Aminoalkylindoles: Structure-Activity Relationships of Novel Cannabinoid Mimetics

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Aminoalkylindoles (AAIs) are a novel series of cannabinoid receptor ligands. In this report we disclose the structural features of AAIs which are important for binding to this receptor as measured by inhibition of binding of [^{3}H]Win 55212-2 (**5**). Functional activity in the mouse vas deferens is also noted and used to distinguish agonists from potential antagonists. The key structural features for potent cannabinoid activity in this series are a bicyclic (naphthyl) substituent at the 3-position, a small (H) substituent at the 2-position, and an aminoethyl (morpholinoethyl) substituent at the 1-position. A 6-bromo analog, Win 54461 (**31**), has been identified as a potential cannabinoid receptor antagonist. Modeling experiments were done to develop a pharmacophore and also to compare AAI structures with those of classical cannabinoids. The fact that the cannabinoid AAIs arose out of work on a series of cyclooxygenase inhibitors makes sense now that an endogenous cannabinoid ligand has been identified which is a derivative of arachidonic acid. Because of their unique structures and physical properties, AAIs provide useful tools to study the structure and function of the cannabinoid receptor(s).

Introduction

Constituents of marijuana such as Δ^1-THC (**1**) have long been of interest because of their central nervous system (CNS) activity. Among the most interesting features of cannabinoids are their psychotropic,[1] analgesic,[2] antiemetic,[3] and ocular pressure lowering properties.[4] These properties of cannabinoids have been extensively explored in the search for therapeutic utilities, but clinical utility has been limited.[5]

Considerable effort has gone into modifying the structure of cannabinoids, particularly in an attempt to dissociate their therapeutic properties from their psychotropic effects.[6] Among the compounds which were explored clinically are nabilone (**2**)[7] and levonantradol (**3**),[8] both of which were associated with undesired side effects. These structures as well as many others were the result of selective modifications of the cannabinoid structure. The work of the Pfizer group led to some exquisitely potent analogs.[8] With the development of such compounds, significant advances in the understanding of cannabinoid pharmacology were possible. Analogs of levonantradol were shown to be highly stereoselective and potent. These compounds and those developed in our work (*vide infra*) were used in the development of radioligand binding assays and in the localization of cannabinoid binding sites in brain.[9] These efforts pointed to the presence of a specific cannabinoid receptor. The cloning and expression of such a receptor has been reported.[10] The presence of a cannabinoid receptor suggested the likelihood of an endogenous ligand. Anandamide (**4**), the ethanolamide of arachidonic acid, has been proposed to be an endogenous ligand for the cannabinoid receptor (Figure 1).[11]

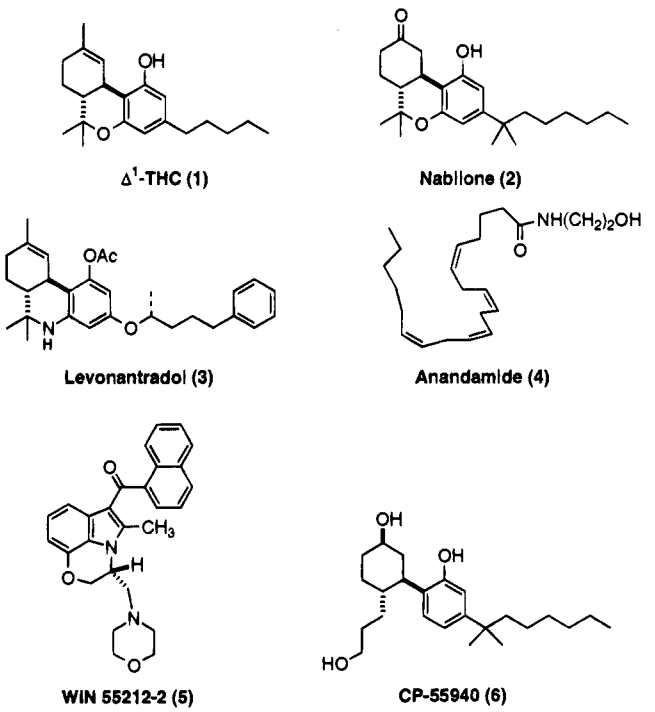

Figure 1.

Concurrent with the work described above, we demonstrated that a series of aminoalkylindole (AAI) antinociceptive agents, originally designed as nonulcerogenic non-steroidal antiinflammatory drugs (NSAIDS),

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is also associated with a second mechanism of action, manifested by potent activity at inhibiting electrically-induced contractions of mouse vas defera (MVD).[12] A potent member of this series, Win 55212–2 (**5**), demonstrated activity in only one of its optical antipodes, and a tritiated version of this compound was used to develop a radioligand binding assay.[13] In the course of profiling a variety of CNS-active compounds through this binding assay, it was discovered that cannabinoids and cannabinoid mimetics bound with high affinity. A receptor binding assay using the synthetic cannabinoid mimetic CP 55940 (**6**) has also been recently developed and a series of AAIs profiled in this assay also showed high affinity.[14] AAIs were also shown to bind to the cloned cannabinoid receptor.[15] In autoradiographic studies, the distribution of AAI binding sites was similar to that reported for classically identified cannabinoid binding sites.[16] These results together with data from functional assays[17] suggest that the activity of aminoalkylindoles and cannabinoids is mediated via a common receptor.

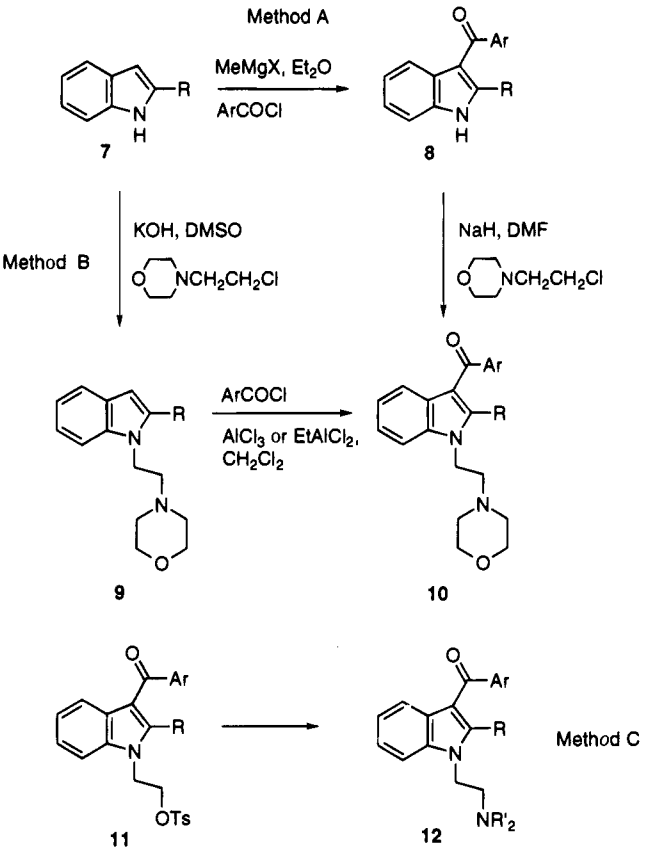
The finding that such apparently structurally different classes of compounds interact with a common receptor is striking.[18] This report describes the structural features of AAIs which are important for binding to this receptor as measured by inhibition of binding of [^{3}H]Win 55212-2.[19] Structural determinants of agonist/antagonist character, defined using the MVD assay, are also discussed.

Chemistry

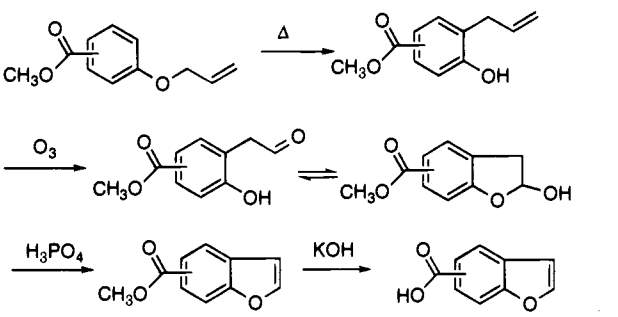
Many of the new compounds described herein were synthesized in a manner similar to our earlier work.[12b] An appropriately functionalized indole was aroylated in the first step followed by N-alkylation (Scheme 1, method A). Alternatively, N-alkylation could be accomplished first, followed by acylation of the indole at C_3 (Scheme 1, method B). For acid-sensitive analogs, $EtAlCl_2$ was used in place of $AlCl_3$ in the Friedel–Crafts acylation. A third approach to the targets was reaction of the 1-(2-(tosyloxy)ethyl) analog with amines to give aminoethyl analogs (Scheme 1, method C).[12b]

Acylation generally utilized the aroyl chloride which was generated using standard conditions from the carboxylic acid. Most of the carboxylic acids were commercially available or were prepared using literature conditions. 4-Methylnaphthoic acid[20] and benzofuran-3-carboxylic acid[21] were prepared by lithiation and carboxylation of the corresponding bromides. 4-Methoxynaphthoic acid[22] and pyrene-1-carboxylic acid[23] were synthesized via oxidation of the corresponding aldehydes. 4-Bromonaphthoic acid[24] was synthesized by acetylation of 1-bromonaphthalene followed by oxidative cleavage. Anthracene-1-carboxylic acid[25] was prepared by reduction of the anthraquinone analog. 1,2,3,4-Tetrahydronaphthoic acid[26] was obtained by reduction of naphthoic acid with sodium in butanol. Quinoline-5-carboxylic acid[27] was synthesized via the Skraup method. Quinoline-7- and -8-carboxylic acids were synthesized by oxidation of the corresponding methyl compounds.[28] A new method of synthesizing benzofuran-4-, -5-, -6-, and -7-carboxylic acids was developed which utilizes the well-studied[29] Claisen rearrangement of allyl ethers of hydroxybenzoates to provide 2-allylphenols which are ozonolyzed and cyclized

