PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/41	A1	(11) International Publication Number: WO 97/20556
		(43) International Publication Date: 12 June 1997 (12.06.97)

(21) International Application Number: PCT/US96/19390

(22) International Filing Date: 5 December 1996 (05.12.96)

(30) Priority Data:

60/008,318	7 December 1995 (07.12.95)	US
60/008,298	7 December 1995 (07.12.95)	US
60/008,306	7 December 1995 (07.12.95)	US
60/008,313	7 December 1995 (07.12.95)	US
60/008,319	7 December 1995 (07.12.95)	US
60/008,312	7 December 1995 (07.12.95)	US
60/008,295	7 December 1995 (07.12.95)	US

(71) Applicant *(for all designated States except US)*: ELI LILLY AND COMPANY [US/US]; Lilly Corporate Center, Indianapolis, IN 46285 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: MITCH, Charles, H. [US/US]; 3210 Grove Parkway, Columbus, IN 47203 (US). SHANNON, Harlan, E. [US/US]; 4229 Rolling Springs Drive, Carmel, IN 46234 (US).

(74) Agents: VORNDRAN-JONES, MaCharri et al.; Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: METHOD FOR TREATING PAIN

(57) Abstract

The present invention provides a method and composition for treating pain using a composition comprising an azabicyclic or tetrahydropyridine compound and a classical analgesic compound.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	**GB**	United Kingdom	**MW**	Malawi
AT	Austria	**GE**	Georgia	**MX**	Mexico
AU	Australia	**GN**	Guinea	**NE**	Niger
BB	Barbados	**GR**	Greece	**NL**	Netherlands
BE	Belgium	**HU**	Hungary	**NO**	Norway
BF	Burkina Faso	**IE**	Ireland	**NZ**	New Zealand
BG	Bulgaria	**IT**	Italy	**PL**	Poland
BJ	Benin	**JP**	Japan	**PT**	Portugal
BR	Brazil	**KE**	Kenya	**RO**	Romania
BY	Belarus	**KG**	Kyrgystan	**RU**	Russian Federation
CA	Canada	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CF	Central African Republic			**SE**	Sweden
CG	Congo	**KR**	Republic of Korea	**SG**	Singapore
CH	Switzerland	**KZ**	Kazakhstan	**SI**	Slovenia
CI	Côte d'Ivoire	**LI**	Liechtenstein	**SK**	Slovakia
CM	Cameroon	**LK**	Sri Lanka	**SN**	Senegal
CN	China	**LR**	Liberia	**SZ**	Swaziland
CS	Czechoslovakia	**LT**	Lithuania	**TD**	Chad
CZ	Czech Republic	**LU**	Luxembourg	**TG**	Togo
DE	Germany	**LV**	Latvia	**TJ**	Tajikistan
DK	Denmark	**MC**	Monaco	**TT**	Trinidad and Tobago
EE	Estonia	**MD**	Republic of Moldova	**UA**	Ukraine
ES	Spain	**MG**	Madagascar	**UG**	Uganda
FI	Finland	**ML**	Mali	**US**	United States of America
FR	France	**MN**	Mongolia	**UZ**	Uzbekistan
GA	Gabon	**MR**	Mauritania	**VN**	Viet Nam

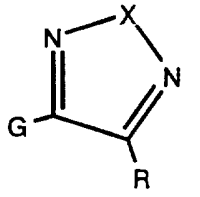
METHOD FOR TREATING PAIN

The present invention relates to a method for using azacyclic, azabicyclic, or tetrahydropyridine compounds for treating pain.

This invention relates to a therapeutic combination of compounds to provide analgesic activity.

More active analgesic combinations effects are in constant demand because they offer the attractive possibility of relieving pain with reduced dosages, thereby diminishing the expected side effects and toxicity that would otherwise result from higher dosages. It would be particularly desirable to acquire a synergistic combination effect. Such a composition is the subject of the present invention.

The present invention provides a method for treating pain comprising administering to a patient in need thereof, an anagesic composition comprising a compound of Formula I



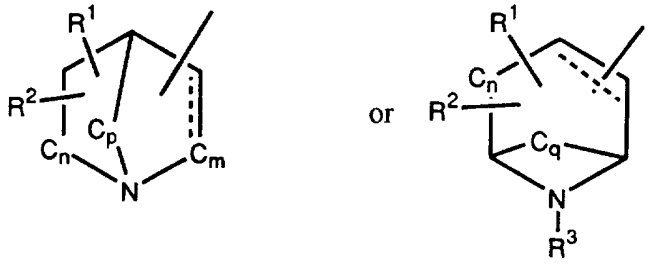
I

wherein

X is oxygen or sulphur;

R is hydrogen, amino, halogen, -CHO, $-NO_2$, $-OR^4$, $-SR^4$, $-SOR^4$, $-SO_2R^4$, C_{3-7}-cycloalkyl, C_{4-8}-(cycloalkylalkyl), -Z-C_{3-7}-cycloalkyl, and -Z-C_{4-8}-(cycloalkylalkyl) wherein R^4 is straight or branched C_{1-15}-alkyl, straight or branched C_{2-15}-alkenyl, straight or branched C_{2-15}-alkynyl, each of which is optionally substituted with one or more halogens, $-CF_3$, -CN,

phenyl or phenoxy wherein phenyl or phenoxy is optionally substituted with halogen, -CN, C_{1-4}-alkyl, C_{1-4}-alkoxy, $-OCF_3$, $-CONH_2$ or $-CSNH_2$; or R is phenyl or benzyloxycarbonyl, each of which is optionally substituted with halogen, -CN, C_{1-4}-alkyl, C_{1-4}-alkoxy, $-OCF_3$, $-CONH_2$ or $-CSNH_2$; or R is $-OR^5Y$, $-SR^5Y$, $-OR^5ZY$, $-SR^5ZY$, $-O-R^4-Z-R^5$ or $-S-R^4-Z-R^5$ wherein Z is oxygen or sulphur, R^5 is straight or branched C_{1-15}-alkynyl, and Y is a 5 or 6 membered heterocyclic group containing one to four N, O or S atom(s) or a combination thereof, which heterocyclic group is optionally substituted at carbon or nitrogen atom(s) with straight or branched C_{1-6}-alkyl, phenyl or benzyl, or which heterocyclic group is optionally fused with a phenyl group; and G is selected from one of the following azabicyclic rings

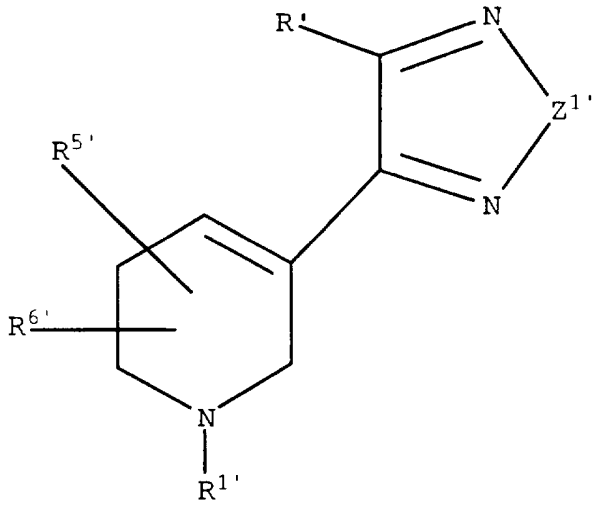


wherein the thiadiazole or oxadiazole ring can be attached at any carbon atom of the azabicyclic ring; R^1 and R^2 may be present at any position, including the point of attachment of the thiadiazole or oxadiazole ring, and independently are hydrogen, straight or branched C_{1-5}-alkyl, straight or branched C_{2-5} alkenyl, straight or branched C_{2-5}-alkynyl, straight or branched C_{1-10}-alkoxy, straight or branched C_{1-5}-alkyl substituted with -OH, OR^4, halogen, $-NH_2$ or carboxy; R^3 is H, straight or branched C_{1-5}-alkyl, straight or branched C_{2-5}-alkenyl or straight or branched C_{2-5}-alkynyl; n is 0, 1 or 2; m is 0, 1 or 2; p is 0, 1 or 2; q is 1 or 2; and --- is a single or double bond; or

a pharmaceutically acceptable salt thereof;

and a nonsteroidal anti-inflammatory drug in a weight ratio of Formula I to nonsteroidal anti-inflammatory drug of from about 1 to about 1000.

The present invention provides a method for treating pain comprising administering to a patient in need thereof, an anagesic composition comprising a compound of Formula II



(II)

wherein

$Z^{1'}$ is oxygen or sulphur;

R' is hydrogen, halogen, amino, $-NHCO-R^{2'}$, C_{3-7}-cycloalkyl, C_{4-10}-(cycloalkylalkyl), $-Z^{2'}-C_{3-7}$-cycloalkyl optionally substituted with C_{1-6}-alkyl, $-Z^{2'}-C_{4-10}$-(cycloalkylalkyl), $-Z^{2'}-C_{4-10}$-(cycloalkenylalkyl), $-Z^{2'}-C_{4-10}$-(methylenecycloalkyl-alkyl), $-NH-R^{2'}$, $-NR^{2'}R^{3'}$, $-NH-OR^{2'}$, phenyl, phenoxy, benzoyl, benzyloxycarbonyl, tetrahydronaphtyl, indenyl, X', $R^{2'}$, $-Z^{2'}R^{2'}$, $-SOR^{2'}$, $-SO_2R^{2'}$, $-Z^{2'}-R^{2'}-Z^{3'}-R^{3'}$, $-Z^{2'}-R^{2'}-Z^{3'}-R^{3'}-Z^{4'}-R^{4'}$, $-Z^{2'}-R^{2'}CO-R^{3'}$, $-Z^{2'}-R^{2'}-CO_2-R^{3'}$, $Z^{2'}-R^{2'}-O_2C-R^{3'}$, $-Z^{2'}-R^{2'}-CONH-R^{3'}$, $-Z^{2'}-R^{2'}-NHCOR^{3'}$, $-Z^{2'}-R^{2'}-X'$, $-Z^{2'}-R^{2'}-Z^{3'}-X'$, wherein $Z^{2'}$, $Z^{3'}$, and $Z^{4'}$ independently are oxygen or sulphur, and $R^{2'}$, $R^{3'}$ and $R^{4'}$ independently are straight or branched C_{1-15}-alkyl, straight or branched C_{2-15}-alkenyl, straight or branched C_{2-15}-alkynyl, each of which is optionally substituted with halogen(s), -OH,

-CN, -CF_3, -SH, -COOH, -NH-$R^{2'}$, -$NR^{2'}R^{3'}$, C_{1-6}alkyl ester, one or two phenyl, phenoxy, benzoyl or benzyloxycarbonyl wherein each aromatic group is optionally substituted with one or two halogen, -CN, C_{1-4}-alkyl or C_{1-4}-alkoxy, and X' is a 5 or 6 membered heterocyclic group containing one to four N, O or S atom(s) or a combination thereof, which heterocyclic group is optionally substituted at carbon or nitrogen atom(s) with straight or branched C_{1-6}-alkyl, phenyl, benzyl or pyridine, or a carbon atom in the heterocyclic group together with an oxygen atom form a carbonyl group, or which heterocyclic group is optionally fused with a phenyl group; and

$R^{5'}$ and $R^{6'}$ may be present at any position, including the point of attachment of the thiadiazole or oxadiazole ring, and independently are hydrogen, straight or branched C_{1-5}-alkyl, straight or branched C_{2-5}-alkenyl, straight or branched C_{2-5}-alkynyl, straight or branched C_{1-10}-alkoxy, straight or branched C_{1-5}-alkyl substituted with -OH, -OH, halogen, -NH_2 or carboxy; $R^{1'}$ is hydrogen, straight or branched C_{1-5}-alkyl, straight or branched C_{2-5}-alkenyl or straight or branched C_{2-5}-alkynyl; or

a pharmaceutically acceptable salt or solvate thereof; and one or more nonsteroidal anti-inflammatory drug in a weight ratio of Formula II to nonsteroidal anti-inflammatory drug of from about 1 to about 1000.

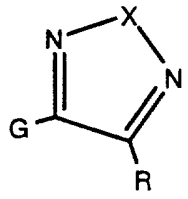
Preferred NSAIDS include, but are in no way limited to salicylates such as aspirin, indomethacin, ibuprofen, naproxen, fenoprofen, tolmetin, sulindac, meclofenamate, keoprofen, piroxicam, flurbiprofen, and diclofenac. Especially preferred NSAIDS include aspirin, ibuprofen, and naproxen. Alternative preferred NSAIDS include ibuprofen and naproxen. Alternative particularly preferred NSAIDS include ibuprofen.

The invention further provides a composition for treating pain comprising a compound selected from the group consisting of Formula I and Formula II; or a

pharmaceutically acceptable salt or solvate thereof; and a a nonsteroidal anti-inflammatory drug in a weight ratio of Compound to a nonsteroidal anti-inflammatory drug of from about 1 to about 1000.

The present invention provides a method for treating pain comprising administering to a patient in need thereof, an anagesic composition comprising a compound selected from the group consisting of Formula I and Formula II; or
a pharmaceutically acceptable salt or solvate thereof; and acetaminophen in a weight ratio of Compound to acetaminophen of from about 1 to about 1000.

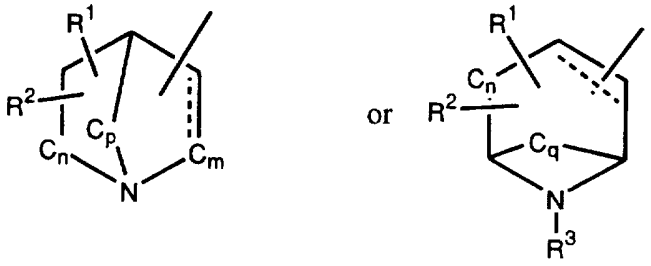
A composition for treating pain comprising an analgesic dose of a compound selected from the group consisting of Formula I



I

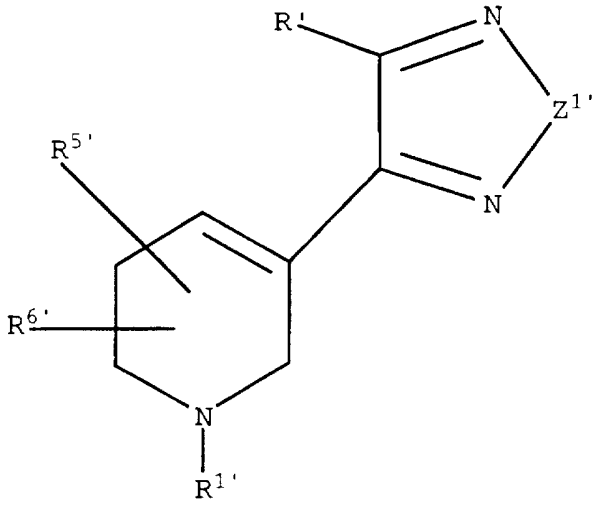
wherein
X is oxygen or sulphur;
R is hydrogen, amino, halogen, -CHO, $-NO_2$, $-OR^4$, $-SR^4$, $-SOR^4$, $-SO_2R^4$, C_{3-7}-cycloalkyl, C_{4-8}-(cycloalkylalkyl), -Z-C_{3-7}-cycloalkyl, and -Z-C_{4-8}-(cycloalkylalkyl) wherein R^4 is straight or branched C_{1-15}-alkyl, straight or branched C_{2-15}-alkenyl, straight or branched C_{2-15}-alkynyl, each of which is optionally substituted with one or more halogens, $-CF_3$, -CN, phenyl or phenoxy wherein phenyl or phenoxy is optionally substituted with halogen, -CN, C_{1-4}-alkyl, C_{1-4}-alkoxy, $-OCF_3$, $-CONH_2$ or $-CSNH_2$; or R is phenyl or benzyloxycarbonyl, each of which is optionally substituted with halogen, -CN, C_{1-4}-alkyl, C_{1-4}-alkoxy, $-OCF_3$, $-CONH_2$ or $-CSNH_2$; or R is $-OR^5Y$, $-SR^5Y$, $-OR^5ZY$, $-SR^5ZY$, $-O-R^4-Z-R^5$ or $-S-R^4-Z-R^5$ wherein Z is oxygen or sulphur, R^5 is straight or branched C_{1-15}-alkynyl, and Y is a 5 or 6 membered heterocyclic group containing one to four

N, O or S atom(s) or a combination thereof, which heterocyclic group is optionally substituted at carbon or nitrogen atom(s) with straight or branched C_{1-6}-alkyl, phenyl or benzyl, or which heterocyclic group is optionally fused with a phenyl group; and G is selected from one of the following azabicyclic rings



wherein the thiadiazole or oxadiazole ring can be attached at any carbon atom of the azabicyclic ring; R^1 and R^2 may be present at any position, including the point of attachment of the thiadiazole or oxadiazole ring, and independently are hydrogen, straight or branched C_{1-5}-alkyl, straight or branched C_{2-5} alkenyl, straight or branched C_{2-5}-alkynyl, straight or branched C_{1-10}-alkoxy, straight or branched C_{1-5}-alkyl substituted with -OH, OR^4, halogen, $-NH_2$ or carboxy; R^3 is H, straight or branched C_{1-5}-alkyl, straight or branched C_{2-5}-alkenyl or straight or branched C_{2-5}-alkynyl; n is 0, 1 or 2; m is 0, 1 or 2; p is 0, 1 or 2; q is 1 or 2; and --- is a single or double bond; and

Formula II



(II)

wherein

$Z^{1'}$ is oxygen or sulphur;

R' is hydrogen, halogen, amino, $-NHCO-R^{2'}$, C_{3-7}-cycloalkyl, C_{4-10}-(cycloalkylalkyl), $-Z^{2'}-C_{3-7}$-cycloalkyl optionally substituted with C_{1-6}-alkyl, $-Z^{2'}-C_{4-10}$-(cycloalkylalkyl), $-Z^{2'}-C_{4-10}$-(cycloalkenylalkyl), $-Z^{2'}-C_{4-10}$-(methylenecycloalkyl-alkyl), $-NH-R^{2'}$, $-NR^{2'}R^{3'}$, $-NH-OR^{2'}$, phenyl, phenoxy, benzoyl, benzyloxycarbonyl, tetrahydronaphtyl, indenyl, X', $R^{2'}$, $-Z^{2'}R^{2'}$, $-SOR^{2'}$, $-SO_2R^{2'}$, $-Z^{2'}-R^{2'}-Z^{3'}-R^{3'}$, $-Z^{2'}-R^{2'}-Z^{3'}-R^{3'}-Z^{4'}-R^{4'}$, $-Z^{2'}-R^{2'}CO-R^{3'}$, $-Z^{2'}-R^{2'}-CO_2-R^{3'}$, $Z^{2'}-R^{2'}-O_2C-R^{3'}$, $-Z^{2'}-R^{2'}-CONH-R^{3'}$, $-Z^{2'}-R^{2'}-NHCOR^{3'}$, $-Z^{2'}-R^{2'}-X'$, $-Z^{2'}-R^{2'}-Z^{3'}-X'$, wherein $Z^{2'}$, $Z^{3'}$, and $Z^{4'}$ independently are oxygen or sulphur, and $R^{2'}$, $R^{3'}$ and $R^{4'}$ independently are straight or branched C_{1-15}-alkyl, straight or branched C_{2-15}-alkenyl, straight or branched C_{2-15}-alkynyl, each of which is optionally substituted with halogen(s), -OH, -CN, $-CF_3$, -SH, -COOH, $-NH-R^{2'}$, $-NR^{2'}R^{3'}$, C_{1-6}alkyl ester, one or two phenyl, phenoxy, benzoyl or benzyloxycarbonyl wherein each aromatic group is optionally substituted with one or two halogen, -CN, C_{1-4}-alkyl or

C_{1-4}-alkoxy, and X' is a 5 or 6 membered heterocyclic group containing one to four N, O or S atom(s) or a combination thereof, which heterocyclic group is optionally substituted at carbon or nitrogen atom(s) with straight or branched C_{1-6}-alkyl, phenyl, benzyl or pyridine, or a carbon atom in the heterocyclic group together with an oxygen atom form a carbonyl group, or which heterocyclic group is optionally fused with a phenyl group; and

$R^{5'}$ and $R^{6'}$ may be present at any position, including the point of attachment of the thiadiazole or oxadiazole ring, and independently are hydrogen, straight or branched C_{1-5}-alkyl, straight or branched C_{2-5}-alkenyl, straight or branched C_{2-5}-alkynyl, straight or branched C_{1-10}-alkoxy, straight or branched C_{1-5}-alkyl substituted with -OH, -OH, halogen, $-NH_2$ or carboxy; $R^{1'}$ is hydrogen, straight or branched C_{1-5}-alkyl, straight or branched C_{2-5}-alkenyl or straight or branched C_{2-5}-alkynyl; or

a pharmaceutically acceptable salt or solvate thereof; and acetaminophen in a weight ratio of Compound to acetaminophen of from about 1 to about 1000.

