Cannabinoid Receptor Bioassay:
A Characterization of UR-144, XLR-11, Their Metabolites and Degradants

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Abstract

Designer drugs, first seen in California in 1979, refer to drugs synthesized with structures not currently scheduled under the Controlled Substances Act (CSA) that intentionally mimic the effects of substances that are scheduled under the CSA.[1,2] These drugs are essentially 'designed' to evade the law. Synthetic cannabinoids, one of the fastest growing and widely divergent groups of designer drugs, have become popular in recent years due to the cannabimimetic, or the hallucinogenic, marijuana-like high they offer to users.[3] The similarities in the effects of synthetic cannabinoids and marijuana (Δ^9-tetrahydrocannabinol) are thought to be the result of these compounds interacting with the same G protein-coupled receptors (GPCRs).[4] These GPCRs are more commonly referred to as the cannabinoid binding receptors, CB1 and CB2, and are located in the human body's central and peripheral nervous systems, respectively. Due to their separate locations, CB1 receptors are generally associated with the hallucinogenic effects of cannabinoids, while the CB2 receptors are linked to the therapeutic effects of cannabinoids.[5] However, current scientific literature reveals little information regarding the potencies of these drugs, or the measure of drug activity expressed as the amount of drug required to produce an effect of a given intensity of these compounds at the CB1 and CB2 receptors. This lack of information regarding the cannabimimetic nature of these drugs and the sheer quantity of divergent compounds in this class makes it difficult for authorities to schedule such compounds.

In order to learn more about how different synthetic cannabinoids interact with the CB1 and CB2 receptors, the potency (EC_{50}) of two of these synthetic cannabinoids, UR-144 and XLR-11, as well as ten of their metabolites and degradants, was investigated using a mammalian

cell-based cannabinoid receptor bioassay. The bioassay, developed by Aegis Sciences Corporation®, was chosen for its ability to detect cannabinoid interactions at the CB1 and CB2 receptors, regardless of the structure of each individual synthetic cannabinoid. For UR-144, EC_{50} values of 8.5 ng/mL and 3.6 ng/mL were found for the CB1 and CB2 receptors, respectively. Two of the remaining UR-144 compounds, the UR-144 degradant and the N-(2-hydroxypentyl) metabolite, were determined to be more potent at the CB1 receptors, while the N-(4-hydroxypentyl) and N-(5-hydroxypentyl) metabolites both were found to be more potent than UR-144 at the CB2 receptors. With XLR-11, the CB1 and CB2 EC_{50} values were found to be 101 ng/mL and 6.6 ng/mL, respectively. All three XLR-11 metabolites and degradants tested proved to be more potent than XLR-11 at the CB2 receptors, with one of these three compounds being more potent at the CB1 receptors as well.

Taking into consideration that seven of the ten metabolized and degraded forms of UR-144 and XLR-11 tested demonstrated greater potencies than the parent compounds, and the fact that the metabolized and degraded forms are more likely to be seen in forensic toxicological samples than UR-144 and XLR-11 themselves, that the bioassay shows great potential as a screening method for toxicological samples. In conclusion, this study demonstrated the cannabimimetic activity of several UR-144 and XLR-11 compounds based on their determined potencies at the CB1 and CB2 receptors. This study is important in assisting federal and state controlled substance scheduling agencies by helping to determine if these drugs should be or continue to be scheduled, while also being useful for the field of medicinal chemistry where cannabinoids with a greater potency at the CB2 receptors than the CB1 receptors are being investigated as potential therapeutic treatments.[6]

Introduction

Synthetic cannabinoids are an exponentially diverse group of designer drugs that have received global attention in recent years. This particular class of drugs has become popular amongst users due to the cannabimimetic high they offer, even though no studies exist that demonstrate the safety of these drugs when consumed by humans.[7] There have been reports of UR-144 and XLR-11 causing kidney injury.[8,9] In addition, a time lag currently exists for scheduling synthetic cannabinoids within the United States.[3] The primary cause of cannabinoid scheduling backlogs is the ease in which "new" synthetic cannabinoids can be synthesized without altering the cannabimimetic high. This alteration of scheduled compounds can be as simple as adding on or changing a single substituent. In Figure 1, the sole structural difference between UR-144 and XLR-11 is the substitution of a fluorine atom for a hydrogen atom on the carbon side-chain.

