Potent Cyano and Carboxamido Side-Chain Analogues of 1′,1′-Dimethyl-Δ^8-Tetrahydrocannabinol

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The synthesis and pharmacological profile of several cyano (**1a**−**e**) and carboxamido (**2a**−**h**) side-chain-substituted analogues of 1′,1′-dimethyl-Δ^8-THC are described. Commercially available cyano compound **3** was transformed to the resorcinol **6** in a three-step sequence. Condensation of **6** with *p*-menth-2-ene-1,8-diol formed the THC **7a** which, with sodium cyanide/DMSO, gave **1b**. Protection of the phenol in **7a** as the MOM derivative provided the common intermediate **8** for the synthesis of **1a**,**c**,**e**. Compound **1d** was also synthesized from **7a** via the aldehyde **9a**. Base hydrolysis of **1b** gave the acid **10** which, via its acid chloride and subsequent treatment with the appropriate amine, formed the target compounds **2a**−**h**. The pharmacological profile indicated that the cyano analogues **1a**−**e** had very high CB1 binding affinity (0.36−13 nM) and high in vivo potency as agonists. Two analogues (**1a**,**b**) had extremely high potency in the mouse tetrad tests. The dimethylcarboxamido analogue **2a** showed a similar profile to **1a**,**b**. The high potency was also retained in analogue **2c**. In contrast the sulfonamide analogue **2d** was unique as it had greater affinity than Δ^9-THC, yet it was practically devoid of agonist effects. This study suggests that the incorporation of a cyano or an amide substituent in the side chain of Δ^8-THC-DMH can enhance potency and can also lead to compounds with a unique profile which have high binding affinity and are practically devoid of agonist effects.

Introduction

Since the discovery of the cannabinoid receptor (CB1) in the brain there has been intense activity in the cannabinoid field.[1,2] CB1 is a G-protein-coupled receptor,[3] and its endogenous ligand has been identified as anandamide,[4] an arachidonic acid derivative. Besides the well-known classical and nonclassical tetrahydrocannabinol (THC) derivatives and the anandamides, other cannabimimetics have been discovered, for example, the indole derivatives (e.g., WIN 55212-2)[5] and the pyrazole derivative CB1 antagonist SR14176A.[6] Another cannabinoid subtype receptor (CB2) has been identified[7] which is expressed mainly in the periphery (macrophages in the spleen) whose specific antagonist[8] is yet another pyrazole derivative. It is evident that compounds derived from a myriad of chemical structures can possess cannabimimetic properties.

We have been examining the structure−activity relationships (SAR) in each chemical class of cannabimimetics. The SAR of the classical THCs still attracts a great deal of attention, and recently we have redirected our attention to the side-chain moiety.[9] In the SAR of THCs it is well-known[10] that the side chain plays a dominant role in the determination of its affinity and effect on the second-messenger system.[2] In particular, the introduction of a methyl or a dimethyl group in the 1′-position, or methyls in the 1′- and 2′-positions, results in a great enhancement in both binding affinity and pharmacological activity.[10,11]

As part of our ongoing program on classical THCs, we have been examining the effect of various substituents in the side chain of THCs in order to develop novel ligands with high affinity and selectivity for the CB1 receptor. With this background we chose Δ^8-THC-DMH as the template for the introduction of various substituents. The cyano group was chosen as it can interact at polar sites of the receptor and there is a precedent for the cyano group to impart significant antagonist activity in the leukotriene B4 class of compounds.[12] We therefore synthesized a cyano analogue (**1b**, 5′-cyano-1′,1′-dimethyl-Δ^8-THC) (Chart 1) which showed very high affinity for the CB1 receptor and which was extremely potent in the mouse tetrad tests (see Table 1). It also shared discriminative stimulus effects with CP55,940. However in antagonist studies, although it attenuated the effects of Δ^9-THC in the mouse behavioral tests, it was difficult to differentiate between antagonism, acute tolerance, or desensitization.[13] These properties of compound **1b** underscored the pharmacological complexity of this class of compounds. However, it provided a lead for exploring the effect of other cyano-substituted Δ^8-THC analogues. To study the effect of other substituents in the side chain, we examined various amides and sulfonamide derivatives. The synthesis and pharmacological profiles of these novel analogues are presented in this paper.

Chemistry

The synthesis of compounds **1a**,**c**−**e** is shown in Scheme 1, and that of compounds **1b** and **2a**−**h** is shown in Scheme 2. The Grignard reagent prepared from 4-bromophenoxybutane in THF was treated with the nitrile **3** (Scheme 1) to furnish the ketone **4** (85%) which on further treatment with dimethylzinc and $TiCl_4$[14] in CH_2Cl_2 at −40 °C gave the resorcinol **5** (63%). After we had carried out this procedure, Tius et al.[15] reported

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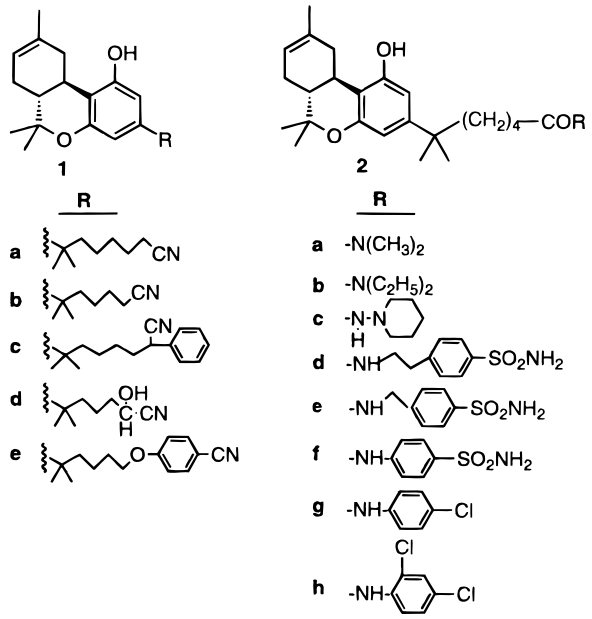
Chart 1



the use of this reagent in the preparation of similar resorcinols. Demethylation and replacement of the phenoxy group by bromine with BBr_3 in CH_2Cl_2 at 5 °C (85%), followed by condensation with *p*-menth-2-ene-1,8-diol in the presence of *p*-toluenesulfonic acid and refluxing in benzene,[9] formed the Δ⁸-tetrahydrocannabinol (THC) analogue **7a** (41%). Treatment of **7a** with sodium cyanide in DMSO furnished **1b** (Scheme 2), whereas the protection of the phenol as the MOM derivative provided the common intermediate **8** for the synthesis of **1a**,**c**,**e**. Thus treatment of **8** with ethyl cyanoacetate in DMF and subsequent heating in DMSO/H_2O at 140 °C formed the cyano analogue **1a**. Similarly, treatment of **8** with benzyl cyanide/BuLi/NaI followed by deprotection of the MOM group gave **1c**, and treatment with *p*-cyanophenol and subsequent deprotection of the MOM group gave **1e**. Analogue **1d** was synthesized from **7a** by conversion to its acetate **7b** (Ac_2O/py) followed by oxidation with DMSO/NaI/$NaHCO_3$ at 110 °C, to form the aldehyde **9a**. Hydrolysis of the acetate gave **9b** which on condensation with NaCN/AcOH/HCl gave the analogue **1d**.

