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DARK Classics in Chemical Neuroscience: Heroin and Desomorphine

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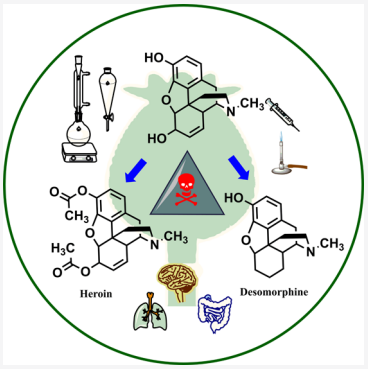
ABSTRACT: Opioids are arguably one of the most important pharmacologic classes, mainly due to their rich history, their useful and potent analgesic effects, and also, just as importantly, their "Dark Side", constituted by their reinforcing properties that have led countless of users to a spiral of addiction, biological dependence, tolerance, withdrawal syndromes, and death. Among the most significant abused and addictive known opioids are heroin and desomorphine, both synthetic derivatives of morphine that belong to the 4,5-epoxymorphinan structural chemical group of the opioid family drugs. These agents share not only structural, pharmacological, and epidemiological features but also a common geographical distribution. A drop in Afghan heroin production and its "exports" to Russia gave rise to widespread consumption of desomorphine in ex-Soviet republics during the first decade of the 21st century, representing an economical and accessible alternative for misusers to this sort of derivative. Herein we review the state of the art of history, chemistry and synthesis, pharmacology, and impact on society of these "cursed cousins".



KEYWORDS: *Opioids, morphine, heroin, desomorphine, krokodil, mu-receptors*

1. HEROIN

1.1. Historical Review. The poppy plant corresponds to an angiosperm species type that gives beautiful flowers. This plant belongs to the *Papaver* genus, Papaveraceae family, specifically, *Papaver somniferum* L. From this species, a dried latex derived from the seed capsules, named opium (the fruit produced by the angiosperms), can be obtained.[1] The earliest history of humanity's romance with opium poppy is found in writings of the Sumerians, dating back to approximately 3300 BC, where they referred to the poppy as "the plant of joy".[2] The story of opium entails several issues, such as addiction, war, the rending of the fabric of entire societies, and mass-scale death through time.[2] For an in-depth review focusing on opium, it is advisable to read *DARK Classics in Chemical Neuroscience: Opium, a Historical Perspective*.[3] Opium produces several alkaloids, and one of opium's main metabolites is morphine (**1**) (*principium somniferum* meaning the sleep-making principle), which was isolated by the German pharmacist Friedrich Wilhelm Adam Sertürner in 1803.[2,4−6] Morphine's correct structure (**1**) was elucidated in 1925 by the Nobel laureate in chemistry Robert Robinson,[7] and by 1952, Gates and Tschudi synthesized morphine for the first time.[8] *DARK Classics in Chemical Neuroscience: Morphine* addresses its history, current synthesis and production routes, and pharmacology, among other features.[9] The efforts to elucidate morphine's structure (**1**) have contributed to the development and synthesis of many derivatives that are structurally much simpler and also have fewer side effects shown by opioid agonists, such as dependence, tolerance, euphoria, and excitement.

Charles Romley Alder Wright, an English chemist working at St. Mary's Hospital Medical School in London, synthesized several morphine esters in 1874, including 3,6-diacetylmorphine (**2**).[10] Wright introduced the two esters into morphine, boiling it with acetic anhydride for several hours. Then he dissolved the product in water, adding ammonia and shaking it up with ether. The ethereal solution obtained was shaken in the presence of hydrochloric acid, yielding a new potent morphine called diamorphine (3,6-diacetylmorphine).[10] Scheme 1 shows the reaction performed by Wright to synthesize the 3,6-diacetylmorphine from morphine, as well as the numerical assignment, cycle allocations, and chiral carbons of morphine.

After the synthesis of 3,6-diacetylmorphine, the physician F. M. Pierce tested the hydrochloride of this new derivative in a dog and a rabbit.[11,12] Nonetheless, results were discouraging and inconclusive, since no direct comparison with morphine was made, decreasing the utility for the drug; therefore, the studies were abandoned. In 1888, Dott and Stockman investigated 3,6-diacetylmorphine in frogs and rabbits,[13] observing a much more intense action and potency than morphine. Later, the physician Joseph von Mering corrobo-

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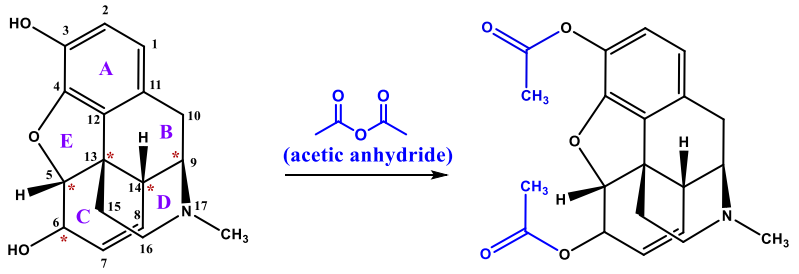
Scheme 1. Synthesis of 3,6-Diacetylmorphine (Heroin, 2) Performed by Wright Starting from Morphine (1)[10a]



Morphine (1) 3,6-Diacetylmorphine - Heroin - (2)

[a]Morphine's numerical assignment, cycle allocations, and chiral carbons (represented by asterisks) are also shown. In heroin's chemical structure (**2**), both acetyl groups are depicted in blue to highlight the structural difference from morphine (**1**).

rated the findings of Dott and Stockman and confirmed the pharmacological effects in dogs.[14]

In 1897, German pharmacist Felix Hoffmann from Friedrich Bayer & Co., one of the most powerful chemical companies in the world at that time, recorded in his laboratory notebook that he had synthesized 3,6-diacetylmorphine on August 21, 1897.[15] However, there has been controversy over who was in charge of Bayer & Co. at the point at which heroin was developed. In light of the date from Hoffman's notes about the 3,6-diacetylmorphine synthesis, de Ridder[15] and Schadewald[16] postulated that the instigator of the experiments to obtain the 3,6-diacetylmorphine in Bayer was Heinrich Dreser, who was appointed head of the pharmacology laboratory in 1897.[17] Nonetheless, Walter Sneader states that this is unlikely considering that Bayer & Co. had been under Arthur Eichengrün's supervision since 1895. Thus, the 3,6-diacetylmorphine synthesis performed by Hoffmann must have happened before Heinrich Dreser was appointed in late 1897.[17]

Once 3,6-diacetylmorphine was synthesized at Bayer & Co., Heinrich Dreser had the intention to test this derivative for the relief of human respiratory diseases; therefore, Dreser started to investigate the drug first in rabbits and then moved on to human beings. Dreser's findings revealed that 3,6-diacetylmorphine alleviated coughing, as well as was slowed and deepened respiration, concluding that this new agent was extremely valuable in clearing the lungs of excess phlegm.[17] Later, in 1898, Dreser reported his findings; however, in none of his published articles did he mention the contributions made by Wright, Pierce, Dott and Stockmann, Eichengrün, or Hoffmann in 3,6-diacetylmorphine development.[18,19]

By June 1898, Bayer registered 3,6-diacetylmorphine with the name heroin, although the original approved name was acetomorphine.[17] The word "heroin" was closely related to the German term *heros*, which refers to an ancient Greek hero.[17] Furthermore, the name's heroic overtones were also related to its anxiolytic effect and to the curing of tuberculosis, the great white plague.

When heroin was launched in September 1898, Bayer & Co. made no attempt to suggest that it had any clinical role other than to afford relief in respiratory disease (Figure 1). That is to say, the depressive effects on the respiratory system of heroin were dismissed or not considered, and it was not until 1911 that von Issekutz published evidence to show that Dreser had been mistaken.[20] Given this, Carmen Ferreiro questioned Dreser's scientific behavior and stressed in her book *Heroin (Drugs: The Straight Facts)*: "His was not a broad investigation

Figure 1. Bayer heroin commercial advertisement prescribed for cough relief. Reprinted from ref 17, The Lancet, Copyright 1998, with permission from Elsevier.

of the drug effects, but a clear example of a scientist setting his experiments to get the answer he is looking for. When Dreser started his tests on the Bayer employees, he narrowed his search to see the effects of the drug on the lungs and minimized the importance of any unwanted results."[6]

The 1911 edition of the *British Pharmaceutical Codex* observed that it was nearly as easy to become addicted to acetomorphine as to morphine. The cases of heroin addiction among people who used the drug did not take long to appear, especially as it was available over-the-counter, as well as having higher water solubility, which facilitated its administration by inhalation, smoking, swallowing, and injection. In 1924, an outright ban on prescribed heroin was declared in the United States,[21] as well as many other countries. However, heroin's formula (**2**) was so well-known that many illegal production operations quickly sprung up to satisfy the public's craving for the drug.[6]

While heroin can produce many benefits and relief, it also can torture and cause much damage to whomever chooses to use it and, above all, misuse it. As was previously mentioned, in ancient times, opium brought about greed, war, and death, among other misfortunes. Synthetic heroin, obtained mainly from morphine, which is extracted from opium, has also caused great harm to humanity. It has taken many lives, in spite of the good intentions in its development.

1.2. Pharmacolgy and Toxicology. The endogenous pain relief system is composed by the opioid receptors, which are denoted by the Greek letters μ (mu), δ (delta), and κ

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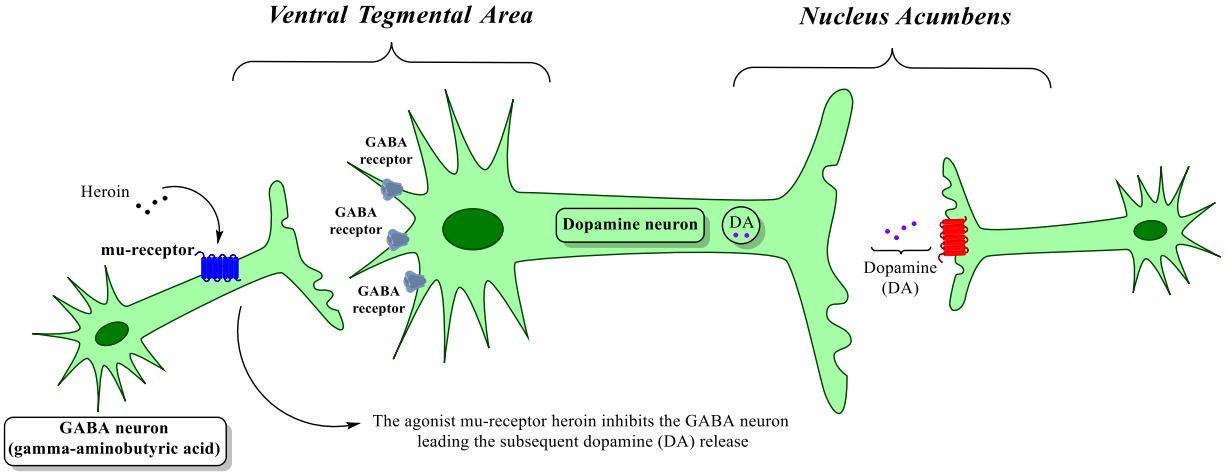

Figure 2. Heroin exerts its agonist action in the μ-opioid receptor of the GABA neurons at the ventral tegmental area (VTA) leading to inhibition of these neurons, which results in an increased release of the neurotransmitter dopamine (DA) in the nucleus accumbens.[34]

(kappa).[22] All opioid receptors have been well characterized,[23] belong to the G-protein coupled receptors family (GPCR), and are located in pre- and postsynaptic neurons.[24] The endogenous ligands for these receptors are peptides called endorphins, dynorphins, and enkephalins, such as Leu-enkephalin and Met-enkephalin, which were isolated in 1975.[25] The activation of opioid receptors produces analgesic effects but also creates euphoria and causes dependence, respiratory depression, drowsiness, dysphoria, hallucinations, and alteration of spatial perception.[26] The best-known intracellular actions when these receptors are activated correspond to the inhibition of neurotransmitter release due to the inhibition of adenylate cyclase, activation of K^+ conductance, and inhibition of Ca^{2+} conductance, as well as activation of phospholipase A_2/C and protein kinase C (PKC). Furthermore, the activation of opiate receptors exerts deferred actions on gene expression, which, under the abuse of agonists such as heroin, could lead to tolerance and dependence.

