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Structure–Activity Relationships for 1′,1′-dimethylalkyl-Δ^8-tetrahydrocannabinols

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Abstract—A series of 1′,1′-dimethylalkyl-Δ^8-tetrahydrocannabinol analogues with C-3 side chains of 2–12 carbon atoms has been synthesized and their in vitro and in vivo pharmacology has been evaluated. The lowest member of the series, 1′,1′-dimethylethyl-Δ^8-THC (**8**, $n=0$) has good affinity for the CB_1 receptor, but is inactive in vivo. The dimethylpropyl (**8**, $n=1$) through dimethyldecyl (**8**, $n=8$) all have high affinity for the CB_1 receptor and are full agonists in vivo. 1′,1′-Dimethylundecyl-Δ^8-THC (**8**, $n=9$) has significant affinity for the receptor ($K_i=25.8\pm5.8$ nM), but has reduced potency in vivo. The dodecyl analogue (**8**, $n=10$) has little affinity for the CB_1 receptor and is inactive in vivo. A quantitative structure–activity relationship study of the side chain region of these compounds is consistent with the concept that for optimum affinity and potency the side chain must be of a length which will permit its terminus to loop back in proximity to the phenolic ring of the cannabinoid.

Introduction

Nearly 40 years ago, Gaoni and Mechoulam identified Δ^9-tetrahydrocannabinol (Δ^9-THC, 1) as the major psychoactive constituent of marijuana.[1] Subsequently, a body of empirical structure–activity relationships (SARs) was developed for those cannabinoids structurally related to Δ^9-THC.[2–4] These SAR include a phenolic hydroxyl group at C-1, an alkyl side chain at C-3, the absolute stereochemistry depicted in **1** and substituent effects at C-9. These SAR were incorporated in the three-point receptor model suggested by both Binder et al.[5] and Howlett et al. which also includes a C-9 or C-11 hydroxyl group.[4,6] Although the nature of the substituent at C-9 has an effect upon the potency of cannabinoids structurally related to Δ^9-THC 1, as noted by Martin et al., these effects are considerably more complex than simply the presence or absence of a hydroxyl group in this region of the molecule.[7–9]

Δ^9-THC (**1**) has good affinity for the CB_1 receptor ($K_i=41\pm1.7$ nM), and its double bond isomer, Δ^8-THC (**2**) has similar receptor affinity.[10] It is known that the nature of the alkyl side chain has a profound effect upon the pharmacological activity and CB_1 receptor affinities of cannabinoids related to THC.[2–5,10] Reducing the length of the side chain by one carbon atom to butyl (**3**) results in a reduction in affinity ($K_i=65\pm13$ nM) while incrementally increasing the length of the side chain to hexyl (**4**), heptyl (**5**) and octyl (**6**), provides a systematic increase in affinity from 41 ± 3.8 to 8.5 ± 1.4 nM. The in vivo potencies of these Δ^8-THC homologues are consistent with their relative affinities for the CB_1 receptor.[10]

Many years ago, Roger Adams found that a 1′,2′-dimethylheptyl side chain provides greatly increased potency in the $\Delta^{6a,10a}$-THC series, however the substitution pattern of this side chain introduces two additional chiral centers.[11] Adams et al. carried out their studies using a mixture of stereoisomers. Ultimately the four isomers of 3-(1′,2′-dimethylheptyl)-Δ^8-THC were prepared and their stereochemistry elucidated.[12]

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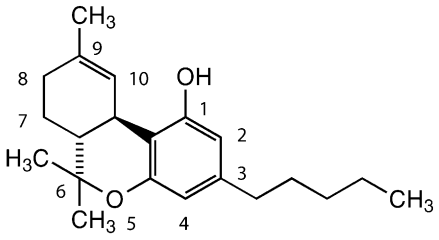

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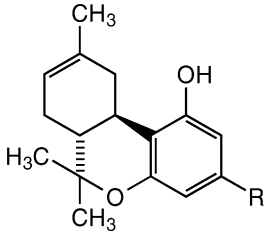


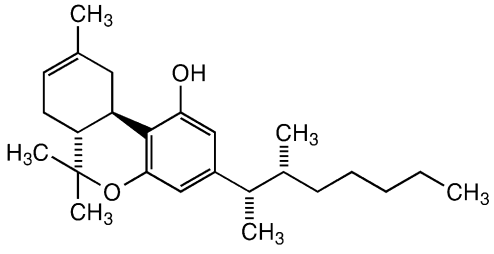
2 R = n-C_5H_{11}
3 R = n-C_4H_9
4 R = n-C_6H_{13}
5 R = n-C_7H_{15}
6 R = n-C_8H_{17}

Although all four are very potent cannabinoids, the (1′*S*,2′*R*) isomer (**7**) has the greatest affinity for the CB_1 ($K_i = 0.46 \pm 0.04$ nM) receptor and is the most potent in vivo. Subsequently an enantioselective synthesis of the resorcinol precursor to this exceptionally potent cannabinoid was developed.[13]

1′,1′-Dimethylheptyl-$\Delta^{6a,10a}$-THC was prepared by Adams et al., and, although it was found to be some 20 times more potent than the *n*-pentyl analogue, it was at least an order of magnitude less potent than a mixture of 1′,2′-dimethylheptyl isomers.[11,14] Subsequently, it was found that 1′,1′-dimethylheptyl-Δ^8-THC (Δ^8-THC-DMH, 8, $n = 5$) is an exceptionally potent cannabinoid in vivo, with very high affinity for the CB_1 receptor ($K_i = 0.77 \pm 0.11$ nM).[15] In connection with the synthesis of the synthetic cannabinoid nabilone (**9**),[16] the Lilly group developed a short, efficient synthesis of 2-(3,5-dihydroxyphenyl)-2-methyloctane (**10**), which has provided a convenient approach to the synthesis of cannabinoids with a 1′,1′-dimethylheptyl side chain.[17] The 1′,1′-dimethylheptyl side chain provides a level of cannabinoid potency only slightly less than that of the 1′,2′-dimethylheptyl group, however it does not contain a chiral center, and is thus considerably more accessible synthetically.

In connection with a quantitative structure–activity relationship (QSAR) analysis of the side chain conformation of a variety of Δ^8-THC analogues, Keimowitz et al. found that not only is the length of the cannabinoid side chain important, but that its ability to fold back to place the terminus close to the polycyclic nucleus is critical.[18] This conclusion agrees with the conformation of the 1′,1′-dimethylheptyl side chain of the bicyclic nonclassical cannabinoid cannabinoid CP-47,497 which was determined by NMR[19] and the compact conformation of Δ^8-THC in a model membrane system.[20] The study by Keimowitz et al. included 36 compounds with side chains of four to eight carbon atoms, and all but one, Δ^8-THC-DMH (**8**, $n = 5$), contain unsaturation in the side chain.[18]

Classical empirical cannabinoid SAR state that a seven-carbon side chain is optimum for cannabinoid potency and that 1′,1′- and 1′,2′-dimethylation greatly increases potency.[2,4] However, recent data show that 3-octyl-Δ^8-THC (**6**) has somewhat greater affinity for the CB_1



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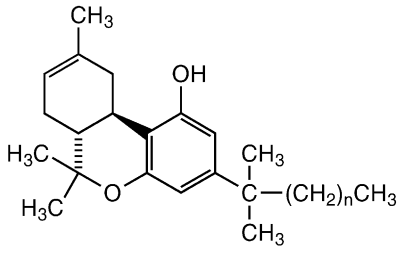

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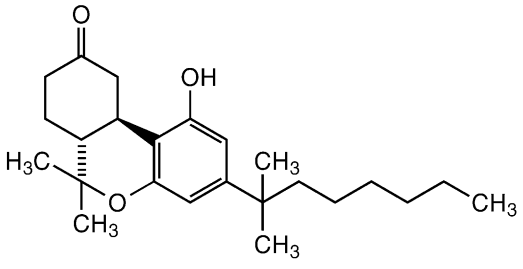

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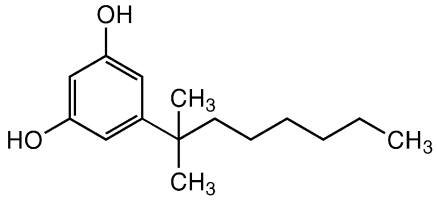

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receptor than 3-heptyl-Δ^8-THC (**5**), and both compounds have comparable potency in vivo.[10] However, little is known concerning the SAR of cannabinoids with 1′,1′-dimethylalkyl groups other than Δ^8-THC-DMH (**8**, $n=5$) and the dimethylpentyl analogue (**8**, $n=3$) which was prepared many years ago by Petrzilka et al. and was found to be more potent than Δ^8-(**2**) or Δ^9-THC (**1**) in vivo.[21,22] In order to define the relationship between length of the cannabinoid side chain and biological activity, we now describe the preparation, pharmacology and QSAR for a series of 1′,1′-dimethylalkyl-Δ^8-THC homologues (**8**, $n=0$–10).

