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(54) **Title:** COMPOSITIONS AND METHODS OF ENHANCING OPIOID RECEPTOR ENGAGEMENT BY OPIOID HEXADIENOATES AND OPTIONALLY SUBSTITUTED HEXADIENOATES

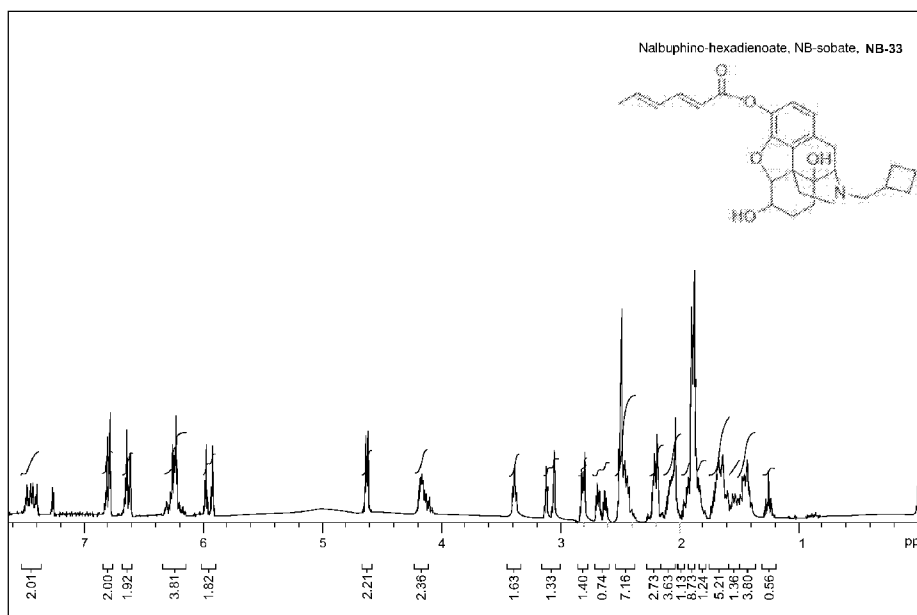


FIG. 2

(57) **Abstract:** The present invention relates to opiate derived compositions and their antagonists useful in therapeutic areas associated with opioid receptor modulation. A 3-hexadienoate modification of the opioids is formulated to improve opiates' engagement of the opioid receptors when given orally. A 3-hexadienoate modification of Nalbuphine or a pharmaceutically acceptable salt of thereof to improve quality of pain management when given intravenously, intranasally, transdermally, sublingually, rectally, topically, intramuscularly, subcutaneously or via inhalation. A 3-hexadienoate modification of the opioids antagonists is formulated to improve inhibition of the opioid receptors when given orally. A 3-hexadienoate modification of Naloxone or a pharmaceutically acceptable salt of thereof to improve quality of Sobering when given intravenously, intranasally, transdermally, sublingually, rectally, topically, intramuscularly,



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**TITLE: COMPOSITIONS AND METHODS OF ENHANCING OPIOID RECEPTOR ENGAGEMENT BY OPIOID HEXADIENOATES AND OPTIONALLY SUBSTITUTED HEXADIENOATES**

[00001] This application is a PCT Application of a Non-Provisional U.S. Patent Application No. 16/540,058, filed on August 14, 2019 and claiming priority under 35 U.S.C. § 119 of prior U.S. Provisional Patent Serial No. 62/885,311, entitled "COMPOSITIONS AND METHODS OF ENHANCING OPIOID RECEPTOR ENGAGEMENT BY OPIOID HEXADIENOATES AND OPTIONALLY SUBSTITUTED HEXADIENOATES" filed on August 11, 2019.

Field of the Invention

[00002] The present invention relates to opiate derived compositions, used in therapeutic areas associated with opioid receptor modulation.

BACKGROUND

[00003] **Nalbuphine** (Nubain) was launched in 1979 as an analgesic for moderate to severe pain and has effectively been used in the clinic since. It is primarily used in conjunction with anesthetics for pre- and post-operative analgesia and in labor and delivery for acute and chronic pain management. Recently its uses have been expanded to the treatment of locomotive disorders, dermatological conditions such as pruritus and addiction management.

[00004] It has also been recently shown that Nalbuphine could prevent opiate tolerance and dependence in chronic pain management. It is the only narcotic analgesic of its type that is not subject to the Controlled Substances Act, an indication of its safe utility. Nalbuphine has a low oral bioavailability.

[00005] There are known Nalbuphine prodrugs designed to improve its pharmacokinetic and pharmacodynamic properties. Merriam-Webster defines a prodrug as a pharmacologically inactive substance that is the modified form of a pharmacologically active drug to which it is converted (as by enzymatic action) in the body. Thus, Franklin (WO 2010-GB52211) teaches that Nalbuphine

could be modified at phenolic hydroxyl residue.

[00006] Furthermore, Nalbuphine could be coupled to an amino acid or short peptide (WO 2011007247, A1). Also, Nalbuphine could be modified with dicarboxylic acid linked amino acid and peptide (WO 2010112942, A1). Further yet, Nalbuphine could be modified with carbamate moiety linked amino acid and peptide (WO 2009092071, A2). Moreover, Jenkins (WO 2007022535, A2) teaches that Nalbuphine could be further modified on its phenolic or nitrogen moiety.

[00007] Wang teaches that Nalbuphine could be converted to ester prodrug (Journal of Controlled Release, Volume: 115, Issue: 2, Pages: 140-149, Journal, 2006,). Hu (Jan 11, 2005, TW 226239, B) teaches that delivery systems and Nalbuphine prodrugs which increase its bioavailability. More specifically, formulation to increase Nalbuphine's bioavailability includes vegetable oils, a co-solvent, and an effective amount of a Nalbuphine ester prodrug or a pharmaceutically acceptable salt thereof. One objective of prodrugs is to increase the oral bioavailability of Nalbuphine and prolong the retention time of Nalbuphine in a body, thereby maintaining a longer analgesic period of time, as well as reducing the analgesic cost.

[00008] Hilfinger (US 20050137141, A1) teaches of Nalbuphine including a pharmaceutical species and an amino acid having a covalent bond to the pharmaceutical species. Huang (International Journal of Pharmaceutics, Volume: 297, Issue: 1-2, Pages: 162-171, Journal, 2005) teaches of the effects of iontophoresis and electroporation on transdermal delivery of Nalbuphine (NA) and its two novel prodrugs: Nalbuphine benzoate (NAB) and sebacoyl dinalbuphine ester (SDN) from solutions as well as from hydrogels.

[00009] Crooks (WO 2005009377, A2) teaches that forming duplex prodrugs including Nalbuphine can provide significant increase in the transdermal flux of drugs across human skin. Uhrich (WO 2002009768, A2) teaches of therapeutic polyesters and polyamides of Nalbuphine. Hu (EP 1149836, A1) teaches of preparation of polynalbuphine derivatives. Pao (Journal of Chromatography, B: Biomedical

Sciences and Applications, Volume: 746, Issue: 2, Pages: 241-247, Journal, 2000) teaches of bioavailability of sebacoyl dinalbuphine ester.

[000010] Han (International Journal of Pharmaceutics, Volume: 177, Issue: 2, Pages: 201-209, Journal, 1999) teaches of Mucoadhesive buccal disks for novel Nalbuphine prodrug controlled delivery: effect of formulation variables on drug release and mucoadhesive performance. Sung (International Journal of Pharmaceutics, Volume: 172, Issue: 1-2, Pages: 17-25, Journal, 1998) teaches of controlled release of nalbuphine prodrugs from biodegradable polymeric matrixes: influence of prodrug hydrophilicity and polymer composition. Yoa-Pu (US 5750534, A) teaches of Nalbuphine esters having long-acting analgesic action.

[000011] Shami (EP 85108258.6) teaches that Nalbuphine can be further modified into 3-acetylsalicylate. Additional Nalbuphine prodrugs are disclosed in US 6569449, B1; CN 1107333, A; EP 615756, A1; and International Journal of Pharmaceutics, Volume: 38, Issue: 1-3, Pages: 199-209, Journal, 1987.

[000012] Pharmacokinetic and pharmacodynamic properties of Nalbuphine, its pharmaceutically acceptable salt, or ester, or its prodrug could be further modulated by various delivery systems. Thus Liu (International Journal of Pharmaceutics, Volume: 257, Issue: 1-2, Pages: 23-31, Journal, 2003) teaches that biodegradable polymeric microspheres for Nalbuphine prodrug controlled delivery. Sung (European Journal of Pharmaceutical Sciences, Volume: 18, Issue: 1, Pages: 63-70, Journal, 2003) teaches of transdermal delivery of nalbuphine and its prodrugs by electroporation. Fang (Arzneimittel-Forschung, Volume: 51, Issue: 5, Pages: 408-413, Journal, 2001) teaches of Transdermal delivery of nalbuphine and nalbuphine pivalate from hydrogels by passive diffusion and iontophoresis.

[000013] A distinction must be made between an improvement of oral bioavailability and an increase in opioid receptor engagement for these opioid derivatives. For example, esterification of phenoxy moiety of Nalbuphine (e.g. 3-docosanoate derivative of Nalbuphine) (NB-39) has been previously claimed

to have improved oral bioavailability. However, when given orally, the cumulative analgesia produced by NB-39 was inferior to the equivalent dose of Nalbuphine in rats and humans. Furthermore, NB-39 did not significantly affect pupil dilation (miosis) in humans after oral administration that is indicative of inferior opioid receptor engagement.

[000014] **Naloxone**, sold under the brandname **Narcan** (and others), is a medication used to block the effects of opioids, especially in overdose situations. Naloxone may also be combined with an opioid (in the same pill or compound), to decrease the risk of opioid misuse. For instance, it could be added to the coating for a sustained release opiate compound, to prevent crushing of the sustained release compound, which could lead to an overdose.

[000015] When given intravenously, Naloxone typically works within two minutes, and when injected into a muscle, it works within five minutes. It may also be used as a nasal spray. The effects of Naloxone typically last for about half an hour to an hour. Thus, multiple doses and administration of Naloxone may be required, as the duration of action of most opioids is greater than that of Naloxone.

[000016] Administration of Naloxone to opioid-dependent individuals may cause symptoms of opioid withdrawal, such as, for example, restlessness, agitation, nausea, vomiting, increased heart rate and perspiration. To prevent this, small doses of Naloxone can be given every few minutes until the desired effect is reached.

[000017] In the individuals with prior history of heart disease or persons who take medications that negatively affect the heart, further heart problems have occurred. Naloxone appears to be safe in pregnancy, after having been given to and tested on a limited number of subjects.

[000018] Naloxone is a non-selective and competitive opioid receptor antagonist. It works by reversing the depression of the central nervous system and respiratory system caused by opioids. Naloxone was originally patented in 1961 and approved for opioid overdose treatment in the United States in 1971.

[000019] Naloxone, also known as N-allylnoroxymorphone or as 17-allyl-4,5 $\alpha$ -epoxy-3,14-dihydroxymorphinan-6-one, is a synthetic morphinan derivative and was derived from oxymorphone (14-hydroxydihydromorphinone), an opioid analgesic. Oxymorphone, in turn, was derived from morphine, an opioid analgesic and naturally occurring constituent of the opium poppy.

[000020] Naloxone is a racemic mixture of two enantiomers, (-)-naloxone (levonalozone) and (+)-naloxone (dextronaloxone), only the former of which is active at opioid receptors. The drug is a highly lipophilic, allowing it to rapidly penetrate the brain and to achieve a far greater brain to serum ratio than that of morphine. Opioid antagonists related to Naloxone include cyprodime, nalmeffene, nalodeine, naloxol, and naltrexone.

[000021] The chemical half-life of Naloxone is such that injection and nasal forms have been marketed with 24-month and 18-month shelf-lives, respectively. A 2018 study noted that the nasal and injection forms presented as chemically stable to 36- and 28-months, respectively, which prompted an as yet incomplete five-year stability study to be initiated. This suggests that expired caches of material in community and healthcare settings may still be efficacious substantially beyond their labeled expiration dates.

[000022] Certain articles about opioid antagonists emphasize the shortcomings and problems with currently known formulations, and the need for an improved and more stable compound that may be used safely on patients suffering from opioid addiction.

[000023] An article by Adam Bisaga, entitled "What Should Clinicians Do As Fentanyl Replaces Heroin?" (published in *Addiction*, Vol. 114, pp. 781-86, at <https://onlinelibrary.wiley.com/doi/epdf/10.1111/add.14522>) describes that a high affinity antagonists may not suffice to block effects of fentanyl and their higher doses that border concerns over systematic safety may be required. Furthermore, fentanyl overdose prevention requires higher doses of naloxone and repeated dosing that is encumbered by much shorter overdose prevention window for fentanyl than heroin.

[000024] Roger Chou et al. describes in the article entitled "Management of Suspected Opioid Overdose With Naloxone by Emergency Medical Services Personnel" (published at In Comparative Effectiveness Review No. 193, at [https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/cer-193-naloxone-final\\_1.pdf](https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/cer-193-naloxone-final_1.pdf)) that existing dosing guidelines of naloxone may not be sufficient to prevent overdose by fentanyl and fentanyl analogues.

[000025] Rachael Rzasa Lynn et al. describes in the article entitled "Naloxone Dosage for Opioid Reversal: Current Evidence and Clinical Implications" (published in Therapeutic Advances in Drug Society Review, Vol. 9(1), pp. 63-88, 2018 at [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5753997/pdf/10.1177\\_2042098617744161.pdf](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5753997/pdf/10.1177_2042098617744161.pdf)) that double dose of naloxone administered to patient anesthetized with fentanyl produced no improvement in oxygen intake, while quadruple dose of naloxone produced significant improvements. Further he teaches that the interactions between the opioid agonist and the mu-opioid receptor may be the greatest determinant of the speed of recovery from the respiratory effects of many opioids, which may not markedly accelerate with increasing doses of naloxone, but rather respond to a minimum effective dose, while for compounds like buprenorphine, higher doses of naloxone may even lose efficacy. Then he cites numerous reports describe fentanyl overdoses initially unresponsive to IN naloxone and only transiently reversed with IV naloxone (if at all), requiring additional IV doses or continuous infusions to prevent recurrence of toxicity and respiratory depression.

[000026] IA. Elkiweri et al. describes in the article entitled "Competitive substrates for P-glycoprotein and organic anion protein transporters differentially reduce blood organ transport of fentanyl and loperamide: pharmacokinetics and pharmacodynamics in Sprague-Dawley rats" (published online in 2009 at <https://www.ncbi.nlm.nih.gov/pubmed/19095843>) that naloxone and fentanyl share a transporter for cellular influx that becomes saturated by a high plasma concentration of fentanyl, preventing rapid influx of naloxone across the BBB regardless of dose.

[000027] Rebecca McDonald et al. describes in the article entitled “Pharmacokinetics of concentrated naloxone nasal spray for opioid overdose reversal: Phase I healthy volunteer study” (published in *Addiction*, 113, pp. 484-93 at ) that high concentration 2 mg Naloxone intranasal (i.n.) spray has early absorption rate that is comparable to intramuscular (i.m.) 0.4 mg injection and could be used as a take-home antidote. He suggests that high dose i.n. Naloxone could be given without risk of “overantagonism”.

[000028] Jiten Ranchhodbhai Patel et al. discloses (Publication No. WO 2013093931 – application PCT/IN20 12/00590, filed Sep. 6, 2012) a novel hydrazide group containing carbamates of naloxone.

[000029] Baohua Huang et al. describes in the article entitled “Human plasma-mediated hypoxic activation of indolequinone-based naloxone pro-drugs” (published in *Bioorganic & Medicinal Chemistry Letters* in 2009, 19(17), 5016-5020) that indolequinone based naloxone pro-drug can reverse opiate induced hypoxia.

[000030] I. Ukrainets et al. discloses in the publication *Chemistry of Heterocyclic Compounds* (2009), 45(4), pp. 405-416) studies of 3-O-acyl derivatives of naloxone as its potential prodrugs.

[000031] Xuemei Peng et al. describes in the article “Pharmacological Properties of Bivalent Ligands Containing Butorphan Linked to Nalbuphine and Nalaxone at  $\mu$ ,  $\delta$  and  $\kappa$  Opioid Receptors” (published in the *Journal of Medicinal Chemistry* (May 2007), 50(9), 2254-2258) discloses bivalent ligands containing butorphan linked to naloxone.

[000032] I. Romanov et al. describes in the Russian Patent Publication (RU 2221566 – published 01/20/2004) that esters of N-substituted 14-hydroxymorphinans could be used as highly effective low toxic an antirelapse agent with prolonged opioid protective effect being after a single s.c. or i.m. injection.

[000033] I. Romanov et al. describes in the Russian Patent Publication (RU 2215741 –

published 11/10/2003) the methods of preparation N-substituted 14-hydroxymorphinane esters.

[000034] Euro-Celtique, S.a., Chevchuk et al. describe in the Patent Publication No. WO 2003070191 (PCT/US/2003/004999 – published 08/28/2003) the methods of preventing pain with a tamper-resistant transdermal device containing 3-acyl- substituted antagonists.

[000035] Lu Zhengtang discloses in the Chinese Patent No. CN 1204649 (published 01-13-1999) preparation of naloxone esters.

[000036] S. Lazar et al. describes in the article entitled “Synthesis and biological activity of the phosphate and sulfate esters of naloxone and naltrexone” (published in the European Journal of Medicinal Chemistry (1994), vol. 29(1), pp. 45-53) the synthesis and biological activity of the phosphate and sulfate esters of naloxone.

[000037] Hussein et al. describes (in Pharmaceutical Research (1988), vol. 5(9), pp. 615-18) that various prodrugs of naloxone where 3-phenoxy group is esterified lacked a bitter taste and had better buccal bioavailability in dogs.

[000038] Elie Gabriel Shami describes in European Patent Publication No. EP 170090 that benzoate ester prodrug derivatives of 3-hydroxymorphinans. The aforementioned publications are incorporated herein, as part of the specification.

[000039] None of these cited publications describes Naloxone combination with a hexadienoate included in the molecule, or indicates that such molecule will result and provide substantially more effective and long-lasting neutralizing/sobering effect when administered to a person.

#### DESCRIPTION OF INVENTION

[000040] The present invention involves a novel modification of opioids and their antagonists that leads to higher opioid receptor engagement when given orally. More specifically, the present invention involves modification of the appropriate opiate receptor modulators (e.g. Nalbuphine, Buprenorphine, Hydromorphone, Morphine, Pentazocine, Butorphanole, Naloxone, etc.) or related

compounds to improve opiates' engagement of the opioid receptors when given orally.

[000041] The present invention further involves methods of mitigating opiate low oral bioavailability when opiates are used, without limitation, for the following conditions: pain management, palliative care, anesthesiology (e.g. postoperatively), skin disorders (e.g. pruritus), addictions (detox or management), certain locomotive disorders (e.g. levodopa-induced dyskinesias (LID) in Parkinson's disease, the dyskinesias associated with Tourette's syndrome, tardive dyskinesia, Huntington's disease, etc.

[000042] The present invention involves a novel modification of the opioid agent (e.g. Nalbuphine) that provides unexpected results of increasing the engagement of opioid receptors when given orally. Thus, this novel modification provides superior quality of care and allows for a wider range of therapeutic indications, including chronic conditions that require oral administration of the opioid.

[000043] The present invention involves a novel modification of the opioid antagonist, such as Naloxone combination with a hexadienoate included in the molecule, which provides substantially more effective and long-lasting neutralizing/sobering effect when administered to a person or patient.

[000044] The novel features of the present invention will be further described with reference to the following drawings.

#### BRIEF DESCRIPTION OF THE DRAWINGS

[000045] The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

[000046] FIGURE 1 illustrates NMR 1H spectrum of NB-20 compound, formulated in accordance with at least one embodiment of the present invention.

[000047] FIGURE 2 illustrates NMR 1H spectrum of NB-33 compound, formulated in accordance with at least one embodiment of the present invention.

[000048] FIGURE 3 illustrates NMR 1H spectrum of NB-39 compound, formulated in accordance with at least one embodiment of the present invention.

[000049] FIGURE 4 illustrates NMR 1H spectrum of NB-51 compound, formulated in accordance with at least one embodiment of the present invention.

[000050] FIGURE 5 illustrates NMR 1H spectrum of NB-52 compound, formulated in accordance with at least one embodiment of the present invention.

[000051] FIGURE 6 illustrates NMR 1H spectrum of NB-56 compound, formulated in accordance with at least one embodiment of the present invention.

[000052] FIGURE 7 illustrates NMR 1H spectrum of NB-58 compound, formulated in accordance with at least one embodiment of the present invention.

[000053] FIGURE 8 illustrates NMR 1H spectrum of NB-78 compound, formulated in accordance with at least one embodiment of the present invention.

[000054] FIGURE 9A illustrates the binding mode and molecular interactions of the most energetically favored conformer of nalbuphine superposed with co-crystallized ligand  $\beta$ -FNA.

[000055] FIGURE 9B illustrates the binding mode and molecular interactions of the most energetically favored conformer of naloxone superposed with co-crystallized ligand  $\beta$ -FNA.

[000056] FIGURE 10A illustrates the binding mode and molecular interactions of the most energetically favored conformer of NX-90 in the binding site of 4DKL.

[000057] FIGURE 10B illustrates the binding mode and molecular interactions of the most energetically favored conformer of NB-33 in the binding site of 4DKL.

[000058] FIGURE 10C illustrates molecular interaction with Met 151 shown by the conformer of NB-33 with the binding mode similar to the most energetically favored conformer.

[000059] FIGURE 10D illustrates the binding mode and molecular interactions of the most energetically favored conformer of NB-39 in the binding site of 4DKL.

[000060] FIGURE 11A illustrates the most energetically favored conformer of nalbuphine (yellow), naloxone (pink) and co-crystalized  $\beta$ -FNA (white) superposed in the opioid binding site of 4DKL.

[000061] FIGURE 11B illustrates the most energetically favored conformers of NX-90 (blue), NB-33 (red), NB-39 (cyan) and co-crystalized  $\beta$ -FNA (white) superposed in the opioid binding site of 4DKL.

[000062] FIGS. 12A-C show Hydrophobic (red) and hydrophilic (yellow) contact preference areas on the molecular surface of the binding site of 4DKL with the docked conformer of NX-90, NB-33 and NB-39, respectively, in accordance with at least one embodiment.

[000063] FIG. 13 shows Graph 1, illustrating superior analgesic properties of the NB-33, according to at least one embodiment, in comparison to the equimolar dose of the parent opioid NB.

#### DETAILED DESCRIPTION

[000064] The present invention includes formation of an opiate derived compositions including hexadienoate and opioid residue in a single molecule, which is used in therapeutic areas associated with opioid receptor modulation.

[000065] The various aspects and features of the present invention and the composition is described with reference to TABLE 1, which illustrates the selected properties of compounds NB, NB-20, NB-28, NB-31, NB-32, NB-33, NB-39, NB-46, NB-51, NB-52, NB-56, NB-58, NB-76, NB-78.

[000066] Examples of NMR 1H spectrums of selected compounds (examples including NB-20, NB-33, NB-39, NB-51, NB-52, NB-56, NB-58, NB-78), formulated in accordance with at least one embodiment of the present invention are shown in FIGS 1-8, respectively.

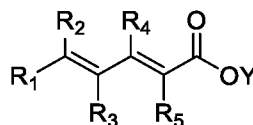
[000067] Surprisingly, 3-hexadienoate derivative of an opioid, created in accordance with at least one embodiment of the present invention, produced higher opioid receptor engagement than the parent opioid compound. Thus, for example, Nalbuphine 3-hexadienoate (NB-33) produced superior to the equivalent dose of both Nalbuphine 3-docosanoate (NB-39) and Nalbuphine (NB) analgesia in rats and humans, when given orally. Furthermore, a significant effect of NB-33 on pupil dilation (miosis) was

observed in humans, which indicated superior receptor engagement.

[000068] Unexpectedly, when examining the effects of at least one embodiment of the present invention, was found that the position and the number of unsaturated sites of the ester of the phenoxy moiety is unique for hexadienic backbone and required for a superior engagement of opioid receptors. Thus, Nalbuphine 3-alkenoate (e.g. NB-33) produced better analgesia than the parent opioid, while other unsaturated acid derivatives of Nalbuphine (e.g. NB-31, NB-32, NB-52, or NB-78) produced no analgesia in rats.

[000069] Moreover, evaluating at least one embodiment of the present invention, it was found that Nalbuphine 3-hexadienoate has a unique and distinct opiate receptor signature of its own with human recombinant opiate receptors expressed in cells.

[000070] In accordance with at least one embodiment, the compounds of present invention comprise a general formula I or pharmaceutically acceptable salt of thereof



Formula I

wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> or R<sub>5</sub> are selected from a group comprising H, optionally substituted C1-3 and OAlk), double bonds have E or Z geometry, and Y is an opioid residue.

