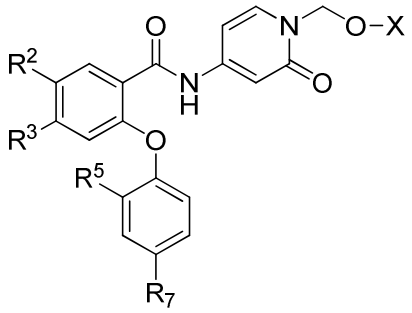
Claims

1. A compound of formula I:



I

wherein, independently for each occurrence:

R^2 and R^3 are independently hydrogen, halogen, or C_1-C_6 alkyl wherein said C_1-C_6 alkyl is substituted with 0-6 halogen;

R^5 is hydrogen, halogen, OH, or C_1-C_6 alkyl wherein said C_1-C_6 alkyl is substituted with 0-6 halogen and wherein up to two non-adjacent CH_2 units of said C_1-C_6 alkyl may be replaced with -O-;

R^7 is hydrogen, halogen, or C_1-C_6 alkyl wherein said C_1-C_6 alkyl is substituted with 0-6 halogen and wherein up to two non-adjacent CH_2 units of said C_1-C_6 alkyl may be replaced with -O-; and

X is $–PO(OH)_2$, $–PO(OH)O^-M^+$, $–PO(O^-)_2•2M^+$, or $–PO(O^-)_2•D^{2+}$; M^+ is a pharmaceutically acceptable monovalent cation; and D^{2+} is a pharmaceutically acceptable divalent cation;

provided that R^2, R^3, R^5, and $R^7$are not simultaneously hydrogen.

2. The compound according to claim 1, wherein R^2 is hydrogen, Cl or CF_3.

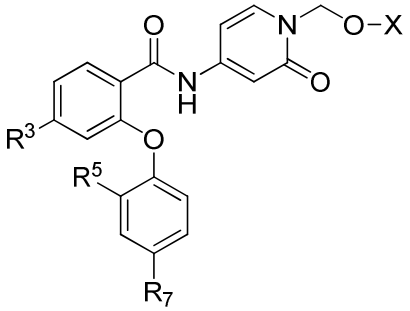
3. The compound according to claim 1 or 2, wherein R^3 is hydrogen, Cl, CF_3 or CF_2CF_3.

4. The compound according to any one of claims 1 to 3, wherein R^5 is hydrogen, Cl, F, CH_3, OCH_3 or OCF_3.

5. The compound according to any one of claims 1 to 4, wherein R^7 is hydrogen, fluorine or OCF_3.

6. The compound according to any one of claims 1 to 5, wherein X is $–PO(OH)_2$.

7. The compound according to claim 1, wherein the compound has formula I-B:



I-B

wherein, independently for each occurrence:

R^3 is halogen, or C_1-C_6 alkyl wherein said C_1-C_6 alkyl is substituted with 0-6 halogen;

R^5 is halogen, OH, or C_1-C_6 alkyl wherein said C_1-C_6 alkyl is substituted with 0-6 halogen and wherein up to two non-adjacent CH_2 units of said C_1-C_6 alkyl may be replaced with -O-;

R^7 is halogen, or C_1-C_6 alkyl wherein said C_1-C_6 alkyl is substituted with 0-6 halogen and wherein up to two non-adjacent CH_2 units of said C_1-C_6 alkyl may be replaced with -O-; and

X is $–PO(OH)_2$, $–PO(OH)O^-M^+$, $–PO(O^-)_2•2M^+$, or $–PO(O^-)_2•D^{2+}$; M^+ is a pharmaceutically acceptable monovalent cation; and D^{2+} is a pharmaceutically acceptable divalent cation.

8. The compound according to claim 7, wherein R^3 is CF_3, Cl or CF_2CF_3.

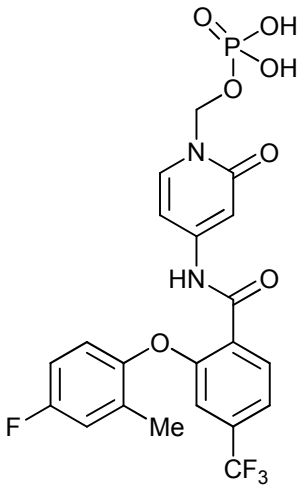
9. The compound according to claim 7 or 8, wherein R^5 is F, CH_3 or OCH_3.

10. The compound according to any one of claims 7 to 9, wherein R^7 is F.

11. The compound according to any one of claims 7 to 10, wherein X is $–PO(OH)_2$.

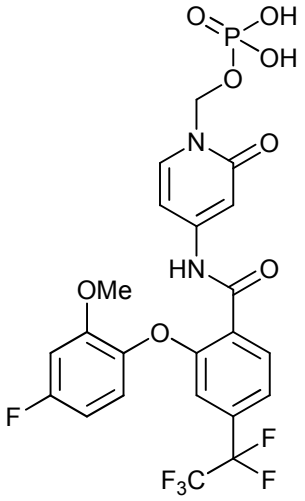
12. The compound according to any one of claims 7 to 10, wherein X is $–PO(OH)O^-M^+$, $-PO(O^-)_2•2M^+$, or $–PO(O^-)_2•D^{2+}$; M^+ is Li^+, Na^+ or K^+ and D^{2+} is Mg^{2+} or Ca^{2+}.

13. The compound according to claim 7, wherein the compound is



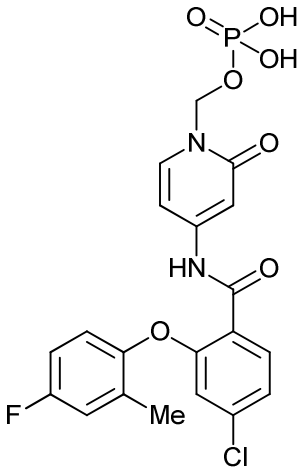
(4-(2-(4-fluoro-2-methylphenoxy)-4-(trifluoromethyl)benzamido)-2-oxopyridin-1(2*H*)-yl)methyl dihydrogen phosphate.

14. The compound according to claim 7, wherein the compound is



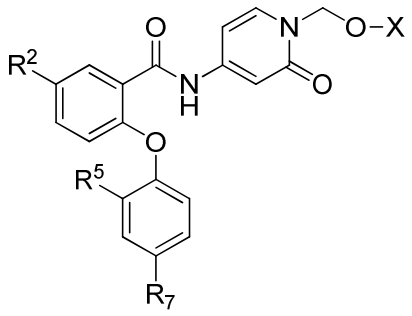
(4-(2-(4-fluoro-2-methoxyphenoxy)-4-(perfluoroethyl)benzamido)-2-oxopyridin-1(2*H*)-yl)methyl dihydrogen phosphate.