Analogues **2a**−**h** were prepared from the acid **10** (Scheme 2) which was synthesized from **1b** by base hydrolysis (KOH/H_2O) in refluxing ethanol. Treatment of **10**, via its acid chloride (oxalyl chloride), and subsequent treatment with diethylamine or 1-aminopiperidine formed **2b**,**c**, respectively. Similarly, **2e**,**f** were synthesized from the corresponding sulfonamides and **2g**,**h** from the corresponding amines. The analogue **2d** was prepared from the acid **10** by condensation with the appropriate sulfonamide in the presence of 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide and DMAP. It was also prepared from the acid **10** via the acid chloride route. During this reaction compound **2a** was formed as a byproduct (see Experimental Section).

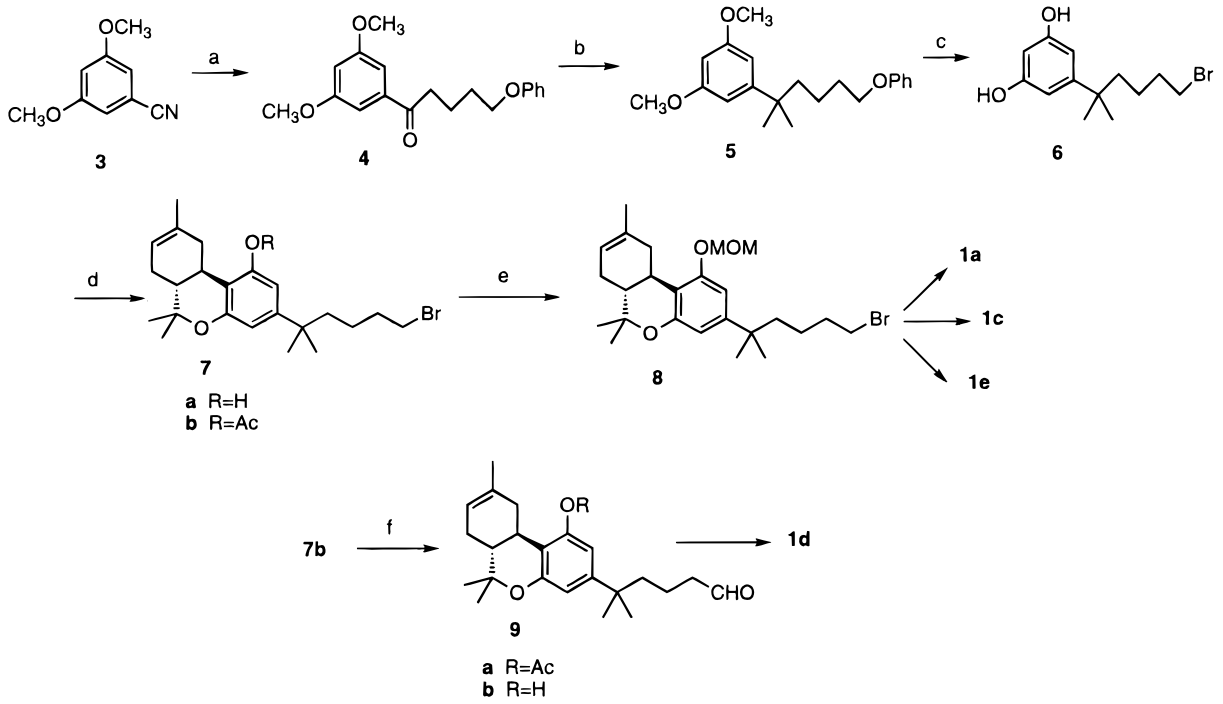
Pharmacology and Discussion of Results

The CB1 binding affinities and the results of the mouse tetrad tests are shown in Table 1. Changing the C5 side chain by a 1′,1′-dimethylheptyl (DMH) side chain in THCs increased the binding affinity 53-fold, and this enhancement was also reflected in spontaneous activity (14-fold), tail flick (35-fold), hypothermia (35-fold), and ring immobility (30-fold).[16] However, substituting a cyano group for the terminal carbon in Δ⁸-THC-DMH, which resulted in the same number of carbons in the chain, i.e., **1a**, had little effect on the binding affinity but showed a further enhancement in both SA (12-fold) and TF (4-fold) tests. The hypothermia measure also showed an 8-fold enhancement. Shortening the side chain of **1a** by one carbon led to **1b** which retained both high receptor affinity and high pharmacological potency. The affinity of **1b** was approximately 2 times greater than that of Δ⁸-THC-DMH, yet its potencies in the SA and TF assays exceeded those of Δ⁸-THC-DMH almost 10-fold. Conversely, **1b** was 2- and 4-fold less potent than Δ⁸-THC-DMH in producing immobility and hypothermia. Comparing **1a**,**b** revealed similar high potencies in the SA and TF procedures that were consistent with their affinities. In contrast, **1b** differed from **1a**, as well as from Δ⁹-THC and Δ⁸-THC-DMH, in that its hypothermic potency was 30−40-fold less than that in SA and TF. Further exploration of **1b** was made possible with a phenyl (**1c**) and hydroxyl (**1d**) substitution. Addition of the phenyl (**1c**) markedly attenuated receptor affinity (∼30-fold compared to that of **1b**) and produced an even greater reduction in the hypomotility (>900-fold) and antinociceptive (∼300-fold) potencies. The 20-fold reduction in hypothermic potency was commensurate with the receptor affinities. Interestingly, the hydroxyl substitution (**1d**) produced a comparable attenuation in receptor affinity (40-fold compared to that of **1b**) and in spontaneous activity potency (∼70-fold), whereas antinociceptive potency was decreased 23-fold and hypothermia potency only 7-fold. The addition of a *p*-cyanophenoxy moiety at the terminal carbon of a 1′,1′-dimethylpentyl side chain (**1e**) resulted in receptor affinity somewhat higher than that for either **1c** or **1d**. The spontaneous activity potency was increased 65-fold compared to that of **1c** and 5-fold compared to that of **1d**. However, there were minimal changes in potencies in both the TF and RT tests. These results show that incorporation of a cyano group at the terminus of the side chain can have a dramatic impact on pharmacological potency with relatively little influence on binding affinity. Furthermore, the cyano addition does not affect all pharmacological effects to the same degree.