Scheme 1



Scheme 2

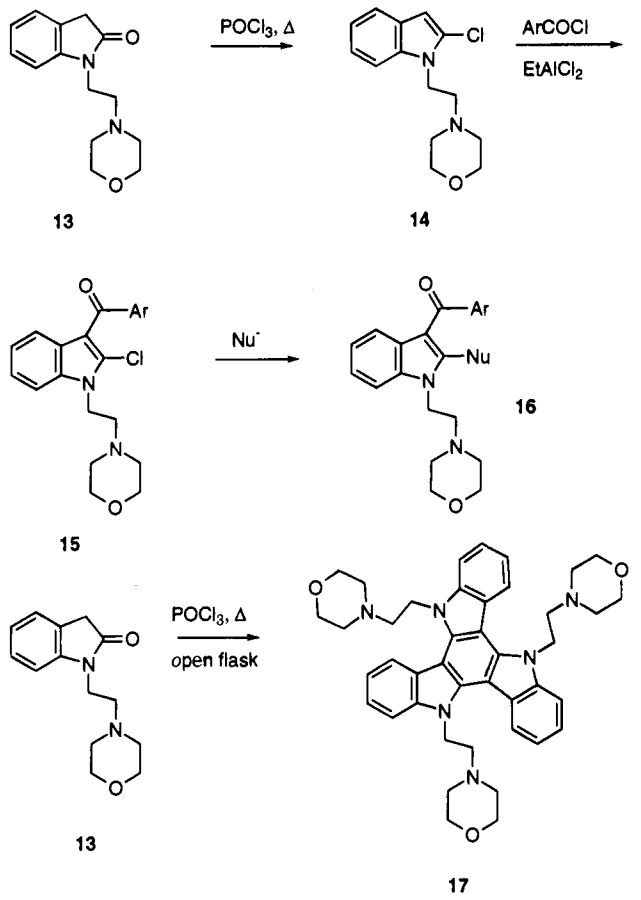


to give the desired benzofuran carboxylic acids (Scheme 2).[30,31] Aneja et al. have used a similar approach in the synthesis of khellin.[32]

The 4-cyanonaphthyl analogs were synthesized by reacting the 4-bromonaphthyl compounds with CuCN. The 4-hydroxynaphthyl analog was derived from the 4-methoxy analog by heating with pyridine hydrochloride. The morpholine *N*-oxide was a microbial oxidation product. The thiomorpholine *S*-oxide was synthesized by oxidation of the thiomorpholine (Table 2).

The indole starting materials that were not commercially available were synthesized using known procedures. The Madelung synthesis provided 2,4- and 2,6-dimethylindole.[33] The Leimgruber–Batcho synthesis was used for 6-methylindole.[34] The Fischer indole synthesis was used to provide 5-fluoro-2-methylindole.[35] The variation which uses (phenylthio)acetone followed by reductive cleavage of the 3-(phenylthio)indole was used for the preparation of 6-methoxy-2-methyl-, 7-methoxy-2-methyl-, and 6-(benzyloxy)-2-methylindole.[36] The Gassman procedure was used for 7-fluoro-2-methylindole.[37]

Scheme 3



2-Ethyl-1-[2-(4-morpholinyl)ethyl]-1*H*-indole (**9**, R = Et) was synthesized by lithiation–alkylation of **1**-[2-(4-morpholinyl)ethyl]-1*H*-indole (**9**, R = H). The 2-chloro analog **14** was made by reacting 1,3-dihydro-1-[2-(4-morpholinyl)ethyl]indol-2-one (**13**) with $POCl_3$. However, a slight modification of the reaction conditions gave the structurally interesting symmetrical trimer **17**.[38] After acylation, the 2-chloro substituent could be displaced by nucleophiles to provide the corresponding 2-substituted analogs **16** (Scheme 3). The hydroxy analog was obtained by treating the methoxy analog with acid.

The 5-hydroxy analog derived from Ra-Ni treatment of 5-(benzyloxy)-3-(phenylthio)-2-methylindole. The 6-bromo analog **31** (Table 2) was synthesized by reacting pravadoline with *N*-bromosuccinimide. The regiochemistry of the bromination was established by difference NOE experiments in which the protons on the methylene next to the indole were irradiated and a significant NOE seen with the indole 7-H which showed only meta coupling, indicating the presence of the 6-substituent.

Structure–Activity Relationships

We have described the structure–activity relationships (SAR) for selected AAIs as prostaglandin synthetase inhibitors and as antinociceptive agents.[12b] We have also described the selection of [^{3}H]Win 55212-2 (**5**) as the radioligand for a binding assay which detected the cannabinoid activity in this series.[13] We now disclose the activity of some of the early AAIs as well as some more recent analogs as inhibitors of binding of [^{3}H]Win 55212-2 reflective of cannabinoid receptor binding and inhibition of electrically induced contractions of the MVD as a functional assay.[19] Although we will not discuss the PG synthetase activity of the compounds, as we have noted previously,[12b,13a] the SAR for PG synthetase inhibitory potency is very different from that for [^{3}H]Win 55212-2 binding activity.

The biological activities of the AAIs are summarized in Table 1. Using pravadoline (**21**) as a benchmark, substitution of the 3-aroyl nucleus was explored. The *o*-methoxy analog **19** was somewhat more potent than pravadoline, but other *ortho* derivatives (**62, 65, 67, 70,** and **73**) were uninteresting. *Meta*, or *para* substitution of the aromatic nucleus led to compounds of moderate potency (**20, 21, 63, 64, 71,** and **72**), compounds with less lipophilic (**66, 68,** and **69**) or with electron-withdrawing (**74** and **75**) substituents being less active. For the more extensively studied *para*-substituted analogs, increasing the lipophilicity slightly by introduction of an ethyl group (**76**) resulted in a potency increase, but further increases in lipophilic bulk (**77–79**) were detrimental. Increasing lipophilicity by addition of a second methyl group to the *m*-methyl compound (**63**) at the *ortho* (**81**) and especially the *para* (**83**) positions also gave a potency increase. A second methyl substituent placed at the *meta* position on the other edge of the phenyl ring was detrimental to binding activity (**82**). Although the 2-naphthyl analog (**119**) was comparable in potency to the dimethyl analog (**83**), the 1-naphthyl analog (**84**) was a major breakthrough in that it provided a better than 1 order of magnitude increase in potency. The potent activity of tetrahydronaphthyl analog (**143**) suggests that the enhancement in potency of the 1-naphthyl analogs is due to the extra ring rather than any specific new aromatic interactions.

The SAR of the 2-position of the indole was initially explored in the pravadoline series. We found that there was a severe restriction to what was tolerated at that position. Increasing the bulk to ethyl (**57**) destroyed activity, while reducing it to H (**54**) enhanced potency. Even when the bulk was maintained within this narrow range, substituents which varied electronically (**58, 60,** and **61**) were inactive, with the exception of the chloro analog (**59**). These results were applied to the 3-(1-naphthyl) analogs and the trends were similar, but differences smaller, the 2-H compound (**98**) being slightly more potent than the 2-methyl (**84**) or 2-chloro (**109**) analogs.

At the 1-position of the indole aminoethyl substitution was optimum. Several potential metabolites (**33–35, 53, 88,** and **89**) were inactive. Displacing the amine from the indole nucleus diminished activity (**45, 46, 93,** and **103**). The nature of the amine was also important. Acyclic amines prepared lacked activity (**35–37**). Among the cyclic amines, morpholine (**21** and **84**), thiomorpholine (**42**), and piperidine (**38** and **90**) were the most active. Piperazines, which contain an additional basic nitrogen in the ring, were inactive (**40, 41, 91,** and **92**). Quaternizing the morpholine by oxidation (**53**) or alkylation (**52** and **90**) destroyed activity, as did oxidizing the sulfur of the thiomorpholine compounds (**43** and **44**). Methyl substitution was explored along the chain and in the morpholine ring (**47–52, 94–97,** and **104–108**). The α-methyl compounds **47, 94, 95,** and **104–106** were

the only ones which retained significant activity, and the activity appeared somewhat stereoselective (**105, 106**).

Using the morpholinoethyl 1-substituent and H or methyl at the 2-position we pursued the SAR of the naphthyl lead. In contrast to the monocyclic aromatic analogs, the naphthyl group was relatively tolerant to diverse substituents (**110–118**). Reduction of the ring of the naphthyl group attached to the carbonyl to give a tetrahydro analog (**142**) resulted in slightly decreased potency. Quinoline derivatives (**121–128**) were uniformly less active. Benzofuryl derivatives (**129–136**) were intermediate in activity between the naphthyls and the quinolines. Analogous to the naphthyl analogs attachment at the peri position (**131** and **136**) to the fused ring gave optimum potency. Fusion of a third aromatic ring onto the naphthyl ring (**137–140**) led to a decrease in potency, most dramatically for the 9-anthracenyl analogs. The carbonyl group in these compounds would have to adopt a significantly different conformation so as to avoid peri interactions. A single tetracyclic pyrene analog (**141**) was a less potent agonist.

Scattered examples of 4- through 7-subsituted indole analogs were prepared. Substituents at the 5-position (**23, 26, 29, 55,** and **100–102**) were generally detrimental to activity. Substitution of pravadoline at the 6-position (**24, 27,** and **31**) gave binding activity but no functional activity in the MVD assay. The naphthyl analog (**99**) retained potent activity in the functional assay. Substitution at the 7-position (**28, 30,** and **86**) gave a modest improvement in binding potency, probably because of restriction of the aminoethyl group to a more bioactive conformation pointing toward the 2-substituent. Potent compounds have been generated by forming a ring between the 1- and 7-substituents which restricts the 1-substituent in a similar way.[13a]

The 9-anthracenyl derivative (**137**), though inactive in the binding assay, was shown to be an apparently competitive antagonist of pravadoline in the MVD and other functional assays.[14,17a] The lack of activity in the binding assay makes interpretation of its importance difficult.

