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Synthesis and pharmacology of 1-deoxy analogs of CP-47,497 and CP-55,940

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Abstract—A series of 1-deoxy analogs of CP-47,497 (**8** and **13**, $n = 0$–7) and 1-deoxy analogs of CP-55,940 (**9**, $n = 0$–7) have been synthesized and their affinities for the cannabinoid CB_1 and CB_2 receptors have been determined. Although the majority of these compounds exhibit selectivity for the CB_2 receptor, none have greater than modest affinity for either receptor. The interactions of these 1-deoxy nontraditional cannabinoids with the CB_2 receptor are discussed.

1. Introduction

In the years following the elucidation of the structure of Δ^9-tetrahydrocannabinol (Δ^9-THC, **1**) and its recognition as the principal psychoactive constituent of marijuana, a number of analogs were synthesized and structure–activity relationships (SAR) based upon the dibenzopyran structure of THC were developed.[1–4] In the early 1980s a group at Pfizer explored the development of analgesics using the potent synthetic cannabinoid, (−)-9-nor-9β-hydroxyhexahydrocannabinol (HHC, **2**), as a template.[5–7] This led to a series of nontraditional cannabinoids in which the oxygen containing pyran ring of THC was removed to provide a bicyclic system that retained the phenolic hydroxyl group of THC and the 9-hydroxyl of HHC. In common with the SAR developed for traditional cannabinoids, it was found that potency was maximum with a 1,1-dimethylheptyl substituent at the 3-position of the aromatic ring and the 9-hydroxyl had the β-orientation.[8] The least complex molecule that fulfilled these requirements was CP-47,497 (**3**, DMH = 1,1-dimethylheptyl), which was found to be more potent than THC in vivo. The addition of a hydroxypropyl group at C-4 of the cyclohexanol ring, as in CP-55,940 (**4**), led to enhanced potency. In 1988 [^{3}H]CP-55,940 was used in work from Howlett's laboratory to identify a cannabinoid receptor in rat brain.[9] This G-protein-coupled, transmembrane receptor is now designated as the CB_1 receptor and is located primarily in the central nervous system.[10–12]

A second receptor, designated CB_2, was originally identified from macrophages present in the spleen,[13] and is expressed primarily in the immune system.[14–18] It has been suggested that this receptor is responsible for the immunomodulatory effects of cannabinoids,[14] a conclusion that is supported by the fact that these effects are absent in CB_2 receptor knockout mice.[19] CB_1 and CB_2 receptors are expressed in a variety of cancer cells and both CB_1 and CB_2 receptor agonists have been found to inhibit tumor growth.[20,21] CB_2 receptors are expressed in C6 glioma cells[22] and both CB_1 and CB_2 receptors are expressed in nonmelanoma skin cancer cells.[23] There is also evidence that the CB_2 receptor is involved in inflammatory pain[24–31] and it has been implicated in cardioprotection.[32] A highly selective CB_2 receptor ligand, JWH-133 (1′,1′-dimethylbutyl)-Δ^8-tetrahydrocannabinol, **5**, causes the regression of both glioma tumors and nonmelanoma skin tumors[22,23] and very recently the CB_2 selective cannabimimetic indole AM1241 (**6**) was found to delay disease progression in a mouse model of amyotrophic lateral sclerosis.[33] Two recent reviews have pointed out the potential of the endocannabinoid system as a therapeutic target and indicate that developing new, selective ligands for the CB_2 receptor in particular may lead to the development of new useful drugs for the treatment of a number diseases.[34,35]

Keywords: CB_1 receptor; CB_2 receptor; Nontraditional cannabinoids; 1-Deoxy cannabinoids.
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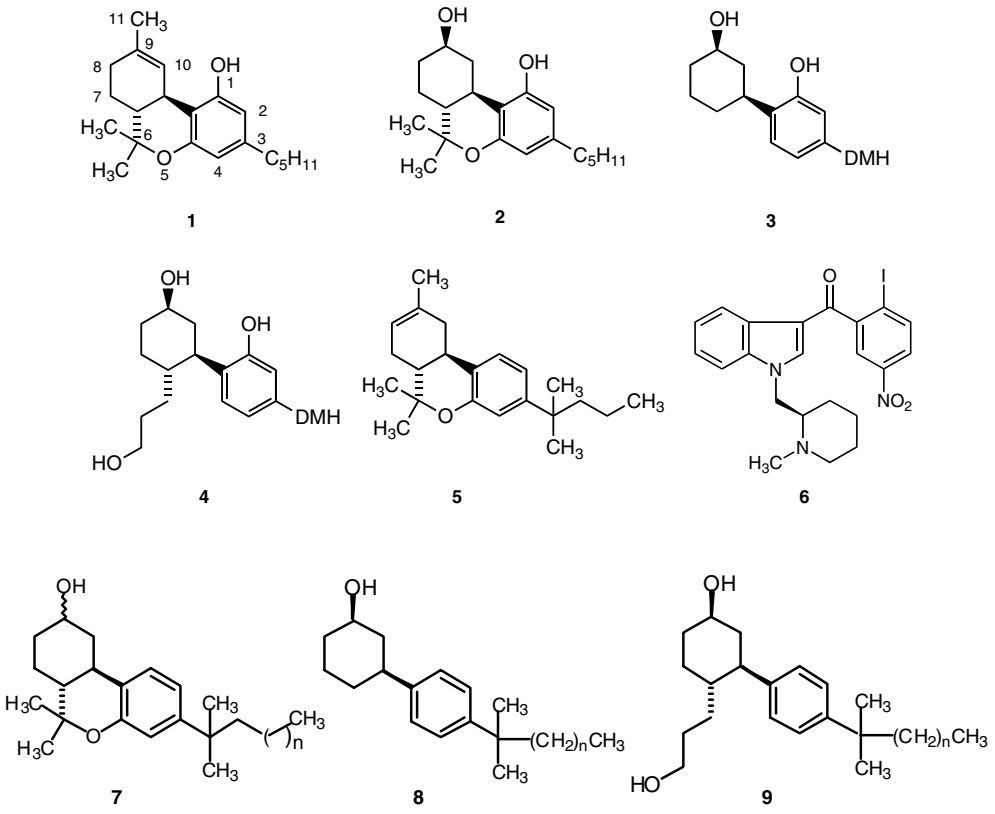
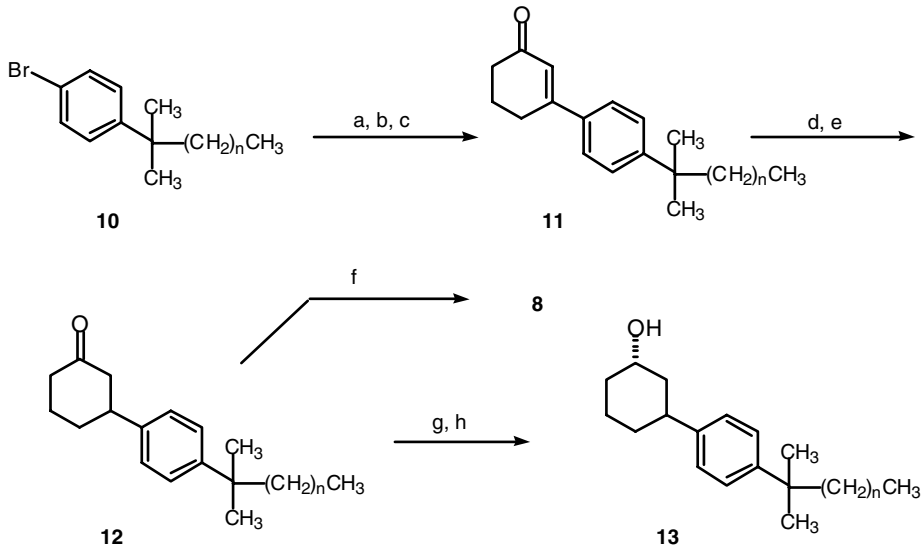


Most of the CB_2 selective agonists currently available are either 1-methoxy or 1-deoxy analogs of Δ^8-THC or are indole derivatives.[36,37] Among these CB_2 selective cannabinoids, the 9-hydroxy-1-deoxyhexahydrocannabinols (**7**, $n = 1$–4, both epimers at C-9), which we described recently, are structurally similar to hexahydrocannabinol (**2**), which is a very potent cannabinoid.[38] Compound **2** was used as a template to develop the potent Pfizer bicyclic nontraditional cannabinoids such as CP-47,497 (**3**) and CP-55,940 (**4**) and it appeared promising to employ hexahydrocannabinols **7** as a template for a series of 1-deoxy analogs of CP-47,497 (**8**, $n = 0$–5) and CP-55,940 (**9**, $n = 0$–5). In analogy to the highly CB_2 selective 1-deoxy-3-(1,1-dimethylalkyl)-Δ^8-THC series we reported several years ago, of which JWH-133 (**5**) is an example, the length of the alkyl side chain in the deoxy analogs of the Pfizer compounds was to range from *tert*-butyl to 1,1-dimethylheptyl.[39] During the course of the present study, the synthetic goals were extended to include the dimethyloctyl and dimethylnonyl analogs (**8**, and **9**, $n = 6$ and 7). The 1-deoxy analog of CP-55,940 (**9**, $n = 5$) was described previously by Melvin et al. and was reported to have moderate affinity for the CB_1 receptor ($K_i = 40.2 \pm 13.5$ nM), although it lacked potency in vivo.[40] The affinity of this compound for the CB_2 receptor was not reported.

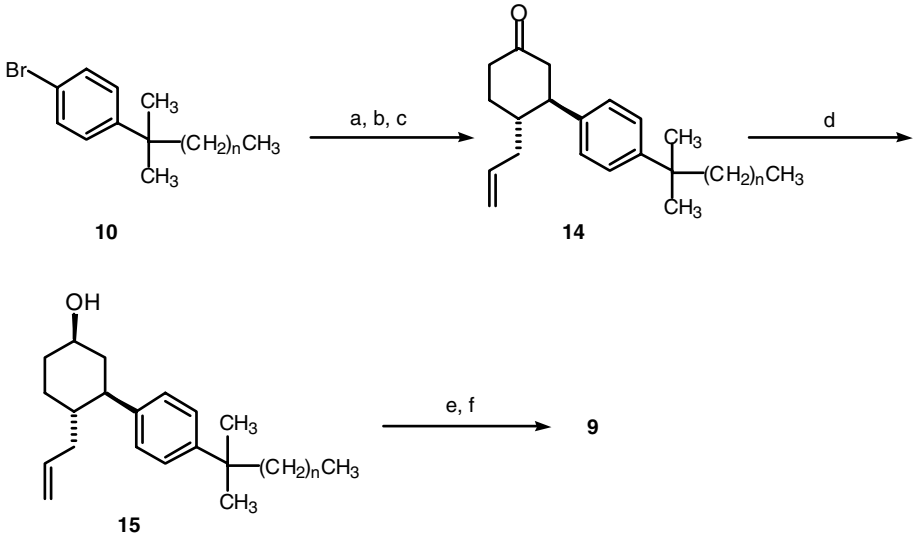
2. Results

The synthesis of the 1-deoxy CP-47,497 analogs is outlined in Scheme 1. This synthesis required a series of 1-bromo-4-(1,1-dimethylalkyl)benzenes (**10**, $n = 0$–7); however, the only compound of this type that is commercially available is 1-bromo-4-*tert*-butylbenzene (**10**, $n = 0$). The synthesis of the other members of this series from the trifluoromethanesulfonate ether of the corresponding phenol via a borate ester was carried out using a sequence developed in our laboratory for the conversion of phenols to the corresponding aryl bromide.[41] Halogen–metal interconversion was applied to aryl bromides **10**, followed by reaction of the organolithium compound with 3-ethoxy-2-cyclohexen-1-one and mild acid treatment to provide 3-arylcyclohexeneones **11**. Dissolving metal reduction using Li in liquid NH_3 gave 3-arylcyclohexanones **12**. Reduction of the carbonyl group of ketones **12** with $NaBH_4$ gave the racemic *cis*-3-arylcyclohexanols (**8**, $n = 0$–7) in which the hydroxyl group has the equatorial conformation. The *trans*-alcohols (**13**, $n = 0$–7) with an axial hydroxyl group were prepared by stereoselective reduction of ketones **12** with K-Selectride® (potassium tri-*sec*-butylborohydride).

