APPENDIX

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APPENDIX A — OPINION OF THE UNITED STATES COURT OF APPEALS FOR THE NINTH CIRCUIT, FILED DECEMBER 27, 2023

UNITED STATES COURT OF APPEALS
FOR THE NINTH CIRCUIT

No. 20-10288, D.C. No. 2:15-cr-00285-APG-EJY-2
No. 20-10296, D.C. No. 2:15-cr-00285-APG-EJY-1

UNITED STATES OF AMERICA,

Plaintiff-Appellee,

v.

BENJAMIN GALECKI, AKA Zencense Ben,

Defendant-Appellant.

UNITED STATES OF AMERICA,

Plaintiff-Appellee,

v.

CHARLES BURTON RITCHIE, AKA Burton Ritchie,

Defendant-Appellant.

Appeal from the United States District Court
for the District of Nevada
Andrew P. Gordon, District Judge, Presiding

Appendix A

Argued and Submitted December 6, 2021
San Francisco, California

Filed December 27, 2023

Before: Ronald M. Gould and Daniel P. Collins, Circuit Judges, and Roslyn O. Silver,* District Judge.
Opinion by Judge Collins.

Opinion by Daniel P. Collins

OPINION

COLLINS, Circuit Judge:

Defendants Benjamin Galecki and Charles Burton Ritchie were convicted of drug trafficking, mail fraud, wire fraud, and money laundering in connection with their distribution of "spice," a synthetic cannabinoid product that, when smoked, produces a high. The drug-trafficking charges were based on the premise that, although the particular cannabinoid that Defendants used had not yet been specifically listed as a prohibited controlled substance under federal law, that cannabinoid was nonetheless treated as a controlled substance because it was an "analogue" of a listed substance. On appeal, Defendants raise multiple challenges to their analogue-based drug-trafficking convictions, but we reject these

* The Honorable Roslyn O. Silver, United States District Judge for the District of Arizona, sitting by designation.

contentions and affirm those convictions. We likewise affirm their money laundering convictions, but we reverse their mail and wire fraud convictions.

I

A

Defendants Galecki and Ritchie manufactured and distributed spice through their company, Zencense Incenseworks, LLC ("Zencense"), which was formed in Florida in 2010. Although headquartered in Florida, Zencense also manufactured spice at a warehouse that the company leased in Nevada. Zencense was highly successful, and mid-2012, it employed approximately 140 people.

At trial, several former Zencense employees testified concerning the company's spice operations. For example, Robert Biggerstaff testified that Galecki taught him how to manufacture spice that contained a cannabinoid known alternatively as "XLR-11" or "5F-UR-144." The "point of adding" the XLR-11, Biggerstaff explained, was to "create a product that would actually get you high." Rachel Templeman, a sales employee, testified that Zencense customized the product with various flavorings, including blueberry, cherry, vanilla, chocolate, and pineapple.

Although both Templeman and Biggerstaff stated that they knew that end users were ingesting Zencense's products, the company maintained an official position that its products were simply "potpourri," which it sold in

packets labeled "not for human consumption." Consistent with this company position, Biggerstaff testified that Zencense staff were instructed not to refer to the various versions of the product as "flavors," because that could "invoke[] a connotation of being orally ingested." Rather, staff were expected to use the words "aroma" or "fragrance." Biggerstaff stated that, if a Zencense employee did not use the "language of fragrance" or "aroma," and instead "refer[red] to something involving taste," that employee "would have been terminated" by Galecki or Ritchie. Templeman agreed that "we weren't able to call [the options] flavors" and that she instead referred to them as "[a]romas" or "scents."

However, rather than sell its "potpourri" to home goods stores such as "Bed Bath & Beyond" or to general retailers such as Target or Walmart, Zencense marketed its products primarily to "either smoke shops or alternative adult emporiums" or "independent convenience stores." Templeman testified that when she referred to "spice or incense or potpourri" on sales calls to such potential retailers, "they knew what you were talking about," because those names were "standard in the industry." Asked why Zencense did not market its potpourri to stores like Target or Walmart, Biggerstaff explained that "[w]e didn't believe they would be a good customer for our product" because they would be expecting "an air freshener," and "that's not the product that we were selling."

To illustrate the stark contrast between Zencense's products and actual potpourri, the Government introduced

testimony from the CEO of a genuine potpourri company, Aromatique. The CEO testified that Aromatique typically sold its conventional potpourri to retailers such as Anthropologie and Macy's for as much as $18 per 8-ounce package. Zencense "potpourri," by contrast, sold to smoke shops and other similar stores for around $7.50 per *gram*—*i.e.*, more than 90 times the price of ordinary potpourri at Aromatique.[1] The potpourri options available to shoppers at Aromatique included "Smell of Spring," "Tarocco & Clove," and "Valencia Orange." The Zencense "potpourri" options included "Bizarro," "Shockwave," "Headhunter," "Sonic Boom," and "DefCon 5 Total Annihilation."

The Government also introduced Zencense's written sales script into evidence, and it confirmed the company's focus on selling to smoke shops while simultaneously maintaining the nominal position that the products were "not for human consumption." For example, if a potential retailer responded that it did not carry "spice" and was not familiar with it, the script stated that the Zencense salesperson should then explain that spice was "an herbal incense blend that you burn" and then immediately ask, "Do you sell pipes?" If the retailer responded that it did *not* sell pipes, the script stated that "[m]ost likely this will not be a potential customer" and the salesperson should "[e]nd [the] call, mark 'Not Interested,' explain in notes, and mark for deletion." But if the retailer stated that it did sell pipes, then the caller was to immediately

1. A wholesale price of $18 for an 8-ounce package works out to approximately $2.25 per ounce. By contrast, a wholesale price of $7.50 per gram works out to more than $212 per ounce.

respond by saying, "You know how pipes are for tobacco use only? Well, spice is not for human consumption." An associated note in the script reminded the caller that the company's "stance" was "always that it is not for human consumption." But the script also noted that retailers "that are in this business understand that language is very important and will usually not press the issue too much."

In addition, the Government presented testimony to show that Galecki and Ritchie were aware that customers were smoking Zencense products to get high. The owner of a chain of smoke shops who purchased spice from Zencense testified that Ritchie told him that if someone smoked spice, "it would knock you out for a couple of hours on the floor." And Jayson Lang, who owned a business that sold XLR-11 to Zencense, testified that "[i]t was common knowledge that people were consuming the product" and that Galecki had told him "people liked the 5F-UR-144 [XLR-11] more than" another similar cannabinoid because XLR-11 was "fluorinated," which "made it stronger."

In July 2012, employees of an apparel shop that was located next to Zencense's Nevada warehouse contacted the Las Vegas police about what they considered to be suspicious activities at the warehouse. Ultimately, federal authorities sought and obtained a search warrant, which was executed on July 25, 2012. Numerous items were seized, including substantial quantities of XLR-11.

Notified of the Nevada raid, Ritchie responded the same day by calling a Florida police officer whom he knew from middle school and who in turn referred him to a DEA

agent named Claude Cosey. On July 26, Ritchie took Cosey and another DEA employee on a "tour" of the company's Florida facilities, and he gave them free samples. During the tour, Cosey told Ritchie "[y]ou know people smoke this, correct?" Ritchie responded: "Hey, I sell it as either incense or potpourri. . . . Whatever they do with it after that, I don't know and I don't want to know."

Defendants were charged with conducting a continuing criminal enterprise in violation of the Controlled Substances Act ("CSA"), *see* 21 U.S.C. § 848; violations of the CSA relating to alleged drug trafficking; and various financial crimes including money laundering, mail fraud, and wire fraud.

B

At the time Defendants engaged in the charged conduct, XLR-11 had not yet been listed on the federal schedules of controlled substances governed by the CSA.[2] Accordingly, the Government's drug-trafficking charges proceeded on the theory that XLR-11 fell within the CSA's provisions addressing "analogues" of listed substances. To set the relevant context concerning the Government's analogue theory, we first review what it means to be an "analogue" under the CSA, and we then summarize the Government's trial evidence concerning whether XLR-11 was an analogue.

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2. Effective May 16, 2013, XLR-11 was formally added to Schedule I. *See* 78 Fed. Reg. 28735 (May 16, 2013).

Appendix A

1

The CSA provides for five "schedules" of controlled substances that are regulated under the Act. *See* 21 U.S.C. § 812. The schedules are numbered in decreasing levels of perceived dangerousness, with "Schedule I" listing the most dangerous substances that have no accepted medical use. *See id.* § 812(b)(1), (c). The various schedules, however, are not set in stone: the CSA expressly "authorizes the Attorney General to add or remove substances, or to move a substance from one schedule to another." *Touby v. United States*, 500 U.S. 160, 162, 111 S. Ct. 1752, 114 L. Ed. 2d 219 (1991) (citing 21 U.S.C. § 811(a)). Unsurprisingly, violations of the CSA that involve Schedule I substances "carry the most severe penalties." *Id.*

The listed-chemical approach of the CSA gave rise to a significant loophole. By taking a substance listed on the federal schedules and making modifications to its chemical structure, drug designers were able to "develop subtle chemical variations of controlled substances" that were functionally similar to a listed chemical without actually *being* a listed chemical. *Grinspoon v. DEA*, 828 F.2d 881, 891 (1st Cir. 1987) (citation omitted). Congress responded to this problem by passing the Controlled Substance Analogue Enforcement Act of 1986 ("the Analogue Act"). *See* Pub. L. No. 99-570, title I, subtitle E, 100 Stat. 3207-13-3207-14 (Oct. 27, 1986). The Analogue Act accomplishes this goal through two amendments to the CSA. First, the Analogue Act added a new definition of the term "controlled substance analogue." 21 U.S.C. § 802(32)(A). Second, the Analogue Act added a new section establishing

the substantive rule governing such "controlled substance analogues." *See id.* § 813. In its current form, the key subsection of that latter provision states: "A controlled substance analogue shall, to the extent intended for human consumption, be treated, for the purposes of any Federal law[,] as a controlled substance in schedule I." *Id.* § 813(a). Thus, any substance falling within the definition of a controlled substance analogue must be treated, if "intended for human consumption," as equivalent to the most serious controlled substances with the most severe penalties. *McFadden v. United States*, 576 U.S. 186, 188, 135 S. Ct. 2298, 192 L. Ed. 2d 260 (2015) (citations omitted).

Given this draconian rule, the statutory definition of "controlled substance analogue" is obviously crucial. That definition states that, subject to certain limited exceptions:

> [T]he term "controlled substance analogue" means a substance—
>
> > (i) the chemical structure of which is substantially similar to the chemical structure of a controlled substance in schedule I or II;
> >
> > (ii) 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

> (iii) 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.

21 U.S.C. § 802(32)(A).

Although the three components of this definition are written in the disjunctive, most courts have read the statute as requiring proof of *both* (1) component (i) *and* (2) *either* component (ii) or component (iii). *See United States v. Makkar*, 810 F.3d 1139, 1142–43, 1146 (10th Cir. 2015) (concluding that this reading was confirmed by "the plain language of the statute" and also noting the potential vagueness concerns presented by a broader, fully disjunctive reading); *see also United States v. Turcotte*, 405 F.3d 515, 521–22 (7th Cir. 2005); *United States v. Klecker*, 348 F.3d 69, 71 (4th Cir. 2003); *United States v. Hodge*, 321 F.3d 429, 435–39 (3d Cir. 2003); *United States v. Washam*, 312 F.3d 926, 930 n.2 (8th Cir. 2002). With the acquiescence of both sides, that reading was explicitly embodied in the jury instructions that were given at Defendants' trial, and the Government confirmed at oral argument in this court that it does not contest that construction of the statute for purposes of this case. In view of that concession, "we need not decide in this case whether that interpretation is correct," and therefore "we

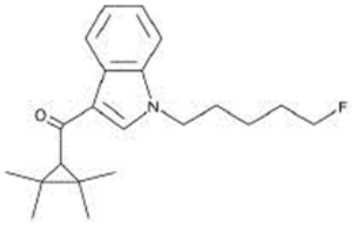
assume for the sake of argument that it is." *McFadden*, 576 U.S. at 194 n.2 (declining to address this very same issue).

2

The indictment charged that XLR-11 was an analogue of "JWH-018," a substance that was added to Schedule I effective March 1, 2011. *See* 76 Fed. Reg. 11075 (Mar. 1, 2011); *see also* 21 C.F.R. § 1308.11(g)(3). At trial, the Government relied on expert testimony to establish that XLR-11 satisfied both elements of the definition of an analogue with respect to JWH-018.

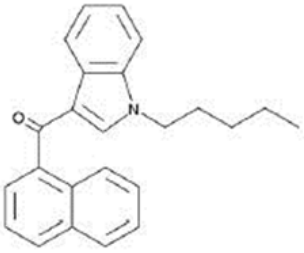
First, Dr. Gregory Endres, an expert in "organic forensic and medicinal chemistry," testified that XLR-11 had a substantially similar chemical structure to JWH-018. Dr. Endres prepared the following diagram depicting XLR-11 and JWH-018 side-by-side:

Chemical structure of XLR11:



Appendix A

Chemical structure of JWH 018:



Dr. Endres stated that "[t]o make a determination on structural similarity I look at the chemical as a whole." Dr. Endres explained that XLR-11 and JWH-018 have "exactly the same" "acylindole core," including the "same atoms" in the "same locations" with the "exact same structure." In Dr. Endres's view, the "substitution of a fluorine atom" in the tail part of XLR-11's structure was not a significant change from JWH-018. Dr. Endres also noted that the "naphthyl group" in JWH-018 was replaced by a "tetramethylcyclopropyl" group in XLR-11. He stated that the naphthyl group is an aromatic that can engage in "pi stacking," a phenomenon that he described as providing a "weak electrostatic interaction . . . that can contribute to better binding affinity." However, he stated that he did not view this "as a significant enough change," because "pi stacking is not required for binding affinity in the cannabinoid receptors."

Second, Dr. Jordan Trecki, a pharmacological expert, opined that "XLR-11 has a substantially similar hallucinogenic effect on the central nervous system of that of JWH-018." Dr. Trecki testified that chemical differences between JWH-018 and XLR-11 "retained and actually intensified the pharmacological effect of the substance." Substances like XLR-11 "continued to work [as] well [as] or greater than the original JWH substance," and the changes from JWH-018 to XLR-11 "enhanced" the substance's effect by, among other things, adding a fluorine atom. Because fluorine "reduce[s] the metabolism of [a] substance," it allows substances to "stay[] in your body longer," meaning that less of the substance is necessary to trigger the same effect over time.

C

Zencense employee Ryan Eaton—who had been sent to assist Zencense's warehouse operations in Las Vegas—was tried alongside Galecki and Ritchie as a co-defendant. However, the jury acquitted Eaton on all six counts with which he was charged. The jury also acquitted Galecki and Ritchie on two drug-trafficking counts involving a *different* alleged analogue, known as "AM 2201" (Counts 20–21), but it convicted both men on all remaining counts, including all five drug-trafficking charges involving XLR-11 (Counts 22–26).[3] Galecki and Ritchie were each

3. Specifically, the jury convicted Galecki and Ritchie of the following five drug-trafficking offenses: (1) conspiracy to manufacture, possess with intent to distribute, and distribute XLR-11, in violation of 21 U.S.C. § 846 (Count 22); (2) manufacture of XLR-11, in violation of 21 U.S.C. § 841(a)(1) (Count 23); (3) distribution

sentenced to 20 years in prison, followed by three years of supervised release, and a criminal forfeiture order was entered against both of them. Galecki and Ritchie timely appealed, and we have jurisdiction under 28 U.S.C. § 1291.

II

We first address Defendants' contention that all of their convictions should be set aside on the ground that the district court erred in refusing to suppress evidence seized during or as a result of the raid at Zencense's Nevada warehouse.

In June 2016, Galecki filed a motion to suppress, asserting that the search warrant affidavit contained false and misleading information in violation of *Franks v. Delaware*, 438 U.S. 154, 98 S. Ct. 2674, 57 L. Ed. 2d 667 (1978). The district court denied this motion on the ground that Galecki had not established that he had Fourth Amendment "standing" to challenge a search of a warehouse leased, not by him, but by Zencense. *See United States v. SDI Future Health, Inc.*, 568 F.3d 684, 695 (9th Cir. 2009) (holding that, as "a matter of substantive

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of XLR-11, in violation of 21 U.S.C. § 841(a)(1) (Count 24); (4) maintaining drug-involved premises, in violation of 21 U.S.C. § 856(a)(1) (Count 25); and (5) possession of a "listed chemical" (*viz.*, acetone) with intent to manufacture a substance containing a detectable amount of XLR-11, in violation of 21 U.S.C. § 841(c) (Count 26). (The statutory definition of "listed chemical" refers to a distinct list of chemicals that are used in the manufacture of controlled substances, and that term therefore does not correspond to the above-described schedules of controlled substances. *See* 21 U.S.C. § 802(33), (35)(B).)

Fourth Amendment law," a person challenging a search or seizure must show that there has been a violation of that Amendment "*as to him, personally*" (emphasis added) (simplified)); *see also Byrd v. United States*, 138 S. Ct. 1518, 1530, 200 L. Ed. 2d 805 (2018) (noting that "Fourth Amendment 'standing'" "should not be confused with Article III standing, which is jurisdictional"). Ritchie subsequently filed his own motion to suppress—which Galecki later joined—arguing that the search warrant affidavit both was defective under *Franks* and failed to establish probable cause. The district court denied this motion as to both Defendants on the ground that it was an improper motion to reconsider the earlier order denying Galecki's motion to suppress.

We need not decide whether the district court erred in treating Ritchie's motion as an improper motion for reconsideration. Reviewing the merits of the Fourth Amendment standing de novo as to both Defendants, *see United States v. Lopez-Cruz*, 730 F.3d 803, 807 (9th Cir. 2013), we conclude that the district court correctly denied the motions.

In arguing that they have standing to challenge the search of Zencense's Nevada warehouse, Defendants assert that they each had a "reasonable expectation of privacy" in those premises. *See Byrd*, 138 S. Ct. at 1526–27 (noting that this test for Fourth Amendment standing "was derived from the second Justice Harlan's concurrence in *Katz v. United States*, 389 U.S. 347, 88 S. Ct. 507, 19 L. Ed. 2d 576 (1967)"). To establish standing under this test, Defendants had to show that

they "manifested a subjective expectation of privacy" in the Nevada warehouse that "society is willing to recognize . . . as reasonable." *California v. Ciraolo*, 476 U.S. 207, 211, 106 S. Ct. 1809, 90 L. Ed. 2d 210 (1986). We conclude that Defendants failed to make that showing.

As we have recognized, determining *who* may assert a reasonable expectation of privacy with respect to specific *commercial* spaces "requires analysis of reasonable expectations 'on a case-by-case basis.'" *SDI Future Health*, 568 F.3d at 695 (quoting *O'Connor v. Ortega*, 480 U.S. 709, 718, 107 S. Ct. 1492, 94 L. Ed. 2d 714 (1987) (plurality)). The need for such a case-by-case inquiry arises from two considerations. First, because "the expectation of privacy that the owner of commercial property enjoys in such property differs significantly from the sanctity accorded an individual's home," *Donovan v. Dewey*, 452 U.S. 594, 598–99, 101 S. Ct. 2534, 69 L. Ed. 2d 262 (1981), the "expectation of privacy in commercial premises" is "less than[] a similar expectation in an individual's home." *New York v. Burger*, 482 U.S. 691, 700, 107 S. Ct. 2636, 96 L. Ed. 2d 601 (1987); *see also Minnesota v. Carter*, 525 U.S. 83, 90, 119 S. Ct. 469, 142 L. Ed. 2d 373 (1998) ("Property used for commercial purposes" is thus "treated differently for Fourth Amendment purposes from residential property."). Second, in light of the "great variety of work environments," any given company officer, manager, or owner may not have the same personal reasonable expectation of privacy in *all* of the commercial spaces of the organization. *SDI Future Health*, 568 F.3d at 695.

Appendix A

In *SDI Future Health*, we identified a number of considerations that inform the determination as to whether a particular individual has a reasonable expectation of privacy in a specific company space. First, we noted that, under our decision in *United States v. Gonzalez, Inc.*, 412 F.3d 1102 (9th Cir. 2005), the joint owners and managers of a "small business," particularly one that is "family-run," may exercise such complete "day-to-day" personal control over, and "full access" to, the company's facilities that those owner/managers would have a reasonable expectation of privacy over the relevant spaces. *SDI Future Health*, 568 F.3d at 696 (citing *Gonzalez, Inc.*, 412 F.3d at 1116–17); *see also Gonzalez, Inc.*, 412 F.3d at 1117 (noting, by contrast, that "the hands-off executives of a major corporate conglomerate might lack standing to challenge all intercepted conversations at a commercial property that they owned, but rarely visited").

Second, we stated in *SDI Future Health* that a further "crucial" threshold factor is whether the particular place searched in the commercial facility was "given over to the *defendant's* exclusive use," 568 F.3d at 695-96 (emphasis added) (simplified), because a showing of such exclusivity would indicate that, absent countervailing considerations, the person's expectation of privacy was reasonable.

Third, *SDI Future Health* held that, outside "the case of a small business over which an individual exercises daily management and control, an individual challenging a search of workplace areas beyond his own internal office must generally show some *personal connection* to the places searched and the materials seized." 568 F.3d at

698 (emphasis added). We further stated that whether the requisite personal connection has been shown should be assessed "with reference to the following factors," which we said are not exclusive, *id.* at 698 & n.8:

> (1) whether the item seized is personal property or otherwise kept in a private place separate from other work-related material; (2) whether the defendant had custody or immediate control of the item when officers seized it; and (3) whether the defendant took precautions on his own behalf to secure the place searched or things seized from any interference without his authorization.

Id. at 698 (footnotes omitted). "Absent such a personal connection or exclusive use, a defendant cannot establish standing for Fourth Amendment purposes to challenge the search of a workplace beyond his internal office." *Id.*

Under this framework, Galecki and Ritchie did not establish Fourth Amendment standing with respect to the Nevada warehouse. First, this case does not fall within the distinctive scenario, typified by *Gonzalez, Inc.*, in which the defendants personally exercise day-to-day physical access to and control over the facilities as part of their daily management of a closely held small business. Indeed, the record does not affirmatively indicate that Galecki and Ritchie had ever actually visited the Nevada warehouse, much less exercised personal day-to-day control over the physical plant. Second, the Nevada warehouse is not the personal office of either Defendant. Because this case

thus does not fall into either of these two scenarios, we consider whether Defendants established that, in light of the factors identified in *SDI Future Health*, they had the requisite "personal connection to the places searched and the materials seized." 568 F.3d at 698.

As to the first *SDI Future Health* factor, the items seized from Zencense's Nevada warehouse were not the "personal property" of Galecki or Ritchie, nor were they "kept in a private place separate from other work-related material." *Id.* Rather, they were materials used in the manufacture of Zencense's products, such as XLR-11, plant material, acetone, and flavorings; physical equipment, such as drying racks; or documents, such as packing slips, handwritten notes concerning flavorings, and a document relating to rental of a facility. Because "the first factor really addresses whether the item seized was personal property without any relationship to work," *id.* at 697, it provides no support for finding the requisite personal connection to the warehouse.

The second *SDI Future Health* factor likewise provides no basis for finding standing, because neither Galecki nor Ritchie had personal "custody or immediate control" of the items at the time that they were seized. *Id.* at 698. As noted earlier, there does not appear to be any record evidence that either Defendant ever even visited the warehouse, which was thousands of miles from Zencense's Florida headquarters. Moreover, Defendants concede that neither of them was present at the warehouse at the time it was searched.

The third *SDI Future Health* factor addresses whether the defendant "took precautions *on his own behalf* to secure the place searched or things seized from any interference without his authorization." *Id.* (emphasis added). This "third factor involves actions the employee takes on his own behalf, *not as an agent of the* [*company*]." *Id.* at 697 (emphasis added). Defendants have pointed to no such evidence in the record. Instead, they point to the fact that *Eaton* took steps to keep the warehouse locked and secure and that Defendants had the legal right, as managers of Zencense, to prohibit others from entering the property. At best, those actions show only that Defendants took steps *as agents of Zencense* to ensure the security of the company's property, and not that they took any steps to secure the warehouse or its contents on their own behalf. As we made clear in *SDI Future Health*, it is not enough that Defendants set "general policy" over company premises, "put in place significant security measures" there, or took "steps to protect the privacy" of the building. *Id.* Under this factor, there must be some showing that actions were taken for the benefit of Galecki or Ritchie personally, as opposed to the benefit of the company as a whole. There is no such evidence.

Nor does the record disclose any other factor, beyond the three we identified in *SDI Future Health*, that would support finding the required "personal connection" to the Nevada warehouse. *See id.* at 698 n.8.[4] Accordingly,

4. Defendants point to the general factors that we used to analyze Fourth Amendment standing in *Lopez-Cruz*, such as whether the defendant has a property interest in the placed searched, whether the defendant has the right to exclude others from it, and whether

we hold that Galecki and Ritchie failed to establish that they have Fourth Amendment standing to challenge the search of the Nevada warehouse and that the district court therefore properly denied their motions to suppress.

III

We reject Defendants' challenges to their convictions for drug trafficking in violation of the CSA.

A

Defendants argue that the evidence was insufficient to establish the scienter required in a CSA prosecution resting on the Analogue Act. We disagree.

In *McFadden v. United States*, 576 U.S. 186, 135 S. Ct. 2298, 192 L. Ed. 2d 260 (2015), the Supreme Court addressed "the knowledge necessary for conviction" under the principal drug-trafficking statute, 21 U.S.C. § 841(a)(1), "when the controlled substance at issue" is "an analogue" rather than a scheduled controlled substance. 576 U.S. at 188. The Court held that such knowledge could be established in either of two ways. First, the Government may establish the requisite scienter "by evidence that a

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he took "normal precautions to maintain privacy." 730 F.3d at 808 (citation omitted). In light of these factors, *Zencense* would clearly have standing to challenge the search of the warehouse had it been prosecuted. *See SDI Future Health*, 568 F.3d at 694 n.3. But in the specific context of an owner, manager, or employee of a company, these factors must be viewed within the context of the *SDI Future Health* framework.

defendant knew that the substance with which he was dealing is some controlled substance—that is, one actually listed on the federal drug schedules or treated as such by operation of the Analogue Act—regardless of whether he knew the particular identity of the substance." *Id.* at 194. Second, the Government may prove scienter "by evidence that the defendant knew the specific analogue he was dealing with, even if he did not know its legal status as an analogue." *Id.*

The Court also elaborated on the actual sorts of proof that might satisfy these two alternatives. As to the first—*i.e.*, knowledge that the substance is a "controlled substance"—the Government can rely on either "direct evidence," such as "past arrests that put a defendant on notice of the controlled status of a substance," or "circumstantial evidence," such as, "a defendant's concealment of his activities, evasive behavior with respect to law enforcement, knowledge that a particular substance produces a 'high' similar to that produced by controlled substances, and knowledge that a particular substance is subject to seizure at customs." *Id.* at 192 n.1; *see also id.* at 195 n.3. As to the second alternative, the Court explained that the requisite scienter exists if the Government shows that the defendant had knowledge of the features of the substance that make it an analogue under the Analogue Act's definition. *Id.* at 194. In such a case, it is the knowledge of the *features* that counts; the "defendant need not know of the existence of the Analogue Act." *Id.* at 195.

