

# Phenazepam and cannabinomimetics sold as herbal highs in New Zealand

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A smokeable product called Kronic, is legally available, sold under five product names, and marketed in New Zealand as containing natural extracts. Two such products called *Pineapple Express* and *Purple Haze* were purchased from shops in Auckland city. They were investigated for the presence of synthetic drugs specifically synthesized for recreational purposes. The synthetic cannabinomimetics identified were JWH-018, JWH-073, JWH-122, JWH-250, and 1-pentyl-3-(4-methoxybenzoyl)indol. A compound not previously reported in such designer drug preparations 1-butyl-3-(4-methoxybenzoyl)indol was also seen. There was a marked variation in the content of these compounds within a named brand. The pharmaceutical benzodiazepine phenazepam (fenazepam) was identified as a constituent, along with certain cannabinomimetics, in nearly all of the Kronic samples examined. Phenazepam has not previously been reported as a constituent of designer drug or herbal high products. The amount of phenazepam was approximately 1 mg per gram of Kronic leaf material. Use of these products could result in severe toxicity. Copyright © 2011 John Wiley & Sons, Ltd.

**Keywords:** Phenazepam; Cannabinomimetics; Herbal Highs; Kronic; Spice; JWH compounds

## Introduction

For centuries, cannabis has been used for both therapeutic and recreational purposes. More recently it was stated that compounds which modulate the endocannabinoid system hold therapeutic promise in a wide variety of pathological conditions such as mood and anxiety disorders, neuropathic pain, and obesity/metabolic syndrome.<sup>[1]</sup> The binding of cannabinoids to, and consequent activation of, the neuronal cannabinoid receptor CB<sub>1</sub> is believed to be responsible for the psychoactive effects associated with cannabinoids.<sup>[2]</sup> Further, it was the identification and cloning of the cannabinoid binding sites on CB<sub>1</sub> and CB<sub>2</sub>, the peripheral cannabinoid receptor, that led to a significant advance in understanding the mechanism of action of cannabinoids and their interaction with biological systems.<sup>[3]</sup> Research in the study of appropriate ligands for the CB<sub>1</sub> and CB<sub>2</sub> led to the development of over 100 synthetic cannabinomimetic compounds. These are referred to as the JWH series and also the CP, HU, and WIN series of compounds. They have been synthesized in research laboratories over the last 40 years as ligands to the cannabinoid receptors.<sup>[4]</sup>

Compounds synthesized and marketed for recreational purposes are colloquially termed designer drugs.<sup>[5]</sup> The designer drug product *Spice* has been available in Europe since about 2004 and perhaps the equivalent brand name in New Zealand is *Kronic*. It is very likely that the published data of CB<sub>1</sub> binding affinities were exploited by the producers of these *Spice* and *Kronic* products. In December 2008 chemical analysis of *Spice* by a German company, THC Pharma, reported JWH-018 as the active ingredient.<sup>[6,7]</sup> The ability of *Spice* to produce marijuana-like effects was attributed to JWH-018, which is a potent and efficacious CB<sub>1</sub> receptor agonist.<sup>[8]</sup> Later, several of the JWH, CP, HU and WIN series of compounds were identified in herbal products.<sup>[9–12]</sup>

Our laboratory is accredited to carry out workplace drug testing under an Australian and New Zealand Standard titled AS/NZS 4308:2008. Drug prevention programmes have been introduced in schools in New Zealand since 2006. As a part of

these prevention programmes, we offer school cannabinoid screening that we refer to as 'non-evidential' work.<sup>[13]</sup> We are in communication with school principals who informed us that they suspect children are using *Kronic* instead of cannabis. Also a physician at the Emergency Department at Auckland Hospital informed us that about 10 patients per week have a psychotic presentation attributed to the use of *Kronic*, often together with alcohol. This problem is exacerbated by the fact that *Kronic* can be legally obtained in New Zealand by those over the age of 18.

