Disclosure herein are methods of treating a patient suffering from one or more types of chronic pain using the following compounds:
METHODS FOR TREATING CHRONIC PAIN USING 1-BEN2YL-1-
HYDROXY-2,3-DIAMINO-PROPYL AMINES, 3-BENZYL-3-HYDROXY-2-
AMINO-PROPIONIC ACID AMIDES AND RELATED COMPOUNDS

BACKGROUND OF THE INVENTION

Field of the invention

The present invention is directed to methods of treating a patient
suffering from one or more types of chronic pain using using 1-benzyl-1-
hydroxy-2,3-diamino-propyl amines, 3-benzyl-3-hydroxy-2-amino-propionic
acid amides and related compounds.

Background of the invention

1-Phenyl-2-decanoylamino-3-morpholino-1-propanol (PDMP) was
discovered by Vunam, R. R. and Radin, N., Chem. Phys. Lipids, 26, 265-278,
1980. Preparation of PDMP is described in Inokuchi, J. et al., J. Lipid Res.

PDMP
mixture of DL-erythro and
DL-threo isomers

These derivatives inhibit glucosylerceramide (GlcCer) formation by inhibiting the
enzyme GlcCer synthase, thereby lowering the level of glycosphingolipids.)

The isomers most active have the R,R-(D-threo)-configuration. Four
enantiomers are produced during the synthesis. Because only the ù-threo
enantiomers are active in inhibiting the glucosylerceramide synthase, resolution
of the active ù-threo inhibitors was performed by chiral chromatography.

Moreover, D-threo-PDkλ,P has antitumor activity via inhibition of
glycosphingolipid biosynthesis as described by Inokuchi J., Cancer Letters
Furthermore, it was also reported that *D-three-PDMP* suppresses synaptic function by Mizutani *et al.*, Biochem. Biophys. Res. Commun., 222, 494-498, 1996.


*L-threo-PDMP* is an agent for treating neuronal diseases WO 95/05177. This compound is also described to be an agent for protecting brain in US 6407064. Moreover treatment with *L-three-PDMP* after transient forebrain ischemia in rats ameliorated the deficit of a well learned spatial memory by an 8-arm maze task, suggesting a potential for neurodegenerative disorders as described by Inokuchi *et al.*, *Ann. N. Y. Acad. Sci.*, 845(1), 219-224, 1998 and JP 10324671 (Seikagaku Kogyo Co.).

A stereoselective synthesis of enantiomerically pure *D-threo-PDMP* has also been described by Shin, S. *et al.*, *Tetrahedron asymmetry*, 11, 3293-3301, 2000 and WO 2002012185 the key step is the regioselective cleavage by nitrogen nucleophiles, as morpholine, of the C(3)-N-bond of non-activated enantiomerically pure aziridine-2-methanols.

![Chemical Structures](image)

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![Chemical Structures](image)
On the other hand, the synthesis of enantiomerically pure (1S,2S)-1-phenyl-2-decanoylamino-3-morpholino-1-propanol (L-threo-PDMP) from L-serine has also been described by Mitchell, Scott A., J. Org. Chem., 63 (24), 8837-8842, 1998.


L-threo-PDMP is an agent for treating neuronal diseases WO 95/05177. This compound is also described to be an agent for protecting brain in US 6407064. Moreover, treatment with L-threo-PDMP after transient forebrain ischemia in rats ameliorated the deficit of a well learned spatial memory by an 8-arm maze task, suggesting a potential for neurodegenerative disorders as described by Inokuchi et al., Ann. N.Y. Acad. Sci., 845(1), 219-224, 1998 and JP 10324671 (Setkagaku Kogyo Co.).

Synthesis of (1S,2S)-threo- and (1R,2S)-erythro-1-phenyl-2-palmitoylamino-3-N-morpholino-1-propanol (PPMP) were described starting from Garner aldehyde of L-serine, by Nishida, A., Synlett, 4, 389-390, 1998.

Compounds with longer chain fatty acyl groups (than decanoyl) have been found to be substantially more effective as inhibitor of GCS. D-threo-1-phenyl-2-palmitoylamino-3-pyrrolidino-1-propanoi (P4 or PPPP) analogues were first obtained by a Mannich reaction as described Abe, A. et al., J. Biochem., 111, 191-196, 1992 or US 5916911 and WO 2001004108.
Preparation of D-threo-4'-hydroxy-P4, one of the most potent inhibitor of GCS, was described by Lee, L. et al., *J. Biol. Chem.*, 274, 21, 14662-14669, 1999. In addition, a series of dioxane substitutions was designed and tested. These included 3',4'-methyleneoxyphenyl-3',4'-ethylenedioxyphenyl- and 3',4'-trimethylenedioxyphenyl-substituted homologues.

Novel prodrugs of P4 derivatives were described in US 20020198240 andWO 2002062777.


![Diagram of synthesis](image)

Diastereoselective synthesis of P4 analogues were described in US 03/0153768 and WO 2003045928 (Genzyme Corp.); Oxazolines [R1 = (un)substituted aryl; R2, R3 = H, (un)substituted aliphatic; NR2R3 = heterocyclic] are prepared as intermediates for P4 glucosyltransferase inhibitors from R1CHO and R2R3NCOCH2CN. Thus, methyl isocyanoacetate CNCH2CO2Me was treated with pyrrolidine and the amide was treated with 1,4-benzodioxane-6-carboxaldehyde, followed by hydrolysis of the oxazoline using HCl in methanol, reduction of the keto group of amide II using LiAlH4, and acylation with palmitoyl chloride to give D,L-tfjreo-ethylenedioxy-P4 III.
Synthesis of enantiopure P4 analogues were described in WO 2003008399 (Genzyrne Corp.).

P4 derivatives, such as I \([R^1, R^5 = \text{substituted}]\) aromatic; R2, R3 = H, un(substituted) aliphatic; NR2R3 = (un)substituted non-aromatic heterocyclic ring; R4 = O, H2, were prepared for their therapeutic use as GCS inhibitors. Thus, D-3',4'-ethylenedioxy-P4 was prepared via a multistep synthetic sequence starting from S-(+)-Ph gyicine, phenyl-\(\alpha\)-bromoacetate, 1,4-benzodioxan-6-carboxaldehyde, pyrrolidine and palmitoyl chloride.

New D-threo-P \(\Lambda\) analogues that bear ether substituents on the aromatic ring have been recently synthesized from D-serine and found to suppress neurite extension in an embryonic insect cell line as described by Slavish, J. P. et al., Bioorg. Med. Chem. Lett., 14, 1487-1490, 2004.

Further references which serve as background to the present invention are United States Patent Nos. 5,945,442; 5,952,370; 6,030,995 and 6,051,598; Journal of Labelled Compounds & Radiopharmaceuticals (1996), 38(3), 285-97; Published PCT application WO 01/38228; and Kastron et al. Latvijas PSR Zinatnu Akademijas Vestis, Kimijas Serija (1965) (4), 474-7.

SUMMARY OF THE INVENTION

The present invention is directed to methods of treating a patient suffering from one or more types of chronic pain using the compounds set forth below:
DETAILED DESCRIPTION OF THE INVENTION

All of compounds useful in the methods of the present invention have two asymmetric carbons adjacent to one another and therefore, generally speaking, can exist in erythro or threo form, with each of these two forms having dextrorotatory (D) or levorotary (L) enantiomers. Nevertheless, most compounds presently used in the methods of the present invention are in the threo form which itself can have dextrorotatory (D) or levorotary (L)
enantiomers. The scope of the present invention includes use of the *threo* and *erythro* isomers, mixtures of *erythro* and *threo* isomers, both enantiomers of the isomers in optically pure form, racemic mixtures and mixtures where the enantiomers are not present in equal amounts. In light of the foregoing, it should be clearly understood that the designation "DL" or "(+/-)" or "(±)" in this application includes the pure dextrorotatory enantiomer, the pure levorotatory enantiomer and all racemic mixtures, including mixtures where the two enantiomers are present in equal or in unequal proportions. Moreover, for simplicity sake in many of the structural formulas, such as in the example below, only one of the enantiomers is actually shown but when the designation "DL" (or "(+/-)" or "(±)") appears below the formula, its optical isomer (mirror image) of the structure actually shown in the formula.

For Example:

\[
\begin{align*}
\text{DL-} & \text{threo} \\
\hline
\text{OH} & \text{O} \\
\text{NH}_2 & \\
\text{N} \\
\text{phenyl}
\end{align*}
\]

In the example above, only one enantiomer is shown, but because the designation "DL" (or "(+/-)" or "(±)") appears below the formula, its optical isomer

\[
\begin{align*}
\text{OH} & \text{O} \\
\text{NH}_2 & \\
\text{N} \\
\text{phenyl}
\end{align*}
\]

and all racemic mixtures of the two optical isomers are also included.

Keeping the foregoing example in mind a person of ordinary skill in the art should readily understand the scope of each described example, although in a broad sense all enantiomers and racemic mixtures are within the scope of the invention.

Generally speaking the compounds used in the methods of the present invention may already be shown as hydrochloride salts. However, the
compounds may also exist in salt free form or may form salts with pharmaceutically acceptable acids, other than hydrochloric acid, and such pharmaceutically acceptable salts are also within the scope of the invention.

The compounds used in the method of the invention have analgesic activity in mammals.

BIOLOGICAL ACTIVITY, MODES OF ADMINISTRATION

The compounds described here may be used to treat a patient suffering from one or more types of chronic pain, including neuropathic pain, inflammatory pain, headache pain, somatic pain, visceral pain, and referred pain.

To "treat," as used here, means to deal with medically. It includes, for example, administering a compound of the invention to prevent a pain, to alleviate its severity, and to prevent its reoccurrence.

The term "pain," as used here, means any unpleasant sensory experience, usually associated with a physical disorder. The physical disorder may or may not be apparent to a clinician. Pain is of two types: chronic and acute. An "acute pain" is a pain of short duration having a sudden onset. One type of acute pain, for example, is cutaneous pain felt on injury to the skin or other superficial tissues, such as caused by a cut or a burn. Cutaneous nociceptors terminate just below the skin, and due to the high concentration of nerve endings, produce a well-defined, localized pain of short duration. "Chronic pain" is a pain other than an acute pain. Chronic pain includes neuropathic pain, inflammatory pain, headache pain, somatic pain visceral pain and referred pain.

/ Neuropathic Pain

The compounds of the invention may be used to treat pain caused by or otherwise associated with any of the following neuropathic pain conditions. "Neuropathic pain" means abnormal sensory input, resulting in discomfort, from the peripheral nervous system, central nervous systems, or both.

A. Symptoms of neuropathic pain

Symptoms of neuropathic pain can involve persistent, spontaneous pain, as well as allodynia (a painful response to a stimulus that normally is not
painful), hyperalgesia (an accentuated response to a painful stimulus that usually causes only a mild discomfort, such as a pin prick), or hyperpathia (where a short discomfort becomes a prolonged severe pain).

B. Causes of neuropathic pain

Neuropathic pain may be caused by any of the following.

1. A traumatic insult, such as, for example, a nerve compression injury (e.g., a nerve crush, a nerve stretch, a nerve entrapment or an incomplete nerve transsection); a spinal cord injury (e.g., a hemisection of the spinal cord); a limb amputation; a contusion; an inflammation (e.g., an inflammation of the spinal cord); or a surgical procedure.

2. An ischemic event, including, for example, a stroke and heart attack.

3. An infectious agent

4. Exposure to a toxin, including, for example, a drug, an alcohol, a heavy metal (e.g., lead, arsenic, mercury), an industrial agent (e.g., a solvent, fumes from a glue) or nitrous oxide.

5. A disease, including, for example, an inflammatory disorder, a neoplastic tumor, an acquired immune deficiency syndrome (AIDS), Lymes disease, a leprosy, a metabolic disease, a neurodegenerative disease, a spinal stenosis, a mononeuropathy, a polyneuropathy, and a peripheral nerve disorder, such as a neuroma.

C. Types of neuropathic pain

1. Neuralgia.

A neuralgia is a pain that radiates along the course of one or more specific nerves usually without any demonstrable pathological change in the nerve structure. The causes of neuralgia are varied. Chemical irritation, inflammation, trauma (including surgery), compression by nearby structures (for instance, tumors), and infections may all lead to neuralgia. In many cases, however, the cause is unknown or unidentifiable. Neuralgia is most common in elderly persons, but it may occur at any age. A neuralgia, includes, without limitation, a trigeminal neuralgia, a spinal stenosis, a post-herpetic neuralgia, a postherpetic neuralgia, a glossopharyngeal neuralgia, pain associated with nerve entrapment disorders, a sciatica and an atypical facial pain.
Neuralgia is a painful disorder of the cranial nerves. Falling under the category of neuralgia are trigeminal neuralgia (TN), atypical facial pain, and postherpetic neuralgia (caused by shingles or herpes). The affected nerves are responsible for sensing touch, temperature and pressure in the facial area from the jaw to the forehead. The disorder generally causes short episodes of excruciating pain, usually for less than two minutes and on only one side of the face. The pain can be described in a variety of ways such as "stabbing," "sharp," "like lightning," "burning," and even "itchy". In the atypical form of TN, the pain can also present as severe or merely aching and last for extended periods. The pain associated with TN is recognized as one the most excruciating pains that can be experienced.

