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The challenge of New Psychoactive Substances

A technical update 2024

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Laboratory and Scientific Services
Drugs, Laboratory and Scientific Services Branch
United Nations Office on Drugs and Crime
P.O. Box 500
1400 Vienna
Austria

Tel.: (+43) 1 26060 0
E-mail: unodc-lab@un.org
Website: www.unodc.org/lab

Contents

Introduction

A New Psychoactive Substance (NPS) is a substance 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". In this context, the term *"new"* does not necessarily refer to novel inventions but to substances that have recently become available.

Since their emergence, NPS have been known in the market by terms such as *"designer drugs," "legal highs," "herbal highs,"* and/or *"bath salts."* The term *"designer drugs"* had been traditionally used to identify synthetic substances. However, it has recently been broadened to include other psychoactive substances that mimic the effects of illicit and, prescription drugs. They are produced by introducing slight modifications to the chemical structure of controlled substances to circumvent drug controls[1, 2]. *"Legal highs," "herbal highs," "research chemicals"* and *"bath salts"* are also common names used to refer to NPS offered as a legal alternative to controlled drugs.

Psychoactive substances controlled under the international drug control conventions produce their effects through a small number of pharmacological mechanisms including activation of cannabinoid receptors (e.g., cannabinoid receptor agonists); modulating the levels and action of monoamine neurotransmitters such as dopamine, epinephrine and serotonin to induce excitatory responses in the central nervous system; acting as *N*-methyl-*D*-aspartate (NMDA) receptor antagonists; interaction with opioid receptors or inhibitory neurotransmitters, and facilitating the action of the neurotransmitter *gamma*-aminobutyric acid (GABA) at the GABAA receptor to induce sedative, hypnotic and anxiolytic effects. It is important to note that some psychoactive substances may induce their physiological effects through one or more of these pharmacological mechanisms[3].

For the purpose of this document and, due to the significant chemical diversity within NPS, we will assign the functional categorisation (or *"effect group"*) classification and discuss synthetic NPS within **six** groups: (i) synthetic cannabinoid receptor agonists; (ii) classic hallucinogens; (iii) stimulants; (iv) opioid receptor agonists; (v) sedatives/hypnotics and (vi) dissociatives; based on the features related to their chemical structure and purported psychopharmacological effects **(Figure 1)**.

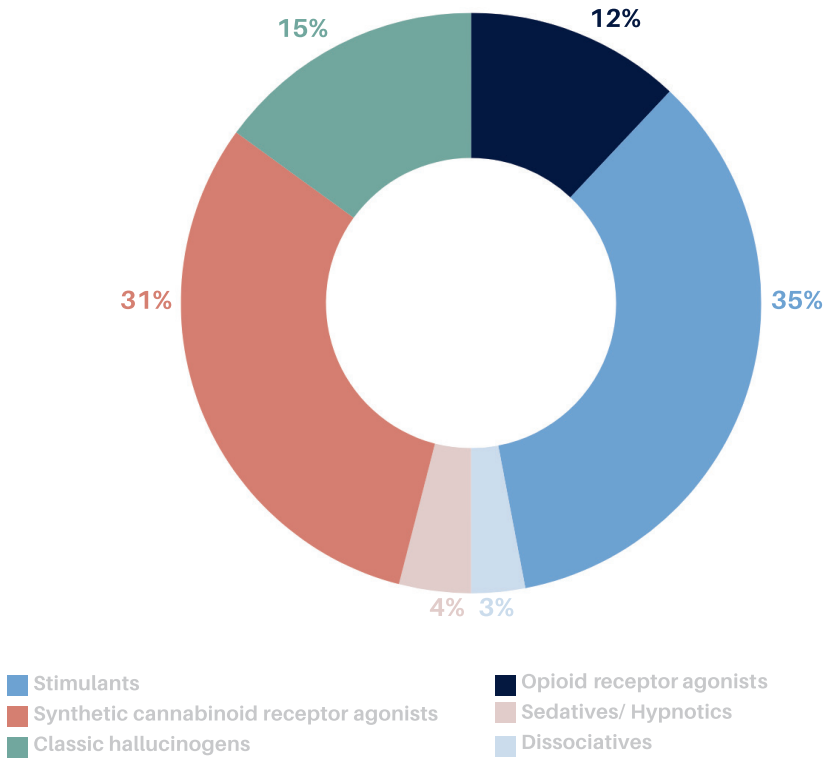


Figure 1: Distribution of NPS reported to the UNODC Early Warning Advisory on NPS by effect group.

Synthetic Cannabinoid Receptor Agonists

This group of NPS is a class of substances with structural features that allow binding to the cannabinoid type-1 (CB_1) and/or type-2 (CB_2) receptors. These receptors are abundant in the central and peripheral nervous system, respectively, and display a pharmacological profile like (-)-*trans*-Δ^9-tetrahydrocannabinol (Δ^9-THC), the principal psychoactive component in Cannabis [4–8]. Activity at the CB_1 receptor produces a characteristic group of psychoactive effects including euphoria, enhancement of sensory perception, antinociception, appetite stimulation, and impairment of memory.

Synthetic cannabinoids are a particularly innovative, dynamic, and evolving group, evidenced by more than 300 individual substances having been reported to UNODC. The number and rapid evolution of this group are also reflected in the NPS market, where the content of products containing SCRAs can vary both in terms of the actual cannabinoid or mixture of cannabinoids present and their concentration(s) between batches of SCRAs or products sold under a specific street name – contributing to the significant health risk posed by these compounds and their products [9, 10]. More than 20 SCRAs have been placed under international control since 2015 **(Figure 2)**.

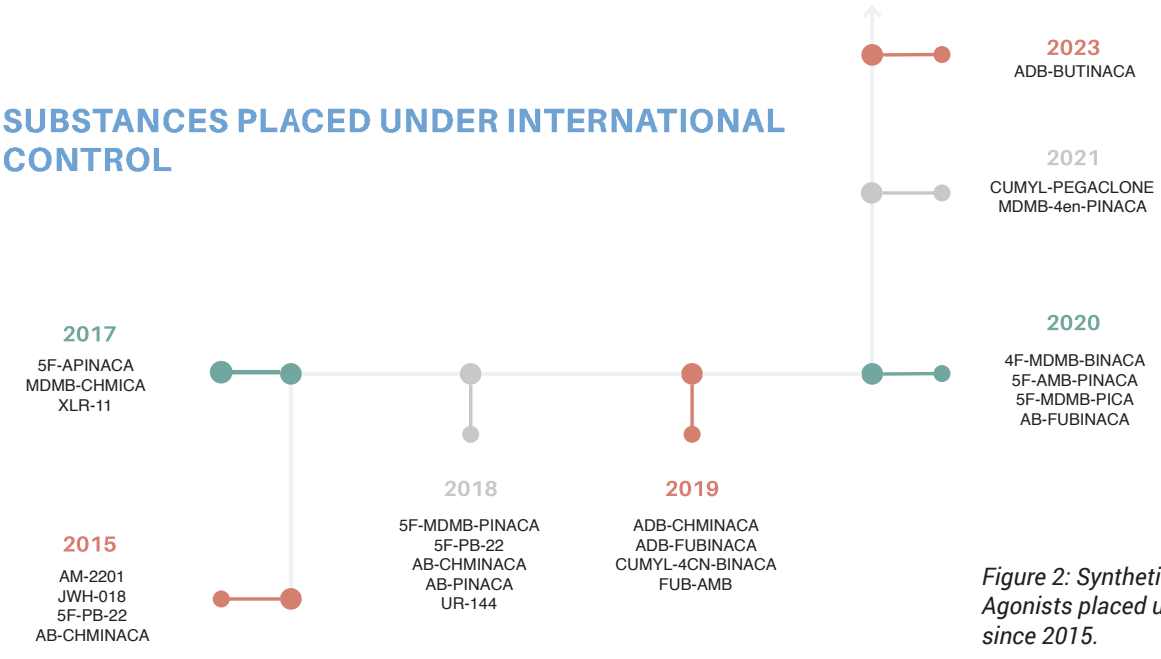


Figure 2: Synthetic Cannabinoid Receptor Agonists placed under international control since 2015.

The first examples of SCRAs were produced in the 1980s to research cannabinoid receptor pharmacology and to investigate the therapeutic potential of drugs interacting with the cannabinoid receptor system. HU-210, a synthetic analogue of Δ^9-THC, was first synthesized in 1988 and is considered to have a potency of at least 100x greater than Δ^9-THC [11–14]. Due to the similarity of its chemical structure to Δ^9-THC, HU-210 is considered a *"classical cannabinoid."* Another group of SCRAS, are cyclohexylphenols (3-arylcyclohexanols, CP-series) which were developed by the pharmaceutical industry as potential analgesics and were termed *"non-classical cannabinoids"* **(Figure 3)** [6]. The most potent SCRA within this sub-family is CP-47,497 and is regarded as one of the first SCRA NPS.

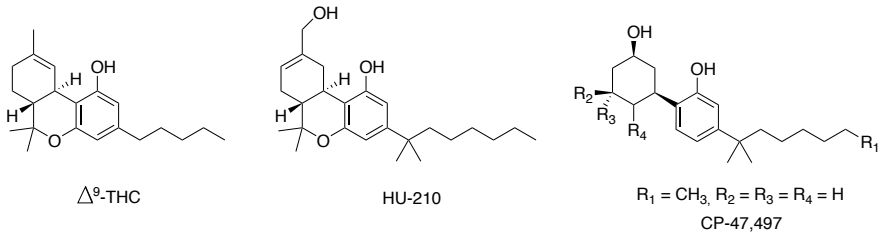
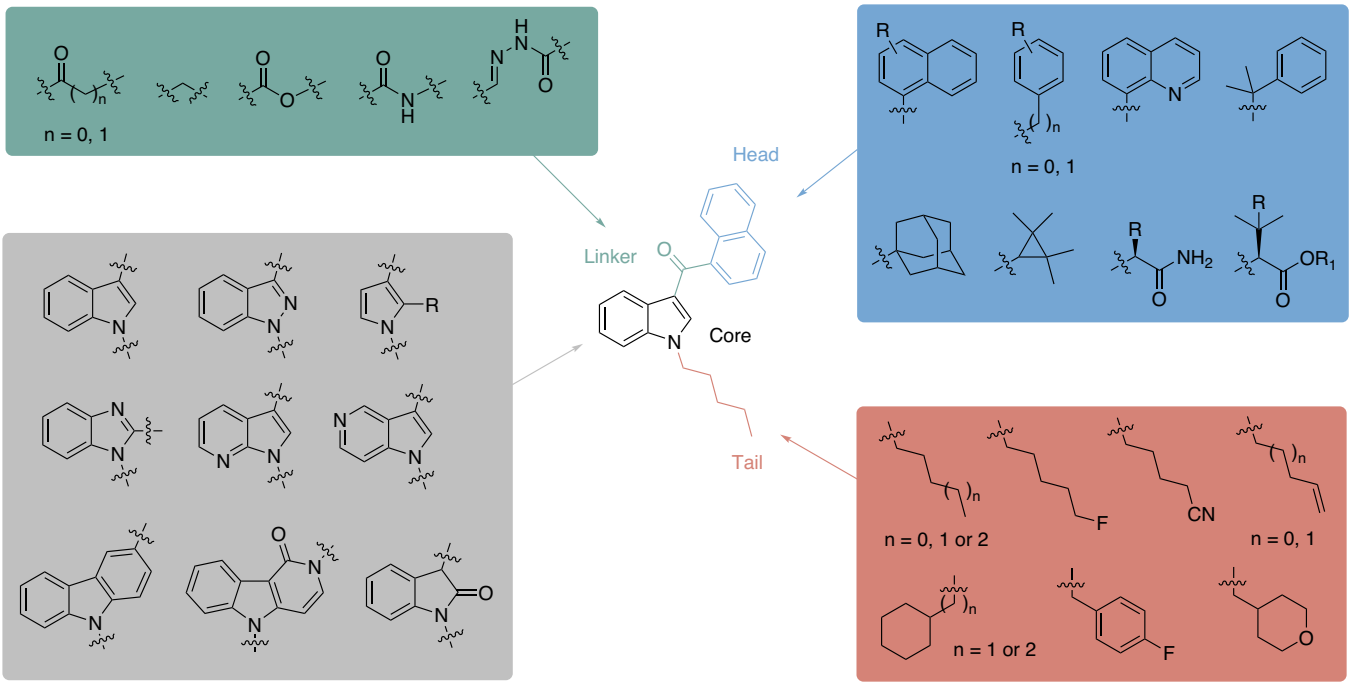


Figure 3: Chemical structures of Δ^9-THC, classical synthetic cannabinoid, HU-210 and the non-classical cannabinoid CP-47,497.

Both *classical* and *non-classical* cannabinoids have significant challenges in their synthesis and consequently, these compounds have been supplanted within the NPS market by simpler synthetic cannabinoid receptor agonists such as those described herein. The variation, evolution, and extensive production of SCRAs have been achieved by systematic modification of one or more of the four regions (core, linker, head, and tail) of the basic structure (**Figure 4**), using common inexpensive precursors or equipment and relatively simple synthetic chemistry methods [15, 16].

Figure 4: Generic structural representation of synthetic cannabinoid receptor agonists (SCRAs) obtained by modification of the key regions (core, linker, head, and tail) and using JWH-018 as the template.



Synthetic cannabinoids can be further sub-divided into **eight** distinct sub-groups: (i) naphthoylindoles; (ii) phenylacetyl- and benzoylindoles; (iii) acylindoles; (iv) acylindazoles; (v) indole- and indazolecarboxylates; (vi) indole- and indazolecarboxamides; (vii) carbazoles and g-carbolines and (viii) *N*-alkylisatin-acylhydrazones [4, 5, 15, 16] **(Figure 5)**.

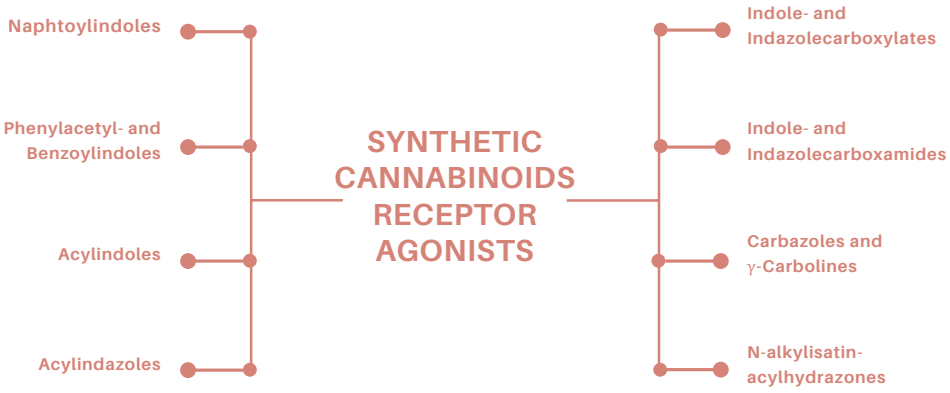


Figure 5: Synthetic cannabinoid receptor agonists receptor (SCRA) sub-groups.

Naphthoylindoles

The naphthoylindole sub-group of SCRA's was independently synthesized by John W Huffman (JWH-series) and Alexandros Makriyannis (AM-series) to identify the structural requirements for selective binding affinity (expressed as K_i) to the cannabinoid type-1 (CB_1) receptor [6, 17–21]. Despite a negligible selectivity for CB_1, synthetic cannabinoids containing *N*-alkylated tail groups bearing 4 to 6 carbon atoms demonstrated effective hydrophobic interactions with the binding pocket of the receptor, leading to an increase in affinity, whereas shorter (or longer) *N*-alkyl groups decreased affinity significantly [22–24]. Replacement of the *N*-pentyl group, with either an *N*-5-fluoropentyl- or *N*-5-cyanopentyl group resulted in substantial increase in CB_1 affinity[19, 20, 25, 26].

Chemical substitution of the ketone bridge with a methylene linker led to naphthylmethylindoles (e.g. JWH-175) that have a weaker affinity for the CB_1 receptor compared to their naphthoylindole counterparts[17]. However, modification of the 1-naphthyl head group, through the introduction of 4-alkoxy- (JWH-081) [20, 24, 27] or 4-halo-substituents (JWH-398) [20, 27, 28] provided access to active cannabimimetics. The most marked increase in potency was observed in 4-alkyl-substituted naphthoylindoles [27], which led to the JWH- and AM-series (specifically JWH-018 and AM-2201) **(Figure 6)** dominating the synthetic cannabinoid market for a period [6].

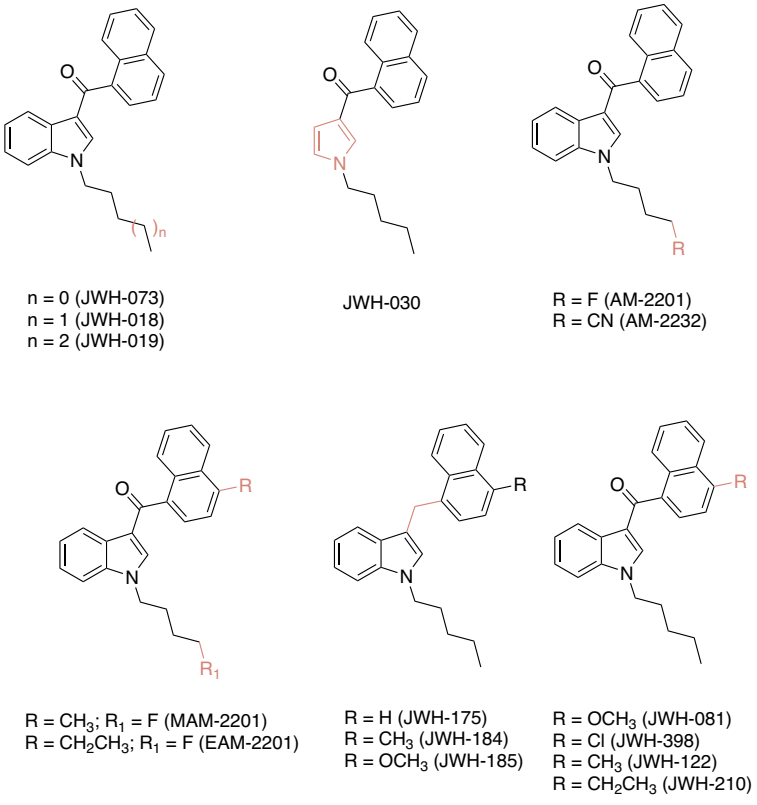
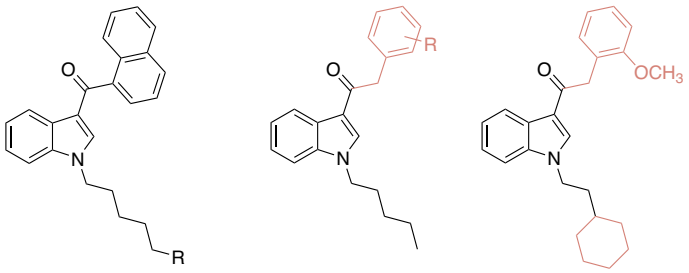


Figure 6: Chemical structures of naphthoylindole-based synthetic cannabinoids. The structural differences between the derivatives and JWH-018 are highlighted in red.

Phenylacetyl- and benzoylindoles

Simplified naphthoylindole derivatives, where the 1-napthyl group was replaced with either a phenylacetyl or benzoyl group were also developed to probe binding to the CB_1 receptor **(Figure 7)**. In the case of the phenylacetylindole, JWH-167, the affinity for the CB_1-receptor was 10x less than observed for JWH-018 [29, 30]. However, the introduction of 2-alkyl- (JWH-251), 2-alkoxy- (JWH-250) or 2-halo-substituents (JWH-311, JWH-203, and JWH-249,) led to improved binding [29, 31].



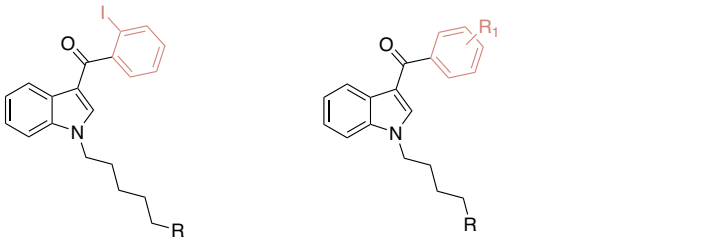
R = H (JWH-018)
R = F (AM-2201)

R = H (JWH-167)
R = 2-F (JWH-311)
R = 2-OCH_3 (JWH-250)
R = 3-OCH_3 (JWH-302)
R = 2-CH_3 (JWH-251)

RCS-8

Figure 7: Chemical structures of phenylacetyl -derived synthetic cannabinoids. The structural differences between the naphthyl- and phenylacetyl -derivatives are highlighted in red.

Substitution of the naphthalene group of JWH-018, with a 2-iodophenyl- motif results in the benzoylindole derivative AM-679, which exhibits a similar level of binding to CB_1 as JHW-018. [19, 32, 33]. As with the naphthoylindole family, subsequent replacement of the *N*-pentyl group, in the AM-679 with an *N*-5-fluoropentyl- tail, resulted in a substantial increase in CB_1 affinity (AM-694) **(Figure 8)** [34].



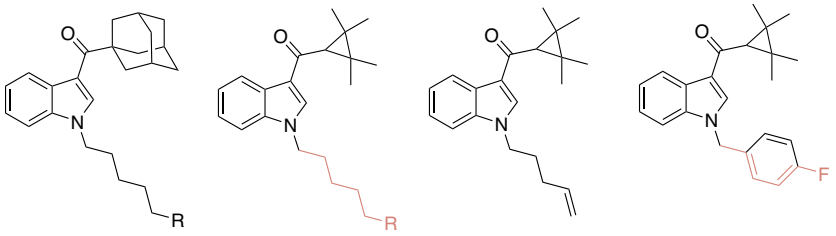
R = H (AM-679)
R = F (AM-694)

R = CH_3, R_1 = 2-OCH_3 (RCS-4, *ortho* isomer)
R = CH_3, R_1 = 4-OCH_3 (RCS-4)
R = H, R_1 = 4-OCH_3 (RCS-4, butyl homologue)

Figure 8: Chemical structures of benzoylindole-derived synthetic cannabinoids. The structural differences between the naphthyl- and benzoylindole-derivatives are highlighted in red.

Acylindoles

Novel 3-acylindole derivatives of SCRAs such as JWH-018 and AM-2201 emerged in several countries in Asia, Europe, and the Americas, in the late 2000s. They feature non-aromatic, bulky alicyclic head groups, such as the adamantylindoles (e.g., AB-001) [33, 35, 36] and tetramethylcyclopropylindoles (e.g., UR-144) [25, 36] (**Figure 9**). As with the naphthoylindole series, the replacement of the *N*-pentyl group with an *N*-5-fluoropentyl-tail resulted in substantial increase in CB_1 affinity and led to the emergence of cannabinoids such as 5F-AB-001 and XLR-11 [37].



