NMDA RECEPTOR ANTAGONISTS FOR NEUROPROTECTION

This application claims priority to U.S. Provisional Application No. 60/947,276, filed June 29, 2007; U.S. Provisional Application No. 60/949,120, filed July 11, 2007; U.S. Provisional Application No. 60/985,082, filed November 2, 2007; and U.S. Provisional Application No. 61/127,105, filed May 9, 2008.

FIELD OF THE INVENTION

The present invention is in the area of NMDA receptor blockers, including pH-sensitive NMDA receptor blockers, as neuroprotective drugs, and includes methods and compositions for the treatment of neurodegeneration resulting from NMDA-receptor activation.

BACKGROUND OF THE INVENTION

The NMDA subtype of glutamate-gated ion channels mediates excitatory synaptic transmission between neurons in the central nervous system (Dingledine et al. (1999), Pharmacological Reviews 51:7-61). Animal models of stroke and brain trauma confirm that glutamate released from affected neurons can overstimulate N-methyl-D-aspartate (NMDA) receptors, which in turn causes neuronal death. Therefore, compounds that block NMDA receptors have been considered candidates for treatment of stroke and head injuries.

NMDA receptors are composed of NR1, NR2 (A, B, C, and D), and NR3 (A and B) subunits, which determine the functional properties of native NMDA receptors. Expression of the NR1 subunit alone does not produce a functional receptor. Co-expression of one or more NR2 subunits is required to form functional channels. In addition to glutamate, the NMDA receptor requires the binding of a co-agonist, glycine, to allow the receptor to function. A glycine binding site is found on the NR1 and NR3 subunits, whereas the glutamate binding site is found on NR2 subunits. At resting membrane potentials, NMDA receptors are largely inactive due to a voltage-dependent block of the channel pore by magnesium ions. Depolarization releases this channel block and permits passage of calcium as well as other ions.

The NMDA receptor is modulated by a number of endogenous and exogenous

compounds including, sodium, potassium and calcium ions that can not only pass through the NMDA receptor channel but also modulate the activity of receptors. Zinc blocks the channel through NR2A- and NR2B-containing receptors noncompetitive and voltage-independent manner. Polyamines can also either potentiate or inhibit glutamate-mediated responses.

Stroke is the third leading cause of death in the United States and the most common cause of adult disability. In an ischemic stroke, which is the cause of approximately 80% of strokes, a blood vessel becomes occluded and the blood supply to part of the brain is blocked. Ischemic stroke is commonly divided into thrombotic stroke, embolic stroke, systemic hypoperfusion (Watershed or Border Zone stroke), or venous thrombosis. NMDA antagonists have been studied as neuroprotective agents for acute stroke. However, these agents, including Dextrorphan, Selfotel and aptiganel HCl (Cerestat) all showed certain toxicity profiles that required halting trials of these agents. Early clinical studies suggest that psychomimetic side effects occur less frequently with glycine site NMDA antagonists, however clinical studies have not supported a protective role for these agents (http://www.emedicine.com/neuro/topic488.htm, Lutsep & Clark "Neuroprotective Agents in Stroke", Apr. 30, 2004).

Epilepsy has also long been considered a potential therapeutic target for glutamate receptor antagonists. NMDA receptor antagonists are known to be anti-convulsant in many experimental models of epilepsy (Bradford (1995) Progress in Neurobiology 47:477-511; McNamara, J. O. (2001) Drugs effective in the therapy of the epilepsies. In Goodman & Gilman's: The pharmacological basis of therapeutics [Eds. J. G. Hardman and L. E. Limbird] McGraw Hill, New York).

NMDA receptor antagonists may also be beneficial in the treatment of chronic pain. Chronic pain, including neuropathic pain such as that due to injury of peripheral or central nerves, has often proved very difficult to treat. Treatment of chronic pain with ketamine and amantadine has proven beneficial, and it is believed that the analgesic effects of ketamine and amantadine are mediated by block of NMDA receptors. Several case reports have indicated that systemic administration of amantadine or ketamine substantially reduces the intensity of trauma-induced neuropathic pain. Small-scale double blind, randomized clinical trials corroborated that amantadine could significantly reduce neuropathic pain in cancer patients (Pud et al. (1998), Pain 75:349-354) and ketamine could reduce pain in patients with peripheral nerve injury (Felsby et al. (1996), Pain 64:283-291), peripheral vascular disease (Perrson et al. (1998), Acta Anaesthesiol Scand 42:750-758), or kidney donors (Stubhaug et

al. (1997), Acta Anaesthesiol Scand 41:1124-1132). "Wind-up pain" produced by repeated pinpricking was also dramatically reduced. These findings suggest that central sensitization caused by nociceptive inputs can be prevented by administration of NMDA receptor anatagonists.

NMDA receptor antagonists can also be beneficial in the treatment of Parkinson's Disease (Blandini and Greenamyre (1998), Fundam Clin Pharmacol 12:4-12). The anti-Parkinsonian drug, amantadine, is an NMDA receptor channel blocker (Blanpied et al. (1997), J Neurophys 77:309-323). In a small clinical trial, Amantadine reduced the severity of dyskinesias by 60% without reducing the antiparkinsonian effect of L-DOPA (Verhagen Metman et al. (1998), Neurology 50:1323-1326). Likewise, another NMDA receptor antagonist, CP-101,606, potentiated the relief of Parkinson's symptoms by L-DOPA in a monkey model (Steece-Collier et al., (2000) Exper. Neurol., 163:239-243).

NMDA receptor antagonists may in addition be beneficial in the treatment of brain cancers. Rapidly-growing brain gliomas can kill adjacent neurons by secreting glutamate and overactivating NMDA receptors such that the dying neurons make room for the growing tumor, and may release cellular components that stimulate tumor growth. Studies show NMDA receptor antagonists can reduce the rate of tumor growth in vivo as well as in some in vitro models (Takano, T., et al. (2001), Nature Medicine 7:1010-1015; Rothstein, J. D. and Bren, H. (2001) Nature Medicine 7:994-995; Rzeski, W., et al. (2001), Proc. Nat'l Acad. Sci 98:6372).

While NMDA-receptor antagonists might be useful to treat a number of very challenging disorders, to date, dose-limiting side effects have prevented clinical use of NMDA receptor antagonists for these conditions. Thus, despite the tremendous potential for glutamate antagonists to treat many serious diseases, the severity of the side effects have caused many to abandon hope that a well-tolerated NMDA receptor antagonist could be developed (Hoyte L. et al (2004) "The Rise and Fall of NMDA Antagonists for Ischemic Stroke Current Molecular Medicine" 4(2): 131-136; Muir, K. W. and Lees, K. R. (1995) Stroke 26:503-513; Herrling, P. L., ed. (1997) "Excitatory amino acid clinical results with antagonists" Academic Press; Parsons et al. (1998) Drug News Perspective II: 523 569).

pH Sensitive NMDA Receptors

Two of the most prevalent subtypes of NMDA receptors (including the NR2A and NR2B subunits or an alternatively spliced NR1 subunit) have the unusual property of being normally inhibited by protons by about 50% at physiological pH (Traynelis, S. F. and Cull-Candy, S. G. (1990) Nature 345:347; Traynelis et al. (1995) Science 268: 873-876; Traynelis et al. (1998), J Neurosci 18:6163-6175).

The extracellular pH is highly dynamic in mammalian brain, and influences the function of a multitude of biochemical processes and proteins, including glutamate receptor function. The pH-sensitivity of the NMDA receptor has received increasing attention for at least two reasons. First, the IC_{50} value for proton inhibition of pH 7.4 places the receptor under tonic inhibition at physiological pH. Second, pH changes are extensively documented in the central nervous system during synaptic transmission, glutamate receptor activation, glutamate receptor uptake, and prominently during pathological states such as ischemia and seizures (Siesjo, BK (1985), Progr Brain Res 63:121-154; Chesler, M (1990), Prog Neurobiol 34:401-427; Chesler and Kaila (1992), Trends Neurosci 15:396-402; Amato et al. (1994), J Neurophysiol 72:1686-1696).

During stroke, transient ischemia leads to a dramatic drop of pH to 6.4-6.5 in the core region of the infarct, with a modest drop in regions surrounding the core. The penumbral region, which surrounds the core and extends outward, suffers significant neuronal loss. The pH in this region drops to around pH 6.9. The pH-induced drops are exaggerated in presence of excess glutamate, and attenuated in hypoglycemic condition (see, for example, Mutch & Hansen (1984) J Cereb Blood Flow Metab 4: 17-27, Smith et al. (1986) J Cereb Blood Flow Metab 6: 574-583; Nedergaard et al. (1991) Am J Physiol 260(Pt3): R581-588; Katsura et al (1992a) Euro J Neursci 4: 166-176; and Katsura & Siesjo (1998) "Acid base metabolism in ischemia" in pH and Brain function (Eds Kaila & Ransom) Wiley-Liss, New York).

In addition to ischemia, there are various other examples of conditions in which pH changes can be associated with pathological processes, including neuropathic pain, Parkinsons disease, epilepsy and traumatic brain injuries.

Neuropathic pain, which is due to hyperactivity of nerve fibers in the dorsal horn of the spinal chord can be associated with pH changes in the spinal cord. Single electrical stimulation of isolated spinal cord from rat pups produces an alkaline shift of 0.05 pH units, and a 0.1 pH unit shift following 10 Hz stimulation which is followed by acidification after cessation of the stimuli. This acidification is greater in older animals (Jendelova & Sykova (1991) Glia 4: 56-63), indicating an increased pH differential underlying the stimuli.

Similarly, 30-40 Hz stimulation of the dorsal root in frog produced in vivo a transient extracellular acidification reaching a maximum ceiling of 0.25 pH unit reduction in the lower dorsal horn. Extracellular pH changes increased with stimulus intensity and frequency (Chvatal et al. (1988) Physiol Bohemoslov 37: 203-212). Further, high frequency (10-100 Hz) nerve stimulation in adult rat spinal cord in vivo produced triphasic alkaline-acid-alkaline shifts in extracellular pH (Sykova et al. (1992) Can J Physiol Pharmacol 70: Suppl S301-309). Additionally, it has been shown that acute nociceptive stimuli (pinch, press, heat) applied to the rat hindpaw produced transient acidification of 0.01-0.05 pH units in the lower dorsal horn in vivo (laminae III-VII). Chemical or thermal peripheral injury produced prolonged 2 hour decreases in interstitial pH of 0.05-0.1 pH units. High frequency nerve stimulation produced an alkaline pH shift followed by a dominating 0.2 pH unit acid shift (Sykova & Svoboda (1990) Brain Res 512: 181-189). Thus, increased firing of pain fibers can cause a decrease in pH (acidification) of the dorsal horn of the spinal cord.

Subthalamic neurons are overactive in Parkinson's disease, which may result in a lower local pH. There is a correlation in brain regions between neuronal activity and extracellular pH, with activity causing acidification. High frequency stimulation of brain slices gives an initial acidification followed by an alkalinization, followed by a slow acidification (See, for example, Chesler (1990) Prog Neurobiol 34: 401-427, Chesler & Kaila (1992) Tr Neurosci 15: 396-402, and Kaila & Chesler (1998) "Activity evoked changes in extracellular pH" in pH and Brain function (eds Kaila and Ransom). Wiley-Liss, New York).

Acidification also occurs during seizures. Electrographic seizures in a wide range of preparations have been shown to cause a change in extracellular pH. For example, up to a 0.2-0.36 drop in pH can occur in cat fascia dentata or rat hippocampal CA1 or dentate during an electrically or chemically evoked seizure. Deeper drops in pH approaching 0.5 can occur under hypoxic conditions (Siesjo et al (1985) J Cereb Blood Flow Metab 5: 47-57; Balestrino & Somjen (1988) J Physiol 396: 247-266; and Xiong & Stringer (2000) J Neurophysiol 83: 3519-3524).

In addition, other types of brain injury can result in acidification. "Spreading depression" is a term used to describe a slowly moving wave of electrical inactivity that occurs following a number of traumatic insults to brain tissue. Spreading depression can occur during a concussion or migraine. Acidic pH changes occur with spreading depression. Systemic alkalosis can occur with reduction in overall carbon dioxide content (hypocapnia) through, for example, hyperventilation. Conversely, systemic acidosis can occur with an increase in blood carbon dioxide (hypercapnia) during respiratory distress or conditions that

impair gas exchange or lung function. Diabetic ketoacidosis and lactic acidosis represent three of the most serious acute complications of diabetes and can result in brain acidification. Further, fetal asphyxia during parturition occurs in 25 per 1000 births at term. It involves hypoxia and brain damage that is similar but not identical to ischemia.

The acidification associated with pathological situations can partially inhibit NMDA receptors, which provides negative feedback that reduces their contribution to neurotoxicity and seizure maintenance (Kaku et al. (1993), Science 260:1516-1518; Munir and McGonigle (1995), J Neurosci 15:7847-7860; Vornov et al. (1996), J Neurochem 67:2379-2389; Gray et al. (1997), J Neurosurg Anesthesiol 9:180-187; O'Donnell and Bickler (1994), Stroke 25:171-177; reviewed by Tombaugh and Sapolsky (1993), J Neurochem 61:793-803; (Balestrino and Somjen (1988), J Physiol (Lond) 396:247-266; Velisek et al. (1994), Exp Brain Res 101:44-52). However, the pH sensitivity of glutamate transporters increases the likelihood that extracellular glutamate levels will be high during a period of acidification (Billups and Attwell (1996), Nature (Lond) 379:171-173), which enhances the opportunity for post-insult treatment of, for example, stroke with NMDA receptor antagonists (Tombaugh and Sapolsky (1993), J Neurochem 61:793-803).

Until 1995, it was not known whether the proton-sensitive property of the NMDA receptor could be exploited as a target for small molecule modulation of the receptor to develop therapeutics. Traynelis et al. (1995 Science 268:873) reported for the first time that the small molecule spermine could modulate NMDA receptor function through relief of proton inhibition. Spermine, a polyamine, shifts the pKa of the proton sensor to acidic values, reducing the degree of tonic inhibition at physiological pH, which appears as a potentiation of function (Traynelis et al. (1995), Science 268:873-876; Kumamoto, E (1996), Magnes Res 9(4):317-327).

In 1998, it was determined that the mechanism of action of the phenylethanolamine NMDA antagonists involved the proton sensor. Ifenprodil and CP-101,606 increased the sensitivity of the receptor to protons, thereby enhancing the proton inhibition. By shifting the pKa for proton block of NMDA receptors to more alkaline values, ifenprodil binding causes a larger fraction of receptors to be protonated at physiological pH and, thus, inhibited. In addition, ifenprodil was found to be more potent at lower pH (6.5) than higher pH (7.5) as tested in an in vitro model of NMDA-induced excitotoxicity in primary cultures of rat cerebral cortex (Mott et al. 1998 Nature Neuroscience 1:659). These compounds have exhibited neuroprotective properties in preclinical models and lack the severe side-effect

liability of other types of NMDA antagonists (e.g. PCP-like psychotic symptoms and cardiovascular effects). Other NMDA receptor-selective derivatives of ifenprodil are being considered for clinical development, including CP101,606 (Menniti et al. (1997), Eur J Pharmacol 331:117-126), Ro 25-6981 (Fischer et al. (1997), J Pharmacol Exp Ther 283:1285-1292) and Ro 8-4304 (Kew et al. (1998), Br J Pharmacol 123:463-472). Unfortunately, ifenprodil and several of its analogs, including eliprodil and haloperidol (Lynch and Gallagher (1996), J Pharmacol Exp Ther 279:154-161; Brimecombe et al. (1998), J Pharmacol Exp Ther 286(2):627-634), block certain serotonin receptors and calcium channels in addition to NMDA receptors, limiting their clinical usefulness (Fletcher et al. (1995), Br J Pharmacol 116(7):2791-2800; McCool and Lovinger (1995), Neuropharmacology 34:621-629; Barann et al. (1998), Naunyn Schmiedebergs Arch Pharmacol 358:145-152).

WO 02/072542 to Emory University describes a class of pH-dependent NMDA receptor antagonists that exhibit pH sensitivity tested in vitro using an oocyte assay and in an experimental model of epilepsy.

WO 06/023957 to Emory University describes processes for selection of a compound which may be useful in the treatment of an ischemic injury or a disorder that lowers the pH in a manner that activates the NMDA receptor antagonist.

There remains a need for improved neuroprotective compounds and methods for the treatment of neuropathologies that have reduced toxicity. In particular there is a need for improved treatments for neuropathic pain, inflammatory pain, stroke, traumatic brain injury, global ischemia, hypoxia, spinal cord trauma, epilepsy, and other neurodegenerative diseases and disorders.

It is therefore an object of the present invention to provide new compounds, pharmaceutical compositions and methods for the treatment of neuropathic and neurodegenerative diseases and disorders.

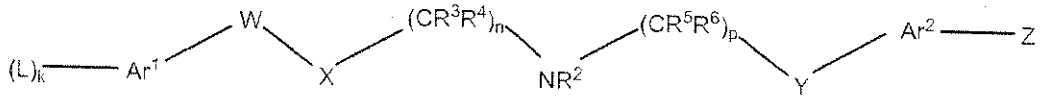
SUMMARY

NMDA receptor antagonists of Formula I, II, III, IV and V are provided, as well as compositions and methods of use of these compounds in the treatment or prophylaxis of neuropathic pain, stroke, traumatic brain injury, epilepsy, and neurologic events or neurodegeneration resulting from NMDA receptor activation. In particular, the compounds described herein are useful as neuroprotective agents. In one embodiment, the compounds,

compositions and methods are useful in the treatment of neuropathic pain. Compounds described herein are also useful in preventing neurodegeneration in patients with Parkinson's, Alzheimer's, Huntington's chorea, ALS, and other neurodegenerative conditions known to the art to be responsive to treatment using NMDA receptor antagonists.

In particular embodiments, certain NMDA receptor antagonists described herein have enhanced activity in brain tissue having lower-than-normal pH due to pathological conditions. Conditions that can alter the regional pH include hypoxia resulting from stroke, traumatic brain injury, global ischemia that may occur during cardiac surgery, hypoxia that may occur following cessation of breathing, pre-eclampsia, spinal cord trauma, epilepsy, status epilepticus, neuropathic pain, inflammatory pain, chronic pain, vascular dementia or glioma tumors.

In one embodiment, compounds, pharmaceutical compositions and methods of treatment or prophylaxis of neuropathic pain, stroke, traumatic brain injury, epilepsy, and other neurologic events or neurodegeneration resulting from NMDA receptor activation comprising administering a compound to a host in need thereof are provided, wherein the compounds is of Formula I, or a pharmaceutically acceptable salt, ester, prodrug or derivative thereof:



Formula I

wherein:

each L is independently C_1-C_6 alkyl, C_1-C_6 alkoxy, C(=O)-(C_1-C_6)-alkyl, C_1-C_6 haloalkyl, hydroxy, fluoro, chloro, bromo, iodo, nitro, or cyano; or two L groups may be taken together with Ar^1 to form: a dioxolane ring or a cyclobutane ring;

k = 0, 1, 2, 3, 4 or 5;

each Ar^1 and Ar^2 is independently aryl or heteroaryl;

W is a bond, C_1-C_4 alkyl, or C_2-C_4 alkenyl;

X is a bond, NR^1 or O;

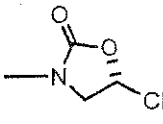
each R^1 and R^2 is independently H, C_1-C_6 alkyl, C_2-C_6 alkenyl or C_6-C_{12} aralkyl; or

R^1 and R^2 can be taken together to form a 5-8 membered ring;

each R^3 and R^4 is independently H, C_1-C_6 alkyl, C_1-C_6 alkoxy, C(=O)-(C_1-C_6)-alkyl, C_1-C_6 haloalkyl, hydroxy, fluoro, chloro, bromo, iodo, nitro, or cyano; or CR^3R^4 is C=O;

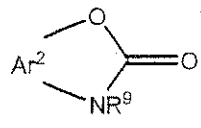
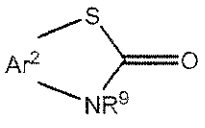
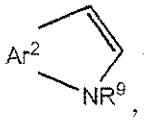
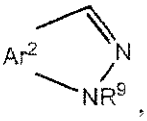
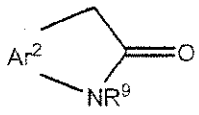
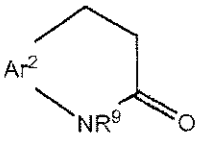
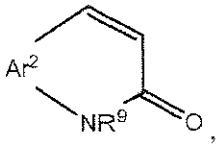
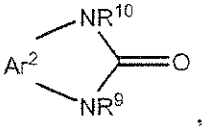
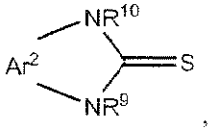
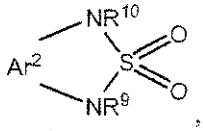
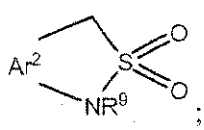
n = 1, 2, 3 or 4;

each R^5 and R^6 is independently H, C_1-C_6 alkyl, C_1-C_6 alkoxy, C(=O)-(C_1-C_6)-alkyl, C_1-C_6 haloalkyl, hydroxy, fluoro, chloro, bromo, iodo, nitro, or cyano; or CR^5R^6 is C=O or $C=CH_2$;

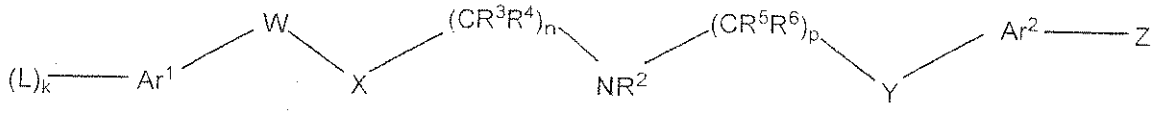
or wherein -NR^2- (CR^5R^6)$_p$- can be ;

Y is a bond, O, S, SO, SO_2, CH_2, NH, N(C_1-C_6 alkyl), or NHC(=O);

Z is OH, NR^6R^7, NR^8SO_2(C_1-C_6 alkyl), $NR^8C(O)NR^6R^7$, $NR^8C(S)NR^6R^7$, $NR^8C(O)O$(C_1-C_6 alkyl), NR^8-dihydrothiazole, or NR^8-dihydroimidazole; wherein each R^6, R^7 and R^8 is independently H, C_1-C_6 alkyl or C_6-C_{12} aralkyl; or

Ar^2—Z is , , , , , , , , , , ; wherein R^9 and R^{10} are each independently H, C_1-C_6 alkyl, aralkyl.

In a first aspect, there is provided a compound of Formula I, or a pharmaceutically acceptable salt, ester, prodrug, or derivative thereof:



Formula I

wherein:

each L is independently C_1-C_6 alkyl, C_1-C_6 alkoxy, C(=O)-(C_1-C_6)-alkyl, C_1-C_6 haloalkyl, alkaryl, hydroxy, -O-alkyl, -O-aryl, -SH, -S-alkyl, -S-aryl, fluoro, chloro, bromo, iodo, nitro, or cyano; or two L groups may be taken together with Ar^1 to form: a dioxolane ring or a cyclobutane ring;

k = 0, 1, 2, 3, 4 or 5;

each Ar^1 and Ar^2 is independently aryl or heteroaryl;

W is a bond, C_1-C_4 alkyl, or C_2-C_4 alkenyl;

X is NR^1;

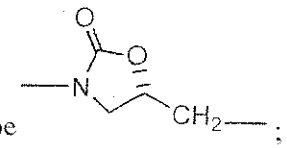
each R^1 and R^2 is independently H, C_1-C_6 alkyl, C_2-C_6 alkenyl or C_6-C_{12} aralkyl; or

R^1 and R^2 can be taken together to form a 5-8 membered ring;

each R^3 and R^4 is independently H, C_1-C_6 alkyl, C_1-C_6 alkoxy, C(=O)-(C_1-C_6)-alkyl, C_1-C_6 haloalkyl, hydroxy, fluoro, chloro, bromo, iodo, nitro, or cyano; or CR^3R^4 is C=O;

n = 1, 2, 3 or 4;

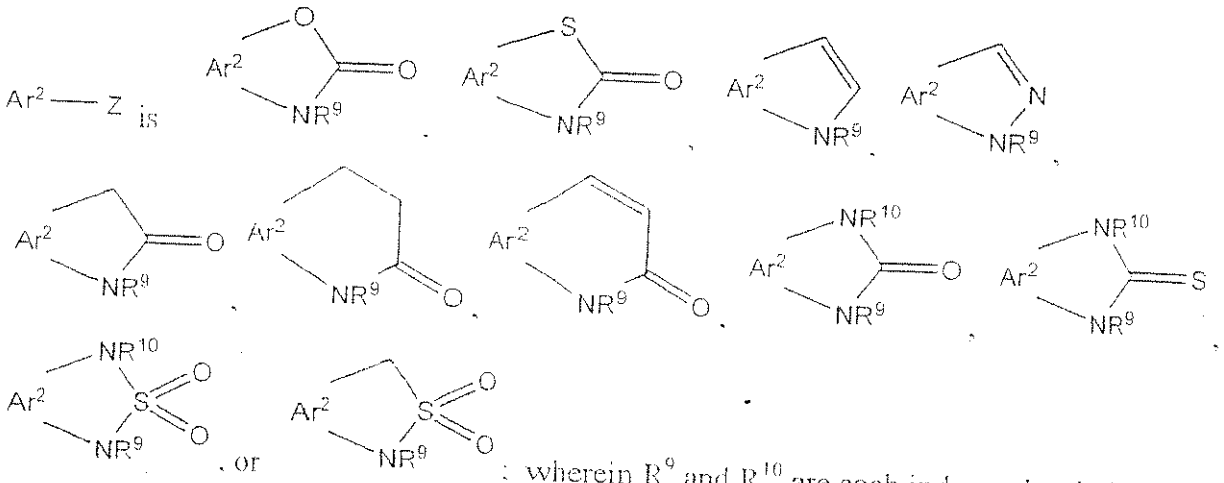
each R^5 and R^6 is independently H, C_1-C_6 alkyl, C_1-C_6 alkoxy, C(=O)-(C_1-C_6)-alkyl, C_1-C_6 haloalkyl, hydroxy, fluoro, chloro, bromo, iodo, nitro, or cyano; or CR^5R^6 is C=O or $C=CH_2$;

or wherein -NR^2-$(CR^5R^6)_p$- can be ;

p is 1, 2, 3 or 4;

Y is a bond, O, S, SO, SO_2, CH_2, NH, N(C_1-C_6 alkyl), or NHC(=O);

Z is OH, NR^6R^7, NR^8SO_2(C_1-C_6 alkyl), $NR^8C(O)NR^6R^7$, $NR^8C(S)NR^6R^7$, $NR^8C(O)O$(C_1-C_6 alkyl), NR^8-dihydrothiazole, or NR^8-dihydroimidazole; wherein each R^6, R^7 and R^8 is independently H, C_1-C_6 alkyl or C_6-C_{12} aralkyl; or



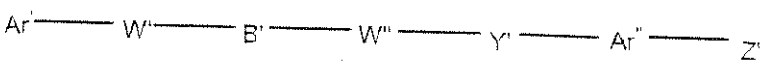
wherein R^9 and R^{10} are each independently H, C_1-C_6 alkyl, aralkyl;

wherein when X is a bond, Y is O and Ar^2 is phenyl, Z is not $NR^8SO_2(C_1$-C_6 alkyl); and when X is O, $-NR^2-(CR^5R^6)_p-$ is not -NH-C(=O)-.

In a second aspect, there is provided a pharmaceutical composition comprising a compound of the first aspect in a pharmaceutically acceptable carrier.

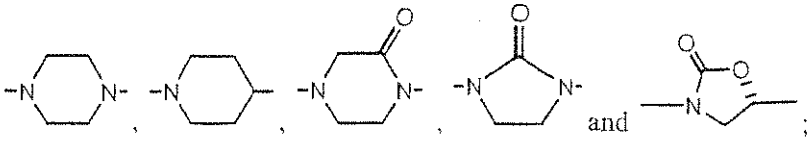
In a third aspect, there is provided a compound of the first aspect, optionally in a pharmaceutically acceptable carrier, for use in the treatment or prophylaxis of neuropathic pain, stroke, traumatic brain injury, epilepsy, and other neurologic events or neurodegeneration resulting from NMDA receptor activation.

In certain embodiments, it has been found that certain aryl substitutions enhance activity and safety of tri-cyclic substituted amine NMDA receptor antagonist compounds by decreasing secondary effects such as hERG binding and α1 adrenergic receptor activation. Thus, in certain embodiments, compounds, pharmaceutical compositions and methods of treatment or prophylaxis of neuropathic pain, stroke, traumatic brain injury, epilepsy, and other neurologic events or neurodegeneration resulting from NMDA receptor activation are provided comprising administering a compound to a host in need thereof are provided, wherein the compound is of Formula V, or a pharmaceutically acceptable salt, ester, prodrug or derivative thereof:



Formula V

wherein B' is selected from the group consisting of:



W' is a bond or C_1-C_4 alkyl;

W'' is C_1-C_4 alkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 haloalkyl or C(=O)-C_1-C_4 alkyl;

Y' is selected from a bond, O, S, CH_2 and N;

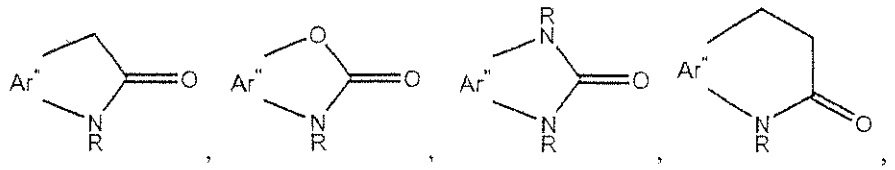
Ar' is an substituted or unsubstituted aromatic or nonaromatic cycloalkyl which optionally may include 0-3 heteroatoms;

Ar'' is an aromatic or nonaromatic cycloalkyl which optionally may include 0-3 heteroatoms;

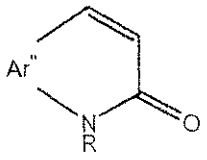
Z' is $NRC(O)NR_2$ wherein each R is independently selected from H, C_1-C_6 alkyl or C_6-C_{12} aralkyl; or

Ar''-Z' are taken together and selected from the group consisting

of:

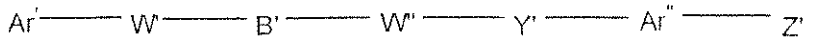


and



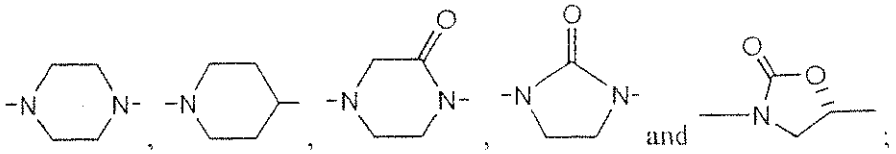
In one embodiment, Ar' is substited by $(L')_{k'}$ wherein each L' is independently C_1-C_6 alkyl, C_1-C_6 alkoxy, C(=O)-(C_1-C_6)-alkyl, C_1-C_6 haloalkyl, alkaryl, hydroxy, -O-alkyl, -O-aryl, -SH, -S-alkyl, -S-aryl, fluoro, chloro, bromo, iodo, nitro, or cyano; or two L' groups may be taken together with Ar' to form a dioxolane ring or a cyclobutane ring; and k' = 1, 2, 3, 4 or 5.

In a fourth aspect, there is provided a compound of Formula V or a pharmaceutically acceptable salt, ester, prodrug or derivative thereof:



Formula V

wherein B' is selected from the group consisting of:



W' is a bond or C_1-C_4 alkyl;

W'' is C_1-C_4 alkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 haloalkyl or C(=O)-C_1-C_4 alkyl;

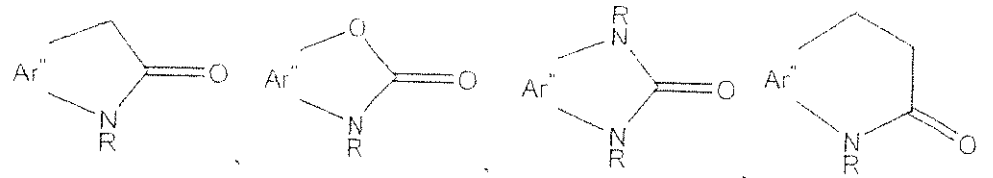
Y' is selected from a bond, O, S, CH_2 and N;

Ar' is a substituted or unsubstituted aromatic or nonaromatic cycloalkyl which optionally may include 0-3 heteroatoms;

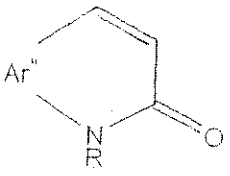
Ar'' is an aromatic or nonaromatic cycloalkyl which optionally may include 0-3 heteroatoms;

Z' is $NRC(O)NR_2$; wherein each R is independently selected from H, C_1-C_6 alkyl or C_6-C_{12} aralkyl; or

Ar''-Z' are taken together and selected from the group consisting of:



and



In a fifth aspect, there is provided a pharmaceutical composition comprising a compound of the fourth aspect, in a pharmaceutically acceptable carrier.

In a sixth aspect, there is provided a compound of the fourth aspect, optionally in a pharmaceutically acceptable carrier, for use in the treatment or prophylaxis of neuropathic pain, stroke, traumatic brain injury, epilepsy, and other neurologic events or neurodegeneration resulting from NMDA receptor activation.

In certain embodiments, the compounds are used for the treatment of neuropathic pain, stroke, traumatic brain injury, epilepsy, other neurologic events or neurodegeneration resulting from NMDA receptor activation, Parkinson's disease, Alzheimer's disease, Huntington's chorea, ALS, and other neurodegenerative conditions known to the art to be responsive to treatment using NMDA receptor blockers. In particular embodiments, the compounds are used for the prophylaxis of neuropathic pain, stroke, traumatic brain injury, epilepsy, other neurologic events or neurodegeneration resulting from NMDA receptor activation, Parkinson's disease, Alzheimer's disease, Huntington's chorea, ALS, and other

neurodegenerative conditions known to the art to be responsive to treatment using NMDA receptor blockers. The compounds can be administered on a prophylactic basis to a patient at risk of a disorder associated with NMDA receptor overactivation, and in particular a disorder associated with a reduced pH. In particular embodiments, the compounds act as neuroprotective agents.

In certain embodiments, the compounds are administered to a host in need thereof. In certain other embodiments, the compounds are administered in combination or alternation with other compounds that are useful in the treatment or prophylaxis of other neurologic events or neurodegeneration resulting from NMDA receptor activation, Parkinson's disease, Alzheimer's disease, Huntington's chorea, ALS, and other neurodegenerative conditions known to the art to be responsive to treatment using NMDA receptor blockers.

DETAILED DESCRIPTION OF THE INVENTION

It has been discovered that certain NMDA receptor antagonists are useful in the treatment or prophylaxis of neuropathic pain, stroke, traumatic brain injury, epilepsy, and other neurologic events or neurodegeneration resulting from NMDA receptor activation as well as Parkinson's disease, Alzheimer's disease, Huntington's chorea, ALS, and other neurodegenerative conditions known in the art to be responsive to treatment using NMDA receptor blockers. In particular, compounds described below are useful as neuroprotective agents. In one specific embodiment, the compounds, compositions and methods are useful in the treatment of neuropathic pain. In certain embodiments, the compounds provided herein are allosteric NMDA inhibitors.

In one embodiment, the IC_{50} value of the compound is 0.01 to 10 μM, 0.01 to 9 μM, 0.01 to 8 μM, 0.01 to 7 μM, 0.01 to 6 μM, 0.01 to 5 μM, 0.01 to 4 μM, 0.01 to 3 μM, 0.01 to 2 μM, 0.01 to 1 μM, 0.05 to 7 μM, 0.05 to 6 μM, 0.05 to 5 μM, 0.05 to 4 μM, 0.05 to 3 μM, 0.05 to 2 μM, 0.05 to 1 μM, 0.05 to 0.5 μM, 0.1 to 7 μM, 0.1 to 6 μM, 0.1 to 5 μM, 0.1 to 4 μM, 0.1 to 3 μM, 0.1 to 2 μM, 0.1 to 1 μM, 0.1 to 0.5 μM, 0.1 to 0.4 μM, 0.1 to 0.3 μM, or 0.1 to 0.2 μM.

Certain NMDA receptor antagonists described herein have enhanced activity in tissue having lower-than-normal pH. The acidic environment generated by ischemic tissue during stroke or by other disorders is harnessed as a switch to activate the neuroprotective agents described herein. In this way side effects are minimized in unaffected tissue since drug at these sites are less active.

In particular embodiments, the compound is pH sensitive. In specific embodiments, the compound exhibits a potency boost of at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 15 or at least 20 when comparing the IC_{50} at physiological pH versus the IC_{50} diseased pH (i.e., (IC_{50} at phys pH/IC_{50} at Dis pH)). In certain embodiments, the compound exhibits at least a 30%, 35%, 40%, 45%, 50%, 55%, or 60% decrease in infarct volume when a patient is suffering from a stroke or related condition.

In one embodiment, the compound has an IC_{50} value of less than 10 μM at a pH of about 6 to about 9. In one embodiment, the compound has an IC_{50} value of less than 10 μM at a pH of about 6.9. In another embodiment, the compound has an IC_{50} value of less than 10 μM at a pH of about 7.6. In one embodiment, the compound has an IC_{50} value of less than 10 μM at physiological pH. In one embodiment, the compound has an IC_{50} value of less than 10 μM at diseased pH.

In one embodiment, the IC_{50} value of the compound at pH 6.9 is 0.01 to 10 μM, 0.01 to 9 μM, 0.01 to 8 μM, 0.01 to 7 μM, 0.01 to 6 μM, 0.01 to 5 μM, 0.01 to 4 μM, 0.01 to 3 μM, 0.01 to 2 μM, 0.01 to 1 μM, 0.05 to 7 μM, 0.05 to 6 μM, 0.05 to 5 μM, 0.05 to 4 μM, 0.05 to 3 μM, 0.05 to 2 μM, 0.05 to 1 μM, 0.05 to 0.5 μM, 0.1 to 7 μM, 0.1 to 6 μM, 0.1 to 5 μM, 0.1 to 4 μM, 0.1 to 3 μM, 0.1 to 2 μM, 0.1 to 1 μM, 0.1 to 0.5 μM, 0.1 to 0.4 μM, 0.1 to 0.3 μM, or 0.1 to 0.2 μM, and the ratio of the IC_{50} values at pH 7.6 to pH 6.9 for the compound is greater than 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, 60, 70, 80, 90, or 100.

In one embodiment, the IC_{50} value of the compound at pH 6.9 is 0.01 to 10 μM, 0.01 to 9 μM, 0.01 to 8 μM, 0.01 to 7 μM, 0.01 to 6 μM, 0.01 to 5 μM, 0.01 to 4 μM, 0.01 to 3 μM, 0.01 to 2 μM, 0.01 to 1 μM, 0.05 to 7 μM, 0.05 to 6 μM, 0.05 to 5 μM, 0.05 to 4 μM, 0.05 to 3 μM, 0.05 to 2 μM, 0.05 to 1 μM, 0.05 to 0.5 μM, 0.1 to 7 μM, 0.1 to 6 μM, 0.1 to 5 μM, 0.1 to 4 μM, 0.1 to 3 μM, 0.1 to 2 μM, 0.1 to 1 μM, 0.1 to 0.5 μM, 0.1 to 0.4 μM, 0.1 to 0.3 μM, or 0.1 to 0.2 μM, and the ratio of the IC_{50} values at pH 7.6 to pH 6.9 for the compound is between 1 and 100, 2 and 100, 3 and 100, 4 and 100, 5 and 100, 6 and 100, 7 and 100, 8 and 100, 9 and 100, 10 and 100, 15 and 100, 20 and 100, 25 and 100, 30 and 100, 40 and 100, 50 and 100, 60 and 100, 70 and 100, 80 and 100, or 90 and 100.

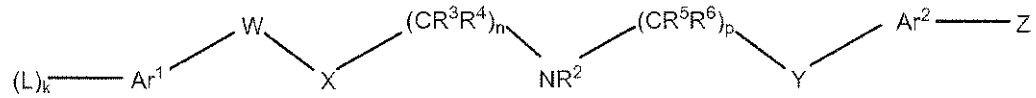
In other embodiments, the IC_{50} value of the compound at pH about 7.6 is 0.01 to 10 μM, 0.01 to 9 μM, 0.01 to 8 μM, 0.01 to 7 μM, 0.01 to 6 μM, 0.01 to 5 μM, 0.01 to 4 μM, 0.01 to 3 μM, 0.01 to 2 μM, 0.01 to 1 μM, 0.05 to 7 μM, 0.05 to 6 μM, 0.05 to 5 μM, 0.05 to 4 μM, 0.05 to 3 μM, 0.05 to 2 μM, 0.05 to 1 μM, 0.05 to 0.5 μM, 0.1 to 7 μM, 0.1 to 6 μM,

0.1 to 5 μM, 0.1 to 4 μM, 0.1 to 3 μM, 0.1 to 2 μM, 0.1 to 1 μM, 0.1 to 0.5 μM, 0.1 to 0.4 μM, 0.1 to 0.3 μM, or 0.1 to 0.2 μM, In certain of these embodiments, the compound exhibits a ratio of the IC_{50} values at pH 7.6 to pH 6.9 between 1 and 100, 2 and 100, 3 and 100, 4 and 100, 5 and 100, 6 and 100, 7 and 100, 8 and 100, 9 and 100, 10 and 100, 15 and 100, 20 and 100, 25 and 100, 30 and 100, 40 and 100, 50 and 100, 60 and 100, 70 and 100, 80 and 100, or 90 and 100. In certain other embodiments, the compound exhibits a ratio below 10, or below 5, or 4, 3, 2 or 1.

Compounds

Formula I

In one embodiment, compounds, pharmaceutical compositions and methods of treatment or prophylaxis of neuropathic pain, stroke, traumatic brain injury, epilepsy, and other neurologic events or neurodegeneration resulting from NMDA receptor activation, comprising administering to a host in need thereof a compound of Formula I, or a pharmaceutically acceptable salt, ester, prodrug or derivative thereof are provided:



FORMULA I

wherein:

each L is independently C_1-C_6 alkyl, C_1-C_6 alkoxy, C(=O)-(C_1-C_6)-alkyl, C_1-C_6 haloalkyl, alkaryl, hydroxy, -O-alkyl, -O-aryl, -SH, -S-alkyl, -S-aryl, fluoro, chloro, bromo, iodo, nitro, or cyano; or two L groups may be taken together with Ar^1 to form: a dioxolane ring or a cyclobutane ring;

k = 0, 1, 2, 3, 4 or 5;

each Ar^1 and Ar^2 is independently aryl or heteroaryl;

W is a bond, C_1-C_4 alkyl, or C_2-C_4 alkenyl;

X is a bond, NR^1 or O;

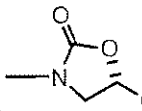
each R^1 and R^2 is independently H, C_1-C_6 alkyl, C_2-C_6 alkenyl or C_6-C_{12} aralkyl; or

R^1 and R^2 can be taken together to form a 5-8 membered ring;

each R^3 and R^4 is independently H, C_1-C_6 alkyl, C_1-C_6 alkoxy, C(=O)-(C_1-C_6)-alkyl, C_1-C_6 haloalkyl, hydroxy, fluoro, chloro, bromo, iodo, nitro, or cyano; or CR^3R^4 is C=O;

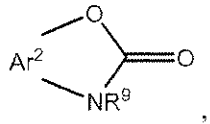
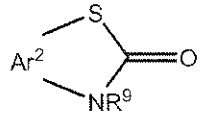
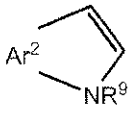
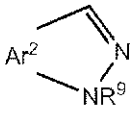
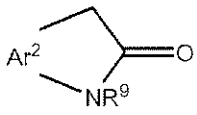
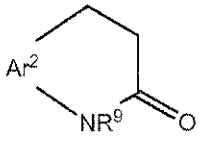
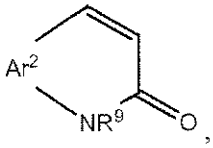
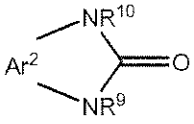
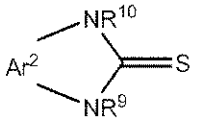
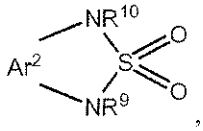
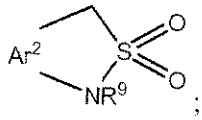
n = 1, 2, 3 or 4;

each R^5 and R^6 is independently H, C_1-C_6 alkyl, C_1-C_6 alkoxy, C(=O)-(C_1-C_6)-alkyl, C_1-C_6 haloalkyl, hydroxy, fluoro, chloro, bromo, iodo, nitro, or cyano; or CR^5R^6 is C=O or $C=CH_2$;

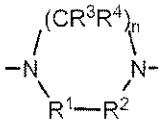
or wherein -NR^2- $(CR^5R^6)_p$- can be ;

Y is a bond, O, S, SO, SO_2, CH_2, NH, N(C_1-C_6 alkyl), or NHC(=O);

Z is OH, NR^6R^7, NR^8SO_2(C_1-C_6 alkyl), $NR^8C(O)NR^6R^7$, $NR^8C(S)NR^6R^7$, $NR^8C(O)O$(C_1-C_6 alkyl), NR^8-dihydrothiazole, or NR^8-dihydroimidazole; wherein each R^6, R^7 and R^8 is independently H, C_1-C_6 alkyl or C_6-C_{12} aralkyl; or

Ar^2—Z is , , , , , , , , , , ; wherein R^9 and R^{10} are each independently H, C_1-C_6 alkyl, aralkyl.

In specific embodiments of the Formula I when X is a bond, Y is O and Ar^2 is phenyl, Z is not NR^8SO_2(C_1-C_6 alkyl); and when X is O, -NR^2-$(CR^5R^6)_p$- is not -NH-C(=O)-.

In one embodiment, when Y is NHC(=O), Z is not OH or NR^8SO_2(C_1-C_6 alkyl). In one subembodiment, when R^1 and R^2 are taken together to form a 5-8 membered ring so that -NR^1-$(CR^3R^4)_n$-NR^2- is , Y-Ar^2 is not NH-heteroaryl. In another subembodiment, when R^1 and R^2 are taken together to form a 5-8 membered ring so that -NR^1-$(CR^3R^4)_n$-NR^2- is , Y is not NHC(=O).

In one embodiment, X is NR^1. In another embodiment, X is O. In another embodiment, X is a bond. In a particular subembodiment, X is a bond, n is 1, R^3 and R^4 are both H, and W is C_2 alkenyl. In certain embodiments, X is not a bond.

In particular subembodiment, Ar^1 is phenyl, pyridyl, pyrimidinyl, thiophenyl, imidazolyl, furanyl, indolyl, benzothiophenyl, benzofuranyl, or benzoimidazolyl.

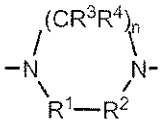
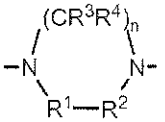
In another particular subembodiment, L is C_1-C_4 alkyl, C_1-C_4 alkoxy, C(=O)-(C_1-C_4)-alkyl, C_1-C_6 haloalkyl, hydroxy, fluoro, chloro, bromo, iodo, nitro, or cyano. In a further subembodiment, L is methyl, trifluoromethyl, methoxy, nitro, fluoro, chloro or hydroxy. In one further subembodiment, there are one, two or three L groups substituting Ar^1. In one subembodiment, Ar^1 is substituted with one fluoro group. In one subembodiment, Ar^1 is substituted with two fluoro groups. In one subembodiment, Ar^1 is substituted with one fluoro group and one chloro group. In one subembodiment, Ar^1 is substituted with one chloro group. In one subembodiment, Ar^1 is substituted with two chloro groups. In one subembodiment, Ar^1 is substituted with one methyl group. In one subembodiment, Ar^1 is substituted with one trifluoromethyl group.

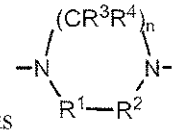
In one subembodiment, Ar^1 is phenyl. In one subembodiment, Ar^1 is phenyl and is substituted with an L group at the 2, 3, or 4 position. In another subembodiment, Ar^1 is phenyl and is substituted with L groups at the 2 and 4 positions. In another subembodiment, Ar^1 is phenyl and is substituted with L groups at the 3 and 4 positions.

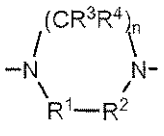
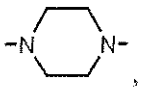
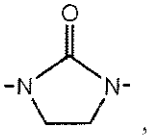
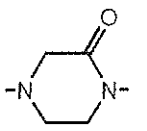
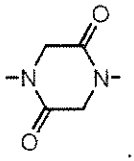
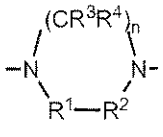
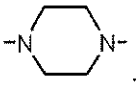
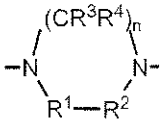
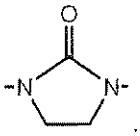
In one subembodiment, Ar^1 is pyridyl. In another subembodment, Ar^1 is 2-pyridyl, 3-pyridyl, or 4-pyridyl.

In one embodiment, Ar^1 is a bicyclic group wherein the W group is attached to the heterocyclic ring.

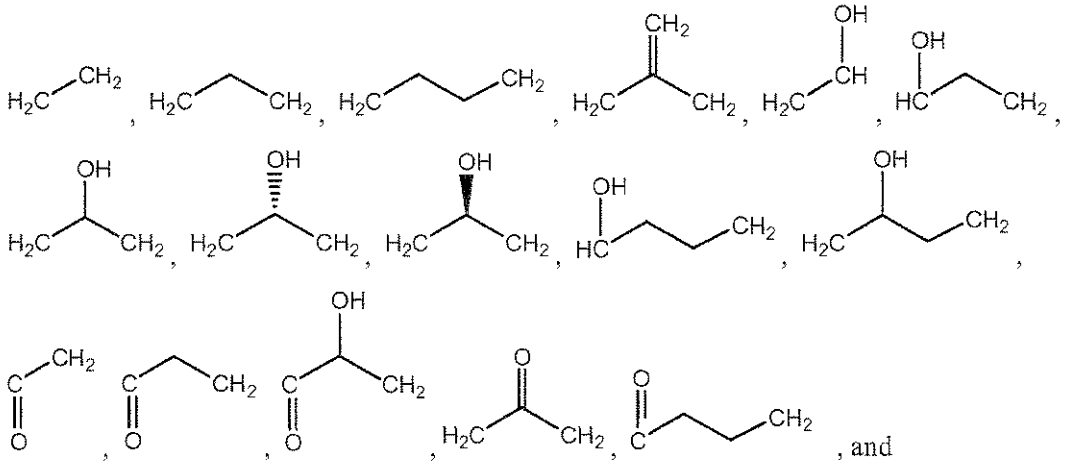
In one embodiment, W is a bond. In another embodiment, W is CH_2. In another embodiment, W is C_2-C_4 alkenyl.

In one embodiment, each R^1 and R^2 is independently H or C_1-C_4 alkyl, for example, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl or *tert*-butyl. In one embodiment, R^1 and R^2 are both H. In one embodiment, R^1 and R^2 are both C_1-C_4 alkyl, for example *n*-butyl. In another embodiment, R^1 and R^2 can be taken together to form a 5-8 membered ring so that $-NR^1-(CR^3R^4)_n-NR^2-$ is . In one subembodiment, when R^1 and R^2 are taken together to form a 5-8 membered ring so that $-NR^1-(CR^3R^4)_n-NR^2-$ is , Y-Ar^2 is not NH-heteroaryl. In another subembodiment, when R^1 and R^2 are taken together to form a

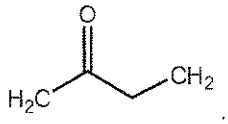
5-8 membered ring so that -NR^1-$(CR^3R^4)_n$-NR^2- is , Y is not NHC(=O). In one embodiment, n is 2. In one embodiment, n is 3. In another embodiment, R^1 and R^2 are each CH_2. In a subembodiment, CR^3R^4 is CH_2 and n is 2. In a subembodiment, CR^3R^4 in CH_2 and n is 3. In a subembodiment, CR^3R^4 is C=O and n is 1.

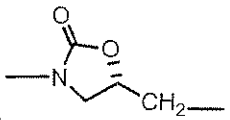
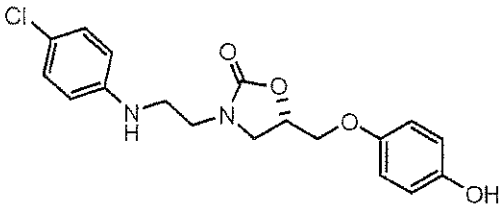
In one embodiment,  is , ,  or . In one embodiment,  is . In another embodiment,  is .

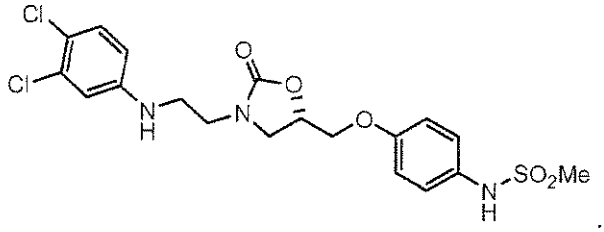
In one embodiment, each R^5 and R^6 is independently H, C_1-C_4 alkyl, C_1-C_4 alkoxy, C(=O)-(C_1-C_4)-alkyl, C_1-C_4 haloalkyl, hydroxy, fluoro, chloro, bromo, iodo, nitro, or cyano. In one embodiment, CR^5R^6 is C=O or $C=CH_2$. In one embodiment, p is 2, 3, or 4. In another embodiment, p is 3. In one embodiment, R^5 and R^6 are H. In another embodiment, one of R^5 and R^6 is hydroxy. In another embodiment, CR^5R^6 is $C=CH_2$. In another embodiment, CR^5R^6 is C=O. In one embodiment, $(CR^5R^6)_p$ is selected from the group consisting of



, and


. Compounds of Formula I can include compounds wherein when p is greater than 1, each (CR^5R^6) can be independently selected, for example, in one embodiment p is 2 and one (CR^5R^6) is C=O and the other (CR^5R^6) is CH_2. In one embodiment, R^5 is not fluoro. In another embodiment, R^6 is not fluoro.

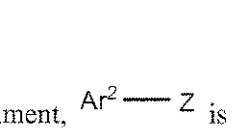
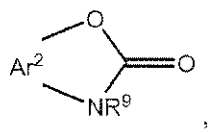
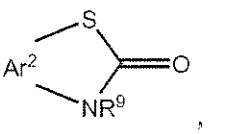
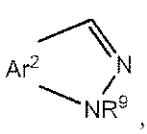
In one embodiment, -NR^2- (CR^5R^6)$_p$- is . In a particular subembodiment, the compound is . In another particular subembodiment, the compound is

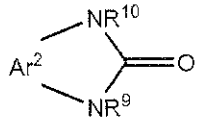
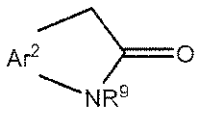
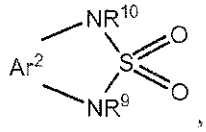
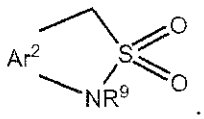
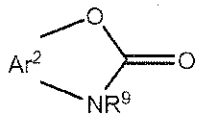
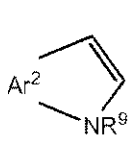
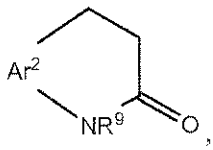
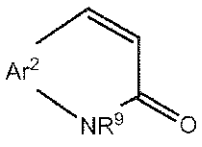
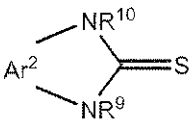

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In one embodiment, Y is a bond, O or CH_2. In one embodiment, Y is O. In another embodiment, Y is CH_2. In one embodiment, Y is not NH. In another embodiment, Y is not NHC(=O).

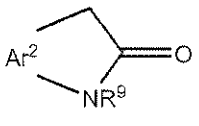
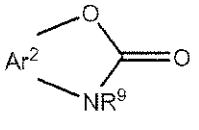
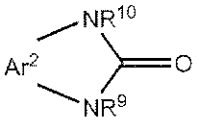
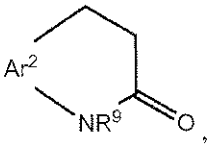
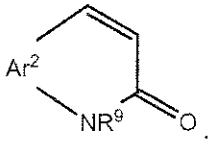
In one embodiment, Ar^2 is aryl. In one embodiment, Ar^2 is aryl, but not phenyl or heteroaryl. In one embodiment Ar^2 is phenyl. In one subembodiment, Ar^2 is phenyl and is substituted with a Z group at the 4 position. In one embodiment, Ar^2 is not heteroaryl. In one embodiment, Ar^2 is aryl, but not phenyl or heteroaryl.

In one embodment, Z is OH, NR^6R^7, $NR^8SO_2(C_1\text{-}C_6$ alkyl), $NR^8C(O)NR^6R^7$, $NR^8C(S)NR^6R^7$, $NR^8C(O)O(C_1\text{-}C_6$ alkyl), NR^8-dihydrothiazole, or NR^8-dihydroimidazole.

In one embodiment, 



,




, or . In one subembodiment, . In one subembodiment, 


, or . In one subembodiment, R^9 and R^{10} are each H.

In one embodiment, Z is $NR^8C(O)NR^6R^7$, for example $NHC(O)NH_2$ or $NHC(O)N(CH_3)_2$.

In another embodiment, Z and Ar^2 are taken together and selected from the group consisting of: 




and .

In one embodiment, the compound is a compound of Formula I, or a pharmaceutically acceptable salt, ester, prodrug or derivative thereof, wherein:

L is C_1-C_6 alkyl, C_1-C_6 alkoxy, C(=O)-(C_1-C_6)-alkyl, C_1-C_6 haloalkyl, alkaryl, hydroxy, -O-alkyl, -O-aryl, -SH, -S-alkyl, -S-aryl, fluoro, chloro, bromo, iodo, nitro, or cyano; or two L groups may be taken together with Ar^1 to form a dioxolane ring or a cyclobutane ring;

k = 0, 1, 2, 3, 4 or 5;

Ar^1 is phenyl, pyridyl, pyrimidinyl, thiophenyl, imidazolyl, furanyl, indolyl, benzothiophenyl, benzofuranyl, benzoimidazolyl;

Ar^2 is phenyl;

W is a bond, C_1-C_4 alkyl, or C_2-C_4 alkenyl;

each R^1 and R^2 is independently H, C_1-C_4 alkyl; or

R^1 and R^2 can be taken together to form a 5-8 membered ring;

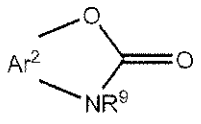
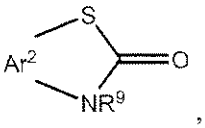
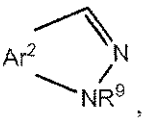
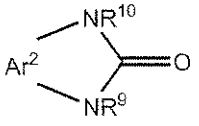
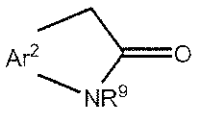
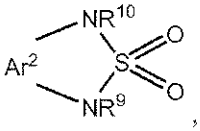
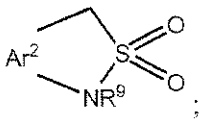
each R^3 and R^4 is independently H, C_1-C_6 alkyl, C_1-C_6 alkoxy, C(=O)-(C_1-C_6)-alkyl, C_1-C_6 haloalkyl, hydroxy, fluoro, chloro, bromo, iodo, nitro, or cyano; or CR^3R^4 is C=O;

n = 1, 2, 3 or 4;

each R^5 and R^6 is independently H, C_1-C_6 alkyl, C_1-C_6 alkoxy, C(=O)-(C_1-C_6)-alkyl, C_1-C_6 haloalkyl, hydroxy, fluoro, chloro, bromo, iodo, nitro, or cyano; or CR^5R^6 is C=O, $C=CH_2$;

Y is a bond, O, S, SO, SO_2, CH_2, NH, N(C_1-C_6 alkyl), NHC(=O);

Z is OH, NH_2, $NHSO_2$(C_1-C_4 alkyl), $NHC(O)NR^6R^7$, $NR^8C(S)NR^6R^7$, $NHC(O)O(C_1$-C_4 alkyl), NH-dihydrothiazole, or NH-dihydroimidazole; wherein each R^6 and R^7 is independently H, C_1-C_6 alkyl; or

Ar^2—Z is , , , , , , or ; wherein R^9 and R^{10} are each independently H or C_1-C_4 alkyl.

In one embodiment, the compound is a compound of Formula I, or a pharmaceutically acceptable salt, ester, prodrug or derivative thereof, wherein:

L is C_1-C_6 alkyl, C_1-C_6 alkoxy, C(=O)-(C_1-C_6)-alkyl, C_1-C_6 haloalkyl, alkaryl, hydroxy, -O-alkyl, -O-aryl, -SH, -S-alkyl, -S-aryl, fluoro, chloro, bromo, iodo, nitro, or cyano; or two L groups may be taken together with Ar^1 to form a dioxolane ring or a cyclobutane ring;

k = 0, 1, 2, 3, 4 or 5;

Ar^1 is phenyl, pyridyl, pyrimidinyl, thiophenyl, imidazolyl, furanyl, indolyl, benzothiophenyl, benzofuranyl, benzoimidazolyl;

Ar^2 is phenyl;

W is a bond, C_1-C_4 alkyl, or C_2-C_4 alkenyl;

each R^1 and R^2 is independently H, C_1-C_4 alkyl; or

R^1 and R^2 can be taken together to form a 5-8 membered ring;

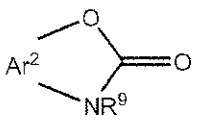
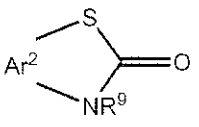
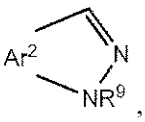
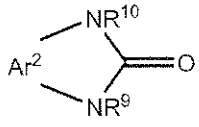
each R^3 and R^4 is independently H, C_1-C_6 alkyl, C_1-C_6 alkoxy, C(=O)-(C_1-C_6)-alkyl, C_1-C_6 haloalkyl, hydroxy, fluoro, chloro, bromo, iodo, nitro, or cyano; or CR^3R^4 is C=O;

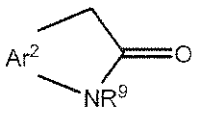
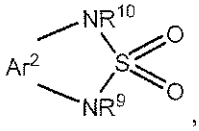
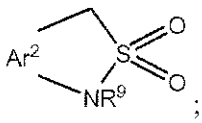
n = 1, 2, 3 or 4;

each R^5 and R^6 is independently H, C_1-C_6 alkyl, C_1-C_6 alkoxy, C(=O)-(C_1-C_6)-alkyl, C_1-C_6 haloalkyl, hydroxy, fluoro, chloro, bromo, iodo, nitro, or cyano; or CR^5R^6 is C=O, $C=CH_2$;

Y is a bond, O, S, SO, SO_2, CH_2, NH, N(C_1-C_6 alkyl), NHC(=O);

Z is OH, NH_2, $NHSO_2(C_1\text{-}C_4$ alkyl), $NHC(O)NR^6R^7$, $NR^8C(S)NR^6R^7$, $NHC(O)O(C_1\text{-}C_4$ alkyl), NH-dihydrothiazole, or NH-dihydroimidazole; wherein each R^6 and R^7 is independently H, $C_1\text{-}C_6$ alkyl; or

$Ar^2\text{—}Z$ is  ,  ,  ,  ,

 ,  , or  ; wherein R^9 and R^{10} are each independently H or $C_1\text{-}C_4$ alkyl.

In one embodiment, the compound is a compound of Formula I, or a pharmaceutically acceptable salt, ester, prodrug or derivative thereof, wherein:

L is $C_1\text{-}C_4$ alkyl, $C_1\text{-}C_4$ alkoxy, C(=O)-($C_1\text{-}C_4$)-alkyl, $C_1\text{-}C_4$ haloalkyl, alkaryl, hydroxy, -O-alkyl, -O-aryl, -SH, -S-alkyl, -S-aryl, fluoro, chloro, bromo, iodo, or nitro; or

two L groups may be taken together to form a dioxolane ring with Ar^1;

k = 0, 1, 2, 3, 4 or 5;

Ar^1 is phenyl or pyridyl;

Ar^2 is phenyl;

W is a bond or $C_1\text{-}C_4$ alkyl;

X is NR^1;

each R^1 and R^2 is independently H or $C_1\text{-}C_4$ alkyl; or

R^1 and R^2 can be taken together to form a 5-8 membered ring;

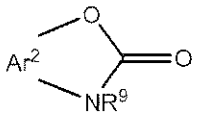
each R^3 and R^4 is independently H or $C_1\text{-}C_4$ alkyl; or CR^3R^4 is C=O;

n = 2 or 3;

each R^5 and R^6 is independently H, $C_1\text{-}C_4$ alkyl or OH; or CR^4R^5 is C=O or $C{=}CH_2$;

Y is O or CH_2;

Z is OH, NH_2, $NHSO_2(C_1\text{-}C_4$ alkyl), $NHC(O)NR^6R^7$, $NR^8C(S)NR^6R^7$, $NHC(O)O(C_1\text{-}C_4$ alkyl), NH-dihydrothiazole, or NH-dihydroimidazole; wherein each R^6 and R^7 is independently H or $C_1\text{-}C_4$ alkyl; or

$Ar^2\text{—}Z$ is  ;

R^9 is H or $C_1\text{-}C_4$ alkyl.

In one embodiment, the compound is a compound of Formula I, or a pharmaceutically acceptable salt, ester, prodrug or derivative thereof, wherein:

L is C_1-C_4 alkyl, C_1-C_4 alkoxy, C(=O)-(C_1-C_4)-alkyl, C_1-C_4 haloalkyl, alkaryl, hydroxy, -O-alkyl, -O-aryl, -SH, -S-alkyl, -S-aryl, fluoro, chloro, bromo, iodo, or nitro; or

two L groups may be taken together to form a dioxolane ring with Ar^1;

k = 0, 1, 2, 3, 4 or 5;

Ar^1 is phenyl or pyridyl;

Ar^2 is phenyl;

W is a bond or C_1-C_4 alkyl;

X is O;

R^2 is H or C_1-C_4 alkyl;

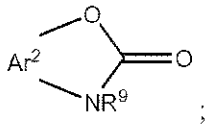
each R^3 and R^4 is independently H or C_1-C_4 alkyl; or CR^3R^4 is C=O;

n = 2 or 3;

each R^5 and R^6 is independently H, C_1-C_4 alkyl or OH; or CR^4R^5 is C=O or $C=CH_2$;

Y is O or CH_2;

Z is OH, NH_2, $NHSO_2$(C_1-C_4 alkyl), $NHC(O)NR^6R^7$, $NHC(O)O$(C_1-C_4 alkyl), NH-dihydrothiazole, or NH-dihydroimidazole; wherein each R^6 and R^7 is independently H or C_1-C_4 alkyl; or

Ar^2—Z is 

;

R^9 is H or C_1-C_4 alkyl.

In one embodiment, the compound is a compound of Formula I, or a pharmaceutically acceptable salt, ester, prodrug or derivative thereof, wherein:

L is C_1-C_4 alkyl, C_1-C_4 alkoxy, C(=O)-(C_1-C_4)-alkyl, C_1-C_4 haloalkyl, hydroxy, fluoro, chloro, bromo, iodo, or nitro; or

two L groups may be taken together to form a dioxolane ring with Ar^1;

k = 0, 1, 2, 3, 4 or 5;

Ar^1 is phenyl or pyridyl;

Ar^2 is phenyl;

W is C_2-C_4 alkenyl;

X is a bond;

R^2 is H or C_1-C_4 alkyl;

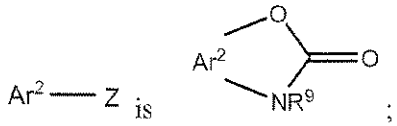
each R^3 and R^4 is independently H or C_1-C_4 alkyl; or CR^3R^4 is C=O;

n = 1, 2 or 3;

each R^5 and R^6 is independently H, C_1-C_4 alkyl or OH; or CR^4R^5 is C=O or $C=CH_2$;

Y is O or CH_2;

Z is OH, NH_2, $NHSO_2(C_1$-C_4 alkyl), $NHC(O)NR^6R^7$, $NR^8C(S)NR^6R^7$, $NHC(O)O(C_1$-C_4 alkyl), NH-dihydrothiazole, or NH-dihydroimidazole; wherein each R^6 and R^7 is independently H or C_1-C_4 alkyl; or

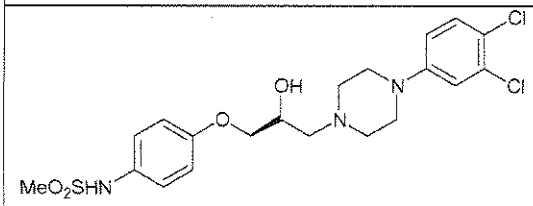
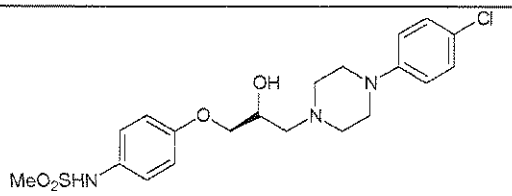
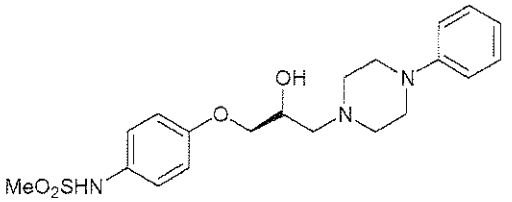


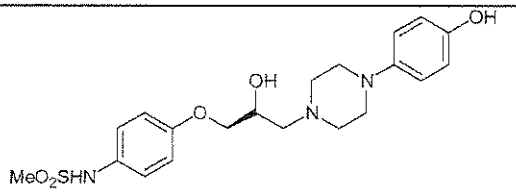
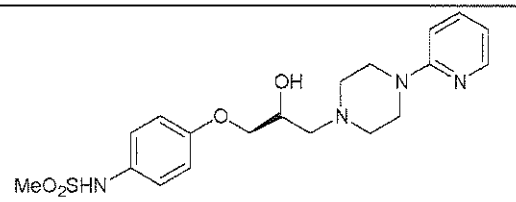
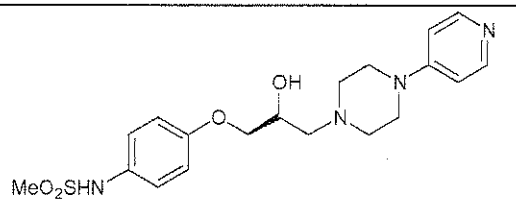
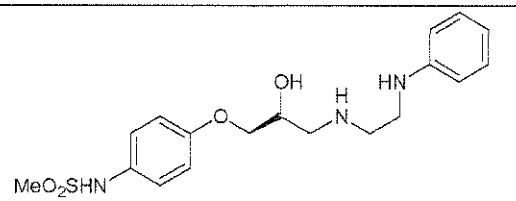
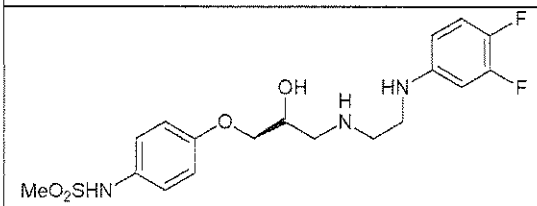
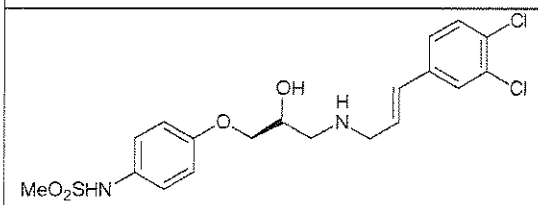
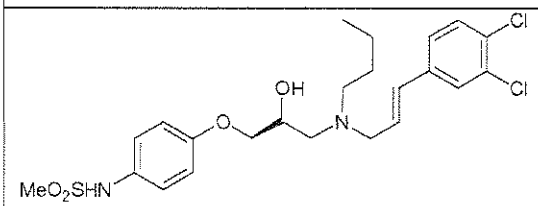
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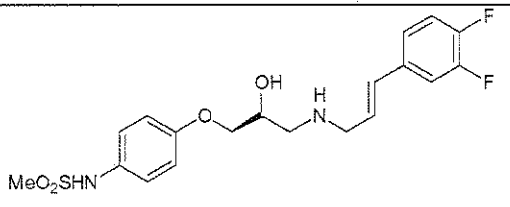
R^9 is H or C_1-C_4 alkyl.

In one embodiment, the compound is selected from the compounds in Table 1.

Table 1.

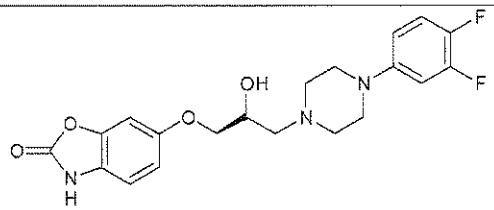
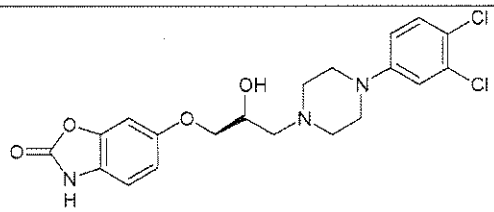
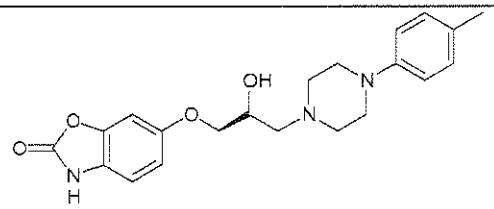
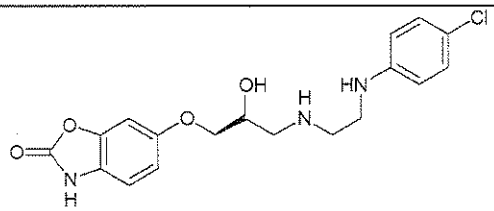
Compound	NAME
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	N-(4-{3-[4-(4-Chloro-phenyl)-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-phenyl)-methanesulfonamide
	N-(4-{3-[4-phenyl-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-phenyl)-methanesulfonamide

	N-(4-{3-[4-(4-Hydroxy-phenyl)-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-phenyl)-methanesulfonamide
	N-(4-{3-[4-(2-Pyridyl)-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-phenyl)-methanesulfonamide
	N-(4-{3-[4-(4-Pyridyl)-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-phenyl)-methanesulfonamide
	N-{4-[2-(*S*)-Hydroxy-3-(2-phenylamino-ethylamino)-propoxy]-phenyl}-methanesulfonamide
	N-{4-[2-(*S*)-Hydroxy-3-(2-(3,4-difluoro-phenyl)amino-ethylamino)-propoxy]-phenyl}-methanesulfonamide
	N-(4-{3-[3-(3,4-Dichloro-phenyl)-allylamino]-2-(*S*)-hydroxy-propoxy}-phenyl)-methanesulfonamide
	N-[4-(3-{Butyl-[3-(3,4-dichloro-phenyl)-allyl]-amino}-2-(*S*)-hydroxy-propoxy)-phenyl]-methanesulfonamide

	N-(4-{3-[3-(3,4-Difluoro-phenyl)-allylamino]-2-(*S*)-hydroxy-propoxy}-phenyl)-methanesulfonamide

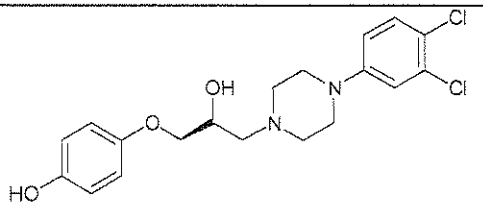
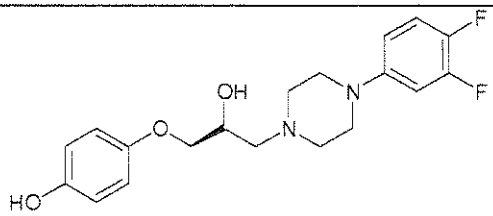
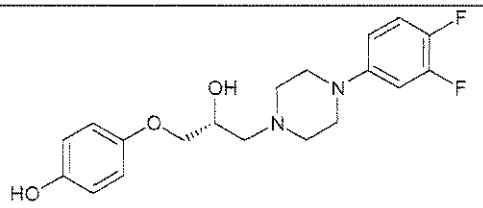
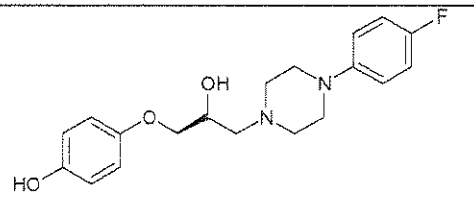
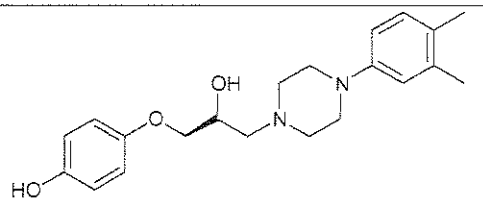
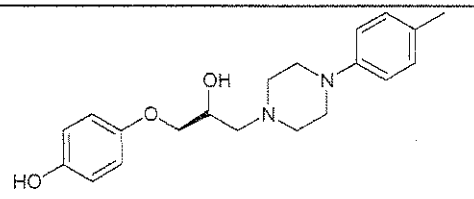
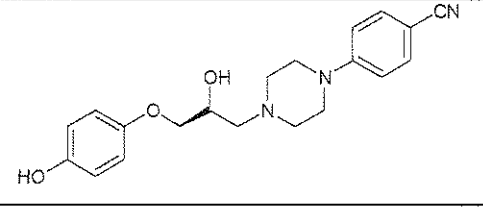
In one embodiment, the compound is selected from the compounds in Table 2.