[000071] In at least one embodiment, the present invention further relates to methods of mitigating opiate low oral bioavailability when opiates are used in the following, but not limited to, conditions: pain management, palliative care, anesthesiology (e.g. postoperatively), skin disorders (e.g. pruritus), addictions (detox or management), certain locomotive disorders (e.g. levodopa-induced dyskinesias (LID) in Parkinson's disease, and the dyskinesias associated with Tourette's syndrome, tardive dyskinesia and Huntington's disease), etc.

[000072] In at least one embodiment, the present invention is an optionally substituted

hexadienoate of a phenoxy moiety modification of the appropriate opiate receptor modulators or related compounds to improve opiates' engagement of the opioid receptors when given orally.

[000073] In another embodiment, the present invention is a is an optionally substituted hexadienoate of a 3-phenoxy moiety modification of the appropriate opiate receptor modulators, including, but not limited to, Hydromorphone, Morphine, Nalbuphine, Pentazocine, Butorphanol, Buprenorphine, Naloxone or related compounds, formulated to improve opiates' engagement of the opioid receptors when given orally.

[000074] In at least one further embodiment, the present invention is a 3-hexadienoate modification of the appropriate opiate receptor modulators or related compounds, formulated to improve opiates' engagement of the opioid receptors when given orally.

[000075] In at least one embodiment, the present invention is a 3-hexadienoate modification of Nalbuphine or a pharmaceutically acceptable salt of thereof to improve engagement of the opioid receptors when given orally.

[000076] In yet another embodiment, the present invention is a 3-hexadienoate modification of Nalbuphine or a pharmaceutically acceptable salt of thereof to improve quality of pain management when given orally.

[000077] In a further one or more embodiments, the present invention is a 3-hexadienoate modification of Nalbuphine or a pharmaceutically acceptable salt of thereof to improve quality of pain management when given intravenously, intranasally, transdermally, sublingually, rectally, topically, intramuscularly, subcutaneously or via inhalation.

[000078] The following are further examples of compounds prepared in accordance with at least one embodiment of the present invention. The chemical name, composition and coding name for each of the compounds in Examples 1 is shown in TABLE 1 below.

EXAMPLES 1

[000079] (E)-3-(cyclobutylmethyl)-9-((3,7-dimethylocta-2,6-dien-1-yl)oxy)-1,2,3,4,5,6,7,7a-octahydro-4aH-4,12-methanobenzofuro[3,2-e]isoquinoline-4a,7-diol, Nalbuphino-Geranyl, (NB-20).

Potassium bicarbonate (280 mg, 2.0 mmol) was added to suspension of nalbuphine hydrochloride (400 mg, 1.0 mmol) in acetone (20 mL) and toluene (20 mL) at room temperature. Geranyl bromide (320 mg, 1.5 mmol) was added. The reaction mixture was stirred under reflux for 4 h and overnight at room temperature. The reaction mixture was evaporated and the residue was purified by column chromatography (silicagel, EtOAc/Heptanes/MeOH, 1:1:0.10). The colorless oil was formed after evaporation of selected fractions, yield 45%, purity 91% by HPLC. The structure was confirmed by NMR <sup>1</sup>H.

[000080] 3-(cyclobutylmethyl)-9-(((2E,6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)oxy)-1,2,3,4,5,6,7,7a-octahydro-4aH-4,12-methanobenzofuro[3,2-e]isoquinoline-4a,7-diol, Nalbuphino-Farnesyl, (NB-28). This compound was prepared according to the procedure of NB-20, by substituting geranyl bromide for farnesyl bromide. The crude material was purified by column chromatography (silicagel, EtOAc/Heptanes, 1:1). The colorless oil was obtained after evaporation of selected fractions, yield 53%, purity 93% by HPLC. The structure was confirmed by NMR <sup>1</sup>H.

[000081] 3-(cyclobutylmethyl)-4a,7-dihydroxy-2,3,4,4a,5,6,7,7a-octahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinolin-9-yl undec-10-enoate, Nalbuphino-undecelenoate, (NB-31). EDCI (1.04 g, 5.4 mmol) was added to undecylenic acid (1.0 g, 5.4 mmol) in THF (30 mL) at 0 °C with stirring. The reaction mixture was stirred for 10 min and Nalbuphine hydrochloride (2.13 g, 5.4 mmol), trimethylamine (1.1 g, 10.9 mmol) and 4-dimethylaminopyridine (0.22 g, 1.8 mmol) were added at 0 °C. The stirring was continued for 1 h at 0 °C and at room temperature overnight. The reaction mixture was filtered, filtrate was evaporated, and the residue was purified by column chromatography (silicagel, EtOAc/Heptanes, 1:1). The white solid was formed after evaporation of selected fractions, yield 2.2 g (78%), purity 95% by HPLC. The structure was confirmed by NMR <sup>1</sup>H.

[000082] 3-(cyclobutylmethyl)-4a,7-dihydroxy-2,3,4,4a,5,6,7,7a-octahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinolin-9-yl (E)-3,7-dimethylocta-2,6-dienoate, Nalbuphino-geranoate, (NB-32). This compound was prepared according to the procedure of NB-31, by substituting undecylenic acid for geranic acid. The crude material was purified by column chromatography (silicagel, EtOAc/Heptanes, 1:1). The white solid was formed after evaporation of selected fractions, yield 67%, and purity 96% by HPLC. The structure was confirmed by NMR <sup>1</sup>H.

[000083] 3-(cyclobutylmethyl)-4a,7-dihydroxy-2,3,4,4a,5,6,7,7a-octahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinolin-9-yl (2E,4E)-hexa-2,4-dienoate, Nalbuphino-sorbate, (NB-33). EDCI (1.16 g, 6.1 mmol) was added to hexadienoic acid (0.68 g, 6.1 mmol) in THF (30 mL) at 0 °C with stirring. The reaction mixture was stirred for 10 min and Nalbuphine hydrochloride (2.39 g, 6.1 mmol), trimethylamine (1.2 g, 12 mmol) and 4-dimethylaminopyridine (0.25 g, 2 mmol) were added at 0 °C. The stirring was continued for 1 h at 0 °C and at room temperature overnight. The reaction mixture was filtered, filtrate was evaporated, and the residue was purified by column chromatography (silicagel, EtOAc/Heptanes, 1:1). The white crystals were formed after evaporation of selected fractions, yield 2.05 g (75%), purity 98% by HPLC. The structure was confirmed by NMR <sup>1</sup>H.

[000084] 3-(cyclobutylmethyl)-9-(((2E,4E)-hexa-2,4-dienoyl)oxy)-4a,7-dihydroxy-2,3,4,4a,5,6,7,7a-octahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinolin-3-ium chloride, Nalbuphino-sorbate, hydrochloride, (NB-56). HCl (gas) was bubbled into the solution of nalbuphino-sorbate (NB-33) (0.4 g, 0.89 mmol) in MTBE (15 mL) at 0 °C. The white precipitate was formed immediately. The reaction mixture was stirred for 1 h and the solid was filtered, washed with MTBE and dried in vacuum. The yield 0.35 g (81%), purity 98% by HPLC. The structure was confirmed by NMR <sup>1</sup>H.

[000085] 3-(cyclobutylmethyl)-4a,7-dihydroxy-2,3,4,4a,5,6,7,7a-octahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinolin-9-yl docosanoate, Nalbuphino-docosanoate, (NB-39). EDCI (0.56 g, 2.9 mmol) was added to behenic acid (1.0 g, 2.9 mmol) in THF (50 mL) at 0 °C with stirring. The reaction

mixture was stirred for 30 min and Nalbuphine hydrochloride (1.16 g, 2.9 mmol), trimethylamine (0.29 g, 2.9 mmol) and 4-dimethylaminopyridine (0.12 g, 1.0 mmol) were added at 0 °C. The stirring was continued for 1 h at 0 °C and at room temperature overnight. The reaction mixture was filtered, filtrate was evaporated, and the residue was purified by column chromatography (silicagel, EtOAc/Heptanes, 1:2). The white solid was formed after evaporation of selected fractions, yield 1.45 g (73%), purity 97% by HPLC. The structure was confirmed by NMR <sup>1</sup>H. Synthesis and properties of NB-39 was also described in US Patent 5750534.

[000086] 3-(cyclobutylmethyl)-4a,7-dihydroxy-2,3,4,4a,5,6,7,7a-octahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinolin-9-yl isobutyrate, Nalbuphino-isobutyrate, NB-isovaleroate, (NB-46). This compound was prepared according to the procedure of NB-31, by substituting undecylenic acid for isovaleric acid. The crude material was purified by column chromatography (silicagel, EtOAc/Heptanes, 1:1). The white crystals were formed after evaporation of selected fractions, yield 54%, and purity 95% by HPLC. The structure was confirmed by NMR <sup>1</sup>H.

[000087] 3-(cyclobutylmethyl)-4a,7-dihydroxy-2,3,4,4a,5,6,7,7a-octahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinolin-9-yl 3-methylbut-2-enoate, Nalbuphino-3,3-dimethylacrylate, (NB-51). This compound was prepared according to the procedure of NB-31, by substituting undecylenic acid for 3,3-dimethyl acrylic acid. The crude material was purified by column chromatography (silicagel, EtOAc/Heptanes, 1:1). The white crystals were formed after evaporation of selected fractions, yield 77%, purity 95% by HPLC. The structure was confirmed by NMR <sup>1</sup>H.

[000088] 3-(cyclobutylmethyl)-4a,7-dihydroxy-2,3,4,4a,5,6,7,7a-octahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinolin-9-yl (E)-2-methylbut-2-enoate, Nalbuphino-2,3-dimethylacrylate, (52). This compound was prepared according to the procedure of NB-31, by substituting undecylenic acid for 2,3-dimethyl acrylic acid. The crude material was purified by column chromatography (silicagel, EtOAc/Heptanes, 1:1). The white crystals were formed after evaporation of selected fractions, yield 75%, purity 96% by HPLC. The structure was confirmed by NMR <sup>1</sup>H.

[000089] 3-(cyclobutylmethyl)-4a,7-dihydroxy-2,3,4,4a,5,6,7,7a-octahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinolin-9-yl 2-methoxybut-2-enoate, Nalbuphino-2-methoxycrotonate, (NB-58). This compound was prepared according to the procedure of NB-31, by substituting undecylenic acid for 2-methoxy-crotonic acid. The crude material was twice purified by column chromatography (silicagel, EtOAc/Heptanes, 1:1). The white oils were formed after evaporation of selected fractions, yield 27%, purity 94% by HPLC. The structure was confirmed by NMR <sup>1</sup>H.

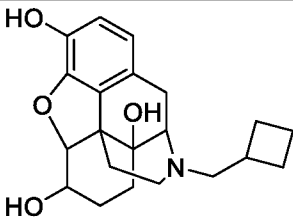
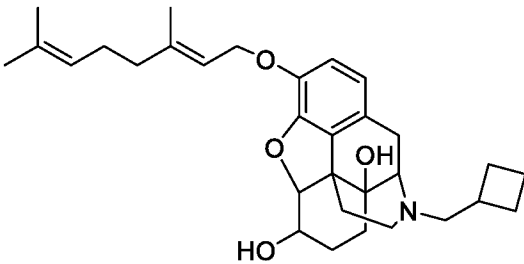
[000090] 7-acetoxy-3-(cyclobutylmethyl)-4a-hydroxy-2,3,4,4a,5,6,7,7a-octahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinolin-9-yl-(2E,4E)-hexa-2,4-dienoate, Nalbuphino-hexadienoate-acetate (NB-76). NB-33 (0.5 g, 1.1 mmol) was stirred in acetic anhydride (7.0 mL) at 40-50 °C overnight. EtOH (20 mL) was added and the reaction mixture was evaporated. The residue was twice purified by column chromatography (silicagel, EtOAc/Heptanes, 1:2). The white crystals were formed after evaporation of selected fractions, yield 1.45 g (50%), purity 97% by HPLC. The structure was confirmed by NMR <sup>1</sup>H.

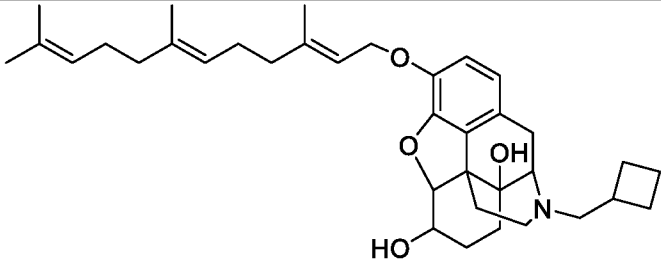
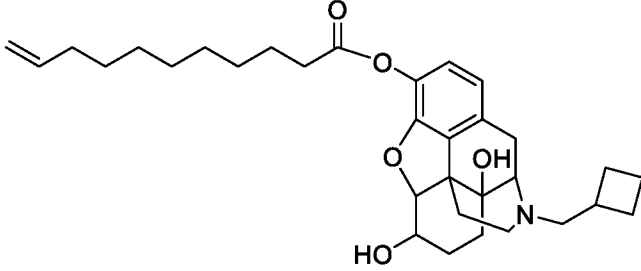
[000091] 3-(cyclobutylmethyl)-4a,7-dihydroxy-2,3,4,4a,5,6,7,7a-octahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinolin-9-yl cinnamate, Nalbuphino-cinnamate, (NB-78). This compound was prepared according to the procedure of NB-31, by substituting undecylenic acid for 2-trans-cinnamic acid. The crude material was purified by column chromatography (silicagel, EtOAc/Heptanes, 1:1). The white crystals were formed after evaporation of selected fractions, yield 67%, purity 94% by HPLC. The structure was confirmed by NMR <sup>1</sup>H.

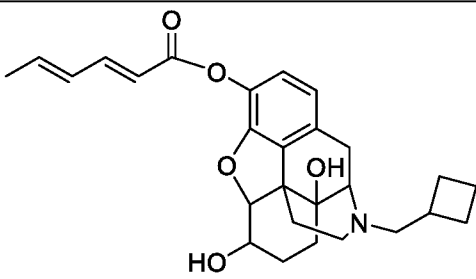
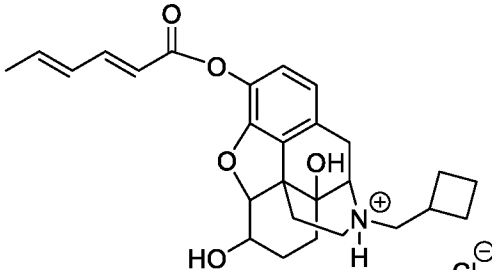
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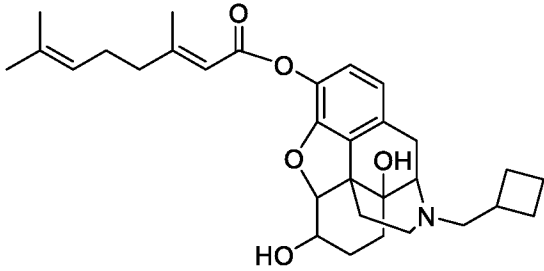
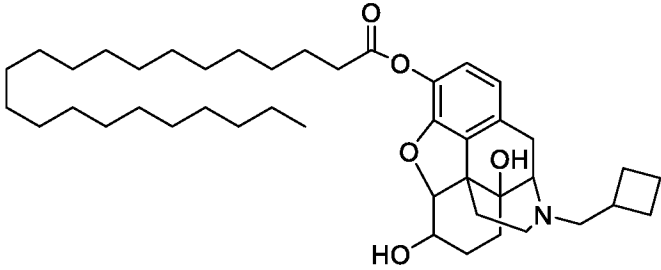
TABLE 1

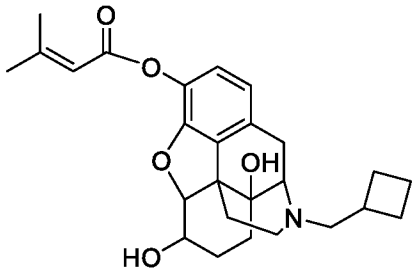
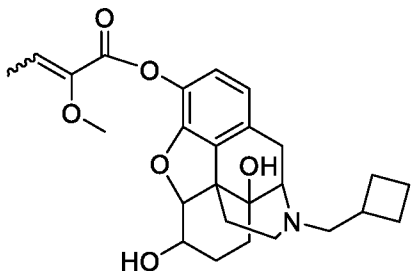
N	Name, Structure	Code	Stable in sGIF	Stable in plasma	Analgesia (rat)
1	Nalbuphine	NB	n/a	n/a	moderate

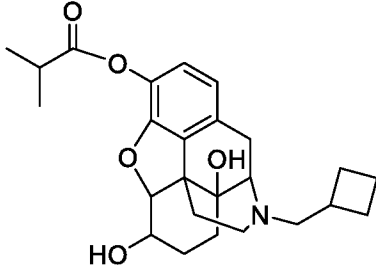
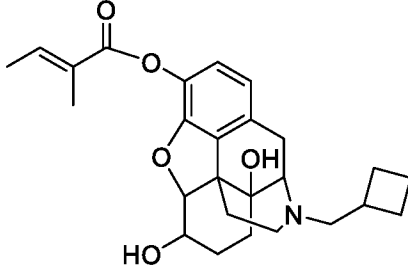
	 <p>3-(cyclobutylmethyl)-1,2,3,4,5,6,7,7a-octahydro-4aH-4,12-methanobenzofuro[3,2-e]isoquinoline-4a,7,9-triol</p> <p>Chemical Formula: C<sub>21</sub>H<sub>27</sub>NO<sub>4</sub></p> <p>Molecular Weight: 357.45</p>				
2	<p>Nalbuphino-Geranyl, NB-geranyl,</p>  <p>(E)-3-(cyclobutylmethyl)-9-((3,7-dimethylocta-2,6-dien-1-yl)oxy)-1,2,3,4,5,6,7,7a-octahydro-4aH-4,12-methanobenzofuro[3,2-e]isoquinoline-4a,7-diol</p> <p>Chemical Formula: C<sub>31</sub>H<sub>43</sub>NO<sub>4</sub></p> <p>Molecular Weight: 493.69</p>	NB-20	No	No	No
3	<p>Nalbuphino-Farnesyl, NB-farnesyl,</p>	NB-28	No	No	No

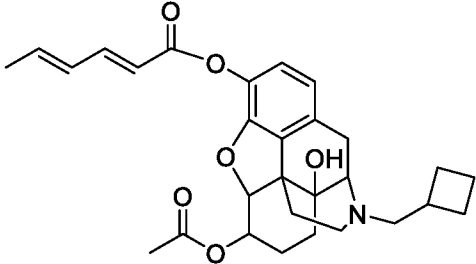
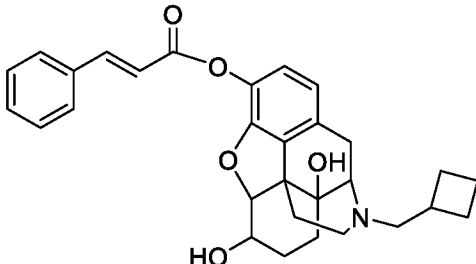
	 <p>3-(cyclobutylmethyl)-9-(((2E,6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)oxy)-1,2,3,4,5,6,7,7a-octahydro-4aH-4,12-methanobenzofuro[3,2-e]isoquinoline-4a,7-diol</p> <p>Chemical Formula: C<sub>36</sub>H<sub>51</sub>NO<sub>4</sub></p> <p>Molecular Weight: 561.81</p>				
4	 <p>3-(cyclobutylmethyl)-4a,7-dihydroxy-2,3,4,4a,5,6,7,7a-octahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinolin-9-yl undec-10-enoate</p> <p>Chemical Formula: C<sub>32</sub>H<sub>45</sub>NO<sub>5</sub></p> <p>Molecular Weight: 523.71</p>	NB-31	Yes	No	Inactive
5	Nalbuphino-hexadienoate, NB-sorbate,	NB-33	Yes	No	Excellent

	 <p>3-(cyclobutylmethyl)-4a,7-dihydroxy-2,3,4,4a,5,6,7,7a-octahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinolin-9-yl (2E,4E)-hexa-2,4-dienoate</p> <p>Chemical Formula: C<sub>27</sub>H<sub>33</sub>NO<sub>5</sub></p> <p>Molecular Weight: 451.56</p>				
6	<p>Nalbuphino-hexadienoate, hydrochloride; NB-sorbate, HCl salt</p>  <p>3-(cyclobutylmethyl)-9-(((2E,4E)-hexa-2,4-dienoyl)oxy)-4a,7-dihydroxy-2,3,4,4a,5,6,7,7a-octahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinolin-3-ium chloride</p> <p>Chemical Formula: C<sub>27</sub>H<sub>34</sub>ClNO<sub>5</sub></p> <p>Molecular Weight: 488.02</p>	NB-56	Yes	No	No

7	<p>Nalbuphino-geranoate, NB-geranoate,</p>  <p>3-(cyclobutylmethyl)-4a,7-dihydroxy-2,3,4,4a,5,6,7,7a-octahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinolin-9-yl (E)-3,7-dimethylocta-2,6-dienoate</p> <p>Chemical Formula: C<sub>31</sub>H<sub>41</sub>NO<sub>5</sub></p> <p>Molecular Weight: 507.67</p>	NB-32	Yes	No	Inactive
8	<p>Nalbuphino-docosanoate, NB-behenoate,</p>  <p>3-(cyclobutylmethyl)-4a,7-dihydroxy-2,3,4,4a,5,6,7,7a-octahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinolin-9-yl docosanoate</p> <p>Chemical Formula: C<sub>43</sub>H<sub>69</sub>NO<sub>5</sub></p>	NB-39	Yes	No	Inactive

	Molecular Weight: 680.03					
9	Nalbuphino-3,3-dimethylacrylate, dimethylacrylate, NB-senecioate    3-(cyclobutylmethyl)-4a,7-dihydroxy-2,3,4,4a,5,6,7,7a-octahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinolin-9-yl 3-methylbut-2-enoate  Chemical Formula: C <sub>26</sub> H <sub>33</sub> NO <sub>5</sub>  Molecular Weight: 439.55	NB-3,3-	NB-51	Yes	No	Inactive
10	Nalbuphino-2-methoxycrotonate, NB-2-methoxycrotonate    3-(cyclobutylmethyl)-4a,7-dihydroxy-2,3,4,4a,5,6,7,7a-		NB-58	No	No	No

	<p>octahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinolin-9-yl 2-methoxybut-2-enoate</p> <p>Chemical Formula: C<sub>26</sub>H<sub>33</sub>NO<sub>6</sub></p> <p>Molecular Weight: 455.55</p>				
11	<p>Nalbuphino-isobutyrate, NB-isovaleroate</p>  <p>3-(cyclobutylmethyl)-4a,7-dihydroxy-2,3,4,4a,5,6,7,7a-octahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinolin-9-yl isobutyrate</p> <p>Chemical Formula: C<sub>25</sub>H<sub>33</sub>NO<sub>5</sub></p> <p>Molecular Weight: 427.54</p>	NB-46	Yes	Yes	No
12	<p>Nalbuphino-2,3-dimethylacrylate, NB-Tiglate</p>  <p>3-(cyclobutylmethyl)-4a,7-dihydroxy-2,3,4,4a,5,6,7,7a-</p>	NB-52	Yes	No	Inactive

	<p>octahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinolin-9-yl (E)-2-methylbut-2-enoate</p> <p>Chemical Formula: C<sub>26</sub>H<sub>33</sub>NO<sub>5</sub></p> <p>Molecular Weight: 439.55</p>				
13	<p>Nalbuphino-hexadienoate-acetate,</p>  <p>7-acetoxy-3-(cyclobutylmethyl)-4a-hydroxy-2,3,4,4a,5,6,7,7a-octahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinolin-9-yl (2E,4E)-hexa-2,4-dienoate</p> <p>Chemical Formula: C<sub>29</sub>H<sub>35</sub>NO<sub>6</sub></p> <p>Molecular Weight: 493.60</p>	NB-76	Yes	No	moderate
14	<p>Nalbuphino-cinnamate</p> 	NB-78	Yes	No	Inactive

	3-(cyclobutylmethyl)-4a,7-dihydroxy-2,3,4,4a,5,6,7,7a- octahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinolin- 9-yl cinnamate Chemical Formula: C <sub>30</sub> H <sub>33</sub> NO <sub>5</sub> Molecular Weight: 487.60				
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EXAMPLE 2 -- Stability in the simulated gastro-intestinal fluid (sGIF).

[000093] Stability of NB-33 in the simulated gastro-intestinal fluid (sGIF) was evaluated as below and individual compound data was summarized in Table 1.

[000094] sGIF is 0.5% solution of pepsine(Alfa Aesar, Pepsin, porcine stomach) in 0.1N aqueous HCl . Each derivative (50mg) was mixed with sGIF (50 mL) and incubated at 37 °C on a shaker. The hydrolysis and release of Nalbuphine was monitored by HPLC at T = 0 hr,

[000095] 0.5 hr, 1 hr, 2 hr, and 4 hr. The acceptance criteria was defined as NLT 80% of the derivative still intact after 4 hrs.