A preferred composition is a weight ratio of Compound to acetaminophen of from about 1 to about 100. An especially preferred ratio is from about 1 to about 30. A further preferred ratio may be from about 1 to about 10. A final preferred ratio may be from about 1 to about 3.

The invention further provides a composition for treating pain comprising a Compound selected from the group consisting of Formula I and Formula II or a pharmaceutically acceptable salt or solvate thereof and a acetaminophen in a weight ratio of Compound to acetaminophen of from about 1 to about 1000.

The present invention provides a composition for treating pain comprising a Compound selected from the group consisting of Formula I and Formula II; or

a pharmaceutically acceptable salt thereof;

and a central alpha-adrenergic active compound in a weight ratio of Compound to central alpha-adrenergic active compound of from about 1 to about 1000.

A preferred composition is a weight ratio of Compound to central alpha-adrenergic active compound of from about 1 to about 100. An especially preferred ratio is from about 1 to about 30. A further preferred ratio may be from about 1 to about 10.

A particularly preferred central alpha-adrenergic active compound is Clonidine or a pharmaceutically acceptable salt thereof. The chemical name for clonidine is 2-(2,6-dichlorophenylamino)-2-imidazoline.

The invention further provides a method for treating pain comprising administering an effective amount of a compound selected from the group consisting of Formula I and Formula II; or a pharmaceutically acceptable salt or solvate thereof; and a central alpha-adrenergic active compound in a weight ratio of Compound to central alpha-adrenergic active compound of from about 1 to about 1000.

The present invention provides a method for treating pain comprising administering to a patient in need thereof, an anagesic composition comprising a Compound selected from the group consisting of Formula I and Formula II; or a pharmaceutically acceptable salt or solvate thereof; and one or more opioid compounds in a weight ratio of Compound to an opioid active compound of from about 1 to about 1000.

A preferred composition is a weight ratio of Compound to opioid compound of from about 1 to about 100. An especially preferred ratio is from about 1 to about 30. A further preferred ratio may be from about 1 to about 10.

Preferred an opioid compounds are morphine, codeine, meperidine, methadone, propoxyphene, levorphanol, hydromorphone, oxymorphone, oxycodone, brompton's cocktail,

naloxone, naltrexone, pentazocine, butorphanol, nabuphine, and buprenorphine.

Especially preferred opioid compounds are selected from the group consisting of hydromorphone, hydrocodone, meperidone, buprenorphine, butorphenol, nalbuphine, pentazocine, oxymorphine, oxycodone, levorphanol, fentanyl, and alphaprodine.

Particularly preferred opioid compounds are selected from the group consisting of propoxyphene, methadone, morphine, hydrocodone, hydromorphine, and codeine. The especially particularly preferred opioid compounds are selected from morphine and codeine.

The invention further provides a composition for treating pain comprising a Compound selected from the group consisting of Formula I and Formula II; or a pharmaceutically acceptable salt or solvate thereof; and a one or more opioid compounds in a weight ratio of Compound to opioid compound of from about 1 to about 1000.

The term "NSAIDS", as used herein, represents a nonsteroidal anti-inflammatory drug which can be identified as such by the skilled artisan. For example, the Merck Manual, 16th Edition, Merck Research Laboratories (1990) pp 1308 - 1309 provide well known examples of NSAIDS. The term is intended to include, but is not limited to salicylates such as aspirin, indomethacin, ibuprofen, naproxen, fenoprofen, tolmetin, sulindac, meclofenamate, keoprofen, piroxicam, flurbiprofen, and diclofenac. Especially preferred NSAIDS include aspirin, ibuprofen, and naproxen. Alternative preferred NSAIDS are indomethacin, ibuprofen, naproxen, fenoprofen, tolmetin, sulindac, meclofenamate, keoprofen, piroxicam, flurbiprofen, and diclofenac. Particularly preferred NSAIDS include aspirin and ibuprofen. The salicylates may include acetylsalicylic acid, sodium acetylsalicylic acid, calcium acetylsalicylic acid, salicylic

acid, and sodium salicylate. An especially preferred NSAID is ibuprofen.

The term "acetaminophen", as used herein, shall have the art accepted meaning and refers to N-(4-Hydroxyphenyl)acetamide and 4'-hydroxyacetanilide. The compound is claimed in U.S. Patent No. 2,998,450 and is known to the skilled artisan.

The term "central alpha-adrenergic active compounds", as used herein, represents a compound having central alpha-adrenergic receptor activity. The most preferred central alpha-adrenergic active compound is clonidine or a pharmaceutically acceptable salt thereof having the chemical name: 2-(2,6-dichlorophenylamino)-2-imidazoline.

Clonidine is known to be useful for treating hypertension. *see* Physicians' Desk Reference, 45th Ed. (1991) p. 673.

The term "opioid", as used herein, represents opioid analgesics and antagonists including natural opioid analgesics, synthetic opioid analgesics, opioid antagonists and opioid agonist-antagonists. Preferred an opioid compounds are selected from the group consisting of morphine, codeine, meperidine, methadone, propoxyphene, levorphanol, hydromorphone, oxymorphone, oxycodone, brompton's cocktail, naloxone, naltrexone, pentazocine, butorphanol, nabuphine, and buprenorphine. More preferred opioid compounds are selected from the group consisting of codeine, nabuphine, naloxone, and naltrexone.

Preferred an opioid compounds are morphine, codeine, meperidine, methadone, propoxyphene, levorphanol, hydromorphone, oxymorphone, oxycodone, brompton's cocktail, naloxone, naltrexone, pentazocine, butorphanol, nabuphine, and buprenorphine.

Especially preferred opioid compounds are selected from the group consisting of hydromorphone, hydrocodone, meperidone, buprenorphine, butorphenol,

nalbuphine, pentazocine, oxymorphine, oxycodone, levorphanol, fentanyl, and alphaprodine.

Particularly preferred opioid compounds are selected from the group consisting of propoxyphene, methadone, morphine, hydrocodone, hydromorphine, and codeine. The especially particularly preferred opioid compounds are selected from morphine and codeine.

As used herein, the phrase "one or more" most preferredly refers to one; however, two, three, or more may be used.

We have discovered that a group of compounds having muscarinic cholinergic activity can be particular useful for treating pain when used in combination with non-steroidal antiinflammatory agents (NSAIDS). More specifically, the invention provides a method of treating pain in humans using a specified azacyclic, azabicyclic or tetrahydropyridine compounds (collectively referred to herein as "selected muscarinic compounds") in combination with a NSAIDS to provide a synergistic effect. The Selected Muscarinic Compounds are believed to be active based on activity at muscarinic cholinergic receptors; however, the present invention is in no way limited by the mechanism of action.

There are many NSAIDS known in the literature and to the skilled artisan.

We have discovered that a group of compounds having muscarinic cholinergic activity can be particular useful for treating pain when used in combination with acetaminophen. More specifically, the invention provides a method of treating pain in humans using a specified Selected Muscarinic Compounds in combination with acetaminophen to provide a synergistic effect.

Further, we have discovered that a group of compounds having muscarinic cholinergic activity can be particularly useful for treating pain when used in combination with central alpha-adrenergic active compounds. More specifically, the invention provides a method of

treating pain in humans using Selected Muscarinic Compounds in combination with a central alpha-adrenergic active compound to provide a synergistic effect.

Oral combinations of aspirin with codeine or other narcotic analgesics are known to provide additive analgesic effects in man. The Pharmacological Basis of Therapeutics, 5th edition, Macmillan Publishing Co., 1975, pp 325-358.

In the composition of this invention a compound of Formula I or Formula II or a pharmaceutically acceptable salt thereof and NSAIDS compound are combined in a weight ratio of Compound to NSAIDS of from about 1 to about 1000.

A preferred composition is a weight ratio of Compound to NSAIDS of from about 1 to about 100. An especially preferred ratio is from about 1 to about 30. A further preferred ratio may be from about 1 to about 10. A final preferred ratio may be from about 1 to about 3.

In the composition of this invention a Compound of Formula or Formula II and acetaminophen are combined in a weight ratio of Formula I or Formula II to acetaminophen of from about 1 to about 1000.

A preferred composition is a weight ratio of Formula I or Formula II to acetaminophen of from about 1 to about 100. An especially preferred ratio is from about 1 to about 30. A further preferred ratio may be from about 1 to about 10. A final preferred ratio may be from about 1 to about 3.

The compounds of Formula I and Formula II are effective over a wide dosage range; however, it is desirable to administer a dosage that is as low as possible. The amount of NSAIDS present in the composition is adjusted as described above in ratio to the Formula I or Formula II dosage. The amount of acetaminophen present in the composition is adjusted as described above in ratio to the Formula I or Formula II dosage. For example, dosages per day of the Formula II compounds will normally fall

within the range of about 0.005 to about 100 mg/kg of body weight and the acetaminophen in the composition would be from 3 to 1000 times this amount. For example, dosages per day of the Formula I compounds will normally fall within the range of about 0.005 to about 100 mg/kg of body weight and the NSAIDS in the composition would be from 3 to 1000 times this amount.

In the composition of this invention a Compound selected from the group consisting of Formula I and Formula II; or a pharmaceutically acceptable salt thereof and one or more opioid compounds are combined in a weight ratio of Compound to opioid compound of from about 1 to about 1000.

A preferred composition is a weight ratio of Compound to opioid compound of from about 1 to about 100. An especially preferred ratio is from about 1 to about 30. A further preferred ratio may be from about 1 to about 10. A final preferred ratio may be from about 1 to about 3.

The Compounds are effective over a wide dosage range; however, it is desirable to administer a dosage that is as low as possible. The amount of opioid compound present in the composition is adjusted as described above in ratio to the Compound dosage. For example, dosages per day of the Formula I compounds will normally fall within the range of about 0.005 to about 100 mg/kg of body weight and the opioid compound in the composition would be from 3 to 1000 times this amount.

However, for each composition claimed herein, it will be understood that the amount of the Compound actually administered will be determined by a physician, in the light of the relevant circumstances including the condition to be treated, the choice of Compound to be administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the chosen route of administration, and therefore the above dosage ranges are not intended to limit the scope of the invention in any way. While the present compounds are preferably administered orally to humans susceptible to or suffering from pain, the

compounds may also be administered by a variety of other routes such as the transdermal, parenterally, subcutaneous, intranasal, intramuscular and intravenous routes. Such formulations may be designed to provide delayed or controlled release using formulation techniques which are known in the art.

Transdermal formulations containing the composition claimed herein most preferably deliver the active substances in an effective amount for from about three days to about seven days. However, for chronic pain such as arthritis or cancer pain, a transdermal delivery of from about three days to up to about two weeks is desirable. Alternatively, it may be preferred to deliver the claimed compositions transdermally in an effective amount for from about one day to about three days.

As used herein the term "treating" includes prophylaxis of a physical and/or mental condition or amelioration or elimination of the developed physical and/or mental condition once it has been established or alleviation of the characteristic symptoms of such condition.

The compounds of Formula I and Formula II employed in the invention are not believed to act via the GABA/benzodiazepine, 5HT1A, or D1 receptor systems in humans. Rather, the activity of the present Formula I and Formula II compounds as analgesic agents is believed to be based upon modulation of muscarinic cholinergic receptors. However, the mechanism by which the present compounds function is not necessarily the mechanism stated *supra.*, and the present invention is not limited by any mode of operation.

The compounds of Formula I and Formula II are described in Sauerberg *et al.* in U.S. Patents 5,043,345, 5,041,455 and 5,260,314 (collectively herein "Sauerberg Patents"), each of which is herein incorporated by reference. The Sauerberg Patents teach the artisan how to make the compounds of Formula I and Formula II used herein for the claimed analgesic composition.

Examples of pharmaceutically acceptable salts include inorganic and organic acid addition salts such as hydrochloride, hydrobromide, sulphate, phosphate, acetate, fumarate, maleate, citrate, lactate, tartrate, oxalate, or similar pharmaceutically-acceptable inorganic or organic acid addition salts, and include the pharmaceutically acceptable salts listed in Journal of Pharmaceutical Science, **66**, 2 (1977) which are known to the skilled artisan. The compounds of this invention may form solvates with standard low molecular weight solvents using methods known to the skilled artisan.

The route of administration may be any route, which effectively transports the active compound to the appropriate or desired site of action, such as oral or parenteral e.g. rectal, transdermal, depot, subcutaneous, intravenous, intramuscular or intranasal, the oral route being preferred.

The dosage administered will, of course, vary depending on known factors such as the pharmacodynamic characteristics of the particular agent, and it smode and route of administration; age, health, and weight of the recipient; nature and extent of the symptoms, kind of concurrent treatment, frequency of treatment, and the effect desired. Usually, the daily dosage can be such that the active ingredient is administered at a daily dosage of from about 0.2 mg/kg to about 100 mg/kg of body weight Formula I or Formula II compound and from about 0.6 to about 200 mg/kg of NSAIDS.

Compositions suitable for internal administration contain from about one half (0.5) milligrams to about 600 milligrams of active ingredient per unit. In these pharmaceutical compositions, the active ingredient will ordinarily be present in an amount of from about 0.5% to about 95% by weight based on the total weight of the composition.

For compositions containing acetaminophen, usually, the daily dosage can be such that the active ingredient is administered at a daily dosage of from about 0.2 mg/kg to about 100 mg/kg of body weight Formula II compound and from about 0.6 to about 200 mg/kg of acetaminophen.

Typical compositions include a compound of Formula I or Formula II or a pharmaceutically acceptable acid addition salt thereof and one or more NSAIDSs, associated with a pharmaceutically acceptable excipient which may be a carrier, or a diluent or be diluted by a carrier, or enclosed within a carrier which can be in the form of a capsule, sachet, paper, or other container. In making the compositions, conventional techniques for the preparation of pharmaceutical compositions may be used. For example, the active compound will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a ampoule, capsule, sachet, paper, or other container. When the carrier serves as a diluent, it may be solid, semi-solid, or liquid material which acts as a vehicle, excipient, or medium for the active compound. The active compound can be adsorbed on a granular solid container for example in a sachet. Some examples of suitable carriers are water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, gelatine, lactose, amylose, magnesium stearate, talc, silicic acid, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, hydroxymethylcellulose and polyvinylpyrrolidone. The formulations may also include wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents, or flavoring agents. The formulations of the invention may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

Typical compositions include a compound of Formula I or Formula II or a pharmaceutically acceptable acid addition salt thereof and acetaminophen, associated with a pharmaceutically acceptable excipient which may be a carrier, or a diluent or be diluted by a carrier, or enclosed within a carrier which can be in the form of a capsule, sachet, paper, or other container. In making the compositions, conventional techniques for the preparation of pharmaceutical compositions may be used, as described above.

A preferred composition is a weight ratio of Compound to central alpha-adrenergic active compound of from about 1 to about 100. An especially preferred ratio is from about 1 to about 30. A further preferred ratio may be from about 1 to about 10. A final preferred ratio may be from about 1 to about 3.

The compounds of Formula I and Formula II are effective over a wide dosage range; however, it is desirable to administer a dosage that is as low as possible. The amount of central alpha-adrenergic active compound present in the composition is adjusted as described above in ratio to the Formula I or Formula II dosage. For example, dosages per day of the Formula I compounds will normally fall within the range of about 0.005 to about 100 mg/kg of body weight and the central alpha-adrenergic active compound in the composition would be from 3 to 1000 times this amount.

Usually, the daily dosage can be such that the active ingredient is administered at a daily dosage of from about 0.2 mg/kg to about 100 mg/kg of body weight Formula I or Formula II compound and from about 0.6 to about 200 mg/kg of central alpha-adrenergic active compound.

Typical compositions include a compound of formula I or Formula II or a pharmaceutically acceptable acid addition salt thereof; and one or more central alpha-adrenergic active compounds, associated with a pharmaceutically acceptable excipient which may be a

carrier, or a diluent or be diluted by a carrier, or enclosed within a carrier which can be in the form of a capsule, sachet, paper, or other container. In making the compositions, conventional techniques for the preparation of pharmaceutical compositions may be used.

The pharmaceutical preparations can be sterilized and mixed, if desired, with auxiliary agents, emulsifiers, salt for influencing osmotic pressure, buffers and/or coloring substances and the like, which do not deleteriously react with the active compounds.

For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like are particularly suitable for oral application. Preferable carriers for tablets, dragees, or capsules include lactose, corn starch, and/or potato starch. A syrup or elixir can be used in cases where a sweetened vehicle can be employed.

Generally, the Formula I or Formula II compounds are dispensed in unit form comprising from about 0.1 to about 100 mg in a pharmaceutically acceptable carrier per unit dosage.

The compositions of this invention may be suitable for administration to an animal. Such animals include both domestic animals, for example livestock, laboratory animals, and household pets, and non-domestic animals such as wildlife. More preferredly, the animal is a vertebrate. Most preferredly, a compound of this invention shall be administered to a mammal. It is especially preferred that the animal is a domestic mammal or a human. The most preferred mammal is a human. For

such purposes, a compound of this invention may be administered as a feed additive.