In assessing the sufficiency of the trial evidence of scienter under these standards,[5] we ask only "whether, after viewing the evidence in the light most favorable to the prosecution, *any* rational trier of fact could have found the essential elements of the crime beyond a reasonable doubt." *Jackson v. Virginia*, 443 U.S. 307, 319, 99 S. Ct. 2781, 61 L. Ed. 2d 560 (1979); *see also United States v. Nevils*, 598 F.3d 1158, 1163–64 (9th Cir. 2010) (en banc). Here, we conclude that the evidence was sufficient to permit a rational jury to find scienter under *McFadden*'s first alternative—namely, that Defendants dealt with a substance with "knowledge that [it] is listed [under the CSA] or treated as listed by operation of the Analogue Act." *McFadden*, 576 U.S. at 196.[6] In particular, the record in this case includes evidence of each of the four types of circumstantial evidence that *McFadden* identified as supporting a finding of scienter under this first alternative. *Id.* at 192 n.1; *see also id.* at 195 n.3.

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5. We note that *McFadden* addressed only a prosecution under § 841(a)(1), whereas in Defendants' case, only two of the five relevant drug-trafficking charges rested specifically on that statute. *See supra* note 3. Nonetheless, the parties and the district court proceeded on the assumption that the same scienter requirements that apply under *McFadden* in a § 841(a)(1) case are also applicable to the charges against Defendants under §§ 841(c), 846, and 856(a)(1). We will proceed, *arguendo*, on the same assumption.

6. We therefore need not consider whether sufficient evidence supported finding scienter under *McFadden*'s second alternative. *See Griffin v. United States*, 502 U.S. 46, 56–60, 112 S. Ct. 466, 116 L. Ed. 2d 371 (1991).

First, the Government presented evidence that Galecki and Ritchie each knew that XLR-11 "produces a 'high' similar to that produced by controlled substances." *Id.* at 192 n.1. As noted earlier, a retailer who purchased spice from Zencense testified that Ritchie told him that if a person smoked spice, "it would knock you out for a couple of hours on the floor." And the owner of a business that sold XLR-11 to Zencense testified that Galecki had told him that XLR-11 was more popular than another cannabinoid because the former was "fluorinated," which "made it stronger" so that the "high lasts longer."

Second, there was evidence of "evasive behavior with respect to law enforcement." *McFadden*, 576 U.S. at 192 n.1. In particular, Biggerstaff testified that, to address the possibility that Zencense's products would be "seized" or "confiscated" by law enforcement, the company maintained "secret" storage locations "that just the higher-ups in the company knew about so that if we ever had an interruption in business, we could continue to sell because we still had product that hadn't been confiscated." Biggerstaff stated that, on at least one occasion, Ritchie personally took him once to these storage facilities, and he also testified that Ritchie told him not to say anything to anyone else about these units. Cory Finch, a Zencense employee, testified that Galecki sent him a text message regarding a Dodge work truck that appeared to have expired registration tags. Galecki stated that the truck could get "pulled over" and informed Finch that if he did get pulled over in the truck, there was a receipt showing the registration had been renewed. In the meantime, Galecki instructed Finch not to place "product in the Dodge until we have the new sticker."

Defendants emphasize that Ritchie freely gave DEA Agent Cosey a tour of Zencense's Florida facility, but that tour was given only *after* DEA agents had already raided the Nevada warehouse. Weighing the competing inferences that may be drawn from the record, the jury could reasonably conclude that this tour, which was given only after the cat was already out of the bag, reflected simply a disingenuous and opportunistic shift in strategy towards law enforcement. That inference is further bolstered by the fact that, during the tour, Ritchie implausibly claimed to Agent Cosey that he was unaware that customers were smoking Zencense products.

Third, there was evidence from which the jury could rationally infer that Defendants knew that the substances involved were "subject to seizure at customs." *McFadden*, 576 U.S. at 192 n.1. Specifically, Defendants were well aware that the XLR-11 that they imported from China was mislabeled as containing other products, such as "cytidine-5' monophosphate." A rational jury could conclude that the products were mislabeled in this way precisely to avoid their seizure by customs. Defendants argue that this practice was standard throughout the spice industry, but that point does not *preclude* the jury from drawing a permissible adverse inference from the use of such mislabeling. Moreover, as noted earlier, Defendants were aware of, and planned for, the possibility that some of their products might be seized or confiscated. In addition, even prior to the search of the Nevada warehouse, Ritchie was informed of raids on retail establishments, and at one point Zencense had a policy of reshipping an order if the product that it shipped to a retailer was seized.

Fourth, there was ample evidence that Defendants took additional steps to "conceal[]," to the extent that they could, the nature of their "activities." *McFadden*, 576 U.S. at 192 n.1. As we have explained, the evidence readily supports the inference that Defendants knew that their products would be consumed by those who purchased them from smoke shops and other retailers. Defendants, however, sought to obscure that fact by labeling their products as "potpourri" or "incense" and "not for human consumption." They similarly instructed their employees not to refer to the spice as having "flavors," which could connote ingestion. Defendants were also aware that their "potpourri" products sold for very high prices that vastly exceeded what a home aromatic would actually fetch, which further supports a reasonable inference that Defendants were engaged in a charade that sought to avoid formally admitting what they knew that they were selling.

The record also contains additional circumstantial evidence beyond the four types that *McFadden* identified. Because Templeman testified that Ritchie explained the concept of an "analogue" to her, the jury could infer that Ritchie was specifically familiar with the Analogue Act. There was also testimony that, during the relevant timeframe, spice distributors, including Zencense, serially switched the cannabinoids they used as one after another was formally added to the CSA's schedules. When asked to explain why Zencense kept changing the cannabinoid it used, Templeman stated that "we knew that we were just staying one step ahead of legality."

Considering the record evidence as a whole, we have little difficulty concluding that a rational jury could find,

beyond a reasonable doubt, that both Galecki and Ritchie had the scienter required for an Analogue Act case under *McFadden*. *See United States v. Anwar*, 880 F.3d 958, 967–68 (8th Cir. 2018).

B

We next address Defendants' contention that the district court erred in giving a "deliberate ignorance" instruction modeled on this court's en banc decision in *United States v. Jewell*, 532 F.2d 697 (9th Cir. 1976) (en banc). Under *Jewell*, the Government can satisfy the scienter requirement in a drug-trafficking case by showing that "[1] the defendant [was] aware" that it was "highly probable" that he was dealing with a controlled substance but [2] he acted with "a conscious purpose to avoid learning the truth." *Id.* at 704 (citation omitted); *see also United States v. Heredia*, 483 F.3d 913, 919–21 (9th Cir. 2007) (en banc). Defendants contend that there was insufficient evidence to support giving such an instruction here. *See United States v. Yi*, 704 F.3d 800, 804 (9th Cir. 2013) ("An instruction is appropriate if it is 'supported by law and has foundation in the evidence.'" (citation omitted)).[7] We review the district court's conclusion that the evidence supported a *Jewell* instruction only for an abuse of discretion, *see Heredia*, 483 F.3d at 921–22, and

7. Defendants do not contend that *Jewell*'s deliberate-ignorance standard is inapplicable to Analogue Act cases under *McFadden*, and we therefore assume *arguendo* that the district court's *Jewell* instruction correctly stated the law. *Cf. Anwar*, 880 F.3d at 967–68 (upholding a "deliberate ignorance" instruction in an Analogue Act case).

in conducting that review, we "must view the evidence in the light most favorable to the party requesting it," *Yi*, 704 F.3d at 804 (citation omitted). We find no abuse of discretion.

As framed in the jury instructions here, the first element of the *Jewell* standard is that "the defendants . . . were aware of a high probability that the charged controlled substance analogue or analogues were treated as a controlled substance by the Analogue Act." This element is amply supported in the trial record. As we have explained, there was substantial evidence to support a finding that Defendants *actually knew* that XLR-11 was treated as a controlled substance under the Analogue Act. It necessarily follows that the evidence was likewise sufficient to support the conclusion that Defendants knew, at a minimum, that there was a high probability that XLR-11 was a controlled substance analogue.

There was also sufficient evidence to support the second element of the *Jewell* standard—*i.e.*, that Defendants "deliberately avoided learning the truth" about XLR-11. As set forth earlier, Defendants were well aware that their trafficking in XLR-11 had to be concealed, at all stages, from law enforcement in order to avoid seizure of the XLR-11 and their smokable products containing it. Defendants also changed the cannabinoid that they used as earlier ones were listed on the CSA's schedules, which further supports an inference that they deliberately attempted to select close-to-the-edge substances that they could superficially claim were not yet *obviously* illegal but that would undoubtedly produce the high that their

ultimate consumers wanted. On this record, a jury could reasonably conclude that Defendants deliberately avoided learning whether XLR-11 was treated as a controlled substance under the Analogue Act.

We therefore hold that the district court did not abuse its discretion in concluding that its *Jewell* instruction had a sufficient foundation in the evidence.

C

Defendants contend that, as applied in this case, the Analogue Act's requirement that the substance in question have a "chemical structure" that is "substantially similar to the chemical structure of a controlled substance in schedule I or II," *see* 21 U.S.C. § 802(32)(A)(i), is unconstitutionally vague. "As generally stated, the void-for-vagueness doctrine requires that a penal statute define the criminal offense with sufficient definiteness that ordinary people can understand what conduct is prohibited and in a manner that does not encourage arbitrary and discriminatory enforcement." *Kolender v. Lawson*, 461 U.S. 352, 357, 103 S. Ct. 1855, 75 L. Ed. 2d 903 (1983). Defendants argue that the underlying standard for determining chemical structural similarity is impermissibly vague and that "[n]o person of ordinary intelligence would have a reasonable opportunity to 'know' that XLR-11 is 'substantially similar' in chemical structure to JWH-018." We reject Defendants' as-applied vagueness challenge.

Because the phrase "substantially similar" "is not further defined by the statute, we give that phrase its ordinary meaning." *United States v. Kuzma*, 967 F.3d 959, 968 (9th Cir. 2020). In common parlance, "similar" means "having characteristics in common" or "alike in substance or essentials." *Similar*, WEBSTER'S THIRD NEW INTERNATIONAL DICTIONARY 2120 (1981 ed.) ("WEBSTER'S THIRD"). The word "substantial," as relevant here, means that the thing "specified" is present "to a large degree or in the main." *Substantial*, WEBSTER'S THIRD, *supra*, at 2280. Accordingly, the chemical structures of two substances are "substantially similar" if they share common essential characteristics "to a large degree or in the main." Further, the term "structure," as used in the context of a chemical, refers to "the arrangement of particles or parts in a substance," as in "the arrangement and mode of union of the atoms in a molecule." *Structure*, WEBSTER'S THIRD, *supra*, at 2267. The statute thus requires, at a minimum, that the two chemicals share, to a large degree or in the main, common components in terms of the arrangement of atoms and the chemical bonds between those atoms. However, because the statute only requires "substantial" similarity, it clearly contemplates that two substances may contain *some* differences in their chemical structures and yet still be sufficiently "alike" in their "essentials" to remain "substantially similar." Under these standards, Defendants' as-applied vagueness challenge fails.

As an initial matter, the trial evidence in this case provided an ample basis to conclude that XLR-11 satisfies the statutory requirement that, at a minimum, it must share common chemical structural features, in terms of

the arrangement of atoms and chemical bonds, with JWH-018. As set forth earlier, the Government presented expert testimony that XLR-11 and JWH-018 share a common "acylindole core," including the "same atoms" in the "same locations" with the "exact same structure." *See supra* section I(B)(2). Defendants note that, despite this common chemical core, there are also some structural differences between the two substances. Specifically, as we have explained, the Government's chemical expert noted two differences in the respective chemical structures of XLR-11 and JWH-018: (1) in contrast to JWH-018, "a fluorine atom" was substituted in the tail portion of XLR-11's structure; and (2) the "naphthyl group" in JWH-018 was replaced by a "tetramethylcyclopropyl" group in XLR-11. *See supra* section 1(B)(2). Accordingly, the question here is whether the statute provides an adequate basis for assessing whether these particular differences in the two substances' chemical structures are sufficiently significant that, despite their common chemical core, XLR-11 and JWH-018 should *not* be considered "substantially similar" in "chemical structure."

In addressing that question, we agree with the Second Circuit's observation that, in judging similarity of chemical structure, what matters is whether the particular structural differences between two otherwise similar chemicals make a difference "in the substance's *relevant* characteristics." *United States v. Roberts*, 363 F.3d 118, 124 (2d Cir. 2004) (emphasis added). In *Roberts*, the court noted that, apart from "only two atoms," the two substances in question had otherwise identical chemical structures, as reflected in "two-dimensional diagrams

of the molecules." *Id.* The Government argued that this high percentage of overlapping chemical structural similarity should be enough, "standing alone," to "establish substantial similarity in chemical structure." *Id.* (simplified). The court declined to adopt this argument, noting that it would not be the "appropriate rule to apply in every situation" because, "[i]n another case, it might well be that a one-or two-atom difference in a molecule made such a radical difference in the substance's relevant characteristics that any similarity in two-dimensional charts would not be 'substantial' enough to satisfy the definition of 'controlled substance analogue.'" *Id.* This analysis indicates that at least *one* way to establish the required substantial similarity in chemical structure would be to show that (1) the alleged analogue shares a significant core of common chemical structural features with a listed substance, in terms of arrangement of atoms and chemical bonds; and (2) any residual differences in the analogue's chemical structure, as compared to that of a listed substance, do not result in a material "difference in the substance's relevant characteristics." *Id.*[8]

Under that standard, Defendants' as-applied vagueness challenge must be rejected. Here, the trial evidence provides a sufficient basis for concluding that XLR-11 and JWH-018 share a common core of identical

8. There may well be other ways to establish the required substantial similarity in chemical structure, and our decision should not be understood as foreclosing other possible approaches that may be appropriate in other cases with different facts. For purposes of the as-applied challenge presented here, the approach suggested by the Second Circuit's *Roberts* decision is sufficient to resolve this case.

chemical structural features and that the subset of differences between the two chemicals does not make a difference in the substance's "relevant characteristics." Here, the Government's expert on chemical structure testified that the replacement of the "naphthyl group" in JWH-018 with a "tetramethylcyclopropyl" group in XLR-11 was not a "significant enough change," because it would not materially affect the substance's chemical "binding affinity in the cannabinoid receptors." *Cf. Roberts*, 363 F.3d at 125 (considering, in judging chemical similarity, how the body metabolized the analogue). As for the "addition of a fluorine atom" in XLR-11, the Government presented expert testimony at trial that the only relevant resulting difference in chemical interaction and processing inside the body was that the presence of a fluorine atom "help[s] the drug stay in the body and not be metabolized or excreted too quickly."

Moreover, as the Supreme Court noted in *McFadden*, the *other* elements of an offense, such as scienter, can serve to alleviate vagueness concerns by independently narrowing the potential range of conduct covered by the statute. 576 U.S. at 197. As noted earlier, there is ample evidence in the record to permit a jury to conclude that Defendants were aware that XLR-11 was a controlled substance under the Analogue Act, even if they did not know its precise chemical structure. *See supra* section III(A). As a result, Defendants are poorly positioned to contend that they could not be expected to discern, through ordinary intelligence, the line between lawful and unlawful conduct that is reflected in the substantially-similar-chemical-structure element of the statutory

definition of an analogue. *See Grayned v. City of Rockford*, 408 U.S. 104, 108, 92 S. Ct. 2294, 33 L. Ed. 2d 222 (1972). Additionally, Defendants are simply wrong in contending that vagueness doctrine precludes Congress from ever drawing legal lines that take account of the complexities of the underling subject matter being regulated. Those who traffic in substances that they know will be ingested by consumers and will have significant pharmacological effects can hardly be heard to complain that the relevant line-drawing may involve a level of complexity that, as here, may call for expert testimony.

The asserted vagueness of the substantially-similar-chemical-structure element is further significantly mitigated by the additional requirement that there be substantial similarity in the actual or represented pharmacological *effect* of the alleged analogue.[9] Even though the two elements of substantial similarity in chemical structure and substantial similarity in pharmacological effect are separate and distinct, the two elements can operate in tandem to adequately narrow the as-applied scope of the statute in a particular case. For example, in a case—such as this one—in which the jury is instructed to use the *same* listed substance (here, JWH-018) in evaluating both elements of the definition of an "analogue," the requirement that there be a substantial

9. As we have observed, *see supra* at 12–13, the statute actually phrases this additional requirement in the disjunctive, which might suggest that it is an *alternative* element rather than an additional one. However, the Government has repeatedly conceded, in this case and elsewhere, that it is an additional requirement. *See McFadden*, 576 U.S. at 194 n.2.

similarity in pharmacological effect will have the *practical* consequence of placing an outer limit on the range of relevant differences in chemical structure. That is, in such a case, the statute's elements will *not* all be met if the difference in chemical structure in the analogue—even if it seems superficially trivial—substantially alters the analogue's pharmacological effect. This additional element places a significant outer limit on the range of chemical variations that will fall within the statutory definition of the offense *as a whole*, thereby further mitigating any vagueness concerns.

Here, the expert testimony presented by the Government at trial was that the two above-identified differences in chemical structure between XLR-11 and JWH-018 did not impede XLR-11 from having a substantially similar pharmacological effect as JWH-018. Specifically, Dr. Trecki described the concept of an "activity cliff," which refers to a structural change to a chemical that causes it to "lose the pharmacological activity, meaning, in more layman's terms, if you make a certain change, the drug will stop working." Dr. Trecki then explained that the chemical differences between XLR-11 and JWH-018 did *not* result in such an activity cliff:

> So when we look at the differences in the functional groups between . . . JWH-018 and XLR-11, the changes that scientists used to make these new molecules, it retained and actually intensified the pharmacological effect of the substance. The activity cliff phenomena

> or theory did not apply here. The substances all continued to work well or greater than the original JWH substance.

Indeed, neither of Defendants' experts affirmatively opined that the differences in chemical structure on which they focused would lead to XLR-11 having overall materially reduced pharmacological effects than JWH-018.

Taking all of the foregoing points together, we reject Defendants' as-applied vagueness challenge to the statutory definition of a "controlled substance analogue."

D

Defendants argue that their due process rights were violated by the district court's failure to compel the Government to grant use immunity to two potential defense witnesses who would have testified as to Defendants' scienter concerning whether XLR-11 was covered by the Analogue Act. Specifically, Defendants sought to call Timothy Dandar, a lawyer who would have testified that he advised Defendants that XLR-11 was "not an illegal product under the Controlled Substance Analogue Act," and Adam Libby, a chemist who would have testified that he advised Defendants that XLR-11 was not substantially similar in chemical structure to JWH-018. The parties agreed below that, if called as witnesses, Dandar and Libby would assert their Fifth Amendment rights. The Government declined to grant Dandar and Libby use immunity and the trial court denied a motion by

the defense to compel the Government to do so. Reviewing de novo, *see United States v. Straub*, 538 F.3d 1147, 1156 (9th Cir. 2008), we conclude the trial court did not err.

"[F]or a defendant to compel use immunity[,] the defendant must show that: (1) the defense witness's testimony was relevant; and (2) either (a) the prosecution intentionally caused the defense witness to invoke the Fifth Amendment right against self-incrimination with the purpose of distorting the fact-finding process; or (b) the prosecution granted immunity to a government witness in order to obtain that witness's testimony, but denied immunity to a defense witness whose testimony would have directly contradicted that of the government witness, with the effect of so distorting the fact-finding process that the defendant was denied his due process right to a fundamentally fair trial." *Id.* at 1162. There is no dispute that Dandar's and Libby's testimony would have been "relevant" at step one of the *Straub* test. *Id.* The only question is whether the district court correctly concluded that the Defendants failed to establish either of the two *Straub* alternatives at step two. It did.

Defendants rely on the second *Straub* alternative, which focuses on the *effect* of the Government's actions in denying immunity to defense witnesses while granting it to prosecution witnesses. Although Defendants do not point to any witnesses who were formally granted immunity in this case, the Government concedes in its answering brief that we have held "that government witnesses who are granted favorable plea deals in return for their testimony are encompassed by *Straub*['s] use

of the term 'immunized.'" *United States v. Wilkes*, 744 F.3d 1101, 1105 n.1 (9th Cir. 2014). Defendants, however, failed to show, as *Straub* requires, that Libby and Dandar would have given testimony that "directly contradicted" the testimony of one of the Government cooperating witnesses in a way that impermissibly distorted the fact-finding process.

This case bears no resemblance to *Straub*, in which we found the requisite direct contradiction when the defense witness sought to be immunized would have given directly contradictory testimony concerning the critical content of a specific conversation that occurred at a particular place and during a particular timeframe. 538 F.3d at 1162–63. No Government witness here testified to the contents of any communications between Defendants and Dandar or Libby, much less that the contents of those communications were the opposite of what Defendants claimed. Moreover, although (as we have explained) the testimony of the Government's witnesses supplied evidence from which a rational jury could circumstantially conclude that Galecki and Ritchie knew that XLR-11 was treated as a controlled substance by virtue of the Analogue Act, those witnesses' testimony also included other elements that refute any suggestion that the refusal to immunize Dandar and Libby resulted in such a distortion of the fact-finding process that the trial was rendered fundamentally unfair. For example, Templeman also testified that she was specifically told by Ritchie and Galecki that the products they were selling were legal. Indeed, after testifying that Ritchie had explained the concept of an analogue to her, Templeman added that she was not worried that they

might actually be selling analogues because *she* "believed the product was legal" based on her conversations with Defendants.

Defendants are not entitled to insist on immunity for any witness that might provide additional testimony that, from Defendants' point of view, might helpfully contribute to the overall assessment of the circumstantial evidence. They were required, under *Straub*, to show a direct contradiction in testimony that resulted in a fundamentally unfair distortion of the fact-finding process. The district court correctly held that they failed to make that showing.

IV

Defendants contend that the evidence was insufficient to support their convictions for operating a continuing criminal enterprise ("CCE") in violation of the CSA. *See* 21 U.S.C. § 848. "In order to prove that a defendant is guilty of engaging in a continuing criminal enterprise in violation of 21 U.S.C. § 848, the government must establish (1) that the defendant's conduct constituted a felony violation of federal narcotics law; (2) that the described conduct occurred as part of a continuing series of violations of federal narcotics law; (3) that the defendant undertook the activity in concert with five or more persons; (4) that the defendant acted as the organizer, supervisor, or manager of the criminal enterprise; and (5) that the defendant obtained substantial income or resources from the purported enterprise." *United States v. Hernandez-Escarsega*, 886 F.2d 1560, 1570 (9th Cir. 1989). A "continuing series" for purposes of the second element means "three or more

federal narcotics violations." *Id.* "It is not necessary," for purposes of the third "in concert with" element, that the defendant "act in concert with five or more persons at the same time, or that five or more persons be engaged in any single criminal transaction." *United States v. Burt*, 765 F.2d 1364, 1366 (9th Cir. 1985). However, the "in concert with" element does "require[] proof of a conspiracy" sufficient to violate 21 U.S.C. § 846. *Rutledge v. United States*, 517 U.S. 292, 300, 116 S. Ct. 1241, 134 L. Ed. 2d 419 (1996). We conclude that the evidence was sufficient under these standards.

Defendants contend that there was insufficient evidence to support the jury's conclusion that they acted "in concert" (*i.e.*, criminally conspired) with five or more persons. We disagree. The evidence was sufficient to permit a rational jury to conclude that Defendants acted in concert with the following five Zencense employees: Ryan Eaton, Rachel Templeman, Robert Biggerstaff, Corey Finch, and Diana Duty.

Defendants assert that Eaton cannot be counted as one of the five requisite conspirators given that the jury acquitted him on all charges. That is wrong. "It is well established that a person may be convicted of conspiring with a co-defendant even when the jury acquits that co-defendant of conspiracy." *United States v. Ching Tang Lo*, 447 F.3d 1212, 1226 & n.8 (9th Cir. 2006) (citing *United States v. Powell*, 469 U.S. 57, 65–66, 105 S. Ct. 471, 83 L. Ed. 2d 461 (1984), and *United States v. Valles-Valencia*, 823 F.2d 381, 381–82 (9th Cir. 1987)). As we explained, "inconsistent verdicts do not necessarily lead

to the conclusion that the guilty verdict was the incorrect verdict," because "inconsistent verdicts can just as easily be the result of jury lenity as a determination of the facts." *Id.* at 1226 n.8 (citation and internal quotation marks omitted). Consequently, "the acquittal of all conspirators but one does not necessarily indicate that the jury found no agreement to act." *Id.* (citation omitted).