Results

All of the target cannabinoids were prepared by the acid catalyzed condensation of an appropriately substituted resorcinol (**11**) and *trans-para*-menthadienol (**12**, Scheme 1).[21] Several of these compounds (**8**, $n=0$–4 and $n=6$, 7) had been prepared previously as intermediates in the synthesis of a series of CB_2 selective 1-deoxycannabinoids.[23] The substituted resorcinols were prepared from the appropriate tertiary alcohol and 2,6-dimethoxyphenol using a modification of the procedure of Dominianni et al.[17,24]

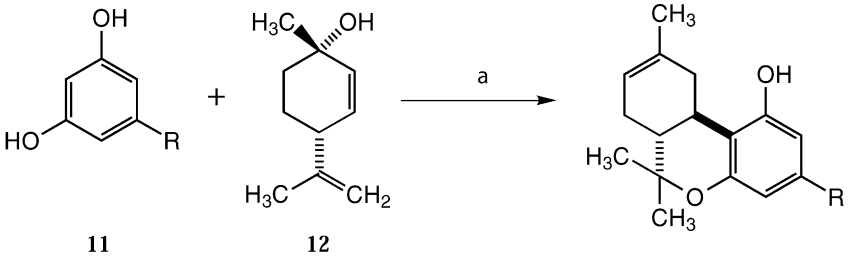
The affinities of cannabinoids **8**, $n=0$–4 and 6–10, for the CB_1 receptor were measured by determining their ability to displace [^{3}H]CP 55,940 from its binding site in a rat brain membrane preparation as described by Compton et al.[25] The in vivo pharmacology was evaluated using the mouse model of cannabinoid activity which measures spontaneous activity (SA), antinociception (as tail flick, TF) and rectal temperature (RT).[26,27]

For those cannabinoids with an unsubstituted alkyl substituent at C-3, the affinity for the CB_1 receptor is maximum for 3-octyl-Δ^8-THC (**6**, $K_i=8.5\pm1.4$ nM), decreases for the heptyl analogue (**5**, $K_i=22\pm3.9$ nM) and then decreases further for 3-hexyl-Δ^8-THC (4, $K_i=41\pm3.8$ nM) and Δ^8-THC (**2**, $K_i=44\pm12$ nM). 3-Butyl-Δ^8-THC (**6**) has significantly lower affinity for the receptor with $K_i=65\pm13$ nM. The in vivo potency of these compounds is consistent with their respective affinities for the CB_1 receptor, and the details of their pharmacology have been discussed previously (Table 1).[10]

In the 3-(1′,1′-dimethylalkyl)-Δ^8-THC series (**8**, $n=0$–4 and 6–10), although the 1′,1′-dimethylethyl (**8**, $n=0$) has significant affinity for the receptor with $K_i=14\pm1.8$ nM, it is inactive in vivo. Since this compound is inactive in vivo, but has high affinity for the CB_1 receptor, the possibility that it was an antagonist was explored. Mice were pretreated with 1, 3 or 10 mg/kg of the ligand and 10 min later were injected with 3 mg/kg of Δ^9-THC. The behavioral effects were evaluated in the usual manner (see the Experimental). 1′,1′-Dimethylethyl-Δ^8-THC (**8**, $n=0$) had no effect on Δ^9-THC induced hypothermia or depression of spontaneous activity. However, in the tail flick protocol to evaluate antinociception at the 10 mg/kg level this ligand reduced the per cent maximum possible effect (% MPE) for 3 mg/kg of Δ^9-THC from 90 to 11%. At the 3 mg/kg level of dimethylethyl-Δ^8-THC (**8**, $n=0$), the% MPE was reduced to 67%, however there was no discernible effect at the 1 mg/kg level. Thus, dimethylethyl-Δ^8-THC (**8**, $n=0$) appears to be either devoid of activity or a very weak agonist in the spontaneous activity and rectal temperature procedures, and to have antagonist properties in the tail flick protocol.

1′,1′-Dimethylpropyl-Δ^8-THC (**8**, $n=1$, $K_i=14\pm0.9$ nM) is an agonist in all three in vivo procedures, however it is considerably less potent than Δ^8-THC (Table 1). The 1′,1′-dimethylbutyl analogue (**8**, $n=2$) also has significant affinity for the CB_1 receptor ($K_i=10.9\pm1.7$ nM) and is more potent than Δ^8-THC (**2**) in the tail flick measure of antinociception. It is approximately equipotent to Δ^8-THC in its ability to decrease rectal temperature, however this analogue does not show a dose-dependent response in the depression of spontaneous activity.

1′,1′-Dimethylpentyl-Δ^8-THC (**8**, $n=3$) through 1′,1′-dimethylnonyl-Δ^8-THC (**8**, $n=7$) all have high affinity for the CB_1 receptor with K_i values of 0.77–3.9 nM. The dimethylheptyl (**8**, $n=5$, $K_i=0.77$ nM) and dimethyloctyl (**8**, $n=6$, $K_i=0.9\pm0.1$) analogues exhibited the highest affinities. The affinities of these two compounds are virtually identical, within experimental error. The 1′,1′-dimethylpentyl (**8**, $n=3$, $K_i=3.9\pm0.9$ nM), 1′,1′-dimethylhexyl (**8**, $n=4$, $K_i=2.7\pm1.3$ nM) and 1′,1′-dimethylnonyl (**8**, $n=7$, $K_i=1.6\pm0.4$ nM) analogues have only slightly lower affinities for the CB_1 receptor. The CB_1 receptor affinities of these three cannabinoids are effectively identical, within experimental error. All five of these compounds are full agonists in the mouse and with the exception of the 1′,1′-dimethylnonyl-Δ^8-THC, all are considerably more potent than Δ^8-THC. The 1′,1′-dimethylnonyl analogue is approximately equal



11 **12**

Scheme 1. (a) HOTs/C_6H_6, 80 °C.

Table 1. In vitro and in vivo pharmacology of Δ^8-THC (**2**) and 3-(1′,1′-dimethylalkyl)-Δ^8-THC analogues (**8**, $n=0$–10)

Compd	K_i (nM)	ED50 (95% CL)		
		SA (μmol/kg)	TF (μmol/kg)	RT (μmol/kg)
Δ^8-THC (**2**)	44±12[a]	2.9[a]	4.8[a]	4.5[a]
3-Butyl-Δ^8-THC (**3**)	65±13[b]	9.0[b]	10.1[b]	6.3[b]
3-Hexyl-Δ^8-THC (**4**)	41±3.8[b]	1.2[b]	1.8[b]	0.10[b]
3-Heptyl-Δ^8-THC (**5**)	22±3.9[b]	0.14[b]	0.61[b]	0.16[b]
3-Octyl-Δ^8-THC (**6**)	8.5±1.4[b]	0.39[b]	0.34[b]	0.24[b]
3-(1′,1′-Dimethylethyl-Δ^8-THC (**8** $n=0$)	14±1.8	[c]	>100	[d]
3-(1′,1′-Dimethylpropyl)Δ^8-THC (**8** $n=1$)	14±0.9	[e]	24.5 (14.0–43.3)	[f]
3-(1′,1′-Dimethylbutyl)Δ^8-THC (**8** $n=2$)	10.9±1.7	[g]	19. (1.3–2.8)	4,2 (3.2–5.6)
3-(1′,1′-Dimethylpentyl)Δ^8-THC (**8** $n=3$)	3.9±0.9	1.1 (0.6–2.1)	0.4 (0.4–0.6)	1.5 (1.0–2.1)
3-(1′,1′-Dimethylhexyl)Δ^8-THC (**8** $n=4$)	2.7±1.2	0.17 (0.01–0.28)	0.21 (0.11–0.28)	0.11 (0.06–0.2)
3-(1′,1′-Dimethylheptyl)Δ^8-THC (**8** $n=5$)	0.77[a]	0.27[a]	0.14[a]	0.15[a]
3-(1′,1′-Dimethyloctyl)Δ^8-THC (**8** $n=6$)	0.09±0.1	0.24 (0.14–0.4)	0.3 (0.19–0.49)	1.2 (0.68–2.0)
3-(1′,1′-Dimethylnonyl)Δ^8-THC (**8** $n=7$)	1.6±0.4	2.1 (0.4–10.8)[h]	5.1 (3.6–7.0)	3.2 (2.4–4.1)
3-(1′,1′-Dimethyldecyl)Δ^8-THC (**8** $n=8$)	6.1±1.8	5.5[i]	37.6 (15.4–92.0)	9.4 (6.0–14.8)
3-(1′,1′-Dimethylundecyl)Δ^8-THC (**8** $n=9$)	25.8±5.8	73[j]	73[k]	73[l]
3-(1′,1′-Dimethyldodecyl)Δ^8-THC (**8** $n=10$	126±18	[m]	Inactive	Inactive

[a]Ref. 15.
[b]Ref. 10.
[c]Active only at 3.3 μmol/kg, inactive at higher doses.
[d]Max −2 °C, not dose responsive.
[e]Max 84% at 95 μmol/kg.
[f]Decreased from −2 to −3.4 °C over a dose range of 0.95–31.8 μmol/kg, no effect at 95.5 μmol/kg.
[g]Max 78% at 91 μmol/kg, not dose dependent.
[h]Max 76%.
[i]Max 64%.
[j]Max 56%.
[k]Max 25%.
[l]Max −3 °C.
[m]Stimulation at 68, 22.7 and 68 μmol/kg.

in potency to Δ^8-THC. None of these cannabinoids show any selectivity among the three pharmacological measures of the in vivo protocol.

1′,1′-Dimethyldecyl-Δ^8-THC (**8**, $n=8$, $K_i=6.1\pm1.8$ nM) has only slightly lower affinity for the CB_1 receptor than the lower homologues: however, it is considerably less potent than the dimethylnonyl analogue in the tail flick measure of antinociception and somewhat less potent in its ability to produce hypoactivity or hypothermia. It also failed to produce complete suppression of spontaneous activity. The 1′,1′-dimethylundecyl analogue (**8**, $n=9$) has moderate affinity for the CB_1 receptor ($K_i=25.8\pm5.8$ nM), but greatly reduced potency in the mouse. This compound is a partial agonist in the three procedures of the in vivo protocol, with maximum effects of 56% in the measure of hypoactivity, 25% in the tail flick measure of antinociception and a maximum decrease in temperature of 3 °C. The 1′,1′-dimethyldodecyl analogue (**8**, $n=10$) has considerably diminished affinity for the CB_1 receptor ($K_i=126\pm18$ nM), and is inactive in the tail flick measure of antinociception. It is also inactive in causing hypothermia and is a stimulant rather than a depressant.