15. The compound according to claim 7, wherein the compound is



(4-(4-chloro-2-(4-fluoro-2-methylphenoxy)benzamido)-2-oxopyridin-1(2*H*)-yl)methyl dihydrogen phosphate.

16. The compound according to claim1, wherein the compound has formula **I-A**



I-A

wherein, independently for each occurrence:

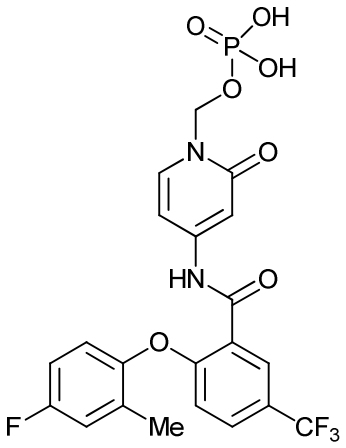
R^2 is halogen, or C_1-C_6 alkyl wherein said C_1-C_6 alkyl is substituted with 0-6 halogen;

R^5 is halogen, OH, or C_1-C_6 alkyl wherein said C_1-C_6 alkyl is substituted with 0-6 halogen and wherein up to two non-adjacent CH_2 units of said C_1-C_6 alkyl may be replaced with -O-;

R^7 is halogen, or C_1-C_6 alkyl wherein said C_1-C_6 alkyl is substituted with 0-6 halogen and wherein up to two non-adjacent CH_2 units of said C_1-C_6 alkyl may be replaced with -O-; and

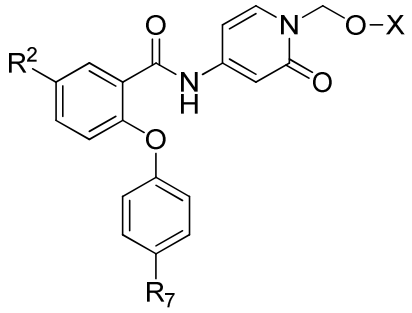
X is $–PO(OH)_2$, $–PO(OH)O^-M^+$, $–PO(O^-)_2•2M^+$, or $–PO(O^-)_2•D^{2+}$; M^+ is a pharmaceutically acceptable monovalent cation; and D^{2+} is a pharmaceutically acceptable divalent cation.

17. The compound according to claim 16, wherein the compound is



(4-(2-(4-fluoro-2-methylphenoxy)-5-(trifluoromethyl)benzamido)-2-oxopyridin-1(2*H*)-yl)methyl dihydrogen phosphate.

18. The compound according to claim1, wherein the compound has formula **I-C**



I-C

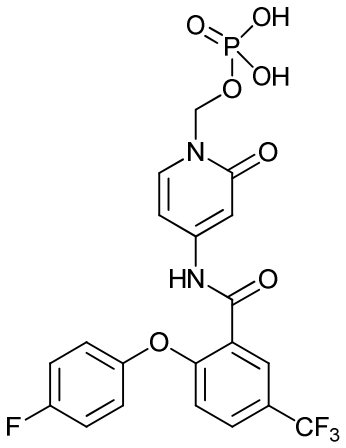
wherein, independently for each occurrence:

R^2 is halogen, or C_1-C_6 alkyl wherein said C_1-C_6 alkyl is substituted with 0-6 halogen;

R^7 is halogen, or C_1-C_6 alkyl wherein said C_1-C_6 alkyl is substituted with 0-6 halogen and wherein up to two non-adjacent CH_2 units of said C_1-C_6 alkyl may be replaced with -O-; and

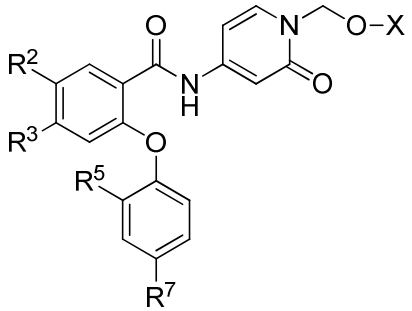
X is $–PO(OH)_2$, $–PO(OH)O^-M^+$, $–PO(O^-)_2•2M^+$, or $–PO(O^-)_2•D^{2+}$; M^+ is a pharmaceutically acceptable monovalent cation; and D^{2+} is a pharmaceutically acceptable divalent cation.

19. The compound according to claim 18, wherein the compound is



(4-(2-(4-fluorophenoxy)-5-(trifluoromethyl)benzamido)-2-oxopyridin-1(2*H*)-yl)methyl dihydrogen phosphate.

20. The compound according to claim 1, wherein the compound has formula **I-G**



I-G

wherein, independently for each occurrence:

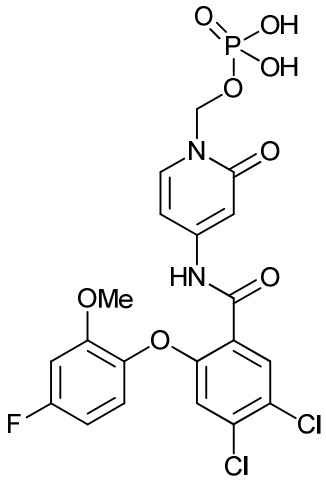
R^2 and R^3 are independently halogen, or C_1-C_6 alkyl wherein said C_1-C_6 alkyl is substituted with 0-6 halogen;

R^5 is halogen, OH, or C_1-C_6 alkyl wherein said C_1-C_6 alkyl is substituted with 0-6 halogen and wherein up to two non-adjacent CH_2 units of said C_1-C_6 alkyl may be replaced with -O-;

R^7 is halogen, or C_1-C_6 alkyl wherein said C_1-C_6 alkyl is substituted with 0-6 halogen and wherein up to two non-adjacent CH_2 units of said C_1-C_6 alkyl may be replaced with -O-; and

X is $–PO(OH)_2$, $–PO(OH)O^-M^+$, $–PO(O^-)_2•2M^+$, or $–PO(O^-)_2•D^{2+}$; M^+ is a pharmaceutically acceptable monovalent cation; and D^{2+} is a pharmaceutically acceptable divalent cation.

