

**COMPOUNDS, NANOPARTICLES, AND PHARMACEUTICAL COMPOSITIONS
FOR THE TREATMENT OF DRUG ADDICTION**

Related Applications

This application claims the benefit of and priority to U.S. Provisional Patent
5 Application No. 63/470,480, filed June 2, 2023, which application is hereby incorporated by
reference in its entirety.

Funding

This invention was made with government support under P01 DA028555 awarded by
the National Institutes of Health. The government has certain rights in the invention.

10 **Background**

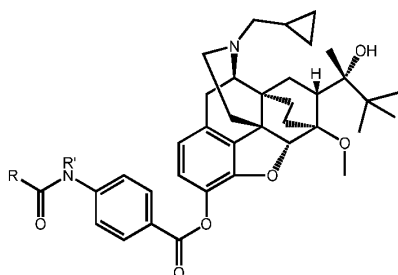
The means to treat opioid use disorder (OUD) is timely. For example, buprenorphine
(BUP) is an agonist of the μ -opioid receptors (MOR) that can be administered in sublingual
pill or film form that requires daily dosing. Use of long-acting (LA) formulations of BUP are
a preferred route of administration to overcome variability, dose diversion, misuse, and non-
15 adherence. The first BUP implant was approved as a non-degradable ethylene vinyl acetate
rod for subdermal insertion. Duration can last for up to 6-month termination necessitates its
removal with numerous reported adverse events.

Two injectable, LA BUP formulations are available for monthly subcutaneous
injection forming a solid slow dissolving release. After administration of LA BUP, complete
20 blockade of hydromorphone effects and improved patient-reported outcomes and abstinence
are reported. However, existing formulations have shown limitations towards wide-spread
application. Such limitations include, but are not limited to, withdrawal, misuse and limited
adherence to repeated injections, implantation/removal, and injection/implant site-associated
adverse events underscoring the need for better treatments with improved efficacy and safety.

25 Therefore, there is an immediate need for a long duration, safe and efficacious LA
formulations that can effectively treat drug and alcohol dependencies while greatly
overcoming the above drawbacks.

Summary

The present application provides a compound of Formula (I):

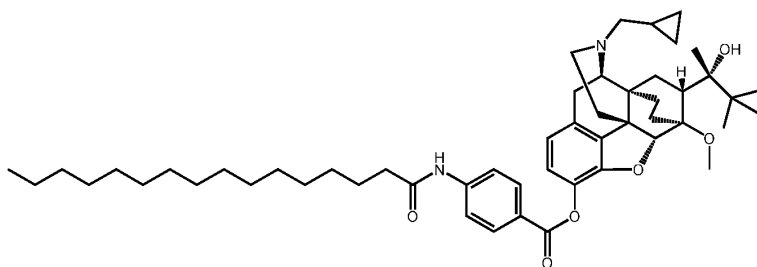


(Formula (I)), or a pharmaceutically acceptable salt thereof, wherein: R is C₁₋₃₀ alkyl, C₂₋₃₀ alkenyl, C₁₋₃₀ heteroalkyl, C₂₋₃₀ heteroalkenyl, phenyl, heteroaryl, or amino acid moiety; and R' is hydrogen, C₁₋₆ alkyl, C₁₋₆ heteroalkyl, C₁₋₆ alkoxy, C₁₋₆ heteroalkoxy, or C₃₋₈ carbocyclyl.

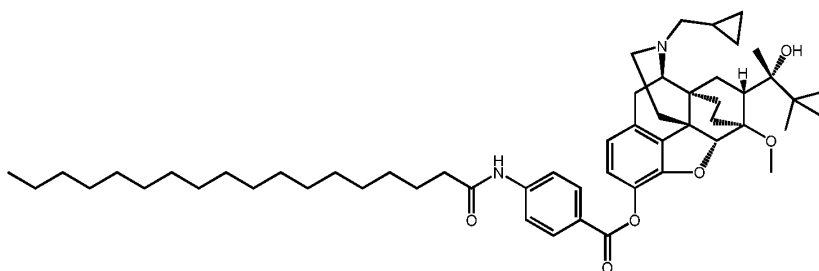
In certain embodiments, R' is hydrogen. In certain embodiments, R' is C₁₋₆ alkyl. In certain embodiments, R' is methyl.

In certain embodiments, R is C₁₋₃₀ alkyl. In certain embodiments, R is C₁₁₋₁₉ alkyl. In certain embodiments, R is C₁₃₋₁₇ alkyl. In certain embodiments, R is C₁₅ alkyl. In certain embodiments, R is C₁₇ alkyl.

The present application provides a compound selected from:

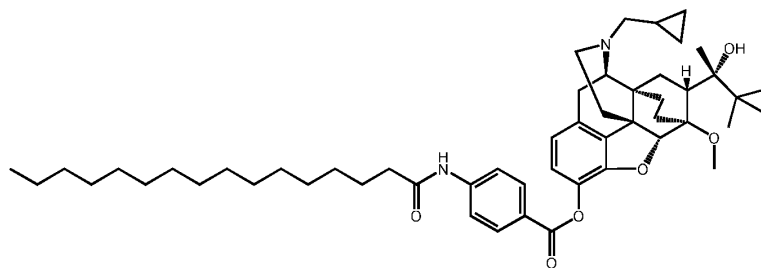


(M4BUP) and



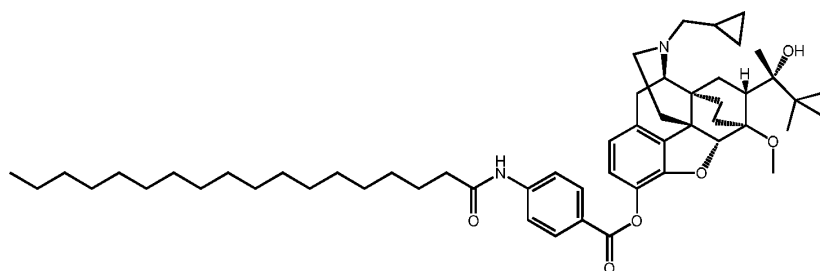
(M6BUP), or

a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is



(M4BUP), or a

pharmaceutically acceptable salt thereof. In certain embodiments, the compound is



(M6BUP), or

a pharmaceutically acceptable salt thereof.

5 In certain embodiments, the compound (e.g., a compound of formula I, such as M4BUP or M6BUP) is complexed with a hydrophobic counterion selected the group consisting of pamoic acid, myristic acid, palmitic acid, stearic acid, behenic acid, napsylate, mandelic acid, tosylate, benzenesulfonate, benzoate, besylate, hydroxynaphthoate, and isethionate. In certain embodiments, the pharmaceutically acceptable salt is a pamoate salt.

10 The present application further provides a nanoparticle comprising a compound as disclosed herein (e.g., a compound of formula I, such as M4BUP or M6BUP), or a pharmaceutically acceptable salt thereof, and one or more polymer or surfactant.

The present application further provides a nanoparticle comprising a pharmaceutically acceptable salt of a compound as disclosed herein (e.g., a compound of formula I, such as M4BUP or M6BUP), and one or more polymer or surfactant. In certain embodiments, the pharmaceutically acceptable salt of the compound is a pamoate salt.

In certain embodiments of the nanoparticles disclosed herein, the one or more polymer or surfactant is an amphiphilic block copolymer. In certain such embodiments, the amphiphilic block copolymer comprises at least one block of poly(oxyethylene) and at least one block of poly(oxypropylene). In certain embodiment of the nanoparticles disclosed herein s, the one or more polymer or surfactant is a poloxomer. In certain embodiments of the

nanoparticles disclosed herein, the one or more polymer or surfactant is P407. In certain
embodiments of the nanoparticles disclosed herein, the one or more polymer or surfactant
comprises a polyoxyethylene sorbitan fatty acid ester. In certain such embodiments, the one
or more polymer or surfactant comprises polyoxyethylene (20) sorbitan monolaurate. In
5 certain embodiments of the nanoparticles disclosed herein, the one or more polymer or
surfactant further comprises polyethylene glycol (PEG). In certain such embodiments, the
one or more polymer or surfactant further comprises PEG 3350. In certain embodiments of
the nanoparticles disclosed herein, the one or more polymer or surfactant comprises
polyethylene glycol (PEG). In certain such embodiments, the one or more polymer or
10 surfactant comprises PEG 3350.

In certain embodiments of the nanoparticles disclosed herein, the diameter of the
nanoparticle is about 100 nm to 1 μ m.

The present application further provides a pharmaceutical composition comprising a
compound as disclosed herein (e.g., a compound of formula I, such as M4BUP or M6BUP),
15 or a pharmaceutically acceptable salt thereof, or a nanoparticle as disclosed herein, and a
pharmaceutically acceptable carrier.

The present application further provides a method of treating drug addiction, drug
dependence, drug overdose, opioid use disorder, pain, chronic pain, fibromyalgia, arthritis, or
obesity in a subject in need thereof, wherein said method comprises administering to said
20 subject a therapeutically effective amount of a compound as disclosed herein (e.g., a
compound of formula I, such as M4BUP or M6BUP), or a pharmaceutically acceptable salt
thereof, a nanoparticle as disclosed herein, or a pharmaceutical composition as disclosed
herein. In certain embodiments, the disease or disorder is opioid use disorder.

In certain embodiments of the foregoing methods, the compound (e.g., a compound of
25 formula I, such as M4BUP or M6BUP), nanoparticle, or composition as disclosed herein is
administered via injection. In certain embodiments of the foregoing methods, the compound
(e.g., a compound of formula I, such as M4BUP or M6BUP), nanoparticle, or composition as
disclosed herein is administered one time in a 1 to 12 month period. In certain embodiments
of the foregoing methods, the compound (e.g., a compound of formula I, such as M4BUP or
30 M6BUP), nanoparticle, or composition as disclosed herein is administered one time in a 3
month period. In certain embodiments of the foregoing methods, the compound (e.g., a
compound of formula I, such as M4BUP or M6BUP), nanoparticle, or composition as

disclosed herein is administered one time in a 6 month period. In certain embodiments of the foregoing methods, the compound (e.g., a compound of formula I, such as M4BUP or M6BUP), nanoparticle, or composition as disclosed herein is administered one time in a 9 month period. In certain embodiments of the foregoing methods, the compound (e.g., a
5 compound of formula I, such as M4BUP or M6BUP), nanoparticle, or composition as disclosed herein is administered one time in a 12 month period.

Brief Description of the Drawings

FIG. 1A and **FIG. 1B** depict ^1H -NMR and ^{13}C -NMR spectra, respectively, for M4BUP.

10 **FIG. 2A** and **FIG. 2B** depict ^1H -NMR and ^{13}C -NMR spectra, respectively, for M6BUP.

FIG. 3A and **FIG. 3B** depict drug uptake and drug retention in monocyte derived macrophages (MDM), respectively.

FIG. 4 depicts the weight analysis of male SD rats administered a single IM dose of
15 NM4BUP (20 or 30 mg BUP eq./kg) in the caudal thigh.

FIG. 5A and **FIG. 5B** depict plasma levels of BUP and M4BUP, respectively, in male SD rats administered a single IM dose of NM4BUP (20 or 30 mg BUP eq./kg) in the caudal thigh.

FIG. 6 depicts plasma levels of BUP in male SD rats administered a single IM dose
20 of NM6BUP (45 or 90 mg BUP eq./kg) in the caudal thigh.

FIG. 7 depicts brain levels of BUP in male SD rats administered a single IM dose of NM6BUP (45 BUP eq./kg) in the caudal thigh.

FIG. 8A and **FIG. 8B** depict drug uptake and drug retention in MDM, respectively.

FIG. 9 depicts a time course evaluation of average particle sizes and polydispersity
25 indices (PDIs) of NM6BUP.

Detailed Description

As generally described herein, the present disclosure provides compounds, nanoparticles, and pharmaceutical compositions comprising the same, and their use for

treating drug addiction, drug dependence, drug overdose, opioid use disorder, pain, chronic pain, fibromyalgia, arthritis, or obesity.

Definitions

To facilitate an understanding of the present disclosure, a number of terms and
5 phrases are defined below.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. The abbreviations used herein have their conventional meaning within the chemical and biological arts. The chemical structures and formulae set forth herein are constructed
10 according to the standard rules of chemical valency known in the chemical arts.

Throughout the present disclosure, where compositions are described as having, including, or comprising specific components, or where processes and methods are described as having, including, or comprising specific steps, it is contemplated that, additionally, there are compositions of the present disclosure that consist essentially of, or consist of, the recited
15 components, and that there are processes and methods according to the present disclosure that consist essentially of, or consist of, the recited processing steps.

In the present disclosure, where an element or component is said to be included in and/or selected from a list of recited elements or components, it should be understood that the element or component can be any one of the recited elements or components, or the element
20 or component can be selected from the group consisting of two or more of the recited elements or components.

