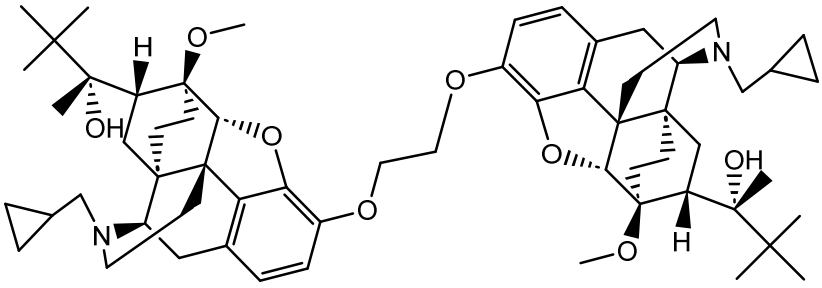
WHAT IS CLAIMED IS:

1. A method of treating a disease in a human subject in need thereof, comprising orally administering to the subject a therapeutically effective amount of a buprenorphine dimer represented by formula (I):



(I),

or a pharmaceutically acceptable salt thereof, wherein

the therapeutically effective amount of the buprenorphine dimer is a total daily dose of at least about 100 mg per day on a salt-free and anhydrous basis; and

the administering achieves a plasma concentration of at least about 700 ng/mL in the subject.

2. The method of claim 1, wherein the buprenorphine dimer is in a neutral form, represented by formula (I).

3. The method of claim 1 or 2, wherein the therapeutically effective amount of the buprenorphine dimer is a total daily dose of at least about 200 mg per day on a salt-free and anhydrous basis.

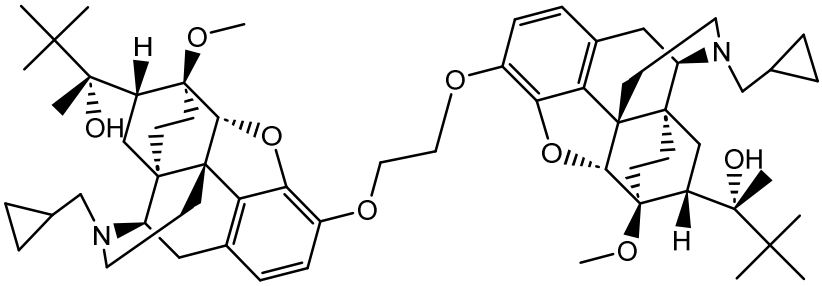
4. The method any one of claims 1-3, wherein the buprenorphine dimer is administered once daily; or

wherein the buprenorphine dimer is administered twice daily.

5. The method of any one of claims 1-4, wherein the disease is chronic pain; or

wherein the disease is Irritable Bowel Syndrome with Diarrhea (IBS-D).

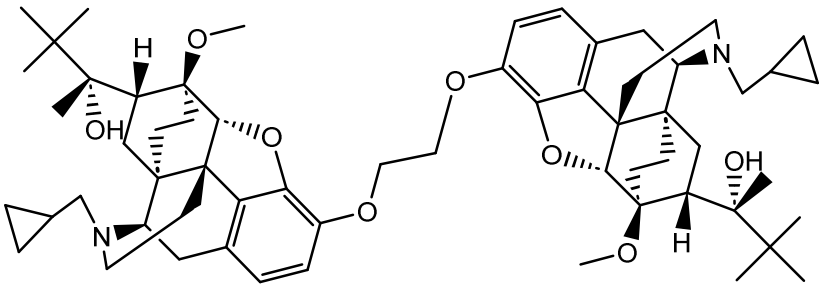
6. A method of treating a chronic pain in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a buprenorphine dimer represented by formula (I):



(I),

or a pharmaceutically acceptable salt thereof, wherein the buprenorphine dimer is administered orally.

7. A method of treating a chronic pain in a subject in need thereof, comprising administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of a buprenorphine dimer in a neutral form represented by formula (I):



(I),

wherein the pharmaceutical composition is administered orally.

8. The method of claim 6 or 7, wherein the chronic pain is a nociceptive pain, a neuropathic pain, or a combination thereof; or

wherein the chronic pain is a peripheral chronic pain; or

wherein the chronic pain is peripheral neuropathic pain.

