Importance of the C-1 Substituent in Classical Cannabinoids to CB_2 Receptor Selectivity: Synthesis and Characterization of a Series of *O*,2-Propano-Δ^8-tetrahydrocannabinol Analogs

Patricia H. Reggio,*,† Tiansheng Wang,‡ Amy E. Brown,‡ Denise N. Fleming,‡ Herbert H. Seltzman,‡ Graeme Griffin,§ Roger G. Pertwee,§ David R. Compton,|| Mary E. Abood,|| and Billy R. Martin||

Department of Chemistry, Kennesaw State University, Kennesaw, Georgia 30144, Research Triangle Institute, Research Triangle Park, North Carolina 27709-2194, Department of Biomedical Sciences, Institute of Medical Sciences, Aberdeen University, Foresterhill, Aberdeen AB25 2ZD, Scotland, United Kingdom, and Department of Pharmacology and Toxicology, Medical College of Virginia, Virginia Commonwealth University, Richmond, Virginia 23298

Received March 5, 1997[⊗]

The separation of the mood-altering effects of cannabinoids from their therapeutic effects has been long sought. Results reported here for a series of C-9 analogs of the cyclic ether *O*,2-propano-Δ^8-tetrahydrocannabinol (*O*,2-propano-Δ^8-THC) point to the C-1 position in classical cannabinoids as a position for which CB_2 subtype selectivity occurs within the cannabinoid receptors. *O*,2-Propano-11-nor-Δ^8-THC, *O*,2-propano-$\Delta^{9,11}$-THC, *O*,2-propano-9-oxo-11-nor-hexahydrocannabinol (*O*,2-propano-9-oxo-11-nor-HHC), and *O*,2-propano-9α- and *O*,2-propano-9β-OH-11-nor-HHC were synthesized and evaluated in radioligand displacement assays for affinity at the CB_1 and CB_2 receptors and in the mouse vas deferens *in vitro* assay and the mouse tetrad *in vivo* assay for cannabinoid activity. Evaluation of binding affinity at the CB_1 and CB_2 receptors revealed that each compound possesses a modest increased affinity for the CB_2 receptor. Analogs which contained an oxygen attached to C-9 (i.e., oxo and hydroxy derivatives) showed the highest affinity and selectivity for CB_2 (for *O*,2-propano-9-oxo-11-nor-HHC, $K_i(CB_1) = 90$ nM, $K_i(CB_2) = 23$ nM, selectivity ratio 3.9; for *O*,2-propano-9β-OH-11-nor-HHC, $K_i(CB_1) = 26$ nm, $K_i(CB_2) = 5.8$ nM, selectivity ratio 4.5). Each compound was found to produce a dose-dependent inhibition of electrically-evoked contractions of the mouse isolated vas deferens when administered at submicromolar concentrations. This inhibition could readily be prevented by the selective CB_1 cannabinoid receptor antagonist SR-141716A. The analogs exhibited unique *in vivo* profiles with *O*,2-propano-$\Delta^{9,11}$-THC exhibiting antinociception with reduced activity in three other *in vivo* measures and *O*,2-propano-9β-OH-HHC exhibiting lack of dose responsiveness in all measures. The CB_2 selectivities of the *O*,2-propano analogs may be due to differences in solvation/desolvation that occur when the ligands enter the CB_1 vs CB_2 binding site. Alternatively, the CB_2 selectivities may be the result of an amino acid change from a hydrogen bond-accepting residue in CB_1 to a hydrogen bond-donating residue in CB_2.

The separation of the therapeutic effects of the cannabinoids from their psychotropic effects has been long sought. With the discovery and cloning of the first two cannabinoid receptors (CB_1 and CB_2),[1,2] both G-protein-coupled receptors, the cannabinoid field may have moved closer toward this goal. Central nervous system (CNS) responses to cannabinoid compounds are believed to be mediated exclusively by the CB_1 receptor, as transcripts of the CB_2 receptor have not been found in brain tissue by either Northern analysis or *in situ* hybridization studies.[2] The work of Galiegue and co-workers[3] has suggested that cannabinoids may exert specific receptor-mediated actions on the immune system specifically through the CB_2 receptor. Thus, given the immune system modulation produced by cannabinoids, a cannabinoid with low CB_1 affinity (and therefore devoid of mood-altering effects), but with high CB_2 affinity, might have therapeutic potential.

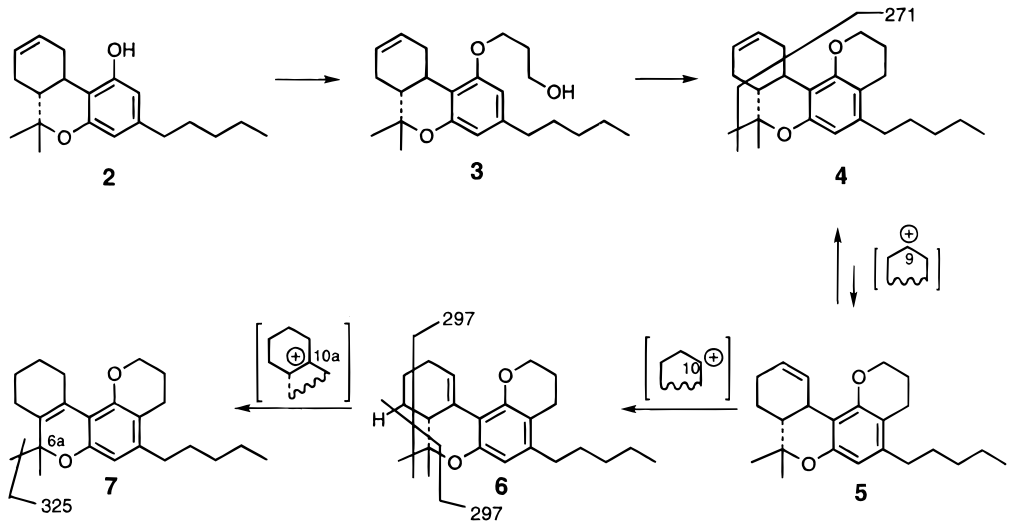
To date, few studies have focused on what molecular features produce selectivity for the CB_2 receptor. Very recent results (including those to be reported here) point to the C-1 position in classical cannabinoids as a modulation site for cannabinoid receptor subtype selectivity. In their recent study of analogs of 11-hydroxy-Δ^8-tetrahydrocannabinol 1′,1′-dimethylheptyl (11-OH-Δ^8-THC DMH), Huffman et al.[4] reported that replacement of the phenolic hydroxyl at C-1 with a hydrogen produces a CB_2 selective ligand ($K_i(CB_1) = 1.2$ nM, $K_i(CB_2) = 0.032$ nM; selectivity ratio 37.5). In addition, Gareau et al.[5] reported that the conversion of the C-1 phenolic hydroxyl of a classical cannabinoid to a methoxy group (i.e., etherification) also produced CB_2 selective ligands. In both of these recent studies, analogs possessed a longer side chain than natural cannabinoids, a 1′,1′-dimethylhelptyl (DMH) side chain at C-3.