21. The compound according to claim 20, wherein the compound is



(4-(4,5-dichloro-2-(4-fluoro-2-methoxyphenoxy)benzamido)-2-oxopyridin-1(2*H*)-yl)methyl dihydrogen phosphate.

22. An amorphous Form C of (4-(2-(4-fluoro-2-methylphenoxy)-4-(trifluoromethyl)benzamido)-2-oxopyridin-1(2*H*)-yl)methyl dihydrogen phosphate.

23. The amorphous Form C of claim 22, characterized by an X-ray powder diffraction pattern, as measured by Cu K_α radiation, substantially similar to Figure 5.

24. A crystalline Form B of (4-(2-(4-fluoro-2-methylphenoxy)-4-(trifluoromethyl)benzamido)-2-oxopyridin-1(2*H*)-yl)methyl dihydrogen phosphate, which is characterized by an X-ray powder diffraction pattern (XRPD) comprising approximate peak positions (degrees 2 theta $\pm$ 0.2) when measured using Cu K_α radiation, selected from the group consisting of 22.2, 23.5 and 26.3, when the XRPD is collected from about 4 to about 40 degrees 2 theta (2 θ).

25. The crystalline Form B of claim 24, characterized by an X-ray powder diffraction pattern, as measured by Cu K_α radiation, substantially similar to Figure 2.

26. The crystalline Form B of claim 25, further characterized by an endothermic peak having an onset temperature at about 210^{o}C degrees as measured by differential scanning calorimetry in which the temperature is scanned at about 10^{o}C per minute.

27. A process for preparing crystalline Form B of claim 24, comprising contacting (4-(2-(4-fluoro-2-methylphenoxy)-4-(trifluoromethyl)benzamido)-2-oxopyridin-1(2*H*)-yl)methyl dihydrogen phosphate with water, an organic solvent, a mixture of organic solvents or a mixture of an organic solvent and water at a suitable temperature, stirring for up to 4 weeks and isolating the solid.

28. A pharmaceutical composition comprising the compound according to any one of claims 1 to 21 and 39, the compound or salt any one of claims 45-51, the amorphous Form C of claim 22 or 23, or the crystalline Form B of any one of claims 24, 25, and 26, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

29. A compound of any one of claims 1 to 21 and 39, a compound or salt of any one of claims 45-51, an amorphous Form C of claim 22 or 23, a crystalline Form B of any one of claims 24, 25, and 26, or a pharmaceutical composition according to claim 28 for use in treating or lessening the severity of chronic pain, gut pain, neuropathic pain, musculoskeletal pain, acute pain, inflammatory pain, cancer pain, idiopathic pain, postsurgical pain, visceral pain, multiple sclerosis, Charcot-Marie-Tooth syndrome, incontinence, pathological cough, or cardiac arrhythmia in a subject, wherein said treating or lessening the severity of chronic pain, gut pain, neuropathic pain, musculoskeletal pain, acute pain, inflammatory pain, cancer pain, idiopathic pain, postsurgical pain, visceral pain, multiple sclerosis, Charcot-Marie-Tooth syndrome, incontinence, pathological cough, or cardiac arrhythmia comprises inhibiting a voltage-gated sodium channel in the subject.

30. The compound, compound or salt, amorphous Form C, crystalline Form B, or pharmaceutical composition of claim 29, wherein the voltage-gated sodium channel is $Na_V1.8$.

31. A compound of any one of claims 1 to 21 and 39, a compound or salt of any one of claims 45-51, an amorphous Form C of claim 22 or 23, a crystalline Form B of any one of claims 24, 25, and 26, or a pharmaceutical composition of claim 28 for use in treating or lessening the severity of chronic pain, gut pain, neuropathic pain, musculoskeletal pain, acute pain, inflammatory pain, cancer pain, idiopathic pain, postsurgical pain, visceral pain, multiple sclerosis, Charcot-Marie-Tooth syndrome, incontinence, pathological cough, or cardiac arrhythmia in a subject.

32. The compound, compound or salt, amorphous Form C, crystalline Form B, or pharmaceutical composition for use according to claim 31, wherein said use comprises treating or lessening the severity of gut pain in a subject, wherein the gut pain comprises inflammatory bowel disease pain, Crohn's disease pain or interstitial cystitis pain.

33. The compound, compound or salt, amorphous Form C, crystalline Form B, or pharmaceutical composition for use according to claim 31, wherein said use comprises treating or lessening the severity of neuropathic pain in a subject, wherein the neuropathic pain comprises post-herpetic neuralgia, diabetic neuralgia, painful HIV-associated sensory neuropathy, trigeminal neuralgia, burning mouth syndrome, post-amputation pain, phantom pain, painful neuroma, traumatic neuroma, Morton's neuroma, nerve entrapment injury, spinal stenosis,

carpal tunnel syndrome, radicular pain, sciatica pain, nerve avulsion injury, brachial plexus avulsion injury, complex regional pain syndrome, drug therapy induced neuralgia, cancer chemotherapy induced neuralgia, anti-retroviral therapy induced neuralgia, post spinal cord injury pain, idiopathic small-fiber neuropathy, idiopathic sensory neuropathy or trigeminal autonomic cephalalgia.

34. The compound, compound or salt, amorphous Form C, crystalline Form B, or pharmaceutical composition for use according to claim 31, wherein said use comprises treating or lessening the severity of neuropathic pain in a subject, wherein the neuropathic pain comprises trigeminal neuralgia.

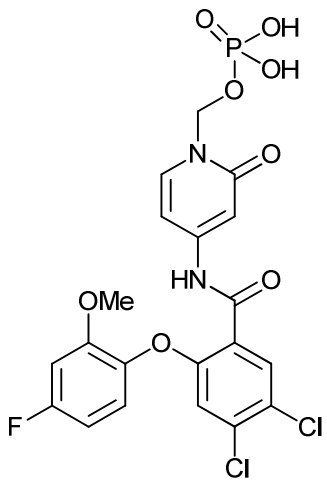
35. The compound, compound or salt, amorphous Form C, crystalline Form B, or pharmaceutical composition for use according to claim 31, wherein said use comprises treating or lessening the severity of musculoskeletal pain in a subject, wherein the musculoskeletal pain comprises osteoarthritis pain, back pain, cold pain, burn pain or dental pain.

