

[0006] Hydrocodone is an opioid analgesic and antitussive and occurs as fine, white crystals or as crystalline powder. Hydrocodone is a semisynthetic narcotic analgesic prepared from codeine with multiple actions qualitatively similar to those of codeine. It is mainly used for relief of moderate to moderately severe pain. Additionally, it is used as an antitussive in cough syrups and tablets in sub-analgesic doses (2.5-5 mg).

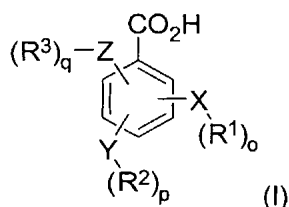
[0007] Patients taking opioid analgesics such as hydrocodone for pain relief can become unintentionally addicted. As tolerance to the opioids develops more drug is needed to alleviate the pain and generate the sense of well being initially achieved with the prescribed dose. This leads to dose escalation, which if left unchecked can lead rapidly to addiction. In some cases patients have become very addicted in as little as thirty days.

BRIEF SUMMARY

[0008] The present technology utilizes covalent conjugation of the opioid hydrocodone with certain aryl carboxylic acids to decrease its potential for causing overdose or abuse by requiring the active hydrocodone to be released through enzymatic or metabolic breakdown of the conjugate *in vivo*. The present technology also provides methods of delivering hydrocodone as conjugates that release the hydrocodone following oral administration while being resistant to abuse by circuitous routes such as intravenous ("shooting") injection and intranasal administration ("snorting").

[0009] The presently described technology in at least one embodiment provides a slow/sustained/controlled release composition of conjugated hydrocodone that allows slow/sustained/controlled delivery of the hydrocodone and/or its active metabolite, 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 and/or other common side effects associated with hydrocodone and similar compounds.

[0010] The present technology provides a composition comprising at least one conjugate of hydrocodone and at least one benzoic acid or derivative thereof, a salt thereof, or a combination thereof, the benzoic acid or derivative thereof having the following formula I:



where X, Y and Z are independently selected from the group consisting of H, O, S, NH and $-(\text{CH}_2)_x-$; R^1 , R^2 and R^3 are independently selected from the group consisting of H, alkyl, alkoxy, aryl, alkenyl, alkynyl, halo, haloalkyl, alkylaryl, arylalkyl, heterocycle, arylalkoxy, cycloalkyl, cycloalkenyl and cycloalkynyl; o, p, q are independently selected from 0 or 1; and x is an integer between 1 and 10. In some embodiments, the benzoic acid or derivative thereof is an aminobenzoate, a hydroxybenzoate, an aminohydroxybenzoate, a derivative thereof, or combination thereof.

[0011] In an embodiment, the present technology provides a composition comprising at least one conjugate of hydrocodone and at least one benzoic acid, a derivative thereof, or a combination thereof.

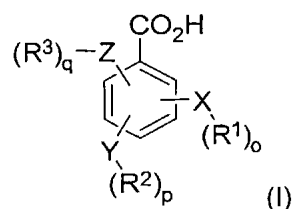
[0012] In yet another embodiment, the present technology provides conjugates of hydrocodone for use to treat pain, preferably moderate to severe pain, or for use to reduce or prevent oral, intranasal or intravenous drug abuse. In some embodiments, the conjugates provide oral, intranasal or parenteral drug abuse resistance.

[0013] In another embodiment, the present technology provides at least one conjugate of hydrocodone that exhibits a slower rate of release over time and a greater or equal AUC when compared to an equivalent molar amount of unconjugated hydrocodone over the same time period. In other embodiments, the conjugate of hydrocodone exhibits less variability in the oral PK profile when

compared to unconjugated hydrocodone. In yet another embodiment, at least one conjugate has reduced side effects when compared with unconjugated hydrocodone or prevents drug tampering by either physical or chemical manipulation.

[0014] In another embodiment, at least one conjugate is provided in an amount sufficient to provide a therapeutically bioequivalent AUC when compared to an equivalent molar amount of unconjugated hydrocodone. In further embodiments, at least one conjugate is provided in an amount sufficient to provide a therapeutically bioequivalent AUC when compared to an equivalent molar amount of unconjugated hydrocodone but does not provide a $C_{\max}$ spike or has a lower $C_{\max}$ than a therapeutically equivalent amount of unconjugated hydrocodone. In yet a further embodiment, at least one conjugate is provided in an amount sufficient to provide a therapeutically bioequivalent AUC when compared to an equivalent molar amount of unconjugated hydrocodone, but does not provide an equivalent $C_{\max}$ spike. In some embodiments, at least one conjugate provides an equivalent $C_{\max}$ spike when compared to unconjugated hydrocodone.

