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Chemical classification of new psychoactive substances (NPS)

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Abstract

This work comprehensively reviews some fundamental concepts about drugs, especially focusing on new psychoactive substances (NPS), and their typical classifications based on either their effects (hallucinogens, stimulants or depressants), their origin (natural, synthetic, or semisynthetic), or legal situation (lawful, illicit, or unregulated). These classifications are highly useful in the medicine/legal field, but completely useless for the chemical determination of drugs. Hence, a classification of NPS based on their chemical composition is revised and discussed. This classification seeks to merge those recent and dispersed chemical groupings of NPS found in scientific literature and/or health/drugs reports from World/European/American Institutions facing the illicit use of drugs (WHO, UNODC, EMCDDA, OEDA, DEA, etc.) into a unique general classification, which might be useful for every forensic practitioner/researcher dealing with the identification of new psychoactive substances.

Keywords: New psychoactive substances; Classification of drugs; Chemical classification.

1. New psychoactive substances

New psychoactive substances (NPS) are defined by the United Nations Office on Drugs and Crime (UNODC) as "substances of abuse, either in a pure form or a preparation, that are not controlled by the 1961 Single Convention on Narcotic Drugs or the 1971 Convention on Psychotropic Substances, but which may pose a public health threat" [1]. UNODC also specifies that "the term "new" does not necessarily refer to new inventions but to substances that have recently become available on the market" [1]. In fact, some NPS were first synthesized more than 80 years ago. As an example, methcathinone (CAS 5650-44-2) was already known, synthesized and investigated by scientists since 1928 [2], but the concern about its abuse arose in the former USSR in the 1970s, and later in the USA in the 1990s [3]. Because of this, methcathinone was included in 1994 in the Schedule I of controlled substances of the Convention on Psychotropic Substances of 1971 (green list of controlled substances) [4]. Schedule I includes substances presenting "a high risk of abuse, posing a particularly serious threat to public health, which are of very little or no therapeutic value" [3]. In this respect, a significant number of NPS were primarily developed for therapeutic purposes, but then started being misused and extensively abused for their euphoric effects, as legal alternatives to "traditional" illicit psychoactive substances [1,3,5-7].

Despite the strict control of psychoactive substances worldwide, a great diversity (in type and number) of NPS are continuously emerging in the recreational drug market, in the attempt of manufacturers to evade drug legislation [6-18]. Actually, the situation is the opposite, legislation desperately and belatedly attempts to discover and control the large number of NPS that freely circulate on the drug market. In Europe, at least 50 substances are detected every year on the drug market, and more than 700 new substances are being monitored by the European Monitoring Centre for Drugs and Drug

Addiction (EMCDDA) since 1997, through the EU Early Warning System (EWS) [19,20]. In addition, legislation is often useless because for each specific substance that gets legally controlled, one or more structurally modified analogues are introduced into the legal market, becoming a never-ending process [1,6-10,21-23]. For example, the NPS naphyrone (CAS 850352-53-3) appeared in UK as the legal replacement to mephedrone (CAS 1189805-46-6), which had been schedule as an illicit substance a few months earlier [24,25].

Besides the public health problems of traditional illicit drugs, NPS pose an additional serious public health threat, mainly because of the huge lack of knowledge about their toxicity, about the limit between a “safe” dose and a fatal dose, and about the unknown adverse health effects they produce [6,10,18,26-28]. Furthermore, the identity of the NPS is generally unknown by the drug users because the new products containing NPS provide no or little information about their composition [10,28-30]. In addition, specially concerning but common cases involve the consumption of NPS in combination with other drugs (including other NPS and/or traditional illicit drugs) either consciously or unconsciously (as “adulterants” of these drugs of abuse) [10,28-31].

Due to all these reasons, since 2008 UNODC has launched the global SMART program (Synthetics Monitoring: Analyses, Reporting and Trends) to improve the capacity of countries to generate, manage, analyse and report information on new illicit synthetic drugs [32]. At European level, the emergence of NPS is controlled through the EMCDDA and EWS. In addition, in 2017, the Parliament and the Council of the European Union approved new legislation to speed up the response procedure to NPS, also including NPS in the official definition of "drug" at the European level [33]. This legislation focuses on early warning measures, risk assessment, and NPS control, while promoting the streamlining, speeding up and increase of knowledge regarding NPS

including toxicological studies, development of analytical chemical methodologies for NPS detection, etc.

Particularly, the development of versatile analytical methodologies that are able to simultaneously detect not only known NPS, but also any new analogue, is essential to face NPS trafficking. In this respect, a major effort is made by numerous academic, research and forensic institutions, which continually update their analytical methodologies for the detection of emerging NPS. This is evidenced by the extensive number of publications reported in literature focused on the analytical determination of NPS [34-45]. However, the development of such robust analytical methods is difficult and slow because of the huge number of potential compounds that emerge as NPS and the lack of available reference standards [6-10,43]. As stated by Couto *et al.* [44], "due to the lack of standard analytical methods for NPS, their identification has definitely become an analytical toxicology challenge, because whenever an analytical method is applied to a new drug, a different derivative rapidly emerges, frequently capable of bypassing the existing methods in a stealth manner". This involves that a significant number of analyses worldwide might be false negative analyses.

In authors' opinion, the main problem when controlling/detecting NPS relies on the lack of knowledge about the chemical structures and the chemical similarities/differences among NPS. Both, the regulation and the analytical detection of NPS would improve whether some efforts were focused on unifying and sharing fundamental chemical data of NPS. According to the 2019-report of the Global Commission on Drug Policy entitled "Classification of psychoactive substances – when science was left behind", the current classification of psychoactive substances needs to be urgently reviewed because it is full of incoherence [46].

This review has accepted this challenge and aims to return chemistry to the classification of psychoactive substances. Particularly, the review focuses on the classification of NPS. First, this review aims to provide an overview of the different current classifications of NPS -based on different criteria- that are available in the scientific literature and/or health/drugs reports from World/European/American Institutions. Those criteria are: (i) the pharmacological effect that NPS produce when consumed; (ii) the origin; and (iii) the legal situation. In addition, some classifications of NPS simultaneously based on previous criteria, but also combined with preliminary chemical groupings are also reviewed and discussed. As the reader will realize, none of these classifications of NPS is consistent from a chemical approach. Consequently, this manuscript aims to revise, propose and discuss a classification of NPS exclusively based on their chemical structure.

2. Current classifications of new psychoactive substances – when chemistry was left behind

Different criteria may be considered when classifying psychoactive substances, thus there exist multiple forms of classification. Perhaps, the classification most usually found in literature is the one based on the pharmacological effect they produce when consumed, which is significantly relevant in the medicine/health fields. In addition, classifications based on their origin or legal situation are also common, which are significantly relevant in the forensic/legal fields. The most relevant classifications of NPS found in literature for each criterium are summarized in Table 1.

Table 1. Classifications of NPS found in literature based on different criteria (pharmacological effect, origin, or legal situation) [3,4,8,32,46-50].

<table>
<tr><th>Criteria</th><th>Reference</th><th colspan="8">Classes</th></tr>
<tr><td rowspan="3">Pharmacological effect</td><td>Global Commission on Drug Policy [46]</td><td colspan="3"><u>Hallucinogens</u> (dissociatives, cannabinoids)</td><td><u>Stimulants</u> (psychedelics)</td><td colspan="2"><u>Depressants</u> (narcotics, hypnotics, sedatives)</td><td><u>Anti-psychotics</u></td></tr>
<tr><td>DEA [47]</td><td colspan="3"><u>Hallucinogens</u></td><td><u>Stimulants</u></td><td><u>Depressants</u></td><td><u>Narcotics</u></td><td><u>Anabolic steroids</u></td></tr>
<tr><td>UNODC [32]</td><td><u>Hallucinogens</u></td><td><u>Dissociatives</u></td><td><u>Cannabinoids</u></td><td><u>Stimulants</u></td><td colspan="2"><u>Hypnotics/Sedatives</u></td><td><u>Opioids</u></td></tr>
<tr><td>Origin</td><td>[3,8,46,48]</td><td colspan="3"><u>Natural</u></td><td colspan="2"><u>Synthetic</u></td><td colspan="2"><u>Semisynthetic</u></td></tr>
<tr><td rowspan="2">Legal situation</td><td rowspan="2">[4, 46, 49, 50]</td><td colspan="2"><u>Legal</u></td><td colspan="4"><u>Illicit (controlled substances)</u></td><td><u>Unregulated</u></td></tr>
<tr><td>Medicines</td><td>Freely consumed legal drugs without therapeutic purposes</td><td colspan="2">Yellow list (1961)
▪ Schedule I
▪ Schedule II
▪ Schedule III
▪ Schedule IV</td><td>Green list (1971)
▪ Schedule I
▪ Schedule II
▪ Schedule III
▪ Schedule IV</td><td>Red list (1988)
▪ Table I
▪ Table II</td><td></td></tr>
</table>

DEA - Drug Enforcement Administration; UNODC - United Nations Office on Drugs and Crime.

Psychoactive substances have been traditionally classified based on the **pharmacological effect** they produce in the human body when consumed into three main classes [32,46,47]: (i) hallucinogens, (ii) stimulants, and (iii) depressants.

- **Hallucinogens**. Hallucinogenic substances are those psychoactive substances that alter human sensory perceptions in such a way that the user perceives a distorted reality in which time, space, colours and forms are deformed. Examples: LSD (CAS 50-37-3), and psilocybin (CAS 520-52-5).
- **Stimulants**. Stimulating psychoactive substances speed up the activity of the central nervous system, often resulting in the user feeling more alert, euphoric and energetic. Examples: amphetamine (CAS 300-62-9), cocaine (CAS 50-36-2), and methylone (CAS 186028-79-5).
- **Depressants**. Depressing psychoactive substances slow down the activity of the central nervous system, often resulting in the user feeling more relaxed, sleepier,

and less sensitive to pain. Examples: heroin (CAS 561-27-3), methadone (CAS 76-99-3), and fentanyl (CAS 437-38-7).

As summarized in Table 1, a fourth class is stablished by the Global Commission on Drug Policy [46] to include **anti-psychotic** substances, which are those psychoactive substances (generally pharmaceutical drugs) used for the medication of different psychotic disorders, but that are sometimes recreationally abused, such as quetiapine (CAS 111974-69-7).

On the contrary, the U.S. Drug Enforcement Administration (DEA) [47] stablishes five classes: (i) hallucinogens, (ii) stimulants, (iii) depressants, (iv) narcotics, and (v) anabolic steroids; because differentiates between depressants and narcotics, and includes a new class to cover anabolic steroids. **Anabolic steroids** are synthetic substances simulating natural male hormones that are abused to promote muscle growth and/or enhance athletic /physical capabilities.

Another classification of NPS also based on their psychopharmacological activity is the one adopted by UNODC, in which NPS are grouped into six major categories: (i) sedative/hypnotics, (ii) dissociatives, (iii) hallucinogens, (iv) stimulants, (v) cannabinoids, and (vi) opioids [32]. Dissociative drugs and cannabinoids are considered hallucinogenic substances whereas opioids are depressants. Nevertheless, UNODC stablishes them as independent classes, probably because of their relevance and the different receptors they have in the nervous system.

In fact, many classifications of drugs based on their pharmacological effect might be found in literature with slight differences among them. However, since this review is not intended to thoroughly revise the pharmacologic effects of drugs, a general, yet fundamental vision of the classification of psychoactive substances based on this

criterium is provided. For more information about the pharmacological effects of NPS, the interested reader is referred to specialized literature [6,51-57].

