UNODC
United Nations Office on Drugs and Crime

The challenge of New Psychoactive Substances

A technical update 2024

UNODC LABORATORY AND SCIENTIFIC SERVICES

UNITED NATIONS OFFICE ON DRUGS AND CRIME
Vienna

The challenge of New Psychoactive Substances

A technical update

June 2024

Acknowledgments
The UNODC Drugs, Laboratory and Scientific Services Branch, headed by Justice Tettey, wishes to express its appreciation and thanks to Dr. Oliver Sutcliffe of the Manchester Metropolitan University, United Kingdom, for the preparation of the final draft of the present report.

The preparation of The challenge of New Psychoactive Substances - A technical update, was coordinated by Martin Raithelhuber and Conor Crean, staff members of the UNODC Laboratory and Scientific Services. The contribution of other UNODC staff members, Anna Carolina De Azevedo Barbosa, Katarzyna Berkowicz, Dominik Bumberger and Sabrina Levissianos is gratefully acknowledged.

The Laboratory and Scientific Services would like to thank the following Governments who made the development of this report possible through their contributions to the SMART Forensics Programme:
Government of Australia
Government of Canada
Government of China
Government of Japan
Government of New Zealand
Government of the Republic of Korea
Government of Thailand
Government of the United Kingdom
Government of the United States

Suggested citation:
UNODC, The challenge of New Psychoactive Substances - A technical update (United Nations publication, 2024)

Comments on the report are welcome and can be sent to:

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)**.

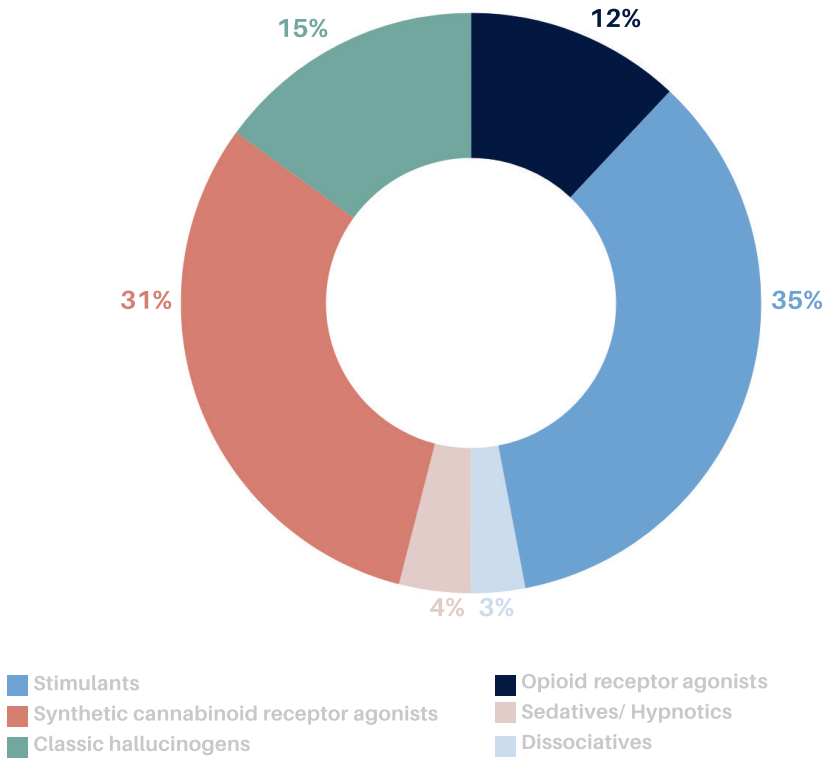


Figure 1: Distribution of NPS reported to the UNODC Early Warning Advisory on NPS by effect group.

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)**.

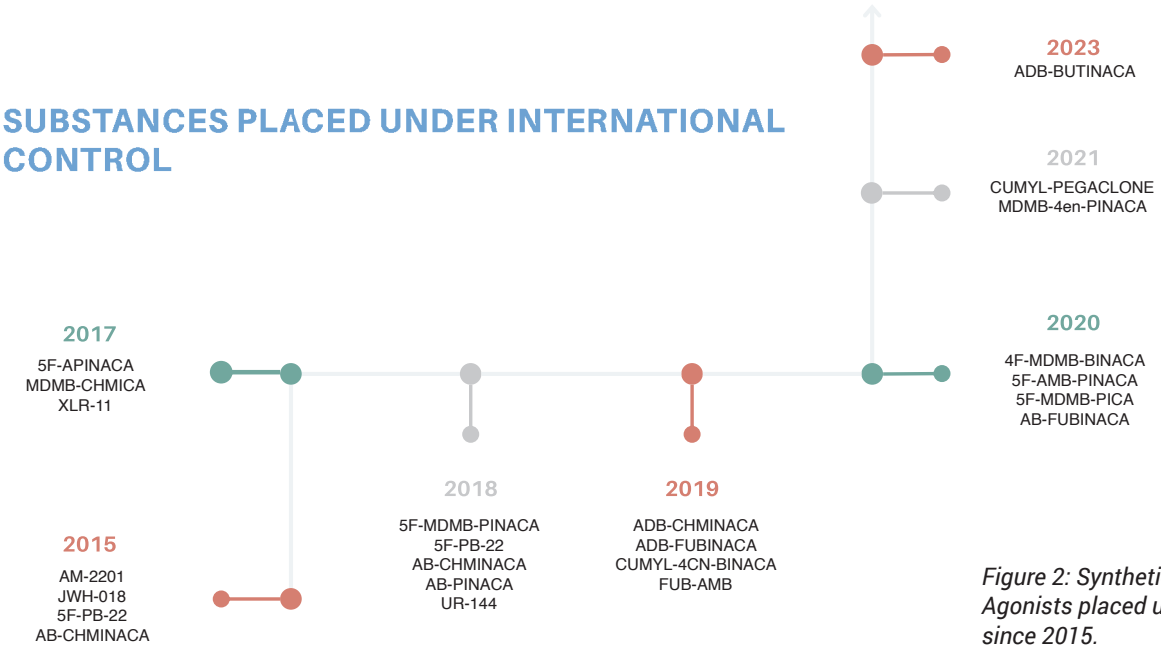


Figure 2: Synthetic Cannabinoid Receptor Agonists placed under international control since 2015.

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.

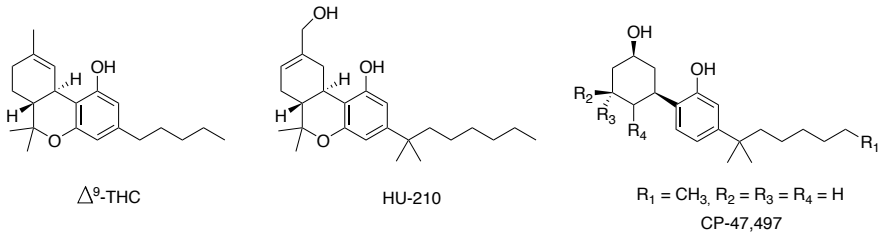
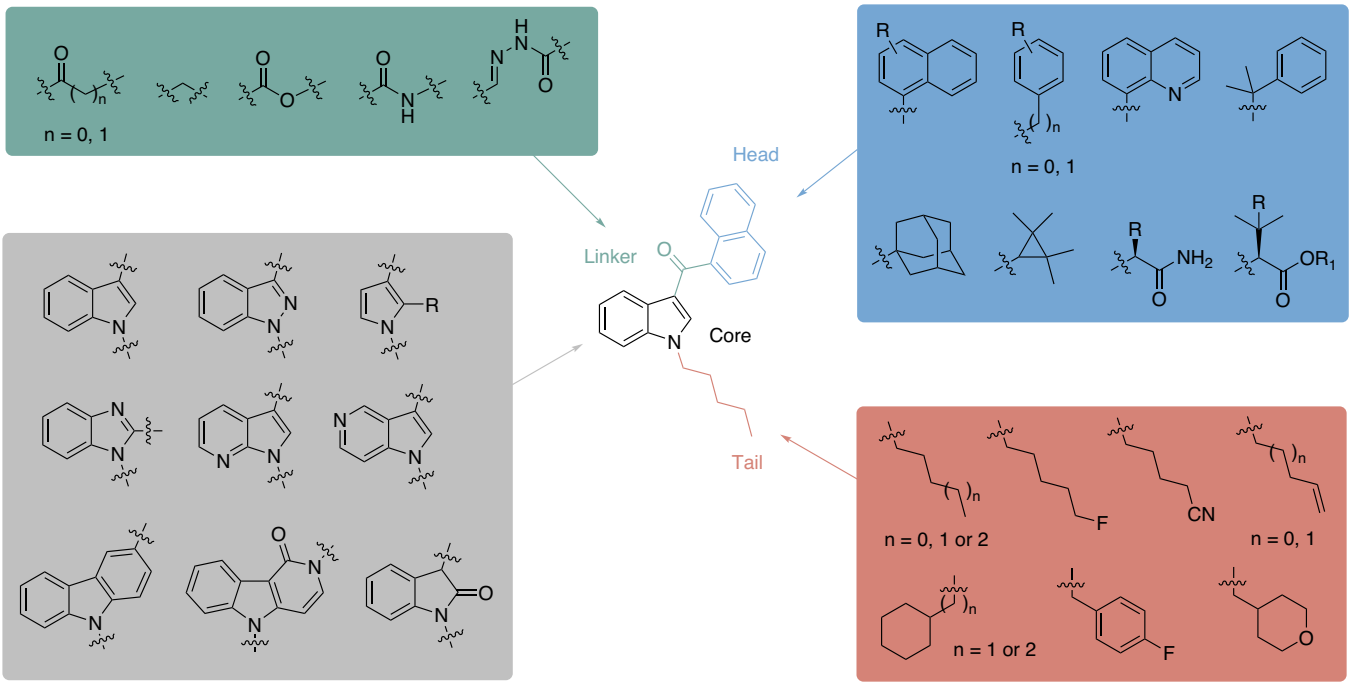


Figure 3: Chemical structures of Δ^9-THC, classical synthetic cannabinoid, HU-210 and the non-classical cannabinoid CP-47,497.

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)**.

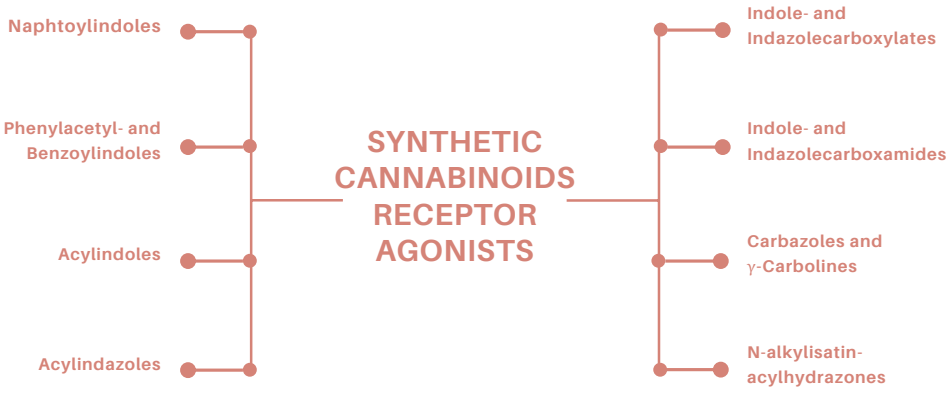


Figure 5: Synthetic cannabinoid receptor agonists receptor (SCRA) sub-groups.

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].

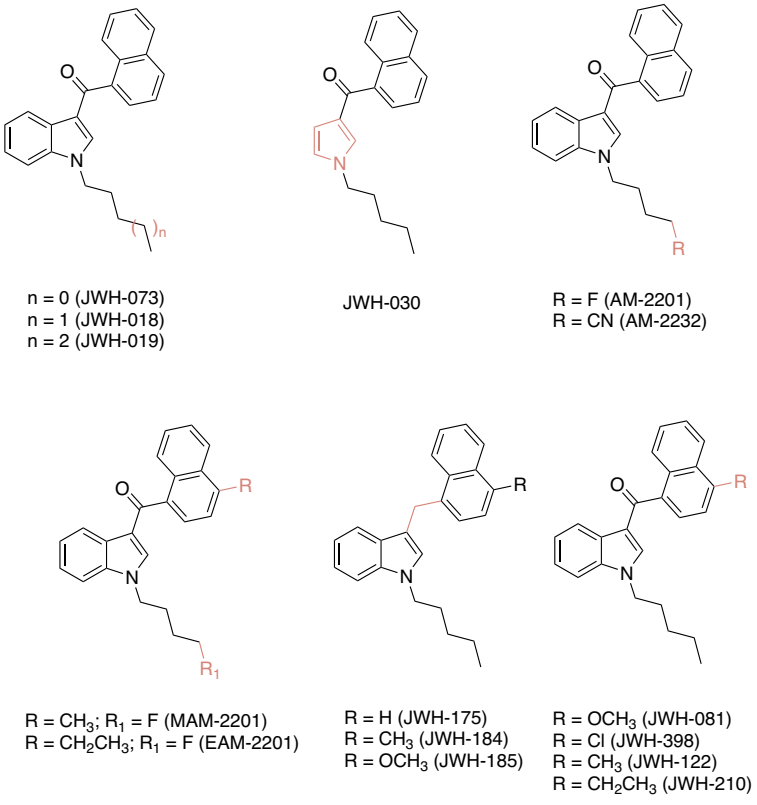
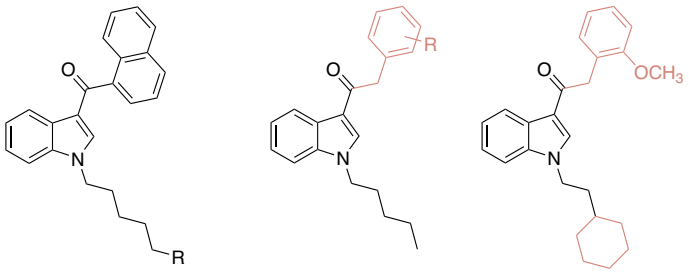


Figure 6: Chemical structures of naphthoylindole-based synthetic cannabinoids. The structural differences between the derivatives and JWH-018 are highlighted in red.

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].



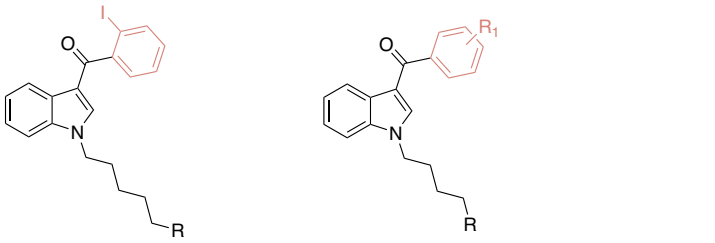
R = H (JWH-018)
R = F (AM-2201)

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].



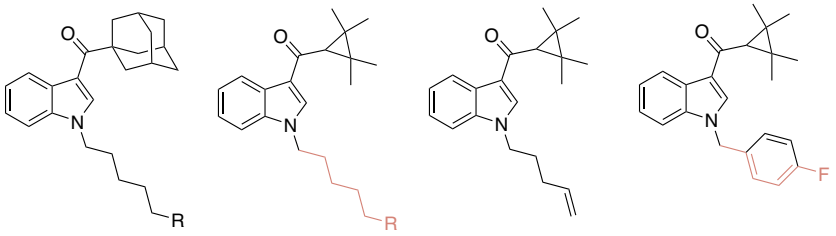
R = H (AM-679)
R = F (AM-694)

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)

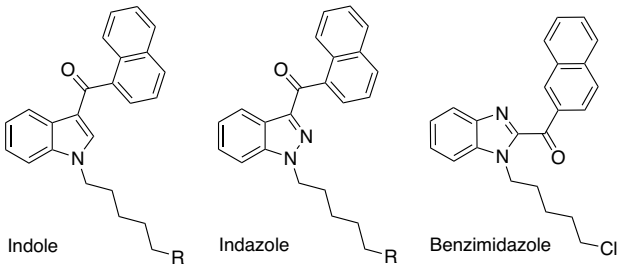
UR-144 N-(4-pentenyl)

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].

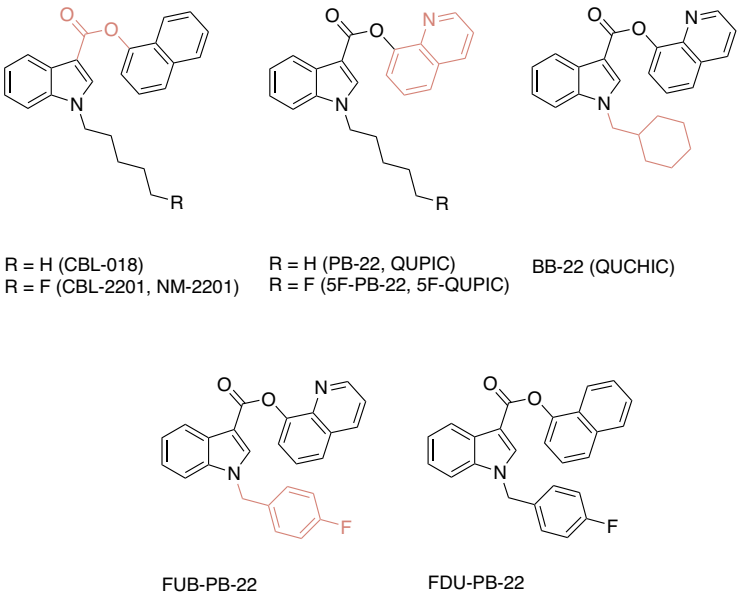


Figure 11: Chemical structures of indolecarboxylate synthetic cannabinoids. The structural differences and evolution from CBL-018 to FUB-PB-22 are highlighted in red.

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)**.

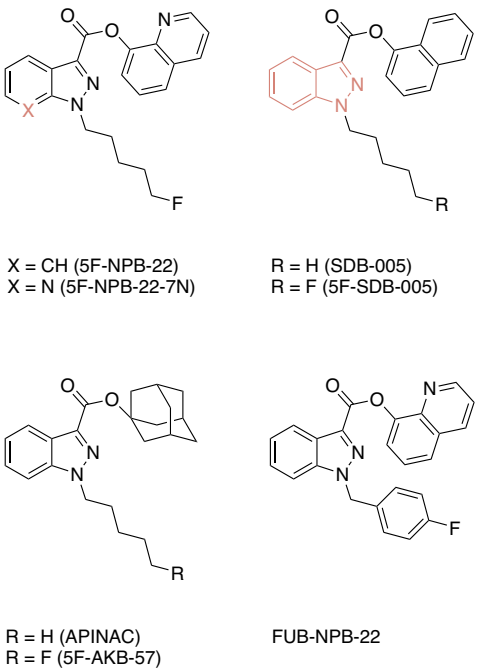


Figure 12: Chemical structures of indazolecarboxylate-derived SCRAs.

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].

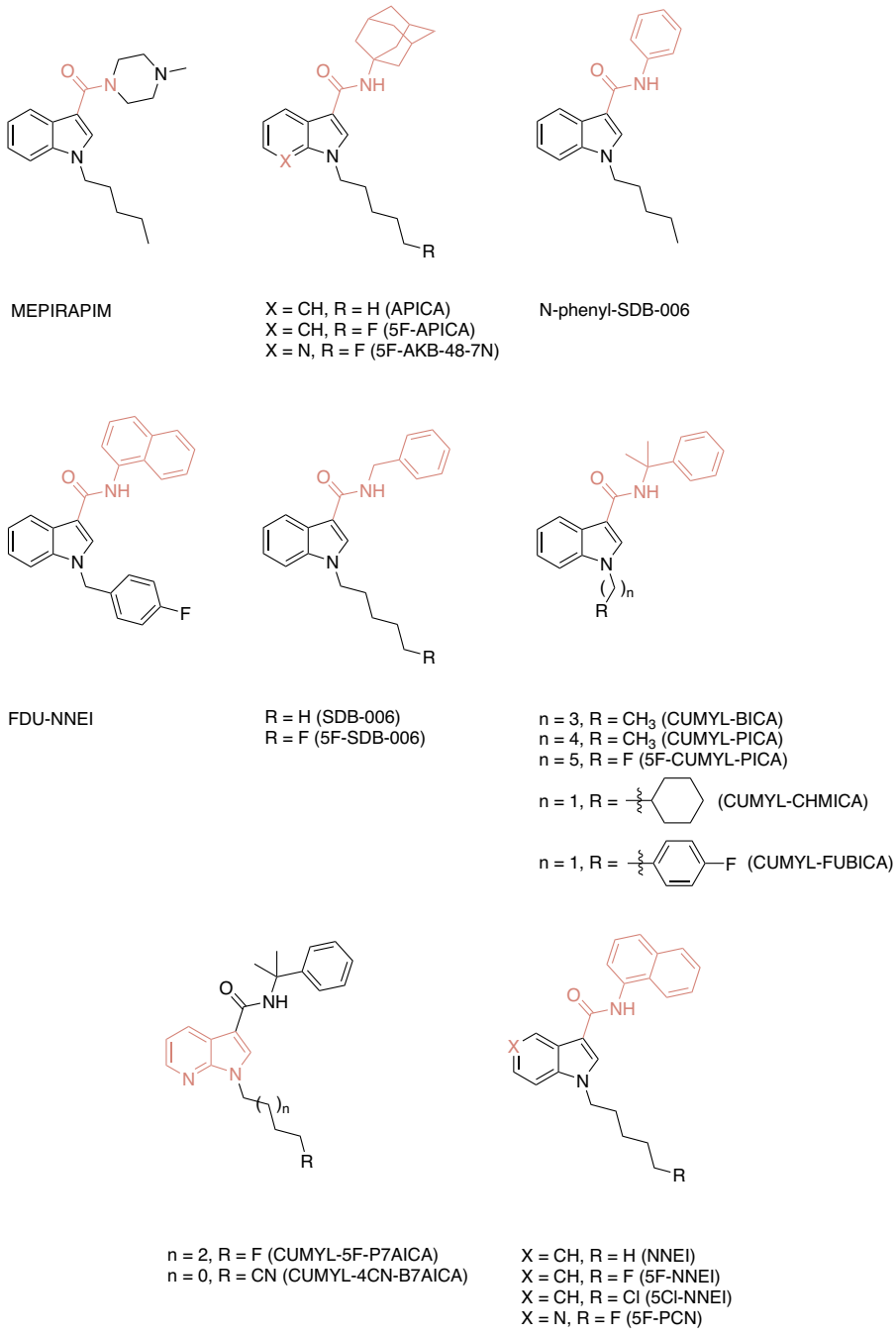


Figure 13: Chemical structures of indolecarboxamide synthetic cannabinoids. The structural differences are highlighted in red.

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.