The following models and assays are useful for illustrating the effectiveness of the compositions claimed herein.

Nociceptive pain model:

Acetic acid-induced writhing: A standard procedure for detecting and comparing the analgesic activity of different classes of analgesic drugs for which there is a good correlation with human analgesic activity is the prevention of acetic acid-induced writhing in mice. Mice, are subcutaneously administered various doses of the claimed composition and are injected injected intraperitoneally with acetic acid (0.5% solution, 10 ml/kg) 5 min prior to a designated observation period. For scoring purposes a "writhe" is indicated by whole body stretching or contraction of the abdomen during the observation period beginning 5 min after receiving the acetic acid. Inhibition of writhing behavior is demonstrative of analgesic activity.

See, Haubrich, D.R., Ward, S.J., Baizman, E., Bell, M.R., Bradford, J., Ferrari, R., Miller, M., Perrone, M., Pierson, A.K., Saelens, J.K. and Luttinger, D.: Pharmacology of pravadoline: a new analgesic agent. The Journal of Pharmacology and Experimental Therapeutics 255 (1990) 511-522.

Neuropathic pain model:

Sciatic nerve ligation model: Rats are anesthetized and a nerve ligation procedure performed. The common sciatic nerve is exposed and 4 ligatures tied loosely around it with about 1 mm spacing. One day to 10 weeks after surgery, the nociceptive testing is performed. Responses to noxious heat are determined by placing the rats in a chamber with a clear glass floor and aiming at the plantar surface of the affected foot a radiant heat source from beneath the floor. Increased latency to withdraw the hindpaw is demonstrative of analgesic

activity. Responses to normally innocuous mechanical stimuli is determined by placing the rats in a chamber with a screen floor and stimulating the plantar surface of the hind paw with graduated von Frey hairs which are calibrated by the grams of force required to bend them. Rats with sciatic nerve ligation respond to lower grams of mechanical stimulation by reflexive withdrawal of the foot than unoperated rats. This response to stimuli which are normally innocuous is termed allodynia. Increases in the grams of mechanical force required to produce foot withdrawal is demonstrative of antiallodynic activity.

See, Bennett, G.J. and Xie, Y.-K. A peripheral mononeuropathy in rat that produces disorders of pain sensation like those seen in man. Pain 33 (1988) 87-107. See also, Lee, Y.-W., Chaplan, S.R. and Yaksh, T.L.: Systemic and supraspinal, but not spinal, opiates suppress allodynia in a rat neuropathic pain model. Neuroci Lett 186 (1995) 111-114.

Formalin paw test: Rats are anesthetized and when there is a loss of spontaneous movement the rats are injected subcutaneously in the dorsal surface of the hindpaw with 50 ul of 5% formalin solution using a 30 gauge needle. Rats are then individually placed in an open Plexiglas chamber for observation, and within a maximum interval of 1 to 2 min, the animal displays recovery from anesthesia with spontaneous activity and normal motor function. Pain behavior is quantified by periodically counting the incidents of spontaneous flinching/shaking of the injected paw. The flinches are counted for 1-min periods at 1- to 2-, 5- to 6- and 5min intervals during the interval from 10 to 60 min. Inhibition of the pain behavior is demonstrative of an analgesic activity.

See, Malmberg, A.B. and Yaksh, T.L.: Antinociceptive actions of spinal nonsteroidal anti-inflammatory agents on the formalin test in the rat. The Journal of Pharmacology and Experimental Therapeutics 263 (1992) 136-146.

Inflammatory pain model:

Brewer's yeast-induced hyperalgesia (Randall-Selitto Test): To assess nociceptive threshold in rats, ascending pressure is applied gradually to the paw with a motor driven weight of a Ugo Basile Analgesy Meter. Rats respond to the pressure by either pulling free of the device, struggling or vocalizing. Hyperalgesia is induced by a hind paw subplantar injection of 0.1 ml of 1% suspension of brewer's yeast in 0.9% saline. The composition of this invention is administered at varying times (0 - 4 hr) after injection of brewer's yeast and pressure threshold for the inflamed paw again determined at varying times. Increases in the pressure which produces a behavioral response is demonstrative of analgesic activity.

See, Haubrich, D.R., Ward, S.J., Baizman, E., Bell, M.R., Bradford, J., Ferrari, R., Miller, M., Perrone, M., Pierson, A.K., Saelens, J.K. and Luttinger, D.: Pharmacology of pravadoline: a new analgesic agent. The Journal of Pharmacology and Experimental Therapeutics 255 (1990) 511-522.

Utility Test Methods

The unexpectedly enhanced analgesic activity of the composition of the invention is evidenced by tests intially conducted on mice. Male mice are fasted for 16-22 hours and weighed. Mice weighing from about 18-22 grams at the time of testing are used for the following studies. All mice are dosed sequentially by the oral route with suspensions of a composition of this invention. Doses are coded using a code unknown to the observer.

A stock suspension of the test composition is prepared by mixing the active ingredients with about 40 mL of an aqueous vehicle containing about 2% Tween 80 (R), a pharmacological dispersant and containing 100% polysorbate 80, and 1% by weight Methocel (R) MC powder, and containing 100% methylcellulose, in distilled water. The mixture may be sonicated for about 10 to about 15 seconds using an

ultrasound sytem. All dosing suspensions are prepared by dilution of the stock suspension with Methocel/Tween 80. All suspensions are used within two hours of preparation.

Mouse Writhing Test

An accepted standard for detecting and comparing the analgesic activity of different classes of analgesic compounds for which there is a good correlation with human analgesic activity is the prevention of phenyl-p-benzoquinone induced writhing in mice. [H. Blumberg et al. Proc. Soc. Exp. biol. Med., 118, 763-766 (1965)].

Mice, treated with various doses of compound of Formula I or Formula II, composition or vehicle are injected intraperitoneally with a standard challenge dose of phenyl-p-benzoquinone 5 minutes prior to a designated observation period. The pheyl-p-benzoquinone is prepared as about 0.1 mg/ml solution in about 5% by volume of ethanol in water. The writhing dose is 1.25 mg/kg injected at a volume of about 0.25ml/10g. For scoring purposes a "writhe" is indicated by whole body stretching or contracting of the abdomen during an observation period beginning about five minutes after the phenyl-p-benzoquinone dose.

All ED50 values and their 95% confidence limits are determined using accepted numerical methods. For example, *see* W.F. Thompson, Bacteriological Rev., **11**, 115-145 (1947). The interaction of the dosages on phenyl-p-benzoquinone induced writhing in mice is demonstrated by the Loewe isobologram (S. Loewe, Pharm. Rev. 9, 237-242 (1957).

The solid line connecting the ED50 dosages of Formula I or Formula II (alone) and classical analgesic as claimed herein (alone) represents the "ED50 addition line" which indicates the expected location of the ED50's for Formula I or Formula II and classical analagesic combinations if simple additivity were to describe their combined effects. The 95% confidence range for the ED50

addition line is shown by the area between the broken lines above and below the ED50 addition line.

According to Loewe's isobolic theory, if the analgesic effects are simply additive to one another, then the expected location of the ED50's of the Formula I or Formula II and classical analgesic component of each fixed dosage ratio would be contained within or overlap the region of the ED50 addition line. Combination ED50's located significantly below the ED50 addition line would represent unexpectedly enhanced analgesic activity and combination ED50's located above the line would represent unexpected diminished analgesic effect.

One method to establish the significance of such unexpected enhanced or diminished activity is to calculate the best fitting polynomial regression line to the observed ED50's using standard mathematical techniques.

Such experiments demonstrate that compositions comprised of a compound of Formula I or Formula II and one or more classical analgesics provides a statistically significant synergistic analgesic effect.

Preferred compounds of Formula I for use in the analesic compositions are selected from the following:

3-CHLORO-3-(3-CHLORO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[2.2.2]OCTANE;

3-(3-CHLORO-1,2,5-THIADIAZOL-4-YL)-3-HYDROXY-1-AZABICYCLO[2.2.2]OCTANE;

3-METHOXY-3-(3-METHOXY-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[2.2.2]OCTANE;

3-(3-METHOXY-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[2.2.2]OCT-2-ENE;

3-(3-HEXYLOXY-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[2.2.2]OCT-2-ENE;

3-HEXYLOXY-3-(3-HEXYLOXY-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO-[2.2.2]OCTANE;

3-(3-HEXYLOXY-1,2,5-THIADIAZOL-4-YL)-3-HYDROXY-1-AZABICYCLO[2.2.2]OCTANE;

3-(3-CHLORO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[2.2.2]OCTANE;

3-(3-ETHOXY-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCL0[2.2.2]OCTANE;

3-(3-PROPOXY-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCL0[2.2.2]OCTANE;

3-(3-BUTOXY-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCL0[2.2.2]OCTANE;

3-(3-PENTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCL0-[2.2.2]OCTANE;

3-(3-ETHOXY-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCL0[2.2.2]OCTANE;

3-(3-HEXYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCL0[2.2.2]OCTANE;

3-(3-(3-PHENYLPROPYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCL0[2.2.2]OCTANE;

3-(3-HEXYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCL0[2.2.2]OCTANE;

3-(3-(4-CYANOBENZYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCL0[2.2.2]OCTANE;

EXO-6-(3-CHLORO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[3.2.1]OCTANE;

ENDO-6-(3-CHLORO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[3.2.1]OCTANE;

ENDO-6-(3-HEXYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[3.2.1]OCTANE;

ENDO-6-(3-(5-HEXENYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[3.2.1]OCTANE;

ENDO-6-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[3.2.1]OCTANE;

ENDO-6-(3-PENTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[3.2.1]OCTANE;

ENDO-6-(3-ETHYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[3.2.1]OCTANE;

ENDO-6-(3-(3-PHENYLPROPYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[3.2.1]OCTANE;

Particularly preferred compounds of Formula I include:

3-(3-HEXYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCL0[2.2.2]OCTANE;

3-(3-(3-PHENYLPROPYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCL0[2.2.2]OCTANE;

3-(3-CHLORO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO(2.2.2)OCTANE

(EXO(+-))-6-(3-CHLORO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO-(3.2.1)OCTANE

3-(3-ETHOXY-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO(2.2.2)OCTANE

3-(3-PROPOXY-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO(2.2.2)OCTANE

3-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO(2.2.2)OCTANE

3-(3-PENTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO(2.2.2)OCTANE

ENDO(+-)-6-(3-ETHYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO-(3.2.1)OCTANE

ENDO(+-)-6-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO-(3.2.1)OCTANE

EXO(+-)-6-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO-(3.2.1)OCTANE

3-(3-(BUTOXY-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO(2.2.2)OCTANE

EXO-3-(3-PROPYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO-(2.2.1)HEPTANE

EXO-3-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO(2.2.1)-HEPTANE

ENDO-3-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO(2.2.1)-HEPTANE

3-(3-ETHYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO(2.2.2)OCTANE

3-(3-PROPYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO(2.2.2)OCTANE

4-CHLORO-3-(3-PROPYLOXY-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO-(3.3.1)NON-2-ENE

3-(3-ISOPENTYLOXY-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO(2.2.2)-

OCTANE

ENDO(+-)3-(3-PROPYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO-(3.2.1)OCTANE

EXO(+-)3-(3-PROPYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO-(3.2.1)OCTANE

-)3-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO(2.2.2)-OCTANE

(+)3-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO(2.2.2)-OCTANE

3-(3-CHLORO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO(2.2.2)OCTANE

(EXO(+-))-6-(3-CHLORO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO-(3.2.1)OCTANE

3-(3-ETHOXY-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO(2.2.2)OCTANE

3-(3-PROPOXY-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO(2.2.2)OCTANE

3-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO(2.2.2)OCTANE

3-(3-PENTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO(2.2.2)OCTANE

ENDO(+-)-6-(3-ETHYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO-(3.2.1)OCTANE

ENDO(+-)-6-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO-(3.2.1)OCTANE

EXO(+-)-6-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO-(3.2.1)OCTANE

3-(3-(BUTOXY-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO(2.2.2)OCTANE

EXO-3-(3-PROPYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO(2.2.1)-HEPTANE

3-(3-ETHYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO(2.2.2)OCTANE

EXO-3-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO(2.2.1)-HEPTANE

ENDO-3-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO(2.2.1)-HEPTANE

3-(3-ETHYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO(2.2.2)OCTANE

3-(3-PROPYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO(2.2.2)OCTANE

4-CHLORO-3-(3-PROPYLOXY-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO-(3.3.1)NON-2-ENE

3-(3-ISOPENTYLOXY-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO-(2.2.2)OCTANE

ENDO(+-)3-(3-PROPYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO-(3.2.1)OCTANE

BIS-1,4-(3-(1-METHYL-1,2,5,6-TETRAHYDROPYRIDIN-3-YL)-1,2,5-THIADIAZOL-4-YL)BUTANEDITHIOL

EXO(+-)3-(3-PROPYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO-(3.2.1)OCTANE

(-)3-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO-(2.2.2)OCTANE

(+)3-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO-(2.2.2.)OCTANE; AND
a pharmaceutically acceptable salt or solvate thereof.

More preferred compounds include the following:
3-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO(2.2.2)OCTANE

3-(3-PENTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO(2.2.2)OCTANE

ENDO(±)-6-(3-ETHYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO-(3.2.1)OCTANE

ENDO(±)-6-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO-(3.2.1)OCTANE

EXO(±)-6-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO-(3.2.1)OCTANE

3-(3-PROPYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO(2.2.2)OCTANE; or
a pharmaceutically acceptable salt or solvate thereof.

The most especially preferred compound of Formula I is 3-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCL0[2.2.2]OCTANE; or
a pharmaceutically acceptable salt or solvate thereof.

Preferred compounds of Formula II for the analgesic composition are selected from the following:
3-(3-METHOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-ETHOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-PROPOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-BUTOXY-1,2,5-THIADIAZOL-4-YL)1,2,5,6-TETTRAHYDRO-1-METHYLPYRIDINE

3-(3-ISOPROPOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-CYCLOPROPYLMETHOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-PENTOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-ISOBUTOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3-BUTENOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(BUT-2-YNOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3-METHYLBUTOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-HEXYLOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(PROP-2-YNOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-BENZYLOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-CHLORO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-CHLORO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE

3-(3-BUTOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE

3-(3-ETHOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-ETHYLPYRIDINE

3-(3-CHLORO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-ETHYLPYRIDINE

3-(3-METHOXYETHOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-HEPTYLOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3-PENTYNYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(4-PENTENYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(2-PROPENYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-OCTYLOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3-HEXYNYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3-BUTENYL-2-OXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYL-PYRIDINE

3-(3-(4-HEXENYLOXY(-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

TRANS-3-(3-(3-HEXENYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

CIS-3-(3-(2-PENTENYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

CIS-3-(3-(2-HEXENYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(5-HEXENYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

CIS-3-(3-(3-HEXENYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,4,5-TETRAHYDRO-1-METHYLPYRIDINE

TRANS-3-(3-(2-HEXENYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(4-METHYLPIPERIDINO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-MORPHOLINO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-DIMETHYLAMINO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-HEXYLAMINO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-HEXYLOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-DEUTEROMETHYLPYRIDINE

1,2,5,6-TETRAHYDRO-3-(3-HEXYLOXY-1,2,5-THIADIAZOL-4-YL)PYRIDINE

3-(3-(2-(2-METHOXYETHOXY)-ETHOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3-ETHOXY-1-PROPOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6,-TETRAHYDRO-1-METHYLPYRIDINE

3-(2-ETHOXYETHOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(2-BUTOXYETHOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(2-(2-BUTOXYETHOXY)-ETHOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(2-(2-ETHOXYETHOXY)-ETHOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-METHYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-PENTYL-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-PROPYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-HEXYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-PENTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-ETHYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-OCTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-PROPYL-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-HEPTYL-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(5-HEXENYL)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-OCTYL-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYPYRIDINE

3-(3-(2-METHYL)-BUTYL-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-METHYLCYCLOPROPYL-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-CYCLOPENTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(1-ETHYLTHIO-2-METHOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3-CHLORO-1-PROPYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(2-METHOXYETHOXY)-ETHYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3-CYANO-1-PROPYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-BENZYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(2-ETHOXY-1-ETHYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(4-PENTYNYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(2-(2-ETHOXYMETHOXY)-ETHYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(5-CYANO-1-PENTYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3-PHENYL-1-PROPYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(2-PHENOXYETHYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(4-CYANOBUTYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(2-ETHYLBUTYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-CYCLOHEXYLMETHYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(8-HYDROXYOCTYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(7-OCTENYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-CYCLOPROPYLMETHYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3(3-CYCLOPROPYLMETHYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3-BUTENYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(4-PENTENYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(4-ISOHEXYLOXY-1,2,5-THIADIAZOL-3-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

1-METHYL-1,2,5,6-TETRAHYDRO-3-((4-CYCLOPENTYLPROPYL)OXY)-1,2,5-THIADIAZOL-3-YL)PYRIDINE

1-METHYL-1,2,5,6-TETRAHYDRO-3-(4-ISOHEPTYLOXY-1,2,5-THIADIAZOL-3-YL)PYRIDINE

1-METHYL-1,2,5,6-TETRAHYDRO-3-(4((2-CYCLOHEXYLETHYL)OXY)-1,2,5-THIADIAZOL-3-YL)PYRIDINE

1,2,5,6-TETRAHYDRO-1-METHYL-3-(4-(1-METHYLHEXLOXY)-1,2,5-THIADIAZOL-3-YL)PYRIDINE

3-(4-(1-ETHYLPENTYLOXY)-1,2,5-THIADIAZOL-3-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(4-(1-ETHYLBUTOXY)-1,2,5-THIADIAZOL-3-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

1,2,5,6-TETRAHYDRO-1-METHYL-3-(4-(1-METHYLPENTYLOXY)-1,2,5-THIADIAZOL-3-)YL)PYRIDINE

1-METHYL-3-(4-(5-HEXENYLOXY)-1,2,5-THIADIAZOL-3-YL)-1,2,5,6-TETRAHYDROPYRIDINE

1,2,5,6-TETRAHYDRO-1-METHYL-3-(4-(2-METHYLBUTOXY)-1,2,5-THIADIAZOL-3-YL)PYRIDINE

1,2,5,6-TETRAHYDRO-1-METHYL-3-(4-(2-METHYLPENTYLOXY)-1,2,5-THIADIAZOL-3-YL)PYRIDINE

1,2,5,6-TETRAHYDRO-1-METHYL-3-(4-(2,2,2-TRIFLUOROETHOXY)-1,2,5-THIADIAZOL-3-YL)PYRIDINE

1-METHYL-1,2,5,6-TETRAHYDRO-3-(4-(3-METHYLPENTYLOXY)-1,2,5-THIADIAZOL-3-YL)PYRIDINE

3-(3-(3-METHYL-2-BUTENYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDO-1-METHYLPYRIDINE

3-(3-ISOBUTOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

1,2,5,6-TETRAHYDRO-1-METHYL-3-(4-(2-METHYLBUTOXY)-1,2,5-THIADIAZOL-3-YL)PYRIDINE

3-(3-(3-HYDROXYPROPOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

(+-)1,6-DIMETHYL-3-(3-HEXYLOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE

3-(3-(3-PHENYL-ETHYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

BIS-1,4-(3-(1-METHYL-1,2,5,6-TETRAHYDROPYRIDIN-3-YL)-1,2,5-THIADIAZOL-4-YL)BUTANEDITHIOL

3-(3-(4,4,4-TRIFLUOROBUTOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3,3,3-TRIFLUOROPROPYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-PROPYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE

3-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE

3-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1,1-DIMETHYLPYRIDINIUM IODIDE

(+-)1,6-DIMETHYL-3-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE

(+-)1,6-DIMETHYL-3-(3-BUTOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE

3-(3-(3-METHYL-2-BUTENYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDO-1-METHYL PYRIDINE

3-(3-ISOBUTOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

1,2,5,6-TETRAHYDRO-1-METHYL-3-(4-(2-METHYLBUTOXY)-1,2,5-THIADIAZOL-3-YL)PYRIDINE

3-(3-(3-HYDROXYPROPOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

(+-)1,6-DIMETHYL-3-(3-HEXYLOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE

3-(3-(3-PHENYL-ETHYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

BIS-1,4-(3-(1-METHYL-1,2,5,6-TETRAHYDROPYRIDIN-3-YL)-1,2,5-THIADIAZOL-4-YL)BUTANEDITHIOL

3-(3-(4,4,4-TRIFLUOROBUTOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3,3,3-TRIFLUOROPROPYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-PROPYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-PROPYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE

3-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE

3-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1,1-DIMETHYLPYRIDINIUM IODIDE

(+-)1,6-DIMETHYL-3-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE

(+-)1,6-DIMETHYL-3-(3-BUTOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE; or
a pharmaceutically acceptable salt thereof.