The CP-55,940 analogs (**9**, $n = 0$–7) were prepared by a modification of the procedure described by the Pfizer group for the synthesis of CP-55,940 and its homologs.[42] Copper catalyzed conjugate addition of the Grignard reagents derived from aryl bromides **10** to 4-(2-propenyl)-2-cyclohexen-1-one provided racemic ketones **14** as shown in Scheme 2. 4-(2-Propenyl)-2-cyclohexen-1-one was prepared from 3-ethoxy-2-cyclohexen-1-one by the Pfizer procedure and has spectroscopic properties identical to those reported recently by Tanyeli and Özdemirhan.[43] Stereoselective $NaBH_4$ reduction of ketones **14** gave alcohols **15**, which upon hydroboration–oxidation provided 1-deoxy CP-55,940 analogs **9**.



Scheme 1. Reagents and conditions: (a) *n*-BuLi, THF −78 °C; (b) 3-ethoxy-2-cylohexen-1-one, THF, reflux; (c) 10% HCl, 25 °C; (d) Li, NH_3, *t*-BuOH, Et_2O, −78 °C; (e) NH_4Cl, 25 °C; (f) $NaBH_4$, EtOH, 25 °C; (g) K(*sec*-butyl)$_3$BH, THF, −78 °C then 25 °C; (h) NaOH, H_2O_2, EtOH, 25 °C.



Scheme 2. Reagents and conditions: (a) Mg, THF, 35 °C; (b) CuI, −20 °C; (c) 4-(2-propenyl)-cyclohexen-1-one, 25 °C; (d) $NaBH_4$, 0–25 °C; (e) BH_3–THF, THF, 25 °C; (f) H_2O_2, NaOH, H_2O.

The affinities of alcohols **8**, **9**, and **13** for the CB_1 receptor were determined by measuring their ability to displace the potent cannabinoid [^{3}H]CP-55,940 from its binding site in a membrane preparation from rat brain as described by Compton et al.[44] Affinities for the CB_2 receptor were determined by measuring the ability of the compounds to displace [^{3}H]CP-55,940 from a cloned human receptor preparation using the procedure described by Showalter et al.[45] The results of these determinations are summarized in Tables 1 and 2. Also included in Table 1 are the receptor affinities for Δ^8-THC (**1**) and CP-47,497 (**3**). The CB_1 and CB_2 receptor affinities for CP-55,940 are included in Table 2.

The data summarized in Table 1 indicate that none of the CP-47,497 analogs have better than modest affinity for either the CB_1 or CB_2 receptor. The compounds with a β-hydroxyl group (series **8**) have little (**8**, $n = 4$–7) or no affinity (**8**, $n = 0$–3) for the CB_1 receptor. Further, none of this series of compounds has high affinity for the CB_2 receptor (maximum affinity: $K_i = 231 \pm 48$ nM for JWH-324 (**8**, $n = 5$)).

The CB_1 receptor affinities of most of the 9-α-alcohols (series **13**, Table 1) are similar to those of the 9-β-alcohols, having little or no affinity for this receptor. The one exception is JWH-405 (**13**, $n = 6$) with $K_i = 193 \pm 3$ nM. While CB_2 receptor affinities are somewhat better than CB_1 affinities for most compounds of series **13** [exceptions are JWH-232 (**13**, $n = 0$) and JWH-402 (**13**, $n = 7$)], they are still only modest at best. The three 9α-ols (JWH-406, JWH-342, and JWH-405, **13**, $n = 4$, 5, and 6, respectively) have the highest CB_2

Table 1. Receptor affinities (mean ± SEM) of CP-47,497 analogs (**8** and **13**), Δ^9-THC (**1**) and CP-47,497 (**3**)

Compound	K_i (nM)		
	CB_1	CB_2	CB_1/CB_2
Δ^9-THC (**1**)	41 ± 2[a]	36 ± 10[b]	1.1
CP-47,497 (**3**)	2.20 ± 0.47[b]	ND	
8, *n* = 0, JWH-231	>10,000	>10,000	
8, *n* = 1, JWH-294	>10,000	3972 ± 228	>2.5
8, *n* = 2, JWH-296	>10,000	2060 ± 71	>4.9
8, *n* = 3, JWH-323	>10,000	639 ± 45	>16
8, *n* = 4, JWH-403	2113 ± 178	460 ± 28	4.6
8, *n* = 5, JWH-324	2954 ± 191	231 ± 48	13
8, *n* = 6, JWH-404	786 ± 67	672 ± 1.2	1.2
8, *n* = 7, JWH-401	1707 ± 82	1120 ± 40	1.5
13, *n* = 0, JWH-232	>10,000	>10,000	
13, *n* = 1, JWH-295	>10,000	3759 ± 170	>2.7
13, *n* = 2, JWH-297	8626 ± 459	1506 ± 191	5.7
13, *n* = 3, JWH-407	1731 ± 378	546 ± 73	3.2
13, *n* = 4, JWH-406	1028 ± 81	215 ± 6	4.8
13, *n* = 5, JWH-342	645 ± 29	178 ± 15	3.6
13, *n* = 6, JWH-405	193 ± 3	154 ± 8	1.3
13, *n* = 7, JWH-402	749 ± 56	1077 ± 25	0.7

[a] Ref. 44.
[b] Ref. 45.

Table 2. Receptor affinities (mean ± SEM) of CP-55,940 analogs (**9**), CP-55,940 (**4**) and 1-deoxy CP-55,940 (**9**, *n* = 5) reported by Melvin et al. (Ref. 40)

Compound	K_i (nM)		
	CB_1	CB_2	CB_1/CB_2
CP-55,940 (**4**)	0.58 ± 0.07[a]	0.69 ± 0.02[a]	0.8
9, *n* = 5	40.2 ± 13.5[b]	ND	
9, *n* = 0, JWH-384	>10,000	>10,000	
9, *n* = 1, JWH-343	>10,000	1362 ± 112	>7.3
9, *n* = 2, JWH-392	3795 ± 409	1782 ± 196	2.1
9, *n* = 3, JWH-325	579 ± 79	700 ± 15	0.8
9, *n* = 4, JWH-344	308 ± 21	221 ± 5	1.4
9, *n* = 5, JWH-337, Sample 1	547 ± 57	238 ± 41	2.3
9, *n* = 5, JWH-337, Sample 2	203 ± 12	118 ± 3	1.7
9, *n* = 6, JWH-345	266 ± 18	173 ± 18	1.5
9, *n* = 7, JWH-385	566 ± 69	421 ± 36	1.3

[a] Ref. 45.
[b] Ref. 40.

receptor affinities with K_i = 215 ± 6, 178 ± 8, and 154 ± 8 nM, respectively.

None of these CP-47,497 analogs (Table 1, series **8** and **13**) has high affinity for the CB_2 receptor; however, the efficacy of one of them, JWH-406 (**13**, *n* = 4), was evaluated for [^{35}S]GTPγS binding, a functional assay that measures G-protein-coupled receptor activation.[46] Chinese hamster ovary (CHO) cells stably expressing the human CB_2 receptor were employed in this determination (see Section 5). The stimulation is normalized to that produced by a maximally effective concentration (3 μM) of the standard cannabinoid agonist CP-55,940 (**4**). CP-55,940 stimulated [^{35}S]GTPγS binding with an E_{max} value of 85 ± 6.3% above basal (normalized to 100%) and an EC_{50} value of 0.69 ± 0.23 nM. Although JWH-406 has modest affinity for the CB_2 receptor, it is a moderately efficacious partial agonist relative to CP-55,940 with EC_{50} = 39.6 ± 17.9 nM and E_{max} = 66 ± 0.1 % of that produced by CP-55,940.

The CB_1 and CB_2 receptor affinities for 1-deoxy-CP-55940 analogs (series **9**, *n* = 0–7) are summarized in Table 2. Although none of this series of compounds has high affinity for the CB_1 receptor [highest affinity: K_i = 203 ± 12 nM for sample 2 of JWH-337 (**9**, *n* = 5)], all of these compounds have equal or higher CB_1 receptor affinities than the corresponding series of CP-47,497 analogs (**8**, *n* = 0–7). CB_2 receptor affinities for the 1-deoxy-CP-55940 analogs with shorter side chains (series **9**, *n* = 0–3, Table 2) are poor. In contrast, analogs with longer side chains (series **9**, *n* = 4–7, Table 2) show modest affinities for this receptor, ranging from K_i = 118 to 221 nM for sample 2 of JWH-337 to K_i = 421 ± 36 nM for JWH-385.

The dimethylheptyl homolog, JWH-337 (**9**, *n* = 5), had been reported previously to have moderate affinity for the CB_1 receptor.[40] However, in our hands this compound was found to have very little affinity for the CB_1 receptor, with K_i = 547 ± 57 nM. The synthesis was independently repeated after an interval of several months and the second sample had somewhat greater affinity for the CB_1 receptor (K_i = 203 ± 12 nM). The two samples of JWH-337 also had somewhat different CB_2 receptor affinities, with K_i = 238 ± 41 nM for the first sample and K_i = 118 ± 3 nM for the second. Because of the considerable difference in receptor affinities from that reported previously, we were concerned that our CP-55,940 analogs did not have the correct structure, although our synthetic protocol followed closely that described by the Pfizer group.[42] The lowest member of this series, JWH-384 (**9**, *n* = 0) is a crystalline solid and the structure was confirmed by X-ray crystallography.[47] We have no explanation for the considerable difference in CB_1 receptor affinities obtained in this work and the data reported in the earlier work.

3. Discussion

Several compounds in the 1-deoxy-HHC series, which served as a template for the CP-47,947 (**8** and **13**, *n* = 0–7) and CP-55,940 (**9**, *n* = 0–7) analogs, have the desirable combination of good affinity for the CB_2 receptor and modest to poor affinity for the CB_1 receptor.[38] However, none of the CP-47,497 and CP-55,940 analogs (**8**, **13**, and **9**, respectively) have high affinity for the CB_1 receptor or better than modest affinity for the CB_2 receptor. For example, the greatest selectivity for the CB_2 receptor (13-fold) is found in JWH-324 (**8**, *n* = 5), but this compound still has only modest affinity for the CB_2 receptor with K_i = 231 ± 48 nM.

In the 1-deoxy-HHC series (**7**, *n* = 1–3), the 9β-hydroxy compounds have higher affinity for both the CB_1 and CB_2 receptors than their 9α-epimers.[39] Several years ago, Reggio et al. demonstrated that 9β-substituted THC analogs were also more potent than their 9α-epimers.[48] This conclusion was supported by our observa-

tion that, while 9β-methyl-Δ^7-THC had moderate affinity for the CB_1 receptor (K_i = 72 ± 7 nM) and was comparable to Δ^9-THC in potency in the mouse tetrad, the 9α-epimer had little affinity for the CB_1 receptor with K_i = 304 ± 131 nM and lacked potency in vivo.[49] In contrast to these findings, the 9α-isomers have greater affinity than the 9β-hydroxy compounds in the CP-47,497 series presented here. Analysis of the basis for this difference in optimal orientation of CP-47,497 analogs versus those of the THC and 1-deoxy-HHC series requires a review of relevant molecular modeling and site-directed mutagenesis studies carried out on the CB_2 receptor.