R = H (AB-001)
R = F (5F-AB-001)

R = H (UR-144)
R = F (XLR-11)
R = Cl (5Cl-UR-144)

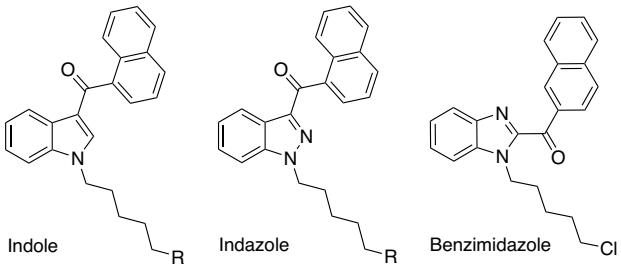
UR-144 N-(4-pentenyl)

FUB-144

Figure 9: Chemical structures of acylindole-based synthetic cannabinoids. The structural similarity between XLR-11 and FUB-144 is highlighted in red.

Acylindazoles

Similar to the emergence of acylindoles, a variety of acylindazole SCRAs also emerged. These substances such as (THJ-018, and THJ-2201) **(Figure 10)** feature a modified indazole core but retain specific head and tail groups for optimal CB_1-receptor affinity [38–40].



Indole

Indazole

Benzimidazole

R = H (JWH-018)
R = F (AM-2201)

R = H (THJ-018)
R = F (THJ-2201)
R = Cl (5Cl-THJ-018)

R = H (BIM-018)
R = F (FUBIMINA)

Figure 10: Chemical structures of acylindole-, acylindazole- and benzimidazole- based synthetic cannabinoids.

Indole- and indazolecarboxylates

In the early-mid 2010s, the NPS market pivoted towards SCRA analogues where the acyl-linker was substituted by either an *ester* or an *amide* linker (e.g., indole-an indazole carboxylates or carboxamides), **(Figure 11)**. As with previous classes, structural features for efficacious CB_1-receptor binding were retained [4, 41, 42].

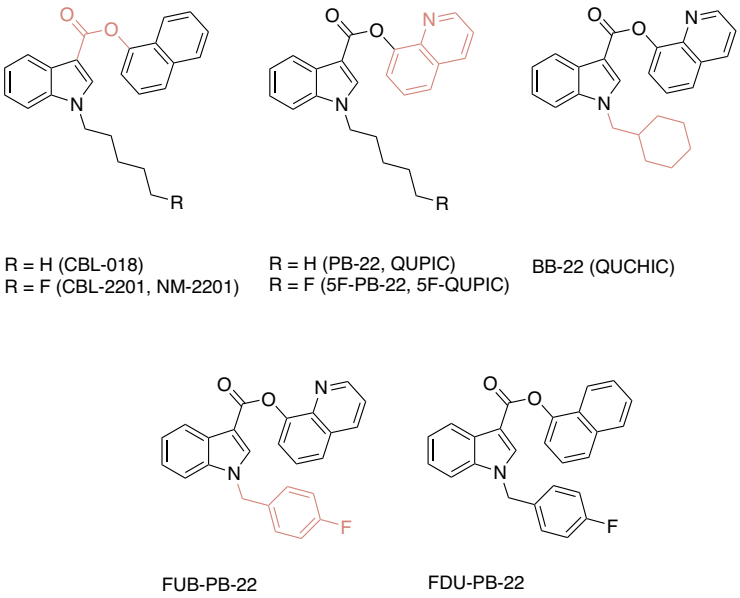


Figure 11: Chemical structures of indolecarboxylate synthetic cannabinoids. The structural differences and evolution from CBL-018 to FUB-PB-22 are highlighted in red.

In 2013, the first two indolecarboxylate synthetic cannabinoids reported were the quinoline-8-yl derivatives, BB-22 (QUCHIC) [25, 39, 43] and PB-22 (QUIPIC) [25, 43–46]. Cannabimimetic binding of PB-22 was improved by sequential replacement of the quinoline-8-yl- group for a 1-naphthyl-group (CBL-018) and subsequent introduction of terminal fluorine into the *N*-pentyl tail leading to a ten-fold increase in CB_1 affinity (NM-2201) [39, 47]. Replacing the *N*-pentyl tail (in PB-22) with either an *N*-4-fluorobenzyl- group or with an *N*-5-fluoropentyl- chain resulted in FDU-PB-22, FUB-PB-22 [39, 48] and 5F-PB-22 [49, 50] **(Figure 11)**.

Indazolecarboxylates are closely related to the indolecarboxylate family of cannabinoids, and some derivatives have been reported to UNODC, including the CBL-018, CBL-2201 analogues, SDB-005, 5F-SDB-005 [25], quinoline-8-yl analogues, 5F-NPB-22 [51, 52], FUB-NPB-22 [53], adamantan-1-yl-*1H*-indazole-3-carboxylates: APINAC [54–57] and 5F-AKB-57 [58–60] **(Figure 12)**.

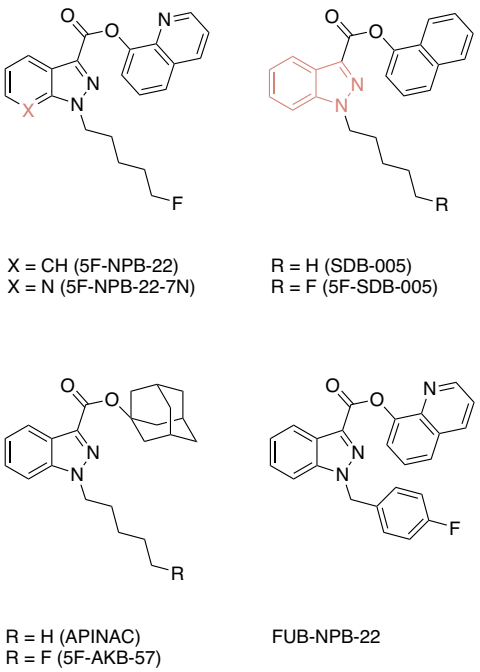


Figure 12: Chemical structures of indazolecarboxylate-derived SCRAs.

As a result of their inherent metabolic instability/toxicity, both the indole- and indazolecarboxylate families were entirely replaced by the more stable amide (indole- and indazolecarboxamide) classes.

Indole- and Indazolecarboxamides

In 2012, the first indolecarboxamide SCRAs that were reported within the NPS market were APICA [25, 61–67] and its fluorinated derivative, 5F-APICA [25, 63, 65], which both exhibited moderate CB_1 receptor affinity. MEPIRAPIM another indole carboxamide also emerged at that time, however it acts as a T-type calcium channel inhibitor and has minimal CB_1 affinity [68, 69].

Subsequently, a *"mix and match"* modification of the *N*-alkyl tails and replacement of the bulky adamantyl- head group for either phenyl- (*N*-phenyl-SDB-006) [35], benzyl- (SDB-006 and 5F-SDB-006,) [35, 53, 70–74] or 1-naphthyl-(NNEI, 5F-NNEI; 5Cl-NNEI, and FDU-NNEI) [48, 74–79] groups led to a wide variety of products (**Figure 13 and 14**).

Phenyl- and benzyl-substituted indolecarboxamides generally exhibit weaker binding to the CB_1 receptor compared to their adamantyl- and 1-naphthyl counterparts. The exception to this trend is the sub-family of (2-phenylpropan-2-yl)- (or cumyl-) CB_1 agonists: CUMYL-BICA CUMYL-PICA, 5F-CUMYL-PICA, CUMYL-CHMICA, and CUMYL-FUBICA. All these CB_1 agonists show significant increases in potency compared to their progenitors SDB-006 and 5F-SDB-006 [25, 70, 80, 81]. Several 7-azaindole-3-carboxamide derivatives (also known as the 7AICA-series) have also emerged in the synthetic cannabinoid market, including 5F-AKB-48-7N [82], CUMYL-5F-P7AICA [80, 83], CUMYL-4CN-B7AICA [84–87] and 5F-PCN [88].

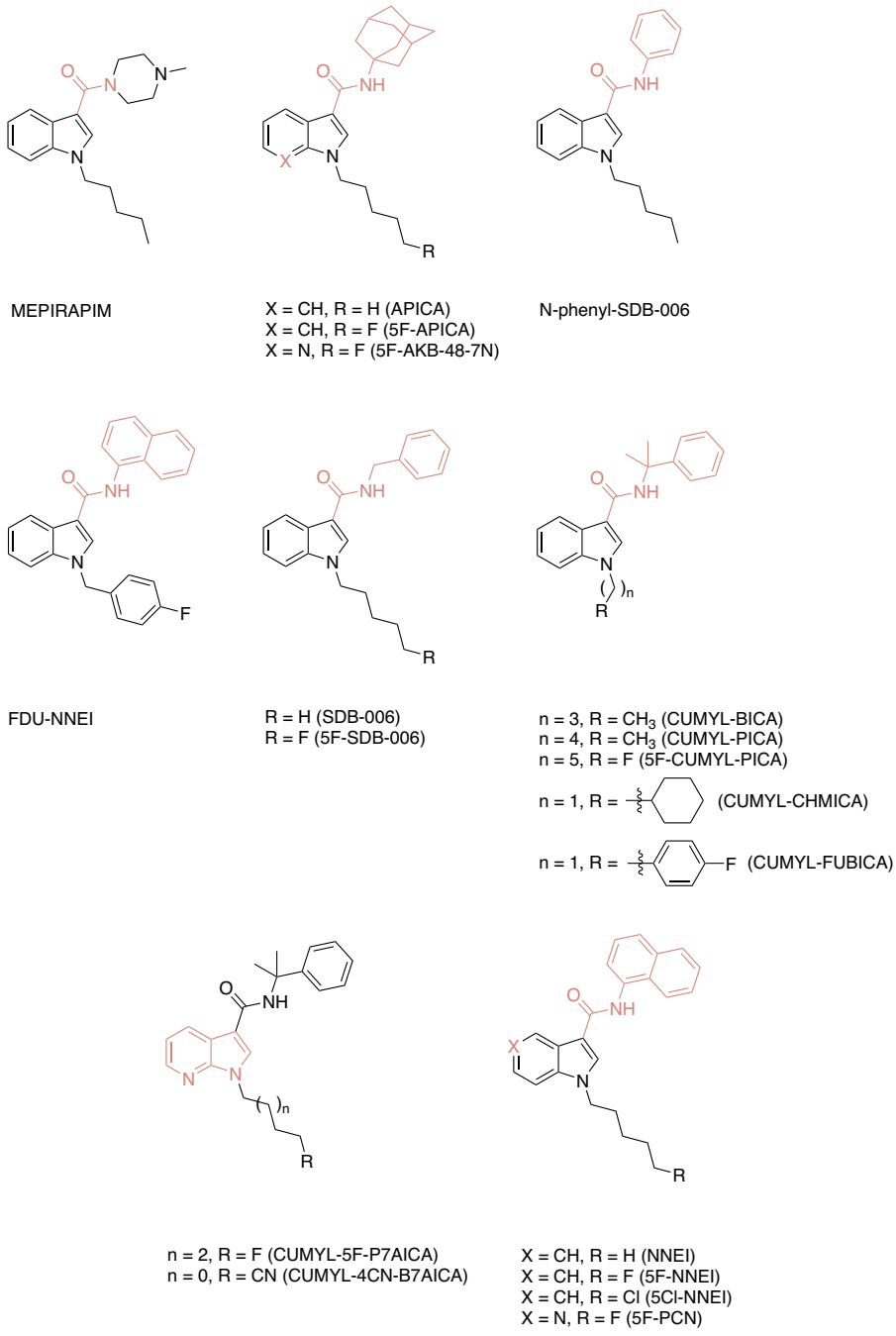


Figure 13: Chemical structures of indolecarboxamide synthetic cannabinoids. The structural differences are highlighted in red.

Figure 14: Further chemical structures of indolecarboxamide synthetic cannabinoids. The structural differences are highlighted in red.

Indazolecarboxamides are a direct extension of the indolecarboxamide family of cannabinoids, where the indole core is replaced with an indazole. Since 2012, various derivatives have been reported, for example SDB-005, 5F-SDB-005 (and analogues); MN-18, and 5F-MN-18 [48, 76, 79, 89, 90]. Other examples are the adamantan-1-yl-*1H*-indazole-3-carboxamides: APINACA (AKB-48) [37, 56, 61, 66, 67, 75, 91–112], 5F-APINACA (5F-AKB-48) [61, 94, 95, 98, 99, 101, 104–107, 110, 112], FUB-AKB-48 [39] and Adamantyl-THPINACA [61, 80, 113] (**Figure 15**). Cumyl-derivatives like CUMYL-BINACA [4], CUMYL-4CN-BINACA [84, 87, 114–116], CUMYL-PINACA [80, 81, 84, 87, 117–119], 5F-CUMYL-PINACA [84, 87, 95, 117, 120], CUMYL-CHMINACA, CUMYL-FUBINACA [4, 81] and CUMYL-THPINACA [80, 113] are also known. These derivatives all show significant increases in cannabimimetic CB_1 potency compared to their indole counterparts.

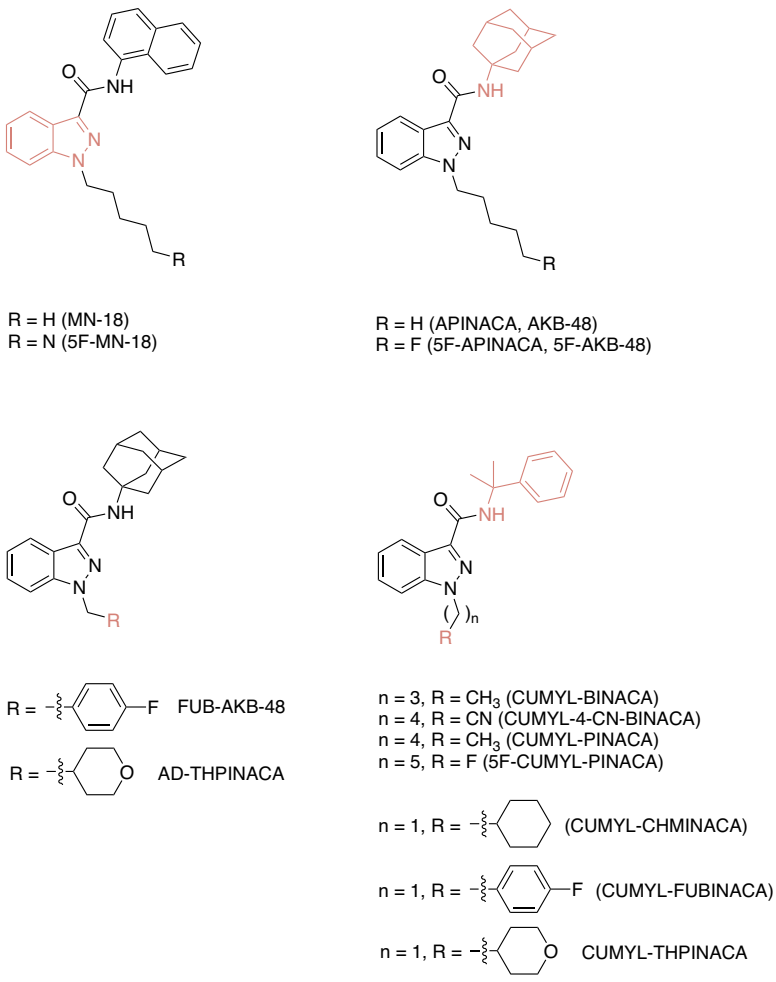


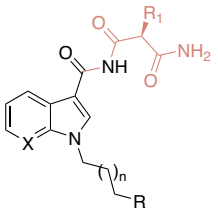
Figure 15: Chemical structures of indazolecarboxamide synthetic cannabinoids.

Amino Acid amides

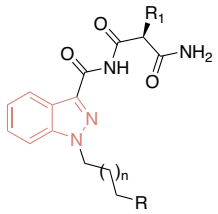
This is an important sub-family within the broader indole- and indazole-carboxamide series of synthetic cannabinoids e.g., valinamides [AB-series] [42, 121–123], *tert*-leucinamides [ADB-series] [42, 122–124] and/or phenylalaninamide [APP-series] [122, 123] (**Figure 16**). The incorporation of *esters* like, methyl valinate [AMB- or MMB-series], ethyl valinate [AEB- or EMB-series], methyl *tert*-leucinate [MDMB-series], and/or ethyl *tert*-leucinate [EDMB-series] is also possible (**Figure 15**) [41, 122, 125–132].

Unlike the previously discussed cannabimimetics, which are achiral, these SCRAs contain an asymmetric carbon. In theory, these compounds are present in two enantiomeric forms – depending upon the source and enantio-purity of the precursor chemicals used. In most cases, a higher potency at the CB_1 receptor is observed for the (*S*)-enantiomer over the (*R*)-enantiomers. In seized samples, the more active enantiomer appears to predominate [125–127, 133].

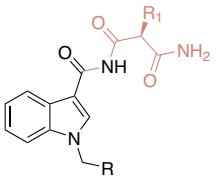
As with previous generations, the indole-valinamide synthetic cannabinoids with *N*-alkylated tail groups bearing 4 or 5 carbons exhibit nanomolar CB_1 affinity (e.g., AB-PICA) (**Figure 16**). Modification of the *N*-pentyl group, with either an *N*-5-fluoropentyl- (5F-AB-PICA) or aromatic

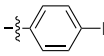
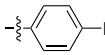


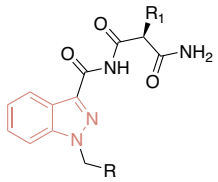
X = CH, n = 1, R = CH_3, R_1 = ^{i}Pr (AB-BICA)
X = CH, n = 2, R = CH_3, R_1 = ^{i}Pr (AB-PICA)
X = CH, n = 2, R = CN, R_1 = ^{i}Pr (4CN-AB-BUTICA)
X = CH, n = 3, R = F, R_1 = ^{i}Pr (5F-AB-PICA)
X = CH, n = 3, R = C=C, R_1 = ^{i}Pr (AB-4en-PICA)
X = CH, n = 2, R = CH_3, R_1 = ^{t}Bu (ADBICA, ADB-PICA)
X = CH, n = 3, R = F, R_1 = ^{t}Bu (5F-ADBICA, 5F-ADB-PICA)
X = CH, n = 3, R = F, R_1 = Bz (5F-APP-PICA, PX-1)
X = N, n = 2, R = CH_3, R_1 = ^{t}Bu (ADB-P7AICA)



n = 2, R = CH_3, R_1 = ^{i}Pr (AB-PINACA)
n = 3, R = F, R_1 = ^{i}Pr (5F-AB-PINACA)
n = 3, R = Cl, R_1 = ^{i}Pr (5Cl-AB-PINACA)
n = 1, R = CH_3, R_1 = ^{t}Bu (ADB-BUTINACA)
n = 2, R = CH_3, R_1 = ^{t}Bu (ADB-PINACA)
n = 3, R = F, R_1 = ^{t}Bu (5F-ADB-PINACA)
n = 3, R = C=C, R_1 = ^{t}Bu (ADB-4en-PINACA)
n = 4, R = CH_3, R_1 = ^{t}Bu (ADB-HEXINACA)
n = 3, R = F, R_1 = Bz (5F-APP-PINACA, PX-2)



R =  , R_1 = ^{i}Pr (AB-CHMICA)
R =  , R_1 = ^{t}Bu (ADB-CHMICA)
R =  , R_1 = Bz (APP-CHMICA)
R =  F, R_1 = ^{i}Pr (AB-FUBICA)
R =  F, R_1 = ^{t}Bu (ADB-FUBICA)



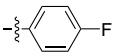
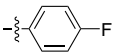
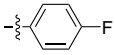
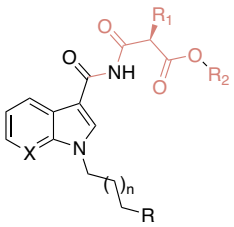
R =  , R_1 = ^{i}Pr (AB-CHMINACA)
R =  , R_1 = ^{t}Bu (ADB-CHMINACA)
R =  , R_1 = Bz (APP-CHMINACA, PX-3)
R =  F, R_1 = ^{i}Pr (AB-FUBINACA)
R =  F, R_1 = ^{t}Bu (ADB-FUBINACA)
R =  F, R_1 = Bz (APP-FUBINACA)
R =  , R_1 = ^{t}Bu (ADB-BINACA)

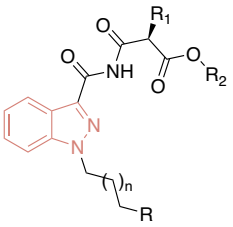
Figure 16: Chemical structures of indazolecarboxamide synthetic cannabinoids.

N-4-fluorobenzyl- (AB-FUBICA), tail resulted in substantial increase in CB_1 affinity. Compounds containing other side chains such as *N*-4-cyanobutyl- (4CN-AB-BUTICA), *N*-cyclohexylmethyl- (AB-CHMICA), and *N*-penten-4yl- (AB-4en-PICA) have also been reported. Replacement of the indole core with an indazole (e.g., AB-PICA *versus* AB-PINACA) leads to a 10x increase in potency in each congeneric derivative [4, 25, 41, 42]. A similar increase in CB_1-binding affinity was seen within the analogous indole- and indazole-*tert*-leucinamide [ADB-series] derivatives, [4, 41, 42, 123, 125, 126]. The same was not observed in the APP-series derived from phenylalanidamide (e.g., 5F-APP-PICA, 5F-APP-PINACA, APP-CHMICA, APP-CHMINACA, and APP-FUBINACA), where the presence of the bulky aromatic group significantly reduces CB_1 cannabimimetic activity in many cases [122, 123, 134]. Further chemical modification of the tail groups (e.g., 5Cl-AB-PINACA; ADB-4en-PINACA, ADB-HEXINACA, and ADB-BINACA) or replacement of the core with a 7-azaindole scaffold (ADB-P7IACA) in the most active ADB-series resulted in an increase in the variety of potent and potentially more harmful analogues on the market [122, 124, 134–137].

An extension of this sub-family has also emerged, where the amino acid amide group was replaced with either a commercially available, chiral methyl valinate [AMB- or MMB-series], ethyl valinate [AEB- or EMB-series], methyl *tert*-leucinate [MDMB-series] or ethyl *tert*-leucinate [EDMB-series] group. Similar to the AB-, ADB-, and APP-series, in most cases, a higher potency at the CB_1 receptor is observed for the (*S*)-enantiomer over the (*R*)-enantiomers. In seized samples, the active enantiomer appears to predominate [4, 15, 70, 125–128, 133]. The AMB-/MMB- and MDMB-series of derivatives bearing *N*-4-fluoropentyl-, *N*-5-fluoropentyl- and *N*-penten-4-yl-groups show the same trends, except for in terms of binding affinity as their amide counterparts with indazoles observed to be more potent than indoles and the *tert*-leucinate derivatives more potent than the valinate derivatives (**Figure 17**).