The 6-substituted compounds (**24, 27,** and **31**) which had reasonable binding affinities, but which did not inhibit contractions of the MVD, were shown to antagonize the activity of pravadoline in this assay. The most potent of these, the 6-bromo derivative (**31**), was a competitive inhibitor in the binding assay and an apparently competitive antagonist of AAI agonists in the MVD (Figure 2).[14] It was also found to antagonize the effects of THC and levonantradol in this assay, suggesting that it is a cannabinoid receptor antagonist. This compound has not demonstrated antagonist effects on representative aminoalkylindoles or cannabinoids *in vivo*.[39]

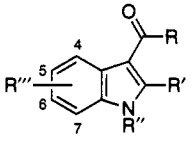
Discussion

In attempting to develop a unifying hypothesis for the cannabinoid-like activity of the AAIs we performed various modeling experiments. In one such set of experiments a pharmacophoric model was developed using the MVD data in which nine AAI agonists were selected to represent the structural diversity present in the database of pravadoline analogs. Three key structural features were identified as being crucial for MVD activity within the database: 1) the nitrogen atom in the aminoalkyl side chain, 2) the 3-aroyl ring, represented by a dummy atom placed at its centroid, and 3) a heterocyclic nucleus, represented by a dummy atom placed at the end of a 3Å normal passing through its centroid (Figure 3). The conformational space of each of the nine reference molecules was systematically examined by rotating each exocyclic bond in the aminoalkyl and aroyl side chains by 5° increments. The distances between the three reference points were recorded, provided that the van der Waals radii did not overlap with any other atom by more than 40%. This distance map, expressed as a series of triangles, was then used as an additional constraint on the conformational search of the next molecule. By repeating this technique, the distance-based pharmacophore was refined to the set of 11 triangles shown. The apices of the triangles represent the allowed positions of each pharmacophoric point common to all of the molecules used in the search. While a facial bias for the aroyl substituent was not established, the amine moiety is restricted to lie on one face of the indole plane, reflecting the stereospecificity of AAIs for the receptor. No AAI agonists were identified which did not conform to the requirements of this pharmacophore, but not every molecule which fit the pharmacophore was active in the MVD assay.

A second approach to modeling these compounds looked at potential commonality between aminoalkylindoles and cannabinoids. In looking at such apparently dissimilar structures we picked out what we thought were the most likely common functionalities. We compared Win 55212-2 (**5**) and Δ^1-THC (**1**). Both compounds possess a polar functionality (amine vs hydroxy), a central ring system (indole vs dibenzopyran), and a lipophilic substituent (naphthyl vs pentyl). Because we had previously observed that a hydroxy did not mimic the morpholine nitrogen in the pravadoline series (**34**), we proposed that the amine of the AAIs and the phenol of the cannabinoids might interact with the same point on the receptor via a hydrogen bond. We thus overlaid the two different series using (1) a dummy atom to the amine and phenol at hydrogen bonding distance, (2) the central rings of each system, and (3) the lipophilic substituent of each system. The results of this exercise are shown in Figure 4. Conformations of both components used in the overlay are energetically accessible. However, the relevance of such an overlay remains speculative.

The recent identification of anandamide (**4**) as a putative endogenous ligand for the cannabinoid receptor makes it a little easier to accept that AAIs structurally may resemble cannabinoids in some way. After all, the original AAIs were designed as cycloogenase inhibitors and might be expected to mimic arachidonic acid in the binding pocket of PG synthetase. The fact that close structural analogs of the cyclooxygenase-inhibiting AAIs bind to the cannabinoid receptor seems eminently reasonable now that an amide of arachidonic acid has been shown to be an endogenous ligand. It would seem likely that the amine of the AAIs interacts with the cannabinoid receptor in a similar fashion to the amide functionality of anandamide, perhaps via a hydrogen bond as described in the overlay experiment. The rest of the AAI apparently mimics an appropriately folded

Table 1. Inhibition of [^{3}H]Win 55212-2 Binding and MVD Activities of AAIs



compd	R	R′	R″[a]	R‴	IC_{50} (nM) inhibition of [^{3}H]Win 55212-2 binding[b]	IC_{50} (nM) MVD[c]
18	H	CH_3	$(CH_2)_2$morph	H	37% at 3000	656 ± 202
19	*o*-OCH_3Ph	CH_3	$(CH_2)_2$morph	H	800	91 ± 18
20	*m*-OCH_3Ph	CH_3	$(CH_2)_2$morph	H	76% at 3000	206 ± 46
21	*p*-OCH_3Ph	CH_3	$(CH_2)_2$morph	H	3155 ± 54	319 ± 63
22	*p*-OCH_3Ph	CH_3	$(CH_2)_2$morph	4-CH_3	42% at 3000	>10000
23	*p*-OCH_3Ph	CH_3	$(CH_2)_2$morph	5-CH_3	7% at 1000	>10000
24	*p*-OCH_3Ph	CH_3	$(CH_2)_2$morph	6-CH_3	1883 ± 125	>10000
25	*p*-OCH_3Ph	CH_3	$(CH_2)_2$morph	7-CH_3	1533 ± 138	178 ± 64
26	*p*-OCH_3Ph	CH_3	$(CH_2)_2$morph	5-OCH_3	14% at 1000	>10000
27	*p*-OCH_3Ph	CH_3	$(CH_2)_2$morph	6-OCH_3	1451 ± 106	>10000
28	*p*-OCH_3Ph	CH_3	$(CH_2)_2$morph	7-OCH_3	64% at 1000	266 ± 49
29	*p*-OCH_3Ph	CH_3	$(CH_2)_2$morph	5-F	19% at 1000	119 ± 15
30	*p*-OCH_3Ph	CH_3	$(CH_2)_2$morph	7-F	571	73 ± 40
31	*p*-OCH_3Ph	CH_3	$(CH_2)_2$morph	6-Br	515 ± 73	>10000
32	*p*-OCH_3Ph	CH_3	H	H	−12% at 1000	27 ± 16
33	*p*-OCH_3Ph	CH_3	CH_2CO_2H	H	−11% at 1000	>10000
34	*p*-OCH_3Ph	CH_3	$(CH_2)_2OH$	H	−6% at 1000	>10000
35	*p*-OCH_3Ph	CH_3	$(CH_2)_2NH_2$	H	−14% at 1000	>10000
36	*p*-OCH_3Ph	CH_3	$(CH_2)_2NMe_2$	H	11% at 1000	
37	*p*-OCH_3Ph	CH_3	$(CH_2)_2NEt_2$	H	−31% at 1000	>10000
38	*p*-OCH_3Ph	CH_3	$(CH_2)_2$pip	H	34% at 3000	1426 ± 130
39	*p*-OCH_3Ph	CH_3	$(CH_2)_2$pyr	H	7% at 1000	241 ± 119
40	*p*-OCH_3Ph	CH_3	$(CH_2)_2$piperaz	H	−16% at 1000	>10000
41	*p*-OCH_3Ph	CH_3	$(CH_2)_2$4-Me-piperaz	H	−22% at 1000	
42	*p*-OCH_3Ph	CH_3	$(CH_2)_2$thiomorph	H	622 ± 79	
43	*p*-OCH_3Ph	CH_3	$(CH_2)_2$thiomorph *S*-oxide	H	−24% at 1000	
44	*p*-OCH_3Ph	CH_3	$(CH_2)_2$thiomorph *S*,*S*-dioxide	H	−4% at 1000	
45	*p*-OCH_3Ph	CH_3	$(CH_2)_3$morph	H	−6% at 1000	360 ± 120
46	*p*-OCH_3Ph	CH_3	$(CH_2)_4$morph	H	−19% at 1000	>10000
47	*p*-OCH_3Ph	CH_3	$CH(CH_3)CH_2$morph	H	34% at 1000	1356 ± 805
48	*p*-OCH_3Ph	H	$CH(CH_3)CH_2$morph	H	35% at 1000	3668 ± 2325
49	*p*-OCH_3Ph	CH_3	$CH_2CH(CH_3)$morph	H	−21% at 1000	>10000
50	*p*-OCH_3Ph	CH_3	$(CH_2)_2$2-Me-morph	H	−12% at 1000	>10000
51	*p*-OCH_3Ph	CH_3	$(CH_2)_2$3-Me-morph	H	−25% at 1000	>10000
52	*p*-OCH_3Ph	CH_3	$(CH_2)_2$N-Me-morph	H	−16% at 1000	4314 ± 2499
53	*p*-OCH_3Ph	CH_3	$(CH_2)_2$morph *N*-oxide	H	−9% at 1000	>10000
54	*p*-OCH_3Ph	H	$(CH_2)_2$morph	H	390 ± 9	101 ± 6
55	*p*-OCH_3Ph	H	$(CH_2)_2$morph	5-Br	−26% at 1000	
56	*p*-OCH_3Ph	H	$(CH_2)_2$morph	6-Br	21% at 1000	17 ± 1
57	*p*-OCH_3Ph	CH_2CH_3	$(CH_2)_2$morph	H	−12% at 1000	>10000
58	*p*-OCH_3Ph	F	$(CH_2)_2$morph	H	7% at 1000	
59	*p*-OCH_3Ph	Cl	$(CH_2)_2$morph	H	47% at 1000	176 ± 20
60	*p*-OCH_3Ph	CN	$(CH_2)_2$morph	H	3% at 1000	
61	*p*-OCH_3Ph	OH	$(CH_2)_2$morph	H	1% at 1000	
62	*o*-CH_3Ph	CH_3	$(CH_2)_2$morph	H	13% at 1000	715 ± 13
63	*m*-CH_3Ph	CH_3	$(CH_2)_2$morph	H	606 ± 91	
64	*p*-CH_3Ph	CH_3	$(CH_2)_2$morph	H	1773 ± 187	442 ± 294
65	*o*-OHPh	CH_3	$(CH_2)_2$morph	H	−2% at 1000	
66	*p*-OHPh	CH_3	$(CH_2)_2$morph	H	15% at 1000	>10000
67	*o*-FPh	CH_3	$(CH_2)_2$morph	H	15% at 1000	1944 ± 598
68	*m*-FPh	CH_3	$(CH_2)_2$morph	H	38% at 3000	
69	*p*-FPh	CH_3	$(CH_2)_2$morph	H	12% at 1000	
70	*o*-ClPh	CH_3	$(CH_2)_2$morph	H	59% at 3000	92 ± 40
71	*m*-ClPh	CH_3	$(CH_2)_2$morph	H	1315 ± 113	
72	*p*-ClPh	CH_3	$(CH_2)_2$morph	H	62% at 3000	564 ± 108
73	*o*-CNPh	CH_3	$(CH_2)_2$morph	H	0% at 1000	
74	*m*-CNPh	CH_3	$(CH_2)_2$morph	H	1% at 1000	
75	*p*-CNPh	CH_3	$(CH_2)_2$morph	H	−1% at 1000	>10000
76	*p*-CH_2CH_3Ph	CH_3	$(CH_2)_2$morph	H	306 ± 28	71 ± 5
77	*p*-$(CH_2)_2CH_3$Ph	CH_3	$(CH_2)_2$morph	H	1134	
78	*p*-$C(CH_3)_3$Ph	CH_3	$(CH_2)_2$morph	H	56% at 3000	
79	*p*-C_6H_5Ph	CH_3	$(CH_2)_2$morph	H	9% at 1000	10000
80	*o*,*o*-$(CH_3)_2$Ph	CH_3	$(CH_2)_2$morph	H	−5% at 1000	1573 ± 623
81	*o*,*m*-$(CH_3)_2$Ph	CH_3	$(CH_2)_2$morph	H	373 ± 53	
82	*m*,*m*-$(CH_3)_2$Ph	CH_3	$(CH_2)_2$morph	H	42% at 1000	390 ± 70
83	*m*,*p*-$(CH_3)_2$Ph	CH_3	$(CH_2)_2$morph	H	140	
84	1-naphthyl	CH_3	$(CH_2)_2$morph	H	19 ± 2	15 ± 2
85	1-naphthyl	CH_3	$(CH_2)_2$morph	6-CH_3	11	15 ± 3