Further, it should be understood that elements and/or features of a composition or a method described herein can be combined in a variety of ways without departing from the spirit and scope of the present disclosure, whether explicit or implicit herein. For example,
25 where reference is made to a particular compound, that compound can be used in various embodiments of compositions of the present disclosure and/or in methods of the present disclosure, unless otherwise understood from the context. In other words, within this application, embodiments have been described and depicted in a way that enables a clear and concise application to be written and drawn, but it is intended and will be appreciated that
30 embodiments may be variously combined or separated without parting from the present teachings and disclosure(s). For example, it will be appreciated that all features described and depicted herein can be applicable to all aspects of the disclosure(s) described and depicted herein.

The articles “a” and “an” are used in this disclosure to refer to one or more than one (i.e., to at least one) of the grammatical object of the article, unless the context is inappropriate. By way of example, “an element” means one element or more than one element.

5 The term “and/or” is used in this disclosure to mean either “and” or “or” unless indicated otherwise.

It should be understood that the expression “at least one of” includes individually each of the recited objects after the expression and the various combinations of two or more of the recited objects unless otherwise understood from the context and use. The expression
10 “and/or” in connection with three or more recited objects should be understood to have the same meaning unless otherwise understood from the context.

The use of the term “include,” “includes,” “including,” “have,” “has,” “having,” “contain,” “contains,” or “containing,” including grammatical equivalents thereof, should be understood generally as open-ended and non-limiting, for example, not excluding additional
15 unrecited elements or steps, unless otherwise specifically stated or understood from the context.

Where the use of the term “about” is before a quantitative value, the present disclosure also includes the specific quantitative value itself, unless specifically stated otherwise. As used herein, the term “about” refers to a $\pm 10\%$ variation from the nominal
20 value unless otherwise indicated or inferred from the context. For example, the term “about 10 mg” means 10 mg with a $\pm 10\%$ variation from 10 mg, i.e., an amount in the range of 9 mg to 11 mg.

At various places in the present specification, variable or parameters are disclosed in groups or in ranges. It is specifically intended that the description include each and every
25 individual sub-combination of the members of such groups and ranges. For example, an integer in the range of 0 to 40 is specifically intended to individually disclose 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, and 40, and an integer in the range of 1 to 20 is specifically
30 intended to individually disclose 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, and 20.

The use of any and all examples, or exemplary language herein, for example, “such as” or “including,” is intended merely to illustrate better the present disclosure and does not pose a limitation on the scope of the disclosure unless claimed. No language in the

specification should be construed as indicating any non-claimed element as essential to the practice of the present disclosure.

As a general matter, compositions specifying a percentage are by weight unless otherwise specified. Further, if a variable is not accompanied by a definition, then the
5 previous definition of the variable controls.

As used herein, “pharmaceutical composition” or “pharmaceutical formulation” refers to the combination of an active agent with an excipient or a carrier, inert or active, making the composition especially suitable for diagnostic or therapeutic use *in vivo* or *ex vivo*.

“Pharmaceutically acceptable” means approved or approvable by a regulatory agency
10 of the federal or a state government or the corresponding agency in countries other than the United States, or that is listed in the U.S. Pharmacopoeia or other generally recognized pharmacopoeia for use in animals, and more particularly, in humans.

As used herein, “pharmaceutically acceptable salt” refers to any salt of an acidic or a basic group that may be present in a compound of the present disclosure (*e.g.*, the compound
15 of Formula (I)), which salt is compatible with pharmaceutical administration.

As is known to those of skill in the art, “salts” of compounds may be derived from inorganic or organic acids and bases. Examples of acids include, but are not limited to, hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycolic, lactic, salicylic, succinic, toluene-p-sulfonic, tartaric, acetic, citric, methanesulfonic,
20 ethanesulfonic, formic, benzoic, malonic, naphthalene-2-sulfonic and benzenesulfonic acid. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds described herein and their pharmaceutically acceptable acid addition salts.

Examples of bases include, but are not limited to, alkali metal (*e.g.*, sodium and
25 potassium) hydroxides, alkaline earth metal (*e.g.*, magnesium and calcium) hydroxides, ammonia, and compounds of formula NW_4^+ , wherein W is C₁₋₄ alkyl, and the like.

Examples of salts include, but are not limited, to acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate,
30 flucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, palmoate, pectinate, persulfate, phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, undecanoate, and the like. Other examples of salts include anions of the compounds of the present disclosure

compounded with a suitable cation such as Na^+ , K^+ , Ca^{2+} , NH_4^+ , and NW_4^+ (where W can be a C_{1-4} alkyl group), and the like.

For therapeutic use, salts of the compounds of the present disclosure are contemplated as being pharmaceutically acceptable. However, salts of acids and bases that are non-pharmaceutically acceptable may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound.

As used herein, “pharmaceutically acceptable carrier” refers to a substance that aids the administration of an active agent to and/or absorption by a subject and can be included in the compositions of the present disclosure without causing a significant adverse toxicological effect on the patient. Non-limiting examples of pharmaceutically acceptable carriers include water, NaCl, normal saline solutions, such as a phosphate buffered saline solution, emulsions (*e.g.*, such as an oil/water or water/oil emulsions), lactated Ringer’s, normal sucrose, normal glucose, binders, fillers, disintegrants, lubricants, coatings, sweeteners, flavors, salt solutions (such as Ringer’s solution), alcohols, oils, gelatins, carbohydrates such as lactose, amylose or starch, fatty acid esters, hydroxymethylcellulose, polyvinyl pyrrolidone, and colors, and the like. Such preparations can be sterilized and, if desired, mixed with auxiliary agents such as lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, and/or aromatic substances and the like that do not deleteriously react with the compounds of the disclosure. For examples of carriers, *see* Martin, Remington’s Pharmaceutical Sciences, 15th Ed., Mack Publ. Co., Easton, PA (1975).

A “subject” to which administration is contemplated includes, but is not limited to, humans (*i.e.*, a male or female of any age group, *e.g.*, a pediatric subject (*e.g.*, infant, child, adolescent) or adult subject (*e.g.*, young adult, middle-aged adult or senior adult)) and/or a non-human animal, *e.g.*, a mammal such as primates (*e.g.*, cynomolgus monkeys, rhesus monkeys), cattle, pigs, horses, sheep, goats, rodents, cats, and/or dogs. In certain embodiments, the subject is a human. In certain embodiments, the subject is a non-human animal. “Subject,” “patient,” or “individual” are used interchangeably herein. None of these terms requires supervision of medical personnel.

As used herein, “administering” means oral administration, administration as a suppository, topical contact, intravenous administration, parenteral administration, intraperitoneal administration, intramuscular administration, intralesional administration, intrathecal administration, intracranial administration, intranasal administration or subcutaneous administration, transmucosal (*e.g.*, buccal, sublingual, nasal, or transdermal) administration, or the implantation of a slow-release device, *e.g.*, a mini-osmotic pump, to a

subject. Parenteral administration includes, *e.g.*, intravenous, intramuscular, intra-arterial, intradermal, subcutaneous, intraperitoneal, intraventricular, and intracranial. Other modes of delivery include, but are not limited to, the use of liposomal formulations, intravenous infusion, transdermal patches, etc.

5 As used herein, and unless otherwise specified, the terms “treat,” “treating” and “treatment” contemplate an action that occurs while a subject is suffering from a specified disease, disorder or condition, which action reduces the severity of the disease, disorder or condition, or retards or slows the progression of the disease, disorder or condition or an action that occurs before a subject begins to suffer from the specified disease, disorder or
10 condition, which action prevents a disease, disorder or condition, or one or more symptoms associated with the disease, disorder or condition, or prevents its recurrence.

 The phrase “therapeutically effective amount” as used herein means an amount of a composition (*e.g.*, a composition described herein), or a compound of Formula (I), or a pharmaceutically acceptable salt thereof, which is effective for producing the desired
15 therapeutic effect in a subject.

 Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, *Handbook of Chemistry and Physics*, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general
20 principles of organic chemistry, as well as specific functional moieties and reactivity, are described in Thomas Sorrell, *Organic Chemistry*, University Science Books, Sausalito, 1999; Smith and March, *March’s Advanced Organic Chemistry*, 5th Edition, John Wiley & Sons, Inc., New York, 2001; Larock, *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, 1989; and Carruthers, *Some Modern Methods of Organic Synthesis*, 3rd
25 Edition, Cambridge University Press, Cambridge, 1987.

 Compounds described herein can comprise one or more asymmetric centers, and thus can exist in various isomeric forms, *e.g.*, enantiomers and/or diastereomers. For example, the compounds described herein can be in the form of an individual enantiomer, diastereomer or geometric isomer, or can be in the form of a mixture of stereoisomers, including racemic
30 mixtures and mixtures enriched in one or more stereoisomer. Isomers can be isolated from mixtures by methods known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts; or preferred isomers can be prepared by asymmetric syntheses. See, for example, Jacques *et al.*, *Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, 1981); Wilen *et*

al., *Tetrahedron* 33:2725 (1977); Eliel, *Stereochemistry of Carbon Compounds* (McGraw–Hill, NY, 1962); and Wilen, *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972). The disclosure additionally encompasses compounds described herein as individual isomers substantially free of other
5 isomers, and alternatively, as mixtures of various isomers.

As used herein a pure enantiomeric compound is substantially free from other enantiomers or stereoisomers of the compound (*i.e.*, in enantiomeric excess, “ee”). In other words, an “S” form of the compound is substantially free from the “R” form of the compound and is, thus, in enantiomeric excess of the “R” form. For example, a compound of the
10 application may have greater than 30% ee, 40% ee, 50% ee, 60% ee, 70% ee, 80% ee, 90% ee, or even 95% or greater ee. The term “enantiomerically pure” or “pure enantiomer” denotes that the compound comprises more than 75% by weight, more than 80% by weight, more than 85% by weight, more than 90% by weight, more than 91% by weight, more than 92% by weight, more than 93% by weight, more than 94% by weight, more than 95% by
15 weight, more than 96% by weight, more than 97% by weight, more than 98% by weight, more than 98.5% by weight, more than 99% by weight, more than 99.2% by weight, more than 99.5% by weight, more than 99.6% by weight, more than 99.7% by weight, more than 99.8% by weight or more than 99.9% by weight, of the enantiomer. In certain embodiments, the weights are based upon total weight of all enantiomers or stereoisomers of the compound.

20 In the compositions provided herein, an enantiomerically pure compound can be present with other active or inactive ingredients. For example, a pharmaceutical composition comprising enantiomerically pure R–compound can comprise, for example, about 90% excipient and about 10% enantiomerically pure R–compound. In certain embodiments, the enantiomerically pure R–compound in such compositions can, for example, comprise, at least
25 about 95% by weight R–compound and at most about 5% by weight S–compound, by total weight of the compound. For example, a pharmaceutical composition comprising enantiomerically pure S–compound can comprise, for example, about 90% excipient and about 10% enantiomerically pure S–compound. In certain embodiments, the enantiomerically pure S–compound in such compositions can, for example, comprise, at least about 95% by
30 weight S–compound and at most about 5% by weight R–compound, by total weight of the compound. In certain embodiments, the active ingredient can be formulated with little or no excipient or carrier.

In certain embodiments, compounds of the application may have more than one stereocenter. In certain such embodiments, compounds of the application may be enriched in

one or more diastereomer (*i.e.*, in diastereomeric excess, “de”). For example, a compound of the application may have greater than 30% de, 40% de, 50% de, 60% de, 70% de, 80% de, 90% de, or even 95% or greater de.

5 In certain embodiments, the therapeutic preparation may be enriched to provide predominantly one diastereomer of a compound (e.g., of formula (I), or a pharmaceutically acceptable salt thereof). A diastereomerically enriched mixture may comprise, for example, at least 60 mol percent of one diastereomer, or more preferably at least 75, 90, 95, or even 99 mol percent.

Compound described herein may also comprise one or more isotopic substitutions.
10 For example, H may be in any isotopic form, including ^1H , ^2H (D or deuterium), and ^3H (T or tritium); C may be in any isotopic form, including ^{12}C , ^{13}C , and ^{14}C ; O may be in any isotopic form, including ^{16}O and ^{18}O ; F may be in any isotopic form, including ^{18}F and ^{19}F ; and the like. For example, in certain embodiments, in compounds (e.g., of formula (I), or pharmaceutically acceptable salts thereof), hydrogen atoms are replaced or substituted by one
15 or more deuterium or tritium (e.g., hydrogen atoms on a C_{1-6} alkyl or a C_{1-6} alkoxy are replaced with deuterium, such as d_3 -methoxy or 1,1,2,2- d_4 -3-methylbutyl).

The compounds of the application, including their pharmaceutically acceptable salts, can also exist as various solvates, such as with water (also known as hydrates), methanol, ethanol, dimethylformamide, diethyl ether, acetamide, and the like. Mixtures of such
20 solvates can also be prepared. The source of such solvate can be from the solvent of crystallization, inherent in the solvent of preparation or crystallization, or adventitious to such solvent.