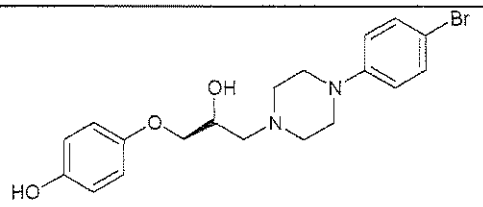
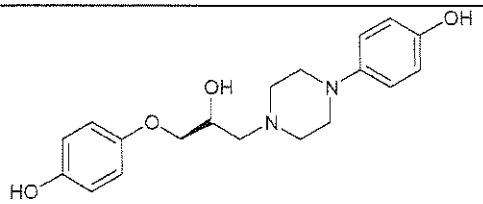
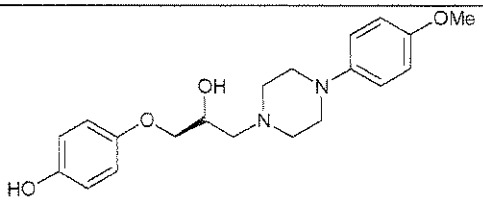
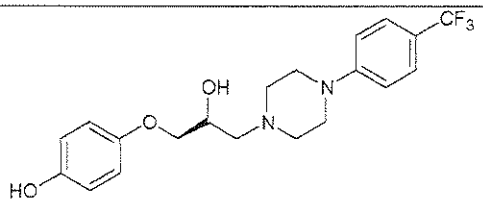
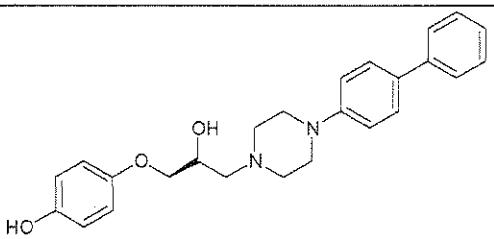
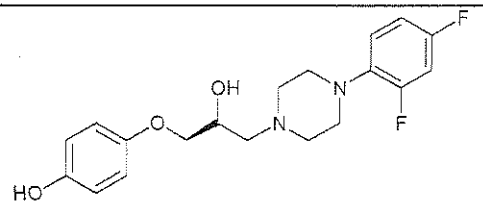
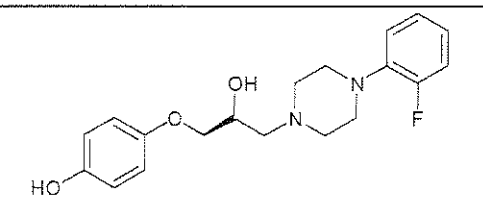
Table 2.

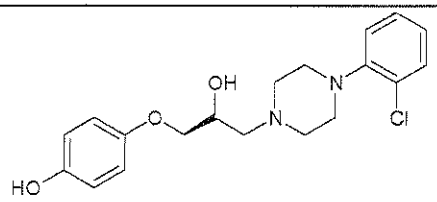
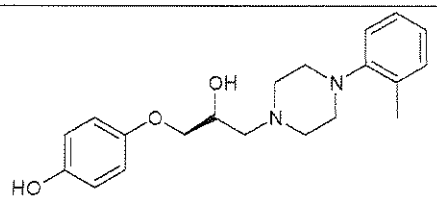
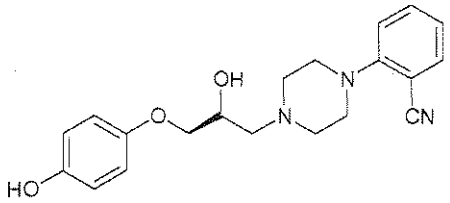
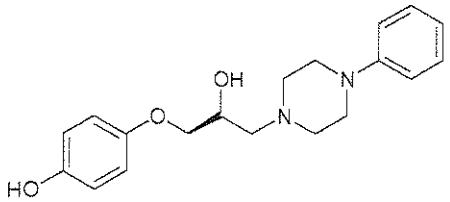
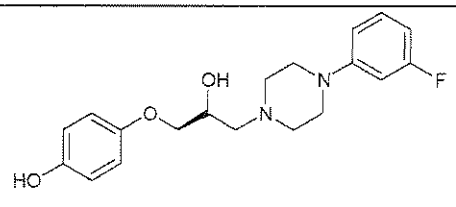
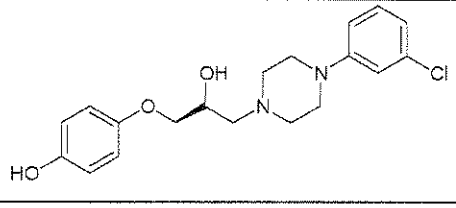
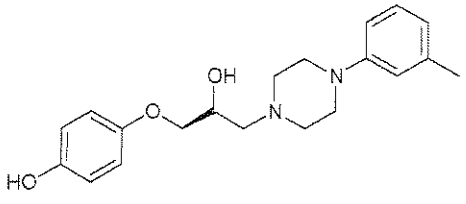
Compound	NAME
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	6-{3-[4-(3,4-Dichloro-phenyl)-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-3H-benzooxazol-2-one
	6-{3-[4-(4-Methyl-phenyl)-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-3H-benzooxazol-2-one
	6-{3-[2-(4-Chloro-phenylamino)-ethylamino]-2-(*S*)-hydroxy-propoxy}-3H-benzooxazol-2-one

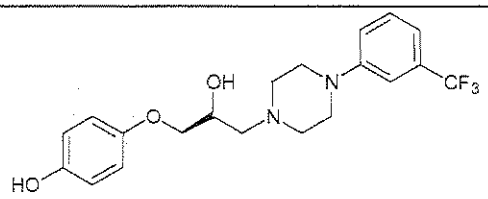
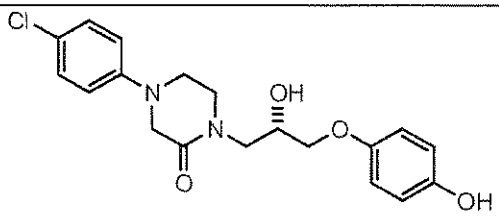
In one embodiment, the compound is selected from the compounds in Table 3.

Table 3.

Compound	NAME
	4-{3-[4-(3,4-Dichloro-phenyl)-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-phenol
	4-{3-[4-(3,4-Difluoro-phenyl)-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-phenol
	4-{3-[4-(3,4-Difluoro-phenyl)-piperazin-1-yl]-2-(*R*)-hydroxy-propoxy}-phenol
	4-{3-[4-(4-Fluoro-phenyl)-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-phenol
	4-{3-[4-(3,4-Dimethyl-phenyl)-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-phenol
	4-{3-[4-(4-Methyl-phenyl)-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-phenol
	4-{3-[4-(4-Cyano-phenyl)-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-phenol

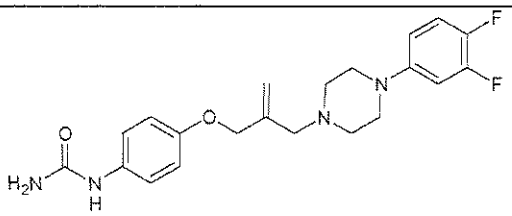
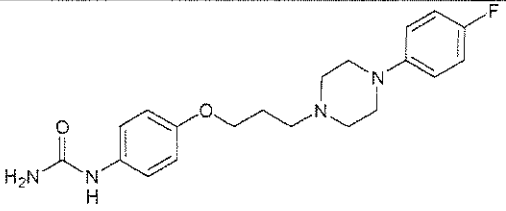
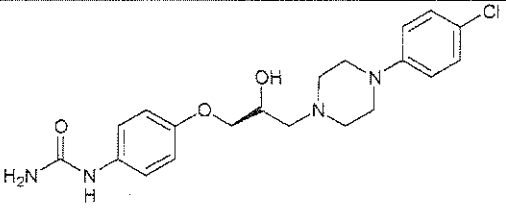
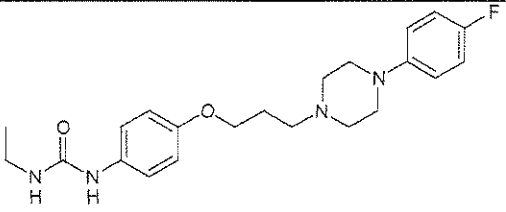
	4-{3-[4-(4-Bromo-phenyl)-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-phenol
	4-{3-[4-(4-Hydroxy-phenyl)-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-phenol
	4-{3-[4-(4-Methoxy-phenyl)-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-phenol
	4-{3-[4-(4-Trifluoromethyl-phenyl)-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-phenol
	4-{3-[4-(4-Biphenyl)-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-phenol
	4-{3-[4-(2,4-Difluoro-phenyl)-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-phenol
	4-{3-[4-(2-Fluoro-phenyl)-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-phenol

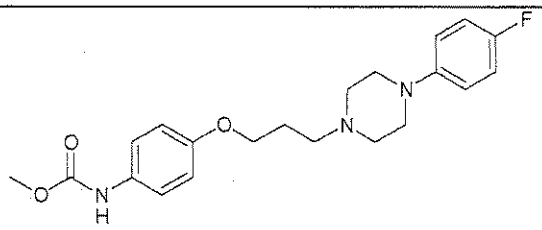
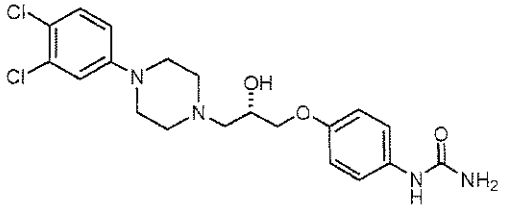
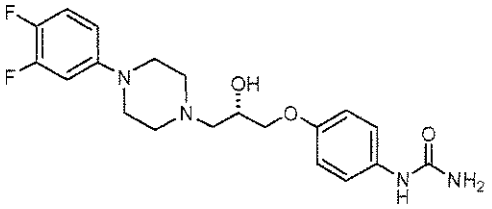
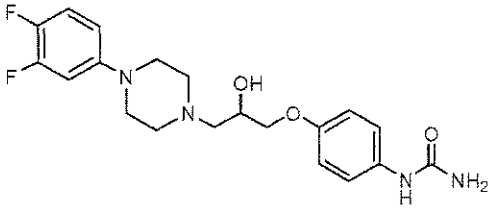
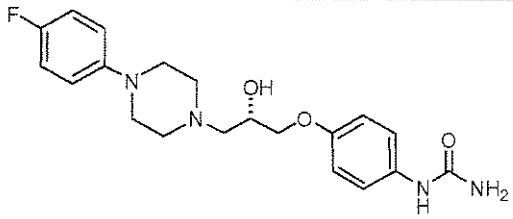
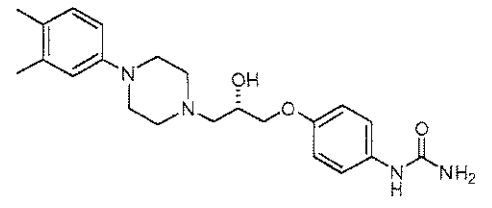
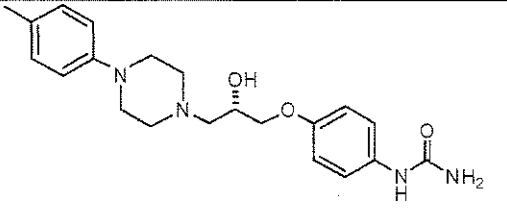
	4-{3-[4-(2-Chloro-phenyl)-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-phenol
	4-{3-[4-(2-Chloro-phenyl)-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-phenol
	4-{3-[4-(2-Cyano-phenyl)-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-phenol
	4-{3-[4-Phenyl-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-phenol
	4-{3-[4-(3-Fluoro-phenyl)-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-phenol
	4-{3-[4-(3-Chloro-phenyl)-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-phenol
	4-{3-[4-(3-Methyl-phenyl)-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-phenol

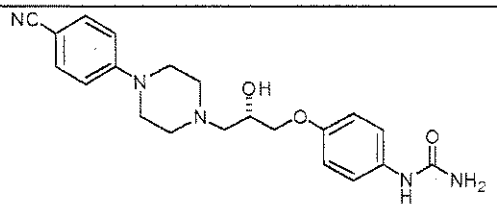
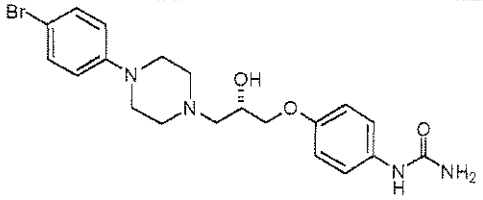
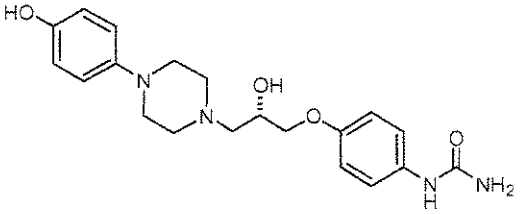
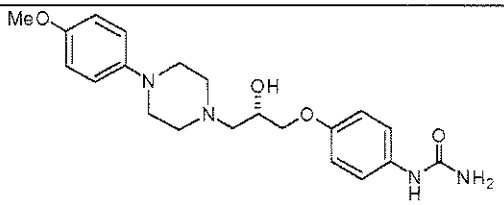
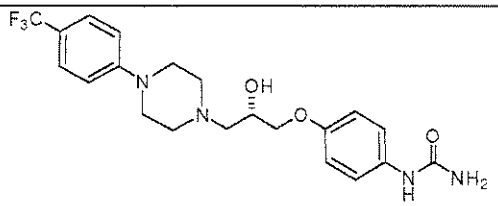
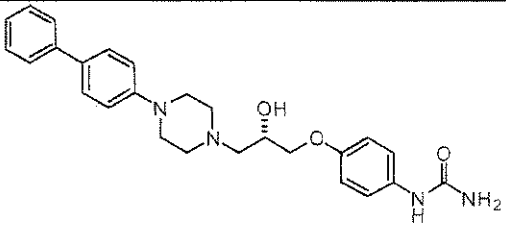
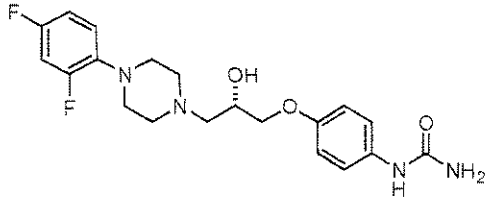
	4-{3-[4-(3-Trifluoromethyl-phenyl)-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-phenol
	

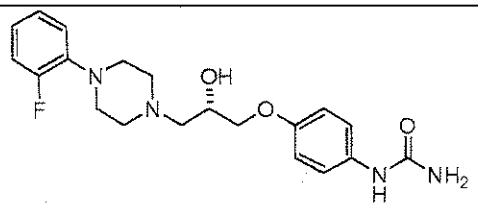
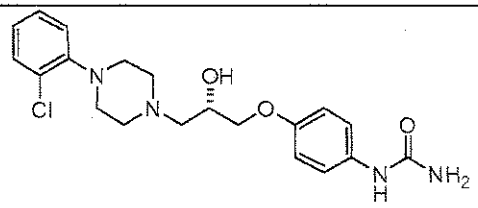
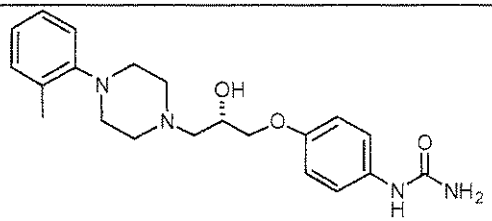
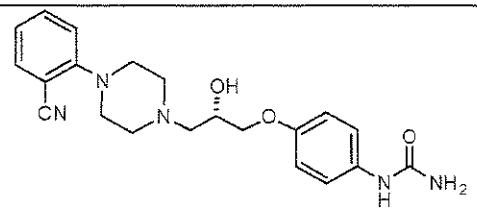
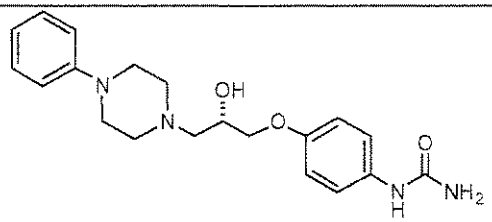
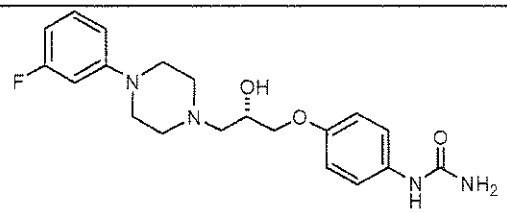
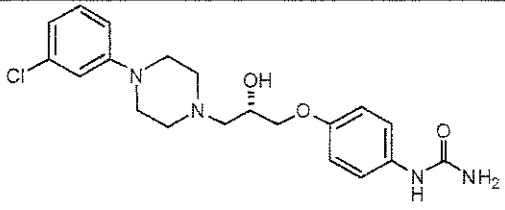
In one embodiment, the compound is selected from the compounds in Table 4.

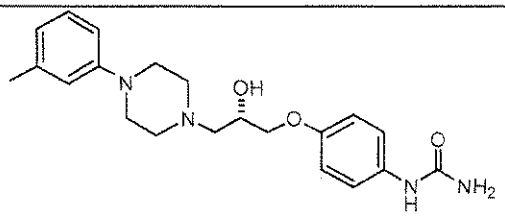
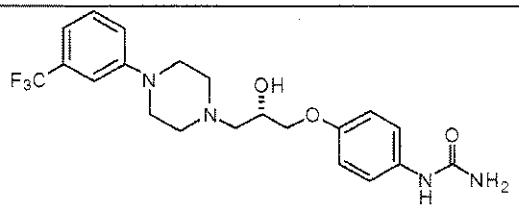
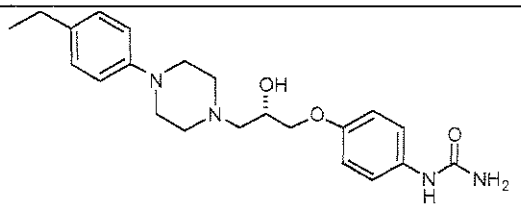
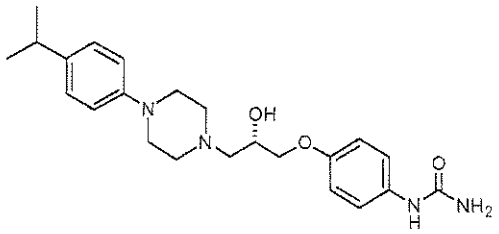
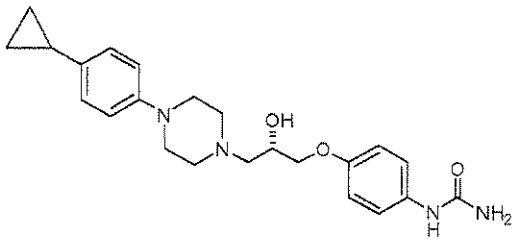
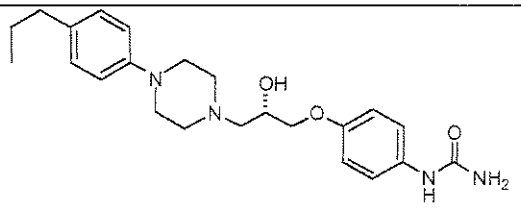
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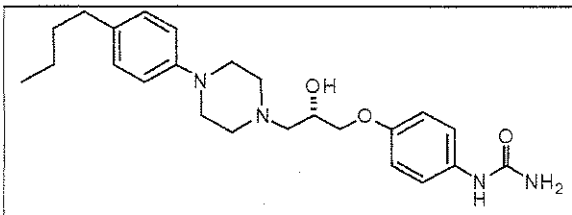
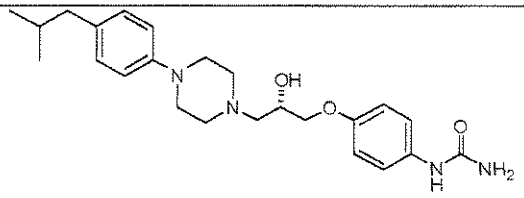
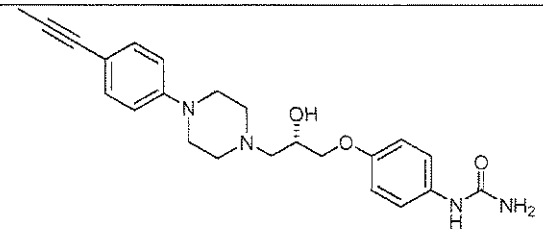
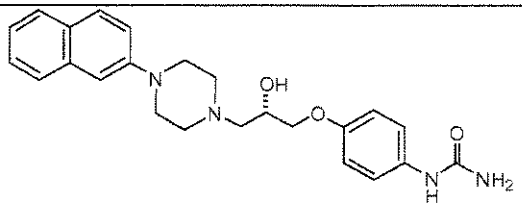
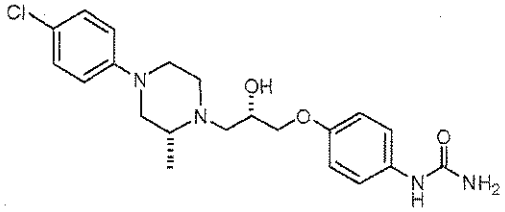
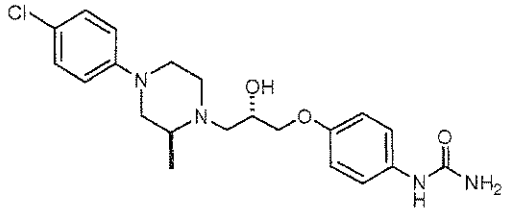
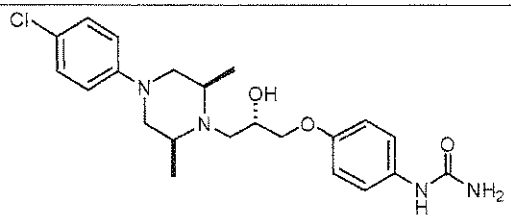
Compound	NAME
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	(4-{3-[4-(4-Fluoro-phenyl)-piperazin-1-yl]-propoxy}-phenyl)-urea
	(4-{3-[4-(4-Chloro-phenyl)-piperazin-1-yl]-2-hydroxy-propoxy}-phenyl)-urea
	1-Ethyl-3-(4-{3-[4-(4-fluoro-phenyl)-piperazin-1-yl]-propoxy}-phenyl)-urea

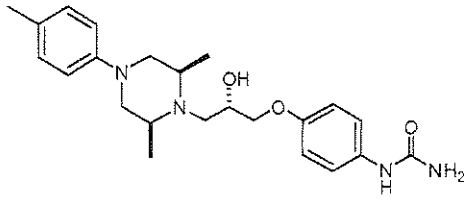
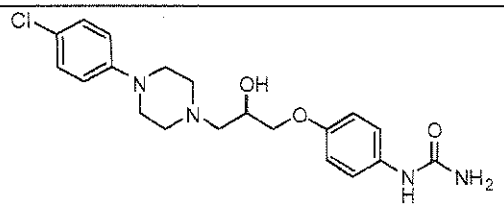
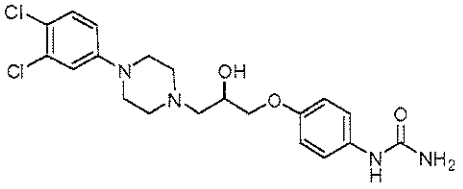
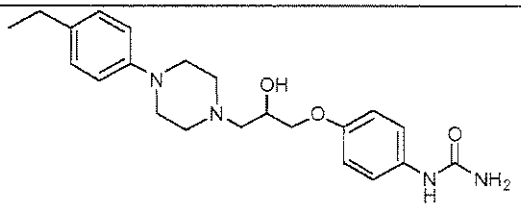
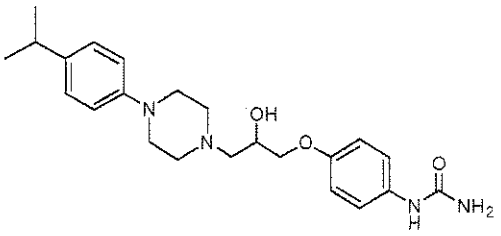
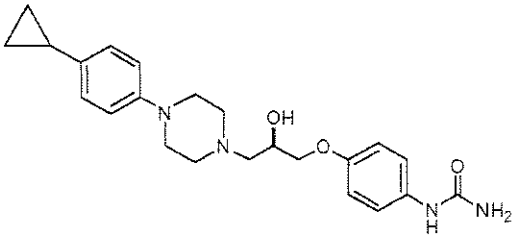
	(4-{3-[4-(4-Fluoro-phenyl)-piperazin-1-yl]-propoxy}-phenyl)-carbamic acid methyl ester
	(*S*)-1-(4-(3-(4-(3,4-dichlorophenyl)piperazin-1-yl)-2-hydroxypropoxy)phenyl)urea
	(*S*)-1-(4-(3-(4-(3,4-difluorophenyl)piperazin-1-yl)-2-hydroxypropoxy)phenyl)urea
	(*R*)-1-(4-(3-(4-(3,4-difluorophenyl)piperazin-1-yl)-2-hydroxypropoxy)phenyl)urea
	(*S*)-1-(4-(3-(4-(4-fluorophenyl)piperazin-1-yl)-2-hydroxypropoxy)phenyl)urea
	(*S*)-1-(4-(3-(4-(3,4-dimethylphenyl)piperazin-1-yl)-2-hydroxypropoxy)phenyl)urea
	(*S*)-1-(4-(2-hydroxy-3-(4-*p*-tolylpiperazin-1-yl)propoxy)phenyl)urea

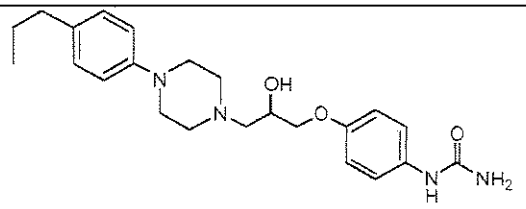
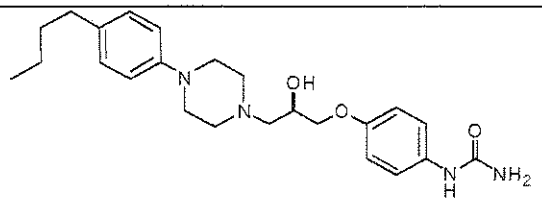
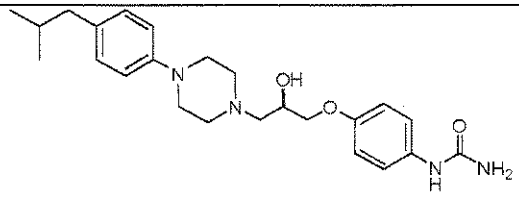
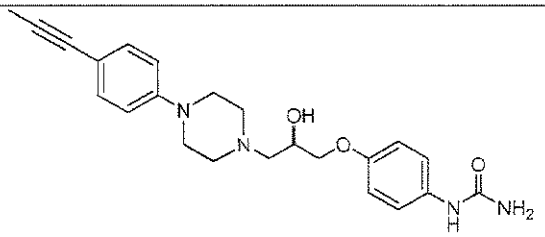
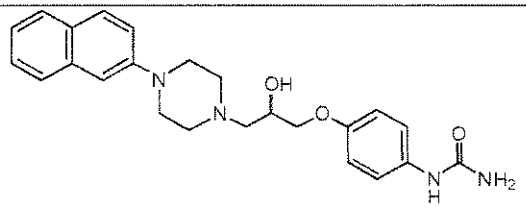
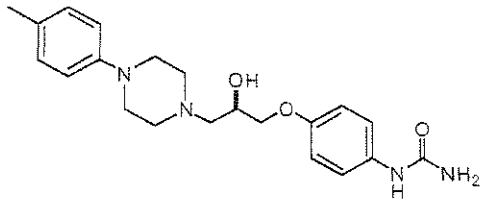
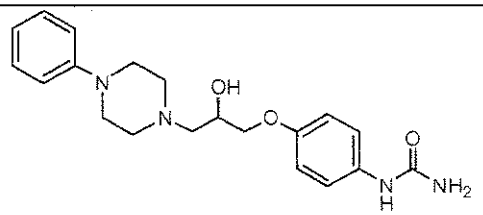
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	(*S*)-1-(4-(3-(4-(4-bromophenyl)piperazin-1-yl)-2-(*S*)-hydroxypropoxy)phenyl)urea
	(*S*)-1-(4-(2-hydroxy-3-(4-(4-hydroxyphenyl)piperazin-1-yl)propoxy)phenyl)urea
	(*S*)-1-(4-(2-hydroxy-3-(4-(4-methoxyphenyl)piperazin-1-yl)propoxy)phenyl)urea
	(*S*)-1-(4-(2-hydroxy-3-(4-(4-(trifluoromethyl)phenyl)piperazin-1-yl)propoxy)phenyl)urea
	(*S*)-1-(4-(3-(4-(biphenyl-4-yl)piperazin-1-yl)-2-hydroxypropoxy)phenyl)urea
	(*S*)-1-(4-(3-(4-(2,4-difluorophenyl)piperazin-1-yl)-2-hydroxypropoxy)phenyl)urea

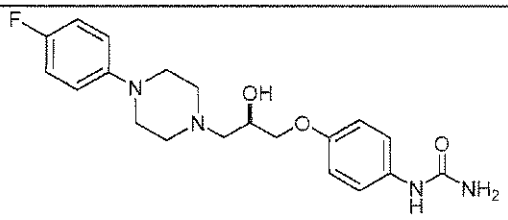
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	(*S*)-1-(4-(3-(4-(2-chlorophenyl)piperazin-1-yl)-2-hydroxypropoxy)phenyl)urea
	(*S*)-1-(4-(2-hydroxy-3-(4-*o*-tolylpiperazin-1-yl)propoxy)phenyl)urea
	(*S*)-1-(4-(3-(4-(2-cyanophenyl)piperazin-1-yl)-2-hydroxypropoxy)phenyl)urea
	(*S*)-1-(4-(2-hydroxy-3-(4-phenylpiperazin-1-yl)propoxy)phenyl)urea
	(*S*)-1-(4-(3-(4-(3-fluorophenyl)piperazin-1-yl)-2-hydroxypropoxy)phenyl)urea
	(*S*)-1-(4-(3-(4-(3-chlorophenyl)piperazin-1-yl)-2-(*S*)-hydroxypropoxy)phenyl)urea

	(*S*)-1-(4-(2-hydroxy-3-(4-*m*-tolypiperazin-1-yl)propoxy)phenyl)urea
	(*S*)-1-(4-(2-hydroxy-3-(4-(3-(trifluoromethyl)phenyl)piperazin-1-yl)propoxy)phenyl)urea
	(*S*)-1-(4-(3-(4-(4-ethylphenyl)piperazin-1-yl)-2-hydroxypropoxy)phenyl)urea
	(*S*)-1-(4-(3-(4-(4-isopropylphenyl)piperazin-1-yl)-2-hydroxypropoxy)phenyl)urea
	(*S*)-1-(4-(3-(4-(4-cyclopropylphenyl)piperazin-1-yl)-2-hydroxypropoxy)phenyl)urea
	(*S*)-1-(4-(3-(4-(4-propylphenyl)piperazin-1-yl)-2-hydroxypropoxy)phenyl)urea

	(*S*)-1-(4-(3-(4-(4-butylphenyl)piperazin-1-yl)-2-hydroxypropoxy)phenyl)urea
	(*S*)-1-(4-(3-(4-(4-isobutylphenyl)piperazin-1-yl)-2-hydroxypropoxy)phenyl)urea
	(*S*)-1-(4-(2-hydroxy-3-(4-(4-(prop-1-ynyl)phenyl)piperazin-1-yl)propoxy)phenyl)urea
	(*S*)-1-(4-(3-(4-(2-naphthyl)piperazin-1-yl)-2-hydroxypropoxy)phenyl)urea
	1-(4-((*S*)-3-((*R*)-4-(4-chlorophenyl)-2-methylpiperazin-1-yl)-2-hydroxypropoxy)phenyl)urea
	1-(4-((*S*)-3-((*S*)-4-(4-chlorophenyl)-2-methylpiperazin-1-yl)-2-hydroxypropoxy)phenyl)urea
	1-(4-((*S*)-3-4-(4-chlorophenyl)-cis-2,6-dimethylpiperazin-1-yl)-2-hydroxypropoxy)phenyl)urea

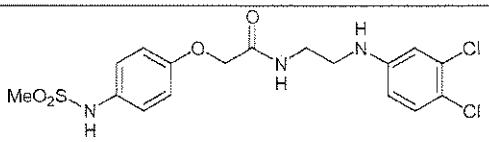
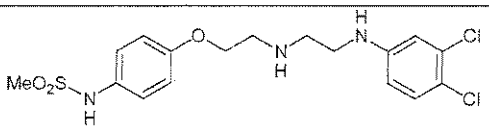
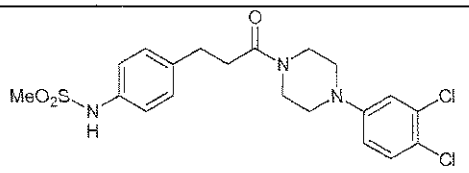
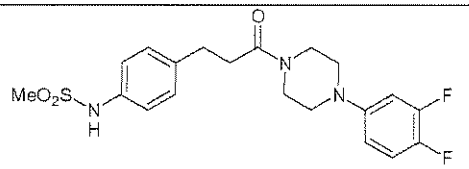
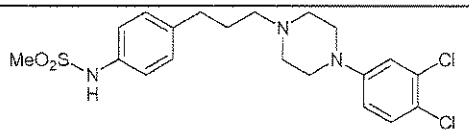
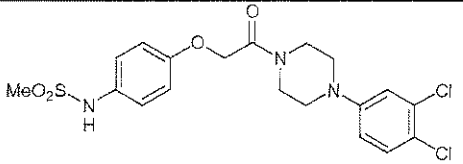
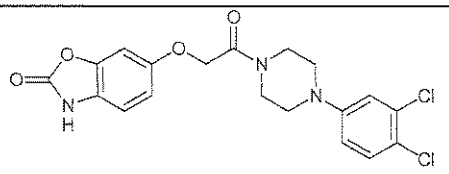
	1-(4-((*S*)-3-(cis-2,6-dimethyl-4-p-tolylpiperazin-1-yl)-2-hydroxypropoxy)phenyl)urea
	(*R*)-1-(4-(3-(4-(4-chlorophenyl)piperazin-1-yl)-2-hydroxypropoxy)phenyl)urea
	(*R*)-1-(4-(3-(4-(3,4-dichlorophenyl)piperazin-1-yl)-2-hydroxypropoxy)phenyl)urea
	(*R*)-1-(4-(3-(4-(4-ethylphenyl)piperazin-1-yl)-2-hydroxypropoxy)phenyl)urea
	(*R*)-1-(4-(3-(4-(4-isopropylphenyl)piperazin-1-yl)-2-hydroxypropoxy)phenyl)urea
	(*R*)-1-(4-(3-(4-(4-cyclopropylphenyl)piperazin-1-yl)-2-hydroxypropoxy)phenyl)urea

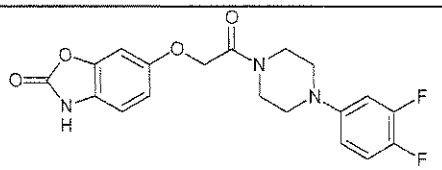
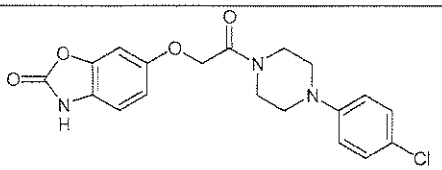
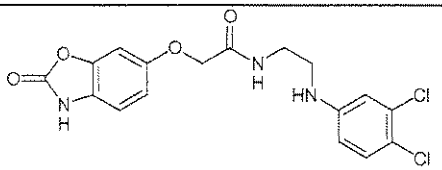
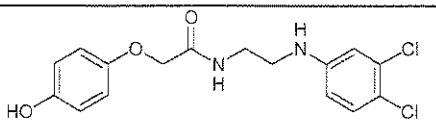
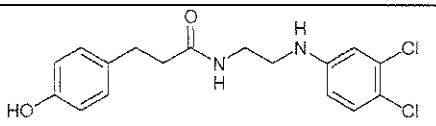
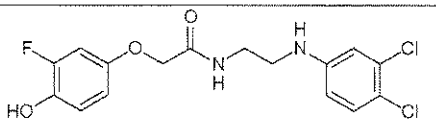
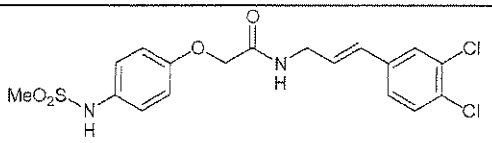
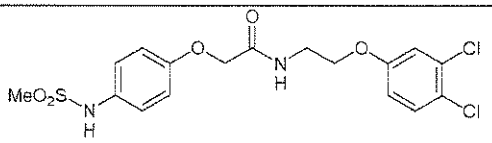
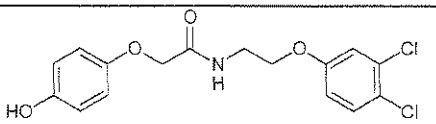
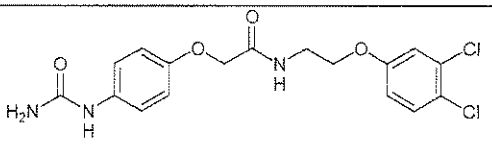
	(*R*)-1-(4-(3-(4-(4-propylphenyl)piperazin-1-yl)-2-hydroxypropoxy)phenyl)urea
	(*R*)-1-(4-(3-(4-(4-butylphenyl)piperazin-1-yl)-2-hydroxypropoxy)phenyl)urea
	(*R*)-1-(4-(3-(4-(4-isobutylphenyl)piperazin-1-yl)-2-hydroxypropoxy)phenyl)urea
	(*R*)-1-(4-(2-hydroxy-3-(4-(4-(prop-1-ynyl)phenyl)piperazin-1-yl)propoxy)phenyl)urea
	(*R*)-1-(4-(3-(4-(2-naphthyl)piperazin-1-yl)-2-hydroxypropoxy)phenyl)urea
	(*R*)-1-(4-(3-(4-(4-methylphenyl)piperazin-1-yl)-2-hydroxypropoxy)phenyl)urea
	(*R*)-1-(4-(3-(4-phenyl-piperazin-1-yl)-2-hydroxypropoxy)phenyl)urea

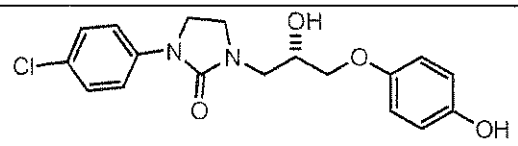
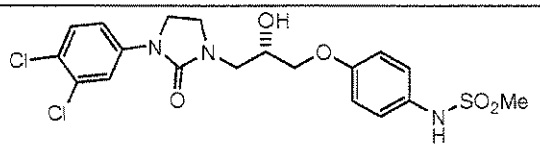
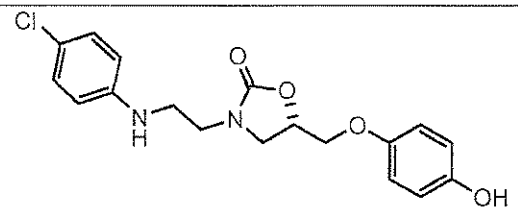
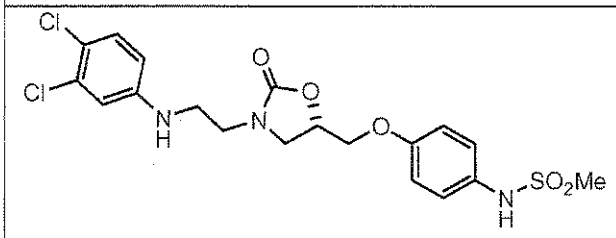
	(*R*)-1-(4-(3-(4-(4-fluorophenyl)piperazin-1-yl)-2-hydroxypropoxy)phenyl)urea

In one embodiment, the compound is selected from the compounds in Table 5.

Table 5.

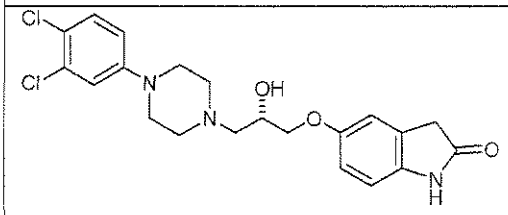
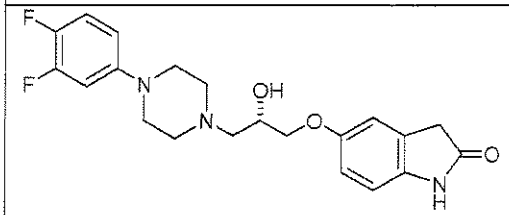
Compound	Name
	N-[2-(3,4-Dichloro-phenylamino)-ethyl]-2-(4-methanesulfonylamino-phenoxy)-acetamide
	N-(4-{2-[2-(3,4-Dichloro-phenylamino)-ethylamino]-ethoxy}-phenyl)-methanesulfonamide
	N-(4-{3-[4-(3,4-Dichloro-phenyl)-piperazin-1-yl]-3-oxo-propyl}-phenyl)-methanesulfonamide
	N-(4-{3-[4-(3,4-DiFluoro-phenyl)-piperazin-1-yl]-3-oxo-propyl}-phenyl)-methanesulfonamide
	N-(4-{3-[4-(3,4-Dichloro-phenyl)-piperazin-1-yl]-propyl}-phenyl)-methanesulfonamide
	N-(4-{2-[4-(3,4-Dichloro-phenyl)-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-methanesulfonamide
	6-{2-[4-(3,4-Dichloro-phenyl)-piperazin-1-yl]-2-oxo-ethoxy}-3H-benzooxazol-2-one

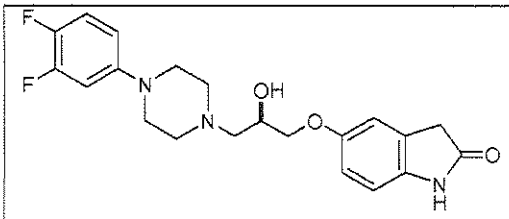
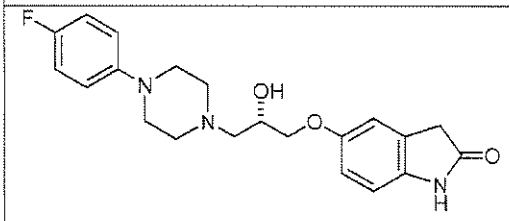
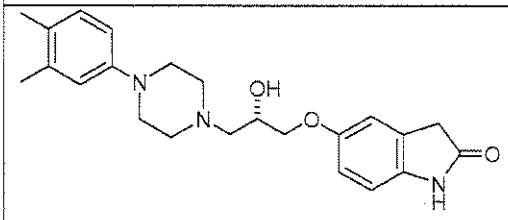
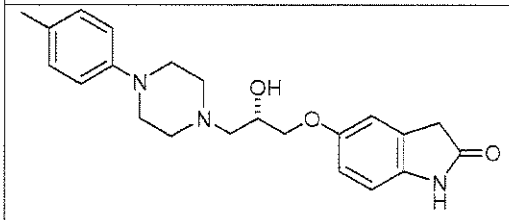
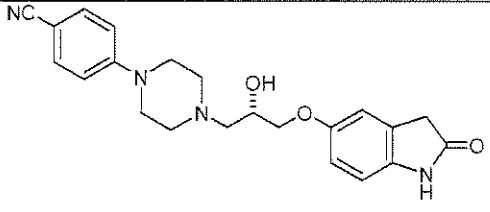
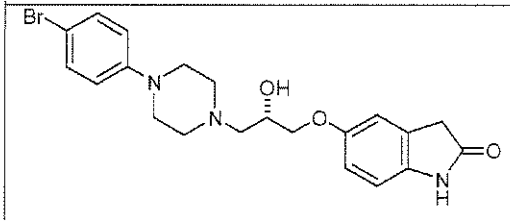
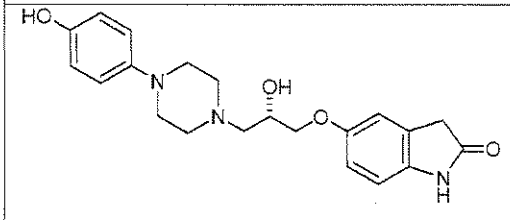
	6-{2-[4-(3,4-DiFluoro-phenyl)-piperazin-1-yl]-2-oxo-ethoxy}-3H-benzooxazol-2-one
	6-{2-[4-(4-Chloro-phenyl)-piperazin-1-yl]-2-oxo-ethoxy}-3H-benzooxazol-2-one
	N-[2-(3,4-Dichloro-phenylamino)-ethyl]-2-(2-oxo-2,3-dihydro-benzooxazol-6-yloxy)-acetamide
	N-[2-(3,4-Dichloro-phenylamino)-ethyl]-2-(4-hydroxy-phenoxy)-acetamide
	N-[2-(3,4-Dichloro-phenylamino)-ethyl]-3-(4-hydroxy-phenyl)-propionamide
	N-[2-(3,4-Dichloro-phenylamino)-ethyl]-2-(3-fluoro-4-hydroxy-phenoxy)-acetamide
	N-[3-(3,4-Dichloro-phenyl)-allyl]-2-(4-methanesulfonylamino-phenoxy)-acetamide
	N-[2-(3,4-Dichloro-phenoxy)-ethyl]-2-(4-methanesulfonylamino-phenoxy)-acetamide
	N-[2-(3,4-Dichloro-phenoxy)-ethyl]-2-(4-hydroxy-phenoxy)-acetamide
	N-[2-(3,4-Dichloro-phenoxy)-ethyl]-2-(4-ureido-phenoxy)-acetamide

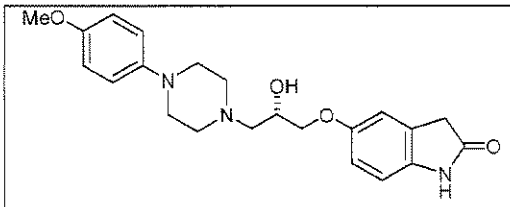
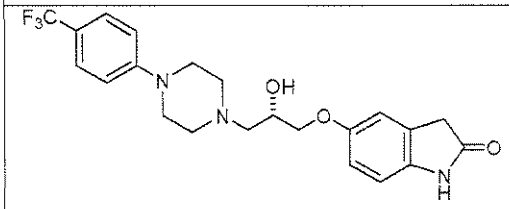
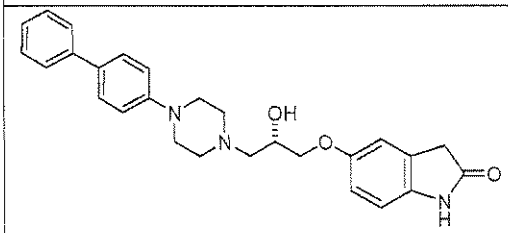
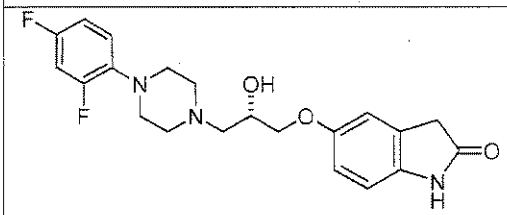
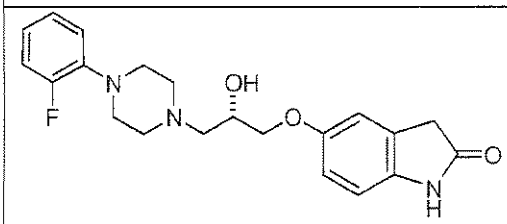
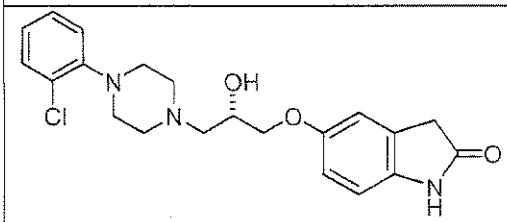
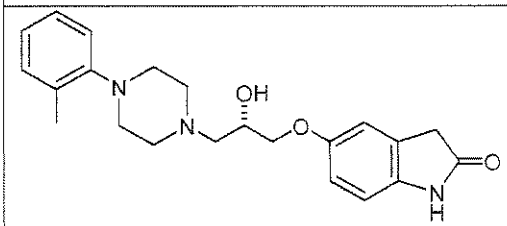
	(S)-1-(4-chlorophenyl)-3-(2-hydroxy-3-(4-hydroxyphenoxy)propyl)imidazolidin-2-one
	(S)-N-(4-(3-(3-(3,4-dichlorophenyl)-2-oxoimidazolidin-1-yl)-2-hydroxypropoxy)phenyl)methanesulfonamide
	(S)-3-(2-(4-chlorophenylamino)ethyl)-5-((4-hydroxyphenoxy)methyl)oxazolidin-2-one
	(S)-N-(4-((3-(2-(3,4-dichlorophenylamino)ethyl)-2-oxooxazolidin-5-yl)methoxy)phenyl)methanesulfonamide

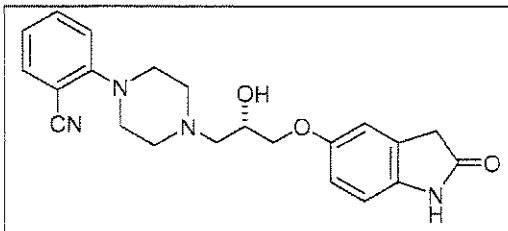
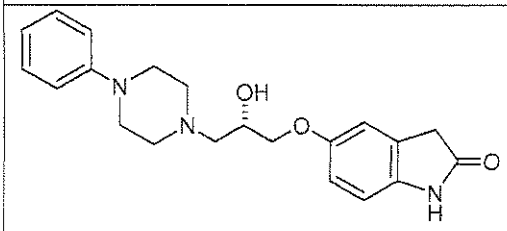
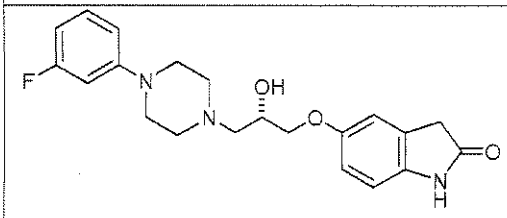
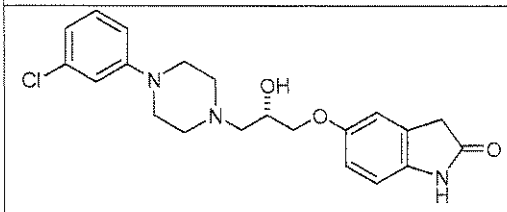
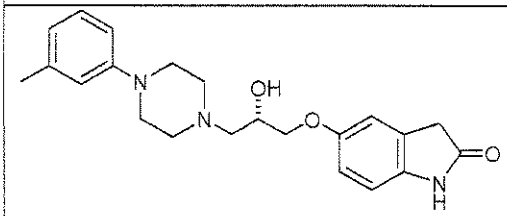
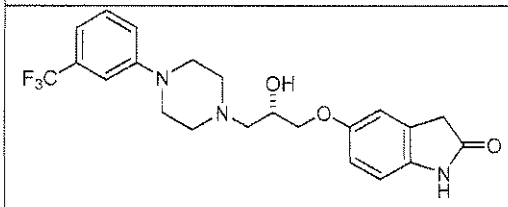
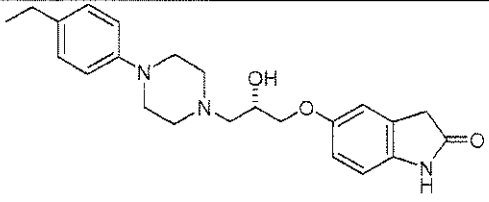
In one embodiment, the compound is selected from Table 6.

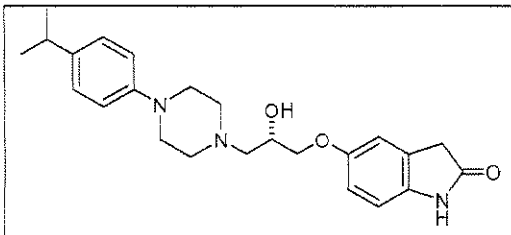
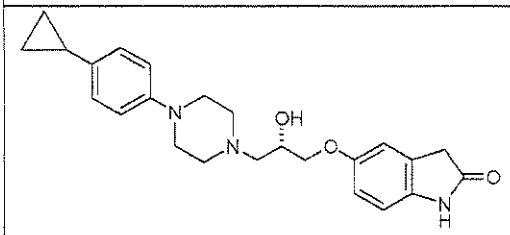
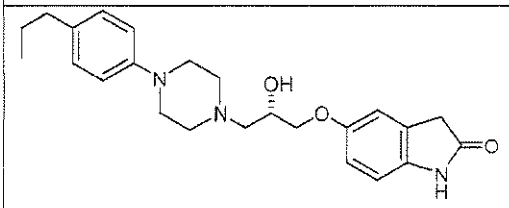
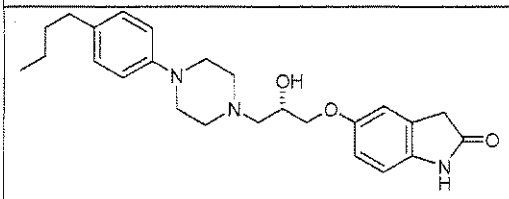
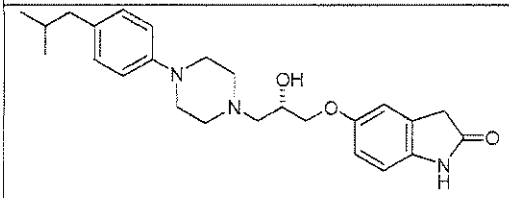
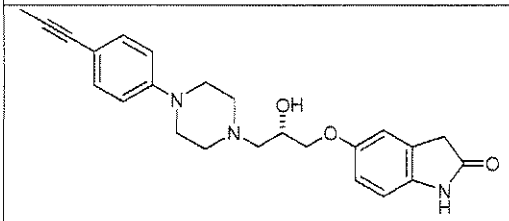
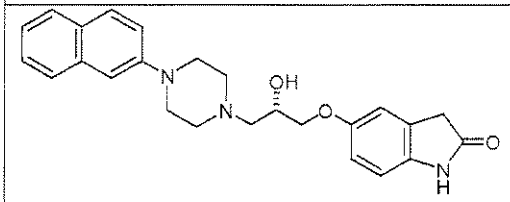
Table 6.

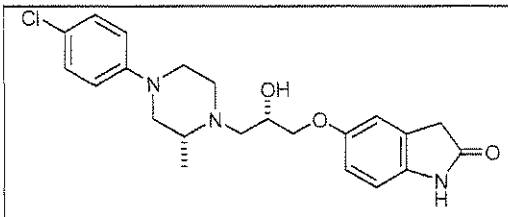
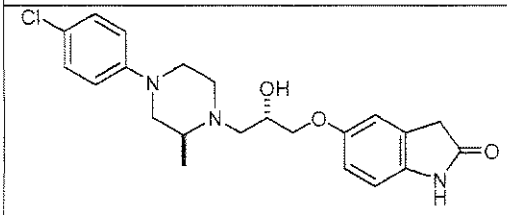
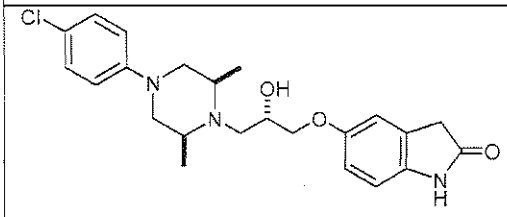
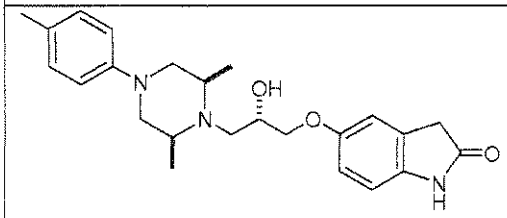
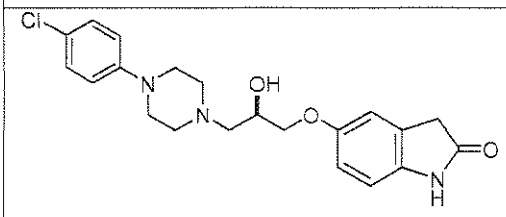
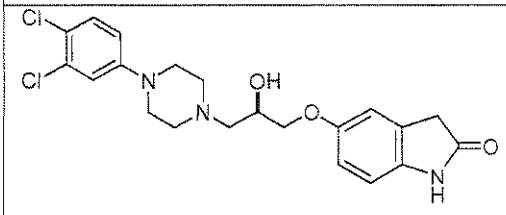
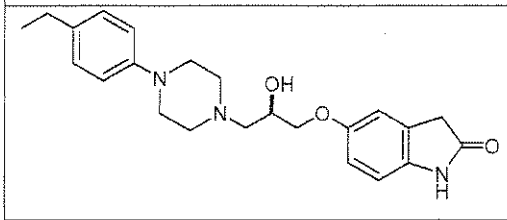
Compound	NAME
	(*S*)-5-(3-(4-(3,4-dichlorophenyl)piperazin-1-yl)-2-hydroxypropoxy)indolin-2-one
	(*S*)-5-(3-(4-(3,4-difluorophenyl)piperazin-1-yl)-2-hydroxypropoxy)indolin-2-one

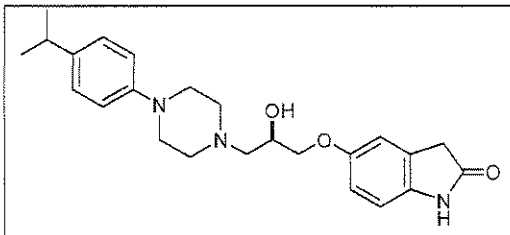
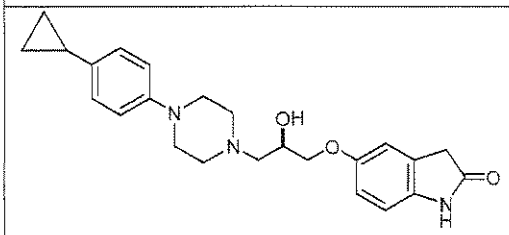
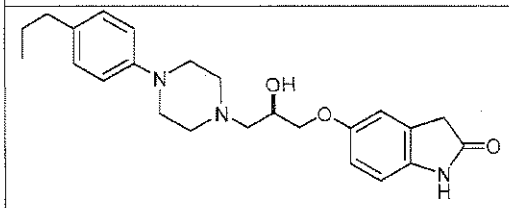
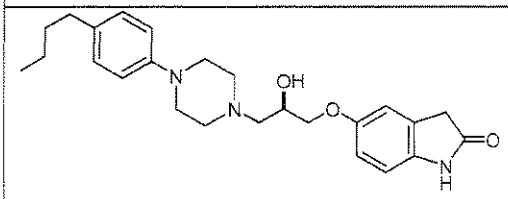
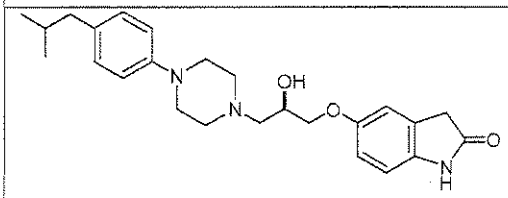
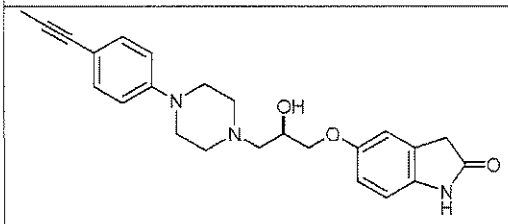
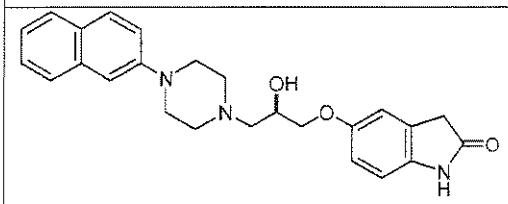
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	(*S*)-5-(3-(4-(4-fluorophenyl)piperazin-1-yl)-2-hydroxypropoxy)indolin-2-one
	(*S*)-5-(3-(4-(3,4-dimethylphenyl)piperazin-1-yl)-2-hydroxypropoxy)indolin-2-one
	(S)-5-(2-hydroxy-3-(4-*p*-tolylpiperazin-1-yl)propoxy)indolin-2-one
	(*S*)-4-(4-(2-hydroxy-3-(2-oxoindolin-5-yloxy)propyl)piperazin-1-yl)benzonitrile
	(*S*)-5-(3-(4-(4-bromophenyl)piperazin-1-yl)-2-hydroxypropoxy)indolin-2-one
	(*S*)-5-(2-hydroxy-3-(4-(4-hydroxyphenyl)piperazin-1-yl)propoxy)indolin-2-one

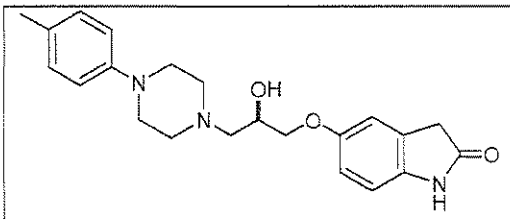
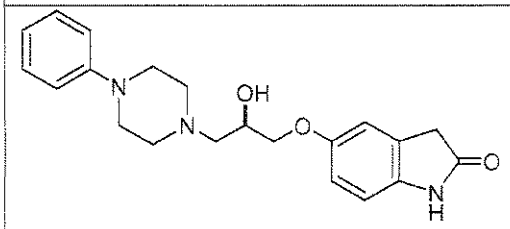
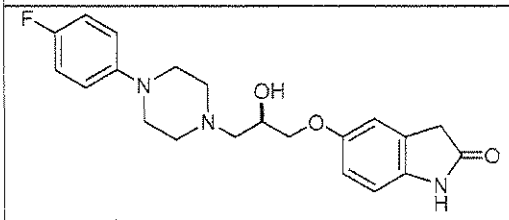
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	(*S*)-5-(2-hydroxy-3-(4-(4-(trifluoromethyl)phenyl)piperazin-1-yl)propoxy)indolin-2-one
	(*S*)-5-(3-(4-(biphenyl-4-yl)piperazin-1-yl)-2-hydroxypropoxy)indolin-2-one
	(*S*)-5-(3-(4-(2,4-difluorophenyl)piperazin-1-yl)-2-hydroxypropoxy)indolin-2-one
	(*S*)-5-(3-(4-(2-fluorophenyl)piperazin-1-yl)-2-hydroxypropoxy)indolin-2-one
	(*S*)-5-(3-(4-(2-chlorophenyl)piperazin-1-yl)-2-hydroxypropoxy)indolin-2-one
	(*S*)-5-(2-hydroxy-3-(4-*o*-tolylpiperazin-1-yl)propoxy)indolin-2-one

	(*S*)-2-(4-(2-hydroxy-3-(2-oxoindolin-5-yloxy)propyl)piperazin-1-yl)benzonitrile
	(*S*)-5-(2-hydroxy-3-(4-phenylpiperazin-1-yl)propoxy)indolin-2-one
	(*S*)-5-(3-(4-(3-fluorophenyl)piperazin-1-yl)-2-hydroxypropoxy)indolin-2-one
	(*S*)-5-(3-(4-(3-chlorophenyl)piperazin-1-yl)-2-hydroxypropoxy)indolin-2-one
	(*S*)-5-(2-hydroxy-3-(4-*m*-tolypiperazin-1-yl)propoxy)indolin-2-one
	(*S*)-5-(2-hydroxy-3-(4-(3-(trifluoromethyl)phenyl)piperazin-1-yl)propoxy)indolin-2-one
	(*S*)-5-(3-(4-(4-ethylphenyl)piperazin-1-yl)-2-hydroxypropoxy)indolin-2-one

	(*S*)-5-(2-hydroxy-3-(4-(4--isopropylphenyl)piperazin-1-yl)propoxy)indolin-2-one
	(*S*)-5-(3-(4-(4-cyclopropylphenyl)piperazin-1-yl)-2-hydroxypropoxy)indolin-2-one
	(*S*)-5-(2-hydroxy-3-(4-(4-propylphenyl)piperazin-1-yl)propoxy)indolin-2-one
	(*S*)-5-(3-(4-(4-butylphenyl)piperazin-1-yl)-2-hydroxypropoxy)indolin-2-one
	(*S*)-5-(2-hydroxy-(3-(4-(4-isobutylphenyl)piperazin-1-yl)propoxy)indolin-2-one
	(*S*)-5-(2-hydroxy-3-(4-(4-(prop-1-ynyl)phenyl)piperazin-1-yl)propoxy)indolin-2-one
	(*S*)-5-(2-hydroxy-3-(4-(naphthalen-2-yl)piperazin-1-yl)propoxy)indolin-2-one

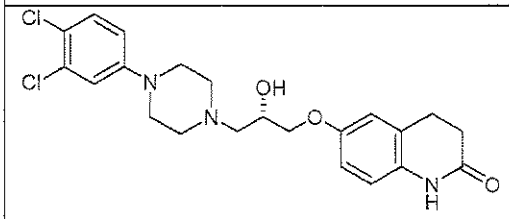
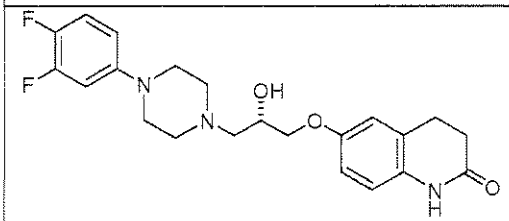
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	5-((*S*)-3-((*S*)-4-(4-chlorophenyl)-2-methylpiperazin-1-yl)-2-hydroxypropoxy)indolin-2-one
	5-((*S*)-3-((2S,6R)-4-(4-chlorophenyl)-2,6-dimethylpiperazin-1-yl)-2-hydroxypropoxy)indolin-2-one
	5-((*S*)-3-((2*S*,6*R*)-2,6-dimethyl-4-*p*-tolylpiperazin-1-yl)-2-hydroxypropoxy)indolin-2-one
	(*R*)-5-(3-(4-(4-chlorophenyl)piperazin-1-yl)-2-hydroxypropoxy)indolin-2-one
	(*R*)-5-(3-(4-(3,4-dichlorophenyl)piperazin-1-yl)-2-hydroxypropoxy)indolin-2-one
	(*R*)-5-(3-(4-(4-ethylphenyl)piperazin-1-yl)-2-hydroxypropoxy)indolin-2-one

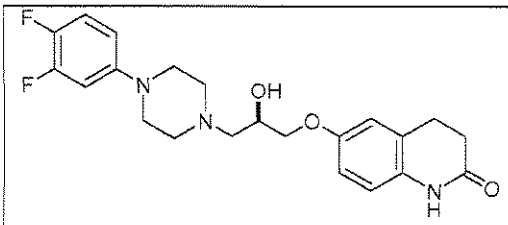
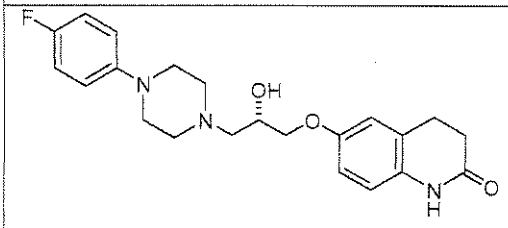
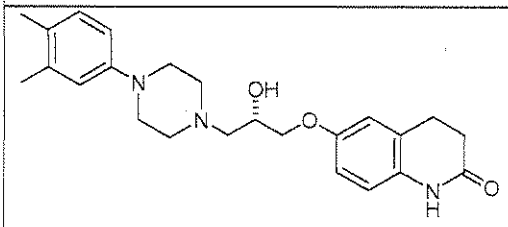
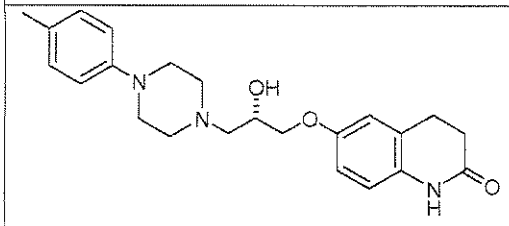
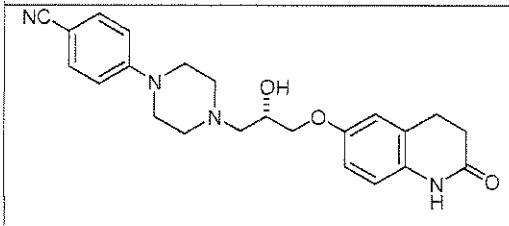
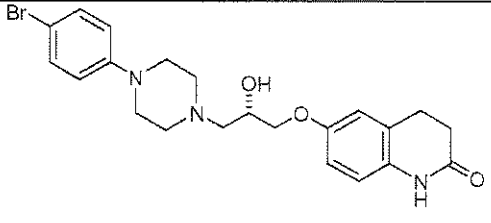
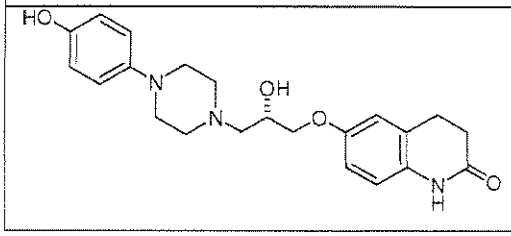
	(*R*)-5-(2-hydroxy-3-(4-(4-isopropylphenyl)piperazin-1-yl)propoxy)indolin-2-one
	(*R*)-5-(3-(4-(4-cyclopropylphenyl)piperazin-1-yl)-2-hydroxypropoxy)indolin-2-one
	(*R*)-5-(2-hydroxy-3-(4-(4-propylphenyl)piperazin-1-yl)propoxy)indolin-2-one
	(*R*)-5-(3-(4-(4-butylphenyl)piperazin-1-yl)-2-hydroxypropoxy)indolin-2-one
	(*R*)-5-(2-hydroxy-3-(4-(4-isobutylphenyl)piperazin-1-yl)propoxy)indolin-2-one
	(*R*)-5-(2-hydroxy-3-(4-(4-(prop-1-ynyl)phenyl)piperazin-1-yl)propoxy)indolin-2-one
	(*R*)-5-(2-hydroxy-3-(4-(naphthalen-2-yl)piperazin-1-yl)propoxy)indolin-2-one

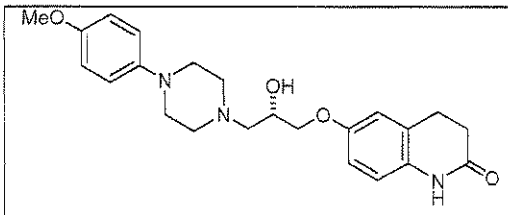
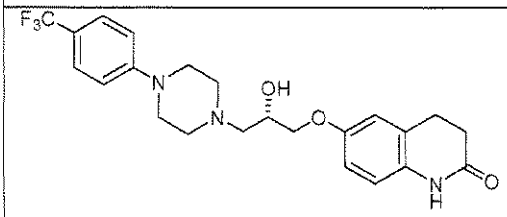
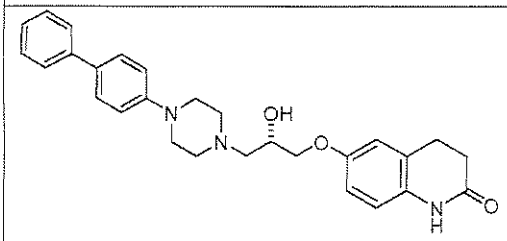
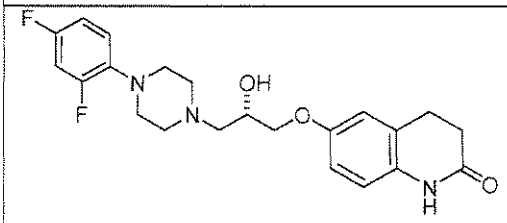
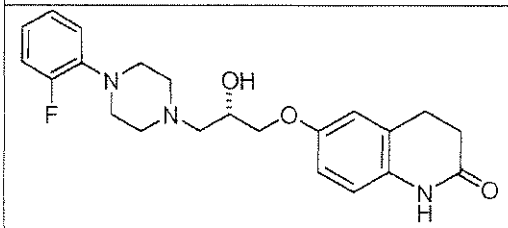
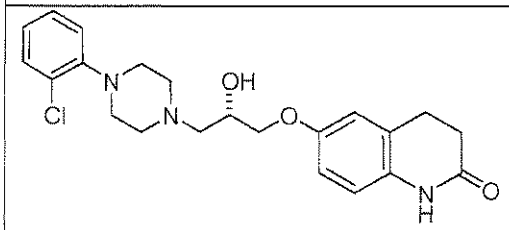
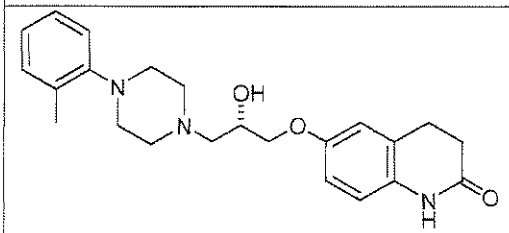
	(*R*)-5-(2-hydroxy-(3-(4-*p*-tolylpiperazin-1-yl)propoxy)indolin-2-one
	(*R*)-5-(2-hydroxy-3-(4-phenylpiperazin-1-yl)propoxy)indolin-2-one
	(*R*)-5-(3-(4-(4-fluorophenyl)piperazin-1-yl)-2-hydroxypropoxy)indolin-2-one

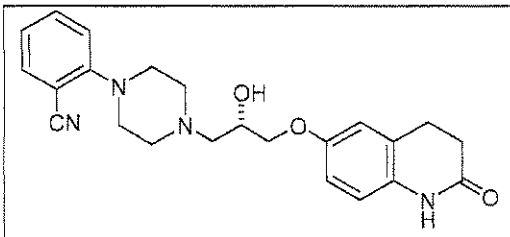
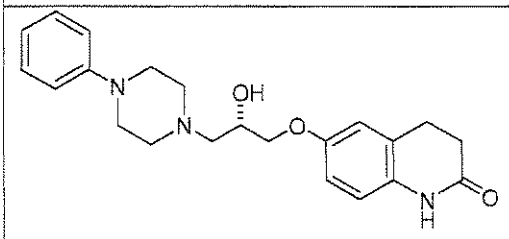
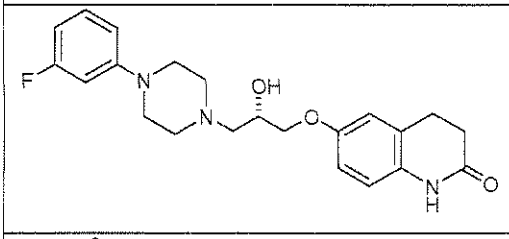
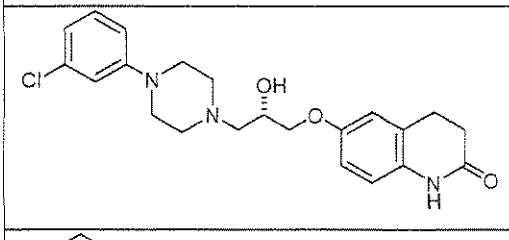
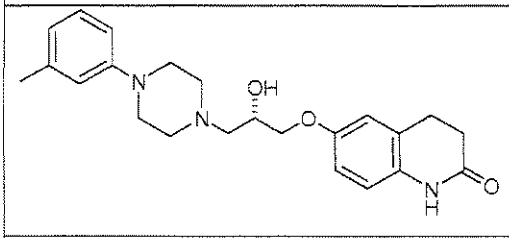
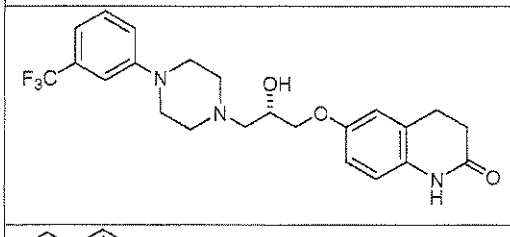
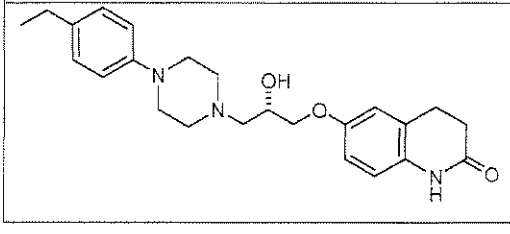
In one embodiment, the compound is selected from Table 7.