Table 1 (Continued)

compd	R	R′	R″[a]	R‴	IC_{50} (nM) displacement of [^{3}H]Win 55212-2 binding[b]	IC_{50} (nM) MVD[c]
86	1-naphthyl	CH_3	$(CH_2)_2$morph	7-OCH_3	10	
87	1-naphthyl	CH_3	$(CH_2)_2$morph	6-Br	10	
88	1-naphthyl	CH_3	H	H	3% at 1000	>10000
89	1-naphthyl	CH_3	CH_2CO_2H	H	21% at 1000	9745 ± 4400
90	1-naphthyl	CH_3	$(CH_2)_2$pip	H	37	66 ± 41
91	1-naphthyl	CH_3	$(CH_2)_2$piperaz	H	−9% at 1000	
92	1-naphthyl	CH_3	$(CH_2)_2$4-Me-piperaz	H	−28% at 1000	>10000
93	1-naphthyl	CH_3	$(CH_2)_3$morph	H	150	112 ± 53
(±)-**94**	1-naphthyl	CH_3	$CH(CH_3)CH_2$morph	H	13	11 ± 2
(−)-**95**	1-naphthyl	CH_3	$CH(CH_3)CH_2$morph	H	79% at 1000	56 ± 19
96	1-naphthyl	CH_3	$(CH_2)_2$2-Me-morph	H	59	30 ± 11
97	1-naphthyl	CH_3	$(CH_2)_2$3-Me-morph	H	384 ± 43	207 ± 24
98	1-naphthyl	H	$(CH_2)_2$morph	H	7.8 ± 0.3	6.3 ± 1.2
99	1-naphthyl	H	$(CH_2)_2$morph	6-CH_3	3.5	1.7 ± 0.0
100	1-naphthyl	H	$(CH_2)_2$morph	5-F	35	7.3 ± 4.7
101	1-naphthyl	H	$(CH_2)_2$morph	5-Br	186 ± 29	19 ± 10
102	1-naphthyl	H	$(CH_2)_2$morph	5-OH	70 ± 6	20 ± 4
103	1-naphthyl	H	$(CH_2)_3$morph	H	43	9.8 ± 2.4
(±)-**104**	1-naphthyl	H	$CH(CH_3)CH_2$morph	H	94% at 1000	19 ± 5
(+)-**105**	1-naphthyl	H	$CH(CH_3)CH_2$morph	H	114 ± 10	60 ± 3
(−)-**106**	1-naphthyl	H	$CH(CH_3)CH_2$morph	H	33 ± 7	12 ± 0.7
107	1-naphthyl	H	$CH_2CH(CH_3)$morph	H	124 ± 20	60 ± 9
108	1-naphthyl	H	$(CH_2)_2$N-Me-morph	H	14% at 1000	180 ± 40
109	1-naphthyl	Cl	$(CH_2)_2$morph	H	10	6.1 ± 1.2
110	4-CH_3-1-naphthyl	H	$(CH_2)_2$morph	H	2.8 ± 1.1	3.6 ± 1.3
111	4-CH_3-1-naphthyl	CH_3	$(CH_2)_2$morph	H	5.9	9.6 ± 2.5
112	4-OCH_3-1-naphthyl	H	$(CH_2)_2$morph	H	1.4	
113	4-OCH_3-1-naphthyl	CH_3	$(CH_2)_2$morph	H	55	23 ± 4
114	4-OH-1-naphthyl	H	$(CH_2)_2$morph	H	3.4	
115	4-CN-1-naphthyl	H	$(CH_2)_2$morph	H	96% at 1000	4.8 ± 2.3
116	4-CN-1-naphthyl	CH_3	$(CH_2)_2$morph	H	15	15 ± 1
117	4-Br-1-naphthyl	H	$(CH_2)_2$morph	H	98% at 1000	5.5 ± 1.4
118	4-Br-1-naphthyl	CH_3	$(CH_2)_2$morph	H	6.9	34 ± 3
119	2-naphthyl	CH_3	$(CH_2)_2$morph	H	128	50 ± 9
120	2-naphthyl	H	$(CH_2)_2$morph	H	59	31 ± 4
121	2-quinolinyl	CH_3	$(CH_2)_2$morph	H	331	99 ± 45
122	3-quinolinyl	CH_3	$(CH_2)_2$morph	H	28% at 1000	571 ± 88
123	4-quinolinyl	CH_3	$(CH_2)_2$morph	H	283 ± 84	115 ± 25
124	5-quinolinyl	CH_3	$(CH_2)_2$morph	H	828 ± 94	79 ± 33
125	6-quinolinyl	CH_3	$(CH_2)_2$morph	H	499 ± 101	103 ± 3
126	6-quinolinyl	H	$(CH_2)_2$morph	H	491 ± 100	142 ± 9
127	7-quinolinyl	CH_3	$(CH_2)_2$morph	H	177	88 ± 32
128	8-quinolinyl	CH_3	$(CH_2)_2$morph	H	274	129 ± 34
129	2-benzofuryl	CH_3	$(CH_2)_2$morph	H	416	324 ± 18
130	3-benzofuryl	CH_3	$(CH_2)_2$morph	H	110	52 ± 15
131	4-benzofuryl	H	$(CH_2)_2$morph	H	24	7.7 ± 2.4
132	5-benzofuryl	CH_3	$(CH_2)_2$morph	H	357	126 ± 41
133	5-benzofuryl	H	$(CH_2)_2$morph	H	138	28 ± 10
134	6-benzofuryl	H	$(CH_2)_2$morph	H	304	40 ± 11
135	7-benzofuryl	CH_3	$(CH_2)_2$morph	H	71	17 ± 10
136	7-benzofuryl	H	$(CH_2)_2$morph	H	18 ± 2	4.6 ± 1.0
137	9-anthracenyl	CH_3	$(CH_2)_2$morph	H	−26% at 1000	>10000
138	9-anthracenyl	H	$(CH_2)_2$morph	H	2965	>10000
139	1-anthracenyl	CH_3	$(CH_2)_2$morph	H	74% at 1000	57 ± 3
140	9-phenanthrenyl	CH_3	$(CH_2)_2$morph	H	75% at 1000	175 ± 8
141	1-pyrenyl	CH_3	$(CH_2)_2$morph	H	89% at 1000	42 ± 30
142	1,2,3,4-H_4-naphthyl	H	$(CH_2)_2$morph	H	38 ± 2	11 ± 3
143	5,6,7,8-H_4-naphthyl	H	$(CH_2)_2$morph	H	97% at 1000	6.0 ± 3.8
1					5.8 ± 0.7	4.0 ± 0.5

[a] Abbreviations: morph = 4-morpholinyl, pip = 1-piperidinyl, pyr = 1-pyrrolidinyl, piperaz = 1-piperazinyl, thiomorph = 4-thiomorpholinyl. [b] Concentration of compound required to inhibit 50% of 0.5 nM [^{3}H]WIN-55212-2 (**5**) binding in rat cerebellum membranes as described in ref 13b. Values are the IC_{50} ± SE or percent inhibition at the highest tested dose (nM). Negative values connote stimulation rather than inhibition. Confidence limits for certain compounds could not be retrieved due to gaps in the archiving. [c] Concentration of compound required to inhibit electrically induced contractions in isolated mouse vas deferens preparations *in vitro* as described in ref 12a. Values are the IC_{50} ± SE or the highest tested dose (nM).

form of anandamide which allows potent binding to the receptor.