The compounds of the application, including their pharmaceutically acceptable salts, can also exist as various polymorphs, pseudo-polymorphs, or in amorphous state. As used
25 herein, the term “polymorph” refers to different crystalline forms of the same compound and other solid state molecular forms including pseudo-polymorphs, such as hydrates, solvates, or salts of the same compound. Different crystalline polymorphs have different crystal structures due to a different packing of molecules in the lattice, as a result of changes in temperature, pressure, or variations in the crystallization process. Polymorphs differ from
30 each other in their physical properties, such as x-ray diffraction characteristics, stability, melting points, solubility, or rates of dissolution in certain solvents. Thus, crystalline polymorphic forms are important aspects in the development of suitable dosage forms in pharmaceutical industry.

The following terms are intended to have the meanings presented therewith below and are useful in understanding the description and intended scope of the present disclosure.

When describing the disclosure, which may include compounds and pharmaceutically acceptable salts thereof, pharmaceutical compositions containing such compounds and methods of using such compounds and compositions, the following terms, if present, have the following meanings unless otherwise indicated. It should also be understood that when described herein any of the moieties defined forth below may be substituted with a variety of substituents, and that the respective definitions are intended to include such substituted moieties within their scope as set out below. Unless otherwise stated, the term “substituted” is to be defined as set out below. It should be further understood that the terms “groups” and “radicals” can be considered interchangeable when used herein. The articles “a” and “an” may be used herein to refer to one or to more than one (*i.e.* at least one) of the grammatical objects of the article. By way of example “an analogue” means one analogue or more than one analogue.

When a range of values is listed, it is intended to encompass each value and sub-range within the range. For example, “C₁₋₆ alkyl” is intended to encompass, C₁, C₂, C₃, C₄, C₅, C₆, C₁₋₆, C₁₋₅, C₁₋₄, C₁₋₃, C₁₋₂, C₂₋₆, C₂₋₅, C₂₋₄, C₂₋₃, C₃₋₆, C₃₋₅, C₃₋₄, C₄₋₆, C₄₋₅, and C₅₋₆ alkyl.

As used herein, “alkyl” refers to a radical of a straight-chain or branched saturated hydrocarbon group, *e.g.*, having 1 to 30 carbon atoms (“C₁₋₃₀ alkyl”). In some embodiments, an alkyl group has 1 to 10 carbon atoms (“C₁₋₁₀ alkyl”). In some embodiments, an alkyl group has 1 to 9 carbon atoms (“C₁₋₉ alkyl”). In some embodiments, an alkyl group has 1 to 8 carbon atoms (“C₁₋₈ alkyl”). In some embodiments, an alkyl group has 1 to 7 carbon atoms (“C₁₋₇ alkyl”). In some embodiments, an alkyl group has 1 to 6 carbon atoms (“C₁₋₆ alkyl”).

In some embodiments, an alkyl group has 1 to 5 carbon atoms (“C₁₋₅ alkyl”). In some embodiments, an alkyl group has 1 to 4 carbon atoms (“C₁₋₄ alkyl”). In some embodiments, an alkyl group has 1 to 3 carbon atoms (“C₁₋₃ alkyl”). In some embodiments, an alkyl group has 1 to 2 carbon atoms (“C₁₋₂ alkyl”). In some embodiments, an alkyl group has 1 carbon atom (“C₁ alkyl”). Examples of C₁₋₆ alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, and the like.

The term “heteroalkyl” as used herein refers to an “alkyl” group in which at least one carbon atom has been replaced with an O, S, or N atom. The heteroalkyl may be, for example, an -O-C₁-C₁₀alkyl group, an -C₁-C₆alkylene-O-C₁-C₆alkyl group, or a C₁-C₆alkylene-OH group. In certain embodiments, the “heteroalkyl” may be 2-8 membered

heteroalkyl, indicating that the heteroalkyl contains from 2 to 8 atoms selected from the group consisting of carbon, oxygen, nitrogen, and sulfur. In yet other embodiments, the heteroalkyl may be a 2-6 membered, 4-8 membered, or a 5-8 membered heteroalkyl group (which may contain for example 1 or 2 heteroatoms selected from the group oxygen and nitrogen). In certain embodiments, the heteroalkyl is an “alkyl” group in which 1-3 carbon atoms have been replaced with oxygen atoms. One type of heteroalkyl group is an “alkoxy” group.

As used herein, “alkenyl” refers to a radical of a straight-chain or branched hydrocarbon group having from 2 to 30 carbon atoms, one or more carbon-carbon double bonds (*e.g.*, 1, 2, 3, or 4 carbon-carbon double bonds), and optionally one or more carbon-carbon triple bonds (*e.g.*, 1, 2, 3, or 4 carbon-carbon triple bonds) (“C₂₋₃₀ alkenyl”). In certain embodiments, alkenyl does not contain any triple bonds. In some embodiments, an alkenyl group has 2 to 10 carbon atoms (“C₂₋₁₀ alkenyl”). In some embodiments, an alkenyl group has 2 to 9 carbon atoms (“C₂₋₉ alkenyl”). In some embodiments, an alkenyl group has 2 to 8 carbon atoms (“C₂₋₈ alkenyl”). In some embodiments, an alkenyl group has 2 to 7 carbon atoms (“C₂₋₇ alkenyl”). In some embodiments, an alkenyl group has 2 to 6 carbon atoms (“C₂₋₆ alkenyl”). In some embodiments, an alkenyl group has 2 to 5 carbon atoms (“C₂₋₅ alkenyl”). In some embodiments, an alkenyl group has 2 to 4 carbon atoms (“C₂₋₄ alkenyl”). In some embodiments, an alkenyl group has 2 to 3 carbon atoms (“C₂₋₃ alkenyl”). In some embodiments, an alkenyl group has 2 carbon atoms (“C₂ alkenyl”). The one or more carbon-carbon double bonds can be internal (such as in 2-butenyl) or terminal (such as in 1-butenyl). Examples of C₂₋₄ alkenyl groups include ethenyl (C₂), 1-propenyl (C₃), 2-propenyl (C₃), 1-butenyl (C₄), 2-butenyl (C₄), butadienyl (C₄), and the like. Examples of C₂₋₆ alkenyl groups include the aforementioned C₂₋₄ alkenyl groups as well as pentenyl (C₅), pentadienyl (C₅), hexenyl (C₆), and the like. Additional examples of alkenyl include heptenyl (C₇), octenyl (C₈), octatrienyl (C₈), and the like.

As used herein, “alkynyl” refers to a radical of a straight-chain or branched hydrocarbon group having from 2 to 30 carbon atoms, one or more carbon-carbon triple bonds (*e.g.*, 1, 2, 3, or 4 carbon-carbon triple bonds), and optionally one or more carbon-carbon double bonds (*e.g.*, 1, 2, 3, or 4 carbon-carbon double bonds) (“C₂₋₃₀ alkynyl”). In certain embodiments, alkynyl does not contain any double bonds. In some embodiments, an alkynyl group has 2 to 10 carbon atoms (“C₂₋₁₀ alkynyl”).

In some embodiments, an alkynyl group has 2 to 9 carbon atoms (“C₂₋₉ alkynyl”). In some embodiments, an alkynyl group has 2 to 8 carbon atoms (“C₂₋₈ alkynyl”). In some embodiments, an alkynyl group has 2 to 7 carbon atoms (“C₂₋₇ alkynyl”). In some embodiments, an alkynyl group has 2 to 6 carbon atoms (“C₂₋₆ alkynyl”). In some
5 embodiments, an alkynyl group has 2 to 5 carbon atoms (“C₂₋₅ alkynyl”). In some
embodiments, an alkynyl group has 2 to 4 carbon atoms (“C₂₋₄ alkynyl”). In some
embodiments, an alkynyl group has 2 to 3 carbon atoms (“C₂₋₃ alkynyl”). In some
embodiments, an alkynyl group has 2 carbon atoms (“C₂ alkynyl”). The one or more carbon–
carbon triple bonds can be internal (such as in 2–butynyl) or terminal (such as in 1–butynyl).
10 Examples of C₂₋₄ alkynyl groups include, without limitation, ethynyl (C₂), 1–propynyl (C₃),
2–propynyl (C₃), 1–butynyl (C₄), 2–butynyl (C₄), and the like. Examples of C₂₋₆ alkenyl
groups include the aforementioned C₂₋₄ alkynyl groups as well as pentynyl (C₅), hexynyl
(C₆), and the like. Additional examples of alkynyl include heptynyl (C₇), octynyl (C₈), and
the like.

15 As used herein, “alkylene,” “alkenylene,” and “alkynylene,” refer to a divalent radical
of an alkyl, alkenyl, and alkynyl group respectively. When a range or number of carbons is
provided for a particular “alkylene,” “alkenylene,” or “alkynylene,” group, it is understood
that the range or number refers to the range or number of carbons in the linear carbon
divalent chain. “Alkylene,” “alkenylene,” and “alkynylene,” groups may be substituted or
20 unsubstituted with one or more substituents as described herein.

 As used herein, “heteroalkylene” refers to a divalent radical of a heteroalkyl group.
When a range or number of carbons is provided for a particular “heteroalkylene” group, it is
understood that the range or number refers to the range or number of carbons in the linear
carbon divalent chain. “Heteroalkylene” group may be substituted or unsubstituted with one
25 or more substituents as described herein.

 As used herein, “heteroaryl” refers to a radical of a 5–10 membered monocyclic or
bicyclic 4n+2 aromatic ring system (*e.g.*, having 6 or 10 electrons shared in a cyclic array)
having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system,
wherein each heteroatom is independently selected from nitrogen, oxygen and sulfur (“5–10
30 membered heteroaryl”). In heteroaryl groups that contain one or more nitrogen atoms, the
point of attachment can be a carbon or nitrogen atom, as valency permits. Heteroaryl bicyclic
ring systems can include one or more heteroatoms in one or both rings. “Heteroaryl” includes
ring systems wherein the heteroaryl ring, as defined above, is fused with one or more
carbocyclyl or heterocyclyl groups wherein the point of attachment is on the heteroaryl ring,

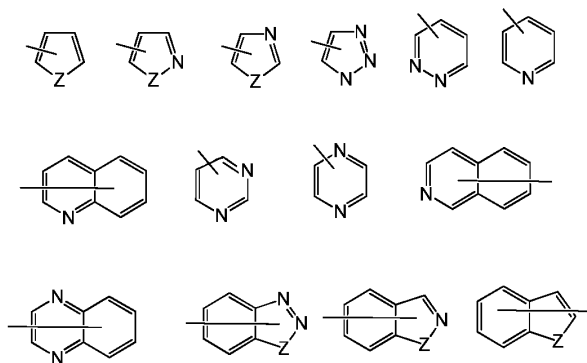
and in such instances, the number of ring members continue to designate the number of ring members in the heteroaryl ring system. "Heteroaryl" also includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more aryl groups wherein the point of attachment is either on the aryl or heteroaryl ring, and in
5 such instances, the number of ring members designates the number of ring members in the fused (aryl/heteroaryl) ring system. Bicyclic heteroaryl groups wherein one ring does not contain a heteroatom (*e.g.*, indolyl, quinoliny, carbazolyl, and the like) the point of attachment can be on either ring, *i.e.*, either the ring bearing a heteroatom (*e.g.*, 2-indolyl) or the ring that does not contain a heteroatom (*e.g.*, 5-indolyl).

10 In some embodiments, a heteroaryl group is a 5–10 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–10 membered heteroaryl"). In some embodiments, a heteroaryl group is a 5–8 membered aromatic ring system having ring carbon atoms
15 and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–8 membered heteroaryl"). In some embodiments, a heteroaryl group is a 5–6 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from
20 nitrogen, oxygen, and sulfur ("5–6 membered heteroaryl"). In some embodiments, the 5–6 membered heteroaryl has 1–3 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5–6 membered heteroaryl has 1–2 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5–6 membered heteroaryl has 1 ring heteroatom selected from nitrogen, oxygen, and
25 sulfur.

Exemplary 5-membered heteroaryl groups containing one heteroatom include, without limitation, pyrrolyl, furanyl and thiophenyl. Exemplary 5-membered heteroaryl groups containing two heteroatoms include, without limitation, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, and isothiazolyl. Exemplary 5-membered
30 heteroaryl groups containing three heteroatoms include, without limitation, triazolyl, oxadiazolyl, and thiadiazolyl. Exemplary 5-membered heteroaryl groups containing four heteroatoms include, without limitation, tetrazolyl. Exemplary 6-membered heteroaryl groups containing one heteroatom include, without limitation, pyridinyl. Exemplary 6-membered heteroaryl groups containing two heteroatoms include,

- without limitation, pyridazinyl, pyrimidinyl, and pyrazinyl. Exemplary 6-membered heteroaryl groups containing three or four heteroatoms include, without limitation, triazinyl and tetrazinyl, respectively. Exemplary 7-membered heteroaryl groups containing one heteroatom include, without limitation, azepinyl, oxepinyl, and thiepinyl. Exemplary 5,6-bicyclic heteroaryl groups include, without limitation, indolyl, isoindolyl, indazolyl, benzotriazolyl, benzothiophenyl, isobenzothiophenyl, benzofuranyl, benzoisofuranyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzoxadiazolyl, benzthiazolyl, benzisothiazolyl, benzthiadiazolyl, indoliziny, and purinyl. Exemplary 6,6-bicyclic heteroaryl groups include, without limitation, naphthyridinyl, pteridinyl, quinolinyl, isoquinolinyl, cinnolinyl, quinoxalinyl, phthalazinyl, and quinazolinyl.