[8,9]

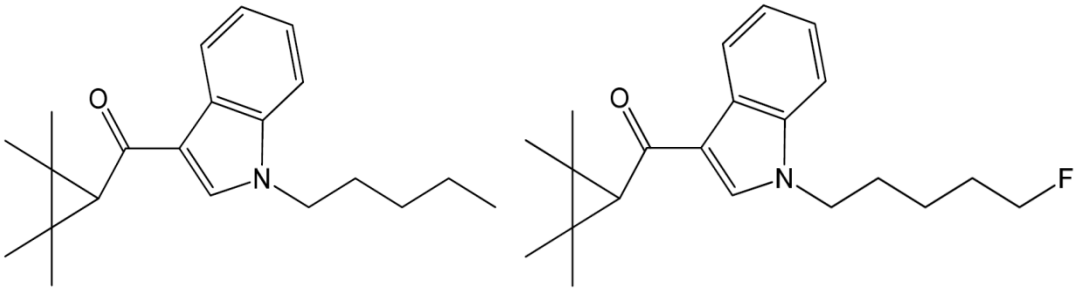

Figure 1. Molecular structures of UR-144 (left) and XLR-11 (right)

The ease with which these compounds are generated results in a vast variety of compounds to be considered for scheduling. In addition, the structural diversity makes it challenging to individually identify these drugs in forensic samples without the use of multiple techniques. This is because current forensic methods, such as gas chromatography-mass spectrometry (GC-MS) and liquid chromatography-tandem mass spectrometry (LC-MS-MS), rely

on identifying compounds based on the mass of the fragments of the molecule generated in the mass spectrometer. When compounds have highly similar structures, like many synthetic cannabinoids, similar fragments will be generated when these compounds are fragmented by a mass spectrometer, making it difficult for analysts to definitively identify one synthetic cannabinoid from another. Essentially, even if a sample comes in that is positive for synthetic cannabinoids, shortcomings in current forensic testing methods may result in a lack of substance identification, while the scheduling lag in current legal standards may result in a lack of consequences for the abuse of the substance.

The cannabimimetic effects synthetic cannabinoids generally possess can actually be attributed to the G protein-coupled receptors (GPCRs) that synthetic cannabinoids and marijuana (Δ^9-tetrahydrocannabinol) both interact with in the body.[4] These specific GPCRs are more commonly referred to as the cannabinoid binding receptors, CB1 and CB2, and are located in the body's central and peripheral nervous systems, respectively. Due to their separate locations, CB1 receptors are generally associated with the hallucinogenic effects of cannabinoids, while the CB2 receptors are linked to therapeutic effects.[5] There is a lack of current scientific data regarding the binding or potencies of these compounds at the CB1 and CB2 receptors, aside from knowing that UR-144 was designed to function as a CB2 receptor agonist by Abbott Laboratories.[8] The consequence is that scheduling synthetic cannabinoids can be difficult when there is minimal scientific data regarding the pharmacology of these drugs.

The aim of this project is to generate scientific information about different synthetic cannabinoids' interactions with the CB1 and CB2 receptors, particularly UR-144, XLR-11, and

several of their associated metabolites and degradants. To characterize how these drugs are interacting with the receptors, cyclic adenosine monophosphate (cAMP) levels within cells can be monitored, due to a link in their pathways. This pathway, in Figure 2, links cannabinoid activity at CB1 and CB2 receptors to a decrease in cells' cAMP levels.

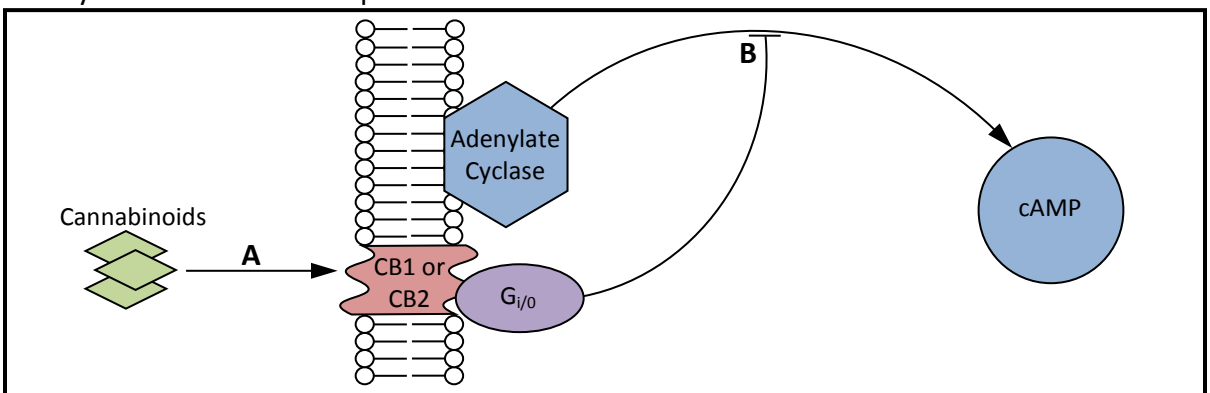

Figure 2. Pathway linking cannabinoid activity at the CB1 and CB2 receptors to cAMP levels within a cell in two parts: (**A**) cannabinoids interact with CB1/2 receptors, which stimulates $G_{i/0}$, (**B**) $G_{i/0}$ inhibits adenylate cyclase from stimulating cAMP production