[0015] In yet another embodiment, the present technology provides a method for treating a patient having a disease, disorder or condition requiring or mediated by binding of an opioid to the opioid receptors of the patient, comprising orally administering to the patient a pharmaceutically effective amount of at least one conjugate of hydrocodone and at least one benzoic acid or derivative thereof, a salt thereof, or a combination thereof, the benzoic acid or derivative thereof having formula I:

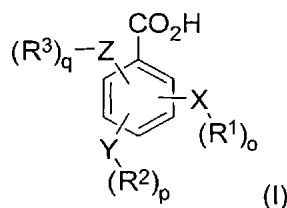


where X, Y and Z are independently selected from the group consisting of H, O, S, NH and $-(CH_2)_x-$; R^1 , R^2 and R^3 are independently selected from the group

consisting of H, alkyl, alkoxy, aryl, alkenyl, alkynyl, halo, haloalkyl, alkylaryl, arylalkyl, heterocycle, arylalkoxy, cycloalkyl, cycloalkenyl and cycloalkynyl; o, p, q are independently selected from 0 or 1; and x is an integer between 1 and 10.

[0016] In another embodiment, at least one conjugate binds irreversibly to the opioid receptors of the patient. In yet another embodiment, at least one conjugate binds irreversibly to the opioid receptors of the patient without a CNS depressive effect.

[0017] In a further embodiment, the present technology provides a method for treating a patient having a disease, disorder or condition requiring or mediated by inhibiting binding of an opioid to the opioid receptors of the patient, comprising orally administering to the patient a pharmaceutically effective amount of at least one conjugate of hydrocodone and at least one benzoic acid or derivative thereof, a salt thereof, or a combination thereof, the benzoic acid or derivative thereof having formula I:



wherein

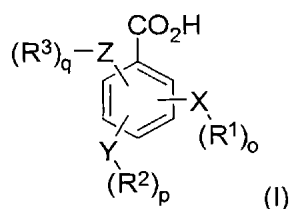
X, Y and Z are independently selected from the group consisting of H, O, S, NH and $-(CH_2)_x-$; R^1 , R^2 and R^3 are independently selected from the group consisting of H, alkyl, alkoxy, aryl, alkenyl, alkynyl, halo, haloalkyl, alkylaryl, arylalkyl, heterocycle, arylalkoxy, cycloalkyl, cycloalkenyl and cycloalkynyl; o, p, q are independently selected from 0 or 1; and x is an integer between 1 and 10.

[0018] In some embodiments, the present technology provides at least one conjugate that reversibly inhibits binding of an opioid to the opioid receptor of the patient. In other embodiments, at least one conjugate reversibly inhibits binding of an opioid to the opioid receptor of the patient without a CNS depressive effect.

[0019] In a further embodiment, the present technology provides a method for treating a patient having a disease, disorder or condition (such as pain) which can be treated by binding of an opioid to the opioid receptors of the patient, the method comprising orally administering to the patient a pharmaceutically effective amount of at least one conjugate of hydrocodone and at least one benzoic acid, a salt thereof, a derivative thereof or a combination thereof.

[0020] In another embodiment, the present technology provides a method for treating a patient having a disease, disorder or condition (such as addiction) which can be treated by inhibiting binding of an opioid to the opioid receptors of the patient, comprising orally administering to the patient a pharmaceutically effective amount of at least one conjugate of hydrocodone and at least one benzoic acid, a salt thereof, a derivative thereof or a combination thereof.

[0021] In yet another embodiment, the present technology provides a pharmaceutical kit including a specified amount of individual doses in a package containing a pharmaceutically effective amount of at least one conjugate of hydrocodone and at least one benzoate, a salt thereof, a derivative thereof or a combination thereof, the benzoate having the formula I:



wherein X, Y and Z are independently selected from the group consisting of H, O, S, NH and $-(\text{CH}_2)_x-$; R^1 , R^2 and R^3 are independently selected from the group consisting of H, alkyl, alkoxy, aryl, alkenyl, alkynyl, halo, haloalkyl, alkylaryl, arylalkyl, heterocycle, arylalkoxy, cycloalkyl, cycloalkenyl and cycloalkynyl; o, p, q can be independently selected from 0 or 1; and x is an integer between 1 and 10. In some embodiments, the kit further comprises instructions for use of the kit in a

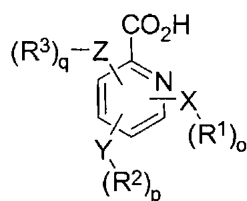
method for treating or preventing drug withdrawal symptoms or pain in a human or animal patient.

