

Synthetic Cannabinoids

Robyn Somerville

Institute of Environmental Science and Research (ESR) Limited Private Bag 92 021 Auckland
(e-mail: robyn.somerville@esr.cri.nz)

Jacob Bertie

Forensic Programme, School of Chemical Sciences, University of Auckland

Synthetic cannabinoids are a new phenomenon in the designer drug market worldwide. They are compounds that were developed over the last 40 years mainly as therapeutic agents for use in the management of pain. They are not structurally similar to any of the psychoactive cannabinoids, including tetrahydrocannabinol THC (Fig. 1) found in cannabis.

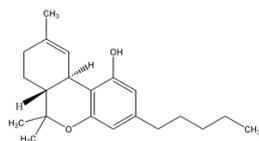


Fig. 1. THC

Synthetic cannabinoids have found a place in the drug market as they give the users a 'high' that mimics that obtained when smoking cannabis. This is because they bind to the cannabinoid receptors in the human brain and so are called cannabinoid receptor agonists. These receptors are responsible for many physiological processes including mood, pain sensation, memory and appetite.

The synthetic cannabinoids were first sold on the streets as synthetic cannabis blends. They were often marketed and sold as herbal blends or herbal smoking blends. The earlier brands on the market were "K2" and "Spice" (Fig. 2). The name "Spice" is now a generic trade name widely used in Europe to describe a herbal high product. In New Zealand and Australia the generic word "Kronic" was used when referring to the herbal blends, after one of the commercially available products being sold.



Fig. 2. Packaging and appearance of "Spice" herbal blend

The presence of synthetic cannabinoids in products being sold to the general public as herbal smoking blends first occurred in 2008. The European Monitoring Centre for Drugs and Drug Addiction reported in *Understanding the "Spice" phenomenon* that at the end of 2008 German and Austrian authorities had both found the synthetic cannabinoid known as JWH-018 in "Spice" products.¹ In early 2009 two groups in Germany and Japan reported the detection of a second synthetic cannabinoid called the C8 homologue of CP 47,497.^{2,3} In March 2009 the US Drugs

Enforcement Administration (DEA) confirmed the presence of another synthetic cannabinoid called HU-210 in "Spice" products.⁴ The synthetic cannabinoid JWH-073 was detected in powders seized in Europe.

These first three synthetic cannabinoids, reported in the scientific literature to be present in herbal smoking blends, have been synthesized along with many others, by different pharmaceutical companies and university research groups, for use as potential pharmaceutical compounds.

Since the 1990s Professor John W Huffman from the University of Clemson has led a research team developing compounds that could target the endocannabinoid receptors of the body. The team has synthesized over 450 compounds, which are commonly referred to as JWH compounds.

The structure of JWH-018, which was the first JWH compound detected in herbal blends, is given Fig. 3, and it can easily be seen that neither it nor JWH-073 (Fig. 4) are structurally similar to THC (Fig. 1)

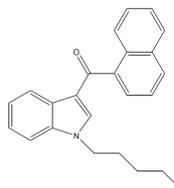


Fig. 3. JWH-018

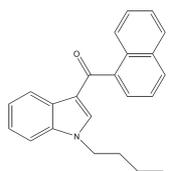


Fig. 4. JWH-073

HU-210, the synthetic cannabinoid detected in the "Spice" products analyzed in the US, (Fig. 5) is one of a series of compounds developed by Dr. Mechoulam's group at the Hebrew University in Israel and is named after the initials of the university.

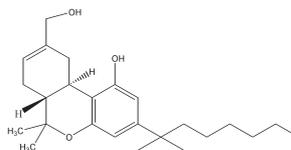


Fig. 5. HU-210

In the early 1980's a research group at the pharmaceutical company Pfizer investigated several synthetic cannabinoids for use as analgesics⁵. The compounds were known as the CP series. It was the C8 homologue of CP49,497

(Fig. 6) that was detected in the “Spice” products.

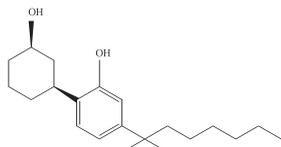


Fig. 6. C8 homologue of CP49,497

By June 2009 ESR had advised the Ministry of Health that in their opinion both HU-210 and CP47,497 and its homologues were structurally similar to THC and as such they would be defined as controlled drug analogues. In the case of JWH-018 and JWH-073, they were not structurally similar to THC and as such would not be controlled under the legislation of the time.

Over the next two years the number of herbal blends on the New Zealand and worldwide markets grew. The products could be easily bought on the internet or from “party shops”. In most countries the synthetic cannabinoids found in these products, and there was often more than one per product, were not controlled. As the regulatory authorities of countries and states moved to control specific synthetic cannabinoids, initially JWH-018 and JWH-073, the composition of the products available for sale changed to replace those that became illegal. There was now a ready market for legal herbal blends and because there are large number of synthetic cannabinoids, many with known activity as cannabinoid receptors, so once one was banned, it was easy for the “industry” to use a replacement.

