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Fentanyl and other synthetic opioids

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Abstract

Opioids are a diverse group of chemical compounds that bind to opioid receptors. They are an important group of drugs used in pain management, but their abuse leads to addiction and serious health risks. Synthetic opioids, one of the fastest growing groups of New Psychoactive Substances, pose a particular risk. The rapid and cheap production of fentanyl, its analogues, and nitazens contributes to their spread on the illegal drug market. This article presents the current global situation regarding opioids, discusses their classification, chemical structure, and mechanisms of action, as well as methods of obtaining fentanyl, methadone, and selected nitazens.

Keywords: fentanyl, fentanyl analogues, nitazene, synthetic opioids

1. Introduction

Opioids are a diverse group of chemical compounds that exhibit affinity for opioid receptors located in the central nervous system (CNS) and peripheral tissues (including the gastrointestinal tract) (Zaporowska-Stachowiak et al., 2020). Their mechanism of action involves binding to opioid receptors coupled with G proteins, which leads to the opening of potassium channels and inhibition of calcium ion influx. The result is hyperpolarization of the neuronal membrane and inhibition of pain signal conduction. Some opioids additionally affect the nervous system by inhibiting the reuptake of neurotransmitters. Furthermore, they can exhibit a variety of pharmacological properties, with some acting as agonists or partial agonists of opioid receptors (activating them completely or partially), others as antagonists (blocking their activity completely), and some substances exhibiting a mixed profile, stimulating some types of receptors and blocking others. (Przewłocka, 2017; Trescot et al., 2008). Thus, they mediate the human body's response to most hormones and neurotransmitters and participate in the sensory perception of sight, taste, and smell. To date, three main types of opioid receptors have been described: MOR (μ), responsible for analgesic and euphoric effects, respiratory depression, and strong addictive potential; KOR (κ), associated with sedative and dysphoric effects; and DOR (δ), involved in mood regulation and pain modulation. In addition, there is the NOP (ORL-1) receptor, activated by nociceptin. (Al-Hasani & Bruchas, 2011; Le Merrer et al., 2009; Pathan & Williams, 2012; Stein, 2016). Their natural ligands are endogenous opioid peptides such as dynorphins, enkephalins, and endorphins (Pathan & Williams, 2012). Exogenous opioids are a group of chemical compounds that

include opiates, their semi-synthetic and synthetic analogues, which include new psychoactive substances (NPS) (Fig. 1). Opiates are natural alkaloids of opium obtained from the dried milk of immature poppy heads (Latin: Papaver somniferum L.). Opium is a complex mixture containing, among other things, flavonoids, phenolic acids, sterols, and alkaloids. There are about 50 alkaloids, the main components of which are morphine, codeine, thebaine, and papaverine. Semi-synthetic opioids are produced from extracted and purified opiates through chemical reactions, including heroin, oxycodone, buprenorphine, and drotaverine. Synthetic opioids include methadone, tramadol, fentanyl, and nitazene, which have a chemical structure that does not resemble opiates but have a similar effect (Fig. 1) (*Lexicon of Alcohol and Drug Terms*, 1994; *Terminology and Information on Drugs*, 2016; Szukalski, 2005). Exogenous opioids play a key role in medicine as effective analgesics used in the treatment of acute and chronic pain, as well as in anesthesiology and palliative care. They are also used to treat shortness of breath, coughing, and diarrhea (Krajnik & Żylicz, 2003; Nadeau et al., 2021; Zaporowska-Stachowiak et al., 2020). However, their use is associated with numerous adverse effects, including respiratory depression, cardiac arrhythmias, and symptoms affecting the gastrointestinal tract and central nervous system (Kocot-Kępska et al., 2016; Radwan-Kwiatek, 2011). Their high risk of addiction is particularly dangerous, especially with prolonged or improper use. The euphoria caused by opioids encourages abuse and can lead to both physical and psychological dependence (The Lancet Regional Health – Americas, 2023; Zaporowska-Stachowiak et al., 2020).

This article aims to summarize the global situation regarding opioids, present their classification, and discuss the synthesis of selected synthetic opioids.

2. The history and current situation of opioids worldwide

The oldest information about the use of poppy seeds comes from ancient Mesopotamia and Egypt, as evidenced by archaeological discoveries and written records (Bartnik, 2021). In those cultures, it was used both for practical purposes, as a sedative, painkiller, and sleeping aid, as well as for ritual purposes. Until the 1990s, doctors avoided prescribing opioid medications for the treatment of chronic non-cancer pain due to fears of addiction, limiting their use mainly to palliative care (Hill, 1993; Paice et al., 1998; Weissman, 1993). Some researchers refer to this period as “opioid phobia.” The problem of opioid abuse emerged during the American Civil War, when the widespread use of morphine led to numerous addictions, later referred to as “soldiers’ disease” or “war morphine addiction” (Oliveira Júnior, 2018). An additional impetus for the development of the crisis was the introduction of heroin in 1898 by Bayer as a supposedly safer substitute for morphine, which quickly proved to be even more addictive (W. M. Compton & Jones, 2019). In the 1990s, organizations such as the American Pain Society and The Joint Commission promoted the concept of pain as the “fifth vital sign” (alongside heart rate, blood pressure, respiration, and body temperature), which led to the intensification of pain therapy and the belief that

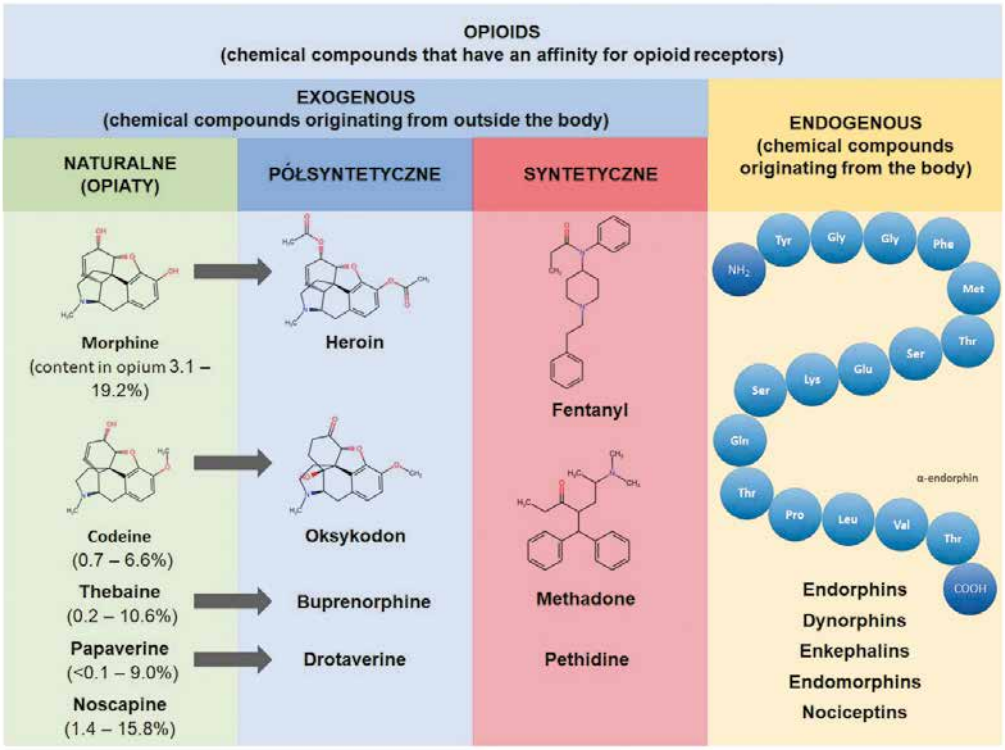

Fig. 1. Classification of opioids according to their origin, with selected representatives of the group

inadequate pain treatment is inhumane (P. Compton, 2023; Levy et al., 2018; Owen et al., 2018; Scher et al., 2018). In 1996, OxyContin (extended-release oxycodone), manufactured by the American company Purdue Pharma, was launched on the market (Haffajee & Mello, 2017). Despite the lack of evidence of its superior efficacy compared to other opioid drugs (Hale et al., 1999; Heiskanen & Kalso, 1997; Kaplan et al., 1998; Mucci- LoRusso et al., 1998; Stambaugh et al., 2001) and earlier reports of abuse of a similar drug, MS Contin (extended-release morphine) (Crews & Denson, 1990), an aggressive marketing campaign led to widespread prescribing of the drug for chronic non-cancer pain. The number of prescriptions rose from 300 000 in 1996 to 6 million in 2001 (Van Zee, 2009). It quickly became apparent that the extended-release mechanism could be easily circumvented by crushing the tablets, leading to a sharp increase in poisoning and deaths due to overdose (Maclean et al., 2022). According to the Centers for Disease Control and Prevention (CDC), between 2000 and 2014, the number of deaths related to opioid overdose increased by 200% (Rudd et al., 2016). This period is considered to be the beginning of the so-called "first wave of the opioid epidemic" in the United States. In 2010, Purdue Pharma introduced a new tamper-resistant formula that made it impossible to crush and dissolve OxyContin (Larance et al., 2018; Leece et al., 2015). This change caused an increase in the price of the drug on the black market and prompted addicts to seek alternatives, which contributed to an increase in heroin use (Alpert et al., 2018). At the same time, heroin prices began to fall and its availability increased as Mexico took over the dominant role in supply, displacing Colombian cartels and becoming the main supplier of this drug to the United States (Felbab-Brown, 2020). Between 2010 and 2013, the number of heroin-related deaths increased by 286% (Hedegaard et al., 2018). This period is referred to as the "second wave of the opioid epidemic" in the United States. Over time, high-quality heroin, known since the 1970s as "China White" (originating in Southeast Asia), was used by traffickers as a marketing tool to sell low-quality heroin mixed with fentanyl, which marked the beginning of the "third wave of the opioid epidemic" (Martin et al., 1991; Mounteney et al., 2015). Fentanyl was first introduced to the market in 1963 in the United Kingdom as an intravenous anesthetic under the trade name Sublimaze, used both before and after surgery. Five years later, the drug arrived in the United States under the name Innovar. In the 1990s, the American company Alza developed transdermal patches containing fentanyl, marketed as Durogesic. These patches released the drug gradually, providing continuous analgesia for three days. In the mid-1990s, this method became the preferred form of opioid administration for cancer patients suffering from severe chronic pain. The first cases of fentanyl abuse were reported as early as the 1970s, but they mainly involved anesthesiologists, surgeons, and nurses who had access to the drug through their work (Stanley, 2014). Fentanyl has now become a street substitute for heroin, mainly because it is cheaper and its production does not require poppy cultivation, which is susceptible to drought or disease, nor does it depend on the plant's growing cycle. Between 2013 and 2016, the number of deaths related to fentanyl overdose in the United States increased by more than 500% (Scholl et al., 2018). Illegal fentanyl laboratories first appeared in the United States in the 1990s, and their number and reach increased in the mid-to-late 2000s (Henderson, 1991; McKeown et al., 2023). Initially, seizures of illegal fentanyl were rare, and drug epidemics were local and short-lived (Fodale et al., 2008). Between 2000 and 2005, the US Drug Enforcement Administration (DEA) searched five illegal laboratories producing fentanyl. During one of the operations, a 27-year-old chemistry student from San Diego State University was arrested for using the university's laboratories to synthesize the substance (San Diego Union-Tribune, 2005). During the same period, Mexican authorities shut down a clandestine laboratory in Toluca responsible for nearly all of the illegal fentanyl entering the United States at that time (Pardo, 2019). In 2013, China became the main producer of fentanyl smuggled into the United States, mainly through Mexico and Canada, where tablet pressing operations were conducted, as well as directly by mail and courier. To avoid detection by customs authorities, Chinese manufacturers and distributors often exploited legal loopholes and, when necessary, resorted to overt deception such as mislabeling shipments. Typical fentanyl seizures from China weighed less than a kilogram, and the purity of the fentanyl often exceeded 90%. Loopholes in the United Nations drug convention system allowed Chinese manufacturers to freely export fentanyl precursors, although substances such as N-phenethyl-4 -piperidinone (NPP) and 4-anilino-N-phenethylpiperidine (ANPP) had been controlled in the United States for over a decade and were only brought under international regulation in October 2017 (Drug Enforcement Administration, 2018). When the Chinese authorities began to impose restrictions on further chemical precursors, Mexican transnational criminal organizations began to diversify their sources of supply. This reduced China's share in the illegal production of fentanyl, but at the same time led to the transfer of criminal activity to neighboring India (Felbab-Brown, 2022; Wang et al., 2022), (Drug Enforcement Administration, 2020b). A 2020 DEA intelligence report indicates that this shift was a direct consequence of restricted access to NPP and ANPP in China. This was confirmed by the increasing number of precursor seizures and dismantling of illegal fentanyl laboratories in India, where Indian and Chinese nationals linked to Mexican transnational criminal organizations were cooperating. Over time, India has taken on a greater role in the illicit production and distribution of fentanyl, both in cooperation with Chinese traffickers and acting independently (Drug Enforcement Administration, 2020a). At the same time, Mexican cartels increased their own production of fentanyl and illegal tablets containing this drug. Some of them began to use increasingly sophisticated laboratories equipped with professional chemical glassware, unregulated substances, and industrial