Although the jury's acquittal of Eaton is thus not dispositive, we must still undertake an "independent review of the sufficiency of the evidence" as to whether Galecki and Ritchie conspired with Eaton. *Powell*, 469 U.S. at 67. We conclude that the evidence on that point was indeed sufficient. Finch testified that he trained Eaton how to make spice, including teaching him the same "knowledge of the process and the additives and things like that" that had originally been conveyed to Finch by Galecki. Finch testified that Eaton, after some time working with Zencense in Florida, left for Las Vegas. Shipping records showed that Ritchie then shipped packages to and from Eaton in Las Vegas, with shipping costs to "send[] packages between Burton Ritchie and Ryan Eaton at the warehouse" alone totaling just over $14,000. When agents raided the Nevada warehouse where Eaton worked, they found industrial cement mixers, drying tables, jugs of flavoring, a large safe, mylar bags, documentation from Zencense's Chinese exporters, and large drums of acetone for processing spice. The Government also presented evidence that Eaton texted an acquaintance that "I do nothing but make itchy spice in a hot warehouse and float in my pool." A special agent testified that Eaton said that he received instructions

that "the word 'flavoring' should never be used," that "it should always be referred to as a fragrance rather than a flavor," and that if anyone joked about the phrase "[n]ot for human consumption," that employee could "potentially be fired on the spot." Based on this evidence, a rational jury could find, beyond a reasonable doubt, that Galecki and Ritchie acted in concert with Eaton in undertaking the underlying drug-trafficking activity.[10]

The same is true of Templeman, Biggerstaff, and Finch, all of whom testified at trial. Templeman's testimony provided substantial evidence from which a rational jury could conclude that she and Defendants acted in concert. Templeman testified that she was aware of instructions to use euphemistic language when describing the flavors of Zencense products; that she was aware Zencense shipments had been raided by law enforcement and that she had conveyed that information to Ritchie; that Ritchie told her what an analogue was; and that she, a single Zencense "potpourri" salesperson, made a 5 percent commission on sales, with her commission amounting to between $100,000 and $125,000, in the months of May to August 2012 *alone*. Biggerstaff's testimony likewise established that he was aware of the company's requirement to use euphemistic language to describe its products' flavors; was aware Zencense products had been

10. For the same reason, we reject Defendants' contention that, because he was acquitted, Eaton cannot serve as a supervisee for purposes of establishing that Defendants acted in concert with at least one or more of the five supervisees in undertaking "three or more federal narcotics violations." *Hernandez-Escarsega*, 886 F.2d at 1570.

raided by law enforcement; was aware that Defendants controlled what Biggerstaff called "secret" storage units to replace "confiscated" product; had been taught by Galecki to manufacture spice, which Biggerstaff knew contained XLR-11; and that Galecki told him XLR-11 was just "one molecule off" from another synthetic drug. And Finch testified that although he initially thought he was making incense, he later learned he was in fact producing spice; that he had originally been trained to produce spice by Galecki; that he placed "not for human consumption" stickers on Zencense products; and that he was aware of "the flavor versus fragrance rule" in talking about Zencense products. While Finch testified that he began to believe the product was questionable when interviewed by law enforcement, implying that he had *not* believed the product was illegal prior to that point in time, the jury was not required to credit Finch's self-serving statements about his own state of mind.

The record evidence is less robust as to Diana Duty, who did not testify at trial. But we must affirm Defendants' CCE conviction so long as, "viewing the evidence in the light most favorable to the prosecution, *any* rational trier of fact could have found the essential elements of the crime beyond a reasonable doubt." *Jackson*, 443 U.S. at 319. According to Finch, Duty conducted Finch's job interview, and she chose to conduct it, not at Zencense's offices, but at a nearby McDonald's. After he "passed the interview," Finch was then "taken back to a unit where I was given the job." Finch also stated that, after he was hired, it was Duty who instructed him as to "exactly" what "was the terminology we should use." She stated that

"[a]ll plant material" was to be called "product" and that "[t]here's no flavor; there's fragrance." Finch did not think that it was unusual to call plant material "product," but he thought it seemed "a little odd" that "it was pretty harsh on the flavor versus fragrance rule," but since "it was a new job," he "did what [he] was told." Duty thus had the role of interviewing and clearing a prospective employee off-campus before bringing him back to Zencense's facility, and she was the one who then instructed that employee in the crucial euphemistic language that was employed by Defendants to describe their products. The nature of Duty's knowledge and role in the company provides a sufficient circumstantial basis to permit a rational jury to conclude, beyond a reasonable doubt, that Defendants acted in concert with Duty.

V

Defendants also challenge their convictions for mail fraud, wire fraud, and money laundering (Counts 2–19). We reverse Defendants' convictions for mail fraud and wire fraud, but we affirm their convictions for money laundering.

A

Defendants argue that the evidence was insufficient to prove all of the elements necessary to sustain their convictions for mail and wire fraud (Counts 9–19).[11]

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11. Specifically, these charges included conspiracy to commit mail fraud in violation of 18 U.S.C. § 1349 (Count 9); conspiracy to

"The elements of mail and wire fraud are: (1) proof of a scheme to defraud; (2) using the mails or wires to further the fraudulent scheme; and (3) specific intent to defraud." *United States v. Sullivan*, 522 F.3d 967, 974 (9th Cir. 2008) (citing 18 U.S.C. §§ 1341, 1343). "In order to prove a 'scheme to defraud,' the jury must find that the defendant employed '*material* falsehoods.'" *United States v. Lindsey*, 850 F.3d 1009, 1013 (9th Cir. 2017) (quoting *Neder v. United States*, 527 U.S. 1, 20, 119 S. Ct. 1827, 144 L. Ed. 2d 35 (1999)). However, "'the government does not have to prove actual reliance upon the defendant's misrepresentations' to satisfy materiality." *Id.* at 1014 (quoting *Neder*, 527 U.S. at 25). Rather, "a false statement is material if it has 'a natural tendency to influence, or [is] capable of influencing,'" the decisionmaker to whom the statement "was addressed." *Id.* at 1013 (quoting *Neder*, 527 U.S. at 16). We agree that, under these standards, the Government's evidence at trial was insufficient to prove the mail fraud and wire fraud offenses charged in the indictment.

The scheme to defraud that was charged in the indictment and that was the basis for all of the mail fraud and wire fraud counts was that, "for the purposes of obtaining money from others," Defendants "made materially false and fraudulent pretenses, representations, and promises that Zencense manufactured and distributed 'herbal incense,' 'potpourri,' and 'aromatherapy' not for

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commit wire fraud in violation of 18 U.S.C. § 1349 (Count 14); four substantive counts of mail fraud in violation of 18 U.S.C. § 1341 (Counts 10–13); and five substantive counts of wire fraud in violation of 18 U.S.C. § 1343 (Counts 15–19).

human consumption to conceal that they then and there well knew that the 'herbal incense,' 'potpourri,' and 'aromatherapy' was synthetic cannabinoid products for human consumption." The jury was likewise expressly instructed, nearly verbatim, that all of the fraud charges rested on these alleged false material representations.

The problem with the Government's theory is that, in assessing whether Defendants made a "material falsehood" for the purpose of obtaining money or property, materiality is judged in relation to the persons *to whom the statement is addressed. Lindsey*, 850 F.3d at 1013; *see also Universal Health Servs., Inc. v. United States ex rel. Escobar*, 579 U.S. 176, 193, 136 S. Ct. 1989, 195 L. Ed. 2d 348 (2016) ("Under any understanding of the concept, materiality looks to the effect on the likely or actual behavior of the recipient of the alleged misrepresentation." (simplified)); *Neder*, 527 U.S. at 16 (holding that, in cases charging materially false statements to a government agency or officer, "a false statement is material if it has a natural tendency to influence, or is capable of influencing, the decision of the decisionmaking body t*o which it was addressed*." (emphasis added) (simplified)). Here, the persons to whom the charged statements were made for the purpose of obtaining money or property were the retailers and end consumers of Zencense's products. But the Government presented no evidence at trial that the specific alleged misrepresentations were materially false to anyone who bought Zencense's products.

The Government presented no evidence whatsoever that the labeling of Zencense's products as "potpourri" and

"not for human consumption" had *any* natural tendency to influence retailers or consumers into thinking that they were purchasing extraordinarily expensive high-end home aromatics. All of the Government's evidence, in fact, pointed in precisely the opposite direction—*i.e.*, that the purchasers all understood, and were in on, the charade. For example, the Government introduced testimony from Ryan Yarbro, an employee of a company with a chain of smoke shops that sold Zencense products, and he stated that "everyone, at least in the company I worked for, knew that people would be smoking it." Victor Nottoli, who owned another chain of smoke shops that sold Zencense products, testified that his understanding of Zencense products' use by consumers was that "[t]hey were smoking it." Templeman, a Zencense sales employee, testified that when she used the words "spice or incense or potpourri" to refer to Zencense's products on sales calls to retailers, they "knew what you were talking about."

Moreover, the Government introduced testimony showing that Defendants deliberately *avoided* marketing their products to retailers who were interested in purchasing true potpourri or incense. Asked why the company did not market Zencense potpourri to stores like Target or Walmart, Biggerstaff explained that "[w]e didn't believe they would be a good customer for our product" because they would be expecting "an air freshener," and "that's not the product that we were selling." Templeman testified that most of Zencense's customers "were either smoke shops or alternative adult emporiums, just not your run of the mill products," and that sales staff did *not* try to market to "Walmart or Bed Bath & Beyond."

The Government also introduced Zencense's sales script into evidence, and that document instructed salespersons making calls that, if a potential client was unfamiliar with spice, they were to ask if the store sold pipes. If the answer was no, the script explained, "[m]ost likely this will not be a potential customer" because "they are not the kind of store we want to sell to." In such cases, the script instructed, the salesperson should "[e]nd call, mark 'Not Interested,' . . . and mark for deletion."

At no point did the Government introduce evidence that Defendants intentionally marketed or sold their products as real "spice" to cooking shops, as "incense" to yoga studios, or as "potpourri" to home improvement stores—in other words, directed their products, in any way, toward any retailers or consumers as to whom the "potpourri" label might have had "a natural tendency" to influence them to believe they were purchasing something other than drugs. *Lindsey*, 850 F.3d at 1013. Indeed, the Government underscored the point by bringing the CEO of an actual potpourri company to trial, who testified that he sold his potpourri for 1/90th the price of Zencense's product, used fundamentally different ingredients in crafting his potpourri, sold his products to an entirely different set of retailers, and did not use secret code words to describe his potpourri products.

On this record, the Government simply failed to prove that Defendants made any materially false statement to purchasers for the purpose of obtaining money or property. The Government's evidence confirmed that *both* Defendants *and* the purchasers whose money Defendants

were trying to obtain understood the labels "potpourri" and "not for human consumption" as a code for "smokable synthetic cannabinoids." While "[a] misrepresentation may be material without inducing any actual reliance," *United States v. Blixt*, 548 F.3d 882, 889 (9th Cir. 2008) (citation omitted)—as in the case of a false statement to an undercover law enforcement officer who is *secretly* aware of the defendant's fraudulent scheme—there can be no materially false statement when *both* the listener and the hearer *know and intend* that the words being used have the same distinctive meaning.

While Defendants were properly convicted under the CSA, the Government's effort to shoehorn this case into the mail fraud and wire fraud statutes failed as a matter of law. Defendants were entitled to a judgment of acquittal on these counts.[12]

12. At oral argument, the Government suggested that the fraud convictions could be sustained on the alternative theory that Defendants falsely stated or implied to retailers that Zencense's products were *legal*, thereby inducing retailers to purchase products they would otherwise have refrained from purchasing. This contention fails because, as the district court correctly recognized, the jury cannot properly convict a defendant of mail fraud based on different misrepresentations from those that were charged in the indictment. *See United States v. Adamson*, 291 F.3d 606, 614–16 (9th Cir. 2002).

B

We next address Defendants' convictions for money laundering offenses (Counts 2–8).[13] Each of these charges required the Government to prove either that Defendants carried out (Counts 4–7) or conspired to carry out (Counts 2–3, and 8) financial activity involving "specified unlawful activity." *See* 18 U.S.C. § 1956(a)(1), (a)(2)(A), (h). The indictment listed, as the predicate "unlawful activity" for these charges, all of the *other* charged offenses, including both the CSA offenses and the fraud offenses. The jury instructions likewise permitted the jury to rely on the conduct underlying any of the charged violations of the CSA or the fraud offenses. The jury returned general verdicts of guilt on the money laundering charges, without specifying which predicate the jury had relied on in convicting.

Given that we have affirmed Defendants' convictions as to the CSA offenses but reversed their convictions mail fraud and wire fraud offenses, the question arises whether the jury's general verdict on the money laundering offenses—which could have rested on any of these predicate offenses—may stand. The Supreme Court has

13. Specifically, the indictment charged one count of conspiracy to engage in financial transactions to promote unlawful activity, in violation of 18 U.S.C. § 1956(h) (Count 2); one count of conspiracy to transport funds to promote unlawful activity, in violation of 18 U.S.C. § 1956(h) (Count 3); four substantive counts of transporting funds to promote unlawful activity, in violation of 18 U.S.C. § 1956(a)(2)(A) (Counts 4–7); and one count of conspiracy to launder monetary instruments in violation of 18 U.S.C. § 1956(h) (Count 8).

held that, in certain circumstances, a general verdict of guilt must be set aside "where the verdict is supportable on one ground, but not on another, and it is impossible to tell which ground the jury selected." *Yates v. United States*, 354 U.S. 298, 312, 77 S. Ct. 1064, 1 L. Ed. 2d 1356 (1957). This rule applies, for example, where the unsupportable ground for the verdict was time-barred by a statute of limitations, *see Yates*, 354 U.S. at 304–11, or was tainted by constitutional error, *see Stromberg v. California*, 283 U.S. 359, 367–68, 51 S. Ct. 532, 75 L. Ed. 1117 (1931). However, in *Griffin v. United States*, 502 U.S. 46, 112 S. Ct. 466, 116 L. Ed. 2d 371 (1991), the Supreme Court distinguished *Yates* and *Stromberg* and upheld a general verdict of conviction for conspiracy, even though the verdict could have rested on "either one of the two objects of the conspiracy" and one of those objects was supported by insufficient evidence. *Id.* at 48, 60 (emphasis omitted). Indeed, the Court described any such proposed extension of *Yates* to the insufficiency context as "unprecedented and extreme." *Id.* at 56. Moreover, the Court noted that it had previously squarely held that "when a jury returns a guilty verdict on an indictment charging several acts in the conjunctive, . . . the verdict stands if the evidence is sufficient with respect to any one of the acts charged." *Turner v. United States*, 396 U.S. 398, 420, 90 S. Ct. 642, 24 L. Ed. 2d 610 (1970) (quoted in *Griffin*, 502 U.S. at 56–57). The Court held that the resulting "distinction between legal error (*Yates*) and insufficiency of proof (*Turner*)" is one that "makes good sense":

> Jurors are not generally equipped to determine whether a particular theory of conviction

> submitted to them is contrary to law—whether, for example, the action in question is protected by the Constitution, is time barred, or fails to come within the statutory definition of the crime. When, therefore, jurors have been left the option of relying upon a legally inadequate theory, there is no reason to think that their own intelligence and expertise will save them from that error. Quite the opposite is true, however, when they have been left the option of relying upon a factually inadequate theory, since jurors are well equipped to analyze the evidence.

Griffin, 502 U.S. at 58–59.

Because we have reversed the mail fraud and wire fraud convictions for insufficiency of the evidence, this case would appear to be governed by the *Griffin/Turner* insufficiency rule rather that the *Yates* legal-error rule. On the other hand, the jury here arguably was not "well equipped" to detect the insufficiency of the evidence as to the mail fraud and wire fraud predicates, *see Griffin*, 502 U.S. at 59, because the jury *did* convict Defendants of those offenses despite the evidentiary insufficiency that we have identified. Moreover, we have previously recognized that, in some cases, a conclusion that the evidence was insufficient may actually rest more on a legal determination than a factual one—*i.e.*, it may rest on the conclusion that the *amply proved conduct* simply "fails to come within the statutory definition of the crime" as

charged in the indictment. *Griffin*, 502 U.S. at 59 (stating that such a legal determination is subject to the *Yates* rule); *see United States v. Gonzalez*, 906 F.3d 784, 791 (9th Cir. 2018) (characterizing our prior decision in *United States v. Manarite*, 44 F.3d 1407, 1413 (9th Cir. 1995), as an example of an insufficiency determination that actually rests on a "legal deficiency" that, under *Griffin*, would be subject to the *Yates* rule). We conclude that we need not decide whether this case is governed by the *Griffin/Turner* rule or the *Yates* rule. Even assuming that *Yates* applies, the Supreme Court has squarely held that "errors of the *Yates* variety are subject to harmless-error analysis." *Skilling v. United States*, 561 U.S. 358, 414, 130 S. Ct. 2896, 177 L. Ed. 2d 619 (2010). We conclude that any *Yates* error here was harmless.

Skilling held that "[h]armless error analysis," which was described in the context of "collateral review" in *Hedgpeth v. Pulido*, 555 U.S. 57, 129 S. Ct. 530, 172 L. Ed. 2d 388 (2008), "applies equally to cases on direct review." 561 U.S. at 414 n.46. *Hedgpeth* held that *Yates* errors are governed by the same harmless-errors standards that otherwise govern instructional errors, including the omission of an element, *see Hedgpeth*, 555 U.S. at 60–62, and in the context of direct review, those standards were set forth in *Neder*, 527 U.S. at 18–19. Under *Neder*'s standards, a *Yates* error is harmless if, after a "thorough examination of the record," we are able to "conclude beyond a reasonable doubt that the jury verdict would have been the same absent the error." *Id.* at 19. As we shall explain, that standard is met here.

As noted earlier, the money laundering counts on which Defendants were convicted consisted of four substantive counts of transporting funds to promote unlawful activity, in violation of 18 U.S.C. § 1956(a)(2)(A) (Counts 4–7), and three different conspiracy counts charged under 18 U.S.C. § 1956(h). Each of the four substantive counts rested on a specific monetary transfer from a Zencense account to a bank account in Jiaojiang, China. Given that these large payments to a Chinese account were clearly in payment for the XLR-11 that was being purchased by Zencense from China, these four particular monetary transactions were *directly* tied to the drug-trafficking activity underlying the CSA charges and only derivatively and indirectly tied to the domestic sales activities that underlay the mail fraud and wire fraud charges. Given that fact, we have little difficulty concluding, beyond a reasonable doubt, that the jury's conviction on these four substantive accounts "would have been the same absent" the asserted *Yates* error in giving the jury the alternative option of relying on the fraud charges. *Neder*, 527 U.S. at 19. And because Count 3 explicitly charged a conspiracy to transfer money "from a place in the United States to and through a place outside of the United States, namely, China," the same reasoning readily leads us to conclude that any *Yates* error with respect to that conspiracy count was likewise harmless.

That leaves only the conspiracy charges in Count 2, which alleged a conspiracy to "conduct financial transactions . . . which involved the *proceeds* of [the] specified unlawful activity," and Count 8, which alleged a conspiracy to "engage in a monetary transaction . . .

in criminally derived property," namely, the "deposit, withdrawal, transfer, and exchange of funds and monetary instruments, such property having been *derived from* [the] specified unlawful activity" (emphasis added). As charged, these two conspiracies focused on the funds obtained from Zencense's *overall* operations, and so, unlike the other five charges, they are not similarly focused directly on the purchase of XLR-11. In support of these charges, the Government introduced evidence of domestic transactions involving Zencense's revenues, and the Government expressly relied on both the drug trafficking and fraud predicates in urging the jury to convict on these counts. Despite that difference, we nonetheless conclude beyond a reasonable doubt that the "jury verdict" on these two counts "would have been the same absent" any *Yates* error. *Neder*, 527 U.S. at 19.

As noted earlier, the theory of mail fraud and wire fraud charged in the indictment was that Defendants made materially false representations about their products "to conceal that they then and there well knew that the 'herbal incense,' 'potpourri,' and 'aromatherapy' *was synthetic cannabinoid products for human consumption*" (emphasis added). The Government's fraud-based theory was thus explicitly intertwined with the drug-trafficking activity. Moreover, the jury here *did* properly convict Defendants on all of the drug-trafficking charges asserted under the CSA. Given these two key facts, we have no reasonable doubt that the jury's verdict would have been the same had the jury understood that a conviction on Counts 2 and 8 could only be based on the charged

drug-trafficking activity. Indeed, on this record, there is no reasonable possibility that the jury here rested its convictions on Counts 2 and 8 on a determination that Zencense's ultimate revenues were derived *only* from mail fraud and wire fraud and *not* also from drug-trafficking. *See United States v. Jefferson*, 674 F.3d 332, 361 (4th Cir. 2012) ("[I]f the evidence that the jury 'necessarily credited in order to convict the defendant under the instructions given . . . is such that the jury must have convicted the defendant on the legally adequate ground in addition to or instead of the legally inadequate ground, the conviction may be affirmed.'" (citation omitted)); *see also United States v. Reed*, 48 F.4th 1082, 1090 (9th Cir. 2022) (holding, in the context of a collateral challenge, that an instructional error in allowing a jury to base a conviction on alternative conspiracy predicates, one of which is legally invalid, is nonetheless harmless when the resulting alternative "conspiracies" are "inextricably intertwined" such that "no rational juror could have" convicted based on "one predicate but not the other" (citations omitted)).

Because any *Yates* error in allowing the money laundering convictions to be based on the mail fraud and wire fraud conduct was harmless beyond a reasonable doubt, we affirm Defendants' money laundering convictions.

VI

Defendants' convictions on Counts 1–8 and 22–26 are affirmed. Defendants' convictions on counts 9–19 are reversed, and the district court is instructed to enter a judgment of acquittal on those counts. We remand to the

district court for further proceedings consistent with this opinion.

AFFIRMED IN PART, REVERSED IN PART, AND REMANDED.

APPENDIX B — REPORT OF PROFESSOR GREGORY DUDLEY, WEST VIRGINIA UNIVERSITY, DOC. 776, *USA V. THE GAS PIPE*, CASE NO. 14-CR-00298 (N.D. TX.)

EXHIBIT 21

Delivered for the use of attorney Jim Felman

1,3-DISUBSTITUTED INDOLES IN MEDICINAL CHEMISTRY

Overview

ODE focuses on the 1,3-disubstituted indole core as the defining structural feature that links the controlled substance JWH-018 to other substances being considered for potential treatment as controlled substance analogues (e.g., JWH-250).

From Office of Diversion Control, Drug & Chemical Evaluation Section (ODE):

> "*The chemical structures of JWH-250 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 bicyclic ring system.*"

ODE 'core':
1,3-disubstituted indole

Appendix B

The 1,3-disubstituted indole core is not an especially distinguishing or defining structural feature in medicinal chemistry. Experts in medicinal chemistry recognize that the '1,3-disubstituted indole core' can be identified in a vast array of chemical structures of interest for diverse pharmacological properties. Indoles are common building blocks in medicinal chemistry, and the 1- and 3-positions are the easiest to modify and diversify. I and other experts have addressed this previously, as outlined below.

Previous Dudley written opinion

One of my very first reports in this area, prepared in connection to the Fedida case in Florida, contained the excerpt reproduced below. The report supports my opinion that identification of a common structural core is not sufficient to establish that substances are "substantially similar" in chemical structure, especially as applied to indole-based structures. The excerpt begins with discussion of a series of 3-substituted indoles—starting with the essential dietary amino acid, tryptophan—in which specific changes at specific locations result in significant differences in properties. The excerpt then focuses on a subset of 1,3-disubstituted indoles published and/or patented prior to 2013 in which (a) the substituent at the 1-position was specifically an "alkyl" group (as opposed to acyl, aryl, heteroatom-based, etc); (b) the substituent at the 3-position was specifically an "acyl" group (as opposed to alkyl, aryl, heteroatom-based, etc); and (c) the indole is not further substituted at any other positions.

Note that for this previous report I defined the core of interest more narrowly than ODE is doing here; my

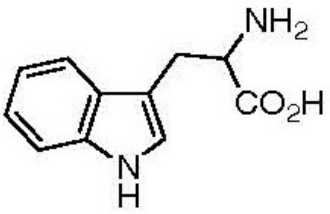
research and comparisons therefore identified a smaller collection of substances than would be captured under ODE's broader '1,3-disubstituted indole' classification.

Excerpt from 2013-01-09DudleyCSAreport:

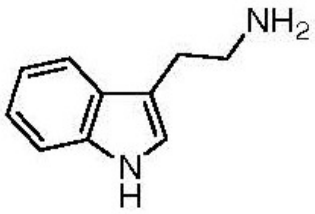
Part 3: Common, biologically relevant indoles

In Part 3 of my analysis, I focus on indole rings, which are found in both JWH-018 and UR-144/XLR-11. In fact, indoles are extremely common in chemical and pharmaceutical research, and indoles with a wide range of biological activities are known. Although all indole derivatives by definition share a common substructure, *it is not feasible to correlate the indole system with any particular pharmacological activity.* For example, consider the following series of common and structurally related indoles depicted in the graphic below.

Examples of common indoles:

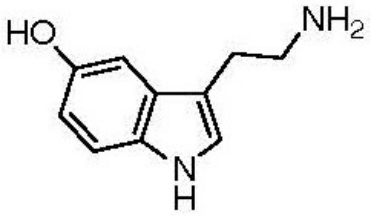


tryptophan
essential amino acid
(found in turkey)

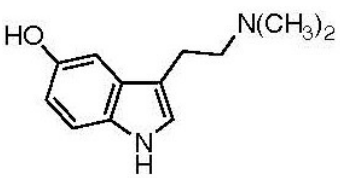


tryptamine
metabolic derivative
of tryptophan

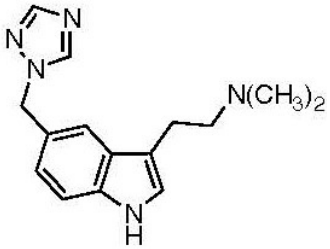
Appendix B



serotonin
neurotransmitter, regulates
sleep, mood, and appetite



bufotenin
frog toxin with
psychedelic properties



Maxalt
(rizatriptan)
migraine drug

Taken in series, each indole differs from the previous one by relatively small compositional changes, but these subtle differences alter the pharmacological effects dramatically. Tryptophan (top left) is one of the 20 essential amino acids used to make proteins in biochemistry. Our bodies metabolize some of the available tryptophan into tryptamine by "decarboxylation" (replacement of the carboxylic acid functional group with hydrogen), and then oxidize it to serotonin. Serotonin is an important neurotransmitter that plays a regulatory role in

sleep, mood, and appetite. (The depression drug duloxetine is thought to influence serotonin levels, for example.) Replacing the primary amine ($-NH_2$) hydrogens of serotonin with methyl groups gives bufotenin, a frog toxin with psychedelic properties, but further substitution leads to rizatriptan, a migraine drug. These indoles are structurally similar but functionally distinct, because the small changes in structure are highly significant.

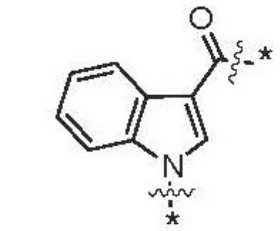
Concluding remarks: The similarities and differences between the chemical structures of JWH-018 and UR-144/XLR-11 have been presented and analyzed. In my opinion, it is not appropriate to designate these compounds as structural analogs.

