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(54) Title: ION CHANNEL MODULATORS

(57) Abstract: The invention relates to compounds, compositions comprising the compounds, and methods of using the compounds and compound compositions. The compounds, compositions, and methods described herein can be used for the therapeutic modulation of ion channel function, and treatment of disease and disease symptoms, particularly those mediated by certain calcium channel subtype targets.

ION CHANNEL MODULATORS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims benefit of U.S. patent applications 60/551,606, filed March 8, 2004, and 60/579,193, filed June 10, 2004, the contents of which are incorporated by
5 reference in their entirety.

BACKGROUND

All cells rely on the regulated movement of inorganic ions across cell membranes to perform essential physiological functions. Electrical excitability, synaptic plasticity, and signal transduction are examples of processes in which changes in ion concentration play a
10 critical role. In general, the ion channels that permit these changes are proteinaceous pores consisting of one or multiple subunits, each containing two or more membrane-spanning domains. Most ion channels have selectivity for specific ions, primarily Na^+ , K^+ , Ca^{2+} , or Cl^- , by virtue of physical preferences for size and charge. Electrochemical forces, rather than active transport, drive ions across membranes, thus a single channel may allow the passage of
15 millions of ions per second. Channel opening, or "gating" is tightly controlled by changes in voltage or by ligand binding, depending on the subclass of channel. Ion channels are attractive therapeutic targets due to their involvement in so many physiological processes, yet the generation of drugs with specificity for particular channels in particular tissue types remains a major challenge.

20 Voltage-gated ion channels open in response to changes in membrane potential. For example, depolarization of excitable cells such as neurons result in a transient influx of Na^+ ions, which propagates nerve impulses. This change in Na^+ concentration is sensed by voltage-gated K^+ channels, which then allow an efflux of K^+ ions. The efflux of K^+ ions repolarizes the membrane. Other cell types rely on voltage-gated Ca^{2+} channels to generate
25 action potentials. Voltage-gated ion channels also perform important functions in non-excitable cells, such as the regulation of secretory, homeostatic, and mitogenic processes. Ligand-gated ion channels can be opened by extracellular stimuli such as neurotransmitters (e.g., glutamate, serotonin, acetylcholine), or intracellular stimuli (e.g. cAMP, Ca^{2+} , and phosphorylation).

30 The Ca_v2 family of voltage-gated calcium channels consists of 3 main subtypes $\text{Ca}_v2.1$ (P or Q-type calcium currents), $\text{Ca}_v2.2$ (N-type calcium currents) and $\text{Ca}_v2.3$ (R-type calcium currents). These currents are found almost exclusively in the central nerves system (CNS),

peripheral nerves system (PNS) and neuroendocrine cells and constitute the predominant forms of presynaptic voltage-gated calcium current. Presynaptic calcium entry is modulated by many types of G-protein coupled receptors (GPCRs) and modulation of Ca_v2 channels is a widespread and highly efficacious means of regulating neurotransmission. The subunit composition of the Ca_v2 channels is defined by their α_1 subunit, which forms the pore and contains the voltage-sensing gates ($\alpha_{1.2.1}$, $\alpha_{1.2.2}$ and $\alpha_{1.2.3}$, also known as α_{1A} , α_{1B} and α_{1E} respectively) and the β , $\alpha_2\delta$ and γ subunits.

Genetic or pharmacological perturbations in ion channel function can have dramatic clinical consequences. Long QT syndrome, epilepsy, cystic fibrosis, and episodic ataxia are a few examples of heritable diseases resulting from mutations in ion channel subunits. Toxic side effects such as arrhythmia and seizure which are triggered by certain drugs are due to interference with ion channel function (Sirois, J.E. and, Atchison, W.D., *Neurotoxicology* 1996; 17(1):63-84; Keating, M.T., *Science* 1996 272:681-685). Drugs are useful for the therapeutic modulation of ion channel activity, and have applications in treatment of many pathological conditions, including hypertension, angina pectoris, myocardial ischemia, asthma, bladder overactivity, alopecia, pain, heart failure, dysmenorrhea, type II diabetes, arrhythmia, graft rejection, seizure, convulsions, epilepsy, stroke, gastric hypermotility, psychoses, cancer, muscular dystrophy, and narcolepsy (Coghlan, M.J., et al. *J. Med. Chem.* 2001, 44:1627-1653; Ackerman, M.J., and Clapham, D.E. *N. Eng. J. Med.* 1997, 336:1575-1586). The growing number of identified ion channels and understanding of their complexity will assist in future efforts at therapies, which modify ion channel function.

Therapeutic modulation of Ca_v2 channel activity has applications in treatment of many pathological conditions. All primary sensory afferents provide input to neurons in the dorsal horns of the spinal cord and in dorsal root ganglia neurons in the dorsal horn and calcium influx through $Ca_v2.2$ channels triggers the release of neurotransmitters from presynaptic nerve terminals in the spinal cord. Hence blockade of $Ca_v2.2$ channels is expected to be broadly efficacious because these channels are in a common pathway downstream from the wide variety of receptors that mediate pain (Julius, D. and Basbaum, A.I. *Nature* 2001, 413:203-216). Indeed, intrathecal injection of $Ca_v2.2$ selective conopeptide ziconotide (SNX-111) has been shown to be broadly effective against both neuropathic pain and inflammatory pain in animals and man (Bowersox, S.S. et al, *J Pharmacol Exp Ther* 1996, 279:1243-1249). Ziconotide has also been shown to be highly effective as a neuroprotective agent in rat models of global or focal ischemia (Colburne, F. et al, *Stroke* 1999, 30:662-668). Thus it is

reasonable to conclude that modulation of Ca_v2.2 has implications in the treatment of neuroprotection / stroke.

Ca_v2.2 channels are found in the periphery and mediate catecholamine release from sympathetic neurons and adrenal chromaffin cells. Some forms of hypertension result from elevated sympathetic tone and Ca_v2.2 modulators could be particularly effective in treating this disorder. Although complete block of Ca_v2.2 can cause hypotension or impair baroreceptor reflexes, partial inhibition by Ca_v2.2 modulators might reduce hypertension with minimal reflex tachycardia (Uneyama, O.D. *Int. J. Mol. Med.* 1999 3:455-466).

Overactive bladder (OAB) is characterized by storage symptoms such as urgency, frequency and nocturia, with or without urge incontinence, resulting from the overactivity of the detrusor muscle in the bladder. OAB can lead to urge incontinence. The etiology of OAB and painful bladder syndrome is unknown, although disturbances in nerves, smooth muscle and urothelium can cause OAB (Steers, W. *Rev Urol*, 4:S7-S18). There is evidence to suggest that reduction of bladder hyperactivity may be indirectly effected by inhibition of Ca_v2.2 and/or Ca_v1 channels.

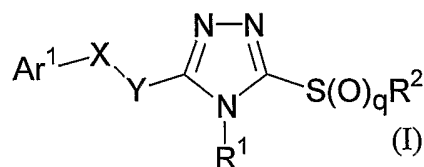
The localization of Ca_v2.1 channels in the superficial laminae of the dorsal horn of the spinal cord suggests involvement of these channels in the perception and maintenance of certain forms of pain (Vanegas, H. and Schaible, H. *Pain* 2000, 85:9-18. Complete elimination of Ca_v2.1 calcium currents alters synaptic transmission, resulting in severe ataxia. Gabapentin has been used clinically for many years as an add-on therapy for the treatment of epilepsy. In recent years, it has emerged as a leading treatment of neuropathic pain. Clinical trials have shown gabapentin to be effective for the treatment of post-herpetic neuralgia, diabetic neuropathy, trigeminal neuralgia, migraine and fibromyalgia (Mellegers, P.G. et al *Clin J Pain* 2001, 17:284-295). Gabapentin was designed as a metabolically stable GABA mimetic, but most studies find no effect on the GABA receptors. The $\alpha_2\delta$ subunit of the Ca_v2.1 channel has been identified as a high affinity binding site for gabapentin in the CNS. There is evidence that suggests that gabapentin could inhibit neurotransmission in the spinal cord by interfering with the function of the $\alpha_2\delta$ subunits thereby inhibiting presynaptic calcium currents.

SUMMARY

The invention relates to heterocyclic compounds, compositions comprising the compounds, and methods of using the compounds and compound compositions. The

compounds and compositions comprising them are useful for treating disease or disease symptoms, including those mediated by or associated with ion channels.

One aspect is a method of treating a disease or disease symptom in a subject including administering to the subject an effective amount of a compound of formula I or pharmaceutical salt thereof:



wherein,

Ar¹ is cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents;

X is NR³, C(R³)₂, S, a bond or O, or together with Y forms -CH=CH-;

Y is C=O, a bond, or lower alkyl, or together with X forms -CH=CH-;

R¹ is Ar², alkenyl, or lower alkyl optionally substituted with Ar²;

each Ar² is independently cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents;

q is 0, 1 or 2;

each R² is independently (CH₂)_mCO₂R³, (CH₂)_mCOAr³, (CH₂)_mCONR³R⁴, (CH₂)_mAr³, (CH₂)₃Ar³, (CH₂)_nNR³R⁴, (CH₂)_nOR⁴; (CH₂)_mCN; alkyl; alkynyl, (CR³R³)_mCONR³R⁴, Ar⁴, (CR³R³)_mN(R³)C(O)Ar³, or (CH₂)_mC(NO₂)NH₂;

each R³ is independently H, or lower alkyl;

each R⁴ is independently H, lower alkyl, alkoxy, (CH₂)_nNR⁵R⁶, or (CH₂)_pAr³;

m is 1 or 2;

n is 2 or 3;

p is 0 or 1;

each Ar³ is cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents;

each substituent for Ar¹, Ar² and Ar³ is independently halogen, CN, NO₂, OR⁶, SR⁶, S(O)₂OR⁵, NR⁵R⁶, cycloalkyl, C₁-C₂ perfluoroalkyl, C₁-C₂ perfluoroalkoxy, 1,2-methylenedioxy, C(O)OR⁵, C(O)NR⁵R⁶, OC(O)NR⁵R⁶, NR⁵C(O)NR⁵R⁶, C(NR⁶)NR⁵R⁶, NR⁵C(NR⁶)NR⁵R⁶, S(O)₂NR⁵R⁶, R⁷, C(O)R⁷, NR⁵C(O)R⁷, S(O)R⁷, or S(O)₂R⁷;

each R⁵ is independently hydrogen or lower alkyl optionally substituted with one or more substituents independently selected from halogen, OH, C₁-C₄ alkoxy, NH₂, C₁-C₄ alkylamino, C₁-C₄ dialkylamino or C₃-C₆ cycloalkyl;

each R⁶ is independently hydrogen, (CH₂)_pAr⁴, or lower alkyl optionally substituted with one or more substituents independently selected from halogen, OH, C₁-C₄ alkoxy, NH₂, C₁-C₄ alkylamino, C₁-C₄ dialkylamino or C₃-C₆ cycloalkyl;

each R⁷ is independently (CH₂)_pAr⁴ or lower alkyl optionally substituted with one or more substituents independently selected from halogen, OH, C₁-C₄ alkoxy, NH₂, C₁-C₄ alkylamino, C₁-C₄ dialkylamino or C₃-C₆ cycloalkyl; and

each Ar⁴ is independently C₃-C₆ cycloalkyl, heterocyclyl, aryl or heteroaryl, each optionally substituted with one to three substituents independently selected from halogen, OH, C₁-C₄ alkoxy, NH₂, C₁-C₄ alkylamino, C₁-C₄ dialkylamino or 1,2-methylenedioxy.

In other aspects, the methods are those of any of the formulae herein (including any combinations thereof):

Wherein,

Ar¹ is aryl or heteroaryl, each optionally substituted with one or more substituents;

X is NR³;

Y is lower alkyl;

R¹ is aryl optionally substituted with one or more substituents; and

each R² is independently (CH₂)_mCO₂R³, (CH₂)_mCOAr³, (CH₂)_mCONR³R⁴, (CH₂)_mAr³, (CH₂)₃Ar³, or (CH₂)_nNR³R⁴.

Wherein,

Ar¹ is aryl or heteroaryl, each optionally substituted with one or more substituents;

X is a bond;

wherein,

Ar¹ is cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents, and each attached to X by a carbon atom;

X is CH₂;

5 Y is a bond;

R¹ is Ar², alkenyl, or lower alkyl optionally substituted with Ar²;

each Ar² is independently cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents;

q is 0, 1 or 2;

10 each R² is independently (CH₂)_mCO₂R³, (CH₂)_mCOAr³, or (CH₂)_mCONR³R⁴;

each R³ is independently H, or lower alkyl;

each R⁴ is independently H, lower alkyl, alkoxy, (CH₂)_nNR⁵R⁶, or (CH₂)_pAr³;

m is 2;

n is 2 or 3;

15 p is 0 or 1;

each Ar³ is cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents;

20 each substituent for Ar¹, Ar² and Ar³ is independently halogen, CN, NO₂, OR⁶, SR⁶, S(O)₂OR⁵, NR⁵R⁶, cycloalkyl, C₁-C₂ perfluoroalkyl, C₁-C₂ perfluoroalkoxy, 1,2-methylenedioxy, C(O)OR⁵, C(O)NR⁵R⁶, OC(O)NR⁵R⁶, NR⁵C(O)NR⁵R⁶, C(NR⁶)NR⁵R⁶, NR⁵C(NR⁶)NR⁵R⁶, S(O)₂NR⁵R⁶, R⁷, C(O)R⁷, NR⁵C(O)R⁷, S(O)R⁷, or S(O)₂R⁷;

each R⁵ is independently hydrogen or lower alkyl optionally substituted with one or more substituents independently selected from halogen, OH, C₁-C₄ alkoxy, NH₂, C₁-C₄ alkylamino, C₁-C₄ dialkylamino or C₃-C₆ cycloalkyl;

25 each R⁶ is independently hydrogen, (CH₂)_pAr⁴, or lower alkyl optionally substituted with one or more substituents independently selected from halogen, OH, C₁-C₄ alkoxy, NH₂, C₁-C₄ alkylamino, C₁-C₄ dialkylamino or C₃-C₆ cycloalkyl;

each R⁷ is independently (CH₂)_pAr⁴ or lower alkyl optionally substituted with one or more substituents independently selected from halogen, OH, C₁-C₄ alkoxy, NH₂, C₁-C₄ alkylamino, C₁-C₄ dialkylamino or C₃-C₆ cycloalkyl; and

5 each Ar⁴ is independently C₃-C₆ cycloalkyl, heterocyclyl, aryl or heteroaryl, each optionally substituted with one to three substituents independently selected from halogen, OH, C₁-C₄ alkoxy, NH₂, C₁-C₄ alkylamino, C₁-C₄ dialkylamino or 1,2-methylenedioxy.

In other aspects, the compounds are those of any of the formulae herein (including any combinations thereof):

10 Wherein,

Ar¹ is cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents, and each attached to X by a carbon atom;

X is a bond;

Y is a bond;

15 R¹ is Ar²;

each Ar² is independently cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents;

each R² is 4-pyridylmethyl;

20 Wherein,

Ar¹ is cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents, and each attached to X by a carbon atom, however, Ar¹ is not 4-pyridyl;

X is a bond;

25 Y is a bond;

R¹ is Ar²;

each Ar² is independently cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents; and

each R² is 3-pyridylmethyl;

Wherein,

Ar¹ is cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with
5 one or more substituents, and each attached to X by a carbon atom;

X is a bond;

Y is a bond;

R¹ is Ar²;

each Ar² is independently cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally
10 substituted with one or more substituents; and

each R² is 2-pyridylmethyl;

Wherein:

Ar¹ is cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with
one or more substituents;

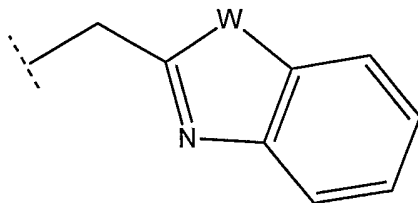
15 X is a bond;

Y is a bond;

R¹ is Ar²;

each Ar² is independently cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally
substituted with one or more substituents; and

20 each R² is:



wherein W is NR³, S or O.

Wherein,

Ar¹ is cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents;

5 X is a bond;

Y is a bond;

R¹ is Ar²;

each Ar² is independently cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents;

10 each R² is (CH₂)_mAr³; and

each Ar³ is aryl substituted with NH₂, S(O)₂OR³, COOH, or C(O)NH₂ ;

Another aspect is a method of treating a Cav2 calcium channel mediated disease or disease symptom in a subject comprising administering to the subject an effective amount of a compound, or pharmaceutical salt, (or composition thereof) of any of the formulae herein.

Another aspect is a method of treating a mediated disease or disease symptom in a subject comprising administering to the subject an effective amount of a compound, or pharmaceutical salt, (or composition thereof) of any of the formulae herein. The disease or disease symptom is angina, hypertension, congestive heart failure, myocardial ischemia, arrhythmia, diabetes, urinary incontinence, stroke, pain, traumatic brain injury, or a neuronal disorder.

Another aspect is a composition including a compound of any of the formulae herein, or pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier. The composition can further include an additional therapeutic agent.

Another aspect is a method of making a compound of formula I, including reacting an intermediate delineated herein with a reagent to provide a compound of formula I as defined herein.

Another aspect is a method of modulating (e.g., inhibiting, antagonism, agonism) calcium channel activity in a subject in need thereof comprising administering to the subject an effective amount of a compound of any of the formulae herein, or pharmaceutically acceptable salt thereof, or composition thereof.

In other aspects, the invention relates to a composition comprising a compound of any of the formulae herein, an additional therapeutic agent, and a pharmaceutically acceptable carrier. The additional therapeutic agent can be a cardiovascular disease agent and/or a nervous system disease agent. A nervous system disease agent refers to a peripheral nervous system (PNS) disease agent and/or a central nervous system (CNS) disease agent.

Yet another aspect of this invention relates to a method of treating a subject (e.g., mammal, human, horse, dog, cat) having a disease or disease symptom (including, but not limited to angina, hypertension, congestive heart failure, myocardial ischemia, arrhythmia, diabetes, urinary incontinence, stroke, pain, traumatic brain injury, or a neuronal disorder). The method includes administering to the subject (including a subject identified as in need of such treatment) an effective amount of a compound described herein, or a composition described herein to produce such effect. Identifying a subject in need of such treatment can be in the judgment of a subject or a health care professional and can be subjective (e.g. opinion) or objective (e.g. measurable by a test or diagnostic method).

Yet another aspect of this invention relates to a method of treating a subject (e.g., mammal, human, horse, dog, cat) having an ion channel mediated disease or disease symptom (including, but not limited to angina, hypertension, congestive heart failure, myocardial ischemia, arrhythmia, diabetes, urinary incontinence, stroke, pain, traumatic brain injury, or a neuronal disorder). The method includes administering to the subject (including a subject identified as in need of such treatment) an effective amount of a compound described herein, or a composition described herein to produce such effect. Identifying a subject in need of such treatment can be in the judgment of a subject or a health care professional and can be subjective (e.g. opinion) or objective (e.g. measurable by a test or diagnostic method).

The invention also relates to a method of making a compound described herein, the method including any reactions or reagents as delineated in the schemes or examples herein. Alternatively, the method includes taking any one of the intermediate compounds described herein and reacting it with one or chemical reagents in one or more steps to produce a compound described herein.

Also within the scope of this invention is a packaged product. The packaged product includes a container, one of the aforementioned compounds in the container, and a legend (e.g., a label or an insert) associated with the container and indicating administration of the compound for treating a disorder associated with ion channel modulation.

In other embodiments, the compounds, compositions, and methods delineated herein are any of the compounds of the Tables herein or methods including them.

The details of one or more embodiments of the invention are set forth in the accompanying drawings and the description below. Other features, objects, and advantages of the invention will be apparent from the description and from the claims.

DETAILED DESCRIPTION

As used herein, the term "halo" refers to any radical of fluorine, chlorine, bromine or iodine.

The term "alkyl" refers to a hydrocarbon chain that may be a straight chain or branched chain, containing the indicated number of carbon atoms. For example, C₁-C₅ indicates that the group may have from 1 to 5 (inclusive) carbon atoms in it. The term "lower alkyl" refers to a C₁-C₆ alkyl chain. The term "arylalkyl" refers to a moiety in which an alkyl hydrogen atom is replaced by an aryl group.

The term "alkoxy" refers to an -O-alkyl radical. The term "alkylene" refers to a divalent alkyl (i.e., -R-). The term "alkylenedioxy" refers to a divalent species of the structure -O-R-O-, in which R represents an alkylene.

The term "cycloalkyl" as employed herein includes saturated and partially unsaturated cyclic hydrocarbon groups having 3 to 12 carbons, preferably 3 to 8 carbons, and more preferably 3 to 6 carbon. The term "cycloalkylalkyl" refers to alkyl substituted with a cycloalkyl. The term "cycloalkylalkoxy" refers to an alkoxy substituted with cycloalkyl.

The term "heterocyclyl" refers to a nonaromatic 5-8 membered monocyclic, 8-12 membered bicyclic, or 11-14 membered tricyclic ring system having 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S (e.g., carbon atoms and 1-3, 1-6, or 1-9 heteroatoms of N, O, or S if monocyclic, bicyclic, or tricyclic, respectively), wherein 0, 1, 2 or 3 atoms of each ring may be substituted by a substituent. The term "heterocyclylalkyl" refers to alkyl substituted with a heterocyclyl. The term "heterocyclylalkoxy" refers to an alkoxy substituted with heterocyclyl.

