Firman, JW, Belfield, SJ, Chen, G, Jackson, M, Lam, FH, Richmond, C, Smith, J, Steinmetz, FP and Cronin, MTD

Chemoinformatic Consideration of Novel Psychoactive Substances: Compilation and Preliminary Analysis of a Categorised Dataset

Chemoinformatic Consideration of Novel Psychoactive Substances: Compilation and Preliminary Analysis of a Categorised Dataset

Dr James W. Firman[1*], Samuel J. Belfield[1], George Chen[1], Megan Jackson[1], Fai Hou Lam[1], Callum Richmond[1], James Smith[1], Dr Fabian P. Steinmetz[2], Professor Mark T.D. Cronin[1]

1. School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University, Liverpool, UK
2. Delphic HSE, Farnborough, UK

* Corresponding author

E-mail address: j.w.firman@ljmu.ac.uk (James W. Firman)

Postal address:

James Firman
School of Pharmacy and Biomolecular Sciences
Liverpool John Moores University
Byrom Street
Liverpool
L3 3AF
United Kingdom

Keywords:

Biological activity, neurological agents, toxicology

Conflict of interest declaration:

The authors can confirm that no conflicts of interest are present relating the reported work.

Abstract

Recent years have seen the emergence into circulation of a growing array of novel psychoactive substances (NPS). Knowledge of the pharmacological profiles and risk liability of these compounds is typically very scarce. Development of chemoinformatic tools enabling prediction of properties within uncharacterised analogues has potential be of particular use. In order to facilitate this, compilation of a chemical inventory comprising known NPS is a necessity.

Sourcing a variety of published governmental and analytical reports, a dataset composed of 690 distinct acknowledged NPS, complete with defined chemical structures, has been constructed. This is supplemented by a complementary series of 155 established psychoactive drugs of abuse (EPDA). Classification was performed in accordance with their key molecular structural features, subjective effect profiles and pharmacological mechanisms of action. In excess of forty chemical groupings, spanning seven subjective effect categories and six broad mechanisms of pharmacological action, were identified. Co-occurrence of NPS and EPDA within specific classes was common, showcasing inherent scope both for chemical read-across and for the derivation of structural alerts.

1. Introduction

Over the course of the previous decade, the emergence onto the unregulated market of novel, predominantly synthetic psychoactive compounds – referred to henceforth as "novel psychoactive substances" (NPS) – has grown to constitute an increasing public health concern across much of the developed world.[1] Such agents are typically intended to mimic closely the effects associated with established, very often illicit, psychotropic drugs of abuse (examples of which are provided within Figure 1.). Their initial presence outside of the boundaries of substance control schedules within many legislative areas has led to their acquisition of the popular descriptor "legal highs".[2] Whilst numerous nations have since taken action to bring under control the broad chemical classes within which these compounds typically fall, emergence of new analogues is continuous. The yet incomplete knowledge concerning their pharmacological and toxicological profiles ensures therefore that their presence and use continues to form an ever-evolving and potentially substantial risk towards consumers.[3]

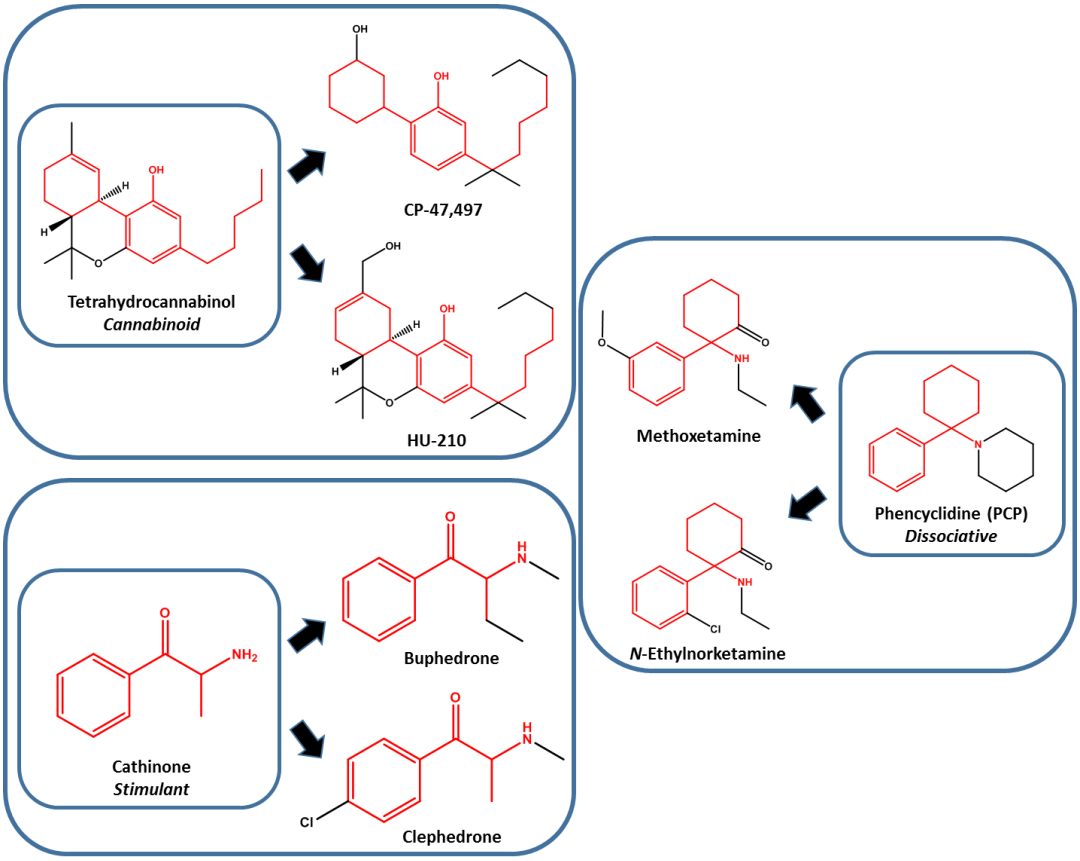


Figure 1.Scheme outlining identity and chemical structure of a selection of established psychoactive drugs of abuse, accompanied by relevant novel analogues.

NPS may be sourced in practice through an assortment of routes, and in an array of formulations. "Head shops", present both as traditional street-side locations and increasingly online, offer a variety of products either individually or as constituents within mixtures.[4] Sold typically under descriptions such as "herbal incense" or "pot pourri", and further commonly referred to as "Spice", cannabimimetic blends composed of a variety of synthetic cannabinoid species are acknowledged as constituting a significant proportion of this market.[5] Stimulant and empathogenic compounds (distributed classically as "bath salts" or "plant food") additionally find wide availability, as do psychedelic tryptamines and lysergamides, opioid agonists and sedatives.[6] Commonly sold as "research chemicals", their unregulated sourcing and production allied to the undefined nature of many formulations contributes to the uncertainty which surrounds identification of single NPS. The discerning of pharmacological and toxicological properties attributable to them is therefore rendered a demanding and non-trivial task.[7] Challenge is additionally posed to the analytical chemist, who must define routes towards the characterisation of an ever-expanding library of structures.[8]

Attempts to understand in greater depth the impacts upon physical and mental wellbeing associated with the abuse of specific NPS are confounded by a variety of factors. These derive both from the inherent novelty of the compounds, and from the unregulated, often clandestine nature of their production and distribution. Owing to the rapid and continuing emergence of novel substances, there exists in general a paucity of reliable experimental and clinical data concerning their toxicological potential. Case studies acquired from patients who have presented following acute ingestion of a cocktail of NPS – either in the presence or absence of established illicit psychoactive drugs – constitute the dominant testimony apparent within the literature.[9-12] Such reports display obvious limitations with regards to the characterisation of individual compounds, most notably with regards to specific cellular and organ-level toxicities and dependency profiles over extended periods of use.

Although it is noted that both *in vivo* and *in vitro* experimental data are largely non-existent for the great majority of compounds which have emerged over the preceding 10-15 years, appreciation of

relevant structure-activity relationships may allow for the inference of the capacity of a substance to react towards given adverse outcomes. As such, there exists significant scope for the input of chemoinformatic and predictive toxicological approaches within characterisation of the properties possessed by this diverse range of chemical subtypes. Pooling of related molecules into relevant groups further has the capacity to assist in predicting pharmacology, drawing upon similarity with established drugs whilst simultaneously permitting extrapolation to novel substances as their presence becomes known.

