opioid medication. Additionally, patients suffering from OIC may become resistant to laxative treatments. Although the mechanism is not yet fully understood, it is assumed that the binding of agonists to the peripheral μ-opioid receptors in the gastrointestinal (GI) tract is the primary cause of OIC. This opioid receptor activation impairs the coordination of the GI function by the enteric nervous system (ENS) resulting in decreased gut motility by delaying the transit time of fecal content through interference with the normal tone and contractility of the bowels. While the contractions of the circular muscles are increased causing non-propulsive kneading and churning (stasis) and increased fluid absorption, the longitudinal smooth muscle tone is decreased causing reduced forward peristalsis and additional time for desiccating fecal matter. Furthermore, the anal sphincter tone is increased making defecation more difficult. The clinical presentation of these effects typically manifests itself in symptoms of hard/dry stool, straining, incomplete evacuation, bloating and abdominal distention.

BRIEF SUMMARY OF THE INVENTION

[010] The present technology utilizes conjugation of the opioid hydromorphone with certain aryl carboxylic acids to decrease its potential for causing overdose or abuse by requiring the active hydromorphone to be released through enzymatic or metabolic breakdown of the conjugate *in vivo*. The present technology also provides methods of delivering hydromorphone as conjugates that release the hydromorphone following oral administration while being resistant to abuse by circuitous routes such as intravenous ("shooting") injection and intranasal administration ("snorting").

[011] Advantages of certain ~~embodiments~~ examples of the hydromorphone prodrugs of the present technology include, but are not limited to, reduced drug abuse potential, reduced or eliminated opioid induced constipation (OIC), reduced risk of chemical or physical manipulation resulting in full dosage of hydromorphone release, reduced patient to patient variability in plasma concentrations compared to free hydromorphone, improved dosage forms through modifications of the physical and chemical properties of the prodrugs and improved side effect profile through reduced conversion of the hydromorphone prodrug to undesirable hydromorphone-3-glucuronide.

[012] In some ~~aspects~~examples, the present technology provides an immediate release composition of conjugated hydromorphone that allows delivery of the hydromorphone into the blood system of a human or animal in a therapeutically bioequivalent manner upon oral administration. In at least one ~~aspect~~example, the compositions/formulations of the current technology can lessen common side effects associated with unconjugated hydromorphone and similar compounds. The presently described technology, in at least one ~~aspect~~example, provides a slow/sustained/controlled release composition of conjugated hydromorphone that allows slow/sustained/controlled delivery of the hydromorphone into the blood system of a human or animal within a safe therapeutic window upon, for example, oral administration. At least some compositions/formulations of the current technology can lessen addiction/abuse potential associated with unconjugated hydromorphone and similar compounds.

[013] In additional ~~aspects~~examples, the present technology utilizes conjugation of natural non-toxic ligands to hydromorphone to create a new class of prodrugs. The prodrugs of the present technology can be easily recognized by the metabolic systems and hydrolyzed to release the active opioid in a controlled fashion upon oral administration. Other routes of administration render the compounds of the present technology ineffective or less effective, thereby preventing or decreasing drug abuse. Additional methods of drug abuse are also averted due to the physical tampering resistance and prevention or reduction of euphoria upon ingestion of high doses of the prodrugs of the present technology. Depending on the choice of ligand, pharmacokinetic (PK) profiles of hydromorphone liberated from the prodrugs of the present technology can be modulated to optimize blood levels versus time for a specific indication and to improve its safety profile. Additionally, by selecting appropriate ligands, the prodrugs of the present technology can deliver hydromorphone into the systemic circulation without interacting with the opioid receptors in the enteric nervous system thus reducing or preventing opioid induced constipation (OIC).

[014] In another ~~aspect~~example, the present technology provides aryl carboxylic acids chemically attached to hydromorphone to create prodrugs that can release the

active opioid. The prodrugs of the present technology do not exhibit significant analgesic activity and by choosing suitable ligands significantly reduce the amounts of

hydromorphone released into the systemic circulation when administered intranasally or intravenously. Moreover, the narcotic cannot be "extracted" from the prodrugs of the present technology by simple physical tampering due to the nature of the covalent enol ester and/or phenol ester bond between hydromorphone and the aryl carboxylic acid. This class of compounds, of the present technology, may be viewed as less attractive to potential drug abusers than traditionally formulated drugs and may provide an improved safety profile and reduced side effects.

