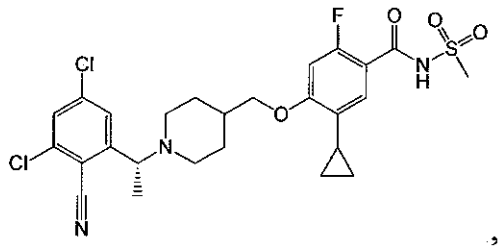
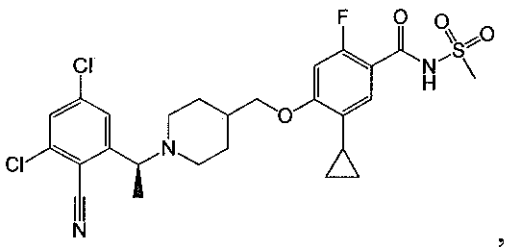
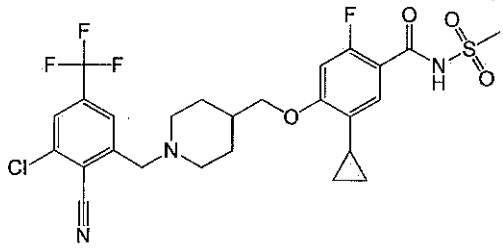
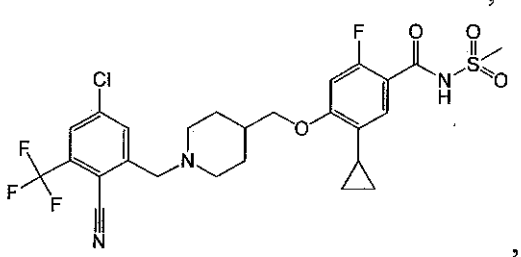
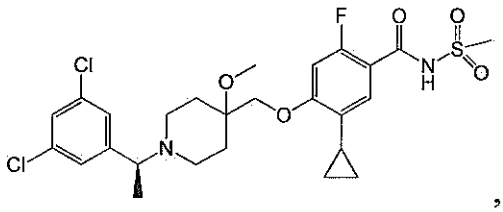
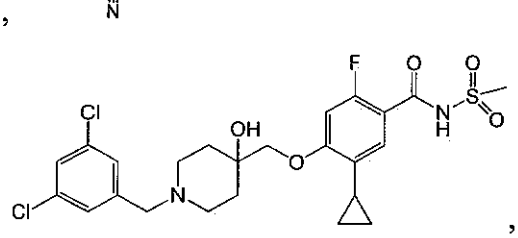
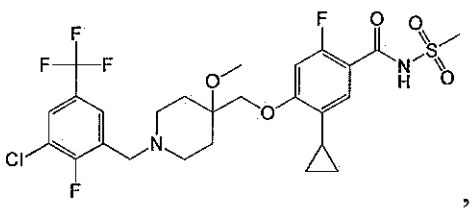
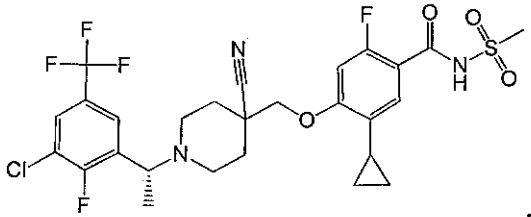
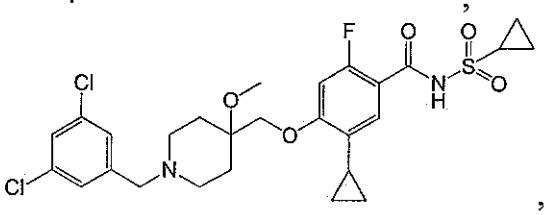
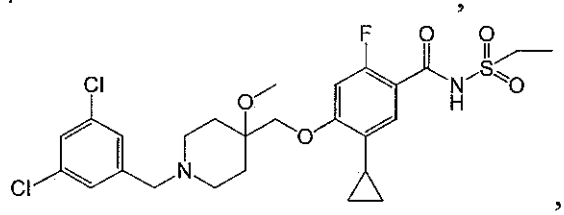
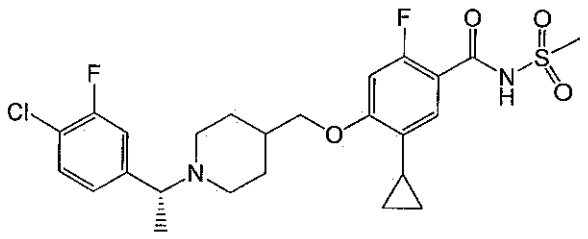
lower back pain, phantom limb pain, and pain resulting from cancer and chemotherapy, chronic pelvic pain, complex regional pain syndrome and related neuralgias.