tablet presses, often imported from China. Fentanyl was entering the United States in large quantities, usually in the form of low-concentration powder (below 10%) or as tablets (Drug Enforcement Administration, 2020b). DEA reports consistently indicate that the Cártel de Sinaloa and Cártel de Jalisco Nueva Generación are primarily responsible for production and trafficking. The dismantled laboratories were located exclusively in areas controlled by these groups or were run by their members and associates. Furthermore, these cartels control the main smuggling routes through California and Arizona, which means that the transport of drugs through these corridors requires their consent (Drug Enforcement Administration, 2024). As Mexican criminal groups intensified their activities, there was a growing need to introduce regulations on further precursors, such as 4-anilinopiperidine (4-AP) and 4-piperidone. Since 2019, new compounds have also begun to appear, reflecting the evolution of fentanyl synthesis methods, including phenethyl-4-anilino-N-phenethylpiperidine (phenethyl-4-ANPP), ethyl-4-anilino-N-phenethylpiperidine (ethyl-4-ANPP) and impurities with a tert-butoxycarbonyl (t-BOC) group (Toske et al., 2023).

For a long time, Europe seemed to have avoided the opioid health crisis, as confirmed by numerous reports from the European Monitoring Center for Drugs and Drug Addiction (EMCDDA) (European Monitoring Centre for Drugs and Drug Addiction, 2021, 2022, 2023). Heroin remains the biggest problem, accounting for a significant number of drug-related deaths (European Monitoring Centre for Drugs and Drug Addiction & Europol, 2024b, 2024a). This substance is most prevalent among high-risk groups who inject opioids. It is used to a much lesser extent by recreational users, who more often choose opioids such as tramadol (European Monitoring Centre for Drugs and Drug Addiction, 2025). Afghanistan is of key importance to the heroin market in Europe. Since the 1990s, it has been the world's largest producer of illegal opium, accounting for 86% of global production in 2021 (Kreutzmann, 2007). This production was fueled by armed conflicts, which financed various factions and prolonged the civil war, while degrading agriculture and economic infrastructure. As a result, poppy cultivation became a widely accepted source of livelihood for many farms in rural Afghanistan (United Nations Office for Drug Control and Crime Prevention, 2001). However, after the Taliban took power in 2021, a ban on poppy cultivation and drug production was introduced in April 2022, leading to a sharp decline in opium production of 95% in 2023. According to data from the United Nations Office on Drugs and Crime (UNODC), production decreased from 6,200 tons in 2022 to 333 tons in 2023. This amount could have been processed into 350–580 tons of export-quality heroin, while in 2023 this figure fell to just 24–38 tons (United Nations Office on Drugs and Crime, 2023). This is not the first time the Taliban has banned poppy cultivation. They introduced a similar ban in June 2000, which led to heroin shortages in Europe and an increase in fentanyl use in Estonia, the United Kingdom, Germany, Finland, Sweden, and Lithuania (Caulkins et al., 2024; Kreutzmann, 2007; Mounteney et al., 2015). There is evidence that he may have come from Russia and China (Pardo et al., 2019). Currently, this ban coincided with Russia's invasion of Ukraine in 2022, which blocked one of the main heroin smuggling routes from Central Asia and other Eastern regions to Europe. The closure of airports and seaports prevented transit, and the destabilization of the route caused heroin shortages in Europe. As a result, prices rose, purity declined, and alternative substances and new sources of supply began to fill the gap (United Nations Office on Drugs and Crime, 2025). In 2024, Italian authorities seized heroin from the Golden Triangle, which shows that Myanmar is beginning to fill the gap, although its production does not match that of Afghanistan. The heroin shortage has also accelerated the expansion of synthetic opioids: fentanyl, methadone, and buprenorphine. There has also been an increase in the number of detections of cyclorphenamine (a benzimidazolone derivative) and spirochlorphene (a spirotriazole derivative) (European Monitoring Centre for Drugs and Drug Addiction, 2025), and especially compounds from the nitazene group, developed in the 1950s by the Swiss company CIBA, but not approved for clinical use. Since 2022, the number of nitazene seizures in Europe has been growing: in 2022, only 430 tablets were seized, in 2023, 24,000, and preliminary data from 2024 indicate over 50,000. Although the scale of seizures remains relatively limited, the trend clearly suggests a gradual expansion of the market (European Monitoring Centre for Drugs and Drug Addiction, 2025). New opioids come in various forms, such as powders, capsules, or counterfeit prescription drugs, such as oxycodone or benzodiazepines (diazepam, alprazolam). They are also sometimes found as adulterants in heroin or other drugs, and even in non-opioid substances such as cocaine. In some cases, they are mixed with other substances, such as methonitazene with bromazolam (benzo-dope) or a combination of protonitazene, methonitazene, and xylazine (tranq-dope). As a result, many consumers take them unknowingly, which significantly increases the risk of overdose. In the United Kingdom, in the second half of 2023 alone, the National Crime Agency (NCA) confirmed 54 deaths related to the presence of nitazens in post-mortem toxicology. Similar signals are coming from other European countries, especially the Baltic states, with the number of deaths rising sharply in Estonia and Latvia, reaching 62 and 102 cases, respectively (Holland et al., 2024). The sources of these substances vary. Nitazene and other new opioids are likely to be produced mainly in China, while carfentanil originates mainly from Russia, and India remains the main supplier of tramadol. The production of synthetic opioids in the European Union is rare and is mainly limited to fentanyl and methadone (European Monitoring Centre for Drugs and Drug Addiction & Europol, 2024a). Some of the methadone enters the market as a result of leaks from substitution therapy programs, while the rest comes

from illegal laboratories controlled by organized crime groups such as KhimProm (United Nations Office on Drugs and Crime, 2025). According to GI-TOC data, fentanyl laboratories operate in France and Estonia, and it is suspected they also operate in Latvia and the Netherlands (European Monitoring Centre for Drugs and Drug Addiction & Europol, 2024a). Changes in the availability and structure of the opioid market, as well as the emergence of new substances, underscore the need to maintain a high level of preparedness in control systems. Rapid detection and monitoring of new nitazene derivatives and other synthetic opioids is becoming crucial to limit the risk of a further increase in overdoses and deaths in Europe.

3. Chemical structure and characteristics of selected opioids

Opioids are a broad group of chemical compounds belonging to different classes. Understanding their biological activity requires consideration of specific structural elements that are common to them. They are divided into eight main subgroups. These include: phenanthrenes, benzomorphans, diphenylheptanes, phenylpiperidines, benzimidazoles, U-series compounds, piperazines, and other substances that are not structurally related to any of the previous groups.

3.1. Phenanthrenes

Phenanthrene derivatives, known as morphinan derivatives, are a key group of opioids, which include morphine, heroin, codeine, oxycodone, buprenorphine, and nalbuphine. Their pharmacological activity results from the presence of an aromatic nitrogen ring and a bridge connecting them in the phenanthrene core at positions 9, 10, and 11.

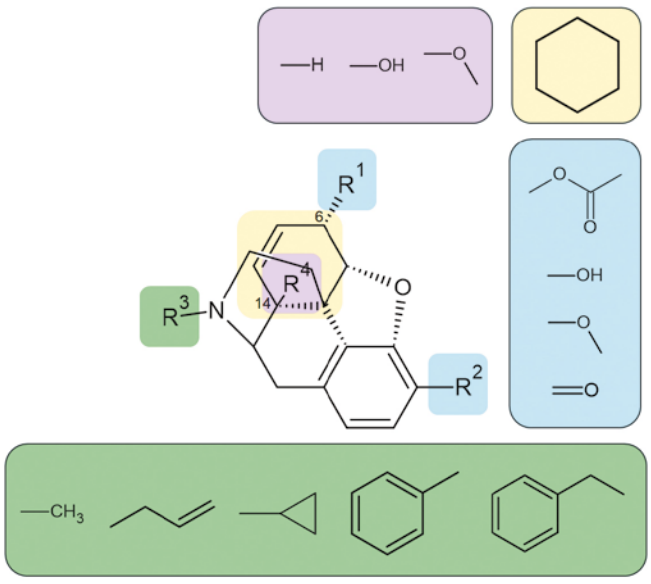

Fig. 2. Possible modifications in the structure of morphine

Stereochemistry plays an important role – levorotatory forms, where the nitrogen ring is above the core, have analgesic effects, while dextrorotatory forms are inactive. Modifications of nitrogen atom substitution can transform an agonist into an antagonist, which was used in the design of naloxone, a compound used to combat poisoning caused by opioid overdose (Goldberg, 2010). The chemical structure also affects side effects – the presence of a hydroxyl group in position 6 increases the risk of nausea or hallucinations, which explains the differences between morphine and oxycodone (Trescot et al., 2008). The introduction of an ethano or ethen bridge between carbons 6 and 14 significantly increases potency, leading to the discovery of Bentley compounds such as buprenorphine and etorphine, which can be up to 10 000 times more potent than morphine (Marton et al., 2022).

3.2. Benzomorphans

Benzomorphans, also known as benzazocines, are compounds with a simplified morphine structure in which the benzene ring is connected to the azocine ring. This group includes 6,7-benzomorphan derivatives such as pentazocine and metazocine. Modifications of functional groups at the nitrogen atom, changes in positions 6 and 7, and substitution of the phenol hydroxyl group (8-OH) have led to the creation of a broad class of compounds with varying affinities for receptors.