Several years ago, in an effort to ascertain whether the phenolic oxygen at C-1 serves as a proton donor or acceptor in its interaction with cannabinoid receptors, we designed, synthesized, and tested *O*,2-propano-Δ^8-THC, **1**.[6] Like the compounds made by Gareau et al.,[5] **1** is a C-1 ether. Unlike the compounds reported by Gareau et al.,[5] however, the C-1 hydroxyl in **1** has been etherified by incorporation into a fourth ring, producing a more rigid structure. We report here the synthesis

* Address correspondence to this author at: Department of Chemistry, Kennesaw State University, 1000 Chastain Rd., Kennesaw, GA 30144.
† Kennesaw State University.
‡ Research Triangle Institute.
§ Aberdeen University.
|| Medical College of Virginia.
⊗ Abstract published in *Advance ACS Abstracts,* September 1, 1997.

S0022-2623(97)00136-2 CCC: $14.00

Scheme 1



and pharmacological evaluation of a series of etherified cannabinoids based on *O*,2-propano-Δ^8-THC (**1**): compounds **4**, **8**, **9**, and **10a,b**. Consistent with results reported by Gareau et al.,[5] these etherified compounds exhibit selectivity for the CB_2 receptor. This selectivity is discussed here in terms of cannabinoid ligand structure−activity relationships (SAR) and in terms of its possible implication for models of the CB_1 and CB_2 receptors.

Results and Discussion

Synthesis of *O*,2-Propano Cannabinoids. Two routes were pursued to prepare the series of *O*,2-propano cannabinoids with different, though complementary, aims. The first route (Scheme 1) targeted *O*,2-propano-11-nor-Δ^8-THC (**4**) by the most direct route of alkylation/cyclization via the known 11-nor-Δ^8-THC (**2**). The second route (Scheme 2) followed parallel chemistry but with the introduction of the pyran ring first, thus providing a series of new *O*,2-propano intermediates that were of interest for SAR studies. Modifications of the second route sought to enhance the yields of the problematic chemistry of the *O*,2-propano intermediates and to obtain the epimeric alcohols (**10a,b**) to address the issue of chirality versus activity. Compound **4** was first prepared from 11-nor-Δ^8-THC (**2**)[7] by the route of alkylation with 3-bromopropanol and subsequent cyclodehydration shown inScheme 1, similar to the reported *O*,2-propano-Δ^8-THC.[8] Three isomeric compounds were generated in the cyclodehydration with P_2O_5 in the ratio 50:42:6 as shown by GC−MS. The major isomer was **4** as determined by its ^{1}H NMR spectrum, which included vinyl resonances for the Δ^8-unsaturation that were consistent with those reported for 11-nor-Δ^8-THC and its MS which exhibited a base peak fragment at *m*/*z* 271 for the combined retro-Diels−Alder loss of butadiene and cleavage of one of the geminal methyls indicative of Δ^8-cannabinoids. The second most prominent product was identified as the $\Delta^{6a,10a}$-olefin **7** by the equivalent geminal methyls, the absence of vinyl resonances, and the general symmetry of the cyclohexene ring resonances in the ^{1}H NMR spectrum for this achiral compound and by the MS. The latter was remarkable in that the M^+−methyl base peak fragment at *m*/*z* 325 was unusually prominent at 10 × the M^+ ion explicable by facilitated cleavage of the now allylic methyl fragment. The minor component was not isolated but is tentatively assigned the $\Delta^{10,10a}$-olefin **6** by its MS which shows a relatively large *m*/*z* 297 (64% of M^+ base ion) for loss of ethylene from a retro-Diels−Alder followed by loss of a geminal methyl to generate a further aromatized fragment. An alternative fragmentation scheme, similarly dependant on a $\Delta^{10,10a}$-unsaturation, would be loss of the allylic isopropyl moiety and a hydrogen. Structure **6** is also supported by its logical intermediacy in the clockwise migration of the double bond from the Δ^8- to the $\Delta^{6a,10a}$-position, a process that is driven by the stabilities of the intermediate carbocations and the olefins (Scheme 1).

The second route provided the cannabinoids **8**−**10a,b**, in addition to **4**, as outlined in Scheme 2. The desired **8** was obtained in 33% chromatographed yield by photochemical isomerization of **1** similar to that reported for $\Delta^{9,11}$-THC.[9] Oxidative cleavage of the impure olefin **8** with potassium permanganate/sodium periodate gave *O*,2-propano-9-oxo-11-nor-HHC (**9**) in 9−13% chromatographed yield in contrast with the 91% yield obtained with $\Delta^{9,11}$-THC methyl ether.[10] Experiments showed that the oxidation of **8** to the 9,11-diol, as the first of the two-stage oxidation, was the poor step; cleavage of the diol to **9** proceeded in 96% unpurified yield. Improved conditions involved the use of osmium tetraoxide and potassium ferricyanide[11] to generate the diol followed by addition of sodium periodate to cleave the diol and provide **9** in 57% chromatographed yield.

Reduction of **9** with sodium borohydride gave a single epimer of the alcohol **10b** in 72% yield. The use of potassium tri-*sec*-butyl borohydride (K-Selectride) as the reducing agent gave the other epimer **10a** as essentially the only isomer. The epimers were identified by the coupling of their resonances in the ^{1}H NMR spectra which reflects the different orientations of the relevant C-9 proton (α or β) versus the adjacent C-8 and C-10 protons. Thus, as with the corresponding cannabinoids without the *O*,2-propano ether,[12] the 9β-H of the 9α-alcohol exhibited a lesser peak width at half-height (6.9 Hz) and was further downfield (4.20 ppm) than the 9α-H of the 9β-alcohol (21.9 Hz, 3.82 ppm) which exhibited greater coupling constants due to the trans-diaxial relationship of the 9α-H to its neighbors.