The essential first step towards any chemoinformatic consideration of NPS is in the curation of a compound inventory, complete with defined, unambiguous structure relating each constituent molecule. A variety of national and supra-national government and advisory agencies have, over the preceding ten years, issued periodical lists of named compounds considered by their experts to fall within the bracket of NPS. It is from these, complemented by a variety of independent analytical sources, that we have sought to construct an expansive compendium of NPS acknowledged as constituting wider concern. As such, the aim of this study was to compile and categorise known NPS and provide basis for comparison – both structurally and mechanistically – with established psychoactive compounds. Presented is a dataset composed of 690 novel psychoactive substances, classified according to their purported effect profiles, neuropharmacological mode of action and structural composition. Comparison was made with an accessory compilation consisting of 155 established psychoactive drugs of abuse, generally possessive of recognised pharmacological and toxicological profiles.

2. Materials and methods

2.1. Compilation of database

Two distinct datasets, one composed solely of recorded NPS and another consisting of established psychoactive drugs of abuse (EPDA), were developed in accordance with protocols described below. In instances whereby compounds were found to occupy both classifications, placement preferentially within the latter grouping was ensured. Each may be found located in its entirety within Supplementary Table 1.

Novel psychoactive substances

Information concerning the identities of compounds acknowledged as NPS was accumulated from sources as outlined within Table 1. Amongst the literature drawn upon were reports issued through governmental and supra-governmental entities including the United Nations Office on Drugs and Crime (UNODC) and the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), alongside a selection of original research publications and reviews developed by independent groups. A comprehensive index of source material, incorporating assignment of origin for each substance, is present within Supplementary Table 1.

Established psychoactive drugs of abuse

Substances constituting "illicit" grouping within the DrugBank resource (www.drugbank.ca) were examined for their purported psychoactive properties.[13[Those adjudged as possessing no such liability (primarily steroidal compounds utilised for physical effect) were removed from consideration, furnishing a 155-member established psychoactive drug of abuse set.

Reference	Entries	Reference	Entries
UNODC, 2013[14]	234	Debruyne & Le Boisselier, 2015[28]	122
EMCDDA, 2006[15]	12	Banister *et al.*, 2015[29]	12
EMCDDA, 2007[16]	6	Banister *et al.*, 2016[30]	18
EMCDDA, 2008[17]	14	Qian *et al.*, 2017[31]	9
EMCDDA, 2009[18]	12	Shevyrin *et al.*, 2014[32]	3
EMCDDA, 2010[19]	24	Shevyrin *et al.*, 2016[33]	1
EMCDDA, 2011[20]	39	Uchiyama, Matsuda *et al.*, 2014[34]	13
EMCDDA, 2012[21]	46	Uchiyama, Shimokawa *et al.*, 2014[35]	8
EMCDDA, 2013[22]	73	Uchiyama *et al.*, 2015[36]	11
EMCDDA, 2014[23]	74	Nakajima *et al.*, 2015[37]	4
EMCDDA, 2015[24]	94	Blakey *et al.*, 2016[38]	8
EMCDDA, 2016[25]	101	Lai *et al.*, 2015[39]	6
EMCDDA, 2017[26]	60	Coppola & Mondola, 2012[40]	5
NFL Slovenia[27]	77		

Table 1. Summary of literature sources from which NPS identities were drawn.

2.2. Acquisition and visualisation of chemical structures

In instances where not provided explicitly within source publications, molecular structures corresponding to listed compounds were obtained through online resources including PubChem (www.pubchem.gov), ChemSpider (www.chemspider.com) and the New Synthetic Drugs Database (http://www.nsddb.eu/).[41, 42] Details concerning structural composition were coded for each entry as SMILES strings.[43] Visualisation was achieved subsequently through use of ChemAxon MarvinView software (version 1.6).[44]

2.3. Grouping and classification of compounds

Grouping with respect to psychoactive effect

Classification as regards psychotropic influence was performed with reference to descriptions present within source literature. Ancillary information, as required, was obtained through use of the Erowid online resource (www.erowid.org).[45]

Grouping with respect to pharmacological mechanism of action

Assorted literature sources, referenced in the text, were employed in order to attribute the dominant neuropharmacological mechanism to constituent compounds.

Grouping with respect to molecular structural features

Molecules were visualised in accordance with protocols described above. Chemical and pharmacological knowledge was employed in order constitute groups related by shared, biologically-relevant structural motifs. Those falling outside of such categories were termed “unclassified”.

2.4. Principal component analysis of chemical space

Descriptors relating to the physicochemical and structural properties of compounds contained within NPS and EPDA sets were determined through use of CORINA Symphony Descriptors Community Edition (v. 2, MN-AM, Nuremberg, Germany: www.mn-am.com/services/corinasymphonydescriptors). Further series of parameters, centred upon the presence within structures of definitive chemical fingerprints, were developed through assistance of the ChemoTyper application (v. 1.1, MN-AM, Nuremberg, Germany) with reference to established ToxPrint chemotypes.[46] Physicochemical and structural descriptors (in total 31, refer to Supplementary Table 3 for their identity) were integrated into combined arrays, from which principal components were extracted using Principal Component Analysis within the Minitab Statistical software (v. 18.1, State College PA, USA). Visualisation, in the form of scatter plots, was achieved through use of this same program.

3. Results

3.1. Overview and analysis of dataset

A total of 690 compounds characterised as NPS were identified from within the aforementioned sources. With regards to purported psychoactive properties (as displayed visually within Figure 2), 223 were distinguished as cannabinoids, 192 as stimulants, 118 as psychedelics, 63 as empathogens, 39 as sedatives, 25 as opioids, and 20 as dissociatives. Owing to insufficient attestation coupled with structural obscurity, 10 compounds, labelled "uncertain", had no definitive effect or effects attributed. 367 of these compounds influenced monoaminergic transmission, 223 cannabinergic, 36 GABAergic, 25 opioidergic, 19 glutamatergic and 6 cholinergic (with 14 uncertain). Substances were further partitioned, where appropriate, into one of 35 distinct chemical groupings. A selection of 43 isolated compounds defied such categorisation, and were in turn listed "unclassified". From the Drugbank "Illicit" dataset, a sum of 155 psychoactive compounds was gathered. In all, 70 could be identified as opioids, 40 as sedatives, 21 as stimulants, 15 as psychedelics, 4 as dissociatives, 4 as empathogens and 1 as cannabinoid. These entries spanned 23 distinct chemical classifications, incorporating six absent amongst NPS.

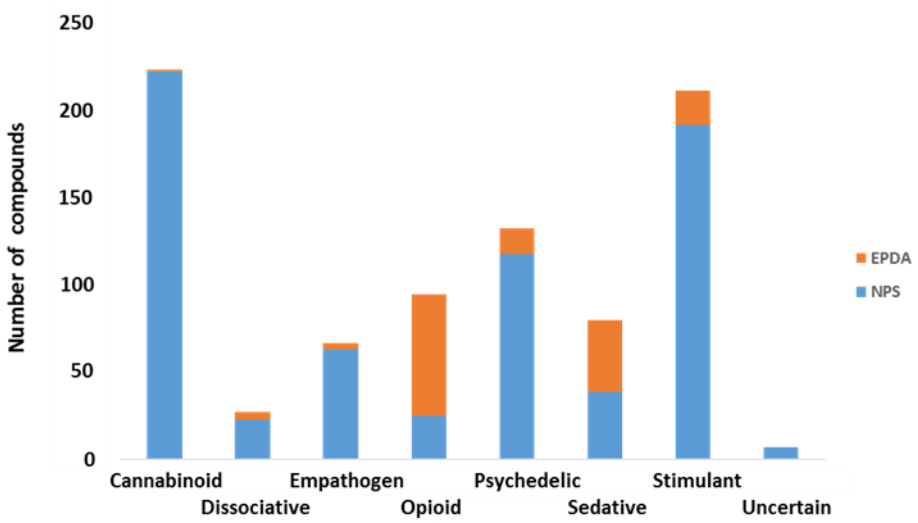


Figure 2. Numerical composition of psychoactive effect groups.