[015] Additionally, by choosing appropriate ligands, all or most of the inactive prodrugs of the present technology can survive the transit through the gastrointestinal (GI) tract until they are absorbed, thus preventing hydromorphone from interacting with the opioid receptors in the enteric nervous system. This lack of binding to the peripheral opioid receptors can significantly reduce or even prevent opioid induced constipation.

[016] In at least one ~~aspect~~example, the present technology provides at least one prodrug composition comprising at least one conjugate, the conjugate comprising at least one hydromorphone, and at least one aryl carboxylic acid.

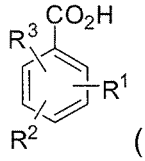
[017] In another ~~aspect~~example, the present technology provides at least one hydromorphone prodrug comprising an aryl carboxylic acid chemically bonded to hydromorphone by reacting the carboxylic acid moiety of the aryl carboxylic acid with the C-6 enol tautomer of hydromorphone.

[018] In another ~~aspect~~example, the present technology provides at least one prodrug comprising the at least one hydromorphone chemically bonded to the at least one aryl carboxylic acid by reacting the carboxylic acid moiety of the aryl carboxylic acid with the C-3 hydroxyl of hydromorphone.

[019] In another ~~aspect~~example, the present technology provides a prodrug comprising at least one hydromorphone chemically bonded to at least one aryl carboxylic acid by reacting the carboxylic acid moiety of one aryl carboxylic acid with the C-6 enol tautomer of hydromorphone and reacting at least one aryl carboxylic acid with the C-3 hydroxyl of hydromorphone.

[020] In other ~~aspects~~examples, the present technology provides at least one prodrug with at least one aryl carboxylic acid comprising a carboxylic group attached directly to at least one aryl moiety.

[021] In another ~~aspect~~example, the present technology provides at least one prodrug with at least one hydromorphone chemically attached to at least one benzoate of the general formula I:

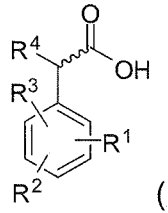


(I)

where R^1, R^2 and R^3 are independently selected from the group consisting of hydrogen, hydroxyl, amino, amine, amide, thiol, cyano, nitro, halogen, imine, alkyl, alkoxy, aryl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, heterocycle, arylalkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, carbonyl, thioether, selenoether, silyl, silyloxy, sulfonyl, phosphonate.

[022] In at least one ~~aspect~~example, the present technology provides a hydromorphone prodrug with at least one aryl carboxylic acid comprising a carboxylic group that is connected by a one-carbon linker to the aryl moiety.

[023] In another ~~aspect~~example, the present technology provides at least one hydromorphone prodrug chemically attached to at least one phenylacetate of the following general formula II:

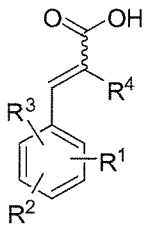


(II)

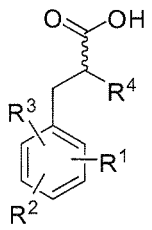
where R^1, R^2, R^3 and R^4 are independently selected from the group consisting of hydrogen, hydroxyl, amino, amine, amide, thiol, cyano, nitro, halogen, imine, alkyl, alkoxy, aryl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, heterocycle, arylalkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, carbonyl, thioether, selenoether, silyl, silyloxy, sulfonyl, phosphonate.

[024] In other ~~aspects~~examples, the present technology provides hydromorphone prodrugs containing at least one aryl carboxylic acid comprising a carboxylic group that is connected by a two-carbon linker to the aryl moiety.

