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Synthesis and Pharmacology of a Hybrid Cannabinoid

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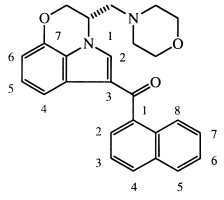
Abstract—A pentacyclic hybrid cannabinoid (**4**) has been synthesized, which combines structural elements of traditional cannabinoids and cannabmimetic indoles. Cannabinoid **4** contains a 1-pentylindole structure fused to the 2,3-positions of the partially reduced hydroxydibenzopyran system of THC. The successful approach to **4** employed 9-benzoyl-5,7-dimethoxy-1,2,3,4-tetrahydrocarbazole (**17**) as the starting material. Dehydrogenation to carbazole **18**, followed by demethylation and condensation with *trans-p*-menthadienol gave *N*-benzoyl hybrid cannabinoid **22**, *N*-alkylation of which afforded target cannabinoid **4**. The hybrid cannabinoid had affinity for the CB_1 receptor approximately equal to that of Δ^8-THC ($K_i = 19.3 \pm 3$ nM), and shows comparable potency in vivo.

Introduction

During the course of a program directed toward the development of nonsteroidal anti-inflammatory drugs, a group at Sterling Winthrop found that a variety of 1-aminoalkylindole derivatives inhibited contractions of the electrically stimulated mouse vas deferens, inhibited adenylate cyclase and interacted with a G-protein coupled receptor in the brain.[1] Subsequent studies demonstrated that these indole derivatives, of which WIN-55,212-2 (**1**) is perhaps the best known example, were in fact interacting with a cannabinoid (CB_1) receptor and demonstrated typical cannabinoid pharmacology in vivo.[2,3] In further studies, the Winthrop group prepared over 100 compounds in the aminoalkyl series and suggested structure–activity relationships (SAR) for this class of cannabinoids.[4,5]



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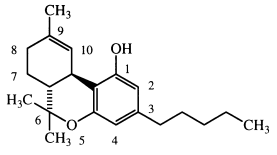

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A pharmacophore for the aminoalkylindoles was developed which included three structural elements: the nitrogen atom of an aminoalkyl side chain, an indole nucleus and a 3-aroyl group appended to the indole.[5] A recent study employed comparative molecular field analysis (CoMFA) to develop three dimensional quantitative SAR for the aminoalkyl indoles.[6] Acting on the assumption that traditional cannabinoids such as Δ^9-THC (**2**) and cannabimimetic indoles related to WIN-55,212-2 (**1**) interact with the cannabinoid receptor at the same site, tentative alignments of these two diverse classes of cannabinoids were proposed.[5,7] One suggested alignment assumed that the phenolic hydroxyl of THC and the morpholino nitrogen of **1** have hydrogen bonding interactions with the same point on the receptor. In this alignment the 3-aroyl substituent of the indole and the C-3 side chain of traditional cannabinoids were considered to overlap. A similar alignment was employed by Razdan's group to design several 4-alkoxy-(aminoalkyl)indole derivatives, some of which had cannabimimetic activity in vivo, but none had particularly high affinity for the CB_1 receptor.[8] A modification of this proposed alignment assumed that the ketonic carbonyl of **1** corresponded to the phenolic hydroxyl of THC, and the naphthalene rings corresponded to the lipophilic side chain of the traditional cannabinoids.[7] A very similar alignment was suggested recently by Shim et al. who employed 3-D pharmacophore mapping and CoMFA to develop a unified pharmacophore for cannabimimetic indoles and traditional cannabinoids.[9]

Keywords: cannabinoid; aminoalkylindole; CB_1 receptor; cannabimimetic indoles.
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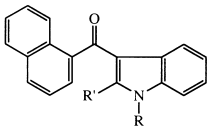
On the basis of modeling studies in 1994, we suggested an alignment in which the carbonyl group of WIN-55,212-2 corresponds to the phenolic hydroxyl of traditional cannabinoids, and C-7 and C-8 of the naphthalene are aligned with C-9 and C-10 of THC (**2**).[10–12] On the basis of the modeling, it was concluded that the aminoalkyl group characteristic of the Winthrop aminoalkylindoles is not necessary for cannabinoid activity. This alignment was then employed as a template for the design and synthesis of a number of 1-alkyl-3-(l-naphthoyl)indoles (**3**), some of which are very potent cannabinoids, both in vitro and in vivo. In particular, 1-butyl through 1-hexyl indole analogues of **3**, either unsubstituted at C-2, or with a 2-methyl group (**3**, R = C_4H_9–C_5H_{11}, R′ = H or CH_3) have affinities for the CB_1 receptor in the range of 10–48 nM. The in vivo potencies of these cannabimimetic indoles are consistent with their receptor affinities.[11]