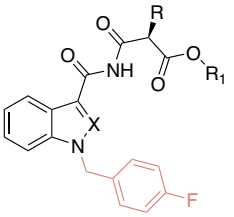


X = CH, n = 2, R = CH_3, R_1 = ^{i}Pr, R_2- = Me (AMB-PICA)
X = CH, n = 3, R = F, R_1 = ^{i}Pr, R_2 = Me (5F-AMB-PICA)
X = CH, n = 3, R = F, R_1 = ^{i}Pr, R_2 = Et (5F-EMB-PICA)
X = CH, n = 3, R = C=C, R_1 = iPr, R_2 = Me (MMB-4en-PICA)
X = CH, n = 2, R = F, R_1 = ^{t}Bu, R_2 = Me (4F-MDMB-BICA)
X = CH, n = 2, R = CH_3, R_1 = ^{t}Bu, R_2 = Me (MDMB-PICA)
X = CH, n = 3, R = F, R_1 = ^{t}Bu, R_2 = Me (5F-MDMB-PICA)
X = CH, n = 3, R = F, R_1 = ^{t}Bu, R_2 = Et (5F-EDMB-PICA)
X = CH, n = 3, R = C=C, R_1 = ^{t}Bu, R_2 = Me (MDMB-4en-PICA)
X = N, n = 3, R = F, R_1 = tBu, R_2 = Me (5F-MDMB-P7AICA)

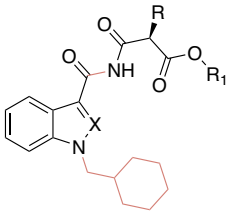


n = 2, R = CH_3, R_1 = ^{i}Pr, R_2- = Me (AMB-PINACA)
n = 2, R = CN, R_1 = ^{i}Pr, R_2 = Me (4CN-MMB-BUTINACA)
n = 3, R = F, R_1 = ^{i}Pr, R_2 = Me (5F-AMB-PINACA)
n = 3, R = F, R_1 = ^{i}Pr, R_2 = Et (5F-EMB-PINACA)
n = 3, R = C=C, R_1 = iPr, R_2 = Me (MMB-4en-PINACA)
n = 2, R = F, R_1 = ^{t}Bu, R_2 = Me (4F-MDMB-BINACA)
n = 2, R = CN, R_1 = ^{t}Bu, R_2 = Me (4CN-MDMB-BUTINACA)
n = 2, R = CH_3, R_1 = ^{t}Bu, R_2 = Me (MDMB-PINACA)
n = 3, R = F, R_1 = ^{t}Bu, R_2 = Me (5F-MDMB-PINACA)
n = 2, R = CH_3, R_1 = ^{t}Bu, R_2 = Et (EDMB-PINACA)
n = 3, R = F, R_1 = ^{t}Bu, R_2 = Et (5F-EDMB-PINACA)
n = 3, R = Cl, R_1 = ^{t}Bu, R_2 = Me (5Cl-MDMB-PINACA)
n = 3, R = C=C, R_1 = ^{t}Bu, R_2 = Me (MDMB-4en-PINACA)

Figure 17: Chemical structures of (S)-amino acid ester derivatives (AMB-/MMB-, EMB-, MDMB and EMDB-series) of the indole- and indazolecarboxamide families.



X = CH, R = ^{i}Pr, R_1 = Me (AMB-FUBICA)
X = CH, R = ^{t}Bu, R_1 = Me (MDMB-FUBICA)
X = N, R = ^{i}Pr, R_1 = Me (AMB-FUBINACA)
X = N, R = ^{t}Bu, R_1 = Me (MDMB-FUBINACA)
X = N, R = ^{i}Pr, R_1 = Et (EMB-FUBINACA)



X = CH, R = ^{i}Pr, R_1 = Me (AMB-CHMICA)
X = CH, R = ^{t}Bu, R_1 = Me (MDMB-CHMICA)
X = N, R = ^{i}Pr, R_1 = Me (AMB-CHMINACA)
X = N, R = ^{t}Bu, R_1 = Me (MDMB-CHMINACA)

The N-4-fluorobenzyl- (AMB-FUBICA, MDMB-FUBICA, AMB-FUBINACA and MDMB-FUBINACA), *N*-cyclohexylmethyl- (AMB-CHMICA, MDMB-CHMICA, AMB-CHMINACA, and MDMB-CHMINACA), *N*-4-cyanobutyl- (4CN-MMB-BUTINACA), *N*-5-chloropentyl- (5Cl-MDMB-PINACA) and 7-azaindole (5F-MDMB-P7AICA) derivatives show similar trends in terms of their CB_1-binding affinities as their corresponding amide counterparts. Recently a small number of ethyl valinate (EMB-) and *tert*-leucinate (EDMB-) derivatives have also been reported.

Carbazoles and γ-Carbolines

After the national control of some indoles, indazole, and benzimidazole-derived synthetic cannabinoids, the NPS market again shifted towards previously unexplored chemical structures. In 2014, tricyclic synthetic cannabinoids, such as the carbazole (e.g., EG-018 [82, 112, 138, 139], EG-2201 [140, 141], MDMB-PCZCA and MDMB-CHMCZCA [141–143]) and γ-carboline (e.g., CUMYL-PEGACLONE) [112, 144, 145] were first identified and exhibited moderate CB_1 affinity (**Figure 18**). Between 2017 – 2020 several γ-carboline analogues, where the *N*-pentyl tail has been replaced with either a *N*-5-halopentyl- (e.g., 5F-CUMYL-PEGACLONE and 5Cl-CUMYL-PEGACLONE) or cycloalkyl- group (e.g., CUMYL-CH-MEGACLONE, CUMYL-CB-MEGACLONE and CUMYL-BC-HPMEGACLONE) have emerged in Europe [112, 144–153].

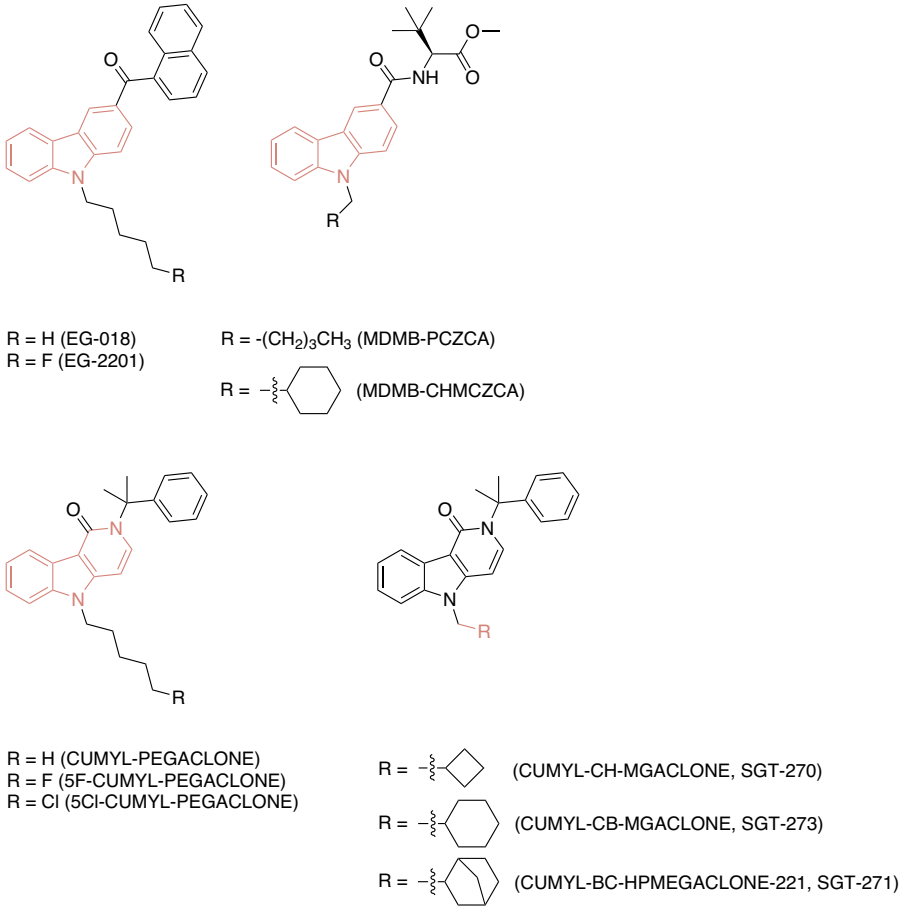


Figure 18: Chemical structures of tricyclic synthetic cannabinoids.

N-alkylisatin-acylhydrazones

In 2021, new substances with previously unencountered and/or not well characterized structural modifications appeared on the market, including the weak CB1 binding *N*-alkylisatin-acylhydrazone, MDA-19 (also known

as BZO-HEXOXIZID) [154], and its related analogues (5Cl-MDA-19, BZO-POXIZID, 5F-MDA-19, 5F-BZO-POXIZID and CHM-MDA-19, BZO-CHMOXIZID) (**Figure 19**). At the time of writing, these compounds have been identified in smoking blends (Americas and Asia) and reported in the literature [154, 155].

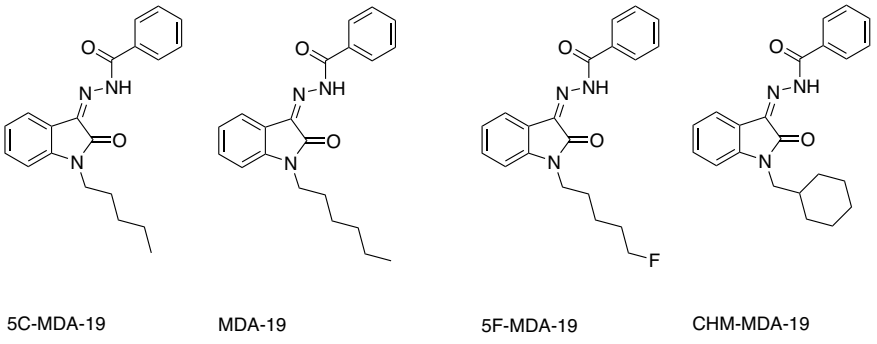


Figure 19: Chemical structures of N-alkylisatin-acylhydrazone derived synthetic cannabinoids.

Commonly Used Forms

SCRAs as bulk crystalline powders are generally dissolved in a volatile organic solvent such as acetone, methanol, or ethanol. They can be infused directly onto inert plant material (resembling traditional herbal cannabis), paper/card, clothing, or dispersed within e-liquids for smoking (either directly or mixed with tobacco) or vaping [15, 16, 117, 125, 130, 145, 156, 157]. Though the most common route of administration is inhalation (*via* water pipe/bong, cigarette, blunt, pipe, or vaping), oral, rectal, and intravenous administration routes have been reported **(Figure 20)** [117].

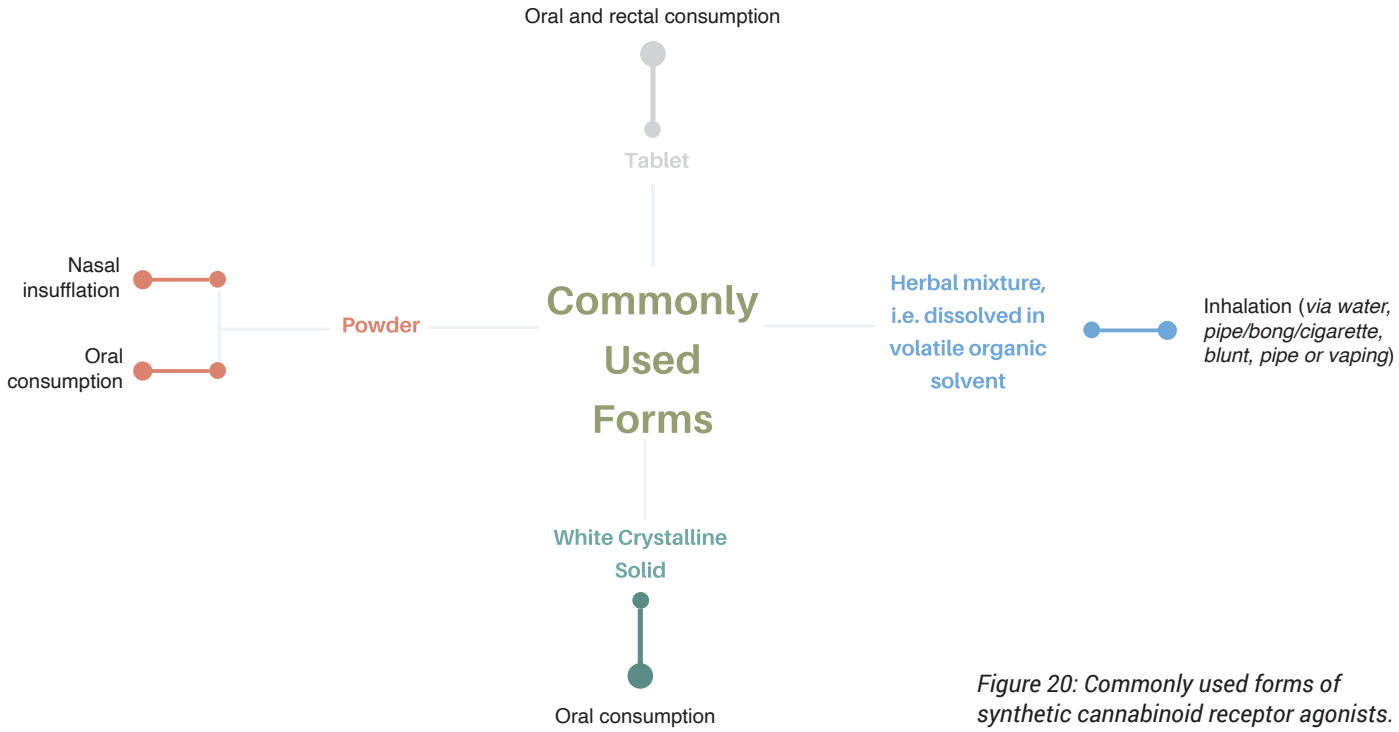


Figure 20: Commonly used forms of synthetic cannabinoid receptor agonists.

Reported Effects

Desired Effects

- *Euphoria - Sense of well being*
- *Enhancement of sensory experiences (i.e. more vivid sense of sight, smell, taste and hearing)*
- *Merriment*
- *Relaxation*

Undesired Acute Effects

- *Agitation, hot flushes*
- *As effects subside, may lead to quietness, reflectiveness, depression or sleepiness*
- *Bloodshot eyes, dilatation of pupils, dry mouth*
- *Memory and cognitive impairment*
- *Impairment of psychomotor performance (i.e. motor coordination, complex tasks)*
- *Increased heart rate*
- *Loss of consciousness, seizures, convulsions*
- *Potential anxiety, panic, paranoia, or acute psychosis*
- *Sensations may be distorted, thinking becomes slow and confused*
- *Vomiting, drowsiness, chest pain*

Effects of Chronic Use

- *Development of tolerance*
- *Loss of drive and interest*
- *May pose a risk for lung cancer, acute and chronic bronchitis, lung inflammation, impaired pulmonary defence, respiratory Insufficiency*
- *Potential development of psychological dependence*
- *Possible mental health problems*
- *Potential development of cannabinoid hyperemesis*
- *Psychosis or schizophrenia in vulnerable individuals*
- *Severe risk during use in pregnancy, e.g. impaired foetal development*

Figure 21: Reported effects of synthetic cannabinoid receptor agonists [a].

a The reported effects of the substances mentioned in this document are taken from the literature referenced herein and from the UNODC Terminology and Information on Drugs (ST/NAR/51) link.

Classic hallucinogens

Hallucinogens are a diverse group of naturally occurring and synthetic drugs that induce distorted states of consciousness, perception, thinking, and feeling, accompanied by different degrees of auditory or visual hallucinations. They are also referred as "psychedelics," which ultimately produce altered perceptions of reality [158] . Classic hallucinogenic substances elicit their pharmacological effect through their interaction with the serotonin (5-HT_{2A}, 5-HT_{2B}, and/or 5-HT_{2C}) and dopamine (D_1, D_2, and/or D_3) receptors in the central nervous system. Classic hallucinogens can be divided into three chemically related sub-groups: (i) hallucinogenic phenethylamines, (ii) tryptamines and (iii) lysergamides (Figure 22).

Figure 22: Classic hallucinogens sub-groups.

There are a number of substances with classic hallucinogenic effects under international control. Examples include (+)-Lysergide (LSD), DMT (*N*,*N*-dimethyltryptamine), psilocybine, mescaline, brolamfetamine (DOB), and 2C-B.

NPS with classic hallucinogenic effects that have been placed under international control since 2015 include 25B-NBOMe, 25C-NBOMe, 25I-NBOMe and DOC (**Figure 23)**.

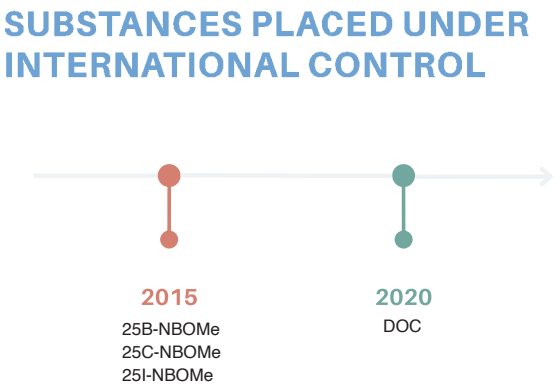
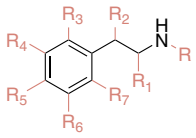


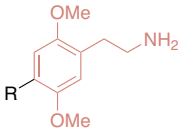
Figure 23: Classic hallucinogens placed under international control since 2015.

Hallucinogenic Phenethylamines

Phenethylamines (PEA) refer to a class of substances that can have stimulant, and/or hallucinogenic effects depending on the position and identity of functional group substituents on the phenethylamine core. The eight positions of the phenethylamine scaffold that can be modified to generate a wide range of substituted phenethylamine analogues are highlighted (**Figure 24).** More than 180 phenethylamines have been reported to UNODC, with 80 of them being classified as classical hallucinogens. Among these, 63 examples possess a 2,5-dimethoxy substitution pattern on the aromatic ring (80%). This is characteristic of phenethylamines classified as "classic hallucinogens," and they are represented by the 2C-, 2D - and NBOMe sub-family. The remaining compounds contain the 2,5-dimethoxy substitution, -3,5-dimethoxy substitution, and trimethoxy substitution, or are NBOMe variations of amphetamines, mescaline analogues, and the "Fly" compounds.

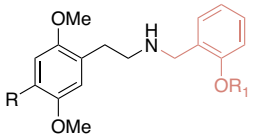


PEA Scaffold



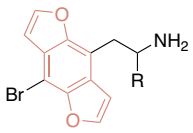
2C-Series

R = Cl (2C-C)
R = I (2C-I)
R = Me (2C-D)
R = Et (2C-E)



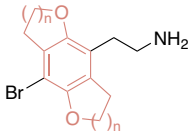
NBOMe- and NBOH-Series

R = H, R_1 = Me (25H-NBOMe)
R = Cl, R_1 = Me (25C-NBOMe)
R = Br, R_1 = Me (25B-NBOMe)
R = I, R_1 = Me (25I-NBOMe)
R = H, R_1 = H (25H-NBOH)
R = Cl, R_1 = H (25C-NBOH)
R = Br, R_1 = H (25B-NBOH)
R = I, R_1 = H (25I-NBOH)



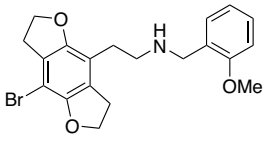
Fly-Series

R = H (2CB-Fly)
R = Me (DOB-Fly,
Bromo-DragonFly)

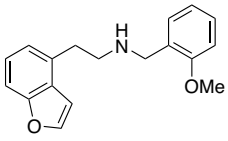


DragonFly- and
ButterFly-series

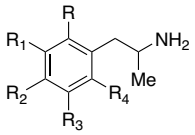
n = 1 (2C-B-DragonFly)
n = 2 (2C-B-ButterFly)



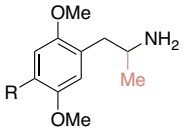
2CBFly-NBOMe



5-APB-NBOMe



R = R_2 = R_3 = OMe, R_3 = H (TMA-2)
R = R_2 = R_4 = OMe, R_2 = H (TMA-6)
R = R_4 = H, R_1 = R_2 = R_3 = OMe (Mescaline)



D-Series

R = Cl (DOC)
R = I (DOI)

Figure 24: Chemical structures of phenethylamine and the structural related analogues. The eight positions of the phenethylamine core and the key structural differences between the analogues are highlighted in red.

2C-series

The largest of these three sub-families is known as the *"2C-series"*. These compounds have a similar structure to mescaline (3,4,5-trimethoxyphenethylamine), and are characterised by methoxy groups situated at the 2- and 5-positions of the aromatic ring with a variety of substituents at the 4- position for example 4-iodo-2,5-dimethoxyphenethylamine (2C-I). The psychoactive effects have been reported to be dose-dependent, ranging from mild stimulation at lower doses, to hallucinogenic and entactogenic (empathogenic) effects at higher doses[159].

2D-series

The introduction of a methyl-group in the alpha position of 2C series substances provides access to ring-substituted amphetamine derivatives, known as the *"D-series",* sometimes referred to as phenylisopropylamines*,* such as 4-iodo-2,5-dimethoxyamphetamine (DOI) and, the trimethoxyamphetamines (TMA-2 and TMA-6). The D-series are more potent with a longer duration of action, due to their metabolic stability to monoamine oxidases in the body, compared to their 2C-progenitors. For example, the duration of action for 2C-I is reported to be 6 – 10h versus 16 – 30h for DOI[159]. Although some of the 2C and 2D series substances are under international control, an increasing number of NPS within these groups have been reported in recent years.

NBOMe-series

Since 2010, several novel 2C-phenethylamine analogues, containing an *N*-(2-methoxybenzyl)- group, have emerged and are commonly referred to as either 25X-NBOMes, NBOMes, or simply *"N-Bombs"*. The NBOMe-series substances can be directly synthesised from their 2C-progenitors, and are potent, selective, and highly efficacious agonists of 5-HT_{2A} and 5-HT_{2C} receptors [160] [161]. Recently, over 30 related substances within this subgroup have been reported to UNODC. Out of this, 15 were identified as NBOMes, while others are the *para*-isomers of 25C-NBOMe and 25B-NBOMe.

Among other potent hallucinogenic phenethylamines that have been reported to UNODC, several contain either a benzodifuranyl- (e.g., 2C-B-FLY) or tetrahydrobenzodifuranyl group (e.g., Bromo-DragonFLY, which has been implicated in several fatalities in Europe). Hybrids of these families, such as 2CBFly-NBOMe and 5-APB-NBOMe, have also been reported.

Tryptamines

Hallucinogenic tryptamines are a group of substances related structurally and in action to both internationally controlled hallucinogens, (+)-lysergide (LSD) and psilocybin. The seven positions of the tryptamine core that can be modified to generate a wide range of substituted analogues are highlighted (**Figure 25)**. Like the phenethylamines, they can be accessed using common inexpensive precursors or equipment and relatively straightforward synthetic strategies.