Simple stimuli such as eating, talking, washing the face, or any light touch or sensation can trigger an attack (even the sensation of a gentle breeze). The attacks can occur in clusters or as an isolated attack.

Symptoms include sharp, stabbing pain or constant, burning pain located anywhere, usually on or near the surface of the body, in the same location for each episode; pain along the path of a specific nerve; impaired function of affected body part due to pain, or muscle weakness due to concomitant motor nerve damage; increased sensitivity of the skin or numbness of the affected skin area (feeling similar to a local anesthetic such as a Novacaine shot); and any touch or pressure is interpreted as pain. Movement may also be painful.

Trigeminal neuralgia is the most common form of neuralgia. It affects the main sensory nerve of the face, the trigeminal nerve ("trigeminal" literally means "three origins", referring to the division of the nerve into 3 branches). This condition involves sudden and short attacks of severe pain on the side of the face, along the area supplied by the trigeminal nerve on that side. The pain attacks may be severe enough to cause a facial grimace, which is classically referred to as a painful tic (tic douloureux). Sometimes, the cause of trigeminal neuralgia is a blood vessel or small tumor pressing on the nerve. Disorders such as multiple sclerosis (an inflammatory disease affecting the brain and spinal cord), certain forms of arthritis, and diabetes (high blood
sugar) may also cause trigeminal neuralgia, but a cause is not always identified. In this condition, certain movements such as chewing, talking, swallowing, or touching an area of the face may trigger a spasm of excruciating pain.

A related but rather uncommon neuralgia affects the glossopharyngeal nerve, which provides sensation to the throat. Symptoms of this neuralgia are short, shock-like episodes of pain located in the throat.

Neuralgia may occur after infections such as shingles, which is caused by the varicella-zoster virus, a type of herpesvirus. This neuralgia produces a constant burning pain after the shingles rash has healed. The pain is worsened by movement of or contact with the affected area. Not all of those diagnosed with shingles go on to experience postherpetic neuralgia, which can be more painful than shingles. The pain and sensitivity can last for months or even years. The pain is usually in the form of an intolerable sensitivity to any touch but especially light touch. Postherpetic neuralgia is not restricted to the face; it can occur anywhere on the body but usually occurs at the location of the shingles rash. Depression is not uncommon due to the pain and social isolation during the illness.

Postherpetic neuralgia may be debilitating long after signs of the original herpes infection have disappeared. Other infectious diseases that may cause neuralgia are syphilis and Lyme disease.

Diabetes is another common cause of neuralgia. This very common medical problem affects almost 1 out of every 20 Americans during adulthood. Diabetes damages the tiny arteries that supply circulation to the nerves, resulting in nerve fiber malfunction and sometimes nerve loss. Diabetes can produce almost any neuralgia, including trigeminal neuralgia, carpal tunnel syndrome (pain and numbness of the hand and wrist), and meralgia paresthetica (numbness and pain in the thigh due to damage to the lateral femoral cutaneous nerve). Strict control of blood sugar may prevent diabetic nerve damage and may accelerate recovery in patients who do develop neuralgia.
Other medical conditions that may be associated with neuralgias are chronic renal insufficiency and porphyria - a hereditary disease in which the body cannot rid itself of certain substances produced after the normal breakdown of blood in the body. Certain drugs may also cause this problem.

2. Deafferentation.

Deafferentation indicates a loss of the sensory input from a portion of the body, and can be caused by interruption of either peripheral sensory fibres or nerves from the central nervous system. A deafferentation pain syndrome, includes, without limitation, an injury to the brain or spinal cord, a post-stroke pain, a phantom pain, a paraplegia, a brachial plexus avulsion injuries, lumbar radiculopathies.

3. Complex regional pain syndromes (CRPs)

CRPS is a chronic pain syndrome with two forms. CRPS 1 currently replaces the term "reflex sympathetic dystrophy syndrome". It is a chronic nerve disorder that occurs most often in the arms or legs after a minor or major injury. CRPS 1 is associated with severe pain; changes in the nails, bone, and skin; and an increased sensitivity to touch in the affected limb. CRPS 2 replaces the term causalgia, and results from an identified injury to the nerve. A CRPS, includes, without limitation, a CRPS Type I (reflex sympathetic dystrophy) and a CRPS Type II (causalgia).


A neuropathy is a functional or pathological change in a nerve and is characterized clinically by sensory or motor neuron abnormalities.

Central neuropathy is a functional or pathological change in the central nervous system.

Peripheral neuropathy is a functional or pathological change in one or more peripheral nerves. The peripheral nerves relay information from your central nervous system (brain and spinal cord) to muscles and other organs and from your skin, joints, and other organs back to your brain. Peripheral neuropathy occurs when these nerves fail to carry information to and from the brain and spinal cord, resulting in pain, loss of sensation, or inability to control muscles. In some cases, the failure of nerves that control blood vessels,
intestines, and other organs results in abnormal blood pressure, digestion problems, and loss of other basic body processes. Risk factors for neuropathy include diabetes, heavy alcohol use, and exposure to certain chemicals and drugs. Some people have a hereditary predisposition for neuropathy.

Prolonged pressure on a nerve is another risk for developing a nerve injury. Pressure injury may be caused by prolonged immobility (such as a long surgical procedure or lengthy illness) or compression of a nerve by casts, splints, braces, crutches, or other devices. Polyneuropathy implies a widespread process that usually affects both sides of the body equally. The symptoms depend on which type of nerve is affected. The three main types of nerves are sensory, motor, and autonomic. Neuropathy can affect any one or a combination of all three types of nerves. Symptoms also depend on whether the condition affects the whole body or just one nerve (as from an injury).

The cause of chronic inflammatory polyneuropathy is an abnormal immune response. The specific antigens, immune processes, and triggering factors are variable and in many cases are unknown. It may occur in association with other conditions such as HIV, inflammatory bowel disease, lupus erythematosus, chronic active hepatitis, and blood cell abnormalities.

Peripheral neuropathy may involve a function or pathological change to a single nerve or nerve group (mononeuropathy) or a function or pathological change affecting multiple nerves (polyneuropathy).

**Peripheral neuropathies**

**Hereditary disorders**

- Charcot-Marie-Tooth disease
- Friedreich’s ataxia

**Systemic or metabolic disorders**

- Diabetes (diabetic neuropathy)
- Dietary deficiencies (especially vitamin B-12)
- Excessive alcohol use (alcoholic neuropathy)
- Uremia (from kidney failure)
- Cancer (including bone cancer and other cancers)
infectious or inflammatory conditions

AIDS
Hepatitis
Colorado tick fever
Diphtheria
Guillain-Barre syndrome
HIV infection without development of AIDS
Leprosy
Lyme disease
Polyarteritis nodosa
Rheumatoid arthritis
Sarcoidosis
Sjogren's syndrome
Syphilis
Systemic Lupus erythematosus
amyloid

Exposure to toxic compounds
Sniffer glue or other toxic compounds
Nitrous oxide
Industrial agents -- especially solvents
Heavy metals (lead, arsenic, mercury, etc.)
Neuropathy secondary to drugs like analgesic nephropathy
Rhabdomyolysis
Macrophagic myofascitis

Highly Active Anti-Retroviral Therapy (HAART)-induced neuropathy
Chemotherapy induced Neuropathy

Miscellaneous causes
Ischemia (decreased oxygen/decreased blood flow)
Prolonged exposure to cold temperature
a. Polyneuropathy
Polyneuropathy is a peripheral neuropathy involving the loss of movement or sensation to an area caused by damage or destruction to
multiple peripheral nerves. Polyneuropathic pain, includes, without limitation, post-polio syndrome, postmastectomy syndrome, diabetic neuropathy, alcohol neuropathy, amyloidosis, toxin exposure, AIDS, hypothyroidism, uremia, vitamin deficiencies, chemotherapy-induced pain, 2',3'-didexoyctydine (ddC) treatment, exposure to the anticonvulsant phenytoin, exposure to antibiotics including chloramphenicol, nitrofurantoin and sulfonamides, exposure to sedatives including barbital and hexobarbital, Guillain-Barre syndrome, Fabry's disease or polyneuropathy secondary to cancers such as multiple myeloma.

b. Mononeuropathy

Mononeuropathy is a peripheral neuropathy involving loss of movement or sensation to an area caused by damage or destruction to a single peripheral nerve or nerve group. Mononeuropathy is most often caused by damage to a local area resulting from injury or trauma, although occasionally systemic disorders may cause isolated nerve damage (as with mononeuritis multiplex). The usual causes are direct trauma, prolonged pressure on the nerve, and compression of the nerve by swelling or injury to nearby body structures. The damage includes destruction of the myelin sheath (covering) of the nerve or of part of the nerve cell (the axon). This damage slows or prevents conduction of impulses through the nerve.

Mononeuropathy may involve any part of the body, Mononeuropathic pain, includes, without limitation, a sciatic nerve dysfunction, a common peroneal nerve dysfunction, a radial nerve dysfunction, an ulnar nerve dysfunction, a cranial mononeuropathy VI, a cranial mononeuropathy VII, a cranial mononeuropathy III (compression type), a cranial mononeuropathy III (diabetic type), an axillary nerve dysfunction, a carpal tunnel syndrome, a femoral nerve dysfunction, a tibial nerve dysfunction, a Bell's palsy, a thoracic outlet syndrome, a carpal tunnel syndrome, and a sixth (abducent) nerve palsy.

c. Generalized peripheral neuropathies

Generalized peripheral neuropathies are symmetrical, and usually due to various systematic illnesses and disease processes that affect the
peripheral nervous system in its entirety. They are further subdivided into several categories:

i. **Distal axonopathies** are the result of some metabolic or toxic derangement of neurons. They may be caused by metabolic diseases such as diabetes, renal failure, deficiency syndromes such as malnutrition and alcoholism, or the effects of toxins or drugs. Distal axonopathy (aka dying back neuropathy) is a type of peripheral neuropathy that results from some metabolic or toxic derangement of peripheral nervous system (PNS) neurons. It is the most common response of nerves to metabolic or toxic disturbances, and as such may be caused by metabolic diseases such as diabetes, renal failure, deficiency syndromes such as malnutrition and alcoholism, or the effects of toxins or drugs. The most common cause of distal axonopathy is diabetes, and the most common distal axonopathy is diabetic neuropathy.

ii. **Myelinopathies** are due to a primary attack on myelin causing an acute failure of impulse conduction. The most common cause is acute inflammatory demyelinating polyneuropathy (AIDP; aka Guillain-Barre syndrome), though other causes include chronic inflammatory demyelinating syndrome (CIDP), genetic metabolic disorders (e.g., leukodystrophy), or toxins. Myelinopathy is due to primary destruction of myelin or the myelinating Schwann cells, which leaves the axon intact, but causes an acute failure of impulse conduction. This demyelination slows down or completely blocks the conduction of electrical impulses through the nerve. The most common cause is acute inflammatory demyelinating polyneuropathy (AIDP, better known as Guillain-Barre syndrome), though other causes include chronic inflammatory demyelinating polyneuropathy (CIDP), genetic metabolic disorders (e.g., leukodystrophy or Charcot-Marie-Tooth disease), or toxins.

iii. **Neuronopathies** are the result of destruction of peripheral nervous system (PNS) neurons. They may be caused by motor neurone diseases, sensory neuronopathies (e.g., Herpes zoster), toxins or autonomic dysfunction. Neurotoxins may cause neuronopathies, such as the chemotherapy agent vincristine. Neuronopathy is dysfunction due to damage to neurons of the peripheral nervous system (PNS), resulting in a peripheral
neuropathy. It may be caused by motor neurone diseases, sensory neuronopathies (e.g., Herpes zoster), toxic substances or autonomic dysfunction. A person with neuronopathy may present in different ways, depending on the cause, the way it affects the nerve cells, and the type of nerve cell that is most affected.

iv. Focal entrapment neuropathies (e.g., carpal tunnel syndrome) represent an additional category of generalized peripheral neuropathies.

//. inflammatory pain

The compounds of the invention may be used to treat pain caused by or otherwise associated with any of the following inflammatory conditions.

