, in a solvent such as benzene to give compound B. Compound B is treated with bromine in a suitable solvent such as acetic acid to give the alpha-bromo ketone, which is cyclized to give the quaternary salt by

treatment with a suitable base such as ammonium hydroxide. Hydrogenolysis of the quaternary salt in the presence of hydrogen and a suitable catalyst such as palladium on carbon in a suitable solvent such as acetic acid gives the amino ketone C.

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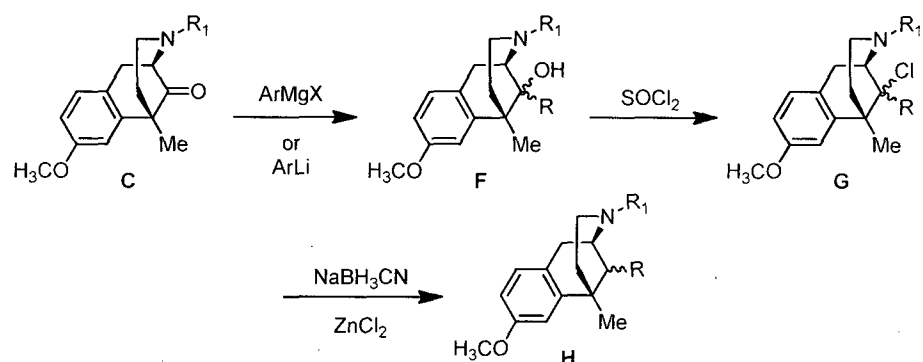
Scheme B

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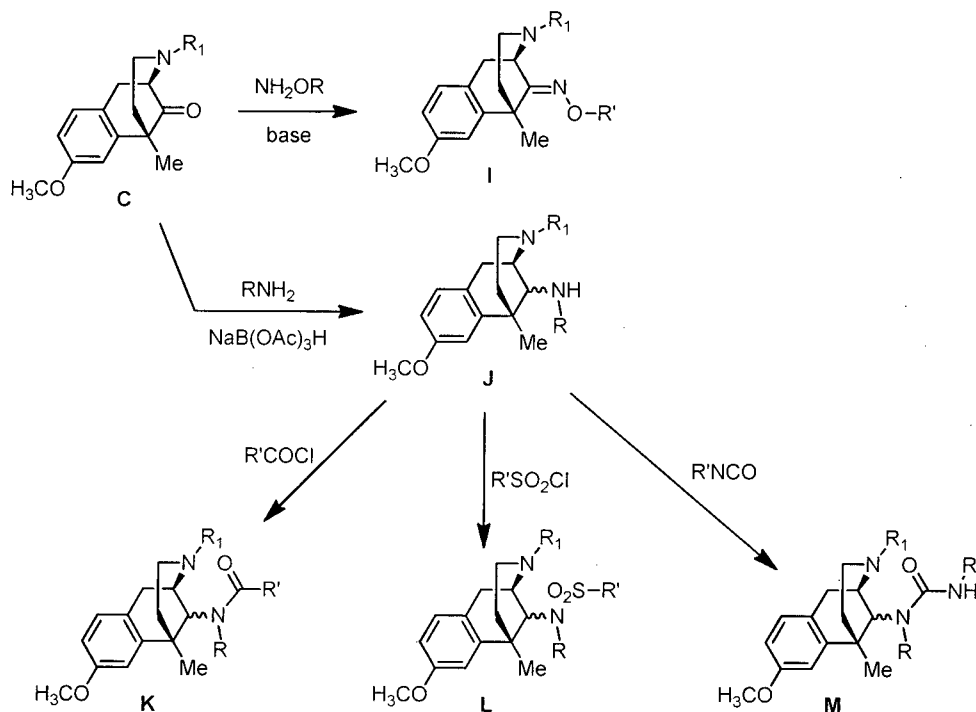
Ketone C is reduced with a suitable reducing agent such as sodium borohydride in a suitable solvent such as methanol (MeOH) to give alcohol D. Compound D can be converted into ether E by alkylation using a suitable base such as sodium hydride in a suitable solvent such as dimethylformamide (DMF). An alternate method of ether

15 formation is via a Mitsunobu reaction (e.g. Hughes, D.L. *Org. Prep.* **1996**, 28, 127) using the appropriate phenol and suitable reagents such as triphenylphosphine and diisopropyl azodicarboxylate (DIAD) in a suitable solvent such as tetrahydrofuran (THF).

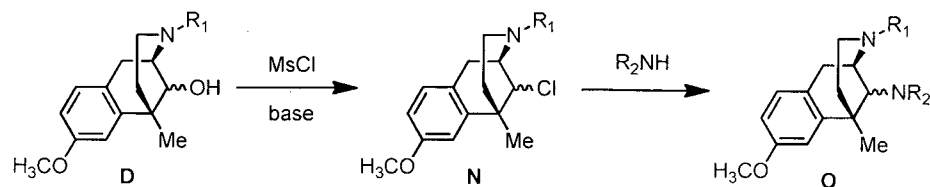
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Scheme C

- 5 Ketone C is reacted with an organometallic reagent (organomagnesium or organolithium) in a suitable solvent such as THF to give alcohol F. Conversion of the alcohol to the chloride G is accomplished with thionyl chloride or other suitable reagent. Conversion to compound H is accomplished by treatment with a reducing reagent such as sodium cyanoborohydride and a Lewis acid such as zinc chloride in a
- 10 suitable solvent such as THF.

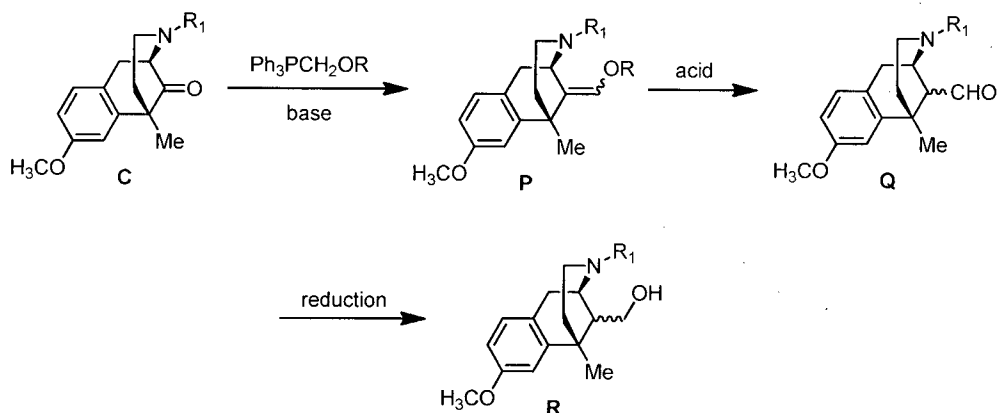
Scheme D

- 5 Ketone C is reacted with a hydroxyl amine in a suitable solvent such as ethanol (EtOH) in the presence of a suitable base such as sodium acetate to form oxime I. Ketone C is reacted with an amine under reductive amination conditions with a suitable reducing agent such as sodium triacetoxyborohydride in a suitable solvent such as acetonitrile (AcCN) to give amine J, which can be functionalized with suitable
- 10 reagents such as acid chlorides, sulfonyl chlorides and isocyanates in a suitable solvent such as dichloromethane (DCM) in the presence of a suitable base such as triethyl amine (TEA) to obtain compound K, L, or M.

Scheme E

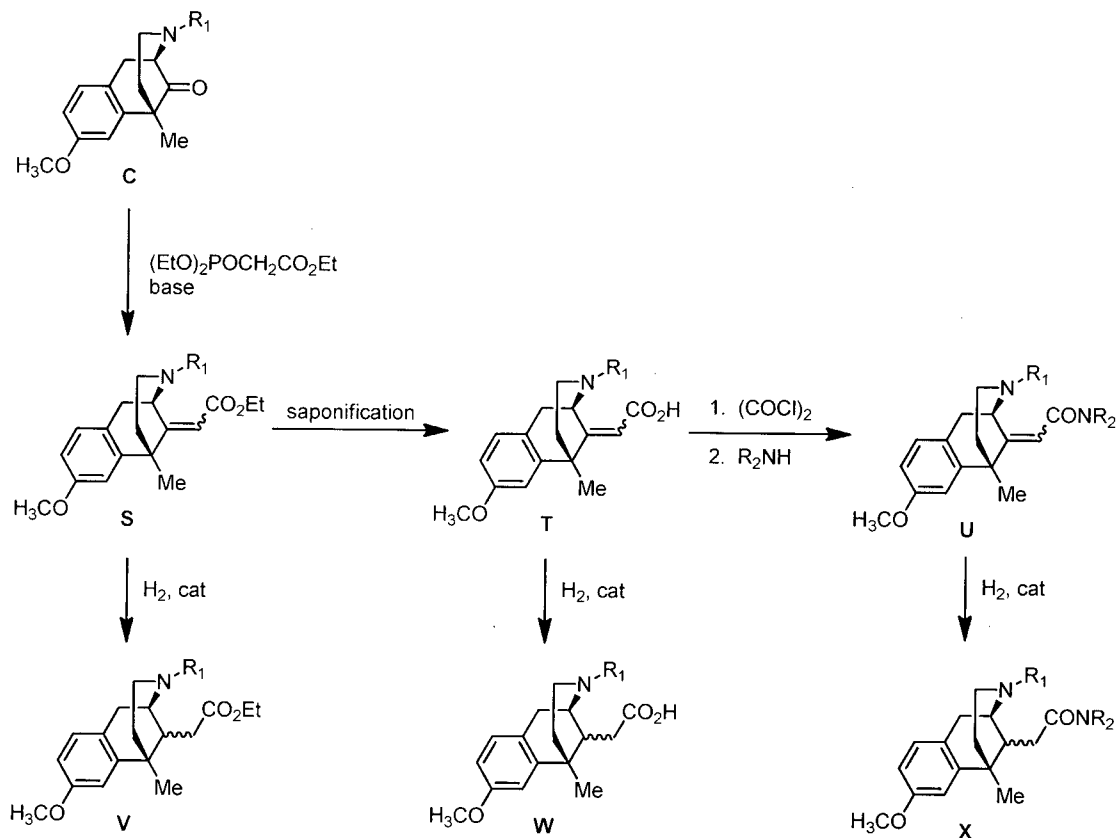
- 5 Alcohol is converted to chloride N by treatment with methanesulfonyl chloride in the presence of a suitable base such as triethyl amine (TEA) in a suitable solvent such as DCM. Reaction of compound N with an amine in the presence of a suitable base such as TEA in a suitable solvent such as DCM gives compound O.

10

Scheme F

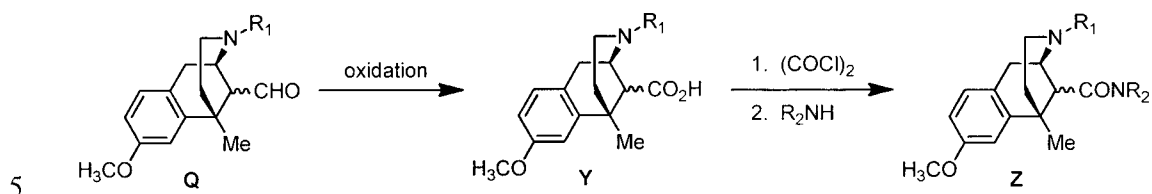
- 15 Ketone C is converted to aldehyde P by reaction with a suitable phosphonium salt in the presence of a suitable base such as potassium tert-butoxide (KOtBu) in a suitable solvent such as THF. Treatment of compound P with acid gives the aldehyde Q which can be converted to the alcohol R by treatment with a suitable reducing agent such as NaBH₄ in a suitable solvent such as EtOH.

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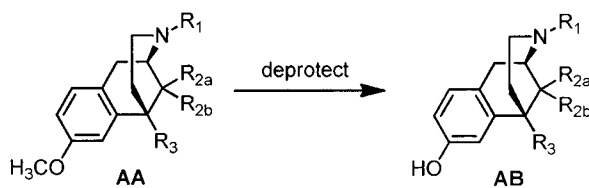
Scheme G

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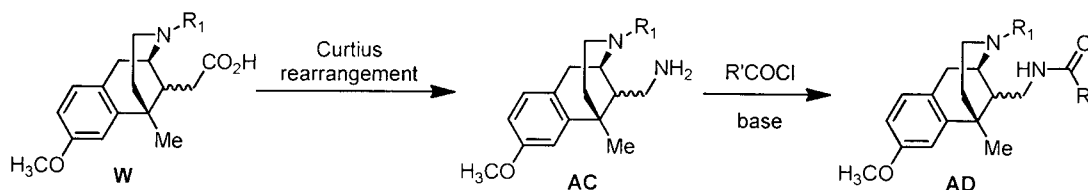
- Ketone C is converted to ester S by reaction with an appropriate phosphonate ester in the presence of a suitable base such as sodium hexamethylsilazide (NaHMDS) in a suitable solvent such as THF. Ester S is saponified to acid T by reaction with a suitable base such as potassium hydroxide (KOH) in a suitable solvent such as MeOH/water. Acid T is converted to amide U by conversion to an acid chloride by treatment with a suitable chlorinating agent such as oxalyl chloride and subsequent reaction with an appropriate amine in the presence of a suitable base such as diisopropylethylamine (DIPEA) in a suitable solvent such as DCM. Each of the unsaturated compounds (S, T and U) can be converted to their saturated analogs by reduction with hydrogen in the presence of a suitable catalyst such as Pd/C in a suitable solvent such as MeOH.

Scheme H

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Scheme I

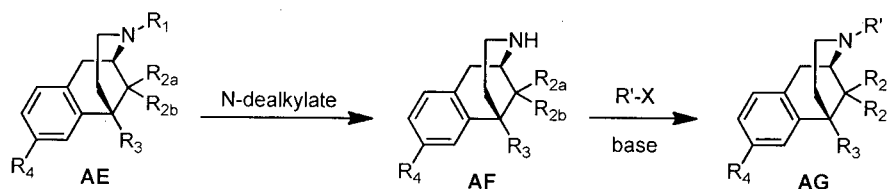
20 boron tribromide (BBr₃) in a suitable solvent such as DCM (e.g. Greene, T.W. "Protective Groups in Organic Synthesis", J. Wiley & Sons, NY, 1981).

Scheme J

5

Acid **W** is converted to amine **AC** by Curtius rearrangement using a suitable reagent such as diphenylphosphoryl azide (DPPA) in the presence of a base such as TEA in a suitable solvent such as toluene, followed by an aqueous workup. Coupling with a suitable acid chloride in the presence of a suitable base such as TEA in a suitable solvent such as DCM gives the amide **AD**.

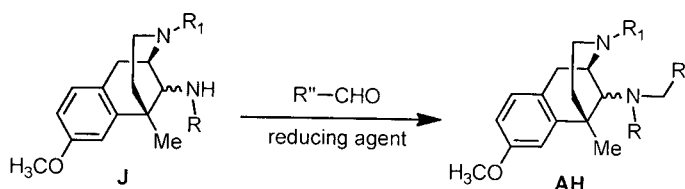
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Scheme K

15

Amine **AE** is N-dealkylated to give the secondary amine **AF** by any number of different methods known to one skilled in the art such as treatment with *m*-chloroperoxybenzoic acid (MCPBA) in the presence of iron (II) chloride ($FeCl_2$) (Monkovic *et al.* Secondary Amines from the Iron(II) Ion-Catalyzed Reaction of

20 Amine Oxides: A General Method for the Dealkylation of Tertiary Amines. *Synthesis*, 1985, 770). Amine **AF** is alkylated to give amine **AG** by treatment with an appropriate alkyl halide in the presence of a suitable base such as TEA in a suitable solvent such as DCM.

Scheme L

Compound **J** is reacted with an aldehyde under reductive amination conditions with a suitable reducing agent such as sodium triacetoxyborohydride in a suitable solvent such as ACN to give Compound **AH**.

Testing of Compounds

μ -opioid Receptor Binding Assay Procedures: Radioligand dose-displacement binding assays for μ -opioid receptors used 0.3 nM [^3H]-diprenorphine (Perkin Elmer, Shelton, CT), with 5 mg membrane protein/well in a final volume of 500 μl binding buffer (10 mM MgCl_2 , 1 mM EDTA, 5% DMSO, 50 mM HEPES, pH 7.4). Reactions were carried out in the absence or presence of increasing concentrations of unlabeled naloxone. All reactions were conducted in 96-deep well polypropylene plates for 2 hr at room temperature. Binding reactions were terminated by rapid filtration onto 96-well Unifilter GF/C filter plates (Perkin Elmer, Shelton, CT), presoaked in 0.5% polyethylenimine using a 96-well tissue harvester (Perkin Elmer, Shelton, CT.) followed by performing three filtration washes with 500 μl of ice-cold binding buffer. Filter plates were subsequently dried at 50°C for 2-3 hours. BetaScint scintillation cocktail (Perkin Elmer, Shelton, CT) was added (50 μl /well), and plates were counted using a Packard Top-Count for 1 min/well. The data were analyzed using the one-site competition curve fitting functions in GraphPad PRISM™ v. 3.0 or higher (San Diego, Calif.), or an in-house function for one-site competition curve-fitting.

μ-opioid Receptor Binding Data: Generally, the lower the K_i value, the more effective the Compounds of the Invention will be at treating or preventing pain or another Condition. Typically, the Compounds of the Invention will have a K_i (nM) of about 1000 or less for binding to μ-opioid receptors. In one embodiment the

- 5 Compounds of the Invention will have a K_i (nM) of about 300 or less for binding to μ-opioid receptors. In one embodiment, Compounds of the Invention will have a K_i (nM) of about 100 or less. In another embodiment, Compounds of the Invention will have a K_i (nM) of about 10 or less. In still another embodiment, Compounds of the Invention will have a K_i (nM) of about 1 or less. In still another embodiment,
- 10 Compounds of the Invention will have a K_i (nM) of about 0.1 or less.

- μ-Opioid Receptor Functional Assay Procedures:** [^{35} S]GTPγS functional assays were conducted using freshly thawed μ-receptor membranes prepared in-house from a cell line expressing recombinant μ opioid receptor in a HEK-293, CHO or U-2 OS cell background, or purchased from a commercial source (Perkin Elmer, Shelton, CT; or DiscovRx, Fremont, CA). Assay reactions were prepared by sequentially
- 15 adding the following reagents to binding buffer (100 mM NaCl, 10 mM $MgCl_2$, 20 mM HEPES, pH 7.4) on ice (final concentrations indicated): membrane protein (0.026 mg/mL), saponin (10 mg/mL), GDP (3mM) and [^{35} S]GTPγS (0.20 nM; Perkin Elmer, Shelton, CT). The prepared membrane solution (190 μl/well) was transferred to 96-
- 20 shallow well polypropylene plates containing 10 μl of 20x concentrated stock solutions of the agonist [D-Ala², N-methyl-Phe⁴ Gly-ol⁵]-enkephalin (DAMGO) prepared in dimethyl sulfoxide (DMSO). Plates were incubated for 30 min at about 25°C with shaking. Reactions were terminated by rapid filtration onto 96-well Unifilter GF/B filter plates (Perkin Elmer, Shelton, CT) using a 96-well tissue harvester (Perkin
- 25 Elmer, Shelton, CT.) followed by three filtration washes with 200 μl of ice-cold wash buffer (10 mM NaH_2PO_4 , 10 mM Na_2HPO_4 , pH 7.4). Filter plates were subsequently dried at 50°C for 2-3 hr. BetaScint scintillation cocktail (Perkin Elmer, Shelton, CT) was added (50 μl/well) and plates were counted using a Packard Top-Count for 1 min/well. Data were analyzed using the sigmoidal dose-response curve fitting
- 30 functions in GraphPad PRISM v. 3.0, or an in-house function for non-linear, sigmoidal dose-response curve-fitting.

μ-Opioid Receptor Functional Data: μ GTP EC₅₀ is the concentration of a compound providing 50% of the maximal response for the compound at a μ-opioid receptor. Compounds of the Invention will typically have a μ GTP EC₅₀ (nM) of about 5000 or less. In certain embodiments, Compounds of the Invention will have a μ GTP EC₅₀ (nM) of about 2000 or less; or about 1000 or less; or about 100 or less; or about 10 or less; or about 1 or less; or about 0.1 or less.

μ GTP E_{max} (%) is the maximal effect elicited by a compound relative to the effect elicited by DAMGO, a standard μ agonist. Generally, the μ GTP E_{max} (%) value measures the efficacy of a compound to treat or prevent pain or other Conditions. Typically, Compounds of the Invention will have a μ GTP E_{max} (%) of greater than about 10%; or greater than about 20%. In certain embodiments, Compounds of the Invention will have a μ GTP E_{max} (%) of greater than about 50%; or greater than about 65%; or greater than about 75%; or greater than about 85%; or greater than about 100%.

κ-opioid Receptor Binding Assay Procedures: Membranes from recombinant HEK-293 cells, CHO or U-2 OS cells expressing the recombinant human κ opioid receptor (κ) were prepared by lysing cells in ice cold hypotonic buffer (2.5 mM MgCl₂, 50 mM HEPES, pH 7.4) (10 mL/10 cm dish) followed by homogenization with a tissue grinder/Teflon pestle. Membranes from a cell line naturally expressing kappa opioid receptors can also be used. Membranes were collected by centrifugation at 30,000 x g for 15 min at 4°C and pellets were resuspended in hypotonic buffer to a final concentration of 1-3mg/mL. Protein concentrations were determined using the BioRad protein assay reagent with bovine serum albumen as standard. Aliquots of κ receptor membranes were stored at -80 °C.

Radioligand dose displacement assays used 0.4 nM [³H]-U69,593 (GE Healthcare, Piscataway, NJ; 40 Ci/mmol) with 15 μg membrane protein (recombinant κ opioid receptor expressed in HEK 293 cells; in-house prep) in a final volume of 200 μl binding buffer (5% DMSO, 50 mM Trizma base, pH 7.4). Non-specific binding was determined in the presence of 10 μM unlabeled naloxone or U69,593. All reactions were performed in 96-well polypropylene plates for 1 hr at a temperature of about 25°C. Binding reactions were terminated by rapid filtration onto 96-well

Unifilter GF/C filter plates (Perkin Elmer, Shelton, CT) presoaked in 0.5% polyethylenimine (Sigma). Harvesting was performed using a 96-well tissue harvester (Perkin Elmer, Shelton, CT) followed by five filtration washes with 200 μ l ice-cold binding buffer. Filter plates were subsequently dried at 50°C for 1-2 hours. Fifty
5 μ l/well scintillation cocktail (Perkin Elmer, Shelton, CT) was added and plates were counted in a Packard Top-Count for 1 min/well.

κ -opioid Receptor Binding Data: In certain embodiments, the Compounds of the Invention will have a K_i (nM) for κ receptors of about 10,000 or more (which, for purposes of this invention, is interpreted as having no binding to the κ receptors).
10 Certain Compounds of the Invention will have a K_i (nM) of about 20,000 or less for κ receptors. In certain embodiments, Compounds of the Invention will have a K_i (nM) of about 10,000 or less; or about 5000 or less; or about 1000 or less; or about 500 or less; or about 450 or less; or about 350 or less; or about 200 or less; or about 100 or less; or about 50 or less; or about 10 or less; or about 1 or less; or about 0.1 or less.

κ -Opioid Receptor Functional Assay Procedures: Functional [^{35} S]GTP γ S binding assays were conducted as follows. κ opioid receptor membrane solution was prepared by sequentially adding final concentrations of 0.026 μ g/ μ l κ membrane protein (in-house), 10 μ g/mL saponin, 3 μ M GDP and 0.20 nM [^{35} S]GTP γ S to binding
15 buffer (100 mM NaCl, 10 mM MgCl₂, 20 mM HEPES, pH 7.4) on ice. The prepared membrane solution (190 μ l/well) was transferred to 96-shallow well polypropylene plates containing 10 μ l of 20x concentrated stock solutions of agonist prepared in DMSO. Plates were incubated for 30 min at a temperature of about 25°C with shaking. Reactions were terminated by rapid filtration onto 96-well Unifilter GF/B
20 filter plates (Perkin Elmer, Shelton, CT) using a 96-well tissue harvester (Packard) and followed by three filtration washes with 200 μ l ice-cold binding buffer (10 mM NaH₂PO₄, 10 mM Na₂HPO₄, pH 7.4). Filter plates were subsequently dried at 50°C for 2-3 hours. Fifty μ l/well scintillation cocktail (Perkin Elmer, Shelton, CT) was
25 added and plates were counted in a Packard Top-Count for 1 min/well.

κ -Opioid Receptor Functional Data: κ GTP EC₅₀ is the concentration of a
30 compound providing 50% of the maximal response for the compound at a κ receptor. Certain Compounds of the Invention will have a κ GTP EC₅₀ (nM) of about 20,000 or

less to stimulate κ opioid receptor function. In certain embodiments, Compounds of the Invention will have a κ GTP EC_{50} (nM) of about 10,000 or less; or about 5000 or less; or about 2000 or less; or about 1500 or less; or about 1000 or less; or about 600 or less; or about 100 or less; or about 50 or less; or about 25 or less; or about 10 or less; or about 1 or less; or about 0.1 or less.

κ GTP E_{max} (%) is the maximal effect elicited by a compound relative to the effect elicited by U69,593. Certain Compounds of the Invention will have a κ GTP E_{max} (%) of greater than about 1%; or greater than about 5%; or greater than about 10%; or greater than about 20%. In certain embodiments, Compounds of the Invention will have a κ GTP E_{max} (%) of greater than about 50%; or greater than about 75%; or greater than about 90%; or greater than about 100%.

δ -opioid Receptor Binding Assay Procedures: δ -opioid Receptor Binding Assay Procedures can be conducted as follows. Radioligand dose-displacement assays use 0.3 nM [^{3} H]-Naltrindole (Perkin Elmer, Shelton, CT; 33.0 Ci/mmol) with 5 μ g membrane protein (Perkin Elmer, Shelton, CT) in a final volume of 500 μ l binding buffer (5 mM $MgCl_2$, 5% DMSO, 50 mM Trizma base, pH 7.4). Non-specific binding is determined in the presence of 25 μ M unlabeled naloxone. All reactions are performed in 96-deep well polypropylene plates for 1 hr at a temperature of about 25°C. Binding reactions are terminated by rapid filtration onto 96-well Unifilter GF/C filter plates (Perkin Elmer, Shelton, CT) presoaked in 0.5% polyethylenimine (Sigma). Harvesting is performed using a 96-well tissue harvester (Perkin Elmer, Shelton, CT) followed by five filtration washes with 500 μ l ice-cold binding buffer. Filter plates are subsequently dried at 50°C for 1-2 hours. Fifty μ l/well scintillation cocktail (Perkin Elmer, Shelton, CT) is added and plates are counted in a Packard Top-Count for 1 min/well.

δ -opioid Receptor Binding Data: In certain embodiments, the Compounds of the Invention will have a K_i (nM) for δ receptors of about 10,000 or more (which, for the purposes of this invention, is interpreted as having no binding to the δ receptors). Certain Compounds of the Invention will have a K_i (nM) of about 20,000 or less for δ receptors. In one embodiment, the Compounds of the Invention will have a K_i (nM) of about 10,000 or less; or of about 9000 or less. In another embodiment, the

Compounds of the Invention will have a K_i (nM) of about 7500 or less; or of about 6500 or less; or of about 5000 or less; or of about 3000 or less; or of about 2500 or less. In another embodiment, the Compounds of the Invention will have a K_i (nM) of about 1000 or less; or of about 500 or less; or of about 350 or less; or of about 250 or less; or of about 100 or less; or of about 10 or less.

δ -Opioid Receptor Functional Assay Procedures: Functional [^{35} S]GTP γ S binding assays can be conducted as follows. δ opioid receptor membrane solution is prepared by sequentially adding final concentrations of 0.026 μ g/ μ l δ membrane protein (Perkin Elmer, Shelton, CT), 10 μ g/mL saponin, 3 μ M GDP and 0.20 nM [^{35} S]GTP γ S to binding buffer (100mM NaCl, 10mM MgCl₂, 20mM HEPES, pH 7.4) on ice. The prepared membrane solution (190 μ l/well) is transferred to 96-shallow well polypropylene plates containing 10 μ l of 20x concentrated stock solutions of agonist prepared in DMSO. Plates are incubated for 30 min at a temperature of about 25°C with shaking. Reactions are terminated by rapid filtration onto 96-well Unifilter GF/B filter plates (Perkin Elmer, Shelton, CT) using a 96-well tissue harvester (Packard) and followed by three filtration washes with 200 μ l ice-cold binding buffer (10 mM NaH₂PO₄, 10 mM Na₂HPO₄, pH 7.4). Filter plates are subsequently dried at 50°C for 1-2 hours. Fifty μ l/well scintillation cocktail (Perkin Elmer, Shelton, CT) is added and plates are counted in a Packard Top-count for 1 min/well.

δ -Opioid Receptor Functional Data: δ GTP EC₅₀ is the concentration of a compound providing 50% of the maximal response for the compound at a δ receptor. Certain Compounds of the Invention will have a δ GTP EC₅₀ (nM) of about 20,000 or less; or about 10,000 or less. In certain embodiments, the Compounds of the Invention will have a δ GTP EC₅₀ (nM) of about 3500 or less; or of about 1000 or less; or of about 500 or less; or of about 100 or less; or of about 90 or less; or of about 50 or less; or of about 25 or less; or of about 10 or less.

δ GTP E_{max} (%) is the maximal effect elicited by a compound relative to the effect elicited by met-enkephalin. Certain Compounds of the Invention of the invention will have a δ GTP E_{max} (%) of greater than about 1%; or of greater than about 5%; or of greater than about 10%. In one embodiment, the Compounds of the Invention will have a δ GTP E_{max} (%) of greater than about 30%. In other

embodiments, the Compounds of the Invention will have a δ GTP $E_{\max}$ (%) of greater than about 50%; or of greater than about 75%; or of greater than about 90%. In another embodiment, the Compounds of the Invention will have a δ GTP $E_{\max}$ (%) of about 100% or greater.

- 5 **ORL-1 Receptor Binding Assay Procedure:** Membranes from recombinant HEK-293 cells expressing the human opioid receptor-like receptor (ORL-1) (Perkin Elmer, Shelton, CT) are prepared by lysing cells in ice-cold hypotonic buffer (2.5 mM MgCl_2 , 50 mM HEPES, pH 7.4) (10 ml/10 cm dish) followed by homogenization with a tissue grinder/Teflon pestle. Membranes are collected by centrifugation at 30,000 x
- 10 g for 15 min at 4°C and pellets resuspended in hypotonic buffer to a final concentration of 1-3 mg/ml. Protein concentrations are determined using the BioRad protein assay reagent with bovine serum albumen as standard. Aliquots of the ORL-1 receptor membranes are stored at -80°C.

- Radioligand binding assays (screening and dose-displacement) use 0.1 nM
- 15 [^3H]-nociceptin (Perkin Elmer, Shelton, CT; 87.7 Ci/mmol) with 12 μg membrane protein in a final volume of 500 μl binding buffer (10 mM MgCl_2 , 1 mM EDTA, 5% DMSO, 50 mM HEPES, pH 7.4). Non-specific binding is determined in the presence of 10 nM unlabeled nociceptin (American Peptide Company). All reactions are performed in 96-deep well polypropylene plates for 1 h at room temperature. Binding
- 20 reactions are terminated by rapid filtration onto 96-well Unifilter GF/C filter plates (Perkin Elmer, Shelton, CT) presoaked in 0.5% polyethylenimine (Sigma). Harvesting is performed using a 96-well tissue harvester (Perkin Elmer, Shelton, CT) followed by three filtration washes with 500 μl ice-cold binding buffer. Filter plates are
- 25 subsequently dried at 50°C for 2-3 hours. Fifty μl /well scintillation cocktail (Perkin Elmer, Shelton, CT) is added and plates are counted in a Packard Top-Count for 1 min/well. The data from screening and dose-displacement experiments are analyzed using Microsoft Excel and the curve fitting functions in GraphPad PRISM™, v. 3.0 or higher, respectively, or an in-house function for one-site competition curve-fitting.

- ORL-1 Receptor Binding Data:** Certain Compounds of the Invention will
- 30 have a K_i (nM) of about 1000 or less. In one embodiment, the Compounds of the Invention will have a K_i (nM) of about 500 or less. In other embodiments, the

Compounds of the Invention will have a K_i (nM) of about 300 or less; or of about 100 or less; or of about 50 or less; or of about 20 or less. In yet other embodiments, the Compounds of the Invention will have a K_i (nM) of about 10 or less; or of about 1 or less; or of about 0.1 or less.

- 5 **ORL-1 Receptor Functional Assay Procedure:** Membranes from recombinant HEK-293 cells expressing the human opioid receptor-like (ORL-1) (Perkin Elmer, Shelton, CT) are prepared by lysing cells in ice-cold hypotonic buffer (2.5 mM Mg Cl₂, 50 mM HEPES, pH 7.4) (10 ml/10 cm dish) followed by homogenization with a tissue grinder/Teflon pestle. Membranes are collected by
- 10 centrifugation at 30,000 x g for 15 min at 4°C, and pellets resuspended in hypotonic buffer to a final concentration of 1-3 mg/ml. Protein concentrations are determined using the BioRad protein assay reagent with bovine serum albumen as standard. Aliquots of the ORL-1 receptor membranes are stored at -80°C.

- Functional [³⁵S]GTPγS binding assays are conducted as follows. ORL-1
- 15 membrane solution is prepared by sequentially adding final concentrations of 0.026 μg/μl ORL-1 membrane protein, 10 μg/ml saponin, 3 μM GDP and 0.20 nM [³⁵S]GTPγS to binding buffer (100 mM NaCl, 10 mM MgCl₂, 20 mM HEPES, pH 7.4) on ice. The prepared membrane solution (190 μl/well) is transferred to 96-shallow well polypropylene plates containing 10 μl of 20x concentrated stock solutions of
- 20 agonist/nociceptin prepared in DMSO. Plates are incubated for 30 min at room temperature with shaking. Reactions are terminated by rapid filtration onto 96-well Unifilter GF/B filter plates (Perkin Elmer, Shelton, CT) using a 96-well tissue harvester (Packard) and followed by three filtration washes with 200 μl ice-cold binding buffer (10 mM NaH₂PO₄, 10 mM Na₂HPO₄, pH 7.4). Filter plates are
- 25 subsequently dried at 50°C for 2-3 hours. Fifty μl/well scintillation cocktail (Perkin Elmer, Shelton, CT) is added and plates are counted in a Packard Top-Count for 1 min/well. Data are analyzed using the sigmoidal dose-response curve fitting functions in GraphPad PRISM v. 3.0 or higher, or an in-house function for non-linear, sigmoidal dose-response curve-fitting.

- 30 **ORL-1 Receptor Functional Data:** ORL-1 GTP EC₅₀ is the concentration of a compound providing 50% of the maximal response for the compound at an ORL-1

receptor. In certain embodiments, the Compounds of the Invention that have a high binding affinity (i.e. low K_i value) will have an ORL-1 GTP EC_{50} (nM) of greater than about 10,000 (i.e. will not stimulate at therapeutic concentrations) In certain embodiments Compounds of the Invention will have an ORL-1 GTP EC_{50} (nM) of about 20,000 or less. In one embodiment, the Compounds of the Invention will have an ORL-1 GTP EC_{50} (nM) of about 10,000 or less; or of about 5000 or less; or of about 1000 or less. In still other embodiments, the Compounds of the Invention will have an ORL-1 GTP EC_{50} (nM) of about 100 or less; or of about 10 or less; or of about 1 or less; or of about 0.1 or less. .

10 ORL-1 GTP E_{max} % is the maximal effect elicited by a compound relative to the effect elicited by nociceptin, a standard ORL-1 agonist. In certain embodiments, Compounds of the Invention will have an ORL-1 GTP E_{max} of less than 10% (which, for the purposes of this invention, is interpreted as having antagonist activity at ORL-1 receptors). Certain Compounds of the Invention will have an ORL-1 GTP E_{max} (%) of
15 greater than 1%; or of greater than 5%; or of greater than 10%. In other embodiments the Compounds of the Invention will have an ORL-1 GTP E_{max} of greater than 20%; or of greater than 50%; or of greater than 75%; or of greater than 88%; or of greater than 100%.

20 *In Vivo Assays for Prevention or Treatment of Pain*

Test Animals: Each experiment uses rats weighing between 200-260 g at the start of the experiment. The rats are group-housed and have free access to food and water at all times, except prior to oral administration of a Compound of the Invention when food is removed for about 16 hours before dosing. A control group acts as a
25 comparison to rats treated with a Compound of the Invention. The control group is administered the carrier for the Compound of the Invention. The volume of carrier administered to the control group is the same as the volume of carrier and Compound of the Invention administered to the test group.

Acute Pain: To assess the actions of a Compound of the Invention for the
30 treatment or prevention of acute pain, the rat tail flick can be used. Rats are gently restrained by hand and the tail exposed to a focused beam of radiant heat at a point 5

cm from the tip using a tail flick unit (Model 7360, commercially available from Ugo Basile of Italy). Tail flick latencies are defined as the interval between the onset of the thermal stimulus and the flick of the tail. Animals not responding within 20 seconds are removed from the tail flick unit and assigned a withdrawal latency of 20 seconds.

- 5 Tail flick latencies are measured immediately before (pre-treatment) and 1, 3, and 5 hours following administration of a Compound of the Invention. Data are expressed as tail flick latency(s) and the percentage of the maximal possible effect (% MPE), *i.e.*, 20 seconds, is calculated as follows:

10

$$\% \text{ MPE} = \frac{[(\text{post administration latency}) - (\text{pre-administration latency})]}{(20 \text{ s} - \text{pre-administration latency})} \times 100$$

The rat tail flick test is described in F.E. D'Amour *et al.*, "A Method for Determining Loss of Pain Sensation," *J. Pharmacol. Exp. Ther.* 72:74-79 (1941).

- 15 To assess the actions of a Compound of the Invention for the treatment or prevention of acute pain, the rat hot plate test can also be used. Rats are tested using a hot plate apparatus consisting of a clear plexiglass cylinder with a heated metal floor maintained at a temperature of 48-52 °C (Model 7280, commercially available from Ugo Basile of Italy). Rats are placed into the cylinder on the hot plate apparatus for a maximum duration of 30 s, or until it exhibits a nocifensive behavior (behavioral
- 20 endpoint), at which time it is removed from the hot plate, and the response latency recorded. Hot plate latencies are measured immediately before (pre-treatment) and 1, 3, and 5 hours following administration of a Compound of the Invention. The nocifensive behavioral endpoint is defined as any of the following: 1) paw withdrawal, either as a sustained lift or with shaking or licking; 2) alternating foot lifting; 3) escape
- 25 or attempted escape from the testing device; or 4) vocalization. Data are expressed as response latency(s) and the percentage of the maximal possible effect is calculated as described above for the tail flick test. The hot plate test is described in G. Woolfe and A.D. Macdonald, *J. Pharmacol. Exp. Ther.* 80:300-307 (1944).

Inflammatory Pain: To assess the actions of a Compound of the Invention for the treatment or prevention of inflammatory pain, the Freund's complete adjuvant ("FCA") model of inflammatory pain can be used. FCA-induced inflammation of the rat hind paw is associated with the development of persistent inflammatory mechanical hyperalgesia and provides reliable prediction of the anti-hyperalgesic action of clinically useful analgesic drugs (L. Bartho *et al.*, "Involvement of Capsaicin-sensitive Neurones in Hyperalgesia and Enhanced Opioid Antinociception in Inflammation," *Naunyn-Schmiedeberg's Archives of Pharmacol.* 342:666-670 (1990)). The left hind paw of each animal is administered a 50 µL intraplantar injection of 50% FCA. Prior to injection of FCA (baseline) and 24 hour post injection, the animal is assessed for response to noxious mechanical stimuli by determining the PWT, as described below. Rats are then administered a single injection of 1, 3, or 10 mg/kg of either a Compound of the Invention; 30mg/kg of a control drug selected from Celebrex, indomethacin or naproxen; or carrier. Responses to noxious mechanical stimuli are determined 1, 3, 5 and 24 hours post administration. Percentage reversal of hyperalgesia for each animal is defined as:

$$\% \text{ Reversal} = \frac{[(\text{post administration PWT}) - (\text{pre-administration PWT})]}{[(\text{baseline PWT}) - (\text{pre-administration PWT})]} \times 100$$

Neuropathic Pain: To assess the actions of a Compound of the Invention for the treatment or prevention of neuropathic pain, either the Seltzer model or the Chung model can be used.

In the Seltzer model, the partial sciatic nerve ligation model of neuropathic pain is used to produce neuropathic hyperalgesia in rats (Z. Seltzer *et al.*, "A Novel Behavioral Model of Neuropathic Pain Disorders Produced in Rats by Partial Sciatic Nerve Injury," *Pain* 43:205-218 (1990)). Partial ligation of the left sciatic nerve is performed under isoflurane/O₂ inhalation anaesthesia. Following induction of anesthesia, the left thigh of the rat is shaved and the sciatic nerve exposed at high thigh level through a small incision and is carefully cleared of surrounding connective

tissues at a site near the trochanter just distal to the point at which the posterior biceps semitendinosus nerve branches off of the common sciatic nerve. A 7-0 silk suture is inserted into the nerve with a 3/8 curved, reversed-cutting mini-needle and tightly ligated so that the dorsal $\frac{1}{3}$ to $\frac{1}{2}$ of the nerve thickness is held within the ligature. The wound is closed with a single muscle suture (4-0 nylon (Vicryl)) and vetbond tissue glue. Following surgery, the wound area is dusted with antibiotic powder. Sham-treated rats undergo an identical surgical procedure except that the sciatic nerve is not manipulated. Following surgery, animals are weighed and placed on a warm pad until they recover from anesthesia. Animals are then returned to their home cages until behavioral testing begins. The animal is assessed for response to noxious mechanical stimuli by determining PWT, as described below, prior to surgery (baseline), then immediately prior to and 1, 3, and 5 hours after drug administration. Percentage reversal of neuropathic hyperalgesia is defined as:

$$\% \text{ Reversal} = \frac{[(\text{post administration PWT}) - (\text{pre-administration PWT})]}{[(\text{baseline PWT}) - (\text{pre-administration PWT})]} \times 100$$

In the Chung model, the spinal nerve ligation model of neuropathic pain is used to produce mechanical hyperalgesia, thermal hyperalgesia and tactile allodynia in rats. Surgery is performed under isoflurane/O₂ inhalation anaesthesia. Following induction of anaesthesia, a 3 cm incision is made and the left paraspinal muscles are separated from the spinous process at the L₄ - S₂ levels. The L₆ transverse process is carefully removed with a pair of small rongeurs to identify visually the L₄ - L₆ spinal nerves. The left L₅ (or L₅ and L₆) spinal nerve(s) is isolated and tightly ligated with silk thread. A complete hemostasis is confirmed and the wound is sutured using non-absorbable sutures, such as nylon sutures or stainless steel staples. Sham-treated rats undergo an identical surgical procedure except that the spinal nerve(s) is not manipulated. Following surgery animals are weighed, administered a subcutaneous (s.c.) injection of saline or ringers lactate, the wound area is dusted with antibiotic powder and they are kept on a warm pad until they recover from the anesthesia. Animals are then returned

to their home cages until behavioral testing begins. The animals are assessed for response to noxious mechanical stimuli by determining PWT, as described below, prior to surgery (baseline), then immediately prior to and 1, 3, and 5 hours after being administered a Compound of the Invention. The animal can also be assessed for response to noxious thermal stimuli or for tactile allodynia, as described below. The Chung model for neuropathic pain is described in S.H. Kim, "An Experimental Model for Peripheral Neuropathy Produced by Segmental Spinal Nerve Ligation in the Rat," *Pain* 50(3):355-363 (1992).

Response to Mechanical Stimuli as an Assessment of Mechanical

10 **Hyperalgesia:** The paw pressure assay can be used to assess mechanical hyperalgesia. For this assay, hind paw withdrawal thresholds (PWT) to a noxious mechanical stimulus are determined using an analgesymeter (Model 7200, commercially available from Ugo Basile of Italy) as described in C. Stein, "Unilateral Inflammation of the Hindpaw in Rats as a Model of Prolonged Noxious Stimulation: Alterations in Behavior and Nociceptive Thresholds," *Pharmacol. Biochem. and Behavior* 31:451-455 (1988). The maximum weight that is applied to the hind paw is set at 250 g and the end point is taken as complete withdrawal of the paw. PWT is determined once for each rat at each time point and either only the affected (ipsilateral; same side as the injury) rear paw is tested, or both the ipsilateral and contralateral (non-injured; opposite to the injury) rear paw are tested.

Response to Thermal Stimuli as an Assessment of Thermal Hyperalgesia:

The plantar test can be used to assess thermal hyperalgesia. For this test, hind paw withdrawal latencies to a noxious thermal stimulus are determined using a plantar test apparatus (commercially available from Ugo Basile of Italy) following the technique described by K. Hargreaves *et al.*, "A New and Sensitive Method for Measuring Thermal Nociception in Cutaneous Hyperalgesia," *Pain* 32(1):77-88 (1988). The maximum exposure time is set at 32 seconds to avoid tissue damage and any directed paw withdrawal from the heat source is taken as the end point. Three latencies are determined at each time point and averaged. Either only the affected (ipsilateral) paw is tested, or both the ipsilateral and contralateral (non-injured) paw are tested.

Assessment of Tactile Allodynia: To assess tactile allodynia, rats are placed in clear, plexiglass compartments with a wire mesh floor and allowed to habituate for a period of at least 15 minutes. After habituation, a series of von Frey monofilaments are presented to the plantar surface of the affected (ipsilateral) foot of each rat. The series of von Frey monofilaments consists of six monofilaments of increasing diameter, with the smallest diameter fiber presented first. Five trials are conducted with each filament with each trial separated by approximately 2 minutes. Each presentation lasts for a period of 4-8 seconds or until a nociceptive withdrawal behavior is observed. Flinching, paw withdrawal or licking of the paw are considered nociceptive behavioral responses.

Assessment of Respiratory Depression: To assess respiratory depression, rats can be prepared by implanting a femoral artery cannula via which blood samples are taken. Blood samples are taken prior to drug administration, then 1, 3, 5 and 24 hours post-treatment. Blood samples are processed using an arterial blood gas analyzer (e.g., IDEXX VetStat with Respiratory/Blood Gas test cartridges). Comparable devices are a standard tool for blood gas analysis (e.g., D. Torbati et al., 2000 *Intensive Care Med.* (26) 585-591).

Assessment of Gastric Motility: Animals are treated with vehicle, reference compound or test article by oral gavage at a volume of 10 mL/kg. At one hour post-dose, all animals are treated with charcoal meal solution (5% non-activated charcoal powder in a solution of 1 % carboxymethylcellulose in water) at a volume of 10 mL/kg. At two hours post-dose (one hour post-charcoal), animals are sacrificed by carbon dioxide inhalation or isoflurane overdose and the transit of charcoal meal identified. The stomach and small intestine are removed carefully and each placed on a saline-soaked absorbent surface. The distance between the pylorus and the furthest progression of charcoal meal is measured and compared to the distance between the pylorus and the ileocecal junction. The charcoal meal transit is expressed as a percentage of small intestinal length traveled.

30

Pharmaceutical Compositions

Due to their activity, the Compounds of the Invention are advantageously useful in human and veterinary medicine. As described above, the Compounds of the Invention are useful for treating or preventing a Condition in a subject in need thereof.

5 The Compounds of the Invention can be administered to any animal requiring modulation of the opioid and/or ORL-1 receptors.

When administered to a subject, a Compound of the Invention can be administered as a component of a composition that comprises a pharmaceutically acceptable carrier or excipient. A Compound of the Invention can be administered by
10 any appropriate route, as determined by the medical practitioner. Methods of administration may include intradermal, intramuscular, intraperitoneal, parenteral, intravenous, subcutaneous, intranasal, epidural, oral, sublingual, buccal, intracerebral, intravaginal, transdermal, transmucosal, rectal, by inhalation, or topical (particularly to the ears, nose, eyes, or skin). Delivery can be either local or systemic. In certain
15 embodiments, administration will result in the release of a Compound of the Invention into the bloodstream.

Pharmaceutical compositions of the invention can take the form of solutions, suspensions, emulsions, tablets, pills, pellets, multi-particulates, capsules, capsules containing liquids, capsules containing powders, capsules containing multi-
20 particulates, lozenges, sustained-release formulations, thin films, suppositories, aerosols, sprays, or any other form suitable for use. In one embodiment, the composition is in the form of a capsule (*see, e.g.*, U.S. Patent No. 5,698,155). Other examples of suitable pharmaceutical excipients are described in *Remington's Pharmaceutical Sciences* 1447-1676 (Alfonso R. Gennaro ed., 19th ed. 1995),
25 incorporated herein by reference.

Pharmaceutical compositions of the invention preferably comprise a suitable amount of a pharmaceutically acceptable excipient so as to provide the form for proper administration to the subject. Such a pharmaceutical excipient can be a diluent, suspending agent, solubilizer, binder, disintegrant, preservative, coloring agent,
30 lubricant, and the like. The pharmaceutical excipient can be a liquid, such as water or an oil, including those of petroleum, animal, vegetable, or synthetic origin, such as

peanut oil, soybean oil, mineral oil, sesame oil, and the like. The pharmaceutical excipient can be saline, gum acacia, gelatin, starch paste, talc, keratin, colloidal silica, urea, and the like. In addition, auxiliary, stabilizing, thickening, lubricating, and coloring agents can be used. In one embodiment, the pharmaceutically acceptable excipient is sterile when administered to an animal. Water is a particularly useful excipient when a Compound of the Invention is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid excipients, particularly for injectable solutions. Suitable pharmaceutical excipients also include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene glycol, water, ethanol, and the like. The invention compositions, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. Specific examples of pharmaceutically acceptable carriers and excipients that can be used to formulate oral dosage forms are described in the *Handbook of Pharmaceutical Excipients*, American Pharmaceutical Association (1986).

In certain embodiments, the Compounds of the Invention are formulated for oral administration. A Compound of the Invention to be orally delivered can be in the form of tablets, capsules, gelcaps, caplets, lozenges, aqueous or oily solutions, suspensions, granules, powders, emulsions, syrups, or elixirs, for example. When a Compound of the Invention is incorporated into oral tablets, such tablets can be compressed, tablet triturates, enteric-coated, sugar-coated, film-coated, multiply compressed or multiply layered.

An orally administered Compound of the Invention can contain one or more additional agents such as, for example, sweetening agents such as fructose, aspartame or saccharin; flavoring agents such as peppermint, oil of wintergreen, or cherry; coloring agents; and preserving agents, and stabilizers, to provide stable, pharmaceutically palatable dosage forms. Techniques and compositions for making solid oral dosage forms are described in *Pharmaceutical Dosage Forms: Tablets* (Lieberman, Lachman and Schwartz, eds., 2nd ed.) published by Marcel Dekker, Inc. Techniques and compositions for making tablets (compressed and molded), capsules

(hard and soft gelatin) and pills are also described in *Remington's Pharmaceutical Sciences* 1553-1593 (Arthur Osol, ed., 16th ed., Mack Publishing, Easton, PA 1980).

Liquid oral dosage forms include aqueous and nonaqueous solutions, emulsions, suspensions, and solutions and/or suspensions reconstituted from non-effervescent

5 granules, optionally containing one or more suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, coloring agents, flavoring agents, and the like. Techniques and compositions for making liquid oral dosage forms are described in *Pharmaceutical Dosage Forms: Disperse Systems*, (Lieberman, Rieger and Banker, eds.) published by Marcel Dekker, Inc.

10 When a Compound of the Invention is formulated for parenteral administration by injection (*e.g.*, continuous infusion or bolus injection), the formulation can be in the form of a suspension, solution, or emulsion in an oily or aqueous vehicle, and such formulations can further comprise pharmaceutically necessary additives such as one or more stabilizing agents, suspending agents, dispersing agents, and the like. When a
15 Compound of the Invention is to be injected parenterally, it can be, *e.g.*, in the form of an isotonic sterile solution. A Compound of the Invention can also be in the form of a powder for reconstitution as an injectable formulation.

In certain embodiments, a Compound of the Invention is formulated into a pharmaceutical composition for intravenous administration. Typically, such
20 compositions comprise sterile isotonic aqueous buffer. Where necessary, the compositions can also include a solubilizing agent. A Compound of the Invention for intravenous administration can optionally include a local anesthetic such as benzocaine or prilocaine to lessen pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry
25 lyophilized powder or water free concentrate in a hermetically sealed container such as an ampule or sachette indicating the quantity of active agent. Where a Compound of the Invention is to be administered by infusion, it can be dispensed, for example, with an infusion bottle containing sterile pharmaceutical grade water or saline. Where a Compound of the Invention is administered by injection, an ampule of sterile water for
30 injection or saline can be provided so that the ingredients can be mixed prior to administration.

When a Compound of the Invention is to be administered by inhalation, it can be formulated into a dry aerosol, or an aqueous or partially aqueous solution.

In another embodiment, a Compound of the Invention can be delivered in a vesicle, in particular a liposome (*see* Langer, *Science* 249:1527-1533 (1990); and Treat
5 *et al.*, *Liposomes in the Therapy of Infectious Disease and Cancer* 317-327 and 353-365 (1989)).

In certain embodiments, a Compound of the Invention is administered locally. This can be achieved, for example, by local infusion during surgery, topical application, *e.g.*, in conjunction with a wound dressing after surgery, by injection, by
10 means of a catheter, by means of a suppository or enema, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers.

In certain embodiments, a Compound of the Invention can be delivered in an immediate release form. In other embodiments, a Compound of the Invention can be
15 delivered in a controlled-release system or sustained-release system. Controlled- or sustained-release pharmaceutical compositions can have a common goal of improving drug therapy over the results achieved by their non-controlled or non-sustained-release counterparts. In one embodiment, a controlled- or sustained-release composition comprises a minimal amount of a Compound of the Invention to treat or prevent the
20 Condition (or a symptom thereof) in a minimum amount of time. Advantages of controlled- or sustained-release compositions include extended activity of the drug, reduced dosage frequency, and increased compliance. In addition, controlled- or sustained-release compositions can favorably affect the time of onset of action or other characteristics, such as blood levels of the Compound of the Invention, and can thus
25 reduce the occurrence of adverse side effects.

Controlled- or sustained-release compositions can initially release an amount of a Compound of the Invention that promptly produces the desired therapeutic or prophylactic effect, and gradually and continually release other amounts of the Compound of the Invention to maintain a level of therapeutic or prophylactic effect
30 over an extended period of time. To maintain a constant level of the Compound of the Invention in the body, the Compound of the Invention can be released from the dosage

form at a rate that will replace the amount of Compound of the Invention being metabolized and excreted from the body. Controlled- or sustained-release of an active ingredient can be stimulated by various conditions, including but not limited to, changes in pH, changes in temperature, concentration or availability of enzymes, concentration or availability of water, or other physiological conditions or compounds.

Controlled-release and sustained-release means for use according to the present invention may be selected from those known in the art. Examples include, but are not limited to, those described in U.S. Patent Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; 4,008,719; 5,674,533; 5,059,595; 5,591,767; 5,120,548; 5,073,543; 5,639,476; 5,354,556; and 5,733,566, each of which is incorporated herein by reference. Such dosage forms can be used to provide controlled- or sustained-release of one or more active ingredients using, for example, hydropropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, multiparticulates, liposomes, microspheres, or a combination thereof to provide the desired release profile in varying proportions. Suitable controlled- or sustained-release formulations known in the art, including those described herein, can be readily selected for use with the active ingredients of the invention in view of this disclosure. See also Goodson, "Dental Applications" (pp. 115-138) in *Medical Applications of Controlled Release, Vol. 2, Applications and Evaluation*, R.S. Langer and D.L. Wise eds., CRC Press (1984). Other controlled- or sustained-release systems that are discussed in the review by Langer, *Science* 249:1527-1533 (1990) can be selected for use according to the present invention. In one embodiment, a pump can be used (Langer, *Science* 249:1527-1533 (1990); Sefton, *CRC Crit. Ref. Biomed. Eng.* 14:201 (1987); Buchwald *et al.*, *Surgery* 88:507 (1980); and Saudek *et al.*, *N. Engl. J. Med.* 321:574 (1989)). In another embodiment, polymeric materials can be used (see *Medical Applications of Controlled Release* (Langer and Wise eds., 1974); *Controlled Drug Bioavailability, Drug Product Design and Performance* (Smolen and Ball eds., 1984); Ranger and Peppas, *J. Macromol. Sci. Rev. Macromol. Chem.* 23:61 (1983); Levy *et al.*, *Science* 228:190 (1985); During *et al.*, *Ann. Neurol.* 25:351 (1989); and Howard *et al.*, *J. Neurosurg.* 71:105 (1989)). In yet another embodiment, a controlled- or sustained-release system can be placed in

proximity of a target of a Compound of the Invention, *e.g.*, the spinal column, brain, or gastrointestinal tract, thus requiring only a fraction of the systemic dose.

When in tablet or pill form, a pharmaceutical composition of the invention can be coated to delay disintegration and absorption in the gastrointestinal tract thereby providing a sustained action over an extended period of time. Selectively permeable membranes surrounding an osmotically active driving compound are also suitable for orally administered compositions. In these latter platforms, fluid from the environment surrounding the capsule is imbibed by the driving compound, which swells to displace the agent or agent composition through an aperture. These delivery platforms can provide an essentially zero order delivery profile as opposed to the spiked profiles of immediate release formulations. A time-delay material such as glycerol monostearate or glycerol stearate can also be used. Oral compositions can include standard excipients such as mannitol, lactose, starch, magnesium stearate, sodium saccharin, cellulose, and magnesium carbonate. In one embodiment, the excipients are of pharmaceutical grade.

Pharmaceutical compositions of the invention include single unit dosage forms suitable for oral administration such as, but not limited to, tablets, capsules, gelcaps, and caplets that are adapted for controlled- or sustained-release.

The amount of the Compound of the Invention that is effective for the treatment or prevention of a condition can be determined by standard clinical techniques. In addition, *in vitro* and/or *in vivo* assays can optionally be employed to help identify optimal dosage ranges. The precise dose to be employed will also depend on, *e.g.*, the route of administration and the extent of the Condition to be treated, and can be decided according to the judgment of a practitioner and/or each animal's circumstances. Variations in dosing may occur depending upon typical factors such as the weight, age, gender and physical condition (*e.g.*, hepatic and renal function) of the animal being treated, the affliction to be treated, the severity of the symptoms, the frequency of the dosage interval, the presence of any deleterious side-effects, and the particular compound utilized, among other things.

Suitable effective dosage amounts can range from about 0.01mg/kg of body weight to about 3000 mg/kg of body weight of the animal per day, although they are

typically from about 0.01mg/kg of body weight to about 2500 mg/kg of body weight of the animal per day or from about 0.01mg/kg of body weight to about 1000 mg/kg of body weight of the animal per day. In one embodiment, the effective dosage amount is about 100 mg/kg of body weight of the animal per day or less. In another
5 embodiment, the effective dosage amount ranges from about 0.01mg/kg of body weight to about 100 mg/kg of body weight of the animal per day of a Compound of the Invention, in another embodiment, about 0.02 mg/kg of body weight to about 50 mg/kg of body weight of the animal per day, and in another embodiment, about 0.025 mg/kg of body weight to about 20 mg/kg of body weight of the animal per day.

10 Administration can be as a single dose or as a divided dose. In one embodiment, an effective dosage amount is administered about every 24h until the Condition is abated. In another embodiment, an effective dosage amount is administered about every 12h until the Condition is abated. In another embodiment, an effective dosage amount is administered about every 8h until the Condition is
15 abated. In another embodiment, an effective dosage amount is administered about every 6h until the Condition is abated. In another embodiment, an effective dosage amount is administered about every 4h until the Condition is abated. The effective dosage amounts described herein refer to total amounts administered; that is, if more than one Compound of the Invention is administered, the effective dosage amounts
20 correspond to the total amount administered.

Where a cell capable of expressing the ORL-1 receptor is contacted with a Compound of the Invention *in vitro*, the amount effective for inhibiting or activating the ORL-1 receptor function in a cell will typically range from about 10^{-12} mol/L to about 10^{-4} mol/L, or from about 10^{-12} mol/L to about 10^{-5} mol/L, or from about 10^{-12}
25 mol/L to about 10^{-6} mol/L, or from about 10^{-12} mol/L to about 10^{-9} mol/L of a solution or suspension of the compound in a pharmaceutically acceptable carrier or excipient. In one embodiment, the volume of solution or suspension comprising the Compound of the Invention will be from about 0.01 μ L to about 1mL. In another embodiment, the volume of solution or suspension will be about 200 μ L.

30 Where a cell capable of expressing the μ -opioid receptors is contacted with a Compound of the Invention *in vitro*, the amount effective for inhibiting or activating

the μ -opioid receptors function in a cell will typically range from about 10^{-12} mol/L to about 10^{-4} mol/L, or from about 10^{-12} mol/L to about 10^{-5} mol/L, or from about 10^{-12} mol/L to about 10^{-6} mol/L, or from about 10^{-12} mol/L to about 10^{-9} mol/L of a solution or suspension of the Compound of the Invention in a pharmaceutically acceptable carrier or excipient. In one embodiment, the volume of solution or suspension comprising the Compound of the Invention will be from about 0.01 μ L to about 1 mL. In another embodiment, the volume of solution or suspension will be about 200 μ L.

Where a cell capable of expressing the δ -opioid receptors is contacted with a Compound of the Invention *in vitro*, the amount effective for inhibiting or activating the δ -opioid receptors function in a cell will typically range from about 10^{-12} mol/L to about 10^{-4} mol/L, or from about 10^{-12} mol/L to about 10^{-5} mol/L, or from about 10^{-12} mol/L to about 10^{-6} mol/L, or from about 10^{-12} mol/L to about 10^{-9} mol/L of a solution or suspension of the Compound of the Invention in a pharmaceutically acceptable carrier or excipient. In one embodiment, the volume of solution or suspension comprising the Compound of the Invention will be from about 0.01 μ L to about 1 mL. In another embodiment, the volume of solution or suspension will be about 200 μ L.

Where a cell capable of expressing the κ -opioid receptors is contacted with a Compound of the Invention *in vitro*, the amount effective for inhibiting or activating the κ -opioid receptors function in a cell will typically range from about 10^{-12} mol/L to about 10^{-4} mol/L, or from about 10^{-12} mol/L to about 10^{-5} mol/L, or from about 10^{-12} mol/L to about 10^{-6} mol/L, or from about 10^{-12} mol/L to about 10^{-9} mol/L of a solution or suspension of the Compound of the Invention in a pharmaceutically acceptable carrier or excipient. In one embodiment, the volume of solution or suspension comprising the Compound of the Invention will be from about 0.01 μ L to about 1 mL. In another embodiment, the volume of solution or suspension will be about 200 μ L.

The Compounds of the Invention can be assayed *in vitro* or *in vivo* for the desired therapeutic or prophylactic activity prior to use in humans. Animal model systems can be used to demonstrate safety and efficacy. Certain Compounds of the Invention will have an ED₅₀ for treating pain ranging from about 0.5 mg/kg to about 20 mg/kg. Certain Compounds of the Invention will produce significant analgesia and/or anti-hyperalgesia at doses that do not induce respiratory depression. In

contrast, oxygen tension, oxygen saturation and pH are significantly decreased, while carbon dioxide is significantly increased, in blood samples from rats given effective doses of conventional opioids, such as morphine.

According to the invention, methods for treating or preventing a Condition in
5 an animal in need thereof can further comprise co-administering to the animal an effective amount of a second therapeutic agent in addition to a Compound of the Invention (*i.e.*, a first therapeutic agent). An effective amount of the second therapeutic agent will be known or determinable by a medical practitioner in view of this disclosure and published clinical studies. In one embodiment of the invention, where a
10 second therapeutic agent is administered to an animal for treatment of a Condition (*e.g.*, pain), the minimal effective amount of the Compound of the Invention (*i.e.*, the first therapeutic agent) will be less than its minimal effective amount would be in circumstances where the second therapeutic agent is not administered. In this embodiment, the Compound of the Invention and the second therapeutic agent can act
15 either additively or synergistically to treat or prevent a Condition. Alternatively, the second therapeutic agent may be used to treat or prevent a disorder that is different from the Condition for which the first therapeutic agent is being administered, and which disorder may or may not be a Condition as defined hereinabove. In one embodiment, a Compound of the Invention is administered concurrently with a second
20 therapeutic agent as a single composition comprising an effective amount of a Compound of the Invention and an effective amount of the second therapeutic agent. Alternatively, a composition comprising an effective amount of a Compound of the Invention and a second composition comprising an effective amount of the second therapeutic agent are concurrently administered. In another embodiment, an effective
25 amount of a Compound of the Invention is administered prior or subsequent to administration of an effective amount of the second therapeutic agent. In this embodiment, the Compound of the Invention is administered while the second therapeutic agent exerts its therapeutic effect, or the second therapeutic agent is administered while the Compound of the Invention exerts its therapeutic effect for
30 treating or preventing a Condition.

The second therapeutic agent can be, but is not limited to, an opioid agonist, a non-opioid analgesic, a non-steroidal anti-inflammatory agent, an antimigraine agent, a Cox-II inhibitor, a 5-lipoxygenase inhibitor, an anti-emetic, a β -adrenergic blocker, an anticonvulsant, an antidepressant, a Ca^{2+} -channel blocker, an anti-cancer agent, an agent for treating or preventing UI, an agent for treating or preventing anxiety, an agent for treating or preventing a memory disorder, an agent for treating or preventing obesity, an agent for treating or preventing constipation, an agent for treating or preventing cough, an agent for treating or preventing diarrhea, an agent for treating or preventing high blood pressure, an agent for treating or preventing epilepsy, an agent for treating or preventing anorexia/cachexia, an agent for treating or preventing drug abuse, an agent for treating or preventing an ulcer, an agent for treating or preventing IBD, an agent for treating or preventing IBS, an agent for treating or preventing addictive disorder, an agent for treating or preventing Parkinson's disease and parkinsonism, an agent for treating or preventing a stroke, an agent for treating or preventing a seizure, an agent for treating or preventing a pruritic condition, an agent for treating or preventing psychosis, an agent for treating or preventing Huntington's chorea, an agent for treating or preventing ALS, an agent for treating or preventing a cognitive disorder, an agent for treating or preventing a migraine, an agent for treating, preventing or inhibiting vomiting, an agent for treating or preventing dyskinesia, an agent for treating or preventing depression, or any mixture thereof.

Examples of useful opioid agonists include, but are not limited to, alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, desomorphine, dextromoramide, dezocine, diampromide, diamorphine, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, fentanyl, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levorphanol, levophenacymorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, nalbuphine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan,

phenazocine, phenoperidine, piminodine, piritramide, proheptazine, promedol, properidine, propiram, propoxyphene, sufentanil, tilidine, tramadol, pharmaceutically acceptable derivatives thereof, or any mixture thereof.

- In certain embodiments, the opioid agonist is selected from codeine,
 5 hydromorphone, hydrocodone, oxycodone, dihydrocodeine, dihydromorphone, morphine, tramadol, oxymorphone, pharmaceutically acceptable derivatives thereof, or any mixture thereof.

- Examples of useful non-opioid analgesics include, but are not limited to, non-steroidal anti-inflammatory agents, such as aspirin, ibuprofen, diclofenac,
 10 naproxen, benoxaprofen, flurbiprofen, fenoprofen, flubufen, ketoprofen, indoprofen, piroprofen, carprofen, oxaprozin, pramoprofen, muprofen, trioxaprofen, suprofen, aminoprofen, tiaprofenic acid, fluprofen, bucloxic acid, indomethacin, sulindac, tolmetin, zomepirac, tiopinac, zidometacin, acetaminophen, fentiazac, clidanac, oxpinac, mefenamic acid, meclofenamic acid, flufenamic acid, niflumic acid, tolfenamic acid,
 15 diflurisal, flufenisal, piroxicam, sudoxicam, isoxicam, a pharmaceutically acceptable derivative thereof, or any mixture thereof. Other suitable non-opioid analgesics include the following, non-limiting, chemical classes of analgesic, antipyretic, nonsteroidal anti-inflammatory drugs: salicylic acid derivatives, including aspirin, sodium salicylate, choline magnesium trisalicylate, salsalate, diflunisal, salicylsalicylic
 20 acid, sulfasalazine, and olsalazin; para-aminophenol derivatives including acetaminophen and phenacetin; indole and indene acetic acids, including indomethacin, sulindac, and etodolac; heteroaryl acetic acids, including tolmetin, diclofenac, and ketorolac; anthranilic acids (fenamates), including mefenamic acid and meclofenamic acid; enolic acids, including oxicams (piroxicam, tenoxicam), and
 25 pyrazolidinediones (phenylbutazone, oxyphenthartazone); alkanones, including nabumetone; a pharmaceutically acceptable derivative thereof; or any mixture thereof. For a more detailed description of the NSAIDs, see Paul A. Insel, *Analgesic-Antipyretic and Anti-inflammatory Agents and Drugs Employed in the Treatment of Gout*, in Goodman & Gilman's *The Pharmacological Basis of*
 30 *Therapeutics* 617-57 (Perry B. Molinoff and Raymond W. Ruddon eds., 9th ed 1996); and Glen R. Hanson, *Analgesic, Antipyretic and Anti-Inflammatory Drugs in*

Remington: The Science and Practice of Pharmacy Vol IA 1196-1221 (A.R. Gennaro ed. 19th ed. 1995), which are hereby incorporated by reference in their entireties.

Examples of useful Cox-II inhibitors and 5-lipoxygenase inhibitors, as well as combinations thereof, are described in U.S. Patent No. 6,136,839, which is hereby incorporated by reference in its entirety. Examples of useful Cox-II inhibitors include, but are not limited to, celecoxib, DUP-697, flosulide, meloxicam, 6-MNA, L-745337, rofecoxib, nabumetone, nimesulide, NS-398, SC-5766, T-614, L-768277, GR-253035, JTE-522, RS-57067-000, SC-58125, SC-078, PD-138387, NS-398, flosulide, D-1367, SC-5766, PD-164387, etoricoxib, valdecoxib, parecoxib, a pharmaceutically acceptable derivative thereof, or any mixture thereof.

Examples of useful antimigraine agents include, but are not limited to, alpiropride, bromocriptine, dihydroergotamine, dolasetron, ergocornine, ergocorninine, ergocryptine, ergonovine, ergot, ergotamine, flumetrolone acetate, fonazine, ketanserin, lisuride, lomerizine, methylergonovine, methysergide, metoprolol, naratriptan, oxetorone, pizotyline, propranolol, risperidone, rizatriptan, sumatriptan, timolol, trazodone, zolmitriptan, a pharmaceutically acceptable derivative thereof, or any mixture thereof.

Examples of useful anticonvulsants include, but are not limited to, acetylpheneturide, albutoin, aloxidone, aminoglutethimide, 4-amino-3-hydroxybutyric acid, atrolactamide, beclamide, buramate, calcium bromide, carbamazepine, cinromide, clomethiazole, clonazepam, decimemide, diethadione, dimethadione, doxenitroin, eterobarb, ethadione, ethosuximide, ethotoin, felbamate, fluorenone, gabapentin, 5-hydroxytryptophan, lamotrigine, magnesium bromide, magnesium sulfate, mephentoin, mephobarbital, metharbital, methetoin, methsuximide, 5-methyl-5-(3-phenanthryl)-hydantoin, 3-methyl-5-phenylhydantoin, narcobarbital, nimetazepam, nitrazepam, oxcarbazepine, paramethadione, phenacetamide, phenetharbital, pheneturide, phenobarbital, phensuximide, phenylmethylbarbituric acid, phenytoin, phethenylate sodium, potassium bromide, pregabalin, primidone, progabide, sodium bromide, solanum, strontium bromide, suclofenide, sulthiame, tetrantoin, tiagabine, topiramate, trimethadione, valproic acid, valpromide, vigabatrin, zonisamide, a pharmaceutically acceptable derivative thereof, or any mixture thereof.