More than 60 individual tryptamine NPS in which the aromatic ring has been modified at the 4- and 5-positions (R_2 and R_3) and the ethylamino-sidechain (R and R_1) substituted with the following groups have been reported to UNODC:

– symmetrical groups (e.g., 5-AcO-DMT,5-MeO-DPT, 5-MeO-DALT),

– unsymmetrical groups (e.g., MALT or 5-MeO-MALT),

– alkyl-, branched alkyl-, cycloalkyl- or allyl- groups in a wide variety of combinations, though *N,N*-dimethyl-substituted tryptamines appear to be the most common within this group.

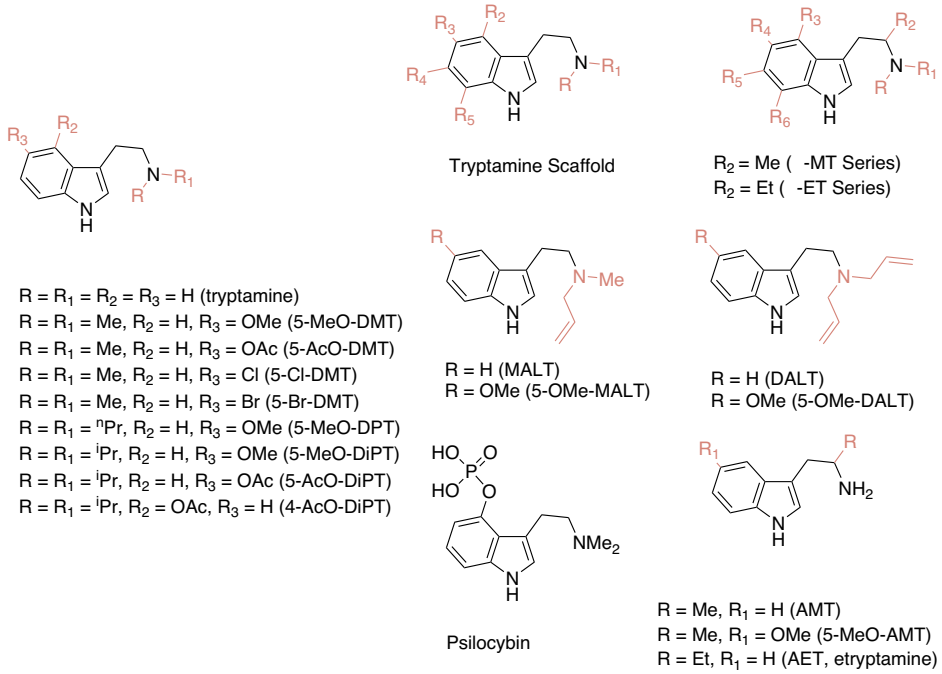


Figure 25: Chemical structures of tryptamines and the structural related analogues. The seven positions of the tryptamine core and the key structural differences between the analogues are highlighted in red.

Based on the site of ring substitution, tryptamines can be divided into three groups: unsubstituted, 4-substituted, and 5-substituted. Substitutions in the 6- and 7-positions of the tryptamine scaffold (R_4 and R_5) also may occur but are not commonly observed and they have been associated with a decrease in hallucinogenic activity. Introduction of methyl-

or ethyl-branching into the ethylamino- sidechain, provides access to *alpha*-methyl- and *alpha*-ethyltryptamines, referred to as the α-MT- and α-ET-series respectively, and include: α-methyltryptamine (AMT), 5-MeO-AMT and the internationally controlled etryptamine (AET) which exhibits both hallucinogenic and stimulant effects.

Lysergamides

Another group of NPS with hallucinogenic properties are derivatives of the internationally controlled (+)-Lysergide (LSD). While the molecules have a complex structure, they all share a common motif with simpler tryptamines (**Figure 26**).

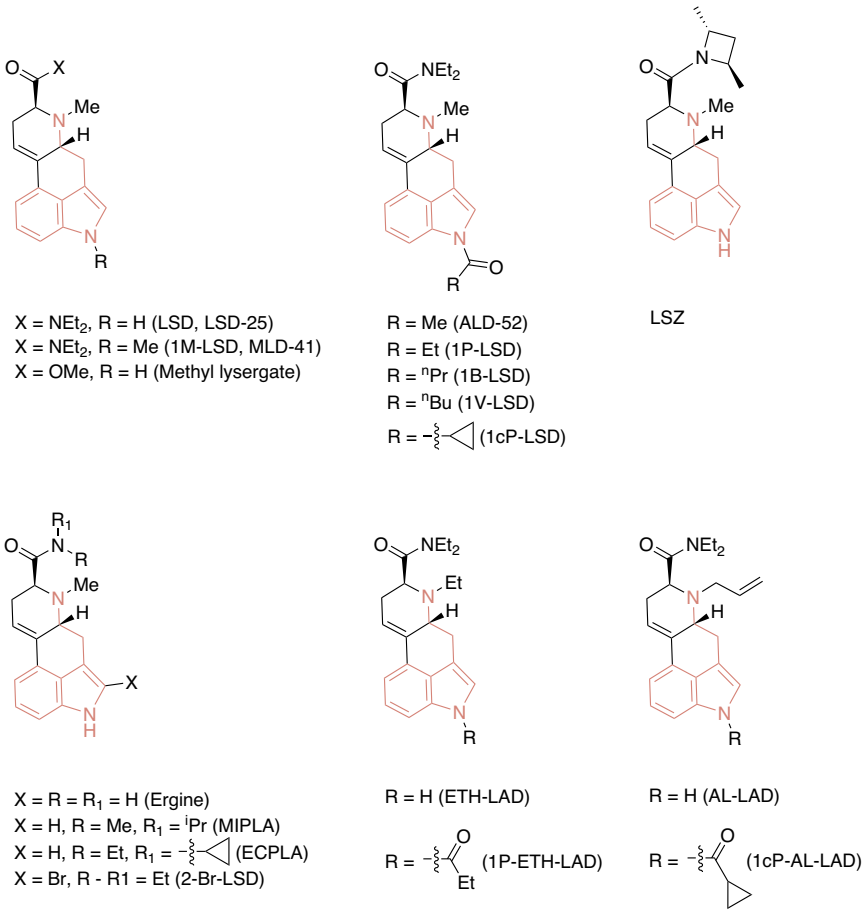


Figure 26: Chemical structures of lysergamides. The key structural similarity between these analogues and tryptamine is highlighted in red.

A number of lysergamides have been reported to UNODC including analogues with structural modifications of LSD such as 1-acetyl-LSD (ALD-52), 1-methyl-LSD (1M-LSD, MLD-41), 1-cyclopropylmethanoyl-LSD (1cP-LSD), 1-propionyl-LSD (1P-LSD), 1-butyryl-LSD (1B-LSD), 1-valeryl-LSD (1V-LSD) and lysergic acid 2,4-dimethylazetidide (LSZ).

Commonly Used Forms

Routes of administration for classic hallucinogens, as either pills or powders, include nasal insufflation, inhalation, ingestion, and intravenous injection. These routes can also be used for the delivery of potent psychedelic hallucinogens, such as (+)-Lysergide (LSD) or *N*-(2-methoxybenzyl)-substituted phenethylamines. These substances are normally consumed *via* the sublingual/buccal route employing *"blotters"* impregnated with the psychoactive substance **(Figure 27)**.

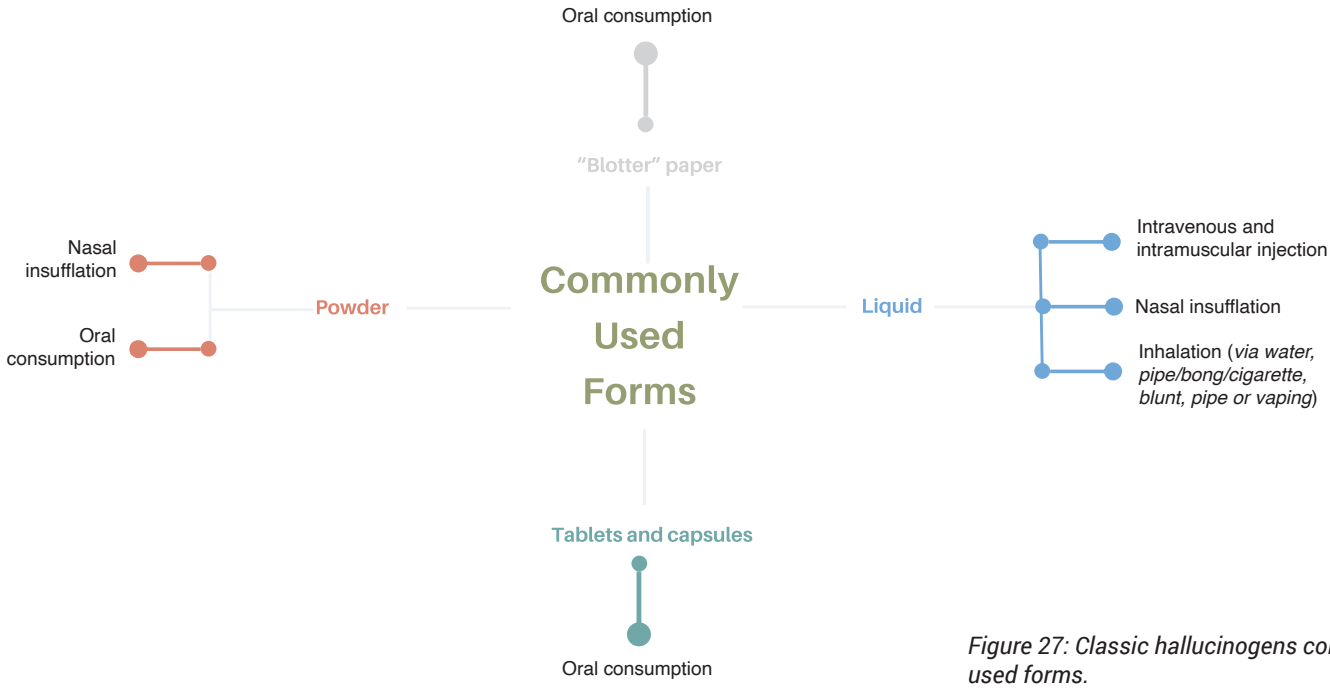


Figure 27: Classic hallucinogens commonly used forms.

Reported Effects

Desired Effects

- *Alterations in thought, mood and sensory perception, "mind expansion"*
- *Sense of empathy, facilitation of communication and increased sociability*

Undesired Acute Effects

- *Change in perception of time, time dilation, sleepiness*
- *Difficulty focusing*
- *General change in consciousness*
- *Looping, recursive, out of control thinking*
- *Hot flushes and/ or cold chills*
- *Nausea, vomiting*
- *Pupil dilation*
- *Scrambled communication*
- *Slight increase in heart rate*
- *Unusual body sensations (body energy, chills, facial flushing, goosebumps)*
- *Vasoconstriction, swelling of feet, hands and face, peripheral numbness,*
- *Yawning*

Effects of Chronic Use

- *Risk of neurological damage, such as progressive encephalopathy and muscle weakness in the limbs ("quadriparesis")*
- *Increased heart rate, high blood pressure, exceptionally high fever*
- *Excessive acid in blood*
- *Seizures, involuntary, muscular contractions and relaxations in rapid succession*
- *Rapid destruction of muscle tissue*
- *Acute kidney injury*
- *Potential violent, erratic behaviour, agitation and aggression*
- *Further effects are not yet known, but are potentially similar to those of LSD*

Figure 28: Reported effects of classic hallucinogens.

Stimulants

Substances within this effect group produce a stimulatory effect on the central nervous system and modulate the levels and activity of important neurotransmitters such as dopamine, norepinephrine, and serotonin. The action of these neurotransmitters induces a range of excitatory responses in the central nervous system. The differing degrees to which a substance affects these neurotransmitters contribute to the psychostimulant properties of individual substances.

Examples of the stimulant class include a variety of structural subgroups such as aminoindanes, oxazolines (e.g., aminorex-derivatives), phenethylamines, phenidates, phenylmorpholines (phenmetrazines), piperazines and synthetic cathinones. These compounds represent the largest category of NPS with almost 400 individual substances having been reported to UNODC (**Figure 29**).

Figure 29: Stimulant sub-groups.

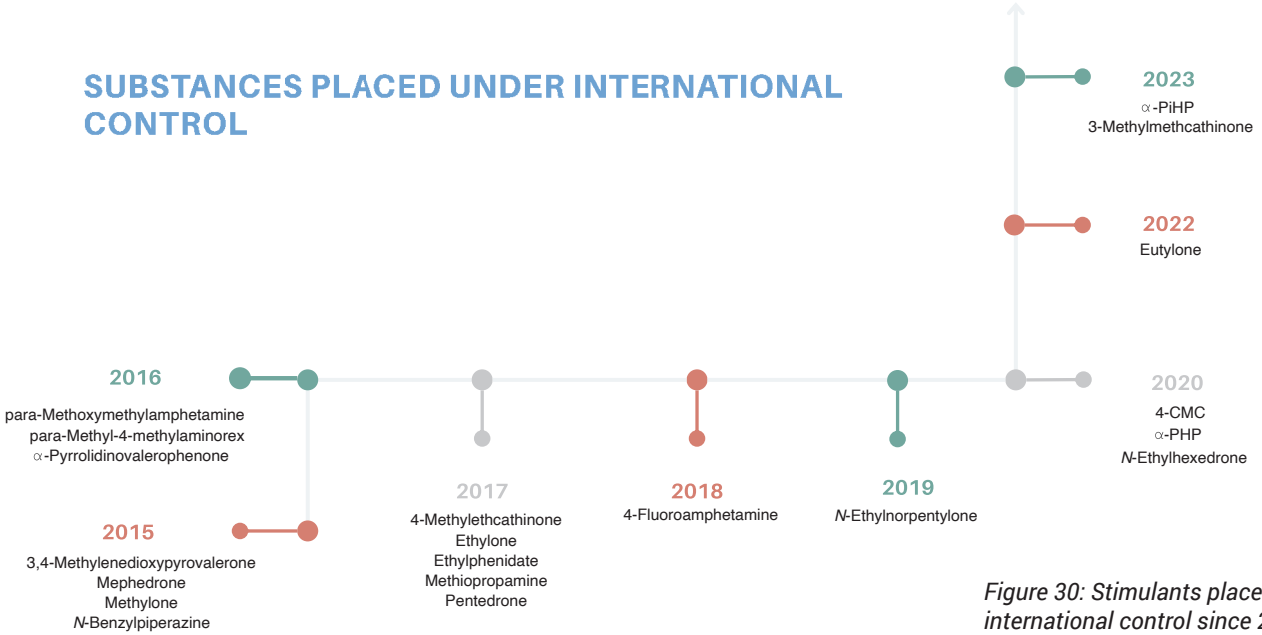


Figure 30: Stimulants placed under international control since 2015.

Prior to 2015, there were 40 stimulants under international control. From 2015-2023, a further 20 stimulants were placed under international control including 14 synthetic cathinones **(Figure 30)**.

Aminoindanes

In the 1970s, 2-aminoindane (2-AI) and its substituted derivatives were reported to possess significant broncho-dilating and analgesic properties. Recent research has indicated that they also have effects on serotonin release and reuptake [6, 162–165]. These substances have been sold as NPS for their ability to produce empathogenic and entactogenic effects of serotonin releasing drugs, such as MDMA. Within this class, specifically, MDAI [166–171] and 5-IAI [172] are reported to be highly potent agents. Currently, nine aminoindanes (**Figure 31**) have been reported to UNODC.

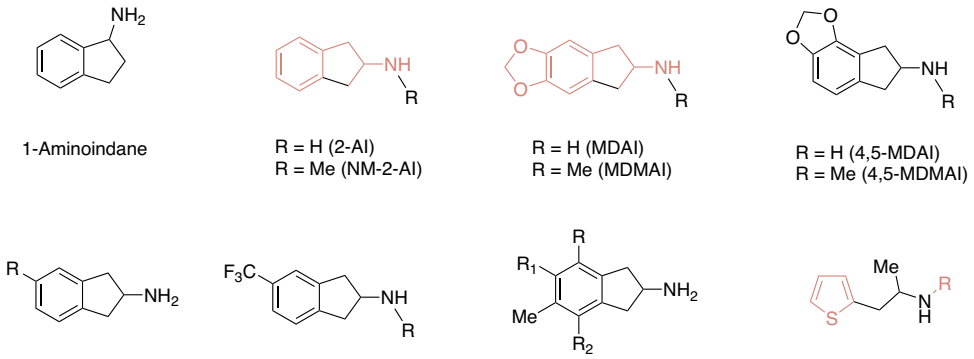


Figure 31: Common aminoindane NPS. The structural similarity between aminoindanes and amphetamines (e.g., amphetamine, methamphetamine and MDMA) are highlighted in red.

2-Amino-5-aryl-2-oxazolines

The 2-amino-5-aryl-2-oxazoline family of stimulants encompasses three distinct sub-families: 2-amino-5-phenyl-2-oxazolines (e.g., aminorex), 4-alkyl-2-amino-5-aryl-2-oxazolines (e.g., 4-MAR, and 4,4′-DMAR) and 2-oxazolidinimines (e.g., 3,4-DMAR) (**Figure 32**) [173]. Since the 1990's, both aminorex and 4-methylaminorex have been under international control, and 4,4'-dimethylaminorex (4,4′-DMAR) was scheduled internationally in 2016. An additional six aminorex derivatives that are NPS have been reported to UNODC.

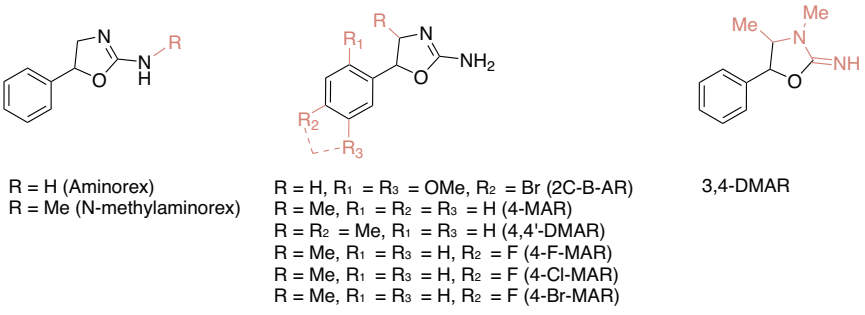


Figure 32: Chemical structures of 2-amino-5-aryl-2-oxazoline derived NPS. The structural differences between Aminorex, 4-MAR and, 3,4-DMAR sub-families are highlighted in red.

Phenethylamines

Phenethylamines (and phenylisopropylamines, which are more commonly known as amphetamines) are well-documented classes of psychoactive substances which possess stimulant, and/or hallucinogenic effects. These compounds are structurally related to amphetamine, methamphetamine, and 3,4-methylenedioxymethamphetamine (MDMA). Phenethylamine-based stimulants modulate monoaminergic neurotransmission by inhibiting norepinephrine, dopamine, and serotonin transporters. In addition, they interact with monoaminergic receptors and other targets that mediate non-exocytotic monoamine efflux.

The principal positions of the phenethylamine or phenylisopropylamine core that can be modified to generate a wide range of substituted analogues are highlighted (**Figure 33**) [159, 174, 175]. Trisubstituted phenethylamines with hallucinogenic properties such as the 2C and 2D -series, have been previously discussed.

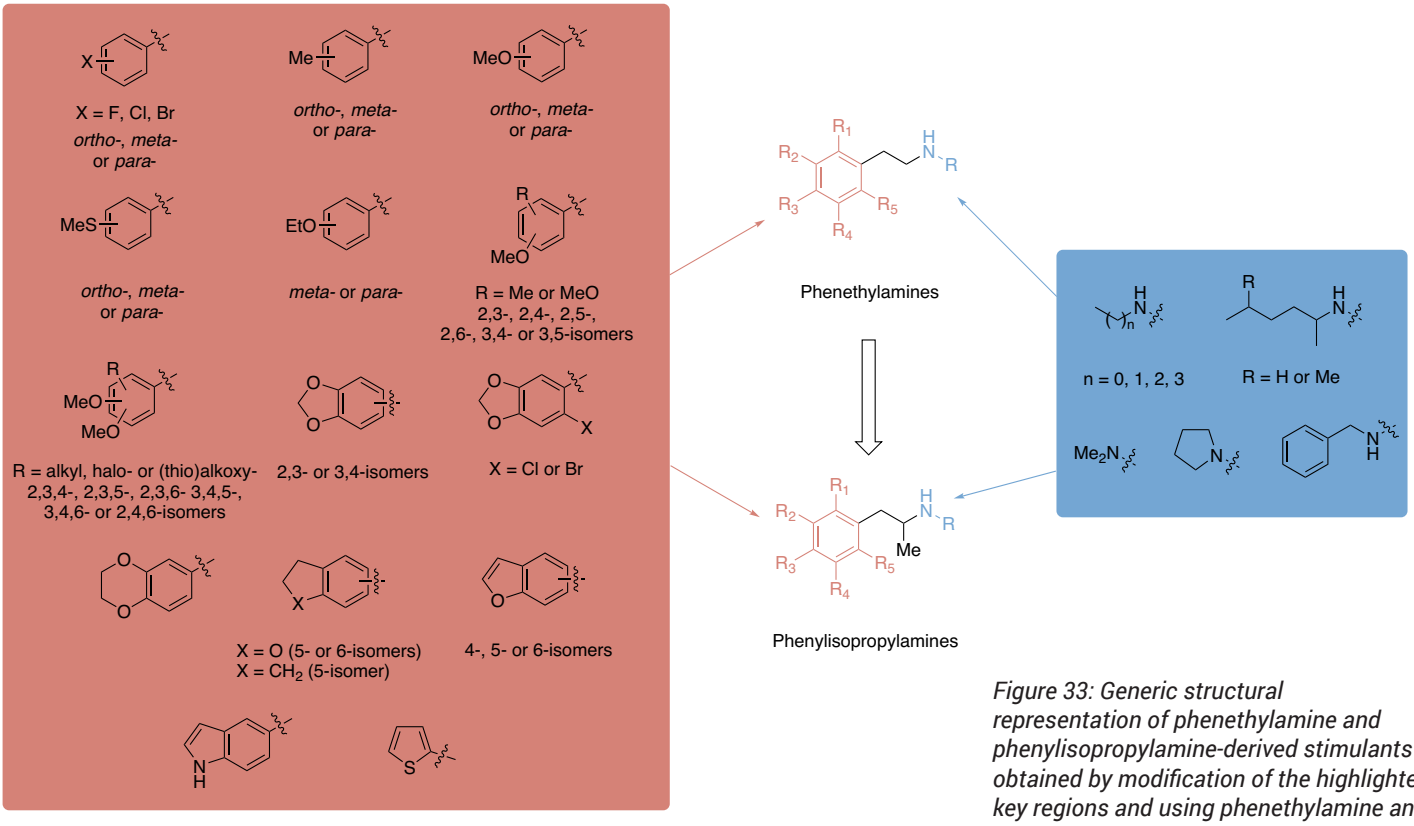


Figure 33: Generic structural representation of phenethylamine and phenylisopropylamine-derived stimulants obtained by modification of the highlighted key regions and using phenethylamine and amphetamine as the progenitor template.