36. The compound, compound or salt, amorphous Form C, crystalline Form B, or pharmaceutical composition for use according to claim 31, wherein said use comprises treating or lessening the severity of inflammatory pain in a subject, wherein the inflammatory pain comprises rheumatoid arthritis pain.

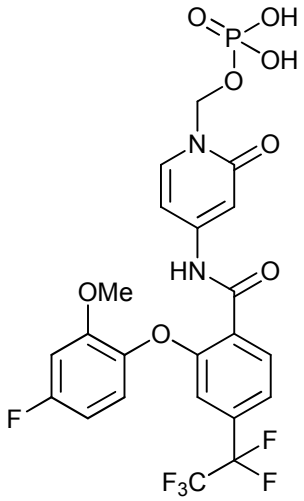
37. The compound, compound or salt, amorphous Form C, crystalline Form B, or pharmaceutical composition for use according to claim 31, wherein said use comprises treating or lessening the severity of idiopathic pain in a subject, wherein the idiopathic pain comprises fibromyalgia pain.

38. The compound, compound or salt, amorphous Form C, crystalline Form B, or pharmaceutical composition for use according to any one of claims 31 to 37, 40 to 44, 52 and 54, wherein said subject is to be treated with one or more additional therapeutic agents administered concurrently with, prior to, or subsequent to treatment with the compound, amorphous Form C, crystalline Form B, or pharmaceutical composition.

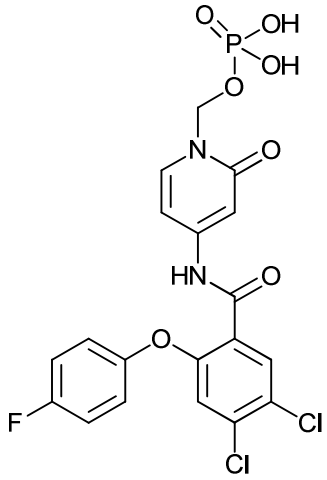
39. A compound selected from the group consisting of:



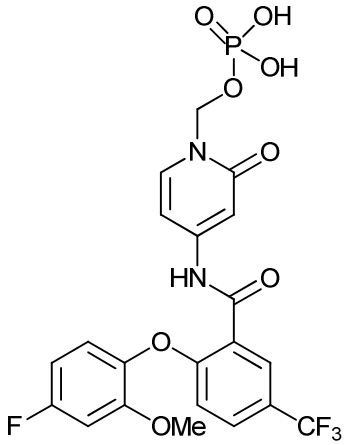
(4-(4,5-dichloro-2-(4-fluoro-2-methoxyphenoxy)benzamido)-2-oxopyridin-1(2*H*)-yl)methyl dihydrogen phosphate;



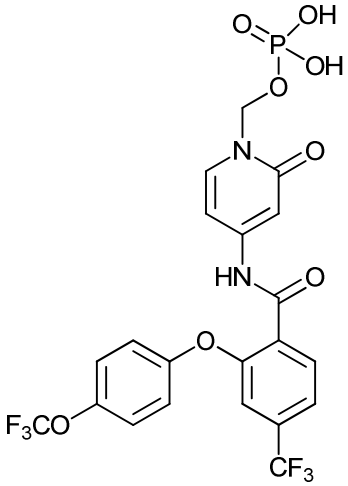
(4-(2-(4-fluoro-2-methoxyphenoxy)-4-(perfluoroethyl)benzamido)-2-oxopyridin-1(2*H*)-yl)methyl dihydrogen phosphate;



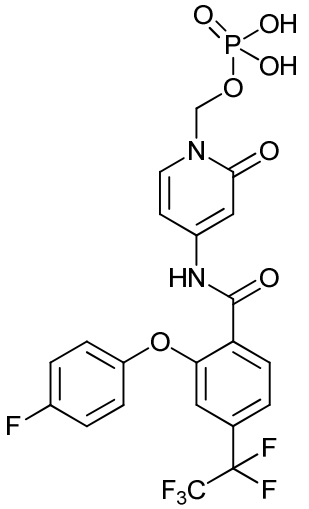
(4-(4,5-dichloro-2-(4-fluorophenoxy)benzamido)-2-oxopyridin-1(2*H*)-yl)methyl dihydrogen phosphate;



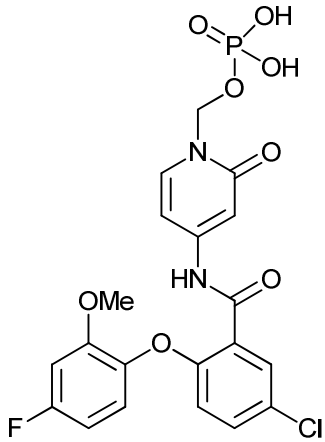
(4-(2-(4-fluoro-2-methoxyphenoxy)-5-(trifluoromethyl)benzamido)-2-oxopyridin-1(2*H*)-yl)methyl dihydrogen phosphate;



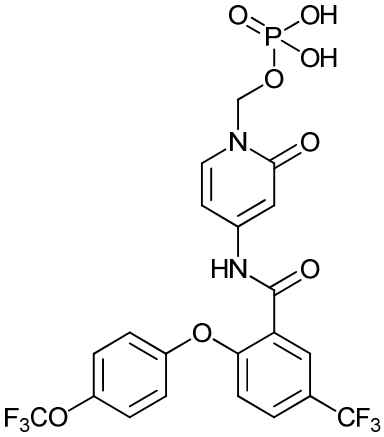
(2-oxo-4-(2-(4-(trifluoromethoxy)phenoxy)-4-(trifluoromethyl)benzamido)pyridin-1(2*H*)-yl)methyl dihydrogen phosphate;



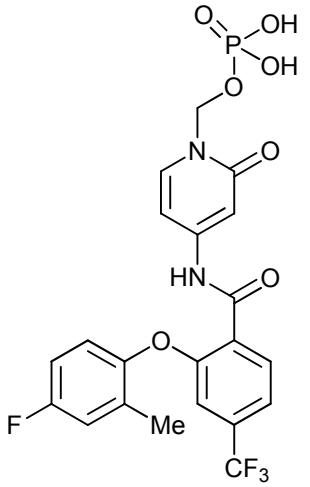
(4-(2-(4-fluorophenoxy)-4-(perfluoroethyl)benzamido)-2-oxopyridin-1(2*H*)-yl)methyl dihydrogen phosphate;