Since about 2006, the product with the brand name *Kronic* has been available in New Zealand and Australia. Packaging states that the products *Kronic Pineapple Harvest* and *Kronic Purple Haze* contain 'a unique blend of all natural, organic extracts and concentrates'. As already mentioned, *Spice* contains several synthetic designer drugs. This therefore raised suspicions that synthetic compounds added to *Kronic*, but undeclared on the packaging, may be the main cause for the pharmacological psychoactive properties of *Kronic* products.

This paper aims to identify the designer type compounds in *Kronic* products that were readily available from shops in Auckland. It will also describe the identification of the unexpected phenazepam drug in the *Kronic* products named *Pineapple Express* and *Purple Haze*. Along with phenazepam identification, four JWH type designer cannabinomimetics and two methoxybenzoylindol compounds were also identified.

Unlike the cannabinomimetics, phenazepam is not a designer drug. It is a benzodiazepine that was first synthesized in the Soviet Union in 1978 and is presently a prescription-only medication in Russia. Baselt<sup>[14]</sup> states that it has been used as a sedative

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Figure 1. Previously Legal Kronic Products.

hypnotic and that adverse effects include somnolence, dizziness, incoordination and asthenia.

## Materials and methods

### Reagents and chemicals

JWH 018 and JWH 073, products of Lipomed AG, Switzerland, were purchased from PM Separations, Australia. Phenazepam (7-bromo-5-(2-chlorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one) CAS No 51753-57-2, was purchased as a crystalline solid, from BDG Synthesis (Wellington, New Zealand). High performance liquid chromatography (HPLC) grade ethanol, Scharlau, was obtained from Global Science and Technology Auckland, New Zealand.

### Samples

Five products labelled as Kronic Pineapple Express (Figure 1); one as Kronic Purple Haze (Figure 1), and one as Kronic Purple Haze in a cigarette form, were purchased from various shops in the city of Auckland, New Zealand.

A further sample of Kronic Pineapple Express and Kronic Purple Haze was obtained from LightYears Ahead Ltd, the company who produces the Kronic products in New Zealand. All the products were in dried-leaf form. The packaging did not indicate any batch details.

### Extraction of compounds

We were informed (Medsafe, pers. comm.) that the designer compounds were simply layered over the leaf material by a spray procedure. Therefore for qualitative analysis each of the products (0.5 gram) was placed in a 30 ml glass vial; 10 ml of ethanol was added and solubilization-extraction of the product constituents was achieved by rapid rotation mixing for 1 h. The

solutions were then centrifuged at 2000 rev/min for 5 min. The ethanolic solutions were refrigerated at 4 °C.

### GC-MS analysis

One hundred µl of each supernatant solution was transferred to an auto-sample vial for mass spectral analysis. Gas chromatography-mass spectrometry (GC-MS) was performed on a Hewlett Packard HP 6890 gas chromatograph interfaced to an HP 5973 Quadrupole mass spectrometer and Chemstation software. The gas chromatograph was operated in the splitless mode using helium as carrier gas. The column was an HP-5MS capillary (30 m, 0.25 mm id; 0.25 µm film thickness). An HP 7683 series auto sampler was used for automatic sample injection. The injector temperature was 225 °C. The oven was held at 150 °C for 1 min, then ramped at 20 °C/min to 290 °C and held for 6 min. The overall run time was 16 min. The retention times of all the compounds detected are listed in Table 1. The relative content was calculated from the area of the target compound peak to that of the standard sample (1 mg/ml acetonitrile) from the GC-MS profile.

## Results

Representative chromatograms from two of the Kronic Pineapple Express products are presented in Figures 2A and 2B. The summary of our findings is presented in Table 1. The chemical structures of all the compounds identified in the Kronic products are presented in Figure 3: A–G.