Heroin (3,6-diacetylmorphine, **2**) is a potent opioid agonist that is structurally modified to morphine in serum or tissues, binding predominantly to the μ-receptors. Likewise, just like morphine, heroin is also a weak agonist over the δ and κ opioid receptor subtypes.[27] Heroin's effects are more pronounced and are reached sooner than morphine's.[28] That is to say, it acts faster as an analgesic due its greater lipid solubility and subsequent penetration through the blood–brain barrier.[29]

Pure heroin hydrochloride is a white powder with a bitter taste. It can be diluted and administered by injection into veins or muscles or under the skin, but also it can be smoked or snorted.[30] Heroin is highly addictive. Once it has been consumed, it produces flushing of the skin, dry mouth, itching, and nausea but also causes intense euphoria due its easy access to the primitive mammalian reward system of the brain, where it is rapidly converted to morphine, stimulating the release of the neurotransmitter dopamine, which in turn causes a sensation of pleasure.[31] The positive reinforcement caused by heroin is achieved because dopamine is released from the terminals of the neurons that originate in the ventral tegmental area (VTA) and project forward to the nucleus accumbens, leaving the neurotransmitter on dopamine receptors of the nucleus accumbens neurons. Large amounts of dopamine become available due the suppression of the release γ-aminobutyric acid (GABA), therefore causing stimulation by disinhibition (Figure 2).[32,33]

It has been well demonstrated that heroin is 2–4 times more potent than morphine as an analgesic and faster in onset of action.[35,36] Administered orally, heroin is approximately 1.5 times more potent than morphine in controlling chronic pain in terminal cancer patients.[29] However, in mice experiments when heroin is administered by intracerebroventricular injection, it was shown to be less potent. Specifically, morphine was 2.5–3.1 times more potent than heroin and 6-acetylmorphine (**3**) (an active metabolite of heroin, see Scheme 2).[37] Inturrisi and colleagues demonstrated by *in vitro* receptor binding assays that heroin was much less potent compared to morphine in displacing the radioactive ligand from binding sites (IC_{50} = 53 nM for morphine and a IC_{50} = 483 nM for heroin). Also, other experiments have suggested that all heroin binding results could be attributed to a breakdown to 6-acetylmorpline (**3**) during the experiments and not to the heroin itself.[38] The data mentioned above establish that the potency of heroin is attributed to its pharmacokinetic properties, and that is the reason why its pharmacological target (μ-receptors) shows high IC_{50} values compared to morphine (see section 1.5).

Regarding new findings within the pharmacology of opioid receptors, it is noteworthy that in the recent years some efforts have been made to develop vaccines for addiction management and as potential agents for reducing overdose. Some attempts have been made by Bremer, Schlosburg, Matyas, Sulima and Ohia-Nwoko.[39−44] In 2019, Natori and colleagues[45] identified key considerations for the construction of a chemically contiguous heroin–fentanyl vaccine. A vaccine could stimulate an immune response, generating antibodies capable of binding the targeted drug. Thus, when a user consumes heroin, the antibodies circulating in the bloodstream can block the effects by forming a drug–antibody complex incapable of passing through the blood–brain barrier, which would be a promising result for heroin abuse treatment.[45]

With respect to conventional heroin management treatments, behavioral and pharmacological treatments are available, with both types of treatments being effective approaches when they are integrated.[46] Medications developed to treat heroin addiction work through the same morphine physiological receptors, but they are safer and less likely to

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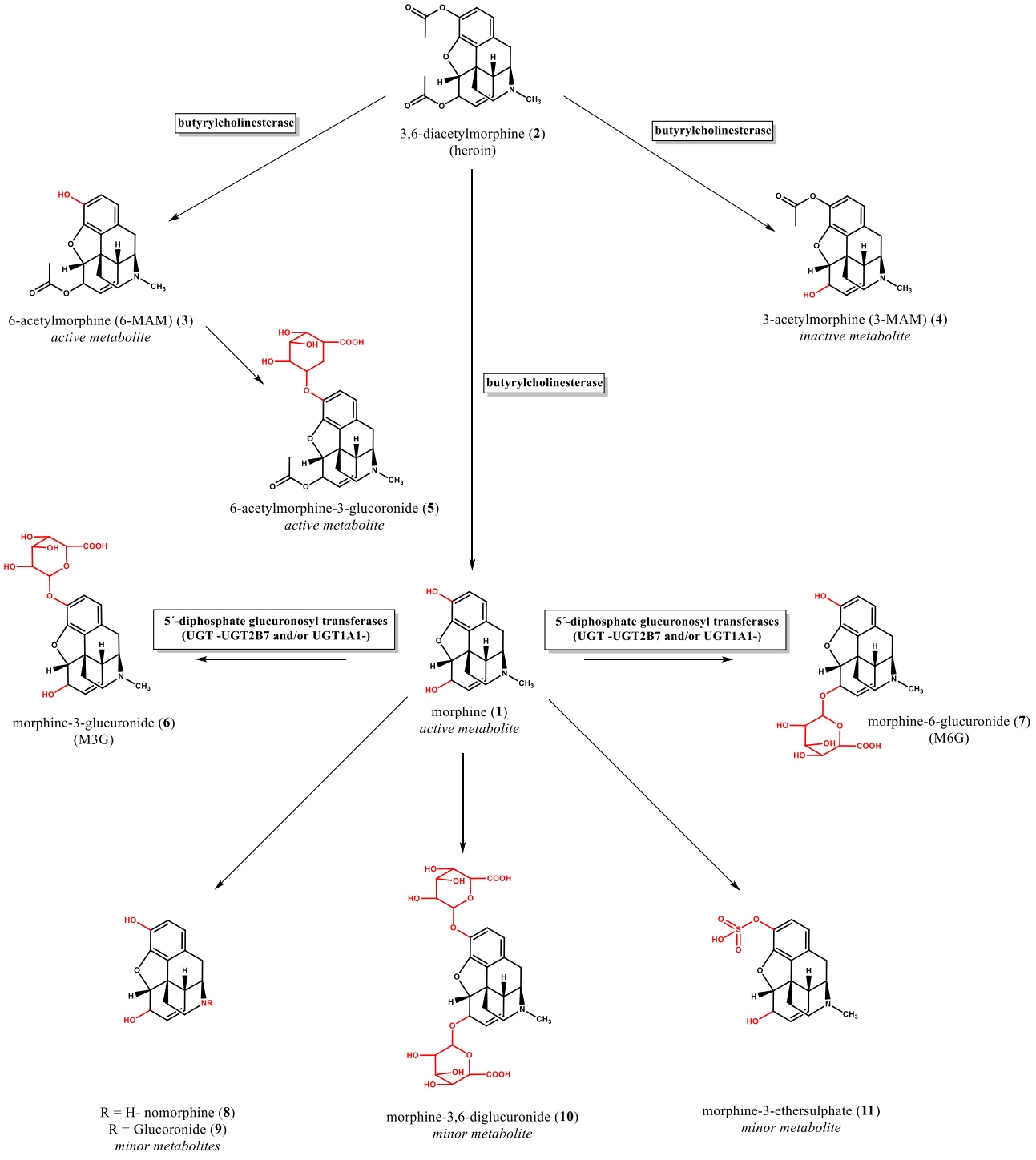
Scheme 2. Metabolic Transformation Routes of Heroin (2) and Metabolic Enzymes Involved[54−66]



produce the harmful behaviors. The pharmacological management of heroin could involve agonists, partial agonists, and antagonists.[24] The most common agents to treat patients who misuse heroin are the slow-acting opioid agonist methadone, the partial opioid agonist buprenorphine, which relieves drug cravings, and the opioid antagonist naltrexone, which has the ability to block the action of opioids without causing physical dependence.[24,25] A combination of buprenorphine and naloxone can also be administered to treat heroin addiction, where naloxone would prevent attempts to get "high" by injecting both drugs in association.[47] Finally, approaches such as contingency management and cognitive-behavioral therapy have been shown to effectively treat heroin addiction, especially when applied in concert with medications.

Concerning the toxicity of heroin and the harm caused by its forms of administration, it is well-known that it can be smoked, snorted, inhaled, or injected subcutaneously, intravenously, or intramuscularly. When it is snorted, nasal necrosis and septal perforation have been described. Furthermore, a mechanism mediated by antineutrophil cytoplasmic antibodies can possibly occur in many addicts.[48] Another problem that is gaining importance is the dramatic increase in the use of

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inhaled heroin.[49] This route of administration has serious health consequences, such as aggressive and toxic leukoencephalopathy, movement disorders, and hydrocephalus.[50] One of the hypotheses regarding the great brain toxicity that this form of consumption is causing is the concomitant inhalation of aluminum from the paper in which the heroin is heated.[51] The administration of tetrahydrobiopterin associated with coenzyme Q10 has been suggested as a treatment to slow down the deterioration of the brain in these cases.[52]

1.3. Drug Metabolism and Pharmacokinetics. The high lipophilicity and basic profile of heroin allow it to be well absorbed and distributed in bodily tissues. As mentioned above, it can be consumed or administrated via many routes, such as intravenous injection, intramuscular injection, smoking, snorting, and even orally. Regardless, it undergoes extensive first-pass metabolism.[53]

Heroin has a short half-life due its fast conversion to the active metabolites 6-acetylmorphine (**3**) (abbreviated as 6-MAM because it is sometimes called 6-monoacetylmorphine) and morphine, by the action of the esterase enzymes present in many body tissues (Scheme 2).[54−56] 6-MAM is an active metabolite due to the free hydroxyl phenolic group, which produces respiratory depressant activity.[57] Plasma butyrylcholinesterase is the primary enzyme responsible for the conversion of heroin to **3** and also for obtaining the inactive metabolite 3-acetylmorphine (**4**) (3-MAM). Both metabolites are submitted to conjugation by the action of uridine 5′-diphosphate glucuronosyl transferases (UGT), specifically the UGT2B7 and UGT1A1 subtypes,[58,59] to yield 6-acetylmorphine-3-glucuronide (**5**), as well as morphine-3- (**6**) and -6 glucuronide (**7**), with morphine-3-gluronide (**6**) (M3G) as the major metabolite.[60] Once heroin is completely transformed into morphine,[61] other minor routes can occur, such as deamination to produce normorphine (**8**)[62,63] and formation of normorphine-glucuronide (**9**),[63] morphine-3,6-diglucuronide (**10**), and morphine-3-ethersulfate (**11**).[64] All these metabolites are hydrophilic and subsequently excreted in urine and in minor amounts in bile.[63,65]

After intravenous heroin administration, about 70% of the total dose is recovered in urine, mainly as conjugated morphine (55%).[65,66] Indeed, Elliot and colleagues could recover 0.13% of unchanged heroin from the total dose after long-term continuous infusion.[65]

It is important to highlight that when heroin was administered orally or rectally, no heroin or **3** was detected in plasma.[67−69]

Considering what we previously discussed about the biotransformation of heroin and the fact that after an oral administration of this drug, morphine, but not heroin or **3**, is detected in blood, heroin would correspond to a prodrug.[29] In addition, taking into account that the affinity for μ-opioid receptors requires a free phenolic hydroxyl group in the 4,5-epoxymorphinan opioid structure, heroin cannot exhibit activity as an agonist, corroborating its prodrug character.[38,70]

The pharmacokinetic parameters of heroin remain a difficult issue to determine due to its short half-life in plasma leading to conversion of the aforementioned metabolites, rapid absorption, several routes of administration, and the concurrent use of other medications or illicit drugs from consumers and patients. Furthermore, in the metabolism and excretion of heroin and its metabolites, the livers and kidneys of the consumers are usually damaged, leading to imprecise information.[71]

Heroin is a useless drug for chronic administration because it is too short-acting and requires intravenous injection several times daily. This pharmacokinetic defect makes heroin use difficult to reconcile with a stable, productive lifestyle.[72]

Some reports have been written by Sawynok,[29] Kendall and Latter,[74] and Rook and colleagues[73] in order to review the pharmacokinetics data of heroin and its metabolites. Herein, we provide a summary of the most relevant information concerning the available pharmacokinetic data.