Supplement to
COMPARATIVE STRUCTURAL ANALYSIS OF JWH-018, UR-144, AND XLR-11

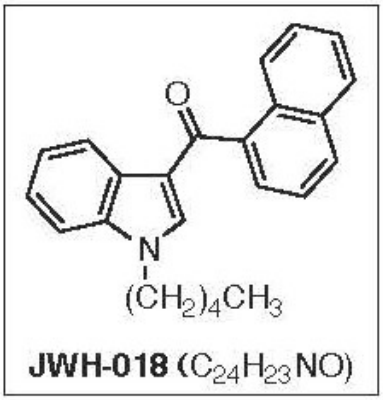
CHEMISTRY RESEARCH INVOLVING *N*-ALKYL-3-ACYL-INDOLES

JWH-018 and UR-144/XLR-11 can be broadly categorized as *N*-alkyl-3-acyl-indoles. Based on my research, it is not possible to generalize the pharmacological data associated with *N*-alkyl-3-acyl-indoles, because their pharmacological properties are too diverse. The Reaxys database of chemistry research compounds provides information and references to 2399 *N*-alkyl-3-acyl-indoles, including JWH-018 and UR-144/XLR-11. Of these 2399 compounds, 610 were associated with some

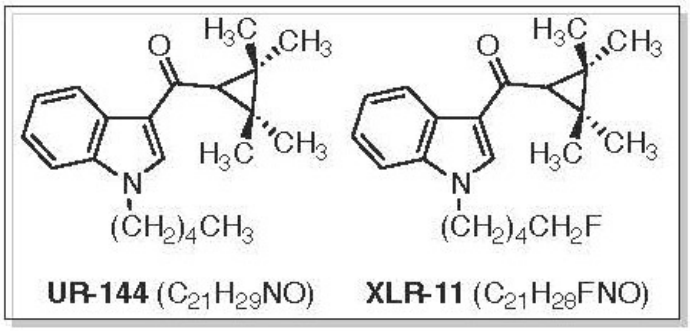
pharmacological data, as reported in patents, peer-reviewed publications, and/or other scientific outlets. Selected examples of important research compounds from this search are illustrated below, along with recent references to the primary literature; the full 1047-page report on the 610 compounds from this search is available upon request.



2399 *N*-alkyl-3-acyl-indoles found in Reaxys database; 610 with known pharmacological data

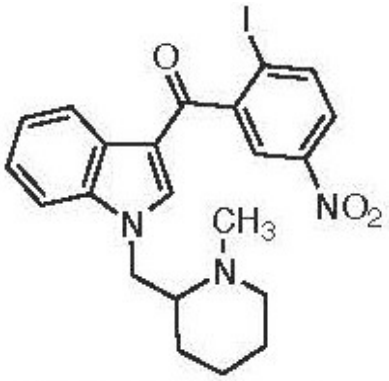


JWH-018 ($C_{24}H_{23}NO$)

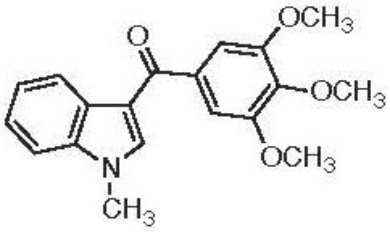


UR-144 ($C_{21}H_{29}NO$) **XLR-11** ($C_{21}H_{28}FNO$)

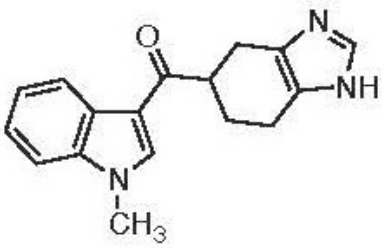
Appendix B



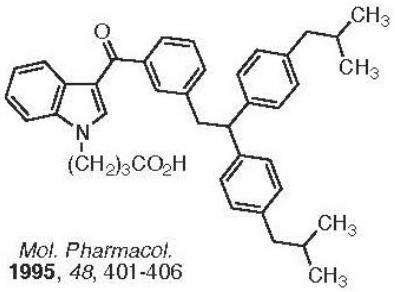
British J. Pharmacol.
2010, *160*, 561-573



J. Org. Chem.
2011, *76*, 4753-4758
Bioorg. Med. Chem.
2006, *14*, 4410-4426



Eur. J. Pharmacol.
2008, *587*, 281-284



Mol. Pharmacol.
1995, *48*, 401-406

These and other *N*-alkyl-3-acyl-indoles are important chemical research tools with diverse biological activities. The first compound on the left reportedly binds the cannabinoid CB_2 receptor and has been investigated as a potential treatment for pain, cancer, amyotrophic lateral sclerosis, and other indications. The second compound inhibits tubulin polymerization, which is a property of interest for cancer research. The third compound shows potential in mouse models as a treatment for diarrhea and other intestinal problems. The fourth compound has been studied for breast and bladder cancers.

Considering the wide range of pharmacological effects known for various *N*-alkyl-3-acyl-indoles, it is not appropriate to make generalizations or assumptions about their properties without careful consideration of the entire structure. In my opinion, the structures of JWH-018 and UR-144/XLR-11 bear very little structural resemblance to each other, beyond the fact that they all fall within the broad category of *N*-alkyl-3-acyl-indoles.

Discussion

N-Alkyl-3-acyl-indoles without further substitution can be objectively identified and researched, but this structure class is too broad to be associated with any particular pharmacological property. If *N*-alkyl-3-acyl-indoles is too broad of a structural category to be useful for Analogue determinations (at least not without further refinement and narrowing of the scope), then the even broader classification of 1,3-substituted indoles is

more emphatically too broad to be useful for Analogue determinations. Other experts have expressed similar opinions, as follows.

Mark Erickson—In a thorough and detailed report, Prof Erickson outlines the difference between objective and subjective determinations and dissects the fundamental problems with a "substantially similar" standard that is not objectively defined. He identifies particular methods that have been employed for structure comparisons—including Tanimoto scores, structure class designations, shared core and/or fragments—but also notes that there is no legal or scientific guidance as to which method to apply:

> "*the term "substantially similar" when used to modify the term "structure" has no accepted measurand (parameter to measure) nor threshold (boundary conditions) to identify where simple similarity ends and substantial similarity begins.*"

He contrasts the Analogue regulatory framework (which lacks methodology and standards) with the traffic safety regulatory framework. Automotive speed is identified as a measurand; speed limits provide clear boundary conditions between what are considered safe and unsafe speeds; and speedometers, radar, and other techniques objectively determine (within error) whether or not a violation has occurred. No such clarity is available for making Analogue determinations, as outlined in Figure 3 of his report. The lack of a designated comparison method creates uncertainty and leaves room for bias:

Appendix B

> "*Reliable and accurate structural similarity comparison methods must have a universally accepted rubric guiding how molecules are to be compared so analysts are evaluating structural comparisons within the same context, boundary conditions, and definitions. Without standard methodology and boundary conditions, bias can guide each analyst and therefore, divergent conclusions will result. Uncertainty from the application of unique methodologies and criteria used by each analyst for each compound evaluated is further exacerbated by the lack of objectivity and insular nature of the current similarity analysis environment.*"

Prof Erickson goes on to examine how various structure comparison methods fail to differentiate Schedule I/II substances from food ingredients and over-the-counter medicines. For example, Prof Erickson notes that the active ingredient in the diarrhea medicine Imodium (loperamide) shares much of its structural core with difenoxin, a Schedule I drug. He also identifies several substances that are regularly consumed in foods—like nutmeg (elemicin and myristicin) and chocolate (phenethylamine)—yet that are "one non-hydrogen atom" different from Schedule I/II controlled substances. His examples help illustrate the problems and challenges associated with any attempt to interpret and apply the Analogue statute consistently.

Prof Erickson's search of the Chemical Abstracts database (likely performed through the SciFinder platform) for

indoles bearing substituents at the 1- and 3-positions produced thousands of hits, including over 9700 qualifying indoles listed for sale from registered vendors.

Adam Renslo—From his search of the chemical literature, Dr. Renslo identified "a total of 10,068 unique N-alkyl-3-acyl indoles, for which a total of 5,244 bioactivities were reported in the associated publications", and he catalogues the diverse biological activities associated with this structure class. Note that his search excluded indoles with additional substitution, and some of the indoles he identified were associated with more than one biological activity in SciFinder.

Neil Garg—Prof Garg, in support of his opinion that XLR-11 is not substantially similar to JWH-018, employed the Reaxys platform (the same software database referenced in my previous report) to identify as many as 525 distinct substances that the platform identifies as meeting certain criteria for being structurally similar to JWH-018: "XLR-11 was not one of the 'similarity' hits (although, indeed XLR-11 is in the REAXYS database)."

Richmond Sarpong—Prof Sarpong, in support of his opinion that UR-144 and XLR-11 are not substantially similar to JWH-018, noted that the structural similarities are not particularly unique to these substances, and that the differences are significant in size, shape, and properties. He identified ondansetron (an anti-nausea medication) and indomethacin (an NSAID for rheumatoid arthritis) among common substituted indoles of value to modern medicine.

These experts articulate their opinions in different ways, but they are consistent in identifying significant structural changes within the broad category of 1,3-disubstituted indoles. Moreover, if there were a desire to regulate 1,3-disubstituted indoles (or narrower subcategories like *N*-alkyl-3-acyl-indoles without further substitution), then it would be straightforward to write clear legislation to define this coverage objectively. Such legislation would likely be met with resistance from the university and pharmaceutical research communities due to the importance of such indoles to medicinal chemistry research efforts aimed at improving human health.

APPENDIX C — AFFIDAVIT OF PROFESSOR PAUL DOERING, UNIVERSITY OF FLORIDA, DOC. 776, *USA V. THE GAS PIPE*, CASE NO. 14-CR-00298 (N.D. TX.)

IN THE UNITED STATES DISTRICT COURT
MIDDLE DISTRICT OF FLORIDA
TAMPA DIVISION

Case No. 8:12-MJ-1457 TGW

IN RE SEIZURE OF FUNDS ON DEPOSIT AT AMERIPRISE GROUP IN ACCOUNTS 072372469001, AT PERSHING INVESTMENT IN ACCOUNT 3FB300824, AT MORGAN KEEGAN/RAYMOND JAMES IN ACCOUNT NUMBER 32772063, AND AT CAPITAL ONE BANK IN ACCOUNT NUMBER 8077989170

TIMOTHY HUMMEL,

Movant

v.

UNITED STATES OF AMERICA,

Respondent

Appendix C

AFFIDAVIT OF PAUL L. DOERING SUPPORTING THE MOTION FOR RETURN OF SEIZED PROPERTY AND REQUEST FOR HEARING

STATE OF FLORIDA

COUNTY OF ALACHUA

Before me appeared the undersigned Affiant, PAUL DOERING, MS, who after being duly sworn, stated as follows:

1. My name is PAUL DOERING, MS. I am a Distinguished Service Professor Emeritus in the Department of Pharmacotherapy and Translational Research at the University of Florida, College of Pharmacy. I am a pharmacy expert with a broad knowledge of drugs and their effects on the human body. I have a Bachelor of Science in Pharmacy and a Master's of Science in Clinical Pharmacy. For 28 years I was Director or Co-director of the statewide Drug Information and Pharmacy Resource Center. Attached as Exhibit A is an accurate curriculum vitae which outlines my education, training, experience, publications and credentials.

2. I have served as an expert witness in litigation. In fact, I have recently served as an expert witness for the United States Department of Justice in matters relating to the illegal prescription and dispensing of controlled substances by physicians and pharmacists. Attached as Exhibit B is a list of the cases in which I have testified.

3. On September 18, 2012, I was contacted by Attorney James E. Felman, counsel for movant Timothy Hummel, and was asked to evaluate whether two chemical compounds, namely UR-144 and XLR-11 met the definition of "controlled substance analogue" under Title 21 U.S.C. § 813. More specifically, I was asked whether these two substances were analogues of Compound JWH-018.

4. Compound UR-144 is known more precisely by its chemical name, 1-pentyl-3-(2,2,3,3-tetramethylcyclopropoyl) indole. Compound XLR-11 is known by its chemical designation, 1-(5-fluoropentyl)-3-(2,2,3,3-tetramethylcyclopropoyl) indole. Compound JWH-018 is also known as 1-pentyl-3-(1-naphthoyl) indole.

5. Title 21 U.S.C. § 841(a) makes it unlawful for any person to knowingly and intentionally manufacture, distribute, or dispense, or possess with intent to manufacture, distribute, or dispense, a controlled substance. Title 21 U.S.C. § 813 provides that a controlled substance analogue shall, to the extent intended for human consumption, be treated as a controlled substance. The term con-trolled substance analogue is defined by Title 21 U.S.C. § 802(32)(A) to mean a substance–

> (i) the chemical structure of which is substantially similar to the chemical structure of a controlled substance in schedule I or II;
>
> (ii) 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
>
> (iii) 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.

7. It is my opinion that compounds UR-144 and XLR-11 are not analogues of compound JWH-018. First, although the chemical structures contain elements common to all, this alone does not make them chemical analogues. In fact, there are many compounds that share similar chemical structures that are vastly different in their pharmacologic and toxic effects. The definitions in the Controlled Substance Analogue law under Title 21 U.S.C. § 813 lacks adequate precision to determine what is meant by the term "substantially similar." Without a more precise definition scientists are forced to apply their own interpretation of this term, and as such, are prone to disagreement on just how similar they have to be to be considered similar under this vague definition. To illustrate, one of the common structural elements of these three compounds is an indole ring structure. Indole is a common component of fragrances and the precursor to many pharmaceuticals.

While indole is a building block of these three compounds, it by itself is devoid of pharmacologic effects that would make it dangerous to ingest. It is only by adding additional molecular groupings (known as side-chains) that the substances take on particular pharmacologic and/or toxic profiles.

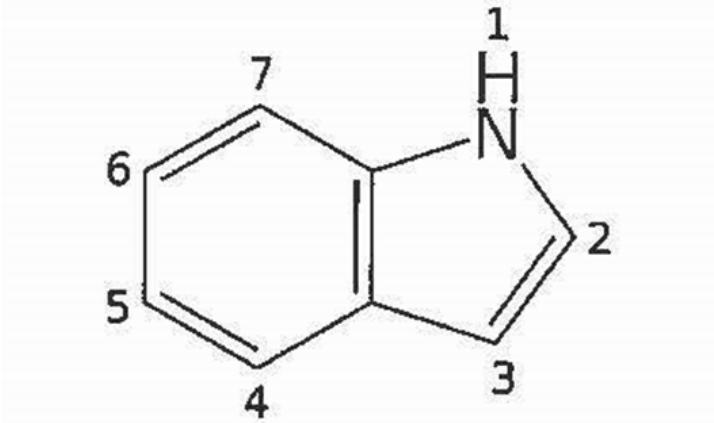


Figure. Chemical structure of indole.

8. The second part of the Analogue Statute says that the compound must have a stimulant, depressant, or hallucinogenic effect on the central nervous system that is sub-stantially 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. Inasmuch as these compounds have not been tested for their pharmacologic properties in humans (it would be illegal to do so outside of an Investigational New Drug Permit), it is therefore impossible to know if it has stimulant, depressant, or hallucinogenic effects

that are similar or greater than those of a controlled substance in schedule I or II. Notwithstanding anecdotal reports appearing in non-scientific outlets (e.g., web blogs, list serves, and e-mail exchanges), there has been no legitimate characterization of the pharmacologic effects, if any, of UR-144 and XLR-11.

9. Animal studies have shown that these two compounds have much less affinity for binding at the site(s) of action of JWH-018. While animal studies do not adequately characterize how a drug would act in the human organism, they can give insight into how the drug might work if it was to be given to human beings. Compounds UR-144 and XLR-11 bind weakly at the cannabinoid receptor CB-1, the receptor in the brain that, when stimulated, produces the mind altering effects of cannabis.

10. It is my opinion that the Analogue Statue is fatally flawed and cannot, in its current form, be reliably used as a rubric to determine the chemical and pharmacological relationship of drug molecules under Title 21 U.S.C. § 802(32)(A).

11. To summarily conclude that compounds UR-144 and XLR-11 are chemical analogues to JWH-018 would not comport with generally accepted scientific principles and methods nor would such methods have been subject to peer review. Any such conclusion would not have general acceptance by the scientific community of pharmacologists, toxicologists, chemists, and pharmacists.

Appendix C

FURTHER AFFIANT SAYETH NAUGHT

/s/ Paul Doering
PAUL DOERING, MS

The foregoing instrument was sworn and subscribed before me this 18th day of October, 2012 by PAUL DOERING, MS.

NOTARY PUBLIC:

sign: /s/ Ingrid T. Cox

print: Ingrid T. Cox

State of Florida
My Commission Expires: 1/16/14
Commission No.: DD 950027
Personally known ☒ OR produced identification ____
Type of Identification Produced _____

APPENDIX D — REPORT OF PROFESSOR NEIL GARG, UNIVERSITY OF CALIFORNIA-LOS ANGELES, DOC. 776, *USA v. THE GAS PIPE*, CASE NO. 14-CR-00298 (N.D. TX.)

EXHIBIT 27

Privileged & Confidential Communication—Expert Report

Research and Structural Analysis of JWH-018 and XLR-11

Neil Garg, PhD
Professor & Vice Chair
University of California, Los Angeles
Department of Chemistry and Biochemistry

I. Overview

The purpose of this report is to provide a scientific analysis as to whether or not **XLR-11** is an analogue of **JWH-018** within the meaning of the Federal Analogue Act. My opinion is that **XLR-11** and **JWH-018** should not be considered analogues because of the reasons described in this report.

II. Introduction

A) The Federal Analogue Act, 21 U.S.C. § 802(32)(A), defines a controlled substance:

(i) the chemical structure of which is substantially similar to the chemical structure of a controlled substance in schedule I or II;

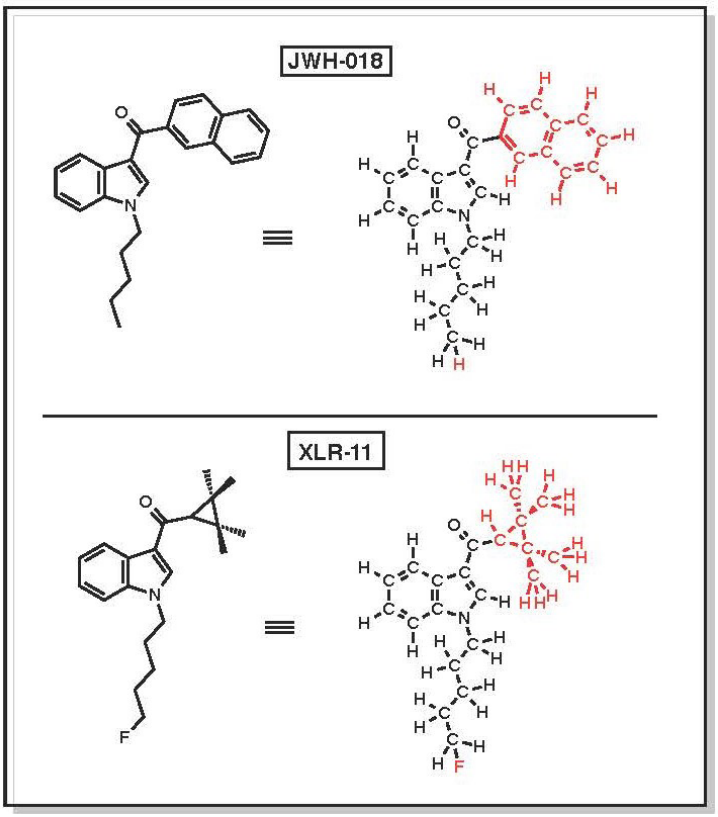
(ii) which has a stimulant, depressant, or hallucinogenic effect on the central nervous system that is substantially similar to or greater than the stimulant, depressant, or hallucinogenic effect on the central nervous system of a controlled substance in schedule I or II; or

(iii) 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.

This report focuses on item **(i)**, which pertains to questions regarding chemical structure similarity. I hold a PhD in Organic Chemistry from the California Institute of Technology and am currently a full professor at UCLA. My research lies at the heart of synthesizing and understanding organic molecules, so this is an area of my expertise where I am qualified to provide a scientific opinion.

B) The specific chemicals requiring analysis are **XLR-11** and **JWH-018**. These are organic molecules, which means they are mostly comprised of the elements carbon and hydrogen. The chemical structures for these molecules are shown below in two different 2-dimensional forms. On the left-hand side, the images reflect abbreviated structures that are commonly used by organic chemists to simplify the drawings. On the right-hand side, the images show all of the atoms. The parts of the molecules highlighted in

red represent the structural differences between **XLR-11** and **JWH-018**.



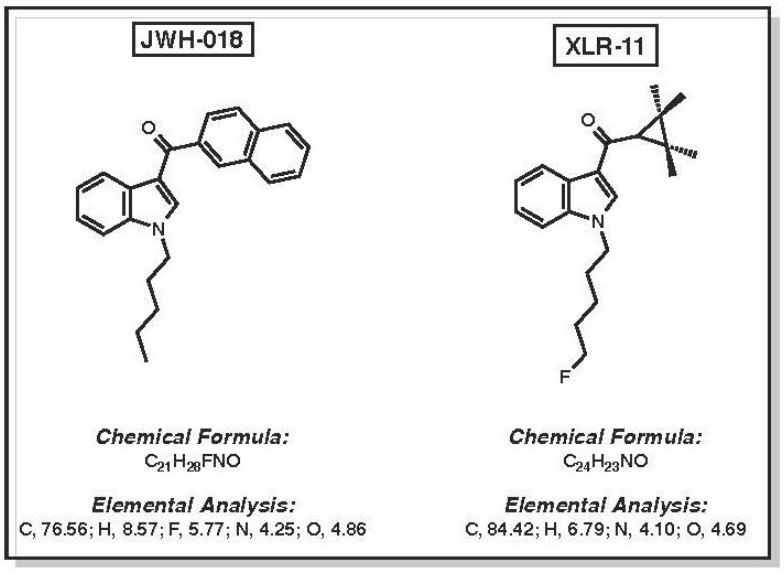
C) The question being asked is: *Are the chemical structures of **JWH-018** and **XLR-11** "substantially similar" to one another?* This wording leaves the matter open to interpretation. In the subsequent section, I explain the criteria I have used to determine that **JWH-018** and **XLR-11** are not "substantially similar" to one another.

Appendix D

III. Analysis

A) Molecular Formula and Evlemental Composition

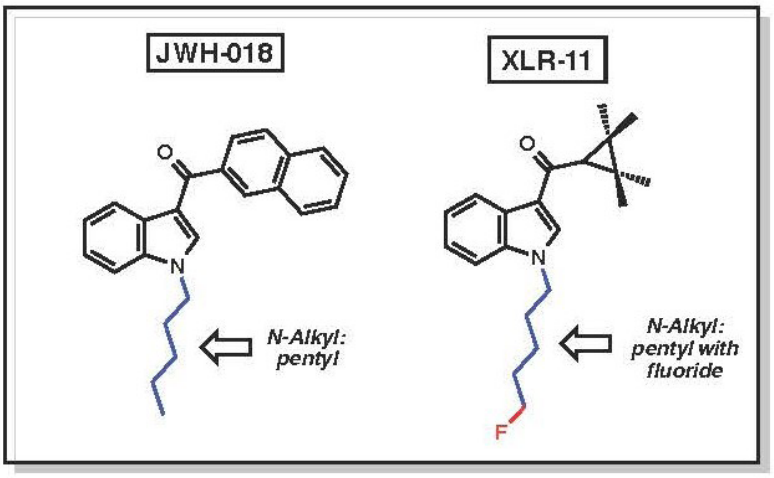
One key criterion to consider is chemical composition. **JWH-018** and **XLR-11** are both organic molecules, primarily consisting of carbon and hydrogen. However, there are several key differences: i) **XLR-11** has three additional carbon atoms compared to **JWH-018**. ii) **XLR-11** contains five fewer hydrogen atoms compared to **JWH-018**. iii) **XLR-11** possesses one fluorine atom, while **JWH-018** does not have any fluorine atoms. This information is reflected in the chemical formulas shown below. Exact percentages of elemental composition are also provided and reflect the same differences.



Appendix D

B) *N*-Alkyl substituent

One of the specific points of difference between the two structures involves the *N*-alkyl chains present on **JWH-018** and **XLR-11**. **JWH-018** contains a pentyl chain, whereas the alkyl chain in **XLR-11** is similar, but possesses a fluoride substituent. Overall, I would classify this is a relatively less critical difference between the two structures, particularly in comparison to what is described in the subsequent section, Section C.

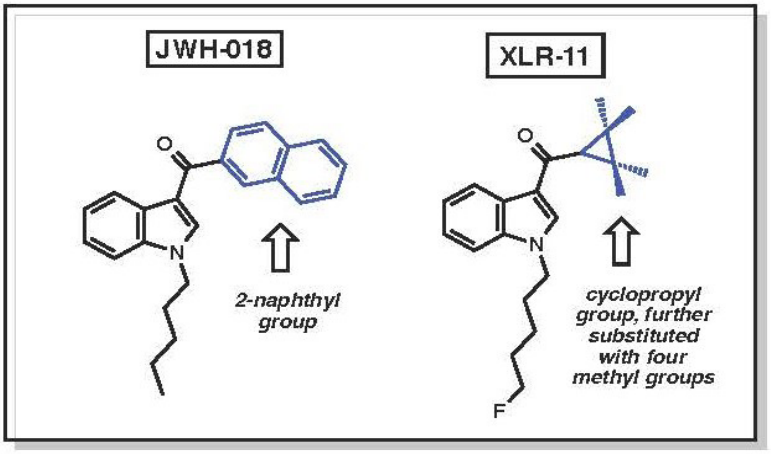


C) Naphthyl vs tetramethylcyclopropyl

The major discrepancy between the two structures involves the substituent on the right-hand side of the ketone, as it is drawn in this document. In the case of

Appendix D

JWH-018, the substituent is a 2-naphthyl group. However, **XLR-11** contains a cyclopropyl group, which, in turn, bears four methyl groups. These two groups (i.e., a 2-naphthyl group and a substituted cyclopropyl group) are entirely dissimilar.