EXAMPLE 3 - Stability in human plasma.

[000096] Stability of NB-56 in human plasma was evaluated as below and the individual compound data was summarized in Table 1.

[000097] NB-56 (1.0 mg) was dissolved in 10 mL of plasma (Plasma Pooled Normal Human Plasma, Na-citrate, Innovative Research) with stirring for 10 min at 20 °C. The solution was incubated at 37 °C. 1 mL of solution was taken for each test sample. MeCN (0.05 mL) was added to sample solution. Shaking for 1 min followed by centrifugation (15 min, 14,000r/m). Supernatant was filtered off and extracted with EtOAc (2x20 mL). The combined extract was dried over MgSO<sub>4</sub> and concentrated in vacuum. The residue was dissolved in MeOH (20 µL). The solution was used for HPLC injection.

[000098] The hydrolysis and release of Nalbuphine was monitored by HPLC at T = 0 hr, 0.5 hr, 1 hr, 2 hr, and 4 hr. The acceptance criteria was defined as NLT than 20% of hydrolysis after 4 hrs.

#### EXAMPLE 4

TABLE 2 - Human recombinant opiate receptor data for NB-33

Assay	NB-33	
	< 1 uM	> 1 uM
mu (MOR) (h) (agonist effect)		
mu (MOR) (h) (antagonist effect)	X	X
kappa (KOR) (h) (agonist effect)		X
kappa (KOR) (h) (antagonist effect)		
delta (DOR) (h) (agonist effect)		X
delta (DOR) (h) (antagonist effect)		

[000099] Human recombinant opiate receptor (mu, kappa or delta) expressed in CHO-K1 cells were used. Test compound (NB-33)/or vehicle was incubated with the cells (4 x 10E5/mL) in modified HBSS pH 7.4 buffer at 370C for 30 min. The reaction was evaluated for cAMP levels by TR-FRET. Compounds were screened at 0.3, 1 and 3 uM. by Eurofins Pharma Discovery Services.

[0000100] Data for compound NB-33 is summarized in Table 2.

EXAMPLE 5

[0000101] Tests on Sprague-Dawley rats were conducted using Nalbuphine, NB-31, NB-32, NB-33, NB-33, NB39, NB-51, NB-52, NB-76 and NB-78.

[0000102] Thirty Sprague-Dawley rats (12 week old; male) were randomly assigned to 10 groups and each group was gavaged with one of the following treatments: 1. Sesame oil; 2. Nalbuphine (in sesame oil; 60 uM/kg), 3. NB-31 (in sesame oil; 60 uM/kg), 4. NB-32 (in sesame oil; 60 uM/kg), 5. NB-33 (in sesame oil; 60 uM/kg), 6. NB-39 (in sesame oil; 60 uM/kg), 7. NB-51 (in sesame oil; 60 uM/kg), 8. NB-52 (in sesame oil; 60 uM/kg), 9. NB-76 (in sesame oil; 60 uM/kg), 10. NB-78 (in sesame oil; 60 uM/kg). Each rat received only one oral dose.

[0000103] The antinociceptive activity was assessed as in Anesth Analg 2003; 97; 806–9 using the cold ethanol tail-flick test. The testing temperature was set at -20° C and the cutoff time was 40 seconds. All rats were tested at T= 0 immediately before medication. Measurements of the antinociceptive thresholds of saline, nalbuphine and nalbuphine derivatives were done at T = 0 hr, 0.25 hr, 0.5 hr, 1 hr, 1.5 hr, 2 hr, 3 hr and 5 hr followed oral administration.

[0000104] The data, as illustrated in the last column of Table 1 indicates excellent and superior results for NB-33.

[0000105]

EXAMPLE 6

[0000106] Double-blind, NB hydrochloride and NB-39 controlled, trial of the antinociceptive effect of oral NB-33 in healthy volunteers. Each of the three healthy volunteers was assigned a set of 6 non-transparent gelatin capsules as follows: 2 x NB hydrochloride (MW = 393.4; 39mg), 2 x NB-33 (MW = 451.6; 45mg) and 2 x NB-39 (MW = 680.0; 68mg). Each week a healthy volunteer would receive a pill from the assigned set in a random fashion and take it orally. At T = 0 hr, 0.25 hr, 0.5 hr, 1 hr, 1.5 hr, 2 hr, 3 hr and 5 hr followed oral administration a heat pain threshold was measured (hot water at 50°C) as well as

miosis.

[0000107] Following one week of a wash out period, each volunteer repeated the protocol until all pills from the assigned set were administered. The individual data for heat pain threshold as %MPE =  $[(\text{test latency} - \text{baseline latency})/(\text{baseline latency})] \times 100$  and for miosis as %MPE =  $[(\text{test diameter} - \text{baseline diameter})/(\text{baseline diameter})] \times 100$  are shown in Table 2 and Table 3 respectively.

[0000108] Tables 3, 4, and 5A-D illustrate that NB-33 resulted in analgesia and miosis superior to both the parent opioid NB and the parent opioid prodrug NB-39 when given orally. The differences in analgesia and miosis were statistically significant as indicated in Table 5A-D.

[0000109]

TABLE 3

	%MPE (analgesia)								
	0hr	0.25 hr	0.5 hr	1 hr	1.5 hr	2 hr	2.5 hr	3 hr	5 hr
33 (45mg)	0.0	0.0	24.0	80.0	140.0	124.0	96.0	60.0	24.0
33 (45mg)	0.0	8.3	66.7	183.3	87.5	191.7	112.5	45.8	20.8
33 (45mg)	0.0	3.7	48.1	59.3	114.8	185.2	133.3	118.5	44.4
33 (45mg)	0.0	31.3	37.5	50.0	68.8	81.3	31.3	25.0	18.8
33 (45mg)	0.0	30.0	37.5	67.5	97.5	157.5	112.5	27.5	22.5
33 (45mg)	0.0	0.0	19.2	100.0	115.4	111.5	119.2	157.7	115.4
NB (35mg)	0.0	0.0	5.6	50.0	100.0	94.4	66.7	22.2	-5.6
NB (35mg)	0.0	29.5	39.3	34.4	54.1	54.1	82.0	32.8	27.9
NB (35mg)	0.0	5.3	10.5	42.1	68.4	94.7	57.9	68.4	5.3
NB (35mg)	0.0	56.3	50.0	87.5	112.5	162.5	106.3	37.5	26.7
NB (35mg)	0.0	5.3	21.1	47.4	73.7	57.9	36.8	57.9	5.3
NB (35mg)	0.0	21.4	35.7	57.1	78.6	50.0	35.7	0.0	0.0
39 (68mg)	0.0	0.0	10.0	10.0	15.0	10.0	5.0	10.0	0.0
39 (68mg)	0.0	17.6	11.8	5.9	11.8	23.5	0.0	11.8	0.0
39 (68mg)	0.0	13.3	40.0	73.3	93.3	93.3	46.7	40.0	6.7
39 (68mg)	0.0	6.2	6.2	10.8	-7.7	33.8	-6.2	9.2	-9.2
39 (68mg)	0.0	8.3	55.6	11.1	19.4	0.0	16.7	0.0	-2.8
39 (68mg)	0.0	0.0	15.0	5.0	5.0	0.0	5.0	0.0	5.0

[0000110]

TABLE 4

	%MPE (miosis)								
	0hr	0.25 hr	0.5 hr	1 hr	1.5 hr	2 hr	2.5 hr	3 hr	5 hr
33 (45mg)	0.0	-8.8	3.4	24.0	20.6	37.8	46.4	3.4	3.4
33 (45mg)	0.0	0.3	26.7	40.4	36.5	46.2	63.7	36.5	36.5
33 (45mg)	0.0	20.0	33.3	42.2	42.2	42.2	29.5	15.6	9.3
33 (45mg)	0.0	0.0	-6.3	33.9	33.9	42.9	33.9	25.0	17.2
33 (45mg)	0.0	-5.0	26.7	26.7	36.5	46.2	46.2	36.5	33.7
33 (45mg)	0.0	26.7	26.7	40.4	46.2	55.9	65.7	29.0	32.1
NB (35mg)	0.0	3.1	9.4	21.9	17.2	18.8	18.8	6.2	6.2
NB (35mg)	0.0	9.4	37.5	46.9	65.6	31.3	3.1	6.2	3.1
NB (35mg)	0.0	6.7	0.0	6.7	25.0	55.6	50.0	33.3	22.2
NB (35mg)	0.0	0.0	9.4	21.9	17.2	31.3	25.0	21.9	6.2
NB (35mg)	0.0	3.2	9.7	45.2	45.2	58.1	25.8	16.1	9.7
NB (35mg)	0.0	2.9	8.8	-2.9	29.4	11.8	26.5	20.6	7.8
39 (68mg)	0.0	10.3	14.9	37.9	37.9	14.9	14.9	24.1	3.4
39 (68mg)	0.0	0.0	0.0	6.7	6.7	0.0	6.7	0.0	0.0
39 (68mg)	0.0	25.0	16.7	22.2	33.3	25.0	11.1	11.1	11.1
39 (68mg)	0.0	12.5	9.4	18.8	21.9	17.2	6.2	0.0	0.0
39 (68mg)	0.0	20.0	26.7	36.7	23.3	16.7	13.3	3.3	13.3
39 (68mg)	0.0	3.1	9.4	21.9	25.0	6.2	9.4	0.0	3.1

[0000111] Independent samples t-test was used to compare the means of %MPE analgesia and miosis in the two pairs of samples: NB-33 and NB and NB-33 and NB-39. All analyses were made using SPSS (v.25).

\* Bold indicates statistical significance at  $\alpha=0.05$

[0000112] Tables 5A-D illustrate comparison of analgesia and miosis between NB-33 and NB, NB-39.

TABLE 5A

TABLE 5B

Analgesia, NB-33 vs. NB			Analgesia, NB-33 vs. NB-39		
hrs	T	p-value	hrs	t	p-value
0.25	- .705	.497	0.25	.700	.506
0.5	1.182	.264	0.5	1.467	.173
1	1.730	.114	<b>1</b>	<b>3.110</b>	<b>.011</b>
1.5	1.699	.120	<b>1.5</b>	<b>4.558</b>	<b>.001</b>
<b>2</b>	<b>2.258</b>	<b>.048</b>	<b>2</b>	<b>5.027</b>	<b>.001</b>
2.5	1.982	.076	<b>2.5</b>	<b>5.380</b>	<b>.000</b>
3	1.486	.168	<b>3</b>	<b>2.656</b>	<b>.039</b>
5	1.895	.087	<b>5</b>	<b>2.642</b>	<b>.025</b>

TABLE 5C

TABLE 5D

Miosis, NB-33 vs. NB			Miosis, NB-33 vs. NB-39		
hrs	t	p-value	hrs	t	p-value
0.25	.217	.836	0.25	-.893	.393
0.5	.716	.491	0.5	.751	.470
1	1.295	.224	1	1.843	.095
1.5	.318	.757	1.5	1.985	.075
2	1.328	.232	<b>2</b>	<b>7.253</b>	<b>.000</b>
<b>2.5</b>	<b>2.624</b>	<b>.025</b>	<b>2.5</b>	<b>5.982</b>	<b>.001</b>
3	1.022	.331	<b>3</b>	<b>2.713</b>	<b>.022</b>
5	2.018	.071	<b>5</b>	<b>2.732</b>	<b>.031</b>

[0000113] Table 6A and Graph 1 in FIG. 13 below illustrate additional testing results for the NB-33 on Randall-Selitto rats, demonstrating its efficacy and benefits (including greater stability) in comparison to base compound.

[0000114] Table 6A and Graph 1 in FIG. 13 below illustrate additional testing results for the NB-33 on Randall-Selitto rats, demonstrating its efficacy and benefits (including greater stability) in comparison to base compound.

[0000115]

TABLE 6A

WO# 10656913 AB137003

Species/Strain/Sex: Rate

Treatment	Route	Dose	No.	Randall-Selitto (g)					
				Pre-treatment	Post-dose				
					0.5 hr	1hr	2 hr	4 hr	6 hr
Vehicle (0.9% NaCl)	SC	5 mL/kg	1	92	73	98	92	65	75
			2	97	68	88	72	69	62
			3	86	68	76	92	97	97
			4	91	86	82	77	83	53
			5	83	91	57	69	64	61
			Mean	<b>89.8</b>	<b>77.2</b>	<b>80.2</b>	<b>80.4</b>	<b>75.6</b>	<b>69.6</b>
			SEM	2.4	4.8	6.8	4.9	6.3	7.7
PT#1225608 AFC-2 NB.HCl	SC	3 mg/kg	1	89	78	63	58	64	50
			2	92	89	62	71	66	71
			3	100	93	92	103	93	82
			4	80	107	90	69	93	69
			5	91	134	96	93	61	85
			Mean	<b>90.4</b>	<b>100.2</b>	<b>80.6</b>	<b>78.8</b>	<b>75.4</b>	<b>71.4</b>
			SEM	3.2	9.6	7.5	8.3	7.2	6.2
PT#1225607 AFC-1 NB-33.HCl	SC	3.9 mg/kg	1	93	121	98	99	83	79
			2	82	120	103	94	71	64
			3	98	207	199	214	136	101
			4	80	161	73	102	63	65
			5	96	96	86	85	97	85

			Mean	89.8	141.0*	111.8	118.8	90.0	78.8
			SEM	3.7	19.5	22.4	24.0	12.9	6.9

[0000116] The data on the Graph 1 in FIG. 13 shows that NB-33 has superior analgesic properties to the equimolar dose of the parent opioid NB. FIG. 13 illustrate in the graphical form the results for 1310 NB-33, marked 1310, in comparison to the base NB compound NB, marked 1320 in FIG. 13.

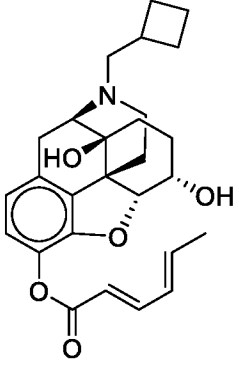
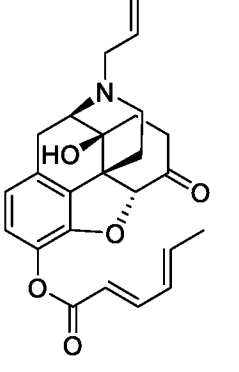
[0000117]

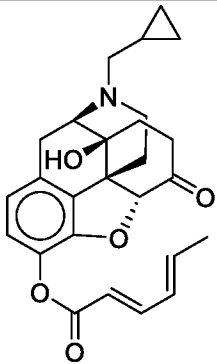
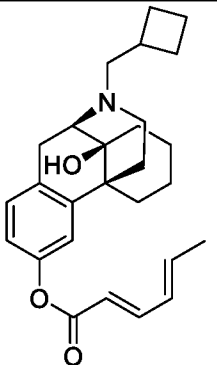
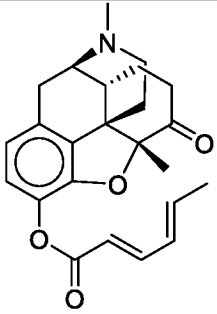
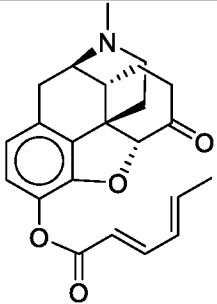
#### EXAMPLE 7

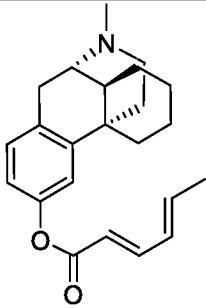
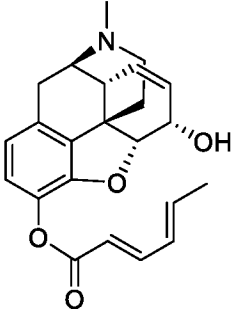
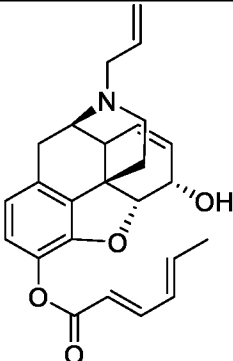
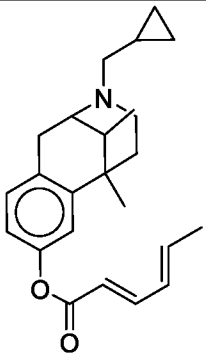
[0000118] This invention is exemplified by but not limited to the following compounds, illustrated below. The following compounds, shown in TABLE 7 below, provide non-limiting examples of various opioids, modified by hexadienoate in accordance with at least one embodiment.

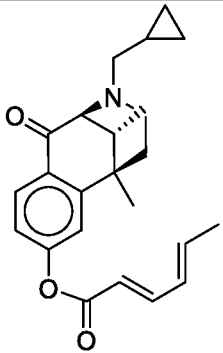
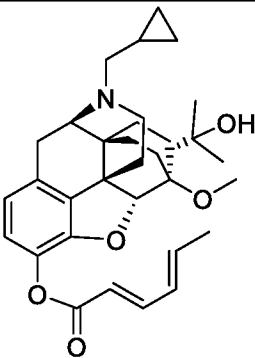
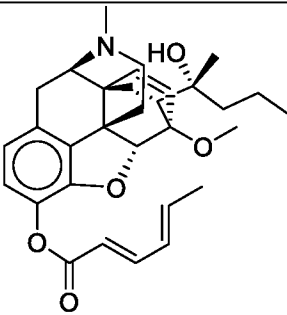
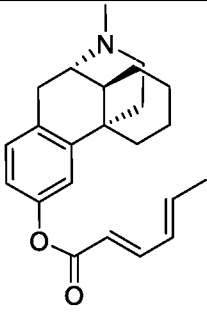
[0000119]

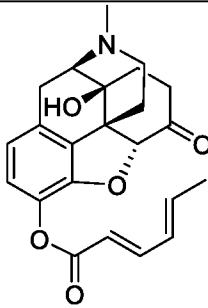
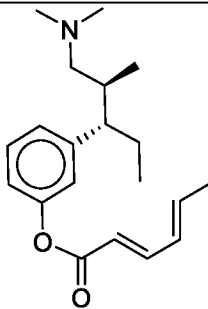
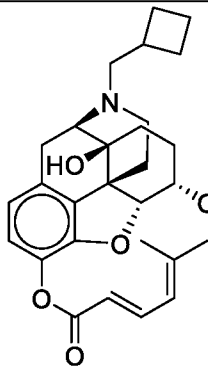
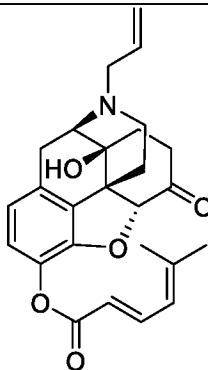
TABLE 7

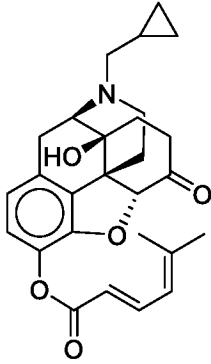
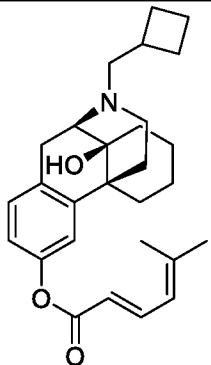
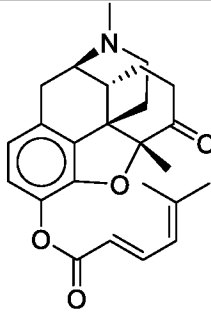
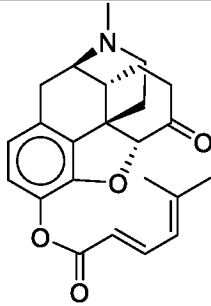
	Nalbuphino-3-hexadienoate
	Naloxone-3-hexadienoate

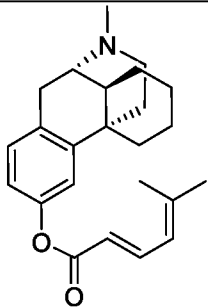
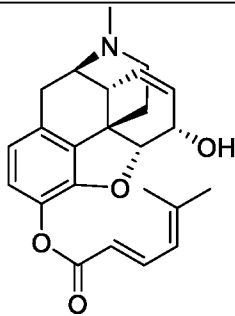
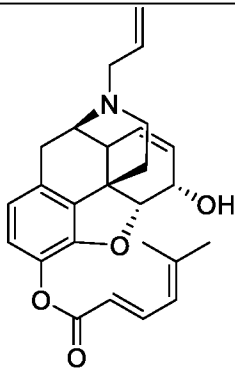
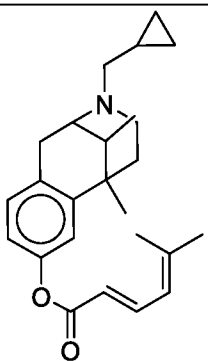
 <p>The structure shows a pentacyclic morphinan core with a hydroxyl group at C3 and a ketone at C6. The nitrogen atom is substituted with a propyl group. At the 3-position, there is an ester linkage to a hexadienoic acid chain.</p>	<p>Naltrexone-3-hexadienoate</p>
 <p>The structure shows a pentacyclic morphinan core with a hydroxyl group at C3 and a ketone at C6. The nitrogen atom is substituted with a butyl group. At the 3-position, there is an ester linkage to a hexadienoic acid chain.</p>	<p>Butorphanolo-3-hexadienoate</p>
 <p>The structure shows a pentacyclic morphinan core with a ketone at C6. The nitrogen atom is substituted with a methyl group. At the 3-position, there is an ester linkage to a hexadienoic acid chain.</p>	<p>Metopon hexadienoate</p>
 <p>The structure shows a pentacyclic morphinan core with a ketone at C6. The nitrogen atom is substituted with a methyl group. At the 3-position, there is an ester linkage to a hexadienoic acid chain.</p>	<p>Hydromorphone hexadienoate</p>

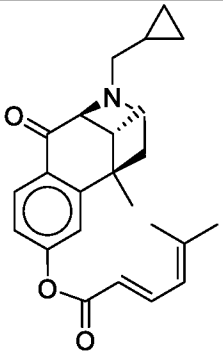
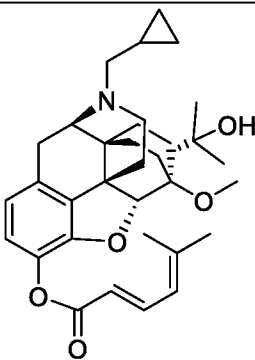
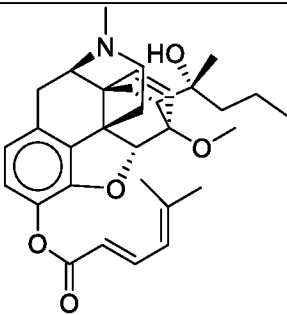
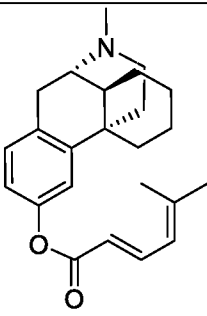
 <p>The structure shows a pentacyclic morphine-like core with a methyl group on the nitrogen atom. A hexadienoate ester group is attached to the 3-position of the morphine ring system.</p>	<p>Levorphanol hexadienoate</p>
 <p>The structure shows a pentacyclic morphine-like core with a methyl group on the nitrogen atom and a hydroxyl group at the 3-position. A hexadienoate ester group is attached to the 3-position of the morphine ring system.</p>	<p>Morphino-3-hexadienoate</p>
 <p>The structure shows a pentacyclic morphine-like core with a methyl group on the nitrogen atom and a hydroxyl group at the 3-position. A propyl group is attached to the nitrogen atom. A hexadienoate ester group is attached to the 3-position of the morphine ring system.</p>	<p>Nalorphino-3-hexadienoate</p>
 <p>The structure shows a pentacyclic morphine-like core with a methyl group on the nitrogen atom and a cyclopropylmethyl group attached to the nitrogen atom. A hexadienoate ester group is attached to the 3-position of the morphine ring system.</p>	<p>Cyclazocine hexadienoate</p>