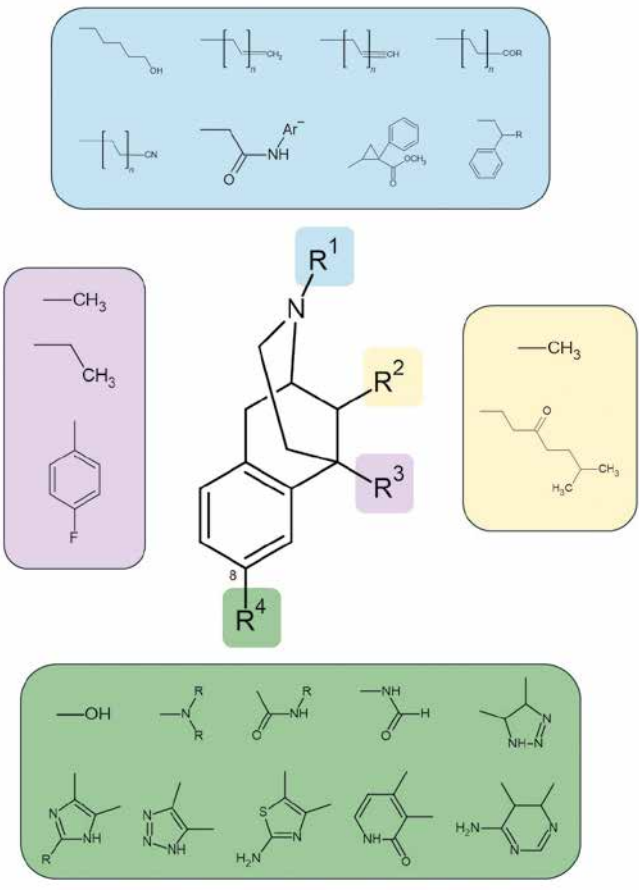

Fig. 3. Possible modifications in the structure of benzomorphan

Unlike morphinan derivatives, the presence of the 8-OH hydroxyl group is not crucial for the interaction of benzomorphans with receptors. Studies have shown that its replacement with hydrogen bond donor groups, such as amino, amide, or thioamide groups, leads to the formation of long-acting derivatives that interact with MOR (μ) and KOR (κ) receptors. Furthermore, the introduction of hydrophobic substituents at position 8 further enhances the affinity for opioid receptors, and the electronic and steric properties of these modifications play a key role in determining the pharmacological profile of a given molecule (Turnaturi, Marrazzo, et al., 2018; Turnaturi, Montenegro, et al., 2018).

3.3. Diphenylheptanes

Diphenylheptanes include methadone and propoxyphene—structurally related compounds with different pharmacological properties (Barkin et al., 2006). They are derivatives of diphenylpropylamine. Methadone is used to treat chronic pain and as an adjunct in the treatment of opioid addiction, relieving opioid cravings, inhibiting withdrawal symptoms, and blocking the euphoric effects caused by other opioids. Despite its effectiveness, long-term use leads to the development of tolerance and dependence, requiring controlled gradual dose reduction [16]. In terms of its mechanism of action, methadone binds to the MOR (μ) receptor, although it also shows affinity for the DOR (δ) and KOR (κ) receptors (Gorman et al., 1997; Joseph et al., 2000).

3.4. Phenylpiperidines

Phenylpiperidines are a group of opioids derived from 4-phenylpiperidine, which includes pethidine, fentanyl, and its numerous analogues. Four of these compounds—fentanyl, alfentanil, remifentanil, and sufentanil – have been approved for medical use as powerful analgesics and anesthetics. Many other fentanyl analogues, although studied for potential pharmaceutical use, have never reached the market. To date, more than 80 such substances have been reported to UNODC (United Nations Office for Drug Control and Crime Prevention, 2024). Uncontrolled use of fentanyl carries a huge risk of overdose; even a dose of 4 μg per kilogram of body weight can cause symptoms of poisoning, such as respiratory depression, and the lethal dose is only 2 mg (Rzasa Lynn & Galinkin, 2018). Fentanyl is about 50 times stronger than heroin, and 0.5 mg administered intranasally is equivalent to 25 mg of heroin. It acts faster but for a shorter period of time – its effect lasts 30–90 minutes, while heroin lasts about 4 hours (Kacela et al., 2022). Minor changes in the chemical structure of fentanyl can significantly affect its properties (Fig. 4). Fentanyl induces euphoria accompanied by bliss and a characteristic semi-conscious state, cutting the user off from reality but without any stimulating effects. Regular use leads to the development of tolerance, resulting in the need to take increasingly larger doses to achieve the same effect. On the black market, fentanyl is often mixed with other substances to prolong its action or enhance its effects. One popular additive is xylazine, a veterinary muscle relaxant and sedative that intensifies the depressive effect of fentanyl on the respiratory center and also causes tissue necrosis and ulceration. A characteristic effect of xylazine is “freezing,” which involves the user remaining in one position for a long time. Another commonly used additive is gabapentin, a drug that affects the GABAergic system, which in high doses has euphoric and sedative effects (Silva-Torres & Mozayani, 2024). Fentanyl and its derivatives have also been used as chemical weapons.

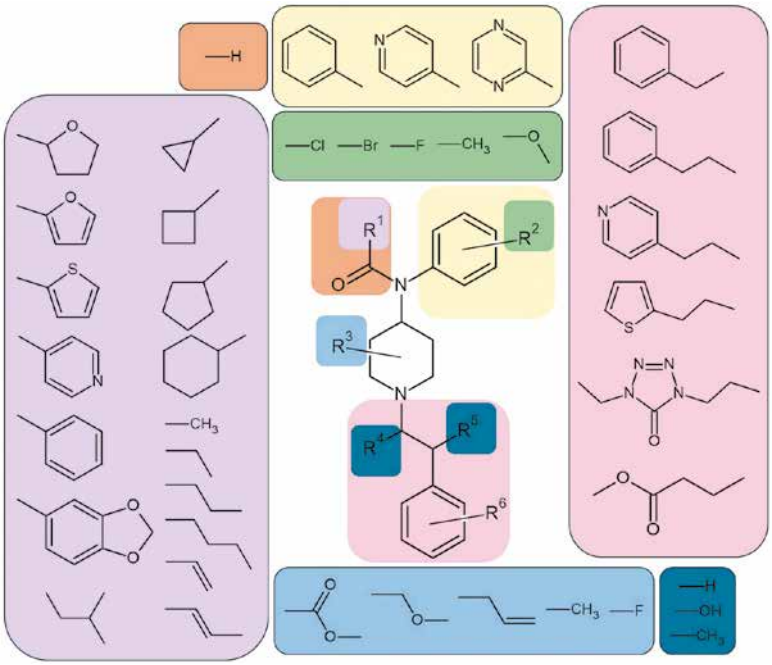

Fig. 4. Possible modifications in the structure of fentanyl

One of the most famous cases was the hostage rescue at the Dubrovka Theater in Moscow in 2002, when Russian security forces used sleeping gas. The mixture probably contained halothane as a carrier in which fentanyl analogues such as remifentanil and carfentanil were dissolved. As a result of the use of the gas and the lack of adequate medical care, 129 hostages died (Partridge, 2012; Riches et al., 2012). There are also reports of the use of fentanyl by the Israelet altelligence agency Mossad in attempts to assassinate Hamas leaders, including Khaled Meshaal (Crowley, 2014). In the United States, fentanyl is sometimes used as a murder weapon. One example is the Fentanyl Murder Crew, which operated in 2022 and used the substance at least 26 times to drug and rob New York partygoers, causing the deaths of six people. In 2023, the first sentence for a fentanyl-related murder was handed down in California (*In first of its kind verdict in California, man found guilty in fentanyl-related homicide*, 2023).

3.5. Benzimidazoles

Nitazene is a group of synthetic opioids that are derivatives of 2-benzylbenzimidazole. They are selective agonists of the μ-opioid receptor (MOR) and were intended to be a simpler alternative to phenanthrene opioids such as morphine (Pardeshi et al., 2021). Despite their high potency and potential medical applications, due to their high toxicity, numerous side effects, and high risk of overdose, no drugs in this class have been approved for medical use (Ujváry et al., 2021). Between 1966 and 2003, the only 2-benzylbenzimidazole opioid occasionally identified on the illegal drug market was etonitazene. It is one of the strongest representatives of this group, and its pharmacological activity is enhanced by the presence of a nitro (-NO_2) and alkoxy (-OR) group. The strength of its action is also influenced by substitutions in position 4 of the benzyl ring – the introduction of a diethylaminoethyl group (Clayton et al., 2024). The situation on the illegal drug market changed in 2019 with the emergence of isotonicitazene. Its presence marked the beginning of a rapid expansion of 2-benzylbenzimidazole opioids in recreational use. In the first half of 2020, isotonicitazene dominated the market for new synthetic opioids (NSO) (Pardeshi et al., 2021). However, after it was added to the international register of controlled substances in June 2021, its popularity began to decline. In response to regulatory action, other nitazene analogues (Fig. 5) began to appear, such as metonitazene, which was identified on the recreational drug market during the COVID-19 pandemic (United Nations Office for Drug Control and Crime Prevention, 2024; Zawilska et al., 2023). Nitazenes are distributed on the black market in powder form, tablets, or in the form of joints with plant material. They are often mixed with other substances, such as heroin, ketamine, or synthetic cannabinoids, which increases the risk of accidental overdose. Many of them have been identified in counterfeit OxyContin, Xanax, and Valium tablets (Ujváry et al., 2021).

3.6. Compounds from the U series

Compounds belonging to this group are referred to as “U compounds” or “U series compounds,” and informally also as “Utopioids.” The letter “U” refers to the Upjohn Company (Hastings, Michigan, United States), where they were developed (Baumann et al., 2020). These substances can be divided into two main groups: cyclohexylbenzamides (e.g., U-47700 and AH-7921) and phenylacetamides (e.g., U-48800, U-50488, and U-51754). U-47700 is a selective μ-receptor (MOR) agonist. Due to the presence of two chiral centers, its synthesis can lead to four potential stereoisomers. However, obtaining the desired active trans-(1R,2R)-isomer (both for U-47700 and its phenylacetamide derivatives) is relatively simple (United Nations Office for Drug Control and Crime Prevention, 2024). U-47700 was first identified in Sweden in October 2014. In subsequent years, it was confiscated in various countries

