ACMD

Advisory Council on the Misuse of Drugs

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Rt. Hon. Theresa May MP
Home Office
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13 September 2011

Dear Home Secretary,

Re: Desoxypipradrol (2-DPMP) advice

I write further to my correspondence of 29 October 2010 in relation to the compound desoxypipradrol (2-diphenylmethyl-piperidine, 2-DPMP). In its advice the Advisory Council on the Misuse of Drugs (ACMD) recommended that desoxypipradrol, identified in samples of a product known as 'Ivory Wave', should be subject to an immediate ban under the Open General Import Licence. This advice was accepted by the Government and a ban was implemented on 4 November 2011.

The ACMD has considered the available evidence and can now provide you with substantive consideration of the compound desoxypipradrol and its related compounds. A short report is annexed to this letter.

The National Poisons Information Service in Edinburgh highlighted that a number of individuals had presented to the Royal Edinburgh Infirmary in the summer of 2010 following use of desoxypipradrol with symptoms that were similar to amphetamine toxicity, but with predominant neuropsychiatric features including:

- Hallucinations
- Paranoia
- Severe Agitation

In some cases these effects persisted for several days after ingestion.

In the attached report the ACMD has considered the available evidence from forensic providers, the National Programme on Substance Abuse Deaths, Clinical Toxicology Services, scientific research and Government Departments on the harms and sales of desoxypipradrol.

The ACMD advises that the harms of desoxypipradrol are commensurate with other Class B drugs and recommend that it is controlled under the Misuse of Drugs Act 1971 as a Class B substance and in Schedule 1 of the Misuse of Drugs Regulations 2001 (as amended). In addition, the ACMD recommends that the structurally related compounds diphenylprolinol (diphenyl-2-pyrrolidinyl-methanol, D2PM) and its desoxy form 2-diphenylmethylpyrrolidine are controlled under the Misuse of Drugs Act 1971 as Class B substances and scheduled under the Misuse of Drugs Regulations 2001. The proposed generic definition will ensure that desoxypipradrol and all its related compounds, e.g. diphenylprolinol and diphenylmethylpyrrolidine, are fully captured (see annex 1 & 2). The ACMD understands that desoxypipradrol and its related compounds do not have any medicinal uses; however, the ACMD has not formally consulted with the industry.

The ACMD believes that there would be no conflicting issues with placing the generic definition in the Act as the three main drugs, desoxypipradrol, diphenylprolinol (D2PM) and 2-diphenylmethylpyrrolidine can all be analytically distinguished from one another and from other drugs in Schedule 2 Part II.

The positional isomers of pipradrol (diphenyl-2-piperidinemethanol), i.e. the diphenyl-3-piperidinemethanol and diphenyl-4-piperidinemethanol isomers would be Class B and in the absence of reference standards may not be readily distinguished from pipradrol (Class C) using routine methods of analysis (medicinal products containing pipradrol are no longer widely used and are not, as far as the ACMD are aware, available in the UK). Whilst, it should be possible to distinguish between pipradrol isomers using techniques such as NMR, in the long term it would be support forensic analysis to have reference standards of all the pipradrol positional isomers. The ACMD recommends that the Home Office considers commissioning the production of standards through the Forensic Early Warning System.

Yours sincerely,

Professor Les Iversen FRS

cc: Anne Milton – Parliamentary Under Secretary of State, Department of Health

Consideration of Desoxypipradrol (2-DPMP) and related pipradrol compounds

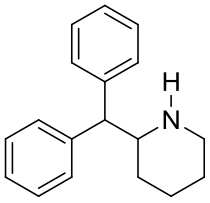
Background

In October 2010 the ACMD recommended to the Government that, 2-diphenylmethyl-piperidine (2-DPMP, here referred to as desoxypipradrol), which was being marketed at that time as 'Ivory Wave', should be subject to an immediate ban under the Open General Import Licence (OGIL). This advice was accepted by the Government and a ban was implemented on 4 November 2011.

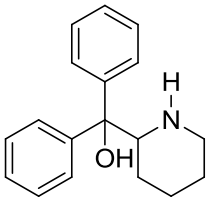
Published data on the effects of 2-DPMP are limited, although research on derivatives of desoxypipradrol show that they exhibit a cocaine-like binding profile (Schmitt *et al*., 2008).

Currently, there is no known medicinal use for this compound, although it was originally developed by Ciba-Geigy (Novartis) in 1953 to be used to wake patients following anaesthesia (Belucci, 1955).