A. Arthritic disorder

Arthritic disorders include, for example, a rheumatoid arthritis; a juvenile rheumatoid arthritis; a systemic lupus erythematosus (SLE); a gouty arthritis; a scleroderma; an osteoarthritis; a psoriatic arthritis; an ankylosing spondylitis; a Reiter's syndrome (reactive arthritis); an adult Still's disease; an arthritis from a viral infection; an arthritis from a bacterial infection, such as, e.g., a gonococcal arthritis and a non-gonococcal bacterial arthritis (septic arthritis); a Tertiary Lyme disease; a tuberculous arthritis; and an arthritis from a fungal infection, such as, e.g., a blastomycosis

B. Autoimmune diseases

Autoimmune diseases include, for example, a Guillain-Barre syndrome, a Hashimoto's thyroiditis, a pernicious anemia, an Addison's disease, a type I diabetes, a systemic lupus erythematosus, a dermatomyositis, Sjogren's syndrome, a lupus erythematosus, a multiple sclerosis, a myasthenia gravis, a Reiter's syndrome, a Grave's disease, and a rheumatoid arthritis. C.

Connective tissue disorder

Connective tissue disorders include, for example, a spondylarthrosis, a dermatomyositis, and a fibromyalgia syndrome.

D. Injury

Inflammation caused by injury, including, for example, a crush, puncture, stretch of a tissue or joint, may cause chronic inflammatory pain.

E. Infection
Inflammation caused by infection, including, for example, a tuberculosis or an interstitial keratitis may cause chronic inflammatory pain. Infection may also result in inflammatory bowel diseases and irritable bowel syndromes.

F. Neuritis

Neuritis is an inflammatory process affecting a nerve or group of nerves. Symptoms depend on the nerves involved, but may include pain, paresthesias, paresis, or hypesthesia (numbness).

Examples include:

a. Brachial neuritis

b. Retrobulbar neuropathy, an inflammatory process affecting the part of the optic nerve lying immediately behind the eyeball.

c. Optic neuropathy, an inflammatory process affecting the optic nerve causing sudden, reduced vision in the affected eye. The cause of optic neuritis is unknown. The sudden inflammation of the optic nerve (the nerve connecting the eye and the brain) leads to swelling and destruction of the myelin sheath. The inflammation may occasionally be the result of a viral infection, or it may be caused by autoimmune diseases such as multiple sclerosis. Risk factors are related to the possible causes.

d. Vestibular neuritis, a viral infection causing an inflammatory process affecting the vestibular nerve.

G. Joint inflammation

Inflammation of the joint, such as that caused by bursitis or tendonitis, for example, may cause chronic inflammatory pain.

/// Headache Pain

The compounds of the invention may be used to treat pain caused by or otherwise associated with any of the following headache conditions. A headache (medically known as cephalgia) is a condition of mild to severe pain in the head; sometimes neck or upper back pain may also be interpreted as a headache. It may indicate an underlying local or systemic disease or be a disorder in itself.

A. Muscular/myogenic headache
Muscular/myogenic headaches appear to involve the tightening or
tensing of facial and neck muscles; they may radiate to the forehead. Tension
headache is the most common form of myogenic headache.

A tension headache is a condition involving pain or discomfort in the
head, scalp, or neck, usually associated with muscle tightness in these areas.
Tension headaches result from the contraction of neck and scalp muscles.
One cause of this muscle contraction is a response to stress, depression or
anxiety. Any activity that causes the head to be held in one position for a long
time without moving can cause a headache. Such activities include typing or
use of computers, fine work with the hands, and use of a microscope.
Sleeping in a cold room or sleeping with the neck in an abnormal position may
also trigger this type of headache. A tension-type headache, includes, without
limitation, an episodic tension headache and a chronic tension headache.

B. Vascular headache

The most common type of vascular headache is migraine. Other kinds
of vascular headaches include cluster headaches, which cause repeated
episodes of intense pain, and headaches resulting from high blood pressure

1. Migraine

A migraine is a heterogeneous disorder that generally involves
recurring headaches. Migraines are different from other headaches because
they occur with other symptoms, such as, e.g., nausea, vomiting, or sensitivity
to light. In most people, a throbbing pain is felt only on one side of the head.
Clinical features such as type of aura symptoms, presence of prodromes, or
associated symptoms such as vertigo, may be seen in subgroups of patients
with different underlying pathophysiological and genetic mechanisms. A
migraine headache, includes, without limitation, a migraine without aura
(common migraine), a migraine with aura (classic migraine), a menstrual
migraine, a migraine equivalent (acephalic headache), a complicated
migraine, an abdominal migraine and a mixed tension migraine.

2. Cluster headache

Cluster headaches affect one side of the head (unilateral) and may be
associated with tearing of the eyes and nasal congestion. They occurs in
clusters, happening repeatedly every day at the same time for several weeks and then remitting.

D. High blood pressure headache
E. Traction and inflammatory headache

Traction and inflammatory headaches are usually symptoms of other disorders, ranging from stroke to sinus infection.

F. Hormone headache
G. Rebound headache

Rebound headaches, also known as medication overuse headaches, occur when medication is taken too frequently to relieve headache. Rebound headaches frequently occur daily and can be very painful.

H. Chronic sinusitis headache

Sinusitis is inflammation, either bacterial, fungal, viral, allergic or autoimmune, of the paranasal sinuses. Chronic sinusitis is one of the most common complications of the common cold. Symptoms include: Nasal congestion; facial pain; headache; fever; general malaise; thick green or yellow discharge; feeling of facial ‘fullness’ worsening on bending over. In a small number of cases, chronic maxillary sinusitis can also be brought on by the spreading of bacteria from a dental infection. Chronic hyperplastic eosinophilic sinusitis is a noninfective form of chronic sinusitis.

I. An organic headache
J. Lctal headaches

Lctal headaches are headaches associated with seizure activity.

IV. Somatic pain

The compounds of the invention may be used to treat pain caused by or otherwise associated with any of the following somatic pain conditions. Somatic pain originates from ligaments, tendons, bones, blood vessels, and even nerves themselves. It is detected with somatic nociceptors. The scarcity of pain receptors in these areas produces a dull, poorly-localized pain of longer duration than cutaneous pain; examples include sprains and broken bones. Additional examples include the following.

A. Excessive muscle tension
Excessive muscle tension can be caused, for example, by a sprain or a strain.

B. Repetitive motion disorders

Repetitive motion disorders can result from overuse of the hands, wrists, elbows, shoulders, neck, back, hips, knees, feet, legs, or ankles.

C. Muscle disorders

Muscle disorders causing somatic pain include, for example, a polymyositis, a dermatomyositis, a lupus, a fibromyalgia, a polymyalgia rheumatica, a macrophagic myofascitis, and a rhabdomyolysis. Muscle pain can also be secondary to neurological and neuromuscular disorders including without limitation Parkinson's disease, Huntington's chorea, dystonias, tardive dyskinesias, drug-induced dyskinesias and dystonias, dyskinesias (paroxysmal), amyotrophic lateral sclerosis, multiple sclerosis, myoclonus, progressive supranuclear palsy, corticobasal degeneration, choreoathetosis, spasticity, Wilson disease, multiple system atrophy (including Shy-Drager syndrome, striatonigral degeneration and olivopontocerebellar atrophy), and hereditary spastic paraplegia (including familial spastic paraparesis, familial spastic paraplegia, hereditary spastic paraparesis, Strumpell-Lorraine syndrome, and StrumpelPs disease).

D. Myalgia

Myalgia is muscle pain and is a symptom of many diseases and disorders. The most common cause for myalgia is either overuse or overstretching of a muscle or group of muscles. Myalgia without a traumatic history is often due to viral infections. Longer-term myalgias may be indicative of a metabolic myopathy, some nutritional deficiencies or chronic fatigue syndrome.

E. Infection

Infection can cause somatic pain. Examples of such infection include, for example, an abscess in the muscle, a trichinosis, an influenza, a Lyme disease, a malaria, a Rocky Mountain spotted fever, Avian influenza, the common cold, community-acquired pneumonia, meningitis, monkeypox,
Severe Acute Respiratory Syndrome, toxic shock syndrome, trichinosis, typhoid fever, and upper respiratory tract infection.

F. Drugs

Drugs can cause somatic pain. Such drugs include, for example, cocaine, statins for lowering cholesterol (such as atorvastatin, simvastatin, and lovastatin), and ACE inhibitors for lowering blood pressure (such as enalapril and captopril).

G. Prolonged nociceptive pain including without limitation to bone fracture pain, spinal stenosis, and post-surgical pain.

V. Visceral pain

The compounds of the invention may be used to treat pain caused by or otherwise associated with any of the following visceral pain conditions. Visceral pain originates from body's viscera, or organs. Visceral nociceptors are located within body organs and internal cavities. The even greater scarcity of nociceptors in these areas produces pain that is usually more aching and of a longer duration than somatic pain. Visceral pain is extremely difficult to localise, and several injuries to visceral tissue exhibit "referred" pain, where the sensation is localised to an area completely unrelated to the site of injury.

Examples of visceral pain include the following.

A. Functional visceral pain

Functional visceral pain includes, for example, an irritable bowel syndrome and a chronic functional abdominal pain (CFAP), a functional constipation and a functional dyspepsia, a non-cardiac chest pain (NCCP) and a chronic abdominal pain.

B. Chronic gastrointestinal inflammation

Chronic gastrointestinal inflammation includes, for example, a gastritis, an inflammatory bowel disease, e.g., a Crohn's disease, an ulcerative colitis, a microscopic colitis, a diverticulitis and a gastroenteritis; an interstitial cystitis; an intestinal ischemia; a cholecystitis; an appendicitis; a gastroesophageal reflux; an ulcer, a nephrolithiasis, an urinary tract infection, a pancreatitis and a hernia.

C. Autoimmune pain
Autoimmune pain includes, for example, a sarcoidosis and a vasculitis.

D. Organic visceral pain

Organic visceral pain includes, for example, pain resulting from a traumatic, inflammatory or degenerative lesion of the gut or produced by a tumor impinging on sensory innervation.

E. Treatment-induced visceral pain

Treatment-induced visceral pain includes, for example, a pain attendant to chemotherapy therapy or a pain attendant to radiation therapy.

vi. Referred pain

The compounds of the invention may be used to treat pain caused by or otherwise associated with any of the following referred pain conditions.

Referred pain arises from pain localized to an area separate from the site of pain stimulation. Often, referred pain arises when a nerve is compressed or damaged at or near its origin. In this circumstance, the sensation of pain will generally be felt in the territory that the nerve serves, even though the damage originates elsewhere. A common example occurs in intervertebral disc herniation, in which a nerve root arising from the spinal cord is compressed by adjacent disc material. Although pain may arise from the damaged disc itself, pain will also be felt in the region served by the compressed nerve (for example, the thigh, knee, or foot). Relieving the pressure on the nerve root may ameliorate the referred pain, provided that permanent nerve damage has not occurred. Myocardial ischaemia (the loss of blood flow to a part of the heart muscle tissue) is possibly the best known example of referred pain; the sensation can occur in the upper chest as a restricted feeling, or as an ache in the left shoulder, arm or even hand.

Pain Reversal

An art-accepted model or assay for measuring an analgesic effect of a compound in chronic pain (in particular peripheral neuropathy) is the model known as Kim and Chung 1992, Pain 150, pp 355-363 (Chung model). This model involves the surgical ligation of the L5 (and optionally the L6) spinal nerves on one side in experimental animals. Rats recovering from the surgery gain weight and display a level of general activity similar to that of
normal rats. However, these rats develop abnormalities of the foot, wherein
the hindpaw is moderately everted and the toes are held together. More
importantly, the hindpaw on the side affected by the surgery appears to
come sensitive to low-threshold mechanical stimuli and will perceive pain
instead of the faint sensation of touch. This sensitivity to normally non-painful
touch, called "tactile allodynia", develops within the first week after surgery
and lasts for at least two months. The allodynia response includes lifting the
affected hindpaw to escape from the stimulus, Sicking the paw and holding it in
the air for many seconds. None of these responses is normally seen in the
control group.

To produce the tactile allodynia, rats are anesthetized before surgery.
The surgical site is shaved and prepared either with betadine or Novacain.
Incision is made from the thoracic vertebra XIII down toward the sacrum.
Muscle tissue is separated from the spinal vertebra (left side) at the L4 - S2
levels. The L6 vertebra is located and the transverse process is carefully
removed with a small rongeur to expose the L4 - L6 spinal nerves. The L5 and
L6 spinal nerves are isolated and tightly ligated with 6-0 silk thread. The same
procedure is done on the right side as a control, except no ligation of the
spinal nerves is performed.

After a complete hemostasis is confirmed, the wounds are sutured. A
small amount of antibiotic ointment is applied to the incised area, and the rat
is transferred to the recovery plastic cage under a regulated heat-temperature
lamp.