Principal component analysis of physicochemical and structural properties was performed upon the NPS dataset. Outcomes are expressed visually within plots (Figure 3), detailing comparison of scores obtained between principal components 1 and 2. Evident within Figure 3A, the dominant groupings of cannabinergic and monoaminergic agents are seen to occupy areas of chemical space largely distinct from one-another. Grouping according to psychoactive effect (Figure 3B) illustrates extent of overlap between monoamine-like stimulant, empathogen and psychedelic agents.

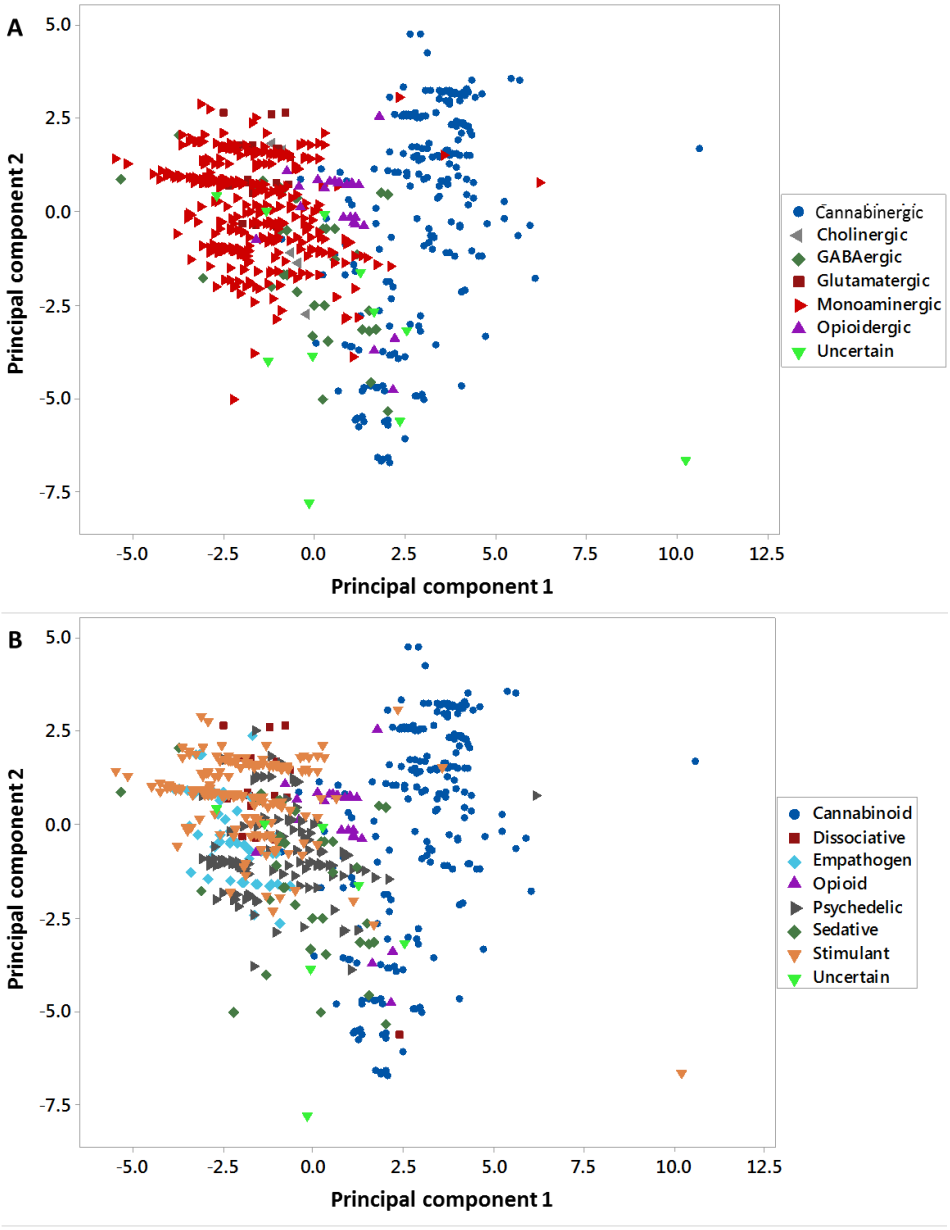


Figure 3. Principal component analyses of NPS dataset. Scores relating first principal components, with compounds grouped In accordance with their pharmacological mechanism of action (A) and psychoactive effect profile (B).

Substance inventories may be viewed in their entirety through accessing of Supplementary Data. Supplementary Table 1 incorporates the sum of relevant data concerning compound nomenclature, structure and classification. For summary of chemical and psychoactive effect classification overlap, Supplementary Table 2 should be consulted.

3.2. Consideration of psychoactive categories

3.2.1. Monoaminergic

Pathways of dopaminergic, adrenergic and serotonergic transmission hold integral roles within regulation of cognition, perception and emotion. Perturbation in the functioning of these systems relates closely, dependent upon mechanistic specificity, to a range of psychoactive influences extending from therapeutic alleviation of depression to induction of intense psychedelic and hallucinogenic experience. There are in practice numerous physiological processes associated with neurotransmitter regulation as modulated through the actions of neuroactive substances, and as such the pharmacology of such compounds is varied. Whilst receptor agonism and antagonism is a feature within selected classes, enhancement of synaptic neurotransmitter concentration through induction of release or inhibition of reuptake forms a generally dominant mode of action.[47, 48]

In the overwhelming majority of instances, a close chemical similarity to endogenous neurotransmitters is apparent (as highlighted within Figure 4). Functionalisation of the phenylethylamine unit central within catecholamines dopamine (DA) and NA permits rational design of compounds possessive of a spectrum of stimulant, empathogenic and psychedelic effects. Tryptamine-derived serotonin (5-HT) mimics, as direct 5-HT receptor agonists, are further notable for their hallucinogenic influence.

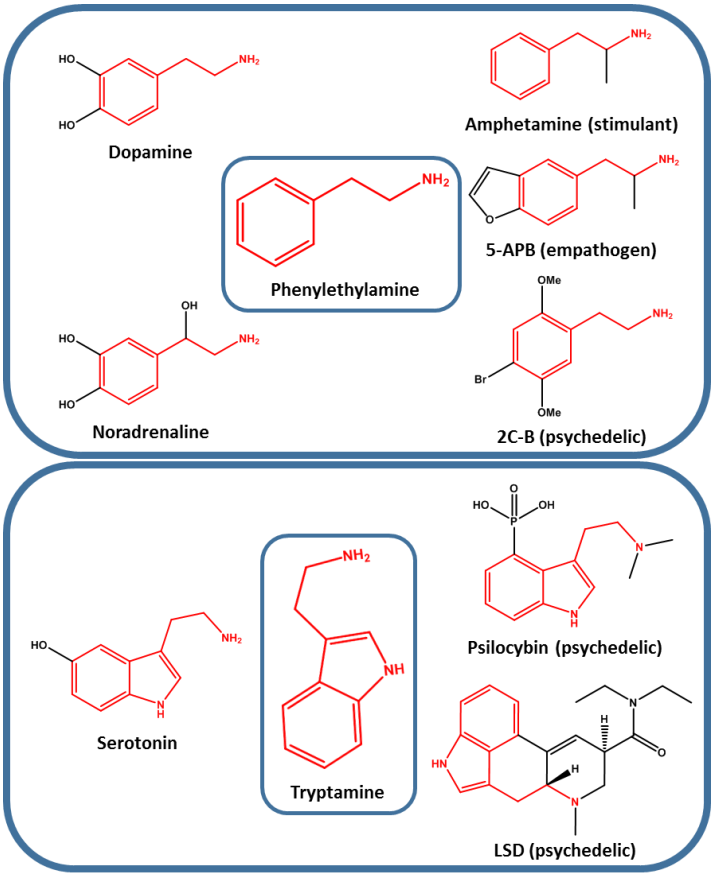
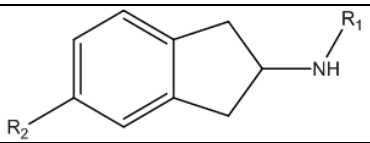
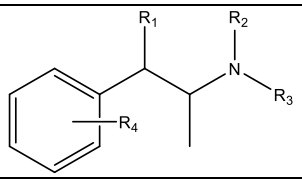
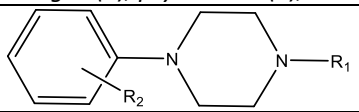
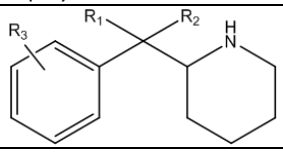
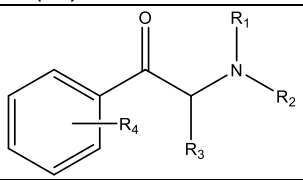
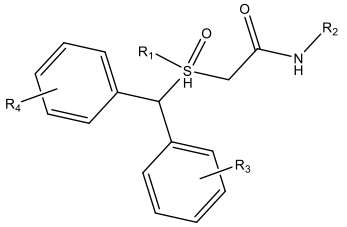
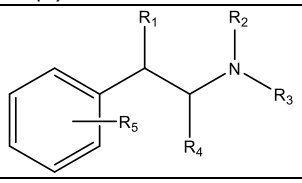
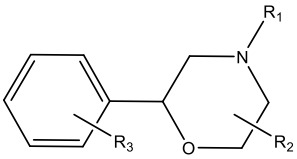


Figure 4. Overview of shared structural motifs common to endogenous neurotransmitters and monoaminergic NPS.