Examples of useful Ca²⁺-channel blockers include, but are not limited to, bepridil, clentiazem, diltiazem, fendiline, gallopamil, mibefradil, prenylamine, semotiadil, terodiline, verapamil, amlodipine, aranidipine, barnidipine, benidipine, cilnidipine, efonidipine, elgodipine, felodipine, isradipine, lacidipine, lercanidipine, 5 manidipine, nicardipine, nifedipine, nilvadipine, nimodipine, nisoldipine, nitrendipine, cinnarizine, flunarizine, lidoflazine, lomerizine, bencyclane, etafenone, fantofarone, perhexiline, a pharmaceutically acceptable derivative thereof, or any mixture thereof.

Examples of useful therapeutic agents for treating or preventing UI include, but are not limited to, propantheline, imipramine, hyoscyamine, oxybutynin, dicyclomine, 10 a pharmaceutically acceptable derivative thereof, or any mixture thereof.

Examples of useful therapeutic agents for treating or preventing anxiety include, but are not limited to, benzodiazepines, such as alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepate, demoxepam, diazepam, estazolam, flumazenil, flurazepam, halazepam, lorazepam, midazolam, nitrazepam, 15 nordazepam, oxazepam, prazepam, quazepam, temazepam, and triazolam; non-benzodiazepine agents, such as buspirone, gepirone, ipsapirone, tiospirone, zolpicone, zolpidem, and zaleplon; tranquilizers, such as barbituates, *e.g.*, amobarbital, aprobarbital, butabarbital, butalbital, mephobarbital, methohexital, pentobarbital, phenobarbital, secobarbital, and thiopental; propanediol carbamates, such as 20 meprobamate and tybamate; a pharmaceutically acceptable derivative thereof; or any mixture thereof.

Examples of useful therapeutic agents for treating or preventing diarrhea include, but are not limited to, diphenoxylate, loperamide, a pharmaceutically acceptable derivative thereof, or any mixture thereof.

25 Examples of useful therapeutic agents for treating or preventing epilepsy include, but are not limited to, carbamazepine, ethosuximide, gabapentin, lamotrigine, phenobarbital, phenytoin, primidone, valproic acid, trimethadione, benzodiazepines, γ vinyl GABA, acetazolamide, felbamate, a pharmaceutically acceptable derivative thereof, or any mixture thereof.

30 Examples of useful therapeutic agents for treating or preventing drug abuse include, but are not limited to, methadone, desipramine, amantadine, fluoxetine,

buprenorphine, an opiate agonist, 3-phenoxypropidine, levomethadyl acetate hydrochloride, serotonin antagonists, a pharmaceutically acceptable derivative thereof, or any mixture thereof.

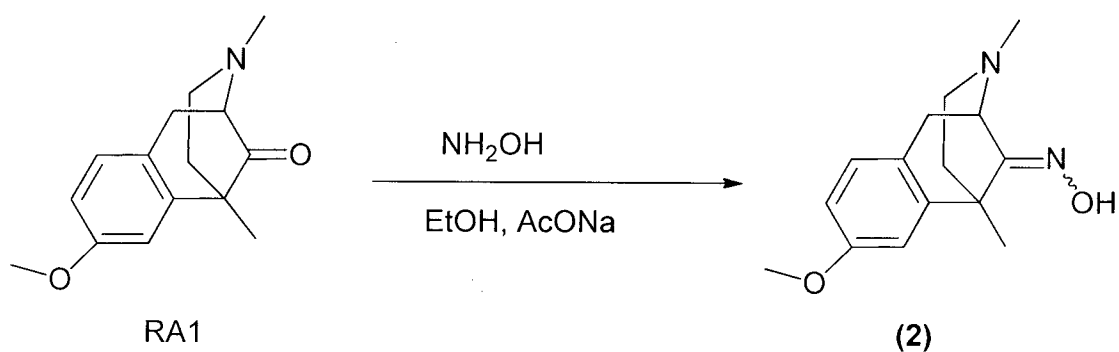
5 Examples of non-steroidal anti-inflammatory agents, 5-lipoxygenase inhibitors, anti-emetics, β adrenergic blockers, antidepressants, and anti-cancer agents are known in the art and can be selected by those skilled in the art. Examples of useful therapeutic agents for treating or preventing memory disorder, obesity, constipation, cough, high blood pressure, anorexia/cachexia, an ulcer, IBD, IBS, addictive disorder, Parkinson's disease and parkinsonism, a stroke, a seizure, a pruritic condition,
10 psychosis, Huntington's chorea, ALS, a cognitive disorder, a migraine, dyskinesia, depression, and/or treating, preventing or inhibiting vomiting include those that are known in the art and can be selected by those skilled in the art.

A composition of the invention is prepared by a method comprising admixing a Compound of the Invention (or a pharmaceutically acceptable salt, prodrug or solvate
15 thereof) with a pharmaceutically acceptable carrier or excipient. Admixing can be accomplished using methods known for admixing a compound (or derivative) and a pharmaceutically acceptable carrier or excipient. In one embodiment, the Compound of the Invention (or pharmaceutically acceptable salt, prodrug or solvate thereof) is present in the composition in an effective amount.

20

EXAMPLE 2

8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-one
 5 oxime (Compound 2)

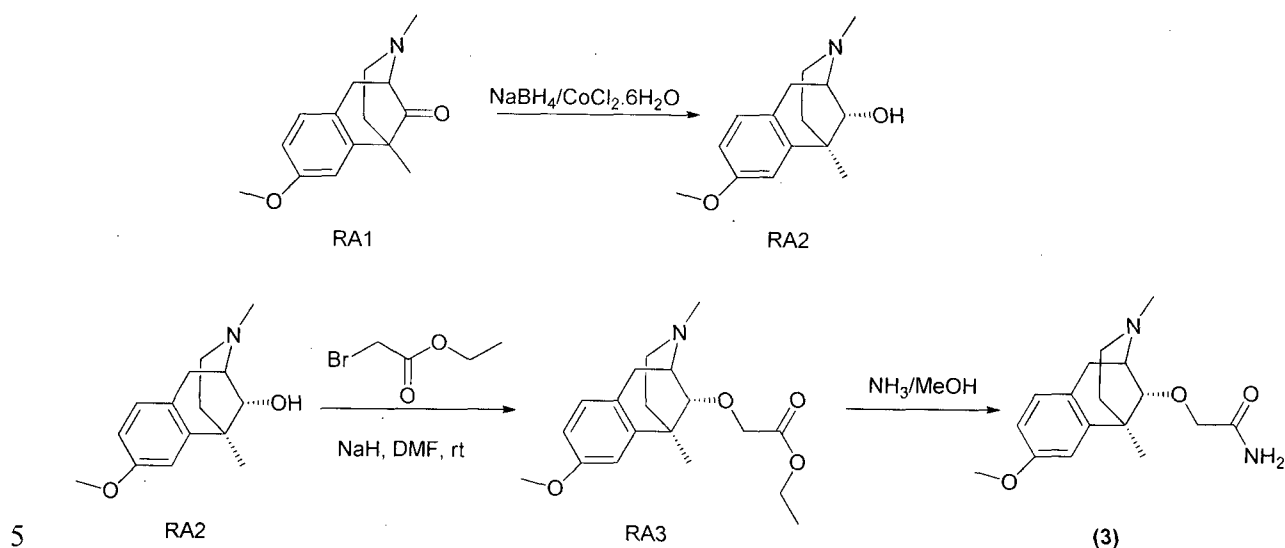


10 In a similar manner **Compound 2** was prepared from **RA1** (0.37mmol) and hydroxylamine hydrochloride (0.56mmol, Aldrich) following the procedure for **Compound 1**. **Compound 2** was obtained as a white solid (70%).

¹H NMR δ_{H} (400 MHz, CDCl₃) 7.43 (br., 1H), 7.03 (d, J = 8.3 Hz, 1H), 6.81 (d, J = 2.6 Hz, 1H), 6.73 (dd, J = 2.6 and 8.3 Hz, 1H), 4.62 (d, J = 6.1Hz, 2H), 3.79 (s, 3H),
 15 3.28 (d, J = 18.0 Hz, 1H), 2.96 (dd, J = 6.1 and 17.8 Hz, 1H), 2.48 – 2.56 (m, 2H), 2.46 (s, 3H), 2.08 – 2.15 (m, 1H), 1.55 (s, 3H), 1.5 – 1.54 (m, 1H); LC/MS, *m/z* = 261.1 [M + H]⁺ (Calc: 260.3).

EXAMPLE 3

2-(((6*R*,11*R*)-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)oxy)acetamide (Compound 3)



RA2 was prepared from **RA1** following the literature procedure (0.5g, 2.0mmol) (T. A. Montzka, and J. D. Matiskella US 3956336, May 11, 1976), and purified by column chromatography (Silica gel).

10 **RA2** (CHCl₃/MeOH 10/0.5, white solid, 0.35g): ¹H NMR δ_H (400 MHz, CDCl₃) 7.05 (d, J = 8.3Hz, 1H), 6.81 (d, J = 2.6 Hz, 1H), 6.73 (dd, J = 2.6 and 8.3 Hz, 1H), 3.79 (s, 3H), 3.76 – 3.78 (m, 1H), 3.19 (t, J = 5.5 Hz, 1H), 3.02 (d, J = 18.8 Hz, 1H), 2.82 (dd, J = 5.9 and 18.2Hz, 1H), 2.43 (s, 3H), 2.32 – 2.37 (m, 1H), 2.04 (dt, J = 3.1 and 12.2 Hz, 1H), 1.85 (dt, J = 4.8 and 12.9 Hz, 1H), 1.74 (br., s, 1H), 1.51 (s, 3H), 1.41 – 1.46 (m, 1H); LC/MS, *m/z* = 248.3 [M + H]⁺ (Calc: 247.3).

15

NaH (1mmol, 60% in mineral oil) was added to a solution of **RA2** (0.28mmol) in 2mL DMF at 0 °C under nitrogen. The reaction mixture was stirred at 0 °C for 1h, then a solution of ethyl 2-bromoacetate (60mg, in 1mL DMF) was added. The reaction mixture was warmed to RT for 24h. After aqueous work-up, the crude product **RA3**,
 20 LC/MS, *m/z* = 334.4 [M + H]⁺ (Calc: 333.4) was treated with ammonia (~ 7N in MeOH, 4mL) at 0 °C. The reaction mixture was shaken at RT for 48h, then concentrated and purified by reverse-phase prep HPLC (C18, 0-100% 0.1 % TFA in

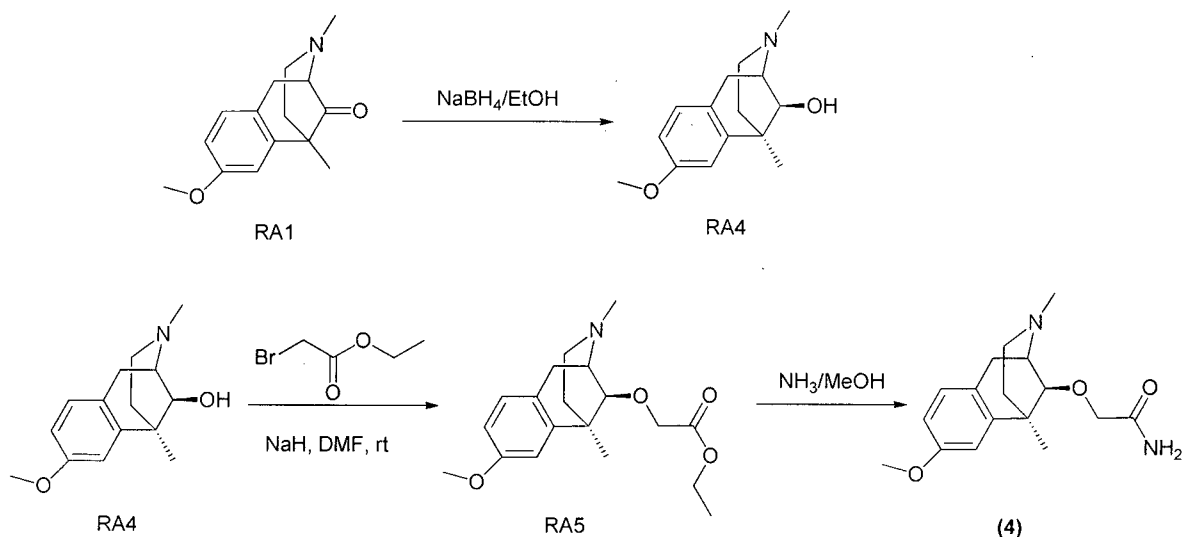
water/0.1 % TFA in ACN) to yield **Compound 3** (TFA-salt, white solid, 30mg, 36%).

^1H NMR δ_{H} (400 MHz, CD_3OD) 7.14 - 7.18 (m, 1H), 6.89 - 6.93 (m, 1H), 6.83 - 6.87 (m, 1H), 4.88 - 4.90 (m, 1H), 4.1 - 4.25 (m, 3H), 3.7 - 3.82 (m, 4H), 3.12 - 3.26 (m, 2H), 2.97 - 3.02 (m, 3H), 2.62 - 2.70 (m, 1H), 1.9 - 2.2 (m, 1H), 1.7 - 1.76 (m, 1H),
5 1.54 - 1.64 (m, 3H); LC/MS, m/z = 305.2 $[\text{M} + \text{H}]^+$ (Calc: 304.4).

EXAMPLE 4

2-(((6*R*,11*S*)-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)oxy)acetamide (**Compound 4**)

10



15 **RA4** was prepared from RA1 following the literature procedure (0.5g, 2.0mmol) (T. A. Montzka, and J. D. Matiskella US Patent No. 3956336, May 11, 1976), and purified by column chromatography (Silica gel).

RA4: ($\text{CHCl}_3/\text{MeOH}$ 10/0.3, white solid, 0.4g): ^1H NMR δ_{H} (400 MHz, CDCl_3) 7.02 (d, J = 8.6Hz, 1H), 6.85 (d, J = 2.6 Hz, 1H), 6.71 (dd, J = 2.6 and 8.5 Hz, 1H), 3.79 (s, 3H), 3.57 - 3.59 (m, 1H), 3.4 - 3.5 (br, 1H), 3.19 (d, J = 18.2 Hz, 1H), 3.11 - 3.14 (m, 1H), 2.77 (dd, J = 6.4 and 18.4Hz, 1H), 2.37 (s, 3H), 2.31 - 2.36 (m, 1H), 1.98 - 2.14
20

(m, 2H), 1.43 (s, 3H), 1.12 – 1.16 (m, 1H); LC/MS, m/z = 248.6 $[M + H]^+$ (Calc: 247.3).

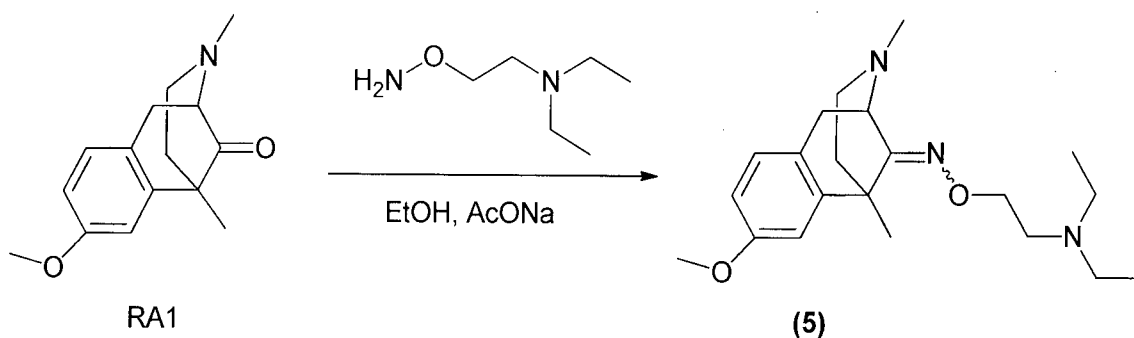
In a similar manner **Compound 4** (TFA-salt, white solid, 25mg, 30%) was prepared from RA4 following the procedure for **Compound 3**.

- 5 **Compound 4**: ^1H NMR δ_{H} (400 MHz, CD_3OD) 7.03 (d, J = 8.5Hz, 1H), 6.78 – 6.81 (m, 1H), 6.3 (dd, J = 2.4 and 8.3Hz, 1H), 4.74 – 4.75 (m, 1H), 4.06 – 4.44 (m, 4H), 3.67 (s, 1H), 3.34 – 3.46 (m, 4H), 2.97 – 3.02 (m, 3H), 3.02 – 3.12 (m, 1H), 2.74 – 2.84 (m, 1H), 2.08 – 2.22 (m, 1H), 1.44 – 1.54 (m, 4H); LC/MS, m/z = 305.2 $[M + H]^+$ (Calc: 304.4).

10

EXAMPLE 5

8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-one
***O*-(2-(diethylamino)ethyl) oxime (Compound 5)**



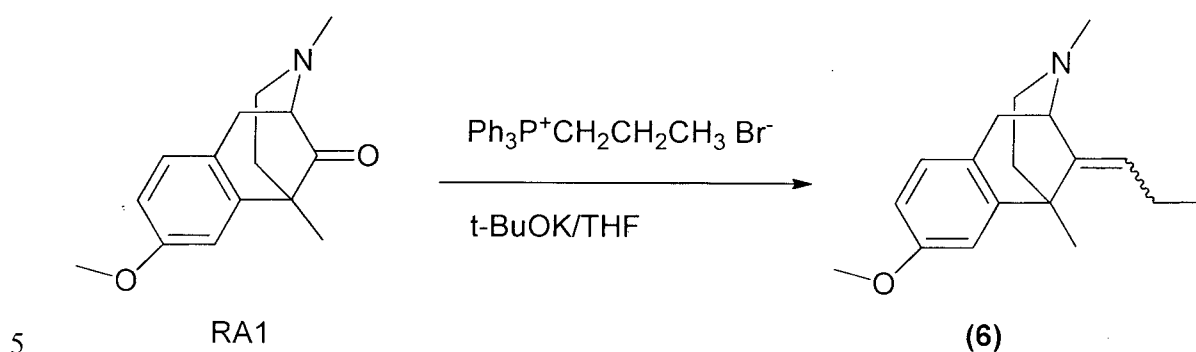
In a similar manner **Compound 5** (TFA-salt, yellow oil, 57%) was prepared from RA1 and *O*-(2-diethylamino-ethyl) hydroxylamine (Hulu Technology) following the procedure for **Compound 3**.

- 20 **Compound 5**: ^1H NMR δ_{H} (400 MHz, CD_3OD) 7.07 (d, J = 8.3 Hz, 1H), 6.83 (d, J = 2.4 Hz, 1H), 6.79 (dd, J = 2.4 and 8.6 Hz, 1H), 5.16 (d, J = 6.6 Hz, 1H), 4.4 (t, J = 5.1Hz, 2H), 3.69 (s, 3H), 3.4 – 3.48 (m, 3H), 3.24 – 3.31 (m, 1H), 3.14 – 3.18 (m, 5H), 2.9 – 2.94 (m, 1H), 2.89 (s, 3H), 2.12 – 2.18 (m, 1H), 1.79 – 1.83 (m, 1H), 1.57 (s, 3H), 1.2 (t, J = 7.1 Hz, 6H); LC/MS, m/z = 360.3 $[M + H]^+$ (Calc: 359.5).

25

EXAMPLE 6

8-methoxy-3,6-dimethyl-11-propylidene-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[d]azocine (Compound 6)

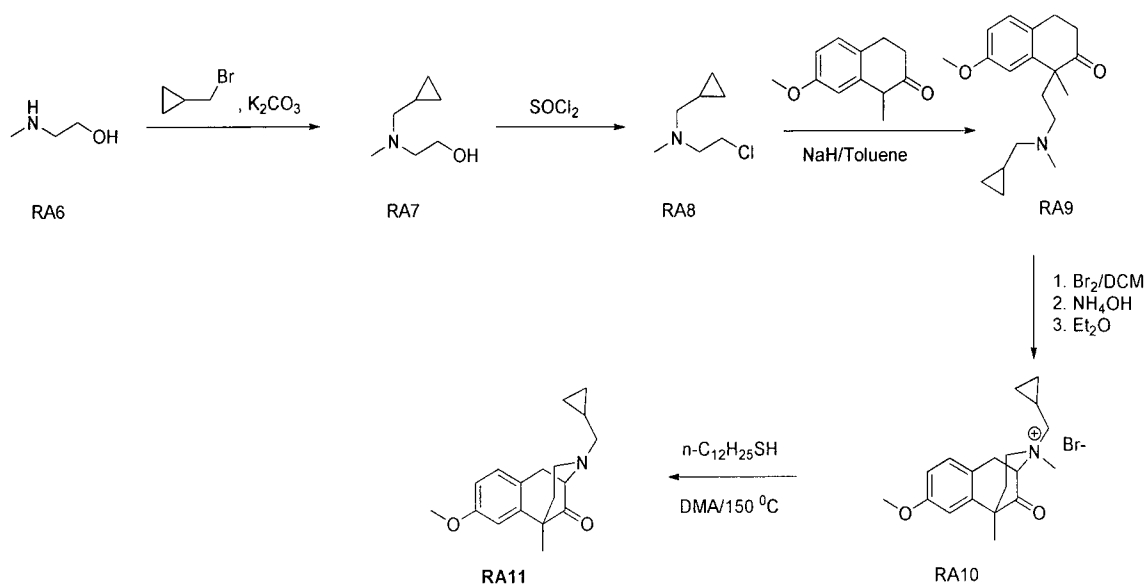


t-BuOK (1M in THF) was added to a mixture of RA1 (0.1g, 0.4mmol) and propyltriphenylphosphonium bromide (0.8mmol) in 5mL THF at rt. After stirring at
10 RT for 12h, the reaction was quenched with water (10mL), extracted with EtOAc (40mL), concentrated and purified by reverse-phase prep HPLC (C18, 0-100% 0.1 % TFA in water/0.1 % TFA in ACN) to yield **Compound 6** as yellow oil (TFA-salt, 80mg, 50%).

Compound 6: ¹H NMR δ_H (400 MHz, CD₃OD) 7.02 (dd, J = 8.5 and 8.6 Hz, 1H), 6.7
15 – 6.8 (m, 2H), 5.58 (dd, J = 7.2 and 7.4 Hz, 1H), 3.86 – 3.96 (m, 1H), 3.68 (s, 3H), 3.3 – 3.36 (m, 1H), 3.06 – 3.14 (m, 2H), 2.7 – 2.84 (m, 4H), 1.98 – 2.4 (m, 3H), 1.74 – 1.78 (m, 3H), 1.36 – 1.56 (m, 1H); LC/MS, *m/z* = 272.2 [M + H]⁺ (Calc: 271.4).

EXAMPLE 7

20 3-(cyclopropylmethyl)-8-methoxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[d]azocin-11-one (RA11)



- (Bromomethyl)cyclopropane (80g, 0.59mol, Combi_Blocks) was added dropwise to a suspension of compound RA6 (1.1mol, Aldrich) and K₂CO₃ (0.58mol) in CH₃CN/water (400mL/ 1mL) under nitrogen over 30 min at RT. The reaction mixture was heated at 50 °C for 24h. After cooling to RT, the reaction mixture was concentrated under vacuum (< 25 °C) to remove most of the solvent, then quenched with water (400mL), and extracted with EtOAc (2x300mL). The combined organic layer was washed with brine (100mL), concentrated and purified by column chromatography (silica gel, EtOAc/MeOH/NH₄OH 10/1.5/0.1) to give RA7 as a colorless oil (60g, 80%): ¹H NMR δ_H (400 MHz, CDCl₃) 3.45 (t, J = 5.4 Hz, 2H), 3.19 (br., 1H), 2.44 (t, J = 5.3 Hz, 2H), 2.22 (s, 3H), 2.2 (d, J = 6.6 Hz, 2H), 0.73 – 0.81 (m, 1H), 0.38 – 0.43 (m, 2H), -0.08 – 0.1 (m, 2H).
- Thionyl chloride (0.68mol, 50mL in 100mL CHCl₃) was added to a solution of RA7 (0.47mol, 60g in 400mL CHCl₃) at 0 °C over 2h. The reaction mixture was warmed to RT, and stirred at RT for 16 h. The reaction mixture was concentrated under vacuum to give a yellow oil, which was washed with Et₂O (100mL), and toluene (100mL). The solid was collected under argon, washed with hexanes, and dried under vacuum to give RA8 (HCl-salt, yellow solid, 75g): ¹H NMR δ_H (400 MHz, CD₃OD) 4.02 (dd, J = 1.1 and 6.1Hz, 2H), 3.75 (dt, J = 6.3 and 13.8 Hz, 1H), 3.56 (dt, J = 5.7

and 13.8 Hz), 3.22 (dd, $J = 7.4$ and 13.5 Hz, 1H), 3.14 (dd, $J = 7.3$ and 13.4 Hz, 1H), 3.01 (s, 3H), 1.15 – 1.22 (m, 1H), 0.78 – 0.82 (m, 2H), 0.46 – 0.52 (m, 2H). The HCl-salt (50g) was suspended in 200mL CHCl_3 under nitrogen, cooled with ice-water, and neutralized to pH ~ 9 with NH_4OH (14% aqueous). The CHCl_3 layer was separated,
5 washed with brine and concentrated under vacuum ($< 15^\circ\text{C}$) to give RA8 as a colorless oil (40g, used immediately).

7-Methoxy-1-methyl-2-tetralone (0.16mol in 100mL toluene) was added to a suspension of NaH (60%, 8g, 0.2mol) in 300mL toluene at 80°C over 1 h. After 1 h at 80°C , this reaction mixture was treated with RA8 (0.18mol, 26g in 60mL of
10 toluene), and continued at 80°C for 5 h. The reaction mixture was cooled to RT, and poured over to ice-water (300g). The aqueous layer was extracted with toluene (2x200mL). The combined toluene layer was washed with brine, concentrated under vacuum to about 300mL, cooled to 0°C with ice-water, and treated with 6N HCl (60mL aqueous). The reaction mixture was stirred at RT for 30min. The aqueous layer
15 was separated, cooled with ice-water, and neutralized with NH_4OH (14% aqueous solution) to pH ~ 9. The toluene layer was separated, washed with brine, concentrated, and purified by column chromatography (silica gel, DCM/MeOH 10/0.8) to give RA9 as a colorless oil (30g, 62%): ^1H NMR δ_{H} (400 MHz, CDCl_3) 7.10 (d, $J = 8.3$ Hz, 1H), 6.84 (d, $J = 2.6$ Hz, 1H), 6.76 (dd, $J = 2.6$ and 8.3 Hz, 1H), 3.82 (s, 3H), 3.06 (dt, $J =$
20 7.3 and 15.5 Hz, 1H), 2.96 (dt, $J = 6.1$ and 15.6 Hz, 1H), 2.66 (dd, $J = 6.1$ and 7.6 Hz, 2H), 2.5 (dt, $J = 8.3$ and 13.8 Hz, 1H), 2.1 – 2.14 (m, 4H), 1.98 – 2.05 (m, 3H), 1.76 – 1.82 (m, 1H), 1.42 (s, 3H), 0.64 – 0.72 (m, 1H), 0.39 – 0.43 (m, 2H), -0.01 – 0.02 (m, 2H).

Bromine (0.11mol, 17g in 20mL DCM and 8mL AcOH) was added to a
25 solution of RA9 (Yao-012d) (0.1mol, 30g in 200mL DCM and 10mL AcOH) over 30min at 0°C . The reaction mixture was warmed to RT over 4 h, and stirred at RT for 24 h. The reaction mixture was poured over ice-water (40g), and neutralized with NH_4OH (14% aqueous solution) to pH ~9. The organic layer was washed with brine, and concentrated under vacuum ($<20^\circ\text{C}$) to give a brown oil. Ether (100mL) was
30 added to the brown oil, and the mixture was stirred at RT under nitrogen for 4 h. The

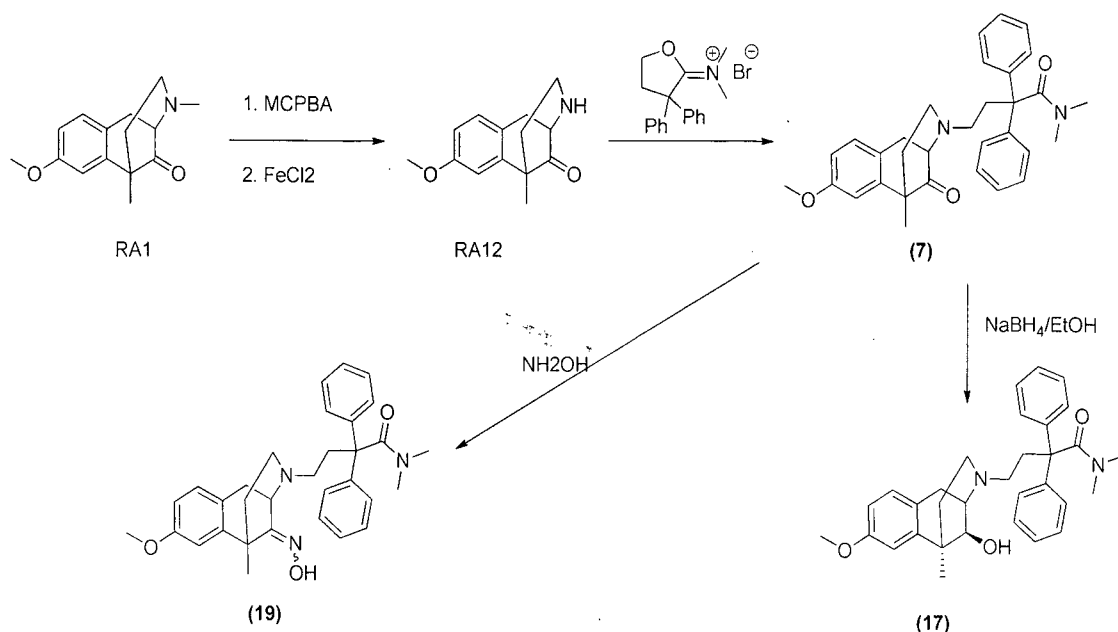
solid was collected under nitrogen, washed with Et₂O and dried under vacuum to give RA10 as a yellow solid (15g, 40%): ¹H NMR δ_H (400 MHz, CD₃OD) 7.2 – 7.4 (m, 1H), 6.93 – 6.97 (m, 1H), 6.89 – 6.91 (m, 1H), 4.42 (dt, J = 1.3 and 5.9 Hz, 0.3H), 4.27 (dt, J = 1.3 and 5.9 Hz, 0.7H), 3.94 – 3.98 (m, 1H), 3.78 – 3.81 (m, 1H), 3.45 – 3.65 (3H), 3.35 – 3.42 (m, 1.7H), 3.27 (m, 2.3H), 2.53 – 2.63 (m, 1H), 2.02 – 2.14 (m, 1H), 1.62 (s, 2.2H), 1.59 (s, 0.8H), 1.2 – 1.26 (m, 1H), 0.82 – 0.94 (m, 2H), 0.51 – 0.64 (m, 2H).

1-Dodecanethiol (25mmol, 6mL, Aldrich) was added to a suspension of RA10 (32mmol, 12g in 30mL DMA) at 150 °C under nitrogen over 2 min. After 30 min, the reaction mixture was cooled to RT, diluted with 200mL EtOAc, and washed with water (150mL, and 2N NaOH 25mL). The organic layer was washed with brine (100mL), concentrated and purified by column chromatography (EtOAc/hexane 2/11) to yield RA11 (yellow solid, 4.1g, 40%). ¹H NMR δ_H (400 MHz, CDCl₃) 6.91 (d, J = 8.3Hz, 1H), 6.63 (dd, J = 2.6 and 8.3 Hz, 1H), 6.61 (d, J = 2.4 Hz, 1H), 3.66 (s, 3H), 3.53 (d, J = 6.1 Hz, 1H), 3.32 (d, J = 17.6Hz, 1H), 2.98 (dd, J = 6.4 and 17.8 Hz, 1H), 2.64 (ddd, J = 1.5, 5.2 and 12.9 Hz, 1H), 2.35 (d, J = 6.6 Hz, 2H), 2.03 – 2.11 (m, 1H), 1.56 – 1.61 (m, 1H), 1.34 (s, 3H), 0.68 – 0.74 (m, 1H), 0.38 – 0.42 (m, 2H), -0.04 - 0.05 (m, 2H); LC/MS, *m/z* = 304.2 [M + H₂O + H]⁺ (Calc: 285.4).

20

EXAMPLE 8

4-(11,11-dihydroxy-8-methoxy-6-methyl-1,2,5,6-tetrahydro-2,6-methanobenzo[d]azocin-3(4*H*)-yl)-*N,N*-dimethyl-2,2-diphenylbutanamide (Compound 7); 4-((6*R*,11*S*)-11-hydroxy-8-methoxy-6-methyl-1,2,5,6-tetrahydro-2,6-methanobenzo[d]azocin-3(4*H*)-yl)-*N,N*-dimethyl-2,2-diphenylbutanamide (Compound 17); and 4-(11-(hydroxyimino)-8-methoxy-6-methyl-1,2,5,6-tetrahydro-2,6-methanobenzo[d]azocin-3(4*H*)-yl)-*N,N*-dimethyl-2,2-diphenylbutanamide (Compound 19)



MCPBA (2mmol, 85% pure, in 5mL of DCM) was added to a solution of RA1 (0.25g, 2mmol) in 4mL DCM at -5 to 0 °C. After 30 min, a solution of FeCl₂ (1M aqueous, 0.2mL) was added. The reaction mixture was stirred at 0 °C for 1h, and 2 h at RT. The reaction was quenched with NaOH (2N aqueous, 2mL). The organic layer was separated, and concentrated to yield crude RA12 as yellow oil {LC/MS, m/z = 232.4 [M + H₂O + H]⁺ (Calc: 231.3)}.

Dihydro-*N,N*-dimethyl-3,3-diphenyl-2(3H)-furaniminium bromide (0.2g, 0.58mmol) was added to a solution of RA12 (0.1g, 0.43mmol) and TEA (1 mmol) in CHCl₃ (2mL) at 0 °C. The reaction mixture was warmed to RT, and stirred at RT for 48 h. The reaction was quenched with NaOH (0.5N aqueous, 4mL). The organic layer was separated, concentrated and purified by HPLC to give **Compound 7** (TFA-salt, white solid, 20mg, 8% in two steps). ¹H NMR δ_H (400 MHz, CD₃CN) 10.2 (br., 1H), 7.24 – 7.38 (m, 10H), 6.98 (d, J = 8.5 Hz, 0.2H), 6.83 (d, J = 8.5 Hz, 0.8H), 6.62 – 6.78 (m, 2H), 3.62 (s, 3H), 3.42 (d, J = 6.0Hz, 1H), 2.18 – 3.05 (m, 15H), 1.3 – 1.42 (m, 4H); LC/MS, m/z = 515.2 [M + H₂O + H]⁺ (Calc: 496.6).

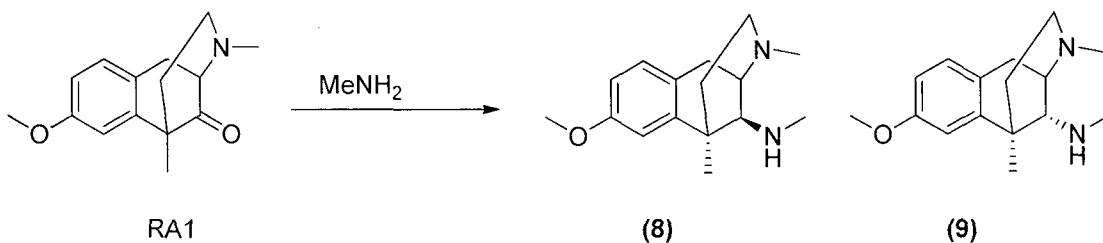
NaBH₄ (0.1g, 33mmol) was added to a solution of **Compound 7** (0.1g, 0.2mmol) in 4mL of EtOH at 0 °C. The reaction mixture was stirred at RT for 1h,

quenched with water, extracted with CHCl_3 , and purified by HPLC to yield **Compound 17** (TFA-salt, white solid, 40mg). ^1H NMR δ_{H} (400 MHz, CD_3OD) 7.28 – 7.46 (m, 10H), 6.9 – 6.94 (m, 1H), 6.66 – 6.8 (m, 2H), 3.7 – 3.75 (m, 1H), 3.64 – 3.66 (m, 3H), 3.44 – 3.48 (m, 1H), 2.93 – 3.15 (m, 6H), 2.3 – 2.75 (m, 6H), 2.25 (s, 3H), 1.23 – 1.45 (m, 4H); LC/MS, $m/z = 499.2$ $[\text{M} + \text{H}]^+$ (Calc: 498.7).

In a similar manner **Compound 19** was prepared from **Compound 7** (0.2mmol) and hydroxylamine hydrochloride (0.3mmol, Aldrich) following the procedure for **Compound 1**. **Compound 19** was purified by reverse-phase prep HPLC (C18, 0-100% 0.1 % TFA in water/0.1 % TFA in ACN) (white solid, TFA-salt, 40mg). ^1H NMR δ_{H} (400 MHz, CD_3OD) 7.22 – 7.42 (m, 10H), 7.02 (d, $J = 8.3$ Hz, 0.6H), 6.88 (d, $J = 8.3$ Hz, 0.4H), 6.67 – 6.8 (m, 2H), 5.02 – 5.07 (m, 1H), 3.64 (s, 3H), 3.22 – 3.25 (m, 1H), 3.0 – 3.05 (m, 2H), 2.87 (s, 3H), 2.4 – 2.8 (m, 5H), 2.22 (s, 3H), 1.56 – 1.96 (m, 2H), 1.52 (s, 1.2H), 1.42 (s, 1.8H); LC/MS, $m/z = 512.3$ $[\text{M} + \text{H}]^+$ (Calc: 511.7).

EXAMPLE 9

(6*R*,11*S*)-8-methoxy-*N*,3,6-trimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-amine (**Compound 8**); and (6*R*,11*R*)-8-methoxy-*N*,3,6-trimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-amine (**Compound 9**)



A mixture of RA1 (0.1g, 0.4mmol), MeNH_2 (2N in THF, 0.5mL, 1mmol), and 4A Molecular Sieve in CH_3CN (1mL) was shaken at RT. After 2 h, sodium triacetoxyborohydride (0.8mmol) was added, and the reaction mixture was shaken at

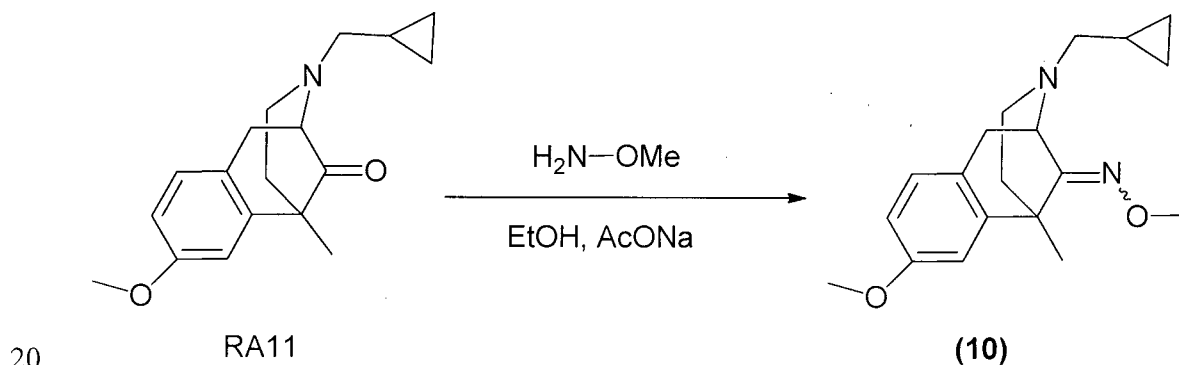
RT for 16 h. The reaction was quenched with NaOH (1N aqueous, 2mL), extracted with EtOAc (10mL), concentrated and purified by HPLC to yield **Compound 8** and **Compound 9**.

Compound 8 (white solid, TFA-salt, 15%, RT 0.865 min): ^1H NMR δ_{H} (400 MHz, CD₃OD) 7.55 (d, J = 8.9Hz, 1H), 6.95 – 6.99 (m, 2H), 4.38 (dd, J = 3.7 and 5.9 Hz, 1H), 3.8 – 3.86 (m, 4H), 3.48 (d, J = 20.1 Hz, 1H), 3.22 – 3.3 (m, 2H), 3.07 (s, 3H), 2.85 (s, 3H), 2.72 – 2.81 (m, 1H), 2.18 – 2.22 (m, 1H), 1.8 – 1.85 (m, 1H), 1.72 (m, 3H); LC/MS, m/z = 261.3 $[\text{M} + \text{H}]^+$ (Calc: 260.4).

Compound 9 (white solid, TFA-salt, 40%, RT 1.717 min): ^1H NMR δ_{H} (400 MHz, CD₃OD) 7.05 (d, J = 8.5Hz, 1H), 6.86 (d, J = 2.2 Hz, 1H), 6.76 (dd, J = 2.6 and 8.3 Hz, 1H), 3.78 – 3.8 (m, 1H), 3.68 (s, 3H), 3.28 – 3.38 (m, 2H), 3.04 (dd, J = 5.1 and 19.5 Hz, 1H), 2.74 – 2.8 (m, 1H), 2.72 (s, 3H), 2.63 (s, 3H), 2.32 – 2.4 (m, 1H), 2.02 – 2.1 (m, 1H), 1.48 (m, 3H), 1.4 – 1.43 (m, 1H); LC/MS, m/z = 261.3 $[\text{M} + \text{H}]^+$ (Calc: 260.4).

EXAMPLE 10

3-(cyclopropylmethyl)-8-methoxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[d]azocin-11-one *O*-methyl oxime (Compound 10)



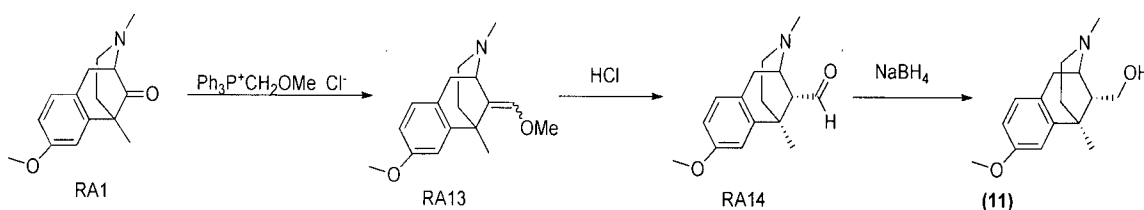
In a similar manner **Compound 10** was prepared from RA11 (0.1g, 0.35mmol) and *o*-methylhydroxylamine hydrochloride (0.5mmol, Aldrich) following the same procedure for **Compound 1**. **Compound 10** was purified by reverse-phase prep HPLC

25

(C18, 0-100% 0.1 % TFA in water/0.1 % TFA in ACN) (TFA-salt, white solid, 80%).
 ^1H NMR δ_{H} (400 MHz, CD_3OD) 7.05 (d, $J = 8.5\text{Hz}$, 1H), 6.83 (d, $J = 2.6\text{ Hz}$, 1H),
 6.78 (dd, $J = 2.6$ and 8.3 Hz , 1H), 5.33 (s, 1H), 3.86 (s, 3H), 3.68 (s, 3H), 3.0 – 3.38
 (m, 5H), 2.6 – 2.8 (m, 1H), 2.0 – 2.18 (m, 1H), 1.7 – 1.82 (m, 1H), 1.56 (s, 3H), 1.0 -
 5 1.04 (m, 1H), 0.66 – 0.71 (m, 2H), 0.36 – 0.41 (m, 2H); LC/MS, $m/z = 315.1$ $[\text{M} + \text{H}]^+$
 (Calc: 314.4).

EXAMPLE 11

10 ((6*S*,11*R*)-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-
 methanobenzo[*d*]azocin-11-yl)methanol (Compound 11)



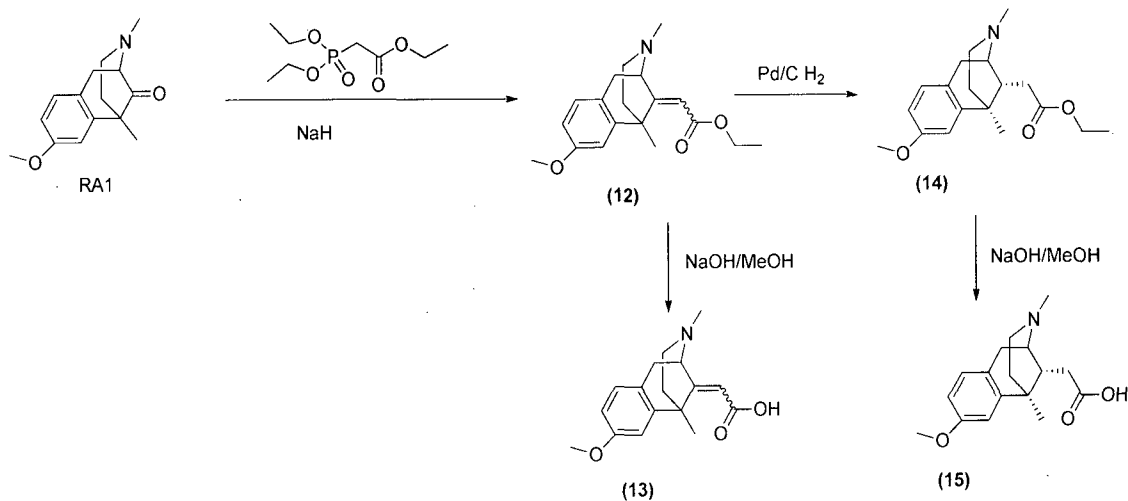
15 $t\text{-BuOk}$ (1M in THF, 2.2mL, 2.2mmol) was added to a solution of RA1 (0.3g,
 1.2mmol) and (methoxymethyl)triphenylphosphonium chloride (0.6g, 1.7 mmol,
 Aldrich) in 10mL of THF at RT. The reaction mixture was stirred at RT for 16 h. After
 aqueous work-up, the resulting mixture was extracted with EtOAc, and purified by
 column (silica gel, $\text{CHCl}_3/\text{MeOH}$ 10/0.3) to yield RA13 [yellow oil, 0.25g, LC/MS,
 20 $m/z = 274.2$ $[\text{M} + \text{H}]^+$ (Calc: 273.4)].

A mixture of RA13 (0.12g, 0.4mmol) and *p*-toluenesulfonic acid
 monohydrate (0.15g, 0.8mmol) in 5mL 1,4-di-oxane was shaken at RT for 2 h, then
 100 °C for 14 h. After cooling to 0 °C, the reaction mixture was diluted with EtOAc
 (15mL), and neutralized with saturated NaHCO_3 . The organic layer was concentrated
 25 to yield the crude RA14 [LC/MS, $m/z = 260.4$ $[\text{M} + \text{H}]^+$ (Calc: 259.3)], which was
 dissolved in 2mL EtOH and treated with NaBH_4 (50mg) at RT for 30min. The
 reaction was quenched with water, and purified by reverse-phase prep HPLC (C18, 0-
 100% 0.1 % TFA in water/0.1 % TFA in ACN) to yield **Compound 10** (TFA-salt,

white solid, 60mg, 42%). ^1H NMR δ_{H} (400 MHz, CD_3OD) 6.92 (d, $J = 8.5\text{ Hz}$, 1H), 6.65 (d, $J = 2.6\text{ Hz}$, 1H), 6.62 (dd, $J = 2.6$ and 8.5 Hz , 1H), 3.65 (dd, $J = 5.2$ and 13.3 Hz , 1H), 3.62 (s, 3H), 3.2 – 3.4 (m, 1H), 3.35 (dd, $J = 10.5$ and 11.8 Hz , 1H), 2.94 (d, $J = 18.3\text{ Hz}$, 1H), 2.64 (dd, $J = 5.9$ and 18.6 Hz , 1H), 2.34 – 2.39 (m, 1H), 2.32 (s, 3H),
 5 2.0 – 2.07 (m, 1H), 1.89 – 1.95 (m, 1H), 1.72 – 1.78 (m, 1H), 1.29 (s, 3H), 1.19 – 1.24 (m, 1H); LC/MS, $m/z = 262.4$ $[\text{M} + \text{H}]^+$ (Calc: 261.4).

EXAMPLE 12

(*Z*)-ethyl 2-(8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-ylidene)acetate (Compound 12); (*Z*)-2-(8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-ylidene)acetic acid (Compound 13); ethyl 2-((6*S*,11*R*)-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)acetate (Compound 14); and 2-((6*S*,11*R*)-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)acetic acid (Compound 15)



20 RA1 (0.8 mmol, 0.2g, in 3mL THF) was added to a mixture of triethyl phosphonoacetate (1.3mmol, 0.3g in 10mL THF) and NaH (5 mmol, 0.2g, 60% in mineral oil) at RT under argon. The reaction mixture was stirred at RT for 16 h. After

it was cooled to 0 °C, the reaction mixture was quenched with water (20mL), extracted with EtOAc (2x50mL). The combined organic layer was concentrated, and purified by reverse-phase prep HPLC (C18, 0-100% 0.1 % TFA in water/0.1 % TFA in ACN) to yield **Compound 12** (TFA-salt, white solid, 0.2g, 58%). ¹H NMR δ_H (400 MHz, CD₃OD) 7.12 (s, 1H), 6.93 (d, J = 2.3 Hz, 1H), 6.88 (dd, J = 2.6 and 8.5 Hz, 1H), 6.24 (d, J = 42.2 Hz, 1H), 5.91 (d, J = 4.8 Hz, 1H), 4.18 - 4.25 (m, 2H), 3.78 (s, 3H), 3.4 - 3.6 (m, 2H), 3.1 - 3.21 (m, 2H), 2.99 (s, 3H), 1.8 - 2.3 (m, 2H), 1.67(s, 3H), 1.27 - 1.31 (m, 3H); LC/MS, m/z = 316.2 [M + H]⁺ (Calc: 315.4).

NaOH (1 mmol, 2N in water, 0.5mL) was added to a solution of **Compound 12** (0.05mmol, 20mg, TFA-salt) in 2mL MeOH at 0 °C. The reaction mixture was shaken at RT for 5 h. The solvent was evaporated under vacuum, the residue was dissolved in 4mL CHCl₃, and neutralized to pH ~ 2 with 1N HCl. The organic layer was separated, concentrated, and purified by reverse-phase prep HPLC (C18, 0-100% 0.1 % TFA in water/0.1 % TFA in ACN) to give **Compound 13** as TFA-salt (white solid, 15mg, 80%). ¹H NMR δ_H (400 MHz, CD₃OD) 7.04 (d, J = 8.1Hz, 1H), 6.84 (d, J = 2.4 Hz, 1H), 6.78 (dd, J = 2.2 and 8.5 Hz, 1H), 6.14 (d, J = 35.3 Hz, 1H), 5.82 (d, J = 6.3 Hz, 1H), 3.68 (s, 3H), 3.24 - 3.5 (m, 2H), 3.0 - 3.16 (m, 2H), 2.89 (s, 3H), 1.8 - 2.2 (m, 2H), 1.58(s, 3H); LC/MS, m/z = 288.1 [M + H]⁺ (Calc: 287.4).

A mixture of **Compound 12** (0.1 mmol, 50mg, TFA-salt) and Pd/C (10%, 0.2g) in EtOH/CHCl₃ (2mL/6mL) was shaken under hydrogen (10PSI) for 12 h. The catalyst was filtered, and the product was purified by reverse-phase prep HPLC (C18, 0-100% 0.1 % TFA in water/0.1 % TFA in ACN) to give **Compound 14** (white solid, TFA-salt, 30mg).

¹H NMR δ_H (400 MHz, CD₃OD) 7.07 (d, J = 9.2 Hz, 1H), 6.75 - 6.77 (m, 2H), 4.04 - 4.07 (m, 2H), 3.74 - 3.77 (m, 1H), 3.69 (s, 3H), 3.03 - 3.15 (m, 3H), 2.86 (s, 3H), 2.59 - 2.66 (m, 1H), 2.41 - 2.46 (m, 2H), 1.89 - 2.07 (m, 2H), 1.58 - 1.63 (m, 1H), 1.37(s, 3H), 1.17 (t, J = 7.2 Hz, 3H); LC/MS, m/z = 318.1 [M + H]⁺ (Calc: 317.4).

In a similar manner **Compound 15** (TFA-salt, white solid)was prepared from **Compound 14** (0.05mmol) following the same procedure for **Compound 13**.

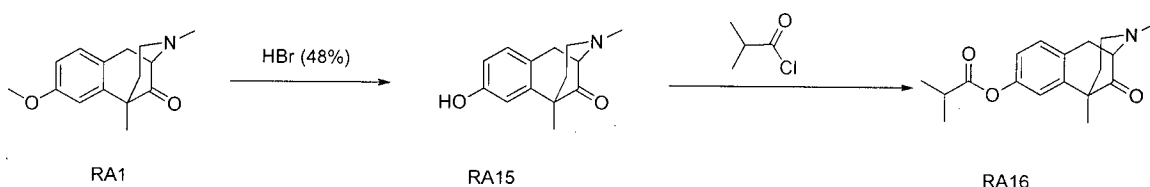
^1H NMR δ_{H} (400 MHz, CD_3OD) 7.07 (d, $J = 8.2$ Hz, 1H), 6.74 – 6.78 (m, 2H), 3.77 – 3.8 (m, 1H), 3.69 (s, 3H), 3.03 – 3.15 (m, 3H), 2.85 (s, 3H), 2.58 – 2.64 (m, 1H), 2.39 – 2.45 (m, 2H), 1.88 – 2.02 (m, 2H), 1.56 – 1.63 (m, 1H), 1.38 (s, 3H); LC/MS, $m/z = 290.1$ $[\text{M} + \text{H}]^+$ (Calc: 289.4).

5

EXAMPLE 13

3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[d]azocine-8,11,11-triol (RA15); and 11,11-dihydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[d]azocin-8-yl isobutyrate (RA16)

10



HBr (1.5mL 48% aqueous) was added to RA1 (0.8 mmol, 0.2g) at RT. The mixture was stirred under argon at 100 °C for 16 h. The reaction mixture was poured over ice-water, neutralized with NH_4OH (14% aqueous) to pH ~ 9, and extracted with CHCl_3 . The organic layer was concentrated and purified by reverse-phase prep HPLC (C18, 0-100% 0.1 % TFA in water/0.1 % TFA in ACN) to yield **RA15** (TFA-salt, 120mg, white solid).

^1H NMR δ_{H} (400 MHz, CD_3OD) 7.01 (d, $J = 8.2$ Hz, 0.6H), 6.92 (d, $J = 8.3$ Hz, 0.4H), 6.54 – 6.68 (m, 2H), 3.28 – 3.8 (m, 3H), 2.58 – 3.18 (m, 5H), 2.16 – 2.24 (m, 1H), 1.28 – 1.96 (m, 4H); LC/MS, $m/z = 250.2$ $[\text{M} + \text{H}]^+$ (Calc: 249.3).

Isobutyryl chloride (0.55mmol, 60mg) was added to a solution of crude RA15 (0.5mmol, 120mg) and triethylamine (1 mmol) in 3mL DCM at 0 °C. The reaction mixture was warmed to RT overnight. After aqueous work-up, the product was purified by flash column chromatography (silica gel, EtOAc/Hexanes 7/3) to yield 100mg of **RA16** as white solid (53%). ^1H NMR δ_{H} (400 MHz, CDCl_3) 7.15 (d, $J = 8.1$ Hz, 1H), 6.93 (dd, $J = 2.3$ and 8.3 Hz, 1H), 6.91 (d, $J = 2.2$ Hz, 1H), 3.56 (d, $J =$

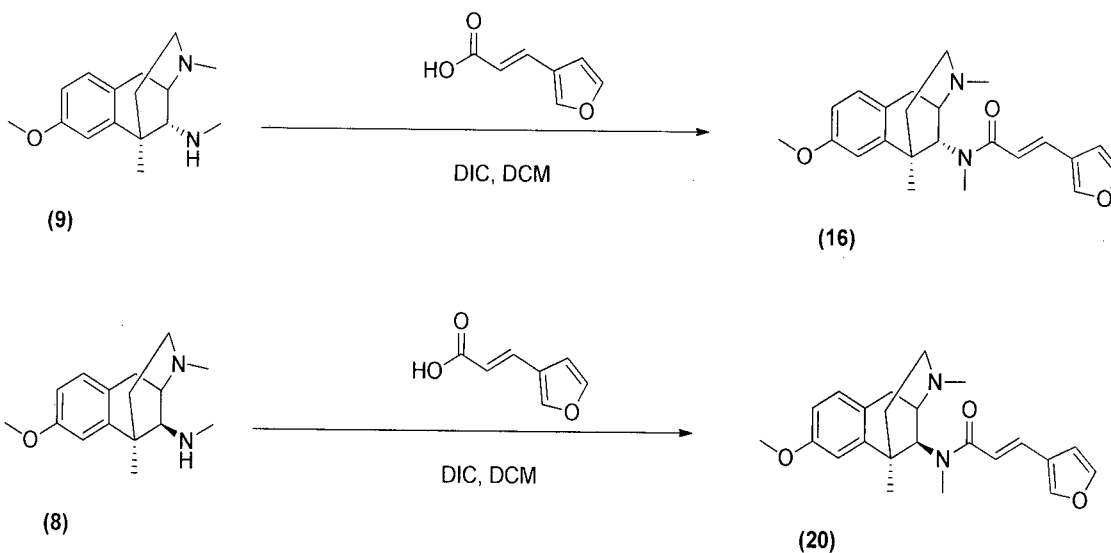
18.2 Hz, 1H), 3.39 (d, $J = 6.2$ Hz, 1H), 3.14 (dd, $J = 6.4$ and 18.2 Hz, 1H), 2.72 – 2.83 (m, 2H), 2.52 – 2.57 (m, 1H), 2.47 (s, 3H), 2.2 – 2.28 (m, 1H), 1.71 – 1.76 (m, 1H), 1.47 (s, 3H), 1.33 (s, 3H), 1.30 (s, 3H); LC/MS, $m/z = 320.2$ $[M + H]^+$ (Calc: 319.4).

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EXAMPLE 14

(*E*)-3-(furan-3-yl)-*N*-((6*R*,11*R*)-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-*N*-methylacrylamide (Compound 16); and (*E*)-3-(furan-3-yl)-*N*-((6*R*,11*S*)-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-*N*-methylacrylamide (Compound 20)

10



15

1,3- Diisopropylcarbodiimide (DIC, 0.12mmol, Aldrich) was added to a solution of **Compound 9** (0.1 mmol, 25mg), 3-(3-furyl)acrylic acid (0.12mmol) and 1-hydroxybenzotriazole (0.05mmol) in 4mL DCM at 0 °C. The reaction mixture was shaken at RT for 48 h. The solid was filtered, the filtrate was washed with NaOH (1N 1mL), and purified by reverse-phase prep HPLC (C18, 0-100% 0.1 % TFA in

20

water/0.1 % TFA in ACN) to yield 15mg of **Compound 16** (TFA-salt, white solid).

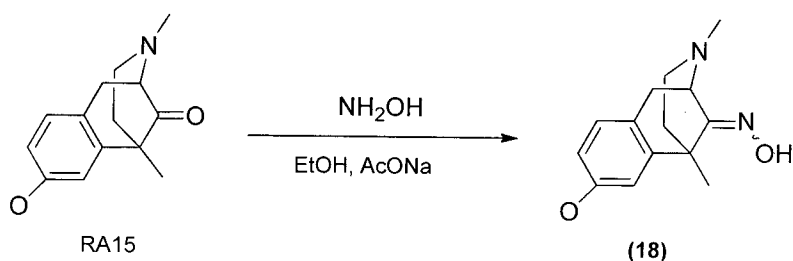
^1H NMR δ_{H} (400 MHz, CD_3OD) 7.75 (s, 1H), 7.48 (d, $J = 15.1$ Hz, 1H), 7.44 (s, 1H), 7.11 (d, $J = 8.6$ Hz, 1H), 6.86 (d, $J = 2.4$ Hz, 1H), 6.8 (dd, $J = 2.4$ and 8.3 Hz, 1H), 6.74 (s, 1H), 6.69 – 6.71 (m, 2H), 3.66 – 3.74 (m, 4H), 3.24 – 3.32 (m, 1H), 3.02 –

3.16 (m, 3H), 2.87 (s, 3H), 2.77 (s, 3H), 2.56 – 2.64 (m, 1H), 1.98 – 2.06 (m, 1H), 1.62 – 1.68 (m, 1H), 1.45 (s, 3H); LC/MS, m/z = 381.5 $[M + H]^+$ (Calc: 380.5).

In a similar manner **Compound 20** was prepared from **Compound 8** (0.1mmol) and 3-(3-furyl)acrylic acid (0.12mmol). The product was purified by reverse-phase prep HPLC (C18, 0-100% 0.1 % TFA in water/0.1 % TFA in ACN) (TFA-salt, white solid, 10mg). ^1H NMR δ_{H} (400 MHz, CD_3OD) 7.8 (s, 1H), 7.62 (d, J = 14.9 Hz, 1H), 7.44 (s, 1H), 7.05 (d, J = 8.3 Hz, 1H), 6.76 – 6.84 (m, 4H), 4.01 (s, 1H), 3.89 (s, 1H), 3.69 (s, 3H), 3.36 – 3.39 (m, 2H), 3.28 (s, 3H), 3.15 – 3.19 (m, 1H), 2.84 (s, 3H), 2.64 – 2.72 (m, 1H), 2.08 – 2.36 (m, 1H), 1.48 (s, 3H), 1.4 – 1.46 (m, 1H); LC/MS, m/z = 381.5 $[M + H]^+$ (Calc: 380.5).

EXAMPLE 15

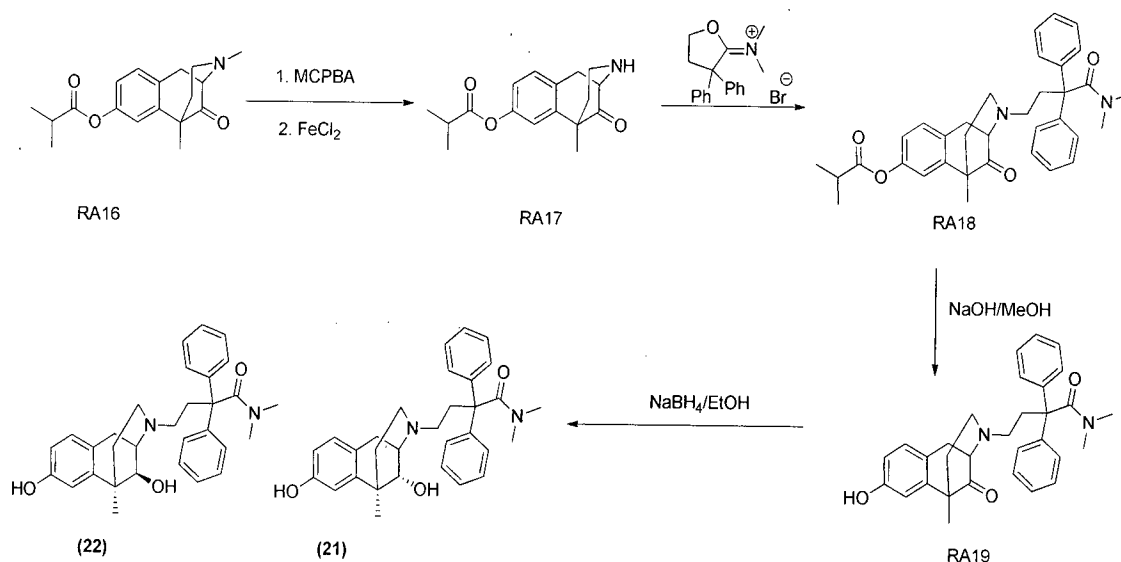
8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[d]azocin-11-one oxime (Compound 18)



In a similar manner **Compound 18** was prepared from RA15 (0.4 mmol) and hydroxylamine hydrochloride (0.6 mmol, Aldrich) following the procedure for **Compound 1**. **Compound 18** was purified by reverse-phase prep HPLC (C18, 0-100% 0.1 % TFA in water/0.1 % TFA in ACN) to obtain a brown oil (TFA-salt, 40%). ^1H NMR δ_{H} (400 MHz, CD_3OD) 7.96 (d, J = 8.6 Hz, 1H), 6.72 (d, J = 2.4 Hz, 1H), 6.63 (dd, J = 2.4 and 8.3 Hz, 1H), 5.24 (d, J = 5.9 Hz, 1H), 3.24 – 3.28 (m, 1H), 3.04 – 3.18 (m, 3H), 2.88 (s, 3H), 1.68 – 2.08 (m, 2H), 1.52 (s, 3H); LC/MS, m/z = 247.2 $[M + H]^+$ (Calc: 246.3).

EXAMPLE 16

4-((6*R*,11*R*)-8,11-dihydroxy-6-methyl-1,2,5,6-tetrahydro-2,6-methanobenzo[d]azocin-3(4*H*)-yl)-*N,N*-dimethyl-2,2-diphenylbutanamide (Compound 21); and 4-((6*R*,11*S*)-8,11-dihydroxy-6-methyl-1,2,5,6-tetrahydro-2,6-methanobenzo[d]azocin-3(4*H*)-yl)-*N,N*-dimethyl-2,2-diphenylbutanamide (Compound 22)



10

In a similar manner compound RA18 was prepared from RA16 following the procedure for **Compound 7**. The crude product RA18 {0.09mmol, 50mg, LC/MS m/z = 571.3 $[M + H_2O + H]^+$ (Calc: 552.7)} was dissolved in MeOH/water (1mL/1mL), and treated with HBr (48% aqueous, 0.1mL) at 65 °C for 4h. After cooling to RT, the product was purified by reverse-phase prep HPLC (C18, 0-100% 0.1 % TFA in water/0.1 % TFA in ACN) to yield RA19 {TFA-salt, 30mg, LC/MS m/z = 501.5 $[M + H_2O + H]^+$ (Calc: 482.6)}.

NaBH₄ (40mg, 1mmol) was added to a solution of RA19 (0.05 mmol, 30mg) in CHCl₃/EtOH (4mL/2mL) at 0 °C. The reaction mixture was stirred for 2 h at 0 °C ~ RT. After aqueous work-up, the product was purified by reverse-phase prep HPLC

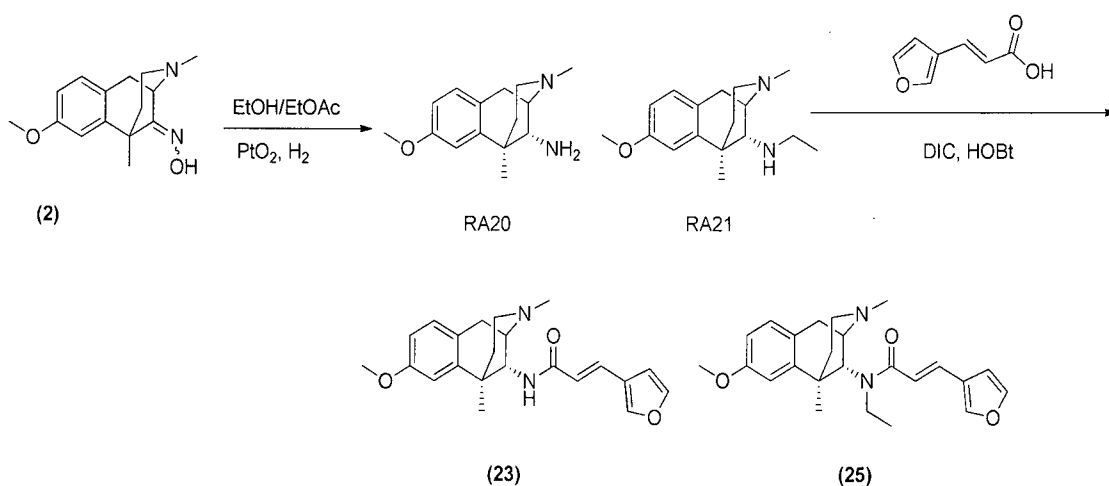
(C18, 0-100% 0.1 % TFA in water/0.1 % TFA in ACN) to yield **Compound 21** and **Compound 22**.

Compound 21 (white solid, 12mg, RT 2.734min): ^1H NMR δ_{H} (400 MHz, CD_3OD) 7.22 – 7.42 (m, 10H), 6.89 (d, $J = 8.3$ Hz, 0.1H), 6.81 (d, $J = 8.3$ Hz, 0.9H), 6.63 – 6.65 (m, 1H), 6.52 (dd, $J = 2.3$ and 8.1 Hz, 1H), 3.7 (d, $J = 3.7$ Hz, 1H), 3.48 (t, $J = 5.2$ Hz, 1H), 3.0 – 3.08 (m, 2H), 2.95 (s, 3H), 2.62 – 2.72 (m, 3H), 2.32 – 2.48 (m, 2H), 2.24 (s, 3H), 1.8 – 1.9 (m, 2H), 1.48 – 1.54 (m, 1H), 1.4 (s, 2.7 H), 1.33 (s, 0.3H); LC/MS, $m/z = 485.2$ $[\text{M} + \text{H}]^+$ (Calc: 484.6).

Compound 22 (white solid, 8mg, RT 2.901min): ^1H NMR δ_{H} (400 MHz, CD_3OD) 7.23 – 7.42 (m, 10H), 6.8 – 6.84 (m, 1H), 6.53 – 6.62 (m, 2H), 3.69 – 3.74 (m, 1H), 3.41 – 3.48 (m, 1H), 2.88 – 3.08 (m, 6H), 2.52 – 2.72 (m, 3H), 2.3 – 2.42 (m, 2H), 2.24 (s, 3H), 1.5 – 1.9 (m, 2H), 1.3 – 1.4 (m, 3H), 1.18 – 1.25 (m, 1H); LC/MS, $m/z = 485.2$ $[\text{M} + \text{H}]^+$ (Calc: 484.6).

EXAMPLE 17

(*E*)-3-(furan-3-yl)-*N*-((2*R*,6*R*,11*S*)-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)acrylamide (**Compound 23**); and (*E*)-*N*-ethyl-3-(furan-3-yl)-*N*-((2*R*,6*R*,11*S*)-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)acrylamide (**Compound 25**)



A mixture of **Compound 2** (0.2g, 0.7 mmol) and PtO₂ (25mg, 0.1 mmol) in AcOH (10mL) was shaken under H₂ (30PSI) for 30 h. CHCl₃ (100mL) was added, and the catalyst was filtered. The filtrate was neutralized to pH ~ 9 with NH₄OH (28% aqueous). The CHCl₃ layer was concentrated under vacuum to yield crude product

5 RA20, LC/MS, m/z = 247.5 [M + H]⁺ (Calc: 246.4); and RA21, LC/MS, m/z = 275.4 [M + H]⁺ (Calc: 274.4)].

1,3- Diisopropylcarbodiimide (DIC, 0.12mL, 0.8 mmol) was added to the above crude product, 3-(3-furyl)acrylic acid (0.11g, 0.8 mmol) and 1-hydroxybenzotriazole (0.07 mmol) in 4mL DCM at 0 °C. The reaction mixture was

10 shaken at RT for 14 h. The solid was filtered, the filtrate was washed with NaOH (1N 1mL), and purified by reverse-phase prep HPLC (C18, 0-100% 0.1 % TFA in water/0.1 % TFA in ACN) to yield **Compound 23** and **Compound 25**.

