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Illicit Street Drugs?! Recent Trends and Chemistry

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Abstract

This mini-review describes recent trends in illicit drug market. The COVID-19 pandemic has changed the habits of many young adults, but still the uses of (novel) illicit substances remain high. Drug addiction and tolerance seem to be a major worldwide burden. Multiple drug use is not infrequent and it was associated with a higher incidence of major adverse events than single drug use. The emerging illicit substances will be discussed including their pharmacological effects and their chemical synthesis/structure. The goal of this review is to shed more light on such important aspects of illegality, commonly occurring in urban life. Better drug education, increased law enforcement, and rehabilitation programs should be undertaken to tackle a foremost world burden.

Keywords: Illicit drugs; Street drugs; Side effects; Life-threatening molecules; COVID-19; Synthesis

Abbreviations

α-PVP: α-Pyrrolidinopentiophenone; CNS: Central Nervous System; COPD: Chronic Obstructive Pulmonary Disease; COVID-19: Coronavirus Disease 2019; DCM: Dichloromethane; DMSO: Dimethyl Sulfoxide; EEDQ: N-Ethoxycarbonyl-2-Ethoxy-1,2-Dihydroquinoline; EMCDDA: European Monitoring Centre for Drugs and Drug Addiction; FDA: Food and Drug Administration; GABA: Gamma-Aminobutyric Acid; LSD: Lysergic Acid Diethylamide; m-CPBA: meta-Chloroperoxybenzoic Acid; PEA: Phenethylamine; TFA: Trifluoroacetic Acid; TFE: 2,2,2-Trifluoroethanol; TEA: Triethylamine; THC: Tetrahydrocannabinol; THF: Tetrahydrofuran; TMEDA: Tetramethylethylenediamine

Introduction

Illicit drugs are substances that either stimulate (such as cocaine or amphetamines) or depress (such as sedative-hypnotics or heroin) the Central Nervous System (CNS) or cause hallucinogenic effects (such as marijuana (cannabis) or Lysergic Acid Diethylamide (LSD)) to the effect that their use has been forbidden globally for recreational use (Figure 1) [1]. In the case of marijuana, the definition of illicit would be not completely appropriate given the fact it has been legalized in many states for therapeutic purposes [2].

In March 2022, The Guardian reported that "there has been a substantial rise in overdose deaths, with 100,000 Americans dying in a recent 12-month period, which is three times the number of traffic accident deaths and twice as many as those killed by guns" [3].

Almost ten years earlier, in 2010, it was reported that cocaine was the second most widely trafficked drug in the world, following only cannabis in this regard. Over the past decade, its recreational use has increased in most European countries [4].

In Europe, from 1997 to early 2000s a particular derivative of amphetamine, methamphetamine, was abused in the USA [5], Australia [6] or Asia [7]. Most of the European use occurs in Central Europe and is based on production in the Czech Republic and Slovakia [8].

Benzodiazepines (sedative/hypnotics) are mostly used illegally in combination with alcohol and opioids [9]. LSD use has been on the rise within the last decades, particularly among those who are well educated [10].

The more recent COVID-19 pandemic has forced governments across the world to take measures that have affected the illegal drug market. For example, pandemic has led to the widespread disruption of trafficking routes for illegal drugs, mainly by air and on land, thus impeding transport of many synthetic substances such as methamphetamine. On the other side, heroin market (mainly

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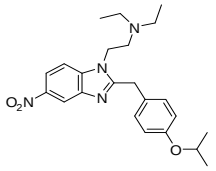
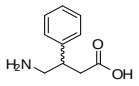
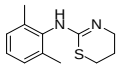
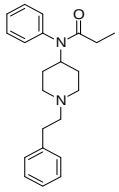
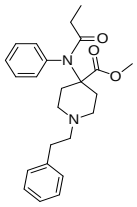
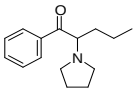
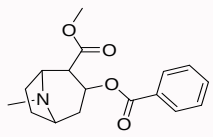
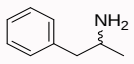
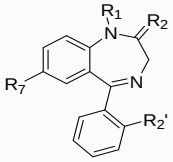
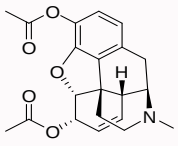
Table 1: Name and chemical structure of the six emerging illicit drugs.

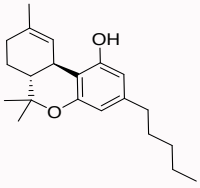
Name of emerging illicit drug	Chemical structure
Isotonitazene	
Phenibut	
Xylazine	
Fentanyl	
Carfentanil	
α-pyrrolidinopentiophenone	











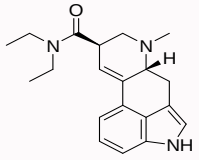


Figure 1: Structure of well-known CNS stimulating agents (cocaine, racemic amphetamine), CNS depressing agents (benzodiazepines and heroin) and hallucinogens [THC (main component of marijuana) and LSD].

black-marketed by land) is pushing it towards being trafficked along maritime routes. Marijuana is often produced near places where

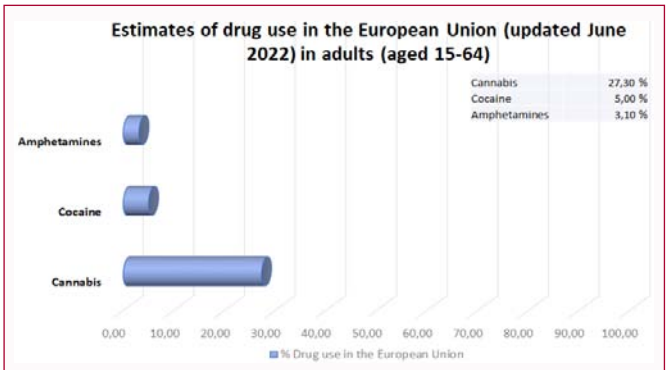


Figure 2: Lifetime estimated use of marijuana (cannabis), cocaine and amphetamines in adults (aged 15-64) in Europe [12].