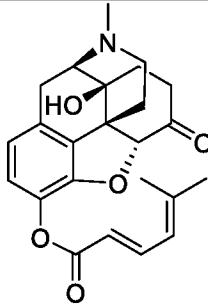
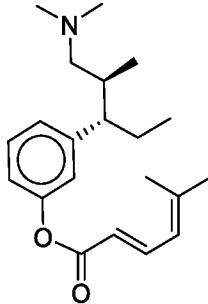
 <p>The structure shows a complex bicyclic core with a nitrogen atom. A cyclopropylmethyl group is attached to the nitrogen. A benzene ring is fused to the core, with a hexadienoate ester group attached at the para position. The hexadienoate chain is shown in a cis configuration.</p>	<p>Ketocyclazocine hexadienoate</p>
 <p>The structure features a pentacyclic core with a nitrogen atom. It has a cyclopropylmethyl group on the nitrogen, a hydroxyl group, and a methoxy group. A benzene ring is fused to the core, with a hexadienoate ester group attached at the para position. The hexadienoate chain is in a cis configuration.</p>	<p>Diprenorphine hexadienoate</p>
 <p>The structure shows a pentacyclic core with a nitrogen atom. It has a hydroxyl group and a propyl group. A benzene ring is fused to the core, with a hexadienoate ester group attached at the para position. The hexadienoate chain is in a cis configuration.</p>	<p>Etorphine hexadienoate</p>
 <p>The structure shows a pentacyclic core with a nitrogen atom. A benzene ring is fused to the core, with a hexadienoate ester group attached at the para position. The hexadienoate chain is in a cis configuration.</p>	<p>Levorphanol hexadienoate</p>

 <p>The structure shows the oxycodone core with a hydroxyl group at C3 and a morphine ring system. It is esterified with a hexadecanoic acid chain at the C6 position.</p>	<p>Oxymorphone hexadecanoate</p>
 <p>The structure features a benzene ring with a hydroxyl group at the para position and a propyl chain at the other para position. The propyl chain is substituted with a dimethylamino group and is esterified with a hexadecanoic acid chain.</p>	<p>Tapentadol hexadecanoate</p>
 <p>The structure is a pentacyclic morphine derivative with hydroxyl groups at C3 and C6. It has a cyclobutylmethyl group at C7 and is esterified with a hexadecanoic acid chain at C6.</p>	<p>Nalbuphino-3-(5-methyl)hexadecanoate</p>
 <p>The structure is a pentacyclic morphine derivative with a hydroxyl group at C3 and a methyl group at C5. It is esterified with a hexadecanoic acid chain at C6.</p>	<p>Naloxone-3-(5-methyl)hexadecanoate</p>

 <p>The structure shows a pentacyclic morphinan core. The nitrogen atom is substituted with a propyl chain ending in a cyclopropyl ring. A hydroxyl group is attached to the 3-position of the morphinan ring. The 6-position is a ketone. The 3-position is esterified with a 5-methylhexadienoate group.</p>	<p>Naltrexone-3-(5-methyl)hexadienoate</p>
 <p>The structure shows a pentacyclic morphinan core. The nitrogen atom is substituted with a propyl chain ending in a cyclobutyl ring. A hydroxyl group is attached to the 3-position of the morphinan ring. The 6-position is a ketone. The 3-position is esterified with a 5-methylhexadienoate group.</p>	<p>Butorphanolo-3-(5-methyl)hexadienoate</p>
 <p>The structure shows a pentacyclic morphinan core. The nitrogen atom is substituted with a methyl group. A hydroxyl group is attached to the 3-position of the morphinan ring. The 6-position is a ketone. The 3-position is esterified with a 5-methylhexadienoate group.</p>	<p>Metopon 5-methylhexadienoate</p>
 <p>The structure shows a pentacyclic morphinan core. The nitrogen atom is substituted with a methyl group. A hydroxyl group is attached to the 3-position of the morphinan ring. The 6-position is a ketone. The 3-position is esterified with a 5-methylhexadienoate group.</p>	<p>Hydromorphone 5-methylhexadienoate</p>

 <p>The structure shows the levorphanol moiety, a pentacyclic morphine derivative, linked via an ester bond to a 5-methylhexadienoate chain. The levorphanol part includes a benzene ring fused to a pentacyclic system with a nitrogen atom at the bridgehead.</p>	<p>Levorphanol 5-methylhexadienoate</p>
 <p>The structure shows a morphine derivative with a hydroxyl group at the 3-position, linked via an ester bond to a 5-methylhexadienoate chain. The morphine part includes a benzene ring fused to a pentacyclic system with a nitrogen atom at the bridgehead.</p>	<p>Morphino-3-(5-methyl)hexadienoate</p>
 <p>The structure shows a nalorphine derivative with a hydroxyl group at the 3-position and a vinyl group at the 4-position, linked via an ester bond to a 5-methylhexadienoate chain. The nalorphine part includes a benzene ring fused to a pentacyclic system with a nitrogen atom at the bridgehead.</p>	<p>Nalorphino-3-(5-methyl)hexadienoate</p>
 <p>The structure shows the cyclazocine moiety, a pentacyclic system with a nitrogen atom at the bridgehead and a cyclopropylmethyl group, linked via an ester bond to a 5-methylhexadienoate chain. The cyclazocine part includes a benzene ring fused to a pentacyclic system.</p>	<p>Cyclazocine 5-methylhexadienoate</p>

 <p>The structure shows a bicyclic core consisting of a benzene ring fused to a six-membered ring containing a nitrogen atom. The nitrogen atom is substituted with a cyclopropylmethyl group. The benzene ring has a methyl group at the 2-position and a 5-methylhexadienoate ester group at the 4-position.</p>	<p>Ketocyclazocine 5-methylhexadienoate</p>
 <p>The structure is a complex pentacyclic system. It features a benzene ring fused to a bicyclic system with a nitrogen atom. The nitrogen atom is substituted with a cyclopropylmethyl group. The benzene ring has a methyl group at the 2-position and a 5-methylhexadienoate ester group at the 4-position. There is a hydroxyl group and a methoxy group on the bicyclic system.</p>	<p>Diprenorphine 5-methylhexadienoate</p>
 <p>The structure is a complex pentacyclic system similar to Diprenorphine. It features a benzene ring fused to a bicyclic system with a nitrogen atom. The nitrogen atom is substituted with a methyl group. The benzene ring has a methyl group at the 2-position and a 5-methylhexadienoate ester group at the 4-position. There is a hydroxyl group and a propyl group on the bicyclic system.</p>	<p>Etorphine 5-methylhexadienoate</p>
 <p>The structure is a complex pentacyclic system similar to Diprenorphine. It features a benzene ring fused to a bicyclic system with a nitrogen atom. The nitrogen atom is substituted with a methyl group. The benzene ring has a methyl group at the 2-position and a 5-methylhexadienoate ester group at the 4-position.</p>	<p>Levorphanol 5-methylhexadienoate</p>

	<p>Oxycodone 5-methylhexadecanoate</p>
	<p>Tapentadol 5-methylhexadecanoate</p>

[0000120]

**EXAMPLE 8** - Molecular docking of nalbuphine/naloxone opioid antagonists into  $\mu$ -opioid receptor.

[0000121] The human  $\mu$ -opioid receptor crystal structures were downloaded from the RCSB Protein Data Bank [PDB entry: 4DKL, <https://www.rcsb.org/structure/4DKL>]. The in silico screening was carried out with the MOE Dock program, part of the MOE Simulation module 2014.0901. The dissociation constants ( $K_i$ ) were calculated from the equation  $\Delta G = RT \ln(K_i)$ , where  $\Delta G$  represents binding free energy which is equivalent to GBVI/WSA dG scoring function, R is the gas constant and T the temperature. The  $K_i$  was computed starting from the binding free energy values at a fixed temperature (300 K).

[0000122] Both antagonists nalbuphine and naloxone demonstrate the key interaction of Asp 147 with their ammonium group. It is known that this bonding to Asp 147 is typical for the most known opioid agonists/antagonists. The other duplicate interaction of nalbuphine and naloxone is bonding of the hydroxyl group attached to the aryl ring (3-position) to the water molecule, which contributes in stabilizing the inactive state of opioid receptors. Differently from nalbuphine, the hydroxyl group of naloxone attached to the tertiary carbon atom (14-position) participates in additional hydrogen bonding to Asp 147.

[0000123] FIGURE 9A illustrates the binding mode and molecular interactions of the most energetically favored conformer of nalbuphine superposed with co-crystallized ligand  $\beta$ -FNA. FIGURE 9B illustrates the binding mode and molecular interactions of the most energetically favored conformer of naloxone superposed with co-crystallized ligand  $\beta$ -FNA.

[0000124] Nalbuphine and naloxone is bonding of the hydroxyl group attached to the aryl ring (3-position) to the water molecule, which contributes in stabilizing the inactive state of opioid receptors. Differently from nalbuphine, the hydroxyl group of naloxone attached to the tertiary carbon atom (14-position) participates in additional hydrogen bonding to Asp 147.

[0000125] FIGURE 10A illustrates the binding mode and molecular interactions of the most energetically favored conformer of **NX-90** in the binding site of 4DKL.

[0000126] FIGURE 10B illustrates the binding mode and molecular interactions of the most energetically favored conformer of **NB-33** in the binding site of 4DKL.

[0000127] FIGURE 10C illustrates molecular interaction with Met 151 shown by the conformer of **NB-33** with the binding mode similar to the most energetically favored conformer.

[0000128] FIGURE 10D illustrates the binding mode and molecular interactions of the most energetically favored conformer of **NB-39** in the binding site of 4DKL.

[0000129] FIGURE 11A illustrates the most energetically favored conformer of nalbuphine (yellow), naloxone (pink) and co-crystalized  $\beta$ -FNA (white) superposed in the opioid binding site of 4DKL. FIGURE 11B illustrates the most energetically favored conformers of NX-90 (blue), NB-33 (red), NB-39 (cyan) and co-crystalized  $\beta$ -FNA (white) superposed in the opioid binding site of 4DKL.

[0000130] Computed dissociation constants ( $K_i$ ) of NX-90, NB-33, NB-39 established the higher affinity to the m-receptor (NB-33, NB-39) or a little lower affinity (NX-90) in comparison to the affinities of nalbuphine and naloxone. Analogously to the most energetically favored conformers of naloxone and nalbuphine, NX-90, NB-33 and NB-39 retain the crucial hydrogen bonding to the residue of

Asp147. In this docking mode the “message” attached to the nitrogen atom is delivered to the correct “address” sited on the exact area of the binding pocket of the m-receptor. However, unlike the binding mode of known m-antagonists (e.g. nalbuphine and naloxone; Figure 11A) the rigid frames of NX-90, NB-33 and NB-39 are rotated by 180° in the binding site (Figure 11B). Conversely, the binding mode that describes binding of nalbuphine and naloxone *is not possible* for all computed conformers of NB-33, NB-39 and NX-90.

[0000131] Furthermore, both NX-90 and NB-33 have the unique hydrogen bonding to Met 151 through the hydroxyl group attached to the tertiary carbon atom (14-position). This interaction makes both NX-90 and NB-33 different from NB-39 which hydroxyl group at cyclohexane fragment (6-position) forms the hydrogen bond with Lys A233 instead. The second differentiating factor for both NX-90 and NB-33 is that the rigid conjugated system of the residue of hexadienoic acid has the extraordinary hydrophobic cylindrical molecular surface. Simultaneously, the residues Cys217, Thr218, Asn127, Gln124, Trp133, Leu219 build the extra complementary hydrophobic molecular surface surrounding this hexadienyl “tail” inside the binding pocket (Figure 12A and 12B), whereas no discernible hydrophobic surface exists in the areas of binding site surrounding the highly flexible and lacking conjugation docosanoyl “tail” (Figure 12C).

[0000132] FIGS. 12A-C show Hydrophobic (red) and hydrophilic (yellow) contact preference areas on the molecular surface of the binding site of 4DKL with the docked conformer of NX-90, shown in FIG. 12A; NB-33, shown in FIG. 12B and NB-39, shown in FIG. 12C.

[0000133] These examples, particularly in FIGURES 9-12 confirm at least one feature of the present invention, i.e., that modifying an opioid with a lipophilic moiety with at least two conjugated double bonds improves interactions with the opioid receptor.

[0000134] These examples also confirm another feature of the present invention, i.e., that modifying an opioid with a lipophilic moiety with at least two conjugated double bonds improves interactions with the opioid receptor by rotating the opioid in the active site by 180°C and creating additional modes of

interactions with the receptor including a unique hydrophobic pocket.

[0000135] These examples further confirm another feature of the present invention, i.e., that modifying an opioid with a lipophilic moiety with at least two conjugated double bonds changes properties of the opioid at least in some embodiments of the present invention.

[0000136] These examples confirm yet another feature of the present invention, i.e., that modifying an opioid with a lipophilic moiety with at least two conjugated double bonds improves antagonistic properties of the opioid at least in some embodiments of the present invention.

[0000137] Improved Performance of Opioid Receptor Antagonists

[0000138] As described above, in addition to the improved performance and analgesic qualities of opiates, the present invention also includes at least one embodiment where hexadienoate improves performance of opioid receptor antagonists, such as, for example, Naloxone.

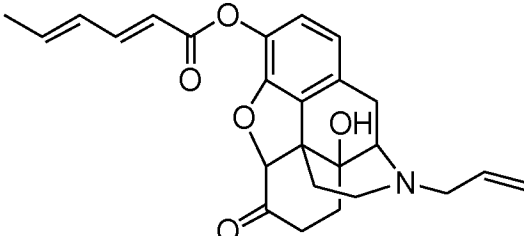
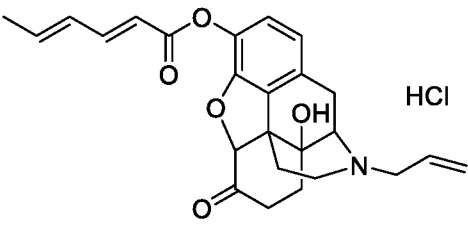
[0000139] In at least one embodiment, the present invention, and particularly the hexadienoate has been combined and tested with at least one specie (or multiple species) from the Naloxone group or compound.

[0000140] In at least one embodiment of the present invention, the Naloxone, having hexadienoate, is included in the molecule, and provides substantially more effective and long-lasting neutralizing/sobering effect when administered to a subject.

[0000141] In at least one embodiment of the present invention, a compound NX-90 and NX-97 having the below formula has been synthesized and analyzed, as shown in TABLE 8 below.

[0000142]

TABLE 8

1	 <p>3-allyl-4a-hydroxy-7-oxo-2,3,4,4a,5,6,7,7a-octahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinolin-9-yl (2E,4E)-hexa-2,4-dienoate          Chemical Formula: C<sub>25</sub>H<sub>27</sub>NO<sub>5</sub>          Molecular Weight: 421.49</p>	NX-90
2	 <p>3-allyl-4a-hydroxy-7-oxo-2,3,4,4a,5,6,7,7a-octahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinolin-9-yl (2E,4E)-hexa-2,4-dienoate hydrochloride          Chemical Formula: C<sub>25</sub>H<sub>28</sub>ClNO<sub>5</sub>          Molecular Weight: 457.95</p>	NX-97

[0000143] Sobering effect may be noted when administered to a subject. This compound may be utilized and synthesized in accordance with at least one embodiment of the present invention is referenced and named Naloxone-sorbate, (NX-90). The preparation of the compound based on at least one embodiment may proceed as follows.

[0000144] EDCI.HCl (1.36 g, 7.12 mmol) was added to hexadienoic acid (0.74 g, 6.61 mmol) in THF (50 mL) at 0 °C with stirring. Triethylamine (1.39 g, 13.8 mmol) was added. Stirring for 2 h at 0 °C. Naloxone hydrochloride (2.00 g, 5.5 mmol) and 4-dimethylaminopyridine (0.10 g, 0.82 mmol) were added at 0 °C. The stirring was continued for 1 h at 0 °C and at room temperature overnight. The reaction mixture was filtered, filtrate was evaporated, and the residue was twice purified by column chromatography (silicagel, EtOAc/Heptanes/Triethylamine, 2:1:0.5%). The white crystals were formed after evaporation of

selected fractions, yield 0.75 g (32%), purity 98% by HPLC. The structure was confirmed by NMR <sup>1</sup>H.

[0000145] The properties of the NX-90 compound have been studied and the following results and specific benefits, including stability data, have been obtained and confirmed.

[0000146]

TABLE 9 – NX-90 Stability (GIF) Batch Number Alpha-1-91 (Tested by Alfacheminvent LLC).

PRODUCT NAME: NX-90			
BATCH NO.: Alpha-1-91	MFG DATE: 03/21/2019	SAMPLE SIZE: 5.0 MG/2.0 ML	PACKAGING TYPE: Glass vial (upright)
ASSAY CONDITIONS: GIF, 37 °C, shaker	STABILITY TESTING INTERVALS: INITIAL, 1, 2, 4, 8, 24 HRS		STATUS: COMPLETED: 03.22.2019

TEST	Specifications	Initial	1 h	2 h	4 h	8 h	24 h
Product Appearance	Clear solution	Conforms	Conf.	Conf.	Conf.	Conf.	Conf.
HPLC Assay: (Area %)	Report results	99.3	99.2	99.3	98.4	95.1	93.0
Single impurity: RRT=0.93	Report results	0.6	0.7	0.6	0.6	0.7	0.6

(Area %)						
Single impurity: RRT=0.67 (Area %)	Report results	-	-	-	0.9	2.3 5.5

[0000147] Based on the results and observations, shown in Table 9, the NX-90 has shown significant improvements over the well-known drug Naloxone.

[0000148] Examples of the combination of NB-33 or similar compounds with different opiates and NX-90 with opiate antagonists in accordance with at least one embodiment of the present invention is further shown in *Table 11* below.

[0000149] It is well documented and commonly known that opioids can be used for the treatment of the following medical conditions: pain management, a palliative care, a postoperative anesthesiology, a skin disorder, an addiction, a locomotive disorder, a levodopa-induced dyskinesias (LID) in Parkinson’s disease, a dyskinesias associated with Tourette’s syndrome, a tardive dyskinesia and a Huntington’s disease and others. The potency and effectiveness of the opioids used for the treatment of these medical conditions affects how successful the treatment is.

[0000150] Respectively, the higher engagement of opioid receptors produces more effective results for the treating such conditions in accordance with at least one embodiment of the present invention. For example, opioids modified with Hexadienoates will be more effective in treating the aforementioned conditions, because they have higher engagement of opioid receptors.

[0000151] Thus, in at least one embodiment of the present invention, one of the composition compounds that is formulated based on the present invention, as for example NB-33 or NX-90 (or others)

may be utilized for treatment of one of the medical conditions such as a pain management, a palliative care, a postoperative anesthesiology, a skin disorder (e.g. pruritus), an addiction (detox or management), and/or a locomotive disorder (e.g. levodopa-induced dyskinesias (LID) in Parkinson's disease, and the dyskinesias associated with Tourette's syndrome, tardive dyskinesia and Huntington's disease).

[0000152] EXAMPLE 9

[0000153] TABLE 10 demonstrates human recombinant opiate receptor data for NX 90.

Assay	NX-90	
	< 1uM	> 1 uM
mu (MOR) (h) (agonist effect)		
mu (MOR) (h) (antagonist effect)	X	X
kappa (KOR) (h) (agonist effect)		
kappa (KOR) (h) (antagonist effect)	X	X
delta (DOR) (h) (agonist effect)		
delta (DOR) (h) (antagonist effect)		X

[0000154] Human recombinant opiate receptor (mu, kappa or delta) expressed in CHO-K1 cells were used. Test compound (NX-90)/or vehicle was incubated with the cells (4 x 10E5/mL) in modified HBSS pH 7.4 buffer at 37°C for 30 min. The reaction was evaluated for cAMP levels (cAMP and/or calcium flux) by TR-FRET. Compounds were screened at 0.1, 0.3 and 1 uM by Eurofins Pharma Discovery Services.

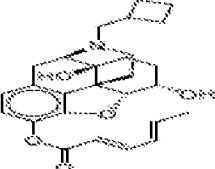
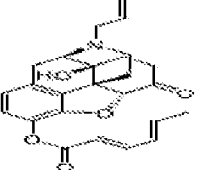
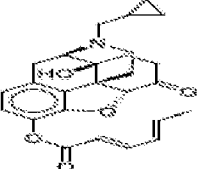
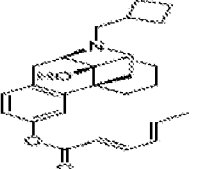
[0000155] Data for compound NX-90 is summarized in Table 10. It shows that NX-90 is not

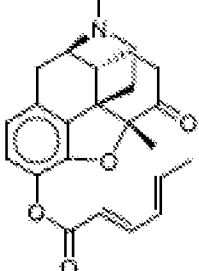
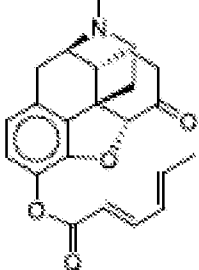
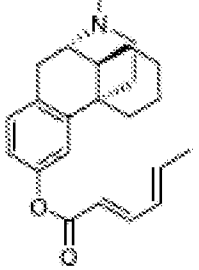
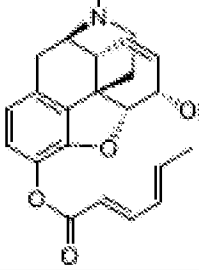
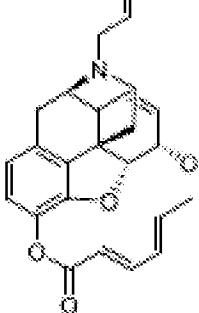
a pharmacologically inert compound and has a distinct opioid signature of its own, similar to the pharmacological profile of naloxone. Separately, it shown that NB-33 is not a pharmacologically inert compound and has a distinct opioid signature of its own, similar to the pharmacological profile of NB.

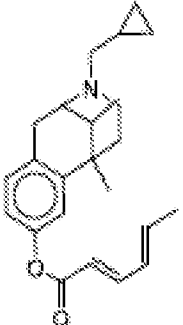
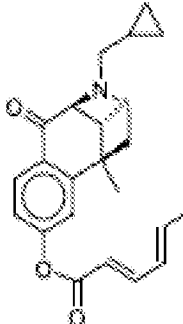
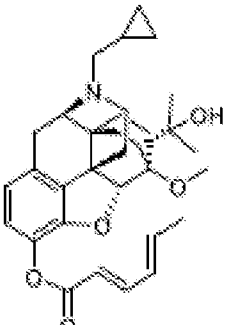
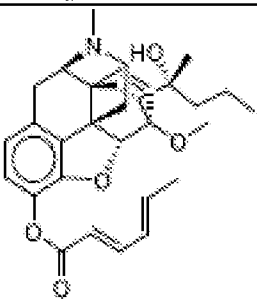
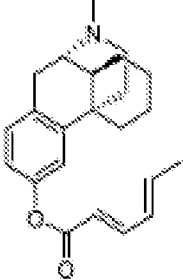
[0000156] These results are highly surprising as the prior art suggests that such modifications of 3-phenoxy position with fatty acids (e.g. NB-39) are pro-drugs and by definition are pharmacologically inert compounds. In accordance with at least one embodiment of the present invention, the NX-90 and NB-33 are shown not pharmacologically inert and are not pro-drugs.

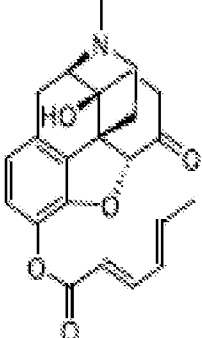
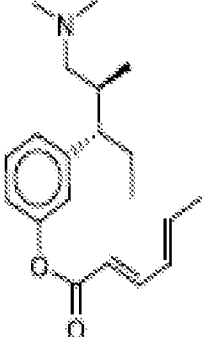
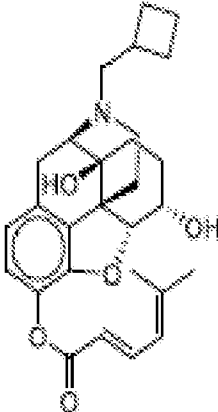
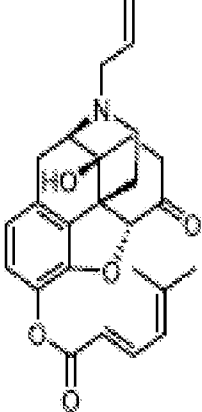
[0000157] In all cases it is understood that the above-described examples and compounds are merely illustrative of the many possible specific embodiments which represent applications of the present invention. Numerous and varied other arrangements can be readily devised in accordance with the principles of the present invention without departing from the spirit and the scope of the invention.

