Novel Cannabinol Probes for CB1 and CB2 Cannabinoid Receptors

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The observation that the phenolic hydroxyl of THCs was important for binding to the CB1 receptor but not as critical for binding to the CB2 receptor prompted us to extend this finding to the cannabinol (CBN) series. To study the SAR of CBN analogues, CBN derivatives with substitution at the C-1, C-3, and C-9 positions were chosen since these positions have played a key role in the SAR of THCs. CBN-3-(1′,1′-dimethylheptyl) analogues were prepared by sulfur dehydrogenation of Δ^8-THC-3-(1′,1′-dimethylheptyl) analogues. 9-Substituted CBN analogues were prepared by the standard sulfur dehydrogenation of 9-substituted Δ^8-THC analogues (Scheme 1), which in turn were prepared following our previous procedure using selenium dioxide oxidation of the corresponding Δ^8-THCs followed by sodium chlorite oxidation to give the 9-carboxy-Δ^8-THC derivatives. 11-Hydroxy-CBN analogues were prepared from the corresponding 9-carbomethoxy-CBN analogues by reduction with $LiAlH_4$. Deoxy-CBN analogue **14** was prepared from the corresponding Δ^8-THC analogue **11** by conversion of the phenolic hydroxyl to the phosphate derivative **12**, followed by lithium ammonia reduction to provide the deoxy-Δ^8-THC analogue **13**, which in turn was dehydrogenated with sulfur to provide the deoxy-CBN analogue **14** (Scheme 2). The various analogues were assayed for binding both to the brain and the peripheral cannabinoid receptors (CB1 and CB2). We have found that the binding profile differs widely between the CBN and the THC series. Specifically, in the CBN series the removal of the phenolic hydroxyl decreases binding affinity to both the CB1 and CB2 receptors, whereas in the THC series, CB1 affinity is selectively reduced. Thus, in the CBN series, the selectivity of binding observed with the removal of the hydroxy group is decreased severalfold as compared to what occurs in the THC series. Generally, high affinity for the CB2 receptor was found in analogues when the phenolic hydroxyl was present. The 3-(1′,1′-dimethylheptyl) derivatives were found to have much higher affinities than the CBN analogues, which is in complete agreement with previously reported work by Rhee et al.[16]

Introduction

It is well-known that Δ^9-tetrahydrocannabinol (Δ^9-THC) (**1**), which is the active constituent of marijuana, produces its unique pharmacological profile by interaction with the G-protein-coupled CB1 receptor.[1] Anandamide (arachidonylethanolamide, AN) has been identified as the endogenous ligand which binds to the central cannabinoid CB1 receptor.[2] Another peripherally expressed cannabinoid receptor subtype CB2 was identified from macrophages in the spleen; its ligand is shown to be 2-arachidonyl glycerol (2-Ara-Gl).[3−6] Pyrazole derivatives *N*-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichloro-phenyl)-4-methyl-1*H*-pyrazole-3-carboxamide (SR141716A) and *N*-[(1*S*)-endo-1,3,3-trimethyl-bicyclo-[2.2.1]heptan-2-yl]-5-(4-chloro-3-methylphenyl)-1-(4-methylbenzyl)-pyrazole-3-carboxamide (SR144528) have been found to be antagonists for the CB1 and CB2 receptors, respectively.[7,8] The discovery of the antagonists and other key developments in this field has enabled us to have a much better understanding of the mechanism by which cannabinoids act.[9−12] Considerable effort has been directed toward the SAR of compounds binding to the CB1 receptor;[13] however, less is known about the SAR of CB2-active compounds. Hence, the emphasis is placed on separation of CB1 activity from CB2, since the development of compounds which bind selectively to the CB2 receptor could lead to potential therapeutic agents in the immune response field.[14]

Limited information is available with regard to the SAR of CB2-active compounds. Aminoalkylindole (AAI) analogues synthesized by Huffman's group were found to have a 7−28-fold CB2 selectivity.[15] In the original report by Munro et al. about the characterization of the peripheral CB2 receptor,[3] it was reported that the affinity of cannabinol (CBN) (**2**) to the CB2 receptor was greater than that of Δ^9-THC (**1**). This finding has also been reported by Showalter et al.[15] Rhee et al. reported that the 3-(1′,1′-dimethylheptyl) analogue of CBN (**18a**) was much more potent than CBN (**2**),[16] and in their studies, 11-hydroxy cannabinol-3-(1′,1′-dimethylheptyl) (**24**) was found to be a very potent agonist for both the CB1 and CB2 receptors. Gareau et al. reported that replacement of C-1 hydroxyl in THCs with the methyl ether gave compounds which were CB2-selective,[17] and some biphenyl analogues were found to show potent CB2 activity with good selectivity. Huffman et al. reported that replacement of C-1 hydroxyl in THCs with hydrogen showed potent CB2 activity with good selectivity.[18] More recently, Huffman et al. reported that 3-(1′,1′-dimethylbutyl)-1-deoxy-Δ^8-THC has very high

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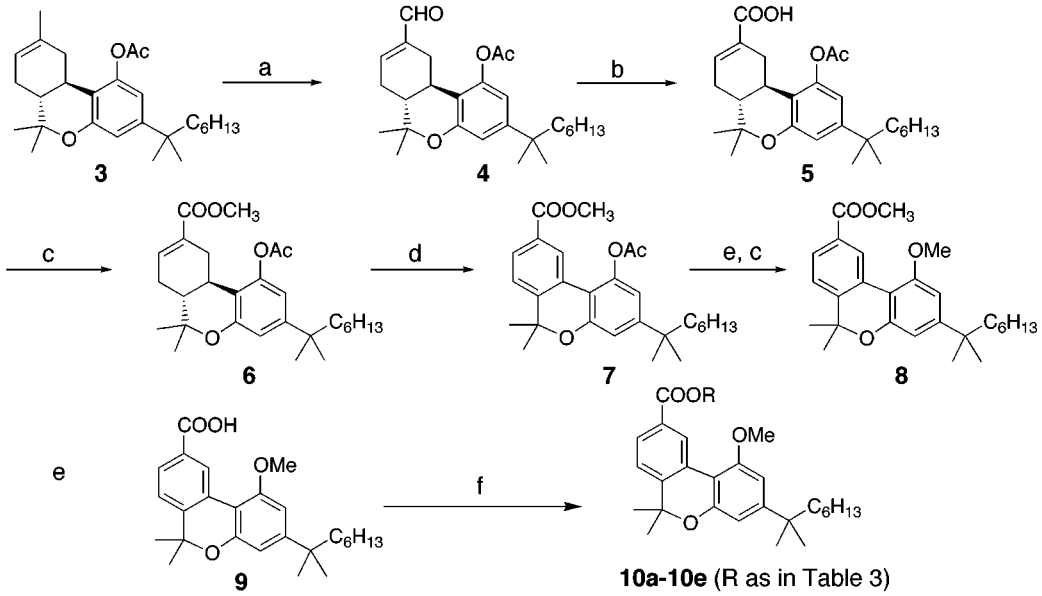
Scheme 1[a]



[a] Reagents and conditions: (a) SeO_2/ethanol, reflux, 24 h, 30%; (b) $NaClO_2$/*tert*-butanol, 25 °C, 2.5 h, 99%; (c) CH_3I/K_2CO_3, acetone, 60 °C, 5 h, 100%; (d) S, 250 °C, 0.5 h, 69%; (e) NaOH, ethanol, 25 °C, 97%; (f) RBr/K_2CO_3, acetone, 60 °C, 4 h, 80-97%.

binding affinity for the CB2 receptor and weak binding affinity for the CB1 receptor (3.4 nM versus 677 nM).[19]

The above observations of CB2-selective compounds in the THC series prompted us to extend these findings to the CBN series. CBN derivatives with substitution in the C-1, C-3, and C-9 positions were chosen since these positions have played a key role in the SAR of THCs.[13] With this background, we synthesized 1-methoxy- and deoxy-CBN-3-(1′,1′-dimethylheptyl) analogues, 3-(1′,1′-dimethylbutyl)-CBN analogues, and 9-carbomethoxy- and 11-hydroxy-CBN-3-(1′,1′-dimethylheptyl) analogues, which are discussed in this paper.