The synthetic cannabinoids can be grouped on the basis of their structures, as shown in Table 1.

Table 1. Synthetic cannabinoids

	Chemical name	Examples*
1	Naphthoylindoles	JWH-018, JWH-073
2	Naphthylmethylindoles	JWH-175, JWH-184
3	Naphthoylpyrroles	JWH-145, JWH-307
4	Naphthylmethylindenes	JWH-176
5	Phenylacetylindoles	JWH-250, RCS-08
6	Benzoylindoles	AM-694 (see Fig. 7)
7	Cyclohexylphenols	CP 47,497 and its homologues
8	Classical cannabinoids	HU-210

* The synthetic cannabinoids are usually referred to by their non-scientific names, and these have come about largely based on either by whom or where they were synthesized: JWH – John W. Huffman, CP – Charles Pfizer, WIN – Winthrop Pharmaceutical (Stirling-Winthrop), HU – Hebrew University, AM – Alexandros Makriyannis, RCS – believed to be “Research Chemical Supplier”, an internet company selling chemicals

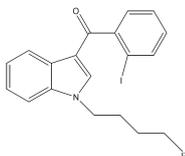


Fig. 7. AM-694

The herbal blends and smoking incenses are sold on the market as herbal mixtures in either a sealed pouch or a plastic bag held within a cardboard packet. The synthetic cannabinoids are either dissolved in a solvent and then sprayed onto the herbal mixture or the herbal mixture is soaked in the solvent which is then left to evaporate. The herbal mixtures used appear varied and are not usually specified on the packets, and have been reported to include some potentially psychoactive plants including: marshmallow, blue lotus and rosehip.¹ The wording on the packets to describe the contents often uses phrases like “natural organic extracts” and “100% legal herbs”. Most of the packets are labeled “R18” and also inform the user to use in a well ventilated room. The packaging of herbal blends generally seems to be intentionally misleading and uninformative, but very eye-catching. Using ambiguous statements and labeling allows the manufacturers to avoid restrictions that would otherwise be imposed on their products. The use of imagery and wording relating to cannabis appears to be a method of indirectly informing the user of the effects of these products

In a survey carried out by the ESR Drugs laboratory in July 2011^{6,43} legal herbal blend products were purchased from NZ websites and shops. (Figs 8 and 9) Eleven synthetic cannabinoids were detected in these products: JWH-018 was present in most herbal blends and there were often two or more synthetic cannabinoids in a single product. The survey also detected the presence of the prescription medicine phenazepam in two products, which were subsequently withdrawn from the market.



Fig. 8.



Fig. 9.

In August 2011, the New Zealand Government decided to list sixteen synthetic cannabinoids as Temporary Class Drugs. These sixteen synthetic cannabinoids had all been detected in the products analyzed as part of the ESR survey. In October 2011 three further synthetic cannabinoids were listed as Temporary Class Drugs.

The sixteen synthetic cannabinoids controlled in New Zealand in August 2011 were JWH-018, JWH-022, JWH-073, JWH-081, JWH-122, JWH-201, JWH-203, JWH-210, JWH-250, JWH-302, AM-694, AM-2201, RCS-04, butyl analogue of RCS-04, 2-methoxy isomer of RCS-04 and the 2-methoxy isomer of butyl analogue of RCS-04. The three further synthetic cannabinoids listed as controlled were JWH-019, JWH-200 and AM-1220,

Being listed as Temporary Class Drugs means that it is currently illegal in New Zealand to import or sell these synthetic cannabinoids or products that contain them. As a result of this legislation the numerous herbal blend products that had been available to purchase from websites or in shops were withdrawn from the market.

References

1. European Monitoring Centre for Drugs and Drug Addiction **2009**. Understanding the Spice phenomenon. <http://www.emcdd.europa.eu>
2. Auwarter, V.; Dresen, S.; Weinmann, W.; Muller, M.; Putz, M.; Ferreiros, N. *JMS Letters J. Mass. Spectrom.* **2009**, *44*, 832.
3. Uchiyama, N.; Kikura-Hanajiri, R.; Kawahara, N.; Haishima, Y.; Goda, Y. *Chem. Pharm. Bull.* **2009**, *57* (4), 439.
4. "Spice"-Plant Material(s) laced with Synthetic Cannabinoids or Cannabinoid Mimicking Compounds. *Microgram Bulletin*, **2009**, *42*(3) March.
5. Melvin, L.; Johnson, M.; Harbert, C.; Milne, G.; Weissman, A. *J. Med. Chem.* **1984**, *27*, 67-71.
6. Somerville, R. Unpublished work.