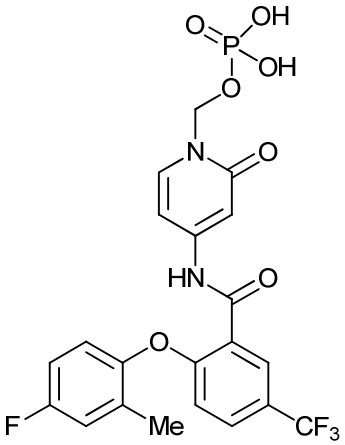
(4-(5-chloro-2-(4-fluoro-2-methoxyphenoxy)benzamido)-2-oxopyridin-1(2*H*)-yl)methyl dihydrogen phosphate;



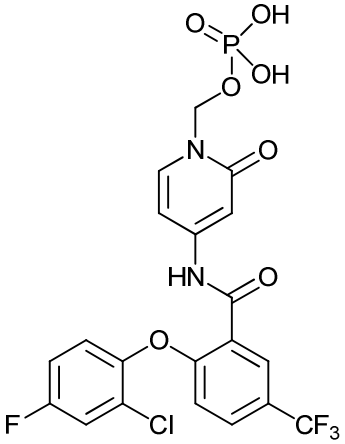
(2-oxo-4-(2-(4-(trifluoromethoxy)phenoxy)-5-(trifluoromethyl)benzamido)pyridin-1(2*H*)-yl)methyl dihydrogen phosphate;



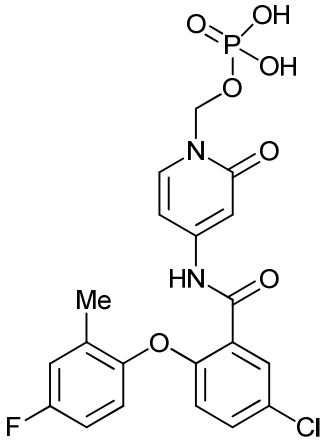
(4-(2-(4-fluoro-2-methylphenoxy)-4-(trifluoromethyl)benzamido)-2-oxopyridin-1(2*H*)-yl)methyl dihydrogen phosphate;



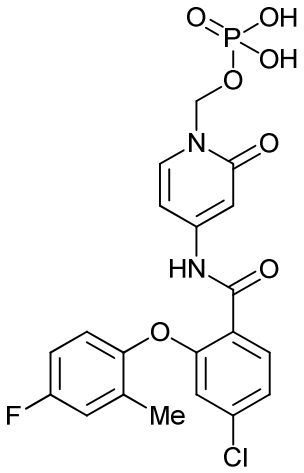
(4-(2-(4-fluoro-2-methylphenoxy)-5-(trifluoromethyl)benzamido)-2-oxopyridin-1(2*H*)-yl)methyl dihydrogen phosphate;



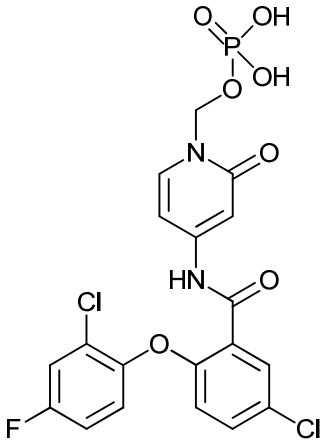
(4-(2-(2-chloro-4-fluorophenoxy)-5-(trifluoromethyl)benzamido)-2-oxopyridin-1(2*H*)-yl)methyl dihydrogen phosphate;



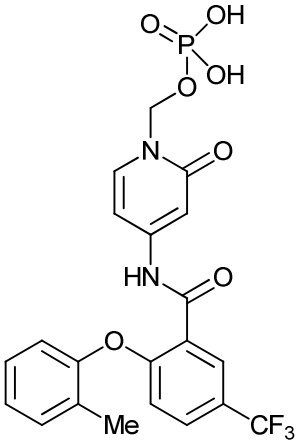
(4-(5-chloro-2-(4-fluoro-2-methylphenoxy)benzamido)-2-oxopyridin-1(2*H*)-yl)methyl dihydrogen phosphate;



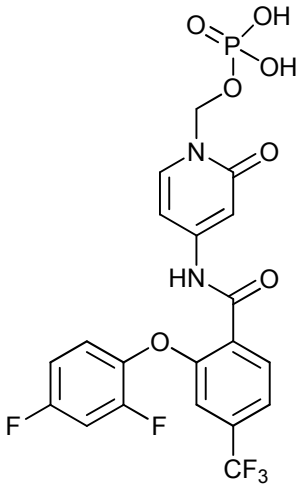
(4-(4-chloro-2-(4-fluoro-2-methylphenoxy)benzamido)-2-oxopyridin-1(2*H*)-yl)methyl dihydrogen phosphate;



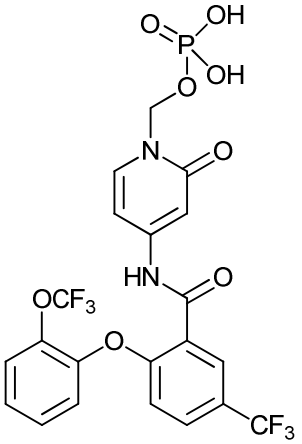
(4-(5-chloro-2-(2-chloro-4-fluorophenoxy)benzamido)-2-oxopyridin-1(2*H*)-yl)methyl dihydrogen phosphate;



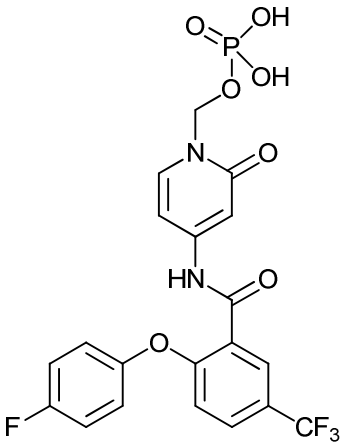
(2-oxo-4-(2-(o-tolyloxy)-5-(trifluoromethyl)benzamido)pyridin-1(2*H*)-yl)methyl dihydrogen phosphate;



(4-(2-(2,4-difluorophenoxy)-4-(trifluoromethyl)benzamido)-2-oxopyridin-1(2*H*)-yl)methyl dihydrogen phosphate;



(2-oxo-4-(2-(2-(trifluoromethoxy)phenoxy)-5-(trifluoromethyl)benzamido)pyridin-1(2*H*)-yl)methyl dihydrogen phosphate; and



(4-(2-(4-fluorophenoxy)-5-(trifluoromethyl)benzamido)-2-oxopyridin-1(2*H*)-yl)methyl dihydrogen phosphate.