Chemistry

CBN-3-(1′,1′-dimethylheptyl) analogues were prepared by sulfur dehydrogenation of Δ^8-THC-3-(1′,1′-dimethylheptyl) analogues, which have previously been prepared in our labs in large quantities.[19a] Thus, Δ^8-THC-3-(1′,1′-dimethylheptyl) was synthesized from 5-(1′,1′-dimethylheptyl) resorcinol[20] by condensation with *p*-menth-2-ene-1,8-diol/*p*-TSA/benzene.[21] Further treatment with pyridine/acetic anhydride formed the starting material Δ^8-THC-3-(1′,1′-dimethylheptyl) acetate (**3**) (Scheme 1). Similarly, 3-(1′,1′-dimethylbutyl)-CBN analogues were prepared by sulfur dehydrogenation of Δ^8-THC-3-(1′,1′-dimethylbutyl) analogues. 1-Methoxy-CBN analogues were prepared by alkylation of the corresponding 1-hydroxy-CBN analogues with methyl iodide (**8**, Scheme 1). Deoxy-CBN analogues were prepared from the corresponding Δ^8-THC analogue **11** by conversion of the phenolic hydroxyl to the phosphate derivative **12** with diethylchlorophosphate. Reduction of the phosphate derivative with lithium in ammonia[22] provided the deoxy-Δ^8-THC analogue **13**, which in turn was dehydrogenated with sulfur to provide the deoxy-CBN analogue **14** (Scheme 2). When we tried to synthesize the deoxy-CBN analogues by conversion of the phenolic hydroxyl of CBN **18a,b** to the phosphate derivative **19a,b**, followed by reduction with lithium in ammonia, it was observed that the open ring analogues

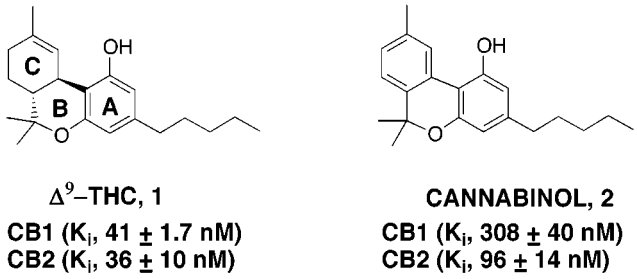


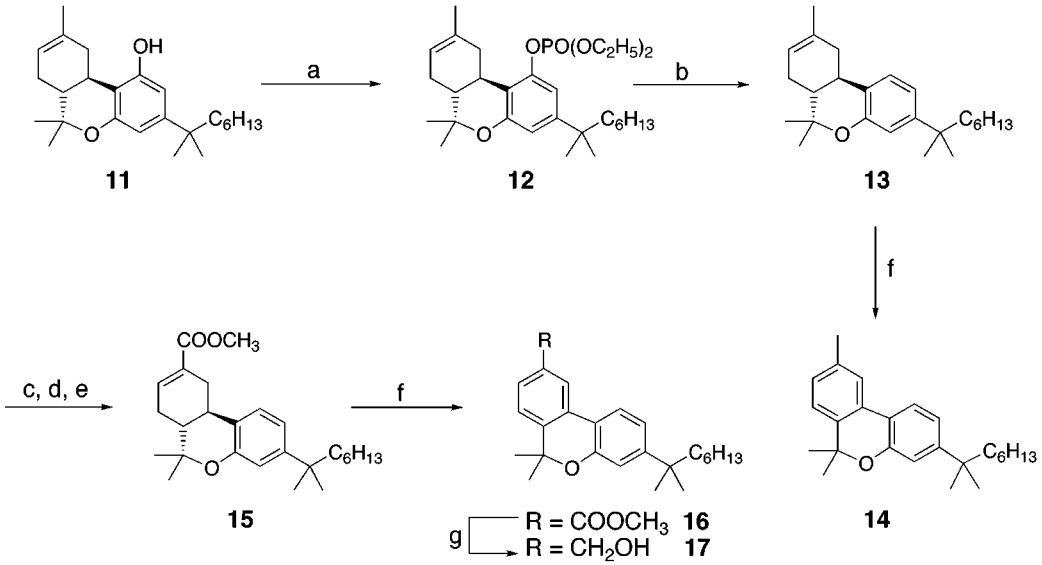
Figure 1. Structures of Δ^9-THC and cannabinol and their binding affinities to CB1 and CB2 receptors.

20a,b were formed instead (Scheme 3). 9-Substituted CBN analogues were prepared by the standard sulfur dehydrogenation of 9-substituted Δ^8-THC analogues (Scheme 1). 9-Carbomethoxy-Δ^8-THC-3-(1′,1′-dimethylheptyl) (**6**) was prepared by selenium dioxide oxidation to aldehyde **4**, followed by sodium chlorite oxidation to give 9-carboxy-Δ^8-THC-3-(1′,1′-dimethylheptyl) acetate (**5**).[23] The acid was then converted into the methyl ester **6** using methyl iodide. Sulfur dehydrogenation then provided 9-carbomethoxy-CBN analogue **7**. 11-Hydroxy-CBN analogues were prepared from the corresponding 9-carbomethoxy-CBN analogues by reduction with LAH (Scheme 2).[21]

Results and Discussion

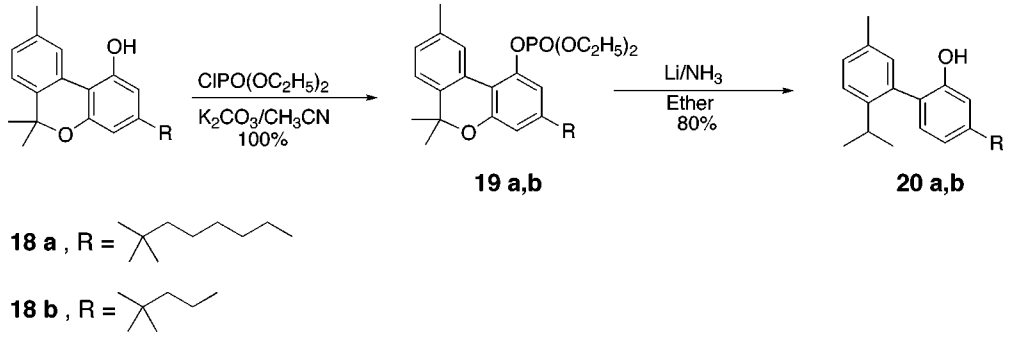
The phenolic hydroxyl of THCs is known to be important for binding to the CB1 receptor but is not as critical for binding to the CB2 receptor.[18,19] Based on this evidence, we decided to investigate the effect of changing the functionality at the C-1 position of CBN on the binding affinities to both the CB1 and CB2 receptors. Showalter et al. Reported (Figure 1) that CBN has a 7−8-fold lower binding affinity than Δ^9-THC in binding to the CB1 receptor and a 3-fold lower binding affinity than Δ^9-THC in binding to the CB2 receptor.[15] Removal of the phenolic hydroxyl in the THC series decreases CB1 binding affinity by almost 30-fold (0.77 nM versus 23 nM) as reported by Huffman et al.[18] and

Scheme 2[a]



[a] Reagents and conditions: (a) $CIPO(OC_2H_5)_2/K_2CO_3/CH_3CN$, 100%; (b) Li/NH_3, ether, 85%; (c) SeO_2/ethanol, 44%; (d) $NaClO_2$/*tert*-butanol, 99%; (e) CH_3I/acetone, 100%; (f) S, 250 °C, 0.5 h, 53%; (g) $LiAlH_4$/ether, 25 °C, 3 h, 86%.

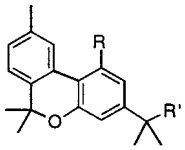
Scheme 3



300-fold (0.83 nM versus 248 nM) as reported by Gareau et al.[17] Gareau et al. also reported a 40-fold decrease (0.49 nM versus 20.8 nM) in the CB2 binding affinity.[17] Huffman et al. have suggested that this difference in binding data may be due to the data being obtained using rat brain homogenates and from human CB1 preparation of unspecific origin.[17,18] Under our experimental conditions, removal of the phenolic hydroxyl in the CBN series **14** and **18a** decreases CB1 binding affinity almost 400-fold (1 nM versus 434 nM), and the CB2 binding affinity decreases 75-fold (2.2 nM versus 167 nM) as shown in Table 1. In the THC series, both Huffman et al. and Gareau et al. have reported that replacement of the phenolic group with a methoxy group resulted in very weak binding affinity to the CB1 receptor (0.83 nM versus either 924 nM or 15 850 nM), whereas the changes in binding affinity to the CB2 receptor were not as dramatic (0.49 nM versus either 65 nM or 20 nM), hence leading to a more CB2 selective compound.[17,18] However, in the CBN series, we observed that replacement of hydroxyl group **18a** with a methoxy group **21** resulted in weak binding affinity to both the CB1 (1 nM versus 681 nM) and CB2 receptors (2.2 nM versus 286 nM).