While *"classic hallucinogens"* are derived from their respective progenitors: 2,5-dimethoxyphenethylamine and 2,5-dimethoxyphenylisopropylamine (2,5-dimethoxyamphetamine), the substitution of these key 2- and 5-methoxy groups for other functional groups can dramatically shift the subjective effects from hallucinogenic to stimulatory. Over 170 phenethylamines, falling into three distinct subfamilies (ring-substituted phenethylamines, amphetamines, and methylenedioxyphenethylamines)

have been reported to UNODC. The largest group is the ring-substituted phenethylamines followed by substances having the amphetamine core and various substituents on either the aromatic ring, the isopropyl-amino- sidechain, or both. The remainder are classified as methylenedioxyphenethylamines. Mono-substituted substances can exist as either their 2-, 3- or 4-positional isomers (commonly known as the *ortho*-, *meta*- and *para*-regioisomers).

The types of substituents that can be added to the amino group of amphetamine are relatively restricted (**Figure 34**). *N*-Methyl and *N*-ethyl groups are tolerated, but larger *N*-alkyl (e.g., *n*-propyl-, *n*-butyl-, benzyl-, 1-methylpentyl-, 1,4-dimethylpentyl- and pyrrolidinyl-) groups have reduced catecholamine-releasing activity.

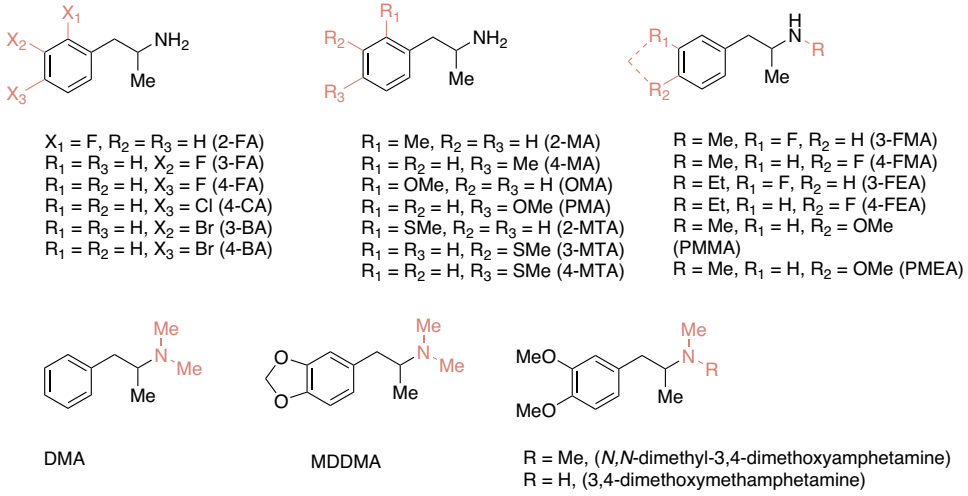


Figure 34: Chemical structures of mono- and N-alkyl-substituted phenethylamines.

Tertiary amine analogues (e.g., *N,N*-dimethylamphetamine, *N,N*-dimethylmethylenedioxyamphetamine, and *N,N*-dimethyl-3,4-dimethoxyamphetamine) are believed to act as prodrugs. They undergo *N*-dealkylation *in vivo* to generate methamphetamine, MDMA, and 3,4-dimethoxyamphetamine respectively. Replacement of the phenyl-ring for 2-thiophene in amphetamine (or methamphetamine) leads to the stimulants, thiopropamine and methiopropamine which are less potent than their phenylisopropylamine progenitors. However, they have been sold on the NPS market in their pure form and combination.

The phenethylamines grouped as *"methylenedioxyphenethylamines"* reported to UNODC also include the related 2,3-dihydro-1,4-benzodioxin-6-yl- (e.g., 3,4-EMDA), tetrahydrobenzodifuranyl- (5-APDB; 5-MAPDB and 6-APDB); and benzodifuranyl- (4-EAPB; 5-APB; 5-MAPB; 5-MBPB; 5-EAPB and 6-APB or *"Benzofury"*) analogues. Disubstituted substances such as the dimethoxy- (e.g., 2,4-DMA and 3,4-DMA), indanyl- (e.g., 5-APDI and 5-MAPDI); and 5-indolyl- (e.g., 5-IT or *"5-API"*) analogues also fall within this sub-family (**Figure 35**). 5-Methoxy- and 6-halo-derivatives

of MDMA, such as MMDMA, 6-Cl-MDMA, and 6-Br-MDMA have been reported, however, data on their prevalence, pharmacology, and toxicity remain unreported. Many of these compounds share common structural features and have been sold as NPS for their purported ability to produce effects like other dopamine and serotonin-releasing drugs (e.g., MDA and MDMA).

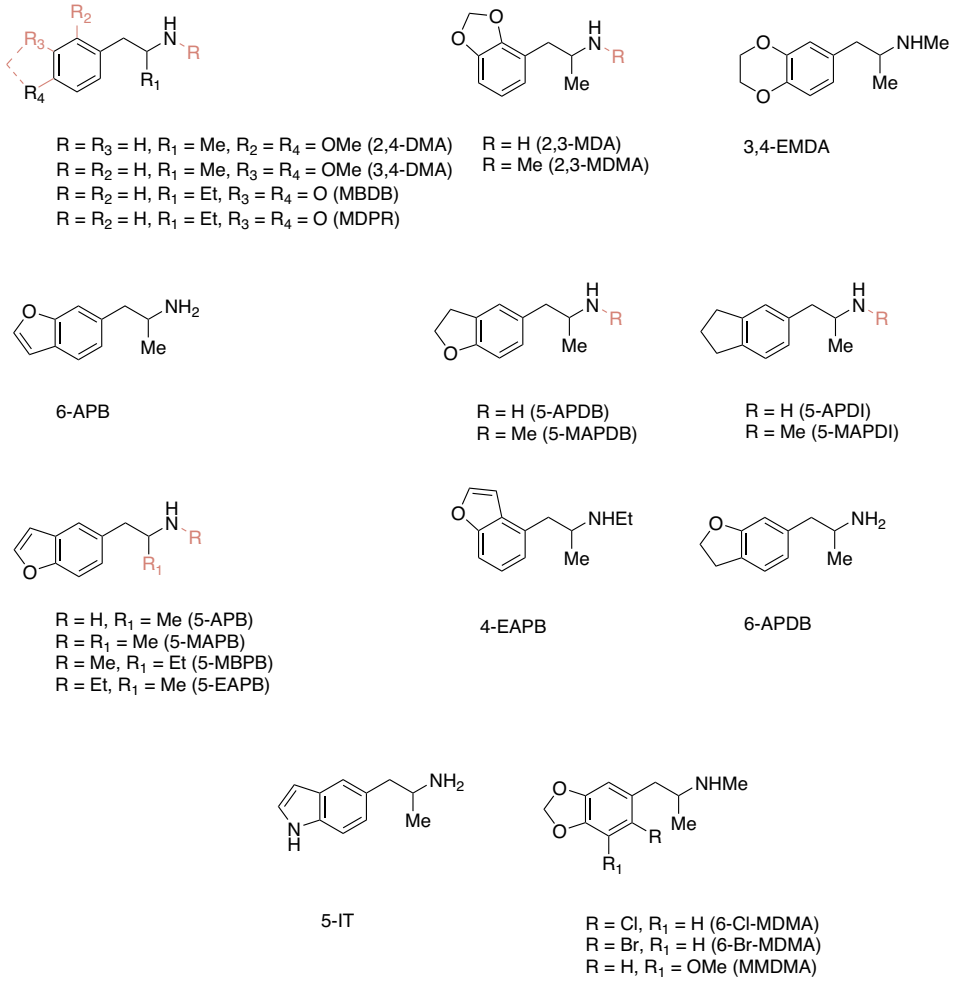


Figure 35: Chemical structures of di-substituted phenethylamines.

Phenidates

Methylphenidate (Ritalin®) is a potent orally active reuptake inhibitor of norepinephrine and dopamine used to treat attention deficit-hyperactivity disorder (ADHD) and narcolepsy. Some analogues of methylphenidate [2, 176–178] have emerged, with an extension of the carbon side chain (e.g., ethylphenidate, propylphenidate, and isopropylphenidate). Structural modification of the phenidate core provides access to the related pipradrol, desoxypipradrol, and desoxyprolinol psychostimulants (**Figure 36**). Replacement of the phenyl ring with a 1-naphthyl ring has also been reported. Ten examples of this class of NPS (specifically seven phenidates, two prolinol, and one pipradrol derivative) have been reported to UNODC.

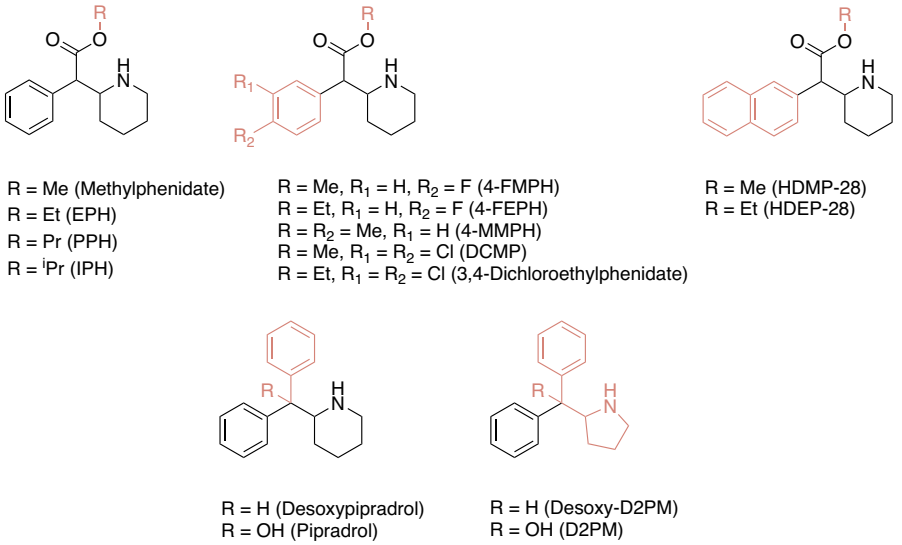


Figure 36: Chemical structures of methylphenidate derived NPS. The structural differences are highlighted in red.

Phenylmorpholines

Phenylmorpholines are a family of orally active stimulants derived from the controlled substance phenmetrazine (Preludin) which was developed in the mid-1950s as an appetite suppressant [179] and is a potent substrate for dopamine and norepinephrine transporters. The synthetic approaches to phenylmorpholines can easily be adapted to access ring-modified analogues. Subsequently, eight novel phenmetrazines have been reported to UNODC. (**Figure 37**).

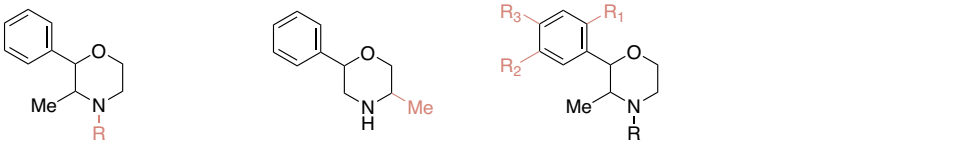
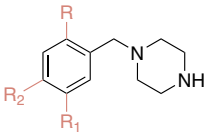


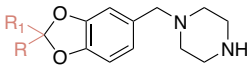
Figure 37: Chemical structures of phenylmorpholine derived NPS. The structural differences are highlighted in red.

Piperazines

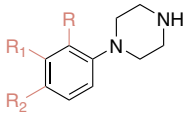
Piperazines are a group of stimulants that have been considered *"failed pharmaceuticals."* Some of them had been evaluated as potential therapeutic agents by pharmaceutical companies but never brought to the market [6, 180–193]. While the best-known piperazine that has been used as an NPS is 1-benzylpiperazine (BZP), more than 20 analogues (including five 1-benzylpiperazines and sixteen 1-phenylpiperazines) have been reported to UNODC (**Figure 38**). Pharmacological studies of piperazines have focused on BZP and have indicated that it is approximately one-tenth of the potency of amphetamine and produces similar toxic effects. The substances trigger the release of dopamine and norepinephrine whilst inhibiting the uptake of dopamine, norepinephrine, and serotonin.



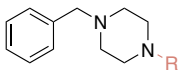
R = R_1 = R_2 = H (BZP)
R = R_2 = H, R_1 = Me (3-MeBZP)
R = R_1 = OMe, R_2 = Br (2C-B-BZP)
R = R_1 = H, R_2 = F (4-FBZP)



R = R_1 = H (MDBZP)
R = R_1 = F (DFMDBZP)



R = R_1 = R_2 = H (1-Phenylpiperazine)
R = F, R_1 = R_2 = H (2-FPP)
R = OMe, R_1 = R_2 = H (2-MeOPP)
R = Me, R_1 = R_2 = H (2-MePP)
R = R_1 = Cl, R_2 = H (2,3-Dichlorophenylpiperazine)
R = R_2 = H, R_1 = F (mFPP)
R = R_2 = H, R_1 = Cl (mCPP)
R = R_2 = H, R_1 = Me (3-MePP)
R = R_2 = H, R_1 = CF_3 (TFMPP)
R = R_1 = H, R_2 = F (4-FPP)
R = R_1 = H, R_2 = Cl (4-CPP)
R = R_1 = H, R_2 = Br (4-BPP)
R = H, R_1 = Cl, R_2 = F (3,4-CFP)



R = Bn (DBZP)
R = Me (MBZP)

Figure 38: Chemical structures of piperazine derived NPS.

Synthetic cathinones

Synthetic cathinones are a group of psychostimulants closely related to phenethylamines but with the additional presence of a carbonyl or β-keto (or *"bk"*) group on the side chain of the phenethylamine scaffold.

In the mid-2000s, a variety of synthetic cathinones (**Figure 39**) appeared in drug markets. However, since the late 1920s, substances such as *N,N*-diethylcathinone, and 4-methylmethcathinone (4-MMC, mephedrone) have been reported in the literature. Although, some compounds were investigated for potential medicinal applications such as antidepressants, appetite suppressants, and treatment of chronic fatigue or lethargy, only bupropion (Wellbutrin® or Zyban®), is currently available in the market.

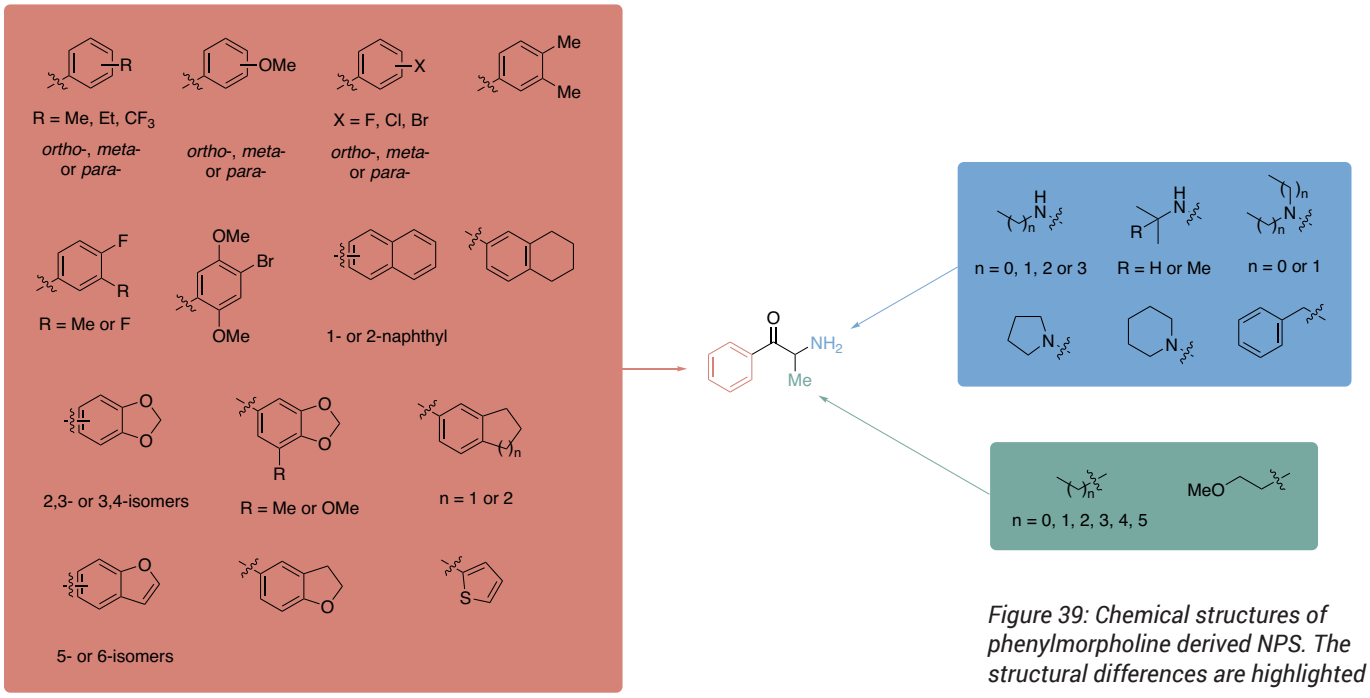
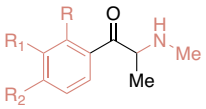


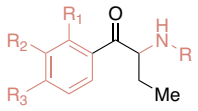
Figure 39: Chemical structures of phenylmorpholine derived NPS. The structural differences are highlighted in red.

Depending on the modification made on the cathinone scaffold, the respective synthetic cathinones can be separated into four different structural sub-families: (i) *N*-alkylcathinones: characterized by alkyl substitutions in the amino group and possible alkyl or halogen substitutions in the aromatic ring, and/or alkyl substitutions in the a-carbon of the side chain (**Figure 40 and 41**); (ii) *N*-pyrrolidino cathinones: characterized by a pyrrolidinyl substitution in the amino group and possible alkyl- or halogen substitutions in the aromatic ring and/or alkyl substitutions in the a-carbon of the side chain (**Figure 40 and 41**); (iii) the methylenedioxy-*N*-alkyl cathinones: characterized by the addition of a methylenedioxy- group to the aromatic ring (either the 2,3- or 3,4-isomer) and alkyl-substitutions in the amino group, and possible alkyl- substitutions both in the a-carbon of the side chain and in the aromatic ring (**Figure 42**); and (iv) methylenedioxy-*N*-pyrrolidine cathinones: characterized by the addi-

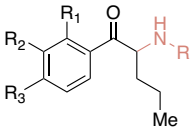
tion of a methylenedioxy- group to the aromatic ring (either the 2,3- or 3,4-isomer) and a pyrrolidinyl substitution in the amino group and possible alkyl substitutions both in the α-carbon of the side chain and in the aromatic ring (**Figure 40 and 41**). Additionally, synthetic cathinone presenting unique structures such as bk-2C-B, 1-naphythyl- (α-naphyrone), 2-naphthyl- (β–naphyrone, O-2482), indanyl- 5,6,7,8-tetrahydronaphthalen-2-yl- and 2-thiophenyl- derivatives can be aggregated in a chemical sub-family (**Figure 40 and 41**). Many are partially or fully effective substrate-type releasers at one or several of the monoamine transporters. Some compounds, such as the *N*-pyrrolidine- and methylenedioxy-*N*-pyrrolidine derivatives (e.g., *alpha*-PVP and MDPV) are transporter inhibitors that increase the monoamine content in the synaptic cleft and consequently lead to the hyperstimulation of post-synaptic receptors.



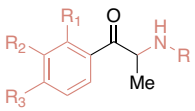
R = = R_1 = R_2 = H (Methcathinone)
R = F, R_1 = R_2 = H (2-FMC)
R = R_2 = H, R_1 = F (3-FMC)
R = R_1 = H, R_2 = F (4-FMC)
R = Cl, R_1 = R_2 = H (2-CMC)
R = R_2 = H, R_1 = Cl (3-CMC)
R = R_1 = H, R_2 = Cl (4-CMC)
R = R_2 = H, R_1 = Br (3-BMC)
R = R_1 = H, R_2 = Br (4-BMC)
R = Me, R_1 = R_2 = H (2-MMC)
R = R_2 = H, R_1 = Me (3-MMC)
R = R_1 = H, R_2 = Me (4-MMC)
R = Et, R_1 = R_2 = H (2-EMC)
R = R_2 = H, R_1 = Et (3-EMC)
R = R_1 = H, R_2 = Et (4-EMC)
R = R_2 = H, R_1 = OMe (3-MeOMC)
R = R_1 = H, R_2 = OMe (4-MeOMC)
R = R_2 = Me, R_1 = H (2,4-DMMC)
R = H, R_1 = R_2 = Me (3,4-DMMC)
R = H, R_1 = Me, R_2 = F (3-Me-flephedrone)



R = Me, R_1 = R_2 = R_3 = H (Buphedrone)
R = Me, R_1 = R_2 = H, R_2 = F (4-F-buphedrone)
R = R_2 = Me, R_1 = R_2 = H (4-Me-buphedrone)
R = Et, R_1 = R_2 = R_3 = H (*N*-ethylbuphedrone)
R = Et, R_1 = R_2 = H, R_3 = F (4-F-*N*-ethylbuphedrone)
R = Et, R_1 = R_2 = H, R_3 = Me (4-Me-*N*-ethylbuphedrone)
R = Bn, R_1 = R_2 = H, R_3 = Me (4-Me-*N*-benzylbuphedrone)



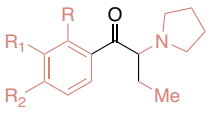
R = Me, R_1 = R_2 = R_3 = H (Pentedrone)
R = Me, R_1 = R_2 = H, R_3 = F (4-F-pentedrone)
R = Me, R_1 = R_2 = H, R_3 = Cl (4-Cl-pentedrone)
R = R_3 = Me, R_1 = R_2 = H (4-Me-pentedrone)
R = Et, R_1 = R_2 = R_3 = H (*N*-ethylpentedrone)
R = Et, R_1 = R_2 = H, R_3 = F (4-F-*N*-ethylpentedrone)
R = Et, R_1 = R_2 = H, R_3 = Me (4-Me-*N*-ethylpentedrone)
R = Pr, R_1 = R_2 = R_3 = H (*N*-propylpentedrone)
R = ^{i}Pr, R_1 = R_2 = H, R_3 = F (4-F-*N*-isopropylpentedrone)



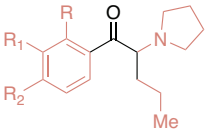
R = Et, R_1 = R_2 = R_3 = H (Ethcathinone)
R = Et, R_1 = F, R_2 R_3 = H (2-FEC)
R = Et, R_1 = R_3 = H, R_2 = F (3-FEC)
R = Et, R_1 = R_2 = H, R_3 = F (4-FEC)
R = Et, R_1 = Cl, R_2 R_3 = H (2-CEC)
R = Et, R_1 = R_3 = H, R_2 = Cl (3-CEC)
R = Et, R_1 = R_2 = H, R_3 = Cl (4-CEC)
R = Et, R_1 = R_2 = H, R_3 = Br (4-BEC)
R = Et, R_1 = Me, R_2 R_3 = H (2-MEC)
R = Et, R_1 = R_3 = H, R_2 = Me (3-MEC)
R = Et, R_1 = R_2 = H, R_3 = Me (4-MEC)
R = R_1 = Et, R_2 = R_3 = H (2-EEC)
R = R_3 = Et, R_1 = R_2 = H (4-EEC)
R = Et, R_1 = R_2 = H, R_3 = OMe (4-MeOEC)
R = Bn, R_1 = R_2 = H; R_3 = Me (Benzedrone)
R = Et, R_1 = H, R_2 = R_3 = Me (3,4-DMEC)
R = Et, R_1 = H, R_2 = R_3 = Cl (3,4-DCEC)

Figure 40: Chemical structures of N-alkyl- and N-pyrrolidine cathinone derived NPS. The structural differences are highlighted in red.

