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Testimony concerning HB 2353
Committee on House Corrections and Juvenile Justice
Presented by Debra Billingsley
On behalf of
The Kansas Board of Pharmacy
February 25, 2013

Chairman Rubin and Members of the Committee:

My name is Debra Billingsley and I am the Executive Secretary of the Kansas State Board of Pharmacy. The Board is created by statute and is comprised of seven members, each of whom is appointed by the Governor. Of the seven, six are licensed pharmacists and one is a member of the general public. The Board of Pharmacy, pursuant to K.S.A. 65-4102(b), is required to submit an annual report on controlled substances proposed by the Board for scheduling, rescheduling or deletion by the legislature.

In proposing to the Legislature that any drugs be classified as a scheduled controlled substance, the Board relies on the following factors set forth in K.S.A. 65-4102(b). Specifically, the proposal must state the reasons that the Board makes their recommendations by considering the following factors: 1) Potential for abuse; 2) the scientific evidence of its pharmacological effect, if known; 3) the state of current scientific knowledge regarding the substance; 4) the history and current pattern of abuse; 5) the scope, duration and significance of abuse; 6) the risk to the public health; 7) the potential of the substance to produce psychological or physiological dependence liability; and 8) whether the substance is an immediate precursor of a substance already controlled under this article.

The Drug Enforcement Administration (DEA) also issues their rulings based on information provided by the DEA's Deputy Administrator and the Department of Health and Human Services using the same factors and criteria that the state uses. The DEA has already reviewed the pharmacology, chemistry, trafficking, actual abuse, pattern of abuse and the relative potential for abuse of 3-tetramethylcyclopropanoylindole compounds.

The Board of Pharmacy recommends that the 3-tetramethylcyclopropanoylindole compounds be added to Schedule I. Schedule I drugs have a high potential for abuse, no currently accepted medical use in treatment in the United States and are not safe for use under medical supervision. The Board adopted an emergency regulation on July 23, 2012 until we could come to the legislature and ask that the drug be placed on the Controlled Substance Schedule I list.

Thank you for permitting me to testify. I will yield to any questions from the committee.

Drug Enforcement Administration
Office of Diversion Control
Drug & Chemical Evaluation Section
8701 Morrisette Drive
Springfield, Virginia 22152
(202) 307-7183

1-Pentyl-3-(2,2,3,3-tetramethycyclopropoyl)indole (UR-144) Analogue Status

April 2012

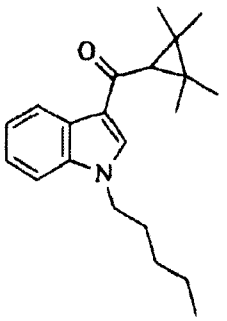
Analogue Statute of the Controlled Substances Act

The Controlled Substances Act (CSA) was amended in 1986 by enactment of the Controlled Substance Analogue Enforcement Act. This law provides for controlled substance analogues, to the extent that they are intended for human consumption, to be treated as Schedule I controlled substances for the purposes of criminal prosecution. The term "controlled substance analogue" means a substance which: (1) the chemical structure of which is substantially similar to the chemical structure of a controlled substance in schedule I or II; (2) which has a stimulant, depressant, or hallucinogenic effect on the central nervous system that is substantially similar to or greater than the stimulant, depressant, or hallucinogenic effect on the central nervous system of a controlled substance in schedule I or II; or (3) with respect to a particular person, which such person represents or intends to have a stimulant, depressant, or hallucinogenic effect on the central nervous system that is substantially similar to or greater than the stimulant, depressant, or hallucinogenic effect on the central nervous system of a controlled substance in schedule I or II. [Title 21 United States Code 802(32)(A)].

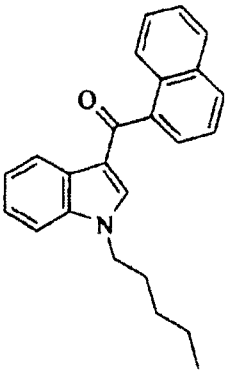
If evidence can be accumulated that the substance in question is intended for human consumption and is not already controlled under the CSA or legally marketed in the United States, the use of the analogue provision of the CSA should be considered (Title 21 United States Code 813).