Both the in vitro and in vivo pharmacology data are consistent with the model suggested by Keimowitz et al. which concludes that for dibenzopyran-based cannabinoids, receptor affinity and potency are enhanced by a side chain of sufficient length that it can wrap backward along either side of the molecule.[18] Those 1′,1′-dimethylalkyl-Δ^8-THC analogues with side chains of less than four carbon atoms (**8**, $n=0$, 1) in which the side chains are too short to wrap around the molecule are inactive or weakly active in vivo, although they have significant affinity for the CB_1 receptor. The 1′,1′-dimethylbutyl to 1′,1′-dimethylnonyl-Δ^8-THC analogues (**8**, $n=2$–7) all have high receptor affinity, and potent in vivo activity. It would appear that these ligands have side chains of sufficient length to wrap around the molecule to give the requisite compact conformation. As the length of the side chain increases from 10 to 12 carbon atoms (**8**, $n=8$–10) the receptor affinity decreases incrementally and the in vivo potency decreases to the point that 1′,1′-dimethyldodecyl-Δ^8-THC is effectively inactive. It seems probable that as the side chain extends beyond nine or 10 carbon atoms it can no longer adopt the compact conformation necessary for cannabinoid activity. In order to investigate the possible validity of this hypothesis a QSAR study employing methodology similar to that used by Keimowitz et al. was carried out.[18]

Quenched molecular dynamics

The quenched molecular dynamics approach used for conformational sampling generated 100 low-energy conformations for each molecule. The conformations were quite diverse for certain molecules, while other molecules repeatedly yielded a small number of similar conformations. These differences in conformational mobility can be visualized graphically by overlaying the conformations for a particular molecule (Fig. 1).

Figure 1. Stereoviews of the conformational ensembles for the compounds in Table 1.

CoMFA

The cross-validated analysis of the relationship between the CoMFA molecular fields and the pharmacological affinity and potency measurements generally indicated that a model derived with five components was optimal. The strength of the cross-validated and final models can be demonstrated through comparison with similar relationships derived with random pharmacological data that spanned the same range as the real pharmacological data. In all but one instance, the cross-validated or final r-squared values obtained with the real pharmacological data were higher (indicating a better model) than when derived using random pharmacological data (Table 2).

Table 2. Comparison of the ability of each QSAR model to fit actual biological data or randomly generated biological data

	Actual data r^2	Random data r^2	Actual data r^2	Random data r^2
	Cross-validated		Final	
CB1 (K_I)	0.464	0.449	0.692	0.580
SA (ED_{50})	0.408	0.035	0.596	0.331
TF (ED_{50})	0.454	0.296	0.638	0.430
RT (ED_{50})	0.370	0.430	0.603	0.550

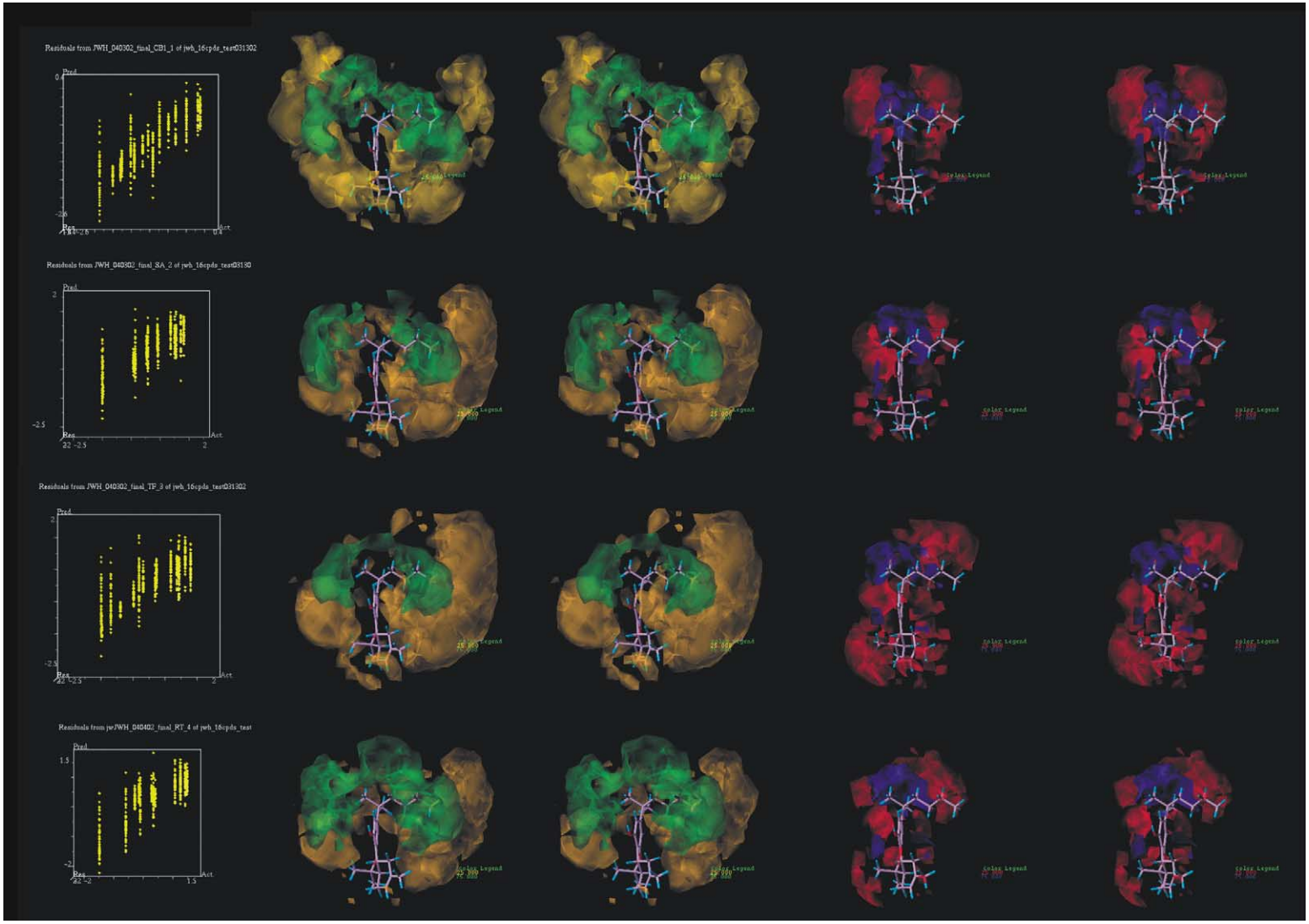


Figure 2. Predicted versus actual plots and stereoviews of the QSARS derived for the steric fields (yellow and green contours) and eletrostatic fields (blue and red) as defined for cannabinoid receptor (CB_1) binding affinity (A) and as defined for cannabinoid-induced changes in spontaneous locomotor activity (B), tail-flick latency (TF) and rectal temperature (RT). For each model, a 75/25 level of contribution is shown. The steric plots are depicted so that steric bulk should be moved closer to areas contoured in green and farther from regions in yellow in order to increase the target property being contoured (i.e., affinity or potency). The electrostatic plots are contoured such that positive charge should be moved closer to regions contoured in blue and farther from regions contoured in red in order to increase the target property being contoured.

Although there was not a single instance of a model derived with random data possessing a higher r^2 value than a model derived with the actual pharmacological data, the ability of the model to fit the potency of these compounds in the rectal temperature assay was quite similar to that determined for random data. The utilization of several conformations for each analogue allows for unbiased analyses to occur. However, it often can also produce various estimated potencies for one particular compound (see predicted vs actual plots in Fig. 2), and therefore can present a greater challenge for the CoMFA approach in deriving an accurate QSAR model. However, it has been reported that use of multiple conformers generated by molecular dynamics to determine and compare conformationally accessible regions can lead to better results in QSAR studies than that determined utilizing single conformations of each analogue.[31]

Visualization of CoMFA fields

Three-dimensional contour plots of the CoMFA model allow the visualization of regions where changes in steric or electrostatic properties are correlated with experimentally determined differences in biological properties. The contour plots in Figure 2 display the QSAR model for both receptor affinity and pharmacological potency. Inspection of the steric contour plots reveals a relatively consistent side-chain SAR for both receptor affinity and behavioral potency. A large contour in yellow surrounds a smaller contour in green in the side chain region of the analogues. The green contour, in most of the models, actually starts on one side of the aromatic ring and wraps around the side-chain end of the molecule at approximately the level of the C-3′ atom until ending on the opposite face of the aromatic ring. Thus, the model predicts decreased affinity and potency for molecules whose side chains prefer an extended conformation. Conversely, analogues whose conformational mobility allows their side chain to bend so that the terminus is alongside the aromatic ring are associated with increased predicted affinity and potency. The electrostatic plots reveal blue contours that indicate that compounds with positive charge density in this region would be predicted to possess increased pharmacological activity. This area corresponds to the increased positive point charges (derived by simple Gassteiger–Huckle calculations) in this region when methyl groups are placed at the C-1 position of the alkyl side chain.