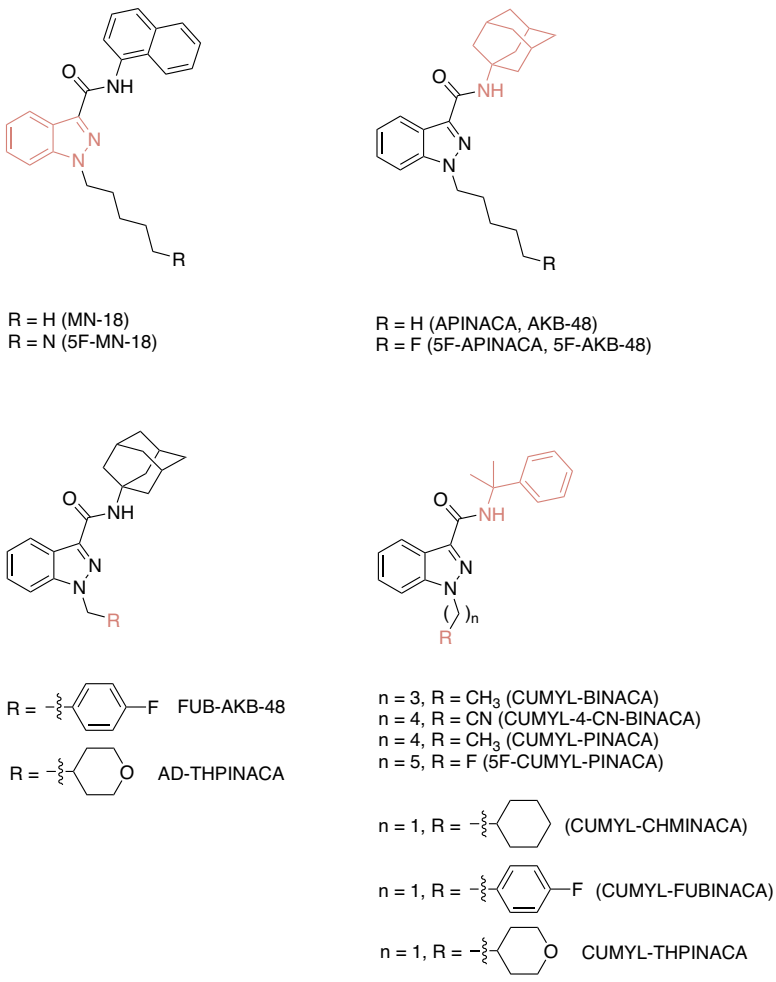


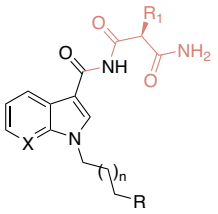
Figure 15: Chemical structures of indazolecarboxamide synthetic cannabinoids.

Amino Acid amides

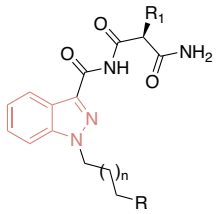
This is an important sub-family within the broader indole- and indazole-carboxamide series of synthetic cannabinoids e.g., valinamides [AB-series] [42, 121–123], *tert*-leucinamides [ADB-series] [42, 122–124] and/or phenylalaninamide [APP-series] [122, 123] (**Figure 16**). The incorporation of *esters* 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].

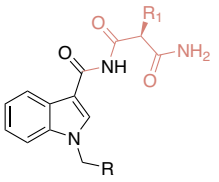
As with previous generations, the indole-valinamide synthetic cannabinoids with *N*-alkylated tail groups bearing 4 or 5 carbons exhibit nanomolar CB_1 affinity (e.g., AB-PICA) (**Figure 16**). Modification of the *N*-pentyl group, with either an *N*-5-fluoropentyl- (5F-AB-PICA) or aromatic

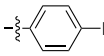
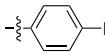


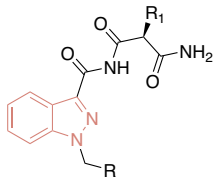
X = CH, n = 1, R = CH_3, R_1 = ^{i}Pr (AB-BICA)
X = CH, n = 2, R = CH_3, R_1 = ^{i}Pr (AB-PICA)
X = CH, n = 2, R = CN, R_1 = ^{i}Pr (4CN-AB-BUTICA)
X = CH, n = 3, R = F, R_1 = ^{i}Pr (5F-AB-PICA)
X = CH, n = 3, R = C=C, R_1 = ^{i}Pr (AB-4en-PICA)
X = CH, n = 2, R = CH_3, R_1 = ^{t}Bu (ADBICA, ADB-PICA)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



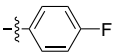
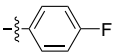
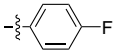
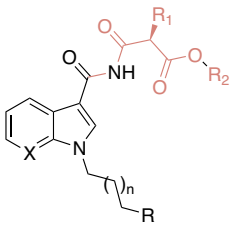
R =  , R_1 = ^{i}Pr (AB-CHMINACA)
R =  , R_1 = ^{t}Bu (ADB-CHMINACA)
R =  , R_1 = Bz (APP-CHMINACA, PX-3)
R =  F, R_1 = ^{i}Pr (AB-FUBINACA)
R =  F, R_1 = ^{t}Bu (ADB-FUBINACA)
R =  F, R_1 = Bz (APP-FUBINACA)
R =  , R_1 = ^{t}Bu (ADB-BINACA)

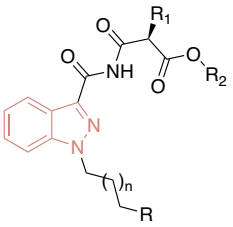
Figure 16: Chemical structures of indazolecarboxamide synthetic cannabinoids.

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**).

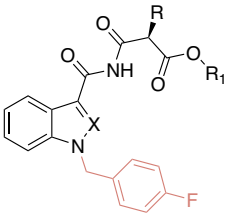


X = CH, n = 2, R = CH_3, R_1 = ^{i}Pr, R_2- = Me (AMB-PICA)
X = CH, n = 3, R = F, R_1 = ^{i}Pr, R_2 = Me (5F-AMB-PICA)
X = CH, n = 3, R = F, R_1 = ^{i}Pr, R_2 = Et (5F-EMB-PICA)
X = CH, n = 3, R = C=C, R_1 = iPr, R_2 = Me (MMB-4en-PICA)
X = CH, n = 2, R = F, R_1 = ^{t}Bu, R_2 = Me (4F-MDMB-BICA)
X =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

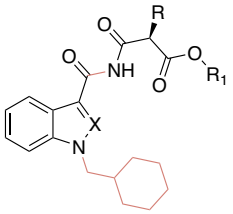


n = 2, R = CH_3, R_1 = ^{i}Pr, R_2- = Me (AMB-PINACA)
n = 2, R = CN, R_1 = ^{i}Pr, R_2 = Me (4CN-MMB-BUTINACA)
n = 3, R = F, R_1 = ^{i}Pr, R_2 = Me (5F-AMB-PINACA)
n = 3, R = F, R_1 = ^{i}Pr, R_2 = Et (5F-EMB-PINACA)
n = 3, R = C=C, R_1 = iPr, R_2 = Me (MMB-4en-PINACA)
n = 2, R = F, R_1 = ^{t}Bu, R_2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

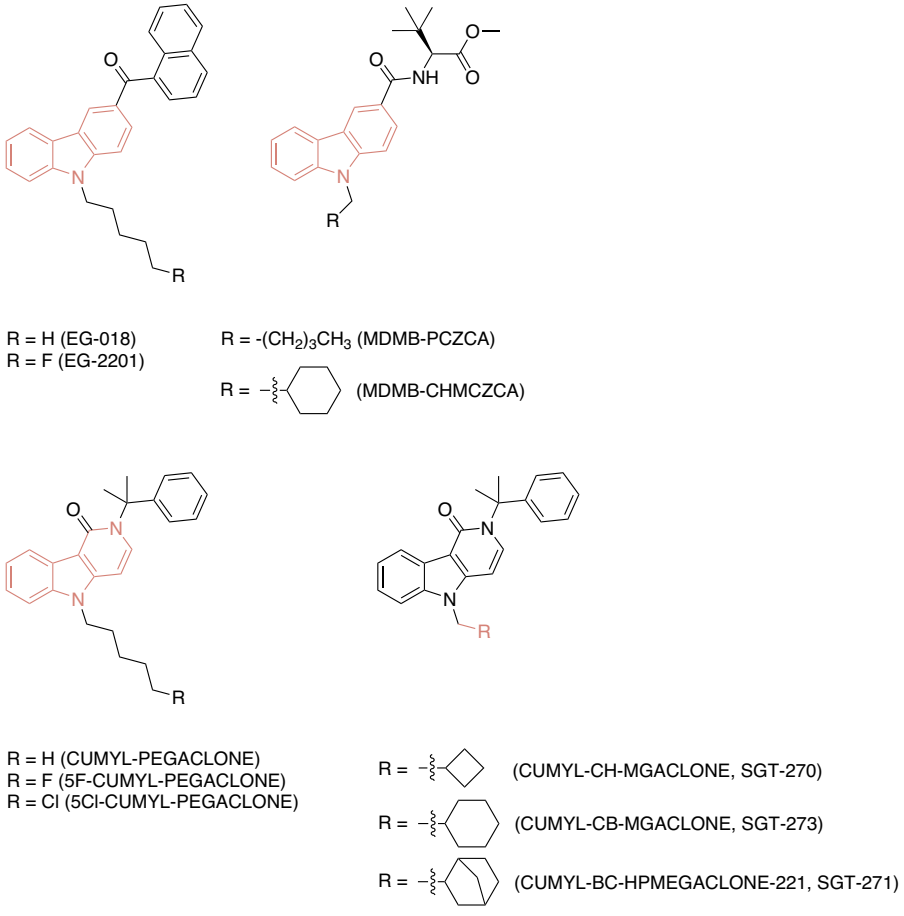


Figure 18: Chemical structures of tricyclic synthetic cannabinoids.

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].

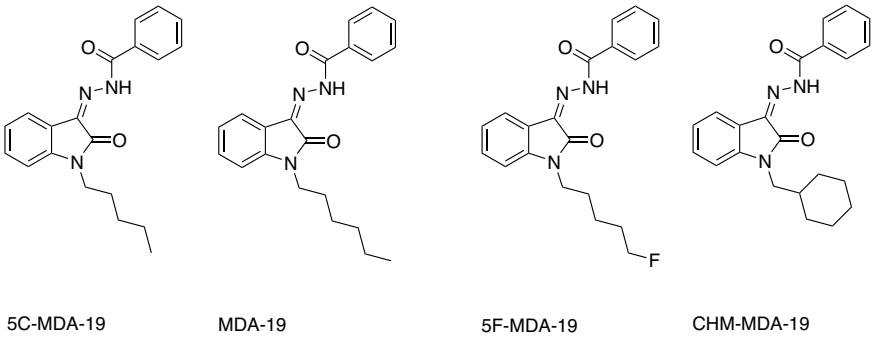


Figure 19: Chemical structures of N-alkylisatin-acylhydrazone derived synthetic cannabinoids.

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].

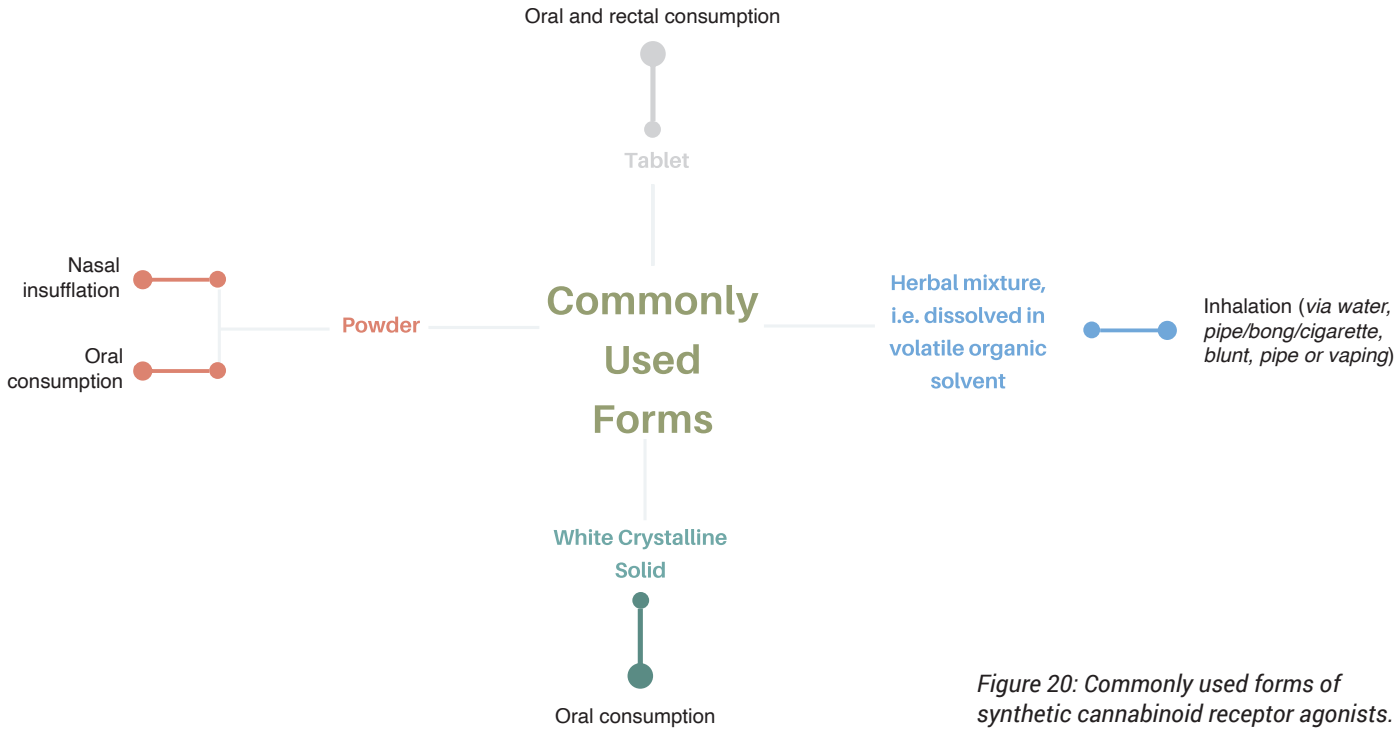


Figure 20: Commonly used forms of synthetic cannabinoid receptor agonists.

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)**.

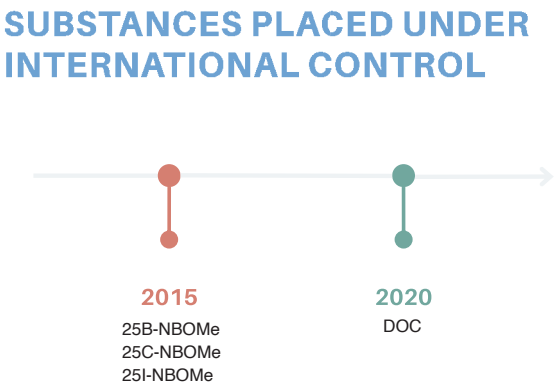
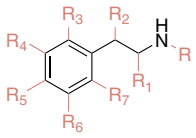


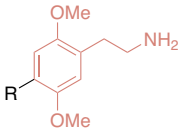
Figure 23: Classic hallucinogens placed under international control since 2015.

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.

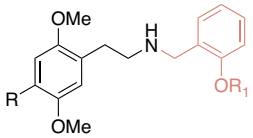


PEA Scaffold



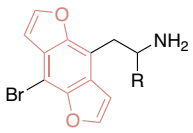
2C-Series

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



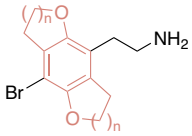
NBOMe- and NBOH-Series

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)



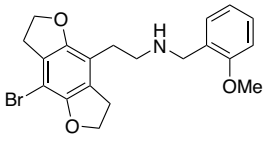
Fly-Series

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

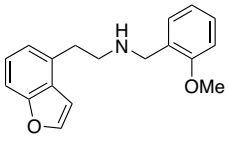


DragonFly- and
ButterFly-series

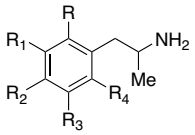
n = 1 (2C-B-DragonFly)
n = 2 (2C-B-ButterFly)



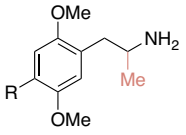
2CBFly-NBOMe



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.

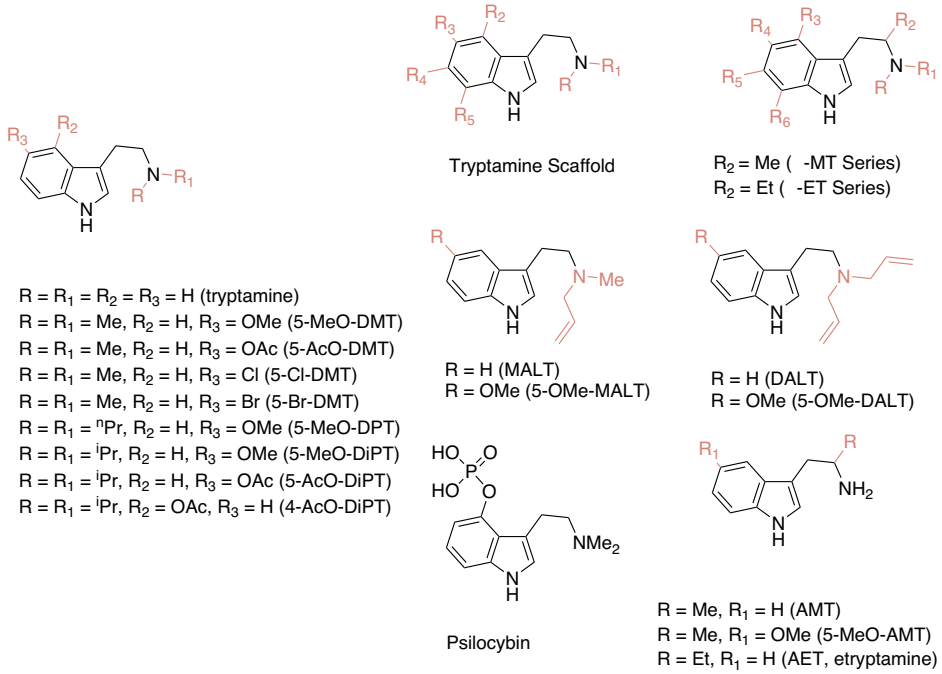


Figure 25: Chemical structures of tryptamines and the structural related analogues. The seven positions of the tryptamine core and the key structural differences between the analogues are highlighted in red.

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**).

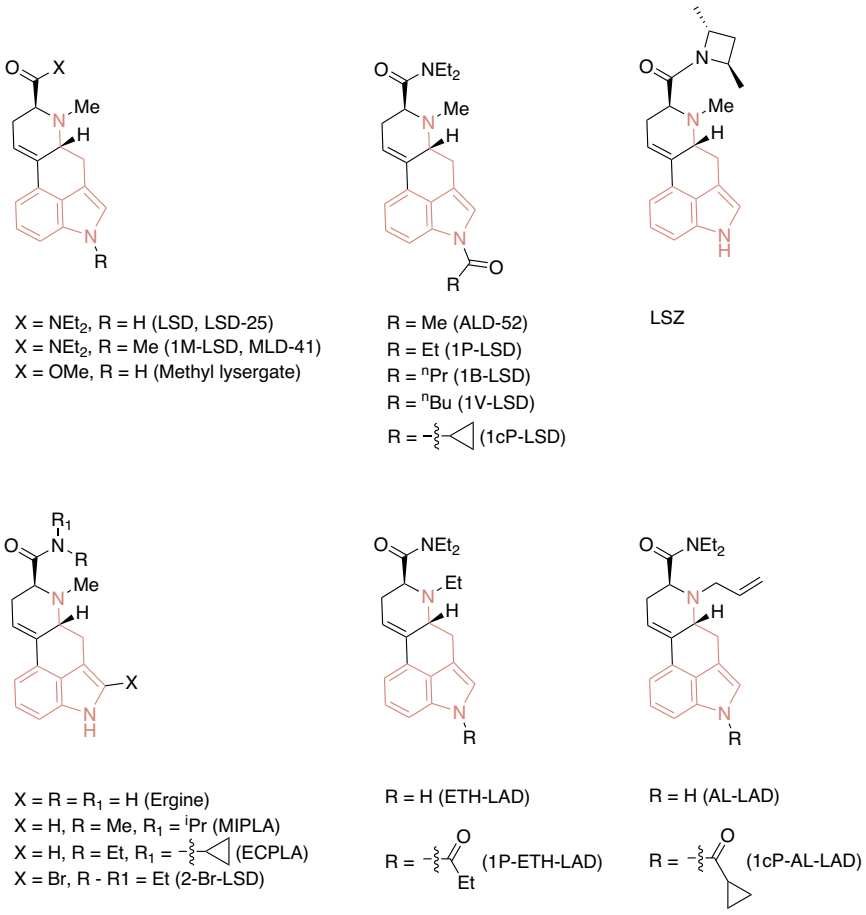


Figure 26: Chemical structures of lysergamides. The key structural similarity between these analogues and tryptamine is highlighted in red.

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)**.

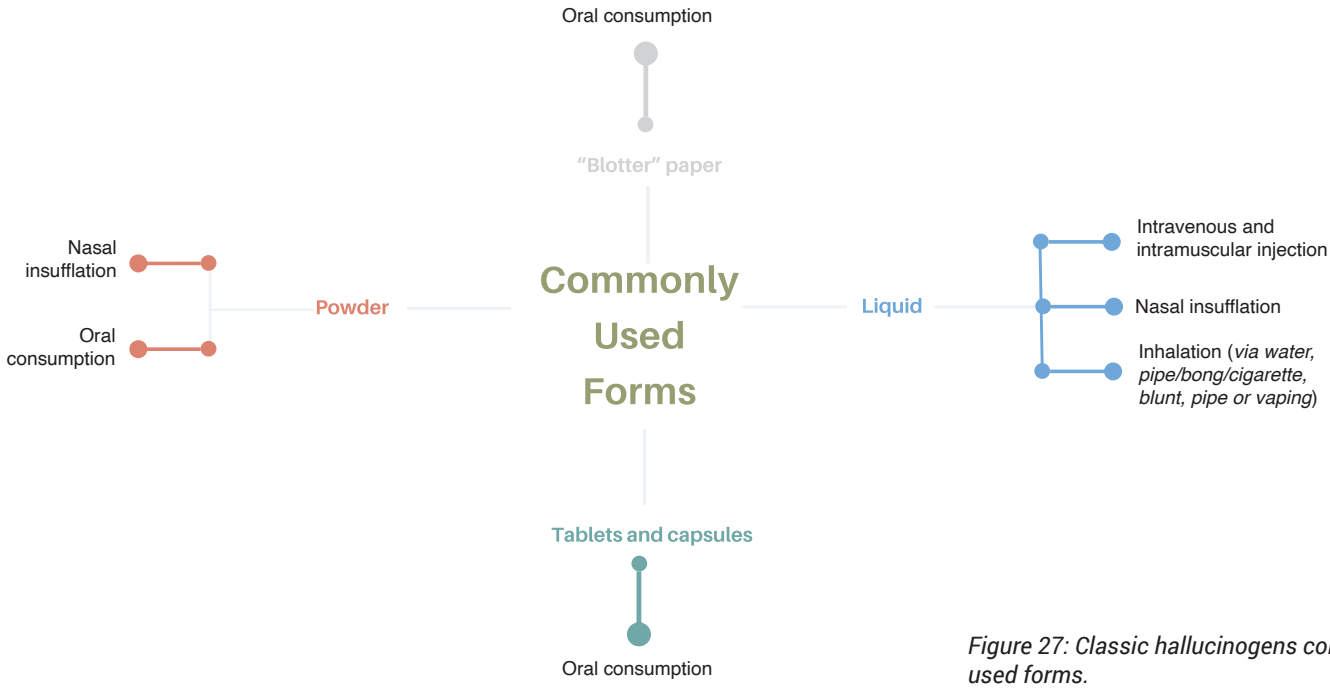


Figure 27: Classic hallucinogens commonly used forms.

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.