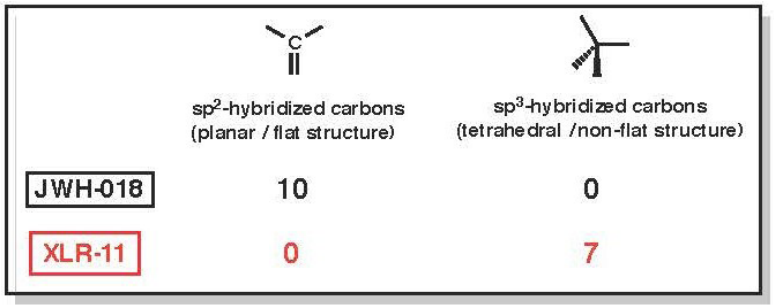


Selected differences between 2-naphthyl and cyclopropyl group s are as follows:

i) A naphthyl group in **JWH-018** is considered aromatic (meaning it has 10 pi electrons that are conjugated to one another via overlapping p orbitals). On the other hand, a cyclopropyl group, as seen in **XLR-11**, is not aromatic.

2. One can also consider the hybridization of the carbon atoms of these two groups. The hybridization of a given carbon atom determines how the substituents on the

carbon atom are oriented in 3-dimensions. In the case of the 2-naphthyl group in **JWH-018**, this has ten sp2-hybridized carbons and zero sp3-hybridized carbons. On the other extreme, the tetra methylcyclo p ropyl group of **XLR-11** has zero sp2-hybridized carbons and seven sp3-hybridized carbons.



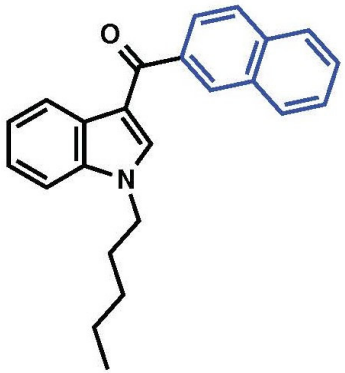
3. Also related to the points above, is a term called bioisostere that is worth noting. Bioisosteres are chemical groups that can commonly be substituted in drug design. Simple cyclopropyl groups are commonly used as 'bioisosteres' for *aliphatic* groups, not *aromatic naphthyl* groups (*J. Med. Chem.* **2011**, *54*, 2529). This highlights the fact that cyclopropyl and naphthyl groups are substantially different. The presence of the 4 methyl groups on the cyclopropyl group of **XLR-11** makes the differences between **JWH-018** and **XLR-11** even more pronounced.

Appendix D

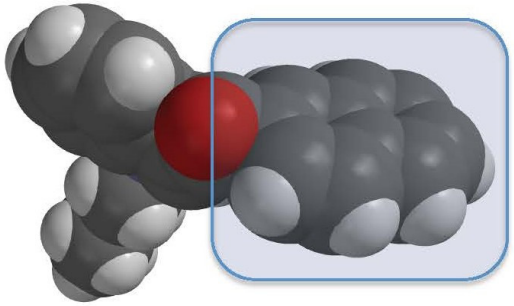
D) Comparison of 3D Structures

The drawings of **JWH-018** and **XLR-11** presented thus far have been in 2D format. However, organic molecules are 3-dimensional and their shape, size, and overall structures play a dramatic role in how chemists compare structures (and how molecules function). Thus, one should compare 3D depictions of **JWH-018** and **XLR-11**. Shown below are geometry optimized structures of the two molecules using Molecular Mechanics calculations (using Spartan '10) software. The substantial differences between the cyclopropyl and 2-naphthyl groups are readily apparent. These groups constitute a large portion of the molecules in question.

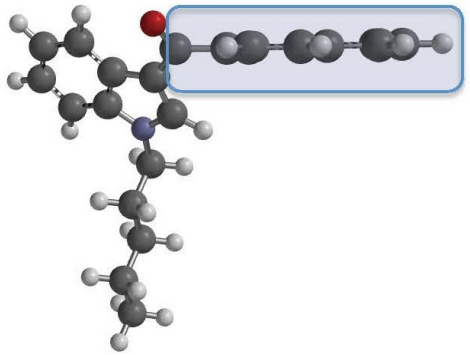
JWH-018



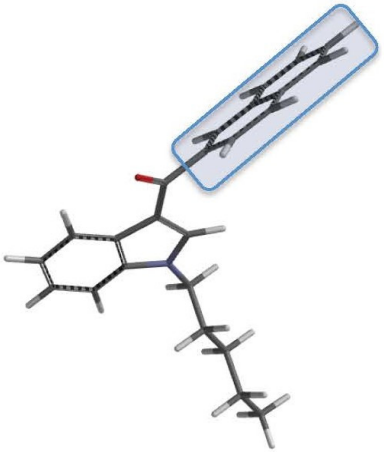
Space Filling Model



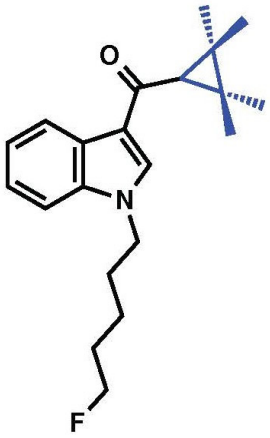
Ball and Stick Model



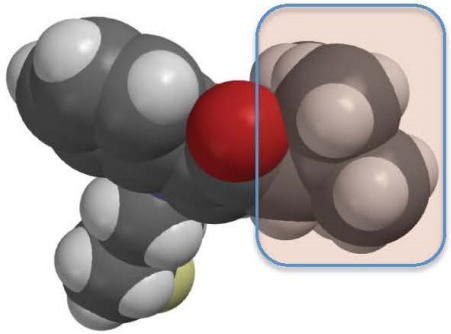
Tube Model



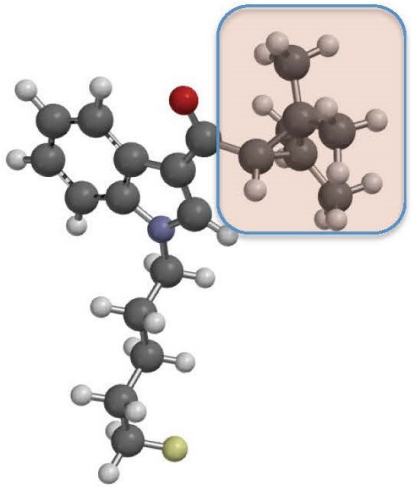
XLR-11



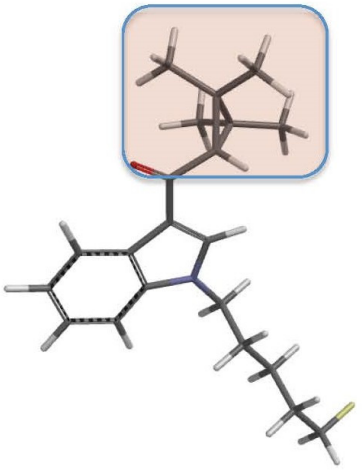
Space Filling Model



Ball and Stick Model



Tube Model



Appendix D

D) Reaxys similarity search

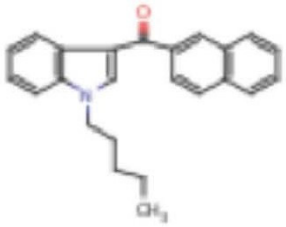
Modern technology allows chemists to perform structure similarity searches. Using REAXYS, state-of-the-art software that is widely used in academia and industry, a structural 'similarity' search was performed for **JWH-018**. As shown in the software screen shot, 525 hits were found (40% similar or higher) under the widest similarity search available. **XLR-11** was not one of the 'similarity' hits (although, indeed **XLR-11** is in the REAXYS database).

IV. Conclusion

On the basis of the analysis described above, I conclude that **JWH-018** and **XLR-11** are not "substantially similar" to one another.

Reaxys: Find Similar Compounds...

Click on one of the hyperlinks below for getting similar compounds according to the selected scope:

Query Structure	Position/Stereo Isomers	Near	Medium	Wide	Widest
	0	0	67	182	525

JWH-018

APPENDIX E — REPORT OF FORENSIC CHEMIST, HEATHER HARRIS, DOC. 776, *USA V. THE GAS PIPE*, CASE NO. 14-CR-00298 (N.D. TX.)

EXHIBIT 29

Heather L. Harris, MFS, JD, D-ABC

February 8, 2018

TO: James E. Felman, Esq.
Kynes, Markman & Felman, P.A. Attorneys at Law

RE: ***Amy Herrig***

Dear Mr. Felman,

You have retained me, Heather L. Harris, MFS, JD, D-ABC, as a consultant to review documentation and provide an opinion in the above captioned case. I have been asked to prepare this report to address two matters: (1) a review of the Advisory Committee on Controlled Substance Analogues, and (2) whether any generally accepted scientific methodology for Prong 1 determinations under the Federal Analogue Act exists or could possibly exist. The Prong 1 determination distills down to the phrase "substantially similar," which is the only criterion present in the statutory definition of controlled substance analogue. It is my opinion that this phrase has no basis in a scientific method and that such a method of evaluation, if one exists, is unlikely to be generally accepted. Therefore, the phrase "substantially similar" possesses no generally accepted scientific meaning.

Appendix E

The Advisory Committee on Controlled Substance Analogues

Any determination of a controlled substance analogue is problematic due to the ambiguity surrounding the term analogue in the statutes as well as the lack of consensus in the forensic chemistry community regarding the proper method for defining, comparing and evaluating potential analogues. In the absence of any legal or scientific guidelines for the definition or determination of an analogue, any claim that a particular compound is an analogue of a currently controlled substance would be simply a subjective opinion with no basis in an objective, peer-reviewed method of evaluation.

A significant problem with an analogue determination under the current statute is that the term analogue is defined by reference to an equally ambiguous phrase, "substantially similar." In the absence of guidance from the statute, the court could look to the relevant scientific community to provide a definition of analogue and a method of evaluation to determine substantial similarity. However, in the forensic chemistry community, no general consensus exists as to what defines an analogue, let alone how to determine if two compounds are properly considered analogues or substantially similar. Only two entities have made public comments about this issue: SWGDRUG (Scientific Working Group for the Analysis of Seized Drugs) and ACECSA (Advisory Committee for the Evaluation of Controlled Substance Analogues). Neither group has provided the clarity and guidance on this issue that the legal and scientific communities are seeking.

Appendix E

SWGDRUG (Scientific Working Group for the Analysis of Seized Drugs) is a DEA sponsored working group that establishes minimum recommendations for the sampling, testing and reporting of forensic drug evidence that are followed by most forensic scientists working in the field. SWGDRUG has issued a set of recommendations to address the issue of analogues.[1] The recommendations stay away from prescribing a methodology for scientific evaluation and instead advise that this is a subjective determination where opinions will differ. SWGDRUG does indicate that a scientific evaluation should include structure, chemical properties and biochemical or pharmacological activity. It also suggests that an evaluation should include a discussion of similarities alongside differences. However, SWGDRUG does not provide any criteria for determining when two compounds are substantially similar.

In early 2012, the Advisory Committee for the Evaluation of Controlled Substance Analogs (ACECSA) was established to address the lack of consensus and standards for evaluating molecules for analog consideration. ACECSA was an independent group of forensic scientists, pharmaceutical scientists, and academics whose mission was to establish a methodology for the evaluation of alleged controlled substance analogues.[2] The primary objectives of ACECSA were to develop a rigorous scientific method for the evaluation of non-controlled substances for analogue consideration that is scientifically valid and

1. SWGDRUG Recommendations, Version 7. 1, Part IIID.2, June 9, 2016, available at www.swgdrug.org

2. See Appendix A for core committee roster.

peer-reviewed and to establish a working definition of "analogue" within the scope of Forensic Drug Analysis. The mission of the ACECSA also sought to address an area of concern addressed in the 2009 National Academy of Sciences' report on Forensic Science (NAS Report) that identified the lack of standardization in the reporting and testimony of forensic experts.

I was a founding member of ACECSA and I also served as the subcommittee chair for the Structure Evaluation committee. The purpose of this subcommittee was to develop a protocol for an objective and consistent comparison between the structures of alleged controlled substance analogs and listed scheduled drugs. Other subcommittees, for example those on pharmacology, computational chemistry, and synthetic pathways, conducted similar work to develop evaluation protocols.

Unfortunately, ACECSA was unable to adopt a formal methodology. The group was able to agree upon a number of different factors that should be considered in an analogue determination, but we were unable to establish criteria that make one compound substantially similar to another. The fact that we were unable to garner consensus among the relatively small group of ACECSA members demonstrates the challenge in achieving a method of evaluation that would be generally accepted by the broader interested communities. By 2014, the complexity of the challenge had frustrated ACECSA's efforts and broader interest in their work had waned.

Appendix E

Methodology for Controlled Substance Analogue Prong 1 Determination

Under the statutory provision set out in 21 U.S.C. §802(32)(a)(i), a controlled substance analogue is a compound

> "*(i) the chemical structure of which is substantially similar to the chemical structure of a controlled substance in schedule I or II.*"

This provision sounds simple on its face, but it is a complex and unsettled area in forensic chemistry. The phrase "substantially similar" has no quantifiable meaning and thus no objective criteria for its measurement exist. The adjective "similar" has no objective scientific meaning but neither does the modifier "substantially." Furthermore, the primary source for internationally accepted definitions for terms in chemistry does not provide a definition for the phrases "substantially similar" or "substantial similarity."[3]

Neither the field of forensic chemistry nor any major academic, government or technical forensic science entity has developed or promoted a standard definition for "substantially similar." This is because the phrase "substantially similar" is inherently vague. This vagueness results in disparate opinions dependent on choices made

3. The Compendium of Chemical Terminology contains internationally accepted definitions for terms in chemistry and is published by the International Union of Pure and Applied Chemistry, available at http://goldbook.iupac.org/, accessed January 30, 2018.

by the chemist conducting the evaluation rather than a generally accepted scientific definition with measurable criteria.

In the absence of any objective, pre-defined meaning, this statutory language demands a compound-by-compound evaluation and interpretation, often based on little more than one person's subjective feelings about the appearance of two-dimensional diagrams.[4] Opinions regarding similarity swing from strict allowances of substitutions to generously broad substitutions, due to vast differences in the interpretation of "substantially similar" and self-chosen criteria for evaluation. A singular, subjective opinion of a chemist may consider scientific elements of the compounds at issue, but that does not mean the evaluation and formation of the opinion has been derived through the scientific method.

One important foundation of scientific knowledge is that it is based upon a testable hypothesis. A testable hypothesis predicts the correlation between variables. Altering one of the variables and measuring the subsequent results can test the hypothesis. If a variable cannot be measured, then the hypothesis cannot be proved or disproved because it is impossible to discern the impact of the testing. In the context of the evaluation of potential analogues, no measurement can indicate if two molecules are substantially similar or what makes them so.

When applying this idea to an opinion regarding the substantial similarity of compounds, it becomes clear

4. *U.S. v. Brown*, 415 F. 3d. 1257. 2005.

that it is simply subjective and is not scientific knowledge acquired through the scientific method. The hypothesis that two molecules are substantially similar is not testable. There is no objective method by which to test the molecules to generate data to determine if the hypothesis is true. An individual's feeling about similarity cannot be subjected to proper scientific testing and it is impossible to establish standardized and objective acceptance criteria for an individual's opinion.

Since a determination of substantial similarity cannot be distilled into a scientific method based on a testable hypothesis proven by objective data, it is impossible to know the potential error rate. It is actually impossible to establish an error rate for an opinion; an opinion is neither right nor wrong. An opinion provided absent an objective methodology and without valid scientific data to support it is not based in scientific knowledge.

Peer review is a natural part of the scientific method. Neither the field of forensic chemistry nor any major academic, government or technical forensic science entity has developed a standard method for evaluation of alleged analogs. Only the field of cosmetic product development has provided a tested, accessible and peer-reviewed method for comparison, and even this method utilizes subjective criteria that are not truly testable according to the scientific method.[5]

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5. S. Wu, K. Blackburn, J. Amburgey, J. Jaworska, T. Federle. "A framework for using structural, reactivity, metabolic and physicochemical similarity to evaluate the suitability of analogs for SAR-based toxicological assessments." Regulatory Toxicology and Pharmacology 56 (2010) 67-81.

Thus, it is clear from the lack of peer-reviewed publications and standard methods and definitions that there is no generally accepted method for the determination of analogues. As discussed above, SWGDRUG acknowledges that evaluation of similarity is a subjective process.[6] Their recommendations stay away from prescribing a methodology for evaluation and instead advise that this is a subjective determination where opinions will differ. This is a realistic assessment of the present state of a Prong 1 determination under the Federal Analogue Act.

Conclusion

In summary, it is my opinion that no generally accepted scientific methodology exists for the determination of potential analogues under the Federal Analog Act. The phrase "substantially similar" is the key to this determination, but this phrase has no scientific definition and its evaluation is based in subjective opinion rather than measured by objective criteria. Therefore, the phrase "substantially similar" possesses no generally accepted scientific meaning.

If any additional information is forthcoming concerning this issue, I would be happy to reevaluate my opinions and conclusions. Feel free to contact me if you have any further questions or concerns.

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6. SWGDRUG Recommendations, Version 7. 1, Part IIID.2, June 9, 2016, available at www.swgdrug.org

Appendix E

Respectfully,

/s/ Heather L Harris

Heather L. Harris, MFS, JD, D-ABC
Forensic Chemistry Consultant

Appendix E

APPENDIX A

ACECSA Core Committee Roster

Officer	Name	Organization
	Barry Logan	NMS Labs
	Dale Forrester	United States Postal Inspection Service / NEAFS
	Deb Calhoun	Pennsylvania State Police
	Fran Diamond	NMS Labs
Recording Secretary	Graham Rankin	Marshall University
	Heather Harris	Functional Group Forensics
	John Meyers	Independent Consultant/Retired DEA
	Karen Phinney	NIST
	Kevin Minbiole	Villanova University
Co-Chair	Kevin Shanks	AIT Laboratories
	Kevin Steele	Montgomery County (PA) District Attorney
	Laura Ciolino	FDA Forensic Chemistry Center
Chair	Lindsay Reinhold	NMS Labs

Appendix E

Sponsor Liaison	Peter Stout	RTI
	Randall Clark	Auburn University
	Ron Porche	Louisiana State Police
	Roscoe Bennett	Pennsylvania State Police
	Steve Reid	Washington State Police
	Vincent Desiderio	United States Postal Inspection Service / NEAFS
Archivist	Warren Samms	Harris County (TX) Institute of Forensic Sciences

APPENDIX F — REPORT OF PROFESSOR MICHAEL HILINSKI, UNIVERSITY OF VIRGINIA, DOC. 776, *USA V. THE GAS PIPE*, CASE NO. 14-CR-00298 (N.D. TX.)

STRUCTURAL COMPARISON OF AM-2201, JWH-018, JWH-250, XLR-11, PB-22, 5F-PB-22, FUB-PB-22, AND THJ-2201

Professor Michael Hilinski, Ph.D.
Department of Chemistry, University of Virginia
Charlottesville, VA 22904

Objective

This report provides an analysis of the structures of several chemical compounds and an opinion on whether they can be described as "substantially similar" in chemical structure to particular comparison compounds, for the purpose of defining them as "controlled substance analogues" as defined by Title 21 U.S.C. § 802(32)(A).

Definitions

An "analogue" or "analog" of a chemical compound is defined accurately, in terms of its common usage by chemical professionals, by the Merriam-Webster dictionary:

> *usually* **analog:** a chemical compound that is structurally similar to another but differs slightly in composition (as in the replacement of one atom by an atom of a different element or in the presence of a particular functional group).

Appendix F

Title 21 U.S.C. § 802(32)(A) defines a "controlled substance analogue" using less precise criteria:

> A substance, the chemical structure of which is substantially similar to the chemical structure of a controlled substance in schedule I or II.

The sole criteria laid out in Title 21 U.S.C. § 802(32)(A) is that the two compounds be "substantially similar" in chemical structure. This is essentially meaningless as "substantially similar" is not a term used in chemical parlance in the context of chemical structure, and lends itself to open-ended subjective interpretation rather than objective analysis. Thus, the comparisons of structural similarity made in this document are guided by Merriam-Webster definition and by the author's expertise in evaluating chemical structures.

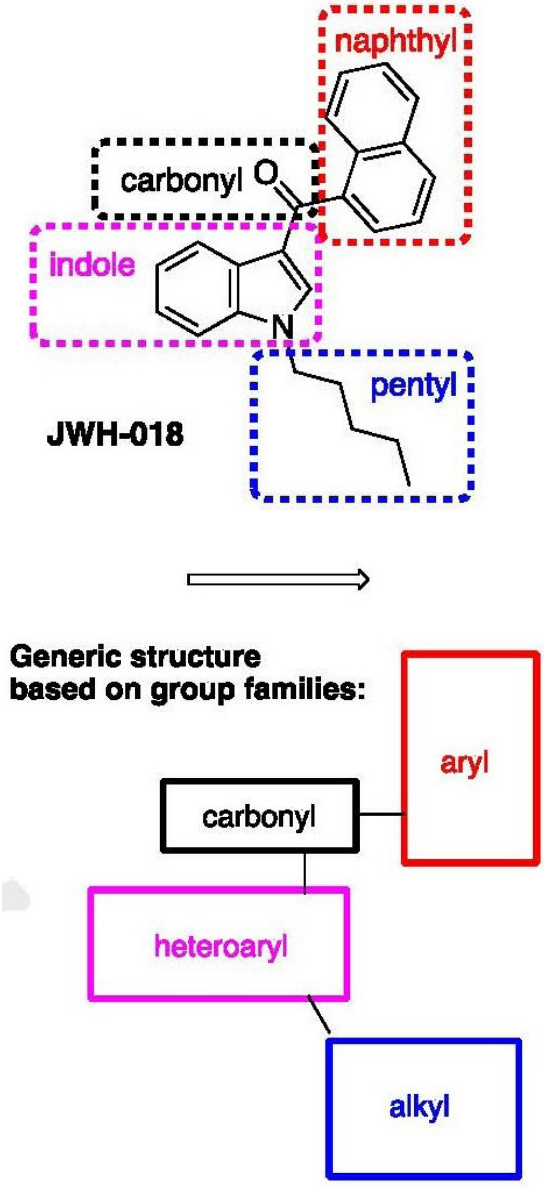
Preliminary Analysis

The chemical structure of JWH-018 is provided below, in a two-dimensional shorthand that portrays the connectivity between atoms but not their position in three-dimensional space. The structure can be broken up into four distinct structural subunits, which can be referred to as either "functional groups" or "groups", which have the characteristic of sharing essentially the same chemical properties no matter where or in what type of molecule they appear. In the case of JWH-018 the specific names of these groups are a pentyl group, an indole group, a carbonyl group, and a naphthalene (or naphthyl) group. These classifications can be further

simplified by assigning each group to a larger family of chemical structures that it belongs to. For JWH-018, the pentyl group falls into the alkyl family (saturated hydrocarbon), the indole group into the heteroaryl family (aromatic ring containing at least one non-carbon atom), the carbonyl group is a fundamental functional group not part of a larger family, and the naphthyl group is considered an aryl group (all-carbon aromatic ring).

Any compound reasonably fitting the definition of "analogue" commonly used in chemical parlance would retain this general structure, substituting atoms or making minor changes to these groups but retaining the overall chemical characteristics of these groups, which could be referred to as "family-level" characteristics. Thus, if the assessment is that these four groups on a chemical compound in question fit into the same broad families as groups in the comparison compound, the two could be considered "controlled substance analogues". However, if at least one of the four groups is better categorized into a different broad family than the group occupying the same region in space as the comparison compound, the two could not be considered analogues. For example, aryl groups have structural, electronic, and other chemical features that make them easily distinguishable from alkyl groups in terms of their properties and reactivity, and in terms of how they would interact with a biological target. Thus changing an aryl group to an alkyl group does not fit the Merriam-Webster definition of structural similarity.

Appendix F

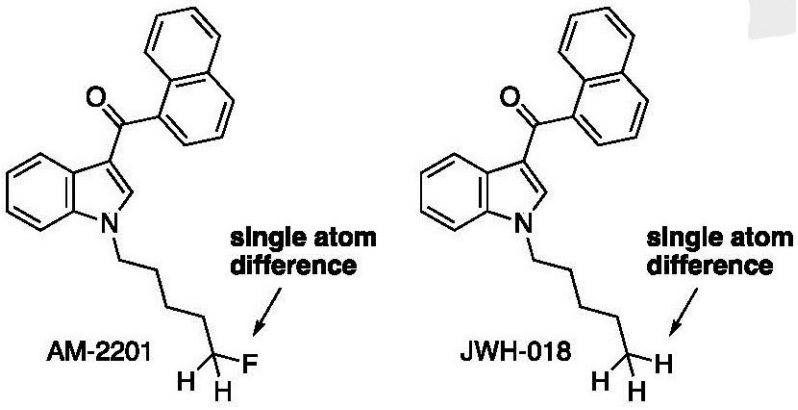

naphthyl
carbonyl
O
indole
N
pentyl
JWH-018
Generic structure
based on group families:
aryl
carbonyl
heteroaryl
alkyl

Appendix F

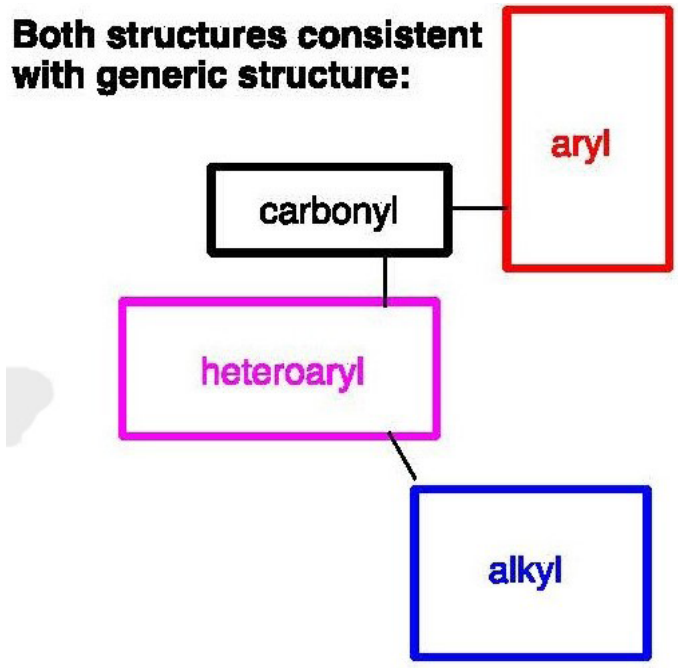
Detailed Analysis

(a) Comparison of AM-2201 with JWH-018

AM2201 and JWH-018 differ in structure by only a single atom. Specifically, the pentyl group in JWH-018, which terminates in a methyl, or $-CH_3$ group, is replaced in AM-2201, with a fluoropentyl group, the only difference being that it terminates in a fluoromethyl, or $-CH_2F$ group. This "replacement of one atom by an atom of a different element" is consistent with the Merriam-Webster definition and thus AM-2201 and JWH-018 should be considered "controlled substance analogues".