[0022] In another embodiment, the present technology provides a pharmaceutical kit including a specified amount of individual doses in a package containing a pharmaceutically effective amount of at least one conjugate of hydrocodone and at least one benzoic acid, a salt thereof, a derivative thereof or a combination thereof. In some embodiments, the kit further includes instructions for use of the kit in a method for treating or preventing drug withdrawal symptoms or pain in a human or animal patient.

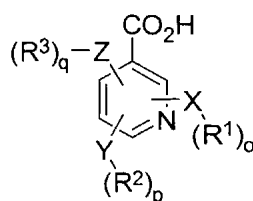
[0023] In yet another embodiment, the present technology provides a composition comprising at least one conjugate of hydrocodone and at least one heteroaryl carboxylic acid, a derivative thereof, or a combination thereof.

[0024] In yet another embodiment, the present technology provides at least one conjugate of hydrocodone and at least one heteroaryl carboxylic acid, a derivative thereof, or a combination thereof where at least one heteroaryl carboxylic acid is selected from formula II, formula III or formula IV,

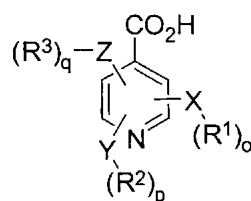
wherein formula II, formula III and formula IV are:



(II)



(III)



(IV)

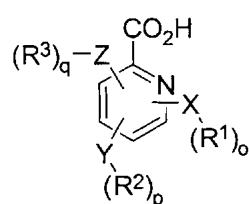
wherein X, Y and Z are independently selected from the group consisting of H, O, S, NH and $-(CH_2)_x-$; R^1 , R^2 and R^3 are independently selected from the group consisting of H, alkyl, alkoxy, aryl, alkenyl, alkynyl, halo, haloalkyl, alkylaryl, arylalkyl, heterocycle, arylalkoxy, cycloalkyl, cycloalkenyl and cycloalkynyl; o, p, q

are independently selected from 0 or 1; and x is an integer from 1 to 10. In some embodiments, at least one heteroaryl carboxylic acid is a pyridine derivative.

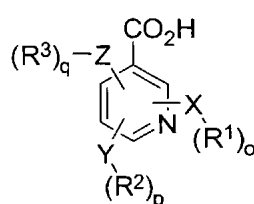
[0025] In some embodiments, the present technology provides at least one conjugate that prevents drug tampering by either physical or chemical manipulation.

[0026] In another embodiment, the present technology provides a method for treating a patient having a disease, disorder or condition requiring or mediated by binding of an opioid to the opioid receptors of the patient, comprising orally administering to the patient a pharmaceutically effective amount of at least one conjugate of hydrocodone and at least one heteroaryl carboxylic acid.

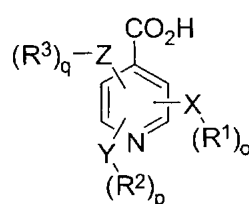
[0027] In a further embodiment, the present technology provides a method for treating a patient having a disease, disorder or condition requiring or mediated by binding of an opioid to the opioid receptors of the patient, comprising orally administering to the patient a pharmaceutically effective amount of at least one conjugate of hydrocodone and at least one heteroaryl carboxylic acid, where the heteroaryl carboxylic acid is selected from formula II, formula III or formula IV, wherein formula II, formula III and formula IV are:



(II)



(III)

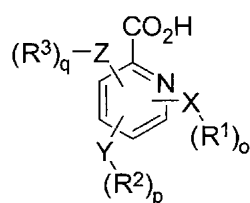


(IV)

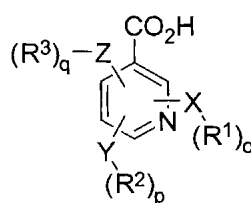
where X, Y and Z are independently selected from the group consisting of H, O, S, NH and $-(CH_2)_x-$; R^1 , R^2 and R^3 are independently selected from the group consisting of H, alkyl, alkoxy, aryl, alkenyl, alkynyl, halo, haloalkyl, alkylaryl, arylalkyl, heterocycle, arylalkoxy, cycloalkyl, cycloalkenyl and cycloalkynyl; o, p, q are independently selected from 0 or 1; and x is an integer from 1 to 10.

