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Synthesis, Pharmacology, and Molecular Modeling of Novel 4-Alkyloxy Indole Derivatives Related to Cannabimimetic Aminoalkyl Indoles (AAIs)

A. K. Dutta,[a] W. Ryan,[a] B. F. Thomas,[b] M. Singer,[a] D. R. Compton,[c] B. R. Martin[c] and R. K. Razdan[a,*]

[a]*Organix Inc., 65 Cummings Park, Woburn, MA 01801, U.S.A.*
[b]*Research Triangle Institute, Research Triangle Park, NC 27709, U.S.A.*
[c]*Medical College of Virginia, Richmond, VA 23298, U.S.A.*

Abstract—Several novel 4-alkyloxy-aminoalkyl indole derivatives **3** were synthesized from 4-benzyloxyindole (**1**). Alkylation of **1** with 4-(2-chloroethyl)morpholine (NaH/HMPA) formed **2**. Deprotection using palladium hydroxide on carbon/hydrogen followed by alkylation with the appropriate alkyl bromide gave the target compounds **3b–3j**. In the synthesis of **3i** and **3j**, the appropriate alkyl bromides **13** and **17** were prepared from the commercially available 1-naphthylethyl bromide **9** using the chain lengthening sequences as shown in Scheme 3. In receptor binding assay and in vivo testing, the long chain alkoxy compounds **3g** and **3h** (K_i = 127 nM) showed affinity for the CB1 receptor which was approximately 16–35-fold less than that of WIN 55,225. However, the pharmacological profile of **3h** mimics that of WIN 55,212. An examination of the SAR of these analogues shows that translocating the napthyl group in AAIs from the C-3 position to C-4 via an oxygen (ether linkage) decreases activity which is in contrast to previous findings that a naphthylcarbonyl at C-4 retains activity. The present work points to the importance of the role of a keto group in the interaction with the receptor. Molecular modeling work suggests that, although reasonable superposition of key structural features between Δ^9-THC and AAIs can be made, the overlay is not straightforward. The present study also illustrates the difficulty in accommodating AAIs into the cannabinoid pharmacophore and it seems likely that a unique pharmacophore will need to be developed. Only then will the similarities to and differences from the classical cannabinoid pharmacophore be clearly delineated. © 1997 Elsevier Science Ltd.

Introduction

In the last few years it has been firmly established that aminoalkylindoles (AAIs) are a novel series of cannabinoid receptor ligands. The AAIs resulted from the extensive work carried out by the Sterling Winthrop group on analogues of pravadoline, an AAI analgesic which was originally designed as a non-ulcerogenic non-steroidal antiinflammatory drug.[1–10b] The most widely studied compound of the series is (+)-WIN-55,212-2 (hence referred to as WIN 55,212) (Fig. 1). It was demonstrated that the cannabimimetic activity resides in only one optical antipode and is more active than Δ^9-tetrahydrocannabinol (THC) in several pharmacological and behavioral assays.[11,12] This is a significant development since AAIs have dramatically different structures from THCs. We have been intrigued by the comparative topological features of both AAIs and THCs. One of our objectives, therefore, has been to accommodate the AAIs within our ongoing studies of the cannabinoid pharmacophores.[11,13] Based on our experience in structure–activity relationships (SAR) of THCs,[14] we aligned the structures in a manner which results in the lipophilic naphthoyl group of AAIs mimicking the side chain of THCs, and the morpholine in AAIs mimicking the C-11 position in THCs. Using this alignment, we found similar overlay patterns which suggested to us the synthesis and an examination of the pharmacological activity of these indole derivatives. We thought that translocating the napthyl substituent from position 3 to 4, albeit via an oxygen, would provide a possible means of determining the required spatial orientation of this functional group for cannabinoid activity. We were not particularly concerned about the presence of an ether linkage in these compounds since it is well known in the SAR of THCs that the lipid side chain, via an oxygen (ether linkage) at C-3, retains activity; a good example of such a compound is nantradol.[14]

It is noteworthy that since we started work in this area, reports from Makriyannis and coworkers[15] and the Sterling Winthrop group[10a] have appeared on the molecular modeling of AAIs and THCs using similar alignment strategies. On the other hand, Huffman and coworkers[16] have reported on indole derivatives which were designed using an entirely different molecular alignment between THCs and AAIs. In addition, there has been some evidence produced through receptor mutation studies[17] that suggests that AAIs interact with the CB1 receptor differently than do classical and nonclassical cannabinoids.

*Author to whom inquiries should be addressed. Tel: (617) 932-4142; Fax: (617) 933-6695

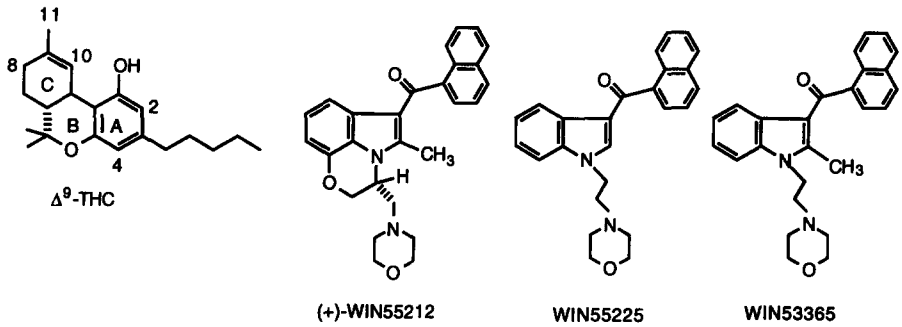


Figure 1.