There are a limited number of effective sodium channel blockers for the treatment of pain with a minimum of adverse side effects which are currently in the clinic. There is also an unmet medical need to treat neuropathic pain and other sodium channel associated pathological states effectively and without adverse side effects due to the blocking of sodium channels not involved in nociception. The present invention provides methods to meet these critical needs.

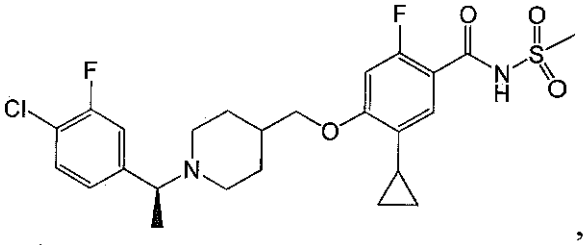
SUMMARY

In one aspect the present invention provides for novel compounds selected from the group consisting of:


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and



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and salts thereof.

In another example, there is described a compound selected from the compounds of Examples 1-40 and the free bases and salts thereof.

In another aspect the present invention refers to a pharmaceutical composition comprising a compound as provided herein or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

In another example, there is described a method of treating a disease or condition in a mammal selected from the group consisting of pain, depression, cardiovascular diseases, respiratory diseases, and psychiatric diseases, and combinations thereof, wherein the method comprises administering to the mammal in need thereof a therapeutically effective amount of a compound as provided herein, or a pharmaceutically acceptable salt thereof. In another aspect of the present invention said disease or condition is selected from the group consisting of neuropathic pain, inflammatory pain, visceral pain, cancer pain, chemotherapy pain, trauma pain, surgical pain, post-surgical pain, childbirth pain, labor pain, neurogenic bladder, ulcerative colitis, chronic pain, persistent pain, peripherally mediated pain, centrally mediated pain, chronic headache, migraine headache, sinus headache, tension headache, phantom limb pain, dental pain, peripheral nerve injury or a combination thereof. In another aspect of the present invention said disease or condition is selected from the group consisting of pain associated with HIV, HIV treatment induced neuropathy, trigeminal neuralgia, post-herpetic neuralgia, eudynia, heat sensitivity, tosarcoidosis, irritable bowel syndrome, Crohns disease, pain associated with multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), diabetic neuropathy, peripheral neuropathy, arthritis, rheumatoid arthritis, osteoarthritis, atherosclerosis, paroxysmal dystonia, myasthenia syndromes, myotonia, malignant hyperthermia, cystic fibrosis, pseudoaldosteronism, rhabdomyolysis, hypothyroidism, bipolar depression, anxiety, schizophrenia, sodium channel toxi related illnesses, familial

erythromelalgia, primary erythromelalgia, familial rectal pain, cancer, epilepsy, partial and general tonic seizures, restless leg syndrome, arrhythmias, fibromyalgia, neuroprotection under ischaemic conditions cause by stroke or neural trauma, tach-arrhythmias, atrial fibrillation and ventricular fibrillation.

In another example, there is disclosed a method of treating pain in a mammal by the inhibition of ion flux through a voltage-dependent sodium channel in the mammal, wherein the method comprises administring to the mammal in need thereof a therapeutically effective amount of a compound as provided herein, or a pharmaceutically acceptable salt thereof.

In another example, there is disclosed a method of decreasing ion flux through a voltage-dependent sodium channel in a cell in a mammal, wherein the method comprises contacting the cell with a compound as provided herein, or a pharmaceutically acceptable salt thereof.

In another example, there is disclosed a method of treating pruritus in a mammal, wherein the method comprises administering to the mammal in need thereof a therapeutically effective amount of a compound as provided herein, or a pharmaceutically acceptable salt thereof.

In another example, there is disclosed a method of treating cancer in a mammal, wherein the method comprises administering to the mammal in need thereof a therapeutically effective amount a compound as provided herein, or a pharmaceutically acceptable salt thereof.