Besides the pharmacological effect, psychoactive substances might be also classified based on their **origin** [3,8,46,48] into (i) natural, (ii) synthetic, and (iii) semisynthetic drugs (see Table 1).

- **Natural drugs**. Natural drugs are those psychoactive substances that are extracted directly from plants or fungi to be consumed after no or little physical processes. Examples: salvia (salvinorin A, CAS 83729-01-5), scopolamine (CAS 51-34-3), and psilocin (CAS 520-53-6).
- **Synthetic drugs**. Synthetic drugs are chemical compounds produced in the laboratory from chemical precursors through advanced chemical reactions usually composed of multiple steps. Examples: carfentanil (CAS 59708-52-0), benzylpiperazine (CAS 2759-28-6), and JWH-200 (CAS 103610-04-4).
- **Semisynthetic drugs.** Semisynthetic drugs are chemical compounds obtained in the laboratory from natural precursors through simple chemical reactions. The precursor and the semisynthetic drug have the same core chemical structure, being usually differentiable by the addition/substitution of one or few radical groups. Example: cocaine hydrochloride (CAS 53-21-4), synthesized from *erythroxylum coca* ("coca"); or heroin (CAS 561-27-3) from *papaver somniferum* ("adormidera").

As summarized in Table 1, psychoactive substances might be also classified based on their **legal situation** [4,46,49,50]. Three main classes are usually stablished: (i) legal, (ii) illicit, and (iii) unregulated drugs.

- **Legal drugs**. Legal drugs are those psychoactive substances whose consumption and trade are allowed by national and/or international laws in force. Examples of legal drugs are tobacco, alcohol (*i.e.* ethanol), caffeine, and medicines. Why are some drugs allowed whilst others not? According to the Global Commission on Drug Policy "the distinction between legal and illegal substances is the result of a long history of cultural and political domination" [46]. For example, alcohol is legal because it has been consumed in Europe and Asia for thousands of years. Alcohol is part of its historical tradition. On the contrary, coca is illegal because it was culturally and traditionally consumed only in south America [46]. Two sub-classes of legal drugs are usually differentiated depending on whether they are consumed with or without therapeutic purposes (*i.e.* medicines or not).
  - **Medicines** (**therapeutic drugs**): Those substances that are consumed for the treatment of disease, pain and/or any other health problem. A medical prescription is usually required to acquire these substances from a drugstore. The synthesis and trade of these substances exclusively correspond to pharmaceutical laboratories and drugstores. The dose is precisely indicated. Any misuse or abuse of psychoactive medicines as well as their synthesis and/or trade by clandestine laboratories is illicit. Examples: lorazepam (CAS 846-49-1), oxycodone (CAS 76-42-6).
  - **Freely consumed legal drugs without therapeutic purposes**: Those legal psychoactive substances that are consumed for cultural and/or recreational purposes. Examples: ethanol, tobacco, caffeine (CAS 58-08-2).
- **Illicit drugs** (**controlled substances**). Illicit drugs are those psychoactive substances whose consumption and/or trade are strictly controlled by national and/or international laws in force, because of posing a serious Public Health threat.

Most countries keep track of the international regulations on this topic, translating and making no or little adaptions from them to prepare national regulations. As summarized in Figure 1, three main international regulations on psychoactive substances are predominant: (i) the 1961 Single Convention on Narcotic Drugs, (ii) the 1971 Convention on Psychotropic Substances, and (iii) the 1988 United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances; from which three lists of controlled substances were derived:

- **Yellow list ("narcotics")**: The "yellow list" refers to the list of psychoactive substances reported and controlled by the 1961 Single Convention on Narcotic Drugs and its subsequent updated editions [49]. In 2019, the 58th edition was published. Yellow list is further sub-categorized into four schedules depending on the potential abuse and addiction of psychoactive substances (See Figure 1).
- **Green list ("psychotropics")**: The "green list" refers to the list of psychoactive substances reported and controlled by the 1971 Convention on Psychotropic Substances and its subsequent updated editions [4]. In 2019, the 30th edition was published. As previously did for yellow list, green list is further sub-categorized into four schedules depending on the potential abuse, addiction and therapeutic value of psychoactive substances (See Figure 1).
- **Red list ("precursors")**: The "red list" refers to the list of precursors and chemical reagents frequently used in the illicit manufacture of psychotropic substances reported and controlled by the 1988 United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances and its subsequent updated editions [50]. In 2020, the 17th edition was published. Red list is further sub-categorized into two tables depending on whether they are

precursors of psychoactive substances or reagents/solvents commonly used in the illicit production of drugs (See Figure 1).

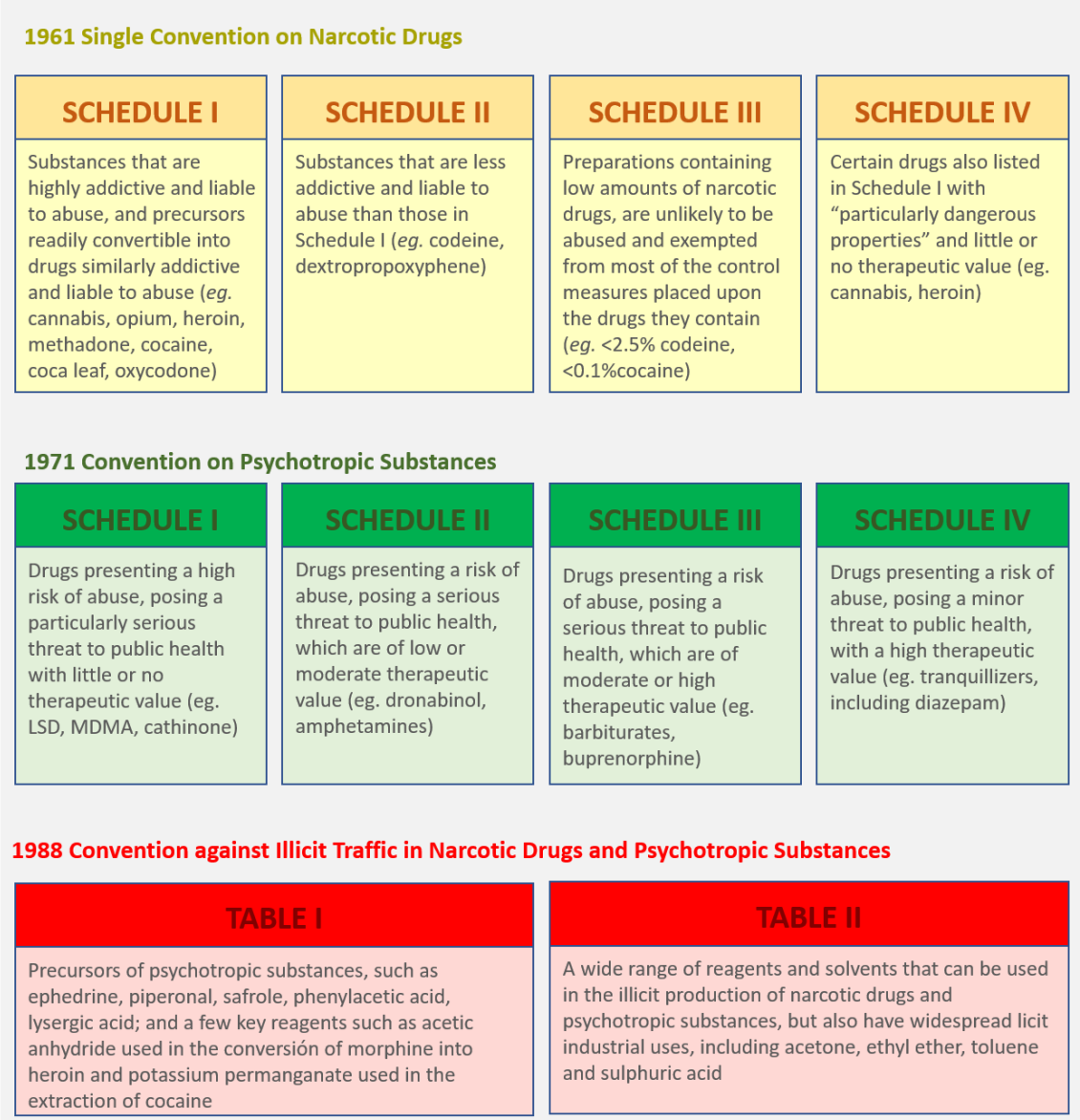

Figure 1. Scheduling of illicit psychoactive substances under the UN Drug Conventions. Adapted with permissions from [46].

- **Unregulated drugs**. Unregulated drugs are psychoactive substances that are not legalized/unlegalized yet. Most NPS are initially unregulated drugs, which finally, after some time, end up being regulated and included in one of the Schedules of controlled illicit substances previously revised. Examples of current unregulated

drugs: Butylone (CAS 802575-11-7), JWH-203 (CAS 864445-54-5), and HU-210 (CAS 112830-95-2).

Previous classifications might be relevant in certain fields such as medicine or law. However, they lack chemistry. The knowledge about the chemical structures of psychoactive substances is essential in analytical toxicology and forensics. Probably for this reason, in the need of chemical information, some classifications of NPS found in literature have started to group NPS not only based on their origin/effect but also preliminary considering their chemical structure. In this respect, five relevant classifications of NPS found in literature are summarized in Table 2 and discussed below. These five classifications, especially the third and the fifth ones, have been the basis from which developing the classification of NPS exclusively based on chemical structure finally proposed in this manuscript.

The classification adopted by UNODC [58] establishes nine families including (i) synthetic cannabinoids, (ii) synthetic cathinones, (iii) phenethylamines, (iv) aminoindanes, (v) tryptamines, (vi) piperazines, (vii) phencyclidine-type substances, (viii) plant-based substances, and (ix) other substances. Interestingly, it should be noted that six of these families are grouped based on their chemical structure (*i.e.* cathinones, phenethylamines, aminoindanes, tryptamines, piperazines, and phencyclidine-type substances); whereas the other three classes are still based on the effect/origin of NPS (*i.e.* synthetic cannabinoids, plant-based substances, and other substances).

Table 2. Classifications of NPS found in literature based on miscellaneous criteria (combining pharmacological effect, origin, and chemical structure) [19,58-61].

