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LETTER TO THE EDITOR

The "pharmacophore rule" and the "spices"

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Dear Editor

In the mid-1990s, synthetic cannabinoids (SCBs) were first synthesized in an attempt to discover novel pharmacologic modulators of the endocannabinoid system with the potential for therapeutic utility [1]. In 2004, the synthetic cannabinoid, JWH-018 [1-pentyl-3-(1-naphthoyl)indole; Fig. 1] began to be sold over the Internet as a "spice" commonly referred to as K2 [2]. In 2011, the Drug Enforcement Agency (DEA), utilizing its emergency scheduling privileges, placed JWH-018 into schedule I [3]. In order to circumvent this DEA scheduling, illicit drug users began to chemically modify and sell versions of JWH-018. In many instances, these chemical modifications enhanced the pharmacologic and toxicologic potency of these agents [4]. In addition, crime laboratories and law enforcement were having difficulty staying ahead of the chemically modified SCBs. Here, we describe the scientific approach utilized by the State of Ohio to schedule current and future yet unidentified SCBs.

Drugs elicit their mechanism of action through biochemical and physiological interactions with drug targets. The pharmacophore of a drug molecule is the portion responsible for producing a pharmacological response, and provides the core scaffold to which functional groups are added. The core scaffold for JWH-018 is the aminoalkylindole ring structure [5]. Functional groups provide atoms for interacting with drug targets, such as receptors [6]. The binding of a drug to a receptor produces most of the pharmacologic and toxicologic effects of the drug.

In 1964, Δ^9-tetrahydrocannabinol (THC) was isolated and found to be the major psychoactive substance in marijuana [7]. In the mid-1980s, the drug target for THC was identified and named the cannabinoid (CB) receptor [8]. Currently, two CB receptors have been identified, the CB1 and CB2 receptors (CB1R and CB2R, respectively). The CB1R is found primarily in brain areas associated with memory, motor coordination, and emotion. THC acts as a partial agonist and JWH-018 as a full agonist at the CB1R [5].

Endogenous (e.g., anandamide) or exogenous (e.g., SCBs) ligand binding to the CB1R and CB2R results in the biochemical or physiological response. The CB1R is a cell surface receptor composed of 473 amino acids. These amino acids are arranged in such a way that the receptor contains seven transmembrane spanning units with an extracellular *N*-terminus and intracellular carboxy terminus; it is classified as a G-protein coupled receptor [9]. The amino acids: aspartic acid, glutamic acid, arginine, lysine, and histidine, are charged at a physiological pH and therefore can interact with the functional groups added to the core scaffold [6]. Functional groups participate in the drug receptor interaction by providing hydrogen bond donors or hydrogen bond acceptors. Common functional groups include the aldehydes, ketones (as in JWH-018), esters, amides, etc. In addition, functional groups can modify the lipophilic nature of the drug.

The strength of the reversible interaction of a drug and its receptor is referred to as affinity. Both the affinity of the drug for its receptor and its ability to produce a response is determined by the drug's chemical structure. Drug affinity is measured with an affinity coefficient (K_i, usually

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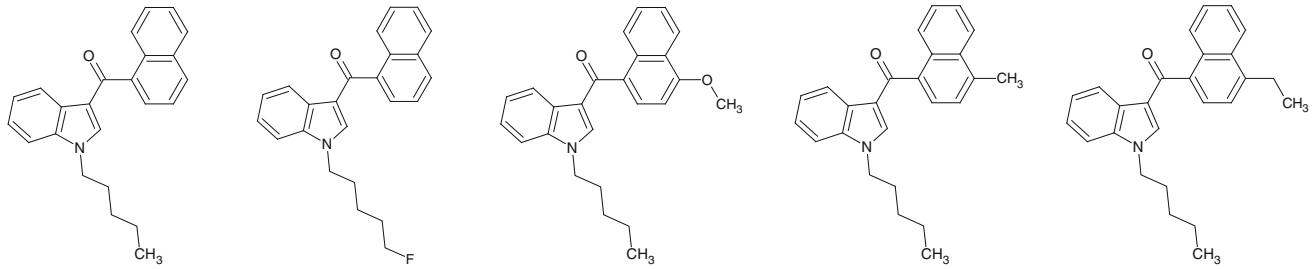

Fig. 1 Chemical structures of JWH-018 and examples of chemical modifications seen in products sold in head shops in Ohio. CB1 receptor K_i (nM) values are listed in parentheses from lowest affinity (JWH-018) to highest affinity (JWH-210). K_i values have been previously reported in the literature [18–21]

expressed in units of nM), where a lower value of K_i reflects stronger binding of the drug to the receptor.