Examples of representative heteroaryls include the following:



- wherein each Z is selected from carbonyl, N, NR⁶⁵, O, and S; and R⁶⁵ is independently hydrogen, C₁-C₈ alkyl, C₃-C₁₀ carbocyclyl, 4-10 membered heterocyclyl, C₆-C₁₀ aryl, and 5-10 membered heteroaryl.

- As used herein, “carbocyclyl” or “carbocyclic” refers to a radical of a non-aromatic cyclic hydrocarbon group having from 3 to 10 ring carbon atoms (“C₃₋₁₀ carbocyclyl”) and zero heteroatoms in the non-aromatic ring system. In some embodiments, a carbocyclyl group has 3 to 8 ring carbon atoms (“C₃₋₈ carbocyclyl”). In some embodiments, a carbocyclyl group has 3 to 6 ring carbon atoms (“C₃₋₆ carbocyclyl”). In some embodiments, a carbocyclyl group has 5 to 10 ring carbon atoms (“C₅₋₁₀ carbocyclyl”). Exemplary C₃₋₆ carbocyclyl groups include, without limitation, cyclopropyl (C₃), cyclobutyl (C₄), cyclobutenyl (C₄), cyclopentyl (C₅), cyclopentenyl (C₅), cyclohexyl (C₆), cyclohexenyl (C₆), cyclohexadienyl (C₆), and the like. Exemplary C₃₋₈ carbocyclyl groups include, without limitation, the aforementioned C₃₋₆ carbocyclyl groups as well as cycloheptyl (C₇), cycloheptenyl (C₇), cycloheptadienyl (C₇), cycloheptatrienyl (C₇), cyclooctyl (C₈), cyclooctenyl (C₈),

bicyclo[2.2.1]heptanyl (C₇), bicyclo[2.2.2]octanyl (C₈), and the like. Exemplary C₃₋₁₀ carbocyclyl groups include, without limitation, the aforementioned C₃₋₈ carbocyclyl groups as well as cyclononyl (C₉), cyclononenyl (C₉), cyclodecyl (C₁₀), cyclodecenyl (C₁₀), octahydro-1*H*-indenyl (C₉), decahydronaphthalenyl (C₁₀), spiro[4.5]decanyl (C₁₀), and the like. As the foregoing examples illustrate, in certain embodiments, the carbocyclyl group is either monocyclic ("monocyclic carbocyclyl") or contain a fused, bridged or spiro ring system such as a bicyclic system ("bicyclic carbocyclyl") and can be saturated or can be partially unsaturated. "Carbocyclyl" also includes ring systems wherein the carbocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups wherein the point of attachment is on the carbocyclyl ring, and in such instances, the number of carbons continue to designate the number of carbons in the carbocyclic ring system.

"Hetero" when used to describe a compound or a group present on a compound means that one or more carbon atoms in the compound or group have been replaced by a nitrogen, oxygen, or sulfur heteroatom. Hetero may be applied to any of the hydrocarbyl groups described above such as alkyl, *e.g.*, heteroalkyl; carbocyclyl, *e.g.*, heterocyclyl; aryl, *e.g.*, heteroaryl; and the like having from 1 to 5, and particularly from 1 to 3 heteroatoms.

As used herein, "halo" or "halogen" refers to fluoro (F), chloro (Cl), bromo (Br) and iodo (I). In certain embodiments, the halo group is either fluoro or chloro.

As used herein, "haloalkyl" refers to an alkyl group substituted with one or more halogen atoms.

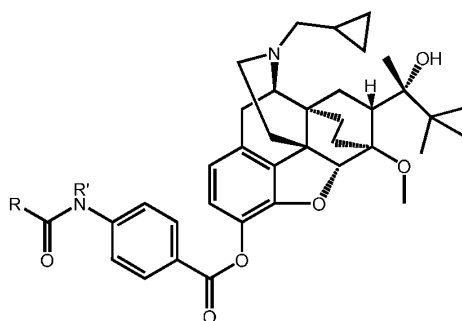
In general, the term "substituted", whether preceded by the term "optionally" or not, means that at least one hydrogen present on a group (*e.g.*, a carbon or nitrogen atom) is replaced with a permissible substituent, *e.g.*, a substituent which upon substitution results in a stable compound, *e.g.*, a compound which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, or other reaction. Unless otherwise indicated, a "substituted" group has a substituent at one or more substitutable positions of the group, and when more than one position in any given structure is substituted, the substituent is either the same or different at each position.

Nitrogen atoms can be substituted or unsubstituted as valency permits, and include primary, secondary, tertiary, and quarternary nitrogen atoms. Exemplary nitrogen atom substituents include, but are not limited to, hydrogen, -OH, -OR^{aa}, -N(R^{cc})₂, -CN, -C(=O)R^{aa}, -C(=O)N(R^{cc})₂, -CO₂R^{aa}, -SO₂R^{aa}, -C(=NR^{bb})R^{aa}, -

$C(=NR^{cc})OR^{aa}$, $-C(=NR^{cc})N(R^{cc})_2$, $-SO_2N(R^{cc})_2$, $-SO_2R^{cc}$, $-SO_2OR^{cc}$, $-SOR^{aa}$, $-C(=S)N(R^{cc})_2$, $-C(=O)SR^{cc}$, $-C(=S)SR^{cc}$, $-P(=O)_2R^{aa}$, $-P(=O)(R^{aa})_2$, $-P(=O)_2N(R^{cc})_2$, $-P(=O)(NR^{cc})_2$, C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} carbocyclyl, 3–14 membered heterocyclyl, C_{6-14} aryl, and 5–14 membered heteroaryl, or two R^{cc} groups attached to a nitrogen atom are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups, and wherein R^{aa} , R^{bb} , R^{cc} and R^{dd} are as defined above.

Compounds

Disclosed herein, in certain embodiments, are compounds of Formula (I):



Formula (I),

or a pharmaceutically acceptable salt thereof, wherein:

R is C_{1-30} alkyl, C_{2-30} alkenyl, C_{1-30} heteroalkyl, C_{2-30} heteroalkenyl, phenyl, heteroaryl, or amino acid moiety; and

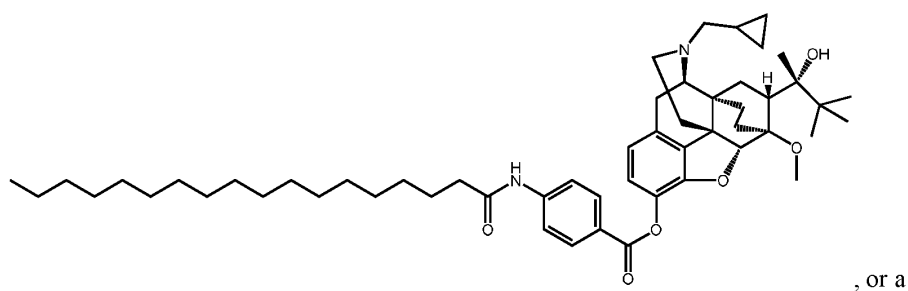
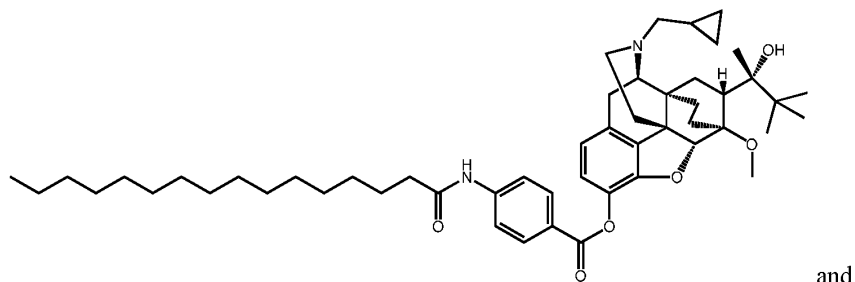
R' is hydrogen, C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{1-6} alkoxy, C_{1-6} heteroalkoxy, or C_{3-8} carbocyclyl.

In certain embodiments, R' is hydrogen. In certain embodiments, R' is C_{1-6} alkyl. In certain embodiments, R' is methyl.

In certain embodiments, R is C_{1-30} alkyl. In certain embodiments, R is C_9-C_{25} alkyl. In certain embodiments, R is $C_{11}-C_{21}$ alkyl. In certain embodiments, R is $C_{11}-C_{19}$ alkyl. In certain embodiments, R is $C_{11}-C_{15}$ alkyl. In certain embodiments, R is $C_{13}-C_{19}$ alkyl. In certain embodiments, R is $C_{13}-C_{17}$ alkyl. In certain embodiments, R is C_{13} alkyl. In certain embodiments, R is C_{14} alkyl. In certain embodiments, R is C_{15} alkyl. In certain embodiments, R is C_{16} alkyl. In certain embodiments, R is C_{17} alkyl. In certain embodiments, R is C_{18} alkyl. In certain embodiments, R is linear C_9-C_{25} alkyl. In certain embodiments, R is linear $C_{11}-C_{21}$ alkyl. In certain embodiments, R is linear $C_{11}-C_{19}$ alkyl. In certain embodiments, R is

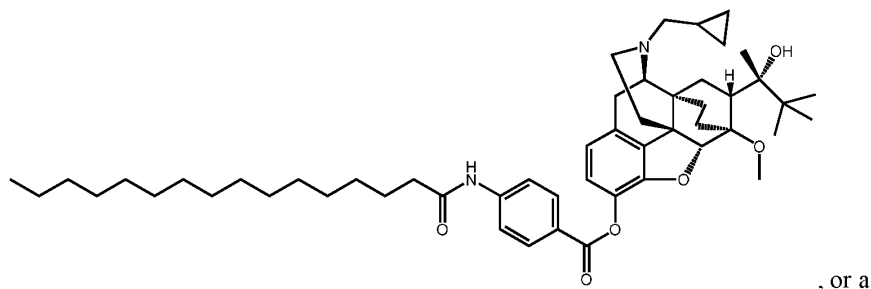
- linear C₁₁-C₁₅ alkyl. In certain embodiments, R is linear C₁₃-C₁₉ alkyl. In certain embodiments, R is linear C₁₃-C₁₇ alkyl. In certain embodiments, R is linear C₁₃ alkyl. In certain embodiments, R is linear C₁₄ alkyl. In certain embodiments, R is linear C₁₅ alkyl. In certain embodiments, R is linear C₁₆ alkyl. In certain embodiments, R is linear C₁₇ alkyl. In certain embodiments, R is linear C₁₈ alkyl.

In certain embodiments, the compound is selected from one of the following:



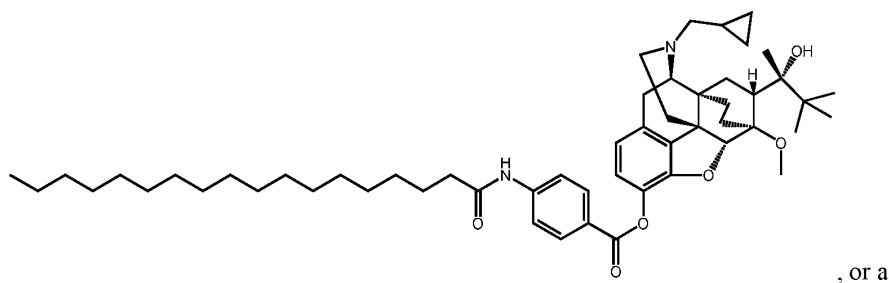
pharmaceutically acceptable salt thereof.

In certain embodiments, the compound is



pharmaceutically acceptable salt thereof.

In certain embodiments, the compound is



pharmaceutically acceptable salt thereof.

In various embodiments, the pharmaceutically acceptable salt of the compound of Formula (I) is a salt of the compound of Formula (I) with physiologically compatible mineral acids, such as hydrochloric acid, sulphuric acid, sulphurous acid or phosphoric acid; or with organic acids, such as methanesulphonic acid, p-toluenesulphonic acid, acetic acid, lactic acid, trifluoroacetic acid, citric acid, fumaric acid, maleic acid, tartaric acid, succinic acid or salicylic acid.

In some embodiments, the compounds of Formula (I) are formed into nanocrystals or other crystalline forms. In certain embodiments, the compounds are complexed with a hydrophobic counterion, including but not limited to pamoic acid, myristic acid, palmitic acid, stearic acid, behenic acid, napsylate, mandelic acid, tosylate, benzenesulfonate, benzoate, besylate, hydroxynaphthoate and isothionates used to form a crystalline and/or solid salt compound forms. In certain embodiments, the pharmaceutically acceptable salt is a pamoate salt.

In certain embodiments, the pharmaceutically acceptable salt can be characterized by a ratio of drug to counterion of 1:1 or 2:1. The compound salt can be crystalline or an amorphous solid.