Reference	Classes
UNODC [58]	**Plant-based substances** | **Synthetic cannabinoids** | **Synthetic cathinones** | **Phenethyl-amines** | **Aminoindanes** | **Tryptamines** | **Piperazines** | **Phencyclidine-type substances** | **Other substances**
EMCDDA [19]	**Plants and extracts** | **Synthetic cannabinoids** | **Cathinones** | **Aryl-alkyl-amines** | **Arylcyclohexyl-amines** | **Phenethyl-amines** | **Amino-indanes** | **Opioids** | **Tryptamines** | **Piperazines** | **Piperidines & pyrrolidines** | **Benzo-diazepines** | **Other substances**
Shevyrin *et al.* [59]	**Cannabinoids** ▪ Phytocannabinoids: - Tricyclic terpenoids - Bicyclic terpenoids - Other ▪ Endocannabinoids - AEA pathway - 2-AG pathway - Other eicosanoids ▪ Synthetic cannabinoids: - Phytocannabinoid-similar ○ Tricyclics ○ Bicyclics ○ Other - Endocannabinoid-related ○ Eicosanoid-similar ○ Endocannabinoid modulators - Indole-similar ○ Indoles • 3-Carbonylindoles ❖ Naphthoylindoles ❖ Phenylacetylindoles ❖ Benzoylindoles ❖ Cycloalkanecarbonylindoles ➢ Adamantanecarbonyl-indoles ➢ Cyclopropanecarbonyl-indoles ❖ Indole-3-carboxamides ❖ Indole-3-carboxylates ❖ Other 3-carbonylindoles - Indole-similar (cont.) ○ Indazoles • 3-Carbonylindazoles ❖ Naphthoylindazoles ❖ Indazole-3-carboxamides ❖ Indazole-3-carboxylates ○ Benzimidazoles • 2-Carbonylbenzimidazoles ❖ 2-Naphthoylbenzimidazoles ○ Other azaindoles - Indenes ○ Naphthylmethylindenes - Pyrrole-similar ○ Pyrroles • 3-Naphthoylpyrroles ○ Pyrazoles • Diarylpyrazoles - Carbazole-similar - Miscellaneous
Zloh *et al.* [60]	**Experimental hierarchical clustering of NMR spectra of 478 NPS into 13 superclusters (79 clusters)**
Zawilska [61]	**Synthetic cannabinomimetics** ▪ JWH compounds: - Naphthoylindoles - Naphthylmethylindoles - Naphthoylpyrroles - Naphthylmethylindenes - Phenacetylindoles ▪ Adamantoylindoles ▪ Aminoalkylindoles ▪ Benzoylindoles ▪ Cyclohexylphenols ▪ Classical cannabinoids (dibenzopyrans) ▪ Indazoles ▪ TMCP compounds ▪ Other **Psychostimulants** ▪ Synthetic cathinones ▪ Piperazines ▪ Piperidines and pyrrolidines ▪ Tryptamines ▪ 2,5-dimethoxyamphetamines ▪ 2-aminoindanes ▪ Benzofurans **Psychedelic hallucinogens** ▪ Tryptamines - Simple tryptamines - Lysergamides ▪ Phenethylamines - 2,5-dimethoxy-phenethylamines - N-(methoxybenzyl)-2,5-dimethoxy-phenethylamines - Dibenzodifurans **Dissociative hallucinogens** ▪ Arylcyclohexylamines ▪ Diarylethylamines **Opioids** ▪ Fentanyl analogues ▪ Other **Benzodiazepines**

Similarly, in the last report of EMCDDA [19], NPS were classified into 13 families including: (i) synthetic cannabinoids, (ii) cathinones, (iii) phenethylamines, (iv) opioids, (v) tryptamines, (vi) arylalkylamines, (vii) benzodiazepines, (viii) arylcyclohexylamines, (ix) piperazines, (x) piperidines and pyrrolidines, (xi) plants and extracts, (xii) aminoindanes, and (xiii) other substances. Interestingly, nine of these families are grouped based on their chemical structure; whereas the other four classes are still based on the effect/origin of NPS (*i.e.* synthetic cannabinoids, opioids, plants and extracts, and other substances).

These classifications present the following chemical lacks: (i) cathinones are one type of phenethylamines; (ii) some plant-based substances are tryptamines; and (iii) no chemical information is provided by indicating "synthetic cannabinoids" because a significant number of chemically different molecules are synthetic cannabinoids. Nevertheless, the incorporation of chemical families in previous classifications, though preliminary and incongruous, is a significant first step towards a thorough and consistent chemical classification of NPS.

A specific classification for cannabinoids was reasoned and proposed by Shevyrin *et al.* [59], after revising the extremely different NPS usually included in this miscellaneous group. According to these authors, cannabinoids might be first classified into: (i) phytocannabinoids, (ii) endocannabinoids, and (iii) synthetic cannabinoids (see Table 2). Phytocannabinoids might be further subclassified into tricyclic terpenoids, bicyclic terpenoids and other. Endocannabinoids might be further subclassified into AEA pathway, 2-AG pathway and other eicosanoids. Finally, synthetic cannabinoids might be further subclassified into: (i) phytocannabinoid-similar, (ii) endocannabinoid-related, (iii) indole-similar, (iv) indenes, (v) pyrrole-similar, (vi) carbazole-similar, and (vii) miscellaneous. Interestingly, indole-similar cannabinoids might be further subclassified

into indoles, indazoles, benzimidazoles and other azaindoles, with subsequent subclassifications each, depending on their chemical structures (see Table 2).

A curious experimental approach for grouping and classifying NPS, based on their "chemical structure", was adopted by Zloh *et al.* [60]. Particularly, these authors calculated a hierarchical cluster based on the NMR spectra of 478 NPS using chemometrics. This way, NPS were grouped in 79 different clusters (13 superclusters) exclusively based on their NMR-spectroscopic differences, which theoretically depend on their chemical structure. A representative molecule of each cluster was selected. Negatively, some representative molecules from different superclusters had the same chemical structure (*e.g.*, superclusters 2 and 7 were both benzofuran-amphetamines; while superclusters 4 and 6 were both carbonyl-indoles) [60]. This result evidences that such NMR-spectroscopic clustering does not necessarily coincide with the chemical structures of NPS. It seems to be very useful for the classification of any novel NPS as long as it is analysed by NMR spectroscopy. However, it is not applicable when using a different analytical detection technique such as mass spectrometry, infrared or Raman spectroscopy, or when simply observing the chemical structure of the NPS.

A further promising attempt for a thorough classification of NPS, based on chemical groups, was proposed by Zawilska in 2018 [61], as summarized in Table 2. In such an extensive classification, Zawilska first differentiates among (i) synthetic cannabinomimetics, (ii) psychostimulants, (iii) psychedelic hallucinogens, (iv) dissociative hallucinogens, (v) benzodiazepines, and (vi) opioids.

- According to Zawilska, synthetic cannabinomimetics might be further sub-categorized into nine chemical families: JWH-compounds, adamantoylindoles, aminoalkylindoles, benzoylindoles, cyclohexylphenols, classical cannabinoids

(*i.e.* dibenzopyrans), indazoles, TMCP compounds, and others. In addition, JWH-compounds might be further sub-classified into five chemical groups: naphthoylindoles, naphthylmethylindoles, naphthoylpyrroles, naphthylmethylindenes, and phenacetylindoles.

- Psychostimulants might be further sub-categorized into seven chemical families: synthetic cathinones, piperazines, piperidines and pyrrolidines, tryptamines, 2,5-dimethoxyamphetamines, 2-aminoindanes, and benzofurans.
- Psychedelic hallucinogens might be further sub-categorized into tryptamines (composed in turn by simple tryptamines and lysergamides), and phenethylamines (further subclassified into 2,5-dimethoxyphenethylamines, N-(methoxybenzyl)-2,5-dimethoxy-phenethylamines, and dibenzodifurans).
- Dissociative hallucinogens might be further sub-categorized into arylcyclohexylamines, and diarylethylamines.
- Finally, opioids might be further sub-categorized into fentanyl analogues, and others.

These five classifications (especially the Zawilska's [61] and Shevyrin's ones [59]) certainly propose a significant number of new chemical families of NPS, but still present several chemical incongruences, and combines miscellaneous criteria (effect and origin together with chemical groups). Nevertheless, they have been an excellent starting point to which continue building the chemical classification of NPS discussed in the next section.

3. Classification of NPS exclusively based on their chemical structure

Despite the multiple classifications of NPS available in literature and revised in previous section, up to date there is not a global chemical classification of NPS. On the contrary, a broad terminology based on different criteria, are used to name families of molecules that sometimes have the same core chemical structure, and sometimes have not. Furthermore, different terminology is sometimes used to name the same chemical family. In this respect, it should be also mentioned that the IUPAC names of most NPS are extremely long to be handled and thus, abbreviations or acronyms are normally used instead by forensic laboratories. Unfortunately, more than one acronym/abbreviation usually exist for each NPS in such a way that the communication between forensic practitioners from different institutions becomes sometimes difficult and slow. To avoid misunderstandings and time-consuming explanations about a certain NPS, we propose that the identifying CAS number and/or the chemical structure of the NPS should always accompany the acronym/abbreviated name of the NPS in forensic reports. For example, the NPS commonly known as FUBIMINA is called [1-(5-Fluoropentyl)-1H-benzimidazol-2-yl]-1-naphthalenylmethanone (according to IUPAC), but it also has other abbreviated names such as BIM-2201 or BZ-2201. Advantageously, the CAS number is unique (1984789-90-3), and thus it can be used for the unequivocal reference of this NPS.

This situation of multiple names greatly complicates the communication between researchers, practitioners and institutions, sometimes delaying and making difficult to share any information about NPS. Some authors are aware of this lack of unification, and intelligent promising proposals for a standardized systematic chemical nomenclature of NPS have been reported in literature. Perhaps, the most recent,

consistent and comprehensive nomenclature of NPS is the one revised by Potts *et al.* [62]. According to this nomenclature, every NPS could be named by placing the chemical name of (i) the core group, (ii) the tail group, (iii) the linker group and (iv) the linked group of the NPS-molecule in a systematic order, in such a way that the systematic name for a NPS would be "Linked group-tail-core-linker". Potts et al. [62] schematically explain this nomenclature with two examples (see Figure 2).

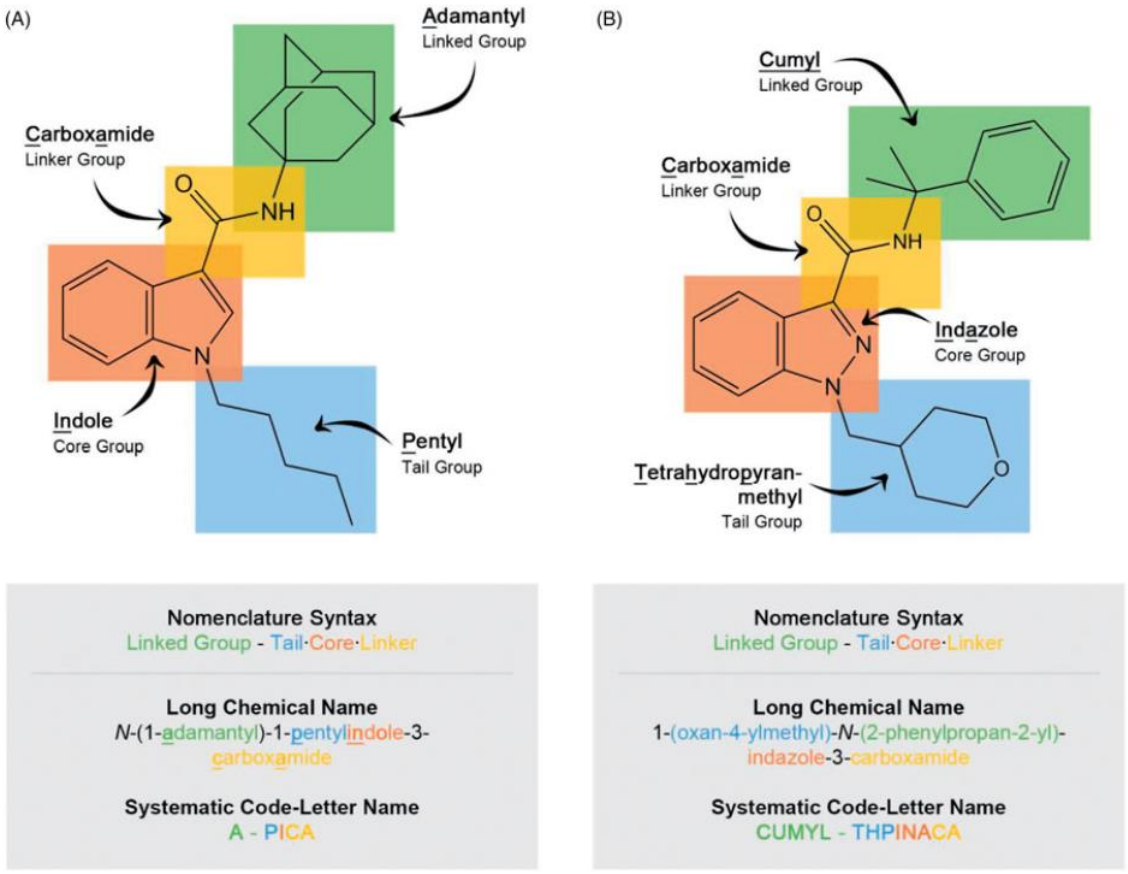

Figure 2. Chemical systematic nomenclature for NPS reported by Potts et al. Reprinted with permissions from [62].