The QSAR results are consistent with the concept that for optimum affinity and potency the side chain's conformational freedom must include conformations where its terminus loops back and comes in closer proximity to the phenolic ring. Thus alkyl chains of only certain lengths can achieve this 'active' conformation, and side-chains which are too short are unable to adopt these conformations. For side chains that are too long, it is likely that these conformations are energetically unfavorable. This conclusion is consistent with the multiple linear regression analysis of Keimowitz et al.[18] where two descriptive variables describing side chain length and terminus position were able to fit the pharmacological data for receptor affinity (correlation coefficient for pK_d of 0.82). In this study, chain length was directly related to receptor affinity, yet the angle made by the side chain from its attachment point to its terminus was found to be inversely related to affinity. Thus, this study indicated that while increased side-chain length can be associated with increased affinity, the side-chain's conformation mobility must not be restricted to extending straight away from the ring system, but must allow its wrapping back around towards the ring system. One might further conclude from the studies presented here that the addition of the 1,1-dimethyl group on alkyl chains of sufficient length induces the bent conformations that appear to be most associated with potent cannabinoid ligands of high CB1 receptor affinity.

It is intriguing that the analogues with long side chains, 1′,1′-dimethyldecyl-Δ^8-THC and 1′,1′-dimethylundecyl-Δ^8-THC, retained receptor affinity while losing biological activity. It is possible that these analogues were able to interact with the receptor when in a broken cell preparation but not in intact tissue. However, the analogue with the shortest side chain, 1′,1′-dimethylethyl-Δ^8-THC also bound with excellent affinity but lacked in vivo efficacy. Therefore, a more likely explanation is that the length of the side chain has a greater influence on receptor activation than on receptor recognition. As such, these side-chain analogues demonstrate structural features that distinguish between receptor affinity and receptor activation.

Experimental

General

IR spectra were obtained using Nicolet 5DX or Magna spectrometers; ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 300AC spectrometer. Mass spectral analyses were performed on a Hewlett-Packard 5890A gas chromatograph with a mass sensitive detector and HRMS data were obtained in the Mass Spectrometry Laboratory, School of Chemical Sciences, University of Illinois. Ether and THF were distilled from Na-benzophenone ketyl immediately before use, and other solvents were purified using standard procedures. Column chromatography was carried out on Universal silica gel (32–63 μ) using the indicated solvents as eluents. All compounds were homogeneous to ^{13}C NMR TLC and/or glc.

3-(1′,1′-Dimethylethyl)-Δ^8-tetrahydrocannabinol (8, $n=0$). The cannabinoid was prepared as described previously:[23] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.12 (s, 3H), 1.23 (s, 9H), 1.40 (s, 3H), 1.70 (s, 3H), 1.75–1.94 (m, 3H), 2.14 (m, 1H), 2.72 (dt, $J=4.6$, 10.8 Hz, 1H), 3.22 (dd, $J=4.6$, 16.3 Hz, 1H), 5.04 (s, 1H), 5.43 (d, $J=4.0$ Hz, 1H), 6.30 (d, $J=1.6$ Hz, 1H), 6.46 (d, $J=1.6$ Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 18.5, 23.5, 27.6, 27.8, 31.1, 31.4, 34.3, 35.9, 44.8, 76.7, 104.9, 107.3, 110.3, 119.3, 134.7, 151.1, 154.4, 154.5; MS (EI) m/z 301 (30), 300 (90), 217 (100);$[\alpha]_D^{20}$ −83° (c0.10, $CHCl_3$); HRMS, calcd for $C_{20}H_{28}O_2$: 300.2084, found 300.2089..

2-Methyl-2-(3,5-dimethoxyphenyl)butane. A mixture of 2.0 g (22.7 mmol) of tertiary amyl alcohol, and 3.5 g (22.7 mmol) of 2,6-dimethoxyphenol was warmed to approximately 50 °C with stirring to effect solution, cooled to 0 °C, and 5.9 mL (81.0 mmol) of methanesulfonic acid was added. The mixture was stirred at 0 °C for 3 h, allowed to warm to ambient temperature and stirred for an additional 14 h. The reaction mixture was poured onto ice, extracted with CH_2Cl_2, and the extracts were washed with water, saturated aqueous $NaHCO_3$ and dried ($MgSO_4$). The solvent was removed in vacuo to give 4.8 g (94%) of 2-methyl-2-(3,5-dimethoxy-4-hydroxyphenyl)butane as a brown oil which was used in the subsequent step without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.67 (t, J = 7.3 Hz, 3H), 1.24 (s, 6H), 1.58 (q, J = 7.3 Hz, 2H), 3.86 (s, 6H), 6.52 (s, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 9.0, 28.5, 36.9, 37.8, 56.2, 103.0, 132.4, 140.6, 146.4.

To a stirred solution of 2.1 g (9.4 mmol) of the above phenol in 5 mL of CCl_4 at 0 °C was added 1.5 mL (11.6 mmol) of diethyl phosphite, followed by the dropwise addition of 1.8 mL (12.9 mmol) of Et_3N. The reaction mixture was stirred at 0 °C for 1 h and at ambient temperature for 16 h. After dilution with CH_2Cl_2, the reaction was washed with water, 10% aqueous NaOH, water, 10% aqueous HCl, brine and dried ($MgSO_4$). The solvent was removed in vacuo to afford 3.1 g (92%) of phosphate ester as an orange-cream solid which was used in the next step without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82 (t, J = 7.1 Hz, 3H), 1.25 (s, 6H), 1.35–1.43 (m, 6H), 1.52 (q, J = 7.1 Hz, 2H), 3.82 (s, 6H), 4.18–4.35 (m, 4H), 6.53 (s, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 15.90, 15.94, 16.5, 28.9, 36.4, 45.2, 55.8, 64.0, 102.3, 127.1, 148.2, 151.0.

To 50 mL of liquid NH_3 at −78 °C was added 0.35 g (50 mg atoms) of lithium. The solution was stirred for 10 min, and 3.0 g (8.3 mmol) of the above phosphate in 3 mL of dry THF was added dropwise. The reaction mixture was stirred at −78 °C for 2 h followed by the careful addition of solid NH_4Cl to destroy the excess lithium. The ammonia was allowed to evaporate at ambient temperature. The solid residue was slurried with water, extracted with ether and the combined organic extracts were washed with brine and dried ($MgSO_4$). The solvent was evaporated in vacuo to give 1.1 g (63%) of 2-methyl-2-(3,5-dimethoxyphenyl)butane as a pale yellow oil after distillation (110 °C/0.5 mmHg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.72 (t, J = 7.4 Hz, 3H), 1.28 (s, 6H), 1.64 (q, J = 7.4 Hz, 2H), 3.81 (s, 6H), 6.33 (t, J = 2.2 Hz, 1H), 6.52 (d, J = 2.2 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 9.1, 28.4, 36.7, 38.1, 55.0, 96.5, 104.7, 152.1, 160.4; MS (EI) m/z 208 (25), 179 (100).

3-(1′,1′-Dimethylpropyl)-Δ^8-tetrahydrocannabinol (8, n = 1). To 0.18 g (0.87 mmol) of 2-methyl-2-(3,5-dimethoxyphenyl)butane at 0 °C was added 2.2 mL (22 mmol) of 1.0 M BBr_3 in CH_2Cl_2. The reaction mixture was warmed to ambient temperature, stirred for 18 h and carefully poured into ice water. After extraction with CH_2Cl_2, the organic extracts were washed with water, and dried ($MgSO_4$). The solvent was removed to give 0.15 g (96%) of crude substituted resorcinol as a brown oil which was used in the next step without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.58 (t, J = 7.3 Hz, 3H), 1.09 (s, 6H), 1.47 (q, J = 7.3 Hz, 2H), 6.22 (s, 1H), 6.42 (s, 2H), 6.70 (br s, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 9.0, 28.1, 36.5, 37.9, 100.2, 106.3, 153.5, 155.7.

The cannabinoid was prepared using the procedure described above for the synthesis of 3-(1′, 1′-dimethylethyl)-Δ^8-tetrahydrocannabinol (**8**, n = 0). From 0.15 g (0.83 mmol) of crude resorcinol, 0.13 g (0.86 mmol) of *trans-p*-menthadienol and 0.02 g (10 mol%) of *p*-toluenesulfonic acid monohydrate, there was obtained 0.18 g (69%) of cannabinoid as a viscous pale brown oil: R_f 0.15 (petroleum ether/ethyl acetate 25:1), 0.32 (petroleum ether/ethyl acetate 10:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.66 (t, J = 7.4 Hz, 3H), 1.11 (s, 3H), 1.16 (s, 6H), 1.39 (s, 3H), 1.52 (q, J = 7.4 Hz, 2H), 1.68 (s, 3H), 1.74–1.90 (m, 3H), 2.12 (m, 1H), 2.71 (dt, J = 4.7, 11.0 Hz, 1H), 3.20 (dd, J = 4.7, 16.5 Hz, 1H), 5.09 (s, 1H), 5.42 (d, J = 4.0 Hz, 1H), 6.23 (d, J = 1.6 Hz, 1H), 6.39 (d, J = 1.6 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 9.2, 18.5, 23.4, 27.5, 27.8, 28.2, 31.5, 35.9, 36.6, 37.5, 44.8, 76.7, 105.6, 108.0, 110.2, 119.3, 134.7, 149.5, 154.3, 154.5; MS (CI) m/z 315 (15), 57 (100); $[\alpha]_D^{20}$ −126° (c0.57, $CHCl_3$); HRMS, calcd for $C_{21}H_{30}O_2$: 314.2251, found 314.2246.