The term "aryl" refers to a hydrocarbon monocyclic, bicyclic or tricyclic aromatic ring system wherein 0, 1, 2, 3, or 4 atoms of each ring may be substituted by a substituent. Examples of aryl groups include phenyl, naphthyl and the like. The term "arylalkyl" or the

term "aralkyl" refers to alkyl substituted with an aryl. The term "arylalkoxy" refers to an alkoxy substituted with aryl.

The term "heteroaryl" refers to an aromatic 5-8 membered monocyclic, 8-12 membered bicyclic, or 11-14 membered tricyclic ring system having 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S (e.g., carbon atoms and 1-3, 1-6, or 1-9 heteroatoms of N, O, or S if monocyclic, bicyclic, or tricyclic, respectively), wherein 0, 1, 2, 3, or 4 atoms of each ring may be substituted by a substituent. The term "heteroarylalkyl" refers to alkyl substituted with an heteroaryl. The term "heteroarylalkoxy" refers to an alkoxy substituted with a heteroaryl.

The term "oxo" refers to an oxygen atom, which forms a carbonyl when attached to carbon, an N-oxide when attached to nitrogen, and a sulfoxide or sulfone when attached to sulfur.

The term "acyl" refers to an alkylcarbonyl, cycloalkylcarbonyl, arylcarbonyl, heterocyclylcarbonyl, or heteroarylcarbonyl substituent, any of which may be further substituted by substituents.

The term "substituents" refers to a group "substituted" on an alkyl, cycloalkyl, aryl, heterocyclyl, or heteroaryl group at any atom of that group. Suitable substituents include, without limitation halogen, CN, NO₂, OR⁵, SR⁵, S(O)₂OR⁵, NR⁵R⁶, C₁-C₂ perfluoroalkyl, C₁-C₂ perfluoroalkoxy, 1,2-methylenedioxy, C(O)OR⁵, C(O)NR⁵R⁶, OC(O)NR⁵R⁶, NR⁵C(O)NR⁵R⁶, C(NR⁶)NR⁵R⁶, NR⁵C(NR⁶)NR⁵R⁶, S(O)₂NR⁵R⁶, R⁷, C(O)R⁷, NR⁵C(O)R⁷, S(O)R⁷, or S(O)₂R⁷. Each R⁵ is independently hydrogen, C₁-C₄ alkyl or C₃-C₆ cycloalkyl. Each R⁶ is independently hydrogen, C₃-C₆ cycloalkyl, aryl, heterocyclyl, heteroaryl, C₁-C₄ alkyl or C₁-C₄ alkyl substituted with C₃-C₆ cycloalkyl, aryl, heterocyclyl or heteroaryl. Each R⁷ is independently C₃-C₆ cycloalkyl, aryl, heterocyclyl, heteroaryl, C₁-C₄ alkyl or C₁-C₄ alkyl substituted with C₃-C₆ cycloalkyl, aryl, heterocyclyl or heteroaryl. Each C₃-C₆ cycloalkyl, aryl, heterocyclyl, heteroaryl and C₁-C₄ alkyl in each R⁵, R⁶ and R⁷ can optionally be substituted with halogen, CN, C₁-C₄ alkyl, OH, C₁-C₄ alkoxy, NH₂, C₁-C₄ alkylamino, C₁-C₄ dialkylamino, C₁-C₂ perfluoroalkyl, C₁-C₂ perfluoroalkoxy, or 1,2-methylenedioxy.

In one aspect, the substituents on a group are independently, hydrogen, hydroxyl, halogen, nitro, SO₃H, trifluoromethyl, trifluoromethoxy, alkyl (C₁-C₆ straight or branched), alkoxy (C₁-C₆ straight or branched), O-benzyl, O-phenyl, phenyl, 1,2-methylenedioxy,

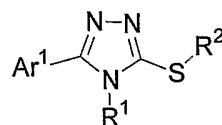
carboxyl, morpholinyl, piperidinyl, amino or OC(O)NR⁵R⁶. Each R⁵ and R⁶ is as described above.

The term “treating” or “treated” refers to administering a compound described herein to a subject with the purpose to cure, heal, alleviate, relieve, alter, remedy, ameliorate, improve, or affect a disease, the symptoms of the disease or the predisposition toward the disease.

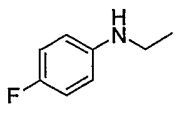
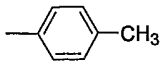
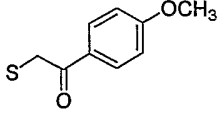
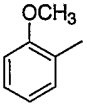
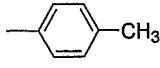
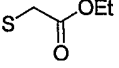
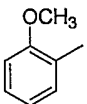
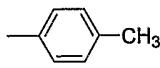
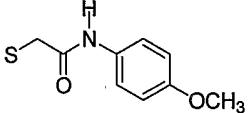
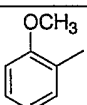
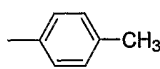
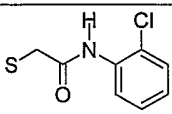
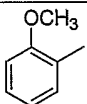
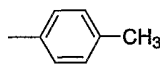
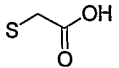
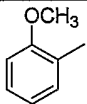
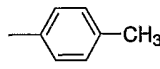
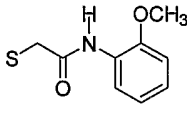
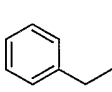
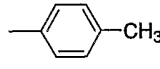
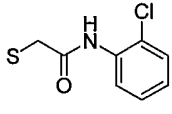
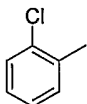
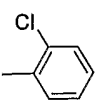
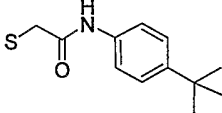
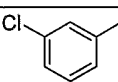
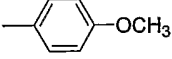


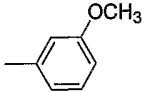

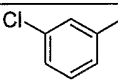
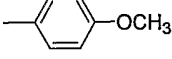
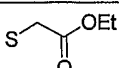
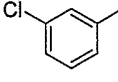
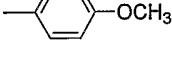
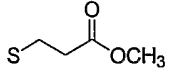
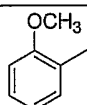
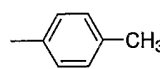
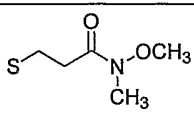
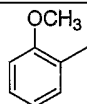
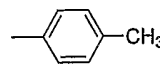
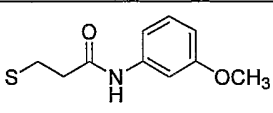
“An effective amount” refers to an amount of a compound, which confers a therapeutic effect on the treated subject. The therapeutic effect may be objective (i.e., measurable by some test or marker) or subjective (i.e., subject gives an indication of or feels an effect). An effective amount of the compound described above may range from about 0.1 mg/Kg to about 500 mg/Kg. Effective doses will also vary depending on route of administration, as well as the possibility of co-usage with other agents.

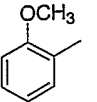
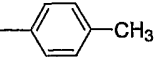
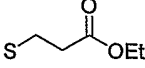
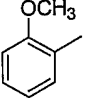
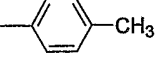
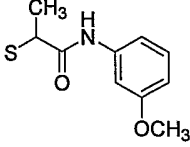
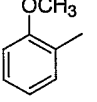
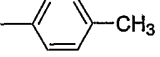
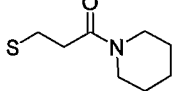
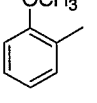
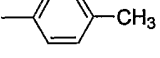
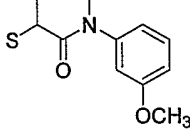
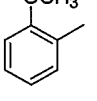
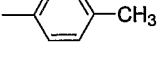
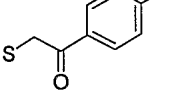
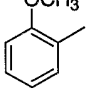
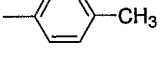
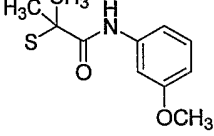
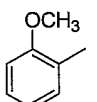
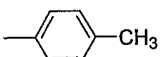
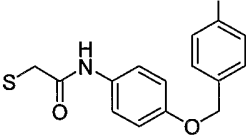
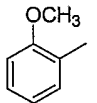
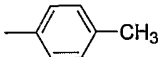
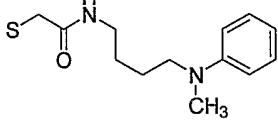
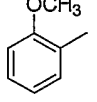
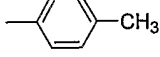
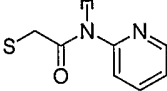
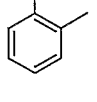
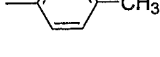
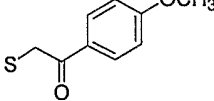

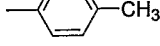
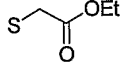
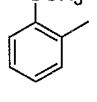
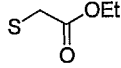
Representative compounds useful in the compositions and methods are delineated herein:

Table 1A

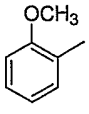
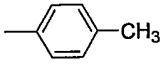
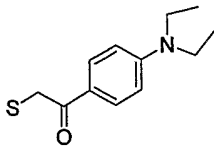
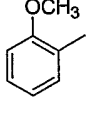
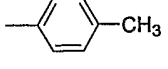
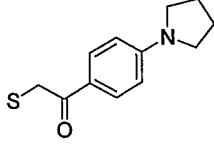
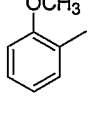
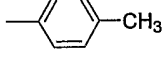
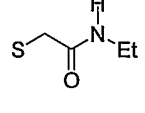
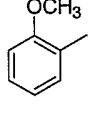
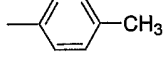
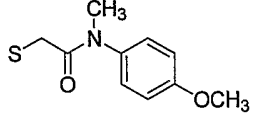
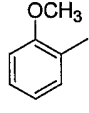
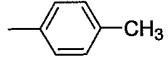
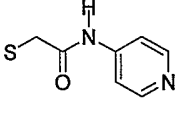
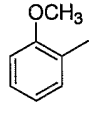
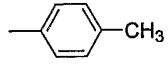
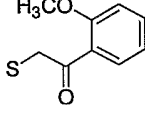
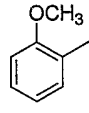
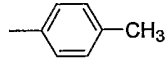
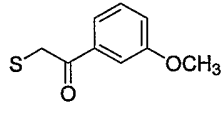
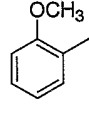
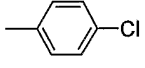
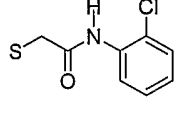
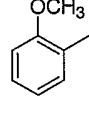
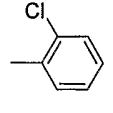
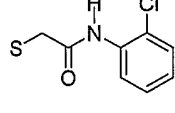
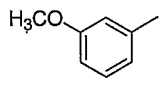
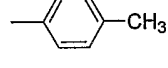
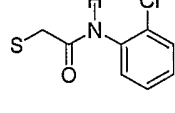
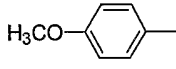
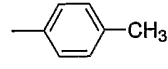
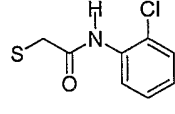
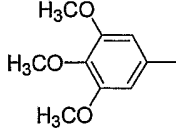
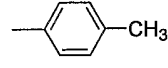
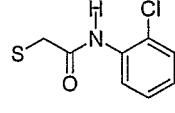


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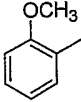
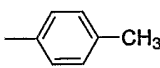
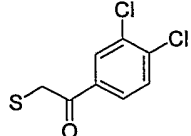
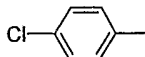
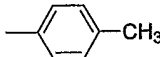
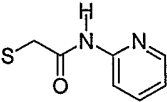
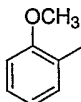
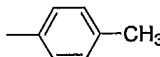
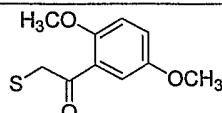
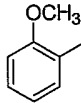
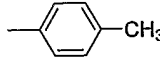
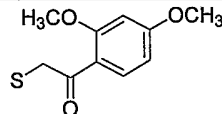
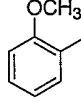
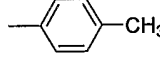
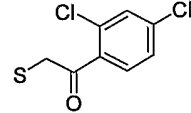
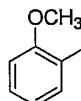
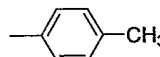
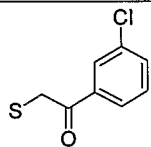
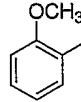
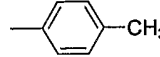
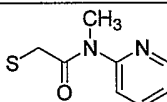
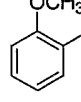
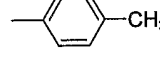
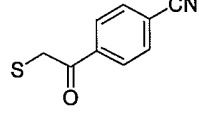
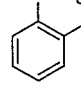
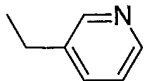
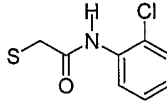
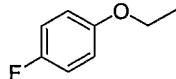
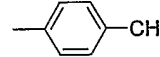
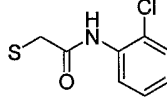
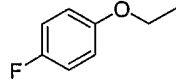
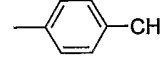
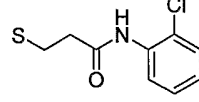
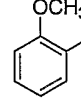
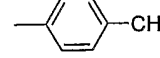
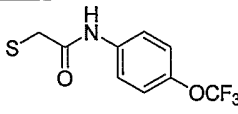
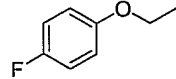
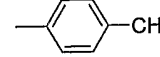
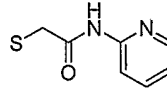
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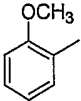
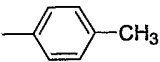
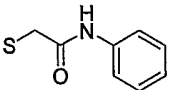
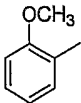
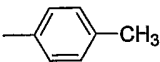
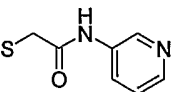
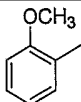
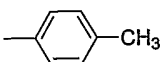
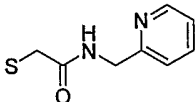
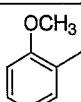
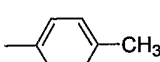
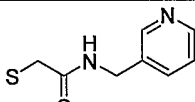
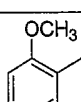
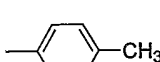
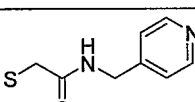
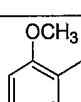
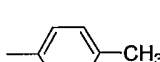
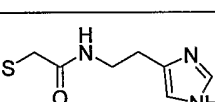
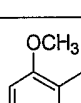
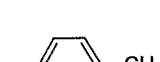
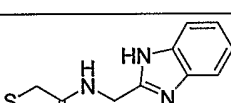
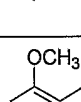
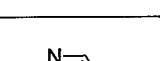
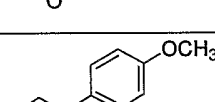
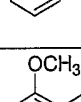
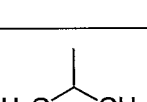
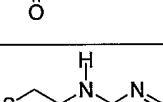
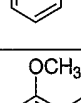

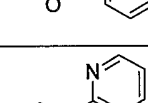
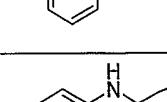
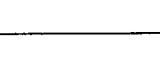
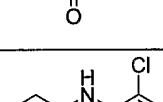
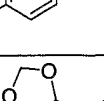
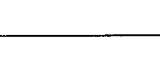
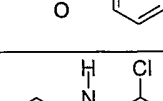
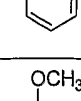

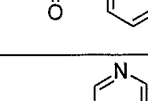
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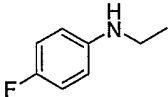
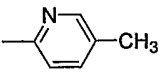
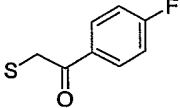
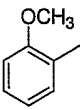
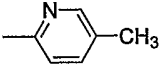
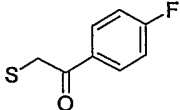
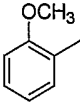
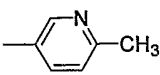
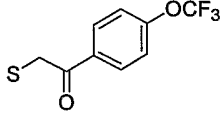
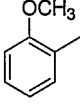
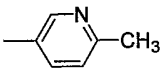
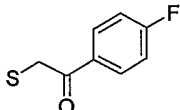