9. The method of any one of claims **6** to **8**, wherein:

(a) the subject has a sickle cell disease (SCD), cancer and/or under chemotherapy, HIV, diabetes, shingles, a traumatic injury, a surgery, an amputation, a burn, or a combination thereof; and/or the subject has or had a coronavirus disease;

and/or

(b) wherein the chronic pain is any one of 1) to 10):

1) associated with a sickle cell disease (SCD) in the subject;

2) a chemotherapeutic induced neuropathic pain in the subject who has cancer and under chemotherapy;

3) HIV sensory neuropathy;

4) a diabetic neuropathy pain;

5) a post-herpetic neuralgia in the subject who has or had shingles;

6) a post-trauma chronic pain;

7) a post-surgical pain;

8) a post-amputation pain;

9) a post-burn pain; and

10) associated with a long-term effect in the subject who had a coronavirus disease.

10. The method of any one of claims **6** to **9**, wherein the therapeutically effective amount is a total daily dosage of from about 50 mg to about 800 mg, from about 50 mg to about 700 mg, from about 50 mg to about 600 mg, from about 50 mg to about 500 mg, from about 50 mg to about 400 mg, from about 50 mg to about 300 mg, or from about 50 mg to about 250 mg of the buprenorphine dimer on a salt-free and anhydrous basis; or

wherein the therapeutically effective amount is a total daily dosage of about 100 mg of the buprenorphine dimer on a salt-free and anhydrous basis; or

wherein the therapeutically effective amount is a total daily dosage of about 200 mg of the buprenorphine dimer on a salt-free and anhydrous basis.

11. The method of any one of claims **6** to **10**, wherein the buprenorphine dimer is administered once, twice, three times, or four times daily; or

wherein the buprenorphine dimer is administered once daily; or

wherein the buprenorphine dimer is administered twice daily.

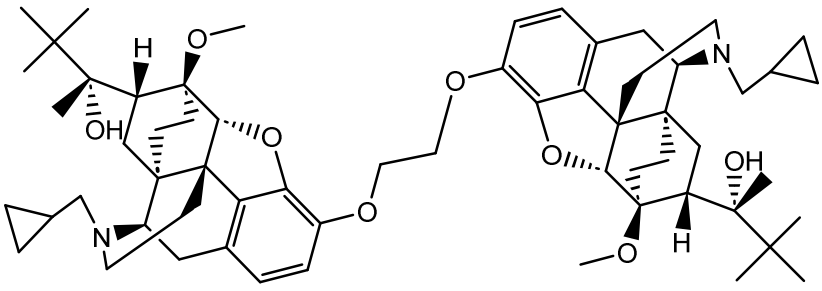
12. The method of any one of claims **7** to **11**, wherein the pharmaceutical composition comprising the buprenorphine dimer is a tablet; or

wherein the tablet comprising buprenorphine dimer is an immediate-release tablet.

13. The method of any one of claims **6** to **12**, wherein the therapeutically effective amount of the buprenorphine dimer reduces the chronic pain, measured by one or more criteria selected from the group consisting of:

1) a reduced monthly average score on a 0-10 Likert scale over past 1, 3, or 6 months, relative to a monthly average score prior to the treating;
2) a reduced monthly average score of characteristic pain intensity and/or disability over past 1, 3, or 6 months, relative to a monthly average score prior to the treating; and
3) a reduced pain severity over past 1, 3, or 6 months relative to a pain severity prior to the treating, wherein the reduced pain severity is selected from the group consisting of:
   i) from Grade 4 (high disability-severely limiting) to any one of Grade 3 (high disability-moderately limiting), Grade 2 (low disability-high intensity), Grade 1 (low disability-low intensity), and Grade 0 (no pain);
   ii) from Grade 3 to any one of Grade 2, Grade 1, and Grand 0;
   iii) from Grade 2 to Grade 1 or Grade 0; and
   iv) from Grade 1 to Grade 0.

14. A method of treating Irritable Bowel Syndrome with Diarrhea (IBS-D) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a buprenorphine dimer represented by formula (I):



(I),

or a pharmaceutically acceptable salt thereof, wherein the subject has 7α-hydroxy-4-cholesten-3-one (C4) at a level of no more than 50 milligrams per deciliter (mg/dL) in blood.