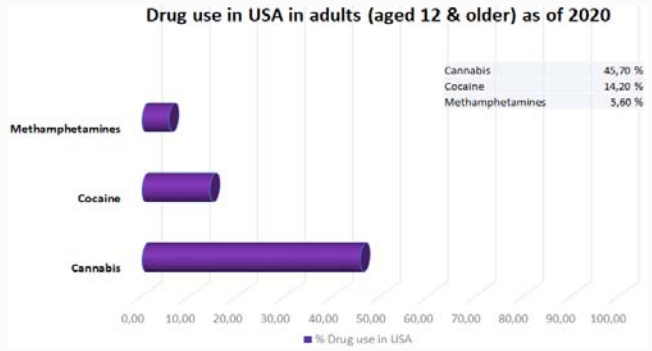


Figure 3: Lifetime use of marijuana (cannabis), cocaine and methamphetamines in adults (aged 12 & older) in USA as of 2020 [13].

it is bought and sold, traffickers of the drug, which is mostly still illegal worldwide, are less dependent on shipping it across regions and borders which may be under coronavirus lockdown [11]. Cannabis use is increasing [12] in many European countries that have legalized it, and that more countries are considering legalizing cannabis for medical and recreational purposes. The lifetime uses of marijuana (27.30%) largely over-came that of cocaine (5.00%) and amphetamines (3.10%) in adults (Figure 2). In USA, a similar trend was observed in adults aged older than 12 as of 2020 (Figure 3). Lifetime use of cannabis totaled 45.70% followed by cocaine (14.20%) and methamphetamines (5.60%) [13].

COVID-19 has caused some illegal drug prices to surge forcing some drug users to seek out for emerging, cheaper illicit drugs. A study conducted in Georgia has shown that COVID-19-related restrictive measures mediated specific changes in supply models and drug-use behaviors [14]. Given the large amount of knowledge, information and data on illegal substances reported in Figure 1, this review will not focus on such molecules and derivatives, but on the emerging drugs on the street [15]. According to Addiction Resource, the six most emerging chemical substances in this field are: Isotonitazene, phenibut, xylazine, fentanyl, carfentanil and α-pyrrolidinopentiophenone.

Emerging Illicit Drugs: Chemistry and Biological Effects

A description for each of the 6 emerging illicit drugs (Table 1) will be provided. The pharmacological effect and the chemical synthesis will be given. When available, more synthetic pathways will be provided.

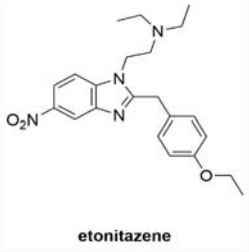


Figure 4: Structure of etonitazene, a potent benzimidazole-based opioid analgesic.

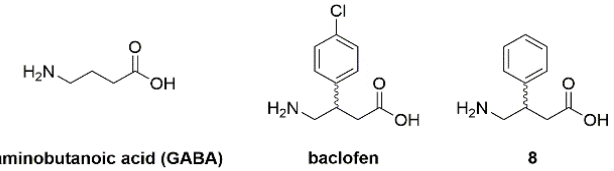


Figure 5: Structure of GABA (4-aminobutyric acid, γ-aminobutyric acid), racemic baclofen and racemic phenibut (8).

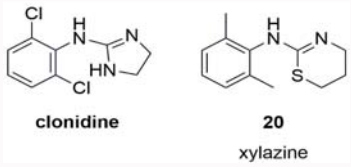


Figure 6: Structure of clonidine and xylazine (20).

Isotonitazene

Isotonitazene (5) is a derivative of benzimidazole and an opioid analgesic that is not medically authorized. It was first synthesized and patented in 1959 as part of research carried out by the Swiss pharmaceutical company CIBA [16,17]. Effects are similar to those caused by morphine and fentanyl, causing relaxation, euphoria, and respiratory depression [16]. It is a μ-opioid receptor agonist [18]. Its potency is about 500 times stronger than morphine [19]. Isotonitazene was formally notified to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) [19]. Isotonitazene is a risk to public health and a real danger to those who misuse drugs, especially both heroin and cocaine users. The extent of its use is still emerging in the UK and its existence should be known to staff at emergency departments [16]. This type of compound is not new. Similar benzimidazole derivatives with analgesic activity were first reported in 1957 [20]. The parent compound, etonitazene (Figure 4) is the most potent compound in this class, with an estimated reported potency of a hundred to a thousand times that of morphine [21]. Interestingly, given their similarity, isotonitazene was sold under the name etonitazene.

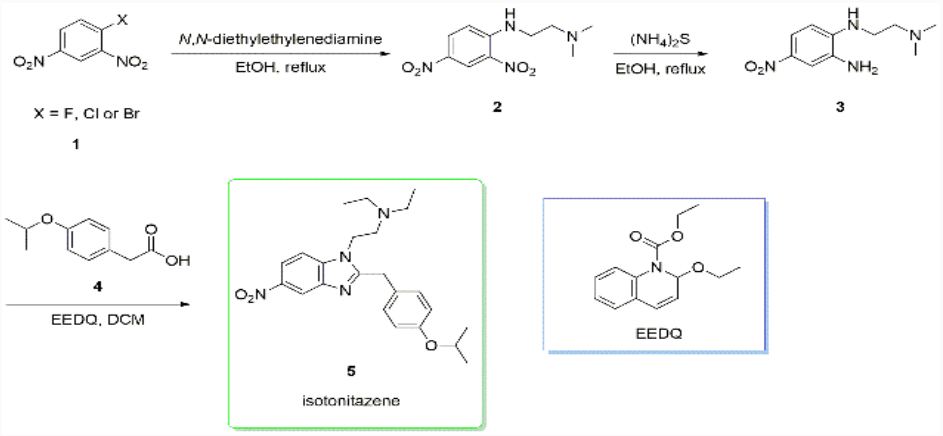
The synthesis of isotonitazene (Scheme 1) is quite straightforward [22]. It starts from halo-dinitrobenzene 1 which is treated with N,N-diethylethylenediamine in ethanol under re-flux in a SNAr to afford intermediate 2. The ortho nitro group to the aromatic amine was selectively reduced to primary amino group by Ammonium Sulfide [$(NH_4)_2S$] to give substituted aniline 3 (Zinin reduction). This was condensed with 2-(4-isopropoxyphenyl) acetic acid 4 under activation of carboxylic acid by N-Ethoxycarbonyl-2-Ethoxy-1,2-Dihydroquinoline (EEDQ) in DCM to provide benzimidazole isotonitazene (5).