Compound 23 (TFA-salt, white solid, 20mg): ¹H NMR δ_H (400 MHz, CD₃OD) 7.68 (s, 1H), 7.36-7.41 (m, 2H), 7.11 (d, J = 8.3 Hz, 1H), 6.84 (d, J = 2.4 Hz, 1H), 6.81 (dd, J = 2.4 and 8.3 Hz, 1H), 6.48 (d, J = 2.2 Hz, 1H), 6.33 (d, J = 15.8 Hz, 1H), 4.26 (d, J = 2.6 Hz, 1H), 3.82 (s, 1H), 3.65 (s, 3H), 3.04 – 3.18 (m, 3H), 2.84 (s, 3H), 2.56 – 2.62 (m, 1H), 1.96 – 2.03 (m, 1H), 1.64 – 1.71 (m, 1H), 1.42 (s, 3H); LC/MS, m/z = 367.2 [M + H]⁺ (Calc: 366.4).

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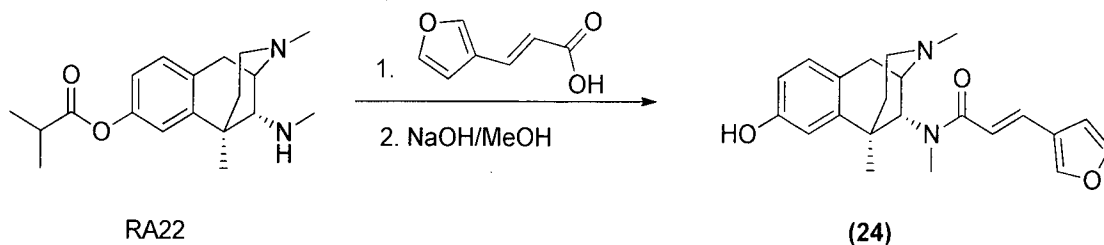
Compound 25 (TFA-salt, white solid, 30mg): ¹H NMR δ_H (400 MHz, CD₃OD) 7.76 (s, 1H), 7.52 (d, J = 15.2 Hz, 1H), 7.45 (s, 1H), 7.13 (d, J = 8.6 Hz, 1H), 6.8 – 6.91 (m, 2H), 6.68 (s, 1H), 6.63 (d, J = 15.2 Hz, 1H), 4.82 – 4.85 (m, 1H), 3.82 (s, 1H), 3.72 (s, 3H), 3.24 – 3.36 (m, 2H), 2.94 – 3.16 (m, 3H), 2.88 (s, 3H), 2.6 – 2.68 (m, 1H), 1.96 – 2.04 (m, 1H), 1.62 – 1.68 (m, 1H), 1.44 (s, 3H), 0.92 (t, J = 7.1Hz, 3H); LC/MS, m/z = 395.2 [M + H]⁺ (Calc: 394.5).

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EXAMPLE 18

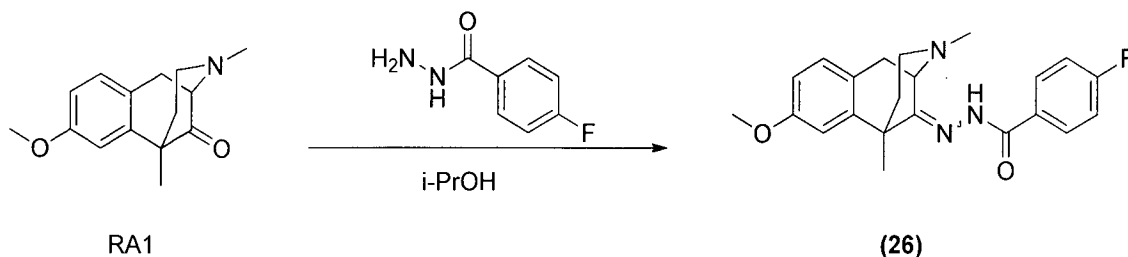
(E)-3-(furan-3-yl)-N-((2R,6R,11S)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[d]azocin-11-yl)-N-methylacrylamide (Compound 24)



1,3- Diisopropylcarbodiimide (DIC, 0.1g, 0.8 mmol) was added to a solution of
 5 RA22 (0.25g, 0.8 mmol), 3-(3-furyl)acrylic acid (0.2g, 1.4mmol) and 1-
 hydroxybenzotriazole (0.14 mmol) in 4mL DCM at 0 °C. The reaction mixture was
 shaken at RT for 14 h. The solid was filtered, the filtrate was washed with NaOH (1N
 1mL), and concentrated under vacuum. The residue was dissolved in 4mL MeOH, and
 treated with 0.5mL NaOH (2N aqueous) at RT for 14 h. After being concentrated
 10 under vacuum, the residue was dissolved in CHCl₃ (10mL), and neutralized to pH ~ 3
 with 1N HCl. The organic layer was concentrated and purified by reverse-phase prep
 HPLC (C18, 0-100% 0.1 % TFA in water/0.1 % TFA in ACN) to yield **Compound 24**
 (TFA-salt, white solid, 60mg). ¹H NMR δ_H (400 MHz, CD₃OD) 7.76 (s, 0.1H), 7.74
 (s, 0.9H), 7.47 (d, J = 15.1 Hz, 1H), 7.43 (s, 1H), 6.99 (d, J = 8.5 Hz, 1H), 6.68 – 6.76
 15 (m, 3H), 6.64 (dd, J = 2.2 and 8.3 Hz, 1H), 4.76 – 4.8 (m, 1H), 3.68 – 3.72 (m, 1H),
 2.98 – 3.16 (m, 3H), 2.86 (s, 3H), 2.78 (s, 3H), 2.58 – 2.64 (m, 1H), 1.98 – 2.05 (m,
 1H), 1.58 – 1.64 (m, 1H), 1.41 (s, 3H); LC/MS, *m/z* = 367.2 [M + H]⁺ (Calc: 366.4).

EXAMPLE 19

20 **4-fluoro-*N'*-((2*S*,6*R*)-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-
 methanobenzo[*d*]azocin-11-ylidene)benzohydrazide (Compound 26)**



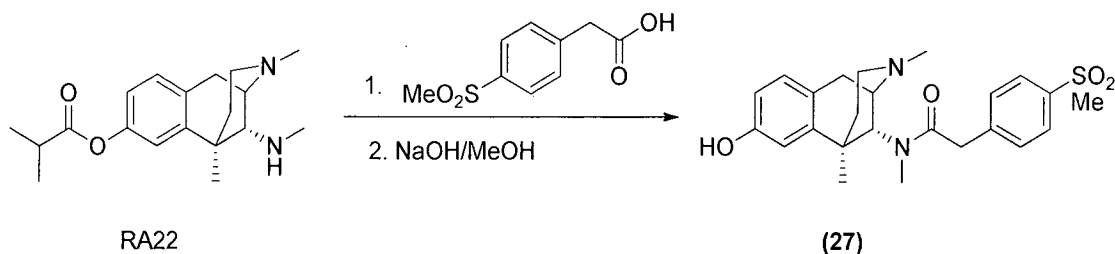
A mixture of RA1 (120mg, 0.48 mmol) and 4-fluorobenzhydrazide (0.52 mmol, 80mg, Oakwood) in *i*-PrOH/AcOH (2mL/0.2mL) was shaken at 60 °C for 3 h. The solvents were removed under vacuum, and the product was purified by reverse-phase prep HPLC (C18, 0-100% 0.1 % TFA in water/0.1 % TFA in ACN).

Compound 26 (TFA-salt, white solid, 30mg): ^1H NMR δ_{H} (400 MHz, CD_3OD) 7.8 (dd, $J = 5.2$ and 8.5 Hz, 2H), 7.14 (t, $J = 7.2$ Hz, 2H), 6.97 (d, $J = 8.3$ Hz, 1H), 6.79 (d, $J = 1.9$ Hz, 1H), 6.68 (dd, $J = 2.6$ and 8.3 Hz, 1H), 4.2 (d, $J = 5.9$ Hz, 1H), 3.68 (s, 3H), 3.24 – 3.3 (m, 1H), 2.98 – 3.04 (m, 1H), 2.44 – 2.48 (m, 2H), 2.36 (s, 3H), 2.0 – 2.08 (m, 1H), 1.58 (s, 3H), 1.2 – 1.54 (m, 1H); LC/MS, $m/z = 382.2$ [$\text{M} + \text{H}$] $^+$ (Calc: 381.4).

15

EXAMPLE 20

***N*-((2*R*,6*R*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-*N*-methyl-2-(4-(methylsulfonyl)phenyl)acetamide (Compound 27)**



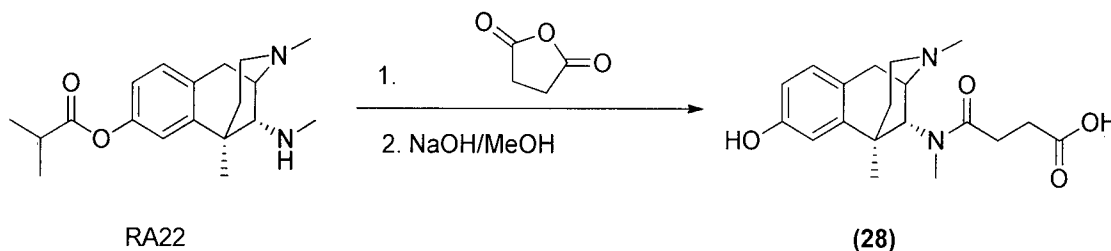
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In a similar manner, **Compound 27** was prepared following the procedure for **Compound 24** using 4-(methylsulfonyl)phenylacetic acid (Aldrich) instead of 3-(3-furyl)acrylic acid. **Compound 27** was purified by reverse-phase prep HPLC (C18, 0-100% 0.1 % TFA in water/0.1 % TFA in ACN) (TFA-salt, 30mg, white solid). ¹H NMR δ_H (400 MHz, CD₃OD) 7.8 – 7.86 (m, 2H), 7.5 (d, J = 8.5 Hz, 0.5H), 7.41 (d, J = 8.5 Hz, 1.5H), 6.96 – 7.01 (m, 1H), 6.68 – 6.74 (m, 1H), 6.6 – 6.65 (m, 1H), 4.6 – 4.9 (m, 1H), 3.64 – 3.96 (m, 3H), 3.24 – 3.32 (m, 1H), 3.0 – 3.1 (m, 6H), 2.6 – 2.86 (m, 6H), 1.94 – 2.2 (m, 1H), 1.58 – 1.62 (m, 1H), 1.38 – 1.44 (m, 3H); LC/MS, *m/z* = 443.1 [M + H]⁺ (Calc: 442.6).

10

EXAMPLE 21

4-(((2*R*,6*R*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)(methyl)amino)-4-oxobutanoic acid (**Compound 28**)



15

Succinic anhydride (50mg, 0.5 mmol) was added to a solution of RA22 (0.1g, 0.3 mmol) in CHCl₃ (2mL) at 0 °C. The reaction mixture was shaken at RT for 24 h. After aqueous work-up, the crude product was dissolved in 4mL of MeOH, and treated with 0.5mL NaOH (2N aqueous) at RT for 14 h. The solvent was removed under vacuum. The residue was dissolved in CHCl₃ (10mL), and neutralized to pH ~ 3 with 1N HCl. The organic layer was concentrated and purified by reverse-phase prep HPLC (C18, 0-100% 0.1 % TFA in water/0.1 % TFA in ACN) to yield **Compound 28** as TFA-salt (white solid, 30mg). ¹H NMR δ_H (400 MHz, CD₃OD) 6.98 (d, J = 8.3 Hz, 1H), 6.73 (d, J = 2.4 Hz, 1H), 6.63 (dd, J = 2.4 and 8.3 Hz, 1H), 4.62 – 4.9 (m, 1H), 3.58 – 3.82 (m, 1H), 2.9 – 3.18 (m, 4H), 2.83 (s, 3H), 2.65 (s, 3H), 2.5 – 2.57 (m, 4H),

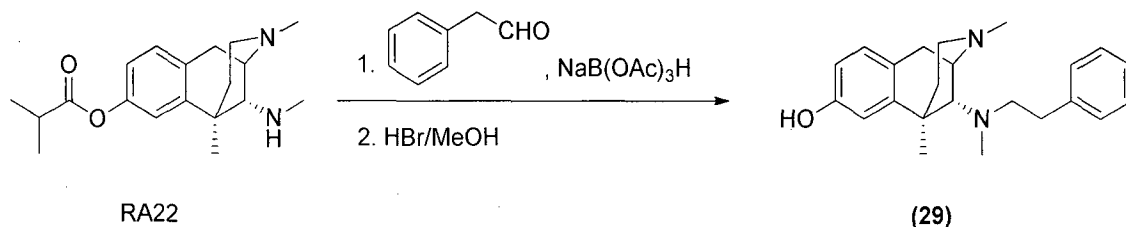
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1.92 – 2.02 (m, 1H), 1.57 – 1.62 (m, 1H), 1.36 – 1.45 (m, 3H); LC/MS, m/z = 347.1
 $[M + H]^+$ (Calc: 346.4).

EXAMPLE 22

- 5 **(2R,6R,11S)-3,6-dimethyl-11-(methyl(phenethyl)amino)-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[d]azocin-8-ol (Compound 29)**



10

A mixture of RA22 (0.15g, 0.47 mmol), phenylacetaldehyde (0.1g, 0.8 mmol), and 4A MS (0.2g) in 1mL CH₃CN was shaken at RT for 2 h. Then, NaB(OAc)₃H (0.2g, 0.9 mmol) was added. The reaction mixture was shaken at RT for 16 h. The solid was filtered, and washed with CHCl₃ (10mL). The filtrate was washed with water, and concentrated. The residue was dissolved in MeOH (4mL)/HBr (48% aqueous, 0.4mL), and the mixture was heated at 60 °C for 14 h. The solvent was evaporated under vacuum and purified by reverse-phase prep HPLC (C18, 0-100% 0.1 % TFA in water/0.1 % TFA in ACN) to yield **Compound 29** as TFA-salt (32mg, white solid). ¹H NMR δ_H (400 MHz, CD₃OD) 7.12 – 7.17 (m, 2H), 7.04 – 7.09 (m, 1H), 6.99 – 7.02 (m, 2H), 6.92 (d, J = 8.3 Hz, 1H), 6.68 (d, J = 2.6 Hz, 1H), 6.6 (dd, J = 2.6 and 8.3 Hz, 1H), 3.86 (s, 1H), 2.88 – 3.18 (m, 6H), 2.84 (s, 3H), 2.6 – 2.76 (m, 3H), 2.36 (s, 3H), 1.84 – 1.88 (m, 1H), 1.43 – 1.46 (m, 1H), 1.38 (s, 3H); LC/MS, m/z = 351.1 $[M + H]^+$ (Calc: 350.5).

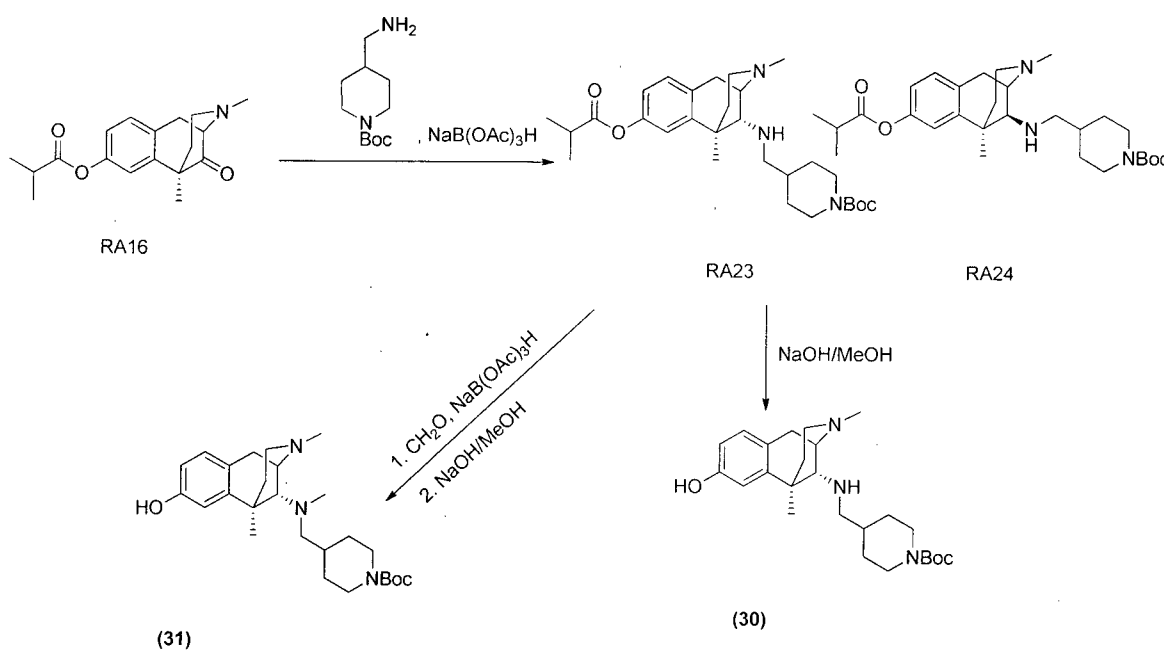
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EXAMPLE 23

tert-butyl 4-((((2R,6S,11R)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[d]azocin-11-yl)amino)methyl)piperidine-1-carboxylate

(Compound 30); and *tert*-butyl 4-(((2*R*,6*S*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)(methylamino)methyl)piperidine-1-carboxylate (Compound 31)



5

A mixture of RA16 (0.2g, 0.6 mmol), 1-Boc-4-(aminomethyl)piperidine (200mg, 0.9 mmol), and 4A MS in 1mL CH₃CN was shaken at RT for 2 h, then NaB(OAc)₃H (0.3g, 1.4 mmol) was added. The reaction mixture was shaken at RT for 16 h. The solid was filtered, and washed with CHCl₃ (10mL). The filtrate was washed with water, concentrated and purified by reverse-phase prep HPLC (C18, 0-100% 0.1 % TFA in water/0.1 % TFA in ACN) to give the desired product RA23 (100mg, RT 0.907min, and 90mg of RA24, RT 1.201min) as TFA-salt.

A mixture of RA23 (20mg, 0.04 mmol in 1mL of MeOH) and 2N NaOH aqueous (0.1mL) was shaken at RT for 24 h. After the reaction was quenched with TFA (2N in CH₃CN 0.1mL), the product was purified by reverse-phase prep HPLC (C18, 0-100% 0.1 % TFA in water/0.1 % TFA in ACN) to yield **Compound 30** as TFA-salt (white solid, 10mg). ¹H NMR δ_H (400 MHz, CD₃OD) 7.03 (d, J = 8.3 Hz, 1H), 6.73 (d, J = 2.4 Hz, 1H), 6.69 (dd, J = 2.4 and 8.3 Hz, 1H), 4.12 (s, 1H), 3.99 (d, J = 13.4 Hz, 2H), 3.58 (s, 1H), 3.24 – 3.3 (m, 1H), 3.1 – 3.18 (m, 2H), 2.94 (s, 3H), 2.9

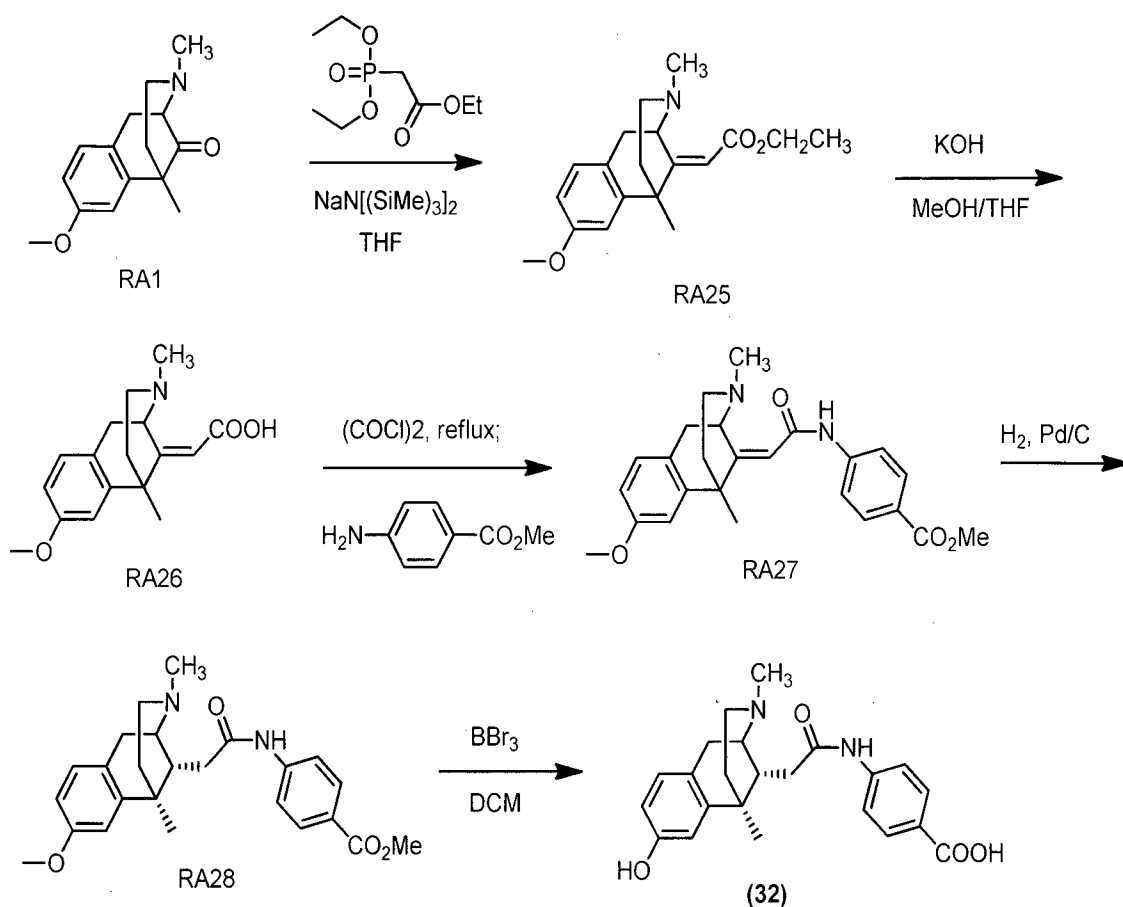
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(d, $J = 5.3$ Hz, 1H), 2.79 (dd, $J = 8.6$ and 12.5 Hz, 1H), 2.62 – 2.72 (m, 3H), 2.06 – 2.13 (m, 1H), 1.82 – 1.88 (m, 1H), 1.62 – 1.68 (m, 3H), 1.56 (s, 3H), 1.34 (s, 9H), 0.99 – 1.09 (m, 2H); LC/MS, $m/z = 430.2$ $[M + H]^+$ (Calc: 429.6).

NaB(OAc)₃H (80mg, 0.37 mmol) was added to a solution of RA23 (20mg, 0.04 mmol) and formaldehyde (36% aqueous, 0.05mL, 0.6 mmol) in 0.4mL CH₃CN at RT. The reaction mixture was shaken at RT for 12 h. The reaction was quenched with MeOH (2mL) and NaOH (2N aqueous, 0.4mL). The resulting mixture was shaken at RT for 24 h. After the solvents were evaporated under vacuum, the residue was dissolved in CHCl₃ (6mL), and neutralized to pH ~ 2 with TFA (2N in CH₃CN). The organic layer was concentrated and purified by reverse-phase prep HPLC (C18, 0-100% 0.1 % TFA in water/0.1 % TFA in ACN) to yield **Compound 31** as TFA-salt (white solid, 6mg). ¹H NMR δ_H (400 MHz, CD₃OD) 6.92 (d, $J = 8.6$ Hz, 1H), 6.69 (d, $J = 2.4$ Hz, 1H), 6.54 (dd, $J = 2.4$ and 8.3 Hz, 1H), 3.92 (d, $J = 12.9$ Hz, 2H), 3.82 (s, 1H), 3.02 – 3.18 (m, 4H), 2.86 (s, 3H), 2.56 – 2.68 (m, 3H), 2.36 – 2.42 (m, 2H), 2.05 (s, 3H), 1.82 – 1.86 (m, 1H), 1.56 – 1.65 (m, 3H), 1.46 – 1.52 (m, 1H), 1.44 (s, 3H), 1.34 (s, 9H), 0.76 – 0.88 (m, 2H); LC/MS, $m/z = 444.3$ $[M + H]^+$ (Calc: 443.6).

EXAMPLE 24

4-(2-((6*S*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)acetamido)benzoic acid (Compound 32); and 2-(2-((6*S*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)acetamido)benzoic acid (Compound 35)



To an ice-cooled solution of triethyl phosphonoacetate (112 mg, 1.2 eq, 0.54 mmol) in anhydrous THF (2 mL), sodium bis(trimethylsilyl)amide (1.0 M in THF, 0.68 mL, 1.5 eq, 0.68 mmol) was added dropwise. After stirring for 15 min, compound RA1 (104 mg, 0.42 mmol) in THF (1 mL) was slowly added. The resulting mixture was stirred at RT overnight, quenched with water (2 mL) and extracted with EtOAc (50 mL x 2). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated. The crude material was purified by flash column chromatography (silica gel, 0-50% EtOAc/hexanes) to give 89 mg of RA25 as an oil.

¹H NMR δ_H (400 MHz, CDCl₃) 7.05 (d, J = 8.55 Hz, 1H), 6.85 (d, J = 2.85 Hz, 1H), 6.77 (dd, J = 2.85 and 8.55 Hz, 1H), 5.93 (s, 1H), 5.23 (d, J = 5.92 Hz, 1H), 4.18 (m, 3H), 3.78 (s, 3H), 3.38 (m, 1H), 2.94 (dd, J = 6.36 and 18.20 Hz, 1H), 2.51 (m, 2H), 2.45 (s, 3H), 2.00 (m, 1H), 1.57 (m, 1H), 1.29 (t, J = 7.02 Hz, 3H).

LC/MS, *m/z* = 316 [M + H]⁺ (Calc: 315).

To a solution of compound RA25 (320 mg, 1 mmol) in MeOH/THF (2 mL, 1:1) was added KOH (2 mL, 2N in water). The resulting mixture was stirred at RT for 3 h and the MeOH evaporated. After cooling to 0°C, the solution was neutralized to pH = 4 by
5 using 1N HCl. The precipitate was filtered, washed with Et₂O, and dried to give 244 mg of RA26 as a white solid.

¹H NMR δ_H (400 MHz, DMSO-*d*₆) 12.90 (br s, 1H), 7.11 (d, J = 8.55 Hz, 1H), 6.90 (d, J = 2.63 Hz, 1H), 6.86 (dd, J = 8.55 Hz, 1H), 6.07 (br s, 1H), 5.59 (d, J = 6.36 Hz, 1H), 3.75 (s, 3H), 3.60 (m, 1H), 3.20-3.40 (m, 3H), 2.15 (m, 1H), 1.71 (m, 1H), 1.58 (s,
10 3H).

LC/MS, *m/z* = 288 [M + H]⁺ (Calc: 287).

To a round-bottomed flask were added RA26 (200 mg, 0.70 mmol), oxalyl chloride (2 mL) and 1-2 drops of DMF. The resulting mixture was heated to reflux for 30 min,
15 then the oxalyl chloride was removed in vacuo. The residue was dissolved in anhydrous DCM (4 mL) and methyl 4-aminobenzoate (88 mg, 1.2 eq, 0.84 mmol) and diisopropylethylamine (DIEA, 1 mL) were added. The mixture was stirred at RT overnight and then concentrated. The crude material was purified by flash column chromatography (silica gel, 0-5% MeOH/DCM) to give 222 mg of RA27 as a brown
20 foam.

LC/MS, *m/z* = 421 [M + H]⁺ (Calc: 420).

To a solution of RA27 (200 mg, 0.48 mmol) in MeOH (5 mL) was added 10% Pd in charcoal (50 mg). The reaction bottle was sealed, de-gassed, and then subjected to a H₂
25 balloon. After stirring at RT overnight, the solution was filtered and concentrated to give RA28. The crude material was used directly in the next step without further purification.

¹H NMR δ_H (400 MHz, DMSO-*d*₆) 10.41 (br s, 1H), 7.91 (d, J = 8.77 Hz, 2H), 7.27 (d, J = 8.77 Hz, 2H), 7.16 (d, J = 8.11 Hz, 1H), 6.88 (m, 2H), 3.82 (s, 3H), 3.75 (s, 3H),
30 3.70 (m, 1H), 2.93-3.25 (m, 4H), 2.81 (s, 3H), 2.71 (m, 1H), 2.39-2.57 (m, 2H), 2.13 (m, 1H), 1.99 (m, 1H), 1.56 (d, J = 14.25 Hz, 1H), 1.40 (s, 3H).

LC/MS, $m/z = 423$ $[M + H]^+$ (Calc: 422).

To a dry ice-cooled solution (-78°C) of RA28 (200 mg, 0.47 mmol) in DCM (4 mL) was added BBr_3 (0.5 mL in DCM). The reaction mixture was slowly warmed to room temperature over 3 h, and then quenched with sat. NH_4Cl (1 mL). After evaporation of the DCM, the residue was dissolved in MeOH (2 mL) and purified by reverse phase column chromatography (C18, ACN/water with 0.1% TFA, 0-95%) to give 79 mg of **Compound 32 TFA salt** as a white powder.

^1H NMR δ_{H} (400 MHz, MeOD) 10.02 (s, 1H), 7.87 (m, 2H), 7.57 (m, 2H), 7.00 (d, $J = 8.33$ Hz, 1H), 6.71 (d, $J = 2.41$ Hz, 1H), 6.63 (dd, $J = 2.41$ and 8.33 Hz, 1H), 3.78 (m, 1H), 3.03-3.16 (m, 3H), 2.86 (s, 3H), 2.16 (m, 1H), 1.95 (dt, $J = 4.82$ and 14.25 Hz, 1H), 1.61 (m, 1H), 1.40 (s, 3H).

LC/MS, $m/z = 395$ $[M + H]^+$ (Calc: 394).

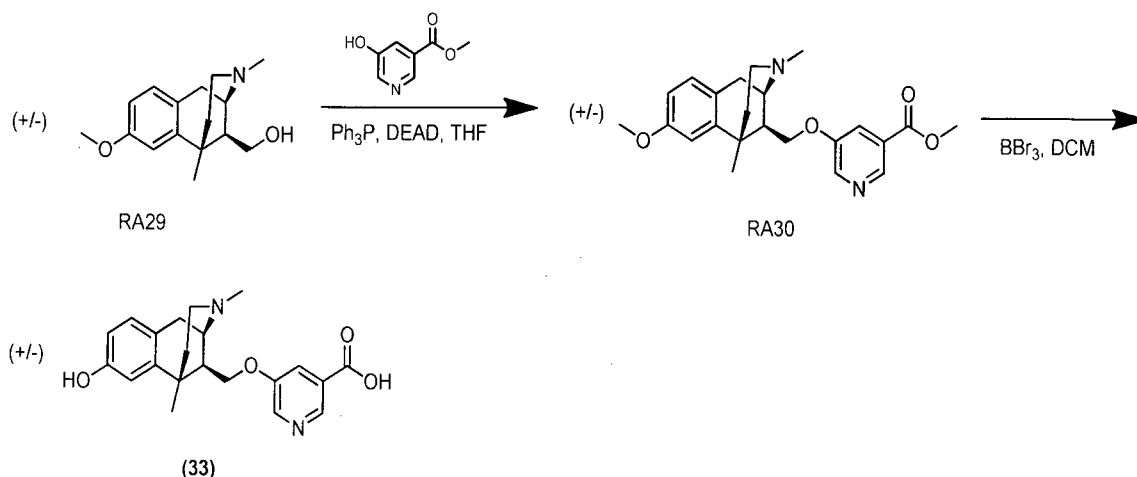
In a similar manner **2-(2-((6*S*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)acetamido)benzoic acid (Compound 35)** was prepared from RA26 using methyl 2-aminobenzoate rather than methyl 4-aminobenzoate. Purification by reverse phase column chromatography (C18, ACN/water with 0.1% TFA, 0-95%) gave **Compound 35 TFA salt** as a white powder.

^1H NMR δ_{H} (400 MHz, MeOD) 8.37 (d, $J = 8.33$ Hz, 1H), 7.96 (dd, $J = 1.53$ and 8.11 Hz, 1H), 7.46 (dt, $J = 1.53$ and 7.23 Hz, 1H), 7.07 (dt, $J = 1.10$ and 7.23 Hz, 1H), 6.99 (d, $J = 8.11$ Hz, 1H), 6.69 (d, $J = 2.63$ Hz, 1H), 6.63 (dd, $J = 2.63$ and 8.33 Hz, 1H), 3.78 (m, 1H), 3.06-3.18 (m, 3H), 2.84 (s, 3H), 2.49-2.70 (m, 3H), 2.12 (m, 1H), 1.93 (m, 1H), 1.59 (d, $J = 13.81$ Hz, 1H), 1.40 (s, 3H).

LC/MS, $m/z = 395$ $[M + H]^+$ (Calc: 394).

EXAMPLE 25

5-(((2*R*,6*S*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)methoxy)nicotinic acid (Compound 33); 3-(((2*R*,6*S*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)methoxy)benzoic acid (Compound 41)



To a mixture of Ph_3P (0.262 g, 1.00 mmol, 1.5 eq) in THF (5 mL) was added diethyl azodicarboxylate (DEAD) (40% in toluene, 0.45 mL, 0.99 mmol, 1.5 eq). This was stirred for 2 min then methyl 5-hydroxynicotinate (0.106 g, 0.692 mmol, 1.05 eq) was added. After 2 more min a solution of compound RA29 (0.172 g, 0.658 mmol, 1 eq) in THF (5 mL) was added. After stirring overnight the reaction mixture was chromatographed over silica gel with 0-25% EtOAc in hexanes. The product fractions were evaporated in vacuo to give the product RA30 as a tan solid (0.141 g). LC/MS, $m/z = 397 [\text{M} + \text{H}]^+$ (Calc: 396).

Compound RA30 (0.141 g, 0.356 mmol) was suspended in DCM (5 mL) and cooled on an ice-salt bath. BBr_3 (0.32 mL, 3.3 mmol, 9 eq) was added. The ice-salt bath was removed after 10 min and the reaction stirred for 3 days. The reaction mixture was diluted with an additional 10 mL DCM and quenched with 5 mL 5N NaOH. The layers were separated and the aqueous portion washed once more with 10 mL DCM. The combined organics were back extracted once with 5 mL water and the second aqueous portion combined with the first aqueous portion. The aqueous portion was adjusted to pH ~ 7 with 5N HCl then evaporated in vacuo. The residue was triturated with 15 mL ACN, filtered and washed successively with 10 mL ACN then twice with 10 mL MeOH. The filtrates were evaporated in vacuo to a residue, acidified with TFA and purified via reverse-phase chromatography (C18, ACN /water with 0.1% TFA, 0-

50%). The product fractions were frozen and lyophilized to give the product **Compound 33 TFA salt** as a cream-colored powder (0.046 g).

¹H NMR δ_H (400 MHz, DMSO-*d*₆) 13.57 (br s, 1H), 9.32 (br s, 1H), 9.17 (br s, 1H), 8.72 (d, J = 1.5 Hz, 1H), 8.61 (d, J = 2.9 Hz, 1H), 7.95 (dd, J = 2.9, 1.8 Hz, 1H), 7.02 (d, J = 8.3 Hz, 1H), 6.80 (d, J = 2.4 Hz, 1H), 6.68 (dd, J = 8.3, 2.4 Hz, 1H), 4.52-4.43 (m, 2H), 4.14 (br d, J = 5.0 Hz, 1H), 3.37-3.29 (m, 1H), 3.22-3.14 (m, 1H), 3.14-3.06 (m, 1H), 2.86 (d, J = 4.4 Hz, 3H), 2.57-2.43 (m, 2H), 2.11 (dt, J = 14.0, 3.9 Hz, 1H), 1.46-1.38 (m, 4H).

LC/MS, m/z = 369 [M + H]⁺ (Calc: 368).

10

In a similar manner **3-(((2*R*,6*S*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)methoxy)benzoic acid (Compound 41)** was prepared from RA29 using methyl 3-hydroxybenzoate rather than methyl 5-hydroxynicotinate. Purification by reverse-phase chromatography (C18, ACN /water with 0.1% TFA, 0-60%) gave **Compound 41 TFA salt** as a white powder.

15

¹H NMR δ_H (400 MHz, DMSO-*d*₆) 13.08 (br s, 1H), 9.31 (s, 1H), 9.10 (br s, 1H), 7.62-7.60 (m, 1H), 7.60-7.57 (m, 1H), 7.46 (t, 1H), 7.33-7.29 (m, 1H), 7.02 (d, J = 8.3 Hz, 1H), 6.80 (d, J = 2.4 Hz, 1H), 6.67 (dd, J = 8.1, 2.4 Hz, 1H), 4.43-4.34 (m, 2H), 4.13 (br d, J = 4.6 Hz, 1H), 3.36-3.28 (m, 1H), 3.23-3.14 (m, 1H), 3.12-3.05 (m, 1H), 2.87 (d, J = 4.6 Hz, 3H), 2.53-2.43 (m, 2H), 2.09 (dt, J = 13.8, 4.6 Hz, 1H), 1.46-1.37 (m, 4H).

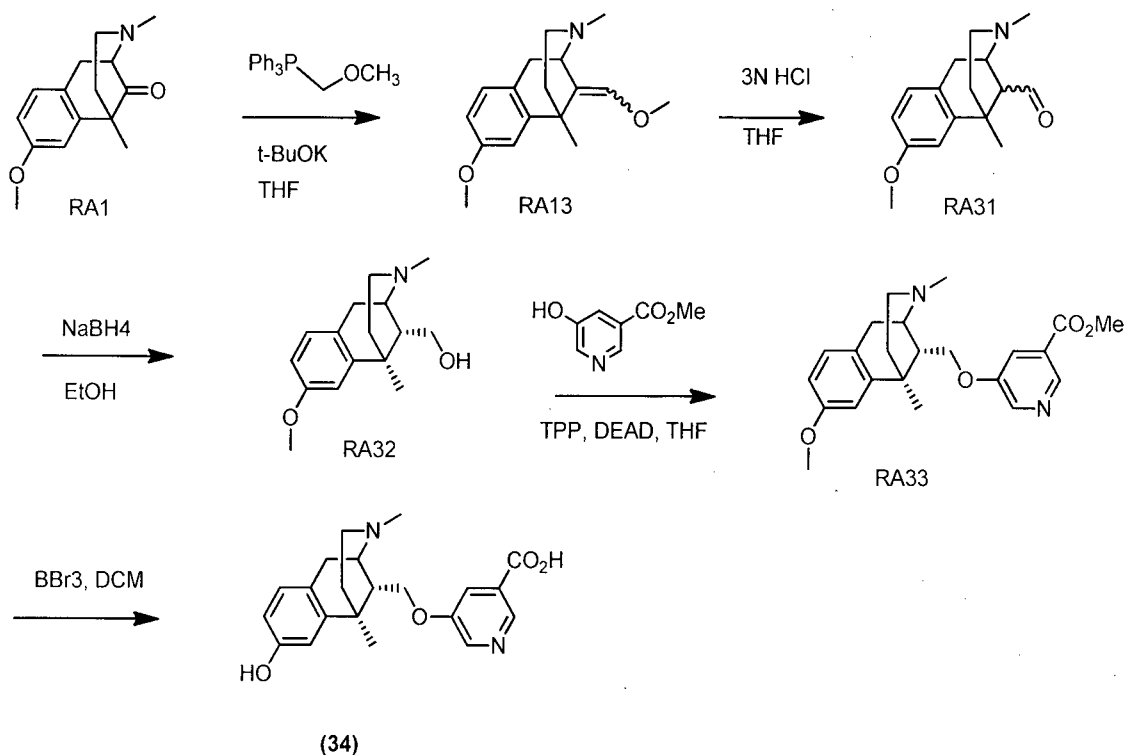
20

LC/MS, m/z = 368 [M + H]⁺ (Calc: 367).

25

EXAMPLE 26

5-(((6*S*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)methoxy)nicotinic acid (Compound 34)



To a solution of compound RA1, (5.00 g, 20.41 mmol, 1 eq) and (methoxymethyl)triphenylphosphonium chloride (9.79 g, 28.57 mmol, 1.4 eq) in THF (148 mL) cooled in an ice bath was added potassium t-butoxide (36.7 mL of a 1M solution in THF, 36.7 mmol). The ice bath was removed and the mixture was stirred at room temperature for 5 h.

The reaction mixture was poured onto cold H₂O and extracted twice with EtOAc, washed with brine, concentrated and purified by flash chromatography (silica gel, 50-100% EtOAc in hexane followed by 10-30% MeOH in DCM) to afford 4.08 g of RA13 as a syrup.

LC/MS, $m/z = 274$ $[M + H]^+$ (Calc: 273).

To a solution of RA13 (2.78 g, 10.18 mmol, 1.0 eq) in THF (25 mL) was added 3N HCl (34 mL, 101.8 mmol, 10.0 eq). The mixture was stirred for 6 h at 50 °C and then it was poured onto cold H₂O (50 mL) and 2M NaOH (50 mL) was added to adjust the pH to 8. The mixture was extracted twice with DCM, dried over Na₂SO₄ and concentrated to afford 2.1 g of RA14 as a mixture of isomers. LC/MS, $m/z = 260$ $[M + H]^+$ (Calc: 259).

To a solution of RA14 (3.34 g, 12.85 mmol, 1.0 eq) in EtOH (36 mL) at 0 °C was added NaBH₄ (0.53 g, 14.13 mmol, 1.1 eq). The mixture was stirred for 10 min, H₂O (10 mL) was added, the EtOH was removed under reduced pressure and the organic
5 portion was extracted with DCM, dried over Na₂SO₄ and concentrated to 2.6 g of a light yellow solid as a mixture of diastereomers which was purified by flash column chromatography (silica gel, 5-25% MeOH (1N NH₃)/ DCM) to afford 1.48 gm of RA32 as the more polar isomer.

¹H NMR δ_H (300 MHz, DMSO-d₆) 7.00 (d, J = 7.9 Hz, 1H), 6.69-6.65 (m, 2H), 4.39
10 (t, J = 4.82 Hz, 1H), 3.69 (s, 3H), 3.56-3.50 (m, 1H), 3.10 (m, 1H), 2.98-2.92 (m, 1H), 2.88 (d, J = 19.1 Hz, 1H), 2.55-2.48 (m, 1H), 2.30 (m, 1H), 2.27 (s, 3H), 1.94-1.81 (m, 2H), 1.70 (td, J = 4.4, 12.3 Hz, 1H), 1.30 (s, 3H), 1.18 (d, J = 13.4 Hz, 1H), LC/MS, m/z = 262 [M + H]⁺ (Calc: 261).

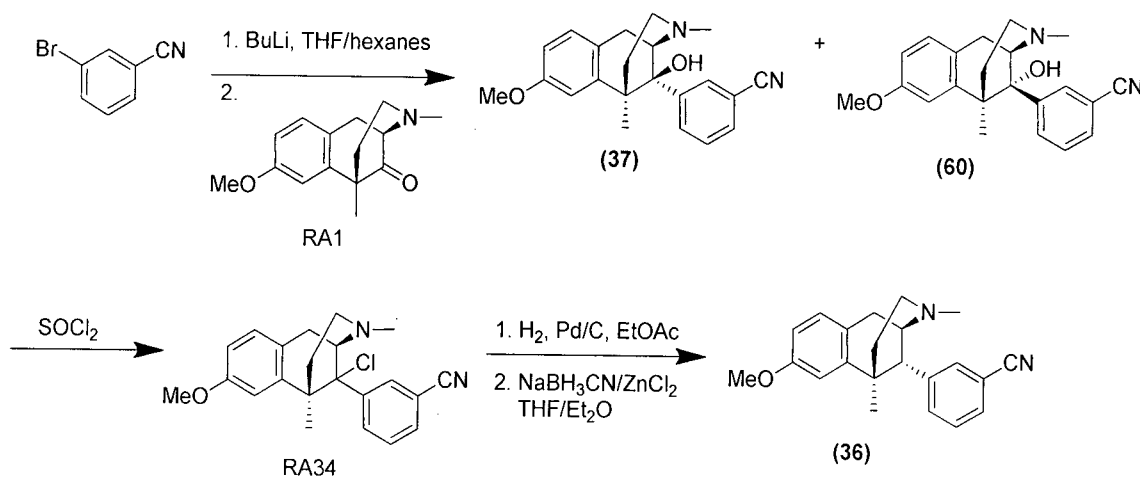
15 To a mixture of RA32 (0.319 g, 1.22 mmol, 1.0 eq), methyl-5-hydroxy-3-pyridine carboxylate (0.46 g, 3.63 mmol, 3.0 eq), and triphenylphosphine (0.80 g, 3.63 mmol, 3.0 eq) in THF (6.4 mL) at 0 °C was added DEAD (1.58 g, 3.63 mmol, 3.0 eq). The ice bath was removed and the mixture was stirred for 16 h. H₂O was added and the organic
20 portion was extracted twice with EtOAc, dried over Na₂SO₄ and concentrated to 2.2 g of a crude mixture which was purified by flash column chromatography (silica gel, 5-25% MeOH (1N NH₃) in DCM) to afford 0.090 g of RA33. LC/MS, m/z = 397 [M + H]⁺ (Calc: 396).

A solution of RA33 (0.042 g, 0.106 mmol, 1.0 eq), in DCM (0.4 mL) at 0 °C was
25 added a solution of boron tribromide (0.041 mL) in DCM (0.15 mL). After 5 h additional boron tribromide (0.020 mL) was diluted with DCM (0.10 mL) and added to the reaction. It was stirred for 16 h at room temperature, cooled in an ice bath and slowly neutralized with saturated NaHCO₃. The organic portion was separated, concentrated and purified on silica gel with 5-25% MeOH (1N NH₃) in DCM to afford
30 8.0 mg of **Compound 34**.

¹H NMR δ_H (300 MHz, CD₃OD) 8.66 (s, 1H), 8.23 (d, *J* = 2.8 Hz, 1H), 7.82 (m, 1H), 7.03 (d, *J* = 8.3 Hz, 1H), 6.79 (d, *J* = 2.4 Hz, 1H), 6.68 (dd, *J* = 2.6 and 8.3 Hz, 1H), 4.93 (s, 2H), 4.36-4.32 (m, 1H), 3.92-3.88 (m, 1H), 3.82 (t, *J* = 10.1 Hz, 1H), 3.20 (d, *J* = 19.3 Hz, 1H), 3.05-2.95 (m, 2H), 2.83 (s, 3H), 2.65-2.54 (m, 2H), 2.10-2.00 (td, *J* = 4.6 and 15.6 Hz, 1H), 1.59-1.56 (m, 1H), 1.56 (s, 3H), LC/MS, *m/z* = 369 [M + H]⁺ (Calc: 368).

EXAMPLE 27

3-((6*R*,11*S*)-11-hydroxy-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)benzonitrile (Compound 37); 3-((6*R*,11*R*)-11-hydroxy-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)benzonitrile (Compound 60); 3-((6*S*,11*R*)-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)benzonitrile (Compound 36); and (6*S*,11*R*)-11-(3-(benzyloxy)phenyl)-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocine (Compound 61)



20

n-BuLi (2.5 *M* in hexanes, 4.2 mL, 10.5 mmol, 1.05 eq) was added slowly to 3-bromobenzonitrile (1.82g, 10 mmol, 1 eq) in 24 mL THF at -78 °C and the solution stirred at -78 °C for 10 min. A solution of RA1 (1.23g, 5 mmol, 0.5 eq) in 5 mL THF

was added and the solution was allowed to warm from -78 °C to RT. After 90 min, EtOAc was added and the solution washed with sat. NaHCO₃, dried with Na₂SO₄, and concentrated. The resulting material was purified by Medium Pressure Liquid Chromatography (MPLC) (0-50% EtOAc/hexanes, 40g) to give **Compound 60**, 550 mg and **Compound 37**, 1.18 g as yellow oils.

Compound 60: ¹H NMR δ_H (400 MHz, DMSO-d₆) 8.77 (s, 1H), 8.64 (d, *J* = 8.1 Hz, 1H), 8.26 (bs, 2H), 8.22 (s, 1H), 7.89 (d, *J* = 7.0 Hz, 1H), 7.74 (d, *J* = 7.0 Hz, 1H), 7.66 (t, *J* = 7.2 Hz, 1H), 7.55 (t, *J* = 7.2 Hz, 1H), 7.11 (d, *J* = 7.4 Hz, 1H), 7.02 (d, *J* = 7.4 Hz, 1H), 6.91 (s, 1H), 6.86-6.75 (m, 2H), 6.69 (d, *J* = 7.4 Hz, 1H), 6.21 (s, 1H), 5.32 (bs, 1H), 4.0 (s, 1H), 3.75 (s, 3H), 3.71 (s, 3H), 3.34 (ABq, *J* = 65.8, 18.4 Hz, 2H), 3.18-2.87 (m, 4H), 2.83 (s, 3H), 2.63-2.53 (m, 1H), 2.40 (s, 3H), 2.08 (t, *J* = 10.8 Hz, 1H), 1.61 (s, 3H), 1.09 (s, 3H).

LC/MS, *m/z* = 349 [M + H]⁺ (Calc: 348).

Compound 37: ¹H NMR δ_H (400 MHz, DMSO-d₆) 9.36 (bs, 1H), 7.80-7.74 (m, 2H), 7.45-7.34 (m, 2H), 7.05 (d, *J* = 8.6 Hz, 1H), 7.02 (d, *J* = 2.5 Hz, 1H), 6.96 (s, 1H), 6.88 (dd, *J* = 8.6, 2.5 Hz, 1H), 3.88 (d, *J* = 5.5 Hz, 1H), 3.80 (s, 3H), 3.26 (d, *J* = 19.7 Hz, 1H), 3.03 (d, *J* = 11.0 Hz, 1H), 2.84 (d, *J* = 4.6 Hz, 3H), 2.46-2.27 (m, 3H), 1.49 (s, 3H), 1.33 (d, *J* = 12.0 Hz, 1H).

LC/MS, *m/z* = 349 [M + H]⁺ (Calc: 348).

Thionyl chloride (35 mL, excess) was added to a mixture of **Compound 37** and **Compound 60** (2.24 g, 1 eq) and the solution heated at 70 °C for 90 min. The solution was concentrated and EtOAc was added. The solution was washed with sat. NaHCO₃, dried with Na₂SO₄, concentrated, and purified by MPLC (0-50% EtOAc/hexanes, 40g) to give RA34 as a yellow oil, 1.0 g. EtOAc (50 mL) was added and the solution run with the Pd/C cartridge on the H-Cube [ThalesNano, model HC-2.SS] at 10 bar in a recirculating fashion at 1 mL/min. After 45 min. the pressure was increased to 30 bar and after 3.5 h the pressure increased to 60 bar and the flow rate dropped to 0.5 mL/min. The reaction was stopped after 6 h with very little conversion to product seen. The recovered RA34 (700 mg, 1 eq) was dissolved in 8 mL THF and a pre-

mixed solution of NaBH₃CN (1 M in THF, 1 eq) and ZnCl₂ (1 M in Et₂O, 0.5 eq) was added. The solution was stirred at RT, and after 3 days 8 mL Et₂O was added, followed by a pre-mixed solution of NaBH₃CN (1 M in THF, 1 eq) and ZnCl₂ (1 M in Et₂O, 0.5 eq). After 8 days EtOAc was added and the solution washed with sat.

- 5 NaHCO₃, dried with Na₂SO₄, and concentrated. The resulting material is purified by MPLC (0-40% EtOAc/hexanes, 12g) to yield **Compound 36** as a pale yellow solid, 235 mg.

¹H NMR δ_H (400 MHz, DMSO-d₆) 9.39 (bs, 1H), 8.56 (bs, 1H), 7.99 (s, 1H), 7.92 (d, *J* = 8.3 Hz, 1H), 7.84 (d, *J* = 7.7 Hz, 1H), 7.74 (s, 1H), 7.72-7.68 (m, 1H), 7.65 (t, *J* = 7.7 Hz, 1H), 7.48-7.39 (m, 2H), 7.36 (d, *J* = 8.3 Hz, 1H), 7.25 (d, *J* = 8.3 Hz, 1H),
10 6.93 (d, *J* = 2.0 Hz, 1H), 6.83 (td, *J* = 7.0, 2.4 Hz, 3H), 6.61 (d, *J* = 2.4 Hz, 1H), 4.00 (t, *J* = 10.3 Hz, 1H), 3.77 (s, 3H), 3.70 (s, 3H), 3.63 (d, *J* = 17.3 Hz, 2H), 3.49-3.30 (m, 6H), 3.29-3.09 (m, 4H), 2.93 (d, *J* = 4.4 Hz, 3H), 2.83-2.67 (m, 3H), 2.66 (d, *J* = 4.4 Hz, 6H), 2.62-2.38 (m, 2H), 1.91 (d, *J* = 16.6 Hz, 1H), 1.83-1.68 (m, 1H), 1.06 (s, 3H),
15 0.97 (s, 3H).

LC/MS, *m/z* = 333 [M + H]⁺ (Calc: 332).

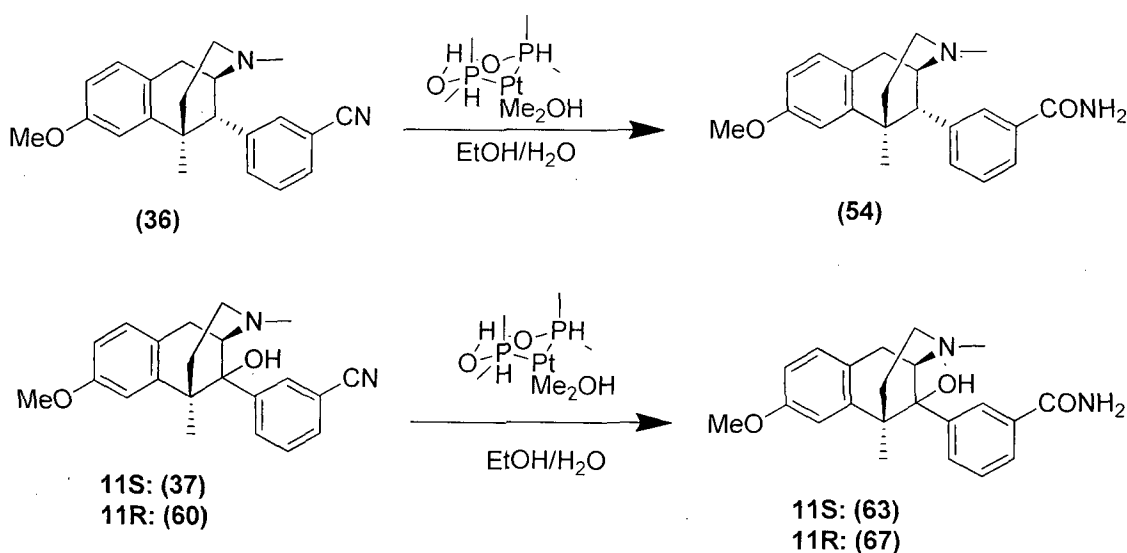
- In a similar manner **Compound 61** was synthesized from RA1 using 3-benzyloxybromobenzene rather than 3-bromobenzonitrile. The material was purified
20 by preparative HPLC [0-60% MeCN/H₂O (0.01% TFA)] to yield **Compound 61 TFA salt**.

¹H NMR δ_H (400 MHz, DMSO-d₆) 9.21 (bs, 1H), 8.38 (bs, 1H), 7.48 (d, *J* = 7.4 Hz, 2H), 7.42 (t, *J* = 7.4 Hz, 3H), 7.39-7.33 (m, 6H), 7.31 (d, *J* = 7.9 Hz, 2H), 7.24 (d, *J* = 7.9 Hz, 1H), 7.16 (d, *J* = 7.2 Hz, 1H), 7.13-7.08 (m, 2H), 7.03 (dd, *J* = 8.1, 2.0 Hz, 1H), 6.91-6.76 (m, 5H), 6.74 (d, *J* = 8.3 Hz, 1H), 6.60 (d, *J* = 2.2 Hz, 1H), 5.17 (s, 2H), 4.95 (s, 2H), 3.93 (dd, *J* = 13.8, 10.5 Hz, 2H), 3.73 (d, *J* = 23.9 Hz, 6H), 3.59 (d, *J* = 16.0 Hz, 3H), 3.45-3.19 (m, 6H), 3.08 (d, *J* = 16.2 Hz, 2H), 2.93 (d, *J* = 4.6 Hz, 3H), 2.81-2.67 (m, 2H), 2.65 (d, *J* = 4.6 Hz, 5H), 1.8 (d, *J* = 14.8 Hz, 2H), 1.76-1.65 (m, 2H), 0.99 (d, *J* = 55.4 Hz, 6H).

- 30 LC/MS, *m/z* = 414 [M + H]⁺ (Calc: 413).

EXAMPLE 28

3-((6*S*,11*R*)-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)benzamide (Compound 54); 3-((6*R*,11*S*)-11-hydroxy-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)benzamide (Compound 63); and 3-((6*R*,11*R*)-11-hydroxy-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)benzamide (Compound 67).



10

A 4:1 mixture of EtOH:H₂O was added to **Compound 36** (100 mg, 0.3 mmol, 1 eq) and hydrido(dimethylphosphinous acid-kP)[hydrogen bis(dimethylphosphinito-kP)]platinum(II) [Strem] (13 mg, 0.03 mmol, 10 mol%). The solution was heated at 80 °C for 16 h, then concentrated. Purification by MPLC (0-100% EtOAc/hexanes) yielded **Compound 54** as a white foam. A small portion was further purified by preparative HPLC [0-60% MeCN/H₂O (0.01% TFA)] to yield **Compound 54 TFA salt**.

¹H NMR δ_H (400 MHz, DMSO-*d*₆) 9.26 (bs, 1H), 8.49 (bs, 1H), 8.07 (s, 1H), 7.98 (s, 1H), 7.90 (s, 1H), 7.87-7.79 (m, 2H), 7.74 (d, *J* = 8.3 Hz, 1H), 7.67 (t, *J* = 4.0 Hz, 1H), 7.52 (t, *J* = 7.9 Hz, 1H), 7.49 (s, 1H), 7.41 (s, 1H), 7.34 (d, *J* = 7.9 Hz, 1H), 7.30-7.22

20

(m, 3H), 6.94 (d, $J = 2.4$ Hz, 1H), 6.81 (ddd, $J = 15.4, 8.3, 2.4$ Hz, 2H), 6.59 (d, $J = 2.4$ Hz, 1H), 4.00 (t, $J = 13.4$ Hz, 2H), 3.73 (d, $J = 29.8$ Hz, 6 H), 3.67-3.57 (m, 2H), 3.48-3.26 (m, 6H), 3.16 (dd, $J = 16.7, 5.0$ Hz, 2H), 2.96 (d, $J = 4.6$ Hz, 3H), 2.84-2.66 (m, 3H), 2.65-2.57 (m, 6H), 1.89 (d, $J = 15.1$ Hz, 1H), 1.03 (d, $J = 32.2$ Hz, 6H).

5 LC/MS, $m/z = 351$ [$M + H$]⁺ (Calc: 350).

In a similar manner **Compound 63** and **Compound 67** were prepared from **Compound 37** and **Compound 60**, respectively.

Compound 63 : ¹H NMR δ_H (400 MHz, DMSO-d₆) 9.32 (bs, 1H), 8.11 (s, 1H), 7.92
10 (s, 1H), 7.72 (d, $J = 8.1$ Hz, 1H), 7.39 (s, 1H), 7.20 (t, $J = 7.7$ Hz, 1H), 7.09 (d, $J = 8.1$ Hz, 1H), 7.03 (d, $J = 5.9$ Hz, 1H), 7.01 (s, 1H), 6.85 (dd, $J = 8.1, 2.6$ Hz, 1H), 6.83 (s, 1H), 3.83-3.77 (m, 2H), 3.80 (s, 3H), 3.24 (d, $J = 18.9$ Hz, 2H), 3.03 (d, $J = 8.8$ Hz, 1H), 2.85 (d, $J = 5.3$ Hz, 3H), 2.48-2.43 (m, 6H), 1.75 (s, 1H), 1.51 (s, 3H), 1.31 (d, $J = 11.4$ Hz, 1H).

15 LC/MS, $m/z = 367$ [$M + H$]⁺ (Calc: 366).

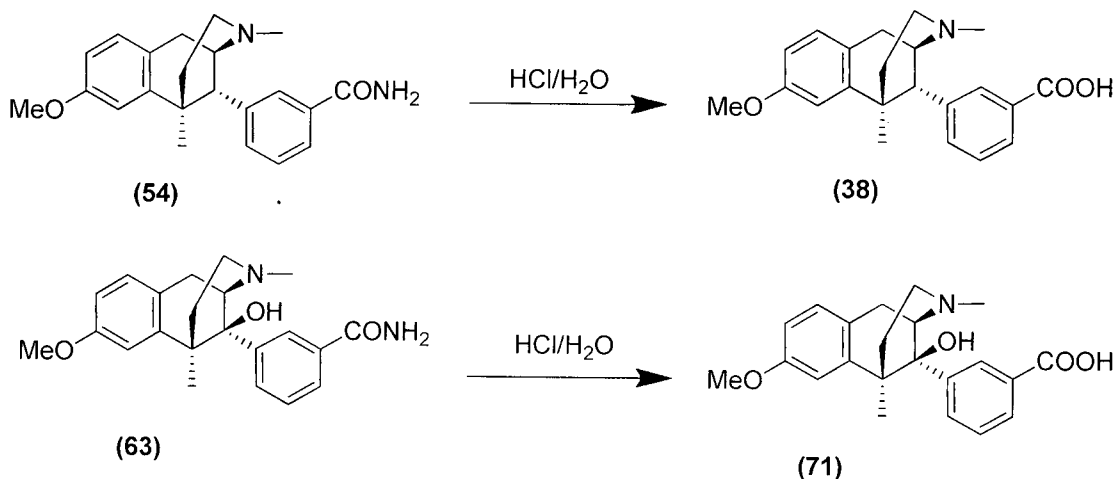
Compound 67: ¹H NMR δ_H (400 MHz, DMSO-d₆) 8.64-8.58 (m, 1H), 8.28 (s, 1H),
8.13 (bs, 1H), 8.02 (s, 1H), 7.94 (d, $J = 7.5$ Hz, 1H), 7.84 (d, $J = 7.5$ Hz, 1H), 7.49 (d,
20 $J = 7.7$ Hz, 1H), 7.45 (d, $J = 3.9$ Hz, 1H), 7.36-7.14 (m, 1H), 7.05 (d, $J = 8.1$ Hz, 1H),
6.86 (d, $J = 2.2$ Hz, 1H), 6.75 (dd, $J = 8.1, 2.2$ Hz, 1H), 6.67-6.59 (m, 1H), 6.00 (s,
1H), 3.97 (d, $J = 4.4$ Hz, 1H), 2.67 (s, 3H), 3.64 (s, 1H), 3.39 (dd, $J = 19.3, 5.3$ Hz,
1H), 3.20 (d, $J = 18.9$ Hz, 1H), 3.10-2.95 (m, 1H), 2.74 (d, $J = 4.6$ Hz, 3H), 2.66-2.46
(m, 1H), 1.69 (s, 2H), 1.61 (s, 3H).

LC/MS, $m/z = 367$ [$M + H$]⁺ (Calc: 366).

25

EXAMPLE 29

3-((6*S*,11*R*)-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-
methanobenzo[d]azocin-11-yl)benzoic acid (**Compound 38**); and 3-((6*R*,11*S*)-11-
hydroxy-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-
30 methanobenzo[d]azocin-11-yl)benzoic acid
(**Compound 71**)



Compound 54 (50 mg, 0.14 mmol) was heated at 70 °C in 1.5 mL 6 M HCl for 21 h.

- 5 Concentration followed by preparative HPLC purification [0-60% MeCN/H₂O (0.01% TFA)] gave **Compound 38** TFA salt.

¹H NMR δ_H (400 MHz, DMSO-d₆) 13.13 (bs, 1H), 13.03 (bs, 1H), 9.30 (bs, 1H), 8.55 (bs, 1H), 8.11 (s, 1H), 7.92 (d, *J* = 7.8 Hz, 1H), 7.89 (s, 1H), 7.84 (d, *J* = 8.5 Hz, 1H), 7.76 (d, *J* = 7.8 Hz, 1H), 7.57 (t, *J* = 7.8 Hz, 1H), 7.43-7.29 (m, 3H), 7.27 (d, *J* = 8.5 Hz, 1H), 6.94 (d, *J* = 2.2 Hz, 1H), 6.82 (dd, *J* = 11.8, 2.2 Hz, 2H), 6.60 (d, *J* = 2.4 Hz, 1H), 4.02 (t, *J* = 11.6 Hz, 1H), 3.73 (d, *J* = 28.9 Hz, 6 H), 3.67 (dd, *J* = 15.0, 12.2 Hz, 2H), 3.44-3.27 (m, 6H), 3.25-3.08 (m, 2H), 2.96 (d, *J* = 4.4 Hz, 3H), 2.84-2.63 (m, 4H), 1.89 (d, *J* = 15.0 Hz, 1H), 1.80-1.67 (m, 1H), 1.0 (d, *J* = 28.7 Hz, 6H).

LC/MS, *m/z* = 352 [M + H]⁺ (Calc: 351).

15

In a similar manner **Compound 71** was prepared from **Compound 63**. Purification by MPLC (0-20% (10% NH₄OH/MeOH)/DCM, 12g) gave **Compound 71** as its ammonium carboxylate salt as a clear oil.

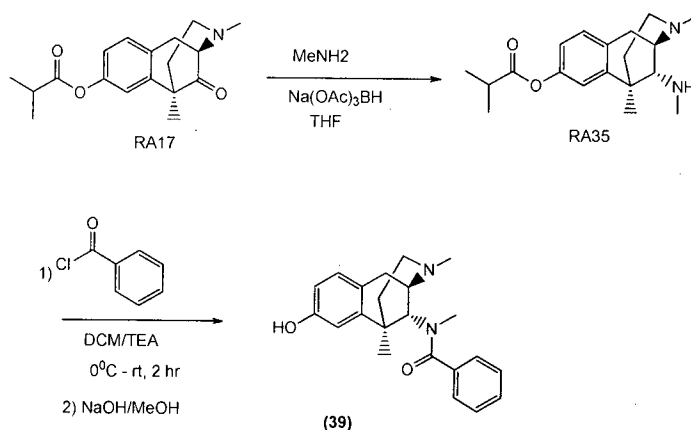
¹H NMR δ_H (400 MHz, DMSO-d₆) 8.11 (s, 1H), 7.74 (d, *J* = 7.5 Hz, 1H), 7.38-7.08 (m, 5H), 7.00 (d, *J* = 8.7 Hz, 1H), 6.93 (d, *J* = 2.2 Hz, 1H), 6.79 (dd, *J* = 8.3, 2.2 Hz, 1H), 3.77 (s, 3H), 3.34 (s, 2H), 3.10 (d, *J* = 17.3 Hz, 1H), 2.39-2.08 (m, 4H), 1.38 (s, 3H), 1.23-1.07 (m, 1H).

LC/MS, *m/z* = 368 [M + H]⁺ (Calc: 367).

EXAMPLE 30

N-((2*R*,6*R*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-*N*-methylbenzamide (Compound 39); 3-(((2*R*,6*R*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)(methyl)carbamoyl)benzoic acid (Compound 47);
 3-(((2*R*,6*R*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)(methyl)carbamoyl)benzoic acid (Compound 48);
 and 4-(((2*R*,6*R*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)(methyl)carbamoyl)benzoic acid (Compound 59)

10



- A mixture of RA17 (500 mg, 1.66 mmol), MeNH₂ (2M in THF, 1 mL, 2 mmol) and 0.1 g 4A molecular sieves in anhydrous ACN (5 mL) was stirred at RT for 2 h.
- Na(OAc)₃BH [704 mg, 2.32 mmol] was added and the resulting mixture stirred at RT overnight. The reaction mixture was basified using sat. NaHCO₃ and extracted with EtOAc. The EtOAc solution was dried over MgSO₄ and the solvent evaporated under reduced pressure. The crude compound RA35 was used in the next step without further purification.
- Crude RA35 (36 mg, 0.11 mmol) was dissolved in DCM (5 mL) and TEA (0.2 mL, 1.43 mmol) was added. The mixture was cooled to 0 °C with an ice bath and then benzoyl chloride (0.038 mL, 0.12 mmol) was added dropwise via a syringe. After the addition was complete the reaction mixture was slowly warmed to RT over 2 h. The

reaction mixture was loaded onto a silica gel column using hexanes/acetone (5:1) as eluent to give the ester intermediate, which was stirred in a mixture of 2N NaOH/MeOH (2 mL/2 mL) at 50 °C for 1 h. The resulting mixture was cooled with an ice bath and the pH adjusted to 7 using 1N HCl, and then extracted with EtOAc. The EtOAc solution was dried over MgSO₄ and the solvent evaporated under reduced pressure. The crude material was subjected to flash column using DCM/MeOH (95: 5) as eluent to give 20 mg of **Compound 39** as a white solid.

¹H NMR δ_H (400 MHz, CD₃OD) 7.30-7.60 (m, 5H), 7.10 (m, 1H), 6.80 (s, 1H), 6.70 (m, 1H), 5.05 (s, 1H), 4.05 (s, 1H), 2.50-3.50 (m, 10H), 1.70-2.10 (m, 2H), 1.55 (s, 3H).

LC/MS, *m/z* = 351 [M + H]⁺ (Calc: 350).

In a similar manner **Compound 47** was prepared from RA35 using methyl 3-(chlorocarbonyl)benzoate rather than benzoyl chloride. Purification by reverse phase column chromatography (C18, ACN/water with 0.1% TFA, 0-95%) gave **Compound 47 TFA salt** as a white solid.

¹H NMR δ_H (400 MHz, CD₃OD) 8.10 (m, 2H), 7.70 (m, 1H), 7.50 (m, 1H), 7.05 (m, 1H), 6.80 (s, 1H), 6.65 (m, 1H), 4.15 (s, 1H), 3.95 (s, 1H), 3.40 (s, 2H), 2.30-3.30 (m, 8H), 1.60 (s, 3H), 1.40 (m, 1H).

LC/MS, *m/z* = 395 [M + H]⁺ (Calc: 394).

In a similar manner **Compound 48** was prepared from RA35 using methyl 3-(chlorocarbonyl)benzoate rather than benzoyl chloride. Purification by reverse phase column chromatography (C18, ACN/water with 0.1% TFA, 0-95%) gave **Compound 48 TFA salt** as a white solid.

¹H NMR δ_H (400 MHz, CD₃OD) 7.90-8.00 (m, 2H), 7.40-7.60 (m, 2H), 6.90 (m, 1H), 6.70 (m, 1H), 6.50 (m, 1H), 4.90 (s, 1H), 3.95 (s, 1H), 2.30-3.30 (m, 9H), 2.10 (m, 1H), 1.65 (m, 1H), 1.50 (s, 3H).

LC/MS, *m/z* = 395 [M + H]⁺ (Calc: 394).

In a similar manner **Compound 59** was prepared from RA35 using methyl 4-(chlorocarbonyl)benzoate rather than benzoyl chloride. Purification by reverse phase column chromatography (C18, ACN/water with 0.1% TFA, 0-95%) gave **Compound 59 TFA salt** as a white solid.