This compound is related to pipradrol, a previously-licensed medicine for treatment of Attention Deficit Hyperactivity Disorder (ADHD), obesity and narcolepsy. Pipradrol is classified under the Misuse of Drugs Act as a Class C substance. Pipradrol still used is some countries, but its use is limited due to its abuse potential; it is a dopamine and norepinephrine reuptake inhibitor.



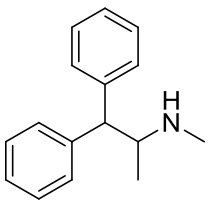
Desoxypipradrol



Pipradrol

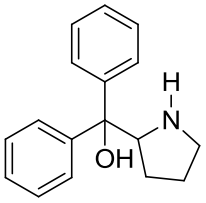
Pipradrol and its desoxy form have structurally related pyrrolidine analogues (see below) such as diphenylprolinol (diphenyl-2-pyrrolidinylmethanol, D2PM), for which there have been a number of recorded cases of cardiovascular and neuropsychiatric toxicity associated with recreational use (Lidder *et al*., 2008, Wood *et al*., 2008, Wood *et al*., 2011), and 2-diphenylmethyl-pyrrolidine, currently marketed, along with D2PM and various analogues, as chemical reagents for use as chiral catalysts in organic synthesis (Bertelsen *et al*., 2005, Sigma-Aldrich, 2007).

The two pairs of materials differ only by the size of the nitrogen-containing ring. Diphenylprolinol and its desoxy form have a five-membered (pyrrolidine) ring, while pipradrol and its desoxy form have a six-membered (piperidine) ring. It seems that the two desoxy forms have particularly long-lasting effects as

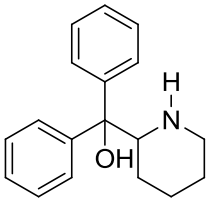


β-phenylmethylamphetamine

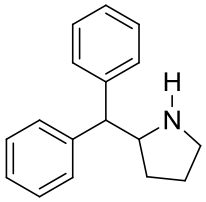
their structures are resistant to metabolism, meaning that they have longer half-lives in the body. A common feature of these compounds is that they are structurally related to β-phenylmethylamphetamine, which is also a potent stimulant with a long half life. However, these compounds differ from β-phenylmethylamphetamine in that the nitrogen atom is linked to the α-methyl group by two or three carbon atoms to form a ring.



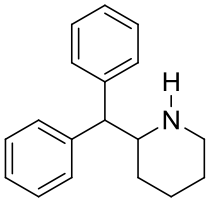
Diphenylprolinol



Pipradrol



Diphenylmethylpyrrolidine



Desoxypipradrol

Various analogues of these compounds have been investigated and found to have stimulant properties (Isbell, 1970 and US Patents). Simple modifications, for example, addition of halogen, alkyl or alkoxy groups on one or both of the phenyl rings or addition of alkyl, alkenyl, haloalkyl and hydroxyalkyl groups on the nitrogen atom have been reported to produce compounds having a stimulant effect on the CNS, which could lead to a range of 'designer' forms.

Other modifications that have been reported in the literature include replacing the piperidine ring with an azepane ring (7-membered ring), a morpholine ring or a pyridine ring (Winthrop, 1961; Enyedy, 2003). The piperidine ring has also been modified by substitution in the ring with an hydroxy group (Nodine, 1960), fusion of the piperidine ring with a benzene ring (Winthrop, 1961) and by substitution at the nitrogen atom with an ethano bridge to form a bicyclic ring system (Wikipedia, 2011).

Almost all of the analogues investigated are structurally related to the 2-isomer of desoxypipradrol, with 2 carbon atoms between the phenyl rings and the nitrogen atom. The only exceptions being the *N*-haloalkyl derivatives of desoxypipradrol and the pyridine analogue in which the 2-, 3- and 4-isomers were all reported to be active. No examples were found of compounds related to 1-diphenylmethylpiperidine (*N*-diphenylmethyl-piperidine).

Whilst, it should be possible to distinguish between pipradrol isomers using techniques such as NMR, in the long term it would be support forensic analysis to have reference standards of all the pipradrol positional isomers. The ACMD recommends that the Home Office considers commissioning the production of standards through the Forensic Early Warning System.

Use and prevalence

The National Poisons Information Service in Edinburgh highlighted that a number of individuals had presented to the Royal Edinburgh Infirmary in the summer of 2010 following their use of desoxypipradrol with symptoms that

were similar to amphetamine toxicity, but with predominant neuropsychiatric features including:

- Hallucinations
- Paranoia
- Severe Agitation

In some patients the symptoms were still being manifested 5-7 days after ingestion and some patients presented directly to psychiatric services, bypassing A&E. There were approximately 12 cases over this period. It was subsequently reported that 4 out of 5 of the Edinburgh cases in whom confirmatory toxicological screening was carried out were positive for desoxypipradrol in urine/blood confirming exposure.