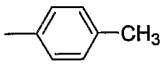
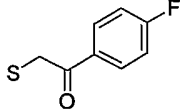
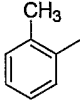
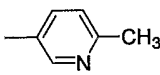
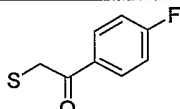
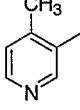
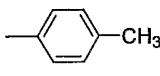
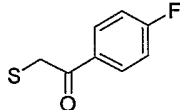
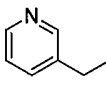
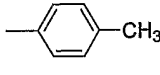
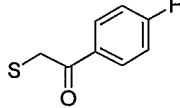
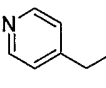
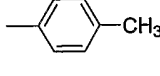
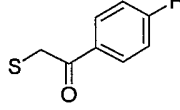
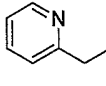
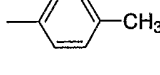
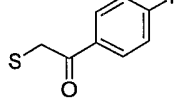
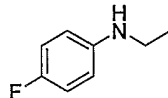
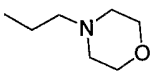
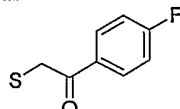
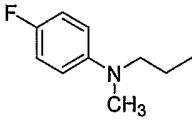
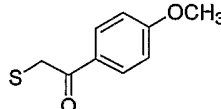
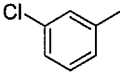
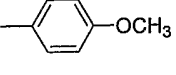
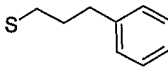
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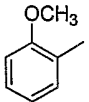
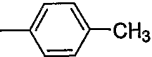
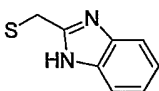
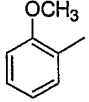
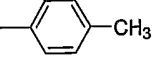
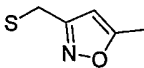
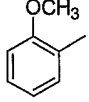
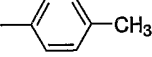
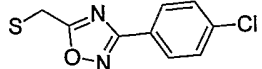
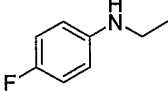
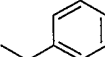
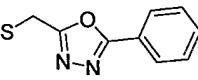
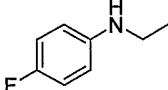
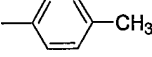
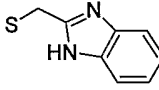
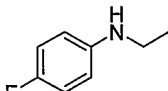
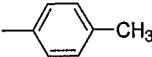
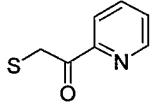
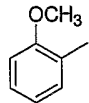
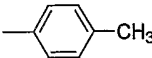
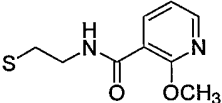
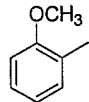
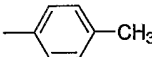
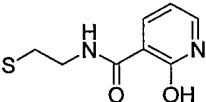
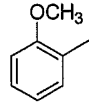
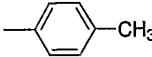
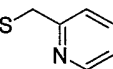
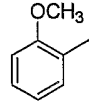
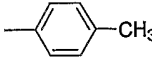
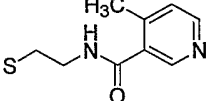
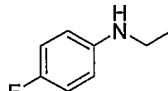
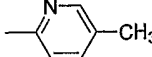
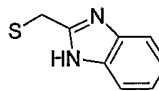
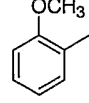
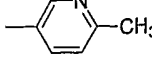
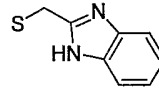
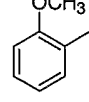
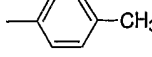
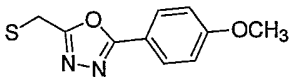
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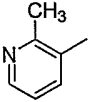
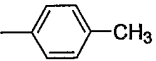
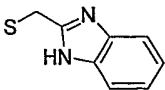
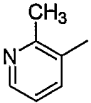
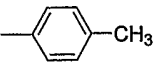
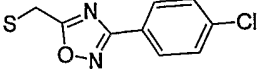
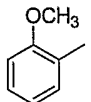
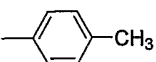
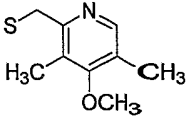
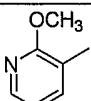
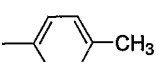
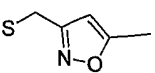
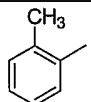
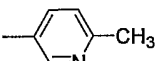
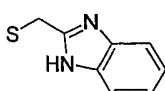
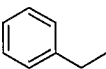
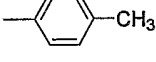
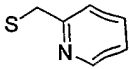
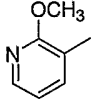
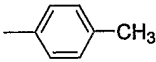
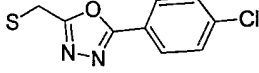
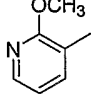
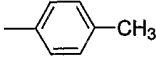
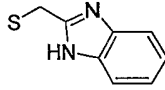
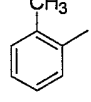
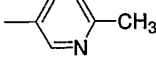
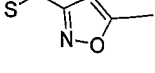
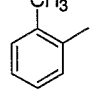
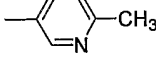
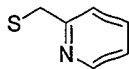
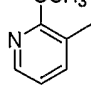
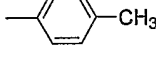
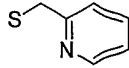
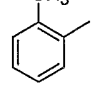
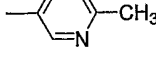
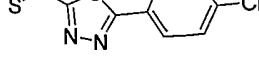
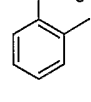
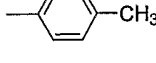
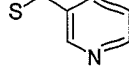
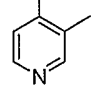
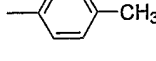
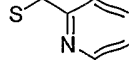
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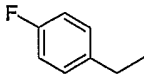
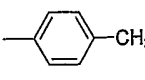
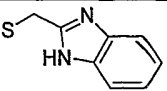
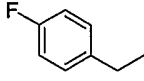
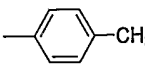
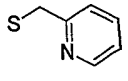
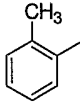
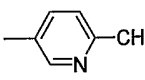
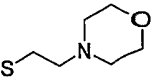
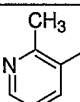
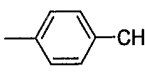
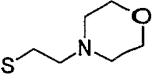
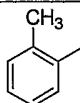
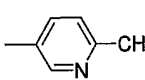
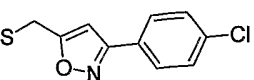
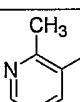
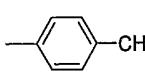
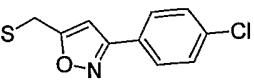
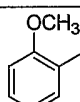
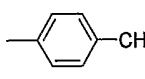
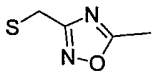
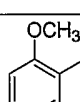
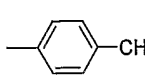
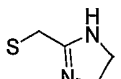
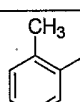
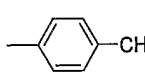
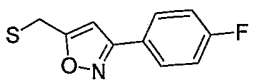
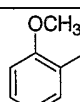
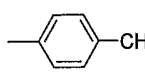
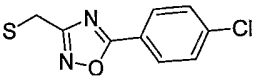
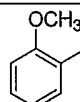
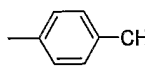
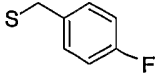
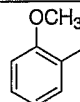
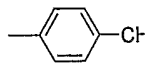
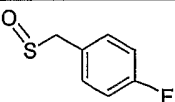
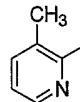
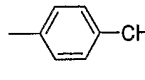
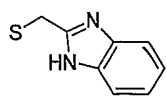
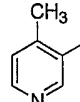
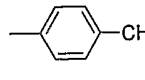
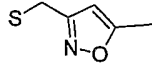
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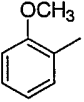
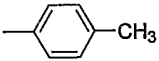
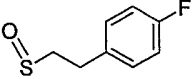
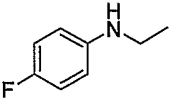
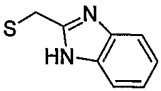
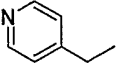
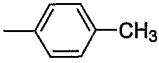
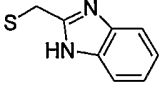
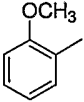
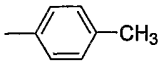
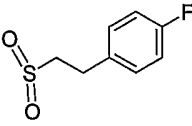
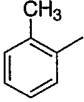
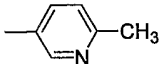
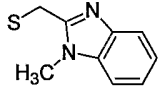
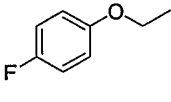
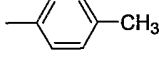
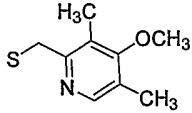
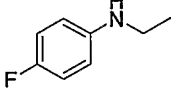
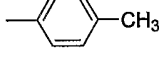
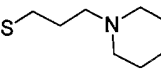
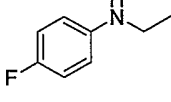
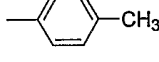
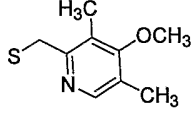
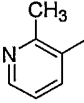
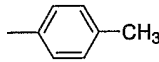
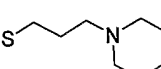
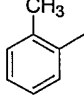
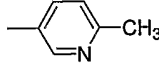
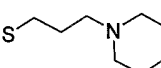
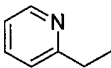
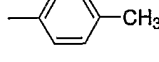
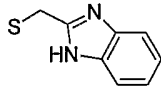
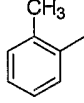
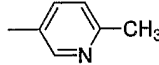
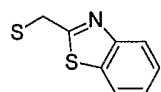
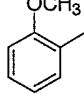
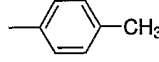
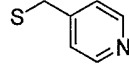
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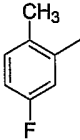
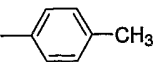
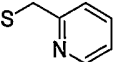
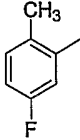
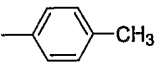
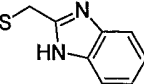

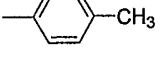
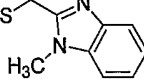
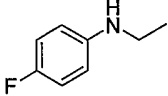
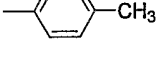
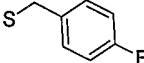

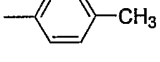
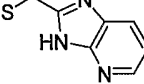
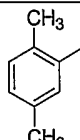
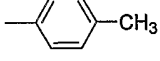
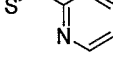
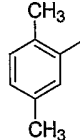
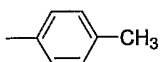
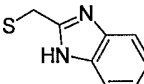
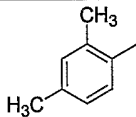
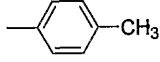
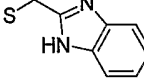
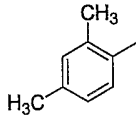
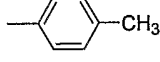
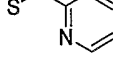
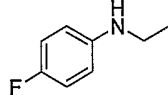
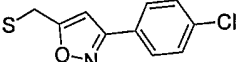
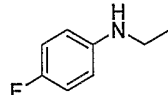
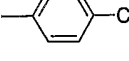
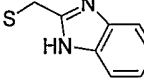

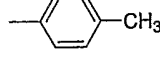
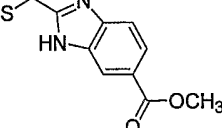
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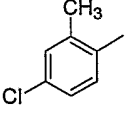
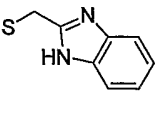
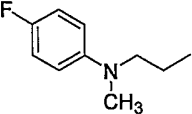
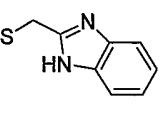
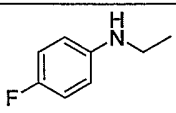
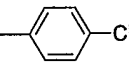
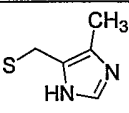
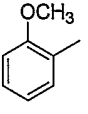
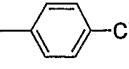
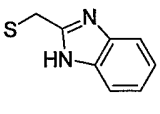
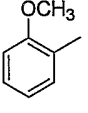
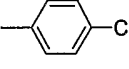
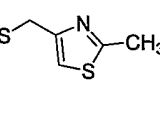
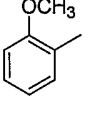
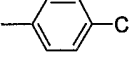
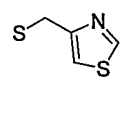
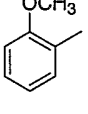
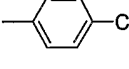
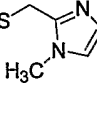
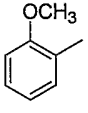
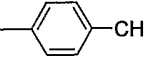

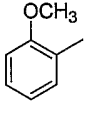
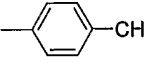

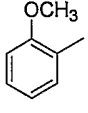
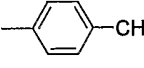
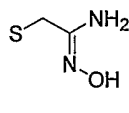
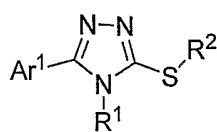
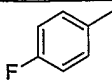
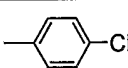
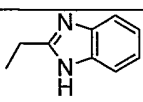
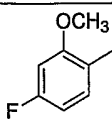
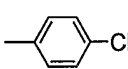
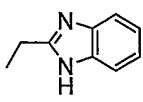
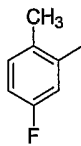
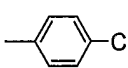
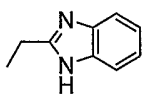
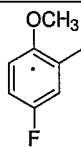
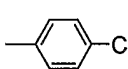
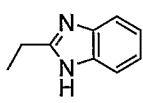
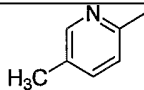
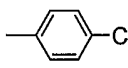
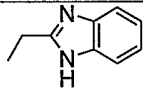

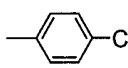
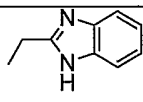
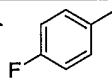
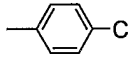
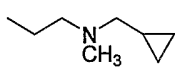
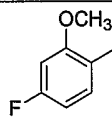
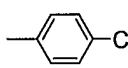
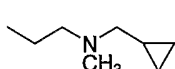
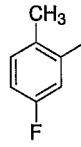
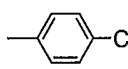
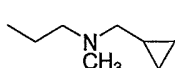
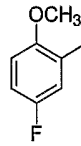
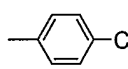
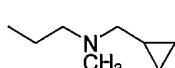
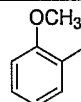
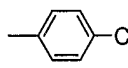
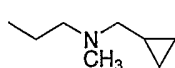
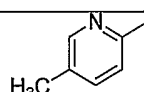
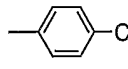
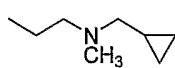

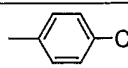
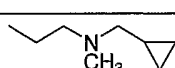
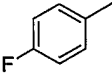
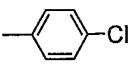
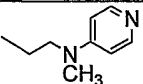
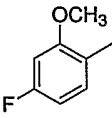
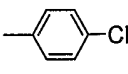
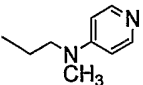
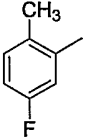
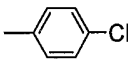
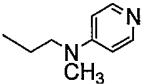
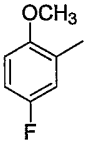
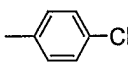
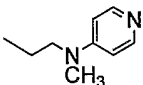
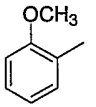
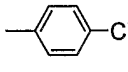
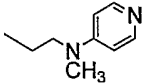
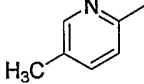
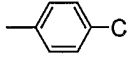
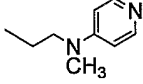

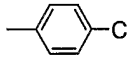
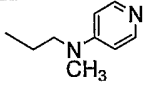
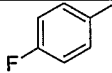
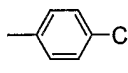
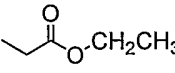
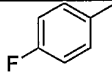
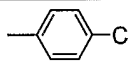
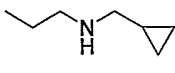
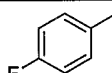
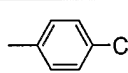
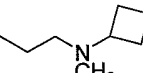
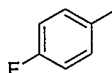
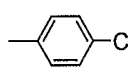
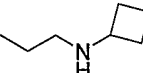
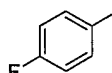
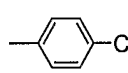
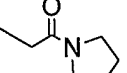
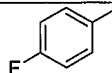
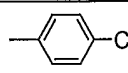
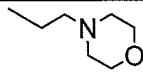
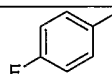
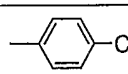
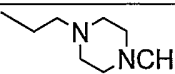
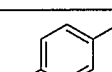
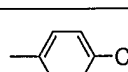
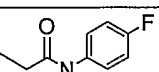
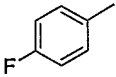
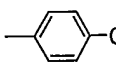
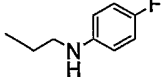
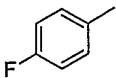
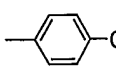
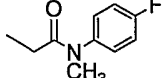
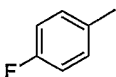
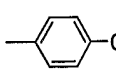
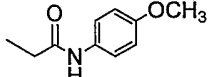
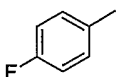
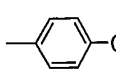
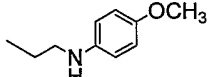
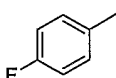
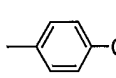
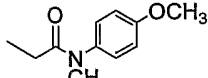
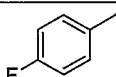
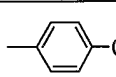
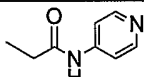
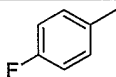
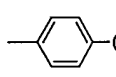
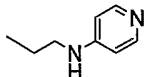
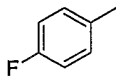
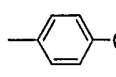
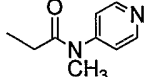
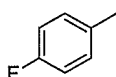
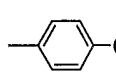
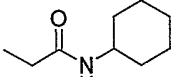
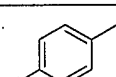
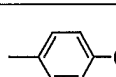
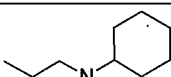
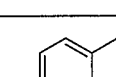
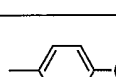
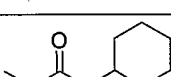
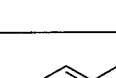

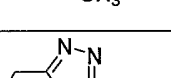
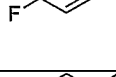
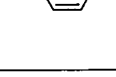
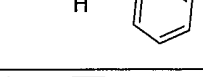
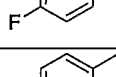
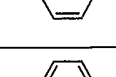
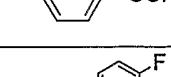
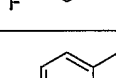

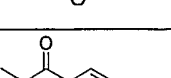
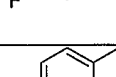

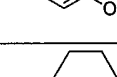
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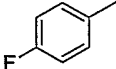
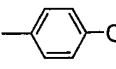
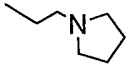
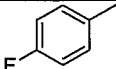
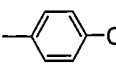
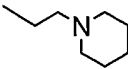
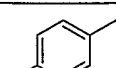
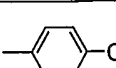
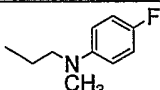
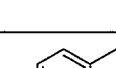
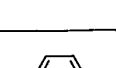
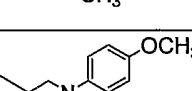
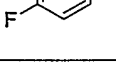

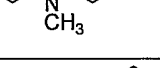
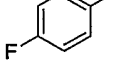
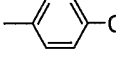
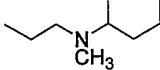
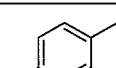
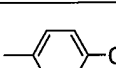
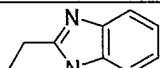
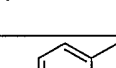


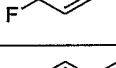
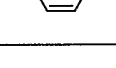

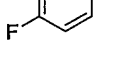
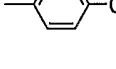
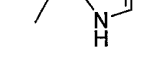
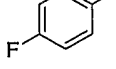
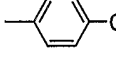

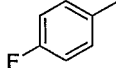
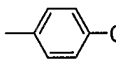

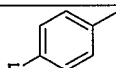
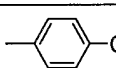

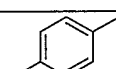
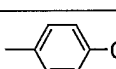
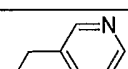
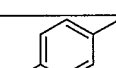
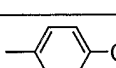
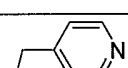
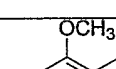
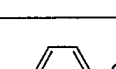
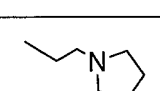
Table 1B



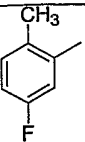
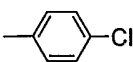
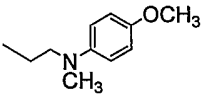
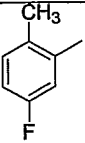
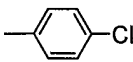
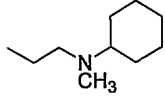
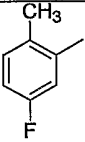
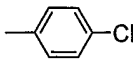
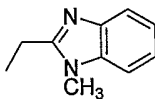
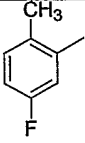
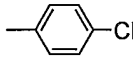
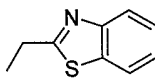
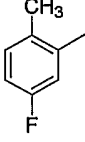
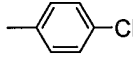
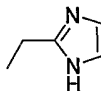
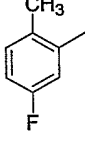
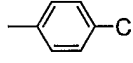
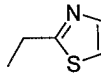
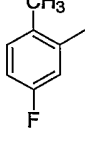
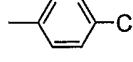
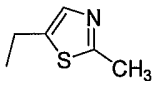
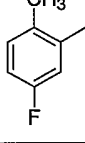
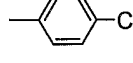
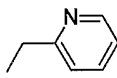
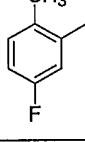
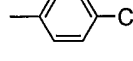
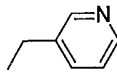
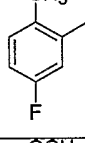
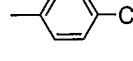
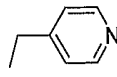
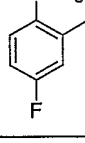
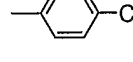
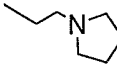
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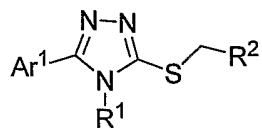
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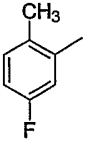
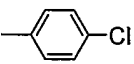
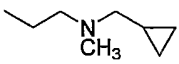
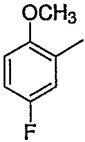
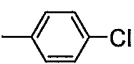
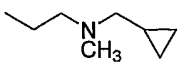
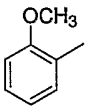
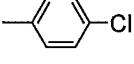
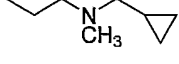
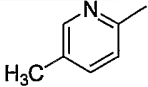
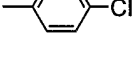
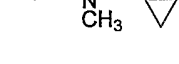

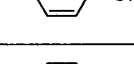
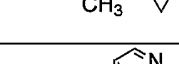

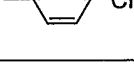
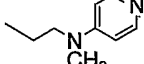
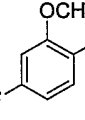
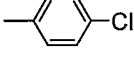
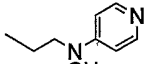
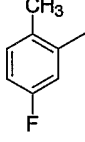
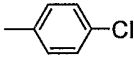
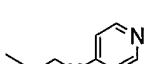
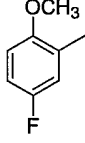
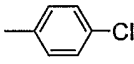
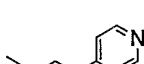

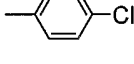
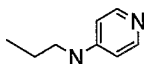
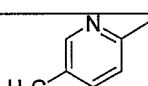
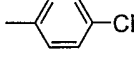
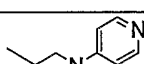

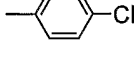
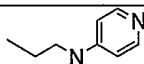

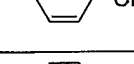
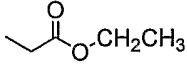

