2018

Opioids History and Chemical Structures

This is the first of a four-part Drug Testing Matters series on opioids.

"Opiates" v. "Opioids"

For clarity, the term "opiates" is defined as those compounds that are naturally occurring alkaloids from the opium plant (e.g., codeine; morphine; heroin, which is produced synthetically by the acetylation of morphine). The term "opioids," often used interchangeably with the term "opiates," is defined simply as those compounds that have agonist or partial agonist activity at the opioid receptor and may or may not have structural similarity to the principle opium alkaloids. The category opioids includes opiates (e.g., codeine, morphine, heroin); semi-synthetic compounds (e.g., hydrocodone, hydromorphone, oxycodone, oxymorphone); and synthetic compounds (e.g., fentanyl). This article focuses on six commonly prescribed opioids: morphine, codeine, hydrocodone, hydromorphone, oxycodone, and oxymorphone, which may be tested in federal and federally regulated drug testing programs.

Historical Background

The use of opiates for the treatment of pain dates back thousands of years. As early as the third century B.C., recorded in the writings of Theophrastus, opium was used as an analgesic compound. In 1680, Sydenham wrote, "Among the remedies which pleased Almighty God to give man to relieve his sufferings, none is so universal and so efficacious as opium" (1). During the American Civil War, a significant number of soldiers developed an addiction to morphine, known as "soldier's disease," aided by the introduction of the hypodermic needle (2). Today, opioids remain the principle drugs of choice for pain management. Opium is obtained from the unripe seed capsules of the poppy plant, *Papaver somniferum*, as a milky juice that is dried and powdered to make powdered opium. There are several naturally occurring opium alkaloids, and they fall into two major classes: phenanthrenes (see Figure 1) and benzylisoquinolines (see Figure 2). The primary phenanthrenes are morphine, codeine, and thebaine, and the common benzylisoquinolines are papaverine and noscapine (1).

Figure 1. Phenanthrene Structure

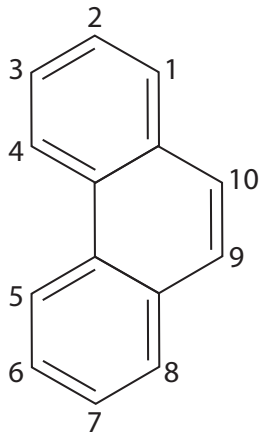


Figure 2. Benzylisoquinoline Structure

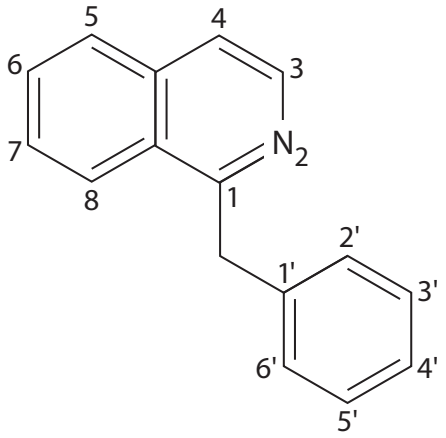
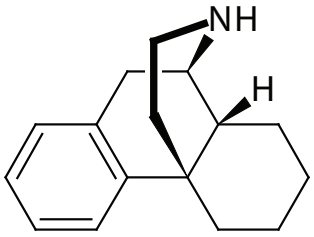


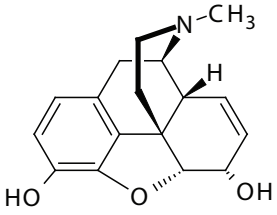
Figure 3. Morphinan Structure



Six Common Opioids and Their Molecular Structures

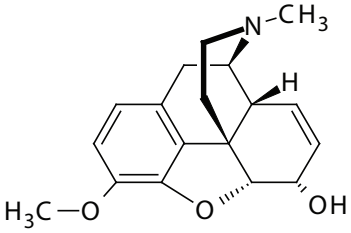
The descriptions of the six opioids below use morphinan as the starting nucleus (3).

Morphine



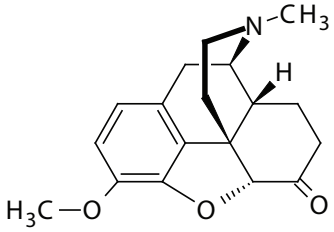
Morphine is the prototype opiate and opioid compound and has a strong affinity for the mu (μ) opioid receptor and a weak affinity for the kappa (κ) opioid receptor (1). It was first isolated in 1804 by Freidrich Wilhelm Adam Serturner, who named it "Morphium" after the Greek god of dreams. It is classified as a Schedule II substance used to control moderate to severe pain (4). The structure of morphine is a hexahydrogenated (5,6; 9,10; and 13,14 positions) phenanthrene nucleus with an ethereal oxygen joining the 4 and 5 (α) carbons, a phenolic hydroxyl group at position 3, an α-alcoholic hydroxyl group at position 6, and a methyl group on the nitrogen atom in the 9,13 carbon-carbon-nitrogen bridge (5). Using the morphinan system, morphine is named (5α,6α)-7,8-didehydro-4,5-epoxy-17-methylmorphinan-3,6-diol.