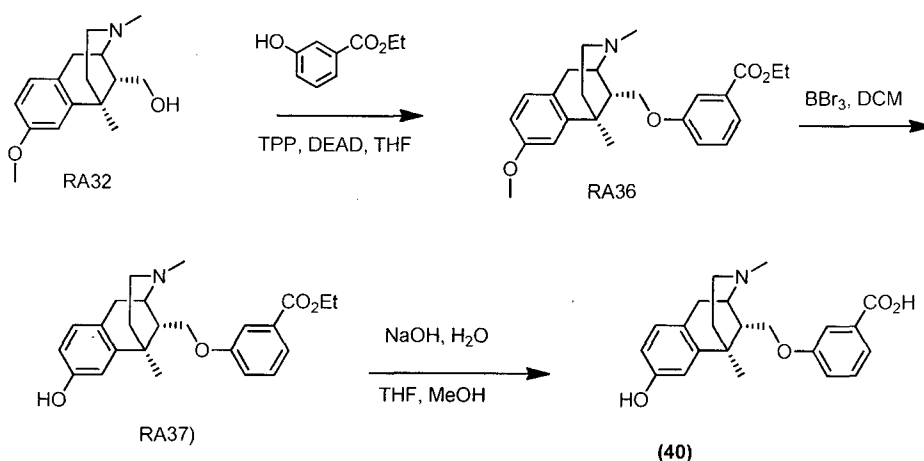
¹H NMR δ_H (400 MHz, CD₃OD) 7.95 (m, 2H), 7.40 (m, 2H), 6.90 (m, 1H), 6.65 (m, 1H), 6.50 (m, 1H), 4.90 (s, 1H), 3.95 (s, 1H), 2.30-3.30 (m, 9H), 2.10 (m, 1H), 1.65 (m, 1H), 1.50 (s, 3H).

LC/MS, m/z = 395 [M + H]⁺ (Calc: 394).

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EXAMPLE 31

3-(((6S,11R)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[d]azocin-11-yl)methoxy)benzoic acid (Compound 40)



15

To a mixture of RA32 (0.316 g, 1.21 mmol, 1.0 eq), ethyl-3-hydroxybenzoate (0.50 g, 3.02 mmol, 2.5 eq), and triphenylphosphine (0.79 g, 3.02 mmol, 2.5 eq) in THF (5.1 mL) at 0 °C was added DEAD (1.40 mL, 3.02 mmol, 2.5 eq). The ice bath was removed and the mixture was stirred for 16 h. H₂O was added and the organic portion was extracted twice with EtOAc, dried over Na₂SO₄ and concentrated. The crude product was purified by flash column chromatography (silica gel, 0-90% EtOAc in hexanes and 0-15% MeOH in DCM) to afford 46 mg of RA36. LC/MS, m/z = 410 [M + H]⁺ (Calc: 409).

20

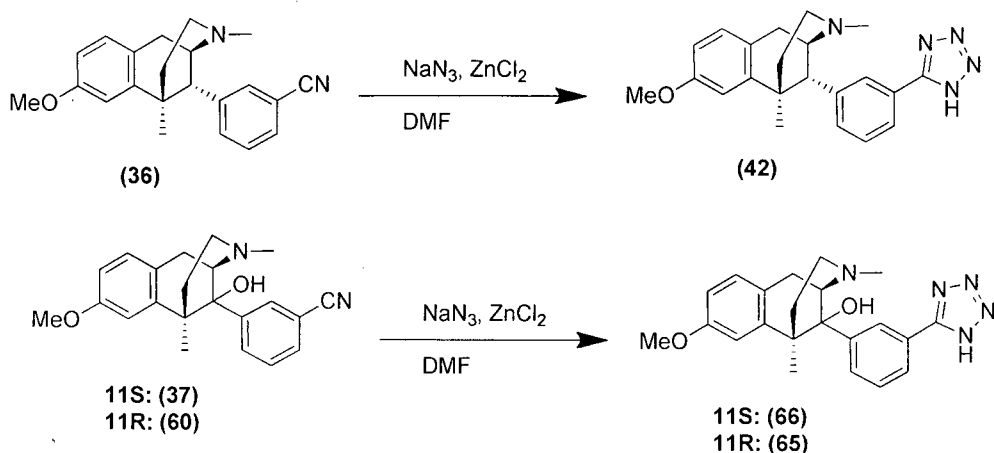
To a solution of RA36 (0.046 g, 0.112 mmol, 1.0 eq), in DCM (0.5 mL) at 0°C was added a solution of boron tribromide (0.043 mL) in DCM (0.10 mL). The ice bath was removed and the mixture was stirred for 16 h at room temperature. It was cooled in an ice bath, slowly neutralized with saturated NaHCO₃, concentrated to dryness to afford crude RA37 which was reacted "as is" in the next step. LC/MS, m/z = 396 [M + H]⁺ (Calc: 395).

To a mixture of crude RA37 from the previous step in THF (0.5 mL) was added a solution of NaOH (0.18 g, 0.448 mmol, 4.0 eq) in H₂O (0.5 mL). MeOH (0.5 mL) was added and the mixture was stirred for 16 h at room temperature. Additional NaOH (0.18 g, 0.448 mmol, 4.0 eq) was added and the mixture was stirred for 6 h at room temperature. It was neutralized with dilute hydrochloric acid and concentrated to dryness on silica gel and purified by flash chromatography with 0-20% MeOH(1N NH₃) in DCM to afford a solid which was triturated with MeOH and dried to afford 14.7 mg of **Compound 40** ammonium salt as a white solid.

¹H NMR δ_H (300 MHz, D₂O) 7.32-7.30 (d, J = 7.7 Hz, 1H), 7.23-7.17 (m, 2H), 6.94 (d, J = 8.3 Hz, 1H), 6.84 (d, J = 8.3 Hz, 1H), 6.72 (s, 1H), 6.64 (d, 8.3 Hz, 1H), 4.20-4.15 (m, 1H), 3.95-3.91 (m, 1H), 3.59-3.52 (t, 10.1 Hz, 1H), 3.04-2.95 (m, 3H), 2.78 (s, 3H), 2.68-2.58 (m, 1H), 2.46-2.39 (m, 1H), 1.91 (t, J = 16.9 Hz, 1H), 1.50 (d, J = 15.6 Hz, 1H), 1.37 (s, 3H), LC/MS, m/z = 368 [M + H]⁺ (Calc: 367).

EXAMPLE 32

(6*S*,11*R*)-11-(3-(1*H*-tetrazol-5-yl)phenyl)-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocine (**Compound 42**); (6*R*,11*R*)-11-(3-(1*H*-tetrazol-5-yl)phenyl)-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-ol (**Compound 65**); and (6*R*,11*S*)-11-(3-(1*H*-tetrazol-5-yl)phenyl)-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-ol (**Compound 66**)



A solution of **Compound 36** (33 mg, 0.1 mmol, 1 eq), NaN₃ (10 mg, 0.15 mmol, 1.5 eq), and ZnCl₂ (20 mg, 0.15 mmol, 1.5 eq) in 0.4 mL DMF was heated at 140 °C for 18 h. The solution was cooled to RT and 2 mL of water was added. The resulting solid was filtered, washed with hexanes and dried under vacuum to yield **Compound 42** as a white solid.

¹H NMR δ_H (400 MHz, ACN-d₃) 8.20 (s, 1H), 8.11 (d, *J* = 7.5 Hz, 1H), 7.73 (d, *J* = 8.1 Hz, 1H), 7.66 (t, *J* = 7.9 Hz, 1H), 7.28 (d, *J* = 8.1 Hz, 1H), 6.86 (d, *J* = 8.1 Hz, 1H), 6.82 (s, 1H), 3.80 (s, 3H), 3.79-3.71 (m, 1H), 3.67 (d, *J* = 15.6 Hz, 1H), 3.41 (d, *J* = 14.7 Hz, 1H), 3.06 (d, *J* = 15.3 Hz, 1H), 2.89 (d, *J* = 13.4 Hz, 1H), 2.82-2.73 (m, 1H), 2.71 (s, 3H), 2.62 (td, *J* = 14.5, 3.8 Hz, 1H), 2.57-2.49 (m, 1H), 0.99 (s, 3H). LC/MS, *m/z* = 376 [M + H]⁺ (Calc: 375).

In a similar manner **Compound 66** and **Compound 65** were prepared from **Compound 37** and **Compound 60**, respectively.

Compound 66

¹H NMR δ_H (400 MHz, ACN-d₃) 8.45 (s, 1H), 7.98-7.67 (m, 2H), 7.28 (t, *J* = 8.1 Hz, 1H), 7.17 (d, *J* = 8.1 Hz, 1H), 7.08-6.99 (m, 2H), 6.88 (dd, *J* = 8.6, 2.6 Hz, 1H), 3.90-3.83 (m, 1H), 3.85 (s, 3H), 3.19 (d, *J* = 19.5 Hz, 1H), 3.12 (d, *J* = 11.0 Hz, 1H), 2.87 (s, 3H), 2.79-2.49 (m, 3H), 1.55 (s, 3H), 1.40 (d, *J* = 11.0 Hz, 1H). LC/MS, *m/z* = 392 [M + H]⁺ (Calc: 391).

Compound 65

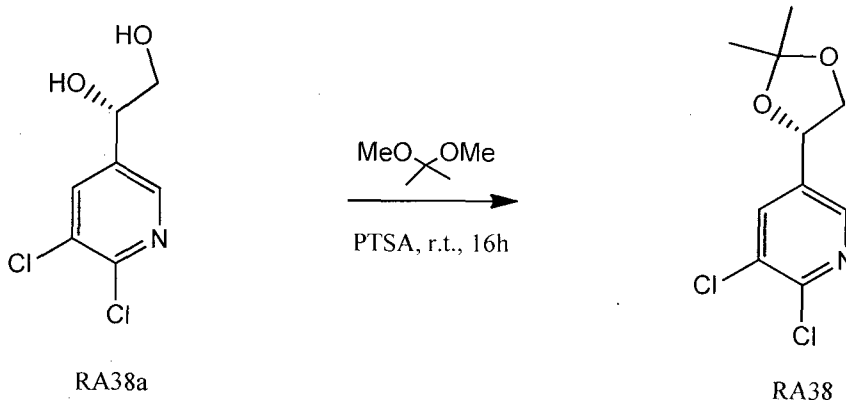
¹H NMR δ_{H} (400 MHz, ACN-d₃) 8.53 (s, 1H), 8.12 (d, J = 8.3 Hz, 1H), 7.67 (t, J = 2.9 Hz, 1H), 7.16 (d, J = 8.3 Hz, 1H), 6.97 (d, J = 2.6 Hz, 1H), 6.85 (dd, J = 8.3, 2.6 Hz, 1H), 3.95 (bs, 1H), 3.79 (s, 3H), 3.80-3.77 (m, 1H), 3.58 (dd, J = 21.0, 6.8 Hz, 1H), 3.25 (d, J = 18.9 Hz, 2H), 2.81 (s, 3H), 2.78-2.67 (m, 2H), 1.80-1.69 (m, 2H), 1.68 (s, 3H).

LC/MS, m/z = 392 [M + H]⁺ (Calc: 391).

10

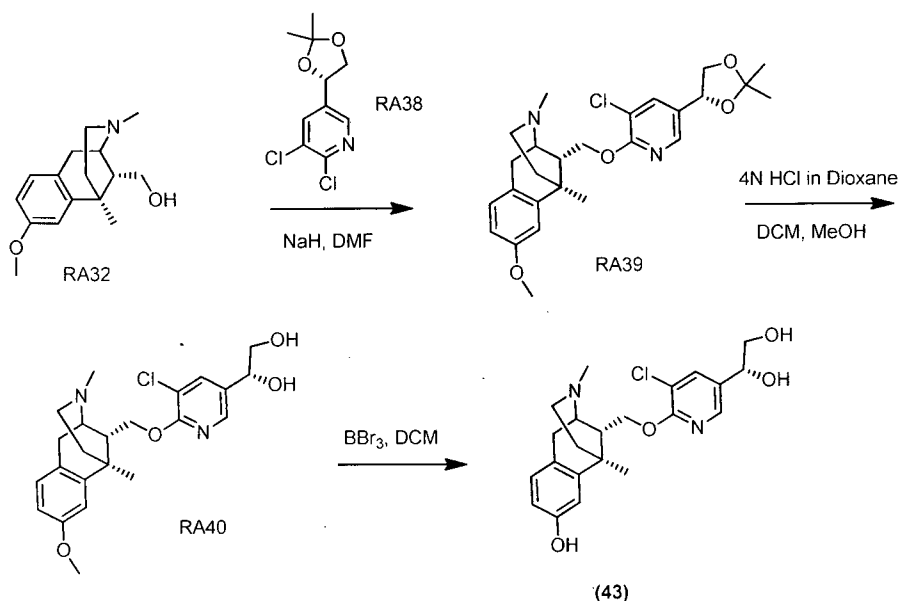
EXAMPLE 33

(1*S*)-1-(5-chloro-6-(((6*S*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)methoxy)pyridin-3-yl)ethane-1,2-diol (Compound 43)



15

Into a flask containing a mixture of RA38a (1.00 gm, 4.81 mmol) in 2,2-dimethoxypropane (9.8 ml) at room temperature was added paratoluenesulfonic acid mono hydrate (0.09 gm, 0.481 mmol). The solution was stirred for 16 hours at room temperature then cooled down with an ice bath and quenched with saturated aqueous sodium bicarbonate and extracted with ethyl acetate. The organic layer was separated, washed with brine, dried over sodium sulfate and concentrated to afford RA38 (99% yield, 1.18 gm) as an oil.



To a solution of RA32 (0.05 g, 0.192 mmol, 1.0 eq), in DMF (0.4 mL) at room temperature was added 60% sodium hydride in mineral oil (0.011 g, 0.287 mmol, 1.5 eq). The mixture was stirred for 45 min at room temperature and then it was cooled with an ice bath and a solution of RA38 (0.095 g, 0.384 mmol, 2.0 eq) in DMF (0.5 mL) was added and the mixture stirred for 16 h at room temperature. H₂O was added and the organic portion was extracted twice with EtOAc, dried over Na₂SO₄ and concentrated. The crude product was purified by flash chromatography (silica gel, 0-7% MeOH in DCM) to afford 70 mg of RA39. LC/MS, m/z = 473 [M + H]⁺ (Calc: 472).

To a solution of RA39 (0.025 g, 0.0529 mmol, 1.0 eq) in DCM (0.12 mL) and MeOH (0.02 mL) was added 4N HCl in dioxane (0.07 mL, 0.265 mmol, 5.0 eq). The solution was stirred for 16 h at room temperature and then concentrated to dryness to afford RA40 which was used "as is" in the next step. LC/MS, m/z = 433 [M + H]⁺ (Calc: 432).

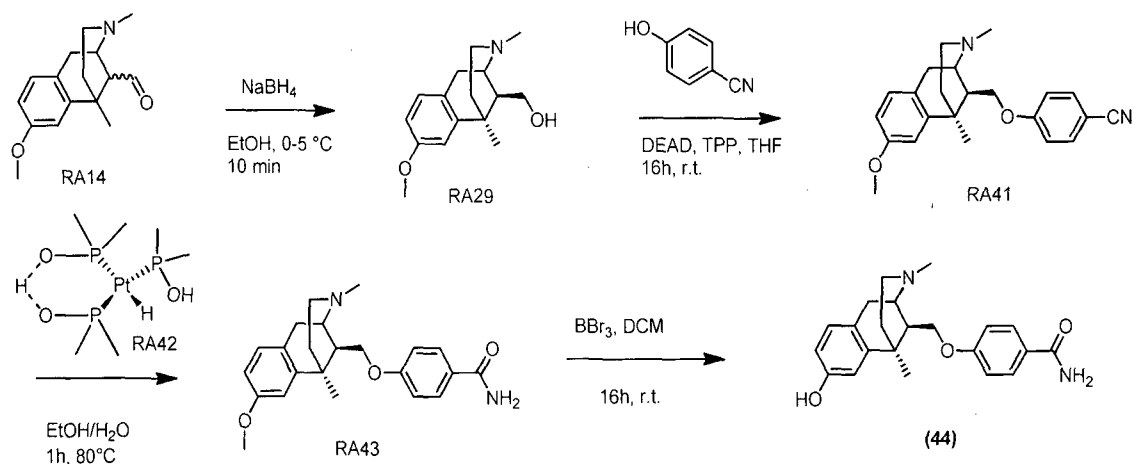
A solution of RA40 (0.023 gm, .045 mmol, 1.0 eq) was dissolved in DCM (0.2 mL), cooled with an ice bath and treated with boron tribromide (0.018 mL, 0.182 mmol, 4.0

eq). The ice bath was removed and the mixture was stirred for 16 h at room temperature. It was quenched with H₂O and neutralized with solid NaHCO₃, concentrated to dryness and purified by flash chromatography (silica gel, 0-10% MeOH (1N NH₃) in DCM) to afford 4.3 mg of **Compound 43**: ¹H NMR δ_H (300 MHz, CD₃OD) 7.88 (s, 1H), 7.68 (s, 1H), 6.85 (d, J = 8.3 Hz, 1H), 6.62 (s, 1H), 6.50 (dd, J = 2.6, 8.3 Hz, 1H), 4.52 (t, J = 5.9 Hz, 1H), 4.49-4.44 (m, 1H), 3.92 (t, J = 10.7 Hz, 1H), 3.55-3.46 (m, 2H), 3.30-3.27 (m, 1H), 3.25 (s, 1H), 2.97 (d, J = 18.6 Hz, 1H), 2.59 (dd, J = 5.9, 18.4 Hz, 1H), 2.39 (dd, J = 5.3, 12.1 Hz, 1H), 2.33 (s, 3H), 2.31 (m, 1H), 2.09 (td, J = 3.1, 12.5 Hz, 1H), 1.80 (td, J = 4.6, 12.7 Hz, 1H), 1.38 (s, 3H), 1.27 (d, 14.2 Hz, 1H) LC/MS, m/z = 419 [M + H]⁺ (Calc: 418).

EXAMPLE 34

4-(((6*S*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)methoxy)benzamide (Compound 44)

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To a solution of RA14 (3.34 g, 12.85 mmol, 1.0 eq) in EtOH (36 mL) at 0 °C was added NaBH₄ (0.53 g, 14.13 mmol, 1.1 eq). The mixture was stirred for 10 min, H₂O (10 mL) was added, the EtOH was removed under reduced pressure and the organic portion was extracted with DCM, dried over Na₂SO₄ and concentrated to 2.6 g of a light yellow solid as a mixture of diastereomers which was purified by flash column

chromatography (silica gel, 5-25% MeOH (1N NH₃)/ DCM) to afford 0.8 g of RA29 as the less polar isomer.

¹H NMR δ_H (300 MHz, (CD₃)₂SO) 7.02 (d, J = 8.3 Hz, 1H), 6.82 (d, J = 2.6 Hz, 1H), 6.70 (dd, J = 2.6, 8.3 Hz, 1H), 4.63 (brs, 1H), 3.87-3.82 (m, 1H), 3.74 (d, J = 4.6 Hz, 1H), 3.70 (s, 3H), 3.22-3.16 (m, 1H), 3.09 (d, J = 18.0 Hz, 1H), 2.57-2.49(m, 1H), 2.32-2.26 (m, 1H), 2.25 (s, 3H), 1.92-1.77 (m, 1H), 1.62-1.56 (m, 1H), 1.33 (s, 3H), 1.08 (d, J = 11.2 Hz, 1H), LC/MS, m/z = 262 [M + H]⁺ (Calc: 261).

To a mixture of RA29 (0.100 g, 0.383 mmol, 1.0 eq), 4-cyanophenol (0.114 g, 0.958 mmol, 2.5 eq), and triphenylphosphine (0.251 g, 0.958 mmol, 2.5 eq) in THF (1.3 mL) at 0 °C was added DEAD (0.17 g, 0.958 mmol, 2.5 eq). The ice bath was removed and the mixture was stirred for 16 h. H₂O was added and the organic portion was extracted twice with EtOAc, dried over Na₂SO₄ and concentrated to 0.72 g of a crude mixture which was purified by flash column chromatography (silica gel, 5-60% EtOAc in hexanes) to afford 0.038 g of RA41. LC/MS, m/z = 363 [M + H]⁺ (Calc: 362).

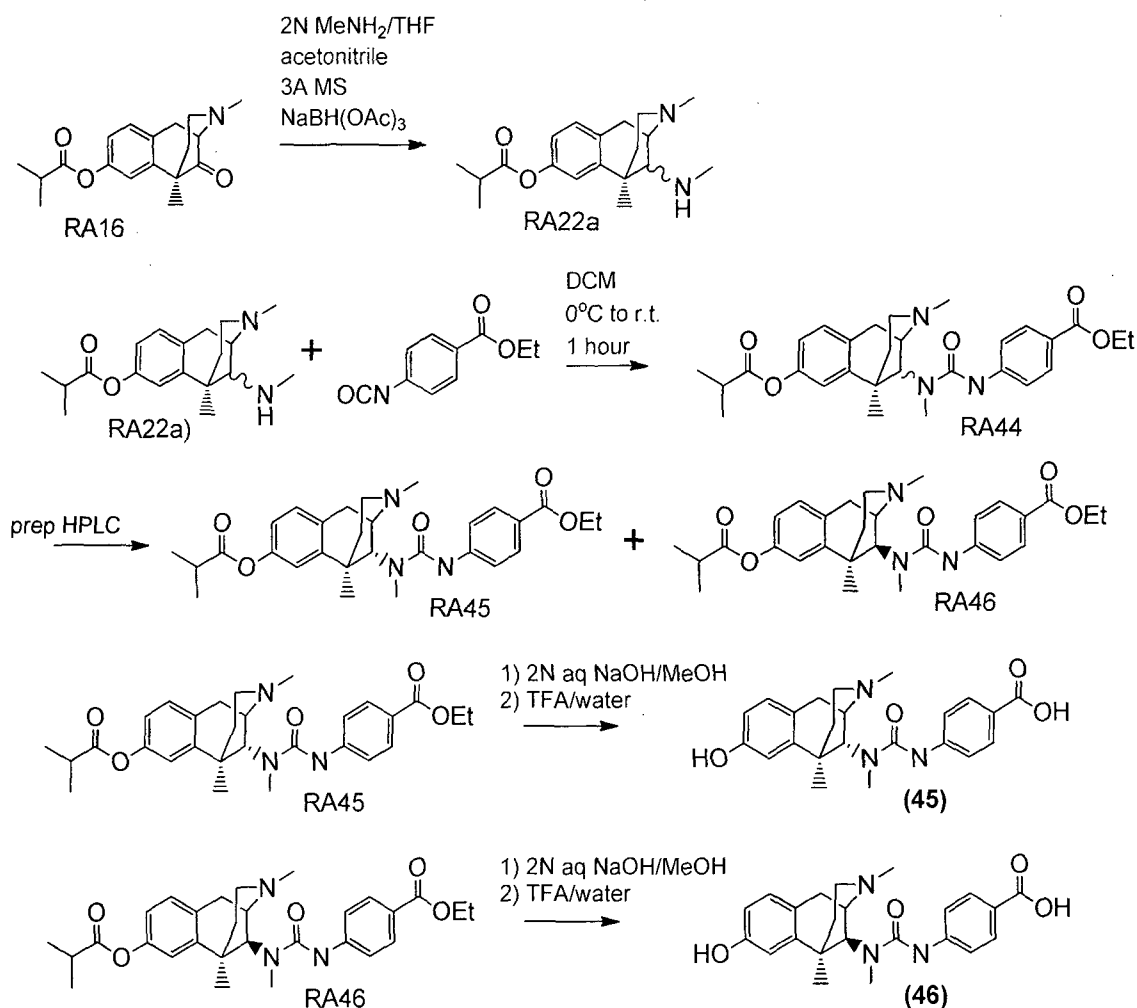
To a suspension of RA41 (0.015 g, .0414 mmol, 1.0 eq) in ethanol (0.4 mL) was added RA42 0.002 g, 0.0041 mmol, 0.10 eq) and H₂O (0.1 mL). The mixture was stirred for 1 h at 80 °C and concentrated to dryness to afford RA43. LC/MS, m/z = 381 [M + H]⁺ (Calc: 380).

A solution of RA43 (0.015 g, 0.039 mmol, 1.0 eq) in DCM (0.16 mL), cooled with an ice bath was treated with boron tribromide (0.015 mL, 0.156 mmol, 4.0 eq). The ice bath was removed and the mixture was stirred for 16 h at room temperature. It was quenched with H₂O, neutralized with solid NaHCO₃, concentrated to dryness and purified by flash chromatography (silica gel, 0-10% MeOH (1N NH₃) in DCM) to afford 4.0 mg of **Compound 44**. ¹H NMR δ_H (300 MHz, CD₃OD) 7.76 (d, J = 9.0 Hz, 2H), 6.95 (d, J = 9.0 Hz, 2H), 6.86 (d, J = 8.3 Hz, 1H), 6.71 (d, J = 2.6 Hz, 1H), 6.51 (dd, J = 2.6, 8.3 Hz, 1H), 4.38-4.28 (m, 2H), 3.38 (m, 1H), 3.14 (d, J=17.8 Hz, 1H), 2.68 (dd, J= 6.1, 18.8 Hz, 1H), 2.40(m, 1H), 2.32 (s, 3H), 2.15 (m, 1H), 2.18 (m,

1H), 1.91 (td, J = 4.6, 13.2 Hz, 1H), 1.33 (s, 3H), 1.18(d, J = 12.1 Hz, 1H), LC/MS, $m/z = 367 [M + H]^+$ (Calc: 366).

EXAMPLE 35

- 5 4-(3-((2*R*,6*R*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-3-methylureido)benzoic acid (Compound 45); 4-(3-((2*R*,6*R*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-3-methylureido)benzoic acid (Compound 46); and
- 10 3-(3-((2*R*,6*R*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-3-methylureido)propanoic acid (Compound 68)



11,11-dihydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-8-yl isobutyrate (RA16) (0.300 g, 0.940 mmol, 1 eq) was dissolved in dry ACN (3 mL) and 2N methylamine in THF (1.41 mL, 2.82 mmol, 3 eq) was added dropwise to the solution at room temperature. The mixture was shaken with 3Å molecular sieves for 2 h at room temperature. Then, solid sodium triacetoxyborohydride (0.837 g, 3.95 mmol) was added in one portion. The mixture was shaken for 16 h at room temperature. The reaction mixture was quenched with 1 mL water and extracted with 2 x 6 mL DCM. The organic layers were combined, dried over Na₂SO₄, and concentrated under reduced pressure to provide 270 mg of crude RA22a as a dark gum.

LC/MS, $m/z = 317$ [M + H]⁺ (Calc: 316).

RA22a (50 mg, 0.157 mmol) was dissolved in DCM (3 mL) and cooled in a brine/ice bath. Ethyl 4-isocyanatobenzoate (30 mg, 0.157 mmol) was dissolved in DCM (1 mL) and added dropwise to the cooled solution. The bath was removed and the reaction mixture stirred for 1 h. The mixture was quenched with water (1 mL) and extracted with DCM (3 mL). The organic layer was dried over Na₂SO₄ and concentrated to give 52 mg of RA44. The crude residue was chromatographed by prep HPLC to give RA45 and RA46. RA45 and RA46 were each dissolved in MeOH (3 mL) and hydrolyzed by adding 2N aq NaOH (0.5 mL) to the solutions and stirring for 16 h at room temperature. The reaction mixtures were concentrated to dryness and redissolved in 2 mL water. The solutions were cooled in an ice bath and acidified with TFA (2 mL) added dropwise. The acid solutions were chromatographed by prep HPLC to give **Compound 45 TFA salt** and **Compound 46 TFA salt** as brown oils.

Compound 45 TFA salt

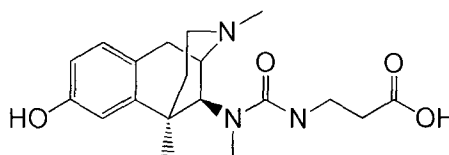
¹H NMR δ_H (400 MHz, CD₃OD) 7.98-7.90 (m, 2H), 7.61-7.52 (m, 2H), 7.14-7.07 (m, 1H), 6.89-6.81 (m, 1H), 6.78-6.70 (m, 1H), 4.69-4.61 (m, 1H), 3.88-3.80 (m, 1H), 3.39-3.34 (m, 1H), 3.27-3.15 (m, 1H), 2.97 (s, 3H), 2.79 (s, 3H), 2.77-2.66 (m, 1H), 2.18-2.00 (m, 1H), 1.77-1.68 (m, 1H), 1.56 (s, 3H).

LC/MS, $m/z = 410$ [M + H]⁺ (Calc: 409);

Compound 46 TFA salt

¹H NMR δ_H (400 MHz, CD₃OD) 8.01-7.93 (m, 2H), 7.64-7.55 (m, 2H), 7.12-7.04 (m, 1H), 6.84-6.78 (m, 1H), 6.74-6.69 (m, 1H), 4.15-4.11 (m, 1H), 3.95-3.90 (m, 1H), 3.50-3.40 (m, 2H), 3.38-3.20 (m, 4H), 2.95 (s, 3H), 2.83-2.73 (m, 1H), 2.51-2.39 (m, 1H), 1.57 (s, 3H), 1.55-1.46 (m, 1H).
 LC/MS, m/z = 410 [M + H]⁺ (Calc: 409).

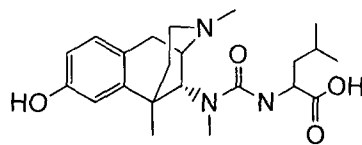
3-(3-((2*R*,6*R*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-3-methylureido)propanoic acid (Compound 68)



(68)

In a similar manner, 3-(3-((2*R*,6*R*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-3-methylureido)propanoic acid (Compound 68) was prepared from RA22a (86 mg, 0.272 mmol) using ethyl 3-isocyanatopropionate (39 mg, 0.272 mmol) rather than ethyl 4-isocyanatobenzoate. Purification by preparatory HPLC gave **Compound 68 TFA salt** as a brown oil.
¹H NMR δ_H (400 MHz, CD₃OD) 7.12-7.03 (m, 1H), 6.84-6.78 (m, 1H), 6.76-6.68 (m, 1H), 4.61-4.52 (m, 1H), 3.76-3.65 (m, 1H), 3.52-3.37 (m, 2H), 3.29-2.99 (m, 4H), 2.98-2.89 (m, 2H), 2.75-2.61 (m, 1H), 2.59-2.48 (m, 5H), 2.13-1.99 (m, 1H), 1.73-1.60 (m, 1H), 1.46 (s, 3H).
 LC/MS, m/z = 362 [M + H]⁺ (Calc: 361).

2-(3-((2*R*,6*S*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-3-methylureido)-4-methylpentanoic acid (Compound 76)



(76)

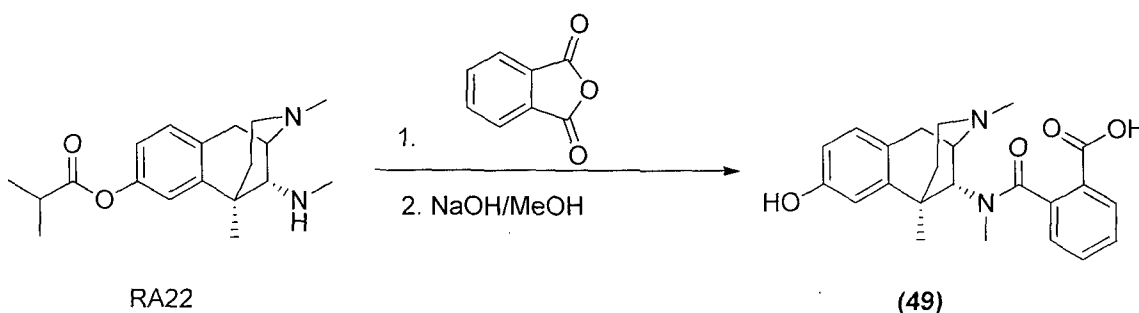
In a similar manner, **Compound 76** was prepared from RA22a (396 mgs, 1.25 mmol) using ethyl 2-isocyanato-4-methylvalerate (278 mgs, 1.5 mmol) rather than ethyl 4-isocyanato-benzoate. Purification by preparatory HPLC gave **Compound 76 TFA salt** as a brown oil.

^1H NMR δ_{H} (400 MHz, CD₃OD) 7.04-6.95 (m, 1H), 6.76-6.69 (m, 1H), 6.67-6.60 (m, 1H), 4.53-4.44 (m, 1H), 4.32-4.23 (m, 1H), 3.64-3.57 (m, 1H), 3.23-3.19 (m, 2H), 3.11-2.98 (m, 3H), 2.86-2.81 (m, 3H), 2.59-2.49 (m, 4H), 1.71-1.50 (m, 1H), 1.43-1.34 (m, 3H), 0.92-0.81 (m, 6H).

LC/MS, $m/z = 404$ [$\text{M} + \text{H}$]⁺ (Calc: 403).

EXAMPLE 36

2-(((2*R*,6*R*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)(methyl)carbamoyl)benzoic acid (**Compound 49**)

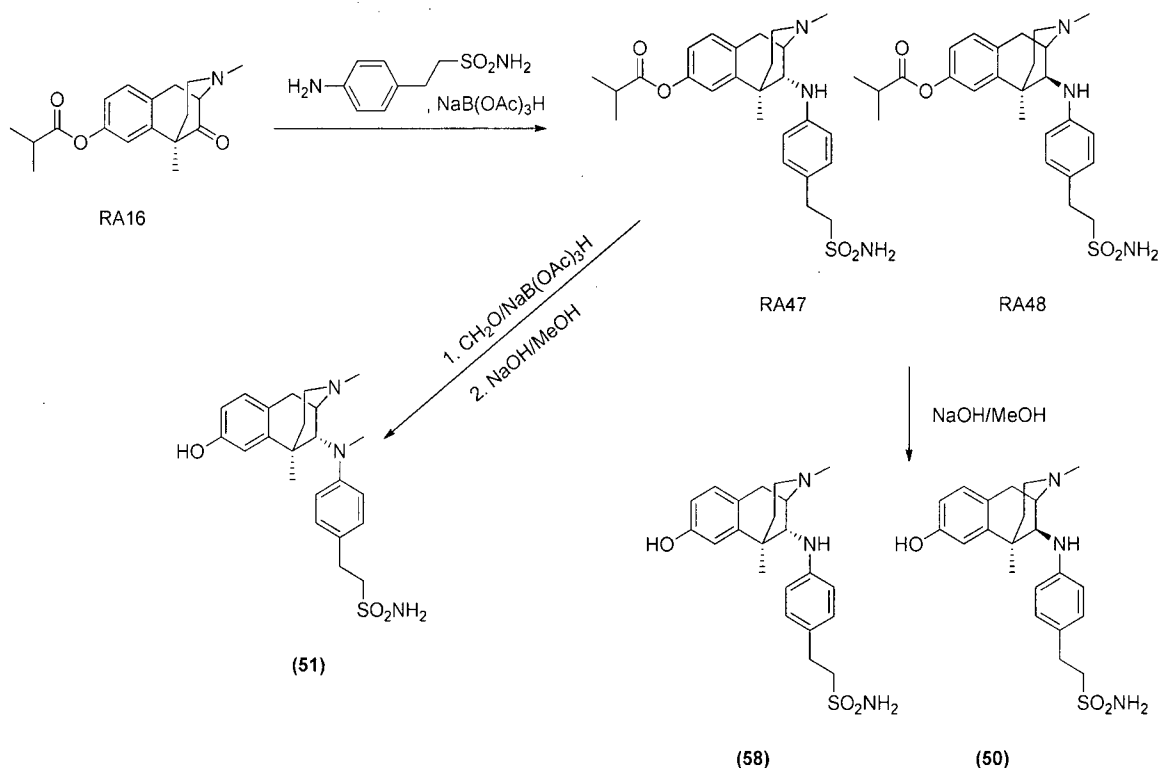


In a similar manner, **Compound 49** was prepared following the procedure for **Compound 24** using phthalic anhydride (Aldrich) instead of succinic anhydride. **Compound 49** was purified by reverse-phase prep HPLC (C18, 0-100% 0.1 % TFA in water/0.1 % TFA in ACN) as TFA-salt (20mg, white solid). ^1H NMR δ_{H} (400 MHz,

CD₃OD) 7.99 (d, J = 7.9 Hz, 1H), 7.59 (dt, J = 1.3 and 7.9 Hz, 1H), 7.45 (dt, J = 1.3 and 7.9 Hz, 1H), 7.22 (d, J = 7.7 Hz, 1H), 6.97 (d, J = 8.1 Hz, 1H), 6.73 (d, J = 2.4 Hz, 1H), 6.61 (dd, J = 2.4 and 8.3 Hz, 1H), 3.96 – 4.01 (m, 1H), 3.23 – 3.31 (m, 1H), 2.98 – 3.18 (m, 3H), 2.91 (s, 3H), 2.64 – 2.72 (m, 1H), 2.36 (s, 3H), 2.02 – 2.08 (m, 1H),
 5 1.64 – 1.68 (m, 1H), 1.52 (s, 3H); LC/MS, m/z = 395.2 [M + H]⁺ (Calc: 394.5).

EXAMPLE 37

2-(4-(((2*R*,6*R*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-
 10 methanobenzo[*d*]azocin-11-yl)amino)phenyl)ethanesulfonamide (Compound 58);
 2-(4-(((2*R*,6*R*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-
 methanobenzo[*d*]azocin-11-yl)amino)phenyl)ethanesulfonamide (Compound 50);
 and 2-(4-(((2*R*,6*R*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-
 methanobenzo[*d*]azocin-11-yl)(methyl)amino)phenyl)ethanesulfonamide
 15 (Compound 51)



In a similar manner **Compound 58** and **Compound 50** were prepared following the procedure for **Compound 30** using 4-(2-aminoethyl)benzenesulfonamide (0.9 mmol, Aldrich) instead of 1-Boc-4-(aminomethyl)piperidine.

Compound 58 (white solid, 15mg, RT 0.845min): ^1H NMR δ_{H} (400 MHz, CD_3OD) 7.76 (d, $J = 8.3$ Hz, 2H), 7.35 (d, $J = 8.3$ Hz, 2H), 7.02 (d, $J = 8.6$ Hz, 1H), 6.74 (d, $J = 2.4$ Hz, 1H), 6.7 (dd, $J = 2.4$ and 8.3 Hz, 1H), 4.16 (s, 1H), 3.64 (s, 1H), 3.22 – 3.28 (m, 3H), 3.0 – 3.16 (m, 3H), 2.92 (s, 3H), 2.64 – 2.72 (m, 1H), 2.02 – 2.08 (m, 1H), 1.65 (d, $J = 12.5$ Hz, 1H), 1.56 (s, 3H); LC/MS, $m/z = 416.2$ $[\text{M} + \text{H}]^+$ (Calc: 415.6).

Compound 50 (white solid, 12mg, RT 2.081min): ^1H NMR δ_{H} (400 MHz, CD_3OD) 7.77 (d, $J = 8.6$ Hz, 2H), 7.38 (d, $J = 8.3$ Hz, 2H), 6.94 (d, $J = 8.6$ Hz, 1H), 6.73 (d, $J = 2.4$ Hz, 1H), 6.58 (dd, $J = 2.4$ and 8.3 Hz, 1H), 3.68 (s, 1H), 3.24 – 3.28 (m, 1H), 2.88 – 3.16 (m, 7H), 2.69 (s, 3H), 2.52 – 2.56 (m, 1H), 2.08 – 2.36 (m, 1H), 1.34 (s, 3H), 1.29 (d, $J = 13.5$ Hz, 1H); LC/MS, $m/z = 416.2$ $[\text{M} + \text{H}]^+$ (Calc: 415.6).

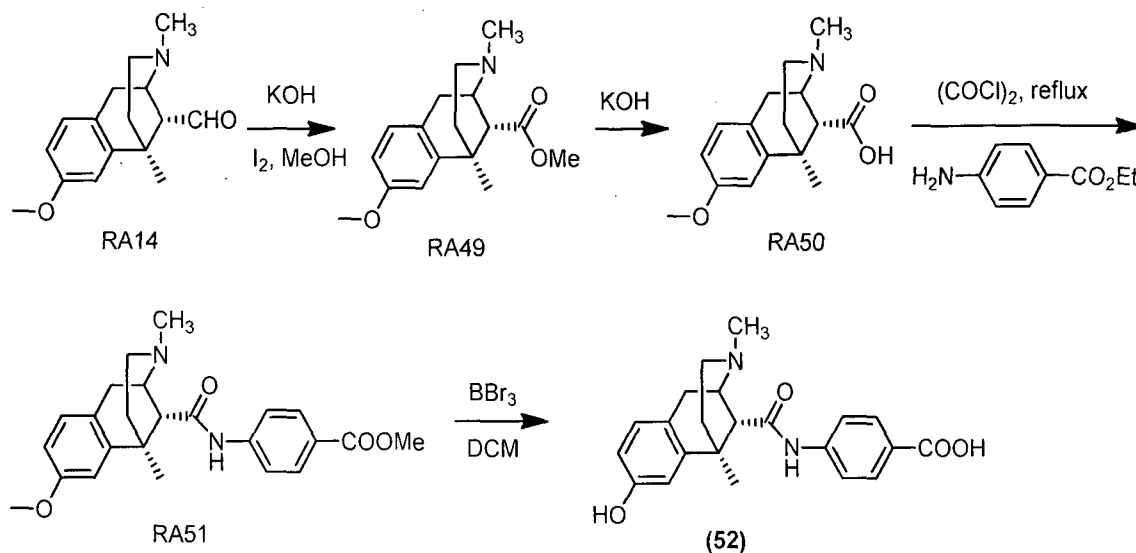
In a similar manner **Compound 51** was prepared following the procedure for **Compound 31**. **Compound 51** was purified by reverse-phase prep HPLC (C18, 0-100% 0.1 % TFA in water/0.1 % TFA in ACN), and obtained as a TFA-salt, white solid, 10mg.

Compound 51: ^1H NMR δ_{H} (400 MHz, CD_3OD) 7.68 (d, $J = 8.5$ Hz, 2H), 7.16 (d, $J = 8.3$ Hz, 2H), 6.89 (d, $J = 8.6$ Hz, 1H), 6.65 (d, $J = 2.4$ Hz, 1H), 6.58 (dd, $J = 2.4$ and 8.3 Hz, 1H), 3.68 (s, 1H), 3.24 – 3.28 (m, 1H), 2.88 – 3.16 (m, 7H), 2.69 (s, 3H), 2.52 – 2.56 (m, 1H), 2.08 – 2.36 (m, 1H), 1.34 (s, 3H), 1.29 (d, $J = 13.5$ Hz, 1H); LC/MS, $m/z = 430.2$ $[\text{M} + \text{H}]^+$ (Calc: 429.6).

25

EXAMPLE 38

4-((6*S*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[d]azocine-11-carboxamido)benzoic acid (**Compound 52**)



Compound RA14 ((600 mg, 2.32 mmol) was dissolved in MeOH (10 mL) and a solution of KOH (2.6 eq, 336 mg, 6.0 mmol) and iodine (1.3 eq, 766 mg, 3.0 mmol) in MeOH (each 2 mL) was successively added at RT. After 2 h, the solution was neutralized to pH = 7 using AcOH. The mixture was diluted with DCM (50 mL), washed with 10% Na₂S₂O₃ (20 mL) and brine, dried over Na₂SO₄, and concentrated. The residue was purified by flash column chromatography (silica gel, 0-50% EtOAc/hexanes) to give 536 mg of RA49 as an oil.

¹H NMR δ_H (400 MHz, MeOD) 7.04 (d, J = 8.33 Hz, 1H), 6.84 (d, J = 2.63 Hz, 1H), 6.76 (dd, J = 2.63 and 8.33 Hz, 1H), 3.78 (s, 3H), 3.73 (m, 1H), 3.62 (s, 3H), 3.13 (m, 1H), 3.01 (m, 1H), 2.79 (dd, J = 3.73 and 12.28 Hz, 1H), 2.44 (dt, J = 3.51 and 12.93 Hz, 1H), 1.88-1.98 (m, 2H), 1.57 (s, 3H), 1.47 (m, 1H).

LC/MS, *m/z* = 290 [M + H]⁺ (Calc: 289).

Compound RA49 (200 mg, 0.69 mmol) was dissolved in MeOH (4 mL) and then aq. KOH (2 N, 2 mL) was added. The resulting mixture was stirred at RT for 2 h, neutralized with aq HCl (1N) to pH = 3, and diluted with DCM (50 mL). The organic layer was washed with brine, dried over Na₂SO₄, and concentrated to give RA50. The residue was used directly in the next step.

LC/MS, *m/z* = 276 [M + H]⁺ (Calc: 275).

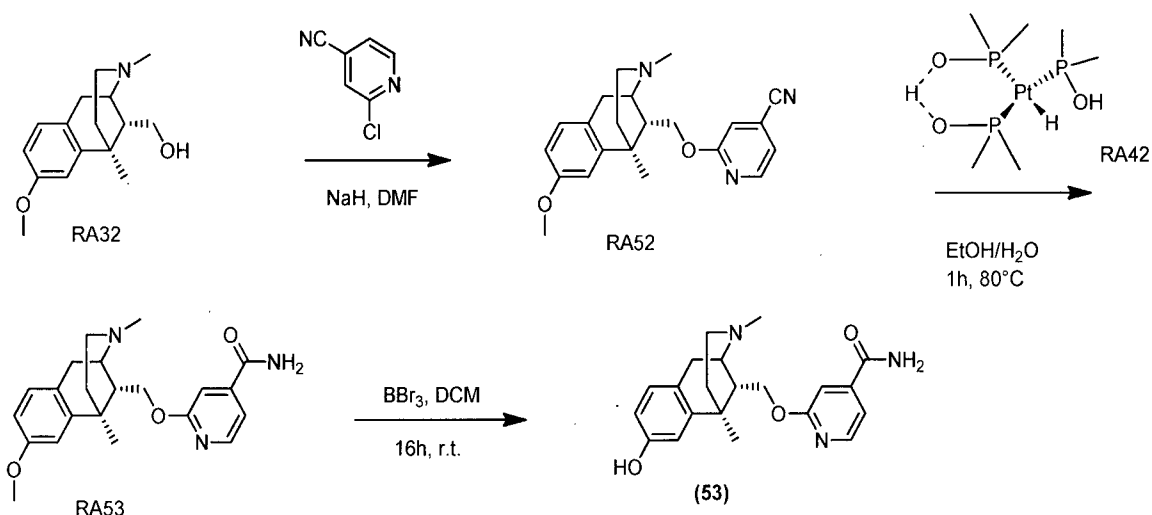
In a similar manner to **Compound 32**, **Compound 52** was prepared using RA50 rather than RA26. Purification by reverse phase column chromatography (C18, ACN/water with 0.1% TFA, 0-95%) gave **Compound 52 TFA salt** as a white powder.

- 5 ^1H NMR δ_{H} (400 MHz, MeOD) 7.85 (m, 2H), 7.51 (m, 2H), 6.93 (m, 2H), 6.69 (d, $J = 2.41$ Hz, 1H), 6.58 (dd, $J = 2.41$ and 8.55 Hz, 2H), 4.02 (m, 1H), 2.91-3.17 (m, 4H), 2.89 (s, 3H), 2.72 (m, 1H), 1.92 (m, 1H), 1.57 (d, $J = 14.25$ Hz, 1H), 1.48 (s, 3H).
LC/MS, $m/z = 381$ $[\text{M} + \text{H}]^+$ (Calc: 380).

10

EXAMPLE 39

2-(((6*S*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)methoxy)isonicotinamide (Compound 53)



- To a solution of RA32 (0.05 g, 0.192 mmol, 1.0 eq), in DMF (0.4 mL) at room temperature was added 60% sodium hydride in mineral oil (0.011 g, 0.287 mmol, 1.5 eq). The mixture was stirred for 45 min at room temperature and then it was cooled with an ice bath and a solution of 2-chloroisonicotinonitrile (0.053 g, 0.384 mmol, 2.0 eq) in DMF (0.4 mL) was added and the mixture was stirred for 1 h at room
- 20

temperature. H₂O was added and the organic portion was extracted twice with EtOAc, dried over Na₂SO₄ and concentrated. The crude product was purified by flash chromatography (silica gel, 0-10% MeOH in DCM) to afford 58 mg of RA52. LC/MS, $m/z = 364 [M + H]^+$ (Calc: 363).

5

To a suspension of RA52 (0.042 g, 0.116 mmol, 1.0 eq) in ethanol (1.1 mL) was added RA42 (0.005 g, .012 mmol, 0.10 eq) and H₂O (0.3 mL). The mixture was stirred for 1.5 h at 80 °C and concentrated to dryness to afford RA53. LC/MS, $m/z = 382 [M + H]^+$ (Calc: 381).

10

A solution of RA53 (0.044 g, 0.115 mmol, 1.0 eq) in DCM (0.80 mL), cooled with an ice bath was treated with boron tribromide (0.045 mL, 0.461 mmol, 4.0 eq). The ice bath was removed and the mixture stirred for 16 h at room temperature. It was quenched with H₂O, neutralized with solid NaHCO₃, concentrated to dryness and

15

purified by flash chromatography (silica gel, 0-10% MeOH (1N NH₃) in DCM) to afford 15 mg of **Compound 53**. ¹H NMR δ_H (300 MHz, CD₃OD) 8.08 (d, $J = 5.3$ Hz, 1H), 7.19 (dd, $J = 1.3, 5.3$ Hz, 1H), 7.08 (s, 1H), 6.84 (d, $J = 8.3$ Hz, 1H), 6.62 (d, $J = 2.6$ Hz, 1H), 6.50 (dd, $J = 2.6, 1.5$ Hz 1H), 4.45-4.40 (m, 1H), 3.89 (t, $J = 10.1$ Hz, 1H), 3.26 (m, 1H), 2.96(d, $J = 18.6$ Hz, 1H), 2.59 (dd, $J = 5.9, 18.6$ Hz, 1H), 2.39 (dd, $J = 3.3, 12.3$ Hz, 1H), 2.33 (s, 3H), 2.32-2.27 (m, 1H), 2.09 (td, $J = 3.1, 12.5$ Hz, 1H), 1.79 (td, $J = 5.9, 14.0$ Hz, 1H), 1.38(s, 3H), 1.27(d, $J = 11.8$ Hz, 1H), LC/MS, $m/z = 368 [M + H]^+$ (Calc: 367).

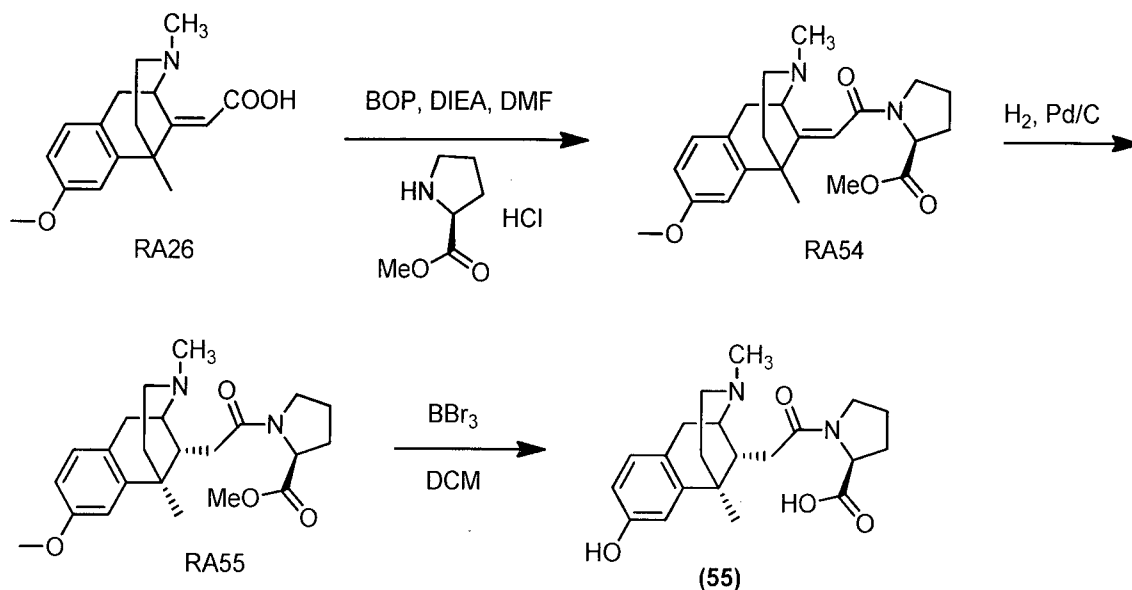
20

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EXAMPLE 40

(2*S*)-1-(2-(((6*S*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)acetyl)pyrrolidine-2-carboxylic acid (Compound 55); and 1-(2-(((6*S*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)acetyl)piperidine-4-carboxylic acid (Compound 72)

30



To a solution of RA26 (200 mg, 0.70 mmol) in DMF (4 mL) were added benzotriazol-
 5 1-yloxy-tri(dimethylamino)phosphonium hexafluorophosphate (BOP, 354 mg, 1.2 eq,
 0.84 mmol), DIEA (1 mL) and (S)-methyl pyrrolidine-2-carboxylate hydrochloride
 (116 mg, 0.7 mmol). The resulting mixture was stirred at room temperature overnight
 and then diluted with EtOAc (50 mL). The organic layer was washed with water (20
 mL x 2), brine (20 mL), dried over Na₂SO₄, and concentrated. The crude material was
 10 purified by flash column chromatography (silica gel, 0-5% MeOH/DCM) to give 167
 mg of RA54 as a pale yellow foam which was used directly in the next step.
 LC/MS, $m/z = 399$ [M + H]⁺ (Calc: 398).

To a solution of RA54 (150 mg, 0.38 mmol) in MeOH (5 mL) was added 10% Pd in
 15 charcoal (50 mg). The reaction bottle was sealed, de-gassed, and then subjected to a H₂
 balloon. After stirring at RT overnight, the solution was filtered and concentrated to
 give RA55. The crude material RA55 was used directly in the next step without further
 purification.

20 To an dry ice-cooled solution (-78°C) of RA55 (150 mg, 0.37 mmol) in DCM (4 mL)
 was added BBr₃ (0.5 mL in DCM). The reaction mixture was slowly warmed to room

temperature over 3 h, and then quenched with sat. NH_4Cl (1 mL). After evaporation of the DCM, the residue was dissolved in MeOH (2 mL) and purified by reverse phase column chromatography (C18, ACN/water with 0.1% TFA, 0-95%) to give 21 mg of **Compound 55 TFA salt** as a white powder.

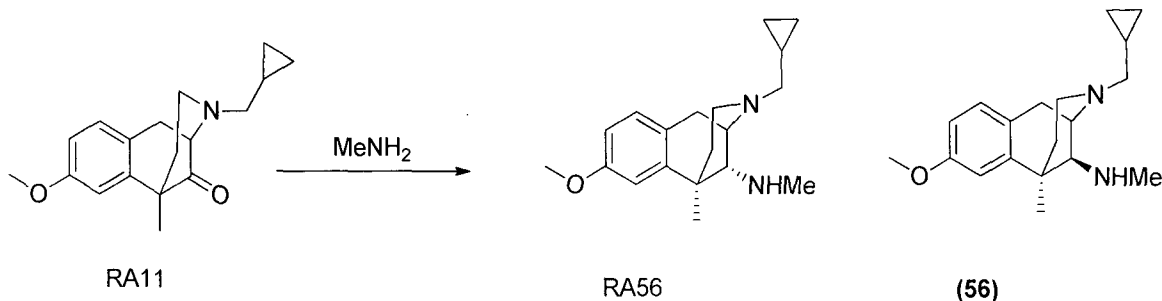
- 5 ^1H NMR δ_{H} (400 MHz, MeOD) 6.97 (t, $J = 8.55$ Hz, 1H), 6.67 (d, $J = 2.19$ Hz, 1H), 6.61 (m, 1H), 4.33 (m, 1H), 3.76 (m, 1H), 3.29-3.44 (m, 2H), 2.98-3.12 (m, 3H), 2.82 (s, 3H), 2.40-2.71 (m, 3H), 1.77-2.21 (m, 6H), 1.57 (m, 1H), 1.35 (d, $J = 8.77$ Hz, 3H). LC/MS, $m/z = 373$ $[\text{M} + \text{H}]^+$ (Calc: 372).

- 10 In a similar manner, **1-(2-((6*S*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)acetyl)piperidine-4-carboxylic acid (Compound 72)** was prepared from RA26 using ethyl piperidine-4-carboxylate rather than (S)-methyl pyrrolidine-2-carboxylate hydrochloride. Purification by reverse phase column chromatography (C18, ACN/water with 0.1% TFA, 0-95%) gave **Compound 72 TFA salt** as a white powder.

- 15 ^1H NMR δ_{H} (400 MHz, MeOD) 6.97 (dd, $J = 3.51$ and 8.33 Hz, 1H), 6.67 (t, $J = 2.41$ Hz, 1H), 6.60 (dd, $J = 2.41$ and 8.33 Hz, 1H), 4.26 (m, 1H), 3.73 (m, 1H), 3.62 (m, 1H), 2.91-3.11 (m, 2H), 2.83 (s, 3H), 2.41-2.78 (m, 5H), 1.75-2.08 (m, 4H), 1.38-1.60 (m, 3H), 1.35 (d, $J = 9.43$ Hz, 1H).
- 20 LC/MS, $m/z = 387$ $[\text{M} + \text{H}]^+$ (Calc: 386).

EXAMPLE 41

- (2*R*,6*R*,11*S*)-3-(cyclopropylmethyl)-8-methoxy-*N*,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-amine (Compound 56)
- 25



A mixture of RA11 (0.1g, 0.4 mmol), MeNH₂ (2N in THF, 2mL, 4mmol) and 4A MS
 5 was shaken at RT for 24 h. The solvent was evaporated under vacuum, then CH₃CN
 (1mL) and NaB(OAc)₃H (0.2g, 0.9 mmol) were added. The reaction mixture was
 shaken at RT for 24 h. The solid was filtered and washed with CHCl₃ (6mL). The
 filtrate was washed with 0.2 N of NaOH aqueous (1mL), concentrated and purified by
 reverse-phase prep HPLC (C18, 0-100% 0.1 % TFA in water/0.1 % TFA in ACN) to
 10 yield RA56 and **Compound 56**.

RA56 (TFA-salt, 20mg, 10%, RT 1.101min): ¹H NMR δ_H (400 MHz, DMSO-d₆) 10.5
 (br., 1H), 9.0 (br., 1H), 8.6 (br., 1H), 6.96 – 7.0 (m, 1H), 6.88 – 6.96 (m, 2H), 4.42 (s,
 1H), 3.77 (s, 3H), 3.72 – 3.75 (m, 1H), 3.2 – 3.2 (m, 5H), 2.7 (s, 3H), 2.38 – 2.46 (m,
 15 1H), 1.98 – 2.08 (m, 1H), 1.7 (d, J = 13.8 Hz, 1H), 1.62 (s, 3H), 1.06 – 1.12 (m, 1H),
 0.632 – 0.68 (m, 2H), 0.36 – 0.42 (m, 2H); LC/MS, *m/z* = 301.4 [M + H]⁺ (Calc:
 300.4).

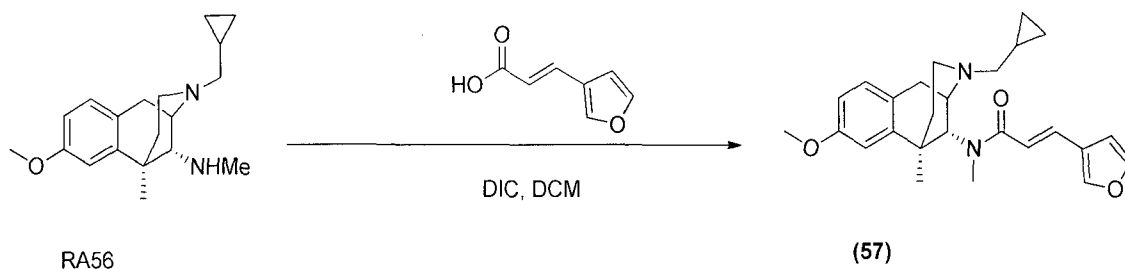
Compound 56 (TFA-salt, 70mg, 40%, 1.363min): ¹H NMR δ_H (400 MHz, CD₃CN,) 7.05 (d, J = 8.5 Hz, 1H), 6.85 (d, J = 2.6 Hz, 1H), 6.78 (dd, J = 2.6 and 8.5 Hz, 1H),
 20 4.2 (s, 1H), 3.69 (s, 3H), 3.42 (s, 1H), 3.0 – 3.22 (m, 4H), 2.69 – 2.72 (m, 1H), 2.67 (s,
 3H), 2.36 – 2.43 (m, 1H), 2.16 – 2.24 (m, 1H), 1.48 (s, 3H), 1.44 (d, J = 14.2 Hz, 1H),
 0.98 – 1.03 (m, 1H), 0.54 – 0.66 (m, 2H), 0.28 – 0.34 (m, 2H); LC/MS, *m/z* = 301.4
 [M + H]⁺ (Calc: 300.4).

25

EXAMPLE 42

(*E*)-*N*-((2*R*,6*R*,11*S*)-3-(cyclopropylmethyl)-8-methoxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-3-(furan-3-yl)-*N*-methylacrylamide (Compound 57)

5



In a similar manner **Compound 57** was prepared following the procedure for **Compound 16**. The product was purified by reverse-phase prep HPLC (C18, 0-100% 0.1 % TFA in water/0.1 % TFA in ACN), to obtain **Compound 57** as a TFA-salt, white solid. ¹H NMR δ_H (400 MHz, CD₃OD) 7.74 (s, 1H), 7.48 (d, *J* = 14.1 Hz, 1H), 7.44 (s, 1H), 7.09 (d, *J* = 8.6 Hz, 1H), 6.86 (d, *J* = 2.4 Hz, 1H), 6.8 (dd, *J* = 2.4 and 8.3 Hz, 1H), 6.74 (s, 1H), 6.68 – 6.74 (m, 2H), 4.96 (s, 0.2H), 4.84 (s, 0.8H), 3.96 (s, 1H), 7.72 (s, 3H), 3.2 – 3.34 (m, 3H), 2.94 – 3.12 (m, 2H), 2.77 (s, 3H), 2.52 – 2.6 (m, 1H), 2.02 – 2.12 (m, 1H), 1.64 – 1.68 (m, 1H), 1.45 (s, 3H), 1.0 – 1.08 (m, 1H), 0.67 – 0.72 (m, 2H), 0.36 – 0.4 (m, 2H); LC/MS, *m/z* = 421.2 [M + H]⁺ (Calc: 420.5).

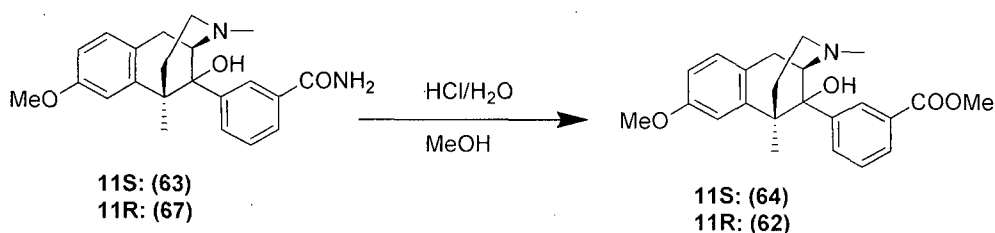
In a similar manner, (*E*)-*N*-((2*R*,6*R*,11*S*)-3-(cyclopropylmethyl)-8-methoxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-3-(furan-3-yl)-*N*-methylacrylamide (**Compound 85**) was prepared.

¹H NMR δ_H (400 MHz, CD₃OD) 7.87 (s, 1H), 7.64 (d, *J* = 16.8 Hz, 1H), 7.49 (s, 1H), 7.08 (d, *J* = 8.4 Hz, 1H), 6.75 – 6.84 (m, 4H), 4.21 (s, 1H), 3.88 (s, 1H), 3.69 (s, 3H), 3.32 – 3.66 (m, 3H), 3.25 (s, 3H), 2.98 – 3.12 (m, 2H), 2.61 – 2.68 (m, 1H), 2.28 – 2.37 (m, 1H), 1.49 (s, 3H), 1.45 (d, *J* = 15.2 Hz, 1H), 1.01 – 1.13 (m, 1H), 0.62 – 0.73 (m, 2H), 0.35 – 0.45 (m, 2H).

LC/MS, *m/z* = 421.2 [M + H]⁺ (Calc: 420.5).

EXAMPLE 43

methyl 3-((6*R*,11*S*)-11-hydroxy-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)benzoate (Compound 64); and methyl 3-((6*R*,11*R*)-11-hydroxy-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)benzoate (Compound 62)



To **Compound 63** (70 mg, 0.19 mmol) was added 1 mL of 6 *M* HCl and the resulting suspension stirred at 80 °C. After 90 min, a few drops of MeOH were added to help solubilize **Compound 63**. After 3 h, 1 mL H₂O was added. After 6 h the solution was cooled to RT and concentrated. To the resulting residue was added 0.5 mL MeOH and 0.5 mL 1 *M* NaOH (0.5 mmol, 2.5 equiv.). The solution was stirred at RT for 16 h and at reflux for 3 h. Excess HCl/Et₂O was added and the solution concentrated. The resulting material was purified by preparative HPLC [0-60% MeCN/H₂O (0.01% TFA)] to yield **Compound 64 TFA salt**.

¹H NMR δ_H (400 MHz, ACN-d₃) 8.38 (bs, 1H), 8.04 (s, 1H), 7.82 (d, *J* = 6.6 Hz, 1H), 7.46 (d, *J* = 8.1 Hz, 1H), 7.30 (t, *J* = 8.1 Hz, 1H), 7.05 (t, *J* = 2.6 Hz, 1H), 7.02 (s, 1H), 6.87 (dd, *J* = 8.1, 2.6 Hz, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 3.76 (d, *J* = 5.3 Hz, 1H), 3.22-3.09 (m, 2H), 2.85 (s, 3H), 2.72-2.47 (m, 4H), 1.84 (s, 1H), 1.51 (s, 3H), 1.40 (dd, *J* = 15.1, 3.0 Hz, 1H).

LC/MS, *m/z* = 382 [*M* + *H*]⁺ (Calc: 381).

In a similar manner **Compound 62 TFA salt** was synthesized analogously from **Compound 67**.

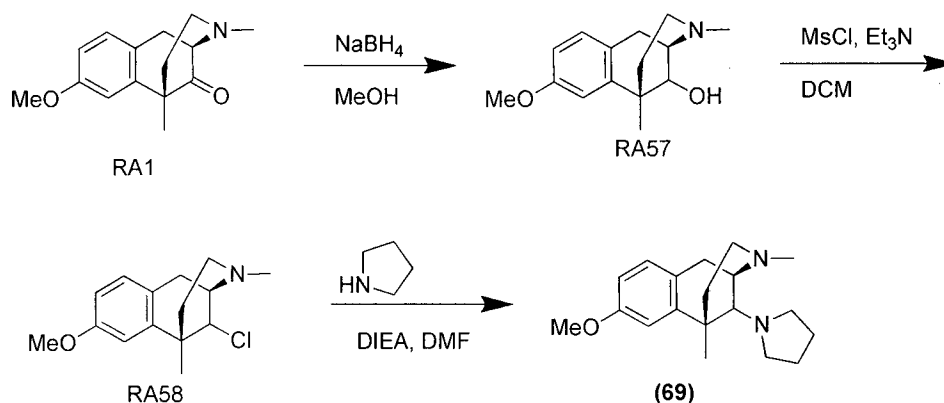
¹H NMR δ_H (400 MHz, DMSO-d₆) 8.91 (s, 1H), 8.74 (d, *J* = 8.1 Hz, 1H), 8.45 (s, 1H), 8.23-8.12 (m, 2H), 8.00 (d, *J* = 8.3 Hz, 1H), 7.85 (d, *J* = 8.1 Hz, 1H), 7.63 (t, *J* =

8.1 Hz, 1H), 7.45 (t, $J = 7.6$ Hz, 1H), 7.12 (d, $J = 8.6$ Hz, 1H), 7.01 (d, $J = 8.6$ Hz, 1H), 6.92 (s, 1H), 6.79 (d, $J = 2.2$ Hz, 1H), 6.68 (d, $J = 8.1$ Hz, 1H), 6.15 (s, 1H), 3.99 (d, $J = 6.6$ Hz, 1H), 3.90 (s, 1.5 H), 3.85 (s, 1.5H), 3.75 (s, 1.5H), 3.70 (s, 1.5H), 3.45 (dd, $J = 20.2, 6.6$ Hz, 2H), 3.26 (d, $J = 19.3$ Hz, 2H), 3.14 (d, $J = 5.9$ Hz, 1H), 3.10 (d, $J = 9.9$ Hz, 1H), 3.04-2.89 (m, 2H), 2.81 (d, $J = 4.2$ Hz, 3H), 2.10 (td, $J = 12.4, 3.9$ Hz, 2H), 1.71 (d, $J = 13.2$ Hz, 2H), 1.66 (s, 3H), 1.09 (s, 3H), 1.08-1.01 (m, 1H).
 LC/MS, $m/z = 382$ $[M + H]^+$ (Calc: 381).

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EXAMPLE 44

(6R)-8-methoxy-3,6-dimethyl-11-(pyrrolidin-1-yl)-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[d]azocine (Compound 69)



15

NaBH₄ (83 mg, 2.2 mmol, 1.2 eq) was added to RA1 (450 mg, 1.8 mmol, 1 eq) in 10 mL of MeOH and the solution stirred at RT for 90 min. EtOAc was added, the solution washed with sat. NaHCO₃, dried with Na₂SO₄, and concentrated to yield RA57 as a clear oil.

To RA57 (630 mg, 2.6 mmol, 1 eq) and Et₃N (1.1 mL, 7.9 mmol, 3 eq) in 12 mL DCM was added MsCl (0.24 mL, 3.1 mmol, 1.2 eq) and the solution stirred at RT. After 90 min. additional MsCl (0.24 mL, 3.1 mmol, 1.2 eq) was added. After 3 h additional MsCl (0.24 mL, 3.1 mmol, 1.2 eq) was added. After 19 h DCM was added and the solution washed with sat. NaHCO₃, dried with Na₂SO₄, and concentrated. The

resulting residue was purified by MPLC (0-20% MeOH/DCM, 12g) to yield RA58 as a yellow oil, 260 mg.

Pyrrolidine (13 μ L, 0.16 mmol, 1.2 eq) was added to RA58 (35 mg, 0.13 mmol, 1 eq) and DIEA (69 μ L, 0.39 mmol, 3 eq) in 0.5 mL DMF and the solution heated at 60 °C for 2 h. The temperature was increased to 120 °C for 1 h, then lowered again to 60 °C. After 46 h the reaction was concentrated and purified by MPLC (0-20% MeOH/DCM, 12g) and further purified by preparative HPLC [0-60% MeCN/H₂O (0.01% TFA)] to yield **Compound 69 TFA salt**.

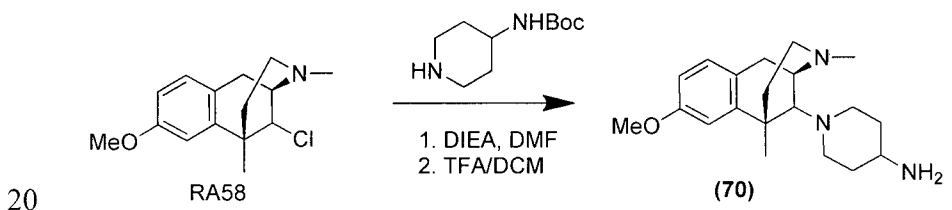
¹H NMR δ_H (400 MHz, MeOH-d₄) 7.13 (d, J = 8.6 Hz, 1H), 6.92 (d, J = 2.4 Hz, 1H), 6.78 (dd, J = 8.6, 2.4 Hz, 1H), 3.88-3.77 (m, 1H), 3.71 (s, 3H), 3.66-3.61 (m, 1H), 3.60-3.52 (m, 1H), 3.35-3.23 (m, 5H), 3.11-3.05 (m, 2H), 3.01 (s, 3H), 2.32-2.24 (m, 1H), 2.17-2.06 (m, 1H), 2.01-1.90 (m, 4H), 1.57 (s, 3H).