2-Methyl-2-(3,5-dimethoxyphenyl)pentane. The dimethyl ether was prepared using the procedure described for the synthesis of 2-methyl-2-(3,5-dimethoxyphenyl)propane. From 3.31 g (32.75 mmol) of 2-methyl-2-pentanol and 5.0 g (32.4 mmol) of 2,6-dimethoxyphenol, there was obtained 7.1 g (92%) of a brown oil which was used in the subsequent step without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80 (t, J = 7.4 Hz, 3H), 1.00–1.30 (m, 2H), 1.21 (s, 6H), 1.45–1.57 (m, 2H), 3.86 (s, 6H), 5.40 (s, 1H), 6.52 (s, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.7, 17.9, 29.0, 37.7, 47.2, 56.2, 102.9, 132.5, 141.1, 146.5.

From 5.0 g (21.0 mmol) of phenol, there was obtained 7.5 g (95%) of phosphate ester as a yellow oil which was used in the next step without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80 (t, J = 7.2 Hz, 3H), 1.03–1.11 (m, 2H), 1.19 (s, 6H), 1.37 (t, J = 7.2 Hz, 6H), 1.49–1.54 (m, 2H), 3.84 (s, 6H), 4.25–4.34 (m, 4H), 6.52 (s, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.67, 15.96, 16.1, 17.8, 28.9, 38.0, 47.0, 56.0, 64.0, 64.1, 103.0, 127.1, 147.1, 151.1.

From 6.0 g (16.0 mmol) of phosphate, there was obtained 3.30 g (93%) of 2-methyl-2-(3,5-dimethoxyphenyl)pentane as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81 (t, J = 7.3 Hz, 3H), 1.04–1.11 (m, 2H), 1.25 (s, 6H), 1.53 (m, 2H), 3.79 (s, 6H), 6.29 (t, J = 2.2 Hz, 1H), 6.49 (d, J = 2.2 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.8, 18.0, 28.9, 38.0, 47.0, 55.2, 96.5, 104.7, 152.6, 160.4.

3-(1′,1′-Dimethylbutyl)-Δ^8-tetrahydrocannabinol (8, n = 2). The cannabinoid was prepared using the procedure

described for the synthesis of 3-(1′,1′-dimethylethyl)-Δ^8-tetrahydrocannabinol. From 3.20 g (14.4 mmol) of 2-methyl-2-(3,5-dimethoxyphenyl)pentane, there was obtained 2.80 g (100%) of crude substituted resorcinol as a brown oil which was used in the next step without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.75 (t, $J=7.3$ Hz, 3H), 0.97–1.03 (m, 2H), 1.14 (s, 6H), 1.40–1.46 (m, 2H), 6.22 (br s, 3H), 6.42 (s, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.6, 17.8, 28.6, 37.7, 46.8, 100.1, 106.1, 153.7, 155.9.

From 2.70 g (13.9 mmol) of crude resorcinol, 2.20 g (14.5 mmol) of *trans*-*p*-menthadienol and 0.20 g (10 mol%) of *p*-toluenesulfonic acid monohydrate, there was obtained 3.50 g (77%) of cannabinoid as a viscous pale yellow oil: R_f 0.19 (petroleum ether/ethyl acetate 25:1), 0.38 (petroleum ether/ethyl acetate 10:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82 (t, $J=7.3$ Hz, 3H), 1.05–1.31 (m, 2H), 1.12 (s, 3H), 1.22 (s, 6H), 1.40 (s, 3H), 1.47–1.52 (m, 2H), 1.71 (s, 3H), 1.75–1.94 (m, 3H), 2.14 (m, 1H), 2.62–2.75 (m, 1H), 3.12–3.28 (m, 1H), 4.65 (s, 1H), 5.44 (br s, 1H), 6.24 (s, 1H), 6.40 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.7, 17.9, 18.5, 23.4, 27.5, 27.8, 28.6, 28.7, 31.5, 35.9, 37.3, 44.9, 46.9, 76.8, 105.5, 107.8, 110.2, 119.2, 134.7, 149.8, 154.2, 154.5; MS (EI) *m*/*z* 329 (20), 328 (40), 286 (100); $[\alpha]_D^{20}$ −258° (*c*2.2, $CHCl_3$); HRMS, calcd for $C_{22}H_{32}O_2$: 238.2402, found 328.2392.

3-(1′,1′-Dimethylpentyl)-Δ^8-tetrahydrocannabinol (8, *n*=3). The cannabinoid was prepared from 1.06 g (5.08 mmol) of 2-(3,5-dihydroxyphenyl)-2-methylhexane, 0.690 g (4.53 mmol) of *trans*-*p*-menthadienol and 0.096 g (10 mol%) of *p*-toluenesulfonic acid monohydrate as described by Petrzilka and Sikemeier[21] to give 1.36 g (78%) of cannabinoid as a viscous pale yellow oil after chromatography (Petroleum ether/ethyl acetate 8:1): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82 (t, $J=7.3$ Hz, 3H), 0.98–1.34 (m, 4H), 1.11 (s, 3H), 1.20 (s, 6H), 1.39 (s, 3H), 1.42–1.56 (m, 2H), 1.70 (s, 3H), 1.73–1.96 (m, 3H), 2.06–2.22 (m, 1H), 2.62–2.77 (m, 1H), 3.12–3.27 (m, 1H), 4.90 (s, 1H), 5.40–5.48 (m, 1H), 6.23 (d, $J=1.7$ Hz, 1H), 6.39 (d, $J=1.6$ Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1, 18.5, 23.4, 23.5, 26.9, 27.6, 28.7, 31.5, 36.0, 37.2, 44.2, 44.9, 76.6, 105.4, 108.0, 110.2, 119.3, 134.7, 150.0, 154.5; HRMS, calcd for $C_{23}H_{34}O_2$: 342.2559, found 342.2558; $[\alpha]_D^{20}$ −212° (*c*0.857, $CHCl_3$), lit.[9] $[\alpha]_D^{20}$ −237°. The ^{1}H NMR data are consistent with those reported by Petrzilka and Sikemeier.[21]

2-Methyl-2-(3,5-dimethoxyphenyl)heptane. The reaction of 3.86 g (28.7 mmol) of 2-methyl-2-heptanol,[28] prepared from 2-heptanone and methylmagnesium bromide, with 4.42 g (28.7 mmol) of 2,6-dimethoxyphenol was carried out as described above to give 7.51 g of 2-methyl-2-(4-hydroxy-3,5-dimethoxyphenyl)heptane as an oil which was used in the subsequent step without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (t, $J=7.0$ Hz, 3H), 1.26 (s, 6H), 0.97–1.36 (m, 6H), 1.48–1.60 (m, 2H), 3.87 (s, 6H), 5.50 (br s, 1H), 6.54 (s, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.9, 22.4, 24.2, 29.0, 32.4, 37.5, 44.5, 56.1, 102.9, 132.4, 140.9, 146.4.

The phenol was converted to the phosphate ester as described above. From 7.50 g (28.2 mmol) of phenol, there was obtained 11.9 g of crude ester as a yellow solid which was used in the next step without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (t, $J=7.1$ Hz, 3H), 1.00–1.50 (m, 6H), 1.50–1.68 (m, 2H), 1.26 (s, 6H), 1.39 (t, $J=6.9$ Hz, 6H), 3.86 (s, 6H), 4.19–4.46 (m, 4H), 6.54 (s, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.8, 15.8, 15.9, 22.2, 24.0, 28.8, 32.3, 37.8, 44.3, 55.8, 63.8, 63.9, 102.8, 127.1, 146.9, 151.0.

The phosphate ester was reduced as described above. From 11.88 g (28.4 mmol) of phosphate, there was obtained 5.81 g (81% from 2-heptanone) of 2-methyl-2-(3,5-dimethoxyphenyl)heptane as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82 (d, $J=7.0$ Hz, 3H), 0.98–1.36 (m, 6H), 1.26 (s, 6H), 1.50–1.65 (m, 2H), 3.79 (s, 6H), 6.30 (t, $J=2.2$ Hz, 1H), 6.49 (d, $J=2.3$ Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1, 22.5, 24.3, 28.9, 32.5, 37.9, 44.4, 55.1, 96.5, 104.6, 152.5, 160.4.[29]

3-(1′,1′-Dimethylhexyl)-Δ^8-tetrahydrocannabinol (8, *n*=4). The cannabinoid was prepared from 1.16 g (4.6 mmol) of 2-methyl-2-(3,5-dimethoxyphenyl)heptane by the procedure described above for the synthesis of 3-(1′,1′-dimethylbutyl)-Δ^8-tetrahydrocannabinol. There was obtained after chromatography (petroleum ether/ethyl acetate 8:1) 1.44 g (86%) of cannabinoid as a viscous pale yellow oil: R_f 0.25 (hexanes/ethyl acetate 25:1), 0.45 (hexanes/ethyl acetate 10:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81 (t, $J=7.1$ Hz, 3H), 0.97–1.30 (m, 6H), 1.10 (s, 3H), 1.17 (s, 6H), 1.39 (s, 3H), 1.68 (s, 3H), 1.41–1.54 (m, 2H), 1.70–1.97 (m, 3H), 2.06–2.23 (m, 1H), 2.62–2.79 (m, 1H), 3.18–3.32 (m, 1H), 5.40 (s, 1H), 5.98 (s, 1H), 6.27 (d, $J=1.6$ Hz, 1H), 6.38 (d, $J=1.7$ Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0, 18.4, 22.5, 23.4, 24.2, 27.5, 27.8, 28.5, 28.6, 31.5, 32.5, 35.9, 37.1, 44.3, 44.9, 79.6, 105.4, 107.5, 110.2, 119.2, 134.7, 149.7, 154.2, 154.8; $[\alpha]_D^{20}$ −174° (*c*1.38, $CHCl_3$); HRMS, calcd for $C_{24}H_{36}O_2$: 356.2715, found 356.2713.