15. The method of claim 14, wherein

(a) the subject has a C4 level of from about 15 mg/dL to about 45 mg/dL in blood; and/or

(b) prior to the treating, the subject has worst abdominal pain over past 24 hours in a weekly average score of more than 3, based on a 1-10 numeric rating scale; and/or

(c) prior to the treating, the subject has stool consistency in a weekly average score of greater than 5, as assessed via Bristol Stool Form Score (BSFS); and/or

(d) wherein the subject has cholecystectomy.

16. The method of claim **14** or **15**, wherein, during the treating, the subject receives loperamide; or

wherein, during the treating, the subject receives loperamide in a total dosage of no more than any one of 8 mg over 24 hours, 14 mg over 48 hours, and 22 mg over 7 days.

17. The method of claim **14** or **15**, wherein, during the treating, the subject does not receive loperamide.

18. The method of any one of claims **14** to **16**, wherein the therapeutically effective amount of the buprenorphine dimer

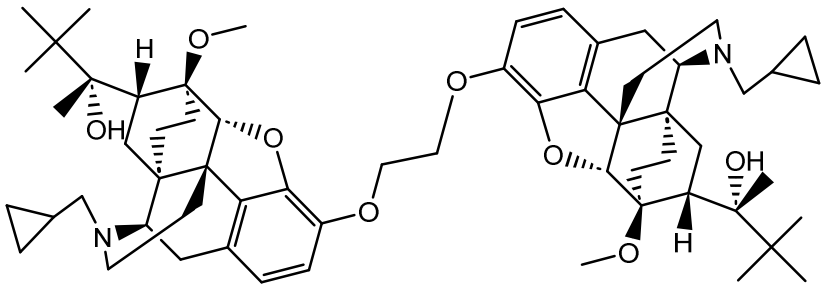
1) reduces a weekly average score of worst abdominal pain over past 24 hours by at least 30%, relative to the weekly average score prior to the treating; and/or

2) improves stool consistency, measured by i) a reduced average BSFS score to less than 6, or ii) an absence of a bowel movement provided that features of 1) are met.

19. The method of any one of claims **6** to **18**, wherein the subject is human; or

wherein the human is an adult in an age of at least 18 years old.

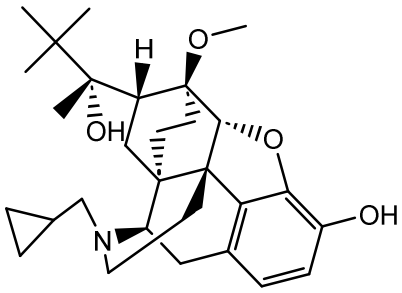
20. A process for preparing a buprenorphine dimer in a neutral form, represented by formula (I):



(I),

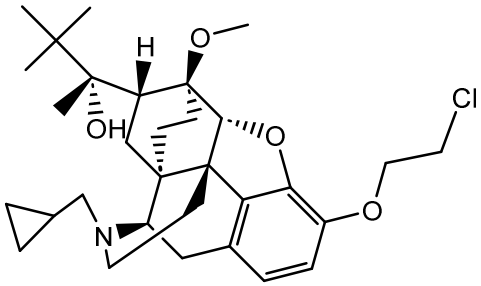
comprising:

a) combining buprenorphine or a salt thereof, represented by the formula:



,

a first inorganic base, water, and a first phase-transfer agent in 1,2-dichloroethane to form a compound of formula (II):



(II); and

b) combining the compound of formula (II), buprenorphine or a salt thereof, a second inorganic base, water, and a second phase-transfer agent in an aprotic solvent to provide the buprenorphine dimer of formula (I) in a neutral form.

21. The process of claim **20**, wherein the buprenorphine in steps a) and b) are each a buprenorphine HCl salt.

22. The process of claim **20** or **21**, wherein the first and second inorganic bases are each an alkali hydroxide independently selected from the group consisting of LiOH, NaOH, KOH, and CsOH; or

wherein the first and second inorganic bases are each NaOH.