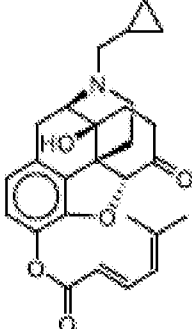
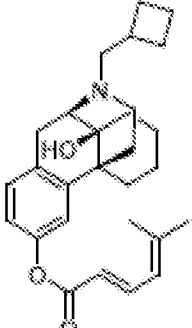
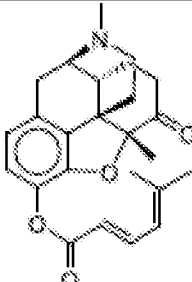
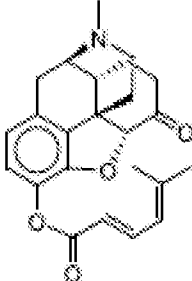
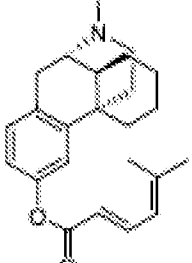
[0000158] TABLE 11

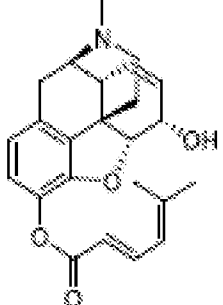
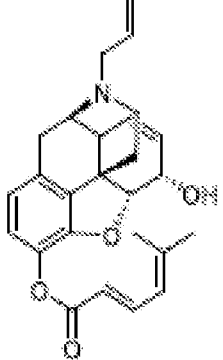
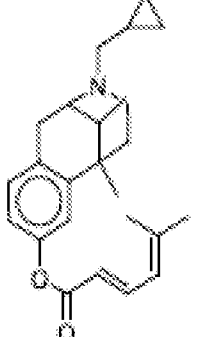
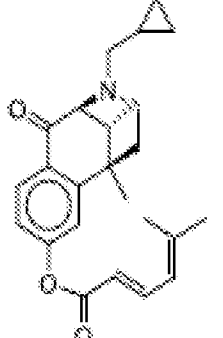
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	Naloxone-3-hexadecanoate
	Naltrexone-3-hexadecanoate
	Butorphanolo-3-hexadecanoate

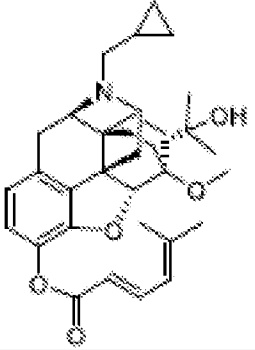
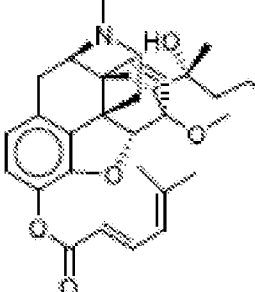
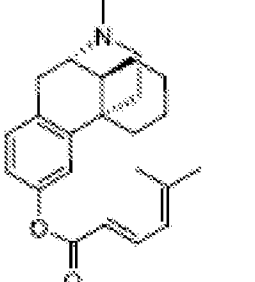
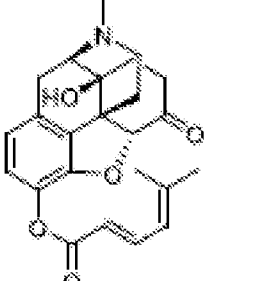
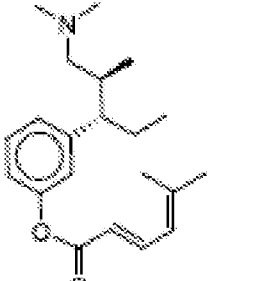
 <p>The structure shows a morphine-like pentacyclic core with a hexadienoate ester group at the 3-position and a methyl group at the 6-position.</p>	<p>Metopon hexadienoate</p>
 <p>The structure is identical to Metopon hexadienoate, featuring a morphine-like pentacyclic core with a hexadienoate ester group at the 3-position and a methyl group at the 6-position.</p>	<p>Hydromorphone hexadienoate</p>
 <p>The structure shows a morphine-like pentacyclic core with a hexadienoate ester group at the 3-position and a methyl group at the 6-position, but with a different stereochemistry at the 5-position compared to the previous structures.</p>	<p>Levorphanol hexadienoate</p>
 <p>The structure shows a morphine-like pentacyclic core with a hexadienoate ester group at the 3-position, a methyl group at the 6-position, and a hydroxyl group at the 4-position.</p>	<p>Morphino-3-hexadienoate</p>
 <p>The structure shows a morphine-like pentacyclic core with a hexadienoate ester group at the 3-position, a methyl group at the 6-position, and a hydroxyl group at the 4-position. It also features a propyl group at the 17-position.</p>	<p>Nalorphino-3-hexadienoate</p>

 <p>The structure shows a complex polycyclic system with a benzene ring fused to a bicyclic nitrogen-containing ring system. A cyclopropyl group is attached to the nitrogen. A hexadienoate ester group is attached to the benzene ring.</p>	<p>Cycloazocine hexadienoate</p>
 <p>The structure is similar to Cycloazocine hexadienoate but includes a ketone group on the nitrogen-containing ring system.</p>	<p>Ketocycloazocine hexadienoate</p>
 <p>The structure features a complex polycyclic system with multiple stereocenters, a hydroxyl group, and a methoxy group. A cyclopropyl group is attached to the nitrogen. A hexadienoate ester group is attached to the benzene ring.</p>	<p>Diprenorphine hexadienoate</p>
 <p>The structure is a complex polycyclic system with multiple stereocenters, a hydroxyl group, and an ethyl group. A cyclopropyl group is attached to the nitrogen. A hexadienoate ester group is attached to the benzene ring.</p>	<p>Etorphine hexadienoate</p>
 <p>The structure shows a complex polycyclic system with a benzene ring fused to a bicyclic nitrogen-containing ring system. A hexadienoate ester group is attached to the benzene ring.</p>	<p>Levorphanol hexadienoate</p>

 <p>The image shows the chemical structure of Oxycodone, a semi-synthetic opioid. It features a pentacyclic morphinan skeleton with a hydroxyl group at the 4-position, a ketone at the 3-position, and a methyl group at the 17-position. The 6-position is substituted with a propyl chain that is esterified to a (Z)-hex-5-enoic acid moiety.</p>	<p>Oxycodone hexadienoate</p>
 <p>The image shows the chemical structure of Tapentadol, a mu-opioid receptor agonist and norepinephrine reuptake inhibitor. It consists of a benzene ring with a methyl group at the 3-position and a propyl chain at the 4-position. The propyl chain is esterified to a (Z)-hex-5-enoic acid moiety.</p>	<p>Tapentadol hexadienoate</p>
 <p>The image shows the chemical structure of Nalbuphine, a mixed mu-opioid receptor agonist and kappa-opioid receptor antagonist. It has a pentacyclic morphinan skeleton with hydroxyl groups at the 4 and 14 positions, a ketone at the 3-position, and a methyl group at the 17-position. The 6-position is substituted with a propyl chain that is esterified to a (Z)-hex-5-enoic acid moiety.</p>	<p>Nalbuphine-3-(5-methyl)hexadienoate</p>
 <p>The image shows the chemical structure of Naloxone, an opioid antagonist. It has a pentacyclic morphinan skeleton with hydroxyl groups at the 4 and 14 positions, a ketone at the 3-position, and a methyl group at the 17-position. The 6-position is substituted with a propyl chain that is esterified to a (Z)-hex-5-enoic acid moiety.</p>	<p>Naloxone-3-(5-methyl)hexadienoate</p>

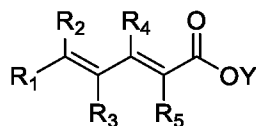
 <p>The structure shows a pentacyclic morphinan skeleton with a hydroxyl group at C3 and a nitrogen atom at C17. A propyl chain is attached to the nitrogen, ending in a cyclopropyl ring. At C3, there is an ester linkage to a 5-methylhexadienoate chain.</p>	<p>Naltrexone-3-(5-methyl)hexadienoate</p>
 <p>The structure shows a pentacyclic morphinan skeleton with a hydroxyl group at C3 and a nitrogen atom at C17. A propyl chain is attached to the nitrogen, ending in a cyclobutyl ring. At C3, there is an ester linkage to a 5-methylhexadienoate chain.</p>	<p>Butorphanolo-3-(5-methyl)hexadienoate</p>
 <p>The structure shows a pentacyclic morphinan skeleton with a nitrogen atom at C17. A methyl group is attached to the nitrogen. At C3, there is an ester linkage to a 5-methylhexadienoate chain.</p>	<p>Metopon 5-methylhexadienoate</p>
 <p>The structure shows a pentacyclic morphinan skeleton with a hydroxyl group at C3 and a nitrogen atom at C17. A methyl group is attached to the nitrogen. At C3, there is an ester linkage to a 5-methylhexadienoate chain.</p>	<p>Hydromorphone 5-methylhexadienoate</p>
 <p>The structure shows a pentacyclic morphinan skeleton with a nitrogen atom at C17. A methyl group is attached to the nitrogen. At C3, there is an ester linkage to a 5-methylhexadienoate chain.</p>	<p>Levorphanol 5-methylhexadienoate</p>

 <p>The structure shows a morphine skeleton with a 5-methylhexadienoate group attached to the 3-position. The 6-position has a hydroxyl group, and the 4-position has a methyl group.</p>	<p>Morphino-3-(5-methyl)hexadienoate</p>
 <p>The structure is similar to morphine but has a nitrogen atom at the 4-position instead of an oxygen atom, forming a piperidine ring. It features a 5-methylhexadienoate group at the 3-position and a hydroxyl group at the 6-position.</p>	<p>Nalorphino-3-(5-methyl)hexadienoate</p>
 <p>The structure features a cycloazocine skeleton with a 5-methylhexadienoate group at the 3-position and a cyclopropylmethyl group at the 4-position. The 6-position has a hydroxyl group.</p>	<p>Cycloazocine 5-methylhexadienoate</p>
 <p>The structure is similar to cycloazocine but has a ketone group at the 6-position instead of a hydroxyl group. It has a 5-methylhexadienoate group at the 3-position and a cyclopropylmethyl group at the 4-position.</p>	<p>Ketocycloazocine 5-methylhexadienoate</p>

 <p>The structure shows a complex pentacyclic morphine skeleton. It features a tertiary amine bridgehead nitrogen, a secondary amine at the 4-position, and a hydroxyl group at the 3-position. A 5-methylhexadienoate ester group is attached to the 6-position of the morphine ring system.</p>	<p>Diprenorphine 5-methylhexadienoate</p>
 <p>The structure shows a pentacyclic morphine skeleton with a tertiary amine bridgehead nitrogen and a secondary amine at the 4-position. A hydroxyl group is present at the 3-position. A 5-methylhexadienoate ester group is attached to the 6-position.</p>	<p>Etorphine 5-methylhexadienoate</p>
 <p>The structure shows a pentacyclic morphine skeleton with a tertiary amine bridgehead nitrogen and a secondary amine at the 4-position. A hydroxyl group is present at the 3-position. A 5-methylhexadienoate ester group is attached to the 6-position.</p>	<p>Levorphanol 5-methylhexadienoate</p>
 <p>The structure shows a pentacyclic morphine skeleton with a tertiary amine bridgehead nitrogen and a secondary amine at the 4-position. Hydroxyl groups are present at the 3 and 6 positions. A 5-methylhexadienoate ester group is attached to the 6-position.</p>	<p>Oxymorphone 5-methylhexadienoate</p>
 <p>The structure shows a pentacyclic morphine skeleton with a tertiary amine bridgehead nitrogen and a secondary amine at the 4-position. A hydroxyl group is present at the 3-position. A 5-methylhexadienoate ester group is attached to the 6-position.</p>	<p>Tapentadol 5-methylhexadienoate</p>

## CLAIMS:

1. A compound of general formula I or pharmaceutically acceptable salt of thereof

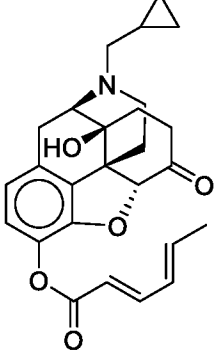
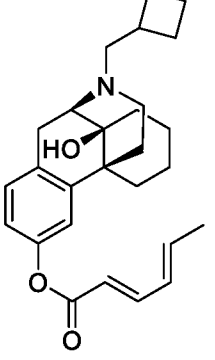
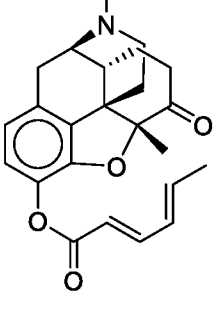
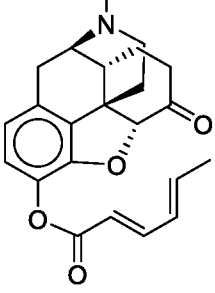


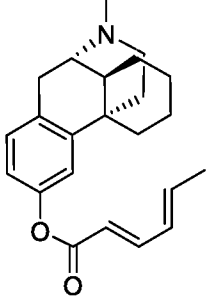
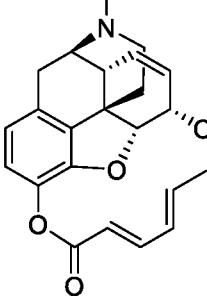
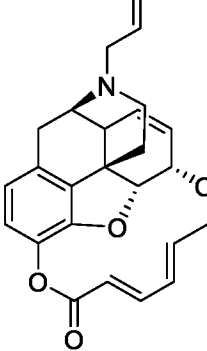
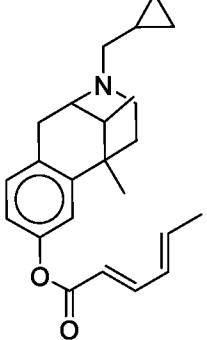
Formula I

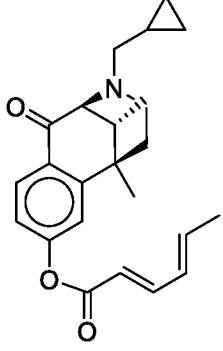
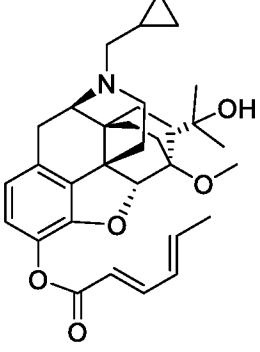
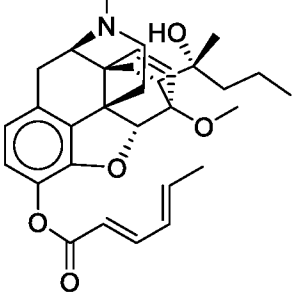
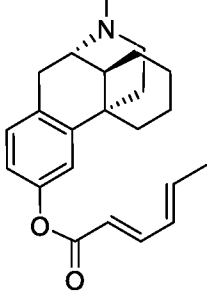
wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> or R<sub>5</sub> are selected from a group comprising H, optionally substituted C1-3 and OAlk), and Y is an opioid residue.

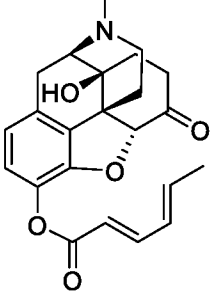
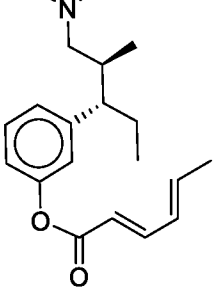
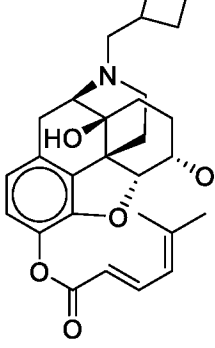
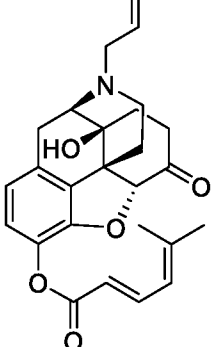
2. The compound of Claim 1, wherein the opioid residue is an opioid antagonist.
3. The compound of Claim 1, wherein said compound of Formula I is selected from the list of:

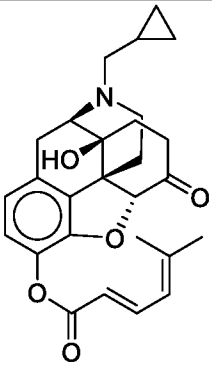
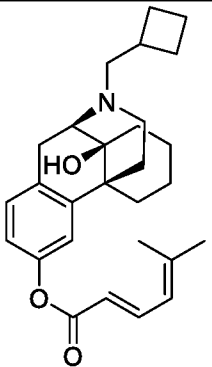
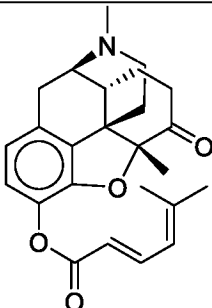
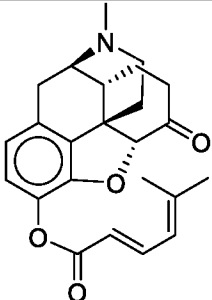
	Nalbuphino-3-hexadienoate
	Naloxone-3-hexadienoate

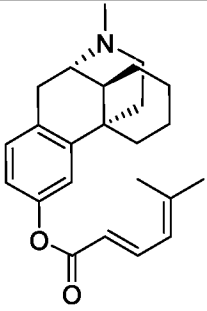
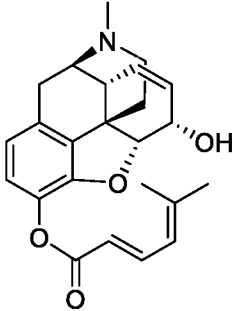
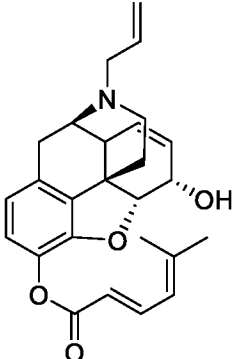
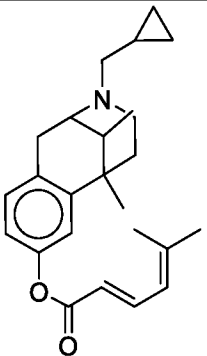
 <p>The structure shows a pentacyclic morphinan core. The nitrogen atom is substituted with a propyl group. A hydroxyl group is attached to the ring system. A hexadienoate ester group is attached to the 3-position of the morphine ring.</p>	<p>Naltrexone-3-hexadienoate</p>
 <p>The structure shows a pentacyclic morphinan core. The nitrogen atom is substituted with a butyl group. A hydroxyl group is attached to the ring system. A hexadienoate ester group is attached to the 3-position of the morphine ring.</p>	<p>Butorphanolo-3-hexadienoate</p>
 <p>The structure shows a pentacyclic morphinan core. The nitrogen atom is substituted with a methyl group. A hydroxyl group is attached to the ring system. A hexadienoate ester group is attached to the 3-position of the morphine ring.</p>	<p>Metopon hexadienoate</p>
 <p>The structure shows a pentacyclic morphinan core. The nitrogen atom is substituted with a methyl group. A hydroxyl group is attached to the ring system. A hexadienoate ester group is attached to the 3-position of the morphine ring.</p>	<p>Hydromorphone hexadienoate</p>

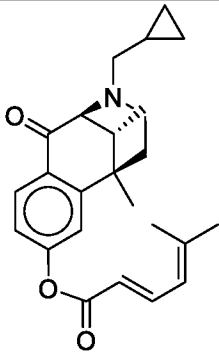
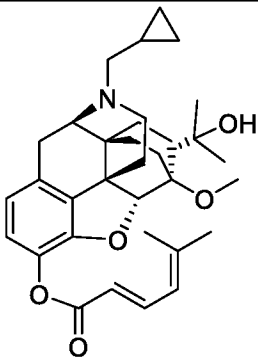
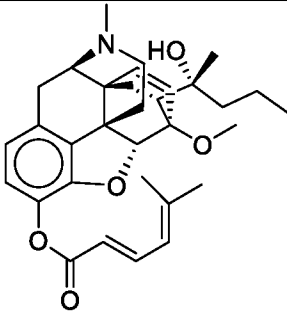
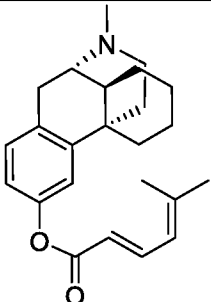
 <p>The structure shows the levorphanol moiety, a pentacyclic morphine-like skeleton with a methyl group on the nitrogen atom, attached to a hexadienoate ester group at the 3-position.</p>	<p>Levorphanol hexadienoate</p>
 <p>The structure shows the morphino moiety, a pentacyclic morphine-like skeleton with a methyl group on the nitrogen atom and a hydroxyl group at the 3-position, attached to a hexadienoate ester group at the 3-position.</p>	<p>Morphino-3-hexadienoate</p>
 <p>The structure shows the nalorphino moiety, a pentacyclic morphine-like skeleton with a methyl group on the nitrogen atom, a hydroxyl group at the 3-position, and an allyl group at the 4-position, attached to a hexadienoate ester group at the 3-position.</p>	<p>Nalorphino-3-hexadienoate</p>
 <p>The structure shows the cyclazocine moiety, a pentacyclic morphine-like skeleton with a methyl group on the nitrogen atom and a cyclopropylmethyl group at the 4-position, attached to a hexadienoate ester group at the 3-position.</p>	<p>Cyclazocine hexadienoate</p>

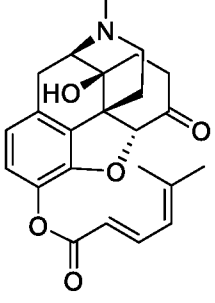
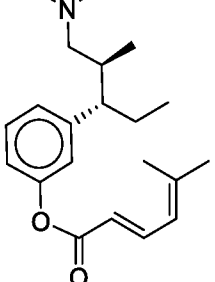
	<p>Ketocyclazocine hexadienoate</p>
	<p>Diprenorphine hexadienoate</p>
	<p>Etorphine hexadienoate</p>
	<p>Levorphanol hexadienoate</p>

 <p>The structure shows the oxycodone core with a hydroxyl group at C4, a methyl group at C5, and a hexadenoate ester group at C3. The hexadenoate chain is shown with a double bond at the 3-position.</p>	Oxymorphone hexadenoate
 <p>The structure shows a benzene ring with a methyl group at C1, a propyl chain at C2, and a hexadenoate ester group at C3. The hexadenoate chain is shown with a double bond at the 3-position.</p>	Tapentadol hexadenoate
 <p>The structure shows the nalbuphine core with hydroxyl groups at C4 and C14, a methyl group at C5, and a hexadenoate ester group at C3. The hexadenoate chain is shown with a double bond at the 3-position.</p>	Nalbuphino-3-(5-methyl)hexadenoate
 <p>The structure shows the naloxone core with a hydroxyl group at C4, a methyl group at C5, and a hexadenoate ester group at C3. The hexadenoate chain is shown with a double bond at the 3-position.</p>	Naloxone-3-(5-methyl)hexadenoate

 <p>The structure shows a pentacyclic morphinan skeleton. The nitrogen atom is substituted with a propyl group. A hydroxyl group is attached to the 3-position of the pentacyclic ring system. The 6-position is substituted with a 3-(5-methyl)hexadienoate ester group.</p>	<p>Naltrexone-3-(5-methyl)hexadienoate</p>
 <p>The structure shows a pentacyclic morphinan skeleton. The nitrogen atom is substituted with a butyl group. A hydroxyl group is attached to the 3-position of the pentacyclic ring system. The 6-position is substituted with a 3-(5-methyl)hexadienoate ester group.</p>	<p>Butorphanolo-3-(5-methyl)hexadienoate</p>
 <p>The structure shows a pentacyclic morphinan skeleton. The nitrogen atom is substituted with a methyl group. A hydroxyl group is attached to the 3-position of the pentacyclic ring system. The 6-position is substituted with a 5-methylhexadienoate ester group.</p>	<p>Metopon 5-methylhexadienoate</p>
 <p>The structure shows a pentacyclic morphinan skeleton. The nitrogen atom is substituted with a methyl group. A hydroxyl group is attached to the 3-position of the pentacyclic ring system. The 6-position is substituted with a 5-methylhexadienoate ester group.</p>	<p>Hydromorphone 5-methylhexadienoate</p>

 <p>The structure shows the levorphanol moiety, a pentacyclic morphine-like skeleton with a methyl group on the nitrogen atom, esterified to a 5-methylhexadienoic acid derivative.</p>	<p>Levorphanol 5-methylhexadienoate</p>
 <p>The structure shows the morphino moiety, a pentacyclic morphine-like skeleton with a hydroxyl group at the 3-position and a methyl group on the nitrogen atom, esterified to a 5-methylhexadienoic acid derivative.</p>	<p>Morphino-3-(5-methyl)hexadienoate</p>
 <p>The structure shows the nalorphino moiety, a pentacyclic morphine-like skeleton with a hydroxyl group at the 3-position, a vinyl group on the nitrogen atom, and a methyl group on the nitrogen atom, esterified to a 5-methylhexadienoic acid derivative.</p>	<p>Nalorphino-3-(5-methyl)hexadienoate</p>
 <p>The structure shows the cyclazocine moiety, a pentacyclic morphine-like skeleton with a cyclopropylmethyl group on the nitrogen atom, esterified to a 5-methylhexadienoic acid derivative.</p>	<p>Cyclazocine 5-methylhexadienoate</p>

 <p>The structure shows a bicyclic core consisting of a benzene ring fused to a six-membered ring containing a nitrogen atom. The nitrogen atom is substituted with a propyl group. A carbonyl group is attached to the benzene ring, and a 5-methylhexadienoate ester group is attached to the six-membered ring.</p>	<p>Ketocyclazocine 5-methylhexadienoate</p>
 <p>The structure shows a complex pentacyclic core with a benzene ring and a nitrogen atom. The nitrogen atom is substituted with a propyl group. There is a hydroxyl group and a methoxy group on the structure. A carbonyl group is attached to the benzene ring, and a 5-methylhexadienoate ester group is attached to the core.</p>	<p>Diprenorphine 5-methylhexadienoate</p>
 <p>The structure shows a complex pentacyclic core with a benzene ring and a nitrogen atom. The nitrogen atom is substituted with a propyl group. There is a hydroxyl group and a methoxy group on the structure. A carbonyl group is attached to the benzene ring, and a 5-methylhexadienoate ester group is attached to the core.</p>	<p>Etorphine 5-methylhexadienoate</p>
 <p>The structure shows a bicyclic core consisting of a benzene ring fused to a six-membered ring containing a nitrogen atom. The nitrogen atom is substituted with a propyl group. A carbonyl group is attached to the benzene ring, and a 5-methylhexadienoate ester group is attached to the six-membered ring.</p>	<p>Levorphanol 5-methylhexadienoate</p>

	<p>Oxycodone 5-methylhexadienoate</p>
	<p>Tapentadol 5-methylhexadienoate</p>

4. The compound of Claim 1, wherein said compound of Formula I is selected from the group of (Nalbuphino-3-hexadienoate, Buprenorphino-3-hexadienoate, Hydromorphino-3-hexadienoate, Morphino-3-hexadienoate, Pentazocino-4-hexadienoate, Butorphanolo-3-hexadienoate, Naloxone-3-hexadienoate).