The number of patients presenting after confirmed ingestion of desoxypipradrol after the summer of 2010 has dramatically reduced in Edinburgh with no cases in 2011 and data from the National Poisons Information Service (NPIS) suggests that there has also been a significant reduction nationally. However, as noted below cases of diphenylprolinol (D2PM) toxicity continue to occur.

So far 3 deaths have been linked to the use of desoxypipradrol (awaiting final reports).

Data provided by the Home Office Centre for Applied Science and Technology (CAST) under its Forensic Early Warning System (FEWS) reported one sample of 2-DPMP (from a head-shop), 10 samples of D2PM and 4 samples of desoxy-D2PM (from test purchases) during the pilot study.

LGC Forensics reported those samples of 'Ivory Wave' it had seen in 2009-2011 contained different active ingredients including the cathinone MDPV (methylenedioxypyrovalerone) then, after this became controlled, naphyrone, and when this too was controlled, desoxypipradrol. More recently, diphenylprolinol has begun to appear in 'legal high' products.

Desoxypipradrol has been found as a white powder that is generally taken by nasal insufflation (sniffing the powder into the nose) or swallowing after wrapping the powder in a cigarette paper ("bombing") to avoid any unpleasant taste.

It is considered that 2-DPMP and its related compounds, as captured under the generic definition (see recommendation), have potential social harms. It appears to the ACMD that such harms are likely in relation to the impairment of function through drug use (mood disorders, changes to lifestyle), loss of relationships and the potential harm to others (directly and indirectly).

Preclinical Data

In the 1950's, Ciba-Geigy investigated the effects of desoxypipradrol, amphetamine and d-methylamphetamine on small animals (report kindly provided by Novartis). The LD_{50} is the dose, which kills 50% of the animals:

Table 1. Toxicity of desoxypipradrol and other compounds, measured as LD_{50}, to small animals (*iv – intravenous, sc – subcutaneous, po – orally).

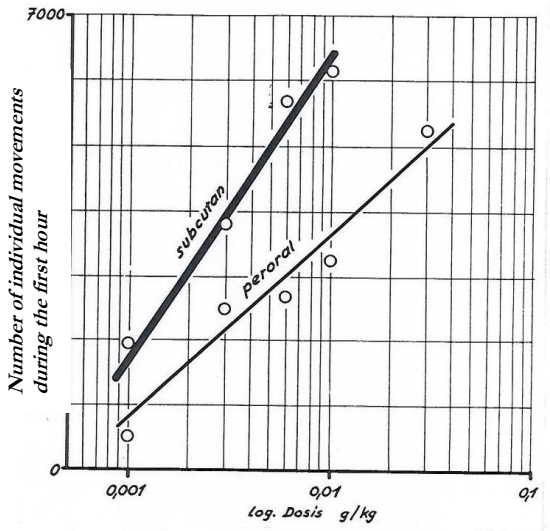
	Desoxypipradrol LD_{50} g/kg	**amphetamine LD_{50} g/kg**	**d-methylamphetamine LD_{50} g/kg**
Mouse iv*	0.020	0.050	0.020
" sc	0.047	0.060	0.080
" po	0.050	0.070	0.150
Rat iv	0.015	0.012	0.023
" sc	0.030	0.012	0.015
" po	0.080	0.013	0.025
Rabbit iv	0.006	0.040	0.030
" sc	0.007	0.045	0.020
" po	0.080	0.170	0.200

Table 1 shows that desoxypipradrol is, in many cases, more toxic than amphetamine and d-methylamphetamine.

The Ciba-Geigy report (from the 1950's) also noted that desoxypipradrol:

" produced a marked central arousal in various, non-anaesthetised animals, consisting initially of general agitation, subsequently a greater degree of increase in co-ordinated motility, heightened reflexes, compelled movements and relatively slight respiratory stimulation.
This was easily discernible objectively in the normal mouse with the aid of the cage movement registration method. With this method the individual movements are registered directly and added up by means of a totaliser".