On the day of the experiment, at least seven days after the surgery,
typically six rats per test group are administered the test drugs by
intraperitoneal (i.p.) injection or oral gavage (p.o.). For i.p. administration, the
compounds are formulated in H₂O and given in a volume of 1 ml/kg body
weight by injecting into the intraperitoneal cavity. For p.o. administration, the
compounds are formulated in H₂O and given in a volume of 1 ml/kg body
weight using an 18-gauge, 3 inch gavage needle that is slowly inserted
through the esophagus into the stomach.
Tactile allodynia is assessed via von Frey hairs, which are a series of fine hairs with incremental differences in stiffness. Rats are placed in a plastic cage with a wire mesh bottom and allowed to acclimate for approximately 30 minutes. To establish the pre-drug baseline, the von Frey hairs are applied perpendicularly through the mesh to the mid-plantar region of the rats' hindpaw with sufficient force to cause slight buckling and held for 6-8 seconds. The applied force has been calculated to range from 0.41 to 15.1 grams. If the paw is sharply withdrawn, it is considered a positive response. A normal animal will not respond to stimuli in this range, but a surgically ligated paw will be withdrawn in response to a 1-2 gram hair. The 50% paw withdrawal threshold is determined using the method of Dixon, W.J., *Ann. Rev. Pharmacol. Toxicol.* 20:441-462 (1980) hereby incorporated by reference. Tactile allodynia is measured prior to and 15, 30, and 60 minutes after drug administration. The post-drug threshold is compared to the pre-drug threshold and the percent reversal of tactile sensitivity is calculated based on a normal threshold of 15.1 grams.

**Table 1** below indicates the degree of pain reversal obtained in the Chung model with exemplary compounds used in accordance with the invention. The intraperitoneal (Lp.) and/or intravenous (iv) administration of the compounds was in doses ranging from 1µg/kg to 300µg/kg or 3mg/kg PO and the peak percentage of reversal of allodynia was measured at 15, 30 or 60 minutes after administration, as is indicated in the table. Data are expressed as the highest % allodynia reversal (out of 3 time points: 15 min, 30 min, or 60 min, post-drug) with a minimum of a 20% allodynia reversal in the rat Chung model. Comparisons between groups (drug treated vs. saline treated) were made using a two-tailed, 2-sample, unpaired t-test. Compounds that are not shown which were not statistically analgesic following an IP dose of 300 µg/kg, but may still be analgesic. Compounds that do not exhibit significant analgesia at 100 mg/kg are not considered to be analgesic.
<table>
<thead>
<tr>
<th>Compound or compound no.</th>
<th>Chemical Formula</th>
<th>Peak% Pain reversal; time post dose</th>
<th>Dose (µg/kg), mode of administ.</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-threo-PDMP</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>100% 30 min</td>
<td>30 µg/kg PO</td>
</tr>
<tr>
<td>Available from Matreya, LLC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DL-erythro-PDMP</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>68% 30 min</td>
<td>1000 µg/kg IP</td>
</tr>
<tr>
<td>Available from Matreya, LLC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D-threo-PDMP</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>77% 60 min</td>
<td>1000 µg/kg IP</td>
</tr>
<tr>
<td>Available from Matreya, LLC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>91% 60 min</td>
<td>100 µg/kg IP</td>
</tr>
<tr>
<td>1 : 1 Racemic mixture of 2 and 4</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>87% 30 min</td>
<td>30 µg/kg IP</td>
</tr>
<tr>
<td>Compound or compound no.</td>
<td>Chemical Formula</td>
<td>Peak% Pain reversal; time post dose</td>
<td>Dose (µg/kg), mode of administ.</td>
</tr>
<tr>
<td>-------------------------</td>
<td>-----------------</td>
<td>------------------------------------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="Chemical Structure" /> 2HCl</td>
<td>85% 60 min</td>
<td>300 µg/kg IP</td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="Chemical Structure" /> DL-threo</td>
<td>92% 60 min</td>
<td>30 µg/kg IP</td>
</tr>
<tr>
<td>7</td>
<td><img src="image" alt="Chemical Structure" /> DL-threo</td>
<td>26% 30 min</td>
<td>1 µg/kg IP</td>
</tr>
<tr>
<td>9</td>
<td><img src="image" alt="Chemical Structure" /> DL-threo</td>
<td>88% 60 min</td>
<td>30 µg/kg IP</td>
</tr>
<tr>
<td>15</td>
<td><img src="image" alt="Chemical Structure" /> HCl DL-threo</td>
<td>42% 60 min</td>
<td>300 µg/kg IP</td>
</tr>
<tr>
<td>16</td>
<td><img src="image" alt="Chemical Structure" /> HCl DL-threo</td>
<td>93% 60 min</td>
<td>300 µg/kg IP</td>
</tr>
<tr>
<td>17</td>
<td><img src="image" alt="Chemical Structure" /> HCl DL-threo</td>
<td>100% 60 min</td>
<td>300 µg/kg IP</td>
</tr>
</tbody>
</table>
Modes of Administration:

Compounds useful in the methods of the invention are administered at pharmaceutically effective dosages. Such dosages are normally the minimum dose necessary to achieve the desired therapeutic effect; in the treatment of chronic pain, this amount would be roughly that necessary to reduce the discomfort caused by the pain to tolerable levels. For human adults such doses generally will be in the range of 0.1 - 5,000 mg/day; more preferably in the range of 1 to 3,000 mg/day, 10 mg to 500 mg/day, 500 to 1,000 mg/day, 1,000 to 1,500 mg/day, 1,500 to 2,000 mg/day, 2,000 to 2,500 mg/day, or 2,500 to 3,000 mg/day. However, the actual amount of the compound to be administered in any given case will be determined by a physician taking into account the relevant circumstances, such as the severity of the pain, the age and weight of the patient, the patient's general physical condition, the cause of the pain, and the route of administration.

Preferably, the patient will be given the compound in a composition orally in any pharmaceutically acceptable form, such as a tablet, liquid, capsule, powder and the like. However, other routes may be desirable or necessary, particularly if the patient suffers from nausea. Such other routes may include, without exception, transdermal, intraperitoneal, parenteral, subcutaneous, intranasal, intrathecal, intramuscular, intravenous and intrarectal modes of delivery and the present invention extends to pharmaceutical compositions adapted for such deliveries. Pharmaceutical compositions tend to contain a pharmaceutically acceptable excipient. Such excipient are well known in the art and may be a carrier or a diluent; this is usually mixed with the active compound, or permitted to dilute or enclose the active compound. If a diluent, the carrier may be solid, semi-solid, or liquid material that acts as an excipient or vehicle for the active compound. The formulations of the compositions may also include wetting agents, emulsifying agents, preserving agents, sweetening agents, and/or flavoring agents. If used as in an ophthalmic or infusion format, the formulation will usually contain one or more salt to influence the osmotic pressure of the formulation.
METHODS FOR OBTAINING COMPOUNDS USEFUL FOR
THE METHOD OF THE INVENTION

Compounds useful in the methods of the invention are known in the art and can be obtained from commercial sources or by the synthetic processes described in the pertinent references (primarily in Shin, S. et al, [Tetrahedron asymmetry, 11, 3293-3301, 2000] and US 200301 53768) and noted in the Background Art section of the present application. For the purposes of the present invention the majority of the compounds were nevertheless synthesized and their preparations are described below.

GENERAL

$^1$H NMR spectra were recorded at ambient temperature with an Avance 300 (Bruker) spectrometer. The compounds were analyzed by reverse phase high performance liquid chromatography (HPLC) using a Waters Autopurification System equipped with a Waters 2525 Pump, a Waters 2696 photodiode array detector, and a XTerra column (Part. No. 186000482, 5 $\mu$m, C18, 4.5 x 50 mm).

The HPLC method used was a gradient of 5 % solvent B to 100 % in 7 min. Solvent A was H$_2$O with 0.05 % TFA and solvent B was CH$_3$CN with 0.05 % TFA (Method A).

Melting points were measured with a Büchi B-545 melting point apparatus and were uncorrected. To isolate reaction products the solvent were removed by evaporation using a vacuum rotatory evaporator, the water bath temperature not exceeding 40 °C.

Preparation of Compound 6, Compound 7, Compound 8 and Compound 9

2-Isocyano-1-(pyrrolidin-1-yl)ethanone BLE 04098.

To stirred and cooled (0°C) methyl isocyanoacetate (96 % technical grade, 5.0 g, 47.8 mmol) was slowly added in 0.75 h pyrrolidine (6.5 mL, 78 mmol). The mixture was stirred for 1.5 h with continued cooling and then concentrated. The resulting oil was co-evaporated twice from CH$_2$Cl$_2$:hexane to remove residual pyrrolidine. 2-Isocyano-1-(pyrrolidin-1-yl)ethanone BLE
04098 was obtained as a yellow solid (6.85 g, 98 % yield) and used in the next step without purification.

\[
\begin{align*}
\text{C}_2\text{N}\text{-}\text{N} \quad \text{BLE 04098} \\
\text{MW: 138.17; Yield: 98 \%; yellow solid; Mp (°C) = 73.9.} \\
^{1}\text{H-NMR (CDCl}_3, \delta): & \quad 1.81-2.08 (m, 4H, 2\times \text{CH}_2), 3.35-3.45 (m, 2\text{H, -NCH}_2), \\
& \quad 3.50-3.60 (m, 2\text{H, -NCH}_2\text{J}, 4.23 (s, 2\text{H, CH}_2\text{CO}).
\end{align*}
\]

To a stirred and cooled (0°C) solution of potassium hydroxide (0.43 mg, 7.60 mmol) in MeOH (6.5 mL) were added successively 1,4-benzodioxan-6-carboxaldehyde (1.31 g, 7.96 mmol) and 2-isocyano-1-(pyrrolidin-1-yl)ethanone BLE 04098 (1.0 g, 6.57 mmol). The solution was stirred 3 h at 0°C and then concentrated. The residue was partitioned between EtOAc (100 mL) and water. The organic layer was combined with 2 additional EtOAc extracts (2 x 100 mL), washed with brine, dried over MgSO\textsubscript{4}, filtered and evaporated. Concentration afford to a crude product which was purified by column chromatography on silica (EtOAc) to yield, after evaporation and drying, to fra/is-4,5-dihydro-5-(2,3-dihydrobenzo[i][1,4]dioxin-6-yl)oxazol-4-yl)(pyrrolidin-1-yl)methanone BLE 041 00 as a colourless oil (1.76 g, 89 % yield).

\[
\begin{align*}
\text{MW: 440.49; Yield: 89 \%; colourless oil.}
\end{align*}
\]
1H-NMR (CDCl3, δ): 1.75-2.10 (m, 4H, 2xCH2), 3.40-3.59 (m, 6H, 3xCH2N), 3.85-4.00 (m, 1H, CHN), 4.26 (s, 4H, CH2O), 4.59 (dd, 1H, J = 7.5 Hz, J = 2.2 Hz, CH-N), 6.00 (d, 1H, J = 7.5 Hz, CH-O), 6.75-6.90 (m, 3H, ArH), 7.00 (d, 1H, J = 2.2 Hz, CH=N).

To a stirred and cooled (0°C) solution of potassium hydroxide (0.37 g, 6.57 mmol) in methanol (30 ml) was added a mixture of 4-methoxy-benzaldehyde (0.88 mL, 7.23 mmol) and 2-isocyano-1-(pyrrolidin-1-yl)ethanone BLE 04098 (1.0 g, 6.57 mmol). The solution was stirred 4 h with continued cooling and then concentrated. The residue was partitioned between ethyl acetate and water. The organic layer was combined with additional ethyl acetate extracts, washed with aqueous sodium chloride and dried over MgSO4. Concentration afforded a crude product as a glassy solid. Flash chromatography over silica (ethyl acetate) yielded to trans-(4,5-dihydro-5-(4-methoxyphenyl)oxazol-4-yl)(pyrrolidin-1-yl)methanone SLA 07074 as a pale yellow solid (1.2 g, 90.5%).

SLA 07074

MW: 274.32; Yield: 90.5 %; pale yellow solid; Mp (°C): 91.2.

Rf: 0.30 (EtOAc).

1H-NMR (CDCl3, δ): 1.75-2.08 (m, 4H, 2xCH2), 3.40-3.58 (m, 3H, CH2N), 3.52 (s, 3H, CH3O), 3.88-3.98 (m, 1H, CH2N), 4.59 (dd, 1H, J = 7.6 Hz, J = 2.2 Hz, CH-N), 6.06 (d, 1H, J = 7.6 Hz, CH-O), 6.90 (d, 2H, J = 8.7 Hz, ArH), 7.01 (d, 1H, J = 2.2 Hz, CH=N), 7.25 (d, 2H, J = 8.7 Hz, ArH).

MS-ESI m/z (% rel. Int.): 275.1 ([MH]+, 10), 247.1 (100).
HPLC: Method A, detection UV 280 ran, SLA 07074 RT = 5.2 min, peak area 92%.