The intensity of the effects of heroin is related to the pharmacokinetic parameters of the drug, as well as to the different routes of administration. Inhalation and intranasal administration most resemble intravenous pharmacokinetics. Hence, intense euphoria (a warm and intensively pleasant sensation known as "flashes") can be felt after administration by these three routes.[75] Oral, rectal, or intramuscular administration routes are less intense and probably more suitable for the treatment of withdrawal symptoms. In this sense, the most well studied pharmacokinetic parameters are those from intravenous injection, inhalation, and intranasal consumption, although intramuscular reports are also available.[69,76,77]

Heroin's peak plasma concentration (C_{max}), which has been attributed to the intensity of the "flashes", is difficult to determine. In this sense, it is advisable to consider the C_{max} as an apparent parameter because it is subject to variation due to each patient's characteristics and sample timing with regard to dosing.

Rook and colleagues[73] reviewed the pharmacokinetic parameter of heroin peak plasma concentration (C_{max}) obtained from several published works.[67,69,76] The C_{max} values were obtained according to the route of administration of heroin: intravenously, intramuscularly, intranasal snorting, or inhalation of vapors after heating the drug. Table 1 summarizes the C_{max} in ng/mL values reported by Rook, Gyr, Girardin, and Skopp and their routes of administration.

Table 1. C_{max} Pharmacokinetic Parameter[a] of Heroin Administered by Different Routes

	source			
route of administration	Rook et al.[75]	Gyr et al.[67]	Girardin et al.[69]	Skopp et al.[76]
intravenous, bolus injection (ng/mL)	3119 ± 60	1530 ± 2270	3960 ± 1369	
intramuscular (ng/mL)			3293 ± 888	45.7
intranasal, inhalation of vapors (ng/mL)				0–44.3
inhalation, snorted (ng/mL)	685 ± 29			

[a]Mean ± SD or range.

As was expected, the highest peak plasma concentrations (C_{max}) are obtained when heroin is administered by bolus injection (3960 ± 1369 ng/mL, the highest reported value).[67,69,75] Girardin and colleagues reported a C_{max} value of 3293 ± 888 ng/mL in patients under heroin-assisted treatment via intramuscular administration at similar doses to bolus injection, which also represents a high serum concentration. In addition, Skopp and colleagues reported a low value of 45.7 ng/mL at low dose for the same administration route in patients who are regular heroin users

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after 3 days of abstinence.[76] The main difference between bolus injection and the intramuscular route is that in the latter, heroin circulates for a longer time due a sustained release of the drug into circulation. The C_{max} is quite low when the drug is administered via inhalation, as well as via the intranasal route.[75,76]

As heroin undergoes biotransformation, its elimination half-life ($t_{1/2}$), which indicates the time that heroin's concentration takes to be reduced by 50% in the plasma, is very low. Sawynok determined that following acute intravenous administration, heroin appears transiently in blood with a $t_{1/2}$ of about 3 min.[29] By infusion or bolus injection, the $t_{1/2}$ reported by many authors was about 3.0 min on average; thus, blood levels of heroin decline rapidly and cannot be detected after 10 min. When it was administered intramuscularly, via intranasal snorting, or by inhalation of the vapors after heating, the $t_{1/2}$ proved to be a little higher but not extremely different compared to intravenous or bolus injection. Indeed, the highest $t_{1/2}$ value was reported by Girardin and colleagues in intramuscular administration with a time of 7.8 ± 4.2 min, which is not of great significance.[69]

The clearance parameter in every administration route was shown to be variable depending on the dose, but it is reported to be higher when the drug is inhaled (1255 ± 1183 to 1939 ± 30 L/h at doses of 2.6−10.5 mg and 133−450 mg, respectively).[75,78] Rook and colleagues[73] expose an interesting finding, which indicates that the estimates of mean heroin clearance of 128−1939 L/h exceeded by far the hepatic and renal blood flow (on average 80 and 60 L/h, respectively, in a standard 70 kg human), indicating that heroin is metabolized primarily in peripheral tissue and in circulation. The high clearance of heroin from plasma is mainly due to the rapid elimination by esterases, spontaneous hydrolysis of heroin in the basic environment of body fluid, and extensive distribution.[75]

Based on the dosage, when heroin is sometimes used for assisted maintenance treatment in patients with severe dependence and where alternative treatments like methadone maintenance therapy have failed, the course of the treatment must consist of prescribed heroin doses based on individual titration, taking into account the clinical effects and the personal responses as the main dose defining indicators.[75] In patients responding to heroin-assisted treatment, prescription must be continued for several months or even years.[79]

However, the problem of tolerance is always present in heroin addiction treatment. This results in increased sensitivity to pain. A single heroin administration induces an enhanced pain sensitivity for several days.[80] An unlimited elevation of the dose to counteract tolerance is not possible. The estimated lethal dose of heroin is about 200 mg. Nonetheless, some addicted users can tolerate up to ten times this amount, but fatal tragedies have occurred after doses of 10 mg.[81] Trials of NMDA receptor antagonists have shown efficacy in reducing pain sensitivity.[82]

1.4. Chemical Properties and Synthesis. Heroin belongs to the opiate classification, sharing structural homology with opium alkaloids.[83] Heroin also emulates the activity of the body's natural pain relievers, α-endorphin, β-endorphin, γ-endorphin, Leu-enkephalin, and Met-enkephalin, among others.[34] As was shown in Scheme 1 in the case of morphine, heroin (specifically (5α,6α)-7,8-didehydro-4,5-epoxy-17-methylmorphinan-3,6-diol diacetate; CAS register number 561-27-3) also possesses a pentacyclic scaffold (cycles A, B, C, D, and E) but is diacetylated in the phenolic hydroxyl group at position 3 and in the secondary hydroxyl function at position 6 of the morphine framework.

Heroin is a lipophilic substance with a slightly lower partition coefficient (log P = 5.2) compared to morphine (log P = 6.0).[81] Due to the nitrogen atom in its piperidine ring, heroin exhibits basic properties (pK_a = 7.6),[84] allowing it to form salts with strong acids and making it a water-soluble derivative. Indeed, heroin is considerably more water-soluble than morphine (500 mg/mL for heroin hydrochloride compared with approximately 60 mg/mL for morphine sulfate and hydrochloride), making it able to be injected in smaller amounts as necessary.[28] As a matter of fact, since the pK_a is close to physiological pH (pH = 7.4), a fairly equal balance between the lipophilic nonionized form and the hydrophilic ionized form exists, resulting in rapid absorption after administration and good distribution (accessible for membrane transport).[75]

Two polymorphic forms have been reported for heroin's free base: rod-shaped oblique plates and needles with a melting point of 172−173 °C and sperulites with a melting point of 168 °C. However, the latter form is readily converted into the former.[85]

The straightforward way to synthesize heroin is to use morphine as a starting substrate (as Wright did), because its structure possesses five different chiral centers, making its total synthesis difficult and expensive. Isolation from the latex of unripe capsules of the poppy is currently the most practical source to obtain morphine as a starting material instead of total chemical synthesis.

1.4.1. Heroin Semisynthesis from the Natural Source. From the poppy plant biosynthesis of morphine, which has been very well described and reviewed by Labanca and colleagues and by Schaefer,[1,26] the raw material could be taken in order to obtain heroin with the precise stereochemistry.

As Chambers and colleagues have reported,[86] the procedure above-described for heroin's semisynthesis is illegal, and the Counter-Narcotics Police of Afghanistan (CNPA) offered German authorities the opportunity to observe and document the whole process.[87]

The method starts with the crushing and stirring of the raw opium in hot water and CaO. Then, NH_4Cl is added, and the precipitate is filtered, obtaining morphine as a free base. The solid is treated with acetic anhydride to achieve morphine diacetylation (heroin). The subsequent addition of Na_2CO_3 makes it possible to obtain heroin as a free base. The solid is then dissolved with HCl and filtered with activated carbon. The supernatant is neutralized with NH_3, and the heroin solid is filtered, repeating the process once more. Finally, the suspension of the solid in HCl and subsequent evaporation of the solvent generates heroin hydrochloride.

The method described above reports 11% yield of morphine extraction in terms of the weight of the raw opium, as well as a 6% yield of white heroin hydrochloride, also in terms of the weight of the raw opium.[87]

Some authors have used alternative modifications to the method reported here, such as Odell and others who have used trifluoroacetic anhydride and acetic acid as reagents.[88] Karlsen and colleagues have used four equivalents of acetyl chloride labeled with ^{13}C isotope ([^{13}C]acetyl chloride) as the esterification reagent, aiming to obtain ^{13}C-heroin and ^{13}C-heroin metabolites, providing references for the quantification of drug content in biological samples.[89]

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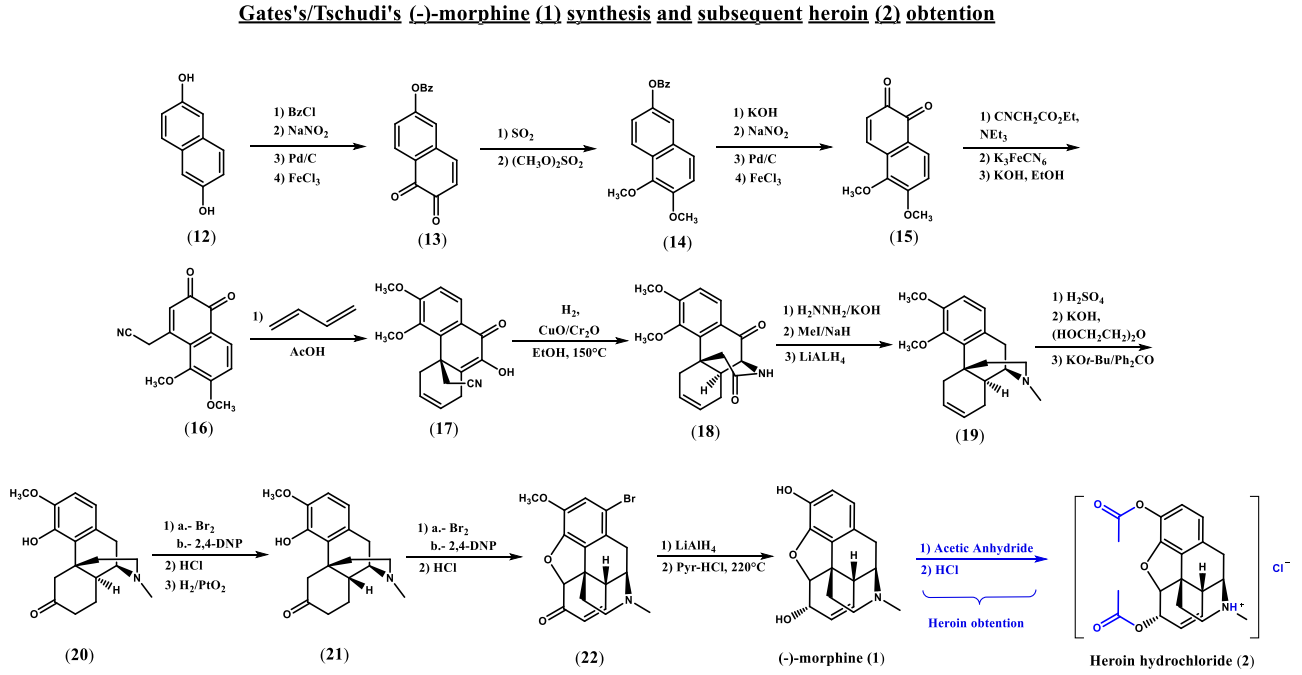
Scheme 3. Gates and Tschudi's Strategy[8] That Yields (−)-Morphine (1)[a]



[a]Subsequently, (−)-morphine (**1**) can be acetylated with acetic anhydride and hydrochloric acid in order to obtain heroin (**2**) hydrochloride.[8,102]