[025] In additional ~~aspects~~examples, the present technology provides hydromorphone prodrug compositions comprising benzylacetates and cinnamates having the following general formula III or IV or combinations thereof:



(III)



(IV)

where R^1, R^2, R^3 and R^4 are independently selected from the group consisting of hydrogen, hydroxyl, amino, amine, amide, thiol, cyano, nitro, halogen, imine, alkyl, alkoxy, aryl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, heterocycle, arylalkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, carbonyl, thioether, selenoether, silyl, silyloxy, sulfonyl, phosphonate.

[026] In other ~~aspects~~examples, the hydromorphone prodrugs of the present technology include at least one aryl carboxylic acid comprising a carboxylic group attached to an aryl moiety ring by an alkyl chain.

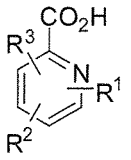
[027] In other ~~aspects~~examples, the hydromorphone prodrugs of the present technology include at least one aryl carboxylic acid comprising a carboxylic group attached to an aryl moiety ring by an alkenyl chain.

[028] In additional ~~aspects~~examples, the hydromorphone prodrugs of the present technology contain at least one aryl carboxylic acid that comprises a carbon chain between the aryl ring and the carboxyl group with one or more side chains.

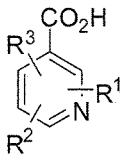
[029] In additional ~~aspects~~examples, the hydromorphone prodrugs of the present technology contain at least one aryl carboxylic acid that comprises one or more functional groups in addition to at least one carboxyl group.

[030] In other ~~aspects~~examples, the hydromorphone prodrugs of the present technology contain at least one aryl carboxylic acid that comprises at least one heteroraryl carboxylic acid.

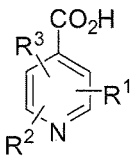
[031] In additional ~~aspects~~examples, the present technology provides hydromorphone prodrug compositions comprising heteroraryl carboxylic acid of the following general formula V, VI, VII, VIII, IX, X, XI, XII, or XIII or combinations thereof:



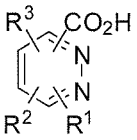
(V)



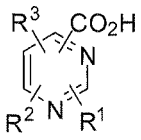
(VI)



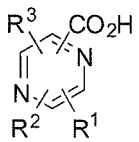
(VII)



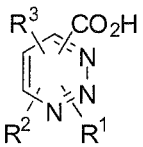
(VIII)



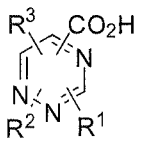
(IX)



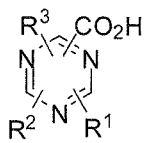
(X)



(XI)



(XII)



(XIII)

where R^1, R^2 and R^3 are independently selected from the group consisting of hydrogen, hydroxyl, amino, amine, amide, thiol, cyano, nitro, halogen, imine, alkyl, alkoxy, aryl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, heterocycle, arylalkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, carbonyl, thioether, selenoether, silyl, silyloxy, sulfonyl, phosphonate.

[032] In other ~~aspects~~examples, the present technology provides at least one hydromorphone prodrug that contains an aryl carboxylic acid comprising a six-membered ring.

[033] In other examples~~aspects~~, the present technology provides at least one hydromorphone prodrug that contains an aryl carboxylic acid comprising only one free carboxylic acid group.

[034] In additional examples~~aspects~~, the present technology provides at least one hydromorphone prodrug that contains an aryl carboxylic acid comprising between 1 to 4 phenyl substituents.

[035] In certain examples~~aspects~~, the present technology provides at least one hydromorphone prodrug conjugate that is a neutral prodrug.

[036] In certain examples~~aspects~~, the present technology provides at least one hydromorphone prodrug conjugate that is a free acid.

[037] In certain examples~~aspects~~, the present technology provides at least one hydromorphone prodrug conjugate that is a free base.

[038] In additional examples~~aspects~~, the present technology provides at least one hydromorphone prodrug conjugate that is a pharmaceutically acceptable anionic or cationic salt form or salt mixtures thereof.

[039] In certain examples~~aspects~~, the hydromorphone prodrug compositions of the present technology are broken down *in vivo* releasing active hydromorphone and an aryl carboxylic acid or derivatives or metabolites thereof.