The lipophilic side chain at the C-3 position of THCs is known to play a key role in their binding affinity and potency. When we compared CBN (**2**) to 3-(1′,1′-dimethylheptyl)-CBN (**18a**), it was found that changing

Table 1. Cannabinol Analogues and Their Binding Affinities to CB1 and CB2 Receptors

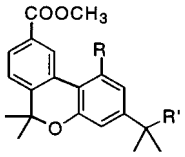


compound	R	R′	CB1	CB2	CB1/CB2
18a	OH	C_6H_{13}	1 ± 0.1 2 ± 0.3[a]	2.24 ± 0.4 1.5 ± 0.5[a]	0.4
21	OMe	C_6H_{13}	681 ± 82	286 ± 25	2.4
14	H	C_6H_{13}	434 ± 69	167 ± 4	2.6
18b	OH	C_3H_7	42 ± 2	6 ± 2	7.0

[a] Reference 16.

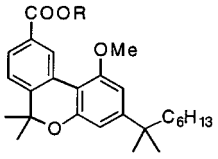
the lipophilic side chain at the C-3 position from 5 to 7 carbons increased the binding affinity to both the CB1 (308 nM versus 1 nM) and the CB2 (96 nM versus 2.2 nM) receptors, resulting in a much higher affinity compound in agreement with the findings of Rhee et al.[16] This observation is consistent with what was observed in the THC series. Huffman et al. have reported that 3-(1′,1′-dimethylbutyl)-1-deoxy-Δ^8-THC binds with good affinity to the CB2 receptor (3.4 nM) and binds weakly to the CB1 receptor (677 nM), thus resulting in a highly CB2 selective compound (CB1/CB2 = 199).[19] When we examined the 3-(1′,1′-dimethylbutyl)

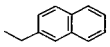
Table 2. 9-Carbomethoxy Cannabinol Analogues and Their Binding Affinities to CB1 and CB2 Receptors



compound	R	R′	CB1	CB2	CB1/CB2
22	OH	C_6H_{13}	14 ± 5	3.8 ± 0.1	3.7
8	OMe	C_6H_{13}	>10 000	529 ± 270	~18.9
16	H	C_6H_{13}	558 ± 54	276 ± 125	2.0
23	H	C_3H_7	>10 000	611 ± 155	16.4

Table 3. 1-Methoxy-3-(1′,1′-dimethylheptyl)-11-oicester-cannabinol Analogues and Their Binding Affinities to CB1 and CB2 Receptors

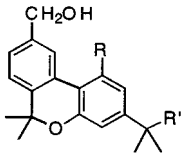


Compound	R	CB1	CB2	CB1/CB2
8	CH3	>10,000	529±270	~18.9
10a	$CH(CH_3)_2$	>10,000	>10,000	~1.0
10b	$CH_2(CH_2)_4CH_3$	>10,000	>10,000	~1.0
10c	CH_2Ph	>10,000	>10,000	~1.0
10d		>10,000	>10,000	~1.0
10e	$CH_2CH_2CH_3$	1727±388	214±1.2	8.1

side chain **18b** in the CBN series, it was observed that there was a 40-fold decrease in the binding affinity to the CB1 receptor when compared to 3-(1′,1′-dimethylheptyl)-CBN (1 nM versus 42 nM), and a 2−3-fold decrease in the binding affinity to the CB2 receptor (2.2 nM versus 6 nM). Hence in the CBN series, only 7-fold CB2 selectivity was observed.

The CBN derivatives with substitution in the C-9 position were investigated. First, we synthesized the CBN-3-(1′,1′-dimethylheptyl) methyl ester **22** and the corresponding acid and looked at their binding affinities to the CB1 and CB2 receptors. It is interesting to note that the conversion of the acid to the methyl ester enhanced the binding affinity for both the CB1 (2760 nM versus 14 nM) and the CB2 (395 nM versus 3.8 nM) receptors and was ∼4-fold selective to the CB2 receptor. Maintaining the C-9 position as the methyl ester, we then varied the functionality at the C-1 and C-3 positions (Table 2). In this series, we observed that replacement of the hydroxyl group **22** with a methoxy group **8** resulted in weak binding affinity to both the CB1 (14 nM versus >10 000 nM) and the CB2 receptors (3.8 nM versus 529 nM); however, the compound was found to be ∼19-fold CB2-selective. Based on the above results, several different esters **10a**−**10e** were synthesized (Table 3). However, all the different ester analogues **10a**−**10e** showed relatively little binding to both the CB1 and the CB2 receptors. The effect of removal of the phenolic group was next investigated, and it was found that the deoxy compound **16** showed poor binding affinity to both the CB1 (558 nM) and the CB2 (276 nM) receptors. The deoxy compound **23**, which has a shorter side chain [3-(1′,1′-dimethylbutyl)], showed no binding affinity to the CB1 receptor and weak binding affinity to the CB2 receptor, leading to a 16-fold CB2-selective compound.

Table 4. 11-Hydroxy Cannabinol Analogues and Their Binding Affinities to CB1 and CB2 Receptors



compound	R	R′	CB1	CB2	CB1/CB2
24	OH	C_6H_{13}	0.1 ± 0.05[a]	0.2 ± 0.04[a]	0.5
17	H	C_6H_{13}	2 ± 0.1	1 ± 0.2	2.0
25	H	C_3H_7	204 ± 27	67 ± 10	3.0

[a] Reference 16.

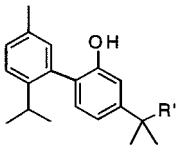
Rhee et al. have reported that 11-hydroxy-CBN-3-(1′,1′-dimethylheptyl) derivative **24** showed very good binding affinity with high potency to both the CB1 and CB2 receptors (0.1 nM, 0.2 nM).[16] Hence, we examined C-11-hydroxy-CBN-3-(1′,1′-dimethylheptyl) derivatives (Table 4). In this series, we observed that replacement of a hydroxyl group **24** with hydrogen **17** resulted in decreased binding affinity to both the CB1 (0.1 nM versus 2 nM) and the CB2 receptors (0.2 nM versus 1 nM); however, the compound was still found to have high binding affinity to both the CB1 and CB2 receptors. The deoxy compound with a 3-(1′,1′-dimethylbutyl) side chain **25** showed decreased binding affinity to both the CB1 and the CB2 receptors, leading to a 3-fold CB2 selective compound.

During the course of trying to synthesize the deoxy CBN analogues, the open ring analogues **20a,b** were formed (Scheme 3). When compared to the CBN-3-(1′,1′-dimethylheptyl) analogue **18a**, the open ring analogue **20a** shows decreased binding affinity to the CB1 receptor (1 nM versus 33 nM); however, binding affinity to the CB2 receptor was unaffected (2.2 nM versus 3 nM). Thus in the open ring compound **20a**, a better selectivity (10-fold) in favor of the CB2 receptor was achieved. The open ring analogue **20b**, which has a shorter side chain [3-(1′,1′-dimethylbutyl)], showed decreased binding affinity to both the CB1 and CB2 receptors and was ∼7-fold CB2 selective. Furthermore, it was also noted that the presence of a hydroxyl group either at ring C or ring A enhances binding affinity to the CB2 receptor (compare **17**, **18a**, and **20a**).