DL-7reo-2-Amino-3-hydroxy-3-(4-methoxyphenyl)-1-(pyrrolidin-1-yl)propan-1-one hydrochloride SLA 07078.

To a stirred solution of trans-(4,5-dihydro-5-(4-methoxyphenyl)oxazol-4-yl)(pyrrolidin-1-yl)methanone SLA 07074 (1.61 g, 5.93 mmol) in methanol (13 mL) was added hydrochloric acid (1 mL). After heating at 50°C for 3 h the mixture reaction was concentrated and the resulting yellow oil was co-evaporated twice with ethyl acetate before solidifying. Trituration (ethyl acetate) and drying afforded DL-7reo-2-amino-3-hydroxy-3-(4-methoxyphenyl)-1-(pyrrolidin-1-yl)propan-1-one hydrochloride SLA 07078 as a white solid (1.64 g, 93%).

MW: 300.78; Yield: 93%; white Solid; Mp (°C): 177.0.

\[
\begin{align*}
\text{1H-NMR (CD}_3\text{OD, } & \delta: 1.32-1.50 (m, 1H, CH}_2, 1.50-1.88 (m, 3H, CH}_2, 2.15-2.28 (m, 1H, CH}_2N), 3.15-3.42 (m, 4H, 2xCH}_2N), 3.79 (s, 3H, CH}_3O), 4.06 (d, 1H, J = 9.2 Hz, CH-N), 4.78 (d, 1H, J = 9.2 Hz, CHO), 6.94 (d, 2H, J = 8.5 Hz, \text{ArH}), 7.34 (d, 2H, J = 8.5 Hz, ArH). \\
\text{13C-NMR (CD}_3\text{OD, } & \delta: 24.8, 26.6, 47.2, 47.6, 55.9, 59.6, 73.9, 115.0 (2xC), 128.9 (2xC), 132.5, 161.7, 166.4.
\end{align*}
\]

DL-7/eo-2-amino-3-(2,3-dihydrobenzo[b]11,4)dioxin-6-yl)-3-hydroxy-1-(pyrrolidin-1-yl)propan-1-one hydrochloride Compound 12

To a stirred solution of trans-4,5-dihydro-5-(2,3-dihydrobenzo[b]11,4)dioxin-6-yl)oxazol-4-yl)(pyrrolidin-1-yl)methanone BLE
04100 (1.74 g, 5.77 mmol) in methanol (15 mL) was added hydrochloric acid (1 mL). After heating at 50°C for 3 h the mixture reaction was concentrated and the resulting yellow oil was co-evaporated twice with ethyl acetate before solidifying. Trituration (ethyl acetate) and drying afforded DL-f/?reo-2-amino-3-(2,3-dihydrobenzo[ib][1,4]dioxin-6-yl)-3-hydroxy-1-(pyrrolidin-1-yl)propan-1-one hydrochloride Compound 12 as a white solid (1.85 g, 95%).

\[
\text{Compound 12}
\]

MW: 328.79; Yield: 95.0%; White Solid; Mp (°C): 176.2.

\[\text{H-NMR (CD}_3\text{OD, } \delta): 1.42-1.58 (m, 1H, CH}_2, 1.58-1.70 (m, 1H, CH}_2, 1.70-1.88 (m, 2H, CH}_2), 3.20-3.45 (m, 4H, N-CH}_2, 4.06 (d, 1H, J = 9.1 Hz, CH-N), 4.25 (s, 2H, CH}_2), 4.75 (d, 1H, J = 9.2 Hz, CH-O), 4.89 (s, 2H, CH}_2), 6.82-6.95 (m, 3H, ArH).\]

\[\text{C-NMR (CD}_3\text{OD, } \delta): 24.9, 26.7, 47.3, 47.6, 59.5, 65.7, 73.6, 116.4, 118.3, 120.3, 133.7, 145.1, 145.6, 166.4.\]

DL-f/?reo-2-Amino-1-(2,3-dihydrobenzof[1,4]dioxin-6-yl)-3-fpyrrolidin-1-yl)propan-1-ol Compound 6.

To a stirred suspension of trans-(4,5-dihydro-5-(4-methoxyphenyl)oxazol-4-yl)pyrrolidin-1-yl)methanone SLA 07074 (1.79 g, 5.44 mmol) in THF (220 mL) was slowly added at 0°C, in two portions, UAIH4 (1.28 g, 33.7 mmol). The mixture was stirred at RT for 3.5 h and quenched by a slow addition of water at 0°C (350 mL). The white suspension was concentrated to remove THF and taken back in a mixture of CH\textsubscript{2}Cl\textsubscript{2} (300 mL) and 1 N aqueous HCl (50 mL). The aqueous layer was basified to pH = 10-11 by slow addition of 1 N aqueous NaOH. The organic layer was removed; two more extracts were combined and dried over MgSO\textsubscript{4}, filtered and evaporated. Concentration afforded to a crude product as a yellow oil. This material was
purified by column chromatography on silica (CH\(_2\)Cl\(_2\):MeOH:NH\(_4\)OH 20% – 94:5:1) to lead to DL-threo-2-amino-1-(2,3-dihydrobenzo[\(b\)][1,4]dioxin-6-yl)-3-(pyrrolidin-1-yl)propan-1-ol Compound 6 (0.705 g, 46.5 % yield) as a near colorless gum.

MW: 278.35; Yield: 46.5 %; Colorless Gum. 
Rf: 0.20 (CH\(_2\)Cl\(_2\):MeOH:NH\(_4\)OH 20% = 94:5:1).

\(^1\)H-NMR (CDCl\(_3\), \(\delta\)): 1.70-1.85 (m, 4H, 2xCH\(_2\)), 2.40-2.70 (m, 6H, 3xCH\(_2\)N-), 3.05-3.15 (m, 1H, CH-N), 4.25 (s, 4H, CH\(_2\)O), 4.55 (d, 1H, \(J = 2.2 \) Hz, CH-O), 5.30 (s, 1H, -OH), 6.75-6.90 (m, 3H, ArH).

\(N-(DL\)-threo-1-(2,3-dihydrobenzo[\(b\]][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)palmitamide Compound 7.

To a stirred solution of DL-threo-2-amino-1-(2,3-dihydrobenzo[\(b\)][1,4]dioxin-6-yl)-3-(pyrrolidin-1-yl)propan-1-ol Compound 12 (0.186 g, 0.67 mmol) in 10 mL CH\(_2\)Cl\(_2\) were added, in order, \(N\)-hydroxysuccinimide (0.081 g, 0.70 mmol) in 2 mL CH\(_2\)Cl\(_2\), triethylamine (112 µL, 0.80 mmol) and decanoyl chloride (125 µL, 0.60 mmol). The mixture was stirred overnight at RT and then partitioned between CH\(_2\)Cl\(_2\) and 1 N aqueous sodium hydroxide. The organic layer was dried over MgSO\(_4\), filtered and evaporated and the residue obtained was purified by column chromatography on silica (CH\(_2\)Cl\(_2\):MeOH = 95:5). A white solid \(N-(DL\)-threo-1-(2,3-dihydrobenzo[\(E\)][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)palmitamide Compound 7 was obtained (126 mg, 43.5 % yield).
MW: 516.76; Yield: 43.5 %; White Solid; Mp (°C): 84.6.

R/: 0.40 (MeOHhCH₂Cl₂ = 10:90).

1H-NMR (CDCl₃, δ): 0.88 (t, 3H, J = 6.7 Hz, CH₃), 1.12-1.39 (m, 12 H), 1.40-1.60 (m, 2H, CH₂), 1.72-1.90 (m, 4H, 2xCH2), 2.10 (t, 2H, J = 6.7 Hz, CH₂), 2.55-2.90 (m, 6H), 4.13-4.30 (m, 12 H), 5.90 (d, 1H, J = 7.4 Hz, NH), 6.75-6.88 (m, 3H, ArH), OH not seen.

13C-NMR (CDCl₃, δ): 14.1, 22.7, 23.6 (2xC), 25.6, 29.1, 29.3, 31.9, 36.8, 52.3, 55.1 (2xC), 57.7, 64.3 (2xC), 75.2, 77.2, 115.0, 117.0, 118.9, 134.4, 142.8, 143.4, 173.5, 174.8.

MS-ESi m/z (% rel. Int.): 433.1 ([MH]+, 100).

HPLC: Method A, detection UV 280 nm, Compound 7, RT = 5.2 min, peak area 96.2 %.

N-(DL-threo 1-(2,3-Dihydrobenzo[b,ir.41dioxin-6-yl]-1-hydroxy-3-pyrrolidin-1-vi)propan-2-yl)paimitamid β Compound 8.

To a stirred solution of DL-threo-2-amino-1-(2,3-dihydrobenzo[fr][1,4]dioxin-6-yl)-3-(pyrrolidin-1-yl)propan-1-ol Compound 12 (0.158 g, 0.57 mmol) in 10 ml CH2Cl₂ were added, in order, N-hydroxysuccinimide (0.068 g, 0.59 mmol) in 2 ml CH2Cl₂, triethylamine (95 µL, 0.68 mmol) and paimitoyl chloride (155 µL, 0.51 mmol) in 3 mL CH2Cl₂. The mixture was stirred overnight at RT and then partitioned between CH2Cl₂ and 1 N aqueous sodium hydroxyde. The organic layer was purified by column chromatography on silica using as eluent CH2Cl₂:MeOH = 95:5. A white solid /V-(DL-threo-1-(2,3-dihydrobenzo[7][1,4]dioxin-6-yl]-1-hydroxy-3-
Compound 8 was obtained (148 mg, 50.4 % yield).

MW: 516.7; Yield: 50.4 %; White Solid; Mp (°C): 66.4.

R<sub>f</sub>: 0.50 (MeOH:CH<sub>2</sub>Cl<sub>2</sub> = 10:90).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, δ): 0.88 (t, 3H, J = 6.7 Hz, CH<sub>3</sub>), 1.15-1.35 (m, 24 H), 1.45-1.58 (m, 2H, CH<sub>2</sub>), 1.75-1.90 (m, 4H, 2xCH<sub>2</sub>), 2.10 (t, 2H, J = 7.4 Hz, CH<sub>2</sub>), 2.61 (s, 1H, CHN), 2.52-2.72 (m, 4H), 2.72-2.92 (m, 2H), 4.15-4.22 (m, 2H, CH<sub>2</sub>N), 4.92 (d, 1H, J = 3.3 Hz, CH-O), 6.08 (d, 1H, J = 7.4 Hz, NH), 6.75-6.90 (m, 3H, ArH).

MS-ESI m/z <rel. Int.>: 517.2 ([MH]<sup>+</sup>, 100).

HPLC: Method A, detection UV 280 nm, Compound 8 RT = 6.60 min, peak area 97.2 %.

DL-tf7reo-2-Amino-1-(4-methoxyphenyl)-3-(pyrrolidin-1-yl)propan-1-ol

Compound 9.

To a stirred suspension of DL-tf[re σ-[5-(4-methoxy-phe πyl)-4,5-dihydrooxazol-4-yl]-pyrrolidin-1-yl]-methanone SLA 07078 (1.61 g, 5.35 mmol) in tetrahydrofuran (200 mL) under nitrogen atmosphere was slowly added, in two portions, lithium aluminium hydride (1.22 g, 32.12 mmol) at 0°C. The mixture reaction was stirred at RT for 17 h, and then quenched by a slow, dropwise addition of water (50 mL). The white suspension was then concentrated to remove THF and taken back up in a mixture of 300 mL CH<sub>2</sub>Cl<sub>2</sub> and 1N aqueous hydrochloric acid (50 mL). The aqueous layer was basified to pH = 10 - 11 by a slow addition of 1N aqueous sodium hydroxide.
The organic layer was removed, combined with additional CH\textsubscript{2}Cl\textsubscript{2} extracts (4 x 200 mL) and dried over MgSO\textsubscript{4}, filtered and evaporated. The crude product was purified by column chromatography on silica (CH\textsubscript{2}Cl\textsubscript{2}:MeOH:NH\textsubscript{3} = 94:05:01). After evaporation and drying, DL-threo2-amino-1-(4-methoxyphenyl)-3-(pyrroldin-1-yl)propan-1-ol Compound 9 was obtained (0.62 g, 46 %) as a pale yellow solid.

\[
\begin{align*}
\text{OH} \\
\text{NH}_2 \\
(+/-)
\end{align*}
\]

Compound 9

MW: 250.34; Yield: 46 %; Pale Yellow Solid; Mp (°C): 77.7.

\[ R_f: 0.35 \text{ (CH}_2\text{Cl}_2:\text{MeOH:NH}_3 = 94:05:01) \]

\[
\begin{align*}
^{1}\text{H-NMR (CDCl}_3, \delta): & \text{ 1.65-1.87 (s, 4H, 2xCH}_2), 2.40-2.90 \text{ (m, 9H, CH}_2\text{N, NH}_2 \\
& \text{& OH), 3.11-3.17 (m, 1H, CH}_2 \text{-N), 3.81 (s, 3H, CH}_3\text{O), 4.61 (d, 1H, J = 3.8 Hz,} \\
& \text{CH-O), 7.89 (d, 2H, J = 8.6 Hz, ArH), 7.26 (d, 2H, J = 8.5 Hz, ArH).} \\
^{13}\text{C-NMR (CDCl}_3, \delta): & \text{ 23.6 (2xC), 54.5, 54.7 (2xC), 55.3, 60.1, 75.9, 113.6,} \\
& \text{127.4, 134.4, 158.8.} \\
\text{MS-ESI m/z (% rel. Int.): 251.1 ([ MH\text{+}], 100).}
\end{align*}
\]

Preparation of Compound 2.4 and 5

Benzyl (S)-3-hydroxy-1-oxo-1-phenylpropan-2-ylcarbamate TTA 0801 OB.