A global core chemical classification of NPS would help in the nomenclature of NPS in such a way that a rapid understanding and communication between different institutions would be possible. In addition, the knowledge about the chemical structure of NPS may provide useful information to properly focus their determination selecting the

appropriate mass spectrometric methodology according to their molecular mass, presence of heteroatoms, potential ion fragments, etc. Thus, for the sake of completeness and clarity, and considering including all the chemical NPS-families already published in scientific literature or already established by UNODC and EMCDDA, a chemically consistent classification of NPS is proposed below. This classification is summarized in Table 3, and the corresponding chemical structures are displayed in Figures 3-5. The chemical structure of all the NPS classes and subclasses and some corresponding examples are described in more detail in supplementary Table S1. First, NPS might be classified in **four fundamental chemical groups**: (i) polycyclic hydrocarbons; (ii) amines; (iii) alcohols/ethers; and (iv) other NPS (See Figure 3).

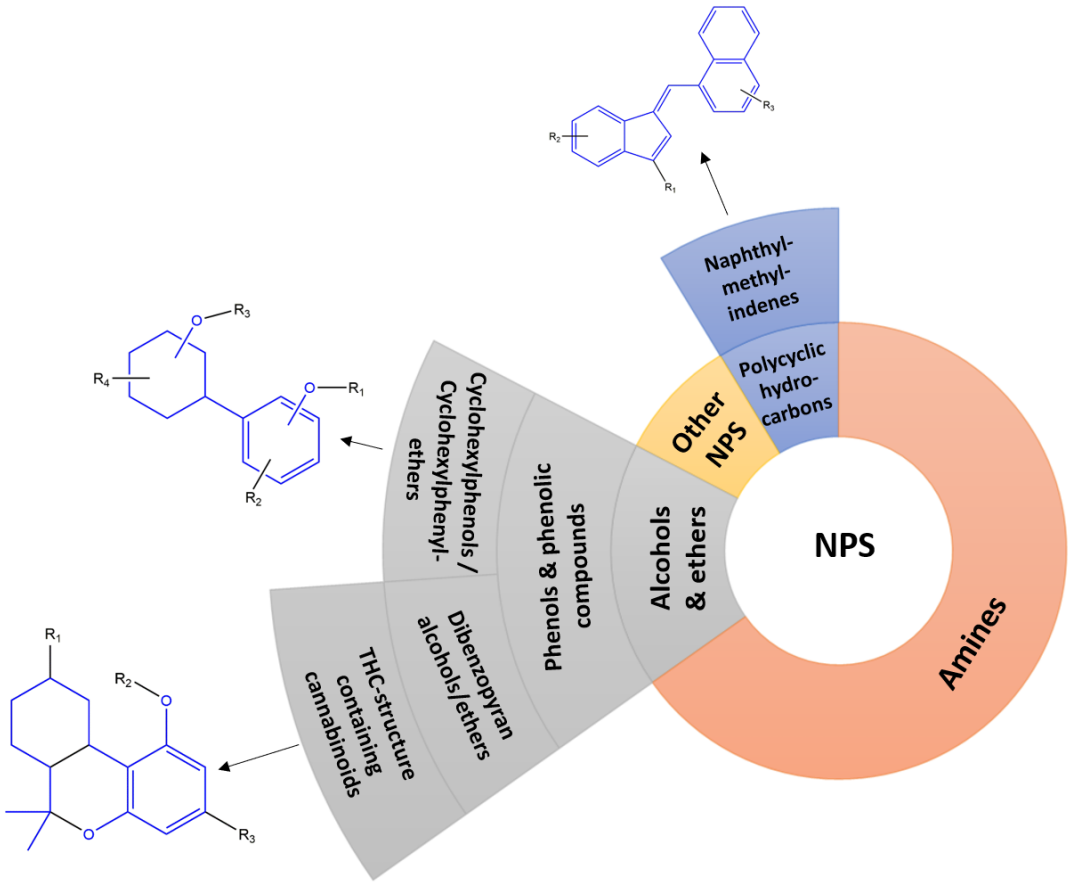

Figure 3. Classification of NPS based on their core chemical structures. For clarification purposes, amines are further described in Figure 4.

Table 3. Proposed classification of NPS exclusively based on their chemical structure.

CHEMICAL CLASSES OF NPS	
Polycyclic hydrocarbons	▪ **NAPHTHYLMETHYLINDENES**
Amines	▪ **ARYLALKYLAMINES** - PHENETHYLAMINES ○ *Alpha-substituted phenethylamines* • Amphetamines • Diarylethylamines • 2-aminoindanes ○ *Beta-substituted phenethylamines* • Cathinones ○ *Phenyl-substituted phenethylamines* • Dialkyloxy-phenethylamines • Methylenedioxy-phenethylamines • Benzofuran-ethylamines • Benzodifuran-ethylamines - DIPHENYLHEPTANAMINES - ARYLCYCLOHEXYLAMINES ○ *Phenylcyclohexylamines* ○ *Aminocyclohexylbenzamides* - THIAMBUTENES ▪ **HETEROCYCLIC AMINES** - HETERO-MONOCYCLIC AMINES ○ *Pyrroles* • Naphthoylpyrroles ○ *Pyrrolidines* ○ *Pyrazoles* ○ *Imidazoles* ○ *Piperidines* • Phenylpiperidines • Fentanyls ❖ Phenethylfentanyls ○ *Piperaz*ines - HETERO-POLYCYCLIC AMINES ○ *Benzodiazepines* ○ *Indoles* • Indolealkylamines ❖ Tryptamines & tryptamine-structure-containing alkaloids ➢ Psilocin & derivatives ➢ Mitragynine (kratom) & derivatives ➢ Lysergamides ❖ Aminoalkylindoles • Arylalkylindoles ❖ Naphthylmethylindoles • Carbonylindoles ❖ Naphthoylindoles ❖ Phenacetylindoles ❖ Benzoylindoles ❖ Adamantoylindoles ❖ Tetramethylcyclopropanoylindoles (TMCP) ❖ Indolecarboxilate esters ❖ Indolecarboxamides ○ I*ndazoles* ○ *Benzimidazoles* ○ *Carbazoles* ○ *Xanthines* ○ *Bridged azapolycyclic compounds* • Tropane-structure-containing alkaloids • Morphine-structure-containing alkaloids
Alcohols & ethers	▪ **PHENOLS & PHENOLIC COMPOUNDS:** - CYCLOHEXYLPHENOLS / CYCLOHEXYLPHENYLETHERS - DIBENZOPYRAN ALCOHOLS/ETHERS ○ *THC-structure-containing cannabinoids*
Other NPS	

Polycyclic hydrocarbons

Some NPS are polycyclic hydrocarbons. In other words, their main chemical structure (*i.e.*, the molecule that is the essential core of the NPS) is only composed of carbon and hydrogen elements, though they might have functional groups including another element (mainly halogens and oxygen). Within these new psychoactive polycyclic hydrocarbons, a sub-category would be the naphthylmethylindenes, a widely known family of NPS.

- **NAPHTHYLMETHYLINDENES.** Naphthylmethylindenes are those NPS based upon the core chemical structure displayed in Figure 3, and supplementary Table S1. Example: JWH-176 (CAS 619294-62-1).

Amines

Most NPS are amines, as summarized in Table 3 and supplementary Table S1. Particularly, the molecule that is the essential core of the NPS is a primary ($-NH_2$), secondary (-NH-) or tertiary (-N-) amine, though they might have additional functional groups bounded to the molecule. New psychoactive amines might be subclassified into: (i) arylalkylamines (Figure 4), and (ii) heterocyclic amines (Figure 5).

- **ARYLALKYLAMINES**

Arylalkylamines are those molecules whose essential core is based upon an alkyl group simultaneously bounded to an amino group and an aryl group. They might be further subclassified into: (i) phenethylamines, (ii) diphenyl-heptanamines, (iii) arylcyclohexyl-amines, and (iv) thiambutenes. See Figure 4.

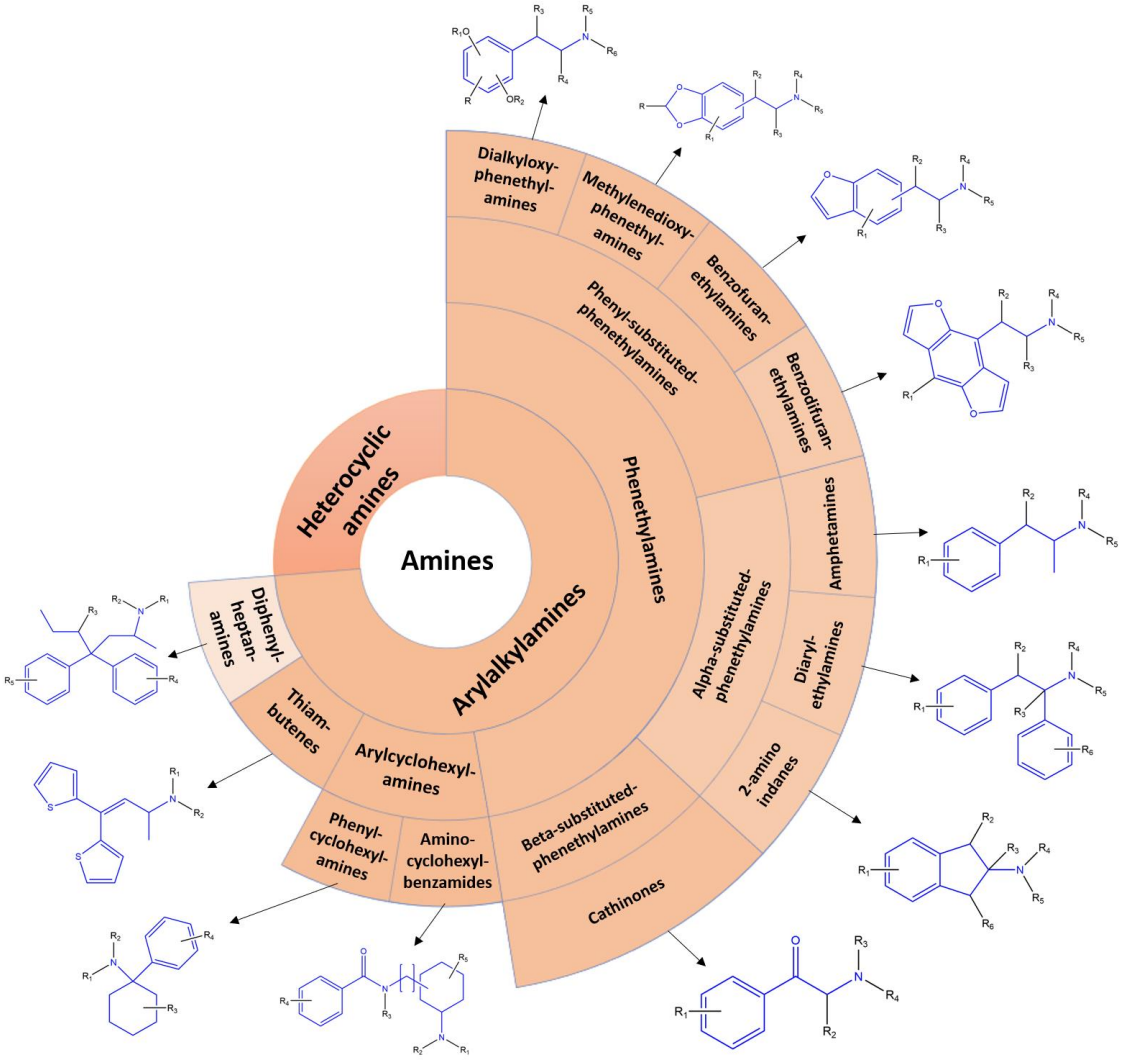

Figure 4. Classification of NPS amines based on their core chemical structures. For clarification purposes, heterocyclic amines are further described in Figure 5.