Scheme 2

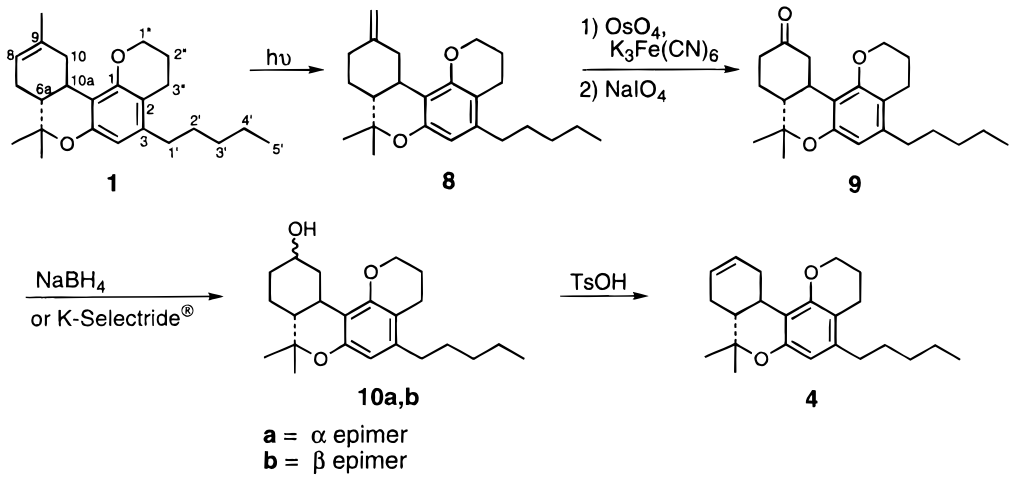


Table 1. Receptor Binding and Pharmacological Results for *O*,2-Propano-Δ^8-THC Analogs

	$K_i \pm$ SEM (nM)			MVD (95% confidence limit)		mouse tetrad[c] (mg/kg)			
compound	CB_1	CB_2	CB_1/CB_2	K_d (nM)[a]	EC_{50} (nM)[b]	SA	TF	RT	RI
(−)-Δ^9-THC	41 ± 2[d]	36 ± 10[d]	1.1	2.66[e] (1.43−4.96)	8.18[f] (6.16−10.88)	1.0[g]	1.4[g]	1.4[g]	1.5[g]
O,2-propano-11-nor-Δ^8-THC (**4**)	364 ± 56	128 ± 21	2.8	2.97 (1.23−7.70)	16.5 (11.36−24.0)	22% at 100	12% at 100	−1.2°C at 100	4% at 100
O,2-propano-$\Delta^{9,11}$-THC (**8**)	884 ± 39	200 ± 60	4.4	2.49 (0.92−7.17)	28.60 (8.39−97.46)	46% at 30	23 ± 2	−3.6°C at 30	54% at 30
O,2-propano-9-oxo-11-nor-HHC (**9**)	90 ± 14	23 ± 4	3.9	1.72 (0.66−9.33)	7.23 (2.67−19.61)	9.2 ± 3.3	1.9 ± 0.5	−2.9°C at 60	43 ± 19
O,2-propano-9α-OH-11-nor-HHC (**10a**)	ND	ND	ND	1.67 (0.62−5.94)	83.5 (49.0−142)	ND	ND	ND	ND
O,2-propano-9*β*-OH-11-nor-HHC (**10b**)	26 ± 2	5.8 ± 2.9	4.5	3.26 (2.13−5.07)	5.70 (2.29−14.17)	34% at 30	74% at 30	−2.4°C at 30	38% at 30

[a] Dissociation constant (K_d) of SR-141716A determined in the presence of various CB receptor agonists using the mouse vas deferens (MVD). [b] EC_{50} for inhibition of electrically-evoked contractions of the MVD. [c] Data for spontaneous activity (SA), tail flick (TF), rectal temperature (RT), and ring immobility (RI) are expressed as either $ED_{50} \pm$ SE from ALLFIT analysis or percent effect at the indicated dose (mg/kg). [d] Reference 21. [e] Reference 28. [f] Reference 15. [g] Reference 33.

Dehydration with toluenesulfonic acid yielded the target, compound **4**. The identities of the intermediates and the target **4** were determined by ^{1}H NMR and MS and were consistent with spectra of **1** and the corresponding *O*,2-propano cannabinoid analogs lacking the *O*,2-propano ring.

CB_1 Receptor Affinities. The affinity of each compound for the cannabinoid CB_1 receptor is presented in Table 1. Here the affinity of (−)-Δ^9-THC, a free phenolic classical cannabinoid, is reported as a reference. With the exception of compound **10b**, the CB_1 affinities of the series were reduced relative to that of the free phenolic compound, (−)-Δ^9-THC.[13] *O*,2-Propano-$\Delta^{9,11}$-THC (**8**) exhibited the lowest CB_1 affinity. The introduction of an electronegative atom at C-9 in *O*,2-propano-9-oxo-11-nor-HHC (**9**) resulted in an improvement in CB_1 affinity within the *O*,2-propano series. *β*-Hydroxylation at C-9 (**10b**) resulted in the highest CB_1 affinity. These results parallel the rank order of CB_1 affinities exhibited by free phenolic THCs with substitution at C-9 with one exception. In free phenolic THCs, nabilone (9-oxo-11-nor-HHC DMH, which corresponds to **9**) has a higher CB_1 affinity than 9*β*-OH-11-nor-HHC (which corresponds to **10b**).[13] However, the dimethylheptyl C-3 side chain of nabilone may account for its higher CB1 affinity relative to 9*β*-OH-11-nor-HHC which possesses a pentyl C-3 side chain.

Mouse Vas Deferens (MVD) Assay. The pharmacological activities of compounds **4**, **8**, **9**, and **10a,b** were also measured using the mouse isolated vas deferens, a preparation which is thought to contain cannabinoid receptors that can mediate an inhibitory effect of cannabinoid receptor agonists on electrically-evoked contractions.[14−16] All studied compounds were found to produce concentration-related inhibitions of electrically-evoked contractions of the vas deferens and to have log concentration−response curves that are sigmoid in shape ($r^2 = 0.972-0.998$). The mean EC_{50} values of the drugs, with their 95% confidence limits shown in parentheses, are given in Table 1. Each compound appeared to be a full agonist in the vas deferens. At a concentration of 31.62 nM, the CB_1 receptor antagonist SR-141716A[17] behaved as a competitive surmountable antagonist of all five agonists, producing parallel rightward shifts in each of these log concentration−response curves. The susceptibility of these agonists to antagonism by the antagonist SR-141716A was no different from that of (−)-Δ^9-THC (Table 1). The K_d values (with their 95% confidence limits) for SR-141716A in the presence of **4**, **8**, **9**, **10a**, or **10b**, listed in Table 1, show the K_d for SR-141716A to be essentially unchanged, thus supporting the conclusion that all of the agonists are acting on the same receptor. Taken together, these results provide strong support for the hypothesis that analogs **4**, **8**, **9**, and **10a,b** are CB_1 cannabinoid receptor agonists. The trends shown in the MVD results for **4**, **8**, **9**, and **10b** parallel their CB_1 affinities reported in Table 1. *O*,2-Propano-9α-OH-11-nor-HHC (**10a**) was evaluated solely in the MVD. The MVD EC_{50} results for **10a** vs **10b** parallel earlier activity results for 9α-

and 9β-OH-11-nor-HHC[12,18] with the β-analog exhibiting greater activity than the α-analog.