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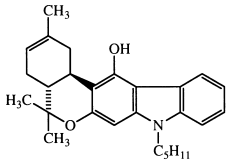

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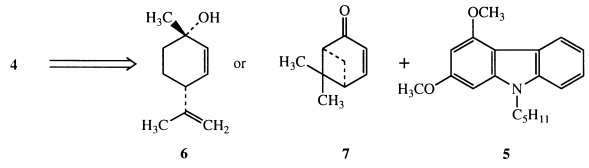
Subsequent experiments using mutant CB_1 receptors suggest that traditional cannabinoids and cannabimimetic indoles bind to different, but partially overlapping, sites on the receptor.[13,14] These mutant receptor experiments, combined with modeling studies have led to the hypothesis that the hydrogen bonding interaction of a lysine on the third transmembrane domain of the CB_1 receptor is important in the binding of traditional cannabinoids, such as THC (**2**), with the receptor, but is not important for the aminoalkylindole WIN-55,212-2 (**1**), and presumably other cannabimimetic indoles.[15,16] However, the direct alignment of indoles and THC which led to the development of a number of potent cannabimimetic indoles derived from **3** implies that there is a possibility that a single pharmacophore for both classes of cannabinoids could be developed.[10–12] In support of this hypothesis, the SAR for indoles **3** indicated a correlation between the nature and length of the *N*-alkyl substituent and cannabinoid activity reminiscent of the effect of side-chain structure upon the activity of THC analogues. In order to test this proposed alignment between cannabimimetic indoles and traditional cannabinoids, and to explore the possibility of a unified pharmacophore for both types of cannabinoids, a hybrid cannabinoid (**4**) was designed. Compound **4** combines the hydroxydibenzopyran ring system of THC with the 1-pentylindole moiety present in the most potent of the cannabimimetic indoles which lack an aminoalkyl group.[10–12]

Results

A retrosynthetic analysis of **4** indicated that the most promising approach would involve a derivative of 2,4-dimethoxycarbazole (**5**) for the indole portion of the target molecule, with an appropriate monoterpene for the alicyclic portion, as outlined in Scheme 1. The synthesis would proceed either via a classical Petrzilka synthesis which entails the acid catalyzed condensation of **5**, or the corresponding bis-phenol with *trans-p*-menthadienol (**6**)[17] or from the reaction of the 3-lithio derivative of **5** with apoverbenone (**7**) followed by subsequent elaboration of the cannabinoid nucleus using methodology developed in our laboratories.[18,19]

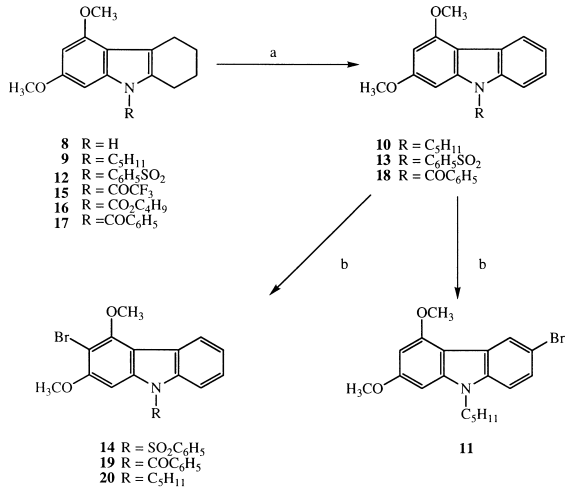
Although a number of syntheses of carbazoles are available, a particularly promising approach appeared to be via dehydrogenation of 5,7-dimethoxy-1,2,3,4-tetrahydrocarbazole (**8**; Scheme 2). Tetrahydrocarbazole **8** has been prepared by cyclization of 4-(4,6-dimethoxyindol-3-yl)-1-butanol;[20] however, the synthesis of **8** in a single step via a Bischler reaction between commercially available 2-chlorocyclohexanone and 3,5-dimethoxyaniline is considerably more concise. Initially the reaction was attempted using conditions developed by Campaigne and Lake for the Bischler reaction (124 °C in refluxing 2-methoxyethanol).[21] Although the starting materials were consumed under these conditions, no recognizable products could be obtained. Assuming that the extremely electron rich aminocyclohexanone intermediate in this synthesis would undergo cyclization under mild conditions, the uncatalyzed reaction of 2-chlorocyclohexanone and 3,5-dimethoxyaniline was carried out in the absence of solvent at 42 °C to provide tetrahydrocarbazole **8** in modest, but acceptable (51%) yield. As reported by earlier workers, this compound is quite sensitive to air oxidation.[20]

Dehydrogenation of **8** using a palladium catalyst proceeded in very poor yield; however, *N*-alkylation of **8**



6 **7** **5**

Scheme 1.