The discovery that **1a** retained excellent receptor affinity prompted us to prepare a series of carboxamides with diverse N-substituents. Introducing a dimethylamine substituent at the terminal carbonyl (**2a**) retained high receptor affinity and high potency in TF and RT comparable to that of Δ⁸-THC-DMH. However, this structural modification increased SA potency 45-fold as compared to that of Δ⁸-THC-DMH. The receptor affinity was decreased an order of magnitude with a diethylamine substitution (**2b**) along with attenuated pharmacological potency. However, receptor affinity was restored with a piperidinylamido substituent (**2c**). This analogue was also a full agonist.

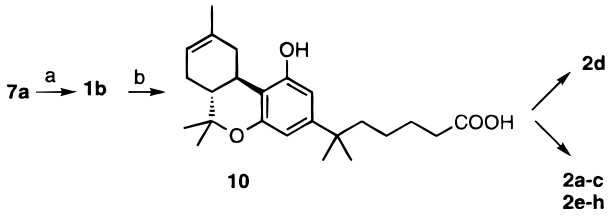
The final series of compounds had an *N*-phenyl with either sulfonamides or chlorophenyl substituents. The ethylphenylsulfonamide derivative (**2d**) had a receptor affinity that was much lower than that of **2a** but

Scheme 1[a]



[a] (a) Grignard of 4-bromophenoxybutane, THF, reflux, 80%; (b) $TiCl_4$, $Zn(CH_3)_2$, −40 to −10 °C, 63%; (c) BBr_3, benzene, 5−23 °C, 85%; (d) *p*-menth-2-ene-1,8-diol, benzene, *p*-TSA, reflux, 41%; (e) K_2CO_3, CH_3CN, 79%; (f) NaI, $NaHCO_3$, DMSO, 110 °C, 63%.

Scheme 2[a]



[a] (a) NaCN, DMSO, 50 °C, 76%; (b) KOH, ethanol, water, reflux, 77%.

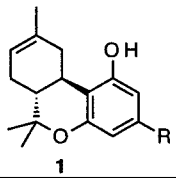
comparable to that of Δ^9-THC, yet this analogue was practically devoid of pharmacological activity at a dose of 100 mg/kg. Decreasing the distance between the nitrogen and phenyl by one carbon (**2e**) improved potency slightly with no improvement in receptor affinity. Further reducing the nitrogen−phenyl distance (**2f**) improved both receptor affinity and potency. This latter compound was one-half as potent as Δ^9-THC, although its receptor affinity exceeded that of Δ^9-THC. Substitution of a chloro for the sulfonamide in **2f** led to **2g** which had very low receptor affinity and pharmacological activity. Incorporation of a second chlorine in the phenyl group of **2g** resulted in **2h** and an improvement in receptor affinity by an order of magnitude. Compound **2h** exhibited moderate activity in TF and RT but was very weak in SA.

Conclusions

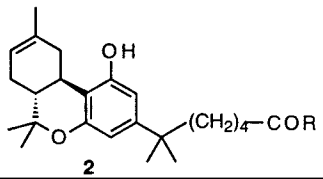
There are several inferences which can be drawn from the examination of these analogues. Their profile suggests that (a) the incorporation of a cyano or an amide substituent in the side chain of Δ^8-THC-DMH can enhance potency, (b) the distance of the substituent from the THC phenolic ring is important for high binding affinity, (c) the introduction of an aminosulfonylphenyl moiety in the amides diminishes agonist effects, and (d) the distance between the amide group and the aminosulfonylphenyl moiety is important for the decrease in agonist effects. The results from all these analogues underscore the importance of the THC side chain in determining the activity. There are two aspects of this study that are intriguing. First, receptor affinity did not always coincide with alterations in potency. Second, many of these structural alterations produced differential effects in the various pharmacological measures. If all of these analogues are interacting with a single receptor to produce these pharmacological effects, as it is currently assumed, then it would appear that the pharmacological selectivity may be achieved by manipulating the nature of this receptor−agonist interaction. With any structure−activity relationship study, there is always the possibility that metabolism can contribute to discrepancies between in vitro and in vivo data. On the other hand, metabolism of the side chain represents a minor metabolic pathway for THC. Additionally, metabolism would appear unlikely to account for differential changes in pharmacological selectivity.

We are continuing the design and synthesis of second-generation analogues based on these structures since the above results have provided us with a useful lead for the development of a potent antagonist with a different template than the CB1 antagonist SR14176A. Furthermore, these derivatized side chains should provide some insight into the furthur development of the cannabinoid receptor pharmacophore. Traditionally, it has been assumed that a hydrophobic pocket accommodates the side chain. Our study suggests that in this region the presence of a nitrile or a carboxamide group, which is polar but not negatively charged, enhances the interaction between the ligand and the

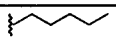
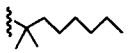
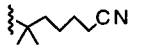
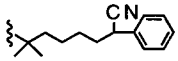
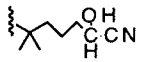
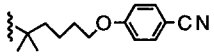
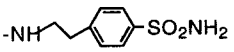
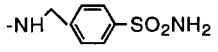
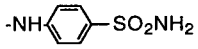
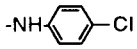
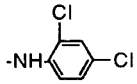
Table 1. Receptor Affinity and Pharmacological Effects of Analogues[a]



1



2

#	Structure (R)	Ki (nM)	SA	TF	RT	RI
Δ^9-THC		41±2 [b]	1.0[b]	1.4[b]	1.4[b]	1.5[b]
Δ^8–THC-DMH		0.77±0.11[b]	0.07[b]	0.04[b]	0.04[b]	0.05[b]
1a		0.6±0.05	0.006	0.01	0.005	ND
1b		0.36±0.14[c]	0.007[c]	0.0047[c]	0.19[c]	0.095[c]
1c		9.2±0.3	6.51	1.4	4.2	5.05
1d		13±2	0.52	0.11	1.50	1.07
1e		3±2	0.10	1.15	4.24	ND
2a	-N(CH$_3$)$_2$	0.86±0.06	0.0015	0.031	0.12	ND
2b	-N(C$_2$H$_5$)$_2$	13±5	0.09	0.10	0.40	ND
2c		1.2±0.2	0.04	0.16	0.17	ND
2d		29±6	60%@100	>100	>100	>100
2e		60±3	31	60%@60	37	ND
2f		19±3	2.03	3.2	1.7	ND
2g		187±6	39%@30	15%@30	-1.6° C @30	ND
2h		18±1.9	27%@30	14	3.7	ND

[a] K_i's (nM) were determined and are expressed as means ± SE for at least three experiments. The pharmacological measures included inhibition of spontaneous activity (SA), antinociception as measured by the tail-flick response (TF), hypothermia as changes in rectal temperature (RT), and ring immobility (RI). The pharmacological data are expressed as the ED_{50} (mg/kg); ND, not determined. [b] Reported previously.[16] [c] Reported previously.[13]

receptor. Hence changes in receptor affinity and pharmacological potency that accompany the incorporation of specific functional groups in the side chain provide an opportunity for refinement of this ill-defined hydrophobic pocket.