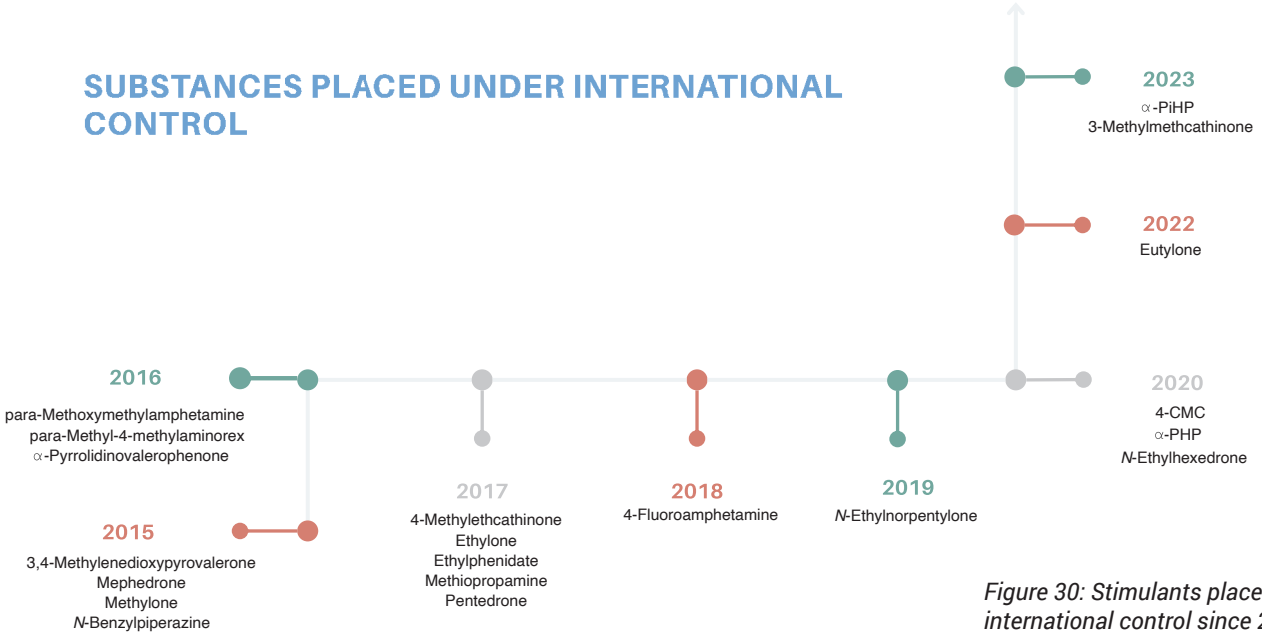


Figure 30: Stimulants placed under international control since 2015.

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.

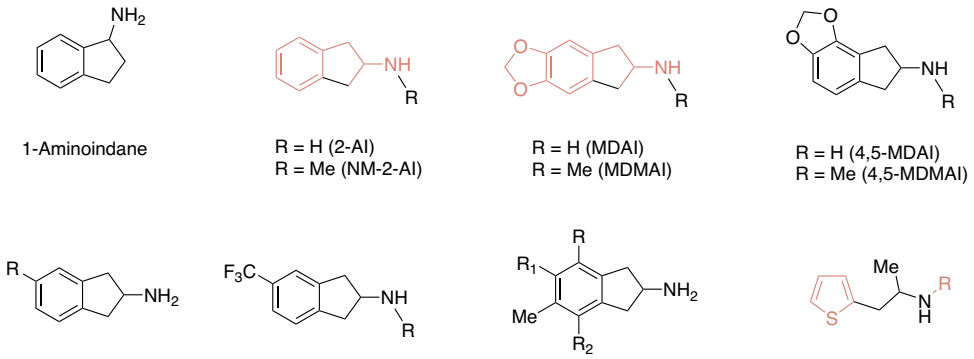


Figure 31: Common aminoindane NPS. The structural similarity between aminoindanes and amphetamines (e.g., amphetamine, methamphetamine and MDMA) are highlighted in red.

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.

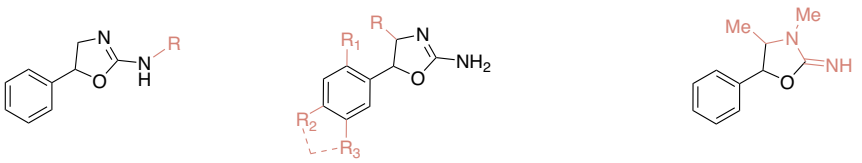


Figure 32: Chemical structures of 2-amino-5-aryl-2-oxazoline derived NPS. The structural differences between Aminorex, 4-MAR and, 3,4-DMAR sub-families are highlighted in red.

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.

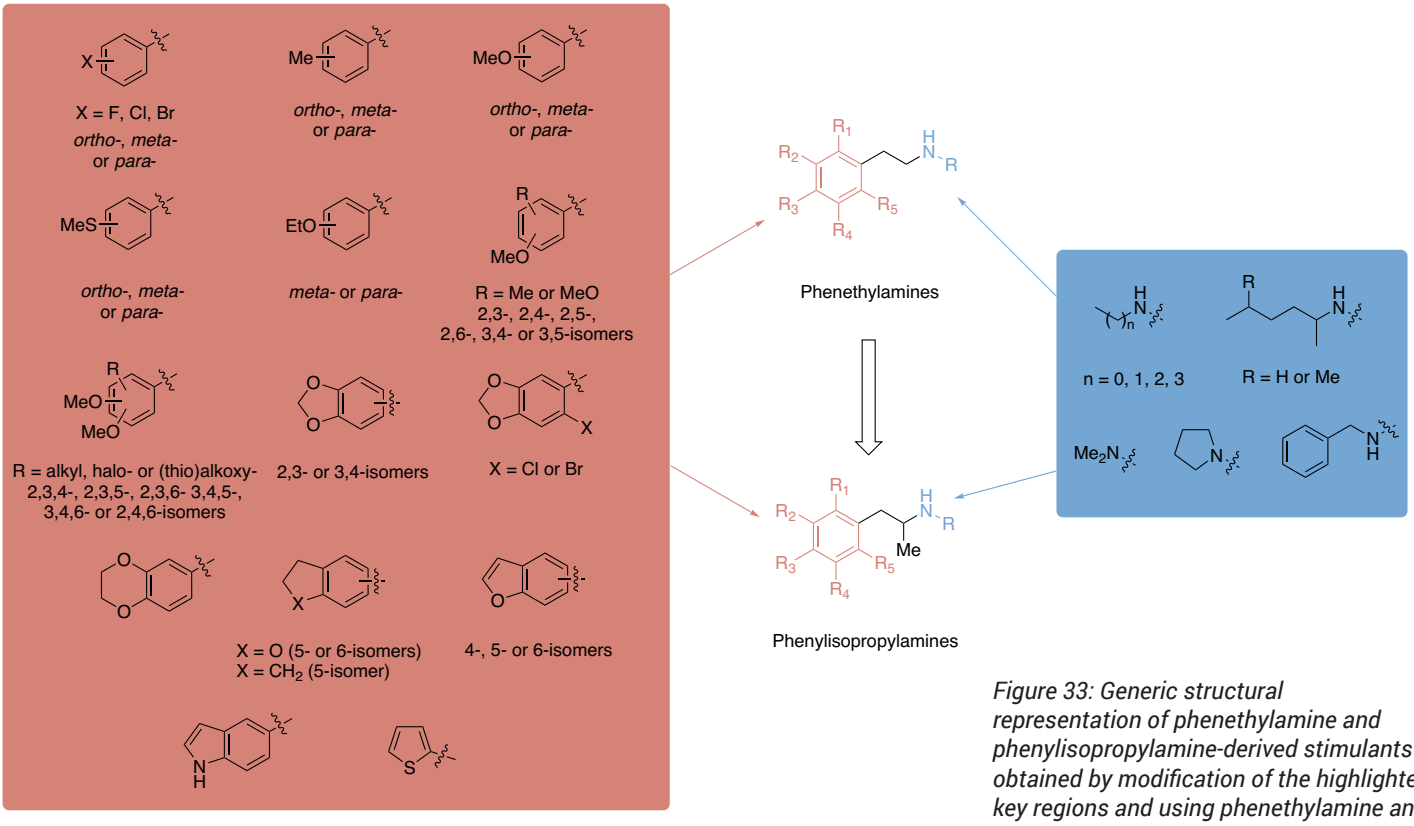


Figure 33: Generic structural representation of phenethylamine and phenylisopropylamine-derived stimulants obtained by modification of the highlighted key regions and using phenethylamine and amphetamine as the progenitor template.

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.

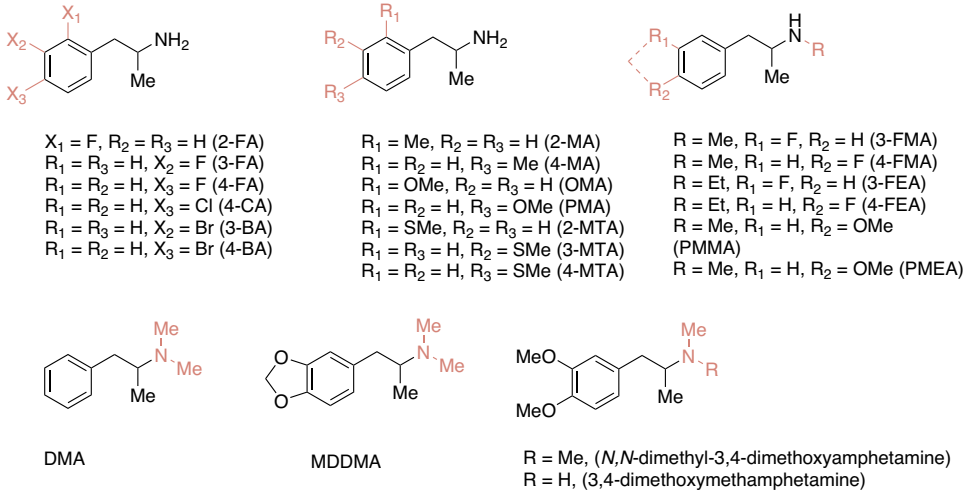


Figure 34: Chemical structures of mono- and N-alkyl-substituted phenethylamines.

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).

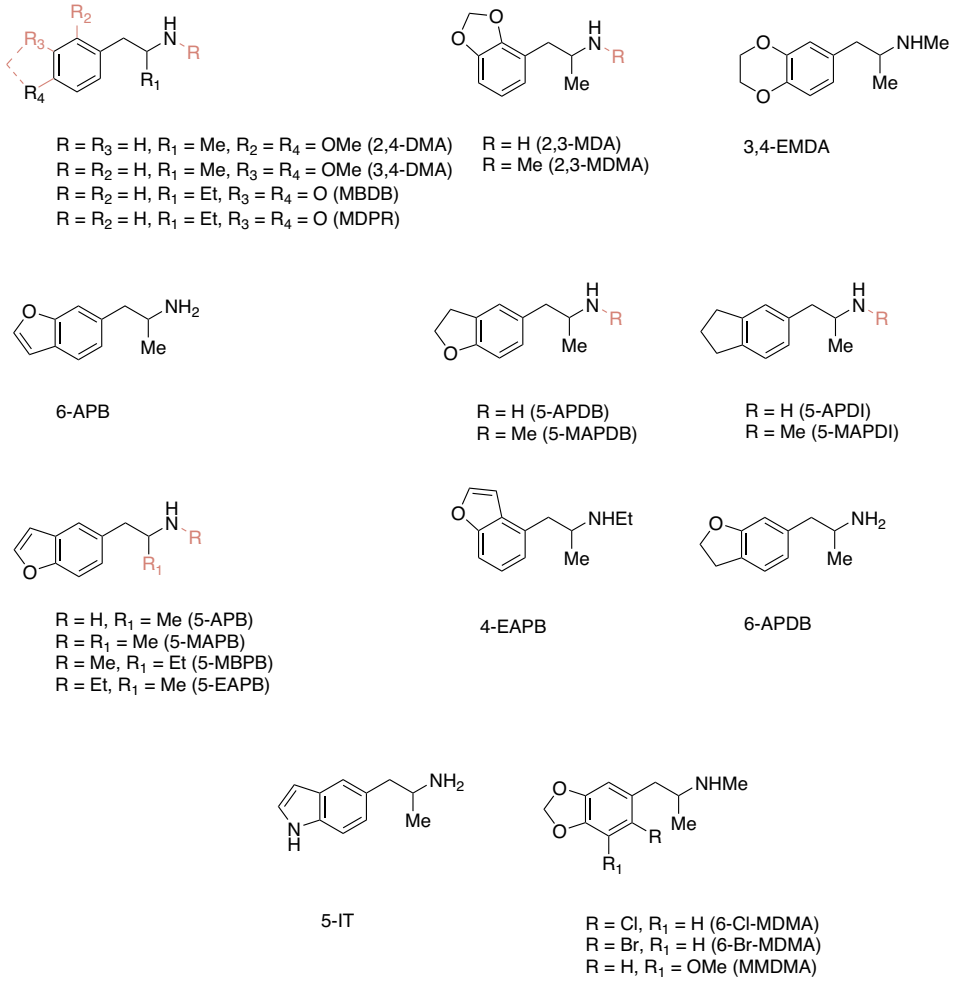


Figure 35: Chemical structures of di-substituted phenethylamines.

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.

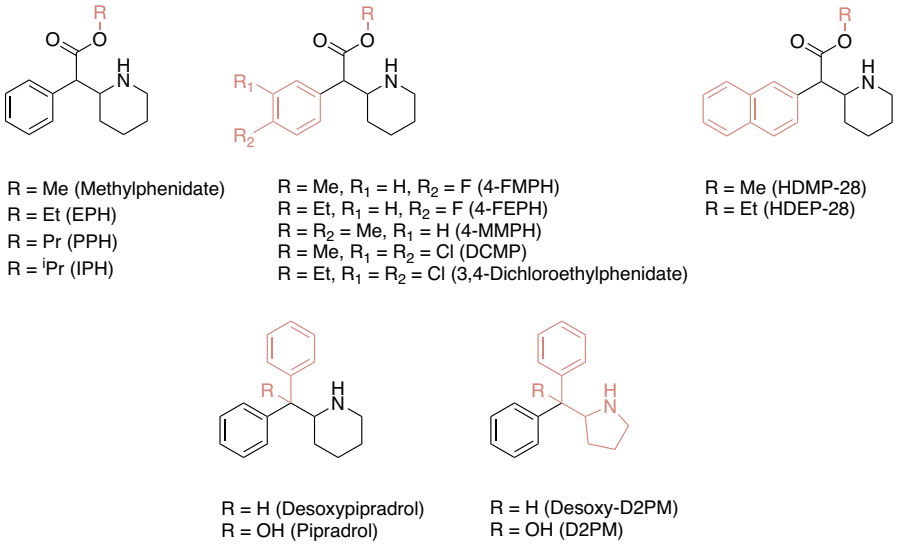


Figure 36: Chemical structures of methylphenidate derived NPS. The structural differences are highlighted in red.

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**).

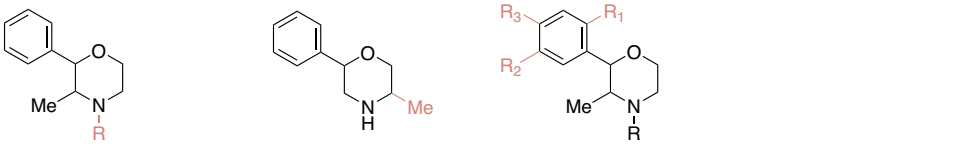
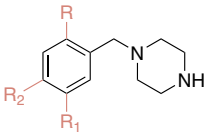


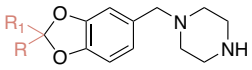
Figure 37: Chemical structures of phenylmorpholine derived NPS. The structural differences are highlighted in red.

Piperazines

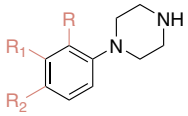
Piperazines are a group of stimulants that have been considered *"failed pharmaceuticals."* Some of them had been evaluated as potential therapeutic agents by pharmaceutical companies but never brought to the market [6, 180–193]. While the best-known piperazine that has been used as an NPS is 1-benzylpiperazine (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.



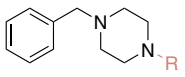
R = R_1 = R_2 = H (BZP)
R = R_2 = H, R_1 = Me (3-MeBZP)
R = R_1 = OMe, R_2 = Br (2C-B-BZP)
R = R_1 = H, R_2 = F (4-FBZP)



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.

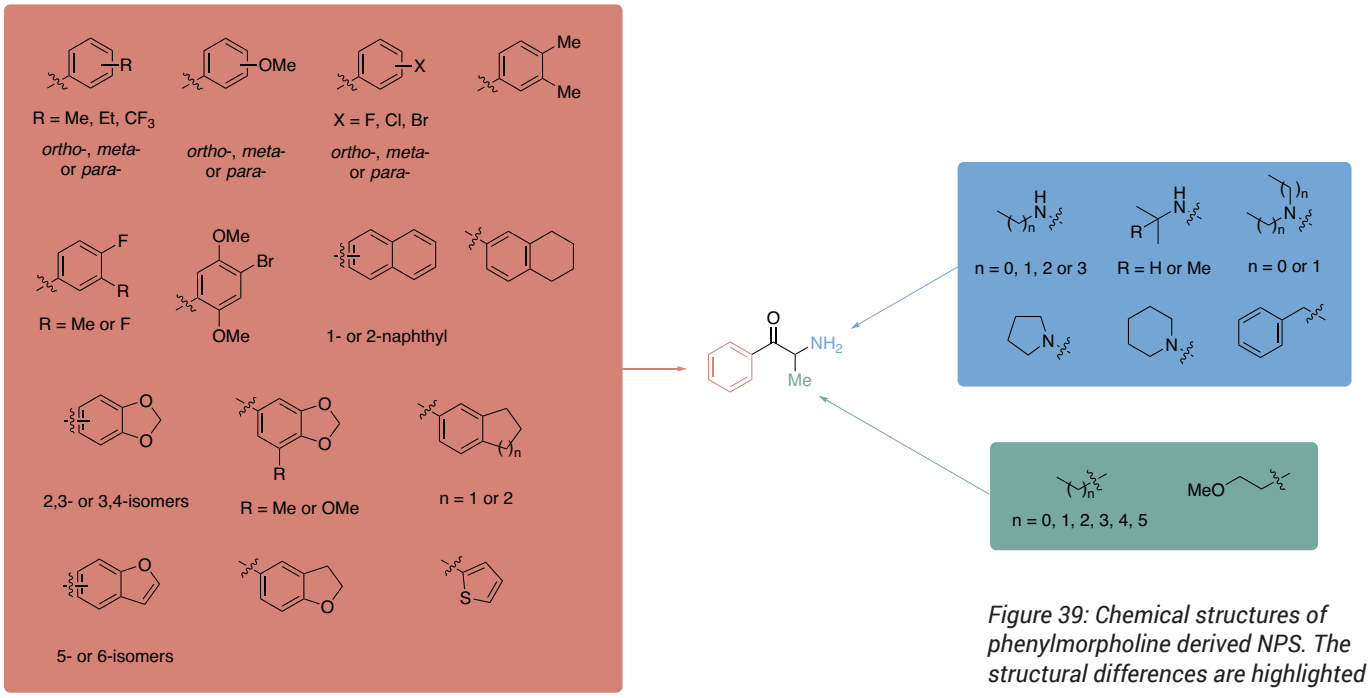
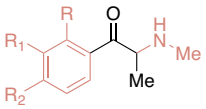


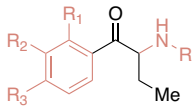
Figure 39: Chemical structures of phenylmorpholine derived NPS. The structural differences are highlighted in red.

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-

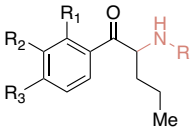
tion of a methylenedioxy- group to the aromatic ring (either the 2,3- or 3,4-isomer) and a pyrrolidinyl substitution in the amino group and possible alkyl substitutions both in the a-carbon of the side chain and in the aromatic ring (**Figure 40 and 41**). Additionally, synthetic cathinone presenting unique structures such as bk-2C-B, 1-naphythyl- (a-naphyrone), 2-naphthyl- (b-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.



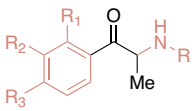
R = = R_1 = R_2 = H (Methcathinone)
R = F, R_1 = R_2 = H (2-FMC)
R = R_2 = H, R_1 = F (3-FMC)
R = R_1 = H, R_2 = F (4-FMC)
R = Cl, R_1 = R_2 = H (2-CMC)
R = R_2 = H, R_1 = Cl (3-CMC)
R = R_1 = H, R_2 = Cl (4-CMC)
R = R_2 = H, R_1 = Br (3-BMC)
R = R_1 = H, R_2 = Br (4-BMC)
R = Me, R_1 = R_2 = H (2-MMC)
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)



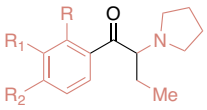
R = Me, R_1 = R_2 = R_3 = H (Pentedrone)
R = Me, R_1 = R_2 = H, R_3 = F (4-F-pentedrone)
R = Me, R_1 = R_2 = H, R_3 = Cl (4-Cl-pentedrone)
R = R_3 = Me, R_1 = R_2 = H (4-Me-pentedrone)
R = Et, R_1 = R_2 = R_3 = H (*N*-ethylpentedrone)
R = Et, R_1 = R_2 = H, R_3 = F (4-F-*N*-ethylpentedrone)
R = Et, R_1 = 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)



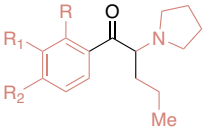
R = Et, R_1 = R_2 = R_3 = H (Ethcathinone)
R = Et, R_1 = F, R_2 R_3 = H (2-FEC)
R = Et, R_1 = R_3 = H, R_2 = F (3-FEC)
R = Et, R_1 = R_2 = H, R_3 = F (4-FEC)
R = Et, R_1 = Cl, R_2 R_3 = H (2-CEC)
R = Et, R_1 = R_3 = H, R_2 = Cl (3-CEC)
R = Et, R_1 = R_2 = H, R_3 = Cl (4-CEC)
R = Et, R_1 = R_2 = H, R_3 = 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.

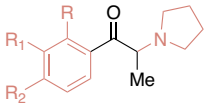
The history, chemistry, and pharmacological action of synthetic cathinones have been the subject of several reviews [6, 185, 194–228]. Currently, synthetic cathinones represent the largest group of psychostimulants that are monitored by UNODC, with over 200 individual substances having been reported.



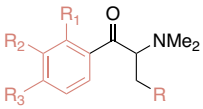
R = R_1 = R_2 = H (-PBP)
R = R_1 = H, R_2 = F (4-F-PBP)
R = R_1 = H, R_2 = OMe (4-MeO- -PBP)



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

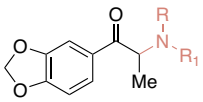


R = R_1 = H, R_2 = Cl (4-Cl- -PPP)
R = R_1 = H, R_2 = Br (4-Br- -PPP)
R = R_2 = H, R_1 = Me (3-MePPP)
R = R_1 = H, R_2 = Me (MPPP)
R = R_2 = H, R_1 = Me (3-MeO- -PPP)
R = R_1 = H, R_2 = OMe (MOPPP)

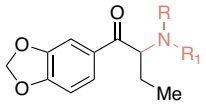


R = R_1 = R_2 = R_3 = H (Metamfepramone)
R = R_1 = R_2 = H, R_3 = Cl (4-CDMC)
R = R_1 = R_2 = H, R_3 = Me (4-MDMC)
R = R_3 = Me, R_1 = R_2 = H (4-Me-*N*-methylbuphedrone)
R = Et, R_1 = R_2 = H, R_3 = Me (4-Me-*N*-methylpentedrone)

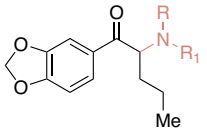
Figure 41: Chemical structures of N-alkyl- and N-pyrrolidine cathinone derived NPS. The structural differences are highlighted in red.