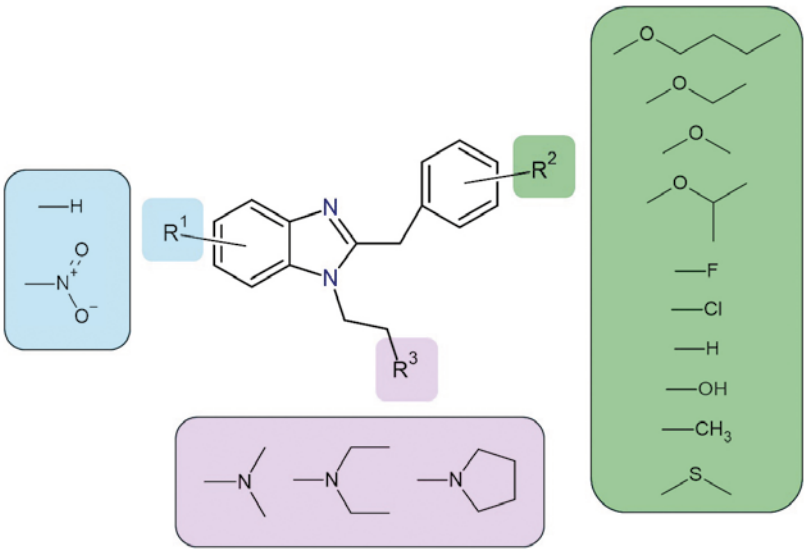

Fig. 5. Possible modifications in the structure of nitazens

in Europe and the US in the form of powder, tablets, and liquids. It is sold as an alternative to heroin and morphine. Structurally related to AH-7921, which belongs to the cyclohexylbenzamides, it was developed by the pharmaceutical company Allen & Hanburys (London, UK), but never reached the market. The reasons for this were its highly addictive properties and the risk of respiratory depression observed in animal studies. AH-7921 was first detected in Europe in July 2012 in a sample purchased from an online retailer. Shortly thereafter, the substance was also identified in Japan in a sample containing synthetic cannabinoids and cathinones (Zawilska, 2017). In 2015, AH-7921 was placed under international control as a Schedule I substance under the 1961 Single Convention on Narcotic Drugs. Similarly, in 2017, U-47700 was placed under the same convention. Since then, numerous derivatives of this group have appeared (Fig. 6), including cyclohexylbenzamides (e.g., isopropyl-U-47700, 3,4-methylenedioxy-U-47700, U-47931E – "bromadoline," U-49900), phenylacetamides (e.g., U-48800, U-50488, U-51754) (United Nations Office for Drug Control and Crime Prevention, 2024). All these compounds contain two nitrogen atoms with different chemical and electrochemical properties, which allows them to be better classified as N-(2-ethylamino)amides. Structurally, they have a strongly basic sp^3 hybridized nitrogen atom and an amide sp^2 hybridized nitrogen atom that does not have a free electron pair capable of protonation (Baumann et al., 2020).

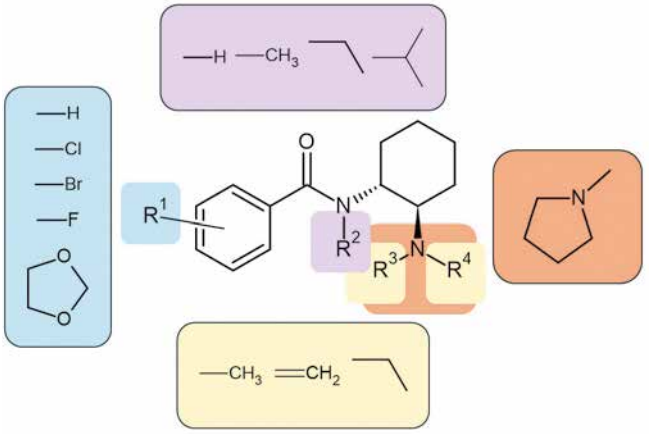

Fig. 6. Possible modifications in the structure of compounds from the U series

3.7. Piperazines

The group of synthetic opioids classified as piperazines includes cinnamylpiperazines (2-methyl-AP-237 and para-methyl-AP-237, also known as AP-238) and phenylethylpiperazines (MT-45). AP-237 (also known as bucinnazine) is a pharmaceutical opioid used to treat pain in cancer patients. It can be used as a precursor for two structural analogues, 2-methyl-AP-237 and para-methyl-AP-237, the former of which appeared on the NPS market in 2019. MT-45 occurs in two racemic forms, with both racemic MT-45 and its S-enantiomer exhibiting opioid-like analgesic effects in animals. Its pharmacological activity is complex and includes stimulation of the DOR (δ) and KOR (κ) opioid receptors. MT-45 was first reported to the EMCDDA in December 2013 in Sweden (United Nations Office for Drug Control and Crime Prevention, 2024).

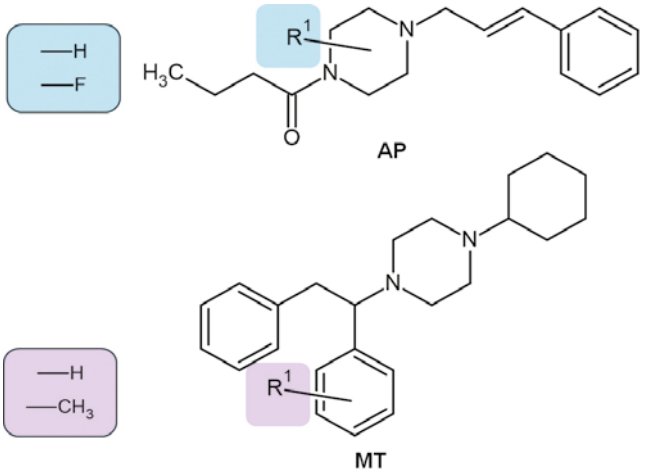

Fig. 7. Possible modifications in the structure of piperazine

3.8. Other synthetic opioids

Tramadol is an atypical opioid that does not fit into the standard classifications of this group. It is a 4-phenylpiperidine analogue of codeine, exhibiting partial activity as a μ-receptor agonist. In addition to its opioid effects, it also affects the GABAergic, catecholaminergic, and serotonergic systems, contributing to its complex mechanism of action (Wilder-Smith et al., 1994).

4. Mechanism of interaction between molecules and opioid receptors

The mechanism of action of substances on opioid receptors was developed based on research into the interactions of endogenous opioid peptides with these receptors, taking into account their chemical structure. This mechanism is based on the classic "ligand-receptor" principle, in which endogenous opioids such as endomorphins, enkephalins, and dynorphins exhibit selectivity for specific subtypes of opioid receptors – MOR (μ), DOR (δ), and KOR (κ). A common amino acid sequence at the N-terminus of the peptide chain plays a key role in this selectivity: Tyr-Pro-Phe/Trp-Phe (Okada et al., 2002). This specific sequence is responsible for transmitting the signal ("message") to the receptor, while the rest of the peptide determines specificity for a particular type of receptor ("address") (Portoghese et al., 1990). It has been established that the structure of tyramine, present in both endogenous opioid peptides and natural alkaloids (e.g., morphine, codeine), plays a key role in transmitting the signal ("message") to the MOR receptor. The rest of the molecule acts as

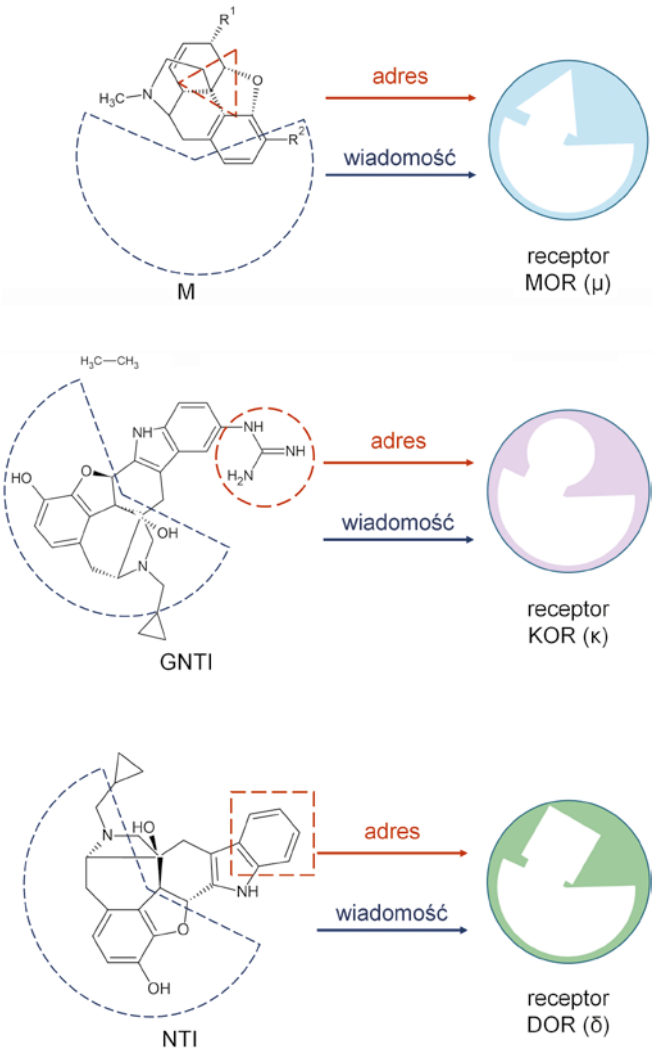

Fig. 8. Proposed concept of the "message-addressee" model in selective opioid receptor ligands – morphine (M), 5'-guanidinonaltridol (GNTI), and naltrindol (NTI)

a structural link, resembling a skeleton –Gly-Gly–, and is responsible for selectivity ("address") towards a specific opioid receptor subtype. According to the "message-address" model, the opioid receptor has a domain that recognizes the common pharmacophore of ligands (i.e., the spatial arrangement of atoms and functional groups necessary to bind to the receptor) and a site responsible for selectivity (Fig. 8) (Chavkin & Goldstein, 1981; Lipkowski et al., 1986; Portoghese, 1993).

The chemical structure of fentanyl allows for additional interactions that stabilize its binding to the MOR (μ) receptor, which translates into a significantly greater potency compared to morphine. The presence of a piperidine ring allows the fentanyl molecule to penetrate deeper into the receptor pocket and form additional hydrogen bonds with histidine H297, which leads to stabilization of the ligand-receptor complex. In addition, fentanyl can interact via a salt bridge with Asp147, which is another interaction that enhances its binding, which morphine does not exhibit. The greater number of hydrophobic interactions also plays an important role – the phenylethyl fragment of fentanyl occupies a special pocket in the receptor that is inaccessible to morphine, which further enhances its affinity for MOR. In addition, the structure of fentanyl allows for π-π interactions of the benzene ring, which are absent in morphine. Ultimately, the specific shape of the fentanyl molecule, which takes on a Y-shaped conformation, fits better into the orthosteric receptor pocket, while morphine has a more compact, elliptical structure (Vo et al., 2021; Zhuang et al., 2022). Nitazenes, like fentanyl, use a tertiary amine to form a salt bridge with Asp147, which anchors the molecule in the central cavity of the receptor. However, the more hydrophilic nitro-substituted benzimidazole of nitazene occupies a pocket between TM2 and TM7, interacting with Tyr75, His319, and Ile322. The nitro group of nitazene forms a hydrogen bond with Tyr75, which stabilizes the ligand-receptor complex (Clayton et al., 2024).

Table 1. Comparison of the relative potency of selected opioids compared to morphine.

Opioid class	Opioid	Potency relative to morphine	Literature
Phenanthrene derivatives	morphine	1	(World Health Organization, 2018)
	codeine	0,1	
	heroin	3	
	buprenorphine	80-100	
	oxycodone	1,5	(World Health Organization, 2018)
Phenylpiperidine derivatives	pethidine	0,125	
	fentanyl	100	(Vardanyan & Hruby, 2014)
	carfentanyl	10000	
	acetylfentanyl	15-45	
	sulfentanyl	4521	
	alfentanil	72	
	remifentanil	200	
Diphenylheptanes	methadone	5-10	(World Health Organization, 2018)
Benzomorphans	pentazocine	0,167	(Beaver et al., 1966)

Table 1. Cont.