2-Methyl-2-(3,5-dimethoxyphenyl)nonane. The reaction of 4.39 g (27.7 mmol) of 2-methyl-2-nonanol,[30] prepared from 2-nonanone and methylmagnesium bromide, with 4.40 g (28.5 mmol) of 2,6-dimethoxyphenol was carried out as described above to give 8.83 g of crude 2-methyl-2-(4-hydroxy-3,5-dimethoxyphenyl)-nonane as an oil which was used in the subsequent step without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, $J=7.1$ Hz, 3H), 1.26 (s, 6H), 0.96–1.35 (m, 10H), 1.47–1.61 (m 2), 3.88 (s, 6H), 6.54 (s, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0, 22.5, 24.6, 29.1, 30.2, 31.8, 37.6, 44.6, 56.2, 102.9, 132.4, 141.0, 146.4.

The phenol was converted to the phosphate ester as described above. From 8.83 g (27.7 mmol) of phenol, there was obtained 11.5 g of ester as a yellow solid which was used in the next step without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, $J=7.2$ Hz, 3H), 1.26 (s, 6H), 0.97–1.33 (m, 10H), 1.38 (t, $J=7.1$ Hz, 3H), 1.39 (t, $J=7.1$ Hz, 3H), 1.50–1.63 (m, 2H), 3.85 (s, 6H), 4.30 (q, $J=7.2$ Hz, 2H), 4.32 (q, $J=7.2$ Hz, 2H), 6.53 (s, 2H); ^{13}C NMR (75.5 MHz,

$CDCl_3$) δ 13.9, 15.9, 16.0, 22.5, 24.5, 28.9, 30.1, 31.7, 37.9, 44.4, 55.9, 63.9, 64.0, 103.0, 127.0, 147.0, 151.1.

The phosphate ester was reduced as described above for the synthesis of 3-pentylmethoxybenzene. From 11.5 g (26.7 mmol) of phosphate there was obtained 7.3g (93% from 2-nonanone) of 2-methyl-2-(3,5-dimethoxyphenyl)nonane as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (t, J = 7.0 Hz, 3H), 0.98–1.35 (m, 10H), 1.25 (s, 6H), 1.48–1.62 (m, 2H), 3.79 (s, 6H), 6.30 (t, J = 2.2 Hz, 1H), 6.48 (d, J = 2.2 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1, 22.6, 24.7, 29.0, 29.2, 30.3, 31.9, 38.0, 44.5, 55.2, 96.6, 104.7, 152.8, 160.4. Anal. calcd for $C_{18}H_{30}O_2$: C, 77.65; H, 10.86; Found: C, 77.78; H, 10.88.

3-(1′,1′-Dimethyloctyl)-Δ^8-tetrahydrocannabinol (8, *n* = 6). The cannabinoid was prepared from 0.737 g (2.65 mmol) of 2-methyl-2-(3,5-dimethoxyphenyl)nonane as described above for the synthesis of 3-(1′,1′-dimethylbutyl)-Δ^8-THC. There was obtained after chromatography (petroleum ether/ethyl acetate 8:1) 0.784 g (77%) of cannabinoid as a viscous pale yellow oil: R_f 0.27 (hexanes/ethyl acetate 25:1), 0.47 (hexanes/ethyl acetate 10:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (t, J = 7.0 Hz, 3H), 1.11 (s, 3H), 0.98–1.35 (m, 10H), 1.18 (s, 6H), 1.39 (s, 3H), 1.44–1.55 (m, 2H), 1.69 (s, 3H), 1.64–1.96 (m, 3H), 2.13–2.24 (m, 1H), 2.62–2.79 (m, 1H), 3.13–3.31 (m, 1H), 5.16 (s, 1H), 5.36–5.47 (m, 1H), 6.23 (d, J = 1.8 Hz, 1H), 6.38 (d, J = 1.6 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1, 18.5, 22.6, 23.5, 24.6, 27.6, 27.9, 28.6, 29.2, 30.3, 31.5, 31.9, 35.9, 37.2, 44.4, 44.8, 76.7, 105.4, 107.8, 110.2, 119.3, 134.7, 149.9, 154.4, 154.5; MS (EI) *m*/*z* (rel intensity) 385 (18), 328 (11), 301 (23), 286 (100), 217 (13); $[\alpha]_D^{20}$ −152° (*c*1.24, $CHCl_3$); HRMS, calcd for $C_{26}H_{40}O_2$: 384.3028, found 384.3026.

2-Methyl-2-(3,5-dimethoxyphenyl)decane. The reaction of 5.30 g (27.5 mmol) of 2-methyl-2-decanol, prepared from 2-decanone and methylmagnesium bromide with 4.23 g (27.4 mmol) of 2,6-dimethoxyphenol was carried out as described above to give 8.62 g of crude 2-methyl-2-(4-hydroxy-3,5-dimethoxyphenyl)decane as an oil which was used in the subsequent step without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, J = 7.0 Hz, 3H), 0.96–1.38 (m, 12H), 1.26 (s, 6H), 1.50–1.63 (m, 2H), 3.87 (s, 6H), 6.54 (s, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0, 22.5, 24.6, 29.0, 29.2, 29.4, 30.2, 31.8, 37.5, 44.6, 56.1, 102.9, 132.4, 141.0, 146.4.

The phenol was converted to the phosphate ester as described above for the preparation of 3-pentylphenol. From 8.6 g (27.5 mmol) of phenol, there was obtained 7.4 g of crude ester as a yellow solid which was used in the next step without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, J = 6.2 Hz, 3H), 0.96–1.34 (m, 12H), 1.25 (s, 6H), 1.38 (t, J = 7.1 Hz, 3H), 1.39 (t, J = 7.1 Hz, 3H), 1.47–1.62 (m, 2H), 3.85 (s, 6H), 4.30 (q, J = 7.3 Hz, 2H), 4.32 (q, J = 7.3 Hz, 2H), 6.53 (s, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0, 16.0, 16.1, 22.6, 24.6, 29.0, 29.3, 29.4, 30.3, 31.8, 38.0, 44.5, 56.0, 64.1, 64.2, 103.1, 147.1, 151.2.

Reduction of 7.43 g (16.7 mmol) of phosphate ester by the method described above gave, after chromatography, (petroleum ether/ethyl acetate 7:1) 3.69 g of recovered phosphate ester and 2.48 g (31% from 2-decanone, based on starting material consumed) of 2-methyl-2-(3,5-dimethoxyphenyl)nonane as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, J = 6.7 Hz, 3H), 0.99–1.37 (m, 12H), 1.25 (s, 6H), 1.50–1.63 (m, 2H), 3.78 (s, 6H), 6.29 (t, J = 2.1 Hz, 1H), 6.49 (d, J = 2.2 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0, 22.6, 24.6, 28.9, 29.3, 29.4, 30.3, 31.8, 37.9, 44.4, 55.0, 96.5, 104.5, 152.4, 160.4. Anal. calcd for $C_{19}H_{32}O_2$: C, 78.03; H, 11.03; Found: C, 77.89; H, 10.90.

3-(1′,1′-Dimethylnonyl)-Δ^8-tetrahydrocannabinol (8, *n* = 7). The cannabinoid was prepared from 0.829 g (2.83 mmol) of 2-methyl-2-(3,5-dimethoxyphenyl)-decane by the method described above for the synthesis of 3-(1′,1′-dimethylbutyl)-Δ^8-THC. There was obtained after chromatography (petroleum ether/ethyl acetate 8:1) 0.573 g (69%) of cannabinoid as a viscous pale yellow oil: R_f 0.29 (hexanes/ethyl acetate 25:1), 0.50 (hexanes/ethyl acetate 10:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, J = 7.0 Hz, 3H), 1.11 (s, 3H), 1.18 (s, 6H), 1.39 (s, 3H), 1.69 (s, 3H), 0.96–1.39 (m, 12H), 1.42–1.57 (m, 2H), 1.75–1.98 (m, 3H, 2.06–2.23 (m, 1H), 2.61–2.78 (m, 1H), 3.13–3.30 (m, 1H), 5.41 (br s, 1H), 5.44 9s, 1H), 6.24 (d, J = 1.6 Hz, 1H), 6.38 (d, J = 1.6 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1, 18.4, 22.6, 23.4, 27.5, 27.8, 28.6, 28.7, 29.3, 29.5, 30.3, 31.5, 31.8, 35.9, 37.2, 44.4, 44.8, 76.6, 105.4, 107.7, 110.2, 119.2, 134.7, 149.9, 154.3, 154.6; MS (EI) *m*/*z* (rel intensity) 399 (20), 316 (15), 286 (100), 217 (17); $[\alpha]_D^{20}$ −122° (*c*0.57, $CHCl_3$); HRMS, calcd for $C_{27}H_{42}O_2$: 398.3185, found 398.3181.

2-(3,5-Dimethoxyphenyl)-2-methylundecane. The reaction of 5.56 g (24.2 mmol) of 2-methyl-2-undecanol[30] with 3.70 g (24.2 mmol) of 2,6-dimethylphenol was carried out as described above for the synthesis of 2-methyl2-(3,5-dimethoxyphenyl)propane to give 4.68 g (67%) of 2-(3,5-dimethoxy-4-hydroxyphenyl)undecane as a pale yellow oil after chromatography (petroleum ether/ether 2:1): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (t, J = 7.4 Hz, 3H), 0.97–1.37 (m, 14H), 1.26 (s, 6H), 1.50–1.62 (m, 2H), 3.87 (s, 6H), 5.48 (br s, 1H), 6.54 (s, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0, 22.5, 24.6, 29.1, 29.2, 29.4, 29.5, 30.2, 31.8, 37.6, 44.6, 56.2, 102.9, 132.4, 140.9, 146.4.