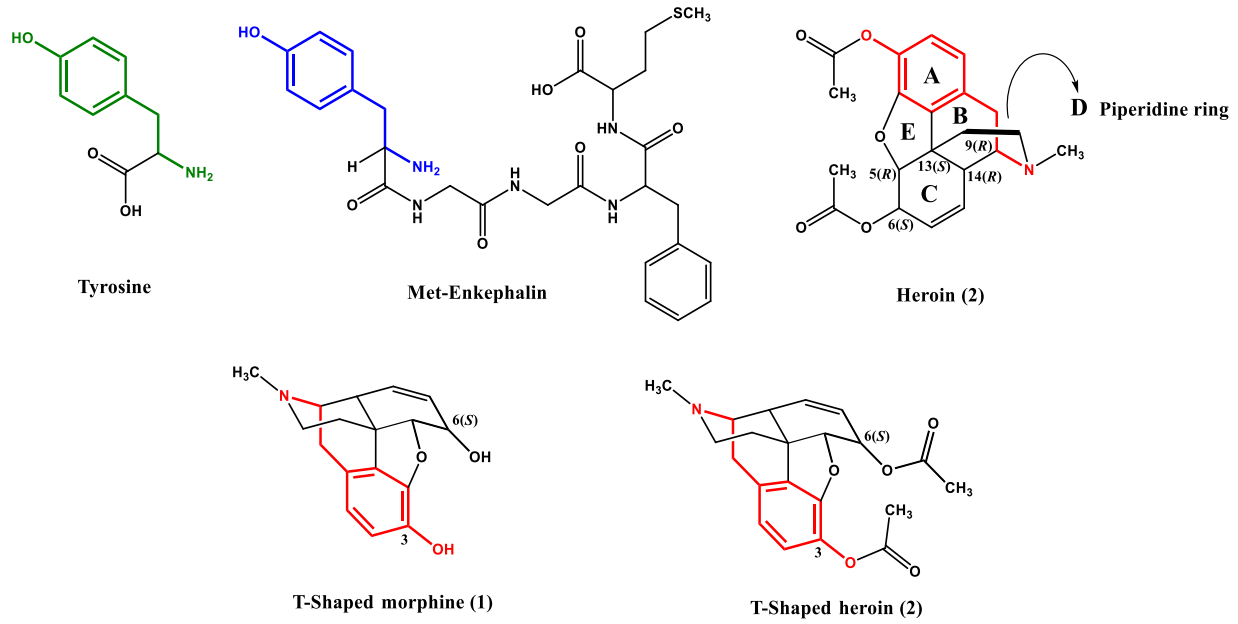


Figure 3. Tyrosine scaffold is the structural commonality among many endogenous opioid agonists, such as Met-enkephalin, and the exogenous opioid agonist heroin (**2**). T-Shaped structures of (−)-morphine (**1**) and (−)-heroin (**2**).[26]

Taken together, this discussion shows that the synthesis of heroin from morphine as a starting reagent represents a useful method.

1.4.2. Complete Heroin Synthesis. Complete heroin synthesis can be achieved by obtaining the morphine scaffold and subsequent acetylation. Since total morphine synthesis was developed by Gates and Tschudi, which commences with 2,6-dihydroxynaphthalene (**12**),[8] several efforts have been made to improve the synthetic conditions to obtain this analgesic. Since this review involves heroin, we will not emphasize or deepen the distinguished and rich morphine synthetic methods that have been developed to date. A great deal of the extant literature has reviewed morphine and 4,5-epoxymorphinan alkaloids synthesis,[86,90−94] and it is undeniable that many of the released racemic or enantioselective synthetic routes are elegant and well thought-out. Some of the most well-known and outstanding morphine synthetic contributions, in addition to Gates and Tschudi's synthetic procedure, are those reported by Elad,[95] Morrison,[96] Kametani,[97] Lie,[98] Rice,[92] Evans,[99] Fuchs,[100] Parker,[101] Overman (first enantioselective synthesis that did not contain resolution),[102] White (first enantioselective (+)-morphine),[103] Trost,[104] Taber,[105] Fukuyama (who

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also informed the enantioselective synthesis of (−)-morphine in 2017),[106,107] Stork,[108] Gaunt,[109] Smith,[110] and Zhang,[111] among others. Moreover, in 2018, *DARK Classics in Chemical Neuroscience: Morphine*[9] emphasized the total synthesis reported by Rice, indicating that it corresponds to the most practical process for generating bulk quantities of morphine from nonbiologic starting material. Scheme 3 depicts the precedent established by Gates and Tschudi of the classic first morphine synthesis method and the next acetylation and hydrochloride steps with acetic anhydride and HCl to obtain heroin hydrochloride.

Due the relatively low overall yields, the large number of reaction steps, the high costs of the routes, their complexity, and the relative easy accessibility of morphine from natural sources, all methods mentioned above, including the Gates−Tschudi synthesis, are not of industrial interest. Nevertheless, every year, novel and effective synthetic methods are studied in order to obtain morphine and heroin, contributing to the organic synthesis discipline.

1.5. Structure−Activity Relationship. The amino acid tyrosine represents an important core for the agonist character of endogenous and exogenous opioids and opiates, since it seems that opioid receptors can recognize this framework. The residue of Tyr, which also is the starting material for benzylisoquinoline alkaloids,[112−114] can be detected in the Met-enkephalin structure and the morphine structure (**1**) and masked in the heroin structure (**2**) (Figure 3). It is clear that the phenolic group and the basic amine group linked by an ethyl linkage play a key role in the μ-opioid receptor affinity.

Opioid agonists and antagonists are enantioselective, and therefore only the optical isomer (−)-heroin is recognized at the binding site of the μ-opioid receptor. For example, in (−)-morphine, the active enantiomer (−)-heroin contains five chiral centers with absolute stereochemistry 5(*R*), 6(*S*), 9(*R*), 13(*S*), and 14(*R*).[34] The ring that exhibits the double bond (ring C) is forced into a pseudoboat conformation due to the presence of the restraining furan ring and the alkene itself.

The 13(*S*) and 14(*R*) chiral centers are very important because they force the heroin to a T-shaped conformation. Both stereocenters allow the B/C ring fusion in heroin to be *cis*, placing rings B and C at right angles to one another. Because the absolute configuration at C-14 and C-13 influences molecular conformation and the degree of fit at the μ-receptor, it is not surprising that the degree of fit also impacts biological activity.[34] On the other hand, rings A, B, and E are in a vertical arrangement, and rings C/D possess a *trans* disposition allowing them into a horizontal plane. Crystal structure analysis and quantum mechanical calculations confirm the T-shape of (−)-morphine, which can be extrapolated to (−)-heroin.[26]

The tertiary amine group in piperidine ring D is of great importance in heroin activity. The tertiary amine must not be quaternized, since a quaternary amine would not have the ability to pass through the blood−brain barrier, and therefore, it would not exert its action. Furthermore, the tertiary amine has basic properties, and its basicity is an essential feature because at physiological pH (7.4), heroin is extensively protonated, promoting an electrostatic bond between the cationic protonated amino group and an aspartate residue conserved in all G-protein-coupled receptors (Asp147).[115]

The methyl group over the nitrogen atom in the piperidine ring D promotes hydrophobic interactions in the μ-opioid receptor's active site, and methyl lipophilicity contributes to increasing the passage through the blood−brain barrier, as well. The N-substituent comprises the "agonist or antagonist message".[9] In this sense, the methyl group at N-17 of piperidine ring D, due its small size and low steric hindrance, occupies an axial position, leading to an agonist response of heroin.[116] On the other hand, long and bulky chemical substituents containing electron-donating or high electron density groups occupy an equatorial position at N-17 (e.g phenylethyl), shifting the activity from agonist to antagonist, as long substituents interact with aspartate, methionine, tyrosine, isoleucine, and glycine.[115]

The phenolic hydroxyl is essential for the activity; hence, if this hydroxyl group is functionalized, the biological activity decreases. When the hydroxyl group at position 6 of (−)-morphine is modified, the pharmacokinetic behavior of the new opioid derivative (heroin) is altered. Moreover, if it is completely removed, the lipophilicity increases, and the eventual new derivative could cross the blood−brain barrier easily.[4]

Heroin has a relatively low affinity for μ-opioid receptors because both hydroxyl groups are protected with acetyl groups. The lack of a free phenolic hydroxyl group in heroin is consistent with the data obtained from codeine (**23**), which also exhibits low binding affinity for μ-opioid receptors.[117] However, it is well-known that the acetyl groups ease the crossing through biological membranes and enhance the penetration of the blood−brain barrier, as well as increasing the analgesic power, as was detailed in section 1.2. It has been suggested that heroin could be viewed as a lipid-soluble prodrug that determines the distribution of its active metabolites through the action of serum and tissue esterases, such as plasma butyrylcholinesterase, which generates the active metabolites 6-monoacetylmorphine (**3**) (6-MAM) and morphine, as well (see section 1.3).[61] The combination of rapid penetration into the brain after an intravenous dose and rapid conversion to active μ-agonist metabolites provides the euphoric rush that users who inject this drug describe.

1.6. Social, Health, and Industrial Aspects. Drug crises reflect two known and recurrent facts: First, a drug appears to be more addictive in one society or period than in others,[118] and second, drug abuse tends to be constructed (given and perceived) in the form of epidemics or cycles, with clear ups and downs, rather than gradual or constant trends. This has obvious demographic, cultural, and even economic reasons. In the case of heroin, the first epidemic consumption of this drug occurred after the Second World War. However, the abuse of this substance has occurred since the end of the 19th century. According to the United Nations (UN), more than 30 million people around the world use heroin every year, which represents a significant fraction of opioid users.[119] Heroin consumption over the last 20 years has increased by more than 70%,[120] and at the end of 2015, a new heroin consumption epidemic broke out in the United States.[121] The causes of heroin addiction have been classified variously, with scholars citing psychological, pharmacological, genetic, sociological, social protest, poverty, and family causes, among others, all of which have been extensively reviewed.[122−125]

It is estimated that more than 66% of the 63 000 overdose deaths that occur each year in the US are due to the use of opiates, including heroin.[126,127] The World Health Organization (WHO) estimates that more than 69 000 people die each year from opioid overdose worldwide.[128] The cause of death is due to severe heroin-induced respiratory depres-

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sion.[129] Naloxone, an *N*-allyl synthetic derivative of oxymorphone, is used to reverse these effects and is an effective agent to treat cardiovascular and respiratory depression associated with narcotic and possibly some non-narcotic overdoses.[130] However, naloxone alone may be insufficient in some cases to revive the victim, and cardiopulmonary resuscitation (CPR), especially rescue breathing, may also be needed. Complications following resuscitation from heroin overdose may frequently need in-hospital care.[131] Other alternatives to treat addiction and reverse the effects of heroin abuse are combined buprenorphine/naloxone agents,[47] as well as the use of methadone.[132] A meta-analysis study found that supervised injectable heroin is an effective way to treat its dependence, refractory to standard treatment.[133] This strategy may be less safe than oral methadone maintenance treatment and therefore requires more clinical attention to manage greater safety issues. However, this intensive intervention is only for patients who previously were unresponsive to conventional treatment.

It should be noted that these therapies for the containment of heroin addiction are not without serious adverse effects for the patient's health. For example, methadone has been associated with QT prolongation in the electrocardiogram and also with higher syncope reports in individuals misusing heroin.[134] Moreover, deaths from both methadone and buprenorphine overdoses have been reported.[135] Losses of tolerance and the concomitant use of alcohol and other central nervous system (CNS) depressants play a major role in fatalities.

Among social and physiological problems associated with heroin abuse is concomitant use with cocaine (a mixture named "speedball"). Heroin alone can reduce anxiety and cause somnolence, and to counterbalance the soporific effects of the drug, it is sometimes mixed with cocaine.[136] There is evidence that the subjective effects of cocaine are boosted when heroin is also consumed. The use of cocaine by heroin-dependent individuals or by patients on methadone or buprenorphine maintenance treatment is substantial and has negative consequences on health, social adjustment, and the outcome of opioid addiction treatment.[137] The pharmacological reasons for cocaine use in opioid-dependent individuals, however, are poorly understood, and little is known about the patterns of concomitant heroin and cocaine use.[136] Heroin is also consumed in association with other drugs—as varied as alcohol, marijuana, LSD, other psychedelics, sedatives, tranquilizers, opioids, and crack. These associations and their effects have been extensively reviewed in the literature.[138−140]

Other health problems associated with heroin use are the development of asthma, reduction in lung function,[141] nephropathy,[142] development of bipolar disorder,[143] masking of myocardial damage in concomitant use with cocaine,[144] and a reduction in pain tolerance. Management of pain therapy in patients addicted to heroin and cocaine is complex, and the use of strong opioids should be avoided.[145]

Among the main social consequences for individuals misusing heroin, discrimination is one of the most important, because their drug consumption is associated with the presence of diseases such as AIDS[146] and hepatitis C,[147] as well as criminal behavior.[148] Moreover, the mental consequences, especially the damage to the user's ability to concentrate,[149] make it more difficult for users to return to their jobs. Regarding sexuality and affectivity, individuals who are misusing heroin with sexual partners suffer great harm, such as damage to reproductive function (reduction of testosterone in men),[150] as well as to normal sexual relations.[151,152]

A final public health problem has to do with the management of heroin addiction and therapeutic and pharmacological treatment.[153] The medical curriculum in the United States (US) does not invest enough time in addiction education; thus, many doctors lack the necessary knowledge for the management of opioid abuse.[154] This is the reason why medical researchers are calling for the inclusion of this growing problem in medical schools.[155]

Manufacturing, possessing, or selling heroin in the US and the United Kingdom (UK) is illegal. However, under the name of diamorphine (diamorphine hydrochloride), heroin can be prescribed legally in the UK, and it is manufactured by Wockhardt Pharmaceuticals.[156] Some countries, such as Switzerland, the Netherlands, Germany, Spain, Denmark, Belgium, Canada, and Luxembourg, have approved its use in particular cases of treatment of addicts who are resistant to conventional therapies (heroin-assisted treatment programs).[157]

Ninety-five percent of illegal heroin production comes from three sources: the Afghanistan network,[158] the Golden Triangle network (Myanmar, Laos, and Thailand),[159] and the Mexico−Colombia network.[160] To identify the provenance of a certain heroin sample, techniques based on the detection of strontium[161] have been developed, as well as detection for porphyroxine, a trace alkaloid in opium.[162] For the rapid detection of heroin in street samples, strategies using square wave voltammetry at bare graphite electrodes have been proposed.[163] Another novel strategy that has been recently reported for the detection of heroin consumption is a noninvasive method based on fingerprint detection.[164] The method consists of printing the person's fingerprints on filter paper, from which the biological fluid is extracted and subsequently identified through ultrahigh-performance liquid chromatography and mass spectrometry (UHPLC-MS). This method has been reported to give 0% false positives in healthy patients and a 100% detection rate in individuals misusing heroin.