Especially preferred compounds include the following:
3-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-METHYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-PENTYL-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-PROPYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-HEXYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-PENTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-ETHYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-OCTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-METHOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-ETHOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-PROPOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-BUTOXY-1,2,5-THIADIAZOL-4-YL)1,2,5,6-TETTRAHYDRO-1-METHYLPYRIDINE

3-(3-ISOPROPOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-CYCLOPROPYLMETHOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-PENTOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-ISOBUTOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3-BUTENOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(BUT-2-YNOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3-METHYLBUTOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-HEXYLOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(PROP-2-YNOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE; or
a pharmaceutically acceptable salt or solvate thereof.

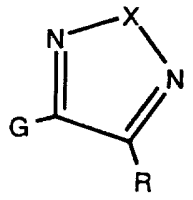
Compound which are particularly preferred include:
3-(3-HEXYLOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE; and

3-(3-HEXYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE; or

a pharmaceutically acceptable salt or solvate thereof.

Claims

1. A composition for treating pain comprising an analgesic dose of a Compound selected from the group consisting of formula I

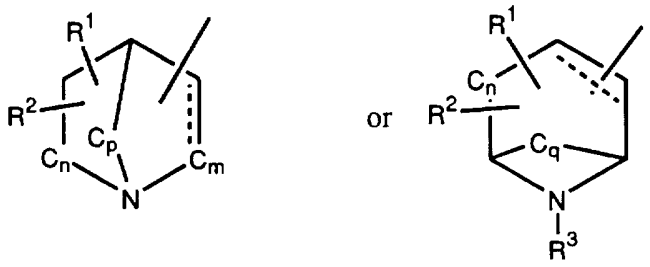


I

wherein

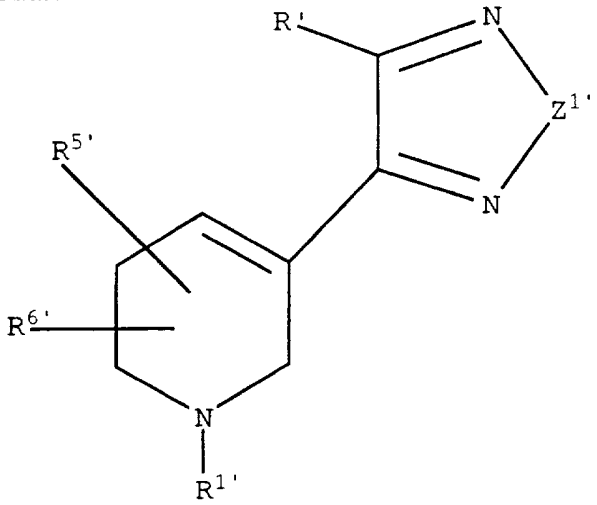
X is oxygen or sulphur;

R is hydrogen, amino, halogen, -CHO, $-NO_2$, $-OR^4$, $-SR^4$, $-SOR^4$, $-SO_2R^4$, C_{3-7}-cycloalkyl, C_{4-8}-(cycloalkylalkyl), -Z-C_{3-7}-cycloalkyl, and -Z-C_{4-8}-(cycloalkylalkyl) wherein R^4 is straight or branched C_{1-15}-alkyl, straight or branched C_{2-15}-alkenyl, straight or branched C_{2-15}-alkynyl, each of which is optionally substituted with one or more halogens, $-CF_3$, -CN, phenyl or phenoxy wherein phenyl or phenoxy is optionally substituted with halogen, -CN, C_{1-4}-alkyl, C_{1-4}-alkoxy, $-OCF_3$, $-CONH_2$ or $-CSNH_2$; or R is phenyl or benzyloxycarbonyl, each of which is optionally substituted with halogen, -CN, C_{1-4}-alkyl, C_{1-4}-alkoxy, $-OCF_3$, $-CONH_2$ or $-CSNH_2$; or R is $-OR^5Y$, $-SR^5Y$, $-OR^5ZY$, $-SR^5ZY$, $-O-R^4-Z-R^5$ or $-S-R^4-Z-R^5$ wherein Z is oxygen or sulphur, R^5 is straight or branched C_{1-15}-alkynyl, and Y is a 5 or 6 membered heterocyclic group containing one to four N, O or S atom(s) or a combination thereof, which heterocyclic group is optionally substituted at carbon or nitrogen atom(s) with straight or branched C_{1-6}-alkyl, phenyl or benzyl, or which heterocyclic group is optionally fused with a phenyl group; and G is selected from one of the following azabicyclic rings



wherein the thiadiazole or oxadiazole ring can be attached at any carbon atom of the azabicyclic ring; R^1 and R^2 may be present at any position, including the point of attachment of the thiadiazole or oxadiazole ring, and independently are hydrogen, straight or branched C_{1-5}-alkyl, straight or branched C_{2-5} alkenyl, straight or branched C_{2-5}-alkynyl, straight or branched C_{1-10}-alkoxy, straight or branched C_{1-5}-alkyl substituted with -OH, OR^4, halogen, $-NH_2$ or carboxy; R^3 is H, straight or branched C_{1-5}-alkyl, straight or branched C_{2-5}-alkenyl or straight or branched C_{2-5}-alkynyl; n is 0, 1 or 2; m is 0, 1 or 2; p is 0, 1 or 2; q is 1 or 2; and --- is a single or double bond; or a pharmaceutically acceptable salt or solvate thereof; and

Formula II



(II)

wherein

$Z^{1'}$ is oxygen or sulphur;

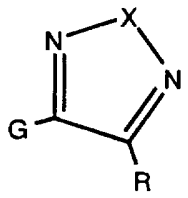
R' is hydrogen, halogen, amino, -NHCO-$R^{2'}$, C_{3-7}-cycloalkyl, C_{4-10}-(cycloalkylalkyl), -$Z^{2'}$-C_{3-7}-cycloalkyl optionally substituted with C_{1-6}-alkyl, -$Z^{2'}$-C_{4-10}-(cycloalkylalkyl), -$Z^{2'}$-C_{4-10}-(cycloalkenylalkyl), -$Z^{2'}$-C_{4-10}-(methylenecycloalkyl-alkyl), -NH-$R^{2'}$, -$NR^{2'}R^{3'}$, -NH-$OR^{2'}$, phenyl, phenoxy, benzoyl, benzyloxycarbonyl, tetrahydronaphtyl, indenyl, X', $R^{2'}$, -$Z^{2'}R^{2'}$, -$SOR^{2'}$, -$SO_2R^{2'}$, -$Z^{2'}$-$R^{2'}$-$Z^{3'}$-$R^{3'}$, -$Z^{2'}$-$R^{2'}$-$Z^{3'}$-$R^{3'}$-$Z^{4'}$-$R^{4'}$, -$Z^{2'}$-$R^{2'}$CO-$R^{3'}$, -$Z^{2'}$-$R^{2'}$-CO_2-$R^{3'}$, $Z^{2'}$-$R^{2'}$-O_2C-$R^{3'}$, -$Z^{2'}$-$R^{2'}$-CONH-$R^{3'}$, -$Z^{2'}$-$R^{2'}$-NHCO$R^{3'}$, -$Z^{2'}$-$R^{2'}$-X', -$Z^{2'}$-$R^{2'}$-$Z^{3'}$-X', wherein $Z^{2'}$, $Z^{3'}$, and $Z^{4'}$ independently are oxygen or sulphur, and $R^{2'}$, $R^{3'}$ and $R^{4'}$ independently are straight or branched C_{1-15}-alkyl, straight or branched C_{2-15}-alkenyl, straight or branched C_{2-15}-alkynyl, each of which is optionally substituted with halogen(s), -OH, -CN, -CF_3, -SH, -COOH, -NH-$R^{2'}$, -$NR^{2'}R^{3'}$, C_{1-6}alkyl ester, one or two phenyl, phenoxy, benzoyl or benzyloxycarbonyl wherein each aromatic group is optionally substituted with one or two halogen, -CN, C_{1-4}-alkyl or C_{1-4}-alkoxy, and X' is a 5 or 6 membered heterocyclic group containing one to four N, O or S atom(s) or a combination thereof, which heterocyclic group is optionally substituted at carbon or nitrogen atom(s) with straight or branched C_{1-6}-alkyl, phenyl, benzyl or pyridine, or a carbon atom in the heterocyclic group together with an oxygen atom form a carbonyl group, or which heterocyclic group is optionally fused with a phenyl group; and

$R^{5'}$ and $R^{6'}$ may be present at any position, including the point of attachment of the thiadiazole or oxadiazole ring, and independently are hydrogen, straight or branched C_{1-5}-alkyl, straight or branched C_{2-5}-alkenyl, straight or branched C_{2-5}-alkynyl, straight or branched C_{1-10}-alkoxy, straight or branched C_{1-5}-alkyl substituted with -OH, -OH, halogen, -NH_2 or carboxy; $R^{1'}$ is hydrogen, straight or branched C_{1-5}-alkyl, straight or branched C_{2-5}-alkenyl or straight or branched

C_{2-5}-alkynyl; or

a pharmaceutically acceptable salt or solvate thereof; and a nonsteroidal anti-inflammatory drug in a weight ratio of Compound to nonsteroidal anti-inflammatory drug (NSAIDS) of from about 1 to about 1000.

2. A composition as claimed by **Claim 1** wherein the Compound is of the formula I

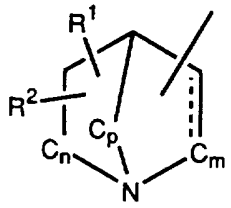


I

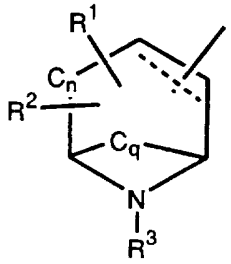
wherein

X is oxygen or sulphur;

R is hydrogen, amino, halogen, -CHO, $-NO_2$, $-OR^4$, $-SR^4$, $-SOR^4$, $-SO_2R^4$, C_{3-7}-cycloalkyl, C_{4-8}-(cycloalkylalkyl), -Z-C_{3-7}-cycloalkyl, and -Z-C_{4-8}-(cycloalkylalkyl) wherein R^4 is straight or branched C_{1-15}-alkyl, straight or branched C_{2-15}-alkenyl, straight or branched C_{2-15}-alkynyl, each of which is optionally substituted with one or more halogens, $-CF_3$, -CN, phenyl or phenoxy wherein phenyl or phenoxy is optionally substituted with halogen, -CN, C_{1-4}-alkyl, C_{1-4}-alkoxy, $-OCF_3$, $-CONH_2$ or $-CSNH_2$; or R is phenyl or benzyloxycarbonyl, each of which is optionally substituted with halogen, -CN, C_{1-4}-alkyl, C_{1-4}-alkoxy, $-OCF_3$, $-CONH_2$ or $-CSNH_2$; or R is $-OR^5Y$, $-SR^5Y$, $-OR^5ZY$, $-SR^5ZY$, $-O-R^4-Z-R^5$ or $-S-R^4-Z-R^5$ wherein Z is oxygen or sulphur, R^5 is straight or branched C_{1-15}-alkynyl, and Y is a 5 or 6 membered heterocyclic group containing one to four N, O or S atom(s) or a combination thereof, which heterocyclic group is optionally substituted at carbon or nitrogen atom(s) with straight or branched C_{1-6}-alkyl, phenyl or benzyl, or which heterocyclic group is optionally fused with a phenyl group; and G is selected from one of the following azabicyclic rings

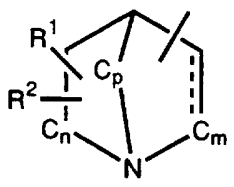


or



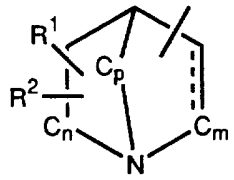
wherein the thiadiazole or oxadiazole ring can be attached at any carbon atom of the azabicyclic ring; R^1 and R^2 may be present at any position, including the point of attachment of the thiadiazole or oxadiazole ring, and independently are hydrogen, straight or branched C_{1-5}-alkyl, straight or branched C_{2-5} alkenyl, straight or branched C_{2-5}-alkynyl, straight or branched C_{1-10}-alkoxy, straight or branched C_{1-5}-alkyl substituted with -OH, OR^4, halogen, $-NH_2$ or carboxy; R^3 is H, straight or branched C_{1-5}-alkyl, straight or branched C_{2-5}-alkenyl or straight or branched C_{2-5}-alkynyl; n is 0, 1 or 2; m is 0, 1 or 2; p is 0, 1 or 2; q is 1 or 2; and --- is a single or double bond; or a pharmaceutically acceptable salt or solvate thereof; and a nonsteroidal anti-inflammatory drug in a weight ratio of Formula I to nonsteroidal anti-inflammatory drug (NSAIDS) of from about 1 to about 1000.

3. A composition of **Claim 2** wherein X is S, G is



wherein n is 1, p is 1 or 2 and m is 1 or 2, R^1 and R^2 independently are hydrogen, methyl, hydroxy, halogen or amino; or a pharmaceutically acceptable salt or solvate thereof.

4. A composition of **Claim 2** wherein X is S, G is



wherein n is 1, p is 1 or 2 and m is 1 or 2.

5. A composition according to **Claim 2** wherein the compound of Formula I is selected from the group consisting of the following:

3-CHLORO-3-(3-CHLORO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[2.2.2]OCTANE;

3-(3-CHLORO-1,2,5-THIADIAZOL-4-YL)-3-HYDROXY-1-AZABICYCLO[2.2.2]OCTANE;

3-METHOXY-3-(3-METHOXY-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[2.2.2]OCTANE;

3-(3-METHOXY-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[2.2.2]OCT-2-ENE;

3-(3-HEXYLOXY-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[2.2.2]OCT-2-ENE;

3-HEXYLOXY-3-(3-HEXYLOXY-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO-[2.2.2]OCTANE;

3-(3-HEXYLOXY-1,2,5-THIADIAZOL-4-YL)-3-HYDROXY-1-AZABICYCLO[2.2.2]OCTANE;

3-(3-CHLORO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[2.2.2]OCTANE;

3-(3-ETHOXY-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCL0[2.2.2]OCTANE;

3-(3-PROPOXY-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCL0[2.2.2]OCTANE;

3-(3-BUTOXY-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCL0[2.2.2]OCTANE;

3-(3-PENTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCL0-[2.2.2]OCTANE;

3-(3-ETHOXY-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCL0[2.2.2]OCTANE;

3-(3-HEXYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCL0[2.2.2]OCTANE;

3-(3-(3-PHENYLPROPYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCL0[2.2.2]OCTANE;

3-(3-HEXYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCL0[2.2.2]OCTANE;

3-(3-(4-CYANOBENZYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCL0[2.2.2]OCTANE;

EXO-6-(3-CHLORO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[3.2.1]OCTANE;

ENDO-6-(3-CHLORO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[3.2.1]OCTANE;

ENDO-6-(3-HEXYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[3.2.1]OCTANE;

ENDO-6-(3-(5-HEXENYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[3.2.1]OCTANE;

ENDO-6-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[3.2.1]OCTANE;

ENDO-6-(3-PENTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[3.2.1]OCTANE;

ENDO-6-(3-ETHYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[3.2.1]OCTANE;

ENDO-6-(3-(3-PHENYLPROPYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[3.2.1]OCTANE; or
a pharmaceutically acceptable salt or solvate thereof.

6. A composition of **Claim 2** wherein compound is 3-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCL0[2.2.2]OCTANE; or
a pharmaceutically acceptable salt or solvate thereof.

7. A composition of **Claim 2** wherein the the non-steroidal antiinflammatory drug is selected from the group consisting of salicylates, indomethacin, ibuprofen, naproxen, fenoprofen, tolmetin, sulindac, meclofenamate, keoprofen, piroxicam, flurbiprofen, and diclofenac.

8. A composition of **Claim 7** wherein the non-steroidal antiinflammatory drugs is selected from the group consisting of aspirin, ibuprofen, and naproxen.

9. A composition of **Claim 2** wherein the weight ratio of a compound of Formula I to NSAIDS is from about .1 to about 100.

10. A composition of **Claim 7** wherein the weight ratio is from about 1 to about 30.

11. A composition of **Claim 10** wherein the weight ratio is from about 1 to about 10.

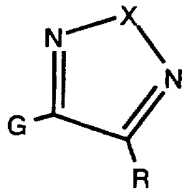
12. A composition of **Claim 11** wherein the weight ratio is from about 1 to about 3.

13. A composition of **Claim 9** wherein the non-steroidal antiinflammatory drug is selected from the group consisting of aspirin and ibuprofen.

14. A composition of **Claim 7** wherein the weight ratio of compound of Formula I to NSAIDS is from about 1 to about 100.

15. A composition of **Claim 8** wherein the weight ratio of compound of Formula I to NSAIDS is from about 1 to about 100.