Mouse Tetrad. The *in vivo* pharmacology of compounds **4**, **8**, **9**, and **10b** was evaluated in the mouse model of cannabimimetic activity which consists of spontaneous activty (SA), antinociception (as tail flick, TF), rectal temperature (RT), and ring immobility (RI) assays.[19] The analogs demonstrated differences in potencies, as well as in their spectrum of action. The *O*,2 propano-11-nor-Δ^8-THC analog (**4**) which exhibited low affinity for the CB_1 receptor (almost 10-fold less than that of Δ^9-THC) demonstrated, as expected, very low potency in the behavioral assay. *O*,2-Propano-$\Delta^{9,11}$-THC (**8**) had the least affinity for the CB_1 receptor yet produced a unique pharmacological profile. As can be seen in Table 1, this compound was capable of producing maximal effects in the tail-flick assay that were dose-responsive as evidenced by an ED_{50} of 23 mg/kg. There is good agreement between the *O*,2-propano-$\Delta^{9,11}$-THC to Δ^9-THC CB_1 receptor affinity ratio (21-fold) and for tail-flick activity (16-fold). However, this analog (**8**) produced approximately 50% effect in the SA, RT, and RI assays at a high dose of 30 mg/kg with these effects being non-dose-responsive. These data reveal a separation in the pharmacological effects of this analog, although failure to produce dose-responsive effects in SA, RT, and RI make it difficult to establish the degree of this separation. *O*,2-Propano-9-oxo-11-nor-HHC (**9**) exhibited a CB_1 receptor affinity approximately one-half that of Δ^9-THC and produced dose-responsive effects in SA, TF, and RI. The unique finding with analog **9** is the large differences in potencies for production of these different behaviors. Most cannabinoids behave in a fashion similar to that of Δ^9-THC in that there is relatively little separation in potencies for production of these four behaviors (i.e., see Table 1). Analog **9** was capable of lowering RT by almost 3 °C at a high dose of 60 mg/kg, but its effects were non-dose-responsive. *O*,2-Propano-9β-OH-11-nor-HHC (**10b**) had a CB_1 affinity somewhat greater than that of Δ^9-THC, yet it was incapable of producing dose-responsive effects in any of the *in vivo* pharmacological assays. We chose to show the percent effect that a dose of 30 mg/kg produced merely to underscore the lack of pharmacological effectiveness.

An explanation for the discrepancy between the CB_1 receptor affinities and *in vivo* pharmacological potencies is not readily apparent. However, several should be discussed. There is always the possibility that pharmacokinetic factors play a role. In such a case, the most likely candidate would be metabolism. It is unlikely that tissue distribution would be a major factor because the physiochemical characteristics of the four analogs do not differ to a great degree. Of course, *O*,2-propano-$\Delta^{9,11}$-THC (**8**) and *O*,2-propano-9-oxo-11-nor-HHC (**9**) were effective in at least one pharmacological assay demonstrating their ability to reach the receptor. A more plausible explanation may be that these compounds are not interacting with the CB_1 receptor in a fashion identical to that of Δ^9-THC. Regardless of the mechanism, these analogs appear to be logical targets for separation of actions that are thought to occur solely at the CB_1 receptor.

CB_2 Receptor Affinities. The CB_2 affinities of compounds **4**, **8**, **9**, and **10b** (see Table 1) follow the same general trend as seen in the CB_1 affinities, i.e., the introduction of an electronegative atom at C-9 results in compounds with better CB_2 affinities. The inclusion of a 9β-hydroxyl substituent (**10b**) produces the highest CB_2 affinity, while inclusion of a 9-oxo substitutent (**9**) produces a slightly lower CB_2 affinity. The $\Delta^{9,11}$-derivative **8** has the lowest CB_2 affinity in the series. For each compound, the third column in Table 1 presents the ratio of the K_i at the CB_1 receptor to the K_i at the CB_2 receptor. This ratio reveals that compounds **4**, **8**, **9**, and **10b** have 3−4 times higher affinity for the CB_2 receptor, no matter the functionality or lack of functionality at C-9. The free phenolic reference compound, (−)-Δ^9-THC (Table 1), exhibits essentially equal affinity for both receptor subtypes (i.e., ratio = 1.1). Very recently, Skaper et al.[20] have suggested that cerebellar granule cells and cerebellum express genes encoding both the CB_1 and CB_2 receptors. This is the first report that the CB_2 receptor may be present in brain. The CB_1 binding assay results reported here were obtained using brain homogenate[13] rather than a CB_1 cloned receptor, while the CB_2 assays results reported here used a cloned receptor. It is possible that the magnitude of selectivity reported here for the *O*,2-propano series, in fact, may be larger, if there is indeed a CB_2 receptor present in brain.

Conclusions

Many free phenolic cannabinoids such as Δ^9-THC, Δ^8-THC, and CP-55,940 exhibit similar affinities for the CB_1 and CB_2 receptors.[21,22] Our results point to the C-1 functional group in classical cannabinoids as a ligand site which results in CB_2 receptor subtype selectivity. The modest CB_2 selectivity of the *O*,2-propano cannabinoids is consistent with the 4.7-fold CB_2 selectivity for the C-1 methyl ether of nabilone reported by Gareau et al.[5] It is possible that the CB_2 selectivities of the *O*,2-propano series are due simply to differences in solvation/desolvation that occurs when the ligands enter the CB_1 vs the CB_2 binding site. On the other hand, the CB_2 selectivities exhibited by the series may be the result of an amino acid change in the binding pocket from a hydrogen bond-accepting residue in CB_1 to a hydrogen bond-donating residue in CB_2.

Experimental Section

Synthesis. ^{1}H NMR spectra were recorded on a Bruker AM-250 MHz or a Bruker AMX-500 MHz spectrometer. The chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) in $CDCl_3$ unless otherwise specified. GC−MS were obtained on an HP 5890 series 2 GC with a DB-17 column coupled to a Hewlett-Packard 5989A spectrometer in the electron impact (EI) mode with a 70 eV ionization voltage. GC chromatograms were obtained on a Varian 3300 gas chromatograph with a FI detector on a 2% OV-17 column. TLCs were run on Whatman K5F silica gel plates with detection by phosphomolybdic acid−ceric sulfate sprays. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, GA, and were within ±0.4% of the value for the given empirical formula.