In another example, there is disclosed a method of treating, but not preventing, pain in a mammal, wherein the method comprises administering to the mammal in need thereof a therapeutically effective amount of a compound as provided herein, or a pharmaceutically acceptable salt thereof. In another aspect of the present invention the pain is selected from the group consisting of neuropathic pain, inflammatory pain, visceral pain, cancer pain, chemotherapy pain, trauma pain, surgical pain, post-surgical pain, childbirth pain, labor pain, neurogenic bladder, ulcerative colitis, chronic pain, persistent pain, peripherally mediated pain, centrally mediated pain, chronic headache, migraine headache, sinus headache, tension headache, phantom limb pain, dental pain, peripheral nerve injury or a combination thereof. In another example the pain is associated with a disease or condition selected from the group consisting of HIV, HIV treatment induced neuropathy, trigeminal neuralgia, post-herpetic neuralgia, eudynia, heat sensitivity, tosarcoidosis, irritable bowel syndrome, Crohns disease, pain associated with multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), diabetic neuropathy, peripheral neuropathy, arthritis, rheumatoid arthritis, osteoarthritis, atherosclerosis, paroxysmal dystonia, myasthenia syndromes, myotonia, malignant

hyperthermia, cystic fibrosis, pseudoaldosteronism, rhabdomyolysis, hypothyroidism, bipolar depression, anxiety, schizophrenia, sodium channel toxi related illnesses, familial erythromelalgia, primary erythromelalgia, familial rectal pain, cancer, epilepsy, partial and general tonic seizures, restless leg syndrome, arrhythmias, fibromyalgia, neuroprotection under ischaemic conditions cause by stroke or neural trauma, tach-arrhythmias, atrial fibrillation and ventricular fibrillation.

In another example, there is disclosed a method of treating, but not preventing, acute pain or chronic pain in a mammal, wherein the method comprises administering to the mammal in need thereof a therapeutically effective amount of a compound as provided herein, or a pharmaceutically acceptable salt thereof.

In another example, there is disclosed a method of treating, but not preventing, neuropathic pain or inflammatory pain in a mammal, wherein the method comprises administering to the mammal in need thereof a therapeutically effective amount of a compound as provided herein, or a pharmaceutically acceptable salt thereof.

In another example, there is disclosed a method for the treatment or prophylaxis of pain, depression, cardiovascular disease, respiratory disease, or psychiatric disease, or a combinations thereof, in an animal which method comprises administering an effective amount of a compound as provided herein, or a pharmaceutically acceptable salt thereof.

In another aspect the present invention provides for a compound as provided herein, or a pharmaceutically acceptable salt thereof for the use as a medicament for the treatment of diseases and disorders selected from the group consisting of pain, depression, cardiovascular diseases, respiratory diseases, and psychiatric diseases, or a combination thereof.

In another aspect the present invention provides for the use of a compound as provided herein, or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of diseases and disorders selected from the group consisting of pain, depression, cardiovascular diseases, respiratory diseases, and psychiatric diseases, or a combination thereof.

In another example, there is disclosed the invention as described herein.