Conclusions

The successful development of selective ligands for cannabinoid receptor subtypes provides the impetus for characterizing unique pharmacophores for CB1 and CB2 receptors. Earlier observations that the phenolic hydroxyl of THCs was important for CB1 but not CB2 binding[18,19] prompted us to extend this finding to the CBN series. Several noteworthy conclusions can be drawn from these analogues which highlight the differences between THCs and their corresponding CBN analogues: (1) The binding profile differs in the CBN and the THC series and shows that, in the CBN series, the removal of the phenolic hydroxyl decreases CB1 binding affinity much more than in the THC series. Thus in the CBN series [CBN-3-(1′,1′-dimethylheptyl)]

Table 5. Open Ring Cannabinol Analogues and Their Binding Affinities to CB1 and CB2 Receptors



compound	R′	CB1	CB2	CB1/CB2
20a	C_6H_{13}	33 ± 4	3 ± 0.4	10.0
20b	C_3H_7	875 ± 21	113 ± 21	7.7

(**18a**) binds with high affinity to the CB1 receptor (K_i = 1 nM). Its deoxy analogue **14** has a 400-fold decreased binding affinity to the CB1 receptor (K_i = 434 nM; Table 1), while a similar change in Δ^8-THC analogues[18] shows a mere 30-fold decrease in binding affinity to the CB1 receptor [K_i = 0.77 nM for Δ^8-THC-3-(1′,1′-dimethylheptyl)] versus [K_i = 23 nM for deoxy-Δ^8-THC-3-(1′,1′-dimethylheptyl)]. Deoxy-CBN-3-(1′,1′-dimethylheptyl) (**14**) has a 57-fold decreased binding affinity to the CB2 receptor (K_i = 167 nM; Table 1) compared to its THC analogue, deoxy-Δ^8-THC-3-(1′,1′-dimethylheptyl) (K_i = 2.9 nM).[18] (2) Unlike the THC series, in the CBN series when a hydroxyl group is present at position C11, the side chain length of deoxy-CBN analogues has relatively little influence on the selectivity; i.e., ratio of CB1/CB2 binding affinity. (3) Increasing the planarity of ring C as in CBN analogues, compared to THCs, is detrimental to the enhancement of CB1/CB2 selectivity. (4) High potency for CB2 binding was found only when the phenolic hydroxyl was present, with one exception in compound **17** (Table 4) where the hydroxyl was present at C11. (5) The presence of a hydroxyl group either in ring C as in compound **17** (Table 4) or in ring A as in compounds **18a** and **20a** (Tables 1 and 5) enhances binding affinity to the CB2 receptor since all the compounds have high CB2 binding affinities (**17**, K_i = 1 nM; **18a**, K_i = 2.24 nM; and **20a**, K_i = 3 nM). (6) The high CB2 binding affinity of **22** (Table 2) compared to the corresponding acid (395 nM) suggests that the receptor has a lipophilic site near the C11 position. However, the influence of this site appears to be minimal since none of the various esters prepared (Table 3) showed any significant enhancement of CB2 binding affinity.

In summary, it is evident that structural requirements for CB1 and/or CB2 receptor binding differ between THC and CBN, thus providing a new strategy for further pharmacophore characterization. It also suggests that to achieve CB1/CB2 selectivity and high binding affinity to the CB2 receptor it is important for the alicyclic ring in THCs (i.e. ring C) to be nonplanar and to have the presence of a hydoxyl group either at ring A or C. Consideration of these factors may prove helpful in the designing of new ligands which bind potently and selectively to the CB2 receptor.

Experimental Section

All reagents were of commercial quality, reagent grade, and used without further purification. Anhydrous solvents were purchased from Aldrich and used without further purification. All reactions were carried out under a N_2 atmosphere. Organic solutions were dried with sodium sulfate. ^{1}H NMR spectra were recorded on either a Bruker 100 MHz or a JEOL Eclipse 300 MHz spectrophotometer using $CDCl_3$ as the solvent with tetramethylsilane as an internal standard. Thin-layer chromatography (TLC) was carried out on Baker Si 250F plates and was developed upon treatment with phosphomolybdic acid (PMA). Flash column chromatography was carried out on EM Science silica gel 60. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, GA, and were found to be within ±0.4% of calculated values for the elements shown, unless otherwise noted.

1-Acetoxy-3-(1′,1′-dimethylheptyl)-9-carbomethoxy-Δ^8-tetrahydrocannabinol (6). It was prepared from Δ^8-THC-DMH acetate **3** using our previously published procedure.[23c] It was obtained in an overall yield of 29% and used without further purification in the subsequent step.

1-Acetoxy-3-(1′,1′-dimethylheptyl)-9-carbomethoxy-cannabinol (7). Dehydrogenation was carried out by heating compound **6** (2.7 g, 5.9 mmol) with sulfur (0.378 g, 11.8 mmol) at 245−255 °C, for 0.5 h, under a nitrogen atmosphere. Purification of the crude product by flash chromatography on SiO_2 eluting with varying amounts of ethyl acetate in hexanes (3−5% EtOAc/hexanes) afforded compound **7** (1.84 g, 69%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.7 (d, J = 1.6 Hz, 1 H), 7.9 (dd, J = 8.4, 1.6 Hz, 1 H), 7.29 (d, J = 8.4 Hz, 1 H), 6.85 (d, J = 1.6 Hz, 1 H), 6.7 (d, J = 1.6 Hz, 1 H), 3.9 (s, 3 H), 2.4 (s, 3 H), 1.6 (s, 6 H), 1.5 (m, 2 H), 1.3 (s, 6 H), 1.1−0.8 (m, 11 H).

1-Methoxy-3-(1′,1′-dimethylheptyl)-9-carbomethoxy-cannabinol (8). To a degassed solution of **7** (1.84 g, 4 mmol) in absolute ethanol (20 mL) was added a degassed solution of sodium hydroxide (0.95 g, 23.7 mmol) in water (10 mL), and the mixture was stirred under N_2 for 5 min. The reaction mixture was concentrated, and the residue was dissolved in 10 mL water and acidified with 4 N HCl. A white precipitate was obtained, which was dissolved in ether. The aqueous layer was separated and extracted (2×) with ether. The combined ether extracts were washed with water, dried, and concentrated to afford the corresponding 9-carboxy-1-hydroxy derivative as a white foam (1.54 g, 95%).

To a solution of the white foam (1.38 g, 3.48 mmol) in acetone (20 mL) was added K_2CO_3 (2 g, 14.4 mmol), followed by iodomethane (2 mL, 32.3 mmol). The reaction mixture was then stirred at 50 °C overnight. The precipitate obtained was filtered and washed with acetone. The acetone solution was concentrated, and the residue was partitioned between water and ether. The aqueous layer was separated and extracted (2×) with ether. The combined ether extracts were washed with water, dried, and concentrated to afford a colorless gum. Purification of the crude product by flash chromatography on SiO_2 eluting with varying amounts of ethyl acetate in hexanes (100% hexanes − 2% EtOAc/hexanes) afforded compound **8** (1.21 g, 82%). ^{1}H NMR (100 MHz, $CDCl_3$) δ 9.1 (d, J = 2.7 Hz, 1 H), 7.9 (dd, J = 9.0, 2.7 Hz, 1 H), 7.3 (d, J = 9.0 Hz, 1 H), 6.6 (s, 2 H), 4.0 (s, 3 H), 3.95 (s, 3 H), 1.65 (s, 6 H), 1.4 (s, 6 H), 1.2−0.8 (m, 13 H). Anal. ($C_{27}H_{36}O_4$) C, H.

1-Methoxy-3-(1′,1′-dimethylheptyl)-9-carboxy-cannabinol (9). To a solution of **8** (1.3 g, 3 mmol) in absolute ethanol (25 mL) was added a solution of sodium hydroxide (0.72 g, 18 mmol) in water (7 mL), and the mixture was stirred under N_2 for 4 h. The reaction mixture was concentrated, and the residue was acidified with 4 N HCl. A white gum was obtained, which was partitioned between water and ether. The aqueous layer was then separated and extracted (2×) with ether. The combined ether extracts were washed with water, dried, and concentrated to afford compound **9** as a white foam (1.22 g, 97%). ^{1}H NMR (100 MHz, $CDCl_3$) δ 9.2 (d, J = 2.7 Hz, 1 H), 8.0 (dd, J = 9.0, 2.7 Hz, 1 H), 7.35 (d, J = 9.0 Hz, 1 H), 6.6 (s, 2 H), 4.0 (s, 3 H), 1.7 (s, 6 H), 1.3 (s, 6 H), 1.2−0.8 (m, 13 H).