16. A method for treating pain comprising administering an analgesic dose of a composition comprising a compound of Formula I



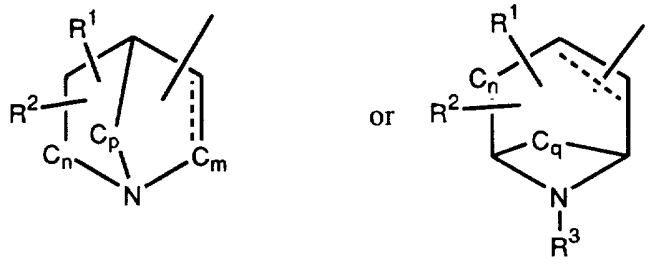
I

wherein

X is oxygen or sulphur;

R is hydrogen, amino, halogen, -CHO, $-NO_2$, $-OR^4$, $-SR^4$, $-SOR^4$, $-SO_2R^4$, C_{3-7}-cycloalkyl, C_{4-8}-(cycloalkylalkyl), -Z-C_{3-7}-cycloalkyl, and -Z-C_{4-8}-(cycloalkylalkyl) wherein R^4 is straight or branched C_{1-15}-alkyl, straight or branched C_{2-15}-alkenyl, straight or branched C_{2-15}-alkynyl, each of which is optionally substituted with one or more halogens, $-CF_3$, -CN, phenyl or phenoxy wherein phenyl or phenoxy is optionally substituted with halogen, -CN, C_{1-4}-alkyl, C_{1-4}-alkoxy, $-OCF_3$, $-CONH_2$ or $-CSNH_2$; or R is phenyl or benzyloxycarbonyl, each of which is optionally substituted with halogen, -CN, C_{1-4}-alkyl, C_{1-4}-alkoxy, $-OCF_3$, $-CONH_2$ or $-CSNH_2$; or R is $-OR^5Y$, $-SR^5Y$, $-OR^5ZY$, $-SR^5ZY$, $-O-R^4-Z-R^5$ or $-S-R^4-Z-R^5$ wherein Z is oxygen

or sulphur, R^5 is straight or branched C_{1-15}-alkynyl, and Y is a 5 or 6 membered heterocyclic group containing one to four N, O or S atom(s) or a combination thereof, which heterocyclic group is optionally substituted at carbon or nitrogen atom(s) with straight or branched C_{1-6}-alkyl, phenyl or benzyl, or which heterocyclic group is optionally fused with a phenyl group; and G is selected from one of the following azabicyclic rings



wherein the thiadiazole or oxadiazole ring can be attached at any carbon atom of the azabicyclic ring; R^1 and R^2 may be present at any position, including the point of attachment of the thiadiazole or oxadiazole ring, and independently are hydrogen, straight or branched C_{1-5}-alkyl, straight or branched C_{2-5} alkenyl, straight or branched C_{2-5}-alkynyl, straight or branched C_{1-10}-alkoxy, straight or branched C_{1-5}-alkyl substituted with -OH, OR^4, halogen, $-NH_2$ or carboxy; R^3 is H, straight or branched C_{1-5}-alkyl, straight or branched C_{2-5}-alkenyl or straight or branched C_{2-5}-alkynyl; n is 0, 1 or 2; m is 0, 1 or 2; p is 0, 1 or 2; q is 1 or 2; and --- is a single or double bond; or a pharmaceutically acceptable salt or solvate thereof; and one or more NSAIDS in a weight ratio of Formula I to NSAIDS of from about 1 to about 1000.

17. A method of **Claim 16** wherein the non-steroidal antiinflammatory drug is selected from the group consisting of salicylates, indomethacin, ibuprofen, naproxen, fenoprofen, tolmetin, sulindac, meclofenamate, keoprofen, piroxicam, flurbiprofen, and diclofenac.

18. A method of **Claim 17** wherein the non-steroidal antiinflammatory drug is selected from the group consisting of ibuprofen, and naproxen.

19. A method of **Claim 16** wherein the weight ratio of a compound of Formula I to NSAIDS of from about 1 to about 100.

20. A method of **Claim 19** wherein the weight ratio is from about 1 to about 30.

21. A method of **Claim 20** wherein the weight ratio is from about 1 to about 10.

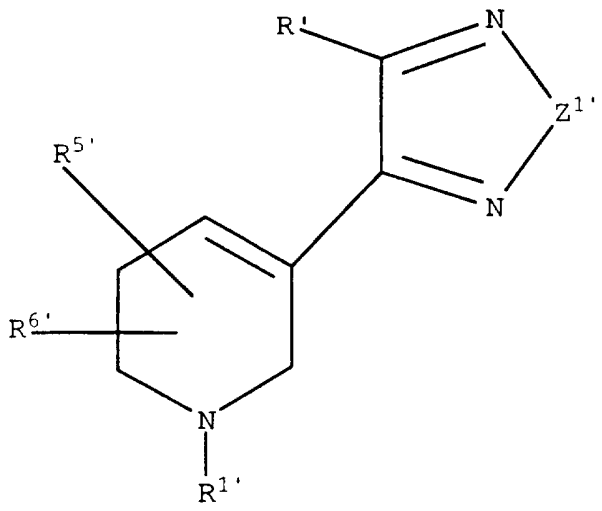
22. A method of **Claim 21** wherein the weight ratio is from about 1 to about 3.

23. A method of **Claim 22** wherein the compound of Formula I is 3-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCL0[2.2.2]OCTANE; or

a pharmaceutically acceptable salt or solvate thereof.

24. A method of **Claim 22** wherein the composition is administered using a transdermal formulation.

25. A composition of **Claim 1** wherein the compound is a compound of the formula II



(II)

wherein

$Z^{1'}$ is oxygen or sulphur;

R' is hydrogen, halogen, amino, $-NHCO-R^{2'}$, C_{3-7}-cycloalkyl, C_{4-10}-(cycloalkylalkyl), $-Z^{2'}-C_{3-7}$-cycloalkyl optionally substituted with C_{1-6}-alkyl, $-Z^{2'}-C_{4-10}$-(cycloalkylalkyl), $-Z^{2'}-C_{4-10}$-(cycloalkenylalkyl), $-Z^{2'}-C_{4-10}$-(methylenecycloalkyl-alkyl), $-NH-R^{2'}$, $-NR^{2'}R^{3'}$, $-NH-OR^{2'}$, phenyl, phenoxy, benzoyl, benzyloxycarbonyl, tetrahydronaphtyl, indenyl, X', $R^{2'}$, $-Z^{2'}R^{2'}$, $-SOR^{2'}$, $-SO_2R^{2'}$, $-Z^{2'}-R^{2'}-Z^{3'}-R^{3'}$, $-Z^{2'}-R^{2'}-Z^{3'}-R^{3'}-Z^{4'}-R^{4'}$, $-Z^{2'}-R^{2'}CO-R^{3'}$, $-Z^{2'}-R^{2'}-CO_2-R^{3'}$, $Z^{2'}-R^{2'}-O_2C-R^{3'}$, $-Z^{2'}-R^{2'}-CONH-R^{3'}$, $-Z^{2'}-R^{2'}-NHCOR^{3'}$, $-Z^{2'}-R^{2'}-X'$, $-Z^{2'}-R^{2'}-Z^{3'}-X'$, wherein $Z^{2'}$, $Z^{3'}$, and $Z^{4'}$ independently are oxygen or sulphur, and $R^{2'}$, $R^{3'}$ and $R^{4'}$ independently are straight or branched C_{1-15}-alkyl, straight or branched C_{2-15}-alkenyl, straight or branched C_{2-15}-alkynyl, each of which is optionally substituted with halogen(s), -OH, -CN, $-CF_3$, -SH, -COOH, $-NH-R^{2'}$, $-NR^{2'}R^{3'}$, C_{1-6}alkyl ester, one or two phenyl, phenoxy, benzoyl or benzyloxycarbonyl wherein each aromatic group is optionally substituted with one or two halogen, -CN, C_{1-4}-alkyl or C_{1-4}-alkoxy, and X' is a 5 or 6 membered heterocyclic group containing one to four N, O or S atom(s) or a combination thereof, which heterocyclic group is optionally substituted

at carbon or nitrogen atom(s) with straight or branched C_{1-6}-alkyl, phenyl, benzyl or pyridine, or a carbon atom in the heterocyclic group together with an oxygen atom form a carbonyl group, or which heterocyclic group is optionally fused with a phenyl group; and

$R^{5'}$ and $R^{6'}$ may be present at any position, including the point of attachment of the thiadiazole or oxadiazole ring, and independently are hydrogen, straight or branched C_{1-5}-alkyl, straight or branched C_{2-5}-alkenyl, straight or branched C_{2-5}-alkynyl, straight or branched C_{1-10}-alkoxy, straight or branched C_{1-5}-alkyl substituted with -OH, -OH, halogen, $-NH_2$ or carboxy; $R^{1'}$ is hydrogen, straight or branched C_{1-5}-alkyl, straight or branched C_{2-5}-alkenyl or straight or branched C_{2-5}-alkynyl; or

a pharmaceutically acceptable salt or solvate thereof; and one or more nonsteroidal anti-inflammatory drugs in a weight ratio of Formula II to nonsteroidal anti-inflammatory drug of from about 1 to about 1000.

26. A composition of **Claim 25** wherein Z' is sulfur.

27. A composition of **Claim 25** wherein Z' is sulfur, $R^{1'}$ is hydrogen or straight or branched C_{1-5}-alkyl, $R^{5'}$ and $R^{6'}$ independently are selected from the group consisitng of hydrogen, methyl, methoxy, hydroxy, halogen, and amino.

28. A composition according to **Claim 25** wherein the compound of Formula II is selected from the group consisting of the following:

3-(3-METHOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-ETHOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-PROPOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-BUTOXY-1,2,5-THIADIAZOL-4-YL)1,2,5,6-TETTRAHYDRO-1-METHYLPYRIDINE

3-(3-ISOPROPOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-CYCLOPROPYLMETHOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-PENTOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-ISOBUTOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3-BUTENOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(BUT-2-YNOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3-METHYLBUTOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-HEXYLOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(PROP-2-YNOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-BENZYLOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-CHLORO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-CHLORO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE

3-(3-BUTOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE

3-(3-ETHOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-ETHYLPYRIDINE

3-(3-CHLORO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-ETHYLPYRIDINE

3-(3-METHOXYETHOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-HEPTYLOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3-PENTYNYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(4-PENTENYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(2-PROPENYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-OCTYLOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3-HEXYNYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3-BUTENYL-2-OXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYL-PYRIDINE

3-(3-(4-HEXENYLOXY(-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

TRANS-3-(3-(3-HEXENYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

CIS-3-(3-(2-PENTENYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

CIS-3-(3-(2-HEXENYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(5-HEXENYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

CIS-3-(3-(3-HEXENYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,4,5-TETRAHYDRO-1-METHYLPYRIDINE

TRANS-3-(3-(2-HEXENYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(4-METHYLPIPERIDINO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-MORPHOLINO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-DIMETHYLAMINO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-HEXYLAMINO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-HEXYLOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-DEUTEROMETHYLPYRIDINE

1,2,5,6-TETRAHYDRO-3-(3-HEXYLOXY-1,2,5-THIADIAZOL-4-YL)PYRIDINE

3-(3-(2-(2-METHOXYETHOXY)-ETHOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3-ETHOXY-1-PROPOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6,-TETRAHYDRO-1-METHYLPYRIDINE

3-(2-ETHOXYETHOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(2-BUTOXYETHOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(2-(2-BUTOXYETHOXY)-ETHOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(2-(2-ETHOXYETHOXY)-ETHOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-METHYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-PENTYL-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-PROPYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-HEXYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-PENTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-ETHYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-OCTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-PROPYL-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-HEPTYL-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(5-HEXENYL)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-OCTYL-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYPYRIDINE

3-(3-(2-METHYL)-BUTYL-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-METHYLCYCLOPROPYL-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-CYCLOPENTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(1-ETHYLTHIO-2-METHOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3-CHLORO-1-PROPYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(2-METHOXYETHOXY)-ETHYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3-CYANO-1-PROPYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-BENZYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(2-ETHOXY-1-ETHYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(4-PENTYNYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(2-(2-ETHOXYMETHOXY)-ETHYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(5-CYANO-1-PENTYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3-PHENYL-1-PROPYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(2-PHENOXYETHYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(4-CYANOBUTYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(2-ETHYLBUTYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-CYCLOHEXYLMETHYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(8-HYDROXYOCTYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(7-OCTENYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-CYCLOPROPYLMETHYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3(3-CYCLOPROPYLMETHYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3-BUTENYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(4-PENTENYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(4-ISOHEXYLOXY-1,2,5-THIADIAZOL-3-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

1-METHYL-1,2,5,6-TETRAHYDRO-3-((4-CYCLOPENTYLPROPYL)OXY)-1,2,5-THIADIAZOL-3-YL)PYRIDINE

1-METHYL-1,2,5,6-TETRAHYDRO-3-(4-ISOHEPTYLOXY-1,2,5-THIADIAZOL-3-YL)PYRIDINE

1-METHYL-1,2,5,6-TETRAHYDRO-3-(4((2-CYCLOHEXYLETHYL)OXY)-1,2,5-THIADIAZOL-3-YL)PYRIDINE

1,2,5,6-TETRAHYDRO-1-METHYL-3-(4-(1-METHYLHEXLOXY)-1,2,5-THIADIAZOL-3-YL)PYRIDINE

3-(4-(1-ETHYLPENTYLOXY)-1,2,5-THIADIAZOL-3-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(4-(1-ETHYLBUTOXY)-1,2,5-THIADIAZOL-3-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

1,2,5,6-TETRAHYDRO-1-METHYL-3-(4-(1-METHYLPENTYLOXY)-1,2,5-THIADIAZOL-3-)YL)PYRIDINE

1-METHYL-3-(4-(5-HEXENYLOXY)-1,2,5-THIADIAZOL-3-YL)-1,2,5,6-TETRAHYDROPYRIDINE

1,2,5,6-TETRAHYDRO-1-METHYL-3-(4-(2-METHYLBUTOXY)-1,2,5-THIADIAZOL-3-YL)PYRIDINE

1,2,5,6-TETRAHYDRO-1-METHYL-3-(4-(2-METHYLPENTYLOXY)-1,2,5-THIADIAZOL-3-YL)PYRIDINE

1,2,5,6-TETRAHYDRO-1-METHYL-3-(4-(2,2,2-TRIFLUOROETHOXY)-1,2,5-THIADIAZOL-3-YL)PYRIDINE

1-METHYL-1,2,5,6-TETRAHYDRO-3-(4-(3-METHYLPENTYLOXY)-1,2,5-THIADIAZOL-3-YL)PYRIDINE

3-(3-(3-METHYL-2-BUTENYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDO-1-METHYLPYRIDINE

3-(3-ISOBUTOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

1,2,5,6-TETRAHYDRO-1-METHYL-3-(4-(2-METHYLBUTOXY)-1,2,5-THIADIAZOL-3-YL)PYRIDINE

3-(3-(3-HYDROXYPROPOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

(+-)1,6-DIMETHYL-3-(3-HEXYLOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE

3-(3-(3-PHENYL-ETHYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

BIS-1,4-(3-(1-METHYL-1,2,5,6-TETRAHYDROPYRIDIN-3-YL)-1,2,5-THIADIAZOL-4-YL)BUTANEDITHIOL

3-(3-(4,4,4-TRIFLUOROBUTOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3,3,3-TRIFLUOROPROPYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-PROPYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE

3-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE

3-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1,1-DIMETHYLPYRIDINIUM IODIDE

(+-)1,6-DIMETHYL-3-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE

(+-)1,6-DIMETHYL-3-(3-BUTOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE

3-(3-(3-METHYL-2-BUTENYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDO-1-METHYL PYRIDINE

3-(3-ISOBUTOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

1,2,5,6-TETRAHYDRO-1-METHYL-3-(4-(2-METHYLBUTOXY)-1,2,5-THIADIAZOL-3-YL)PYRIDINE

3-(3-(3-HYDROXYPROPOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

(+-)1,6-DIMETHYL-3-(3-HEXYLOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE

3-(3-(3-PHENYL-ETHYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

BIS-1,4-(3-(1-METHYL-1,2,5,6-TETRAHYDROPYRIDIN-3-YL)-1,2,5-THIADIAZOL-4-YL)BUTANEDITHIOL

3-(3-(4,4,4-TRIFLUOROBUTOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3,3,3-TRIFLUOROPROPYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-PROPYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-PROPYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE

3-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE

3-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1,1-DIMETHYLPYRIDINIUM IODIDE

(+-)1,6-DIMETHYL-3-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE; and

(+-)1,6-DIMETHYL-3-(3-BUTOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE; or a pharmaceutically acceptable salt or solvate thereof.

29. A composition of **Claim 25** wherein the the non-steroidal antiinflammatory drug is selected from the group consisting of salicylates, indomethacin, ibuprofen, naproxen, fenoprofen, tolmetin, sulindac, meclofenamate, keoprofen, piroxicam, flurbiprofen, and diclofenac.

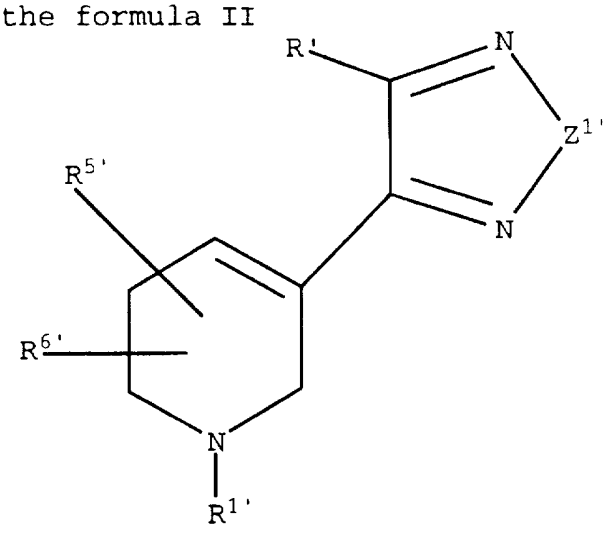
30. A composition of **Claim 29** wherein the non-steroidal antiinflammatory drugs is selected from the group consisting of aspirin, ibuprofen, and naproxen.

31. A composition of **Claim 25** wherein the weight ratio of a compound of Formula II to NSAIDS is from about 1 to about 100.

32. A composition of **Claim 30** wherein the non-steroidal antiinflammatory drug is ibuprofen.

33. A composition of **Claim 2** wherein the weight ratio of compound of Formula I to NSAIDS is from about 1 to about 100.