In certain embodiments, the compounds disclosed herein modulate the opioid receptor. For example, buprenorphine (BUP) is a high affinity partial agonist for the μ -opioid receptor (MOR). Buprenorphine greatly reduces the effect of most other MOR agonists, can cause precipitated withdrawal when used in actively opioid dependent subjects, and has a lower incidence of respiratory depression and fatal overdose relative to full MOR agonists. See, e.g., Gudín, Jeffrey; Fudin, Jeffrey, "A Narrative Pharmacological Review of Buprenorphine: A Unique Opioid for the Treatment of Chronic Pain" *Pain and Therapy*, 2020, 9 (1): 41–54; Robinson SE, "Buprenorphine: an analgesic with an expanding role in the treatment of opioid addiction" *CNS Drug Reviews*, 2002, 8 (4): 377–90; and Khanna, Ish K.; Pillarisetti, Sivaram "Buprenorphine - an attractive opioid with underutilized potential in treatment of chronic pain" *Journal of Pain Research*, 2015, 8: 859–870. Buprenorphine is also hypothesized to be a high affinity antagonist of κ -opioid receptor (KOR), a high affinity antagonist for δ -opioid receptor (DOR), and a weak affinity, weak partial agonist of nociception receptor (NOP, ORL-1).

In certain embodiments, the compounds disclosed herein are very high affinity partial agonist of MOR. In certain embodiments, the compounds disclosed herein are high affinity antagonist of KOR. In certain embodiments, the compounds disclosed herein are high affinity antagonist of DOR. In certain embodiments, the compounds disclosed herein are weak partial agonist of NOP or ORL-1.

In certain embodiments, the compounds disclosed herein reduce the severity of or prevent adverse events associated with administration of opioid receptor modulators such as buprenorphine. Exemplary adverse events associated with administration of opioid receptor modulators such as buprenorphine includes, but are not limited to, constipation, dizziness, drowsiness, headache, nausea, drug withdrawal, fatigue, vomiting, hyperhidrosis, xerostomia, stomach pain, difficulty falling asleep or staying asleep, blurred vision, back pain, hives, rash, itching, overdose, and respiratory depression. In certain embodiments, administration of a compound disclosed herein provides for a controlled release of opioid receptor modulators such as buprenorphine relative to the administration of opioid receptor modulators such as buprenorphine.

Nanoparticles

Disclosed herein, in certain embodiments, are nanoparticles, comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and one or more polymer or surfactant. Typically, the compound (including any crystalline or solid salt form of the

compound) maybe encapsulated by a coating comprising one or more polymer or surfactant to form nanoparticles (or nanoformulations).

In certain embodiments, the compound:polymer (or surfactant) ratio (by weight) is about 10:1, about 10:6 to about 1000:6, about 20:6 to about 500:6, about 50:6 to about 200:6, or about 100:6. In certain embodiments wherein the nanoparticle comprises two polymers or surfactants, the compound:polymer (or surfactant):polymer (or surfactant) ratio (by weight) is about 10:1:1 to about 20:1:1, about 500:1:1 to about 50:1:1, about 200:1:1 to about 100:1:1, 5:1:1 to about 10:1:1, or 5:1:1 to about 7:1:1. In certain embodiments wherein the nanoparticle comprises two polymers or surfactants, the compound:polymer (or surfactant):polymer (or surfactant) ratio (by weight) is about 5:1:1, about 6:1:1, about 7:1:1, about 8:1:1, about 9:1:1, or about 10:1:1. In certain embodiments wherein the nanoparticle comprises two polymers or surfactants, the compound:polymer (or surfactant):polymer (or surfactant) ratio (by weight) is about 7:1:1.

In certain embodiments, the nanoparticles comprise a pharmaceutically acceptable salt of the compound of Formula (I), and one or more polymer or surfactant. In certain embodiments, the nanoparticles comprise a pharmaceutically acceptable salt of the compound of Formula (I), and more than one polymer or surfactant, such as two surfactants.

In a particular embodiment, the nanoparticles are a submicron colloidal dispersion of nanosized compound crystals or solid salt forms of the compound stabilized by polymers (or surfactants) (*e.g.*, polymer-coated compound crystals; a nanoformulation). In a particular embodiment, the compound of the nanoparticles may be crystalline or a solid salt form complexed with a hydrophobic counterion. In certain embodiments, the nanoparticles containing the compound are crystalline. In certain embodiments, the nanoparticles and/or the compound may be crystalline, amorphous, or are solid-state nanoparticles of the compound that is formed as crystal that combines the compound and polymer (or surfactant). As used herein, the term “crystalline” refers to an ordered state (*i.e.* non-amorphous) and/or a substance exhibiting long-range order in three dimensions. In a particular embodiment, the majority (*e.g.*, at least 50%, 60%, 70%, 80%, 90%, 95% or more) of the compound (and, optionally the hydrophobic portion of the polymer (or surfactant) are crystalline or a solid salt form complexed with a hydrophobic counterion.

In certain embodiments, the resultant nanoparticle is up to about 2 or 3 μm in diameter (*e.g.*, average diameter) or its longest dimension, particularly up to about 1 μm (*e.g.*, about 100 nm to about 1 μm). For example, the diameter or longest dimension of the nanoparticle may be about 50 to about 800 nm. In a particular embodiment, the diameter or

longest dimension of the nanoparticle is about 50 to about 750 nm, about 50 to about 500 nm, about 200 nm to about 500 nm, or about 200 nm to about 400 nm. The nanoparticles may be, for example, rod shaped, elongated rods, irregular, or round shaped. The nanoparticles of the instant disclosure may be neutral or charged. The nano particles may be charged positively or negatively.

Methods of synthesizing the nanoparticles of the instant disclosure are known in the art. In certain embodiment, the methods generate nanoparticles comprising a compound (*e.g.*, crystalline or amorphous) coated (either partially or completely) with a polymer (or surfactant). Examples of synthesis methods include, without limitation, milling (*e.g.*, wet milling), homogenization (*e.g.*, high pressure homogenization), particle replication in nonwetting template (PRINT) technology, and/or sonication techniques. For example, U.S. Patent Application Publication No. 2013/0236553, incorporated by reference herein, provides methods suitable for synthesizing nanoparticles of the instant disclosure. In a particular embodiment, the polymers (or surfactants) are firstly chemically modified with targeting ligands and then used directly or mixed with non-targeted polymers (or surfactants) in certain molar ratios to coat on the surface of drug suspensions - *e.g.*, by using a nanoparticle synthesis process (*e.g.*, a crystalline nanoparticle synthesis process) such as milling (*e.g.*, wet milling), homogenization (*e.g.*, high pressure homogenization), particle replication in nonwetting template (PRINT) technology, and/or sonication techniques, thereby preparing targeted nanoformulations. The nanoparticles may be used with or without further purification, although the avoidance of further purification is desirable for quicker production of the nano particles. In a particular embodiment, the nanoparticles are synthesized using milling and/or homogenization.

In a particular embodiment, the nanoparticles are synthesized by adding the compound to solution comprising one or more polymers (or surfactants) (described below) and then generating the nanoparticles (*e.g.*, by wet milling or high pressure homogenization). The compound and polymer(s) (or surfactant(s)) solution may be agitated prior to wet milling or high pressure homogenization to form nanoparticles.

Examples of polymers (or surfactants) include, without limitation, synthetic or natural phospholipids, PEGylated lipids (*e.g.*, PEGylated phospholipid), lipid derivatives, polysorbates, amphiphilic copolymers, amphiphilic block copolymers, poly(ethylene glycol)-co-poly(lactide-co-glycolide) (PEG-PLGA), their derivatives, ligand-conjugated derivatives and combinations thereof. Further examples of surfactants include, without limitation: 1) nonionic surfactants (*e.g.*, pegylated and/or polysaccharide-conjugated polyesters and other

- hydrophobic polymeric blocks such as poly(lactide-co-glycolide) (PLGA), polylactic acid (PLA), polycaprolactone (PCL), other polyesters, poly(propylene oxide), poly(1,2-butylene oxide), poly(n-butylene oxide), poly(tetrahydrofuran), and poly(styrene); glyceryl esters, polyoxyethylene fatty alcohol ethers, polyoxyethylene sorbitan fatty acid esters,
- 5 polyoxyethylene fatty acid esters, sorbitan esters, glycerol monostearate, polyethylene glycols, polypropyleneglycols, cetyl alcohol, cetostearyl alcohol, stearyl alcohol, aryl alkyl polyether alcohols, polyoxyethylene-polyoxypropylene copolymers, poloxamines, cellulose, methylcellulose, hydroxymethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, polysaccharides, starch and their derivatives,
- 10 hydroxyethylstarch, polyvinyl alcohol (PVA), polyvinylpyrrolidone, and their combination thereof); and 2) ionic surfactants (*e.g.*, phospholipids, amphiphilic lipids, 1,2-dialkylglycero-3-alkylphosphocholines, 1, 2- distearoyl-sn-glycero-3-phosphocholine (DSPC), 1,2-distearoyl-sn-glycero-3- phosphoethanolamine-N[carboxy(polyethylene glycol) (DSPE-PEG), dimethylaminoethanecarbamoyl cholesterol (DC-Chol), N-[1-(2,3-Dioleoyloxy)propyl]-
- 15 N,N,N-trimethylammonium (DOTAP), alkyl pyridinium halides, quaternary ammonium compounds, lauryldimethylbenzylammonium, acyl carnitine hydrochlorides, dimethyldioctadecylammonium (DDAB), n-octylamines, oleylamines, benzalkonium, cetyltrimethylammonium, chitosan, chitosan salts, poly(ethylenimine) (PEI), poly(N-isopropyl acrylamide(PNIPAM), and poly(allylamine) (PAH), poly
- 20 (dimethyldiallylammonium chloride) (PDDA), alkyl sulfonates, alkyl phosphates, alkyl phosphonates, potassium laurate, triethanolamine stearate, sodium lauryl sulfate, sodium dodecylsulfate, alkyl polyoxyethylene sulfates, alginic acid, alginic acid salts, hyaluronic acid, hyaluronic acid salts, gelatins, dioctyl sodium sulfosuccinate, sodium carboxymethylcellulose, cellulose sulfate, dextran sulfate and carboxymethylcellulose,
- 25 chondroitin sulfate, heparin, synthetic poly(acrylic acid) (PAA), poly (methacrylic acid) (PMA), poly(vinyl sulfate) (PVS), poly(styrene sulfonate) (PSS), bile acids and their salts, cholic acid, deoxycholic acid, glycocholic acid, taurocholic acid, glycodeoxycholic acid, derivatives thereof, and combinations thereof). In certain embodiments, the one or more polymer or surfactant comprises a polyoxyethylene sorbitan fatty acid ester, such as
- 30 polyoxyethylene (20) sorbitan monolaurate (*i.e.*, polysorbate 20 or Tween 20). In certain embodiments, the one or more polymer or surfactant comprises polyethylene glycol, such as PEG 3350. In certain embodiments, the one or more polymer or surfactant comprises a polyoxyethylene sorbitan fatty acid ester, such as polyoxyethylene (20) sorbitan monolaurate (*i.e.*, polysorbate 20 or Tween 20), and polyethylene glycol, such as PEG 3350.

The polymer (or surfactant) of the instant disclosure may be charged or neutral. In a particular embodiment, the polymer (or surfactant) is neutral or negatively charged (*e.g.*, poloxamers, polysorbates, phospholipids, and their derivatives).

In a particular embodiment, the polymer (or surfactant) is an amphiphilic block copolymer or lipid derivative. In a particular embodiment, at least one polymer (or surfactant) of the nanoparticle is an amphiphilic block copolymer, particularly a copolymer comprising at least one block of poly(oxyethylene) and at least one block of poly(oxypropylene). In a particular embodiment, the polymer (or surfactant) is a triblock amphiphilic block copolymer. In a particular embodiment, the polymer (or surfactant) is a triblock amphiphilic block copolymer comprising a central hydrophobic block of polypropylene glycol flanked by two hydrophilic blocks of polyethylene glycol.

In a particular embodiment, the amphiphilic block copolymer is a copolymer comprising at least one block of poly(oxyethylene) and at least one block of poly(oxypropylene).

Examples of poloxamers include, without limitation, Pluronic® L31, L35, F38, L42, L43, L44, L61, L62, L63, L64, P65, F68, L72, P75, F77, L81, P84, P85, F87, F88, L92, F98, L101, P103, P104, P10S, F108, L121, L122, L123, F127, 10RS, 10R8, 12R3, 17R1, 17R2, 17R4, 17R8, 22R4, 25R1, 25R2, 2SR4, 2SR5, 2SR8, 31R1, 31R2, and 31R4.

In a particular embodiment, the polymer (or surfactant) is poloxamer 407 (Pluronic® F127).

In a particular embodiment of the disclosure, the polymer (or surfactant) is present in the nanoparticle and/or surfactant solution to synthesize the nanoparticle (as described hereinabove) at a concentration ranging from about 0.0001% to about 10% or 15% by weight. In a particular embodiment, the concentration of the polymer (or surfactant) ranges from about 0.01% to about 15%, about 0.01% to about 10%, or about 0.1% to about 6% by weight. In a particular embodiment, the nanoparticle comprises at least about 50%, 75%, 80%, 85%, 90%, 95%, 97%, 98%, 99% or higher therapeutic agent by weight.