40. The compound, compound or salt, amorphous Form C, crystalline Form B, or pharmaceutical composition for use according to claim 33, wherein the neuropathic pain comprises idiopathic small-fiber neuropathy.

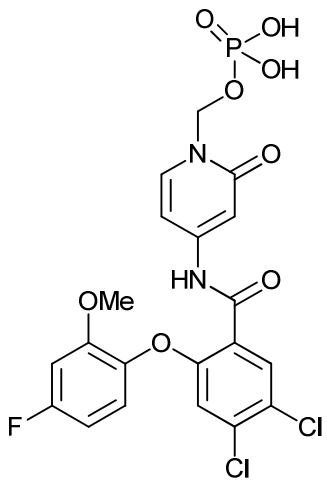
41. The compound, compound or salt, amorphous Form C, crystalline Form B, or pharmaceutical composition for use according to claim 35, wherein the musculoskeletal pain comprises osteoarthritis pain.

42. The compound, compound or salt, amorphous Form C, crystalline Form B, or pharmaceutical composition for use according to claim 31, wherein said use comprises treating or lessening the severity of acute pain in a subject.

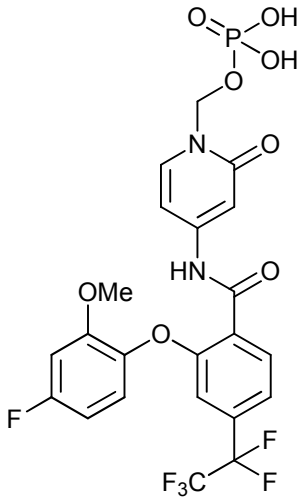
43. The compound, compound or salt, amorphous Form C, crystalline Form B, or pharmaceutical composition for use according to claim 42, wherein the acute pain comprises acute post-operative pain.

44. The compound, compound or salt, amorphous Form C, crystalline Form B, or pharmaceutical composition for use according to claim 31, wherein said use comprises treating or lessening the severity of postsurgical pain in a subject.

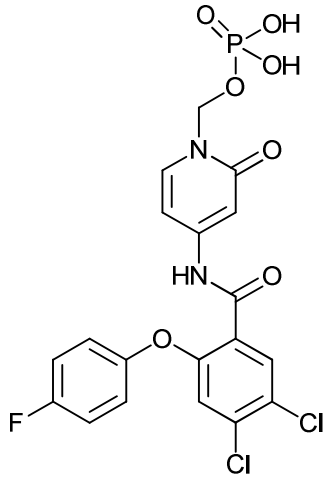
45. A compound selected from the group consisting of:



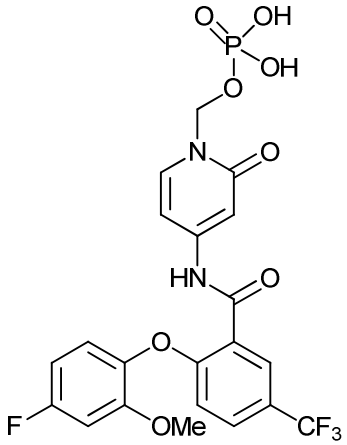
(4-(4,5-dichloro-2-(4-fluoro-2-methoxyphenoxy)benzamido)-2-oxopyridin-1(2*H*)-yl)methyl dihydrogen phosphate;



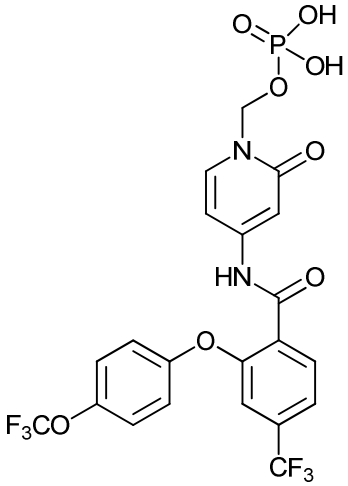
(4-(2-(4-fluoro-2-methoxyphenoxy)-4-(perfluoroethyl)benzamido)-2-oxopyridin-1(2*H*)-yl)methyl dihydrogen phosphate;



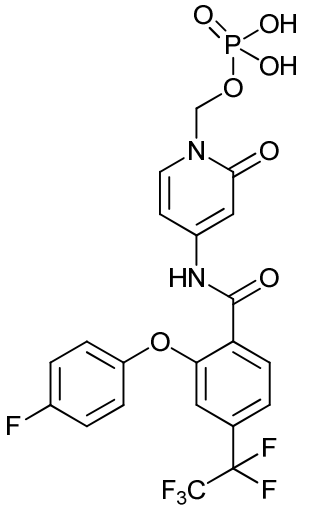
(4-(4,5-dichloro-2-(4-fluorophenoxy)benzamido)-2-oxopyridin-1(2*H*)-yl)methyl dihydrogen phosphate;



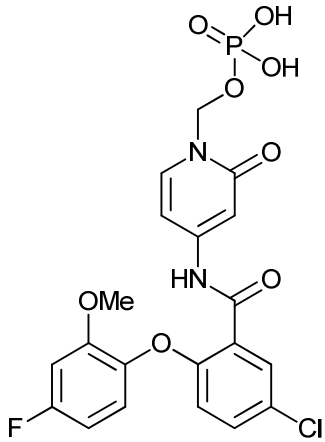
(4-(2-(4-fluoro-2-methoxyphenoxy)-5-(trifluoromethyl)benzamido)-2-oxopyridin-1(2*H*)-yl)methyl dihydrogen phosphate;



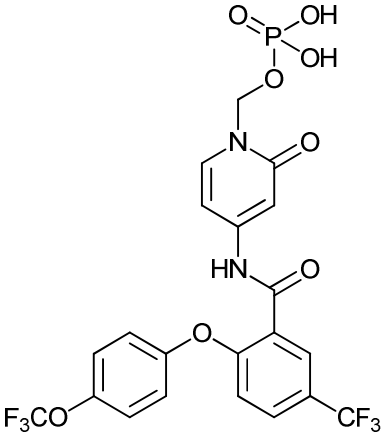
(2-oxo-4-(2-(4-(trifluoromethoxy)phenoxy)-4-(trifluoromethyl)benzamido)pyridin-1(2*H*)-yl)methyl dihydrogen phosphate;