34. A method for treating pain comprising administering an analgesic dose of a composition comprising a compound of the formula II



(II)

wherein

$Z^{1'}$ is oxygen or sulphur;
R' is hydrogen, halogen, amino, $-NHCO-R^{2'}$, C_{3-7}-cycloalkyl, C_{4-10}-(cycloalkylalkyl), $-Z^{2'}-C_{3-7}$-cycloalkyl optionally substituted with C_{1-6}-alkyl, $-Z^{2'}-C_{4-10}$-(cycloalkylalkyl), $-Z^{2'}-C_{4-10}$-(cycloalkenylalkyl), $-Z^{2'}-C_{4-10}$-(methylenecycloalkyl-alkyl), $-NH-R^{2'}$, $-NR^{2'}R^{3'}$, $-NH-OR^{2'}$, phenyl, phenoxy, benzoyl, benzyloxycarbonyl, tetrahydronaphtyl, indenyl, X', $R^{2'}$, $-Z^{2'}R^{2'}$, $-SOR^{2'}$, $-SO_2R^{2'}$, $-Z^{2'}-R^{2'}-Z^{3'}-R^{3'}$, $-Z^{2'}-R^{2'}-Z^{3'}-R^{3'}-Z^{4'}-R^{4'}$, $-Z^{2'}-R^{2'}CO-R^{3'}$, $-Z^{2'}-R^{2'}-CO_2-R^{3'}$, $Z^{2'}-R^{2'}-O_2C-R^{3'}$, $-Z^{2'}-R^{2'}-CONH-R^{3'}$, $-Z^{2'}-R^{2'}-NHCOR^{3'}$, $-Z^{2'}-R^{2'}-X'$, $-Z^{2'}-R^{2'}-Z^{3'}-X'$, wherein $Z^{2'}$, $Z^{3'}$, and $Z^{4'}$ independently are oxygen or sulphur, and $R^{2'}$, $R^{3'}$ and $R^{4'}$ independently are straight or branched C_{1-15}-alkyl, straight or branched C_{2-15}-alkenyl, straight or branched C_{2-15}-alkynyl, each of which is optionally substituted with halogen(s), -OH, -CN, $-CF_3$, -SH, -COOH, $-NH-R^{2'}$, $-NR^{2'}R^{3'}$, C_{1-6}alkyl ester, one or two phenyl, phenoxy, benzoyl or benzyloxycarbonyl wherein each aromatic group is optionally substituted with one or two halogen, -CN, C_{1-4}-alkyl or C_{1-4}-alkoxy, and X' is a 5 or 6 membered heterocyclic group containing one to four N, O or S atom(s) or a combination thereof, which heterocyclic group is optionally substituted at carbon or nitrogen atom(s) with straight or branched C_{1-6}-alkyl, phenyl, benzyl or pyridine, or a carbon atom in the heterocyclic group together with an oxygen atom form a carbonyl group, or which heterocyclic group is optionally fused with a phenyl group; and
$R^{5'}$ and $R^{6'}$ may be present at any position, including the point of attachment of the thiadiazole or oxadiazole ring, and independently are hydrogen, straight or branched C_{1-5}-alkyl, straight or branched C_{2-5}-alkenyl, straight or branched C_{2-5}-alkynyl, straight or branched C_{1-10}-alkoxy, straight or branched C_{1-5}-alkyl substituted with -OH, -OH, halogen, $-NH_2$ or carboxy; $R^{1'}$ is hydrogen, straight or branched C_{1-5}-alkyl, straight or branched C_{2-5}-alkenyl or straight or branched

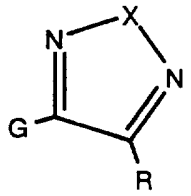
C_{2-5}-alkynyl; or
a pharmaceutically acceptable salt or solvate thereof; and one or more NSAIDS in a weight ratio of Formula II to NSAIDS of from about 1 to about 1000.

35. A method of **Claim 34** wherein the non-steroidal antiinflammatory drug is selected from the group consisting of salicylates, indomethacin, ibuprofen, naproxen, fenoprofen, tolmetin, sulindac, meclofenamate, keoprofen, piroxicam, flurbiprofen, and diclofenac.

36. A method of **Claim 34** wherein the non-steroidal antiinflammatory drug is selected from the group consisting of ibuprofen, and naproxen.

37 . A method of **Claim 35** wherein the composition is administered using a transdermal formulation.

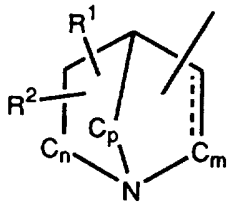
38. A composition for treating pain comprising an analgesic dose of a Compound selected from the group consisting of Formula I



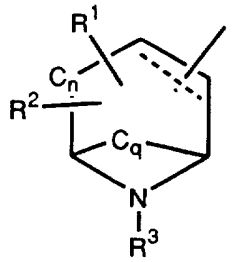
I

wherein
X is oxygen or sulphur;
R is hydrogen, amino, halogen, -CHO, $-NO_2$, $-OR^4$, $-SR^4$, $-SOR^4$, $-SO_2R^4$, C_{3-7}-cycloalkyl, C_{4-8}-(cycloalkylalkyl), -Z-C_{3-7}-cycloalkyl, and -Z-C_{4-8}-(cycloalkylalkyl) wherein R^4 is straight or branched C_{1-15}-alkyl, straight or branched C_{2-15}-alkenyl, straight or branched C_{2-15}-alkynyl, each of which is optionally substituted with one or more halogens, $-CF_3$, -CN, phenyl or phenoxy wherein phenyl or phenoxy is optionally substituted with halogen, -CN, C_{1-4}-alkyl, C_{1-4}-alkoxy, $-OCF_3$,

$-CONH_2$ or $-CSNH_2$; or R is phenyl or benzyloxycarbonyl, each of which is optionally substituted with halogen, -CN, C_{1-4}-alkyl, C_{1-4}-alkoxy, $-OCF_3$, $-CONH_2$ or $-CSNH_2$; or R is $-OR^5Y$, $-SR^5Y$, $-OR^5ZY$, $-SR^5ZY$, $-O-R^4-Z-R^5$ or $-S-R^4-Z-R^5$ wherein Z is oxygen or sulphur, R^5 is straight or branched C_{1-15}-alkynyl, and Y is a 5 or 6 membered heterocyclic group containing one to four N, O or S atom(s) or a combination thereof, which heterocyclic group is optionally substituted at carbon or nitrogen atom(s) with straight or branched C_{1-6}-alkyl, phenyl or benzyl, or which heterocyclic group is optionally fused with a phenyl group; and G is selected from one of the following azabicyclic rings

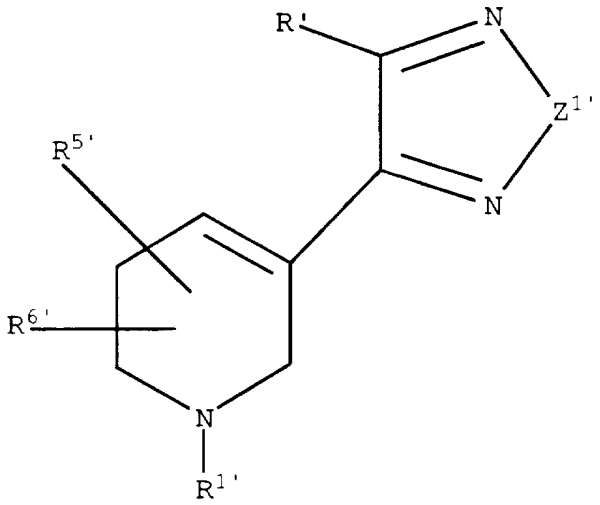


or



wherein the thiadiazole or oxadiazole ring can be attached at any carbon atom of the azabicyclic ring; R^1 and R^2 may be present at any position, including the point of attachment of the thiadiazole or oxadiazole ring, and independently are hydrogen, straight or branched C_{1-5}-alkyl, straight or branched C_{2-5} alkenyl, straight or branched C_{2-5}-alkynyl, straight or branched C_{1-10}-alkoxy, straight or branched C_{1-5}-alkyl substituted with -OH, OR^4, halogen, $-NH_2$ or carboxy; R^3 is H, straight or branched C_{1-5}-alkyl, straight or branched C_{2-5}-alkenyl or straight or branched C_{2-5}-alkynyl; n is 0, 1 or 2; m is 0, 1 or 2; p is 0, 1 or 2; q is 1 or 2; and --- is a single or double bond; and

Formula II



(II)

wherein

$Z^{1'}$ is oxygen or sulphur;

R' is hydrogen, halogen, amino, $-NHCO-R^{2'}$, C_{3-7}-cycloalkyl, C_{4-10}-(cycloalkylalkyl), $-Z^{2'}-C_{3-7}$-cycloalkyl optionally substituted with C_{1-6}-alkyl, $-Z^{2'}-C_{4-10}$-(cycloalkylalkyl), $-Z^{2'}-C_{4-10}$-(cycloalkenylalkyl), $-Z^{2'}-C_{4-10}$-(methylenecycloalkyl-alkyl), $-NH-R^{2'}$, $-NR^{2'}R^{3'}$, $-NH-OR^{2'}$, phenyl, phenoxy, benzoyl, benzyloxycarbonyl, tetrahydronaphtyl, indenyl, X', $R^{2'}$, $-Z^{2'}R^{2'}$, $-SOR^{2'}$, $-SO_2R^{2'}$, $-Z^{2'}-R^{2'}-Z^{3'}-R^{3'}$, $-Z^{2'}-R^{2'}-Z^{3'}-R^{3'}-Z^{4'}-R^{4'}$, $-Z^{2'}-R^{2'}CO-R^{3'}$, $-Z^{2'}-R^{2'}-CO_2-R^{3'}$, $Z^{2'}-R^{2'}-O_2C-R^{3'}$, $-Z^{2'}-R^{2'}-CONH-R^{3'}$, $-Z^{2'}-R^{2'}-NHCOR^{3'}$, $-Z^{2'}-R^{2'}-X'$, $-Z^{2'}-R^{2'}-Z^{3'}-X'$, wherein $Z^{2'}$, $Z^{3'}$, and $Z^{4'}$ independently are oxygen or sulphur, and $R^{2'}$, $R^{3'}$ and $R^{4'}$ independently are straight or branched C_{1-15}-alkyl, straight or branched C_{2-15}-alkenyl, straight or branched C_{2-15}-alkynyl, each of which is optionally substituted with halogen(s), -OH, -CN, $-CF_3$, -SH, -COOH, $-NH-R^{2'}$, $-NR^{2'}R^{3'}$, C_{1-6}alkyl ester, one or two phenyl, phenoxy, benzoyl or benzyloxycarbonyl wherein each aromatic group is optionally substituted with one or two halogen, -CN, C_{1-4}-alkyl or

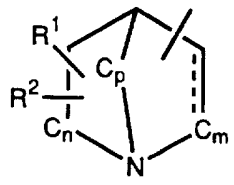
C_{1-4}-alkoxy, and X' is a 5 or 6 membered heterocyclic group containing one to four N, O or S atom(s) or a combination thereof, which heterocyclic group is optionally substituted at carbon or nitrogen atom(s) with straight or branched C_{1-6}-alkyl, phenyl, benzyl or pyridine, or a carbon atom in the heterocyclic group together with an oxygen atom form a carbonyl group, or which heterocyclic group is optionally fused with a phenyl group; and

$R^{5'}$ and $R^{6'}$ may be present at any position, including the point of attachment of the thiadiazole or oxadiazole ring, and independently are hydrogen, straight or branched C_{1-5}-alkyl, straight or branched C_{2-5}-alkenyl, straight or branched C_{2-5}-alkynyl, straight or branched C_{1-10}-alkoxy, straight or branched C_{1-5}-alkyl substituted with -OH, -OH, halogen, $-NH_2$ or carboxy; $R^{1'}$ is hydrogen, straight or branched C_{1-5}-alkyl, straight or branched C_{2-5}-alkenyl or straight or branched C_{2-5}-alkynyl; or

a pharmaceutically acceptable salt or solvate thereof; and acetaminophen in a weight ratio of Compound to acetaminophen of from about 1 to about 1000.

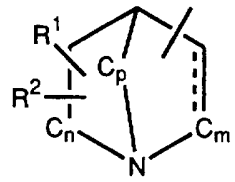
39. A composition of **Claim 38** wherein the compound is a compound of Formula I; or a pharmaceutically acceptable salt or solvate thereof.

40. A composition of **Claim 39** wherein X is S, G is



wherein n is 1, p is 1 or 2 and m is 1 or 2, R^1 and R^2 independently are hydrogen, methyl, hydroxy, halogen or amino; or a pharmaceutically acceptable salt or solvate thereof.

41. A composition of **Claim 39** wherein X is S, G is



wherein n is 1, p is 1 or 2 and m is 1 or 2.

42. A composition according to **Claim 39** wherein the compound of Formula I is selected from the group consisting of the following:

3-CHLORO-3-(3-CHLORO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[2.2.2]OCTANE;

3-(3-CHLORO-1,2,5-THIADIAZOL-4-YL)-3-HYDROXY-1-AZABICYCLO[2.2.2]OCTANE;

3-METHOXY-3-(3-METHOXY-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[2.2.2]OCTANE;

3-(3-METHOXY-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[2.2.2]OCT-2-ENE;

3-(3-HEXYLOXY-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[2.2.2]OCT-2-ENE;

3-HEXYLOXY-3-(3-HEXYLOXY-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO-[2.2.2]OCTANE;

3-(3-HEXYLOXY-1,2,5-THIADIAZOL-4-YL)-3-HYDROXY-1-AZABICYCLO[2.2.2]OCTANE;

3-(3-CHLORO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[2.2.2]OCTANE;

3-(3-ETHOXY-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCL0[2.2.2]OCTANE;

3-(3-PROPOXY-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCL0[2.2.2]OCTANE;

3-(3-BUTOXY-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCL0[2.2.2]OCTANE;

3-(3-PENTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCL0-[2.2.2]OCTANE;

3-(3-ETHOXY-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCL0[2.2.2]OCTANE;

3-(3-HEXYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCL0[2.2.2]OCTANE;

3-(3-(3-PHENYLPROPYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCL0[2.2.2]OCTANE;

3-(3-HEXYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCL0[2.2.2]OCTANE;

3-(3-(4-CYANOBENZYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCL0[2.2.2]OCTANE;

EXO-6-(3-CHLORO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[3.2.1]OCTANE;

ENDO-6-(3-CHLORO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[3.2.1]OCTANE;

ENDO-6-(3-HEXYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[3.2.1]OCTANE;

ENDO-6-(3-(5-HEXENYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[3.2.1]OCTANE;

ENDO-6-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[3.2.1]OCTANE;

ENDO-6-(3-PENTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[3.2.1]OCTANE;

ENDO-6-(3-ETHYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[3.2.1]OCTANE; and

ENDO-6-(3-(3-PHENYLPROPYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[3.2.1]OCTANE; or a pharmaceutically acceptable salt or solvate thereof.

43. A composition of **Claim 42** wherein the Compound of Formula I is 3-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCL0[2.2.2]OCTANE; or

a pharmaceutically acceptable salt or solvate thereof.

44. A composition of **Claim 43** wherein the weight ratio is from about 1 to about 30.

45. A composition of **Claim 38** wherein the compound is of Formula II.

46. A composition of **Claim 45** wherein Z is sulfur.

47. A composition of **Claim 45** wherein Z is sulfur, R^1 is hydrogen or straight or branched C_{1-5}-alkyl, R^5 and R^6 independently are selected from the group consisitng of hydrogen, methyl, methoxy, hydroxy, halogen, and amino.

48. A composition according to **Claim 45** wherein the compound of Formula II is selected from the group consisting of the following:

3-(3-METHOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-ETHOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-PROPOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-BUTOXY-1,2,5-THIADIAZOL-4-YL)1,2,5,6-TETTRAHYDRO-1-METHYLPYRIDINE

3-(3-ISOPROPOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-CYCLOPROPYLMETHOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-PENTOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-ISOBUTOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3-BUTENOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(BUT-2-YNOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3-METHYLBUTOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-HEXYLOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(PROP-2-YNOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-BENZYLOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-CHLORO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-CHLORO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE

3-(3-BUTOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE

3-(3-ETHOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-ETHYLPYRIDINE

3-(3-CHLORO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-ETHYLPYRIDINE

3-(3-METHOXYETHOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-HEPTYLOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3-PENTYNYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(4-PENTENYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(2-PROPENYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-OCTYLOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3-HEXYNYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3-BUTENYL-2-OXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYL-PYRIDINE

3-(3-(4-HEXENYLOXY(-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

TRANS-3-(3-(3-HEXENYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

CIS-3-(3-(2-PENTENYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

CIS-3-(3-(2-HEXENYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(5-HEXENYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

CIS-3-(3-(3-HEXENYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,4,5-TETRAHYDRO-1-METHYLPYRIDINE

TRANS-3-(3-(2-HEXENYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(4-METHYLPIPERIDINO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-MORPHOLINO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-DIMETHYLAMINO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-HEXYLAMINO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-HEXYLOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-DEUTEROMETHYLPYRIDINE

1,2,5,6-TETRAHYDRO-3-(3-HEXYLOXY-1,2,5-THIADIAZOL-4-YL)PYRIDINE

3-(3-(2-(2-METHOXYETHOXY)-ETHOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3-ETHOXY-1-PROPOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6,-TETRAHYDRO-1-METHYLPYRIDINE

3-(2-ETHOXYETHOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(2-BUTOXYETHOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(2-(2-BUTOXYETHOXY)-ETHOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(2-(2-ETHOXYETHOXY)-ETHOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-METHYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-PENTYL-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-PROPYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-HEXYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-PENTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-ETHYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-OCTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-PROPYL-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-HEPTYL-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(5-HEXENYL)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-OCTYL-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYPYRIDINE

3-(3-(2-METHYL)-BUTYL-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-METHYLCYCLOPROPYL-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-CYCLOPENTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(1-ETHYLTHIO-2-METHOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3-CHLORO-1-PROPYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(2-METHOXYETHOXY)-ETHYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3-CYANO-1-PROPYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-BENZYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(2-ETHOXY-1-ETHYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(4-PENTYNYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(2-(2-ETHOXYMETHOXY)-ETHYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(5-CYANO-1-PENTYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3-PHENYL-1-PROPYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(2-PHENOXYETHYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(4-CYANOBUTYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(2-ETHYLBUTYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-CYCLOHEXYLMETHYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(8-HYDROXYOCTYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(7-OCTENYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-CYCLOPROPYLMETHYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3(3-CYCLOPROPYLMETHYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3-BUTENYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(4-PENTENYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(4-ISOHEXYLOXY-1,2,5-THIADIAZOL-3-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

1-METHYL-1,2,5,6-TETRAHYDRO-3-((4-CYCLOPENTYLPROPYL)OXY)-1,2,5-THIADIAZOL-3-YL)PYRIDINE

1-METHYL-1,2,5,6-TETRAHYDRO-3-(4-ISOHEPTYLOXY-1,2,5-THIADIAZOL-3-YL)PYRIDINE

1-METHYL-1,2,5,6-TETRAHYDRO-3-(4((2-CYCLOHEXYLETHYL)OXY)-1,2,5-THIADIAZOL-3-YL)PYRIDINE

1,2,5,6-TETRAHYDRO-1-METHYL-3-(4-(1-METHYLHEXLOXY)-1,2,5-THIADIAZOL-3-YL)PYRIDINE

3-(4-(1-ETHYLPENTYLOXY)-1,2,5-THIADIAZOL-3-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(4-(1-ETHYLBUTOXY)-1,2,5-THIADIAZOL-3-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