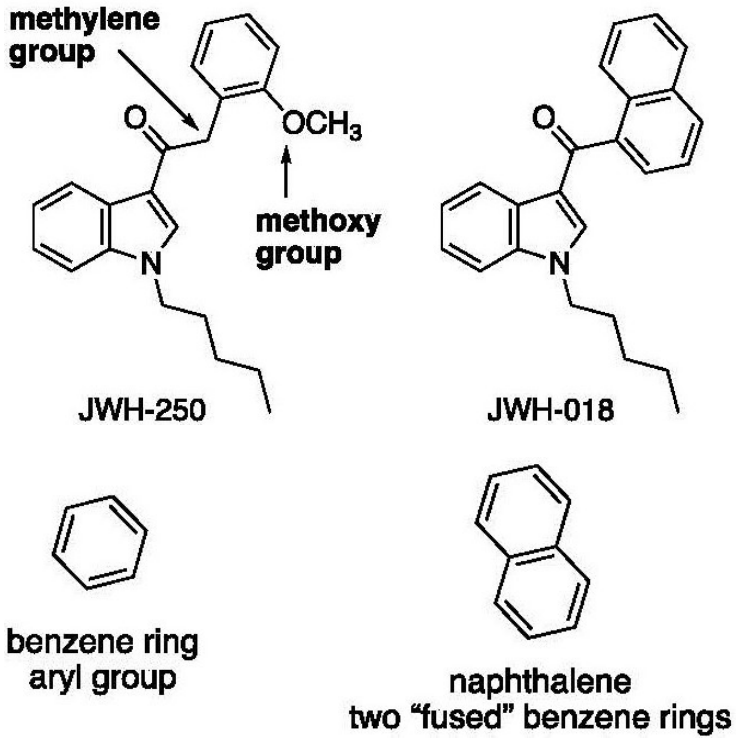
Appendix F



(b) Comparison of JWH-250 with JWH-108

JWH-250 and JWH-018 differ only in the "aryl" region of the generic structure. When considering whether the new group found in JWH-250 is sufficiently similar to the naphthyl group found in JWH-018 to warrant a designation of JWH-250 as an "analogue" of JWH-018, I first looked to whether the group fits in general "aryl" family of groups. This is indeed the case. Whereas JWH-018 contains a napthyl group in this region, JWH-250 contains a phenyl group (also called a benzene ring). Benzene is widely considered to be the parent member of the aryl family. Thus, the two are both aryl groups and in

that way meet the basic standard for similarity. A more in-depth analysis would consider whether the substitution of the one benzene ring found in JWH-018 (as one half of the naphthyl group) with one methylene group and one methoxy group as found in JWH-250. Since these are bound to an aryl group (the benzene ring) they can still be considered part of that group. Therefore, they are best considered as atom substitutions rather than family-level substitutions. By this analysis, I conclude that JWH-250 and JWH-018 should be considered "controlled substance analogues".



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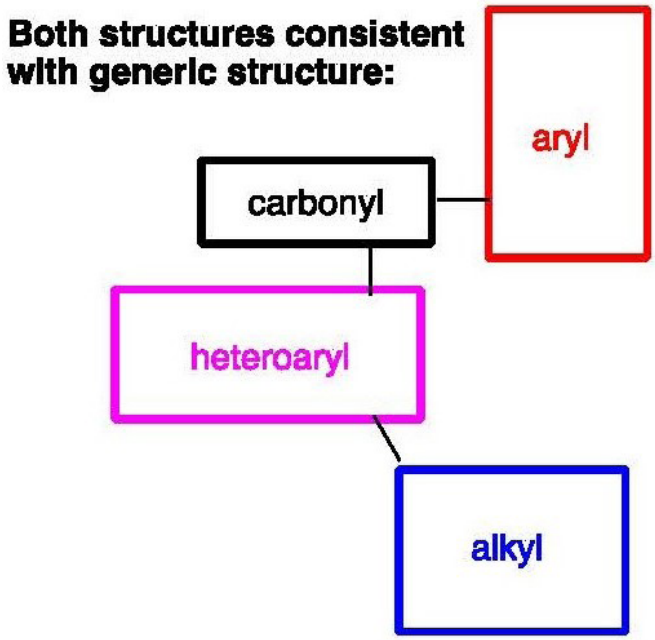
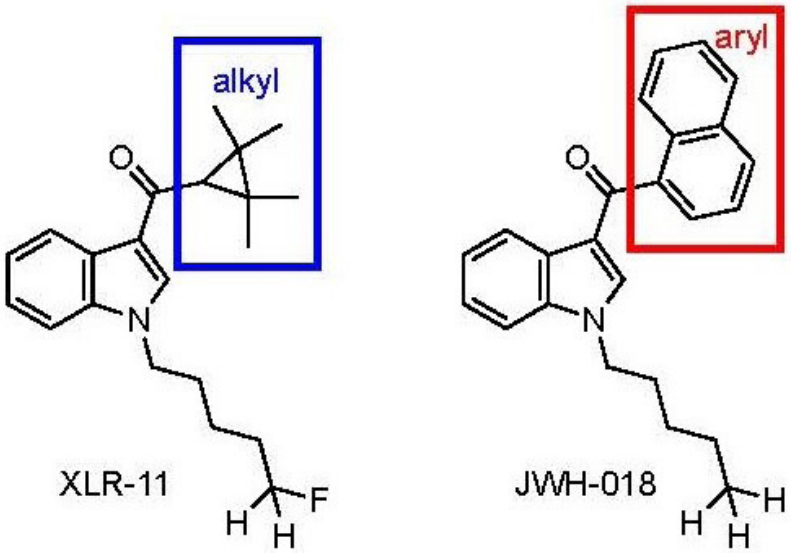


(c) Comparison of XLR-11 with JWH-018

XLR-11 and JWH-018 differ substantially in what would be considered the "aryl" region of JWH-018. In fact, the group that is present in that region of XLR-11 does not fit into the aryl family, and is considered an alkyl group. The differences between alkyl groups and aryl groups are considerable. For example, in an alkyl group such as tetramethylcyclopropyl (the group found in XLR-11), all of the carbon atoms (which in the 2d representation are where lines meet or terminate) are bound to four other atoms. In an aryl group (such as the naphthalene found in JWH-018) all of the carbon atoms are bound to three other atoms. One consequence of this that is apparent from the

Appendix F

3D structures shown is that the tetramethylcyclopropyl group is bulbous in shape whereas the naphthalene is perfectly planar. Other than size and shape, one other way to measure the degree of difference between two groups or types of groups is to consider their chemical reactivity. In this regard, alkyl groups and aryl groups are very different. For example, under certain conditions any alkyl group would be expected to react with molecular bromine in the absence of any other chemical reagents. In the case of aryl groups such as naphthalene, when exposed to the same reagent no reaction would occur. For these reasons and others, alkyl and aryl groups are considered to be members of distinct chemical families, and thus I conclude that XLR-11 and JWH-018 should not be considered "controlled substance analogues" of each other.



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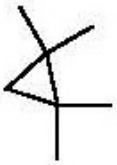
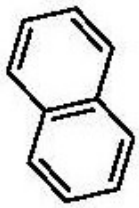
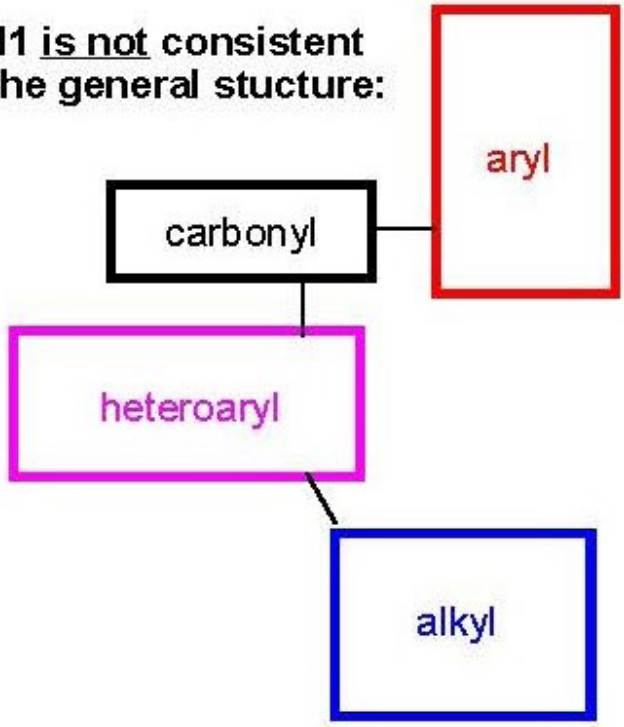


tetramethylcyclopropyl
an alkyl group

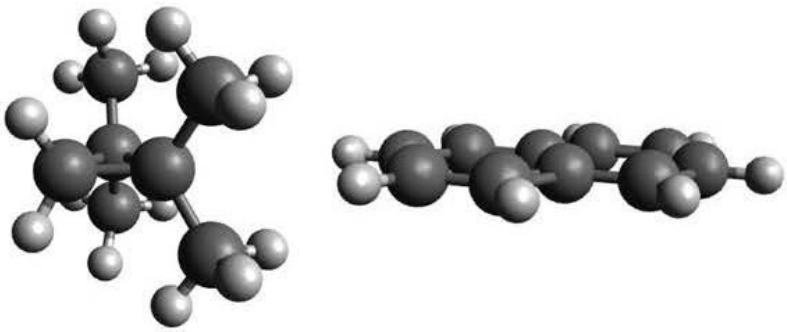


naphthalene
an aryl group

XLR-11 <u>is not</u> consistent with the general stucture:



Appendix F



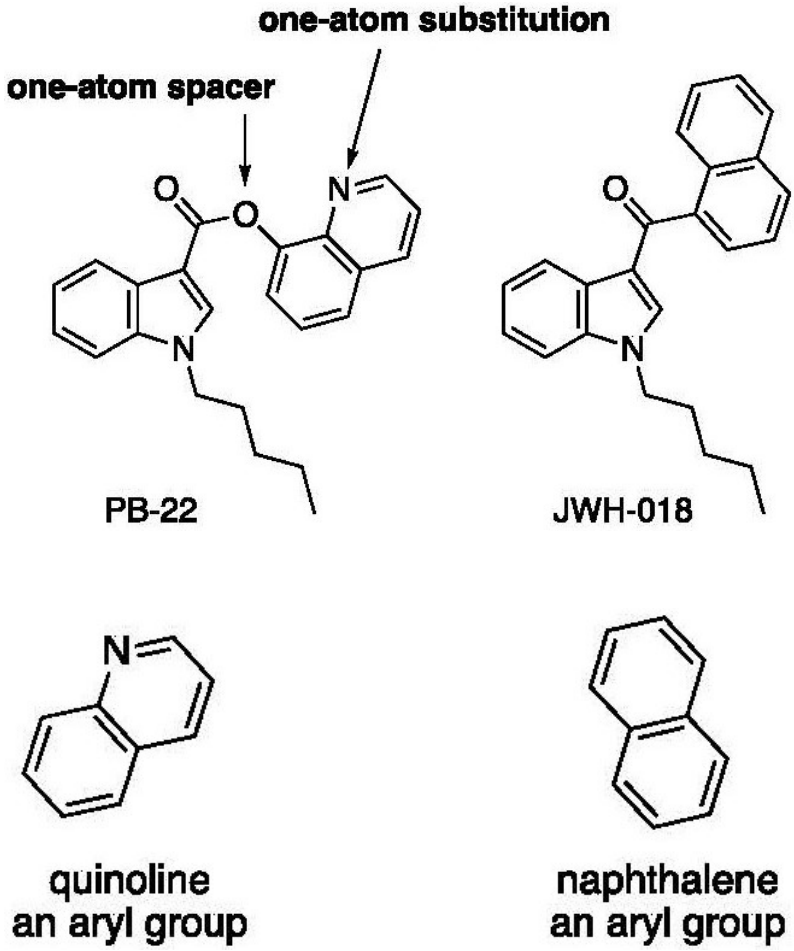
tetramethylcyclopropyl
3D representation

naphthalene
3D representation

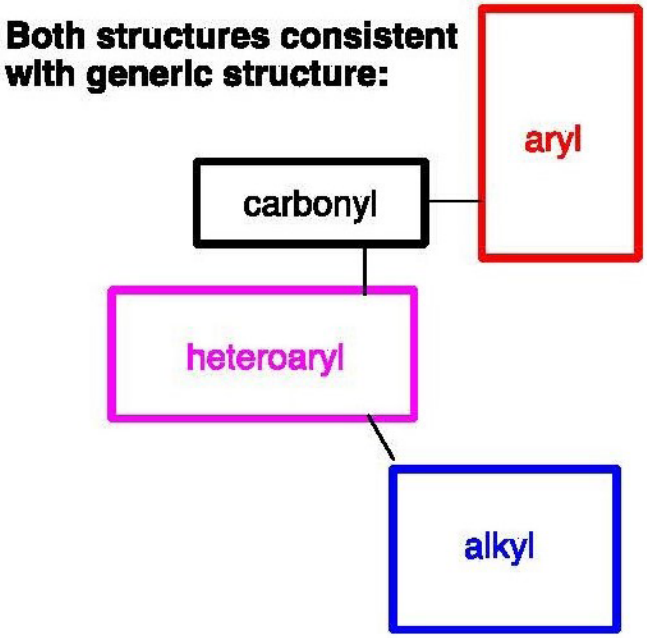
(d) Comparison of PB-22 with JWH-018

PB-22 and JWH-018 differ only in the "aryl" region of the general structure. As before, a precise way to determine similarity would be to consider whether the substructure in the "aryl" region of PB-22 qualifies as an aryl group. The only two differences between PB-22 and JWH-018 are the presence of a one-atom substitution (carbon to nitrogen) and the addition of a one-atom spacer between the carbonyl group and what would be referred to as a quinoline group. The quinoline group is aromatic like the naphthalene, and thus qualifies as an aryl group. More precisely, one would consider it a heteroaryl group, because one carbon of the aryl group is replaced with a noncarbon atom. Heteroaryl groups are a subset of the aryl family and to a first approximation there are no substantial differences in properties, structure, or reactivity. Therefore, I conclude that PB-22 and JWH-018 should be considered "controlled substance analogues".

Appendix F


one-atom substitution
one-atom spacer
O
O
N
N
PB-22
O
N
JWH-018
N
quinoline
an aryl group
naphthalene
an aryl group

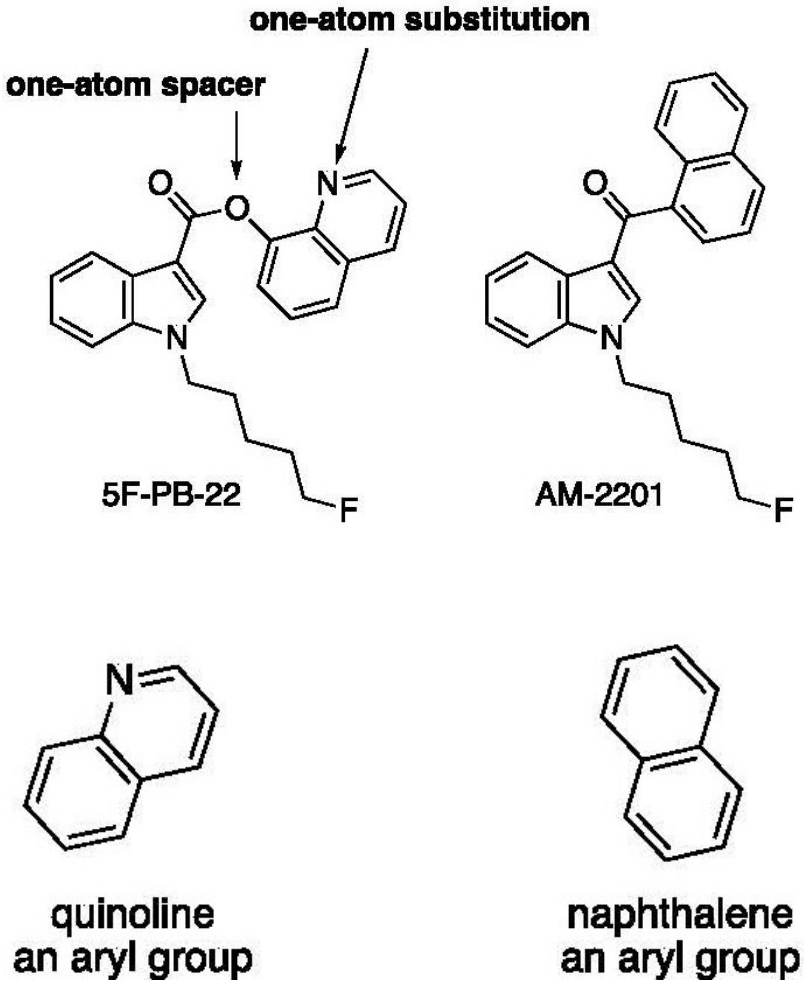
Appendix F



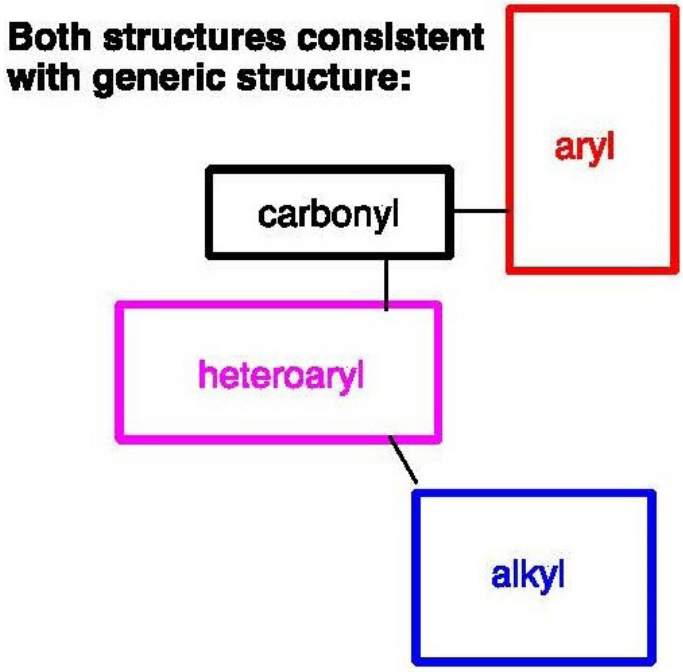
(e) Comparison of 5F-PB-22 with AM-2201

5F-PB-22 ad AM-2201 differ in exactly the same way as PB-22 and JWH-018 [see section **(d)** above] and therefore should be considered "controlled substance analogues"

Appendix F


one-atom substitution
one-atom spacer
O
O
N
N
F
5F-PB-22
O
N
F
AM-2201
N
quinoline
an aryl group
naphthalene
an aryl group

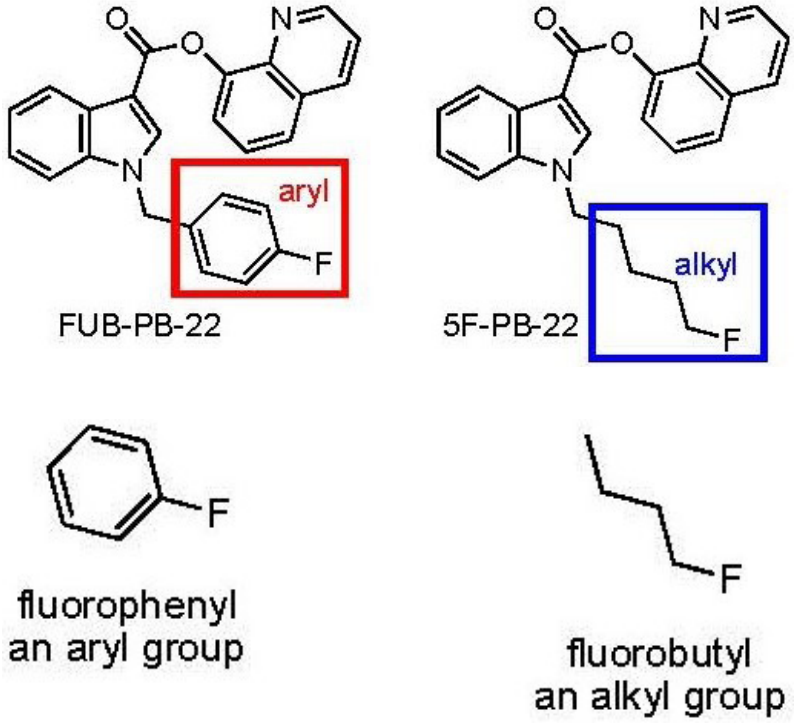
Appendix F



(f) Comparison of FUB-PB-22 with 5F-PB-22

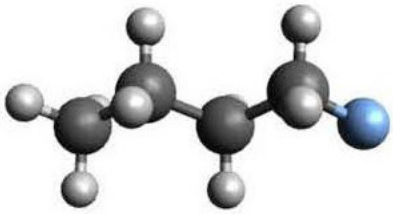
FUB-PB-22 and 5F-PB-22 differ in the "alkyl" region of the general structure. As was the case with the earlier comparison of XLR-11 and JWH-018 [see section **(c)**] the way in which the structures differ in this region is quite substantial, given that the group found in 5F-PB-22 (fluorobutyl group) is categorized as part of the alkyl family and the group found in FUB-PB-22 (fluorophenyl group) is categorized as part of the aryl family. For all the reasons outlined in section **(c)**, the differences that lead to distinct family classifications for these two groups

(structure, shape, reactivity, etc.) are substantial and therefore they lack any reasonable degree of similarity. A person lacking chemical knowledge might be tempted to assert similarity based on the presence of a fluorine atom in each substructure, however the influence of a fluorine atom on chemical structure and properties pales in comparison to the influence of the family to which the substructure belongs. For these reasons, I conclude that FUB-PB-22 and 5F-PB-22 should not be considered "controlled substance analogues" of each other.

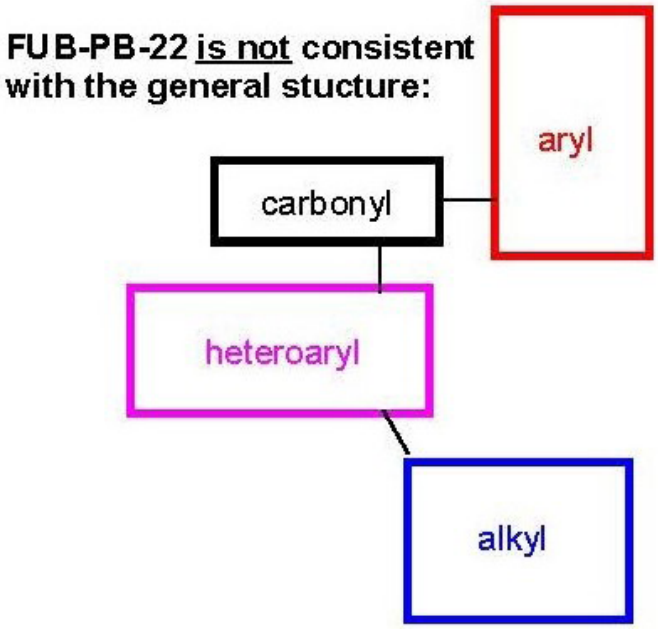


Appendix F

fluorophenyl
3D representation



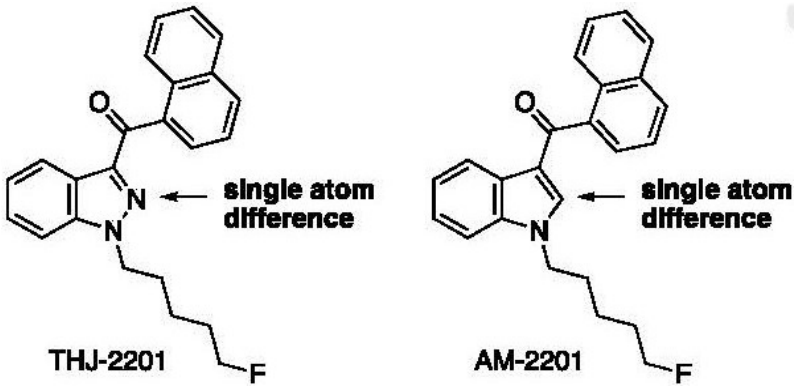
fluorobutyl
3D representation



Appendix F

(g) Comparison of THJ-2201 with AM-2201

THJ-2201 and AM-2201 differ in structure only by a single atom. This difference occurs in the heteroaryl region of the general structure. This change (carbon vs. nitrogen) does not change the fact that THJ-2201 still contains a group in this reason that is categorized as a heteroaryl group. As such, this single atom difference fits the Merriam-Webster definition of "analogue". Therefore, I conclude that THJ-2201 and AM-2201 should be considered "controlled substance analogues" of each other.



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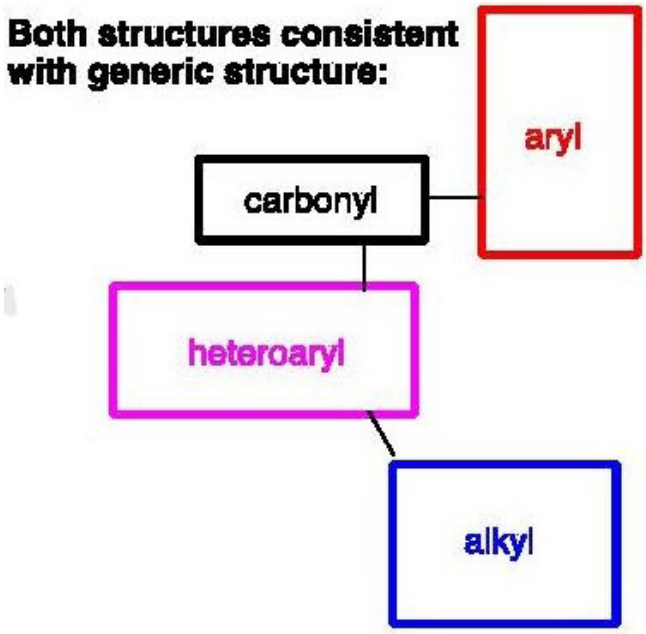


Summary and Conclusions

Guided by the Merriam-Webster definition of a chemical "analogue" and my expertise in evaluating chemical structures, I reach the following conclusions with regards to whether the following chemical compounds should be considered "controlled substance analogues" as defined by Title 21 U.S.C. § 802(32)(A).