A one-pot, three-component coupling reactions for the syntheses of benzimidazoles has been reported [23]. Conditions employ 2-iodo- or 2-bromoanilines (1.0 equiv), aldehydes (1.2 equiv), NaN3 (2.0 equiv), 5 mol% of Copper Chloride (CuCl), and 5 mol% of Tetramethylethylenediamine (TMEDA) in DMSO as solvent at 120°C for 12 h.

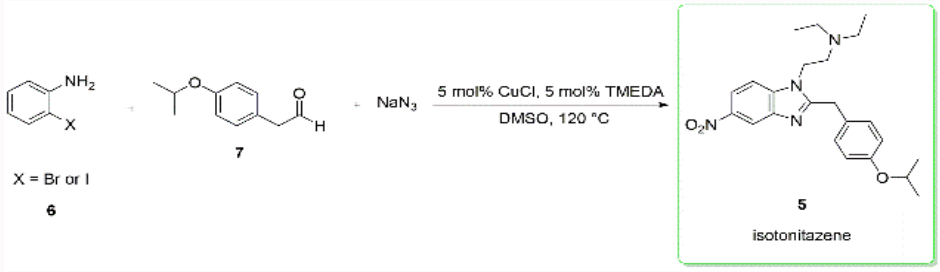
This strategy could be applied to obtain isotonitazene (Scheme 2) using 2-iodo- or 2-bromoanilines 6 and aldehyde 7. This system shows several advantages: It requires no preparation of the starting materials as they are commercially available, it does not require the isolation of intermediates and it is applicable for a wide range of substrates. The proposed mechanism is supposed to progress *via* halobenzene followed by insertion of copper and cyclization [23].

Phenibut

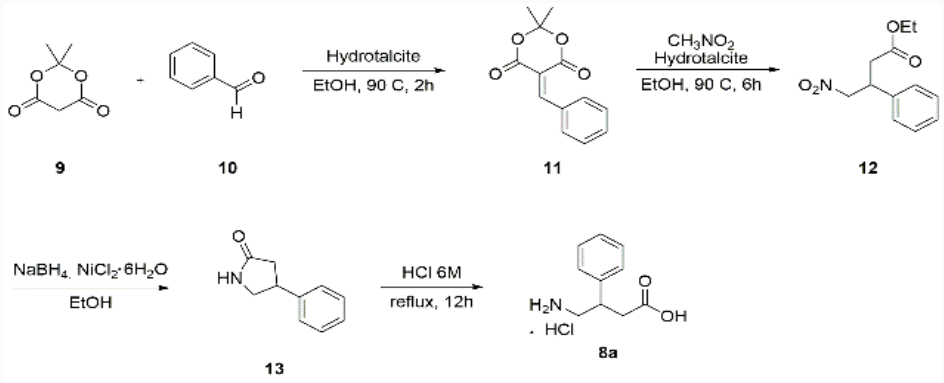
Phenibut (8), (Figure 5) is a psychoactive substance. Phenibut (β-phenyl-γ-aminobutyric acid) is a GABAB agonist; therefore, most of the pharmacological studies with PB were linked to its GABA-like properties (Figure 5) [21,22]. It was introduced in Russia and there licensed for the treatment of anxiety, alcohol withdrawal, stammering and insomnia [25]. A study with a patient taking phenibut showed that dependence including tolerance and significant withdrawal symptoms appeared [26]. Phenibut is an analogue of baclofen (Figure 5). The incorporation of a phenyl ring into GABA scaffold is expected to improve the entry of the molecule into the brain. Besides acting on GABA system, phenibut also stimulates dopamine receptors



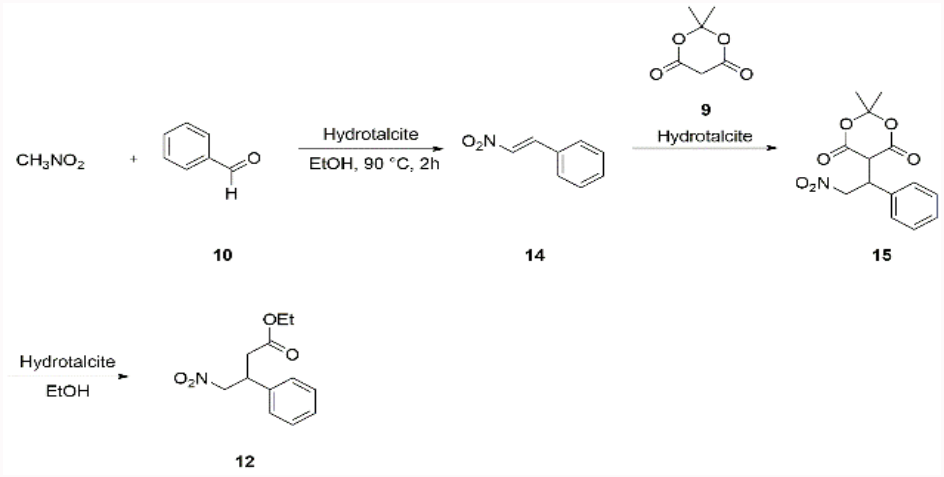
Scheme 1: Preparation of isotonitazene (5) [3]. EEDQ is shown in blue box.