The compounds and nanoformulations thereof of the present disclosure may be used for the treatment and or prevention of drug and alcohol addiction, drug abuse, abstinence or overdose. In one embodiment the compounds and/or nanoformulations thereof are used for the treatment of opioid use disorders such as opioid dependence/addiction. In addition, the compounds and nanoformulations thereof of the present disclosure can also be used for treating diseases/disorders not related to drug addiction including but not limited to cancer, pain {including chronic pain, degenerative pain, inflammatory pain, visceral pain,

neuropathic pain or trauma-related (broken bones, dental, burns, surgery) pain, fibromyalgia, arthritis and obesity.

The compounds may also be packaged with additional drugs or compounds into nanoparticles (or nanoformulations) or co-administered with other drugs.

5 **Pharmaceutical Compositions**

Disclosed herein, in certain embodiments, are pharmaceutical compositions, comprising a compound of Formula (I) or a nanoparticle comprising the same, and a pharmaceutically acceptable carrier. The compounds and nanoformulations of the present disclosure may be conveniently formulated for administration with any pharmaceutically acceptable carrier(s).

In certain embodiments, the pharmaceutical composition comprises a pharmaceutically acceptable salt of the compound of Formula (I) or a nanoparticle comprising the same, and a pharmaceutically acceptable carrier. In certain embodiments, the pharmaceutical composition is an aqueous suspension.

The pharmaceutical compositions provided herein can be administered by a variety of routes including, but not limited to, oral (enteral) administration, parenteral (by injection) administration, rectal administration, transdermal administration, intradermal administration, intrathecal administration, subcutaneous (SC) administration, intravenous (IV) administration, intramuscular (IM) administration, and intranasal administration. In certain embodiments, the pharmaceutical compositions disclosed herein are administered orally. In certain embodiments, the pharmaceutical compositions disclosed herein are administered via injection.

The pharmaceutical compositions provided herein may also be administered chronically ("chronic administration"). Chronic administration refers to administration of a compound or pharmaceutical composition thereof over an extended period of time, *e.g.*, for example, over 3 months, 6 months, 1 year, 2 years, 3 years, 5 years, etc., or may be continued indefinitely, for example, for the rest of the subject's life. In certain embodiments, the compound or nanoparticle is administered one time in a 1 to 12 month period. In certain embodiments, the compound or nanoparticle is administered one time in a 1 month period. In certain embodiments, the compound or nanoparticle is administered one time in a 2 month period. In certain embodiments, the compound or nanoparticle is administered one time in a 3 month period. In certain embodiments, the compound or nanoparticle is administered one time in a 4 month period. In certain embodiments, the compound or nanoparticle is

administered one time in a 5 month period. In certain embodiments, the compound or nanoparticle is administered one time in a 6 month period. In certain embodiments, the compound or nanoparticle is administered one time in a 7 month period. In certain embodiments, the compound or nanoparticle is administered one time in a 8 month period. In certain embodiments, the compound or nanoparticle is administered one time in a 9 month period. In certain embodiments, the compound or nanoparticle is administered one time in a 10 month period. In certain embodiments, the compound or nanoparticle is administered one time in a 11 month period. In certain embodiments, the compound or nanoparticle is administered one time in a 12 month period. In certain embodiments, the chronic administration is intended to provide a constant level of the compound in the blood, *e.g.*, within the therapeutic window over the extended period of time.

It is envisioned that the compounds and nanoformulations of the compounds will be useful as long acting slow release treatments for diseases. The compounds and nanoformulations will allow for decreased dosing regimens. For example it is envisioned that the compounds and/or nanoformulations of the compounds can be given once every month to once a year. Examples include administration once every month, once every two months, once every three months, once every four months, once every five months, once every six months, once every seven months, once every 8 months, once every 9 months, once every 10 months, once every 11 months, and once every 12 months.

The pharmaceutical compositions provided herein may be presented in unit dosage forms to facilitate accurate dosing. The term “unit dosage forms” refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient. In various embodiments, the pharmaceutical dosage forms described herein can be administered as a unit dose. Typical unit dosage forms include prefilled, premeasured ampules or syringes of the liquid compositions or pills, tablets, capsules or the like in the case of solid compositions.

In various embodiments, the pharmaceutical compositions provided herein comprise the compound of Formula (I) as the sole active agent, or in combination with other active agents. For example, in certain embodiments, the application relates to a pharmaceutical composition comprising (1) a compound according to formula (I), or a pharmaceutically acceptable salt of the compound of formula (I), (2) an additional therapeutic agent, or a pharmaceutically acceptable salt thereof, and (3) pharmaceutically acceptable excipients, carriers or diluents.

In the treatment of any of the disorders disclosed herein, different compounds of the application may be (e.g., conjointly) administered with one or more other compounds of the application. Moreover, compounds of formula (I), or a pharmaceutically acceptable salt of the compound of formula (I), or certain combinations thereof, may be conjointly administered
5 with other conventional therapeutic agents in treating one or more disease conditions referred to herein.

In certain embodiments, compounds of the application may be used alone or conjointly administered with another type of therapeutic agent. As used herein, the phrase “conjoint administration” refers to any form of administration of two or more different
10 therapeutic compounds such that the second compound is administered while the previously administered therapeutic compound is still effective in the body (e.g., the two compounds are simultaneously effective in the patient, which may include synergistic effects of the two compounds). For example, the different therapeutic compounds can be administered either in the same formulation or in a separate formulation, either simultaneously, sequentially, or by
15 separate dosing of the individual components of the treatment. In certain embodiments, the different therapeutic compounds can be administered within one hour, 12 hours, 24 hours, 36 hours, 48 hours, 72 hours, or a week of one another. Thus, an individual who receives such treatment can benefit from a combined effect of different therapeutic compounds.

In certain embodiments, conjoint administration of compounds of the application with
20 one or more additional therapeutic agent(s) provides improved efficacy relative to each individual administration of the compound of the application (e.g., compound of formula (I), or a pharmaceutically acceptable salt of the compound of formula (I)) or the one or more additional therapeutic agent(s). In certain such embodiments, the conjoint administration provides an additive effect, wherein an additive effect refers to the sum of each of the effects
25 of individual administration of the compound of the application and the one or more additional therapeutic agent(s).

Such conventional therapeutics may include one or more of the following categories of agents: drug addiction and drug dependence therapeutics; drug overdose therapeutics; pain
30 therapeutics (e.g., therapeutics for acute pain, chronic pain, neuropathic pain, nociceptive pain, or radicular pain); fibromyalgia therapeutics; arthritis therapeutics; and/or obesity therapeutics.

Such combination products employ the compounds of this application within the dosage range described herein and the other pharmaceutically active compound or

compounds within approved dosage ranges and/or the dosage described in the publication reference.

Although the descriptions of pharmaceutical compositions provided herein are principally directed to pharmaceutical compositions which are suitable for administration to humans, it will be understood by the skilled artisan that such compositions are generally suitable for administration to animals of all sorts. Modification of pharmaceutical compositions suitable for administration to humans in order to render the compositions suitable for administration to various animals is well understood, and the ordinarily skilled veterinary pharmacologist can design and/or perform such modification with ordinary experimentation. General considerations in the formulation and/or manufacture of pharmaceutical compositions can be found, for example, in *Remington: The Science and Practice of Pharmacy* 21st ed., Lippincott Williams & Wilkins, 2005.

Methods of treatment

The compounds, nanoparticles, and pharmaceutical compositions of the present disclosure are useful in treating drug addiction, drug dependence, drug overdose, opioid use disorder, pain, acute pain, chronic pain, fibromyalgia, arthritis, or obesity.

Drug Addiction and Drug Dependence

Drug addiction, also called substance use disorder, refers to a disease that affects an individual's brain and behavior and leads to an inability to control the use of a legal or illegal drug or medication. When addicted, the individual may continue using the drug despite the harm it causes. As drug use increases, the individual may need larger doses of the drug to feel its effect or find that it is increasingly difficult to go without the drug (drug dependence). Attempts to stop drug use may cause intense cravings and make the individual feel physically ill (withdrawal symptoms). Drug addiction symptoms or behaviors include, among others:

- feeling of having to use the drug regularly — daily or even several times a day; having intense urges for the drug that block out any other thoughts; needing more of the drug to get the same effect, over time; taking larger amounts of the drug over a longer period of time than intended; ensuring a supply of the drug; not meeting obligations and work responsibilities, or cutting back on social or recreational activities because of drug use;
- continuing to use the drug, despite knowledge that it causes social problems or physical or psychological harm; failing to stop using the drug; and experiencing withdrawal symptoms upon attempt to stop taking the drug. Exemplary drugs where the individual has an addiction or dependence include, but are not limited to, marijuana, hashish and other cannabis-

containing substances, K2, Spice, bath salts, barbiturates (such as phenobarbital and secobarbital (Seconal)), benzodiazepines, (sedatives, such as diazepam (Valium), alprazolam (Xanax), lorazepam (Ativan), clonazepam (Klonopin) and chlordiazepoxide (Librium)), hypnotics (such as prescription sleeping medications such as zolpidem (Ambien, Intermezzo, others) and zaleplon (Sonata)), methamphetamine, cocaine and other stimulants (such as methylphenidate (Ritalin, Concerta, others) and amphetamine-dextroamphetamine (Adderall, Adderall XR, others)), inhalants (such as glue, paint thinners, correction fluid, felt tip marker fluid, gasoline, cleaning fluids and household aerosol products), and opioids (such as heroin, morphine, codeine, methadone and oxycodone).

10 *Drug Overdose*

A drug overdose (overdose or OD) refers to the ingestion or application of a drug or other substance in quantities greater than are recommended. Drug overdose may be accidental overuse or intentional misuse. A drug overdose may result in a toxic state or death. Signs and symptoms of a drug overdose vary depending on the drug or exposure to toxins.

15 Generally, in an overdose, the effects of the drug may be a heightened level of the therapeutic effects seen with regular use. In overdose, side effects become more pronounced, and other effects can take place, which would not occur with normal use. Large overdoses of some medications cause only minimal effects, while smaller overdoses of other medications can cause severe effects, possibly death. A single dose of some medications can be lethal to a

20 young child. Some overdoses may worsen a person's chronic disease. Symptoms of opioid overdoses include slow breathing, heart rate and pulse. Opioid overdoses can also cause pinpoint pupils, and blue lips and nails due to low levels of oxygen in the blood. An individual experiencing an opioid overdose might also have muscle spasms, seizures and decreased consciousness. A individual experiencing an opiate overdose usually will not wake

25 up even if their name is called or if they are shaken vigorously.

Opioid use disorder refers to use (*e.g.*, chronic use) of opioids that causes clinically significant distress or impairment in a subject. Opioid use disorder diagnosis is generally based on the American Psychiatric Association DSM-5 and includes a desire to obtain and take opioids despite social and professional consequences. Examples of opioids include, but

30 are not limited to, heroin, morphine, codeine, fentanyl, and synthetic opioids such as oxycodone. Symptoms of opioid use disorder includes, but are not limited to, an overpowering desire to use opioids, increased opioid tolerance, withdrawal syndrome when discontinued, dependence and addiction with addiction representing the most severe form of the disorder.

Pain

Pain refers to an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage. Pain includes acute pain, chronic pain, neuropathic pain, nociceptive pain, and radicular pain.

5 *Acute pain*

Acute pain refers to pain is short in duration, lasting from minutes to about three months (sometimes up to six months). Acute pain is typically related to a soft-tissue injury or a temporary illness. Acute pain from an injury may evolve into chronic pain if the injury does not heal correctly or if the pain signals malfunction.

10 *Chronic pain*

Chronic pain refers to pain that lasts longer in duration. It can be constant or intermittent. For example, headaches can be considered chronic pain when they continue over many months or years – even if the pain is not always present. Chronic pain is often due to a health condition, such as arthritis, fibromyalgia, or a spine condition.

15 *Neuropathic pain*

Neuropathic pain is generally due to damage to the nerves or other parts of the nervous system. It is often described as shooting, stabbing, or burning pain, or it feels like pins and needles. It can also affect sensitivity to touch and can make someone have difficulty feeling hot or cold sensations. Neuropathic pain is a common type of chronic pain. It may be
20 intermittent (meaning it comes and goes), and it can be so severe that it makes performing everyday tasks difficult. Because the pain can interfere with normal movement, it can also lead to mobility issues.

Nociceptive pain

Nociceptive pain refers to a type of pain caused by damage to body tissue. It is often
25 described as being a sharp, achy, or throbbing pain. It is often caused by an external injury. This type of pain is often experienced in the joints, muscles, skin, tendons, and bones. It can be both acute and chronic.

Radicular pain

Radicular pain refers to a specific type of pain can occur when the spinal nerve gets
30 compressed or inflamed. It radiates from the back and hip into the leg(s) by way of the spine and spinal nerve root. Individuals who have radicular pain may experience tingling, numbness, and muscle weakness. Pain that radiates from the back and into the leg is called radiculopathy. It is commonly known as sciatica because the pain is due to the sciatic nerve being affected. This type of pain is often steady, and individuals can feel it deep in the leg.