[040] In certain examples~~aspects~~, the hydromorphone prodrug compositions of the present technology are administered orally and hydrolyzed *in vivo* releasing hydromorphone from the prodrug.

[041] In other examples~~aspects~~, the hydromorphone prodrug compositions of the present technology exhibit no or limited pharmacological activity upon administration.

[042] In other examplesaspects, the hydromorphone prodrug compositions of the present technology release hydromorphone in a manner that is similar to free or unmodified hydromorphone upon administration at equimolar dosages.

[043] In additional examplesaspects, the hydromorphone prodrug compositions of the present technology control and limit the release of hydromorphone into the systemic circulation when the prodrug is administered via routes other than oral.

[044] In certain examplesaspects, the hydromorphone prodrug compositions of the present technology release hydromorphone in a controlled or sustained manner upon administration.

[045] In other examplesaspects, the hydromorphone prodrug compositions of the present technology exhibit no or decreased side effects compared to unmodified hydromorphone upon administration at equimolar dosages.

[046] In additional examplesaspects, administration of the hydromorphone prodrug compositions of the present technology results in hydromorphone concentrations in the plasma or blood that are significantly decreased compared to unmodified hydromorphone upon administration at equimolar dosages by intravenous or intranasal routes.

[047] In other examplesaspects, administration of the hydromorphone prodrug compositions of the present technology does not cause or results in reduced euphoria or drug liking effect compared to unmodified hydromorphone upon intranasal or intravenous administration at equimolar dosages.

[048] In some examplesaspects, administration of the hydromorphone prodrug compositions of the present technology does not result in a rapid hydromorphone concentration spike (C_{max}) in the blood or plasma upon oral administration.

[049] In other examplesaspects, administration of the hydromorphone prodrug compositions of the present technology results in a delayed T_{max} compared to unmodified hydromorphone when administered orally at equimolar dosages.

[050] In additional examplesaspects, administration of the hydromorphone prodrug compositions of the present technology results in a lower C_{max} value compared to unmodified hydromorphone when administered orally at equimolar dosages.

[051] In further examplesaspects, physical manipulation of the hydromorphone prodrug compositions of the present technology does not result in the liberation of free hydromorphone.

[052] In other examplesaspects, the hydromorphone prodrug compositions of the present technology exhibit resistance to certain chemical manipulations intended to liberate free hydromorphone.

[053] In other examplesaspects, administration of the hydromorphone prodrug compositions of the present technology does not cause or results in insignificant activity at μ-opioid receptors.

[054] In other examplesaspects, the hydromorphone prodrug compositions of the present technology are not or are limitedly subjected to enzymatic hydrolysis until absorbed in the gut.

[055] In further examplesaspects, the hydromorphone prodrug compositions of the present technology exhibit decreased conversion to hydromorphone-3-glucuronide (H3G) compared to unmodified hydromorphone when administered orally at equimolar dosages.

[056] In other examplesaspects, the hydromorphone prodrug compositions of the present technology prevent or decrease opioid induced constipation (OIC) compared to unmodified hydromorphone when administered orally at equimolar dosages.

[057] In other examplesaspects, the hydromorphone prodrug compositions of the present technology comprise additional active pharmaceutical ingredients (APIs), including, for example, ibuprofen, acetaminophen, or aspirin.

[058] In certain examplesaspects, the hydromorphone prodrug compositions of the present technology may be 3-aspirin-hydromorphone, 3,6-di-aspirin-hydromorphone, 6-o-salicylate-hydromorphone, 3-cinnamate-hydromorphone, 6-naproxen-hydromorphone,

3-isoniacin-hydromorphone, 3-*p*-salicylic-hydromorphone, 3-fenamate-hydromorphone, 3-benzoate-hydromorphone, and 3,6-di-benzoate-hydromorphone.

[058A] In one aspect, there is provided a prodrug composition comprising at least one conjugate, wherein the at least one conjugate is 3,6-di-aspirin-hydromorphone.