Scheme 2: Proposed preparation of isotonitazene (5) *via* one-pot copper catalyzed strategy [23].



Scheme 3: Preparation of phenibut (8a, as hydrochloride) [28].



Scheme 4: Preparation of intermediate 12(alternative procedure), useful for the preparation of phenibut [28].

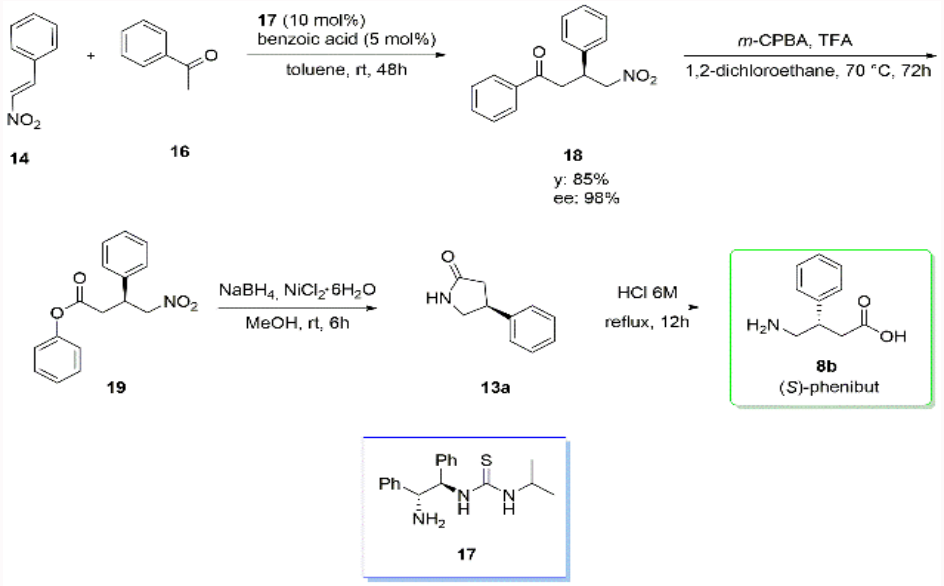
and antagonizes β-Phenethylamine (PEA), a putative endogenous anxiogenic, thus showing nootropic effects as well [25]. Both baclofen and phenibut are used clinically in their racemic forms even though they could be separated into R- and S-enantiomers [27].

A multicomponent preparation of phenibut intermediate has been reported [28]. The preparation involves the use of Meldrum's acid (9), benzaldehyde (10) and nitromethane with the employment of calcined hydrotalcite (a magnesium-aluminum hydroxycarbonate) as a catalyst. The hydrotalcite-like compounds exhibit dual basic/acid properties and thus exhibit interesting feature for catalysis [28].

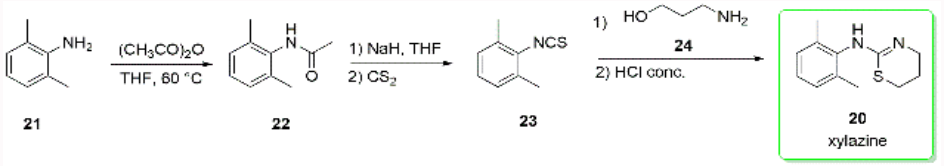
Two possible mechanisms are envisioned. The first (Scheme 3) involves a Knoevenagel condensation between 9 and 10 with the formation of benzylidene intermediate 11. This is subjected to attack by nitromethane to form nitro derivative 12 (loss of acetone and CO_2). Reduction of nitro of 12 mediated by $NaBH_4$ and $NiCl_2$ yielded lactam 13 which is eventually converted into phenibut (8a as hydrochloride) *via* acidic hydrolysis.

The second (Scheme 4) involves the Knoevenagel condensation between 8 and 10 to form nitro styrene 14. This was attacked by Meldrum's acid 9 (Michael addition) in the presence of hydrotalcite to form nitro compound 15. This was transformed into intermediate 12 upon addition of ethanol (loss of acetone and CO_2). The synthesis then proceeds in the same way as seen in Scheme 3.

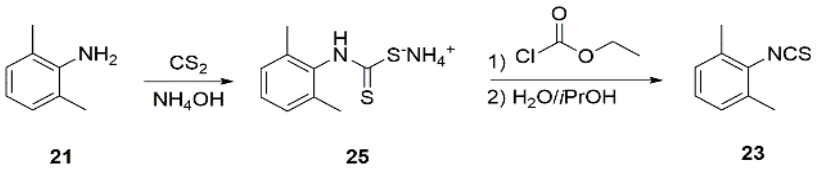
Another organocatalytic, asymmetric Michael addition of ketones to α, β-unsaturated nitro compounds have been reported (Scheme 5) [29]. (E)-Nitro styrene 14 and acetophenone 16 were mixed in toluene



Scheme 5: Organocatalytic, asymmetric Michael preparation of (S)-phenibut [29].



Scheme 6: Preparation of xylazine [34].



Scheme 7: Preparation of intermediate isothiocyanate 23 useful for the synthesis of xylazine [35].

in the presence of thiourea catalyst 17 and additive benzoic acid to form nitro ketone 18 in a very good yield and enantiomeric excess (85% and 98%, respectively). The oxidation of ketone group of 18 to corresponding benzoic ester mediated by meta-Chloroperoxybenzoic Acid (m-CPBA) and TFA provided compound 19. This was treated with similar conditions seen in Scheme 3 ($NaBH_4$ followed by HCl 6M) to afford (S)-phenibut 8b. The use of benzoic acid as additive leads to improved yields and enantioselectivities.