Experimental Section

^{1}H NMR spectra were recorded on either a Bruker 100 or a Varian XL400 spectrophotometer using $CDCl_3$ as the solvent unless otherwise stated, with tetramethylsilane as an internal standard. Thin-layer chromatography (TLC) was carried out on Baker Si 250F plates. Visualization was accomplished with either iodine vapor, UV exposure, or treatment with phosphomolybdic acid (PMA). Flash chromatography was carried out on EM Science silica gel 60. Elemental analyses were performed by Atlantic Microlab, Atlanta, GA, and were found to be within ±0.4% of calculated values for the elements shown. The purity of the products on which the high-resolution mass spectral data are reported were determined by TLC in two solvent systems and ^{1}H NMR analysis. All reactions were carried out under nitrogen, and sodium sulfate was used as the drying agent.

5-Phenoxy-(3′,5′-dimethoxyphenyl)pent-1-one (4). To a mechanically stirred Grignard solution (prepared from 91.60 g, 0.4 mol, of 4-bromophenoxybutane and 14.60 g, 0.6 mol, of magnesium turnings in 400 mL of anhydrous THF) was added 48.90 g (0.3 mol) of 3,5-dimethoxybenzonitrile (**3**) all at once, and the mixture was heated to reflux for 3 h. The reaction was cooled to 0 °C with an ice bath for 15 min followed by the slow addition of 6 N HCl (150 mL) and then allowed to stir at reflux overnight. The THF was removed in vacuo and the residue dissolved in EtOAc (300 mL) and 6 N HCl (50 mL). The layers were separated, and the aqueous was extracted with EtOAc (4 × 150 mL). The combined EtOAc extract was washed with saturated $NaHCO_3$, followed by water and brine. After drying it was concentrated, and the residue was chromatographed on silica gel (650 g), eluting with 5−25% ether/hexanes, to yield 79.80 g (85%) of compound **4**: ^{1}H NMR δ 7.35−6.6 (m, 8H), 4.0(t, J = 7 Hz, 2H), 3.82 (s, 6H), 3.0 (t, J = 7 Hz, 2H), 2.0−1.8 (m, 4H).

1-Phenoxy-5-methyl-(3′,5′-dimethoxyphenyl)hexane (5). In a dry three-necked flask equipped with a mechanical stirrer, a thermometer, and an addition funnel was added anhydrous CH_2Cl_2 (300 mL), and the mixture was cooled to −40 °C. A 1 M solution of $TiCl_4$ in CH_2Cl_2 (382 mL, 0.382 mol) was transferred to the addition funnel (cannula) and added slowly to the cold CH_2Cl_2 solution maintaining a temperature of −40 °C. After the addition the solution was cooled to −50 °C, and via the addition funnel, a 2 M solution of dimethylzinc in

toluene (191 mL, 0.382 mol) was added as rapidly as possible, maintaining the mixture temperature between −40 and −50 °C. Upon complete addition the viscous red suspension was stirred vigorously for 10 min, after which a solution of compound **4** (20.00 g, 63.6 mmol) in dry CH_2Cl_2 (50 mL) was added rapidly maintaining the temperature between −40 and −50 °C. The mixture (bright orange) was stirred vigorously for 2 h at −45 to −35 °C; then the temperature was allowed to rise slowly to −10 °C over 2 h with continued stirring. The mixture was poured onto ice/water (600 mL), and the aqueous layer was extracted with CH_2Cl_2 (4 × 200 mL). The combined CH_2Cl_2 extract was washed with brine (200 mL), dried, and concentrated, and the residue was chromatographed on silica gel (500 g), eluting with 1.5−30% ethyl acetate/hexanes, to give 13.70 g (63%) of compound **5**: ^{1}H NMR δ 7.45−7.20 (m, 2H), 7.0−6.8 (m, 3H), 6.50 (d, J = 2 Hz, 2H), 6.30 (t, J = 2 Hz, 1H), 3.88 (t, J = 7 Hz, 2H), 3.79 (s, 6H), 1.9−1.6 (m, 6H), 1.28 (s, 6H).

5′-Bromo-1′,1′-dimethyl-3,5-benzenediol (6). A solution of compound **5** (10.00 g, 30 mmol) in benzene (100 mL) was azeotroped for 2.5 h. After the mixture cooled to 5 °C, a 1 M solution of boron tribromide in CH_2Cl_2 (70 mL, 70 mmol) was added dropwise via an addition funnel over 20 min, and the mixture stirred overnight at 23 °C. The mixture was poured onto ice/water (500 mL), and the aqueous layer was extracted with ether (5 × 200 mL). The combined ether extract was washed with 5% Na_2SO_3 solution (300 mL), followed by water (2 × 300 mL) and brine (200 mL), and then dried and concentrated in vacuo. The viscous residue was chromatographed on silica gel (300 g), eluting with 20% and then with 50% ether/hexanes mixture, to yield 7.47 g (85%) of the resorcinol **6**: ^{1}H NMR δ 6.39 (d, J = 2 Hz, 1H), 6.19 (d, J = 2 Hz, 1H), 5.62 (br s, 1H, D_2O exchangeable), 3.31 (t, J = 7 Hz, 2H), 1.80−1.30 (m, 6H), 1.21 (s, 6H).

5′-Bromo-1′,1′-dimethyl-Δ^8-tetrahydrocannabinol (7a). It was prepared by condensing the resorcinol **6** (6.13 g, 21.3 mmol) with *p*-menth-2-ene-1,8-diol (5.70 g, 33.4 mmol) in the presence of *p*-toluenesulfonic acid (0.13 g, 0.68 mmol) in benzene (1.2 L) according to our previously described procedure.[9] The gum obtained after workup was chromatographed on silica gel (600 g), eluting with 30% ethyl acetate/hexanes, to yield 3.72 g (41%) of **7a**: ^{1}H NMR δ 6.38 (d, J = 2 Hz, 1H), 6.20 (d, J = 2 Hz, 1H), 5.42 (br s, 1H), 4.74 (br s, 1H, D_2O exchangeable), 3.32 (t, J = 7 Hz, 2H), 3.19 (dd, J = 4 and 17 Hz, 1H), 1.73 (br s, 3H), 1.36 (s, 3H), 1.22 (s, 6H), 1.10 (s, 3H).