1-Methoxy-3-(1′,1′-dimethylheptyl)-11-oicester-cannabinol (10a−e). To a solution of **9** (0.103 g, 0.25 mmol) in acetone (3 mL) was added K_2CO_3 (0.138 g, 0.99 mmol), followed by 2-iodopropane (0.85 g, 5 mmol). The reaction mixture was then stirred at 60 °C under N_2 for 4 h. The precipitate obtained was filtered and washed with acetone. The acetone solution was concentrated, and the residue was partitioned between water and ether. The aqueous layer was separated and

extracted (2×) with ether. The combined ether extracts were washed with water, dried, and concentrated to afford a gum. Purification of the crude product by flash chromatography on SiO_2 eluting with varying amounts of ethyl acetate in hexanes (100% hexanes − 1% EtOAc/hexanes) afforded compound **10a** as a gum (0.092 g, 82%). ^{1}H NMR (100 MHz, $CDCl_3$) δ 9.1 (d, J = 2.4 Hz, 1 H), 7.9 (dd, J = 9.5, 2.4 Hz, 1 H), 7.3 (d, J = 9.5 Hz, 1 H), 6.6 (s, 2 H), 5.3 (m, 1 H), 4.0 (s, 3 H), 1.6 (s, 6 H), 1.4 (m, 6 H), 1.3 (s, 6 H), 1.2−0.85 (m, 13 H). Anal. ($C_{29}H_{40}O_4$) C, H.

10b: Prepared as described above for **10a** using iodohexane, (82%). ^{1}H NMR (100 MHz, $CDCl_3$) δ 9.1 (d, J = 2.4 Hz, 1 H), 7.9 (dd, J = 9.5, 2.4 Hz, 1 H), 7.3 (d, J = 9.5 Hz, 1 H), 6.6 (s, 2 H), 4.35 (m, 2 H), 4.0 (s, 3 H), 1.65 (s, 6 H), 1.3 (m, 24 H), 0.9 (m, 6 H). Anal. ($C_{32}H_{46}O_4$) C, H.

10c: Prepared as described above for **10a** using benzyl bromide, (91%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.15 (d, J = 1.9 Hz, 1 H), 7.95 (dd, J = 8.3, 1.9 Hz, 1 H), 7.35 (m, 6 H), 6.6 (d, J = 1.6 Hz, 2 H), 5.38 (s, 2 H), 3.93 (s, 3 H), 1.61 (s, 6 H), 1.35 (s, 6 H), 1.2−0.85 (m, 13 H). Anal. ($C_{33}H_{40}O_4$) C, H.

10d: Prepared as described above for **10a** using 2-bromomethyl naphthalene, (80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.18 (d, J = 1.9 Hz, 1 H), 7.92 (m, 5 H), 7.51 (m, 3 H), 7.29 (d, J = 8.0 Hz, 1 H), 6.57 (d, J = 1.9 Hz, 2 H), 5.54 (s, 2 H), 3.92 (s, 3 H), 1.61 (s, 6 H), 1.28 (s, 6 H), 1.15−0.85 (m, 13 H). Anal. ($C_{37}H_{42}O_4$) C, H.

10e: Prepared as described above for **10a** using iodopropane, (100%). ^{1}H NMR (100 MHz, $CDCl_3$) δ 9.15 (d, J = 2.4 Hz, 1 H), 7.95 (dd, J = 9.5, 2.4 Hz, 1 H), 7.3 (d, J = 9.5 Hz, 1 H), 6.6 (s, 2 H), 4.3 (t, 2 H), 4.0 (s, 3 H), 1.65 (s, 6 H), 1.3 (m, 18 H), 0.9 (m, 6 H). Anal. ($C_{29}H_{40}O_4$) C, H.

3-(1′,1′-Dimethylheptyl)-Δ^8-tetrahydrocannabinol-1-diethyl Phosphate (12). To a solution of **11** (4.95 g, 13.3 mmol) in anhydrous acetonitrile (100 mL) was added K_2CO_3 (16 g, 110 mmol) followed by diethylchlorophosphate (3.4 g, 19.7 mmol).[22] The reaction mixture was then stirred at 90 °C under N_2 for 4 h and concentrated, and the residue was partitioned between water and ether. The aqueous layer was separated and extracted (2×) with ether. The combined ether extracts were washed with water, dried, and concentrated to afford **12** (7 g) as a golden gum which was used directly in the next step without further purification.

1-Deoxy-3-(1′,1′-dimethylheptyl)-Δ^8-tetrahydrocannabinol (13). A solution of **12** (7 g) in dry ether (70 mL) was added to ∼300 mL of liquid NH_3. The reaction mixture was stirred vigorously and small pieces of Li wire (0.16 g) were added until blue color persisted for >5 min.[22] Excess Li was then decomposed by addition of NH_4Cl, and NH_3 was allowed to evaporate using a stream of nitrogen. The residue was partitioned between water and ether. The aqueous layer was separated and extracted (2×) with ether. The combined ether extracts were washed with water, dried, and concentrated to afford a gum. Purification of the crude product by flash chromatography on SiO_2 eluting with varying amounts of ethyl acetate in hexanes (100% hexanes − 0.8% EtOAc/hexanes) afforded **13** (4 g, 85%) as a colorless gum. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.1 (d, J = 8.0 Hz, 1 H), 6.84 (dd, J = 8.0, 2.0 Hz, 1 H), 6.74 (d, J = 1.9 Hz, 1 H), 5.45 (m, 1 H), 2.64 (m, 2 H), 1.95 (m, 3 H), 1.7 (m, 3 H), 1.53 (m, 4 H), 1.4 (s, 3 H), 1.23 (s, 6 H), 1.2 (m, 4 H), 1.14 (s, 3 H), 1.06−0.85 (m, 6 H), 0.85 (t, 3 H).

1-Deoxy-3-(1′,1′-dimethylheptyl)-cannabinol (14). A mixture of **13** (0.45 g, 1.3 mmol) and sulfur (0.83 g, 2.6 mmol) was heated at 250 °C under N_2 for 0.5 h, in a flask fitted with condenser (no water) and connected to a dilute NaOH trap. Purification of the crude product by flash chromatography on SiO_2 eluting with varying amounts of ethyl acetate in hexanes (100% hexanes − 1.5% EtOAc/hexanes) afforded **14** (0.236 g, 53%) as an oily solid. ^{1}H NMR (100 MHz, $CDCl_3$) δ 7.65 (d, J = 9.0 Hz, 1 H), 7.5 (s, 1 H), 7.15 (s, 2 H), 7.05 (m, 2 H), 2.4 (s, 3 H), 1.6 (s, 6 H), 1.5 (m, 2 H), 1.3 (s, 6 H), 1.15−0.83 (m, 11 H). Anal. ($C_{25}H_{34}O$) C, H.

1-Deoxy-3-(1′,1′-dimethylheptyl)-9-carbomethoxy-Δ^8-tetrahydrocannabinol (15). To a solution of **13** (3.65 g, 10.29 mmol) in ethanol (43 mL) was added dropwise a solution of SeO_2 (2.75 g, 24.78 mmol) in EtOH/H_2O (43 mL/4.3 mL) over 0.5 h at 25 °C. After the addition was complete, the reaction mixture was refluxed overnight. The reaction mixture was then cooled, filtered through a Celite pad, and washed with MeOH. The filtrate was concentrated, and the residue was dissolved in ether. The ether layer was then successively washed with water, sodium bicarbonate solution, and water. It was then dried and concentrated. Purification of the crude product by flash chromatography on SiO_2 eluting with varying amounts of ethyl acetate in hexanes (5% EtOAc/hexanes − 7% EtOAc/hexanes) afforded the intermediate 11-oxo derivative (1.5 g, 40%) as a yellow solid.

A three-neck round-bottom flask fitted with a condenser and nitrogen inlet was charged with the 11-oxo derivative (1.66 g, 4.5 mmol), *t*-BuOH (69 mL), and 2-methyl-2-butene (68.5 mL; technical grade). To this was added in portions a solution of $NaClO_2$ and NaH_2PO_4 in water (4.69 g, 4.47 g, 45.5 mL) over 0.5 h. The biphasic mixture was then vigorously stirred for 2.5 h. The reaction mixture was then concentrated, and the residue was partitioned between water and ether. The aqueous layer was separated and extracted (2×) with ether. The combined ether extracts were washed with 1 N HCl and water, dried, and concentrated to afford the corresponding 9-carboxy derivative (1.72 g, 99%) as a solid which was used in the next step without further purification.