Xylazine

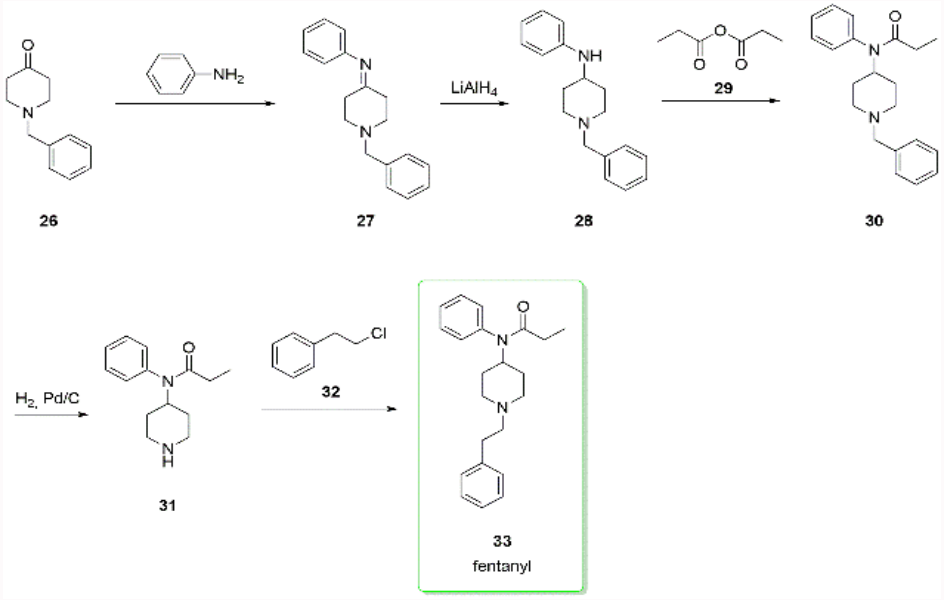
Xylazine (20) (Figure 6) is an alpha-2-adrenergic agonist used for its sedative and analgesic properties in veterinary medicine. While not approved by the FDA for use in humans, there are evidences that an exposure in humans is increasing [30].

In the recent times, xylazine was noted in the street opioid supply of Puerto Rico and Philadelphia [31]. Employments of veterinary anesthetics as recreational drugs have gained popularity. If used in humans, it is known to produce remarkable hypotension and bradycardia [32]. In the event of a suspected xylazine overdose, experts recommend giving the naloxone (opioid overdose reversal medication) because xylazine is frequently combined with opioid [33]. Reports have appeared of people using xylazine-containing fentanyl to lengthen its euphoric effects [31].

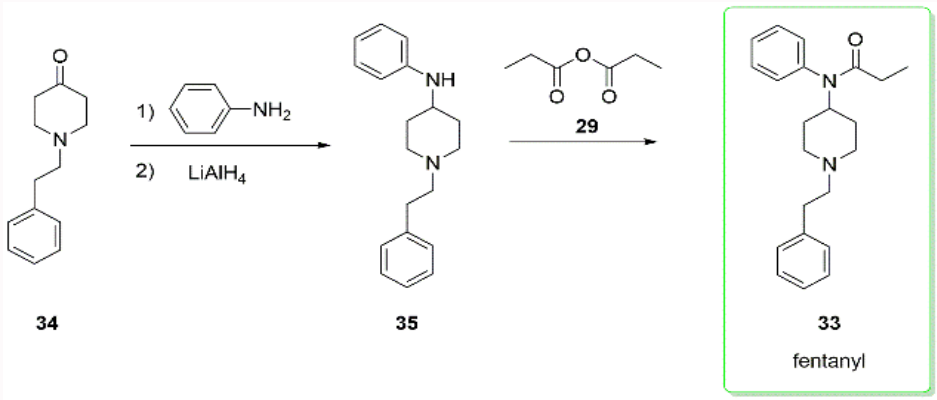
It is similar to clonidine in terms of structure and pharmacological effects [32]. The two chlorine atoms in clonidine are replaced by two methyl groups in xylazine. Moreover, the dihydroimidazole ring in clonidine is replaced by a dihydrothiazine ring in 20.

An American patent published in 1986 describes the preparation of xylazine (Scheme 6) [34]. The synthesis starts from 2,6-dimethylaniline 21 which is firstly converted into corresponding acetylated intermediate 22. This was then treated with Sodium Hydride suspension (NaH) in THF to generate the nucleophilic anion that attacks Carbon Disulfide (CS_2) to make isothiocyanate 23. This is attacked by 3-aminopropan-1-ol 24 followed by concentrated HCl to make xylazine (20) passing *via* the thiourea intermediate. Last step yield was ranging from 80% to 93%.

A later patent [35] reported the preparation of intermediate 23 avoiding the acetylation step. In particular 2,6-dimethylaniline 21 was treated directly with carbon disulfide and ammonium hydroxide



Scheme 8: Preparation of fentanyl (33) by Janssen [44,45].



Scheme 9: More expeditious preparation of fentanyl (33) [46].

to afford ammonium dithiocarbamate salt 25. This decomposed to 23 upon treatment with ethyl chloroformate in water and 2-propanol (Scheme 7). Authors reported that other formats and alcohols can be used instead of chloroformate and 2-propanol, respectively.