Since the SARs for inhibition of PG synthetase and binding to the cannabinoid receptor differ within the AAI series, it allows some speculation about the relative conformations of anandamide bound to the cannabinoid receptor vis-à-vis arachidonic acid bound to PG synthetase. AAIs containing more lipophilic and bulky 3-substituents (naphthyl) are potent cannabinoid binders but inactive as cyclooxygenase inhibitors, suggesting that anandamide may be in a more extended conformation when bound to the cannabinoid receptor than is arachidonic acid when bound to PG synthetase. Furthermore, the limited variation tolerated on the amine

Table 2. New Compounds Synthesized

compd	method[a]	% yield[b]	formula	recrystn solvent	mp, °C	anal.
22	A	31 (2 steps)	$C_{24}H_{28}N_2O_3 \cdot CH_3SO_3H$	2-PrOH	214–216	C,H,N
23	A	77 (80)	$C_{24}H_{28}N_2O_3$	EtOAc	153–154	C,H,N
24	A	57 (40)	$C_{24}H_{28}N_2O_3$	EtOAc	101–104	C,H,N
25	A	83 (74)	$C_{24}H_{28}N_2O_3$	2-PrOH	149–151	C,H,N
26	A	45	$C_{24}H_{28}N_2O_4$	EtOAc	118–120	C,H,N
27	A	63 (53)	$C_{24}H_{28}N_2O_4 \cdot HCl$	EtOAc/CH_2Cl_2/Et_2O	222–224	C,H,N
28	A	25 (68)	$C_{24}H_{28}N_2O_4 \cdot HCl$	CH_3OH/Et_2O	203–204	C,H,N,Cl
29	A	59 (53)	$C_{23}H_{25}FN_2O_3 \cdot HCl$	CH_3OH/Et_2O	198–200	C,H,N,F
30	A	23 (42)	$C_{23}H_{25}FN_2O_3$	2-PrOH	120–121	C,H,N,F
31	D	38	$C_{23}H_{25}BrN_2O_3$	Toluene	137.5–139.5	C,H,N,Br
42	C	50	$C_{23}H_{26}N_2O_2S$	EtOAc	124–125	C,H,N
43	E	31	$C_{23}H_{26}N_2O_2S \cdot C_4H_4O_4$	EtOH	179–180	C,H,N
44	C	15	$C_{23}H_{26}N_2O_4S$	CH_3CN	181–182	C,H,N
49	A	45	$C_{24}H_{28}N_2O_3$	EtOAc/hexane	128–130	C,H,N
50	C	41	$C_{24}H_{28}N_2O_3 \cdot HCl$	CH_3CN	239–241	C,H,N
51	C	56	$C_{24}H_{26}N_2O_3 \cdot C_4H_4O_4 \cdot {}^1/_2EtOAc$	EtOAc	135–140	C,(H),N[c]
52	F	46	$C_{24}H_{29}N_2O_4 \cdot C_7H_7SO_3$	MeOH	228–231	C,H,N
53	G	43	$C_{23}H_{26}N_2O_4$	acetone/Et_2O	142–144	C,H,N
55	B	71 (58)	$C_{22}H_{23}BrN_2O_3$	EtOAc	155–156	C,H,N,Br
56	D	1	$C_{22}H_{23}BrN_2O_3$	EtOAc	137–138	C,H,N
58	H	45	$C_{22}H_{23}FN_2O_3$	EtOH	134–135	C,H,N
59	B	85	$C_{22}H_{23}ClN_2O_3 \cdot HCl$	EtOH	170–173	C,H,N
60	H	83	$C_{23}H_{23}N_3O_3$	EtOH	123–124	C,H,N
61	I	35	$C_{22}H_{24}N_2O_4 \cdot HCl$	MeOH	225–227	C,H,N
65	J	23	$C_{22}H_{24}N_3O_3$	2-PrOH	115–116	C,H,N
70	B	64	$C_{22}H_{23}ClN_2O_2$	Et_2O	104–107	C,H,N
71	B	38	$C_{22}H_{23}ClN_2O_2$	EtOAc/Et_2O	116–118	C,H,N
72	A	54 (34)	$C_{22}H_{23}ClN_2O_2$	EtOAc	148–150	C,H,N
73	B	19	$C_{22}H_{23}N_3O_2 \cdot C_4H_4O_4$	EtOAc	185–186	C,H,N
74	B	26	$C_{22}H_{23}N_3O_2$	Et_2O	122–124	C,H,N
75	A	89 (67)	$C_{22}H_{23}N_3O_2$	EtOAc	156.5–158.5	C,H,N
76	A	70 (70)	$C_{24}H_{26}N_2O_2$	EtOAc	124–126	C,H,N
77	B	68	$C_{25}H_{30}N_2O_2$	EtOAc/Et_2O	86.5–87.5	C,H,N
78	B	57	$C_{26}H_{32}N_2O_2 \cdot HCl$	MeOH	235–236	C,H,N,Cl
79	A	59 (56)	$C_{28}H_{28}N_2O_2$	CH_3CN	131.5–133.0	C,H,N
80	A	59 (95)	$C_{24}H_{26}N_2O_2 \cdot HCl$	EtOAc/Et_2O	275–280	C,H,N
81	B	46	$C_{24}H_{26}N_2O_2 \cdot HCl \cdot {}^3/_4H_2O$	EtOH	241–244	C,H,N[d]
82	B	51	$C_{24}H_{28}N_2O_2$	EtOAc/hexane	142–144	C,H,N
83	B	83	$C_{24}H_{28}N_2O_2$	2-PrOH	145–147	C,H,N
85	A	74 (29)	$C_{27}H_{28}N_2O_2$	EtOAc	154.5–156.0	C,H,N
86	B	11 (31)	$C_{27}H_{26}N_2O_3$	EtOAc/Et_2O	225–227	C,H,N
87	D	24	$C_{26}H_{25}BrN_2O_2$	EtOAc/hexane	131.5–135.0	C,H,N
89	A, K	30	$C_{22}H_{16}NO_3Na$	EtOH/Et_2O	>300	C,H,N
90	C	32	$C_{27}H_{28}N_2O$	EtOAc	119–121	C,H,N
91	C	38	$C_{26}H_{27}N_3O_2 \cdot HCl$	CH_3OH	237.5–241.0	C,H,N
92	C	27	$C_{26}H_{27}N_3O_2 \cdot 2HCl \cdot {}^1/_2H_2O$	CH_3OH	195.5–199.5	C,H,N[e]
93	A	71	$C_{27}H_{28}N_2O_2$	Et_2O	135–138	C,H,N
(±)-**94**	B	36	$C_{27}H_{28}N_2O_2 \cdot C_4H_4O_4$	MeOtBu	87	C,H,N
(−)-**95**[f]	B	49	$C_{27}H_{28}N_2O_2 \cdot HCl$	EtOAc	246–250	C,H,N,Cl
96	C	5	$C_{27}H_{28}N_2O_2 \cdot HCl$	MeOtBu	149–154	C,H,N
97	C	21	$C_{27}H_{28}N_2O_2$	Et_2O	144–145	C,H,N
99	B	54	$C_{26}H_{26}N_2O_2$	EtOAc	163–165	C,H,N
100	A	34 (54)	$C_{25}H_{23}FN_2O_2 \cdot CH_3SO_3H$	2-PrOH/Et_2O	210–212	C,H,N,F,S
101	A	37 (40)	$C_{25}H_{25}BrN_2O_2$	EtOAc	153–155	C,H,N
102	L	24	$C_{25}H_{24}N_2O_3$	EtOAc	200–202	C,H,N
103	B	57	$C_{26}H_{26}N_2O_2$	EtOAc	143–144	C,H,N
(±)-**104**	B	26	$C_{26}H_{26}N_2O_2$	Et_2O	116–119	C,H,N
(+)-**105**[g]	B	72	$C_{26}H_{26}N_2O_2$	Et_2O	143–144	C,H,N
(−)-**106**[h]	B	52	$C_{26}H_{26}N_2O_2$	Et_2O	140–142	C,H,N
107	A	35	$C_{26}H_{26}N_2O_2$	EtOAc/hexane	145–147	C,H,N
108	C	67	$C_{26}H_{27}N_2O_2 \cdot C_7H_7SO_3$	2-PrOH	192–194	C,H,N,S
109	B	48	$C_{25}H_{23}ClN_2O_2$	EtOAc	144–145	C,H,N
110	B	91	$C_{26}H_{26}N_2O_2$	CH_2Cl_2/toluene	158.5–160.5	C,H,N
111	B	78	$C_{27}H_{28}N_2O_2$	CH_2Cl_2/toluene	171–173	C,H,N
112	B	88	$C_{26}H_{26}N_2O_3$	CH_2Cl_2/toluene	137.0–140.5	C,H,N
113	A	26 (50)	$C_{27}H_{26}N_2O_2 \cdot CH_3SO_3H \cdot 0.4(2\text{-PrOH})$	2-PrOH	145–147	C,H,N[i]
114	I	42	$C_{25}H_{24}N_2O_3$	EtOAc/hexane	185–186	C,H,N
115	M	77	$C_{26}H_{26}N_3O_2$	EtOAc	186.5–189.0	C,H,N
116	M	57	$C_{27}H_{25}N_3O_2$	EtOAc	180.5–183.5	C,H,N
117	B	82	$C_{25}H_{23}BrN_2O_2$	Acetone	164–166	C,H,N,Br
118	B	73	$C_{26}H_{25}BrN_2O_2$	EtOAc/Et_2O	126.5–128.5	C,H,N,Br
119	A	35 (57)	$C_{26}H_{26}N_2O_2 \cdot CH_3SO_3H$	2-PrOH	195–198	C,H,N
120	B	49	$C_{25}H_{24}N_2O_2$	EtOAc	170–172	C,H,N
121	B	51	$C_{25}H_{25}N_3O_2$	CH_2Cl_2/CH_3OH	163–164	C,H,N
122	B	34	$C_{25}H_{25}N_3O_2$	CH_2Cl_2/CH_3OH	165–166	C,H,N
123	B	63	$C_{25}H_{25}N_3O_2$	EtOH	142–143	C,H,N
124	B	38	$C_{25}H_{25}N_3O_2$	EtOAc	174–175	C,H,N