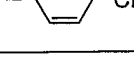
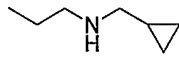
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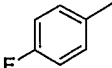
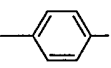
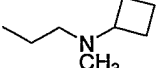
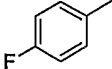
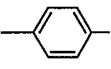
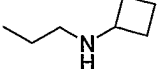
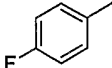
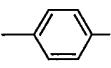
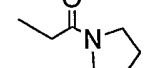
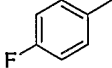
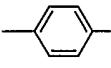
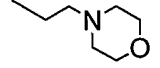
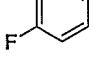
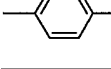
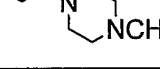
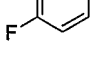
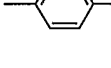
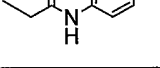
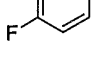
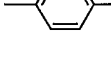
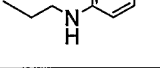
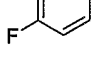
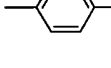
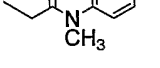
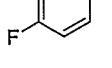
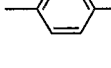
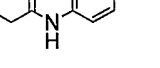
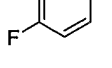
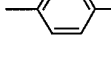
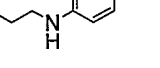
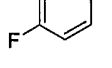
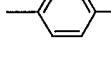
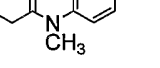
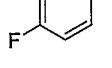
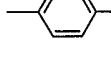
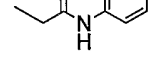
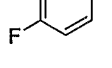
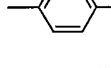
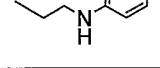
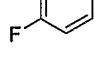
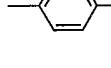
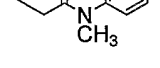
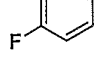
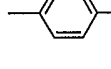
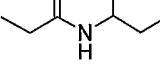
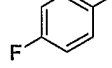
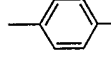
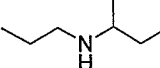
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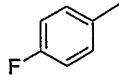
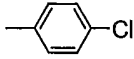
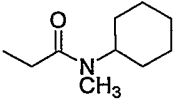
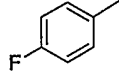
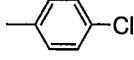
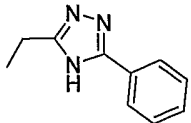
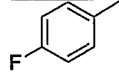
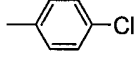
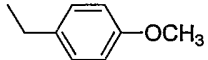
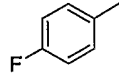
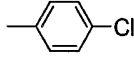
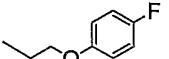
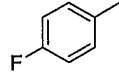
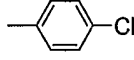
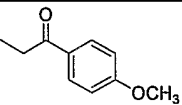
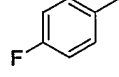
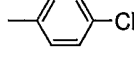
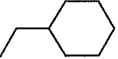
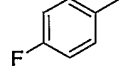
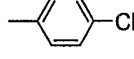
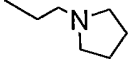
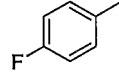
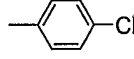
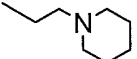
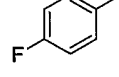
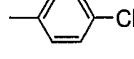
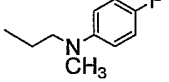
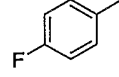
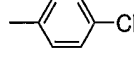
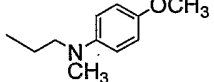
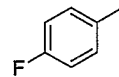
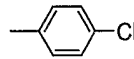
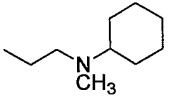
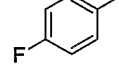
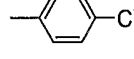
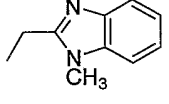
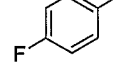
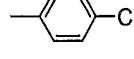
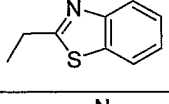
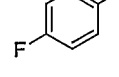
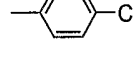
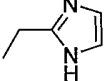
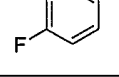
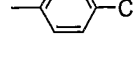
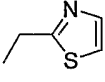
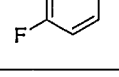
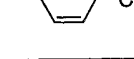
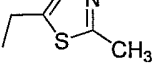


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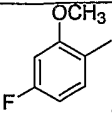
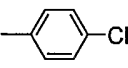
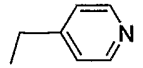
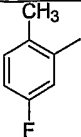
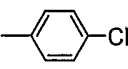
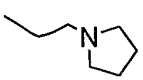
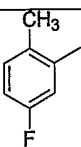
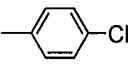
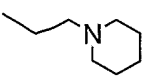
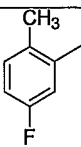
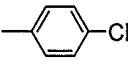
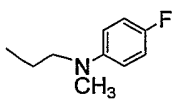
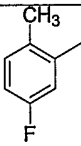
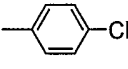
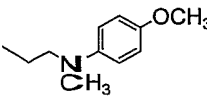
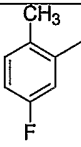
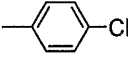
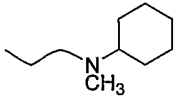
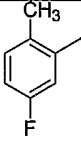
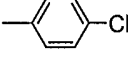
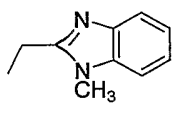
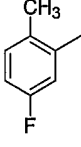
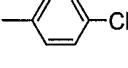
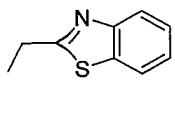
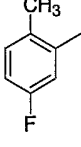
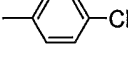
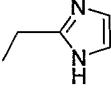
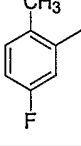
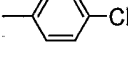
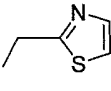
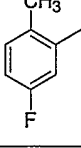
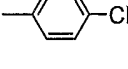
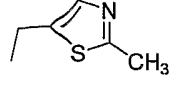
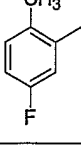
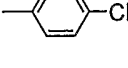
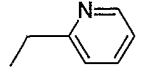
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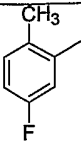
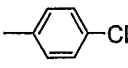
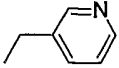
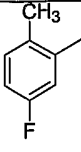
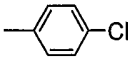
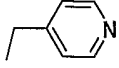
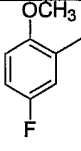
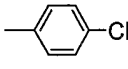
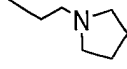
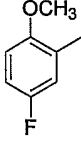
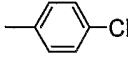
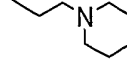
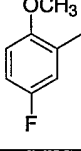
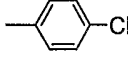
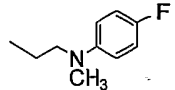
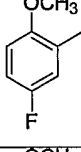
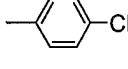
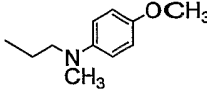
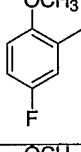
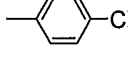
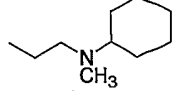
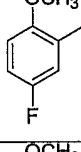
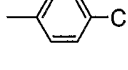
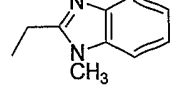
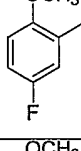
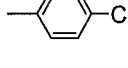
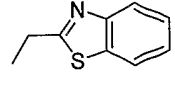
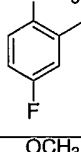
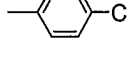
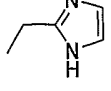
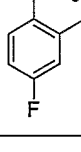
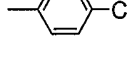
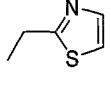
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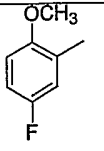
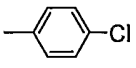
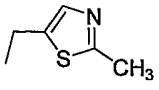
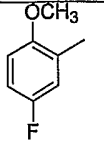
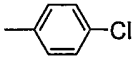
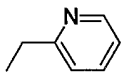
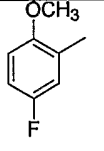
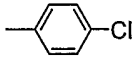
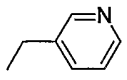
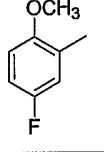
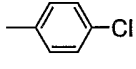
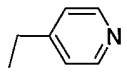
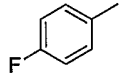
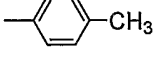
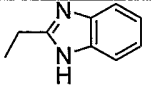
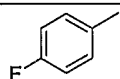
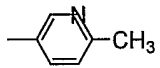
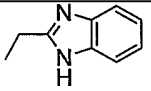
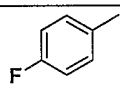
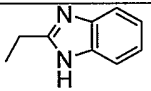
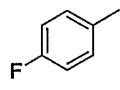

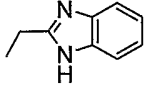
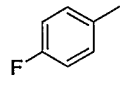
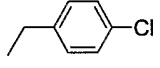
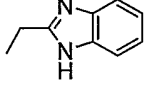
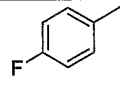
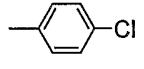
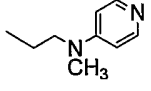
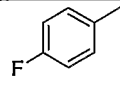
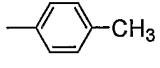
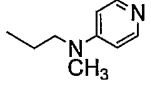
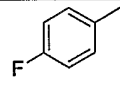
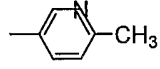
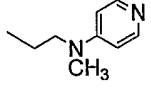
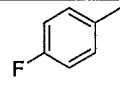
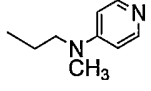
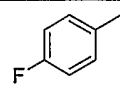

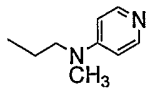
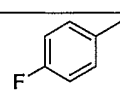
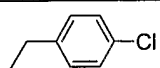
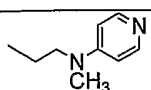
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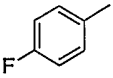
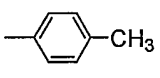
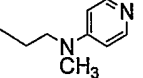
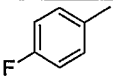
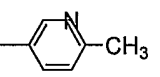
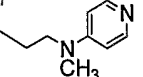
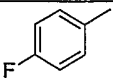
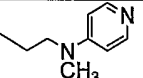
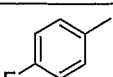

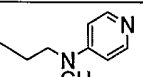
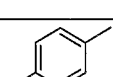
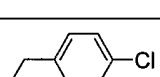
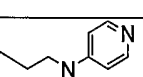
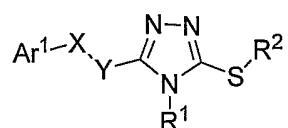
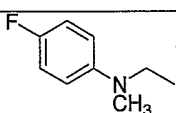
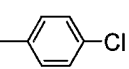
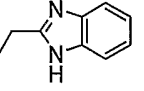
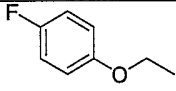
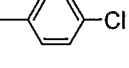
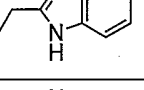
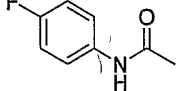
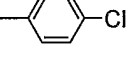
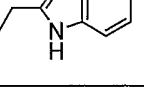
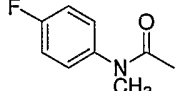
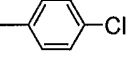
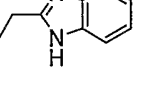
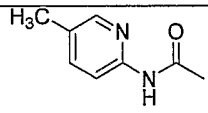
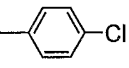
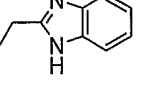
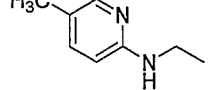
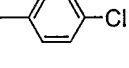
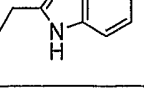
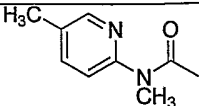
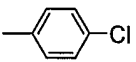
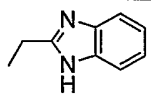
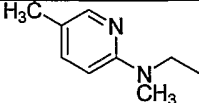
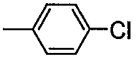
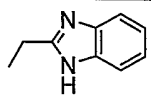
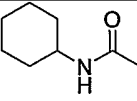
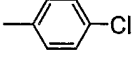
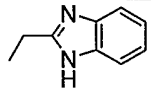
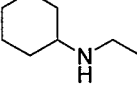
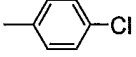
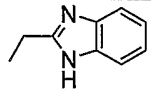
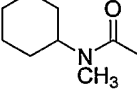
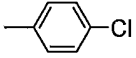
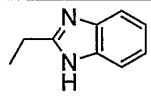
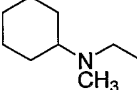
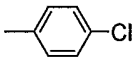
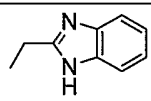
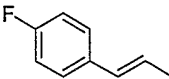
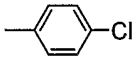
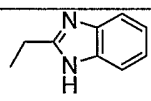
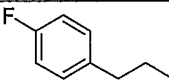
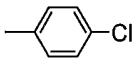
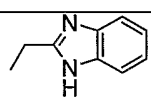
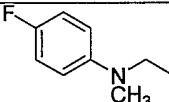
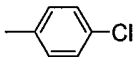
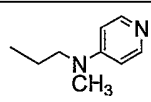
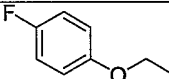
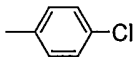
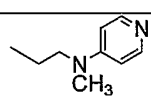
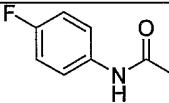
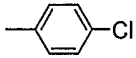
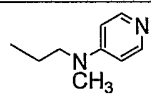
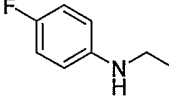
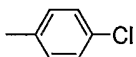
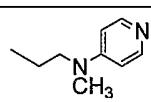
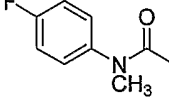
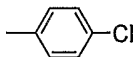
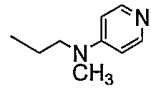
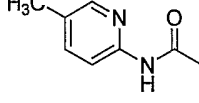
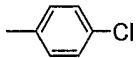
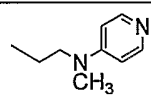
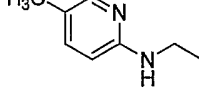
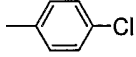
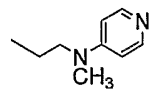
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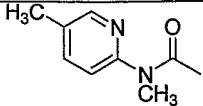
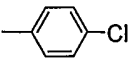
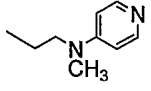
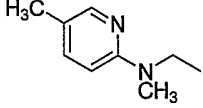
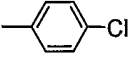
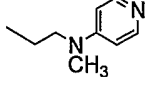
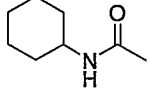
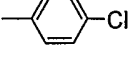
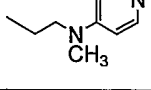
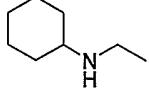
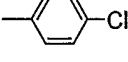
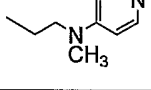
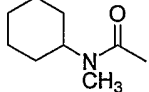
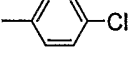
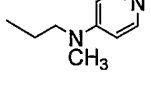
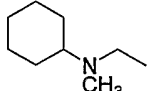
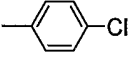
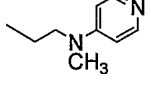
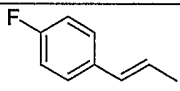
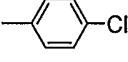
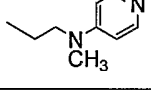
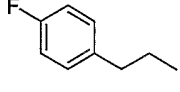
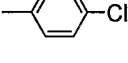
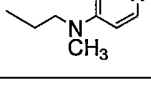
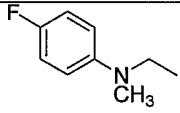
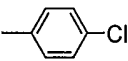
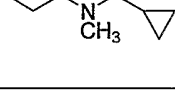
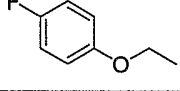
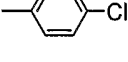
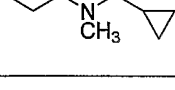
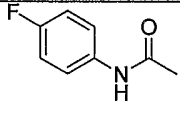
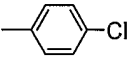
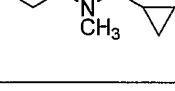
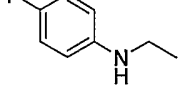
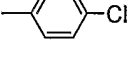
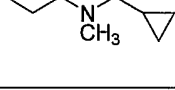
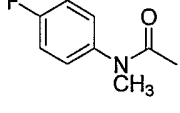
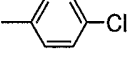
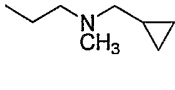
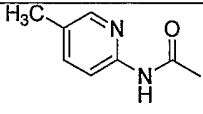
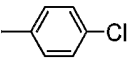
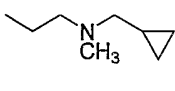
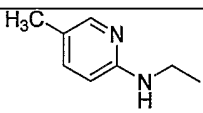
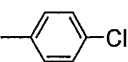
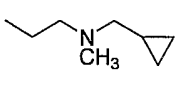
Table 1D

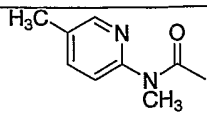
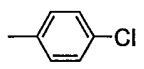
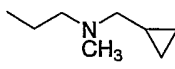
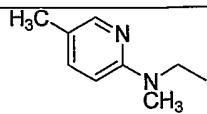
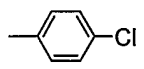
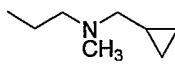
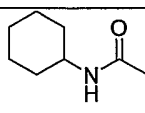
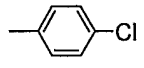
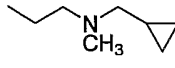
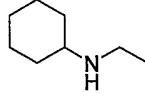
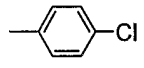
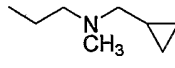
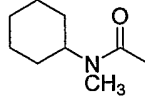
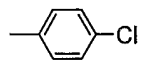
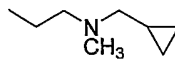
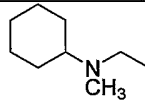
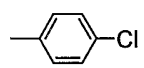
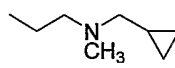
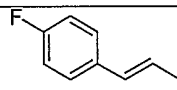
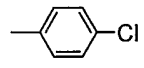
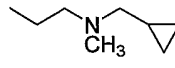
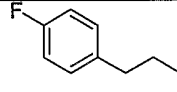
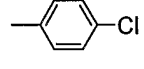
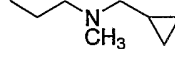
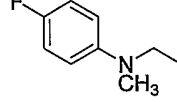
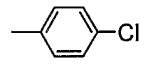
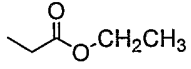
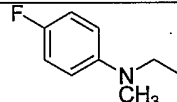
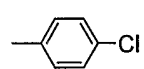
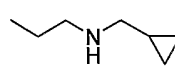
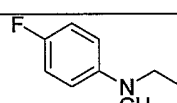
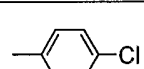
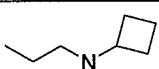
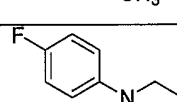
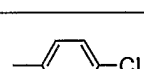
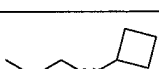
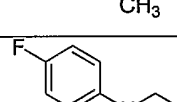

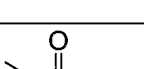
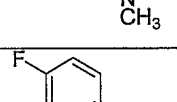
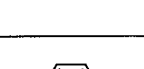
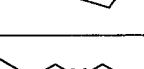
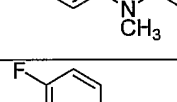
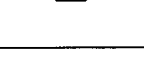
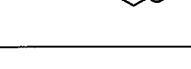


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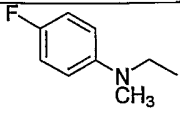
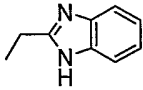
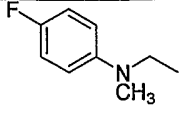

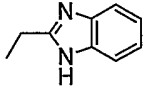
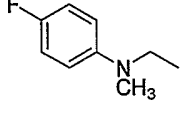
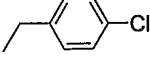
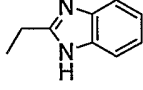
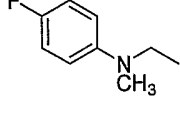
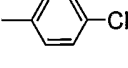
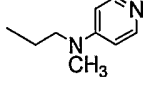
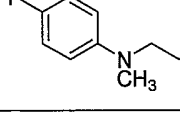
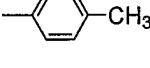
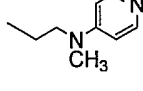
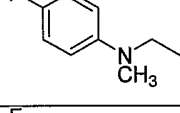
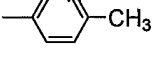
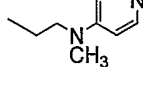
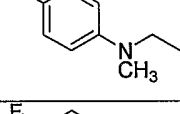
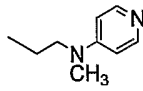
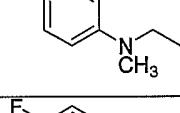

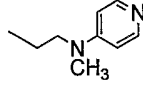
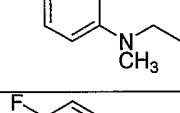
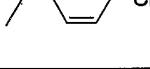
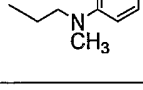
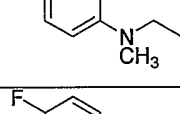
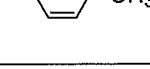
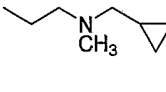
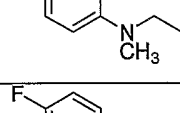
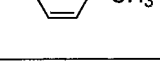
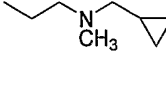
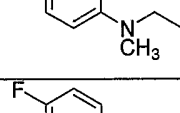
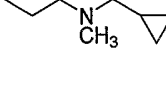
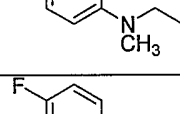