5′-Cyano-1′,1′-dimethyl-Δ^8-tetrahydrocannabinol (1b). To a warm solution (50 °C) of **7a** (2.90 g, 6.8 mmol) in DMSO (55 mL) was added NaCN (1.20 g, 24.5 mmol), and the mixture stirred at 50 °C for 3 h. The solvent was removed in vacuo, and the residue was treated with water and extracted with ether. The combined ether extract was washed with brine, dried, and concentrated, and the residue was chromatographed on silica gel (80 g). Elution with 30% ether/hexanes gave 1.90 g (76%) of **1b**: ^{1}H NMR δ 6.38 (d, J = 2 Hz, 1H), 6.21 (d, J = 2 Hz, 1H), 5.45 (br s, 1H), 4.75 (s, 1H, D_2O exchangeable), 3.35−3.05 (m, 1H), 2.25 (t, J = 8.2 Hz, 2H), 1.70 (br s, 3H), 1.36 (s, 3H), 1.24 (s, 6H), 1.12 (s, 3H). Anal. ($C_{24}H_{33}NO_2$) C, H, N.

5′-Bromo-1′,1′-dimethyl-Δ^8-tetrahydrocannabinol Methoxymethyl Ether (8). To a stirred solution of **7a** (1.05 g, 2.37 mmol) in anhydrous CH_3CN (10 mL) was added K_2CO_3 (200 mesh, 1.30 g. 9.4 mmol), and the mixture was cooled to 0 °C for 20 min. Chloromethylmethyl ether (0.72 mL, 9.46 mmol) was added, and the reaction mixture was allowed to stir overnight at 23 °C. The mixture was added to water (50 mL) and extracted with several portions of ether. The combined ether extract was washed with water, followed by brine, then dried, and concentrated in vacuo to give a viscous oil which was chromatographed on silica gel (100 g). On elution with 2.5% ethyl acetate/hexanes it gave 0.87 g (79%) of **8**: ^{1}H NMR δ 6.57 (d, J = 2 Hz, 1H), 6.45 (d, J = 2 Hz, 1H), 5.41 (br s, 1H), 5.18 (s, 2H), 3.50 (s, 3H), 3.33 (t, J = 7 Hz, 2H), 3.19 (dd, J = 4 and 17 Hz, 1H), 1.76 (br s, 3H), 1.38 (s, 3H), 1.24 (s, 6H), 1.10 (s, 3H).

Norpentyl-6′-cyano-1′,1′-dimethylhexyl-Δ^8-tetrahydrocannabinol (1a). To a solution of ethyl cyanoacetate (364 mg, 0.34 mL, 3.22 mmol) in DMF (dry over sieves, 10 mL) was added NaH (60% oil dispersion, 86 mg, 2.15 mmol), and the solution was stirred at room temperature for 30 min. Compound **8** (1.00 g, 2.15 mmol) was then added, and the reaction was heated to 110 °C (oil bath) for 1.5 h. After the mixture cooled, saturated NH_4Cl solution (5 mL) was added, and the DMF was removed in vacuo. The residue was partitioned between water and EtOAc. The aqueous layer was extracted several times with EtOAc, and the combined EtOAc extract was washed with water and brine and then dried. After concentration in vacuo, the residue was chromatographed on silica gel (150 g), eluting with 10% ethyl acetate/hexanes, to give 0.67 g (63%) of norpentyl-6′-carbethoxy-6′-cyano-1′,1′-dimethylhexyl-Δ^8-tetrahydrocannabinol methoxymethyl ether: ^{1}H NMR δ 6.57 (d, J = 2 Hz, 1H), 6.45 (d, J = 2 Hz, 1H), 5.41 (br s, 1H), 5.17 (s, 2H), 4.19 (q, J = 7 Hz, 2H), 3.49 (s, 3H), 3.41 (t, J = 7 Hz, 1H), 3.18 (dd, J = 4 and 17 Hz, 1H), 1.70 (br s, 3H), 1.38 (s, 3H), 1.23 (s, 6H), 1.11 (s, 3H).

The above methoxymethyl ether (200 mg, 0.40 mmol) was dissolved in anhydrous DMSO (1 mL), H_2O (0.1 mL) was added, and the solution was heated to 140 °C for 16 h. The solution was partitioned between H_2O and CH_2Cl_2. The aqueous layer was extracted several times with CH_2Cl_2, and the combined CH_2Cl_2 extract was washed with water and brine and then dried and evaporated in vacuo. The residue was chromatographed on silica gel (40 g), eluting with 10% ethyl acetate/hexanes, to give 80 mg (54%) of **1a**: ^{1}H NMR δ 6.36 (d, J = 2 Hz, 1H), 6.22 (d, J = 2 Hz, 1H), 5.43 (br s, 1H), 4.79 (br s, 1H, D_2O exchangeable), 3.20 (dd, J = 4 and 17 Hz, 1H), 2.26 (t, J = 7 Hz, 2H), 1.74 (br s, 3H), 1.38 (s, 3H), 1.22 (s, 6H), 1.12 (s, 3H); HRMS calcd for $C_{25}H_{35}NO_2$ (M + 1) 381.2667, found 381.2652.

Norpentyl-6′-cyano-1′,1′-dimethyl-6′-phenylhexyl-Δ^8-tetrahydrocannabinol (1c). To a solution of benzyl cyanide (59.6 mg, 0.51 mmol) in anhydrous THF (3 mL) at 0 °C was added dropwise 1.7 M BuLi in hexanes (0.3 mL, 0.51 mmol), and the mixture stirred for 15 min. This was added via a cannula to a solution of compound **8** (250 mg, 0.53 mmol) and lithium iodide (71 mg, 0.53 mmol) in anhydrous THF (3 mL). After the mixture stirred at room temperature for 1 h, saturated NH_4Cl (2 mL) was added to quench the reaction and the solvents were removed in vacuo. The residue was partitioned between EtOAc and water, and the aqueous layer was extracted several times with EtOAc. The combined EtOAc extract was washed with water and then with brine and dried. After concentration in vacuo the residue was chromatographed on silica gel (40 g), eluting with 5% ethyl acetate/hexanes, to yield 190 mg (75%) of 6′-cyano-1′,1′- dimethyl-6′-phenylhexyl-Δ^8-tetrahydrocannabinol methoxymethyl ether: ^{1}H NMR δ 7.32 (br s, 5H), 6.55 (d, J = 2 Hz, 1H), 6.43 (s, J = 2 Hz, 1H), 5.41 (br s, 1H), 5.15 (s, 2H), 3.71 (t, J = 7 Hz, 1H), 3.51 (s, 3H), 3.18 (dd, J = 4 and 17 Hz, 1H), 1.70 (br s, 1H), 1.37 (s, 3H), 1.21 (s, 6H), 1.10 (s, 1H).