5. A composition of claim 1, where said composition increases opioid receptor engagement of an opiate when administered orally to a patient.

6. A method of use of composition of claim 1 for the treatment of one of the medical conditions from the group of (a pain management, a palliative care, a postoperative anesthesiology, a skin disorder, an addiction, a locomotive disorder, a levodopa-induced dyskinesias (LID) in Parkinson's disease, a dyskinesias associated with Tourette's syndrome, a tardive dyskinesia and a Huntington's disease.

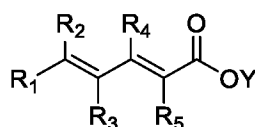
7. A composition comprising a hexadienoate and opioid residue.

8. The compound of claim 7, wherein said hexadienoate attached to the 3<sup>hydroxy</sup> position of

the opioid residue.

9. The compound of claim 7, wherein said hexadienoate attached to the phenoxy radical of the opioid residue.

10. The compound of claim 7, wherein said compound is based on a general formula I or pharmaceutically acceptable salt



Formula I

wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> or R<sub>5</sub> are selected from H, optionally substituted C1-3, OAlk; and Y is selected from an opioid residue.

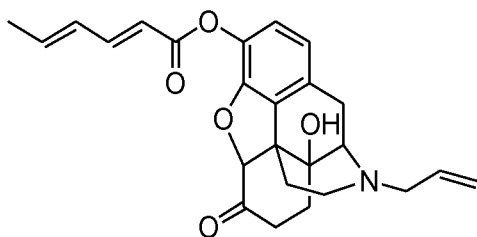
11. The compound of Claim 7, wherein the opioid residue is an opioid antagonist.

12. The compound as claimed in Claim 7, wherein the opioid residue Y is selected from a group comprising (Nalbuphine, Naloxone, Naltrexone, Butorphanol, Metopon, Hydromorphone, Levorphanol, Morphine, Nalorphine, Ketocyclazocine, Diprenorphine, Etorphine, Levorphanol, Oxymorphone, Tapentadol, Nalbuphino-3-(5-methyl)hexadienoate, Naloxone-3-(5-methyl)hexadienoate, Naltrexone-3-(5-methyl)hexadienoate, Butorphanolo-3-(5-methyl)hexadienoate, Metopon 5-methylhexadienoate, Hydromorphone 5-methylhexadienoate, Levorphanol 5-methylhexadienoate, Morphino-3-(5-methyl)hexadienoate, Nalorphino-3-(5-methyl)hexadienoate, Cyclazocine5-methylhexadienoate, Ketocyclazocine 5-methylhexadienoate, Diprenorphine 5-methylhexadienoate, Etorphine 5-methylhexadienoate, Oxymorphone5-methylhexadienoate, Tapentadol 5-methylhexadienoate).

13. The compound of claim 7, wherein the opioid residue is 3-allyl-4a-hydroxy-7-oxo-

2,3,4,4a,5,6,7,7a-octahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinolin-9-yl (2E,4E).

14. The compound of claim 7, having the chemical formula



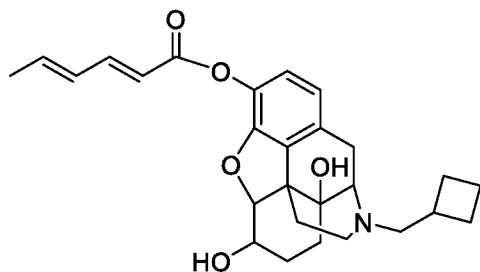
3-allyl-4a-hydroxy-7-oxo-2,3,4,4a,5,6,7,7a-octahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinolin-9-yl (2E,4E)-hexa-2,4-dienoate

Chemical Formula: C<sub>25</sub>H<sub>27</sub>NO<sub>5</sub>

Molecular Weight: 421.49

15. The compound of claim 7, wherein the opioid residue is 3-(cyclobutylmethyl)-4a,7-dihydroxy-2,3,4,4a,5,6,7,7a-octahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinolin-9-yl (2E,4E).

16. The compound of claim 15, having the chemical formula



3-(cyclobutylmethyl)-4a,7-dihydroxy-2,3,4,4a,5,6,7,7a-octahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinolin-9-yl (2E,4E)-hexa-2,4-dienoate

17. A method of increasing opioid receptor engagement comprising an administering to the subject an effective amounts of the compound of claim 7.

18. A method of pain management comprising an administering to the subject an effective amounts of compound of claim 7.

19. A method of treatment of a skin disorder, an addiction, a locomotive disorder, a levodopa-induced dyskinesias (LID) in Parkinson's disease, a dyskinesias associated with Tourette's syndrome, a tardive dyskinesia or a Huntington's disease by administering to a patient an effective amounts of the compound of claim 7.

20. A method of treatment of an opioid overdose comprising the steps of administering to a subject an effective amounts of the compound of claim 7.







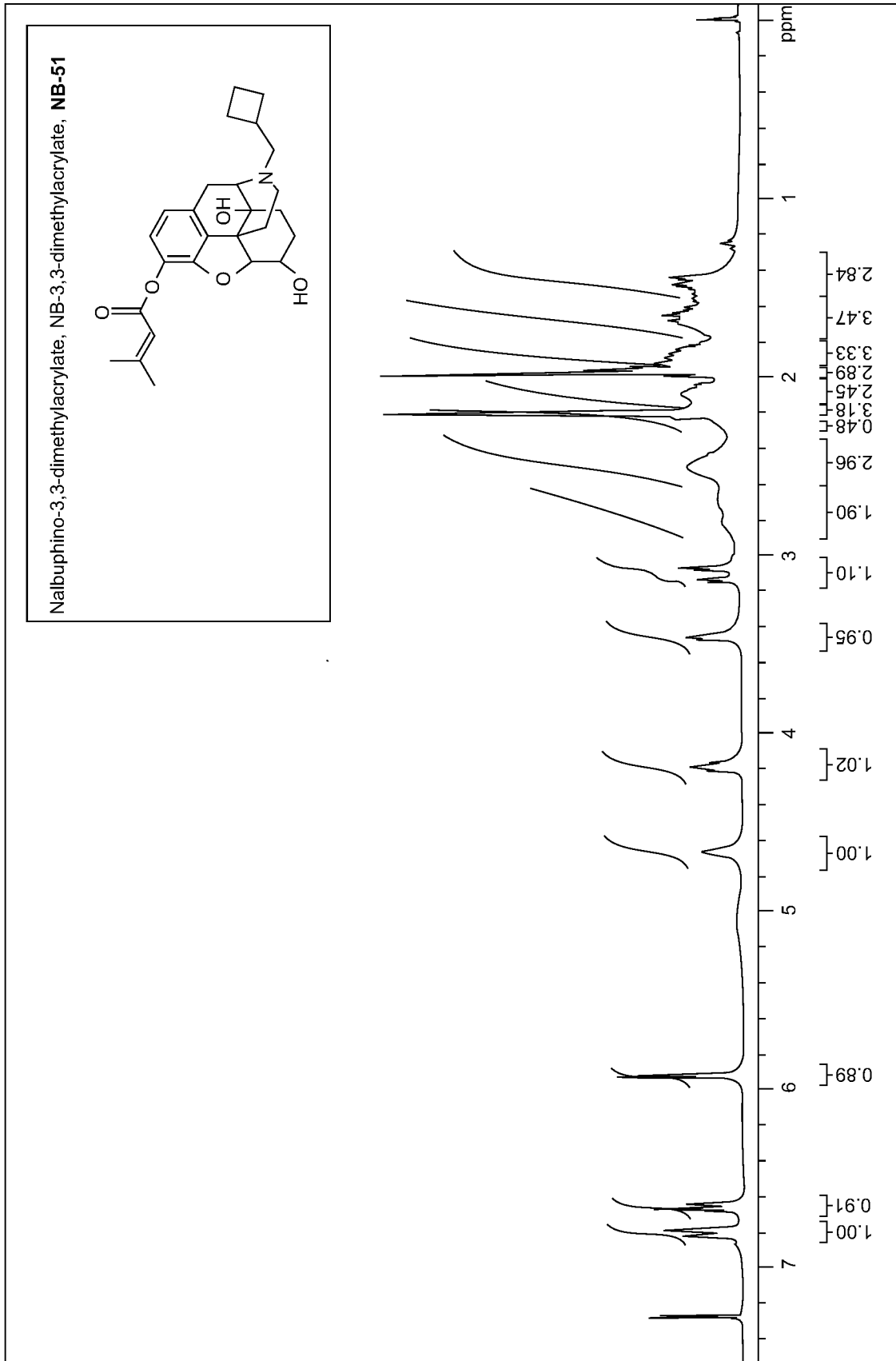


FIG. 4

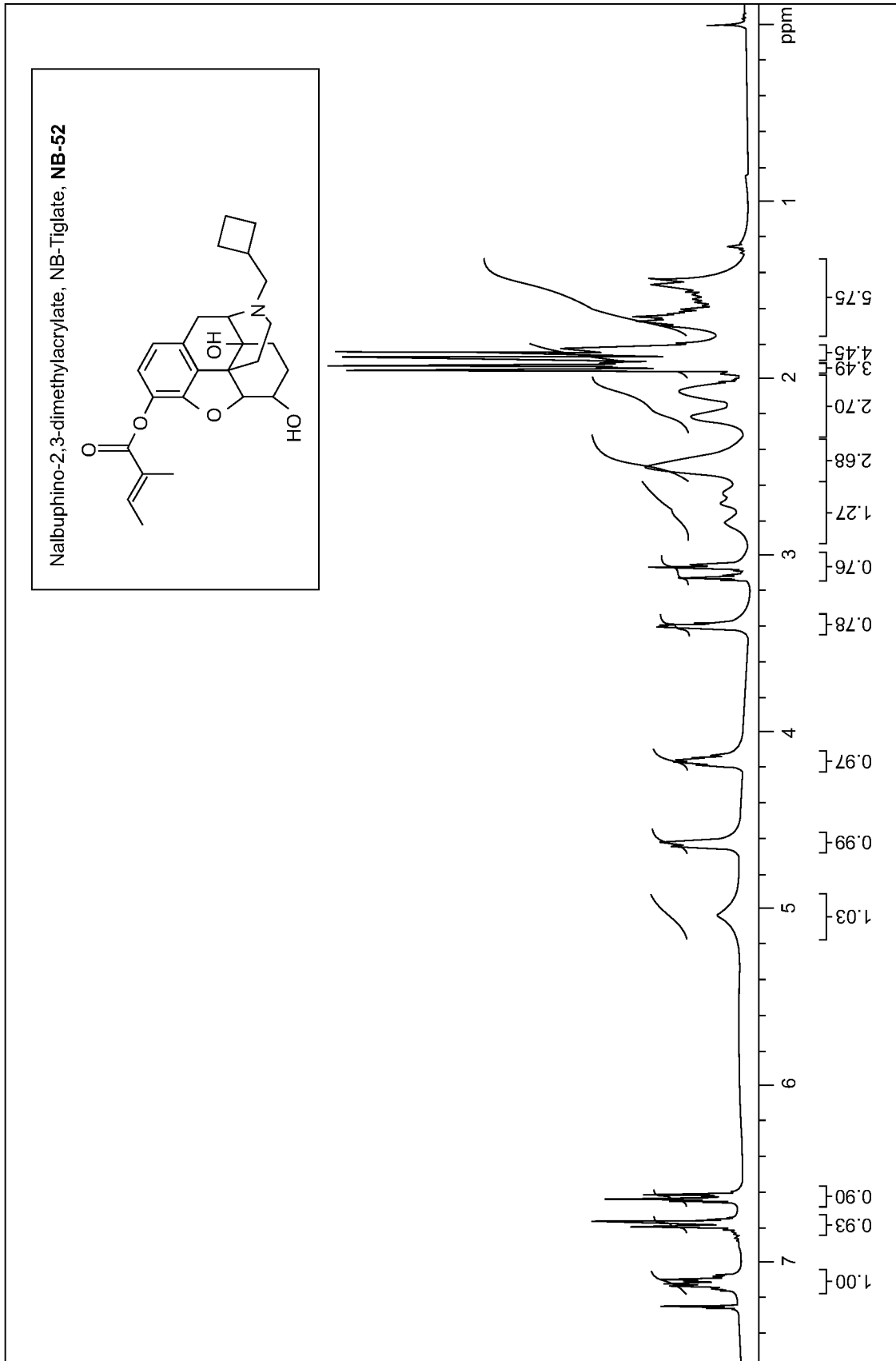


FIG. 5

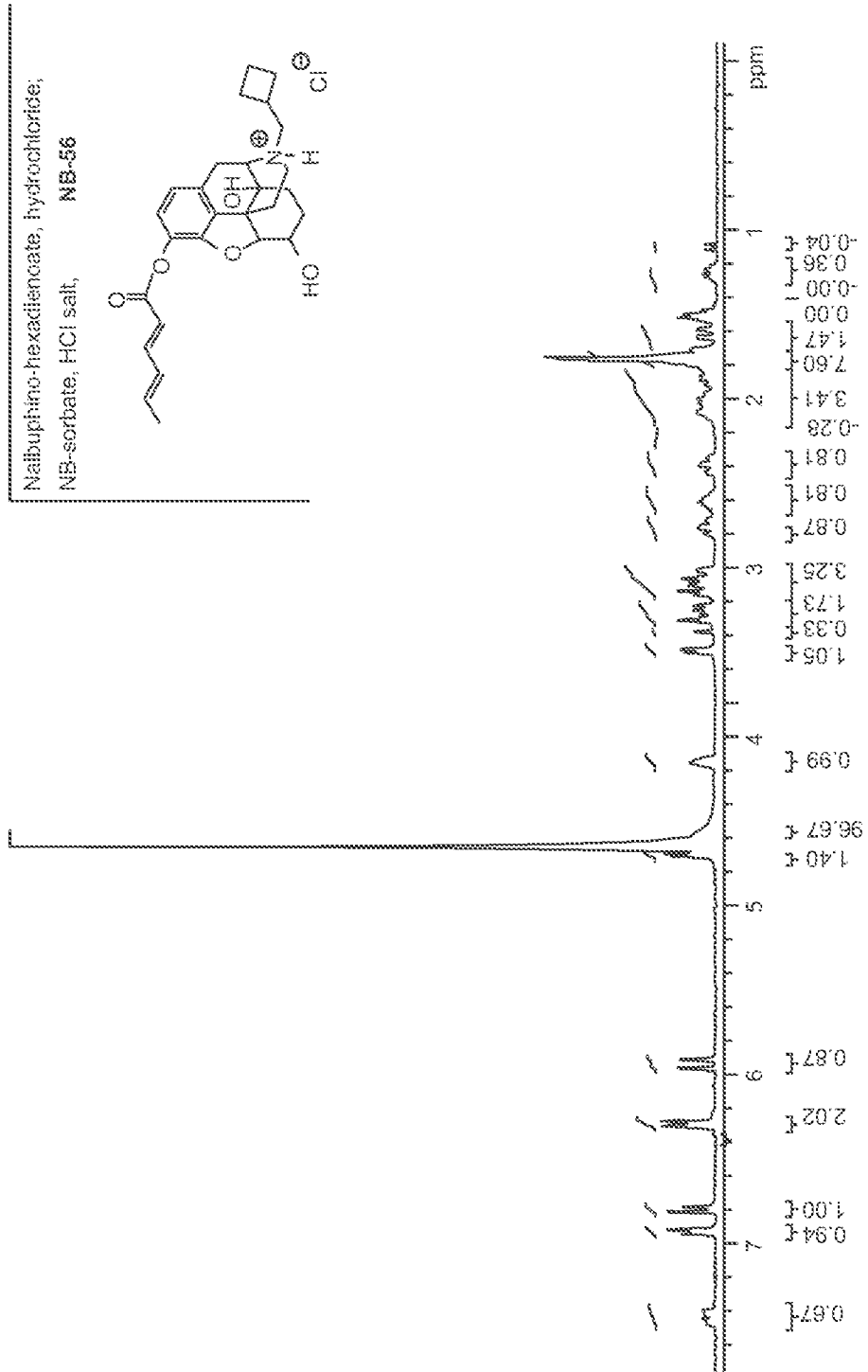


FIG. 6

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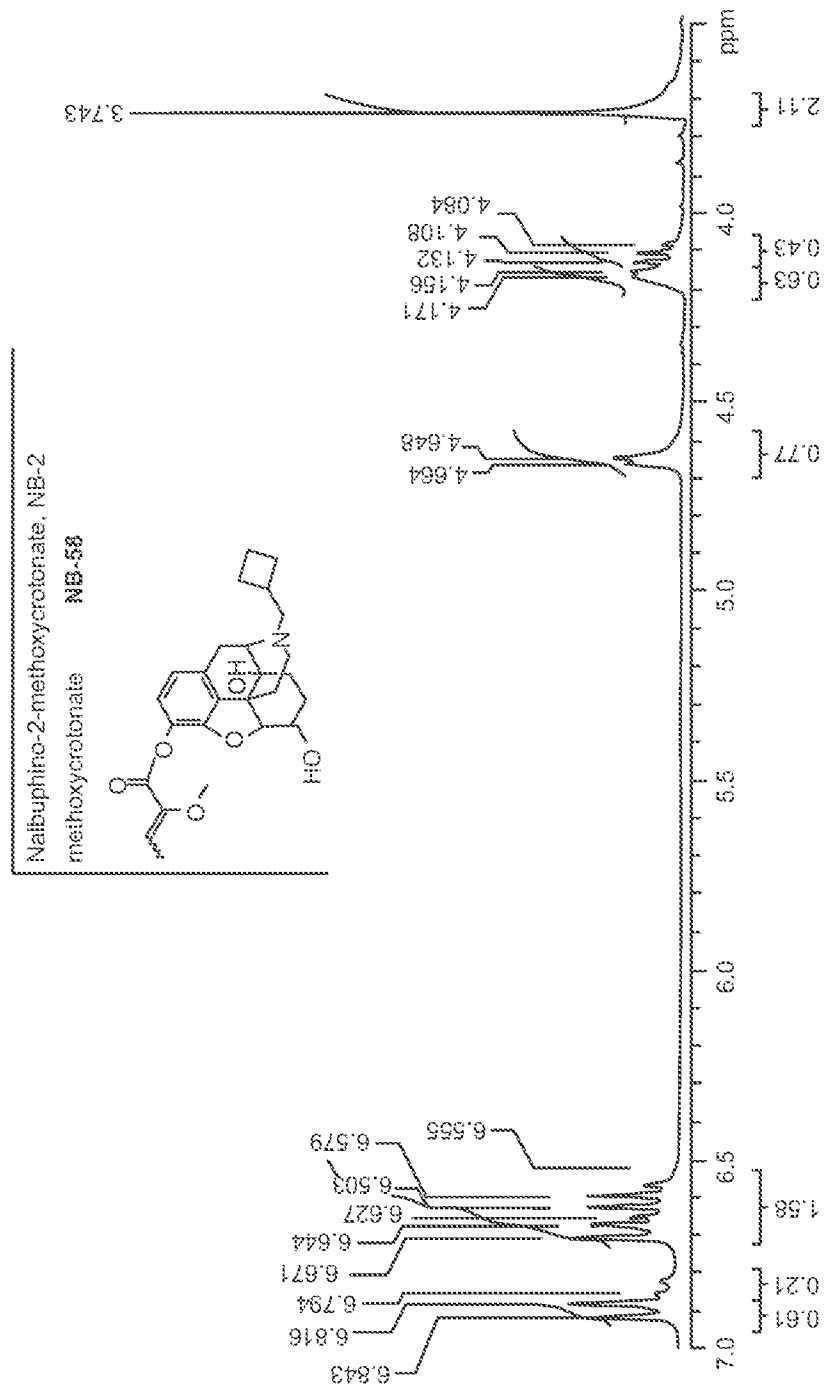


FIG. 7

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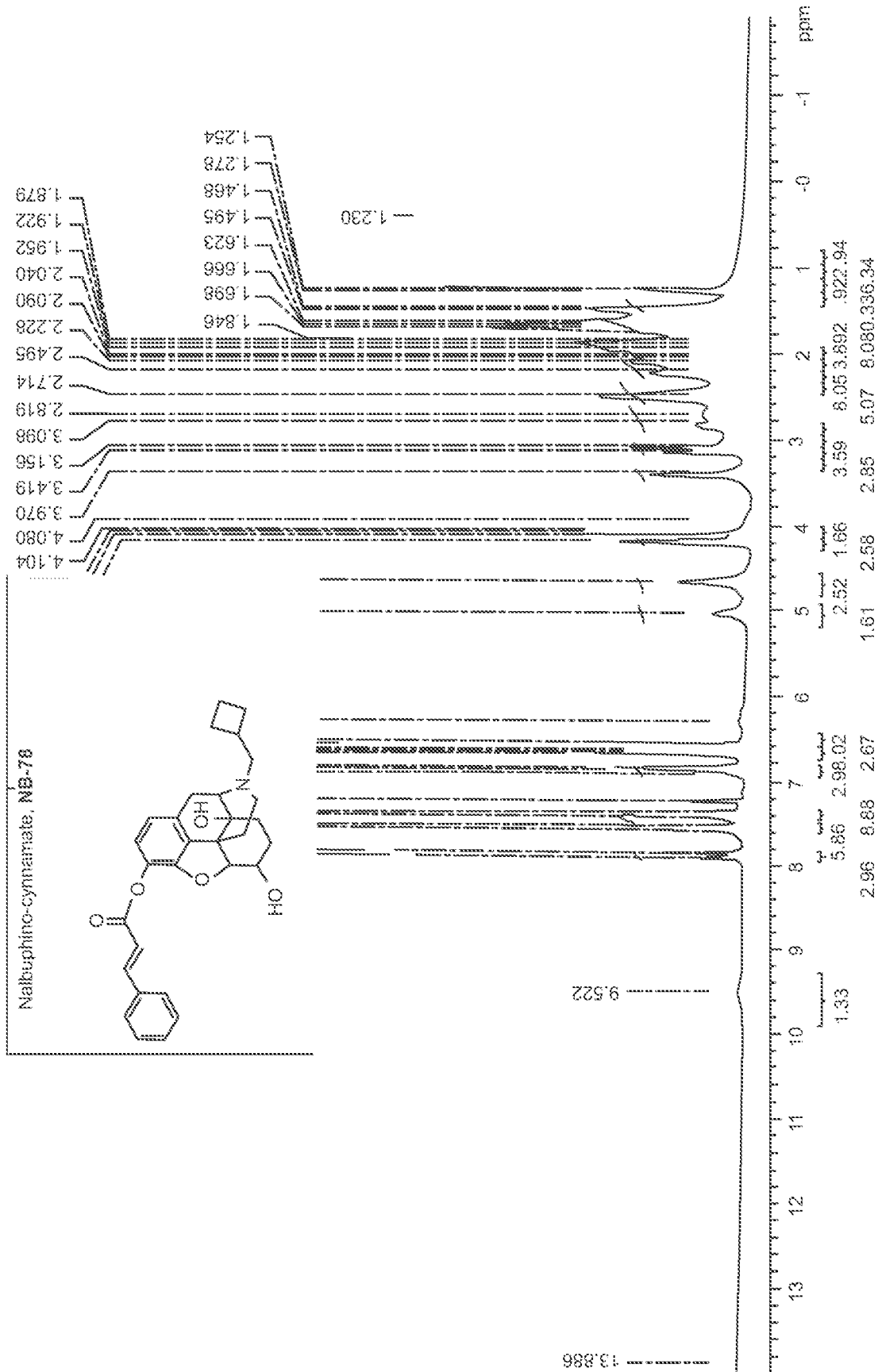