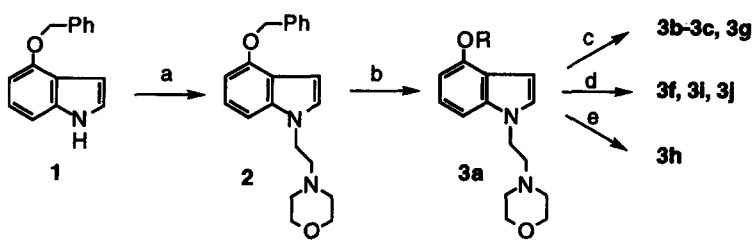
Chemistry

The synthesis of compounds **3b–3j** from commercially available 4-benzyloxyindole **1** is described below. 4-Benzyloxyindole **1** (Scheme 1) was alkylated to **2** with 4-(2-chloroethyl)morpholine in the presence of sodium hydride and HMPA. It was deprotected using palladium hydroxide on carbon/H_2 in methanol to give the phenol **3a**. Target compounds **3b–3e** and **3g** were synthesized by the treatment of freshly prepared **3a** with the appropriate alkyl bromide in the presence of NaH/DMF. Compound **3f** was similarly prepared except for using finely ground K_2CO_3 in DMF in place of NaH. For the synthesis of **3h**, 1-naphthylacetic acid (Scheme 2) was converted to the diazoketone **7** via its acid chloride (oxalyl chloride/benzene) followed by treatment with HBr at 0 °C to form the bromide **8**.[18] Subjecting compound **8** to phase-transfer-catalysis conditions in the presence of tetra-*n*-butylammonium iodide/K_2CO_3/tetra-*n*-butylammonium hydroxide and **3a** afforded **3h**, albeit in 11% yield. Most of the loss in yield was encountered during purification of **3h**. For the synthesis of **3i** and **3j** (Scheme 3), 1-naphthylethyl bromide **9** was converted to the appropriate bromides **13** and **17** using the standard chain lengthening sequences as shown. Bromination of **12** to **13** was carried out in 95% yield using CBr_4 in ether at 0 °C in the presence of tri-*n*-octylphosphine.[19] Similarly **17** was obtained from **16** in 84% yield. Treatment of **13** and **17** with **3a** using the same conditions as in the preparation of **3f** formed **3i** and **3j**, respectively.

Pharmacology

The pharmacological profiles of WIN 55,212, WIN 55,225, and WIN 53,365 are presented in Table 1. WIN 55,212, which has high affinity for the CB1 receptor and is active in all four pharmacological assays, serves as the reference compound.[12] Although a full agonist in all assays, it is considerably more potent in attenuating spontaneous activity and producing antinociception than in lowering body temperature. The other lead compound, WIN 55,225, also exhibits high receptor affinity and high pharmacological potency in these mouse procedures. The homolog WIN 53,365 differs from WIN 55,225 by the addition of a methyl at position 2. These three indoles are similar in that they exhibit greater potency in the spontaneous activity and antinociceptive assays. This pattern contrasts with that of Δ^9-THC which is equipotent in all four pharmacological assays.[12]

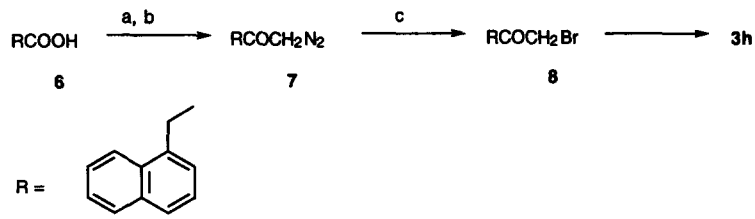
The parent phenol **3a** did not bind to the receptor (K_i > 10,000 nM) and as for the analogues reported herein, the addition of long chain alkoxy groups at position 4



R

a, H	f, CH_2-2-naphthyl
b, $CH(CH_3)C_5H_{11}$	g, CH_2CO-1-naphthyl
c, $(CH_2)_8CH_3$	h, CH_2COCH_2-1-naphthyl
d, $CH(CH_3)C_3H_6Ph$	I, $(CH_2)_3$-1-naphthyl
e, CH_2-1-napthyl	J, $(CH_2)_4$-1-naphthyl

Scheme 1. (a) NaH, HMPA, 4-(2-chloroethyl)morpholine, 94%; (b) H_2/$Pd(OH)_2$/C, MeOH; (c) RBr, Bu_4NI, Bu_4NOH, K_2CO_3, CH_2Cl_2, H_2O, 25 °C, 2 h, 11%.



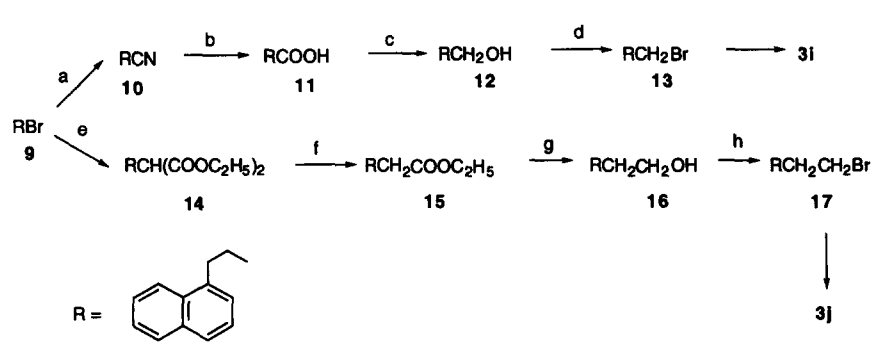
Scheme 2. (a) oxalyl chloride, benzene, 25 °C, 16 h; (b) CH_2N_2, ether, 0 °C, 2.5 h; (c) HBr gas, 0 °C, 1.5 h, 66%.

resulted in analogues **3b** and **3c** that neither bound to the receptor nor produced any pharmacological effects at doses up to 100 mg/kg (Table 1). Likewise, the addition of a phenylpentyloxy substituent (**3d**) did not impart pharmacological activity. On the other hand, the 1-naphthylmethoxy analogue **3e** did exhibit weak affinity for the receptor and was pharmacologically active. Its spectrum of activity resembles that of WIN 55,212 regarding spontaneous activity, tail-flick response and rectal temperature. However, its failure to produce immobility at doses up to 30 mg/kg is in contrast to the actions of WIN 55,212. Obviously, the orientation of the naphthyl is critical as demonstrated by the weak affinity of the 2-naphthylmethoxy analogue (**3f**) for the cannabinoid receptor. This analogue also failed to produce 50% maximal effects at doses up to 30 mg/kg. Two additional 1-naphthyl analogues also exhibited weak receptor affinity and cannabinoid effects. The acetoyloxy-1-naphthyl derivative (**3g**) bound with somewhat lower affinity than **3e** and was less potent. While **3g** was a full agonist regarding attenuation of spontaneous activity and antinociception, it failed to produce significant hypothermia and immobility at doses up to 30 mg/kg. However, incorporation of an additional carbon unit in the 3-(1-naphthyl)-2-oxopropoxy derivative (**3h**) resulted in full agonist effects in all four behaviors. The pharmacological profile of **3h** mimics that of WIN 55,225 with regard to its high potency in the spontaneous activity and antinociceptive assays and low potency in the hypothermia and immobility tests. The receptor affinity of **3h** is greater than that of **3g** which probably accounts for our ability to obtain a complete pharmacological profile for the former. In contrast to **3h**, **3i** (1-naphthyl-propoxy) has extremely low receptor affinity (200-fold less than that of **3h**) and is incapable of producing significant pharmacological effects at doses up to 30 mg/kg. A comparison of **3h** and **3i** suggests a role for the keto group, despite the fact that **3e** lacks a carbonyl and retains pharmacological effects. Extending the carbon chain length, as in **3j** (1-naphthyl-butoxy), had no influence on receptor affinity. Sufficient quantities of **3j** were available so that we could extend the dose range up to 100 mg/kg. Although **3j** was extremely weak, it was capable of lowering spontaneous activity and body temperature and in producing antinociception. It was not evaluated in the immobility assay.