- PHENETHYLAMINES

Phenethylamines are those NPS whose core chemical structure consists of a 2-phenyl-ethylamine, as displayed in Table 4. Examples: 2C-C (CAS 88441-15-0), 25I-NBOME (CAS 919797-19-6). Phenethylamines might be further sub-classified depending on the positioned substituents, into: (i) alpha-substituted-phenethylamines, (ii) beta-substituted-phenethylamines, and (iii) phenyl-substituted-phenethyl-amines. Examples of NPS including different phenethylamines are given in Table S1.

- **Alpha-substituted-phenethylamines**. Phenethylamines with any substituent in alpha position.
  - ***Amphetamines***. Alpha-substituted-phenethylamines in which the substituent is a methyl group. Examples: amphetamine (CAS 300-62-9), methamphetamine (CAS 537-46-2), MDMA (CAS 42542-10-9), DOM (CAS 15588-95-1), MDA (CAS 4764-17-4). Amphetamines are usually further subclassified considering the substituents in phenyl position (*e.g.* dialkyloxy-amphetamines, methylenedioxy-amphetamines, etc.) as explained below for phenyl-substituted-phenethylamines.
  - ***Diarylethylamines***. Alpha-substituted-phenethylamines in which the substituent is an aryl group, typically a phenyl group (Figure 4). Examples: Ephenidine (CAS 60951-19-1), diphenidine (CAS 36794-52-2), lefetamine (CAS 7262-75-1).
  - ***2-Aminoindanes***. Alpha-substituted-phenethylamines in which the substituent is a (-CH_2-) group that is also bounded to the benzene ring, thus forming an indane (Figure 4). Examples: 2-AI (CAS 2975-41-9), MDAI (CAS 132741-81-2).
- **Beta-substituted-phenethylamines**. Phenethylamines with any substituent in beta position.
  - ***Cathinones***. Beta-substituted-phenethylamines in which the substituent is an oxo group. Examples: Cathinone (CAS 71031-15-7), buphedrone (CAS 408332-79-6), mephedrone (CAS 1189805-46-6), 4-MEC (CAS 1225617-18-4), methylone (CAS 186028-79-5). Like amphetamines, cathinones are usually further

subclassified considering the substituents in phenyl position (*e.g.* dialkyloxy-cathinones, methylenedioxy-cathinones, etc.) as explained below for phenyl-substituted-phenethylamines. For a more complete sub-categorization of cathinones, the reader is referred to references [3,8].

- **Phenyl-substituted-phenethylamines**. Phenethylamines with any substituent in phenyl position.
  - ***Dialkyloxy-phenethylamines***. Phenethylamines in which two alkyloxy groups are bounded to the benzene ring. Examples: 2C-E (CAS 71539-34-9), DOB (CAS 64638-07-9).
  - ***Methylendioxy-phenethylamines***. Phenethylamines in which a methylenedioxy group is bounded to the benzene ring (Figure 4). Examples: MDPEA (CAS 1484-85-1), MDA (CAS 4764-17-4).
  - ***Benzofuran-ethylamines***. Phenethylamines in which the benzene ring has been replaced by a benzofuran ring. Examples: 5-AEDB (CAS 910400-71-4), 6-APB (CAS 286834-85-3).
  - ***Benzodifuran-ethylamines***. Phenethylamines in which the benzene ring has been replaced by a benzodifuran ring. Because of their structure, they are colloquially known as "dragonFLY" drugs. Examples: 2C-B-FLY (CAS 733720-95-1).

- DYPHENYLHEPTANAMINES

The core chemical structure of dyphenylheptanamines is based upon a heptanamine chain to which two phenyl groups are bounded (usually both phenyls to the same position). Examples: Methadone (CAS 76-99-3), acetylmethadol (CAS 509-74-0).

- ARYLCYCLOHEXYLAMINES

Arylcyclohexylamines are those NPS whose core chemical structure consists of a 1-aryl-cyclohexilamine (Figure 4 and supplementary Table S1). Two well-known NPS subcategories within this group are (i) phenylcyclohexylamines, and (ii) aminocyclohexylbenzamides.

- ***Phenylcyclohexylamines***. Those arylcyclohexylamines in which the aryl group is a phenyl. Examples: Phencyclidine (CAS 77-10-1), MXE (CAS 1239943-76-0), 4-MeO-PCP (CAS 2201-35-6).
- ***Aminocyclohexylbenzamides***. Those cyclohexylamines which are bounded to a benzamide rather than a phenyl. Examples: U-47700 (CAS 82657-23-6), AH-7921 (CAS 55154-30-8).

- THIAMBUTENES

The core chemical structure of thiambutenes is based upon a 3-aminobut-1-ene chain to which two thiophene rings are bounded (usually both to position 1). Examples: DMTB (CAS 524-84-5), Piperidylthiambutene (CAS 54160-31-5).

▪ HETEROCYCLIC AMINES

Heterocyclic amines are those molecules whose essential core is based upon a cycle (ring structure) in which at least one of the atoms constituting the ring is a nitrogen. They might be further subclassified into: (i) mono-heterocyclic amines, and (ii) hetero-polycyclic amines; depending on the number of bounded cycles (See Figure 5 and supplementary Table S1). Examples of the NPS classified in the different groups and subgroups of heterocyclic amines are summarized in Table S1.

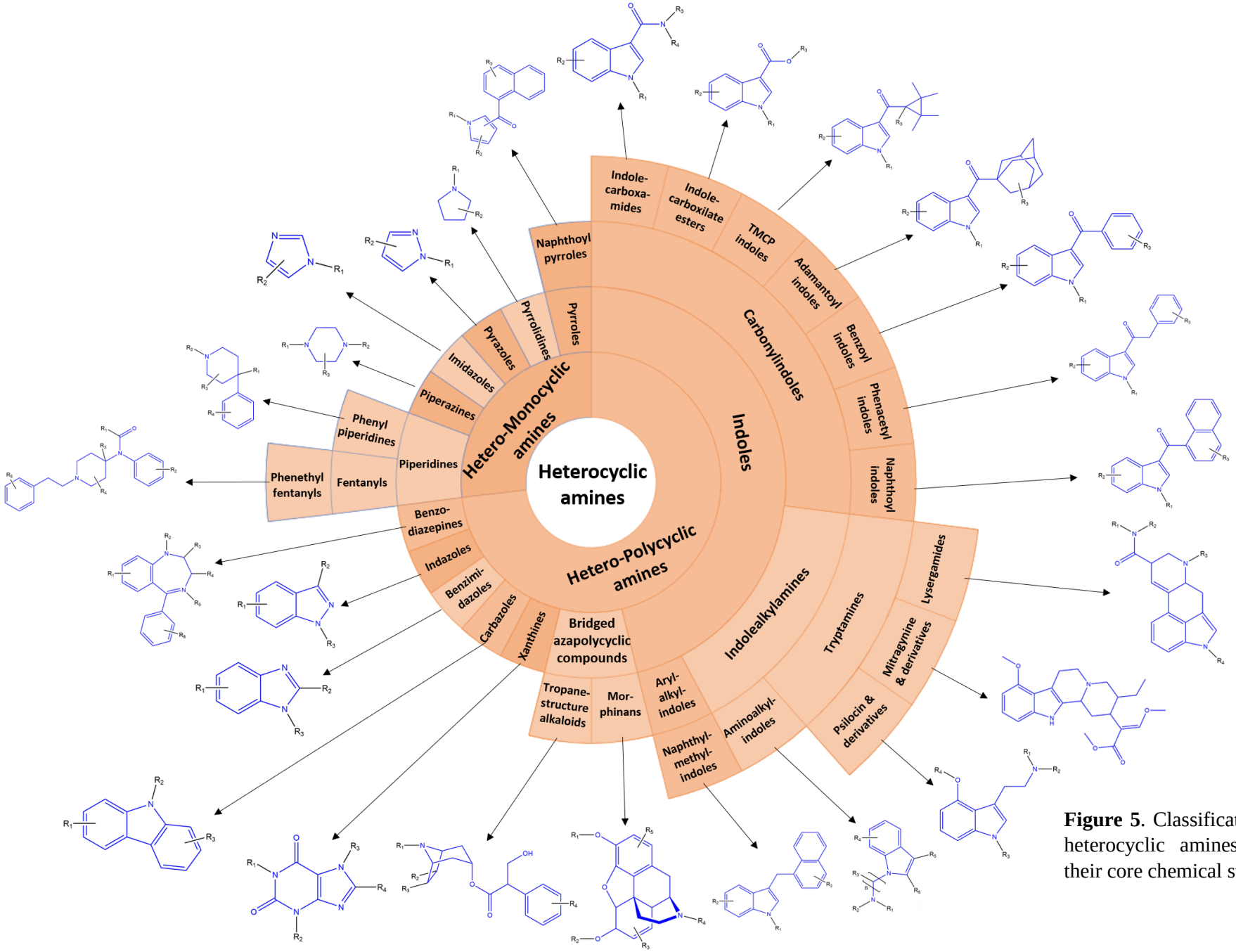

Figure 5. Classification of NPS heterocyclic amines based on their core chemical structures.

- HETERO-MONOCYCLIC AMINES

Mono-heterocyclic amines are those NPS whose core chemical structure consists of one heterocyclic amine ring. They might be further subclassified into: (i) pyrroles, (ii) pyrrolidines, (iii) pyrazoles, (iv) imidazoles, (v) piperidines, and (vi) piperazines; depending on whether they are five- or six-membered heterocyclic amines, whether they have one or more nitrogen atoms constituting the ring, depending on the position of nitrogen atoms, and/or the presence or absence of double bonds. See Figure 5.

- ***Pyrroles***. Every NPS whose core chemical structure is based upon a pyrrole ring might be included in this class. The family of NPS known as naphthoylpyrroles is a subcategory within pyrroles class.
  - **Naphthoylpyrroles.** Their core chemical structure is based on a naphthylcarbonyl group bounded to a pyrrole ring (Figure 5).
- ***Pyrrolidines*.** Every NPS whose core chemical structure is based upon a pyrrolidine ring might be included in this class (Figure 5). Examples: D2PM (CAS 22348-32-9).
- ***Pyrazoles*.** Every NPS whose core chemical structure is based upon a pyrazole ring might be included in this class (Figure 5).
- ***Imidazoles*.** Every NPS whose core chemical structure is based upon an imidazole ring might be included in this class (Figure 5).
- ***Piperidines***. Every NPS whose core chemical structure is based upon a piperidine ring might be included in this class. In addition, two subcategories of well-known families of NPS might be further established within piperidines: phenylpiperidines and fentanyls. Examples: 2-DPMP (CAS 519-74-4), Brorphine (CAS 2244737-98-0).