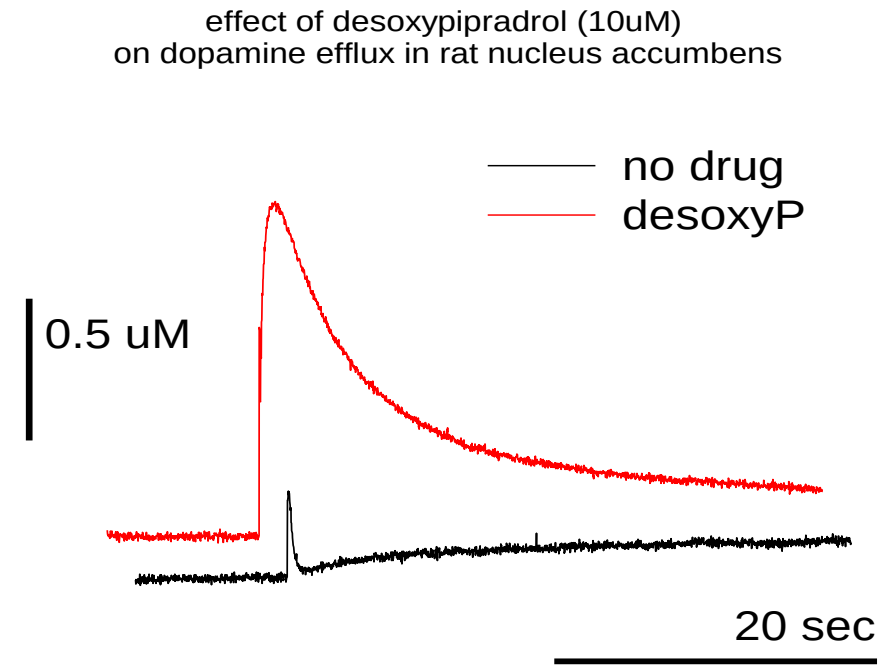
Figure 1. Effectiveness of desoxypipradrol in stimulating activity in mice when administered subcutaneously (heavy line) or orally (thin line) (Figure reproduced with kind permission of Novartis)



The data show that desoxypipradrol is effective as a stimulant in doses comparable to those for amphetamine or methylamphetamine – from 1 mg/kg upwards. For the purposes of its research at the time, Novartis recommended an initial human dose of 1mg or less, (ca 0.014 mg/kg). Anecdotal information would suggest that the human dose is only a few mg, with 10mg or more being considered harmful.

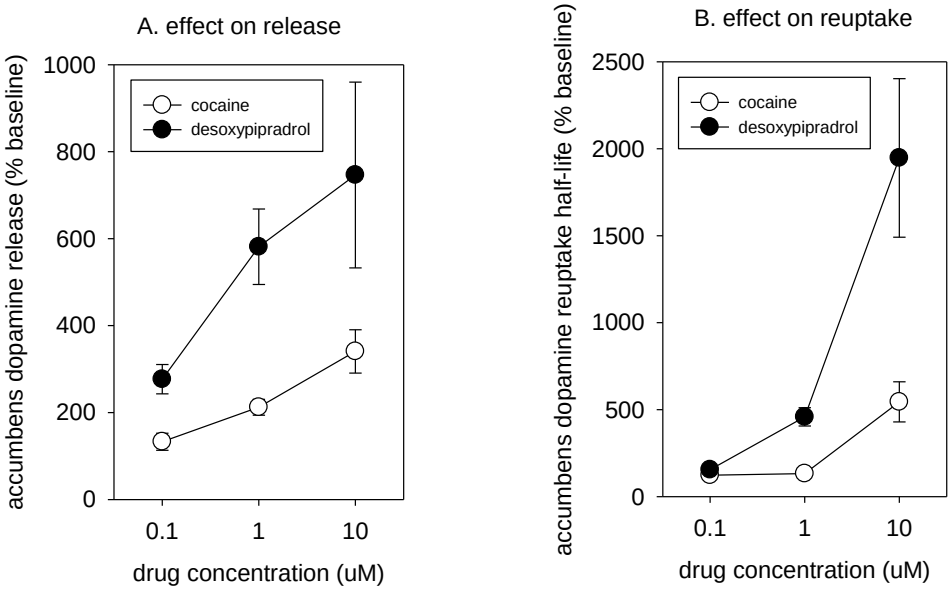
Experimental data supplied by Dr Colin Davidson (St Georges, University of London, 2011) demonstrated that desoxypipradrol potently stimulated dopamine release from rat brain slices *in vitro*. Dopamine release was measured from the region of the nucleus accumbens, using carbon fibre microelectrodes and fast cyclic voltammetry to electrically measure the oxidations of dopamine. The rate of recovery of stimulated dopamine release also allowed measurement of the action of the drug as an inhibitor of the dopamine reuptake mechanism. Dopamine release in the nucleus accumbens is considered to be a key target for psychostimulant drugs.

Figure 2



It also proved possible to compare the potency of desoxypipradrol with the psychostimulant drug cocaine in the brain slice preparation. The results (Figure 3) indicate that desoxypipradrol is both more effective and more potent than cocaine in stimulating dopamine release and in inhibiting its reuptake.