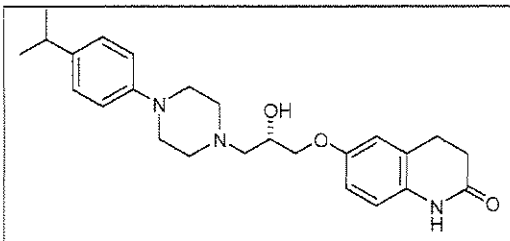
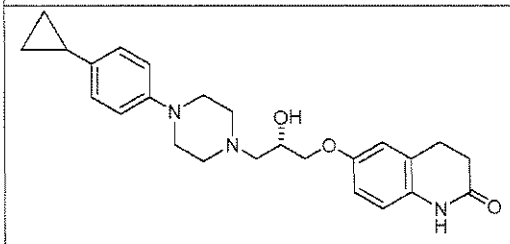
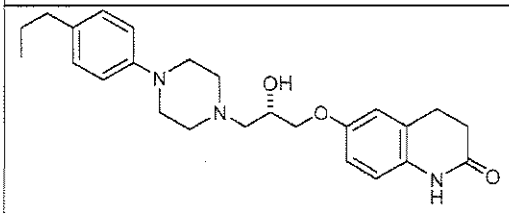
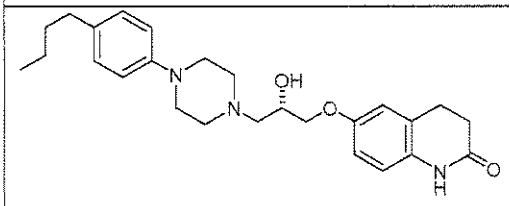
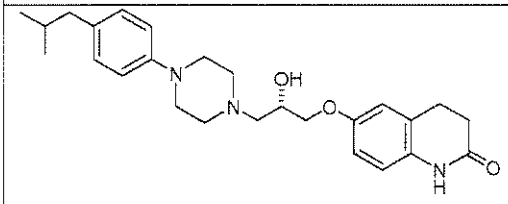
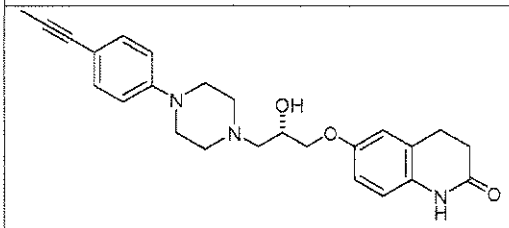
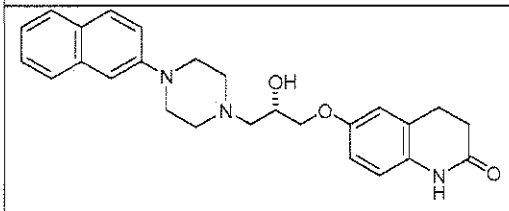
Table 7.

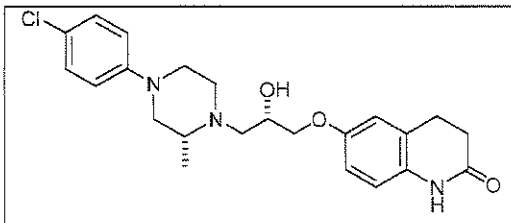
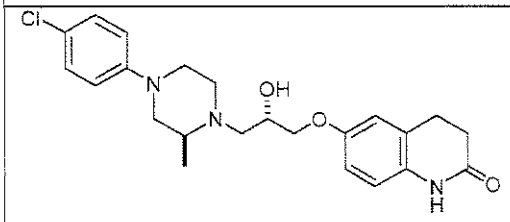
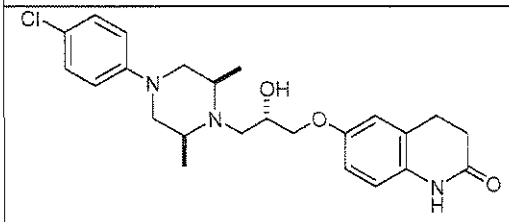
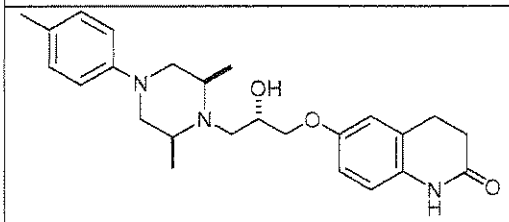
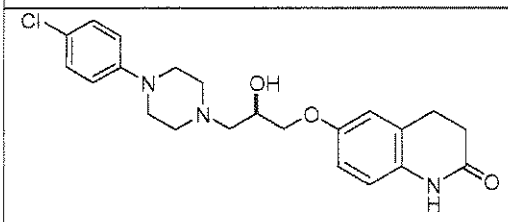
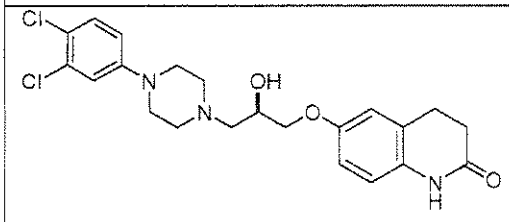
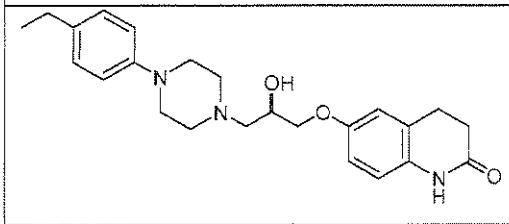
Compound	NAME
	(*S*)-6-(3-(4-(3,4-dichlorophenyl)piperazin-1-yl)-2-hydroxypropoxy)-3,4-dihydroquinolin-2(1*H*)-one
	(*S*)-6-(3-(4-(3,4-difluorophenyl)piperazin-1-yl)-2-hydroxypropoxy)-3,4-dihydroquinolin-2(1*H*)-one

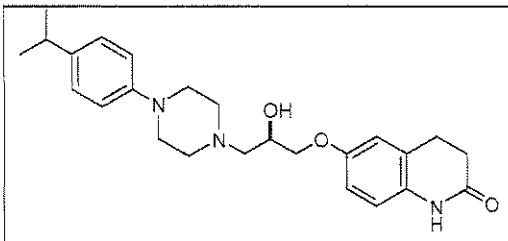
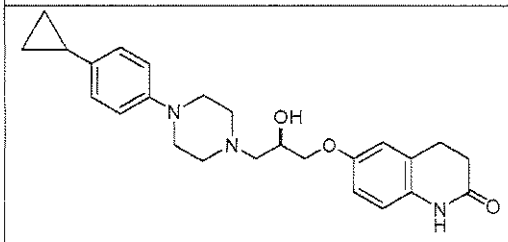
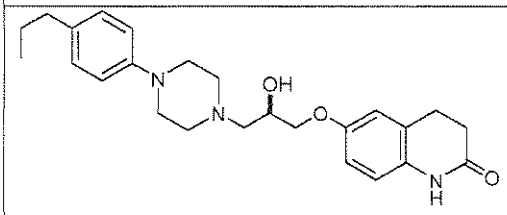
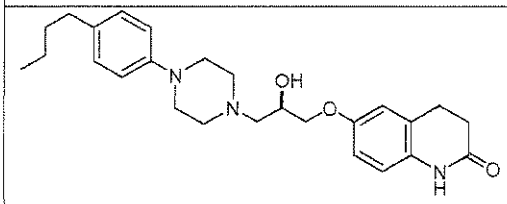
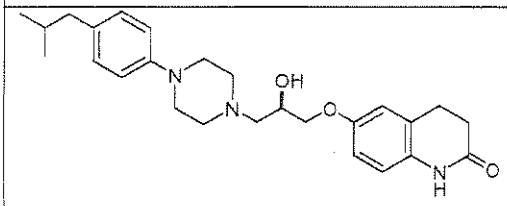
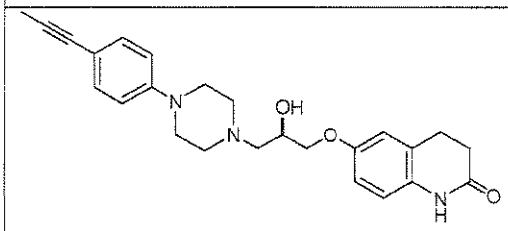
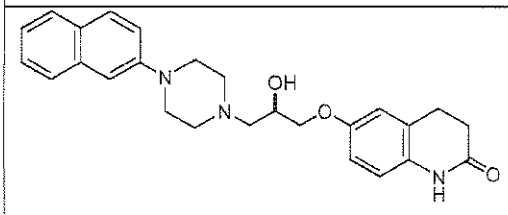
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	(*S*)-6-(3-(4-(4-fluorophenyl)piperazin-1-yl)-2-hydroxypropoxy)-3,4-dihydroquinolin-2(1*H*)-one
	(*S*)-6-(3-(4-(3,4-dimethylphenyl)piperazin-1-yl)-2-hydroxypropoxy)-3,4-dihydroquinolin-2(1*H*)-one
	(*S*)-6-(2-hydroxy-3-(4-*p*-tolylpiperazin-1-yl)propoxy)-3,4-dihydroquinolin-2(1*H*)-one
	(*S*)-4-(4-(2-hydroxy-3-(2-oxo-1,2,3,4-tetrahydroquinolin-6-yloxy)propyl)piperazin-1-yl)benzonitrile
	(*S*)-6-(3-(4-(4-bromophenyl)piperazin-1-yl)-2-hydroxypropoxy)-3,4-dihydroquinolin-2(1*H*)-one
	(*S*)-6-(2-hydroxy-3-(4-(4-hydroxyphenyl)piperazin-1-yl)propoxy)-3,4-dihydroquinolin-2(1*H*)-one

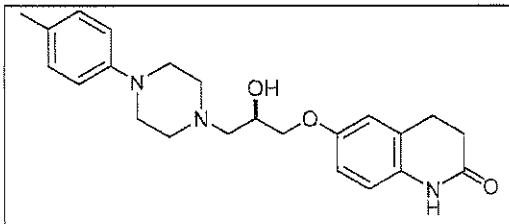
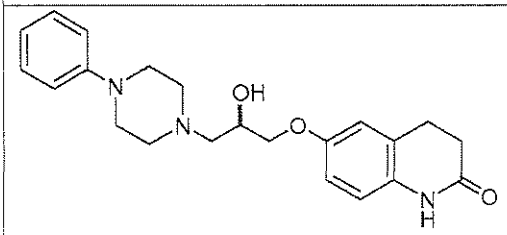
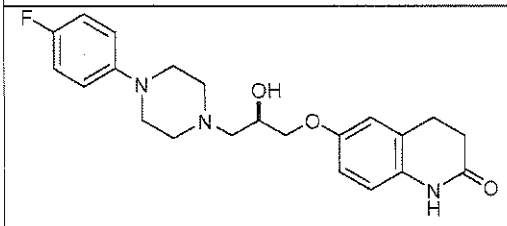
	(*S*)-6-(2-hydroxy-3-(4-(4-methoxyphenyl)piperazin-1-yl)propoxy)-3,4-dihydroquinolin-2(1*H*)-one
	(*S*)-6-(2-hydroxy-3-(4-(4-(trifluoromethyl)phenyl)piperazin-1-yl)propoxy)-3,4-dihydroquinolin-2(1*H*)-one
	(*S*)-6-(3-(4-(biphenyl-4-yl)piperazin-1-yl)-2-hydroxypropoxy)-3,4-dihydroquinolin-2(1*H*)-one
	(*S*)-6-(3-(4-(2,4-difluorophenyl)piperazin-1-yl)-2-hydroxypropoxy)-3,4-dihydroquinolin-2(1*H*)-one
	(*S*)-6-(3-(4-(2-fluorophenyl)piperazin-1-yl)-2-hydroxypropoxy)-3,4-dihydroquinolin-2(1*H*)-one
	(*S*)-6-(3-(4-(2-chlorophenyl)piperazin-1-yl)-2-hydroxypropoxy)-3,4-dihydroquinolin-2(1*H*)-one
	(*S*)-6-(2-hydroxy-3-(4-*o*-tolylpiperazin-1-yl)propoxy)-3,4-dihydroquinolin-2(1*H*)-one

	(*S*)-2-(4-(2-hydroxy-3-(2-oxo-1,2,3,4-tetrahydroquinolin-6-yloxy)propyl)piperazin-1-yl)benzonitrile
	(*S*)-6-(2-hydroxy-3-(4-phenylpiperazin-1-yl)propoxy)-3,4-dihydroquinolin-2(1*H*)-one
	(*S*)-6-(3-(4-(3-fluorophenyl)piperazin-1-yl)-2-hydroxypropoxy)-3,4-dihydroquinolin-2(1*H*)-one
	(*S*)-6-(3-(4-(3-chlorophenyl)piperazin-1-yl)-2-hydroxypropoxy)-3,4-dihydroquinolin-2(1*H*)-one
	(*S*)-6-(2-hydroxy-3-(4-*m*-tolypiperazin-1-yl)propoxy)-3,4-dihydroquinolin-2(1*H*)-one
	(*S*)-6-(2-hydroxy-3-(4-(3-(trifluoromethyl)phenyl)piperazin-1-yl)propoxy)-3,4-dihydroquinolin-2(1*H*)-one
	(*S*)-6-(3-(4-(4-ethylphenyl)piperazin-1-yl)-2-hydroxypropoxy)-3,4-dihydroquinolin-2(1*H*)-one

	(*S*)-6-(2-hydroxy-3-(4-(4-isopropylphenyl)piperazin-1-yl)propoxy)-3,4-dihydroquinolin-2(1*H*)-one
	(*S*)-6-(3-(4-(4-cyclopropylphenyl)piperazin-1-yl)-2-hydroxypropoxy)-3,4-dihydroquinolin-2(1*H*)-one
	(*S*)-6-(2-hydroxy-3-(4-(4-propylphenyl)piperazin-1-yl)propoxy)-3,4-dihydroquinolin-2(1*H*)-one
	(*S*)-6-(3-(4-(4-butylphenyl)piperazin-1-yl)-2-hydroxypropoxy)-3,4-dihydroquinolin-2(1*H*)-one
	(*S*)-6-(2-hydroxy-3-(4-(4-isobutylphenyl)piperazin-1-yl)propoxy)-3,4-dihydroquinolin-2(1*H*)-one
	(*S*)-6-(2-hydroxy-3-(4-(4-(prop-1-ynyl)phenyl)piperazin-1-yl)propoxy)-3,4-dihydroquinolin-2(1*H*)-one
	(*S*)-6-(2-hydroxy-3-(4-(naphthalen-2-yl)-piperazin-1-yl)propoxy)-3,4-dihydroquinolin-2(1*H*)-one

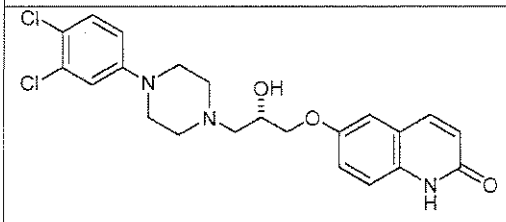
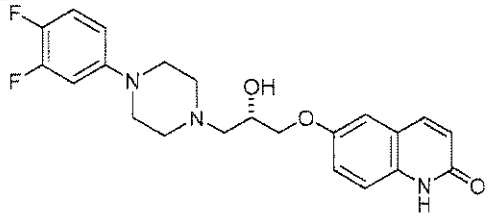
	6-((*S*)-3-((*R*)-4-(4-chlorophenyl)-2-methylpiperazin-1-yl)-2-hydroxypropoxy)-3,4-dihydroquinolin-2(1*H*)-one
	6-((*S*)-3-((*S*)-4-(4-chlorophenyl)-2-methylpiperazin-1-yl)-2-hydroxypropoxy)-3,4-dihydroquinolin-2(1*H*)-one
	6-((*S*)-3-((2*S*,6*R*)-4-(4-chlorophenyl)-2,6-dimethylpiperazin-1-yl)-2-hydroxypropoxy)-3,4-dihydroquinolin-2(1*H*)-one
	6-((*S*)-3-((2*S*,6*R*)-2,6-dimethyl-4-*p*-tolylpiperazin-1-yl)-2-hydroxypropoxy)-3,4-dihydroquinolin-2(1*H*)-one
	(*R*)-6-(3-(4-(4-chlorophenyl)piperazin-1-yl)-2-hydroxypropoxy)-3,4-dihydroquinolin-2(1*H*)-one
	(*R*)-6-(3-(4-(3,4-dichlorophenyl)piperazin-1-yl)-2-hydroxypropoxy)-3,4-dihydroquinolin-2(1*H*)-one
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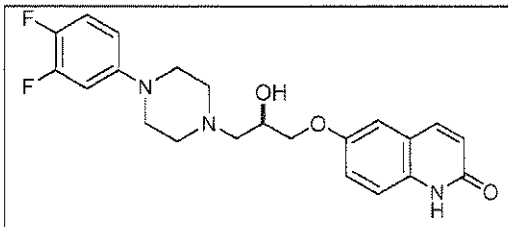
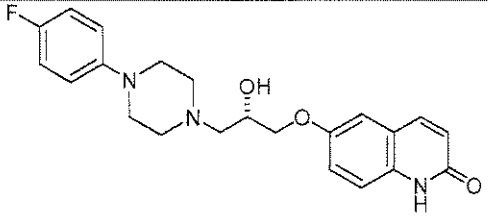
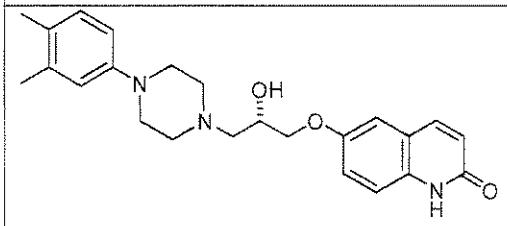
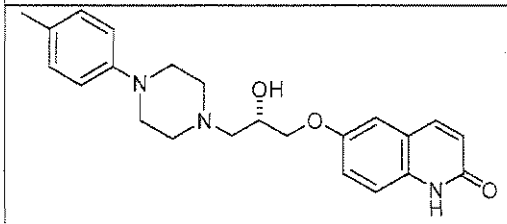
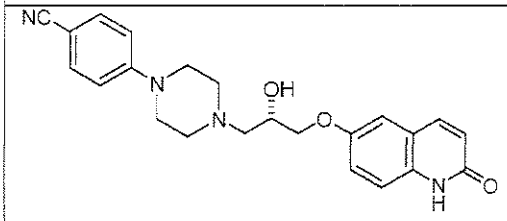
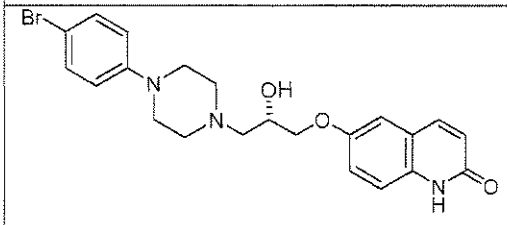
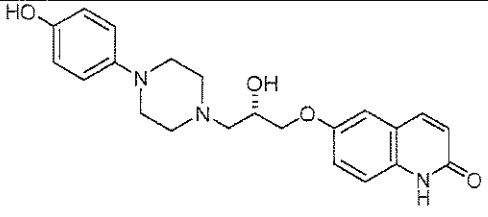
	(*R*)-6-(2-hydroxy-3-(4-(4-isopropylphenyl)piperazin-1-yl)propoxy)-3,4-dihydroquinolin-2(1*H*)-one
	(*R*)-6-(3-(4-(4-cyclopropylphenyl)piperazin-1-yl)-2-hydroxypropoxy)-3,4-dihydroquinolin-2(1*H*)-one
	(*R*)-6-(2-hydroxy-3-(4-(4-propylphenyl)piperazin-1-yl)propoxy)-3,4-dihydroquinolin-2(1*H*)-one
	(*R*)-6-(3-(4-(4-butylphenyl)piperazin-1-yl)-2-hydroxypropoxy)-3,4-dihydroquinolin-2(1*H*)-one
	(*R*)-6-(2-hydroxy-3-(4-(4-isobutylphenyl)piperazin-1-yl)propoxy)-3,4-dihydroquinolin-2(1*H*)-one
	(*R*)-6-(2-hydroxy-3-(4-(4-(prop-1-ynyl)phenyl)piperazin-1-yl)propoxy)-3,4-dihydroquinolin-2(1*H*)-one
	(*R*)-6-(2-hydroxy-3-(4-(naphthalen-2-yl)piperazin-1-yl)propoxy)-3,4-dihydroquinolin-2(1*H*)-one

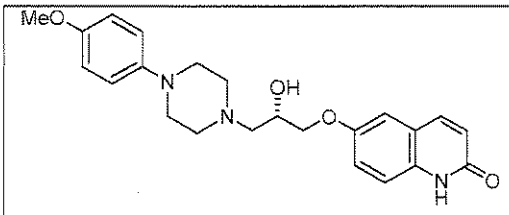
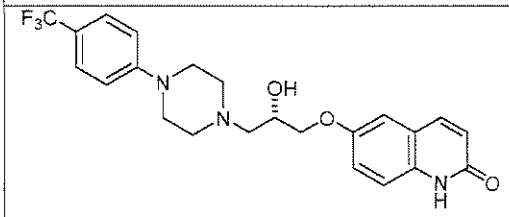
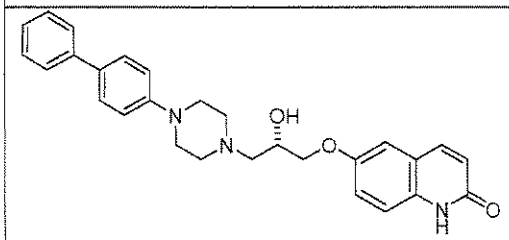
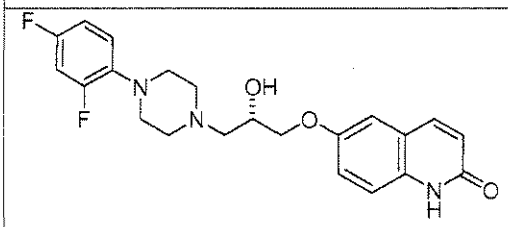
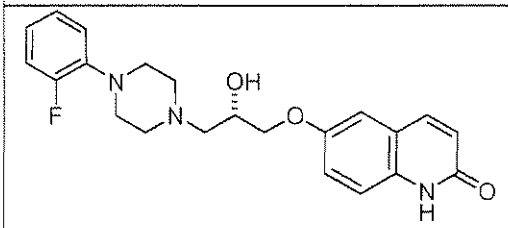
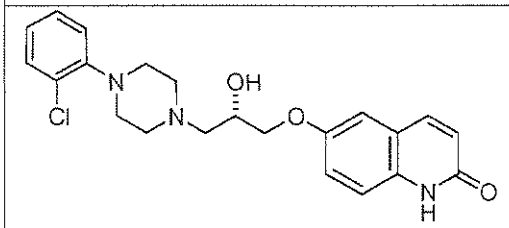
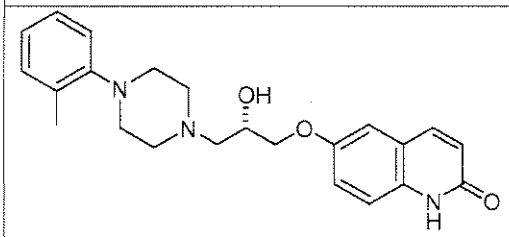
	(*R*)-6-(2-hydroxy-3-(4-*p*-tolylpiperazin-1-yl)propoxy)-3,4-dihydroquinolin-2(1*H*)-one
	(*R*)-6-(2-hydroxy-3-(4-phenylpiperazin-1-yl)propoxy)-3,4-dihydroquinolin-2(1*H*)-one
	(*R*)-6-(3-(4-(4-fluorophenyl)piperazin-1-yl)-2-hydroxypropoxy)-3,4-dihydroquinolin-2(1*H*)-one

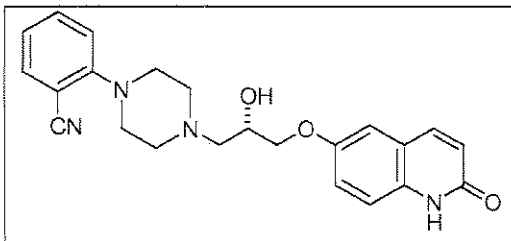
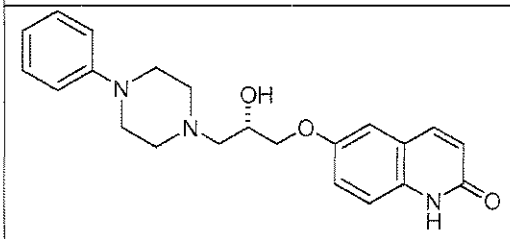
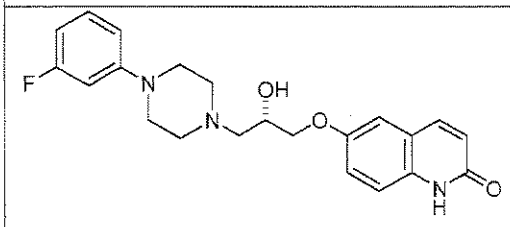
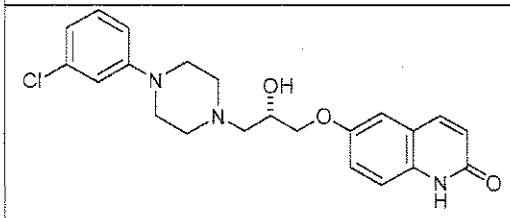
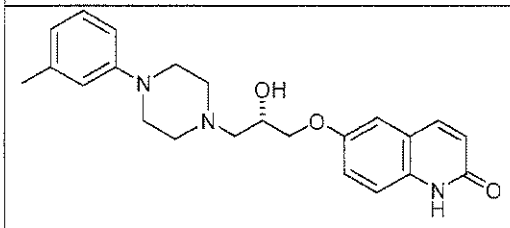
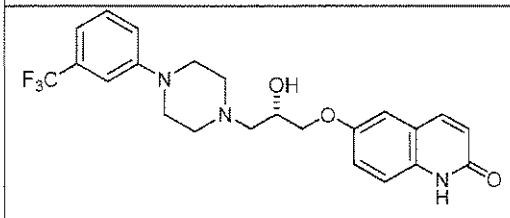
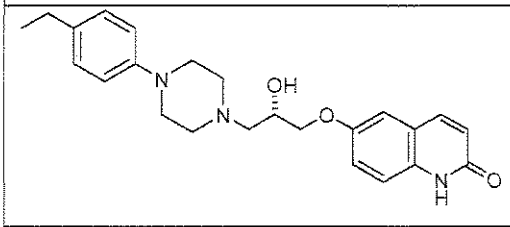
In another embodiment, the compound is selected from Table 8.

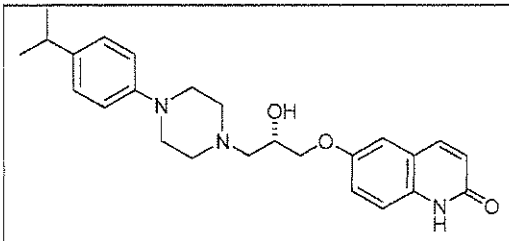
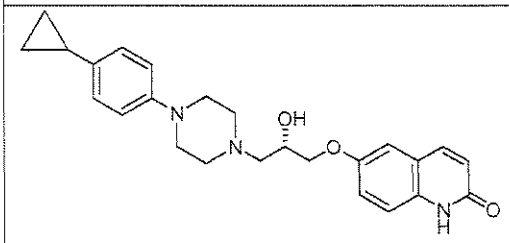
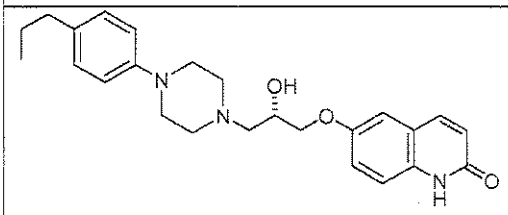
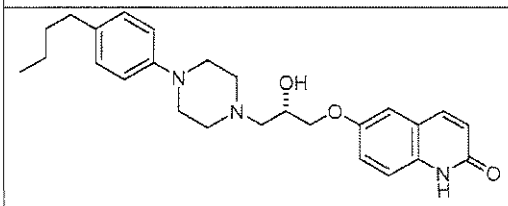
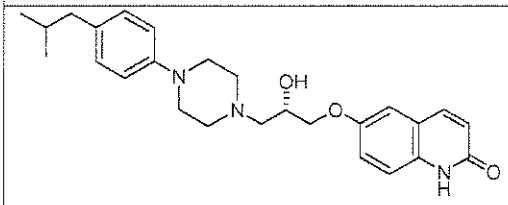
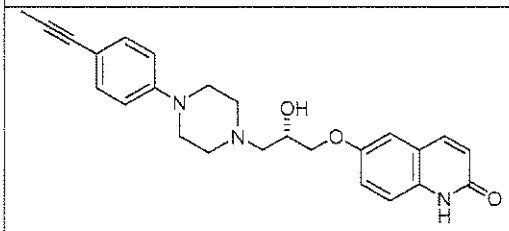
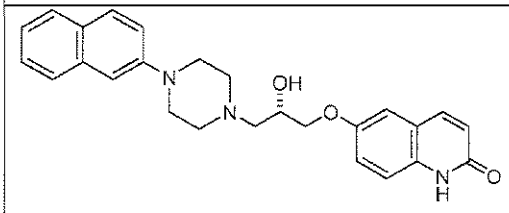
Table 8.

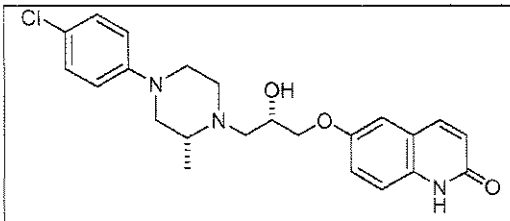
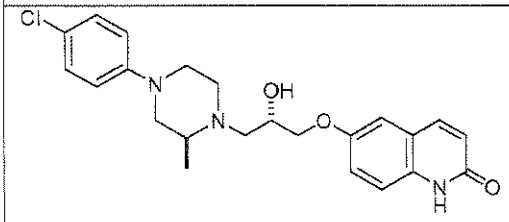
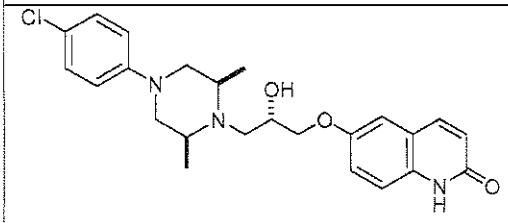
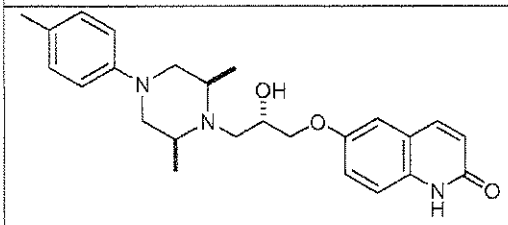
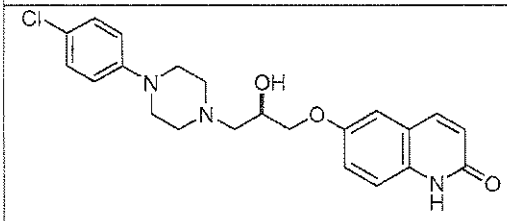
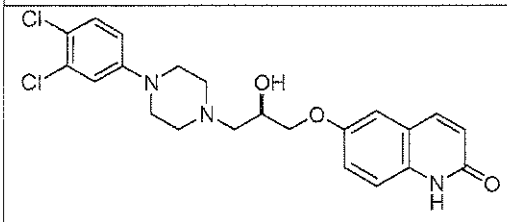
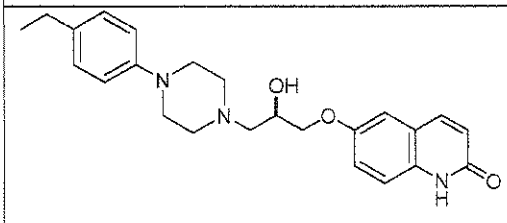
Compound	NAME
	(*S*)-6-(3-(4-(3,4-dichlorophenyl)piperazin-1-yl)-2-hydroxypropoxy)quinolin-2(1*H*)-one
	(*S*)-6-(3-(4-(3,4-difluorophenyl)piperazin-1-yl)-2-hydroxypropoxy)quinolin-2(1*H*)-one

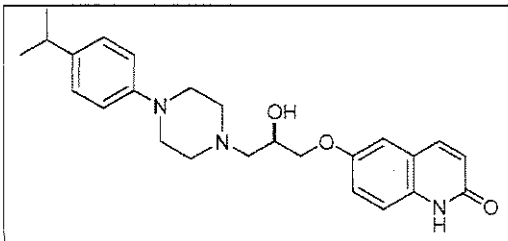
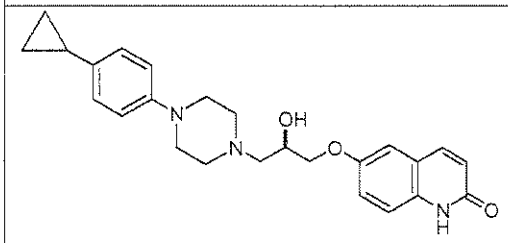
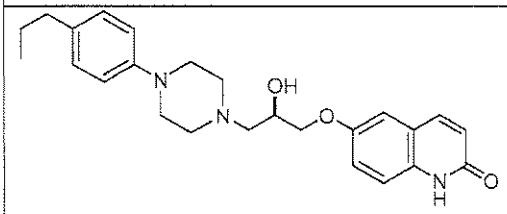
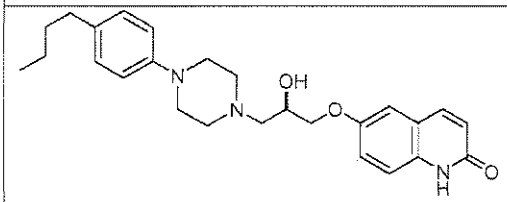
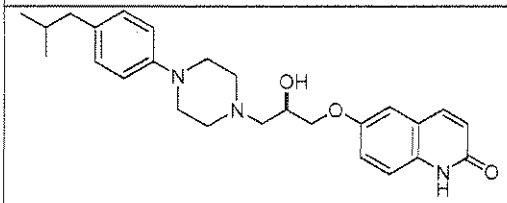
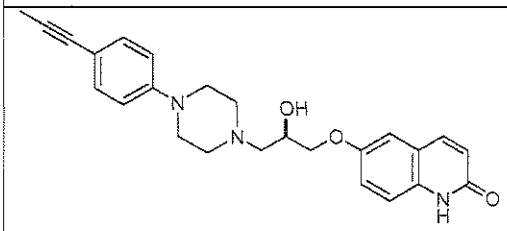
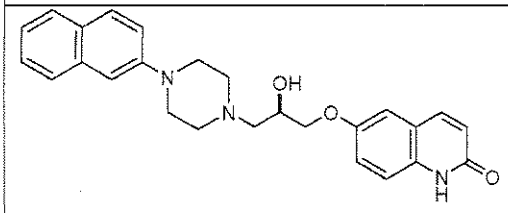
	(*R*)-6-(3-(4-(3,4-difluorophenyl)piperazin-1-yl)-2-hydroxypropoxy)quinolin-2(1*H*)-one
	(*S*)-6-(3-(4-(4-fluorophenyl)piperazin-1-yl)-2-hydroxypropoxy)quinolin-2(1*H*)-one
	(*S*)-6-(3-(4-(3,4-dimethylphenyl)piperazin-1-yl)-2-hydroxypropoxy)quinolin-2(1*H*)-one
	(*S*)-6-(2-hydroxy-3-(4-*p*-tolylpiperazin-1-yl)propoxy)quinolin-2(1*H*)-one
	(*S*)-4-(4-(2-hydroxy-3-(2-oxo-1,2-dihydroquinolin-6-yloxy)propyl)piperazin-1-yl)benzonitrile
	(*S*)-6-(3-(4-(4-bromophenyl)piperazin-1-yl)-2-hydroxypropoxy)quinolin-2(1*H*)-one
	(*S*)-6-(2-hydroxy-3-(4-(4-hydroxyphenyl)piperazin-1-yl)propoxy)quinolin-2(1*H*)-one

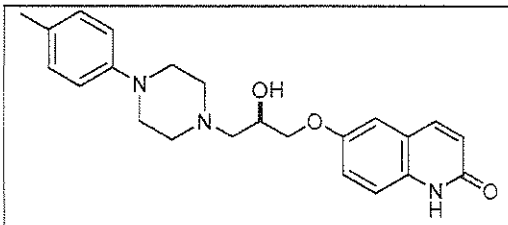
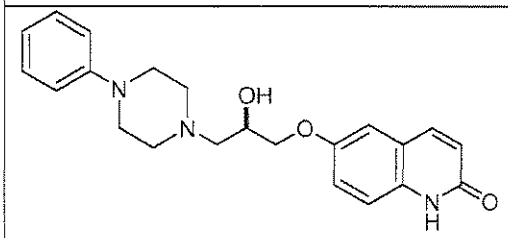
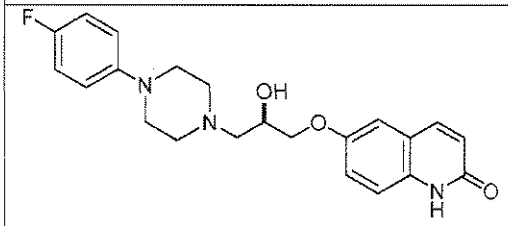
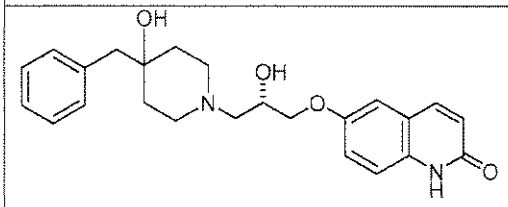
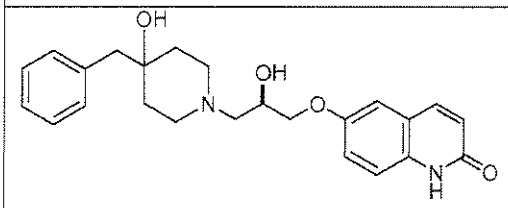
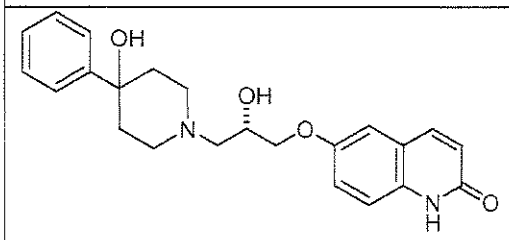
	(*S*)-6-(2-hydroxy-3-(4-(4-methoxyphenyl)piperazin-1-yl)propoxy)quinolin-2(1*H*)-one
	(*S*)-6-(2-hydroxy-3-(4-(4-(trifluoromethyl)phenyl)piperazin-1-yl)propoxy)quinolin-2(1*H*)-one
	(*S*)-6-(3-(4-(biphenyl-4-yl)piperazin-1-yl)-2-hydroxypropoxy)quinolin-2(1*H*)-one
	(*S*)-6-(3-(4-(2,4-difluorophenyl)piperazin-1-yl)-2-hydroxypropoxy)quinolin-2(1*H*)-one
	(*S*)-6-(3-(4-(2-fluorophenyl)piperazin-1-yl)-2-hydroxypropoxy)quinolin-2(1*H*)-one
	(*S*)-6-(3-(4-(2-chlorophenyl)piperazin-1-yl)-2-hydroxypropoxy)quinolin-2(1*H*)-one
	(*S*)-6-(2-hydroxy-3-(4-*o*-tolylpiperazin-1-yl)propoxy)quinolin-2(1*H*)-one

	(*S*)-2-(4-(2-hydroxy-3-(2-oxo-1,2-dihydroquinolin-6-yloxy)propyl)piperazin-1-yl)benzonitrile
	(*S*)-6-(2-hydroxy-3-(4-phenylpiperazin-1-yl)propoxy)quinolin-2(1*H*)-one
	(*S*)-6-(3-(4-(3-fluorophenyl)piperazin-1-yl)-2-hydroxypropoxy)quinolin-2(1*H*)-one
	(*S*)-6-(3-(4-(3-chlorophenyl)piperazin-1-yl)-2-hydroxypropoxy)quinolin-2(1*H*)-one
	(*S*)-6-(2-hydroxy-3-(4-*m*-tolypiperazin-1-yl)propoxy)quinolin-2(1*H*)-one
	(*S*)-6-(2-hydroxy-3-(4-(3-(trifluoromethyl)phenyl)piperazin-1-yl)propoxy)quinolin-2(1*H*)-one
	(*S*)-6-(3-(4-(4-ethylphenyl)piperazin-1-yl)-2-hydroxypropoxy)quinolin-2(1*H*)-one

	(*S*)-6-(2-hydroxy-3-(4-(4-isopropylphenyl)piperazin-1-yl)propoxy)quinolin-2(1*H*)-one
	(*S*)-6-(3-(4-(4-cyclopropylphenyl)piperazin-1-yl)-2-hydroxypropoxy)quinolin-2(1*H*)-one
	(*S*)-6-(2-hydroxy-3-(4-(4-propylphenyl)piperazin-1-yl)propoxy)quinolin-2(1*H*)-one
	(*S*)-6-(3-(4-(4-butylphenyl)piperazin-1-yl)-2-hydroxypropoxy)quinolin-2(1*H*)-one
	(*S*)-6-(2-hydroxy-3-(4-(4-isobutylphenyl)piperazin-1-yl)propoxy)quinolin-2(1*H*)-one
	(*S*)-6-(2-hydroxy-3-(4-(4-(prop-1-ynyl)phenyl)piperazin-1-yl)propoxy)quinolin-2(1*H*)-one
	(*S*)-6-(2-hydroxy-3-(4-(naphthalen-2-yl)piperazin-1-yl)propoxy)quinolin-2(1*H*)-one

	6-((*S*)-3-((*R*)-4-(4-chlorophenyl)-2-methylpiperazin-1-yl)-2-hydroxypropoxy)quinolin-2(1*H*)-one
	6-((*S*)-3-((*S*)-4-(4-chlorophenyl)-2-methylpiperazin-1-yl)-2-hydroxypropoxy)quinolin-2(1*H*)-one
	6-((*S*)-3-((2*S*,6*R*)-4-(4-chlorophenyl)-2,6-dimethylpiperazin-1-yl)-2-hydroxypropoxy)quinolin-2(1*H*)-one
	6-((*S*)-3-((2*S*,6*R*)-2,6-dimethyl-4-*p*-tolylpiperazin-1-yl)-2-hydroxypropoxy)quinolin-2(1*H*)-one
	(*R*)-6-(3-(4-(4-chlorophenyl)piperazin-1-yl)-2-hydroxypropoxy)quinolin-2(1*H*)-one
	(*R*)-6-(3-(4-(3,4-dichlorophenyl)piperazin-1-yl)-2-hydroxypropoxy)quinolin-2(1*H*)-one
	(*R*)-6-(3-(4-(4-ethylphenyl)piperazin-1-yl)-2-hydroxypropoxy)quinolin-2(1*H*)-one

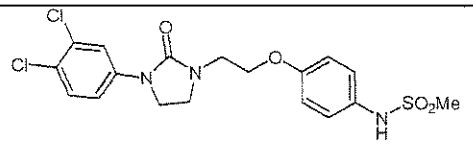
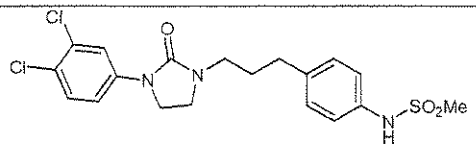
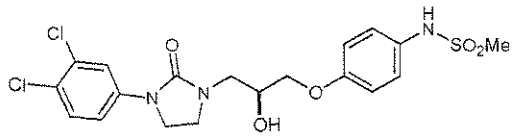
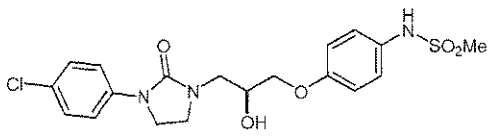
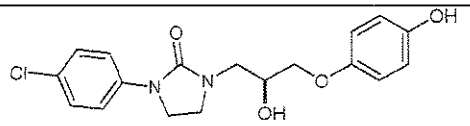
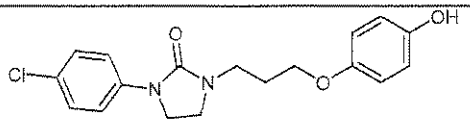
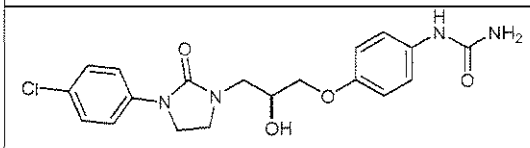
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	(*R*)-6-(3-(4-(4-cyclopropylphenyl)piperazin-1-yl)-2-hydroxypropoxy)quinolin-2(1*H*)-one
	(*R*)-6-(2-hydroxy-3-(4-(4-propylphenyl)piperazin-1-yl)propoxy)quinolin-2(1*H*)-one
	(*R*)-6-(3-(4-(4-butylphenyl)piperazin-1-yl)-2-hydroxypropoxy)quinolin-2(1*H*)-one
	(*R*)-6-(2-hydroxy-3-(4-(4-isobutylphenyl)piperazin-1-yl)propoxy)quinolin-2(1*H*)-one
	(*R*)-6-(2-hydroxy-3-(4-(4-(prop-1-ynyl)phenyl)piperazin-1-yl)propoxy)quinolin-2(1*H*)-one
	(*R*)-6-(2-hydroxy-3-(4-(naphthalen-2-yl)piperazin-1-yl)propoxy)quinolin-2(1*H*)-one

	(*R*)-6-(2-hydroxy-3-(4-*p*-tolylpiperazin-1-yl) propoxy)quinolin-2(1*H*)-one
	(*R*)-6-(2-hydroxy-3-(4-phenylpiperazin-1-yl)propoxy)quinolin-2(1*H*)-one
	(*R*)-6-(3-(4-(fluorophenyl)piperazin-1-yl)-2-hydroxypropoxy)quinolin-2(1*H*)-one
	(*S*)-6-(3-(4-benzyl-4-hydroxypiperidin-1-yl)-2-hydroxypropoxy)quinolin-2(1H)-one
	(*R*)-6-(3-(4-benzyl-4-hydroxypiperidin-1-yl)-2-hydroxypropoxy)quinolin-2(1H)-one
	(*S*)-6-(2-hydroxy-3-(4-hydroxy-4-phenylpiperidin-1-yl)propoxy)quinolin-2(1H)-one

In another embodiment, the compound is selected from Table 9.

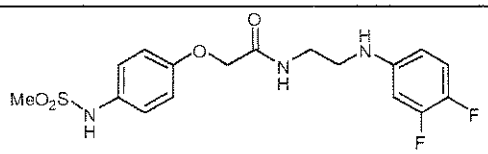
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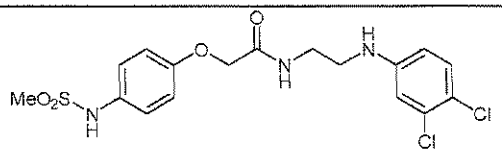
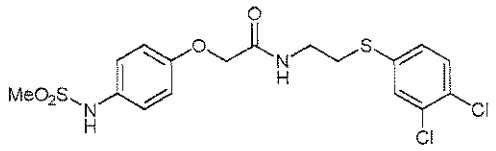
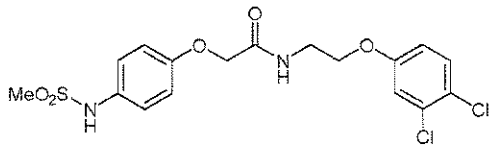
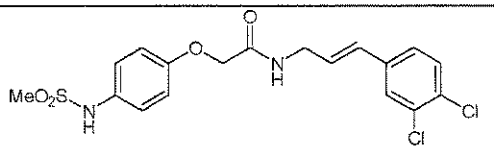
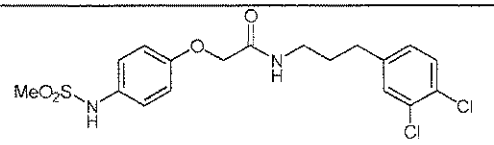
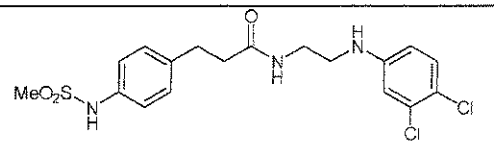
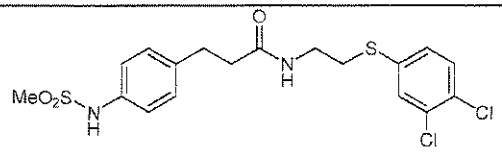
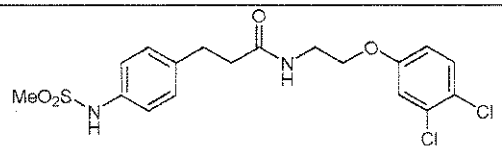
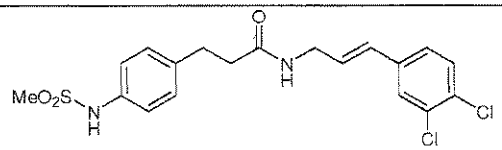
Compound	Name

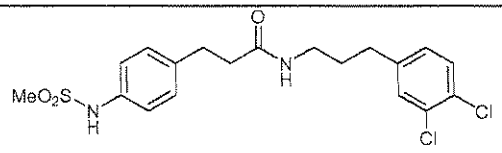
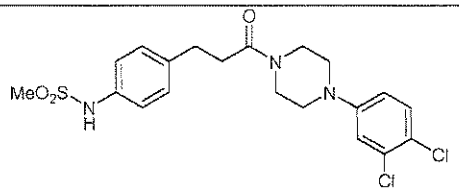
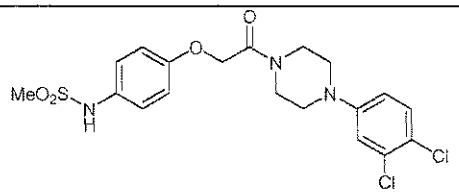
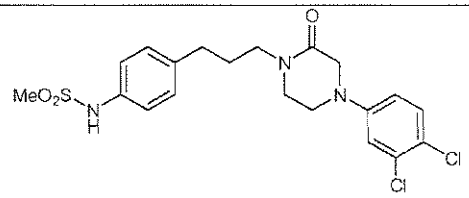
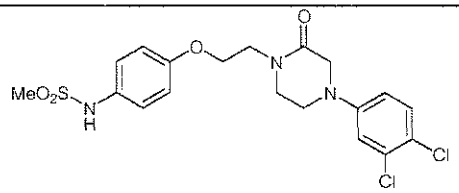
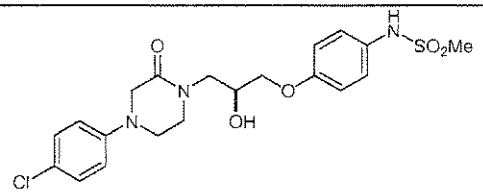
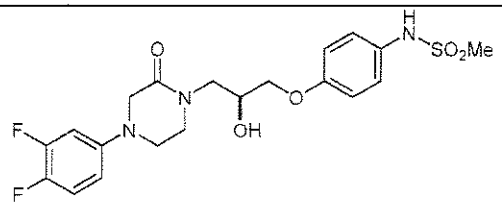
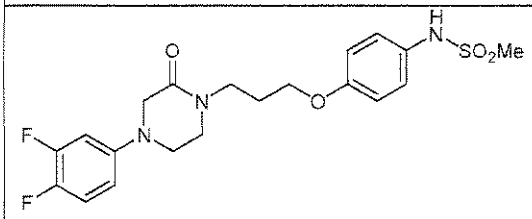
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	N-(4-(3-(3-(3,4-dichlorophenyl)-2-oxoimidazolidin-1-yl)propyl)phenyl)methanesulfonamide
	(S)-N-(4-(3-(3-(3,4-dichlorophenyl)-2-oxoimidazolidin-1-yl)-2-hydroxypropoxy)phenyl)methanesulfonamide
	(S)-N-(4-(3-(3-(4-chlorophenyl)-2-oxoimidazolidin-1-yl)-2-hydroxypropoxy)phenyl)methanesulfonamide
	(S)-1-(4-chlorophenyl)-3-(2-hydroxy-3-(4-hydroxyphenoxy)propyl)imidazolidin-2-one
	1-(4-chlorophenyl)-3-(3-(4-hydroxyphenoxy)propyl)imidazolidin-2-one
	(S)-1-(4-(3-(3-(4-chlorophenyl)-2-oxoimidazolidin-1-yl)-2-hydroxypropoxy)phenyl)urea

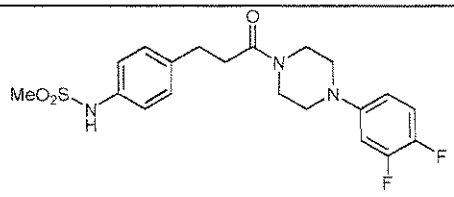
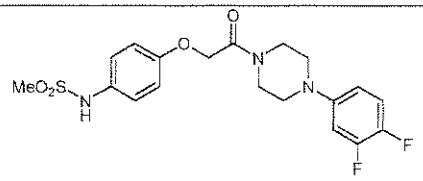
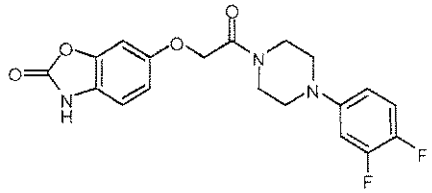
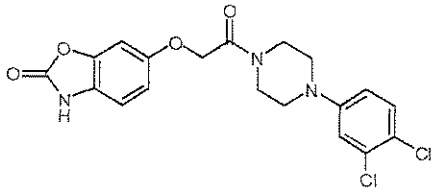
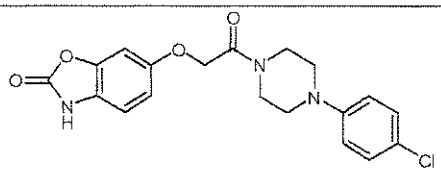
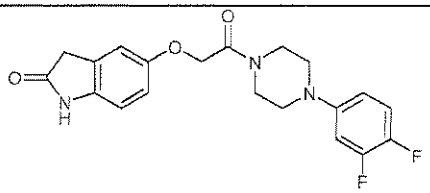
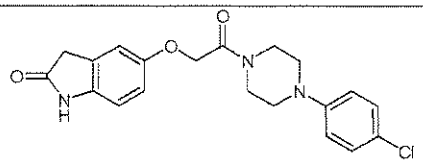
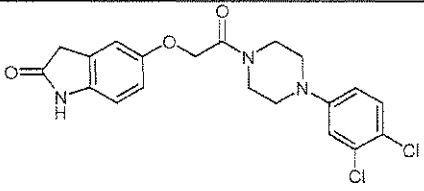
In another embodiment, the compound is selected from Table 10.

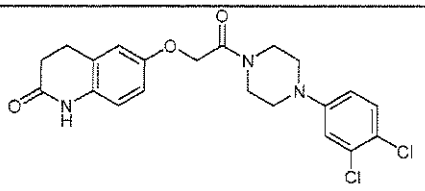
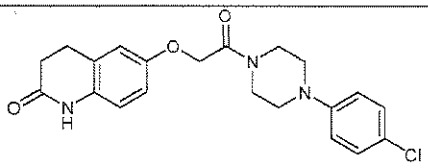
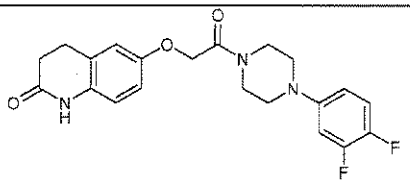
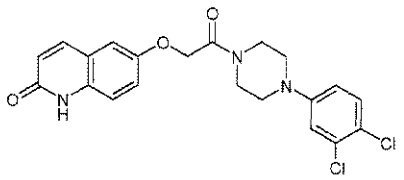
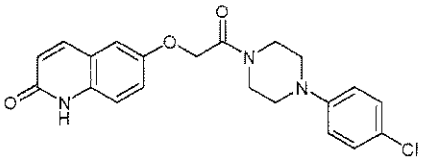
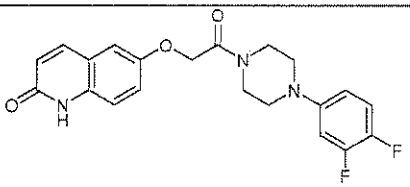
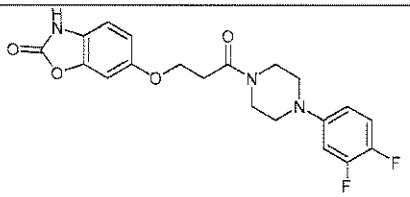
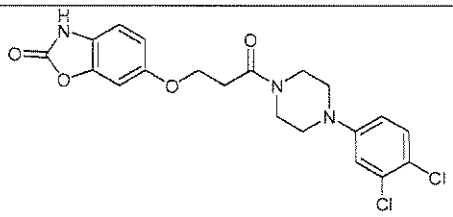
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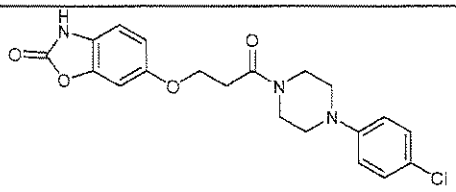
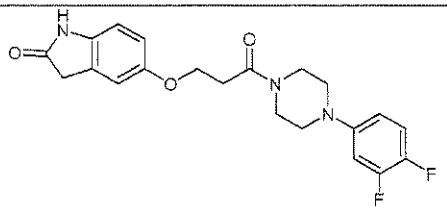
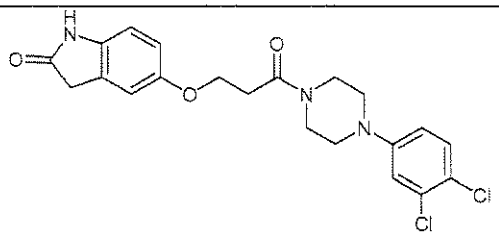
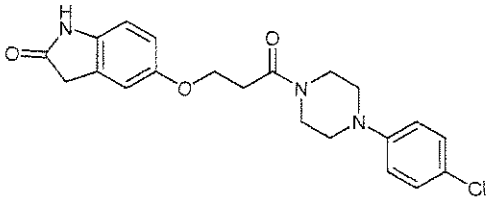
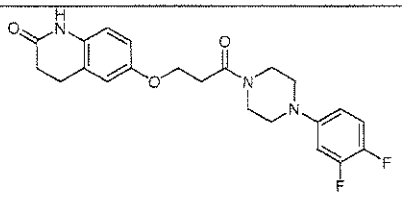
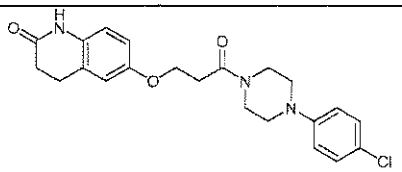
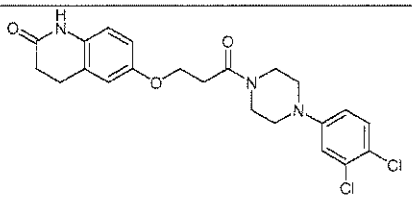
Compound	Name
	*N*-(2-(3,4-difluorophenylamino)ethyl)-2-(4-(methylsulfonamido)phenoxy)acetamide

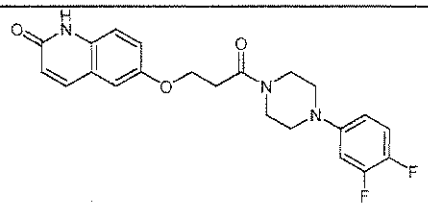
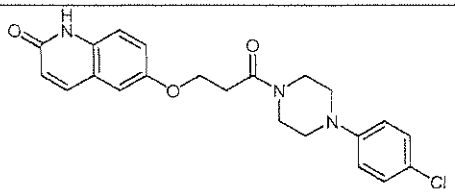
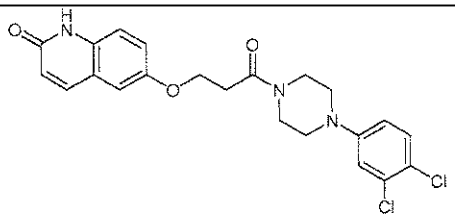
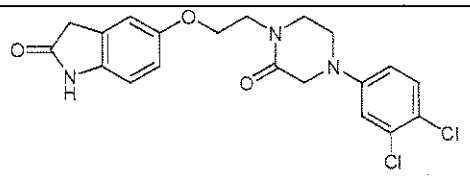
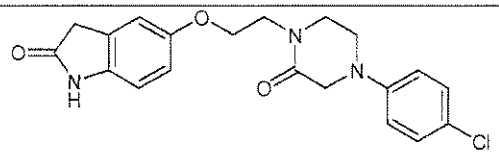
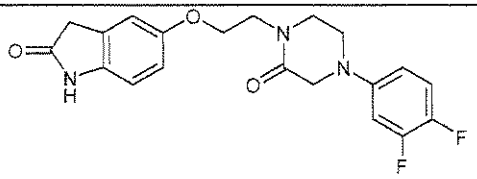
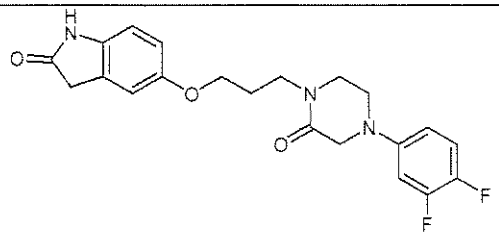
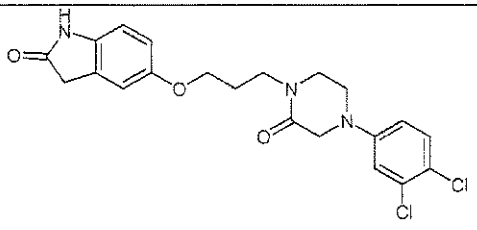
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	N-(2-(3,4-dichlorophenylthio)ethyl)-2-(4-(methylsulfonamido)phenoxy)acetamide
	N-(2-(3,4-dichlorophenoxy)ethyl)-2-(4-(methylsulfonamido)phenoxy)acetamide
	(E)-N-(3-(3,4-dichlorophenyl)allyl)-2-(4-(methylsulfonamido)phenoxy)acetamide
	N-(3-(3,4-dichlorophenyl)propyl)-2-(4-(methylsulfonamido)phenoxy)acetamide
	N-(2-(3,4-dichlorophenylamino)ethyl)-3-(4-(methylsulfonamido)phenyl)propanamide
	N-(2-(3,4-dichlorophenylthio)ethyl)-3-(4-(methylsulfonamido)phenyl)propanamide
	N-(2-(3,4-dichlorophenoxy)ethyl)-3-(4-(methylsulfonamido)phenyl)propanamide
	(E)-N-(3-(3,4-dichlorophenyl)allyl)-3-(4-(methylsulfonamido)phenyl)propanamide

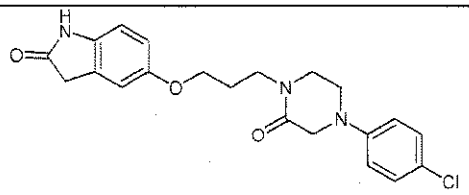
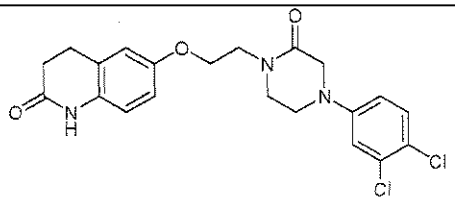
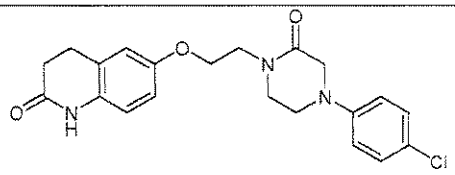
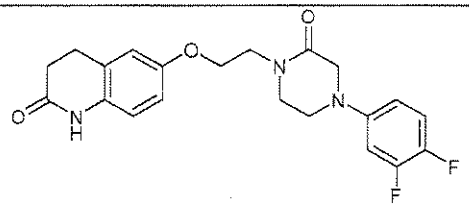
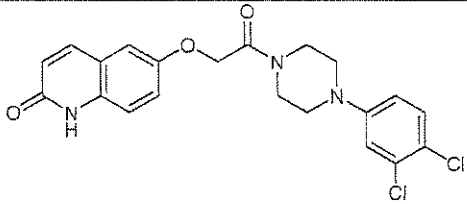
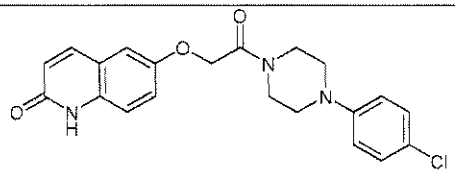
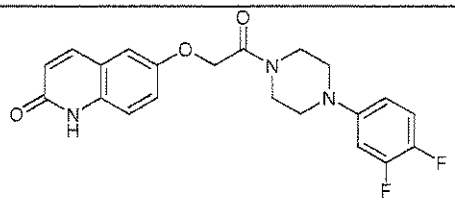
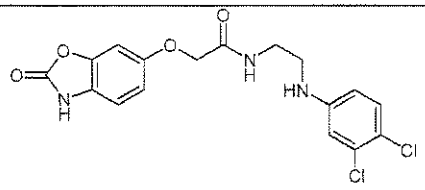
	N-(3-(3,4-dichlorophenyl)propyl)-3-(4-(methylsulfonamido)phenyl)propanamide
	N-(4-(3-(4-(3,4-dichlorophenyl)piperazin-1-yl)-3-oxopropyl)phenyl)methanesulfonamide
	N-(4-(2-(4-(3,4-dichlorophenyl)piperazin-1-yl)-2-oxoethoxy)phenyl)methanesulfonamide
	N-(4-(3-(4-(3,4-dichlorophenyl)-2-oxopiperazin-1-yl)propyl)phenyl)methanesulfonamide
	N-(4-(2-(4-(3,4-dichlorophenyl)-2-oxopiperazin-1-yl)ethoxy)phenyl)methanesulfonamide
	(S)-N-(4-(3-(4-(4-chlorophenyl)-2-oxopiperazin-1-yl)-2-hydroxypropoxy)phenyl)methanesulfonamide
	(S)-N-(4-(3-(4-(3,4-difluorophenyl)-2-oxopiperazin-1-yl)-2-hydroxypropoxy)phenyl)methanesulfonamide
	N-(4-(3-(4-(3,4-difluorophenyl)-2-oxopiperazin-1-yl)propoxy)phenyl)methanesulfonamide

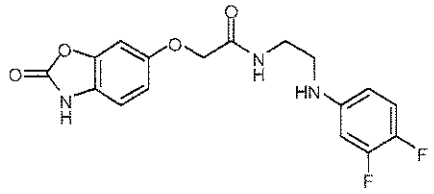
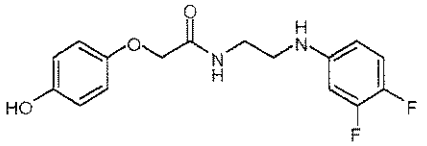
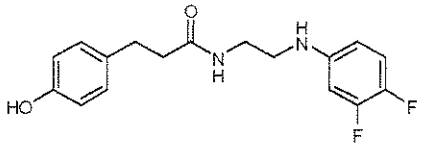
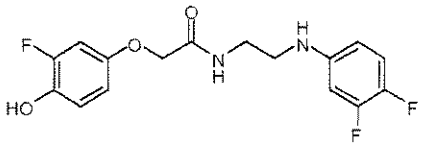
	*N*-(4-(3-(4-(3,4-difluorophenyl)piperazin-1-yl)-3-oxopropyl)phenyl)methanesulfonamide
	*N*-(4-(2-(4-(3,4-difluorophenyl)piperazin-1-yl)-2-oxoethoxy)phenyl)methanesulfonamide
	6-(2-(4-(3,4-difluorophenyl)piperazin-1-yl)-2-oxoethoxy)benzo[*d*]oxazol-2(3*H*)-one
	6-(2-(4-(3,4-dichlorophenyl)piperazin-1-yl)-2-oxoethoxy)benzo[*d*]oxazol-2(3*H*)-one
	6-(2-(4-(4-Chlorophenyl)piperazin-1-yl)-2-oxoethoxy)benzo[*d*]oxazol-2(3*H*)-one
	5-(2-(4-(3,4-difluorophenyl)piperazin-1-yl)-2-oxoethoxy)indolin-2-one
	5-(2-(4-(4-chlorophenyl)piperazin-1-yl)-2-oxoethoxy)indolin-2-one
	5-(2-(4-(3,4-dichlorophenyl)piperazin-1-yl)-2-oxoethoxy)indolin-2-one

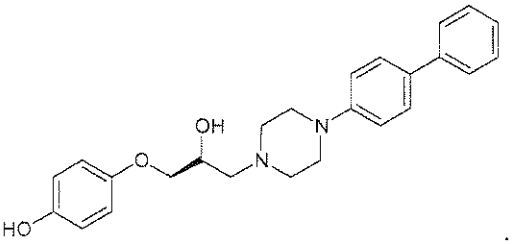
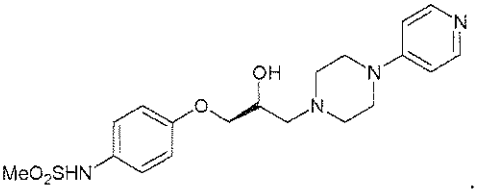
	6-(2-(4-(3,4-dichlorophenyl)piperazin-1-yl)-2-oxoethoxy)-3,4-dihydroquinolin-2(1H)-one
	6-(2-(4-(4-chlorophenyl)piperazin-1-yl)-2-oxoethoxy)-3,4-dihydroquinolin-2(1H)-one
	6-(2-(4-(3,4-difluorophenyl)piperazin-1-yl)-2-oxoethoxy)-3,4-dihydroquinolin-2(1H)-one
	6-(2-(4-(3,4-dichlorophenyl)piperazin-1-yl)-2-oxoethoxy)quinolin-2(1H)-one
	6-(2-(4-(4-chlorophenyl)piperazin-1-yl)-2-oxoethoxy)quinolin-2(1H)-one
	6-(2-(4-(3,4-difluorophenyl)piperazin-1-yl)-2-oxoethoxy)quinolin-2(1H)-one
	6-(3-(4-(3,4-difluorophenyl)piperazin-1-yl)-3-oxopropoxy)benzo[d]oxazol-2(3H)-one
	6-(3-(4-(3,4-dichlorophenyl)piperazin-1-yl)-3-oxopropoxy)benzo[d]oxazol-2(3H)-one

	6-(3-(4-(4-chlorophenyl)piperazin-1-yl)-3-oxopropoxy)benzo[d]oxazol-2(3H)-one
	5-(3-(4-(3,4-difluorophenyl)piperazin-1-yl)-3-oxopropoxy)indolin-2-one
	5-(3-(4-(3,4-dichlorophenyl)piperazin-1-yl)-3-oxopropoxy)indolin-2-one
	5-(3-(4-(4-chlorophenyl)piperazin-1-yl)-3-oxopropoxy)indolin-2-one
	6-(3-(4-(3,4-difluorophenyl)piperazin-1-yl)-3-oxopropoxy)-3,4-dihydroquinolin-2(1H)-one
	6-(3-(4-(4-chlorophenyl)piperazin-1-yl)-3-oxopropoxy)-3,4-dihydroquinolin-2(1H)-one
	6-(3-(4-(3,4-dichlorophenyl)piperazin-1-yl)-3-oxopropoxy)-3,4-dihydroquinolin-2(1H)-one

	6-(3-(4-(3,4-difluorophenyl)piperazin-1-yl)-3-oxopropoxy)quinolin-2(1H)-one
	6-(3-(4-(4-chlorophenyl)piperazin-1-yl)-3-oxopropoxy)quinolin-2(1H)-one
	6-(3-(4-(3,4-dichlorophenyl)piperazin-1-yl)-3-oxopropoxy)quinolin-2(1H)-one
	5-(2-(4-(3,4-dichlorophenyl)-2-oxopiperazin-1-yl)ethoxy)indolin-2-one
	5-(2-(4-(4-chlorophenyl)-2-oxopiperazin-1-yl)ethoxy)indolin-2-one
	5-(2-(4-(3,4-difluorophenyl)-2-oxopiperazin-1-yl)ethoxy)indolin-2-one
	5-(3-(4-(3,4-difluorophenyl)-2-oxopiperazin-1-yl)propoxy)indolin-2-one
	5-(3-(4-(3,4-dichlorophenyl)-2-oxopiperazin-1-yl)propoxy)indolin-2-one

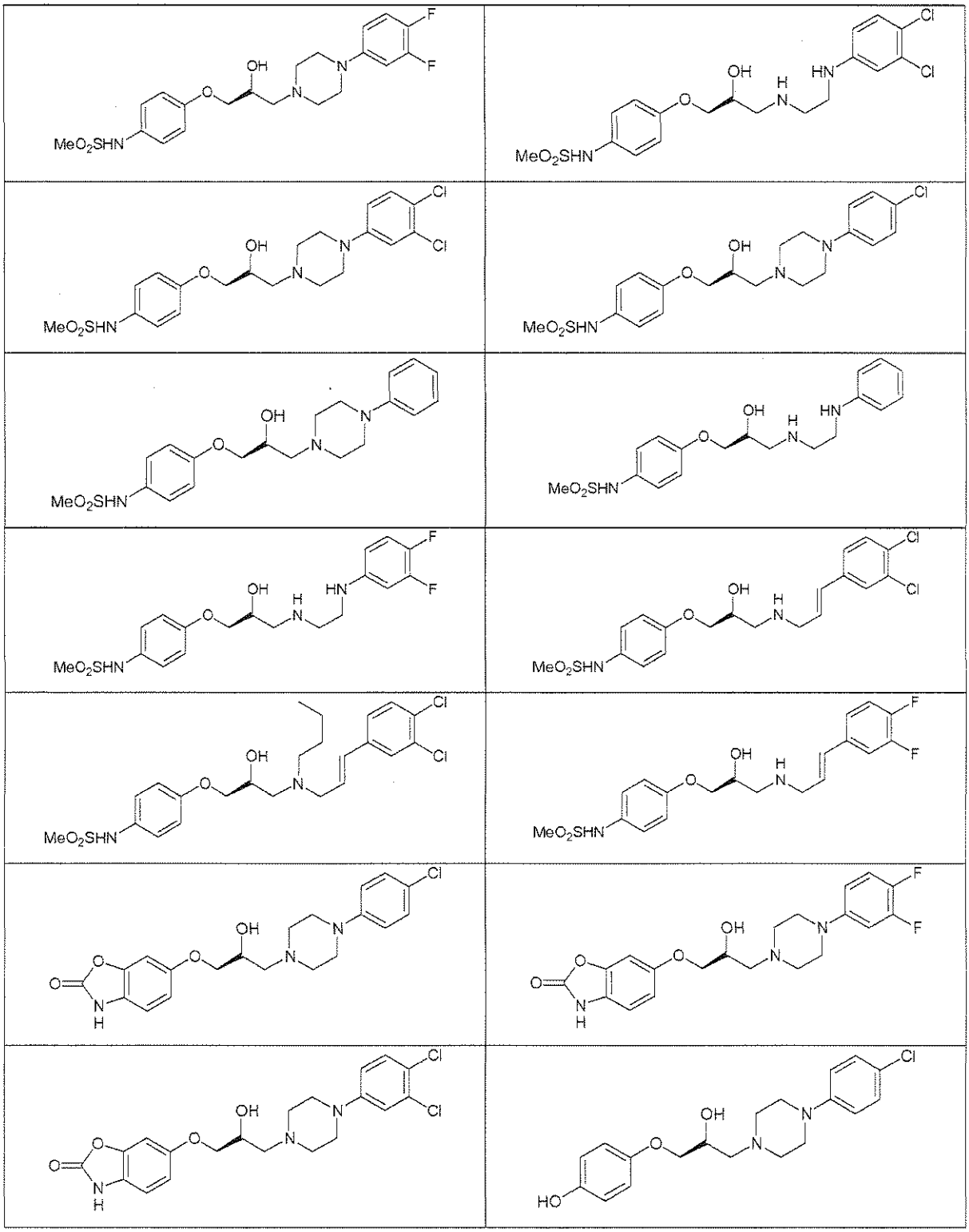
	5-(3-(4-(4-chlorophenyl)-2-oxopiperazin-1-yl)propoxy)indolin-2-one
	6-(2-(4-(3,4-dichlorophenyl)-2-oxopiperazin-1-yl)ethoxy)-3,4-dihydroquinolin-2(1H)-one
	6-(2-(4-(4-chlorophenyl)-2-oxopiperazin-1-yl)ethoxy)-3,4-dihydroquinolin-2(1H)-one
	6-(2-(4-(3,4-difluorophenyl)-2-oxopiperazin-1-yl)ethoxy)-3,4-dihydroquinolin-2(1H)-one
	6-(2-(4-(3,4-dichlorophenyl)piperazin-1-yl)-2-oxoethoxy)quinolin-2(1H)-one
	6-(2-(4-(4-chlorophenyl)piperazin-1-yl)-2-oxoethoxy)quinolin-2(1H)-one
	6-(2-(4-(3,4-difluorophenyl)piperazin-1-yl)-2-oxoethoxy)quinolin-2(1H)-one
	N-(2-(3,4-dichlorophenylamino)ethyl)-2-(2-oxo-2,3-dihydrobenzo[d]oxazol-6-yloxy)acetamide

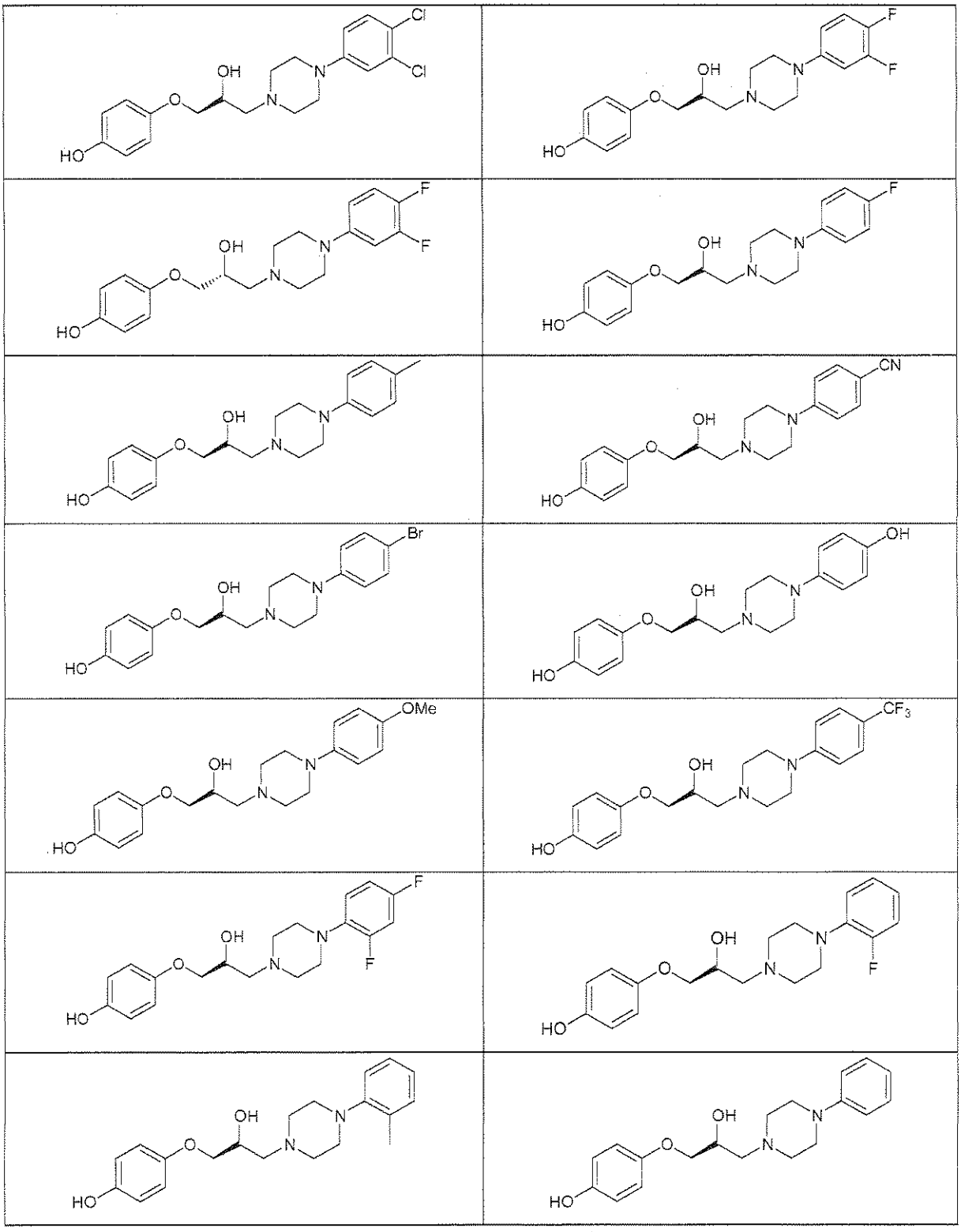
	*N*-(2-(3,4-difluorophenylamino)ethyl)-2-(2-oxo-2,3-dihydrobenzo[*d*]oxazol-6-yloxy)acetamide
	*N*-(2-(3,4-difluorophenylamino)ethyl-2-(4-hydroxyphenoxy)acetamide
	*N*-(2-(3,4-difluorophenylamino)ethyl)-3-(4-hydroxyphenyl)propanamide
	*N*-(2-(3,4-difluorophenylamino)ethyl)-2-(3-fluoro-4-hydroxyphenoxy)acetamide

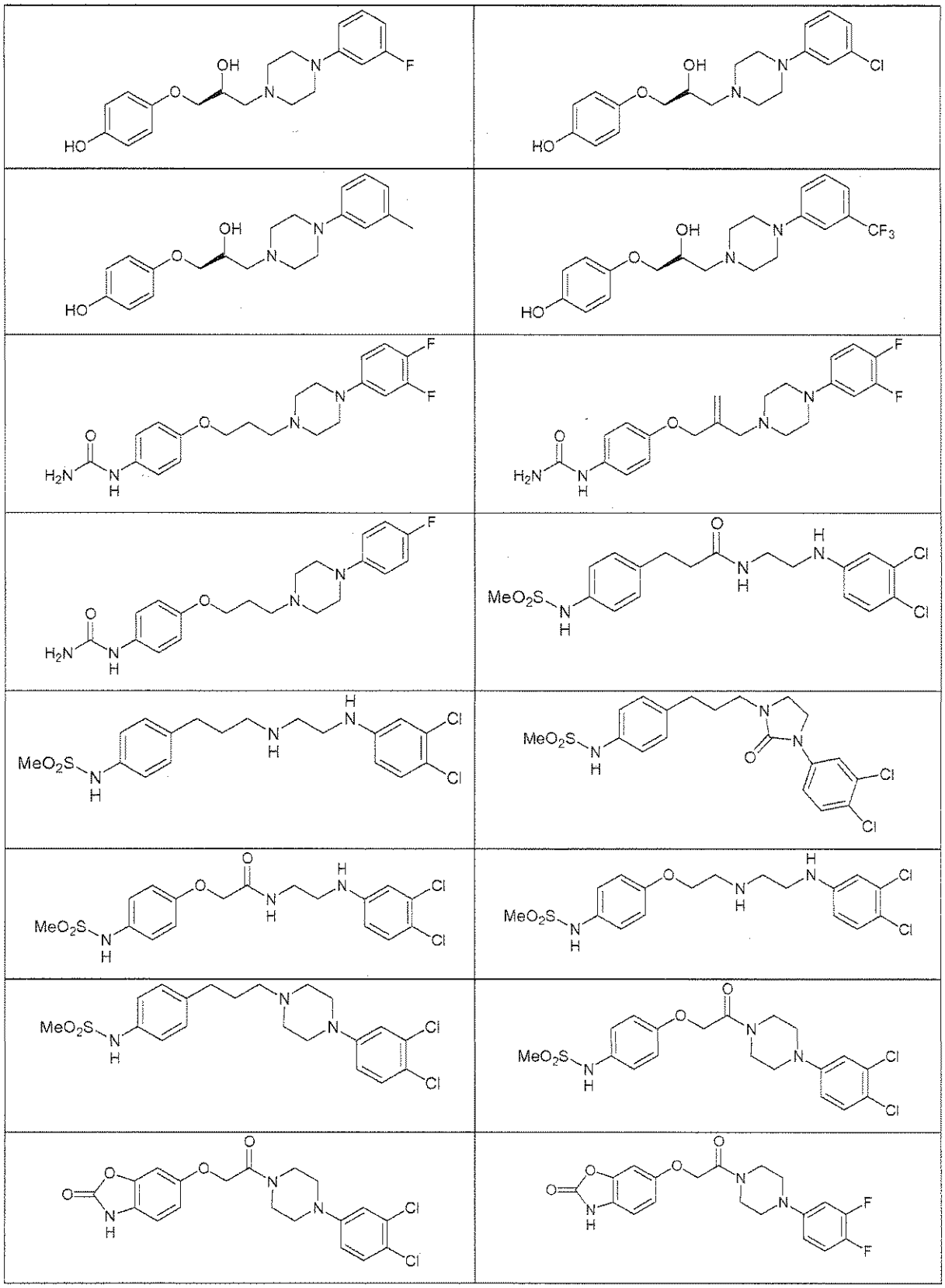
In one embodiment, the compound is not . In another embodiment, the compound is not .

