RCS-4

Critical-Review Report

Agenda item 4.10

Expert Committee on Drug Dependence

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Summary

There is little information available for 4-methoxyphenyl-(1-pentyl-1H-indol-3-yl) methanone (RCS-4). It belongs to the category of synthetic cannabinoid receptor agonists (SCRAs), which have affinity for CB_1 and CB_2 receptors. The affinity of RCS-4 for CB_1 and CB_2 receptors is not known, but RCS-4 is able to stimulate GTP binding to rat brain cortical membranes in a specific CB_1 receptor-mediated binding assay.

RCS-4 is a psychoactive substance and has effects similar to those of delta-9-tetrahydrocannabinol (THC). It has been detected in herbal products marketed under a variety of names via the Internet and in specialised shops. The quantity of RCS-4 among the different packages may vary considerably.

Detailed information on the toxic effects of RCS-4 is not available. In general, SCRAs may produce nausea, vomiting, agitation, hallucinations, panic attacks, tachycardia, hypertension, and occasionally chest pain, myoclonia, acute psychosis, and seizures. Intoxications have led to hospital admissions, but the psychoactive SCRA is rarely identified.

Studies on abuse and dependence potential of RCS-4 have not been performed, but considering its close pharmacological resemblance to THC, abuse of RCS-4 is likely to occur.

1. Substance identification

A. International Nonproprietary Name (INN)

Not applicable.

B. Chemical Abstract Service (CAS) Registry Number

1345966-78-0

C. Other Names

1-pentyl-3-(4-methoxybenzoyl)indole
4-methoxyphenyl-(1-pentyl-1H-indol-3-yl)methanone
RCS-4, RCS-04, SR-19, BTM-4, OBT-199

D. Trade Names

No information available.

E. Street Names

Eric-4 (later shortened to E-4), NRG-4, DD001

F. Physical properties

In pure form RCS-4 is a pale yellow powder.

G. WHO Review History

RCS - 4 was not previously pre-reviewed or critically reviewed. A direct critical review is proposed based on information brought to WHO's attention that RCS - 4 is clandestinely manufactured, of especially serious risk to public health and society, and of no recognized therapeutic use by any party. Preliminary data collected from literature and different countries indicated that this substance may cause substantial harm and that it has no medical use.

2. Chemistry

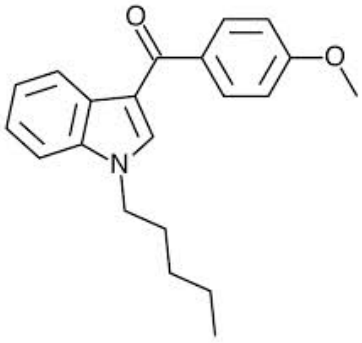
A. Chemical Name

IUPAC Name: 4-methoxyphenyl-(1-pentyl-1H-indol-3-yl)methanone
CA Index Name:

B. Chemical Structure

Free base:

RCS-4



Molecular Formula: $C_{21}H_{23}NO_2$
Molecular Weight: 321.2
Melting point: 116.7
Boiling point: -
Fusion point: -

C. Stereoisomers

No stereoisomers exist.

D. Synthesis

No data available.

E. Chemical description

RCS-4 belongs to the category of compounds with a benzoylindole structure and is structurally related to other synthetic cannabinoid receptor agonists with a core indole structure, such as the Schedule I substances JWH-018 and AM2201.

F. Chemical properties

No data available.

G. Chemical identification

NMR, FTIR and chromatographic methods have been described for the identification of RCS-4.[3;12;13;20;21] For a review of analytical techniques used, see Presley et al (2013).[22]

3. Ease of convertibility into controlled substances

No data available.

4. General pharmacology

4.1. Pharmacodynamics

RCS-4 belongs to the category of synthetic cannabinoid receptor agonists (SCRAs). SCRAs mimic the effects of delta-9- tetrahydrocannabinol (THC) by binding to CB1 and CB2 cannabinoid receptors in the brain and in peripheral organs.

In the early 1990s, two cannabinoid receptors have been identified and named CB1 and CB2. CB1 is primarily localized in the central nervous system (CNS), and CB2 in cells mainly associated with the immune system, such as macrophages, lymph nodes, spleen, and microglia cells.7;17;19;25 CB1 receptors are mainly found in the CNS-regions involved in cognition, short-term memory, movement and motor function.1 Activation of the CB1 receptor by THC or SCRAs modulates amongst others neurotransmitter release in many inhibitory and excitatory synapses in the brain. These effects are mediated through CB1 receptor coupled G-protein activation and finally result in decreased activity of cAMP-dependent protein kinases.