Drug-seeking behavior associated with substances of abuse has been associated with dopamine release in the nucleus accumbens [10]. Although not all SCBs have been evaluated for their ability to activate this dopaminergic system, Δ^9-THC and the aminoalkylindole WIN-55212-2 increase dopamine release [11] and cell burst [12] in the nucleus accumbens. Furthermore, JWH-018, JWH-073, and JWH-210 have been shown to fully substitute for Δ^9-THC in drug discrimination models [13]. These findings are consistent with SCBs producing drug-seeking behavior.

In a retrospective study, Hermanns-Clausen et al. [14] demonstrated that SCBs have potentiated toxic effects over Δ^9-THC. The toxicities associated with SCBs not seen with Δ^9-THC include agitation, seizures, hypertension, emesis, and hypokalemia. These authors further correlated the augmentation of toxicologic effects of the SCBs with their K_i values, which were lower than that of Δ^9-THC (40 nM, [5]).

Since the emergency scheduling of JWH-018 by the DEA, the State of Ohio has proactively taken several steps to combat the growing problems associated with SCBs. Initially (October 2011), the State passed House Bill 64, which permanently scheduled the five SCBs (JWH-018, JWH-073, JWH-200, CP-47,497, CP-47,497 C8) that were emergency scheduled by the DEA. House Bill 64 also created a modified version of the DEA's analog rule where two of three conditions must be met allowing the state to present a case to a jury as an analog to a scheduled compound. The first condition is that a compound must be substantially similar in structure to a Schedule I or II substance. The second condition is that the compound must be one of two things: equal to or greater in stimulant, depressant, or hallucinogenic effect in the central nervous system when compared to a Schedule I or II substance, or have effects purported to be like those of a Schedule I or II substance. This rule also implies that the synthetic compound is intended for human consumption. However, the ability to meet all these criteria proved difficult because of a lack of scientific data on the pharmacology and toxicology of the new SCBs and overall apparent chemical dissimilarities between the emerging SCBs.

In an aggressive effort to stay ahead of clandestine laboratories, the State of Ohio again took action and passed House Bill 334 in December 2012. This bill formally named several compounds that had been seen in forensic laboratories, but were sufficiently different in chemical structure to not fit the standards outlined in House Bill 64. House Bill 334 also created classes for SCBs such that base structures with specific modifications were now deemed illegal. The creation of classes enabled the state to quickly prosecute more compounds that were harmful to the public. Unfortunately, soon after this bill took effect, more compounds began appearing on the market that "tip-toed" around the SCB classes that were created in House Bill 334.

At this point, the Office of the Attorney General sought input from The Ohio State Board of Pharmacy. Working together, these two entities developed the "pharmacophore rule." House Bill 334 created classes around the compounds that were being abused at the time of writing the bill, whereas the "pharmacophore rule" attacked the SCB problem at the level of pharmacology and before the compounds had even been identified in forensic science laboratories. The rule was written such that a chemist could identify the basic structural elements required for a compound to bind to the cannabinoid receptor. If three of the four binding elements, as described in general by Aung et al. [5], are met as determined by the chemist, then the compound is considered a Schedule I substance.

The following language is reprinted in part from Ohio Administrative Code 4729-11-02, which was published for public opinion on 7 August 2014.

Any substance that meets at least three of the following pharmacophore requirements to bind at the CB1 and CB2