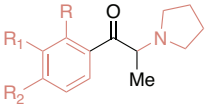
The history, chemistry, and pharmacological action of synthetic cathinones have been the subject of several reviews [6, 185, 194–228]. Currently, synthetic cathinones represent the largest group of psychostimulants that are monitored by UNODC, with over 200 individual substances having been reported.



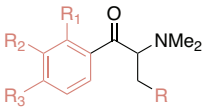
R = R_1 = R_2 = H (α-PBP)
R = R_1 = H, R_2 = F (4-F-PBP)
R = R_1 = H, R_2 = OMe (4-MeO-α-PBP)



R = R_1 = R_2 = H (α-PVP)
R = R_2 = H, R_1 = F (3-F-α-PVP)
R = R_1 = H, R_2 = F (4-F-α-PVP)
R = R_1 = H, R_2 = Cl (4-Cl-α-PVP)
R = R_1 = H, R_2 = Br (4-Br-α-PVP)
R = Me, R_1 = R_2 = H (2-Me-α-PVP)
R = R_1 = H, R_2 = Me (Pyrovalerone)
R = R_1 = H, R_2 = Et (4-Et-α-PVP)
R = R_1 = H, R_2 = MeO (4-MeO-α-PVP)

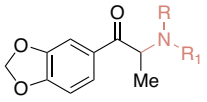


R = R_1 = H, R_2 = Cl (4-Cl-α-PPP)
R = R_1 = H, R_2 = Br (4-Br-α-PPP)
R = R_2 = H, R_1 = Me (3-MePPP)
R = R_1 = H, R_2 = Me (MPPP)
R = R_2 = H, R_1 = Me (3-MeO-α-PPP)
R = R_1 = H, R_2 = OMe (MOPPP)

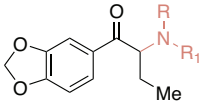


R = R_1 = R_2 = R_3 = H (Metamfepramone)
R = R_1 = R_2 = H, R_3 = Cl (4-CDMC)
R = R_1 = R_2 = H, R_3 = Me (4-MDMC)
R = R_3 = Me, R_1 = R_2 = H (4-Me-*N*-methylbuphedrone)
R = Et, R_1 = R_2 = H, R_3 = Me (4-Me-*N*-methylpentedrone)

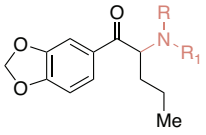
Figure 41: Chemical structures of N-alkyl- and N-pyrrolidine cathinone derived NPS. The structural differences are highlighted in red.



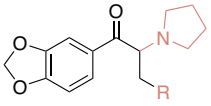
R = R_1 = H (bk-MDA)
R = H, R_1 = Me (Methylone)
R = H, R_1 = Et (Ethylone)
R = H, R_1 = Bn (Benzylone)
R = R_1 = Me (Dimethylone)
R = R_1 = Et (Diethylone)



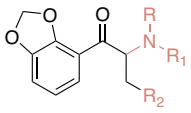
R = H, R_1 = Me (Butylone)
R = H, R_1 = Et (Eutylone)
R = R_1 = Me (Dibutylone)



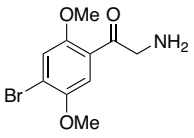
R = H, R_1 = Me (Pentylone)
R = H, R_1 = Et (*N*-ethylpentylone)
R = R_1 = Me (Dipentylone)



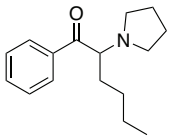
R = H (MDPPP)
R = Me (MDPBP)
R = Et (MDPV)
R = Pr (MDPHP)



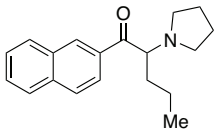
R = R_2 = H, R_1 = Me (2,3-MDMC)
R = H, R_1 = Me, R_2 = Et (2,3-Pentylone)
R = R_1 = Me, R_2 = Et (2,3-Dipentylone)



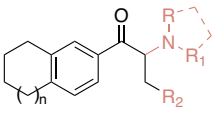
bk-2C-B



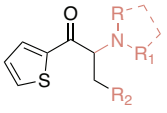
α-PHP



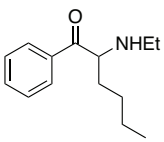
β-Naphryone (O-2482)



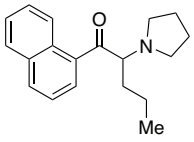
n = 0, R = R_2 = H, R_1 = Me (bk-IMP)
n = 0, R = H, R_2 = Me, R_1 = Et (bk-IBP)
n = 0, R = H, R_1 = R_2 = Et (bk-IVP)
n = 0, R = R_1 = CH_2, R_2 = Me (5-PPDI)
n = 0, R = R_1 = CH_2, R_2 = Et (5-BPDI)
n = 0, R = R_1 = CH_2, R_2 = Pr (5-HPDI)
n = 1, R = R_1 = CH_2, R_2 = Me (TH-PBP)
n = 1, R = R_1 = CH_2, R_2 = Et (TH-PVP)
n = 1, R = R_1 = CH_2, R_2 = Pr (TH-PHP)



R = R_1 = H (Thiothinone)
R = H, R_1 = Me (bk-MPA)
R = R_1 = CH_2, R_2 = H (α-PPT)
R = R_1 = CH_2, R_2 = Me (α-PBT)
R = R_1 = CH_2, R_2 = Et (α-PVT)



N-ethylhexedrone



α-Naphryone

Figure 42: Chemical structures of methylenedioxy-N-alkyl, methylenedioxy-N-pyrrolidine, and miscellaneous cathinone derived NPS. The structural differences are highlighted in red.

Commonly Used Forms

On the illicit market, central nervous system stimulants are normally encountered in orally active solid-dosage forms (e.g., powder or pills) and can be insufflated or inhaled, swallowed (often wrapped in cigarette papers, colloquially known as *"bombing"*), smoked, and less commonly injected or used rectally (Figure 43)

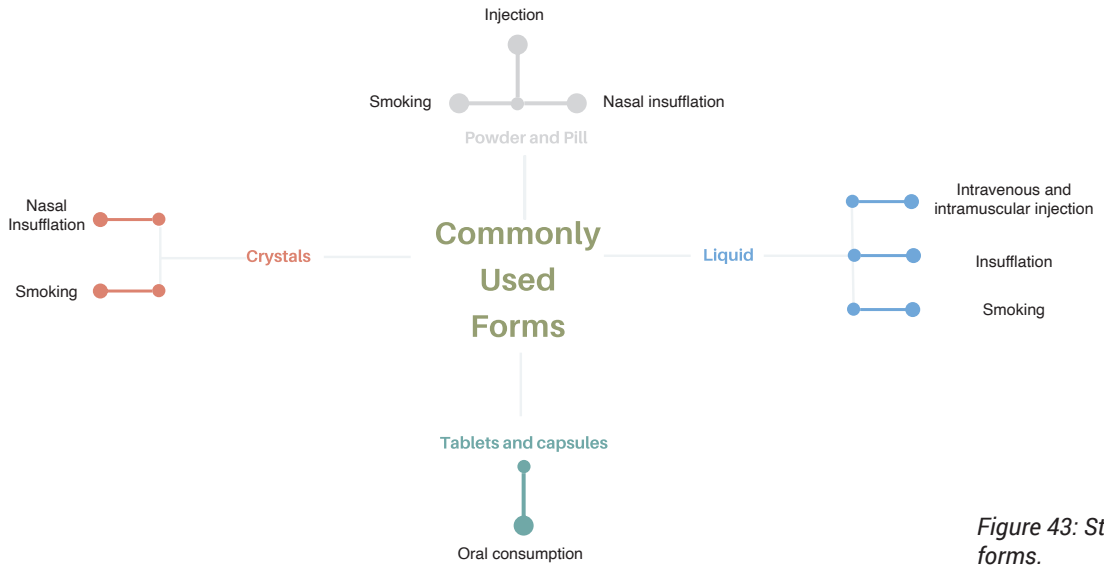


Figure 43: Stimulants commonly used forms.

Reported Effects

Currently, there is limited pharmacological and toxicological data on many aminoindanes. Users report effects including euphoria, empathy, stimulation (not the case with MDAI), and cognitive enhancement after either ingestion or insufflation. Adverse effects described by users include dehydration, increased perspiration, anxiety, depression, panic attacks, and tachycardia with a limited number of MDAI-related deaths reported [167, 171, 230, 231] **(Figure 44)**.

Compared with amphetamine, an increase in serotonergic neurotoxicity has been reported for 4-chloroamphetamine (4-CA). Other halogenated substances, such as 4-fluoroamphetamine have been associated with various mild-to-moderate adverse effects (e.g., agitation, severe headache, anxiety, confusion, hypertension, tachycardia, chest pain, and nau-

sea) and severe adverse effects (e.g., coma, convulsions, cerebral haemorrhage, and cardiac arrest resulting in fatality). 4-Methoxy- (PMA and PMMA) and 4-thiomethyl- (4-MTA) analogues have been more often associated with incidental deaths. Specifically, PMA and PMMA, are known to have a particularly high toxicity and there are many reports of fatalities associated with their use [232–236]. Clinical observations have reported transpiration, tremor, severe nystagmus, headache, and severe hyperthermia following the use of these substances. In the case of 4-MTA, moderate-to-mild clinical effects include headache, stomach pain, sweating, tachycardia, and severe tremors, with more serious intoxication leading to seizures, coma, respiratory failure, and serotonergic toxicity. There is limited pharmacological and toxicological data on many phenidate analogues and most pharmacological studies have focused on methylphenidate and, to a lesser degree, ethylphenidate. Self-reported adverse effects of phenidate derivatives include agitation, anxiety, hypertension, tachycardia, and palpitations.

There is limited pharmacological and toxicological data on many phenmetrazine analogues. Symptoms commonly associated with acute, non-fatal, intoxications involving 3-fluorophenmetrazine include tachycardia, reduced level of consciousness, agitation/anxiety, and delirium. Less common symptoms such as miosis, seizures, and hypertension are also observed. Adverse effects of the use of piperazine-derived NPS include nausea, headache, dizziness, sweating, and potential cardiovascular symptoms. Self-reported psychological problems experienced by users have included trouble sleeping, loss of energy, strange thoughts, mood swings, confusion, and irritability[183, 191, 237–242].

Short-term adverse effects reported following synthetic cathinone use are variable and may include, loss of appetite, blurred vision, anxiety, post-use depression, confusion, hallucinations, short-term psychosis, and mania. Clinical reports have noted that MDPV and its methylenedioxy-*N*-pyrrolidine analogues use may result in anxiety, paranoia, memory loss, and aggression [207, 224, 226, 243–245]. Individuals intoxicated with *N*-ethylpentylone displayed a variety of symptoms common to sympathomimetic toxicity including, palpitations, tachycardia, agitation, aggression, hallucinations, coma, and, in some cases, death. Intoxication by synthetic cathinone may also lead to severe adverse effects including acute

liver failure, acute kidney injury, high blood pressure, and tremor. Habitual users have also reported the development of tolerance, dependence, or withdrawal symptoms with prolonged use [185, 199, 207, 210, 214, 217, 221, 223, 224, 246–249]. Numerous cathinone-related fatalities have been reported and these are mainly attributed to hyperthermia, hypertension, cardiac arrest, and serotonin syndrome [208, 211, 217, 250–254].

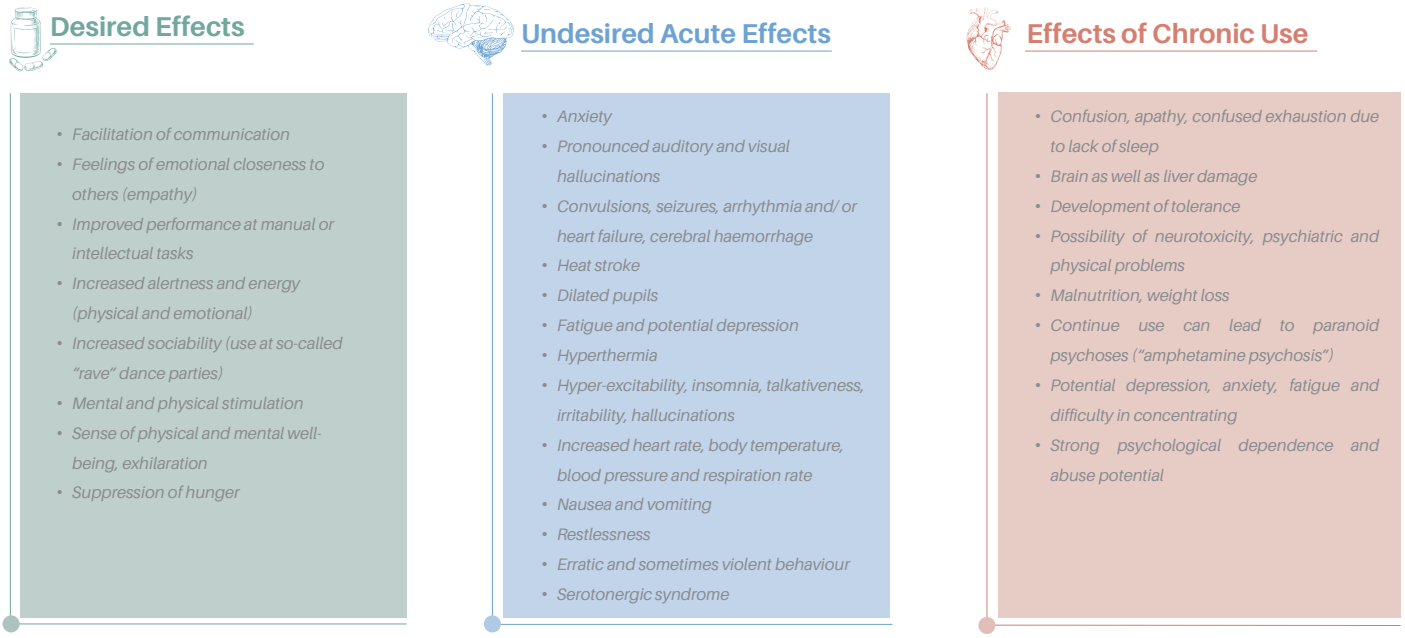


Figure 44: Reported effects of stimulants.

Opioid receptor agonists

Opioid receptor agonists are a chemically diverse groups of substances which are central nervous system depressants. Their effects are mediated through their interaction with inhibitory neurotransmitters and opioid receptors. More generally, an opioid is a generic term applied to a variety of substances including naturally occurring opiates (e.g., opium and morphine), synthetic opioids (e.g., fentanyl and tramadol), semi-synthetic opioids (e.g., heroin), as well as new psychoactive substances (NPS) with opioid effects. Pharmaceutical products range from preparations of codeine or tramadol used in the treatment of mild or medium pain, through essential medicines such as morphine, to very potent substances used in alleviating pain after surgery, such as fentanyl, or in palliative care, diacetylmorphine (heroin).

Before the global emergence of NPS, there were almost 120 opioids under international control. From 2015-2023, a further 24 NPS with opioid like effects were scheduled internationally (**Figure 45**).

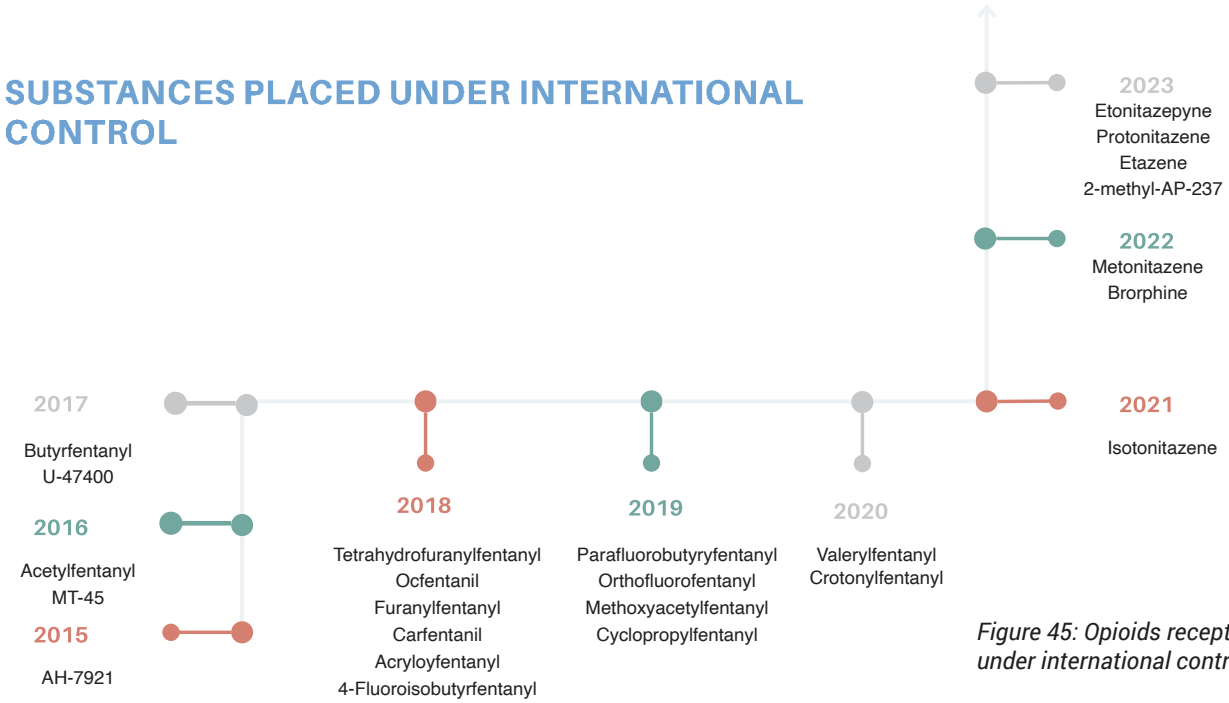


Figure 45: Opioids receptor agonists placed under international control since 2015.

Over 120 opioid receptor agonists, falling into **five** distinct sub-groups, have been reported to UNODC. These substances can be classified as (i) *"Fentanyl analogues;"* (ii) *"U-Series"* substances; (iii) *"Nitazenes;"* (iv) *"Piperazines"* and (v) *"Miscellaneous,"* which include derivatives structurally unrelated to the other four sub-groups **(Figure 46)**.

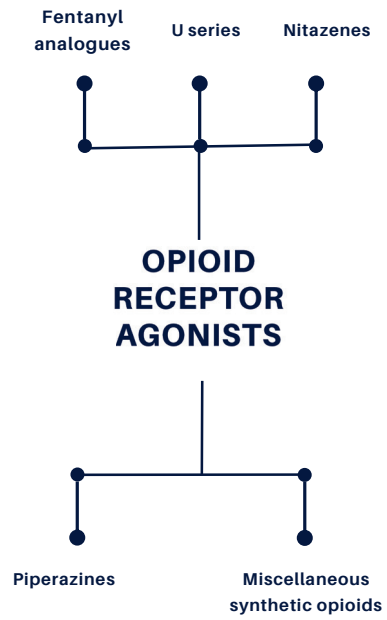


Figure 46: Opioid receptor agonists sub-groups.

Fentanyl analogues

Fentanyl analogues can be described as having the 4-anilinopiperidine structure as its core, with four possible sites of modification (**Figure 47**).

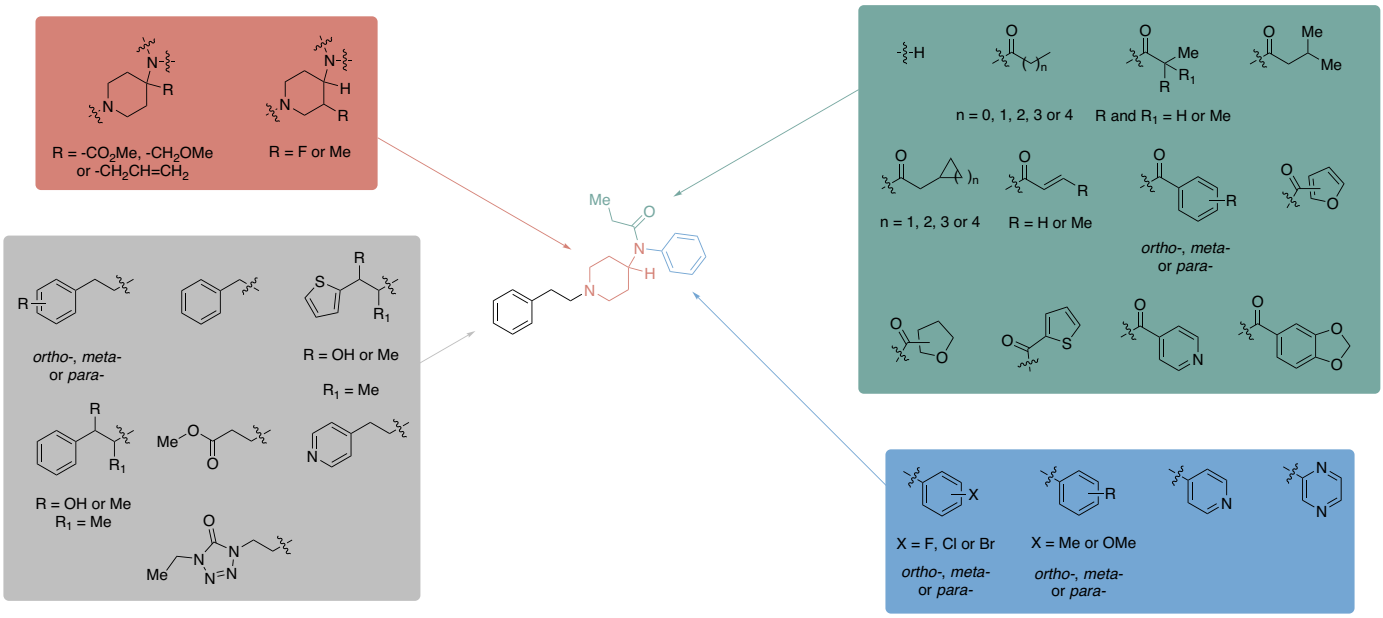
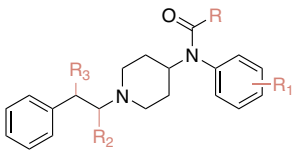
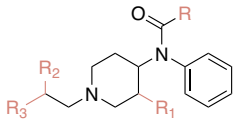


Figure 47: Generic structural representation of fentanyl analogues obtained by modification of the highlighted key regions and using fentanyl as the template.