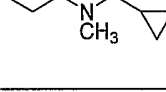
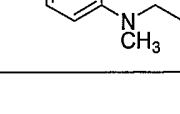
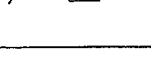
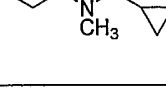
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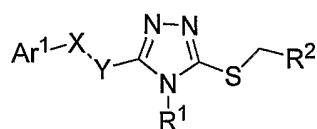
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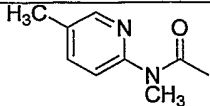
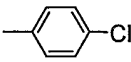
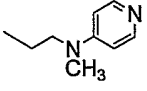
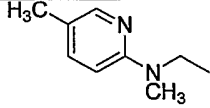
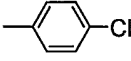
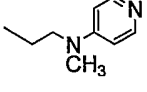
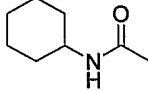
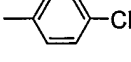
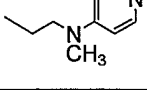
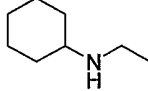
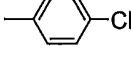
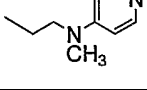
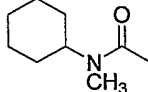
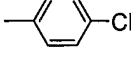
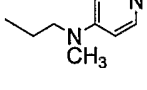
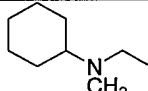
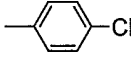
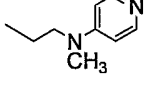
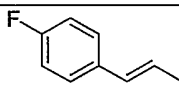
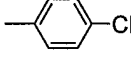
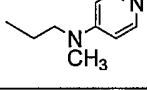
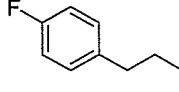
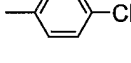
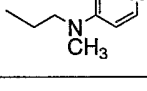
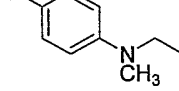
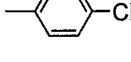
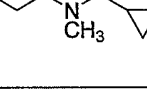
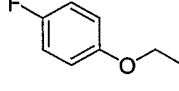
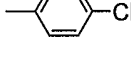
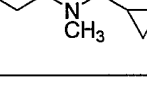
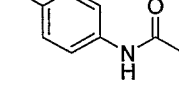
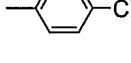
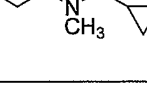
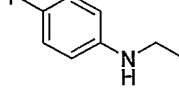
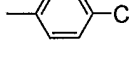
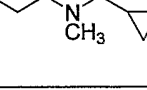
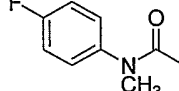
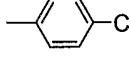
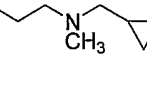
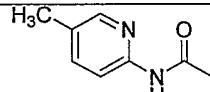
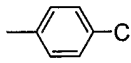
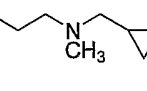
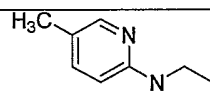
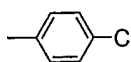
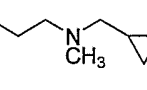
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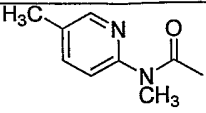
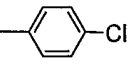
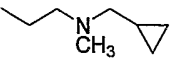
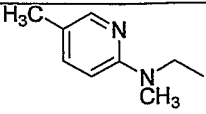
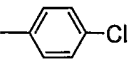
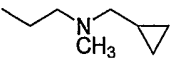
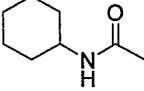
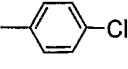
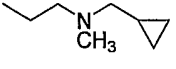
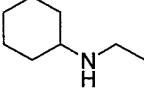
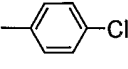
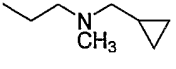
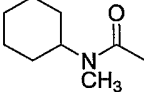
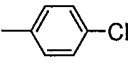
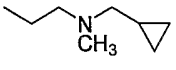
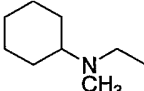
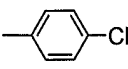
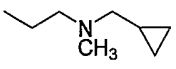
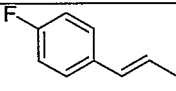
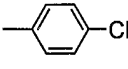
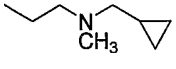
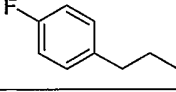
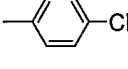
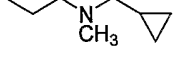
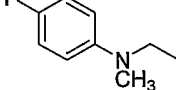
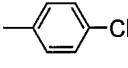
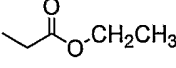
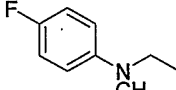
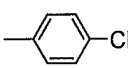
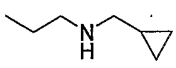
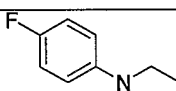
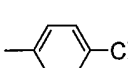
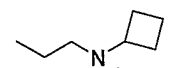
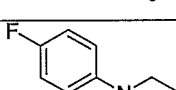
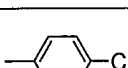
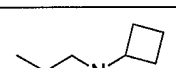
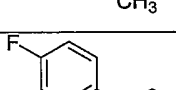

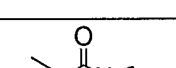
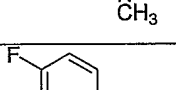
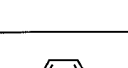
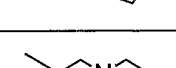
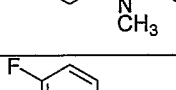

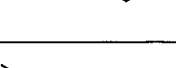


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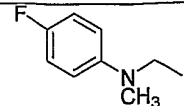
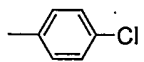
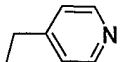
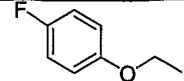
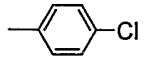
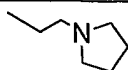
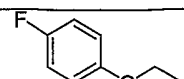
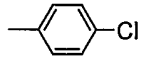
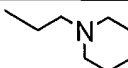
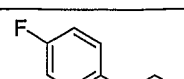
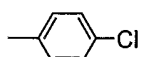
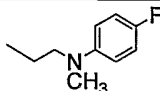
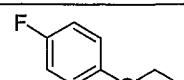
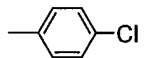
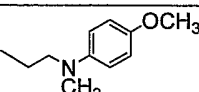
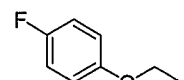
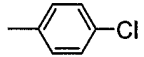
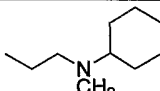
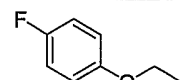
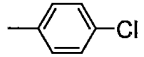
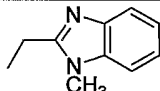
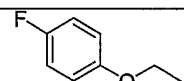
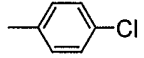
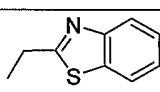
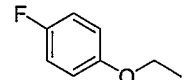
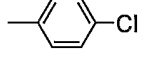

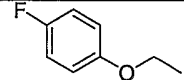
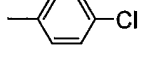

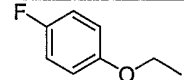
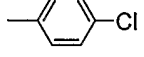
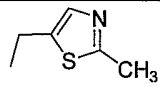
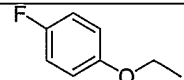
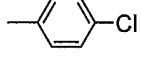
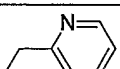
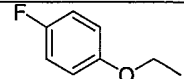
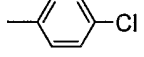
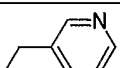
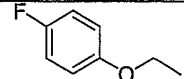
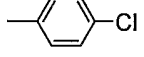
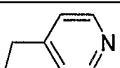
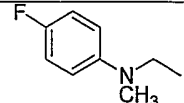
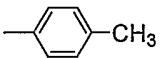
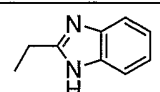
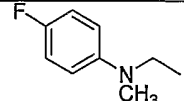
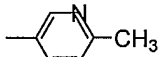
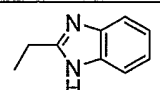
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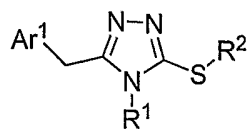
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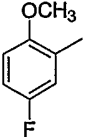
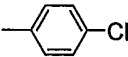
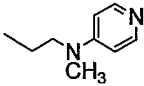
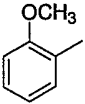
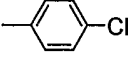
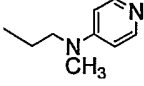
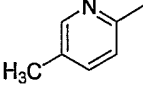
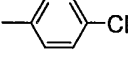
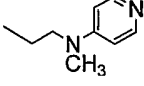

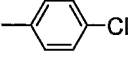
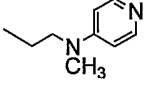
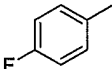
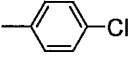
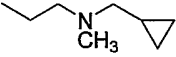
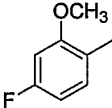
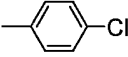
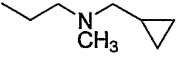
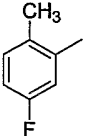
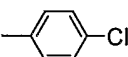
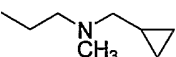
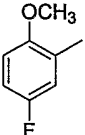
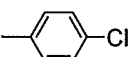
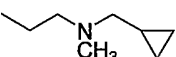
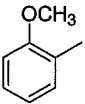
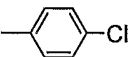
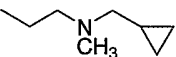
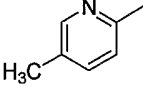
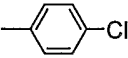
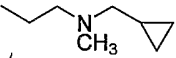

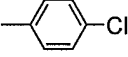
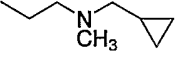
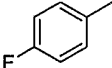
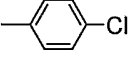
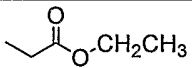
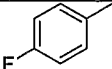
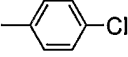
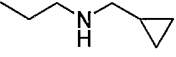
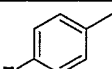
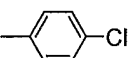
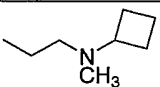
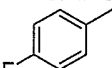
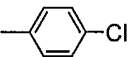
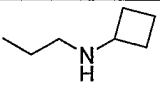
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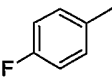
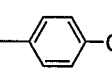
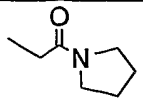
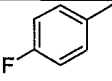
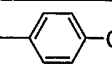
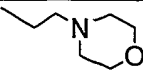
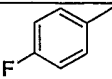
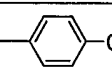
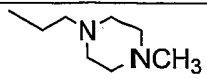
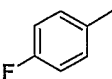
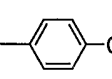
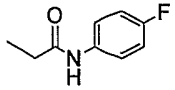
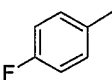
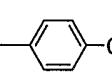
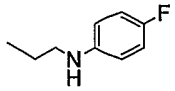
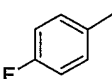
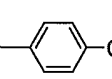
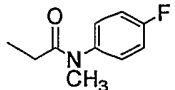
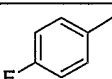
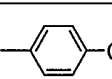
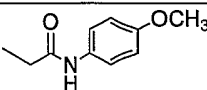
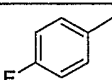
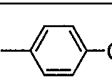
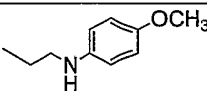
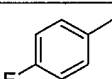
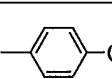
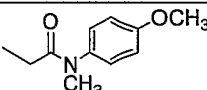
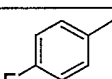
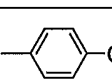
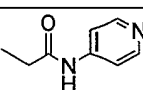
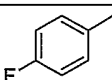
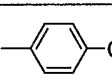
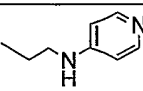
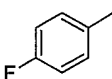
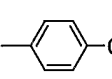
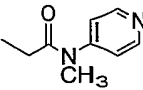
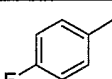
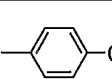
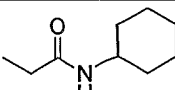
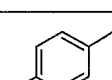
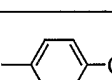
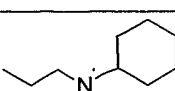
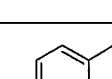
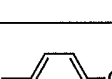
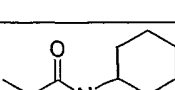
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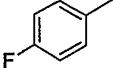
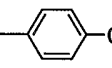
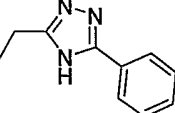
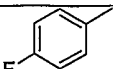
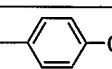
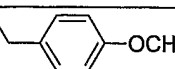
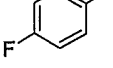
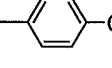
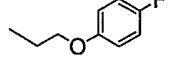
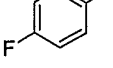
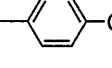
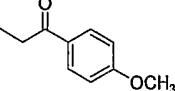
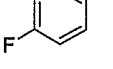
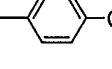
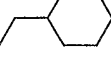
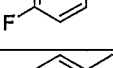
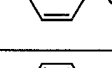
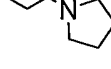
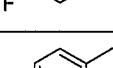
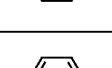
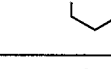
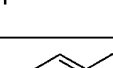
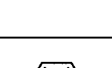
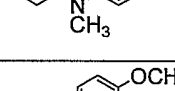
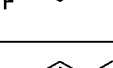
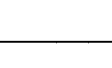
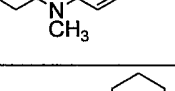
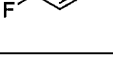

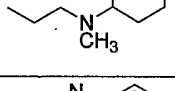
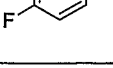
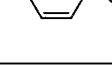
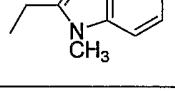
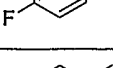

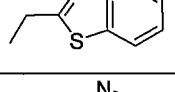
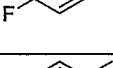
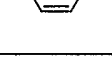
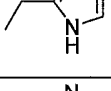
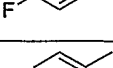

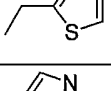
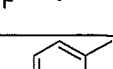

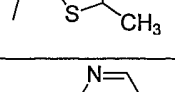
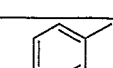
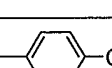
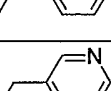


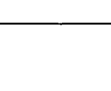
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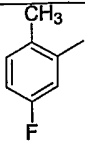
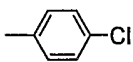
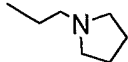
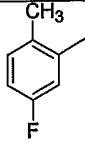
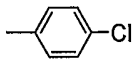
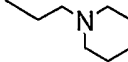
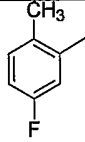
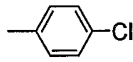
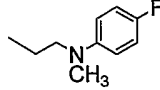
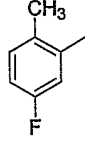
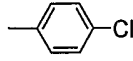
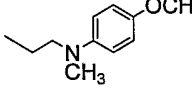
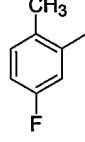
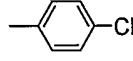
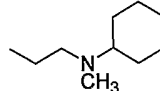
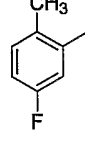
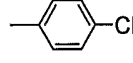
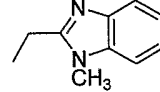
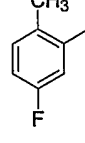
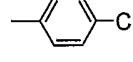
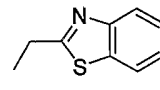
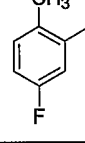
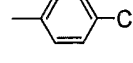

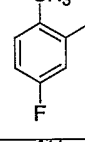
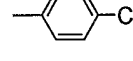

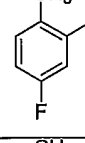
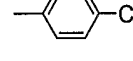
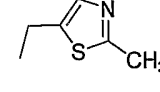
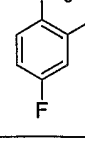
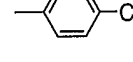
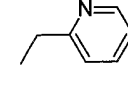
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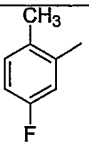
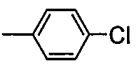
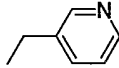
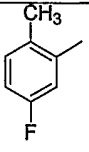
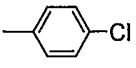
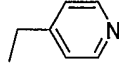
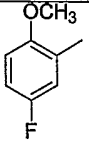
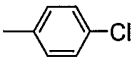
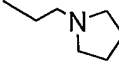
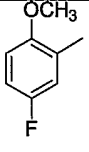
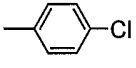
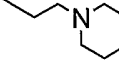
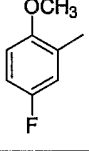
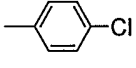
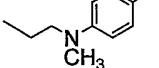
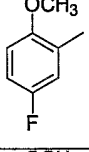
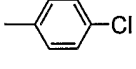
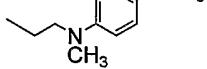
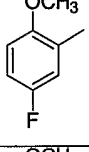
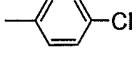
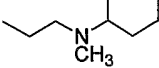
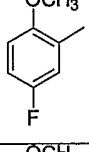
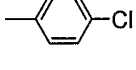
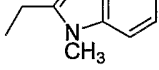
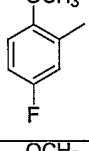
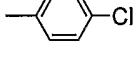
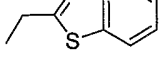
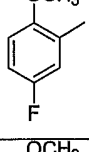
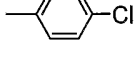
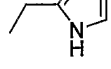
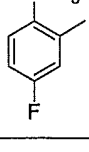
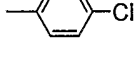
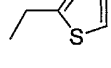
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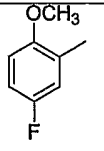
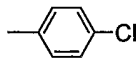
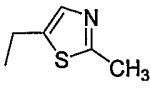
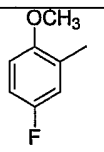
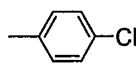
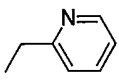
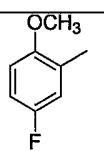
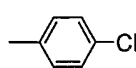
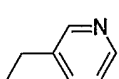
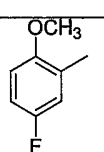
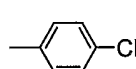
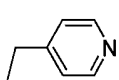
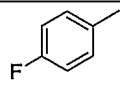
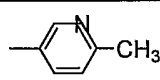
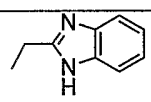
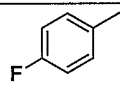
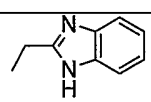
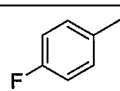

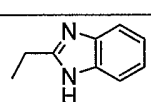
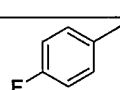
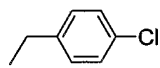
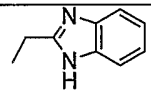
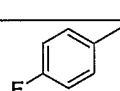
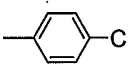
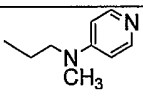
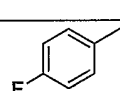
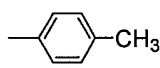
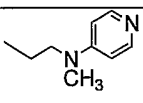
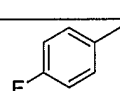
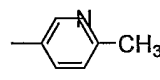
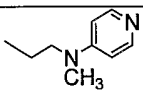
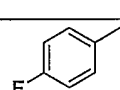
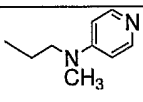
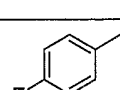

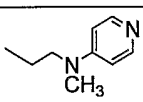
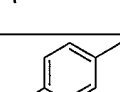
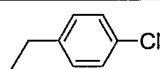
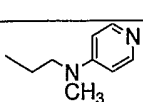
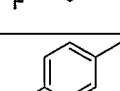
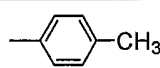
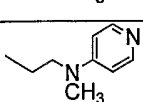
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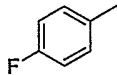
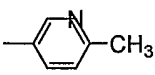
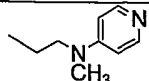
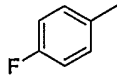
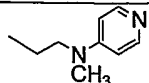
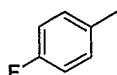
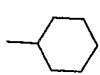
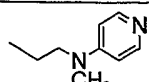
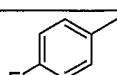
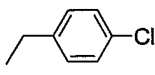
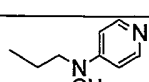
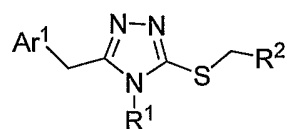
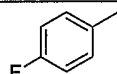
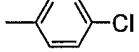
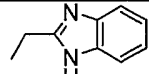
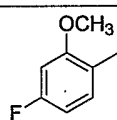
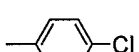
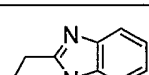
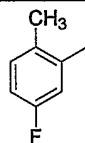
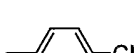
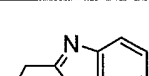
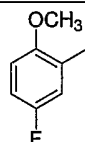

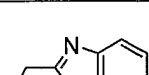
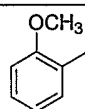
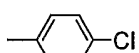
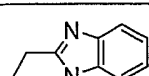
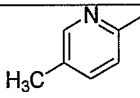
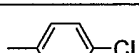
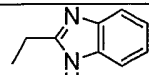

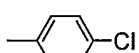
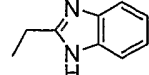
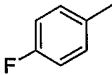
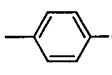
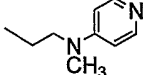
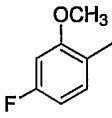
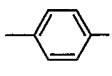
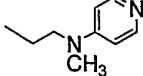
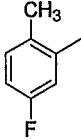
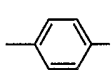
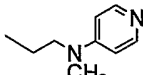
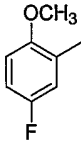
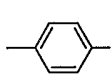
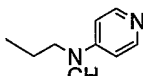
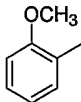
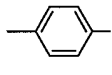
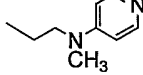
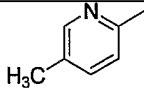
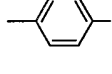
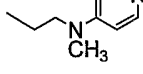