(1) *1-Pentyl-3-(2,2,3,3-tetramethylcyclopropoyl)indole (UR-144) shares substantial chemical structural similarities with the Schedule I substance, 1-pentyl-3-(1-naphthoyl)indole (JWH-018)*

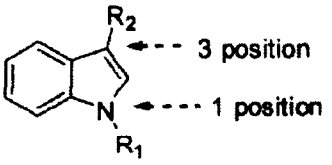
The chemical structures of UR-144 and JWH-018 are substantially similar. Both compounds share the same core indole structure as depicted in Figure 1 with substitutions at the 1 and 3 positions of this fused bi-cyclic ring system.



1-pentyl-3-(2,2,3,3-tetramethylcyclopropoyl)indole
([1-Pentylindol-3-yl]-(2,2,3,3-tetra-methylcyclopropyl)methanone; UR-144)



1-pentyl-3-(1-naphthoyl)indole
(Naphthalen-1-yl-(1-pentylindol-3-yl)methanone; JWH-018)



Indole ring system

Figure 1. Structures of UR-144, JWH-018, and indole ring system

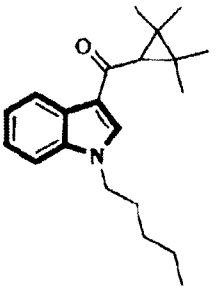
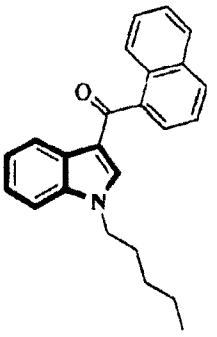
Figure 1 depicts the structures of UR-144, JWH-018, and the indole ring system. The core ring system is substituted at the indole-1 and -3 positions to give both UR-144 and JWH-018. Both substances are substituted at the 3-position with an acyl group, a carbonyl group (ketone) linked to a ring system and at the 1-position with an alkyl group. The alkyl group at the 1-position for both UR-144 and JWH-018 is a five carbon unit chain known as a pentyl group.

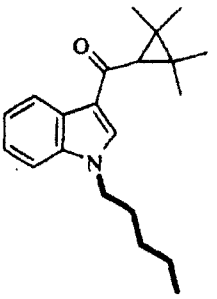
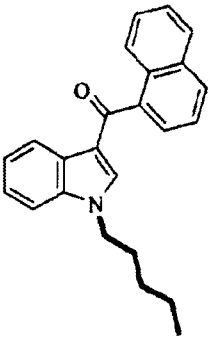
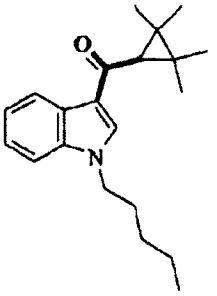
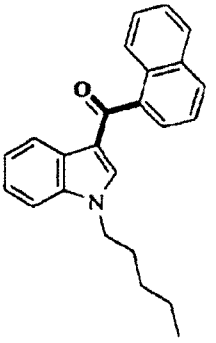
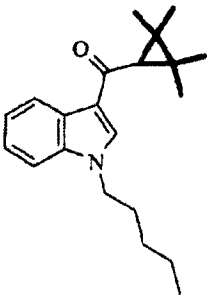
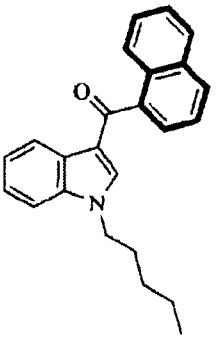
Studies concerning the aminoalkylindole structural class have focused primarily on varying the indole nitrogen and 3-position substituents. The core indole became a framework for continued investigations with the early work by Sterling-Winthrop that led to pravadoline and WIN-55212-2 (D'Ambra *et al.*, 1992). Several other groups expanded this investigation of structure activity relationships including the laboratories of Huffman and co-workers and Makriyannis and co-workers (Huffman, 2009). The scientific