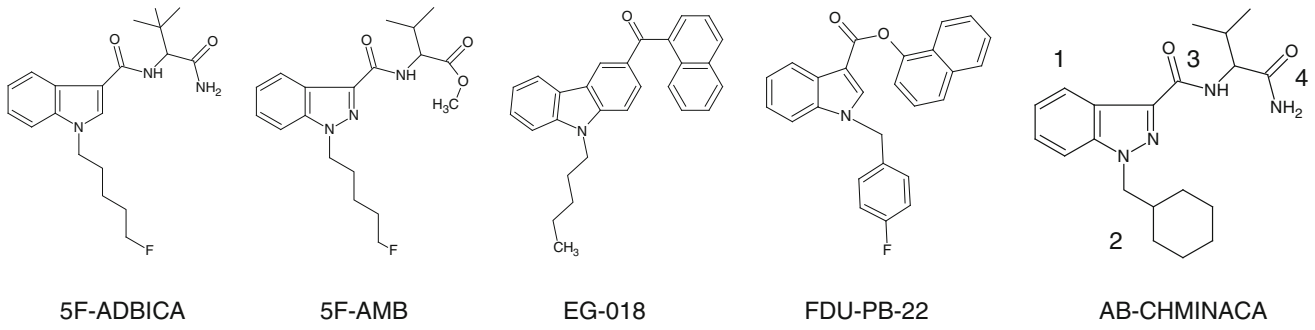

Fig. 2 AB-CHMINACA and other recently identified synthetic cannabinoids from the State of Ohio that fit the "pharmacophore rule"

receptors, as identified by a report from an established forensic laboratory, is a Schedule I controlled substance:

1. A chemical scaffold consisting of substituted or nonsubstituted ring structures that facilitate binding of required elements (such as: indole compounds, indazoles, benzimidazoles, or other ring types)
2. Alkyl or aryl side chain off the chemical scaffold providing hydrophobic interaction with the CB1 and CB2 receptors
3. Carbonyl or ester or equivalent for hydrogen bonding
4. Cyclohexane, naphthalene ring, substituted butanamide, or equivalent for steric requirements for CB1 and CB2 receptor binding

The numbers around AB-CHMINACA (see Fig. 2) correspond to the numbered points below.

1. The indazole structure matches the chemical scaffold requirement
2. Although this alkyl side chain has a cyclic structure, it would provide for hydrophobic interactions
3. Amide substitution that would allow for hydrogen bonding
4. Remainder of the molecule providing steric hindrance

Other recently identified SCBs that were previously unscheduled in the State of Ohio but fall under the scope of the "pharmacophore rule" are also presented in Fig. 2.

The "pharmacophore rule" utilized by the State of Ohio to establish guidelines for the scheduling of SCBs is based upon the scientific principles of drug design. The original synthesis of JWH-018 by John W. Huffman's laboratory was based upon these same scientific principles in an attempt to further our scientific understanding of the endocannabinoid system [15]. Wiley et al. [15] outlined the historical "hijacking" of the legitimate science conducted by Dr. Huffman's research team and the subsequent misuse of this science resulting in the abuse of SCBs. Aung et al. [5], working in Dr. Huffman's laboratory, outlined the structure–activity relationship between the JWH compounds and the CB receptors. Unfortunately, these scientific discoveries provide a "cookbook" for the synthesis of compounds that could be sold as "legal highs."

Original attempts to regulate SCBs based on compounds being substantially similar in chemical structure was fraught with confusion and ignored the pharmacology associated with drug–receptor interactions. That is, not enough attention was paid to pharmacophores consisting of core scaffolds with functional groups for hydrogen bond donors and hydrogen bond acceptors. In addition, SCBs were being released on the street at such a rate that complete pharmacological and toxicological characterization was not complete, leaving this characterization in the hands of the user.

"Protecting Our Youth from Dangerous Synthetic Drugs Act of 2013," introduced by Senator Feinstein has taken measures to also include the pharmacologic effects of the drug [16]. This bill, while still in the editing and approval stages, states, "…the substance is determined by the Committee to be similar to a Schedule I or II controlled substance in either its chemical structure or its predictive effect on the body, in such a manner as to make it likely that the substance will, or can be reasonably expected to have a potential for abuse." Although not stated as the pharmacophore, these predictive effects on the body can only be made by applying the scientific principles of drug design.

Recently, Nutt et al. [17] outlined the constraining effects that the placement of newly identified compounds with therapeutic potential into Schedule I has on scientific discovery. They also suggested that a new scheduling system be implemented for legitimate scientific discovery so as to attenuate the blunting effects scheduling has on drug discovery. We agree that policies and procedures should be established for legitimate scientific research on agents with the potential for abuse and we would support such a system. In the development of policies with regard to the misuse of SCBs, Huffman and his research team state, "like the creation of the problem itself, the foundation of its solution starts with science" [15]. The State of Ohio has attempted to draw the line between legitimate

scientific drug design for disease treatment and street abuse. The State of Ohio's "pharmacophore rule" applies the scientific principles of drug design in establishing the framework for regulation of the SCBs.

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