In addition to the social harm of illegal heroin trafficking, the informal manufacture of this drug carries additional health problems due to the use of adulterants, diluents, and byproducts generated in the manufacturing process.[53] Knowing the most common type of people involved in the illegal production of heroin would allow for a more complete understanding of the adverse effects and more appropriate therapy for patients. According to studies, the addition of adulterants generally occurs at high levels of distribution of the drug, to achieve a greater economic benefit, but it is harmful to the consumer's health. Some compounds used in heroin adulteration include acetaminophen, acetylsalicylic acid, and caffeine.[165] The injectable route was the most common form of use until the discovery of AIDS.[166] To administer via injection, the heroin product is dissolved in heated water in a teaspoon, and after adding a few drops of lemon juice or vinegar, it is introduced into the syringe to be injected, reaching the brain in 15 or 30 s.[75]

Regarding the global market of illicit heroin, it is estimated that trafficking moves more than $50 billion of heroin per year.[167] For comparison, the estimated cost for the health, labor, and prison systems in the US is estimated to be $51.2 billion per year.[168]

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Afghanistan is considered a global hub for heroin production and trafficking (see section 1.4.1).[169,170] The opium poppy crop that is exported from Afghanistan crosses into neighboring Pakistan, Iran, Tajikistan, Uzbekistan, and Turkmenistan. It is estimated that 50% of the opium produced in Afghanistan is consumed in the country and its neighboring countries.[171] According to the UN Drug Control Program (UNDCP) and Europol officials, drug traffickers use three main routes to export the drugs out of Afghanistan: the northern route, the Karachi, Pakistan, route, and the Iran/Turkey truck route.[171] A large portion of Afghanistan's raw opium is converted into heroin in clandestine laboratories in Afghanistan and its bordering countries and shipped to markets in Europe, Asia, and the Middle East through Iran, Pakistan, and Central Asia. It is estimated that 50% of the heroin produced is exported through the northern route.[171] Therefore, Afghan heroin is widely exported to Russia, Ukraine, and all other former Soviet countries. The latter countries have a traditional behavior of "cooking" their own homemade drugs. When Afghanistan started to export heroin to Russia, this served as a replacement for homemade drugs for a while. However, knowing that it was less expensive to obtain codeine (**23**), many drug users with limited funds and resources turned to krokodil (desomorphine (**24**)), an even more harmful drug that is also a homemade injectable opioid.[172] This turns heroin, to a certain extent, into a sort of culprit for the impact of desomorphine use. Therefore, heroin causes many problems that have a high social impact, and prevention, treatment, and cost reduction strategies associated with addiction should be investigated.

2. DESOMORPHINE (KROKODIL)

2.1. History and Geographical Distribution of Krokodil Use. Desomorphine (dihydrodesoxymorphine-D) is a synthetic morphine analog, first described in the US in 1933 by the American chemist Lyndon Frederick Small and patented one year later.[173−175] It was originally synthesized as a more powerful morphine derivative with fewer side effects and, most importantly, improved tolerance and addictive properties. However, expectations were not met, and its use was soon outlawed (1936) in the US.[176] Although its use was banned earlier in the US, desomorphine was introduced and used in Switzerland in 1940 by Hoffman-LaRoche under the commercial name of Permonid, mainly for the postoperative treatment of severe pain.[177] The drug was withdrawn from the market in 1952, although its production continued until 1981 due to the idiosyncratic analgesic requirements of a single patient in Bern.[178,179] In 1961 in the international Single Convention on Narcotic Drugs of the United Nations, desomorphine was listed as a controlled substance.[177,180] To date, desomorphine is controlled as a Schedule I substance under the Controlled Substances Act. This means (a) the drug has a high potential for abuse, (b) the drug has no currently accepted medical use in treatment in the US, and (c) there is a lack of accepted safety for its use under medical supervision.[181] At the beginning of the 21st century, the drug reappeared in Russia (particularly in Siberia) in the context of the use of a homemade drug called krokodil, with the first confirmed report of its use in 2004, although there are unconfirmed earlier reports.[178,182−185] An epidemic increase of its use among Russian addicts has been observed since then. For example, in 2005, the Russian antinarcotics agency reported only isolated instances of the drug; but in 2011, the agency confiscated 65 million doses, a 23-fold increase from two years earlier.[186] At its peak in 2011, krokodil use had expanded to as many as one million users in Russia.[186] The drug generates a powerful opiate-like effect with a fast and short-lasting action, being up to ten times more potent than morphine.[187,188] Because of this effect, it is known in Russia as *Russian magic*.[184] Additionally, because it is cheaper than heroin, it is referred to as the "drug of the poor" in Russia.[187,189] However, the homemade injectable drug mixture is more commonly known on the streets as krokodil or crocodile. This nickname refers both to α-chlorocodide (**25**), a synthetic intermediate in the traditional synthesis of the drug, and to the notable skin injuries reported on users, such as large areas of scale-like, discolored, and ulcerated skin, resembling that of a crocodile.[172,177,190,191] There are several reasons to explain its reappearance and the dramatic increase in its use. First, a drop in the production of heroin imported from Afghanistan led to an increase in its price and a decrease in its availability.[172,184] This was because in the 2007−2010 period, the cultivation and potential production of opium in Afghanistan decreased steadily for the three consecutive years.[192] Additionally, in 2010, production fell by around 48%, apparently due to a fungal disease that affected opium plants at a late stage of plant development.[172] In addition, an increase in police seizures of drugs and government bans also hampered access to opium and heroin.[172,193,194] Furthermore, there was an increase in poverty levels in Russia since the start of the 2008 economic crisis. As a consequence, homemade and pharmacy drugs became significantly cheaper than heroin or other imported drugs and thus became popular among the poorest segment of the drug-using population.[172,189] The second factor in its popularity is the ease of availability of krokodil, resulting from a low-cost, simple, and fast production process starting from codeine that can be accomplished at home.[178] At the end of 2011, 100 000 of the 2.5 million people in Russia with substance dependence appeared to be addicted to krokodil.[178] Due to these dramatic developments, it was determined that in Russia, starting on June 1, 2012, codeine-containing tablets would no longer be over-the-counter medications and would only be available in pharmacies under medical prescription.[178] However, codeine is still available on the black market.[195] Since its appearance in Russia, the drug quickly spread to other neighboring former Soviet republics, especially Ukraine (which had around 20 000 cases in 2011),[172,196] as well as Georgia,[197−200] Armenia,[201,202] and Kazakhstan.[172,203] The first western European country to report cases of krokodil use was Germany in 2011.[178] Subsequently, cases (both confirmed and suspected) have been reported in other European countries, such as France,[204] Italy,[205] Norway,[206] Spain,[207] and Poland,[208,209] with a significant part of them imported from Eastern Europe through immigrants from former Soviet republics.[204] It is noteworthy that various reviews mention cases reported in the Czech Republic, Sweden, Belgium, and Portugal,[190,208,210,211] but reliable information about these cases could not be found by the authors of the current review. In North America, some cases have been reported in both Canada[212,213] and the US[186,191,214−218] (in newspapers and scientific articles), most of which are heavily based on patient history and the admission of krokodil use by drug users.[219] However, the absence of confirmed toxicological results make their veracity doubtful, as some authors have pointed out.[220,221] As a result, the true prevalence of krokodil use in the US is relatively unknown.[180,219] To date, there are no

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reliable reports of the use of the drug in Mexico or Central or South America.

2.2. Chemical Properties and Synthesis. Desomorphine (Figure 4) is the common name for 4,5-α-epoxy-17-methylmorphinan-3-ol (dihydrodesoxymorphine-D; CAS Registry Number 427-00-9). It is a semisynthetic opioid that is structurally related to the 4,5-epoxymorphinan class of opioids: morphine, heroin, and codeine. It is synthetically derived from the latter drug in homemade production and produces opioid-like effects.[190]

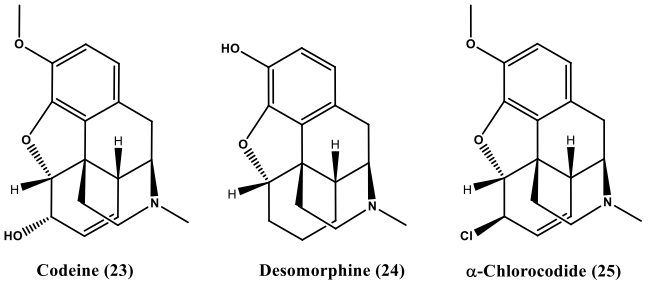
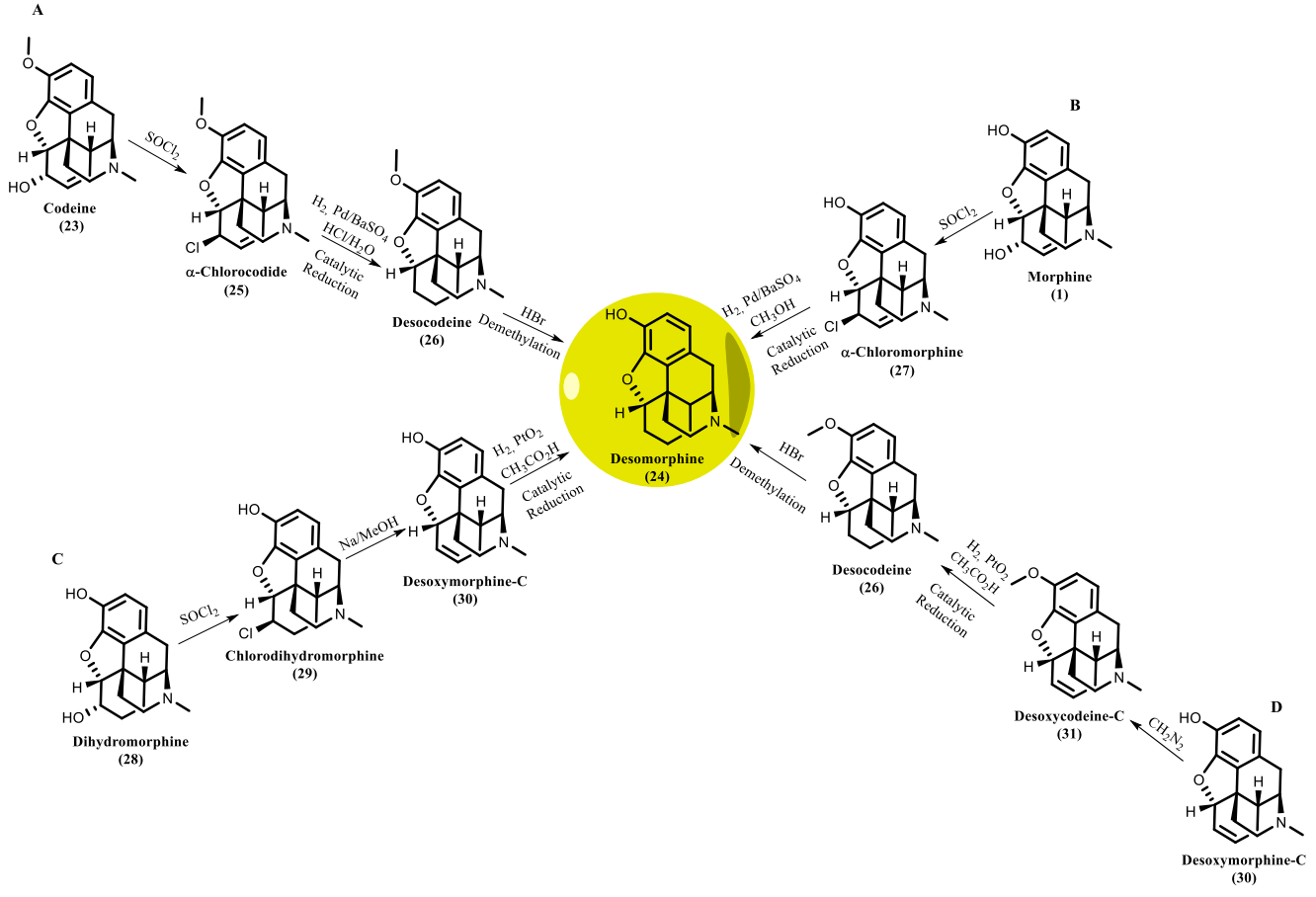


Figure 4. Structure of desomorphine and the structurally related 4,5-epoxymorphinans codeine and α-chlorocodide.