From 4.45 g (15.3 mmol) of the above phenol, there was obtained 6.49 g (93%) of phosphate ester as a yellow solid which was used in the next step without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, J = 6.2 Hz, 3H), 0.96–1.12 (m, 2H), 1.12–1.47 (m, 12H), 1.25 (s, 6H), 1.38 (t, J = 7.1 Hz, 3H), 1.39 (t, J = 7.1 Hz, 3H), 1.47–1.62 (m, 2H), 3.85 (s, 6H), 4.30 (q, J = 7.3 Hz, 2H), 4.32 (q, J = 7.3 Hz, 2H), 6.53 (s, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0, 16.0, 16.1, 22.6, 24.6, 29.0, 29.4, 29.5, 30.3, 31.8, 38.0, 44.5, 56.0, 64.1, 64.2, 103.1, 127.1, 147.1, 151.2.

Reduction of 6.49 g (14.2 mmol) of the phosphate ester by the method described above gave 3.65 g (84%) of 2-(3,5-dimethoxyphenyl)-2-methylundecane as a colorless

oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, J = 6.7 Hz, 3H), 0.99–1.14 (m, 2H), 1.14–1.37 (m, 12H), 1.25 (s, 6H), 1.50–1.63 (m, 2H), 3.78 (s, 6H), 6.29 (t, J = 2.1 Hz, 1H), 6.49 (d, J = 2.2 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1, 22.6, 24.6, 28.9, 29.3, 29.5, 29.6, 30.3, 31.8, 37.9, 44.4, 55.0, 96.5, 104.5, 152.4, 160.4; MS m/z calcd for $C_{20}H_{34}O_2$: 306.2559, found 306.2560.

3-(1′,1′-Dimethyldecyl)-Δ^8-tetrahydrocannabinol (8, n = 8). From 0.462 g (1.51 mmol) of 2-methyl-2-(3,5-dimethoxyphenyl)undecane there was obtained 0.430 g of crude resorcinol as a brown oil which used in the next step without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, J = 6.9 Hz, 3H), 0.95–1.11 (m, 2H), 1.11–1.35 (m, 12H), 1.19 (s, 6H), 1.41–1.56 (m, 2H), 6.23 (t, J = 2.0 Hz, 1H), 6.35 (br s. 2), 6.40 (d, J = 2.1 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0, 22.6, 24.6, 28.8, 29.3, 29.6., 30.4, 31.8, 37.6, 44.4, 99.9, 105.7, 153.2, 156.5.

From 0.43 g (1.51 mmol) of crude resorcinol, 0.207 g (1.36 mmol) of *trans-p*-menthadienol and 0.015 g (10 mol%) of *p*-toluenesulfonic acid monohydrate, there was obtained 0.395 g (71%) of cannabinoid as viscous pale yellow oil: R_f 0.24 (petroleum ether/ether 20:1), 0.39 (petroleum ether/ether 10:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, J = 7.0 Hz, 3H), 1.11 (s, 3H), 1.18 (s, 6H), 1.39 (s, 3H), 1.69 (s, 3H), 0.96–1.39 (m, 14H), 1.42–1.57 (m, 2H), 1.75–1.98 (m, 3H), 2.06–2.23 (m, 1H), 2.61–2.78 (m, 1H), 3.13–3.30 (m, 1H), 5.41 (br s, 1H), 5.44 (s, 1H), 6.24 (d, J = 1.6 Hz, 1H), 6.38 (d, J = 1.6 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1, 18.5, 22.7, 23.5, 24.6, 27.6, 27.9, 28.6, 28.7, 29.3, 29.5, 29.6, 30.4, 31.5, 31.8, 36.0, 37.3, 44.4, 44.9, 76.6, 105.4, 107.7, 110.2, 119.2, 134.7, 149.9, 154.3, 154.6; MS m/z calcd for $C_{28}H_{44}O_2$: 412.3341, Found 412.3340; $[\alpha]_D^{20}$ −128° (c0.56, $CHCl_3$).

2-(3,5-Dimethoxyphenyl)-2-methyldodecane. The reaction of 4.90 g (24.5 mmol) of 2-methyl-2-dodecanol[30] with 3.57 g (23.3 mmol) of 2,6-dimethylphenol was carried out as described above to give 4.45 g (57%) of 2-(3,5-dimethoxy-4-hydroxyphenyl)-2-methyldodecane as an oil after chromatography (petroleum ether/ether 2:1): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, J = 7.0 Hz, 3H), 0.96–1.13 (m, 2H), 1.13–1.38 (m, 14H), 1.26 (s, 6H), 1.50–1.63 (m, 2H), 3.87 (s, 6H), 6.54 (s, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0, 22.5, 24.6, 29.1, 29.2, 29.5, 29.6, 30.3, 31.8, 37.6, 44.6, 56.1, 102.9, 132.4, 141.0, 146.4.

From 4.35 g (12.9 mmol) of phenol, there was obtained 6.43 g (100%) of crude phosphate ester as a yellow solid which was used in the next step without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, J = 6.2 Hz, 3H), 0.96 (m, 2H), 1.12–1.47 (m, 14H), 1.25 (s, 6H), 1.38 (t, J = 7.1 Hz, 3H), 1.39 (t, J = 7.1 Hz, 3H), 1.47–1.62 (m, 2H), 3.85 (s, 6H), 4.30 (q, J = 7.3 Hz, 2H), 4.32 (q, J = 7.3 Hz, 2H), 6.53 (s, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.9, 15.8, 15.9, 22.5, 24.5, 28.8, 29.1, 29.3, 29.4, 29.5, 30.2, 31.7, 37.9, 44.4, 55.9, 63.9, 64.0, 103.0, 127.3, 147.0, 151.1.

From 6.43 g (12.9 mmol) of phosphate ester, there was obtained after chromatography (petroleum ether/ethyl acetate 10:1), 3.12 g (75%) of 2-(3,5-dimethoxyphenyl)-2-methyldodecane as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, J = 6.7 Hz, 3H), 0.99–1.14 (m, 2H), 1.14–1.37 (m, 14H), 1.25 (s, 6H), 1.50–1.63 (m, 2H), 3.78 (s, 6H), 6.29 (t, J = 2.1 Hz, 1H), 6.49 (d, J = 2.2 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1, 22.6, 24.6, 28.9, 29.3, 29.5, 29.6, 30.3, 31.8, 37.9, 44.4, 55.0, 96.5, 104.5, 152.4, 160.4; HRMS calcd for $C_{21}H_{36}O_2$: 320.2715, found 320.2715.

3-(1′, 1′-Dimethylundecyl)-Δ^8-tetrahydrocannabinol (8, n = 9). From 0.262 g (0.819 mmol) of 2-(3,5-dimethoxyphenyl)-2-methyldodecane there was obtained 0.245 g (100%) of crude resorcinol which was used in the subsequent step without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, J = 6.9 Hz, 3H), 0.95–1.11 (m, 2H), 1.11–1.35 (m, 14H), 1.19 (s, 6H), 1.41–1.56 (m, 2H), 6.23 (t, J = 2.0 Hz, 1H), 6.35 (br s, 2H), 6.40 (d, J = 2.1 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1, 22.6, 24.6, 28.8, 29.3, 29.6, 29.7, 30.3, 31.8, 37.6, 44.4, 99.9, 105.7, 153.2, 156.5.

From 0.262 g (0.819 mmol) of resorcinol, there was obtained, after chromatography (petroleum ether/ether 10:1), 0.195 g (62%) of cannabinoid as a viscous pale yellow oil: R_f 0.24 (petroleum ether/ether 20:1), 0.39 (petroleum ether/ether 10:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, J = 7.0 Hz, 3H), 1.11 (s, 3H), 1.18 (s, 6H), 1.39 (s, 3H), 0.96–1.39 (m, 16H), 1.42–1.57 (m, 2H), 1.69 (s, 3H), 1.75–1.98 (m, 3H), 2.06–2.23 (m, 1H), 2.61–2.78 (m, 1H), 3.13–3.30 (m, 1H), 5.41 (br s, 1H), 5.44 (s, 1H), 6.24 (d, J = 1.6 Hz, 1H), 6.38 (d, J = 1.6 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1, 18.4, 22.6, 23.4, 24.6, 27.5, 27.8, 28.6, 28.7, 29.3, 29.6, 29.7, 30.3, 31.5, 31.8, 35.9, 37.2, 44.4, 44.8, 76.6, 105.4, 107.7, 110.2, 119.2, 134.7, 149.9, 154.3, 154.6; MS m/z calcd for $C_{29}H_{46}O_2$: 426.3498, found 426.3494; $[\alpha]_D^{20}$ −110° (c0.57, $CHCl_3$).

2-Methyl-2-(3,5-dimethoxyphenyl)tridecane. The reaction of 4.90 g (24.5 mmol) of 2-methyl-2-tridecanol[30] with 3.19 g of 2,6-dimethoxyphenol was carried out as described above to give, after chromatography (petroleum ether/ether 2:1), 4.51 g (62%) of 2-methyl-2-(3,5-dimethoxy-4-hydroxyphenyl)tridecane as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, J = 7.0 Hz, 3H), 0.96–1.13 (m, 2H), 1.13–1.38 (m, 16H), 1.26 (s, 6H), 1.50–1.63 (m, 2H), 3.87 (s, 6H), 6.54 (s, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0, 22.5, 24.6, 29.1, 29.2, 29.6, 30.3, 31.8, 37.6, 44.6, 56.1, 102.9, 132.4, 141.0, 146.4.