LC/MS, m/z = 301 [M + H]⁺ (Calc: 300).

15

EXAMPLE 45

1-((6*R*)-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)piperidin-4-amine (Compound 70)

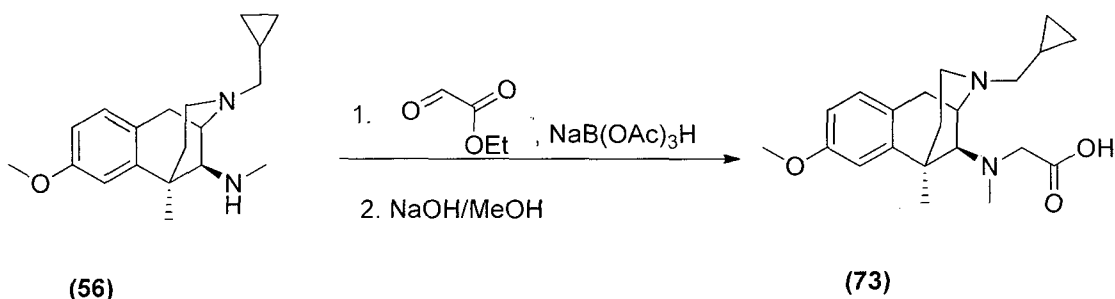


4-Boc-aminopiperidine (45 mg, 0.18 mmol, 1.2 eq) was added to RA58 (40 mg, 0.15 mmol, 1 eq) and DIEA (79 μ L, 0.45 mmol, 3 eq) in 0.5 mL DMF and the solution heated at 60 °C for 40 h. The reaction was concentrated and purified by MPLC (0-20% MeOH/DCM, 12g). To the purified residue was added 0.5 mL of 1:1 TFA:DCM. The reaction was stirred at RT for 1 h and concentrated. The resulting material was purified by preparative HPLC [0-60% MeCN/H₂O (0.01% TFA)] to yield **Compound 70 TFA salt**.

¹H NMR δ_H (400 MHz, MeOH-d₄) 6.96 (d, J = 8.3 Hz, 1H), 6.70 (d, J = 2.4 Hz, 1H), 6.66 (dd, J = 8.3, 2.4 Hz, 1H), 3.73-3.67 (m, 1H), 3.67 (s, 3H), 3.46 (d, J = 11.4 Hz, 1H), 3.33 (td, J = 13.5, 5.7 Hz, 1H), 3.13-3.02 (m, 5H), 2.82-2.67 (m, 4H), 2.56-2.42 (m, 2H), 2.27 (t, J = 10.8 Hz, 1H), 2.09 (td, J = 13.6, 7.0 Hz, 1H), 2.04-1.90 (m, 2H), 1.65 (qd, J = 11.6, 4.8 Hz, 1H), 1.49 (qd, J = 12.0, 4.0 Hz, 1H), 1.42 (s, 3H).
 LC/MS, m/z = 330 [M + H]⁺ (Calc: 329).

EXAMPLE 46

2-(((2*R*,6*R*,11*S*)-3-(cyclopropylmethyl)-8-methoxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)(methyl)amino)acetic acid (Compound 73)



15

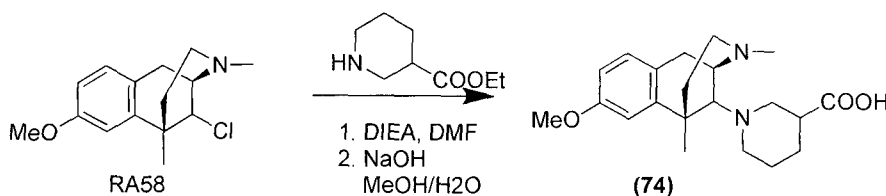
A mixture of **Compound 56** (TFA-Salt, 50mg, 0.12 mmol), glyoxylic acid ethyl ester (0.1g, 1 mmol), TEA (0.05mL, 0.4 mmol) and 4A MS in CH₃CN (0.5mL) was shaken for 2 h; then NaB(OAc)₃H (0.3g, 1.4 mmol) was added. The reaction mixture was shaken at RT for 16 h. The solid was filtered, and washed with CHCl₃ (10mL). The filtrate was washed with water, and concentrated. The residue was dissolved in 1mL MeOH and treated with 0.2mL NaOH (2N aqueous) at RT for 24 h. After aqueous work-up, the product was purified by reverse-phase prep HPLC (C18, 0-100% 0.1 % TFA in water/0.1 % TFA in ACN) to yield **Compound 73** as TFA-salt (15mg, white solid).

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¹H NMR δ_H (400 MHz, CD₃OD) 7.15 (d, J = 8.5 Hz, 1H), 6.95 (d, J = 2.6 Hz, 1H), 6.85 (dd, J = 2.6 and 8.3 Hz, 1H), 4.53 (d, J = 5.3 Hz, 1H), 3.94 (d, J = 18.9 Hz, 1H), 3.79 (s, 3H), 3.72 (d, J = 18.2 Hz, 1H), 3.32 – 3.45 (m, 4H), 3.19 – 3.24 (m, 1H), 2.97 (dd, J = 7.8 and 13.4 Hz, 1H), 2.83 (s, 3H), 2.66 (dt, J = 3.5 and 13.2 Hz, 1H), 2.4 (dt, J = 4.6 and 14.5 Hz, 1H), 1.64 (s, 3H), 1.54 (d, J = 14.7 Hz), 1.16 – 1.23 (m, 1H), 0.75 – 0.84 (m, 2H), 0.49 – 0.53 (m, 2H); LC/MS, m/z = 359.2 [M + H]⁺ (Calc: 358.5).

EXAMPLE 47

1-((6*R*)-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[d]azocin-11-yl)piperidine-3-carboxylic acid (Compound 74)

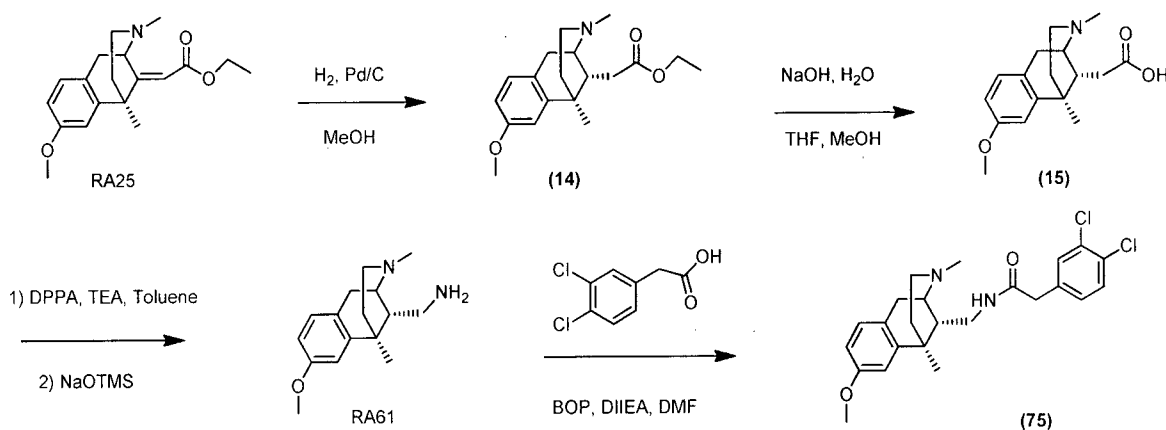


Ethyl nipecolate (35 μ L, 0.18 mmol, 1.2 eq) was added to RA58 (40 mg, 0.15 mmol, 1 eq) and DIEA (79 μ L, 0.45 mmol, 3 eq) in 0.5 mL DMF and the solution heated at 60 °C for 40 h. The reaction was concentrated and purified by MPLC (0-20% MeOH/DCM, 12g). To the purified residue was added 0.4 mL MeOH and 0.2 mL 10 % NaOH. The reaction was stirred at 80 °C for 1 h and concentrated. The resulting material was purified by preparative HPLC [0-60% MeCN/H₂O (0.01% TFA)] to yield Compound 74 TFA salt.

¹H NMR δ_H (400 MHz, MeOH-d₄) 6.97 (d, J = 8.3 Hz, 1H), 6.70 (d, J = 2.4 Hz, 1H), 6.66 (dd, J = 8.3, 2.4 Hz, 1H), 3.70-3.63 (m, 1H), 3.67 (s, 3H), 3.47 (d, J = 11.4 Hz, 1H), 3.37-3.27 (m, 1H), 3.09 (s, 3H), 3.01 (dt, J = 11.6, 3.2 Hz, 1H), 2.79 (dd, J = 14.5, 2.9 Hz, 1H), 2.70 (dd, J = 11.1, 3.0, 2H), 2.66-2.59 (m, 1H), 2.53 (d, J = 13.8 Hz, 1H), 2.46 (dd, J = 13.4, 5.5 Hz, 1H), 2.35-2.18 (m, 2H), 2.07 (td, J = 13.6, 7.0 Hz, 1H), 1.97-01.82 (m, 2H), 1.77-1.65 (m, 1H), 1.56 (q, J = 11.0 Hz, 1H), 1.42 (s, 3H). LC/MS, m/z = 359 [M + H]⁺ (Calc: 358).

EXAMPLE 48

2-(3,4-dichlorophenyl)-N-(((6*S*,11*S*)-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)methyl)acetamide (Compound 75)



5

To a solution of RA25 (3.0 g, 9.51 mmol, 1.0 eq), in MeOH (30 mL) was added wet 10% palladium on carbon (0.50 g). The mixture was stirred for 16 h at room temperature under a balloon of hydrogen, filtered through Celite and concentrated to dryness to afford **Compound 14**. LC/MS, $m/z = 318$ $[M + H]^+$ (Calc: 317).

To a solution of **Compound 14** in THF (30 mL) at room temperature was added a solution of sodium hydroxide (1.06 g, 26.5 mmol, 3.0 eq) in H₂O (20 mL) followed by MeOH (13 mL). The solution was stirred for 2 h, the THF and MeOH were removed under reduced pressure, the pH was adjusted to 7.0 and the aqueous solution was concentrated to dryness. The solid residue was stirred with MeOH and the solid was removed by filtration and discarded. The filtrate was concentrated to afford **Compound 15**. LC/MS, $m/z = 290$ $[M + H]^+$ (Calc: 289).

To a solution of **Compound 15** (0.25 g, 0.865 mmol, 1.0 eq) in toluene (10 mL) was added triethylamine (0.12 mL, 0.865 mmol, 1.0 eq) and diphenylphosphoryl azide (0.186 mL, 0.865 mmol, 1.0 eq). The mixture was heated to reflux for 2 h, cooled with an ice bath and 1.0 M sodium trimethylsilanolate in THF (1.75 mL, 1.73 mmol, 2.0 eq) was added. The mixture was stirred at room temperature for 30 min, cooled

with an ice bath, quenched with 10% citric acid, neutralized with NaHCO₃ and extracted with EtOAc and DCM. The combined organic layers were dried over sodium sulfate and concentrated to dryness and purified by flash chromatography (silica gel, EtOAc then 0-25% MeOH (1N NH₃) in DCM) to afford 0.042 g of RA61.

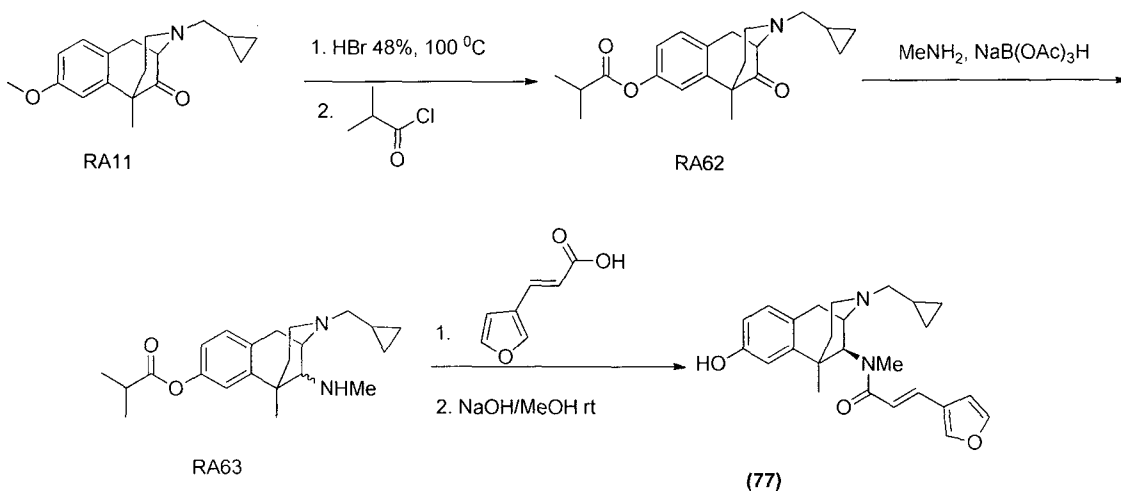
5 ¹H NMR δ_H (300 MHz, CDCl₃) 6.94 (d, J = 8.3 Hz 1H), 6.68 (d, J = 2.6 Hz, 1H), 6.62 (dd, J = 2.6, 8.3 Hz, 1H), 3.71 (s, 3H), 3.23 (m, 1H), 2.95 (d, J = 18.4 Hz, 1H), 2.88 (dd, J = 4.4, 12.9 Hz, 1H), 2.55 (dd, J = 5.9, 18.2 Hz, 1H), 2.40 (m, 1H), 2.37 (s, 3H), 2.25-2.17(t, J = 12.7, 1H), 2.06-1.98 (td, J = 3.3, 12.5 Hz, 1H), 1.84-1.76 (td, J = 4.8, 12.7 Hz, 1H), 1.76-1.70 (m, 1H), 1.33 (s, 3H), 1.28(m, 1H), 1.24(m, 1H), LC/MS, m/z = 261 [M + H]⁺ (Calc: 260).

To a solution of RA61 (0.42 g, 0.162 mmol, 1.0 eq) in DMF (0.9 mL) was added diisopropylethylamine (0.063 g, 0.485 mmol, 3.0 eq), 3,4-dichlorophenylacetic acid (0.040 g, 0.194 mmol, 1.2 eq), and benzotriazole-1-yl-oxy-tris-(dimethylamino)-
 15 phosphonium hexafluorophosphate (0.086 g, 0.194 mmol, 1.2 eq). The mixture was stirred for 16 h at room temperature, brine was added and the mixture extracted with DCM. The organic layers were concentrated and purified by flash chromatography (silica gel, 0-25% MeOH in DCM) to afford 0.018 g of **Compound 75**. ¹H NMR δ_H (300 MHz, CD₃OD) 7.40-7.36 (m, 2H), 7.13 (dd, J = 2.0, 8.1 Hz, 1H),
 20 7.02 (d, J = 8.5 Hz, 1H), 6.75-6.71 (m, 2H), 3.67 (s, 3H), 3.41 (m, 3H), 3.29 (dd, J = 4.8, 14.0 Hz 1H), 3.19-3.10 (m, 1H), 3.07-3.00 (m, 1H), 2.95-2.88 (m, 1H), 2.85-2.78(dd, J = 10.1, 14.0 Hz, 1H), 2.73 (s, 2H), 2.54 (d, J = 9.4, 3H), 2.09 (m, 1H), 1.89-1.79 (td, J = 5.0, 13.8 Hz, 1H), 1.46 (d, J = 13.6 Hz, 1H), 1.41 (s, 3H), LC/MS, m/z = 447 [M + H]⁺ (Calc: 446).

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EXAMPLE 49

(*E*)-*N*-((2*R*,6*R*,11*S*)-3-(cyclopropylmethyl)-8-hydroxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-3-(furan-3-yl)-*N*-methylacrylamide
 30 (Compound 77)



In a similar manner compound RA62 was prepared following the procedure for RA16.

- 5 The product was purified by column (silica gel, EtOAc/Hexane 2/1); to yield RA62 as a colorless oil, 150mg, 40%: ¹H NMR δ_H (400 MHz, CDCl₃) 7.0 (d, J = 8.5Hz, 1H), 6.8 (d, J = 2.4 Hz, 1H), 6.77 (dd, J = 2.6 and 5.4 Hz, 1H), 3.56 (d, J = 6.1 Hz, 1H), 3.37 (d, J = 18.4 Hz, 1H), 3.04 (dd, J = 7.0 and 18.8 Hz), 2.58 – 2.68 (m, 3H), 2.36 (d, J = 6.4 Hz, 2H), 2.04 – 2.12 (m, 1H), 1.56 – 1.62 (m, 1H), 1.33 (s, 3H), 1.18 (d, J = 6.9Hz, 6H), 0.68 – 0.73 (m, 1H), 0.39 – 0.42 (m, 2H), -0.08 – 0.02 (m, 2H).

- 10 A mixture of RA62 (0.15g, 0.44 mmol), methylamine (2N in THF, 2mL, 4 mmol) and 4A MS in CH₃CN was shaken for 12 h, then NaB(OAc)₃H (0.4g, 1.8 mmol) was added. The reaction mixture was shaken at RT for 24 h. The solid was filtered, and washed with CHCl₃ (10mL). The filtrate was washed with 2N NaOH (2mL aqueous). The organic layer was concentrated to yield 0.2g of crude RA63 {(LC/MS, *m/z* = 357.5 [M + H]⁺ (Calc: 356.5)}.

- 15 O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU, Applied Bio, 0.22g, 0.6 mmol) was added to a solution of RA63 (0.2g, 0.56 mmol), 3-(3-furyl)acrylic acid (100mg, 0.7 mmol) and TEA (0.1mL, 0.8 mmol) in DMF (1mL) at RT. The reaction mixture was shaken at RT for 24 h. After aqueous work-up, the product was dissolved in 1mL MeOH and treated with 0.2mL NaOH (2N aqueous) at RT for 24 h. After aqueous work-up, the product was purified by reverse-phase prep HPLC (C18, 0-100% 0.1 % TFA in water/0.1 %

TFA in ACN) to yield **Compound 77** (the major isomer) as TFA-salt (30mg, yellow solid): ^1H NMR δ_{H} (400 MHz, CD_3OD) 7.8 (s, 1H), 7.62 (d, $J = 15.1$ Hz, 1H), 7.48 (s, 1H), 6.98 (d, $J = 8.3$ Hz, 1H), 6.84 (s, 1H), 6.79 (d, $J = 2.8$ Hz, 1H), 6.71 (d, $J = 2.4$ Hz, 1H), 6.62 (dd, $J = 2.6$ and 8.3 Hz, 1H), 4.2 (d, $J = 3.9$ Hz, 1H), 3.87 (s, 1H), 3.3 – 3.36 (m, 3H), 3.28 (s, 3H), 2.98 – 3.08 (m, 2H), 2.62 – 2.7 (m, 1H), 2.28 – 2.36 (m, 1H), 1.46 (s, 3H), 1.41 – 1.43 (m, 1H), 1.04 – 1.12 (m, 1H), 0.65 – 0.7 (m, 2H), 0.38 – 0.42 (m, 2H); LC/MS, $m/z = 407.3$ $[\text{M} + \text{H}]^+$ (Calc: 406.5).

In a similar manner, (*E*)-*N*-((6*R*,11*R*)-3-(cyclopropylmethyl)-8-hydroxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-3-(furan-3-yl)-*N*-methylacrylamide (**Compound 83**) was prepared.

^1H NMR δ_{H} (400 MHz, CD_3OD) 7.74 (s, 1H) 7.48 (d, $J = 15.2$ Hz, 1H), 7.44 (s, 1H), 6.98 (d, $J = 8.8$ Hz, 1H), 6.62 – 6.74 (m, 4H), 4.82 – 4.93 (m, 1H), 3.85 – 3.97 (m, 1H), 3.16 – 3.23 (m, 1H), 2.91 – 3.12 (m, 3H), 2.79 (s, 3H), 2.53 – 2.63 (m, 1H), 2.02 – 2.31 (m, 1H), 1.64 (d, $J = 14.8$ Hz, 1H), 1.44 (s, 3H), 0.96 – 1.13 (m, 1H), 0.68 (d, $J = 7.6$ Hz, 2H), 0.38 – 0.51 (m, 2H).

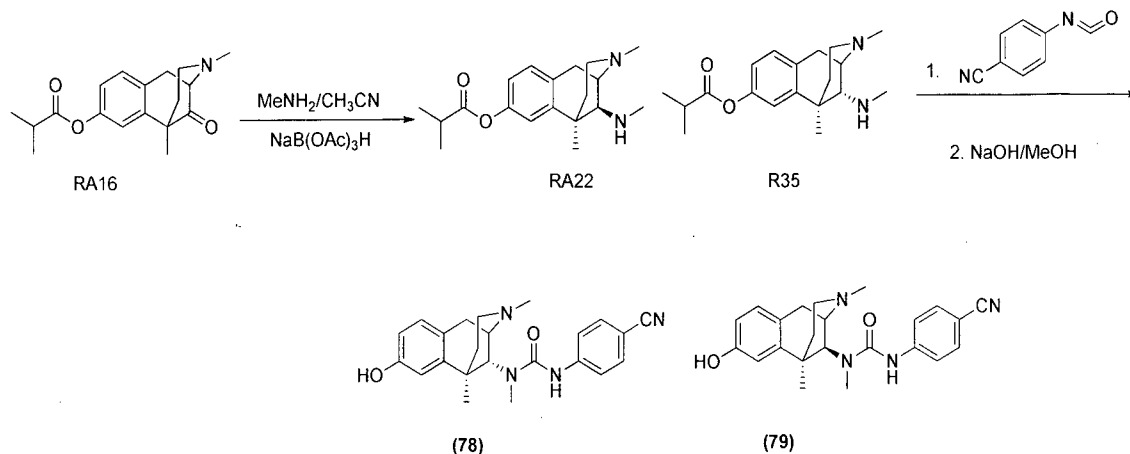
LC/MS, $m/z = 406.5$ $[\text{M} + \text{H}]^+$ (Calc: 407.3).

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EXAMPLE 50

3-(4-cyanophenyl)-1-((2*R*,6*R*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-1-methylurea (**Compound 78**); and 3-(4-cyanophenyl)-1-((2*R*,6*R*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-1-methylurea (**Compound 79**)

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A mixture of RA16 (0.85g, 2.7 mmol), MeNH₂ (33% in EtOH, 1mL, Aldrich, 10
 5 mmol) and 4A MS (0.4g) in 1mL CH₃CN was shaken at RT for 4 h. The solvent was removed under vacuum. The residue was treated with CH₃CN (3mL) and NaB(OAc)₃H (3.4 mmol). The reaction mixture was stirred at RT for 14 h. The solid was filtered. The filtrate was quenched with water (2mL and 2N NaOH 2mL), extracted with EtOAc and concentrated to yield 0.5g of crude RA22 /RA35 {*m/z* =
 10 317.4 [M + H]⁺ (Calc: 316.4)}.

4-Isocyanatobenzonitrile (1.4 mmol, 0.2g, Aldrich) was added to a solution of RA22/RA35 (0.5g, 1.6mmol) in 4mL CHCl₃ at 0 °C. The reaction mixture was warmed to RT over 4 h, and shaken at RT for two days. The reaction mixture was quenched with water (1mL), and the solvent was evaporated under vacuum. The
 15 residue was dissolved in MeOH (6mL), and treated with NaOH (2N in water, 0.5mL). The reaction mixture was shaken at RT for 14 h. After being concentrated under vacuum, the residue was dissolved in CHCl₃ (10mL), and neutralized to pH ~ 3 with 1N HCl. The organic layer was concentrated and purified by column (CHCl₃/MeOH 10/1) to yield compounds **Compound 78** and **Compound 79**.

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Compound 78 (white solid, 110mg, 22%, RT 1.650min): ¹H NMR δ_H (400 MHz, CDCl₃) 7.68 (d, *J* = 8.7 Hz, 2H), 7.58 (d, *J* = 8.8 Hz, 2H), 6.97 (d, *J* = 8.3 Hz, 1H), 6.77 (d, *J* = 2.6 Hz, 1H), 6.68 (dd, *J* = 2.4 and 8.1 Hz, 1H), 3.8 – 4.1 (m, 1H), 3.08 –

3.17 (m, 2H), 2.64 – 2.72 (m, 4H), 2.5 – 2.56 (m, 1H), 2.46 (s, 3H), 2.04 – 2.22 (m, 1H), 1.94 – 2.02 (m, 1H), 1.48 – 1.52 (m, 1H), 1.47 (s, 3H); LC/MS, m/z = 391.2 [$M + H$]⁺ (Calc: 390.5).

- 5 **Compound 79** (white solid, 80mg, 16%, RT 1.805min): ¹H NMR δ_H (400 MHz, CDCl₃) 7.57 (dd, J = 1.9 and 8.7 Hz, 2H), 7.51 (d, J = 8.7 Hz, 2H), 7.0 (d, J = 7.9 Hz, 1H), 6.76 (d, J = 2.6 Hz, 1H), 6.69 (dd, J = 2.4 and 8.1 Hz, 1H), 3.64 – 3.69 (m, 1H), 3.52 – 3.56 (m, 1H), 3.24 – 3.26 (m, 1H), 3.14 (s, 3H), 2.96 – 3.04 (m, 1H), 2.6 – 2.66 (m, 1H), 2.55 (s, 3H), 2.36 – 2.44 (m, 1H), 2.16 – 2.22 (m, 1H), 1.47 (s, 3H), 1.24 –
10 1.32 (m, 1H); LC/MS, m/z = 391.2 [$M + H$]⁺ (Calc: 390.5).

In a similar manner the following compounds were prepared.

- 15 **3-(4-cyanophenyl)-1-((6*R*,11*S*)-3-(cyclopropylmethyl)-8-hydroxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-1-methylurea**
(Compound 81)

¹H NMR δ_H (400 MHz, CD₃OD) 7.58 (s, 4H) 6.98 (d, J = 8.8 Hz, 1H), 6.71 (d, J = 2.8 Hz, 1H), 6.62 (dd, J = 2.8 and 7.6 Hz, 1H), 4.24 (d, J = 5.6 Hz, 1H), 3.27 – 3.40 (m, 1H), 3.23 (s, 3H), 3.00 – 3.11 (m, 1H), 2.62 – 2.70 (m, 1H), 2.28 – 2.37 (m, 1H), 1.47
20 (s, 3H), 1.44 (d, J = 14.8 Hz, 1H), 1.04 – 1.13 (m, 1H), 0.66 – 0.71 (m, 2H), 0.38 – 0.44 (m, 2H).
LC/MS, m/z = 431.3 [$M + H$]⁺ (Calc: 430.5).

- 25 **3-(4-cyanophenyl)-1-((6*R*,11*R*)-3-(cyclopropylmethyl)-8-hydroxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-1-methylurea**
(Compound 80)

¹H NMR δ_H (400 MHz, CD₃OD) 7.52 – 7.59 (m, 4H), 6.99 (d, J = 8.8 Hz, 1H), 6.75 (s, 1H), 6.63 – 6.67 (m, 1H), 6.42 (s, 1H), 3.91 – 3.98 (m, 1H), 2.94 – 3.13 (m, 3H), 2.69 (s, 3H), 2.52 – 2.66 (m, 1H), 2.02 – 2.29 (m, 1H), 1.62 (d, J = 14.0 Hz), 1.45 (s, 3H),
30 0.97 – 1.23 (m, 1H), 0.68 (d, J = 15.6 Hz, 2H), 0.37 – 0.44 (m, 2H).
LC/MS, m/z = 431.3 [$M + H$]⁺ (Calc: 430.5).

EXAMPLE 51

The following Tables provide the compound structures, and the results on the efficacy of binding and activity response of exemplified Compounds of the Invention at the ORL1, μ -, and κ -opioid receptors.

5 In TABLE 1, binding affinity of certain Compounds of the Invention to the ORL-1, μ -, and κ -opioid receptors was determined as described above in HEK-293 or CHO cells.

In TABLE 2, activity response of certain Compounds of the Invention to the μ - and κ -opioid receptors was determined as described above for functional assays using
10 HEK-293 cells.

In TABLE 2A, activity response of certain Compounds of the Invention to the μ - and κ -opioid receptors was determined as described above for functional assays using U-2 OS cells.

In TABLE 3, the structure of the exemplified compounds is shown.

15

TABLE 1: Binding Affinity of Benzomorphan Analog Compounds

Ref. No.	Ki (nM)		
	ORL-1	Opioid Receptor	
		μ	κ
1		> 20 μ M	12098.38
2		> 20 μ M	2581.00 $\pm$ 121.72
3		> 20 μ M	> 20 μ M
4		> 20 μ M	> 20 μ M
5		> 20 μ M	10692.95 $\pm$
6		> 20 μ M	3163.34 $\pm$ 1240.16
7			278.94 $\pm$ 39.80
8			> 20 μ M
9			18852.90 $\pm$ 3125.86
10			2140.72 $\pm$ 150.62
11			> 20 μ M

Ref. No.	K _i (nM)		
	ORL-1	Opioid Receptor	
		μ	κ
12			> 20 μ M
13			> 20 μ M
14			14295.63
15			> 20 μ M
16			186.49 $\pm$ 33.99
17			89.91 $\pm$ 14.68
18			5576.32 $\pm$ 1014.93
19			8516.26 $\pm$ 604.62
20			1946.74 $\pm$ 537.74
21			1220.02 $\pm$ 331.89
22			25.71 $\pm$ 8.74
23			13246.68
24			1.17 $\pm$ 0.09
25			147.19 $\pm$ 18.37
26			> 20 μ M
27			35.22 $\pm$ 9.38
28			18223.59
29			30.07 $\pm$ 11.75
30			7.66 $\pm$ 1.96
31			0.34 $\pm$ 0.09
32			12741.18 $\pm$ 2092.19
33			2835.01 $\pm$ 341.97
34			5985.04 $\pm$ 603.94
35			> 20 μ M
36			4187.46 $\pm$ 1054.00
37			> 20 μ M
38			17400.63 $\pm$ 5983.60
39			81.98 $\pm$ 10.36
40			3121.28 $\pm$ 482.94
41			1884.11 $\pm$ 279.98

Ref. No.	Ki (nM)		
	ORL-1	Opioid Receptor	
		μ	κ
42			> 20 μ M
43			515.84 $\pm$ 126.06
44			166.02 $\pm$ 62.34
45			> 20 μ M
46			> 20 μ M
47			19990.58
48			> 20 μ M
49			> 20 μ M
50			58.34 $\pm$ 10.09
51			7.83 $\pm$ 0.95
52			> 20 μ M
53			700.52 $\pm$ 57.96
54			258.53 $\pm$ 33.55
55			> 20 μ M
56			169.98 $\pm$ 51.94
57		235.73 $\pm$ 70.22	4.61 $\pm$ 1.43
58			336.27 $\pm$ 87.49
59			> 20 μ M
60			> 20 μ M
61			2774.49 $\pm$ 850.38
62			> 20 μ M
63			340.14 $\pm$ 90.93
64			12412.96
65			> 20 μ M
66			> 20 μ M
67			> 20 μ M
68			799.12 $\pm$ 98.16
69			19844.43
70			4716.93 $\pm$ 29.55
71			> 20 μ M

Ref. No.	Ki (nM)		
	ORL-1	Opioid Receptor	
		μ	κ
72			14756.49
73			> 20 μ M
74		229.98 $\pm$ 43.79	24.14 $\pm$ 5.93
75			184.78 $\pm$ 51.34
76			106.69 $\pm$ 1.33
77			4.30 $\pm$ 0.91
78			17.88 $\pm$ 4.33
79			3138.90 $\pm$ 804.72
80			1.19 $\pm$ 0.32
81			36.57 $\pm$ 4.94
82			10157.61
83		1.78 $\pm$ 0.38	0.15 $\pm$ 0.02
84			269.27 $\pm$ 27.74
85			701.28 $\pm$ 94.11
86			978.95 $\pm$ 146.23
87			1.21 $\pm$ 0.24
88			4.74 $\pm$ 1.55
89			9.20 $\pm$ 0.90
90			1.74 $\pm$ 0.45
91			174.45 $\pm$ 25.67
92	> 20 μ M	54.50 $\pm$ 17.3	163.50 $\pm$ 3.83
93	> 20 μ M	3702.00 $\pm$ 91.40	5353.00 $\pm$ 540.70
94	> 20 μ M	36.80 $\pm$ 12.10	16.80 $\pm$ 2.51
95	> 20 μ M	1759.00 $\pm$ 324.20	4602.00 $\pm$ 764.20

**TABLE 2: Activity Response of Benzomorphan Analog Compounds in HEK-293
or CHO Cells**

Ref. No.	GTP γ S (EC ₅₀ : nM, E _{max} : %)			
	μ		κ	
	EC ₅₀	E _{max}	EC ₅₀	E _{max}
7			> 20 μ M	-0.33 $\pm$ 0.67
16			1052.05 $\pm$ 262.24	15.00 $\pm$ 1.53
17			> 20 μ M	
22			> 20 μ M	
24			178.37 $\pm$ 25.08	30.67 $\pm$ 2.60
25			> 20 μ M	-1.00 $\pm$ 0.00
27			> 20 μ M	
29			233.45 $\pm$ 74.94	28.25 $\pm$ 4.66
30	270.32 $\pm$ 33.89	49.67 $\pm$ 3.67	> 20 μ M	0.33 $\pm$ 0.67
31	12.33 $\pm$ 0.95	61.00 $\pm$ 3.00	> 20 μ M	1.00 $\pm$ 0.00
32	335.55 $\pm$ 92.84	23.00 $\pm$ 1.53		
33	2451.89 $\pm$ 166.69	49.00 $\pm$ 3.67		
34	3640.47 $\pm$ 372.93	16.00 $\pm$ 3.46		
35	2568.62 $\pm$ 783.31	23.00 $\pm$ 0.58		
36	> 20 μ M			
37	> 20 μ M			
38	> 20 μ M			
39	321.13 $\pm$ 22.21	89.75 $\pm$ 5.39	> 20 μ M	-1.00 $\pm$ 0.00
40	3068.01 $\pm$ 468.81	25.67 $\pm$ 3.76		
41	1224.96 $\pm$ 234.71	46.00 $\pm$ 3.79		
42	> 20 μ M			

Ref. No.	GTP γ S (EC ₅₀ : nM, E _{max} : %)			
	μ		κ	
	EC ₅₀	E _{max}	EC ₅₀	E _{max}
43	3389.03 $\pm$ 63.44	24.67 $\pm$ 3.28	> 20 μ M	
44	718.03 $\pm$ 249.07	65.00 $\pm$ 2.52	393.84 $\pm$ 88.38	17.67 $\pm$ 1.20
45	3845.14 $\pm$ 838.61	17.00 $\pm$ 3.06		
46	13356.09 $\pm$ 2991.11	36.67 $\pm$ 3.18		
47	8893.34 $\pm$ 654.64	58.67 $\pm$ 5.24		
48	5187.29 $\pm$ 549.08	26.00 $\pm$ 4.16		
49	> 20 μ M	31.33 $\pm$ 5.36		
50	189.38 $\pm$ 13.68	93.75 $\pm$ 2.17	> 20 μ M	
51	1.44 $\pm$ 0.44	100.40 $\pm$ 7.22	> 20 μ M	
52	1029.16 $\pm$ 73.07	72.33 $\pm$ 3.48		
53	1109.86 $\pm$ 209.60	82.67 $\pm$ 1.20		
54	> 20 μ M		> 20 μ M	
55	5911.18 $\pm$ 422.16	71.00 $\pm$ 8.08		
56	3811.28 $\pm$ 725.51	36.67 $\pm$ 7.22	2583.28 $\pm$ 721.00	25.67 $\pm$ 1.67
57	314.67 $\pm$ 47.88	111.67 $\pm$ 7.22	351.43 $\pm$ 115.38	85.67 $\pm$ 3.93
58	750.70 $\pm$ 43.35	110.00 $\pm$ 7.55		
59	3443.33 $\pm$ 183.49	76.33 $\pm$ 10.17		
60	6093.08 $\pm$ 528.96	38.33 $\pm$ 0.88		
61	5758.65 $\pm$ 1554.16	26.67 $\pm$ 0.88		

Ref. No.	GTP γ S (EC ₅₀ : nM, E _{max} : %)			
	μ		κ	
	EC ₅₀	E _{max}	EC ₅₀	E _{max}
62	7450.91 $\pm$ 470.09	24.00 $\pm$ 2.97		
63	> 20 μ M		> 20 μ M	
64	> 20 μ M			
65	5062.97 $\pm$ 1146.61	21.67 $\pm$ 2.85		
66	6605.36 $\pm$ 198.95	20.67 $\pm$ 1.33		
67	> 20 μ M			
68	549.95 $\pm$ 31.63	98.00 $\pm$ 1.73		
69	> 20 μ M	24.33 $\pm$ 2.96		
70	9380.74 $\pm$ 500.59	24.67 $\pm$ 0.88		
71	13019.30 $\pm$ 1144.67	23.00 $\pm$ 4.58		
72	4893.25 $\pm$ 508.01	70.33 $\pm$ 8.33		
73	18050.23 $\pm$ 2716.99	25.00 $\pm$ 2.52		
74	639.16 $\pm$ 147.03	31.67 $\pm$ 0.67	636.58 $\pm$ 65.05	53.00 $\pm$ 2.31
75	62.33 $\pm$ 13.71	111.50 $\pm$ 2.40	> 20 μ M	0.33 $\pm$ 0.67
76	810.87 $\pm$ 52.98	79.33 $\pm$ 3.48	> 20 μ M	-0.33 $\pm$ 0.67
77	144.40 $\pm$ 11.00	56.50 $\pm$ 2.02	> 20 μ M	-1.00 $\pm$ 0.00
78			> 20 μ M	
80	216.09 $\pm$ 38.74	92.40 $\pm$ 3.23	>20 μ M	
81	1225.90 $\pm$ 172.97	31.20 $\pm$ 2.87	>20 μ M	
82				
83	10.55 $\pm$ 1.18	92.67 $\pm$ 5.21	2.67 $\pm$ 0.84	77.67 $\pm$ 1.76
87	5.29 $\pm$ 1.10	96.33 $\pm$ 2.96	24.02 $\pm$ 1.94	10.75 $\pm$ 1.49

Ref. No.	GTP γ S (EC ₅₀ : nM, E _{max} : %)			
	μ		κ	
	EC ₅₀	E _{max}	EC ₅₀	E _{max}
88	7.58 $\pm$ 1.06	74.67 $\pm$ 1.86	24.67 $\pm$ 5.35	18.50 $\pm$ 2.84
89	>20 μ M		>20 μ M	
90	5.92 $\pm$ 1.82	32.67 $\pm$ 5.78	>20 μ M	1.00 $\pm$ 0.00
91	408.78 $\pm$ 19.46	89.67 $\pm$ 5.90	2811.03 $\pm$ 128.63	34.67 $\pm$ 5.93
92	68.90 $\pm$ 16.00	100.50 $\pm$ 3.12	> 20 μ M	3.50 $\pm$ 1.71
93	3137.00 $\pm$ 790.20	92.00 $\pm$ 4.30		
94	40.80 $\pm$ 2.76	85.30 $\pm$ 4.98	> 20 μ M	4.60 $\pm$ 0.40
95	2120.00 $\pm$ 204.30	78.00 $\pm$ 3.06		
128	7.67 $\pm$ 0.79	53.50 $\pm$ 3.52	0.35 $\pm$ 0.15	40.30 $\pm$ 2.19

TABLE 2A: Activity Response of Benzomorphan Analog Compounds in U-2 OS Cells

5

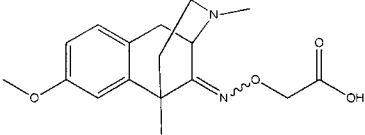
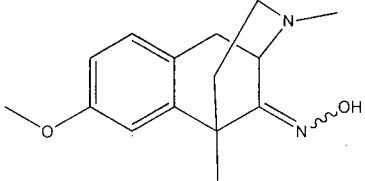
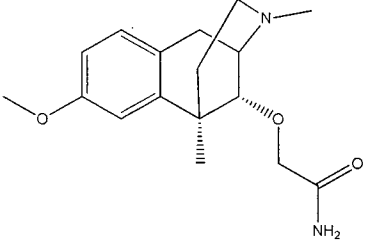
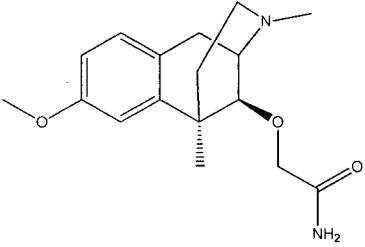
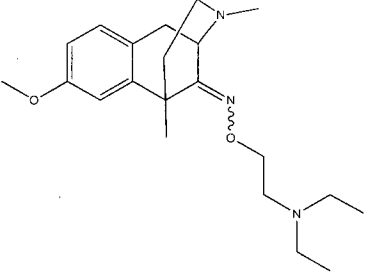
Ref. No.	GTP γ S (EC ₅₀ : nM, E _{max} : %)			
	μ		κ	
	EC ₅₀	E _{max}	EC ₅₀	E _{max}
22	299.80 $\pm$ 45.80	71.00 $\pm$ 3.46		
25	49.80 $\pm$ 12.10	101.70 $\pm$ 1.67		
26	1194.00 $\pm$ 93.90	91.00 $\pm$ 7.09		
27	1.51 $\pm$ 0.24	102.70 $\pm$ 2.33		
28	1562.00 $\pm$ 106.10	74.70 $\pm$ 4.63		
29	0.044 $\pm$ 0.00	100.30 $\pm$ 1.45		
30	33.60 $\pm$ 8.17	91.70 $\pm$ 4.33		
31	0.41 $\pm$ 0.38	94.30 $\pm$ 3.18		
32	232.90 $\pm$ 58.20	39.80 $\pm$ 2.46		

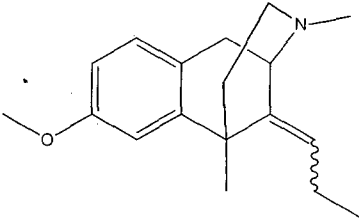
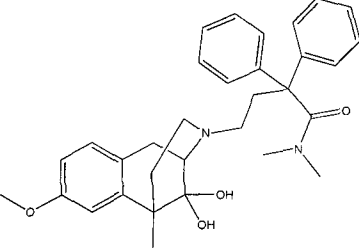
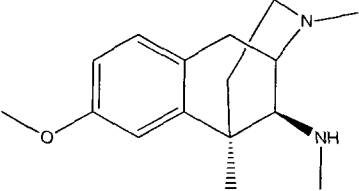
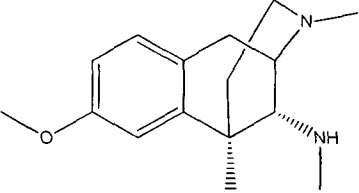
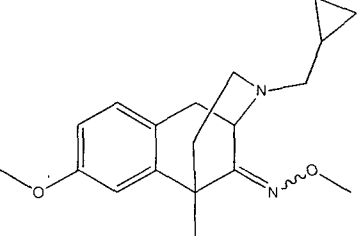
Ref. No.	GTP γ S (EC ₅₀ : nM, E _{max} : %)			
	μ		κ	
	EC ₅₀	E _{max}	EC ₅₀	E _{max}
39	18.30 $\pm$ 1.22	100.70 $\pm$ 3.76		
50	42.00 $\pm$ 10.90	86.50 $\pm$ 4.14	> 20 μ M	9.78 $\pm$ 2.97
51	0.21 $\pm$ 0.021	113.00 $\pm$ 2.65		
75	12.70 $\pm$ 1.52	103.70 $\pm$ 2.67		
77	29.00 $\pm$ 0.86	77.70 $\pm$ 0.88		
78	6.09 $\pm$ 0.45	109.30 $\pm$ 3.28		
79	2198.00 $\pm$ 668.50	49.00 $\pm$ 3.46		
80	0.20 $\pm$ 0.013	112.70 $\pm$ 3.53		
82	> 20 μ M	31.70 $\pm$ 5.36		
84	83.90 $\pm$ 13.30	90.70 $\pm$ 1.86		
85	3238.00 $\pm$ 770.50	19.30 $\pm$ 2.33		
86	2152.00 $\pm$ 210.50	14.70 $\pm$ 0.88		
87	2.08 $\pm$ 0.12	99.30 $\pm$ 2.03		
88	1.67 $\pm$ 0.16	85.70 $\pm$ 2.33		
89	> 20 μ M	1.17 $\pm$ 1.01		
90	7.02 $\pm$ 1.89	14.00 $\pm$ 1.00		
91	377.80 $\pm$ 61.90	71.30 $\pm$ 3.53		
92	149.30 $\pm$ 25.50	97.30 $\pm$ 3.53	> 20 μ M	1.00 $\pm$ 0.00
93	4559.00 $\pm$ 743.20	80.70 $\pm$ 4.48	> 20 μ M	2.00 $\pm$ 0.00
94	27.40 $\pm$ 4.20	85.30 $\pm$ 5.93	> 20 μ M	0.00
95	1437.00 $\pm$ 44.70	79.70 $\pm$ 8.41	> 20 μ M	-1.00
96	6.01 $\pm$ 0.51	32.30 $\pm$ 0.88	6.41 $\pm$ 1.67	
97	> 20 μ M	2.50 $\pm$ 0.00	> 20 μ M	0.00
98	0.30 $\pm$ 0.027	103.70 $\pm$ 3.76	28.60 $\pm$ 3.21	95.30 $\pm$ 3.84
99	0.13 $\pm$ 0.01	71.00 $\pm$ 2.00	1.44 $\pm$ 0.053	72.30 $\pm$ 4.67

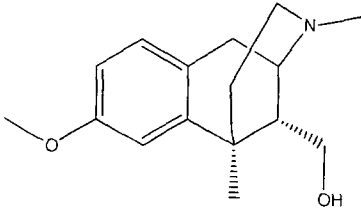
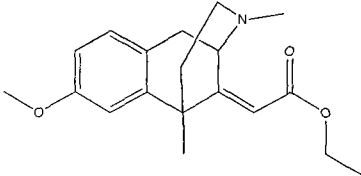
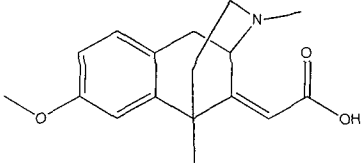
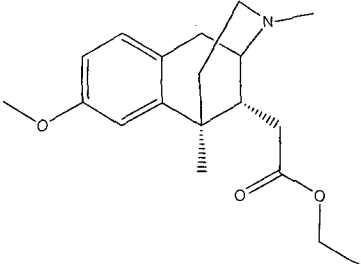
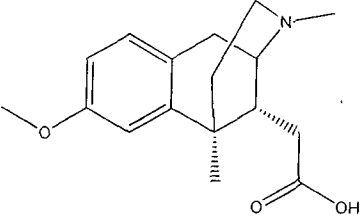
Ref. No.	GTP γ S (EC ₅₀ : nM, E _{max} : %)			
	μ		κ	
	EC ₅₀	E _{max}	EC ₅₀	E _{max}
100	40.00 $\pm$ 3.25	102.30 $\pm$ 1.45	1757.00 $\pm$ 364.50	45.00 $\pm$ 2.08
101	3.73 $\pm$ 0.21	104.00 $\pm$ 2.08	1083.00 $\pm$ 112.90	66.70 $\pm$ 1.20
102	> 20 μ M	2.50 $\pm$ 0.00	> 20 μ M	-1.00
103	116.80 $\pm$ 2.82	77.50 $\pm$ 1.26	287.10 $\pm$ 62.00	83.00 $\pm$ 8.02
104	51.30 $\pm$ 5.26	105.30 $\pm$ 0.88	1260.00 $\pm$ 229.00	79.70 $\pm$ 5.90
105	0.22 $\pm$ 0.052	32.70 $\pm$ 1.76	> 20 μ M	1.00
106	> 20 μ M	2.50	> 20 μ	1.00
107	46.20 $\pm$ 0.35	58.30 $\pm$ 0.33	> 20 μ M	1.00
108	0.39 $\pm$ 0.11	80.80 $\pm$ 2.50	3.27 $\pm$ 0.69	18.80 $\pm$ 1.25
109	29.00 $\pm$ 1.36	100.30 $\pm$ 3.18	191.50 $\pm$ 41.60	36.70 $\pm$ 0.67
110	11.60 $\pm$ 1.55	92.30 $\pm$ 2.03	25.40 $\pm$ 3.38	37.70 $\pm$ 2.03
111	2.23 $\pm$ 0.12	64.00 $\pm$ 4.00	42.60 $\pm$ 7.64	22.70 $\pm$ 2.33
112	7.56 $\pm$ 0.45	83.70 $\pm$ 1.45	23.40 $\pm$ 7.81	26.30 $\pm$ 0.88
113	0.45 $\pm$ 0.036	68.70 $\pm$ 3.71	0.052 $\pm$ 0.013	99.20 $\pm$ 1.65
114	152.10 $\pm$ 16.80	20.70 $\pm$ 0.67	18.90 $\pm$ 2.01	107.00 $\pm$ 4.36
115	159.30 $\pm$ 15.40	37.70 $\pm$ 1.67	53.40 $\pm$ 7.28	76.00 $\pm$ 6.66
116	3.12 $\pm$ 0.15	104.30 $\pm$ 2.96	69.40 $\pm$ 5.37	56.30 $\pm$ 3.93
117	822.40 $\pm$ 93.90	93.70 $\pm$ 5.36	3394.00 $\pm$ 439.20	79.70 $\pm$ 5.46
118	1.32 $\pm$ 0.04	101.00 $\pm$ 2.52	90.80 $\pm$ 7.63	75.20 $\pm$ 4.33
119	32.20 $\pm$ 3.26	100.30 $\pm$ 2.73	382.80 $\pm$ 21.90	96.70 $\pm$ 5.36
120	2938.00 $\pm$ 481.00	76.30 $\pm$ 3.48	2865.00 $\pm$ 231.10	62.30 $\pm$ 4.91
121	126.00 $\pm$ 15.40	91.70 $\pm$ 4.18	604.50 $\pm$ 68.10	18.30 $\pm$ 0.88
122	0.36 $\pm$ 0.01	101.70 $\pm$ 1.20	15.20 $\pm$ 2.63	94.50 $\pm$ 0.65
123	1.85.00 $\pm$ 0.16	104.00 $\pm$ 3.06	112.50 $\pm$ 5.80	74.00 $\pm$ 3.06
124	14.10 $\pm$ 0.48	98.00 $\pm$ 3.06	679.70 $\pm$ 67.70	77.30 $\pm$ 4.63

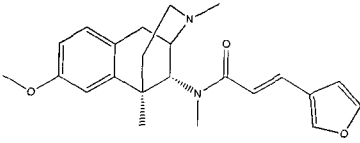
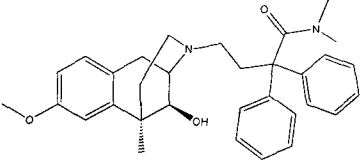
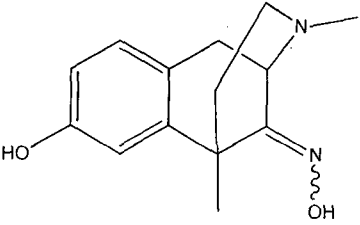
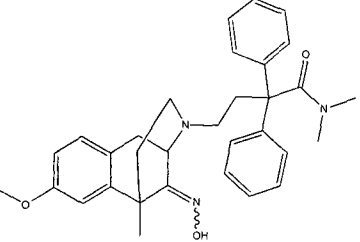
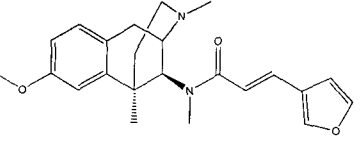
Ref. No.	GTPγS (EC ₅₀ : nM, E _{max} : %)			
	μ		κ	
	EC ₅₀	E _{max}	EC ₅₀	E _{max}
125	2620.00 ± 396.50	70.70 ± 2.33	443.40 ± 73.20	102.00 ± 5.69
126	146.90 ± 9.47	103.30 ± 2.40	1465.00 ± 91.30	63.70 ± 3.93
127	> 20 μ	3.67 ± 1.20	947.10 ± 68.00	93.00 ± 3.51
128	0.18 ± 0.069	47.80 ± 1.25	0.74 ± 0.13	90.70 ± 1.45
129	9.14 ± 1.19	20.00 ± 1.15	0.78 ± 0.070	97.30 ± 1.86
130	373.00 ± 104.60	29.00 ± 2.00	22.80 ± 3.38	71.00 ± 3.11
131	290.00 ± 5.32	69.00 ± 1.00	> 20 μM	0.00
132	3.03 ± 0.17	95.30 ± 2.60	11.40 ± 1.58	89.00 ± 5.69
133	3.90 ± 0.74	22.30 ± 1.20	21.70 ± 3.16	42.00 ± 4.02
134	1.47 ± 0.58	16.00 ± 0.71	> 20 μM	90.00
135	1700.00 ± 112.20	92.00 ± 2.65	2810.00 ± 397.20	22.00 ± 2.52
136	2332.00 ± 236.30	62.30 ± 3.84	3835.00 ± 540.80	22.30 ± 3.71
137	1322.00 ± 177.50	50.30 ± 1.76	3373.00 ± 753.00	30.00 ± 2.31
138	> 20 μM	45.30 ± 2.33	> 20 μM	35.50 ± 2.06
139	12.50 ± 2.18	87.00 ± 3.08	91.80 ± 4.88	48.00 ± 5.13
140	0.10 ± 0.01	82.00 ± 0.91	4.68 ± 0.40	107.20 ± 4.40

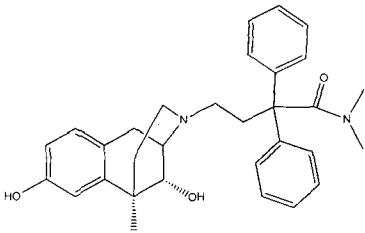
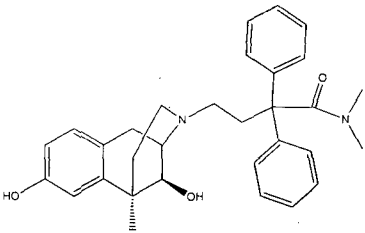
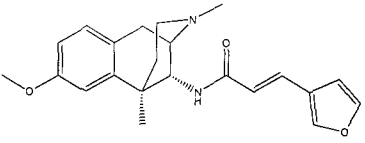
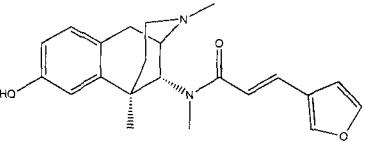
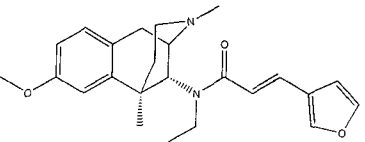
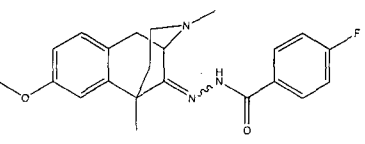
TABLE 3: Structure of Exemplified Compounds

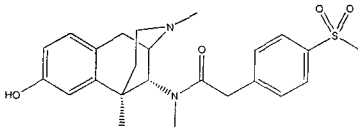
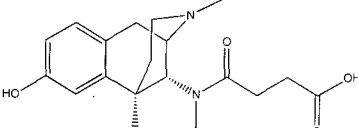
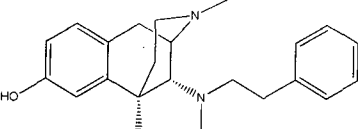
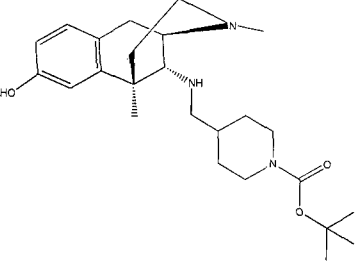
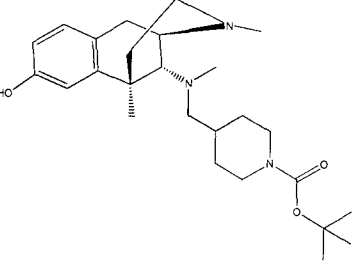
Ref. No.	Compound
1	
2	
3	
4	
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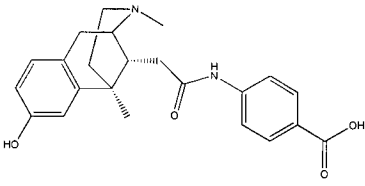
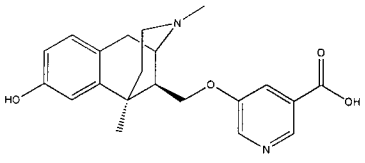
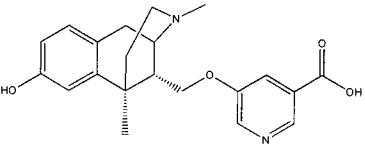
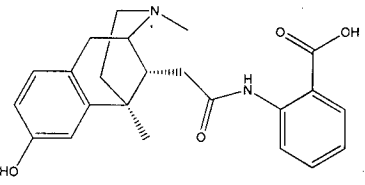
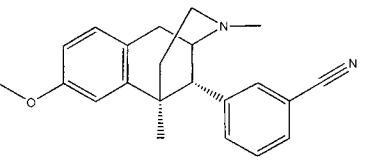
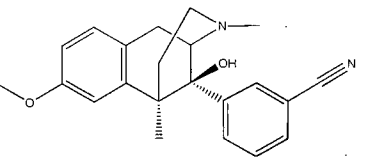
Ref. No.	Compound
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7	
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9	
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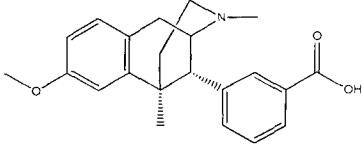
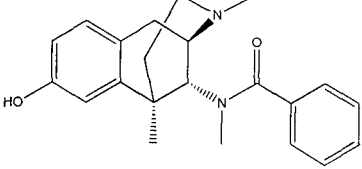
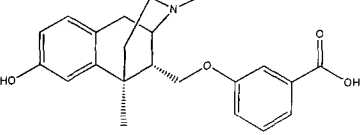
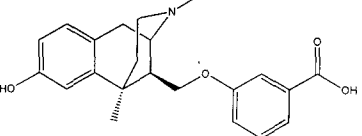
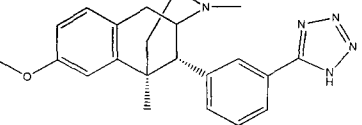
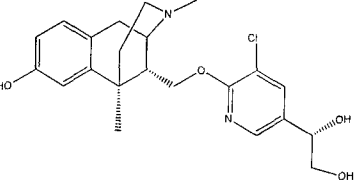
Ref. No.	Compound
11	 <chem>COc1ccc2c(c1)[C@H]3[C@@H](C)[C@H](C[C@@H](C2)C[C@H]4C[C@H](N4C)C)C[C@H](C3)CO</chem>
12	 <chem>COc1ccc2c(c1)[C@H]3[C@@H](C)[C@H](C[C@@H](C2)C[C@H]4C[C@H](N4C)C)C[C@H](C3)C(=O)OCC</chem>
13	 <chem>COc1ccc2c(c1)[C@H]3[C@@H](C)[C@H](C[C@@H](C2)C[C@H]4C[C@H](N4C)C)C[C@H](C3)C(=O)O</chem>
14	 <chem>COc1ccc2c(c1)[C@H]3[C@@H](C)[C@H](C[C@@H](C2)C[C@H]4C[C@H](N4C)C)C[C@H](C3)C(=O)OCC</chem>
15	 <chem>COc1ccc2c(c1)[C@H]3[C@@H](C)[C@H](C[C@@H](C2)C[C@H]4C[C@H](N4C)C)C[C@H](C3)C(=O)O</chem>

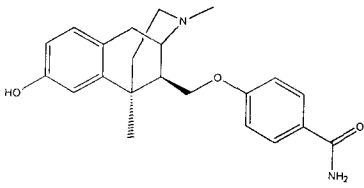
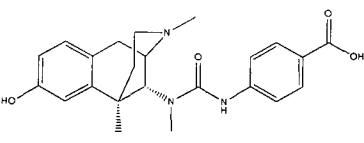
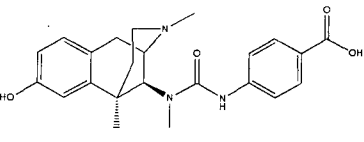
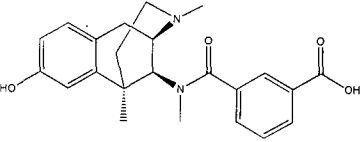
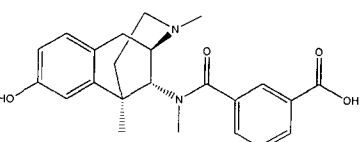
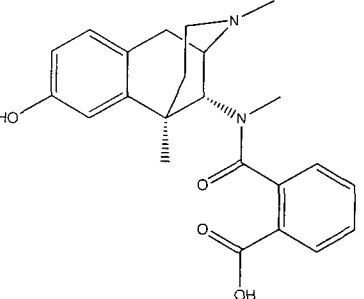
Ref. No.	Compound
16	
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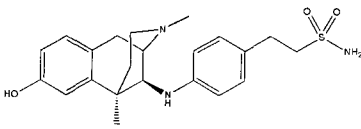
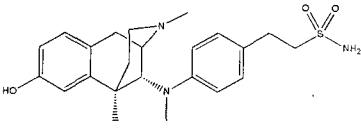
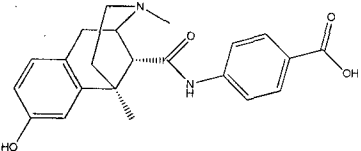
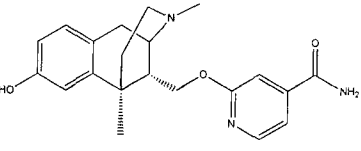
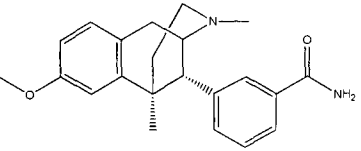
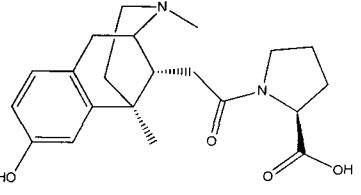
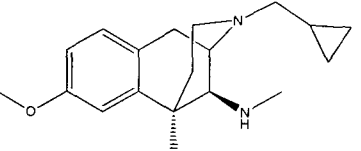
Ref. No.	Compound
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22	
23	
24	
25	
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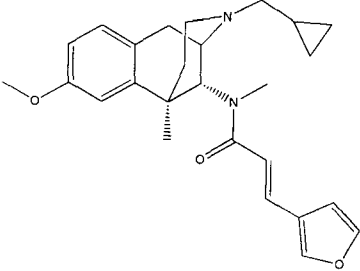
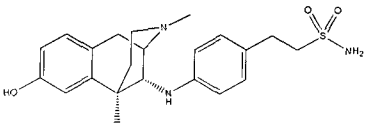
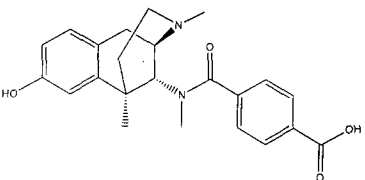
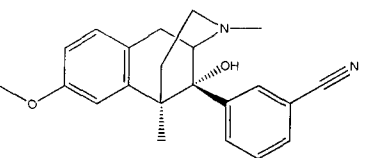
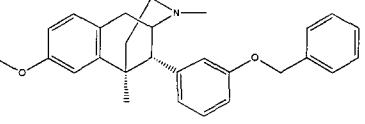
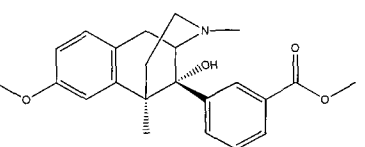
Ref. No.	Compound
27	
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31	

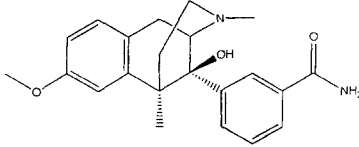
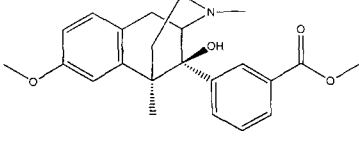
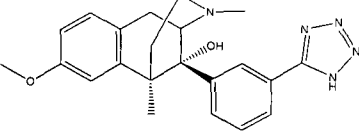
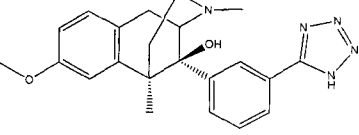
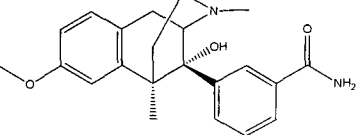
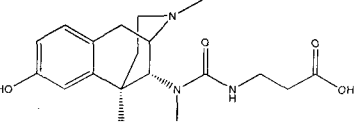
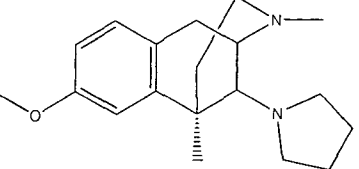
Ref. No.	Compound
32	
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34	
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36	
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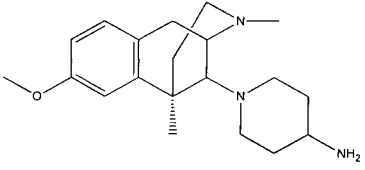
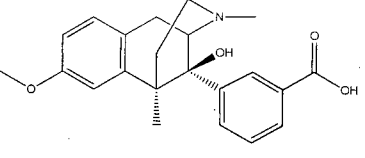
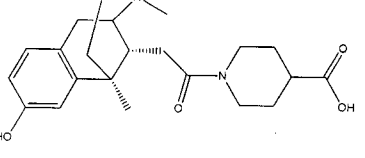
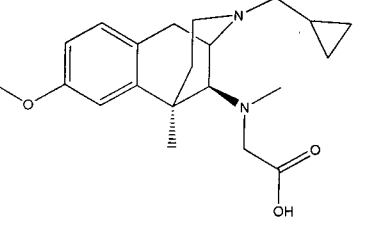
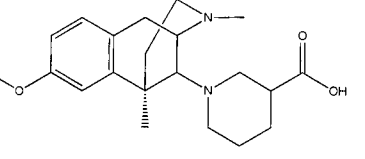
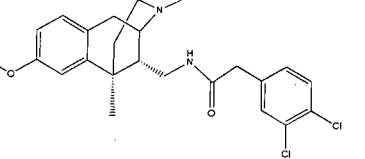
Ref. No.	Compound
38	 <chem>COc1ccc2c(c1)[C@H]3[C@@H](C(=O)N(C)Cc4ccccc4)[C@H](C)[C@H]2C3</chem>
39	 <chem>OC1=CC=C2[C@H]3[C@@H](C(=O)N(C)Cc4ccccc4)[C@H](C)[C@H]2C13</chem>
40	 <chem>OC1=CC=C2[C@H]3[C@@H](COc4ccc(C(=O)O)cc4)[C@H](C)[C@H]2C13</chem>
41	 <chem>OC1=CC=C2[C@H]3[C@@H](COc4ccc(C(=O)O)cc4)[C@H](C)[C@H]2C13</chem>
42	 <chem>COc1ccc2c(c1)[C@H]3[C@@H](c4ccccc4c5nn[nH]5)[C@H](C)[C@H]2C3</chem>
43	 <chem>OC1=CC=C2[C@H]3[C@@H](COc4cc(Cl)cc(CO)c4n)[C@H](C)[C@H]2C13</chem>

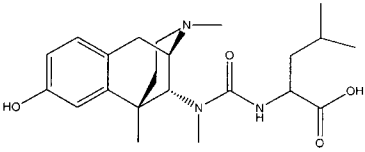
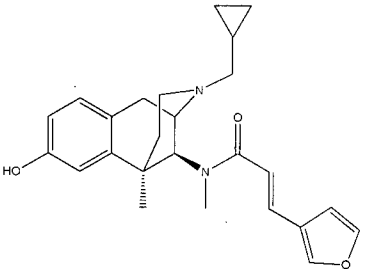
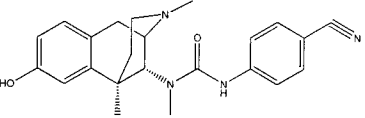
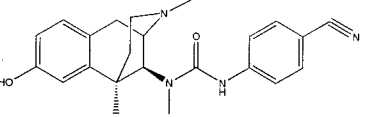
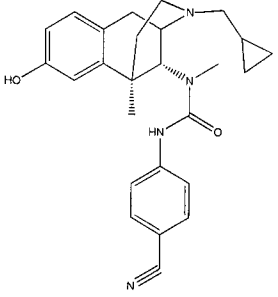
Ref. No.	Compound
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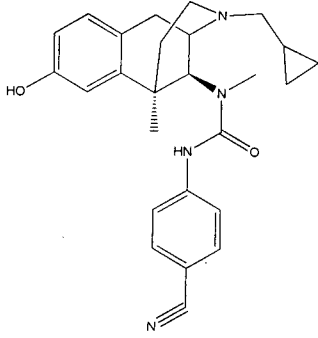
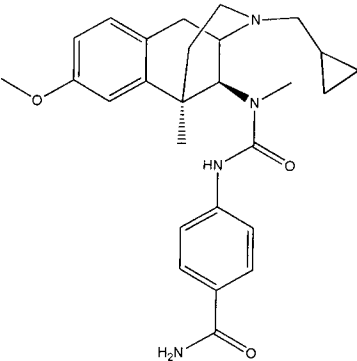
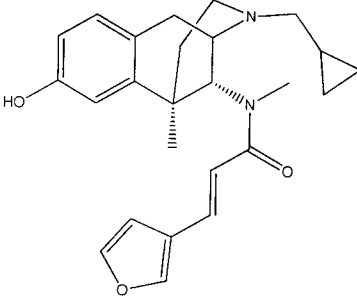
Ref. No.	Compound
50	
51	
52	
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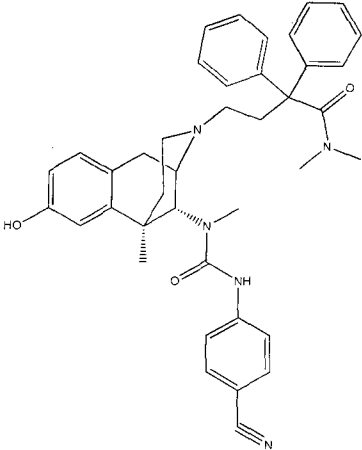
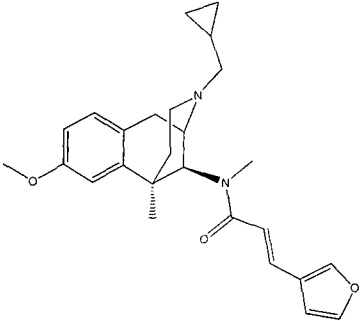
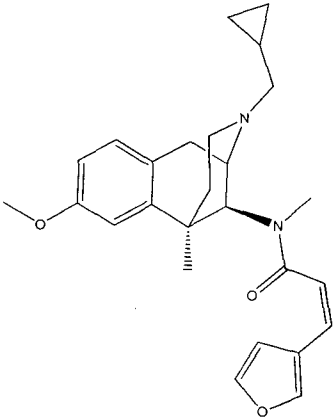
Ref. No.	Compound
57	
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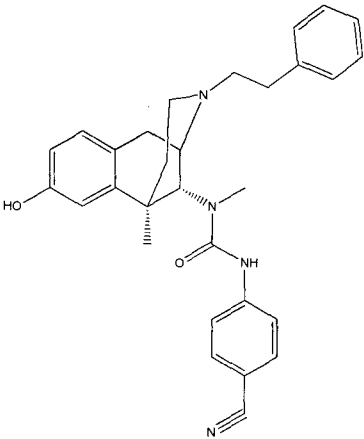
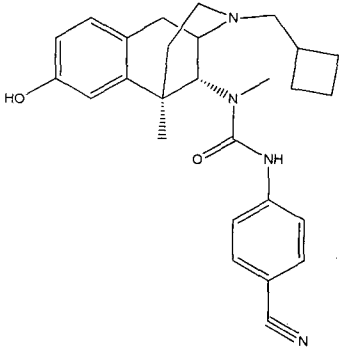
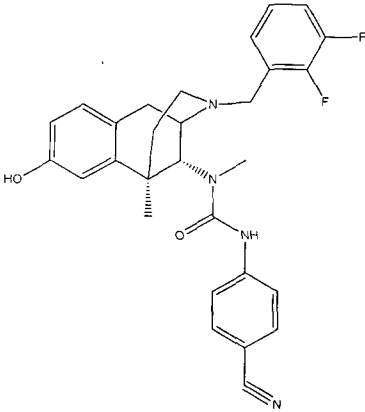
Ref. No.	Compound
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64	
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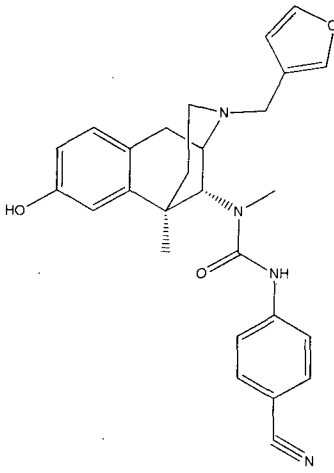
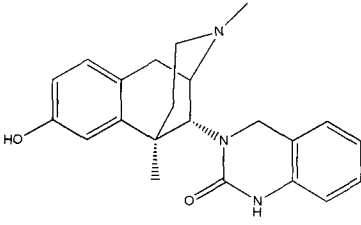
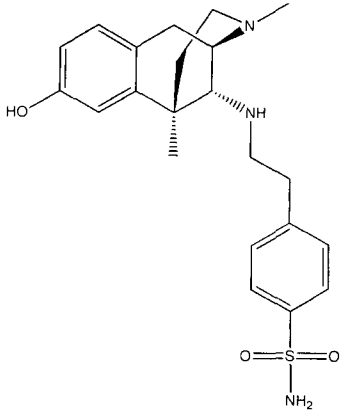
Ref. No.	Compound
70	 <chem>COC1=CC=C2C3=C1[C@H](C2)C4(C3)N(C)CC4C5=CC=C(C=C5)N</chem>
71	 <chem>COC1=CC=C2C3=C1[C@H](C2)C4(C3)N(C)CC4C5=CC=C(C=C5)C(=O)O</chem>
72	 <chem>COC1=CC=C2C3=C1[C@H](C2)C4(C3)N(C)CC4C5=CC=C(C=C5)C(=O)O</chem>
73	 <chem>COC1=CC=C2C3=C1[C@H](C2)C4(C3)N(C)CC4C5=CC=C(C=C5)C(=O)O</chem>
74	 <chem>COC1=CC=C2C3=C1[C@H](C2)C4(C3)N(C)CC4C5=CC=C(C=C5)C(=O)O</chem>
75	 <chem>COC1=CC=C2C3=C1[C@H](C2)C4(C3)N(C)CC4C5=CC=C(C=C5)C(=O)O</chem>

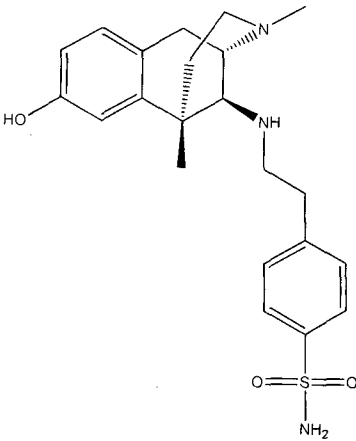
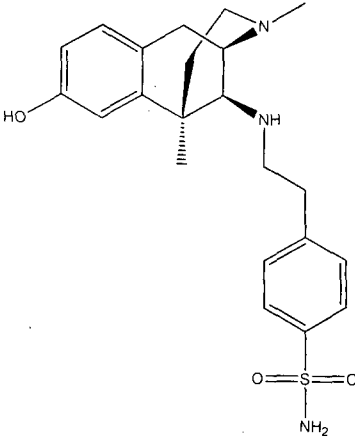
Ref. No.	Compound
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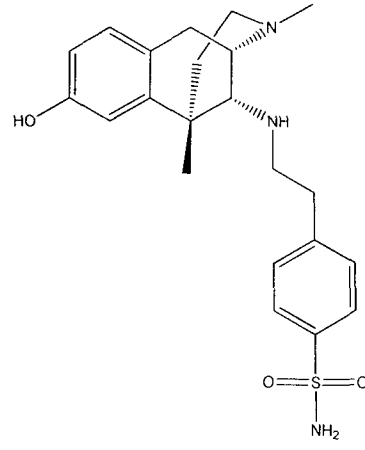
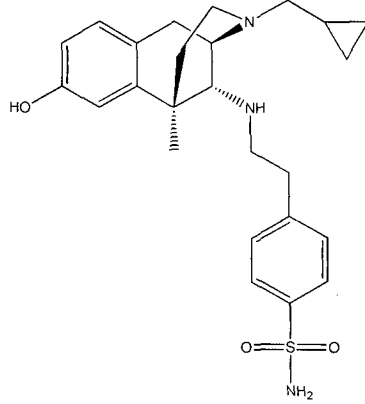
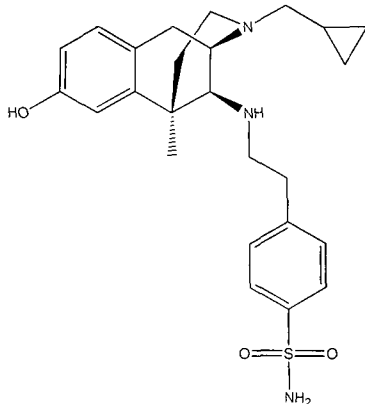
Ref. No.	Compound
81	 <chem>CN(C)C(=O)Nc1ccc(C#N)cc1</chem>
82	 <chem>CN(C)C(=O)Nc1ccc(C(=O)N)cc1</chem>
83	 <chem>CN(C)C(=O)Nc1ccc(C=Cc2ccoc2)cc1</chem>

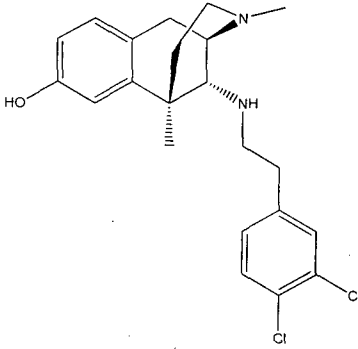
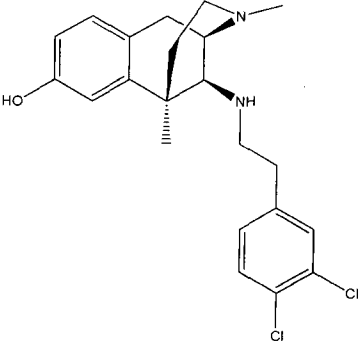
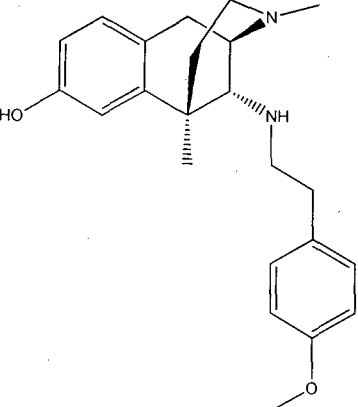
Ref. No.	Compound
84	 Chemical structure of compound 84: A complex molecule featuring a pentacyclic core. It includes a hydroxyl group (HO-), a dimethylamino group (N(CH₃)₂), and a 4-cyanophenyl group (C₆H₄C≡N).
85	 Chemical structure of compound 85: A complex molecule featuring a pentacyclic core. It includes a methoxy group (OCH₃), a cyclopropylmethyl group (C₃H₅), and a 2-furyl group (C₄H₃OC₂H₃).
86	 Chemical structure of compound 86: A complex molecule featuring a pentacyclic core. It includes a methoxy group (OCH₃), a cyclopropylmethyl group (C₃H₅), and a 2-furyl group (C₄H₃OC₂H₃).