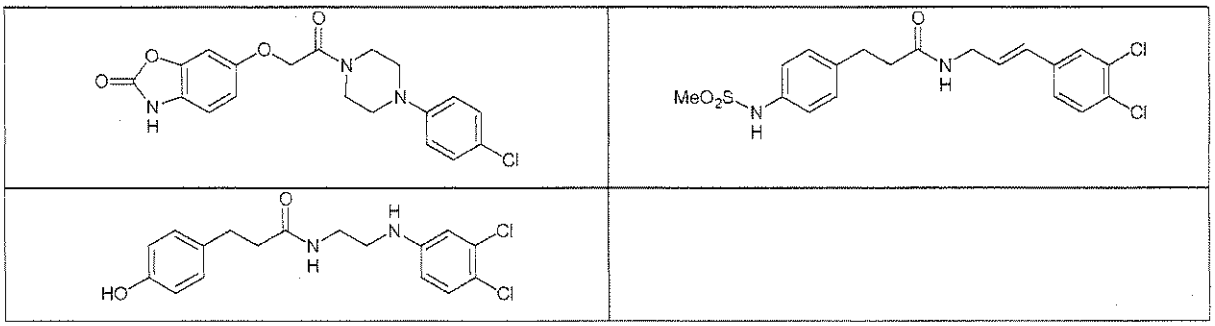
In one embodiment, the compound has an IC_{50} value of 600 nM or less. In one embodiment, the compound has an IC_{50} value of 600 nM or less at pH 6.9 or an ischemic pH. In one embodiment, the compound is selected from Table 11.

Table 11.



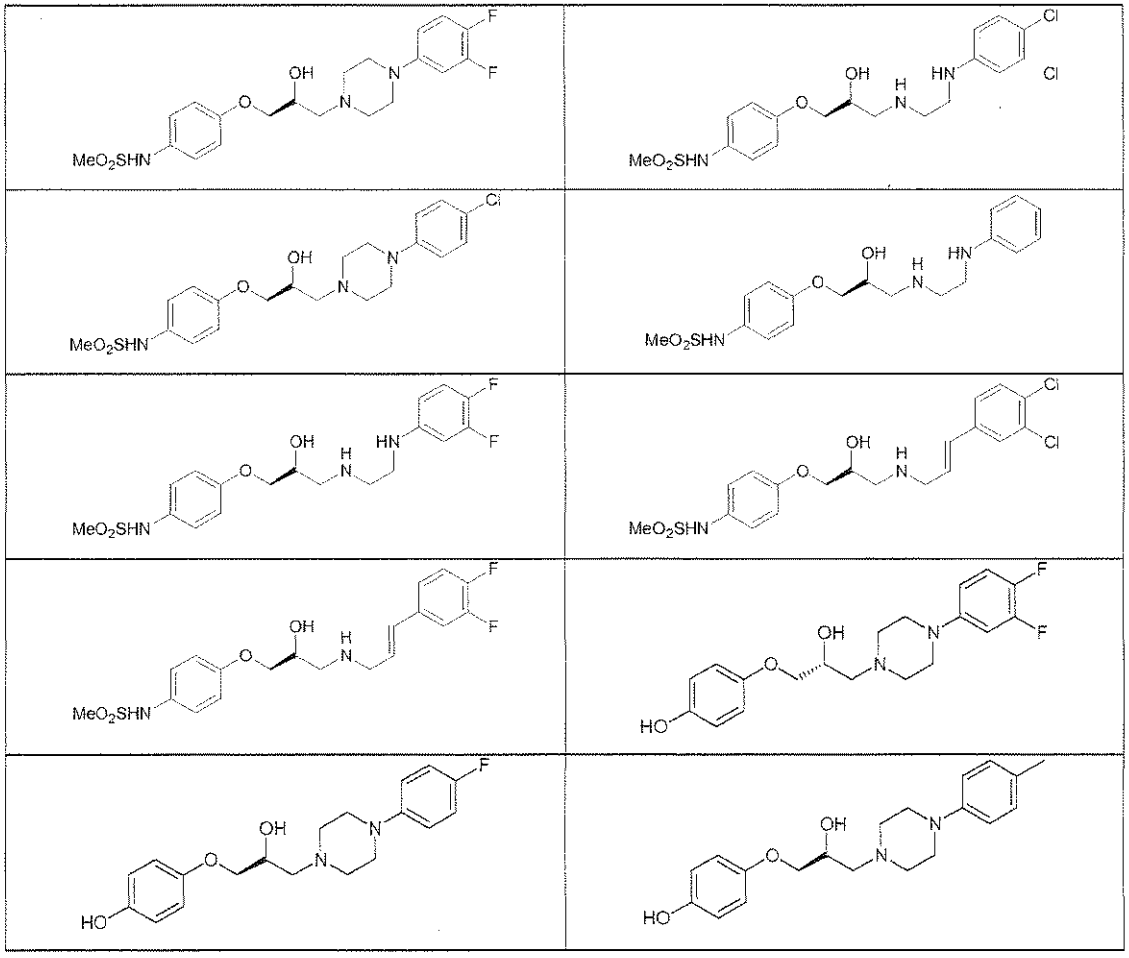


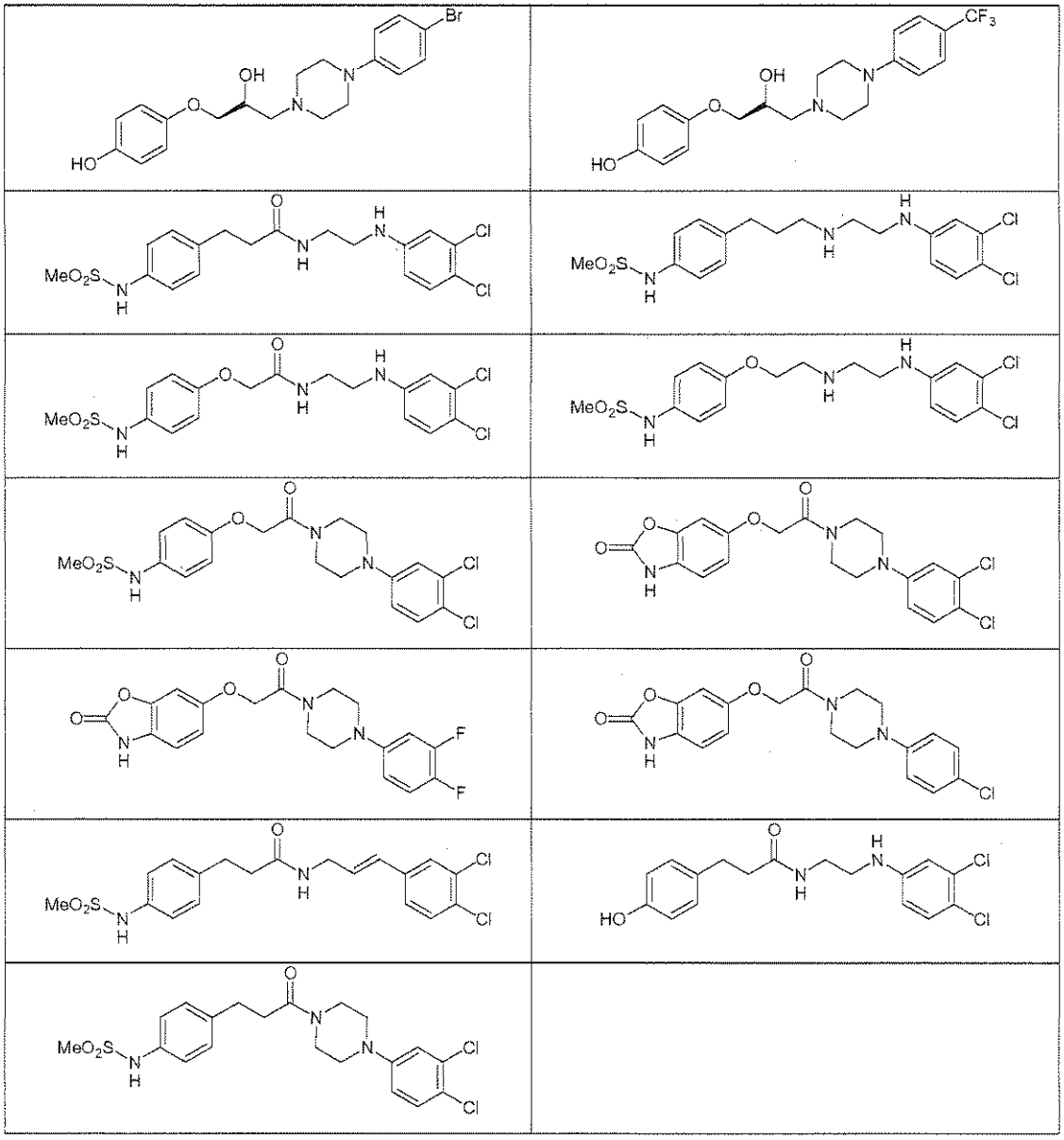




In one embodiment, the compound has an IC_{50} value of 600 nM or less at pH 7.6 or a physiological pH. In one embodiment, the compound is selected from Table 12.

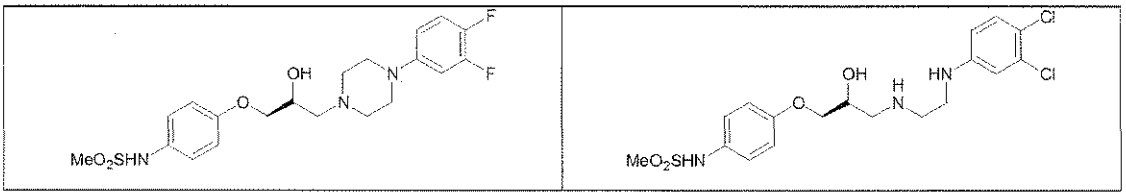
Table 12.

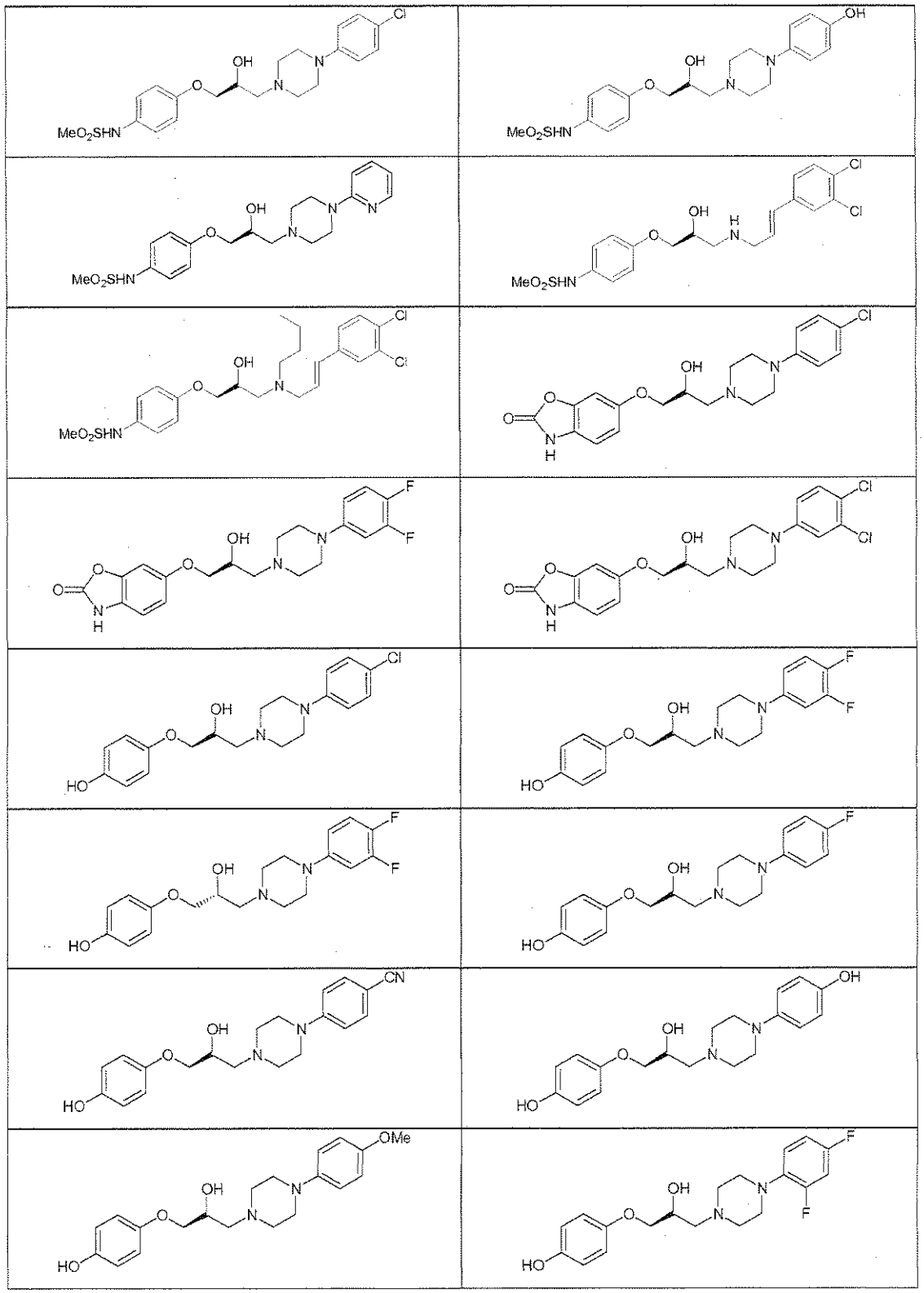


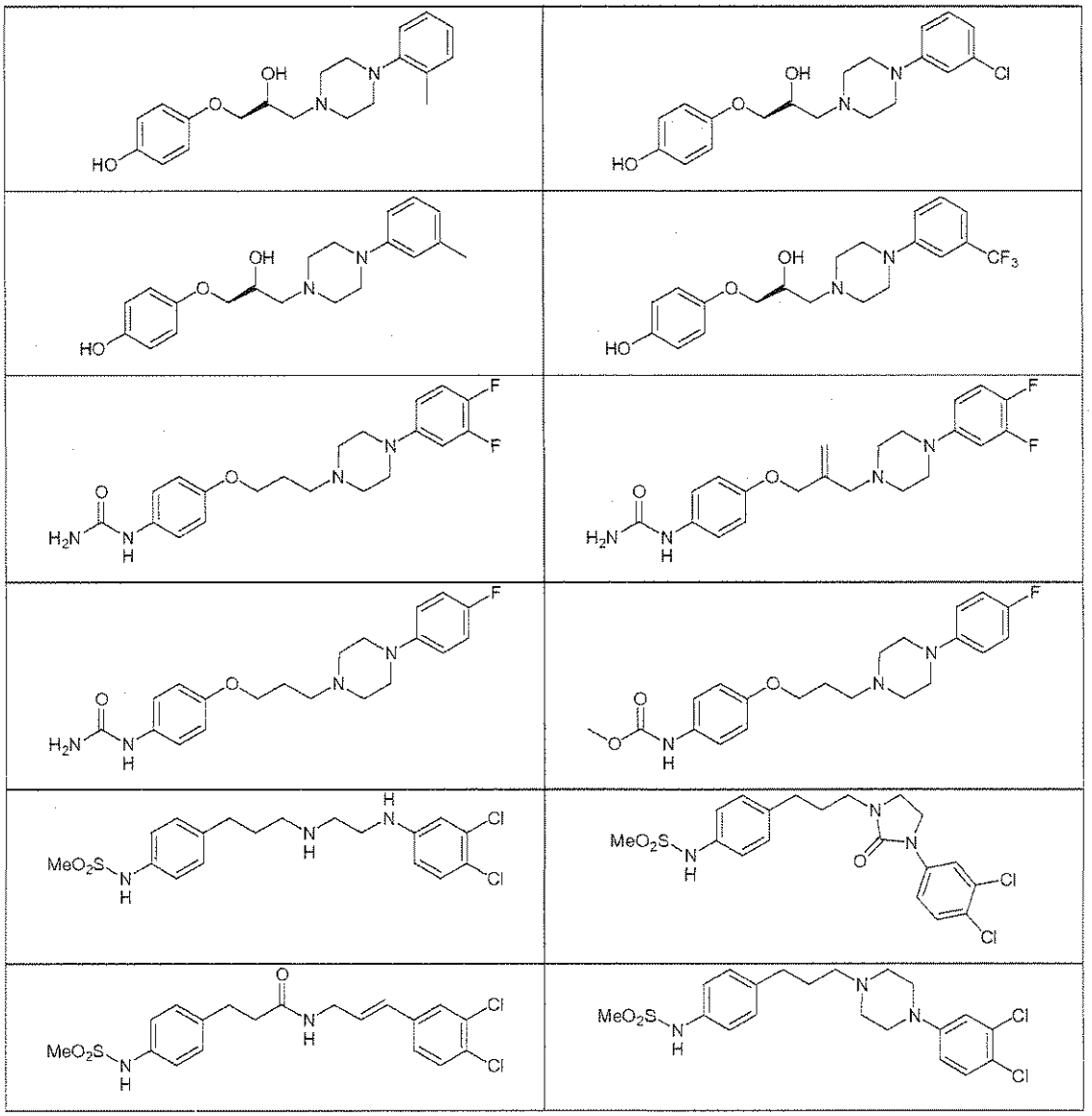


In one embodiment, the compound has a pH boost of 5 or more. In one embodiment, the compound is selected from Table 13.

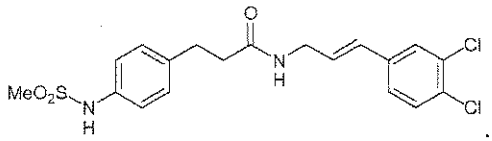
Table 13.



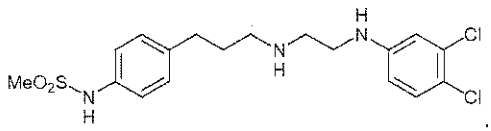




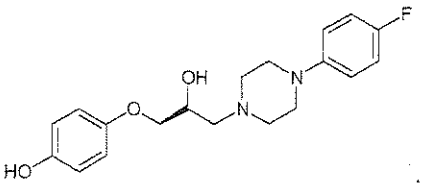
In one embodiment, the compound has an IC_{50} of 600 nM or less and a pH boost of 5 or more. In a particular embodiment, the compound is



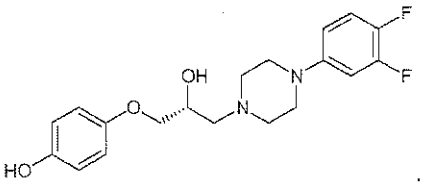
. In another embodiment, the compound is



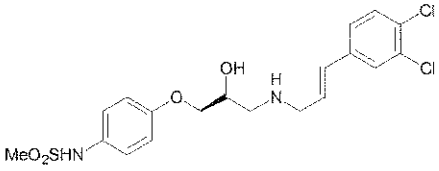
. In another embodiment, the compound is,



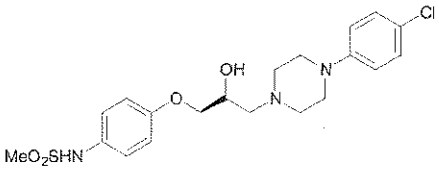
. In another embodiment, the compound is,



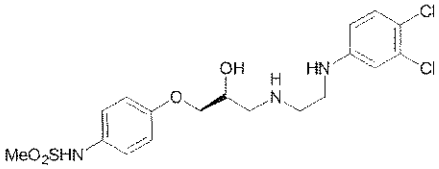
. In a particular embodiment, the compound is



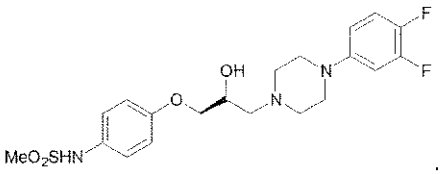
. In another particular embodiment, the compound is



. In another embodiment, the compound is,

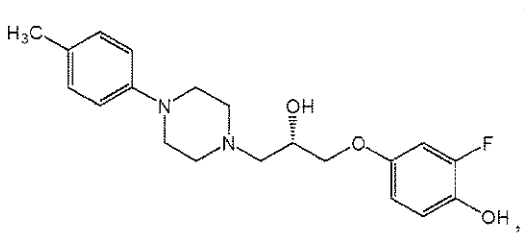


. In another embodiment, the compound is,

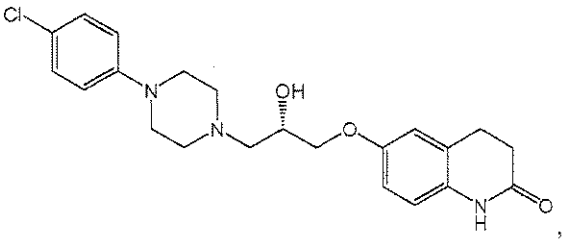


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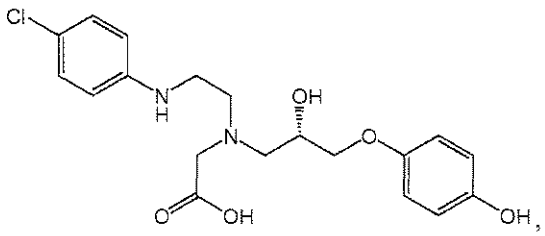
In one embodiment, the compound is selected from the group consisting of:

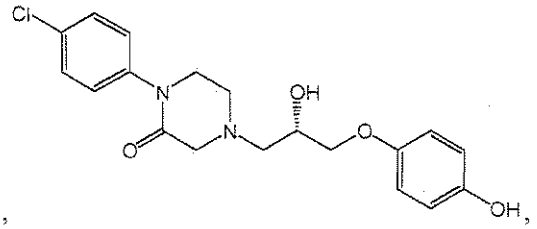


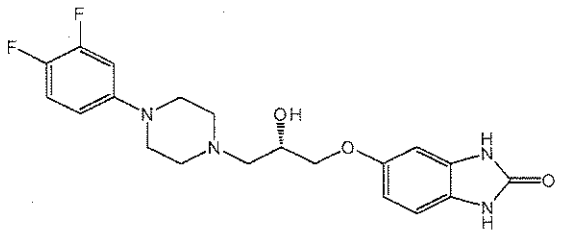
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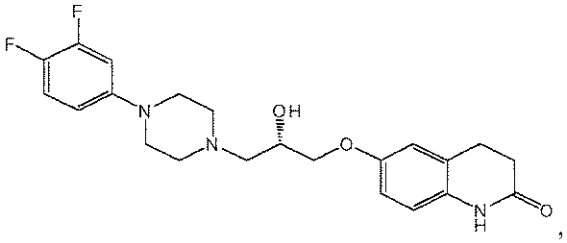


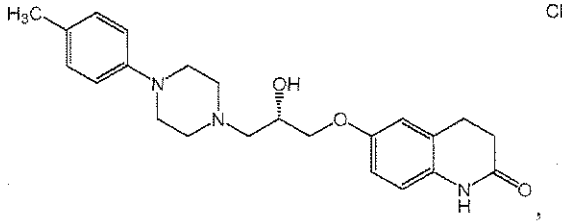
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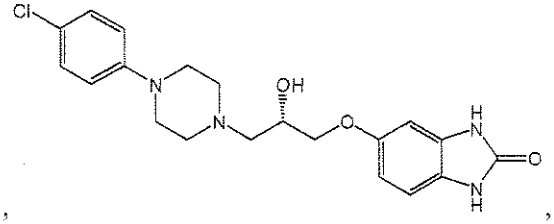


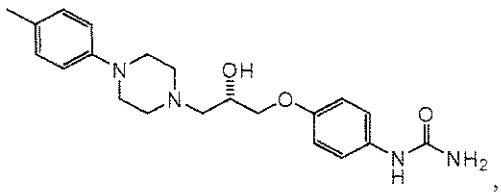


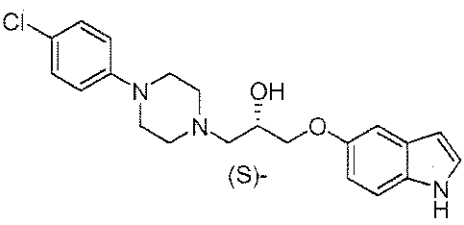


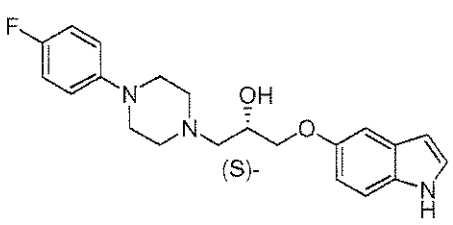


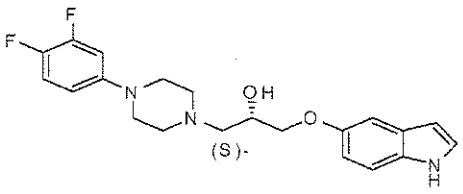


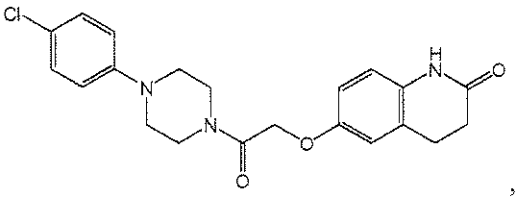


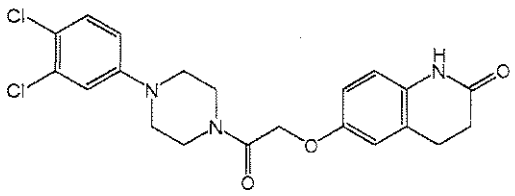




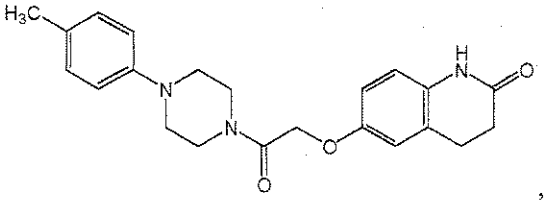




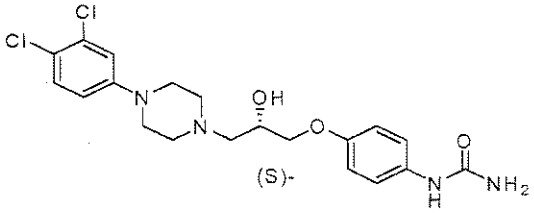




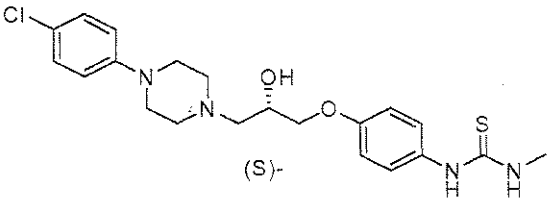
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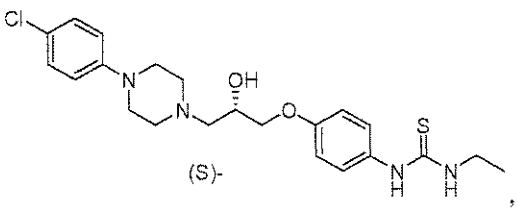
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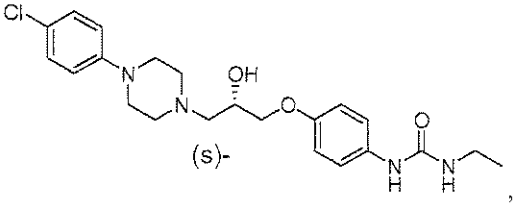
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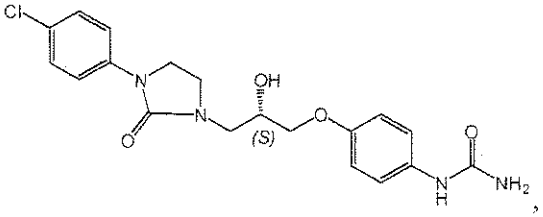
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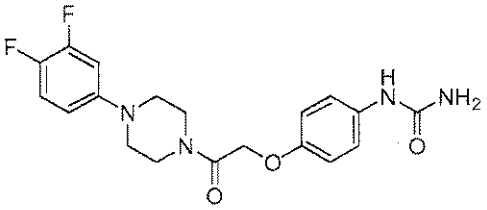
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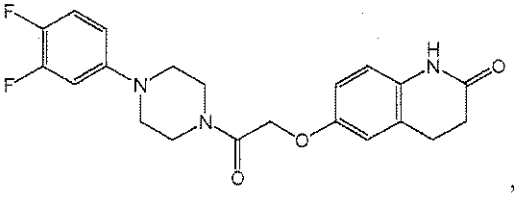
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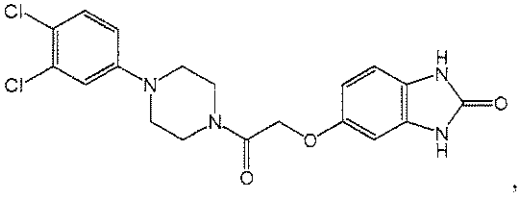
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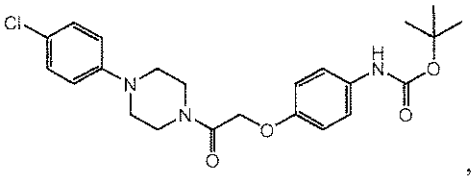
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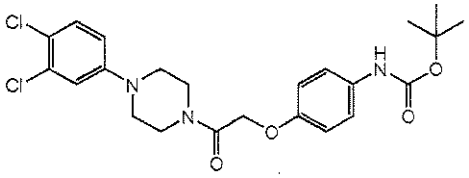
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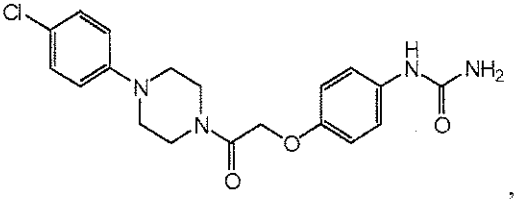
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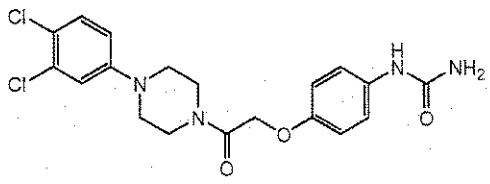
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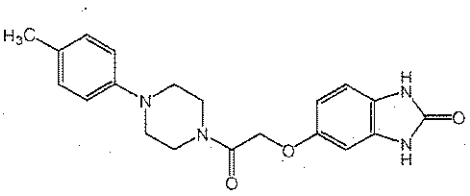


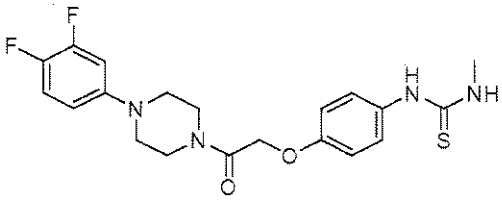
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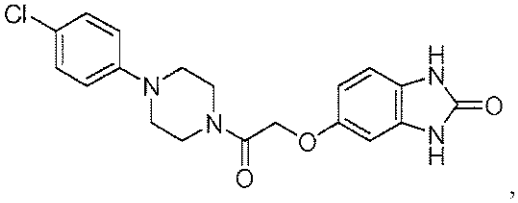


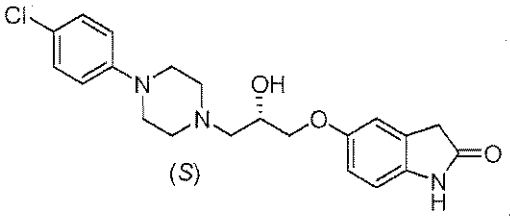
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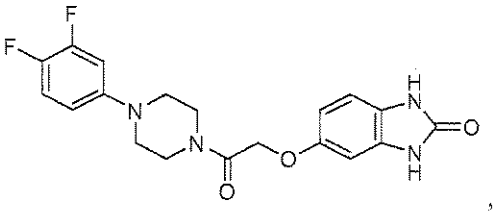


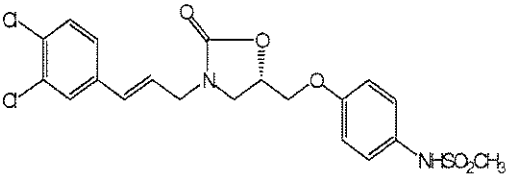


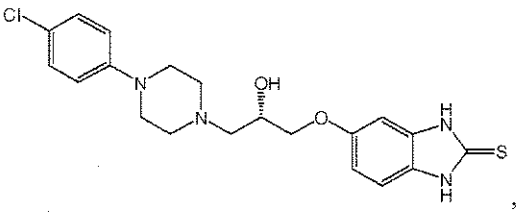


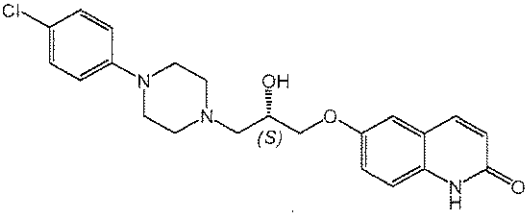


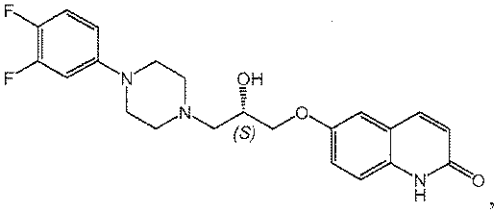

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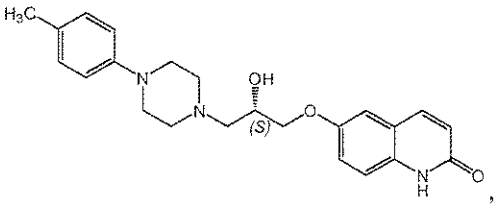


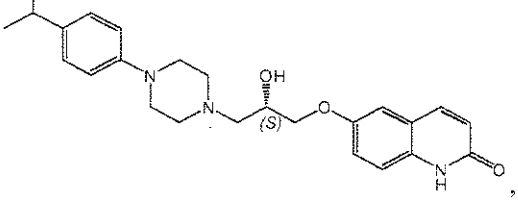


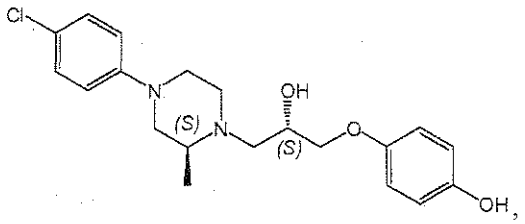


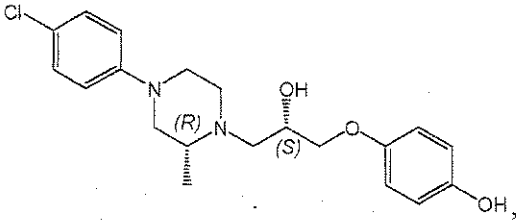

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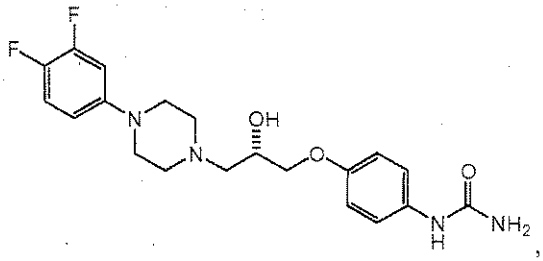

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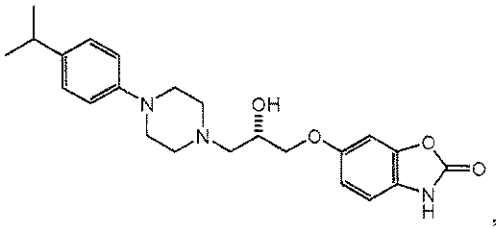

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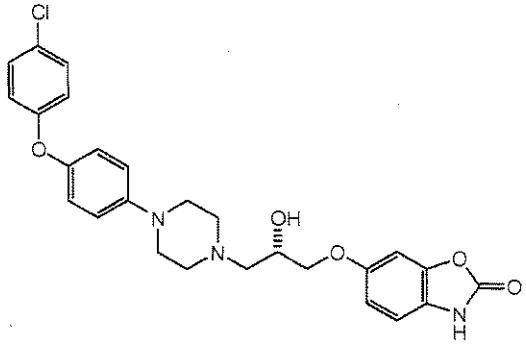

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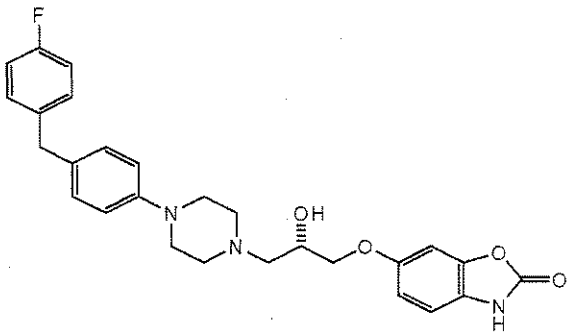


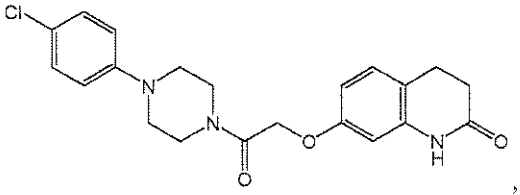


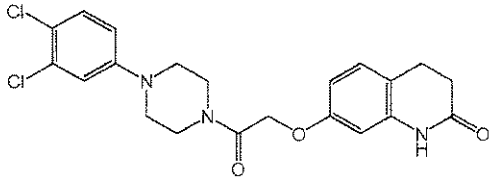


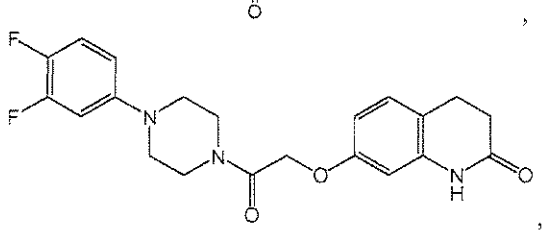


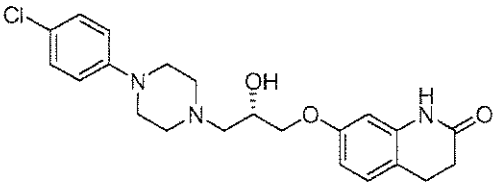


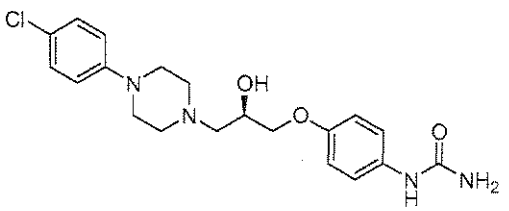


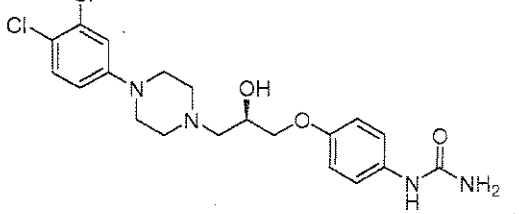


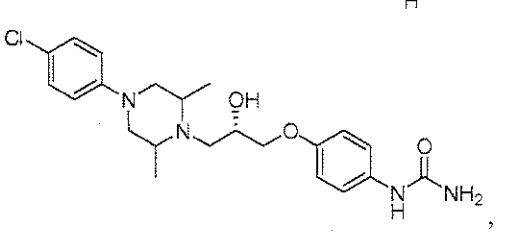


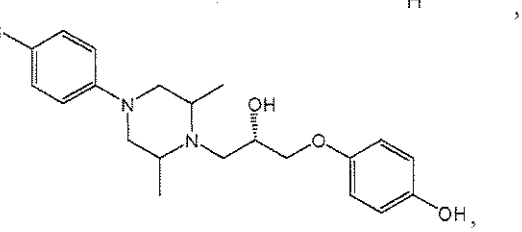


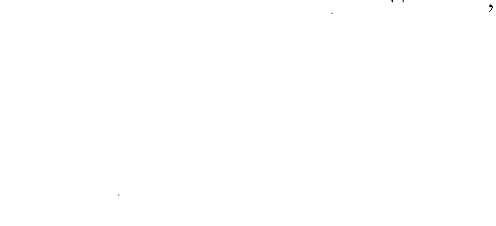




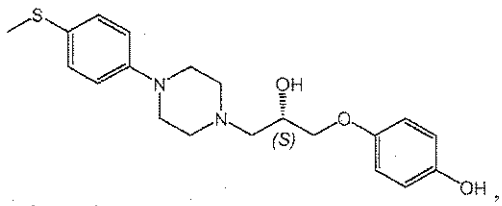


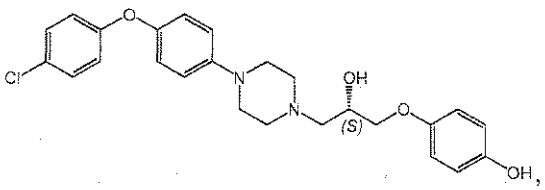


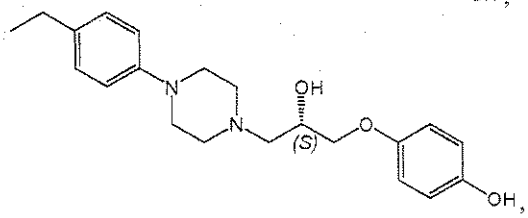


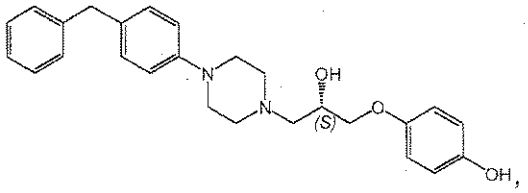


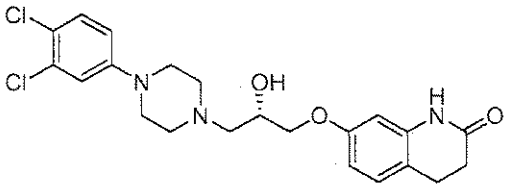


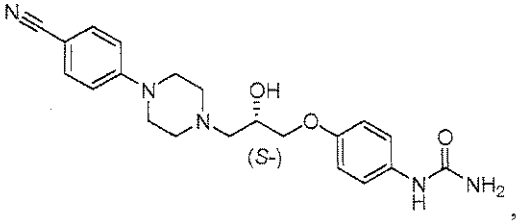


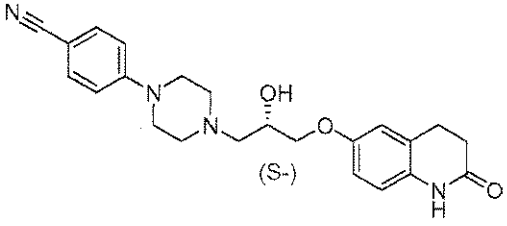


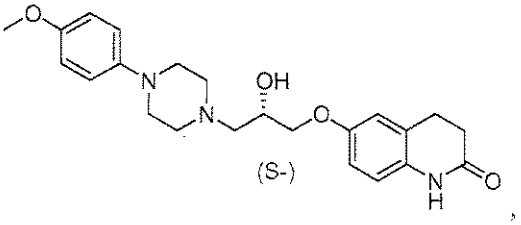


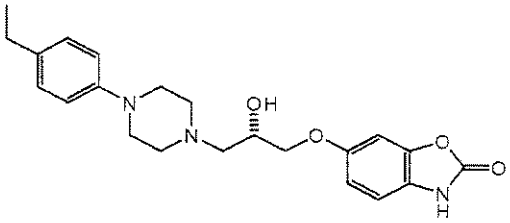


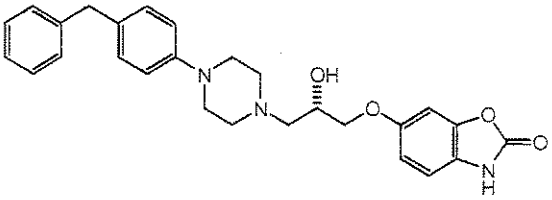


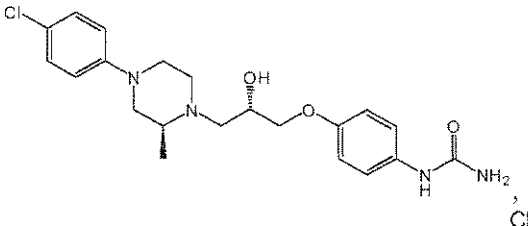


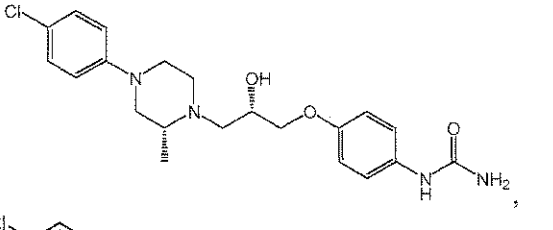


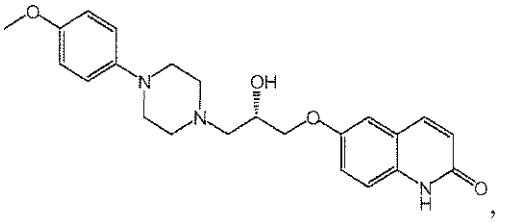


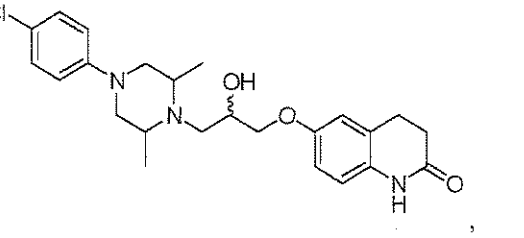






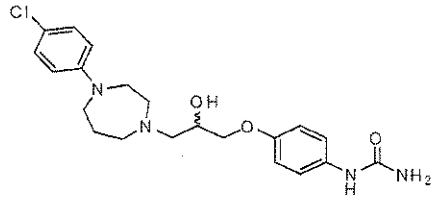
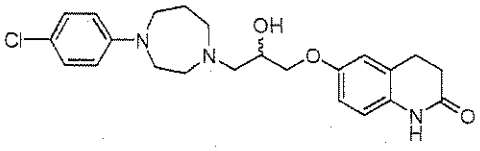
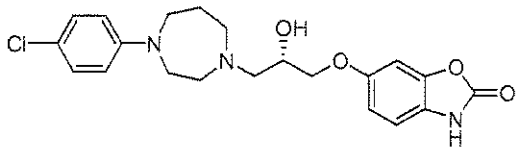
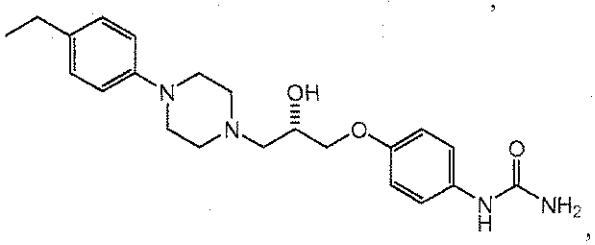
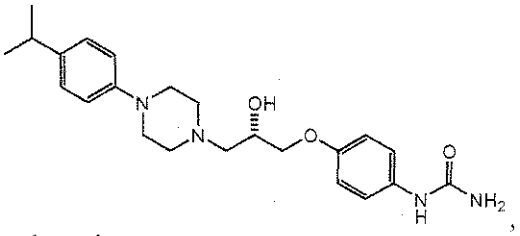
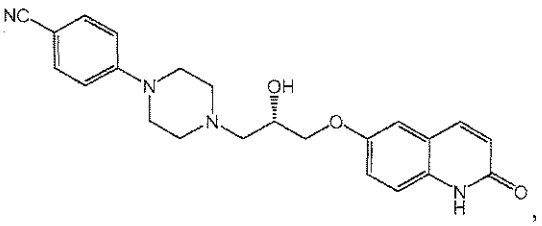
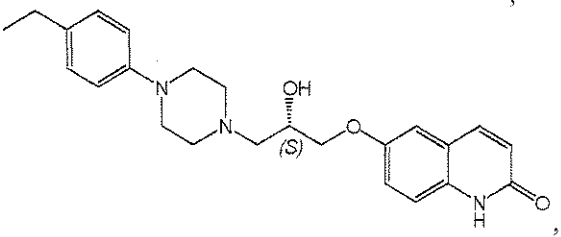
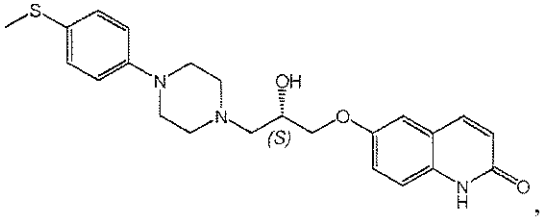
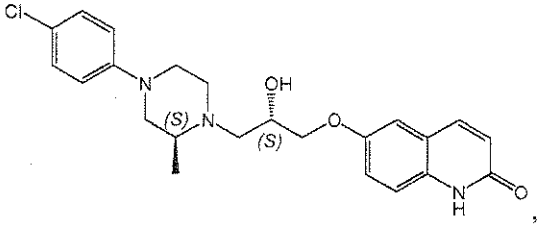
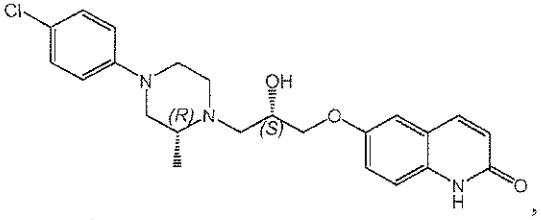
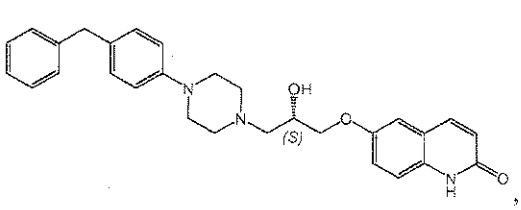




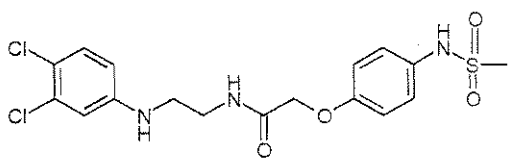
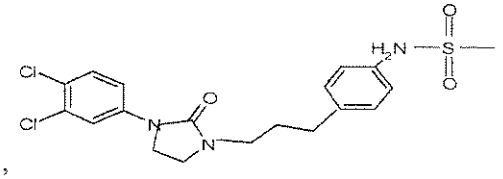


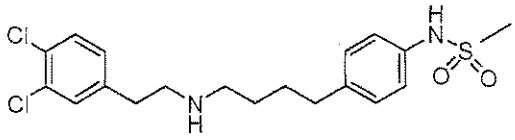
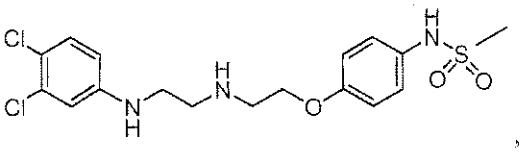
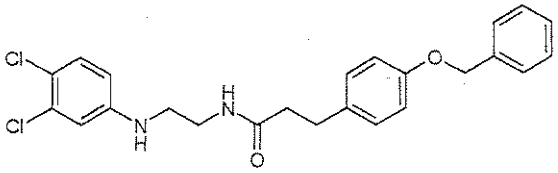
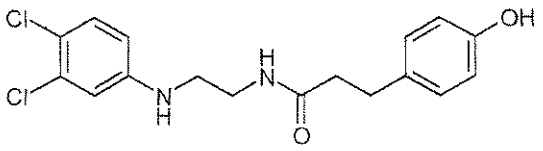
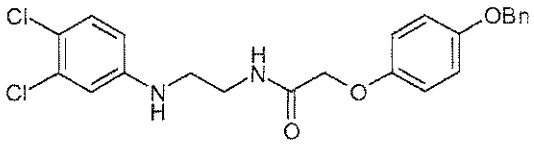
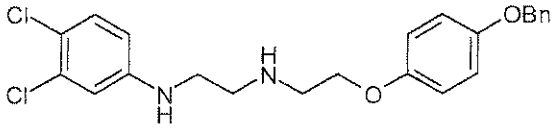
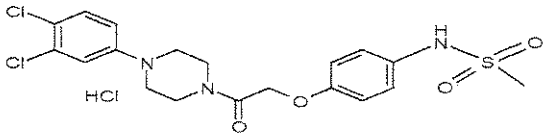
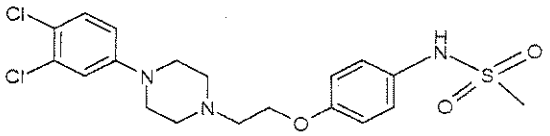
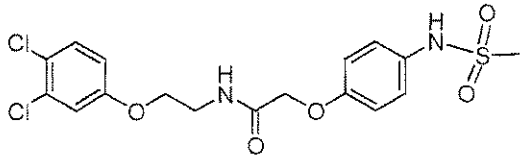
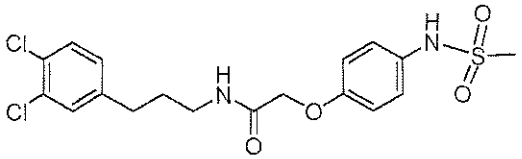
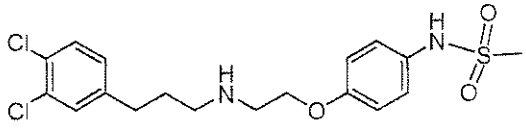
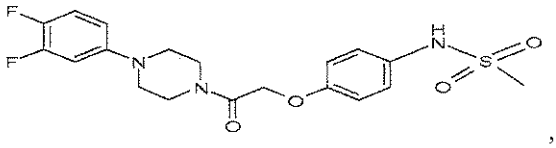


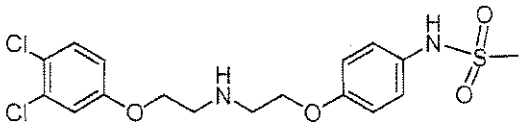


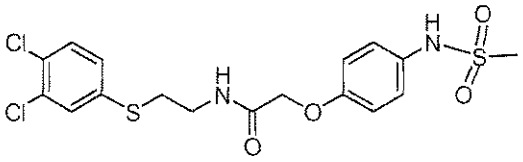

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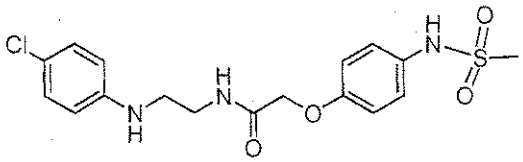
In one embodiment, the compound is selected from the group consisting of:

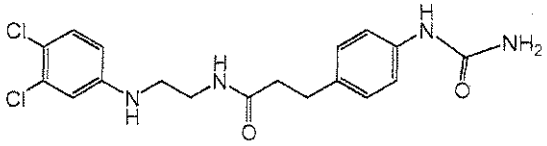

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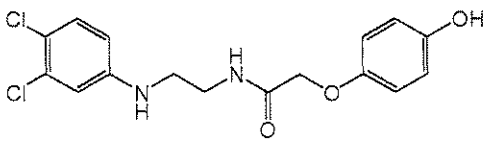

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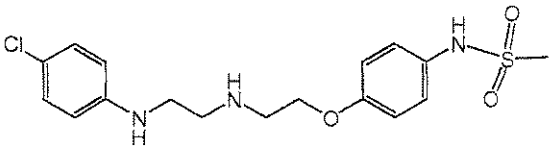


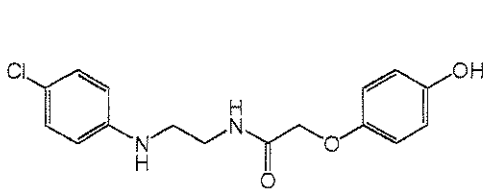


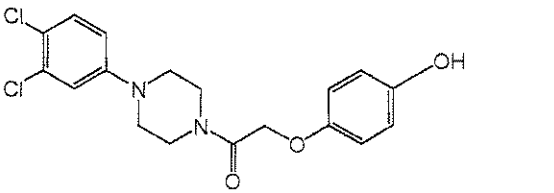


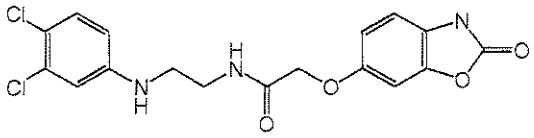


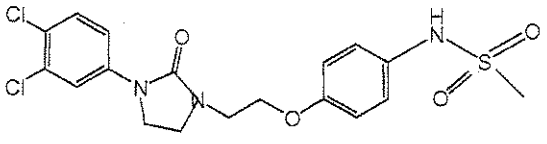


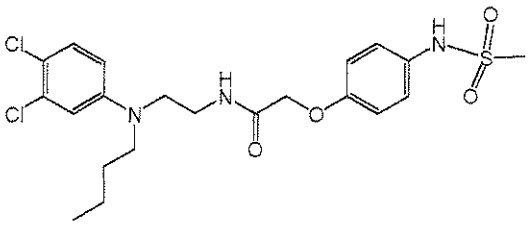


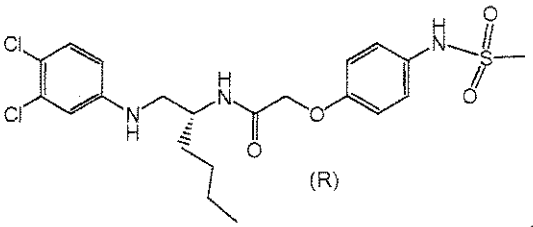




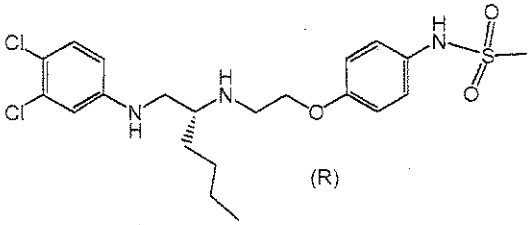






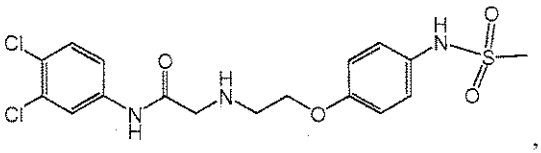


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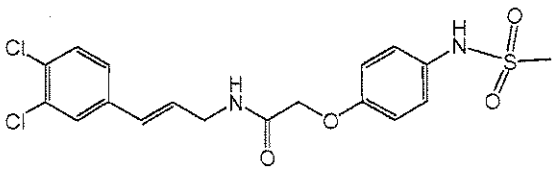


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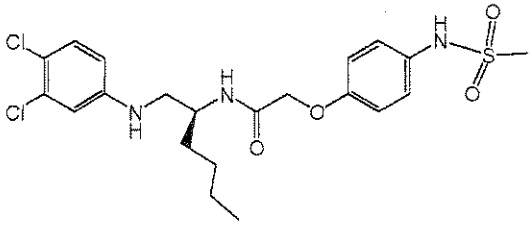
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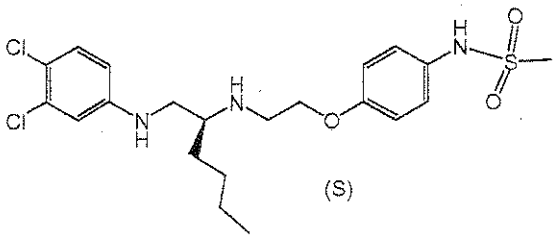
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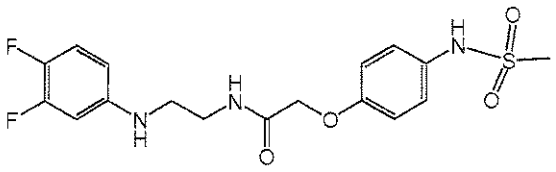


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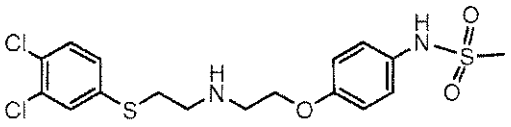


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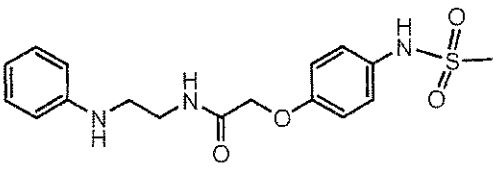
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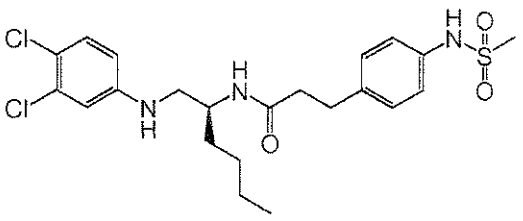
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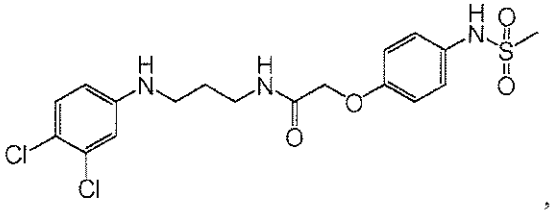
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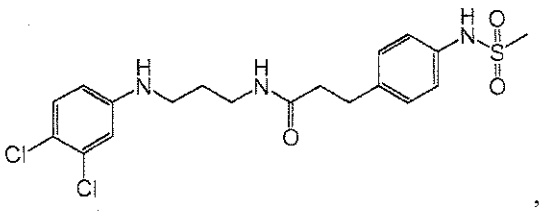
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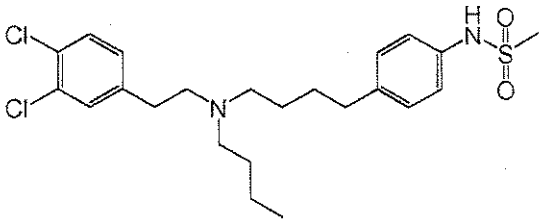


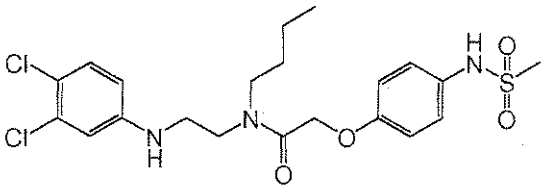
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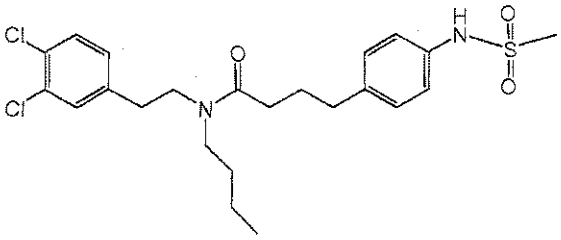


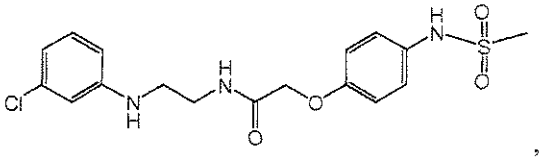
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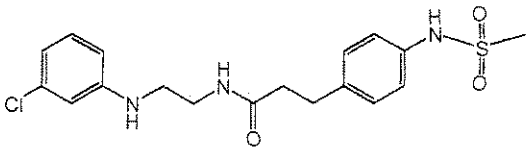


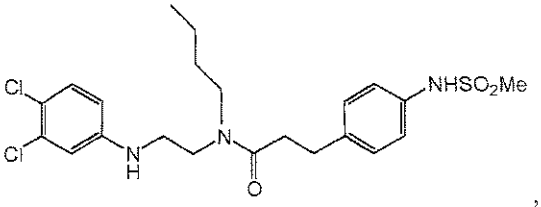


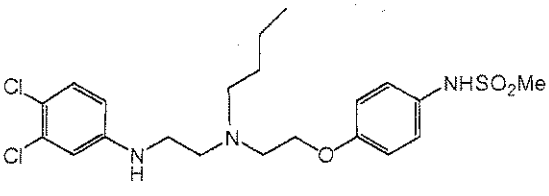


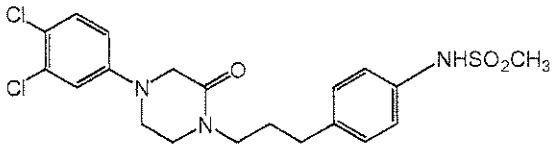




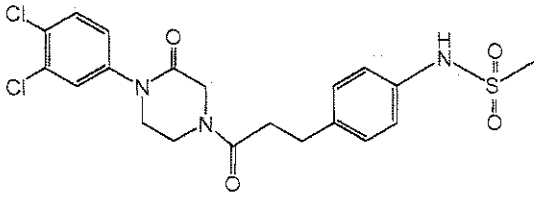




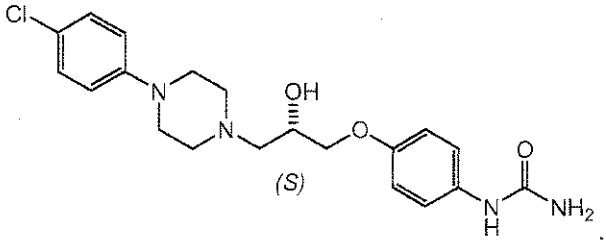




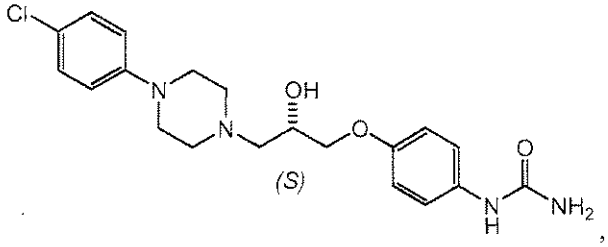
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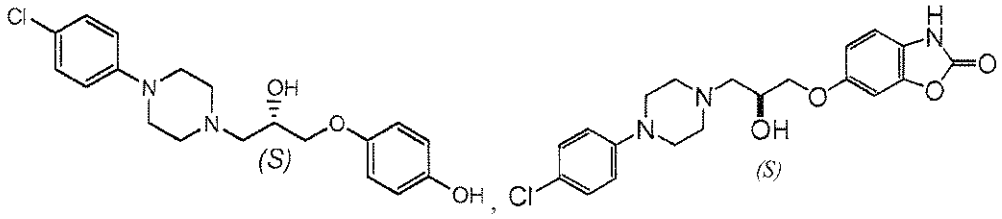
In one embodiment, the compound is



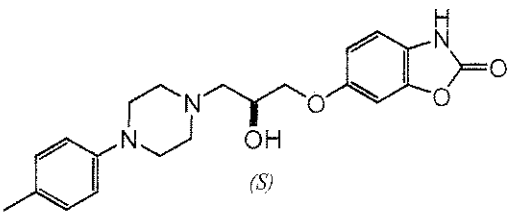
In one embodiment, the compound is selected from the group consisting of:



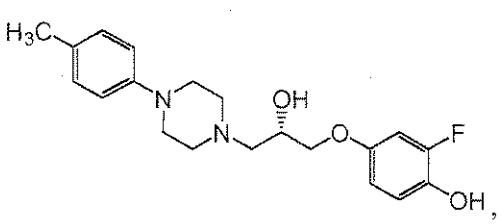
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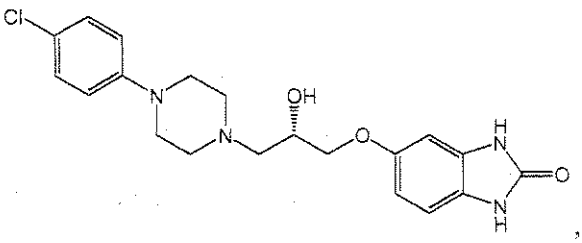
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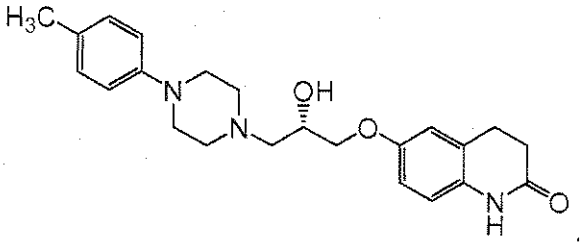
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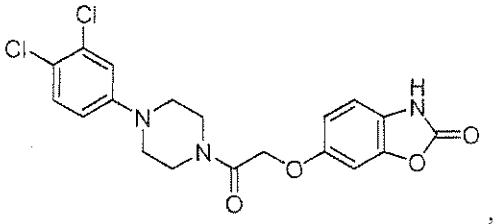
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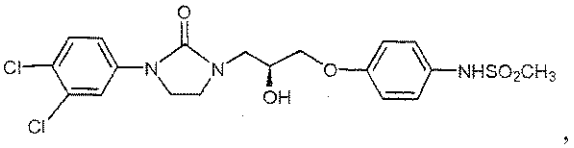
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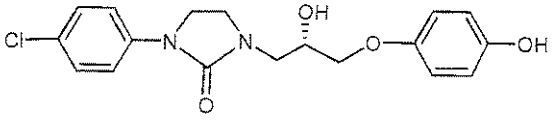
In another embodiment, the compound is selected from the group consisting of:



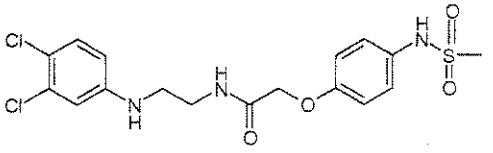
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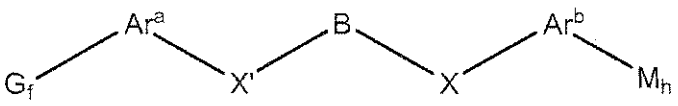


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Formula II

In one embodiment, compounds, pharmaceutical compositions and methods of treatment or prophylaxis of neuropathic pain, stroke, traumatic brain injury, epilepsy, and other neurologic events or neurodegeneration resulting from NMDA receptor activation, comprising administering to a host in need thereof a compound of Formula II, or a pharmaceutically acceptable salt, ester, prodrug or derivative thereof are provided:



FORMULA II

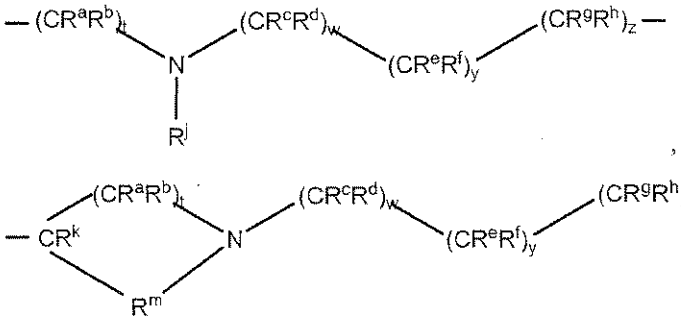
wherein:

each G is independently F, Cl, Br, I, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_6-C_{12} aralkyl, -O-aryl, -S-aryl, -NH-aryl;

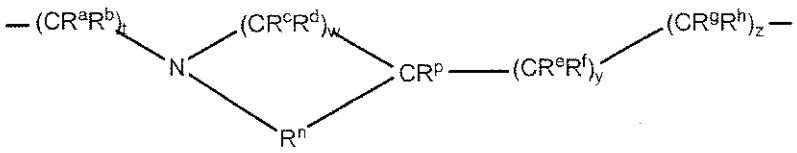
f = 0, 1, 2, 3, 4 or 5;

Ar^a and Ar^b are each independently aryl or heteroaryl;

B is selected from the group consisting of:



, and



;

wherein R^a, R^b, R^c, R^d, R^e, R^f, R^g, R^h, R^k and R^p are each independently selected from H, C_1-C_6 alkyl, C_1-C_6 alkoxy, OH or halo;

R^j is H, C_1-C_6 alkyl, OH or $P(O)(OC_1$-C_4 alkyl$)_2$;

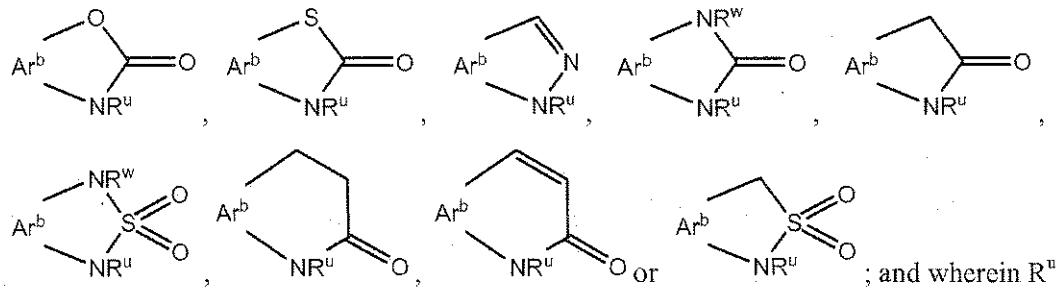
R^m is C_1-C_4 alkyl or C_2-C_4 alkenyl;

R^n is C_1-C_4 alkyl, C_2-C_4 alkenyl, C_6-C_{12} aralkyl, $-CH_2O$-, $-CH(C_1$-C_6 alkyl)O-, $-CH(C_2$-C_{12} aralkyl)O-;

t, w, y and z each = 0, 1, 2, or 3;

X and X' are independently selected from a bond, O, S, SO, SO_2, CH_2, NH, $N(C_1$-C_6 alkyl), and NHC(=O);

M is OH, F, Cl, Br, I, NH_2, NR^qR^r, NO_2, $O(C_1$-C_6 alkyl), OCF_3, CN, C(O)OH, $C(O)O(C_1$-C_6 alkyl), C_6-C_{12} aralkyl, $NR^sC(O)CR^t_3$, or $NR^uC(O)NR^v_2$; wherein each R^q, R^r, R^s, R^u and R^v is each independently H or C_1-C_6 alkyl; and each R^t is independently H, C_1-C_6 alkyl or halo; or two M groups may be taken together with Ar^b to form:



; and wherein R^u and R^w are independently H, C_1-C_6 alkyl or C_6-C_{12} aralkyl; and

h = 1, 2, 3, 4 or 5;

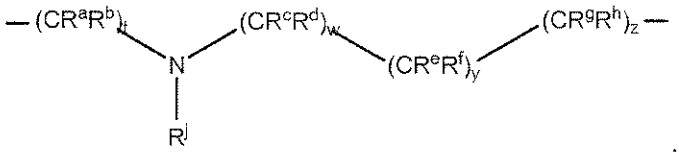
wherein when B contains a piperidin-4-ol or a pyrrolidin-2-ol moiety, and Ar^a and Ar^b are each phenyl, M is not OH at the para position on Ar^b.