A peak was observed by GC-MS at a retention time of 9.1 min (Figure 2A). This was subsequently identified as phenazepam from the mass ion fragmentation data. The Pfleger and Wiley libraries gave a 99% quality match for the phenazepam extracted from the Kronic material. The identity of phenazepam was further confirmed by comparing the mass fragment pattern and the

**Table 1.** Summary of results for products tested

Kronic flavour	Phenazepam	JWH-018	JWH-73	JWH-122	JWH-50	A	B
Pineapple Express Light Years Ltd.	Detected	Detected *	Detected			Detected *	Detected
Pineapple Express Shop 1	Detected	Detected *	Detected *			Detected *	Detected
Pineapple Express Shop 2		Detected		Detected *			Detected *
Pineapple Express Shop 3	Detected	Detected *	Detected *			Detected *	Detected
Pineapple Express Shop 4	Trace amount Detected	Detected *	Detected	Detected *	Detected *	Detected	Detected *
Pineapple Express Shop 5		Detected *		Detected *	Detected *		Detected *
Purple Haze Light Years Ltd	Trace amount Detected	Detected	Detected *			Detected	Detected
Purple Haze Shop 4	Trace amount Detected	Detected	Detected *			Detected	Detected
Purple Haze cigarette form		Detected *	Detected				
Retention time (Minutes) GC-MS Profile	9.1	12.7	11.7	14.5	10.4	10.1	10.7

A. 1-Butyl-3-(4-methoxybenzoyl)indol.  
 B. 1-Pentyl-3-(4-methoxybenzoyl)indol.  
 \* Components detected at substantial amounts as observed from the GC-MS chromatograms.

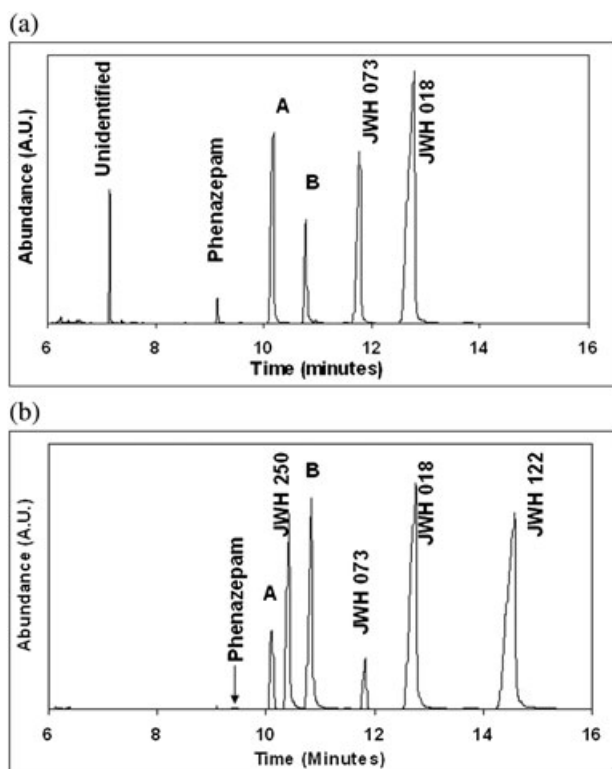
retention time with authentic phenazepam. Phenazepam was identified in six of the nine Kronic products that we analyzed. The concentration of phenazepam was determined as approximately 1 mg per gram of Kronic leaf material obtained from LightYears Ahead Ltd, and from shops 1 and 3. However, in three of the products, phenazepam was detected in only trace amounts (Figure 2B).

1-Pentyl-3-(1-naphthoyl)indole, JWH-018, was identified in all nine products. Its concentration varied 10-fold between these nine products. 1-Butyl-3-(1-naphthoyl)indole, JWH-73, was identified in seven of the Kronic products. JWH-73 was the prominent component in the two Purple Haze products. Its concentration varied 10-fold between the seven products. Both JWH-018 and JWH-73 were confirmed by the retention time