Figure 3. Comparison of potencies of desoxypipradrol and cocaine in releasing dopamine, and inhibiting inactivation in rat brain slice preparations (C. Davidson, unpublished)



The results both from Novartis and from Dr Davidson indicate that desoxypipradrol is very potent and comparable to amphetamine or methylamphetamine in its potential to cause acute toxicity. The available human data also show it to be a long-lasting substance, capable of eliciting agitation lasting for several days after a single dose.

In addition to the reports of toxicity associated with the use of desoxypipradrol noted above, there have also been reports of significant toxicity associated with the recreational use of the related compound diphenylprolinol (D2PM). In addition, reports from forensic providers suggest that D2PM has replaced desoxypipradrol in many 'Ivory Wave' products. The clinical toxicology service at Guy's and St Thomas' Hospital in London have documented 6 cases of analytically confirmed D2PM toxicity: 1 case in 2008 and 5 cases in 2010/2011 (Lidder *et al*., 2008, Wood *et al*., 2008, Wood *et al*., 2011). In these cases patients have presented with a variety of symptoms including:

- chest pain
- agitation
- anxiety
- insomnia
- hallucinations
- paranoia

In many of these cases patients have had ongoing features, in particular neuro-psychiatric features such as anxiety, insomnia and paranoia for up to 48-96 hours after use of D2PM.

Recommendation

The ACMD advises that the harms of desoxypipradrol are commensurate with other Class B drugs and recommend that it is controlled under the Misuse of Drugs Act 1971 as a Class B substance and in Schedule 1 of the Misuse of Drugs Regulations 2001 (as amended). Furthermore, we recommend that the structurally related compounds diphenylprolinol (diphenyl-2-pyrrolidinyl-methanol, D2PM) and its desoxy form 2-diphenylmethylpyrrolidine are similarly controlled under the Misuse of Drugs Act 1971 and scheduled under the Misuse of Drugs Regulations 2001 by virtue of a generic definition (see Annex 1 of the report) to ensure that desoxypipradrol and related compounds, e.g. diphenylprolinol, diphenylmethylpyrrolidine, are fully captured (see annex 1 & 2).

The ACMD understands that desoxypipradrol and its related compounds do not have any medicinal uses; however, the ACMD has not formally consulted with the industry.

The proposed generic definition includes desoxypipradrol and those analogues most likely to be produced as alternatives. Some of the compounds that fall within the scope of the proposed generic definition contain a hydroxy group, which can be converted to an ester or ether. Such compounds may have similar pharmacological properties to the parent

compound and therefore it is recommended that esters and ethers of these compounds are also subject to control under the Misuse of Drugs Act, 1971.

Whilst, ideally, any generic definition would include all possible positional isomers, this may mean that non-active compounds would also be controlled. Further, a definition to cover all of these potential analogues is feasible, but it would be very complex and possibly difficult to understand.

Under the definition that the ACMD propose at Annex 1 esters and ethers of pipradrol would not be controlled. This is because pipradrol is specifically excluded from the generic definition and therefore paragraph 2A would also not apply to pipradrol. For consistency the ACMD advise the inclusion of esters and ethers of pipradrol by moving pipradrol from Schedule 2 Part III paragraph 1(a) to paragraph 1(b) so that paragraph 1(d) regarding esters or ethers would apply to pipradrol.

The ACMD further advise that stereoisomers should be controlled by Schedule 2 Part II paragraph 2. The three main drugs, desoxypipradrol, diphenylprolinol (D2PM) and 2-diphenylmethylpyrrolidine all have stereoisomers and most of the compounds covered by the generic definition will also have stereoisomers.

References

1. Bellucci G. (1955); (2-Diphenylmethyl-piperidine hydrochloride and the methyl ester of 2-chloro-2-phenyl-2-(2-piperidyl)-acetic acid), drugs with waking effect in anaesthesia. *Minerva Anestesiologica* 21: 125–8.

2. Bertelsen S, Halland N, Bachmann S, Marigo M, Braunton A, Jørgensen KA. (2005); Organocatalytic asymmetric α-bromination of aldehydes and ketones. Chemical Communications 4821-4823

3. Enyedy IJ, Sakamuri S, Zaman WA, Johnson KM, Wang S. (2003); Pharmacophore-based discovery of substituted pyridines as novel dopamine transporter inhibitors. Bioorganic & Medicinal Chemistry Letters;13:513–517.