In one embodiment, G is F or Cl. In another embodiment, f is 1 or 2.

In one embodiment, Ar^a is phenyl. In another embodiment, Ar^b is phenyl. In another embodiment, Ar^a and Ar^b are each phenyl.

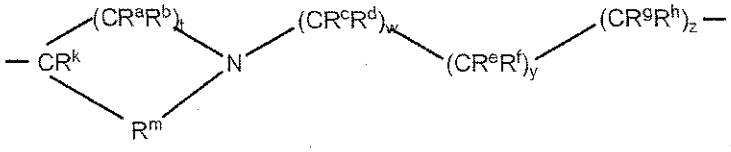
In one embodiment, Ar^a is phenyl and is substituted with two G groups. In a subembodiment, both G groups are Cl. In another subembodiment, both G groups are F. In another subemebodiment, one G group is Cl and the other G group is F. In one embodiment, G is selected from the group consisting of C_6-C_{12} aralkyl, -O-aryl, -S-aryl, and -NH-aryl.

In one embodiment, B is



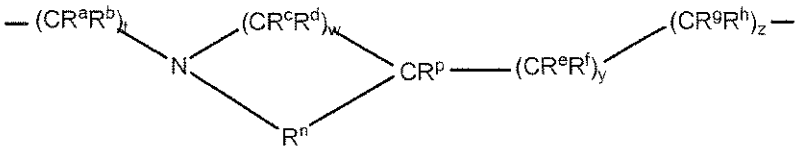
. In a subembodiment, R^a, R^b, R^c, R^d, R^e, R^g and R^h are H; Rj is H, C_1-C_6 alkyl, OH or $P(O)(OC_1$-C_4 alkyl$)_2$; R^f is H, halo or OH; t is 0, 1, 2, or 3; and w, y and z are each 1.

In one embodiment, B is



. In a subembodiment, R^a, R^b, R^c, R^d, R^e, R^g and R^h are H; R^f is H, halo or OH; R^k is H, halo or OH; R^m is C_1-C_4 alkyl; t is 1, 2, or 3; and w, y and z are each 1.

In one embodiment, B is



. In a subembodiment, R^a, R^b, R^c, R^d, R^e, R^g and R^h are H; R^f is H, halo or OH; R^p is H, halo or OH; R^n is -CH_2O-; t is 0, 1, 2, or 3; and w, y and z are each 1.

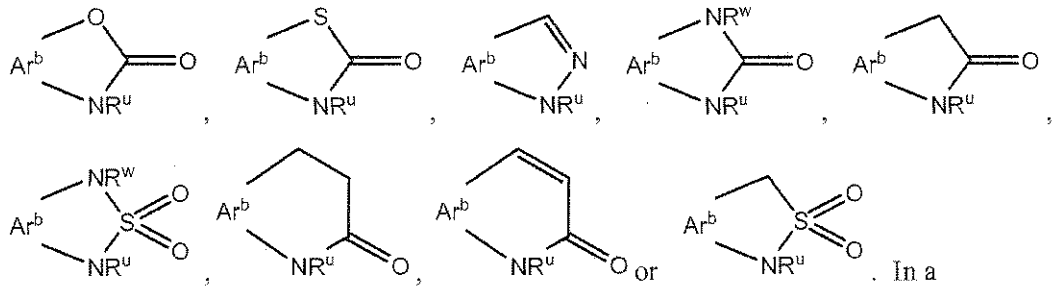
In one embodiment, the sum of w, y and z does not exceed 6. In one embodiment, the sum of w, y and z is 2, 3, 4, 5 or 6.

In one embodiment, X is a bond, O, S or CH_2. In another embodiment, X is O. In another embodiment, X is CH_2.

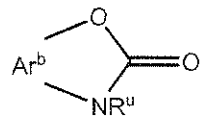
In one embodiment, X' is a bond, NH, S or CH_2. In another embodiment, X' is a bond. In another embodiment, X' is S. In another embodiment, X' is NH. In another embodiment, X' is CH_2.

In one embodiment, M is OH. In another embodiment, M is F or Cl. In another embodiment, M is O(C_1-C_6 alkyl), for example OCH_3, OCH_2CH_3, $O(CH_2)_2CH_3$, $OCH(CH_3)_2$ or $OC(CH_3)_3$. In another embodiment, M is NH_2. In another embodiment, M is NR^qR^r. In another embodiment, M is NO_2. In another embodiment, M is OCF_3. In one embodiment, M is CN. In one embodiment, M is C(O)OH. In one embodiment, M is C(O)O(C_1-C_6 alkyl), for example $C(O)OCH_3$, $C(O)OCH_2CH_3$, $C(O)O(CH_2)_2CH_3$, $C(O)OCH(CH_3)_2$ or $C(O)OC(CH_3)_3$. In one embodiment, M is C_6-C_{12} aralkyl, for example CH_2-phenyl. In one embodiment, M is $NR^sC(O)CR^t_3$. In a subembodiment, R^s is H. In a subembodiment, R^t is H or Cl. In one embodiment, M is $NR^uC(O)NR^v_2$, for example, $NHC(O)NH_2$. In a subembodiment, R^u is H and R^v is H or alkyl.

In one embodiment, two M groups may be taken together with Ar^b to form:



. In a subembodiment, two M groups may be taken together with Ar^b to form:



. In one embodiment, R^u and R^w are both H. In one embodiment, h is 1 or 2.

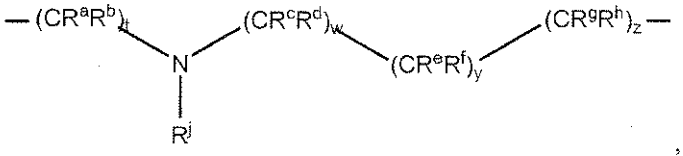
In one embodiment, the compound is a compound of Formula II, or a pharmaceutically acceptable salt, ester, prodrug or derivative thereof, wherein:

each G is independently F, Cl, Br or I;

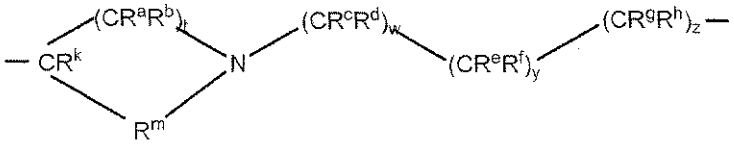
f is 0, 1, 2, 3, 4, or 5;

Ar^a and Ar^b are each independently selected from the group consisting of phenyl, pyridyl, pyrimidinyl, thiophenyl, imidazolyl, furanyl, indolyl, benzothiophenyl, benzofuranyl, benzoimidazolyl;

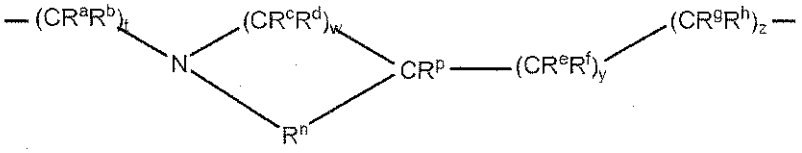
B is selected from the group consisting of:



,



, and



;

wherein R^a, R^b, R^c, R^d, R^e, R^f, R^g, R^h, R^k and R^p are each independently selected from H, C_1-C_6 alkyl, OH, or halo;

R^j is H, C_1-C_6 alkyl, C_7-C_{12} aralkyl, or OH;

R^m is C_1-C_4 alkyl or C_2-C_4 alkenyl;

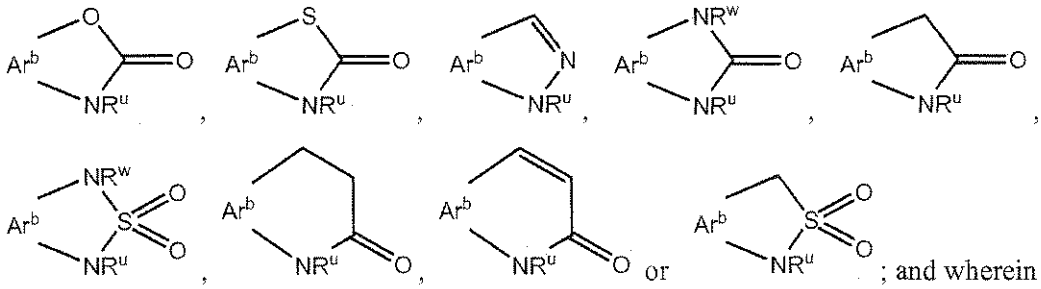
R^n is C_1-C_4 alkyl, C_2-C_4 alkenyl, C_6-C_{12} aralkyl, -CH_2O-, -CH(C_1-C_6 alkyl)O-, -CH(C_2-C_{12} aralkyl)O-;

t, w, y and z each = 0, 1, 2, or 3;

X is a bond, CH_2 or O;

X' is a bond, CH_2, S or NH;

M is OH, F, Cl, Br, I, NH_2, NR^qR^r, NO_2, $O(C_1\text{-}C_6$ alkyl), OCF_3, CN, C(O)OH, $C(O)O(C_1\text{-}C_6$ alkyl), $C_6\text{-}C_{12}$ aralkyl, $NR^sC(O)CR^t_3$, or $NR^uC(O)NR^v_2$; wherein each R^q, R^r, R^s, R^u and R^v is each independently H or $C_1\text{-}C_6$ alkyl; and each R^t is independently H, $C_1\text{-}C_6$ alkyl or halo; or two M groups may be taken together with Ar^b to form:



; and wherein R^u and R^w are independently H or $C_1\text{-}C_4$ alkyl; and

h = 1, 2 or 3.

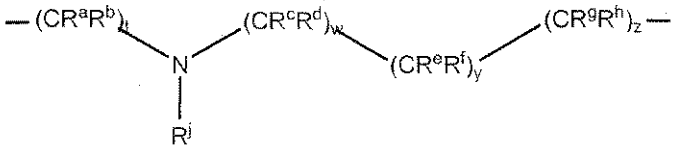
In one embodiment, the compound is a compound of Formula II, or a pharmaceutically acceptable salt, ester, prodrug or derivative thereof, wherein:

each G is independently F, Cl, Br or I;

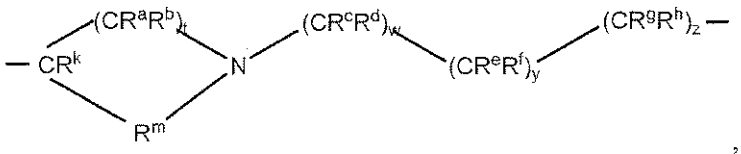
f = 0, 1, 2, 3, 4 or 5;

Ar^a and Ar^b are each phenyl;

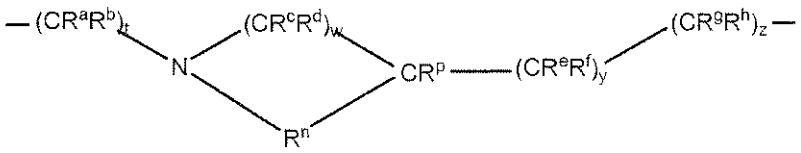
B is selected from the group consisting of:



,



, and



;

wherein R^a, R^b, R^c, R^d, R^e, R^f, R^g, R^h, R^k and R^p are each independently selected from H, $C_1\text{-}C_6$ alkyl, OH, or halo;

R^j is H, $C_1\text{-}C_6$ alkyl, or OH;

R^m is $C_1\text{-}C_4$ alkyl or $C_2\text{-}C_4$ alkenyl;

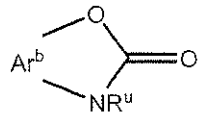
R^n is C_1-C_4 alkyl, C_2-C_4 alkenyl, C_6-C_{12} aralkyl, -CH_2O-, -CH(C_1-C_6 alkyl)O-, -CH(C_2-C_{12} aralkyl)O-;

t, w, y and z each = 0, 1, 2, or 3;

X is a bond, CH_2 or O;

X' is a bond, CH_2, S or NH;

M is OH, F, Cl, Br, I, NH_2, NR^qR^r, NO_2, O(C_1-C_6 alkyl), OCF_3, CN, C(O)OH, C(O)O(C_1-C_6 alkyl), C_6-C_{12} aralkyl, $NR^sC(O)CR^t_3$; wherein each R^q, R^r, and R^s is each independently H or C_1-C_6 alkyl; and each R^t is independently H, C_1-C_6 alkyl or halo; or two M groups may be taken together with Ar^b to form:

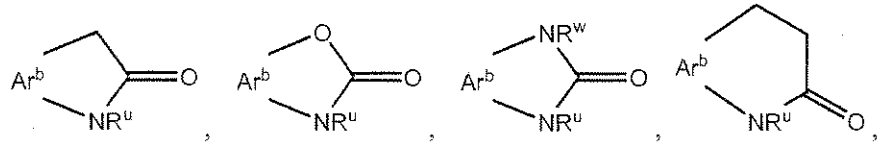


; and wherein R^u is H or C_1-C_4 alkyl; and

h = 1, 2 or 3.

In one embodiment, M is $NR^uC(O)NR^v_2$, for example $NHC(O)NH_2$ or $NHC(O)N(CH_3)_2$.

In another embodiment, Ar^b-M is selected from the group consisting of:

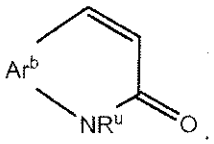


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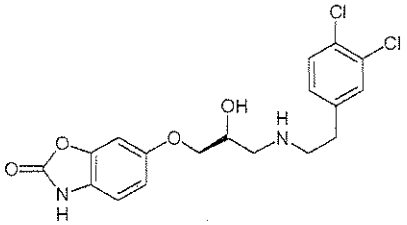
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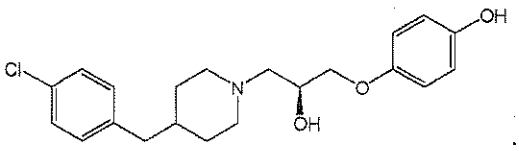
and .

In one embodiment, the compound is



or 6-{3-[2-(3,4-Dichloro-phenyl)-ethylamino]-2-(*S*)-hydroxy-propoxy}-3H-benzooxazol-2-one.

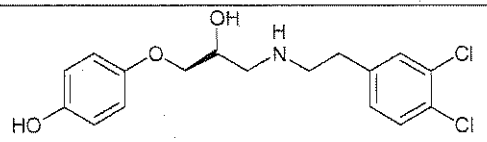
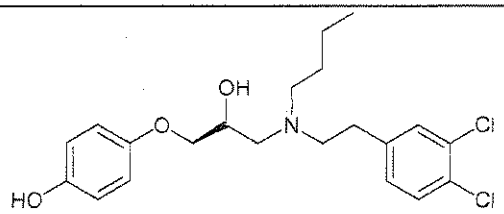
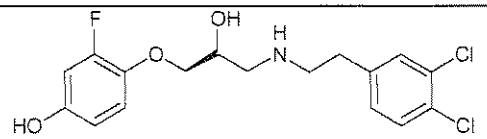
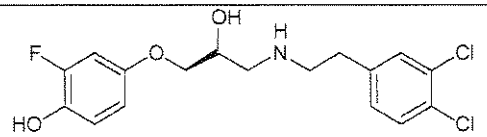
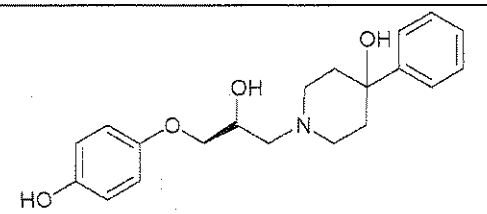
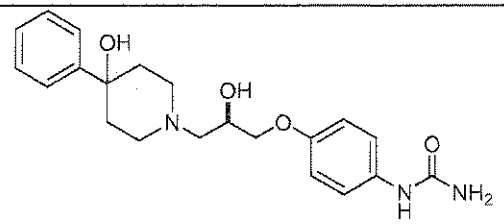
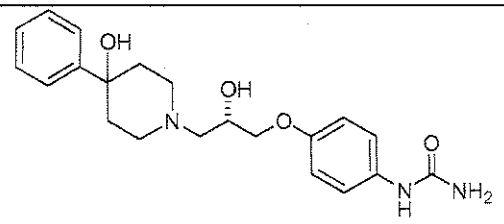
In one embodiment, the compound is

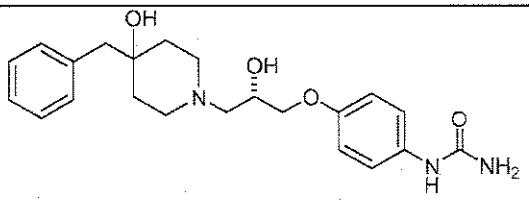
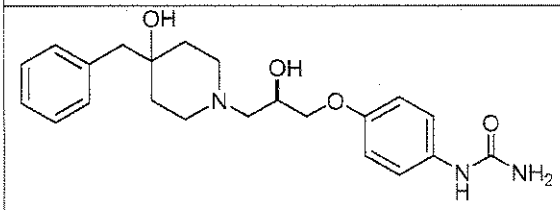
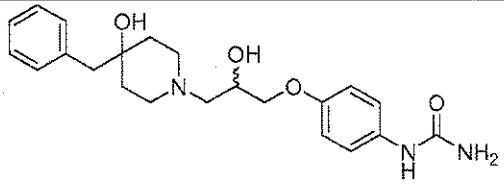
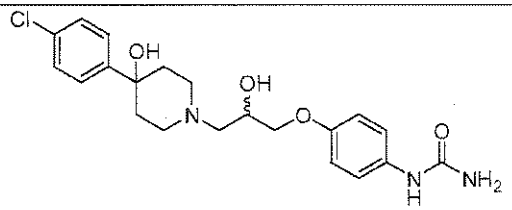
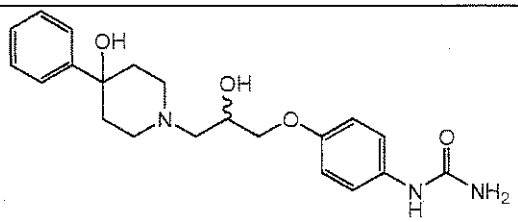
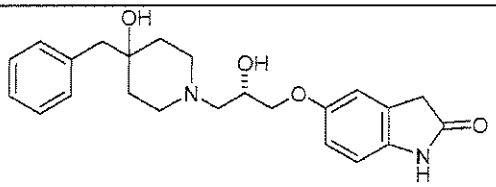
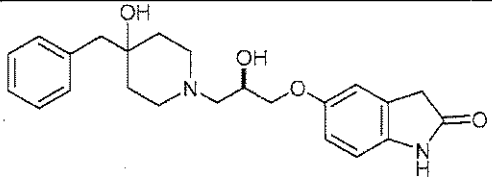


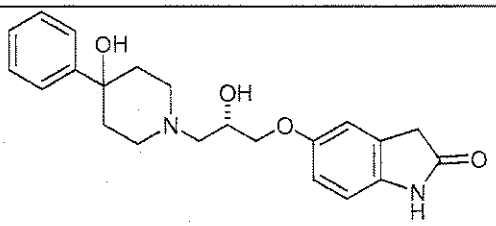
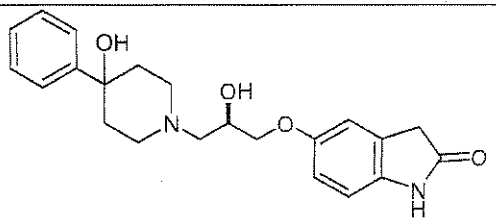
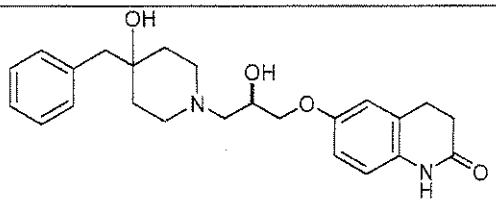
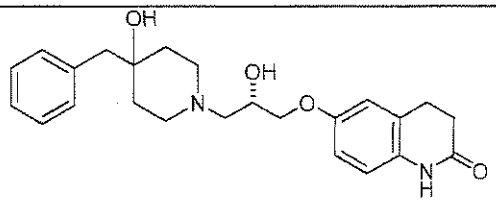
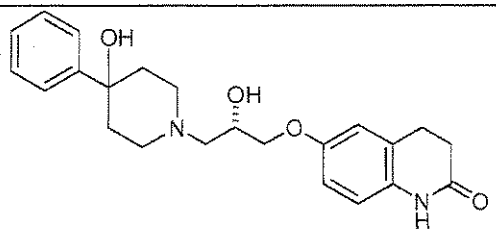
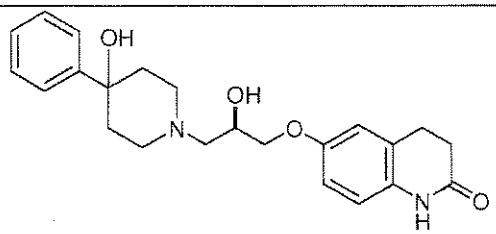
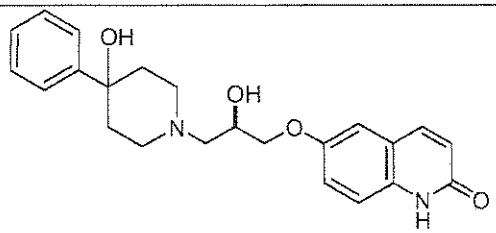
.

In one embodiment, the compound is selected from the compounds in Table 14.

Table 14.

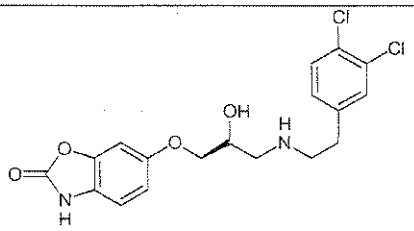
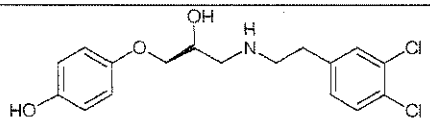
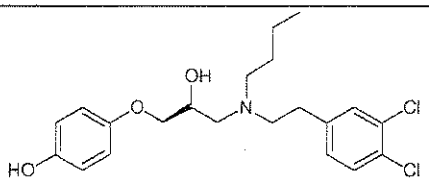
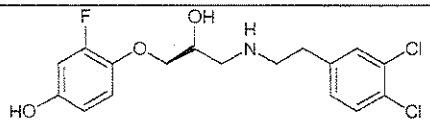
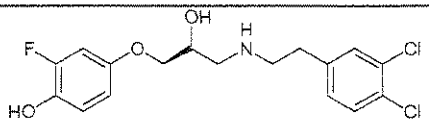
Compound	NAME
	4-{3-[2-(3,4-Dichloro-phenyl)-ethylamino]-2-(*S*)-hydroxy-propoxy}-phenol
	4-(3-{Butyl-[2-(3,4-dichloro-phenyl)-ethyl]-amino}-2-(*S*)-hydroxy-propoxy)-phenol
	4-{3-[2-(3,4-Dichloro-phenyl)-ethylamino]-2-(*S*)-hydroxy-propoxy}-3-fluoro-phenol
	4-{3-[2-(3,4-Dichloro-phenyl)-ethylamino]-2-(*S*)-hydroxy-propoxy}-2-fluoro-phenol
	1-[2-(*S*)-Hydroxy-3-(4-hydroxy-phenoxy)-propyl]-4-phenyl-piperidin-4-ol
	(*R*)-1-(4-(2-hydroxy-3-(4-hydroxy-4-phenylpiperidin-1-yl)propoxy)phenyl)urea
	(*S*)-1-(4-(2-hydroxy-3-(4-hydroxy-4-phenylpiperidin-1-yl)propoxy)phenyl)urea

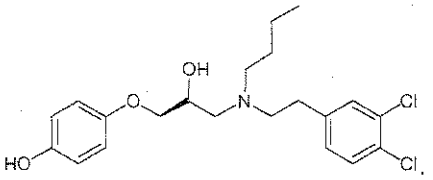
	(*S*)-1-(4-(3-(4-benzyl-4-hydroxypiperidin-1-yl)-2-hydroxypropoxy)phenyl)urea
	(*R*)-1-(4-(3-(4-benzyl-4-hydroxypiperidin-1-yl)-2-hydroxypropoxy)phenyl)urea
	1-(4-(3-(4-benzyl-4-hydroxypiperidin-1-yl)-2-hydroxypropoxy)phenyl)urea
	1-(4-(3-(4-(4-chlorobenzyl)-4-hydroxypiperidin-1-yl)-2-hydroxypropoxy)phenyl)urea
	1-(4-(2-hydroxy-3-(4-hydroxy-4-phenylpiperidin-1-yl)propoxy)phenyl)urea
	(*S*)-5-(3-(4-benzyl-4-hydroxypiperidin-1-yl)-2-hydroxypropoxy)indolin-2-one
	(*R*)-5-(3-(4-benzyl-4-hydroxypiperidin-1-yl)-2-hydroxypropoxy)indolin-2-one

	(*S*)-5-(2-hydroxy-3-(4-hydroxy-4-phenylpiperidin-1-yl)propoxy)indolin-2-one
	(*R*)-5-(2-hydroxy-3-(4-hydroxy-4-phenylpiperidin-1-yl)propoxy)indolin-2-one
	(*R*)-6-(3-(4-benzyl-4-hydroxypiperidin-1-yl)-2-hydroxypropoxy)-3,4-dihydroquinolin-2(1H)-one
	(*S*)-6-(3-(4-benzyl-4-hydroxypiperidin-1-yl)-2-hydroxypropoxy)-3,4-dihydroquinolin-2(1H)-one
	(*S*)-6-(2-hydroxy-3-(4-hydroxy-4-phenylpiperidin-1-yl)propoxy)-3,4-dihydroquinolin-2(1H)-one
	(*R*)-6-(2-hydroxy-3-(4-hydroxy-4-phenylpiperidin-1-yl)propoxy)-3,4-dihydroquinolin-2(1H)-one
	(*R*)-6-(2-hydroxy-3-(4-hydroxy-4-phenylpiperidin-1-yl)propoxy)quinolin-2(1H)-one

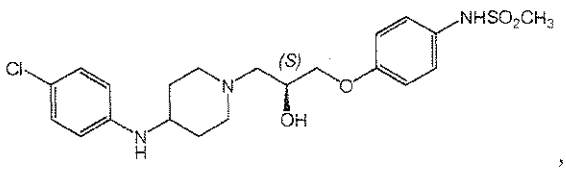
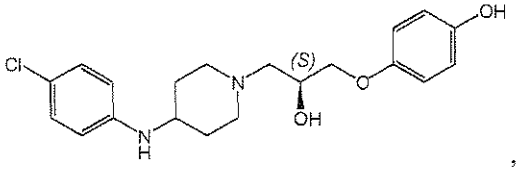
In one embodiment, the compound has an IC_{50} value of 600 nM or less. In one embodiment, the compound has an IC_{50} value of 600 nM or less at pH 6.9 or an ischemic pH. In one embodiment, the compound is selected from Table 15.

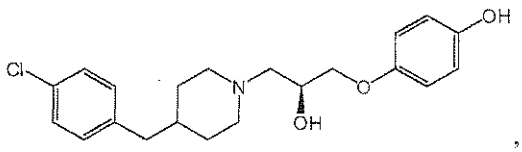
Table 15.

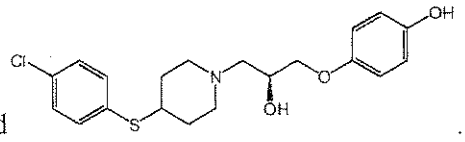
	
	
	

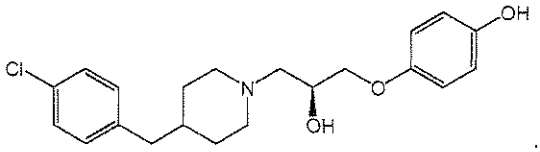
In one embodiment, the compound has a pH boost of 5 or more. In one embodiment, the compound is .

In one embodiment, the compound is selected from the group consisting of:

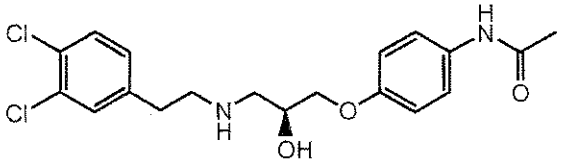
, ,

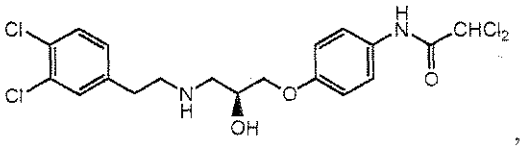
,

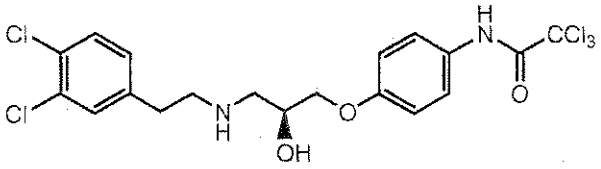
and 

In one embodiment, the compound is .

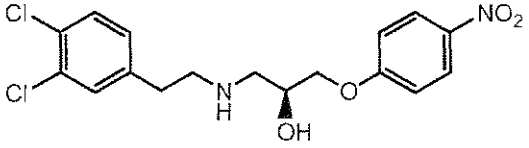
In another embodiment, the compound is selected from the group consisting of:

,

, and

.

In another embodiment the compound is

.

In one embodiment, one or more of R^c, R^d, R^e, R^f, R^g, and R^h is an OH group which creates a stereogenic center. In a particular subembodiment, one of R^c, R^d, R^e, R^f, R^g, and R^h is an OH group which creates a stereogenic center. In another subembodiment, the OH group at one of R^c, R^d, R^e, R^f, R^g, and R^h is in the R configuration. In another subembodiment, the OH group at one of R^c, R^d, R^e, R^f, R^g, and R^h is in the S configuration.

In certain embodiments, the binding to both hERG and alpha-1 adrenergic receptors can be modulated by changing the G substituent or G substituents. In particular, for compounds wherein Ar^a is phenyl, the binding to both hERG and alpha-1 adrenergic

receptors can be modulated by changing the substitution at the 3 and/or 4 positions. In one embodiment, the Ar^a phenyl is substituted at the 3 and/or 4 position with, for example, fluorine or chlorine. In certain embodiments, substitution at the 3 and/or 4 postions of the Ar^a phenyl can increase potency.

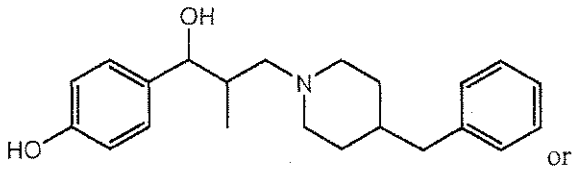
In certain embodiments, both hERG and alpha-1 adrenergic binding can be reduced by substituting N at the R^j position with C_7-C_{12} aralkyl. In a particular subembodiment, R^j is benzyl.

In certain embodiments, alpha-1 adrenergic binding is reduced when R^j is C_1-C_6 alkyl.

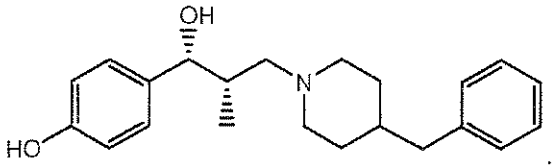
When Ar^b is phenyl, *para* substitution of the M substituent is particularly preferred. Additional M substitutents on the Ar^b phenyl are preferred at one or more *ortho* positions. Additional substitution on the Ar^b phenyl at one or more *meta* positions can reduce potency.

In certain embodiments, the Ar^a phenyl is not substituted by two fluoro groups. In one embodiment, the Ar^a phenyl is not substituted by two methyl groups. In one embodiment, the Ar^a phenyl is not substituted by one halo group. In one embodiment, the Ar^a phenyl is not substituted by one fluoro or alkyl group at the C-2 position. In one embodiment, the Ar^a phenyl is not substituted by a OH or NO_2 group.

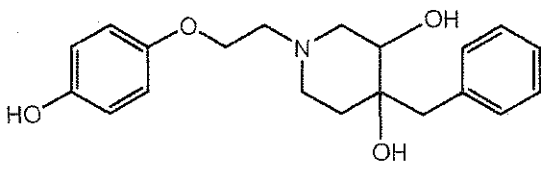
In one embodiment, when Ar^a and Ar^b are both phenyl, at least one of f or h is not 0. In one embodiment, when Ar^a and Ar^b are both phenyl, f is not 0. In one embodiment, when Ar^a and Ar^b are both phenyl, h is not 0. In one embodiment, when Ar^a and Ar^b are both phenyl, X is not CH_2. In one embodiment, when Ar^a and Ar^b are both phenyl, X' is not CH_2. In another embodiment, M is not OH. In one embodiment, the compound is not



or



In one embodiment, M is not aralkoxy. In one embodiment, the compound is not



In one embodiment, B does not contain a piperidinyl moiety. In another embodiment, when B contains a piperidinyl moiety, and Ar^a and Ar^b are both phenyl, M is not OH. In one embodiment, when B contains a piperidinyl moiety, M is $NR^uC(O)NR^v{}_2$, for example, $NHC(O)NH_2$. In a subembodiment, R^u is H and R^v is H or alkyl. In one embodiment, when B contains a piperidinyl moiety, X is not CH_2. In one embodiment, when B contains a piperidinyl moiety, X' is not CH_2. In one embodiment, R^k is not OH. In one embodiment, R^p is not OH.

In one embodiment, when B contains a hydroxy-substituted-piperidinyl moiety, X is not CH_2. In one embodiment, when B contains a hydroxy-substituted-piperidinyl moiety, X' is not CH_2. In one embodiment, B does not contain a hydroxy-substituted-piperidinyl moiety.

In one embodiment, X is not SO_2. In another embodiment, X' is not SO_2. In one embodiment, when B contains a piperidinyl moiety, X is not SO_2. In one embodiment, when B contains a piperidinyl moiety, X' is not SO_2.

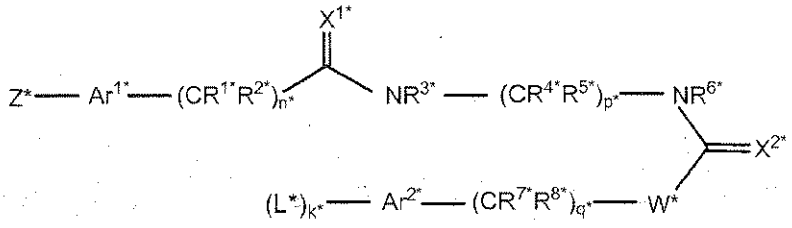
In one embodiment, X is not S. In another embodiment, X' is not S. In one embodiment, when B contains a piperidinyl moiety, X is not S. In one embodiment, when B contains a piperidinyl moiety, X' is not S.

In another embodiment, M is not OCH_3 or OCF_3. In another embodiment, M is not NO_2. In one embodiment, when B contains a nitrogen-containing heterocycle, Ar^b-X is not heteroaryl-NH. In another embodiment, when B contains a nitrogen-containing heterocycle, Ar^a-X' is not heteroaryl-NH.

In one embodiment, when B contains a nitrogen-containing heterocycle, X is not NH(C=O). In another embodiment, when B contains a nitrogen-containing heterocycle, X' is not NH(C=O).

Formula III

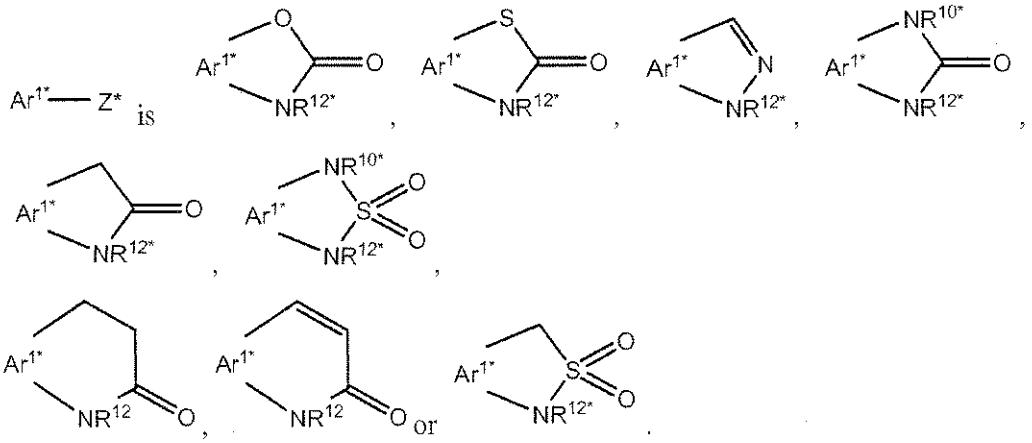
In one embodiment, compounds, pharmaceutical compositions and methods of treatment or prophylaxis of neuropathic pain, stroke, traumatic brain injury, epilepsy, and other neurologic events or neurodegeneration resulting from NMDA receptor activation, comprising administering to a host in need thereof a compound of Formula III, or a pharmaceutically acceptable salt, ester, prodrug or derivative thereof are provided:



FORMULA III

wherein:

Z* is OH, $NR^{10*}R^{11*}$, $NR^{12*}SO_2R^{11*}$, $NR^{12*}C(O)NR^{10*}R^{11*}$, $NR^{12*}C(O)OR^{10*}$, NR^{12*}-dihydrothiazole, or NR^{12*}-dihydroimidazole; wherein each R^{10*}, R^{11*} and R^{12*} is independently H, C_1-C_6 alkyl or C_6-C_{12} aralkyl; or

Ar^{1*}—Z* is 

Ar^{1*} and Ar^{2*} are each independently aryl or heteroaryl;

R^{1*}, R^{2*}, R^{4*}, R^{5*}, R^{7*}, R^{8*} are independently H, OH or C_1-C_4 alkyl;

n^* = 1, 2, 3 or 4;

p^* = 0, 1, 2 or 3;

q^* = 0. 1 or 2;

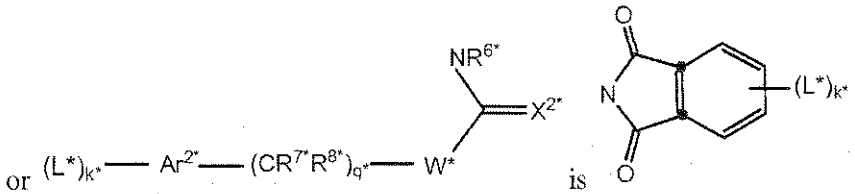
R^{3*} and R^{6*} are each independently H or C_1-C_4 alkyl;

X^{1*} and X^{2*} are each independently O, S, N(C_1-C_4 alkyl) or C(H or C_1-C_4 alkyl)$_2$;

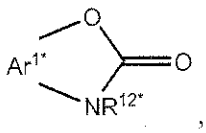
W* is NR^{9*} or $CR^{13*}R^{14*}$; wherein R^{9*}, R^{13*} and R^{14*} are each independently is H or C_1-C_4 alkyl;

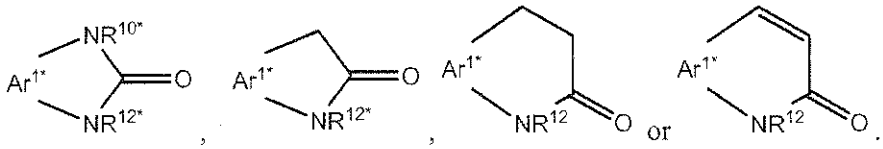
each L^* is independently C_1-C_6 alkyl, C_1-C_6 alkoxy, C(=O)-(C_1-C_6)-alkyl, C_1-C_6 haloalkyl, hydroxy, fluoro, chloro, bromo, iodo, nitro, or cyano; or two L groups may be taken together with Ar^{2*} to form a dioxolane ring or a cyclobutane ring;

k^* = 0, 1, 2, 3, 4 or 5;



In one embodiment, Z^* is OH, $NR^{12*}SO_2R^{11*}$; wherein R^{12*} is H or C_1-C_4 alkyl, and R^{11*} is C_1-C_4 alkyl or C_7-C_{10} aralkyl. In one embodiment, Z^* is OH. In another embodiment, Z^* is $NR^{12*}SO_2R^{11*}$, for example, $NHSO_2CH_3$.

In one embodiment, Z* is $NR^{12*}C(O)NR^{10*}R^{11*}$ or Ar^{1*}—Z^* is ,



In one embodiment, Ar^{1*} and Ar^{2*} are each phenyl.

In one embodiment, R^{1*}, R^{2*}, R^{4*}, R^{5*}, R^{7*}, R^{8*} are H.

In a particular embodiment, n^* is 2.

In one embodiment, p^* is 0, 1 or 2. In another embodiment, p^* is 0. In another embodiment, p^* is 1. In another embodiment, p^* is 2.

In one embodiment, q^* is 0. In another embodiment, q^* is 1. In another embodiment, q^* is 2.

In one embodiment, R^{3*} and R^{6*} are both H. In one embodiment, R^{6*} is C_1-C_4 alkyl, for example methyl, ethyl, propyl, isopropyl, *n*-butyl, *sec*-butyl, or *tert*-butyl.

In one embodiment, X^* is S. In one embodiment, X^* is O.

In one embodiment, W^* is NR^{7*}, for example NH. In another embodiment, W^* is $CR^{13*}R^{14*}$, for example CH_2.

In one embodiment, each L^* is independently selected from C_1-C_4 alkyl, F, Cl, Br, I, or C_1-C_4 haloalkyl, for example, Cl, CH_3 or CF_3. In one embodiment, k^* is 1. In another embodiment, k^* is 2.

In one embodiment, the compound is a compound of Formula III, or a pharmaceutically acceptable salt, ester, prodrug or derivative thereof, wherein:

Z^* is OH, $NHSO_2CH_3$;

Ar^{1*} is phenyl;

R^{1*}, R^{2*}, R^{4*}, R^{5*} are independently H or C_1-C_4 alkyl;

$n^* = 2$;

$p^* = 0$, 1 or 2;

$q^* = 0$, 1 or 2;

R^{3*} and R^{6*} are each independently H or C_1-C_4 alkyl;

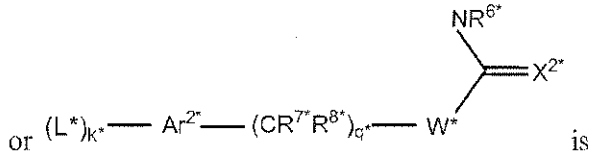
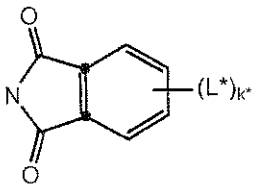
X^* is O or S;

W^* is NR^{7*} or $CR^{13*}R^{14*}$; wherein R^{7*}, R^{13*} and R^{14*} are each independently is H or C_1-C_4 alkyl;

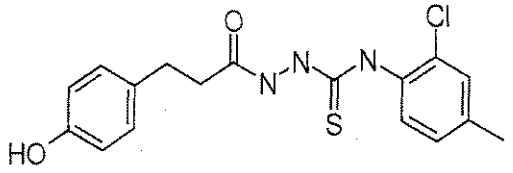
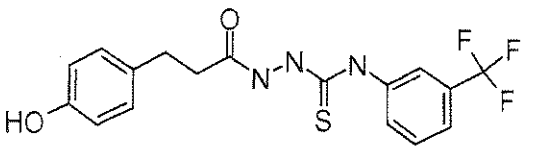
Ar^{2*} is phenyl;

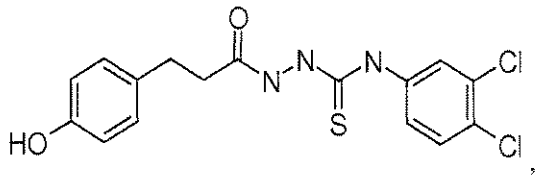
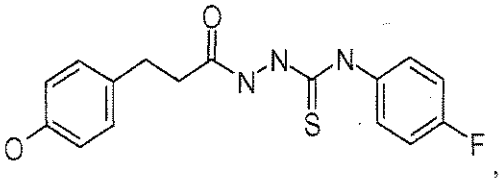
each L^* is independently selected from C_1-C_4 alkyl, F, Cl, Br, I, C_1-C_4 haloalkyl;

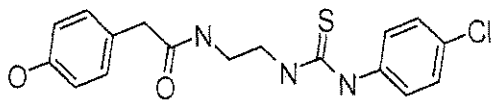
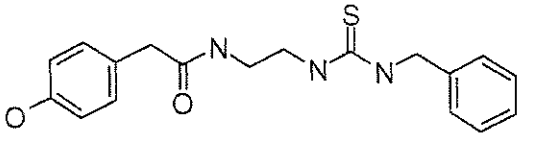
$k^* = 0$, 1, 2, 3, 4 or 5;

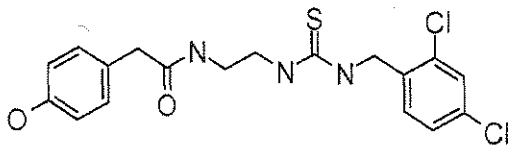
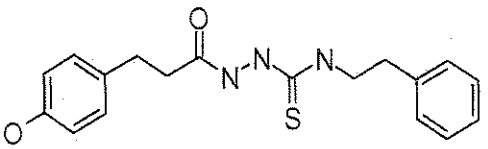
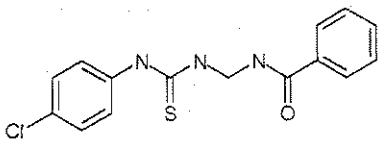
or  is .

In one embodiment, the compound is selected from the group consisting of:

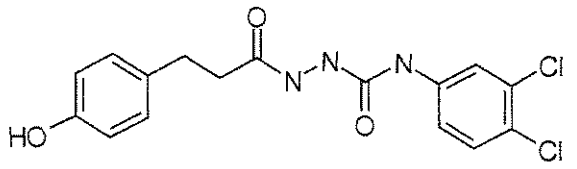
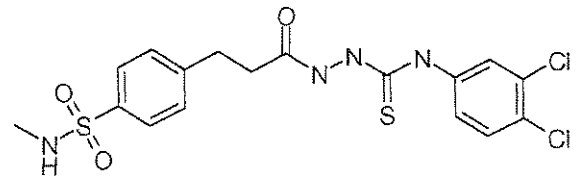
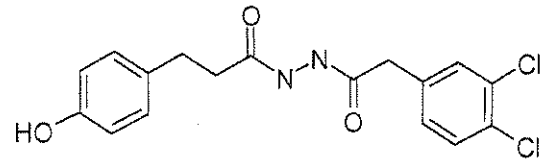
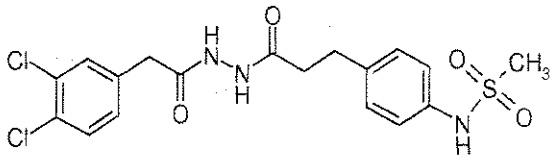
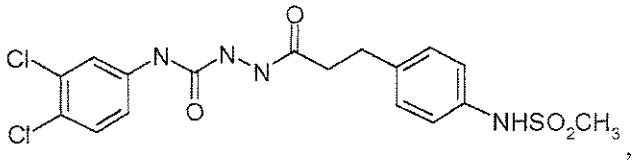
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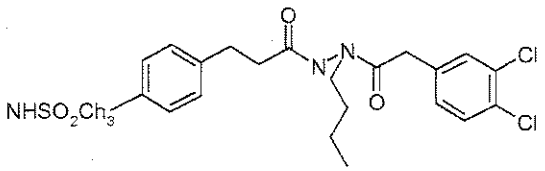
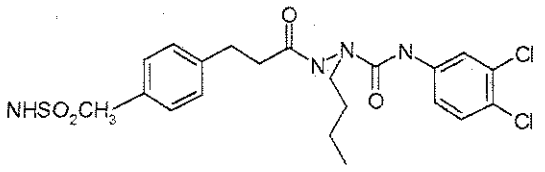
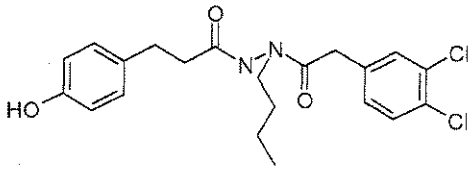
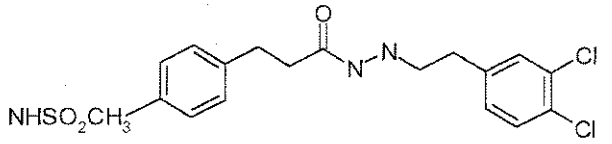
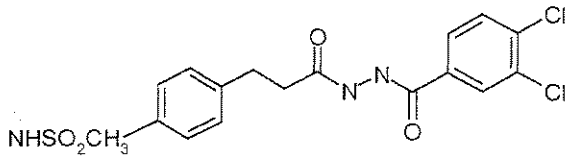
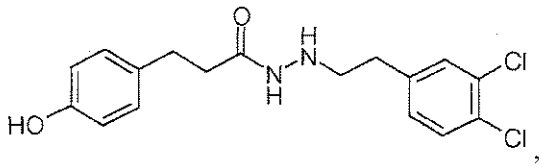
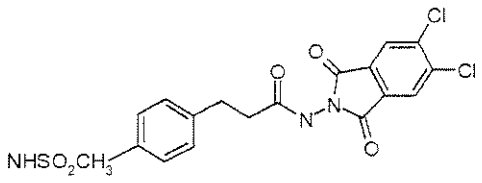
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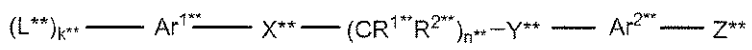
In another embodiment, the compound is selected from the group consisting of:


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, and

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Formula IV

In one embodiment, compounds, pharmaceutical compositions and methods of treatment or prophylaxis of neuropathic pain, stroke, traumatic brain injury, epilepsy, and other neurologic events or neurodegeneration resulting from NMDA receptor activation, comprising administering to a host in need thereof a compound of Formula IV, or a pharmaceutically acceptable salt, ester, prodrug or derivative thereof are provided:



FORMULA IV

wherein:

each L^{**} is independently C_1-C_6 alkyl, C_1-C_6 alkoxy, C(=O)-(C_1-C_6)-alkyl, C_1-C_6 haloalkyl, hydroxy, fluoro, chloro, bromo, iodo, nitro, or cyano; or two L^{**} groups may be taken together with Ar^{1**} to form: a dioxolane ring or a cyclobutane ring;

k^{**} = 0, 1, 2, 3, 4 or 5;

each Ar^{1**} and Ar^{2**} is independently aryl or heteroaryl;

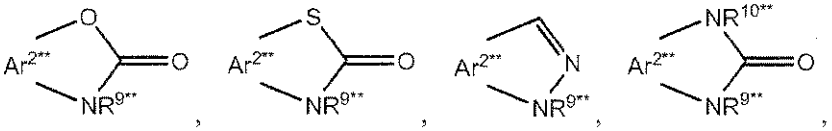
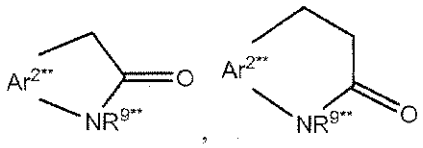
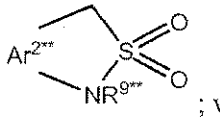
X^{**} is S, O or NR^3; wherein R^3 is H, C_1-C_6 alkyl, or C_6-C_{12} aralkyl;

each R^{1**} and R^{2**} is independently H, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_6-C_{12} aralkyl, C(=O)-(C_1-C_6)-alkyl, C_1-C_6 haloalkyl, hydroxy, fluoro, chloro, bromo, iodo, nitro, or cyano; or CR^1R^2 can be C=O or $C=CH_2$;

n^{**} = 1, 2, 3 or 4;

Y^{**} is a bond, O, S, SO, SO_2, CH_2, NH, N(C_1-C_6 alkyl), or NHC(=O);

Z^{**} is OH, $NR^{6**}R^{7**}$, $NR^{8**}SO_2$(C_1-C_6 alkyl), $NR^{8**}C(O)NR^{6**}R^{7**}$, $NR^{8**}C(O)O$(C_1-C_6 alkyl), NR^{8**}-dihydrothiazole, or NR^{8**}-dihydroimidazole; wherein each R^{6**}, R^{7**} and R^{8**} is independently H, C_1-C_6 alkyl or C_6-C_{12} aralkyl; or

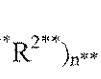
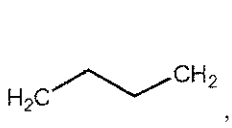
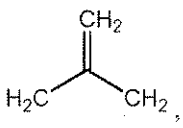
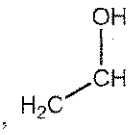
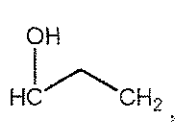
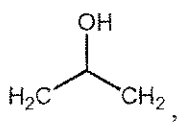
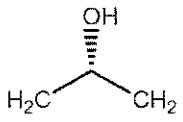
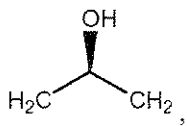
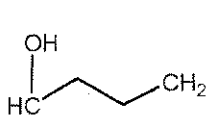
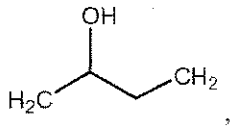
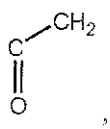
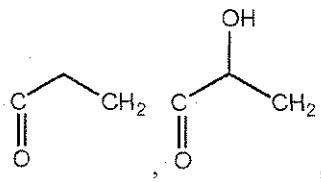
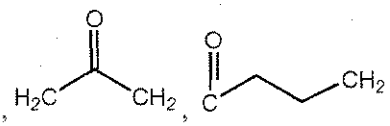
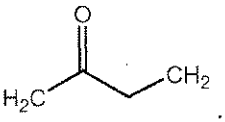
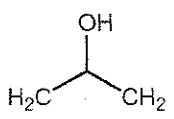
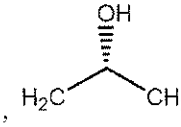
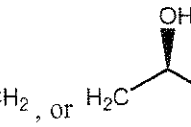
Ar^{2**}—Z^{**} is , , , or ; wherein R^{9**} and R^{10**} are each independently H, C_1-C_6 alkyl, aralkyl.

In particular subembodiment, Ar^{1**} is phenyl, pyridyl, pyrimidinyl, thiophenyl, imidazolyl, furanyl, indolyl, benzothiophenyl, benzofuranyl, or benzoimidazolyl. In one embodiment, Ar^{2**} is phenyl. In another embodiment, Ar^{1**} is benzoimidazolyl. In a particular subembodiment, Ar^{2**} is phenyl and Ar^{1**} is a heteroaryl, for example benzoimidazolyl. In one embodiment, Ar^{1**} is a bicyclic group wherein the X^{**} group is attached to the heterocyclic ring.

In one embodiment, X^{**} is S. In one embodiment, X^{**} is O. In one embodiment, X^{**} is NR^{3**}, for example NH.

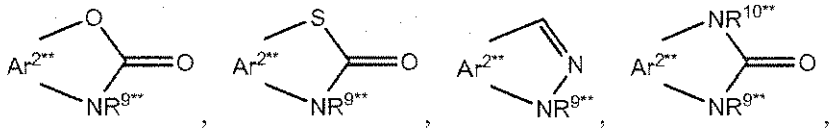
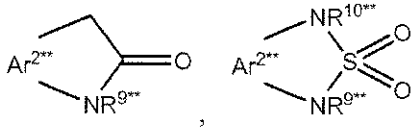
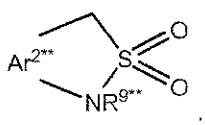
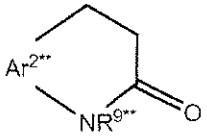
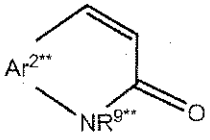
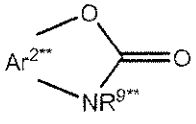
In another particular subembodiment, L^{**} is C_1-C_4 alkyl, C_1-C_4 alkoxy, C(=O)-(C_1-C_4)-alkyl, C_1-C_6 haloalkyl, hydroxy, fluoro, chloro, bromo, iodo, nitro, or cyano. In a further subembodiment, L^{**} is methyl, trifluoromethyl, methoxy, nitro, fluoro, chloro or hydroxy. In one further subembodiment, there are one, two or three L^{**} groups substituting Ar^{1**}. In one subembodiment, Ar^{1**} is substituted with one fluoro group. In one subembodiment, Ar^{1**} is substituted with two fluoro groups. In one subembodiment, Ar^{1**} is substituted with one fluoro group and one chloro group. In one subembodiment, Ar^{1**} is substituted with one chloro group. In one subembodiment, Ar^{1**} is substituted with two chloro groups. In one subembodiment, Ar^{1**} is substituted with one methyl group. In one subembodiment, Ar^{1**} is substituted with one trifluoromethyl group.

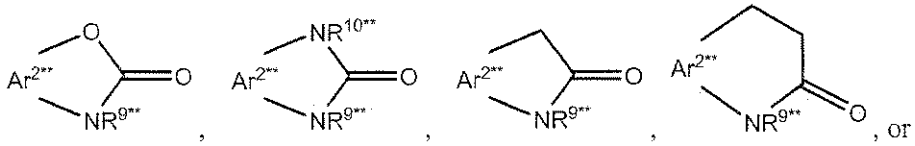
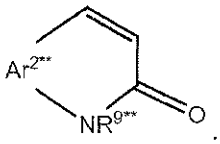
In one embodiment, each R^{1**} and R^{2**} is independently H or C_1-C_4 alkyl, for example, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl or *tert*-butyl. In one embodiment, R^{1**} and R^{2**} are both H. In one embodiment, one R^{1**} or R^{2**} is hydroxy. In one embodiment, n^{**} is 2, 3, or 4. In one embodiment, n^{**} is 3.

In one embodiment, one $CR^{1**}R^{2**}$ is C=O or $C=CH_2$. In one embodiment, $(CR^{1**}R^{2**})_{n**}$ is selected from the group consisting of , , , , , , , , , , , , , , and . In an particular embodiment, $(CR^{1**}R^{2**})_{n**}$ is , , or .

In one embodiment, Y^{**} is a bond, O or CH_2. In one embodiment, Y^{**} is O. In one subembodiment, Ar^{2**} is phenyl and is substituted with a Z^{**} group at the 4 position.

In one embodment, Z^{**} is OH, $NR^{6**}R^{7**}$, $NR^{8**}SO_2(C_1\text{-}C_6$ alkyl), $NR^{8**}C(O)NR^{6**}R^{7**}$, $NR^{8**}C(O)O(C_1\text{-}C_6$ alkyl), NR^{8**}-dihydrothiazole, or NR^{8**}-dihydroimidazole. In one subembodiment, Ar^{2**} is phenyl and is substituted with a Z^{**} group at the 4 position. In one embodiment,

Ar^{2**}—Z^{**} is , , or . In one embodiment, Ar^{2**}—Z^{**} is  or . In one subembodiment, Ar^{2**}—Z^{**} is . In one subembodiment, R^{9**} and R^{10**} are each H.

In another subembodiment, Z^{**} is $NR^{8**}C(O)NR^{6**}R^{7**}$ or Ar^{2**}—Z^{**} is , or .

In one embodiment, the compound is a compound of Formula IV, or a pharmaceutically acceptable salt, ester, prodrug or derivative thereof, wherein:

L^{**} is C_1-C_4 alkyl, C_1-C_4 alkoxy, C(=O)-(C_1-C_4)-alkyl, C_1-C_4 haloalkyl, hydroxy, fluoro, chloro, bromo, iodo, or nitro;

$k^{**} = 0, 1, 2, 3, 4$ or 5;

Ar^{1**} is selected from the group consisting of phenyl, pyridyl, pyrimidinyl, thiophenyl, imidazolyl, furanyl, indolyl, benzothiophenyl, benzofuranyl, or benzoimidazolyl.;

Ar^{2**} is phenyl;

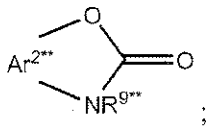
X^{**} is S;

each R^{1**} and R^{2**} is independently H, hydroxy or C_1-C_4 alkyl; or $CR^{1**}R^{2**}$ is C=O;

n^{**} = 2, 3 or 4;

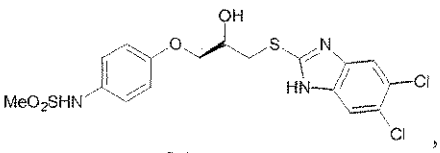
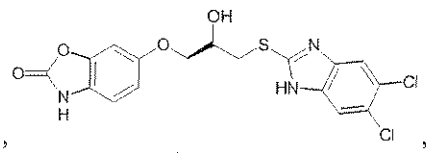
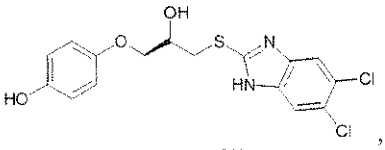
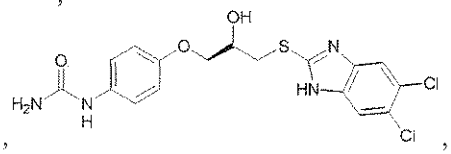
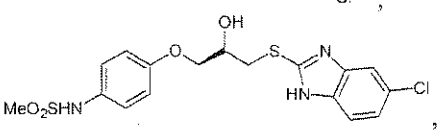
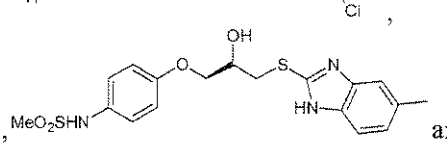
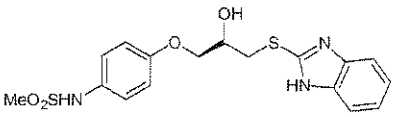
Y^{**} is O;

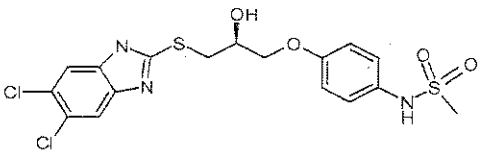
Z^{**} is OH, NH_2, $NHSO_2(C_1$-C_4 alkyl), $NHC(O)NR^{6**}R^{7**}$, $NHC(O)O(C_1$-C_4 alkyl), NH-dihydrothiazole, or NH-dihydroimidazole; wherein each R^{6**} and R^{7**} is independently H or C_1-C_4 alkyl; or

Ar^{2**}—Z^{**} is ;

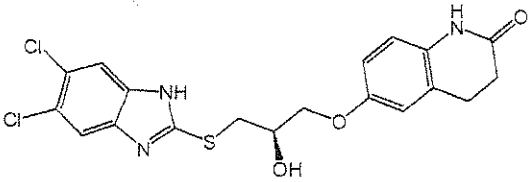
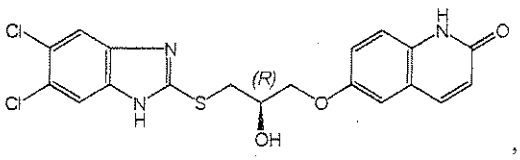
R^{9**} is H or C_1-C_4 alkyl.

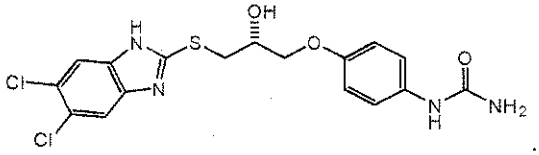
In one embodiment, the compound is selected from the group consisting of:

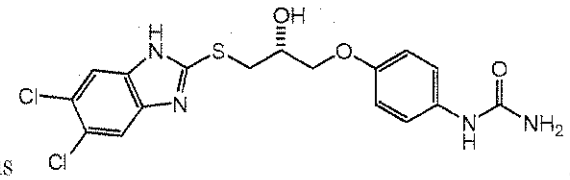
,
,
,
,
,

and


In one embodiment, the compound is .

In one embodiment, the compound is selected from the group consisting of:

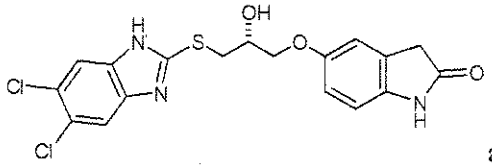
,
,
and



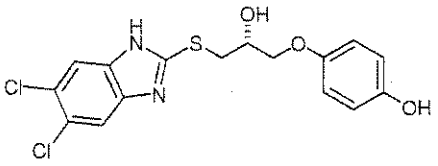


In one embodiment, the compound is .

In another embodiment, the compound is selected from the group consisting of:



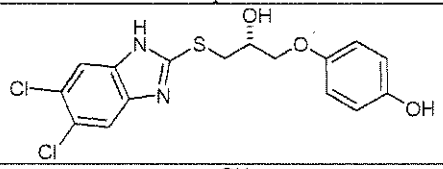
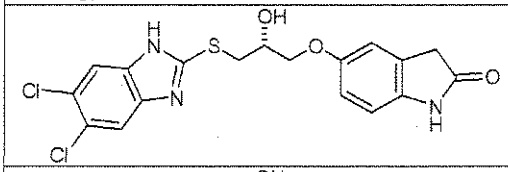
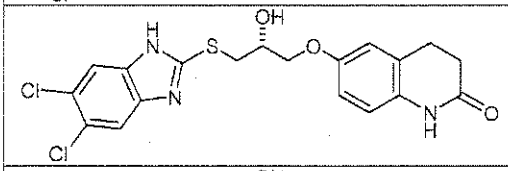
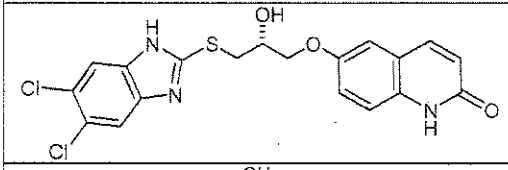
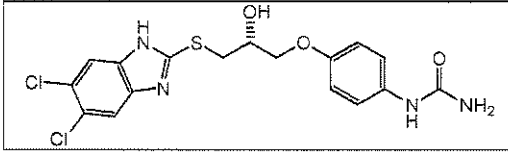
and

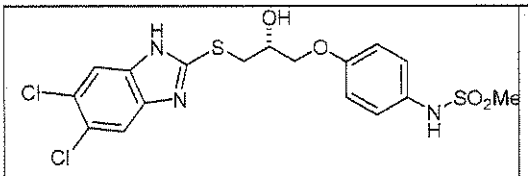
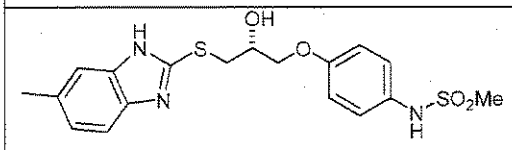


.

In another embodiment, the compound is selected from Table 16.

Table 16.

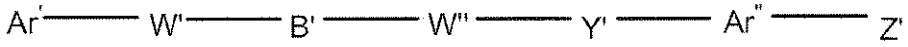
Compound	Name
	(*R*)-4-(3-(5,6-dichloro-1H-benzo[d]imidazol-2-ylthio)-2-hydroxypropoxy)phenol
	(*R*)-5-(3-(5,6-dichloro-1H-benzo[d]imidazol-2-ylthio)-2-hydroxypropoxy)indolin-2-one
	(*R*)-6-(3-(5,6-dichloro-1H-benzo[d]imidazol-2-ylthio)-2-hydroxypropoxy)-3,4-dihydroquinolin-2(1H)-one
	(*R*)-6-(3-(5,6-dichloro-1H-benzo[d]imidazol-2-ylthio)-2-hydroxypropoxy)quinolin-2(1H)-one
	(*R*)-1-(4-(3-(5,6-dichloro-1H-benzo[d]imidazol-2-ylthio)-2-hydroxypropoxy)phenyl)urea

	(*R*)-N-(4-(3-(5,6-dichloro-1H-benzo[d]imidazol-2-ylthio)-2-hydroxypropoxy)phenyl)methanesulfonamide
	(*R*)-N-(4-(2-hydroxy-3-(6-methyl-1H-benzo[d]imidazol-2-ylthio)propoxy)phenyl)methanesulfonamide

.

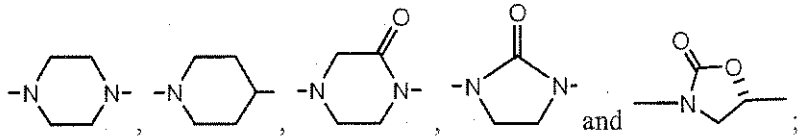
Formula V

In one embodiment, compounds, pharmaceutical compositions and methods of treatment or prophylaxis of neuropathic pain, stroke, traumatic brain injury, epilepsy, and other neurologic events or neurodegeneration resulting from NMDA receptor activation, comprising administering to a host in need thereof a compound of Formula V, or a pharmaceutically acceptable salt, ester, prodrug or derivative thereof are provided:



FORMULA V

wherein B' is selected from the group consisting of:



W' is a bond or C_1-C_4 alkyl;

W'' is C_1-C_4 alkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 haloalkyl or C(=O)-C_1-C_4 alkyl;

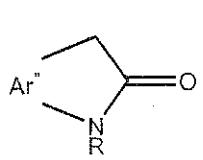
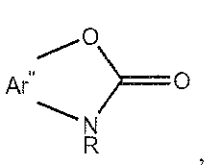
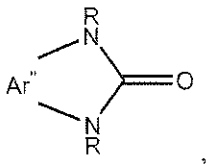
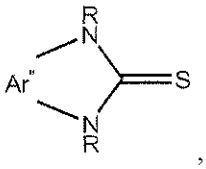
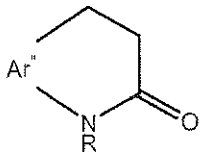
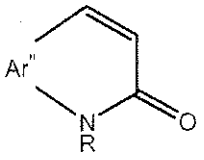
Y' is selected from a bond, O, S, CH_2 and N;

Ar' is an substituted or unsubstituted aromatic or nonaromatic cycloalkyl which optionally may include 0-3 heteroatoms;

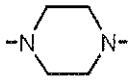
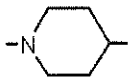
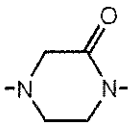
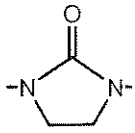
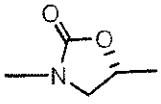
Ar'' is an aromatic or nonaromatic cycloalkyl which optionally may include 0-3 heteroatoms;

Z' is $NRC(O)NR_2$ wherein each R is independently selected from H, C_1-C_6 alkyl or C_6-C_{12} aralkyl; or

Ar''-Z' are taken together and selected from the group consisting

of: , , , , , and .