[0028] In another embodiment, the present technology provides a method for treating a patient having a disease, disorder or condition requiring or mediated by binding of an opioid to the opioid receptors of the patient, comprising orally administering to the patient a pharmaceutically effective amount of at least one conjugate of hydrocodone and at least one nicotinic acid, a derivative thereof, or a combination thereof.

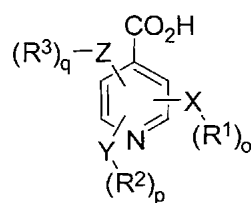
[0029] In another embodiment, the present technology provides a method for treating a patient having a disease, disorder or condition requiring or mediated by inhibiting binding of an opioid to the opioid receptors of the patient, comprising orally administering to the patient a pharmaceutically effective amount of at least one conjugate of hydrocodone and at least one heteroaryl carboxylic acid. In some embodiments, the heteroaryl carboxylic acid is selected from formula II, formula III or formula IV, wherein formula II, formula III and formula IV are:



(II)



(III)



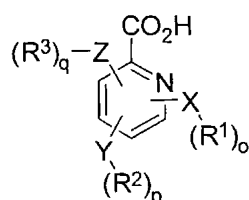
(IV)

wherein X, Y and Z are independently selected from the group consisting of H, O, S, NH and $-(CH_2)_x-$; R^1 , R^2 and R^3 are independently selected from the group consisting of H, alkyl, alkoxy, aryl, alkenyl, alkynyl, halo, haloalkyl, alkylaryl, arylalkyl, heterocycle, arylalkoxy, cycloalkyl, cycloalkenyl and cycloalkynyl; o, p, q are independently selected from 0 or 1; and x is an integer from 1 to 10.

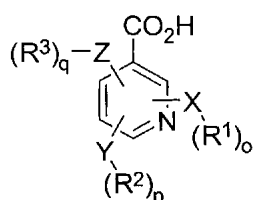
[0030] In another embodiment, the present technology provides a method for treating a patient having a disease, disorder or condition requiring or mediated by inhibiting binding of an opioid to the opioid receptors of the patient, comprising orally administering to the patient a pharmaceutically effective amount of at least

one conjugate of hydrocodone and at least one nicotinic acid, a derivative thereof, or a combination thereof.

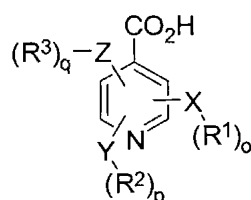
[0031] In yet another embodiment, the present technology provides a pharmaceutical kit including a specified number of individual doses in a package containing a pharmaceutically effective amount of at least one conjugate of hydrocodone and at least one heteroaryl carboxylic acid, a derivative thereof, or a combination thereof, wherein the heteroaryl carboxylic acid is selected from formula II, formula III or formula IV, wherein formula II, formula III and formula IV are:



(II)



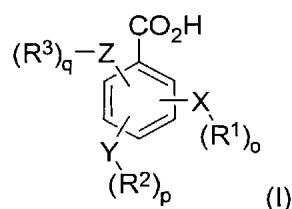
(III)



(IV)

wherein X, Y and Z are independently selected from the group consisting of H, O, S, NH and $-(CH_2)_x-$; R^1 , R^2 and R^3 are independently selected from the group consisting of H, alkyl, alkoxy, aryl, alkenyl, alkynyl, halo, haloalkyl, alkylaryl, arylalkyl, heterocycle, arylalkoxy, cycloalkyl, cycloalkenyl and cycloalkynyl; o, p, q are independently selected from 0 or 1; and x is an integer from 1 to 10. In some embodiments, the kit further comprises instructions for use of the kit in a method for treating or preventing drug withdrawal symptoms or pain in a human or animal patient.