A number of studies of the interaction of cannabinoid ligands with the CB_2 receptor have been reported utilizing molecular modeling and/or site-directed mutagenesis of the CB_2 receptor. While many of these studies were restricted to cannabimimetic indoles or CB_2 receptor antagonists/inverse agonists, several dealt with traditional cannabinoids and CP-55,940.[50–52] Song and Bonner found that binding of CP-55,940 to a mutant CB_1 receptor in which a lysine on helix 3 of the receptor was converted to an alanine, K3.28(192)A, resulted in loss of affinity of CP-55,940 for the receptor.[53] It was concluded that this loss of affinity was caused by the loss of a hydrogen bonding interaction between the lysine of the wild type receptor and the phenolic hydroxyl of CP-55,940. In a similar mutation of the CB_2 receptor in which the conserved lysine residue, K3.28(109), was converted to alanine, K3.28(109)A, Tao et al. found that CP-55,940 binding was not attenuated.[50] This mutant CB_2 receptor was fully functional as indicated by forskolin-stimulated inhibition of cAMP. Molecular modeling suggested that a hydrogen bonding cluster consisting of serine 3.31(112) and threonine 3.35(116) is important for CP-55,940 (**4**) binding to the CB_2 receptor.[50] These modeling studies showed that the secondary hydroxyl group has hydrogen bonding interactions with serine 3.31(112) and tyrosine 3.35(116). The phenolic hydroxyl group interacts with asparagine 7.45(291) and the primary hydroxyl interacts with lysine 3.28(109). These modeling results were supported by the observation that [^{3}H]CP-55,940 showed no appreciable specific binding to a doubly mutant CB_2 receptor, in which the lysine to alanine (K109A) mutant was further transformed by substituting serine 3.31(112) with a glycine (K109AS112G), although specific binding of [^{3}H]WIN-55,212-2 was observed. Similarly, when a tryptophan residue in the fourth transmembrane domain of the CB_2 receptor was transformed to alanine (W172A) or leucine (W172L), Rhee et al. found that HU243, a traditional cannabinoid, did not bind to either mutant receptor.[51] Results of a recent modeling study substantially agreed with the work of Tao and that of Rhee.[52]

Based upon the site-directed mutagenesis and modeling studies, it appears probable that CP-55,940 and traditional cannabinoids interact with the CB_2 receptor by a combination of hydrogen bonding and aromatic stacking.[50–52] In contrast to the usual SAR for 9-hydroxy cannabinoids,[38] the 1-deoxy-9α-hydroxy CP-47,497 analogs (**13**, n = 0–7) have greater affinity for the CB_2 receptor than their 9β-epimers (**8**, n = 0–7, Table 1), implying that these deoxy CP-47,497 and CP-55,940 analogs interact in a different orientation than CP-55,940 and traditional cannabinoids in hydrogen bonding to the CB_2 receptor. Based upon docking studies, it was suggested some years ago that the unexpectedly high affinity (K_i = 23.7 ± 7 nM) of 1-deoxy-3-(1′,1′-dimethylheptyl)-Δ^8-THC for the CB_1 receptor could be explained if the orientation of this compound with the receptor was inverted relative to that of Δ^9-THC so that lysine 3.28(192) would hydrogen bond to the benzopyran oxygen of 1-deoxy-3-(1′,1′-dimethylheptyl)-Δ^8-THC.[54] In the case of 1-deoxy-Δ^8-THCs, many of which have very high affinity for the CB_2 receptor,[38,39,54–56] it appears plausible to suggest that they adopt a similar orientation in binding to the CB_2 receptor, which would facilitate hydrogen bonding with the receptor. For JWH-133 (**5**) and other 1-deoxy-3-(1,1-dimethylalkyl)-Δ^8-THCs, CB_2 receptor affinity is relatively insensitive to the length of the alkyl chain. Although the CB_1 receptor affinities in this series decline from 23 nM for the dimethylheptyl compound to 2290 nM for the dimethylpropyl analog, the CB_2 receptor affinities fall in a very narrow range, from 2.9 to 19 nM, for the same compounds.[39] This indicates that in their orientation with the CB_2 receptor the alkyl side chain of the 1-deoxy-3-(1,1-dimethylalkyl)-Δ^8-THCs apparently has no significant interactions with the receptor. Although no modeling or mutagenesis studies have been reported for the 1-deoxy-3-(1,1-dimethylalkyl)-Δ^8-THCs, it is plausible that their hydrogen bonding interactions with the CB_2 receptor involve the benzopyran oxygen serving as a surrogate for the phenolic hydroxyl of traditional cannabinoids and CP-55,940. In the case of the 1-deoxy CP-47,497 and CP-55,940 analogs, however, there is no oxygen substituent on the aromatic ring equivalent to the benzopyran oxygen of the 1-deoxy-Δ^8-THC analogs, leading to diminished hydrogen bonding to the CB_2 receptor.

4. Conclusions

Although the original goal of this work was the synthesis of new selective ligands for the CB_2 receptor, none of the resulting 1-deoxy CP-47,497 and CP-55,940 analogs have high affinity for the CB_2 receptor. The failure of these compounds to have better than modest affinity for the CB_2 receptor does, however, provide some insight into the manner in which 1-deoxy traditional cannabinoids, other traditional cannabinoids, and the Pfizer nontraditional cannabinoids interact with the CB_2 receptor. These results also indicate that the presence of an oxygen substituent appended to the aromatic ring of a traditional cannabinoid is probably essential for CB_2 receptor binding.

5. Experimental

5.1. General

IR spectra were obtained using Nicolet 5DX or Magna spectrometers; ^{1}H and ^{13}C NMR spectra were recorded

on Bruker 300AC and JEOL 500 spectrometers. Mass spectral analyses were performed on a Hewlett-Packard 5890A capillary gas chromatograph equipped with a mass sensitive detector. HRMS data were obtained in the Mass Spectrometry Laboratory, School of Chemical Sciences, University of Illinois. Ether and THF were distilled from Na-benzophenone ketyl immediately before use, and other solvents were purified using standard procedures. Column chromatography was carried out on Sorbent Technologies silica gel (32–63 μ) using the indicated solvents as eluents. All new compounds were homogeneous to TLC and ^{13}C NMR. All target compounds were homogeneous to GLC or TLC in two different solvent systems. TLC was carried out using 200 μm silica gel plates with the indicated solvents. GLC analyses were performed on the Hewlett-Packard 5890A GC/MS using a 60 m carbowax column and helium gas as a carrier. An initial column temperature of 60 °C was employed and the temperature was increased at a rate of 1.5 °C/min to a maximum temperature of 300 °C.

5.2. 3-(4-*tert*-Butylphenyl)cyclohex-2-en-1-one (11, *n* = 0)

To a solution of 0.21 g (0.98 mmol) of 1-bromo-4-*tert*-butylbenzene in 5 mL of dry THF at −78 °C was added 0.75 mL of *n*-butyllithium (1.6 M solution in cyclohexane, 1.2 mmol) and the mixture was stirred for 30 min. A solution of 0.14 g (1.0 mmol) of 3-ethoxy-2-cyclohexen-1-one in 5 mL of THF was added dropwise and the reaction mixture was heated at reflux for 2 h. After cooling to ambient temperature, the reaction mixture was acidified with 10% aqueous HCl and stirred for 30 min and extracted with three portions of ether. The combined ether layers were washed successively with saturated aqueous $NaHCO_3$, and brine. After drying ($MgSO_4$) the solvent was removed in vacuo. And the residue was chromatographed (petroleum ether/ethyl acetate, 9:1) to give 0.16 g (70%) of **11**, $n = 0$, as an off-white crystalline solid: mp 47.5–49.5 °C; ^1H NMR (300 MHz) δ 1.34 (s, 9H), 2.09–2.20 (m, 2H), 2.44–2.54 (m, 2H), 2.77 (t, $J = 6.0$ Hz, 2H), 6.44 (s, 1H), 7.44 (d, $J = 8.6$ Hz, 2H), 7.50 (d, $J = 8.6$ Hz, 2H); ^{13}C NMR (75.5 MHz) δ 22.8, 27.9, 31.1, 34.7, 37.2, 124.7, 125.7, 125.8, 135.7, 153.5, 159.5, 199.9; MS (EI) *m*/*z* (rel intensity) 228 (44), 213 (100), 185 (21), 171 (35), 157 (6), 144 (27), 128 (8), 115 (12), 92 (5), 78 (10), 67 (11), 57 (16).

5.3. (±)-3-(4-*tert*-Butylphenyl)cyclohexanone (12, *n* = 0)

To 50 mL of liquid NH_3 at −78 °C was added 0.100 g (14.4 g atom) of lithium shot and the solution was stirred for 20 min. A solution of 0.15 g (0.66 mmol) of 3-(4-*tert*-butylphenyl)cyclohex-2-en-1-one and 0.049 g (0.66 mmol) of *tert*-butanol in 5 mL of dry ether was added dropwise and the mixture was stirred at −78 °C for 10 min. The reaction was quenched with NH_4Cl and the ammonia was evaporated at ambient temperature. The mixture was diluted with 20 mL of water and 20 mL of ether. The aqueous layer was diluted with brine and the product was extracted with ether. The ethereal solution was washed with successive portions of 10% HCl and saturated brine, dried ($MgSO_4$), and the solvent was removed in vacuo. The orange liquid was purified by chromatography (petroleum ether/ethyl acetate, 95:5) to give 0.15 g (99%) of **12** ($n = 0$): mp 37.5–39.0 °C; IR (neat, ν/cm^{-1}) 3090 (w), 3070 (w), 3053 (w), 2957 (s), 2858 (m), 1716 (s), 1520 (m), 1461 (m), 1428 (w), 1360 (m), 1321 (w), 1272 (m), 1230 (w), 1122 (m), 1026 (w), 835 (m); ^1H NMR (500 MHz) δ 1.32 (s, 9H), 1.72–1.90 (m, 2H), 2.04–2.11 (m, 1H), 2.11–2.19 (m, 1H), 2.32–2.48 (m, 2H), 2.48–2.63 (m, 2H), 2.99 (dddd, $J = 4.1$, 4.1, 11.9, 11.9 Hz, 1H), 7.16 (d, $J = 7.8$ Hz, 2H), 7.35 (d, $J = 7.4$ Hz, 2H); ^{13}C NMR (75.5 MHz) δ 25.5, 31.3, 32.8, 34.4, 41.2, 44.2, 49.0, 125.5, 126.2, 141.3, 149.4, 211.2; MS (EI) *m*/*z* (rel intensity) 230 (27), 216 (18), 215 (100), 187 (2), 173 (4), 145 (7), 129 (6), 117 (7), 91 (6), 69 (8), 57 (11).

5.4. (1*R**,3*S**)-3-(4-*tert*-Butylphenyl)cyclohexanol (JWH-231, 8, *n* = 0)

To a solution of 0.070 g (0.30 mmol) of (±)-3-(4-*tert*-butylphenyl)cyclohexanone in 10 mL of dry ethanol at 0 °C was added 0.091 g (2.4 mmol) of $NaBH_4$. The mixture was warmed to ambient temperature and stirred for 2 h, quenched with 10 mL of 10% HCl, and extracted with ether. The ethereal extracts were washed with successive portions of saturated aqueous $NaHCO_3$, brine and dried ($MgSO_4$). The solvent was removed in vacuo. The residue was purified by column chromatography (petroleum ether/ethyl acetate, 4:1) to give 0.048 g (68%) of JWH-231 as an off-white solid: mp 95.5–96.5 °C; ^1H NMR (500 MHz) δ 1.20–1.35 (m, 11H), 1.37–1.48 (m, 2H), 1.79–1.85 (m, 2H), 1.88 (dp, $J = 3.3$, 13.2 Hz, 1H), 2.01–2.07 (m, 1H), 2.13–2.20 (m, 1H), 2.55 (dddd, $J = 3.2$, 3.2, 12.2, 12.2 Hz, 1H), 3.71 (dddd, $J = 4.4$, 4.4, 10.8, 10.8 Hz, 1H), 7.14 (d, $J = 8.2$ Hz, 2H), 7.32 (d, $J = 8.7$ Hz, 2H); ^{13}C NMR (125.8 MHz) δ 24.4, 31.4, 33.4, 34.3, 35.3, 42.1, 43.1, 71.0, 125.2, 126.3, 143.1, 148.8; MS (EI) *m*/*z* (rel intensity) 232 (17), 218 (20), 217 (100), 215 (11), 199 (14), 171 (2), 157 (4), 145 (7), 131 (13), 117 (9), 105 (4), 91 (12), 57 (16); HRMS: Calcd for $C_{16}H_{24}O$: 232.1827. Found: 232.1832.