Table 2 (Continued) Continued

compd	method[a]	% yield[b]	formula	recrystn solvent	mp, °C	anal.
125	B	55	$C_{25}H_{25}N_3O_2$	EtOAc	138–139	C,H,N
126	B	37	$C_{24}H_{23}N_3O_2$	Et_2O	123–124	C,H,N
127	B	41	$C_{25}H_{25}N_3O_2$	Et_2O	125–126	C,H,N
128	B	28	$C_{25}H_{25}N_3O_2$	EtOAc	158–159	C,H,N
129	A	60 (62)	$C_{24}H_{24}N_2O_3 \cdot CH_3SO_3H$	EtOH	194–198	C,H,N
130	B	28	$C_{24}H_{24}N_2O_3$	EtOH	134–135	C,H,N
131	B	59	$C_{23}H_{22}N_2O_3$	EtOAc	160–162	C,H,N
132	B	40	$C_{24}H_{24}N_2O_3$	EtOAc/acetone	165.5–167.0	C,H,N
133	B	36	$C_{23}H_{22}N_2O_3$	EtOAc	158–159	C,H,N
134	B	67	$C_{23}H_{22}N_2O_3$	–	125–126	C,H,N
135	B	27	$C_{24}H_{24}N_2O_3$	EtOAc/hexane	161–162	C,H,N
136	B	86	$C_{23}H_{22}N_2O_3$	EtOAc	145–147	C,H,N
137	B	54	$C_{30}H_{28}N_2O_2$	EtOAc/CH_2Cl_2	194–196	C,H,N
138	A	61 (88)	$C_{29}H_{26}N_2O_2$	CH_3CN	202–204	C,H,N
139	A	67 (9)	$C_{30}H_{28}N_2O_2$	EtOAc	126–128	C,H,N
140	A	62 (51)	$C_{30}H_{28}N_2O_2 \cdot HCl$	Et_2O/CH_2Cl_2	180–182	C,H,N,Cl
141	B	30	$C_{32}H_{28}N_2O_2$	toluene	157–159	C,H,N
142	B	59	$C_{25}H_{28}N_2O_2 \cdot HCl$	CH_3OH/Et_2O	198–200	C,H,N
143	B	17	$C_{25}H_{28}N_2O_2 \cdot HCl$	CH_3OH/Et_2O	214–216	C,H,N

[a] Methods A, B, and C are shown in Scheme 1 and are also used in ref 12a, where examples are given. Examples of method B, method D, bromination of the parent indole with NBS, and method H, nucleophilic displacement of the 2-chloro analog, are provided in the Experimental Section. In method E, the corresponding sulfide was oxidized with MCPBA. In method F, the amine was alkylated with methyl tosylate. The *N*-oxide was a microbial transformation product (method G) of pravadoline (see ref 12e). In methods I and J the methyl ethers were deprotected with HCl or pyridine hydrochloride, respectively. Method K involves basic hydrolysis of the ethyl ester. Method L utilized $AlCl_3$-catalyzed debenzylation of the benzyl ether. Method M utilized CuCN-mediated displacement on the 4-bromo analog. [b] For method A, when a new acylation was used the yields for the acylation and the alkylation are given. [c] Anal. Calcd for $C_{24}H_{28}N_2O_3 \cdot HCl \cdot {}^1/_2EtOAc$: C, 65.20; H, 6.57; N, 5.07. Found: C, 65.27; H, 6.12; N, 5.03. [d] Anal. Calcd for $C_{24}H_{28}N_2O_2 \cdot HCl \cdot {}^3/_4H_2O$: C, 67.61; H, 6.92; N, 6.57. Found: C, 67.75; H, 6.88; N, 6.52. [e] Anal. Calcd for $C_{26}H_{27}N_3O_2 \cdot 2HCl \cdot {}^1/_2H_2O$: C, 65.72; H, 6.54; N, 8.52. Found: C, 65.75; H, 6.84; N, 8.31. [f] $[\alpha]^{25}_D = -16.7°$ (1%, MeOH). [g] $[\alpha]^{25}_D = +7.7°$ (1%, $CHCl_3$). [h] $[\alpha]^{25}_D = -7.3°$ (1%, $CHCl_3$). [i] Anal. Calcd for $C_{27}H_{28}N_2O_2 \cdot CH_3SO_3H \cdot 0.4$ (2-PrOH): C, 64.06; H, 6.26; N, 5.12. Found: C, 63.83; H, 6.26; N, 5.18.

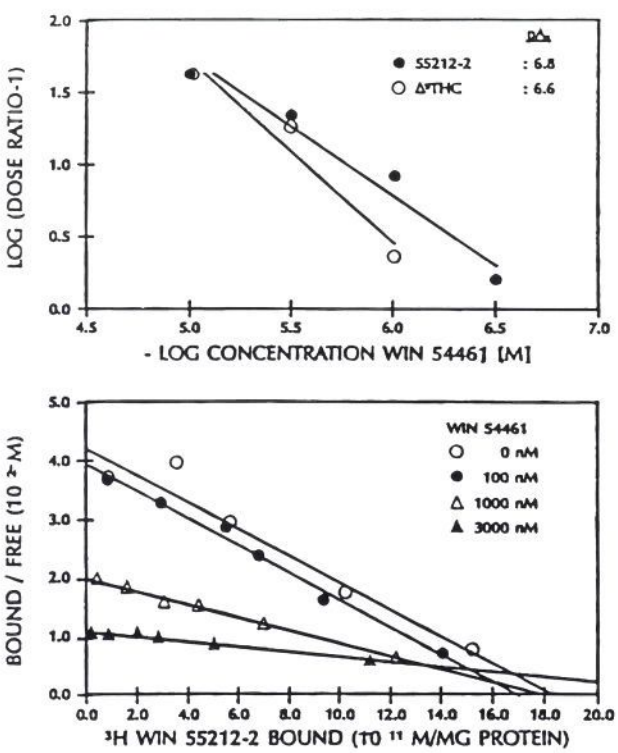


Figure 2.

of the AAIs suggests that minor substitution of the hydroxy amide of anandamide may not be tolerated and that stereoselectivity at this end of the molecule might be expected. Indeed, modest stereoselectivity for anandamide analogs has recently been reported.[18g] Such speculations lead to some obvious hybrid target structures of AAIs and anandamide which may lead to whole new series of cannabinoid agonists and perhaps antagonists.

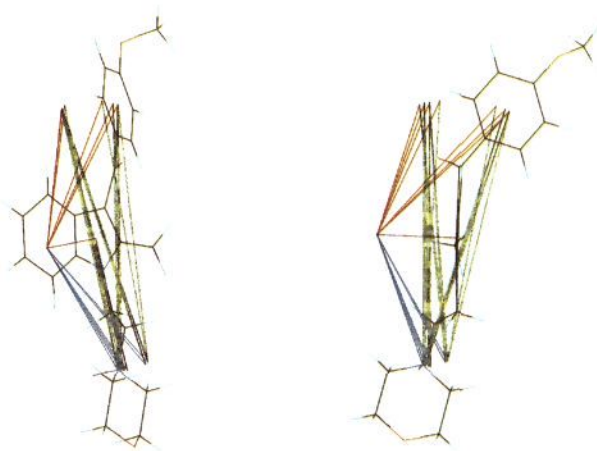


Figure 3.

Summary

Key structural features for potent cannabinoid binding activity of AAIs are a bicyclic (particularly 1-naphthyl) substituent at the 3-position of the indole, a small substituent, or better, no substituent, at the 2-position of the indole, and a morpholinoethyl or other cyclic aminoethyl substituent at the 1-position. Compounds which possess these features have nanomolar potency in a central cannabinoid receptor binding assay and corresponding activity in functional assays.

Win 54461 **(31)**, a compound which has an anisoyl group at the 3-position and a bromo substituent at the 6-position of the indole, is a cannabinoid antagonist. It remains to be seen whether the structural features which contribute to greater agonist potency can be used to synthesize more potent antagonists or merely convert the antagonists into agonists.

We have discovered two different antinociceptive mechanisms for the AAIs: first identifying them as

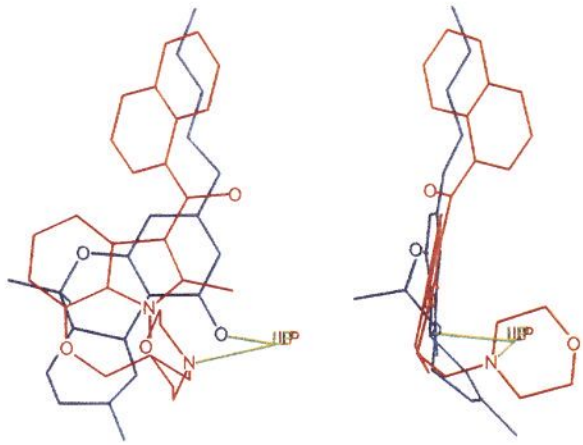


Figure 4.

cyclooxygenase inhibitors and then identifying a second mode of activity subsequently characterized as cannabinoid. In this respect we appear to have mimicked the relevant endogenous systems: arachidonic acid has long been known as the substrate for cyclooxygenase, and anandamide, a (hydroxyethyl)amide of arachidonic acid, has recently been identified as an endogenous cannabinoid.

AAIs should prove useful in the further characterization of the cannabinoid receptor. The recent identification of a peripheral cannabinoid receptor opens up new therapeutic endpoints for such compounds and might help refine our understanding of the SAR. Additionally, the presence of an endogenous cannabinoid ligand begs the question of its function and whether imbalances in ligand or receptor concentration are associated with mood or a disease state. Compounds such as the aminoalkylindoles which have appreciable water solubility as salts and are less lipophilic than classical cannabinoids should prove useful at better characterizing the function of these receptors and may provide templates for future drugs. Additionally, if the antagonists identified can be improved they will contribute greatly to our understanding of the receptors and may in themselves be drug candidates.