4. Hoffmann K, Heer J. (1958); 2-Diphenylmethyl-piperidine compounds. US Patent 2,826,583.

5. Hoffmann K, Heer J. (1958); Piperidines and their manufacture. US Patent 2,849,453.

6. Hoffman K. (1962); 1-Ethyl-2-diphenylmethyl-piperidines. US Patent 3,048,594.

7. Hoffmann K, Heer J. (1960); Substituted 2-diphenylmethyl-piperidine compounds. US Patent 2,957,879.

8. Isbell H, Chrusciel TS. (1970); Dependence Liability of Non-Narcotic Drugs. *Bulletin of the World Health Organisation;* **43**: Supplement, pages 76-77.

9. Lidder S, Dargan P, Sexton M, Button J, Ramsey J, Holt D, Wood D. (2008); Cardiovascular toxicity associated with recreational use of diphenylprolinol (diphenyl-2-pyrrolidinemethanol [D2PM]). Journal of Medical Toxicology; 4(3):167-9

10. Nodine JH, Bodi T, Slap J, Levy HA, Siegler PE. (1960); Preliminary trial of a new stimulant SCH 5472 in ambulatory patients with depression, exhaustion, or hypersomnia syndrome. Antibiotic Medicine and Clinical Therapy ; 7:771-6.

11. Novartis (1955) Information on Prep. No. 14’469 (desoxypipradrol), a new synthetic stimulant with central point of application.

12. Schmitt KC, Zhen J, Kharkar P, Mishra M, Chen N, Dutta AK, Reith ME. (2008); Interaction of cocaine-, benztropine-, and GBR12909-like compounds with wild-type and mutant human dopamine transporters: molecular features that differentially determine antagonist-binding properties; *Journal of Neurochemistry* 107: 928-40.

13. Sigma-Aldrich Co. (2007) "Organocatalysis", Chemistry files, vol 7, No.

14. Wikipedia entry for AL-1095. <http://en.wikipedia.org/wiki/AL-1095>; 2011 [accessed 25.08.11].

15. Winthrop SO. (1960) α-(3-Morpholyl)-benzhydrol and its salts. US Patent 2,947,749.

16. Winthrop SO. (1961); 3-Benzhydrylmorpholine and salts thereof, and method of preparing said compounds. US Patent 2,993,895.

17. Winthrop SO, Humber LG. (1961); Central Stimulants. Cyclized Diphenylisopropylamines. *Journal of Organic Chemistry* **26**: 2834-6.

18. Wood DM, Davies S, Puchnarewicz, Holt DW, Dargan PI. A case series of individuals with analytically confirmed acute diphenyl-2-pyrrolidinemethanol (D2PM) toxicity. *Manuscript submitted for publication*.

19. Wood DM, Puchnarewicz M, Holt DW, Ramsey J, Dargan PI. (2011); Detection of the precursor benzophenone in individuals who have used legal highs containing diphenyl-2-pyyrrolidinemethanol (D2PM). *Basic & Clinical Pharmacology & Toxicology*; 109 (Suppl. 1): 86

Annex 1

Proposed generic definition

Any compound (not being pipradrol) structurally derived from piperidine, pyrrolidine, azepane, morpholine or pyridine by substitution on a ring carbon atom with a diphenylmethyl group, whether or not the compound is further modified in any of the following ways, that is to say,

(i) by substitution in any of the phenyl rings to any extent with alkyl, alkoxy, haloalkyl or halide groups;

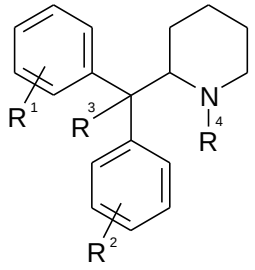
(ii) by substitution on the methyl carbon atom with an alkyl, hydroxyalkyl or hydroxy group;

(iii) by substitution on the ring nitrogen atom with an alkyl, alkenyl, haloalkyl or hydroxyalkyl group.

Annex 2

The generic definition includes, but is not limited to, the following examples:

Compounds structurally derived from piperidine



e.g. 2-piperidine isomer

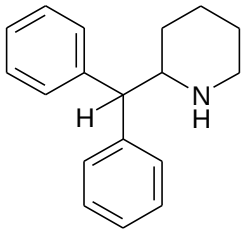
(i) by substitution in any of the phenyl rings to any extent
R^1 = *any number of* H, alkyl, alkoxy, haloalkyl or halide groups
R^2 = *any number of* H, alkyl, alkoxy, haloalkyl or halide groups

(ii) by substitution on the methyl carbon atom
R^3 = H, alkyl, hydroxyalkyl or hydroxy group

(iii) by substitution on the ring nitrogen atom
R^4 = H, alkyl, alkenyl, haloalkyl or hydroxyalkyl group