To a stirred solution of Z-L-Ser-OH (6.00 g, 25.08 mmol) in 32 mL of anhydrous THF at 0°C under nitrogen was added dropwise 1 M phenylmagnesium bromide in THF (32 mL, 200 mmol). The mixture was stirred 15 h at RT under nitrogen. A solution of 2 M HCl (100 mL) was slowly added at 0°C and the mixture was partitioned between ethyl acetate (750 mL) and acidic water. The organic layer was washed with water (2 x 20 mL), 1 N aqueous sodium bicarbonate (2 x 20 mL), brine (2 x 20 mL) and dried over MgSO\textsubscript{4}. After removing ethyl acetate by evaporation at 30-35°C, the crude product (4.50 g, 60 % yield) was crystallized in a mixture of ethyl
acetate:hexane = 25 tssL:20 mL to give benzyl (S)-3-hydroxy-1-oxo-1-phenylpropan-2-ylcarbamate TTA 0801 O B as a white solid (1.40 g, 20 % yield).

\[
\text{\textbf{TTA 08010B}}
\]

MW: 299.32; Yield: 20 %; White Solid; Mp (°C): 106.5.

Rf: 0.75 (CH2Cl2:MeOH = 9:1).

\[\text{\textbf{H-NMR} (CDCl3, } \delta \text{):} 2.78 (s, 1H, OH), 3.85-3.93 (m, 1H, CH2O), 4.00-4.09 (m, 1H, CH2O), 5.14 (s, 2H, ArCH2 θ), 5.40 (t, 1H, J = 3.3 Hz, CH), 6.17 (d, 1H, J = 6.4 Hz, NH), 7.35 (s, 5H, ArH), 7.49 (t, 2H, J = 7.60 Hz, ArH), 7.62 (t, 1H, J = 7.1 Hz, ArH), 8.99 (t, 2H, J = 7.6 Hz, ArH).

\[\text{\textbf{C-NMR} (CDCl3, } \delta \text{):} 58.3, 64.6, 67.3, 128.1, 128.3, 128.6, 128.7, 129.0, 134.1, 136.0, 156.6, 196.6.

\[\text{\textbf{MS-ESI m/z} (\% rel. int.):} 300.1 ([MH]+, 5), 256.1 (100).

\[\text{\textbf{HPLC: Method A, detection UV 254 nm, TTA 0801 O B RT = 5.40 min, peak area 98.5 \%.}

\[\text{[Q]}^{22}_{\text{D}} = -5.8 \text{ (c=1.00, MeOH).}

Benzyl \textit{L-threo}-1,S-dihydroxy-i-phenylpropan\-\textsuperscript{\alpha}-ylcarbamate TTA 08012.

To a stirred solution of benzyl (S)-3-hydroxy-1-oxo-1-phenylpropan-2-ylcarbamate TTA 0801 O B (1.40 g, 4.70 mmol) in 28 mL of anhydrous THF at -78°C under nitrogen was added slowly dropwise 1 M DiBAL-H in hexane (18.8 mL, 18.80 mmol). The mixture was stirred 2 h at -78°C then 1.5 h at RT. A solution of 2 M HCl (35 mL) was slowly added at -20°C and the mixture was partitioned between ethyl acetate (750 mL) and acidic water. The organic phase was washed with water (2x20 mL), brine (2x20 mL) and dried over MgSO\textsubscript{4}. After removing ethyl acetate by evaporation at 30-35 °C, the crude
product was purified by column chromatography on silica (CH2Cl2:MeOH = 98:2 to 97:3) to give benzyl L-threo-1,3-dihydroxy-1-phenyipropan-2-ylcarbamate TTA 08012 as a white solid (1.10 g, 78 % yield).

\[
\text{TTA 08012}
\]

MW: 301.34; Yield: 78 %; White Solid; Mp (°C): 102.5.  
R(f) : 0.30 (CH2Cl2:MeOH = 95/5).  
1H-NMR (CDCl3, δ): 3.08 (t, 1H, J = 5.0 Hz, OH), 3.59 (d, 1H, J = 3.1 Hz, OH), 3.64-3.78 (m, 2H, CH2O), 3.80-3.89 (m, 1H, CH), 4.95 (s, 2H, ArC=O), 5.57 (d, 1H, J = 8.3 Hz, NH), 7.17-7.38 (m, 10H, ArH).  
13C-NMR (CDCl3, δ): 57.5, 63.6, 66.9, 73.8, 126.0, 127.8, 127.9, 128.1, 128.5, 128.6, 136.2, 141.0, 156.9.  
MS-ESI m/z (% rel. Int.): 302.0 ([MH]+, 5); 132.0 (100).  
HPLC: Method A, detection UV 254 nm, TTA 08012 RT = 5.00 min, peak area 99.5 %.  
\([Q]^{22}\text{D} = +39.4 \text{ (c=1.00, MeOH).}

Benzyl L-threo-1,3-dihydroxy-3-morpholino-1-phenyipropan-2-ylcarbamate hydrochloride Compound 1.

To a stirred solution of benzyl L-threo-1,3-dihydroxy-1-phenylpropan-2-ylcarbamate TTA 08012 (1.00 g, 3.30 mmol) in 13 ml of pyridine at -10°C was added dropwise methanesulfonyl chloride (0.27 ml, 3.50 mmol). The mixture was stirred 6 h at 20°C under nitrogen. Pyridine was removed by evaporation at 30-35°C and the residue was partitioned between ethyl acetate (250 mL) and 0.1 N HCl (20 mL). The organic phase was washed with water (20 mL), brine (20 mL), dried over MgSO4 and evaporated to give after drying L-threo-1,3-dihydroxy-3-methanesulfonyl-1-phenylpropan-2-ylcarbamate TTA 08014 (1.25 g, 65% yield).
To a stirred solution of crude benzyl L-threo-1-hydroxy-3-methanesulfonyl-1-phenylpropan-2-ylcarbamate TTA 0801 4 (1.25 g, 3.30 mmol) in 6 ml of DMF at RT was added morpholine (1.2 ml, 13.20 mmol). The mixture was stirred 15 h at 50°C under nitrogen. DMF was evaporated and the residue was partitioned between ethyl acetate (250 mL) and 1 N aqueous sodium bicarbonate (20 mL). The organic phase was washed with water (20 mL), brine (20 mL) and dried over MgSO₄. After evaporation the crude product was purified by column chromatography on silica (CH₂Cl₂:MeOH = 98:2 to 97:3) to give benzyl L-threo-1-hydroxy^-morpholino-i-phenylpropan^-ylcarbamate as an oil (380 mg, 31 % yield). The hydrochloride salt was obtained from 100 mg of the free base in diethylether at 0°C using a solution 0.3 M HCl in diethylether. The precipitate was filtered and dry to give benzyl L-threo-λ-hydroxy-3-morpholino-1-phenylpropan-2-ylcarbamate hydrochloride Compound 1 as a white solid (70 mg, 65 % yield).

![Compound 1](image)

MW: 406.90; Yield: 20 %; White Solid; Mp (°C): 144.5.
Rₛ: 0.40 (CH₂Cl₂:MeOH = 95:5).

¹H-NMR (CD₃OD, δ): 3.14-3.77 (m, 6H, CH₂N), 3.70-4.07 (m, 4H, CH₂O), 4.30-4.33 (m, 1H, CH), 4.90-5.06 (m, 3H, CH, ArC^O), 7.20-7.43 (m, 10H, ArH).


MS-ESI m/z (% rel. Int.): 371.0 ([MH]^+, 100).

HPLC: Method A, detection UV 254 nm, Compound 1 RT = 4.40 min, peak area 96.5 %.

[α]²²_D = +13.9 (c = 1.00, MeOH).
Compound 2.

To a stirred solution of benzyl L-threo-1-hydroxy-3-morpholino-1-phenylpropan-2-ylcarbamate Compound 1 (0.26 g, 0.70 mmol) in 20 ml of MeOH at RT was added Pd-C 10% (140 mg). The mixture was saturated with hydrogen and stirred for 24 h at RT under hydrogen atmosphere (balloon). The catalyst Pd-C 10% was removed by filtration on celite and the solution was evaporated. The crude product was purified by column chromatography on silica (CH2Cl2:MeOH:NaOH = 79:20:1 to 75:20:5) to give L-threo-2-amino-3-morpholino-1-phenylpropan-1-ol as an oil (100 mg, 60% yield). The hydrochloride salt was obtained from 83 mg of the free base in diethylether at 0°C using 0.3 M HCl in diethylether. After precipitation in diethylether, filtration and drying L-threo-2-amino-3-morpholino-1-phenylpropan-1-ol dihydrochloride Compound 2 was obtained as a white solid (80 mg, 74% yield).

\[
\begin{align*}
\text{Compounds 2} \\
\text{OH} & \\
\text{NH}_2 & \\
\text{O} & \\
\text{2.HCl}
\end{align*}
\]

MW: 309.23; Yield: 44.0 %; White Solid; Mp (°C): 166.4-170.9.

R\(_g\): 0.20 (CH2Cl2:MeOH = 9:1).

\(^1\)H-NMR (CD3OD, \(\delta\)): 3.30-3.77 (m, 6H, CH2N), 3.92-4.05 (m, 4H, CH2O), 4.05-4.16 (m, 1H, CH), 4.85-4.98 (m, 1H, CH), 7.35-7.60 (m, 5H, ArH).

\(^13\)C-NMR (CD3OD, \(\delta\)): 53.1, 54.9, 58.5, 64.8, 72.6, 127.2, 128.0, 130.2, 140.3.

MS-ESI m/z (% rel. Int.): 237.0 ([MH]+, 100).

HPLC: Method A, detection UV 254 nm, Compound 2 RT = 0.90 min, peak area 98.0 %.

\([\alpha]^{22}_D = +10.8 \ (c = 1.00, \text{MeOH}), \ \text{free base}: \ [\alpha]^{22}_D = -6.1 \ (c = 0.25, \text{CHCl3})\).

(R)-Methyl 1-((S)-1-phenylethyl)aziridine-2-carboxylate EBE 06044B.

To solution of methyl 2,3-dibromopropionate (25 mL, 198 mmol) in toluene at 50°C was added triethylamine (55 mL, 0.39 mmol) in toluene (100 mL). After stirring for 5 min (S)-(1)-phenethylamine (25 mL, 198 mmol) in toluene (100 mL) was added dropwise. The suspension was refluxed for 3 h and allowed to cool down, filtered and the volatiles were evaporated under reduced pressure to give a residue that was purified by column chromatography (950 g of silica gel) with a gradient of 0-20% EtOAc in cyclohexane to yield to (S)-methyl 1-((S)-1-phenylethyl)aziridine-2-carboxylate EBE 06044A as a yellow oil (17.31 g, 43 % yield) and (R)-methyl 1-((S)-1-phenylethyl)aziridine-2-carboxylate EBE 06044B as a yellow oil (15.14 g, 37 % yield).

MW: 205.3; Yield EBE 06044B: 37 %; Yellow Oil. Yield: EBE 06044A: 43 %, Yellow Oil.

Rf: EBE 06044A = 0.5; Rf: EBE 06044B = 0.35 (EtOAc:cyclohexane = 25:75).

1H-NMR (CDCl3, δ): EBE 06044A: 1.47 (d, 3H, J = 6.6 Hz, CH3), 1.60 (d, 1H, J = 6.4 Hz, CH), 2.13 (d, 1H, J = 2.6 Hz), 2.21 (dd, 1H, J = 3.2 Hz, J = 6.4Hz), 2.54 (q, 1H, J = 6.6 Hz), 3.75 (s, 3H, OCH3) 7.23-7.40 (m, 5H, ArH).
$^1$H-NMR (CDCl$_3$, δ):  EBE 06044B: 1.46 (d, 3H, J = 6.6 Hz, CH$_3$), 1.79 (d, 1H, J = 6.6 Hz, CH), 2.08 (d, 1H, J = 3.1 Hz, 6.6 Hz), 2.34 (dd, 1H, J = 3.1 Hz, J = 1.0 Hz), 2.56 (q, 1H, J = 6.6 Hz), 3.67 (s, 3H, OCH$_3$) 7.24-7.36 (m, 5H, ArH).