Molecular modeling

Modeling and alignment of AAIs to Δ^9-THC.[11,13] The conformation of the prototypical AAI, WIN 55,212, which served as the basis for defining the pharmacophoric alignment, is shown in stereoviews along with that of Δ^9-THC (Fig. 2). These stereoviews reveal the overall shape similarity that can be obtained between these structurally distinct cannabimimetic agents. This conformation of WIN 55,212, when systematically superposed using SPARTAN to maximize the overlap in molecular volume improves the overlay of the hydrophobic side chain with the naphthyl-ring system in the AAI and allows the methyl group of the AAI to superpose with the phenol hydroxyl. This superposition also increases the overlay of the morpholino group with the carbocyclic ring system of tetrahydrocannabinol.

With regard to the electrostatic properties of each compound, our results (Fig. 3) suggest that the electrostatic properties of WIN 55,212 and Δ^9-THC are not as highly superposed as their molecular volumes. Furthermore, although some aspects of the



Scheme 3. (a) KCN, C_2H_5OH, H_2O, reflux, 21 h; (b) 40% H_2SO_4, reflux, 20 h, 94%; (c) LAH, THF, 97%; (d) CBr_4, Oct_3P, ether, 0 °C, 95%; (e) Diethyl malonate, NaH, DMF, 0 °C, 1 h, 85%; (f) DMSO, H_2O, 200 °C, 5 h, 75%; (g) LAH, THF; (h) CBr_4, Oct_3P, ether, 0 °C, 84% (two steps).

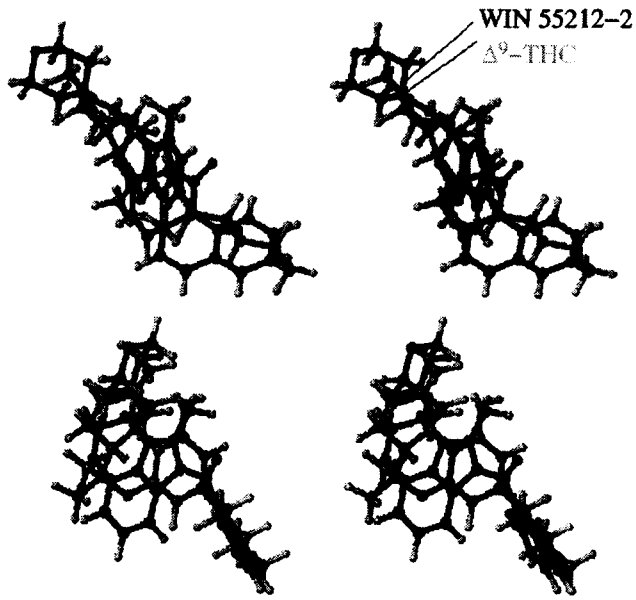
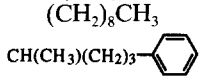
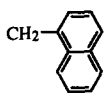
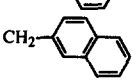
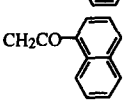
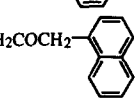
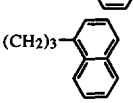
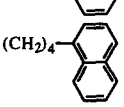


Figure 2. Stereoviews demonstrating the alignment of Δ^9-THC and the prototype aminoalkylindole WIN 55212-2 when overlayed so as to maximize molecular volume overlap. In this figure, two perspectives are shown, the bottom perspective showing the top view after rotating the image 90°.

electrostatic properties of WIN 55,212 are also present in the 4-alkyloxyindoles, molecular electrostatic potentials around the ether region clearly differ from WIN 55,212. Despite this difference in electrostatic properties, one can see that the proposed alignment and shape similarity between WIN 55,212 and Δ^9-THC is also readily obtained with the 4-alkyloxyindole derivatives.

Relationship between conformational mobility and pharmacophoric conformation. The relationship between the conformational mobility of the AAI analogues and their ability to overlay with Δ^9-THC was evaluated by plotting the energies of the conformations obtained for each analogue against their volume difference from Δ^9-THC (results not shown). There appears to be no significant trends in their conformational energies that would result in any one analogue favoring a conformation that can be superposed, or superposes to a greater extent, with Δ^9-THC. The explanation for the uniform ability of these analogues to overlay with Δ^9-THC may partially be explained by the relatively high conformational mobility of these compounds. Hence the identification of a specific conformation to further evaluate is made difficult.

Table 1. Pharmacological activity and receptor affinity of analogues[a]

Analogue	R	K_i (nM)	S.A. ED_{50} (mg/kg)	T.F. ED_{50} (mg/kg)	R.T. ED_{50} (mg/kg)	R.I. ED_{50} (mg/kg)
WIN 55,212		8.7 ± 0.1	0.1[b]	0.4[b]	12[b]	1.1[b]
WIN 55,225		7.4 ± 0.2[c]	0.3	0.3	1.2	2.7
WIN 53,365		16 ± 1[c]	2.0	1.9	7.2	3.9
Δ^9-THC		41 ± 2[d]	1.0[b]	1.4[b]	1.4[b]	1.5[b]
3b	$(CH)CH_3)C_5H_{11}$	>10,000	>100	>100	>100	>100
3c	$(CH_2)_8CH_3$	>10,000	>100	>100	>100	>100
3d	$CH(CH_3)(CH_2)_3$– 	>10,000	>100	>100	>100	>100
3e	CH_2– 	221 ± 14	3.5	3.3	12.3	>25
3f	CH_2– 	1300 ± 60	>30	>30	>30	>30
3g	CH_2CO– 	287 ± 42	4.6	8.4	>30	>30
3h	CH_2COCH_2– 	127 ± 7	6.1	1.7	18.7	20.8
3i	$(CH_2)_3$– 	2220 ± 1450	>30	>30	>30	>30
3j	$(CH_2)_4$– 	3390 ± 1520	55	78	79	N.D.

[a]Spontaneous activity (S.A.), tail-flick (T.F.), rectal temperature (R.T.) and ring immobility (R.I.).
[b]Data reported previously.[11,12]
[c]Data reported previously.[8]
[d]Data reported previously: Compton, et al. *J. Pharmacol. Exp. Ther.* **1992**, *260*, 201.