***O*,2-Propano-$\Delta^{9,11}$-THC (8).** *O*,2-Propano-Δ^8-THC (1.0 g, 2.82 mmol) and 5 mL of *p*-xylene were dissolved in 450 mL of 2-propanol and degassed *in vacuo* with stirring. The solution was added, under argon, to a photolysis apparatus fitted with a water-cooled quartz immersion finger with a Vycor filter and a Hanovia 450 W medium pressure mercury lamp. A slow stream of argon was bubbled into the apparatus from the bottom to blanket the reaction and provide mixing. Irradiation

was monitored by GC (270 °C) until complete consumption of the *O*,2-propano-Δ^8-THC (16 h). Removal of solvent *in vacuo* afforded a pale yellow resin which was chromatographed on silica gel eluting with hexane:methylene chloride (75:25) to afford 330 mg (33%) of the title compound; ^{1}H NMR (550 MHz) δ 6.27 (s, 1H, ArH), 4.76 (brs, 1H, vinyl-H), 4.72 (brs, 1H, vinyl-H′), 4.20 (m, 1H, ArOCH), 4.08 (m, 1H, ArOCH′), 3.65 (d, 1H, J = 11 Hz, 10α-H), 2.63 (m, 2H, 3″-CH_2), 2.42 (m, 3H, 1′-CH_2 + 10a-H), 1.38 (s, 3H, 6β-Me), 1.04 (s, 3H, 6α-Me), 0.90 (m, 3H, 5′-Me); MS (EI) m/z 354 (M^+, base), 339 (M − Me), 271 (M − C_5H_8 − Me); UV ϵ_{287} = 1660 L/M cm; GC (250 °C) t_R = 10.3 min (100%); TLC (2% acetone−hexane) R_f = 0.2.

***O*,2-Propano-9-oxo-11-nor-HHC (9).** To a 7 mL aqueous solution of potassium ferricyanide (918 mg, 2.79 mmol) and potassium carbonate (380 mg, 2.75 mmol) was added a 0.16 M solution of osmium tetraoxide in *tert*-butyl alcohol (0.076 mL, 0.012 mmol). To this yellow solution was added a 7 mL solution of *O*,2-propano-$\Delta^{9,11}$-THC (330 mg, 0.93 mmol) in *tert*-butyl alcohol. The resulting green mixture was stirred at ambient temperature for 40 h to give a bright yellow mixture which was treated with finely-powdered sodium periodate (1.59 g, 7.44 mmol). The reaction cleared and became green in color. After stirring at ambient temperature overnight, a yellow precipitate was observed with a rust-colored supernatant. The volatiles were evaporated *in vacuo*; the residue was diluted with water and extracted with diethyl ether. The organics were washed with brine and dried over sodium sulfate. Evaporation of solvent gave a brown foamy resin (295 mg, 89% yield). Flash chromatography on 12 g of silica gel (75:25 CH_2Cl_2:hexane) gave 190 mg of **9** as a clear resin (57% yield): ^{1}H NMR δ 6.28 (s, 1H, ArH), 4.10 (m, 2H, 1″-CH_2), 3.76 (dq, 1H, J = 15.2, 1.8 Hz, 10α-H), 2.79 (dt, 1H, J = 11.9, 3.2 Hz, 10a-H), 2.60 (t, 2H, J = 6.6 Hz, 3′-CH_2), 2.42 (t, 2H, J = 7.3 Hz, 1′-CH_2), 1.96 (m, 2H, 2″-CH_2), 1.44 (s, 3H, 6β-CH_3), 1.09 (s, 3H, 6α-CH_3), 0.89 (t, 3H, J = 7.0 Hz, 5′-CH_3); ^{13}C NMR δ 211.5 (C9), 153.6[a] (C1), 152.0[a] (C4a), 141.3 (C3), 112.3 (C2 and C10b, overlap), 109.5 (C4), 76.7 (C6), 65.7 (Pr 1″), 47.7 (C6a), 45.8 (C10), 40.7 (C8), 34.6 (C10a), 32.2 (1′), 31.9 (3′), 29.3 (2′), 27.8 (C6β), 26.6 (C7), 22.5 (4′), 22.2 (Pr 2″), 21.7 (Pr 3″), 18.7 (C6α), 14.1((5′) (a, assignments may be reversed).

***O*,2-Propano-9β-OH-11-nor-HHC (10b).** *O*,2-Propano-9-oxo-11-nor-HHC (80 mg, 0.22 mmol) in 2.3 mL of dry methanol was treated with $NaBH_4$ (14 mg, 0.36 mmol) under nitrogen in an ice bath with stirring. After the reaction was complete (TLC) (1 h), the solvent was evaporated and the residue was partitioned between CH_2Cl_2 and 0.1 N HCl. The organic layer was dried over Na_2SO_4 and evaporated *in vacuo* and the residue chromatographed on silica gel (3.5 g) with CH_2Cl_2 as the eluant affording 57 mg (72%) of the title compound as a single isomer: ^{1}H NMR δ 6.26 (s, 1H, ArH), 4.18 (m, 1H, ArO-CH), 4.05 (m, 1H, ArO-CH′), 3.82 (m, 1H, 9α-H), 3.36 (dq, 1H, J = 9.7, 2.2 Hz, 10α-H), 2.62 (t, 2H, J = 6.6 Hz, 3″-CH_2), 2.41 (t, 3H, J = 7.7 Hz, 1′-CH_2 + 10a-H), 2.15 (brd, 1H, J = 9.5 Hz, 8α-H), 1.96 (m, 2H, 2″-CH_2), 1.37 (s, 3H, 6β-CH_3), 1.04 (s, 3H, 6α-CH_3), 0.89 (t, 3H, J = 7.0 Hz, 5′-CH_3); ^{13}C NMR δ 153.8[a] (C1), 152.2[a] (C4a), 140.7 (C3), 111.9[b] (C10b), 110.3[b] (C2), 109.5 (C4), 70.8 (C9), 65.6 (Pr 1″), 48.7 (C6a), 39.3 (C10), 35.8 (C8), 33.7 (C10a), 32.2 (1′), 31.9 (3′), 29.3 (2′), 27.8 (C6β), 26.1 (C7), 22.5 (4′), 22.4 (Pr 2″), 21.7 (Pr 3″), 18.8 (C6α), 14.0 (5′) (C6 not observed due to overlap) (a,b, assignments may be reversed); MS (EI) m/z 358 (M^+, base), 302 (M − C_4H_8), 233, 190; UV ϵ_{287} = 1700 L/M cm; GC (260 °C) t_R = 14.6 min; TLC (CH_2Cl_2) R_f = 0.1.