Walking, sitting, and some other activities can make sciatica worse. It is one of the most common forms of radicular pain.

Fibromyalgia

Fibromyalgia refers to a disorder characterized by widespread musculoskeletal pain accompanied by fatigue, sleep, memory and mood issues. Symptoms include pain and stiffness all over the body, fatigue and tiredness, depression and anxiety, sleep problems, problems with thinking, memory, and concentration, headaches, including migraines, tingling or numbness in hands and feet, pain in the face or jaw, including disorders of the jaw known as temporomandibular joint syndrome (also known as TMJ), and digestive problems, such as abdominal pain, bloating, constipation, and even irritable bowel syndrome (also known as IBS).

Arthritis

Arthritis refers to the swelling and tenderness of one or more joints. The main symptoms of arthritis are joint pain and stiffness, which typically worsen with age. Arthritis includes, but are not limited to, osteoarthritis, fibromyalgia, gout, psoriatic arthritis, rheumatoid arthritis, lupus, ankylosing spondylitis, juvenile arthritis, adult-onset Still's disease, Behçet's Disease, bursitis, Calcium Pyrophosphate Deposition Disease (CPPD), carpal tunnel syndrome, chondromalacia patella, chronic fatigue syndrome, complex regional pain syndrome, Cryopyrin-Associated Periodic Syndromes (CAPS), degenerative disc disease, developmental-dysplasia of hip, Ehlers-Danlos, familial Mediterranean fever, giant cell arteritis, hemochromatosis, infectious arthritis, inflammatory arthritis, inflammatory bowel disease, Juvenile Dermatomyositis (JD), juvenile scleroderma, Kawasaki disease, mixed connective tissue disease, myositis (including polymyositis, dermatomyositis), osteoporosis, Pagets, palindromic rheumatism, patellofemoral pain syndrome, pediatric rheumatic diseases, polymyalgia rheumatica, pseudogout, Rynaud's phenomenon, reactive arthritis, reflex sympathetic dystrophy, Reiter's syndrome, rheumatic fever, rheumatism, scleroderma, Sjögren's disease, spinal stenosis, spondyloarthritis, systemic juvenile idiopathic arthritis, systemic lupus erythematosus, systemic lupus erythematosus, systemic sclerosis, temporal arteritis, tendinitis, vasculitis, and Wegener's granulomatosis.

Obesity

Obesity is a complex disease involving an excessive amount of body fat. Obesity increases the risk of other diseases and health problems, such as heart disease, diabetes, high blood pressure and certain cancers. Animal studies suggest that endogenous opioid system has an important role in the control of appetite. MOR agonists increase and opioid

antagonists decrease food intake and hedonic pleasures caused by palatable foods (Gosnell and Levine, 2009; Peciña and Smith, 2010). Opioid antagonists also prevent food seeking and binge-like eating (Giuliano et al., 2012; Cambridge et al., 2013). Moreover, stimulation of the MOR in the shell of nucleus accumbens increases the pleasure responses for foods and may

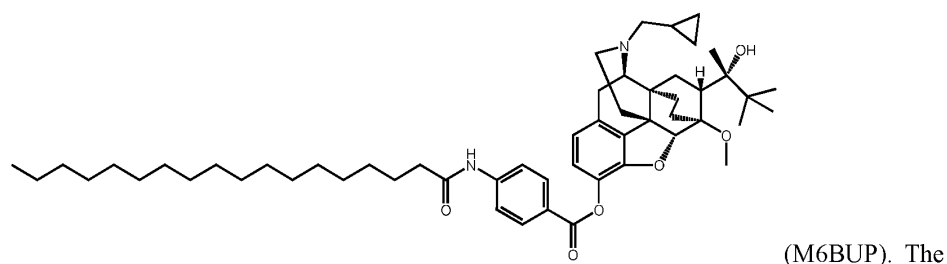
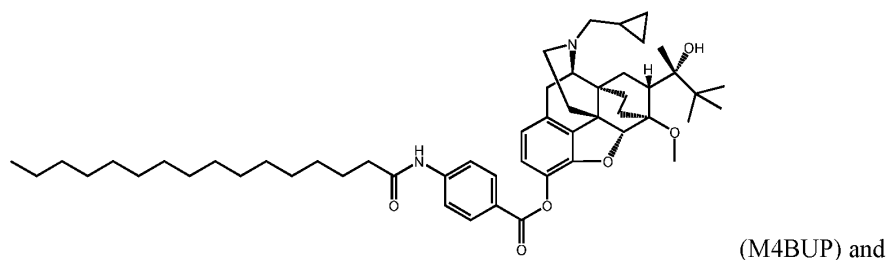
5 also trigger eating behavior (Peciña and Berridge, 2005). The μ -opioid receptor gene OPRM1 also modulates the intake of fat and possibly the risk for gaining weight in humans (Haghighi et al., 2014). Accordingly, changes in MOR rather than D2R availability can maintain excessive energy uptake due to altered hedonic processing of food.

EXAMPLES

10 In order that the disclosure described herein may be more fully understood, the following examples are set forth. The examples described in this application are offered to illustrate the compounds, pharmaceutical compositions, and methods provided herein and are not to be construed in any way as limiting their scope.

Example 1. Synthesis of compounds of Formula (I)

15 BUP was chemically modified to produce M4BUP and M6BUP:



samples were dissolved in CDCl_3 and analyzed on a Varian Unity/Inova-500 NB (500 MHz). Buprenorphine (BUP) (1g, 1.983 mmol, 1.0 equivalents) was added to 10.0 mL of anhydrous pyridine and the resultant slurry was evaporated to dryness on a rotavapor. The BUP powder

20 was then redissolved in anhydrous pyridine (15.0 mL) followed by the addition of 1.2 equivalents of the acylating aryl moiety (as an acyl chloride or free carboxylic acid form

activated using 3 equivalents of EDC as the coupling reagent) on a regular ice bath under an argon atmosphere. The reaction mixture was then warmed to 50 °C under stirring for 24h. The mixture was concentrated and dissolved in dichloromethane (120 ml) and washed with brine (100 mL). The dichloromethane layer was dried over sodium sulfate, concentrated and purified by silica gel column chromatography using an eluent of 4:1 then 2:1 mixture of hexanes and ethyl acetate. The desired compound fractions from the columns were dried on a rotary evaporator to obtain foamy compounds that were further dried under high vacuum to give the desired solid compounds in high chemical yields. **FIG. 1A** and **FIG. 1B** depict ¹H-NMR and ¹³C-NMR spectra, respectively, for M4BUP. **FIG. 2A** and **FIG. 2B** depict ¹H-NMR and ¹³C-NMR spectra, respectively, for M6BUP.

The synthesized solid prodrugs were then either nanoformulated as such or transformed into free flowing pamoate salt powders. To make the pamoate salts, the prodrug and pamoic acid (1:1 or 2:1) were dissolved in DMSO (10.0 mL) and warmed to 75 °C for at least 40 minutes, the salt solution was then poured in a beaker of stirring HPLC grade water (200.0 mL) to form BUP prodrug salt precipitates that were collected and dried under vacuum. Successful synthesis of prodrugs and salts was confirmed by proton and carbon nuclear magnetic resonance (¹H and ¹³C NMR) spectra using Bruker Avance-III HD (Billerica, MA) operating at 500 MHz, a magnetic field strength of 11.7 T.

Nanocrystals of either BUP prodrugs or prodrug pamoate salts were manufactured by high-pressure homogenization in aqueous buffers stabilized by non-ionic surfactants. Specifically, the BUP prodrug salt was dispersed in a surfactant solution of Tween 20 and PEG 3350 in phosphate-buffered saline (PBS) and allowed to form a presuspension. The prodrug to Tween 20 to PEG 3350 ratio was maintained at 7:1:1 (w/w). The presuspensions were homogenized on an Avestin EmulsiFlex-C3 high-pressure homogenizer at 15,000-20,000 psi until the desired particle size of 250-350 nm was achieved. Nanoparticles were characterized for particle size, PDI and zeta potential by dynamic light scattering using a Malvern Zetasizer Nano-ZS.

Example 2. In vitro monocyte-derived macrophage assays – M4BUP

Human monocytes were obtained by leukapheresis from HIV-1/2 and hepatitis B seronegative donors, and then purified by counter-current centrifugal elutriation. Human monocytes were plated in a 12-well plate at a density of 1.0×10^6 cells per well using DMEM supplemented with 10% heat-inactivated pooled human serum, 1% glutamine, 10 µg/mL ciprofloxacin, and 50 µg/mL gentamicin. Cells were maintained at 37 °C in a 5%

CO₂ incubator. After 7 days of differentiation in the presence of 1000 U/mL recombinant human macrophage colony stimulating factor (MCSF), the monocyte derived macrophages (MDM) were then treated. For drug cellular uptake studies, MDM were treated with 10 or 50 μ M of BUP or nanoformulated M4BUP (NM4BUP) and collected at 2, 4, 8, and 24 h following treatment. For retention studies, MDM were treated with 50 μ M NM4BUP for 8 h, then washed with PBS and maintained with half-media changes every other day until collection at days 1, 5, 10 and 20. For both uptake and retention studies, adherent MDM were washed with PBS, then scraped into PBS, and counted at indicated time points using an Invitrogen Countess Automated Cell Counter (Carlsbad, CA). Cells were pelleted by centrifugation at 3000 r.p.m. for 8 min at 4 °C. Cell pellets were briefly sonicated in 200 μ L methanol to extract drug and centrifuged at 14,000 r.p.m. for 10 min at 4 °C to pellet cell debris. BUP and M4BUP drug content were quantified by liquid chromatography tandem mass spectrometry (LC-MS/MS).

FIG. 3A shows drug uptake upon 10 μ M BUP and NM4BUP treatment in MDM. Measurements were obtained over 24 hours after treatment with prodrug nanoformulations. “NM4BUP (BUP)” depicts the BUP forming after treatment with the the nanoformulated M4BUP. “NM4BUP (M4BUP)” depicts the M4BUP level following treatment with the nanoformulated M4BUP. Results are expressed as the mean $\pm$ SEM for $N = 3$ biological replicates.

FIG 3B shows drug retention upon 50 μ M BUP and MN4BUP treatment in MDM. Measurements were obtained over 20 days after treatment with prodrug nanoformulations. Results are expressed as the mean $\pm$ SEM for $N = 3$ biological replicates.

Example 3. Pharmacokinetic analysis of NM4BUP

Male Sprague-Dawley (SD) rats (SASCO, Wilmington, MA, USA) were administered a single intramuscular (IM) dose in the caudal thigh muscle of either 20 or 30 mg BUP-eq./kg of NM4BUP nanosuspension using a 28G x 1/2” needle. Animals were housed under a 12-h light/dark cycle at a temperature of 20–24 °C and humidity range of 30–70%. The animals were maintained on sterilized 7012 Teklad diet (Harlan, Madison, WI), and acidified water was provided ad libitum. Following injection, blood samples were collected into heparinized tubes at day 1, 3 and 7 after administration, then weekly in the ongoing study. Animal weights were taken before dosing and at the time of each blood collection. Blood draws were made through tail vein bleeds. Blood samples were centrifuged at 2,000 $\times$ g for 8 minutes for

plasma collection and quantitation of plasma drug contents by liquid chromatography tandem mass spectrometry (LC-MS/MS).

FIG. 4 shows the weight analysis of male SD rats administered a single IM dose of NM4BUP (20 or 30 mg BUP eq./kg) in the caudal thigh. Results are expressed as mean $\pm$ SEM. *N* = 4 animals for the 20 mg/kg NM4BUP group and 2 animals for the 30 mg/kg NM4BUP group.

FIG. 5A shows plasma levels of BUP in male SD rats administered a single IM dose of NM4BUP (20 or 30 mg BUP eq./kg) in the caudal thigh. The dotted line indicates the average target plasma BUP concentration (2-3 ng/mL). **FIG. 5B** shows plasma levels of prodrug (M4BUP) in male SD rats administered a single IM dose of NM4BUP (20 or 30 mg BUP eq./kg) in the caudal thigh. Data are expressed as mean $\pm$ SEM. *N* = 4 animals for the 20 mg/kg NM4BUP group and 2 animals for the 30 mg/kg NM4BUP group.

Example 4. Pharmacokinetic analysis of NM6BUP

Male Sprague-Dawley (SD) rats (SASCO, Wilmington, MA, USA) were administered a single intramuscular (IM) dose in the caudal thigh muscle of either 45 or 90 mg BUP-eq./kg of NM6BUP nanosuspension using a 28G x 1/2" needle. Animals were housed under a 12-h light/dark cycle at a temperature of 20–24 °C and humidity range of 30–70%. The animals were maintained on sterilized 7012 Teklad diet (Harlan, Madison, WI), and acidified water was provided ad libitum. Following injection, blood samples were collected into heparinized tubes at days 1, 3, 7, and then weekly after administration. Blood draws were made through tail vein bleeds. Blood samples were centrifuged at $2,000 \times g$ for 8 minutes for plasma collection and quantitation of plasma drug contents by liquid chromatography tandem mass spectrometry (LC-MS/MS).