The above compound (130 mg, 0.26 mmol) was then deprotected with trimethylsilyl bromide (130 mg, 0.26 mmol) using the same procedure as described above and gave 61 mg (50%) of compound **1c**: ^{1}H NMR δ 7.32 (br s, 5H), 6.37 (d, J = 2 Hz, 1H), 6.21 (d, J = 2 Hz, 1H), 5.41 (br s, 1H), 4.79 (br s, 1H, D_2O exchangeable), 3.71 (t, J = 7 Hz, 1H), 3.19 (dd, J = 4 and 17 Hz, 1H),1.72 (br s, 3H), 1.36 (s, 3H), 1.25 (s, 6H), 1.12 (s, 3H). Anal. ($C_{31}H_{39}NO_2 \cdot H_2O$) C, H, N.

5′-(*p*-Cyanophenoxy)-1′,1′-dimethyl-Δ^8-tetrahydrocannabinol (1e). To a solution of **8** (350 mg, 0.75 mmol) in anhydrous CH_3CN (5 mL) was added K_2CO_3 (200 mesh, 456 mg, 3.31 mmol) followed by *p*-cyanophenol (98 mg, 0.82 mmol), and the reaction was heated to 60 °C overnight. After the mixture cooled, water (50 mL) was added, and the aqueous mixture was extracted with several portions of ether. The combined ether extract was washed with water followed by brine, then dried, and concentrated. The resulting viscous oil was chromatographed on silica gel (40 g), eluting with 8% ethyl acetate/hexanes, to give 337 mg (89%) of 5′-(*p*-cyanophenoxy)-

1′,1′-dimethyl-Δ⁸-tetrahydrocannabinol methoxymethyl ether: ^{1}H NMR δ 7.55 (d, J = 9 Hz, 2H), 6.87 (d, J = 9 Hz, 2H), 6.57 (d, J = 2 Hz, 1H), 6.46 (d, J = 2 Hz, 1H), 5.43 (br s, 1H), 5.15 (s, 2H), 3.91 (t, J = 7 Hz, 2H), 3.49 (s, 3H), 3.18 (dd, J = 4 and 17 Hz, 1H), 1.70 (br s, 3H), 1.38 (s, 3H), 1.25 (s, 6H), 1.09 (s, 3H).

To a cooled solution (−30 °C) of the above methoxymethyl ether (324 mg, 0.64 mmol) in anhydrous CH_2Cl_2 (2 mL) was added trimethylsilyl bromide (400 mg, 2.6 mmol), and the mixture was stirred at −40 to −25 °C followed by warming to room temperature for 2 h. The reaction was quenched by the addition of saturated $NaHCO_3$ solution, and the mixture was extracted several times with ether. The combined ether extract was washed with water and brine and concentrated in vacuo after drying. The residue was dried in vacuo and dissolved in anhydrous THF (4 mL). After treatment with a 1 M solution of Bu_4NF in THF (1 mL, 1 mmol) and stirring for 4 h at 23 °C, the solvent was removed in vacuo. The residue was chromatographed on silica gel (20 g), eluting with 20% ethyl acetate/hexanes, to give 103 mg (47%) of **1b**: ^{1}H NMR δ 7.55 (d, J = 9 Hz, 2H), 6.87 (d, J = 9 Hz, 2H), 6.38 (d, J = 2 Hz, 1H), 6.22 (d, J = 2 Hz, 1H), 5.41 (br s, 1H), 3.91 (t, J = 7 Hz, 2H), 3.19 (dd, J = 4 and 17 Hz, 1H), 1.72 (br s, 3H), 1.38 (s, 3H), 1.22 (s, 6H), 1.13 (s, 3H). Anal. ($C_{30}H_{37}NO_3$·0.35 CH_2Cl_2) C, H, N. The presence of CH_2Cl_2 was confirmed by NMR.

5′-Oxo-1′,1′-dimethylpentyl-Δ⁸-tetrahydrocannabinol-1-acetate (9a). To a solution of acetate **7b** (1.86 g, 4.0 mmol prepared from the corresponding THC **7a** by treatment with Ac_2O/Py/DMAP/CH_2Cl_2) in anhydrous DMSO (50 mL) were added sodium iodide (900 mg, 6.02 mmol) and $NaHCO_3$ (675 mg, 8.03 mmol), and the mixture was heated to 110 °C for 6 h. After cooling, the mixture was added to water (200 mL), and the aqueous layer was extracted with EtOAc (5 × 200 mL). The combined EtOAc extract was washed with water and then with brine, then dried, and concentrated in vacuo to give a gum which was chromatographed on silica gel (45 g), eluting with 30% ethyl acetate/hexanes, to give 1.02 g (63%) of **9a**: ^{1}H NMR δ 9.68 (t, J = 3 Hz, 3H), 6.68 (d, J = 2 Hz, 1H), 6.50 (d, J = 2 Hz, 1H), 5.42 (br s, 1H), 2.75 (dd, J = 4 and 17 Hz, 1H), 2.30 (s, 3H), 1.72 (br s, 3H), 1.38 (s, 3H), 1.25 (s, 6H), 1.10 (s, 3H).

5′-Cyano-1′,1′-dimethyl-5′-hydroxy-Δ⁸-tetrahydrocannabinol (1d). To a degassed (with N_2) solution of the acetate aldehyde **9a** (528 mg, 1.32 mmol) in methanol (12 mL) was added a degassed (with N_2) solution of Na_2CO_3 (560 mg, 5.30 mmol) in H_2O (3 mL), and the solution was stirred for 0.5 h at 23 °C. The solvent was removed in vacuo, and the residue was partitioned between EtOAc and H_2O. The aqueous layer was extracted several times with EtOAc, and the combined EtOAc extract was washed with H_2O and brine, then dried, and concentrated in vacuo. The residue was chromatographed on silica gel (35 g), eluting with 10% ethyl acetate/hexanes, to yield 436 mg (93%) of **9b**. To a solution of the aldehyde **9b** (200 mg, 0.56 mmol) in anhydrous methanol (8 mL) was added sodium cyanide (165 mg, 3.37 mmol), and the mixture was allowed to stir for 2 h. Glacial acetic acid (200 mg, 192 μL, 3.37 mmol) was then added followed 30 min later by methanolic HCl (2.8 M, 200 μL), and the mixture was allowed to stir overnight. It was concentrated in vacuo and the residue partitioned between CH_2Cl_2 and H_2O. The CH_2Cl_2 layer was dried and evaporated in vacuo to yield a viscous oil which was chromatographed on silica gel (20 g), eluting with 15% ethyl acetate/hexanes, to give 181 mg (87%) of **1d**: ^{1}H NMR δ 6.38 (d, J = 2 Hz, 1H), 6.23 (d, J = 2 Hz, 1H), 5.43 (br s, 1H), 4.79 (br s, 1H, D_2O exchangeable), 4.48−4.25 (m, 1H), 3.21 (dd, J = 4 and 17 Hz, 1H), 2.54 (d, J = 7 Hz, 1H, D_2O exchangeable), 1.70 (br s, 3H), 1.38 (s, 3H), 1.22 (s, 6H), 1.11 (s, 3H). Anal. ($C_{24}H_{33}NO_3$·0.6H_2O) C, H, N.