Within a cell, adenylate cyclase (AC) is the enzyme responsible for stimulating the production of cAMP. When cannabinoids interact with the CB1 or CB2 receptors, the $G_{i/0}$ protein is stimulated, and inhibits AC, which then causes a decrease in the cAMP levels within cannabinoid-dosed cells.[10]

The technique of choice for monitoring cAMP levels in cells is a proprietary mammalian cell-based cannabinoid receptor bioassay developed at Aegis Sciences Corporation®. This is because the bioassay only looks for interactions at the CB1 and CB2 receptors. Current forensic technologies that detect the presence of synthetic cannabinoids, such as enzyme-linked immunosorbent assays (ELISAs) generally rely on the structure of synthetic cannabinoid molecules how certain chemical dyes interact with these structures. With synthetic cannabinoids being so diverse, this means that several ELISAs may need to be run in order to detect the presence of synthetic cannabinoids. The cannabinoid receptor bioassay bypasses

this shortcoming of current technologies and theoretically allows for the detection of any and all synthetic cannabinoids at the same time.

This particular bioassay looks at cAMP levels in cells as an indirect measure of the binding of synthetic cannabinoids to the receptor, which allows for the evaluation of dose-responses of individual analytes. Dose-response curves can then be generated, from which the potency of each compound can be determined for each receptor. Potency here is represented by the EC_{50}, or the effective concentration of a drug required to reach its half-maximal effect.

The basic functionality of the bioassay is due to the use of Perkin Elmer®'s LANCE *Ultra* cAMP Assay kit. The LANCE kit utilizes the principle of time resolved-fluorescence resonance energy transfer (TR-FRET) to measure cAMP levels in a sample. FRET is the process by which fluorescence energy is transferred between an excited donor molecule and an acceptor molecule when these two molecules come together. This particular assay is referred to as time-resolved, because it allows for sequential measurements of fluorescence at different wavelengths. The assay functions by adding cAMP-specific monoclonal antibodies labeled with U*Light*™ dye and europium (Eu)-labeled cAMP tracers to a sample. Then, free cAMP in the sample competes with the Eu-labeled cAMP tracers to bind to the dye-labeled cAMP antibodies, and the sample is excited with a laser at either 320 nm or 340 nm.[11]

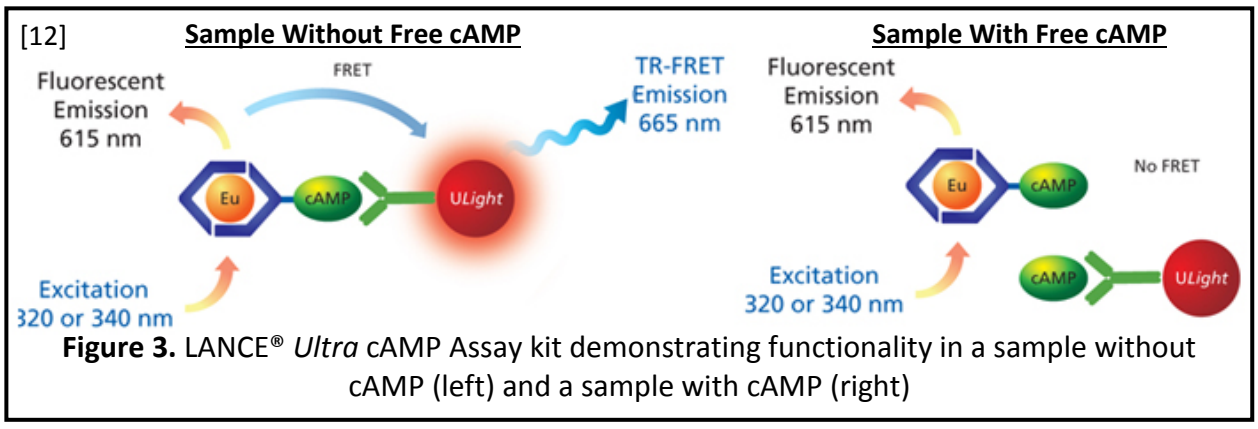

Figure 3. LANCE® *Ultra* cAMP Assay kit demonstrating functionality in a sample without cAMP (left) and a sample with cAMP (right)