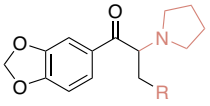
R = R_1 = H (bk-MDA)
R = H, R_1 = Me (Methylone)
R = H, R_1 = Et (Ethylone)
R = H, R_1 = Bn (Benzylone)
R = R_1 = Me (Dimethylone)
R = R_1 = Et (Diethylone)



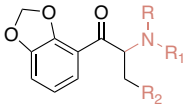
R = H, R_1 = Me (Butylone)
R = H, R_1 = Et (Eutylone)
R = R_1 = Me (Dibutylone)



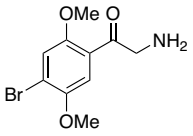
R = H, R_1 = Me (Pentylone)
R = H, R_1 = Et (*N*-ethylpentylone)
R = R_1 = Me (Dipentylone)



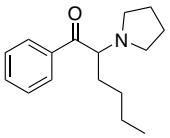
R = H (MDPPP)
R = Me (MDPBP)
R = Et (MDPV)
R = Pr (MDPHP)



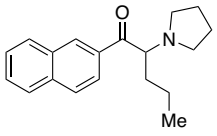
R = R_2 = H, R_1 = Me (2,3-MDMC)
R = H, R_1 = Me, R_2 = Et (2,3-Pentylone)
R = R_1 = Me, R_2 = Et (2,3-Dipentylone)



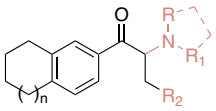
bk-2C-B



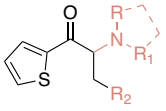
-PHP



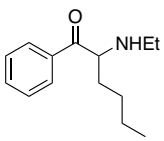
-Naphryone (O-2482)



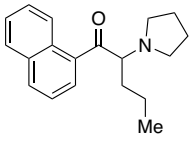
n = 0, R = R_2 = H, R_1 = Me (bk-IMP)
n = 0, R = H, R_2 = Me, R_1 = Et (bk-IBP)
n = 0, R = H, R_1 = R_2 = Et (bk-IVP)
n = 0, R = R_1 = CH_2, R_2 = Me (5-PPDI)
n = 0, R = R_1 = CH_2, R_2 = Et (5-BPDI)
n = 0, R = R_1 = CH_2, R_2 = Pr (5-HPDI)
n = 1, R = R_1 = CH_2, R_2 = Me (TH-PBP)
n = 1, R = R_1 = CH_2,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



N-ethylhexedrone



-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)

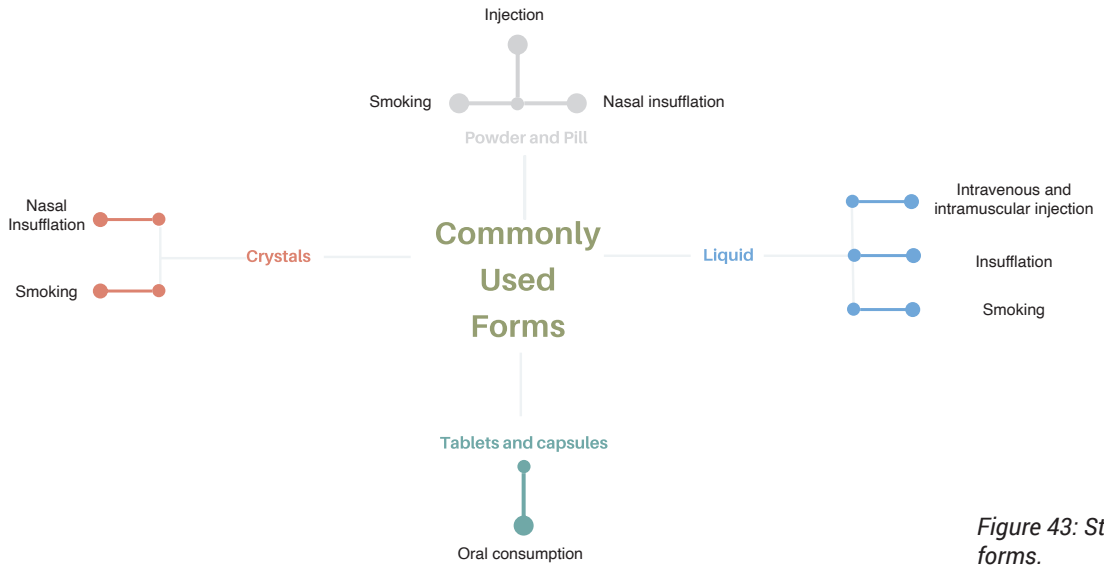


Figure 43: Stimulants commonly used forms.

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].

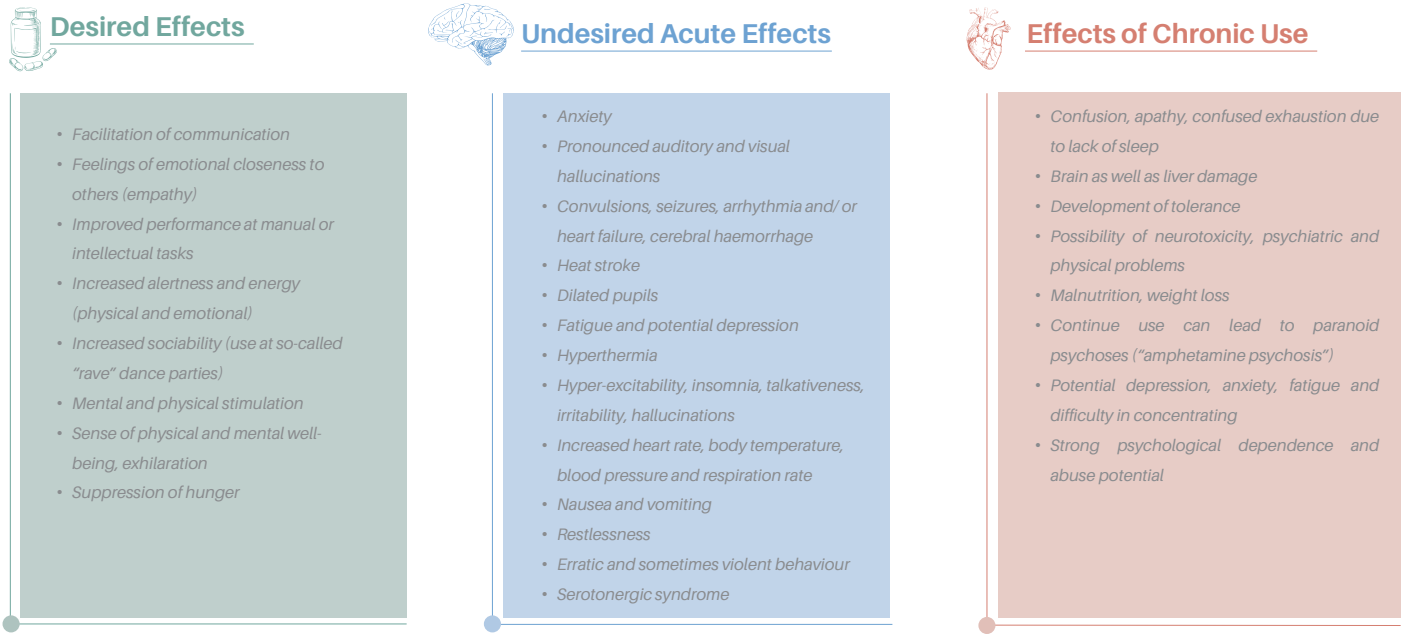


Figure 44: Reported effects of stimulants.

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**).

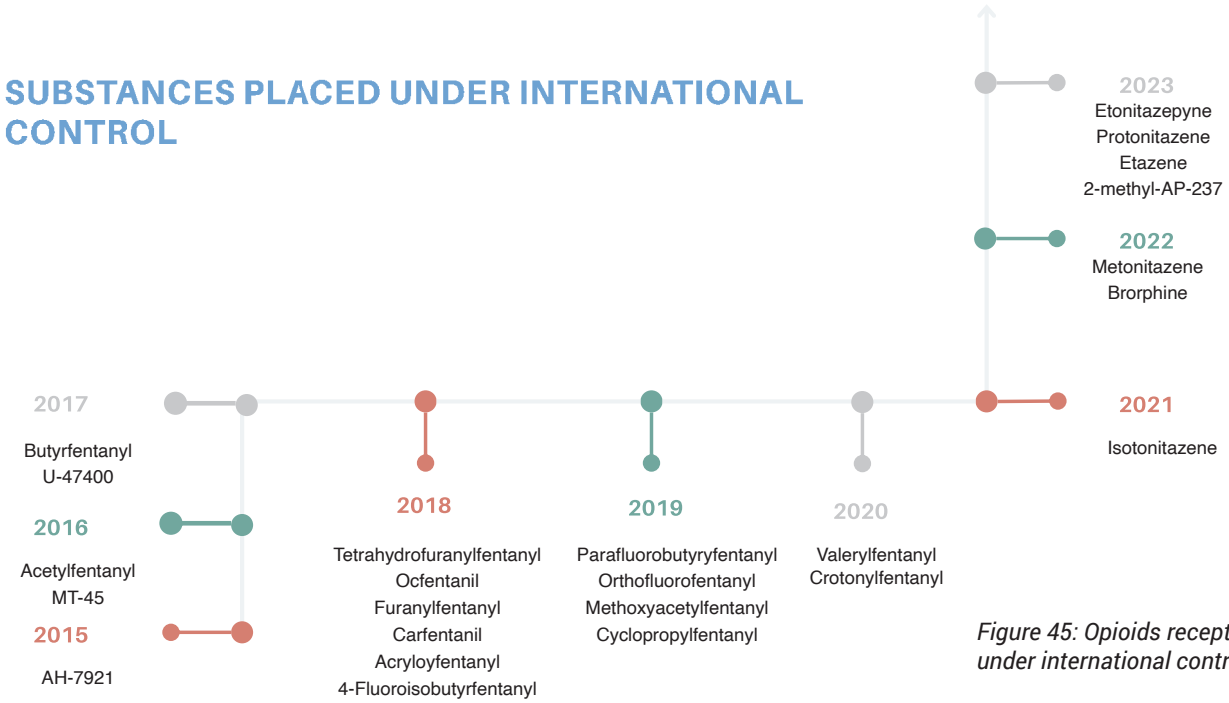


Figure 45: Opioids receptor agonists placed under international control since 2015.

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)**.

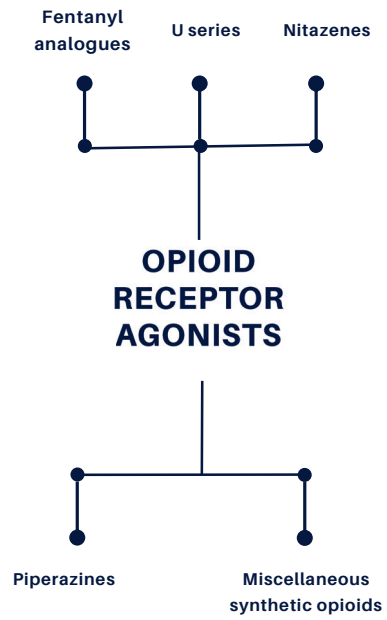


Figure 46: Opioid receptor agonists sub-groups.

Fentanyl analogues

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

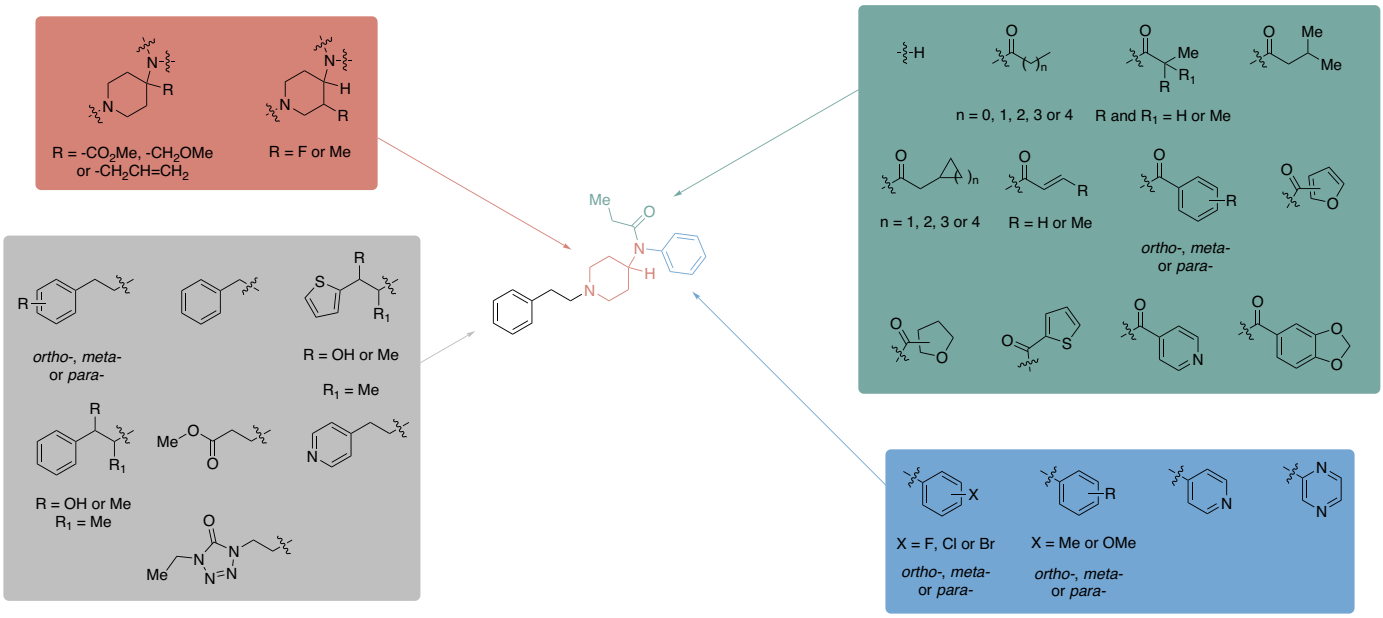
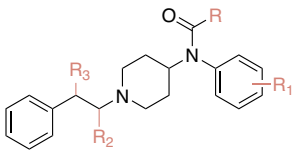
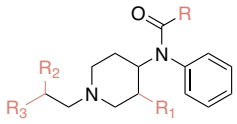


Figure 47: Generic structural representation of fentanyl analogues obtained by modification of the highlighted key regions and using fentanyl as the template.

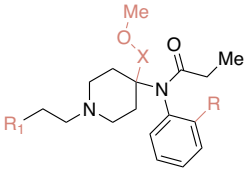
While four fentanyl analogues (alfentanil, remifentanil, sufentanil and fentanyl itself) have been approved for medical use to manage severe pain and in anaesthesia, many fentanyl analogues are derived from substances that have been researched for pharmaceutical use but have never been marketed. More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



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

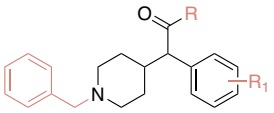


R = Et, R_1 = F, R_2 = H, R_3 = Ph (3-fluorofentanyl)

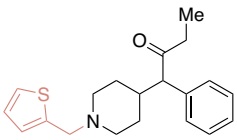


R = H, R_1 = Ph, X = CO (carfentanil)
R = F, R_1 = Ph, X = CH_2 (ocfentanil)

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)

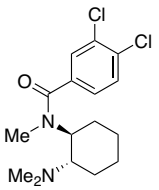


thienylfentanyl

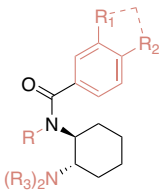
Figure 48: Common fentanyl analogues NPS. Structural differences are highlighted in red.

U-Series

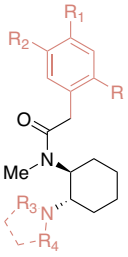
A second sub-group of opioid receptor agonists that have been reported to UNODC are the *"U-Series"* compounds. The substances can be differentiated into two families, the cyclohexylbenzamides (e.g., U-47700 and AH-7921) and phenylacetamides (e.g., U-48800, U-50488, and U-51754) (**Figure 49**).



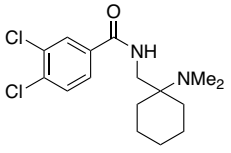
U-47700



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)



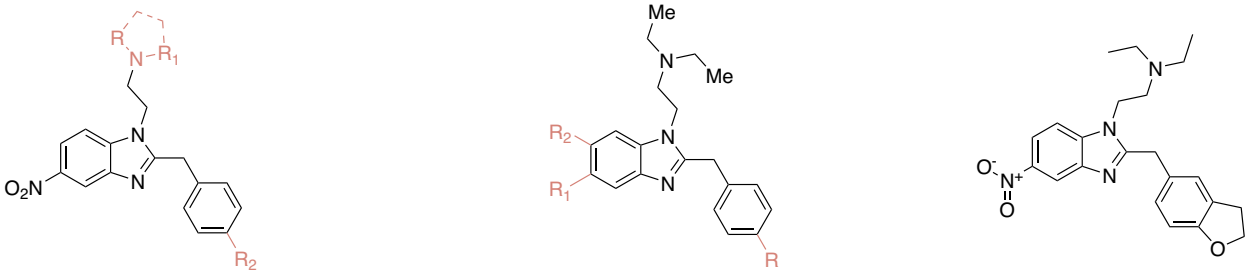
AH-7921

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

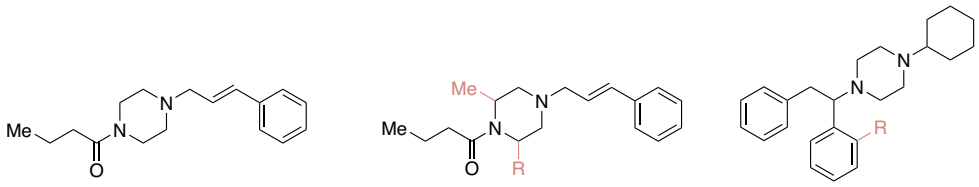
Figure 50: Common nitazene NPS. The structural differences are highlighted in red.

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 more than 10 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.

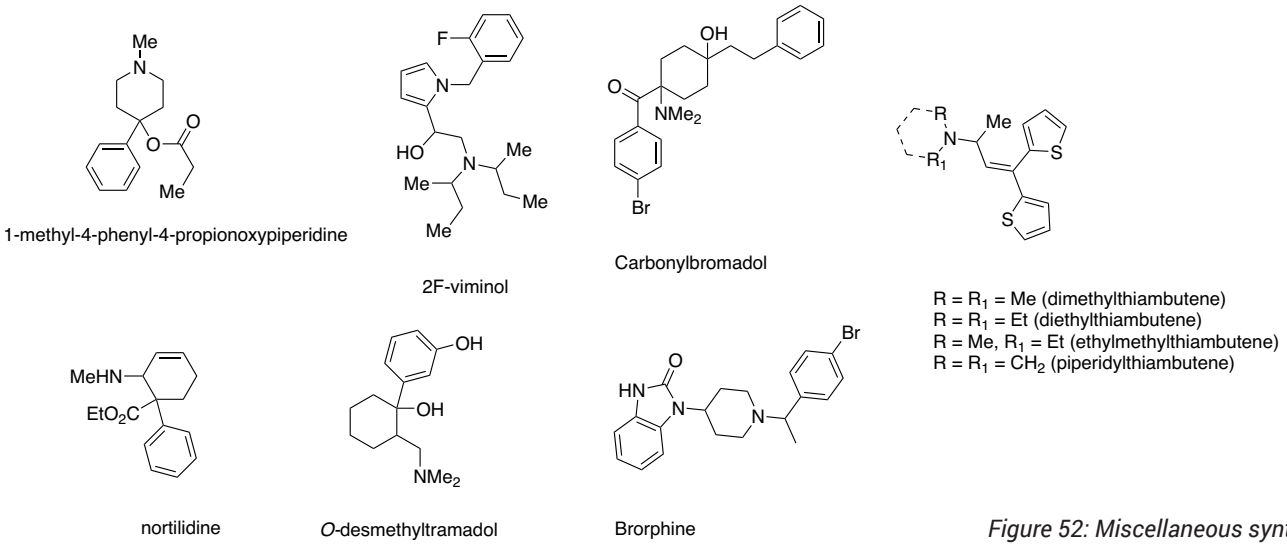


Figure 52: Miscellaneous synthetic opioids.

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.

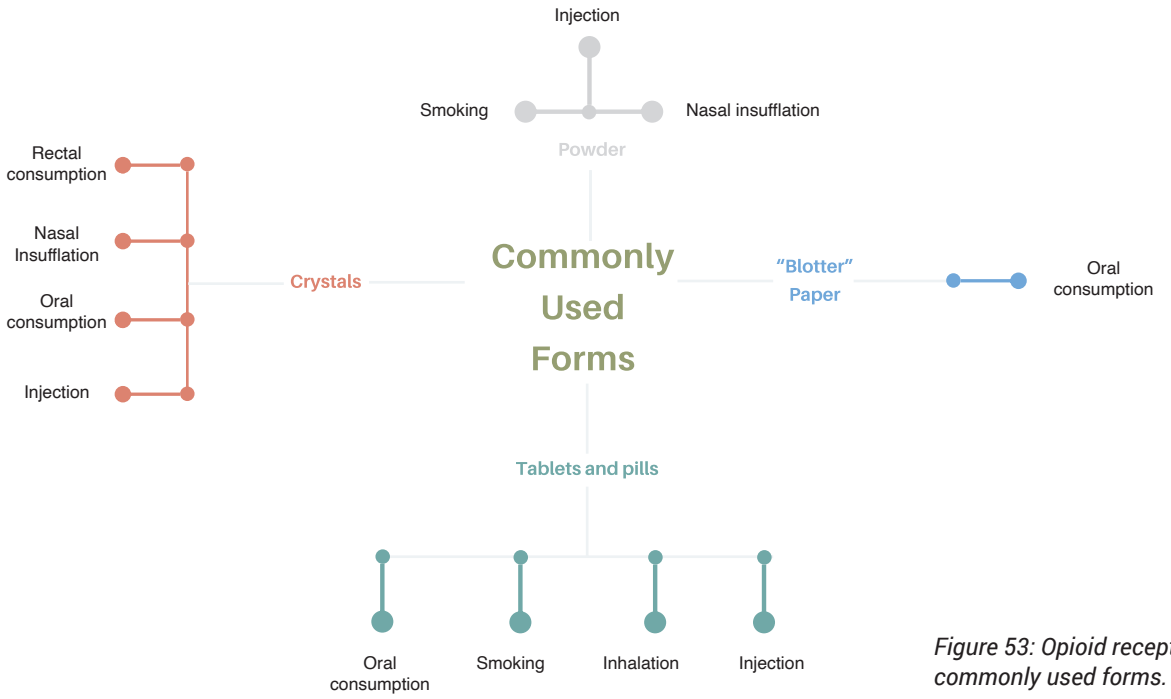


Figure 53: Opioid receptor agonists commonly used forms.