literature and patent literature details further substitutions of the aminoalkylindole structural class with specific substitutions at the 3-position of the indole core structure to incorporate aromatic and non-aromatic ring systems. Bell (1986) reported on the preparation of cyclohexyl ketones and the work of Frost and co-workers is an extension. A series of 3-tetramethylcyclopropyl ketone substituted indoles were prepared and evaluated (Frost *et al.*, 2008). These investigations led to the further synthesis and evaluation of UR-144 and series of structurally related nonaromatic acyl substituted substances (Frost *et al.*, 2010).

Both substances share the core indole ring system. The nitrogen of the indole, 1-position is substituted by an alkyl moiety. The alkyl group attached to the nitrogen for both UR-144 and JWH-018 is a five carbon chain known as a pentyl group. The indole 3-poition incorporates a carbonyl (C=O) group which is further substituted with a cyclic ring system. Table 1 further highlights the structural similarities between UR-144 and JWH-018.

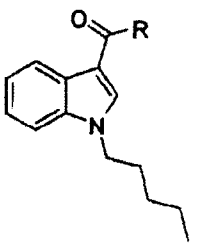
Table 1. Shared structural features

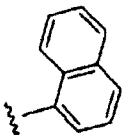
	Structural feature	UR-144	JWH-018
A.	Indole core structure		

B.	Indole 1-position substitution		
C.	Indole 3-position carbonyl substitution		
D.	Carbonyl substitution		

The shared structural features are further highlighted in Figure 2, below. The chemical structures for both UR-144 and JWH-018 are substituted at the same position with a ring system and the overlap of both substances details the high degree of conservation in chemical structure between the two substances. As previously noted, these substances are representative of the aminoalkylindole structural class.

(A)



Substance	R=	Name
JWH-018		naphthyl
UR-144		tetramethylcyclopropyl

(B)

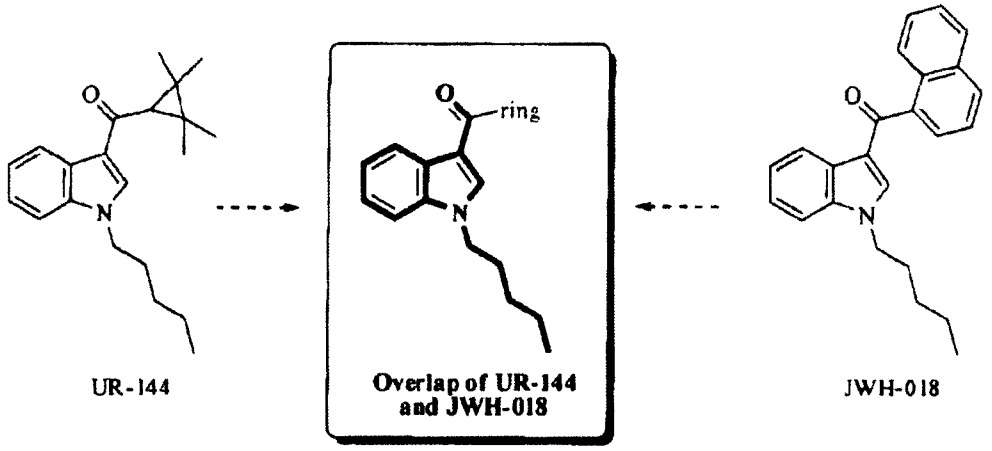


Figure 2. (A) *Comparison of site specific substitution for UR-144 and JWH-018 and* (B) the overlap of the two chemical structures, bold features highlight shared chemical structure.

The difference between these two substances is the ring structure attached to the 3-position the carbonyl group, alicyclic vs. aryl ring system. UR-144 incorporates a tetramethylcyclopropyl group, whereas, JWH-018 incorporates a naphthyl group. Other than this difference, the remainder of the chemical structure for both UR-144 and JWH-018 is the same. Therefore, based on the above analysis, UR-144 is substantially similar in chemical structure to JWH-018 and meets the first criterion of the definition of a controlled substance analogue*.