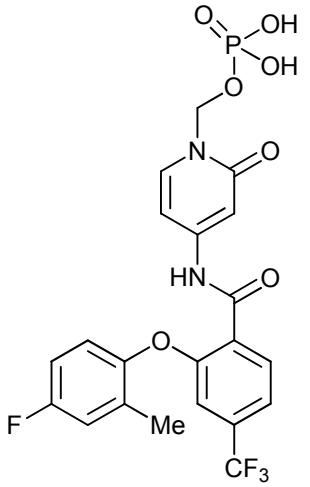
(4-(2-(4-fluorophenoxy)-4-(perfluoroethyl)benzamido)-2-oxopyridin-1(2*H*)-yl)methyl dihydrogen phosphate;



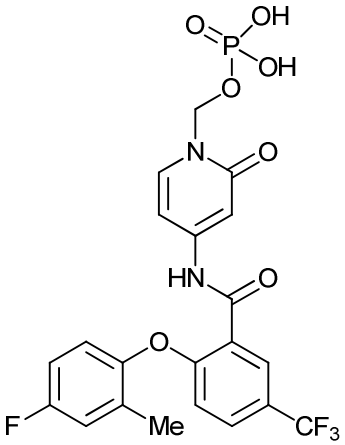
(4-(5-chloro-2-(4-fluoro-2-methoxyphenoxy)benzamido)-2-oxopyridin-1(2*H*)-yl)methyl dihydrogen phosphate;



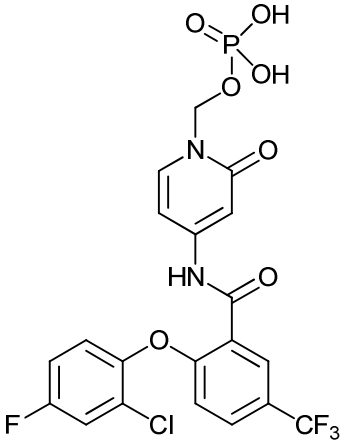
(2-oxo-4-(2-(4-(trifluoromethoxy)phenoxy)-5-(trifluoromethyl)benzamido)pyridin-1(2*H*)-yl)methyl dihydrogen phosphate;



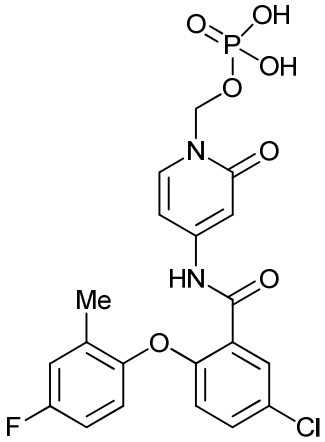
(4-(2-(4-fluoro-2-methylphenoxy)-4-(trifluoromethyl)benzamido)-2-oxopyridin-1(2*H*)-yl)methyl dihydrogen phosphate;



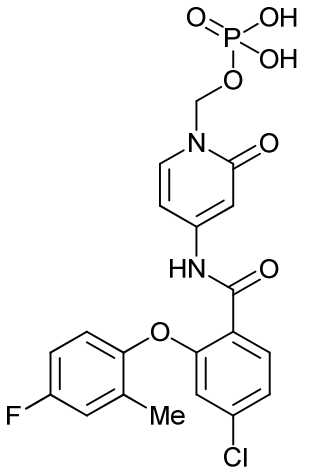
(4-(2-(4-fluoro-2-methylphenoxy)-5-(trifluoromethyl)benzamido)-2-oxopyridin-1(2*H*)-yl)methyl dihydrogen phosphate;



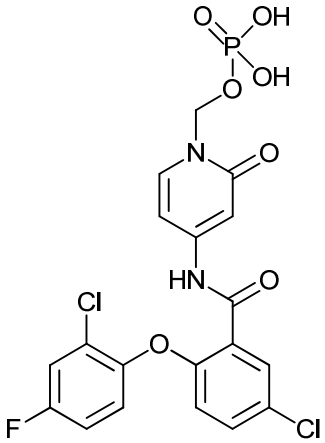
(4-(2-(2-chloro-4-fluorophenoxy)-5-(trifluoromethyl)benzamido)-2-oxopyridin-1(2*H*)-yl)methyl dihydrogen phosphate;



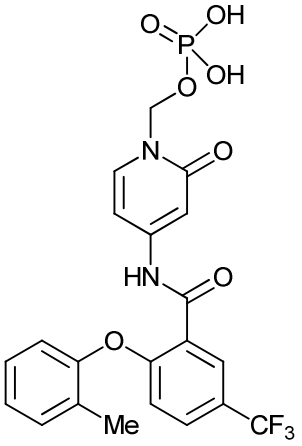
(4-(5-chloro-2-(4-fluoro-2-methylphenoxy)benzamido)-2-oxopyridin-1(2*H*)-yl)methyl dihydrogen phosphate;



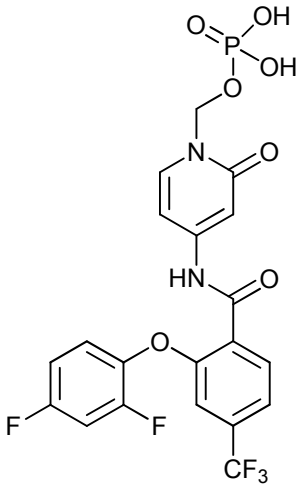
(4-(4-chloro-2-(4-fluoro-2-methylphenoxy)benzamido)-2-oxopyridin-1(2*H*)-yl)methyl dihydrogen phosphate;



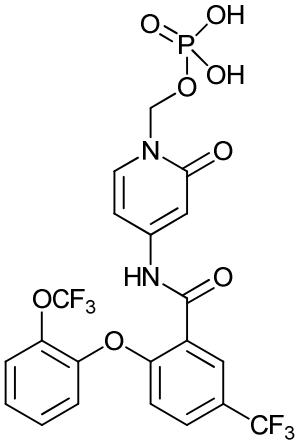
(4-(5-chloro-2-(2-chloro-4-fluorophenoxy)benzamido)-2-oxopyridin-1(2*H*)-yl)methyl dihydrogen phosphate;