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

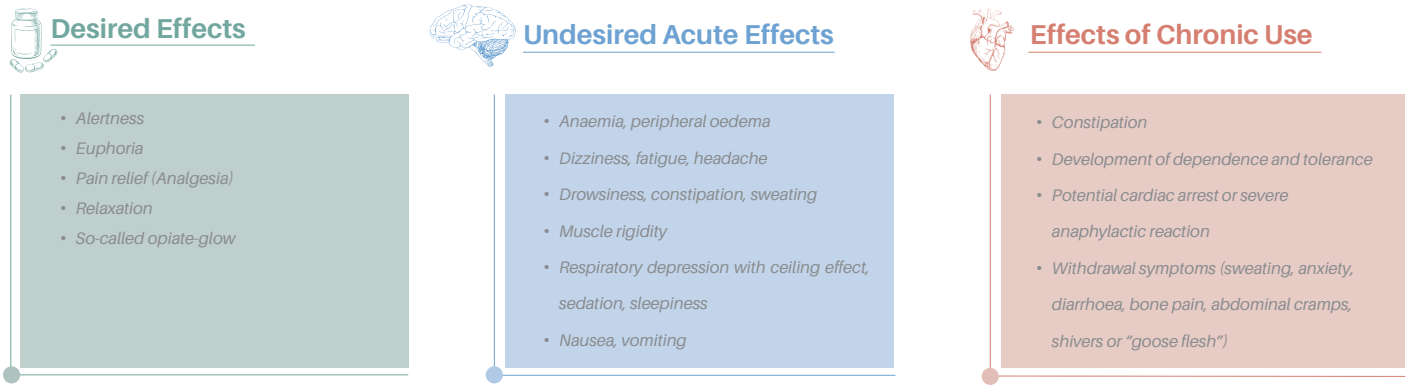


Figure 54: Reported effects of opioid receptor agonists.

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)**.

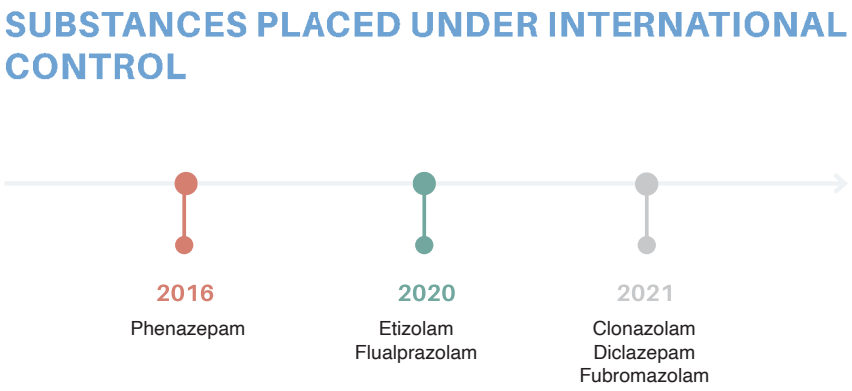


Figure 55: Sedatives placed under international control since 2015.

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**).

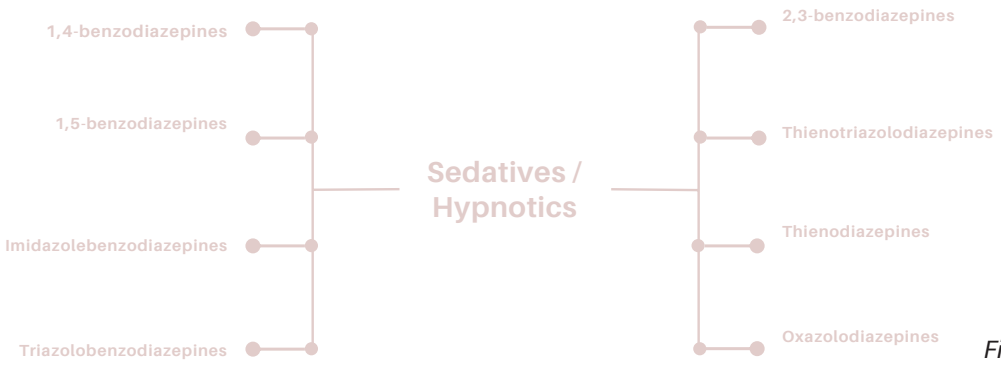


Figure 56: Sedatives sub-groups.

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**).

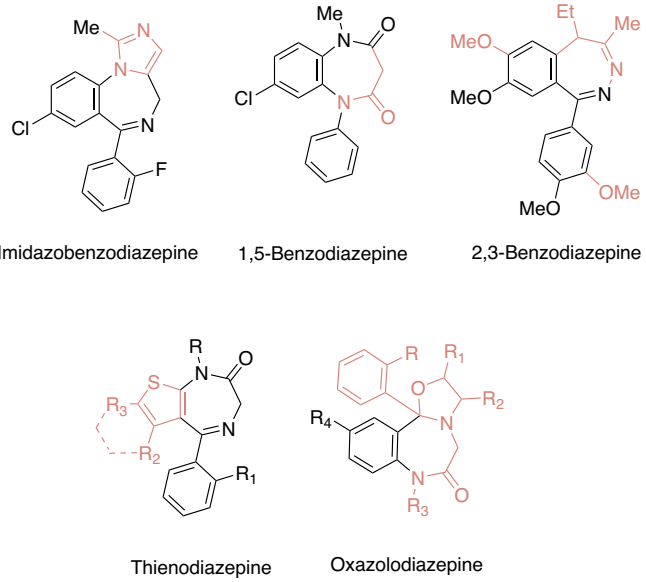
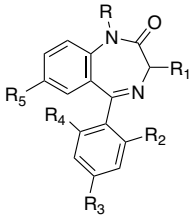


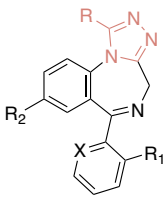
Figure 57: Chemical structures of five sub-families of benzodiazepines (BZDs). The structural differences between these families and the 1,4-benzodiazepine core are highlighted in red.



1,4-Benzodiazepine

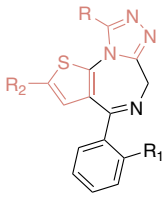
R = Me, R_1 = R_3 = R_4 = H, R_2 = R_5 = Cl (Diclazepam)
R = R_1 = R_3 = R_4 = H, R_2 = F, R_5 = Br (Flubromazepam)
R = R_3 = R_4 = H, R_1 = OH, R_2 = F, R_5 = NO_2 (Nifoxipam)
R = R_3 = R_4 = H, R_1 = Me, R_2 = Cl, R_5 = NO_2 (Meclonazepam)
R = R_3 = R_4 = H, R_1 = OH, R_2 = Cl, R_5 = Br (3-Hydroxyphenazepam)
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)**.

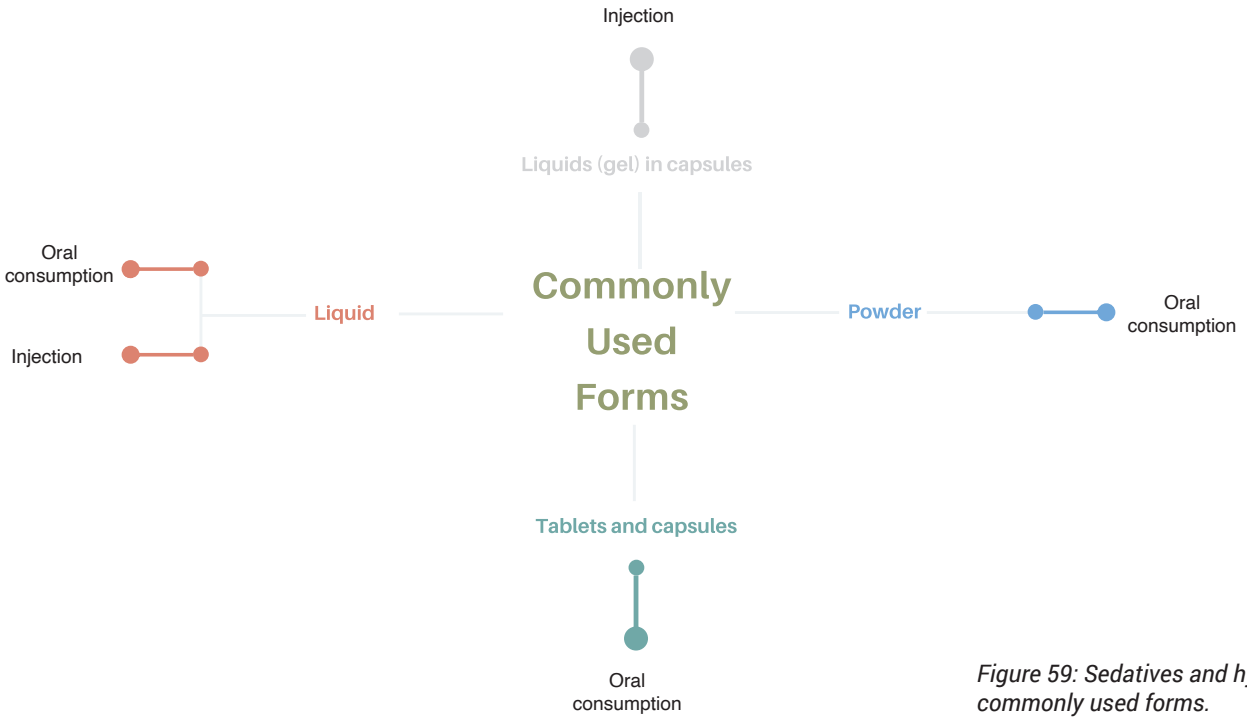


Figure 59: Sedatives and hypnotics commonly used forms.

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)**.

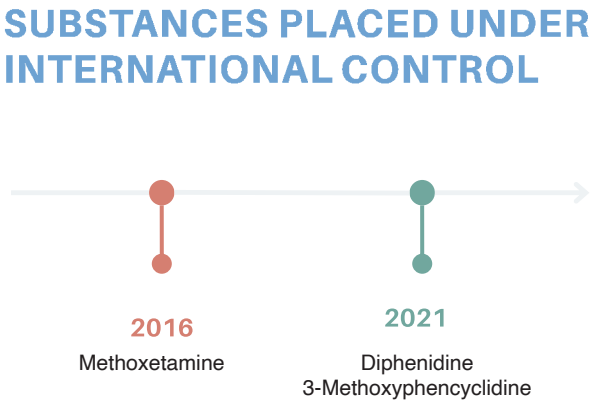


Figure 62: Dissociatives placed under international control since 2015.

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**).

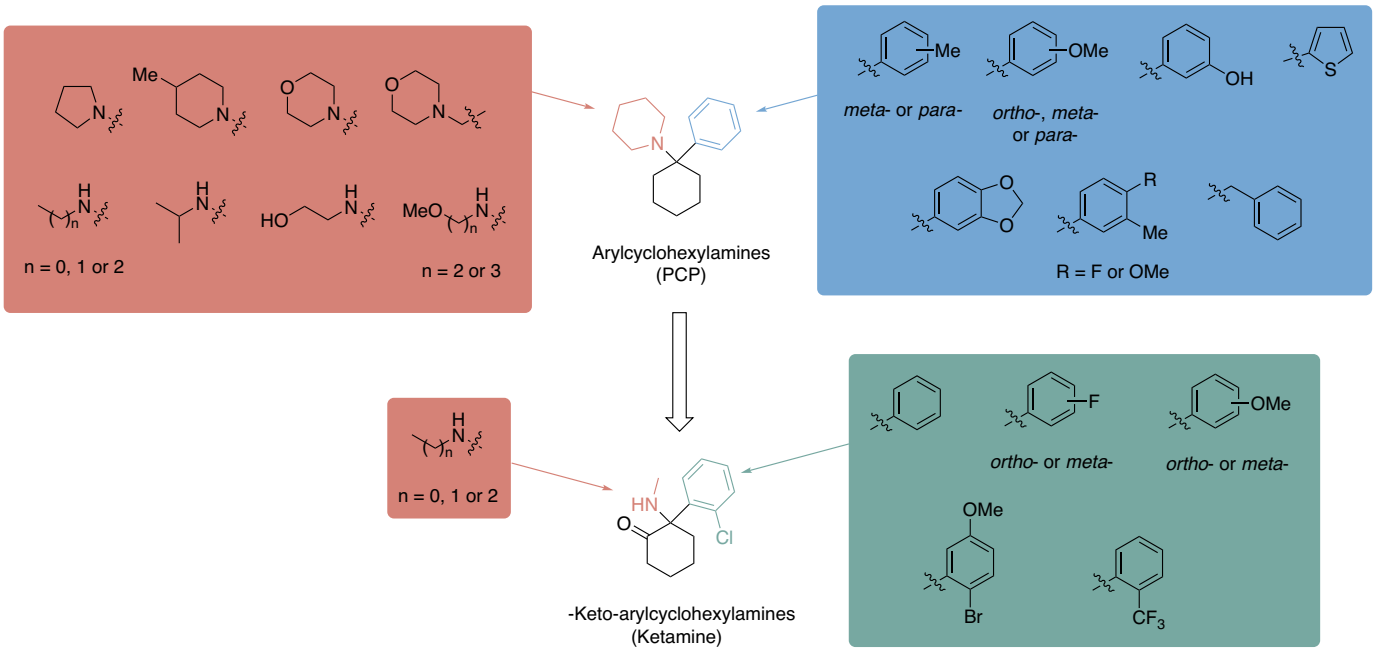


Figure 63: Generic structural representation of phencyclidine and ketamine derived dissociatives obtained by modification of the highlighted key regions and using phencyclidine (PCP) and ketamine as the progenitor template.

-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**).

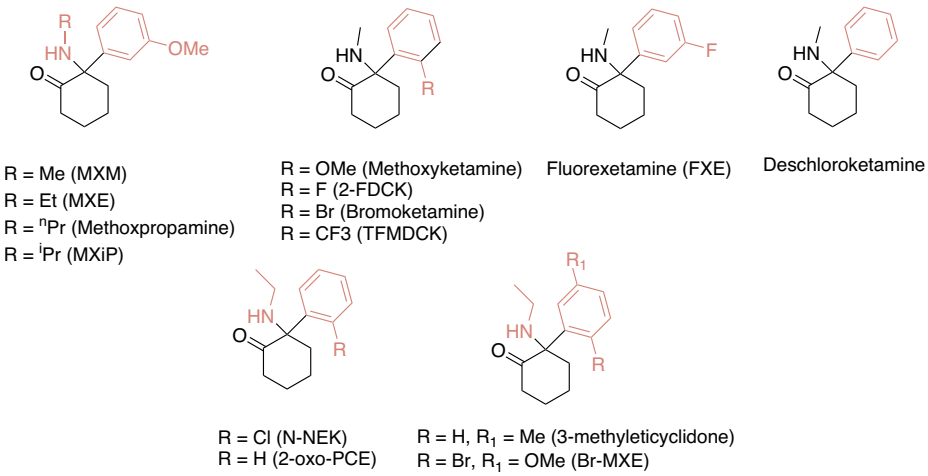


Figure 64: Common ketamine-derived (beta-keto-arylcyclohexylamine) NPS. The structural differences between these compounds and ketamine are highlighted in red.

In the same way that arylcylohexylamines share commonality with PCP, -keto-arylcyclohexylamines, are structurally related to the dissociative anaesthetic, ketamine. Like the PCP-derived NPS, several -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 -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)**.

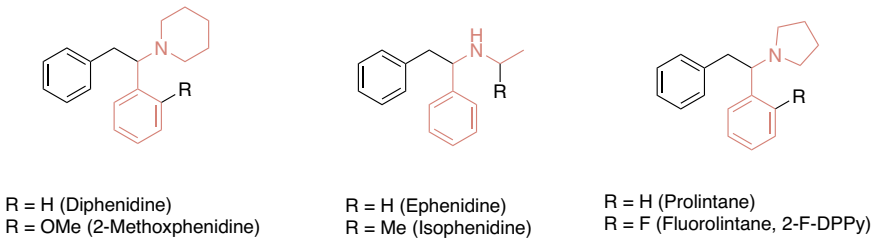


Figure 65: Common 1,2-diarylethylamine-derived NPS. The structural similarity between 1,2-diarylethylamines and arylcyclohexylamines (PCP, PCE and PHP) are highlighted in red.

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).**

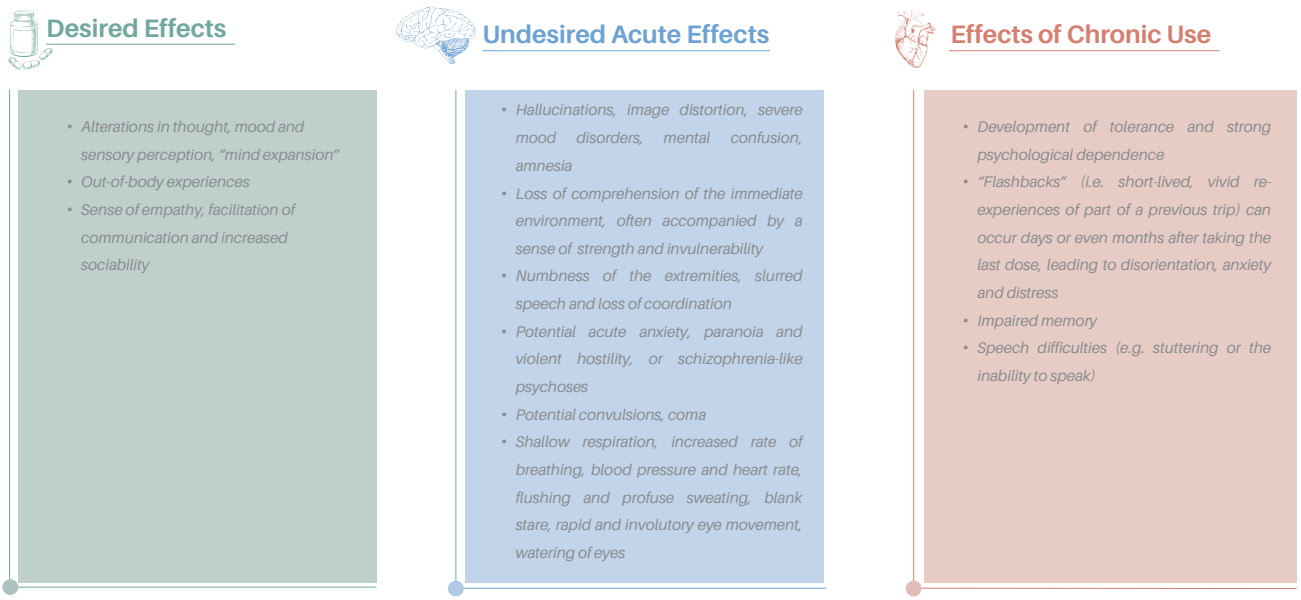


Figure 67: Reported effects of dissociatives.

References

1 Orsolini, L. *et al.* Novel psychoactive substances. *Eur Psychiat* 33, S59-S60 (2016). https://doi.org/10.1016/j.eurpsy.2016.01.945

2 Shafi, A., Berry, A. J., Sumnall, H., Wood, D. M. & Tracy, D. K. New psychoactive substances: a review and updates. *Ther Adv Psychopharm* 10 (2020). https://doi.org/Artn 2045125320967197 10.1177/2045125320967197

3 Tettey, J. N. A., Crean, C., Ifeagwu, S. C. & Raithelhuber, M. Emergence, Diversity, and Control of New Psychoactive Substances: A Global Perspective. *Handb Exp Pharmacol* 252, 51-67 (2018). https://doi.org/10.1007/164_2018_127

4 Banister, S. D. & Connor, M. The Chemistry and Pharmacology of Synthetic Cannabinoid Receptor Agonist New Psychoactive Substances: Evolution. *Handb Exp Pharmacol* 252, 191-226 (2018). https://doi.org/10.1007/164_2018_144

5 Banister, S. D. & Connor, M. The Chemistry and Pharmacology of Synthetic Cannabinoid Receptor Agonists as New Psychoactive Substances: Origins. *Handb Exp Pharmacol* 252, 165-190 (2018). https://doi.org/10.1007/164_2018_143

6 UNODC. The Challenge of New Psychoactive Substances. A Report from the Global SMART programme. (Laboratory and Scientific Section, United Nations Office on Drugs and Crime (UNODC), 2013).

7 Banister, S. D., Arnold, J. C., Connor, M., Glass, M. & McGregor, I. S. Dark Classics in Chemical Neuroscience: Delta(9)-Tetrahydrocannabinol. *Acs Chem Neurosci* 10, 2160-2175 (2019). https://doi.org/10.1021/acschemneuro.8b00651

8 Worob, A. & Wenthur, C. DARK Classics in Chemical Neuroscience: Synthetic Cannabinoids (Spice/K2). *Acs Chem Neurosci* 11, 3881-3892 (2020). https://doi.org/10.1021/acschemneuro.9b00586

9 Corazza, O. *et al.* "Spice," "Kryptonite," "Black Mamba": An Overview of Brand Names and Marketing Strategies of Novel Psychoactive Substances on the Web. *J Psychoactive Drugs* 46, 287-294 (2014). https://doi.org/10.1080/02791072.2014.944291

10 Graziano, S. *et al.* Herbal Highs: Review on Psychoactive Effects and Neuropharmacology. *Curr Neuropharmacol* 15, 750-761 (2017). https://doi.org/10.2174/1570159x14666161031144427

11 Mechoulam, R., Breuer, A., Jarbe, T. U. C., Hiltunen, A. J. & Glaser, R. Cannabimimetic Activity of Novel Enantiomeric, Benzofuran Cannabinoids. *J Med Chem* 33, 1037-1043 (1990). https://doi.org/DOI 10.1021/jm00165a024

12 Mechoulam, R. *et al.* Enantiomeric Cannabinoids - Stereospecificity of Psychotropic Activity. *Experientia* 44, 762-764 (1988). https://doi.org/Doi 10.1007/Bf01959156

13 Mechoulam, R., Lander, N., Breuer, A. & Zahalka, J. Synthesis of the Individual, Pharmacologically Distinct, Enantiomers of a Tetrahydrocannabinol Derivative. *Tetrahedron-Asymmetr* 1, 315-318 (1990). https://doi.org/Doi 10.1016/S0957-4166(00)86322-3

14 Weissman, A., Milne, G. M. & Melvin, L. S., Jr. Cannabimimetic activity from CP-47,497, a derivative of 3-phenylcyclohexanol. *J Pharmacol Exp Ther* 223, 516-523 (1982).

15 Tettey, J. N. A. *et al.* United Nations Office on Drugs and Crime: Recommended methods for the Identification and Analysis of Synthetic Cannabinoid Receptor Agonists in Seized Materials. *Forensic Sci Int Synerg* 3, 100129 (2021). https://doi.org/10.1016/j.fsisyn.2020.11.003

16 Auwärter, V. Synthetic cannabinoids in Europe – a review. (European Monitoring Centre for Drugs and Drug Addiction, Publications Office of the European Union, Luxembourg, 2021).

17 Huffman, J. W. & Padgett, L. W. Recent developments in the medicinal chemistry of cannabimimetic indoles, pyrroles and indenes. *Curr Med Chem* 12, 1395-1411 (2005). https://doi.org/10.2174/0929867054020864

18 Alves, V. L., Goncalves, J. L., Aguiar, J., Teixeira, H. M. & Camara, J. S. The synthetic cannabinoids phenomenon: from structure to toxicological properties. A review. *Crit Rev Toxicol* 50, 359-382 (2020). https://doi.org/10.1080/10408444.2020.1762539

19 Makriyannis, A. Preparation of cannabimimetic indole derivatives with cannabinoid CB1 or CB2 receptor binding affinity (2001).