5′-Carboxy-1′,1′-dimethyl-Δ⁸-tetrahydrocannabinol (10). To a solution of **1a** (3.00 g, 8.17 mmol) in ethanol (340 mL) were added KOH (26.30 g) and water (26 mL) which was refluxed for 24 h. The ethanol was removed in vacuo, and the residue was made acidic (2 M HCl) and extracted with ether (5 × 100 mL). The combined ether extract was washed, dried, and concentrated to leave a residue which was chromatographed on silica gel (300 g), eluting with 30% ethyl acetate/hexanes, to yield 2.45 g (77%) of the acid **10**: IR (KBr) 1705 cm^{-1}; ^{1}H NMR δ 6.38 (d, J = 2 Hz, 1H), 6.22 (d, J = 2 Hz, 1H), 5.45 (br s, 1H), 3.21 (dd, J = 4 and 17 Hz, 1H), 2.28 (t, J = 9.5 Hz, 2H), 1.68 (br s, 3H), 1.39 (s, 3H), 1.21 (s, 6H), 1.13 (s, 3H).

1′,1′-Dimethyl-5′-(*N*,*N*-diethylcarboxamido)-Δ⁸-tetrahydrocannabinol (2b). To a solution of the acid **10** (100 mg, 0.26 mmol) in benzene (4A sieves, 2 mL) were added 1 drop of dry DMF and oxalyl chloride (131 mg, 90 μL, 1.03 mmol). The mixture was allowed to stir at room temperature for 1 h. The solvent was removed in vacuo followed by addition of benzene and evaporation on a rotary evaporator to remove traces of oxalyl chloride. The residue was dissolved in anhydrous CH_2Cl_2 (2 mL), diethylamine (190 mg, 270 μL, 2.6 mmol) was added, and the reaction was allowed to stir for 30 min. The reaction was partitioned between CH_2Cl_2 and H_2O, and the aqueous layer was extracted several times with CH_2Cl_2. The combined CH_2Cl_2 extract was washed with 1 N HCl, H_2O, and brine, dried, and evaporated to yield a viscous oil, which was chromatographed on silica gel (35 g), eluting with 30% ethyl acetate/hexanes, to give 73 mg (64%) of **2b**: ^{1}H NMR δ 6.32 (br s, 2H), 6.15 (s, 1H, D_2O exchangeable), 5.43 (br s, 1H), 3.31 (d of q, J = 7 Hz, 4H), 3.21 (dd, J = 4 and 17 Hz, 1H), 2.24 (t, J = 7 Hz, 2H), 1.68 (br s, 3H), 1.37 (s, 3H), 1.22 (s, 6H), 2.4−0.9 (m, 20H); HRMS calcd for $C_{28}H_{44}NO_3$ (M + 1) 442.3321, found 442.3349.

1′,1′-Dimethyl-5′-[*N*-(piperidin-1-yl)carboxamido]-Δ⁸-tetrahydrocannabinol (2c). The acid **10** (100 mg, 0.26 mmol) was converted to its acid chloride which was treated with 1-aminopiperidine (259 mg, 279 μL, 2.26 mmol) and worked up in the same way as described above. It was purified by chromatography on silica gel (15 g), eluting with 50% ethyl acetate/hexanes, to give 40 mg (33%) of **2c**: ^{1}H NMR δ 6.2−6.4 (m, 3H), 5.45 (br s, 1H), 3.22 (dd, J = 4 and 17 Hz, 1H), 2.90−2.55 (m, 2H), 1.78 (br s, 3H), 1.37 (s, 3H), 1.18 (s, 6H), 1.13 (s, 3H); HRMS calcd for $C_{29}H_{45}N_2O_3$ (M + 1) 469.3430, found 469.3400.

1′,1′-Dimethyl-5′-[*N*-(2-(4-aminosulfonylphenyl)ethyl)-carboxamido]-Δ⁸-tetrahydrocannabinol (2d). To a mixture of the acid **10** (210 mg, 0.54 mmol), 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide (101 mg, 0.65 mmol), DMAP (66 mg, 0.54 mmol), and 4-(2-aminoethyl)benzenesulfonamide (112 mg, 0.56 mmol) in anhydrous CH_2Cl_2 (4 mL) was added anhydrous THF (4 mL), and the mixture was stirred at 23 °C for 24 h. The clear solution was concentrated in vacuo, and the residue was partitioned in ether/1 M HCl solution and extracted with ether (4 × 20 mL). The combined ether extract was washed with 1 M HCl solution, followed by brine, then dried, and concentrated in vacuo. The residue was chromatographed on silica gel (40 g), eluting with 50% ethyl acetate/hexanes, to yield 109 mg (34%) of **2d**: ^{1}H NMR δ 7.8 (d, J = 11 Hz, 2H), 7.25 (d, J = 11 Hz, 2H), 6.4−6.15 (m, 3H, D_2O exchangeable 1H), 5.7−5.5 (m, 1H, D_2O exchangeable), 5.42 (br, 1H), 5.2 (s, 2H, D_2O exchangeable), 3.65−3.10 (m, 3H), 2.95−2.50 (m, 3H), 1.7 (br s, 3H), 1.36 (s, 3H), 1.21 (s, 6H), 1.07 (s, 3H); MS (CI) 569 (M + 1) 99.5%. Anal. ($C_{32}H_{44}N_2O_5S$·0.35$CHCl_3$·H_2O) C, H, N, S. The presence of chloroform was confirmed by NMR.

This compound (**2d**) was also formed by conversion of the acid **10** to its acid chloride as in **2b** and its subsequent treatment with 4-(2-aminoethyl)benzenesulfonamide. However, during the preparation of the acid chloride of the acid **10**, if a larger amount (4−5 drops) of DMF was used as the catalyst, the acid chloride on subsequent treatment with the above sulfonamide formed a different compound which was identified as **1′,1′-dimethyl- 5′-(*N*,*N*-dimethylcarboxamido)-Δ⁸-tetrahydrocannabinol (2a)**, the dimethylamide analogue of **2b**. It was isolated by chromatography (silica gel), eluting with 25% EtOAc/hexanes, in 57% yield: mp 103−106 °C; ^{1}H NMR δ 6.32 (br s, 2H), 6.25 (s, 1H), 5.43 (br s, 1H), 3.21 (dd,

J = 4 and 17 Hz, 1H), 3.0 (s, 3H), 2.97 (s, 3H), 1.68 (br s, 3H), 1.37 (s, 3H), 1.19 (s, 6H), 2.8−0.9 (m, 16 H); MS *m/z* 414 (M + 1) (100), 286 (65). Anal. ($C_{26}H_{39}NO_3$·0.75EtOAc) C, H, N. The presence of EtOAc was confirmed by NMR.