FIG. 8

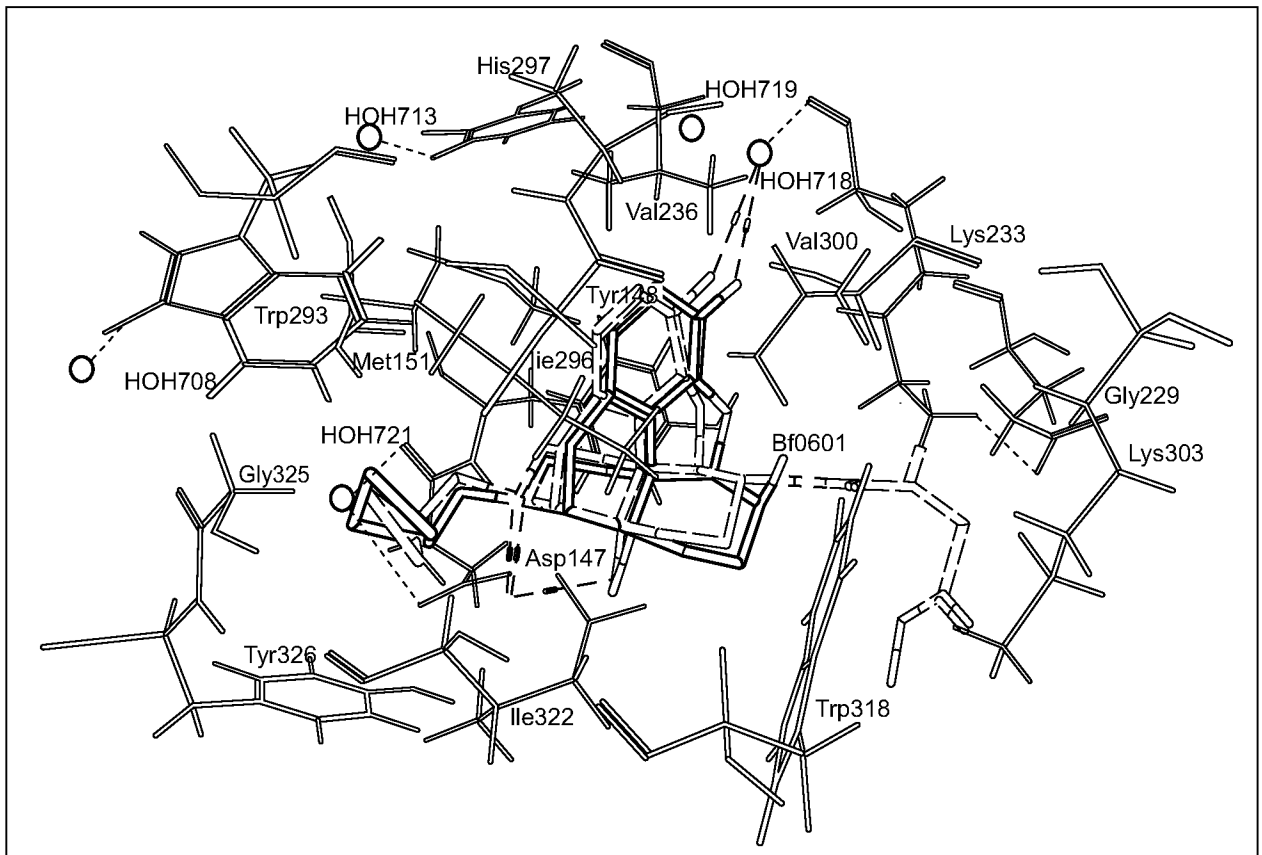


FIG. 9A

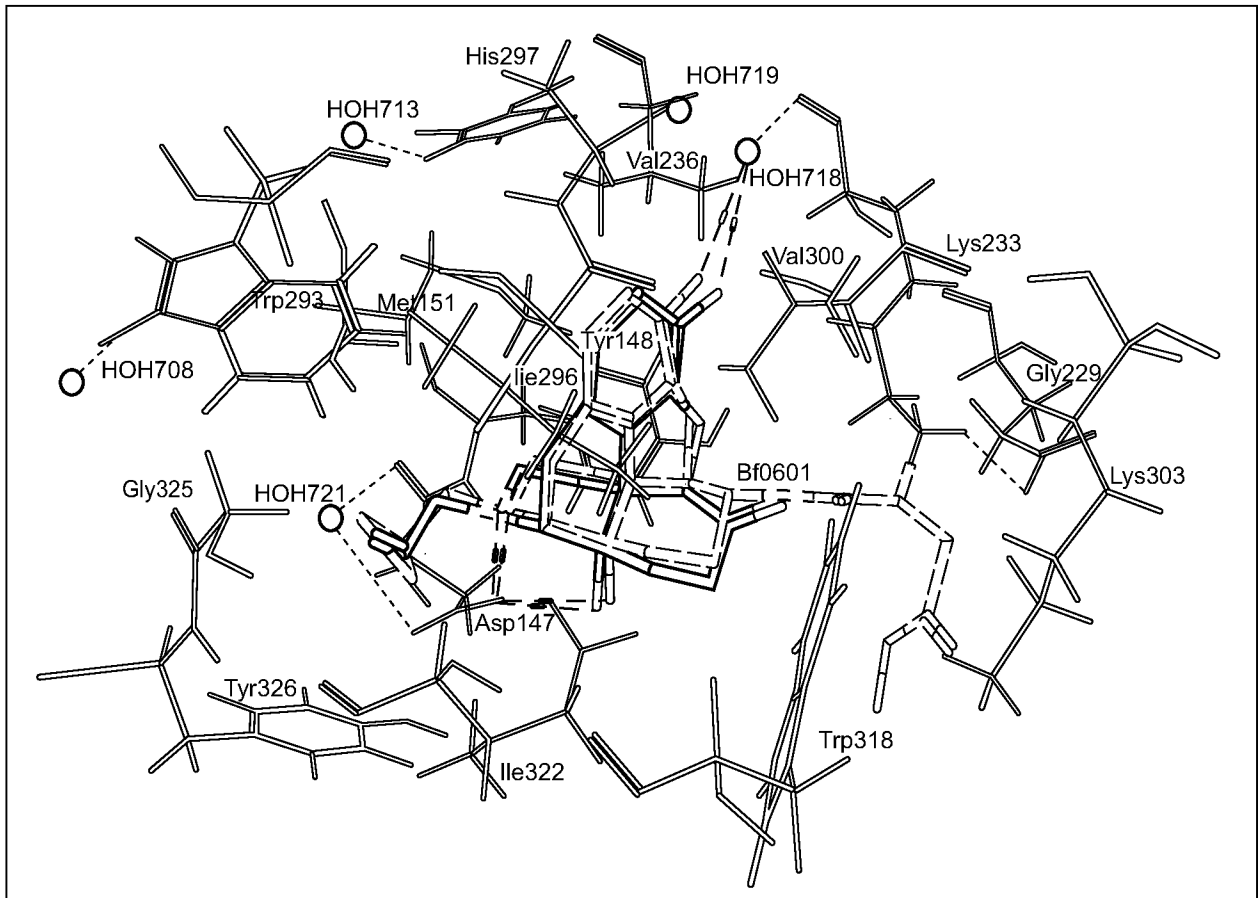


FIG. 9B

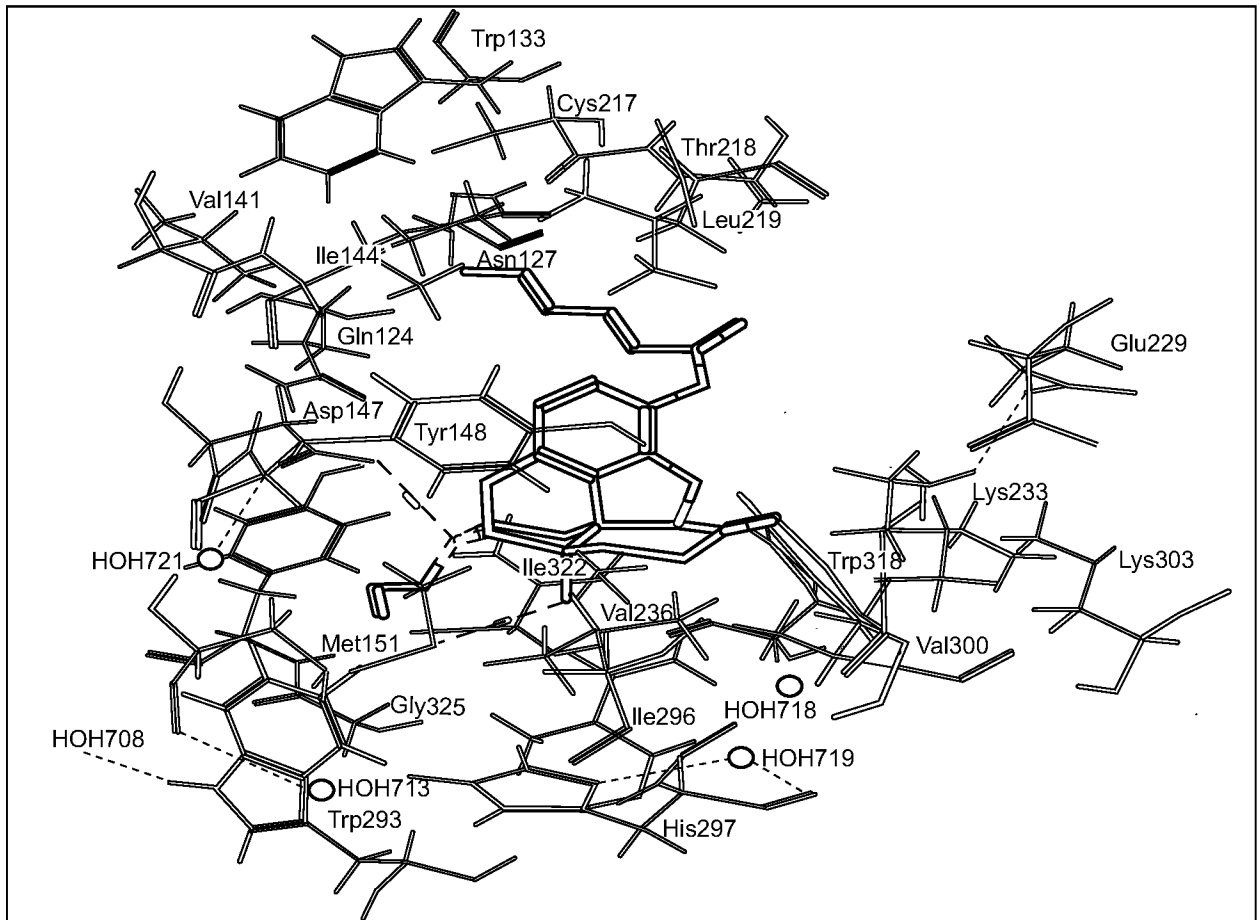


FIG. 10A

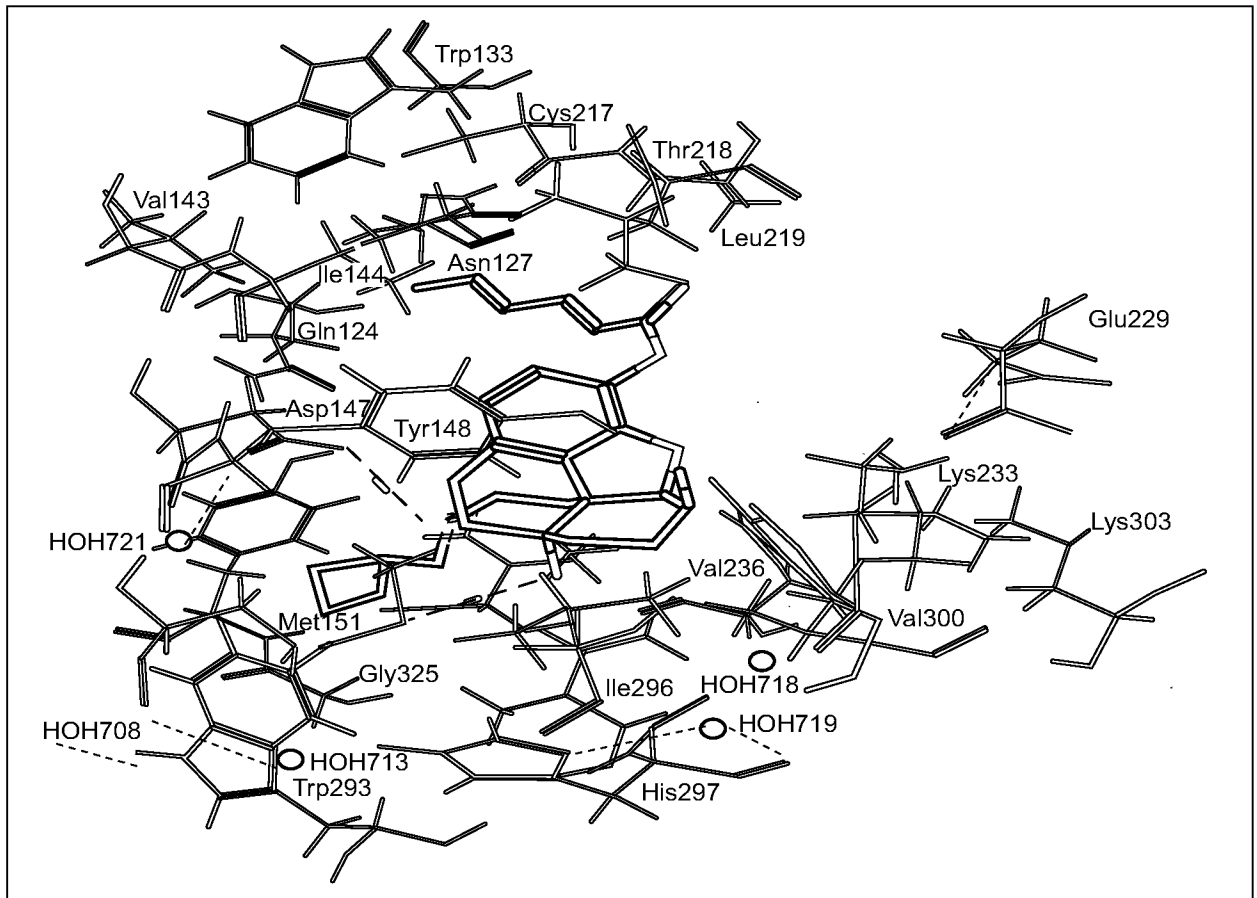


FIG. 10B

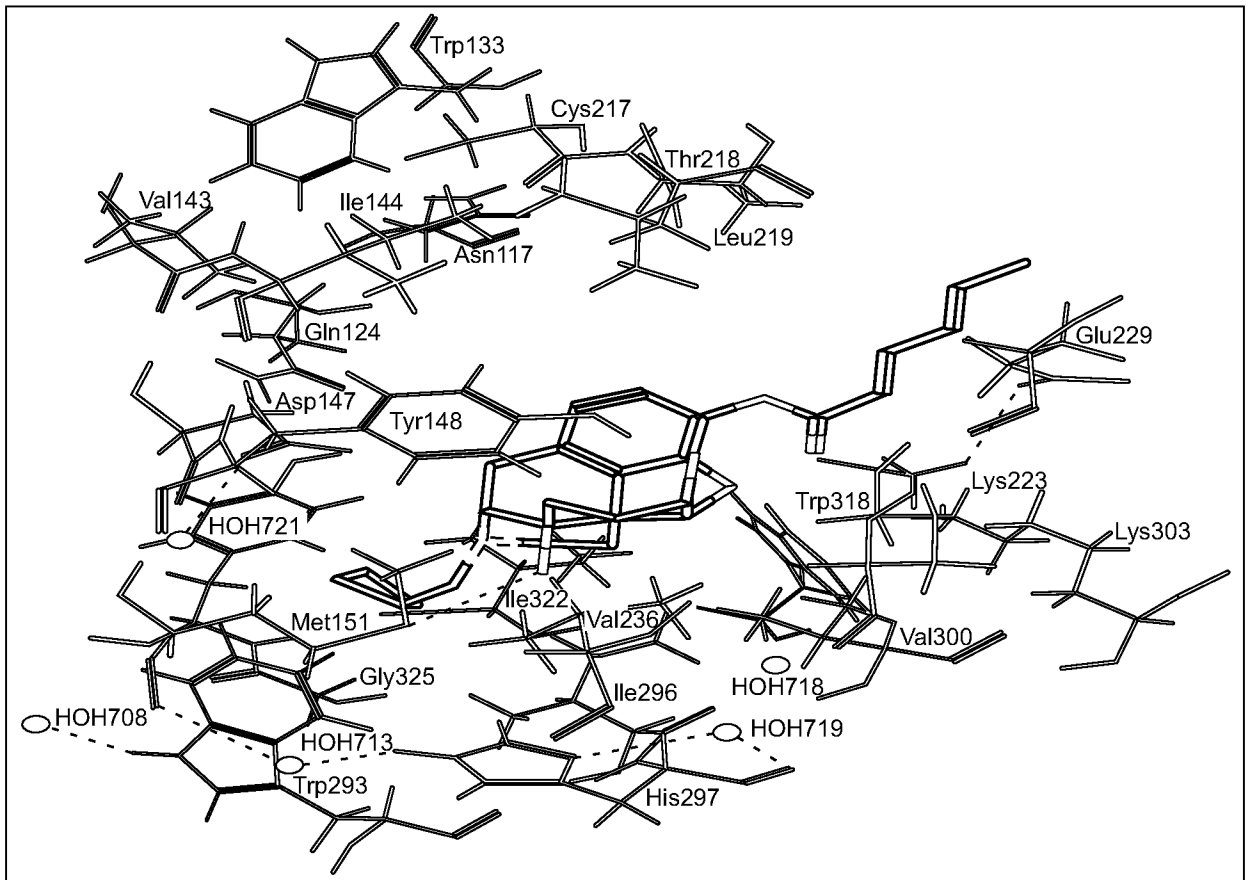


FIG. 10C

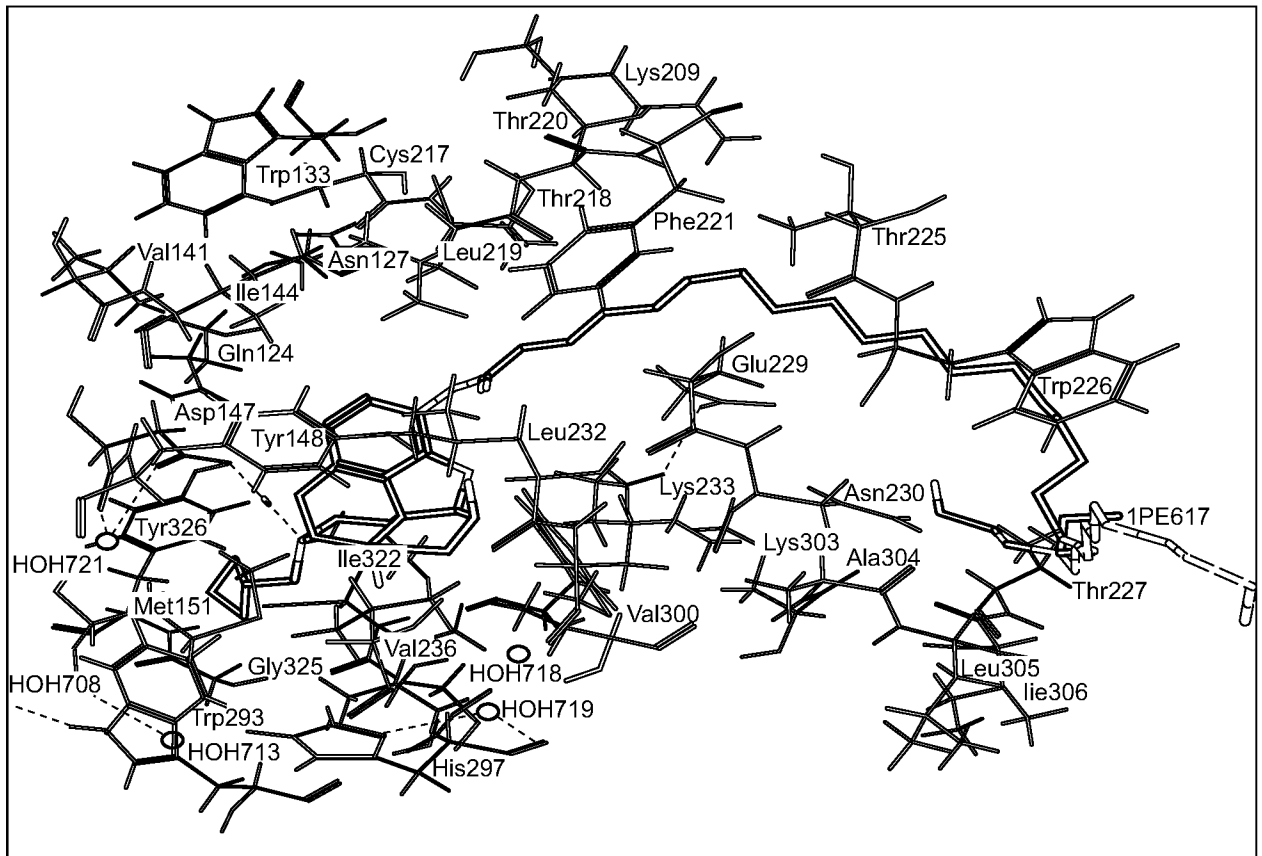


FIG. 10D

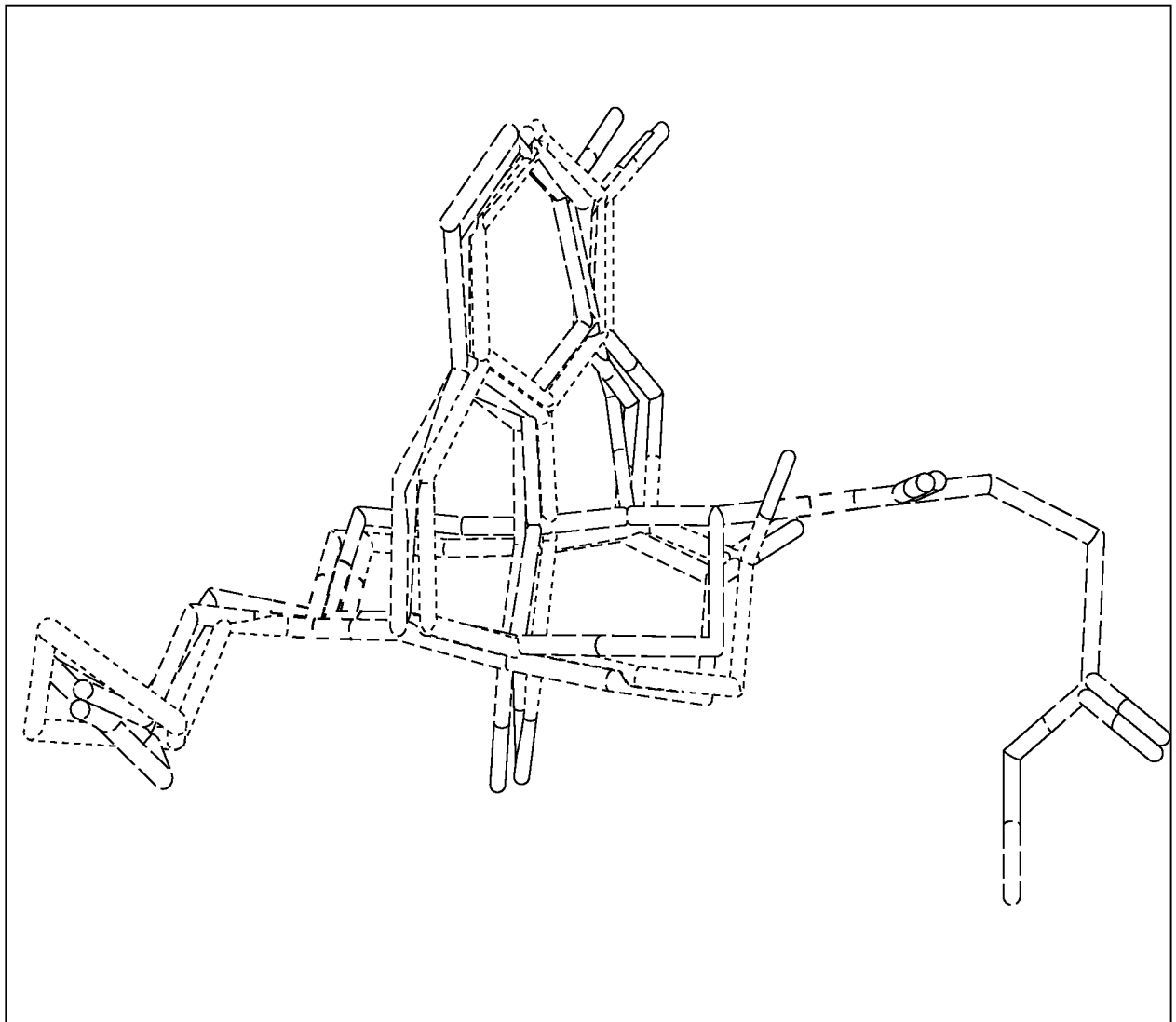


FIG. 11A

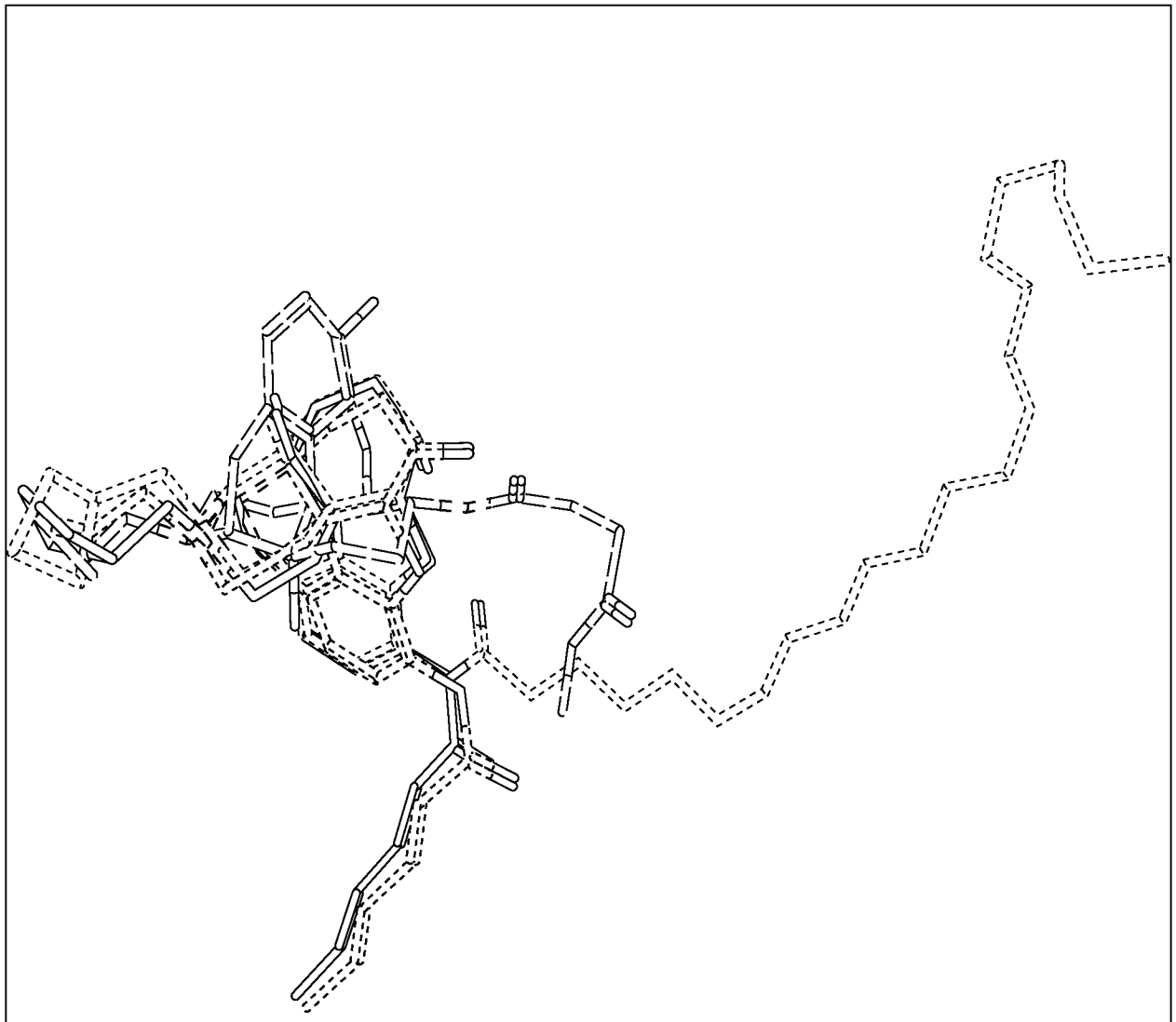


FIG. 11B

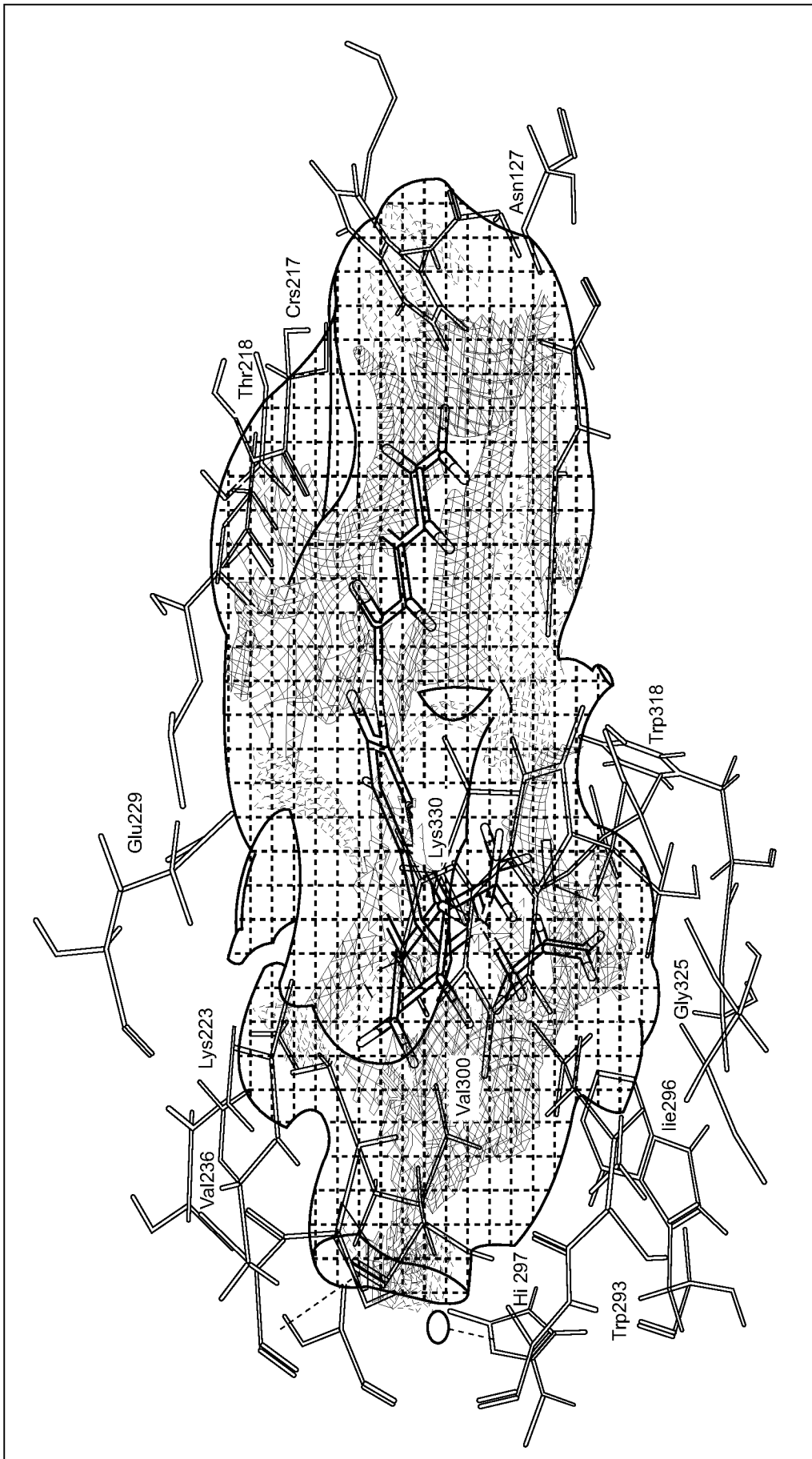


FIG. 12A

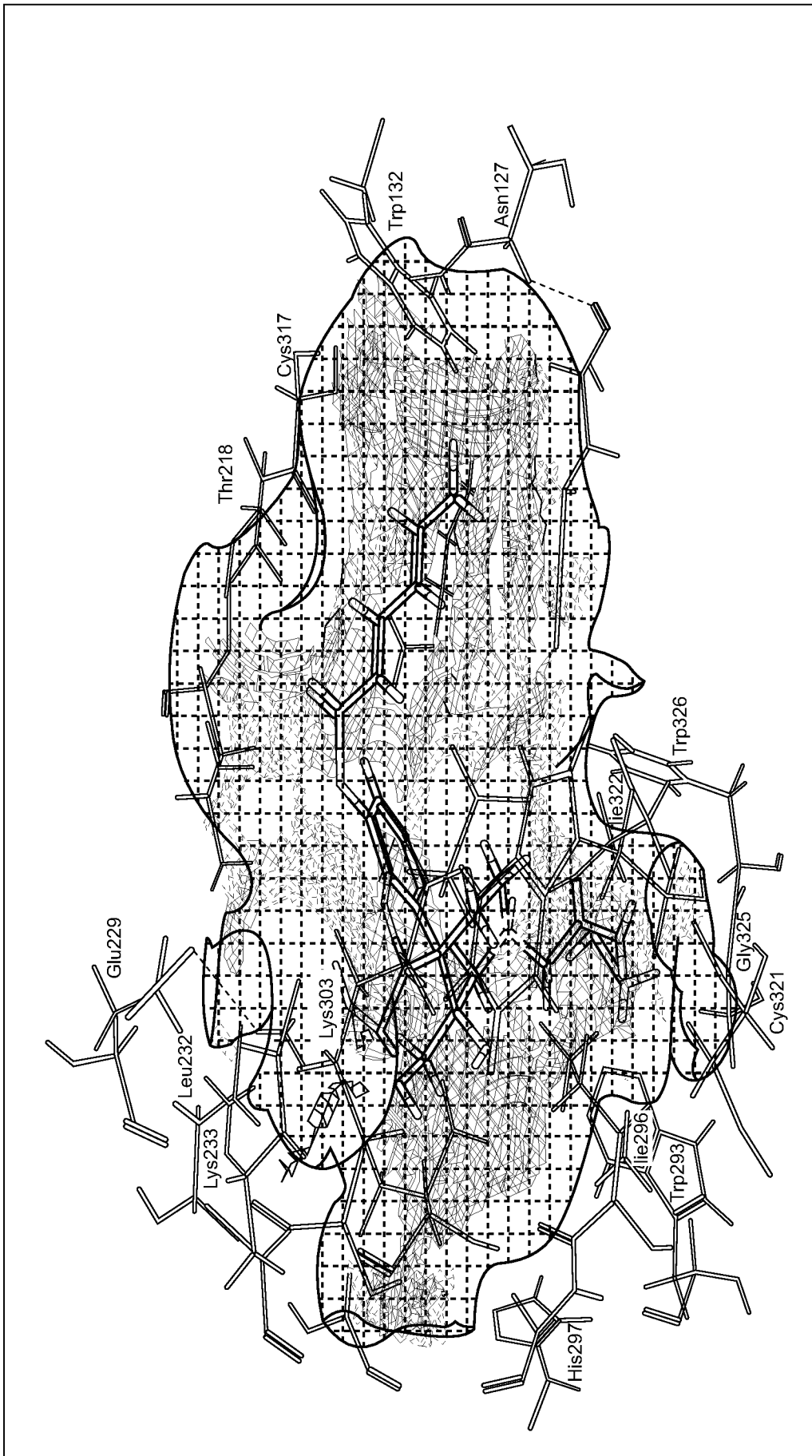


FIG. 12B

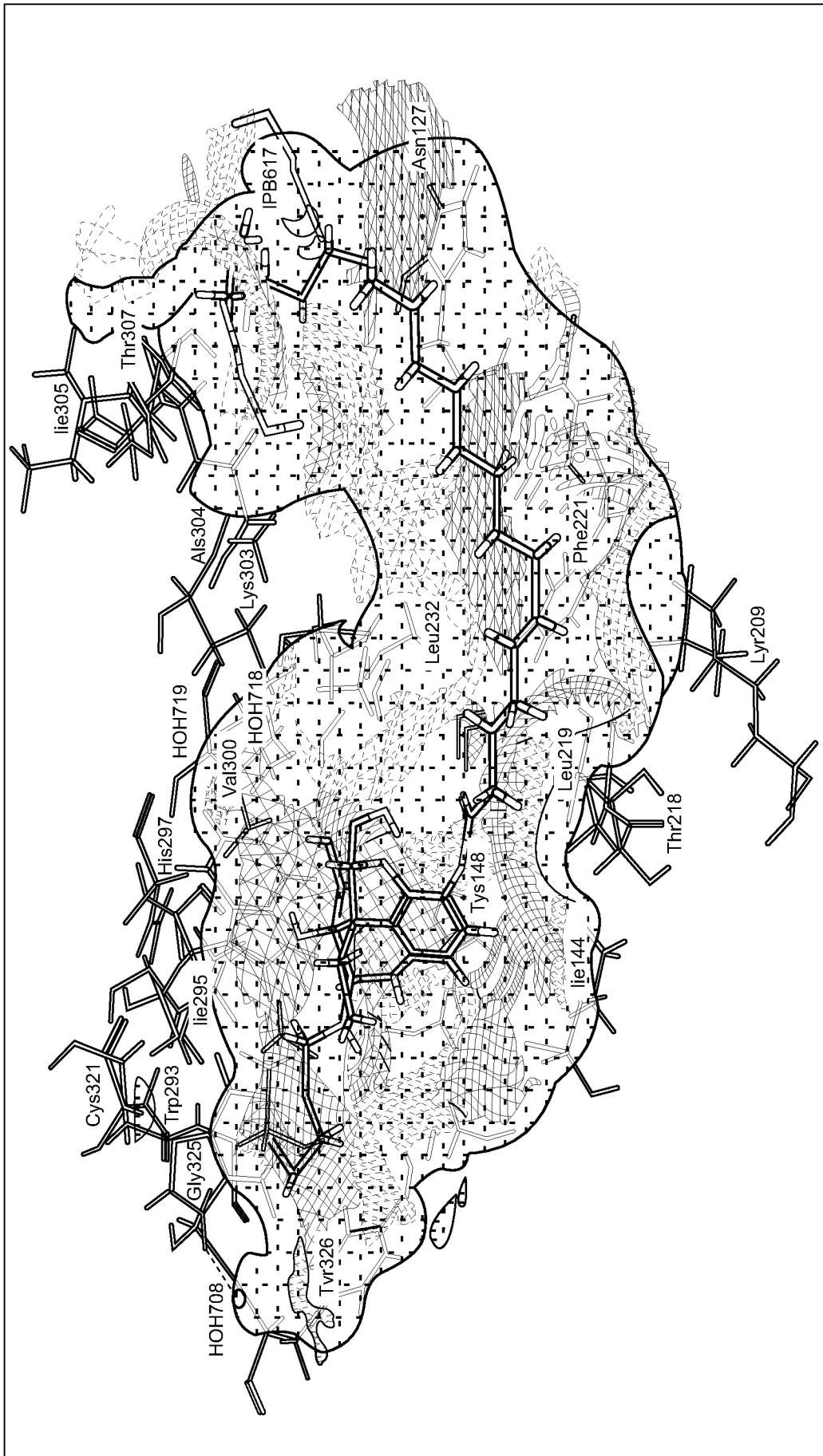


FIG. 12C

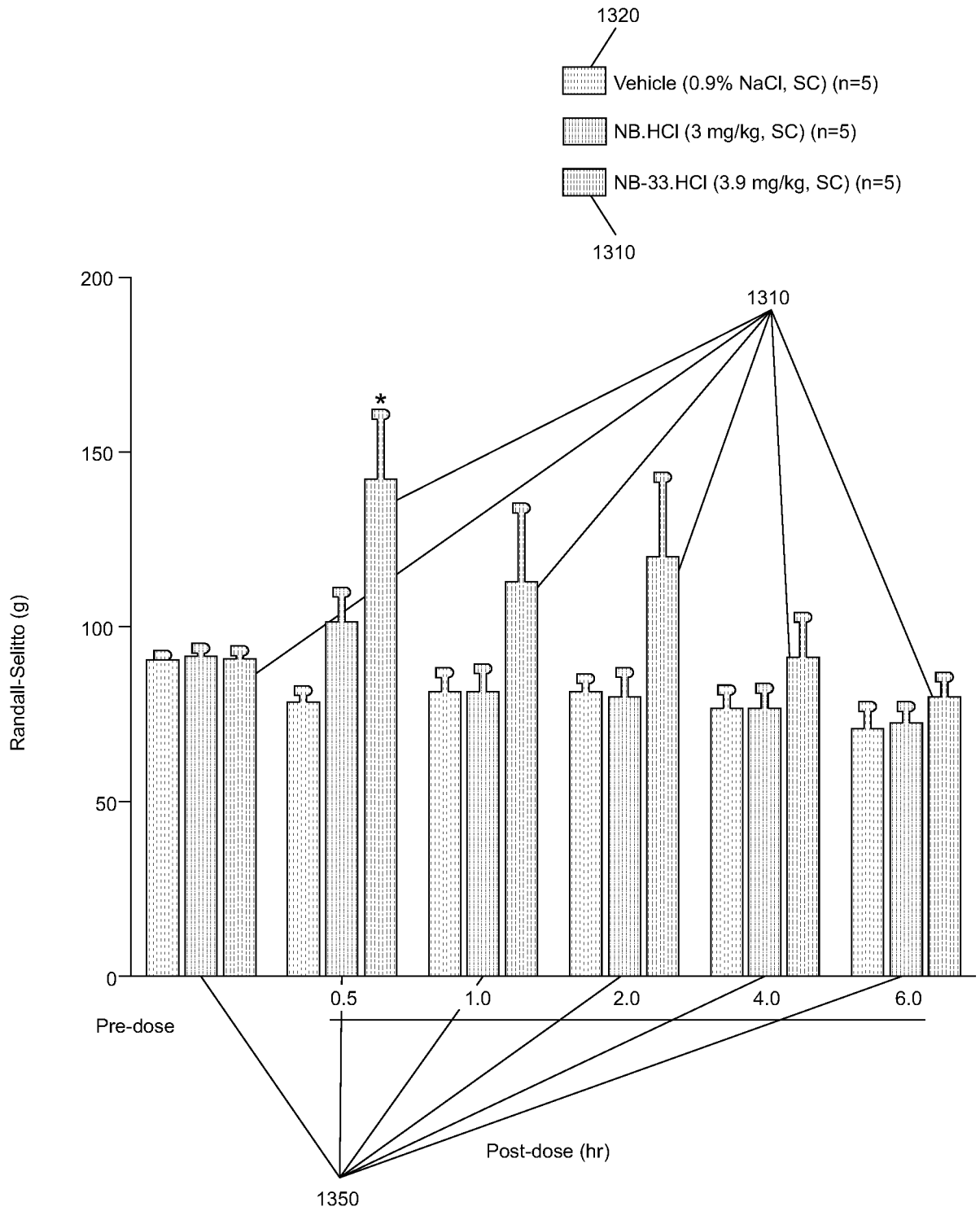


FIG. 13

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 20/21599

A. CLASSIFICATION OF SUBJECT MATTER  
 IPC - A61P 25/36; C07C 229/38; C07D 221/28 (2020.01)  
 CPC - A61P 25/36; C07C 219/28; C07C 229/38

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
 See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched  
 See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
 See Search History document

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Wei et al. 'Synthesis and antitumor activities of sinomenine derivatives on rings A and C',	1, 7, 9-10
---	Journal of Asian Natural Products Research, 01 November 2017 (01.11.2017), Vol.20,	-----
A	pages277-291; p280	2-5, 8, 11-12, 15-16
A	US 2011/0190267 A1 (Franklin et al.) 04 August 2011 (04.08.2011); para[0491]	2-5, 8, 11-12, 15-16
A	Sung et al. 'Controlled release of nalbuphine prodrugs from biodegradable polymeric matrices: influence of prodrug hydrophilicity and polymer composition', International Journal of Pharmaceutics, 07 October 1998 (07.10.1998), Vol.172, pages17-25; p18	2-5, 8, 11-12, 15-16
A	US 2011/0245288 A1 (Stinchcomb et al.) 06 October 2011 (06.10.2011); entire document	1-5, 7-12, 15-16
A	US 2018/0236082 A1 (MEDRx Co Ltd) 23 August 2018 (23.08.2013); entire document	1-5, 7-12, 15-16
P/A	US 2020/0055864 A1 (Kappa - Pharma LLC) 20 February 2020 (20.02.2020); entire document	1-5, 7-12, 15-16

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"D" document cited by the applicant in the international application	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"E" earlier application or patent but published on or after the international filing date	"&" document member of the same patent family
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

07 August 2020

Date of mailing of the international search report

**29 SEP 2020**

Name and mailing address of the ISA/US  
 Mail Stop PCT, Attn: ISA/US, Commissioner for Patents  
 P.O. Box 1450, Alexandria, Virginia 22313-1450  
 Facsimile No. 571-273-8300

Authorized officer

Lee Young

Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 20/21599

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

- 1.  Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
- 2.  Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
  
- 3.  Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

--See Supplemental Box--

- 1.  As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
- 2.  As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
- 3.  As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
- 4.  No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:  
1(in part), 2, 3-4(in part), 5, 7-9, 10(in part), 11, 12(in part), and 15-16

- Remark on Protest**
- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
  - The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
  - No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT  
Information on patent family members

International application No.

PCT/US 20/21599