Desomorphine is a colorless, crystalline alkaloid (pK_a value of 9.69) that is solid at room temperature.[177,190] The compound has a molecular formula of $C_{17}H_{21}NO_2$, a molecular weight of 271.35 g/mol, a melting point of 188−189 °C, and a specific rotation in absolute methanol of $[\alpha]_D^{28}$ −76.8° (c = 1.614).[173,177,190] It is soluble in organic polar solvents such as acetone, ethyl acetate, and alcohols. The free base of the compound is scarcely soluble in water at room temperature (solubility of 1.425 mg/L). However, the salt forms of desomorphine are freely soluble in water.[177,190] The first synthesis of desomorphine was described by Lyndon Frederick Small in 1933[174,175] and in a patent in 1934.[173] In his reports, Small describes four different methods to obtain desomorphine (Scheme 4). These synthetic pathways obtained desomorphine through a common catalytic hydrogenation step starting from different precursors in each case: (A) by catalytic hydrogenation of the halogenocodides, followed by demethylation;[173] (B) by catalytic hydrogenation of the halogenomorphides;[175] (C) by catalytic hydrogenation of desoxymorphine-C (**30**);[174,175] (D) a slight modification of method C.[173,222]

In these reports, Small found that in the preparation of the product, the first and second methods constitute the most feasible and economical routes, while the third and fourth are more difficult and give lower yields of desomorphine.[173] The conditions of the catalytic reduction, that is, using other metal catalysts in different organic solvents or acid solutions, as well as the amounts of catalysts and solvent, can be modified without changing results appreciably.[173] Method A (Scheme 4) represents the traditional synthetic pathway from codeine to desomorphine and, with modifications, is the route used in the home production of krokodil (Scheme 4).[172,190,223,224] On the other hand, a modification of this process has been reported by Srimurugan that achieves a higher yield and purity without obtaining impurities or byproducts (Scheme 5).[225]

Scheme 4. Synthetic Pathways for Desomorphine Described by Small[173−175]



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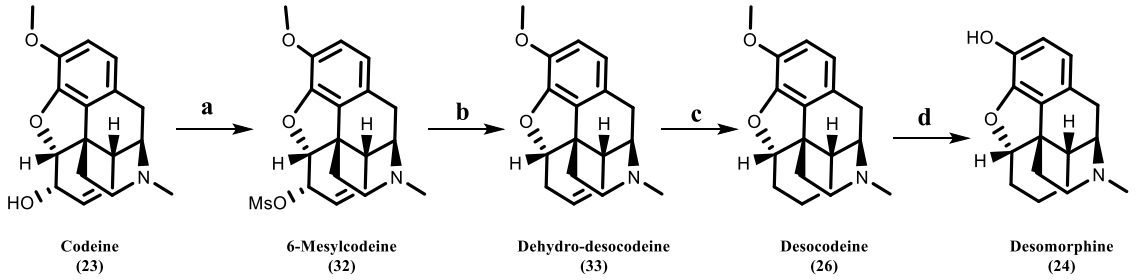
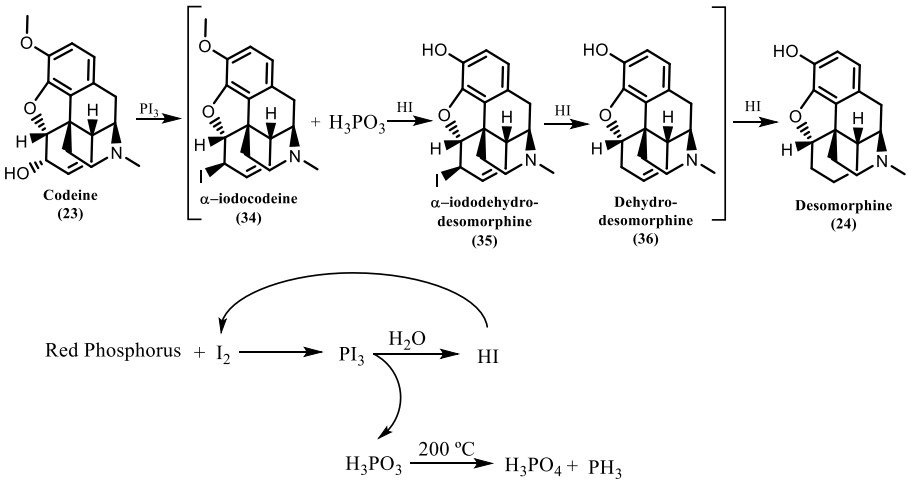
Scheme 5. Synthesis of Desomorphine Reported by Srimurugan[225a]



[a]Conditions: (a) Et_3N, MsCl, CH_2Cl_2, 0 °C, 1 h, 95%; (b) $LiAlH_4$, THF, RT, 1 h, 93%; (c) PtO_2/H_2 (4 bar), MeOH, 1 h, 99%; (d) BBr_3, CH_2Cl_2, RT, 30 min, 43%.

Scheme 6. Mechanism of Formation of Desomorphine from Codeine



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For this synthesis, a codeine free base was generated from codeine phosphate, followed by a reaction with mesyl chloride, affording the corresponding mesylate **32** in excellent yield. The treatment of 6-mesylcodeine (**32**) with 2 equiv of $LiAlH_4$ in THF at room temperature for a short time afforded dehydrodesocodeine (**33**) in high yield. In this way, the 6-hydroxy group of codeine was deoxygenated effectively by converting it into a better leaving group and then displacing it with hydride. Catalytic reduction of dehydrodesocodeine (**33**) over H_2/PtO_2 afforded highly pure desocodeine (**26**) in quantitative yield. The final demethylation of desocodeine (**26**) was performed through an efficient protocol using 1.5 equiv of BBr_3, yielding desomorphine in acceptable yield and very high purity. The overall yield of the synthesis was 38%, and the authors claim that no column purification was required in any step.[225]

As mentioned previously, the catalytic hydrogenation of the halogenocodides, followed by demethylation (method A, Scheme 4), is the synthetic pathway traditionally used in the homemade production of desomorphine (the main active opioid in krokodil), though with some modifications in comparison to the method reported by Small.[172,190,223,224] This homemade process of krokodil production usually employs a nonstandardized technique requiring easily affordable and highly toxic chemical agents and very basic laboratory conditions, generating a synthesis product that is not purified for later use by drug users.[177,186] The raw materials used in this homemade synthesis are typically codeine as the starting opioid precursor, gasoline, hydrochloric acid, alkali solutions, red phosphorus, and iodine.[172,178,186,210,223,224] The overall process involves two simple and clearly differentiated stages:

(a) Extraction of codeine: In this step, codeine is extracted from commercial tablets, after crushing, using gasoline and a strong alkali to obtain the free base. Subsequently, the codeine free base is mixed with acid to form the corresponding hydrochloride. The aqueous solution containing the codeine hydrochloride may be directly used in the subsequent step, or alternatively, the drug may be extracted or dried.[172,224] Although the extraction process can be further repeated, the drug can be used directly in the next step.

(b) Catalytic reduction of codeine to desomorphine: This homemade synthesis of desomorphine is nearly identical to the Nagai process of amphetamine synthesis from ephedrine or pseudoephedrine.[226,227] The key step in this process is the catalytic reduction of the halogenocodide, which is performed using hydriodic acid (HI) formed *in situ* by the reaction between red phosphorus and iodine as the catalyst for the reduction reaction to obtain the opioid derivative.[177,190,223,224,228] A mechanism for this reaction was proposed by Alves and colleagues[223] (Scheme 6), in which codeine reacts with phosphorus triiodide (PI_3), forming α-iodocodeine (**34**) through an S_N2 mechanism. PI_3 would come from the reaction of red phosphorus and iodine.[228,229] Subsequently, PI_3 is converted to HI by reaction with water. HI concomitantly contributes to the methyl ether

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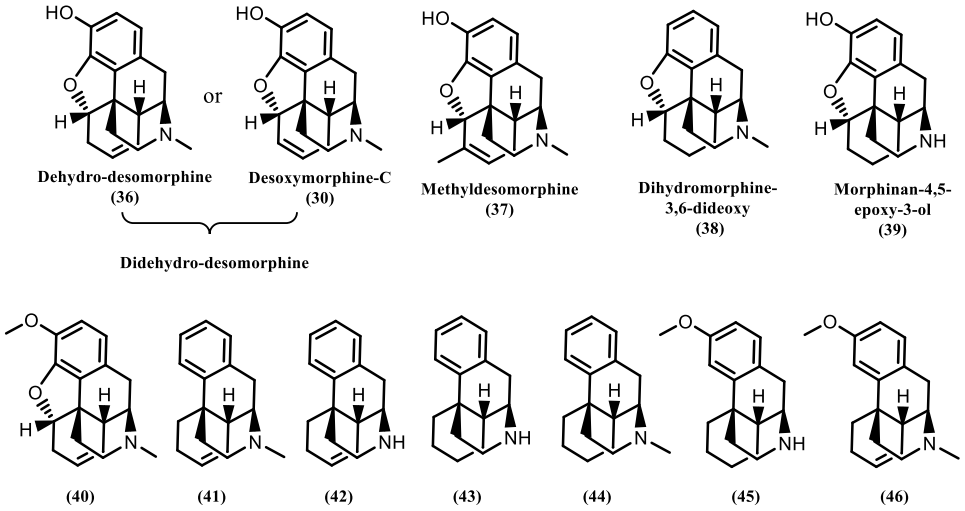

Figure 5. Structures of morphinans and 4,5-epoxymorphinans detected in the work of Savchuk,[185] Alves,[223] and Soares:[210] **30** or **36**, **37**, **38**, and **39** are structures of compounds detected by Savchuk et al.,[185] **38** and **39** are opioids detected in trace amounts by Alves et al.,[223] and some opioid structures detected by Soares et al.[210] include 4,5-epoxymorphinans (**40**) and morphinans **41**, **42**, **43**, **44**, **45**, and **46**.

cleavage[230] and to the dehalogenation of α-iodocodeine to dehydrodesomorphine (**36**).[228] HI is also responsible for the reduction of the 7,8-double bond, carrying out the synthesis of desomorphine and of two other 4,5-epoxymorphinans in trace quantities (detected by gas chromatography-electron impact/mass spectrometry (GC-EI/MS) (compounds **38** and **39** in Figure 5).[185,223] The iodine regenerated in the dehalogenation reaction reacts again with red phosphorus, initiating a new redox cycle.[223] According to krokodil "manufacturers", the krokodil is ready to be injected after approximately 45 min, when a brown to light-yellow color (probably a result of presence of remnant iodine) and an acid odor appear (the resulting krokodil mixture has a strong acidic pH (1.15 ± 0.30)).[190,223,224] Due to the rudimentary laboratory conditions employed and the lack of purifications steps, the final product of this home manufacture is often contaminated with various toxic and corrosive byproducts or residuals.[177,210,224,227] All these substances are considered to be responsible for most of the undesirable or toxic effects that appear after the repeated injections of krokodil, which is a cocktail of all the above substances.[172,178,210]