To a solution of the 9-carboxy derivative (1.72 g, 4.47 mmol) in acetone (30 mL) was added K_2CO_3 (2.47 g, 17.8 mmol), followed by iodomethane (2.5 mL). The reaction mixture was then stirred at 60 °C, for 5 h. The reaction mixture was concentrated, and the residue was partitioned between water and ether. The aqueous layer was separated and extracted (2×) with ether. The combined ether extracts were washed with water, dried, and concentrated to afford **15** (1.82 g, 100%) as a golden gum. Purification of a portion of the crude product (0.12 g) by preparative TLC plate (20 × 20 × 2 mm thickness) eluting with 20% EtOAc/hexanes afforded compound **15** (0.096 g) as a golden gum. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.2 (d, J = 8.2 Hz, 1 H), 7.05 (m, 1 H), 6.85 (dd, J = 8.2, 1.9 Hz, 1 H), 6.7 (d, J = 1.9 Hz, 1 H), 3.8 (s, 3 H), 3.2 (dd, J = 17.0, 3.0 Hz, 1 H), 2.65 (m, 1 H), 2.4 (m, 1 H), 2.05 (m, 2 H), 1.75 (m, 1 H), 1.55 (m, 2 H), 1.45 (s, 3 H), 1.25−0.85 (m, 20 H). Anal. ($C_{26}H_{38}O_3$) C, H.

1-Deoxy-3-(1′,1′-dimethylheptyl)-9-carbomethoxy-cannabinol (16). This was prepared from **15** in a similar manner as described for the synthesis of **14**. The ester **16** was obtained in 73% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 (d, J = 1.6 Hz, 1 H), 7.9 (dd, J = 8.2, 1.6 Hz, 1 H), 7.72 (d, J = 8.2 Hz, 1 H), 7.3 (d, J = 8.0 Hz, 1 H), 7.02 (dd, J = 8.2, 1.6 Hz, 1 H), 6.9 (d, J = 1.9 Hz, 1 H), 3.95 (s, 3 H), 1.65 (s, 6 H), 1.6 (m, 2 H), 1.28 (s, 6 H), 1.2−0.82 (m, 11 H). Anal. ($C_{26}H_{34}O_3$) C, H.

1-Deoxy-3-(1′,1′-dimethylheptyl)-11-hydroxy-cannabinol (17).[21] A three-neck round-bottom flask equipped with addition funnel and nitrogen inlet was charged with $LiAlH_4$ (0.379 g, 10 mmol) and dry ether (30 mL). To this was added dropwise a solution of **16** (0.35 g, 0.88 mmol) in dry ether (10 mL). After the addition was complete, the reaction mixture was stirred at 25 °C for 3 h. Excess $LiAlH_4$ was then decomposed by dropwise addition of EtOAc followed by addition of a saturated solution of NH_4Cl. The aqueous layer was separated and extracted (2×) with ether. The combined ether extracts were washed with aqueous NH_4Cl and water, dried, and concentrated. Purification of the crude product by flash chromatography on SiO_2 eluting with varying amounts of ethyl acetate in hexanes (100% hexanes − 5% EtOAc/hexanes − 10% EtOAc/hexanes) afforded **17** (0.28 g, 86%) as a colorless gum. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.7 (brs, 1 H), 7.64 (d, J = 8.2 Hz, 1 H), 7.24 (m, 2 H), 7.0 (dd, J = 8.2, 1.6 Hz, 1 H), 6.9 (d, J = 1.6 Hz, 1 H), 4.74 (m, 2 H), 1.6 (m, 10 H), 1.32 (s, 6 H), 1.15−0.85 (m, 9 H). Anal. ($C_{25}H_{34}O_2$) C, H.

3-(1′,1′-Dimethylheptyl)-cannabinol (18a). 1-Acetoxy-3-(1′,1′-dimethylheptyl)-cannabinol was prepared (84%) from 1-acetoxy-3-(1′,1′-dimethylheptyl)-Δ^8-tetrahydrocannabinol in a similar manner as described for the synthesis of **14**.

To a solution of 1-acetoxy-3-(1′,1′-dimethylheptyl)-cannabinol (0.83 g, 2 mmol) in MeOH (50 mL) was added a solution of sodium carbonate (0.85 g, 8 mmol) in water (4.5 mL). The reaction mixture was stirred under N_2 for 1 h after which it was evaporated to remove MeOH. The residue was partitioned between water and ethyl acetate. The aqueous layer was separated and extracted (2×) with ethyl acetate. The combined extracts were successively washed with water and brine and then dried and concentrated. Purification of the crude product by flash chromatography on SiO_2 eluting with varying amounts of ethyl acetate in hexanes (100% hexanes − 1.5% EtOAc/hexanes) afforded **18a** (0.59 g, 55% overall) as a gum. ^{1}H NMR (100 MHz, $CDCl_3$) δ 8.15 (d, J = 2.5 Hz, 1 H), 7.13 (m, 2 H), 6.6 (d, J = 2.5 Hz, 1 H), 6.4 (d, J = 2.5 Hz, 1 H), 5.1 (s, 1 H), 2.42 (s, 3 H), 1.65 (s, 6 H), 1.3 (s, 6 H), 1.2−0.85 (m, 13 H). Anal. ($C_{25}H_{34}O$) C, H.

3-(1′,1′-Dimethylbutyl)-cannabinol (18b). 3-(1′,1′-Dimethylbutyl)-Δ^8-tetrahydrocannabinol was prepared (61%) in a similar manner as described for the synthesis of 3-(1′,1′-dimethylheptyl)-Δ^8-tetrahydrocannabinol.

To a solution of 3-(1′,1′-dimethylbutyl)-Δ^8-tetrahydrocannabinol (1.0 g, 3 mmol) in pyridine (5.7 mL) was added acetic anhydride (0.372 g, 3.65 mmol). The reaction mixture was then stirred at 90 °C under N_2 for 2 h. The reaction mixture was concentrated and the residue was partitioned between water and ether. The aqueous layer was separated and extracted (2×) with ether. The combined ether extracts were successively washed with water, saturated $NaHCO_3$, 1 N HCl, and brine. It was then dried and concentrated to afford 1-acetoxy-3-(1′,1′-dimethylbutyl)-Δ^8-tetrahydrocannabinol (1.14 g) as a brown gum, which was used directly in the next step without further purification.

1-Acetoxy-3-(1′,1′-dimethylbutyl)-cannabinol was prepared (67%) from 1-acetoxy-3-(1′,1′-dimethylbutyl)-Δ^8-tetrahydrocannabinol in a similar manner as described for the synthesis of **14**, and then deprotected as in the case of **18a** to give 3-(1′,1′-dimethylbutyl)-cannabinol **18b** (60%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (s, 1 H), 7.1 (m, 2 H), 6.55 (d, J = 1.6 Hz, 1 H), 6.4 (d, J = 1.9 Hz, 1 H), 5.15 (s, 1 H), 2.41 (s, 3 H), 1.6 (s, 6 H), 1.54 (m, 2 H),1.25 (s, 6 H), 1.1−0.81 (m, 5 H). Anal. ($C_{22}H_{28}O_2$) C, H.

3-(1′,1′-Dimethylheptyl)-6-(2-isopropyl-5-methylphenyl)-phenol (20a). To a solution of **18a** (0.085 g, 0.23 mmol) in dry acetonitrile (4 mL) was added K_2CO_3 (0.28 g, 2 mmol), followed by diethylchloro-phosphate (0.058 g, 0.34 mmol). The reaction mixture was then stirred at 25 °C under N_2 for 2 h and concentrated, and the residue was partitioned between water and ether. The aqueous layer was separated and extracted (2×) with ether. The combined ether extracts were washed with water, dried, and concentrated to afford **19a** (0.125 g) as a gum which was used directly in the next step without further purification.

A solution of **19a** (0.25 g) in dry ether (2 mL) was added to ∼20 mL of liquid NH_3. The reaction mixture was stirred vigorously and small pieces of Li wire (0.02 g) were added until a blue color persisted for >5 min.[22] The excess Li was then decomposed by addition of NH_4Cl, and the NH_3 was allowed to evaporate using a stream of nitrogen. The residue was partitioned between water and ether. The aqueous layer was separated and extracted (2×) with ether. The combined ether extracts were washed with water, dried, and concentrated. Purification of the crude product by flash chromatography on SiO_2 eluting with varying amounts of ethyl acetate in hexanes (100% hexanes − 1% EtOAc/hexanes) afforded **20a** (0.118 g, 67%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.3 (d, J = 8.5 Hz, 1 H), 7.21 (dd, J = 8.5, 1.6 Hz, 1 H), 7.06 (m, 2 H), 6.92 (m, 2 H), 4.63 (s,1 H), 2.81 (m, 1 H), 2.33 (s, 3 H), 1.6 (m, 3 H), 1.3 (s, 6 H), 1.13 (brs, 7 H), 1.18 (m, 3 H), 1.13−0.84 (m, 6 H). Anal. ($C_{25}H_{36}O$) C, H.