Opioid class	Opioid	Potency relative to morphine	Literature
Benzimidazoles	flunitazene	1	(Holland et al., 2024)
	metodesnitazene	1	
	nitazene	2	
	clonitazene	3	
	butonitazene	5	
	menitazene	10	
	etazene	70	
	metonitazene	100	
	protonitazene	500	
	etonitazene	1000	
U series	AH-7921	1	(United Nations Office for Drug Control and Crime Prevention, 2024)
	U-4770	10	
Piperazines	MT-45	0,8-1	
Others	tramadol	0,1	(Wilder-Smith et al., 1994)

5. Methods for synthesizing selected synthetic opioids and their markers

5.1. Fentanyl

5.1.1. Janssen method

The first method for synthesizing fentanyl was patented in 1964 by Belgian chemist Paul Janssen, founder of Janssen Pharmaceuticals (Stanley, 2014). This is a five-step process that begins with the reductive amination of 1-benzyl-4-piperidone (1) with aniline and p-toluenesulfonic acid, leading to the formation of an imine derivative (2). The imine is then reduced with lithium aluminum hydride in ether, resulting in 1-benzyl-N-phenylpiperidine-4-amine (3). In the third step, the amine is acylated with propionic anhydride in the presence of toluene. The next, fourth step involves hydrogenolysis, i.e., removal of the benzyl group, using a palladium catalyst on carbon and hydrogen in ethanol, which leads to the formation of norfentanyl (5). In the final stage, norfentanyl (5) reacts with (2-chloroethyl)benzene in the presence of sodium carbonate, potassium iodide, and 4-methyl-2-pentanone (MIBK), undergoing an S_N2 nucleophilic substitution reaction, which results in the formation of fentanyl (6) (Janssen & Gardocki, 1962).

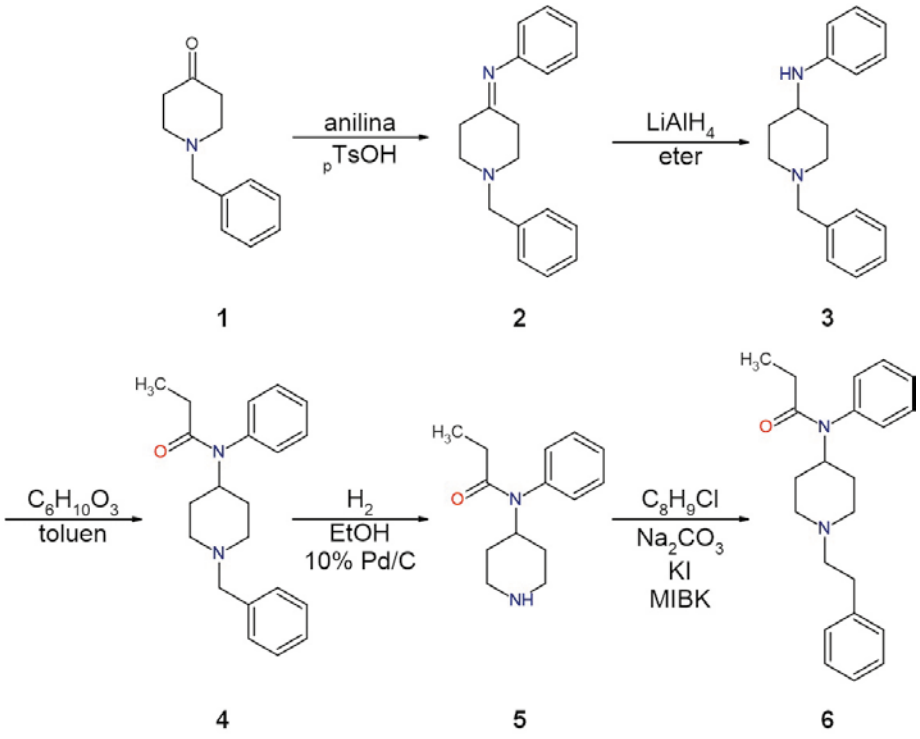

Fig. 9. Janssen's method for the synthesis of fentanyl

The Janssen method requires techniques that may be too complex or costly for production outside of controlled industrial settings [75]. For this reason, it is suspected that fentanyl obtained using this method comes mainly from legal chemical manufacturers in China, rather than from clandestine laboratories in North America (Drug Enforcement Administration, 2018). Data from the US fentanyl profiling program showed that after NPP and ANPP came under international control in 2017, the Janssen method became the dominant method of illicit production of confiscated fentanyl in 2019.

5.1.2. Modified Janssen method

The United States Army Combat Capabilities Development Command Chemical Biological Center (DEVCOM CBC) has developed a modified Janssen method with only four synthesis steps. The first step is the reductive amination of 1-benzyl-4-piperidone (1) using sodium triacetoxyborohydride (STAB), which leads to the formation of 1-benzyl-N-phenylpiperidine-4-amine (2). Next, propionyl chloride and oxalic acid are used to form an amide bond, resulting in N-(1-benzyl-4-piperidinyl)-N-phenylpropionamide oxalate (3). In the next step, catalytic transfer hydrogenation is carried out using ammonium formate, leading to the formation of norfentanyl (4). Finally, norfentanyl is alkylated with 2-chloroethylbenzene, resulting in the formation of fentanyl (5) (Walz & Hsu, 2017).

5.1.3. Siegfried method

In 1998, a simplified four-step method for synthesizing fentanyl, known as the Siegfried method, was published and disseminated on the Internet. Its name comes from the pseudonym “Siegfried” used by the author of the guide describing this method of synthesis. In the first step, which is the alkylation of piperidone, 4-piperidone (1) is used as the substrate, which is mixed at a temperature below boiling point in the presence of a base (potassium carbonate), a phase transfer catalyst (polyethylene glycol, PEG-400) and a solvent (acetonitrile, ACN). The mixture is then heated to boiling with (2-bromoethyl)benzene, which leads to a nucleophilic substitution reaction (SN2) and the formation of N-phenylethyl-4-piperidone (NPP, 2). In the second stage, NPP is reacted with aniline to form an imine derivative (3). This process takes place at room temperature with continuous stirring. Sodium borohydride is then added to the mixture, which reduces the imine to 4-anilino-N-phenylethylpiperidine (ANPP, 4). This reaction takes place at room temperature in the presence of methanol. In the final stage, ANPP is acylated by alkylation of the secondary amino group with propionyl chloride in the presence of pyridine. This reaction produces fentanyl (5) (Casale et al., 2020a).

Before NPP and ANPP were controlled under the US Controlled Substances Act of 1970, in 2008 and 2010 respectively, the Siegfried method was the dominant method of producing illicit fentanyl in local laboratories.

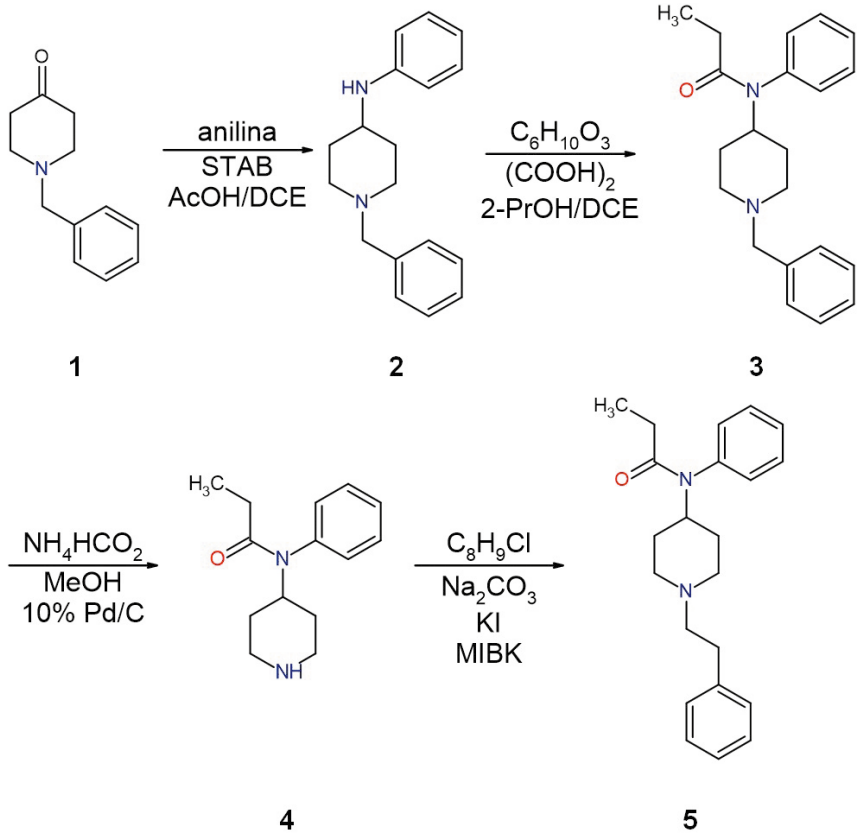

Fig. 10. Modified Janssen method for the synthesis of fentanyl

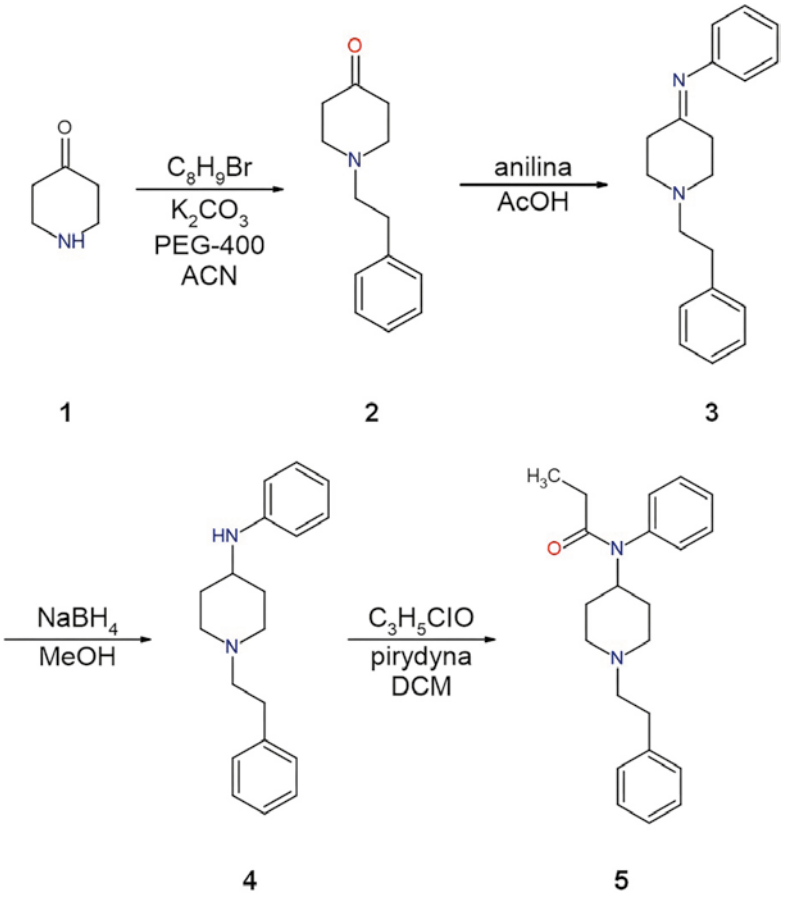

Fig. 11. Siegfried's method for the synthesis of fentanyl

However, after the availability of key substances was restricted, this method gradually lost its importance, giving way to the more advanced Janssen method.