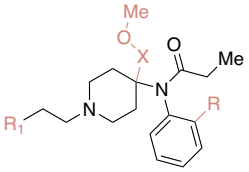
While four fentanyl analogues (alfentanil, remifentanil, sufentanil and fentanyl itself) have been approved for medical use to manage severe pain and in anaesthesia, many fentanyl analogues are derived from substances that have been researched for pharmaceutical use but have never been marketed. More than 80 fentanyl analogues have been reported to UNODC **(Figure 48)**.



R = Et, R_1 = R_2 = R_3 = H (fentanyl)

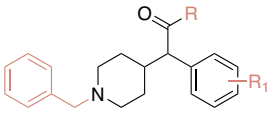


R = Et, R_1 = F, R_2 = H, R_3 = Ph (3-fluorofentanyl)

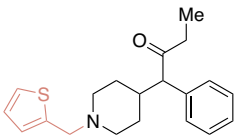


R = H, R_1 = Ph, X = CO (carfentanil)
R = F, R_1 = Ph, X = CH_2 (ocfentanil)

R = Me, R_1 = R_2 = R_3 = H (acetylfentanyl)
R = Et, R_1 = 2-F, R_2 = R_3 = H (orthofluorofentanyl)
R = ^{n}Pr, R_1 = R_2 = R_3 = H (butyrfentanyl)
R = ^{n}Pr, R_1 = 4-F, R_2 = R_3 = H (4-F-butyrfentanyl)
R = ^{i}Pr, R_1 = 4-F, R_2 = R_3 = H (4-F-isobutyrfentanyl)
R = ^{n}Bu, R_1 = R_2 = R_3 = H (valerylfentanyl)
R = -CH=CH_2, R_1 = R_2 = R_3 = H (acrylfentanyl)
R = -CH=CH(Me), R_1 = R_2 = R_3 = H (crotonylfentanyl)
R = CH_2OMe, R_1 = R_2 = R_3 = H (methoxyacetylfentanyl)
R = Ph, R_1 = R_2 = R_3 = H (benzoylfentanyl)
R = cyclopropane, R_1 = R_2 = R_3 = H (cyclopropylfentanyl)
R = 2-furan, R_1 = R_2 = R_3 = H (furanylfentanyl)
R = 2-tetrahydrofuran, R_1 = R_2 = R_3 = H (tetrahydrofuranylfentanyl)



R = Me, R_1 = H (acetylbenzylfentanyl)
R = Et, R_1 = H (benzylfentanyl)
R = Et, R_1 = 4-F (4-F-benzylfentanyl)
R = cyclopropane, R_1 = 4-F (4-F-cyclopropylbenzylfentanyl)
R = Ph, R_1 = H (benzoylbenzylfentanyl)
R = 2-furan, R_1 = H (2-furanylbenzylfentanyl)

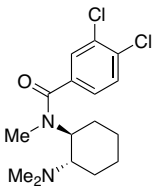


thienylfentanyl

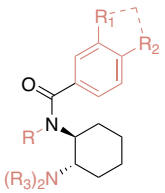
Figure 48: Common fentanyl analogues NPS. Structural differences are highlighted in red.

U-Series

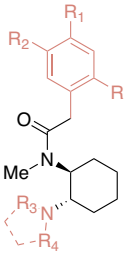
A second sub-group of opioid receptor agonists that have been reported to UNODC are the *"U-Series"* compounds. The substances can be differentiated into two families, the cyclohexylbenzamides (e.g., U-47700 and AH-7921) and phenylacetamides (e.g., U-48800, U-50488, and U-51754) (**Figure 49**).



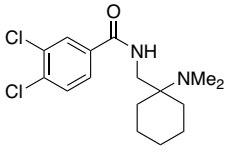
U-47700



R = ^{i}Pr, R_1 = R_2 = Cl, R_3 = Me (isopropyl-U-477700)
R = Et, R_1 = R_2 = Cl, R_3 = Me (*N*-ethyl-U-477700)
R = R_3 = Me, R_1 = R_2 = O (3,4-methylenedioxy-U-47700)
R = H, R_1 = H, R_2 = Br (U-47931E, bromadoline)
R = Me, R_1 = R_2 = Cl, R_3 = Et (U-49900)
R = R_3 = Me, R_1 = R_2 = F (3,4-difluoro-U-47700)



R = R_1 = Cl, R_2 = H, R_3 = R_4 = Me (U-48800)
R = H, R_1 = R_2 = Cl, R_3 = R_4 = CH_2 (U-50488)
R = H, R_1 = R_2 = Cl, R_3 = R_4 = Me (U-51754)



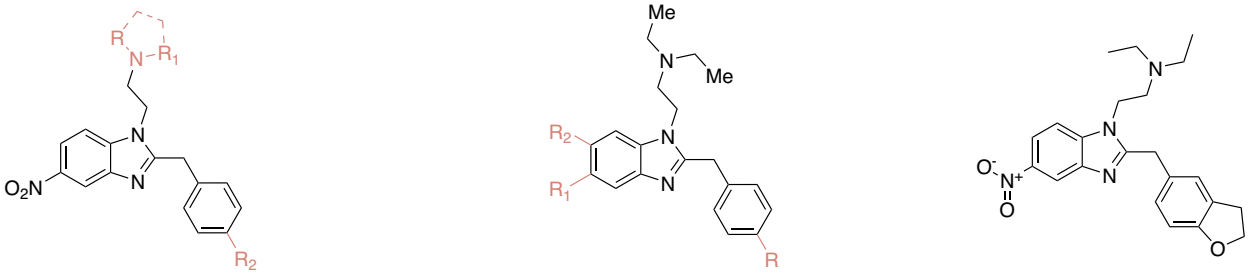
AH-7921

Figure 49: Common cyclohexylbenzamide- and phenylacetamide-derived NPS. The structural differences are highlighted in red.

Due to the presence of two chiral centres the synthesis of U-47700 can lead to four potential stereoisomers. However, the reported synthesis of U-47700 (and its derivative or phenylacetamide analogues) into the desired (and active) *trans*-(*1R*, *2R*)-isomer of this class is straightforward. U-4770 has one-tenth of the potency of fentanyl and about 7.5 times the potency of morphine in animal studies [255, 256].

The structurally related cyclohexylbenzamide analogue, AH-7921, is a synthetic opioid with similar potency to morphine. AH-7921 was never marketed, possibly due to its highly addictive properties and risk of respiratory depression observed in animal studies. In 2015 it was placed under international control as a Schedule I substance within the Single Convention on Narcotic Drugs of 1961, and in 2017, U-47700 was also placed in the same convention. Since then, related derivatives have emerged such as cyclohexylbenzamide- (e.g., isopropyl-U-47700; 3,4-methylenedioxy-U-47700; U-47931E, "bromadoline" and U-49900) and phenylacetamide-derived synthetic opioids (e.g., U-48800; U-50488 and U-51754).

Nitazenes



R = R_1 = Et, R_2 = OMe (metonitazene)
R = R_1 = Et, R_2 = ^{n}Pr (protonitazene)
R = R_1 = Et, R_2 = ^{i}Pr (isotonitazene)
R = R_1 = Et, R_2 = ^{n}Bu (butonitazene)
R = R_1 = Et, R_2 = F (fluonitazene)
R = R_1 = C_2H_4, R_2 = OEt (etonitazepyne)
R = R_1 = C_2H_4, R_2 = OCH_3 (metonitazepyne)
R = R_1 = C_2H_4, R_2 = OPr (protonitazepyne)
R = H, R_1 = Et, R_2 = OEt, (N-desethyl etonitazene)
R = H, R_1 = Et, R_2 = ^{i}Pr, (N-desethyl isotonitazene)
R = R_1 = Cy, R_2 = OEt, (N-piperidinyl etonitazene)

R = OMe, R_1 = H (metodesnitazene)
R = OEt, R_1 = H (etodesnitazene)
R = O^{i}Pr, R_1 = NH_2 (5-aminoisotonitazene)
R = OEt, R_1 = CH_3 (5-methyl etodesnitazene)
R = OEt, R_1 = H, R_2 = CH_3 (6-methyl etodesnitazene)
R = ^{i}Pr, R_1 = R_2 = H (isotodesnitazene)

Ethyleneoxynitazene

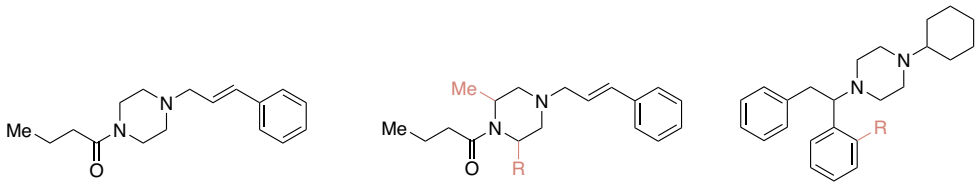
Figure 50: Common nitazene NPS. The structural differences are highlighted in red.

Another group of synthetic opioids that have emerged in recent years are analogues of the internationally controlled substances clonitazene-

and etonitazene. The first nitazene reported to UNODC, isotonitazene, emerged in 2019 and since then 18 substances have emerged. This family of synthetic opioids was initially developed in an attempt to access safer classes of opioid analgesics, but in fact, the substances discovered had a potency several times higher than morphine (e.g., etonitazene, 70x and isotonitazene, 500x)[257]. The reported substances can be differentiated into two sub-families, which include nitrobenzimidazoles (e.g., isotonitazene), and benzimidazoles (e.g., metodesnitazene) (**Figure 50**).

Piperazines

The smallest group of synthetic opioids that have been reported to UNODC are classified as *"piperazines"* and include two cinnamylpiperazines (e.g., 2-methyl-AP-237 and para-methyl-AP-237 or *"AP-238"*) and one phenethylpiperazine (e.g., MT-45). AP-237 (*"bucinnazine"*) **(Figure 51)**, a pharmaceutical opioid prescribed for pain management in cancer patients can be considered the progenitor of the two structural analogues 2-methyl-AP-237 and *para*-methyl-AP-237. In 2019, the 2-methyl-AP-237 appeared on the NPS market. This substance possesses analgesic activity but is less toxic than AP-237 in animal studies [258, 259].



AP-237

R = H (2-methyl-AP-237)
R = Me (*para*-methyl-AP-237, AP-238)

R = H (MT-45)
R = F (2F-MT-45)

Figure 51: Common cinnamylpiperazine- and phenethylpiperazine-derived NPS. The structural differences are highlighted in red.

Miscellaneous synthetic opioids

The fifth group contains a diverse range of synthetic opioids, that in some cases express certain structural similarities to opioid analgesics under international control but have never been marketed as a pharmaceutical and lack a common core.

One example is the phenethylpiperidine, brorphine, **(Figure 52)** which has a similar chemical structure to bezitramide an opioid under international control. It is a full agonist at the μ -opioid receptor with potency in between fentanyl and morphine [260, 261]. Deaths associated with the use of this substance in combination with other opioids or benzodiazepines have been reported by several countries.

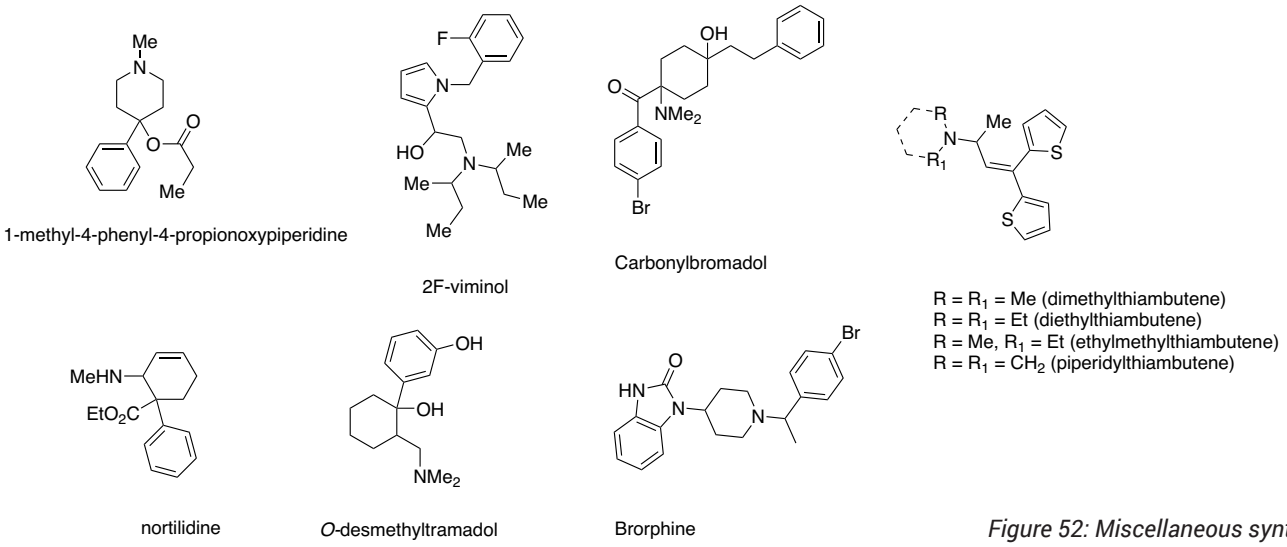


Figure 52: Miscellaneous synthetic opioids.

Commonly Used Forms

The substances in this group appears to be used through the most common routes of administration normally accessible to users **(Figure 53)**. Fentanyl can be injected, snorted/sniffed, smoked, taken orally by pill or tablet, and spiked onto blotter paper. Analogues are typically seen in powder form, which can be used as it is or mixed with another substance and then smoked or taken by the intranasal or intravenous route. They can also be pressed into tablets, often as falsified forms of other pharmaceuticals opioid products (e.g.M30) or mixed into an intranasal spray.

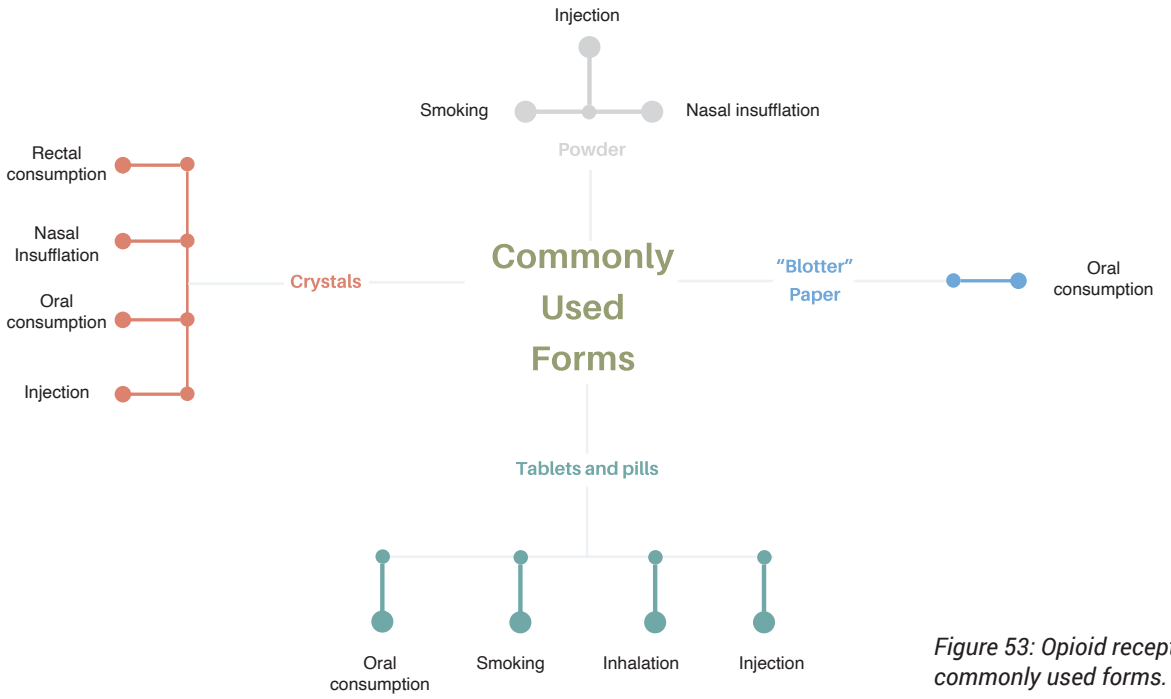


Figure 53: Opioid receptor agonists commonly used forms.

The commonly reported routes of administration of nitazenes are vaping intravenous sublingual and intranasally *via* spray or insufflation.

Reported Effects

The typical side effect profile of opioid agonist use includes euphoria, pupillary constriction, decreased consciousness, impairment of cognition, respiratory depression, sedation, sleepiness, dizziness, nausea, vomiting, fatigue, headache, constipation and hallucinatory or dissociative effects **(Figure 54)**.

Tolerance to the analgesic and euphoric effects of opioids can develop quickly and the euphoric effects of opioids can lead to habituation and dependence. Cessation of opioid agonist use leads to a withdrawal syndrome, characterized by drug craving, dysphoria, anxiety, insomnia, irregular heart rate, loss of appetite, diarrhoea, sweating, nausea, and vomiting. The main mechanism of fatal opioid overdose is respiratory depression, leading to pathological indicators such as froth in the airways, and cerebral and pulmonary oedema. As fentanyl and its analogues have high potency compared to morphine, poor control of dose, polydrug use, and patterns of repeated use are most likely contributors to the high rates of overdose, respiratory depression, and death associated with these drugs. The clinical toxicological properties of many nitazenes have not been studied directly. There are few reports from online user forums on the acute and chronic physical and psychological effects. The

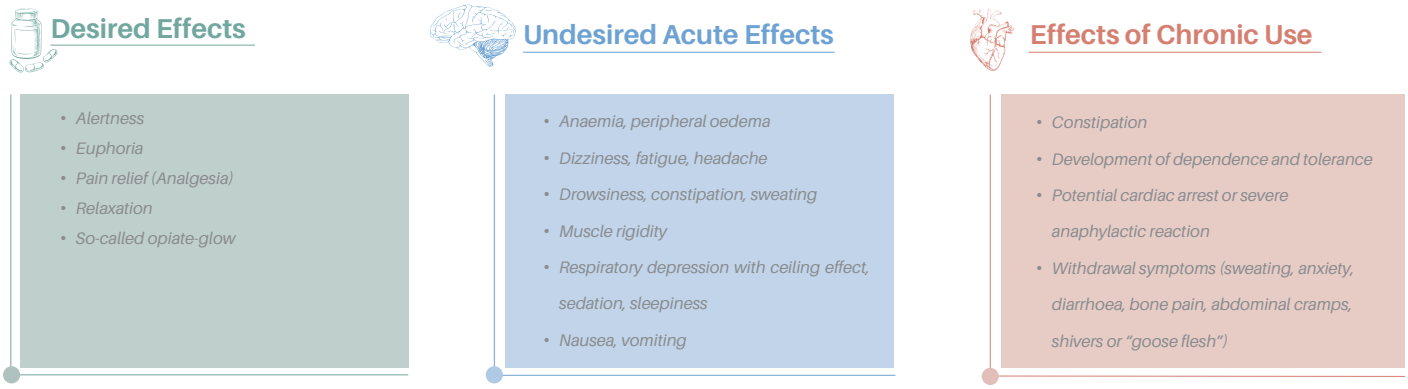


Figure 54: Reported effects of opioid receptor agonists.

adverse effects align with those commonly reported for other synthetic opioid NPS such as incoordination, dizziness, drowsiness, mental confusion, sedation, and profound intoxication.

Sedatives/hypnotics

Sedative/hypnotic substances are central nervous system (CNS) depressants that suppress, inhibit, or decrease brain activity. They are positive allosteric modulators of the central g-aminobutyric acid type A ($GABA_A$) receptors, enhancing inhibitory signalling in the central nervous system to facilitate sedation. The largest structural group of CNS depressants are benzodiazepines, which are widely used in medicine as anticonvulsants, anxiolytics, hypnotics, sedatives, skeletal muscle relaxants, and tranquilizers. Numerous benzodiazepines have been synthesized for use as pharmaceuticals and more than 40 have been placed under international control. However, several benzodiazepine-type NPS have also appeared in recent years, and often marketed in forms of presentation that are similar in appearance to legitimate medicines containing benzodiazepines **(Figure 55)**.

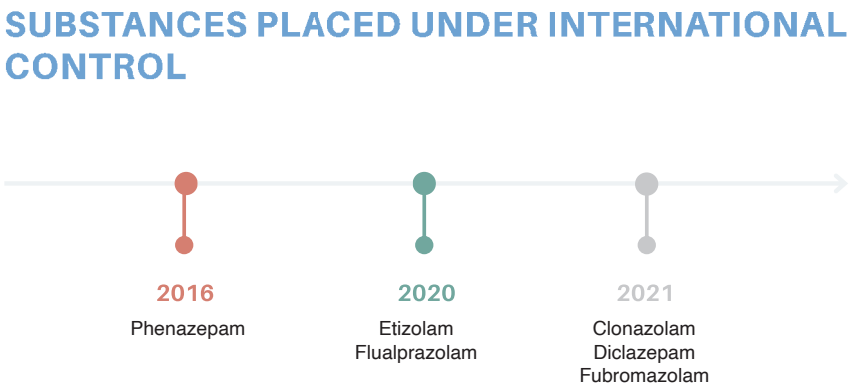


Figure 55: Sedatives placed under international control since 2015.

Benzodiazepines (BZDs) can be classified into **eight** sub-groups, based on their chemical structures: (i) 1,4-benzodiazepines, (ii) 1,5-benzodiazepines, (iii) imidazolobenzodiazepines, (iv) triazolbenzodiazepines, (v) 2,3-benzodiazepines, (vi) thienotriazolodiazepines, (vii) thienodiazepines, and (viii) oxazolodiazepines (**Figure 56**).