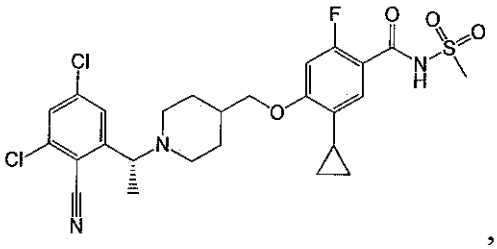
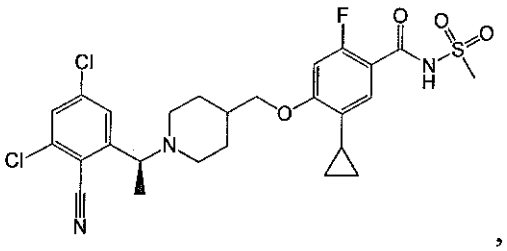
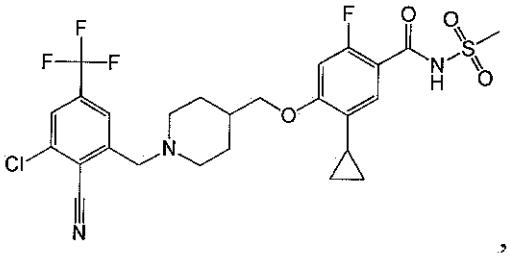
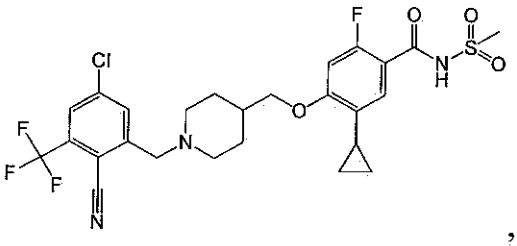
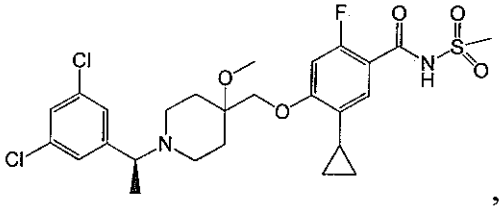
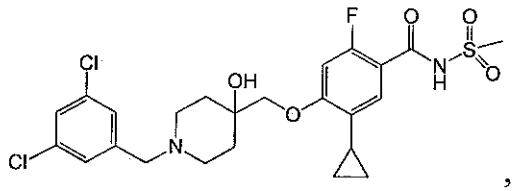
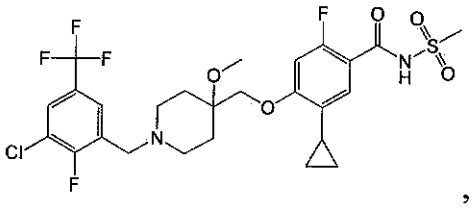
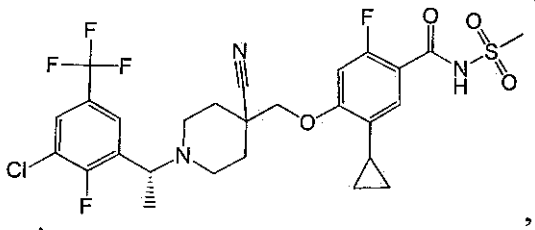
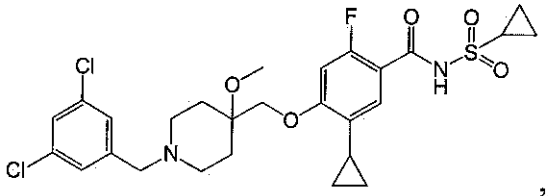
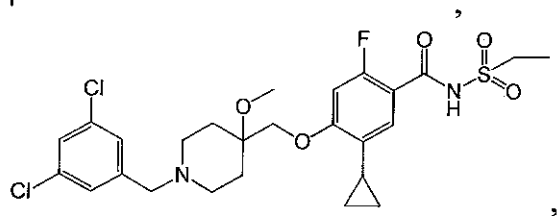
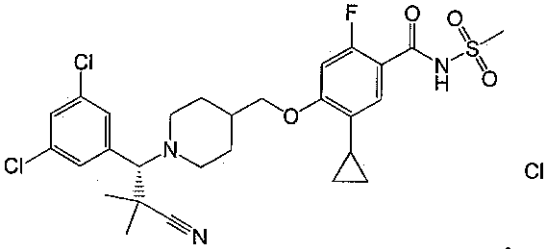
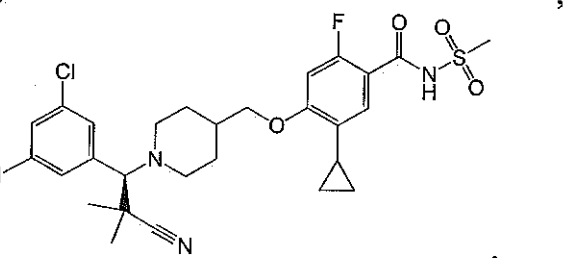
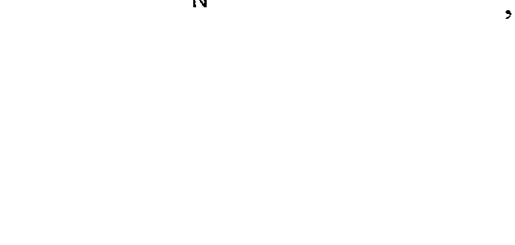
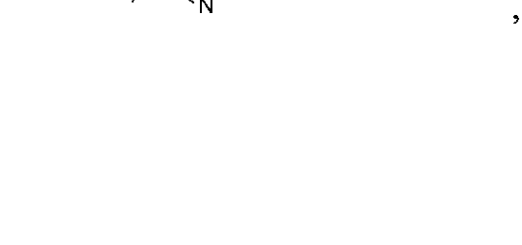
In one aspect, the present invention refers to use of the compound as disclosed herein or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a disease or condition in a mammal selected from the group consisting of pain, depression, cardiovascular diseases, respiratory diseases, and psychiatric diseases, and combinations thereof.