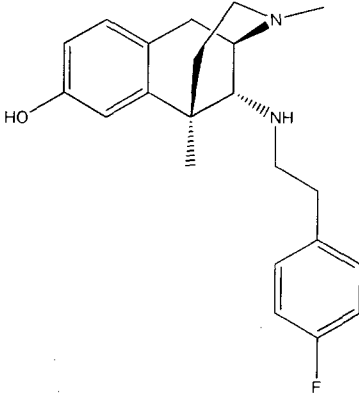
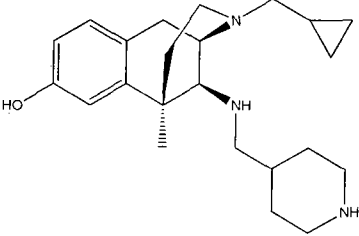
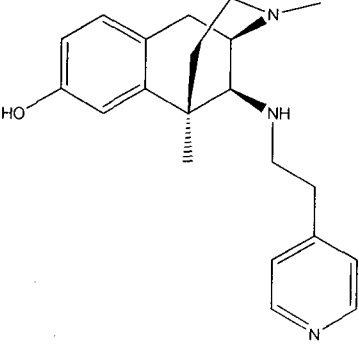
Ref. No.	Compound
87	
88	
89	

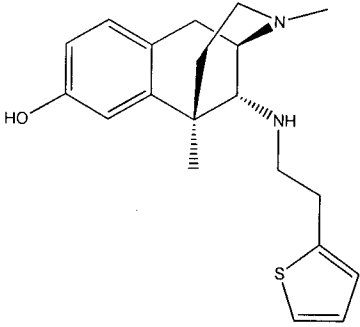
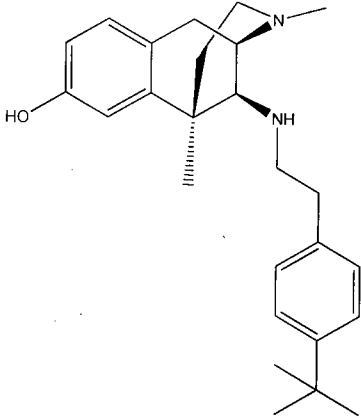
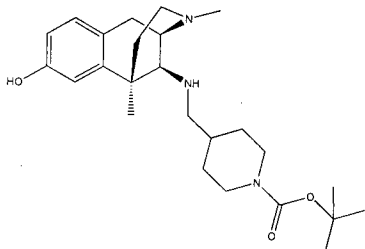
Ref. No.	Compound
90	 <chem>CN(C(=O)Nc1ccc(C#N)cc1)[C@H]2[C@@H]3[C@H](C4=CC=C(C=C4)O)CC[C@H]2CN(C4=CC=CC=C4O)C3</chem>
91	 <chem>CN(C(=O)N1CCc2ccccc2N1C(=O)N)[C@H]2[C@@H]3[C@H](C4=CC=C(C=C4)O)CC[C@H]2CN(C4=CC=CC=C4O)C3</chem>
92	 <chem>NC(=O)S(=O)(=O)c1ccc(cc1)CCN[C@H]2[C@@H]3[C@H](C4=CC=C(C=C4)O)CC[C@H]2CN(C4=CC=CC=C4O)C3</chem>

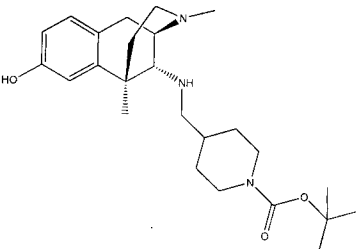
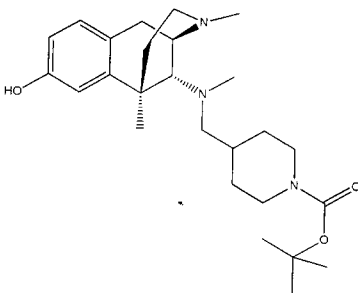
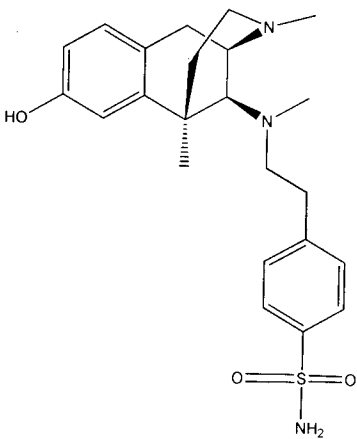
Ref. No.	Compound
93	 <chem>CN(C)[C@H]1CC[C@@H]2[C@@H](C)[C@H](C)[C@H]1Cc3ccc(O)cc3N[C@@H]2CCc4ccc(S(=O)(=O)N)cc4</chem>
94	 <chem>CN(C)[C@H]1CC[C@@H]2[C@@H](C)[C@H]1Cc3ccc(O)cc3N[C@@H]2CCc4ccc(S(=O)(=O)N)cc4</chem>

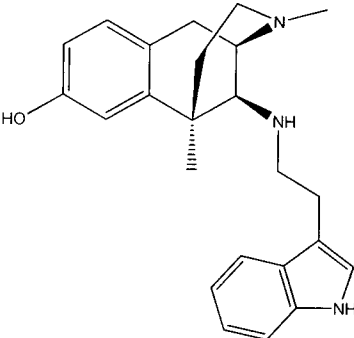
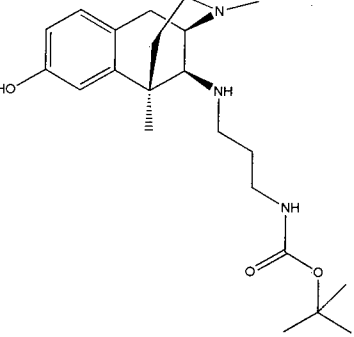
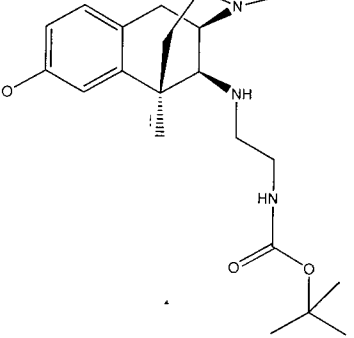
Ref. No.	Compound
95	 <chem>CN(C)[C@H]1[C@@H](C)[C@H](NC2=CC=C(C=C2)S(=O)(=O)N)C[C@H]3[C@@H](C)[C@H](O)C=C[C@H]13</chem>
96	 <chem>CN(C)[C@H]1[C@@H](C2CC2)[C@H](NC3=CC=C(C=C3)S(=O)(=O)N)C[C@H]4[C@@H](C)[C@H](O)C=C[C@H]14</chem>
97	 <chem>CN(C)[C@H]1[C@@H](C2CC2)[C@H](NC3=CC=C(C=C3)S(=O)(=O)N)C[C@H]4[C@@H](C)[C@H](O)C=C[C@H]14</chem>

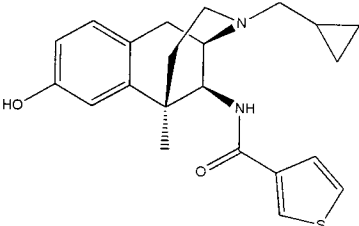
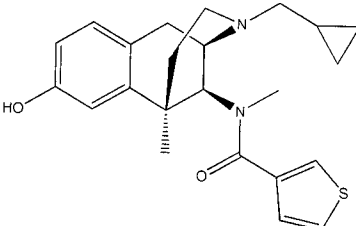
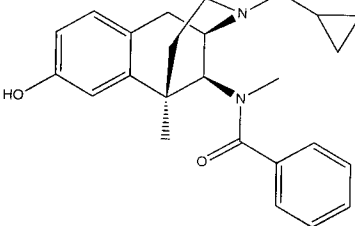
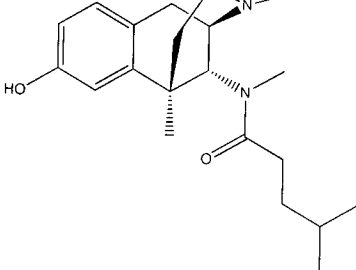
Ref. No.	Compound
98	 <chem>CN(C)[C@H]1CC[C@@H]2[C@@H]1Cc3ccc(O)cc3[C@H]2[C@H](CNCc4cc(Cl)c(Cl)cc4)C</chem>
99	 <chem>CN(C)[C@H]1CC[C@@H]2[C@@H]1Cc3ccc(O)cc3[C@H]2[C@H](CNCc4cc(Cl)c(Cl)cc4)C</chem>
100	 <chem>CN(C)[C@H]1CC[C@@H]2[C@@H]1Cc3ccc(O)cc3[C@H]2[C@H](CNCc4ccc(OC)cc4)C</chem>

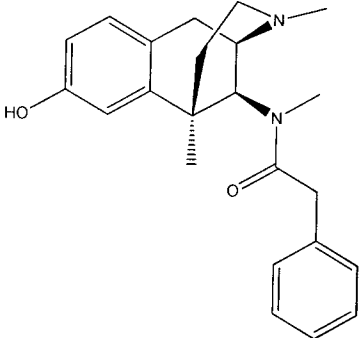
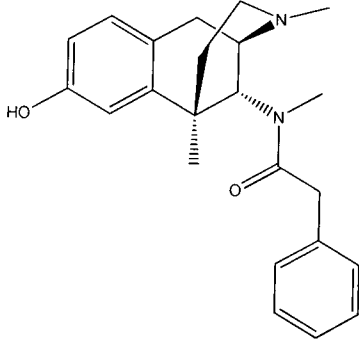
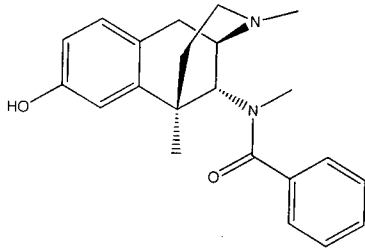
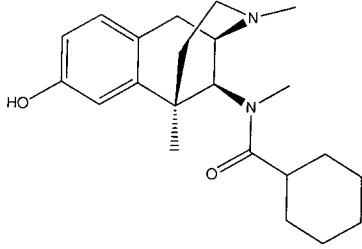
Ref. No.	Compound
101	 <chem>CN1[C@H]2[C@@H](C[C@H]3[C@H](C[C@@H]1[C@H]2Cc4ccc(O)cc4)CCN(Cc5ccc(F)cc5)C3</chem>
102	 <chem>C1CCN1[C@H]2[C@@H](C[C@H]3[C@H](C[C@@H]2[C@H]3Cc4ccc(O)cc4)CCN(Cc5ccncc5)C3</chem>
103	 <chem>CN1[C@H]2[C@@H](C[C@H]3[C@H](C[C@@H]1[C@H]2Cc4ccc(O)cc4)CCN(Cc5ccncc5)C3</chem>

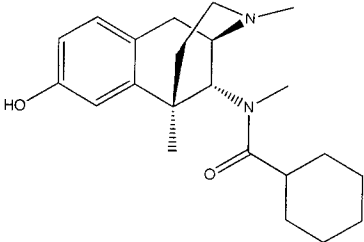
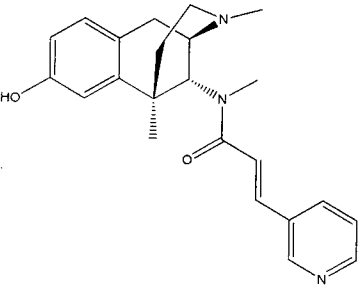
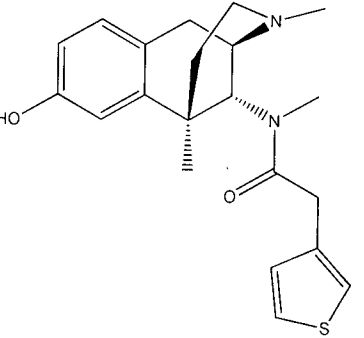
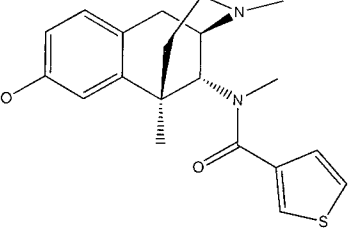
Ref. No.	Compound
104	 <chem>CN1[C@H]2[C@@H](C)[C@H](CNC3CCSC3)[C@H]1Cc1ccc(O)cc1</chem>
105	 <chem>CC(C)(C)c1ccc(cc1)CCNC[C@H]2[C@@H](C)[C@H](C)[C@H]2Cc3ccc(O)cc3</chem>
106	 <chem>CC(C)(C)OC(=O)N1CC[C@H](CNC[C@H]2[C@@H](C)[C@H](C)[C@H]2Cc3ccc(O)cc3)CC1</chem>

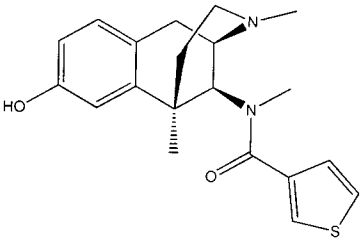
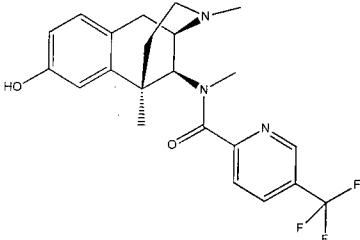
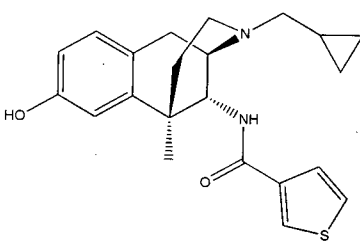
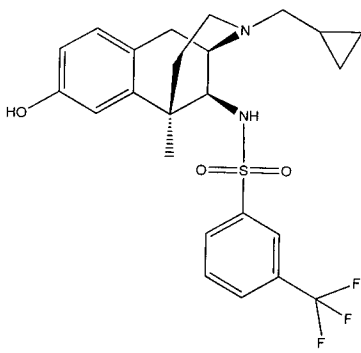
Ref. No.	Compound
107	 <chem>CC12C(CCN1C3=CC=C(C=C3)O)CCN(C2)CCOC(=O)C(C)(C)C</chem>
108	 <chem>CC12C(CCN1C3=CC=C(C=C3)O)CCN(C2)CCOC(=O)C(C)(C)C</chem>
109	 <chem>CC12C(CCN1C3=CC=C(C=C3)O)CCN(C2)CCc4ccc(S(=O)(=O)N)cc4</chem>

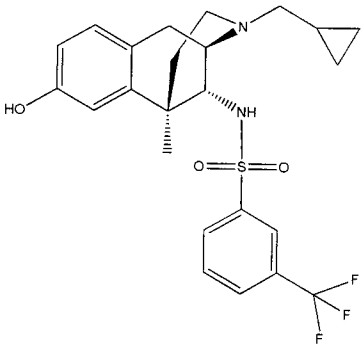
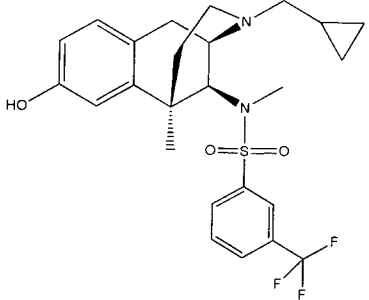
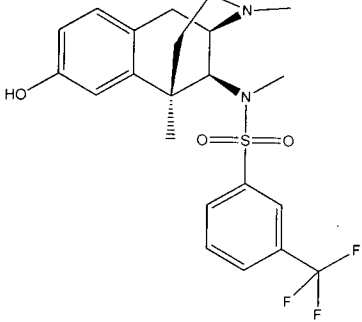
Ref. No.	Compound
110	 <chem>CN1[C@H]2[C@@H](CCN(C2)CC3=CC=C4C(=C3)C=CC=C4O)C5=CC=CC=C5</chem>
111	 <chem>CC1(C)OC(=O)NCCC[C@H]2[C@@H](CCN(C2)C3=CC=CC=C3O)C4=CC=CC=C4</chem>
112	 <chem>CC1(C)OC(=O)NCCC[C@H]2[C@@H](CCN(C2)C3=CC=CC=C3O)C4=CC=CC=C4</chem>

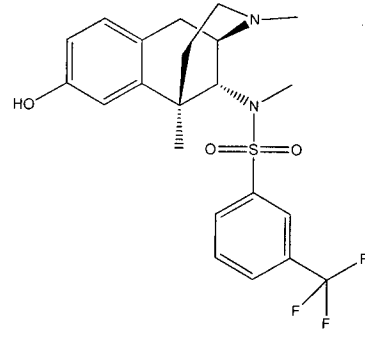
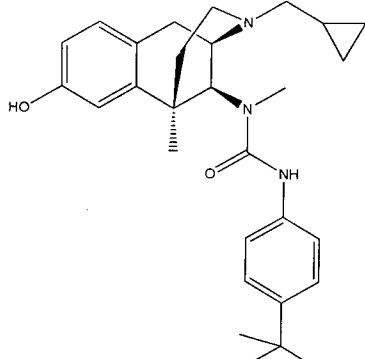
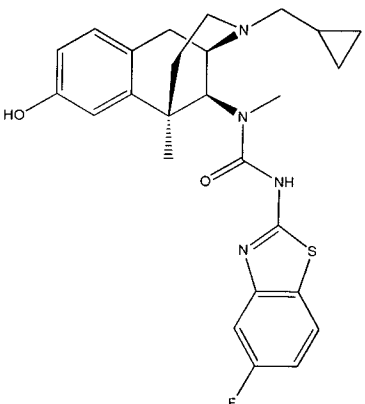
Ref. No.	Compound
113	 <chem>Oc1ccc2c(c1)[C@H]3[C@@H](C(=O)N[C@@H]3CC4CC4)C2</chem>
114	 <chem>CN(C)C(=O)N[C@@H]3CC4CC4[C@H]3C2=CC=C(C=C2)O</chem>
115	 <chem>CN(C)C(=O)N[C@@H]3CC4CC4[C@H]3C2=CC=C(C=C2)O</chem>
116	 <chem>CC(C)CC(=O)N(C)N[C@@H]3CC4CC4[C@H]3C2=CC=C(C=C2)O</chem>

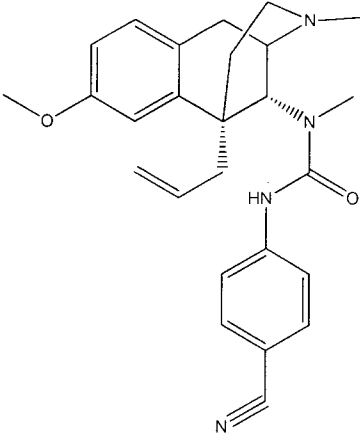
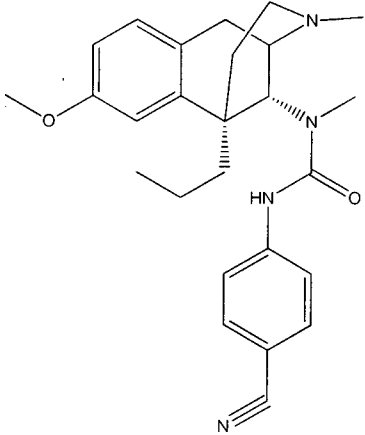
Ref. No.	Compound
117	 <chem>CN(C)[C@H]1CC[C@@H]2[C@@H]1Cc1ccc(O)cc1[C@H]2C(=O)N(C)Cc3ccccc3</chem>
118	 <chem>CN(C)[C@H]1CC[C@@H]2[C@@H]1Cc1ccc(O)cc1[C@H]2C(=O)N(C)Cc3ccccc3</chem>
119	 <chem>CN(C)[C@H]1CC[C@@H]2[C@@H]1Cc1ccc(O)cc1[C@H]2C(=O)N(C)C(=O)c3ccccc3</chem>
120	 <chem>CN(C)[C@H]1CC[C@@H]2[C@@H]1Cc1ccc(O)cc1[C@H]2C(=O)N(C)C(=O)C3CCCCC3</chem>

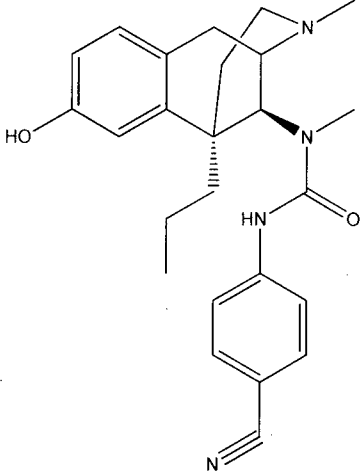
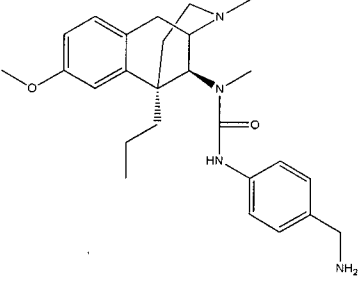
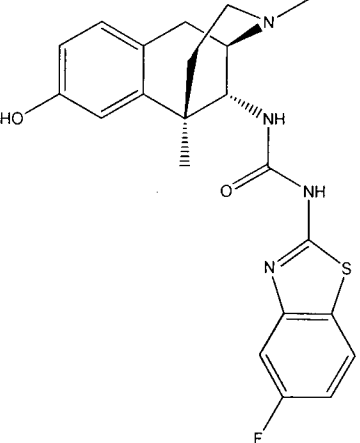
Ref. No.	Compound
121	 <chem>CN(C)[C@H]1[C@@H](C)[C@H]2[C@@H](C1)[C@H](C)[C@@H]3[C@@H](C2)C(=O)N(C)CC4CCCCC4[C@@H]3C5=CC=C(O)C=C5</chem>
122	 <chem>CN(C)[C@H]1[C@@H](C)[C@H]2[C@@H](C1)[C@H](C)[C@@H]3[C@@H](C2)C(=O)N(C)C/C=C/c4cccnc4[C@@H]3C5=CC=C(O)C=C5</chem>
123	 <chem>CN(C)[C@H]1[C@@H](C)[C@H]2[C@@H](C1)[C@H](C)[C@@H]3[C@@H](C2)C(=O)N(C)CCc4ccsc4[C@@H]3C5=CC=C(O)C=C5</chem>
124	 <chem>CN(C)[C@H]1[C@@H](C)[C@H]2[C@@H](C1)[C@H](C)[C@@H]3[C@@H](C2)C(=O)N(C)Cc4ccsc4[C@@H]3C5=CC=C(O)C=C5</chem>

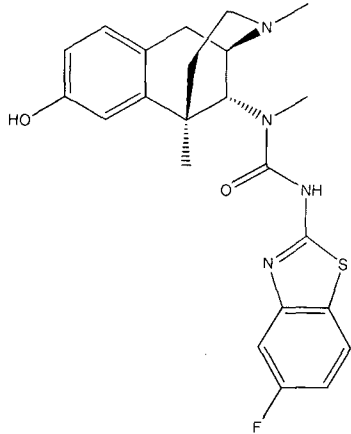
Ref. No.	Compound
125	 <chem>CN1[C@H]2[C@@H](C(=O)N1C3=CC=CC=C3O)C[C@H](C2)C4=CC=CC=C4O</chem>
126	 <chem>CN1[C@H]2[C@@H](C(=O)N1C3=CC=CC=C3O)C[C@H](C2)C4=CC=CC=C4O</chem>
127	 <chem>CN1[C@H]2[C@@H](C(=O)N1C3=CC=CC=C3O)C[C@H](C2)C4=CC=CC=C4O</chem>
128	 <chem>CN1[C@H]2[C@@H](C(=O)N1C3=CC=CC=C3O)C[C@H](C2)C4=CC=CC=C4O</chem>

Ref. No.	Compound
129	 <chem>Oc1ccc2c(c1)[C@H]3[C@@H](C[C@H]2N(C3)CC4CC4)NS(=O)(=O)c5ccc(cc5)C(F)(F)F</chem>
130	 <chem>CN(C)[C@H]1[C@@H](C[C@H]2c3ccc(O)cc3[C@H]12)NS(=O)(=O)c4ccc(cc4)C(F)(F)F</chem>
131	 <chem>CN(C)[C@H]1[C@@H](C[C@H]2c3ccc(O)cc3[C@H]12)NS(=O)(=O)c4ccc(cc4)C(F)(F)F</chem>

Ref. No.	Compound
132	 <chem>CN1[C@H]2[C@@H](C(=O)N(C)S(=O)(=O)c3ccc(C(F)(F)F)cc3)[C@H](c4ccc(O)cc4)[C@H]12</chem>
133	 <chem>CC1(C)[C@H]2[C@@H](C(=O)NC3=CC=C(C(C)(C)C)C=C3)[C@H](c4ccc(O)cc4)[C@H]12N(C)CC5CC5</chem>
134	 <chem>CC1(C)[C@H]2[C@@H](C(=O)NC3=C4C(=C(C=C3)SC4=N)C=C(F)C=C4)[C@H](c5ccc(O)cc5)[C@H]12N(C)CC6CC6</chem>

Ref. No.	Compound
135	 Chemical structure of compound 135: A pentacyclic molecule featuring a 4-methoxyphenyl group, a vinyl group, a dimethylamino group, and a 4-cyanophenyl group. <chem>COc1ccc2c(c1)[C@H]3[C@@H](C=C)[C@@H](C(=O)Nc4ccc(C#N)cc4)[C@H](N(C)C)[C@H]3C2</chem>
136	 Chemical structure of compound 136: A pentacyclic molecule featuring a 4-methoxyphenyl group, an ethyl group, a dimethylamino group, and a 4-cyanophenyl group. <chem>COc1ccc2c(c1)[C@H]3[C@@H](CC)[C@@H](C(=O)Nc4ccc(C#N)cc4)[C@H](N(C)C)[C@H]3C2</chem>

Ref. No.	Compound
137	
138	
139	

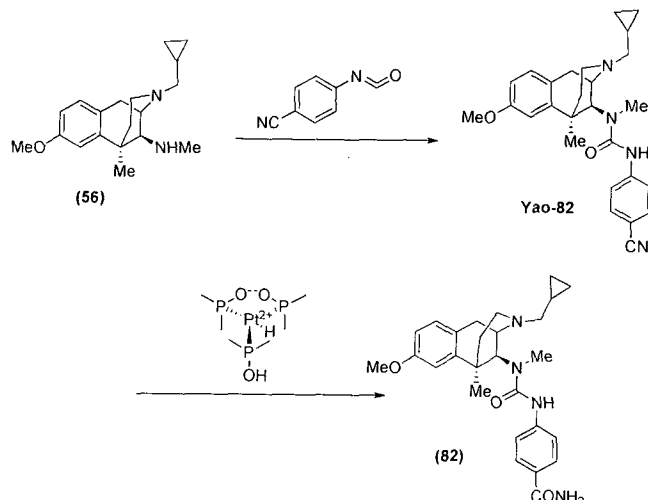
Ref. No.	Compound
140	

The *in vitro* test results of Tables 1, 2, and 2A show that representative Compounds of the Invention generally have high binding affinity for opioid receptors, and that these compounds activate these receptors as partial to full agonists. Compounds of the Invention are therefore expected to be useful to treat Conditions, particularly pain, that are responsive to the activation of one or more opioid receptors.

10

EXAMPLE 52

4-(3-(((6*R*,11*S*)-3-(cyclopropylmethyl)-8-methoxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-3-methylureido)benzamide (Compound 82)



4-isocyanatobenzonitrile (0.4 g, 1.67 mmol, Aldrich) was added to a solution of **Compound 56** (0.5 g, 1.67 mmol) in CHCl₃ (4 mL) at 0 °C. The reaction mixture was warmed to RT, and stirred at RT for 24 h. The reaction was quenched with 2 mL of water and 0.2 mL of conc. NH₄OH, and extracted with CHCl₃. The CHCl₃ layer was separated, concentrated, and purified by flash chromatography (SiO₂, 10% CHCl₃/hexanes) to give **Compound Yao-82** as a colorless oil (0.6 g, 81%).

LC/MS, $m/z = 445.4$ $[M + H]^+$ (Calc: 444.6).

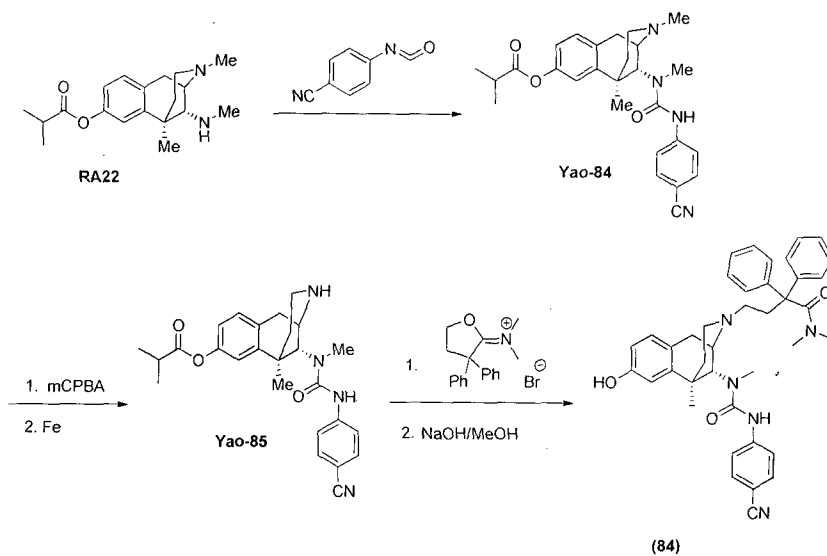
10 A mixture of **Compound Yao-82** (50 mg, 0.09 mmol) and bis(dimethyloxidophosphoranyl) (hydroxydimethylphosphoranyl)platinum(VI) hydride (5 mg, STREM CHEM. Inc.) in 1 mL of EtOH/water (3/1) was shaken at 85 °C for 3 h. The reaction was quenched with water, and extracted with CHCl₃. The CHCl₃ layer was separated, concentrated, and purified by reverse-phase prep HPLC
15 (C18, 0-100% 0.1 % TFA in water/0.1 % TFA in ACN) to yield **Compound 82** as a TFA-salt (white solid, 15 mg, 36%).

¹H NMR δ_H (400 MHz, CD₃OD) 7.87 (d, J = 8.0 Hz, 2H) 6.98 (d, J = 8.8 Hz, 1H), 6.71 (d, J = 2.8 Hz, 1H), 6.62 (dd, J = 2.8 and 7.6 Hz, 1H), 4.24 (d, J = 5.6 Hz, 1H), 3.27 – 3.40 (m, 1H), 3.23 (s, 3H), 3.00 – 3.11 (m, 1H), 2.62 – 2.70 (m, 1H), 2.28 – 2.37 (m, 1H), 1.47 (s, 3H), 1.44 (d, J = 14.8 Hz, 1H), 1.04 – 1.13 (m, 1H), 0.66 – 0.71 (m, 2H), 0.38 – 0.44 (m, 2H).

LC/MS, $m/z = 431.3$ $[M + H]^+$ (Calc: 430.5).

EXAMPLE 53

4-((2*R*,6*R*,11*S*)-11-(3-(4-cyanophenyl)-1-methylureido)-8-hydroxy-6-methyl-1,2,5,6-tetrahydro-2,6-methanobenzo[*d*]azocin-3(4*H*)-yl)-*N,N*-dimethyl-2,2-diphenylbutanamide (Compound 84)



4-isocyanatobenzonitrile (0.40 g, 2.8 mmol) was added to a solution of **Compound RA22** (0.8 g, 2.53 mmol) in CHCl_3 (4 mL) at 0 °C. The reaction mixture was warmed to RT, and stirred at RT for 24 h. The reaction was quenched with 2 mL of water and 0.2 mL of conc. NH_4OH , and extracted with CHCl_3 . The CHCl_3 layer was separated, concentrated, and purified by flash chromatography (SiO_2 , 10% CHCl_3 /hexanes) to give **Compound Yao-84** as an orange solid (0.85 g, 73%).

LC/MS, $m/z = 461.3$ $[\text{M} + \text{H}]^+$ (Calc: 460.5).

mCPBA (80 mg, 85%) was added to a solution of **Compound Yao-084** (0.20 g, 0.43 mmol) in CHCl_3 (4 mL) at 0 °C. After 10 min, 30 μL of HCl (5N) and 100 mg of iron powder were added. The reaction mixture was warmed to RT, and stirred at RT for 16 h. The reaction was filtered through a layer of Na_2SO_4 , then quenched with water and extracted with CHCl_3 . The CHCl_3 layer was washed with saturated aq. sodium sulfite (1 mL), and concentrated to give the crude product **Compound Yao-85** (0.20 g).

LC/MS, $m/z = 447.2$ $[\text{M} + \text{H}]^+$ (Calc: 446.5).

Dihydro-*N,N*-dimethyl-3,3-diphenyl-2(3H)-furaniminium bromide (60 mg, 0.17 mmol) was added to a solution of **Compound Yao-085** (0.15 g, 0.34 mmol) in DCM (15 mL) and TEA (30 μ L) at 0 °C. The reaction mixture was warmed to 36 °C, and
5 shaken at 36 °C for 2 h. The reaction was quenched with 1 mL of water and 1 mL of saturated NaHCO₃. The organic layer was separated, and concentrated under vacuum. The residue was re-dissolved in 2 mL of MeOH, then 0.1 mL of NaOH (2N) was added. The mixture was shaken at 36 °C for 2 h. The reaction mixture was concentrated under vacuum, and purified by reverse-phase prep HPLC (C18, 0-100%
10 0.1 % TFA in water/0.1 % TFA in ACN) to yield **Compound 84** as a TFA-salt (white solid, 15 mg).

¹H NMR δ_H (400 MHz, CD₃OD) 7.52 – 7.60 (m, 4H), 7.28 – 7.42 (m, 10H), 6.88 (d, J = 8.8 Hz, 1H), 6.71 (s, 1H), 6.59 (d, J = 7.6 Hz, 1H), 4.52 (s, 0.8H), 4.34 (s, 0.2H, diastereoisomers of TFA-salt), 3.49 (br, 1H), 2.90 – 3.10 (m, 6H), 2.82 – 2.84 (m, 2H),
15 2.58 – 2.71 (m, 4H), 2.35 – 2.48 (m, 2H), 2.25 (s, 3H), 2.00 – 2.08 (m, 1H), 1.58 (d, J = 15.6 Hz), 1.41 (s, 2.4H), 1.36 (3, 0.6H).

LC/MS, m/z = 642.3 [M + H]⁺ (Calc: 641.8).

In a similar manner the following compounds were prepared.

20

3-(4-cyanophenyl)-1-((2*R*,6*R*,11*S*)-8-hydroxy-6-methyl-3-phenethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[d]azocin-11-yl)-1-methylurea (Compound 87)

¹H NMR δ_H (400 MHz, CD₃OD) 7.55 – 7.60 (m, 4H), 7.18 – 7.28 (m, 5H), 7.02 (d, J = 8.8 Hz, 1H), 6.71 (s, 1H), 6.64 (d, J = 7.6 Hz, 1H), 4.75 (s, 0.2H), 4.59 (s, 0.8H, diastereoisomers of TFA-salt), 3.94 (s, 1H), 3.23 – 3.59 (m, 3H), 2.92 – 3.14 (m, 4H),
25 2.62 – 2.73 (m, 4H), 1.91 – 2.08 (m, 1H), 1.64 (d, J = 12.4 Hz, 1H), 1.46 (s, 3H).

LC/MS, m/z = 481.2 [M + H]⁺ (Calc: 480.6).

**3-(4-cyanophenyl)-1-((6*R*,11*R*)-3-(cyclobutylmethyl)-8-hydroxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-1-methylurea
(Compound 88)**

¹H NMR δ_H (400 MHz, CD₃OD) 7.52 – 7.60 (m, 4H), 6.95 – 7.02 (m, 2H), 6.74 (d, J = 2.8 Hz, 1H), 6.64 (dd, J = 2.8 and 8.8 Hz, 1H), 4.54 (s, 1H), 3.74 (s, 1H), 3.56 – 3.58 (m, 1H), 3.44 – 3.47 (m, 1H), 3.22 – 3.28 (m, 1H), 3.05 – 3.13 (m, 1H), 2.92 – 3.04 (m, 2H), 2.58 – 2.73 (m, 5H), 1.73 – 2.18 (m, 7H), 1.43 – 1.61 (m, 4H).

LC/MS, *m/z* = 445.2 [M + H]⁺ (Calc: 444.6).

**3-(4-cyanophenyl)-1-((6*R*,11*R*)-3-(2,3-difluorobenzyl)-8-hydroxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-1-methylurea
(Compound 89)**

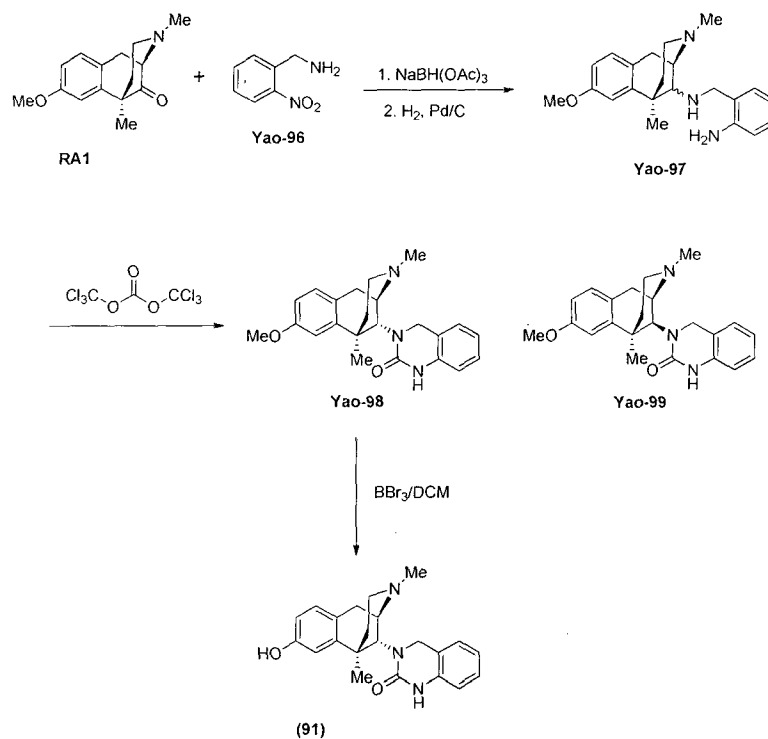
¹H NMR δ_H (400 MHz, CD₃OD) 7.50 – 7.57 (m, 4H), 7.30 – 7.39 (m, 2H), 7.16 – 7.24 (m, 1H), 7.00 – 7.08 (m, 1H), 6.77 (d, J = 3.2 Hz, 1H), 6.64 (dd, J = 2.4 and 8.8 Hz, 1H), 4.50 – 4.56 (m, 2H), 3.84 – 3.91 (m, 1H), 3.56 – 3.58 (m, 1H), 3.44 – 3.47 (m, 1H), 3.05 – 3.19 (m, 2H), 2.76 – 2.85 (m, 1H), 2.68 (s, 3H), 1.98 – 2.11 (m, 1H), 1.62 (d, J = 12.4 Hz, 1H), 1.44 (s, 3H).

LC/MS, *m/z* = 503.3 [M + H]⁺ (Calc: 502.6).

**3-(4-cyanophenyl)-1-((2*R*,6*R*,11*S*)-3-(furan-3-ylmethyl)-8-hydroxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-1-methylurea
(Compound 90)**

¹H NMR δ_H (400 MHz, CD₃OD) 7.67 – 7.73 (m, 4H), 7.58 (d, J = 8.4 Hz, 2H), 7.03 (d, J = 9.2 Hz, 1H), 6.73 (d, J = 2.4 Hz, 1H), 6.63 (dd, J = 2.8 and 8.4 Hz, 1H), 6.51 (s, 1H), 4.23 (br, 1H), 3.46 – 3.56 (m, 3H), 3.05 – 3.12 (m, 2H), 2.67 (s, 3H), 2.46 – 2.52 (m, 1H), 1.85 – 2.05 (m, 2H), 1.38 (s, 3H), 1.31 (d, J = 12.4 Hz, 1H).

LC/MS, *m/z* = 457.2 [M + H]⁺ (Calc: 456.5).

EXAMPLE 54**3-((2*R*,6*R*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-3,4-dihydroquinazolin-2(1*H*)-one (Compound 91)**

5 A mixture of **Compound RA1** (0.36 g, 1.47 mmol), (2-nitrophenyl)methanamine, HCl (**Compound Yao-96**, 0.48 g, 2.5 mmol), TEA (0.4 g, 4 mmol) and Na₂SO₄ (0.5 g) in 4 mL of ACN was shaken at 40 °C for 16 h, then added NaBH(OAc)₃ (0.6 g, 2.9 mmol). The reaction mixture was shaken at RT for 2 h. The reaction was quenched with water
 10 (3 mL), and extracted with 20 mL of CHCl₃. The organic layer was washed with 1N NaOH (6 mL), and concentrated to give an oil, which was dissolved in MeOH (50 mL) and AcOH (2 mL). The MeOH/AcOH solution was passed through H-cube (5 atm, 7.5mL/min, Pd/C 10%) at RT for 1 h. The solvent was removed under vacuum. The residue was dissolved in CHCl₃ (50 mL), cooled with ice-water, and nutralized to pH ~
 15 9 with 2N NaOH. The CHCl₃ layer was dried over Na₂SO₄, and filtered to afford crude **Compound Yao-97** in chloroform (~ 50 mL).

LC/MS, $m/z = 352.4$ [M + H]⁺ (Calc: 351.5).

Triphosgene (0.75 g in 5 mL of CHCl_3) was added to a solution of the crude **Compound Yao-97** (in 50 mL of CHCl_3 and 0.5 mL of TEA at 0 °C. The reaction mixture was warmed to RT over 2 h. The reaction was quenched with water at 0 °C, and neutralized with 1N NaOH. The organic layer was concentrated and purified by flash chromatography (SiO_2 , 5% MeOH/DCM) to give **Compound Yao-98** (120 mg) and **Compound Yao-99** (55 mg). The structures of **Compound Yao-98** and **Compound Yao-99** were confirmed by 2D NMR.

Compound Yao-098:

^1H NMR δ_{H} (400 MHz, CD_3OD) 7.14 (d, $J = 8.4$ Hz, 1H), 7.04 (dd, $J = 7.0$ and 8.4 Hz, 1H), 6.88 (d, $J = 2.8$ Hz, 1H), 6.85 (dd, $J = 2.8$ and 8.8 Hz, 1H), 6.74 – 6.78 (m, 1H), 6.71 (d, $J = 8.0$ Hz, 1H), 6.53 (d, $J = 6.8$ Hz, 1H), 4.56 (s, 1H), 3.86 – 3.98 (m, 3H), 3.75 (s, 3H), 3.44 – 3.58 (m, 1H), 3.30 (d, $J = 19.8$ Hz, 1H), 3.10 – 3.15 (m, 3H), 2.87 (s, 3H), 2.60 – 2.66 (m, 1H), 1.97 – 2.06 (m, 1H), 1.66 (d, $J = 14.8$ Hz, 1H), 1.42 (s, 3H).

15

BBr_3 (1M in DCM, 2 mL, 2 mmol) was added to a solution of **Compound Yao-098** (0.10 g, 0.26 mmol) in DCM (4 mL) at -78 °C. After 2 h at -78 °C, the reaction mixture was warmed to 0 °C for 30 min. The reaction was quenched with water (2 mL), neutralized with saturated aq. NaHCO_3 . The organic layer was separated, and purified by reverse-phase prep HPLC (C18, 0-100% 0.1 % TFA in water/0.1 % TFA in ACN) to yield **Compound 91** as a TFA-salt (white solid, 25 mg).

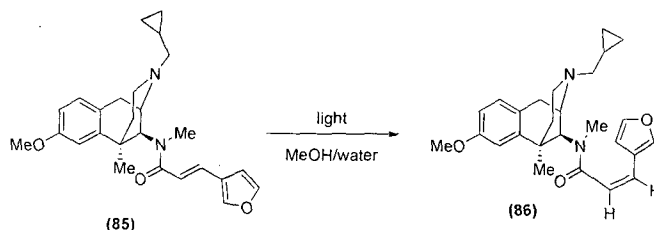
^1H NMR δ_{H} (400 MHz, CD_3OD) 7.03 – 7.07 (m, 2H), 6.75 – 6.79 (m, 2H), 6.71 (d, $J = 8.0$ Hz, 2H), 6.55 (d, $J = 7.6$ Hz, 1H), 4.53 (s, 1H), 3.82 – 4.00 (m, 4H), 3.04 – 3.14 (m, 2H), 2.55 (s, 3H), 2.60 – 2.66 (m, 1H), 1.97 – 2.03 (m, 1H), 1.63 (d, $J = 14.8$ Hz, 1H), 1.38 (s, 3H).

25

LC/MS, $m/z = 364.2$ $[\text{M} + \text{H}]^+$ (Calc: 363.4).

EXAMPLE 55

(Z)-N-((2R,6R,11S)-3-(cyclopropylmethyl)-8-methoxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[d]azocin-11-yl)-3-(furan-3-yl)-N-methylacrylamide
(Compound 86)



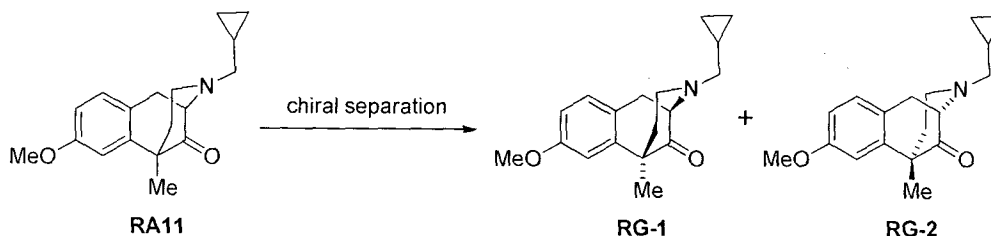
A solution of **Compound 85** (50 mg, 0.12 mmol) in 16 mL of MeOH/water (7/1) was stirred under ambient fluorescent light in a Quartz flask at RT for 24 h. After the solvent was removed under vacuum, the residue was purified by reverse-phase prep HPLC (C18, 0-100% 0.1 % TFA in water/0.1 % TFA in ACN) to yield **Compound 86** as a TFA-salt (white solid, 25 mg).

^1H NMR δ_{H} (400 MHz, CD_3OD) 7.79 (s, 1H), 7.44 (s, 1H), 7.08 (d, $J = 7.8$ Hz, 1H), 6.82 (d, $J = 3.6$ Hz, 1H), 6.79 (dd, $J = 3.2$ and 9.2 Hz, 1H), 6.65 (d, 1H, $J = 12.4$ Hz, 1H), 6.61 (s, 1H), 6.15 (d, $J = 12.4$ Hz, 1H), 4.31 (s, 1H), 3.90 (s, 1H), 3.38 (s, 3H), 3.07 – 3.18 (m, 5H), 2.61 – 2.68 (m, 1H), 2.28 – 2.37 (m, 1H), 1.54 (d, $J = 15.2$ Hz, 1H), 1.49 (s, 3H), 1.01 – 1.13 (m, 1H), 0.62 – 0.73 (m, 2H), 0.35 – 0.41 (m, 2H).

LC/MS, $m/z = 421.2$ [$\text{M} + \text{H}$] $^+$ (Calc: 420.5).

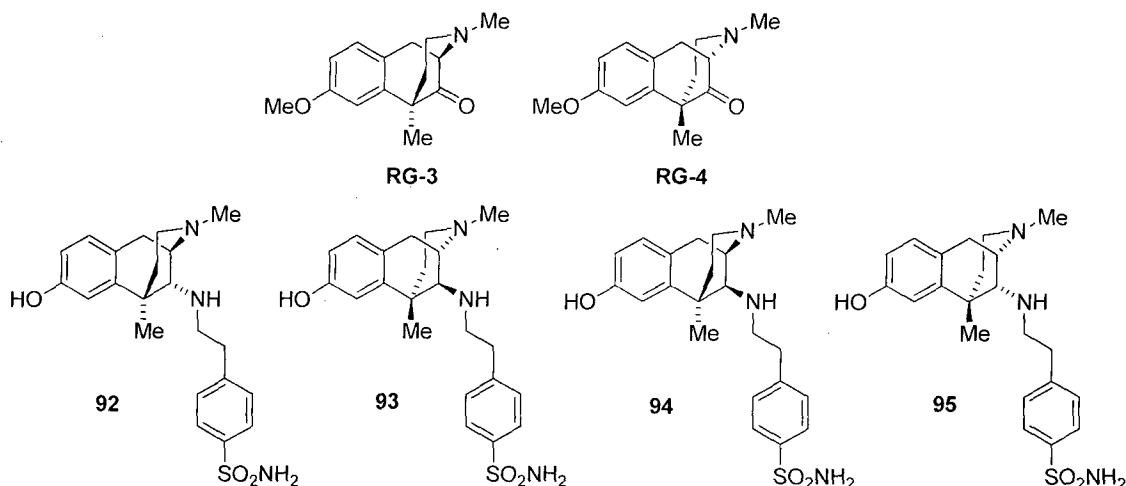
EXAMPLE 56

Resolution of racemic intermediates by chiral column chromatography.



Chiral chromatography was performed on racemic **Compound RA11** using a RegisPack 5 column (250 mm x 50 mm x 5 μ m) eluting with 20:80 EtOH/CO₂ to afford optically pure **Compound RG-1** and **Compound RG-2**.

- 5 In a similar manner the following compounds were isolated by chiral column chromatography.



- 10 **(2R,6S)-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[d]azocin-11-one (Compound RG-3)**

LC/MS, m/z = 246.1 $[M + H]^+$ (Calc: 245.3).

- 15 **(2S,6R)-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[d]azocin-11-one (Compound RG-4)**

LC/MS, m/z = 246.1 $[M + H]^+$ (Calc: 245.3).

- 20 **4-(2-(((2R,6S,11R)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[d]azocin-11-yl)amino)ethyl)benzenesulfonamide (Compound 92)**
- ¹H NMR δ_H (400 MHz, DMSO- d_6) 8.85 (s, 1H, -OH), 7.62 (d, $J=8.4$ Hz, 2H), 7.30 (d, $J=8.4$ Hz, 2H), 7.19 (s, 2H, -NH₂), 6.76 (d, $J=8.4$ Hz, 1H), 6.50 (d, $J=2.4$ Hz, 1H), 6.41 (dd, $J=8.1, 2.4$ Hz, 1H), 2.94-3.04 (m, 1H), 2.77-2.91 (m, 1H), 2.56-2.76 (m, 4H),

2.44-2.54 (m, 2H), 2.09-2.32 (m, 4H), 1.82 (td, $J=11.9$, 2.8 Hz, 1H), 1.64 (td, $J=12.5$, 4.7 Hz, 1H), 1.23 (s, 3H), 1.12 (d, $J=12.1$ Hz, 1H), 0.99 (br. s., 1H).

LC/MS, $m/z = 416.1$ $[M + H]^+$ (Calc: 415.6).

5 **4-(2-(((2*S*,6*R*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)amino)ethyl)benzenesulfonamide (Compound 93)**

^1H NMR δ_{H} (400 MHz, DMSO- d_6) 8.86 (s, 1H), 7.62 (d, $J=8.4$ Hz, 2H), 7.30 (d, $J=8.1$ Hz, 2H), 7.19 (s, 2H), 6.76 (d, $J=8.1$ Hz, 1H), 6.50 (d, $J=2.4$ Hz, 1H), 6.42 (dd, $J=8.1$, 2.4 Hz, 1H), 3.00 (br., 1H), 2.76-2.90 (m, 1H), 2.46-2.75 (m, 6H), 2.21 (br. s., 4H),
10 1.83 (t, $J=10.8$ Hz, 1H), 1.64 (td, $J=12.5$, 4.4 Hz, 1H), 1.24 (s, 3H), 1.13 (d, $J=11.9$ Hz, 1H), 0.99 (br. s., 1H).

LC/MS, $m/z = 416.2$ $[M + H]^+$ (Calc: 415.6).

15 **4-(2-(((2*R*,6*S*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)amino)ethyl)benzenesulfonamide (Compound 94)**

^1H NMR δ_{H} (400 MHz, DMSO- d_6) 8.88 (s, 1H), 7.66 (d, $J=8.4$ Hz, 2H), 7.37 (d, $J=8.4$ Hz, 2H), 7.20 (s, 2H), 6.79 (d, $J=8.1$ Hz, 1H), 6.59 (d, $J=2.4$ Hz, 1H), 6.38-6.50 (m, 1H), 2.86-3.16 (m, 3H), 2.73 (d, $J=7.3$ Hz, 3H), 2.45-2.58 (m, 1H), 2.31 (br. s., 1H),
2.09-2.20 (m, 4H), 1.61-1.98 (m, 3H), 1.22 (s, 3H), 0.84 (d, $J=11.7$ Hz, 1H).

20 LC/MS, $m/z = 416.2$ $[M + H]^+$ (Calc: 415.6).

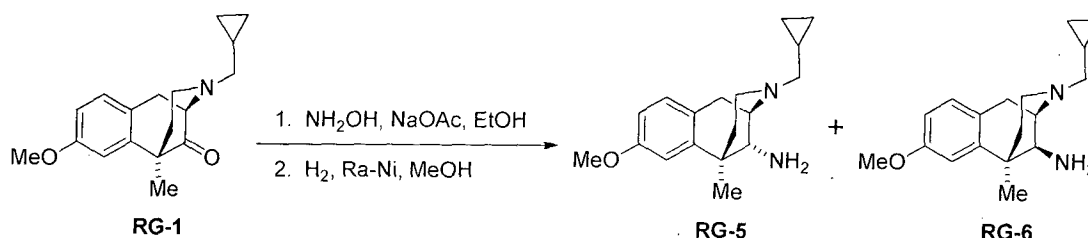
4-(2-(((2*S*,6*R*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)amino)ethyl)benzenesulfonamide (Compound 95)

^1H NMR δ_{H} (400 MHz, DMSO- d_6) 8.96 (s, 1H), 7.73 (d, $J=8.4$ Hz, 2H), 7.44 (d, $J=8.4$ Hz, 2H), 7.27 (s, 2H), 6.86 (d, $J=8.4$ Hz, 1H), 6.66 (d, $J=2.4$ Hz, 1H), 6.51 (dd, $J=8.1$, 2.4 Hz, 1H), 2.95-3.21 (m, 3H), 2.66-2.89 (m, 3H), 2.58 (dd, $J=17.8$, 5.7 Hz, 1H), 2.38 (br. s., 1H), 2.11-2.27 (m, 4H), 1.69-2.01 (m, 3H), 1.29 (s, 3H), 0.92 (d, $J=11.9$ Hz, 1H).

LC/MS, $m/z = 416.2$ $[M + H]^+$ (Calc: 415.6).

EXAMPLE 57

- 5 (2*R*,6*S*,11*S*)-3-(cyclopropylmethyl)-8-methoxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-amine (Compound RG-5) and (2*R*,6*S*,11*S*)-3-(cyclopropylmethyl)-8-methoxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-amine (Compound RG-6)



- 10 A mixture of **Compound RG-1** (0.942 g, 3.30 mmol), sodium acetate (0.54 g, 6.59 mmol) and hydroxylamine hydrochloride (0.46 g, 6.59 mmol) in EtOH (10 mL) was heated at 45 °C for 16 h. The mixture was concentrated and then quenched by the addition of water (15 mL). The mixture was extracted with EtOAc (40 mL) and the organic extracts concentrated to give the crude oxime as a sticky solid, which was used
- 15 directly in the next step.

- The crude oxime was dissolved in MeOH (200 mL) and hydrogenated over Ra-Ni at 40 atm and 40 °C for 4 h. The mixture was filtered and the filtrate concentrated to give a residue that was purified by flash chromatography (SiO₂, 10% (10% NH₄OH in MeOH) in DCM) to give **Compound RG-5** as a colorless oil (0.30 g, 32%) and
- 20 **Compound RG-6** as a colorless oil (0.25 g, 27%).

(2*R*,6*S*,11*S*)-3-(cyclopropylmethyl)-8-methoxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-amine (Compound RG-5)

LC/MS, m/z = 287.4 [M + H]⁺ (Calc: 286.4).

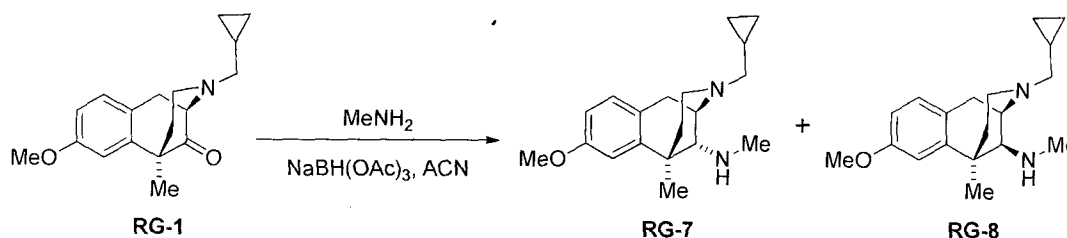
- 25 (2*R*,6*S*,11*S*)-3-(cyclopropylmethyl)-8-methoxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-amine (2*R*,6*S*,11*S*)-3-(cyclopropylmethyl)-8-

**methoxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[d]azocin-11-amine
(Compound RG-6)**

LC/MS, $m/z = 287.4$ $[M + H]^+$ (Calc: 286.4).

EXAMPLE 58

(2*R*,6*S*,11*S*)-3-(cyclopropylmethyl)-8-methoxy-*N*,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-amine (Compound RG-7) and (2*R*,6*S*,11*S*)-3-(cyclopropylmethyl)-8-methoxy-*N*,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-amine (Compound RG-8)



Chiral ketone **Compound RG-1** was converted to chiral amines **Compound RG-7** and **Compound RG-8** according to the same procedure described in **Example 41** for racemic **Compound RA11**.

15 **(2*R*,6*S*,11*S*)-3-(cyclopropylmethyl)-8-methoxy-*N*,6-dimethyl-1,2,3,4,5,6-**
hexahydro-2,6-methanobenzo[*d*]azocin-11-amine (Compound RG-7)

LC/MS, $m/z = 301.4$ $[M + H]^+$ (Calc: 300.4).

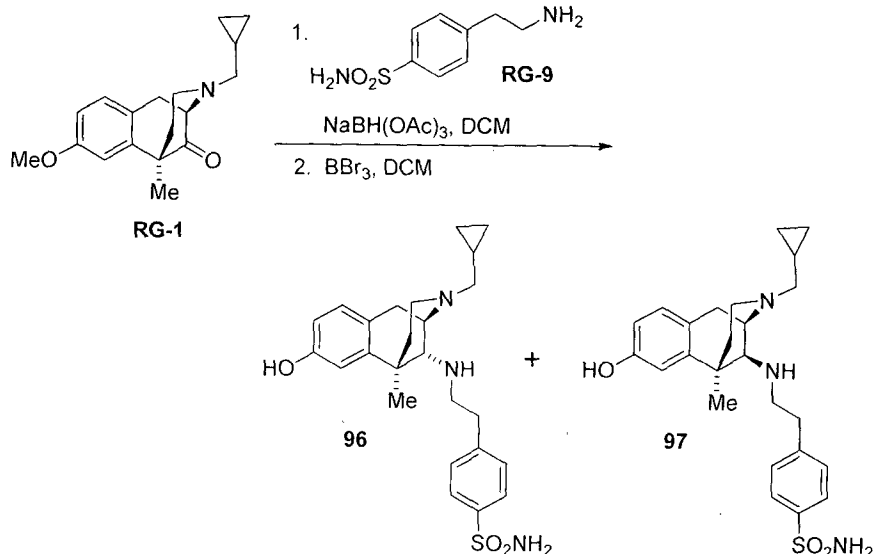
20 **(2*R*,6*S*,11*S*)-3-(cyclopropylmethyl)-8-methoxy-*N*,6-dimethyl-1,2,3,4,5,6-
hexahydro-2,6-methanobenzo[*d*]azocin-11-amine (Compound RG-8)**

LC/MS, $m/z = 301.4$ $[M + H]^+$ (Calc: 300.4).

EXAMPLE 59

25 4-(2-(((2*R*,6*S*,11*R*)-3-(cyclopropylmethyl)-8-hydroxy-6-methyl-1,2,3,4,5,6-
hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)amino)ethyl)benzenesulfonamide
(Compound 96) and 4-(2-(((2*R*,6*S*,11*S*)-3-(cyclopropylmethyl)-8-hydroxy-6-

methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[d]azocin-11-yl)amino)ethyl)benzenesulfonamide (Compound 97)



A mixture of **Compound RG-1** (0.50 g, 1.65 mmol), **Compound RG-9** (0.50 g, 2.47 mmol) and pTSA (0.03 g) in toluene (40 mL) was heated to reflux for 4 h and concentrated to give a brown oil. To this oil was added ACN (20 mL) followed by NaBH(OAc)₃ (1.05 g, 4.94 mmol). The reaction mixture was stirred at RT for 24 h, MeOH (1 mL) was added and the mixture concentrated. Water (10 mL) and EtOAc (100 mL) were added and the pH adjusted to *ca* 9 with conc. NH₄OH. The layers were separated and the organic layer was concentrated and purified by flash chromatography (SiO₂, 10% (10% NH₄OH in MeOH) in DCM) to give the product as a mixture of isomers.

This material was dissolved in DCM (4 mL), cooled to -78 °C and 1 M BBr₃ in DCM (2.0 mL, 2.0 mmol) was added. The mixture was stirred at -78 °C for 1 h allowed to warm to 0 °C and stirred an additional 30 min. The reaction was quenched by the addition of water (2 mL) and the pH adjusted to *ca* 8 with conc. NH₄OH. The layers were separated, the organic layer was concentrated and purified by flash chromatography (SiO₂, 10% (10% NH₄OH in MeOH) in DCM) to give **Compound 96** as a white solid (0.020 g, 3%) and **Compound 97** as a white solid (0.050 g, 7%).

4-(2-(((2*R*,6*S*,11*R*)-3-(cyclopropylmethyl)-8-hydroxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)amino)ethyl)benzenesulfonamide (Compound 96)

¹H NMR δ_H (400 MHz, CD₃OD) 7.77 (d, *J* = 8.36 Hz, 2H), 7.40 (d, *J* = 7.92 Hz, 2H), 7.01 (d, *J* = 7.92 Hz, 1H), 6.70 – 6.76 (m, 2H), 3.18 – 3.52 (m, 6H), 2.84 – 3.04 (m, 4H), 1.98 – 2.03 (m, 1H), 1.60 – 1.64 (m, 1H), 1.53 (s, 3H), 1.04 – 1.12 (m, 1H), 0.62 – 0.69 (m, 2H), 0.36 – 0.41 (m, 2H).