3-(1′,1′-Dimethylbutyl)-6-(2-isopropyl-5-methylphenyl)-phenol (20b). Compound **20b** was prepared in 61% yield from **18b** in a similar manner as described for the synthesis of **20a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, J = 8.5 Hz, 1 H), 7.25 (dd, J = 8.5, 1.6 Hz, 1 H), 6.99 (m, 4 H), 4.68 (s, 1 H), 2.82 (m, 1 H), 2.37 (s, 3 H), 1.55 (m, 3 H), 1.3 (s, 6 H), 1.25 (m, 1 H), 1.16−0.85(m, 9 H). Anal. ($C_{22}H_{30}O$·0.03 $C_4H_8O_2$) C, H. The presence of ethyl acetate was confirmed by NMR.

1-Methoxy-3-(1′,1′-dimethylheptyl)-cannabinol (21). To a solution of **18a** (0.25 g, 0.68 mmol) in acetone (10 mL) was added K_2CO_3 (0.3 g), followed by iodomethane (3 mL). The reaction mixture was then stirred at 45 °C under N_2, overnight. The reaction mixture was concentrated, and the residue was partitioned between water and ether. The aqueous layer was separated and extracted (2mx) with ether. The combined ether extracts were washed with water, dried, and concentrated to afford a gum. Purification of the crude product by flash chromatography on SiO_2 eluting with varying amounts of ethyl acetate in hexanes (100% hexanes − 1% EtOAc/hexanes) afforded compound **21** as a gum (0.199 g, 77%). ^{1}H NMR (100 MHz, $CDCl_3$) δ 8.25 (d, J = 2.5 Hz, 1 H), 7.09 (m, 2 H), 6.55 (m, 2 H), 3.96 (s, 3 H), 2.4 (s, 3 H), 1.59 (s, 6 H), 1.28 (s, 6 H), 1.16−0.82 (m, 13 H). Anal. ($C_{26}H_{36}O_2$) C, H.

3-(1′,1′-Dimethylheptyl)-9-carbomethoxy-cannabinol (22). 3-(1′,1′-Dimethylheptyl)-9-carboxy-Δ^9-tetrahydrocannabinol *tert*-butyldimethylsilyl ether was synthesized by a previously published procedure.[23c]

To a solution of 3-(1′,1′-dimethylheptyl)-9-carboxy-Δ^9-tetrahydrocannabinol *tert*-butyldimethylsilyl ether (1.66 g) in acetone (50 mL) was added K_2CO_3 (1 g), followed by iodomethane (4 mL). The reaction mixture was then stirred at 25 °C overnight. The acetone solution was concentrated, and the residue was partitioned between water and ether. The aqueous layer was separated and extracted (2×) with ether. The combined ether extracts were washed with water, dried, and concentrated to afford 3-(1′,1′-dimethylheptyl)-9-carbomethoxy-Δ^9-tetrahydrocannabinol *tert*-butyldimethylsilyl ether (1.7 g), which was used directly in the next step without further purification.

It was converted to 3-(1′,1′-dimethylheptyl)-9-carbomethoxy-cannabinol *tert*-butyldimethylsilyl ether in a similar manner as described for the synthesis of **14** (72%).

To a solution of 3-(1′,1′-dimethylheptyl)-9-carbomethoxy-cannabinol *tert*-butyldimethylsilyl ether (0.177 g, 0.33 mmol) in THF (3 mL) was added a 1 M solution of Bu_4NF in THF (1 mL). The reaction mixture was stirred at 25 °C for 0.5 h, then 3 mL of 1 N HCl was added (pH 1) followed by ether. The aqueous layer was separated and extracted (2×) with ether. The combined ether extracts were washed with water, dried, and concentrated. Purification of the crude product by preparative TLC plate (20 × 20 × 2 mm thickness) eluting with 10% EtOAc/hexanes afforded compound **22** (0.13 g, 94%) as a gum. ^{1}H NMR (100 MHz, $CDCl_3$) δ 9.3 (d, J = 2.7 Hz, 1 H), 8.1 (dd, J = 9.0, 2.7 Hz, 1 H), 7.5 (d, J = 9.0 Hz, 1 H), 6.8 (m, 2 H), 4.2 (s, 3 H), 1.5 (m, 25 H). Anal. ($C_{26}H_{34}O_4$) C, H.

1-Deoxy-3-(1′,1′-dimethylbutyl)-9-carbomethoxy-cannabinol (23). Compound **23** (73%) was prepared in a similar manner as described for the synthesis of **16**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (d, J = 1.6 Hz, 1 H), 7.9 (dd, J = 8.2, 1.6 Hz, 1 H), 7.71 (d, J = 8.2 Hz, 1 H), 7.28 (d, J = 8.0 Hz, 1 H), 7.02 (dd, J = 8.2, 1.9 Hz, 1 H), 6.9 (d, J = 1.9 Hz, 1 H), 3.93 (s, 3 H), 1.63 (s, 6 H), 1.55 (m, 2 H), 1.31 (s, 6 H), 1.1−0.83 (m, 5 H). Anal. ($C_{23}H_{28}O_3$) C, H.

1-Deoxy-3-(1′,1′-dimethylbutyl)-11-hydroxy-cannabinol (25). Using the same procedure as in the preparation of **17**, compound **23** (0.417 g) afforded **25** (0.33 g, 87%) as a gum. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (m, 2 H), 7.24 (m, 2 H), 6.98 (dd, J = 8.0, 1.9 Hz, 1 H), 6.89 (d, J = 1.9 Hz, 1 H), 4.7 (d, J = 5.8 Hz, 2 H), 1.62 (s, 6 H), 1.6 (m, 3 H),1.27 (s, 6 H), 1.1−0.82 (m, 5 H). Anal. ($C_{22}H_{28}O_2$) C, H.

Pharmacology. 1. Drug Preparation and Administration. For binding assays, the compounds were prepared as 1 mg/mL stock solutions in absolute ethanol and were stored at −20 °C.

2. Binding Assays. Radioligand binding to P_2 membrane preparations using the filtration method was performed as described elsewhere.[15,24] Displacement curves were generated by incubating drugs with 1 nM [^{3}H]CP-55,490. The assays were

performed in triplicate, and the results represent the combined data from the three individual experiments.

3. Data Analysis. IC_{50} values were converted to K_i values as described by Cheng and Prusoff.[25]

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Supporting Information Available: Elemental analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Pertwee, R. G. Phamacological, physiological and clinical implications of the discovery of cannabinoid receptors: an overview. In *Cannabinoid Receptors*; Pertwee, R. G., Ed.; Academic Press: London, 1995; pp 1−29. (b) Reviews. See, for example: Pertwee, R. G. Pharmacology of Cannabinoid CB1 and CB2 Receptors. *Pharmacol. Ther.* **1997**, *74*, 129−180. (c) Huffman, J. W.; Lainton, J. A. H. Recent Developments in the Medicinal Chemistry of Cannabinoids. *Current Med. Chem.* **1996**, *3*, 101−116.

(2) Devane, W. A.; Hannus, L.; Breuer, A.; Pertwee, R. G.; Stevenson, L. A.; Griffin, G.; Gibson, D.; Mandelbaum, A.; Etinger, A.; Mechoulam, R. Isolation and Structure of a Brain Constituent that Binds to the Cannabinoid Receptor. *Science* **1992**, *258*, 1946−1949.

(3) Munro, S.; Thomas, K. L.; Abu-Shaar, M. Molecular Characterization of a Peripheral Receptor for Cannabinoids. *Nature* **1993**, *365*, 61−65.