3.2.1.1 Stimulant

Characterised by a capacity to invoke senses of wakefulness and heightened energy, the typical stimulant belongs to the broad family of substituted phenylethylamines (as outlined within Table 2). Cathinone and pyrrolidinophenone derivatives are notably numerous, forming as they do common constituents within "bath salt" blends.[6] Tropane cocaine analogues and modafinil mimics form notable categories based upon alternative structural motifs.

	Structural basis	NPS	EPDA
Aminoindane		2-AI, 5-IAI, NM-2-AI	**None**
	Varying patterns of DA, NA and 5-HT reuptake inhibition and release.[49] Conformationally-restricted phenylethylamine. *Empathogen (1), stimulant (2)*		

Amphetamine		Methiopopamine, DMA, 4-MA **(Total 21)**	Amphetamine, cathine, methamphetamine **(Total 5)**
	Stimulation of DA release, inhibition DA, NA and 5-HT reuptake.[50] *Empathogen (7), psychedelic (2), stimulant (12)*		
Arylpiperazine		BZP, MBZP, 4-MeOPP **(Total 17)**	**None**
	Varying patterns of DA, NA and 5-HT reuptake inhibition and release.[51, 52] *Stimulant (17)*		
Benzylpiperidine		Ethylphenidate, propylphenidate pipradrol **(Total 15)**	**None**
	Stimulation of DA, NA release with concurrent inhibition of reuptake.[48, 51, 53] Conformationally-restricted phenylethylamine. *Stimulant (15)*		
Cathinone		Ethcathinone, buphedrone, hexedrone **(Total 61)**	Cathinone, diethylpropion
	Stimulation of DA release, inhibition DA, NA and 5-HT reuptake.[54, 55] *Empathogen (8), psychedelic (1), stimulant (52)*		
Modafinil-like		Modafinil, adrafinil, fladrafinil **(Total 5)**	**None**
	Purported perturbation of DA transmission.[56] *Stimulant (5)*		
Phenylalkylamine - other		Phenethylamine, NMPEA, camfetamine **(Total 15)**	Chlorphentermine, oxilofrine, sibutramine **(Total 5)**
	Generally possessive of stimulant activity. Incorporating phenibut, a GABAergic sedative. *Sedative (1), stimulant (14)*		
Phenylmorpholine		Phenetrazine, isophenmetrazine, G-130 **(Total 12)**	Phenmetrazine, phendimetrazine
	Stimulation of DA, NA release.[57] Conformationally-restricted phenylethylamine. *Stimulant (12)*		

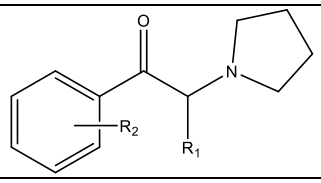
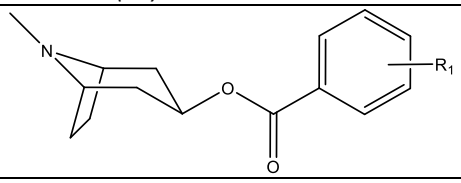
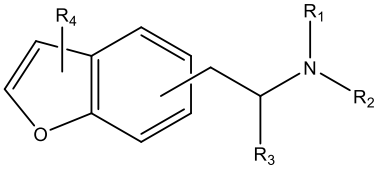
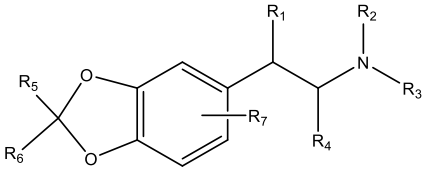
Pyrrolidinophenone		α-PVP, 4'-Fluoro-α-PVP, α-PNP **(Total 44)**	**None**
	Stimulation of DA release, inhibition DA, NA and 5-HT reuptake.[58] *Stimulant (44)*		
Tropane and analogues		Dichloropane, nitracaine, dimethocaine **(Total 8)**	Cocaine, ecgonine, benzoylecgonine
	Inhibition of DA, NA and 5-HT reuptake.[48,59] Hyoscine and hysocamine alternatively function as cholinergic deliriants. *Stimulant (6), psychedelic (2)*		
Minor	Methoxyphenylalkylamine – other (4), non-specified alkaloid (4), unclassified (5)	4-EA NBOMe, 2-MA, vanoxerine **(Total 13)**	Amineptine, aminorex, pemoline **(Total 4)**

Table 2. Overview of key structural features, prominent category entries and recovered EPDA analogues related to chemical groupings prevalent amongst stimulant NPS.

3.2.1.2. Empathogen

Such compounds are characterised by their broad similarity in psychoactive effect to methylenedioxymethamphetamine (MDMA) – described commonly as the induction of stimulation and euphoria accompanied by heightened feelings of social connectivity.[59, 60] Their distinctive properties are associated with increased serotonergic potency, likely a function of the fused tryptamine-like heterocyclic units apparent in benzofurans and methylenedioxyphenylalkylamines (detailed in Table 3).

	Structural basis	NPS	EPDA
Benzofuran		5-APB, 6-APB, 5-EAPB **(Total 15)**	**None**
	Inhibition of reuptake and stimulation of release of DA, NA and 5-HT. Agonism at 5-HT_2 receptor.[60] *Empathogen (14), psychedelic (1)*		
Methylenedioxy-phenylalkylamine		Ethylone, butylone, EDMA **(Total 29)**	MDMA, MMDA, tenamfetamine **(Total 4)**
	Inhibition of reuptake and stimulation of release of DA, NA and 5-HT. Weak agonism at 5-HT_2 receptor.[54, 61] *Empathogen (27), psychedelic (2)*		

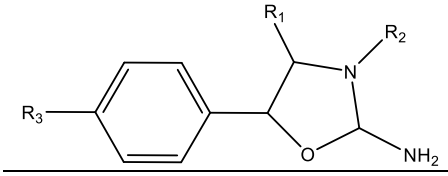
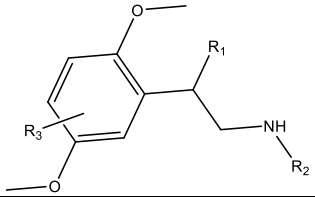
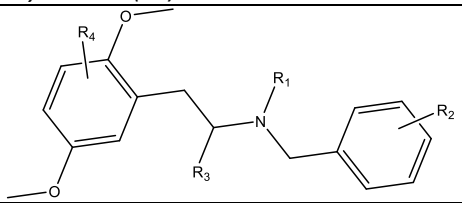
Oxazoline		3,4-DMAR, 4,4'-DMAR, N-Methyl aminorex derivative	Aminorex, 4-methylaminorex, pemoline
	Inhibition of DA, NA and 5-HT reuptake, alongside stimulation of 5-HT release.[62] Bears conformationally-restricted phenylethylamine moiety. *Empathogen (3)*		
Minor	Aminoindane (1), amphetamine (7), cathinone (8), methoxyphenylalkylamine – other (2), tryptamine (1)	Mephedrone, 4-FA, 5-API **(Total 19)**	**None**

Table 3. Overview of key structural features, prominent category entries and recovered EPDA analogues related to chemical groupings prevalent amongst empathogen NPS.