1,2,5,6-TETRAHYDRO-1-METHYL-3-(4-(1-METHYLPENTYLOXY)-1,2,5-THIADIAZOL-3-)YL)PYRIDINE

1-METHYL-3-(4-(5-HEXENYLOXY)-1,2,5-THIADIAZOL-3-YL)-1,2,5,6-TETRAHYDROPYRIDINE

1,2,5,6-TETRAHYDRO-1-METHYL-3-(4-(2-METHYLBUTOXY)-1,2,5-THIADIAZOL-3-YL)PYRIDINE

1,2,5,6-TETRAHYDRO-1-METHYL-3-(4-(2-METHYLPENTYLOXY)-1,2,5-THIADIAZOL-3-YL)PYRIDINE

1,2,5,6-TETRAHYDRO-1-METHYL-3-(4-(2,2,2-TRIFLUOROETHOXY)-1,2,5-THIADIAZOL-3-YL)PYRIDINE

1-METHYL-1,2,5,6-TETRAHYDRO-3-(4-(3-METHYLPENTYLOXY)-1,2,5-THIADIAZOL-3-YL)PYRIDINE

3-(3-(3-METHYL-2-BUTENYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDO-1-METHYLPYRIDINE

3-(3-ISOBUTOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

1,2,5,6-TETRAHYDRO-1-METHYL-3-(4-(2-METHYLBUTOXY)-1,2,5-THIADIAZOL-3-YL)PYRIDINE

3-(3-(3-HYDROXYPROPOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

(+-)1,6-DIMETHYL-3-(3-HEXYLOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE

3-(3-(3-PHENYL-ETHYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

BIS-1,4-(3-(1-METHYL-1,2,5,6-TETRAHYDROPYRIDIN-3-YL)-1,2,5-THIADIAZOL-4-YL)BUTANEDITHIOL

3-(3-(4,4,4-TRIFLUOROBUTOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3,3,3-TRIFLUOROPROPYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-PROPYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE

3-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE

3-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1,1-DIMETHYLPYRIDINIUM IODIDE

(+-)1,6-DIMETHYL-3-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE

(+-)1,6-DIMETHYL-3-(3-BUTOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE

3-(3-(3-METHYL-2-BUTENYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDO-1-METHYL PYRIDINE

3-(3-ISOBUTOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

1,2,5,6-TETRAHYDRO-1-METHYL-3-(4-(2-METHYLBUTOXY)-1,2,5-THIADIAZOL-3-YL)PYRIDINE

3-(3-(3-HYDROXYPROPOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

(+-)1,6-DIMETHYL-3-(3-HEXYLOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE

3-(3-(3-PHENYL-ETHYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

BIS-1,4-(3-(1-METHYL-1,2,5,6-TETRAHYDROPYRIDIN-3-YL)-1,2,5-THIADIAZOL-4-YL)BUTANEDITHIOL

3-(3-(4,4,4-TRIFLUOROBUTOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3,3,3-TRIFLUOROPROPYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-PROPYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-PROPYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE

3-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE

3-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1,1-DIMETHYLPYRIDINIUM IODIDE

(+-)1,6-DIMETHYL-3-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE; and

(+-)1,6-DIMETHYL-3-(3-BUTOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE; or a pharmaceutically acceptable salt or solvate thereof.

49. A composition of **Claim 45** wherein the weight ratio of a compound of Formula II to acetaminophen of from about 1 to about 100.

50. A method for treating pain comprising administering an analgesic dose of a composition comprising a Compound selected from the group consisting of Formula I and Formula II; or
a pharmaceutically acceptable salt or solvate thereof; and acetaminophen in a weight ratio of Compound to acetaminophen of from about 1 to about 1000.

51. A method of **Claim 50** wherein the compound is of Formula I.

52. A method of **Claim 51** wherein the weight ratio of a compound of Formula I to acetaminophen of from about 1 to about 100.

53. A method of **Claim 51** wherein the composition is administered using a transdermal formulation.

54. A method of **Claim 51** wherein the Formula I compound is 3-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCL0[2.2.2]OCTANE; or
a pharmaceutically acceptable salt or solvate thereof.

55. A method of **Claim 50** wherein the compound is of Formula II.

56. A method of **Claim 55** wherein the compound is selected from the group consisting of

3-(3-METHOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-ETHOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-PROPOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-BUTOXY-1,2,5-THIADIAZOL-4-YL)1,2,5,6-TETTRAHYDRO-1-METHYLPYRIDINE

3-(3-ISOPROPOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-CYCLOPROPYLMETHOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-PENTOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-ISOBUTOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3-BUTENOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(BUT-2-YNOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3-METHYLBUTOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-HEXYLOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(PROP-2-YNOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-BENZYLOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-CHLORO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-CHLORO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE

3-(3-BUTOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE

3-(3-ETHOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-ETHYLPYRIDINE

3-(3-CHLORO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-ETHYLPYRIDINE

3-(3-METHOXYETHOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-HEPTYLOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3-PENTYNYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(4-PENTENYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(2-PROPENYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-OCTYLOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3-HEXYNYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3-BUTENYL-2-OXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYL-PYRIDINE

3-(3-(4-HEXENYLOXY(-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

TRANS-3-(3-(3-HEXENYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

CIS-3-(3-(2-PENTENYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

CIS-3-(3-(2-HEXENYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(5-HEXENYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

CIS-3-(3-(3-HEXENYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,4,5-TETRAHYDRO-1-METHYLPYRIDINE

TRANS-3-(3-(2-HEXENYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(4-METHYLPIPERIDINO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-MORPHOLINO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-DIMETHYLAMINO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-HEXYLAMINO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-HEXYLOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-DEUTEROMETHYLPYRIDINE

1,2,5,6-TETRAHYDRO-3-(3-HEXYLOXY-1,2,5-THIADIAZOL-4-YL)PYRIDINE

3-(3-(2-(2-METHOXYETHOXY)-ETHOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3-ETHOXY-1-PROPOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6,-TETRAHYDRO-1-METHYLPYRIDINE

3-(2-ETHOXYETHOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(2-BUTOXYETHOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(2-(2-BUTOXYETHOXY)-ETHOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(2-(2-ETHOXYETHOXY)-ETHOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-METHYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-PENTYL-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-PROPYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-HEXYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-PENTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-ETHYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-OCTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-PROPYL-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-HEPTYL-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(5-HEXENYL)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-OCTYL-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYPYRIDINE

3-(3-(2-METHYL)-BUTYL-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-METHYLCYCLOPROPYL-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-CYCLOPENTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(1-ETHYLTHIO-2-METHOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3-CHLORO-1-PROPYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(2-METHOXYETHOXY)-ETHYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3-CYANO-1-PROPYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-BENZYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(2-ETHOXY-1-ETHYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(4-PENTYNYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(2-(2-ETHOXYMETHOXY)-ETHYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(5-CYANO-1-PENTYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3-PHENYL-1-PROPYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(2-PHENOXYETHYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(4-CYANOBUTYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(2-ETHYLBUTYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-CYCLOHEXYLMETHYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(8-HYDROXYOCTYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(7-OCTENYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-CYCLOPROPYLMETHYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3(3-CYCLOPROPYLMETHYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3-BUTENYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(4-PENTENYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(4-ISOHEXYLOXY-1,2,5-THIADIAZOL-3-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

1-METHYL-1,2,5,6-TETRAHYDRO-3-((4-CYCLOPENTYLPROPYL)OXY)-1,2,5-THIADIAZOL-3-YL)PYRIDINE

1-METHYL-1,2,5,6-TETRAHYDRO-3-(4-ISOHEPTYLOXY-1,2,5-THIADIAZOL-3-YL)PYRIDINE

1-METHYL-1,2,5,6-TETRAHYDRO-3-(4((2-CYCLOHEXYLETHYL)OXY)-1,2,5-THIADIAZOL-3-YL)PYRIDINE

1,2,5,6-TETRAHYDRO-1-METHYL-3-(4-(1-METHYLHEXLOXY)-1,2,5-THIADIAZOL-3-YL)PYRIDINE

3-(4-(1-ETHYLPENTYLOXY)-1,2,5-THIADIAZOL-3-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(4-(1-ETHYLBUTOXY)-1,2,5-THIADIAZOL-3-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

1,2,5,6-TETRAHYDRO-1-METHYL-3-(4-(1-METHYLPENTYLOXY)-1,2,5-THIADIAZOL-3-)YL)PYRIDINE

1-METHYL-3-(4-(5-HEXENYLOXY)-1,2,5-THIADIAZOL-3-YL)-1,2,5,6-TETRAHYDROPYRIDINE

1,2,5,6-TETRAHYDRO-1-METHYL-3-(4-(2-METHYLBUTOXY)-1,2,5-THIADIAZOL-3-YL)PYRIDINE

1,2,5,6-TETRAHYDRO-1-METHYL-3-(4-(2-METHYLPENTYLOXY)-1,2,5-THIADIAZOL-3-YL)PYRIDINE

1,2,5,6-TETRAHYDRO-1-METHYL-3-(4-(2,2,2-TRIFLUOROETHOXY)-1,2,5-THIADIAZOL-3-YL)PYRIDINE

1-METHYL-1,2,5,6-TETRAHYDRO-3-(4-(3-METHYLPENTYLOXY)-1,2,5-THIADIAZOL-3-YL)PYRIDINE

3-(3-(3-METHYL-2-BUTENYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDO-1-METHYLPYRIDINE

3-(3-ISOBUTOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

1,2,5,6-TETRAHYDRO-1-METHYL-3-(4-(2-METHYLBUTOXY)-1,2,5-THIADIAZOL-3-YL)PYRIDINE

3-(3-(3-HYDROXYPROPOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

(+-)1,6-DIMETHYL-3-(3-HEXYLOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE

3-(3-(3-PHENYL-ETHYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

BIS-1,4-(3-(1-METHYL-1,2,5,6-TETRAHYDROPYRIDIN-3-YL)-1,2,5-THIADIAZOL-4-YL)BUTANEDITHIOL

3-(3-(4,4,4-TRIFLUOROBUTOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3,3,3-TRIFLUOROPROPYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-PROPYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE

3-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE

3-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1,1-DIMETHYLPYRIDINIUM IODIDE

(+-)1,6-DIMETHYL-3-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE

(+-)1,6-DIMETHYL-3-(3-BUTOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE

3-(3-(3-METHYL-2-BUTENYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDO-1-METHYL PYRIDINE

3-(3-ISOBUTOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

1,2,5,6-TETRAHYDRO-1-METHYL-3-(4-(2-METHYLBUTOXY)-1,2,5-THIADIAZOL-3-YL)PYRIDINE

3-(3-(3-HYDROXYPROPOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

(+-)1,6-DIMETHYL-3-(3-HEXYLOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE

3-(3-(3-PHENYL-ETHYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

BIS-1,4-(3-(1-METHYL-1,2,5,6-TETRAHYDROPYRIDIN-3-YL)-1,2,5-THIADIAZOL-4-YL)BUTANEDITHIOL

3-(3-(4,4,4-TRIFLUOROBUTOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3,3,3-TRIFLUOROPROPYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-PROPYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-PROPYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE

3-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE

3-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1,1-DIMETHYLPYRIDINIUM IODIDE

(+-)1,6-DIMETHYL-3-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE; and

(+-)1,6-DIMETHYL-3-(3-BUTOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE; or a pharmaceutically acceptable salt thereof.

57. A composition for treating pain comprising a Compound selected from the group consisting of Formula I and Formula II; or
a pharmaceutically acceptable salt or solvate thereof; and a central alpha-adrenergic active compound in a weight ratio of Compound to central alpha-adrenergic active compound of from about 1 to about 1000.

58. A composition of **Claim 57** wherein the Compound is of Formula I.

59. A composition according to **Claim 58** wherein the Compound of Formula I is selected from the group consisting of the following:

3-CHLORO-3-(3-CHLORO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[2.2.2]OCTANE;

3-(3-CHLORO-1,2,5-THIADIAZOL-4-YL)-3-HYDROXY-1-AZABICYCLO[2.2.2]OCTANE;

3-METHOXY-3-(3-METHOXY-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[2.2.2]OCTANE;

3-(3-METHOXY-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[2.2.2]OCT-2-ENE;

3-(3-HEXYLOXY-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[2.2.2]OCT-2-ENE;

3-HEXYLOXY-3-(3-HEXYLOXY-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO-[2.2.2]OCTANE;

3-(3-HEXYLOXY-1,2,5-THIADIAZOL-4-YL)-3-HYDROXY-1-AZABICYCLO[2.2.2]OCTANE;

3-(3-CHLORO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[2.2.2]OCTANE;

3-(3-ETHOXY-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCL0[2.2.2]OCTANE;

3-(3-PROPOXY-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCL0[2.2.2]OCTANE;

3-(3-BUTOXY-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCL0[2.2.2]OCTANE;

3-(3-PENTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCL0-[2.2.2]OCTANE;

3-(3-ETHOXY-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCL0[2.2.2]OCTANE;

3-(3-HEXYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCL0[2.2.2]OCTANE;

3-(3-(3-PHENYLPROPYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCL0[2.2.2]OCTANE;

3-(3-HEXYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCL0[2.2.2]OCTANE;

3-(3-(4-CYANOBENZYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCL0[2.2.2]OCTANE;

EXO-6-(3-CHLORO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[3.2.1]OCTANE;

ENDO-6-(3-CHLORO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[3.2.1]OCTANE;

ENDO-6-(3-HEXYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[3.2.1]OCTANE;

ENDO-6-(3-(5-HEXENYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[3.2.1]OCTANE;

ENDO-6-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[3.2.1]OCTANE;

ENDO-6-(3-PENTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[3.2.1]OCTANE;

ENDO-6-(3-ETHYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[3.2.1]OCTANE; and

ENDO-6-(3-(3-PHENYLPROPYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[3.2.1]OCTANE; or
a pharmaceutically acceptable salt or solvate thereof.

60. A composition of **Claim 59** wherein the Compound of Formula I is 3-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCL0[2.2.2]OCTANE; or
a pharmaceutically acceptable salt thereof.

61. A composition of **Claim 58** wherin the weight ratio of Compound to central alpha-adrenergic active compound of from about 1 to about 30.

62. A composition of **Claim 61** wherein the alpha-adrenergic compound is 2-(2,6-dichlorophenylamino)-2-imidazoline.

63. A composition of **Claim 57** wherein the Compound is of Formula II.

64. A composition of **Claim 63** wherein the Compound of Formula II is selected from the group consisting of

3-(3-METHOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-ETHOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-PROPOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-BUTOXY-1,2,5-THIADIAZOL-4-YL)1,2,5,6-TETTRAHYDRO-1-METHYLPYRIDINE

3-(3-ISOPROPOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-CYCLOPROPYLMETHOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-PENTOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-ISOBUTOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3-BUTENOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(BUT-2-YNOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3-METHYLBUTOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-HEXYLOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(PROP-2-YNOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-BENZYLOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-CHLORO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-CHLORO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE

3-(3-BUTOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE

3-(3-ETHOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-ETHYLPYRIDINE

3-(3-CHLORO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-ETHYLPYRIDINE

3-(3-METHOXYETHOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-HEPTYLOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3-PENTYNYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(4-PENTENYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(2-PROPENYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-OCTYLOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3-HEXYNYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3-BUTENYL-2-OXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYL-PYRIDINE

3-(3-(4-HEXENYLOXY(-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

TRANS-3-(3-(3-HEXENYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

CIS-3-(3-(2-PENTENYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

CIS-3-(3-(2-HEXENYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(5-HEXENYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

CIS-3-(3-(3-HEXENYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,4,5-TETRAHYDRO-1-METHYLPYRIDINE

TRANS-3-(3-(2-HEXENYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(4-METHYLPIPERIDINO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-MORPHOLINO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-DIMETHYLAMINO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-HEXYLAMINO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-HEXYLOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-DEUTEROMETHYLPYRIDINE

1,2,5,6-TETRAHYDRO-3-(3-HEXYLOXY-1,2,5-THIADIAZOL-4-YL)PYRIDINE

3-(3-(2-(2-METHOXYETHOXY)-ETHOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3-ETHOXY-1-PROPOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6,-TETRAHYDRO-1-METHYLPYRIDINE

3-(2-ETHOXYETHOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(2-BUTOXYETHOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(2-(2-BUTOXYETHOXY)-ETHOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(2-(2-ETHOXYETHOXY)-ETHOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-METHYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-PENTYL-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-PROPYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-HEXYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-PENTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-ETHYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-OCTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-PROPYL-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-HEPTYL-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(5-HEXENYL)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-OCTYL-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYPYRIDINE

3-(3-(2-METHYL)-BUTYL-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-METHYLCYCLOPROPYL-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-CYCLOPENTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(1-ETHYLTHIO-2-METHOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3-CHLORO-1-PROPYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(2-METHOXYETHOXY)-ETHYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3-CYANO-1-PROPYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-BENZYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(2-ETHOXY-1-ETHYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(4-PENTYNYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(2-(2-ETHOXYMETHOXY)-ETHYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(5-CYANO-1-PENTYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3-PHENYL-1-PROPYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(2-PHENOXYETHYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(4-CYANOBUTYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(2-ETHYLBUTYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-CYCLOHEXYLMETHYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(8-HYDROXYOCTYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(7-OCTENYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-CYCLOPROPYLMETHYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3(3-CYCLOPROPYLMETHYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3-BUTENYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(4-PENTENYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(4-ISOHEXYLOXY-1,2,5-THIADIAZOL-3-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

1-METHYL-1,2,5,6-TETRAHYDRO-3-((4-CYCLOPENTYLPROPYL)OXY)-1,2,5-THIADIAZOL-3-YL)PYRIDINE

1-METHYL-1,2,5,6-TETRAHYDRO-3-(4-ISOHEPTYLOXY-1,2,5-THIADIAZOL-3-YL)PYRIDINE

1-METHYL-1,2,5,6-TETRAHYDRO-3-(4((2-CYCLOHEXYLETHYL)OXY)-1,2,5-THIADIAZOL-3-YL)PYRIDINE

1,2,5,6-TETRAHYDRO-1-METHYL-3-(4-(1-METHYLHEXLOXY)-1,2,5-THIADIAZOL-3-YL)PYRIDINE

3-(4-(1-ETHYLPENTYLOXY)-1,2,5-THIADIAZOL-3-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(4-(1-ETHYLBUTOXY)-1,2,5-THIADIAZOL-3-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