[*Note: According to 21 U.S.C. 802(32), the first criterion of the definition of a controlled substance analogue requires consideration of physical structure only. While various functional groups at different positions may alter certain physicochemical properties (solubility, polarity, melting point, etc.), these physicochemical properties are not considered in making a determination regarding structural similarity. However, they may be considered in making a determination regarding pharmacological similarity under the second criterion of the definition of an analogue.]

References

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D'Ambra TE, Estep KD, Bell MA, Eissenstat MA, Josef KA, Ward SJ, Haycock DA, Baizman ER, Casiano FM, Beglin NC, Chippari SM, Grego JD, Kullnig RK, and Daley GT (1992). **Conformationally restrained analogues of pravadoline: nanomolar potent, enantioselective, (aminoalkyl)indole agonists of the cannabinoid receptor.** *Journal of Medicinal Chemistry* 35, 124-135.

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Huffman JW (2009). **Cannabimimetic indoles, pyrroles, and indenes: Structure-activity relationships and receptor interactions.** *Cannabinoid Receptors*, Reggio PH, Ed, Chapter 3, 49-98, Humana, New York

(2) ***1-Pentyl-3-(2,2,3,3-tetramethylcyclopropoyl)indole (UR-144) is likely to share substantial pharmacological effects similarity with the Schedule I substance, 1-pentyl-3-(1-naphthoyl)indole (JWH-018)***

- Classical cannabinoids, such as the primary psychoactive constituent of marijuana, Δ9-tetrahydrocannabinol (Δ9-THC) produces pharmacological effects via specific receptors in the body. The complex effects of cannabinoids are considered to be mediated through at least two distinct G-protein coupled transmembrane receptors designated as CB1 and CB2. The CB1 receptors are found predominately in the central nervous system, and are attributed to most of the overt pharmacological effects

of cannabinoids. The CB1 receptors are thought to be responsible for the euphoric and psychoactive effects (Wells and Ott, 2011). The CB2 receptors are found primarily in the periphery and expressed in the immune system.

- UR-144 binds to both CB1 and CB2 receptors with reported binding affinities (Ki) of 150 and 1.8 nM, respectively (Frost *et al.*, 2010). JWH-018 binds to the CB1 and CB2 receptors with reported binding affinities (Ki) of 9.0 and 2.9 nM, respectively (Aung *et al.*, 2000; Wiley *et al.*, 1998).
- CB1 receptor agonists can be divided into four structural classes (1) classic cannabinoids; (2) non-classical cannabinoids; (3) aminoalkylindoles; and (4) endogenous cannabinoids (Reggio, 2003).
- UR-144, similar to JWH-018, is a substance representative of the aminoalkylindole structural class. Aminoalkylindoles are known to exhibit typical cannabinoid pharmacology *in vivo* (D'Ambra *et al.*, 1992; Compton *et al.*, 1992).

Based on the above mentioned receptor binding data and structure-activity relationship information, UR-144 is likely to have cannabinoid agonist properties similar to that of JWH-018.

(3) ***1-Pentyl-3-(2,2,3,3-tetramethylcyclopropoyl)indole (UR-144)*** **was represented by the *seller* to have a pharmacological effect substantially similar to a Schedule I or II controlled substance (example: "this acts just like JWH-018"). These criteria *are* found at 21 U.S.C. § 802(32)(A).**

The third criterion may be established from evidence collected by the investigators (example: conversations or e-mail with suspects).

Conclusion

Based on the above information, UR-144 is substantially similar in chemical structure to JWH-018 and meets the first criterion of the definition of a controlled substance analogue. Based on receptor binding affinities, it is inferred that UR-144 is likely to have substantially similar pharmacological effects on the central nervous system

as the schedule I substance, JWH-018 and meets the second criterion of the definition of a controlled substance analogue. Depending on the individual case history, UR-144 may meet the third criterion of the definition of a controlled substance analogue. The third criterion may be established from evidence collected by the investigators (example: conversations or e-mail with suspects).

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