5.1.4. Gupta I method (also known as the One-Pot method)

In 2005, Pradeep Gupta published an article describing a one-pot synthesis of fentanyl, carried out at room temperature through three consecutive tandem reactions. The process begins with the reductive alkylation of 4-piperidone (1) with phenylacetaldehyde in a dichloroethane and triethylamine environment. The mixture is initially prepared in a dry nitrogen atmosphere, then STAB is added and left to mix at room temperature, leading to the formation of NPP (2). In the next step, aniline is added, which enables the reductive amination of the ketone group, resulting in the formation of ANPP (3). The final step is acylation – the addition of propionyl chloride in the presence of triethylamine, which leads to the formation of fentanyl (4) (Gupta et al., 2005).

5.1.5. Gupta II method (also known as the Gupta patent)

In 2009, Pradeep Gupta published a patent for another simple, environmentally friendly, and inexpensive method for synthesizing fentanyl. The process begins with the reaction of 4-piperidone (1) with aniline in the presence of zinc and acetic acid, leading to the formation of 4-AP (2). In the next step, 4-AP is alkylated with

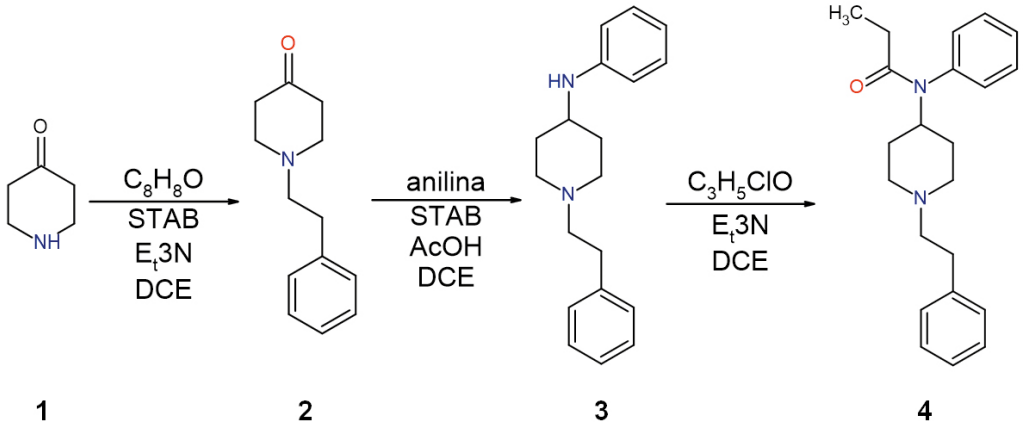

Fig. 12. Gupta I method (One-Pot method) for the synthesis of fentanyl

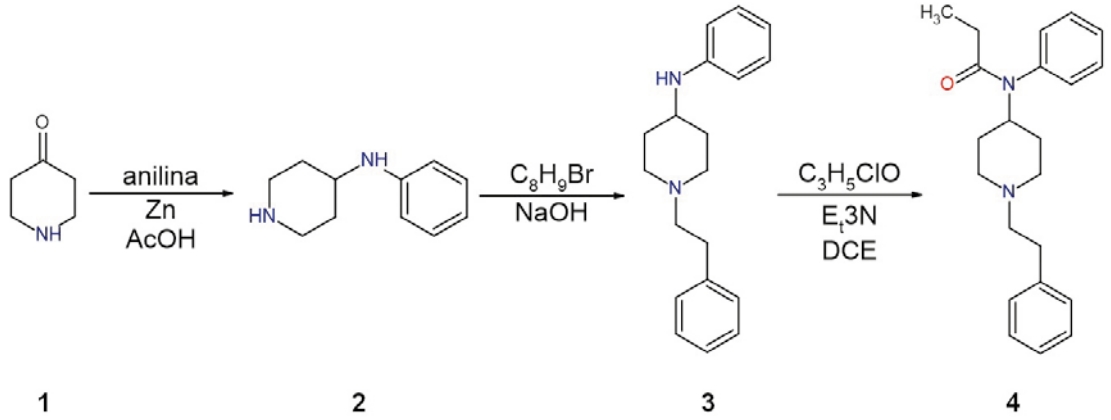

Fig. 13. Gupta II method (Gupta patent) for the synthesis of fentanyl

(2-bromoethyl)benzene and then heated to boiling in an aqueous sodium hydroxide solution. After the reaction is complete, the mixture is filtered and recrystallized to obtain ANPP (3). The final step is to use the Gupta I method (One-Pot method), i.e., adding propionyl chloride in the presence of triethylamine, which leads to the synthesis of fentanyl (4) (Gupta et al., 2009).

However, tighter regulations have once again forced illegal manufacturers and suppliers to move their operations from China to India and to abandon the Janssen method in favor of a synthesis based on a 2005 Indian patent known as the Gupta patent. Data from the US fentanyl profiling program showed that by 2021, this method had become the dominant method of illicit fentanyl production.

5.1.6. Dieckmann method

In 2005 and 2009, Hossein Fakhraian and Babaei Panbeh Riseh published two articles on the two-step reaction of phenylethylamine with methyl acrylate catalyzed by a protic solvent and an improved procedure for obtaining 1-(2-phenethyl)-4-piperidone. In the first step, methyl methacrylate is reacted with phenethylamine (1) in the presence of methanol, leading to a Michael addition and the formation of N,N-bis-(β-carbomethoxyethyl)phenethylamine (2). Next, a Dieckmann condensation is carried out using sodium t-butoxide as a basic catalyst and xylene as the preferred solvent. The reaction is carried out at room temperature, ensuring that the reaction environment is completely dry to avoid unwanted polymerization. The resulting intermediate

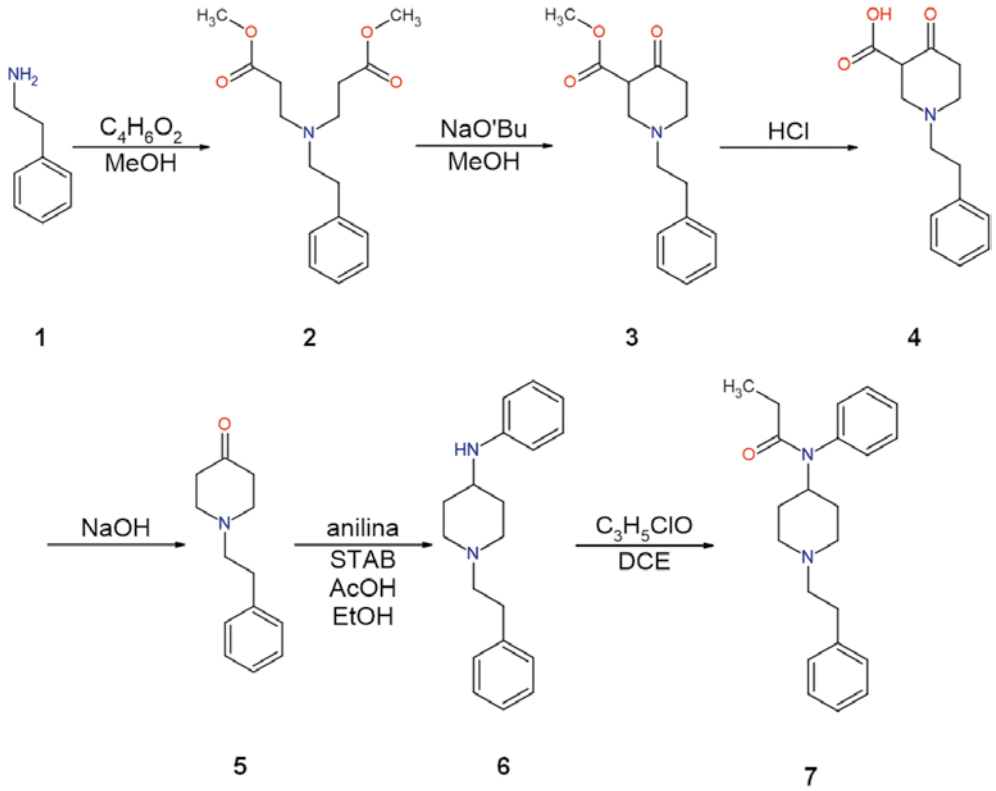

Fig. 14. Dieckmann's method for the synthesis of fentanyl

methyl-4-oxo-1-phenethylpiperidine-3-carboxylate (3) is acidified to pH 3–4 and then refluxed, leading to hydrolysis of the carboxylate ester and its conversion to carboxylic acid (4). The final step is decarboxylation in an alkaline environment using an excess of sodium hydroxide, leading to the formation of NPP (5). Then, in 2016, Yu Xinhong patented the refinement of this method with two additional steps. These involved the addition of aniline in the presence of acetic acid and ethanol to produce ANPP (6), and a fourth step detailed the acylation of ANPP with propionyl chloride in the presence of dichloroethane to produce fentanyl (7) (Fakhraian & Panbeh Riseh, 2005; Fakhraian & Riseh, 2008; Xinhong et al., 2011).

The Dieckmann method does not require piperidone as a starting material, which is commercially expensive compared to methyl acrylate and phenethylamine. For this reason, it is considered an attractive alternative to other methods.

5.7.1. Valdez method

In 2014, Carlos Valdez published an article describing an optimized synthesis of fentanyl, which is a modified version of Siegfried's method. The first key difference is the alkylation of 4-piperidone (1) with (2-bromoethyl) benzene in the presence of cesium carbonate to produce NPP (2). The second difference is the reductive amination with aniline in a STAB and acetic acid environment to obtain ANPP (3). The use of STAB, which does not reduce ketones, in the presence of aniline allows for the reductive amination of NPP directly to ANPP. The final difference is the acylation of ANPP (4) with propionyl chloride in the presence of Hunig's base - N,N-diisopropylethylamine (DIPEA) to produce fentanyl (5) (Valdez et al., 2014).

5.1.7. The t-BOC method

The synthesis of fentanyl using the t-BOC method involves five steps, using tert-butoxycarbonyl (t-BOC) as the starting material. In the first step, t-BOC-piperidone (1) reacts with aniline in 1,2-dichloroethane in the presence of cesium carbonate, acetic acid, and STAB, leading to the formation of t-BOC-4-AP (2). This compound is then acylated with propionyl chloride in dichloromethane, resulting in the formation of t-BOC-norfentanyl (3). In the next step, the t-BOC protecting group is removed with hydrochloric acid in methanol, revealing free norfentanyl (4). In the final step, norfentanyl reacts with (2-bromoethyl)benzene in acetonitrile in the presence of cesium carbonate, leading to the synthesis of fentanyl (5) (Toske et al., 2023).

5.2. Fentanyl synthesis markers

Profiling illicit fentanyl relies on the identification of characteristic synthesis markers, which allow for the determination of the production method used and the potential source of the substance. Several studies on illicit fentanyl profiling have been reported in recent years (Casale et al., 2020b; Lurie et al., 2012; Mayer et al., 2016; Mörén et al., 2019; Toske et al., 2023).