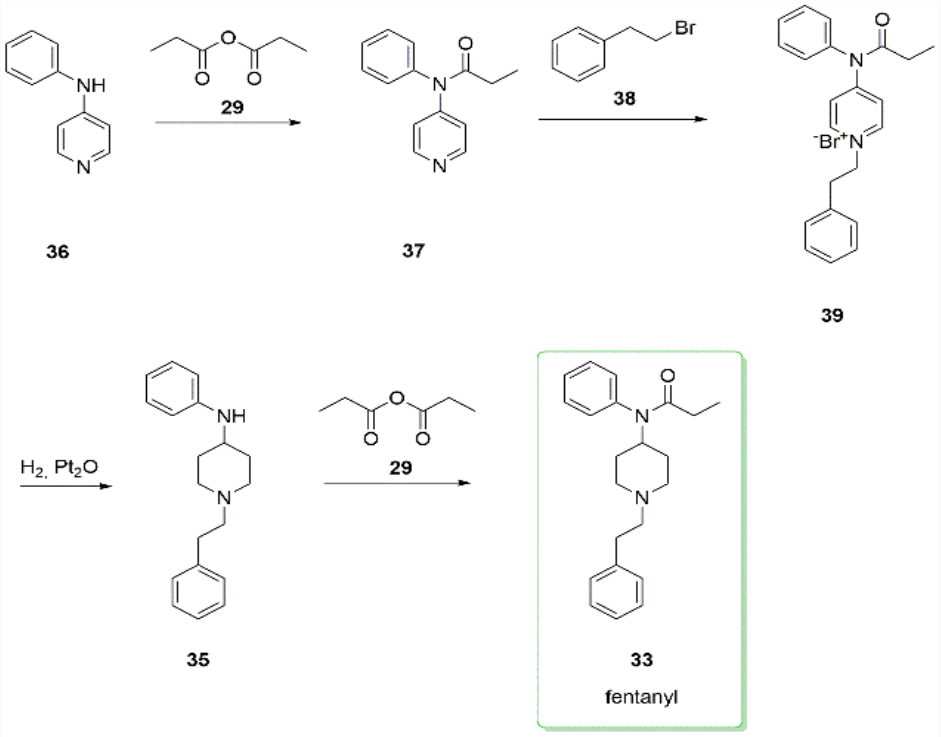
In the formation of isothiocyanate 22, both strategies avoid using thiophosgene whose use is not suitable for scalable processes given its toxicity.

Fentanyl

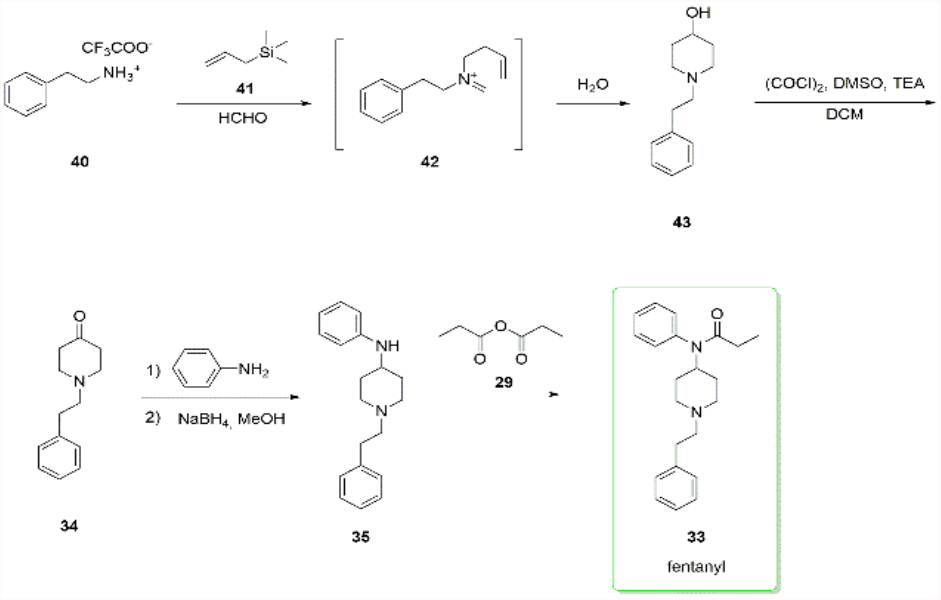
Fentanyl (33), a lipid-soluble synthetic opioid is still the most popular opioid used in the perioperative period in the world. Despite of the development of more potent, safer, faster onset, and both shorter and longer lasting alternative opioids, fentanyl remains the pillar of anesthesiologists [36]. Fentanyl is typically 50 more potent than morphine. It is powerfully addictive, mortal even in tiny amounts, and has become a huge part of America's opioid crisis [37]. Among the recreational names are Fent, fenty, blonde, he-man, murder 8, snowflake, tango and cash, Apache, butter, good fella, dragon, dragon's breath, jack, jackpot, white girl, toe tag dope, blue diamond, China town, Chinese food, king ivory, dance fever, lollipop, crazy one and TNT [38]. Fentanyl acts preferentially on μ receptors [39]. Initial symptoms include extreme happiness and respiratory depression, among the others [40]. The Harvard Gazette reports that "…. fentanyl is so deadly: It stops people's breathing before they even realize it" [41]. It was firstly synthesized in 1960 by Paul Janssen [42], the founder of Janssen Pharmaceutica. The 4-anilidopiperidine and 1-[2(arylethyl)] moiety is fundamental for displaying high μ-affinity and activity [43]. It's firstly developed synthesis (Scheme 8) [44,45] by Janssen starts from 1-benzylpiperidin-4-one 26 which was condensed with aniline to give Schiff base 27. This is subjected to reduction with Lithium Aluminium Hydride ($LiAlH_4$) to yield the secondary amine 28. The treatment of 28 with propionic anhydride 29 gave compound 30. The removal of N-benzyl group mediated by catalytic hydrogenation afforded free piperidine 31. This was alkylated with (2-chloroethyl) benzene32 to generate fentanyl (33).

A shorter pathway (Scheme 9) was shortly after developed [46]. It employed directly the 1-phenethylpiperidin-4-one 34 as starting material. After Schiff base formation and reduction with LiAlH4 compound 35 was obtained. This was acylated by propionic anhydride 29 to afford fentanyl (33).

A different approach utilizing reduction of pyridinium salt was



Scheme 10: Preparation of fentanyl via P_2O hydrogenation of pyridinium ring [47].