[059] In other ~~aspects~~examples, the hydromorphone prodrug compositions of the present technology are in an oral dosage form. In some examples~~aspects~~, the oral dosage forms of the present technology are solid dosage forms. In additional aspects, the excipients of the present technology are antiadherents, binders, coatings, disintegrants, fillers, flavors, colors, glidants, lubricants, preservatives, sorbents and sweeteners.

[060] In additional examples~~aspects~~, the hydromorphone prodrug compositions of the present technology are provided as tablets, capsules, softgel capsules, modified release capsules, extended release tablets, controlled release capsules, suppositories, powders for injection, oral liquids, cough syrups, transdermal film, oral thin film, slurry or injections.

[061] In certain examples~~aspects~~, the hydromorphone prodrug compositions of the present technology are provided at oral dosage strengths that are equimolar to from about 0.1 mg to about 200 mg of unmodified hydromorphone.

[062] In other examples~~aspects~~, the present technology provides a method of treating a patient in need of an analgesic effect by administering an amount of at least one hydromorphone prodrug composition of the present technology that is therapeutically equivalent to an effective amount of unconjugated hydromorphone.

[062A] in another aspect, there is provided use of a pharmaceutically effective amount of the prodrug composition comprising at least one conjugate of claim 1 in the manufacture of a medicament for treating a patient having a disease, disorder or condition mediated by binding of an opioid to opioid receptors of the patient.

[063] In further examples~~aspects~~, the present technology provides a method of synthesizing the hydromorphone prodrug compositions of the present technology.

[064] In other aspects, the present technology provides a method of treating a patient in need of an analgesic effect by administering an amount of 3-aspirin-hydromorphone, 3,6-di-aspirin-hydromorphone, 6-salicylate-hydromorphone, 3-cinnamate-hydromorphone, or 3-benzoate-hydromorphone that is therapeutically equivalent to an effective amount of unconjugated hydromorphone.

[065] In additional aspects, the present technology provides a pharmaceutical kit containing a specified amount of individual doses containing an amount of at least one conjugate that is therapeutically equivalent to an effective amount of unconjugated

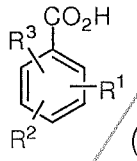
CLAIMS

1. A prodrug composition comprising at least one conjugate, the conjugate comprising at least one hydromorphone, and at least one aryl carboxylic acid.

2. The prodrug composition of claim 1, wherein the at least one aryl carboxylic acid is selected from the group consisting of benzoates and heteroaryl carboxylic acids.

3. The prodrug composition of claim 2, wherein the heteroaryl carboxylic acid is selected from the group consisting of pyridine, diazine and triazine.

4. The prodrug composition of claim 2, wherein the benzoate has the following general formula I:



(I)

wherein R^1, R^2 and R^3 are independently selected from the group consisting of hydrogen, hydroxyl, amino, amine, amide, thiol, cyano, nitro, halogen, imine, alkyl, alkoxy, aryl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, heterocycle, arylalkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, carbonyl, thioether, selenoether, silyl, silyloxy, sulfonyl, phosphonate.

5. The prodrug composition of claim 2, wherein the benzoate is selected from the group consisting of aminobenzoates, hydroxybenzoates and aminohydroxybenzoates, mixtures thereof and derivatives thereof.

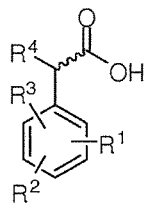
6. The prodrug composition of claim 5, wherein the aminobenzoate is selected from the group consisting of anthranilic acid, 3-aminobenzoic acid, 4,5-dimethylanthranilic acid, *N*-methylanthranilic acid, *N*-acetylanthranilic acid, fenamic acids, 2,4-diaminobenzoic acid (2,4-DABA), 2-acetylamino-4-aminobenzoic acid, 4-acetylamino-2-aminobenzoic acid and 2,4-diacetylaminobenzoic acid, mixtures thereof and derivatives thereof.