1′,1′-Dimethyl-5′-[*N*-((4-aminosulfonylphenyl)methyl)-carboxamido]-Δ⁸-tetrahydrocannabinol (2e). The acid **10** (200 mg, 0.52 mmol) was converted to its acid chloride as described above. It was dissolved in dry CH_2Cl_2 (20 mL) and added dropwise to a stirred suspension of 4-(aminomethyl)-benzenesulfonamide (1.15 g, 5.16 mmol) in dry THF (20 mL). After stirring at 40 °C for 2 h, the mixture was worked up and chromatographed, as described above, to give 120 mg (42%) of **2e**: ^{1}H NMR (CD_3OD) δ 7.85 (d, J = 9 Hz, 2H), 7.42 (d, J = 9 Hz, 2H), 6.35 (d, J = 2 Hz, 1H), 6.25 (d, J = 2 Hz, 1H), 5.42 (br s, 1H), 4.40 (s, 2H), 2.20 (t, J = 7 Hz, 2H), 1.68 (br s, 3H), 1.35 (s, 3H), 1.19 (s, 6H), 1.07 (s, 3H). Anal. ($C_{31}H_{42}N_2O_5S$·0.6H_2O) C, H, N.

1′,1′-Dimethyl-5′-[*N*-(4-aminosulfonylphenyl)carboxamido]-Δ⁸-tetrahydrocannabinol (2f). The acid **10** (215 mg, 0.55 mmol) was converted to its acid chloride. It was dissolved in dry CH_2Cl_2 (15 mL), added dropwise to a stirred suspension of sulfanilamide (890 mg, 5.17 mmol) in dry CH_2Cl_2 (30 mL), and then refluxed for 16 h. After filtering, the filtrate was washed with water, dried, and concentrated in vacuo. The residue was chromatographed on silica gel (23 g), eluting with 25% EtOAc/CH_2Cl_2, to give 140 mg (47%) of **2f**: ^{1}H NMR δ 8.32 (br s, 1H), 7.7 (d, J = 9 Hz, 2H), 7.45 (d, J = 9 Hz, 2H), 6.55 (br s, 1H), 6.3 (br s, 2H), 5.7 (br s, 1H), 5.4 (br s, 1H), 3.4−2.5 (m, 3H), 1.63 (br s, 3H), 1.35 (s, 3H), 1.20 (s, 6H), 1.05 (s, 3H). Anal. ($C_{30}H_{40}N_2O_5S$·0.5H_2O) C, H, N.

1′,1′-Dimethyl-5′-[*N*-(4-chlorophenyl)carboxamido]-Δ⁸-tetrahydrocannabinol (2g). The acid **10** (200 mg, 0.52 mmol) was converted to its acid chloride which was treated with 4-chloroaniline (200 mg, 1.57 mmol) and worked up as described for **2b**. It was purified by preparative TLC (10% EtOAc/CH_2Cl_2) to give 65 mg (17%) of **2g** as a pale-yellow solid: mp 95−96 °C; ^{1}H NMR δ 7.2−7.6 (m, 5H), 6.39 (d, J = 2 Hz, 1H), 6.25 (d, J = 2 Hz, 1H), 5.45 (br s, 1H), 3.22 (dd, J = 4 and 17 Hz, 1H), 2.24 (t, J = 7 Hz, 2H), 1.72 (br s, 3H), 1.08−2.85 (m, 24H); MS *m/z* 497 (M + 1) (100), 286 (78). Anal. ($C_{30}H_{38}NO_3Cl$·0.33$CHCl_3$·0.75H_2O) C, H, N. The presence of chloroform was confirmed by NMR.

1′,1′-Dimethyl-5′-[*N*-(2,4-dichlorophenyl)carboxamido]-Δ⁸-tetrahydrocannabinol (2h). It was similarly prepared as **2g** and obtained as a pale-yellow solid (16%): mp 84−85 °C; ^{1}H NMR δ 8.3 (d, J = 7 Hz, 1H), 7.52 (br s, 1H), 7.4 (d, J = 2 Hz, 1H), 7.2 (dd, J = 2 and 7 Hz, 1H), 6.4 (d, J = 2 Hz, 1H), 5.47 (br s, 1H), 3.2 (dd, J = 4 and 17 Hz, 1H), 2.38 (t, J = 7 Hz, 2H), 1.72 (br s, 3H), 1.08−2.85 (m, 24H); HRMS calcd for $C_{30}H_{37}NO_3Cl_2$ (M + 1) 530.2231, found 530.2264.

Pharmacology. 1. Drug Preparation and Administration. For binding assays, compounds were prepared as 1 mg/mL stock solutions in absolute ethanol and were stored at −20 °C. For behavioral assays, drugs were dissolved in a 1:1:18 mixture of ethanol, emulphor (GAF Corp., Linden, NJ), and saline (0.9% NaCl) and were administered intravenously (iv) in the mouse tail vein in volumes of 0.1 mL/10 g of body weight.

2. Binding Assays. Radioligand binding to P_2 membrane preparations using the filtration method was performed as described elsewhere.[17] Displacement curves were generated by incubating drugs with 1 nM [^{3}H]CP-55490. The assays were performed in triplicate, and the results represent the combined data from three individual experiments.

3. Behavioral Evaluation. Mice received the analogue by tail-vein injection and were evaluated for their ability to produce hypomotility, hypothermia, antinociception, and immobility. These four pharmacological measures were determined in the same mouse as described elsewhere.[17] Spontaneous activity (SA, hypomotility) was expressed as percent of control activity. Antinociception (tail-flick, TF) was expressed as percent of maximum possible effect (MPE) using a 10-s maximum test latency as described earlier.[18] Hypothermia (rectal temperature, RT), and ring immobility (RI) were expressed as Δ°C and % immobility, respectively.

4. Data Analysis. IC_{50} values were converted to K_i values.[19] Statistical evaluation of parallelism between displacement curves generated was performed using ALLFIT.[20] Dose−response relationships were determined for each analogue in the pharmacological assays. Percent effect was determined based upon the maximal effects that are produced by Δ⁹-THC which are 90%, 100%, −6 °C, and 60% for SA, TF, RT, and RI, respectively. The data generated by these tests were converted to probit values, and ED_{50} values were calculated by unweighted least-squares linear regression analysis of the log dose versus the probit values.

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