Discussion and Conclusion

The above pharmacology and molecular modeling description demonstrates that the systematic alteration of the structural backbone of WIN 55,512 provides a unique opportunity to explore the SAR of cannabinoids. As mentioned above there are similarities and differences in the pharmacological profile of Δ^9-THC and AAIs (see Pharmacology). In this respect it is noteworthy that it has been established that AAIs and Δ^8-THC can bind to the same site.[3,4,12]

The Sterling group had shown that the naphthyl substituent was very important for pharmacological activity in AAIs.[10a] Additionally they had noted that by translocating the 1-naphthylcarbonyl or 4-methoxybenzoyl group from C-3 to C-4 it retained activity.[20] The present study illustrates that the naphthyl group and its linkage contributes to the receptor interaction in that translocating the naphthyl from C-3 to C-4 via an oxygen decreases the receptor affinity and biological potency. Although **3e**, **3g**, and **3b** were able to interact with the cannabinoid receptor, their affinities were approximately 16- to 35-fold less than that of Win 55,212. This is in contrast to the findings of the Sterling group when a naphthylcarbonyl is present at C-4. Additionally, a comparison of the activities of **3h** and **3i** in the present study suggests very strongly a role for the keto group in the interaction with the receptor. It is conceivable that the keto group, being planar, could sterically direct and restrict the conformational freedom of the naphthyl group to a position which is important for interaction with the receptor whereas the more flexible ether linkage cannot. An examination of Figure 3 reveals that the ether linkage of the remaining 4-alkyloxyindole analogues is more sterically hindered and not as electronegative as the keto functionality and that its ability to participate in the interaction with the receptor would be less favorable. Recently the Sterling group reported[21] a series of morpholinoalkylindenes which show high CB1 affinities. However, no analogues with a keto group were reported, but interestingly one of the most potent compounds from the series was a naphthylidene analogue. This compound would be expected to have restricted rotation for the naphthalene group and would therefore support our hypothesis that the ketone group in our compounds is perhaps restricting the rotation of the indole substituent. On the other hand it is conceivable that the presence of a ketone group is more important in our indole series than in the morpholinoalkylindene series.

It remains possible that an alternative overlay of AAIs provides the actual superposition of structural features with Δ^9-THC explaining their ability to interact with the same receptor site. Indeed, the AAI analogues described in this report all have ring system substituents which could mimic the carbocyclic B and C ring in classical cannabinoids as proposed by Huffman et al.[16] However, it is also possible that these compounds are interacting at the same site (as suggested by radioligand binding studies)[3,4,12] but in a unique overlapping manner. This hypothesis has received recent support from cannabinoid receptor mutation studies.[17] In these studies, a single amino acid mutation in the cannabinoid receptor resulted in a dramatic loss of affinity for HU-210, CP-55940 and anandamide without altering the binding of WIN-55,212. Thus, there is some experi-

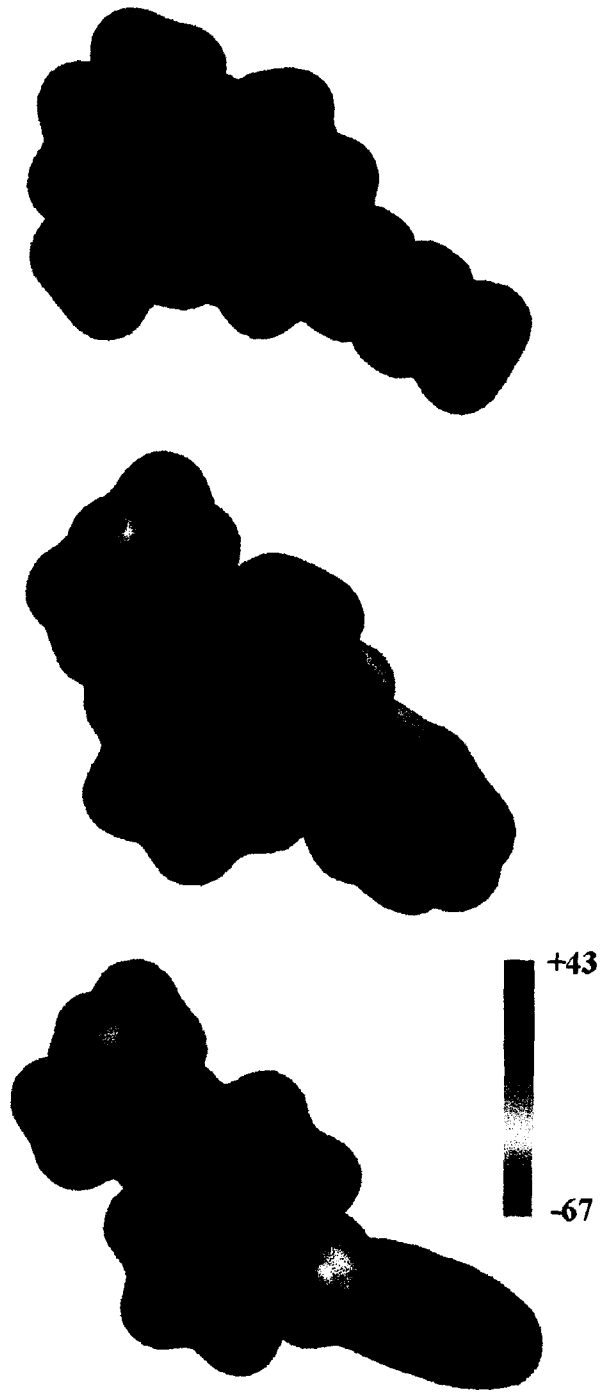


Figure 3. Molecular electrostatic potentials color-coded onto a surface at the 95% electron-density level of Δ^9-THC (top), WIN 55,212 (middle) and compound **3e** (bottom). Each compound has been oriented so as to maximize the molecular volume overlap with Δ^9-THC serving as the template molecule. The color-bar provides an index of the charge and magnitude of the color-coding of the molecular electrostatic potential maps.

mental evidence that the binding site of AAIs requires an area that extends beyond that involved in the recognition of classical, nonclassical and endogenous cannabinoids. If this is the case, it would seem likely that a unique pharmacophore will need to be developed in order to accommodate the AAIs, and that only after the pharmacophore for the AAIs is developed will the similarities to and differences from the classical cannabinoid pharmacophore be clearly delineated. Another interesting point relating to the AAIs has emerged recently which indicates that WIN 55,212 is more selective for the peripheral cannabinoid receptor CB2[22] than the CB1 receptor.[23] This raises the obvious question of how these analogues bind to CB2.