Shown in Figure 3, if no free cAMP is present in the sample, then the Eu-labeled tracer will be bound to the dye-labeled cAMP antibodies. In this case, the Eu-labeled tracer will be excited, FRET will occur exciting the dye bound to the cAMP antibodies, and then the dye will emit at 665 nm. In addition to FRET, minor emissions will occur from the Eu-labeled cAMP tracer itself at 615 nm. However, if free cAMP is present in the sample, it will outcompete the Eu-labeled cAMP tracers and bind to the dye-labeled cAMP antibodies. This means that, when the Eu-labeled cAMP tracer is excited, there will be no pathway for FRET to occur, resulting in all emissions occurring solely from the Eu-labeled cAMP tracer at 615 nm.[11]

Methods

This study looked at characterizing UR-144, XLR-11, and ten of their metabolites and degradants using standards from both Cayman Chemical® and Cerilliant Corporation®. The twelve drugs being characterized are in listed Table 1, with their structures in Figures 1 and 4.

Table 1. Twelve UR-144 and XLR-11 drug standards utilized for the characterization study

Drug Standards	
UR-144	UR-144 N-(5-hydroxypentyl) β-D-glucoronide
UR-144 degradant	UR-144 N-pentanoic acid metabolite
UR-144 degradant N-pentanoic acid metabolite	XLR-11
UR-144 N-(2-hydroxypentyl) metabolite	XLR-11 degradant
UR-144 N-(4-hydroxypentyl) metabolite	XLR-11 4-hydroxypentyl metabolite
UR-144 N-(5-hydroxypentyl) metabolite	XLR-11 6-hydroxyindole metabolite

[13]

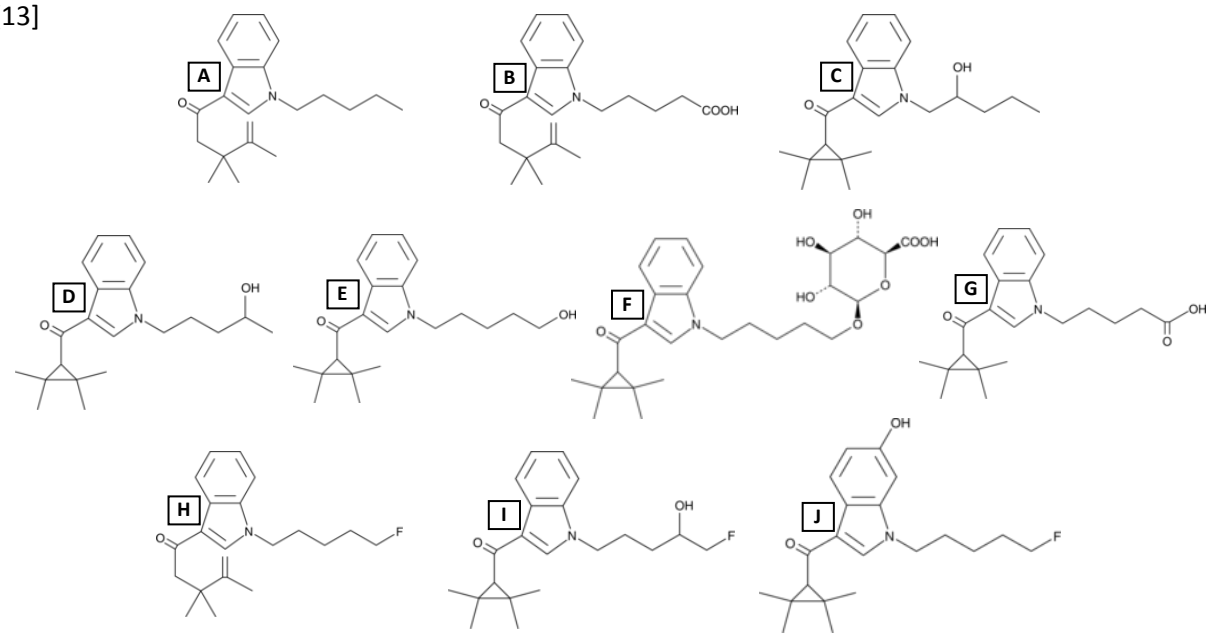

Figure 4. Molecular structures of UR-144 degradant (**A**), UR-144 degradant N-pentanoic acid (**B**), UR-144 N-(2-hydroxypentyl) metabolite (**C**), UR-144 N-(4-hydroxypentyl) metabolite (**D**), UR-144 N-(5-hydroxypentyl) metabolite (**E**), UR-144 N-(5-hydroxypentyl) β-D-glucoronide (**F**), UR-144 N-pentanoic acid metabolite (**G**), XLR-11 degradant (**H**), XLR-11 4-hydroxypentyl metabolite (**I**), and XLR-11 6-hydroxyindole metabolite (**J**).