5.5. (1*R**,3*R**)-3-(4-*tert*-Butylphenyl)cyclohexanol (JWH-232, 13, *n* = 0)

To a solution of 0.070 g (0.30 mmol) (±)-3-(4-*tert*-butylphenyl)cyclohexanone in 10 mL of dry THF at −78 °C was added 0.60 mL of K-selectride® (1.0 M solution in THF, 0.60 mmol) and the mixture was stirred for 2 h. The reaction was allowed to warm to ambient temperature and was stirred for an additional 1 h. To the reaction mixture was added 0.10 mL of water, 0.40 mL of ethanol, 0.15 mL of 15% NaOH, and 0.15 mL of 30% hydrogen peroxide and the reaction mixture was stirred for 5 min. The reaction mixture was extracted with ether and the ethereal extracts were washed with saturated brine, dried ($MgSO_4$), and the solvent was removed in vacuo. The crude product was chromatographed (petroleum ether/ethyl acetate, 4:1) to give 0.063 g (89%) of JWH-232 as an off-white solid: mp 94.0–96.0 °C; ^1H NMR (500 MHz) δ 1.31 (s, 9H), 1.36–1.51 (m, 2H), 1.51–1.73 (m, 3H), 1.76–1.86 (m, 2H), 1.86–1.94 (m,

1H), 1.94–2.01 (m, 1H), 2.98 (dd, J = 12.4, 12.4 Hz, 1H), 4.19–4.26 (m, 1H), 7.16 (d, J = 8.2 Hz, 2H), 7.32 (d, J = 8.2 Hz, 2H); ^{13}C NMR (125.8 MHz) δ 20.4, 31.4, 32.4, 33.7, 34.3, 36.9, 40.5, 66.9, 125.2, 126.5, 143.9, 148.6; MS (EI) m/z (rel intensity) 232 (13), 217 (28), 214 (28), 199 (100), 171 (5), 157 (21), 145 (8), 131 (15), 117 (12), 105 (5), 91 (15), 77 (5), 57 (18); HRMS: Calcd for $C_{16}H_{24}O$: 232.1827. Found: 232.1826.

5.6. (1*R**,3*S**)-3-[4-(1,1-Dimethylpropyl)phenyl]cyclohexanol (JWH-294, 8, *n* = 1)

This compound was prepared by the procedure used for the preparation of JWH-231. From 0.060 g (0.24 mmol) of (±)-3-[4-(1,1-dimethylpropyl)phenyl]cyclohexanone there was obtained, after chromatography (petroleum ether/ethyl acetate, 4:1), 0.054 g (89%) of JWH-294 as an off-white solid: mp 57–58 °C; ^{1}H NMR (300 MHz) δ 0.68 (t, J = 7.4 Hz, 3H), 1.20–1.34 (m, 8H), 1.34–1.52 (m, 2H), 1.62 (q, J = 7.4 Hz, 2H), 1.69–1.96 (m, 3H), 1.96–2.11 (m, 1H), 2.11–2.23 (m, 1H), 2.56 (dd, J = 12.1, 12.1 Hz, 1H), 3.72 (dddd, J = 4.2, 4.2, 10.8, 10.8 Hz, 1H), 7.13 (d, J = 8.3 Hz, 2H), 7.25 (d, J = 8.2 Hz, 2H); ^{13}C NMR (75.5 MHz) δ 9.1, 24.5, 28.4, 33.4, 35.3, 36.8, 37.5, 42.1, 43.2, 71.0, 125.9, 126.2, 142.9, 147.2; MS (EI) m/z (rel intensity) 246 (6), 218 (17), 217 (100), 199 (4), 171 (4), 157 (1), 145 (5), 131 (12), 117 (8), 105 (4), 91 (11), 81 (6); HRMS: Calcd for $C_{17}H_{26}O$: 246.1984. Found: 246.1988.

5.7. (1*R**,3*R**)-3-[4-(1,1-Dimethylpropyl)phenyl]cyclohexanol (JWH-295, 13, *n* = 1)

This compound was prepared by the procedure used for the preparation of JWH-232. From 0.060 g (0.24 mmol) of (±)-3-[4-(1,1-dimethylpropyl)phenyl]cyclohexanone there was obtained after chromatography (petroleum ether/ethyl acetate, 4:1), 0.055 g (91%) of JWH-295 as an off-white solid: mp 82–83 °C; ^{1}H NMR (300 MHz) δ 0.68 (t, J = 7.4 Hz, 3H), 1.26 (s, 6H), 1.44 (qd, J = 3.2, 12.0 Hz, 1H), 1.50–1.73 (m, 6H), 1.74–2.00 (m, 4H), 2.98 (dd, J = 12.1, 12.1 Hz, 1H), 4.18–4.28 (m, 1H), 7.14 (d, J = 8.2 Hz, 2H), 7.25 (d, J = 8.2 Hz, 2H); ^{13}C NMR (75.5 MHz) δ 9.1, 20.4, 28.4, 32.4, 33.7, 36.8, 37.5, 40.5, 66.8, 125.8, 126.4, 143.8, 146.9; MS (EI) m/z (rel intensity) 246 (10), 228 (6), 218 (17), 217 (100), 199 (71), 171 (8), 157 (4), 145 (7), 131 (16), 117 (13), 105 (6), 91 (17); HRMS: Calcd for $C_{17}H_{26}O$: 246.1984. Found: 246.1978.

5.8. (1*R**,3*S**)-3-[4-(1,1-Dimethylbutyl)phenyl]cyclohexanol (JWH-296, 8, *n* = 2)

This compound was prepared by the procedure used for the preparation of JWH-231. From 0.060 g (0.23 mmol) of (±)-3-[4-(1,1-dimethylbutyl)phenyl]cyclohexanone there was obtained, after chromatography (petroleum ether/ethyl acetate, 4:1), 0.052 g (86%) of JWH-296 as an off-white solid: mp 49–50 °C; ^{1}H NMR (300 MHz) δ 0.81 (t, J = 7.2 Hz, 3H), 1.00–1.17 (m, 2H), 1.17–1.34 (m, 8H), 1.34–1.50 (m, 2H), 1.50–1.63 (m, 2H), 1.75–1.93 (m, 2H), 1.94 (br s, 1H), 1.98–2.10 (m, 1H), 2.10–2.22 (m, 1H), 2.54 (dd, J = 12.0, 12.0 Hz, 1H), 3.71 (dddd, J = 4.2, 4.2, 10.8, 10.8 Hz, 1H), 7.12 (d, J = 8.3 Hz, 2H), 7.25 (d, J = 8.3 Hz, 2H); ^{13}C NMR (75.5 MHz) δ 14.7, 17.9, 24.4, 28.9, 33.4, 35.3, 37.3, 42.1, 43.2, 47.1, 71.0, 125.7, 126.2, 142.9, 147.5; MS (EI) m/z (rel intensity) 260 (9), 218 (20), 217 (100), 199 (12), 171 (4), 145 (5), 131 (13), 117 (10), 105 (5), 91 (13), 81 (6), 77 (4); HRMS: Calcd for $C_{18}H_{28}O$: 260.2140. Found: 260.2141.

5.9. (1*R**,3*R**)-3-[4-(1,1-dimethylbutyl)phenyl]cyclohexanol (JWH-297, 13, *n* = 2)

This compound was prepared by the procedure used for the preparation of JWH-232. From 0.060 g (0.23 mmol) of (±)-3-[4-(1,1-dimethylbutyl)phenyl]cyclohexanone there was obtained, after chromatography (petroleum ether/ethyl acetate, 4:1), 0.052 g (86%) of JWH-297 as a white solid: mp 63.5–65.0 °C; ^{1}H NMR (300 MHz) δ 0.81 (t, J = 7.2 Hz, 3H), 0.99–1.16 (m, 2H), 1.27 (s, 6H), 1.44 (qd, J = 3.3, 12.1 Hz, 1H), 1.50–1.60 (m, 4H), 1.62–1.73 (m, 2H), 1.73–2.00 (m, 4H), 2.98 (dd, J = 12.1, 12.1 Hz, 1H), 4.16–4.26 (m, 1H), 7.13 (d, J = 8.2 Hz, 2H), 7.24 (d, J = 8.3 Hz, 2H); ^{13}C NMR (75.5 MHz) δ 14.7, 17.9, 20.4, 28.9, 32.4, 33.6, 36.8, 37.3, 40.5, 47.1, 66.8, 125.6, 126.3, 143.7, 147.2; MS (EI) m/z (rel intensity) 260 (8), 242 (3), 218 (17), 217 (100), 199 (57), 185 (2), 171 (6), 145 (5), 131 (14), 117 (11), 105 (6), 91 (14); HRMS: Calcd for $C_{18}H_{28}O$: 260.2140. Found: 260.2138.

5.10. (1*R**,3*S**)-3-[4-(1,1-Dimethylpentyl)phenyl]cyclohexanol (JWH-323, 8, *n* = 3)

This compound was prepared by the procedure used for the preparation of JWH-231. From 0.055 g (0.20 mmol) of (±)-3-[4-(1,1-dimethylpentyl)phenyl]cyclohexanone there was obtained, after chromatography (petroleum ether/ethyl acetate, 4:1), 0.043 g (78%) of JWH-323 as an off-white solid: mp 46–48 °C; ^{1}H NMR (300 MHz) δ 0.82 (t, J = 7.2 Hz, 3H), 0.97–1.13 (m, 2H), 1.22 (sextet, J = 7.0 Hz, 2H), 1.23–1.34 (m, 8H), 1.34–1.52 (m, 2H), 1.52–1.63 (m, 2H), 1.74 (br s, 1H), 1.78–1.94 (m, 2H), 1.98–2.11 (m, 1H), 2.11–2.23 (m, 1H), 2.48–2.63 (m, 1H), 3.64–3.79 (m, 1H), 7.12 (d, J = 8.3 Hz, 2H), 7.25 (d, J = 8.3 Hz, 2H); ^{13}C NMR (75.5 MHz) δ 14.0, 23.4, 24.5, 26.9, 28.9, 33.4, 35.3, 37.2, 42.1, 43.2, 44.3, 71.0, 125.7, 126.2, 142.9, 147.5; MS (EI) m/z (rel intensity) 274 (4), 218 (16), 217 (100), 199 (4), 171 (3), 145 (6), 131 (13), 117 (11), 105 (6), 91 (14), 81 (6), 77 (4); HRMS: Calcd for $C_{19}H_{30}O$: 274.2297. Found: 274.2296.

5.11. (1*R**,3*R**)-3-[4-(1,1-Dimethylpentyl)phenyl]cyclohexanol (JWH-396, JWH-407, 13, *n* = 3)

This compound was prepared by the procedure used for the preparation of JWH-232. From 0.055 g (0.20 mmol) of (±)-3-[4-(1,1-dimethylpentyl)phenyl]cyclohexanone there was obtained, after chromatography (petroleum ether/ethyl acetate, 4:1), 0.047 g (85%) of JWH-396 as a pale yellow oil: ^{1}H NMR (500 MHz) δ 0.82 (t, J = 7.4 Hz, 3H), 1.00–1.08 (m, 2H), 1.21 (sextet, J = 7.3 Hz, 2H), 1.27 (s, 6H), 1.45 (qd, J = 3.7,

12.4 Hz, 1H), 1.54–1.60 (m, 3H), 1.60–1.67 (m, 2H), 1.67–1.72 (m, 1H), 1.77–1.85 (m, 2H), 1.87–1.93 (m, 1H), 1.93–2.00 (m, 1H), 2.98 (dddd, J = 3.4, 3.4, 12.4, 12.4 Hz, 1H), 4.20–4.25 (m, 1H), 7.14 (d, J = 8.2 Hz, 2H), 7.24 (d, J = 8.2 Hz, 2H); ^{13}C NMR (125.8 MHz) δ 14.0, 20.4, 23.4, 26.9, 28.9, 32.4, 33.6, 36.8, 37.2, 40.5, 44.4, 66.9, 125.7, 126.4, 143.7, 147.3; MS (EI) *m*/*z* (rel intensity) 274 (5), 256 (2), 218 (15), 217 (100), 199 (36), 171 (3), 145 (3), 131 (7), 117 (6), 105 (3), 91 (7); HRMS: Calcd for $C_{19}H_{30}O$: 274.2297. Found: 274.2294.