7. The prodrug composition of claim 5, wherein the hydroxybenzoate is selected from the group consisting of benzoic acid, salicylic acid, acetylsalicylic acid (aspirin), 3-hydroxybenzoic acid, 4-hydroxybenzoic acid, 6-methylsalicylic acid, *o,m,p*-cresotinic acid, anacardic acids, 4,5-dimethylsalicylic acid, *o,m,p*-thymotic acid, diflusinal, *o,m,p*-anisic acid, 2,3-dihydroxybenzoic acid (2,3-DHB), α,β,γ-resorcylic acid, protocatechuic acid, gentisic acid, piperonylic acid, 3-methoxysalicylic acid, 4-methoxysalicylic acid, 5-methoxysalicylic acid, 6-methoxysalicylic acid, 3-hydroxy-2-methoxybenzoic acid, 4-hydroxy-2-methoxybenzoic acid, 5-hydroxy-2-methoxybenzoic acid, vanillic acid, isovanillic acid, 5-hydroxy-3-methoxybenzoic acid, 2,3-dimethoxybenzoic acid, 2,4-dimethoxybenzoic acid, 2,5-dimethoxybenzoic acid, 2,6-dimethoxybenzoic acid, veratric acid (3,4-dimethoxybenzoic acid), 3,5-dimethoxybenzoic acid, gallic acid, 2,3,4-trihydroxybenzoic acid, 2,3,6-trihydroxybenzoic acid, 2,4,5-trihydroxybenzoic acid, 3-*O*-methylgallic acid (3-OMGA), 4-*O*-methylgallic acid (4-OMGA), 3,4-*O*-dimethylgallic acid, syringic acid, and 3,4,5-trimethoxybenzoic acid, mixtures thereof and derivatives thereof.

8. The prodrug composition of claim 5, wherein the aminohydroxybenzoate is selected from the group consisting of 4-aminosalicylic acid, 3-hydroxyanthranilic acid, and 3-methoxyanthranilic acid, mixtures thereof and derivatives thereof.

9. The prodrug composition of claim 1, wherein the at least one aryl carboxylic acid is selected from the group consisting of branched phenylpropionic acids and phenylacetates, mixtures thereof and derivatives thereof.

10. The prodrug composition of claim 9, wherein the phenylacetate has the following general structure II:



(II)

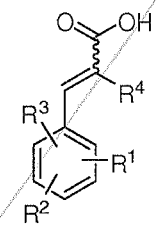
wherein R^1, R^2, R^3 and R^4 are independently selected from the group consisting of hydrogen, hydroxyl, amino, amine, amide, thiol, cyano, nitro, halogen, imine, alkyl,

alkoxy, aryl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, heterocycle, arylalkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, carbonyl, thioether, selenoether, silyl, silyloxy, sulfonyl, phosphonate.

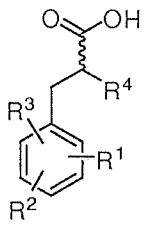
11. The prodrug composition of claim 9, wherein the phenylacetate is selected from the group consisting of phenylacetic acid (hydratropic acid), 2-hydroxyphenylacetic acid, 3-hydroxyphenylacetic acid, 4-hydroxyphenylacetic acid, homoprotocatechuic acid, homogentisic acid, 2,6-dihydroxyphenylacetic acid, homovanillic acid, homoisovanillic acid, homoveratric acid, atropic acid, *d,l*-tropic acid, diclofenac, *d,l*-mandelic acid, 3,4-dihydroxy-*d,l*-mandelic acid, vanillyl-*d,l*-mandelic acid, isovanillyl-*d,l*-mandelic acid, ibuprofen, fenoprofen, carprofen, flurbiprofen, ketoprofen and naproxen, mixtures thereof and derivatives thereof.

12. The prodrug composition of claim 1, wherein the at least one aryl carboxylic acid is selected from the group consisting of benzylacetates and cinnamates, mixtures thereof and derivatives thereof.

13. The prodrug composition of claim 12, wherein the benzylacetates and cinnamates have the following general formula III or IV or combinations thereof:



(III)



(IV)

wherein R^1, R^2, R^3 and R^4 are independently selected from the group consisting of hydrogen, hydroxyl, amino, amine, amide, thiol, cyano, nitro, halogen, imine, alkyl, alkoxy, aryl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, heterocycle, arylalkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, carbonyl, thioether, selenoether, silyl, silyloxy, sulfonyl, phosphonate.