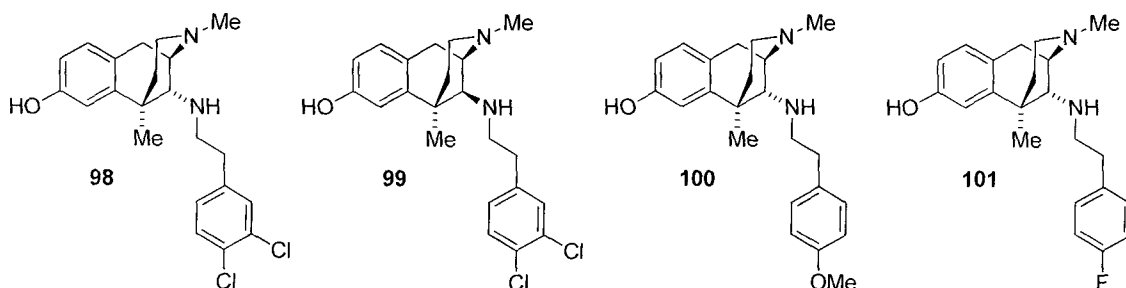
LC/MS, *m/z* = 456.1 [*M* + *H*]⁺ (Calc: 455.6).

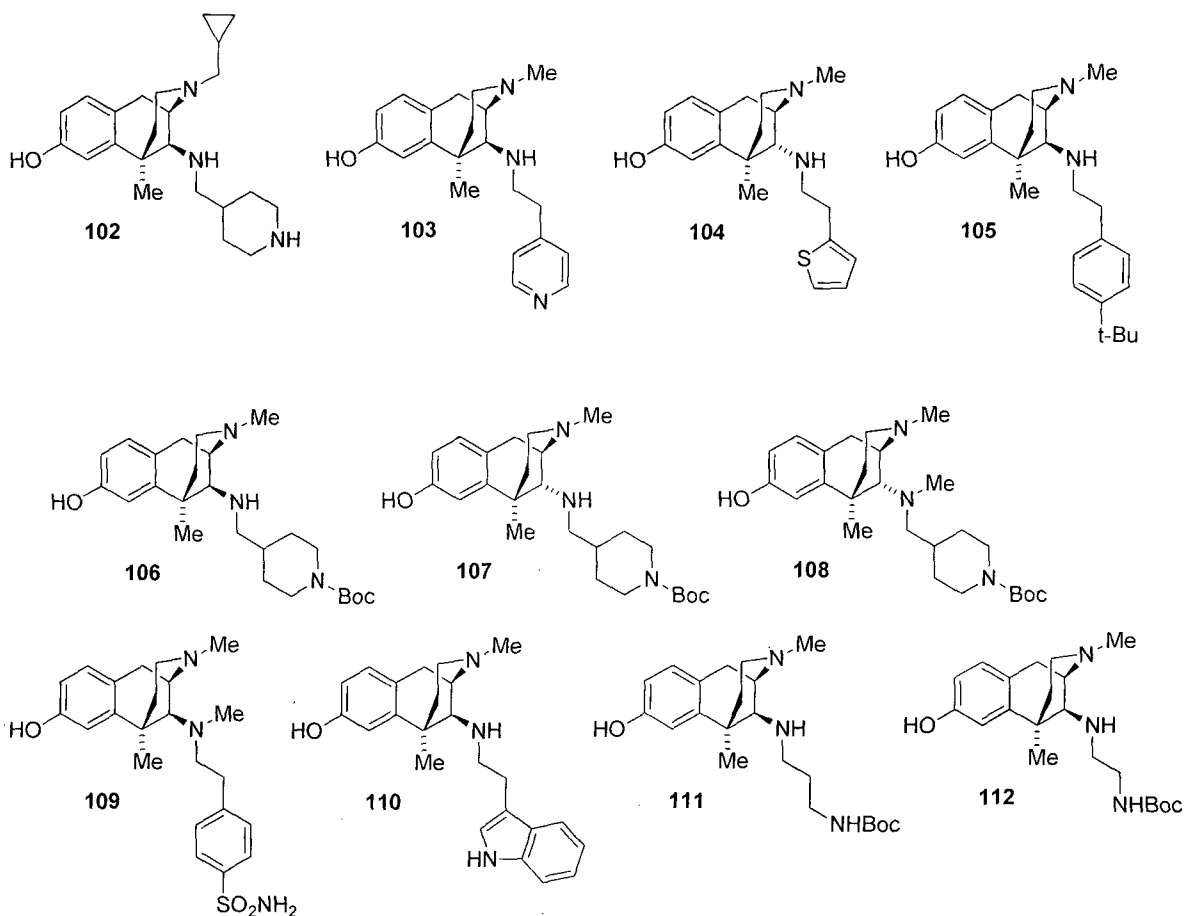
4-(2-(((2*R*,6*S*,11*S*)-3-(cyclopropylmethyl)-8-hydroxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)amino)ethyl)benzenesulfonamide (Compound 97)

¹H NMR δ_H (400 MHz, DMSO-*d*₆) 8.90 (s, 1H), 7.67 (d, *J*=8.1 Hz, 2H), 7.39 (d, *J*=8.4 Hz, 2H), 7.21 (s, 2H), 6.79 (d, *J*=8.4 Hz, 1H), 6.61 (d, *J*=2.4 Hz, 1H), 6.45 (dd, *J*=8.1, 2.4 Hz, 1H), 2.88-3.08 (m, 2H), 2.62-2.84 (m, 3H), 2.53 (dd, *J*=17.9, 5.8 Hz, 1H), 2.29-2.40 (m, 2H), 2.21 (ddt, *J*=19.5, 12.8, 6.4 Hz, 2H), 1.91-2.05 (m, 1H), 1.66-1.89 (m, 2H), 1.25 (s, 3H), 0.87 (d, *J*=12.1 Hz, 1H), 0.52-0.69 (m, 1H), 0.28-0.47 (m, 2H), -0.15-0.10 (m, 2H).

LC/MS, *m/z* = 456.1 [*M* + *H*]⁺ (Calc: 455.6).

In a similar manner the following chiral compounds were prepared from the appropriate chiral ketones.





5

(2*R*,6*S*,11*R*)-11-((3,4-dichlorophenethyl)amino)-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[d]azocin-8-ol (Compound 98)

¹H NMR δ_{H} (400 MHz, CD₃OD) 7.22-7.33 (m, 2H), 7.01 (dd, *J*=8.1, 1.8 Hz, 1H), 6.77 (d, *J*=8.1 Hz, 1H), 6.56 (d, *J*=2.2 Hz, 1H), 6.47 (dd, *J*=8.3, 2.3 Hz, 1H), 3.11 (br. s., 1H), 2.79-2.93 (m, 2H), 2.70-2.77 (m, 1H), 2.62 (d, *J*=3.5 Hz, 4H), 2.32 (s, 3H), 2.23-2.31 (m, 1H), 1.96-2.08 (m, 1H), 1.73 (td, *J*=12.9, 4.7 Hz, 1H), 1.28 (s, 3H), 1.18-1.26 (m, 1H).

LC/MS, *m/z* = 405.1/407.1 [*M*/*M* + 2]⁺ (Calc: 405.4).

(2*R*,6*S*,11*S*)-11-((3,4-dichlorophenethyl)amino)-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[d]azocin-8-ol (Compound 99)

¹H NMR δ_{H} (400 MHz, CD₃OD) 7.36 (s, 1H), 7.31 (d, *J*=8.3 Hz, 1H), 7.10 (dd, *J*=8.3, 1.9 Hz, 1H), 6.80 (d, *J*=8.4 Hz, 1H), 6.64 (d, *J*=2.4 Hz, 1H), 6.45 (dd, *J*=8.3, 2.5 Hz,

1H), 3.03-3.18 (m, 2H), 2.90-3.00 (m, 1H), 2.54-2.75 (m, 4H), 2.42 (br. s., 1H), 2.19-2.27 (m, 4H), 1.90-2.00 (m, 1H), 1.81 (td, J=12.9, 4.6 Hz, 1H), 1.25 (s, 3H), 0.97 (d, J=12.8 Hz, 1H).

LC/MS, m/z = 405.1/407.1 [M/M + 2]⁺ (Calc: 405.4).

5

(2R,6S,11R)-11-((4-methoxyphenethyl)amino)-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[d]azocin-8-ol (Compound 100)

¹H NMR δ_H (400 MHz, CD₃OD) 6.96 (d, J=8.6 Hz, 2H), 6.76 (d, J=8.1 Hz, 1H), 6.69 (d, J=8.6 Hz, 2H), 6.54 (d, J=2.6 Hz, 1H), 6.43-6.50 (m, 1H), 3.65 (s, 3H), 2.99-3.16 (m, 1H), 2.39-2.92 (m, 7H), 2.22 – 2.35 (m, 4H), 1.89-2.11 (m, 1H), 1.72 (d, J=4.8 Hz, 1H), 1.10-1.33 (m, 4H).

10

LC/MS, m/z = 367.2 [M + H]⁺ (Calc: 366.5).

(2R,6S,11R)-11-((4-fluorophenethyl)amino)-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[d]azocin-8-ol (Compound 101)

15

¹H NMR δ_H (400 MHz, CD₃OD) 7.17 (dd, J=8.6, 5.5 Hz, 2H), 7.00 (d, J=8.4 Hz, 1H), 6.94 (t, J=8.8 Hz, 2H), 6.72 (d, J=2.4 Hz, 1H), 6.67 (dd, J=8.4, 2.4 Hz, 1H), 4.07 (br. s., 1H), 3.47 (br. s., 1H), 3.05-3.20 (m, 5H), 2.85-2.97 (m, 4H), 2.65 – 2.8 (m, 2H), 1.94-2.11 (m, 1H), 1.58-1.70 (m, 1H), 1.52 (s, 3H).

20

LC/MS, m/z = 355.2 [M + H]⁺ (Calc: 354.5).

(2R,6S,11S)-3-(cyclopropylmethyl)-6-methyl-11-((piperidin-4-ylmethyl)amino)-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[d]azocin-8-ol (Compound 102)

¹H NMR δ_H (400 MHz, CD₃OD) 7.04 (d, J=8.4 Hz, 1H), 6.85 (d, J=2.4 Hz, 1H), 6.69 (dd, J=8.4, 2.4 Hz, 1H), 4.20 (br. s., 1H), 3.32-3.51 (m, 3H), 3.27 (br. s., 1H), 2.93-3.11 (m, 4H), 2.85 (dd, J=13.4, 8.1 Hz, 1H), 2.75 (d, J=5.3 Hz, 1H), 2.56-2.71 (m, 2H), 2.24 (br., 2H), 1.97-2.09 (m, 1H), 1.79-1.95 (m, 1H), 1.49-1.57 (m, 3H), 1.34-1.48 (m, 3H), 1.05-1.19 (m, 1H), 0.81 (d, J=4.2 Hz, 1H), 0.72 (br. s., 1H), 0.40-0.58 (m, 2H).

25

LC/MS, m/z = 370.4 [M + H]⁺ (Calc: 369.5).

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(2*R*,6*S*,11*S*)-3,6-dimethyl-11-((2-(pyridin-4-yl)ethyl)amino)-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-8-ol (Compound 103)

¹H NMR δ_H (400 MHz, CD₃OD) 8.78 (d, *J*=5.7 Hz, 2H), 8.03 (d, *J*=6.4 Hz, 2H), 7.08 (d, *J*=8.4 Hz, 1H), 6.87 (d, *J*=2.4 Hz, 1H), 6.72 (dd, *J*=8.3, 2.3 Hz, 1H), 3.87-3.96 (m, 1H), 3.35 – 3.41 (m, 1H), 3.20 – 3.25 (m, 4H), 3.07-3.16 (m, 3H), 2.91 (s, 3H), 2.65-2.76 (m, 1H), 2.23-2.39 (m, 1H), 1.50 (s, 3H), 1.44 (d, *J*=12.8 Hz, 1H).

LC/MS, *m/z* = 338.3 [M + H]⁺ (Calc: 337.5).

(2*R*,6*S*,11*R*)-3,6-dimethyl-11-((2-(thiophen-2-yl)ethyl)amino)-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-8-ol (Compound 104)

¹H NMR δ_H (400 MHz, CD₃OD) 7.15 (d, *J*=5.2 Hz, 1H), 6.98 (d, *J*=8.4 Hz, 1H), 6.84 (d, *J*=8.5 Hz, 1H), 6.80 (s, 1H), 6.70 (s, 1H), 6.65 (d, *J*=8.5 Hz, 1H), 4.02 (d, *J*=2.9 Hz, 1H), 3.35 (br. s., 1H), 2.98-3.17 (m, 7H), 2.90 (s, 3H), 2.64 (br. s., 1H), 1.89-2.10 (m, 1H), 1.61 (d, *J*=13.4 Hz, 1H), 1.49 (s, 3H).

LC/MS, *m/z* = 343.2 [M + H]⁺ (Calc: 342.5).

(2*R*,6*S*,11*S*)-11-((4-(*tert*-butyl)phenethyl)amino)-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-8-ol (Compound 105)

¹H NMR δ_H (400 MHz, CD₃OD) 7.20-7.24 (m, *J*=8.1 Hz, 2H), 7.05-7.09 (m, *J*=8.1 Hz, 2H), 6.79 (d, *J*=8.4 Hz, 1H), 6.64 (d, *J*=2.4 Hz, 1H), 6.46 (dd, *J*=8.4, 2.4 Hz, 1H), 3.07 (d, *J*=18.0 Hz, 1H), 2.99 (br. s., 1H), 2.86-2.95 (m, 1H), 2.63-2.77 (m, 3H), 2.56 (dd, *J*=17.9, 5.4 Hz, 1H), 2.43 (br. s., 1H), 2.15-2.26 (m, 4H), 1.79-2.01 (m, 2H), 1.26 (s, 3H), 1.20 (s, 9H), 0.97 (d, *J*=12.5 Hz, 1H).

LC/MS, *m/z* = 393.3 [M + H]⁺ (Calc: 392.6).

***tert*-butyl 4-((((2*R*,6*S*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)amino)methyl)piperidine-1-carboxylate (Compound 106)**

¹H NMR δ_H (400 MHz, CD₃OD) 6.94 (d, *J*=8.4 Hz, 1H), 6.74 (d, *J*=2.4 Hz, 1H), 6.59 (dd, *J*=8.3, 2.5 Hz, 1H), 4.01 (d, *J*=13.4 Hz, 2H), 3.66 (d, *J*=4.6 Hz, 1H), 3.26 (s, 1H), 3.13 (d, *J*=6.2 Hz, 1H), 2.85-2.95 (m, 2H), 2.74 (s, 3H), 2.49-2.71 (m, 5H), 2.14 (td,

$J=13.9$, 5.1 Hz, $1H$), 1.60 - 1.88 (m, $3H$), 1.41 (s, $3H$), 1.35 (s, $9H$), 1.31 (d, $J=13.0$ Hz, $1H$), 0.96 - 1.13 (m, $2H$).

LC/MS, $m/z = 430.2$ $[M + H]^+$ (Calc: 429.6).

5 ***tert*-butyl 4-(((*(2R,6S,11R)*-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)amino)methyl)piperidine-1-carboxylate**
(Compound 107)

^1H NMR δ_H (400 MHz, CD_3OD) 7.00 (d, $J=8.6$ Hz, $1H$), 6.71 (d, $J=2.4$ Hz, $1H$), 6.66 (dd, $J=8.4$, 2.4 Hz, $1H$), 3.91 - 4.07 (m, $3H$), 3.34 (br. s., $1H$), 3.18 (br. s., $1H$), 3.10 (d, $J=10.1$ Hz, $1H$), 2.91 (s, $3H$), 2.58 - 2.84 (m, $5H$), 1.95 - 2.11 (m, $1H$), 1.58 - 1.79 (m, $4H$), 1.53 (s, $3H$), 1.3 - 1.36 (m, $10H$), 0.92 - 1.10 (m, $2H$).

LC/MS, $m/z = 430.4$ $[M + H]^+$ (Calc: 429.6).

15 ***tert*-butyl 4-(((*(2R,6S,11R)*-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)(methyl)amino)methyl)piperidine-1-carboxylate**
(Compound 108)

^1H NMR δ_H (400 MHz, $CDCl_3$) 6.82 (d, $J=8.4$ Hz, $1H$), 6.65 (d, $J=2.4$ Hz, $1H$), 6.51 (dd, $J=8.1$, 2.4 Hz, $1H$), 3.95 (br. s., $2H$), 3.08 (dd, $J=5.4$, 2.3 Hz, $1H$), 3.00 (d, $J=18.5$ Hz, $1H$), 2.69 - 2.75 (m, $1H$), 2.45 - 2.64 (m, $3H$), 2.24 - 2.37 (m, $6H$), 1.90 - 2.06 (m, $4H$), 1.79 (td, $J=12.7$, 5.1 Hz, $2H$), 1.44 - 1.67 (m, $1H$), 1.34 - 1.39 (m, $12H$), 1.06 - 1.29 (m, $2H$), 0.75 - 0.94 (m, $2H$).

LC/MS, $m/z = 444.3$ $[M + H]^+$ (Calc: 443.6).

25 **4-(2-(((*(2R,6S,11S)*-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)(methyl)amino)ethyl)benzenesulfonamide**
(Compound 109)

^1H NMR δ_H (400 MHz, CD_3OD) 7.75 - 7.79 (m, $J=8.4$ Hz, $2H$), 7.36 - 7.40 (m, $J=8.4$ Hz, $2H$), 6.90 (d, $J=8.4$ Hz, $1H$), 6.70 (d, $J=2.4$ Hz, $1H$), 6.57 (dd, $J=8.4$, 2.4 Hz, $1H$), 3.65 (d, $J=5.1$ Hz, $1H$), 3.23 - 3.44 (m, $4H$), 3.03 - 3.11 (m, $5H$), 2.86 (dd, $J=18.4$, 5.8 Hz, $1H$), 2.60 (dd, $J=11.7$, 3.5 Hz, $1H$), 2.45 (s, $3H$), 2.11 - 2.32 (m, $2H$), 1.48 (s, $3H$), 1.32 (d, $J=13.9$ Hz, $1H$).

LC/MS, $m/z = 430.2$ $[M + H]^+$ (Calc: 429.6).

(2*R*,6*S*,11*S*)-11-((2-(1*H*-indol-3-yl)ethyl)amino)-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-8-ol (Compound 110)

- 5 ^1H NMR δ_{H} (400 MHz, CD_3OD) 7.54 (d, $J=7.9$ Hz, 1H), 7.28 (d, $J=8.1$ Hz, 1H), 6.86-7.10 (m, 4H), 6.68 (d, $J=2.4$ Hz, 1H), 6.56 (dd, $J=8.4$, 2.4 Hz, 1H), 3.40 (br. s., 1H), 3.12-3.20 (m, 2H), 3.03-3.10 (m, 4H), 2.85-2.93 (m, 1H), 2.62 (d, $J=8.4$ Hz, 1H), 2.26-2.36 (m, 4H), 1.95-2.05 (m, 1H), 1.21-1.32 (m, 4H).

LC/MS, $m/z = 376.2$ $[M + H]^+$ (Calc: 375.5).

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***tert*-butyl (3-(((2*R*,6*S*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)amino)propyl)carbamate (Compound 111)**

- ^1H NMR δ_{H} (400 MHz, CD_3OD) 7.06 (d, $J=8.4$ Hz, 1H), 6.86 (d, $J=2.4$ Hz, 1H), 6.71 (dd, $J=8.4$, 2.4 Hz, 1H), 3.81 (br. s., 1H), 3.39 (s, 1H), 3.12-3.29 (m, 4H), 2.87-3.05 (m, 3H), 2.81 (s, 3H), 2.58 (td, $J=12.7$, 3.4 Hz, 1H), 2.21-2.30 (m, 1H), 1.82 (quin, $J=6.6$ Hz, 2H), 1.52-1.59 (m, 3H), 1.46 (s, 9H), 1.42-1.45 (m, 1H).

15

LC/MS, $m/z = 390.3$ $[M + H]^+$ (Calc: 389.5).

***tert*-butyl (2-(((2*R*,6*S*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)amino)ethyl)carbamate (Compound 112)**

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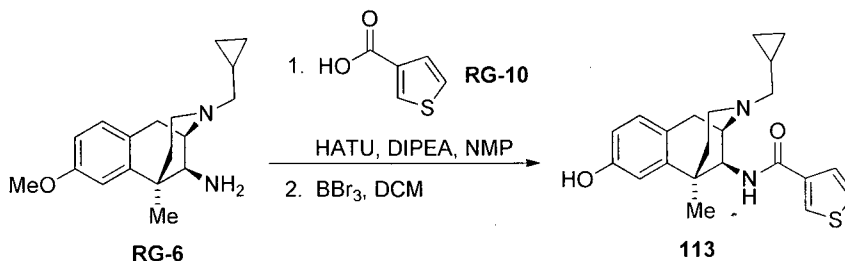
^1H NMR δ_{H} (400 MHz, CD_3OD) 7.06 (d, $J=8.4$ Hz, 1H), 6.86 (d, $J=2.4$ Hz, 1H), 6.71 (dd, $J=8.3$, 2.5 Hz, 1H), 3.77-3.82 (m, 1H), 3.32 – 3.38 (m, 1H), 3.27-3.31 (m, 1H), 3.13-3.26 (m, 2H), 2.98-3.07 (m, 2H), 2.87-2.92 (m, 2H), 2.86 (s, 3H), 2.61-2.71 (m, 1H), 2.21-2.31 (m, 1H), 1.50 (s, 3H), 1.48 (s, 9H), 1.41 (d, $J=14.3$ Hz, 1H).

- 25 LC/MS, $m/z = 376.2$ $[M + H]^+$ (Calc: 375.5).

EXAMPLE 60

***N*-((2*R*,6*S*,11*S*)-3-(cyclopropylmethyl)-8-hydroxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)thiophene-3-carboxamide (Compound 113)**

30



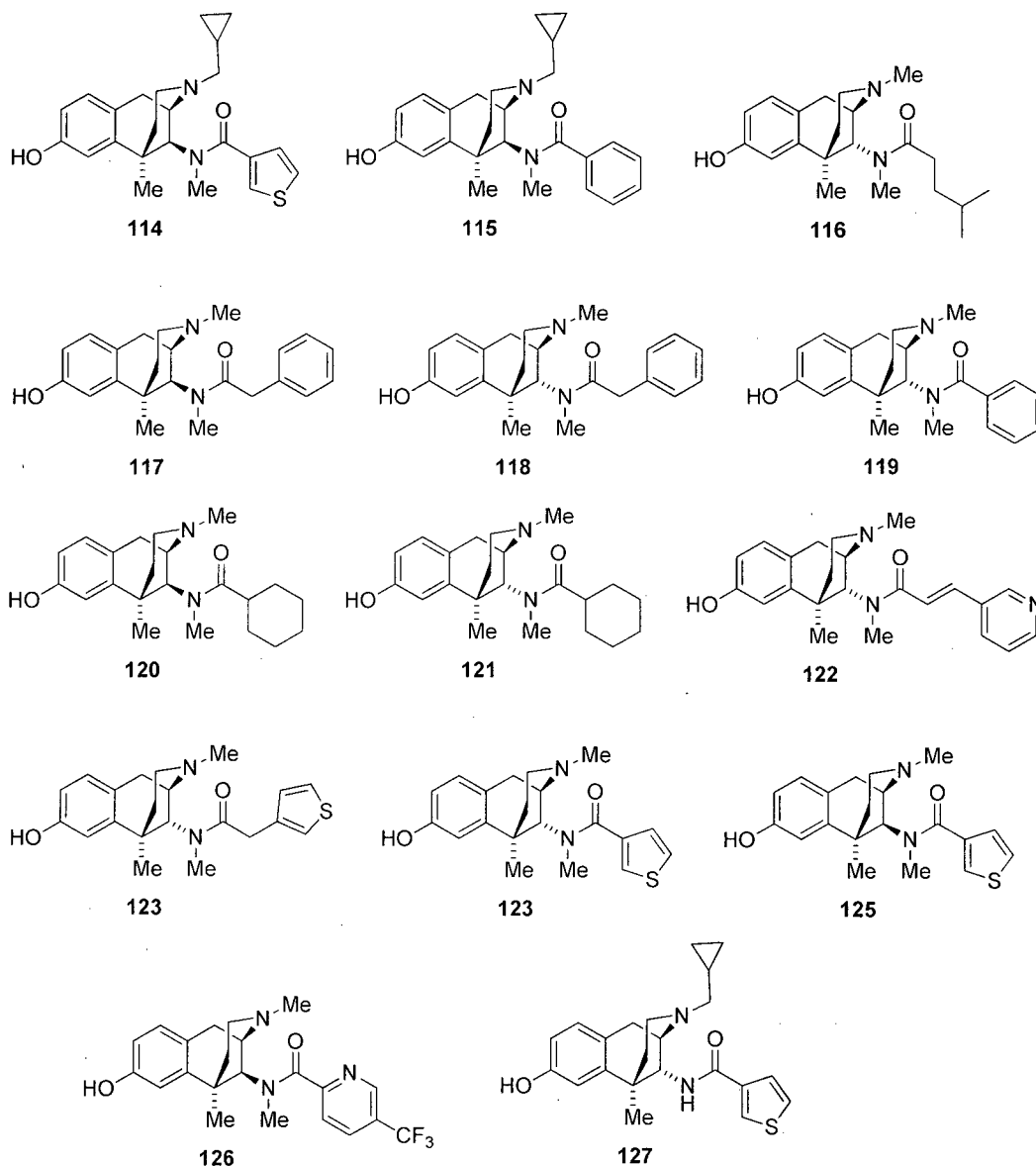
To a mixture of **Compound RG-6** (0.10 g, 0.35 mmol), **Compound RG-10** (0.054 g, 0.42 mmol) and DIPEA (0.045 g, 0.35 mmol) in NMP (1 mL) was added HATU (0.16 g, 0.42 mmol) at RT. The reaction mixture was stirred at RT for 16 h, quenched by the addition of water and the mixture extracted with EtOAc. The organic layer was concentrated and purified by flash chromatography (SiO₂, 10% (10% NH₄OH in MeOH) in DCM) to give the desired product.

This material was dissolved in DCM (8 mL), cooled to -78 °C and 1 M BBr₃ in DCM (2.0 mL, 2.0 mmol) was added. The mixture was stirred at -78 °C for 2 h allowed to warm to 0 °C and stirred an additional 30 min. The reaction was quenched by the addition of water (2 mL) and the pH adjusted to *ca* 8 with conc. NH₄OH. The layers were separated, the organic layer was concentrated and purified by flash chromatography (SiO₂, 10% (7% NH₄OH in MeOH) in DCM) to give **Compound 113** as a white solid (0.040 g, 29%).

¹H NMR δ_H (400 MHz, DMSO-d₆) 8.95 (s, 1H), 8.13 (dd, J=2.6, 1.1 Hz, 1H), 7.47-7.57 (m, 2H), 7.38 (d, J=5.1 Hz, 1H), 6.81 (d, J=8.4 Hz, 1H), 6.59 (d, J=2.4 Hz, 1H), 6.46 (dd, J=8.3, 2.3 Hz, 1H), 4.00 (d, J=7.3 Hz, 1H), 3.14-3.20 (m, 1H), 2.91 (d, J=18.0 Hz, 1H), 2.62 (dd, J=18.0, 6.2 Hz, 1H), 2.47 (d, J=7.0 Hz, 1H), 2.15-2.34 (m, 2H), 1.86-2.01 (m, 2H), 1.10 (s, 3H), 0.99 (d, J=10.1 Hz, 1H), 0.73 (t, J=6.2 Hz, 1H), 0.27-0.39 (m, 2H), 0.01 (d, J=4.6 Hz, 2H).

LC/MS, *m/z* = 383.1 [M + H]⁺ (Calc: 382.5).

In a similar manner the following chiral compounds were prepared from the appropriate chiral amines.



***N*-((2*R*,6*S*,11*S*)-3-(cyclopropylmethyl)-8-hydroxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-*N*-methylthiophene-3-carboxamide**

5 (Compound 114)

^1H NMR δ_{H} (400 MHz, CD_3OD) 6.90 – 7.70 (m, 3H), 6.37 – 6.82 (m, 3H), 4.88 (s, 0.6H), 3.99 (s, 0.4H), 3.58 – 3.60 (m, 3H), 3.41 – 3.52 (m, 1H), 2.95 – 3.1 (m, 1H), 2.34 – 2.72 (m, 3H), 2.08 – 2.22 (m, 3H), 1.09 – 1.29 (m, 4H), 0.72 – 0.82 (m, 1H), 0.35 – 0.42 (m, 2H), -0.04 – 0.04 (m, 2H).

10 LC/MS, $m/z = 397.2$ $[\text{M} + \text{H}]^+$ (Calc: 396.6).

***N*-((2*R*,6*S*,11*S*)-3-(cyclopropylmethyl)-8-hydroxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-*N*-methylbenzamide (Compound 115)**

¹H NMR δ_H (400 MHz, CD₃OD) 7.16 – 7.35 (m, 5H), 6.82 (d, *J* = 8.1 Hz, 0.6H), 6.63 – 6.65 (m, 1H), 6.33 – 6.49 (m, 1.4H), 4.9 (s, 0.6H), 3.85 (s, 0.4H), 3.45 – 3.65 (m, 4H), 2.92 – 3.1 (m, 1H), 2.63 – 2.74 (m, 1.6H), 2.34 – 2.42 (m, 1.4H), 2.0 – 2.22 (m, 3H), 1.08 – 1.34 (m, 4H), 0.65 – 0.8 (m, 1H), 0.35 – 0.43 (m, 2H), -0.04 – 0.04 (m, 2H).

LC/MS, *m/z* = 391.2 [*M* + *H*]⁺ (Calc: 390.5).

10

***N*-((2*R*,6*S*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-*N*,4-dimethylpentanamide (Compound 116)**

¹H NMR δ_H (400 MHz, CD₃OD) 6.86 (d, *J* = 7.7 Hz, 1H), 6.64 (d, *J* = 2.4 Hz, 1H), 6.50 – 6.54 (m, 1H), 4.65 (d, *J* = 2.6 Hz, 0.6H), 3.85 (d, *J* = 2.6 Hz, 0.4H), 2.93 – 3.11 (m, 2H), 2.39 – 2.64 (m, 4H), 2.23 – 2.40 (m, 6H), 1.99 – 2.13 (m, 1H), 1.81 – 1.91 (m, 1H), 1.34 – 1.56 (m, 3H), 1.24 – 1.32 (m, 4H), 0.79 – 0.89 (m, 6H).

15

LC/MS, *m/z* = 345.3 [*M* + *H*]⁺ (Calc: 344.5).

***N*-((2*R*,6*S*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-**

methanobenzo[*d*]azocin-11-yl)-*N*-methyl-2-phenylacetamide (Compound 117)

¹H NMR δ_H (400 MHz, DMSO-*d*₆) 8.97 (s, 1H), 6.92 – 7.32 (m, 5H), 6.83 (d, *J* = 8.4 Hz, 1H), 6.40 – 6.62 (m, 2H), 4.66 (s, 1H), 3.70 (d, *J* = 2.9 Hz, 2H), 3.51 (s, 3H), 2.69 – 3.10 (m, 2H), 2.51 – 2.64 (m, 1H), 2.30 – 2.40 (m, 1H), 2.10 – 2.23 (m, 3H), 1.82 – 2.07 (m, 2H), 0.92 – 1.16 (m, 4H).

20

LC/MS, *m/z* = 365.2 [*M* + *H*]⁺ (Calc: 364.5).

***N*-((2*R*,6*S*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-**

methanobenzo[*d*]azocin-11-yl)-*N*-methyl-2-phenylacetamide (Compound 118)

¹H NMR δ_H (400 MHz, DMSO-*d*₆) 9.04 (d, *J* = 2.4 Hz, 1H), 7.00 – 7.39 (m, 5H), 6.76 – 6.90 (m, 1H), 6.36 – 6.63 (m, 2H), 4.52 (d, *J* = 2.6 Hz, 0.6H), 3.86 (d, *J* = 2.6 Hz, 0.4H), 3.57 – 3.74 (m, 2H), 2.87 – 2.92 (m, 1H), 2.76 – 2.78 (m, 1H), 2.52 (s, 1.8H), 2.38 (s,

30

1.2H), 2.30-2.35 (m, 1H), 2.20-2.26 (m, 1H), 2.18 (s, 3H), 1.55-1.91 (m, 2H), 1.18 (s, 1.8H), 1.03-1.15 (m, 1H), 0.94 (s, 1.2H).

LC/MS, $m/z = 365.2$ $[M + H]^+$ (Calc: 364.5).

5 ***N*-((2*R*,6*S*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-*N*-methylbenzamide (Compound 119)**

^1H NMR δ_{H} (400 MHz, DMSO- d_6) 8.94-9.19 (m, 1H), 7.15-7.54 (m, 5H), 6.86 (t, $J=8.0$ Hz, 1H), 6.55-6.69 (m, 1H), 6.36-6.53 (m, 1H), 4.70 (br. 0.5H), 3.68 (br., 0.5H), 2.88-3.09 (m, 2H), 2.59-2.66 (m, 1H), 2.55 (s, 1.5H), 2.39 (s, 1.5H), 2.24 (br., 2H),
10 2.05 (br., 2H), 1.80 – 1.87 (m, 1.5H), 1.06-1.43 (m, 4.5H).

LC/MS, $m/z = 351.1$ $[M + H]^+$ (Calc: 350.5).

15 ***N*-((2*R*,6*S*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-*N*-methylcyclohexanecarboxamide (Compound 120)**

^1H NMR δ_{H} (400 MHz, DMSO- d_6) 8.96 (s, 1H), 6.83 (d, $J=8.4$ Hz, 1H), 6.55 (d, $J=2.4$ Hz, 1H), 6.47 (dd, $J=8.4$, 2.4 Hz, 1H), 4.67 (s, 1H), 3.52 (s, 3H), 3.05 (d, $J=17.4$ Hz, 1H), 2.96 (d, $J=5.3$ Hz, 1H), 2.50-2.69 (m, 2H), 2.33-2.41 (m, 1H), 2.15-2.28 (m, 3H), 1.90 – 2.05 (m, 2H), 1.55 – 1.85 (m, 5H), 1.06-1.36 (m, 6H), 1.03 (s, 3H).

20 LC/MS, $m/z = 357.1$ $[M + H]^+$ (Calc: 356.5).

25 ***N*-((2*R*,6*S*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-*N*-methylcyclohexanecarboxamide (Compound 121)**

^1H NMR δ_{H} (400 MHz, CD_3OD) 6.87-7.08 (m, 1H), 6.72 (d, $J=2.2$ Hz, 1H), 6.63 (dd, $J=8.3$, 2.3 Hz, 1H), 4.87 (br. s., 0.3H), 4.66 (br., 0.7H), 3.58 (br. s., 1H), 2.90-3.14 (m, 3H), 2.84 (s, 3H), 2.43-2.74 (m, 5H), 1.90 – 2.00 (m, 1H), 1.49-1.79 (m, 6H), 1.06-1.45 (m, 8H).

LC/MS, $m/z = 357.3$ $[M + H]^+$ (Calc: 356.5).

(E)-N-((2R,6S,11R)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[d]azocin-11-yl)-N-methyl-3-(pyridin-3-yl)acrylamide (Compound 122)

¹H NMR δ_{H} (400 MHz, DMSO- d_6) 8.94-9.31 (m, 1H), 8.69-8.87 (m, 1H), 8.47 (dd, J=4.7, 1.4 Hz, 1H), 8.05 (d, J=7.9 Hz, 1H), 7.10-7.55 (m, 3H), 6.87 (d, J=8.4 Hz, 1H), 6.60 (d, J=2.4 Hz, 1H), 6.49 (dd, J=8.1, 2.4 Hz, 1H), 4.63 (d, J=2.6 Hz, 0.7H), 4.11 (d, J = 2.4 Hz, 0.3H), 2.79-3.11 (m, 2H), 2.72 (s, 2H), 2.50 (s, 1H), 2.18-2.30 (m, 4H), 1.72-1.95 (m, 2H), 1.23-1.35 (m, 3H), 1.19 (d, J=11.7 Hz, 1H).

LC/MS, m/z = 378.1 $[M + H]^+$ (Calc: 377.5).

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N-((2R,6S,11R)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[d]azocin-11-yl)-N-methyl-2-(thiophen-3-yl)acetamide (Compound 123)

¹H NMR δ_{H} (400 MHz, DMSO- d_6) 9.05 (s, 1H), 7.39 (dd, J=5.0, 3.0 Hz, 1H), 7.12 (d, J=1.8 Hz, 1H), 6.87-6.98 (m, 1H), 6.83 (d, J=7.9 Hz, 1H), 6.56 (d, J=2.0 Hz, 1H), 6.46 (dd, J=8.3, 1.9 Hz, 1H), 4.51 (br. s., 0.6H), 3.88 (br. s., 0.4H), 3.62-3.81 (m, 1H), 3.61 (s, 1H), 2.89 – 2.95 (m, 1H), 2.72-2.84 (m, 1H), 2.53 (s, 2H), 2.38 (s, 2H), 2.15-2.29 (m, 4H), 1.63-1.93 (m, 2H), 0.94-1.26 (m, 4H).

LC/MS, m/z = 371.1 $[M + H]^+$ (Calc: 370.5).

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N-((2R,6S,11R)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[d]azocin-11-yl)-N-methylthiophene-3-carboxamide (Compound 124)

¹H NMR δ_{H} (400 MHz, DMSO- d_6) 9.07 (s, 1H), 7.41-7.80 (m, 2H), 7.13 (dd, J=5.0, 1.0 Hz, 1H), 6.87 (t, J=7.6 Hz, 1H), 6.36-6.68 (m, 2H), 4.66 (br. s., 0.5H), 3.84 (br. s., 0.5H), 2.90 – 2.95 (m, 2H), 2.56 2.6 (m, 1H), 2.53 (s, 3H), 2.05-2.35 (m, 4H), 1.69-1.96 (m, 1.5H), 1.34-1.48 (m, 0.5H), 1.03-1.33 (m, 4H).

LC/MS, m/z = 357.1 $[M + H]^+$ (Calc: 356.5).

***N*-((2*R*,6*S*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-*N*-methylthiophene-3-carboxamide (Compound 125)**

¹H NMR δ_H (400 MHz, CD₃OD) 7.78-7.93 (m, 1H), 7.48 (dd, J=5.1, 2.9 Hz, 1H), 7.29 (dd, J=5.1, 1.1 Hz, 1H), 7.00 (d, J=8.4 Hz, 1H), 6.73 (d, J=2.4 Hz, 1H), 6.64 (dd, J=8.4, 2.4 Hz, 1H), 4.07-4.27 (m, 1H), 3.92 (br. s., 1H), 3.38 (d, J=3.5 Hz, 2H), 3.21-3.21 (m, 4H), 2.89 (s, 3H), 2.74 (td, J=13.0, 3.4 Hz, 1H), 2.38 (td, J=13.9, 4.7 Hz, 1H), 1.57 (s, 3H), 1.47 (d, J=14.3 Hz, 1H).

LC/MS, *m/z* = 357.1 [M + H]⁺ (Calc: 356.5).

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***N*-((2*R*,6*S*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-*N*-methyl-5-(trifluoromethyl)picolinamide (Compound 126)**

¹H NMR δ_H (400 MHz, CD₃OD) 8.92 (s, 1H), 8.25 (dd, J=8.3, 1.9 Hz, 1H), 7.82 (d, J=8.4 Hz, 1H), 7.01 (d, J=8.4 Hz, 1H), 6.75 (d, J=2.4 Hz, 1H), 6.65 (dd, J=8.1, 2.4 Hz, 1H), 4.21 (br. s., 1H), 4.00 (br. s., 1H), 3.41 (d, J=3.5 Hz, 2H), 3.24-3.30 (m, 1H), 3.07 (s, 3H), 2.93 (s, 3H), 2.76 (td, J=13.0, 3.5 Hz, 1H), 2.40 (td, J=13.9, 4.6 Hz, 1H), 1.62 (s, 3H), 1.51 (d, J=14.5 Hz, 1H).

LC/MS, *m/z* = 420.1 [M + H]⁺ (Calc: 419.4).

20

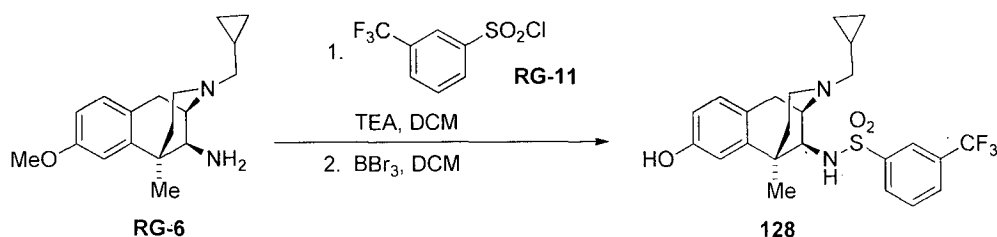
***N*-((2*R*,6*S*,11*R*)-3-(cyclopropylmethyl)-8-hydroxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)thiophene-3-carboxamide (Compound 127)**

¹H NMR δ_H (400 MHz, CD₃OD) 7.96 (t, J=2.0 Hz, 1H), 7.33 (d, J=2.0 Hz, 2H), 7.01 (d, J=8.4 Hz, 1H), 6.77 (d, J=2.4 Hz, 1H), 6.67 (dd, J=8.4, 2.4 Hz, 1H), 4.49 (d, J=3.3 Hz, 1H), 4.12 (br. s., 1H), 3.25-3.70 (m, 2H), 3.07-3.21 (m, 2H), 2.81-3.06 (m, 1H), 2.60 (td, J=13.3, 3.4 Hz, 1H), 2.07 (td, J=13.9, 4.5 Hz, 1H), 1.70 (dd, J=14.5, 1.5 Hz, 1H), 1.47 (s, 3H), 0.96-1.26 (m, 1H), 0.64-0.78 (m, 2H), 0.28-0.62 (m, 2H).

LC/MS, *m/z* = 383.3 [M + H]⁺ (Calc: 382.5).

EXAMPLE 61

N-((2*R*,6*S*,11*S*)-3-(cyclopropylmethyl)-8-hydroxy-6-methyl-1,2,3,4,5,6-hexahydro-
 5 2,6-methanobenzo[*d*]azocin-11-yl)-3-(trifluoromethyl)benzenesulfonamide
 (Compound 128)



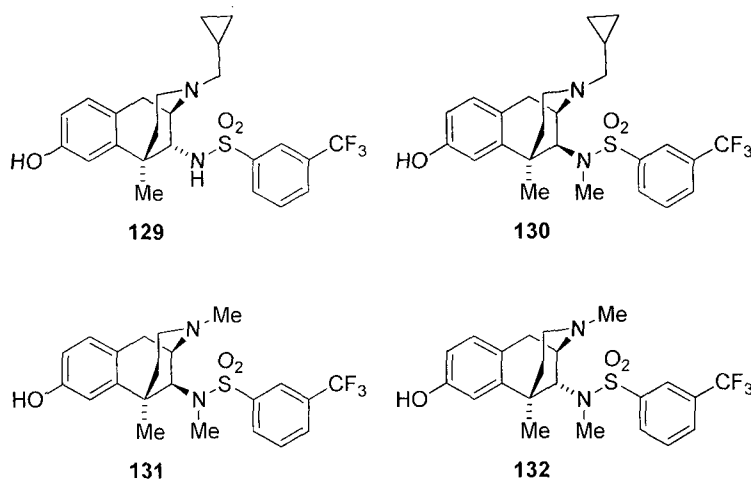
To a mixture of **Compound RG-6** (0.10 g, 0.35 mmol) and TEA (0.035 g, 0.35 mmol) in DCM (2 mL) was added **Compound RG-11** (0.102 g, 0.42 mmol) at 0 °C. The
 10 reaction mixture was stirred at RT for 16 h, quenched by the addition of water and the mixture extracted with CHCl₃. The organic layer was concentrated to give the crude product which was used directly in the next step.

This material was dissolved in DCM (8 mL), cooled to -78 °C and 1 M BBr₃ in DCM (2.0 mL, 2.0 mmol) was added. The mixture was stirred at -78 °C for 2 h allowed to
 15 warm to 0 °C and stirred an additional 30 min. The reaction was quenched by the addition of water (2 mL) and the pH adjusted to *ca* 8 with conc. NH₄OH. The layers were separated and the organic layer was concentrated and purified by flash chromatography (SiO₂, 10% (10% NH₄OH in MeOH) in DCM) to give **Compound 128** as a white solid (0.100 g, 60%).

20 ¹H NMR δ_H (400 MHz, DMSO-*d*₆) 9.12 (br. s., 1H), 8.30 (s, 1H), 8.25 (d, *J*=7.9 Hz, 1H), 8.09 (d, *J*=7.7 Hz, 1H), 7.79-7.95 (m, 1H), 7.56-7.80 (m, 1H), 6.89 (d, *J*=8.4 Hz, 1H), 6.72 (d, *J*=2.2 Hz, 1H), 6.59 (dd, *J*=8.1, 2.4 Hz, 1H), 3.46 (br. s., 1H), 2.87 (d, *J*=17.8 Hz, 1H), 2.77 (dd, *J*=5.5, 2.9 Hz, 1H), 2.45 (td, *J*=17.0, 5.4 Hz, 3H), 1.86-2.03 (m, 3H), 1.27 (s, 3H), 1.09 (d, *J*=9.7 Hz, 1H), 0.44-0.63 (m, 1H), 0.25-0.39 (m, 1H), -
 25 0.15-0.16 (m, 3H).

LC/MS, *m/z* = 481.2 [M + H]⁺ (Calc: 480.5).

In a similar manner the following chiral compounds were prepared from the appropriate chiral amines.



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***N*-((2*R*,6*S*,11*R*)-3-(cyclopropylmethyl)-8-hydroxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-3-(trifluoromethyl)benzenesulfonamide (Compound 129)**

¹H NMR δ_{H} (400 MHz, CD₃OD) 8.25 (s, 1H), 8.21 (d, *J*=7.9 Hz, 1H), 8.02 (d, *J*=7.7 Hz, 1H), 7.75-7.93 (m, 1H), 7.01-7.21 (m, 1H), 6.65-6.87 (m, 2H), 3.88-4.18 (m, 1H), 3.54-3.85 (m, 2H), 3.38 (d, *J*=6.8 Hz, 1H), 2.99-3.31 (m, 3H), 2.36-2.73 (m, 1H), 1.93 (td, *J*=14.0, 4.6 Hz, 1H), 1.43-1.73 (m, 1H), 0.93-1.26 (m, 5H), 0.67-0.87 (m, 2H), 0.34-0.62 (m, 2H).

LC/MS, *m/z* = 481.2 [*M* + *H*]⁺ (Calc: 480.5).

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***N*-((2*R*,6*S*,11*S*)-3-(cyclopropylmethyl)-8-hydroxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-*N*-methyl-3-(trifluoromethyl)benzenesulfonamide (Compound 130)**

¹H NMR δ_{H} (400 MHz, CD₃OD) 8.18 (d, *J*=7.9 Hz, 1H), 8.13 (s, 1H), 8.07 (d, *J*=7.7 Hz, 1H), 7.86-7.96 (m, 1H), 6.97 (d, *J*=8.4 Hz, 1H), 6.82 (d, *J*=2.4 Hz, 1H), 6.67 (dd, *J*=8.1, 2.4 Hz, 1H), 4.17 (s, 1H), 3.51 (s, 3H), 3.09 (d, *J*=17.6 Hz, 1H), 2.99 (br. s.,

1H), 2.53-2.70 (m, 2H), 2.08-2.41 (m, 4H), 1.53 (s, 3H), 1.27-1.41 (m, 1H), 0.58 (br. s., 1H), 0.18-0.42 (m, 2H), -0.10 – 0.10 (m, 2H).

LC/MS, m/z = 495.1 $[M + H]^+$ (Calc: 494.6).

5 ***N*-((2*R*,6*S*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-*N*-methyl-3-(trifluoromethyl)benzenesulfonamide (Compound 131)**

¹H NMR δ_H (400 MHz, CD₃OD) 7.93-8.11 (m, 2H), 7.82-7.91 (m, 1H), 7.72 (t, $J=7.7$ Hz, 1H), 7.32-7.55 (m, 1H), 6.90 (d, $J=8.1$ Hz, 1H), 6.75 (br. s., 1H), 6.62 (dd, $J=8.4$,
10 2.4 Hz, 1H), 4.10 (s, 1H), 3.36 (s, 3H), 3.09 (d, $J=15.6$ Hz, 1H), 2.46-2.71 (m, 2H), 2.39 (d, $J=9.9$ Hz, 1H), 1.97-2.24 (m, 5H), 1.43 (s, 3H), 1.25 (d, $J=10.6$ Hz, 1H).

LC/MS, m/z = 455.1 $[M + H]^+$ (Calc: 454.5).

15 ***N*-((2*R*,6*S*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-*N*-methyl-3-(trifluoromethyl)benzenesulfonamide (Compound 132)**

¹H NMR δ_H (400 MHz, CD₃OD) 7.99-8.16 (m, 2H), 7.90 (d, $J=7.9$ Hz, 1H), 7.64-7.80 (m, 1H), 6.84 (d, $J=8.1$ Hz, 1H), 6.34-6.59 (m, 2H), 3.90 (d, $J=2.6$ Hz, 1H), 2.86-3.08 (m, 2H), 2.57 (dd, $J=18.9$, 5.9 Hz, 1H), 2.51 (s, 3H), 2.19-2.38 (m, 4H), 1.97 (td,
20 $J=12.5$, 3.4 Hz, 1H), 1.70 (td, $J=12.8$, 4.7 Hz, 1H), 1.20 (d, $J=11.7$ Hz, 1H), 0.87 (s, 3H).

LC/MS, m/z = 455.1 $[M + H]^+$ (Calc: 454.5).

EXAMPLE 62

Using methods similar to those described in the previous examples, the
25 following compounds were also made:

3-(4-(*tert*-butyl)phenyl)-1-((2*R*,6*S*,11*S*)-3-(cyclopropylmethyl)-8-hydroxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-1-methylurea (Compound 133);

¹H NMR (400MHz, DMSO-*d*₆) δ : 8.93 (br. s., 1H), 8.01 (br. s., 1H), 7.26 (d, $J=8.8$ Hz, 2H), 7.12 (d, $J=8.8$ Hz, 2H), 6.80 (d, $J=8.1$ Hz, 1H), 6.54 (d, $J=2.4$ Hz, 1H), 6.44 (dd, $J=8.1$, 1.8 Hz, 1H), 4.44 (br. s., 1H), 3.57 (br. s., 3H), 3.34 (br. s., 1H), 2.97 (d, $J=17.4$

Hz, 1H), 2.53 – 2.59 (m, 2H), 2.33 (dd, J=12.2, 6.5 Hz, 1H), 2.13 – 2.25 (m, 1H), 1.94 – 2.07 (m, 2H), 1.00-1.22 (m, 13H), 0.64-0.87 (m, 1H), 0.26-0.49 (m, 2H), -0.09-0.11 (m, 2H).

LC/MS, m/z = 462.3 $[M + H]^+$ (Calc: 461.64)

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1-((2*R*,6*S*,11*S*)-3-(cyclopropylmethyl)-8-hydroxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[d]azocin-11-yl)-3-(5-fluorobenzo[d]thiazol-2-yl)-1-methylurea (Compound 134);

^1H NMR (400MHz, METHANOL- d_4) δ : 7.73 (dd, J=8.6, 5.5 Hz, 1H), 7.27 (dd, J=10.1, 2.4 Hz, 1H), 6.90-7.07 (m, 2H), 6.77 (d, J=2.4 Hz, 1H), 6.66 (dd, J=8.4, 2.4 Hz, 1H), 4.10 (d, J=5.5 Hz, 1H), 3.84 (s, 1H), 3.21 (s, 3H), 3.02-3.14 (m, 2H), 2.77 (d, J=6.8 Hz, 2H), 2.28-2.52 (m, 2H), 1.47 (s, 3H), 1.3 – 1.35 (m, 2H), 1.17-1.29 (m, 1H), 0.42-0.71 (m, 2H), 0.11-0.33 (m, 2H).

LC/MS, m/z = 481.2 $[M + H]^+$ (Calc: 480.6)

15

1-((6*R*,11*R*)-6-allyl-8-methoxy-3-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[d]azocin-11-yl)-3-(4-cyanophenyl)-1-methylurea (Compound 135);

^1H NMR (400MHz, METHANOL- d_4 , TFA-salt) δ : 7.45-7.65 (m, 4H), 7.13 (d, J=8.4 Hz, 1H), 6.90 (d, J=2.2 Hz, 1H), 6.82 (dd, J=8.4, 2.4 Hz, 1H), 5.74-5.94 (m, 1H), 5.20 (d, J=17.2 Hz, 1H), 5.15 (d, J=10.1 Hz, 1H), 4.56 (br. s., 1H), 3.67-3.81 (m, 4H), 3.24-3.35 (m, 1H), 3.03-3.16 (m, 2H), 2.81-2.94 (m, 4H), 2.72 (s, 3H), 2.47-2.66 (m, 2H), 2.27 (td, J=13.9, 4.6 Hz, 1H), 1.50 (d, J=14.3 Hz, 1H).

LC/MS, m/z = 431.3 $[M + H]^+$ (Calc: 430.54)

25 **3-(4-cyanophenyl)-1-((6*R*,11*R*)-8-methoxy-3-methyl-6-propyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[d]azocin-11-yl)-1-methylurea (Compound 136);**

^1H NMR (400MHz, METHANOL- d_4 , TFA-salt) δ : 7.44-7.65 (m, 4H), 7.11 (d, J=8.6 Hz, 1H), 6.89 (d, J=2.2 Hz, 1H), 6.81 (dd, J=8.4, 2.4 Hz, 1H), 4.63 (d, J=2.0 Hz, 1H), 3.65-3.81 (m, 4H), 3.24-3.33 (m, 1H), 3.03-3.16 (m, 2H), 2.86 (s, 3H), 2.69 (s, 3H), 2.60 (td, J=13.2, 3.5 Hz, 1H), 2.28 (td, J=13.8, 4.6 Hz, 1H), 2.08 (td, J=13.1, 3.9 Hz,

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1H), 1.75 (td, J=13.3, 4.4 Hz, 1H), 1.35-1.56 (m, 2H), 1.17-1.33 (m, 1H), 0.92-1.03 (m, 3H).

LC/MS, m/z = 433.2 $[M + H]^+$ (Calc: 432.56)

5 **3-(4-cyanophenyl)-1-((6R,11S)-8-hydroxy-3-methyl-6-propyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[d]azocin-11-yl)-1-methylurea (Compound 137);**

^1H NMR (400MHz, METHANOL- d_4 , TFA-salt) δ : 7.47-7.68 (m, 4H), 6.98 (d, J=8.4 Hz, 1H), 6.52-6.70 (m, 2H), 4.05 (d, J=5.1 Hz, 1H), 3.92 (s, 1H), 3.29-3.45 (m, 2H), 3.26 (s, 3H), 3.13 (dd, J=12.3, 4.0 Hz, 1H), 2.85 (s, 3H), 2.63 (td, J=12.9, 3.7 Hz, 1H),
10 2.40 (td, J=13.8, 4.8 Hz, 1H), 1.85-2.01 (m, 1H), 1.58-1.73 (m, 1H), 1.12-1.49 (m, 3H), 0.95 (t, J=7.3 Hz, 3H).

LC/MS, m/z = 419.2 $[M + H]^+$ (Calc: 418.53)

15 **3-(4-(aminomethyl)phenyl)-1-((6R,11S)-8-methoxy-3-methyl-6-propyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[d]azocin-11-yl)-1-methylurea (Compound 138);**

^1H NMR (400MHz, METHANOL- d_4 , TFA-salt) δ : 7.48 (d, J=8.6 Hz, 2H), 7.32 (d, J=8.6 Hz, 2H), 7.09 (d, J=8.6 Hz, 1H), 6.77 (dd, J=8.5, 2.3 Hz, 1H), 6.69 (d, J=2.2 Hz, 1H), 4.04 (d, J=5.1 Hz, 1H), 3.99 (s, 2H), 3.93 (s, 1H), 3.69 (s, 3H), 3.28-3.45 (m, 2H), 3.25 (s, 3H), 3.11 (dd, J=12.4, 4.3 Hz, 1H), 2.84 (s, 3H), 2.60 (td, J=12.9, 3.5 Hz, 1H),
20 2.40 (td, J=13.6, 4.7 Hz, 1H), 1.89-2.10 (m, 1H), 1.55-1.75 (m, 1H), 1.31-1.48 (m, 2H), 1.15-1.29 (m, 1H), 0.96 (t, J=7.3 Hz, 3H).

LC/MS, m/z = 437.2 $[M + H]^+$ (Calc: 436.59)

25 **1-(5-fluorobenzo[d]thiazol-2-yl)-3-((2R,6S,11R)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[d]azocin-11-yl)urea (Compound 139);**

^1H NMR (400MHz, METHANOL- d_4 , TFA-salt) δ : 7.66 (dd, J=8.6, 5.3 Hz, 1H), 7.24 (dd, J=9.8, 2.3 Hz, 1H), 6.92 (td, J=9.0, 2.5 Hz, 1H), 6.86 (d, J=8.4 Hz, 1H), 6.68 (d, J=2.4 Hz, 1H), 6.51 (dd, J=8.1, 2.4 Hz, 1H), 3.88 (s, 1H), 3.12 (d, J=18.0 Hz, 1H), 2.99 (br. s., 1H), 2.70 (dd, J=17.9, 5.8 Hz, 1H), 2.33-2.41 (m, 1H), 2.31 (s, 3H), 2.06
30 (td, J=12.1, 3.1 Hz, 1H), 1.86 (td, J=12.9, 4.8 Hz, 1H), 1.23 (s, 3H), 1.13 (d, J=13.2 Hz, 1H).

LC/MS, $m/z = 427.2$ $[M + H]^+$ (Calc: 426.51)

3-(5-fluorobenzo[d]thiazol-2-yl)-1-((2*R*,6*S*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[d]azocin-11-yl)-1-methylurea

5 **(Compound 140)**

^1H NMR (CD_3OD) δ : 7.60 (m, 1H), 7.16 (d, $J=8.0$ Hz, 1H), 6.89 (m, 2H), 6.66 (m, 1H), 6.53 (m, 1H), 4.47 (br, 1H), 3.07 (m, 2H), 2.73-2.56 (m, 4H), 2.43-2.33 (m, 4H), 2.10 (m, 1H), 1.91 (m, 1H), 1.39-1.28 (m, 4H) ppm

LC/MS, $m/z = 441.1$ $[M + H]^+$ (Calc: 440.53)

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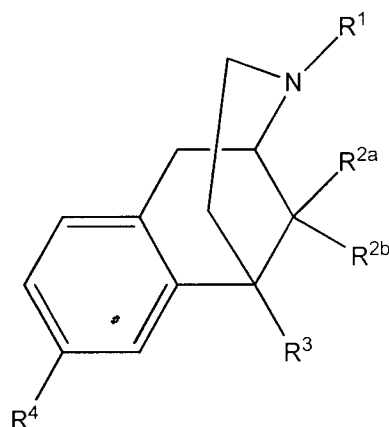
Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

15

All patents and publications cited herein are fully incorporated by reference in their entirety.

What is claimed is:

1. A compound of Formula I':



5

wherein

- 10 R^1 is selected from the group consisting of $-(C_1-C_{10})$ alkyl, $-(C_2-C_{10})$ alkenyl, $-(C_2-C_{10})$ alkynyl, $-(C_3-C_{12})$ cycloalkyl, (C_3-C_{12}) cycloalkyl- (C_1-C_6) alkyl-, $-(C_3-C_{12})$ cycloalkenyl, (C_3-C_{12}) cycloalkenyl- (C_1-C_6) alkyl-, $-(6- \text{ to } 14\text{-membered})$ aryl, $((6- \text{ to } 14\text{-membered})$ aryl)- (C_1-C_6) alkyl-, diphenyl- (C_1-C_6) alkyl-, $-(3- \text{ to } 12\text{-membered})$ heterocycle, $((3- \text{ to } 12 \text{ membered})$ heterocycle)- (C_1-C_6) alkyl-, -
- 15 $(OCH_2CH_2)_5-O-(C_1-C_6)$ alkyl, $-(CH_2CH_2O)_5-(C_1-C_6)$ alkyl, (C_1-C_{10}) alkoxy, $C(\text{halo})_3$, $CH(\text{halo})_2$, $CH_2(\text{halo})$, $C(O)R^5$, $-C(O)O-(C_1-C_{10})$ alkyl, and $-(CH_2)_n-N(R^6)_2$, each of which is optionally substituted by 1, 2 or 3 independently selected R^9 groups;

R^{2a} is hydrogen, OH, or absent;

20 R^{2b} is

- a) $((6- \text{ to } 14\text{-membered})$ aryl), $-(5- \text{ to } 12\text{-membered})$ heteroaryl), or $((3- \text{ to } 12\text{-membered})$ heterocycle), each of which is optionally substituted with one, two, or three independently selected R^{30} groups; or

b) $-Z-G-R^{10}$, provided that $-Z-G-R^{10}$ is other than hydrogen;
 or R^{2a} and R^{2b} together form $=O$;
 Z is absent or $-(CH_2)_m-$, optionally substituted with 1 or 2 $-(C_1-C_6)$ alkyl;

5 G is selected from the group consisting of:

- a) a bond, $-(C_1-C_6)$ alkylene, $-(C_2-C_6)$ alkenylene;
- b) O , $-OCO-$, $-C(=O)$, $=CH$;
- c) NR^8 , $=N-O$, $=N-NH$;
- d) S , SO , SO_2 ; and
- 10 e) $-NH-SO_2$;

and when Z is absent and G is $=CH$, $=N-O$, or $=N-NH$, then R^{2a} is absent;

R^{10} is selected from the group consisting of hydrogen, $-(C_1-C_{10})$ alkyl, $-(C_2-C_{12})$ alkenyl,
 15 $-C(=O)$, $-C(=O)-(C_1-C_6)$ alkyl, $-C(=O)-(C_2-C_6)$ alkenyl, $-C(=O)-(6- to 14-$
 membered)aryl, $-C(=O)-(C_1-C_6)$ alkyl-(6- to 14-membered)aryl, $-(C_2-C_{12})$ alkynyl, $-(C_1-$
 $C_{10})$ alkoxy, $-(OCH_2CH_2)_5-O(C_1-C_6)$ alkyl, $-(CH_2CH_2O)_5-(C_1-C_6)$ alkyl, $-NH_2$,
 $-NH(C_1-C_6)$ alkyl, CN , NR^5R^6 , $-(C_1-C_6)$ alkyl- NR^5R^6 , $-CONR^5R^6$, $-(C_1-C_6)$ alkyl- $CO-$
 NR^5R^6 , $-COOR^7$, $-(C_1-C_6)$ alkyl- $CO-OR^7$, $-(C_1-C_6)$ alkoxy- $COOR^7$, $-CO-(CH_2)_n-$
 20 $COOR^7$, $-CO-(CH_2)_n-CO-NR^5R^6$, $-(C_3-C_{12})$ cycloalkyl, $((C_3-C_{12})$ cycloalkyl)- $(C_1-$
 $C_6)$ alkyl-, $-(C_4-C_{12})$ cycloalkenyl, $((C_4-C_{12})$ cycloalkenyl)- (C_1-C_6) alkyl-, $-(C_6-$
 $C_{14})$ bicycloalkyl, $((C_6-C_{14})$ bicycloalkyl)- (C_1-C_6) alkyl-, $-(C_8-C_{20})$ tricycloalkyl, $((C_8-$
 $C_{20})$ tricycloalkyl)- (C_1-C_6) alkyl-, $-(C_7-C_{14})$ bicycloalkenyl, $((C_7-C_{14})$ bicycloalkenyl)-
 (C_1-C_6) alkyl-, $-(C_8-C_{20})$ tricycloalkenyl, $((C_8-C_{20})$ tricycloalkenyl)- (C_1-C_6) alkyl-, $-(6-$
 25 $to 14-$ membered)aryl, $((6- to 14-$ membered)aryl)- (C_1-C_6) alkyl-, $-SO_2-(C_1-C_6)$ alkyl-,
 $-SO_2-((C_3-C_{12})$ cycloalkyl), $-SO_2-((C_3-C_{12})$ cycloalkyl)- (C_1-C_6) alkyl-, $-SO_2-((5- to 12-$
 membered)heteroaryl), $-SO_2-((5- to 12-$ membered)heteroaryl)- (C_1-C_6) alkyl-, $-C(=O)-$
 $NH-((5- to 12-$ membered)heteroaryl), $-C(=O)-NH-((5- to 12-$ membered)heteroaryl)-
 (C_1-C_6) alkyl-, $-C(=O)-NH-((3- to 12-$ membered)heterocycle), $-C(=O)-NH-((3- to 12-$
 30 membered)heterocycle)- (C_1-C_6) alkyl, $SO_2-((6- to 14-$ membered)aryl), $SO_2-((6- to 14$
 membered)aryl)- (C_1-C_6) alkyl, $-(7- to 12-$ membered)bicyclic ring system, $((7- to 12-$

membered)bicyclic ring system)-(C₁-C₆)alkyl-, -(7- to 12-membered)bicyclic aryl, ((7- to 12-membered)bicyclic aryl)-(C₁-C₆)alkyl-, -(5- to 12-membered)heteroaryl, ((5- to 12-membered)heteroaryl)-(C₁-C₆)alkyl-, -(3- to 12-membered)heterocycle, ((3- to 12-membered)heterocycle)-(C₁-C₆)alkyl-, -(7- to 12-membered)bicycloheterocycle, ((7- to 12-membered)bicycloheterocycle)-(C₁-C₆)alkyl-, phenyl, benzyl and naphthyl; each of which is optionally substituted with one, two, or three substituents independently selected from the group consisting of -OH, (=O), halo, -C(halo)₃, -CH(halo)₂, -CH₂(halo), -(C₁-C₆)alkyl, halo(C₁-C₆)alkyl-, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, hydroxy(C₁-C₆)alkyl-, dihydroxy(C₁-C₆)alkyl-, -(C₁-C₆)alkoxy, ((C₁-C₆)alkoxy)CO(C₁-C₆)alkoxy-, phenyl, benzyl, -NH₂, -NH(C₁-C₆)alkyl, -(C₁-C₆)alkyl-NH(C₁-C₆)alkyl-R¹⁴, -CN, -SH, -OR¹¹, -CONR⁵R⁶, -(C₁-C₆alkyl)-CO-NR⁵R⁶, -COOR⁷, -(C₁-C₆)alkyl-CO-OR⁷, -(C₁-C₆)alkoxy-COOR⁷, -(OCH₂CH₂)_s-O(C₁-C₆)alkyl, -(CH₂CH₂O)_s-(C₁-C₆)alkyl, -SO₂-NR^{5a}R^{6a}, (C₁-C₆)alkyl)sulfonyl, ((C₁-C₆)alkyl)sulfonyl(C₁-C₆)alkyl-, -NH-SO₂(C₁-C₆)alkyl, NH₂-SO₂(C₁-C₆)alkyl-, -N(SO₂(C₁-C₆)alkyl)₂, -C(=NH)NH₂, -NH-CO-(C₁-C₆)alkyl, -NH-CO-NH₂, -NH-C(=O)-NH-(C₁-C₆)alkyl, -NH-C(=O)-(6- to 14- membered)aryl, -NH-C(=O)-(C₁-C₆)alkyl-(6- to 14- membered)aryl, -NH-(C₁-C₆)alkyl-CO-OR⁷, -NH-C(=O)-(C₁-C₆)alkyl-CO-OR⁷, -NH-C(=O)-CH(NH₂)-(C₁-C₆)alkyl-CO-OR⁷, -(C₃-C₁₂)cycloalkyl, ((C₃-C₁₂)cycloalkyl)-(C₁-C₆)alkyl-, -(6- to 14-membered)aryl, -(6- to 14-membered)aryloxy, -(C₁-C₆)alkoxy-C(O)NR⁵R⁶, -NH-(C₁-C₆)alkyl-C(O)-NR⁵R⁶, -C(O)NH-(C₁-C₆)alkyl-COOR⁷, ((6- to 14-membered)aryl)-(C₁-C₆)alkyl-, -(5- to 12-membered)heteroaryl, ((5- to 12-membered)heteroaryl)-(C₁-C₆)alkyl-, -(3- to 12-membered)heterocycle, ((3- to 12-membered)heterocycle)-(C₁-C₆)alkyl-, -(7- to 12-membered)bicycloheterocycle, and ((7- to 12-membered)bicycloheterocycle)-(C₁-C₆)alkyl-;

R³ is selected from:

- a) -H; or
- b) -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, or -(C₂-C₆)alkynyl;

R⁴ is selected from

- a) -H, -OH, halo, -C(halo)₃, -CH(halo)₂, -CH₂(halo), COOH, or CONH₂; or
 b) -(C₁-C₅)alkyl, -(C₂-C₅)alkenyl, -(C₂-C₅)alkynyl, -(CH₂)_n-O-(CH₂)_n-CH₃, or -(C₁-C₅)alkoxy, each of which is optionally substituted with 1, 2, or 3 independently selected R⁹ groups;

5

R⁵ and R⁶ are each independently selected from

- a) hydrogen, -OH, halo, -C(halo)₃, -CH(halo)₂, -CH₂(halo);
 b) -(C₁-C₆)alkyl, -(C₂-C₅)alkenyl, -(C₂-C₅)alkynyl, -(CH₂)_n-O-(CH₂)_n-CH₃, -(C₁-C₆)alkoxy, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from -OH, halo, -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₁-C₁₀)alkoxy, -(C₃-C₁₂)cycloalkyl, -CHO, -C(O)OH, -C(halo)₃, -CH(halo)₂, CH₂(halo), -(CH₂)_n-O-(CH₂)_n-CH₃, phenyl, or CONR^{5a}R^{6a};
 c) -(C₃-C₈)cycloalkyl, ((C₃-C₈)cycloalkyl)-(C₁-C₆)alkyl-, -COOR⁷, -(C₁-C₆)alkyl-COOR⁷, -CONH₂, or (C₁-C₆)alkyl-CONH-;
 d) ((6- to 14-membered)aryl) optionally substituted with 1, 2, or 3 independently selected R³⁰ groups;
 e) -((5- to 12-membered)heteroaryl) optionally substituted with 1, 2, or 3 independently selected R³⁰ groups; or
 f) R⁵ and R⁶ together with the nitrogen atom to which they are attached form a (3- to 12-membered)heterocycle optionally substituted with 1, 2, or 3 independently selected R³⁰ groups;

15
20

R^{5a} and R^{6a} are each independently selected from the group consisting of:

- a) hydrogen, -OH, halo, -C(halo)₃, -CH(halo)₂, and -CH₂(halo);
 b) -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(CH₂)_n-O-(CH₂)_n-CH₃, and -(C₁-C₆)alkoxy, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from -OH, halo, -(C₁-C₁₀)alkyl, -(C₂-C₁₂)alkenyl, -(C₂-C₁₂)alkynyl, -(C₁-C₁₀)alkoxy, -(C₃-C₁₂)cycloalkyl, -CHO, -COOH, -C(halo)₃, -CH(halo)₂, CH₂(halo), -(CH₂)_n-O-(CH₂)_n-CH₃, and phenyl;
 c) -(C₃-C₈)cycloalkyl, ((C₃-C₈)cycloalkyl)-(C₁-C₆)alkyl-, -COOR⁷, -(C₁-C₆)alkyl-COOR⁷, -CONH₂, and (C₁-C₆)alkyl-CONH-;

25
30

- d) -(6- to 14-membered)aryl optionally substituted with 1, 2, or 3 independently selected R^{30} groups;
- e) -((5- to 12-membered)heteroaryl) optionally substituted with 1, 2, or 3 independently selected R^{30} groups; or
- 5 f) R^{5a} and R^{6a} together with the nitrogen atom to which they are attached form a (3- to 12-membered)heterocycle optionally substituted with 1, 2, or 3 independently selected R^{30} groups;

each R^7 is independently selected from the group consisting of hydrogen, -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₃-C₁₂)cycloalkyl, -(C₄-C₁₂)cycloalkenyl, ((C₃-C₁₂)cycloalkyl)-(C₁-C₆)alkyl-, and ((C₄-C₁₂)cycloalkenyl)-(C₁-C₆)alkyl-;

each R^8 is independently selected from H, -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₁-C₁₀)alkoxy, -(C₃-C₁₂)cycloalkyl, -(C₃-C₁₂)cycloalkenyl, ((C₃-C₁₂)cycloalkyl)-(C₁-C₆)alkyl-, ((C₃-C₁₂)cycloalkenyl)-(C₁-C₆)alkyl-, -C(=O)(C₁-C₆)alkyl or SO₂(C₁-C₆)alkyl;

each R^9 is independently selected from -OH, halo, -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₁-C₁₀)alkoxy, -(C₃-C₁₂)cycloalkyl, -CHO, -C(O)OH, -C(halo)₃, -CH(halo)₂, CH₂(halo), -(CH₂)_n-O-(CH₂)_n-CH₃, phenyl, or CONR^{5a}R^{6a};

each R^{11} is independently selected from -C(halo)₃, -CH(halo)₂, -CH₂(halo), -(C₂-C₅)alkenyl, -(C₂-C₅)alkynyl, -(CH₂)_n-O-(CH₂)_n-CH₃, (6- to 14-membered)aryl, ((6- to 14-membered)aryl)-(C₁-C₆)alkyl-, or (5- to 12-membered)heteroaryl, ((5- to 12-membered)heteroaryl)-(C₁-C₆)alkyl-, each of which is optionally substituted with 1, 2, or 3 independently selected R^9 groups;

each R^{14} is independently selected from -COOR⁷, -(C₁-C₆)alkyl-COOR⁷, -C(=O)-(C₁-C₆)alkyl-COOR⁷, -(C₁-C₆)alkyl-C(=O)-(C₁-C₆)alkyl-COOR⁷, CONH₂, or -(C₁-C₆)alkyl-CONH;

each R^{30} is independently selected from COOR^7 , $\text{CONR}^{5a}\text{R}^{6a}$, $-(\text{C}_1\text{-C}_6)\text{alkyl}$, $-\text{C}(=\text{O})$, CN , $-(3\text{- to }12\text{-membered})\text{heteroaryl}$, $((3\text{- to }12\text{-membered})\text{heteroaryl})-(\text{C}_1\text{-C}_6)\text{alkyl}$, NH_2 , halo, and $((6\text{- to }14\text{-membered})\text{aryl})-(\text{C}_1\text{-C}_6)\text{alkoxy}$;

5 m is an integer 1, 2, 3, 4, 5, or 6;

n is an integer 0, 1, 2, 3, 4, 5, or 6;

s in an integer 1, 2, 3, 4, 5, or 6;

provided that when R^4 is $-(\text{C}_1\text{-C}_5)\text{alkoxy}$ then:

- a) R^{2a} and R^{2b} cannot be taken together to form $=\text{O}$; or
- 10 b) R^{2a} cannot be OH when R^{2b} is $-\text{Z-G-R}^{10}$, and $-\text{Z-G-R}^{10}$ is either:
 - a. OH; or
 - b. $-(\text{C}_1\text{-C}_6)\text{alkyl}$;
 - c. 2-propenyl;
 - d. 2-propynyl; or
- 15 c) R^{2a} cannot be H when the combination $-\text{Z-G-R}^{10}$ is either:
 - a. OH;
 - b. $-\text{O-C}(=\text{O})-(\text{C}_1\text{-C}_6)\text{alkyl}$; or
 - c. $-\text{O-C}(=\text{O})-(\text{C}_2\text{-C}_6)\text{alkenyl}$;

20 and provided that when R^4 is OH then:

- a) R^{2a} cannot be OH when R^{2b} is $-\text{Z-G-R}^{10}$, and $-\text{Z-G-R}^{10}$ is:
 - a. methyl;
 - b. ethyl;
 - c. 2-propenyl; or
 - 25 d. 2-propynyl;
- b) R^{2a} cannot be H when R^{2b} is $-\text{Z-G-R}^{10}$, and $-\text{Z-G-R}^{10}$ is either:
 - a. OH;
 - b. $-\text{O-C}(=\text{O})-(\text{C}_1\text{-C}_6)\text{alkyl}$; or
 - c. $-\text{O-C}(=\text{O})-(\text{C}_2\text{-C}_6)\text{alkenyl}$;

30

and provided that when R^3 is (C_1-C_6) alkyl or (C_2-C_6) alkenyl, and R^4 is H, OH, or (C_1-C_5) alkoxy, then R^{2b} is not:

- a) optionally substituted (5- to 12-membered)heteroaryl;
- b) optionally substituted (3- to 12-membered)heterocycle; or
- 5 c) unsubstituted phenyl or phenyl substituted with F or Cl, methyl, CF_3 , hydroxy, methoxy, (3- to 12-membered)heterocycle, or NH_2 ;

and provided that when R^4 is OH and R^1 is (C_1-C_{10}) alkyl, then R^{2a} and R^{2b} cannot be together selected =O;

10

and provided that when R^4 is hydrogen and when R^1 and R^3 are both methyl, then:

- a) R^{2a} and R^{2b} cannot together form =O or =N-OH; or
- b) R^{2b} may not be NH_2 or $NHC(O)CH_3$ if R^{2a} is hydrogen;

15 and provided that when R^{2a} is H, then R^{2b} may not be $-Z-G-R^{10}$, wherein $-Z-G-R^{10}$ is:

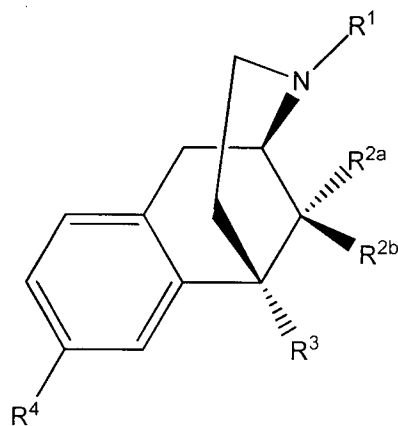
- a) $-CH_2-CHR^{20}-C(=O)R^{21}$, wherein
 R^{20} is H, or $-(C_1-C_6)$ alkyl, and
 R^{21} is selected from the group consisting of H, $-(C_1-C_{10})$ alkyl,
 $-(C_3-C_{12})$ cycloalkyl, $((C_3-C_{12})$ cycloalkyl)- (C_1-C_6) alkyl-, phenyl, and
20 phenyl- (C_1-C_6) alkyl; or

- b) $-CH_2-CHR^{20}-CR^{22}R^{23}OH$, wherein
 R^{20} is defined as above, and
 R^{22} and R^{23} are each independently selected from the group consisting of H,
 $-(C_1-C_{10})$ alkyl, $((C_3-C_{12})$ cycloalkyl)- (C_1-C_6) alkyl-, phenyl, and
25 phenyl- (C_1-C_6) alkyl; or

- c) $-CH_2-CR^{20}=CR^{23}R^{24}$, wherein
 R^{20} and R^{23} are defined as above, and
 R^{24} is selected from the group consisting of H, and $-(C_1-C_6)$ alkyl;

30 and the pharmaceutically acceptable salts and solvates thereof.