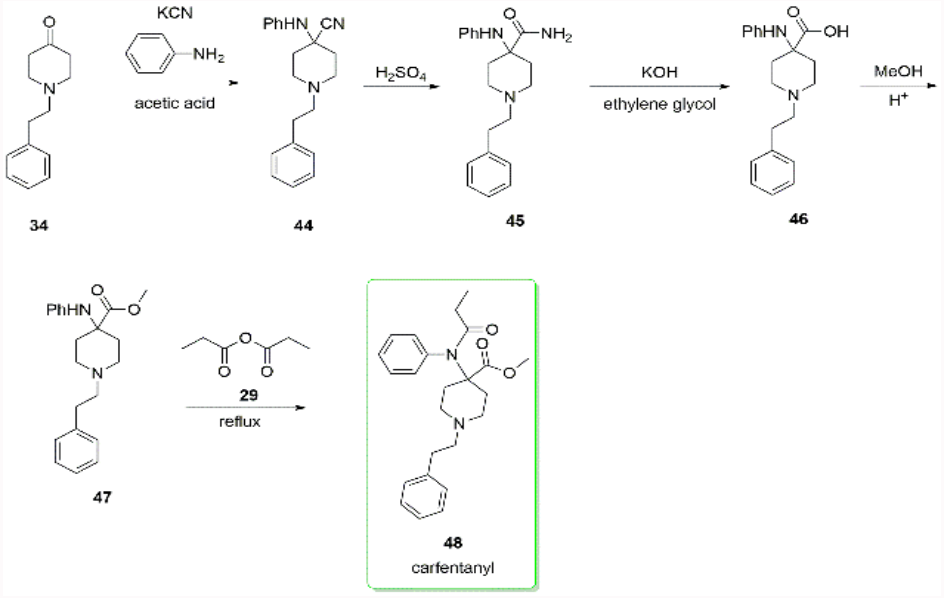
Scheme 11: Preparation of fentanyl via aminomethanodesilylation cyclization [48].

reported (Scheme 10) [47]. The initial N-phenylpyridin-4-amine 36 was propionylated upon addition of 29 to give diaryl amide 37. This was alkylated at the pyridine-nitrogen with (2-bromoethyl) benzene38 to form the pyridinium bromide salt 39. This was treated in hydrogen atmosphere in the presence of catalyst platinum (IV) oxide ($P_{t2}O$) to afford intermediate 35. Lastly, 35 were transformed into fentanyl (33) by propionylation.

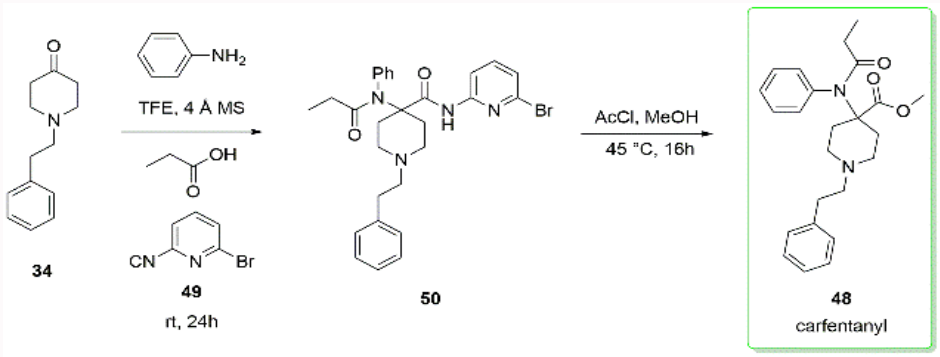
A total synthesis of fentanyl employing an intramolecular Mannich-type reaction was reported (Scheme 11) [48]. The initial phenylethylammonium trifluoroacetate 40 was treated with allyltrimethylsilane (41) and formaldehyde to give the not isolated intermediate 42 which is converted to alcohol 43 upon addition of water. The subsequent Swern oxidation (oxalyl chloride and DMSO in triethylamine) provided ketone 34. This was firstly treated with aniline and secondly with Sodium Borohydride ($NaBH_4$) to give piperidine 35, eventually, propionylation afforded fentanyl (33).

Carfentanil

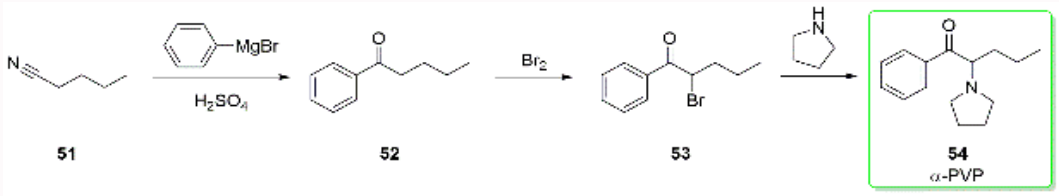
Carfentanil (48, also known as carfentanyl) is a very potent analgesic used for sedation of big-sized animals such as elephants [49]. It is a selective agonist of μ-opioid receptors, with an estimated



Scheme 12: Preparation of carfentanil (48) patented by Janssen [55].



Scheme 13: Preparation of carfentanil (48) *via* Ugi multicomponent strategy [56].



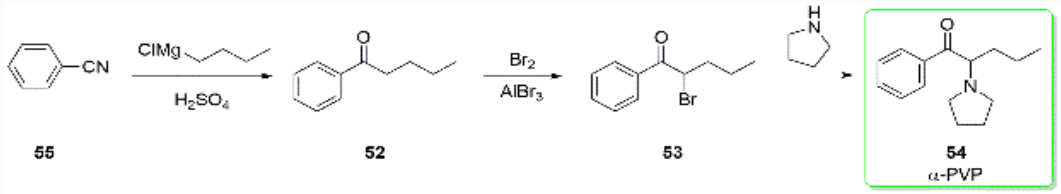
Scheme 14: Preparation of α-PVP (54) by U.S. Department of Justice [60].

quantitative potency approximately 10,000 and 100 times higher than morphine and fentanyl, respectively [50,51]. Increasing reports from North America and Europe have shown that an inflated number of carfentanil-related intoxications in recent years have occurred [52,53].