[0032] In yet another embodiment, the present technology provides a prodrug comprising at least one conjugate of hydrocodone and at least one benzoic acid or benzoic acid derivative, a salt thereof, or a combination thereof, the benzoic acid or benzoic acid derivative having the following formula I:

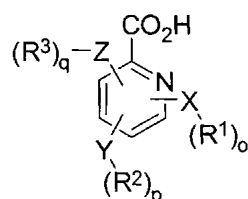


(I)

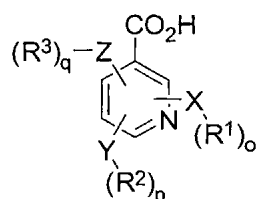
where X, Y and Z are independently selected from the group consisting of H, O, S, NH and $-(CH_2)_x-$; R^1 , R^2 and R^3 are independently selected from the group consisting of H, alkyl, alkoxy, aryl, alkenyl, alkynyl, halo, haloalkyl, alkylaryl, arylalkyl, heterocycle, arylalkoxy, cycloalkyl, cycloalkenyl and cycloalkynyl; o, p, q are independently selected from 0 or 1; and x is an integer between 1 and 10.

[0033] In another embodiment, the present technology provides a prodrug comprising at least one conjugate of hydrocodone and at least one benzoic acid, a derivative thereof, or a combination thereof.

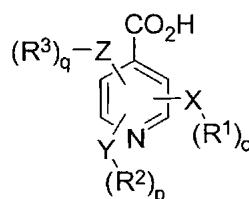
[0034] In yet another embodiment, the present technology provides a prodrug comprising at least one conjugate of hydrocodone and at least one heteroaryl carboxylic acid, a derivative thereof, or a combination thereof. In some embodiments, the prodrug includes at least one heteroaryl carboxylic acid selected from formula II, formula III or formula IV, wherein formula II, formula III and formula IV are:



(II)



(III)



(IV)

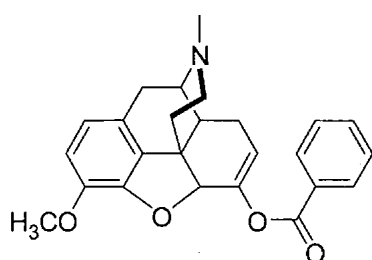
wherein X, Y and Z are independently selected from the group consisting of H, O, S, NH and $-(CH_2)_x-$; R^1 , R^2 and R^3 are independently selected from the group consisting of H, alkyl, alkoxy, aryl, alkenyl, alkynyl, halo, haloalkyl, alkylaryl, arylalkyl, heterocycle, arylalkoxy, cycloalkyl, cycloalkenyl and cycloalkynyl; o, p, q are independently selected from 0 or 1; and x is an integer from 1 to 10.

[0035] In yet another embodiment, the present technology provides a prodrug comprising at least one conjugate of hydrocodone and at least one nicotinic acid, a derivative thereof, or a combination thereof.

[0036] In some embodiments, the prodrug includes an aminobenzoate, a hydroxybenzoate, an aminohydroxybenzoate, a derivative thereof, or combination thereof.

[0037] In some embodiments, at least one conjugate binds reversibly to the opioid receptors of the patient. In some further embodiments, at least one conjugate binds reversibly to the opioid receptors of the patient without a CNS depressive effect. In yet another embodiment, at least one conjugate prevents or reduces at least one constipatory side effect of unconjugated hydrocodone.

[0037a] In an aspect, there is provided a composition comprising a conjugate wherein the conjugate is benzoate-hydrocodone (Bz-HC) having the following structure:



benzoate-hydrocodone
(Bz-HC)

[0037b] In another aspect, there is provided the use of a composition as defined above 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, wherein said condition is selected from the group consisting of narcotic addiction, drug addiction, acute pain or chronic pain.

[0037c] In another aspect, there is provided a composition as defined above for use in therapy.

BRIEF DESCRIPTION OF SEVERAL VIEWS OF THE DRAWINGS

[0038] Figure 1. Chemical structures of hydroxybenzoic acids and benzoic acid derivatives for use in the making of the conjugates of the present technology.

[0039] Figure 2. Chemical structures of aminobenzoic acids for use in the making of the conjugates of the present technology.

[0040] Figure 3. Chemical structures of aminohydroxybenzoic acids for use in the making of conjugates of the present technology.

[0041] Figure 4. Figure 4A is a Table of common hydrocodone products and dosage ranges and Figure 4B is a Table of common hydrocodone products used in cough syrups.

[0042] Figure 5. PK profile graph of plasma concentrations of hydrocodone released from Bz-HC (benzoate-hydrocodone), YYFFI-HC (Tyr-Tyr-Phe-Phe-Ile-Hydrocodone) and Diglycolate-HC over time upon oral administration in rats.

[0043] Figure 6. PK profile graph of plasma concentrations of active metabolite hydromorphone over time upon oral administration of Bz-HC, YYFFI-HC, and Diglycolate-HC in rats.