2. A compound of claim 1 having Formula IA'':



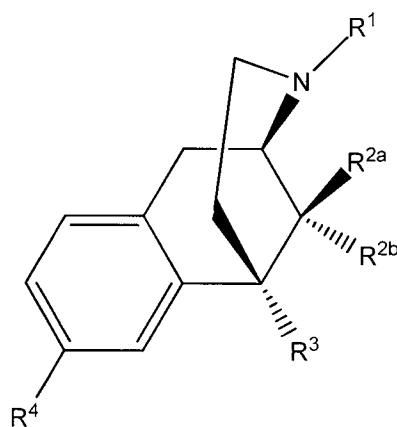
IA'',

5

wherein R¹, R^{2a}, R^{2b}, R³, and R⁴ are defined as in claim 1,

or a pharmaceutically acceptable salt or solvate thereof.

10 3. A compound of claim 1 having Formula IB'':

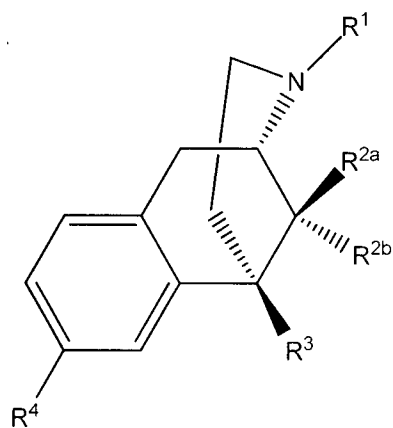


IB'',

15 wherein R¹, R^{2a}, R^{2b}, R³, and R⁴ are defined as in claim 1,

or a pharmaceutically acceptable salt, prodrug, or solvate thereof.

4. A compound of claim having Formula IC'':



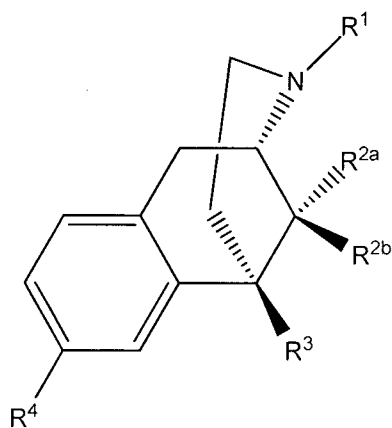
5

IC'',

wherein R^1 , R^{2a} , R^{2b} , R^3 , and R^4 are defined as in claim 1,

10 or a pharmaceutically acceptable salt or solvate thereof.

5. A compound of claim 1 having Formula ID'':



15

ID'',

wherein R^1 , R^{2a} , R^{2b} , R^3 , and R^4 are defined as in claim 1,

or a pharmaceutically acceptable salt or solvate thereof.

- 5 6. A compound of any one of the preceding claims, wherein R^{2a} is hydrogen or OH, or wherein R^{2a} is absent or OH.
7. A compound of any one of claims 1 to 5, wherein R^{2a} is hydrogen.
- 10 8. A compound of any one of claims 1 to 5, wherein R^{2a} is OH.
9. A compound of any one of claims 1 to 5, wherein R^{2a} and R^{2b} together form =O.
10. A compound of any one of claims 1 to 8, wherein R^{2b} is ((6- to 14-membered)aryl)
15 or ((3- to 12-membered)heterocycle), each of which is optionally substituted with one or more R^{30} .
11. A compound of any one of the preceding claims, wherein R^{2b} is -Z-G- R^{10} ,
provided that -Z-G- R^{10} is other than hydrogen.
- 20 12. A compound of any one of the preceding claims, wherein Z is absent.
13. A compound of any one of claims 1 to 11, wherein Z is CH_2 .
- 25 14. A compound of any one of the preceding claims, wherein G is NR^8 .
15. A compound of any one of the preceding claims, wherein G is NR^8 , wherein R^8 is hydrogen.
- 30 16. A compound of any one of claims 1 to 14, wherein G is NR^8 , wherein R^8 is (C_1 - C_6)alkyl.

17. A compound of any one of claims 1 to 14 or 16, wherein G is NR^8 , wherein R^8 is methyl or ethyl.

5 18. A compound of any one of claims 1 to 13, wherein G is a bond.

19. A compound of any one of claims 1 to 13, wherein G is O.

20. A compound of any one of claims 1 to 13, wherein G is $-\text{OCO}-$.

10

21. A compound of any one of claims 1 to 13, wherein G is $-\text{C}(=\text{O})$.

22. A compound of any one of claims 1 to 13, wherein G is $=\text{CH}$.

15 23. A compound of any one of claims 1 to 13, wherein G is $=\text{N}-\text{O}$.

24. A compound of any one of claims 1 to 13, wherein G is S.

25. A compound of any one of claims 1 to 13, wherein G is SO.

20

26. A compound of any one of claims 1 to 13, wherein G is SO_2 .

27. A compound of any one of claims 1 to 13, wherein G is $-\text{NH}-\text{SO}_2$.

25 28. A compound of any one of the preceding claims, wherein R^{10} is a $-(6 \text{ to } 14\text{-membered})\text{aryl}$ or $((6\text{- to } 14\text{-membered})\text{aryl})-(\text{C}_1\text{-C}_6)\text{alkyl}$ -, optionally substituted with one, two, or three substituents independently selected from the group consisting of $-(\text{C}_1\text{-C}_6)\text{alkyl}$, halo, $-\text{C}(\text{halo})_3$, $-\text{CH}(\text{halo})_2$, $-\text{CH}_2(\text{halo})$, $-(\text{C}_1\text{-C}_6)\text{alkyl}-\text{CO}-\text{NR}^{5a}\text{R}^{6a}$, NH_2 , $\text{SO}_2(\text{C}_1\text{-C}_6)\text{alkyl}$ -, or $-\text{SO}_2-\text{NR}^{5a}\text{R}^{6a}$, preferably substituted with $-(\text{C}_1\text{-C}_6)\text{alkyl}$.

30

29. A compound of claim 28, wherein R^{10} is substituted with $-\text{SO}_2-\text{NR}^{5a}\text{R}^{6a}$.

30. A compound of claim 29, wherein at least one of R^{5a} or R^{6a} is hydrogen.
31. A compound of claim 30, wherein both R^{5a} and R^{6a} are hydrogen.
- 5 32. A compound of any one of the preceding claims, wherein R¹⁰ is optionally substituted phenyl or benzyl.
33. A compound of any one of claims 1 to 27, wherein R¹⁰ is -(5- to 12-
10 membered)heteroaryl, ((5- to 12-membered)heteroaryl-(C₁-C₆)alkyl-, -(3- to 12-
membered)heterocycle, ((3- to 12-membered)heterocycle)-(C₁-C₆)alkyl-, (7- to 12-
membered)bicycloheterocycle, or ((7- to 12-membered)bicycloheterocycle)-(C₁-
C₆)alkyl-, each of which is optionally substituted.
- 15 34. A compound of claim 33, wherein R¹⁰ is optionally substituted with one, two or
three substituents independently selected from the group consisting of -(C₁-C₆)alkyl, -
(C₃₋₁₂)cycloalkyl, -(6- to 14-membered)aryl, and -(5- to 12-membered)heteroaryl.
- 20 35. A compound of any one of claims 33 to 34, wherein R¹⁰ is substituted with
COOR⁷.
36. A compound of claim 35, wherein R⁷ is -(C₁-C₆)alkyl.
37. A compound of any one of claims 1 to 27 and 33 to 35, wherein R¹⁰ is piperidinyl
25 optionally substituted with COOR⁷ or NH₂.
38. A compound of any one of claims 1 to 27 and 33 to 35, wherein R¹⁰ is
pyrrolidinyl.
- 30 39. A compound of any one of claims 1 to 27 and 33 to 35, wherein R¹⁰ is -(5- to 12-
membered)heteroaryl.

40. A compound of any one of claims 1 to 27 and 33, wherein R^{10} is optionally substituted pyridinyl.
- 5 41. A compound of any one of claims 1 to 27 and 33, wherein R^{10} is furanyl.
42. A compound of any one of the preceeding claims, wherein R^{10} is optionally substituted $-C(=O)-((6\text{- to }14\text{-membered})\text{aryl})$ or optionally substituted $-C(=O)-NH-(4\text{- to }12\text{-membered})\text{heteroaryl}$.
- 10 43. A compound of any one of claims 1 to 27, wherein R^{10} is $-C(=O)$ or $-C(=O)-(C_2-C_6)\text{alkenyl}$, optionally substituted with $-(C_3-C_{12})\text{cycloalkyl}$, $-(6\text{- to }14\text{-membered})\text{aryl}$ or $-(5\text{- to }12\text{-membered})\text{heteroaryl}$.
- 15 44. A compound of claim 43, wherein R^{10} is substituted with $-(C_3-C_{12})\text{cycloalkyl}$.
45. A compound of any one of claims 1 to 27, wherein R^{10} is $-C(=O)-(C_1-C_6)\text{alkyl}$ -(6- to 14-membered)aryl, optionally substituted with halo.
- 20 46. A compound of any one of claims 1 to 27, wherein R^{10} is NR^5R^6 or $-(C_1-C_6)\text{alkyl}-NR^5NR^6$, each of which is optionally substituted.
47. A compound of claim 46, wherein at least one of R^5 or R^6 is hydrogen.
- 25 48. A compound of claim 46 or 47, wherein at least one of R^5 or R^6 is $-(C_1-C_6)\text{alkyl}$.
49. A compound of claim 46 or 47, wherein at least one of R^5 or R^6 is $-(6\text{- to }14\text{-membered})\text{aryl}$.
- 30 50. A compound of claim 46 or 47, wherein at least one at least one of R^5 or R^6 is $-(5\text{- to }12\text{-membered})\text{heteroaryl}$.

51. A compound of claim 46 or 47, wherein at least one of R⁵ or R⁶ is hydrogen, and the other is $-(C_1-C_6)alkyl-COOR^7$.
- 5 52. A compound of claim 51, wherein R⁷ is hydrogen or $-(C_1-C_6)alkyl$.
53. A compound of any one of claims 1 to 27, wherein R¹⁰ is CONR⁵R⁶.
54. A compound of claim 53, wherein at least one of R⁵ or R⁶ is optionally substituted
10 $-(C_1-C_6)alkyl$.
55. A compound of claim 53 or 54, wherein at least one of R⁵ or R⁶ is substituted with phenyl.
- 15 56. A compound of claim 53, wherein at least one of R⁵ or R⁶ is $-(6- to 14-$
membered)aryl optionally substituted with one, two or three independently selected
R³⁰ groups.
57. A compound of claim 53, wherein at least one of R⁵ or R⁶ is $-(6- to 14-$
20 membered)aryl substituted with one R³⁰ group.
58. A compound of claim 57, wherein R³⁰ is $-(C_1-C_6)alkyl$.
59. A compound of claim 57, wherein R³⁰ is COOR⁷.
25
60. A compound of claim 59, wherein R⁷ is hydrogen.
61. A compound of claim 53, wherein at least one of R⁵ or R⁶ is $-(5- to 12-$
membered)heteroaryl or $-(3- to 12-membered)heterocycle$.
30

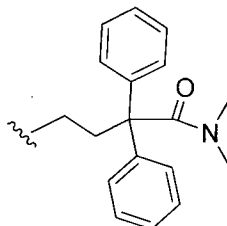
62. A compound of claim 53, wherein R^5 and R^6 together with the nitrogen to which they are attached, form an optionally substituted -(3- to 12-membered)heterocycle.
63. A compound of claim 62, wherein the -(3- to 12-membered) heterocycle is substituted with one, two or three independently selected halo, $C(\text{halo})_3$, $CH(\text{halo})_2$, or $CH_2(\text{halo})$.
64. A compound of any one of the preceeding claims, wherein R^{10} is optionally substituted $-SO_2-(C_1-C_6)\text{alkyl}$.
65. A compound of any one of the preceeding claims, wherein R^{10} is optionally substituted $-SO_2-(C_3-C_{12})\text{cycloalkyl}$.
66. A compound of any one of the preceeding claims, wherein R^{10} is optionally substituted $-SO_2-(5\text{- to }12\text{-membred})\text{heteroaryl}$.
67. A compound of any one of the preceeding claims, wherein R^{10} is optionally substituted $-SO_2-((6\text{- to }14\text{-membered})\text{aryl})$ or optionally substituted $-SO_2-((6\text{- to }14\text{-membered})\text{aryl})-(C_1-C_6)\text{alkyl}$.
68. A compound of claim 65, wherein R^{10} is substituted with one, two or three independently selected halo, $C(\text{halo})_3$, $CH(\text{halo})_2$, or $CH_2(\text{halo})$.
69. A compound of any one of the preceeding claims, wherein R^{10} is optionally substituted $-(C_1-C_6)\text{alkyl}-NR^5R^6$.
70. A compound of claim 69, wherein at least one of R^5 and R^6 is hydrogen.
71. A compound of claim 69 or 70, wherein at least one of R^5 and R^6 is $COOR^7$.
72. A compound of claim 71, wherein R^7 is $-(C_1-C_6)\text{alkyl}$.

73. A compound of any one of the preceding claims, wherein R^1 is $-(C_1-C_{10})$ alkyl, preferably methyl.

5 74. A compound of any one of claims 1 to 72, wherein R^1 is (C_3-C_{12}) cycloalkyl- (C_1-C_6) alkyl-, preferably cyclopropylmethyl or cyclobutylmethyl, preferably cyclopropylmethyl.

75. A compound of any one of claims 1 to 72, wherein R^1 is ((6- to 14-
10 membered)aryl)- (C_1-C_6) alkyl-, preferably difluoro-benzyl or phenylethyl, or ((3- to 12 membered)heterocycle)- (C_1-C_6) alkyl-, preferably furanylmethyl.

76. A compound of any one of claims 1 to 72, wherein R^1 is



15

77. A compound of any one of the preceding claims, wherein R^3 is $-(C_1-C_6)$ alkyl, preferably methyl or propenyl, further preferably methyl.

20 78. A compound of any one of claims 1 to 76, wherein R^3 is $-(C_2-C_6)$ alkenyl, preferably 2-propenyl.

79. A compound of any one of the preceding claims, wherein R^4 is $-(C_1-C_5)$ alkoxy, preferably methoxy.

25

80. A compound of any one of claims 1 to 48, wherein R^4 is OH.

81. A compound of any one of the claims 1 to 6 or 73 to 80, wherein R^{2a} is hydrogen, and R^{2b} is $-Z-G-R^{10}$, wherein Z is absent, G is NR^8 where R^8 is hydrogen, and R^{10} is $-C(=O)-(C_2-C_6)alkenyl$ substituted with a $-(5- \text{ to } 12\text{-membered})heteroaryl$.
- 5 82. A compound of any one of claims 1 to 6 or 73 to 80, wherein R^{2a} is hydrogen, and R^{2b} is $-Z-G-R^{10}$, wherein Z is absent, G is NR^8 where R^8 is $(C_1-C_6)alkyl$, and R^{10} is $((6- \text{ to } 14\text{-membered})aryl)-(C_1-C_6)alkyl$.
83. A compound of any one of claims 1 to 6 or 73 to 80, wherein R^{2a} is hydrogen, and
10 R^{2b} is $-Z-G-R^{10}$, wherein Z is CH_2 , G is a bond, and R^{10} is $CONR^5R^6$, wherein one of R^5 or R^6 is hydrogen and the other is $(6- \text{ to } 14\text{-membered})aryl$ substituted with one R^{30} wherein R^{30} is $COOR^7$ wherein R^7 is hydrogen.
84. A compound of any one of claims 1 to 6 or 73 to 80, wherein R^{2a} is hydrogen, and
15 R^{2b} is $-Z-G-R^{10}$, wherein Z is absent, G is NR^8 wherein R^8 is $(C_1-C_6)alkyl$, and R^{10} is $-C(=O)$ substituted with a $(6- \text{ to } 14\text{-membered})aryl$.
85. A compound of any one of claims 1 to 6 or 73 to 80, wherein R^{2a} is hydrogen, and
20 R^{2b} is $-Z-G-R^{10}$, wherein Z is CH_2 , G is O, and R^{10} is $(6- \text{ to } 14\text{-membered})aryl$ substituted with a $-(C_1-C_6)alkyl-CO-NR^5R^6$, wherein R^5 and R^6 are both hydrogen.
86. A compound of any one of claims 1 to 6 or 73 to 80, wherein R^{2a} is hydrogen, and
25 R^{2b} is $-Z-G-R^{10}$, wherein Z is absent, G is NR^8 wherein R^8 is hydrogen, and R^{10} is $(6- \text{ to } 14\text{-membered})aryl$ substituted with $NH_2-SO_2(C_1-C_6)alkyl$.
87. A compound of any one of claims 1 to 6 or 73 to 80, wherein R^{2a} is hydrogen, and
30 R^{2b} is $-Z-G-R^{10}$, wherein Z is absent, G is NR^8 wherein R^8 is $(C_1-C_6)alkyl$, and R^{10} is $-(6- \text{ to } 14\text{-membered})aryl$ substituted with $NH_2-SO_2(C_1-C_6)alkyl$.
88. A compound of any one of claims 1 to 6 or 73 to 80, wherein R^{2a} is hydrogen, and
 R^{2b} is $-Z-G-R^{10}$, wherein Z is absent, G is NR^8 wherein R^8 is $(C_1-C_6)alkyl$, and R^{10} is $-$

C(=O)-(C₂-C₆)alkenyl substituted with -(5- to 12-membered)heteroaryl or -(3- to 12-membered)heterocycle.

89. A compound of any one of claims 1 to 6 or 73 to 80, wherein R^{2a} is hydrogen, and
 5 R^{2b} is -Z-G-R¹⁰, wherein Z is absent, G is NR⁸ wherein R⁸ is hydrogen, and R¹⁰ is -(6- to 14-membered)aryl substituted with NH₂-SO₂(C₁-C₆)alkyl-.
90. A compound of any one of claims 1 to 6 or 73 to 80, wherein R^{2a} is hydrogen, and
 R^{2b} is -Z-G-R¹⁰, wherein Z is absent, G is NR⁸ wherein R⁸ is (C₁-C₆)alkyl, and R¹⁰ is
 10 CONR⁵R⁶ wherein one of R⁵ or R⁶ is hydrogen and the other is -(C₁-C₆)alkyl-COOR⁷.
91. A compound of any one of claims 1 to 6 or 73 to 80, wherein R^{2a} is hydrogen, and
 R^{2b} is -Z-G-R¹⁰, wherein Z is absent, G is a bond, and R¹⁰ is -(3- to 12-
 membered)heterocycle substituted with -COOR⁷ wherein R⁷ is hydrogen.
 15
92. A compound of any one of claims 1 to 6 or 73 to 80, wherein R^{2a} is hydrogen, and
 R^{2b} is -Z-G-R¹⁰, wherein Z is CH₂, G is NR⁸ wherein R⁸ is hydrogen, and R¹⁰ is -
 C(=O)-(C₁-C₆)alkyl-(6- to 14-membered)aryl substituted with two halo.
- 20 93. A compound of any one of claims 1 to 6 or 73 to 80, wherein R^{2a} is hydrogen, and
 R^{2b} is -Z-G-R¹⁰, wherein Z is absent, G is NR⁸ wherein R⁸ is (C₁-C₆)alkyl, and R¹⁰ is
 CONR⁵R⁶ wherein one of R⁵ or R⁶ is hydrogen and the other is -(C₁-C₆)alkyl-COOR⁷.
94. A compound of any one of claims 1 to 6 or 73 to 80, wherein R^{2a} is hydrogen, and
 25 R^{2b} is -Z-G-R¹⁰, wherein Z is absent, G is NR⁸ wherein R⁸ is (C₁-C₆)alkyl, and R¹⁰ is -
 C(=O)-(C₂-C₆)alkenyl substituted with -(3- to 12-membered)heterocycle.
95. A compound of any one of claims 1 to 6 or 73 to 80, wherein R^{2a} is hydrogen, and
 R^{2b} is -Z-G-R¹⁰, wherein Z is absent, G is NR⁸ wherein R⁸ is -(C₁-C₆)alkyl, and R¹⁰ is
 30 ((3- to 12-membered)heterocycle)-(C₁-C₆)alkyl- substituted with COOR⁷.

96. A compound of claim 95, wherein R^7 is $-(C_1-C_6)\text{alkyl}$.
97. A compound of any one of claims 1 to 6 or 73 to 80, wherein R^{2a} is hydrogen, and R^{2b} is $-Z-G-R^{10}$, wherein Z is absent, G is NR^8 where R^8 is hydrogen, and R^{10} is optionally substituted $-SO_2-((6\text{- to }14\text{-membered})\text{aryl})$.
98. A compound of any one of claims 1 to 6 or 73 to 80, wherein R^{2a} is hydrogen, and R^{2b} is $-Z-G-R^{10}$, wherein Z is absent, G is $-N-SO_2$, and R^{10} is $-(6\text{- to }14\text{-membered})\text{aryl}$ or $((6\text{- to }14\text{-membered})\text{aryl})-(C_1-C_6)\text{alkyl-}$, each of which is optionally substituted.
99. A compound of any one of claims 1 to 6 or 73 to 80, wherein R^{2a} is hydrogen, and R^{2b} is $-Z-G-R^{10}$, wherein Z is absent, G is NR^8 where R^8 is $-(C_1-C_6)\text{alkyl}$, and R^{10} is $-(6\text{- to }14\text{-membered})\text{aryl}$ substituted with $-SO_2-NR^{5a}R^{6a}$.
100. A compound of any one of claims 1 to 6 or 73 to 80, wherein R^{2a} is hydrogen, and R^{2b} is $-Z-G-R^{10}$, wherein Z is absent, G is NR^8 where R^8 is hydrogen, and R^{10} is $-(C_1-C_6)\text{alkyl}-NR^{5R^6}$.
101. A compound of claim 100, wherein at least one of R^5 and R^6 is hydrogen.
102. A compound of claim 100 or 101, wherein at least one of R^5 and R^6 is $-COOR^7$.
103. A compound of claim 102, wherein R^7 is $-(C_1-C_6)\text{alkyl}$.
104. A compound of any one of claims 1 to 6 or 73 to 80, wherein R^{2a} is hydrogen, and R^{2b} is $-Z-G-R^{10}$, wherein Z is absent, G is NR^8 where R^8 is $-(C_1-C_6)\text{alkyl}$, and R^{10} is $CONR^{5R^6}$.
105. A compound of claim 104, wherein R^5 and R^6 taken together with the nitrogen atom to which they are attached form an optionally substituted $-(3\text{- to }12\text{-membered})\text{heterocycle}$.

106. A compound of claim 105, wherein the -(3- to 12-membered) heterocycle is substituted with one R³⁰ group.
- 5 107. A compound of claim 106, wherein R³⁰ is selected from the group consisting of halo, C(halo)₃, CH(halo)₂, and CH₂(halo).
108. A compound of any one of claims 1 to 6 or 73 to 80, wherein R^{2a} is hydrogen, and R^{2b} is -Z-G-R¹⁰, wherein Z is absent, G is NR⁸ where R⁸ is hydrogen, and R¹⁰ is
10 optionally substituted -SO₂-((6- to 14-membered)aryl).
109. A compound of claim 108, wherein R¹⁰ is substituted with one, two or three substituents independently selected from the group consisting of halo, C(halo)₃, CH(halo)₂, and CH₂(halo).
15
110. A compound of any one of claims 1 to 6 or 73 to 80, wherein R^{2a} is hydrogen, and R^{2b} is -Z-G-R¹⁰, wherein Z is absent, G is -N-SO₂, and R¹⁰ is optionally substituted -(6- to 14-membered)aryl.
- 20 111. A compound of claim 110, wherein R¹⁰ is optionally substituted with one, two or three substituents independently selected from the group consisting of halo, C(halo)₃, CH(halo)₂, and CH₂(halo).
112. A compound of any one of claims 1 to 6 or 73 to 80, wherein R^{2a} is hydrogen,
25 and R^{2b} is -Z-G-R¹⁰, wherein Z is absent, G is NR⁸, and R¹⁰ is -CONR⁵R⁶.
113. A compound of claim 112, wherein R⁸ is -(C₁-C₆)alkyl.
114. A compound of claim 112 or 113, wherein at least one of R⁵ and R⁶ is hydrogen.
30

115. A compound of claim any one of claims 112 to 114, wherein at least one of R⁵ and R⁶ is optionally substituted $-(6\text{- to }14\text{-membered})\text{aryl}$.
116. A compound of claim 115, wherein the $-(6\text{ to }14\text{-membered})\text{aryl}$ is substituted
5 with one R³⁰ group.
117. A compound of claim 116, wherein R³⁰ is $-(\text{C}_1\text{-C}_6)\text{alkyl}$.
118. A compound of any one of claims 1 to 6 or 73 to 80, wherein R^{2a} is hydrogen,
10 and R^{2b} is $-\text{Z-G-R}^{10}$, wherein Z is absent, G is NR⁸, and R¹⁰ is optionally substituted
 $((6\text{- to }14\text{-membered})\text{aryl})-(\text{C}_1\text{-C}_6)\text{alkyl}$.
119. A compound of claim 118, wherein R⁸ is hydrogen.
120. A compound of claim 118 or 119, wherein R¹⁰ is substituted with $-(\text{C}_1\text{-C}_6)\text{alkyl}$.
15
121. A compound of any one of claims 1 to 6 or 73 to 80, wherein R^{2a} is hydrogen,
and R^{2b} is $-\text{Z-G-R}^{10}$, wherein Z is absent, G is NR⁸, and R¹⁰ is $-(3\text{- to }12\text{-}$
 $\text{membered})\text{heterocycle}$, $((3\text{- to }12\text{-membered})\text{heterocycle})-(\text{C}_1\text{-C}_6)\text{alkyl}$, $(7\text{- to }12\text{-}$
20 $\text{membered})\text{bicycloheterocycle}$, or $((7\text{- to }12\text{-membered})\text{bicycloheterocycle})-(\text{C}_1\text{-}$
 $\text{C}_6)\text{alkyl}$, each of which is optionally substituted.
122. A compound of claim 121, wherein R⁸ is hydrogen.
123. A compound of claim 121 or 122, wherein R¹⁰ is substituted with $-\text{COOR}^7$.
25
124. A compound of claim 123, wherein R⁷ is $-(\text{C}_1\text{-C}_6)\text{alkyl}$.
125. A compound of any one of claims 1 to 6 or 73 to 80, wherein R^{2a} is hydrogen,
30 and R^{2b} is $-\text{Z-G-R}^{10}$, wherein Z is absent, G is NR⁸, and R¹⁰ is optionally substituted $-\text{C}(=\text{O})\text{-NH-}((3\text{- to }12\text{-membered})\text{heterocycle})$.

126. A compound of claim 125, wherein R^8 is $-(C_1-C_6)\text{alkyl}$.
127. A compound of claim 125 or 126, wherein R^{10} is substituted with one, two or
5 three independently selected halo, $C(\text{halo})_3$, $CH(\text{halo})_2$, and $CH_2(\text{halo})$.
128. A compound of any one of claims 1 to 6 or 73 to 80, wherein R^{2a} is hydrogen,
and R^{2b} is $-Z-G-R^{10}$, wherein Z is absent, G is NR^8 , and R^{10} is optionally substituted
((6- to 14-membered)aryl)-(C₁-C₆)alkyl-.
10
129. A compound of claim 128, wherein R^8 is hydrogen.
130. A compound of claim 128 or 129, wherein R^{10} is substituted with $-SO_2-NR^{5a}R^{6a}$.
131. A compound of claim 130, wherein at least one of R^{5a} and R^{6a} is hydrogen.
15
132. A compound of claim 130, wherein both R^{5a} and R^{6a} are hydrogen.
133. A compound of any one of claims 1 to 6 or 73 to 80, wherein R^{2a} is hydrogen,
20 and R^{2b} is $-Z-G-R^{10}$, wherein Z is absent, G is NR^8 , and R^{10} is optionally substituted $-C(=O)$.
134. A compound of claim 133, wherein R^8 is $-(C_1-C_6)\text{alkyl}$.
135. A compound of claim 133 or 134, wherein R^{10} is substituted with $-(6\text{- to }14\text{-membered})\text{aryl}$.
25
136. A compound of claim 135, wherein R^{10} is substituted with phenyl or benzyl.
137. A compound of claim 133 or 134, wherein R^{10} is substituted with $-(3\text{- to }12\text{-membered})\text{heterocycle}$ or $(5\text{- to }12\text{-membered})\text{heteraryl}$.
30

138. A compound of any one of claims 1 to 6 or 73 to 80, wherein R^{2a} is hydrogen, and R^{2b} is $-Z-G-R^{10}$, wherein Z is absent, G is NR^8 , and R^{10} is (6- to 14-membered)aryl or ((6- to 14-membered)aryl)-(C₁-C₆)alkyl-, each of which is optionally substituted.
- 5 139. A compound of claim 138, wherein R^8 is hydrogen.
140. A compound of claim 138 or 139, wherein R^{10} is substituted by one, two or three independently selected halo, C(halo)₃, CH(halo)₂, or CH₂(halo).
- 10 141. A compound of any one of claims 1 to 6 or 73 to 80, wherein R^{2a} is hydrogen, and R^{2b} is $-Z-G-R^{10}$, wherein Z is absent, G is NR^8 , and R^{10} is optionally substituted – C(=O)-(C₁-C₆)alkyl.
- 15 142. A compound of any one of claims 1 to 6 or 73 to 80, wherein R^{2a} is hydrogen, and R^{2b} is $-Z-G-R^{10}$, wherein Z is absent, G is NR^8 , and R^{10} is NR^5R^6 .
143. A compound of claim 142, wherein R^8 is hydrogen.
- 20 144. A compound of claim 142 or 143, wherein at least one of R^5 or R^6 is hydrogen.
145. A compound of any one of claims 142 to 144, wherein at least one of R^5 or R^6 is $-COOR^7$.
- 25 146. A compound of claim 145, wherein R^7 is $-(C_1-C_6)alkyl$.
147. A compound of any one of claims 1 to 6 or 73 to 80, wherein R^{2a} is hydrogen, and R^{2b} is $-Z-G-R^{10}$, wherein Z is absent, G is NR^8 , and R^{10} is optionally substituted – SO₂-((6- to 14-membered)aryl).
- 30 148. A compound of claim 147, wherein R^8 is hydrogen.

149. A compound of claim 147 or 148, wherein R^{10} is substituted with one, two or three independently selected halo, $C(\text{halo})_3$, $CH(\text{halo})_2$, or $CH_2(\text{halo})$.
- 5 150. A compound of any one of claims 1 to 6 or 73 to 80, wherein R^{2a} is hydrogen, and R^{2b} is $-Z-G-R^{10}$, wherein Z is absent, G is NR^8 , and R^{10} is optionally substituted ((6- to 14-membered)aryl)-(C₁-C₆)alkyl.
151. A compound of claim 150, wherein R^8 is $-(C_1-C_6)\text{alkyl}$.
- 10 152. A compound of claim 150 or 151, wherein R^{10} is substituted with $-\text{SO}_2-NR^{5a}R^{6a}$.
153. A compound of claim 152, wherein at least one of R^{5a} and R^{6a} is hydrogen.
- 15 154. A compound of claim 152, wherein both R^{5a} and R^{6a} are hydrogen.
155. A compound of any one of claims 1 to 6 or 73 to 80, wherein R^{2a} is hydrogen, and R^{2b} is $-Z-G-R^{10}$, wherein Z is absent, G is NR^8 , and R^{10} is optionally substituted $-(C_1-C_6)\text{alkyl}-NR^{5R^6}$.
- 20 156. A compound of claim 155, wherein at least one of R^5 and R^6 is hydrogen.
157. A compound of claim 155 or 156, wherein at least one of R^5 and R^6 is $-\text{COOR}^7$.
- 25 158. A compound of claim 157, wherein R^7 is $-(C_1-C_6)\text{alkyl}$.
159. A compound of any one of the preceding claims, wherein
- R^1 is selected from the group consisting of $-(C_1-C_{10})\text{alkyl}$, $-(C_2-C_{10})\text{alkenyl}$, $-(C_2-$
- 30 $C_{10})\text{alkynyl}$, $-(C_3-C_{12})\text{cycloalkyl}$, $(C_3-C_{12})\text{cycloalkyl}-(C_1-C_6)\text{alkyl}$ -, $-(C_3-$
- $C_{12})\text{cycloalkenyl}$, $(C_3-C_{12})\text{cycloalkenyl}-(C_1-C_6)\text{alkyl}$ -, $-(6- \text{ to } 14\text{-membered})\text{aryl}$, $((6-$

to 14-membered)aryl)-(C₁-C₆)alkyl-, diphenyl(C₁-C₆)alkyl-, -(3- to 12-membered)heterocycle, ((3- to 12 membered)heterocycle)-(C₁-C₆)alkyl-, -(OCH₂CH₂)_s-O-(C₁-C₆)alkyl, -(CH₂CH₂O)_s-(C₁-C₆)alkyl, (C₁-C₁₀)alkoxy, C(halo)₃, CH(halo)₂, CH₂(halo), C(O)R⁵, -C(O)O-(C₁-C₁₀)alkyl, and -(CH₂)_n-N(R⁶)₂, each of
 5 which is optionally substituted by 1, 2 or 3 independently selected R⁹ groups;

R^{2a} is hydrogen, OH, or absent;

R^{2b} is

- 10 a) ((6- to 14-membered)aryl), -((5- to 12-membered)heteroaryl), or ((3- to 12-membered)heterocycle), each of which is optionally substituted with one, two, or three independently selected R³⁰ groups; or
 b) -Z-G-R¹⁰, provided that -Z-G-R¹⁰ is other than hydrogen;
 or R^{2a} and R^{2b} together form =O;

15 Z is absent or -(CH₂)_m-, optionally substituted with 1 or 2 -(C₁-C₆)alkyl;

G is selected from the group consisting of:

- 20 a) a bond, -(C₁-C₆)alkylene, -(C₂-C₆)alkenylene;
 b) O, -OCO-, -C(=O), =CH;
 c) NR⁸, =N-O, =N-NH;
 d) S, SO, SO₂; and
 e) -NH-SO₂;

25 and when Z is absent and G is =CH, =N-O, or =N-NH, then R^{2a} is absent;

R¹⁰ is selected from the group consisting of hydrogen, -(C₁-C₁₀)alkyl, -(C₂-C₁₂)alkenyl, -C(=O), -C(=O)-(C₁-C₆)alkyl, -C(=O)-(C₂-C₆)alkenyl, -C(=O)-(6- to 14-membered)aryl, -C(=O)-(C₁-C₆)alkyl-(6- to 14-membered)aryl, -(C₂-C₁₂)alkynyl, -(C₁-C₁₀)alkoxy, -(OCH₂CH₂)_s-O(C₁-C₆)alkyl, -(CH₂CH₂O)_s-(C₁-C₆)alkyl, -NH₂, -
 30 NH(C₁-C₆)alkyl, CN, NR⁵R⁶, -(C₁-C₆)alkyl-NR⁵R⁶, -CONR⁵R⁶, -(C₁-C₆)alkyl-CO-NR⁵R⁶, -COOR⁷, -(C₁-C₆)alkyl-CO-OR⁷, -(C₁-C₆)alkoxy-COOR⁷, -CO-(CH₂)_n-

COOR⁷, -CO-(CH₂)_n-CO-NR⁵R⁶, -(C₃-C₁₂)cycloalkyl, ((C₃-C₁₂)cycloalkyl)-(C₁-C₆)alkyl-, -(C₄-C₁₂)cycloalkenyl, ((C₄-C₁₂)cycloalkenyl)-(C₁-C₆)alkyl-, -(C₆-C₁₄)bicycloalkyl, ((C₆-C₁₄)bicycloalkyl)-(C₁-C₆)alkyl-, -(C₈-C₂₀)tricycloalkyl, ((C₈-C₂₀)tricycloalkyl)-(C₁-C₆)alkyl-, -(C₇-C₁₄)bicycloalkenyl, ((C₇-C₁₄)bicycloalkenyl)-(C₁-C₆)alkyl-, -(C₈-C₂₀)tricycloalkenyl, ((C₈-C₂₀)tricycloalkenyl)-(C₁-C₆)alkyl-, -(6- to 14-membered)aryl, ((6- to 14-membered)aryl)-(C₁-C₆)alkyl-, -SO₂-(C₁-C₆)alkyl-, -SO₂-((C₃-C₁₂)cycloalkyl), -SO₂-((C₃-C₁₂)cycloalkyl)-(C₁-C₆)alkyl, -SO₂-((5- to 12-membered)heteroaryl), -SO₂-((5- to 12-membered)heteroaryl)-(C₁-C₆)alkyl, -C(=O)-NH-((5- to 12-membered)heteroaryl), -C(=O)-NH-((5- to 12-membered)heteroaryl)-(C₁-C₆)alkyl, -C(=O)-NH-((3- to 12-membered)heterocycle), -C(=O)-NH-((3- to 12-membered)heterocycle)-(C₁-C₆)alkyl, SO₂-((6- to 14-membered)aryl), SO₂-((6- to 14-membered)aryl)-(C₁-C₆)alkyl, -(7- to 12-membered)bicyclic ring system, ((7- to 12-membered)bicyclic ring system)-(C₁-C₆)alkyl-, -(7- to 12-membered)bicyclic aryl, ((7- to 12-membered)bicyclic aryl)-(C₁-C₆)alkyl-, -(5- to 12-membered)heteroaryl, ((5- to 12-membered)heteroaryl)-(C₁-C₆)alkyl-, -(3- to 12-membered)heterocycle, ((3- to 12-membered)heterocycle)-(C₁-C₆)alkyl-, -(7- to 12-membered)bicycloheterocycle, ((7- to 12-membered)bicycloheterocycle)-(C₁-C₆)alkyl-, phenyl, benzyl and naphthyl; each of which is optionally substituted with one, two, or three substituents independently selected from the group consisting of -OH, (=O), halo, -C(halo)₃, -CH(halo)₂, -CH₂(halo), -(C₁-C₆)alkyl, halo(C₁-C₆)alkyl-, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, hydroxy(C₁-C₆)alkyl-, dihydroxy(C₁-C₆)alkyl-, -(C₁-C₆)alkoxy, ((C₁-C₆)alkoxy)CO(C₁-C₆)alkoxy-, phenyl, benzyl, -NH₂, -NH(C₁-C₆)alkyl, -(C₁-C₆)alkyl-NH(C₁-C₆)alkyl-R¹⁴, -CN, -SH, -OR¹¹, -CONR⁵R⁶, -(C₁-C₆)alkyl-CO-NR⁵R⁶, -COOR⁷, -(C₁-C₆)alkyl-CO-OR⁷, -(C₁-C₆)alkoxy-COOR⁷, -(OCH₂CH₂)_s-O(C₁-C₆)alkyl, -(CH₂CH₂O)_s-(C₁-C₆)alkyl, -SO₂-NR^{5a}R^{6a}, (C₁-C₆)alkyl)sulfonyl, ((C₁-C₆)alkyl)sulfonyl(C₁-C₆)alkyl-, -NH-SO₂(C₁-C₆)alkyl, NH₂-SO₂(C₁-C₆)alkyl-, -N(SO₂(C₁-C₆)alkyl)₂, -C(=NH)NH₂, -NH-CO-(C₁-C₆)alkyl, -NH-CO-NH₂, -NH-C(=O)-NH-(C₁-C₆)alkyl, -NH-C(=O)-(6- to 14-membered)aryl, -NH-C(=O)-(C₁-C₆)alkyl-(6- to 14-membered)aryl, -NH-(C₁-C₆)alkyl-CO-OR⁷, -NH-C(=O)-(C₁-C₆)alkyl-CO-OR⁷, -NH-C(=O)-CH(NH₂)-(C₁-C₆)alkyl-CO-OR⁷, -(C₃-C₁₂)cycloalkyl, ((C₃-C₁₂)cycloalkyl)-(C₁-C₆)alkyl-, -(6- to 14-membered)aryl, -(6- to 14-

membered)aryloxy, $-(C_1-C_6)alkoxy-C(O)NR^5R^6$, $-NH-(C_1-C_6)alkyl-C(O)-NR^5R^6$, $-C(O)NH-(C_1-C_6)alkyl-COOR^7$, ((6- to 14-membered)aryl)-(C₁-C₆)alkyl-, -(5- to 12-membered)heteroaryl, ((5- to 12-membered)heteroaryl)-(C₁-C₆)alkyl-, -(3- to 12-membered)heterocycle, ((3- to 12-membered)heterocycle)-(C₁-C₆)alkyl-, -(7- to 12-membered)bicycloheterocycle, and ((7- to 12-membered)bicycloheterocycle)-(C₁-C₆)alkyl-;

R³ is selected from:

- a) -H; or
- 10 b) $-(C_1-C_6)alkyl$, $-(C_2-C_6)alkenyl$, or $-(C_2-C_6)alkynyl$;

R⁴ is selected from

- a) -H, -OH, halo, $-C(halo)_3$, $-CH(halo)_2$, $-CH_2(halo)$, COOH, or CONH₂; or
- b) $-(C_1-C_5)alkyl$, $-(C_2-C_5)alkenyl$, $-(C_2-C_5)alkynyl$, $-(CH_2)_n-O-(CH_2)_n-CH_3$, or $-(C_1-C_5)alkoxy$, each of which is optionally substituted with 1, 2, or 3 independently selected R⁹ groups;
- 15

R⁵ and R⁶ are each independently selected from

- a) hydrogen, -OH, halo, $-C(halo)_3$, $-CH(halo)_2$, $-CH_2(halo)$;
- 20 b) $-(C_1-C_6)alkyl$, $-(C_2-C_5)alkenyl$, $-(C_2-C_5)alkynyl$, $-(CH_2)_n-O-(CH_2)_n-CH_3$, $-(C_1-C_6)alkoxy$, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from -OH, halo, $-(C_1-C_{10})alkyl$, $-(C_2-C_{10})alkenyl$, $-(C_2-C_{10})alkynyl$, $-(C_1-C_{10})alkoxy$, $-(C_3-C_{12})cycloalkyl$, -CHO, $-C(O)OH$, $-C(halo)_3$, $-CH(halo)_2$, $CH_2(halo)$, $-(CH_2)_n-O-(CH_2)_n-CH_3$, phenyl, or $CONR^{5a}R^{6a}$;
- 25 c) $-(C_3-C_8)cycloalkyl$, $((C_3-C_8)cycloalkyl)-(C_1-C_6)alkyl$ -, $-COOR^7$, $-(C_1-C_6)alkyl-COOR^7$, $-CONH_2$, or $(C_1-C_6)alkyl-CONH$ -;
- d) ((6- to 14-membered)aryl) optionally substituted with 1, 2, or 3 independently selected R³⁰ groups;
- e) $-((5- to 12-membered)heteroaryl)$ optionally substituted with 1, 2, or 3
- 30 independently selected R³⁰ groups; or

- f) R^5 and R^6 together with the nitrogen atom to which they are attached form a (3- to 12-membered)heterocycle optionally substituted with 1, 2, or 3 independently selected R^{30} groups;
- 5 R^{5a} and R^{6a} are each independently selected from the group consisting of:
- hydrogen, -OH, halo, -C(halo)₃, -CH(halo)₂, and -CH₂(halo);
 - (C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(CH₂)_n-O-(CH₂)_n-CH₃, and -(C₁-C₆)alkoxy, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from -OH, halo, -(C₁-C₁₀)alkyl, -(C₂-C₁₂)alkenyl, -(C₂-C₁₂)alkynyl, -(C₁-C₁₀)alkoxy, -(C₃-C₁₂)cycloalkyl, -CHO, -COOH, -C(halo)₃, -CH(halo)₂, CH₂(halo), -(CH₂)_n-O-(CH₂)_n-CH₃, and phenyl;
 - (C₃-C₈)cycloalkyl, ((C₃-C₈)cycloalkyl)-(C₁-C₆)alkyl-, -COOR⁷, -(C₁-C₆)alkyl-COOR⁷, -CONH₂, and (C₁-C₆)alkyl-CONH-;
 - (6- to 14-membered)aryl optionally substituted with 1, 2, or 3 independently selected R^{30} groups;
 - (5- to 12-membered)heteroaryl optionally substituted with 1, 2, or 3 independently selected R^{30} groups; or
 - R^{5a} and R^{6a} together with the nitrogen atom to which they are attached form a (3- to 12-membered)heterocycle optionally substituted with 1, 2, or 3 independently selected R^{30} groups;

each R^7 is independently selected from the group consisting of hydrogen, -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₃-C₁₂)cycloalkyl, -(C₄-C₁₂)cycloalkenyl, ((C₃-C₁₂)cycloalkyl)-(C₁-C₆)alkyl-, and ((C₄-C₁₂)cycloalkenyl)-(C₁-C₆)alkyl-;

each R^8 is independently selected from H, -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₁-C₁₀)alkoxy, -(C₃-C₁₂)cycloalkyl, -(C₃-C₁₂)cycloalkenyl, ((C₃-C₁₂)cycloalkyl)-(C₁-C₆)alkyl-, ((C₃-C₁₂)cycloalkenyl)-(C₁-C₆)alkyl-, -C(=O)(C₁-C₆)alkyl or SO₂(C₁-C₆)alkyl;

- each R^9 is independently selected from -OH, halo, $-(C_1-C_{10})$ alkyl, $-(C_2-C_{10})$ alkenyl, $-(C_2-C_{10})$ alkynyl, $-(C_1-C_{10})$ alkoxy, $-(C_3-C_{12})$ cycloalkyl, -CHO, $-C(O)OH$, $-C(halo)_3$, $-CH(halo)_2$, $CH_2(halo)$, $-(CH_2)_n-O-(CH_2)_n-CH_3$, phenyl, or $CONR^{5a}R^{6a}$;
- 5 each R^{11} is independently selected from $-C(halo)_3$, $-CH(halo)_2$, $-CH_2(halo)$, $-(C_2-C_5)$ alkenyl, $-(C_2-C_5)$ alkynyl, $-(CH_2)_n-O-(CH_2)_n-CH_3$, (6- to 14-membered)aryl, ((6- to 14-membered)aryl)- (C_1-C_6) alkyl-, or (5- to 12-membered)heteroaryl, ((5- to 12-membered)heteroaryl)- (C_1-C_6) alkyl-, each of which is optionally substituted with 1, 2, or 3 independently selected R^9 groups;
- 10 each R^{14} is independently selected from $-COOR^7$, $-(C_1-C_6)$ alkyl- $COOR^7$, $-C(=O)-(C_1-C_6)$ alkyl- $COOR^7$, $-(C_1-C_6)$ alkyl- $C(=O)-(C_1-C_6)$ alkyl- $COOR^7$, $CONH_2$, or $-(C_1-C_6)$ alkyl-CONH;
- 15 each R^{30} is independently selected from $COOR^7$, $CONR^{5a}R^{6a}$, $-(C_1-C_6)$ alkyl, $-C(=O)$, CN, $-(3- \text{ to } 12\text{-membered})$ heteroaryl, $((3- \text{ to } 12\text{-membered})$ heteroaryl)- (C_1-C_6) alkyl-, NH_2 , halo, and $((6- \text{ to } 14\text{-membered})$ aryl)- (C_1-C_6) alkoxy-;
- m is an integer 1, 2, 3, 4, 5, or 6;
- 20 n is an integer 0, 1, 2, 3, 4, 5, or 6;
- s is an integer 1, 2, 3, 4, 5, or 6;
- provided that when R^4 is $-(C_1-C_5)$ alkoxy then:
- a) R^{2a} and R^{2b} cannot be taken together to form $=O$; or
- 25 b) R^{2a} cannot be OH when R^{2b} is $-Z-G-R^{10}$, and $-Z-G-R^{10}$ is either:
- a. OH;
- b. $-(C_1-C_6)$ alkyl;
- c. $-(C_2-C_6)$ alkenyl; or
- d. $-(C_2-C_6)$ alkynyl; or
- 30 c) R^{2a} cannot be H when the combination $-Z-G-R^{10}$ is either:
- a. OH;

- b. $-\text{O}-\text{C}(=\text{O})-(\text{C}_1-\text{C}_6)\text{alkyl}$; or
- c. $-\text{O}-\text{C}(=\text{O})-(\text{C}_2-\text{C}_6)\text{alkenyl}$;

and provided that when R^4 is OH then:

- a) R^{2a} cannot be OH when R^{2b} is $-\text{Z}-\text{G}-\text{R}^{10}$, and $-\text{Z}-\text{G}-\text{R}^{10}$ is:
 - 5 a. $-(\text{C}_1-\text{C}_6)\text{alkyl}$;
 - b. $-(\text{C}_2-\text{C}_6)\text{alkenyl}$;
 - c. or $-(\text{C}_2-\text{C}_6)\text{alkynyl}$;
- b) R^{2a} cannot be H when R^{2b} is $-\text{Z}-\text{G}-\text{R}^{10}$, and $-\text{Z}-\text{G}-\text{R}^{10}$ is:
 - a. OH
 - 10 b. $-\text{O}-\text{C}(=\text{O})-(\text{C}_1-\text{C}_6)\text{alkyl}$; or
 - c. $-\text{O}-\text{C}(=\text{O})-(\text{C}_2-\text{C}_6)\text{alkenyl}$;

and provided that when R^3 is $(\text{C}_1-\text{C}_6)\text{alkyl}$ or $(\text{C}_2-\text{C}_6)\text{alkenyl}$, and R^4 is H, OH, or $(\text{C}_1-\text{C}_5)\text{alkoxy}$, then R^{2b} is not

- 15 a) optionally substituted (5- to 12-membered)heteroaryl,
- b) optionally substituted (3- to 12-membered)heterocycle, or
- c) unsubstituted phenyl or phenyl substituted with halo, $(\text{C}_1-\text{C}_6)\text{alkyl}$, $\text{C}(\text{halo})_3$, hydroxy, $(\text{C}_1-\text{C}_6)\text{alkoxy}$, (3- to 12-membered)heterocycle, or NH_2

- 20 and provided that when R^4 is OH and R^1 is $(\text{C}_1-\text{C}_{10})\text{alkyl}$, then R^{2a} and R^{2b} cannot be together selected $=\text{O}$.

and provided that when R^4 is hydrogen and when R^1 and R^3 are both methyl, then

- a) R^{2a} and R^{2b} cannot together form $=\text{O}$ or $=\text{N}-\text{OH}$; or
- 25 b) R^{2b} may not be NH_2 or $\text{NHC}(\text{O})\text{CH}_3$ if R^{2a} is hydrogen.

and provided that when R^{2a} is H, then R^{2b} may not be $-\text{Z}-\text{G}-\text{R}^{10}$, wherein $-\text{Z}-\text{G}-\text{R}^{10}$ is:

- a) $-\text{CH}_2-\text{CHR}^{20}-\text{C}(=\text{O})\text{R}^{21}$, wherein
 - R^{20} is H, or $-(\text{C}_1-\text{C}_6)\text{alkyl}$, and
 - 30 R^{21} is selected from the group consisting of H, $-(\text{C}_1-\text{C}_{10})\text{alkyl}$,

-(C₃-C₁₂)cycloalkyl, ((C₃-C₁₂)cycloalkyl)-(C₁-C₆)alkyl-, -(6- to 14-membered)aryl, and ((6- to 14-membered)aryl)-(C₁-C₆)alkyl-; or

b) -CH₂-CHR²⁰-CR²²R²³OH, wherein

R²⁰ is defined as above, and

5 R²² and R²³ are each independently selected from the group consisting of H, -(C₁-C₁₀)alkyl, ((C₃-C₁₂)cycloalkyl)-(C₁-C₆)alkyl-, -(6- to 14-membered)aryl, and ((6- to 14-membered)aryl)-(C₁-C₆)alkyl-; or

c) -CH₂-CR²⁰=CR²³R²⁴, wherein

R²⁰ and R²³ are defined as above, and

10 R²⁴ is selected from the group consisting of H, and -(C₁-C₆)alkyl.

and the pharmaceutically acceptable salts and solvates thereof.

160. A compound selected from the group consisting of:

15 2-(((8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[d]azocin-11-ylidene)amino)oxy)acetic acid;

8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[d]azocin-11-one oxime;

20 2-(((6*R*,11*R*)-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[d]azocin-11-yl)oxy)acetamide;

2-(((6*R*,11*S*)-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[d]azocin-11-yl)oxy)acetamide;

8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[d]azocin-11-one-*O*-(2-(diethylamino)ethyl) oxime;

25 8-methoxy-3,6-dimethyl-11-propylidene-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[d]azocine;

4-(11,11-dihydroxy-8-methoxy-6-methyl-1,2,5,6-tetrahydro-2,6-methanobenzo[d]azocin-3(4*H*)-yl)-*N,N*-dimethyl-2,2-diphenylbutanamide;

30 (6*R*,11*S*)-8-methoxy-*N*,3,6-trimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[d]azocin-11-amine;

- (6*R*,11*R*)-8-methoxy-*N*,3,6-trimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-amine;
- 3-(cyclopropylmethyl)-8-methoxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-one *O*-methyl oxime;
- 5 ((6*S*,11*R*)-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)methanol;
- (*Z*)-ethyl 2-(8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-ylidene)acetate;
- (*Z*)-2-(8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-
- 10 methanobenzo[*d*]azocin-11-ylidene)acetic acid;
- ethyl 2-((6*S*,11*R*)-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)acetate;
- 2-((6*S*,11*R*)-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)acetic acid;
- 15 (*E*)-3-(furan-3-yl)-*N*-((6*R*,11*R*)-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-*N*-methylacrylamide;
- 4-((6*R*,11*S*)-11-hydroxy-8-methoxy-6-methyl-1,2,5,6-tetrahydro-2,6-methanobenzo[*d*]azocin-3(4*H*)-yl)-*N,N*-dimethyl-2,2-diphenylbutanamide;
- 8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-
- 20 11-one oxime;
- 4-(11-(hydroxyimino)-8-methoxy-6-methyl-1,2,5,6-tetrahydro-2,6-methanobenzo[*d*]azocin-3(4*H*)-yl)-*N,N*-dimethyl-2,2-diphenylbutanamide;
- (*E*)-3-(furan-3-yl)-*N*-((6*R*,11*S*)-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-*N*-methylacrylamide;
- 25 4-((6*R*,11*R*)-8,11-dihydroxy-6-methyl-1,2,5,6-tetrahydro-2,6-methanobenzo[*d*]azocin-3(4*H*)-yl)-*N,N*-dimethyl-2,2-diphenylbutanamide;
- 4-((6*R*,11*S*)-8,11-dihydroxy-6-methyl-1,2,5,6-tetrahydro-2,6-methanobenzo[*d*]azocin-3(4*H*)-yl)-*N,N*-dimethyl-2,2-diphenylbutanamide;
- (*E*)-3-(furan-3-yl)-*N*-((2*R*,6*R*,11*S*)-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-
- 30 hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)acrylamide;

- (*E*)-3-(furan-3-yl)-*N*-((2*R*,6*R*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-*N*-methylacrylamide;
- (*E*)-*N*-ethyl-3-(furan-3-yl)-*N*-((2*R*,6*R*,11*S*)-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)acrylamide;
- 5 4-fluoro-*N*'-((2*S*,6*R*)-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-ylidene)benzohydrazide;
- N*-((2*R*,6*R*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-*N*-methyl-2-(4-(methylsulfonyl)phenyl)acetamide);
- 4-(((2*R*,6*R*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)(methyl)amino)-4-oxobutanoic acid;
- 10 (2*R*,6*R*,11*S*)-3,6-dimethyl-11-(methyl(phenethyl)amino)-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-8-ol;
- tert*-butyl 4-(((2*R*,6*S*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)amino)methyl)piperidine-1-carboxylate;
- 15 *tert*-butyl 4-(((2*R*,6*S*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)(methyl)amino)methyl)piperidine-1-carboxylate;
- 4-(2-(((6*S*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)acetamido)benzoic acid;
- 5-(((2*R*,6*S*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)methoxy)nicotinic acid;
- 20 5-(((6*S*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)methoxy)nicotinic acid;
- 2-(2-(((6*S*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)acetamido)benzoic acid;
- 25 3-(((6*S*,11*R*)-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)benzonitrile;
- 3-((6*R*,11*S*)-11-hydroxy-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)benzonitrile;
- 3-(((6*S*,11*R*)-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)benzoic acid;
- 30

- N*-((2*R*,6*R*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-*N*-methylbenzamide;
- 3-(((6*S*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)methoxy)benzoic acid;
- 5 3-(((2*R*,6*S*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)methoxy)benzoic acid;
- (6*S*,11*R*)-11-(3-(1*H*-tetrazol-5-yl)phenyl)-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocine;
- (1*S*)-1-(5-chloro-6-(((6*S*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)methoxy)pyridin-3-yl)ethane-1,2-diol;
- 10 4-(((6*S*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)methoxy)benzamide;
- 4-(3-((2*R*,6*R*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-3-methylureido)benzoic acid;
- 15 4-(3-((2*R*,6*R*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-3-methylureido)benzoic acid;
- 3-(((2*R*,6*R*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)(methyl)carbamoyl)benzoic acid;
- 3-(((2*R*,6*R*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)(methyl)carbamoyl)benzoic acid;
- 20 2-(((2*R*,6*R*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)(methyl)carbamoyl)benzoic acid;
- 2-(4-(((2*R*,6*R*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)amino)phenyl)ethanesulfonamide;
- 25 2-(4-(((2*R*,6*R*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)(methyl)amino)phenyl)ethanesulfonamide;
- 4-(((6*S*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocine-11-carboxamido)benzoic acid;
- 2-(((6*S*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)methoxy)isonicotinamide;
- 30

- 3-((6*S*,11*R*)-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)benzamide;
- (2*S*)-1-(2-((6*S*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)acetyl)pyrrolidine-2-carboxylic acid;
- 5 (2*R*,6*R*,11*S*)-3-(cyclopropylmethyl)-8-methoxy-*N*,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-amine;
- (*E*)-*N*-((2*R*,6*R*,11*S*)-3-(cyclopropylmethyl)-8-methoxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-3-(furan-3-yl)-*N*-methylacrylamide;
- 2-(4-(((2*R*,6*R*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)amino)phenyl)ethanesulfonamide;
- 10 4-(((2*R*,6*R*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)(methyl)carbamoyl)benzoic acid;
- 3-((6*R*,11*R*)-11-hydroxy-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)benzonitrile;
- 15 (6*S*,11*R*)-11-(3-(benzyloxy)phenyl)-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocine;
- methyl 3-((6*R*,11*R*)-11-hydroxy-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)benzoate;
- 3-((6*R*,11*S*)-11-hydroxy-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)benzamide;
- 20 methyl 3-((6*R*,11*S*)-11-hydroxy-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)benzoate;
- (6*R*,11*R*)-11-(3-(1*H*-tetrazol-5-yl)phenyl)-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-ol;
- 25 (6*R*,11*S*)-11-(3-(1*H*-tetrazol-5-yl)phenyl)-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-ol;
- 3-((6*R*,11*R*)-11-hydroxy-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)benzamide;
- 3-3-((2*R*,6*R*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-3-methylureido)propanoic acid;
- 30

(6*R*)-8-methoxy-3,6-dimethyl-11-(pyrrolidin-1-yl)-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocine;

1-((6*R*)-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)piperidin-4-amine;

5 3-((6*R*,11*S*)-11-hydroxy-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)benzoic acid;

1-(2-((6*S*,11*R*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)acetyl)piperidine-4-carboxylic acid;

10 2-(((2*R*,6*R*,11*S*)-3-(cyclopropylmethyl)-8-methoxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)(methyl)amino)acetic acid;

1-((6*R*)-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)piperidine-3-carboxylic acid;

2-(3,4-dichlorophenyl)-*N*-(((6*S*,11*S*)-8-methoxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)methyl)acetamide;

15 2-(3-((2*R*,6*S*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-3-methylureido)-4-methylpentanoic acid;

(*E*)-*N*-((2*R*,6*R*,11*S*)-3-(cyclopropylmethyl)-8-hydroxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-3-(furan-3-yl)-*N*-methylacrylamide;

20 3-(4-cyanophenyl)-1-((2*R*,6*R*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-1-methylurea;

3-(4-cyanophenyl)-1-((2*R*,6*R*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-1-methylurea; and

the pharmaceutically acceptable salts and solvates thereof.

25 161. A compound selected from the group consisting of:

3-(4-cyanophenyl)-1-((6*R*,11*R*)-3-(cyclopropylmethyl)-8-hydroxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-1-methylurea;

3-(4-cyanophenyl)-1-((6*R*,11*S*)-3-(cyclopropylmethyl)-8-hydroxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-1-methylurea;

30 4-(3-((6*R*,11*S*)-3-(cyclopropylmethyl)-8-methoxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-3-methylureido)benzamide;

(*E*)-*N*-((6*R*,11*R*)-3-(cyclopropylmethyl)-8-hydroxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-3-(furan-3-yl)-*N*-methylacrylamide;
 4-((2*R*,6*R*,11*S*)-11-(3-(4-cyanophenyl)-1-methylureido)-8-hydroxy-6-methyl-1,2,5,6-tetrahydro-2,6-methanobenzo[*d*]azocin-3(4*H*)-yl)-*N,N*-dimethyl-2,2-
 5 diphenylbutanamide;

(*E*)-*N*-((2*R*,6*R*,11*S*)-3-(cyclopropylmethyl)-8-methoxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-3-(furan-3-yl)-*N*-methylacrylamide;

(*Z*)-*N*-((2*R*,6*R*,11*S*)-3-(cyclopropylmethyl)-8-methoxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-3-(furan-3-yl)-*N*-methylacrylamide;

10 3-(4-cyanophenyl)-1-((2*R*,6*R*,11*S*)-8-hydroxy-6-methyl-3-phenethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-1-methylurea;

3-(4-cyanophenyl)-1-((6*R*,11*R*)-3-(cyclobutylmethyl)-8-hydroxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-1-methylurea;

15 3-(4-cyanophenyl)-1-((6*R*,11*R*)-3-(2,3-difluorobenzyl)-8-hydroxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-1-methylurea;

3-(4-cyanophenyl)-1-((2*R*,6*R*,11*S*)-3-(furan-3-ylmethyl)-8-hydroxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-1-methylurea;

3-((2*R*,6*R*,11*S*)-8-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*]azocin-11-yl)-3,4-dihydroquinazolin-2(1*H*)-one; and

20 the pharmaceutically acceptable salts and solvates thereof.

162. A pharmaceutical composition comprising an effective amount of a compound of any one of claims 1 to 161, or a pharmaceutically salt, prodrug, or solvate thereof, and a pharmaceutically acceptable carrier or excipient.

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163. A method for modulating opioid receptor function in a cell, comprising contacting a cell capable of expressing an opioid receptor with an effective amount of a compound of any one of claims 1 to 161, or a pharmaceutically acceptable salt, prodrug or solvate thereof.

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164. The method of claim 163, wherein the compound modulates μ -opioid receptor function.
165. The method of claim 163 or 164, wherein the compound acts as an agonist at the μ -opioid receptor.
166. The method of claim 163 or 164, wherein the compound acts as an antagonist at the μ -opioid receptor.
167. The method of claim 163, wherein the compound acts as an agonist at the κ -opioid receptor.
168. The method of claim 163, wherein the compound modulates ORL-1 receptor function.
169. The method of claim 163 or 168, wherein the compound acts as an antagonist at the ORL-1 receptor.
170. A method of treating a Condition in a mammal, comprising administering to such mammal in need thereof an effective amount of a compound of any one of claims 1 to 161, or a pharmaceutically acceptable salt, prodrug or solvate thereof.
171. The method of claim 170, wherein the Condition is pain.
172. The method of claim 170, wherein the Condition is constipation.
173. A method for preparing a composition, comprising the step of admixing a compound according to any one of claims 1 to 161, or a pharmaceutically acceptable salt, prodrug or solvate thereof, with a pharmaceutically acceptable carrier or excipient.

174. A compound of any one of claims 1 to 161 or a pharmaceutically acceptable salt, prodrug or solvate thereof, for use in the treatment, prevention, or amelioration of a Condition.
- 5 175. The compound for use of claim 174, wherein the Condition is pain.
176. The compound for use of claim 174, wherein the Condition is constipation.
177. Use of a compound according to any one of claims 1 to 161 or a
10 pharmaceutically acceptable salt, prodrug or solvate thereof in the manufacture of a medicament useful for treating or preventing a Condition.
178. The use of claim 177, wherein the Condition is pain.
- 15 179. The use of claim 177, wherein the Condition is constipation.