- **Phenylpiperidines**. Those NPS whose core chemical structure is based upon a piperidine bounded to a phenyl group (usually by position 4). (See Figure 5). Examples: pethidine (CAS 57-42-1), ketobemidone (CAS 469-79-4).
- **Fentanyls**. Fentanyls are those NPS whose core chemical structure is based upon a piperidine (bounded by position 4) to the nitrogen of a N-phenyl-carboxamide. The family of NPS known as phenethylfentanyls might be a subcategory within fentanyl class (Figure 5). Examples: alfentanil (CAS 71195-58-9), FUEF (CAS 802544-02-1), R-32395 (CAS 59708-50-8).
    - ❖ **Phenethylfentanyls**. Phenethylfentanyls (sometimes named phenetylpiperidines) are those fentanyls whose R_5 is a 2-phenyl-ethyl group (see Figure 5 and supplementary Table S1). It should be noted that phenethylfentanyls might be also considered a type of phenethylamines. Examples: Fentanyl (CAS 437-38-7), carfentanil (CAS 59708-52-0), 4-fluorofentanyl (CAS 90736-23-5).

- ***Piperazines*.** Every NPS whose core chemical structure is based upon a piperazine ring might be included in this class (Figure 5). Examples: Benzylpiperazine (CAS 2759-28-6), MT-45 (CAS 52694-55-0).

- HETERO-POLYCYCLIC AMINES

Hetero-polycyclic amines are those NPS whose core chemical structure consists of two or more fused rings in which, at least one of them is a heterocyclic amine ring. In most NPS, the other ring is typically a benzene. They might be further subclassified into: (i) benzodiazepines, (ii) indoles (iii) indazoles, and (iv) benzimidazoles; depending on the type of heterocyclic amine ring fused to benzene. See Figure 5.

- ***Benzodiazepines*.** Benzodiazepines are those molecules whose core chemical structure is the fusion of a benzene ring and a diazepine ring (*i.e.,* a seven-membered heterocycle with two nitrogen atoms). However, some diazepine derivatives have replaced benzene by other aromatic rings. Most new psychoactive benzodiazepines have a phenyl group in the fifth position (see Figure 5 and supplementary Table S1). Examples: Pyrazolam (CAS 39243-02-2), flualprazolam (CAS 28910-91-0), etizolam (CAS 40054-69-1).
- ***Indoles***. Indoles are those molecules whose core chemical structure is the fusion of a benzene ring and a pyrrole ring.
  - **Indolealkylamines**. Indolealkylamines are those molecules whose core chemical structure is an indole ring bounded to an alkylamine. Two subcategories of well-known families of NPS might be further established within indolealkylamines: (i) tryptamines & tryptamine-structure-containing alkaloids, and (ii) aminoalkylindoles (Figure 5). Examples: 5-IT (CAS 3784-30-3).
    - **Tryptamines & tryptamine-structure-containing alkaloids**. Tryptamines are those molecules whose core chemical structure is 2-(indol-3-yl)-ethylamine. See Figure 5.

Besides substituted tryptamines, three additional well-known families of NPS might be included within this class as three subcategories of tryptamine-structure-containing alkaloids: (i) psilocin and derivatives, (ii) mitragynine and derivatives, and (iii) lysergamides. Examples: tryptamine (CAS 61-54-1), DMT (CAS 61-50-7), 4-AcO-DiPT (CAS 936015-60-0).

- **Psilocin & derivatives**. Psilocin is a tryptamine in which R_1 and R_2 are methyl groups; R_3, R_4 and R_5 are hydrogens, and R_6 is a hydroxyl group. Any substituted tryptamine keeping the core chemical structure of psilocin might be included within this category (Figure 5). Examples: psilocin (CAS 520-53-6), psilocybin (CAS 520-52-5).
- **Mitragynine (kratom) & derivatives**. Mitragynine is a tryptamine-structure-containing alkaloid in which R_1, R_2 and R_4 are alkyl groups that cycle within each other forming two six-membered rings fused to the indole ring, as displayed in Figure 5. Every substituted alkaloid keeping the core chemical structure of mitragynine might be included within this class. Examples: mitragynine (CAS 4098-40-2).
- **Lysergamides.** Lysergamides are tryptamine-structure-containing alkaloids in which R_1, R_3 and R_6 are alkyl groups that cycle within each other forming two six-membered rings fused to the indole ring, as displayed in

Figure 5. They are named lysergamides because they have a carboxamide group bounded to the six-membered heterocyclic-amine ring. Examples: LSD (CAS 50-37-3), 1P-LSD (CAS 2349358-81-0).

- ❖ **Aminoalkylindoles.** This is a particular family of NPS, characterized by having an aminoalkyl group bounded to the nitrogen of the indole ring. In a significant number of aminoalkylindoles, this aminoalkyl group is a 2-morpholin-4-ylethyl group (Figure 5). Examples: JWH-200 (CAS 103610-04-4), WIN 55212-2 (CAS 131543-22-1).

- **Arylalkylindoles**. Arylalkylindoles are those molecules whose core chemical structure is an arylalkyl group bounded to an indole ring. Naphthylmethylindoles, a well-known family of NPS, is a sub-category within this class.
  - ❖ **Naphthylmethylindoles**. Those indoles to which a naphthylmethyl group is bounded (Figure 5). Examples: JWH-175 (CAS 619294-35-8).

- **Carbonylindoles.** Carbonylindoles are those molecules whose core chemical structure is an indole ring to which a carbonyl group is bounded. Up to seven subcategories of well-known families of NPS might be further established within carbonylindoles depending on the chemical group also bounded

to the carbonyl (Table 3): (i) naphthoylindoles, (ii) phenacetylindoles, (iii) benzoylindoles, (iv) adamantoylindoles, (v) tetramethyl-cyclopropanoylindoles (TMCP), (vi) indolecarboxilate esters, and (vii) indolecarboxamides.

- **Naphthoylindoles.** Carbonylindoles in which R_3 is a naphthyl group (Figure 5). Examples: JWH-018 (CAS 209414-07-3), JWH-200 (CAS 103610-04-4).
- **Phenacetylindoles.** Carbonylindoles in which R_3 is a benzyl group (Figure 5). Examples: JWH-203 (CAS 864445-54-5), RCS-8 (CAS 1345970-42-4).
- **Benzoylindoles.** Carbonylindoles in which R_3 is a phenyl (Figure 5). Examples: RCS-4 (CAS 1345966-78-0), AM-679 (CAS 335160-91-3).
- **Adamantoylindoles.** Carbonylindoles in which R_3 is an adamantyl group (Figure 5). Examples: AB-001 (CAS 1345973-49-0).
- **Tetramethylcyclopropanoylindoles (TMCP).** Carbonylindoles in which R_3 is a tetramethylcyclopropyl group (Figure 5). Examples: XLR-11 (CAS 1364933-54-9), UR-144 (CAS 1199943-44-6).
- **Indolecarboxilate esters.** Carbonylindoles in which R_3 is an alkoxy group (Figure 5). Examples: NM-2201 (CAS 2042201-16-9), PB-22 (CAS 1400742-17-7).

- **Indolecarboxamides.** Carbonylindoles in which R_3 is an amine group (Figure 5). Examples: NNE1 (CAS 1338925-11-3), CUMYL-PICA (CAS 1400742-32-6).

- ***Indazoles***. Indazoles are those molecules whose core chemical structure is the fusion of a benzene ring and a pyrazole ring. The same seven subcategories of carbonylindoles might be also established for indazoles. Examples: AB-FUBINACA (CAS 1185282-01-2), SDB-005 (CAS 2180934-13-6), FAB-144 (CAS 2180935-79-7).

- ***Benzimidazoles***. Benzimidazoles are those molecules whose core chemical structure is the fusion of a benzene ring and an imidazole ring. The same seven subcategories of carbonylindoles might be also established for benzimidazoles Examples: FUBIMINA (CAS 1984789-90-3), BIM-018 (CAS 2316839-70-8), Etonitazene (CAS 911-65-9), Isotonitazene (CAS 14188-81-9), Brorphine (CAS 2244737-98-0).

- ***Carbazoles***. The core chemical structure of carbazoles is the fusion of two benzene rings to a pyrrole ring. The same seven subcategories of carbonylindoles might be also established for carbazoles. Examples: EG-018 (CAS 2219320-91-7), MDMB-CHMCZCA (CAS 2219324-32-8).

- ***Xanthines***. Xanthines are those molecules whose core chemical structure is a xanthine ring, *i.e.,* a 3,7-dihydropurine with two oxo

groups in positions 2 and 6. See Figure 5 and supplementary Table S1. Examples: caffeine (CAS 58-08-2), DPCPX (CAS 102146-07-6).

- ***Bridged azapolycyclic compounds***. Any compound containing bridged cycles in which, at least, one of the atoms forming any of the rings is a nitrogen, might be included within this class. In addition, two subcategories of well-known families of NPS might be further established within this group: (i) tropane-structure-containing alkaloids, and (ii) morphine-structure-containing opioids. See Table 3 and supplementary Table S1.
  - **Tropane-structure-containing alkaloids**. Every molecule based upon tropane core structure (*i.e.*, a substituted 8-azabicyclo[3.2.1]octane) might be included within this class (Figure 5). Examples: scopolamine (CAS 51-34-3), cocaine (CAS 50-36-2), hyoscyamine (CAS 101-31-5).
  - **Morphine-structure-containing alkaloids ("morphinans")**. Every molecule based upon morphine pentacyclic core structure might be included in this group (Figure 5). Examples: morphine (CAS 57-27-2), heroin (CAS 561-27-3), buprenorphine (CAS 52485-79-7).

⅄ Alcohols & ethers

Some NPS are not amines, but alcohols and/or ethers (see Table 3 and Figure 3). Most psychoactive alcohols/ethers are phenolic compounds, though there are some exceptions such as ethanol or γ-hydroxybutyric acid (GHB).

- **Phenols & phenolic compounds.**

The core chemical structure of these molecules is a benzene ring to which a hydroxy/alkoxy group is bounded. Two subcategories of well-known families of NPS might be further established within phenolic compounds including: (i) cyclohexylphenols, and (ii) dibenzopyran alcohols/ethers.

- CYCLOHEXYLPHENOLS / CYCLOHEXYLPHENYLETHERS

Cyclohexylphenols are those NPS molecules whose core chemical structure is 2-(3-hydroxycyclohexyl)phenol, as displayed in Figure 3 and supplementary Table S1. Examples: Cannabicyclohexanol (CAS 70434-92-3), CP 55,940 (CAS 83002-04-4), Tramadol (CAS 27203-92-5).

- DIBENZOPYRAN ALCOHOLS/ETHERS

Those NPS molecules whose core chemical structure is a dibenzopyran polycyclic ring to which a hydroxy/alkoxy group is bounded. Cannabinoids (a well-known family of NPS) might be a subcategory within dibenzopyran alcohols/ethers.

- ***THC-structure-containing cannabinoids***. Cannabinoids are those molecules whose core chemical structure is based upon tetrahydrocannabinol (THC) structure. See Figure 3. Examples: THC (CAS 1972-08-3), cannabidiol (CAS 13956-29-1), HU-210 (CAS 112830-95-2).

Other NPS

This class would include every NPS whose core chemical structure does not fit into any of the above classes. Examples: Salvinorin A (CAS 83729-01-5) from salvia.