3.2.1.3. Psychedelic

NPS appearing under the description "psychedelic" are noted for their induction of altered states of perception characterised by visual hallucination and profound changes in cognition. As direct agonists at selected 5-HT receptors (refer to Table 4), tryptamine serotonin analogues and dimethoxy-substituted phenylalkylamines constitute the bulk of this class.[63, 64]

	Structural basis	NPS	EPDA
xC-Phenylalkylamine		2C-C, 2C-I, 2C-N **(Total 23)**	2C-B, 2C-T-7
	Agonism and antagonism across 5-HT_2 receptors.[65] Dimethoxy substituent essential in induction of hallucinogenic effect.[66] *Psychedelic (23)*		
xC-NBx-Phenylalkylamine		25B-NBOMe 25C-NBOMe 25N-NBOMe **(Total 21)**	**None**
	Agonism at 5-HT_2 receptors.[67] Dimethoxy substituent essential in induction of hallucinogenic effect. *Psychedelic (21)*		

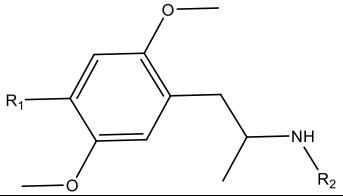
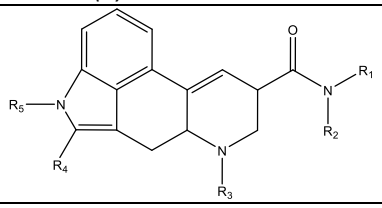
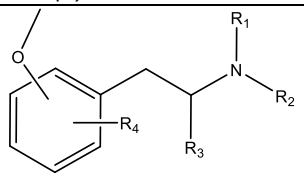
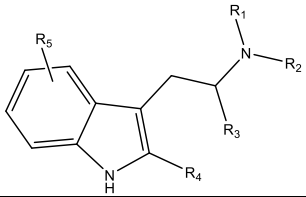
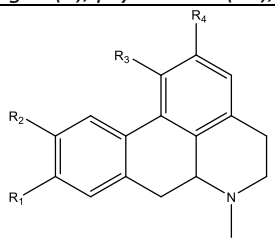
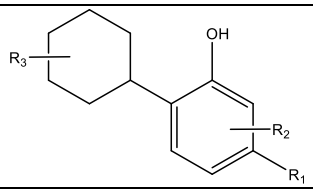
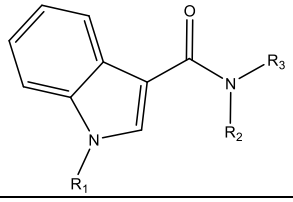
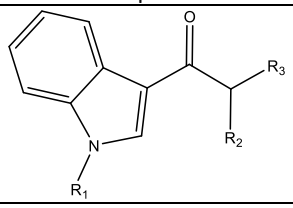
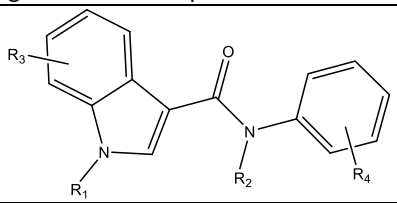
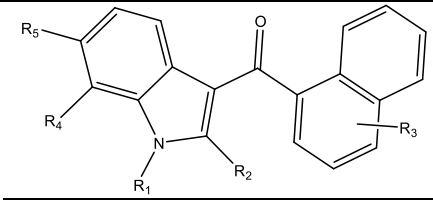
DOx amphetamine		DOC, DOI, DOB-Dragonfly **(Total 9)**	DOET, DOB, DOM **(Total 4)**
	Agonism across 5-HT_2 receptors.[68] Dimethoxy substituent essential in induction of hallucinogenic effect. *Psychedelic (9)*		
Lysergamide		LSA, AL-LAD, ETH-LAD **(Total 7)**	LSD
	Agonism across broad range of 5-HT receptors.[64, 69] Tryptamine unit embedded within polycyclic framework. *Psychedelic (7)*		
Methoxy-phenylalkylamine - other		Mescaline, proscaline, 3C-E **(Total 18)**	3,4,5-Trimethoxy-amphetamine, 4-Methoxy-amphetamine
	Psychedelic effect generally present with dialkoxy and trialkoxy substitution. Monomethoxy associated with stimulant profile. *Psychedelic (12), stimulant (4), empathogen (2)*		
Tryptamine		DPT, α-TMT, MET **(Total 34)**	α-MT, DMT, bufotenine **(Total 6)**
	Agonism across 5-HT_1 and 5-HT_2 receptors.[63, 70, 71] Structural analogue of serotonin. *Empathogen (1), psychedelic (32), sedative (1)*		
Quinoline alklaloid		Nuciferine, aporphine, glaucine	**None**
	Pattern of activity unestablished. DA receptor agonism noted.[72] *Psychedelic (3)*		
Minor	Amphetamine (2), benzofuran (1), cathinone (1), methylenedioxy-phenylalkylamine (2), tropane and analogues (2), unclassified (3)	Hyoscamine, 5-MeO-DiBF, 5-MAPDI **(Total 11)**	**None**

Table 4. Overview of key structural features, prominent category entries and recovered EPDA analogues related to chemical groupings prevalent amongst psychedelic NPS.

3.2.2. Cannabinergic

Cannabinoid

A variety of synthetic agonists active at cannabinoid CB_1 and CB_2 receptors have, through consequence of the popularity of "Spice"-style blends, entered into circulation.[73] With exception of the notable class of THC-like cyclohexylphenols, the great majority of developed compounds display structures – typically carbonyl-substituted indole and indazole derivatives – distinct from natural endogenous or phytochemical activators (listed in full within Table 5).

	Structural basis	NPS	EPDA
Cyclohexylphenol		HU-210, HU-308 CP-47,497 **(Total 10)**	THC
	Agonist at CB receptors.[73] Structural analogues of THC.		
Indole-alkyl carboxamide		ADBICA, STS-135, MN-25 **(Total 57)**	**None**
	Agonist at CB receptors.		
Indole-alkyl ketone		UR-144, AB-001, AM-1248 **(Total 14)**	**None**
	Agonist at CB receptors.		
Indole-aryl carboxamide		SGT-25, MN-24, PX-1 **(Total 28)**	**None**
	Agonist at CB receptors.		
Indole-naphthyl ketone		JWH-018, JWH-200, AM-2201 **(Total 55)**	**None**
	Agonist at CB receptors.		

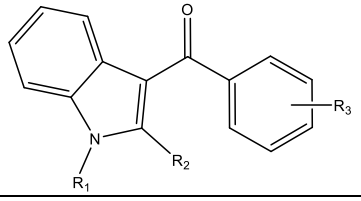
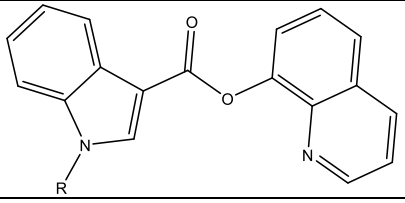
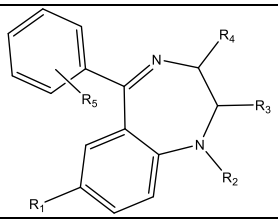
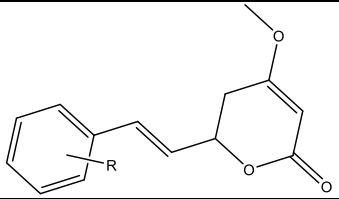
Indole-phenyl ketone		RCS-4, JWH-250, AM-679 **(Total 31)**	**None**
	Agonist at CB receptors. Incorporating benzoylindoles and phenylcacetylindoles.		
Indole-quinoline ester		PB-22, NM-2201, BB-22 **(Total 12)**	**None**
	Agonist at CB receptors.		
Minor	Unclassified (16)	Methanandamide, JWH-175, URB597	**None**

Table 5. Overview of key structural features, prominent category entries and recovered EPDA analogues related to selected chemical groupings prevalent amongst cannabinoid NPS.

3.2.3. GABAergic

Sedative

Exclusively inhibitory in effect, potentiation of signalling through GABA receptors imparts sedative and depressant outcome. GABAergic drug classes, including benzodiazepines and quinazolines, function in general as allosteric receptor agonists, occupying distinct binding sites.[74] Kavalactones – a selection of natural products isolated from the roots of kava (*Piper methysticum*) – exert effects through an apparently distinct mechanism.[75] Further covered, exclusively under the heading of EPDA (and hence omitted from inclusion within Table 6), is the barbiturate class.