5.12. (1*R**,3*S**)-3-[4-(1,1-Dimethylhexyl)phenyl]cyclohexanol (JWH-403, 8, *n* = 4)

This compound was prepared by the procedure used for the preparation of JWH-231. From 0.090 g (0.31 mmol) of (±)-3-[4-(1,1-dimethylhexyl)phenyl]cyclohexanone there was obtained, after chromatography (petroleum ether/ethyl acetate, 4:1), 0.063 g (70%) of JWH-403 as an off-white solid: mp 50–51 °C; ^{1}H NMR (500 MHz) δ 0.81 (t, J = 7.1 Hz, 3H), 1.02–1.11 (m, 2H), 1.13–1.25 (m, 4H), 1.25–1.34 (m, 8H), 1.35–1.47 (m, 2H), 1.53–1.59 (m, 2H), 1.78–1.84 (m, 1H), 1.89 (dp, J = 3.3, 12.8 Hz, 1H), 1.99–2.06 (m, 1H), 2.12–2.21 (m, 2H), 2.54 (dddd, J = 3.2, 3.2, 12.4, 12.4 Hz, 1H), 3.70 (dddd, J = 4.3, 4.3, 11.0, 11.0 Hz, 1H), 7.12 (d, J = 8.2 Hz, 2H), 7.24 (d, J = 8.2 Hz, 2H); ^{13}C NMR (125.8 MHz) δ 14.0, 22.5, 24.3, 24.4, 28.9, 32.5, 33.4, 35.2, 37.2, 42.1, 43.1, 44.5, 70.9, 125.7, 126.2, 142.9, 147.4; MS (EI) *m*/*z* (rel intensity) 288 (2), 218 (16), 217 (100), 199 (3), 171 (2), 145 (4), 131 (10), 117 (8), 105 (4), 91 (10), 81 (5), 77 (2); HRMS: Calcd for $C_{20}H_{32}O$: 288.2453. Found: 288.2455.

5.13. (1*R**,3*R**)-3-[4-(1,1-Dimethylhexyl)phenyl]cyclohexanol (JWH-406, 13, *n* = 4)

This compound was prepared by the procedure used for the preparation of JWH-232. From 0.090 g (0.31 mmol) of (±)-3-[4-(1,1-dimethylhexyl)phenyl]cyclohexanone there was obtained, after chromatography (petroleum ether/ethyl acetate, 4:1), 0.069 g (76%) of JWH-406 as a pale yellow oil: ^{1}H NMR (500 MHz) δ 0.82 (t, J = 7.1 Hz, 3H), 1.02–1.11 (m, 2H), 1.13–1.26 (m, 4H), 1.27 (s, 6H), 1.46 (qd, J = 3.7, 12.4 Hz, 1H), 1.52–1.61 (m, 4H), 1.61–1.73 (m, 2H), 1.77–1.85 (m, 2H), 1.87–1.93 (m, 1H), 1.94–2.00 (m, 1H), 2.97 (dddd, J = 3.4, 3.4, 12.4, 12.4 Hz, 1H), 4.21–4.25 (m, 1H), 7.14 (d, J = 8.2 Hz, 2H), 7.24 (d, J = 8.2 Hz, 2H); ^{13}C NMR (125.8 MHz) δ 14.1, 20.4, 22.5, 24.4, 28.9, 32.4, 32.6, 33.7, 36.9, 37.3, 40.5, 44.6, 66.9, 125.7, 126.4, 143.7, 147.4; MS (EI) *m*/*z* (rel intensity) 288 (3), 218 (16), 217 (100), 199 (40), 171 (3), 145 (5), 131 (7), 117 (6), 105 (3), 91 (7); HRMS: Calcd for $C_{20}H_{32}O$: 288.2453. Found: 288.2451.

5.14. (1*R**,3*S**)-3-[4-(1,1-Dimethylheptyl)phenyl]cyclohexanol (JWH-324, 8, *n* = 5)

This compound was prepared by the procedure used for the preparation of JWH-231. From 0.070 g (0.23 mmol) of (±)-3-[4-(1,1-dimethylheptyl)phenyl]cyclohexanone there was obtained, after chromatography (petroleum ether/ethyl acetate, 4:1), 0.054 g (77%) of JWH-324 as a white solid: mp 59–60 °C; ^{1}H NMR (300 MHz) δ 0.84 (t, J = 6.8 Hz, 3H), 0.98–1.13 (m, 2H), 1.13–1.25 (m, 6H), 1.25–1.35 (m, 8H), 1.35–1.52 (m, 2H), 1.52–1.66 (m, 3H), 1.72–1.96 (m, 2H), 1.98–2.12 (m, 1H), 2.12–2.26 (m, 1H), 2.55 (dd, J = 12.1, 12.1 Hz, 1H), 3.72 (dddd, J = 4.2, 4.2, 10.7, 10.7 Hz, 1H), 7.12 (d, J = 8.2 Hz, 2H), 7.25 (d, J = 8.2 Hz, 2H); ^{13}C NMR (75.5 MHz) δ 14.0, 22.6, 24.5, 24.6, 28.9, 30.0, 31.7, 33.4, 35.3, 37.3, 42.1, 43.2, 44.6, 71.0, 125.7, 126.2, 142.9, 147.5; MS (EI) *m*/*z* (rel intensity) 302 (5), 218 (16), 217 (100), 199 (3), 171 (2), 145 (3), 131 (7), 117 (5), 105 (3), 91 (6), 81 (3); HRMS: Calcd for $C_{21}H_{34}O$: 302.2610. Found: 302.2617.

5.15. (1*R**,3*R**)-3-[4-(1,1-Dimethylheptyl)phenyl]cyclohexanol (JWH-342, 13, *n* = 5)

This compound was prepared by the procedure used for the preparation of JWH-232. From 0.070 g (0.23 mmol) of (±)-3-[4-(1,1-dimethylheptyl)phenyl]cyclohexanone there was obtained, after chromatography (petroleum ether/ethyl acetate, 4:1), 0.063 g (89%) of JWH-342 as an off-white solid: mp 53–54 °C; ^{1}H NMR (500 MHz) δ 0.84 (t, J = 6.9 Hz, 3H), 1.01–1.10 (m, 2H), 1.16–1.26 (m, 6H), 1.27 (s, 6H), 1.46 (qd, J = 3.7, 12.4 Hz, 1H), 1.51 (br s, 1H), 1.52–1.60 (m, 3H), 1.60–1.73 (m, 2H), 1.77–1.85 (m, 2H), 1.87–1.93 (m, 1H), 1.93–2.00 (m, 1H), 2.97 (dddd, J = 3.4, 3.4, 12.4, 12.4 Hz, 1H), 4.19–4.25 (m, 1H), 7.14 (d, J = 8.2 Hz, 2H), 7.24 (d, J = 8.2 Hz, 2H); ^{13}C NMR (125.8 MHz) δ 14.1, 20.4, 22.6, 24.6, 28.9, 30.0, 31.8, 32.4, 33.7, 36.9, 37.3, 40.5, 44.6, 66.9, 125.7, 126.4, 143.7, 147.4; MS (EI) *m*/*z* (rel intensity) 302 (6), 284 (2), 218 (16), 217 (100), 199 (38), 171 (4), 157 (2), 145 (5), 131 (9), 117 (7), 105 (4), 91 (9), 81 (6); HRMS: Calcd for $C_{21}H_{34}O$: 302.2610. Found: 302.2604.

5.16. (1*R**,3*S**)-3-[4-(1,1-Dimethyloctyl)phenyl]cyclohexanol (JWH-404, 8, *n* = 6)

This compound was prepared by the procedure used for the preparation of JWH-231. From 0.095 g (0.30 mmol) of (±)-3-[4-(1,1-dimethyloctyl)phenyl]cyclohexanone there was obtained, after chromatography (petroleum ether/ethyl acetate, 4:1), 0.076 g (79%) of JWH-404 as a white solid: mp 60–61 °C; ^{1}H NMR (500 MHz) δ 0.85 (t, J = 7.1 Hz, 3H), 1.01–1.10 (m, 2H), 1.14–1.21 (m, 6H), 1.21–1.35 (m, 10H), 1.38–1.49 (m, 2H), 1.53–1.59 (m, 2H), 1.62 (br s, 1H), 1.80–1.86 (m, 1H), 1.89 (dp, J = 3.3, 13.3 Hz, 1H), 2.01–2.09 (m, 1H), 2.14–2.22 (m, 1H), 2.56 (dddd, J = 3.3, 3.3, 12.4, 12.4 Hz, 1H), 3.72 (dddd, J = 4.3, 4.3, 10.8, 10.8 Hz, 1H), 7.13 (d, J = 8.2 Hz, 2H), 7.25 (d, J = 8.2 Hz, 2H); ^{13}C NMR (125.8 MHz) δ 14.1, 22.6, 24.5, 24.7, 28.9, 29.2, 30.3, 31.9, 33.4, 35.3, 37.3, 42.1, 43.2, 44.6, 71.1, 125.7, 126.2, 142.9, 147.6; MS (EI) *m*/*z* (rel intensity) 316 (6), 218 (17), 217 (100), 199 (7), 171 (2), 145 (3), 131 (6), 117 (4), 91 (5), 81 (3), 77 (2); HRMS: Calcd for $C_{22}H_{36}O$: 316.2766. Found: 316.2767.

5.17. (1*R**,3*R**)-3-[4-(1,1-Dimethyloctyl)phenyl]cyclohexanol (13, *n* = 6)

This compound was prepared by the procedure used for the preparation of JWH-232. From 0.095 g

(0.30 mmol) of (±)-3-[4-(1,1-dimethyloctyl)phenyl]cyclohexanone there was obtained, after chromatography (petroleum ether/ethyl acetate, 4:1), 0.079 g (83%) of JWH-405 as a white solid: mp 58–59 °C; ^{1}H NMR (500 MHz) δ 0.85 (t, J = 7.1 Hz, 3H), 1.02–1.10 (m, 2H), 1.13–1.21 (m, 6H), 1.21–1.26 (m, 2H), 1.27 (s, 6H), 1.45 (qd, J = 3.2, 12.4 Hz, 1H), 1.52–1.60 (m, 4H), 1.60–1.72 (m, 2H), 1.77–1.85 (m, 2H), 1.87–1.93 (m, 1H), 1.93–2.00 (m, 1H), 2.97 (dddd, J = 3.4, 3.4, 12.4, 12.4 Hz, 1H), 4.20–4.25 (m, 1H), 7.14 (d, J = 8.2 Hz, 2H), 7.24 (d, J = 8.2 Hz, 2H); ^{13}C NMR (125.8 MHz) δ 14.1, 20.4, 22.6, 24.7, 28.9, 29.2, 30.3, 31.9, 32.4, 33.7, 36.8, 37.3, 40.5, 44.6, 66.9, 125.7, 126.4, 143.7, 147.4; MS (EI) *m*/*z* (rel intensity) 316 (2), 218 (16), 217 (100), 199 (32), 171 (3), 145 (2), 131 (6), 117 (4), 105 (2), 91 (4), 81 (3); HRMS: Calcd for $C_{22}H_{36}O$: 316.2766. Found: 316.2773.