Examples

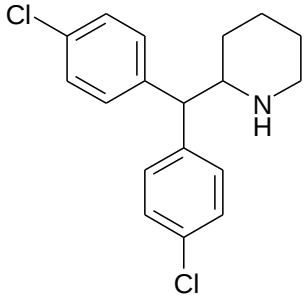
Substitution on a piperidine ring carbon atom at the 2-position



Desoxypipradrol

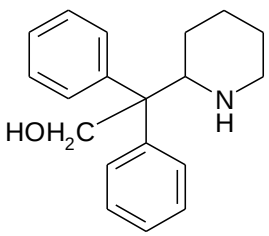
$R^1 = R^2 = R^3 = R^4 = H$
i.e. not further modified

Encountered as a legal high



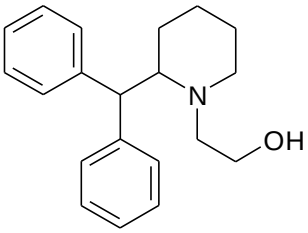
US Patent 2,286,583 (Hoffman 1958)
CNS stimulants

e.g. 2-[bis(4-chlorophenyl)methyl]piperidine
$R^1 = R^2$ = halide
$R^3 = R^4 = H$



US Patent 2,849,453 (Hoffman 1958)
CNS stimulants

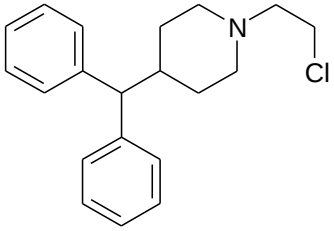
e.g. 2-(1',1'-diphenyl-2'-hydroxy-ethyl)-piperidine
R^3 = hydroxyalkyl
$R^1 = R^2 = R^4 = H$



US Patent 3,048,594 (Hoffman 1962)
Stimulants

e.g. 1-β-hydroxyethyl-2-diphenylmethyl-piperidine
R^4 = hydroxyalkyl
$R^1 = R^2 = R^3 = H$

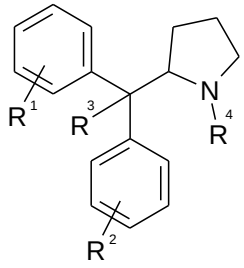
Substitution on a piperidine ring carbon atom at the 4-position



US Patent 3,048,594 (Hoffman 1962)
Stimulants

e.g. 1-β-chloroethyl-4-diphenylmethyl-piperidine
R^4 = haloalkyl
$R^1 = R^2 = R^3 = H$

Compounds structurally derived from pyrrolidine



e.g. 2-pyrrolidine isomer

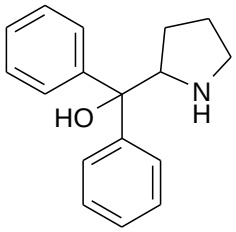
(i) by substitution in any of the phenyl rings to any extent
R^1 = *any number of* H, alkyl, alkoxy, haloalkyl or halide groups
R^2 = *any number of* H, alkyl, alkoxy, haloalkyl or halide groups

(ii) by substitution on the methyl carbon atom
R^3 = H, alkyl, hydroxyalkyl or hydroxy group

(iii) by substitution on the ring nitrogen atom
R^4 = H, alkyl, alkenyl, haloalkyl or hydroxyalkyl group

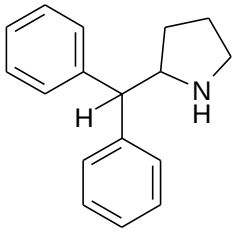
Examples

Substitution on a pyrrolidine ring carbon atom at the 2-position



Diphenylprolinol (diphenyl-2-pyrrolidinyl-methanol, D2PM)
$R^1 = R^2 = R^4 = H$
R^3 = hydroxy

Encountered as a legal high

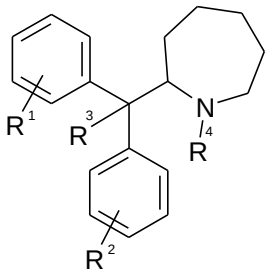


2-diphenylmethylpyrrolidine (desoxy-D2PM)

$R^1 = R^2 = R^3 = R^4 = H$
i.e. not further modified

Encountered as a legal high

Compounds structurally derived from azepane



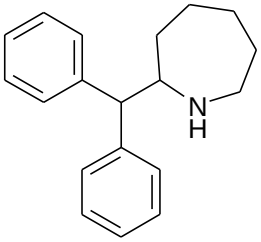
e.g. 2-azepane isomer

(i) by substitution in any of the phenyl rings to any extent
R^1 = *any number of* H, alkyl, alkoxy, haloalkyl or halide groups
R^2 = *any number of* H, alkyl, alkoxy, haloalkyl or halide groups