	Structural basis	NPS	EPDA
Benzodiazepine		Etizolam, nitrazolam, phenazepam **(Total 21)**	Diazepam, midazolam, prazepam **(Total 20)**
	Allosteric agonism of $GABA_A$ receptor.[76] *Sedative (21)*		
Kavalactone		Kavain, methysticin, yangonin **(Total 6)**	**None**
	Potentiation of GABA signalling through undefined mechanism.[77, 78]. *Sedative (6)*		

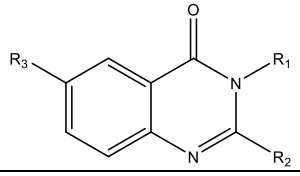
Quinazoline		Etaqualone, afloqualone, mebroqualone **(Total 4)**	Methaqualone
	Allosteric agonism of $GABA_A$ receptor.[79] *Sedative (4)*		
Minor	Non-specified alkaloid (1), phenylalkylamine – other (1), tryptamine (1), unclassified (5)	5-HTP, 1,4-butanediol, zopiclone **(Total 8)**	Pregabalin, fospropofol, GHB **(Total 9)**

Table 6. Overview of key structural features, prominent category entries and recovered EPDA analogues related to chemical groupings prevalent amongst sedative NPS.

3.2.4. Glutamatergic

Dissociative

Whilst three primary classes of excitatory ionotropic glutamate receptor are characterised, it is those of the NMDA variety which are considered of greatest pharmacological relevance. Antagonists, notably analogues of ketamine and phencyclidine (PCP), are associated with unique forms of dissociative anaesthesia – incorporating states typically characterised by hallucination, "out-of-body" experience and sedation.[80, 81] Table 7 details the prominent chemical groupings.

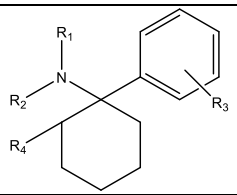
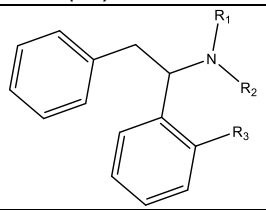
	Structural basis	NPS	EPDA
Aryl-cyclohexylamine		Methoxetamine, deschloroketamine, 4-MeO-PCP **(Total 14)**	PCP, PCPy, tenocyclidine, **(Total 4)**
	Non-competitive antagonism at NMDA receptor.[82] *Dissociative (14)*		
Diarylethylamine		Ephenidine, diphenidine, NPDPA **(Total 5)**	**None**
	Non-competitive antagonism at NMDA receptor.[83] Incorporates opioidergic MT-45. *Dissociative (4), opioid (1)*		
Minor	Unclassified (2)	Salvinorin A, memantine	**None**

Table 7. Overview of key structural features, prominent category entries and recovered EPDA analogues related to chemical groupings prevalent amongst dissociative NPS.

3.2.5. Opioidergic

Opioid

Agonists at the major subclasses of opioid receptor (δ, κ, μ and nociceptin) are capable of inducing potent analgaesic effect, coupled commonly with mild euphoria.[84] Dependence liability is notably high.[85] A variety of categories, including the numerous analogues of morphine, methadone and pethidine (excluded from Table 8) occur exclusively as EPDA.

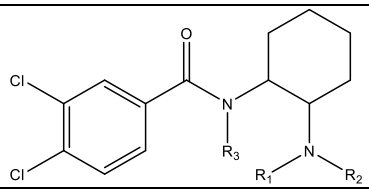
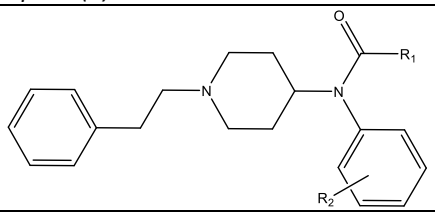
	Structural basis	NPS	EPDA
Dichlorobenzamide		AH-7921, U-47700, U-49900	**None**
	Agonism across range of opioid receptor subtypes.[86] *Opioid (3)*		
Fentanyl derivative		Acetylfentanyl, valerylfentanyl, furanylfentanyl **(Total 16)**	Fentanyl, carfentanil, lofentanil **(Total 22)**
	Agonism across range of opioid receptor subtypes.[87] *Opioid (16)*		
Minor	Diarylethylamine (1), non-specified alklaloid (3), unclassified (2)	W-15, mitragynine, akuammine **(Total 6)**	**None**

Table 8. Overview of key structural features, prominent category entries and recovered EPDA analogues related to chemical groupings prevalent amongst opioid NPS.

4. Discussion

The recent emergence into circulation of an expanding library of novel psychoactive substances (NPS) constitutes an evolving risk to public health. Efforts to define the landscape of identified compounds with respect to their effect profiles and structural features have proved challenging on account both of the novelty and obscurity of many, and further of the generally narrow scope of reports attesting their detection and characterisation. As such, the intentions of this study have been to collate from accessible source material an expansive inventory of definitively-acknowledged NPS. Like entries were classified with respect to chemical, pharmacological and psychoactive similarity and, where appropriate, related to analogous established drugs of abuse.

In total, a sum of 690 distinct novel substances were identified, supplemented by 155 established drugs of abuse. It is apparent that, considered broadly, composition in terms of psychoactive profile amongst the NPS set exhibits significant variation from that noted across EPDA (refer to Section 3.1.). This is illustrated starkly in the preponderance of synthetic cannabinoids present within the former (matching solely in effect against THC), and additionally by the comparative dominance of opioids – notably the exclusive classes of morphine, methadone and pethidine analogues – amongst the latter. Whilst the development and spread of cannabimimetics represents a recent phenomenon, the establishment over many decades of opiate-like substances within clinical practice has contributed towards the characterisation of their liability towards abuse and in turn to their scheduling.[88]

There remains a substantial number of chemical categories co-occurring within both novel and established sets. Contributing substantially towards impetus behind the development of NPS has been the desire to circumvent existing legislation concerning control of well-characterised recreational or abuse-liable drugs.[9] As such, the synthesis of structural analogues through minor modification of known compounds with an intention of retaining or even potentiating desired psychoactive outcome has assisted greatly in spurring the upturn in emergence of new substances (notably amongst the readily-adapted monoaminergic phenylalkylamines). Analogues of amphetamine and cathinone are

accordingly plentiful, whilst similarly well-represented are methylenedioxy entries mimicking configuration of MDMA and hallucinogenic methoxy-substituted 2C- and DOx equivalents.[63, 89] Despite the general obscurity of a great number of these newer molecules, aspects of their psychoactive and toxicological profiles be inferred with confidence through application of the more extensive knowledge accrued within their established relatives – methodology akin to that of "read-across".[90-92] Such a principle which can similarly be extended to function within all chemically-related categories incorporating at least a single EPDA analogue and across which pharmacological mechanism of action can be reliably postulated as shared. This is a list which may include, but would not be limited to, the serotonergic tryptamines and lysergamides, glutaminergic arylcyclohexylamines, GABAergic benzodiazepines and opioid fentanyl analogues.

In contrast to the aforementioned structural mimics, which correspond closely to recognised psychoactive substances, a variety of classes exhibit novelty and distinctness in molecular composition. In such instances the breadth and quality of study data relating the properties of member compounds is typically inferior, and cross-group extrapolation of effects a more substantial challenge. Consideration of attributed pharmacological mechanism of action, alongside governing structure-activity relationships, adopts greater importance. A variety of notable categories fall under this broad description, including benzofuran phenylalkylamines, diaryethylamines and the great majority of synthetic cannabinoids. Uncharacterised benzofurans might reliably be inferred to possess empathogenic qualities as a function of their structural similarity to the methylenedioxy MDMA derivatives, implying a monoaminergic mode of action (common to phenylalkylamines) distinguished by further weak serotonin receptor agonism.[61] Diarylethylamines likewise share great correspondence with NMDA antagonist arylcyclohexylamines – a class of dissociatives including amongst its number the extensively-studied ketamine and PCP.