5.18. (1*R**,3*S**)-3-[4-(1,1-Dimethylnonyl)phenyl]cyclohexanol (JWH-401, 8, *n* = 7)

This compound was prepared by the procedure used for the preparation of JWH-231. From 0.075 g (0.23 mmol) of (±)-3-[4-(1,1-dimethylnonyl)phenyl]cyclohexanone there was obtained, after chromatography (petroleum ether/ethyl acetate, 4:1), 0.036 g (48%) of JWH-401 as a white solid: mp 52–53 °C; ^{1}H NMR (500 MHz) δ 0.86 (t, J = 7.1 Hz, 3H), 1.01–1.10 (m, 2H), 1.16–1.23 (m, 8H), 1.23–1.35 (m, 10H), 1.38–1.49 (m, 2H), 1.53–1.59 (m, 2H), 1.66 (br s, 1H), 1.80–1.86 (m, 1H), 1.89 (dp, J = 3.3, 13.3 Hz, 1H), 2.02–2.08 (m, 1H), 2.14–2.21 (m, 1H), 2.56 (dddd, J = 3.3, 3.3, 12.4, 12.4 Hz, 1H), 3.73 (dddd, J = 4.3, 4.3, 11.0, 11.0 Hz, 1H), 7.13 (d, J = 8.2 Hz, 2H), 7.25 (d, J = 8.2 Hz, 2H); ^{13}C NMR (125.8 MHz) δ 14.1, 22.6, 24.5, 24.7, 28.9, 29.3, 29.5, 30.3, 31.8, 33.4, 35.3, 37.3, 42.1, 43.2, 44.6, 71.1, 125.8, 126.2, 142.9, 147.6; MS (EI) *m*/*z* (rel intensity) 330 (2), 218 (15), 217 (100), 199 (2), 171 (2), 145 (3), 131 (7), 117 (5), 91 (6), 81 (4), 57 (6); HRMS: Calcd for $C_{23}H_{38}O$: 330.2923. Found: 330.2921.

5.19. (1*R**,3*R**)-3-[4-(1,1-Dimethylnonyl)phenyl]cyclohexanol (JWH-402, 13, *n* = 7)

This compound was prepared by the procedure used for the preparation of JWH-232. From 0.075 g (0.23 mmol) of (±)-3-[4-(1,1-dimethylnonyl)phenyl]cyclohexanone there was obtained, after chromatography (petroleum ether/ethyl acetate, 4:1), 0.050 g (66%) of JWH-402 as a pale yellow oil: ^{1}H NMR (500 MHz) δ 0.86 (t, J = 6.8 Hz, 3H), 1.02–1.10 (m, 2H), 1.13–1.23 (m, 8H), 1.23–1.30 (m, 8H), 1.45 (qd, J = 3.6, 12.4 Hz, 1H), 1.51–1.60 (m, 4H), 1.61–1.72 (m, 2H), 1.77–1.87 (m, 2H), 1.87–1.93 (m, 1H), 1.93–2.00 (m, 1H), 2.97 (dddd, J = 3.4, 3.4, 12.2, 12.2 Hz, 1H), 4.20–4.25 (m, 1H), 7.14 (d, J = 8.2 Hz, 2H), 7.24 (d, J = 8.2 Hz, 2H); ^{13}C NMR (125.8 MHz) δ 14.1, 20.4, 22.6, 24.7, 28.9, 29.3, 29.5, 30.3, 31.8, 32.4, 33.7, 36.8, 37.3, 40.5, 44.6, 66.9, 125.7, 126.4, 143.7, 147.4; MS (EI) *m*/*z* (rel intensity) 330 (4), 312 (1), 218 (15), 217 (100), 199 (34), 171 (3), 145 (4), 131 (9), 117 (7), 105 (4), 91 (8); HRMS: Calcd for $C_{23}H_{38}O$: 330.2923. Found: 330.2930.

5.20. (±)-3-Ethoxy-6-(2-propenyl)-2-cyclohexen-1-one

To a solution of 50 mmol of LDA, prepared from 20.0 mL of *n*-butyllithium (2.5 M in hexanes) and 7.4 mL (53 mmol) of diisopropylamine in 5 mL of dry THF at −78 °C under nitrogen, was added dropwise 6.72 g of 3-ethoxy-2-cyclohexen-1-one (47.9 mmol) in 5 mL of THF. The reaction was stirred for 30 min and 17.5 mL (100 mmol) of HMPA and 8.9 mL (100 mmol) of 3-bromo-1-propene were added successively. The reaction was warmed to ambient temperature and stirred for 1.5 h, quenched with water, and most of the solvent was removed in vacuo. The remaining mixture was diluted with 300 mL of ice water and extracted with ether. The ether extracts were washed with water, dried ($MgSO_4$), and the solvent was removed in vacuo. The bright yellow liquid was distilled in vacuo to give 6.08 g (70%) of (±)-3-ethoxy-6-(2-propenyl)-2-cyclohexen-1-one as a yellow liquid: ^{1}H NMR (300 MHz) δ 1.36 (t, J = 7.0 Hz, 3H), 1.63–1.78 (m, 1H), 2.00–2.32 (m, 3H), 2.38–2.47 (m, 2H), 2.57–2.70 (m, 1H), 3.90 (qd, J = 0.8, 6.8 Hz, 2H), 4.99–5.12 (m, 2H), 5.32 (s, 1H), 5.69–5.87 (m, 1H); ^{13}C NMR (75.5 MHz) δ 13.8, 25.5, 27.9, 33.7, 44.4, 63.9, 101.9, 116.2, 136.1, 176.6, 200.0; MS (EI) *m*/*z* (rel intensity) 180 (52), 165 (5), 151 (9), 139 (6), 123 (7), 112 (58), 97 (6), 84 (100), 69 (79), 55 (22). These data agree in all respects with those reported previously.[42]

5.21. (±)-4-(2-Propenyl)-2-cyclohexen-1-one

A solution of 6.00 g (33.3 mmol) of (±)-3-ethoxy-6-(2-propenyl)-2-cyclohexen-1-one in 15 mL of dry ether was added to 0.65 g (17 mmol) of $LiAlH_4$ in 50 mL of ether at 0 °C, and the mixture was stirred for 1 h. The reaction was quenched with 70 mL of 2 M aqueous HCl, stirred for 30 min, and extracted with ether. The ethereal extracts were washed with saturated $NaHCO_3$, dried ($MgSO_4$), and the solvent was removed in vacuo. The yellow liquid was distilled to give 3.55 g (78%) of (±)-4-(2-propenyl)-2-cyclohexen-1-one as a pale yellow liquid: ^{1}H NMR (300 MHz) δ 1.62–1.80 (m, 1H), 2.03–2.18 (m, 1H), 2.24 (t, J = 7.1 Hz, 2H), 2.39 (dd, J = 4.8, 12.4 Hz, 1H), 2.47 (t, J = 4.7 Hz, 1H), 2.49–2.58 (m, 1H), 5.12 (d, J = 12.5 Hz, 2H), 5.71–5.89 (m, 1H), 5.99 (dd, J = 2.4, 10.2 Hz, 1H), 6.88 (d, J = 10.2 Hz, 1H); ^{13}C NMR (75.5 MHz) δ 28.3, 35.6, 36.7, 38.7, 117.3, 129.0, 135.1, 153.9, 199.4; GC/MS (EI) *m*/*z* (rel intensity) 136 (10), 118 (13), 108 (7), 95 (24), 79 (100), 67 (96), 53 (21). These data agree in all respects with those reported previously.[43]

5.22. (3*R**,4*S**)-3-(4-*tert*-Butylphenyl)-4-(2-propenyl)-cyclohexanone 3 (14, *n* = 0)

A solution of 0.43 g (2.0 mmol) of 1-bromo-4-*tert*-butylbenzene in 10 mL of THF and a crystal of iodine were added under N_2 to 0.10 g (4.1 mmol) of Mg ribbon. The mixture was warmed slightly and stirred for 1.5 h, cooled to −20 °C and 0.060 g (0.32 mmol) of CuI was added followed by 0.28 g (2.0 mmol) of (±)-4-(2-propenyl)-2-cyclohexen-1-one in 2 mL of THF. The reaction was stirred for 2 h at ambient temperature, quenched

with 15 mL of saturated NH_4Cl, and the product was extracted with three portions of ether. The combined ether layers were washed with saturated NH_4Cl, brine and dried ($MgSO_4$). The solvent was removed in vacuo and the crude product was chromatographed (petroleum ether/ethyl acetate, 95:5) to give 0.39 g (71%) of (3*R**,4*S**)-3-(4-*tert*-butylphenyl)-4-(2-propenyl)cyclohexanone as a clear pale yellow liquid: ^{1}H NMR (500 MHz) δ 1.31 (s, 9H), 1.41–1.52 (m, 1H), 1.69 (dt, J = 8.6, 13.8 Hz, 1H), 1.98–2.10 (m, 2H), 2.22 (dq, J = 4.3, 13.8 Hz, 1H), 2.44–2.49 (m, 2H), 2.49–2.60 (m, 2H), 2.68 (td, J = 5.0, 11.2 Hz, 1H), 4.92 (d, J = 17.4 Hz, 1H), 4.97 (d, J = 10.1 Hz, 1H), 5.67 (dddd, J = 5.8, 8.4, 10.1, 17.1 Hz, 1H), 7.10 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.2 Hz, 2H); ^{13}C NMR (125.8 MHz) δ 30.8, 31.3, 34.4, 37.3, 41.0, 41.1, 49.3, 49.5, 116.6, 125.6, 126.8, 136.1, 140.0, 149.6, 210.9; MS (EI) *m*/*z* (rel intensity) 270 (7), 255 (44), 228 (70), 214 (23), 213 (100), 185 (10), 145 (64), 131 (20), 117 (28), 105 (12), 91 (29), 79 (18).

5.23. (1*R**,3*R**,4*S**)-3-(4-*tert*-Butylphenyl)-4-(2-propenyl)cyclohexanol (15, *n* = 0)

To a solution of 0.38 g (1.4 mmol) of (3*R**,4*S**)-3-(4-*tert*-butylphenyl)-4-(2-propenyl)cyclohexanone in 5 mL of methanol at 0 °C was added 0.053 g (1.4 mmol) of $NaBH_4$. The reaction was stirred at ambient temperature for 30 min, diluted with 15 mL of saturated brine, and extracted with three portions of ether. The combined ether layers were washed with brine, dried ($MgSO_4$), and the solvent was removed in vacuo. The crude product was chromatographed (petroleum ether/ethyl acetate, 9:1) to give 0.21 g (55%) of (1*R**,3*R**,4*S**)-3-(4-*tert*-Butylphenyl)-4-(2-propenyl)cyclohexanol as a pale yellow liquid: ^{1}H NMR (500 MHz) δ 1.04–1.14 (m, 1H), 1.31 (s, 9H), 1.33–1.41 (m, 1H), 1.47–1.62 (m, 3H), 1.89 (br s, 1H), 1.91–1.99 (m, 2H), 2.03–2.10 (m, 2H), 2.23–2.30 (m, 1H), 3.68 (dddd, J = 4.3, 4.3, 11.0, 11.0 Hz, 1H), 4.86 (d, J = 17.0 Hz, 1H), 4.91 (d, J = 10.1 Hz, 1H), 5.63 (dddd, J = 6.0, 8.2, 10.4, 16.8 Hz, 1H), 7.07 (d, J = 8.2 Hz, 2H), 7.30 (d, J = 8.2 Hz, 2H); ^{13}C NMR (125.8 MHz) δ 29.7, 31.4, 34.3, 35.4, 37.9, 41.4, 44.5, 47.8, 70.8, 115.8, 125.2, 127.1, 137.0, 141.6, 148.9; MS (EI) *m*/*z* (rel intensity) 272 (16), 257 (36), 230 (41), 212 (79), 197 (58), 145 (38), 131 (28), 117 (41), 91 (38), 79 (17), 67 (17), 57 (100).