Experimental Section

Proton (^{1}H) NMR spectra were measured at 270 MHz on a JEOL GSX-270 instrument, at 300 MHz on a General Electric QE-300 instrument, at 200 MHz on a Bruker AC-200 instrument, or at 60 MHz on a Varian T60 instrument using $CDCl_3$ or DMSO-d_6 as solvent. Carbon (^{13}C) NMR spectra were measured at 67.8 MHz using the JEOL GSX instrument or at 75.5 MHz using the QE-300. IR spectra were measured on a Nicolet 20 SX, a BioRad FTS-45 FT IR, or a Perkin-Elmer Model 467 instrument. Optical rotations were obtained on an Autopol III polarimeter (Rudolph Research). Mass spectra were measured on a JEOL JMS-01SC instrument. Elemental analyses were performed by Galbraith Laboratories of Knoxville, TN, Quantitative Technologies, Inc. of Bound Brook, NJ, or Oneida Research Services of Whiteboro, NY. Melting points are uncorrected. All structures were consistent with NMR, IR, MS, and TLC.

Analytical thin layer chromatography (TLC) was performed on E. Merck 5 × 20 Kieselgel 60 F-254 plates. Flash chromatography was performed with Kieselgel 60 (230−400 mesh).

Modeling experiments were run using SYBYL Version 5.10 (Tripos Associates, St. Louis, MO).

Benzofuran-5-carboxylic Acid. A solution of methyl 4-hydroxy-3-(2-propenyl)benzoate[40] (75 g, 391 mol) in 750 mL of MeOH was cooled to −60 °C and ozonolyzed until no starting material remained (3.5 h). Dimethyl sulfide (39 mL) was added and the reaction mixture warmed to 30 °C for 10 min. It was then concentrated *in vacuo*, taken up in ether and washed with 10% Na_2CO_3, H_2O, and brine. The organic layer was dried over $MgSO_4$ and concentrated to a white solid which was reprecipitated from ether−hexane to provide 57.6 g (76%) of methyl 2-hydroxy-2,3-dihydrobenzofuran-5-carboxylate as an amorphous solid. This hemiacetal was treated with 250 mL of 85% H_3PO_4 and heated at 50 °C. After 5 min, the product precipitated out. The reaction was diluted with 300 mL of H_2O and filtered to give 49 g (95%) of methyl benzofuran-5-carboxylate as an off-white solid: mp 69−72 °C;[41] ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.34 (d, J = 1 Hz, 1 H), 8.02 (dd, J = 8, 1 Hz, 1 H), 7.70 (d, J = 1 Hz, 1 H), 7.53 (d, J = 8 Hz, 1 H), 6.83 (d, J = 1 Hz, 1 H), 3.92 (s, 3 H).

A solution of this ester (40 g, 227 mmol) in 250 mL of EtOH was treated with 85% KOH (15.2 g, 260 mmol). The reaction mixture was heated at reflux for 2 h and then poured onto 600 mL of ice−H_2O. It was then acidified with 6 N HCl and the resulting solid collected by filtration to give, after drying, 34.7 g (94%) of benzofuran-5-carboxylic acid: mp 189-191 °C (lit.[42] mp 190−191 °C); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.34 (d, J = 1 Hz, 1 H), 8.02 (dd, J = 8, 1 Hz, 1 H), 7.70 (d, J = 1 Hz, 1 H), 7.52 (d, J = 8 Hz, 1 H), 6.87 (d, J = 1 Hz, 1 H).

Benzofuran-7-carboxylic Acid. Methyl 2-(2-propenyloxy)benzoate (58 g, 302 mmol) was heated at 230 °C for 2.5 h to provide crude methyl 2-hydroxy-3-(2-propenyl)benzoate as an oil (58 g).[43] This material was ozonolyzed as above to give crude aldehyde (59 g). The aldehyde (19 g, 97 mmol) was treated with 85% H_3PO_4 at room temperature to provide after silica gel chromatography (10% EtOAc−hexane) 3.0 g (18% overall) of methyl benzofuran-7-carboxylate[44] which was hydrolyzed as above to give 2.5 g (91%) of benzofuran-7-carboxylic acid: mp 158−159 °C (lit.[42,44] mp 162−163 °C); ^{1}H NMR (60 MHz, $CDCl_3$) δ 11.9 (s, 1 H), 7.6−8.0 (m, 2 H), 7.6 (d, 1 H), 7.0−7.3 (m, 1 H), 7.15 (d, 1 H).

Benzofuran-4- and -6-carboxylic Acids. Methyl 3-(2-propenyloxy)benzoate (25.4 g, 132 mmol) was heated at 230 °C for 1 h after which time no starting material remained. The residue was taken up in Et_2O and extracted three times with 5% KOH. The alkaline layer was allowed to stand for 30 min to allow hydrolysis of the less hindered isomer, then acidified with 6 N HCl, and extracted twice with Et_2O. The Et_2O phase was extracted three times with 10% K_2CO_3 and then concentrated to give 10.4 g (41%) of methyl 3-hydroxy-2-(2-propenyl)benzoate: mp 54−55 °C (hexane) (lit.[29c] mp 72−74 °C). The basic extracts were treated with 6 N HCl, and the resulting precipitate was filtered to give 6.4 g (27%) of 3-hydroxy-4-(2-propenyl)benzoic acid:[45] mp 145−147 °C (H_2O).

Methyl 3-hydroxy-2-(2-propenyl)benzoate (9.5 g, 49.5 mmol) in 50 mL of MeOH was cooled to −70 °C and ozonolyzed until no starting material remained (30 min). Dimethyl sulfide (15 mL) was added and the reaction mixture allowed to gradually warm to room temperature and stand overnight. It was then concentrated *in vacuo* and taken up in Et_2O. The Et_2O layer was washed twice with H_2O and once with brine and then concentrated to 10.7 g of crude methyl 2-hydroxy-2,3-dihydrobenzofuran-4-carboxylate. This material was taken up in 50 mL of 85% H_3PO_4 initially at room temperature for 10 min and then at 100 °C for 15 min. The reaction mixture was allowed to cool, was then diluted with 100 mL of H_2O, and was extracted three times with Et_2O. The Et_2O phase was washed three times with H_2O and twice with 10% K_2CO_3. The basic phase was washed with Et_2O and the combined Et_2O phase washed with brine, dried ($MgSO_4$), and concentrated to 7.8 g of a yellow-green oil which was chromatographed on silica to provide 5.8 g (67%) of methyl benzofuran-4-carboxylate.[46] This material was treated with 10 mL of 35% KOH in 25 mL of MeOH and heated at reflux for 1 h, concentrated *in vacuo*, diluted with H_2O, and extracted with Et_2O. The aqueous phase was acidified with 6 N HCl and then cooled to give a precipitate which was collected by filtration with H_2O washing, which after drying gave 5.2 g (97%) of benzofuran-4-carboxylic acid: mp 200−202 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.07

(bs, 1 H), 8.10 (d, J = 2.0 Hz, 1 H), 7.85 (d, J = 7.3 Hz, 1 H), 7.83 (d, J = 7.9 Hz, **1** H), 7.38 (t, J = 7.9 Hz, 1 H), 7.29 (s, 1 H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 167.52, 155.09, 148.06, 127.86, 125.64, 124.27, 123.79, 116.19, 107.82; HRMS calcd for $C_9H_6O_3$ 163.0395, found **163**.0397.

3-Hydroxy-4-(2-propenyl)benzoic acid (2.7 g, 15 mmol) was mixed with $SOCl_2$ (25 mL, 343 mmol) and 2 drops of DMF for 3 h. The reaction mixture was then concentrated *in vacuo* to a dark oil which was cooled on an ice bath. To this oil was slowly added 50 mL of MeOH. The reaction mixture was stirred in the cold for 30 min and then concentrated *in vacuo* to a solid which was taken up in Et_2O and washed with 10% K_2CO_3, H_2O, and then brine. The resulting solution was treated with DARCO and $MgSO_4$ and filtered. The filtrate was concentrated to 2.9 g (100%) of methyl 3-hydroxy-4-(2-propenyl)benzoate as a white solid.[45] This solid was dissolved in 25 mL of MeOH and cooled to −70 °C. It was then ozonolyzed until starting material was consumed (15 min). Dimethyl sulfide was added and the reaction mixture allowed to gradually warm to room temperature and stir overnight. The reaction mixture was then concentrated *in vacuo* and taken up in Et_2O. The Et_2O phase was washed twice with H_2O and once with brine and concentrated to 3.2 g of crude methyl 2-hydroxy-2,3-dihydrobenzofuran-6-carboxylate. This material was treated with 10 mL of 85% H_3PO_4 initially at room temperature and then for several minutes at 100 °C. After cooling, the reaction mixture was diluted with 25 mL of H_2O and extracted with Et_2O. The Et_2O phase was washed twice with H_2O, once with 10% K_2CO_3, and then an additional three times with H_2O and once with brine. The organic phase was concentrated to 2.1 g (80% overall) of methyl benzofuran-6-carboxylate as a low-melting solid. This ester (4.8 g, 27 mmol) in 50 mL of MeOH and 20 mL of H_2O was treated with 20 mL of 35% KOH at 100 °C. The MeOH was removed *in vacuo* and the resulting aqueous solution acidified with 6 N HCl. The solid that precipitated was collected by filtration, washed with H_2O, and dried to give 3.8 g (87%) of benzofuran-6-carboxylic acid as an off-white solid: mp 180−186 °C (lit.[42] mp 184−185 °C); ^{1}H NMR (60 MHz, $CDCl_3$−DMSO-d_6) δ 9.7 (bs, 1 H), 8.05 (s, 1 H), 7.25−7.90 (m, 3 H), 6.75 (bs, 1 H).