Finally, it should be remarked that a particular NPS-molecule might belong to more than one class because it may contain in their structure chemical groups from different chemical families. For example, the NPS pyrrole-fentanyl (CAS 92064-68-1), belongs to both phenethylfentanyl group and pyrrole group; whereas phencyclidine (CAS 77-10-1) belongs to both phenylcyclohexylamine group and piperidine group.

5. Conclusions

The chemical classification of NPS proposed in this study has aimed to encompass, join, and relate the different core chemical structures of NPS known up to date and referred in scientific literature and/or referred by Forensic and Health institutions dealing with Drugs. In this respect, it is notorious that qualitatively more than 85% of the core chemical structures of NPS are amines (either arylalkylamines or heterocyclic amines). This classification is intended to serve as a global chemical guide of NPS with which the different forensic laboratories across the World, regardless their country and their particular terminology, might communicate within each other using the same chemical language for NPS. In this respect, an urgent call to the forensic and scientific communities for the unification of standard names of NPS and always providing the unique CAS number for every NPS is made.

It should be also noted that the classification of NPS based on the chemical structure does not only facilitate the communication between forensic and scientific institutions, but also helps to: i) better evaluate which trends of chemical modifications and new structural changes are being synthesized, ii) to better follow-up the prevalence of chemical families of NPS in the illegal market, iii) to better know the precursors needed to synthesise the core chemical structure of a particular chemical family of NPS, iv) to

better understand the chemical analogies between different families of NPS, v) to improve the development of analytical spectrometric methodologies to detect NPS based on the characteristic chemical substituents (fragments); and v) to better classify a completely new detected NPS (which does not even have a name or CAS number) into its corresponding chemical family due to its core chemical structure. Although this proposed classification is not intended to be a definitive chemical classification of NPS, it provides a robust foundation on which to complete and update emerging NPS. In this sense, this chemical classification lay the basis to identify NPS analogues and support those legal responses focused on the control of NPS analogues.

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Conflicts of Interest

Authors declare no conflict of interest.

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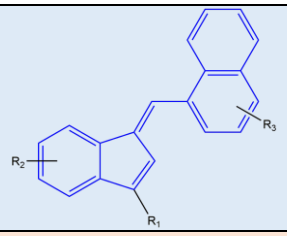
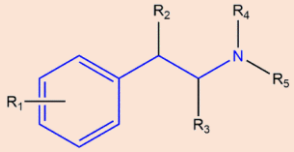
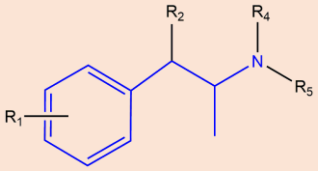
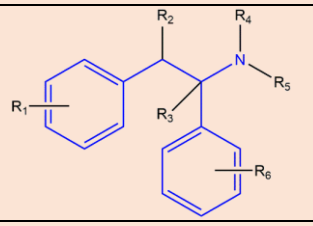
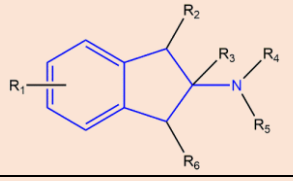
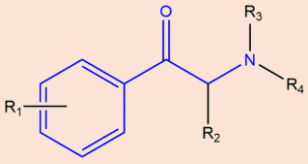
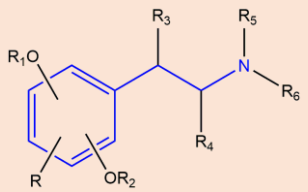
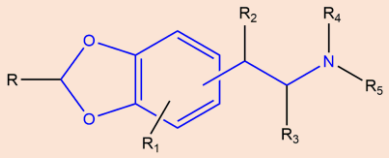
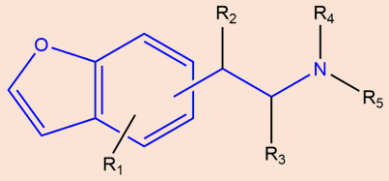
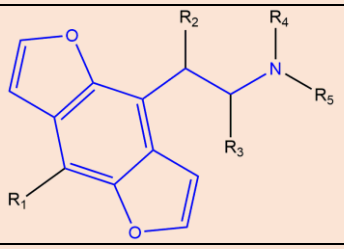
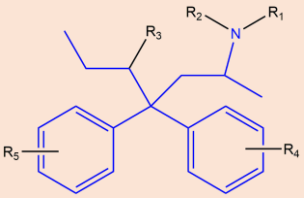
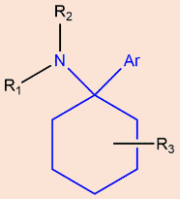
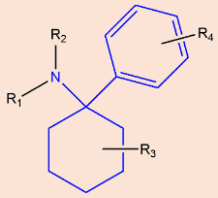
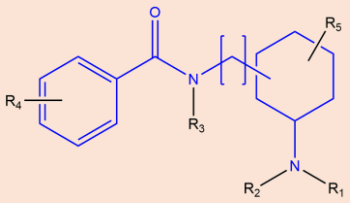
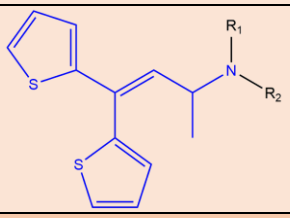
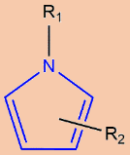
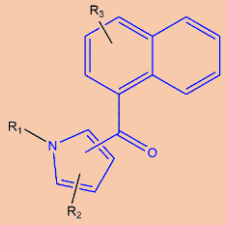
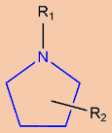
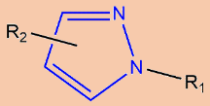
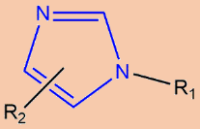
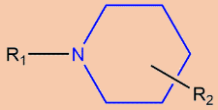
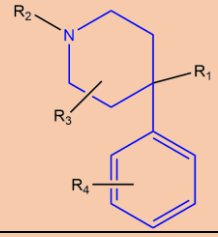
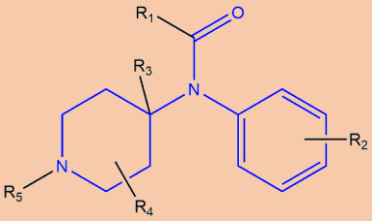
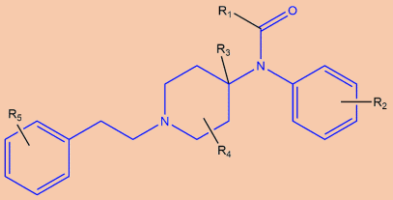
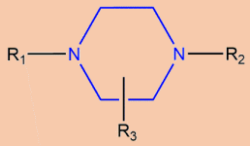
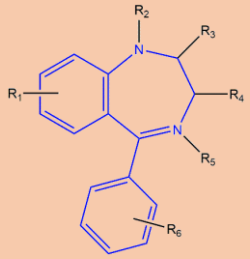
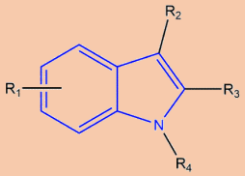
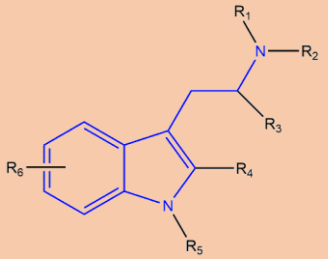
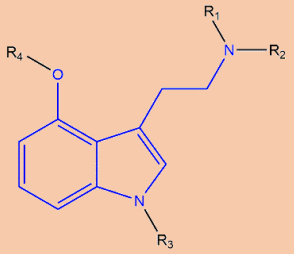
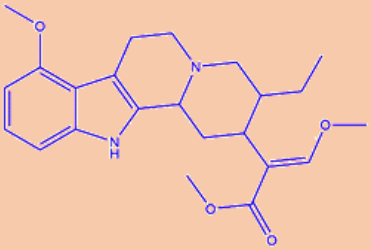
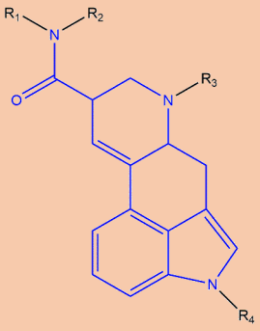
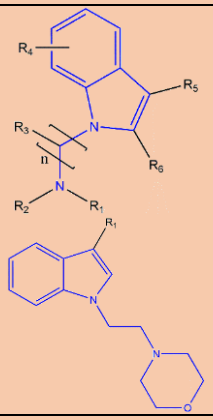
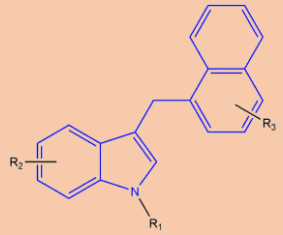
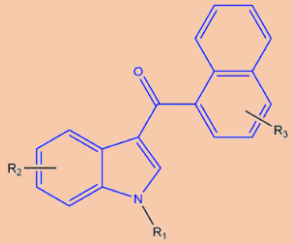
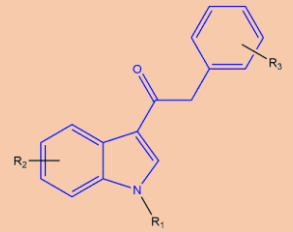
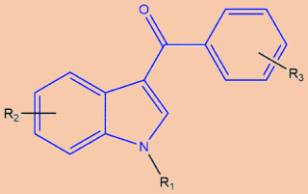
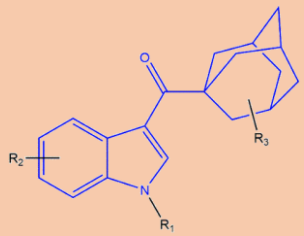
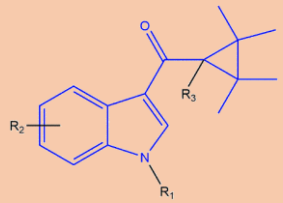
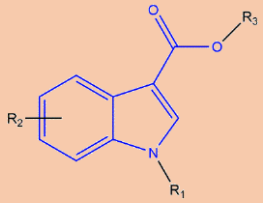
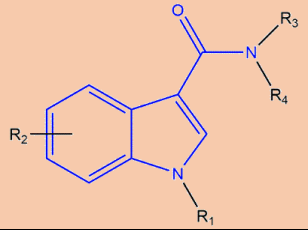
Supplementary Table S1. Proposed classification of NPS exclusively based on their chemical structure including examples of NPS and some classical drugs type and chemical structures.