***O*,2-Propano-9α-OH-11-nor-HHC (10a).** To a solution of *O*,2-propano-9-oxo-11-nor-HHC (250 mg, 0.7 mmol) in THF (8 mL) at −75 °C was added a 1.0 M solution of potassium tri-*sec*-butyl borohydride in THF (2.8 mL). After standing overnight, the cold bath was removed, water (1 mL) was added, and the reaction was brought to ambient temperature. The intermediate organoborane was oxidized with 2 N NaOH (0.36 mL) and 30% hydrogen peroxide (0.36 mL). Potassium carbonate was carefully added to saturation, the THF was evaporated, and the aqueous residue was extracted with diethyl ether. The organic layer was washed with brine and dried over sodium sulfate to give an off-white foamy resin after evaporation of the solvent *in vacuo* (256 mg, 100% crude yield) which was chromatographed on a Lobar SiO_2 column (97:3 toluene:acetone): ^{1}H NMR δ 6.27 (s, 1H, ArH), 4.20 (brs, 1H, 9β-H), 4.11 (m, 2H, 1″-CH_2), 3.19 (dd, 1H, J = 13.8, 2.5 Hz, 10α-H), 2.88 (t, 1H, J = 9.6 Hz, 10a-H), 2.62 (t, 2H, J = 6.7 Hz, 3″-CH_2), 2.42 (t, 2H, J = 8.2 Hz, 1′-CH_2), 1.96 (m, 2H, 2″-CH_2), 1.36 (s, 3H, 6β-CH_3), 1.09 (s, 3H, 6α-CH_3), 0.89 (t, 3H, J = 6.9 Hz, 5′-CH_3); ^{13}C NMR δ 153.8[a] (C1), 152.5[a] (C4a), 140.4 (C3), 111.8[b] (C10b), 110.3[b] (C2), 109.5 (C4), 76.4 (C6), 66.88 (C9), 65.5 (Pr 1″), 49.5 (C6a), 37.3 (C10), 33.2 (C8), 32.2 (1′), 31.9 (3′), 29.3 (2′), 29.2 (C10a), 27.5 (C6β), 22.7[c] (C7), 22.5[c] (4′), 22.4 (Pr 2″), 21.7 (Pr 3″), 18.9 (C6α), 14.0 (5′). (a−c, assignments may be reversed.)

***O*,2-Propano-11-nor-Δ^8-THC (4).** (a) *O*,2-Propano-9β-hydroxy-11-nor-HHC (7 mg) was added to a solution of *p*-toluenesulfonic acid (0.5 mg) in 5 mL of benzene and heated at reflux through a Soxhlet extractor charged with 3 Å sieves. During the next 4 h the benzene was lost leaving a residue that was the target compound as shown by ^{1}H NMR, GC, and TLC comparison to a sample prepared by an alternative route (see b). (b) *O*-(3-Hydroxypropyl)-11-nor-Δ^8-THC (2.4 g, 6.7 mmol) in 40 mL of dry benzene was added to P_2O_5 (2.0 g, 14.0 mmol) in 40 mL of benzene under an atmosphere of dry argon with stirring. The suspension was sonicated briefly to disperse the P_2O_5 and heated at reflux for 20 min. The completed reaction (TLC) was filtered and evaporated *in vacuo*, and the residue was dissolved in EtOAc, washed with aqueous $NaHCO_3$ and brine (2×), and dried over Na_2SO_4. GC (260 °C) showed three products: t_R (%): 7.2 (50), 8.3 (42), and 10.3 (6) min, the GC-MS of which each exhibited a parent ion at m/z 340. The residue from evaporation of solvent was eluted from silica gel with 25% CH_2Cl_2−hexane and a portion rechromatographed on a Merck size B silica gel prepak column with 0−3% CH_2Cl_2−hexane gradient in 1% steps to afford 333 mg of the title compound **4**. The yield from all chromatographies was 18% of theoretical. The resin was distilled at 185 °C and 0.05 mmHg: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.28 (s, 1H, ArH), 5.74, 5.72 (2m, 2H, 8-H/9-H), 4.15 (dd, 1H, J = 3.8, 6.4 Hz, Ar, OCH), 4.08 (dd, 1H, J = 3.8, 6.9 Hz, ArOCH′), 3.32 (brd, 1H, 10α-H), 2.63 (m, 3H, 3″-CH_2 + 10a-H), 2.43 (m, 2H, 1′-CH_2), 1.37 (s, 3H, 6β-Me), 1.10 (s, 3H, 6α-Me), 0.90 (m, 3H, 5′-Me); MS (EI) m/z 340 (M^+), 284 (M − C_4H_8), 271 (M − C_4H_6 − CH_3); UV ϵ_{287} = 1750 L/M cm; GC (260 °C) t_R = 7.1 min (98%); TLC (25% CH_2Cl_2−hexane) R_f = 0.4.

The second major component (GC t_R = 8.3 min) eluted from silica gel before the title compound and was identified spectrally as *O*,2-propano-11-nor-$\Delta^{6a,10a}$-THC: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.31 (s, 1H, ArH), 4.10 (t, 2H, J = 5.2 Hz, 1′-CH_2), 2.64 (t, 2H, J = 6.6 Hz, 3′-CH_2), 2.55 (“p”, 2H, 10-CH_2), 2.43 (t, 2H, J = 7.9 Hz, 1′-CH_2), 2.07 (“p”, 2H, 7-CH_2), 1.97 (“q”, 2H, 2′-CH_2), 1.65, 1.59, 1.55 (m, m, m, 2H, 2H, 2H, 8-CH_2/9-CH_2/2′-CH_2), 1.34 (m, 4H, 3′-CH_2, 4′-CH_2), 1.30 (s, 6H, C-Me_2), 0.89 (m, 3H, 5′-Me); MS (EI) m/z 340 (10, M^+), 325 (base, M − Me).

***O*-(3-Hydroxypropyl)-11-nor-Δ^8-THC (3).** 11-Nor-Δ^8-THC (2.6 g, 8.7 mmol) dissolved in absolute ethanol (30 mL) was treated with 3-bromo-1-propanol (2.5 mL, 26.1 mmol) and DBU (4.1 mL, 26.1 mmol) with stirring and then heated at reflux under argon overnight. A further 26.1 mmol each of 3-bromo-1-propanol and DBU were added, and heating at reflux was continued for another 10 h to bring the reaction to completion (TLC). The ethanol was removed *in vacuo*, and the residue was dissolved in EtOAc, washed with water, 1 N HCl, and brine, and dried over Na_2SO_4. Filtration and evaporation *in vacuo* afforded a resin that was chromatographed on silica gel (175 g) eluting with 85% and 95% CH_2Cl_2−hexane yielding 2.48 g (69%) on the title compound: ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.31 (s, 1H, ArH), 6.27 (s, 1H, ArH′), 5.73 (brs, 2H, 8-H, 9-H), 4.10 (m, 2H, 1″-CH_2), 3.87 (m, 2H, CH_2OH), 3.30 (brd, 1H, J = 16.2 H, 10α-H), 2.64 (“dt”, 1H, 10a-H), 2.49 (t, 2H, J = 7.7 Hz, 1′-CH_2), 1.38 (s, 3H, 6β-Me), 1.10 (s, 3H, 6α-Me), 0.89 (t, 3H, J = 6.6 Hz, 5′-Me); GC (265 °C) t_R = 7.6 min; TLC (75% CH_2Cl_2−hexane) R_f = 0.2.