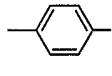
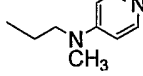
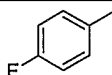
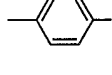
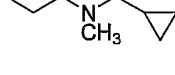
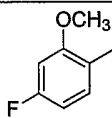
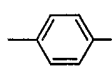
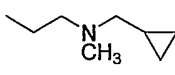
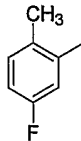
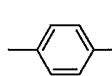
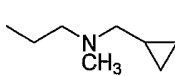
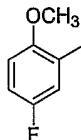
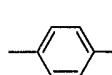
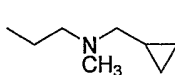
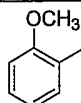
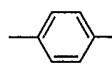
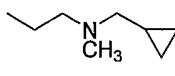
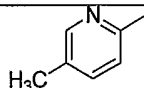
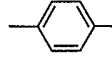
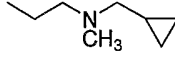
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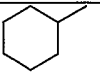
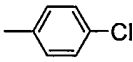
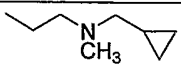
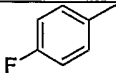
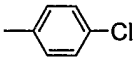
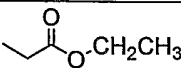
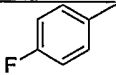
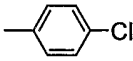
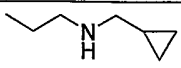
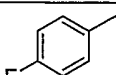
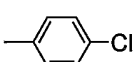
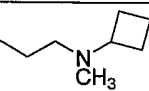
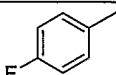
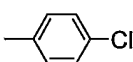
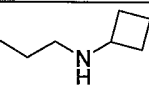
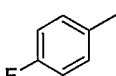
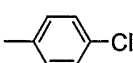
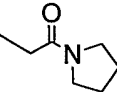
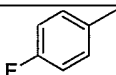
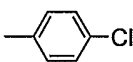
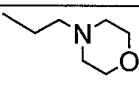
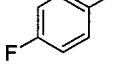
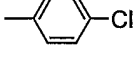
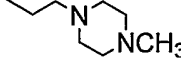
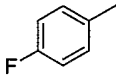
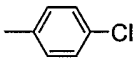
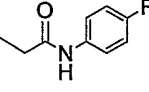
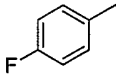
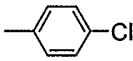
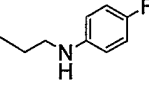
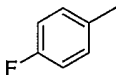
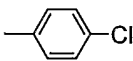
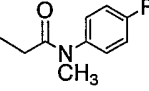
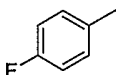
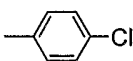
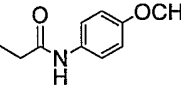
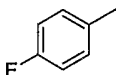
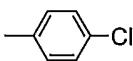
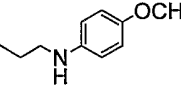
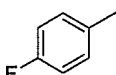
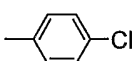
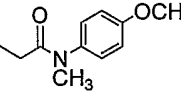
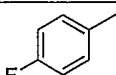
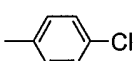
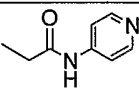
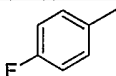
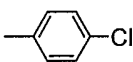
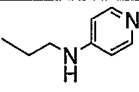
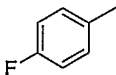
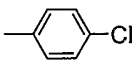
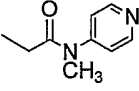
Table 1G

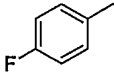
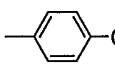
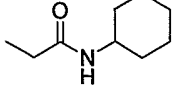
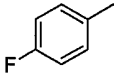
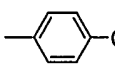
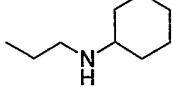
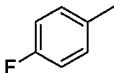
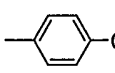
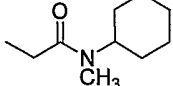
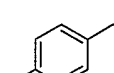
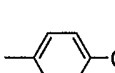
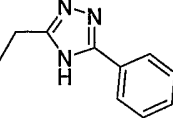
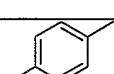
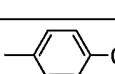
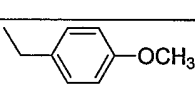
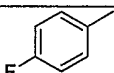
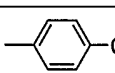
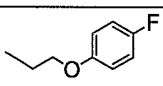
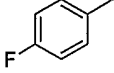
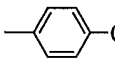
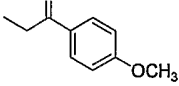
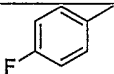
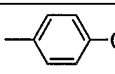
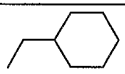
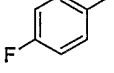
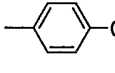
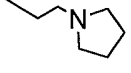
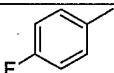
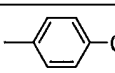
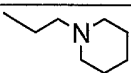
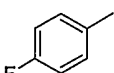
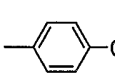
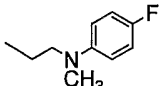
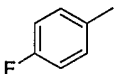
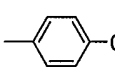
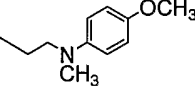
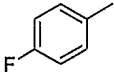
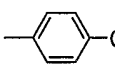
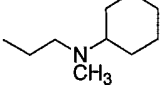
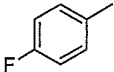
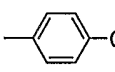
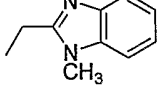
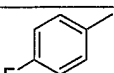
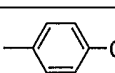
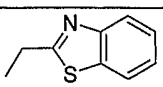
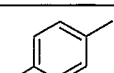
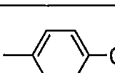
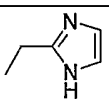


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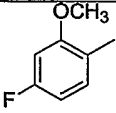
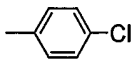
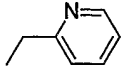
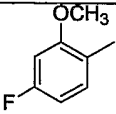
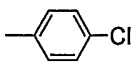
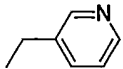
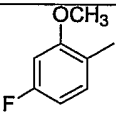
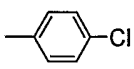
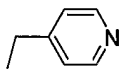
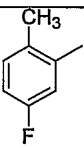
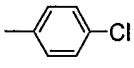
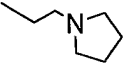
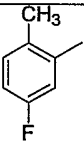
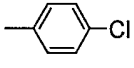
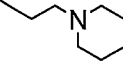
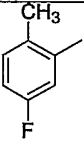
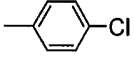
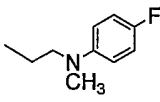
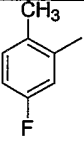
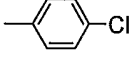
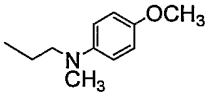
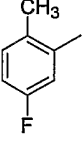
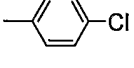
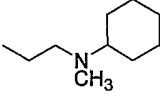
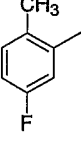
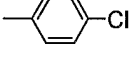
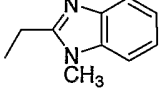
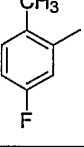
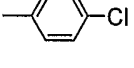
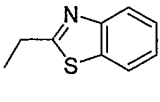
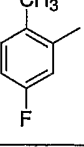
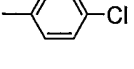
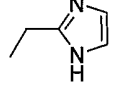
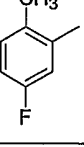
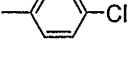
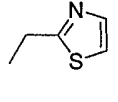
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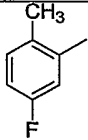
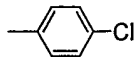
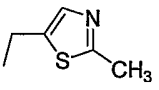
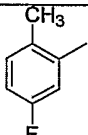
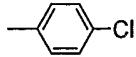
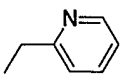
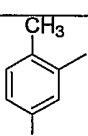
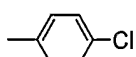
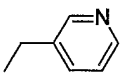
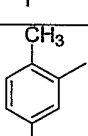
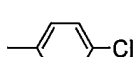
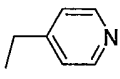
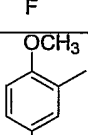
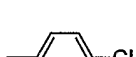
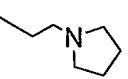
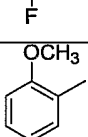
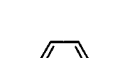
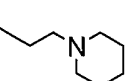
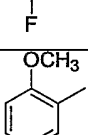

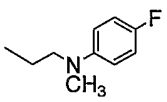
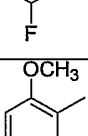
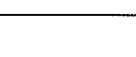
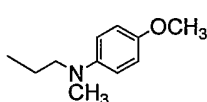
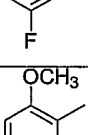
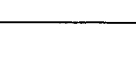
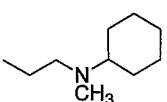
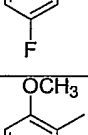
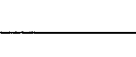
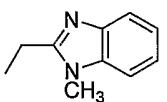
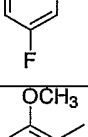
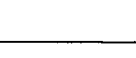
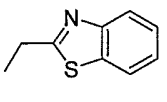
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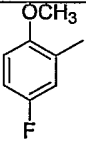
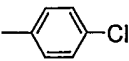
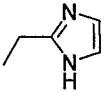
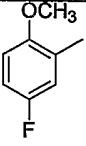
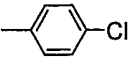
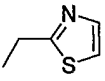
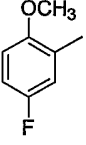
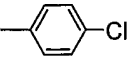
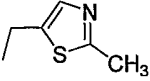
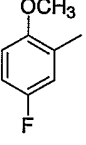
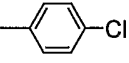
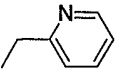
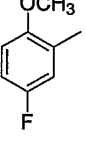
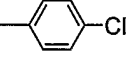
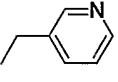
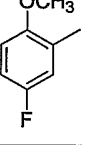
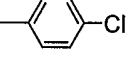
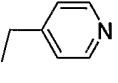
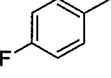
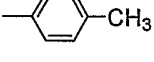
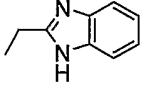
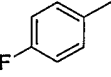
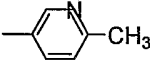
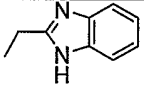
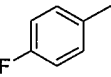
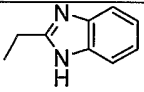
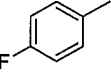

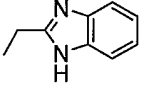
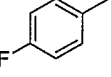
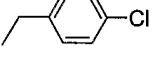
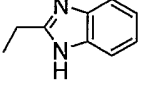
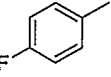
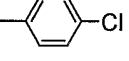
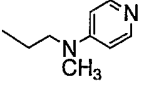
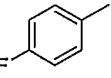
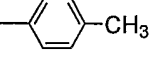
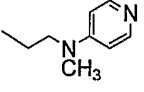
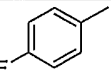
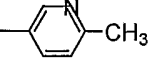
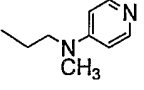
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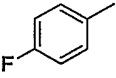
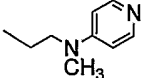
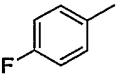

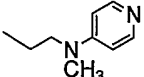
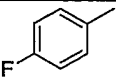
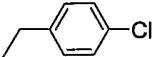
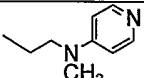
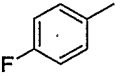
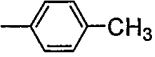
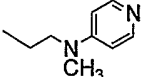
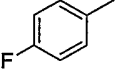
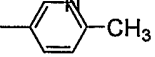
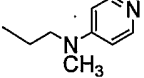
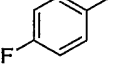
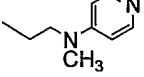
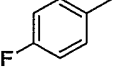

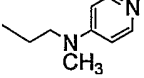
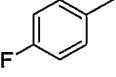
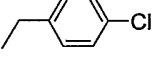
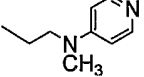
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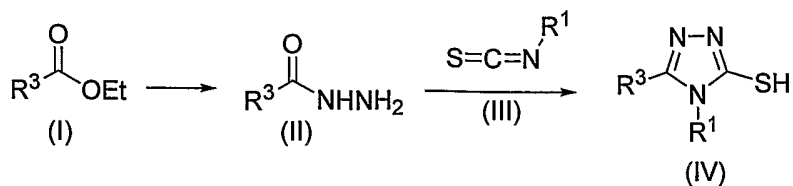
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Ion channel-modulating compounds can be identified through both *in vitro* (e.g., cell and non-cell based) and *in vivo* methods. Representative examples of these methods are described in the Examples herein.

Combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds. The term "stable", as used herein, refers to compounds which possess stability sufficient to allow manufacture and which maintains the integrity of the compound for a sufficient period of time to be useful for the purposes detailed herein (e.g., therapeutic or prophylactic administration to a subject).

The compounds delineated herein can be synthesized using conventional methods, as illustrated in the schemes herein. In the schemes herein, unless expressly to the contrary, variables in chemical formulae are as defined in other formulae herein. For example, Ar¹, Ar³, R¹, R³ and R⁴ in the schemes are defined as in any of the formulae herein, except where defined otherwise in the schemes.

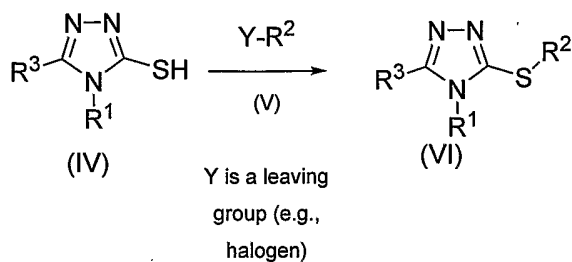
Scheme 1



Treatment of ethyl ester (I) with hydrazine in solvent (e.g., ethanol) provides hydrazide (II). Treatment of (II) with thioisocyanate (III) under aqueous basic conditions gives triazole thiol (IV).

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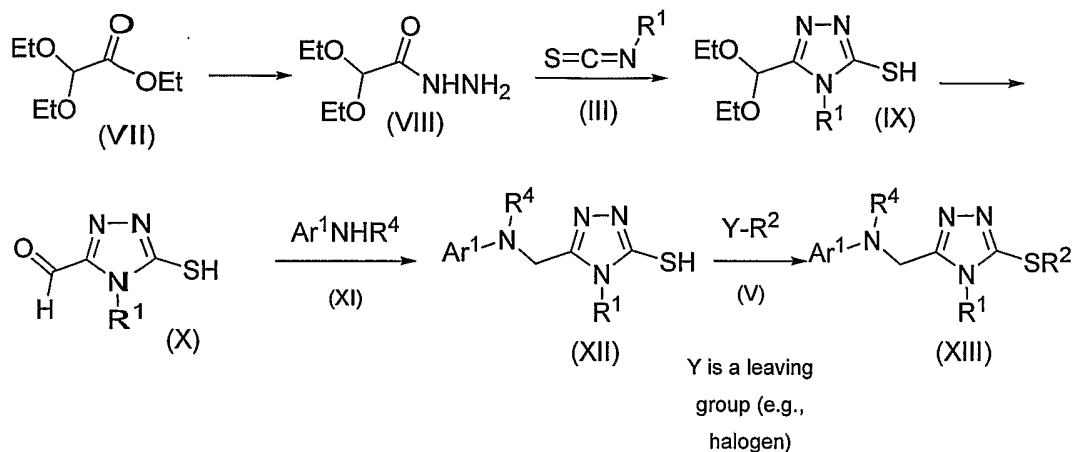
Scheme 2



Treatment of (IV) with (V) under basic conditions (e.g., K₂CO₃ in acetone) gives (VI).

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Scheme 3



Treatment of ethyl diethoxy acetate (VII) with hydrazine in solvent (e.g., ethanol) provides hydrazide (VIII). Treatment of (VIII) with thioisocyanate (III) aqueous basic conditions gives triazole (IX) which turn provides aldehyde (X) upon treatment with aqueous acidic conditions. Treatment of (X) with (V) under basic conditions (e.g., K₂CO₃ in acetone) provides (XIII).

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The synthesized compounds can be separated from a reaction mixture and further purified by a method such as column chromatography, high pressure liquid chromatography, or recrystallization. As can be appreciated by the skilled artisan, further methods of synthesizing the compounds of the formulae herein will be evident to those of ordinary skill in the art. Additionally, the various synthetic steps may be performed in an alternate sequence or order to give the desired compounds. Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing the compounds described herein are known in the art and include, for example, those such as described in R. Larock, *Comprehensive Organic Transformations*, 2nd. Ed., Wiley-VCH Publishers (1999); T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, 3rd. Ed., John Wiley and Sons (1999); L. Fieser and M. Fieser, *Fieser and Fieser's Reagents for Organic Synthesis*, John Wiley and Sons (1999); and L. Paquette, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons (1995), and subsequent editions thereof.

The compounds of this invention may contain one or more asymmetric centers and thus occur as racemates and racemic mixtures, single enantiomers, individual diastereomers and diastereomeric mixtures. All such isomeric forms of these compounds are expressly included in the present invention. The compounds of this invention may also be represented in multiple tautomeric forms, in such instances, the invention expressly includes all tautomeric forms of the compounds described herein (e.g., alkylation of a ring system may result in alkylation at multiple sites, the invention expressly includes all such reaction products). All such isomeric forms of such compounds are expressly included in the present invention. All crystal forms of the compounds described herein are expressly included in the present invention.

As used herein, the compounds of this invention, including the compounds of formulae described herein, are defined to include pharmaceutically acceptable derivatives or prodrugs thereof. A "pharmaceutically acceptable derivative or prodrug" means any pharmaceutically acceptable salt, ester, salt of an ester, or other derivative of a compound of this invention which, upon administration to a recipient, is capable of providing (directly or indirectly) a compound of this invention. Particularly favored derivatives and prodrugs are those that increase the bioavailability of the compounds of this invention when such compounds are administered to a mammal (e.g., by allowing an orally administered compound to be more readily absorbed into the blood) or which enhance delivery of the parent compound to a

biological compartment (e.g., the brain or lymphatic system) relative to the parent species. Preferred prodrugs include derivatives where a group which enhances aqueous solubility or active transport through the gut membrane is appended to the structure of formulae described herein. See, e.g., Alexander, J. et al. *Journal of Medicinal Chemistry* **1988**, *31*, 318-322; Bundgaard, H. *Design of Prodrugs*; Elsevier: Amsterdam, 1985; pp 1-92; Bundgaard, H.; Nielsen, N. M. *Journal of Medicinal Chemistry* **1987**, *30*, 451-454; Bundgaard, H. *A Textbook of Drug Design and Development*; Harwood Academic Publ.: Switzerland, 1991; pp 113-191; Digenis, G. A. et al. *Handbook of Experimental Pharmacology* **1975**, *28*, 86-112; Friis, G. J.; Bundgaard, H. *A Textbook of Drug Design and Development*; 2 ed.; Overseas Publ.: Amsterdam, 1996; pp 351-385; Pitman, I. H. *Medicinal Research Reviews* **1981**, *1*, 189-214; Sinkula, A. A.; Yalkowsky. *Journal of Pharmaceutical Sciences* **1975**, *64*, 181-210; Verbiscar, A. J.; Abood, L. G. *Journal of Medicinal Chemistry* **1970**, *13*, 1176-1179; Stella, V. J.; Himmelstein, K. J. *Journal of Medicinal Chemistry* **1980**, *23*, 1275-1282; Bodor, N.; Kaminski, J. J. *Annual Reports in Medicinal Chemistry* **1987**, *22*, 303-313.

The compounds of this invention may be modified by appending appropriate functionalities to enhance selective biological properties. Such modifications are known in the art and include those which increase biological penetration into a given biological compartment (e.g., blood, lymphatic system, nervous system), increase oral availability, increase solubility to allow administration by injection, alter metabolism and alter rate of excretion.

Pharmaceutically acceptable salts of the compounds of this invention include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acid salts include acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptanoate, glycolate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, palmoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, salicylate, succinate, sulfate, tartrate, thiocyanate, tosylate and undecanoate. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts. Salts derived from appropriate bases include alkali metal (e.g., sodium), alkaline earth metal (e.g., magnesium), ammonium and N-(alkyl)₄⁺ salts. This invention also envisions the quaternization of any basic nitrogen-

containing groups of the compounds disclosed herein. Water or oil-soluble or dispersible products may be obtained by such quaternization.

The compounds of the formulae described herein can, for example, be administered by injection, intravenously, intraarterially, subdermally, intraperitoneally, intramuscularly, or subcutaneously; or orally, buccally, nasally, transmucosally, topically, in an ophthalmic preparation, or by inhalation, with a dosage ranging from about 0.5 to about 100 mg/kg of body weight, alternatively dosages between 1 mg and 1000 mg/dose, every 4 to 120 hours, or according to the requirements of the particular drug. The methods herein contemplate administration of an effective amount of compound or compound composition to achieve the desired or stated effect. Typically, the pharmaceutical compositions of this invention will be administered from about 1 to about 6 times per day or alternatively, as a continuous infusion. Such administration can be used as a chronic or acute therapy. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. A typical preparation will contain from about 5% to about 95% active compound (w/w). Alternatively, such preparations contain from about 20% to about 80% active compound.

Lower or higher doses than those recited above may be required. Specific dosage and treatment regimens for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health status, sex, diet, time of administration, rate of excretion, drug combination, the severity and course of the disease, condition or symptoms, the patient's disposition to the disease, condition or symptoms, and the judgment of the treating physician.

Upon improvement of a patient's condition, a maintenance dose of a compound, composition or combination of this invention may be administered, if necessary.