20 Shevyrin, V. A. & Morzherin, Y. Y. Cannabinoids: structures, effects, and classification. *Russ Chem B+* 64, 1249-1266 (2015). https://doi.org/10.1007/s11172-015-1008-1

21 Lindigkeit, R. *et al.* Spice: A never ending story? *Forensic Sci Int* 191, 58-63 (2009). https://doi.org/10.1016/j.forsciint.2009.06.008

22 Huffman, J. W., Dai, D., Martin, B. R. & Compton, D. R. Design, Synthesis and Pharmacology of Cannabimimetic Indoles. *Bioorg Med Chem Lett* 4, 563-566 (1994). https://doi.org/Doi 10.1016/S0960-894x(01)80155-4

23 Wiley, J. L. *et al.* Structure-activity relationships of indole- and pyrrole-derived cannabinoids. *J Pharmacol Exp Ther* 285, 995-1004 (1998).

24 Aung, M. M. *et al.* Influence of the N-1 alkyl chain length of cannabimimetic indoles upon CB1 and CB2 receptor binding. *Drug Alcohol Depen* 60, 133-140 (2000). https://doi.org/Doi 10.1016/S0376-8716(99)00152-0

25 Banister, S. D. *et al.* Effects of Bioisosteric Fluorine in Synthetic Cannabinoid Designer Drugs JWH-018, AM-2201, UR-144, XLR-11, PB-22, 5F-PB-22, APICA, and STS-135. *Acs Chem Neurosci* 6, 1445-1458 (2015). https://doi.org/10.1021/acschemneuro.5b00107

26 Wilkinson, S. M., Banister, S. D. & Kassiou, M. Bioisosteric Fluorine in the Clandestine Design of Synthetic Cannabinoids. *Aust J Chem* 68, 4-8 (2015). https://doi.org/10.1071/Ch14198

27 Huffman, J. W. *et al.* Structure-activity relationships for 1-alkyl-3-(l-naphthoyl) indoles at the cannabinoid CB1 and CB2 receptors: steric and electronic effects of naphthoyl substituents. New highly selective CB2 receptor agonists. *Bioorgan Med Chem* 13, 89-112 (2005). https://doi.org/10.1016/j.bmc.2004.09.050

28 Huffman, J. W. *et al.* 3-indolyl-1-naphthylmethanes: New cannabimimetic Indoles provide evidence for aromatic stacking interactions with the CB1 cannabinoid receptor. *Bioorgan Med Chem* 11, 539-549 (2003). https://doi.org/Pii S0968-0896(02)00451-0 Doi 10.1016/S0968-0896(02)00451-0

29 Huffman, J. W. *et al.* 1-Pentyl-3-phenylacetylindoles, a new class of cannabimimetic indoles. *Bioorg Med Chem Lett* 15, 4110-4113 (2005). https://doi.org/10.1016/j.bmcl.2005.06.008

30 Manera, C., Tuccinardi, T. & Martinelli, A. Indoles and related compounds as cannabinoid ligands. *Mini-Rev Med Chem* 8, 370-387 (2008). https://doi.org/Doi 10.2174/138955708783955935

31 Wiley, J. L., Marusich, J. A., Martin, B. R. & Huffman, J. W. 1-Pentyl-3-phenylacetylindoles and JWH-018 share in vivo cannabinoid profiles in mice. *Drug Alcohol Depen* 123, 148-153 (2012). https://doi.org/10.1016/j.drugalcdep.2011.11.001

32 Deng, H. F. *et al.* Potent cannabinergic indole analogues as radioiodinatable brain imaging agents for the CB1 cannabinoid receptor. *J Med Chem* 48, 6386-6392 (2005). https://doi.org/10.1021/jm050135l

33 Jankovics, P. *et al.* Detection and identification of the new potential synthetic cannabinoids 1-pentyl-3-(2-iodobenzoyl)indole and 1-pentyl-3-(1-adamantoyl) indole in seized bulk powders in Hungary. *Forensic Sci Int* 214, 27-32 (2012). https://doi.org/10.1016/j.forsciint.2011.07.011

34 Willis, P. G., Katoch-Rouse, R. & Horti, A. G. Regioselective F-18 radiolabeling of AM694, a CB1 cannabinoid receptor ligand. *J Labelled Compd Rad* 46, 799-804 (2003). https://doi.org/10.1002/jlcr.720

35 Banister, S. D. *et al.* The synthesis and pharmacological evaluation of adamantane-derived indoles: cannabimimetic drugs of abuse. *ACS Chem Neurosci* 4, 1081-1092 (2013). https://doi.org/10.1021/cn400035r

36 Frost, J. M. *et al.* Indol-3-yl-tetramethylcyclopropyl ketones: Effects of indole ring substitution on CB(2) cannabinoid receptor activity. *J Med Chem* 51, 1904-1912 (2008). https://doi.org/10.1021/jm7011613

37 Uchiyama, N., Kawamura, M., Kikura-Hanajiri, R. & Goda, Y. URB-754: A new class of designer drug and 12 synthetic cannabinoids detected in illegal products. *Forensic Sci Int* 227, 21-32 (2013). https://doi.org/10.1016/j.forsciint.2012.08.047

38 Diao, X. X., Wohlfarth, A., Pang, S. K., Scheidweiler, K. B. & Huestis, M. A. High-Resolution Mass Spectrometry for Characterizing the Metabolism of Synthetic Cannabinoid THJ-018 and Its 5-Fluoro Analog THJ-2201 after Incubation in Human Hepatocytes. *Clin Chem* 62, 157-169 (2016). https://doi.org/10.1373/clinchem.2015.243535

39 Hess, C., Schoeder, C. T., Pillaiyar, T., Madea, B. & Muller, C. E. Pharmacological evaluation of synthetic cannabinoids identified as constituents of spice. *Forensic Toxicol* 34, 329-343 (2016). https://doi.org/10.1007/s11419-016-0320-2

40 Shevyrin, V. *et al.* 3-Naphthoylindazoles and 2-naphthoylbenzoimidazoles as novel chemical groups of synthetic cannabinoids: Chemical structure elucidation, analytical characteristics and identification of the first representatives in smoke mixtures (vol 242, pg 72, 2014). *Forensic Sci Int* 249, 280-280 (2015). https://doi.org/10.1016/j.forsciint.2015.02.016

41 Banister, S. D. *et al.* Pharmacology of Valinate and tert-Leucinate Synthetic Cannabinoids 5F-AMBICA, 5F-AMB, 5F-ADB, AMB-FUBINACA, MDMB-

FUBINACA, MDMB-CHMICA, and Their Analogues. *ACS Chem Neurosci* 7, 1241-1254 (2016). https://doi.org/10.1021/acschemneuro.6b00137

42 Banister, S. D. *et al.* Pharmacology of Indole and Indazole Synthetic Cannabinoid Designer Drugs AB-FUBINACA, ADB-FUBINACA, AB-PINACA, ADB-PINACA, 5F-AB-PINACA, 5F-ADB-PINACA, ADBICA, and 5F-ADBICA. *ACS Chem Neurosci* 6, 1546-1559 (2015). https://doi.org/10.1021/acschemneuro.5b00112

43 Wohlfarth, A. *et al.* Metabolism of synthetic cannabinoids PB-22 and its 5-fluoro analog, 5F-PB-22, by human hepatocyte incubation and high-resolution mass spectrometry. *Anal Bioanal Chem* 406, 1763-1780 (2014). https://doi.org/10.1007/s00216-014-7668-0

44 Hur, K. H. *et al.* Abuse Potential of Synthetic Cannabinoids: AM-1248, CB-13, and PB-22. *Biomol Ther* 29, 384-391 (2021). https://doi.org/10.4062/biomolther.2020.212

45 Lin, M. L., Ellis, B., Eubanks, L. M. & Janda, K. D. Pharmacokinetic Approach to Combat the Synthetic Cannabinoid PB-22. *Acs Chem Neurosci* 12, 2573-2579 (2021). https://doi.org/10.1021/acschemneuro.1c00360

46 Watanabe, S., Kuzhiumparambil, U., Nguyen, M. A., Cameron, J. & Fu, S. L. Metabolic Profile of Synthetic Cannabinoids 5F-PB-22, PB-22, XLR-11 and UR-144 by Cunninghamella elegans. *Aaps J* 19, 1148-1162 (2017). https://doi.org/10.1208/s12248-017-0078-4

47 Kondrasenko, A. A., Goncharov, E. V., Dugaev, K. P. & Rubaylo, A. I. CBL-2201. Report on a new designer drug: Napht-1-yl 1-(5-fluoropentyl)-1H-indole-3-carboxylate. *Forensic Sci Int* 257, 209-213 (2015). https://doi.org/10.1016/j.forsciint.2015.08.023

48 Uchiyama, N. *et al.* A synthetic cannabinoid FDU-NNEI, two 2H-indazole isomers of synthetic cannabinoids AB-CHMINACA and NNEI indazole analog (MN-18), a phenethylamine derivative N-OH-EDMA, and a cathinone derivative dimethoxy-alpha-PHP, newly identified in illegal products. *Forensic Toxicol* 33, 244-259 (2015). https://doi.org/10.1007/s11419-015-0268-7

49 Shevyrin, V., Melkozerov, V., Nevero, A., Eltsov, O. & Shafran, Y. Analytical characterization of some synthetic cannabinoids, derivatives of indole-3-carboxylic acid. *Forensic Sci Int* 232, 1-10 (2013). https://doi.org/10.1016/j.forsciint.2013.06.011

50 Uchiyama, N., Matsuda, S., Kawamura, M., Kikura-Hanajiri, R. & Goda, Y. Identification of two new-type designer drugs, piperazine derivative MT-45 (I-C6) and synthetic peptide Noopept (GVS-111), with synthetic cannabinoid A-834735, cathinone derivative 4-methoxy-alpha-PVP, and phenethylamine derivative 4-methylbuphedrine from illegal products. *Forensic Toxicol* 32, 9-18 (2014). https://doi.org/10.1007/s11419-013-0194-5

51 Apirakkan, O. *et al.* Evidence of enzyme-mediated transesterification of synthetic cannabinoids with ethanol: potential toxicological impact. *Forensic Toxicol* 38, 95-107 (2020). https://doi.org/10.1007/s11419-019-00491-0

52 Ozseker, P. E. & Daglioglu, N. Simultaneous Determination and Validation of 5F-ADBICA and 5F-NPB-22 in Whole Blood and Urine by LC/MS-MS. *Chromatographia* 83, 1283-1291 (2020). https://doi.org/10.1007/s10337-020-03947-3

53 Hill, S. L. *et al.* Human Toxicity Caused by Indole and Indazole Carboxylate Synthetic Cannabinoid Receptor Agonists: From Horizon Scanning to Notification. *Clin Chem* 64, 346-354 (2018). https://doi.org/10.1373/clinchem.2017.275867

54 Hwang, J. *et al.* Metabolic and pharmacokinetic characterization of a new synthetic cannabinoid APINAC in rats. *Forensic Toxicol* 36, 88-101 (2018). https://doi.org/10.1007/s11419-017-0387-4

55 Kadomura, N. *et al.* In vitro metabolic profiles of adamantyl positional isomers of synthetic cannabinoids. *Forensic Toxicol* 39, 26-44 (2021). https://doi.org/10.1007/s11419-020-00538-7

56 Lee, J. H. *et al.* Identification of new synthetic cannabinoid analogue APINAC (adamantan-1-yl 1-pentyl-1H-indazole-3-carboxylate) with other synthetic cannabinoid MDMB(N)-Bz-F in illegal products. *Forensic Toxicol* 35, 45-55 (2017). https://doi.org/10.1007/s11419-016-0331-z

57 Savchuk, S. *et al.* In vivo metabolism of the new synthetic cannabinoid APINAC in rats by GC-MS and LC-QTOF-MS. *Forensic Toxicol* 35, 359-368 (2017). https://doi.org/10.1007/s11419-017-0364-y

58 Appolonova, S. A. *et al.* In vivo and in vitro metabolism of the novel synthetic cannabinoid 5F-APINAC. *Forensic Toxicol* 38, 160-171 (2020). https://doi.org/10.1007/s11419-019-00503-z

59 Markin, P. A. *et al.* Short- and long-term exposures of the synthetic cannabinoid 5F-APINAC induce metabolomic alterations associated with neurotransmitter systems and embryotoxicity confirmed by teratogenicity in zebrafish. *Comp Biochem Phys C* 243 (2021). https://doi.org/ARTN 109000 10.1016/j.cbpc.2021.109000

60 Shestakova, K. M. *et al.* Pharmacokinetic Properties of the Novel Synthetic Cannabinoid 5F-APINAC and Its Influence on Metabolites Associated with Neurotransmission in Rabbit Plasma. *Pharmaceuticals-Base* 14 (2021). https://doi.org/ARTN 668 10.3390/ph14070668

61 Asada, A., Doi, T., Tagami, T., Takeda, A. & Sawabe, Y. Isomeric discrimination of synthetic cannabinoids by GC-EI-MS: 1-adamantyl and 2-adamantyl isomers of N-adamantyl carboxamides. *Drug Test Anal* 9, 378-388 (2017). https://doi.org/10.1002/dta.2124

62 Cannizzaro, C. *et al.* Behavioural and pharmacological characterization of a novel cannabinomimetic adamantane-derived indole, APICA, and considerations on the possible misuse as a psychotropic spice abuse, in C57bl/6J mice. *Forensic Sci Int* 265, 6-12 (2016). https://doi.org/10.1016/j.forsciint.2015.12.035

63 Longworth, M., Connor, M., Banister, S. D. & Kassiou, M. Synthesis and Pharmacological Profiling of the Metabolites of Synthetic Cannabinoid Drugs APICA, STS-135, ADB-PINACA, and 5F-ADB-PINACA. *Acs Chem Neurosci* 8, 1673-1680 (2017). https://doi.org/10.1021/acschemneuro.7b00116

64 Longworth, M. *et al.* New-generation azaindole-adamantyl-derived synthetic cannabinoids. *Forensic Toxicol* 37, 350-365 (2019). https://doi.org/10.1007/s11419-019-00466-1

65 Sobolevsky, T., Prasolov, I. & Rodchenkov, G. Study on the phase I metabolism of novel synthetic cannabinoids, APICA and its fluorinated analogue. *Drug Test Anal* 7, 131-142 (2015). https://doi.org/10.1002/dta.1756

66 Uchiyama, N., Kawamura, M., Kikura-Hanajiri, R. & Goda, Y. Identification of two new-type synthetic cannabinoids, N-(1-adamantyl)-1-pentyl-1H-indole-3-carboxamide (APICA) and N-(1-adamantyl)-1-pentyl-1H-indazole-3-carboxamide (APINACA), and detection of five synthetic cannabinoids, AM-1220, AM-2233, AM-1241, CB-13 (CRA-13), and AM-1248, as designer drugs in illegal products. *Forensic Toxicol* 30, 114-125 (2012). https://doi.org/10.1007/s11419-012-0136-7

67 Uchiyama, N., Matsuda, S., Kawamura, M., Kikura-Hanajiri, R. & Goda, Y. Two new-type cannabimimetic quinolinyl carboxylates, QUPIC and QUCHIC, two new cannabimimetic carboxamide derivatives, ADB-FUBINACA and ADBICA, and five synthetic cannabinoids detected with a thiophene derivative alpha-PVT and an opioid receptor agonist AH-7921 identified in illegal products. *Forensic Toxicol* 31, 223-240 (2013). https://doi.org/10.1007/s11419-013-0182-9

68 Uchiyama, N. *et al.* Two new synthetic cannabinoids, AM-2201 benzimidazole analog (FUBIMINA) and (4-methylpiperazin-1-yl)(1-pentyl-1H-indol-3-yl) methanone (MEPIRAPIM), and three phenethylamine derivatives, 25H-NBOMe 3,4,5-trimethoxybenzyl analog, 25B-NBOMe, and 2C-N-NBOMe, identified in illegal products. *Forensic Toxicol* 32, 105-115 (2014). https://doi.org/10.1007/s11419-013-0217-2

69 Kevin, R. C. *et al.* Putative Synthetic Cannabinoids MEPIRAPIM, 5F-BEPIRAPIM (NNL-2), and Their Analogues Are T-Type Calcium Channel (CaV3) Inhibitors. *ACS Chem Neurosci* 13, 1395-1409 (2022). https://doi.org/10.1021/acschemneuro.1c00822

70 Ametovski, A. *et al.* Exploring Stereochemical and Conformational Requirements at Cannabinoid Receptors for Synthetic Cannabinoids Related to SDB-006, 5F-SDB-006, CUMYL-PICA, and 5F-CUMYL-PICA. *Acs Chem Neurosci* 11, 3672-3682 (2020). https://doi.org/10.1021/acschemneuro.0c00591

71 Banister, S. D. *et al.* The chemistry and pharmacology of synthetic cannabinoid SDB-006 and its regioisomeric fluorinated and methoxylated analogs. *Drug Test Anal* 10, 1099-1109 (2018). https://doi.org/10.1002/dta.2362

72 Bijlsma, L. *et al.* Mass spectrometric identification and structural analysis of the third-generation synthetic cannabinoids on the UK market since the 2013 legislative ban. *Forensic Toxicol* 35, 376-388 (2017). https://doi.org/10.1007/s11419-017-0368-7

73 Diao, X. X., Carlier, J., Scheidweiler, K. B. & Huestis, M. A. In vitro metabolism of new synthetic cannabinoid SDB-006 in human hepatocytes by high-resolution mass spectrometry. *Forensic Toxicol* 35, 252-262 (2017). https://doi.org/10.1007/s11419-016-0350-9

74 Glatfelter, G. C., Partilla, J. S. & Baumann, M. H. Structure-activity relationships for 5F-MDMB-PICA and its 5F-pentylindole analogs to induce cannabinoid-like effects in mice. *Neuropsychopharmacol* 47, 924-932 (2022). https://doi.org/10.1038/s41386-021-01227-8

75 Apirakkan, O., Gavrilovic, I., Cowan, D. A. & Abbate, V. In Vitro Phase I Metabolic Profiling of the Synthetic Cannabinoids AM-694, 5F-NNEI, FUB-APINACA, MFUBINAC, and AMB-FUBINACA. *Chem Res Toxicol* 33, 1653-1664 (2020). https://doi.org/10.1021/acs.chemrestox.9b00466

76 Kevin, R. C. *et al.* Kinetic and metabolic profiles of synthetic cannabinoids NNEI and MN-18. *Drug Test Anal* 10, 137-147 (2018). https://doi.org/10.1002/dta.2262

77 Tsujikawa, K., Iwata, Y. T., Inoue, M., Higashibayashi, S. & Inoue, H. Comments on "Characterization of four new designer drugs, 5-chloro-NNEI, NNEI indazole analog, alpha-PHPP and alpha-POP, with 11 newly distributed designer drugs in illegal products". *Forensic Sci Int* 251, E15-E17 (2015). https://doi.org/10.1016/j.forsciint.2015.04.008

78 Uchiyama, N. *et al.* Characterization of four new designer drugs, 5-chloro-NNEI, NNEI indazole analog, alpha-PHPP and alpha-POP, with 11 newly distributed designer drugs in illegal products. *Forensic Sci Int* 243, 1-13 (2014). https://doi.org/10.1016/j.forsciint.2014.03.013

79 Uchiyama, N., Shimokawa, Y., Kawamura, M., Kikura-Hanajiri, R. & Hakamatsuka, T. Chemical analysis of a benzofuran derivative, 2-(2-ethylaminopropyl)benzofuran (2-EAPB), eight synthetic cannabinoids, five cathinone derivatives, and five other designer drugs newly detected in illegal products. *Forensic Toxicol* 32, 266-281 (2014). https://doi.org/10.1007/s11419-014-0238-5

80 Asada, A. *et al.* Cannabimimetic activities of cumyl carboxamide-type synthetic cannabinoids. *Forensic Toxicol* 36, 170-177 (2018). https://doi.org/10.1007/s11419-017-0374-9

81 Longworth, M. *et al.* Pharmacology of Cumyl-Carboxamide Synthetic Cannabinoid New Psychoactive Substances (NPS) CUMYL-BICA, CUMYL-PICA, CUMYL-5F-PICA, CUMYL-5F-PINACA, and Their Analogues. *ACS Chem Neurosci* 8, 2159-2167 (2017). https://doi.org/10.1021/acschemneuro.7b00267

82 Liu, C. M., Jia, W., Hua, Z. D. & Qian, Z. H. Identification and analytical characterization of six synthetic cannabinoids NNL-3, 5F-NPB-22-7N, 5F-AKB-48-7N, 5F-EDMB-PINACA, EMB-FUBINACA, and EG-018. *Drug Test Anal* 9, 1251-1261 (2017). https://doi.org/10.1002/dta.2160

83 Walle, N. *et al.* Comparison of in vitro and in vivo models for the elucidation of metabolic patterns of 7-azaindole-derived synthetic cannabinoids exemplified using cumyl-5F-P7AICA. *Drug Test Anal* 13, 74-90 (2021). https://doi.org/10.1002/dta.2899

84 Bovens, M. *et al.* Structural characterization of the new synthetic cannabinoids CUMYL-PINACA, 5F-CUMYL-PINACA, CUMYL-4CN-BINACA, 5F-CUMYL-P7AICA and CUMYL-4CN-B7AICA. *Forensic Sci Int* 281, 98-105 (2017). https://doi.org/10.1016/j.forsciint.2017.10.020

85 Giorgetti, A. *et al.* Detection and phase I metabolism of the 7-azaindole-derived synthetic cannabinoid 5F-AB-P7AICA including a preliminary pharmacokinetic evaluation. *Drug Test Anal* 12, 78-91 (2020). https://doi.org/10.1002/dta.2692

86 Polettini, A. E., Kutzler, J., Sauer, C., Guber, S. & Schultis, W. LC-QTOF-MS Presumptive Identification of Synthetic Cannabinoids without Reference Chromatographic Retention/Mass Spectral Information. II. Evaluation of a Computational Approach for Predicting and Identifying Unknown High-Resolution Product Ion Mass Spectra. *J Anal Toxicol* 45, 440-461 (2021). https://doi.org/10.1093/jat/bkaa127

87 Staeheli, S. N. *et al.* In vitro metabolism of the synthetic cannabinoids CUMYL-PINACA, 5F-CUMYL-PINACA, CUMYL-4CN-BINACA, 5F-CUMYL-P7AICA and CUMYL-4CN-B7AICA. *Drug Test Anal* 10, 148-157 (2018). https://doi.org/10.1002/dta.2298

88 Blaazer, A. R. *et al.* Novel indole and azaindole (pyrrolopyridine) cannabinoid (CB) receptor agonists: Design, synthesis, structure-activity relationships, physicochemical properties and biological activity. *Eur J Med Chem* 46, 5086-5098 (2011). https://doi.org/10.1016/j.ejmech.2011.08.021

89 Diao, X. X., Carlier, J., Zhu, M. S. & Huestis, M. A. Human Hepatocyte Metabolism of Novel Synthetic Cannabinoids MN-18 and Its 5-Fluoro Analog 5F-MN-18. *Clin Chem* 63, 1753-1763 (2017). https://doi.org/10.1373/clinchem.2017.277152

90 Kevin, R. C. *et al.* Toxic by design? Formation of thermal degradants and cyanide from carboxamide-type synthetic cannabinoids CUMYL-PICA, 5F-CUMYL-PICA, AMB-FUBINACA, MDMB-FUBINACA, NNEI, and MN-18 during exposure to high temperatures. *Forensic Toxicol* 37, 17-26 (2019). https://doi.org/10.1007/s11419-018-0430-0