The single largest effect category present within NPS, definitive characterisation of synthetic cannabinoid action presents unique challenges. Of the 223 compounds identified, a mere ten (each of

the cyclohexylphenol class) bear structural relation to THC. Composing the remainder are an array of functionalised nitrogen heterocycle derivatives, distinct in composition from established psychoactives. It therefore follows that whilst the shared mechanism of cannabinergic receptor agonism ensures predictability in short-term subjective effects, inference of the physical and psychological consequences of continued use constitutes a greater trial. Ease of functionalisation ensures that the development of novel analogues remains ongoing, with the composition of cannabimimetic blends showing great variety.[5]

Examples considered across the above text provide broad overviews of how predictive approaches, based upon consideration of molecular similarity, might be employed in order to credibly infer the properties of the multitude of uncharacterised NPS. Drawing and collating from a variety of authoritative sources, an extensive survey of the chemical landscape is presented. A total of 647 of the 690 identified substances (94%) may be placed into one of the 35 defined structural groupings – a practice which greatly orders and simplifies understanding of the set. Of these classes, 17 are seen to co-occur amongst EPDA – thus granting scope for direct comparison of effect profile. Pharmacological system of action is attributable within 676 members (98%) – furnishing mechanistic rationale which will enhance confidence in proposed structure-activity relationships. To the knowledge of the authors, this represents the most thorough unified structural repository of NPS – in terms both of numerical composition and of pharmacological consideration – present within the literature at this time. Provision of unambiguous structural identifiers for each entry, in the form of SMILES strings, allows further for ready research use.

References

[1] M. E. Liechti, *Swiss Med. Wkly*. **2015,** *145*, 1-12

[2] J. Ramsey, P. I. Dargan, M. Smyllie, S. Davies, J. Button, D. W. Holt, D. M. Wood, *QJM* **2010**, *103*, 777-783

[3] J. B. Zawilska, D. Andrzejczak, *Drug Alcohol Depend.* **2015**, *157*, 1-17

[4] S. W. Smith, F. M. Garlich, in *Novel Psychoactive Substances: Classification, Pharmacology and Toxicology*, (P. Dargan, D.M. Wood), **2013**, Academic Press; Boston, pp. 55-77

[5] K. A. Seely, J. Lapoint, J. H. Moran, L. Fattore, *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* **2012**, *39*, 234-243

[6] C. L. German, A. E. Fleckenstein, G. R. Hanson*, Life Sci.* **2014**, 97, *2-8*

[7] L. Karila, B. Megarbane, O. Cottencin, M. Lejoyeux, *Curr. Neuropharmacol.* **2015**, *13*, 12-20

[8] J. P. Smith, O. B. Sutcliffe, C. E. Banks, *Analyst* **2015**, *140*, 4932-4948

[9] S. L. Hill, S. H. L. Thomas, *Clin. Toxicol.* **2011**, *49*, 705-719

[10] S. Elliott, J. Evans, *Forensic Sci. Int.* **2014**, *243*, 55-60

[11] A. V. Larchenko, M. A. Suvorov, V. I. Andryukhin, Y. V. Kaurov, A. V. Suvorov, *Sovremennye Tehnologii v Medicine* **2017**, *9*, 185-196

[12] B. K. Logan, A. L. A. Mohr, M. Friscia, A. J. Krotulski, D. M. Papsun, S. L. Kacinko, J. D. Ropero-Miller, M. A. Huestis, *J. Anal. Toxicol.* **2017**, *41*, 573-610

[13] V. Law, C. Knox, Y. Djoumbou, T. Jewison, A. C. Guo, Y. F. Liu, A. Maciejewski, D. Arndt, M. Wilson, V. Neveu, A. Tang, G. Gabriel, C. Ly, S. Adamjee, Z. T. Dame, B. S. Han, Y. Zhou, D. S. Wishart, *Nucleic Acids Res.* **2014**, *42*, 1091-1097

[14] *The Challenge of New Psychoactive Substances*, United Nations Office on Drugs and Crime

[15] *Europol 2005 Annual Report on the Implementation of Council Decision 2005/387/Jha*, European Monitoring Centre for Drugs and Drug Addiction

[16] *Europol 2006 Annual Report on the Implementation of Council Decision 2005/387/Jha*, European Monitoring Centre for Drugs and Drug Addiction

[17] *Europol 2007 Annual Report on the Implementation of Council Decision 2005/387/Jha*, European Monitoring Centre for Drugs and Drug Addiction

[18] *Europol 2008 Annual Report on the Implementation of Council Decision 2005/387/Jha*, European Monitoring Centre for Drugs and Drug Addiction

[19] *Europol 2009 Annual Report on the Implementation of Council Decision 2005/387/Jha*, European Monitoring Centre for Drugs and Drug Addiction

[20] *Europol 2010 Annual Report on the Implementation of Council Decision 2005/387/Jha*, European Monitoring Centre for Drugs and Drug Addiction

[21] *Europol 2011 Annual Report on the Implementation of Council Decision 2005/387/Jha*, European Monitoring Centre for Drugs and Drug Addiction

[22] *Europol 2012 Annual Report on the Implementation of Council Decision 2005/387/Jha*, European Monitoring Centre for Drugs and Drug Addiction

[23] *Europol 2013 Annual Report on the Implementation of Council Decision 2005/387/Jha*, European Monitoring Centre for Drugs and Drug Addiction

[24] *Europol 2014 Annual Report on the Implementation of Council Decision 2005/387/Jha*, European Monitoring Centre for Drugs and Drug Addiction

[25] *Europol 2015 Annual Report on the Implementation of Council Decision 2005/387/Jha*, European Monitoring Centre for Drugs and Drug Addiction

[26] *Europol 2016 Annual Report on the Implementation of Council Decision 2005/387/Jha*, European Monitoring Centre for Drugs and Drug Addiction

[27] *The List of NPS Identified by the National Forensic Laboratory and Some of Them Verified by NMR at Faculty of Chemistry and Chemical Technology*, University of Ljubljana, National Forensic Laboratory Slovenia
[28] D. Debruyne, R. Le Boisselier, *Subst. Abuse Rehabil.* **2015**, *6*, 113-129
[29] S. D. Banister, M. Moir, J. Stuart, R. C. Kevin, K. E. Wood, M. Longworth, S. M. Wilkinson, C. Beinat, A. S. Buchanan, M. Glass, M. Connor, I. S. McGregor, M. Kassiou, *ACS Chem. Neurosci.* **2015**, *6*, 1546-1559
[30] S. D. Banister, M. Longworth, R. Kevin, S. Sachdev, M. Santiago, J. Stuart, J. B. C. Mack, M. Glass, I. S. McGregor, M. Connor, M. Kassiou, *ACS Chem. Neurosci.* **2016**, *7*, 1241-1254
[31] Z. H. Qian, W. Jia, T. Li, Z. D. Hua, C. M. Liu, *Drug Test. Anal.* **2017**, *9*, 51-60
[32] V. Shevyrin, V. Melkozerov, A. Nevero, O. Eltsov, Y. Morzherin, Y. Shafran, *Forensic Sci. Int.* **2014**, *242*, 72-80
[33] V. Shevyrin, V. Melkozerov, O. Eltsov, Y. Shafran, Y. Morzherin, *Forensic Sci. Int.* **2016**, *259*, 95-100
[34] N. Uchiyama, S. Matsuda, M. Kawamura, Y. Shimokawa, R. Kikura-Hanajiri, K. Aritake, Y. Urade, Y. Goda, *Forensic Sci. Int.* **2014**, *243*, 1-13
[35] N. Uchiyama, Y. Shimokawa, S. Matsuda, M. Kawamura, R. Kikura-Hanajiri, Y. Goda, *Forensic Toxicol.* **2014**, *32*, 105-115
[36] N. Uchiyama, Y. Shimokawa, R. Kikura-Hanajiri, Y. Demizu, Y. Goda, T. Hakamatsuka, *Forensic Toxicol.* **2015**, *33*, 244-259
[37] J. Nakajima, M. Takahashi, N. Uemura, T. Seto, H. Fukaya, J. Suzuki, M. Yoshida, M. Kusano, H. Nakayama, K. Zaitsu, A. Ishii, T. Moriyasu, D. Nakae, *Forensic Toxicol.* **2015**, *33*, 84-92
[38] K. Blakey, S. Boyd, S. Atkinson, J. Wolf, P. M. Slottje, K. Goodchild, J. McGowan*, Forensic Sci. Int.* **2016**, *260*, 40-53
[39] F. Y. Lai, C. Erratico, J. Kinyua, J. F. Mueller, A. Covaci, A. L. N. van Nuijs, *J. Pharm. Biomed. Anal.* **2015**, *114*, 355-375
[40] M. Coppola, R. Mondola, *Toxicol. Lett.* **2012**, *212*, 57-60
[41] S. Kim, P. A. Thiessen, E. E. Bolton, J. Chen, G. Fu, A. Gindulyte, L. Y. Han, J. E. He, S. Q. He, B. A. Shoemaker, J. Y. Wang, B. Yu, J. Zhang, S. H. Bryant, *Nucleic Acids Res.* **2016**, *44*, D1202-D1213
[42] H. E. Pence, A. Williams, *J. Chem. Educ.* **2010**, *87*, 1123-1124
[43] Daylight, www.daylight.com
[44] MarvinView, ChemAxon
[45] Erowid, https://www.erowid.org/
[46] C. H. Yang, A. Tarkhov, J. Marusczyk, B. Bienfait, J. Gasteiger, T. Kleinoeder, T. Magdziarz, O. Sacher, C. H. Schwab, J. Schwoebel, L. Terfloth, K. Arvidson, A. Richard, A. Worth, J. Rothman, *J. Chem. Inf. Model.* **2015**, *55*, 510-528
[47] M. V. Solanto, *Behav. Brain Res.* **1998**, *94*, 127-152
[48] L. Iversen, *Br. J. Pharmacol.* **2006**, *147*, S82-S88
[49] N. Pinterova, R. R. Horsley, T. Palenicek, *Front. Psychiatry* **2017**, *8:236*
[50] L. S. Seiden, K. E. Sabol, *Annu. Rev. Pharmacol. Tox.* **1993**, *33*, 639-677
[51] L. D. Simmler, A. Rickli, Y. Schramm, M. C. Hoener, M. E. Liechti, *Biochem. Pharmacol.* **2014**, *88*, 237-244
[52] D.M. Wood, J. Button, S. Lidder, J. Ramsey, D.W. Holt, P.I. Dargan, *J. Med. Toxicol.* **2008**, *4*, 254-257
[53] M. W. White, J. R. H. Archer, in *Novel Psychoactive Substances: Classification, Pharmacology and Toxicology*, (P. Dargan, D.M. Wood), **2013**, Academic Press; Boston, pp. 233-259