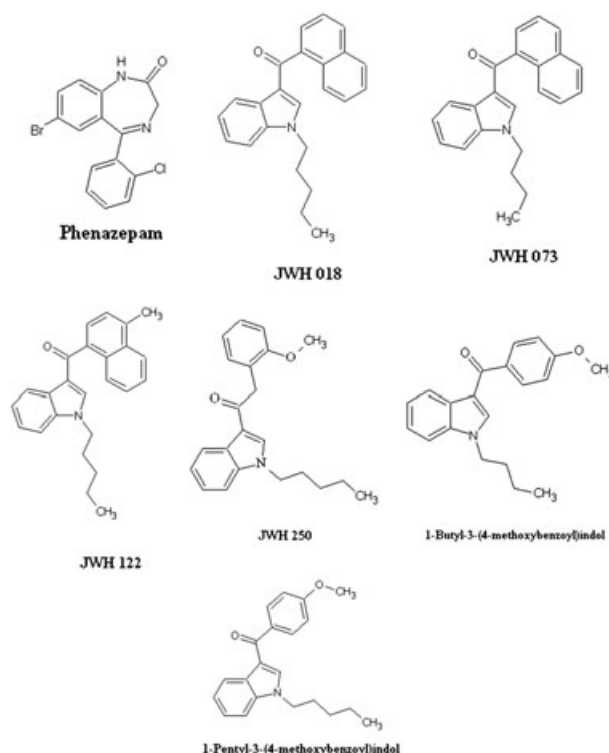
and mass ion fragmentation pattern relative to the data obtained from the two authentic standards.

1-Pentyl-3-[1-(4-methylnaphthoyl)]indole, JWH-122, was identified in substantial amounts in three of the Kronic Pineapple Express products, purchased from shops 2, 4 and 5. 1-Pentyl-3-(2-methoxyphenylacetyl)indole, JWH-250, was identified in two of products. Two other compounds identified were 1-pentyl-3-(4-methoxybenzoyl)indole and 1-butyl-3-(4-methoxybenzoyl)indole.

Since we did not possess authentic standards for JWH-122, JWH-250, 1-pentyl-3-(4-methoxybenzoyl)indole and 1-butyl-3-(4-methoxybenzoyl)indole, we compared published<sup>[9,12,15]</sup> mass ion fragmentation patterns to those observed by us in the



**Figure 2.** (A) Representative GC-MS Chromatogram (B) Phenazepam detected in trace amount.



**Figure 3.** Chemical structures of the compounds identified in the herbal mixtures. (A) Phenazepam. (B) JWH 018. (C) JWH 073. (D) JWH 122. (E) JWH 250. (F) 1-Butyl-3-(4-methoxybenzoyl) indol. (G) 1-Pentyl-3-(4-methoxybenzoyl) indol.

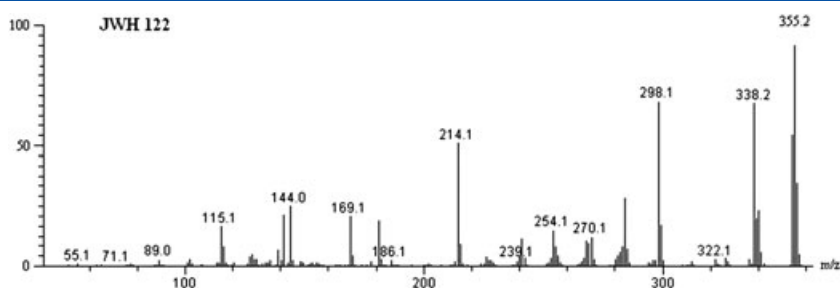


Figure 4. GC-MS mass fragmentation pattern of JWH 122

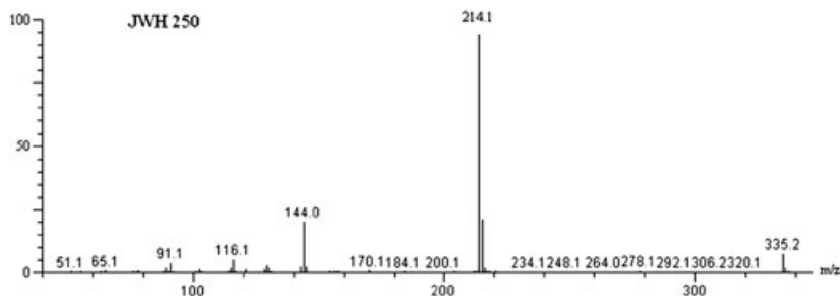


Figure 5. GC-MS mass fragmentation pattern of JWH 250.