Receptor Binding. 1. CB_1. Radiolabeled CP-55,940 was obtained from DuPont NEN. [^{3}H]CP-55,940 binding to P_2 membranes was conducted as described elsewhere[13] except whole brain (rather than cortex only) was used. Displacement

curves were generated by incubating drugs with 1 nM [^{3}H]-CP-55,940. The assays were performed in triplicate, and the results represent the combined data from three independent experiments.

2. CB_2. Human CB_2 cDNA was subcloned into the *Xho*I site of the pcDNA3 mammalian expression vector (Invitrogen, San Diego, CA). Its orientation was confirmed by restriction digest and sequencing. The construct was transfected into CHO cells as described elsewhere.[21] The methods for tissue preparation were essentially those described by Compton et al.[13] with the exception that a cultured cell line was used rather than rat cortex. The methods for [^{3}H]CP-55,940 binding were as described above for the CB_1 binding assay.

3. Binding Data Analysis. The K_i values reported in Table 1 were determined from Scatchard analysis[23,24] using the KELL package of binding analysis programs for the Macintosh computer (Biosoft, Milltown, NJ). The software was modified for the Macintosh by G. A. McPherson based upon the original description of LIGAND[25] and EBDA (equilibrium binding data analysis).[26] Similarly, displacement studies were analyzed using EBDA which provided K_i values for each analog by performing log−logit analysis to determine IC_{50} estimates which were optimized prior to conversion[27] to K_i values.

Biological Evaluations: MVD Assay. The *in vitro* pharmacology of all compounds was investigated using the mouse isolated vas deferens assay in which the measured response is drug-induced inhibition of electrically-evoked contractions.[28] All drugs were mixed with 2 parts of Tween 80 by weight and dispersed in a 0.9% aqueous solution of NaCl (saline).[14] EC_{50} values were calculated by nonlinear regression analysis using GraphPAD InPlot (GraphPAD Software, San Diego, CA). K_d values of SR-141716A were calculated using the equation: $(x - 1) = B/K_d$, where x (the 'dose ratio') is the concentration of a twitch inhibitor that produces a particular degree of inhibition in the presence of SR-141716A at a concentration, B, divided by the concentration of the same twitch inhibitor that produces an identical degree of inhibition in the presence of Tween 80.[28,29] Dose ratio values and their 95% confidence limits have been determined by symmetrical (2 + 2) dose parallel line assay,[30] using responses to pairs of agonist concentrations located on the steepest part of each log concentration−response curve. In none of these assays did pairs of log concentration−response curves show significant deviation from parallelism ($P > 0.05$).

Biological Evaluations: *In Vivo* Pharmacology. The *in vivo* pharmacology of all compounds was evaluated in the mouse model of cannabimimetic activity which measures spontaneous activity (SA), antinociception (as tail flick, TF), ring immobility (RI), and rectal temperature (RT) following iv injection in the tail vein.[19,31] Each compound was dissolved in 1:1:18 (emulphor:ethanol:saline) for tail vein injection administration at a volume of 0.1 mL/10 g of body weight. The ED_{50} values and standard errors (SE) were calculated using ALLFIT analysis, a nonlinear sigmoidal curve-fitting mainframe program.[32]

Acknowledgment. This work was supported by NIDA Grant DA03934 (to P.H.R.) by NIDA Grant DA03672 (to B.R.M.), and by Wellcome Trust Grant 034924 (to R.G.P.). We thank Sanofi Recherche for providing SR-141716A and Dr. Sean Munro, MRC Cambridge, for providing the CB_2 cDNA.

References

(1) (a) Matsuda, L. A.; Lolait, S. J.; Brownstein, M. J.; Young, A. C.; Bonner, T. I. Structure of a Cannabinoid Receptor and Functional Expression of the Cloned cDNA. *Nature* **1990**, *346*, 561−564. (b) Gerard, C. M.; Mollereau, C.; Vassart, G.; Parmentier, M. Molecular Cloning of a Human Cannabinoid Receptor Which Is Also Expressed in Testis. *Biochem. J.* **1991**, *279*, 129−134.

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

(3) Galiegue, S.; Mary, S.; Marchand, J.; Dussossoy, D.; Carriere, D.; Carayon, P.; Bouaboula, M.; Shire, D.; Le Fur, G.; Casellas, P. Expression of Central and Peripheral Cannabinoid Receptors in Human Immune Tissues and Leukocyte Subpopulations. *Eur. J. Biochem.* **1995**, *232*, 54−61.

(4) Huffman, J. W.; Yu, S.; Showalter, V.; Abood, M. E.; Wiley, J. L.; 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 CB_2 Receptor. *J. Med. Chem.* **1996**, *39*, 3875−3877.

(5) Gareau, Y.; Dufresne, 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.

(6) Reggio, P. H.; Seltzman, H. H.; Compton, D. R.; Prescott, W. R., Jr.; Martin, B. R. Investigation of the Role of the Phenolic Hydroxyl in Cannabinoid Activity. *Mol. Pharmacol.* **1990**, *38*, 854−862.

(7) Wilson, R. S.; May, E. L. Analgesic Properties of the Tetrahydrocannabinols, Their Metabolites and Analogs. *J. Med. Chem.* **1975**, *18*, 700−703.

(8) Seltzman, H. H.; Hsieh, Y.-A.; Pitt, C. G.; Reggio, P. H. Synthesis of Rotationally Restricted Tetrahydrocannabinol Ethers. *J. Org. Chem.* **1991**, *56*, 1549−1553.

(9) Nilsson, J. L. G.; Nilsson, I. M.; Agurell, S. Metabolism of Cannabis XI. Synthesis of Delta-7-tetrahydrocannabinol and 7-Hydroxy-tetrahydrocannabinol. *Acta Chem. Scand.* **1971**, *25*, 768−769.

(10) Wildes, J. W.; Martin, N. H.; Pitt, C. G.; Wall, M. E. The Synthesis of (−)-Delta 9,11-trans-Tetrahydrocannabinol. *J. Org. Chem.* **1971**, *36*, 721−723.