[54] L. D. Simmler, T. A. Buser, M. Donzelli, Y. Schramm, L. H. Dieu, J. Huwyler, S. Chaboz, M. C. Hoener, M. E. Liechti, *Br. J. Pharmacol.* **2013**, *168*, 458-470

[55] M. J. Valente, P. G. de Pinho, M. D. Bastos, F. Carvalho, M. Carvalho, *Arch. Toxicol.* **2014**, *88*, 15-45

[56] P. Gerrard, R. Malcolm, *Neuropsychiatr. Dis. Treat.* **2007**, *3*, 349-364

[57] K. N. Ellefsen, E. A. Taylor, P. Simmons, V. Willoughby, B. J. Hall, *J. Anal. Toxicol.* **2017**, *41*, 765-770

[58] K. Zaitsu, M. Katagi, H. Tsuchihashi, A. Ishii, *Forensic Toxicol.* **2014**, *32*, 1-8

[59] S. Singh, *Chem. Rev.* **2000**, *100*, 925-1024

[60] A. Rickli, S. Kopf, M.C. Hoener, M.E. Liechti, *Br. J. Pharmacol.* **2015**, *172*, 3412-3425

[61] A. R. Green, A. O. Mechan, J. M. Elliott, E. O'Shea, M. I. Colado, *Pharmacol. Rev.* **2003**, *55*, 463-508

[62] T. Hofmaier, A. Luf, A. Seddik, T. Stockner, M. Holy, M. Freissmuth, G. F. Ecker, R. Schmid, H. H. Sitte, O. Kudlacek, *Neurochem. Int.* **2014**, *73*, 32-41

[63] W. E. Fantegrossi, K. S. Murnane, C. J. Reissig, *Biochem. Pharmacol.* **2008**, *75*, 17-33

[64] D. E. Nichols, *Pharmacol. Ther.* **2004**, *101*, 131-181

[65] B. V. Dean, S. J. Stellpflug, A. M. Burnett, K. M. Engebretsen*, J. Med. Toxicol.* **2013**, *9*, 172-178

[66] A. T. Shulgin, A. Shulgin, *PiHKAL: A Chemical Love Story*, **1991,** Transform Press; Berkeley

[67] W. Lawn, M. Barratt, M. Williams, A. Horne, A. Winstock, *J. Psychopharmacol.* **2014**, *28*, 780-788

[68] T. S. Ray, *PLoS One* **2010**, *5:e9019*

[69] D. E. Nichols, *Wiley Interdiscip. Rev.: Membr. Transp. Signaling* **2012**, *1*, 559-579

[70] R. Tittarelli, G. Mannocchi, F. Pantano, F. S. Romolo, *Curr. Neuropharmacol.* **2015**, *13*, 26-46

[71] A. T. Shulgin, A. Shulgin, *TiHKAL: The Continuation*, **1997**, Transform Press; Berkeley

[72] S. Ribaric, *Molecules*, **2012**, *17*, 5289-5309

[73] M. S. Castaneto, D. A. Gorelick, N. A. Desrosiers, R. L. Hartman, S. Pirard, M. A. Huestis, *Drug Alcohol Depend.* **2014**, *144*, 12-41

[74] E. Sigel, M. E. Steinmann, *J. Biol. Chem.* **2012**, *287*, 40224-40231

[75] Y. Shao, K. He, B. L. Zheng, Q. Y. Zheng, *J. Chromatogr. A* **1998**, *825*, 1-8

[76] H. Mohler, J. M. Fritschy, U. Rudolph, *J. Pharmacol. Exp. Ther.* **2002**, *300*, 2-8

[77] Y. N. Singh, N. N. Singh, *CNS Drugs* **2002**, *16*, 731-743

[78] J. Sarris, E. LaPorte, I. Schweitzer, *Aust. N. Z. J. Psychiatry* **2011**, *45*, 27-35

[79] H. S. Abulkhair, K. M. El-Gamal, K. El-Adl, M. F. Fadl, *Med. Chem.* **2016**, *6*, 593-603

[80] H. Morris, J. Wallach, *Drug Test. Anal.* **2014**, *6*, 614-632

[81] P. Zarantonello, E. Bettini, A. Paio, C. Simoncelli, S. Terreni, F. Cardullo, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 2059-2063

[82] C. L. Craig, G. H. Loeffler, *Mil. Med.* **2014**, *179*, 1149-1157

[83] H. Kang, P. Park, Z. A. Bortolotto, S. D. Brandt, T. Colestock, J. Wallach, G. L. Collingridge, D. Lodge, *Neuropharmacology* **2017**, *112*, 144-149

[84] C. E. Inturrisi, *Clin. J. Pain* **2002**, *18*, S3-S13

[85] H. G. Birnbaum, A. G. White, M. Schiller, T. Waldman, J. M. Cleveland, C. L. Roland, *Pain Med.* **2011**, *12*, 657-667

[86] D. Fabregat-Safont, X. Carbon, M. Ventura, I. Fornis, E. Guillamon, J. V. Sancho, F. Hernandez, M. Ibanez, *Sci. Rep.* **2017**, *7:6338*

[87] J. C. Chen, E. R. Smith, M. Cahill, R. Cohen, J. B. Fishman, *Life Sci.* **1993**, *52*, 389-396

[88] R. Benyamin, A. M. Trescot, S. Datta, R. Buenaventura, R. Adlaka, N. Sehgal, S. E. Glaser, R. Vallejo, *Pain Physician* **2008**, *11*, S105-S120

[89] J. Welter-Luedeke, H. H. Maurer, *Ther. Drug Monit.* **2016**, *38*, 4-11

[90] T. W. Schultz, K. R. Przybylak, A.-N. Richarz, C. L. Mellor, S. E. Escher, S. P. Bradbury, M. T. D. Cronin, *Comput. Toxicol.* **2017**, *2*, 12-19
[91] K. R. Przybylak, T. W. Schultz, A.-N. Richarz, C. L. Mellor, S. E. Escher, M. T. D. Cronin, *Comput. Toxicol.* **2017**, *1*, 22-32
[92] C. L. Mellor, T. W. Schultz, K. R. Przybylak, A. N. Richarz, S. P. Bradbury, M. T. D. Cronin, *Comput. Toxicol.* **2017**, *2*, 1-11