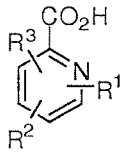
14. The prodrug composition of claim 12, wherein the benzylacetate is selected from the group consisting of benzylacetic acid, melilotic acid, 3-

hydroxyphenylpropanoic acid, 4-hydroxyphenylpropanoic acid, 2,3-dihydroxyphenylpropanoic acid, *d,l*-phenyllactic acid, *o,m,p*-hydroxy-*d,l*-phenyllactic acid and phenylpyruvic acid, mixtures thereof and derivatives thereof.

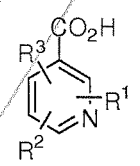
15. The prodrug composition of claim 12, wherein the cinnamate is selected from the group consisting of cinnamic acid, *o,m,p*-coumaric acid, 2,3-dihydroxycinnamic acid, 2,6-dihydroxycinnamic acid, caffeic acid, ferulic acid, isoferulic acid, 5-hydroxyferulic acid, sinapic acid and 2-hydroxy-3-phenylpropenoic acid, mixtures thereof and derivatives thereof.

16. The prodrug composition of claim 1, wherein the at least one aryl carboxylic acid comprises at least one heteroaryl carboxylic acid.

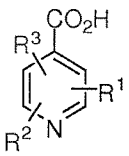
17. The prodrug composition of claim 16, wherein the heteroaryl carboxylic acid has the following general formula V, VI, VII, VIII, IX, X, XI, XII, or XIII or combinations thereof:



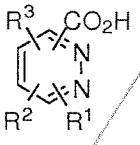
(V)



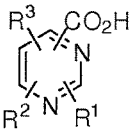
(VI)



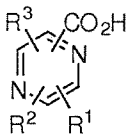
(VII)



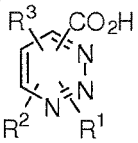
(VIII)



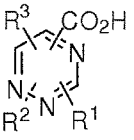
(IX)



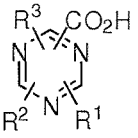
(X)



(XI)



(XII)



(XIII)

wherein R^1, R^2 and R^3 are independently selected from the group consisting of hydrogen, hydroxyl, amino, amine, amide, thiol, cyano, nitro, halogen, imine, alkyl, alkoxy, aryl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, heterocycle, arylalkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, carbonyl, thioether, selenoether, silyl, silyloxy, sulfonyl, phosphonate.

18. The prodrug composition of claim 16, wherein the heteroaryl carboxylic acid is selected from the group consisting of nicotinic acid (niacin), isonicotinic acid, picolinic acid, 3-hydroxypicolinic acid, 6-hydroxynicotinic acid, citrazinic acid, 2,6-dihydroxynicotinic acid, kynurenic acid, xanthurenic acid, 6-hydroxykynurenic acid, 8-methoxykynurenic acid, 7,8-dihydroxykynurenic acid and 7,8-dihydro-7,8-dihydroxykynurenic acid, mixtures thereof and derivatives thereof.

19. The prodrug composition of claim 1, wherein the conjugate is selected from the group consisting of 3-aspirin-hydromorphone, 3,6-di-aspirin-hydromorphone, 6-salicylate-hydromorphone, 3-cinnamate-hydromorphone and 3-benzoate-hydromorphone.

20. The prodrug composition of claim 1, wherein the at least one conjugate is used to treat narcotic or opioid abuse; to prevent narcotic or opioid withdrawal; to treat moderate to severe pain; to reduce or prevent oral, intranasal or intravenous drug abuse; or to provide oral, intranasal or parenteral drug abuse resistance.

21. The prodrug composition of claim 1, wherein oral administration of the at least one conjugate results in an improved AUC and rate of release over time when compared to unconjugated hydromorphone over the same time period.