Qualify as analogues: JWH-018, AM-2201, JWH-250, PB-22, 5F-PB-22, and THJ-2201

Do not qualify as analogues: XLR-11 and FUB-PB-22

APPENDIX G — REPORT OF PROFESSOR ADAM RENSLO, UNIVERSITY OF CALIFORNIA-SAN FRANCISCO, DOC. 776, *USA V. THE GAS PIPE*, CASE NO. 14-CR-00298 (N.D. TX.)

PRIVILEGED & CONFIDENTIAL
COMMUNICATION: ATTORNEY-CLIENT
PRIVILEGE & ATTORNEY WORK PRODUCT
PREPARED IN ANTICIPATION OF LITIGATION

Research and Structural Analysis of JWH-018 and XLR-11

Professor Adam R. Renslo, Ph.D.
Department of Pharmaceutical Chemistry
University of California, San Francisco

Objective: This report provides an analysis of the structures of JWH-018 and XLR-11 and provides an opinion on whether the latter may be considered a structural "*analogue*" of the former as defined by Title 21 U.S.C. § 802(32)(A).

Definitions

Definition of "analogue / analog" *in the context of chemical structure*:

> Merriam-Webster Dictionary: A chemical compound that is structurally similar to another but differs slightly in composition (as in the replacement of one atom by an atom of a different element or in the presence of a particular functional group).

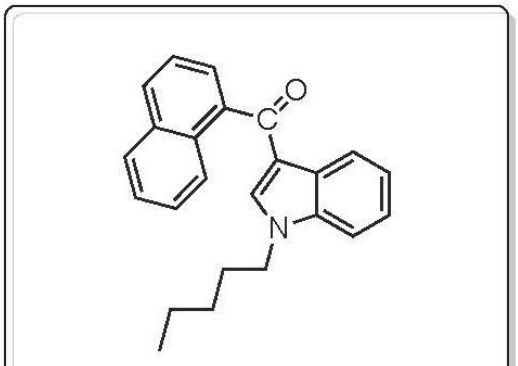
Appendix G

Definition of "controlled substance analogue" *in the context of chemical structure.*

> Title 21 U.S.C. § 802(32)(A): A substance, the chemical structure of which is substantially similar to the chemical structure of a controlled substance in schedule I or II.

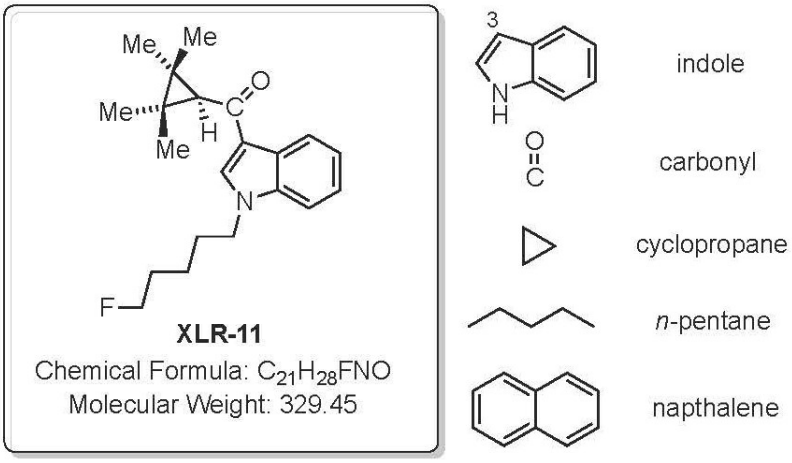
Preliminary Analysis:

The chemical structures, chemical formulae, and molecular weights of JWH-018 and XLR-11 are provided below. The compounds share an indole ring substituted at the 3 position with a carbonyl group that is further joined to a naphthalene (in JWH-018) or a tetramethylcyclopropane ring (in XLR-11). The indole nitrogen atom of both compounds is substituted with an unbranched alkyl chain of five carbons in length (*n*-pentyl). The distal carbon of the *n*-pentyl chain in XLR-11 (but not JWH-018) is further substituted with a fluorine atom (F).



JWH-018
Chemical Formula: $C_{24}H_{23}NO$
Molecular Weight: 341.45

Appendix G



To conclude that JWH-018 and XLR-11 are analogues according to the above definitions requires that they be "structurally similar", "substantially similar", or "differ slightly". The *n*-pentyl side chains in the two compounds differ by a single atom (H or F) and would therefore be considered by most practicing organic/medicinal chemists to be substantially similar. However, the tetra methylcyclopropane and naphthalene ring systems are fundamentally different in composition, bonding, size, and shape, as will be further described later. Therefore, it is my opinion that JWH-018 and XLR-11 cannot be considered structural "analogues" as defined above (Definitions).

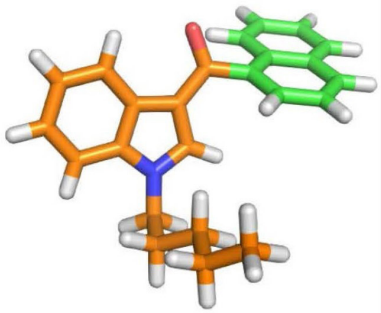
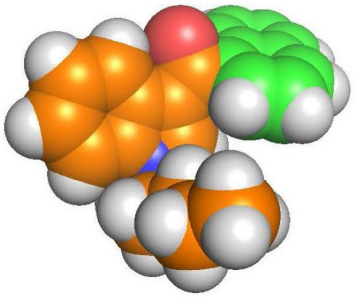
Detailed Analysis:

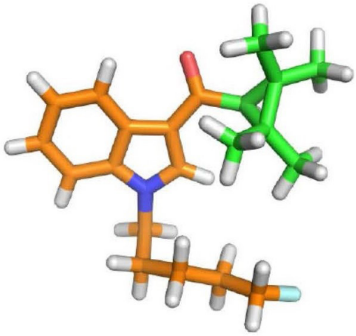
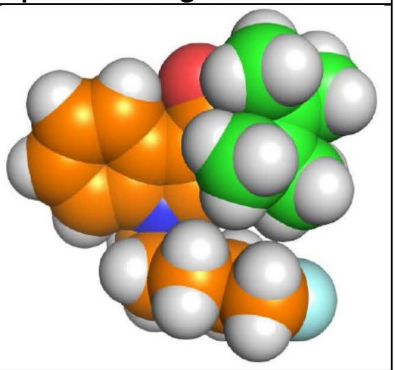
The term "controlled substance analogue" is defined by Title 21 U.S.C. § 802(32)(A) to mean a substance,

> (i) the chemical structure of which is substantially similar to the chemical structure of a controlled substance in schedule I or II;
>
> (ii) 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
>
> (iii) 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.

The present analysis focuses on (i) above and the question of whether the compounds in question are "substantially similar" with respect to their chemical structures. To assist in the analysis and provide a more accurate representation of each molecule, I calculated a low-energy conformation of both JWH-018 and XLR-11 (performed in Marvin from ChemAxon; images prepared in Pymol). A "low-energy" conformation shows the molecule with bond angles and bond rotations that will be significantly present under normal (e.g. physiological) conditions of temperature and pressure. In addition to stick models that emphasize the connectivity of atoms, I have also prepared a space-filling representation of each molecule

to better approximate the shape and space occupied by each molecule.

JWH-018	
stick model	space-filling model
	

XLR-11	
stick model	space-filling model
	

Appendix G

In the above representations, the carbon atoms comprising the napthlene ring in JWH-018 and the tetra methylcyclopropane ring in XLR-11 have been colored green. The carbon atoms of the indole ring and *n*-pentyl side chains of JHW-018 and XLR-11 are presented in orange while the fluorine atom of XLR-11 is shown in cyan. It should be apparent from these representations that parts of the two molecules (those shown in orange) are very similar, while other parts of the molecules (those shown in green) are quite different.

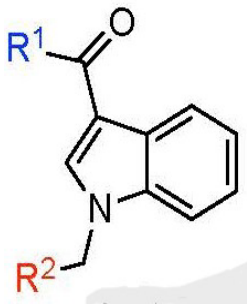
The carbon atoms in organic molecules can exist in distinct 'hybridization' states, which determine the bond angles between atoms and their relative orientation in space. Thus, the carbon atoms of the naphthalene ring in JWH-018 are sp^2 hybridized, with bond angles of ~120 degrees and all atoms in a roughly co-planar relationship. The flat, planar structure of the naphthalene ring should be apparent in the structures of JWH-018 shown above. The carbon atoms of the four methyl groups in tetramethylcyclopropane are sp^3 hybridized and form bonds separated by ~109 degrees, with bonded carbon and hydrogen atoms located roughly at the corners of a tetrahedron. The carbon atoms that make up the cyclopropane ring itself adopt a still different hybridization state that allows even smaller bond angles required to form the three-membered ring structure. Thus, the carbon atoms in naphthalene and tetramethylcyclopropane are found in distinct hybridization states and do not share any of the same bonding angles. The most relevant consequence of these differences is that naphthalene is a flat, planar structure while the tetramethylcyclopropane ring has

a spheroid aspect. Finally, the planar arrangement of sp^2 hybridized carbon atoms in naphthalene affords special "aromatic" stability to this ring system that is not present in tetra methylcyclopropane. Thus, for reasons of structure, carbon hybridization, 3D shape, and aromatic stabilization, the practicing organic or medicinal chemist will consider naphthalene and tetra methylcyclopropane to be very different substituents. It is therefore my opinion that JWH-018 and XLR-11 cannot be considered to be structural "analogues" by the relevant definitions of the term.

I will next consider the *N*-alkyl-3-acyl-indole that is present in both JWH-018 and XLR-11 and ask the question whether the presence of this shared sub-structure can be used to infer, based solely on structure, a similar pharmacological effect of the two compounds. To do this, I performed a search of the scientific literature (using SciFinder from Chemical Abstracts Services) for all reported compounds possessing the *N*-alkyl-3-acylindole substructure shown below. The query was performed in such a way that substitutions of the indole ring other than 3-acyl (R^1) and *N*-alkyl (R^2) were not permitted. In this way, all compounds identified in the search possess the same *N*-alkyl-3-acylindole sub-structure present in JWH-018 and XLR-11 (i.e., the sub-structure shown below).

Appendix G

Search of chemical literature using sub-structure common to JWH-018 and XLR-11



N-alkyl 3-acyl indole ring held constant; R1 and R2 groups variable

- 10,068 unique substances with >= 1 literature reference
- 5,244 bioactivities (see Table 1 for most common activities)

sub-structure queried

The results of the search were further limited to compounds that are described in at least one scientific publication. This produced a total of 10,068 unique *N*-alkyl-3-acyl indoles, for which a total of 5,244 bioactivities were reported in the associated publications (note that specific compounds may have multiple associated bioactivities). The fifteen most common bioactivities reported for *N*-alkyl-3-acyl indoles are provided in the table below, ordered by number of occurrences. As is evident from this analysis, the *N*-alkyl -3-acyl-indole substructure is present in a large number of molecules exhibiting a wide array of bioactivities and pharmacological effects. Thus, the presence of a shared *N*-alkyl-3-acyl-indole structure in JWH-018 and XLR-11 is by itself insufficient structural information to infer a particular pharmacological effect.

Appendix G

Biological activity	**Number of occurrences**
Antiproliferative agents	226
Respiratory system agents	223
Cardiovascular agents	211
Receptor antagonists	159
Gastrointestinal agents	150
Enzyme inhibitors	117
Antiobesity agents	106
Antiosteoporotic agents	67
Receptor agonists	66
Hematologic agents	52
Microtubule-targeting agents	46
Ophthalmic agents	45
Hypolipemic agents	38
Peptidomimetics	36
Ion channel blockers	34

Concluding Remarks: The structures of JWH-018 and XLR-11 have been analyzed and compared for their structural differences and similarities. On the basis of this analysis, it is my opinion that these compounds cannot be considered to be structural analogues.

APPENDIX H — REPORT OF PROFESSOR RICHARD SARPONG, UNIVERSITY OF CALIFORNIA-BERKELEY, DOC. 776, *USA V. THE GAS PIPE*, CASE NO. 14-CR-00298 (N.D. TX.)

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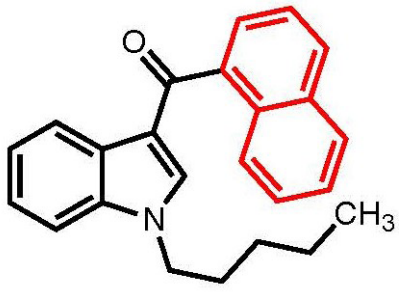
COMMUNICATION: ATTORNEY–CLIENT
PRIVELEGE & ATTORNEY WORK PRODUCT
PREPARED IN ANTICIPATION OF LITIGATION

STRUCTURAL ANALYSIS OF JWH-018, UR-144, AND XLR-11

Professor Richmond Sarpong, Ph. D.
Department of Chemistry, University of California–Berkeley

Purpose: This document provides an analysis of the structures of the chemical compounds **JWH018**, **UR-144** and **XLR-11** and addresses whether these compounds can be described as "substantially similar" or in the language of organic chemistry whether these compounds are "structural analogues" of one another.



JWH-018

Appendix H

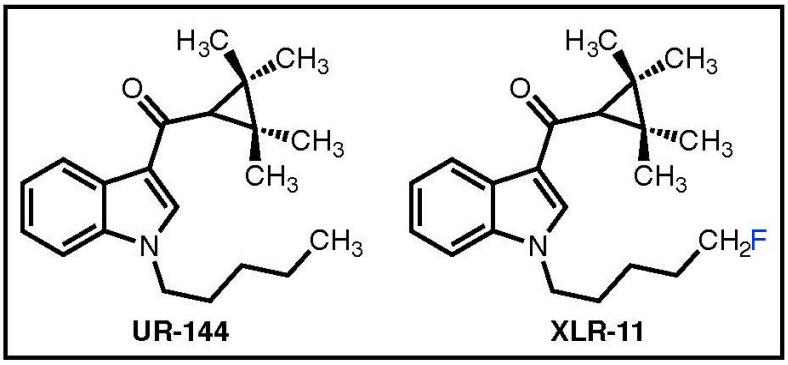


Figure 1. Chemical structures of JWH-018, UR-144 and XLR-11

Structural analogue is a term that is used in chemistry to describe chemical compounds that are structurally 'similar'. The term analogue (or analog in the United States), in my opinion, is best defined by the Merriam-Webster journal (http://www.merriam-webster.com/dictionary/analogue)

Analog: a chemical compound that is structurally similar to another but differs slightly in composition (as in the replacement of one atom by an atom of a different element or in the presence of a particular functional group).

In general usage outside of the chemistry context, the term 'similar' or 'substantially similar' is open to interpretation and is therefore relative. To make the determination of substantial similarity, especially in organic chemistry, this has to be in the context of a comparison group.

Appendix H

Summary

The definition of a 'controlled substance analogue' is well established by Title 21 U.S.C. § 802(32)(A). On the basis of the analysis provided in this document, XLR-11 and UR-144 qualify as structural analogues of each other with 'substantial similarity' whereas JWH-018 can**not** be described as a structural analogue of these two compounds. Thus, in my opinion, XLR-11 and UR-144 are **not** substantially similar to JWH-018 in the context of that comparison group and should therefore not be described as structural analogues of the latter.

Similarities and Differences of JWH-018, UR-144 and XLR-11

On balance, to reach a conclusion of whether two chemical compounds are "substantially similar", their structural similarities and differences need to be considered. Even upon visual inspection of the chemical structural depictions of JWH-018, UR-144 and XLR-11 shown in Figure 1 above, the substantial similarity between the latter two is evident whereas the former deviates from this structural similarity.

Chemical structures of the type illustrated in Figure 1 are a formalism to represent connectivity between atoms. JWH-018, UR-144 and XLR-11 are examples of organic chemical compounds, which are characterized by a carbon and hydrogen (hydrocarbon) framework. Therefore, the lines represent bonds between atoms, which sit at the vertices. In the cases where a letter is not

shown at a vertex, this represents the position of a carbon atom (which may be bound to four other atoms). Where a hydrogen atom is bound to a carbon atom, the hydrogens (H) are often not shown. In some cases, the carbons (C) and hydrogens (H) are shown for emphasis.

Similarities: JWH-018, UR-144 and XLR-11 all contain an indole, carbonyl group, and a butyl group, which is an example of an alkyl chain that possess four carbon atoms (see below for illustrations).

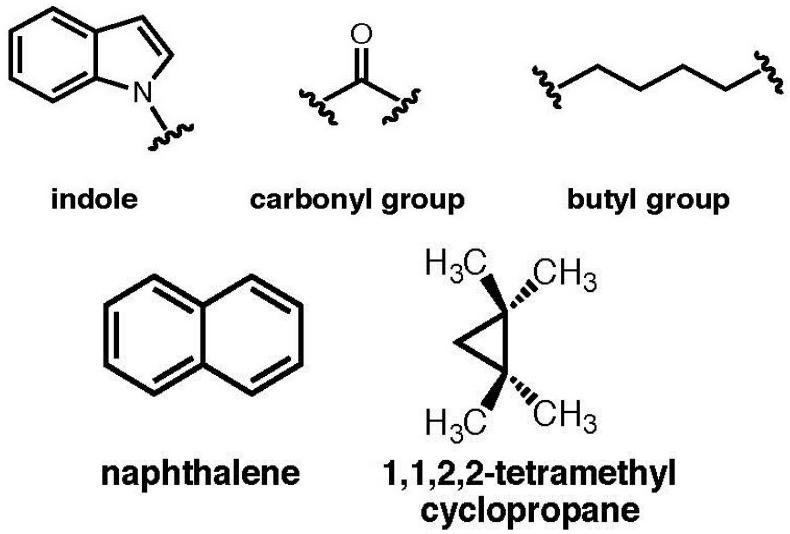
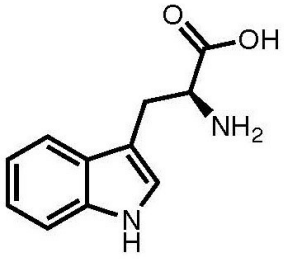


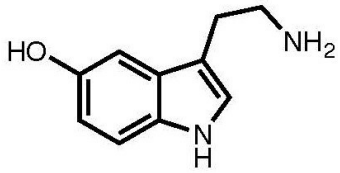
Figure 2. Different groups in JWH-018, UR-144 and XLR-11

Indoles are found in a wide range of organic chemical compounds (see Figure 3). Perhaps the most easily recognized of these is tryptophan, which is an amino-acid

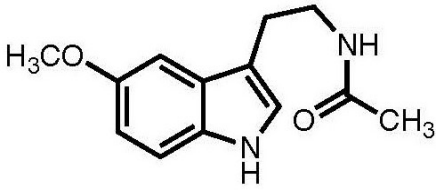
that is relevant to the synthesis of essential peptides and in turn proteins that are basis for many cellular processes. The indole structure also features prominently in many naturally-occuring compounds including serotonin, melatonin, as well as the pharmaceuticals ondansetron and indomethacin. As such, the occurrence of indoles in organic compounds is quite common-place and does not correlate with a particular biological function or pharmaceutical activity. Carbonyl groups and alkyl groups are also quite common in organic chemical structures and do not correlate to a particular biological activity either. Therefore, a determination of substantial structural similarity for JWH-018, UR-144 and XLR-11 cannot be made on the basis of these groups.



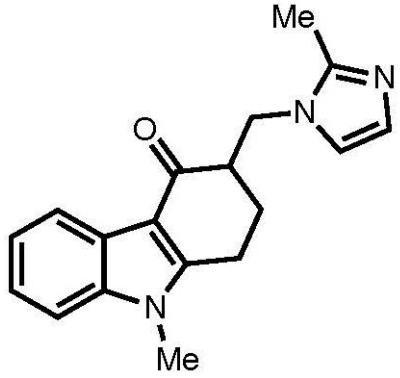
Tryptophan
(amino acid)



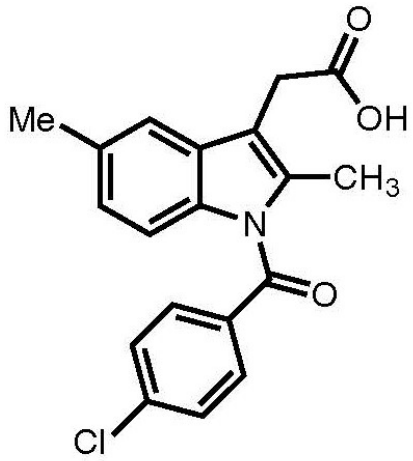
Serotonin
(neurotransmitter)



Melatonin
(hormone/sleep aid)



Ondansetron
(suppression of nausea/vomiting)
used along with chemotherapeutics



Indomethacin
(treatment of rheumatoid
arthritis)

Figure 3. Selected compounds that possess an indole group

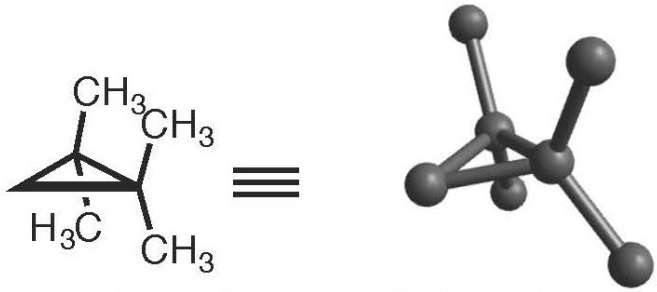
Appendix H

Differences: The difference between UR-144 and XLR-11 is in the substitution of a single hydrogen atom (H) for a fluorine atom (F) on the butyl chain. This structural change is very small ("as in the replacement of one atom by an atom of a different element" –see the Merriam-Webster definition of analog above) and therefore these two compounds, in my opinion, are substantially similar and therefore should be considered as structural analogues. On the hand, the difference between, JWH018 and, for example, UR-144 is the substitution of a naphthalene group for a 1,1,2,2-tetramethyl cyclopropane group. JWH-018 further differs from XLR-11 in the additional substitution of a hydrogen atom by a fluorine atom.

A naphthalene group and a 1,1,2,2,-tetramethyl cyclopropane group are substantially different from a structural standpoint (see Figure 4; minimized structures obtained using Avogadro, http://avogadro.openmolecules.net/). The naphthalene group, by virtue of the bonding of the carbon atoms, is flat. The naphthalene contains alternating double and single bonds between the carbon atoms (indicated by the alternating double and single lines), which enforces a flat structure. It is a one-atom thick molecule and can be regarded as a two-dimensional structure. The 1,1,2,2,- tetramethyl cyclopropane group on the other hand is a three-dimensional structure which projects into space in all three dimensions. This is a substantial difference in structure and in my opinion, these two structures are **not** structural analogues. Another structural difference between the naphthalene and 1,1,2,2-tetramethylcyclopropane groups is in their molecular formula, which reveals differences in the

number of carbon and hydrogen atoms. The molecular formula for naphthalene is C10H8 whereas it is C7H14 for the 1, 1,2,2-tetramethylcyclopropane group.

side-on view of naphthalene
H atoms removed for clarity
(Minimized with Avogadro)



side-on view of tetramethyl cyclopropane
H atoms removed for clarity
(Minimized with Avogadro)

Figure 4. Comparison of three dimensional structures

In chemistry, the differences between structures are often best reflected in their reactivity in chemical reactions. The

naphthalene is an example of what is termed an aromatic group. This is a term that is applied in chemistry to a subset of cyclic molecules that are imbued with added stabilization by virtue of their bonding. They are more stable (i.e., less reactive) than what might be predicted. Cyclopropanes on the other hand are three-membered rings that possess substantial strain, which is destabilizing and makes them reactive. The strain arises because of the substantial deviation of the carbon-carbon angles in a cyclopropane from the ideal angles for carbon-carbon single bonds. The inherent strain makes cyclopropanes more reactive because this 'angle strain' weakens the carbon-carbon bonds.

The analysis of the differences thus far has focused on a portion of the overall structures of JWH-018, UR-144 and XLR-11. This is because from a holistic consideration, the naphthalene and cyclopropane fragments represent substantial portions of these molecules and are significant to the properties of these molecules.

Several criteria are applied in defining a controlled substance analogue as detailed in Title 21 U.S.C. § 802(32)(A). Particularly pertinent to the discussion presented here is the following statement "the chemical structure of which is substantially similar to the chemical structure of a controlled substance in schedule I or II". The interpretation of this statement in the language of chemistry would be whether these chemical structures are structural analogues. On this basis alone and the analysis I have provided here, in my opinion, UR144 and XLR-11 cannot be considered controlled substance analogues.

Appendix H

Conclusion:

An analysis of the structural similarities and differences between UR-144/ XLR-11 and JWH-018 has been presented. A substantial difference in structure between the latter and two former compounds is a 'naphthalene for 1,1,2,2-tetramethyl cyclopropane' group substitution. In my opinion, this difference is significant in the context of these structural types and as such UR-144/ XLR-11 are **not** structural analogues of JWH-018.

APPENDIX I — REPORT OF PROFESSOR RICHARD TAYLOR, UNIVERSITY OF NOTRE DAME, DOC. 776, *USA V. THE GAS PIPE*, CASE NO. 14-CR-00298 (N.D. TX.)

ATTORNEY WORK PRODUCT PREPARED
IN ANTICIPATION OF LITIGATION

Structural Analysis of XLR-11 and JWH-018

I. Introduction

A) The Federal Analogue Act, 21 U.S.C. § 802(32)(A), defines a controlled substance:

(i) the chemical structure of which is substantially similar to the chemical structure of a controlled substance in schedule I or II;

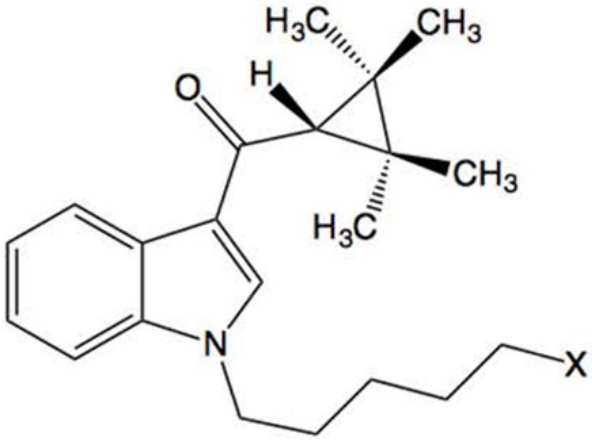
(ii) which has a stimulant, depressant, or hallucinogenic effect on the central nervous system that is substantially similar to or greater than the stimulant, depressant, or hallucinogenic effect on the central nervous system of a controlled substance in schedule I or II; or

(iii) 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.