To carry out the characterization study, the general process of the bioassay began with plating cAMP standards into a 96-well half-area plate to be used for a standard curve. A separate set of 96-well half-area plates was then used to hold collected Chinese Hamster Ovary (CHO) cells that were expressing either CB1 or CB2 receptors. Next, the cells were stimulated with forskolin (FSK) and dosed with differing concentrations of the drug standards seen in Table 1. Each drug was run at sixteen concentrations that could range as high as 150 µg/mL and went down to 0 µg/mL, with all concentrations being run in triplicate. An optimized version of Perkin Elmer's LANCE® *Ultra* cAMP Assay kit was then used on both the plates with cells and the cAMP standards in order to measure the cAMP levels for each cell sample and cAMP standard.

GraphPad *Prism 6* software[14] was used to analyze the fluorescence emissions data using *Prism 6*'s 'log(dose) vs. response curve (four parameter)' curve fit. *Prism 6* was also used to calculate the EC_{50} for each curve via Equation 1.

$$Y = \frac{a-d}{1+(X/c)^b} + d \quad (1)$$

In Equation 1, *Y* refers to the response elicited, *X* is the concentration of drug used to generate the response, *a* is the lower asymptote of the dose-response curve, *b* is the curve's slope factor, *d* is the upper asymptote of the dose-response curve, and *c* is the curve's EC_{50} value.[15] Compounds with smaller EC_{50} values are considered to be more potent than their counterparts, because a smaller value indicates that less of the drug is needed to reach the half-maximal effect when compared to drugs with relatively larger EC_{50} values.

Dose-response curves were considered acceptable if their fit had an R^2 value greater than 0.80, and were optimized based on their bend-points as per Sebaugh.[15] The calculated EC_{50} values were considered to be indicative of cannabimimetic activity if they were found to be less than 1,000 ng/mL.

Results and Discussion

The optimized dose-response curves from characterizations for the CB1 and CB2 receptors can be seen in Figures 5 and 6 respectively. Their corresponding EC_{50} values and R^2 values can be found in Table 2, along with each curve's tested concentration range.

When comparing all twelve dose-response curves between the CB1 and CB2 receptors, seen in Figures 5 and 6, it is noted that there is a great variance in activity, not just different compounds, but between the two receptor types as well. However, the R^2 values for both curves for each of the twelve compounds are equal to 0.96 or higher (Table 2), indicating that

the curves are not only viable, but that there is a good fit between the data points and the curve fit for each of the curves in Figures 5 and 6.

Table 2. Dose-response curve results for UR-144, XLR-11, and their metabolites and degradants, including EC_{50} values and corresponding R^2 values
*'No Activity' is indicative of EC_{50} values greater than 1,000 ng/mL

Drug Standards	CB1		CB2	
	EC_{50} (ng/mL)	R^2	EC_{50} (ng/mL)	R^2
UR-144	8.5	0.99	3.6	0.99
UR-144 degradant	1.9	0.99	6.3	0.99
UR-144 degradant N-pentanoic acid metabolite	No Activity	0.96	No Activity	0.99
UR-144 N-(2-hydroxypentyl) metabolite	2.5	0.99	9.6	0.99
UR-144 N-(4-hydroxypentyl) metabolite	231	0.97	2.4	0.99
UR-144 N-(5-hydroxypentyl) metabolite	273	0.99	0.62	0.99
UR-144 N-(5-hydroxypentyl) β-D-glucoronide	No Activity	0.98	59	0.96
UR-144 N-pentanoic acid metabolite	No Activity	0.98	219	0.99
XLR-11	101	0.99	6.6	0.97
XLR-11 degradant	250	0.98	1.9	0.99
XLR-11 4-hydroxypentyl metabolite	183	0.99	4.7	0.99
XLR-11 6-hydroxyindole metabolite	2.1	0.96	1.2	0.98

For the calculated EC_{50} values, with activity being defined as having an EC_{50} value less than 1000 ng/mL, only one compound out of twelve, UR-144 degradant N-pentanoic acid metabolite, did not demonstrate activity with either of the receptor types. Looking at Table 2, nine of the remaining compounds tested demonstrated some activity at the CB1 receptors, while eleven demonstrated some activity at the CB2 receptors. The highest and lowest

potencies for CB1 corresponded to the UR-144 degradant with an EC_{50} value of 1.9 ng/mL and the UR-144 N-(5-hydroxypentyl) metabolite with an EC_{50} value of 273 ng/mL. For CB2, the highest and lowest potencies were found to belong to the UR-144 N-(5-hydroxypentyl) metabolite and the UR-144 N-pentanoic acid metabolite with EC_{50} values of 0.62 ng/mL and 219 ng/mL, respectively.