1,2,5,6-TETRAHYDRO-1-METHYL-3-(4-(1-METHYLPENTYLOXY)-1,2,5-THIADIAZOL-3-)YL)PYRIDINE

1-METHYL-3-(4-(5-HEXENYLOXY)-1,2,5-THIADIAZOL-3-YL)-1,2,5,6-TETRAHYDROPYRIDINE

1,2,5,6-TETRAHYDRO-1-METHYL-3-(4-(2-METHYLBUTOXY)-1,2,5-THIADIAZOL-3-YL)PYRIDINE

1,2,5,6-TETRAHYDRO-1-METHYL-3-(4-(2-METHYLPENTYLOXY)-1,2,5-THIADIAZOL-3-YL)PYRIDINE

1,2,5,6-TETRAHYDRO-1-METHYL-3-(4-(2,2,2-TRIFLUOROETHOXY)-1,2,5-THIADIAZOL-3-YL)PYRIDINE

1-METHYL-1,2,5,6-TETRAHYDRO-3-(4-(3-METHYLPENTYLOXY)-1,2,5-THIADIAZOL-3-YL)PYRIDINE

3-(3-(3-METHYL-2-BUTENYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDO-1-METHYLPYRIDINE

3-(3-ISOBUTOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

1,2,5,6-TETRAHYDRO-1-METHYL-3-(4-(2-METHYLBUTOXY)-1,2,5-THIADIAZOL-3-YL)PYRIDINE

3-(3-(3-HYDROXYPROPOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

(+-)1,6-DIMETHYL-3-(3-HEXYLOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE

3-(3-(3-PHENYL-ETHYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

BIS-1,4-(3-(1-METHYL-1,2,5,6-TETRAHYDROPYRIDIN-3-YL)-1,2,5-THIADIAZOL-4-YL)BUTANEDITHIOL

3-(3-(4,4,4-TRIFLUOROBUTOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3,3,3-TRIFLUOROPROPYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-PROPYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE

3-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE

3-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1,1-DIMETHYLPYRIDINIUM IODIDE

(+-)1,6-DIMETHYL-3-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE

(+-)1,6-DIMETHYL-3-(3-BUTOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE

3-(3-(3-METHYL-2-BUTENYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDO-1-METHYL PYRIDINE

3-(3-ISOBUTOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

1,2,5,6-TETRAHYDRO-1-METHYL-3-(4-(2-METHYLBUTOXY)-1,2,5-THIADIAZOL-3-YL)PYRIDINE

3-(3-(3-HYDROXYPROPOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

(+-)1,6-DIMETHYL-3-(3-HEXYLOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE

3-(3-(3-PHENYL-ETHYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

BIS-1,4-(3-(1-METHYL-1,2,5,6-TETRAHYDROPYRIDIN-3-YL)-1,2,5-THIADIAZOL-4-YL)BUTANEDITHIOL

3-(3-(4,4,4-TRIFLUOROBUTOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3,3,3-TRIFLUOROPROPYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-PROPYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-PROPYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE

3-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE

3-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1,1-DIMETHYLPYRIDINIUM IODIDE

(+-)1,6-DIMETHYL-3-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE; and

(+-)1,6-DIMETHYL-3-(3-BUTOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE; or a pharmaceutically acceptable salt or solvate thereof.

65. A method for treating pain comprising administering to a patient in need thereof, a composition comprising a Compound selected from the group consisting of Formula I and Formula II; or a pharmaceutically acceptable salt or solvate thereof; and a central alpha-adrenergic active compound in a weight ratio of Compound to central alpha-adrenergic active compound of from about 1 to about 1000.

66. A method of **Claim 65** wherein the Compound is of Formula I.

67. A method of **Claim 66** wherein the Compound is 3-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCL0[2.2.2]OCTANE; or

a pharmaceutically acceptable salt or solvate thereof.

68. A method of **Claim 65** wherein the Compound is of Formula II.

69. A composition for treating pain comprising an analgesic dose of a Compound selected from the group consisting of Formula I and Formula II; or a pharmaceutically acceptable salt or solvate thereof; and one or more opioid compounds in a weight ratio of Compound to opioid compound of from about 1 to about 1000.

70. A composition of **Claim 69** wherein the Compound is of Formula I.

71. A composition of **Claim 70** wherein the compound of Formula I is selected from the group consisting of the following:

3-CHLORO-3-(3-CHLORO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[2.2.2]OCTANE;

3-(3-CHLORO-1,2,5-THIADIAZOL-4-YL)-3-HYDROXY-1-AZABICYCLO[2.2.2]OCTANE;

3-METHOXY-3-(3-METHOXY-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[2.2.2]OCTANE;

3-(3-METHOXY-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[2.2.2]OCT-2-ENE;

3-(3-HEXYLOXY-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[2.2.2]OCT-2-ENE;

3-HEXYLOXY-3-(3-HEXYLOXY-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO-[2.2.2]OCTANE;

3-(3-HEXYLOXY-1,2,5-THIADIAZOL-4-YL)-3-HYDROXY-1-AZABICYCLO[2.2.2]OCTANE;

3-(3-CHLORO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[2.2.2]OCTANE;

3-(3-ETHOXY-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCL0[2.2.2]OCTANE;

3-(3-PROPOXY-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCL0[2.2.2]OCTANE;

3-(3-BUTOXY-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCL0[2.2.2]OCTANE;

3-(3-PENTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCL0-[2.2.2]OCTANE;

3-(3-ETHOXY-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCL0[2.2.2]OCTANE;

3-(3-HEXYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCL0[2.2.2]OCTANE;

3-(3-(3-PHENYLPROPYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCL0[2.2.2]OCTANE;

3-(3-HEXYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCL0[2.2.2]OCTANE;

3-(3-(4-CYANOBENZYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCL0[2.2.2]OCTANE;

EXO-6-(3-CHLORO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[3.2.1]OCTANE;

ENDO-6-(3-CHLORO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[3.2.1]OCTANE;

ENDO-6-(3-HEXYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[3.2.1]OCTANE;

ENDO-6-(3-(5-HEXENYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[3.2.1]OCTANE;

ENDO-6-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[3.2.1]OCTANE;

ENDO-6-(3-PENTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[3.2.1]OCTANE;

ENDO-6-(3-ETHYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[3.2.1]OCTANE; and

ENDO-6-(3-(3-PHENYLPROPYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCLO[3.2.1]OCTANE; or
a pharmaceutically acceptable salt or solvate thereof.

73. A method of **Claim 71** wherein the Compound is 3-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCL0[2.2.2]OCTANE; or
a pharmaceutically acceptable salt or solvate thereof.

74. A composition of **Claim 69** wherein the Compound is of Formula II.

75. A composition of **Claim 74** wherein the Compound of Formula II is selected from the group consisting of

3-(3-METHOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-ETHOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-PROPOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-BUTOXY-1,2,5-THIADIAZOL-4-YL)1,2,5,6-TETTRAHYDRO-1-METHYLPYRIDINE

3-(3-ISOPROPOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-CYCLOPROPYLMETHOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-PENTOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-ISOBUTOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3-BUTENOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(BUT-2-YNOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3-METHYLBUTOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-HEXYLOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(PROP-2-YNOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-BENZYLOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-CHLORO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-CHLORO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE

3-(3-BUTOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE

3-(3-ETHOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-ETHYLPYRIDINE

3-(3-CHLORO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-ETHYLPYRIDINE

3-(3-METHOXYETHOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-HEPTYLOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3-PENTYNYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(4-PENTENYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(2-PROPENYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-OCTYLOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3-HEXYNYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3-BUTENYL-2-OXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYL-PYRIDINE

3-(3-(4-HEXENYLOXY(-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

TRANS-3-(3-(3-HEXENYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

CIS-3-(3-(2-PENTENYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

CIS-3-(3-(2-HEXENYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(5-HEXENYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

CIS-3-(3-(3-HEXENYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,4,5-TETRAHYDRO-1-METHYLPYRIDINE

TRANS-3-(3-(2-HEXENYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(4-METHYLPIPERIDINO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-MORPHOLINO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-DIMETHYLAMINO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-HEXYLAMINO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-HEXYLOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-DEUTEROMETHYLPYRIDINE

1,2,5,6-TETRAHYDRO-3-(3-HEXYLOXY-1,2,5-THIADIAZOL-4-YL)PYRIDINE

3-(3-(2-(2-METHOXYETHOXY)-ETHOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3-ETHOXY-1-PROPOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6,-TETRAHYDRO-1-METHYLPYRIDINE

3-(2-ETHOXYETHOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(2-BUTOXYETHOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(2-(2-BUTOXYETHOXY)-ETHOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(2-(2-ETHOXYETHOXY)-ETHOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-METHYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-PENTYL-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-PROPYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-HEXYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-PENTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-ETHYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-OCTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-PROPYL-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-HEPTYL-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(5-HEXENYL)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-OCTYL-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYPYRIDINE

3-(3-(2-METHYL)-BUTYL-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-METHYLCYCLOPROPYL-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-CYCLOPENTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(1-ETHYLTHIO-2-METHOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3-CHLORO-1-PROPYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(2-METHOXYETHOXY)-ETHYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3-CYANO-1-PROPYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-BENZYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(2-ETHOXY-1-ETHYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(4-PENTYNYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(2-(2-ETHOXYMETHOXY)-ETHYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(5-CYANO-1-PENTYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3-PHENYL-1-PROPYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(2-PHENOXYETHYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(4-CYANOBUTYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(2-ETHYLBUTYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-CYCLOHEXYLMETHYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(8-HYDROXYOCTYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(7-OCTENYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-CYCLOPROPYLMETHYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3(3-CYCLOPROPYLMETHYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3-BUTENYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(4-PENTENYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(4-ISOHEXYLOXY-1,2,5-THIADIAZOL-3-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

1-METHYL-1,2,5,6-TETRAHYDRO-3-((4-CYCLOPENTYLPROPYL)OXY)-1,2,5-THIADIAZOL-3-YL)PYRIDINE

1-METHYL-1,2,5,6-TETRAHYDRO-3-(4-ISOHEPTYLOXY-1,2,5-THIADIAZOL-3-YL)PYRIDINE

1-METHYL-1,2,5,6-TETRAHYDRO-3-(4((2-CYCLOHEXYLETHYL)OXY)-1,2,5-THIADIAZOL-3-YL)PYRIDINE

1,2,5,6-TETRAHYDRO-1-METHYL-3-(4-(1-METHYLHEXLOXY)-1,2,5-THIADIAZOL-3-YL)PYRIDINE

3-(4-(1-ETHYLPENTYLOXY)-1,2,5-THIADIAZOL-3-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(4-(1-ETHYLBUTOXY)-1,2,5-THIADIAZOL-3-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

1,2,5,6-TETRAHYDRO-1-METHYL-3-(4-(1-METHYLPENTYLOXY)-1,2,5-THIADIAZOL-3-)YL)PYRIDINE

1-METHYL-3-(4-(5-HEXENYLOXY)-1,2,5-THIADIAZOL-3-YL)-1,2,5,6-TETRAHYDROPYRIDINE

1,2,5,6-TETRAHYDRO-1-METHYL-3-(4-(2-METHYLBUTOXY)-1,2,5-THIADIAZOL-3-YL)PYRIDINE

1,2,5,6-TETRAHYDRO-1-METHYL-3-(4-(2-METHYLPENTYLOXY)-1,2,5-THIADIAZOL-3-YL)PYRIDINE

1,2,5,6-TETRAHYDRO-1-METHYL-3-(4-(2,2,2-TRIFLUOROETHOXY)-1,2,5-THIADIAZOL-3-YL)PYRIDINE

1-METHYL-1,2,5,6-TETRAHYDRO-3-(4-(3-METHYLPENTYLOXY)-1,2,5-THIADIAZOL-3-YL)PYRIDINE

3-(3-(3-METHYL-2-BUTENYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDO-1-METHYLPYRIDINE

3-(3-ISOBUTOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

1,2,5,6-TETRAHYDRO-1-METHYL-3-(4-(2-METHYLBUTOXY)-1,2,5-THIADIAZOL-3-YL)PYRIDINE

3-(3-(3-HYDROXYPROPOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

(+-)1,6-DIMETHYL-3-(3-HEXYLOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE

3-(3-(3-PHENYL-ETHYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

BIS-1,4-(3-(1-METHYL-1,2,5,6-TETRAHYDROPYRIDIN-3-YL)-1,2,5-THIADIAZOL-4-YL)BUTANEDITHIOL

3-(3-(4,4,4-TRIFLUOROBUTOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3,3,3-TRIFLUOROPROPYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-PROPYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE

3-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE

3-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1,1-DIMETHYLPYRIDINIUM IODIDE

(+-)1,6-DIMETHYL-3-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE

(+-)1,6-DIMETHYL-3-(3-BUTOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE

3-(3-(3-METHYL-2-BUTENYLOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDO-1-METHYL PYRIDINE

3-(3-ISOBUTOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

1,2,5,6-TETRAHYDRO-1-METHYL-3-(4-(2-METHYLBUTOXY)-1,2,5-THIADIAZOL-3-YL)PYRIDINE

3-(3-(3-HYDROXYPROPOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

(+-)1,6-DIMETHYL-3-(3-HEXYLOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE

3-(3-(3-PHENYL-ETHYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

BIS-1,4-(3-(1-METHYL-1,2,5,6-TETRAHYDROPYRIDIN-3-YL)-1,2,5-THIADIAZOL-4-YL)BUTANEDITHIOL

3-(3-(4,4,4-TRIFLUOROBUTOXY)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-(3,3,3-TRIFLUOROPROPYLTHIO)-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-PROPYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINE

3-(3-PROPYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE

3-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE

3-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDRO-1,1-DIMETHYLPYRIDINIUM IODIDE

(+-)1,6-DIMETHYL-3-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE; and

(+-)1,6-DIMETHYL-3-(3-BUTOXY-1,2,5-THIADIAZOL-4-YL)-1,2,5,6-TETRAHYDROPYRIDINE; or a pharmaceutically acceptable salt or solvate thereof.

76. A composition of **Claim 69** wherein the opioid compound is selected from the group consisting of morphine, codeine, meperidine, methadone, propoxyphene, levorphanol, hydromorphone, oxymorphone, oxycodone, brompton's cocktail, naloxone, naltrexone, pentazocine, butorphanol, nabuphine, and buprenorphine.

77. A composition of **Claim 69** wherein the opioid compound is selected from the group consisting of hydromorphone, hydrocodone, meperidone, buprenorphine, butorphenol, nalbuphine, pentazocine, oxymorphine, oxycodone, levorphanol, fentanyl, and alphaprodine.

78. A composition of **Claim 69** wherein the opioid compound is selected from the group consisting of

propoxyphene, methadone, morphine, hydrocodone, hydromorphine, and codeine.

79. A composition of **Claim 78** wherein the opioid compound is selected from morphine and codeine.

80. A method for treating pain comprising administering an analgesic dose of a composition comprising a Compound selected from the group consisting of Formula I and Formula II; or a pharmaceutically acceptable salt or solvate thereof; and one or more opioid compounds in a weight ratio of Compound to opioid compound of from about 1 to about 1000.

81. A method of **Claim 80** wherein the Compound is of Formula I.

82. A method of **Claim 81** wherein the Compound is 3-(3-BUTYLTHIO-1,2,5-THIADIAZOL-4-YL)-1-AZABICYCL0[2.2.2]OCTANE; or

a pharmaceutically acceptable salt or solvate thereof.

83. A method of **Claim 80** wherein the Compound is of Formula II.

81. The use of a composition comprising a Compound selected from the group consisting of Formula I and Formula II; or a pharmaceutically acceptable salt or solvate thereof; and one or more opioid compounds in a weight ratio of Compound to opioid compound of from about 1 to about 1000 for a manufacture of a medicament for therapeutic application in the treatment of pain.

82. The use of a composition comprising a Compound selected from the group consisting of Formula I and Formula II; or a pharmaceutically acceptable salt or

solvate thereof; and one or more alpha-adrenergic compounds in a weight ratio of Compound to alpha-adrenergic compound of from about 1 to about 1000 for a manufacture of a medicament for therapeutic application in the treatment of pain.

83. The use of a composition comprising a Compound selected from the group consisting of Formula I and Formula II; or a pharmaceutically acceptable salt or solvate thereof; and one or more non-steroidal antiinflammatory drug (NSAIDS) in a weight ratio of Compound to NSAIDS compound of from about 1 to about 1000 for a manufacture of a medicament for therapeutic application in the treatment of pain.

84. The use of a composition comprising a Compound selected from the group consisting of Formula I and Formula II; or a pharmaceutically acceptable salt or solvate thereof; and acetaminophen in a weight ratio of Compound to acetaminophen of from about 1 to about 1000 for a manufacture of a medicament for therapeutic application in the treatment of pain.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/19390

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/41

US CL :514/362, 364

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/362, 364

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

USPATFULL, HCAPLUS, MEDLINE- preferred compounds of formula I for the treatment of pain and etc.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,041,455 A (SAUERBERG et al.) 20 August 1991, entire document.	1-24, 33, and 83
Y	US 5,578,602 A (SAUERBERG et al.) 26 November 1996, entire document.	1-24, 33, and 83
Y	US 5,527,813 A (SAUERBERG et al.) 18 June 1996, entire document.	1-24, 33, and 83
Y	DIPIRO et al. Pharmacotherapy A Pathophysiologic Approach. New York: Elsevier Science. 1989, pages 906-909.	1-24, 33, and 83
A, E	US 5,605,701 A (BYMASTER et al.) 25 February 1997, claims.	1-24, 33, and 83

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 12 APRIL 1997	Date of mailing of the international search report 12 MAY 1997
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer IW for M. MOEZIE Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)★

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/19390

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1 (in part-compounds of formula I), 2-24, 33, and 83 (in part-compounds of formula I)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/19390

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

Group I, claim(s) 1-37 and 83, drawn to methods and compositions employing compounds of formula I or II and NSAIDs for the treatment of pain.

Group II, claim(s) 38-56 and 84, drawn to compositions and methods employing compounds of formula I or II and acetaminophen in the treatment of pain.

Group III, claim(s) 57-68 and 82, drawn to methods and compositions employing compounds of formula I or II and an a central alpha adrenergic compound in the treatment of pain.

Group IV, claim(s) 69-81, drawn to methods and compositions employing compounds of formula I or II and an opioid compound in the treatment of pain.

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack Unity of Invention because they are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for more than one species to be searched, the appropriate additional search fees must be paid. The species are as follows:

Compounds of formula I and Compounds of formula II. See e.g., claims 1, 38, 57, and 69.

The inventions listed as Groups I-IV do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the inventions relate to separate and distinct general inventive concepts which are compositions and methods relating to the use of different generic classes of compounds used in combination for the treatment of pain. When multiple products, e.g., compositions and uses e.g., methods of treatment, for the same are claimed, the first invention of the category first mentioned in the claims constitutes the main invention. See 37 CFR 1.475(b) and (d) particularly.

The species listed above do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: The compounds of formula I and II relate to compounds which differ so greatly in chemical structure as to lack even any common central core.