Subsequently, the dosage or frequency of administration, or both, may be reduced, as a function of the symptoms, to a level at which the improved condition is retained when the symptoms have been alleviated to the desired level, treatment should cease. Patients may, however, require intermittent treatment on a long-term basis upon any recurrence of disease symptoms.

The compositions delineated herein include the compounds of the formulae delineated herein, as well as additional therapeutic agents if present, in amounts effective for achieving a modulation of disease or disease symptoms, including ion channel-mediated disorders or symptoms thereof. References which include examples of additional therapeutic agents are:

1) *Burger's Medicinal Chemistry & Drug Discovery* 6th edition, by Alfred Burger, Donald J.

Abraham, ed., Volumes 1 to 6, Wiley Interscience Publication, NY, 2003; 2) *Ion Channels and Disease* by Francis M. Ashcroft, Academic Press, NY, 2000; and 3) *Calcium Antagonists in Clinical Medicine* 3rd edition, Murray Epstein, MD, FACP, ed., Hanley & Belfus, Inc., Philadelphia, PA, 2002. Additional therapeutic agents include but are not limited to agents for the treatment of cardiovascular disease (e.g., hypertension, angina, etc), metabolic disease (e.g., syndrome X, diabetes, obesity), pain (e.g., acute pain, inflammatory pain, neuropathic pain, migraine, etc), renal or genito-urinary disease (e.g. glomerular nephritis, urinary incontinence, nephrotic syndrome), abnormal cell growth (e.g., oncology, fibrotic diseases), nervous system disease (e.g., epilepsy, stroke, migraine, traumatic brain injury or neuronal disorders, etc.), respiratory disease (e.g., asthma, COPD, pulmonary hypertension) and their disease symptoms. Examples of additional therapeutic agents for treatment of cardiovascular disease and disease symptoms include but are not limited to antihypertensive agents, ACE inhibitors, angiotensin II receptor antagonists, statins, β -blockers, antioxidants, anti-inflammatory drugs, anti-thrombotics, anti-coagulants or antiarrhythmics. Examples of additional therapeutic agents for treatment of metabolic disease and disease symptoms include but are not limited to ACE inhibitors, angiotensin II antagonists, fibrates, thiazolidinediones or sulphonylurea anti-diabetic drugs. Examples of additional therapeutic agents for treatment of pain and its symptoms include but are not limited to non-steroidal anti-inflammatory drugs ("NSAIDS", e.g., aspirin, ibuprofen, flumizole, acetaminophen, etc.), opioids (e.g., morphine, fentanyl, oxycodone), and agents such as gabapentin,, ziconitide, tramadol, dextromethorphan, carbamazepine, lamotrigine, baclofen or capsaicin. Examples of additional therapeutic agents for treatment of renal and/or genitor-urinary syndromes and their symptoms include but are not limited to alpha-1 adrenergic antagonists (e.g., doxazosin), anti-muscarinics (e.g., tolterodine), norepinephrine/serotonin reuptake inhibitors (e.g., duloxetine), tricyclic antidepressants (e.g., doxepin, desipramine) or steroids. Examples of additional therapeutic agents for treatment of abnormal cell growth syndromes and their symptoms include but are not limited to anti-cytokine therapies (e.g., anti-TNF and anti-IL-1 biologics, p38 MAPK inhibitors), endothelin-1 antagonists or stem cell therapies (e.g., progenitor cells). Examples of additional therapeutic agents for treatment of stroke disease and disease symptoms include but are not limited to neuroprotective agents and anticoagulants (e.g., alteplase (TPA), abciximab). Examples of additional therapeutic agents for treatment of epilepsy and its symptoms include but are not limited to GABA analogs, hydantoins, barbiturates, phenyl triazines, succinimides, valproic acid, carbamazepin, falbamate, and leveracetam. Examples of additional therapeutic agents for the treatment of

migraine include but are not limited to serotonin/5-HT receptor agonist (e.g., sumatriptan, etc.). Examples of additional therapeutic agents for treatment of respiratory diseases and their symptoms include but are not limited to anticholinergics (e.g., tiotropium), steroids, anti-inflammatory agents, anti-cytokine agents or PDE inhibitors

5 The term “pharmaceutically acceptable carrier or adjuvant” refers to a carrier or adjuvant that may be administered to a patient, together with a compound of this invention, and which does not destroy the pharmacological activity thereof and is nontoxic when administered in doses sufficient to deliver a therapeutic amount of the compound.

10 Pharmaceutically acceptable carriers, adjuvants and vehicles that may be used in the pharmaceutical compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, self-emulsifying drug delivery systems (SEDDS) such as d- α -tocopherol polyethyleneglycol 1000 succinate, surfactants used in pharmaceutical dosage forms such as Tweens or other similar polymeric delivery matrices, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, 15 potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block 20 polymers, polyethylene glycol and wool fat. Cyclodextrins such as α -, β -, and γ -cyclodextrin, or chemically modified derivatives such as hydroxyalkylcyclodextrins, including 2- and 3-hydroxypropyl- β -cyclodextrins, or other solubilized derivatives may also be advantageously used to enhance delivery of compounds of the formulae described herein.

25 The pharmaceutical compositions of this invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir, preferably by oral administration or administration by injection. The pharmaceutical compositions of this invention may contain any conventional non-toxic pharmaceutically-acceptable carriers, adjuvants or vehicles. In some cases, the pH of the formulation may be adjusted with pharmaceutically acceptable acids, bases or buffers to 30 enhance the stability of the formulated compound or its delivery form. The term parenteral as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intraarticular, intraarterial, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques.

The pharmaceutical compositions may be in the form of a sterile injectable preparation, for example, as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, or carboxymethyl cellulose or similar dispersing agents which are commonly used in the formulation of pharmaceutically acceptable dosage forms such as emulsions and or suspensions. Other commonly used surfactants such as Tweens or Spans and/or other similar emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms may also be used for the purposes of formulation.

The pharmaceutical compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, emulsions and aqueous suspensions, dispersions and solutions. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions and/or emulsions are administered orally, the active ingredient may be suspended or dissolved in an oily phase is combined with emulsifying and/or suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents may be added.

The pharmaceutical compositions of this invention may also be administered in the form of suppositories for rectal administration. These compositions can be prepared by mixing a compound of this invention with a suitable non-irritating excipient which is solid at room temperature but liquid at the rectal temperature and therefore will melt in the rectum to release the active components. Such materials include, but are not limited to, cocoa butter, beeswax and polyethylene glycols.

Topical administration of the pharmaceutical compositions of this invention is useful when the desired treatment involves areas or organs readily accessible by topical application. For application topically to the skin, the pharmaceutical composition should be formulated with a suitable ointment containing the active components suspended or dissolved in a carrier. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petroleum, white petroleum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutical composition can be formulated with a suitable lotion or cream containing the active compound suspended or dissolved in a carrier with suitable emulsifying agents. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water. The pharmaceutical compositions of this invention may also be topically applied to the lower intestinal tract by rectal suppository formulation or in a suitable enema formulation. Topically-transdermal patches are also included in this invention.

The pharmaceutical compositions of this invention may be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

A composition having the compound of the formulae herein and an additional agent (e.g., a therapeutic agent) can be administered using an implantable device. Implantable devices and related technology are known in the art and are useful as delivery systems where a continuous, or timed-release delivery of compounds or compositions delineated herein is desired. Additionally, the implantable device delivery system is useful for targeting specific points of compound or composition delivery (e.g., localized sites, organs). Negrin et al., *Biomaterials*, 22(6):563 (2001). Timed-release technology involving alternate delivery methods can also be used in this invention. For example, timed-release formulations based on polymer technologies, sustained-release techniques and encapsulation techniques (e.g., polymeric, liposomal) can also be used for delivery of the compounds and compositions delineated herein.

Also within the invention is a patch to deliver active chemotherapeutic combinations herein. A patch includes a material layer (e.g., polymeric, cloth, gauze, bandage) and the compound of the formulae herein as delineated herein. One side of the material layer can have a protective layer adhered to it to resist passage of the compounds or compositions. The

patch can additionally include an adhesive to hold the patch in place on a subject. An adhesive is a composition, including those of either natural or synthetic origin, that when contacted with the skin of a subject, temporarily adheres to the skin. It can be water resistant. The adhesive can be placed on the patch to hold it in contact with the skin of the subject for an extended period of time. The adhesive can be made of a tackiness, or adhesive strength, such that it holds the device in place subject to incidental contact, however, upon an affirmative act (e.g., ripping, peeling, or other intentional removal) the adhesive gives way to the external pressure placed on the device or the adhesive itself, and allows for breaking of the adhesion contact. The adhesive can be pressure sensitive, that is, it can allow for positioning of the adhesive (and the device to be adhered to the skin) against the skin by the application of pressure (e.g., pushing, rubbing,) on the adhesive or device.

When the compositions of this invention comprise a combination of a compound of the formulae described herein and one or more additional therapeutic or prophylactic agents, both the compound and the additional agent should be present at dosage levels of between about 1 to 100%, and more preferably between about 5 to 95% of the dosage normally administered in a monotherapy regimen. The additional agents may be administered separately, as part of a multiple dose regimen, from the compounds of this invention. Alternatively, those agents may be part of a single dosage form, mixed together with the compounds of this invention in a single composition.

The invention will be further described in the following examples. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting this invention in any manner.

Example 1

Oocyte Assay

Representative compounds of the formulae herein are screened for activity against calcium channel targets in an assay essentially as described in *Neuron* January 1997, 18(11): 153-166, Lin *et. al.*; *J. Neurosci.* July 1, 2000, 20(13):4768-75, J. Pan and D. Lipscombe; and *J. Neurosci.*, August 15, 2001, 21(16):5944-5951, W. Xu and D. Lipscombe, using *Xenopus oocyte* heterologous expression system. The assay is performed on various calcium channels (e.g., $Ca_v2.2$ subfamily) whereby the modulation of the calcium channel is measured for each compound. Table 2 contains IC_{50} 's for representative compounds disclosed in the invention.

Table 2

Example	IC₅₀ (μM)
2	17
11	1.12
18	5.52
33	4.1
45	0.456

5

Example 2HEK Assay

HEK-293T/17 cells are transiently transfected in a similar manner as described in FuGENE 6 Package Insert Version 7, April 2002, Roche Applied Science, Indianapolis, IN. The cells are plated at 2.5×10^5 cells in 2 mL in a 6-well plate in incubator for one night and achieve a 30~40% confluence. In a small sterile tube, add sufficient serum-free medium as diluent for FuGENE Transfection Reagent (Roche Applied Science, Indianapolis, IN), to a total volume of 100 μL. Add 3 μL of FuGENE 6 Reagent directly into this medium. The mixture is tapped gently to mix. 2 μg of DNA solution (0.8-2.0 μg/μL) is added to the prediluted FuGENE 6 Reagent from above. The DNA/Fugene 6 mixture is gently pipeted to mix the contents and incubated for about 15 minutes at room temperature. The complex mixture is then added to the HEK-293T/17 cells, distributing it around the well, and swirled to ensure even dispersal. The cells are returned to the incubator for 24hrs. The transfected cells are then replated at density 2.5×10^5 in a 35mm dish with 5 glass coverslips and grow in low serum(1%) media for 24hrs. Coverslips with isolated cells are then transferred into chamber and calcium channel (e.g., L-type, N-type, etc.) current or other currents for counter screening are recorded from the transiently transfected HEK-293T/17 cells.

The whole-cell voltage clamp configuration of the patch clamp technique is employed to evaluate voltage-dependent calcium currents essentially as described by Thompson and Wong (1991) *J. Physiol.*, 439: 671-689. To record calcium channel (e.g., L-type, N-type, etc.) currents for evaluation of inhibitory potency of compounds (steady-state concentration-response analysis), five pulses of 20-30 ms voltage steps to about +10 mV (the peak of the current voltage relationship) are delivered at five Hz every 30 second from a holding potential at -100mV. Compound evaluations were carried out essentially as described by Sah

DW and Bean BP (1994) *Mol Pharmacol*.45(1):84-92. Table 3 contains IC₅₀'s for representative compounds.

TABLE 3

Example	IC ₅₀ (μM)
5	0.378
27	0.695
28	0.572

5

Example 3Formalin Test

Representative compounds of the formulae herein are screened for activity in the formalin test. The formalin test is widely used as a model of acute and tonic inflammatory pain (Dubuisson & Dennis, 1977 *Pain* 4:161-174; Wheeler-Aceto et al, 1990, *Pain* 40:229-238; Coderre et al, 1993, *Pain* 52:259-285). The test involves the administration to the rat hind paw of a dilute formalin solution followed by monitoring behavioral signs (i.e., flinching, biting and licking) during the "late phase" (11 to 60 minutes post injection) of the formalin response which reflects both peripheral nerve activity and central sensitization.. Male, Sprague-Dawley rats (Harlan, Indianapolis, IN) weighing approximately 225-300 g are used with an n=6-8 for each treatment group.

Depending on pharmacokinetic profile and route of administration, vehicle or a dose of test compound is administered to each rat by the intraperitoneal or oral route 30-120 minutes prior to formalin. Each animal is acclimated to an experimental chamber for 60 minutes prior to formalin administration, which is 50μL of a 5% solution injected subcutaneously into the plantar surface of one hind paw using a 300μL microsyringe and a 29 gauge needle. A mirror is angled behind the chambers to enhance the views of the animals' paws. The number of flinches (paw lifts with or without rapid paw shaking) and the time spent biting and/or licking the injured hind paw are recorded for each rat for 2 continuous minutes every 5 minutes for a total of 60 minutes after formalin administration. A terminal blood sample is harvested for analysis of plasma compound concentrations. Between groups comparisons of the total number of flinches or time spent biting and/or licking during the early or late phase are conducted using one-way analysis of variance (ANOVA).

Representative compounds of the formulae herein were evaluated for activity against calcium channel targets.

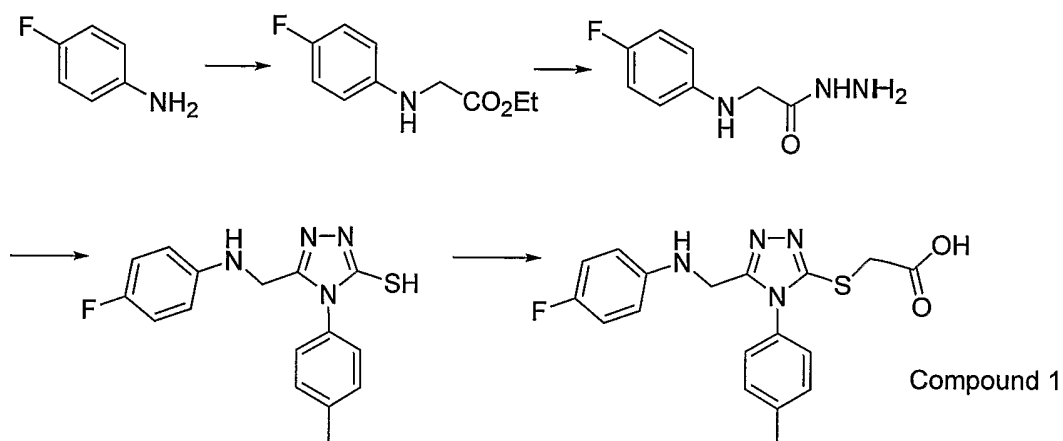
Example 4

Method A

Compound 1

{5-[(4-Fluoro-phenylamino)-methyl]-4-p-tolyl-4H-[1,2,4]triazol-3-ylsulfanyl}-acetic acid

Scheme 4



Part 1. Preparation of (4-Fluoro-phenylamino)-acetic acid ethyl ester

A mixture of 4-fluoroaniline (10 g, 90 mmol), bromoacetate (15 g, 90 mmol), and sodium acetate (11 g, 135 mmol) in ethanol (200 mL) was heated reflux for 2 hours. The cooled reaction was cooled and concentrated under vacuum. The residue was diluted with water and extracted with ethyl acetate. The organics were dried and concentrated under vacuum to give (4-fluoro-phenylamino)-acetic acid ethyl ester (8.46 g, 42.9 mmol) as a white solid.

Part 2. Preparation of (4-Fluoro-phenylamino)-acetic acid hydrazide

A mixture of (4-fluoro-phenylamino)-acetic acid ethyl ester and hydrazine (8.23 g, 257 mmol) in ethanol (200 mL) was refluxed for 3 hours. The reaction was cooled and

concentrated under vacuum. Trituration of the residue with n-hexane (75 mL) gave (4-fluoro-phenylamino)-acetic acid hydrazide (5.5 g, 30.20 mmol) as a white solid.

5 Part 3. Preparation of 5-[(4-Fluoro-phenylamino)-methyl]-4-p-tolyl-2,4-dihydro-[1,2,4]triazole-3-thione

A mixture of (4-fluoro-phenylamino)-acetic acid hydrazide and p-Tolueneisothiocyanate (4.5 g, 30.20 mmol) in aqueous 2N sodium hydroxide (100 mL) and heated for several hours then cooled. The solution was neutralized with 6N hydrochloric acid and extracted with ethyl acetate. The organics were dried and concentrated under vacuum to give a brown residue. Trituration of the residue with n-hexane (100mL) gave 5-[(4-fluoro-phenylamino)-methyl]-4-p-tolyl-2,4-dihydro-[1,2,4]triazole-3-thione (7.6 g, 24.2 mmol) as a white solid.

15 Part 4. Preparation of {5-[(4-Fluoro-phenylamino)-methyl]-4-p-tolyl-4H-[1,2,4]triazol-3-ylsulfanyl}-acetic acid

To a mixture of 5-[(4-fluoro-phenylamino)-methyl]-4-p-tolyl-2,4-dihydro-[1,2,4]triazole-3-thione (0.30 gm, 0.95 mmol), bromoacetic acid (0.13 gm, 0.95 mmol) and potassium carbonate (0.16 gm, 1.14 mmol) in acetone (6 mL) was heated at 40C for 3 hours then cooled. The reaction was diluted with water and extracted with ethyl acetate. The organics were dried and concentrated under vacuum to give a residue. The residue was purified by chromatography on silica (20% methanol in methylene chloride) to give {5-[(4-Fluoro-phenylamino)-methyl]-4-p-tolyl-4H-[1,2,4]triazol-3-ylsulfanyl}-acetic acid (0.27 gm, 0.72 mmol) as a white solid.

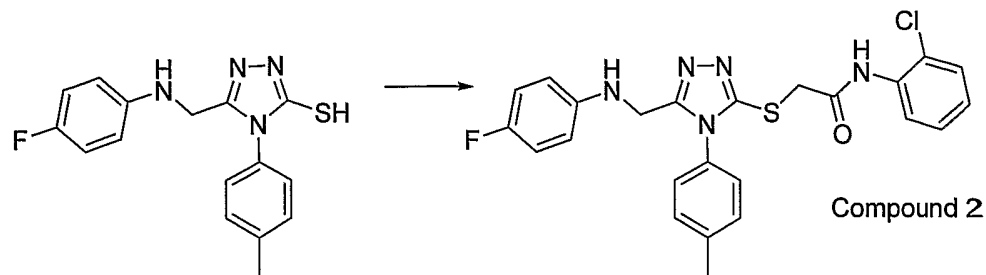
Method B

Compound 2

30

N-(2-Chloro-phenyl)-2- {5-[(4-fluoro-phenylamino)-methyl]-4-p-tolyl-4H-[1,2,4]triazol-3-ylsulfanyl}-acetamide

Scheme 5



Part 1. Preparation of N-(2-Chloro-phenyl)-2-{5-[(4-fluoro-phenylamino)-methyl]-4-p-tolyl-4H-[1,2,4]triazol-3-ylsulfanyl}-acetamide

5

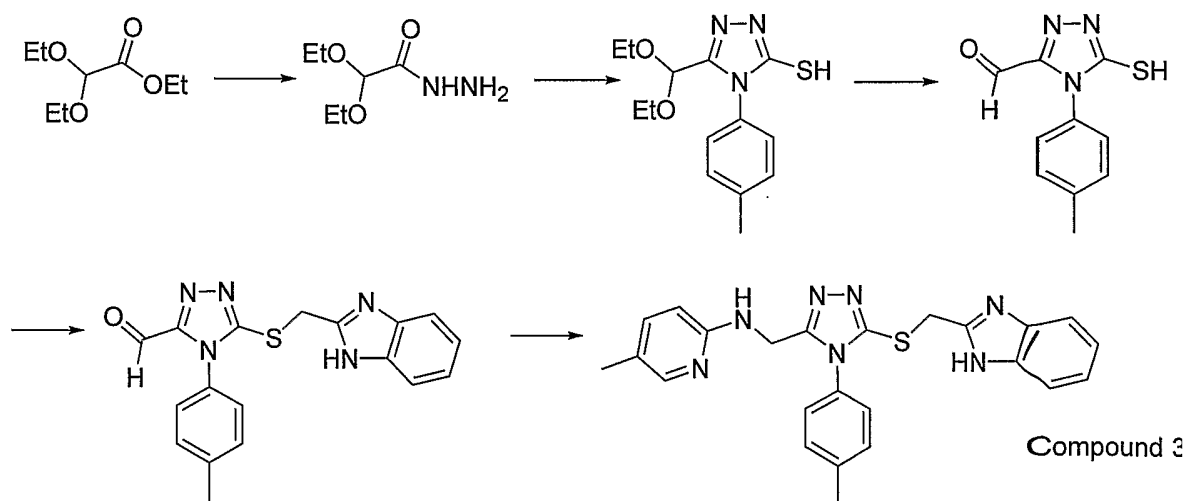
To a mixture of 5-[(4-fluoro-phenylamino)-methyl]-4-p-tolyl-2,4-dihydro-[1,2,4]triazole-3-thione (0.30 gm, 0.95 mmol), 2-bromo-N-(2-chloro-phenyl)-acetamide (0.24 gm, 0.95 mmol) and potassium carbonate (0.16 gm, 1.14 mmol) in acetone (6 mL) was heated at 40C for 3 hours then cooled. The reaction was diluted with water and extracted with ethyl acetate. The organics were dried and concentrated under vacuum to give a residue. The residue was purified by chromatography on silica (20% methanol in methylene chloride) to give N-(2-Chloro-phenyl)-2-{5-[(4-fluoro-phenylamino)-methyl]-4-p-tolyl-4H-[1,2,4]triazol-3-ylsulfanyl}-acetamide (0.10 gm, 0.20 mmol) as a white solid.