Out of the eleven compounds that had some activity for at least one of the two receptors, nine were found to be have lower EC_{50} values at the CB2 receptors than at the CB1 receptors, indicating that these nine compounds are more potent at the CB2 receptors. UR-144 degradant and UR-144 N-(2-hydroxypentyl) metabolite were the only two compounds that went against this trend, as seen in Table 2, with potencies of 1.9 ng/mL and 6.3 ng/mL at the CB1 receptors, and 2.5 ng/mL and 9.6 ng/mL at the CB2 receptors, respectively.

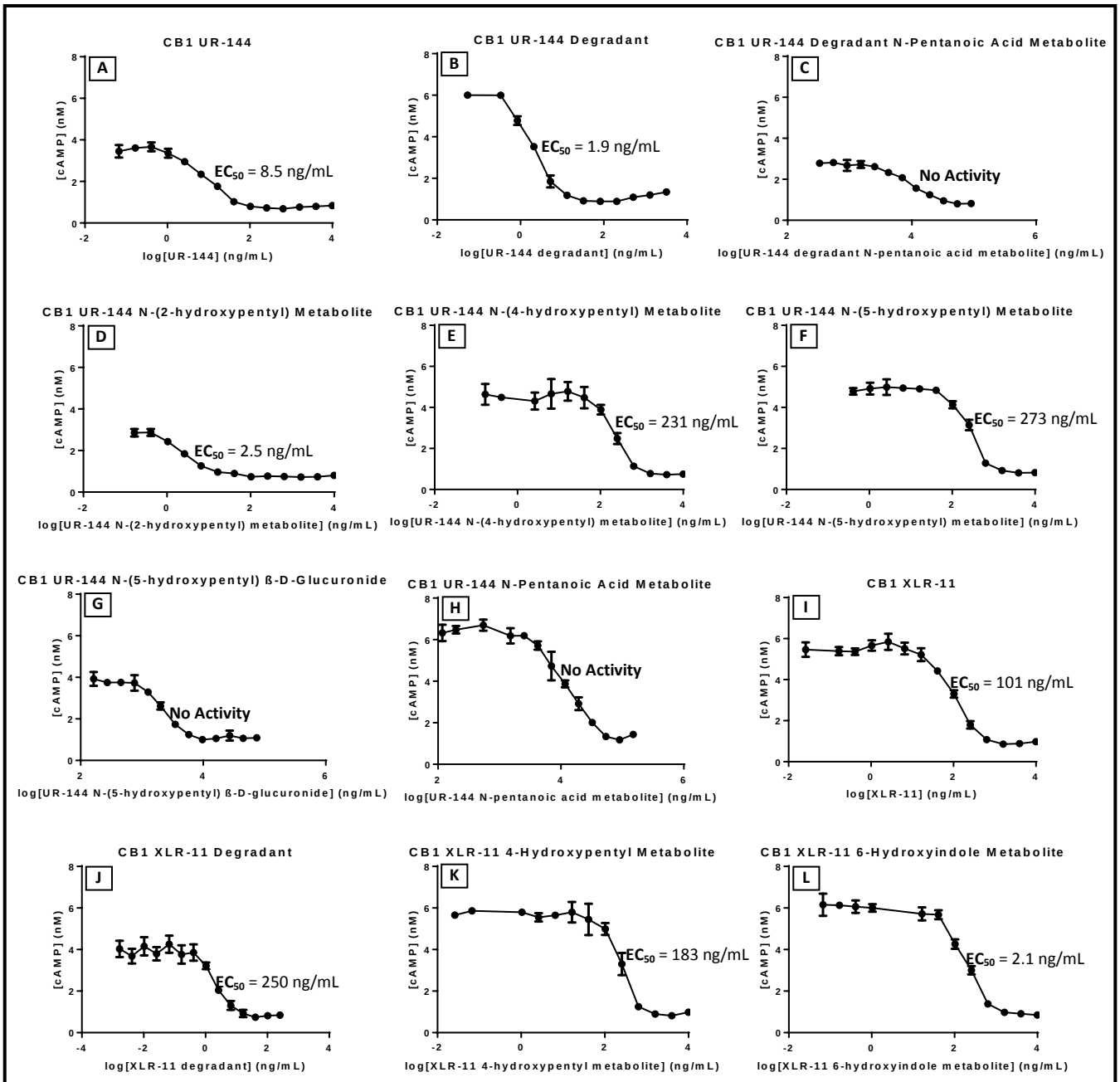

Figure 5. Optimized dose-response curves with their corresponding EC_{50} values from the CB1 receptors for UR-144 (A), UR-144 degradant (B), UR-144 degradant N-pentanoic acid metabolite (C), UR-144 N-(2-hydroxypentyl) metabolite (D), UR-144 N-(4-hydroxypentyl) metabolite (E), UR-144 N-(5-hydroxypentyl) metabolite (F), UR-144 N-(5-hydroxypentyl) β-D-glucoronide (G), UR-144 N-pentanoic acid metabolite (H), XLR-11 (I), XLR-11 degradant (J), XLR-11 4-hydroxypentyl metabolite (K), and XLR-11 6-hydroxyindole metabolite (L).