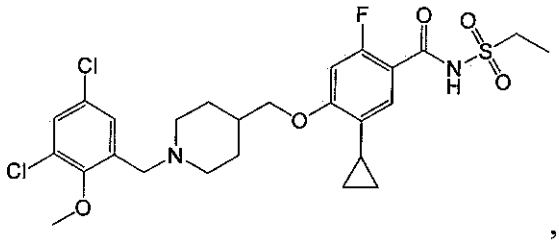
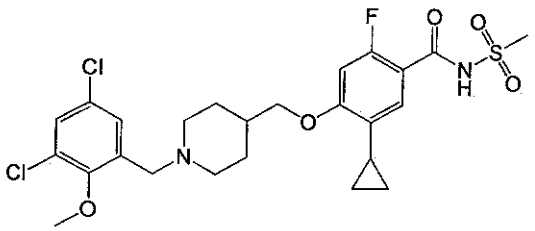
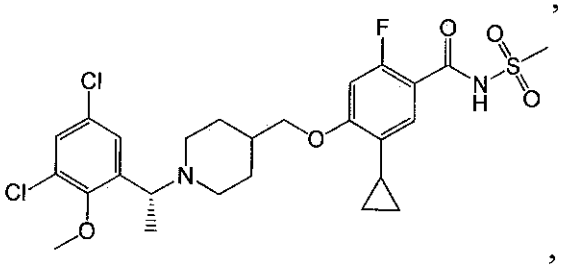
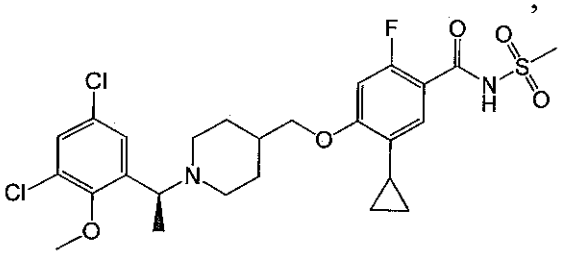
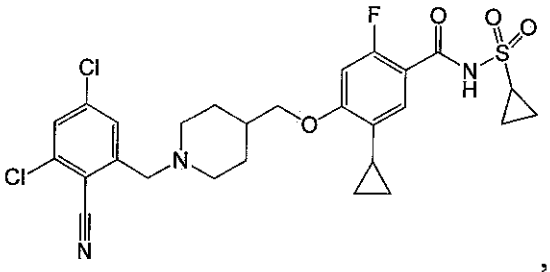
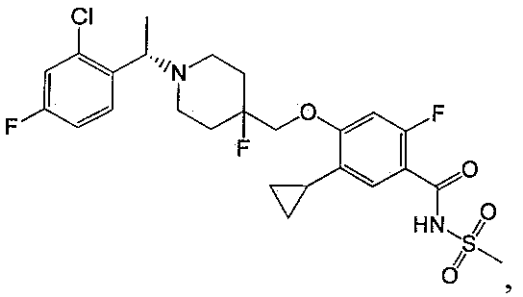
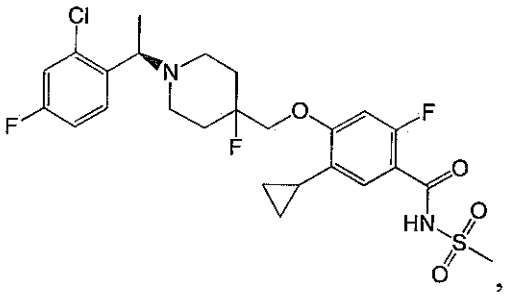
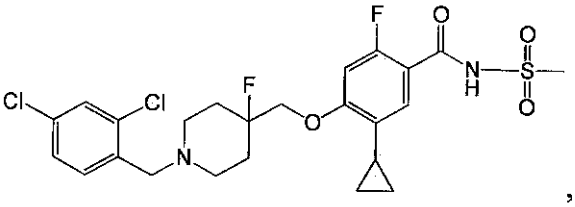
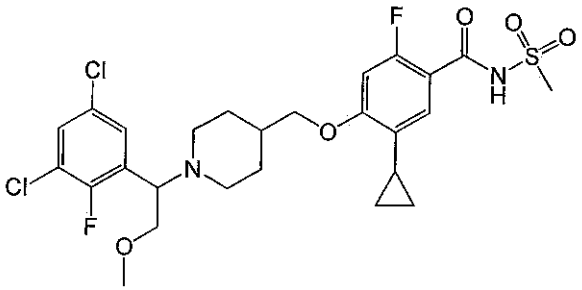
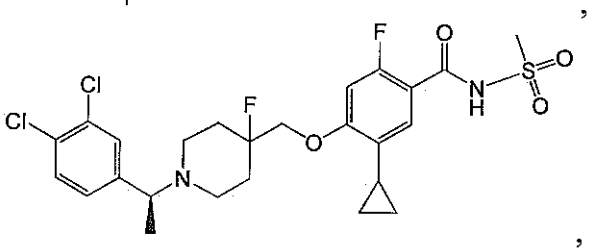
In another aspect, the present invention refers to use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for of treating pruritus in a mammal.