In summary, we conclude that (a) the naphthyl group contributes to the receptor interaction as the Sterling group's work indicated; (b) in the interaction with the receptor, the keto group appears to play an important role; (c) molecular modeling overlay studies, the pharmacological and cannabinoid mutation studies all point to the need for the development of a unique pharmacophore for AAIs.

Experimental

Chemistry

^{1}H NMR spectra were recorded on either a Bruker 100 or a Varian XL400 spectrometer using tetramethylsilane as an internal reference in $CDCl_3$. 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). Preparative TLC was carried out on Analtech uniplates Silica Gel GF 2000 microns. Flash chromatography was carried out on Baker Silica Gel 40 mM. Elemental analyses (performed by Atlantic Microlab, Atlanta, GA) were carried out for the elements shown and were found to agree with the calculated data within ± 0.4%. 4-Benzyloxyindole was purchased from Pharmatech International.

4-Benzyloxy-1-[2-(4-morpholinyl)ethyl]-1H-indole (2). To a cooled (ice bath) solution of 1.0 g (4.48 mmol) of 4-benzyloxyindole in 20 mL of distilled HMPA was added 0.43 g (10.75 mmol) of NaH (60%) under nitrogen and the mixture was stirred at room temperature for 4 h. Then a solution of free base 4-(2-chloroethyl) morpholine, (prepared from 2.5 g (13.4 mmol) of its hydrochloride salt by treatment with saturated $NaHCO_3$ followed by extraction with EtOAc and drying under vacuum for 2 h) in 4 mL of HMPA was added at 0 °C. After stirring at 0 °C for 10 min, the reaction was stirred at room temperature for 20 h and then quenched with 25 mL H_2O. After addition of 25 mL ether, the aqueous layer was separated and extracted with 5 × 40 mL ether. The combined ether extract was washed with 5 × 100 mL, H_2O followed by 2 × 100 mL brine. After drying (Na_2SO_4) the solvent was removed and the residue was chromatographed on 50 g of silica with 1:1 EtOAc:hexanes to yield 1.42 g (94%) of a slightly yellow oil; NMR δ 6.9–7.6 (m, 8H), 6.5–6.7 (m, 2H), 5.24 (s, 2H), 4.25 (t, J = 6.6 Hz, 2H), 3.72 (distorted t, J = 4.8 Hz, 4H), 2.76 (t, J = 7.2 Hz, 2H), 2.49 (distorted t, J = 5.1 Hz, 4H); TLC R_f = 0.27 (1:1 EtOAc:hexanes)

Table 2. Analytical data

Compd	Mol. Formula	Calcd	Found
3b	$C_{21}H_{32}N_2O_2$	C 73.20	C 73.10
		H 9.36	H 9.42
		N 8.13	N 8.11
3c	$C_{23}H_{36}N_2O_2$	C 74.13	C 73.92
		H 9.74	H 9.79
		N 7.52	N 7.51
3d	$C_{25}H_{32}N_2O_2$	C 76.48	C 76.36
		H 8.22	H 8.21
		N 7.13	N 7.08
3e	$C_{25}H_{26}N_2O_2$	C 77.69	C 77.47
		H 6.78	H 6.81
		N 7.25	N 7.13
3f	$C_{25}H_{26}N_2O_2$	C 77.69	C 77.45
		H 6.78	H 6.88
		N 7.25	N 7.17
3g	$C_{26}H_{26}N_2O_3 \cdot 0.9H_2O$	C 72.49	C 72.73
		H 6.51	H 5.96
		N 6.50	N 5.94
3i	$C_{27}H_{30}N_2O_2 \cdot 0.5H_2O$	C 76.75	C 76.63
		H 7.38	H 7.24
		N 6.61	N 6.55
3j	$C_{28}H_{32}N_2O_2 \cdot 0.14EtOAc$	C 77.79	C 77.78
		H 7.57	H 7.53
		N 6.35	N 6.35
8	$C_{13}H_{11}BrO$	C 59.34	C 59.30
		H 4.21	H 4.19
		Br 30.37	Br 30.26

4-Hydroxy-1-[2-(4-morpholinyl)ethyl]-1H-indole (3a). To a suspension of 0.21 g (.624 mmol) of **2** in 25 mL methanol under nitrogen was quickly added 0.063 g of palladium hydroxide on carbon (20% Pd). The flask was sealed and the nitrogen atmosphere was replaced with hydrogen gas (atmospheric pressure). After stirring the mixture for 1 h it was filtered and concentrated in vacuo. The residue, after treatment with dry benzene and removal on the rotory evaporator (to remove traces of water), was placed under vacuum for 1.5 h and used immediately in subsequent alkylation reactions; NMR δ 6.8–7.4 (m, 3H), 6.4–6.7 (m, 2H), 4.23 (t, J = 7.0 Hz, 2H), 3.72 (distorted t, J = 4.6 Hz, 4H), 2.76 (t, J = 7.0 Hz, 2H), 2.50 (distorted t, J = 5.5 Hz, 4H), 2.80 (brs, 1H).

Compounds **3b–e** and **3g** were prepared by following the general procedure described below for **3b**.

4-(2-Heptyloxy)-1-[2-(4-morpholinyl)ethyl]-1H-indole (3b). To a cooled (ice bath) solution of 0.07 g (0.28 mmol) of **3a** in 3 mL of dry DMF was added 0.013 g (0.34 mmol) of NaH (60%) under nitrogen. After stirring for 1 h at 0 °C, a solution of 0.075 g (0.4

mmol) of 2-bromoheptane in 2 mL of DMF was added. After continued stirring for 2 h the reaction was quenched with H_2O. The solution was extracted with 100 mL EtOAc and the extract was washed with H_2O, dried (Na_2SO_4) and evaporated in vacuo. The residue was purified by preparative TLC in 1:1 EtOAc:hexanes. Pure **3b** was obtained as an oil, 0.06 g (62%); NMR δ 6.94–7.27 (m, 3H), 6.52–6.60 (m, 2H), 4.52–4.53 (m, 1H), 4.22 (t, J = 6.5 Hz, 2H), 3.71–3.73 (m, 4H), 2.76 (t, J = 6.5 Hz, 2H), 2.5 (brs, 4H), 1.31–1.9 (m, 11H), 0.94 (t, J = 6.5 Hz, 3H). Anal. ($C_{21}H_{32}N_2O_2$) C, H, N.