(11) Minato, M.; Yamamoto, K.; Tsuji, J. Osmium Tetraoxide Catalyzed Vicinal Hydroxylation of Higher Olefins by Using Hexacyanoferrate(III) Ion as a Cooxidant. *J. Org. Chem.* **1990**, *55*, 766−768.

(12) Wilson, R. S.; May, E. L.; Martin, B. R.; Dewey, W. L. 9-Nor-9-hydroxy-hexahydrocannabinols. Synthesis, Some Behavioral and Analgesic Properties, and Comparison with Tetrahydrocannabinols. *J. Med. Chem.* **1976**, *19*, 1165−1167.

(13) Compton, D. R.; Rice, K. C.; De Costa, B. R.; Razdan, R. K.; Melvin, L. S.; Johnson, M. R.; Martin, B. R. Cannabinoid Structure-Activity Relationships: Correlation of Receptor Binding and *in Vivo* Activities. *J. Pharmacol. Exp. Ther.* **1993**, *265*, 218−226.

(14) Pertwee, R. G.; Stevenson, L. A.; Elrick, D. B.; Mechoulam, R.; Corbett, A. D. Inhibitory Effects of Certain Enantiomeric Cannabinoids in the Mouse Vas Deferens and the Myenteric Plexus Preparation of Guinea-Pig Small Intestine. *Br. J. Pharmacol.* **1992**, *105*, 980−984.

(15) Pertwee, R. G.; Stevenson, L. A.; Griffin, G. Cross-Tolerance Between Delta-9-tetrahydrocannabinol and the Cannabimimetic Agents, CP-55,940, WIN-55,212-2 and Anandamide. *Br. J. Pharmacol.* **1993**, *110*, 1483−1490.

(16) Pertwee, R. The Evidence for the Existence of Cannabinoid Receptors. *Gen. Pharmacol.* **1993**, *24*, 811−824.

(17) Rinaldi-Carmona, M.; Barth, F.; Heaulme, M.; Shire, D.; Calandra, B.; Congy, C.; Martinez, S.; Maruani, J.; Neliat, G.; Caput, D.; Ferrara, P.; Soubrie, P.; Breliere, J. C.; LeFur, G. SR141716A, A Potent and Selective Antagonist of the Brain Cannabinoid Receptor. *FEBS Lett.* **1994**, *350*, 240−244.

(18) Herkenham, M.; Lynn, A. B.; Little, M. D.; Johnson, M. R.; Melvin, L. S.; de Costa, B. R.; Rice, K. C. Cannabinoid Receptor Localization in Brain. *Proc. Natl. Acad. Sci. U.S.A.* **1990**, *87*, 1932−1936.

(19) Little, P. J.; Compton, D. R.; Johnson, M. R.; Melvin, L. S.; Martin, B. R. Pharmacology and Stereoselectivity of Structurally Novel Cannabinoids in Mice. *J. Pharmacol. Exp. Ther.* **1988**, *247*, 1046−1051.

(20) Skaper, S. D.; Buriani, A.; Dal Toso, R.; Petrelli, L.; Romanello, S.; Facci, L.; Leon, A. The ALIAmide Palmitoylethanolamide and Cannabinoids, but not Anandamide, are Protective in a Delayed Postglutamate Paradigm of Excitotoxic Death in Cerebellar Granule Neurons. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 3984−3989.

(21) 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 (CB_2): Identification of Cannabinoid Receptor Subtype Selective Ligands. *J. Pharmacol. Exp. Ther.* **1996**, *278*, 989−999.

(22) Felder, C. C.; Joyce, K. E.; Briley, E. M.; Mansouri, J.; Mackie, K.; Blond, O.; Lai, Y.; Ma, A. L.; Mitchell, R. L. Comparison of the Pharmacology and Signal Transduction of the Human Cannabinoid CB_1 and CB_2 Receptors. *Mol. Pharmacol.* **1995**, *48*, 443−450.

(23) Rosenthal, H. E. A Graphic Method for the Determination and Presentation of Binding Parameters in a Complex System. *Anal. Biochem.* **1967**, *20*, 525−532.

(24) Scatchard, G. The Attractions of Proteins for Small Molecules and Ions. *Ann. N. Y. Acad. Sci.* **1951**, *51*, 660−672.
(25) Munson, P. J.; Rodbard, D. LIGAND: A Versatile Computerized Approach for Characterization of Ligand-Binding Systems. *Anal. Biochem.* **1980**, *107*, 220−239.
(26) McPherson, G. A. A Practical Computer-Based Approach to the Analysis of Radioligand Binding Experiments. *Comput. Programs Biomed.* **1983**, *17*, 107−114.
(27) Cheng, Y. C.; Prusoff, W. H. Relationship Between the Inhibition Constant (K_I) and the Concentration of Inhibitor Which Causes 50 Percent Inhibition (IC_{50}) on an Enzymatic Reaction. *Biochem. Pharmacol.* **1973**, *22*, 3099−3108.
(28) Pertwee, R. G.; Griffin, G.; Lainton, J. A. H.; Huffman, J. W. Pharmacological Characterization of Three Novel Cannabinoid Receptor Agonists in the Mouse Isolated Vas Deferens. *Eur. J. Pharmacol.* **1995**, *284*, 241−247.
(29) Tallarida, R. J.; Cowan, A.; Adler, A. W. pA_2 and Receptor Differentiation: A Statistical Analysis of Competitive Antagonism. *Life Sci.* **1979**, *25*, 637−642.
(30) Colquhoun, D. *Lectures on Biostatistics*; Oxford University Press: Oxford, 1971.
(31) Martin, B. R.; Compton, D. R.; Little, P. J.; Martin, T. J.; Beardsley, P. M. Pharmacological Evaluation of Agonistic and Antagonistic Activity of Cannabinoids. In *Structure-Activity Relationships of the Cannabinoids*; Rapaka, R. S., Makriyannis, A., Eds.; NIDA Research Monograph 79; National Institute on Drug Abuse: Rockville, MD, 1987; pp 108−122.
(32) DeLean, A.; Munson, P.; Rodbard, D. Simultaneous Analysis of Families of Sigmoidal Curves: Application to Bioassay, Radioligand Assay, and Physiological Dose Response Curves. *Am. J. Physiol.* **1987**, *235*, E97−E102.
(33) Compton, D. R.; Johnson, M. R.; Melvin, L. S.; Martin, B. R. Pharmacological Profile of a Series of Bicyclic Cannabinoid Analogs: Classification as Cannabimimetic Agents *J. Pharmacol. Exp. Ther.* **1992**, *260*, 201−209.

JM970136G