(4) Mechoulam, R.; Ben-Shabat, S.; Hanus, L.; Ligumsky, M.; Kaminski, N.; Schatz, A.; Gopher, A.; Almog, S.; Martin, B.; Compton, D.; Pertwee, R. G.; Griffin, G.; Bayewitch, M.; Barg, J.; Vogel, Z. Identification of an Endogenous 2-Monoglyceride, Present in Canine Gut, that Binds to Cannabinoid Receptors. *Biochem. Pharmacol.* **1995**, *50*, 83−90.

(5) Sugiura, T.; Kondo, S.; Sukagawa, A.; Nakane, S.; Shinoda, A.; Itoh, K.; Yamashita, A.; Waku, K. 2- Arachidonoyl-Glycerol: a Possible Endogenous Cannabinoid Receptor Ligand in Brain. *Biochem. Biophys. Res. Commun.* **1995**, *215*, 89−97.

(6) Martin, B. R.; Mechoulam, R.; Razdan, R. K. Discovery and Characterization of Endogenous Cannabinoids. *Life Sci.* **1999**, *65*, 573−595.

(7) Rinaldi-Carmona, M.; Barth, F.; Healume, M.; Shire, D.; Calendra, B.; Congy, C.; Martinez, S.; Maruani, J.; Neliat, G.; Ferrara, P.; Soubrie, P.; Breliere, J. C.; Le Fur, G. SR141716A, a Potent and Selective Antagonist of the Brain Cannabinoid Receptor. *FEBS Lett.* **1994**, *350*, 240−244.

(8) Rinaldi-Carmona, M.; Barth, F.; Millan, J.; Derocq, J. M.; Casellas, P.; Cengy, C.; Oustric, D.; Sarran, M.; Bouaboule, M.; Calandra, B.; Portier, M.; Shire, D.; Breliere, J. C.; Le Fur, G. SR144528, an Antagonist for the Peripheral Cannabinoid Receptor that Behaves as an Inverse Agonist. *J. Pharmacol. Exp. Ther.* **1998**, *284*, 644−650.

(9) Di Marzo, V.; Fontana, A.; Casdas, H.; Schinelli, S.; Cimino, G.; Schwartz, J. C.; Piomelli, D. Formation and Inactivation of Endogenous Cannabinoid Anandamide in Central Neurons. *Nature* **1994**, *372*, 686−691.

(10) Stella, N.; Schweitzer, P.; Piomelli, D. A Second Endogenous Cannabinoid that Modulates Long-Term Potentiation. *Nature* **1997**, *388*, 773−778.

(11) Beltramo, M.; Stella, N.; Calignaro, A.; Lin, S. Y.; Makriyannis, A.; Piomelli, D. Functional Role of High-Affinity Anandamide Transport, as Revealed by Selective Inhibition. *Science* **1997**, *277*, 1094−1097.

(12) Reviews. See, for example: (a) Di Marzo, V.; De Petrocellis, L. *Internet J. Science-Biol. Chem.* **1997**, *1*, 1−21. (b) Mechoulam, R.; Hanus, L.; Fride, E. *Progress in Medicinal Chemistry Vol. 35*; G. P. Ellis, D. K., Luscombe, A. W., Eds.; Oxford: Elsevier Science B. V.; 1998; pp 199−243.

(13) (a) Razdan, R. K. Structure Activity Relationships in Cannabinoids. *J. Pharmacol. Rev.* **1986**, *38*, 75−149. (b) Rapaka, R. S.; Makriyannis, A. *Structure−Activity Relationships of the Cannabinoids*. NIDA Research Monograph 79, National Institute of Drug Abuse, Rockville, MD, 1987. (c) Melvin, L. S.; Milne, G. M.; Johnson, M. R.; Subramanian, B.; Wilken, G. H.; Howlett, A. C. Structure Activity Relationships for Cannabinoid Receptor-Binding and Analgesic Activity: Studies of Bicyclic Cannabinoid Analogues. *Mol. Pharmacol.* **1993**, *44*, 1008−1015.

(14) Kaminski, N. E.; Abood, M. E.; Kessler, M. E.; Martin, B. R.; Schatz, A. R. Identification of a Functionally Relevant Cannabinoid Receptor on Mouse Spleen Cells that is Involved in Cannabinoid-Mediated Immune Modulation. *Mol. Pharmacol.* **1993**, *42*, 736−742.

(15) Showalter, V. M.; Compton, D. R.; Martin, B. R.; Abood, M. E. Evaluation of Binding in a Transfected Cell Line Expressing a Peripheral Cannabinoid Receptor (CB2): Identification of Cannabinoid Receptor Subtype Selective Ligands. *J. Pharmacol. Exp. Ther.* **1996**, *278*, 989−999.

(16) Rhee, M. H.; Vogel, Z.; Barg, J.; Bayewitch, M.; Levy, R.; Hanus, L.; Breuer, A.; Mechoulam, R. Cannabinol Derivatives: Binding to Cannabinoid Receptors and Inhibition of Adenylylcyclase. *J. Med. Chem.* **1997**, *40*, 3228−3233.

(17) Gareau, Y.; Dufrense, C.; Gallant, M.; Rochette, C.; Sawyer, N.; Slipetz, D. M.; Tremblay, N.; Weech, P. K.; Metters, K. M.; Labelle, M. Structure Activity Relationships of Tetrahydrocannabinol Analogues on Human Cannabinoid Receptors. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 189−194.

(18) Huffman, J.; Showalter, V.; Abood, M. E.; Compton, D. R.; Martin, B. R.; Bramblett, R. D.; Reggio, P. H. Synthesis and Pharmacology of a Very Potent Cannabinoid Lacking a Phenolic Hydroxyl with High Affinity for the CB2 Receptor. *J. Med. Chem.* **1996**, *39*, 3875−3877.

(19) Huffman, J. W.; Liddle, J.; Yu, S.; Aung, M. M.; Abood, M. E.; Wiley: J. L.; Martin, B. R. 3-(1′,1′-Dimethylbutyl)-1-deoxy-Δ^8-THC and Related Compounds: Synthesis of Selective Ligands for the CB2 Receptor. *Bioorg. Med. Chem. Lett.* **1999**, *7*, 22905−2914. (a) Adams, R.; Pease, D. C.; Cain, C. K.; Clark, J. H. Structure of Cannabidiol. VI. Isomerisation of Cannabidiol to Tetrahydrocannabinol, a Physiologically Active Product. Conversion of Cannabidiol to Cannabinol. *J. Am. Chem. Soc.* **1940**, *62*, 2402−2405.

(20) Dominianni, S. J.; Ryan, C. W.; De Armitt, C. W. Synthesis of 5-(tert-Alkyl) Resorcinols. *J. Org. Chem.* **1977**, *42*, 344−346.

(21) Siegel, C.; Gordon, P. M.; Uliss, D. B.; Handrick, G. R.; Dalzell, H. C.; Razdan, R. K. Synthesis of Racemic and Optically Active Δ^9-Tetrahydrocannabinol (THC) Metabolites. *J. Org. Chem.* **1991**, *56*, 6865−6872.

(22) Kenner, G. W.; Williams, N. R. A Method of Reducing Phenols to Aromatic Hydrocarbons. *J. Chem. Soc.* **1955**, 522−525.

(23) (a) Ben Zvi, Z.; Mechoulam, R.; Burstein, S. H. Synthesis of $\Delta^{1(6)}$-THC Metabolites. *Tetrahedron Lett.* **1970**, 4495−4497. (b) Inayama. S.; Sawa, A.; Hosoya, E. The oxidation of Δ^1-and Δ^6- THC with Selenium Dioxide. *Chem. Pharm. Bull. Japan* **1974**, *22*, 1519−1525. (c) Siegel, C.; Gordon, P. M.; Razdan, R. K. Studies on the Synthesis of (−)-11-Nor-9-Carboxy-Δ^9-Tetrahydrocannabinol (THC) and Related Compounds: An Improved Oxidative Procedure. *Synthesis* **1991**, 851−853.

(24) Compton, D. R.; Johnson, M. R.; Melvin, L. S.; Martin, B. R. Pharmacological Profile of a Series of Bicyclic Cannabinoid Analogues: Classification as Cannabimimetic Agents. *J. Pharmacol. Exp. Ther.* **1992**, *260*, 201−209.

(25) Cheng, Y. C.; Prusoff, W. H. Relationship between the Inhibition Constant (k_i) and the Concentration of Inhibitor which causes 50% Inhibition (I_{50}) on an Enzymatic Reaction. *Biochem. Pharmacol.* **1973**, *22*, 3099−3108.

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