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I+: Claims 1-5, and 7-16 directed to a compound of general formula I or pharmaceutically acceptable salt of thereof wherein R1, R2, R3, R4 or R5 are selected from a group comprising H, optionally substituted C1-3 and OAlk), and Y is an opioid residue. The compound of general formula I will be searched to the extent that it encompasses the compound of general formula I, wherein said compound of Formula I is Nalbuphino-3-hexadienoate in claim 3. It is believed that claims 1(in part), 2, 3-4(in part), 5, 7-9, 10(in part), 11, 12(in part), and 8-16 read on this first named invention, and thus these claims will be searched without fee. Applicant is invited to elect additional compounds of claim 1, wherein each additional compound elected will require one additional invention fee. Applicants must specify the claims that encompass any additionally elected compound. Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the '+' group(s) will result in only the first claimed invention to be searched. Additionally, an exemplary election wherein different actual variables are selected is suggested. An exemplary election would be the compound of general formula I or pharmaceutically acceptable salt of thereof, wherein said compound of Formula I is Naloxone-3-hexadienoate in claim 3 (i.e., claims 1(in part), 2, 3-4(in part), 5, 7-9, 10(in part), 11, 12(in part), and 8-16).

Group II: claims 6, and 17-20 directed to a method of use of composition of claim 1 for the treatment of one of the medical conditions from the group of (a pain management, a palliative care, a postoperative anesthesiology, a skin disorder, an addiction, a locomotive disorder, a levodopa-induced dyskinesias (LID) in Parkinson's disease, a dyskinesias associated with Tourette's syndrome, a tardive dyskinesia and a Huntington's disease.

The group of inventions listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special Technical Features:

Group I+ includes the technical feature of a unique compound of general formula I or pharmaceutically acceptable salt of thereof containing the same, which is not required by any other invention of Group I+.

Group II includes the technical feature of a method of use of composition of claim 1 for the treatment of one of the medical conditions, not required by Group I+.

Common technical features:

The inventions of Group I+ share the technical feature of compound of general formula I or pharmaceutically acceptable salt of thereof containing the same.

Groups I+ and II share the technical feature of a compound of general formula I or pharmaceutically acceptable salt of thereof.

These shared technical features, however, do not provide a contribution over the prior art, as being anticipated by the journal article entitled 'Synthesis and antitumor activities of sinomenine derivatives on rings A and C' by Wei et al. (hereinafter 'Wei'). Wei discloses a compound of general formula I wherein R1 is OAlk; and R2, R3, R4 or R5 are H, and Y is an opioid residue (p280, Table 1. "Compound 1a R1=H, R2=(CH=CH-CH=CHCH3)").

As said compound and compositions were known in the art at the time of the invention, these cannot be considered special technical features that would otherwise unify the inventions of Groups I+ and II. The inventions of Group I+ and II thus lack unity under PCT Rule 13.

Note:

There is a typo for claims to searched in Form 206. The original Form 206 stated claims 1(in part), 2, 3-4(in part), 5, 7-9, 10(in part), 11, 12(in part), and 8-16. However, the correct claims are claims 1(in part), 2, 3-4(in part), 5, 7-9, 10(in part), 11, 12(in part), and 15-16. Thus, claims 1(in part), 2, 3-4(in part), 5, 7-9, 10(in part), 11, 12(in part), and 15-16 are searched for the group 1.