FIG. 6 shows plasma levels of BUP in male SD rats administered a single IM dose of NM6BUP (45 or 90 mg BUP eq./kg) in the caudal thigh. The dashed lines represent the target steady state BUP plasma concentrations of 1-2 ng/ml, and the dotted line indicates the lower limit of quantitation (LLQ). Data are expressed as mean $\pm$ SEM with *N* = 4 animals per group.

Example 5. Brain BUP levels of NM6BUP

Male Sprague-Dawley (SD) rats (SASCO, Wilmington, MA, USA) were administered a single intramuscular (IM) dose in the caudal thigh muscle of 45 mg BUP-eq./kg of NM6BUP nanosuspension using a 28G x 1/2" needle. Animals were housed under a 12-h light/dark cycle at a temperature of 20–24 °C and humidity range of 30–70%. The animals were maintained on sterilized 7012 Teklad diet (Harlan, Madison, WI), and acidified water

was provided ad libitum. Following injection, brain samples were collected at day 112 after administration. For tissue sample preparation, 35-250 mg of each tissue sample were homogenized in 5-10 volumes (depending on the tissue) of 90% acetonitrile (containing 0.1% FA) using a Tissue Lyzer II (Qiagen, Valencia, CA, USA). 390 μ l of 100% acetonitrile (containing 0.1% FA) and 10 μ l of IS were added to 100 μ l of tissue homogenates. Samples were vortexed for 3 mins and centrifuged at $16,000 \times g$ for 10 min. Then, 400 μ l supernatant was aspirated for drying down using SpeedVac Concentrator. After drying out the solvent completely 100 μ l of 80% methanol (containing 0.1% FA) was added to the tissue samples. After that, samples were vortexed for 3 min and centrifuged at $16,000 \times g$ for 10 min. 5 μ l sample was injected on LC-MS/MS for BUP and M6BUP analysis. Calibration curves in the range of 0.08–80 ng/ml for BUP and M6BUP were prepared the same way in blank tissues.

FIG. 7 shows brain levels of BUP in male SD rats administered a single IM dose of NM6BUP (45 BUP eq./kg) in the caudal thigh. BUP levels were determined by LC-MS/MS. The animal numbers were N=5. Data is expressed as standard errors of the mean (SEM).

15 **Example 6. In vitro monocyte-derived macrophage assays – M6BUP**

Human monocytes were obtained by leukapheresis from HIV-1/2 and hepatitis B seronegative donors, and then purified by counter-current centrifugal elutriation. Human monocytes were plated in a 12-well plate at a density of 1.0×10^6 cells per well using DMEM supplemented with 10% heat-inactivated pooled human serum, 1% glutamine, 10 μ g/mL ciprofloxacin, and 50 μ g/mL gentamicin. Cells were maintained at 37 °C in a 5% CO₂ incubator. After 7 days of differentiation in the presence of 1000 U/mL recombinant human macrophage colony stimulating factor (M-CSF), the monocyte derived macrophages (MDM) were then treated. For drug cellular uptake studies, MDM were treated with nanoformulated M6BUP (NM6BUP) and collected at 2, 4, 8, and 24 h following treatment. For retention studies, MDM were treated with 25 μ M NM6BUP for 8 h, then washed with PBS and maintained with half-media changes every other day until collection at days 1, 5, 10 and 20. For both uptake and retention studies, adherent MDM were washed with PBS, then scraped into PBS, and counted at indicated time points using an Invitrogen Countess Automated Cell Counter (Carlsbad, CA). Cells were pelleted by centrifugation at 3000 r.p.m. for 8 min at 4 °C. Cell pellets were briefly sonicated in 200 μ L methanol to extract drug and centrifuged at 14,000 r.p.m. for 10 min at 4 °C to pellet cell debris. BUP and M6BUP drug content were quantified by UPLC-MS/MS.

FIG. 8A shows drug uptake upon 25 μ M NM6BUP treatment in MDM. Measurements were obtained over 24 hours after treatment with prodrug nanoformulations.

Intracellular BUP (parent drug forming from prodrug/bottom line) and M6BUP (prodrug/top line) levels were quantified by UPLC-MS/MS. The data is expressed as Mean $\pm$ SEM, for n=3.

FIG. 8B shows drug retention by MDMs upon a single 8 hour treatment with 25 μ M MN6BUP. Measurements were obtained over 20 days after treatment with prodrug nanoformulations. Intracellular BUP (parent drug forming from prodrug/bottom line) and M6BUP (prodrug/top line) levels were quantified by UPLC-MS/MS. The data is expressed as Mean $\pm$ SEM, for n=3.

Example 7. Nanoformulation Stability

10 Nanosuspension stability was assessed during storage at RT by dynamic light scattering using a Malvern Zetasizer Nano-ZS. D_{eff} , PdI and ζ -potential were measured at predetermined times.

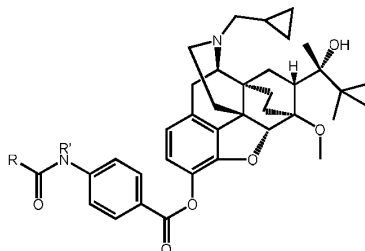
FIG. 9 shows a time course evaluation of average particle sizes and polydispersity indices (PDIs) of NM6BUP. The formulation was monitored at room temperature using dynamic light scattering (DLS) to determine long-term formulation stability and homogeneity.

20 **EQUIVALENTS**

The disclosure may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather than limiting the disclosure described herein. Scope of the disclosure is thus indicated by the appended claims rather than by the foregoing description, and all changes that come within the meaning and range of equivalency of the claims are intended to be embraced therein.

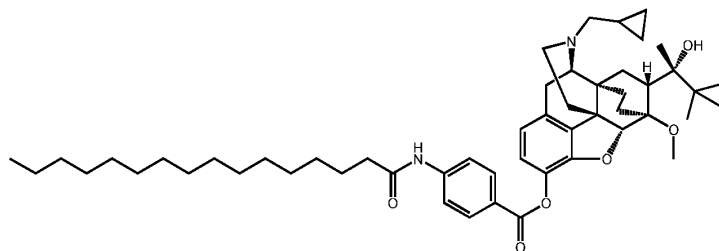
CLAIMS

1. A compound of Formula (I):

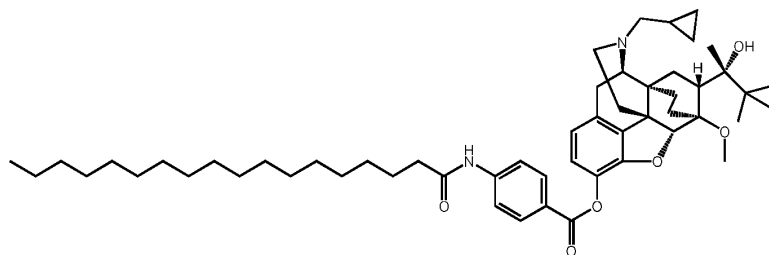


Formula (I),

- 5 or a pharmaceutically acceptable salt thereof, wherein:
- R is C₁₋₃₀ alkyl, C₂₋₃₀ alkenyl, C₁₋₃₀ heteroalkyl, C₂₋₃₀ heteroalkenyl, phenyl, heteroaryl, or amino acid moiety; and
- R' is hydrogen, C₁₋₆ alkyl, C₁₋₆ heteroalkyl, C₁₋₆ alkoxy, C₁₋₆ heteroalkoxy, or C₃₋₈ carbocyclyl.
- 10 2. The compound of claim 1, wherein R' is hydrogen.
3. The compound of claim 1, wherein R' is C₁₋₆ alkyl.
4. The compound of claim 3, wherein R' is methyl.
5. The compound of any preceding claim, wherein R is C₁₋₃₀ alkyl.
6. The compound of claim 5, wherein R is C₁₁₋₁₉ alkyl.
- 15 7. The compound of claim 5, wherein R is C₁₃₋₁₇ alkyl.
8. The compound of claim 5, wherein R is C₁₅ alkyl.
9. The compound of claim 5, wherein R is C₁₇ alkyl.
10. The compound of claim 1, wherein the compound is selected from:



and

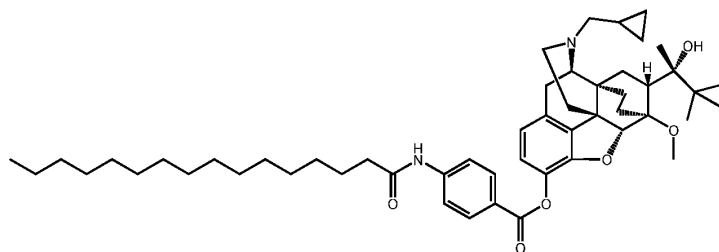


, or a

pharmaceutically acceptable

salt thereof.

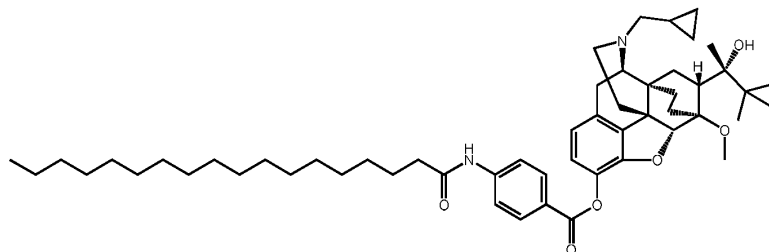
11. The compound of claim 1, wherein the compound is



, or a pharmaceutically

acceptable salt thereof.

12. The compound of claim 1, wherein the compound is



, or a

pharmaceutically acceptable salt thereof.

10 13. The compound of any one of claims 1-12, wherein the compound is complexed with a hydrophobic counterion selected the group consisting of pamoic acid, myristic acid, palmitic acid, stearic acid, behenic acid, napsylate, mandelic acid, tosylate, benzenesulfonate, benzoate, besylate, hydroxynaphthoate, and isethionate.

14. The compound of any one of claims 1-12, wherein the pharmaceutically acceptable
15 salt is a pamoate salt.

15. A nanoparticle, comprising a compound of any one of claims 1-12, or a pharmaceutically acceptable salt thereof, and one or more polymer or surfactant.
16. A nanoparticle, comprising a pharmaceutically acceptable salt of the compound of any one of claims 1-12, and one or more polymer or surfactant.
- 5 17. The nanoparticle of claim 16, wherein the pharmaceutically acceptable salt of the compound is a pamoate salt.
18. The nanoparticle of any one of claims 15-17, wherein the one or more polymer or surfactant is an amphiphilic block copolymer.
19. The nanoparticle of claim 18, wherein the amphiphilic block copolymer comprises at
10 least one block of poly(oxyethylene) and at least one block of poly(oxypropylene).
20. The nanoparticle of claim 18, wherein said one or more polymer or surfactant is a poloxomer.
21. The nanoparticle of claim 18, wherein said one or more polymer or surfactant is P407.
22. The nanoparticle of any one of claims 15-17, wherein the one or more polymer or
15 surfactant comprises a polyoxyethylene sorbitan fatty acid ester.
23. The nanoparticle of claim 22, wherein the one or more polymer or surfactant comprises polyoxyethylene (20) sorbitan monolaurate.
24. The nanoparticle of claim 22 or 23, wherein the one or more polymer or surfactant further comprises polyethylene glycol (PEG).
- 20 25. The nanoparticle of claim 24, wherein the one or more polymer or surfactant further comprises PEG 3350.
26. The nanoparticle of any one of claims 15-17, wherein the one or more polymer or surfactant comprises polyethylene glycol (PEG).
27. The nanoparticle of claim 26, wherein the one or more polymer or surfactant
25 comprises PEG 3350.
28. The nanoparticle of any one of claim 15-27, wherein the diameter of the nanoparticle is about 100 nm to 1 μ m.

29. A pharmaceutical composition, comprising a compound of any one of claims 1-14, or a pharmaceutically acceptable salt thereof, or a nanoparticle of any one of claims 15-28, and a pharmaceutically acceptable carrier.
30. A method of treating drug addiction, drug dependence, drug overdose, opioid use disorder, pain, chronic pain, fibromyalgia, arthritis, or obesity in a subject in need thereof, wherein said method comprises administering to said subject a therapeutically effective amount of a compound of any one of claims 1-14, or a pharmaceutically acceptable salt thereof, a nanoparticle of any one of claims 15-28, or a pharmaceutical composition of claim 29.
31. The method of claim 30, wherein the disease or disorder is opioid use disorder.
32. The method of claim 30, wherein the compound, nanoparticle, or composition is administered via injection.
33. The method of claim 32, wherein the compound, nanoparticle, or composition is administered one time in a 1 to 12 month period.
34. The method of claim 32, wherein the compound, nanoparticle, or composition is administered one time in a 3 month period.
35. The method of claim 32, wherein the compound, nanoparticle, or composition is administered one time in a 6 month period.
36. The method of claim 32, wherein the compound, nanoparticle, or composition is administered one time in a 9 month period.
37. The method of claim 32, wherein the compound, nanoparticle, or composition is administered one time in a 12 month period.