Although it is usually claimed that desomorphine is the main opioid obtained from this method, some authors have proposed that other morphinans and 4,5-epoxymorphinans could be obtained as byproducts and could contribute to the opioid effect of krokodil.[185,210] Savchuk and colleagues studied several forensic and biological samples through gas chromatography−mass spectrometry (GC-MS) analysis, both from instruments used by drug consumers and from urine samples of users from different regions of Russia.[185] In this study, besides desomorphine, the authors found four 4,5-epoxymorphinan derivatives related to desomorphine (Figure 5): didehydrodesomorphine (**30** or **36**), methyldesomorphine (**37**), dihydromorphine-3,6-dideoxy (**38**), and morphinan-4,5-epoxy-3-ol (**39**).[185,223] The latter two derivatives were also detected in trace amount by Alves.[223] It is worth mentioning that the structure of didehydrodesomorphine, which is not given in Savchuk's work, could correspond to desoxymorphine-C (**30**) (previously described by Small[174,175]) or to dehydrodesomorphine (**36**), subsequently proposed as a synthetic intermediate by Alves.[223] The concentration of desomorphine in the urine samples varied from trace amounts to 70−80%.[185] More recently, taking the works of Savchuk[185] and Alves[223] as references, Soares and colleagues have reported the presence of 54 morphinans and 4,5-epoxymorphinans from a street-like synthetic sample, with the majority of them constituting a cluster, forming a complex mixture.[210]

The chemical profiling of this complex mixture was performed by reverse-phase high-performance liquid chromatography coupled with a photodiode array detector (RP-HPLC-DAD) and by liquid chromatography coupled with high resolution tandem mass spectrometry (LC-ESI-IT-Orbitrap-MS). Among the morphinans and 4,5-epoxymorphinans detected, Soares and colleagues found codeine and morphine in trace amounts (the latter being identified for first time in krokodil) and desomorphine as the most abundant 4,5-epoxymorphinan in the mixture.[210] The presence of 51 additional morphinans and 4,5-epoxymorphinans was also reported, among which there were some previously known, as well as new ones.[210] The composition of krokodil in the different batches is very dissimilar even in controlled conditions, with desomorphine being the main opioid in some batches, while in others its amount is less.[210] These results could suggest that the opioid effect of krokodil could be due not only to desomorphine but also to a combination of other opioids present in the mixture in an additive or synergistic effect.[210] Additionally, some detection methods have been developed for desomorphine by several authors. In 2015, Eckart developed and validated a highly sensitive and specific liquid chromatography−tandem mass spectrometry (LC−MS−MS) method using electrospray ionization for the detection of desomorphine and 34 other opioid-type drugs from analytical plasma samples. In this method, the lower limit of quantification for desomorphine was 0.1 ng/mL, and the limit of detection was 0.06 ng/mL.[231] In another work, Kerrigan and Winborn developed a method based on solid phase extraction (SPE) and GC−MS to identify desomorphine in blood and urine samples, achieving limits of quantitation in blood and urine of 5 ng/mL and 8 ng/mL, respectively. To date, this represents the most sensitive method based in GC-

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MS thus far.[232] In a later work, Kerrigan and Winborn, using SPE and LC-MS-MS, were able to quantitatively identify desomorphine in urine analytical samples with limits of detection and quantitation of 0.5 ng/mL.[180]

2.3. Drug Metabolism. To date, the metabolic fate of desomorphine in humans has not been studied (i.e., the complete determination of its phase I and II metabolites). However, a few important works have been published studying its metabolism *in vitro*, as well as *in vivo* in rats.[233,234] These *in vitro* metabolic studies can predict, reasonably well, the metabolites that can potentially form in the human body.[233,235] In the first of these studies, Richter and colleagues performed metabolic studies *in vivo* using rat urine and *in vitro* using pooled human liver microsomes (pHLM) and pooled human liver cytosol (pHLC), as well as human liver cell lines (HepG2 and HepaRG), through Orbitrap (OT)-based liquid chromatography−high-resolution tandem mass spectrometry (LC-HR-MS/MS) or hydrophilic interaction liquid chromatography (HILIC)-HR MS/MS.[233] In their work, the authors were able to identify several phase I and phase II desomorphine metabolites. This allowed the authors to propose a metabolic pathway in which the main steps are *N*-demethylation, *N*-oxidation, and hydroxylation at various positions, as well as glucuronidation and sulfation of the parent compound **24** and glucuronidation of nor-desomorphine (**39**) (morphinan-4,5-epoxy-3-ol) and desomorphine *N*-oxide (**47**) (Figure 6).[233]

All phase I metabolic steps were catalyzed by CYP3A4. Glucuronidation was catalyzed by UDP-glucuronyltransferases: UGT1A1, UGT1A8, UGT1A9, UGT1A10, UGT2B4, UGT2B7, UGT2B15, and UGT2B17.[233] All studied models (*in vivo* and *in vitro*) were able to identify desomorphine glucuronide (**51**), the metabolite with the highest relative abundance.[233] Additionally, desomorphine and its phase I metabolites, namely, nor-desomorphine (**39**) and desomorphine *N*-oxide (**47**), were detected in all investigated models. On the other hand, dihydromorphine (**54**) (the 6-hydroxylated compound) was only identified in the *in vivo* model.[233] In another effort, Kerrigan's group studied the *in vitro* metabolism of desomorphine using recombinant human cytochrome P450 enzymes (rCYPs) and recombinant uridine 5′-diphosphoglucuronosyltransferase (rUGTs) through liquid chromatography/quadrupole time-of-flight mass spectrometry (LC−Q/TOF-MS).[234] The results were concordant with those obtained by Richter, with some slight differences. In Kerrigan's work, a new phase I metabolite (norhydroxydesomorphine (**57**)) was detected that had not previously been described.[234] It is worth mentioning that Kerrigan's work proposes two metabolic products of aromatic hydroxylation, in contrast to Richter, whose work proposes only one.[234] The study of CYP450 isoenzyme activity confirmed the major contribution of CYP3A4 to desomorphine metabolism, as described by Richter, but the major contribution of CYP2C18 in the dealkylation reaction of desomorphine was also evidenced.[234] Furthermore, the minor contribution of other CYP450s in the metabolic reactions of six of the eight identified metabolites was verified. The only phase II metabolite detected by Kerrigan corresponds to desomorphine glucuronide (**51**).[234]

2.4. Pharmacology and Toxicology. Desomorphine was originally synthesized as a more powerful morphine derivative with a more moderate adverse effect profile. In this sense, it is interesting to read what its inventor, Frederick Louis Small, thought about it:

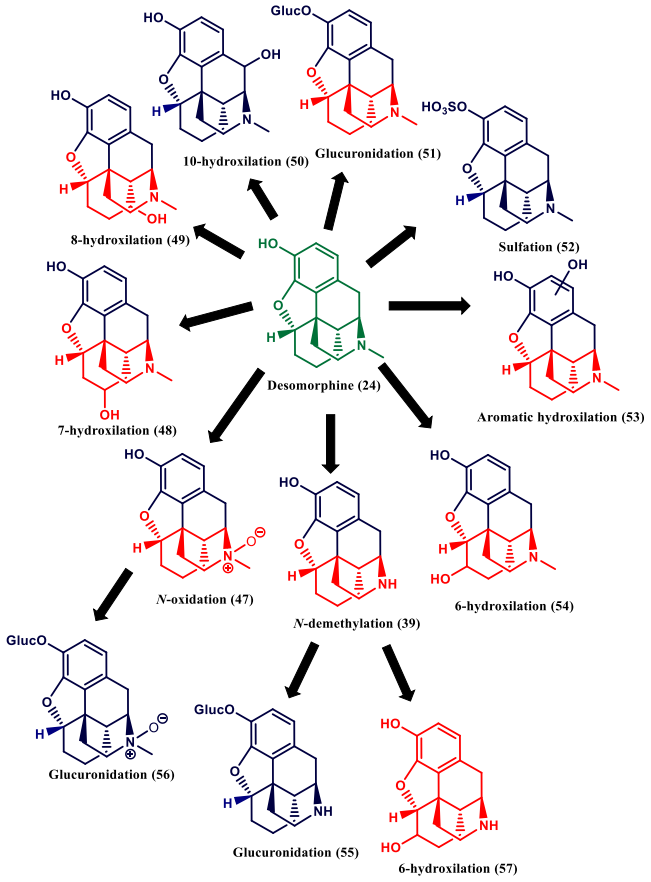

Figure 6. Metabolic fate of desomorphine (**24**) proposed by Richter[233] and Kerrigan.[234] In dark blue, phase I and II metabolites proposed only by Richter. In red, metabolites proposed only by Kerrigan. Bicolor structures represent the metabolites simultaneously detected in both works. The new metabolite detected by Kerrigan corresponds to 6-hydroxylated derivative of nor-desomorphine (norhydroxydesomorphine (**57**)). In addition, Kerrigan proposes two metabolite products of aromatic hydroxylation (**53**), in contrast to Richter, who proposed only one.[234]

> *The present invention is a new product of the morphine series and is superior in physiological action to most present known narcotics related to morphine, codeine and drugs of like action and which may serve to replace morphine, in pharmaceuticals preparations and in medical applications. The invention is more effective in producing analgesia, in effect on respiration and cough, and in general depressant action, but relatively free from convulsant, emetic and toxic effects, and is designed to replace morphine and others drugs of morphine-like action in therapeutic practice.*[173]

The truth is that current knowledge indicates that it is not a useful drug from a therapeutic point of view, which it is mainly due to its powerful addictive properties that preclude its use as a therapeutic tool. Given the chemical structure and clinical effects of desomorphine in diverse animal species (mice, rabbit, cat, primates, humans), it is reasonable to assume that its main pharmacological targets are the opioid μ-, κ-, and δ-receptors, especially the former. The spectrum of these clinical effects is so typical and homogeneous that it appears safe to presume that desomorphine exerts its effects by a common mechanism of action with morphine and other opioid narcotics.[236] However, to date there is no complete *in vitro* pharmacological characterization of the drug, either in terms of its affinity for

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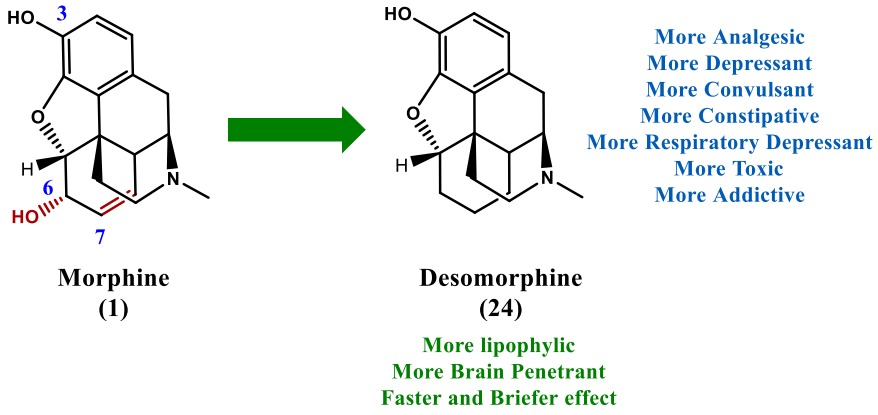

Figure 7. Morphine to desomorphine. Consequences of the clinical, pharmacological, and physicochemical properties of desomorphine.

the aforementioned receptors or of its pharmacological profile. Nevertheless, it has been reported that desomorphine is around ten times more potent than morphine.[188,236−238] The removal of the hydroxyl group at position 6 of desomorphine makes the compound more lipophilic, promoting greater penetration through the blood−brain barrier and to the central nervous system (CNS), allowing it to reach higher concentrations at the action site, and therefore making it more toxic, more analgesic, more powerful as a respiratory depressant, more convulsant, and more of a general depressant than morphine and even more so than heroin (Figure 7).[175,177,188,190,238,239]

The absence of the hydroxyl group at position 6 has a much greater impact on analgesic and depressant actions: that is, desomorphine has 9−10 times the analgesic power (cats,[188,238] mice,[240] human[237,241]) of morphine but is only about 3−5 times more toxic (mice[188,238]). Additionally, desomorphine has nearly 15−21 times the depressant effect (rats,[188,238] human[237]) of morphine and 14 times its suppressor activity on gastrointestinal mobility (rabbit[188]), but it seems to entirely lack an emetic effect and shows less of a sedative effect.[188,237] Additionally, desomorphine exhibits a very limited convulsant effect, as it is more potent than morphine in mice, albeit less efficacious.[188] However, some reports indicate that in mice, desomorphine exhibits approximately 5 times the effect of morphine in convulsant action.[238] Also, a 12-fold increase, compared to morphine, has been reported in the respiratory depressant effect in rabbits generated by desomorphine.[238,242] An interesting effect reported for desomorphine is its potent and efficacious inhibition of cholinesterase from different sources (human, rabbit, and dog serum and human and rabbit brain); this enzyme inhibition is more powerful than that of morphine and codeine in all cases.[243−245]

On the other hand, desomorphine exhibits faster and shorter-lasting action when compared with morphine, a feature that contributes to its great addictive power, which currently precludes its use as a therapeutic agent.[188,236,237,240,241,246] Repeated administration of desomorphine can cause serious health complications that include addiction and physical dependency, tolerance, and a withdrawal syndrome if the substance is no longer consumed. In this respect, it is noteworthy that in a study performed in morphine users, an abrupt withdrawal of desomorphine promptly led them to develop abstinence symptoms more rapidly than an abrupt withdrawal of morphine.[237,246] The withdrawal symptoms generated by both drugs were equally severe, as were their durations.[237,246]

All pharmacological effects exhibited by desomorphine, that is, analgesic effectiveness, side effects (convulsant, constipative, depressant, and toxic effects), physical dependency, tolerance, and addiction liability are archetypal effects, at least qualitatively, of a wide variety of opioid agents.