23. The process of any one of claims **20** to **22**, wherein the first and second phase-transfer agents are each independently a quaternary ammonium salt; or

wherein the first and second phase-transfer agents are each tetrabutylammonium hydroxide; or

wherein, wherein the first and second phase-transfer agents are each tetrabutylammonium hydroxide and in step a), tetrabutylammonium hydroxide is present in an amount of about 5% by weight, based on buprenorphine or the salt thereof; and/or in step b),

tetrabutylammonium hydroxide is present in an amount of about 0.3 equivalents, relative to the compound of formula (II).

24. The process of any one of claims **20** to **23**, wherein, in step b), buprenorphine or the salt thereof is present in an amount of about 0.8 equivalents, relative to the compound of formula (II); and/or

wherein, in step b), the aprotic solvent is toluene.

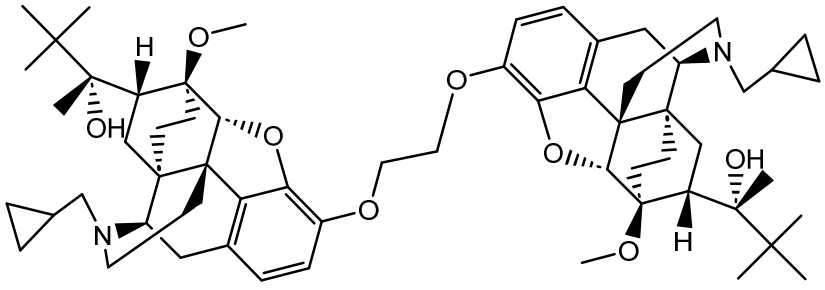
25. The process of any one of claims **20** to **24**, wherein step a) is conducted at a temperature of from about 50°C to about 70°C; and/or step b) is conducted at a temperature of from about 70°C to about 100°C; or

wherein step a) is conducted at a temperature of about 60°C; and/or step b) is conducted at a temperature of from about 85°C.

26. The process of any one of claims **20** to **25**, wherein the compound of formula (II) obtained from step a) is used directly in step b) without purification.

27. The process of any one of claims **20** to **26**, wherein the buprenorphine dimer of formula (I) in a neutral form is further purified by trituration in acetone.

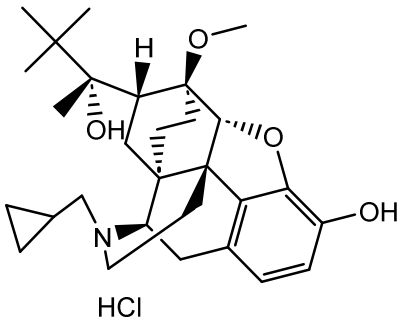
28. A process for preparing a buprenorphine dimer in a neutral form, represented by formula (I):



(I),

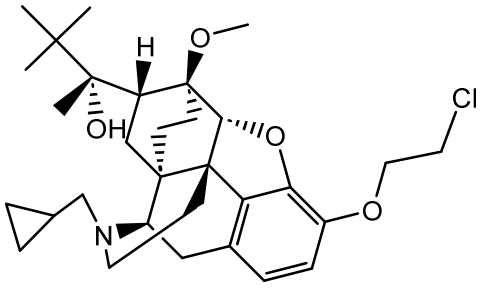
comprising:

a) combining a HCl salt of buprenorphine, represented by the formula:



,

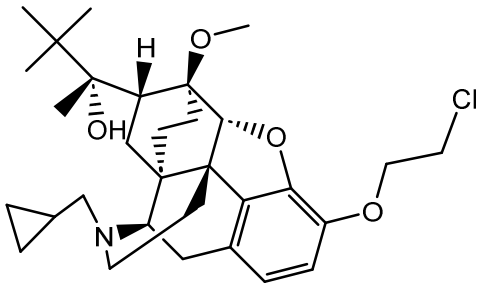
an aqueous NaOH solution, and tetrabutylammonium hydroxide in 1,2-dichloroethane to form a compound of formula (II):



(II); and

b) combining the compound of formula (II), a HCl salt of buprenorphine, an aqueous NaOH solution, and tetrabutylammonium hydroxide in toluene to provide the buprenorphine dimer of formula (I) in a neutral form.

29. A compound, represented by formula (II):



,

or a salt thereof.

30. The compound of claim **29**, in a neutral form.