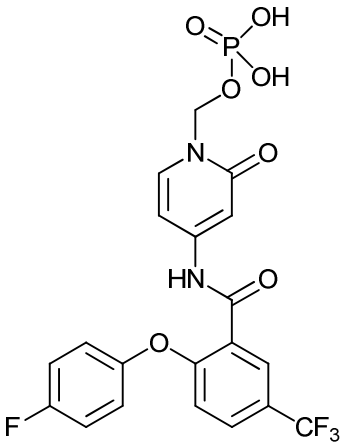
(2-oxo-4-(2-(o-tolyloxy)-5-(trifluoromethyl)benzamido)pyridin-1(2*H*)-yl)methyl dihydrogen phosphate;



(4-(2-(2,4-difluorophenoxy)-4-(trifluoromethyl)benzamido)-2-oxopyridin-1(2*H*)-yl)methyl dihydrogen phosphate;



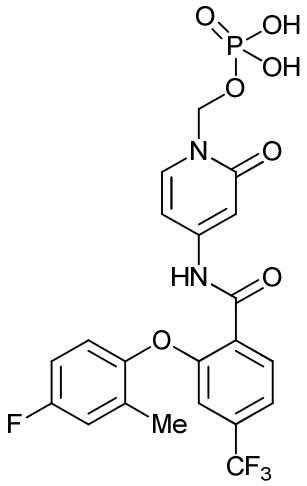
(2-oxo-4-(2-(2-(trifluoromethoxy)phenoxy)-5-(trifluoromethyl)benzamido)pyridin-1(2*H*)-yl)methyl dihydrogen phosphate; and



(4-(2-(4-fluorophenoxy)-5-(trifluoromethyl)benzamido)-2-oxopyridin-1(2*H*)-yl)methyl dihydrogen phosphate;

or a pharmaceutically acceptable salt thereof.

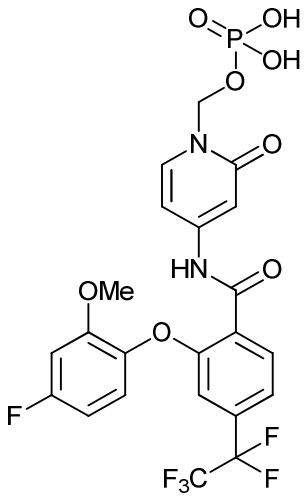
46. A compound that is



(4-(2-(4-fluoro-2-methylphenoxy)-4-(trifluoromethyl)benzamido)-2-oxopyridin-1(2*H*)-yl)methyl dihydrogen phosphate;

or a pharmaceutically acceptable salt thereof.

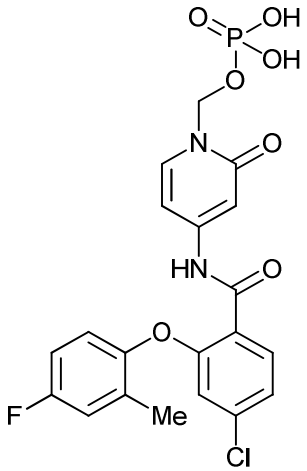
47. A compound that is



(4-(2-(4-fluoro-2-methoxyphenoxy)-4-(perfluoroethyl)benzamido)-2-oxopyridin-1(2*H*)-yl)methyl dihydrogen phosphate;

or a pharmaceutically acceptable salt thereof.

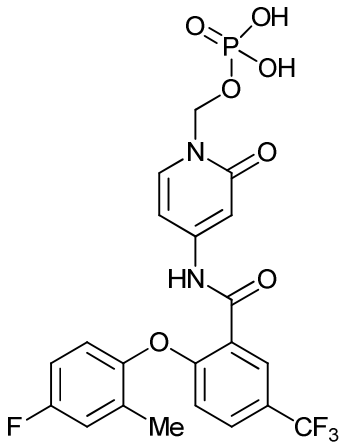
48. A compound that is



(4-(4-chloro-2-(4-fluoro-2-methylphenoxy)benzamido)-2-oxopyridin-1(2*H*)-yl)methyl dihydrogen phosphate;

or a pharmaceutically acceptable salt thereof.

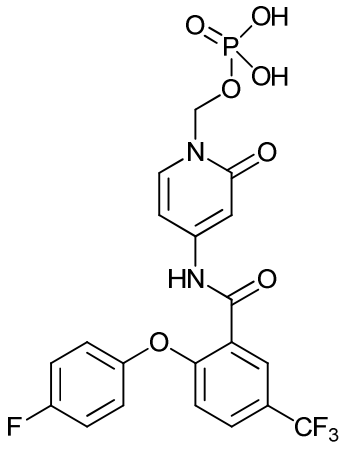
49. A compound that is



(4-(2-(4-fluoro-2-methylphenoxy)-5-(trifluoromethyl)benzamido)-2-oxopyridin-1(2*H*)-yl)methyl dihydrogen phosphate;

or a pharmaceutically acceptable salt thereof.

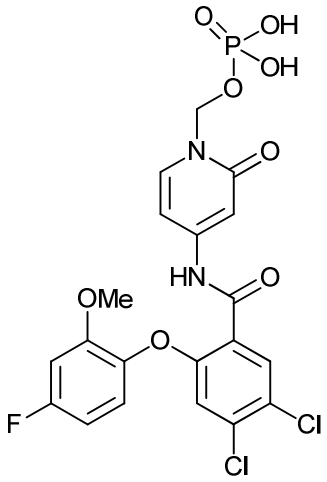
50. A compound that is



(4-(2-(4-fluorophenoxy)-5-(trifluoromethyl)benzamido)-2-oxopyridin-1(2*H*)-yl)methyl dihydrogen phosphate;

or a pharmaceutically acceptable salt thereof.

51. A compound that is



(4-(4,5-dichloro-2-(4-fluoro-2-methoxyphenoxy)benzamido)-2-oxopyridin-1(2*H*)-yl)methyl dihydrogen phosphate;

or a pharmaceutically acceptable salt thereof.

52. A compound of any one of claims 1 to 21 and 39, a compound or salt of any one of claims 45-51, an amorphous Form C of claim 22 or 23, a crystalline Form B of any one of claims 24, 25, and 26, or a pharmaceutical composition of claim 28 for use as a medicament.

53. The compound, compound or salt, amorphous Form C, crystalline Form B, or pharmaceutical composition for use according to claim 33, wherein the neuropathic pain comprises post-herpetic neuralgia.

54. The compound, compound or salt, amorphous Form C, crystalline Form B, or pharmaceutical composition for use according to claim 31, wherein said use comprises treating or lessening the severity of visceral pain in a subject.