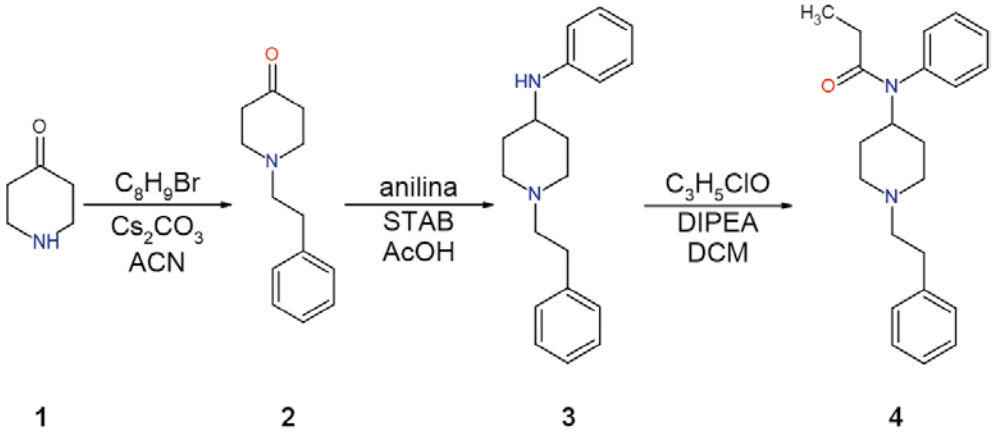

Fig. 15. Valdez method for the synthesis of fentanyl

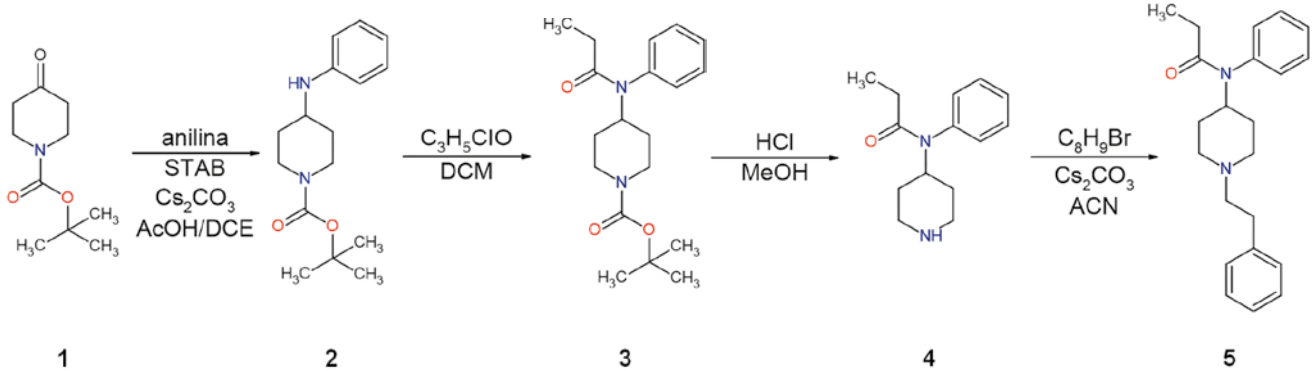

Fig. 16. t-BOC method for the synthesis of fentanyl

Table 2. Markers of individual fentanyl synthesis methods (Casale et al., 2020b; Lurie et al., 2012; Mayer et al., 2016; Mörén et al., 2019; Toske et al., 2023)

Synthesis method	Reagent	Marker
Janssen method	1-benzyl-4-piperidone, aniline, p- toluenesulfonic acid , lithium aluminum hydroxide , propionic anhydride, palladium on carbon catalyst, hydrogen, ethanol, (2-chloroethyl)benzene, sodium carbonate, potassium iodide, 4-methyl-2-pentanone (MIBK)	benzylamine
		N-phenylpiperidin-4-amine
		1-benzyl-4-piperidone
		1-Benzyl-4-hydroxypiperidine
		N-(phenmethyl)-1-phenmethyl-4-piperidinamine
		N-(phenylmethyl)-1-phenyl-4-piperidinamine
		1-benzyl-4-anilinopiperidine
		N-(4-piperidyl)-N- phenylpropamide
		1-benzyl-4-propionyloxypiperidine
		N- benzylpropanamide
		N-(benzyl-4-piperidinyl)-N- phenylpropamide
Siegfried method	4-Piperidone, Potassium Carbonate, PEG-400, Acetonitrile (ACN), (2-Bromoethyl)benzene, Aniline, Sodium Borohydride, Methanol, Propionyl Chloride , Pyridine	phenethylamine
		N,1-bis(2-phenethyl)piperidine-4-amine
		1-phenyl-N-(2-phenethyl)piperidin-4-amine
		phenethylpropanamide
		N-(1-phenethyl-4-piperidyl)-N- phenethylpropanamide
		N-(2-phenethyl)-N-(1-phenyl-4-piperidinyl) propanamic
		N,N- dipropionylphenethylamine
Gupta patent method	4-piperidone, aniline, zinc, acetic acid, (2-bromoethyl) benzene, sodium hydroxide, propionyl chloride , triethylamine	1-benzyl-4-piperidone
		N -propionyl fentanyl
		4-anilino-N-phenethylpiperidine
		Phenethyl- 4-anilino-N-phenethylpiperidine
		N- phenylpropanamide
		N- methylnorfentanyl
		benzylfentanyl
		acetylfentanyl
t-BOC method	t-BOC- piperidone , aniline, 1,2-dichloroethane, cesium carbonate, acetic acid, STAB, propionyl chloride , dichloromethane, hydrogen chloride in methanol, (2-bromoethyl)benzene, acetonitrile	N- phenylpropanamide
		norfentanyl
		4-anilino-N-phenethylpiperidine
		benzylfentanyl
		acetylfentanyl

5.3. Benzimidazole derivatives (nitazenes)

One of the first compounds studied by the CIBA team was 1-(β-diethylaminoethyl)-2-benzylbenzimidazole. This discovery inspired scientists to conduct systematic studies of 2-benzylbenzimidazole derivatives, leading to the development of universal methods for their synthesis (Grimmett & Grimmett, 1997; Pardeshi et al., 2021). The first method was based on the acid-catalyzed cyclocondensation of the appropriate 1,2-phenylenediamine derivatives (1) with para-ethoxy-phenylacetonitrile (2). This reaction, known as the Ladenburg-Phillips reaction, first leads to the formation of anilides, which then cyclize to form 2-benzylbenzimidazole (3). Alternatively, carbonitriles, iminoethers, or amidines can be used as carbonyl equivalents. This process is catalyzed by inorganic acids such as hydrochloric acid, polyphosphoric acid, or boric acid. The resulting benzimidazole was then alkylated with the appropriate 1-chloro-2-dialkylaminoethane (4), yielding the final product (5). In the case of oxidative cyclocondensations, it is also possible to use aldehydes, which in the presence of Cu(II) ions undergo the Weidenhagen reaction (Ujváry et al., 2021), (Hunger et al., 1957, 1960). This particular procedure proved most useful in preparing benzimidazoles that lacked substituents on their benzene rings.

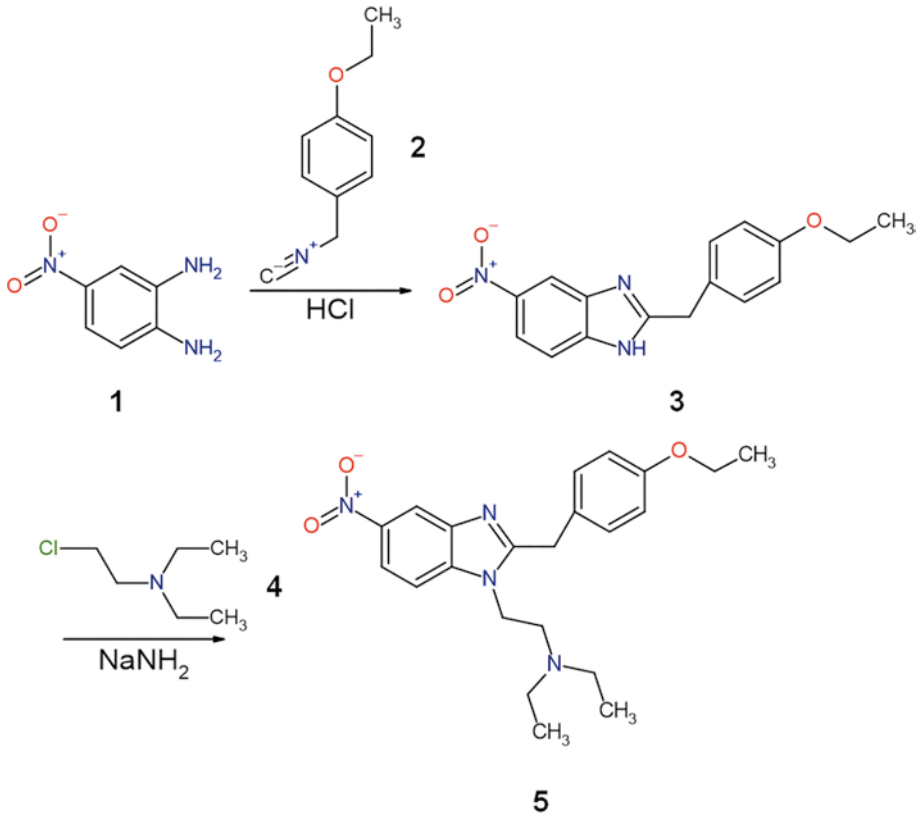

Fig. 17. The first method of nitazenes synthesis, using etonitazene as an example

The second synthesis developed by the Swiss CIBA team first involved the alkylation of 1-chloro-2,4-dinitrobenzene (1), where the activated chlorine atom can be replaced by N,N-dialkylated alkylenediamines, for example 2-diethylaminoethylamine (2). Regioselective reduction of the nitro group adjacent to the alkylamino moiety in 2,4-dinitroaniline (3) to the corresponding primary amine can be accomplished using ammonium sulfide. Condensation of the resulting ortho-phenylenediamine (4) with an appropriately substituted imidate (5) leads to the 5-nitrosubstituted final product (6) (Carroll et al., 1967; Hoffmann et al., 1960). This procedure is particularly useful for the preparation of 4-, 5-, 6-, and 7-nitrobenzimidazoles. By varying the choice of substituted imino ether of phenylacetic acid, compounds with a variety of substituents on the benzene ring at the 2-position are obtained.