In one embodiment, Ar' is substited by $(L')_{k'}$ wherein each L' is independently C_1-C_6 alkyl, C_1-C_6 alkoxy, C(=O)-(C_1-C_6)-alkyl, C_1-C_6 haloalkyl, alkaryl, hydroxy, -O-alkyl, -O-aryl, -SH, -S-alkyl, -S-aryl, fluoro, chloro, bromo, iodo, nitro, or cyano; or two L' groups may be taken together with Ar' to form a dioxolane ring or a cyclobutane ring; and k' = 1, 2, 3, 4 or 5.

In one embodiment B' is . In another embodiment, B' is . In another embodiment, B' is . In another embodiment, B' is . In another embodiment, B' is .

In one embodiment, W' is a bond. In another embodiment, W' is C_1-C_4 alkyl, for example methylene, ethylene, or propylene. In a particular subembodiment, W' is CH_2.

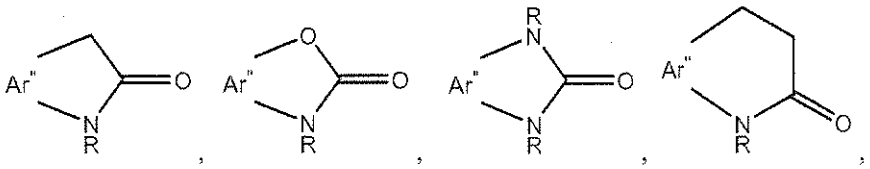
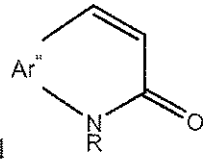
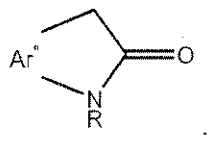
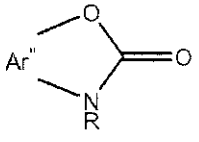
In one embodiment W'' is C_1-C_4 alkyl, for example methylene, ethylene, propylene, methylpropylene, or butylene. In another embodiment, W'' is C_1-C_4 hydroxyalkyl, for example hydroxymethylene, hydroxyethylene, or hydroxypropylene. In a particular subembodiment, W'' is -CH_2, CH(OH)-CH_2-. In another embodiment, W'' is C_1-C_4 haloalkyl, for example fluoroethylene, fluoropropylene, chloroethylene, or chloropropylene. In another embodiment, W'' is C(=O)-C_1-C_4 alkyl, for example -C(=O)-CH_2- or -C(=O)-CH_2-CH_2-.

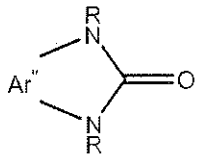
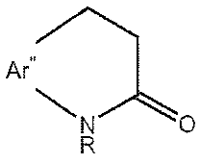
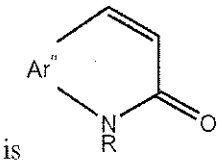
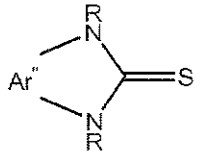
In one embodiment, Ar' is an aromatic cycloalkyl, for example phenyl. In another embodiment, Ar' is an nonaromatic cycloalkyl, for example cyclopentyl or cyclohexyl. In another embodiment, Ar' is an aromatic cycloalkyl including 1-3 heteroatoms, for example pyrrole, furan, thiophene, pyridine, pyrimidine, pyrazine, pyridazine. Heteroatoms include

but are not limited to N, S and O. In another embodiment, Ar' is a nonaromatic cycloalkyl including 1-3 heteroatoms, for example pyrrolidine, pyrroline, dihydrofuran, tetrahydrofuran, dihydrothiophene, tetrahydrothiophene, piperidine, tetrahydropyran, pyran, thiane, thiiine, piperazine, oxazine, dithiane, or dioxane. In another embodiment, Ar' is an aromatic or nonaromatic cycloalkyl including 1 heteroatom. In another embodiment, Ar' is an aromatic or nonaromatic cycloalkyl including 2 heteroatoms. In another embodiment, Ar' is an aromatic or nonaromatic cycloalkyl including 3 heteroatoms.

In one embodiment, Ar'' is an aromatic cycloalkyl, for example phenyl. In another embodiment, Ar'' is an nonaromatic cycloalkyl, for example cyclopentyl or cyclohexyl. In another embodiment, Ar'' is an aromatic cycloalkyl including 1-3 heteroatoms, for example pyrrole, furan, thiophene, pyridine, pyrimidine, pyrazine, or pyridazine. In another embodiment, Ar'' is a nonaromatic cycloalkyl including 1-3 heteroatoms, for example pyrrolidine, pyrroline, dihydrofuran, tetrahydrofuran, dihydrothiophene, tetrahydrothiophene, piperidine, tetrahydropyran, pyran, thiane, thiiine, piperazine, oxazine, dithiane, or dioxane. In another embodiment, Ar'' is an aromatic or nonaromatic cycloalkyl including 1 heteroatom. In another embodiment, Ar'' is an aromatic or nonaromatic cycloalkyl including 2 heteroatoms. In another embodiment, Ar'' is an aromatic or nonaromatic cycloalkyl including 3 heteroatoms.

In one embodiment, Z' is $NRC(O)NR_2$, for example $NHC(O)NH_2$ or $NHC(O)N(CH_3)_2$.

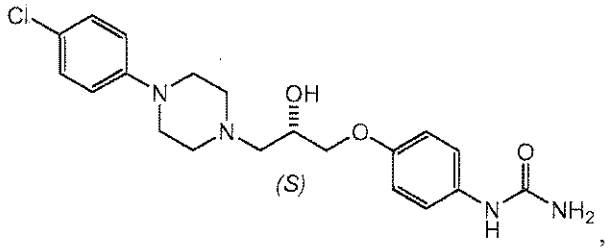
In another embodiment, Z and Ar'' are taken together and selected from the group consisting of: ,  and . In a particular subembodiment, Ar''-Z' is . In another subembodiment, Ar''-Z' is . In another subembodiment, Ar''-Z' is

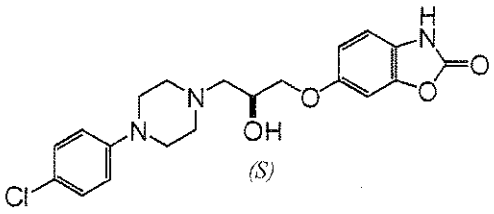

. In another subembodiment, Ar''-Z' is 
. In another subembodiment, Ar''-Z' is 
. In another subembodiment, Ar''-Z' is 
. In a particular subembodiment of any of the above embodiments, R is H. In a particular subembodiment of any of the above embodiments, Ar'' is phenyl.

In one embodiment, each L' is independently halo, C_1-C_6 alkyl, or C_1-C_6 haloalkyl. In a particular subembodiment Ar' has at least one L'. In a particular subembodiment Ar' is phenyl and is substituted with one or more L' groups wherein one L' is in the para position. In a particular embodiment, at least one L' is halo, for example fluoro, chloro, bromo, or iodo. In a particular subembodiment, are least two L' are halo and may be the same or different. In another embodiment, at least one L' is C_1-C_6 alkyl, for example methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, or hexyl. In another embodiment, at least one L' is C_1-C_6 haloalkyl, for example, trifluoromethyl.

In one embodiment, Ar' is unsubstituted. In another embodiment, k' is 1. In a subembodiment, when k' is 1 and Ar' is phenyl, L' is in the para position. In another embodiment, k' is 2. In a subembodiment, when k' is 2 and Ar' is phenyl, one L' is in the para position and one L' is in a meta position. In another embodiment, k' is 3. In another embodiment, k' is 4. In another embodiment, k' is 5.

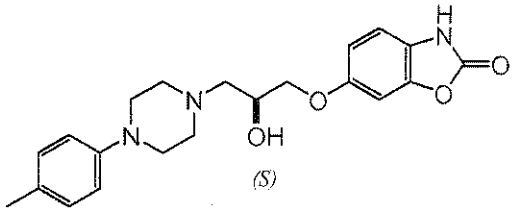
In one embodiment, the compound is selected from the group consisting of:


(S)
,



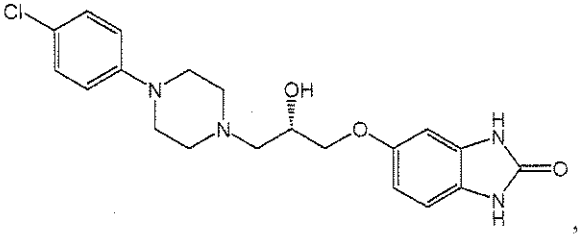
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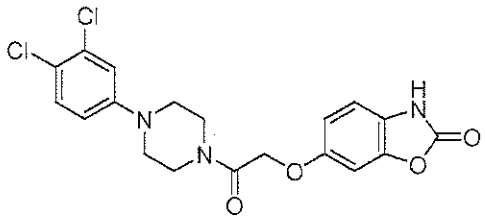


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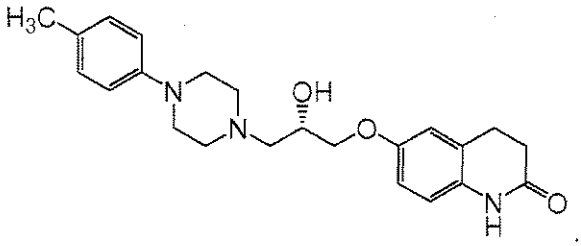
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and



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Enantiomers

In certain embodiments, the compounds are present as enantiomers. In one embodiment, the compound is provided as an enantiomer or mixture of enantiomers. In a particular embodiment, the compound is present as a racemic mixture. The enantiomer can be named by the configuration at the chiral center, such as R or S. In certain embodiments, the compound is present as a racemic mixture of R- and S- enantiomers. In certain embodiments, the compound is present as a mixture of two enantiomers. In one embodiment, the mixture has an enantiomeric excess in R. In one embodiment, the mixture has an enantiomeric excess in S. In certain other embodiments, the compound is in an enantiomeric excess of the R- or S- enantiomer. The enantiomeric excess can be 51% or more, such as

51% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, 98% or more, or 99% or more in the single enantiomer. The enantiomeric excess can be 51% or more, such as 51% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, 98% or more, or 99% or more in the R enantiomer. The enantiomeric excess can be 51% or more, such as 51% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, 98% or more, or 99% or more in the S enantiomer.

In other embodiments, the compound is substantially in the form of a single enantiomer. In some embodiments, the compound is present substantially in the form of the R enantiomer. In some embodiments, the compound is present substantially in the form of the S enantiomer. The phrase "substantially in the form of a single enantiomer" is intended to mean at least 70% or more in the form of a single enantiomer, for example 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, 98% or more, or 99% or more in either the R or S enantiomer.

The enantiomer can be named by the direction in which it rotates the plane of polarized light. If it rotates the light clockwise as seen by the viewer towards whom the light is traveling, the isomer can be labeled (+) and if it rotates the light counterclockwise, the isomer can be labeled (-). In certain embodiments, the compound is present as a racemic mixture of (+) and (-) isomers. In certain embodiments, the compound is present as a mixture of two isomers. In one embodiment, the mixture has an excess in (+). In one embodiment, the mixture has an excess in (-). In certain other embodiments, the compound is in an excess of the (+) or (-) isomer. The isomeric excess can be 51% or more, such as 51% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, 98% or more, or 99% or more in the (+) isomer. The enantiomeric excess can be 51% or more, such as 51% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, 98% or more, or 99% or more in the (-) isomer.

In other embodiments, the compound is substantially in the form of a single optical isomer. In some embodiments, the compound is present substantially in the form of the (+) isomer. In other embodiments, the compound is present substantially in the form of the (-) isomer. The phrase "substantially in the form of a single optical isomer" is intended to mean at least 70% or more in the form of a single isomer, for example 70% or more, 75% or more,

80% or more, 85% or more, 90% or more, 95% or more, 98% or more, or 99% or more of either the (+) or (-) isomer.

Definitions

Whenever a term in the specification is identified as a range (i.e. C_{1-4} alkyl), the range independently refers to each element of the range. As a non-limiting example, C_{1-4} alkyl means, independently, C_1, C_2, C_3 or C_4 alkyl. Similarly, when one or more substituents are referred to as being "independently selected from" a group, this means that each substituent can be any element of that group, and any combination of these groups can be separated from the group. For example, if R^1 and R^2 can be independently selected from X, Y and Z, this separately includes the groups R^1 is X and R^2 is X; R^1 is X and R^2 is Y; R^1 is X and R^2 is Z; R^1 is Y and R^2 is X; R^1 is Y and R^2 is Y; R^1 is Y and R^2 is Z; R^1 is Z and R^2 is X; R^1 is Z and R^2 is Y; and R^1 is Z and R^2 is Z.

The term "alkyl" is used herein, unless otherwise specified, refers to a substituted or unsubstituted, saturated, straight, branched, or cyclic (also identified as cycloalkyl), primary, secondary, or tertiary hydrocarbon, including but not limited to those of C_1 to C_6. Illustrative examples of alkyl groups are methyl, ethyl, propyl, *iso*propyl, cyclopropyl, butyl, secbutyl, isobutyl, *tert*butyl, cyclobutyl, 1-methylbutyl, 1,1-dimethylpropyl, pentyl, cyclopentyl, isopentyl, neopentyl, cyclopentyl, hexyl, isohexyl, and cyclohexyl. Unless otherwise specified, the alkyl group can be unsubstituted or substituted with one or more moieties selected from the group consisting of alkyl, halo, haloalkyl, hydroxyl, carboxyl, acyl, acyloxy, amino, amido, carboxyl derivatives, alkylamino, dialkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, thio, sulfonyl, ester, carboxylic acid, amide, phosphonyl, phosphinyl, thioether, oxime, or any other viable functional group that does not inhibit the pharmacological activity of this compound, either unprotected, or protected as necessary, as known to those skilled in the art, for example, as taught in Greene, *et al.*, Protective Groups in Organic Synthesis, John Wiley and Sons, Third Edition, 2002. In certain embodiments, alkyl may be optionally substituted by one or more fluro, chloro, bromo, iodo, hydroxy, heterocyclic, heteroaryl, carboxy, alkoxy, nitro, NH_2, $N(alkyl)_2$, NH(alkyl), alkoxycarbonyl, -N(H or alkyl)C(O)(H or alkyl), -N(H or alkyl)C(O)N(H or alkyl)$_2$, -N(H or alkyl)C(O)O(H or alkyl), -OC(O)N(H or alkyl)$_2$, -S(O)$_n$-(H or alkyl), -C(O)-N(H or alkyl)$_2$, cyano, alkenyl, cycloalkyl, acyl, hydroxyalkyl, heterocyclic, heteroaryl, aryl, aminoalkyl, oxo, carboxyalkyl, -C(O)-NH_2, -C(O)-N(H)O(H or alkyl), -S(O)$_2$-NH_2, -S(O)$_n$-N(H or alkyl)$_2$ and/or -S(O)$_2$-N(H

or alkyl)$_2$.

The term "cycloalkyl" is used herein, unless otherwise specified, refers to a substituted or unsubstituted, saturated cyclic hydrocarbon, including but not limited to those of C_3 to C_{12}. Illustrative examples of cycloalkyl groups are cyclopropyl, cyclobutyl, cyclopentyl, cyclopentyl, and cyclohexyl. Unless otherwise specified, the cycloalkyl group can be unsubstituted or substituted with one or more moieties selected from the group consisting of alkyl, halo, haloalkyl, hydroxyl, carboxyl, acyl, acyloxy, amino, amido, carboxyl derivatives, alkylamino, dialkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, thio, sulfonyl, ester, carboxylic acid, amide, phosphonyl, phosphinyl, thioether, oxime, or any other viable functional group that does not inhibit the pharmacological activity of this compound, either unprotected, or protected as necessary, as known to those skilled in the art, for example, as taught in Greene, *et al.*, Protective Groups in Organic Synthesis, John Wiley and Sons, Third Edition, 2002. In certain embodiments, the cycloalkyl may be optionally substituted by one or more fluoro, chloro, bromo, iodo, hydroxy, heterocyclic, heteroaryl, carboxy, alkoxy, nitro, NH_2, N(alkyl)$_2$, NH(alkyl), alkoxycarbonyl, -N(H or alkyl)C(O)(H or alkyl), -N(H or alkyl)C(O)N(H or alkyl)$_2$, -N(H or alkyl)C(O)O(H or alkyl), -OC(O)N(H or alkyl)$_2$, -S(O)$_n$-(H or alkyl), -C(O)-N(H or alkyl)$_2$, cyano, alkenyl, cycloalkyl, acyl, hydroxyalkyl, heterocyclic, heteroaryl, aryl, aminoalkyl, oxo, carboxyalkyl, -C(O)-NH_2, -C(O)-N(H)O(H or alkyl), -S(O)$_2$-NH_2, -S(O)$_n$-N(H or alkyl)$_2$ and/or -S(O)$_2$-N(H or alkyl)$_2$.

The term "halo" or "halogen," refers to chloro, bromo, iodo, or fluoro.

The term "heterocyclic" refers to a non-aromatic or aromatic cyclic group wherein there is at least one heteroatom, such as oxygen, sulfur, nitrogen, or phosphorus in the ring. The term "heteroaryl" or "heteroaromatic," refers to an aromatic that includes at least one sulfur, oxygen, nitrogen or phosphorus in the aromatic ring. Nonlimiting examples of heteroaryl and heterocyclic groups include furyl, furanyl, pyridyl, pyrimidyl, thienyl, isothiazolyl, imidazolyl, tetrazolyl, pyrazinyl, benzofuranyl, benzothiophenyl, quinolyl, isoquinolyl, benzothienyl, isobenzofuryl, pyrazolyl, indolyl, isoindolyl, benzimidazolyl, purinyl, carbazolyl, oxazolyl, thiazolyl, isothiazolyl, 1,2,4-thiadiazolyl, isooxazolyl, pyrrolyl, quinazolinyl, cinnolinyl, phthalazinyl, xanthinyl, hypoxanthinyl, thiophene, furan, pyrrole, isopyrrole, pyrazole, imidazole, 1,2,3-triazole, 1,2,4-triazole, oxazole, isoxazole, thiazole, isothiazole, pyrimidine or pyridazine, pteridinyl, aziridines, thiazole, isothiazole, oxadiazole, thiazine, pyridine, pyrazine, piperazine, piperidine, pyrrolidine, oxaziranes, phenazine, phenothiazine, morpholinyl, pyrazolyl, pyridazinyl, pyrazinyl, quinoxalinyl, xanthinyl,

hypoxanthinyl, pteridinyl, 5-azacytidinyl, 5-azauracilyl, triazolopyridinyl, imidazolopyridinyl, pyrrolopyrimidinyl, pyrazolopyrimidinyl, adenine, N^6-alkylpurines, N^6-benzylpurine, N^6-halopurine, N^6-vinypurine, N^6-acetylenic purine, N^6-acyl purine,N^6-hydroxyalkyl purine, N^6-thioalkyl purine, thymine, cytosine, 6-azapyrimidine, 2-mercaptopyrmidine, uracil, N^5-alkylpyrimidines, N^5-benzylpyrimidines, N^5-halopyrimidines, N^5-vinylpyrimidine, N^5-acetylenic pyrimidine, N^5-acyl pyrimidine, N^5-hydroxyalkyl purine, and N^6-thioalkyl purine, and isoxazolyl. The heteroaromatic or heterocyclic group can be optionally substituted with one or more substituent selected from halogen, haloalkyl, alkyl, alkoxy, hydroxy, carboxyl derivatives, amido, amino, alkylamino, dialkylamino. The heteroaromatic can be partially or totally hydrogenated as desired. Nonlimiting examples include dihydropyridine and tetrahydrobenzimidazole. In some embodiment, the heteroaryl may be optionally substituted by one or more fluoro, chloro, bromo, iodo, hydroxy, heterocyclic, heteroaryl, carboxy, alkoxy, nitro, NH_2, $N(alkyl)_2$, NH(alkyl), alkoxycarbonyl, -N(H or alkyl)C(O)(H or alkyl), -N(H or alkyl)C(O)N(H or alkyl)$_2$, -N(H or alkyl)C(O)O(H or alkyl), -OC(O)N(H or alkyl)$_2$, -$S(O)_n$-(H or alkyl), -C(O)-N(H or alkyl)$_2$, cyano, alkenyl, cycloalkyl, acyl, hydroxyalkyl, heterocyclic, heteroaryl, aryl, aminoalkyl, oxo, carboxyalkyl, -C(O)-NH_2, -C(O)-N(H)O(H or alkyl), -$S(O)_2$-NH_2, -$S(O)_n$-N(H or alkyl)$_2$ and/or -$S(O)_2$-N(H or alkyl)$_2$. Functional oxygen and nitrogen groups on the heteroaryl group can be protected as necessary or desired. Suitable protecting groups are well known to those skilled in the art, and include trimethylsilyl, dimethylhexylsilyl, *t*-butyldimethylsilyl, and *t*-butyldiphenylsilyl, trityl or substituted trityl, alkyl groups, acyl groups such as acetyl and propionyl, methanesulfonyl, and *p*-tolylsulfonyl.

The term "aryl," unless otherwise specified, refers to a carbon based aromatic ring, including phenyl, biphenyl, or naphthyl. The aryl group can be optionally substituted with one or more moieties selected from the group consisting of hydroxyl, acyl, amino, halo, alkylamino, alkoxy, aryloxy, nitro, cyano, sulfonic acid, sulfate, phosphonic acid, phosphate, or phosphonate, either unprotected, or protected as necessary, as known to those skilled in the art, for example, as taught in *Greene, et al.* Protective Groups in Organic Synthesis, John Wiley and Sons, Third Edition, 2002. In certain embodiments, the aryl group is optionally substituted by one or more fluro, chloro, bromo, iodo, hydroxy, heterocyclic, heteroaryl, carboxy, alkoxy, nitro, NH_2, $N(alkyl)_2$, NH(alkyl), alkoxycarbonyl, -N(H or alkyl)C(O)(H or alkyl), -N(H or alkyl)C(O)N(H or alkyl)$_2$, -N(H or alkyl)C(O)O(H or alkyl), -OC(O)N(H or alkyl)$_2$, -$S(O)_n$-(H or alkyl), -C(O)-N(H or alkyl)$_2$, cyano, alkenyl, cycloalkyl, acyl, hydroxyalkyl, heterocyclic, heteroaryl, aryl, aminoalkyl, oxo, carboxyalkyl, -C(O)-NH_2, -

C(O)-N(H)O(H or alkyl), $-S(O)_2-NH_2$, $-S(O)_n-N(H \text{ or alkyl})_2$ and/or $-S(O)_2-N(H \text{ or alkyl})_2$.

The term "aralkyl," unless otherwise specified, refers to an aryl group as defined above linked to the molecule through an alkyl group as defined above.

The term "alkaryl," unless otherwise specified, refers to an alkyl group as defind above linked to the molecule through an aryl group as defined above. Other groups, such as acyloxyalkyl, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkylaminoalkyl, alkylthioalkyl, amidoalkyl, aminoalkyl, carboxyalkyl, dialkylaminoalkyl, haloalkyl, heteroaralkyl, heterocyclicalkyl, hydroxyalkyl, sulfonamidoalkyl, sulfonylalkyl and thioalkyl are named in a similar manner.

The term "alkoxy," unless otherwise specified, refers to a moiety of the structure -O-alkyl, wherein alkyl is as defined above.

The term "acyl," refers to a group of the formula C(O)R' or "alkyl-oxy", wherein R' is an alkyl, aryl, alkaryl or aralkyl group, or substituted alkyl, aryl, aralkyl or alkaryl.

The term "alkenyl" The term "alkenyl" means a monovalent, unbranched or branched hydrocarbon chain having one or more double bonds therein. The double bond of an alkenyl group can be unconjugated or conjugated to another unsaturated group. Suitable alkenyl groups include, but are not limited to (C_2-C_8)alkenyl groups, such as vinyl, allyl, butenyl, pentenyl, hexenyl, butadienyl, pentadienyl, hexadienyl, 2-ethylhexenyl,2-propyl-2-butenyl,4-(2-methyl-3-butene)-pentenyl. An alkenyl group can be unsubstituted or substituted with one or two suitable substituents.

The term "carbonyl" refers to a functional group composed of a carbon atom double-bonded to an oxygen atom : -C=O. Similarly, C(O) or C(=O) refers to a carbonyl group.

The term "amino" refers to $-NH_2$, -NH(alkyl) or $-N(alkyl)_2$.

The term "thio" indicates the presence of a sulfur group. The prefix thio- denotes that there is at least one extra sulfur atom added to the chemical. The prefix 'thio-' can also be placed before the name of a ompoundto mean that an oxygen atom in the compound has been replaced by a sulfur atom. Although typically the term "thiol" is used to indicate the presence of -SH, in instances in which the sulfur atom would be have improper valance a radical if the hydrogen is improperly designated, the terms 'thio' and 'thiol' are used interchangeably, unless otherwise indicated.

The term "amido" indicates a group (H or alkyl)-C(O)-NH-.

The term "carboxy" designates the terminal group -C(O)OH.

The term "sulfonyl" indicates an organic radical of the general formula (H or alkyl)-$S(=O)_2$-(H or alkyl'), where there are two double bonds between the sulfur and oxygen.

The term "pharmaceutically acceptable salt" refers to salts or complexes that retain the desired biological activity of the compounds of the present invention and exhibit minimal undesired toxicological effects. Nonlimiting examples of such salts are (a) acid addition salts formed with inorganic acids (for example, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, and the like), and salts formed with organic acids such as acetic acid, oxalic acid, tartaric acid, succinic acid, malic acid, ascorbic acid, benzoic acid, tannic acid, pamoic acid, alginic acid, polyglutamic acid, naphthalenesulfonic acid, naphthalenedisulfonic acid, and polygalcturonic acid; (b) base addition salts formed with metal cations such as zinc, calcium, bismuth, barium, magnesium, aluminum, copper, cobalt, nickel, cadmium, sodium, potassium, and the like, or with a cation formed from ammonia, N,N-dibenzylethylenediamine, D-glucosamine, tetraethylammonium, or ethylenediamine; or (c) combinations of (a) and (b); e.g., a zinc tannate salt or the like. Also included in this definition are pharmaceutically acceptable quaternary salts known by those skilled in the art, which specifically include the quaternary ammonium salt of the formula $-NR^{+}A^{-}$, wherein R is H or alkyl and A is a counterion, including chloride, bromide, iodide, -O-alkyl, toluenesulfonate, methylsulfonate, sulfonate, phosphate, or carboxylate (such as benzoate, succinate, acetate, glycolate, maleate, malate, citrate, tartrate, ascorbate, benzoate, cinnamoate, mandeloate, benzyloate, and diphenylacetate).

The term "protected" as used herein and unless otherwise defined refers to a group that is added to an oxygen, nitrogen, or phosphorus atom to prevent its further reaction or for other purposes. A wide variety of oxygen and nitrogen protecting groups are known to those skilled in the art of organic synthesis.

It should be understood that the various possible stereoisomers of the groups mentioned above and herein are within the meaning of the individual terms and examples, unless otherwise specified. As an illustrative example, "1-methyl-butyl" exists in both (R) and the (S) form, thus, both (R)-1-methyl-butyl and (S)-1-methyl-butyl is covered by the term "1-methyl-butyl", unless otherwise specified.

Methods of Use

The compounds described herein can generally be used to treat neuropathic pain, stroke, traumatic brain injury, epilepsy, and other neurologic events or neurodegeneration resulting from NMDA receptor activation. Methods are provided for the treatment neuropathic pain, stroke, traumatic brain injury, epilepsy, and other neurologic events or

neurodegeneration resulting from NMDA receptor activation comprising administering to a host in need thereof an effective amount of a compound of Formula I, II, III, IV or V, or a pharmaceutical composition thereof. In specific embodiments, the compound is of Formula I or V, or a salt or ester thereof.

In one embodiment, a method of treatment for neuropathic pain, stroke, traumatic brain injury, epilepsy, and other neurologic events or neurodegeneration resulting from NMDA receptor activation comprising administering a neuroprotective agent of Formula I is provided. Compositions and methods comprising the compounds described herein are useful for treating neuropathic pain, stroke, traumatic brain injury, epilepsy, and other neurologic events or neurodegeneration resulting from NMDA receptor activation. In one embodiment, methods are useful in the treatment of neuropathic pain. In another embodiment, the methods are useful in preventing neurodegeneration in patients with Parkinson's, Alzheimer's, Huntington's chorea, ALS, and other neurodegenerative conditions known to the art to be responsive to treatment using NMDA receptor blockers.

The compounds of the invention can generally be administered to a host at risk of, or suffering from, neuropathic pain, stroke, traumatic brain injury, epilepsy, and other neurologic events or neurodegeneration resulting from NMDA receptor activation. In one embodiment, the compounds are administered for the treatment or prophylaxis of an neuropathic pain, stroke, traumatic brain injury, epilepsy, and other neurologic events or neurodegeneration resulting from NMDA receptor activation.

In additional aspects of the present invention, methods are provided to treat patients by administering a compound selected according to the methods or processes described herein. Any disease, condition or disorder which induces a region with a reduced pH (below pH 7.6) can be treated according to the methods described herein.

Certain NMDA receptor antagonists described herein have enhanced activity in tissue having lower-than-normal pH. The tissue can be brain tissue. In certain embodiments, the reduced pH is due to pathological conditions such as hypoxia resulting from stroke, traumatic brain injury, global ischemia, such as global ischemia that may occur during cardiac surgery, hypoxia, including hypoxia that may occur following cessation of breathing, pre-eclampsia, spinal cord trauma, epilepsy, status epilepticus, neuropathic pain, inflammatory pain, chronic pain, vascular dementia and glioma tumors. Because tumors produce an acidic environment, drugs activated by low pH can be useful in slowing tumor growth because they have enhanced activity only at the site of the tumor. In some embodiments, the compounds are

useful in the treatment of tumor growth. In certain embodiments, the compounds reduce tumor mass. In one embodiment, the compounds are useful in the treatment or prophylaxis of a neurologic event involving acidification of brain or spinal cord tissue. In another embodiment, the NMDA receptor antagonists of this invention are useful both in the treatment of stroke and head trauma, and for use as prophylactic agents for at risk patients. The acid generated by ischemic tissue during stroke is harnessed as a switch to activate the neuroprotective agents described herein. In this way side effects are minimized in unaffected tissue since drug at these sites are less active. These compounds may be used to reduce the amount of neuronal death associated with stroke and head trauma. They may be given chronically to individuals with epilepsy or who are at risk for stroke or head trauma, preoperatively in high risk heart/brain surgery, etc., in order to lengthen the window of opportunity for subsequent therapy.

In one embodiment, methods are provided to attenuate the progression of an ischemic or excitotoxic cascade associated with a drop in pH by administering a compound described herein. In addition, methods are provided to decrease infarct volume associated with a drop in pH by administering a compound selected according to the processes or methods described herein. Further, a method is provided to decrease cell death associated with a drop in pH by administering a compound selected according to the processes or methods described herein. Still further, methods are provided to decrease behavioral deficits associated with an ischemic event associated with a drop in pH by administering a compound selected according to the processes or methods described herein.

In additional aspects of the present invention, methods are provided to treat patients in need thereof by administering a compound or composition described herein. Any disease, condition or disorder which induces a low pH can be treated according to the methods described herein.

In one embodiment, methods are provided to treat patients with ischemic injury or hypoxia, or prevent or treat the neuronal toxicity associated with ischemic injury or hypoxia, by administering a compound or composition described herein. In one particular embodiment, the ischemic injury is stroke. In another particular embodiment, the ischemic injury is vasospasm after subarachnoid hemorrhage. In other embodiments, the ischemic injury is selected from, but not limited to, one of the following: traumatic brain injury, cognitive deficit after bypass surgery, cognitive deficit after carotid angioplasty; and/or neonatal ischemia following hypothermic circulatory arrest.

In another embodiment, methods are provided to treat patients with neuropathic pain

or related disorders by administering a compound or composition described herein. In certain embodiments, the neuropathic pain or related disorder can be selected from the group including, but not limited to: peripheral diabetic neuropathy, postherpetic neuralgia, complex regional pain syndromes, peripheral neuropathies, chemotherapy-induced neuropathic pain, cancer neuropathic pain, neuropathic low back pain, HIV neuropathic pain, trigeminal neuralgia, and/or central post-stroke pain.

In another embodiment, methods are provided to treat patients with brain tumors by administering a compound selected according to the methods or processes described herein. In a further embodiment, methods are provided to treat patients with neurodegenerative diseases by administering a compound selected according to the methods or processes described herein. In one embodiment, the neurodegenerative disease can be Parkinson's disease. In another embodiment, the neurodegenerative disease can be Alzheimer's, Huntington's and/or Amyotrophic Lateral Sclerosis.

Further, compounds selected according to the methods or processes described herein can be used prophylactically to prevent or protect against such diseases or neurological conditions, such as those described herein. In one embodiment, patients with a predisposition for an ischemic event, such as a genetic predisposition, can be treated prophylactically with the methods and compounds described herein. In another embodiment, patients that exhibit vasospasms can be treated prophylactically with the methods and compounds described herein. In a further embodiment, patients that have undergone cardiac bypass surgery can be treated prophylactically with the methods and compounds described herein.

In one embodiment, methods are provided to treat patients with ischemic injury or hypoxia, or prevent or treat the neuronal toxicity associated with ischemic injury or hypoxia, by administering a compound selected according to the methods or processes described herein. In one particular embodiment, the ischemic injury can be stroke. In other embodiments, the ischemic injury can be selected from, but not limited to, one of the following: traumatic brain injury, cognitive deficit after bypass surgery, cognitive deficit after carotid angioplasty; and/or neonatal ischemia following hypothermic circulatory arrest.

In another particular embodiment, the ischemic injury can be vasospasm after subarachnoid hemorrhage. A subarachnoid hemorrhage refers to an abnormal condition in which blood collects beneath the arachnoid mater, a membrane that covers the brain. This area, called the subarachnoid space, normally contains cerebrospinal fluid. The accumulation of blood in the subarachnoid space and the vasospasm of the vessels which results from it can lead to stroke, seizures, and other complications. The methods and compounds described

herein can be used to treat patients experiencing a subarachnoid hemorrhage. In one embodiment, the methods and compounds described herein can be used to limit the toxic effects of the subarachnoid hemorrhage, including, for example, stroke and/or ischemia that can result from the subarachnoid hemorrhage. In a particular embodiment, the methods and compounds described herein can be used to treat patients with traumatic subarachnoid hemorrhage. On one embodiment, the traumatic subarachnoid hemorrhage can be due to a head injury. In another embodiment, the patients can have a spontaneous subarachnoid hemorrhage.

In another embodiment, methods are provided to treat patients with neuropathic pain or related disorders by administering a compound selected according to the methods or processes described herein. In certain embodiments, the neuropathic pain or related disorder can be selected from the group including, but not limited to: peripheral diabetic neuropathy, postherpetic neuralgia, complex regional pain syndromes, peripheral neuropathies, chemotherapy-induced neuropathic pain, cancer neuropathic pain, neuropathic low back pain, HIV neuropathic pain, trigeminal neuralgia, and/or central post-stroke pain.

Neuropathic pain can be associated with signals generated ectopically and often in the absence of ongoing noxious events by pathologic processes in the peripheral or central nervous system. This dysfunction can be associated with common symptoms such as allodynia, hyperalgesia, intermittent abnormal sensations, and spontaneous, burning, shooting, stabbing, paroxysmal or electrical-sensations, paresthesias, hyperpathia and/or dysesthesias, which can also be treated by the compounds and methods described herein.

Further, the compounds and methods described herein can be used to treat neuropathic pain resulting from peripheral or central nervous system pathologic events, including, but not limited to trauma, ischemia; infections or from ongoing metabolic or toxic diseases, infections or endocrinologic disorders, including, but not limited to, diabetes mellitus, diabetic neurophathy, amyloidosis, amyloid polyneuropathy (primary and familial), neuropathies with monoclonal proteins, vasculitic neuropathy, HIV infection, herpes zoster--shingles and/or postherpetic neuralgia; neuropathy associated with Guillain-Barre syndrome; neuropathy associated with Fabry's disease; entrapment due to anatomic abnormalities; trigeminal and other CNS neuralgias; malignancies; inflammatory conditions or autoimmune disorders, including, but not limited to, demyelinating inflammatory disorders, rheumatoid arthritis, systemic lupus erythematosus, Sjogren's syndrome; and cryptogenic causes, including, but not limited to idiopathic distal small-fiber neuropathy. Other causes of neuropathic pain that can be treated according to the methods and compositions described

herein include, but are not limited to, exposure to toxins or drugs (such as aresnic, thallium, alcohol, vincristine, cisplatinum and dideoxynucleosides), dietary or absorption abnormalities, immuno-globulinemias, hereditary abnormalities and amputations (including mastectomy). Neuropathic pain can also result from compression of nerve fibers, such as radiculopathies and carpal tunnel syndrome.

In another embodiment, methods are provided to treat patients with brain tumors by administering a compound selected according to the methods or processes described herein. In a further embodiment, methods are provided to treat patients with neurodegenerative diseases by administering a compound selected according to the methods or processes described herein. In one embodiment, the neurodegenerative disease can be Parkinson's disease. In another embodiment, the neurodegenerative disease can be Alzheimer's, Huntington's and/or Amyotrophic Lateral Sclerosis.

In another embodiment, the methods provided herein can be used prophylactically to prevent or protect against such diseases or neurological conditions, such as those described herein. In one embodiment, patients with a predisposition for an ischemic event, such as a genetic predisposition, can be treated prophylactically with the methods and compounds described herein. In another embodiment, patients that exhibit vasospasms can be treated prophylactically with the methods and compounds described herein. In further embodiment, patients that have undergone cardiac bypass surgery can be treated prophylactically with the methods and compounds described herein.

In addition, methods are provided to treat the following diseases or neurological conditions, including, but not limited to: chronic nerve injury, chronic pain syndromes, such as, but not limited to diabetic neuropathy, ischemia, ischemia following transient or permanent vessel occlusion, seizures, spreading depression, restless leg syndrome, hypocapnia, hypercapnia, diabetic ketoacidosis, fetal asphyxia, spinal cord injury, traumatic brain injury, status epilepticus, epilepsy, hypoxia, perinatal hypoxia, concussion, migraine, hypocapnia, hyperventilation, lactic acidosis, fetal asphyxia during parturition, brain gliomas, and/or retinopathies by administering a compound selected according to the methods or processes described herein.

Further provided are methods to attenuate the progression of an ischemic, hypoxic or excitotoxic cascade associated with a drop in pH by administering an effective amount of a compound that exhibits the properties described herein. In addition, methods are provided to decrease infarct volume associated with a drop in pH by administering a compound that exhibits the properties described herein. Further, a method is provided to decrease cell death

associated with a drop in pH by administering a compound that exhibits the properties described herein. Still further, methods are provided to decrease behavioral deficits associated with an ischemic event associated with a drop in pH by administering a compound that exhibits the properties described herein.

In one embodiment, the use of the compounds of the invention reduces symptoms of neuropathic pain, stroke, traumatic brain injury, epilepsy, and other neurologic events or neurodegeneration resulting from NMDA receptor activation.

Side Effects

In an additional aspect of the methods and processes described herein, the compound does not exhibit substantial toxic an/or psychotic side effects. Toxic side effects include, but are not limited to, agitation, hallucination, confusion, stupor, paranoia, delirium, psychotomimetic-like symptoms, rotarod impairment, amphetamine-like stereotyped behaviors, stereotypy, psychosis memory impairment, motor impairment, anxiolytic-like effects, increased blood pressure, decreased blood pressure, increased pulse, decreased pulse, hematological abnormalities, electrocardiogram (ECG) abnormalities, cardiac toxicity, heart palpitations, motor stimulation, psychomotor performance, mood changes, short-term memory deficits, long-term memory deficits, arousal, sedation, extrapyramidal side-effects, ventricular tachycardia. Lengthening of cardiac repolarisation, ataxia, cognitive deficits and/or schizophrenia-like symptoms.

In one embodiment, the compounds are selective NMDA receptor blockers. General blocking of NMDA receptors throughout the brain causes adverse effects such as ataxia, memory deficits, hallucinations and other neurological problems. The compounds provided herein can selectively block NR2B-containing NMDA receptors, have varying activity against receptors containing NR2A or NR2D, and may also be selective for other members of the NMDA receptor family (NR2C, NR3A and NR3B). IIn one embodiment, the compounds are NMDA receptors antagonists selective for NR2B, NR2A, NR2C, NR2D, NR3A, and/or NR3B and do not interact with other receptors or ion channels at therapeutic concentrations. In one embodiment, the compound is a selective NR1/NR2A NMDA receptor and/or a NR1/NR2B NMDA receptor antagonist. In one particular embodiment, the compounds can bind to the NR2B subunit of the NMDA receptor. In another particular embodiment, the

compounds are selective for the NR2B subunit of the NMDA receptor. In one embodiment, the compound is not an NMDA receptor glutamate site antagonist. In another embodiment, the compound is not an NMDA receptor glycine site antagonist.

The compounds selected or identified according to the processes and methods described herein generally avoid substantial side effects associated with other classes of NMDA receptor antagonists. In one embodiments, such compounds do not substantially exhibit the side effects associated with NMDA antagonists of the glutamate site, such as selfotel, D-CPPene (SDZ EAA 494) and AR-R15896AR (ARL 15896AR), including, agitation, hallucination, confusion and stupor (Davis et al. (2000) Stroke 31(2):347-354; Diener et al. (2002), J Neurol 249(5):561-568); paranoia and delirium (Grotta et al. (1995), J Intern Med 237:89-94); psychotomimetic-like symptoms (Loscher et al. (1998), Neurosci Lett 240(1):33-36); poor therapeutic ratio (Dawson et al. (2001), Brain Res 892(2):344-350); amphetamine-like stereotyped behaviors (Potschka et al. (1999), Eur J Pharmacol 374(2):175-187). In another embodiment, such compounds do not exhibit the side effects associated with NMDA antagonists of the glycine site, such as HA-966, L-701,324, d-cycloserine, CGP-40116, and ACEA 1021, including significant memory impairment and motor impairment (Wlaz, P (1998), Brain Res Bull 46(6):535-540). In a still further embodiment, such compounds do not exhibit the side effects of NMDA high affinity receptor channel blockers, such as MK-801 and ketamine, including, psychosis-like effects (Hoffman, D C (1992), J Neural Transm Gen Sect 89:1-10); cognitive deficits (decrements in free recall, recognition memory, and attention; Malhotra et al (1996), Neuropsychopharmacology 14:301-307); schizophrenia-like symptoms (Krystal et al (1994), Arch Gen Psychiatry 51:199-214; Lahti et al. (2001), Neuropsychopharmacology 25:455-467), and hyperactivity and increased stereotpy (Ford et al (1989) Physiology and behavior 46: 755-758.

In a further additional or alternative embodiment, the compound has a therapeutic index equal to or greater than at least 2:1, at least 3:1, at least 4:1, at least 5:1, at least 6:1, at least 7:1, at least 8:1, at least 9:1, at least 10:1, at least 15:1, at least 20:1, at least 25:1, at least 30:1, at least 40:1, at least 50:1, at least 75:1, at least 100:1 or at least 1000:1. The therapeutic index can be defined as the ratio of the dose required to produce toxic or lethal effects to dose required to produce therapeutic responses. It can be the ratio between the the median toxic dose (the dosage at which 50% of the group exhibits the adverse effect of the drug) and the median effective dose (the dosage at which 50% of the population respond to the drug in a specific manner). The higher the therapeutic index, the more safe the drug is considered to be. It simply indicates that it would take a higher dose to invoke a toxic

response that it does to cause a beneficial effect.

The side effect profile of compounds can be determined by any method known to those skilled in the art. In one embodiment, motor impairment can be measured by, for example, measuring locomotor activity and/or rotorod performance. Rotorod experiments involve measuring the duration that an animal can remain on an accelerating rod. In another embodiment, memory impairment can be assessed, for example, by using a passive avoidance paradigm; Sternberg memory scanning and paired words for short-term memory, or delayed free recall of pictures for long-term memory. In a further embodiment, anxiolytic-like effects can be measured, for example, in the elevated plus maze task. In other embodiments, cardiac function can be monitored, blood pressure and/or body temperature measured and/or electrocardiograms conducted to test for side effects. In other embodiments, psychomotor functions and arousal can be measured, for example by analyzing critical flicker fusion threshold, choice reaction time, and/or body sway. In other embodiments, mood can be assessed using, for example, self-ratings. In further embodiments, schizophrenic symptoms can be evaluated, for example, using the PANSS, BPRS, and CGI, side-effects were assessed by the HAS and the S/A scale.

In one embodiment, the compound does not exhibit substantial toxic side effects, such as, for example, motor impairment or cognitive impairment. In a particular embodiment, the compound has a therapeutic index equal to or greater than at least 2. In another embodiment, the compound is at least 10 times more selective for binding to an NMDA receptor than any other glutamate receptor. In certain embodiments, the compound activates hERG receptors at an IC_{50} at least 10 times the IC_{50} of inhibition of an NMDA receptor at either pH 6.9 or 7.6 or both. In certain embodiments, the compound activates adrenergic receptors, in particular α adrenergic such as $\alpha 1$ adrenergic receptors at an IC_{50} at least 10 times the IC_{50} of inhibition of an NMDA receptor at either pH 6.9 or 7.6 or both. In specific embodiments the ratio of IC_{50}'s between either hERG activation or adrenergic receptor activation and NMDA receptor antagonism is greater than 50, or greater than 100, or greater than 500.

Pharmaceutical Compositions

Mammals, and specifically humans, suffering from neuropathic pain, stroke, traumatic brain injury, epilepsy, and other neurologic events or neurodegeneration resulting from NMDA receptor activation, or any of the above-described conditions, and in particular suffering from neuropathic pain, can be treated by either targeted or systemic administration,

via oral, inhalation, topical, trans- or sub-mucosal, subcutaneous, parenteral, intramuscular, intravenous or transdermal administration of a composition comprising an effective amount of the compounds described herein or a pharmaceutically acceptable salt, ester or prodrug thereof, optionally in a pharmaceutically acceptable carrier.

The compounds or composition is typically administered by oral administration. Alternatively, compounds can be administered by inhalation. In another embodiment, the compound is administered transdermally (for example via a slow release patch), or topically. In yet another embodiment, the compound is administered subcutaneously, intravenously, intraperitoneally, intramuscularly, parenterally, or submucosally. In any of these embodiments, the compound is administered in an effective dosage range to treat the target condition.

In one embodiment, compounds of the present invention are administered orally. Oral compositions will generally include an inert diluent or an edible carrier. They may be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition..

When the compound is administered orally in the form of a dosage unit such as a tablets, pills, capsules, troches and the like, these can contain any of the following ingredients, or compounds of a similar nature: a binder (such as microcrystalline cellulose, gum tragacanth or gelatin); an excipient (such as starch or lactose), a disintegrating agent (such as alginic acid, Primogel, or corn starch); a lubricant (such as magnesium stearate or Sterotes); a glidant (such as colloidal silicon dioxide); a sweetening agent (such as sucrose or saccharin); and/or a flavoring agent (such as peppermint, methyl salicylate, or orange flavoring). When the dosage unit form is a capsule, it can contain, in addition to material of the above type, a liquid carrier (such as a fatty oil). In addition, dosage unit forms can contain various other materials which modify the physical form of the dosage unit, for example, coatings of sugar, shellac, or other enteric agents.

The compound or its salts can also be administered orally as a component of an elixir, suspension, syrup, wafer, chewing gum or the like. A syrup may contain, in addition to the active compounds, a sweetening agent (such as sucrose, saccharine, etc.) and preservatives, dyes and colorings and flavors.

The compounds of the invention may be also administered in specific, measured amounts in the form of an aqueous suspension by use of a pump spray bottle. The aqueous

suspension compositions of the present invention may be prepared by admixing the compounds with water and other pharmaceutically acceptable excipients. The aqueous suspension compositions according to the present invention may contain, inter alia, water, auxiliaries and/or one or more of the excipients, such as: suspending agents, e.g., microcrystalline cellulose, sodium carboxymethylcellulose, hydroxpropyl-methyl cellulose; humectants, e.g. glycerin and propylene glycol; acids, bases or buffer substances for adjusting the pH, e.g., citric acid, sodium citrate, phosphoric acid, sodium phospate as well as mixtures of citrate and phosphate buffers; surfactants, e.g. Polysorbate 80; and antimicrobial preservatives, e.g., benzalkonium chloride, phenylethyl alcohol and potassium sorbate.

In a separate embodiment, the compounds of the invention are in the form of an inhaled dosage. In this embodiment, the compounds may be in the form of an aerosol suspension, a dry powder or liquid particle form. The compounds may be prepared for delivery as a nasal spray or in an inhaler, such as a metered dose inhaler. Pressurized metered-dose inhalers ("MDI") generally deliver aerosolized particles suspended in chlorofluorocarbon propellants such as CFC-11, CFC-12, or the non-chlorofluorocarbons or alternate propellants such as the fluorocarbons, HFC-134A or HFC-227 with or without surfactants and suitable bridging agents. Dry-powder inhalers can also be used, either breath activated or delivered by air or gas pressure such as the dry-powder inhaler disclosed in the Schering Corporation International Patent Application No. PCT/US92/05225, published 7 Jan. 1993 as well as the Turbuhaler™ (available from Astra Pharmaceutical Products, Inc.) or the Rotahaler™ (available from Allen & Hanburys) which may be used to deliver the aerosolized particles as a finely milled powder in large aggregates either alone or in combination with some pharmaceutically acceptable carrier e.g. lactose; and nebulizers.

Solutions or suspensions used for parenteral, intradermal, subcutaneous, or topical application can include at least some of the following components: a sterile diluent (such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents); antibacterial agents (such as benzyl alcohol or methyl parabens); antioxidants (such as ascorbic acid or sodium bisulfite); chelating agents (such as ethylenediaminetetraacetic acid); buffers (such as acetates, citrates or phosphates); and/or agents for the adjustment of tonicity (such as sodium chloride or dextrose). The pH of the solution or suspension can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide.

A parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

Suitable vehicles or carriers for topical application can be prepared by conventional techniques, such as lotions, suspensions, ointments, creams, gels, tinctures, sprays, powders, pastes, slow-release transdermal patches, suppositories for application to rectal, vaginal, nasal or oral mucosa. In addition to the other materials listed above for systemic administration, thickening agents, emollients, and stabilizers can be used to prepare topical compositions. Examples of thickening agents include petrolatum, beeswax, xanthan gum, or polyethylene, humectants such as sorbitol, emollients such as mineral oil, lanolin and its derivatives, or squalene.

If administered intravenously, carriers can be physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, NJ) or phosphate buffered saline (PBS).

In one embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) are also preferred as pharmaceutically acceptable carriers. These may be prepared according to methods known to those skilled in the art, for example, as described in U.S. Patent No. 4,522,811 (which is incorporated herein by reference in its entirety). For example, liposome formulations may be prepared by dissolving appropriate lipid(s) (such as stearoyl phosphatidyl ethanolamine, stearoyl phosphatidyl choline, arachadoyl phosphatidyl choline, and cholesterol) in an inorganic solvent that is then evaporated, leaving behind a thin film of dried lipid on the surface of the container. An aqueous solution of the compound is then introduced into the container. The container is then swirled by hand to free lipid material from the sides of the container and to disperse lipid aggregates, thereby forming the liposomal suspension.

Dosing

The compound is administered for a sufficient time period to alleviate the undesired symptoms and the clinical signs associated with the condition being treated. In one embodiment, the compounds are administered less than three times daily. In one

embodiment, the compounds are administered in one or two doses daily. In one embodiment, the compounds are administered once daily. In some embodiments, the compounds are administered in a single oral dosage once a day.

The active compound is included in the pharmaceutically acceptable carrier or diluent in an amount sufficient to deliver to a patient a therapeutic amount of compound *in vivo* in the absence of serious toxic effects. An effective dose can be readily determined by the use of conventional techniques and by observing results obtained under analogous circumstances. In determining the effective dose, a number of factors are considered including, but not limited to: the species of patient; its size, age, and general health; the specific disease involved; the degree of involvement or the severity of the disease; the response of the individual patient; the particular compound administered; the mode of administration; the bioavailability characteristics of the preparation administered; the dose regimen selected; and the use of concomitant medication.

Typical systemic dosages for the herein described conditions are those ranging from 0.01 mg/kg to 1500 mg/kg of body weight per day as a single daily dose or divided daily doses. Preferred dosages for the described conditions range from 0.5-1500 mg per day. A more particularly preferred dosage for the desired conditions ranges from 5-750 mg per day. Typical dosages can also range from 0.01 to 1500, 0.02 to 1000, 0.2 to 500, 0.02 to 200, 0.05 to 100, 0.05 to 50, 0.075 to 50, 0.1 to 50, 0.5 to 50, 1 to 50, 2 to 50, 5 to 50, 10 to 50, 25 to 50, 25 to 75, 25 to 100, 100 to 150, or 150 or more mg/kg/day, as a single daily dose or divided daily doses. In one embodiment, the daily dose is between 10 and 500 mg/day. In another embodiment, the dose is between about 10 and 400 mg/day, or between about 10 and 300 mg/day, or between about 20 and 300 mg/day, or between about 30 and 300 mg/day, or between about 40 and 300 mg/day, or between about 50 and 300 mg/day, or between about 60 and 300 mg/day, or between about 70 and 300 mg/day, or between about 80 and 300 mg/day, or between about 90 and 300 mg/day, or between about 100 and 300 mg/day, or about 200 mg/day. In one embodiment, the compounds are given in doses of between about 1 to about 5, about 5 to about 10, about 10 to about 25 or about 25 to about 50 mg/kg. Typical dosages for topical application are those ranging from 0.001 to 100% by weight of the active compound.

The concentration of active compound in the drug composition will depend on absorption, inactivation, and excretion rates of the drug as well as other factors known to those of skill in the art. It is to be noted that dosage values will also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject,

specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that the dosage ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed composition. The active ingredient may be administered at once, or may be divided into a number of smaller doses to be administered at varying intervals of time.

Combination Treatment

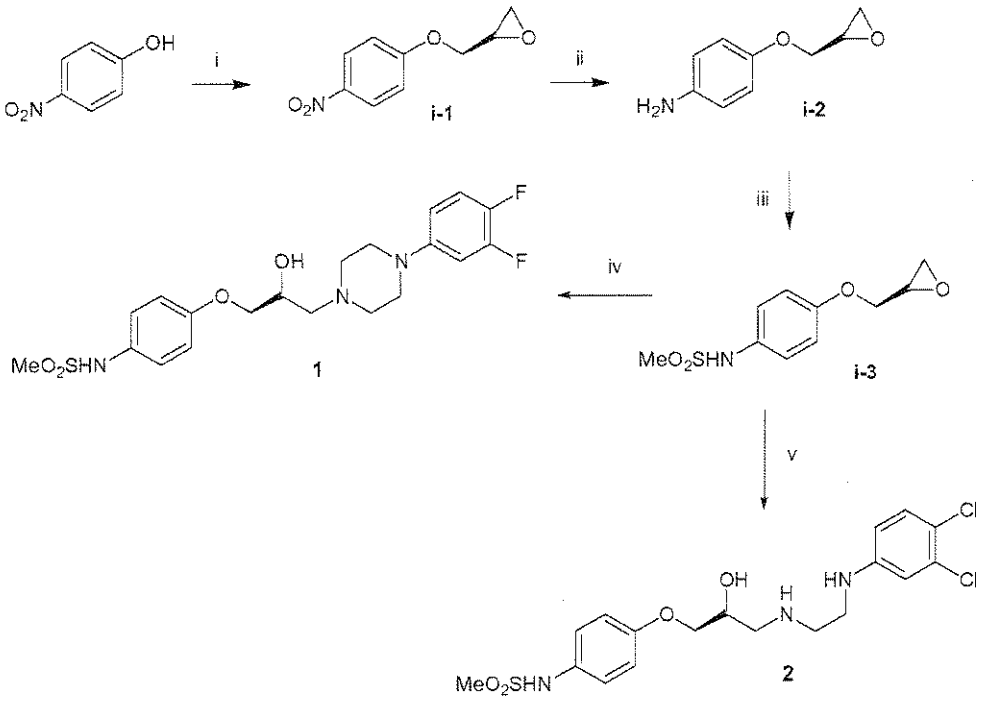
The compound can also be mixed with other active materials which do not impair the desired action, or with materials that supplement the desired action. The active compounds can be administered in conjunction, i.e. combination or alternation, with other medications used in the treatment or prevention neuropathic pain, stroke, traumatic brain injury, epilepsy, and other neurologic events or neurodegeneration resulting from NMDA receptor activation. In another embodiment, the compounds can be administered in conjunction (combination or alternation) with other medications used in treatment or prophylaxis of inflammatory conditions. In certain embodiments, the combination can be synergistic although in other embodiments the combination is not synergistic.

Emergency treatment for an ischemic stroke, particularly when the stroke is diagnosed within 3 hours of the start of symptoms, include thrombolytic, or clot-dissolving, medications such as tissue plasminogen activator (t-PA). Other treatments of an ischemic stroke involve administering to the patient an antiplatelet medication (aspirin, clopidogrel, dipyridamole), or anticoagulant medication (warfarin), dependent on the cause.Dextrorphan, a pharmacologically active metabolite of the cough suppressant dextromethorphan, is an NMDA antagonists studied in human stroke patients. Selfotel, a competitive NMDA antagonist, has also been tested in human patients, however it trends toward higher mortality within treated patients than within placebo-treated cohorts, and therefore, trials were stopped prematurely. A trial of another NMDA receptor antagonist, aptiganel HCl (Cerestat), was terminated. A large, 1367-patient, efficacy trial with the agent GV150526 was completed in 2000. (http://www.emedicine.com/neuro/topic488.htm, Lutsep & Clark "Neuroprotective Agents in Stroke", Apr. 30, 2004).

EXAMPLES

The following examples are provided to illustrate the present invention and are not intended to limit the scope thereof. Those skilled in the art will readily understand that kown variations of the conditions and processes of the following preparative procedures can be used to manufacture the desired compounds. The materials required for the mebodiments and the examples are known in the literature, readily commercially available, or can be made by known methods from the known starting materials by those skilled in the art.

Examples 1 and 2. N-(4-{3-[4-(3,4-Difluoro-phenyl)-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-phenyl)-methanesulfonamide (Compound 1) and N-(4-{3-[2-(3,4-Dichloro-phenylamino)-ethylamino]-2-(*S*)-hydroxy-propoxy}-phenyl)-methanesulfonamide (Compound 2).



Step (i). 3-(4-Nitro-phenoxy)-2-(*S*)-propyleneoxide (**i-1**). 4-Nitrophenol (6.6 mmol) was dissolved in 5 ml anhydrous DMF. Cesium fluoride (19.9 mmol) was added to the reaction. The reaction mixture was stirred for 1 hour at room temperature and (S)-Glycidyl nosylate (6.6 mmol) was added to the reaction mixture. The reaction stirred for 24 hours at room temperature. Water (150 mL) was added and the solution was extracted with ethyl acetate.

The organic phase was dried over $MgSO_4$ and evaporated. The residue was purified with column chromatograph using ethylacetate: hexane (50:50) solvent system to give the desired product **i-1** This step can be substituted with (*R*)-Glycidyl nosylate to get the R isomer.

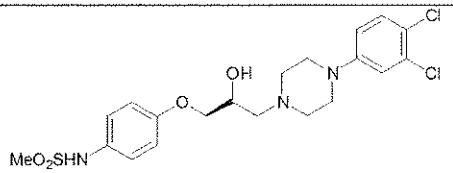
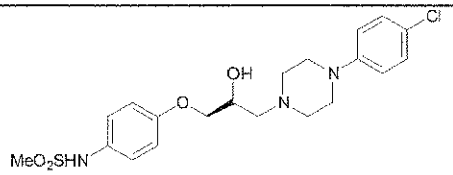
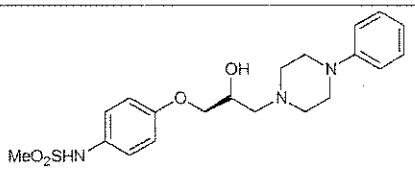
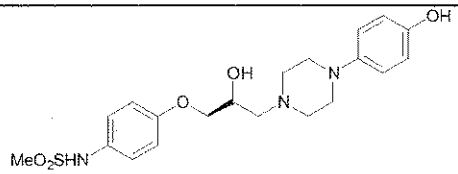
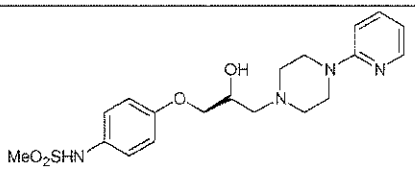
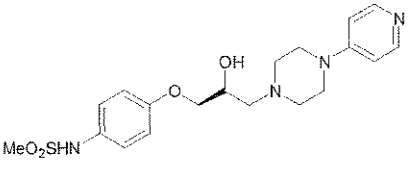
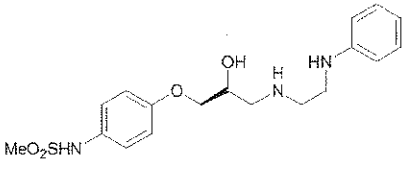
Step (ii). 3-(4-Amino-phenoxy)-2-(*S*)-propyleneoxide (**i-2**). (S)-Glycidyl-4-nitrophenyl ether (2.6 mmol, **i-1**) and 5% Pd/C(en)[{Sajiki et all, Chemistry- a europian journal 6(12):2200-2204 (2000).] (10% of the weight of starting material) in 5 ml anhydrous THF was hydrogenated at ambient pressure and temperature for 3 hours. The reaction mixture was filtered by using membrane filter (13, 0.22 μm) and the filtrate was concentrated in vacuum. The compound was afforded as a crude mixture of amino reduction compound **i-2**.

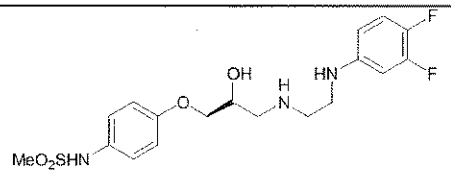
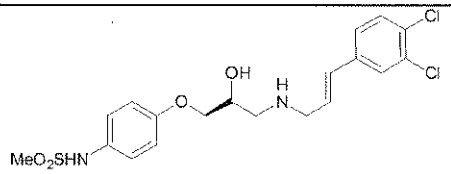
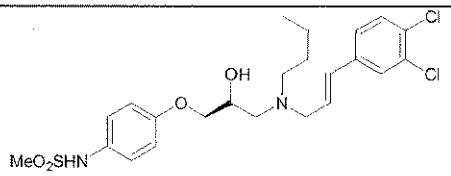
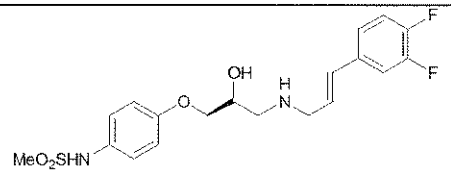
Step (iii). 3-(4-methansufonylamido-phenoxy)-2-(*S*)-propyleneoxide (**i-3**). (S)-Glycidyl-4-aminophenyl ether (2.4 mmol, **i-2**) dissolved in 20 ml anhydrous DCM and N,N-diisopropyl-N-ethylamine (2.6 mmol) was added at 0°C. After stirring 15 minutes methanesulfonyl chloride (2.6 mmol) was added drop wise to the reaction mixture at 0°C. After stirring over night, the reaction extracted with water and washed with brine. Organic phase dried over magnesium sulfate and evaporated. The residue was purified with flash chromatography using Ethyl acetate: DCM (30:70) solvent system to give the desired product **i-3**.

Step (iv). N-(4-{3-[4-(3,4-Difluoro-phenyl)-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-phenyl)-methanesulfonamide (Compound **1**). Compound **i-3** (2.00 mmol) and N-(3,4-Difluorophenyl)piperazine (2.00 mmol) were heated under reflux conditions in 20 ml ethanol for 8 hours. Then solvent was evaporated and residue was purified with flash chromatography using dichloromethane:methanol (90:10) solvent system to get compound **1**. Compound **1** was dissolved in ethanol and bubbled HCl gas to get the HCl salt of the compound **1**.

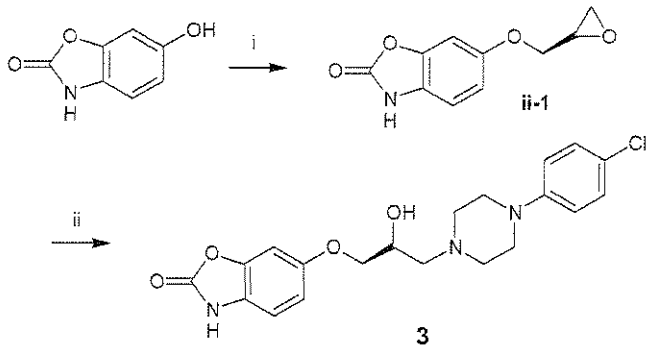
Step (v). N-(4-{3-[2-(3,4-Dichloro-phenylamino)-ethylamino]-2-(*S*)-hydroxy-propoxy}-phenyl)-methanesulfonamide (Compound **2**). The epoxide (**i-3**, 1.58 mmol) was dissolved in EtOH (20 ml), and then the 3,4-dicholoro-ethylene diamine (1.58 mmol) (preparation: Isabel Perillo, M. Cristina Caterina, Julieta López, Alejandra Salerno. Synthesis 2004, 6, 851-856) was added and the solution refluxed for 16 hours. The solvent was evaporated and the product purified with column chromatography using 10% MeOH/DCM + 1% NH_4OH to give compound **2**.

The following compounds were synthesized according to the procedures provided in examples 1 and 2.

COMPOUND	NAME AND PHYSICAL DATA
	N-(4-{3-[4-(3,4-Dichloro-phenyl)-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-phenyl)-methanesulfonamide MS: 475.14486
	N-(4-{3-[4-(4-Chloro-phenyl)-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-phenyl)-methanesulfonamide MS:440.14017
	N-(4-{3-[4-phenyl-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-phenyl)-methanesulfonamide MS:406.20183
	N-(4-{3-[4-(4-Hydroxy-phenyl)-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-phenyl)-methanesulfonamide
	N-(4-{3-[4-(2-Pyridyl)-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-phenyl)-methanesulfonamide
	N-(4-{3-[4-(4-Pyridyl)-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-phenyl)-methanesulfonamide
	N-{4-[2-(*S*)-Hydroxy-3-(2-phenylamino-ethylamino)-propoxy]-phenyl}-methanesulfonamide

	N-{4-[2-(*S*)-Hydroxy-3-(2-(3,4-difluoro-phenyl)amino-ethylamino)-propoxy]-phenyl}-methanesulfonamide MS:416.15842
	N-(4-{3-[3-(3,4-Dichloro-phenyl)-allylamino]-2-(*S*)-hydroxy-propoxy}-phenyl)-methanesulfonamide MS:446.09479
	N-[4-(3-{Butyl-[3-(3,4-dichloro-phenyl)-allyl]-amino}-2-(*S*)-hydroxy-propoxy)-phenyl]-methanesulfonamide MS:501.13871
	N-(4-{3-[3-(3,4-Difluoro-phenyl)-allylamino]-2-(*S*)-hydroxy-propoxy}-phenyl)-methanesulfonamide MS:413.58425

Example 3. 6-{3-[4-(4-Chloro-phenyl)-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-3H-benzooxazol-2-one (Compound 3).

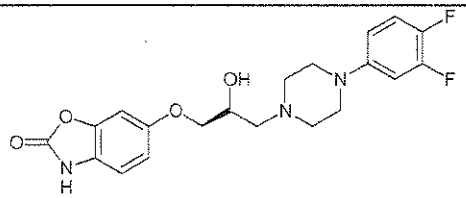
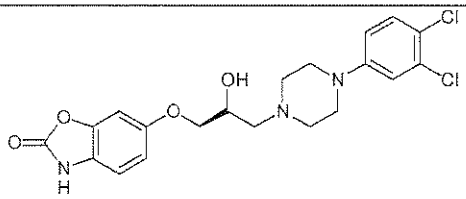
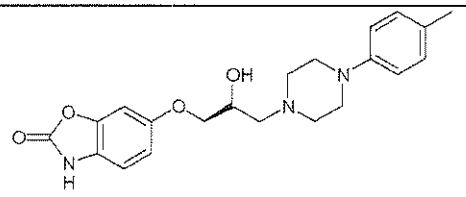


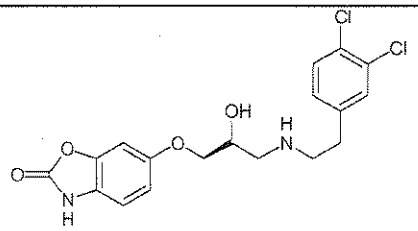
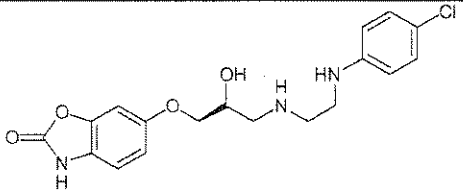
Step (i). 6-(2-(*S*)-Oxiranylmethoxy)-3H-benzooxazol-2-one (**ii-1**). 5-hydroxy-benzoxazole (310 mg) and cesium carbonate (780 mg) were combined in 6 mL of N,N-dimethylformamide. The reaction was stirred for room temperature for 1 hour. (S)-glycidal nosylate (520 mg) was added, and the reaction stiired at room temperature overnight. The reaction was quenched with NH_4Cl(aq) solution and extracted with ethyl acetate. The organic layer was washed with NH_4Cl(aq) and NaCl(aq) solutions, separated, and dried over

Na_2SO_4(s). Filtration and solvent removal was followed by absorption onto silica gel. Elution with an ethyl actate/methanol mixture (4:1) followed by solvent removal gave 445 mg of a yellow, oily solid.

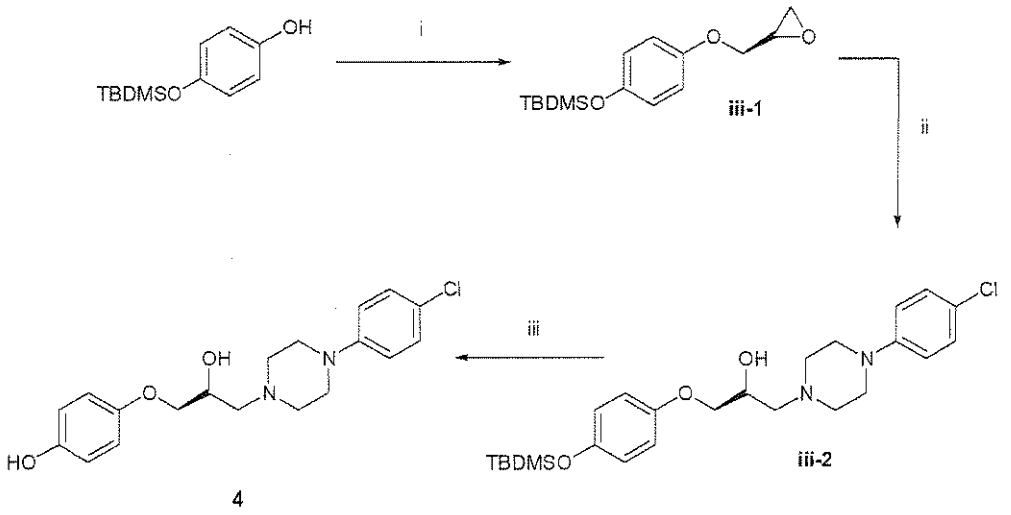
Step (ii). 6-{3-[4-(4-Chloro-phenyl)-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-3H-benzooxazol-2-one (Compound **3**). To a solution of 300 mg of epoxide (ii-1) in 10 mL of absolute ethanol was added 300 mg of 4-(4-chlorophenyl)-piperazine. The solution was heated to 70oC for 8 hours. The reaction was cooled andf the solvent removed under vaccum. The residue was purified by column chromatography on silica gel using ethyl acetate as solvent. Obtained 240 mg of a light brown solid (45% yield). 1HNMR (d6-DMSO, 400 MHz): δ 2.37 (dq, 2H, J=6Hz, J=13Hz), 2.51 (m, 4H), 3.02 (m, 4H), 3.68 (q, 1H, J=8Hz), 3.84 (dd, 1H, J=4Hz, J=14Hz), 4.02 (bs, 1H), 5.07 (d, 1H, J=5Hz), 6.61 (dd, 1H, J=2Hz, J=9Hz), 6.73 (d, 1H, J=2Hz), 6.91 (d, 2H, J=9Hz), 7.05 (d, 1H, J=8Hz), 7.21 (d, 2H, J=9Hz), 9.43 (s, 1H); MS (m/z): 404 (M+H), 406 (M+2+H); HRMS Calcd. for C20H23ClN3O4: 404.13771; Found: 404.13673.

The following compounds were synthesized according to the procedure in Example 3.

COMPOUND	NAME AND PHYSICAL DATA
	6-{3-[4-(3,4-Difluoro-phenyl)-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-3H-benzooxazol-2-one MS: 406.15664
	6-{3-[4-(3,4-Dichloro-phenyl)-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-3H-benzooxazol-2-one
	6-{3-[4-(4-Methyl-phenyl)-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-3H-benzooxazol-2-one MS: 384.19077

	6-{3-[2-(3,4-Dichloro-phenyl)-ethylamino]-2-(*S*)-hydroxy-propoxy}-3H-benzooxazol-2-one
	6-{3-[2-(4-Chloro-phenylamino)-ethylamino]-2-(*S*)-hydroxy-propoxy}-3H-benzooxazol-2-one MS: 378.12089

Example 4. 4-{3-[4-(3,4-Dichloro-phenyl)-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-phenol (Compound 4).

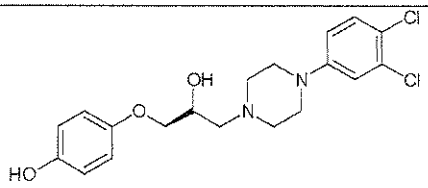
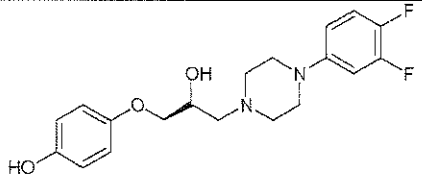
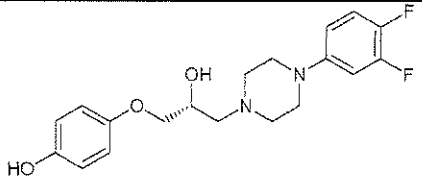


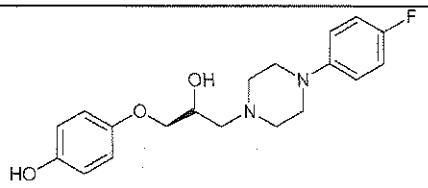
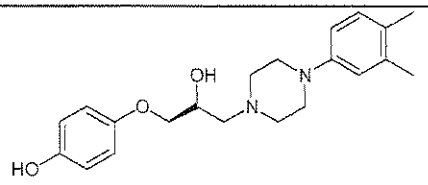
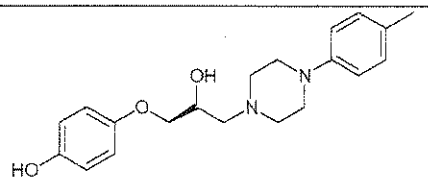
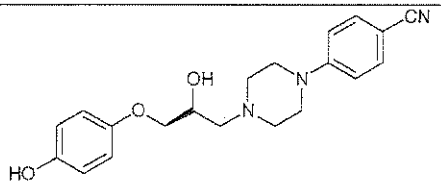
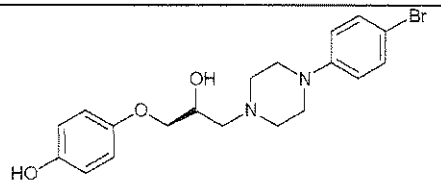
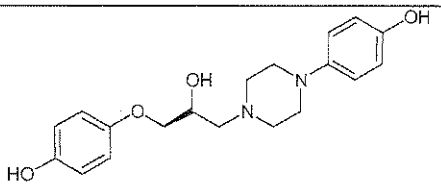
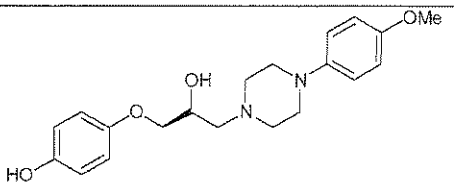
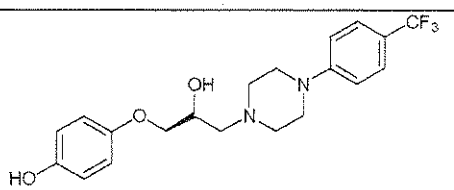
Step (i). 3-(4-tert-Butyldimethylsilyloxy-phenoxy)-2-(*S*)-propyleneoxide (**iii-1**). 4-(tert-Butyldimethylsiloxy)phenol (1.45 g, 6.25 mmol) in 5 ml anhydrous THF was added dropwise to the suspension of NaH (0.158 g, 6.25 mmol) in 5 ml THF. After stirring at room temperature for 2 hours glycidyl nosylate (1.30 g, 5 mmol) and then 15-crown-5 (25 mol%) were added to the reaction mixture. After stirring 24 hours reaction was poured to ice-water and extracted with ethyl acetate. Organic phase was washed with water and brine, then dried over sodium sulfate and evaporated. Product was purified by column chromatography using EtOAc: Hexane (1:9) (yield: 1.06 g 76%). ^{1}H-NMR (400MHz, CDCl3) δ 0.17 (6H, s), 0.98 (9H, s), 2.75 (1H, dd, *J*= 2.4, 4.4 Hz), 2.89 (1H, q, *J*= 4.4Hz), 3.33-3.36 (1H, m), 3.90 (1H, dd, *J*= 5.6, 10.8 Hz), 4.16 (1H, dd, *J*= 3.6, 11.2 Hz), 6.69-6.81 (4H, m).