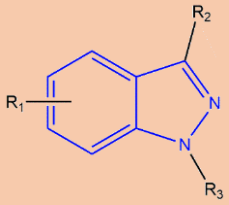
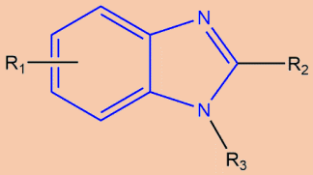
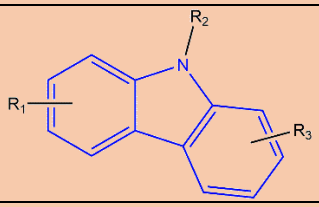
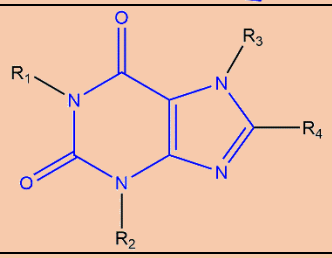
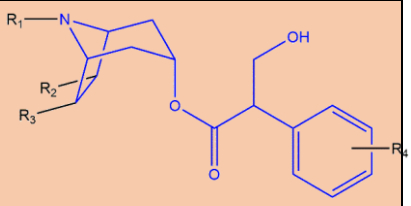
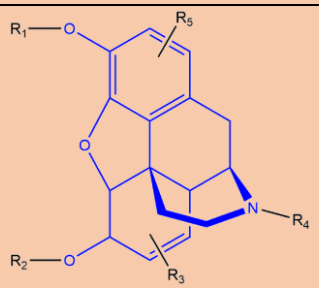
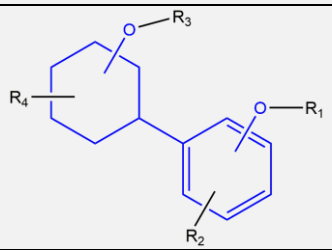
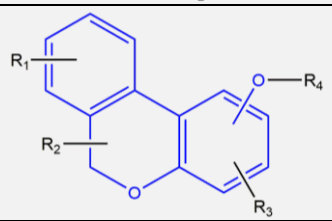
Chemical Classes of NPS		Chemical structure
Polycyclic hydrocarbons	▪ **NAPHTHYLMETHYLINDENES** *Examples:* *JWH-176 (CAS 619294-62-1)*	
Amines	▪ **1. ARYLALKYLAMINES:**	
	- 1.1. PHENETHYLAMINES *Examples:* *2C-C (CAS 88441-15-0),* *25I-NBOME (CAS 919797-19-6),* *2C-B-FLY (CAS 733720-95-1)*	
	○ ***1.1.1. Alpha-substituted-phenethylamines***	
	• **I. Amphetamines** *Examples:* *amphetamine (CAS 300-62-9),* *methamphetamine (CAS 537-46-2),* *4-fluoro amphetamine (459-02-9),* *MDMA (CAS 42542-10-9),* *DOM (CAS 15588-95-1),* *MDA (CAS 4764-17-4)*	
	• **II. Diarylethylamines** *Examples:* *ephenidine (CAS 60951-19-1),* *diphenidine (CAS 36794-52-2),* *lefetamine (CAS 7262-75-1)*	
	• **III. 2-aminoindanes** *Examples:* *2-AI (CAS 2975-41-9),* *MDAI (CAS 132741-81-2),* *5-IAI (CAS 132367-76-1)*	
	○ ***1.1.2. Beta-substituted-phenethylamines***	
	• **I. Cathinones** *Examples:* *cathinone (CAS 71031-15-7),* *buphedrone (CAS 408332-79-6),* *mephedrone (CAS 1189805-46-6),* *4-MEC (CAS 1225617-18-4)* *methylone (CAS 186028-79-5),* *butylone (CAS 802575-11-7)*	
	○ ***1.1.3. Phenyl-substituted-phenethylamines***	
	• I. **Dialkyloxy-phenethylamines** *Examples:* *2C-E (CAS 71539-34-9),* *DOM (CAS 15588-95-1),* *DOB (CAS 64638-07-9),*	

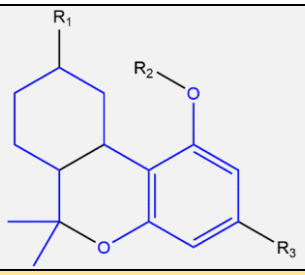
	• **II. Methylenedioxy-phenethylamines** *Examples:* *MDPEA (CAS 1484-85-1)* *MDA (CAS 4764-17-4)* *MDMA (CAS 42542-10-9)* *butylone (CAS 802575-11-7)*	
	• **III. Benzofuran-ethylamines** *Examples:* *5-AEDB (CAS 910400-71-4)* *5-APB (CAS 286834-81-9),* *6-APB (CAS 286834-85-3),* *5-EAPB (CAS 1445566-01-7)*	
	• **IV. Benzodifuran-ethylamines** *Examples:* *2C-B-FLY (CAS 733720-95-1),* *TFM-FLY (CAS 260809-99-2)*	
	- 1.2. DIPHENYLHEPTANAMINES *Examples:* *Methadone (CAS 76-99-3),* *Acetylmethadol (CAS 509-74-0)*	
	- 1.3. ARYLCYCLOHEXYLAMINES *Examples:* *Phencyclidine (CAS 77-10-1),* *MXE (CAS 1239943-76-0),* *U-47700 (CAS 82657-23-6)*	
	○ ***1.3.1. Phenylcyclohexylamines*** *Examples:* *Phencyclidine (CAS 77-10-1),* *MXE (CAS 1239943-76-0),* *4-MeO-PCP (CAS 2201-35-6)*	
	○ ***1.3.2. Aminocyclohexylbenzamides*** *Examples:* *U-47700 (CAS 82657-23-6),* *AH-7921 (CAS 55154-30-8)*	
	- 1.4. THIAMBUTENES *Examples:* *DMTB (CAS 524-84-5), Piperidylthiambutene (CAS 54160-31-5)*	
	▪ **2. HETEROCYCLIC AMINES:**	
	- 2.1. HETERO-MONOCYCLIC AMINES	
	○ ***2.1.1. Pyrroles*** *Examples:* *2F-Viminol (CAS 63880-43-3)*	

	• Naphthoylpyrroles *Examples:* *JWH-030 (CAS 162934-73-8),* *JWH-147 (CAS 914458-20-1)*	
	○ ***2.1.2. Pyrrolidines*** *Examples:* *D2PM (CAS 22348-32-9),* *α-PVP (14530-33-7)*	
	○ ***2.1.3. Pyrazoles*** *Examples:* *AM-251 (CAS 183232-66-8)*	
	○ ***2.1.4. Imidazoles*** *Examples:* *Difluorobenzylidene-6,7-dihydroimidazo-thiazin-3-one (CAS 1628150-69-5)*	
	○ ***2.1.5. Piperidines*** *Examples:* *2-DPMP (CAS 519-74-4)* *Brorphine (CAS 2244737-98-0)*	
	• Phenylpiperidines *Examples:* *Pethidine (CAS 57-42-1), Ketobemidone (CAS 469-79-4)*	
	• Fentanyls *Examples:* *alfentanil (CAS 71195-58-9),* *FUEF (CAS 802544-02-1),* *R-32395 (CAS 59708-50-8)*	
	❖ Phenethylfentanyls *Examples:* *fentanyl (CAS 437-38-7),* *carfentanil (CAS 59708-52-0),* *4-fluorofentanyl (CAS 90736-23-5)*	
	○ ***2.1.6. Piperazines*** *Examples:* *benzylpiperazine (CAS 2759-28-6),* *AP-237 (CAS 17719-89-0)* *MT-45 (CAS 52694-55-0)*	
	- **2.2.** HETERO-POLYCYCLIC AMINES	
	○ ***2.2.1. Benzodiazepines*** *Examples:* *pyrazolam (CAS 39243-02-2),* *flualprazolam (CAS 28910-91-0),* *etizolam (CAS 40054-69-1)*	

	○ ***2.2.2. Indoles*** *Examples:* *5-IT (CAS 3784-30-3)*	
	• I. Indolealkylamines	
	❖ I.1. Tryptamines & tryptamine-structure-containing alkaloids *Examples:* *tryptamine (CAS 61-54-1),* *DMT (CAS 61-50-7),* *4-AcO-DiPT (CAS 936015-60-0)*	
	➢ I.1.1. Psilocin & derivatives *Examples:* *psilocin (CAS 520-53-6),* *psilocybin (CAS 520-52-5)*	
	➢ I.1.2. Mitragynine (kratom) & derivatives *Examples:* *mitragynine (CAS 4098-40-2)*	
	➢ I.1.3. Lysergamides *Examples:* *LSD (CAS 50-37-3),* *1P-LSD (CAS 2349358-81-0)*	
	❖ I.2. Aminoalkylindoles *Examples:* *JWH-200 (CAS 103610-04-4),* *WIN 55212-2 (CAS 131543-22-1)*	
	• II. Arylalkylindoles	

	❖ Naphthylmethylindoles *Examples:* *JWH-175 (CAS 619294-35-8)*	
	• III. Carbonylindoles	
	❖ III.1. Naphthoylindoles *Examples:* *JWH-018 (CAS 209414-07-3),* *JWH-200 (CAS 103610-04-4)*	
	❖ III.2. Phenacetylindoles *Examples:* *JWH-203 (CAS 864445-54-5),* *RCS-8 (CAS 1345970-42-4)*	
	❖ III.3. Benzoylindoles *Examples:* *RCS-4 (CAS 1345966-78-0),* *AM-679 (CAS 335160-91-3)*	
	❖ III.4. Adamantoylindoles *Examples:* *AB-001 (CAS 1345973-49-0)*	
	❖ III.5. Tetramethylcyclopropanoyl-indoles (TMCP) *Examples:* *XLR-11 (CAS 1364933-54-9),* *UR-144 (CAS 1199943-44-6)*	
	❖ III.6. Indolecarboxilate esters *Examples:* *NM-2201 (CAS 2042201-16-9),* *PB-22 (CAS 1400742-17-7)*	
	❖ III.7. Indolecarboxamides *Examples:* *NNE1 (CAS 1338925-11-3),* *APICA (CAS 1345973-50-3),* *CUMYL-PICA (CAS 1400742-32-6)*	

	○ ***2.2.3. Indazoles*** *Examples:* *AB-FUBINACA (CAS 1185282-01-2),* *AB-PINACA (CAS 1445752-09-9),* *SDB-005 (CAS 2180934-13-6),* *FAB-144 (CAS 2180935-79-7)*	
	○ ***2.2.4. Benzimidazoles*** *Examples:* *FUBIMINA (CAS 1984789-90-3),* *BIM-018 (CAS 2316839-70-8),* *etonitazene (CAS 911-65-9)* *Isotonitazene (CAS 14188-81-9),* *Brorphine (CAS 2244737-98-0)*	
	○ ***2.2.5. Carbazoles*** *Examples:* *EG-018 (CAS 2219320-91-7),* *MDMB-CHMCZCA (CAS 2219324-32-8)*	
	○ ***2.2.6. Xanthines*** *Examples:* *Xanthine (CAS 69-89-6),* *Caffeine (CAS 58-08-2),* *DPCPX (CAS 102146-07-6)*	
	○ ***2.2.7. Bridged azapolycyclic compounds***	
	• I. Tropane-structure-containing alkaloids *Examples:* *scopolamine (CAS 51-34-3),* *cocaine (CAS 50-36-2),* *hyoscyamine (CAS 101-31-5),* *atropine (CAS 51-55-8)*	
	• II. Morphine-structure-containing alkaloids (“Morphinans”) *Examples:* *morphine (CAS 57-27-2),* *heroin (CAS 561-27-3),* *codeine (CAS 76-57-3),* *buprenorphine (CAS 52485-79-7)*	
Alcohols & ethers	▪ **PHENOLS & PHENOLIC COMPOUNDS:**	
	- CYCLOHEXYLPHENOLS / CYCLOHEXYLPHENYLETHERS *Examples:* *Cannabicyclohexanol (CAS 70434-92-3),* *CP 55,940 (CAS 83002-04-4),* *Tramadol (CAS 27203-92-5)*	
	- DIBENZOPYRAN ALCOHOLS/ETHERS *Examples:* *Cannabinol (CAS 521-35-7)*	

	○ ***THC-structure-containing cannabinoids*** *Examples:* *THC (CAS 1972-08-3),* *cannabidiol (CAS 13956-29-1),* *HU-210 (CAS 112830-95-2)*	
Other NPS	*Examples:* *Salvinorin A (CAS 83729-01-5)*	