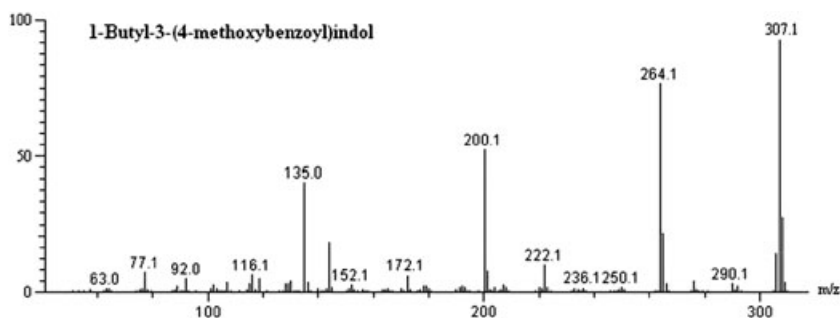


Figure 6. GC-MS mass fragmentation pattern of 1-Butyl-3-(4-methoxybenzoyl)indol.

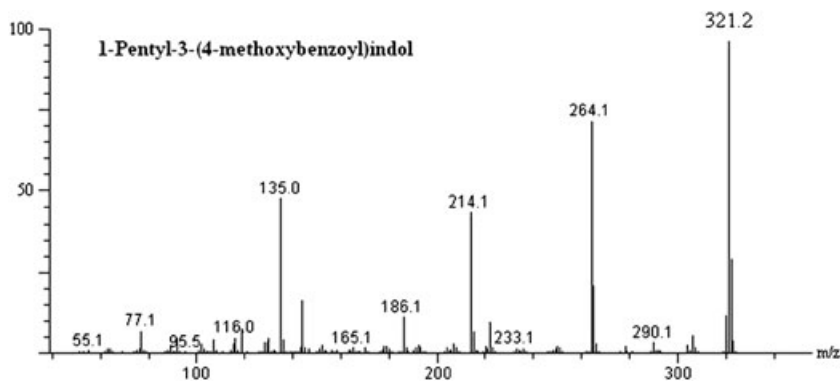


Figure 7. GC-MS mass fragmentation pattern of 1-Pentyl-3-(4-methoxybenzoyl)indol.

GC-MS profile. It is possible, however, that the positional isomers, with regard to the methoxy group, could have similar mass ion fragmentation components. The observed mass ion fragmentation pattern of JWH 122, JWH-250, 1-butyl-3-(4-methoxybenzoyl)indole and 1-pentyl-3-(4-methoxybenzoyl)indole are shown in Figures 4–7, respectively.

In a similar Kronic product – Purple Haze in cigarette form – JWH-018 and JWH-073 were the only compounds detected. However, Purple Haze in a 1.5 g packet was found to contain phenazepam together with JWH-018, JWH-073 and both the 1-butyl and 1-pentyl-3-(4-methoxybenzoyl)indol compounds. Comparing the relative amounts based on the GC-MS profile, the amount

of JWH-073 appeared to be about three times more than JWH-018 and the 1-butyl and 1-pentyl-3-(4-methoxybenzoyl)indol compounds. Phenazepam was detected in trace amounts in this product compared to Kronic Pineapple Express.

## Discussion

This study has demonstrated the presence of six cannabinomimetic compounds and phenazepam in a product labelled Kronic Pineapple Express. Phenazepam was found in four of the six samples. JWH-018, JWH-073, JWH-122, and JWH-250 were detected in 6, 4, 3, and 2 of the 6 samples, respectively. 1-Pentyl-3-(4-methoxybenzoyl)indol was detected in all 6 samples.