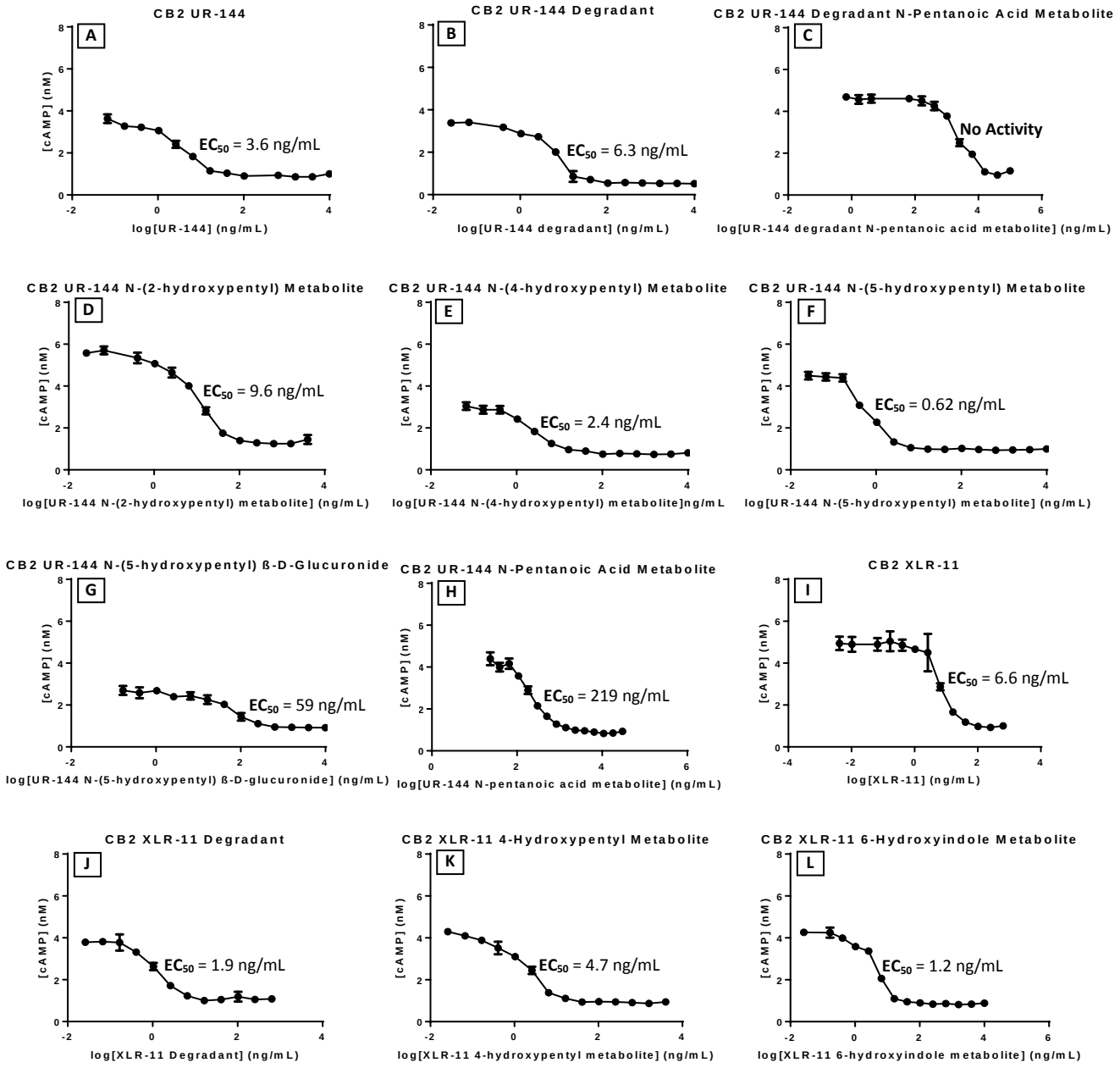

Figure 6. Optimized dose-response curves with their corresponding EC_{50} values from the CB2 receptors for UR-144 (A), UR-144 degradant (B), UR-144 degradant N-pentanoic acid metabolite (C), UR-144 N-(2-hydroxypentyl) metabolite (D), UR-144 N-(4-hydroxypentyl) metabolite (E), UR-144 N-(5-hydroxypentyl) metabolite (F), UR-144 N-(5-hydroxypentyl) β-D-glucoronide (G), UR-144 N-pentanoic acid metabolite (H), XLR-11 (I), XLR-11 degradant (J), XLR-11 4-hydroxypentyl metabolite (K), and XLR-11 6-hydroxyindole metabolite (L)