4-Nonyloxy-1-[2-(4-morpholinyl)ethyl]-1H-indole (3c). It was similarly prepared from 0.2 g (0.8 mmol) of **3a** and 1-bromononane and gave 0.11 g (37%) of **3c**; NMR δ 6.91–7.15 (m, 3H), 6.49–6.60 (m, 2H), 4.21 (t, J = 6.5 Hz, 2H), 4.1 (t, J = 6.5 Hz, 2H), 3.69–3.71 (m, 4H), 2.73 (t, J = 6.7 Hz, 2H), 2.46–2.49 (m, 4H), 1.84–1.88 (m, 2H), 1.23–1.51 (m, 12H), 0.88 (t, J = 6.8 Hz, 3H). Anal. ($C_{23}H_{36}N_2O_2$) C, H, N.

4-[2-(5-phenyl)pentyloxy]-1-[2-(4-morpholinyl)-ethyl]1H-indole (3d). It was synthesized from 0.22 g (0.89 mmol) of **3a** and 2-bromo-4-phenylpentane (prepared from the Grignard of 3-phenylpropyl bromide and acetaldehyde to form 5-phenyl-2-pentanol which was brominated using trimethylsilyl bromide) in 33% yield to give 0.11 g of **3d**; NMR δ 6.96–7.31 (m, 8H), 6.52–6.61 (m, 2H), 4.51 (m, 1H), 4.25 (m, 2H), 3.77 (brs, 4H), 2.77 (t, J = 6.6 Hz, 2H), 2.69 (t, J = 6.5 Hz, 2H), 2.51 (brs, 4H), 1.71–1.92 (m, 9H), 1.30–1.39 (d, 3H). Anal. ($C_{25}H_{32}N_2O_2$) C, H, N.

4-(1-Naphthyl)methoxy-1-[2-(4-morpholinyl)ethyl]-1H-indole (3e). It was formed from 0.34 g (1.3 mmol) of **3a** and 1-bromomethyl-naphthalene in 15% yield to give 0.060 g of **3e**; NMR δ 6.61–8.2 (m, 12H), 5.7 (s, 2H), 4.25 (t, J = 6.5 Hz, 2H), 3.75 (brs, 4H), 2.8 (t, J = 6.6 Hz, 2H), 2.51 (brs, 4H), Anal. ($C_{25}H_{25}N_2O_2$) C, H, N.

4-(Acetoyloxy-1-naphthyl)-1-[2-(4-morpholinyl)-ethyl)-1H-indole (3g). It was synthesized from 0.26 g (1 mmol) of **3a** and freshly prepared 2-bromo-1′-acetonaphthone (prepared by treatment of 1-aceto-naphthone with pyridinum hydrobromide perbromide in THF) in 32% yield to give 0.13 g of **3g**; NMR δ 6.5–8.7 (m, 12H), 5.4 (s, 2H), 4.2 (brt, 2H), 3.7 (brs, 4H), 2.75 (t, J = 6.6 Hz, 2H), 2.5 (brs, 4H); CI-MS *m/e* 415 (M+1). Anal. ($C_{26}H_{26}N_2O_3$·0.9H2O) C, H, N; H: calcd, 6.51; found 5.96; N: calcd, 6.50; found 5.94. The presence of water was confirmed by NMR.

1-2[2-(4-Morpholinyl)ethyl]-4-(2-naphthyl)methoxy-1H-indole (3f). Compound **3a**, prepared from 0.43 g (1.28 mmol) of **2** as described above, was dissolved in 5 mL of dry DMF and treated with 0.36 g (2.61 mmol) of finely ground K_2CO_3 and 0.43 g (1.96 mmol) of 2-naphthylmethylbromide. The reaction was heated with stirring to 105 °C for 1.5 h after which it was cooled and 30 mL of 1:1 EtOAc:H_2O mixture was added. The layers were separated and the aqueous layer was saturated with NaCl, then extracted with 5 × 20 mL EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed on 100 g of silica using 1:1 EtOAc:hexanes as eluent to afford 0.129 g (26%) of **3f** as a white solid, mp 81–83 °C; NMR δ 6.5–8.0 (m, 12H), 5.36 (s, 2H), 4.18 (t, J = 6.6 Hz, 2H), 3.68 (distorted t, J = 5.4 Hz, 4H), 2.70 (t, J = 7.2 Hz, 2H), 2.44 (distorted t, J = 5.3 Hz, 4H). TLC R_f = 0.53 (EtOAc). Anal. ($C_{25}H_{26}N_2O_2$) C, H, N.

1-Bromo-3-(1-naphthyl)acetone (8).[18] A solution of 1.5 g (8 mmol) of 1-naphthylacetic acid in 50 mL of dry benzene was cooled to 5 °C under nitrogen and 1.44 mL (16 mmol) of oxalyl chloride was added dropwise. After stirring overnight at room temperature the reaction mixture was concentrated in vacuo and the residue was placed under vacuum for 1.5 h. A solution of this acid chloride in anhydrous ether was then added dropwise to an etherial solution of diazomethane (excess) at 0 °C and the mixture was stirred for 2.5 h, warming to room temperature.

The diazoketone solution **7** thus obtained was recooled to 0 °C and HBr gas was bubbled through at a slow rate for 1.5 h. The reaction mixture was then poured into 100 mL of 0.1 M NaOH solution containing crushed ice. After shaking, the ether layer was separated and was washed with 2 × 50 mL Na_2CO_3 solution followed by brine and dried and concentrated in vacuo. The residue was chromatographed on 200 g of silica eluting with 5% EtOAc/hexanes mixture to yield 1.40 g (66%) of **8** as a yellow oil; NMR δ 7.7–8.2 (m, 3H), 7.3–7.7 (m, 4H), 4.38 (s, 2H), 3.87 (s, 2H). Anal. ($CH_{11}BrO$) C, H, Br.