1-butyl-3-(4-methoxybenzoyl)indole was identified in 4 of the 6 samples. Kneisel *et al.* [15] reported that 1-pentyl-3-(4-methoxybenzoyl)indol was found as a 'research chemical' on the Internet. There are no previous reports of this compound being found in Kronic or Spice type products.

Labelling was amiss of batch details. Further, all of these compounds were designed for experimental purposes and lack any published *in vivo* testing information. This commercial product Kronic Pineapple Express is not uniform in terms of the synthetic drug content.

Phenazepam has not previously been reported as a constituent of designer drug or herbal high products. Prescribed oral doses of phenazepam are 0.5–2 mg. [14] The half life of phenazepam is 60 h. [14] The packet details on both Pineapple Express and Purple Haze state: 'it emits a pleasant, very relaxing smoke when burned'. Maddeleno *et al.* [16] state that the benzodiazepine, flunitrazepam, can be inhaled. The possible inhalation properties of phenazepam are not documented. Since, the amount of phenazepam present was approximately 1 mg per g of Kronic leaf material, use of these products could result in toxicity if a phenazepam vapour was inhaled.

An Internet purchase of phenazepam was presented as a contributing factor, together with opiates, for the death of a 42-year-old male. [17] Maskell *et al.* [18] reported phenazepam was detected in postmortem blood samples obtained from nine drug misuse cases. Luzhnikov *et al.* [19] have stated that in recent years the most frequent cause of poisoning in children was derivatives of benzodiazepine, mainly phenazepam. They observed that one of the basic symptoms of poisoning by phenazepam is depression of consciousness from somnolence to coma, psychomotor excitement accompanied by visual or acoustic hallucinations in some patients.

The addition of cannabinomimetic designer drugs in products stated as herbal is now worldwide. In 2009, a group at the Braunschweig University of Technology, Germany, isolated JWH-018 and also reported JWH-073 as the first instance of the compound being found as a designer drug. [7] In 2011, this same laboratory characterized JWH-122 as a new cannabinomimetic and isolated it from a 'Spice-like' herbal product. [9] Spice is a more general name for such products as currently detailed by Hudson and Ramsey. [20]

Germany, France, Ireland, Poland, and Japan have made JWH-018 illegal, and Britain has banned all Spice products. In June 2011, Western Australia banned all products containing synthetic cannabinoids, including brands such as Kronic. The synthetic cannabinoid receptor agonists fall into seven major groups. [21] Three of them – Naphthoylindoles (e.g. JWH-018 and JWH-073),

phenylacetylindoles (e.g. JWH-250), and benzoylindoles – were not included within the New Zealand Misuse of Drugs Act as at December 2010. Hence, they are regarded as legal. In June, the New Zealand government restricted the sale of Kronic products to those aged 18 years and older. Following a submission of our findings to the New Zealand Ministry of Health on 24 June 2011, the sale of Kronic Pineapple Express was forbidden from 1 July 2011. This was a directive by the Director-General and Chief Executive, New Zealand Ministry of Health. [22] Another product called *Juicy Puff Super Strength* has also been withdrawn because it contained phenazepam. [23] The New Zealand government laboratory is now investigating other similar marketed products and also investigating the source and occurrence of the prescription medication phenazepam in these previously legal Kronic products.

Our clinical laboratory justified research into this product that was previously deemed as suitable for youth. We are proceeding with methods to identify the presence of phenazepam or its principle metabolite in human urine.

## Conclusion

The data presented indicated that the package labelling, on two brands of a previously legal Kronic product called Pineapple Express and Purple Haze, was not consistent with the actual contents described. Six synthetic cannabinomimetics were identified. In New Zealand many such substances are currently not adequately provided for by any legislative regime and once cleared by New Zealand Customs can be sold as a product destined for human use. The identification of phenazepam, a prescription medication, permitted the New Zealand Ministry of Health to immediately demand that such products be recalled by retailers. Legislation should be implemented to prevent such recreational and prescription compounds being marketed in this manner.

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