Table 3. Potency rankings of the eight UR-144 compounds and the four XLR-11 compounds per each receptor

CB1	Potency Ranking	CB2
UR-144 degradant	**1**	UR-144 N-(5-hydroxypentyl) metabolite
UR-144 N-(2-hydroxypentyl) metabolite	**2**	UR-144 N-(4-hydroxypentyl) metabolite
UR-144	**3**	UR-144
UR-144 N-(4-hydroxypentyl) metabolite	**4**	UR-144 degradant
UR-144 N-(5-hydroxypentyl) metabolite	**5**	UR-144 N-(2-hydroxypentyl) metabolite
Tie: UR-144 degradant N-pentanoic acid metabolite, UR-144 N-(5-hydroxypentyl) β-D-glucoronide, UR-144 N-pentanoic acid metabolite	**6**	UR-144 N-(5-hydroxypentyl) β-D-glucoronide
	7	UR-144 N-pentanoic acid metabolite
	8	UR-144 degradant N-pentanoic acid metabolite
XLR-11 6-hydroxyindole metabolite	**1**	XLR-11 6-hydroxyindole metabolite
XLR-11	**2**	XLR-11 degradant
XLR-11 4-hydroxypentyl metabolite	**3**	XLR-11 4-hydroxypentyl metabolite
XLR-11 degradant	**4**	XLR-11

Another key trend to note is that four of the UR-144 metabolites and degradants and all three of the XLR-11 metabolites and degradants have greater potencies than their parent compound for at least one of the receptor types. The UR-144 compounds and XLR-11 compounds are ranked based on their potencies per receptor in Table 3. This trend particularly important to note because it is more likely that the metabolites and degradants will be seen in forensic toxicological samples than their parent compounds. This is due to the parent compounds being metabolized upon entering the body, as well as degradation from volatilization of compounds for confirmatory analysis.[13]

For the UR-144 compounds, at CB1 receptors, UR-144 degradant and UR-144 N-(2-hydroxypentyl) metabolite are more potent than UR-144 itself. Both UR-144 N-(4-hydroxypentyl) metabolite and UR-144 N-(5-hydroxypentyl) metabolite demonstrated greater potencies than UR-144 at the CB2 receptors. As seen in Table 3, UR-144 actually has the third highest potency at both the CB1 and CB2 receptors. With the XLR-11 compounds, all three metabolites and degradants showed greater potency at the CB2 receptors than XLR-11 itself. In addition, XLR-11 degradant also had a greater potency that XLR-11 at the CB1 receptors. The specific values for all of these compounds can be seen in Table 2.

Conclusions

From this study of the UR-144 and XLR-11 family of synthetic cannabinoids, there are three key findings. First, not every compound demonstrated cannabimimetic activity. While all four XLR-11 compounds were found to be active at both CB1 and CB2, and seven of the eight UR-144 compounds showed activity with the CB2 receptors, only five of those seven UR-144 compounds were active with the CB1 receptors. The one hold-out compound that failed to exhibit activity at either CB1 or CB2 was UR-144 degradant N-pentanoic acid metabolite.

The second key observation from this study is that, as seen in Table 2, the majority of the compounds were found to have lower EC_{50} values, and thus greater potencies, at the CB2 receptors than the CB1 receptors. Across the eleven compounds that demonstrated activity for at least one of the two receptor types, this trend holds true for nine of them, including all four XLR-11 compounds. With the UR-144 and XLR-11 family exhibiting generally higher potencies at the CB2 receptors than the CB1 receptors, it is suggested that this group of synthetic cannabinoids may provide users with stronger therapeutic effects as opposed to hallucinogenic

effects. Therefore this group of synthetic cannabinoids may be of interest for the field of medicinal chemistry as a potential source of alternative therapeutic treatments.[6]

Finally, the third major finding, seen in Table 3, is the general ranking of UR-144 and XLR-11 compounds by their potencies per receptor. From the ten metabolites and degradants tested, seven demonstrated greater potencies than their respective parent compound. Knowing that the metabolized and degraded forms are more likely to be seen in forensic toxicological samples than UR-144 and XLR-11 themselves, this suggests that the cannabinoid receptor bioassay may be a powerful tool for screening toxicological samples for cannabinoids.

Future avenues of work include the characterization of the more UR-144 and XLR-11 metabolites and analogs, as well as the more recent fourth generation synthetic cannabinoids. In addition, the cannabinoid receptor bioassay is undergoing automation for future implementation as a forensic screening method for synthetic cannabinoids at Aegis Sciences Corporation®.

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