$^{13}$C-NMR (CDCl$_3$, δ):  EBE 06044B: 23.5, 35.0, 36.9, 52.2, 69.8, 126.5, 127.2, 128.5, 143.6, 171.1.

HPLC: Method A, detection at 254 nm, EBE 06044B RT = 6.1 min, peak area 92.9 %.

((R)-(S)-phenylethyl)aziridin-2-yl)methanol  EBE 06046.

A 250 mL round bottom flask was charged with anhydrous THF (100mL) and LiAlH$_4$ (2.77 g, 73.1 mmol). While the suspension is stirred at 0°C, a solution of (S)-methyl 1-((S)-1-phenylethyl)aziridine-2-carboxylate  EBE 06044B (10.0 g, 48.7 mmol) in THF (50 mL) was added dropwise over 20 min. The dropping funnel was washed with THF (2 x 3 mL) and allowed to react 20 min at 0°C. Maintaining the reaction mixture at 0°C, a solution of KOH (10 %, 20 mL) was added dropwise for 20 min (caution the reaction is exothermic). The mixture was stirred for 0.5 h at 25 °C and the white precipitate removed by filtration through a celite pad that was washed with diethyl ether (30 mL). The combined organic filtrates were washed with NaH$_2$PO$_4$ and the aqueous layer was extracted with Et$_2$O (3 x 30 mL). The combined organic phase were dried with Na$_2$SO$_4$ and concentrated to give ((R)-1-((S)-1-phenylethyl)aziridin-2-yl)methanol  EBE 06046 as a white solid (10.4 g, 90 % yield).

$$\begin{align*}
\text{OH} \\
\text{N} \\
\text{EBE 06046}
\end{align*}$$

MW: 177.2; Yield: 90%; White Solid; Mp (°C): 37.7.

$^1$H-NMR (CDCl$_3$, δ): 1.43 (d, 3H, J = 6.6 Hz, CH$_3$), 1.49 (d, 1H, J = 6.5 Hz, CH), 1.65-1.71 (m, 1H, CH), 1.92 (d, 1H, J = 3.5 Hz, NCH), 2.26 (s, 1H, OH),
2.53 (q, 1H, J = 6.6 Hz, NCH), 3.32-3.37 (m, 1H, OCH₂), 3.56 (m, 1H, OCH₂), 7.23-7.35 (m, 5H, ArH).

13C-NMR (CDCl₃, δ): 22.9, 31.4, 39.3, 62.5, 69.4, 126.6, 127.3, 128.6, 144.5.

(R)-1-((S)-1-Phenylethyl)aziridine-2-carbaldehyde  EBE 06048

A three neck, 250 mL round bottom flask was equipped with a low temperature thermometer and two (2) equalizing dropping funnels. One of these was connected to a nitrogen line and charged with a solution of ((R)-1-((S)-1-phenylethyl)aziridine-2-yl)methanol  EBE 06046 (7.0 g, 39.5 mmol) in CH₂Cl₂ (75 mL), the other was charged with a solution of DMSO (9.25 g, 118.5 mmol) in CH₂Cl₂ (11 mL). To a solution of oxalyl chloride (7.5 g, 59.3 mmol) in CH₂Cl₂ (90 mL) under N₂ at -78°C, the DMSO solution was added dropwise during 20 min and stirred for 20 min. EBE 06046 (7.0 g, 39.5 mmol) in CH₂Cl₂ (75 mL) was added dropwise over 50 min. then the dropping funnel was charged with DIEA (42.6 mL, 237 mmol) in CH₂Cl₂ (10 mL) and the reaction mixture was stirred for 30 min at -45°C. The DIEA solution was added over 5 min with the reaction mixture at -78°C and the reaction was allowed to warm to room temperature. The reaction mixture was washed with H₂O (3 x 50 mL), dried over MgSO₄, filtered, evaporated. The crude product obtained was purified by column chromatography on silica with a gradient of 0-20 % [v/v] EtOAc in cyclohexane to give ((R)-1-((S)-1-phenylethyl)aziridine-2-carbaldehyde  EBE 06048 as a yellow oil (5.59 g, 81 % yield).

MW: 175.2; Yield: 81 %; Yellow Oil.

Rf: EBE 06048: 0.3 (EtOAc:cyclohexane = 20:80).

1H-NMR (CDCl₃, δ): 1.47 (d, 3H, J = 6.6 Hz, CH₃), 1.94 (d, 1H, J = 6.7 Hz, NCH₂), 2.08 (dt, J = 2.9 Hz, J = 6.4 Hz, NCH), 2.37 (d, 1H, J = 2.6 Hz, NCH₂).
2.61 (q, 1H, J = 6.6 Hz, NCH), 7.20-7.38 (m, 5H, ArH), 8.92 (d, 1H, J = 6.2 Hz).

$^1$C-NMR (CDCl$_3$, δ): 22.7, 32.1, 43.2, 68.1, 125.5, 126.5, 127.6, 142.4, 198.7.

(fl)-Phenyl((fl)-1-((S)-1-phenylethyl)aziridin-2-yl)methanol EBE 06066.

To a solution of bromobenzene (4.93 g, 31.4 mmol) in THF 125 mL under nitrogen at -78°C was added /-BuLi (1.7 M in pentane, 50 mL). The mixture was stirred for 0.5 h at room temperature. The mixture was cooled down to -78°C and a solution of (fl)-1-((S)-1-phenylethyl)aziridine-2-carbaldehyde EBE 06048 (2.5 g, 14.3 mmol) in THF (16.7 mL) at -78°C was added dropwise. The reaction mixture was treated with H$_2$O (20 mL), the organic layer was separated and the aqueous phase was extracted with EtOAc. The combined organic layers were dried over MgSO$_4$, filtered and concentrated in vacuo to give a residue that was purified by column chromatography using a gradient of 0-20% [v/v] EtOAc in cyclohexane to give (R)-phenyl((R)-1-((S)-1-phenylethyl)aziridin-2-yl)methanol EBE 06066 (3.13 g, 86% yield).

MW: 253.3; Yield: 86%.

R$_f$: 0.3 (EtOAc:cyclohexane = 20:80).

$^1$H-NMR (CDCl$_3$, δ): 1.47 (d, 3H, J = 6.6 Hz, CH$_3$), 1.57 (d, 1H, J = 6.5 Hz, CH), 1.79 (t, 1H, J = 3.5 Hz, J = 8.7 Hz, CH), 2.04 (d, 1H, J = 3.5 Hz, OCH), 2.35 (bs, 1H, OH), 2.53 (q, 1H, J = 6.5 Hz, CH), 4.23 (d, 1H, J = 5.7 Hz, OCH), 7.07-7.13 (m, 2H, ArH), 7.16-7.20 (m, 3H, ArH), 7.24-7.34 (m, 5H, ArH).
13C-NMR (CDCl3, δ): 22.4, 32.0, 44.6, 69.4, 74.1, 125.8 (2xC), 126.9 <2xC), 127.3, 127.6, 128.2 (2xC), 128.7 (2xC), 142.0, 144.2.

[Q]22D = -71.53 (c = 0.59, CHCl3).

5 D-threo-2-((S)-1-Phenylethlamino)-3-morpholino-1-phenylpropan-1-ol dihydrochloride Compound 5

To a solution of (S)-phenyl((R)-1-((S)-1-phenylethyl)aziridin-2-yl)methanol EBE 06066 (1.5 g, 5.92 mmol) in CH3CN (19 mL) at RT was added iodon trimethylsilane (3.55 g, 17.8 mmol). The solution was stirred for 2 h and morpholine (1.032 g, 11.84 mmol) was added. After 2 h at reflux, the reaction mixture was treated with HCl (1M) to reach pH = 1 and stirred for 10 min. After a slow addition of NaHCO3 to reach pH = 9, the product was extracted with EtOAc, dried over Na2SO4, filtered to give after evaporation a crude brown oil that was purified by column chromatography using a gradient of 0-20% [v/v] MeOH in EtOAc to give D-threo-2-((S)-1-phenylethlamino)-3-morpholino-1-phenylpropan-1-ol EBE 06068A (0.831 g, 42%) as a pale brown solid. To a solution of D-threo-2-((S)-1-phenylethlamino)-3-morpholino-1-phenylpropan-1-ol EBE 06068A (0.100 g, 0.294 mmol) in ethanol (1 mL) was added a solution of HCl (0.8 M, 0.816 mL) in EtOH.

Evaporation of the volatiles afforded to D-threo-2-((S)-1-phenylethlamino)-3-morpholino-1-phenylpropan-1-ol dihydrochloride Compound 5 as white solid (0.125 g, 100%).

MW: 412.37; Yield: 42%; White Solid; Mp (ºC): 157.2 (dec).

Rf. 0.3 (MeOH:EtOAc = 20:80) EBE 06068A.

1H-NMR (CD3OD, δ): 1.19 (t, 2H, J = 7.0 Hz, NCH2), 1.71 (d, 3H, J = 6.8 Hz, CH3), 3.45 (m, 2H, J = 7.1 Hz, NCH2), 3.62 (q, 2H, J = 7.1 Hz, N-CH2), 3.97 (t,
4H, J = 4.5 Hz, OCH₂), 4.06 (m, 1H, CH-N), 4.75 (q, 1H, J = 6.8 Hz, CH-N), 5.21 (d, 1H, J = 5.1 Hz, CH-O), 7.44-7.56 (m, 1OH, ArH).

MS-ESI m/z (% rel. int.): 341.1 ([MH]⁺, 20).

¹³C-NMR (CD₃OD, δ): 24.4, 54.5 (2xC), 55.5, 55.9, 60.0, 67.0 (2xC), 75.6, 126.3 (2xC), 126.5 (2xC), 127.0, 127.1, 128.1 (2xC), 128.5 (2xC), 142.2, 145.3.

HPLC: Method A, detection at 254 nm, Compound 5 RT = 4.41 min, peak area 99 %.

D-fftreo2-Amino-3-morpholino-1-phenylpropan-1-ol dihydrochloride

Compound 4.

To a solution of D-tf7reo-2-(S)-1-phenylethlamino)-3-morpholino-1-phenylpropan-1-ol EBE 06068A (0.400 g, 1.17 mmol) in MeOH (6 ml) at RT was added acetic acid (0.133 ml, 2.35 mmol). The reaction vessel was flushed with nitrogen and Pd(OH)₂ (25 % weight, 0.150 g) was added. The nitrogen atmosphere was exchanged with hydrogen using three cycle of vacuum and hydrogen addition using a balloon of hydrogen. After stirring for 16 hours under hydrogen the reaction mixture was filtrated through celite to give EBE 06070A the acetate salt of (2R)-amino-3-morpholin-4-yl-(1 R)-phenylpropan-1-ol (0.279 g, 98 % yield). To as solution of EBE 06070A the acetate salt of (2f?)-amino-3-morpholin-4-yl-(1 f?)-phenylpropan-1-ol (0.100 g, 0.338 mmol) in ethanol (1 ml) was added a solution of HCl (0.8 M, 0.930 ml) in EtOH. Evaporation of the volatiles afforded to D-tf7reo-2-amino-3-morpholino-1-phenylpropan-1-ol dihydrochloride Compound 4 (0.104 g, 100 % yield) as an off white solid. (Adapted from Shin, S-H.; Han, E.Y.; Park, CS.; Lee, W.K.; Ha, H.-J. Tetrahedron Asymmetry, 2000, 11, 3293-3301).

![Chemical structure](image)
Compound 4

MW: 309.23; Yield: 99 %; Off White Solid; Mp (0°C): 183.4.

$^1$H-NMR (CD$_3$OD, $\delta$): 3.30-3.77 (m, 6H, CH$_2$N), 3.92-4.05 (m, 4H, CH$_2$O), 4.05-4.16 (m, 1H, CH), 4.85-4.98 (m, 1H, CH), 7.35-7.60 (m, 5H, ArH).

$^{13}$C-NMR (CD$_3$OD): 53.2, 58.3, 58.5 (2xC), 64.9 (2xC), 72.6, 128.0 (2xC), 130.2 (2xC), 140.3.

MS-ESI m/z (% rel. int.): 237.1 (100, [MH$^+$]).

HPLC: Isocratic 10% CH$_3$CN in H$_2$O (pH 10, [NH$_4$OH] = 5 mM), detection UV 254 nm, Compound 4 RT = 6.63 min, peak area 97.3 %.