5.24. (1*R**,3*R**,4*R**)-3-(4-*tert*-Butylphenyl)-4-(3-hydroxypropyl)cyclohexanol (JWH-384, 9, *n* = 0)

To a solution of 0.20 g (0.73 mmol) of (1*R**,3*R**,4*S**)-3-(4-*tert*-butylphenyl)-4-(2-propenyl)cyclohexanol in 5 mL of dry THF at 0 °C under N_2 was added 1.5 mL (1.5 mmol) of BH_3-THF (1.0 M in THF). The reaction was stirred at ambient temperature for 45 min, cooled to 0 °C, and 0.20 mL of water, 0.45 mL of 2 M aqueous NaOH, and 0.25 mL (2.0 mmol) of 30% H_2O_2 were added. The reaction mixture was stirred at ambient temperature for 45 min, quenched with 50 mL of brine, and extracted with ether. The ethereal solution was washed with brine, dried ($MgSO_4$), and the solvent was removed in vacuo. The crude product was chromatographed (petroleum ether/ethyl acetate, 1:1) to give 0.18 g (84%) of JWH-384 as a white crystalline solid: mp 134.8–135.8 °C; ^{1}H NMR (500 MHz) δ 0.84–0.93 (m, 1H), 1.08–1.16 (m, 1H), 1.23–1.28 (m, 2H), 1.28–1.34 (m, 10H), 1.34–1.61 (m, 5H), 2.00 (dq, J = 3.5, 13.5 Hz, 1H), 2.03–2.12 (m, 2H), 2.22–2.30 (m, 1H), 3.39–3.51 (m, 2H), 3.70 (dddd, J = 4.4, 4.4, 10.8, 10.8 Hz, 1H), 7.06 (d, J = 8.2 Hz, 2H), 7.29 (d, J = 8.2 Hz, 2H); ^{13}C NMR (125.8 MHz) δ 29.3, 29.8, 29.9, 31.4, 34.3, 35.4, 41.2, 44.6, 48.3, 63.1, 70.8, 125.3, 127.0, 141.7, 148.9; MS (EI) *m*/*z* (rel intensity) 290 (12), 272 (46), 257 (20), 145 (85), 131 (74), 117 (54), 57 (100); HRMS: Calcd for $C_{19}H_{30}O_2$: 290.2246. Found: 290.2253.

5.25. (1*R**,3*R**,4*R**)-3-[4-(1,1-Dimethylpropyl)phenyl]-4-(3-hydroxypropyl)cyclohexanol (JWH-343, *n* = 1)

The title compound was prepared using the procedure employed for the preparation of JWH-384. From 0.16 g (0.56 mmol) of (1*R**,3*R**,4*S**)-3-[4-(1,1-dimethylpropyl)phenyl]-4-(2-propenyl)cyclohexanol there was obtained, after chromatography (petroleum ether/ethyl acetate, 1:1), 0.15 g (88%) of JWH-343 as a pale yellow liquid: ^{1}H NMR (500 MHz) δ 0.66 (t, J = 7.3 Hz, 3H), 0.80–0.95 (m, 1H), 1.06–1.15 (m, 1H), 1.16–1.30 (m, 8H), 1.30–1.58 (m, 5H), 1.61 (q, J = 7.5 Hz, 2H), 1.99 (dq, J = 3.5, 13.5 Hz, 1H), 2.04–2.12 (m, 2H), 2.22–2.29 (m, 1H), 3.38–3.49 (m, 2H), 3.71 (dddd, J = 4.1, 4.1, 11.0, 11.0 Hz, 1H), 7.06 (d, J = 8.2 Hz, 2H), 7.23 (d, J = 8.2 Hz, 2H); ^{13}C NMR (125.8 MHz) δ 9.1, 28.4, 29.3, 29.8, 30.0, 35.5, 36.9, 37.5, 41.3, 44.6, 48.3, 63.1, 70.8, 126.0, 127.0, 141.6, 147.3; MS (EI) *m*/*z* (rel intensity) 314 (11), 276 (20), 275 (100), 257(24), 239 (11), 207 (16), 197 (14), 171 (14), 157 (11), 145 (27), 131 (34), 121 (15), 91 (14), 71 (9), 55 (10); HRMS: Calcd for $C_{20}H_{32}O_2$: 304.2402. Found: 304.2411.

5.26. (1*R**,3*R**,4*R**)-3-[4-(1,1-Dimethylbutyl)phenyl]-4-(3-hydroxypropyl)cyclohexanol (JWH-392, 9, *n* = 2)

The title compound was prepared using the procedure employed for the preparation of JWH-384. From 0.22 g (0.73 mmol) of (1*R**,3*R**,4*S**)-3-[4-(1,1-dimethylbutyl)phenyl]-4-(2-propenyl)cyclohexanol there was obtained, after chromatography (petroleum ether/ethyl acetate, 1:1), 0.20 g (86%) of JWH-392 as a pale yellow liquid: ^{1}H NMR (500 MHz) δ 0.81 (t, J = 7.3 Hz, 3H), 0.84–0.91 (m, 1H), 1.01–1.16 (m, 3H), 1.24–1.30 (m, 8H), 1.30–1.52 (m, 5H), 1.52–1.57 (m, 3H), 1.99 (dq, J = 3.4, 13.5 Hz, 1H), 2.04–2.12 (m, 2H), 2.22–2.29 (m, 1H), 3.38–3.49 (m, 2H), 3.71 (dddd, J = 4.4, 4.4, 10.8, 10.8 Hz, 1H), 7.05 (d, J = 8.2 Hz, 2H), 7.23 (d, J = 8.7 Hz, 2H); ^{13}C NMR (125.8 MHz) δ 14.8, 18.0, 28.9, 29.4, 29.9, 30.0, 35.5, 37.4, 41.3, 44.6, 47.2, 48.4, 63.1, 70.8, 125.8, 127.0, 141.6, 147.7; MS (EI) *m*/*z* (rel intensity) 318 (12), 276 (24), 275 (100), 257 (31), 239 (10), 207 (21), 171 (15), 157 (18), 145 (31), 131 (48), 121 (26), 91 (15); HRMS: Calcd for $C_{21}H_{34}O_2$: 318.2559. Found: 318.2557.

5.27. (1*R**,3*R**,4*R**)-3-[4-(1,1-Dimethylpentyl)phenyl]-4-(3-hydroxypropyl)cyclohexanol (JWH-325, 9, *n* = 3)

The title compound was prepared using the procedure employed for the preparation of JWH-384. From

0.19 g (0.60 mmol) of (1*R**,3*R**,4*S**)-3-[4-(1,1-dimethylpentyl)phenyl]-4-(2-propenyl)cyclohexanol there was obtained, after chromatography (petroleum ether/ethyl acetate, 1:1), 0.15 g (75%) of JWH-325 as a pale yellow liquid: ^{1}H NMR (500 MHz) δ 0.81 (t, J = 7.3 Hz, 3H), 0.85–0.91 (m, 1H), 0.97–1.05 (m, 2H), 1.05–1.16 (m, 1H), 1.20 (sextet, J = 7.3 Hz, 2H), 1.23–1.30 (m, 8H), 1.30–1.53 (m, 5H), 1.53–1.60 (m, 3H), 1.98 (dq, J = 3.4, 13.5 Hz, 1H), 2.03–2.11 (m, 2H), 2.20–2.28 (m, 1H), 3.35–3.48 (m, 2H), 3.69 (dddd, J = 4.4, 4.4, 11.0, 11.0 Hz, 1H), 7.05 (d, J = 8.2 Hz, 2H), 7.22 (d, J = 8.2 Hz, 2H); ^{13}C NMR (125.8 MHz) δ 14.0, 23.3, 26.9, 28.8, 29.3, 29.8, 29.9, 35.4, 37.2, 41.3, 44.4, 44.5, 48.3, 63.0, 70.7, 125.8, 126.9, 141.6, 147.6; MS (EI) *m*/*z* (rel intensity) 332 (7), 276 (21), 275 (100), 257 (24), 239 (10), 207 (21), 171 (18), 157(19), 145 (36), 131 (65), 121 (19), 117 (22), 91 (23), 57 (20); HRMS: Calcd for $C_{22}H_{36}O_2$: 332.2715. Found: 332.2707.

5.28. (1*R**,3*R**,4*R**)-3-[4-(1,1-Dimethylhexyl)phenyl]-4-(3-hydroxypropyl)cyclohexanol (JWH-344, 9, *n* = 4)

The title compound was prepared using the procedure employed for the preparation of JWH-384. From 0.18 g (0.55 mmol) of (1*R**,3*R**,4*S**)-3-[4-(1,1-dimethylhexyl)-phenyl]-4-(2-propenyl)cyclohexanol there was obtained after, chromatography (petroleum ether/ethyl acetate, 1:1), 0.17 g (90%) of JWH-344 a pale yellow liquid: ^{1}H NMR (300 MHz) δ 0.83 (t, J = 6.9 Hz, 3H), 0.87–0.99 (m, 1H), 0.99–1.12 (m, 2H), 1.12–1.26 (m, 5H), 1.26–1.34 (m, 8H), 1.34–1.51 (m, 4H), 1.51–1.64 (m, 4H), 1.96–2.16 (m, 3H), 2.19–2.35 (m, 1H), 3.36–3.53 (m, 2H), 3.71 (dddd, J = 4.2, 4.2, 10.8, 10.8 Hz, 1H), 7.07 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 8.1 Hz, 2H); ^{13}C NMR (75.5 MHz) δ 14.0, 22.5, 24.3, 28.9, 29.4, 29.9, 30.0, 32.5, 35.5, 37.3, 41.4, 44.6 × 2, 48.4, 63.1, 70.8, 125.8, 127.0, 141.6, 147.7; MS (EI) *m*/*z* (rel intensity) 346 (12), 328 (4), 276 (21), 275 (100), 257 (25), 239 (8), 197 (10), 171 (14), 145 (26), 131 (41), 117 (17), 91 (15); HRMS: Calcd for $C_{23}H_{38}O_2$: 346.2871. Found: 346.2868.

5.29. (1*R**,3*R**,4*R**)-3-[4-(1,1-Dimethylheptyl)phenyl]-4-(3-hydroxypropyl)cyclohexanol (JWH-337, 9, *n* = 5)

The title compound was prepared using the procedure employed for the preparation of JWH-384. From 0.18 g (0.52 mmol) of (1*R**,3*R**,4*S**)-3-[4-(1,1-dimethylheptyl)phenyl]-4-(2-propenyl)cyclohexanol there was obtained, after chromatography (petroleum ether/ethyl acetate, 1:1), 0.16 g (84%) of JWH-337 as a pale yellow liquid: ^{1}H NMR (500 MHz) δ 0.83 (t, J = 6.9 Hz, 3H), 0.86–0.91 (m, 1H), 0.99–1.06 (m, 2H), 1.06–1.14 (m, 1H), 1.14–1.26 (m, 6H), 1.26–1.33 (m, 8H), 1.33–1.52 (m, 4H), 1.52–1.58 (m, 4H), 1.99 (dq, J = 3.4, 13.3 Hz, 1H), 2.04–2.12 (m, 2H), 2.21–2.29 (m, 1H), 3.37–3.49 (m, 2H), 3.70 (dddd, J = 4.2, 4.2, 11.0, 11.0 Hz, 1H), 7.05 (d, J = 8.2 Hz, 2H), 7.22 (d, J = 8.2 Hz, 2H); ^{13}C NMR (125.8 MHz) δ 14.1, 22.6, 24.6, 28.9, 29.3, 29.7, 29.8, 30.0, 31.7, 35.5, 37.3, 41.3, 44.6, 44.7, 48.3, 63.1, 70.8, 125.8, 127.0, 141.6, 147.7; MS(EI) *m*/*z* (rel intensity) 360 (9), 342 (3), 276 (20), 275 (100), 257 (26), 239 (8), 197 (12), 171 (18), 157 (16), 145 (34), 131 (53), 117 (24); HRMS: Calcd for $C_{24}H_{40}O_2$: 360.3028. Found: 360.3028.