91 Al-Matrouk, A., Alqallaf, M., AlShemmeri, A. & BoJbarah, H. Identification of synthetic cannabinoids that were seized, consumed, or associated with deaths in Kuwait in 2018 using GC-MS and LC-MS-MS analysis. *Forensic Sci Int* 303 (2019). https://doi.org/ARTN 109960 10.1016/j.forsciint.2019.109960

92 Alves, V. L. *et al.* Highly sensitive screening and analytical characterization of synthetic cannabinoids in nine different herbal mixtures. *Anal Bioanal Chem* 413, 2257-2273 (2021). https://doi.org/10.1007/s00216-021-03199-6

93 Dinamarca, F. *et al.* Reviewing "apinaca", an emergent synthetic cannabinoid receptor agonist. *Eur Neuropsychopharm* 25, S626-S626 (2015). https://doi.org/Doi 10.1016/S0924-977x(15)30885-3

94 Frinculescu, A., Lyall, C. L., Ramsey, J. & Miserez, B. Variation in commercial smoking mixtures containing third-generation synthetic cannabinoids. *Drug Test Anal* 9, 327-333 (2017). https://doi.org/10.1002/dta.1975

95 Gamage, T. F. *et al.* Synthetic Cannabinoid Hydroxypentyl Metabolites Retain Efficacy at Human Cannabinoid Receptors. *J Pharmacol Exp Ther* 368, 414-422 (2019). https://doi.org/10.1124/jpet.118.254425

96 Gandhi, A. S. *et al.* First Characterization of AKB-48 Metabolism, a Novel Synthetic Cannabinoid, Using Human Hepatocytes and High-Resolution Mass Spectrometry. *Aaps J* 15, 1091-1098 (2013). https://doi.org/10.1208/s12248-013-9516-0

97 Gatch, M. B. & Forster, M. J. Delta(9)-Tetrahydrocannabinol-like effects of novel synthetic cannabinoids found on the gray market. *Behav Pharmacol* 26, 460-468 (2015). https://doi.org/10.1097/Fbp.0000000000000150

98 Hess, C., Stockhausen, S., Kernbach-Wighton, G. & Madea, B. Death due to diabetic ketoacidosis: Induction by the consumption of synthetic cannabinoids? *Forensic Sci Int* 257, E6-E11 (2015). https://doi.org/10.1016/j.forsciint.2015.08.012

99 Holm, N. B., Pedersen, A. J., Dalsgaard, P. W. & Linnet, K. Metabolites of 5F-AKB-48, a synthetic cannabinoid receptor agonist, identified in human urine and liver microsomal preparations using liquid chromatography high-resolution mass spectrometry. *Drug Test Anal* 7, 199-206 (2015). https://doi.org/10.1002/dta.1663

100 Jia, W. *et al.* Identification of three cannabimimetic indazole and pyrazole derivatives, APINACA 2H-indazole analogue, AMPPPCA, and 5F-AMPPPCA. *Drug Test Anal* 9, 248-255 (2017). https://doi.org/10.1002/dta.1967

101 Karinen, R., Tuv, S. S., Oiestad, E. L. & Vindenes, V. Concentrations of APINACA, 5F-APINACA, UR-144 and its degradant product in blood samples from six impaired drivers compared to previous reported concentrations of other synthetic cannabinoids. *Forensic Sci Int* 246, 98-103 (2015). https://doi.org/10.1016/j.forsciint.2014.11.012

102 Kim, S. *et al.* In Vitro Inhibitory Effects of APINACA on Human Major Cytochrome P450, UDP-Glucuronosyltransferase Enzymes, and Drug Transporters. *Molecules* 24 (2019). https://doi.org/ARTN 3000 10.3390/molecules24163000

103 Kim, S., Shin, Y. H., Kim, J. H., Song, I. S. & Lee, H. S. In Vitro Inhibitory Effects of Apinaca, a Synthetic Cannabinoid, on Human Cytochrome P450, Udp-Glucuronosyltransferase Enzymes, and Drug Transporters. *Drug Metab Pharmacok* 35, S45-S45 (2020).

104 Le Boisselier, R., Juteau, S., Lecordier-Maret, F. & Debruyne, D. "Buddah blues" (5F-AKB48=5F-APINACA) in e-smoking: about a case of withdrawal with persistent tachycardia and acute psychotic decompensation. *Therapie* 72, 157-157 (2017). https://doi.org/10.1016/j.therap.2016.11.025

105 Malaca, S., Busardo, F. P., Gottardi, M., Pichini, S. & Marchei, E. Dilute and shoot ultra-high performance liquid chromatography tandem mass spectrometry (UHPLC-MS/MS) analysis of psychoactive drugs in oral fluid. *J Pharmaceut Biomed* 170, 63-67 (2019). https://doi.org/10.1016/j.jpba.2019.02.039

106 Marchei, E. *et al.* Stability and Degradation Pathways of Different Psychoactive Drugs in Neat and in Buffered Oral Fluid. *J Anal Toxicol* 44, 570-579 (2020). https://doi.org/10.1093/jat/bkz114

107 McKinnie, R. J., Darweesh, T., Zito, P. A., Shields, T. J. & Trudell, M. L. Synthesis of the 5-Fluoro-4-hydroxypentyl Side Chain Metabolites of Synthetic Cannabinoids 5F-APINACA and CUMYL-5F-PINACA. *Synthesis-Stuttgart* 50, 4683-4689 (2018). https://doi.org/10.1055/s-0037-1609914

108 Oztas, E., Abudayyak, M., Celiksoz, M. & Ozhan, G. Inflammation and oxidative stress are key mediators in AKB48-induced neurotoxicity in vitro. *Toxicol in Vitro* 55, 101-107 (2019). https://doi.org/10.1016/j.tiv.2018.12.005

109 Pandopulos, A. J. *et al.* Towards an efficient method for the extraction and analysis of cannabinoids in wastewater. *Talanta* 217 (2020). https://doi.org/ARTN 121034 10.1016/j.talanta.2020.121034

110 Pinson, A. O. *et al.* Significance of Competing Metabolic Pathways for 5F-APINACA Based on Quantitative Kinetics. *Molecules* 25 (2020). https://doi.org/ARTN 4820 10.3390/molecules25204820

111 Rossi, S. S. *et al.* An analytical approach to the forensic identification of different classes of new psychoactive substances (NPSs) in seized materials. *Rapid Commun Mass Sp* 28, 1904-1916 (2014). https://doi.org/10.1002/rcm.6969

112 Wouters, E. *et al.* Assessment of Biased Agonism among Distinct Synthetic Cannabinoid Receptor Agonist Scaffolds. *Acs Pharmacol Transl* 3, 285-295 (2020). https://doi.org/10.1021/acsptsci.9b00069

113 Monti, M. C., Scheurer, E. & Mercer-Chalmers-Bender, K. Phase I In Vitro Metabolic Profiling of the Synthetic Cannabinoid Receptor Agonists CUMYL-THPINACA and ADAMANTYL-THPINACA. *Metabolites* 11 (2021). https://doi.org/ARTN 470 10.3390/metabo11080470

114 Astrand, A. *et al.* Metabolism study for CUMYL-4CN-BINACA in human hepatocytes and authentic urine specimens: Free cyanide is formed during the main metabolic pathway. *Drug Test Anal* 10, 1270-1279 (2018). https://doi.org/10.1002/dta.2373

115 Gatch, M. B., Tourigny, A., Shetty, R. A. & Forster, M. J. Behavioral pharmacology of five novel synthetic cannabinoids. *Behav Pharmacol* 33, 175-183 (2022). https://doi.org/10.1097/Fbp.0000000000000618

116 Kevin, R. C. *et al.* CUMYL-4CN-BINACA Is an Efficacious and Potent Pro-Convulsant Synthetic Cannabinoid Receptor Agonist. *Front Pharmacol* 10, 595 (2019). https://doi.org/10.3389/fphar.2019.00595

117 Apirakkan, O. *et al.* Isolation, detection and identification of synthetic cannabinoids in alternative formulations or dosage forms. *Forensic Chem* 18 (2020). https://doi.org/ARTN 100227 10.1016/j.forc.2020.100227

118 Baumann, M., Garibay, N., Partilla, J. & Brandt, S. N-Alkyl Chain Length is a Critical Determinant for the Pharmacological Activity of Cumyl-Pinaca and Related Synthetic Cannabinoids. *Neuropsychopharmacol* 44, 508-508 (2019).

119 Dobaja, M., Grenc, D., Kozelj, G. & Brvar, M. Occupational transdermal poisoning with synthetic cannabinoid cumyl-PINACA. *Clin Toxicol* 55, 193-195 (2017). https://doi.org/10.1080/15563650.2016.1278224

120 Angerer, V., Franz, F., Moosmann, B., Bisel, P. & Auwarter, V. 5F-Cumyl-PINACA in 'e-liquids' for electronic cigarettes: comprehensive characterization of a new type of synthetic cannabinoid in a trendy product including investigations on the in vitro and in vivo phase I metabolism of 5F-Cumyl-PINACA and its non-fluorinated analog Cumyl-PINACA. *Forensic Toxicol* 37, 186-196 (2019). https://doi.org/10.1007/s11419-018-0451-8

121 Longworth, M. *et al.* The 2-alkyl-2H-indazole regioisomers of synthetic cannabinoids AB-CHMINACA, AB-FUBINACA, AB-PINACA, and 5F-AB-PINACA are possible manufacturing impurities with cannabimimetic activities. *Forensic Toxicol* 34, 286-303 (2016). https://doi.org/10.1007/s11419-016-0316-y

122 Pike, E. *et al.* Systematic evaluation of a panel of 30 synthetic cannabinoid receptor agonists structurally related to MMB-4en-PICA, MDMB-4en-PINACA,

ADB-4en-PINACA, and MMB-4CN-BUTINACA using a combination of binding and different CB1 receptor activation assays: Part I-Synthesis, analytical characterization, and binding affinity for human CB1 receptors. *Drug Test Anal* 13, 1383-1401 (2021). https://doi.org/10.1002/dta.3037

123 Sparkes, E. *et al.* Structure-activity relationships of valine, tert-leucine, and phenylalanine amino acid-derived synthetic cannabinoid receptor agonists related to ADB-BUTINACA, APP-BUTINACA, and ADB-P7AICA. *Rsc Med Chem* 13, 156-174 (2022). https://doi.org/10.1039/d1md00242b

124 Kronstrand, R. *et al.* The metabolism of the synthetic cannabinoids ADB-BUTINACA and ADB-4en-PINACA and their detection in forensic toxicology casework and infused papers seized in prisons. *Drug Test Anal* 14, 634-652 (2022). https://doi.org/10.1002/dta.3203

125 Antonides, L. H. *et al.* Shape matters: The application of activity-based in vitro bioassays and chiral profiling to the pharmacological evaluation of synthetic cannabinoid receptor agonists in drug-infused papers seized in prisons. *Drug Test Anal* 13, 628-643 (2021). https://doi.org/10.1002/dta.2965

126 Brandon, A. M. *et al.* A Systematic Study of the In Vitro Pharmacokinetics and Estimated Human In Vivo Clearance of Indole and Indazole-3-Carboxamide Synthetic Cannabinoid Receptor Agonists Detected on the Illicit Drug Market. *Molecules* 26 (2021). https://doi.org/ARTN 1396 10.3390/molecules26051396

127 Doi, T. *et al.* Enantioseparation of the carboxamide-type synthetic cannabinoids N-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(5-fluoropentyl)-1H-indazole-3-carboxamide and methyl [1-(5-fluoropentyl)-1H-indazole-3-carbonyl]-valinate in illicit herbal products. *J Chromatogr A* 1473, 83-89 (2016). https://doi.org/10.1016/j.chroma.2016.10.049

128 Doi, T., Tagami, T., Takeda, A., Asada, A. & Sawabe, Y. Evaluation of carboxamide-type synthetic cannabinoids as CB1/CB2 receptor agonists: difference between the enantiomers. *Forensic Toxicol* 36, 51-60 (2018). https://doi.org/10.1007/s11419-017-0378-5

129 Mogler, L. *et al.* Detection of the recently emerged synthetic cannabinoid 5F-MDMB-PICA in 'legal high' products and human urine samples. *Drug Test Anal* 10, 196-205 (2018). https://doi.org/10.1002/dta.2201

130 Norman, C. *et al.* A transnational perspective on the evolution of the synthetic cannabinoid receptor agonists market: Comparing prison and general populations. *Drug Test Anal* 13, 841-852 (2021). https://doi.org/10.1002/dta.3002

131 Shi, Y. *et al.* Detection of a New Tert-Leucinate Synthetic Cannabinoid 5F-MDMB-PICA and Its Metabolites in Human Hair: Application to Authentic Cases. *Front Chem* 8 (2020). https://doi.org/ARTN 610312 10.3389/fchem.2020.610312

132 Risseeuw, M. D. P. *et al.* Identification of a new tert-leucinate class synthetic cannabinoid in powder and "spice-like" herbal incenses: Methyl 2-[[1-(5-fluoropentyl)indole-3-carbonyl]amino]-3,3-dimethyl-butanoate (5F-MDMB-PICA). *Forensic Sci Int* 273, 45-52 (2017). https://doi.org/10.1016/j.forsciint.2017.01.023

133 Antonides, L. H. *et al.* Enantiospecific Synthesis, Chiral Separation, and Biological Activity of Four Indazole-3-Carboxamide-Type Synthetic Cannabinoid Receptor Agonists and Their Detection in Seized Drug Samples. *Front Chem* 7, 321 (2019). https://doi.org/10.3389/fchem.2019.00321

134 Grafinger, K. E. *et al.* Systematic evaluation of a panel of 30 synthetic cannabinoid receptor agonists structurally related to MMB-4en-PICA, MDMB-4en-PINACA, ADB-4en-PINACA, and MMB-4CN-BUTINACA using a combination of binding and different CB1 receptor activation assays. Part III: The G protein pathway and critical comparison of different assays. *Drug Test Anal* 13, 1412-1429 (2021). https://doi.org/10.1002/dta.3054

135 Gilbert, N. *et al.* Synthesis, characterisation, detection and quantification of a novel hexyl-substituted synthetic cannabinoid receptor agonist: (S)-N-(1-amino-3,3-dimethyl-1-oxobutan-2-yl)-1-hexyl-1H-indazole-3-carboxamide (ADB-HINACA). *Forensic Chem* 26 (2021). https://doi.org/ARTN 100354 10.1016/j.forc.2021.100354

136 Cannaert, A. *et al.* Synthesis and in Vitro Cannabinoid Receptor 1 Activity of Recently Detected Synthetic Cannabinoids 4F-MDMB-BICA, 5F-MPP-PICA, MMB-4en-PICA, CUMYL-CBMICA, ADB-BINACA, APP-BINACA, 4F-MDMB-BINACA, MDMB-4en-PINACA, A-CHMINACA, 5F-AB-P7AICA, 5F-MDMB-P7AICA, and 5F-AP7AICA. *Acs Chem Neurosci* 11, 4434-4446 (2020). https://doi.org/10.1021/acschemneuro.0c00644

137 Qian, Z. H., Hua, Z. D., Liu, C. M. & Jia, W. Four types of cannabimimetic indazole and indole derivatives, ADB-BINACA, AB-FUBICA, ADB-FUBICA, and AB-BICA, identified as new psychoactive substances. *Forensic Toxicol* 34, 133-143 (2016). https://doi.org/10.1007/s11419-015-0297-2

138 Diao, X. X., Carlier, J., Zhu, M. S. & Huestis, M. A. Metabolism of the new synthetic cannabinoid EG-018 in human hepatocytes by high-resolution mass spectrometry. *Forensic Toxicol* 36, 304-312 (2018). https://doi.org/10.1007/s11419-018-0404-2

139 Gamage, T. F. *et al.* In vitro and in vivo pharmacological evaluation of the synthetic cannabinoid receptor agonist EG-018. *Pharmacol Biochem Be* 193 (2020). https://doi.org/ARTN 172918 10.1016/j.pbb.2020.172918

140 Gaunitz, F. *et al.* In vitro metabolic profiling of synthetic cannabinoids by pooled human liver microsomes, cytochrome P450 isoenzymes, and Cunninghamella elegans and their detection in urine samples. *Anal Bioanal Chem* 411, 3561-3579 (2019). https://doi.org/10.1007/s00216-019-01837-8

141 Mogler, L. *et al.* Phase I metabolism of the carbazole-derived synthetic cannabinoids EG-018, EG-2201, and MDMB-CHMCZCA and detection in human urine samples. *Drug Test Anal* 10, 1417-1429 (2018). https://doi.org/10.1002/dta.2398

142 Schoeder, C. T., Hess, C., Madea, B., Meiler, J. & Muller, C. E. Pharmacological evaluation of new constituents of "Spice": synthetic cannabinoids based on indole, indazole, benzimidazole and carbazole scaffolds. *Forensic Toxicol* 36, 385-403 (2018). https://doi.org/10.1007/s11419-018-0415-z

143 Weber, C. *et al.* Characterization of the synthetic cannabinoid MDMB-CHMCZCA. *Beilstein J Org Chem* 12, 2808-2815 (2016). https://doi.org/10.3762/bjoc.12.279

144 Ernst, L. *et al.* Identification and quantification of synthetic cannabinoids in 'spicelike' herbal mixtures: Update of the German situation in early 2017. *Forensic Sci Int* 277, 51-58 (2017). https://doi.org/10.1016/j.forsciint.2017.05.019

145 Norman, C. *et al.* Large-scale evaluation of ion mobility spectrometry for the rapid detection of synthetic cannabinoid receptor agonists in infused papers in prisons. *Drug Test Anal* 13, 644-663 (2021). https://doi.org/10.1002/dta.2945

146 Angerer, V. *et al.* Structural characterization and pharmacological evaluation of the new synthetic cannabinoid CUMYL-PEGACLONE. *Drug Test Anal* 10, 597-603 (2018). https://doi.org/10.1002/dta.2237

147 Gallo, M. *et al.* Severe cardiac and neurological toxic effects due to synthetic cannabinoid cumyl-pegaclone (SGT-151) alone: a case report. *Clin Toxicol* 59, 546-546 (2021).

148 Giorgetti, A. *et al.* Four cases of death involving the novel synthetic cannabinoid 5F-Cumyl-PEGACLONE. *Forensic Toxicol* 38, 314-326 (2020). https://doi.org/10.1007/s11419-019-00514-w

149 Halter, S. *et al.* Cumyl-PEGACLONE: A comparatively safe new synthetic cannabinoid receptor agonist entering the NPS market? *Drug Test Anal* 11, 347-349 (2019). https://doi.org/10.1002/dta.2545

150 Janssens, L., Cannaert, A., Connolly, M. J., Liu, H. L. & Stove, C. P. In vitro activity profiling of Cumyl-PEGACLONE variants at the CB1 receptor: Fluorination versus isomer exploration. *Drug Test Anal* 12, 1336-1343 (2020). https://doi.org/10.1002/dta.2870

151 Mogler, L., Halter, S., Wilde, M., Franz, F. & Auwarter, V. Human phase I metabolism of the novel synthetic cannabinoid 5F-CUMYL-PEGACLONE. *Forensic Toxicol* 37, 154-163 (2019). https://doi.org/10.1007/s11419-018-0447-4

152 Mogler, L. *et al.* Phase I metabolism of the recently emerged synthetic cannabinoid CUMYL-PEGACLONE and detection in human urine samples. *Drug Test Anal* 10, 886-891 (2018). https://doi.org/10.1002/dta.2352

153 Tiemensma, M., Rutherford, J. D., Scott, T. & Karch, S. Emergence of Cumyl-PEGACLONE-related fatalities in the Northern Territory of Australia. *Forensic Sci Med Pat* 17, 3-9 (2021). https://doi.org/10.1007/s12024-020-00334-0

154 Rao, M., Chen, D. F., Zhan, P. & Jiang, J. Q. MDA19, a novel CB2 agonist, inhibits hepatocellular carcinoma partly through inactivation of AKT signaling pathway. *Biol Direct* 14 (2019). https://doi.org/ARTN 9 10.1186/s13062-019-0241-1

155 Liu, C. M., Hua, Z. D., Jia, W. & Li, T. Identification of AD-18, 5F-MDA-19, and pentyl MDA-19 in seized materials after the class-wide ban of synthetic cannabinoids in China. *Drug Test Anal* 14, 307-316 (2022). https://doi.org/10.1002/dta.3185

156 Norman, C. *et al.* Detection and quantitation of synthetic cannabinoid receptor agonists in infused papers from prisons in a constantly evolving illicit market. *Drug Test Anal* 12, 538-554 (2020). https://doi.org/10.1002/dta.2767

157 Ralphs, R., Williams, L., Askew, R. & Norton, A. Adding Spice to the Porridges : The development of a synthetic cannabinoid market in an English prison. *Int J Drug Policy* 40, 57-69 (2017). https://doi.org/10.1016/j.drugpo.2016.10.003

158 UNODC. Terminology and Information on Drugs. (United Nations, New York, 2016).

159 Shulgin, A. S., A. *PIHKAL: A Chemical Love Story*. (Transform Press, 1991).

160 Kyriakou, C. *et al.* NBOMe: new potent hallucinogens - pharmacology, analytical methods, toxicities, fatalities: a review. *Eur Rev Med Pharmaco* 19, 3270-3281 (2015).

161 Marchi, N. C. *et al.* Clinical and Toxicological Profile of NBOMes: A Systematic Review. *Psychosomatics* 60, 129-138 (2019). https://doi.org/DOI 10.1016/j.psym.2018.11.002

162 Deslandes, G. *et al.* "Synthacaines": A mosaic of substances for a wide range of effects, from a case. *Toxicol Anal Clin* 29, 134-138 (2017). https://doi.org/10.1016/j.toxac.2017.01.003

163 King, L. A. New phenethylamines in Europe. *Drug Test Anal* 6, 808-818 (2014). https://doi.org/10.1002/dta.1570

164 Pinterova, N., Horsley, R. R. & Palenicek, T. Synthetic Aminoindanes: A Summary of existing Knowledge. *Front Psychiatry* 8 (2017). https://doi.org/ARTN 236 10.3389/fpsyt.2017.00236

165 Sainsbury, P. D., Kicman, A. T., Archer, R. P., King, L. A. & Braithwaite, R. A.

Aminoindanes - the next wave of 'legal highs'? *Drug Test Anal* 3, 479-482 (2011). https://doi.org/10.1002/dta.318

166 Corkery, J. M., Elliott, S., Schifano, F., Corazza, O. & Ghodse, A. H. MDAI (5,6-methylenedioxy-2-aminoindane; 6,7-dihydro-5H-cyclopenta[f][1,3] benzodioxol-6-amine; "sparkle'; "mindy') toxicity: a brief overview and update. *Hum Psychopharm Clin* 28, 345-355 (2013). https://doi.org/10.1002/hup.2298

167 Deville, M. *et al.* Death following consumption of MDAI and 5-EAPB. *Forensic Sci Int* 299, 89-94 (2019). https://doi.org/10.1016/j.forsciint.2019.03.023

168 Palenicek, T. *et al.* Emerging toxicity of 5,6-methylenedioxy-2-aminoindane (MDAI): Pharmacokinetics, behaviour, thermoregulation and LD50 in rats. *Prog Neuro-Psychoph* 69, 49-59 (2016). https://doi.org/10.1016/j.pnpbp.2016.04.004

169 Palenicek, T. *et al.* The effects of the new synthetic drugs mephedrone, methylone, naphyrone and 5,6-methylenedioxy-2-aminoindane (MDAI) in rats. *Eur Neuropsychopharm* 23, S572-S573 (2013). https://doi.org/Doi 10.1016/S0924-977x(13)70911-8

170 Shimshoni, J. A. *et al.* Toxicological evaluation of 5-methoxy-2-aminoindane (MEAI): Binge mitigating agent in development. *Toxicol Appl Pharm* 319, 59-68 (2017). https://doi.org/10.1016/j.taap.2017.01.018

171 Staeheli, S. N. *et al.* Postmortem distribution and redistribution of MDAI and 2-MAPB in blood and alternative matrices. *Forensic Sci Int* 279, 83-87 (2017). https://doi.org/10.1016/j.forsciint.2017.08.007

172 Coppola, M. & Mondola, R. 5-Iodo-2-aminoindan (5-IAI): Chemistry, pharmacology, and toxicology of a research chemical producing MDMA-like effects. *Toxicol Lett* 218, 24-29 (2013). https://doi.org/10.1016/j.toxlet.2013.01.008

173 Maier, J., Mayer, F. P., Brandt, S. D. & Sitte, H. H. DARK Classics in Chemical Neuroscience: Aminorex Analogues. *Acs Chem Neurosci* 9, 2484-2502 (2018). https://doi.org/10.1021/acschemneuro.8b00415

174 Shulgin, A. M., T.; Daley, P. E. *The Shulgin Index: Volume One, Psychedelic Phenethylamines and Related Compounds*. (Transform Press, 2011).