[Q]$^{22}$D = -10.7 (c = 1.00, MeOH).

Preparation of Compound 13, Compound 14, Compound 15, Compound 16 and Compound 17

Method B:

To a stirred and cooled (0°C) solution of potassium hydroxide (380 mg, 5.80 mmol) in MeOH (5 mL) were added successively aldehyde (5.80 mmol) and 2-isocyanato-1-(pyrrolidin-1-yl)ethanone BLE 04098 (0.8 g, 5.8 mmol). The solution was stirred 3 h at 0°C and then concentrated. The residue was partitioned between CH$_2$Cl$_2$ (100 mL) and water. The organic layer was washed with brine, dried over MgSO$_4$, filtered and evaporated. Concentration afforded a crude product which was purified by column chromatography on silica (cyclohexane:EtOAc = 70/30 to 0:100) to yield, after evaporation and drying, to an intermediate oxazoline. To a stirred solution of oxazoline in methanol (15 mL) was added hydrochloric acid (1 mL, 12 mmol). After heating at 60°C for 2 h, the mixture reaction was then concentrated and the resulting yellow oil was coevaporated twice with MeOH before solidifying. Trituration in EtOAc:MeOH = 10/1 followed by filtration gave title compound as a white solid.

DL-fhrβo-2-Amino-3-hydroxy-3-(4-methoxyphenyl)-1-(pyrrolidin-1-yl)propan-1-one hydrochloride Compound 13.
The compound was prepared according to method B with 4-methoxybenzaldehyde (811 mg, 5.80 mmol). DL-t/reo-2-Amino-3-hydroxy-3-(4-methoxyphenyl)-1-(pyrrolidin-1-yl)propan-1-one hydrochloride. Compound 13 was obtained as a white solid (468 mg, 30% yield).

\[
\text{Compound 13}
\]

MW: 300.78; Yield: 30.0%; White Solid; Mp (°C): 176.6.
R\text{f}: 0.15 (EtOAc:MeOH = 85:15) free base.
\(1^H\)-NMR (CD3OD, \(\delta\)):
- 1.37-1.78 (m, 4H, 2xCH2),
- 2.17-2.25 (m, 1H, CH2N),
- 3.15-3.26 (m, 2H, CH2N),
- 3.34-3.40 (m, 2H, CH2N),
- 3.79 (s, 3H, 1CH3O),
- 4.06 (d, 1H, J = 9.3 Hz, CH-N),
- 4.80 (d, 1H, J = 9.3 Hz, CH-O),
- 6.94 (m, 2H, J = 8.7 Hz, ArH),
- 7.33 (d, 2H, J = 8.6 Hz, ArH).
\(13^C\)-NMR (CD3OD, \(\delta\)):
- 24.8, 26.6, 47.2, 47.6, 55.9, 59.6, 73.8, 115.0, 128.9, 132.5, 161.7, 166.4.
MS-ESI m/z (% rel. Int.): 265.1 ([MH]+, 10), 247.1 (100).
HPLC: Method A, detection UV 254 nm, Compound 13 RT = 3.70 min, peak area 99.00%.

DL-t/reo-2-Amino-3-(4-chlorophenyl)-3-hydroxy-1-(pyrrolidin-1-yl)propan-1-one hydrochloride Compound 14.

The compound was prepared according to method B with 4-chlorobenzaldehyde (837 mg, 5.80 mmol). DL-t/reo-2-Amino-3-(4-chlorophenyl)-3-hydroxy-1-(pyrrolidin-1-yl)propan-1-one hydrochloride. Compound 14 was obtained as a white solid (483 mg, 33% yield).
MW: 321.24; Yield: 33.0 %; White Solid; Mp (°C): 190.1.

Rf: 0.15 (EtOAc:MeOH = 85:15), free base.

1H-NMR (CD3OD, δ): 1.41-1.78 (m, 4H, 2xCH2), 2.24-2.32 (m, 1H, CH2N), 3.16-3.28 (m, 2H, CH2N), 3.34-3.40 (m, 1H, CH2N), 4.11 (d, 1H, J = 9.0 Hz, CH-N), 4.85-4.88 (m, 1H, CH-O), 7.42 <s, 4H, ArH).

13C-NMR (CD3OD, δ): 24.8, 26.6, 47.2, 47.6, 59.2, 73.5, 129.4, 129.8, 135.8, 139.6, 166.1.

MS-ESI m/z (% rel. Int.): 269.1/271.1 ([MH]+, 50/20), 251.1/253.1 (100/30).

HPLC: Method A, detection UV 254 nm, Compound 14 RT = 4.00 min, peak area 99.00 %.

DL-tireo-2-Amino-3-(3,4-dichlorophenyl)-3-hydroxy-1-(pyrrolidin-1-yl)propan-1-one hydrochloride Compound 15.

The compound was prepared according to method B with 3,4-dichlorobenzaldehyde (809 mg, 4.60 mmol). DL-tireo-2-Amino-3-(3,4-dichlorophenyl)-3-hydroxy-1-(pyrrolidin-1-yl)propan-1-one hydrochloride Compound 15 was obtained as a white solid (522 mg, 31 % yield).

MW: 355.69; Yield: 31.0 %; White Solid; Mp (°C): 186.3.

Rf: 0.15 (EtOAc:MeOH = 85:15), free base.

1H-NMR (CD3OD, δ): 1.46-1.82 (m, 4H, 2xCH2), 2.32-2.40 (m, 1H, CH2N), 3.20-3.27 (m, 1H, CH2N), 3.34-3.43 (m, 2H, CH2N), 4.15 (d, 1H, J = 8.7 Hz, CH-N), 4.87-4.90 (m, 1H, CH-O), 7.38 (dd, 1H, J = 8.3 Hz, J = 1.7 Hz, ArH), 7.57-7.59 (m, 2H, ArH).

13C-NMR (CD3OD, δ): 24.9, 26.7, 47.3, 47.8, 59.0, 72.8, 127.5, 129.8, 131.9, 133.6, 133.7, 141.6, 166.0.

MS-ESI m/z (% rel. Int.): 303.1/305.0 ([MH]+, 65/45), 111.0 (100).
HPLC: Method A, detection UV 254 nm, Compound 15 RT = 4.20 min, peak area 99.00 %.

\textit{DL-}$\beta$-2-Amino-3-hydroxy-3-phenyl-1-(pyrrolidin-1-yl)propan-1-one hydrochloride Compound 16.

The compound was prepared according to method B with benzaldehyde (0.613 g, 5.78 mmol). \textit{DL-}$\beta$-2-Amino-3-hydroxy-3-phenyl-1-(pyrrolidin-1-yl)propan-1-one hydrochloride Compound 16 was obtained as a white solid (0.225 g, 14 % yield).

\[
\text{OH} \\
\text{NH}_2 \\
\text{N} \\
(+/−) \text{HCl}
\]

Compound 16

MW: 270.76; Yield: 14 %; White Solid; Mp (°C): 184.9.

$^1$H-NMR (CD$_3$OD, $\delta$): 1.30-1.42 (m, 1H, CH$_2$), 1.50-1.60 (m, 1H, CH$_2$), 1.60-1.80 (m, 2H, CH$_2$), 2.05-2.15 (m, 1H, CH$_2$), 3.12-3.30 (m, 2H, NCH$_2$), 3.30-3.40 (m, 1H, NCH$_2$), 4.09 (d, 1H, $J$ = 9.2 Hz, CH-N), 4.80-4.95 (m, 1H, CH-O), 7.30-7.45 (m, 5H, ArH).

$^{13}$C-NMR (CD$_3$OD, $\delta$): 24.7, 26.5, 47.2, 47.5, 59.5, 74.2, 127.7, 129.7, 130.0, 140.8, 166.3.

MS-ESI m/z (% rel. Int.): 235.2 ([MH$^+$, 100]).

HPLC: Method A, detection UV 254 nm, Compound 16 RT = 3.56 min, peak area 96.4 %.

\textit{DL-}$\beta$-2-Amino-3-hydroxy-1-(pyrrolidin-1-yl)-3-p-tolylpropan-1-one hydrochloride Compound 17.

The compound was prepared according to method B with 4-methylbenzaldehyde (0.694 g, 5.78 mmol). \textit{DL-}$\beta$-2-Amino-3-hydroxy-1-(pyrrolidin-1-yl)-3-p-tolylpropan-1-one hydrochloride Compound 17 was obtained as a white solid (0.044 g, 3 % yield).
MW: 284.78; Yield: 3% ; White Solid; Mp (°C): 184.2.

$^1$H-NMR (CD3OD, δ): 1.28-1.40 (m, 1H, CH$_2$), 1.50-1.60 (m, 1H, CH$_2$), 1.60-1.80 (m, 2H, CH$_2$), 2.10-2.22 (m, 1H, CH$_2$), 2.34 (s, 3H, CH$_3$), 3.10-3.25 (m, 2H, NCH$_2$), 3.25-3.40 (m, 1H, NCH$_2$), 4.07 (d, 1H, J = 9.2 Hz, CH-N), 4.80 (d, 1H, J = 9.2 Hz, CH-O), 7.21 (d, 2H, J = 8.1 Hz, ArH), 7.30 (d, 2H, J = 8.0 Hz, ArH).

$^{13}$C-NMR (CD3OD, δ): 21.2, 24.8, 26.5, 47.2, 47.5, 59.6, 74.1, 127.6, 130.2, 137.7, 140.1, 166.4.

MS-ESi m/z (% rel. Int.): 249.2 ([MH]$^+$, 30).

HPLC: Method A, detection UV 254 nm, Compound 17 RT = 3.90 min, peak area 99.9%.

1-Phenyl-2-decanoylamino-3-morpholino-1~propano! (PDMP) isomers and enantiomers

PDMP mixture of DL-erythro and DL-threo isomers
WHAT IS CLAIMED IS:

1. The use of a compound in the manufacture of a medicament for treating a condition selected from the group consisting of neuropathic pain, inflammatory pain, headache pain, somatic pain, visceral pain, and referred pain, wherein the compound has the following structure
or any pharmaceutically acceptable salt thereof.

2. The use according to claim 1, wherein the compound has the formula
or any pharmaceutically acceptable salt thereof.

3. The use according to claim 1, wherein the compound has the formula

\[
\begin{align*}
&\text{DL-threeo} \\
&2 \text{HCl} \\
&\text{D-threeo}
\end{align*}
\]

or any other pharmaceutically acceptable salt of said compound.

4. The use according to claim 1, wherein the compound has the formula

\[
\begin{align*}
&\text{HCl} \\
&\text{DL-threeo}
\end{align*}
\]

or any other pharmaceutically acceptable salt of said compound.

5. The use according to claim 1, wherein the compound has the formula

\[
\begin{align*}
&\text{HCl} \\
&\text{DL-threeo}
\end{align*}
\]
or any other pharmaceutically acceptable salt of said compound.

6. The use according to claim 1, wherein the compound has the formula

![Chemical Structure]

HCl
DL-threo

or any other pharmaceutically acceptable salt of said compound.

7. The use according to claim 1, wherein the compound has the formula

![Chemical Structure]

HCl
DL-threo

or any other pharmaceutically acceptable salt of said compound.

8. The use according to claim 1, wherein the compound has the formula

![Chemical Structure]

HCl
DL-threo

or any other pharmaceutically acceptable salt of said compound.

9. The use according to claim 1, wherein the compound has the formula

![Chemical Structure]

2 HCl
DL-threo

or any other pharmaceutically acceptable salt of said compound.
10. The use according to claim 1, wherein the compound has the formula

\[
\begin{array}{c}
\text{OH} \\
\text{NH}_2 \\
\text{N} \\
\text{O} \\
\end{array}
\]

\[\text{2 HCl} \]

\[\text{L-threeo} \]

or any other pharmaceutically acceptable salt of said compound.

11. The use according to claim 1, wherein the compound has the formula

\[
\begin{array}{c}
\text{OH} \\
\text{N} \\
\text{H} \text{N} \text{C} \text{H}_3 \\
\text{O} \\
\end{array}
\]

\[\text{L-threeo-PDMP} \]

or a pharmaceutically acceptable salt of said compound.

12. The use according to claim 1, wherein the compound has the formula

\[
\begin{array}{c}
\text{OH} \\
\text{N} \\
\text{H} \text{N} \text{C} \text{H}_3 \\
\text{O} \\
\end{array}
\]

\[\text{DL-ery threeoPDMP} \]

or a pharmaceutically acceptable salt of said compound.

13. The use according to claim 1, wherein the compound has the formula

\[
\begin{array}{c}
\text{OH} \\
\text{N} \\
\text{H} \text{N} \text{C} \text{H}_3 \\
\text{O} \\
\end{array}
\]

\[\text{D-threeo-PDMP} \]

or a pharmaceutically acceptable salt of said compound.