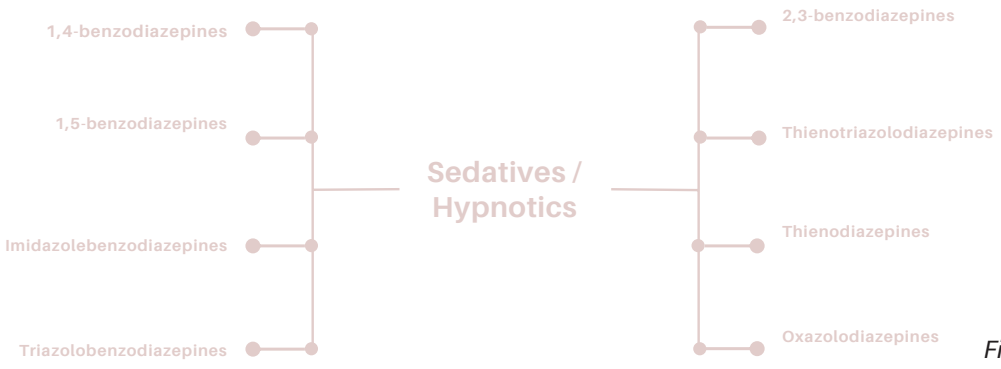


Figure 56: Sedatives sub-groups.

More than 30 benzodiazepine-type NPS have been reported to UNODC. They primarily belong to these three sub-families: 1,4-benzodiazepines, triazolobenzodiazepines and thienotriazolobenzodiazepines (**Figure 57 and 58**).

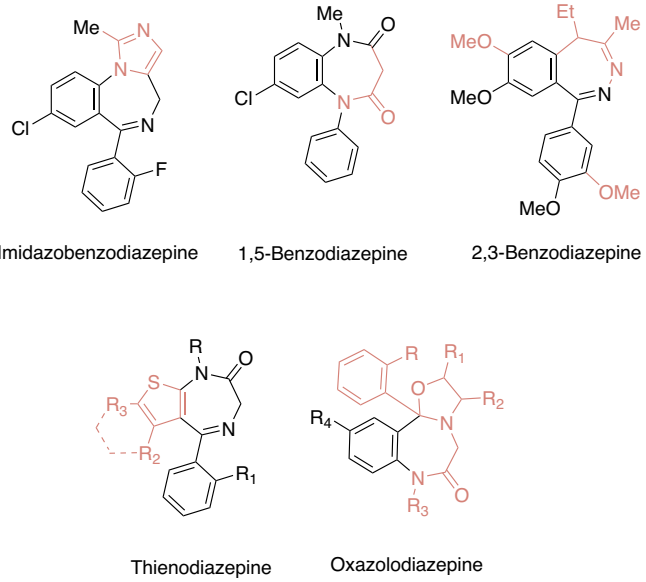
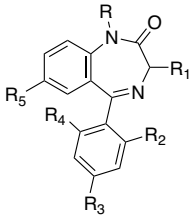


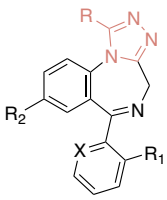
Figure 57: Chemical structures of five sub-families of benzodiazepines (BZDs). The structural differences between these families and the 1,4-benzodiazepine core are highlighted in red.



1,4-Benzodiazepine

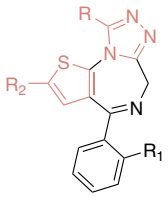
R = Me, R_1 = R_3 = R_4 = H, R_2 = R_5 = Cl (Diclazepam)
R = R_1 = R_3 = R_4 = H, R_2 = F, R_5 = Br (Flubromazepam)
R = R_3 = R_4 = H, R_1 = OH, R_2 = F, R_5 = NO_2 (Nifoxipam)
R = R_3 = R_4 = H, R_1 = Me, R_2 = Cl, R_5 = NO_2 (Meclonazepam)
R = R_3 = R_4 = H, R_1 = OH, R_2 = Cl, R_5 = Br (3-Hydroxyphenazepam)
R = R_1 = R_3 = R_4 = H, R_2 = F, R_5 = Cl (Norflurazepam)
R = Me, R_1 = R_2 = R_4 = H, R_3 = R_5 = Cl (4-chlorodiazepam)
R = Me, R_1 = R_3 = R_4 = H, R_2 = Cl, R_5 = NO_2 (Methylclonazepam)
R = Me, R_1 = R_3 = H, R_2 = R_4 = F, R_5 = Cl (Difludiazepam)
R = R_1 = R_3 = R_4 = H, R_2 = Cl, R_5 = Br (Phenazepam)

R =  R_1 = R_3 = R_4 = H, R_2 = Cl, R_5 = NO_2 (Cloniprazepam)



Triazolobenzodiazepine

X = CH, R = Me, R_1 = H, R_2 = Br (Bromazolam)
X = CH, R = Me, R_1 = H, R_2 = NO_2 (Nitrazolam)
X = CH, R = Me, R_1 = Cl, R_2 = NO_2 (Clonazolam)
X = CH, R = Me, R_1 = F, R_2 = Cl (Flualprazolam)
X = CH, R = Me, R_1 = F, R_2 = Br (Flubromazolam)
X = CH, R = Me, R_1 = F, R_2 = NO_2 (Flunitrazolam)
X = CH, R = CH_2NMe_2, R_1 = H, R_2 = Cl (Adinazolam)
X = N, R = Me, R_1 = H, R_2 = Br (Pyrazolam)



Thienotriazolodiazepine

R = H, R_1 = Cl, R_2 = Et (Metizolam)
R = Me, R_1 = Cl, R_2 = Et (Etizolam)
R = Me, R_1 = H, R_2 = Et (Deschloroetizolam)
R = Me, R_1 = F, R_2 = Cl (Fluclotizolam)

Figure 58: Chemical structures of three further sub-families of benzodiazepines (BZDs). The structural differences between these families and the 1,4-benzodiazepine core are highlighted in red.

A small number of sedative/hypnotic NPS derived from methaqualone have also emerged. Methaqualone is a synthetic central nervous system (CNS) depressant with sedative/hypnotic, anticonvulsant, antispasmodic, and local anaesthetic properties [262]. This substance was withdrawn from the pharmaceutical market in many countries because of problems of abuse and it is under international control. NPS within this group that have been reported to UNODC include etaqualone, mebroqualone, methylmethaqualone, and nitromethaqualone.

Commonly Used Forms

The substances in this group appears to be used through the most common routes of administration normally accessible **(Figure 59)**.

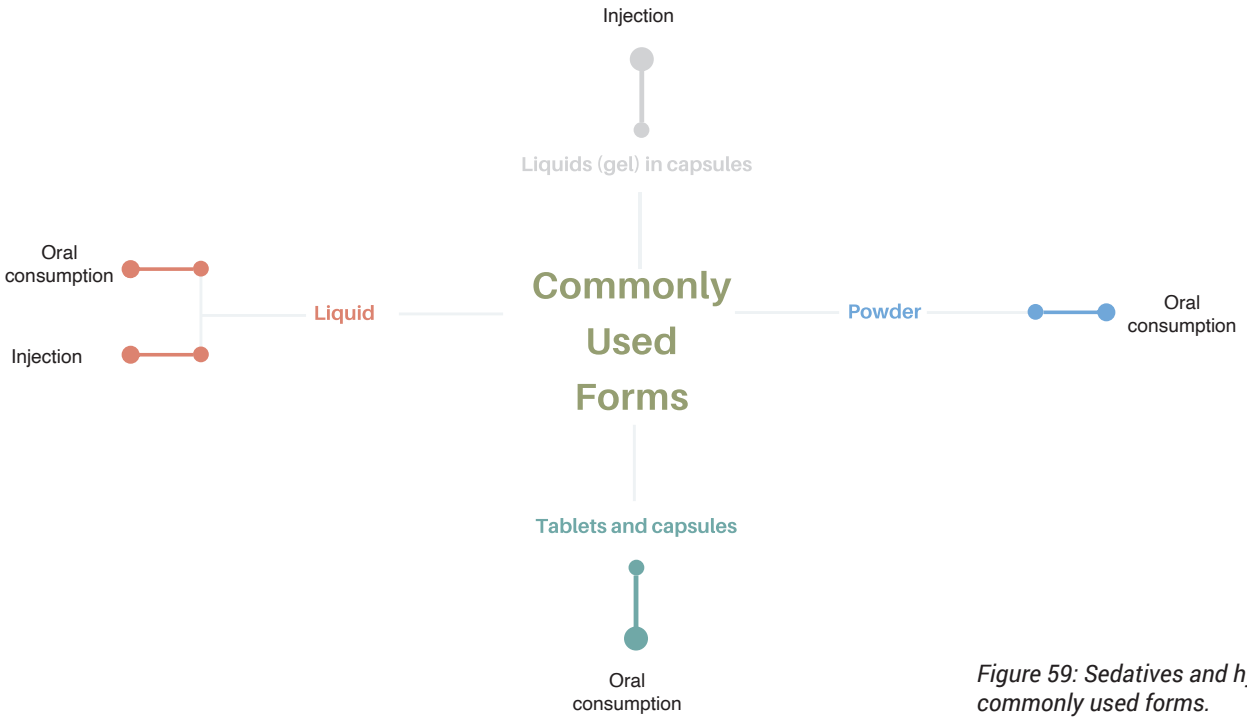


Figure 59: Sedatives and hypnotics commonly used forms.

Reported Effects

While some benzodiazepine-type-NPS have been placed under international control in recent years, there is limited pharmacological and toxicological information on most substances that have emerged. The use of benzodiazepines along with opiates or other CNS-depressant drugs highly increases the risk of overdose and death. Although deaths involving benzodiazepines may be under-reported, they are rare without the concurrent use of other drugs **(Figure 60)**.

Desired Effects

- *Feelings of calmness, relaxation, sociability and well being in individuals with anxiety problems*
- *Improved coping with situational pressure or psychological problems*
- *Promotes growth hormone effects of alleged stimulation of muscle growth*
- *Reduced inhibition, euphoria and mild hallucinations*
- *Relief of tension, mental stress and anxiety*
- *Relief of side effects associated with withdrawal of other drugs or over stimulation*

Undesired Acute Effects

- *Dilation of pupils*
- *Diminished emotional responses to external stimuli, e.g. pain*
- *Extreme, unpredictable emotional reactions and mental confusion, disorientation*
- *Potential impairment of muscle coordination, clumsiness, dizziness, low blood pressure, or fainting*
- *Potential stupor, unconsciousness, coma*
- *Reduced mental activity and alertness, drowsiness, lethargy and impairment of clarity of thought and judgement may occur*
- *Respiratory and cardiac depression, weak and rapid heart rate, suppression of cough reflex*
- *Slurred speech, poor control of speech, impaired judgement*

Effects of Chronic Use

- *Abrupt cessation may lead to withdrawal syndrome which can include insomnia, anxiety, perceptual, hypersensitivity, tremors, irritability, nervousness, faintness, nausea and vomiting, progressive restlessness, temporary sleep disturbances and possible delirium and life-threatening convulsions*
- *Bronchitis, pneumonia*
- *Development of tolerance, strong psychological and physical, dependence*
- *Headache, irritability, confusion, memory impairment, depression, insomnia and tremor*
- *Potential blackouts*
- *Severe depression and amnesia*
- *In conjunction with other central nervous system (CNS) depressants, adverse effects are exacerbated*

Figure 60: Reported effects of sedatives/ hypnotics.

Dissociatives

Dissociative substances form a class of hallucinogens that produce feelings of detachment and dissociation from self and the environment. Dissociatives produce their effects through antagonism of ionotropic *N*-methyl-D-aspartate (NMDA) receptors in the central nervous system [262]. Dissociatives can be classified into **two** sub-groups: (i) phencyclidine-type substances and (ii) 1,2-diarylethylamines (**Figure 61**).

Figure 61: Dissociatives sub-groups.

There are a number of substances with dissociative effects under international control e.g., phencyclidine and three. NPS with dissociative effects have been placed under international control since 2016 **(Figure 62)**.

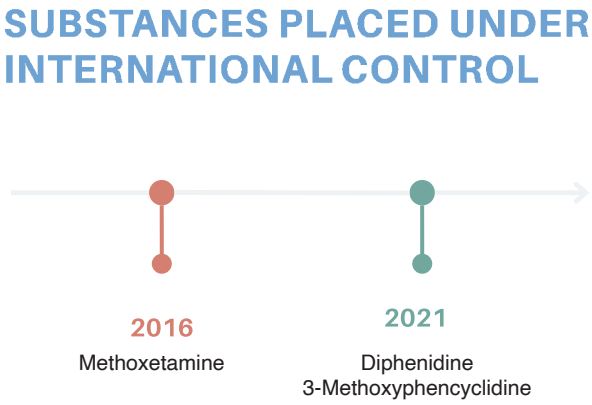


Figure 62: Dissociatives placed under international control since 2015.

Phencyclidine-type substances

Following the discovery of 1-(1-phenylcyclohexyl)piperidine (phencyclidine, PCP) in the mid-1950s, a variety of analogues known as *"arylcyclohexylamines"* have been developed by systematic modification of the two key regions of the PCP structure (**Figure 63**).

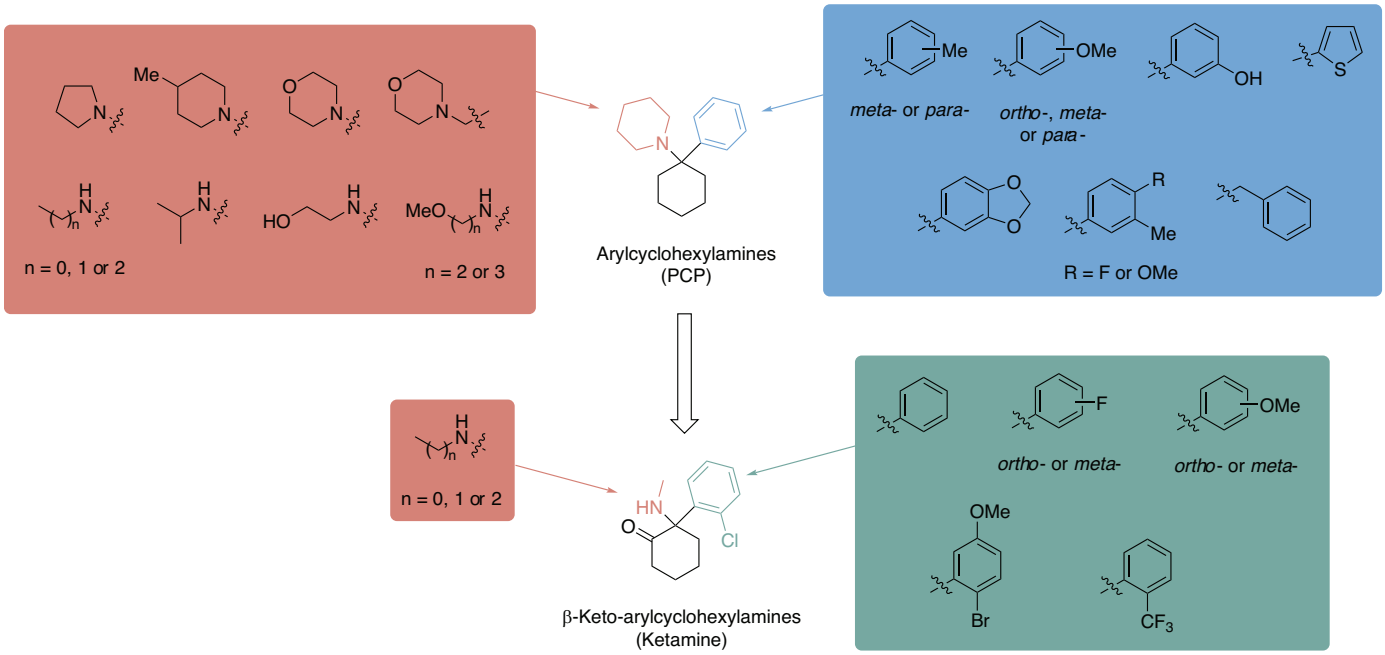


Figure 63: Generic structural representation of phencyclidine and ketamine derived dissociatives obtained by modification of the highlighted key regions and using phencyclidine (PCP) and ketamine as the progenitor template.

β-Keto-arylcyclohexylamines are closely related to the arylcyclohexylamine family of dissociatives, where the cyclohexane ring is substituted with a cyclohexan-2-one group (**Figure 64**).

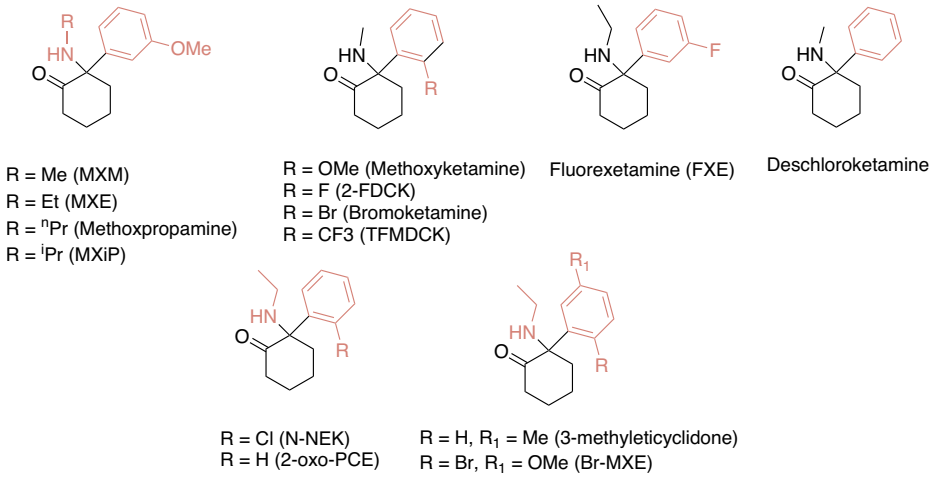


Figure 64: Common ketamine-derived (beta-keto-arylcyclohexylamine) NPS. The structural differences between these compounds and ketamine are highlighted in red.

In the same way that arylcylohexylamines share commonality with PCP, β-keto-arylcyclohexylamines, are structurally related to the dissociative anaesthetic, ketamine. Like the PCP-derived NPS, several β-keto-arylcyclohexylamines have been accessed by systematic modification of the basic structure using well-documented approaches. Ketamine and phencyclidine have similar modes of action, affecting a range of central neurotransmitters. Nevertheless, the structural-activity relationships of β-keto-arylcyclohexylamines relative to their arylcyclohexylamine cous-

ins remain largely unpublished with indications that ketamine-derived NPS are pharmacologically similar. More than 10 β-keto-arylcyclohexylamines have been reported to UNODC.

1,2-Diarylethylamines

Another class of NMDA receptor antagonists to emerge on the NPS market are the 1,2-diarylethylamines, which share structural similarities to arylcyclohexylamines but are less conformationally restricted due to the removal of the cyclohexane core. These compounds have been extensively reviewed [263] and can be easily accessed using common inexpensive, uncontrolled precursors and simple, single-step chemical reactions. The first 1,2-diarylethylamine to appear on the market was 1-(1,2-diphenylethyl)piperidine (diphenidine) in 2013, shortly followed by its 2-methoxy- analogue 1-[1-(2-methoxyphenyl)-2-phenylethyl]piperidine (2-methoxphenidine, 2-MXP) and finally *N*-ethyl-1,2-diphenylethylamine (ephenidine) in 2015 **(Figure 65)**.

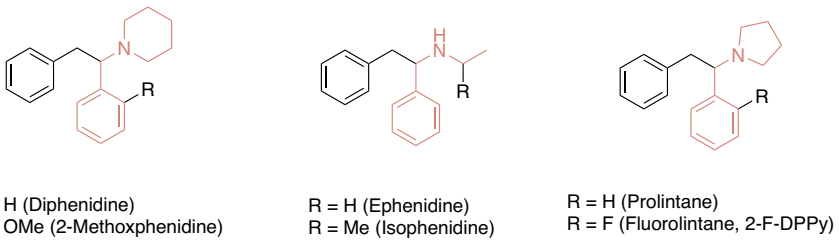


Figure 65: Common 1,2-diarylethylamine-derived NPS. The structural similarity between 1,2-diarylethylamines and arylcyclohexylamines (PCP, PCE and PHP) are highlighted in red.

Commonly Used Forms

The routes of administration for dissociatives are in the form of either pills or powders, including insufflation, inhalation, ingestion, and intravenous injection **(Figure 66)**.

Figure 66: Dissociatives commonly used forms.

Reported Effects

Adverse effects of dissociative-induced intoxication by phencyclidine-type substances include effects on both the cardiovascular (tachycardia, hypotension) and central nervous (impaired or loss of consciousness, coma, slowed psychomotor performance, disorientation, hallucinations, agitation, and aggression) systems **(Figure 67).**

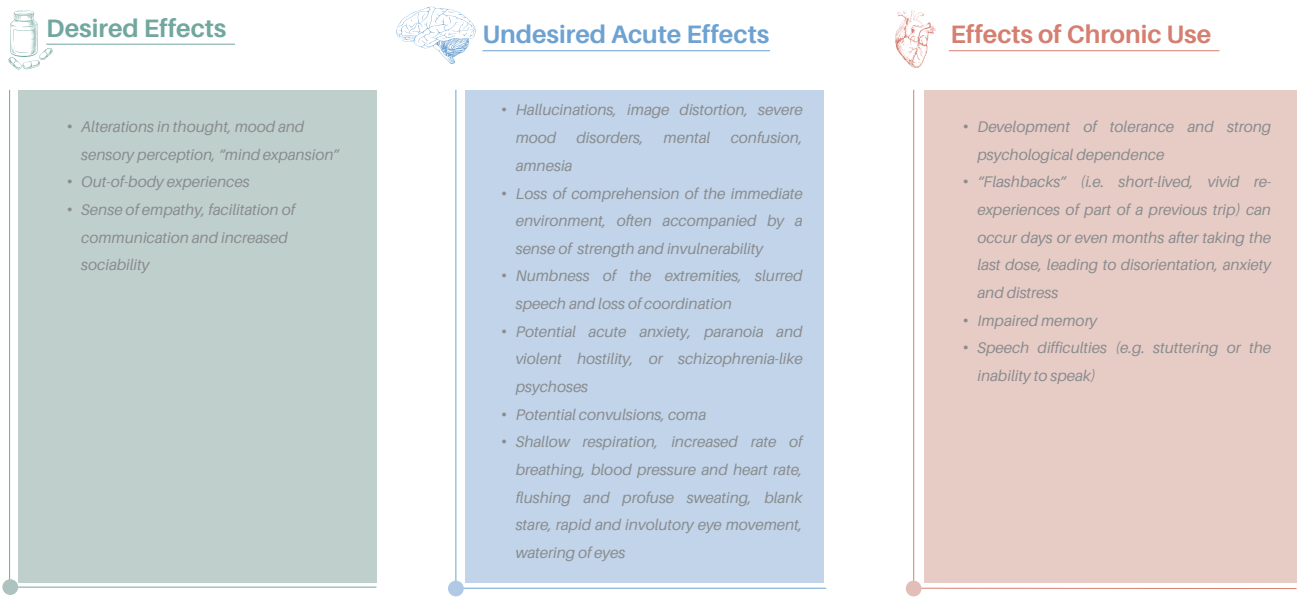


Figure 67: Reported effects of dissociatives.

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UNODC
United Nations Office on Drugs and Crime

Vienna International Centre, P.O. Box 500, 1400 Vienna, Austria
Tel.: (+43-1) 26060-0, Fax: (+43-1) 263-3389, www.unodc.org