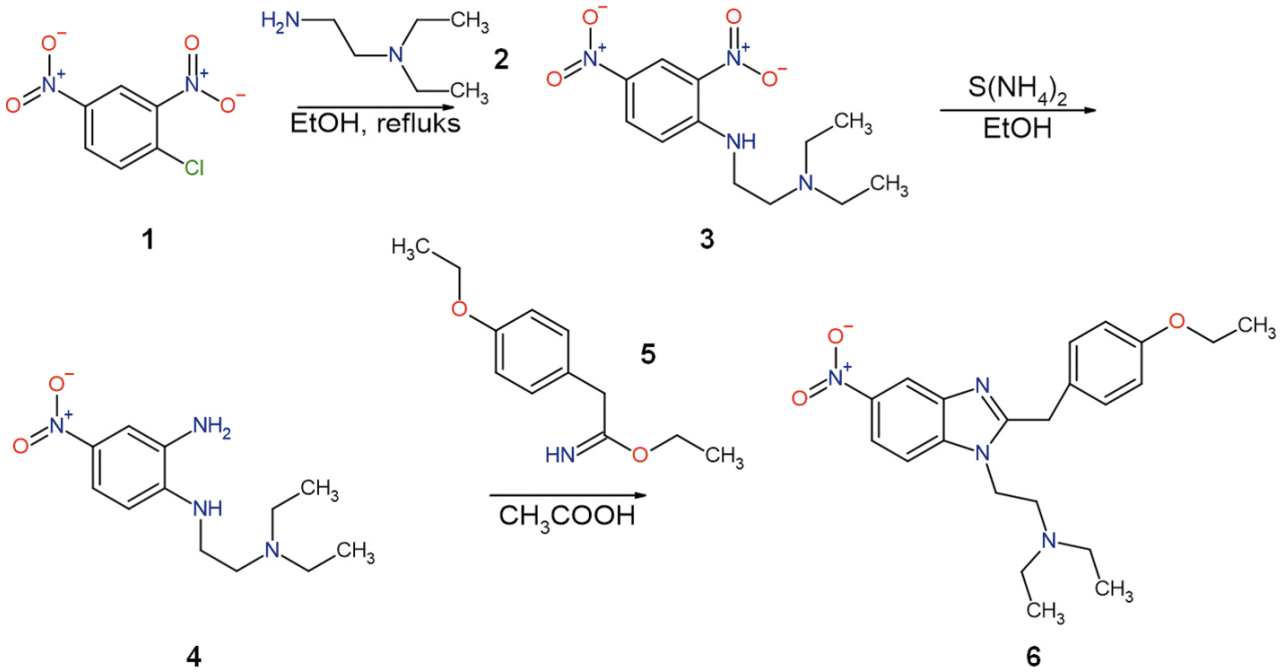

Fig. 18. The second method of nitazenes synthesis using etonitazene as an example

In 1975, Frank Carroll and Michael Coleman developed a novel, high-yield method for the synthesis of etonitazene. They were tasked with preparing large quantities of this compound but found conventional synthesis insufficient. The main problem with the traditional method was the instability of the iminoether reagent – 2-(4-ethoxyphenyl)acetimidoic acid ethyl ester, which was obtained by reacting 4-ethoxyphenylacetonitrile with ethanolic HCl. The iminoether required anhydrous reaction conditions and was difficult to synthesize on a large scale. To address this problem, the authors experimented with the coupling reagent EEDQ (N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline), which promoted the condensation of 2-(2-diethylaminoethylamino)-5-nitroaniline (1) with 4-ethoxyphenylacetic acid (2). The use of EEDQ allowed the acylation and cyclization steps to be carried out in one pot, significantly simplifying the entire process. (Carroll & Coleman, 1975; Thomas et al., 1997). In 1999, it was reported that a chemist involved in the illegal production of etonitazene (3) in Moscow had used this “improved” method (Ujváry et al., 2021).

5.4. Methadone

Methadone (6-dimethylamino-4,4-diphenyl-3-heptanone) was developed during World War II by German chemists Max Bockmühl and Gustav Ehrhart working for the pharmaceutical company IG Farben (Frankfurt am Main, Germany). On September 11, 1941, they filed a patent for this compound, which was given the trade name Polamidon (Defalque & Wright, 2007). In 2024, the Central Bureau of Investigation of the Police and the Anti-Drug Department of the National Police of Ukraine (ukr. Департамент боротьби з наркозлочинністю Національної поліції України) conducted a large-scale operation that led to the dismantling of the largest synthetic opioid production laboratory in Poland to date. During 38 police operations conducted in both countries, law enforcement officers seized a total of 195 kilograms of crystal methadone. (Europol, 2024). The synthesis of methadone begins with the alkylation of the diphenylacetonitrile anion (1), formed by reacting diphenylacetonitrile with a strong base such as NaOH in the presence of sodium amide

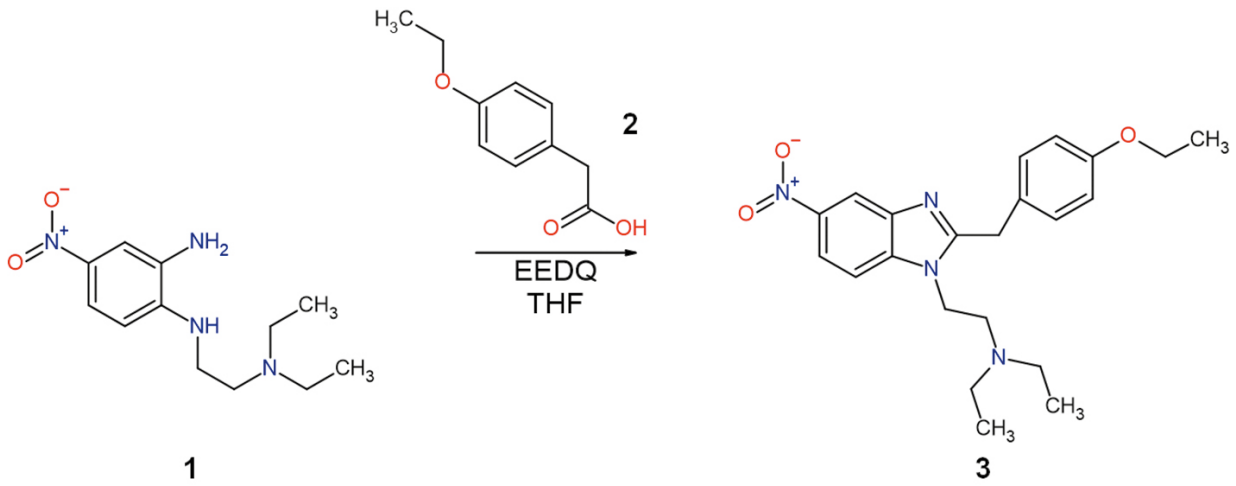

Fig. 19. Method for the synthesis of nitazenes, based on the example of etonitazene using EEDQ

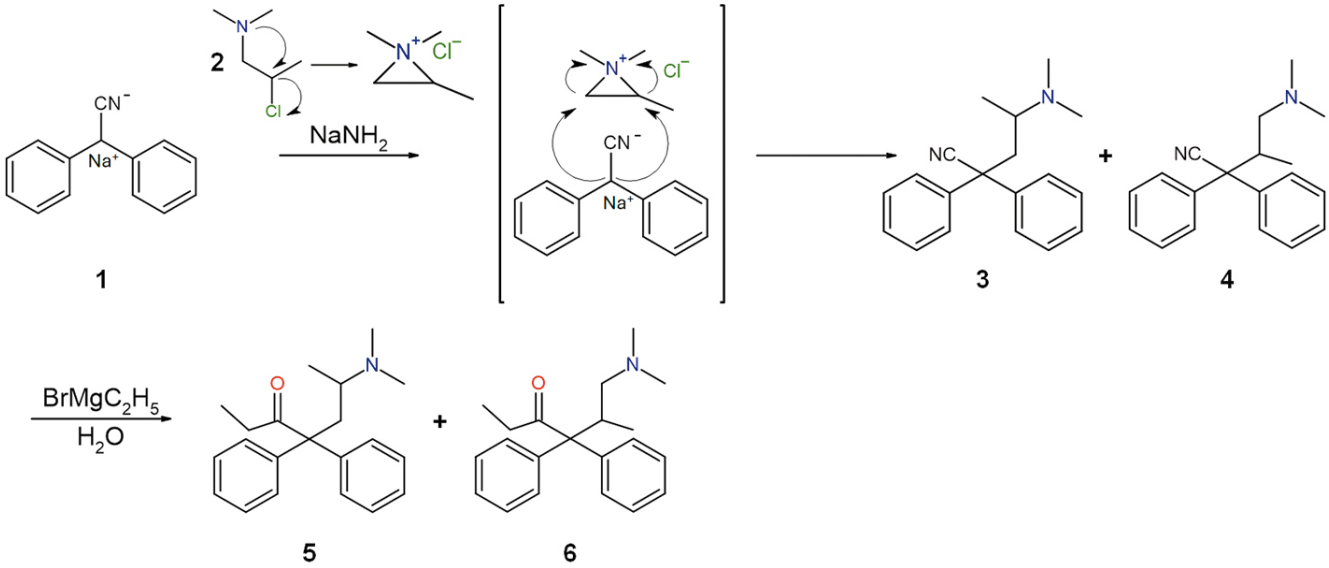

Fig. 20. Methadone synthesis method

(lithium amide, potassium tert-butoxide, and sodium hydroxide have been used interchangeably). 1-Dimethylamino-2-chloropropane (2) is used as the alkylating reagent, which cyclizes under the reaction conditions to form an aziridinium salt (1,1,2-trimethylaziridinium chloride). Depending on the direction of attack of the diphenylacetonitrile anion on the aziridinium cation, ring opening occurs at different positions. This results in the formation of a mixture of two isomeric nitriles. If the diphenylacetonitrile anion attacks from the left, 2,2-diphenyl-4-dimethylaminovaleronitrile (3) (referred to as methadone nitrile) is formed, and if it attacks from the right, 2,2-diphenyl-3-methyl-4-dimethylaminobutyrone (4) (referred to as isomethadone nitrile) is formed. Separation of the isomeric nitriles was not carried out in the original process, but methadone nitrile, having a higher melting point, is less soluble in hexane, while isomethadone nitrile forms less soluble salts with p-toluenesulfonic acid and oxalic acid. 2,2-Diphenyl-4-dimethylaminovaleronitrile, after Grignard reaction with ethylmagnesium bromide formed in situ and subsequent hydrolysis, gives methadone (5), while 2,2-diphenyl-3-methyl-4-dimethylaminobutyrone reacts with ethylmagnesium bromide to give a stable ketimine (3-imino-4,4-diphenyl-5-methyl-6-dimethylaminohexane), which hydrolyzes with difficulty to isomethadone (6). Without separation of the isometric nitriles, a mixture of constitutional isomers is formed in the last step of the synthesis.

Methadone is a racemate containing equimolar amounts of dextromethadone and levomethadone. Levomethadone is approximately twice as potent as the racemic mixture of methadone, but this difference is usually not significant enough to justify routine separation of the isomers. The process of enantiomer separation is not complicated; adding d-tartaric acid to a solution of racemic methadone in a mixture of acetone and water leads to the formation of diastereomeric salts with varying solubility. The less soluble dextromethadone levotartrate salt precipitates and is separated by filtration. Levomethadone can then be isolated from the mother liquor in high yields after alkalization and extraction (Barnett, 1976).

6. Summary

Synthetic opioids pose a significant challenge to both law enforcement and the healthcare system due to their high potency and growing popularity on the black market. Their high potency is determined by their binding mechanisms to opioid receptors, and their synthesis, often conducted under uncontrolled conditions, results in the presence of characteristic chemical markers. Profiling synthetic opioids, including analysis of their impurities and synthesis methods, can be a crucial tool in identifying their sources, which is crucial for forensic activities and countering the threats associated with these substances.

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