In another aspect, the present invention refers to use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating, but not preventing, pain in a mammal.

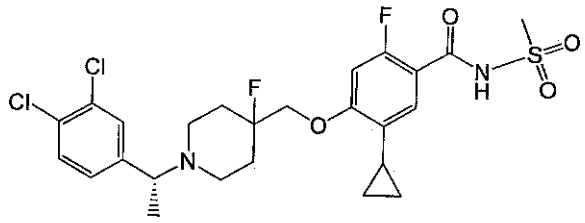
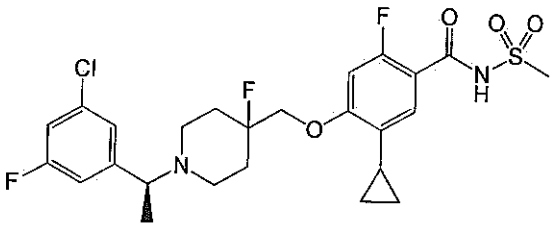
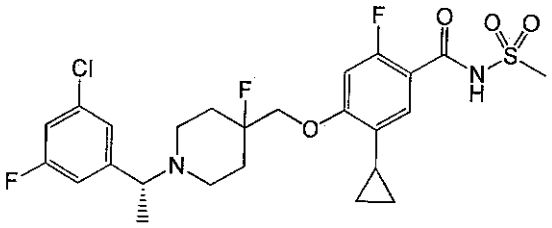
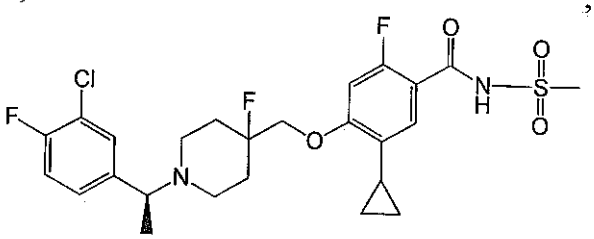
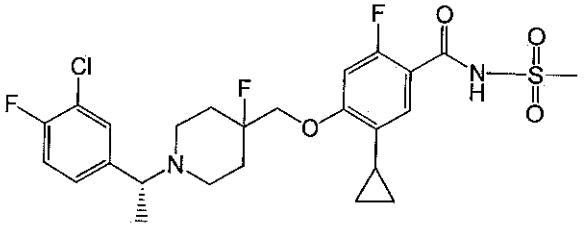
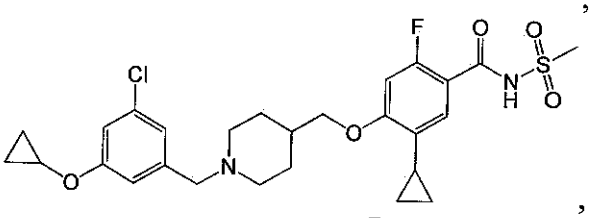
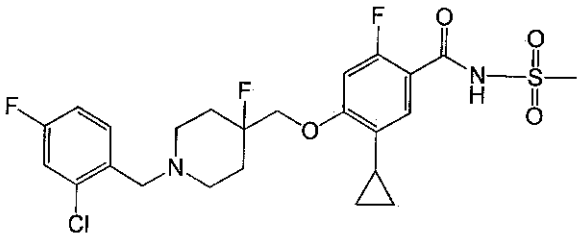
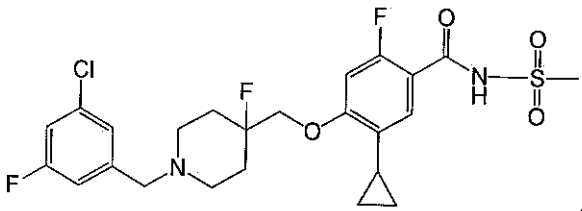
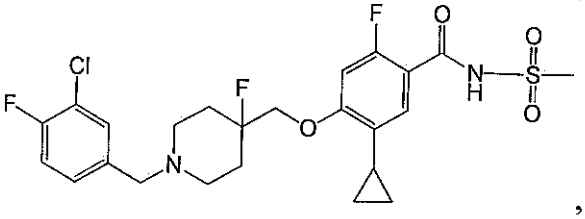
WE CLAIM:

1. A compound selected from the group consisting of:

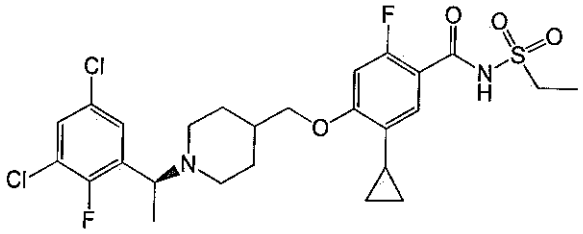
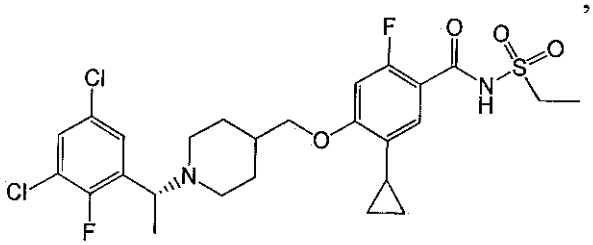
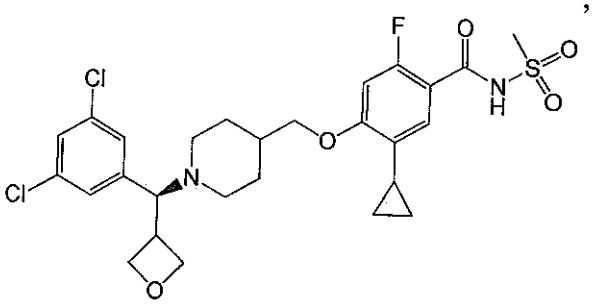
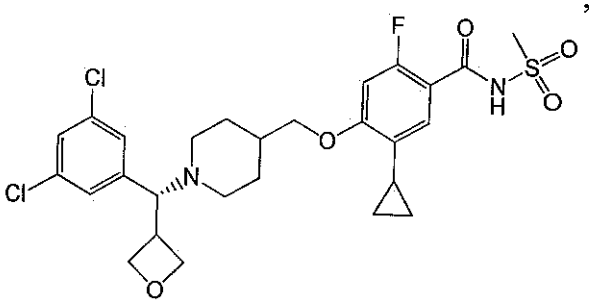
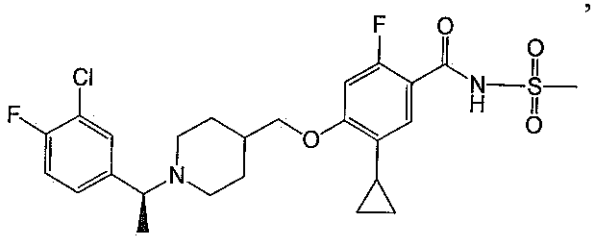
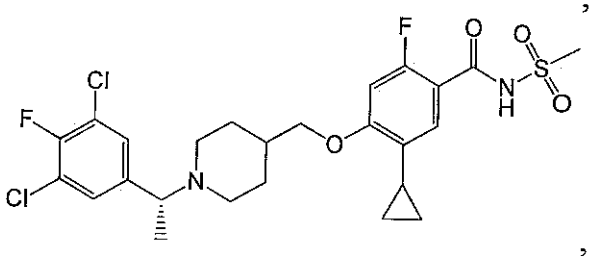

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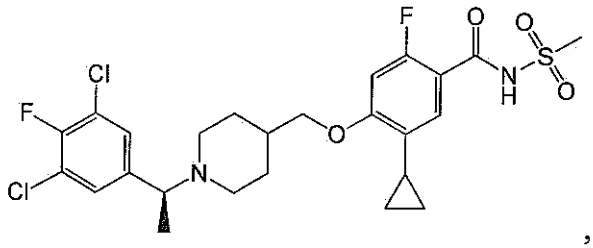

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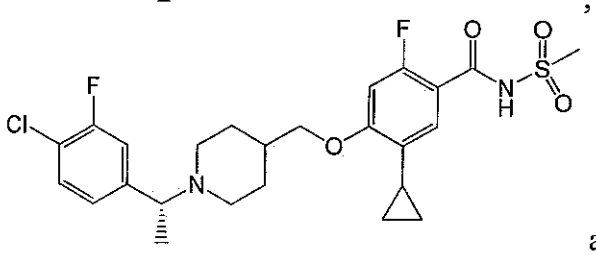

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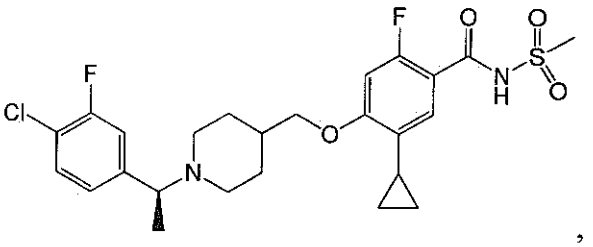

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and salts thereof.