Chemical properties are similar to those of other fentanyl analogues. Carfentanil has a calculated logP value of 3.7, indicating high lipophilicity. Given these physicochemical properties, it can be inferred that carfentanil distributes preferentially throughout extravascular compartments, including the brain and adipose tissue [51].

Its synthesis was firstly described in the literature in 1976 [54]. As in the case of fentanyl, the patent issuer was Janssen. The synthetic route (patented in 1979, Scheme 12) [55] starts from 1-phenethylpiperidin-4-one 34 which is subjected to Strecker synthesis in the presence of aniline and Potassium Cyanide (KCN) in acetic acid to provide α-aminonitrile 44. The nitrile moiety is firstly converted to primary amide (45) upon addition of sulfuric acid and later to carboxylic acid (46) *via* alkaline hydrolysis (KOH in ethylene glycol). 46 was transformed into methyl ester 47 by addition of methanol in acidic conditions. Final propionylation by addition of 29 provided carfentanil (48).

A two-step, Ugi multicomponent, efficient preparation of carfentanil has been reported (Scheme 13) [56].



Scheme 15: Alternative preparation of α-PVP (54).

Ketone 34 and aniline and were firstly dissolved in 2,2,2-Trifluoroethanol (TFE). Then, molecular sieves (4 Å) were added and the resulting mixture was stirred overnight at room temperature before adding propionic acid and 2-bromo-6-isocyanopyridine 49. The resulting bis-amide 50 was converted into carfentanil (48) *via* acidic methanolysis (acetyl chloride in methanol). Yields were excellent for both first step (92%) and the second step (98%). 2-bromo-6-isocyanopyridine combines sufficient nucleophilicity with excellent leaving group properties (charge stabilized between pyridine nitrogen and nitrogen from the resulting leaving amide) [56].

α-pyrrolidinopentiophenone

Synthetic cathinones are an emerging class of novel psychoactive substances. α-Pyrrolidinopentiophenone (α-PVP, 54), or "Flakka", belongs to this class [57]. Cathinone is structurally similar to amphetamines differing from them for having a ketone functional group. Experimental work showed that cathinone, similarly to amphetamine, increases the levels of dopamine in the brain by acting on the catecholaminergic synapses [58]. α-pyrrolidinopentiophenone has been linked to the insurgence of catatonia, a very complex neuropsychiatric disorder whose main traits are abnormal movements, immobility, abnormal behaviors [59]. A case report involving a 20-year-old teen without prior psychiatric showed increasingly bizarre and erratic behavior after reported ingestion of α-PVP [57].

U.S. Department of Justice reported a synthetic pathway (Scheme 14) for α-Pyrrolidinopentiophenone (α-PVP) [60]. It starts from valeronitrile 51 which is treated with phenylmagnesium bromide followed by acidic workup to afford ketone 52. This was brominated with bromine to give α-bromo ketone 53. Lastly, this was mixed with pyrrolidine to give α-pyrrolidinopentiophenone 54. Details on experimental work were not provided.

Alternatively, benzonitrile 55 and n-butylmagnesium chloride can be used as starting material to yield ketone 52. The subsequent bromination catalyzed by AlBr3 afforded α-bromo ketone 53 which was transformed to α-pyrrolidinopentiophenone54 upon addition of pyrrolidine [61] (Scheme 15).

Fentanyl and COVID-19: An Unexpected Therapeutic Activity?

Opioids remain the definitive standard choice for the treatment of pain in critically ill patients, including those with COVID-19. It has been recently reported that fentanyl could help in mitigating the respiratory symptoms which characterize COVID-19. The proposed mechanism of action was that fentanyl decreased the rate of spontaneous respiratory rate, diminished the brain stem chemoreceptor response to hypoxia and hypercarbia, in addition to exhibiting a modulating effect on the brain stem [62]. The effectiveness of nebulized fentanyl in the treatment of refractive dyspnea in a patient with Chronic Obstructive Pulmonary Disease (COPD) with major complications and comorbidities was studied. Nebulized fentanyl was used to successfully decrease the subjective symptoms of refractory dyspnea in these given patients [63]. Given the side effects displayed by fentanyl, nebulized fentanyl could be beneficial in a palliative care setting where patients have refractive dyspnea that has failed other therapies [63].

Concluding Remarks and Future Outlook

This descriptive review summarized the most emerging street illicit drugs. Illicit drugs represent a major burden in USA and in Europe and they are still very popular despite the recent COVID-19 pandemic. The use of cannabis, in particular, is on the rise not only in the EU but also in USA. Furthermore, there was a marked increase in the use of new psychoactive substances. COVID-19 pandemic forced many drug users to change their habits and to look for possibly cheaper substances. Among them six molecular entities are herein described: Isotonitazene, phenibut, xylazine, fentanyl, carfentanyl and α-pyrrolidinopentiophenone.

The synthetic opioids isotonitazene, fentanyl and carfentanil are potent analgesic, are related to morphine and are very frequently abused. Phenibut is an analogue of baclofen having additionally nootropic effects. Xylazine is often cut in combination with opioid painkillers. Lastly, α-Pyrrolidinopentiophenone (α-PVP) is very destructive for human health (may induce catatonia). These substances share a common feature: They can easily induce addiction.

The chemical synthesis of presented street drugs is quite straightforward demonstrating the easiness of process and consequent availability. Unfortunately, this latter aspect favors the black market of such illicit drugs that often are in mixture with other psychedelic substances. Campaigns addressing opioid addiction are emerging. One example is represented by the federal Cumberland County, Pennsylvania which is receiving 1 million dollars funding to help combat the opioid crisis. The funding will be used to support treatment and recovery initiatives such as expanding access to substance use disorder treatment and recovery services [64].

Altogether, the risks connected to the use and abuse of these drugs and the highlight on chemical aspects put lighter on the problems of drug addiction and tolerance, a never-ending problem in nowadays society.

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