(ii) by substitution on the methyl carbon atom
R^3 = H, alkyl, hydroxyalkyl or hydroxy group

(iii) by substitution on the ring nitrogen atom
R^4 = H, alkyl, alkenyl, haloalkyl or hydroxyalkyl group

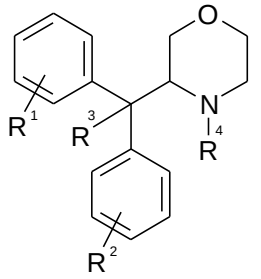
Example
Substitution on an azepane ring carbon atom at the 2-position



(Winthrop 1961)
CNS stimulants

e.g. 2-diphenylmethylazepane
(2-benzhydrylhexamethyleneimine)
$R^1 = R^2 = R^3 = R^4 = H$
i.e. not further modified

Compounds structurally derived from morpholine



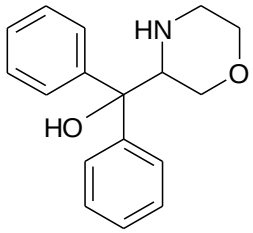
e.g. 3-morpholine isomer
(substitution adjacent to ring nitrogen atom)

(i) by substitution in any of the phenyl rings to any extent
R^1 = *any number of* H, alkyl, alkoxy, haloalkyl or halide groups
R^2 = *any number of* H, alkyl, alkoxy, haloalkyl or halide groups

(ii) by substitution on the methyl carbon atom
R^3 = H, alkyl, hydroxyalkyl or hydroxy group

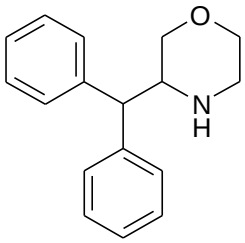
(iii) by substitution on the ring nitrogen atom
R^4 = H, alkyl, alkenyl, haloalkyl or hydroxyalkyl group

Examples
Substitution on a morpholine ring carbon atom at the 3-position



(Winthrop 1961) and US Patent 2,947,749 (Winthrop 1960)
CNS stimulant

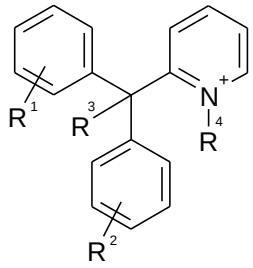
α-(3-morpholyl)-benzhydrol
$R^1 = R^2 = R^4 = H$
R^3 = hydroxy



US Patent 2,993,895 (Winthrop 1961)
CNS stimulant

3-benzhydrylmorpholine
$R^1 = R^2 = R^3 = R^4 = H$
i.e. not further modified

Compounds structurally derived from pyridine



e.g. 2-pyridine isomer

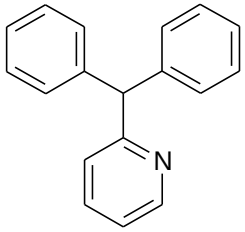
(i) by substitution in any of the phenyl rings to any extent
R^1 = *any number of* H, alkyl, alkoxy, haloalkyl or halide groups
R^2 = *any number of* H, alkyl, alkoxy, haloalkyl or halide groups

(ii) by substitution on the methyl carbon atom
R^3 = H, alkyl, hydroxyalkyl or hydroxy group

(iii) by substitution on the ring nitrogen atom
R^4 = H, alkyl, alkenyl, haloalkyl or hydroxyalkyl group

Examples

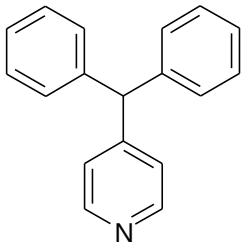
Substitution on a pyridine ring carbon atom at the 2-position



(Enyedy 2003)
Dopamine transporter inhibitors
e.g. 2-diphenylmethylpyridine
$R^1 = R^2 = R^3 = R^4 = H$
i.e. not further modified

The 2-, 3- and 4- isomers show quite potent activities in binding and uptake assays, with K_i values 0.079 – 0.780 μM in binding and 0.255 – 1.067 μM in inhibition of dopamine reuptake, respectively

Substitution on a pyridine ring carbon atom at the 4-position



(Enyedy 2003)
Dopamine transporter inhibitors
e.g. 4-diphenylmethylpyridine

$R^1 = R^2 = R^3 = R^4 = H$

i.e. not further modified

The 4-diphenylmethylpyridine isomer is as potent as cocaine in the dopamine uptake assay, with K_i values of 79 nM in binding and 255nM in inhibition of dopamine reuptake.