4-[3-(1-naphthyl)-2-oxopropoxy]-1-[2-(4-morpholinyl)-ethyl]-1H-indole (3h). To a solution of **3a** (prepared from 0.50 g (1.48 mmol) of **2**) in 10 mL CH_2Cl_2 was added 0.39 g (1.48 mmol) of 1-bromo-3-(1-naphthyl)acetone **8**, 0.56 g (1.52 mmol) tetra-*n*-butylammonium iodide, and 0.62 g (4.49 mmol) of K_2CO_3 in 10 mL H_2O. Thirty drops of tetra-*n*-butyl ammonium hydroxide were added, and the reaction mixture was stirred vigorously for 140 min. The layers were separated and the aqueous layer was extracted with 3 × 10 mL CH_2Cl_2. The combined organic layers were washed with brine, dried and stripped to an orange oil. Repeated careful chromatography on silica using 1:9:0.01 acetone:hexanes:NEt_3 as eluent afforded 0.071 g (11%) of **3h**; NMR δ 7.7–8.0 (m, 3H), 7.3–7.6 (m, 4H), 7.0–7.2 (m, 3H), 6.68 (d, J = 3.0 Hz, 1H), 6.35 (dd, J = 6.0 Hz, 1H), 4.75 (s, 2H), 4.41 (s, 2H), 4.23 (t, J = 6.9 Hz, 2H), 3.69 (distorted t, J = 4.7 Hz, 4H), 2.73 (t, J = 6.9 Hz, 2H), 2.46 (distorted t, J = 4.7 Hz, 4H); TLC R_f = 0.34 (EtOAc). HRMS ($C_{27}H_{28}N_2O_3$) Found 429.2157 g/mol (M+1); calcd 429.2178 g/mol.

1-Bromo-3-(1-naphthyl)propane (13). A mixture of 4.01 g (17.05 mmol) of (1-naphthyl)-ethyl bromide (**9**) in 32 mL alcohol and 1.37 g (21.04 mmol) of KCN

dissolved in 8 mL of H_2O was heated under reflux.[24] After 21 h the alcohol was removed in vacuo and the residue was dissolved in ether/water mixture. The layers were separated and the aqueous solution was extracted three times with ether. The combined ether extract was washed with brine, dried (Na_2SO_4) and concentrated in vacuo to leave a residue which was purified by chromatography on 100 g silica eluting with 1:9 EtOAc:hexanes. It gave 3.09 g (72%) of 3-(1′-naphthyl)propionitrile (**10**) as a colorless oil; NMR δ 7.3–8.0 (m, 7H), 3.44 (t, J = 7.5 Hz, 2H), 2.76 (t, J = 7.6 Hz, 2H); TLC R_f = 0.21 (1:9 EtOAc: hexanes).

Acid hydrolysis[25] (40% dilute H_2SO_4) of **10** at reflux for 20 h and standard workup gave the corresponding acid **11** in 94% yield. It was reduced using the standard $LiAlH_4$/THF conditions to afford the alcohol **12** in 97% yield as a colorless oil.

To a solution of 1.75 g (9.40 mmol) of **12** and 6.25 g (18.85 mmol) of CBr_4 in 20 mL dry ether at 0 °C was added a solution of 6.98 g (18.84 mmol) of tri-*n*-octylphosphine[19] in 20 mL ether, dropwise. After stirring the mixture at room temperature overnight the solvents were removed in vacuo and the residue was chromatographed on 100 g silica eluting with hexanes to yield 2.22 g (95%) of **13** as a colorless oil; NMR δ 7.3–8.1 (m, 7H), 3.43 (t, J = 6.4 Hz, 2H), 3.23 (t, J = 7.4 Hz, 2H), 2.27 (distorted quintet, J = 6.8 Hz, 2H); TLC R_f = 0.17 (hexanes).

4-(1-Naphthyl)propoxy-1-[2-(4-morpholinyl)ethyl]-1H-indole (3i). Compound **3a**, prepared from 0.43 g (1.28 mmol) of **2** as described above was treated with 0.36 g (2.61 mmol) of finely divided K_2CO_3 and 0.45 g (1.81 mmol) of **13** in DMF exactly as described for **3f**. After workup, it afforded 0.23 g (44%) of **3i**; NMR δ 6.4–8.3 (m, 12H), 4.1–4.4 (m, 4H), 2.71 (distorted t, J = 4.7 Hz, 4H), 3.36 (t, J = 7.1 Hz, 2H,), 2.76 (t, J = 6.9 Hz, 2H) 2.2–2.5 (m, 6H); TLC R_f = 0.47 (EtOAc). Anal. ($C_{27}H_{30}N_2O_2 \cdot 0.5H_2O$) C, H, N. The presence of water was confirmed by NMR.

Diethyl-2-[2-(1-naphthyl)ethyl]malonate (14). A solution of 1.27 g (7.9 mmol) diethyl malonate in 20 mL dry DMF was treated with 0.34 g (8.46 mmol) of NaH (60%) at 0 °C under nitrogen and continued stirring for 1 h at 0 °C. A solution of 2.01 g (8.55 mmol) of **9** in 5 mL of DMF was then added and the reaction mixture was refluxed for 1.5 h. After quenching with 10 mL H_2O, the mixture was extracted three times with EtOAc, washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed on 150 g silica eluting with 3% EtOAc/hexanes to give 2.1 g (85%) of **14** as a colorless oil; NMR δ 7.2–8.1 (m, 7H), 4.22 (q, J = 7.1 Hz, 4H), 3.46 (t, J = 7.3 Hz), 3.14 (t, J = 7.9 Hz, 2H), 2.34 (q, J = 7.7 Hz, 2H), 1.28 (t, J = 7.1 Hz, 6H); TLC R_f = 0.34 (1:9 EtOAc:hexanes).

Ethyl-4-(1-naphthyl)butanoate (15).[26] A solution of 0.97 g (3.09 mmol) of **14** in 10 mL DMSO containing 0.24 mL (13.32 mmol) of H_2O was heated at 200 °C for 5 h. The reaction was quenched by the addition of 10 mL H_2O and extracted three times with EtOAc. After washing with brine and drying (Na_2SO_4) the solvent was removed in vacuo and the residue was purified by chromatography on 100 g silica eluting with 5% EtOAc/hexanes. It gave 0.56 g (75%) of **15**; NMR δ 7.2–8.1 (m, 7H), 4.14 (q, J = 7.1 Hz, 2H), 3.12 (t, J = 7.5 Hz, 2H), 2.40 (t, J = 7.1 Hz, 2H), 2.11 (q, J = 7.7 Hz, 2H), 1.25 (t, J = 7.1 Hz, 3H); TLC R_f = 0.52 (1:9 EtOAc:hexanes).

4-(1-Naphthyl)butyl bromide (17). The ester **15** was reduced to the alcohol **16** and then brominated[19] as described for **13** to give **17** (84%) as a colorless oil; NMR δ 7.2–8.1 (m, 7H), 3.44 (t, J = 6.4 Hz, 2H), 3.09 (t, J = 7.2 Hz, 2H), 1.8–2.2 (m, 4H). TLC R_f = 0.31 (hexanes).