(6-Benzofuryl)[1-[2-(4-morpholinyl)ethyl]-1*H*-indol-3-yl]methanone (134). A mixture of benzofuran-6-carboxylic acid (1.6 g, 10 mmol), $SOCl_2$ (25 mL, 343 mmol), and 1 drop of DMF was stirred at room temperature for 2.5 h and then concentrated *in vacuo*. Toluene was added and the solution reconcentrated to remove residual $SOCl_2$. The resulting solid acid chloride was taken up in 50 mL of CH_2Cl_2. 1-[2-(4-Morpholinyl)ethyl]-1*H*-indole (**9**, R = H) (2.5 g, 10.7 mmol) was added and the solution cooled to −78 °C. A solution of 1.8 M $EtAlCl_2$ in toluene (12 mL, 22 mmol) was added dropwise. A precipitate formed as the reaction was allowed to gradually warm to room temperature overnight. The reaction was partitioned between cold H_2O and EtOAc and the aqueous layer extracted with two additional portions of EtOAc. The combined EtOAc phase was washed with H_2O, 10% K_2CO_3, and brine, dried over $MgSO_4$, and concentrated to a solid. This material was flashed through a silica gel column using EtOAc to remove baseline material and provide 2.5 g (67%) of (**134**) as a white solid: mp 125−126 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.43 (m, 1 H), 8.02 (s, 1 H), 7.67−7.82 (m, 4 H), 7.37 (m, 3 H), 6.85 (d, J = 1 Hz, 1 H), 4.25 (t, J = 7 Hz, 2 H), 3.70 (m, 4 H), 2.77 (t, J = 7 Hz, 2 H), 2.49 (m, 4 H). Anal. ($C_{23}H_{22}N_2O_3$) C, H, N.

2-Chloro-1-[2-(4-morpholinyl)ethyl]-1*H*-indole (14). 1,3-Dihydro-1-[2-(4-morpholinyl)ethyl]-2*H*-indol-2-one (**13**)[47,48] (34 g, 121 mmol) in $POCl_3$ (100 mL, 1.07 mol) was heated on a steam bath for 8 h to give a clear dark solution. This solution was concentrated *in vacuo* and then added gradually (caution)[50] to a stirred mixture of 10% K_2CO_3, ice, and Et_2O until the residual $POCl_3$ had decomposed and the product migrated to the organic layer. The layers were separated and the aqueous layer was extracted with an additional portion of Et_2O. The combined Et_2O phase was washed twice with brine, dried over $MgSO_4$ and concentrated. The residue was dissolved in 50 mL of iPrOH and cooled on a ice bath as a solution of ethereal HCl was added. The resulting precipitate was collected by filtration with Et_2O washing to provide, after drying, 30 g (83%) of **14** hydrochloride as a tan powder: mp 200−201 °C; ^{1}H NMR (60 MHz, $CDCl_3$−DMSO-d_6) δ 6.8−7.7 (m, 4 H), 6.35 (s, 1 H), 4.6−5.0 (m, 2 H), 3.8−4.2 (m, 4 H), 2.9−3.6 (m, 7 H).

10,15-Dihydro-5,10,15-tris[2-(4-morpholinyl)ethyl]-1*H*-diindolo[3,2-*a*:3′,2′-*c*]carbazole (17). If conditions were modified slightly a cyclic trimer was obtained instead of the 2-chloro derivative. Thus if a mixture of 1,3-dihydro-1-[2-(4-morpholinyl)ethyl]-2*H*-indol-2-one (**13**) hydrochloride (6.5 g, 23 mmol) and $POCl_3$ (25 mL, 268 mmol) was heated in an open flask on a steam bath overnight, a dark residue remained which was stirred in H_2O (caution)[49] until it dissolved. It was then treated with DARCO and filtered. The filtrate was slowly basified with solid K_2CO_3 and the resulting precipitate washed with 10% K_2CO_3 and H_2O and then taken up in $CHCl_3$. This solution was washed with H_2O, dried over $MgSO_4$, and concentrated to give after recrystallization from $CHCl_3$−EtOH 4.0 g (72%) of white needles of trimer **17** as a 3:1 solvate with $CHCl_3$: mp 190−191 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.39 (d, J = 8 Hz, 3 H), 7.59 (d, J = 8 Hz, 3 H), 7.41 (t, J = 8 Hz, 3 H), 7.30 (t, J = 8 Hz, 3 H), 5.00 (t, J = 7 Hz, 6 H), 3.54 (t, J = 6 Hz, 12 H), 2.78 (t, J = 7 Hz, 6 H), 2.37 (t, J = 6 Hz, 12 H). Anal. ($C_{42}H_{48}N_6O_3 \cdot {}^1/_3CHCl_3$) C, H, N, Cl.

(4-Methoxyphenyl)[2-chloro-1-[2-(4-morpholinyl)ethyl]-1*H*-indol-3-yl]methanone Hydrochloride (59). A suspension of 2-chloro-1-[2-(4-morpholinyl)ethyl]-1*H*-indole (**14**) hydrochloride (40 g, 133 mmol) and *p*-anisoyl chloride (30 g, 177 mmol) in 500 mL of CH_2Cl_2 was cooled in an ice bath, and 1.8 M $EtAlCl_2$ in toluene (160 mL, 288 mmol) was added over $^3/_4$ h. A solution formed, and then an orange-brown solid precipitated. After 24 h the reaction mixture was poured onto ice and H_2O, and the layers were separated. The aqueous layer was washed three times with CH_2Cl_2 and the combined organic phase dried ($MgSO_4$) and concentrated to an oil which was taken up in 50 mL of iPrOH and treated with ethereal HCl. The resulting solid was collected by filtration and washed with iPrOH and then Et_2O, to give, after drying, 49 g (85%) yellow solid. A portion was recrystallized from EtOH to give, after drying, the acylated product **59** as yellow crystals: mp 170−173 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 14.03 (bs, 1 H), 7.89 (d, J = 8 Hz, 1 H), 7.82 (d, J = 9 Hz, 2 H), 7.52 (d, J = 8 Hz, 1 H), 7.38 (t, J = 8 Hz, 1 H), 7.21 (t, J = 8 Hz, 1 H), 6.97 (d, J = 9 Hz, 2 H), 5.02 (t, J = 7 Hz, 2 H), 4.32 (m, 2 H), 4.02 (m, 2 H), 3.93 (s, 3 H), 3.55 (m, 2 H), 3.33 (m, 2H), 3.02 (m, 2 H). Anal. ($C_{22}H_{23}ClN_2O_3 \cdot HCl$) C, H, N. Treatment with NH_4OH in MeOH provided the free base, mp 117 °C.

3-(4-Methoxybenzoyl)-1-[2-(4-morpholinyl)ethyl]-1*H*-indole-2-carbonitrile (60). A solution of the 2-chloro analog **59** (18.5 g, 42 mmol) and NaCN (23.5 g, 480 mmol) in 200 mL of DMSO was heated at 70 °C for 12 h. The warm reaction mixture was poured onto a mixture of ice, H_2O, and EtOAc. The phases were separated, and the aqueous phase was extracted with two additional portions EtOAc. The combined EtOAc phase was washed three times with brine, dried over $MgSO_4$, and concentrated to a yellow solid which was recrystallized from EtOH to provide 13 g (80%) of 2-cyano compound **60** as a yellow solid: mp 123−124 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.89 (d, J = 9 Hz, 2 H), 7.44 (m, 2 H), 7.29 (m, 2 H), 6.98 (d, J = 9 Hz, 2 H), 4.47 (t, J = 7 Hz, 2 H), 3.91 (s, 3 H), 3.69 (m, 2 H), 2.78 (t, J = 7 Hz, 2 H), 2.52 (m, 2 H); IR (KBr) 2319, 1625 cm^{-1}. Anal. ($C_{23}H_{23}N_3O_3$) C, H, N.

(4-Methoxyphenyl)[6-bromo-2-methyl-1-[2-(4-morpholinyl)ethyl]-1*H*-indol-3-yl]methanone (31). (4-Methoxyphenyl)[2-methyl-1-[2-(4-morpholinyl)ethyl]-1*H*-indol-3-yl]methanone (**21**) hydrobromide (23.0 g, 50 mmol) in 650 mL of CH_2Cl_2 was treated with NBS (20.1 g, 113 mmol). The reaction turned orange. It was then heated to reflux and placed under a high-intensity lamp. Gas evolution was observed. The reaction mixture turned brown, and after 2 h TLC (40% acetone−toluene) showed little or no remaining starting material. Aqueous $NaHSO_3$ was added and the resulting mixture extracted with CH_2Cl_2 and $CHCl_3$ (emulsion). The organic phase was dried ($MgSO_4$), filtered, and concentrated to an oil that was flash chromatographed on silica gel using 10% acetone−toluene to 15% acetone−toluene. Minor components

were obtained both prior to and after product. Fractions containing product contaminated with a higher R_f yellow spot were taken up in EtOAc, and the impurity was removed by filtration. The filtrate was combined with pure product fractions, concentrated, and recrystallized from toluene with Et_2O washing to give 8.0 g (35%) of **31**: mp 138.5–140.0 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.77 (d, J = 9 Hz, 2 H), 7.50 (d, J = 1 Hz, 1 H), 7.23 (d, J = 8 Hz, 1 H), 7.17 (dd, J = 8, 1 Hz, 1 H), 6.94 (d, J = 9 Hz, 2 H) 4.23 (t, J = 7 Hz, 2 H), 3.90 (s, 3 H), 3.72 (m, 4 H), 2.71 (t, J = 7 Hz, 2 H), 2.60 (s, 3 H), 2.53 (m, 2 H). Irradiation of the NCH_2 triplet at 4.23 caused a significant NOE of the peak at 7.50 (C_7-H), confirming the placement of the Br at the 6-position; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 191.3, 162.7, 143.8, 136.6, 133.2, 131.5, 126.1, 124.3, 122.2, 115.3, 114.0, 113.4, 112.3, 66.8, 57.4, 55.4, 54.0, 41.4, 12.3. Anal. ($C_{23}H_{25}BrN_2O_3$) C, H, N, Br.

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