Few data for the RCS class of cannabimimetics in terms of their potency are available. RCS-4 stimulated [35S]GTPγS binding in rat brain cortical membranes in vitro with an EC50 value of 199 nM and Emax-value of 72%, indicating partial cannabimimetic activity of the compound via CB1-receptors.20

4.2. Routes of administration and dosage

As a substitute for cannabis, RCS-4 is usually smoked and sometimes ingested. The dose required for the desired effect(s) is unknown.

4.3. Pharmacokinetics

Sixteen metabolites of RCS-4 have been identified in human urine.[14] Metabolism is by aromatic hydroxylation, N- and O-dealkylation, and oxidation of the N-pentyl chain. The major metabolites were found to be predominantly conjugated.

5. Toxicology

No pre-clinical safety data are available about the toxicity, reproductive impact and mutagenic/carcinogenic potential of RCS-4.

6. Adverse reactions in humans

In a conference abstract, Hermanns-Clausen et al. (2012) reported 35 emergency department patients (32 male, 3 female; median age 17.5 years) with analytically verified consumption of SCRAs.[9] In two cases, RCS-4 was identified. Most frequent clinical symptoms (not specified for each SCRA) were tachycardia (74%), nausea/vomiting (66%), somnolence (57%), mydriasis (46%) and hypokalemia (40%). Less frequent were reduced or missing pupillary light reflex (20%), agitation (17%), vertigo (14%), paraesthesia (11%), aphasia (6%), dysphasia (6%), generalised seizures (6%), myoclonia or muscle jerking (6%), hypopnoea with hypoxemia (3%) and

aspiration with respiratory insufficiency (3%). Most symptoms ceased within a few hours.

In a series (closely similar and probably overlapping with the previously reported series of the same group[9;10]), RCS-4 was one of the twelve different SCRAs detected in serum.[8;10] In 65% of the cases, more than one SCRA were identified. At maximum, eight different SCRAs were identified in one patient. Symptoms of intoxications were similar to those reported by this group before (those of RCS-4 were not separately specified).

Kronstrand et al. (2013) presented eight cases of intoxication with SCRAs between 2011 and early 2013, where blood from subjects suspected of innocent drug offence or driving under the influence of drugs (DUI) was analysed.[15] Of 3,078 blood samples analysed, 28% were found positive for one or more SCRAs. In four sera, the mean (median) concentration of RCS-4 was 1.83 (1.81) ng/ml.

Analysis of SCRA exposures reported to the USA National Poison Data System (N=1898; January 1 to October 1, 2010), seven percent were potentially life-threatening. Common clinical effects were tachycardia (40%), agitation/irritability (23%), vomiting (15%), drowsiness/lethargy (13%), confusion (12%), nausea (10%), hallucination/delusion (9.4%), hypertension (8.1%), dizziness/vertigo (7.3%), and chest pain (4.7%).[11] Epileptic seizures were uncommon (4%) and primarily occurred in a single episode. There was one reported fatality (cardiac arrest).

Occasionally, psychotic reactions have been reported following SCRA use. Patients with a history of psychotic illnesses may be at risk.[6] Rarely, myocard infarction has been described following SCRA use.[18]

In 2010, the US Poison Control Centers received an estimated total of 2,977 reports of synthetic cannabinoids were submitted to State and local forensic laboratories in the United States. Synthetic cannabinoids were identified in 32 states. Nearly two-thirds were identified as JWH-018 (1887 reports; 63%). RCS-4 was reported in 16 cases (0.54%).[2]

In summary, it is not possible to draw conclusions about the toxicity of RCS-4 in humans, because no toxicity data are available following overdosing of RCS-4 alone. Signs of toxicity have been described only following consumption of SCRAs in general and have not been specified for RCS-4.

7. Dependence potential

No study data on the dependence potential of RCS-4 is available.

8. Abuse potential

No study data on the abuse potential of RCS-4 is available. Considering its close pharmacological resemblance to THC, abuse of RCS-4 is likely to occur.

9. Therapeutic applications and extent of therapeutic use and epidemiology of medical use

RCS-4 does not have any therapeutic application.

10. Listing on the WHO Model List of Essential Medicines

Not listed.

11. Marketing authorizations (as a medicine)

RCS-4 is not marketed as a medicine.

12. Industrial use

No industrial use known.

13. Non-medical use, abuse and dependence

RCS-4 has been encountered as adulterants in herbal products that are smoked for their psychoactive effects. However, the extent of the use of these products (either or not containing RCS-4) is largely unknown.[4]

Also refer Annex 1: Report on WHO questionnaire for review of psychoactive substances.

14. Nature and magnitude of public health problems related to misuse, abuse and dependence

The general view is that RCS-4, like other SCRAs, is used a substitute for cannabis. In general, adverse effects of SCRA intoxications are more intense than with cannabis, possibly because of their high activity and ease of overdosing.[4] There appears to be a wide variety of herbal products containing a variety and varying quantities of SCRAs.[4]

Also refer Annex 1: Report on WHO questionnaire for review of psychoactive substances.