However, in the context of the homemade-drug krokodil, a series of serious and devastating adverse effects have appeared in users.[172,186,187,189,208,217] As mentioned, krokodil is a homemade injectable drug whose main opioid component appears to be desomorphine. However, given the type and conditions of manufacture and the absence of any kind of purification of the drug, it presents a large quantity and variety of byproducts and highly toxic and corrosive residues (lead, iron, zinc, antimony, iodine, and phosphorus compounds, among others).[172,177,178,186,208,210,223,224]

Just like heroin and many other opioids, desomorphine is administered intravenously (the most common route), intramuscularly, and subcutaneously,[172,177,247] although oral administration has also been reported.[207] The reported harms caused by the drug's administration can be local, systemic, and neurological (Table 2).[172,177] It is noteworthy that the damage described seems to appear relatively soon after the consumption of krokodil begins, and that it is extreme and unprecedented, generally leading to death after 2−3 years.[172,186]

At a local level, the most important clinical manifestations appear to be severe venous damage, including ulcers and thrombophlebitis at and around injection sites, as well as skin and soft tissue infections, rapidly followed by necrosis, which can progress to muscle and cartilaginous tissue destruction, and even gangrene and amputation of limbs if use is continuous (Figure 8).[172,186,191,205,218,224]

Very often, krokodil-induced health complications also involve systemic toxicity, which includes neurological, endocrine, and organ damage.[172,177] Several pathologies have been reported, such as coronary artery bursting, septicemia, and other systemic damage due to infections, such as pneumonia and meningitis.[172,177] The liver, kidneys, and heart are among the organs most affected by the use of krokodil, leading in some cases to multiple organ failure. On this issue, a recent study has reported multiple internal organ toxicity after subcutaneous administration of krokodil in rats.[247] In this study, abnormalities in biomarkers of cardiac and renal toxicity were detected (creatine kinase, creatine

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Table 2. Toxic Effects Related to Krokodil Exposure[172,205,224]

Local Toxic Effects	
•black and open ulcers	•scab formation
•popped skin lesions	•bleeding
•thrombosis of the major vessels	•necrosis
•thrombophlebitis	•gangrene
•skin discoloration	•limb ulcerations and amputations
•skin and soft tissue infections	
Systemic Toxic Effects	
•blood vessel, muscle, cartilage, and bone damage	•meningitis
•liver and kidney inflammation	•multiple organ failure
•swollen hands	•low blood pressure and heart beat
•jaw osteonecrosis	•endocarditis
•hypothyroidism	•death
•pneumonia	
Neurotoxicity	
•motor skill impairments	•loss of memory and concentration
•loss of cognitive functions	•personality changes
•speech impediments	•hallucinations

kinase-MB, and uric acid).[247] In addition, a significant alteration in the levels of oxidized and reduced glutathione was evidenced in the heart and kidneys, suggesting that oxidative stress could mediate the toxicity of the drug.[247] Cardiac congestion is the most important effect of continuous administration of krokodil.[247] Recently, a case of lethal endomyocarditis has been reported in a user of this drug in Italy.[205] The autopsy showed foci of inflammation in the liver and the kidneys.[205] It has also been reported that exposure to lead (from gasoline used as a solvent) could generate liver and renal damage and exposure to iodine could cause thyroid abnormalities.[172,177,184,248]

Another serious health complication presented by users of krokodil is jaw osteonecrosis, whose main feature is jawbone exposure in the oral cavity. Numerous such cases have been reported recently.[201,202,204,249] A possible explanation for this devastating pathology is given in van Kempen and Brand's work.[249] According to their study, symptoms of krokodil-associated osteonecrosis are comparable to phosphorus and bisphosphonate-induced necrosis of the jaw.[184,249] The intravenously administrated homemade drug exposes the user's blood to a high concentration of residual phosphorus compounds, which cannot be efficiently removed by the kidneys. Phosphorus can react with molecules like CO_2, H_2O, and amino acids to produce a powerful amino bisphosphonate, which is responsible for generating the damage.[223,249] It is worth mentioning, as pointed out by other authors, that the generation of toxic phosphonates can also occur during the preparation of the drug, due to the extreme conditions of the synthesis.[223,247]

Some studies have also reported neurological damage, probably due to exposure to residual heavy metals (in particular lead) present in the drug, such as speech difficulties, motor skill impairments, personality changes, hallucinations, and loss of cognitive functions.[172,177,250,251] Neurological harm can occur before or even without obvious physical damage.[186]

2.5. Structure−Activity Relationship. Desomorphine, as reported in several publications, is arguably the most powerful analgesic agent among 4,5-epoxymorphinans derived from morphine.[188,237,238,252,253] Furthermore, the other typical actions of opioids are powerful in desomorphine. For example, its respiratory depressant, exciting, constipative, and depressant properties are in the near maximum activity levels among several morphine derivatives.[188,238] Figure 9 shows the structurally closest changes on desomorphine and their influence on some of its actions.

In most cases, modifications are detrimental to the corresponding pharmacological action. Only the toxic effect, manifested as decrease in lethal doses, is enhanced by one of the structural changes in the desomorphine skeleton (namely, insertion of the C6−C7 double bond).[188,253] For example, *N*-demethylation to produce **39** leads to a substantial decrease in analgesic action, as reported by Sargent.[253] It is noteworthy that no other pharmacological actions have been evaluated for this derivative. On the other hand, the insertion of a C6−C7 double bond (**30**) or a hydroxyl group at C-6 (**28**) also leads to a decrease in the analgesic action as well as the other pharmacological actions of desomorphine. The depressant action is most affected by hydroxylation in C-6, falling 55 times in relation to the parent drug.[188] Another structural modification that was demonstrated to be detrimental for all desomorphine pharmacological actions, and with a high impact on the depressant properties, was the removal of E ring (tetrahydrodesoxymorphine (**58**)). This modification would change desomorphine's structural classification of 4,5-epoxymorphinan to morphinan. Although morphinans, such as levorphanol or butorphanol exhibit good opioid activity, a desomorphine "morphinan-like" drug loses most its agonist characteristics.[188] Finally, methylation of the phenolic hydroxyl

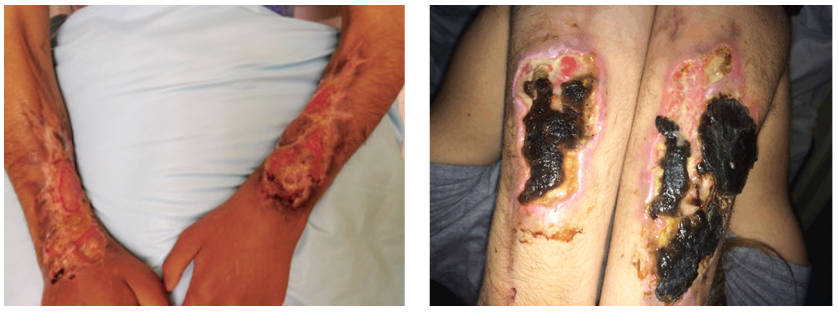

Figure 8. Skin damage in patients suspected of using krokodil.[191,218] (A) Skin damage in a suspected user in Baltimore, Maryland, US (Reproduced with permission from ref 218. Copyright 2016 Elsevier). (B) Necrotic ulcers and scar tissue in bilateral upper extremity in a suspected female user of krokodil in the US (Reprinted from ref 191 under the terms of CC BY 4.0).

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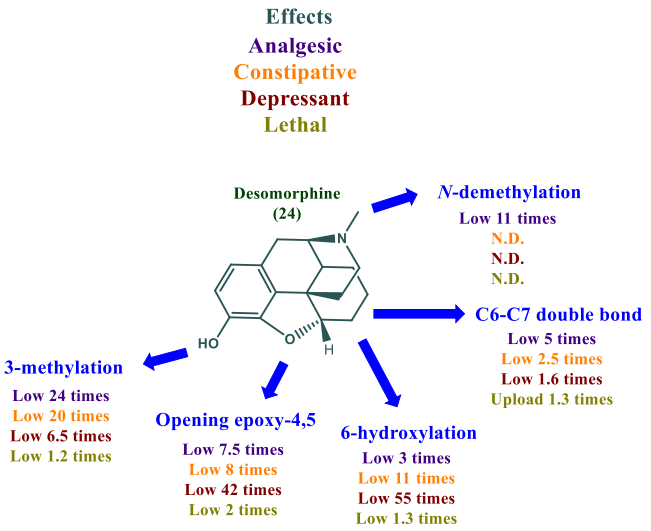

Figure 9. Structure–activity relationship for desomorphine (**24**). Structural changes on desomorphine (**24**) and its analgesic (cats), constipative (rabbits), depressant (rats), and lethal dose (mice) effects are shown.[188,253] 3-Methylation (desocodeine (**26**)), opening of epoxy-4,5 function (tetrahydrodesoxymorphine (**58**)), 6-hydroxylation (dihydromorphine (**28**)), and *N*-demethylation (nor-desomorphine (**39**)) decrease all pharmacological activities of desomorphine. The presence of the C6–C7 double bond (desoxymorphine-C (**30**)) decreases all pharmacological activities of desomorphine (**24**), except lethal effect.[188,253] Analgesic (purple), constipative (orange), depressant (brown), and toxic (green) effects are shown. ND, not determined.

group to produce **26** also leads to a decrease in all drug activities.

3. CONCLUDING REMARKS

Opioids represent a good therapeutic alternative for pain relief, and many of them are currently used as clinical drugs. The "cursed cousins" heroin and desomorphine, which share structural, pharmacological, and epidemiological features, can cause severe and diverse damage; therefore, they cannot be used for pain, coughing, or diarrhea treatment. The most obvious and quickest damage to appear in people who use these drugs are biological dependence, tolerance, withdrawal syndrome, and death. In particular, desomorphine (krokodil) has been shown to cause very extensive skin damage in its users, although it has been proposed that this phenomenon is related to the possibly large quantity and variety of byproducts in its home manufacture. As was mentioned above, since a great deal of heroin production comes from Afghanistan, this country could be considered as a global hub for trafficking. Thus, as a main supplier, any changes in its "heroin exports" would wreak havoc on global consumers. In this manner, a drop in Afghan heroin production encouraged the appearance of desomorphine in order to satisfy consumers and meet heroin demand in its absence. From this geo-economic perspective, we reviewed the historical, pharmacological, pharmacokinetic, chemical, and societal impact of both drugs, which were developed to improve opioid properties, exhibiting fewer side effects in terms of tolerance and addictive profile. Nevertheless, the expectations were not met, and like opium in the early stages of its history, both drugs synthetically created from derivatives of the poppy plant (morphine and codeine) have taken many lives in those who have decided to use them. Therefore, it is necessary to emphasize that the story has not ended and the possibility of creating new better opioid derivatives is still possible.

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Notes

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