From 4.41 g (12.9 mmol) of phenol, there was obtained 8.71 g (100%) of crude phosphate ester which was used in the next step without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, J = 6.2 Hz, 3H), 0.96–1.12 (m, 2H), 1.12–1.47 (m, 16H), 1.25 (s, 6H), 1.38 (t, J = 7.1 Hz, 3H), 1.39 (t, J = 7.1 Hz, 3H), 1.47–1.62 (m, 2H), 3.85 (s, 6H), 4.30 (q, J = 7.3 Hz, 2H), 4.32 (q, 7.3H), 6.53 (s, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.9, 15.8, 15.9, 22.5, 24.5, 28.8, 29.1, 29.3, 29.4, 29.5, 30.2, 31.7, 37.9, 44.4, 55.9, 63.9, 64.0, 103.0, 127.3, 147.0, 151.1.

From 8.71 g (12.9 mmol) of phosphate ester, there was obtained, after chromatography (petroleum ether/ether

10:1), 3.27 g (76%) of 2-methyl-2-(3,5-dimethoxyphenyl)tridecane as a colorless oil: R_f 0.18 (petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, $J=6.7$ Hz, 3H), 0.99–1.14 (m, 2H), 1.14–1.37 (m, 16H), 1.25 (s, 6H), 150–1.63 (m, 2H), 3.78 (s, 6H), 6.29 (t, $J=2.1$ Hz, 1H), 6.49 (d, $J=2.2$ Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1, 22.6, 24.6, 28.9, 29.3, 29.5, 29.6, 30.4, 31.9, 37.9, 44.4, 55.0, 96.5, 104.5, 152.4, 160.4; MS m/z calcd for $C_{22}H_{38}O_2$: 334.2872, found 334.2870.

3-(1′,1′-Dimethyldodecyl)-Δ^8-tetrahydrocannabinol (8, $n=10$). From 0.280 g (0.838 mmol) of 2-methyl-2-(3,5-dimethoxyphenyl)tridecane there was obtained 0.265 g (100%) of resorcinol which was used in the subsequent step without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, $J=6.9$ Hz, 3H), 0.95–1.11 (m, 2H), 1.11–1.35 (m, 16H), 1.19 (s, 6H), 1.41–1.56 (m, 2H), 6.23 (t, $J=2.0$ Hz, 1H), 6.35 (br s, 2H), 6.40 (d, $J=2.1$ Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1, 22.6, 24.6, 28.8, 29.3, 30.3, 31.8, 37.6, 44.4, 99.9, 105.7, 153.2, 156.5.

From 0.28 g (0.84 mmol) of crude resorcinol, 0.13 g (0.86 mmol) of *trans*-*p*-menthadienol and 0.02 g (10 mol%) of *p*-toluenesulfonic acid monohydrate there was obtained 0.23 g of cannabinoid as a viscous pale yellow oil: R_f 0.24 (petroleum ether/ether 20:1), 0.39 (petroleum ether/ether 10:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, $J=7.0$ Hz, 3H), 1.11 (s, 3H), 1.18 (s, 6H), 1.39 (s, 3H), 1.69 (s, 3H), 0.96–1.39 (m, 18H), 1.42–1.57 (m, 2H), 1.75–1.98 (m, 3H), 2.06–2.23 (m, 1H), 2.61–2.78 (m, 1H), 3.13–3.30 (m, 1H), 5.41 (br s, 1H), 5.44 (s, 1H), 6.24 (d, $J=1.6$ Hz, 1H), 6.38 (d, $J=1.6$ Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1, 18.4, 22.6, 23.4, 24.6, 27.5, 27.8, 28.6, 28.7, 29.3, 29.6, 29.7, 30.3, 31.5, 31.9, 35.9, 37.2, 44.4, 44.8, 76.6, 105.4, 107.7, 110.2, 119.2, 134.7, 149.9, 154.3, 154.6; MS m/z calcd for $C_{30}H_{48}O_2$: 440.3654, found 440.3655; $[\alpha]_D^{20}$ −137° (c1.1, $CHCl_3$).

Receptor binding assays

[^{3}H]CP-55,940 ($K_D=690$ nM) binding to P_2 membranes was conducted as described elsewhere,[32] except whole brain (rather than cortex only) was used. Displacement curves were generated by incubating drugs with 1 nM of [^{3}H]CP-55,940. The assays were performed in triplicate, and the results represent the combined data from three individual experiments.

Pharmacology

Male ICR mice (Harlan Laboratories, Dublin, VA, USA) weighing 18–25 g were maintained on a 14:10 h light/dark cycle with free access to food and water. Δ^9-THC and Δ^8-THC were obtained from the National Institute on Drug Abuse. All compounds were dissolved in 1:1:18 (emulphor–ethanol–saline) for in vivo administration. Emulphor (EL-620, a polyoxyethylated vegetable oil, GAF Corporation, Linden, NJ, USA) is currently available as Alkmulphor. All drug injections were administered iv (tail vein) at a volume of 0.1 mL/10 g of body weight. Mice were acclimated in the evaluation room overnight without interruption of food and water. Following drug administration each animal was tested for effects on the following procedures: spontaneous (locomotor) activity at 5–15 min, tail-flick latency (antinociception) response at 20 min, core (rectal) temperature at 30 min.

Spontaneous activity. Inhibition of locomotor activity was accomplished by placing mice into individual activity cages (6.5×11 in), and recording interruptions of the photocell beams (16 beams per chamber) for a 10-min period using a Digiscan Animal Activity Monitor (Omnitech Electronics Inc., Columbus, OH, USA). Activity in the chamber was expressed as the total number of beam interruptions.

Tail-flick latency. Antinociception was assessed using the tail-flick procedure. The heat lamp of the tail-flick apparatus was maintained at an intensity sufficient to produce control latencies of 2–3 s. Control values for each animal were determined prior to drug administration. Mice were then re-evaluated following drug administration and latency (s) to tail-flick response was recorded. A 10-s maximum was imposed to prevent tissue damage. The degree of antinociception was expressed as the% MPE (maximum possible effect) which was calculated as:

$$\%\ \mathrm{MPE} = \left[\frac{(\text{test latency} - \text{control latency})}{10\ \text{s} - \text{test latency}}\right] \times 100$$

Core temperature. Hypothermia was assessed by first measuring baseline core temperatures prior to drug treatment with a telethermometer (Yellow Springs Instrument Co., Yellow Springs, OH, USA) and a rectal thermistor probe inserted to 25 mm. Rectal temperatures were also measured following drug administration. The temperature difference (°C) between values was calculated for each animal.

Computational methods

Molecular modeling and energy minimization. Molecules were modeled using SYBYL (Tripos Inc., St. Louis, MO, USA). Electrostatic charges of each compound were calculated with the Gasteiger–Hückel method. Each compound was energy minimized using the SYBYL force field with a conjugate gradient of 0.001 kcal/mol or a maximum of 100,000 iterations as termination criteria.

Quenched molecular dynamics. In order to characterize the conformational mobility of each analogue, molecular dynamics were computed on each energy-minimized structure at temperatures from 100 to 1000 K. During the molecular dynamics simulation, the molecule was heated at 100 K steps, and allowed to remain at the specified temperature for 1 ps. Upon reaching 1000 K, the molecule was held at this temperature for 100 ps while snapshots were acquired at 1-ps intervals. Each conformation obtained for a particular molecule was energy minimized again using a conjugate gradient of 0.01 kcal/mol or a maximum of 100,000 iterations as

termination criteria, yielding a group of 100 energy-minimized conformers per compound.

Molecular and conformational alignment. All conformations from each of the analogues were overlaid using a single template molecule. Because the phenyl ring systems of all analogues were identical, it was unimportant which molecule or conformation was used for this template, as long as it was applied consistently using the six aromatic carbons of the phenol ring system. The alignment was performed using atom-by-atom root mean square distance minimization. This alignment positioned all of the molecules in the same three-dimensional space and superposed the ring systems to as great an extent as possible. Since the side chains were not part of the alignment rule, this feature of the molecule could be compared between conformers of the same compound as well as between different compounds using the QSAR technique described below.

Quantitative structure–activity relationship analysis. Comparative molecular field analysis was used to characterize the quantitative structure–activity relationships of the compounds shown in Table 1. This technique has previously been used successfully in QSAR studies of cannabinoids.[18,33–37] For the QSAR studies, a total of 50 random conformations from the 100 obtained were selected for each analogue. The descriptive variables were steric and electrostatic descriptions of the three-dimensional structure of the entire set of compounds. The dependent variables for the models were receptor affinity (K_i) and potency (ED_{50}) in the spontaneous activity (SA), tail flick (TF) and rectal temperature (RT) assays. The CoMFA analysis was performed using a proton (H + 1) probe atom positioned at lattice points spaced around the molecules at 1.5Å increments. Cross-validation was performed by randomly selecting 80% of the compounds to form a training set, developing a QSAR model based on their three-dimensional steric and electrostatic properties, and using this model to predict the dependent variables of the remaining 20% of the compounds that were not included in the training set. The predicted dependent variable of the compounds that were omitted from the training set was then compared against the actual dependent variable and a correlation coefficient obtained. This process was repeated randomly until every compound had been omitted from the training set and had its dependent variables predicted at least once. The correlation coefficients of the entire process were tracked throughout this process and the average r-squared value was calculated as a measure of the press, or the goodness/robustness of the model.

Control studies were also run where randomized pharmacological data was used in place of real pharmacological data. These artificial points were random numbers generated to fall within the range of the real data. The same cross-validated and final analyses were performed in the control studies to check that the r^2 values were higher when pharmacological data were used than when artificial data were used.

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