15. Licit production, consumption and international trade

No data available.

16. Illicit manufacture and traffic and related information

As reported to the EMCDD, RCS-4 has been encountered in seized herbal products in Italy, Belgium, Norway, Hungary, Turkey, United Kingdom, Bulgaria, Croatia, Sweden, Germany, Czech Republic, and the European neighbour country Belarus.[5]

It has been detected in 'Puff The Philosophers Stone', 'Puff Super Strength', 'Kronic Pineapple Express', 'Marley Extra Strength 1.5', 'Kronic Tropical Explosion' and

'Kronic Purple Haze'.[23] RCS-4 has also been detected in the products 'Freedom' and 'MTN-787'.[16]

Out of over 2000 samples seized in Polish head shops and from individuals during 3.5-years (2008-2011), 420 samples were analysed for SCRA content and RCS-4 was identified in 92 samples. In 18 of those samples, RCS-4 was found in combination with JWH-081.[26]

The global emergence retrieved from the UNODC Early Warning Advisory on NPS is listed in Table 1.[24]

Table 1. Global emergence of RCS-4.[24]

List of countries (18)	
Australia	Netherlands
Bulgaria	New Zealand
Canada	Norway
Finland	Romania
Hungary	Russian Federation
Ireland	Singapore
Israel	Turkey
Italy	United Kingdom
Latvia	United States

Also refer Annex 1: Report on WHO questionnaire for review of psychoactive substances.

17. Current international controls and their impact

RCS-4 is currently not under international control.

18. Current and past national controls

RCS-4 is a schedule I controlled substance under the US Federal Controlled Substances Act. RCS-4 is under national control in Sweden, Denmark, New Zealand, Germany, Estonia, Hungary, Ireland, Italy, Luxembourg, Slovenia, Portugal, and Poland. Along with UR-144 and AM-2201, RCS-4 has been placed under national control in the UK in 2013.

Also refer Annex 1: Report on WHO questionnaire for review of psychoactive substances.

19. Other medical and scientific matters relevant for a recommendation on the scheduling of the substance

No data available.

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Annex 1:
Report on WHO Questionnaire for Review of Psychoactive Substances for the 36th ECDD: Evaluation of RCS-4

Data were obtained from 72 WHO Member States (18 AFR, 13 AMR, 5 EMR, 29 EUR, 3 SEAR, 4 WPR).

A total of 64 Member States answered the questionnaire for RCS-4. Of these, only 28 respondents (AFR 1, AMR 4, EUR 20, WPR 3) had information on this substance.

LEGITIMATE USE

None reported that RCS-4 was currently authorized or is in the process of being authorized/registered as a medical product in their country. Four respondents stated that this substance was used in medical and scientific research or as analytical standard. There was no stated use for animal/veterinary care.

HARMFUL USE

Nineteen respondents confirmed that there was recreational/harmful use of BZP; common routes of administration were stated as inhaling/sniffing by 10, oral/injecting and inhaling/sniffing by 2, oral by one, and oral, inhaling/sniffing by another one. Thirteen respondents stated this was obtained via trafficking, 2 stated trafficking plus clandestine manufacturing, one each clandestine manufacturing and diversion plus trafficking. Nine reported powder as the common formulation available and one as powder and liquid forms. Two respondents mention RCS-4 being smoked and 4 that it is part of herbal blends. Six respondents stated that it was only used by the general population, one stated only in clubs and another one stated this was used by both these populations. Four respondents reported withdrawal, tolerance and other adverse effects or medical illnesses, similar to other synthetic cannabinoids. Possibility of drug related crime is reported. One emergency room visit is reported for 2012.

CONTROL

Of those with information available on this substance, 21 reported that RCS-4 was controlled under legislation that was intended to regulate its availability - 16 under “controlled substance act”, 4 under “medicines law” and 1 under “other” laws. Only 2 respondents stated that there were challenges with the implementation of this legislation. On illicit activities involving RCS-4, three respondents reported clandestine manufacture but none the synthesis of the product itself. Six respondents reported processing into the consumer product, 14 reported trafficking, 1 reported diversion and 12 an internet market.

Details on seizures are presented below.

	2011 (number of respondents)	2012 (number of respondents)
Total number of seizures	868 (12)	277 (11)
Total quantity seized (kg)	257.16 (8) include other cannabinoids in some cases	16.17 (7) include other cannabinoids in some cases
Others seized	wraps, plant and herbal products	wraps, plant and herbal products

IMPACT OF SCHEDULING

Twenty-four respondents reported that if RCS-4 was placed under international control, they would have the laboratory capacity to identify the substance. It has no reported medical use