175 Shulgin, A. T. & Carter, M. F. Centrally Active Phenethylamines. *Psychopharmacol Comm* 1, 93-98 (1975).

176 Carlier, J. *et al.* Use of cognitive enhancers: methylphenidate analogs. *Eur Rev Med Pharmaco* 23, 3-15 (2019).

177 Markowitz, J. S., Zhu, H. J. & Patrick, K. S. Isopropylphenidate: An Ester Homolog of Methylphenidate with Sustained and Selective Dopaminergic Activity and Reduced Drug Interaction Liability. *J Child Adol Psychop* 23, 648-654 (2013). https://doi.org/10.1089/cap.2013.0074

178 Soussan, C. & Kjellgren, A. "Chasing the High" - Experiences of Ethylphenidate as Described on International Internet Forums. *Subst Abus-Res Treat* 9, 9-16 (2015). https://doi.org/10.4137/Sart.S22495

179 Silverstone, T. Appetite-Suppressants - a Review. *Drugs* 43, 820-836 (1992). https://doi.org/Doi 10.2165/00003495-199243060-00003

180 Adamowicz, P. *et al.* The prevalence of new psychoactive substances in biological material - a three-year review of casework in Poland. *Drug Test Anal* 8, 64-71 (2016). https://doi.org/10.1002/dta.1924

181 Burillo-Putze, G. *et al.* Emergent drugs (I): smart drugs. *An Sist Sanit Navar* 34, 263-274 (2011). https://doi.org/Doi 10.4321/S1137-66272011000200012

182 Cohen, B. M. Z. & Butler, R. BZP-party pills: A review of research on benzylpiperazine as a recreational drug. *Int J Drug Policy* 22, 95-101 (2011). https://doi.org/10.1016/j.drugpo.2010.12.002

183 Elliott, S. Current awareness of piperazines: pharmacology and toxicology. *Drug Test Anal* 3, 430-438 (2011). https://doi.org/10.1002/dta.307

184 Hess, C., Maas, A. & Madea, B. Legal highs . Chemistry, pharmacology, toxicology and forensic importance. *Rechtsmedizin* 24, 291-304 (2014). https://doi.org/10.1007/s00194-014-0964-3

185 Hill, S. L. & Thomas, S. H. L. Clinical toxicology of newer recreational drugs. *Clin Toxicol* 49, 705-719 (2011). https://doi.org/10.3109/15563650.2011.615318

186 Hudson, A., Zepeda, N., Perreault, A. & Lalies, M. 1-Benzylpiperazine: taking ecstasy to a new high. *Can J Physiol Pharm* 90, 671-671 (2012).

187 Kerr, J. R. & Davis, L. S. Benzylpiperazine in New Zealand: brief history and current implications. *J Roy Soc New Zeal* 41, 155-164 (2011). https://doi.org/Pii 935022782 10.1080/03036758.2011.557036

188 Monteiro, M. S., Bastos, M. D., de Pinho, P. G. & Carvalho, M. Update on 1-benzylpiperazine (BZP) party pills. *Arch Toxicol* 87, 929-947 (2013). https://doi.org/10.1007/s00204-013-1057-x

189 Musselman, M. E. & Hampton, J. P. "Not for Human Consumption": A Review of Emerging Designer Drugs. *Pharmacotherapy* 34, 745-757 (2014). https://doi.org/10.1002/phar.1424

190 Sheridan, J., Butler, R., Wilkins, C. & Russell, B. Legal piperazine-containing party pills - a new trend in substance misuse. *Drug Alcohol Rev* 26, 335-343 (2007). https://doi.org/10.1080/09595230701255791

191 Simmler, L. D., Rickli, A., Schramm, Y., Hoener, M. C. & Liechti, M. E. Pharmacological profiles of aminoindanes, piperazines, and pipradrol derivatives. *Biochem Pharmacol* 88, 237-244 (2014). https://doi.org/10.1016/j.bcp.2014.01.024

192 Welz, A. & Koba, M. Piperazine derivatives as dangerous abused compounds. *Acta Pharmaceut* 70, 423-441 (2020). https://doi.org/10.2478/acph-2020-0035

193 Wilkins, C. & Sweetsur, P. The impact of the prohibition of benzylpiperazine (BZP) 'legal highs' On the prevalence of BZP, new legal highs and other drug use in New Zealand. *Drug Alcohol Depen* 127, 72-80 (2013). https://doi.org/10.1016/j.drugalcdep.2012.06.014

194 Airuehia, E., Walker, L. Y. & Nittler, J. A Review of "Bath Salts": Evolving Designer Drugs of Abuse. *J Child Adoles Subst* 24, 186-190 (2015). https://doi.org/10.1080/1067828x.2013.803942

195 Banks, M. L., Worst, T. J., Rusyniak, D. E. & Sprague, J. E. Synthetic Cathinones ("Bath Salts"). *J Emerg Med* 46, 632-642 (2014). https://doi.org/10.1016/j.jemermed.2013.11.104

196 Baumann, M. H. *et al.* Baths Salts, Spice, and Related Designer Drugs: The Science Behind the Headlines. *J Neurosci* 34, 15150-15158 (2014). https://doi.org/10.1523/Jneurosci.3223-14.2014

197 Brandt, S. D., King, L. A. & Evans-Brown, M. The new drug phenomenon. *Drug Test Anal* 6, 587-597 (2014). https://doi.org/10.1002/dta.1686

198 Cottencin, O., Rolland, B. & Karila, L. New Designer Drugs (Synthetic Cannabinoids and Synthetic Cathinones): Review of Literature. *Curr Pharm Design* 20, 4106-4111 (2014). https://doi.org/Doi 10.2174/13816128113199990622

199 De Felice, L. J., Glennon, R. A. & Negus, S. S. Synthetic cathinones: Chemical phylogeny, physiology, and neuropharmacology. *Life Sci* 97, 20-26 (2014). https://doi.org/10.1016/j.lfs.2013.10.029

200 Feng, L. Y., Battulga, A., Han, E., Chung, H. & Li, J. H. New psychoactive substances of natural origin: A brief review. *J Food Drug Anal* 25, 461-471 (2017). https://doi.org/10.1016/j.jfda.2017.04.001

201 Ferreira, B., da Silva, D. D., Carvalho, F., Bastos, M. D. & Carmo, H. The novel psychoactive substance 3-methylmethcathinone (3-MMC or metaphedrone): A review. *Forensic Sci Int* 295, 54-63 (2019). https://doi.org/10.1016/j.forsciint.2018.11.024

202 Fojtikova, L., Holubova, B. & Kuchar, M. New Psycho-active Substances. *Chem Listy* 111, 234-238 (2017).

203 German, C. L., Fleckenstein, A. E. & Hanson, G. R. Bath salts and synthetic cathinones: An emerging designer drug phenomenon. *Life Sci* 97, 2-8 (2014). https://doi.org/10.1016/j.lfs.2013.07.023

204 Goncalves, J. L., Alves, V. L., Aguiar, J., Teixeira, H. M. & Camara, J. S. Synthetic cathinones: an evolving class of new psychoactive substances. *Crit Rev Toxicol* 49, 549-566 (2019). https://doi.org/10.1080/10408444.2019.1679087

205 Gunderson, E. W., Kirkpatrick, M. G., Willing, L. M. & Holstege, C. P. Substituted Cathinone Products: A New Trend in "Bath Salts" and Other Designer Stimulant Drug Use. *J Addict Med* 7, 153-162 (2013). https://doi.org/10.1097/ADM.0b013e31829084b7

206 Karila, L. *et al.* Novel psychoactive substances: A review. *Presse Med* 44, 383-391 (2015). https://doi.org/10.1016/j.lpm.2014.09.020

207 Karila, L., Megarbane, B., Cottencin, O. & Lejoyeux, M. Synthetic Cathinones: A New Public Health Problem. *Curr Neuropharmacol* 13, 12-20 (2015). https://doi.org/10.2174/1570159x13666141210224137

208 La Maida, N. *et al.* A Review of Synthetic Cathinone-Related Fatalities From 2017 to 2020. *Ther Drug Monit* 43, 52-68 (2021). https://doi.org/10.1097/Ftd.0000000000000808

209 Larchenko, A. V., Suvorov, M. A., Andryukhin, V. I., Kaurov, Y. V. & Suvorov, A. V. Synthetic Cathinones and Cannabinoids are New Psychoactive Substances (Review). *Sovrem Tehnol Med* 9, 185-196 (2017). https://doi.org/10.17691/stm2017.9.1.23

210 Majchrzak, M., Celinski, R., Kus, P., Kowalska, T. & Sajewicz, M. The newest cathinone derivatives as designer drugs: an analytical and toxicological review. *Forensic Toxicol* 36, 33-50 (2018). https://doi.org/10.1007/s11419-017-0385-6

211 Mercurio, I. *et al.* Toxicological findings in fatal intoxications from synthetic cathinones: a narrative review. *Aust J Forensic Sci* (2020). https://doi.org/10.1080/00450618.2020.1841291

212 Oliver, C. F. *et al.* Synthetic cathinone adulteration of illegal drugs. *Psychopharmacology* 236, 869-879 (2019). https://doi.org/10.1007/s00213-018-5066-6

213 Pieprzyca, E., Skowronek, R., Niznansy, L. & Czekaj, P. Synthetic cathinones - From natural plant stimulant to new drug of abuse. *Eur J Pharmacol* 875 (2020). https://doi.org/ARTN 173012 10.1016/j.ejphar.2020.173012

214 Radaelli, D. *et al.* Synthetic Cannabinoids and Cathinones Cardiotoxicity: Facts and Perspectives. *Curr Neuropharmacol* 19, 2038-2048 (2021). https://doi.org/10.2174/1570159x19666210412101929

215 Rivera, J. V., Vance, E. G., Rushton, W. F. & Arnold, J. K. Novel Psychoactive Substances and Trends of Abuse. *Crit Care Nurs Q* 40, 374-382 (2017). https://doi.org/10.1097/Cnq.0000000000000174

216 Schifano, F. *et al.* Mephedrone (4-methylmethcathinone; 'meow meow'): chemical, pharmacological and clinical issues. *Psychopharmacology* 214, 593-602 (2011). https://doi.org/10.1007/s00213-010-2070-x

217 Schifano, F. *et al.* New psychoactive substances (NPS) and serotonin syndrome onset: A systematic review. *Exp Neurol* 339 (2021). https://doi.org/ARTN 113638 10.1016/j.expneurol.2021.113638

218 Schifano, F., Papanti, G. D., Orsolini, L. & Corkery, J. M. Novel psychoactive substances: the pharmacology of stimulants and hallucinogens. *Expert Rev Clin Phar* 9, 943-954 (2016). https://doi.org/10.1586/17512433.2016.1167597

219 Simmons, S. J. *et al.* DARK Classics in Chemical Neuroscience: Cathinone-Derived Psychostimulants. *Acs Chem Neurosci* 9, 2379-2394 (2018). https://doi.org/10.1021/acschemneuro.8b00147

220 Soares, J., Costa, V. M., Bastos, M. D., Carvalho, F. & Capela, J. P. An updated review on synthetic cathinones. *Arch Toxicol* 95, 2895-2940 (2021). https://doi.org/10.1007/s00204-021-03083-3

221 Tyrkko, E., Andersson, M. & Kronstrand, R. The Toxicology of New Psychoactive Substances: Synthetic Cathinones and Phenylethylamines. *Ther Drug Monit* 38, 190-216 (2016). https://doi.org/Doi 10.1097/Ftd.0000000000000263

222 Valente, M. J., de Pinho, P. G., Bastos, M. D., Carvalho, F. & Carvalho, M. Khat and synthetic cathinones: a review. *Arch Toxicol* 88, 15-45 (2014). https://doi.org/10.1007/s00204-013-1163-9

223 Wronikowska, O. & Budzynska, B. Toxicological profile and structure-activity relationship of new synthetic cathinones. *Postep Hig Med Dosw* 74, 57-68 (2020). https://doi.org/10.5604/01.3001.0013.9252

224 Zaitsu, K., Katagi, M., Tsuchihashi, H. & Ishii, A. Recently abused synthetic cathinones, alpha-pyrrolidinophenone derivatives: a review of their pharmacology, acute toxicity, and metabolism. *Forensic Toxicol* 32, 1-8 (2014). https://doi.org/10.1007/s11419-013-0218-1

225 Zawilska, J. B. Mephedrone and other cathinones. *Curr Opin Psychiatr* 27, 256-262 (2014). https://doi.org/10.1097/Yco.0000000000000066

226 Zawilska, J. B. & Wojcieszak, J. alpha-Pyrrolidinophenones: a new wave of designer cathinones. *Forensic Toxicol* 35, 201-216 (2017). https://doi.org/10.1007/s11419-016-0353-6

227 Zawilska, J. B. & Wojcieszak, J. Designer cathinones-An emerging class of novel recreational drugs. *Forensic Sci Int* 231, 42-53 (2013). https://doi.org/10.1016/j.forsciint.2013.04.015

228 UNODC. Recommended Methods for the Identification and Analysis of Synthetic Cathinones in Seized Materials. (Laboratory and Scientific Section, United Nations Office on Drugs and Crime (UNODC), Vienna, Austria, 2015).

229 Cumba, L. R. *et al.* Forensic electrochemistry: indirect electrochemical sensing of the components of the new psychoactive substance "Synthacaine". *Analyst* 140, 5536-5545 (2015). https://doi.org/10.1039/c5an00858a

230 Bottei, E., Zellmer, K. & Breiner, J. Death from diffuse alveolar hemorrhage temporally related to the use of MAB-CHMINACA and N-methyl-2-aminoindane. *Clin Toxicol* 54, 709-709 (2016).

231 Deville, M., Dubois, N. & Charlier, C. Potential 2-Aminoindane Fatality Invalidated by Careful Mass Spectrometric Analysis. *J Anal Toxicol* 46, E11-E15 (2022). https://doi.org/10.1093/jat/bkaa172

232 Chen, W. H., Chui, C. & Yin, H. L. The Antemortem Neurobehavior in Fatal Paramethoxymethamphetamine Usage. *Subst Abus* 33, 366-372 (2012). https://doi.org/10.1080/08897077.2011.638736

233 Lin, D. L., Liu, H. C. & Yin, H. L. Recent paramethoxymethamphetamine (PMMA) deaths in Taiwan. *J Anal Toxicol* 31, 109-113 (2007). https://doi.org/DOI 10.1093/jat/31.2.109

234 Lurie, Y. *et al.* Severe paramethoxymethamphetamine (PMMA) and paramethoxyamphetamine (PMA) outbreak in Israel. *Clin Toxicol* 50, 39-43 (2012). https://doi.org/10.3109/15563650.2011.635148

235 Refstad, S. Paramethoxyamphetamine (PMA) poisoning; a 'party drug' with lethal effects. *Acta Anaesth Scand* 47, 1298-1299 (2003). https://doi.org/DOI 10.1046/j.1399-6576.2003.00245.x

236 Vevelstad, M. *et al.* The PMMA epidemic in Norway: Comparison of fatal and non-fatal intoxications. *Forensic Sci Int* 219 (2012). https://doi.org/10.1016/j.forsciint.2011.12.014

237 Antia, U., Lee, H. S., Kydd, R. R., Tingle, M. D. & Russell, B. R. Pharmacokinetics of 'party pill' drug N-benzylpiperazine (BZP) in healthy human participants. *Forensic Sci Int* 186, 63-67 (2009). https://doi.org/10.1016/j.forsciint.2009.01.015

238 Baumann, M. H. *et al.* N-substituted piperazines abused by humans mimic the molecular mechanism of 3,4-methylenedioxymethamphetamine (MDMA, or 'Ecstasy'). *Neuropsychopharmacol* 30, 550-560 (2005). https://doi.org/10.1038/sj.npp.1300585

239 Baumann, M. H. *et al.* Effects of "Legal X" piperazine analogs on dopamine and serotonin release in rat brain. *Ann Ny Acad Sci* 1025, 189-197 (2004). https://doi.org/10.1196/annals.1316.024

240 Bye, C., Munrofau.Ad, Peck, A. W. & Young, P. A. Comparison of Effects of 1-Benzylpiperazine and Dexamphetamine on Human Performance Tests. *Eur J Clin Pharmacol* 6, 163-169 (1973). https://doi.org/Doi 10.1007/Bf00558280

241 Campbell, H., Peck, A. W., Lloyd, J., Clane, W. & Evans, M. Comparison of Effects of Dexamphetamine and 1-Benzylpiperazine in Former Addicts. *Brit J Pharmacol* 44, P369-& (1972).

242 Fantegrossi, W. E., Winger, G., Woods, J. H., Woolverton, W. L. & Coop, A. Reinforcing and discriminative stimulus effects of 1-benzylpiperazine and trifluoromethylphenylpiperazine in rhesus monkeys. *Drug Alcohol Depen* 77, 161-168 (2005). https://doi.org/10.1016/j.drugalcdep.2004.07.014

243 Kolesnikova, T. O., Khatsko, S. L., Demin, K. A., Shevyrin, V. A. & Kalueff, A. V. DARK Classics in Chemical Neuroscience: alpha-Pyrrolidinovalerophenone ("Flakka"). *Acs Chem Neurosci* 10, 168-174 (2019). https://doi.org/10.1021/acschemneuro.8b00525

244 Patocka, J. *et al.* Flakka: New Dangerous Synthetic Cathinone on the Drug Scene. *Int J Mol Sci* 21 (2020). https://doi.org/ARTN 8185 10.3390/ijms21218185

245 Schifano, F. *et al.* The clinical challenges of synthetic cathinones. *Brit J Clin Pharmaco* 86, 410-419 (2020). https://doi.org/10.1111/bcp.14132

246 Baumann, M. H., Walters, H. M., Niello, M. & Sitte, H. H. Neuropharmacology of Synthetic Cathinones. *Handb Exp Pharmacol* 252, 113-142 (2018). https://doi.org/10.1007/164_2018_178

247 Contrucci, R. R., Brunt, T. M., Inan, F., Franssen, E. J. F. & Hondebrink, L. Synthetic Cathinones and Their Potential Interactions with Prescription Drugs. *Ther Drug Monit* 42, 75-82 (2020). https://doi.org/10.1097/Ftd.0000000000000682

248 Meyer, M. R. & Peters, F. T. Analytical Toxicology of Emerging Drugs of Abuse-An Update. *Ther Drug Monit* 34, 615-621 (2012). https://doi.org/10.1097/FTD.0b013e31826d0915

249 Riley, A. L. *et al.* Abuse potential and toxicity of the synthetic cathinones (i.e., "Bath salts"). *Neurosci Biobehav R* 110, 150-173 (2020). https://doi.org/10.1016/j.neubiorev.2018.07.015

250 Braham, M. Y. *et al.* Fatal 4-MEC Intoxication Case Report and Review of Literature. *Am J Foren Med Path* 42, 57-61 (2021). https://doi.org/10.1097/Paf.0000000000000599

251 Busardo, F. P., Kyriakou, C., Napoletano, S., Marinelli, E. & Zaami, S. Mephedrone related fatalities: a review. *Eur Rev Med Pharmaco* 19, 3777-3790 (2015).

252 Ezaki, J., Ro, A., Hasegawa, M. & Kibayashi, K. Fatal overdose from synthetic cannabinoids and cathinones in Japan: demographics and autopsy findings. *Am J Drug Alcohol Ab* 42, 520-529 (2016). https://doi.org/10.3109/00952990.2016.1172594

253 Kraemer, M., Boehmer, A., Madea, B. & Maas, A. Death cases involving certain new psychoactive substances: A review of the literature. *Forensic Sci Int* 298, 186-267 (2019). https://doi.org/10.1016/j.forsciint.2019.02.021

254 Zaami, S. *et al.* Synthetic cathinones related fatalities: an update. *Eur Rev Med Pharmaco* 22, 268-274 (2018). https://doi.org/10.26355/eurrev_201801_14129

255 Beardsley, P. M. & Zhang, Y. Synthetic Opioids. *Handb Exp Pharmacol* 252, 353-381 (2018). https://doi.org/10.1007/164_2018_149

256 Kyei-Baffour, K. & Lindsley, C. W. DARK Classics in Chemical Neuroscience: U-47700. *Acs Chem Neurosci* 11, 3928-3936 (2020). https://doi.org/10.1021/acschemneuro.0c00330

257 Ujvary, I. *et al.* DARK Classics in Chemical Neuroscience: Etonitazene and Related Benzimidazoles. *Acs Chem Neurosci* 12, 1072-1092 (2021). https://doi.org/10.1021/acschemneuro.1c00037

258 Resnik, K., Brandao, P. & Alves, E. A. DARK Classics in Chemical Neuroscience: Bucinnazine. *Acs Chem Neurosci* 12, 3527-3534 (2021). https://doi.org/10.1021/acschemneuro.1c00522

259 Gonzalez, A. & Hinson, D. 2-Methyl AP-237, a new synthetic opioid available via the black market. *Clin Toxicol* 59, 1065-1066 (2021).

260 Vandeputte, M. M., Krotulski, A. J., Papsun, D. M., Logan, B. K. & Stove, C. P. The Rise and Fall of Isotonitazene and Brorphine: Two Recent Stars in the Synthetic Opioid Firmament. *J Anal Toxicol* 46, 115-121 (2022). https://doi.org/10.1093/jat/bkab082

261 Verougstraete, N. *et al.* First Report on Brorphine: The Next Opioid on the Deadly New Psychoactive Substance Horizon? *J Anal Toxicol* 44, 937-946 (2020). https://doi.org/10.1093/jat/bkaa094

262 Wallach, J. & Brandt, S. D. Phencyclidine-Based New Psychoactive Substances. *Handb Exp Pharmacol* 252, 261-303 (2018). https://doi.org/10.1007/164_2018_124

263 Wallach, J. & Brandt, S. D. 1,2-Diarylethylamine- and Ketamine-Based New Psychoactive Substances. *Handb Exp Pharmacol* 252, 305-352 (2018). https://doi.org/10.1007/164_2018_148

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