5.30. (1*R**,3*R**,4*R**)-3-[4-(1,1-Dimethyloctyl)phenyl]-4-(3-hydroxypropyl)cyclohexanol (JWH-345, 9, *n* = 6)

The title compound was prepared using the procedure employed for the preparation of JWH-384. From 0.13 g (0.36 mmol) of (1*R**,3*R**,4*S**)-3-[4-(1,1-dimethyloctyl)phenyl]-4-(2-propenyl)cyclohexanol there was obtained, after chromatography (petroleum ether/ethyl acetate, 1:1), 0.12 g (88%) of JWH-345 as a pale yellow liquid: ^{1}H NMR (500 MHz) δ 0.85 (t, J = 7.1 Hz, 3H), 0.87–0.91 (m, 1H), 0.98–1.06 (m, 2H), 1.06–1.14 (m, 1H), 1.14–1.22 (m, 8H), 1.22–1.32 (m, 8H), 1.32–1.51 (m, 3H), 1.51–1.58 (m, 5H), 1.98 (dq, J = 3.2, 13.8 Hz, 1H), 2.02–2.13 (m, 2H), 2.19–2.29 (m, 1H), 3.35–3.48 (m, 2H), 3.69 (dddd, J = 4.4, 4.4, 10.8, 10.8 Hz, 1H), 7.05 (d, J = 8.2 Hz, 2H), 7.22 (d, J = 8.2 Hz, 2H); ^{13}C NMR (125.8 MHz) δ 14.1, 22.6, 24.7, 28.8, 29.2, 29.3, 29.8, 29.9, 30.2, 31.8, 35.4, 37.3, 41.3, 44.5, 44.6, 48.3, 63.1, 70.8, 125.8, 126.9, 141.6, 147.6; MS (EI) *m*/*z* (rel intensity) 374 (3), 276 (20), 275 (100), 257 (22), 239 (9), 207 (16), 197 (10), 171 (13), 157 (12), 145 (27), 131 (44), 121 (12), 117 (15), 91 (14), 55 (12); HRMS: Calcd for $C_{25}H_{42}O_2$: 374.3185. Found: 374.3182.

5.31. (1*R**,3*R**,4*R**)-3-[4-(1,1-Dimethylnonyl)phenyl]-4-(3-hydroxypropyl)cyclohexanol (JWH-385, 9, *n* = 7)

The title compound was prepared using the procedure employed for the preparation of JWH-384. From 0.12 g (0.32 mmol) of (1*R**,3*R**,4*S**)-3-[4-(1,1-dimethylnonyl)phenyl]-4-(2-propenyl)cyclohexanol there was obtained, after chromatography (petroleum ether/ethyl acetate, 1:1), 0.12 g (95%) of JWH-385 as a pale yellow liquid: ^{1}H NMR (500 MHz) δ 0.86 (t, J = 6.9 Hz, 3H), 0.87–0.91 (m, 1H), 0.99–1.06 (m, 2H), 1.06–1.14 (m, 1H), 1.14–1.23 (m, 10H), 1.23–1.29 (m, 8H), 1.29–1.52 (m, 5H), 1.52–1.60 (m, 3H), 1.99 (dq, J = 3.2, 13.8 Hz, 1H), 2.04–2.11 (m, 2H), 2.21–2.29 (m, 1H), 3.37–3.49 (m, 2H), 3.70 (dddd, J = 4.1, 4.1, 11.0, 11.0 Hz, 1H), 7.05 (d, J = 8.2 Hz, 2H), 7.22 (d, J = 8.2 Hz, 2H); ^{13}C NMR (125.8 MHz) δ 14.1, 22.6, 24.7, 28.9, 29.3, 29.4, 29.5, 29.8, 30.0, 30.3, 31.8, 35.5, 37.3, 41.3, 44.6, 44.7, 48.3, 63.1, 70.8, 125.8, 127.0, 141.6, 147.7; MS (EI) *m*/*z* (rel intensity) 388 (3), 276 (18), 275 (100), 257 (20), 239 (8), 197 (8), 171 (11), 157 (10), 145 (21), 131 (33), 121 (11), 117 (11), 91 (10), 55 (10); HRMS: Calcd for $C_{26}H_{44}O_2$: 388.3341. Found: 388.3350.

5.32. Receptor binding experiments

5.32.1. Materials. Frozen whole brains of male Sprague–Dawley rats were obtained from Harlan (Dublin, VA). CP-55,940 was provided by Pfizer (Groton, CT). [^{3}H]CP-55,940 was purchased from NEN Life Science Products, Inc. (Boston, MA). Lipofectamine reagent was purchased from Life Technologies (Gaithersburg, MD). Human CB_2 cDNA was provided by Dr. Sean Munro (MRC Lab, Cambridge, UK). DMEM and geneticin were purchased from Gibco BRL (Grand Island, NY). Fetal clone II was purchased from Hyclone Laboratories, Inc. (Logan, UT). Aquasil was purchased from Pierce (Rockford, IL). GF/C glass-fiber filters

(2.4 cm) were purchased from Baxter (McGaw Park, IL). Polyethylenimine and bovine serum albumin were purchased from Sigma Chemical Co. (St. Louis, MO). Scintillation vials and Budget Solve scintillation fluid were purchased from RPI Corp. (Mount Prospect, IL).

5.32.2. Development of hCB_2-CHO cell line. Chinese hamster ovary cells were maintained in Dulbecco's modified Eagle's medium (DMEM) with 10% fetal clone II and 5% CO_2 at 37 °C in a Forma incubator. Cell lines were created by transfection of CB_2pcDNA3 into CHO cells by the Lipofectamine reagent. Stable transformants were selected in growth medium containing geneticin (1 mg/mL, reagent). Colonies of about 500 cells were picked (about 2 weeks post transfection) and allowed to expand, then tested for expression of receptor mRNA by Northern blot analysis. Cell lines containing moderate to high levels of receptor mRNA were tested for receptor binding properties. Transfected cell lines were maintained in DMEM with 10% fetal clone II plus 0.3–0.5 mg/mL geneticin and 5% CO_2 at 37 °C in a Forma incubator.

5.32.3. Membrane preparation. hCB_2-CHO cells were harvested in phosphate-buffered saline containing 1 mM EDTA and centrifuged at 500*g*. Cell pellets (for CB_2) or whole rat brains (for CB_1) were homogenized in 10 mL of solution A (50 mM Tris–HCl, 320 mM sucrose, 2 mM EDTA, 5 mM $MgCl_2$, pH 7.4). The homogenate was centrifuged at 1600*g* (10 min), the supernatant saved, and the pellet washed three times in solution A with subsequent centrifugation. The combined supernatants were centrifuged at 100,000*g* (60 min). The (P_2 membrane) pellet was resuspended in 3 mL of buffer B (50 mM Tris–HCl, 1 mM EDTA, 3 mM $MgCl_2$, pH 7.4) to yield a protein concentration of approximately 1 mg/mL. The tissue preparation was divided into equal aliquots, frozen on dry ice, and stored at −70 °C.

5.33. Competition binding assays

5.33.1. CB_1 assay. [H^3]CP-55,940 binding to P_2 membranes was conducted as described elsewhere,[57] except whole brain (rather than cortex only) was used. CP-55,940 and all cannabinoid analogs were prepared by suspension in assay buffer from a 1 mg/mL ethanolic stock without evaporation of the ethanol (final concentration of no more than 0.4%). Displacement curves were generated by incubating drugs with 1 nM of [^{3}H]CP-55,940. [^{3}H]CP-55,940 bound to rat brain membranes with a K_D value of 0.68 ± 0.07 nM and a B_{max} value of 1.7 ± 0.11 pmol/mg. The assays were performed in triplicate, and the results represent the combined data from three individual experiments.

5.33.2. CB_2 assay. Binding was assayed by a modification of Compton et al.[44] CP-55,940 and all cannabinoid analogs were prepared by suspension in assay buffer from a 1 mg/mL ethanolic stock without evaporation of the ethanol (final concentration of no more than 0.4%). The incubation was initiated by the addition of 40–50 μg membrane protein to silanized tubes containing [^{3}H]CP-55,940 (102.9 Ci/mmol) and a sufficient volume of buffer C (50 mM Tris–HCl, 1 mM EDTA, 3 mM $MgCl_2$, and 5 mg/mL fatty acid free BSA, pH 7.4) to bring the total volume to 0.5 mL. The addition of 1 μM unlabeled CP-55,940 was used to assess nonspecific binding. Following incubation (30 °C for 1 h), binding was terminated by the addition of 2 mL of ice cold buffer D (50 mM Tris–HCl, pH 7.4, plus 1 mg/mL BSA) and rapid vacuum filtration through Whatman GF/C filters (pretreated with polyethyleneimine (0.1%) for at least 2 h). Tubes were rinsed with 2 mL of ice cold buffer D, which was also filtered, and the filters subsequently rinsed twice with 4 mL of ice cold buffer D. Before radioactivity was quantitated by liquid scintillation spectrometry, filters were shaken for 1 h in 5 mL of scintillation fluid. [^{3}H]CP-55,940 bound to hCB_2-CHO cells membranes with a K_D value of 0.45 ± 0.07 nM and a B_{max} value of 2.93 ± 0.06 pmol/mg.

5.33.3. Data analysis. Competition assays were conducted with 1 nM [^{3}H]CP-55,940 and 6 concentrations (0.1 nM to 10 μM displacing ligands). Displacement IC_{50} values were originally determined by unweighted least-squares linear regression of log concentration-percent displacement data and then converted to K_i values using the method of Cheng and Prusoff.[58] All experiments were performed in triplicate and repeated 3–6 times. All data are reported as mean values ± SEM.

5.34. [^{35}S]GTPγS binding experiments

5.34.1. Materials. All chemicals were from Sigma (St. Louis, MO) except the following: [^{35}S]GTPγS (1250 Ci/mmol) was purchased from New England Nuclear Group (Boston, MA), GTPγS from Boehringer Mannheim (New York, NY), and DMEM/F-12 from Fischer Scientific (Pittsburgh, PA). Whatman GF/B glass fiber filters were purchased from Fisher Scientific (Pittsburgh, PA).

5.34.2. Membrane preparations. Chinese hamster ovary (CHO) cells stably expressing the human CB_2 receptor (CB_2-CHO) were cultured in a 50:50 mixture of DMEM and Ham F-12 supplemented with 100 U/mL penicillin, 100 Bg/mL streptomycin, 0.25 mg/mL G418, and 5% fetal calf serum. Cells were harvested by replacement of the media with cold phosphate-buffered saline containing 0.4% EDTA followed by agitation. Membranes were prepared by homogenization of cells in 50 mM Tris–HCl, 3 mM $MgCl_2$, 1 mM EGTA, pH 7.4, centrifugation at 50,000*g* for 10 min at 4 °C, and resuspension in the same buffer at 1.5 mg/mL. Membranes were stored at −80 °C until use.

5.34.3. [^{35}S]GTPγS binding assay. Prior to assays, samples were thawed on ice, centrifuged at 50,000*g* for 10 min at 4 °C, and resuspended in assay buffer (50 mM Tris–HCl (pH 7.4), 3 mM $MgCl_2$, 0.2 mM EGTA, and 100 mM NaCl). Reactions containing 10*g* of membrane protein were incubated for 1.5 h at 30 °C in assay buffer containing 10 μM GDP, 0.1 nM [^{35}S]GTPγS, 0.1% bovine serum albumin, and various

concentrations of agonist. Nonspecific binding was determined in the presence of 20 μM unlabeled GTPγS. Reactions were terminated by rapid vacuum filtration through GF/B glass fiber filters, and radioactivity was measured by liquid scintillation spectrophotometry at 95% efficiency for ^{35}S.

5.34.4. Data analysis. Nonspecific [^{35}S]GTPγS binding was subtracted from all data. Basal [^{35}S]GTPγS binding is defined as specific [^{35}S]GTPγS binding in the absence of drug. Net-stimulated [^{35}S]GTPγS binding is defined as [^{35}S]GTPγS binding in the presence of drug minus basal. Percent stimulation is expressed as (net-stimulated [^{35}S]GTPγS binding/basal) × 100%. The net stimulation produced by each concentration of every test compound was normalized to that obtained by a maximally effective concentration of CP-55,940 (3 μM), which was included in one triplicate of each individual experiment as an internal standard, according to the following equation. Percent maximal CP-55,940 stimulation = (net-stimulated [^{35}S]GTPγS binding by test compound/net-stimulated [^{35}S]GTPγS binding by 3 μM CP-55,940) × 100%. In this way, individual concentration–effect curves of the percent maximal CP-55,940 stimulation produced by each test compound were obtained and subjected to nonlinear regression analysis. All data are reported as mean E_{max} or EC_{50} values ± SEM of 3–6 experiments, each performed in triplicate. Nonlinear regression analysis was conducted by iterative fitting of the concentration–effect curves using JMP (SAS for Macintosh: Cary, NC). Statistically significant differences among E_{max} values were determined by analysis of variance followed by post hoc analysis with the unpaired, two-tailed Student's *t*-test using JMP.

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