B) This report focuses on point (i) of the analogue act, which pertains to questions regarding chemical structure

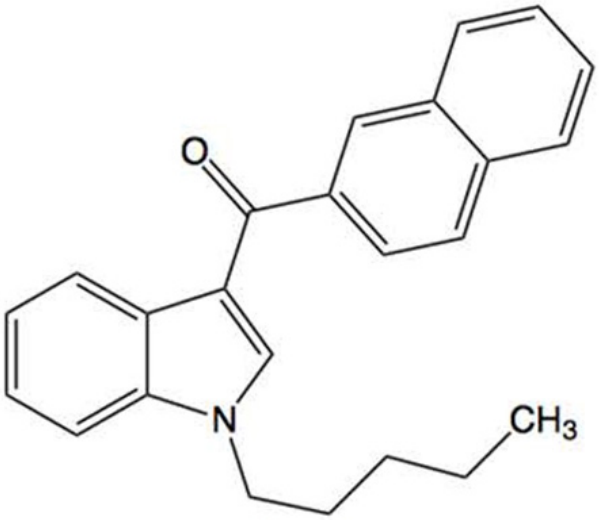
similarity as it pertains to two compounds, XLR-11, a fluorinated derivative of UR-144, and JWH-018 (Figure 1 below). As Professor of Chemistry & Biochemistry at the University of Notre Dame and Director of the Warren Family Research Center for Drug Discovery and Development I have substantial experience in the field. Prior to my current appointments, I received my Ph.D. from Rensselaer Polytechnic Institute and did a three-year postdoctoral appointment at Stanford University. For the past twenty years I have run an active drug discovery research program that explores the therapeutic potential of small organic molecules as potential treatments for cancer and rare disease through the development of chemical and biological synthetic technologies. I am particularly interested in the relationship between chemical structure, molecular conformation (shape) and biological activity and thus I am qualified to provide a scientific opinion in this case.

Figure 1.



XLR-11 (X = F)
UR-144 (X= H)

Appendix I



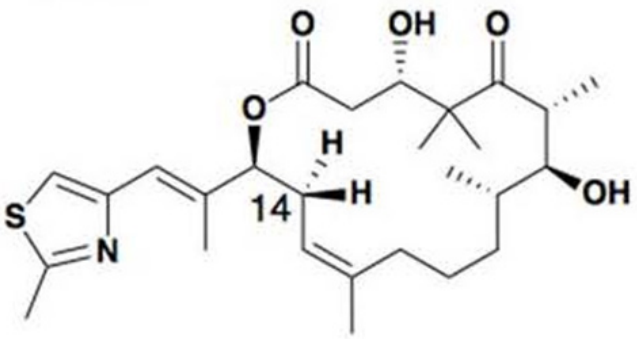
JWH-018

Introductory Example: Epothilone Analogues

As an example from my own experience and perspective with respect to the term "chemical analogue" I present four chemical entities shown in Figure 2. My lab has studied the epothilone class of natural products for the past twenty years. Epothilone D is one of several compounds produced by a myxobacterium, has anti-cancer potential, and was the basis for a FDA-approved cancer drug, Ixempra®. During our studies we developed a unique synthetic route from commercially available and simple chemical entities which allowed us to prepare several naturally occurring epothilones including epothilone D. Minor modifications of the starting materials allowed us to prepare a few structural analogues of epothilone D as shown in Figure 2. Analogue 1 represents a change

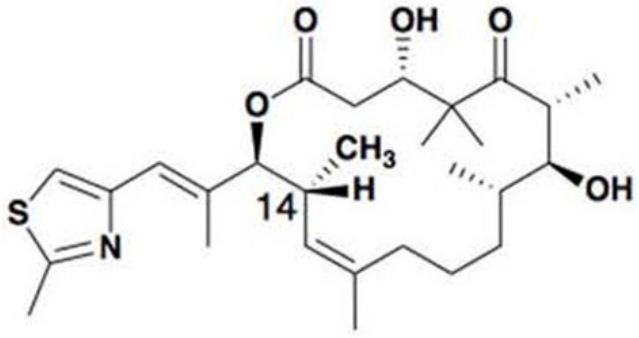
of a single hydrogen atom in epothilone D to a methyl group, a carbon with three hydrogen atoms. Importantly, analogue 1 was prepared as a single stereochemistry at the position labelled 14. In other words, only one of the two hydrogen atoms present in epothilone D have been changed. Quite remarkably, this change eliminated the exciting biological activity against cancer cells observed in epothilone D. Even more surprising was the fact, that the stereoisomer of analogue 1, analogue 2, where the methyl group (R) replaced the other C14-hydrogen, retained the biological anti-cancer activity present in epothilone D. Moreover, we were able to observe enhanced activity in analogue 3 with the addition of a single oxygen atom into analogue 2. Based on the ratio of molecular weights (epothilone D; 491.68), the analogues represent less than a 3% structural change. In other words, 97% of molecule has been unmodified. These compounds, epothilone D and analogues 1-3 represent analogues, from my perspective, due to the fact, the structural modifications are minor and they are prepared by related routes, despite the fact the structural changes may or may not affect the biological activity.

Figure 2.

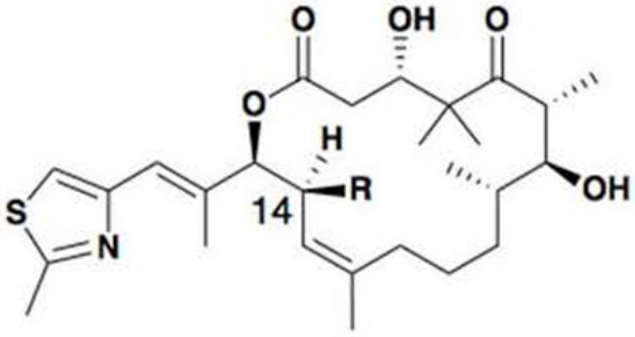


epothilone D

Appendix I



analogue 1



analogue 2 R = -CH_3
analogue 3 R = -OCH_3

Our research has shown that difference in biological activity between analogues 1 and 2 are a result of very different conformational preferences or three-dimensional shape. Despite having identical formulas, analogues 1 and 3 have very different three-dimensional shapes. Thus, despite having identical chemical formulas, some people trained in the art may not consider these

structures as "substantially similar" due to their very different three-dimensional shapes and this results in substantial biological activity differences. One must be very careful in drawing conclusions about the similarities of compounds; the relationship between chemical formula, two-dimensional structure, three-dimensional structure, physical properties, chemical properties, and biological properties are often difficult to predict a priori.

General Chemical Analysis of XLR-11 and JWH-18

An initial analysis of the compounds in question, XLR-11 and JWH-18, first leads us to elemental composition, molecular formula and molecular weight. JWH-018 and XLR-11 are both considered organic molecules, consisting primarily of the elements carbon, hydrogen, nitrogen, and, oxygen. There are several differences with respect to the number of elements, the types of bonding, and the organization of atoms within their structure.

i) XLR-11 has a molecular formula ($C_{24}H_{23}NO$) compared to JWH-18 ($C_{21}H_{28}FNO$). Thus, XLR-11 has three more carbons but five less hydrogens than JWH-18. Based on these molecular formulas the two molecules have a significant difference in degrees of unsaturation. XLR-11 has 14 degrees of unsaturation and JWH-18 having 8 degrees of unsaturation. This type of analysis is valuable to chemists in determining the uniqueness of chemical structure from molecular formula. Degrees of unsaturation are a key feature to structural similarity as it informs the chemist of the number of rings and double

and triple bonds that are possible based upon a unique molecule formula. There is a significant difference between the two compounds in terms of degrees of unsaturation.

ii) XLR-11 possesses one fluorine atom, while JWH-018 does not have any fluorine atoms. Since hydrogen atoms can be substituted for fluorine atoms without affecting degrees of unsaturation, the difference in degrees of unsaturation is exclusively localized in the acyl substituent. Moreover, fluorine and hydrogen have similar steric demands and thus are often exchanged in during medicinal chemistry analogue preparation. However, fluorine incorporation can have dramatic effects on the chemical, physical, and biological properties of an organic molecule. Florine's high electronegativity means it has a large electronic effect at neighboring carbon centers, a substantial effect on the molecule's dipole moment, and the acidity or basicity of other functional groups located near the fluorine atom(s). Fluorine, as well as other halogens are often incorporated into positions susceptible to oxidation due to their poor reactivity with P450 oxidases, metabolic enzymes typically found in the liver, in contrast to hydrogen atoms. In contrast to hydrogen atoms, fluorine substituents can act as a hydrogen bond acceptor. The number of FDA approved drugs which include at least one fluorine atom has significantly increased in recent years. In 2012, 8 of 39 FDA-approved small molecule drugs were fluorinated. Despite the fact of their similar steric size, exchange of a hydrogen atom for a fluorine substituent may often be considered a "substantial structural difference."

Appendix I

Analysis of the Acyl Substituent

The major discrepancy between the two structures involves acyl substituent. In the case of JWH-018, the substituent is a 2-naphthyl group. However, XLR-11 contains a cyclopropyl group, which, in turn, bears four methyl groups. These two groups (i.e., a 2-naphthyl group and a substituted cyclopropyl group) are entirely dissimilar. Selected differences between 2-naphthyl and cyclopropyl groups are as follows:

i) **Aromaticity**: A naphthyl group in JWH-018 is considered aromatic; meaning it is a cyclic system with 10 pi electrons that are conjugated to one another via p orbitals on adjacent atoms. On the other hand, a cyclopropyl group, as seen in XLR-11, has no pi electrons, it's ring atoms do not have p-orbitals and is, thus, not aromatic.

ii) **Ring substituents**: Both acyl substituents contain very different ring structures. JWH-018 contains a planar, fused ring system made up of ten carbon atoms displaying seven additional hydrogen atoms. In a similar position, XLR-11 contains a three membered ring, which this ring is also planar, the cyclopropane displays four methyl substituents and a single hydrogen atom.

iii) **Carbon hybridization**: Beyond the different size of each ring, a significant difference between the two comparative ring systems is the hybridization of their skeletal carbons which affects their structural and chemical properties. The ten carbons of a naphthyl group are all sp2-hybridized, which display bonding

with planar geometry. Carbons that are sp2-hybridized have a significant electron-withdrawing property which affects the rest of the molecule inductively. In contrast, the tetramethyl cyclopropyl group of XLR-11 has zero sp2-hybridized carbons and seven roughly sp3-hybridized carbons. The tetramethylcyclopropyl group is less electron withdrawing and likely has less of an inductive effect on the rest of the molecule. The presence of an sp2 hybridized atom in JWH-018 adjacent to the ketone carbonyl means the naphthyl group is conjugated to carbonyl affecting its physical and chemical properties as well as the rotational barrier between them due to overlapping p-orbitals. This type of strong resonance conjugation is severely diminished in XLR-11.

iv) **Three-dimensional shape**: In contrast to the discussion of the epothilone D and several analogues (Figure 2) prepared and studied in my own laboratory, the two acyl substituents are rigid entities lacking conformational mobility and thus having a single, defined shape. A detailed comparative analysis of the defined size and shape for the naphthyl and cyclopropyl substituents found in JWH-18 and XLR-11 was included in the exhibit prepared by Dr. Terry Stouch. In the report, Figures 2 and 3, demonstrate that the cyclopropyl group is smaller and spherical in shape in comparison to the larger, flat, naphthyl substituent. From a three-dimensional perspective the two substituents are not structurally similar. Dr. Richard Sarpong (UC-Berkeley) continues, "It [naphthyl] is a one-atom thick molecule and can be regarded as a two-dimensional structure. The 1,1,2,2,-tetramethyl cyclopropane group on the other hand

is a three-dimensional structure which projects into space in all three dimensions. This is a substantial difference in structure and in my opinion, these two structures are not structural analogues."

A separate exhibit accurately defines bio-isosteres as chemical groups that can commonly be substituted in drug design. Dr. Garg writes. "[s]imple cyclopropyl groups are commonly used as 'bioisosteres' for aliphatic groups, not aromatic naphthyl groups (J. Med. Chem. 2011, 54, 2529). This highlights the fact that cyclopropyl and naphthyl groups are substantially different." In his report, Dr. Adam Renslo (UCSF) adds generality with, "the practicing organic or medicinal chemist will consider naphthalene and tetramethylcyclopropane to be very different substituents."

v) **Objective measures of similarity**: Using an objective measure of similarity may provide an alternate conclusion. Tanimoto similarity is a chemoinformatic index used in the drug discovery field for the analysis of large groups of compounds. For instance, one may be interested in identifying all the commercially-available compounds that are "similar" to a given lead compound, with the aim of identifying compounds with better biological or pharmacological properties. In the exhibit prepared NMS Labs, forensic chemist Lindsay Reinhold includes the results of a Tanimoto comparison of XLR-11 and JWH-18. The analysis found the two compounds to be outside the typical similarity score cutoffs used by pharmaceutical companies and the NIH screening centers. Moreover, a more detailed analysis of the results showed that

none of the suggested structures identified as above the cutoff, contained cyclopropyl substituents as an isosteric replacement for a naphthyl substructure. The presence of the 4 methyl groups on the cyclopropyl group of XLR-11 makes the differences between JWH-018 and XLR-11 even more pronounced. Thus, based on a fairly objective computational model, Reinhold concluded that XLR-11 and JWH-18 are not substantially similar.

"Substantially similar" is a vague and analysis of its meaning is subjective.

In my analysis of the supporting documentation, I was particularly intrigued by Exhibit 10 which includes correspondence between Cynthia A. Hawkins and the US DOJ Acting US Attorney A. Lee Bentley III and Assistant US Attorney E Jason Boggs, Jr., with regards to United States v. llan Fedida (Case No. 6:12-cr-209-0ri-37DAB). Bentley and Boggs write "As part of its deliberative process, DEA's Office of Diversion Control (OD), specifically the Drug and Chemical Evaluation Section (ODE) consulted with [DEA's Office of Forensic Science (SF)] regarding the chemical structure of UR-144. As part of its analysis ODE recognized this structural distinction and considered it during its deliberative process. On behalf of DEA, ODE determined that UR-144 met the definition of a controlled substance analogue.

Interestingly, Bentley and Boggs also include contradictory evidence; "that [o]ne SF chemist (Senior Research Chemist Dr. Arthur Berrier) opined that UR-144 and JWH-018 were not substantially similar in structure because

JWH-018 has a naphthyl structural group while UR-144 has a tetramethylcyclopropyl group." ODE often consults with SF about the chemical structure of a substance during its analysis and determination of whether or not the substance meets the definition of a controlled substance analogue.

> "***In the opinion of [Dr. Berrier], UR-144 and JWH-018 are not substantially similar in structure and are not analogues***. *While both JWH 018 and UR-144 contain a 1-pentyl-1 H-indol-3-yl ring system as part of their structure, there no similarity in the remaining portion of the molecules. In the case of JWH-018, the substituent attached to the carbonyl carbon is the 1-naphthyl group, a bicyclic aromatic moiety, while with UR-144; the substituent is a tetramethylcyclopropyl group, a three-membered aliphatic ring system. These two substituents are not similar in structure in any manner. The resultant molecules, while having features common to both, also have significant portions that are not similar.*"

Despite Dr. Berrier's perspective the Monograph concluded, "Based upon the comparison of the structures of UR-144 and JWH-018 . . . the two materials are substantially similar." The major argument for this conclusion is the observation that the chemical structures of UR-144 and JWH-018 only differ by the identity of the ring structure attached to the carbonyl group at the 3-position of indole-tetramethylcyclopropyl in the

case of UR-144 and 1-naphthyl in the case of JWH-018. Since classification of a chemical entity as a controlled substance analogue is based upon a chemical structure that is "substantially similar" to the chemical structure of a controlled substance in Schedule I or II we are left to ambiguities present in the term "substantially" and the individual perspectives of chemists.

The subjective nature of the Boos testimony:

The supporting documentation labelled exhibit 8 included testimony from Dr. Terrance Boos, a chemist with the Drug Enforcement Agency. A particular exchange during direct questioning provides evidence for the subjective nature of the analysis he provides:

> *Q: " . . . as part of your preparation for your work with the analogues, did you feel it important to know a little bit about the history of these types of substances?*
>
> *A. Very much so. I think in order to evaluate them and put them in the proper context and arrive at a scientifically sound position, you have to know where they've come from and the history behind them.*

Later, he continues;

> " . . . there's enough of a conserved structure within these two substances, that's why they're part of the same structural class, that they're

> substantially similar in structure. We've just substituted outring structures. [RET: Outring is not a term with which I am familiar but I am inferring that Dr. Boos is using this term to describe the functionality appended to a similar core structure.]
>
> Q. Now, when you make your determinations, do you also – are these determinations also informed by the pharmacology?
>
> A. It is.

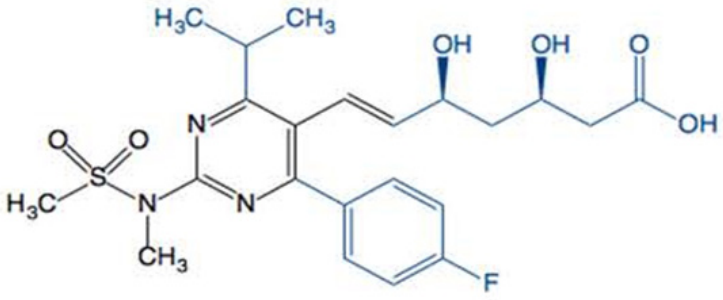
Under cross examination he states;

> "I believe I've arrived at a sound decision based on the science . . . "

These exchanges suggest to me that Dr. Boos' analysis of the chemical structures and their potential structural similarity is being influenced by not only his understanding of their biological properties but potentially the legal ramifications due to relationships to controlled substances. This would not be an objective or even scientifically valid method of analysis. As a final point, I provide two pairs of chemical structures which represent the active pharmaceutical ingredient to four well know, marketed drugs, Figure 4. The first pair of compounds represent "blockbuster drugs" for cholesterol management. Structural similarities are shown in blue. These compounds are marketed by two different companies, each of which hold intellectual property rights to their

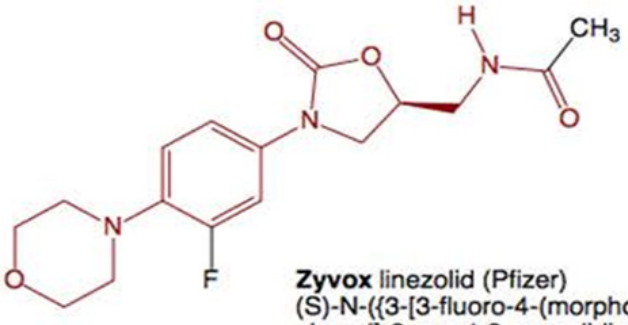
chemical composition. Despite structure similarities in what Dr. Boos would term "outring structures", each molecule has a different heterocyclic core; Crestor has an aminopyrazine core while Lipitor uses a tetrasubstituted pyrrole core. The molecules target the same protein, HMG CoA reductase. It Is reasonable to think that without the knowledge of their shared biological activity that some chemists may view these molecules as substantially similar while others including the USPTO does not.

Figure 4.

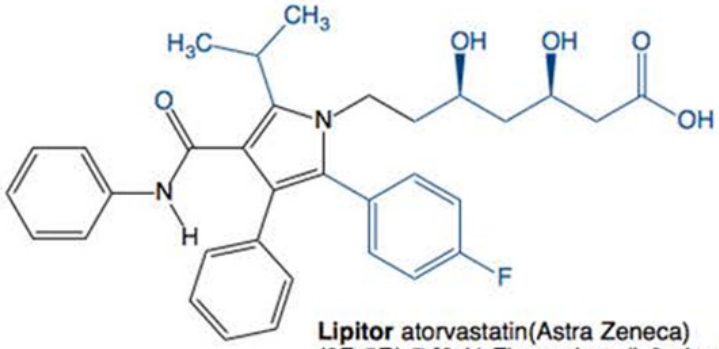


Crestor rosuvastatin (Astra Zeneca)
(3R,5S,6E)-7-[4-(4-fluorophenyl)-2-(N-methylmethanesulfonamido)
-6-(propan-2-yl)pyrimidin-5-yl]-3,5-dihydroxyhept-6-enoic acid

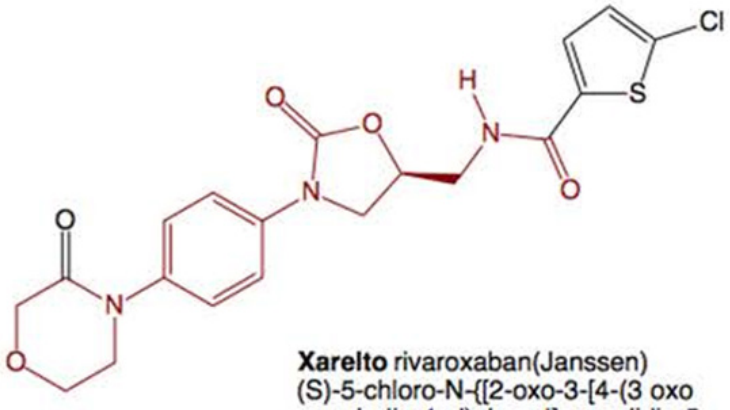
Appendix I



Zyvox linezolid (Pfizer)
(S)-N-({3-[3-fluoro-4-(morpholin-4-yl)
phenyl]-2-oxo-1,3-oxazolidin-5-yl}
methyl)acetamide



Lipitor atorvastatin(Astra Zeneca)
(3R,5R)-7-[2-(4-Fluorophenyl)-3-phenyl-
4-(phenylcarbamoyl)-5-propan-2-ylpyrrol-
1-yl]-3,5-dihydroxyheptanoic acid



Xarelto rivaroxaban(Janssen)
(S)-5-chloro-N-{[2-oxo-3-[4-(3 oxo
morpholin-4-yl)phenyl]oxazolidin-5-
yl]methyl} thiophene-2-carboxamide

The second set of compounds are known as oxazolidinones based on their "substantially similar" core scaffold shown in red. They represent the chemical entities associated with the antibiotic Zyvox and the anticoagulant, Xarelto. These compounds have even more structural overlap, than the previous example except for a different "outring structure". From a biological perspective, Xarelto has no antibiotic activity at all and Zyvox does not show any clinical effects on blood coagulation. These four compounds demonstrate that the relationship between chemical structure and biological function is complicated and is likely to create subjective associations to what should be the more objective chemically-based structural analysis.

In conclusion, it is my opinion that XLR-11 and JWH-018 are not substantially similar in chemical structure based on the detailed analysis of the acyl substituent and its relationship to the overall structure. The term "substantially similar" is vague and there is no scientifically validated, universally accepted method to objectively make comparisons between chemical structures. A chemist is likely to be influenced by his/her experience and perspective and thus such conclusions are inherently subjective. In this report, I have provided an analysis based on my own perspectives, influenced by my own experience, and thus subjective in nature. However, with each point I have tried to declare the influences on that opinion and defend my conclusions with broadly accepted scientific facts and thus as objective as possible.

Appendix I

Richard E. Taylor
May 16, 2016
Associate Vice President for Research
Interim-Director of the Warren Center for
Drug Discovery and Development
Professor of Chemistry & Biochemistry
University of Notre Dame

APPENDIX J — ORDER OF THE UNITED STATES COURT OF APPEALS FOR THE NINTH CIRCUIT, FILED MARCH 4, 2024

UNITED STATES COURT OF APPEALS
FOR THE NINTH CIRCUIT

No. 20-10288
D.C. No. 2:15-cr-00285-APG-EJY-2
District of Nevada, Las Vegas

UNITED STATES OF AMERICA,

Plaintiff-Appellee,

v.

BENJAMIN GALECKI, AKA Zencense Ben,

Defendant-Appellant.

No. 20-10296
D.C. No. 2:15-cr-00285-APG-EJY-1
District of Nevada, Las Vegas

UNITED STATES OF AMERICA,

Plaintiff-Appellee,

v.

CHARLES BURTON RITCHIE, AKA Burton Ritchie,

Defendant-Appellant.

Filed March 4, 2024

Appendix J

ORDER

Before: GOULD and COLLINS, Circuit Judges, and SILVER,* District Judge.

Judge Gould and Judge Collins have voted to deny the petition for rehearing en banc, and Judge Silver so recommends. The full court has been advised of the petition for rehearing en banc, and no judge has requested a vote on whether to rehear the matter en banc. See FED. R. APP. P. 35. The petition for rehearing en banc (20-10288 Dkt. No. 70 and 20-10296 Dkt. No. 58) is denied.

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* The Honorable Roslyn O. Silver, United States District Judge for the District of Arizona, sitting by designation.

APPENDIX K — ORDER OF THE UNITED STATES COURT OF APPEALS FOR THE NINTH CIRCUIT, FILED MARCH 21, 2024

UNITED STATES COURT OF APPEALS
FOR THE NINTH CIRCUIT

No. 20-10288
D.C. No. 2:15-cr-00285-APG-EJY-2
District of Nevada, Las Vegas.

UNITED STATES OF AMERICA,

Plaintiff-Appellee,

v.

BENJAMIN GALECKI, AKA ZENCENSE BEN,

Defendant-Appellant.

No. 20-10296
D.C. No. 2:15-cr-00285-APG-EJY-1
District of Nevada, Las Vegas.

UNITED STATES OF AMERICA,

Plaintiff-Appellee,

v.

CHARLES BURTON RITCHIE,
AKA BURTON RITCHIE,

Defendant-Appellant.

Appendix K

March 21, 2024, Filed

Before: GOULD and COLLINS, Circuit Judges, and SILVER,* District Judge.

ORDER

Appellant Charles Burton Ritchie's' unopposed motion to stay the mandate pending the filing and disposition of a petition for certiorari (20-10288 Dkt. No. 72 and 20-10296 Dkt. No. 60) is GRANTED. *See* FED. R. APP. P. 41(d). To permit the timely filing of a petition for certiorari, the mandate is stayed for 90 days, which time period may be further extended in accordance with Federal Rule of Appellate Procedure 41(d)(2)(A), (B)(i). If a petition for certiorari is timely filed, then the mandate shall be further stayed pending the Supreme Court's disposition of the petition. *See* FED. R. APP. P. 41(d)(2)(B)(ii).

* The Honorable Roslyn O. Silver, United States District Judge for the District of Arizona, sitting by designation.