Codeine



Codeine was first isolated in 1832 and is a prototype weak opioid analgesic with weak affinity for the μ opioid receptor (5,6). In its pure form, codeine is considered a Schedule II compound but is classified as a Schedule III compound when combined with other weak analgesics, such as acetaminophen, and as a Schedule V compound when in liquid cough suppressant preparations (4). Its analgesic potency is approximately 10% that of morphine (6,7). Codeine is produced commercially by the 3-O-methylation of morphine. The structure of codeine is a hexahydrogenated (5,6; 9,10; and 13,14 positions) phenanthrene nucleus with an ethereal oxygen joining the 4 and 5 (α) carbons, a methanolic ether group at position 3, an α-alcoholic hydroxyl group at position 6, and a methyl group on the nitrogen atom in the 9,13 carbon-carbon-nitrogen bridge. Using the morphinan system, codeine is named (5α,6α)-7,8-didehydro-4,5-epoxy-3-methoxy-17-methylmorphinan-6-ol.

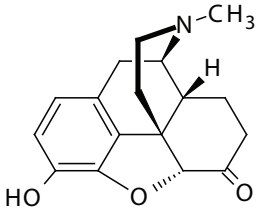
Hydrocodone



Hydrocodone (Vicodin®, Lortab®), a semisynthetic opioid derived from codeine, is indicated for moderate to moderately severe pain and symptomatic relief of a non-productive cough. It has been the most commonly prescribed opioid for several years. Hydrocodone is a Schedule II compound, by itself or when combined with ibuprofen or acetaminophen (4).

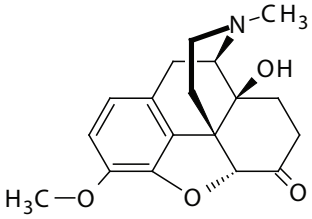
Hydrocodone, like codeine, has weak binding to the μ opioid receptor. Hydrocodone metabolizes to hydromorphone, which has significantly stronger μ opioid receptor binding. The structure of hydrocodone is an octahydrogenated (5,6; 7,8; 9,10; and 13,14 positions) phenanthrene nucleus with an ethereal oxygen joining the 4 and 5 (α) carbons, a methanolic ether group at position 3, a keto group at position 6, and a methyl group on the nitrogen atom in the 9,13 carbon-carbon-nitrogen bridge. Using the morphinan system, hydrocodone is named 4,5-epoxy-3-methoxy-17-methylmorphinan-6-one.

Hydromorphone



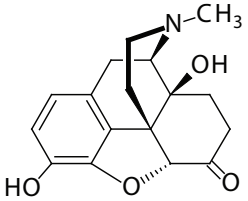
Hydromorphone (Dilaudid®) is a Schedule II semisynthetic opioid that acts as an agonist on the μ opioid receptor with 7 to 10 times the potency of morphine (4,6). Hydromorphone is also a metabolite of hydrocodone via cytochrome P450 2D6 (CYP2D6)-mediated O-demethylation. The structure of hydromorphone is an octahydrogenated (5,6; 7,8; 9,10; and 13,14 positions) phenanthrene nucleus with an ethereal oxygen joining the 4 and 5 (α) carbons, a phenolic hydroxyl at position 3, a keto group at position 6, and a methyl group on the nitrogen atom in the 9,13 carbon-carbon-nitrogen bridge. Using the morphinan system, hydromorphone is named 4,5-epoxy-3-hydroxy-17-methylmorphinan-6-one.

Oxycodone



Oxycodone (Percocet®, Percodan®, Oxycontin®) is a Schedule II semisynthetic opioid in its pure form or in combination with acetaminophen or aspirin (4). Oxycodone has high oral bioavailability with activity at both the κ and μ opioid receptors exhibiting comparable or marginally less analgesic potency than that of morphine (8). Oxycodone has a similar structure to hydrocodone with an added hydroxyl group on the number 14 carbon atom. The structure of oxycodone is an octahydrogenated (5,6; 7,8; 9,10; and 13,14 positions) phenanthrene nucleus with a benzene ring with an ethereal methoxy group at position 3, a ketone group at position 6, a β-alcoholic hydroxyl group at position 14, and a methyl group on the nitrogen atom in the 9,13 carbon-carbon-nitrogen bridge. Using the morphinan system, oxycodone is named 4,5-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one.

Oxymorphone



Oxymorphone is a Schedule II semisynthetic opioid with high affinity for the μ opioid receptor and negligible interactions with the κ and delta (δ) opioid receptors (4, 8). Oxymorphone is a metabolite of oxycodone via phase I CYP2D6-mediated biotransformation. The drug has approximately 10 times the potency of morphine for analgesia and is not affected by CYP2D6- or CYP3A4-specific phase I metabolism. The structure of oxymorphone is a phenanthrene nucleus with a benzene ring with a phenolic hydroxyl group at position 3, a ketone group at position 6, and a β-alcoholic hydroxyl group at position 14, with a methyl group on the nitrogen atom in the 9,13 carbon-carbon-nitrogen bridge. An extended-release version of oxymorphone, sold under the brand name Opana ER®, was removed from the US market in 2017 because of its high abuse potential. Using the morphinan system, oxymorphone is named 4,5-epoxy-3,14-dihydroxy-17-methylmorphinan-6-one.

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The author of the May 2012 Drug Testing Matters article, Opiates Pharmacology, was James Bourland, Ph.D., F-ABFT. ***This article was revised and updated in August 2018 by:***

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