22. The prodrug composition of claim 1, wherein oral administration of the at least one conjugate results in less variability in the oral PK profile when compared to unconjugated hydromorphone.

23. The prodrug composition of claim 1, wherein oral administration of the at least one conjugate results in reduced side effects when compared with unconjugated hydromorphone.

24. The prodrug composition of claim 23, wherein the reduced side effect is reduced opioid induced constipation.

25. The prodrug composition of claim 1, wherein at least one conjugate is provided in a dosage form selected from the group consisting of a tablet, a capsule, a caplet, a suppository, a troche, a lozenge, an oral powder, a solution, an oral film, a thin strip, a slurry, and a suspension.

26. The prodrug composition of claim 1, wherein oral administration of the at least one conjugate provides a therapeutically bioequivalent AUC and/or C_{max} when compared to an equivalent molar amount of unconjugated hydromorphone.

27. The prodrug composition of claim 1, wherein oral administration of the at least one conjugate provides a therapeutically bioequivalent AUC and a lower C_{max} when compared to an equivalent molar amount of unconjugated hydromorphone.

28. The prodrug composition of claim 1, wherein intranasal or intravenous administration of the at least one conjugate provides a lower AUC and/or C_{max} when compared to an equivalent molar amount of unconjugated hydromorphone.

29. The prodrug composition of claim 1, wherein oral administration of the at least one conjugate provides a decreased overdose potential when compared to an equivalent molar amount of unconjugated hydromorphone.

30. The prodrug composition of claim 1, wherein the at least one conjugate provides an increased tamper resistance when compared to unconjugated hydromorphone.

31. A method for treating a patient having a disease, disorder or condition mediated by binding of an opioid to opioid receptors of the patient, comprising orally

administering to the patient a pharmaceutically effective amount of the prodrug composition comprising at least one conjugate of claim 1.

Claims

1. A prodrug composition comprising at least one conjugate, wherein the at least one conjugate is 3,6-di-aspirin-hydromorphone.

2. The prodrug composition of claim 1, wherein the at least one conjugate is used to treat narcotic or opioid abuse; to prevent narcotic or opioid withdrawal; to treat moderate to severe pain; to reduce or prevent oral, intranasal or intravenous drug abuse; or to provide oral, intranasal or parenteral drug abuse resistance.

3. The prodrug composition of claim 1, wherein oral administration of the at least one conjugate results in an improved AUC and rate of release over time when compared to unconjugated hydromorphone over the same time period.

4. The prodrug composition of claim 1, wherein oral administration of the at least one conjugate results in less variability in the oral PK profile when compared to unconjugated hydromorphone.

5. The prodrug composition of claim 1, wherein oral administration of the at least one conjugate results in reduced side effects when compared with unconjugated hydromorphone.

6. The prodrug composition of claim 5, wherein the reduced side effect is reduced opioid induced constipation.

7. The prodrug composition of claim 1, wherein at least one conjugate is provided in a dosage form selected from the group consisting of a tablet, a capsule, a caplet, a suppository, a troche, a lozenge, an oral powder, a solution, an oral film, a thin strip, a slurry, and a suspension.

8. The prodrug composition of claim 1, wherein oral administration of the at least one conjugate provides a therapeutically bioequivalent AUC and/or a bioequivalent or lower C_{max} when compared to an equivalent molar amount of unconjugated hydromorphone.

9. The prodrug composition of claim 1, wherein intranasal or intravenous administration of the at least one conjugate provides a lower AUC and/or C_{max} when compared to an equivalent molar amount of unconjugated hydromorphone.

10. The prodrug composition of claim 1, wherein oral administration of the at least one conjugate provides a decreased overdose potential when compared to an equivalent molar amount of unconjugated hydromorphone.

11. The prodrug composition of claim 1, wherein the at least one conjugate provides an increased tamper resistance when compared to unconjugated hydromorphone.

12. Use of a pharmaceutically effective amount of the prodrug composition comprising at least one conjugate of claim 1 in the manufacture of a medicament for treating a patient having a disease, disorder or condition mediated by binding of an opioid to opioid receptors of the patient.