4-(1-Naphthyl)butoxy-1-[2-(4-morpholinyl)ethyl]-1-H-indole (3j). Compound **3a**, prepared from 0.69 g (2.05 mmol) of **2**, was treated with 0.81 g (3.08 mmol) of **17** in the presence of 0.57 g (4.12 mmol) of finely divided K_2CO_3 in DMF as described for **3f**. It formed 0.6 g (69%) of **3j**; NMR δ 6.4–8.2 (m, 12H), 4.0–4.4 (m, 4H), 3.70 (distorted t, J = 4.6 Hz, 4H), 3.18 (m, 2H), 2.73 (t, J = 7.0 Hz, 2H), 2.47 (distorted t, J = 4.8 Hz, 4H), 2.0 (m, 4H); TLC R_f = 0.33 (EtOAc). Anal. ($C_{28}H_{32}N_2O_2 \cdot 0.14$ EtOAc) C, H, N. The pressence of ethyl acetate was confirmed by NMR.

Pharmacology

Materials. Male ICR mice (22–30 g) and Sprague–Dawley rats (250–275 g) obtained from Dominion Laboratories (Dublin, VA), were maintained on a 14:10-h light:dark cycle, and received food and water ad libitum. Δ^9-THC was obtained from the National Institute on Drug Abuse. ^{3}H-CP-55,940 was purchased from DuPont-NEN (Wilmington, DE).

Drug preparation and administration. Micellular suspensions suitable for injection contained a final vehicle composition of ethanol:emulphor:saline (1:1:18),[27] which were administered via the tail-vein (0.1 mL/10 g) of mice.

Behavioral evaluations. Locomotor activity (% inhibition), antinociception (via tail-flick latency; expressed as %MPE), hypothermia (Δ°C), and catalepsy (i.e., ring-immobility; expressed as % immobility) were evaluated in mice by previously reported methods.[28] The ED_{50} values for agonist activity was determined by unweighted least-squares linear regression of the log dose-probit analysis.

In vitro binding assays. The filtration procedure used for ^{3}H-CP-55,940 binding has been described previously.[28] Rats were decapitated and their cortices

rapidly dissected and homogenized in 0.32 M sucrose which contained 2 mM EDTA and 5 mM $MgCl_2$. The homogenate was centrifuged at 1,600 *g* for 10 min, and the supernatant removed. The pellet was washed twice by resuspending in 0.32 M sucrose/2 mM EDTA/5 mM $MgCl_2$ and centrifuging again as described above. The original supernatant was combined with the wash supernatants and centrifuged at 39,000 *g* for 15 min. The resulting P_2 pellet was suspended in 50 mL of buffer (50 mM Tris–HCl, pH 7.0, 2 mM EDTA, 5 mM $MgCl_2$) and incubated at 37 °C for 10 min before centrifugation at 23,000 *g* for 10 min. The P_2 pellet was resuspended in 50 mL of 50 mM Tris–HCl/2 mM EDTA/5 mM $MgCl_2$ and incubated at 30 °C for 10 min before centrifugation at 11,000 *g* for 15 min. The final pellet was resuspended in 10 mL of 50 mM Tris–HCl (pH 7.4) which contained 1 mM EDTA and 3 mM $MgCl_2$ and then stored at −40 °C.

The binding assay was performed in silanized glass tubes which contained 100 μL of radiolabeled ligand (final concentration 1 nM), 100 μL of competing unlabeled drug, 150 μg of membrane protein (75 μL) and sufficient buffer (50 mM Tris–HCl, pH 7.4, 1 mM EDTA, 3 mM $MgCl_2$ and 5 mg/ mL bovine serum albumin [BSA]) to make a final volume of 1 mL. After a 1-h incubation at 30 °C, the reaction was terminated by the addition of 2 mL of ice cold 50 mM Tris–HCl (pH 7.4) buffer containing 1 mg BSA/mL and rapid filtration through polyethyleneimine-treated Whatman GF/C glass-fiber filters. The reaction tube was washed with a 2-mL aliquot of buffer which was then also filtered. The filters were washed with two 4-mL aliquots of ice cold buffer. The filters were shaken for 60 min in 10 mL of scintillation fluid, and radioactivity quantitated by liquid scintillation spectrometry. Specific binding was defined as the difference between the binding that occurred in the presence and absence of 10 μM unlabeled CP-55,940.

Structure generation and charge calculation. All molecular modeling studies were carried out on a Silicon Graphics Indigo 2XZ workstation using SYBYL (version 6.03, Tripos, St. Louis, MO) and SPARTAN (version 4.0, Wavefunction, Irvine, CA) computational chemistry software. Initially, compounds were constructed within SYBYL. Electrostatic charges for all of the analogues were calculated based on the method of Gasteiger–Huckel. Energy minimization using the SYBYL force field was performed until the difference in energy between successive iterations was < 0.01 kcal/mol. In instances where a racemic mixture was used in biological testing, only the (s)-isomer was modeled. Gasteiger–Huckle charges were included in all molecular dynamics simulations.

Molecular dynamics. Molecular dynamics runs were performed in order to evaluate each compound's conformational mobility. Analogues were simulated at 100, 200, 300 and 400 K for 1 ps each and finally were allowed to remain at 500 K for 100 ps. Once the molecule had reached 500 K, snapshots of its conformation were taken at 1 ps intervals, resulting in 100 separate conformations being obtained. After the molecular dynamics runs had concluded, each recorded conformation was subjected to energy minimization as described above until the difference in energy between successive iterations was < 0.01 kcal/mol, resulting in a set of 'quenched' conformations that were stored for further examination.

Alignment of AAIs to Δ^9-THC. An initial alignment based on previous pharmacophore alignment studies with the prototype AAI (WIN 55,212 and Δ^9-THC[13] was assessed using an automated fitting procedure that minimized the Root Mean Square (RMS) deviation between the six aromatic carbons in the benzene ring of the AAI analogues and the six aromatic carbons in the phenol ring of Δ^9-THC (superposition scheme shown in Fig. 2). This set of analogous atoms could be used in all of the molecules involved in this study, thereby enabling rational conformational comparisons to be made throughout this series of compounds. In order to further evaluate and quantitate the ability of selected conformations of AAIs to overlay with Δ^9-THC, the molecular volume of each conformation was calculated using a three-dimensional grid surrounding each molecule. The molecular volume overlap was then optimized using a reiterative process to maximize the correlation coefficient between the points in the two grids (that of the template molecule, Δ^9-THC, and the molecule to be superposed).

Relationship between conformational mobility and pharmacophoric superposition. The relationship between conformational mobility and ability to be superposed with Δ^9-THC was evaluated by plotting the energies of the conformations obtained for each analogue against their volume difference from Δ^9-THC. These graphs relate the conformational mobility of this series of compounds to the overlapping volume of each conformation when aligned as shown in Figure 2.

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