2. A pharmaceutical composition comprising a compound of claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

3. Use of the compound of claim 1 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a disease or condition in a mammal selected from the group consisting of pain, depression, cardiovascular diseases, respiratory diseases, and psychiatric diseases, and combinations thereof.

4. The use of claim 3, wherein said disease or condition is selected from the group consisting of neuropathic pain, inflammatory pain, visceral pain, cancer pain, chemotherapy pain, trauma pain, surgical pain, post-surgical pain, childbirth pain, labor pain, neurogenic bladder, ulcerative colitis, chronic pain, persistent pain, peripherally mediated pain, centrally mediated pain, chronic headache, migraine headache, sinus headache, tension headache, phantom limb pain, dental pain, peripheral nerve injury or a combination thereof.

5. The use of claim 3, wherein said disease or condition is selected from the group consisting of pain associated with HIV, HIV treatment induced neuropathy, trigeminal neuralgia, post-herpetic neuralgia, eudynia, heat sensitivity, tosarcoidosis, irritable bowel syndrome, Crohns disease, pain associated with multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), diabetic neuropathy, peripheral neuropathy, arthritis, rheumatoid arthritis, osteoarthritis, atherosclerosis, paroxysmal dystonia, myasthenia syndromes, myotonia, malignant hyperthermia, cystic fibrosis, pseudoaldosteronism, rhabdomyolysis, hypothyroidism, bipolar depression, anxiety, schizophrenia, sodium channel toxi related illnesses, familial erythromelalgia, primary erythromelalgia, familial rectal pain, cancer, epilepsy, partial and general tonic seizures, restless leg syndrome, arrhythmias, fibromyalgia, neuroprotection under ischaemic conditions cause by stroke or neural trauma, tach-arrhythmias, atrial fibrillation and ventricular fibrillation.

6. Use of a compound of claim 1, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for of treating pruritus in a mammal.

7. Use of a compound of claim 1, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating, but not preventing, pain in a mammal.

8. The use of claim 7, wherein the pain is selected from the group consisting of neuropathic pain, inflammatory pain, visceral pain, cancer pain, chemotherapy pain, trauma pain, surgical pain, post-surgical pain, childbirth pain, labor pain, neurogenic bladder, ulcerative colitis, chronic pain, persistent pain, peripherally mediated pain, centrally mediated pain, chronic headache, migraine headache, sinus headache, tension headache, phantom limb pain, dental pain, peripheral nerve injury or a combination thereof.

9. The use of claim 8, wherein said pain is acute or chronic pain.

10. The use of claim 8, wherein said pain is neuropathic or inflammatory pain.

11. The use of claim 8, wherein the pain is associated with a disease or condition selected from the group consisting of HIV, HIV treatment induced neuropathy, trigeminal neuralgia, post-herpetic neuralgia, eudynia, heat sensitivity, tosarcoidosis, irritable bowel syndrome, Crohns disease, pain associated with multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), diabetic neuropathy, peripheral neuropathy, arthritis, rheumatoid arthritis, osteoarthritis, atherosclerosis, paroxysmal dystonia, myasthenia syndromes, myotonia, malignant hyperthermia, cystic fibrosis, pseudoaldosteronism, rhabdomyolysis, hypothyroidism, bipolar depression, anxiety, schizophrenia, sodium channel toxi related illnesses, familial erythromelalgia, primary erythromelalgia, familial rectal pain, cancer, epilepsy, partial and general tonic seizures, restless leg syndrome, arrhythmias, fibromyalgia, neuroprotection under ischaemic conditions cause by stroke or neural trauma, tach-arrhythmias, atrial fibrillation and ventricular fibrillation.

12. Use of a compound of claim 1, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment or prophylaxis of pain, depression, cardiovascular disease, respiratory disease, or psychiatric disease, or a combinations thereof, in an animal.

13. A compound of claim 1 for the use as a medicament for the treatment of diseases and disorders selected from the group consisting of pain, depression, cardiovascular diseases, respiratory diseases, and psychiatric diseases, or a combination thereof.