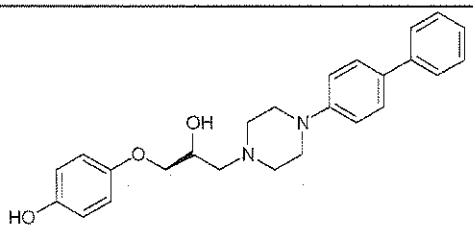
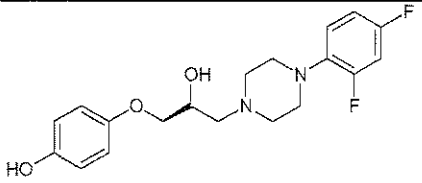
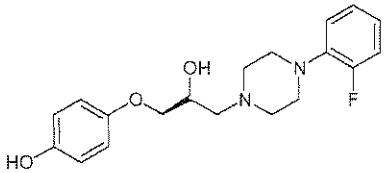
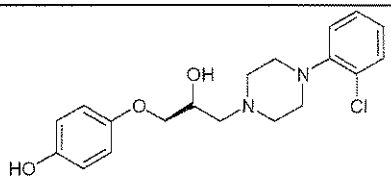
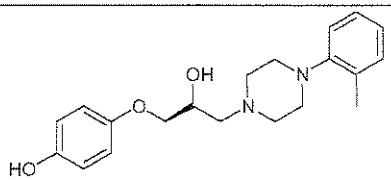
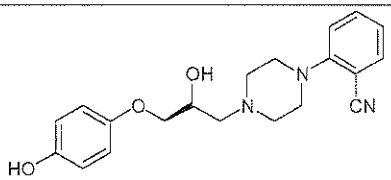
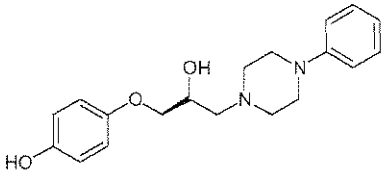
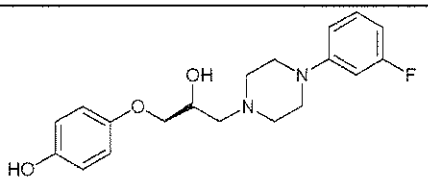
Step (ii). 4-{3-[4-(3,4-Dichloro-phenyl)-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-phenoxy-tert-butyldimethyl silane (**iii-2**). Compound **iii-1** (0.280 g, 1 mmol) and 1-(4-chlorophenyl)piperazine (0.200 g, 1 mmol) were dissolved in 5 ml EtOH and refluxed for 90 minutes. Solvent was evaporated and the material was used in the next step without purification.

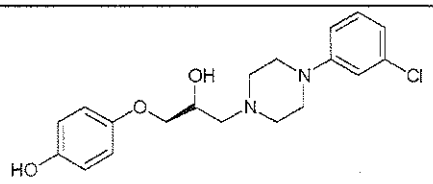
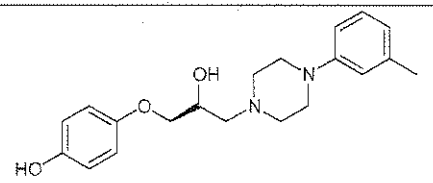
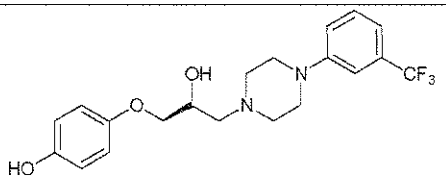
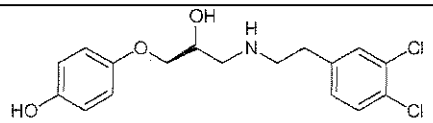
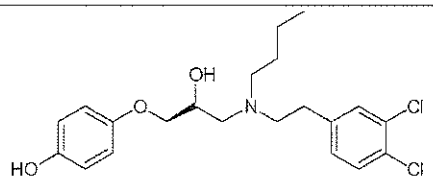
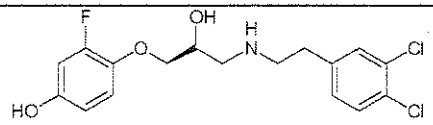
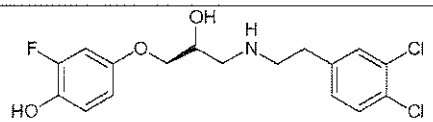
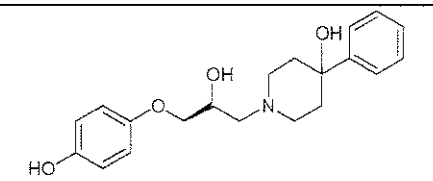
Step (iii). 4-{3-[4-(3,4-Dichloro-phenyl)-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-phenol (Compound **4**). Compound **iii-2** was dissolved in 5 ml THF and 2 ml TBAF in 1.0M THF solution was added, and stirred for 2 hours. Quenched with ammonium chloride solution, extracted with EtOAc. Organic phase was dried over sodium sulfate and evaporated. Product was purified using column chromatography using EtOAc:MeOH (95:5). 1H-NMR (400MHz, DMSO-d6) δ 2.36-2.61 (6H, m), 3.11 (4H, t, *J*= 4.8 Hz), 3.76 (1H, dd, *J*= 4.0, 6.0 Hz), 386(1H, dd, *J*= 4.4, 10.0 Hz), 3.91-3.95 (1H, m), 4.85 (1H, d, *J*= 4.8 Hz), 6.66 (1H, dd, *J*= 2.4, 6.8 Hz), 6.75 (1H, dd, *J*= 2.4, 6.8 Hz), 6.92 (1H, dd, *J*= 2.4, 6.8 Hz), 7.21 (1H, dd, *J*= 2.4, 6.8 Hz), 8.90 (1H, s). HRMS: 362.1397 calculated. 362.14696 found.

The following compounds were synthesized according to Example 4.

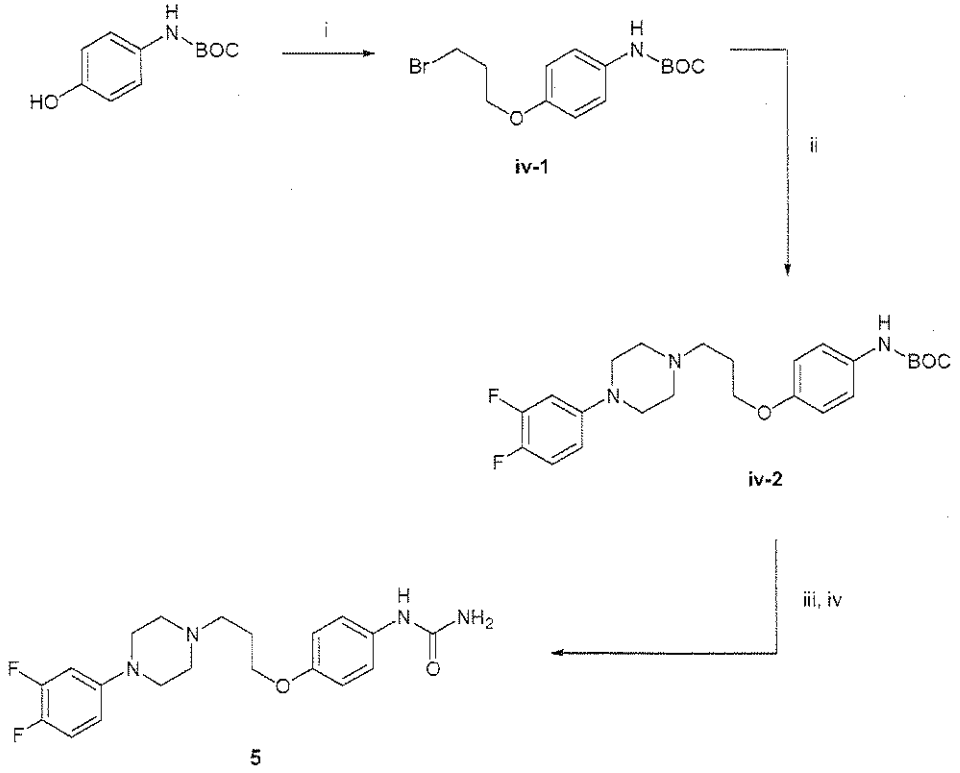
COMPOUND	NAME AND PHYSICAL DATA
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	4-{3-[4-(3,4-Difluoro-phenyl)-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-phenol MS:365.16672
	4-{3-[4-(3,4-Difluoro-phenyl)-piperazin-1-yl]-2-(*R*)-hydroxy-propoxy}-phenol MS: 365.16657

	4-{3-[4-(4-Fluoro-phenyl)-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-phenol MS:347.17602
	4-{3-[4-(3,4-Dimethyl-phenyl)-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-phenol MS:357.21716
	4-{3-[4-(4-Methyl-phenyl)-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-phenol MS:343.20093
	4-{3-[4-(4-Cyano-phenyl)-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-phenol MS:354.18073
	4-{3-[4-(4-Bromo-phenyl)-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-phenol MS:407.09663
	4-{3-[4-(4-Hydroxy-phenyl)-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-phenol MS:345.18061
	4-{3-[4-(4-Methoxy-phenyl)-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-phenol MS:359.19608
	4-{3-[4-(4-Trifluoromethyl-phenyl)-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-phenol MS:397.17327

	4-{3-[4-(4-Biphenyl)-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-phenol MS: 405.21643
	4-{3-[4-(2,4-Difluoro-phenyl)-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-phenol MS:365.16651
	4-{3-[4-(2-Fluoro-phenyl)-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-phenol MS:347.17595
	4-{3-[4-(2-Chloro-phenyl)-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-phenol MS: 363.14695
	4-{3-[4-(2-Chloro-phenyl)-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-phenol MS:343.20108
	4-{3-[4-(2-Cyano-phenyl)-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-phenol MS:354.18070
	4-{3-[4-Phenyl-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-phenol MS:329.18547
	4-{3-[4-(3-Fluoro-phenyl)-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-phenol MS:347.17608

	4-{3-[4-(3-Chloro-phenyl)-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-phenol MS:363.14741
	4-{3-[4-(3-Methyl-phenyl)-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-phenol MS:343.20109
	4-{3-[4-(3-Trifluoromethyl-phenyl)-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-phenol MS:397.17269
	4-{3-[2-(3,4-Dichloro-phenyl)-ethylamino]-2-(*S*)-hydroxy-propoxy}-phenol MS:357.10159
	4-(3-{Butyl-[2-(3,4-dichloro-phenyl)-ethyl]-amino}-2-(*S*)-hydroxy-propoxy)-phenol MS:413.12769
	4-{3-[2-(3,4-Dichloro-phenyl)-ethylamino]-2-(*S*)-hydroxy-propoxy}-3-fluoro-phenol MS:375.03418
	4-{3-[2-(3,4-Dichloro-phenyl)-ethylamino]-2-(*S*)-hydroxy-propoxy}-2-fluoro-phenol MS:375.03409
	1-[2-(*S*)-Hydroxy-3-(4-hydroxy-phenoxy)-propyl]-4-phenyl-piperidin-4-ol MS:344.18509

Example 5a. (4-{3-[4-(3,4-Difluoro-phenyl)-piperazin-1-yl]-propoxy}-phenyl)-urea (Compound 5).



Step (i). [4-(3-Bromo-propoxy)-phenyl]-carbamic acid tert-butyl ester (**iv-1**). To a solution of 2.1g of 4-t-butylcarbonylamino-phenol in 20 mL of acetonitrile was added 3.25g of cesium carbonate. The reaction was stirred for one hour, and then 1.5 mL of 1,3-dibromopropane was added and the reaction stirred for 20 hours. The reaction was then quenched with NH_4Cl(aq.) solution. The mixture was extracted with ethyl acetate and washed with NH_4Cl(aq.) and NaCl(aq.) solutions. The organic layer was separated and dried over Na_2SO_4(s). Filtration and solvent removal gave a light brown oily solid. Hexanes were added and the resulting solids filtered and washed with Hexanes three times. Drying gave 2.4g of an off-white solid.

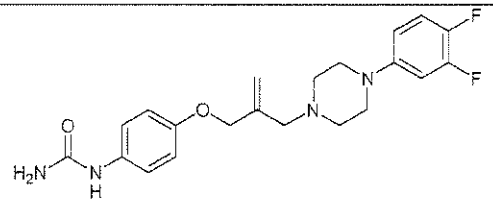
Step (ii). (4-{3-[4-(3,4-Difluoro-phenyl)-piperazin-1-yl]-propoxy}-phenyl)-carbamic acid tert-butyl ester (**iv-2**). To 305 mg of 4-(3,4Difluoro-phenyl)-piperazine and 335 mg of compound **iv-1** was added 5 mL of acetonitrile. The reaction was heated to 65°C overnight. The reaction was cooled, and then extracted with ethyl acetate. The organic layers were washed with $NaHCO_3$(aq.) twice, and the organic layers separated and dried over Na_2SO_4(s).

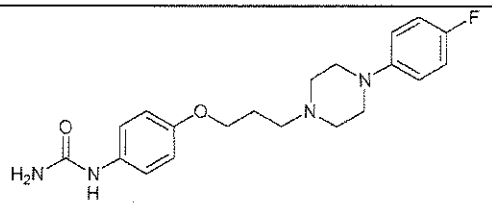
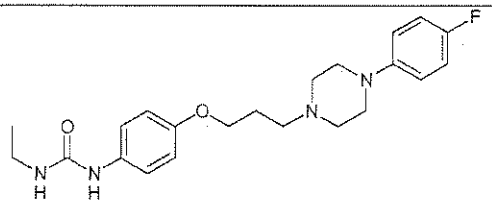
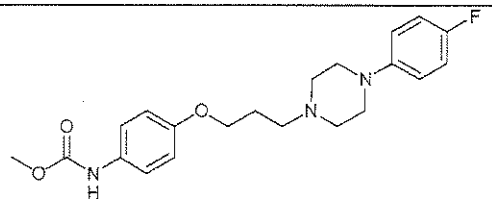
Filtration and solvent removal gave an light brown solid. Dilution with hexanes, filtration, and washing with hexanes gave 458 mg of a white solid (**iv-2**). MS (m/z): 430 (M+H); HRMS: Obsd for $C_{24}H_{33}FN_3O_3$: 430.24951.

Step (iii). Compound **iv-2** (430 mg) was dissolved in 6 mL of dichloromethane. Next, 4 mL of trifluoroacetic acid was added and the reaction was stirred for 6 hours. Then $NaHCO_3$(s) was added until the bubbling stopped. Then water was added to the reaction mixture and the reaction was extracted with dichloromethane and washed with $NaHCO_3$(aq.) twice. The organics were dried over Na_2SO_4(s), and then the solution was filtered and the solvent removed under vacuum. The residue was used in the next step without any purification.

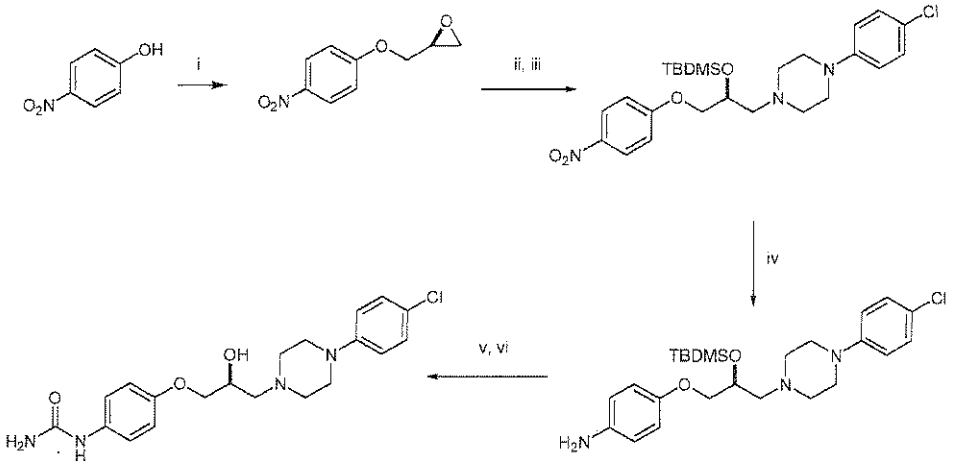
Step (iv). (4-{3-[4-(3,4-Difluoro-phenyl)-piperazin-1-yl]-propoxy}-phenyl)-urea (Compound **5**). The aniline from the previous step was dissolved in 10 mL of N,N-dimethyl formamide. Next, 1 mL of trimethylsilyl isocyanate was added, and the reaction was stirred at room temperature overnight. The reaction was then quenched with $NaHCO_3$(aq.) solution. The reaction was extracted with ethyl acetate and washed with $NaHCO_3$(aq.) solution twice. The organic layer was separated and dried over Na_2SO_4(s). Filtration and solvent removal gave a brown solid. Filtration over a plug of silica gel with ethyl acetate/methanol (4:1) was followed by solvent removal. Trituration of the resulting solids with ethyl ether and filtration gave 98 mg of an off-white solid. MS (m/z): 391 (M+H); HRMS: calcd. for $C_{20}H_{25}F_2N_4O_2$: 391.19456, Found: 391.19184.

The following compounds were synthesized according to the methods and variation s of described for Example 5.

COMPOUND	NAME AND PHYSICAL DATA
	(4-{2-[4-(3,4-Difluoro-phenyl)-piperazin-1-ylmethyl]-allyloxy}-phenyl)-urea MS: 403.19326

	(4-{3-[4-(4-Fluoro-phenyl)-piperazin-1-yl]-propoxy}-phenyl)-urea MS: 373.20319
	1-Ethyl-3-(4-{3-[4-(4-fluoro-phenyl)-piperazin-1-yl]-propoxy}-phenyl)-urea
	(4-{3-[4-(4-Fluoro-phenyl)-piperazin-1-yl]-propoxy}-phenyl)-carbamic acid methyl ester MS: 388.20251

Example 5b. (4-{3-[4-(4-Chloro-phenyl)-piperazin-1-yl]-2-(*S*)-hydroxy-propoxy}-phenyl)-urea.



Step (ii). Epoxide ring opening with p-chlorophenyl-piperazine. To a solution of 1.1g of p-chloro-phenyl-piperazine in 10mL of ethanol was added 0.95 g of the S-epoxide. The solution was heated for 18 hours at 70°C. The reaction was cooled, and extracted with dichloromethane. The organic layers were washed twice with $NaHCO_3$(aq.) solution. The organic layers were separated, and then dried over Na_2SO_4(s). Filtration and solvent removal gave an oily residue. Next, ethyl ether was triturated in and the resulting solids filtered and

dried. Obtained 1.49g of piperazine compound as a light yellow solid. ^{1}H NMR (400 MHz, CDCl3): 2.64 (m, 4H), 2.86 (m, 2H), 3.08 (m, 1H), 3.19 (m, 4H), 4.12 (m, 2H), 4.18 (m, 1H), 6.85 (d, 2H, J=8Hz), 7.01 (d, 2H, J=11Hz), 8.21 (d, 2H, J=9Hz); ms (m/z): 392 (M+H). HRMS: m/z 392.13665 – theoretical for $C_{19}H_{23}O_4N_3Cl$ – 392.13716.

Step (iii). Silyl ether formation p-chlorophenyl-piperazine. To a solution of 1.2g of alcohol i-2 in dichloromethane was added 600mg of *t*-butyldimethylsilyl chloride, 1mL of diisopropylethyl amine, and 600mg of 4-N,N-dimethylaminopyridine. The reaction was stirred for 1 day, then 150mg of *t*-butyldimethylsilyl chloride was added. Stirring for a third day was followed by addition of a third alloquat of 150 mg of *t*-butyldimethylsilyl chloride. Stirring for an additional day was followed by solvent removal and absorption onto silica gel. The residue was filtered with a 3:1-Hexane-ethyl acetate mixture and the solvent was removed under vacuum. 1.1g of a yellow, oily solid was obtained. ^{1}H NMR($CDCl_3$): δ 0.08 (s, 3H), 0.11 (s, 3H), 0.88 (s, 9H), 2.52 (m, 2H), 2.65 (m, 4H), 3.13 (t, 4H, J=4Hz), 3.98 (dd, 1H, J=7Hz, J=9Hz), 4.16 (m, 1H), 4.22 (dd, 1H, J=3Hz, J=9Hz), 6.81 (d, 2H, J=9Hz), 6.96 (d, 2H, J=9Hz), 7.18 (d, 2H, J=9Hz), 8.18 (d, 2H, J=9Hz); MS (m/z): 506 (M+H); HRMS: Calcd. for $C_{25}H_{37}ClN_3O_4Si$: 506.22419; Found: 506.22577.

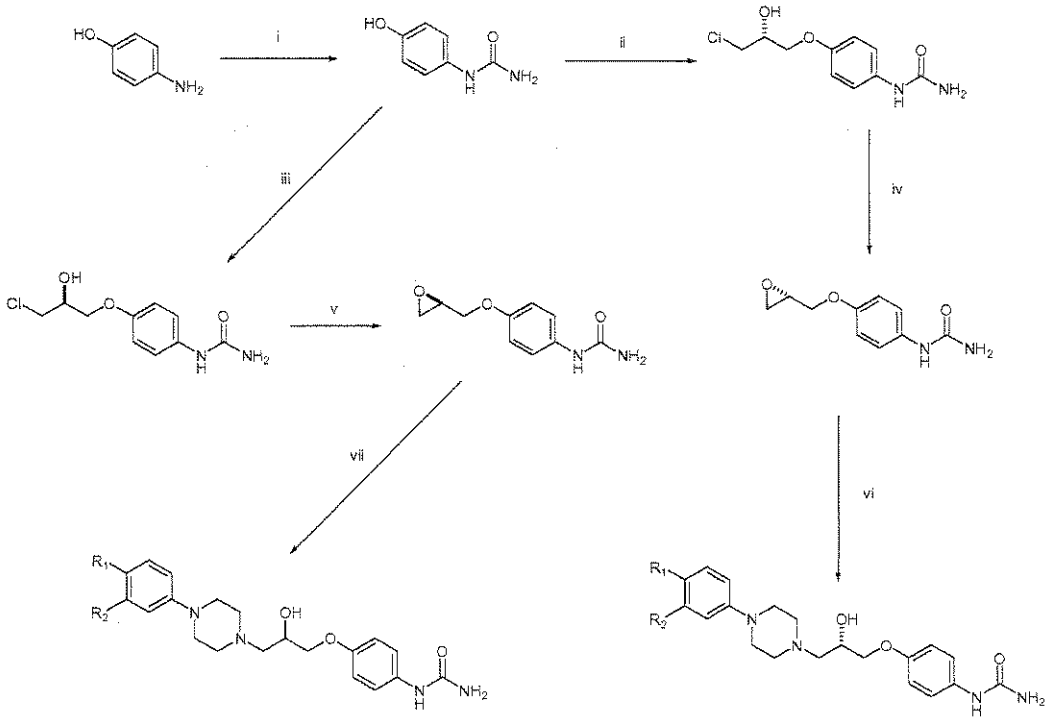
Step (iv). Nitro group reduction. To a solution of 25mg of silyl ether i-3 in 6 mL of N,N-dimethylformamide was added 1g of tin(II)chloride hydrate. The reaction was heated to 65°C for 20 hours. The reaction was cooled and quenched by pouring over $NaHCO_3$(aq.) solution. The mixture bubbled and was allowed to subside. Ethyl acetate was added, and the materials filtered through celite. The organic layer was extracted with NaHCO3(aq.) solution. The aqueous layers were re-extracted with ethyl acetate and the organic layers were combined and dried over sodium sulfate. Filtration, solvent removal, and column chromatography gave 210mg of a clear oil. Repetition with 450mg of nitro compound i-3 gave 290mg of aniline.

Step (v). Urea formation. To a solution of 500mg of aniline in 6 mL of N,N-dimethyl formamide was added 1 mL of trimethylsilyl isocyanate. The reaction was stirred for 2 days. An additional 0.5 mL of trimethylsilyl isocyanate was added and followed by stirring for 2 more days. The reaction was extracted with ethyl acetate, and washed with $NaHCO_3$(aq.) solution. The organic layer was separated and dried over Na_2SO_4(s). Filtration, solvent removal, and column chromatography gave 410mg of a waxy, white solid. 1H NMR(d^6-

DMSO): δ 0.04 (s, 3H), 0.07 (s, 3H), 0.83 (s, 9H), 2.39 (m, 2H), 2.48 (m, 4H), 3.08 (t, 4H, J=4Hz), 3.75 (dd, 1H, J=7Hz, J=10Hz), 3.98 (dd, 1H, J=3Hz, J=10Hz), 4.08 (m, 1H), 5.69 (s, 2H), 6.76 (d, 2H, J=9Hz), 6.89 (d, 2H, J=9Hz), 7.18 (d, 2H, J=9Hz), 7.23 (d, 2H, J=9Hz), 8.28 (s, 1H).

Step (vi). Desilylation. 400mg of silyl ether i-5 was dissolved in 10 mL of tetrahydrofuran. Next, 2 mL of a tetrabutylammonium fluoride solution (1M, in THF, Aldrich) was added. The reaction was stirred overnight, and then saturated NH_4Cl(aq.) solution was added. The mixture was diluted with ethyl acetate, and the resulting solids filtered. The solids were washed with water, ethyl acetate, and ethyl ether (three times each). Drying gave 220mg of an off-white powder. ^{1}H NMR (d^6-DMSO): 2.42 (m, 2H), 2.54 (m, 4H), 3.08 (t, 4H, J=4Hz), 3.77 (dd, 1H, J=6Hz, J=9Hz), 3.89 (m, 2H), 4.85 (d, 1H, J=5Hz), 5.68 (s, 2H), 6.78 (d, 2H, J=9Hz), 6.89 (d, 2H, J=9Hz), 7.18 (d, 2H, J=9Hz), 7.23 (d, 2H, J=9Hz), 8.27 (s, 1H); MS (m/z): 405 (M+H), 407 (M+2+H); HRMS: calcd for $C_{20}H_{26}N_4O_3{}^{35}Cl$: 405.16934; observed: 405.16872. The p-toluene sulfonate salt was formed by taking 70mg of the free base and mixing in 50mg of p-toluene sulfonic acid hydrate. The mixture was diluted with 5 mL tetrahydrofuran and 3 mL ethanol and heated to 60°C until all solids had dissolved. The mixture was cooled, and 90% of the solvent removed under vacuum. Next, ethanol was added and allowed to stand at room temperature for several hours. The resulting solids were filtered, washed with ethanol three times and dried. Obtained 80mg of a fluffy, white solid. ^{1}H NMR (d^6-DMSO): 2.25 (s, 3H), 2.99 (m, 2H), 3.09 (m, 2H), 3.22 (m, 2H), 3.58 (m, 2H), 3,79 (m, 2H), 3.87 (m, 2H), 4.28 (s, 1H), 5.74 (s, 2H), 5.97 (s, 1H), 6.81 (d, 2H, J=8Hz), 6.99 (d, 2H, J=8Hz), 7.08 (d, 2H, J=7Hz), 7.27 (t, 4H, J=8Hz), 7.44 (d, 2H, J=8Hz), 8.36 (s, 1H), 9.58 (s, 1H); Anal. Calc. For $C_{20}H_{25}N_4O_3Cl$-pTsOH-H2O: C, 54.49, H, 5.93, N, 9.41; Found: C, 54.82, H, 5.77, N, 9.42.

Example 5c. Synthesis of *R* and *S* hydroxy-propyl urea piperazines.



Step (i). Preparation of 1-(4-hydroxyphenyl)urea.

To a solution of 10.92 g of 4-hydroxy-aniline in 100 mL of tetrahydrofuran at 65°C was added 20 mL of trimethylsilyl isocyanate (85%, Aldrich). The solution was heated at 65°C for 6 hours. The solution was cooled to room temperature, and then 100 mL of ethanol and 10g of silica gel were added. The reaction was stirred at room temperature overnight. The solvent was removed under vacuum. The solids were diluted with a 1:1 mixture of dichloromethane and ethanol (500 mL). After all the solids had dissolved, the solution was filtered over a plug of silica gel. The solvent was removed under vacuum. Next, dichloromethane was added and the solids were filtered and washed with dichloromethane three times. The resulting solids were then dried. The reaction gave 15.5g of a fine white powder (100% yield). ^{1}H NMR (d^6-DMSO): δ 5.62 (s, 2H), 6.58 (d, 2H, J=9 Hz), 7.1 (d, 2H, J=9 Hz), 8.12 (s, 1H), 8.91 (s, 1H); MS: 187 (M+Cl); HRMS: 187.02821.

Step (ii). Preparation of (*R*)-1-(4-(3-chloro-2-hydroxypropoxy)phenyl)urea. (T. Fujioka *et al. Chem. Pharm. Bull.* **44**(*8*), **1996**, 1596-1598.)

To a solution of 1.52 g (10 mmoles) of 1-(4-hydroxyphenyl)urea in 10 mL of methanol and 10 mL of water was added 0.5 mL of triethylamine, followed by 8 mL of (*R*)-epichlorohydrin. The reaction was homogeneous, and was stirred at room temperature for 20 hours. The reaction was diluted with 50 mL of water and extracted with 5 X 100 mL portions of ethyl acetate. The organics were washed with dilute HCl (aq.) and NaCl (aq.) solutions. The organics were separated and dried over Na_2SO_4(s). Filtration and solvent removal gave an oily residue, which was absorbed onto silica gel. The crude product was then subjected to purification by column chromatography with a gradiant based on a 90:10:1 mixture of dichloromethane:methanol:NH_4OH and dichloromethane. The fractions of interest were combined and the solvent removed under vacuum. The resulting pink solid was dried under vacuum to give 1.62 g of fluffy white solid (66% yield). ^{1}H NMR: (d^6-DMSO): δ 3.62 (dd, 1H, J=6Hz, J=11Hz), 3.71 (dd, 1H, J=5Hz, J=11Hz), 3.86 (d, 2H, J=5Hz), 3.96 (m, 1H), 5.49 (d, 1H, J=6Hz), 5.69 (s, 2H), 6.78 (d, 2H, J=9Hz), 7.24 (d, 2H, J=9Hz), 8.29 (s, 1H); MS: 279 (M+Cl); HRMS: 279.03124.

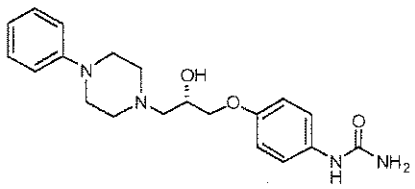
Step (iii). Preparation of (*S*)-1-(4-(3-chloro-2-hydroxypropoxy)phenyl)urea. Following the exact procedure of the *R*-enantiomer, 1.52 g (10 mmoles) of 1-(4-hydroxyphenyl)urea and 8 mL of (*S*)-epichlorohydrin gave 1.39 g (57% yield) of light pink solid. The compound had identical ^{1}HNMR and MS spectra to the (*R*)-enantiomer.

Step (iv). (*S*)-1-(4-(oxiran-2-ylmethoxy)phenyl)urea. (T. Fujioka *et al. Chem. Pharm. Bull.* **44**(*8*), **1996**, 1596-1598.) To a solution of 1.62 g of the (*R*)-chlorohydrin (**3**) in 70 mL of isopropanol and 10 mL of water at 0°C was added a solution of 2 g of KOH dissolved in 12 mL of water. The reaction was stirred for 2 hours at 0°C, during which time a white precipitate formed. After 2.5 hours, 100 mL of ethyl acetate was added and the reaction was allowed to warm to room temperature. The organic layer was washed with NaCl (aq.) solution. The aqueous layer was extracted with 4 X 100 mL of ethyl acetate, and the organic layers were combined and dried over Na_2SO_4(s). Filtration and solvent removal gave a white residue. Ethyl ether was added and the solids were filtered and washed with ethyl ether three times. Drying gave 1.23 g of a white, fluffy solid (89% yield). ^{1}H NMR (d^6-DMSO): δ 2.65 (dd, 1H, J=3Hz, J=5Hz), 2.79 (t, 1H, J=5Hz), 3.25 (m, 1H), 3.71 (dd, 1H, J=7Hz, J=12Hz), 4.2 (dd, 1H, J=3Hz, J=12Hz), 5.7 (s, 2H), 6.79 (d, 2H, J=9Hz), 7.25 (d, 2H, J=9Hz), 8.3 (s, 1H); MS: 243 (M+Cl); HRMS: 243.05458.

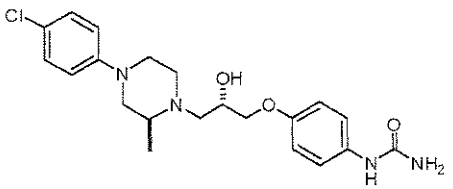
Step (v). (*R*)-1-(4-(oxiran-2-ylmethoxy)phenyl)urea.

Using the same procedure as for the (S)-enantiomer, 1.39 g of the S-chlorohydrin gave 1.11g (93% yield) of the *R*-epoxide as a fluffy, white solid. This compound had identical ^{1}H NMR and MS as the S-enantiomer.

Specific exemplary syntheses for step (vi):

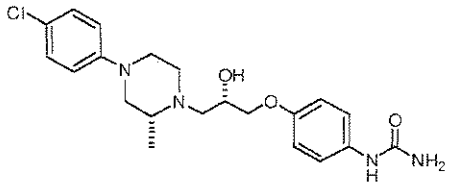


(*S*)-1-(4-(2-hydroxy-3-(4-phenylpiperazin-1-yl)propoxy)phenyl)urea. A mixture of 0.1 g of (*S*)-1-(4-(oxiran-2-ylmethoxy)phenyl)urea, 0.14 g of *N*-phenyl-piperazine, and 6 mL of abosolute ethanol was heated to 70°C for 20 hrs. The reaction was cooled, and the resulting precipitate collected by filtration. The solids were washed three times with ethanol, and dried. 0.126 g of the title compound was obtained as a fluffy white powder was obtained. ^{1}H NMR (d^6-DMSO): δ 2.36 (dd, 1H, J=6Hz, J=13Hz), 2.48 (m, 1H), 2.55 (m, 4H), 3.08 (t, 4H, J=5Hz), 3.78 (dd, 1H, J=6Hz, J=9Hz), 3.89 (m, 1H), 3.93 (m, 1H), 4.84 (d, 1H, J=5Hz), 5.68 (s, 2H), 6.73 (t, 1H, J=8Hz), 6.78 (d, 2H, J=9 Hz), 6.88 (d, 2H, J=8Hz), 7.16 (t, 2H, J=8Hz), 7.24 (d, 2H, J=9Hz), 8.27 (s, 1H); MS: 371 (M+H); HRMS: Observed: 371.20723; HPLC: 100% peak area composition; retention time = 6.64 min.

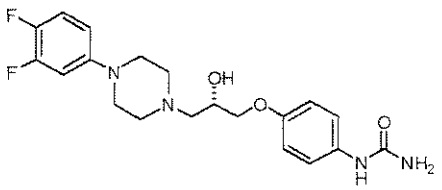


1-(4-((S)-3-((S)-4-(4-chlorophenyl)-2-methylpiperazin-1-yl)-2-hydroxypropoxy)phenyl) urea. A solution of 0.5 mmol of the (S)-epoxide and 0.6 mmol (3S)-1-(4-chlorophenyl)-3-methylpiperazine in 5 ml ethanol was refluxed for overnight. The solvent was evaporated and product was purified with the column chromatography using

dichloromethane:methanol:NH_4OH (90:10:1). After the column it was crystallized with ethyl acetate to give 0.109 g (52% yield). ^1H NMR (400 MHz, d6-DMSO): δ 1.01 (3H, d, J = 6.0 Hz), 2.16 (1H, dd, J = 5.6, 12.8 Hz), 2.34-2.51 (3H, m), 2.78-2.89 (2H, m), 2.99 (1H, d, J = 11.6 Hz), 3.38 (2H, d, J = 11.2 Hz), 3.75-3.79 (1H, m), 3.88-3.92 (2H, m), 4.84, (1H, d, J = 5.2 Hz), 5.67 (2H, s), 6.78 (2H, d, J = 7.2 Hz), 6.88 (2H, d, J = 9.2 Hz), 7.17 (2H, d, J = 7.2 Hz), 7.23 (2H, d, J = 9.2 Hz), 8.25 (1H, s); MS: 419 (M+H); HRMS= 419.18431; HPLC= 96% peak area at 7.7 min. retention time.

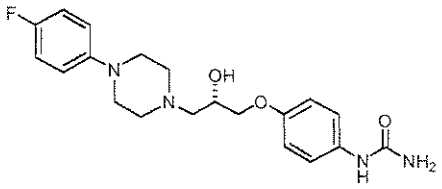


1-(4-((S)-3-((R)-4-(4-chlorophenyl)-2-methylpiperazin-1-yl)-2-hydroxypropoxy)phenyl) urea. A solution of 0.5 mmol of the (S)-epoxide and 0.6 mmol of (3R)-1-(4-chlorophenyl)-3-methylpiperazine in 5 ml ethanol was refluxed overnight. The solvent was evaporated and product was purified with the column chromatography using dichloromethane:methanol:NH_4OH (90:10:1). After the column it was crystallized with ethyl acetate to give 0.099 g (47% yield). ^1H NMR (400 MHz, d^6-DMSO) δ 1.05 (3H, d, J = 6.0 Hz), 2.37 (1H, dd, J = 4.8, 13.2 Hz), 2.46-2.53 (2H, m), 2.71 (1H, dd, J = 6.8, 13.2 Hz), 2.78 (1H, t, J = 8.8 Hz), 2.95 (1H, d, J = 12.0 Hz), 3.40 (2H, d, J = 8.8 Hz), 3.80-3.83 (1H, m), 3.89, (2H, d, J = 6.4 Hz), 4.78 (1H, d, J = 4.4 Hz), 5.71 (2H, s), 6.82 (2H, d, J = 8.8 Hz), 6.91 (2H, d, J = 8.8 Hz), 7.20 (2H, d, J = 8.8 Hz), 7.27 (2H, d, J = 8.8 Hz), 8.29 (1H, s); MS: 419 (M+H); HRMS= 419.18437; HPLC= 95% peak area at 7.6 min. retention time.

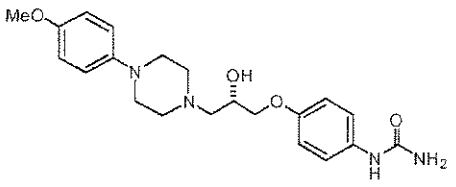


(*S*)-1-(4-(3-(4-(3,4-difluorophenyl)piperazin-1-yl)-2-hydroxypropoxy)phenyl)urea. A solution of 0.106 g of (S)-epoxide, 0.135 g of N-(3,4-difluorophenyl)-piperazine and 6 mL of

absolute ethanol was heated at 70°C for 18 hours. The reaction was cooled, and the resulting precipitate filtered. The solids were washed with ethanol and ethyl ether three times each. Drying gave 0.12 g of a white solid. ^{1}H NMR (d^6-DMSO): 2.36 (dd, 1H, J=7Hz, J=13Hz), 2.45 (m, 1H), 2.53 (m, 4H), 3.06 (m, 4H), 3.77 (dd, 1H, J=6Hz, J=9Hz), 3.88 (m, 1H), 3.91 (m, 1H), 4.83 (d, 1H, J=4Hz), 5.67 (s, 2H), 6.67 (m, 1H), 6.78 (d, 2H, J=9Hz), 6.93 (m, 1H), 7.19 (quart, 1H, J=10Hz), 7.23 (d, 2H, J=9Hz), 8.26 (s, 1H); MS: 407 (M+H); HRMS: 407.18890; HPLC: 100% peak area at 7.1 min. retention time.

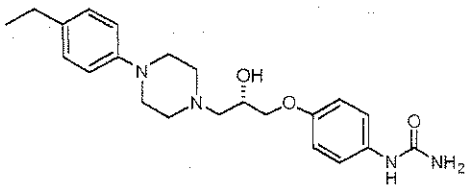


(*S*)-1-(4-(3-(4-(4-fluorophenyl)piperazin-1-yl)-2-hydroxypropoxy)phenyl)urea. A solution of 0.11 g of (S)-epoxide, 0.14 g of N-(4-fluorophenyl)-piperazine, and 6 mL of ethanol was heated to 70°C for 20 hours. The solution was cooled to room temperature. The solids were filtered, washed with ethanol three times, and dried. Gave 0.164 g of a white powder. 1H NMR (d6-DMSO): d 2.36 (dd, 1H, J=6Hz, J=13Hz), 2.47 (m, 1H), 2.55 (m, 4H), 3.02 (t, 4H, J=5Hz), 3.77 (dd, 1H, J=6Hz, J=9Hz), 3.88 (m, 1H), 3.92 (m, 1H), 4.84 (d, 1H, J=5Hz), 5.68 (s, 2H), 6.78 (d, 2H, J=9Hz), 6.89 (m, 2H), 6.99 (t, 2H, J=8Hz), 7.23 (d, 2H, J=9Hz), 8.27 (s, 1H); MS: 389. (M+H); HRMS: 389.19782; HPLC: 99.2% peak area at 6.5 min. retention time.

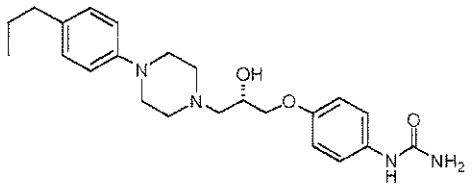


(*S*)-1-(4-(2-hydroxy-3-(4-(4-methoxyphenyl)piperazin-1-yl)propoxy)phenyl)urea. A solution of 0.11 g of (S)-epoxide, 0.155 g of *N*-(4-methoxyphenyl)-piperazine, and 6 mL of ethanol was heated to 70°C for 20 hours. The solution was cooled to room temperature. The solids were filtered, washed with ethanol three times, and dried. Gave 0.18 g of a white powder. ^{1}H NMR (d^6-DMSO): δ 2.36 (dd, 1H, J=7Hz, J=13Hz), 2.45 (m, 1H), 2.55 (m, 4H), 2.96 (t,

4H, J=5Hz), 3.64 (s, 3H), 3.77 (dd, 1H, J=6Hz, J=9Hz), 3.87 (m, 1H), 3.93 (m, 1H), 4.83 (d, 1H, J=5Hz), 5.68 (s, 2H), 6.78 (m, 4H), 6.83 (d, 2H, J=9Hz), 7.23 (d, 2H, J=9Hz), 8.27 (s, 1H); MS: 401 (M+H); HRMS: 401.21861; HPLC: 99% peak area at 6.2 min.

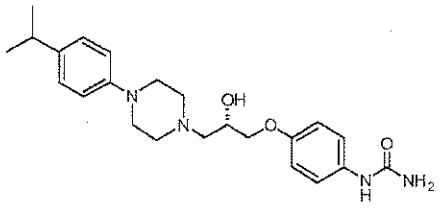


(*S*)-1-(4-(3-(4-(4-ethylphenyl)piperazin-1-yl)-2-hydroxypropoxy)phenyl)urea. A solution of 0.08 g of (S)-epoxide, 0.12 g of N-(4-ethylphenyl)-piperazine, and 5 mL of absolute ethanol were heated at 70oC for 30 hours. The solution was cooled to room temperature. The solvent was removed under vacuum, and the residue subjected to column chromatography on silica gel with a dichloromethane/dichloromethane:methanol:NH_4OH (90:10:1) gradiant. Combination of the fractions and solvent removal, followed by drying under vacuum gave 0.064 g of a white solid. ^1H NMR (d^6-DMSO): δ 1.09 (t, 3H, J=8Hz), 2.36 (dd, 1H, J=6 Hz, J=12Hz), 2.44 (m, 1H), 2.54 (m, 4H), 3.03 (t, 4H, J=5Hz), 3.77 (dd, 1H, J=6Hz, J=10Hz), 3.89 (m, 1H), 3.92 (m, 1H), 4.83 (d, 1H, J=5Hz), 5.67 (s, 2H), 6.78 (d, 2H, J=9Hz), 6.8 (d, 2H, J=8Hz), 7.01 (d, 2H, J=9Hz), 7.23 (d, 2H, J=10Hz), 8.26 (s, 1H); MS: 399 (M+H); HRMS: 399.23896; HPLC: 100% peak area; retention time at 7.8 min. Elemental – formula+0.25 H_2O - theory: C, 65.57, H, 7.63, N, 13.9; Found: C, 65.58, H, 7.51, N, 13.98.

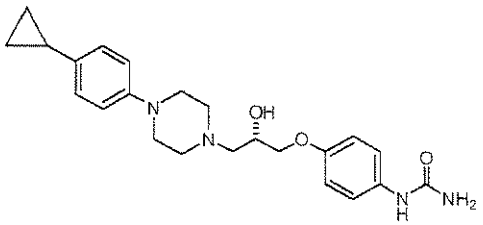


(*S*)-1-(4-(3-(4-(4-propylphenyl)piperazin-1-yl)-2-hydroxypropoxy)phenyl)urea. A solution of 0.11 g of (S)-epoxide, 0.154 g of N-(4-propylphenyl)-piperazine, and 6 mL of ethanol was heated to 70°C for 20 hours. The solution was cooled to room temperature. The solids were filtered, washed with ethanol three times, and dried. Gave 0.094 g of a white powder. ^1H NMR (d^6-DMSO): δ 0.83 (t, 3H, J=7Hz), 1.49 (hextet, 2H, J=7Hz), 2.38 (m, 3H), 2.54 (m, 4H), 3.03 (t, 4H, J=5Hz), 3.77 (dd, 1H, J=6Hz, J=9Hz), 3.89 (m, 1H), 3.92 (m, 1H), 4.83 (d, 1H, J=5Hz), 5.68 (s, 2H), 6.78 (d, 2H, J=9Hz), 6.8 (d, 2H, J=8Hz), 6.98 (d, 2H, J=8Hz), 7.24

(d, 2H, J=9Hz), 8.27 (s, 1H); MS: 413 (M+H); HRMS: 413.25406; HPLC: 99% peak area at 8.6 min. retention time.



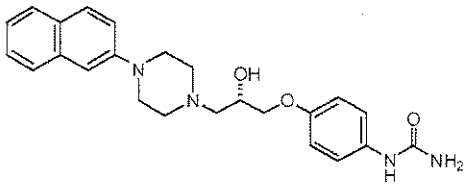
(*S*)-1-(4-(3-(4-(4-isopropyl-phenyl)piperazin-1-yl)-2-hydroxypropoxy)phenyl)urea. A solution of 0.08 g of (S)-epoxide, 0.16 g of N-(4-isopropylphenyl)-piperazine, and 5 mL of absolute ethanol were heated at 70°C for 30 hours. The solution was cooled to room temperature. The solvent was removed under vacuum, and the residue subjected to column chromatography on silica gel with a dichloromethane: dichloromethane:methanol:NH_4OH (90:10:1) gradient. The fractions were combined and the solvent removed under vacuum. Ethyl ether was added to the solids and they were filtered, washed with ethyl ether three times, and then dried. 0.046 g of a white solid was obtained. 1H NMR (400 MHz, d^6-DMSO): δ 1.11 (d, 6H, J=7Hz), 2.36 (dd, 1H, J=7Hz, J=13Hz), 2.45 (m, 1H), 2.54 (m, 4H), 2.74 (quint, 1H, J=7Hz), 3.03 (t, 4H, J=5Hz), 3.77 (dd, 1H, J=6Hz, J=10Hz), 3.88 (m, 1H), 3.92 (m, 1H), 4.84 (d, 1H, J=5Hz), 5.68 (s, 2H), 6.8 (t, 4H, J=10Hz), 7.03 (d, 2H, J=8Hz), 7.24 (d, 2H, J=9Hz), 8.27 (s, 1H); MS: 413 (M+H); HRMS: 413.25458; HPLC: 100% peak area at a retention time of 8.25 min.; Elemental analysis - Theory: C, 66.96, H, 7.82, N, 13.58; Found, C, 66.98, H, 7.82, N, 13.48.



(*S*)-1-(4-(3-(4-(4-cyclopropylphenyl)piperazin-1-yl)-2-hydroxypropoxy)phenyl)urea. A solution of 0.1 g of (S)-epoxide, 0.15 g of N-(4-cyclopropylphenyl)-piperazine, and 6 mL of absolute ethanol were heated at 70°C for 20 hours. The solution was cooled to room temperature. The solvent was removed under vacuum, and the residue subjected to column chromatography on silica gel with a dichloromethane/dichloromethane: methanol:NH_4OH

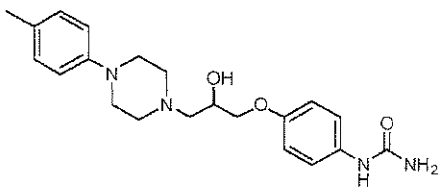
(90:10:1) gradiant. The fractions were combined and the solvent removed under vacuum. Ethanol was added to the solids and they were filtered, washed with ethanol three times, and then dried. 0.067 g of a white solid was obtained. ^{1}H NMR: (d^6-DMSO): δ 0.5 (quart, 2H, J=4Hz), 0.8 (m, 2H), 1.76 (m, 1H), 2.35 (dd, 1H, J=6Hz, J=12Hz), 2.46 (m, 1H), 2.54 (m, 4H), 3.01 (t, 4H, J=5Hz), 3.77 (dd, 1H, J=6Hz, J=10Hz), 3.88 (m, 1H), 3.91 (m, 1H), 4.83 (d, 1H, J=5Hz), 5.68 (s, 2H), 6.78 (m, 4H), 6.88 (d, 2H, J=8Hz), 7.23 (d, 2H, J=9Hz), 8.27 (s, 1H); MS: 411 (M+H); HRMS: 411.23895; HPLC: 100% peak area at 7.8 min. retention time; Elemental analysis: Theory: C, 67.29, H, 7.37, N, 13.65; Found: C, 67.27, H, 7.36, N, 13.54.

(*S*)-1-(4-(3-(4-(4-isobutylphenyl)piperazin-1-yl)-2-hydroxypropoxy)phenyl)urea



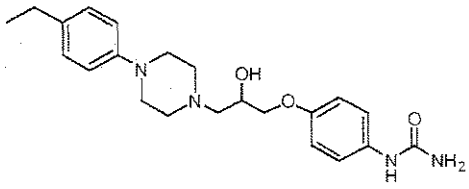
(*S*)-1-(4-(3-(4-(2-naphthyl)piperazin-1-yl)-2-hydroxypropoxy)phenyl)urea. A solution of 0.11 g of (S)-epoxide, 0.175 g of N-(2-naphthyl)-piperazine, and 6 mL of ethanol was heated to 70°C for 20 hours. The solution was cooled to room temperature. The solids were filtered, washed with ethanol three times, and dried. Gave 0.197 g of a white powder. ^{1}H NMR (d^6-DMSO): δ 2.39 (dd, 1H, J=7Hz, J=12Hz), 2.49 (m, 1H), 2.61 (m, 4H), 3.79 (dd, 1H, J=6Hz, J=10Hz), 3.9 (m, 1H), 3.96 (m, 1H), 4.86 (d, 1H, J=5Hz), 5.68 (s, 2H), 6.79 (d, 2H, J=9Hz), 7.11 (d, 1H, J=2Hz), 7.23 (m, 4H), 7.34 (m, 3H), 7.69 (m, 4H), 8.27 (s, 1H); MS: 421 (M+H); HRMS: 421.22338; HPLC: 99.9 % peak area at 7.8 min. retention time.

Specific exemplary syntheses for step (vii):

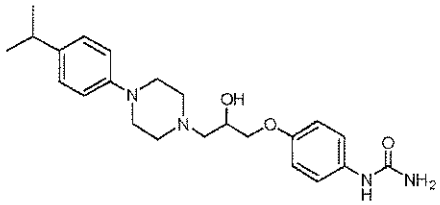


(*R*)-1-(4-(3-(4-(4-methylphenyl)piperazin-1-yl)-2-hydroxypropoxy)phenyl)urea. A solution of 0.11 g of (R)-epoxide, 0.13 g of N-(4-methylphenyl)-piperazine, and 5 mL of absolute

ethanol were heated at 70°C for 30 hours. The solution was cooled to room temperature. The solution was filtered. The solids were washed with ethanol three times and dried. Gave 0.157g of a white solid.

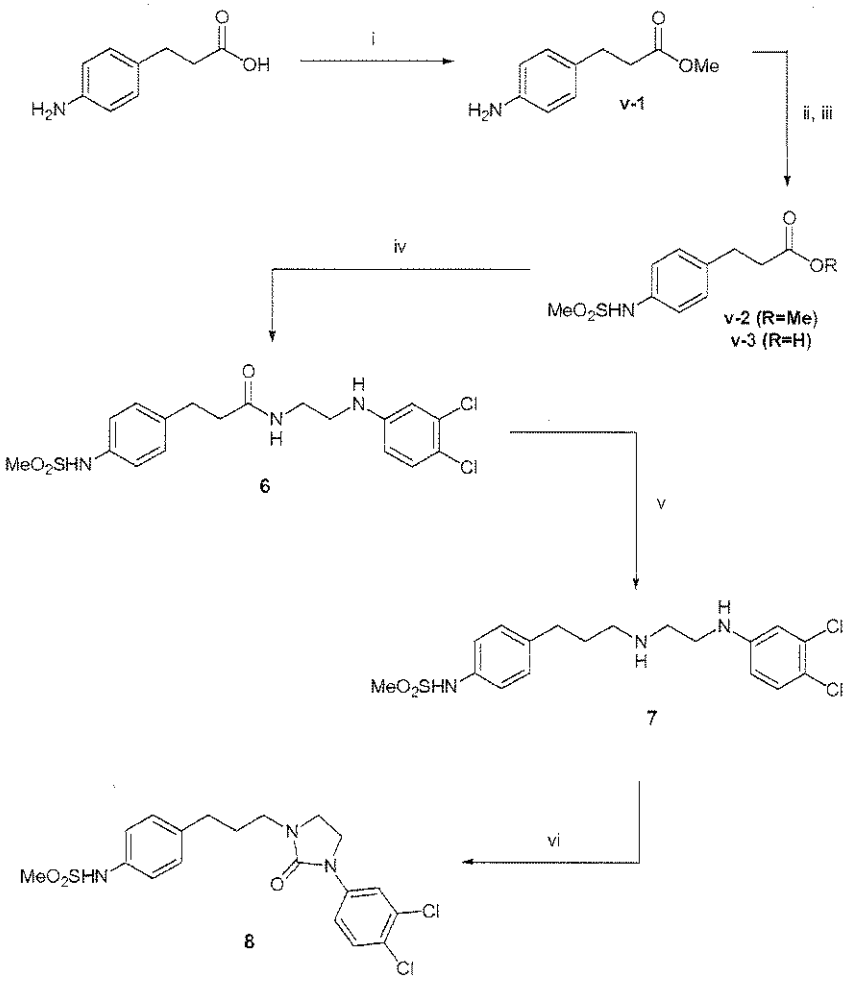


(*R*)-1-(4-(3-(4-(4-ethylphenyl)piperazin-1-yl)-2-hydroxypropoxy)phenyl)urea. A solution of 0.11 g of (S)-epoxide, 0.15 g of N-(4-ethylphenyl)-piperazine, and 5 mL of absolute ethanol were heated at 70°C for 30 hours. The solution was cooled to room temperature. The solids were filtered, washed with ethanol and ethyl ether three times each. Drying gave 0.1g of a white solid.



(*R*)-1-(4-(3-(4-(4-isopropylphenyl)piperazin-1-yl)-2-hydroxypropoxy)phenyl)urea. A solution of 0.11 g of (S)-epoxide, 0.175 g of N-(4-ethylphenyl)-piperazine, and 5 mL of absolute ethanol were heated at 70°C for 30 hours. The solution was cooled to room temperature. The resulting solids were filtered, washed with ethanol and ethyl ether three times each. Drying gave 0.094g of a white solid.

Examples 6, 7, and 8. N-[2-(3,4-Dichloro-phenylamino)-ethyl]-3-(4-methanesulfonylamino-phenyl)-propionamide (Compound 6), N-(4-{3-[2-(3,4-Dichloro-phenylamino)-ethylamino]-propyl}-phenyl)-methanesulfonamide (Compound 7), and N-(4-(3-(3-(3,4-dichlorophenyl)-2-oxoimidazolidin-1 l)propyl)phenyl) methanesulfonamide (Compound 8).



Step (i) Methyl 3-(4-aminophenyl)propanoate (**v-1**). Thionyl chloride (14.6 ml, 200 mmol, 3.3 equiv) was added dropwise to a solution of dry methanol (60 ml, 1453 mmol, 24 equiv) at -10° C. After stirring for 10 minutes, 3-(4-aminophenyl)propanoic acid (10.0 g, 61 mmol) was added to give a yellow suspension. The solution stirred for 1 hour and was slowly warmed to room temperature. The resulting solution was concentrated to give a yellow solid. The solid was suspended in ethyl acetate, and $NaHCO_3$ (aq.) was added until the salt

dissolved fully. Solid sodium bicarbonate was added to give pH 8.The layers were separated and the organics were washed with brine (aq.). The resulting solution was dried over $MgSO_4$, filtered, and concentrated to give a yellow solid (10.6 g, 98%). ^{1}H NMR (300 MHz, $CDCl_3$) 7.00 (d, *J*=8.3 Hz, 2H), 6.63 (d, *J*=8.3 Hz, 2H), 3.67 (s, 3H), 3.59 (bs, NH_2, 2H), 2.85 (t, *J*=7.6 Hz, 2H), 2.58 (t, *J*=8.3 Hz, 2H). ^{13}C NMR (300 MHz, $CDCl_3$) 173. 8, 144.9, 130.7, 129.3, 115.5, 51.8, 36.4, 30.4. M.S. (ESI) m/z=180.102 (M+H).

Step (ii). Methyl 3-(4-(methylsulfonamido)phenyl)propanoate (**v-2**). The ester (7.38 g, 41.2 mmol) was dissolved in pyridine (17.0 ml, excess). After cooling to 0°C, methanesulfonyl chloride (4.55 ml, 57.7 mmol, 1.4 equiv) was added dropwise. The reaction was warmed to room temperature and stirred overnight. The reaction was quenched with water and diluted with DCM. The layers were separated and the organics were washed with brine. The resulting solution was concentrated to give a red solid. The crude material was purified using silica gel chromatography (1 EtOAc/1 Hexanes) to give a white solid (87%). ^{1}H NMR: ($CDCl_3$, 400 MHz) 7.20 (d, *J*=8.6 Hz, 2H), 7.15 (d, *J*=8.6 Hz, 2H), 6.45 (bs, N*H*,1H), 3.68 (s, 3H), 3.00 (s, 3H), 2.94 (t, *J*=7.6 Hz, 2H), 2.63 (t, *J*=7.5 Hz, 2H). ^{13}C NMR ($CDCl_3$, 400 MHz): 173.4, 137.6, 135.2, 129.4, 121.4, 51.7, 38.5, 35.5, 30.1. M.S. (ESI) m/z= 257.56 (M+H)

Step (iii). 3-(4-(methylsulfonamido)phenyl)propanoic acid (**v-3**). The sulfonamide ester (1.16 g, 4.5 mmol) was dissolved in methanol (50 ml). To this solution, 1.0 N NaOH (17.0 ml, 17.0 mmol, 3.8 equiv) was added. The mixture was stirred at room temperature overnight. TLC indicated the reaction was finished. The pH of the solution was adjusted to 3 with a solution of aqueous HCl. The volume of methanol was reduced by rotary evaporation (40 mbar), upon which the product crashed out of solution. The yellow crystals were filtered off and dried (0.900 g, 82%). ^{1}H NMR (400 MHz, CD_3OD) 7.21 (d, *J*=8.6 Hz, 2H), 7.17 (d, *J*=8.6 Hz, 2H), 2.91 (s, 3H), 2.89 (t, *J*=7.6 Hz, 2H), 2.59 (t, *J*=7.6 Hz, 2H). ^{13}C NMR (400 MHz, CD_3OD) 176.7, 139.0, 137.7, 130.5, 122.3, 39.1, 36.8, 31.4. M.S. (ESI) m/z= 242.05 (M-H).

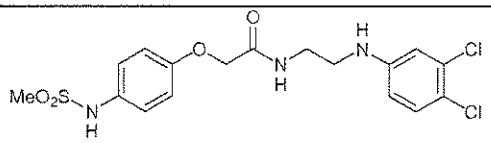
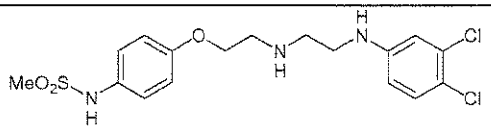
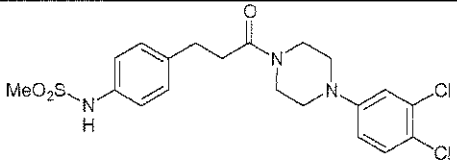
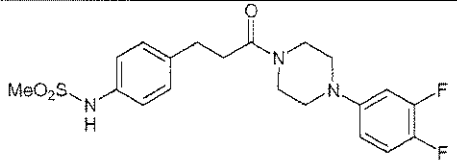
Step (iv). N-(2-(3,4-dichlorophenylamino)ethyl)-3-(4-(methylsulfonamido)phenyl) propanamide Compound **6**). The carboxylic acid (0.700 g, 2.88 mmmol) was dissolved in

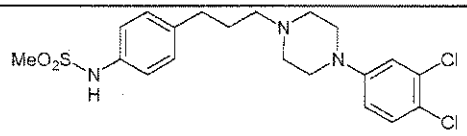
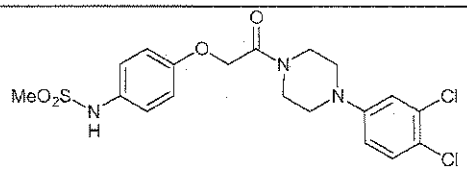
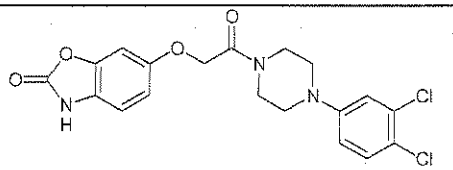
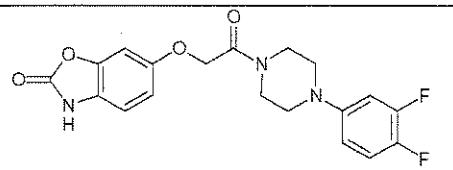
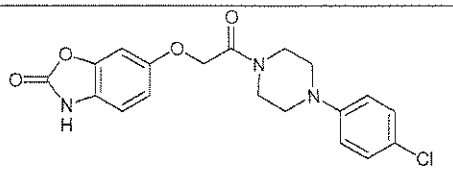
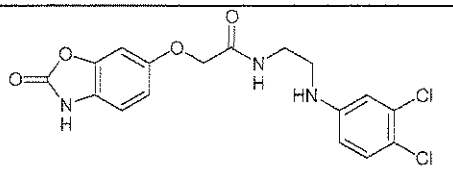
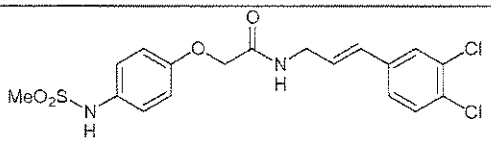
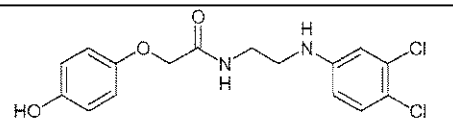
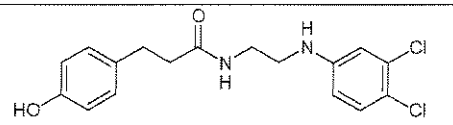
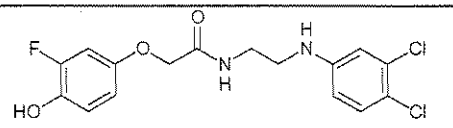
DMF (30.0 ml) and cooled to 0°C. To this solution, DMAP (0.352 g, 2.28 mmol, 1.1 equiv), and EDCI (0.552 g, 2.88 mmol, 1.0 equiv) were added to give a clear suspension. After stirring for 30 minutes, the amine (0.590 g, 2.88 mmol, 1.0 equiv) in THF (5.0 ml) was added dropwise to give a brown solution. The mixture was warmed to room temperature and stirred overnight. The reaction was monitored by TLC. To quench the reaction, 20 mL of 1.0 N HCl was added and the solution was extracted with 3x30 mL of EtOAc. The orgainic layer was dried with $MgSO_4$, filtered, and concentrated to give red oil. The crude material was purified by taking the residue up in DCM and stirring. Immediately a white powder precipitated out (0.920 g, 74%). ^{1}H NMR (400 MHz, CD_3OD) 7.14-7.10 (mult, 5H), 6.72 (d, J=2.9 Hz, 1H), 6.51 (dd, J_1=8.9 Hz, J_2=2.6 Hz, 1H), 3.27 (t, 2H), 3.10 (t, J=6.4 Hz, 2H), 2.88 (s, 3H), 2.87 (t, J=6.5 Hz, 2H), 2.46, (t, J=6.4 Hz, 2H). ^{13}C NMR (300 MHz, $CDCl_3$) 175.8, 150.0, 138.7, 138.3, 131.7, 130.5, 122.3, 114.4, 113.6, 44.0, 39.8, 39.2, 39.0, 32.3. M.S. Calc'd 429.0681 Found (HRMS) 431.08143 (M+H). E.A. Calc'd: C 50.24, H 4.92, N 9.76 Found: C 49.94, H 4.91, N 9.74.

Step (v). N-(4-(3-(2-(3,4-dichlorophenylamino)ethylamino)propyl)phenyl) methanesulfonamide (Compound 7). The sulfonamide amide ((0.500 g, 1.2 mmol) was dissolved in THF (30.0 ml). After cooling to 0°C, a solution of Lithium Aluminum hydride (2.0 M solution in THF, 2.3 ml, 4.6 mmol, 4.0 equiv) was added dropwise. After stirring for 10 minutes at 0°C, the ice bath was removed and the reaction mixed was warmed to room temperature and stirred overnight. The mixture was diluted with DCM and water to give an emulsion. Rochelle's salt (sat'd solution) was added and the mixture stirred for 20 minutes before filtering over a pad of celite. The resulting liquid was separated, and the organics were washed with brine, dried over $MgSO_4$ and concentrated to give a white foam (0.358 g, 74%). The free base was converted to the HCl salt by bubbling HCl (g) through a solution of substrate dissolved in ethanol. The white powder precipitated out and was filtered off. ^{1}H NMR (300 MHz, $CDCl_3$) 7.20-7.11 (mult, 5H), 6.69 (d, J=2.8 Hz, 1H), 6.46 (dd, J_1=8.8 Hz, J_2=2.8 Hz), 4.36 (bs, 1H, NH), 3.156 (mult, 2H), 3.00 (s, 3H), 2.88 (t, J=6.2 Hz, 2H), 2.66 (t, J=7.1 Hz, 4H), 1.86-1.79 (mult, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) 148.1, 139.4, 134.8, 132.8, 130.7, 129.7, 121.6, 119.7, 113.9, 112.9, 49.0, 48.2, 43.2, 39.3, 32.9, 31.5. M.S. Calc'd 416.088. Found (HRMS): 416.069.

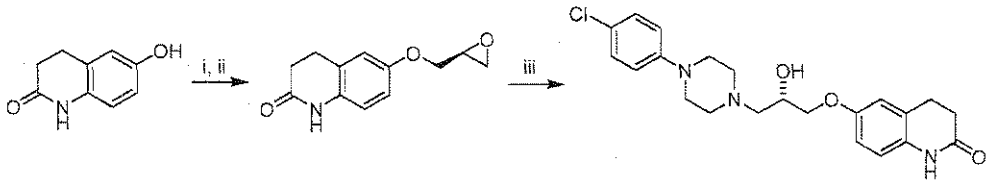
Step (vi). N-(4-(3-(3-(3,4-dichlorophenyl)-2-oxoimidazolidin-1 l)propyl)phenyl) methanesulfonamide (Compound **8**). The starting material diamine (0.113 g, 0.27 mmol) was dissolved in THF (10.0 ml). To this solution 1,1-carbonyldiimidazole (0.048 g, 0.30 mmol, 1.1 equiv) was added. The mixture stirred at room temperature overnight. After completion, the solution was evaporated to dryness and the residue was taken up in ethyl acetate, washed with brine (1x) and dried over Na_2SO_4, filtered, and concentrated to give a clear oil. The crude material was purified using silica gel chromatography (100% EtOAc) to give a white foam (0.070 g, 58%). ^1H (400 MHz, $CDCl_3$) 7.72 (s, 1H), 7.16 (d, *J*=8.6 Hz, 2H), 7.07 (d, *J*=8.6 Hz, 2H), 7.02 (s, 1H), 6.64 (d, *J*=2.9 Hz, 1H), 6.41 (dd, J_1=8.5 Hz, J_2=2.9 Hz), 3.64 (t, *J*=6.0 Hz, 2H), 3.40-3.36 (mult, 4H), 2.97 (s, 3H), 2.57 (t, *J*=7.3 Hz, 2H), 1.26 (t, *J*=7.3 Hz, 2H). ^{13}C (75 MHz, $CDCl_3$) 152.6, 147.1, 137.3, 136.8, 135.6, 130.9, 129.5, 121.6, 118.0, 113.6, 112.5. M.S. (ESI) Calc'd: 441.0681 Found: 442.07527 (M+H).

Compounds in the following table were synthesized according to variations in methods described for Examples 6, 7, and 8.

COMPOUND	NAME
	N-[2-(3,4-Dichloro-phenylamino)-ethyl]-2-(4-methanesulfonylamino-phenoxy)-acetamide
	N-(4-{2-[2-(3,4-Dichloro-phenylamino)-ethylamino]-ethoxy}-phenyl)-methanesulfonamide
	N-(4-{3-[4-(3,4-Dichloro-phenyl)-piperazin-1-yl]-3-oxo-propyl}-phenyl)-methanesulfonamide
	N-(4-{3-[4-(3,4-DiFluoro-phenyl)-piperazin-1-yl]-3-oxo-propyl}-phenyl)-methanesulfonamide

	N-(4-{3-[4-(3,4-Dichloro-phenyl)-piperazin-1-yl]-propyl}-phenyl)-methanesulfonamide
	N-(4-{2-[4-(3,4-Dichloro-phenyl)-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-methanesulfonamide
	6-{2-[4-(3,4-Dichloro-phenyl)-piperazin-1-yl]-2-oxo-ethoxy}-3H-benzooxazol-2-one
	6-{2-[4-(3,4-DiFluoro-phenyl)-piperazin-1-yl]-2-oxo-ethoxy}-3H-benzooxazol-2-one
	6-{2-[4-(4-Chloro-phenyl)-piperazin-1-yl]-2-oxo-ethoxy}-3H-benzooxazol-2-one
	N-[2-(3,4-Dichloro-phenylamino)-ethyl]-2-(2-oxo-2,3-dihydro-benzooxazol-6-yloxy)-acetamide
	N-[3-(3,4-Dichloro-phenyl)-allyl]-2-(4-methanesulfonylamino-phenoxy)-acetamide
	N-[2-(3,4-Dichloro-phenylamino)-ethyl]-2-(4-hydroxy-phenoxy)-acetamide
	N-[2-(3,4-Dichloro-phenylamino)-ethyl]-3-(4-hydroxy-phenyl)-propionamide
	N-[2-(3,4-Dichloro-phenylamino)-ethyl]-2-(3-fluoro-4-hydroxy-phenoxy)-acetamide

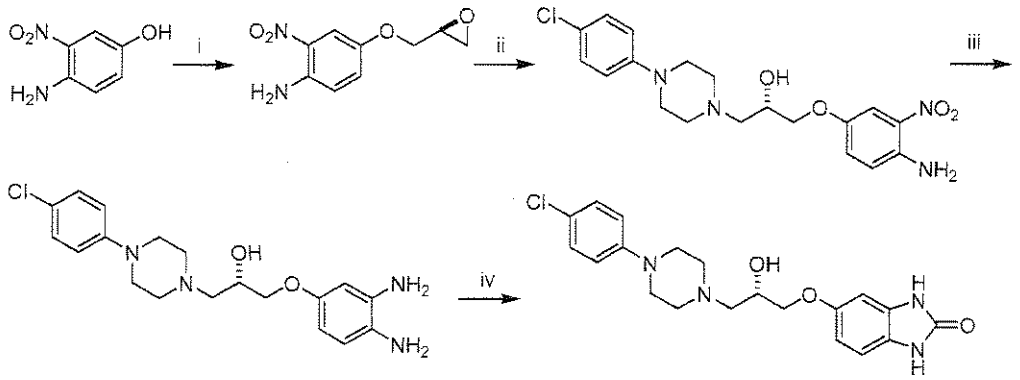
Example 9. General synthesis for quinolinone derivatives. Preparation of (S)-6-(3-(4-(4-chlorophenyl)piperazin-1-yl)-2-hydroxypropoxy)-3,4-dihydroquinolin-2(1H)-one.



Steps (i) and (ii). Preparation of (S)-6-(oxiran-2-ylmethoxy)-3,4-dihydroquinolin-2(1H)-one. Reactions were performed according to the literature (Uno, T. et all; Chem. Pharm. Bull. 43(10) 1724-1733 (1995). Either stereoisomer could be formed from (*S*) or (*R*) epichlorohydrin and 6-hydroxy-3,4-dihydroquinolin-2(1H)-one.

Step (iii). A solution of 2 mmol of the quinolinone epoxide and 3 mmol 1-(4-chlorophenyl)piperazine in 10 ml ethanol was refluxed overnight. The solid was precipitated during the reflux which was filtered, and dried to give 0.42 g of a white solid (51% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.55-2.65 (6H, m), 2.81-2.86 (2H, m), 2.93 (2H, t, J = 7.6 Hz), 2.95-3.23 (4H, m), 3.48 (1H, bs), 3.94-3.99 (2H, m), 4.09-4.15 (1H, m), 6.69-6.77 (3H, m), 6.84 (2H, d, J = 8.8 Hz), 7.21 (2H, d, J = 8.8 Hz), 8.31 (1H, s); MS416 (M+H); HRMS416.17306; Elemental Analysis for $C_{22}H_{26}ClN_3O_3$; Calculated: C, 63.53; H, 6.30; N, 10.10; Found: C, 63.27; H, 6.29; N, 10.05.

Example 10. Preparation of (*S*)-5-(3-(4-(4-chlorophenyl)piperazin-1-yl)-2-hydroxypropoxy)-1H-benzo[d]imidazol-2(3H)-one.



Step (i). A solution of 2-amino-3-nitrophenol (5.08 g, 33 mmol) and (2S)-(+)-glycidyl 3-nitrobenzenesulfonate (8.54 g, 33 mmol) in 75 mL of acetone was treated with K_2CO_3 (5.00

g, 36.3 mmol) and stirred at reflux for 18 hours. The suspension was cooled to ambient temperature; the solids were filtered; and the filtrate concentrated in vacuo to dryness. The resulting solids were partitioned between dichloromethane and water, and the aqueous layer extracted once with DCM. The organic layers were combined and dried over Na_2SO_4 and concentrated in vacuo to give an orange solid (0.3 g, 86.7% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.45 (1H, t, J = 4.8 Hz), 3.86-4.03 (1H, m), 4.64-4.67 (1H, m), 4.79 (1H, dd, J = 2.4, 10.8 Hz), 5.14 (1H, t, J = 5.6), 7.45 (1H, d, J = 9.2 Hz), 7.62 (1H, dd, J = 4.8, 9.2 Hz), 8.36 12H, d, J = 6.8 Hz).