15

Method C

Compound 3

Scheme 6



20

[5-(1H-Benzoimidazol-2-ylmethylsulfanyl)-4-p-tolyl-4H-[1,2,4]triazol-3-ylmethyl]-
(5-methyl-pyridin-2-yl)-amine

Part 1. Preparation of Diethoxy-acetic acid hydrazide

5

A solution of ethyl diethoxyacetate (15.8 g, 90 mmol) ethanol (100 mL) was stirred and hydrazine(8.23 g, 257 mmol) was added. The mixture was heated at reflux for 2 hours. then cooled and concentrated under vacuum. The residue was diluted with water and extracted with ethyl acetate. The organics were dried and concentrated under vacuum to give
10 diethoxy-acetic acid hydrazide (10.53 g, 65 mmol) as a clear oil.

Part 2. Preparation of 5-Diethoxymethyl-4-p-tolyl-2,4-dihydro-[1,2,4]triazole-3-
thione

15

p-Tolueneisothiocyanate (9.7 g, 65mmol) and diethoxy-acetic acid hydrazide (10.53 g, 65 mmol) was dissolved in aqueous 2N sodium hydroxide (100 mL) and heated for several hours then cooled. The solution was neutralized with 6N hydrochloric acid and extracted with ethyl acetate. The organics were dried and concentrated under vacuum to give a yellow residue. Trituration of the residue with n-hexane (100mL) gave 5-diethoxymethyl-4-p-tolyl-
20 2,4-dihydro-[1,2,4]triazole-3-thione (12.3 g, 42mmol) as a yellow solid.

Part 3. Preparation of 5-Thioxo-4-p-tolyl-4,5-dihydro-1H-[1,2,4]triazole-3-
carbaldehyde

25

A solution of 5-diethoxymethyl-4-p-tolyl-2,4-dihydro-[1,2,4]triazole-3-thione (5 g, 17 mmol) and Aqueous 3N HCl (30 mL) in 1,4-dioxane (10 mL) was stirred and heated at 40C for 2 hours then cooled. The mixture was quenched with water and extracted with ethyl acetate. The organics dried and concentrated to give a residue. Purification by flash chromatography (SiO₂, 10% acetone in n-hexane) gave 5-thioxo-4-p-tolyl-4,5-dihydro-1H-
30 [1,2,4]triazole-3-carbaldehyde (2.6 g, 11.8 mmol) as a yellow solid.

Part 4. Preparation of 5-(1H-Benzoimidazol-2-ylmethylsulfanyl)-4-p-tolyl-4H-
[1,2,4]triazole-3-carbaldehyde

A solution of 5-thioxo-4-p-tolyl-4,5-dihydro-1H-[1,2,4]triazole-3-carbaldehyde (2.6 g, 1.8 mmol) and 2-(chloromethyl)benzimidazole (2.15 g, 12.9 mmol) in acetone (10 mL) was stirred and potassium carbonate (2.07 g, 15 mmol) was added. The mixture was heated at 40C for 3 hours then cooled. The mixture was quenched with water and extracted with ethyl acetate. The organics dried and concentrated to give a residue. Purification by flash chromatography (SiO₂, 30% acetone in n-hexane) gave 5-(1H-benzoimidazol-2-ylmethylsulfanyl)-4-p-tolyl-4H-[1,2,4]triazole-3-carbaldehyde (2.50 g, 7.08 mmol) as white solid.

Part 5. Preparation of [5-(1H-Benzoimidazol-2-ylmethylsulfanyl)-4-p-tolyl-4H-[1,2,4]triazol-3-ylmethyl]-(5-methyl-pyridin-2-yl)-amine

A solution of 5-(1H-benzoimidazol-2-ylmethylsulfanyl)-4-p-tolyl-4H-[1,2,4]triazole-3-carbaldehyde (1.0 g, 4.56 mmol) and 2-amino-5-methyl pyridine (0.49 g, 4.56 mmol) in DMF/ HOAc (10/1:v/v) (10 mL) was stirred at room temperature for 1 hour. Sodium cyanoborohydride (0.376 g, 6.0 mmol) was added and mixture was stirred overnight. The mixture was quenched with water and extracted with ethyl acetate. The organics dried and concentrated to give a residue. Purification by flash chromatography (SiO₂, 30% acetone in n-hexane) gave [5-(1H-Benzoimidazol-2-ylmethylsulfanyl)-4-p-tolyl-4H-[1,2,4]triazol-3-ylmethyl]-(5-methyl-pyridin-2-yl)-amine (0.108 g, 0.25 mmol) as an off-white solid.

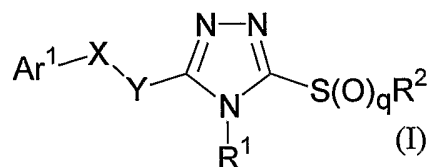
Compounds in the tables herein are prepared in a manner similar as described above and in the general schemes.

All references cited herein, whether in print, electronic, computer readable storage media or other form, are expressly incorporated by reference in their entirety, including but not limited to, abstracts, articles, journals, publications, texts, treatises, internet web sites, databases, patents, and patent publications.

It is to be understood that while the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

1 **WHAT IS CLAIMED IS:**

2 1. A method of treating a disease or disease symptom in a subject comprising
 3 administering to the subject an effective amount a compound of formula I or
 4 pharmaceutical salt thereof:



5

6 wherein,

7 Ar^1 is cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with
 8 one or more substituents;

9 X is NR^3 , $\text{C}(\text{R}^3)_2$, S, a bond or O, or together with Y forms $-\text{CH}=\text{CH}-$;

10 Y is $\text{C}=\text{O}$, a bond, or lower alkyl, or together with X forms $-\text{CH}=\text{CH}-$;

11 R^1 is Ar^2 , alkenyl, or lower alkyl optionally substituted with Ar^2 ;

12 each Ar^2 is independently cycloalkyl, aryl, heterocyclyl, or heteroaryl, each
 13 optionally substituted with one or more substituents;

14 q is 0, 1 or 2;

15 each R^2 is independently $(\text{CH}_2)_m\text{CO}_2\text{R}^3$, $(\text{CH}_2)_m\text{COAr}^3$, $(\text{CH}_2)_m\text{CONR}^3\text{R}^4$,
 16 $(\text{CH}_2)_m\text{Ar}^3$, $(\text{CH}_2)_3\text{Ar}^3$, $(\text{CH}_2)_n\text{NR}^3\text{R}^4$, $(\text{CH}_2)_n\text{OR}^4$; $(\text{CH}_2)_m\text{CN}$; alkyl; alkynyl,
 17 $(\text{CR}^3\text{R}^3)_m\text{CONR}^3\text{R}^4$, Ar^4 , $(\text{CR}^3\text{R}^3)_m\text{N}(\text{R}^3)\text{C}(\text{O})\text{Ar}^3$, or $(\text{CH}_2)_m\text{C}(\text{NOH})\text{NH}_2$;

18 each R^3 is independently H, or lower alkyl;

19 each R^4 is independently H, lower alkyl, alkoxy, $(\text{CH}_2)_n\text{NR}^5\text{R}^6$, or $(\text{CH}_2)_p\text{Ar}^3$;

20 m is 1 or 2;

21 n is 2 or 3;

22 p is 0 or 1;

23 each Ar^3 is cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted
 24 with one or more substituents;

25 each substituent for Ar¹, Ar² and Ar³ is independently halogen, CN, NO₂, OR⁶,
 26 SR⁶, S(O)₂OR⁵, NR⁵R⁶, cycloalkyl, C₁-C₂ perfluoroalkyl, C₁-C₂ perfluoroalkoxy, 1,2-
 27 methylenedioxy, C(O)OR⁵, C(O)NR⁵R⁶, OC(O)NR⁵R⁶, NR⁵C(O)NR⁵R⁶, C(NR⁶)NR⁵R⁶,
 28 NR⁵C(NR⁶)NR⁵R⁶, S(O)₂NR⁵R⁶, R⁷, C(O)R⁷, NR⁵C(O)R⁷, S(O)R⁷, or S(O)₂R⁷;

29 each R⁵ is independently hydrogen or lower alkyl optionally substituted with one
 30 or more substituents independently selected from halogen, OH, C₁-C₄ alkoxy, NH₂, C₁-
 31 C₄ alkylamino, C₁-C₄ dialkylamino or C₃-C₆ cycloalkyl;

32 each R⁶ is independently hydrogen, (CH₂)_pAr⁴, or lower alkyl optionally
 33 substituted with one or more substituents independently selected from halogen, OH, C₁-
 34 C₄ alkoxy, NH₂, C₁-C₄ alkylamino, C₁-C₄ dialkylamino or C₃-C₆ cycloalkyl;

35 each R⁷ is independently (CH₂)_pAr⁴ or lower alkyl optionally substituted with one
 36 or more substituents independently selected from halogen, OH, C₁-C₄ alkoxy, NH₂, C₁-
 37 C₄ alkylamino, C₁-C₄ dialkylamino or C₃-C₆ cycloalkyl; and

38 each Ar⁴ is independently C₃-C₆ cycloalkyl, heterocyclyl, aryl or heteroaryl, each
 39 optionally substituted with one to three substituents independently selected from halogen,
 40 OH, C₁-C₄ alkoxy, NH₂, C₁-C₄ alkylamino, C₁-C₄ dialkylamino or 1,2-methylenedioxy.

41

42 2. The method of claim 1, wherein:

43 Ar¹ is aryl or heteroaryl, each optionally substituted with one or more substituents;

44 X is NR³;

45 Y is lower alkyl;

46 R¹ is aryl optionally substituted with one or more substituents; and

47 each R² is independently (CH₂)_mCO₂R³, (CH₂)_mCOAr³, (CH₂)_mCONR³R⁴,
 48 (CH₂)_mAr³, (CH₂)₃Ar³, or (CH₂)_nNR³R⁴.

49

50 3. The method of claim 1, wherein:

51 Ar¹ is aryl or heteroaryl, each optionally substituted with one or more substituents;

52 X is a bond;

53 Y is a bond;

54 R¹ is aryl optionally substituted with one or more substituents; and

55 each R² is independently selected from (CH₂)_mCO₂R³, (CH₂)_mCOAr³,
56 (CH₂)_mCONR³R⁴, (CH₂)_mAr³, (CH₂)₃Ar³, (CH₂)_nNR³R⁴.

57
58 4. The method of any of claims 1-3, wherein each R² is independently selected
59 from (CH₂)_mAr³.

60
61 5. The method of any of claims 1-3, wherein:

62 each R² is independently selected from (CH₂)_mAr³; and

63 each Ar³ is heteroaryl optionally substituted with one or more substituents.

64
65 6. The method of claim 5, wherein Ar³ is a heteroaryl comprising a five-
66 membered ring having carbon atoms and 1, 2 or 3 heteroatoms selected from N, O and S,
67 optionally substituted with one or more substituents.

68
69 7. The method of claim 5, wherein Ar³ is pyrrolidinyl, pyrazolyl, imidazolyl,
70 oxazolyl, thiazolyl, benzimidazolyl, benzoxazolyl, or benzthiazolyl, each optionally
71 substituted with one or more substituents.

72
73 8. The method of claim 1, wherein the compound of formula I is a compound
74 delineated in any of Tables 1, or pharmaceutical salt thereof.

75
76 9. The method of claim 1, wherein the disease or disease symptom is modulated
77 by calcium channel Cav2.

78
79 10. The method of claim 9, wherein the disease or disease symptom is modulated
80 by calcium channel Cav2.2.

81
82 11. The method of claim 1, wherein the disease or disease symptom is angina,
83 hypertension, congestive heart failure, myocardial ischemia, arrhythmia, diabetes, urinary
84 incontinence, stroke, pain, traumatic brain injury, or a neuronal disorder.

85
86 12. A method of modulating calcium channel activity comprising contacting a
87 calcium channel with a compound of formula I in claim 1.

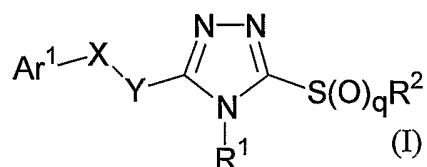
88

89 13. A compound of formula I in claim 1, or pharmaceutical salt thereof.

90

91 14. A compound of formula I or pharmaceutical salt thereof,

92



93

94 wherein,

95 Ar^1 is cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with
96 one or more substituents, and each attached to X by a carbon atom;

97 X is CH_2 ;

98 Y is a bond;

99 R^1 is Ar^2 , alkenyl, or lower alkyl optionally substituted with Ar^2 ;

100 each Ar^2 is independently cycloalkyl, aryl, heterocyclyl, or heteroaryl, each
101 optionally substituted with one or more substituents;

102 q is 0,1 or 2;

103 each R^2 is independently $(\text{CH}_2)_m\text{CO}_2\text{R}^3$, $(\text{CH}_2)_m\text{COAr}^3$, or $(\text{CH}_2)_m\text{CONR}^3\text{R}^4$;

104 each R^3 is independently H, or lower alkyl;

105 each R^4 is independently H, lower alkyl, alkoxy, $(\text{CH}_2)_n\text{NR}^5\text{R}^6$, or $(\text{CH}_2)_p\text{Ar}^3$;

106 m is 2;

107 n is 2 or 3;

108 p is 0 or 1;

109 each Ar^3 is cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted
110 with one or more substituents;

111 each substituent for Ar^1 , Ar^2 and Ar^3 is independently halogen, CN, NO_2 , OR^6 ,
112 SR^6 , $\text{S(O)}_2\text{OR}^5$, NR^5R^6 , cycloalkyl, $\text{C}_1\text{-C}_2$ perfluoroalkyl, $\text{C}_1\text{-C}_2$ perfluoroalkoxy, 1,2-

113 methylenedioxy, C(O)OR⁵, C(O)NR⁵R⁶, OC(O)NR⁵R⁶, NR⁵C(O)NR⁵R⁶, C(NR⁶)NR⁵R⁶,
114 NR⁵C(NR⁶)NR⁵R⁶, S(O)₂NR⁵R⁶, R⁷, C(O)R⁷, NR⁵C(O)R⁷, S(O)R⁷, or S(O)₂R⁷;

115 each R⁵ is independently hydrogen or lower alkyl optionally substituted with one
116 or more substituents independently selected from halogen, OH, C₁-C₄ alkoxy, NH₂, C₁-
117 C₄ alkylamino, C₁-C₄ dialkylamino or C₃-C₆ cycloalkyl;

118 each R⁶ is independently hydrogen, (CH₂)_pAr⁴, or lower alkyl optionally
119 substituted with one or more substituents independently selected from halogen, OH, C₁-
120 C₄ alkoxy, NH₂, C₁-C₄ alkylamino, C₁-C₄ dialkylamino or C₃-C₆ cycloalkyl;

121 each R⁷ is independently (CH₂)_pAr⁴ or lower alkyl optionally substituted with one
122 or more substituents independently selected from halogen, OH, C₁-C₄ alkoxy, NH₂, C₁-
123 C₄ alkylamino, C₁-C₄ dialkylamino or C₃-C₆ cycloalkyl; and

124 each Ar⁴ is independently C₃-C₆ cycloalkyl, heterocyclyl, aryl or heteroaryl, each
125 optionally substituted with one to three substituents independently selected from halogen,
126 OH, C₁-C₄ alkoxy, NH₂, C₁-C₄ alkylamino, C₁-C₄ dialkylamino or 1,2-methylenedioxy.

127

128 15. The compound of claim 13, wherein:

129 Ar¹ is cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with
130 one or more substituents, and each attached to X by a carbon atom;

131 X is a bond;

132 Y is a bond;

133 R¹ is Ar²;

134 each Ar² is independently cycloalkyl, aryl, heterocyclyl, or heteroaryl, each
135 optionally substituted with one or more substituents;

136 each R² is 4-pyridylmethyl.

137

138 16. The compound of claim 13, wherein:

139 Ar¹ is cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with
140 one or more substituents, and each attached to X by a carbon atom, however, Ar¹ is not 4-
141 pyridyl;

142 X is a bond;

143 Y is a bond;

144 R^1 is Ar^2 ;

145 each Ar^2 is independently cycloalkyl, aryl, heterocyclyl, or heteroaryl, each
146 optionally substituted with one or more substituents; and

147 each R^2 is 3-pyridylmethyl.

148

149 17. The compound of claim 13, wherein:

150 Ar^1 is cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with
151 one or more substituents, and each attached to X by a carbon atom;

152 X is a bond;

153 Y is a bond;

154 R^1 is Ar^2 ;

155 each Ar^2 is independently cycloalkyl, aryl, heterocyclyl, or heteroaryl, each
156 optionally substituted with one or more substituents; and

157 each R^2 is 2-pyridylmethyl.

158 18. The compound of claim 13, wherein:

159 Ar^1 is cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with
160 one or more substituents;

161 X is a bond;

162 Y is a bond;

163 R^1 is Ar^2 ;

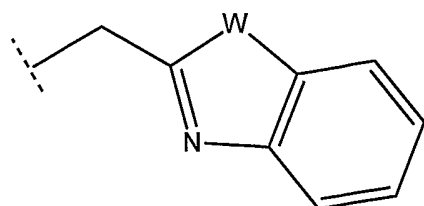
164 each Ar^2 is independently cycloalkyl, aryl, heterocyclyl, or heteroaryl, each
165 optionally substituted with one or more substituents; and

166

167

168 each R² is:

169



170 wherein W is NR³, S or O.

171

172 19. The compound of claim 13, wherein:

173 Ar¹ is cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with
174 one or more substituents;

175 X is a bond;

176 Y is a bond;

177 R¹ is Ar²;

178 each Ar² is independently cycloalkyl, aryl, heterocyclyl, or heteroaryl, each
179 optionally substituted with one or more substituents;

180 each R² is (CH₂)_mAr³; and

181 each Ar³ is aryl substituted with NH₂, S(O)₂OR³, COOH, or C(O)NH₂.

182

183 20. A method of treating a Cav2 calcium channel mediated disease or disease
184 symptom in a subject comprising administering to the subject an effective amount of a
185 compound of any of claims 13-19.

186

187 21. A method of treating a mediated disease or disease symptom in a subject
188 comprising administering to the subject an effective amount of a compound of any of
189 claims 13-19.

190

191 22. The method of claim 21, wherein the disease or disease symptom is angina,
192 hypertension, congestive heart failure, myocardial ischemia, arrhythmia, diabetes, urinary
193 incontinence, stroke, pain, traumatic brain injury, or a neuronal disorder.

194

195 23. A composition comprising a compound of formula I, or pharmaceutically
196 acceptable salt thereof, according to any of claims 13-19 and a pharmaceutically
197 acceptable carrier.

198

199 24. The composition of claim 23, further comprising an additional therapeutic
200 agent.

201

202 25. A method of making a compound of formula I in claim 1, comprising reacting
203 an intermediate delineated herein with a reagent to provide a compound of formula I as
204 defined herein.

205

206 26. A method of modulating calcium channel activity comprising contacting a
207 calcium channel with a compound of formula I in claim 13.

208

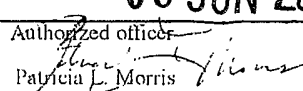
209 27. A method of modulating calcium channel activity in a subject in need thereof
210 comprising administering to the subject an effective amount of a compound of any of
211 claims 13-19.

212

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US05/07920

A. CLASSIFICATION OF SUBJECT MATTER IPC(7) : C07D 249/12 US CL : 548:264.4 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. : 548/264.4 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)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,260,450 A (KANE et al) 9 November 1993 (09.11.1993), see entire document.	14
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
Special categories of cited documents		
"X" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family	
Date of the actual completion of the international search 17 May 2005 (17.05.2005)		Date of mailing of the international search report 08 JUN 2005
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230		Authorized officer  Patricia L. Morris Telephone No. (571) 272-1600

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US05/07

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.: 1-13 and 15-27
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:
Please See Continuation Sheet

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 No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying 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.:

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/US05/07920

Continuation of Box II Reason 2:

In these claims, the numerous variables and their voluminous, complex meanings and their seemingly endless permutations and combinations make it virtually impossible to determine the full scope and complete meaning of the claimed subject matter. As presented, the claimed subject matter cannot be regarded as being a clear and concise description for which protection is sought and as such the listed claims do not comply with the requirements of PCT Article 6. Thus it is impossible to carry out a meaningful search on same. A search will be made on the first discernable invention, i.e., compound 1 on page 96 of the specification.