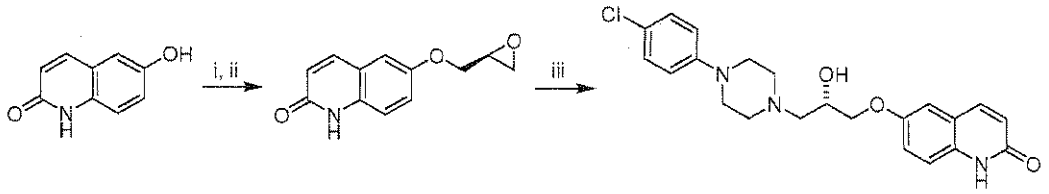
Step (ii). A solution of 2.54 mmol of (S)-2-nitro-4-(oxiran-2-ylmethoxy)aniline and 3.0 mmol of 1-(4-chlorophenyl)piperazine in 10 ml ethanol was refluxed overnight. The solvent was evaporated and product was purified with column chromatography using DCM:MeOH:NH_4OH (95:5:0.5). Gave 1.033 g (100% yield).

Step (iii). (S)-1-(4-amino-3-nitrophenoxy)-3-(4-(4-chlorophenyl)piperazin-1-yl)propan-2-ol (1.033 g, 2.54 mmol) was suspended in 40 ml ethanol and 30 ml water at room temperature and treated with excesses of sodium bicarbonate (2.56 g, 30.48 mmol) and sodium hydrosulfite (6.24 g, 30.48 mmol). The orange reaction mixture slowly became colorless in 3-4 hours, and the mixture was left to stir at room temperature for overnight. The suspension was filtered, and the filtrate concentrated in vacuo to a leave a white solid. This residue was partitioned between DCM and water, and the organic layer washed two times with brine. The combined organic extracts were concentrated in vacuo to give light brown solid (0.43 g, 45% yield). The compound was used directly for the next step without further purification.

Step (iv). The compound from step iii (0.430 g, 1.14 mmol) was suspended in mixture of 8 ml toluene and 14.25 ml 2N HCl at room temperature with vigorous stirring. An excess of triphosgene (3.61 g, 11.93 mmol) was added, and the stirring continued for overnight. The biphasic mixture was cautiously quenched and neutralized with sodium bicarbonate, causing an pinkish-white precipitate to form at the interface. The precipitate was filtered and purified with column chromatography using DCM:MeOH:NH_4OH (90:10:1) to give 0.283 g of a brown solid (47% yield). ^{1}H-NMR (400 MHz, d_6-DMSO): δ 2.32-2.45 (1H, m), 2.53-2.64 (4H, m), 3.11 (4H, t, J = 5.2 Hz), 3.79-3.83 (1H, m), 3.91 (1H, dd, J = 4.0, 9.6 Hz), 3.94-4.01 (1H, m), 4.89 (1H, d, J = 4.4 Hz), 6.51 (1H, d, J = 2.4 Hz), 6.54 (1H, s), 6.79 (1H, d, J =

8.4 Hz), 6.93 (2H, d, J = 9.6 Hz), 7.22 (2H, d, J = 9.2 Hz), 10.39 (1H, s), 10.52 (1H, s); HRMS= 403.15259; HPLC= 2.804 retention time (99% purity); Elemental analysis for $C_{20}H_{23}ClN_4O_3$ x 0.75 mol H_2O: Calculated: C, 57.69; H, 5.93; N, 13.46; Found: C, 57.63; H, 5.63; N, 13.45.

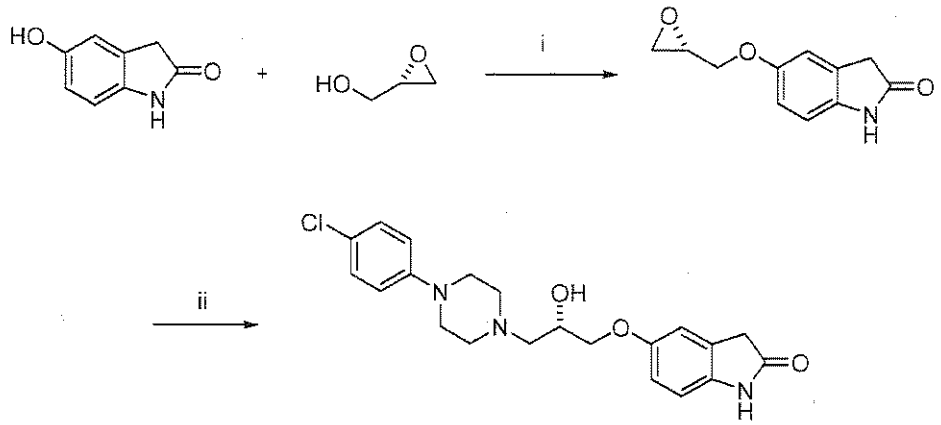
Example 11. Preparation of (S)-6-(3-(4-(4-chlorophenyl)piperazin-1-yl)-2-hydroxypropoxy)quinolin-2(1H)-one.



Steps i and ii. Steps i and ii: Preparation of (S)-6-(oxiran-2-ylmethoxy)-quinolin-2(1H)-one. Reactions were performed according to the literature (Uno, T. et all; Chem. Pharm. Bull. 43(10) 1724-1733 (1995). Either stereoisomer could be formed from (*S*) or (*R*) epichlorohydrin and 6-hydroxy-3,4-dihydroquinolin-2(1H)-one.

Step (iii). A solution of 2 mmol the (S)-dihydroquinolinone epoxide and 3 mmol 1-(4-chlorophenyl)piperazine in 10 ml ethanol was refluxed overnight. The solid was precipitated during the reflux which was filtered, washed with ethanol, and dried to give 0.314g of a white solid (76% yield). ^{1}H-NMR (400 MHz, dmso-d_6) δ 2.42 (1H, dd, J = 6.4, 12.8 Hz), 2.53-2.64 (4H, m), 3.11 (4H, t, J = 5.2 Hz), 3.88-3.92 (1H, m), 4.00 (2H, d, J = 6.4 Hz), 4.94 (1H, d, J = 4.4 Hz), 6.48 (1H, d, J = 9.6 Hz), 6.92 (2H, d, J = 9.2 Hz), 7.15-7.25 (5H, m), 7.83 (1H, d, J = 9.6 Hz), 11.64 (1H, s); HRMS= 414.15720; HPLC= 8.196 retention time (99% purity); Elemental analysis: $C_{22}H_{24}ClN_3O_3$; Calculated: C, 63.84; H, 5.84; N, 10.15; Found: C, 63.42; H, 5.80; N, 10.11.

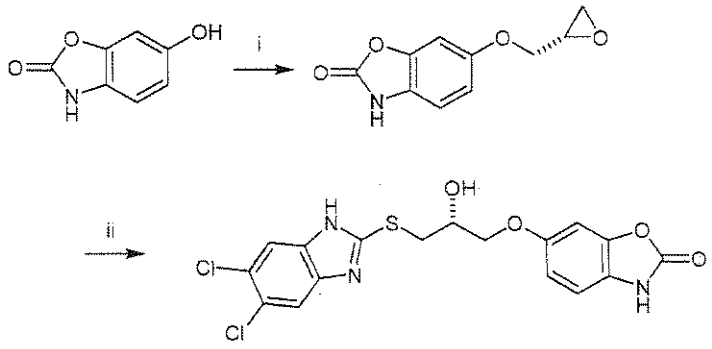
Example 12. Preparation of (S)-5-(3-(4-(4-chlorophenyl)piperazin-1-yl)-2-hydroxypropoxy)indolin-2-one.



Step (i). Diethylazodicarboxylate (40% solution in toluene, 1.9 mL, 4.4 mmol) was added to a mixture of 5-hydroxyoxindole (0.65 g, 4.4 mmol), triphenylphosphine (1.14 g, 4.4 mmol), and (*S*)-glycidol (0.29 mL, 4.4 mmol) in anhydrous tetrahydrofuran at 0 °C. After the addition, the mixture was stirred at 20 °C for 16 h. The volatiles were evaporated on a rotavap and the residue was purified on silica gel using hexane/ethyl acetate solvent mixture. Yield: 0.4 g (impure). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (b.s, 1H), 6.92 (s, 1H), 6.78 (s, 2H), 4.22 (m, 1H), 3.88 (m, 1H), 3.52 (s, 2H), 3.36 (m, 1H), 2.91 (m, 1H), 2.76 (m, 1H).

Step (ii). A mixture of (*S*)-indolinone epoxide (0.35 g, 1.7 mmol) and 4-chlorophenylpiperazine (0.35 g, 1.8 mmol) in ethanol (10 mL) was heated at 70 °C for 16 hours. The reaction mixture was cooled to room temperature and volatiles were evaporated. The residue was purified on silica gel using a dichloromethane:methanol: ammonia solvent mixture. Gave 0.17 g (25 %) of a brown solid. ^{1}H NMR (400 MHz, d^6-DMSO): δ 10.19 (b.s), 7.21 (d, 2H), 6.92 (d, 2H), 6.88 (s, 1H), 6.77 (d, 1H), 6.68 (d, 1H), 4.88 (d, 1H), 3.96 (m, 1H), 3.91 (m, 1H), 3.80 (m, 1H), 3.43 (s, 2H), 3.11 (m, 4H), 2.58 (m, 4H), 2.41 (m, 1H). ES-MS m/z 402.16 $(C_{21}H_{24}ClN_3O_3 + 1)^+$. Analysis Calculated for $C_{21}H_{24}ClN_3O_3$: % C 62.76; % H 6.02; % N 10.46; found: % C 62.62; % H 6.06; % N 10.36.

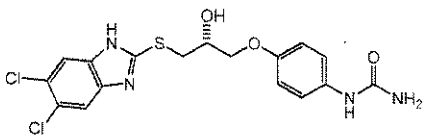
Example 13. Preparation of (*R*)-6-(3-(5,6-dichloro-1H-benzo[d]imidazol-2-ylthio)-2-hydroxypropoxy)benzo[d]oxazol-2(3H)-one.



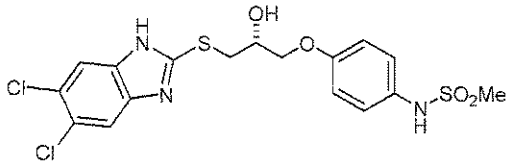
Step i. (S)-6-(oxiran-2-ylmethoxy)benzo[d]oxazol-2(3H)-one. A mixture of 0.6g of 6-hydroxy-2-benzoxazolinone and 0.75g of potassium carbonate was diluted with 8 mL of N,N-dimethylformamide. The reaction was stirred at room temperature for 1 hour, and then 1.2g of (*S*)-glycidyl nosylate was added. The reaction was stirred for 3 days at room temperature. The reaction was then quenched with water, extracted with $NaHCO_3$(aq.) solution and ethyl acetate. The organic layer was separated and dryed over Na_2SO_4(s). Filtration and solvent removal gave a residue that was subjected to column chromatography (hexanes-ethyl acetate gradient). Fraction combination and solvent removal gave 0.39g of a white solid (47% yield). ^{1}H NMR (d^6-DMSO): δ 2.6 (quart, 1H, J=3Hz), 2.76 (t, 1H, J=4Hz), 3.23 (m, 1H), 3.71 (dd, 1H, J=6Hz, J=15Hz), 4.11 (dd, 1H, J=3Hz, J=15Hz), 6.59 (dd, 1H, J=2Hz, J=9Hz), 6.73 (d, 1H, J=2Hz), 7.06 (d, 1H, J=8Hz), 9.48 (s, 1H).

Step (ii). Preparation of (*R*)-6-(3-(5,6-dichloro-1H-benzo[d]imidazol-2-ylthio)-2-hydroxypropoxy)benzo[d]oxazol-2(3H)-one. 5,6-Dichloro-2-thiabenzimidazole. ^{1}H NMR (d6-DMSO): δ 3.59 (dd, 1H, J=6Hz, J=8Hz), 3.7 (d, 2H, J=6Hz), 3.93 (t, 1H, J=25Hz), 4.93 (M, 2h), 6.17 (dd, 1H, J=2Hz, J=8Hz), 6.3 (d, 1H, J=3Hz), 6.94 (d, 1H, J=8Hz), 7.7 (s, 2H), 9.4 (s, 1H), 9.59 (s, 1H), 12.98 (s, 1H); MS (m/z): 426 (M+H), 428 (M+2+H); HRMS: Calcd. for $C_{17}H_{14}{}^{35}Cl_2N_3O_4S$: 426.00821; Found: 426.00739.

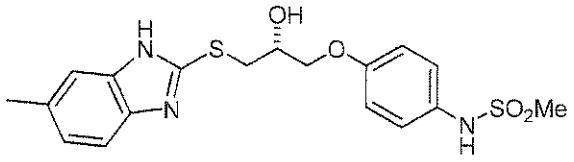
The following compounds were prepared using similar procedures.



(*R*)-1-(4-(3-(5,6-dichloro-1H-benzo[d]imidazol-2-ylthio)-2-hydroxypropoxy)phenyl)urea. To a solution of 0.19 g of 5,6-dichloro-1H-benzo[d]imidazole-2-thiol in 4 mL of *N,N*-dimethylformamide was added 0.36 g of cesium carbonate. The reaction was stirred at room temperature for 2 hours. Next, 0.1 g of the (*S*)-epoxide was added, and the reaction heated to 60°C for 18 hours. The reaction was cooled, extracted with ethyl acetate and washed with $NaHCO_3$ (aq.) solution. The aqueous layer was re-extracted with ethyl acetate, and the organic layers combined and dried over Na_2SO_4(s). Filtration and solvent removal gave a dark yellow solid. Column chromatography with an ethyl acetate /methanol gradient gave an off-white solid after fraction combination and solvent removal. The solids were heated with ethyl acetate to 70°C for 15 minutes. The solution was cooled, filtered, and the solids were washed with ethyl acetate. Drying gave 0.099 g of a white solid. ^{1}H NMR (d^6-DMSO): δ 3.31 (bs, 1H), 3.38 (dd, 1H, J=7Hz, J=13Hz), 3.55 (dd, 1H, J=5Hz, J=13Hz), 3.91 (m, 2H), 4.09 (m, 1H), 5.68 (s, 2H), 6.79 (d, 2H, J=9Hz), 7.24 (d, 2H, J=9Hz), 7.64 (s, 2H), 8.27 (s, 1H); MS: 429 (M+H+2), 427 (M+H); HRMS: 427.03926; HPLC: 100% peak area at 7.1 min. retention time.

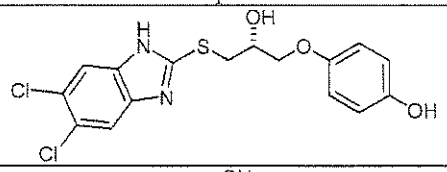
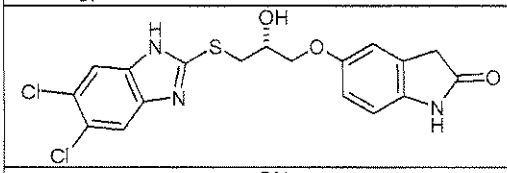
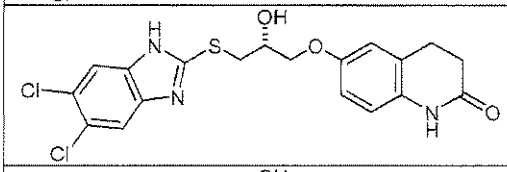
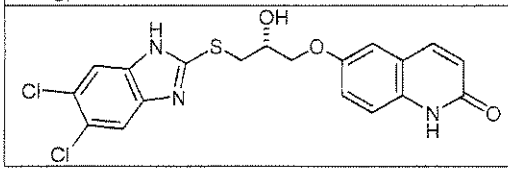


(*R*)-N-(4-(3-(5,6-dichloro-1H-benzo[d]imidazol-2-ylthio)-2-hydroxypropoxy)phenyl)methanesulfonamide. Physical data: ^{1}H NMR (d^6-DMSO): δ 2.84 (s, 3H), 3.99 (dd, 1H, J=7Hz, J=13Hz), 3.56 (dd, 1H, J=5Hz, J=14Hz), 3.96 (m, 2H), 4.12 (m, 1H), 6.9 (d, 2H, J=9Hz), 7.1 (d, 2H, J=9Hz), 7.65 (s, 2H), 9.38 (bs, 1H); MS: 462 (M+H), 464 (M+2+H); HRMS: calcd. for $C_{17}H_{18}{}^{35}Cl_2N_3O_4S_2$: 462.01158; Observed: 462.01045.



(*R*)-N-(4-(2-hydroxy-3-(6-methyl-1H-benzo[d]imidazol-2-ylthio)propoxy)phenyl)methanesulfonamide. A solution of 0.25g of 6-methyl-1H-

benzo[d]imidazol-2-thiol and 0.5g of cesium carbonate in 5 mL of N,N-dimethylformamide was stirred at room temperature for one hour. Next, 0.25g of the sulfonamide (S) epoxide was added and the reaction was heated to 60oC for 8 hours. The reaction was cooled, and diluted with water. The aqueous phase was extracted with ethyl acetate, and Physical data: ^{1}H NMR (d^6-DMSO): δ 2.34 (s, 3H), 2.84 (s, 3H), 3.36 (dd, 1H, J=8Hz, J=13Hz), 3.5 (dd, 1H, J=5Hz, J=13Hz), 3.95 (m, 2H), 4.1 (quint, 1H, J=6Hz), 5.7 (bs, 1H), 6.89 (d, 2H, J=9Hz), 6.9 (m, 1H), 7.1 (d, 2H, J=9Hz), 7.17 (bs, 1H), 7.26 (d, 1H, J=6Hz), 9.39 (bs, 1H); MS m/z: 408 (M+H); HRMS: Calcd. for $C_{18}H_{22}N_3O_4S_2$: 408.10517; Found: 408.10416.

Compound	Name
	(*R*)-4-(3-(5,6-dichloro-1H-benzo[d]imidazol-2-ylthio)-2-hydroxypropoxy)phenol
	(*R*)-5-(3-(5,6-dichloro-1H-benzo[d]imidazol-2-ylthio)-2-hydroxypropoxy)indolin-2-one
	(*R*)-6-(3-(5,6-dichloro-1H-benzo[d]imidazol-2-ylthio)-2-hydroxypropoxy)-3,4-dihydroquinolin-2(1H)-one
	(*R*)-6-(3-(5,6-dichloro-1H-benzo[d]imidazol-2-ylthio)-2-hydroxypropoxy)quinolin-2(1H)-one

Example 14. Expression of glutamate receptors in *Xenopus laevis* oocytes.

cRNA was synthesized from linearized template cDNA for rat glutamate receptor subunits according to manufacturer specifications (Ambion). Quality of synthesized cRNA was assessed by gel electrophoresis, and quantity was estimated by spectroscopy and gel electrophoresis. Stage V and VI oocytes were surgically removed from the ovaries of large, well-fed and healthy *Xenopus laevis* anesthetized with 3-amino-benzoic acid ethyl ester (3 gm/l) as previously described. Clusters of isolated oocytes were incubated with 292 U/ml Worthington (Freehold, NJ) type IV collagenase or 1.3 mg/ml collagenase (Life Technologies, Gaithersburg, MD; 17018–029) for 2 hr in Ca^{2+}-free solution comprised of (in mM) 115 NaCl, 2.5 KCl, and 10 HEPES, pH 7.5, with slow agitation to remove the follicular

cell layer. Oocytes were then washed extensively in the same solution supplemented with 1.8 mM $CaCl_2$ and maintained in Barth's solution comprised of (in mM): 88 NaCl, 1 KCl, 2.4 $NaHCO_3$, 10 HEPES, 0.82 $MgSO_4$, 0.33 $Ca(NO_3)_2$, and 0.91 $CaCl_2$ and supplemented with 100 μg/ml gentamycin, 10 μg/ml streptomycin, and 10 μg/ml penicillin. Oocytes were manually defolliculated and injected within 24 hrs of isolation with 3-5 ng of NR1 subunit cRNA and 7-10 ng of NR2 cRNA subunit in a 50 nl volume, or 5-10 ng of AMPA or kainate receptor cRNAs in a 50 nl volume, and incubated in Barth's solution at 18°C for 1–7 d. Glass injection pipettes had tip sizes ranging from 10-20 microns, and were backfilled with mineral oil.

Example 15. Two electrode voltage clamp recording from *Xenopus laevis* oocytes

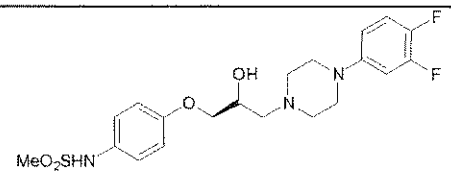
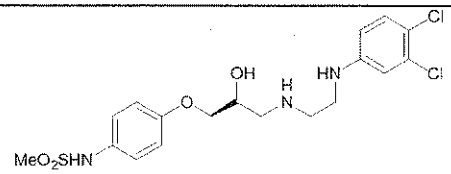
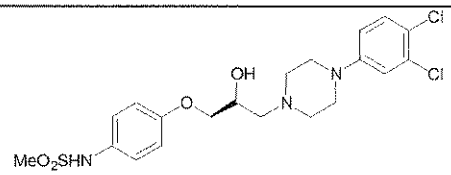
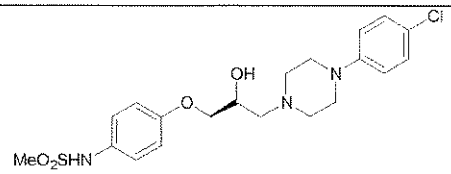
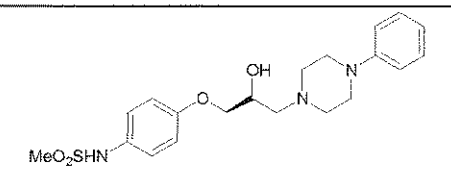
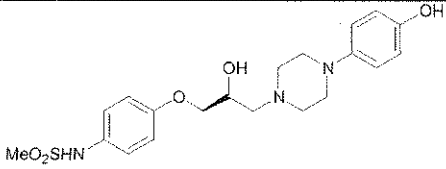
Two electrode voltage-clamp recordings were made 2–7 days post-injection as previously described. Oocytes were placed in a dual-track plexiglass recording chamber with a single perfusion line that splits in a Y-configuration to perfuse two oocytes. Dual recordings were made at room temperature (23°C) using two Warner OC725B two-electrode voltage clamp amplifiers, arranged as recommended by the manufacturer. Glass microelectrodes (1-10 Megaohms) were filled with 300 mM KCl (voltage electrode) or 3 M KCl (current electrode). The bath clamps communicated across silver chloride wires placed into each side of the recording chamber, both of which were assumed to be at a reference potential of 0 mV. Oocytes were perfused with a solution comprised of (in mM) 90 NaCl, 1 KCl, 10 HEPES, and 0.5 $BaCl_2$; pH was adjusted by addition of 1-3 M NaOH of HCl. Oocytes were recorded under voltage clamp at -40 mV. Final concentrations for control application of glutamate (50 μM) plus glycine (30 μM) were achieved by adding appropriate volumes from 100 and 30 mM stock solutions, respectively. In addition, 10 μM final EDTA was obtained by adding a 1:1000 dilution of 10 mM EDTA, in order to chelate contaminant divalent ions such as Zn^{2+}. Concentration-response curves for experimental compounds were obtained by applying in successive fashion maximal glutamate/glycine, followed by glutamate/glycine plus variable concentrations of experimental compounds. Dose response curves consisting of 4 to 8 concentrations were obtained in this manner. The baseline leak current at -40 mV was measured before and after recording, and the full recording linearly corrected for any change in leak current. Oocytes with glutamate-evoked responses smaller than 50 nA were not included in the analysis. The level of inhibition by applied experimental compounds was expressed as a percent of the initial glutamate response, and averaged together across oocytes

from a single frog. Each experiment consisted of recordings from 3 to 10 oocytes obtained from a single frog. Results from 3-6 experiments were pooled, and the average percent responses at antagonist concentrations were fitted by the equation,

$$Percent\ Response = (100 - minimum) / (1 + ([conc] / IC_{50})^{nH}) + minimum$$

where *minimum* is the residual percent response in saturating concentration of the experimental compounds, IC_{50} is the concentration of antagonist that causes half of the achievable inhibition, and *nH* is a slope factor describing steepness of the inhibition curve. *Minimum* was constrained to be greater than or equal to 0.

TABLE A. ASSAY RESULTS FOR COMPOUNDS PREPARED IN EXAMPLES 1 AND 2.

COMPOUND	IC_{50} at pH6.9 (nM)	IC_{50} at pH7.6 (nM)
	31	557
	12	62
	296	1,020
	32	270
	213	1,020
	2,400	28,000

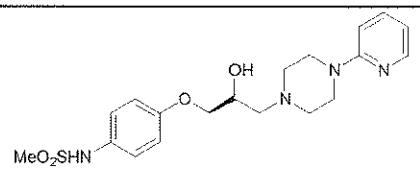
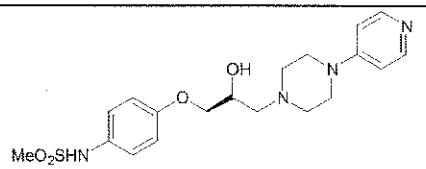
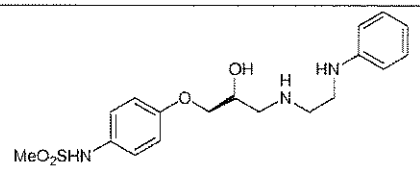
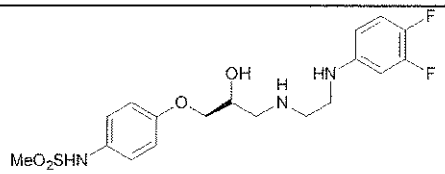
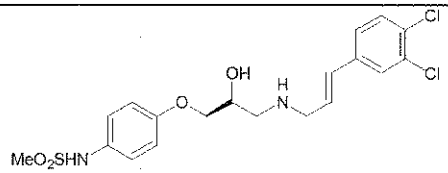
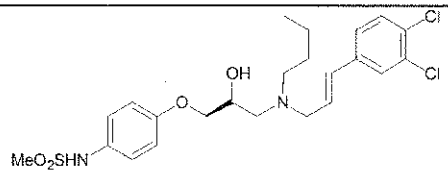
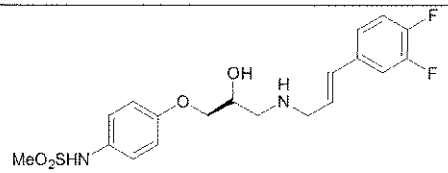
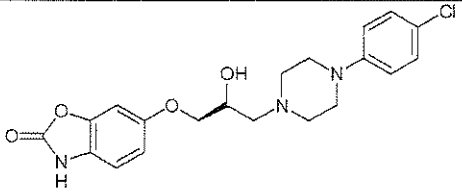
	1,810	12,700
	>30,000	>30,000
	55	133
	108	199
	7	38
	163	2,580
	38	71

TABLE B. ASSAY RESULTS FOR COMPOUNDS PREPARED IN EXAMPLE 3.

COMPOUND	IC_{50} at pH 6.9 (nM)	IC_{50} at pH 7.6 (nM)
	79	726

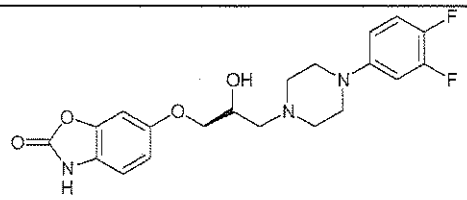
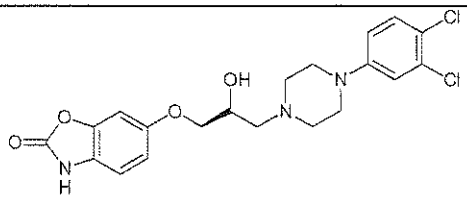
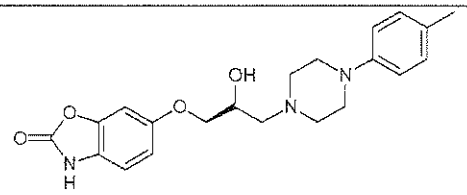
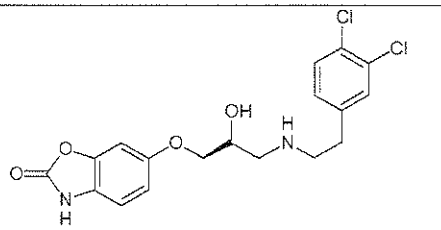
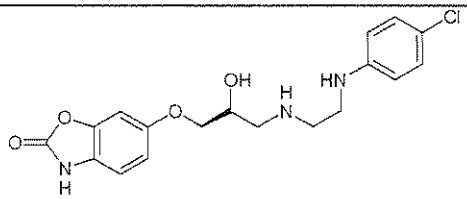
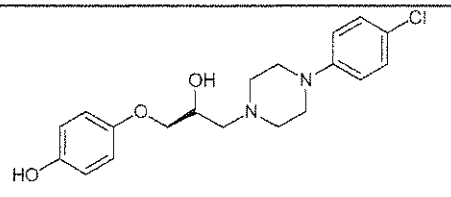
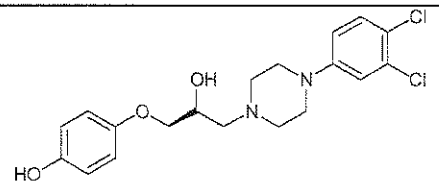
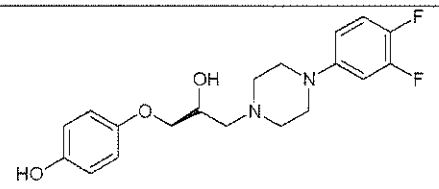
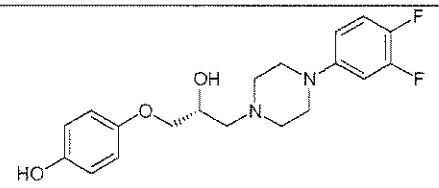
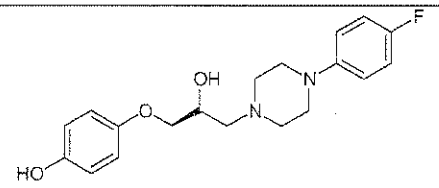
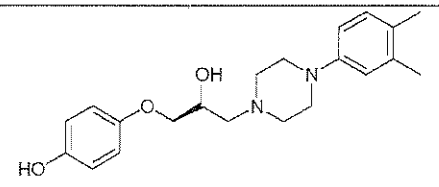
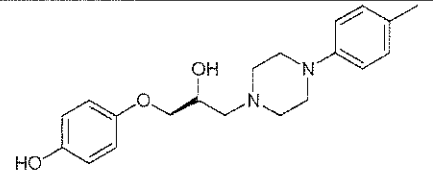
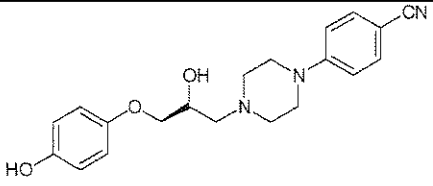
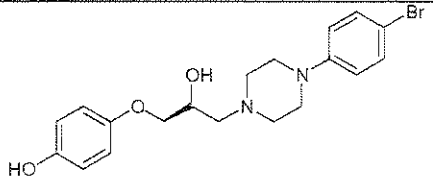
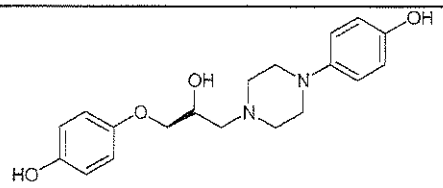
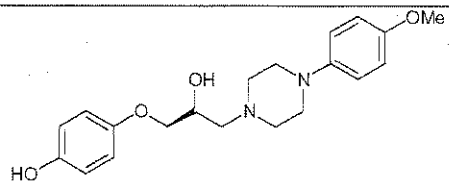
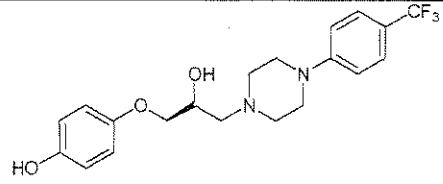
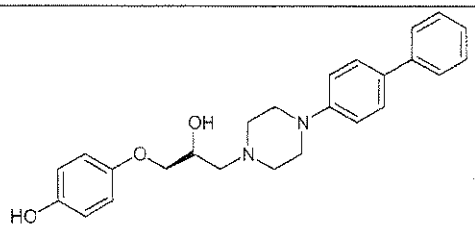
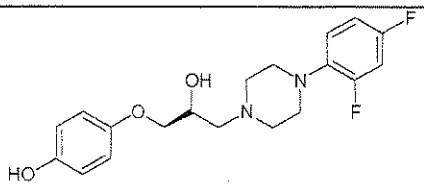
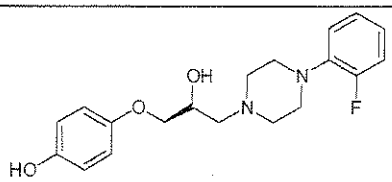
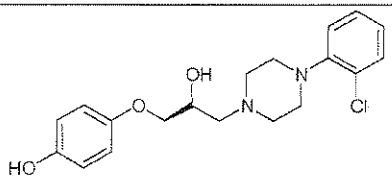
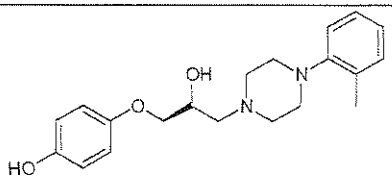
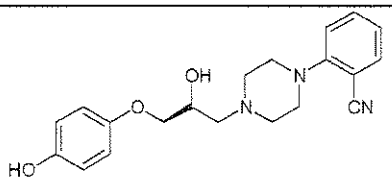
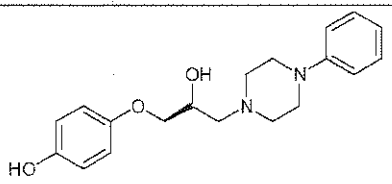
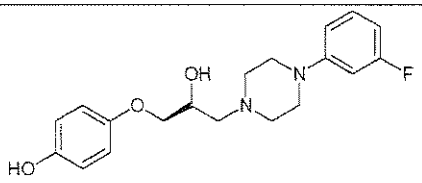
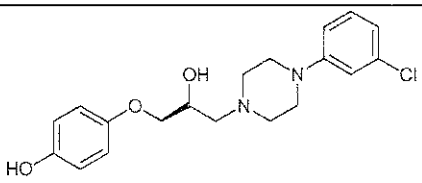
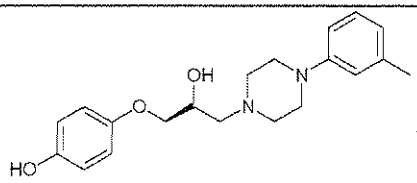
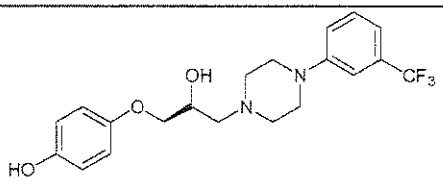
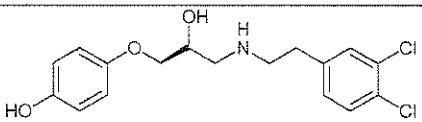
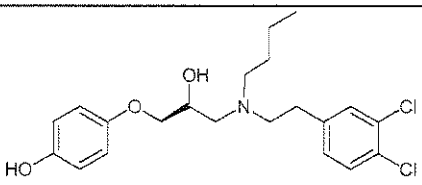
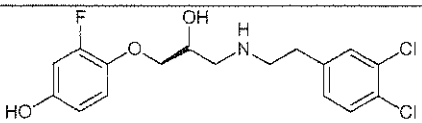
	145	1,700
	185	1,500
	72	644
	185	446
	25	97

TABLE C. ASSAY RESULTS FOR COMPOUNDS PREPARED ACCORDING TO EXAMPLE 4.

COMPOUND	IC_{50} at pH 6.9 (nM)	IC_{50} at pH 7.6 (nM)
	80	814

	131	611
	87	980
	50	272
	87	529
	1,500	5,790
	70	260
	460	4,370
	73	204

	576	4,700
	562	9,740
	113	448
	6,950	191,300
	529	3,560
	541	1,730
	978	4,390
	430	3,930

	3,210	8,330
	217	476
	211	598
	257	4,800
	341	1,740
	386	3,790
	197	501
	585	6,500
	116	330

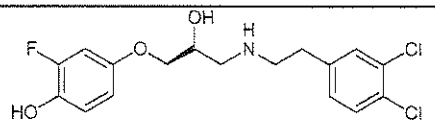
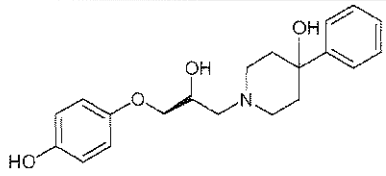
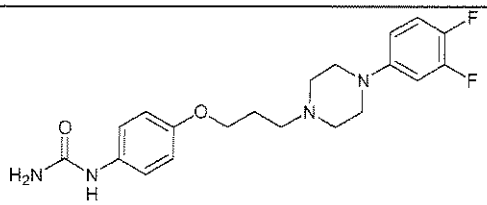
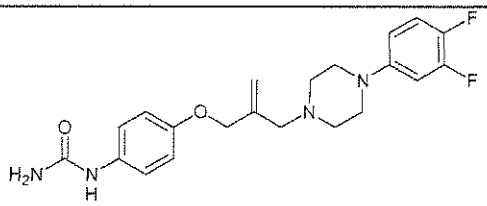
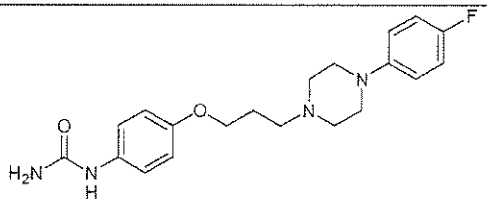
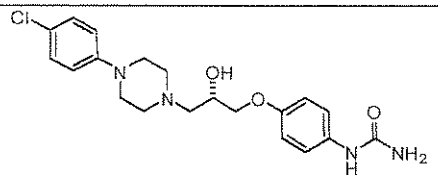
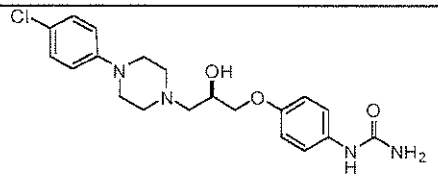
	114	549
	191	298

TABLE D. ASSAY RESULTS FOR COMPOUNDS MADE ACCORDING TO EXAMPLE 5.

COMPOUND	IC_{50} at pH 6.9	IC_{50} at pH 7.6
	82	696
	557	10,400
	117	625
	46	452
	19	60

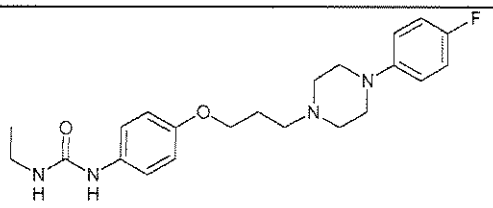
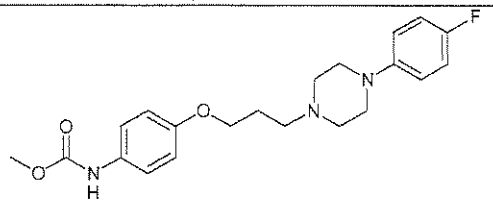
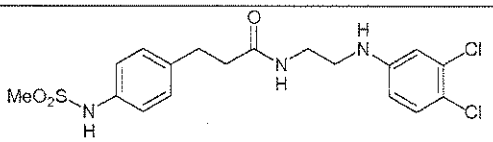
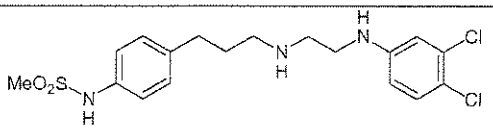
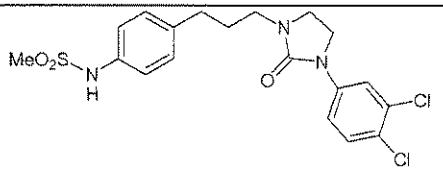
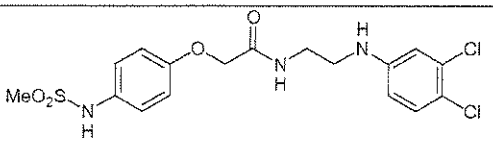
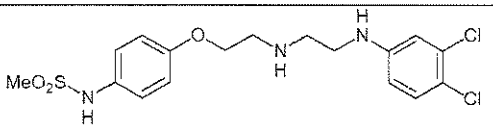
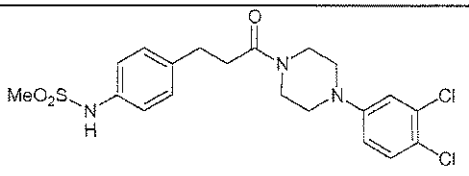
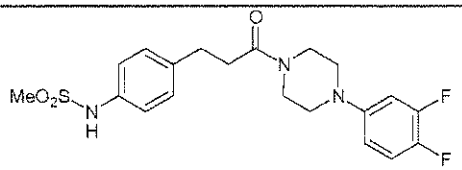
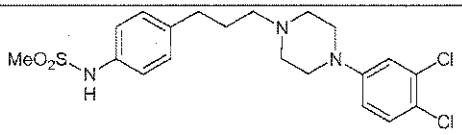
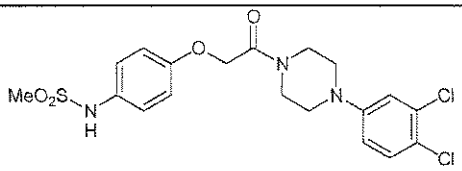
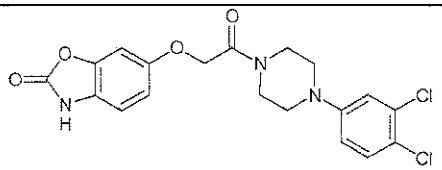
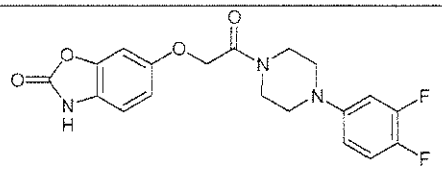
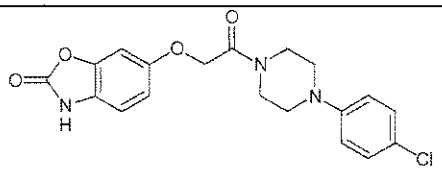
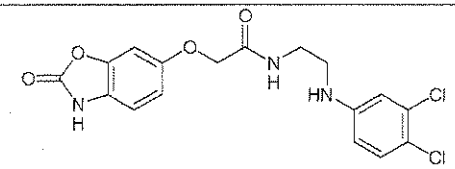
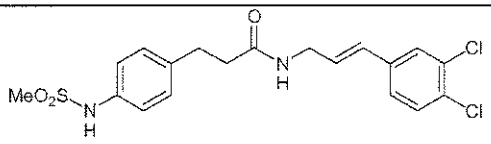
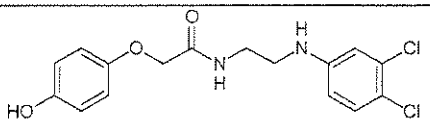
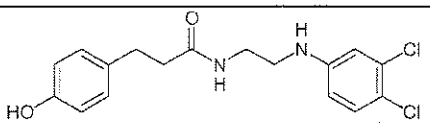
	3,030	15,700
	1,540	16,200

TABLE E. ASSAY RESULTS FOR COMPOUNDS MADE ACCORDING TO EXAMPLES 6, 7, AND 8.

COMPOUND	IC_{50} at pH 6.9	IC_{50} at pH 7.6
	30	55
	2	21
	160	809
	13	58
	14	36
	670	5,330

	2,200	8,400
	230	2,730
	40	129
	41	45
	307	467
	189	243
	80	150
	10	70
	280	515
	210	339

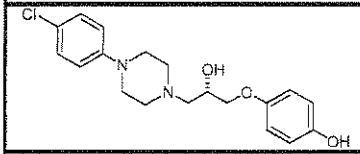
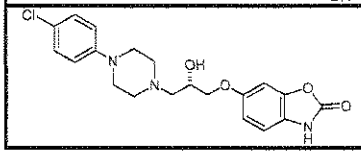
Example 16. In vitro binding studies for secondary effects

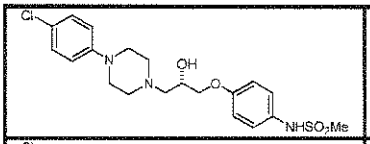
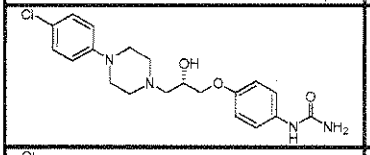
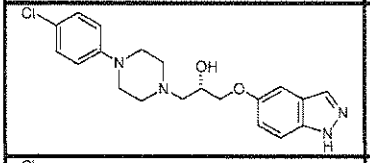
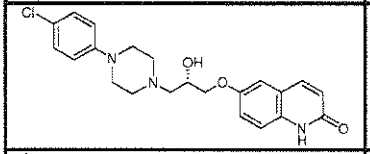
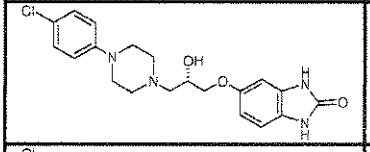
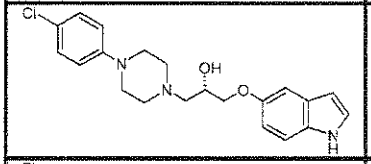
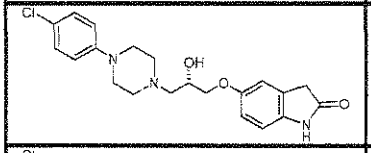
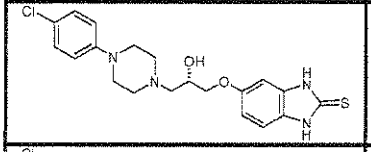
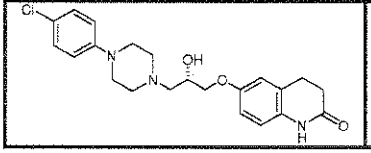
Compounds were evaluated for binding to the human ether-a-go-go potassium channel (hERG) expressed in HEK293 cells by displacement of ^{3}[H]-astemizole according to the methods by Finlayson et al. (K. Finlayson., L. Turnbull, C.T. January, J. Sharkey, J.S. Kelly; [3H]Dofetilide binding to HERG transfected membranes: a potential high throughput preclinical screen. *Eur. J. Pharmacol.* 2001, 430, 147-148). Compounds were incubated at 1 or 10 μM final concentration, in duplicate, and the amount of displaced ^{3}[H]-astemizole determined by liquid scintillation spectroscopy. In some cases, a seven concentration (each concentration in duplicate) displacement curve was generated to determine an IC_{50}.

Binding to the rat alpha-1 adrenergic receptor in rat brain membranes was determined by displacement of ^{3}[H]-prazosin (P. Greengrass and R. Bremner; Binding characteristics of 3H-prazosin to rat brain a-adrenergic receptors. *Eur.J. Pharmacol.* 1979, 55: 323-326). Compounds were incubated at 0.3 or 3 μM final concentration, in duplicate, and the amount of displaced ^{3}[H]-prazosin determined by liquid scintillation spectroscopy.

Binding IC_{50} values were determined from displacement curves (four-six concentrations, each concentration in duplicate) fit by a non-linear, least squares, regression analysis using MathIQ (ID Business Solutions Ltd., UK). The binding Ki's were determined from the IC_{50} according to the method of Cheng and Prusoff (Y. Cheng and W.H. Prusoff; Relationship between the inhibition constant (K1) and the concentration of inhibitor which causes 50 percent inhibition (IC50) of an enzymatic reaction. *Biochem. Pharmacol.* 1973, 22: 3099-3108).

TABLE F: COMPARISON OF IC50 VALUES FOR NMDA ANTAGONISM AT PH 6.9 AND 7.6 AND HERG AND A1 ADRENERGIC RECEPTORS

Compound	IC_{50} pH 6.9 (nM)	IC_{50} pH 7.6 (nM)	hERG Ki (nM)	α1 IC_{50} (nM)
	74	555	39,000	720
	51	447	1,600	620

	32	270	553	350
	46	452	13,000	340
	410	3,830	~1,000	~300
	69	550	~7,500	~350
	14	103	~7,500	~350
	>10,000	>10,000	-	-
	370	29	~10,000	~100
	16	76	~7,500	~150
	12	66	~5,000	~100

Example 17. Metabolic stability

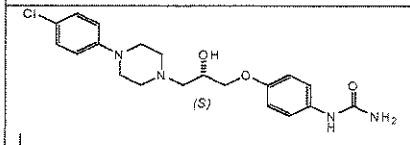
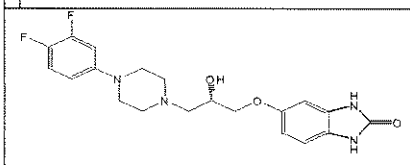
Compounds were incubated with pooled human (from at least 10 donors) or rat liver microsomes, 1.0 mg/ml microsomal protein, and 1 mM NADPH, in buffer at 37 C in a shaking water bath according to the method of Clarke and Jeffrey (S.E. Clarke and P. Jeffrey; Utility of metabolic stability screening: comparison of in vitro and in vivo clearance.

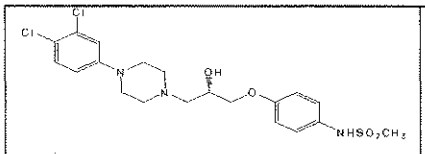
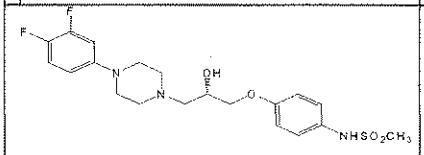
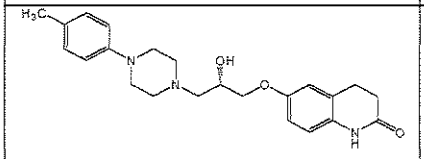
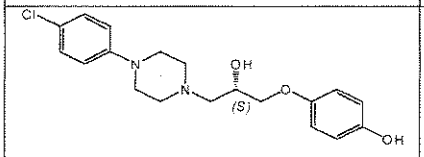
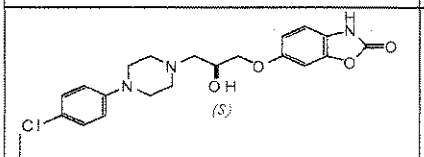
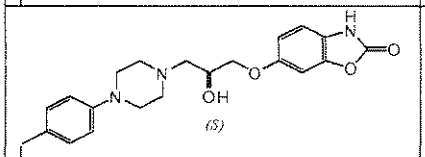
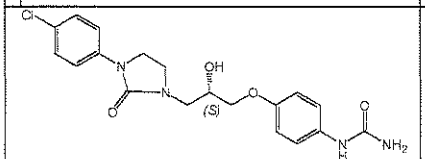
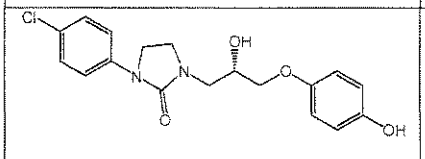
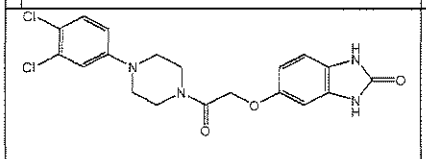
Xenobiotica 2001. 31: 591-598). At 60 min the samples were extracted and analyzed for the presence of the parent compound by LC-MS/MS. The parent material remaining in the sample at 60 min is compared to that at 0 min and expressed as a percentage. A control compound, testosterone, was run in parallel.

Example 18. Plasma half-life and brain exposure

Rats (n=3 per dose) were administered compounds at a doses of 1-4 mg/kg in a single bolus i.v. infusion (2 ml/kg body weight) via the tail vein formulated in 2% dimethyl acetamide/ 98% 2-hydroxy-propyl cyclodextrin (5%). Animals were fasted overnight prior to dose administration and food returned to the animals two hours after dosing. Following IV dosing, blood samples (*ca* 200 µL) were collected into separate tubes containing anticoagulant (K-EDTA) *via* the orbital plexus at various times post administration. Plasma samples were prepared immediately after collection by centrifugation for ten minutes using a tabletop centrifuge, and stored at -80°C. Brain tissue was weighed, homogenized on ice in 50 mM phosphate buffer (2 ml per brain) and the homogenate stored at -80 °C. Plasma and brain homogenate samples were extracted by the addition of 5 volumes of cold acetonitrile, mixed well by vortexing and centrifuged at 4000 rpm for 15 minutes. The supernatant fractions were analyzed by LC-MS/MS operating in multiple reaction monitoring mode (MRM). The amount of parent compound in each sample was calculated by comparing the response of the analyte in the sample to that of a standard curve.

TABLE G: PLASMA STABILITY RESULTS

Compound	PK-i.v. t1/2 (hr)	i.v. Cmax ng/ml	AUC (0-last h) i.v. XMPK (hr*ng/mL)	Dosing	Formu-lation
	**2.7**	252	1031*	(a) 1 MPK, 0-4 hr i.v.;	2% DMA/98% 2-HPBCD (5%in Water)
	**2.4**	241	452	(b) 1 MPK, 0-6 hr i.v.;	5% DMA/95% 2-HPBCD (5%in Water)

	**2.6**	1069	2351	(b) 3MPK, 0-4 hr i.v.;	2% DMA/98% 2-HPBCD (5%in Water)
	**> 2 i.p.****	13403 (30m), 13057 (2hr),		60 MPK, i.p. NP/Ricerca	5% DMA/95% 2-HPBCD (5%in Water)
	**0.8**	464	347	(b) 1 MPK, 0-6 hr i.v.; .	5% DMA/95% 2-HPBCD (5%in Water)
	**0.6**	193	187	(a) 1 MPK, 0-4 hr i.v.;	2% DMA/98% 2-HPBCD (5%in Water)
	**0.6**	288	217	(a) 1 MPK, 0-4 hr i.v.	2% DMA/98% 2-HPBCD (5%in Water)
	**0.6**	568	364	(a) 1 MPK, 0-4 hr i.v.;	2% DMA/98% 2-HPBCD (5%in Water)
	**1.14**	715	787.4	(b) 1MPK, 0-6 hr i.v.; 5MPK, 0-6 hr	10% DMA/10% EtOH/30% 2-HPBCD/50 % water
	**≤ 0.8 hr**	377 (30m)		3 MPK i.v. (Ricerca)	2% DMA/98% 2-HPBCD (5%in Water)
	**1.84**	575.7	1096	(b) 1MPK, 0-6 hr i.v.; 5MPK, 0-6 hr	10% DMA/10% EtOH/30% 2-HPBCD/50 % water

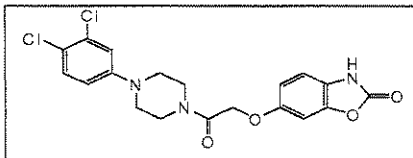
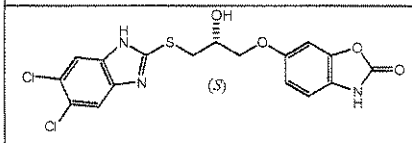
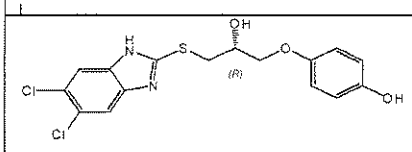
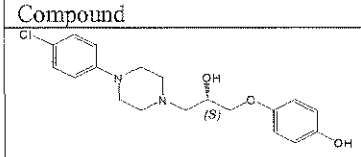
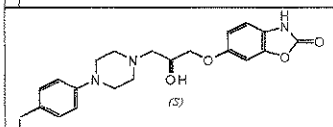
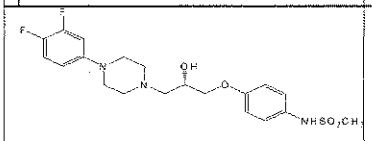
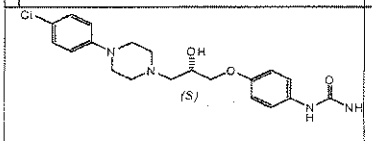
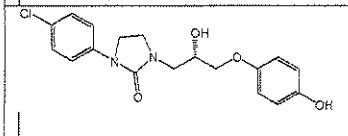
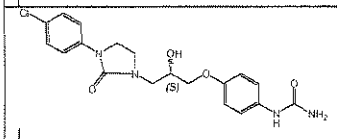
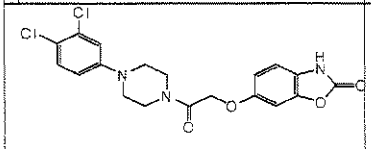
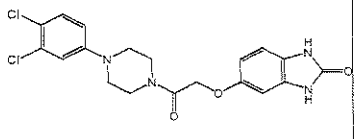
	**~0.83 i.p.**	960 (15m)		10 MPK i.p., (NeurOp/Yerkes)	50% DMSO/50 % saline
	**≤ 0.8 hr**	398 (30m)		3 MPK i.v. (Ricerca)	2% DMA/98% 2-HPBCD (5%in Water)
	**~0.5 hr**	413 (30m)		3 MPK i.v. (Ricerca)	2% DMA/98% 2-HPBCD (5%in Water)

TABLE H: BRAIN PENETRATION

Compound	RATIO: Brain:plasma (Direct)	Dosing	Formulation	BBB Pene Classification
	**10.2 (avg);** 11 (30m), 9.5 (1hr),	3 MPK i.v.	2% DMA/98% 2-HPBCD (5%in Water)	High
	**2.3 (avg);** 2.3 (30m), 2.9 (1hr), 1.7 (2hr)	3 MPK i.v. (Ricerca)	2% DMA/98% 2-HPBCD (5%in Water)	Moderate
	**0.77 (avg);** 0.7 (30m), 0.7 (2hr), 0.9 (4hr)	60 MPK, i.p. NP/Ricerca	5% DMA/95% 2-HPBCD (5%in Water)	Moderate
	**0.42 (avg);** 0.24 (30m), 0.53 (1hr), **0.49 (6hr)**	3 MPK i.v. @ 6hr, 1MPK @ 0.5hr and 2 hr (Ricerca)	2% DMA/98% 2-HPBCD (5%in Water)	Low
	**0.59 (avg);** 0.68 (30m), 0.49 (1hr),	3 MPK i.v. (Ricerca)	2% DMA/98% 2-HPBCD (5%in Water)	High
	**Below Detection limit (~ 0)**	1 MPK i.v., (Absorption)	10% DMA/10% EtOH/30% 2-HPBCD/50 % water	Low
	**0.33 (avg);** 0.25 (15m), 0.49 (30m), 0.30 (1hr), 0.36 (2hr)	10 MPK i.p., (NeurOp/ Yerkes)	50% DMSO/50% saline	Moderate
	**0.07 (avg.);** 0.04 (15m), 0.06 (30m), 0.07 (1hr), 0.10 (3hr)	1 MPG i.v., (Absorption)	10% DMA/10% EtOH/30% 2-HPBCD/50 % water	Moderate

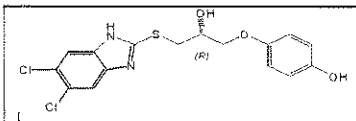
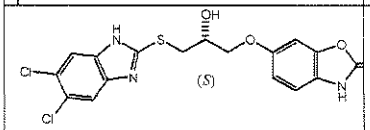
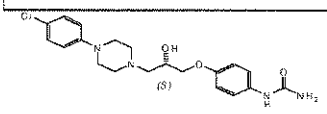
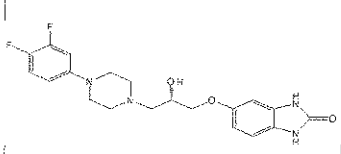
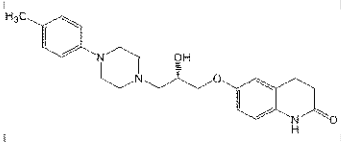
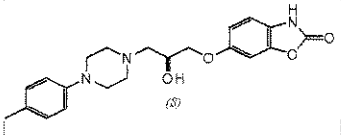
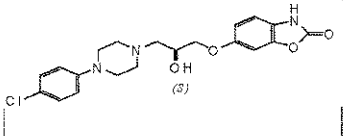
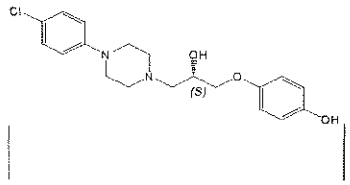
	**0.25 (avg);** 0.15 (30m), 0.35 (1hr), BLQ (2hr)	3 MPK i.v. (Ricerca)	2% DMA/98% 2-HPBCD (5%in Water)	High
	**BLQ (avg);** BLQ (30m), BLQ (1hr),	3 MPK i.v. (Ricerca)	2% DMA/98% 2-HPBCD (5%in Water)	Moderate

TABLE I: ORAL ABSORPTION

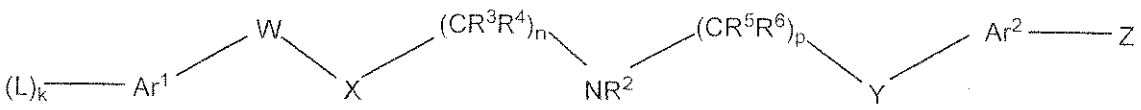
Compound	**% Absorbed (%F)**	p.o. Cmax	p.o. Tmax hr	p.o. t1/2 hr	AUC (0-last h) p.o. (hr*ng /mL)	Dosing	Formulation
	**145.7***	1556.6	2.67	6.46	8451	10 MPK, 0-8 hr p.o.	2% DMA/98% 2-HPBCD (5%in Water)
	**82.2**	558	0.5	3.04	1856	5 MPK, 0-6 hr p.o.	5% DMA/95% 2-HPBCD (5%in Water)
	**31.6**	407	0.33	0.85	549	5 MPK, 0-6 hr p.o.	5% DMA/95% 2-HPBCD (5%in Water)
	**7.9****	57.8	6.7	nc	284	10 MPK, 0-8 hr p.o.	2% DMA/98% 2-HPBCD (5%in Water)
	**6.2****	30.6	8	nc	132	10 MPK, 0-8 hr p.o.	2% DMA/98% 2-HPBCD (5%in Water)

	**3.3****	10.2	5.3	nc	56.4	10 MPK, 0-8 hr p.o.	2% DMA/98% 2-HPBCD (5%in Water)

CLAIMS

We claim:

1. A compound of Formula I, or a pharmaceutically acceptable salt, ester, prodrug or derivative thereof:



Formula I

wherein:

each L is independently C_1-C_6 alkyl, C_1-C_6 alkoxy, C(=O)-(C_1-C_6)-alkyl, C_1-C_6 haloalkyl, alkaryl, hydroxy, -O-alkyl, -O-aryl, -SH, -S-alkyl, -S-aryl, fluoro, chloro, bromo, iodo, nitro, or cyano; or two L groups may be taken together with Ar^1 to form: a dioxolane ring or a cyclobutane ring;

k = 0, 1, 2, 3, 4 or 5;

each Ar^1 and Ar^2 is independently aryl or heteroaryl;

W is a bond, C_1-C_4 alkyl, or C_2-C_4 alkenyl;

X is NR^1;

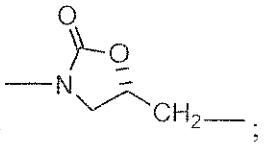
each R^1 and R^2 is independently H, C_1-C_6 alkyl, C_2-C_6 alkenyl or C_6-C_{12} aralkyl; or

R^1 and R^2 can be taken together to form a 5-8 membered ring;

each R^3 and R^4 is independently H, C_1-C_6 alkyl, C_1-C_6 alkoxy, C(=O)-(C_1-C_6)-alkyl, C_1-C_6 haloalkyl, hydroxy, fluoro, chloro, bromo, iodo, nitro, or cyano; or CR^3R^4 is C=O;

n = 1, 2, 3 or 4;

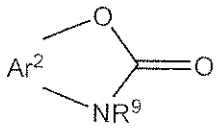
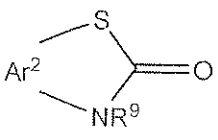
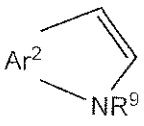
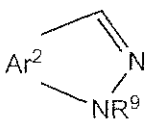
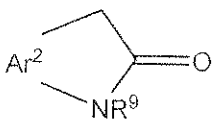
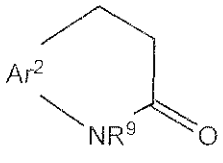
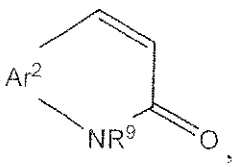
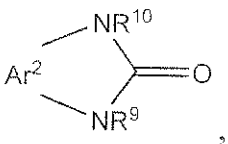
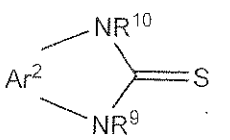
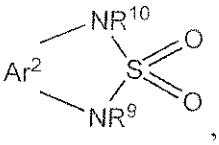
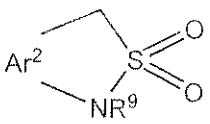
each R^5 and R^6 is independently H, C_1-C_6 alkyl, C_1-C_6 alkoxy, C(=O)-(C_1-C_6)-alkyl, C_1-C_6 haloalkyl, hydroxy, fluoro, chloro, bromo, iodo, nitro, or cyano; or CR^5R^6 is C=O or $C=CH_2$;

or wherein -NR^2- (CR^5R^6)$_p$- can be ;

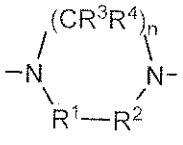
p is 1, 2, 3 or 4;

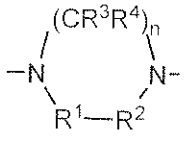
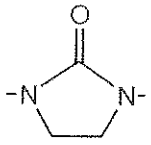
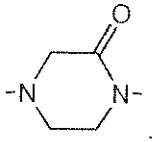
Y is a bond, O, S, SO, SO_2, CH_2, NH, N(C_1-C_6 alkyl), or NHC(=O);

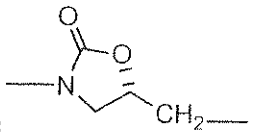
Z is OH, NR^6R^7, NR^8SO_2(C_1-C_6 alkyl), $NR^8C(O)NR^6R^7$, $NR^8C(S)NR^6R^7$, $NR^8C(O)O$(C_1-C_6 alkyl), NR^8-dihydrothiazole, or NR^8-dihydroimidazole; wherein each R^6, R^7 and R^8 is independently H, C_1-C_6 alkyl or C_6-C_{12} aralkyl; or

Ar^2—Z is , , , , , , , , , , or ; wherein R^9 and R^{10} are each independently H, C_1-C_6 alkyl, aralkyl;

wherein when X is a bond, Y is O and Ar^2 is phenyl, Z is not $NR^8SO_2(C_1$-C_6 alkyl); and when X is O, $-NR^2-(CR^5R^6)_p-$ is not -NH-C(=O)-.

2. The compound of claim 1, wherein R^1 and R^2 are taken together to form a 5-8 membered ring so that $-NR^1-(CR^3R^4)_n-NR^2-$ is .

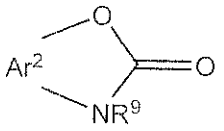
3. The compound of claim 2, wherein  is ,  or .

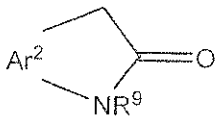
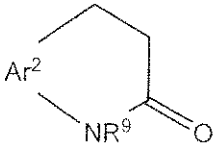
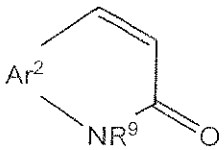
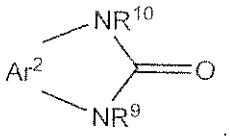
4. The compound of claim 1 wherein $-NR^2-(CR^5R^6)_p-$ is .

5. The compound of claim 1, wherein W is a bond.

6. The compound of claim 1, wherein Y is O.

7. The compound of claim 1, wherein Z is $NR^8C(O)NR^6R^7$.

8. The compound of claim 1, wherein $Ar^2—Z$ is ,

, , , or .

9. The compound of claim 1, wherein the compound is present substantially in the form of a single enantiomer.

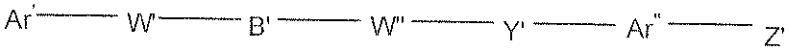
10. A pharmaceutical composition comprising a compound of claim 1 in a pharmaceutically acceptable carrier.

11. A compound of claim 1, optionally in a pharmaceutically acceptable carrier, for use in the treatment or prophylaxis of neuropathic pain, stroke, traumatic brain injury, epilepsy, and other neurologic events or neurodegeneration resulting from NMDA receptor activation.

12. The compound of claim 11, wherein the compound is to be administered for treatment of a host suffering from neuropathic pain.

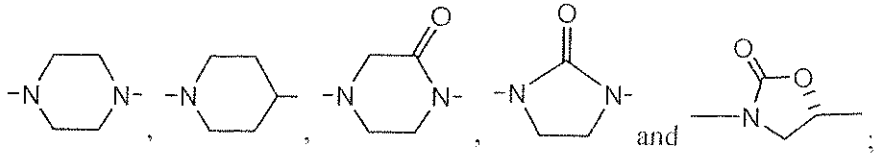
13. The compound of claim 11, wherein the compound is to be administered for reducing neuronal injury in a host suffering from a stroke or a traumatic brain injury.

14. A compound of Formula V or a pharmaceutically acceptable salt, ester, prodrug or derivative thereof:



Formula V

wherein B' is selected from the group consisting of:



W' is a bond or C_1-C_4 alkyl;

W'' is C_1-C_4 alkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 haloalkyl or C(=O)-C_1-C_4 alkyl;

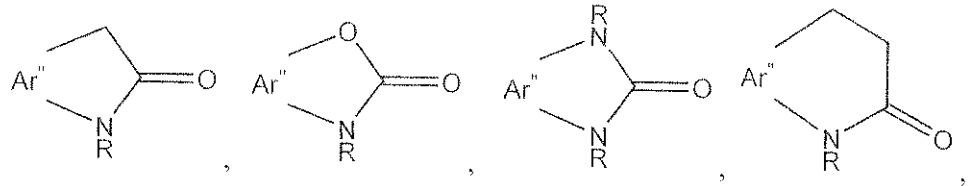
Y' is selected from a bond, O, S, CH_2 and N;

Ar' is a substituted or unsubstituted aromatic or nonaromatic cycloalkyl which optionally may include 0-3 heteroatoms;

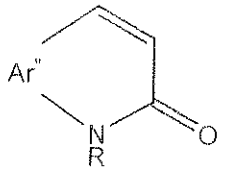
Ar'' is an aromatic or nonaromatic cycloalkyl which optionally may include 0-3 heteroatoms;

Z' is $NRC(O)NR_2$; wherein each R is independently selected from H, C_1-C_6 alkyl or C_6-C_{12} aralkyl; or

Ar''-Z' are taken together and selected from the group consisting of:



and



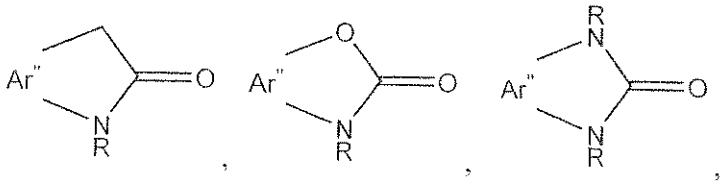
15. The compound of claim 14, wherein B' is .

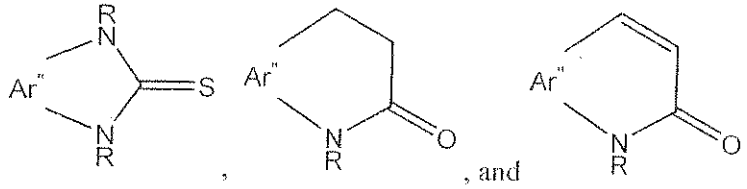
16. The compound of claim 14, wherein W'' is $-CH_2$ or $CH(OH)-CH_2-$.

17. The compound of claim 14, wherein Ar'' is phenyl.

18. The compound of claim 14, wherein Z' is $NRC(O)NR_2$.

19. The compound of claim 14, wherein Z and Ar'' are taken together and selected from the group consisting of:





, and

.

20. The compound of claim 14, wherein Ar' is substituted with $(L')_{k'}$ and each L' is independently C_1-C_6 alkyl, C_1-C_6 alkoxy, $C(=O)$-$(C_1$-$C_6)$-alkyl, C_1-C_6 haloalkyl, alkaryl, hydroxy, -O-alkyl, -O-aryl, -SH, -S-alkyl, -S-aryl, fluoro, chloro, bromo, iodo, nitro, or cyano; or two L' groups may be taken together with Ar' to form: a dioxolane ring or a cyclobutane ring; and

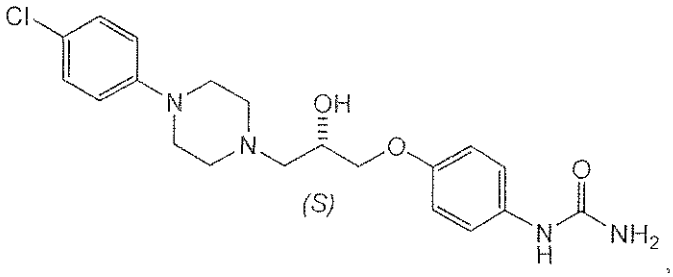
k' = 0, 1, 2, 3, 4 or 5.

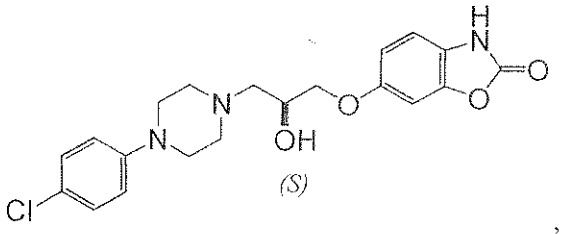
21. The compound of claim 20, wherein an L' group is in the para position on Ar'.

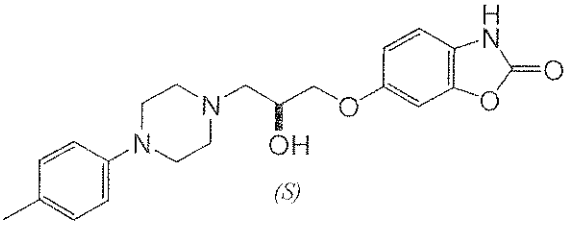
22. The compound of claim 21, wherein L' in the para position is a halogen.

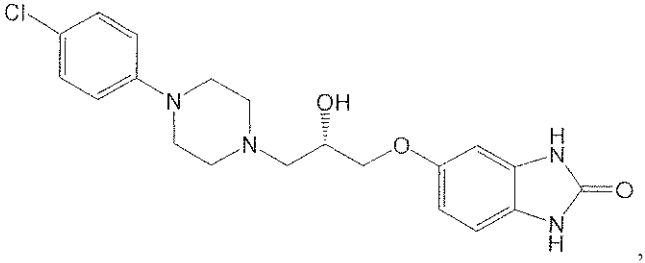
23. The compound of claim 21, wherein L' in the para position is a C_1-C_6 alkyl.

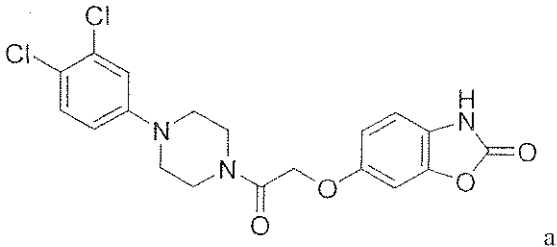
24. The compound of claim 14, wherein the compound is selected from the group consisting of:



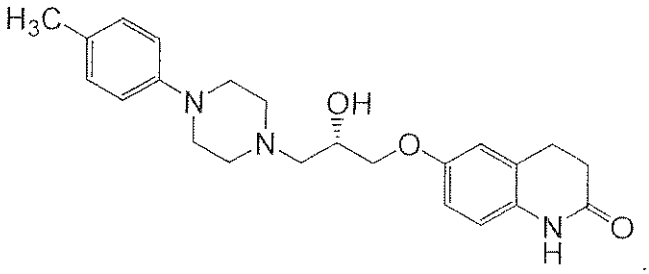








and



25. A pharmaceutical composition comprising a compound of claim 14, in a pharmaceutically acceptable carrier.

26. A compound of claim 14, optionally in a pharmaceutically acceptable carrier, for use in the treatment or prophylaxis of neuropathic pain, stroke, traumatic brain injury, epilepsy, and other neurologic events or neurodegeneration resulting from NMDA receptor activation.