8 R = H
9 R = C_5H_{11}
12 R = $C_6H_5SO_2$
15 R = $COCF_3$
16 R = $CO_2C_4H_9$
17 R = COC_6H_5

10 R = C_5H_{11}
13 R = $C_6H_5SO_2$
18 R = COC_6H_5

14 R = $SO_2C_6H_5$
19 R = COC_6H_5
20 R = C_5H_{11}

11

Scheme 2. (a) Chloranil, benzene, 80 °C; (b) Br_2, HOAc, 25 °C.

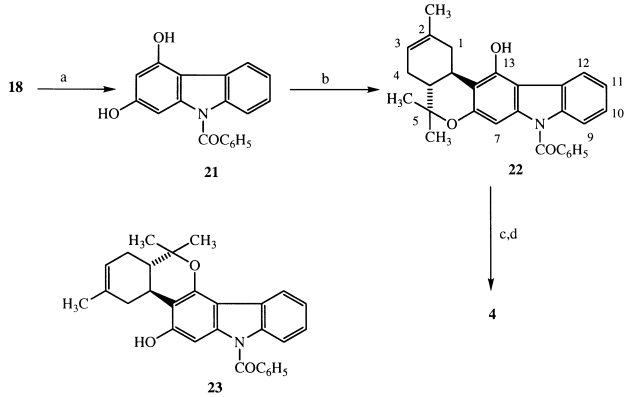
employing 1-bromopentane provided *N*-pentyl derivative **9** in 80% yield, which was considerably less sensitive than the unalkylated tetrahydrocarbazole (Scheme 2). Dehydrogenation employing chloranil gave carbazole **10** in 72% yield. A number of attempts were made to effect the directed lithiation of **10** employing conditions which we had used previously in the lithiation of other substituted resorcinol dimethyl ethers.[18,19] Not only was **10** inert to *n*-butyllithium in ether at reflux, but it also failed to react with *sec*-butyllithium under a variety of conditions, and was inert to *tert*-butyllithium. In an effort to obtain the bis-phenol derived from **10**, a precursor for a Petrzilka synthesis of **4**, the demethylation of carbazole **10** using boron tribromide was attempted; however the starting material was recovered unchanged.

On the basis of the strongly electron donating effects of the methoxy groups, it was expected that bromination of carbazole **10** would occur in the ring containing these two substituents, and that the product would probably be a mixture of 1- and 3-bromo-2,4-dimethoxycarbazoles. The 3-bromo compound would provide the required aryllithium via halogen–metal interconversion. However, reaction of **10** with bromine in acetic acid gave a single substitution product, which on the basis of the ^{1}H NMR spectrum was neither of the expected products. In particular, the characteristic doublets, $J = 1.7$ Hz, at relatively high field (δ 6.31 and 6.43) assigned to H-1 and H-3 in dimethoxycarbazole derivatives **8**–**10** were still present. However, in the bromination product, the rather complex pattern for the other aromatic protons was simplified to a pair of doublets and a doublet of doublets. Based on the coupling constants (see Experimental), this compound was either 6- or 7-bromo-2,4-dimethoxycarbazole. On the basis of the electron donating effect of the nitrogen atom, the structure was tentatively assigned as 6-bromo-2,4-dimethoxycarbazole (**11**), which was confirmed by X-ray crystallography.[22]

It seemed probable that the electron releasing effect of the indole nitrogen, combined with steric effects associated with the tetrasubstituted aromatic ring containing the methoxy groups, led to the exclusive formation of bromination product **11**. To reduce this effect, tetrahydrocarbazole **8** was reacted with sodium hydride, and the derived anion treated with benzenesulfonyl chloride to provide sulfonamide **12** (Scheme 2) in which the electron donating effects of the nitrogen are attenuated. In spite of extensive efforts, acceptable yields of **12** could not be obtained. Although benzenesulfonamide **12** was not a viable intermediate for further synthetic studies, the feasibility of using an amide to modify the electronic effects of the indole nitrogen was explored using this substrate. Dehydrogenation to carbazole **13** proceeded smoothly, and bromination afforded a single monobromination product. It was difficult to assign a structure on the basis of NMR data; however, X-ray crystallography confirmed that bromination had occurred in the desired fashion to afford 3-bromocarbazole **14**.[22] In an effort to obtain acceptable yields of an acyl protected carbazole, tetrahydrocarbazole **8** was treated with trifluoroacetic anhydride in the presence of DMAP which provided a mixture of amide **15** (11%) and a trifluoroacetyl ketone (67%), the result of a Friedel–Crafts acylation reaction. Reaction of **8** with di-*tert*-butyl dicarbonate gave BOC amide **16** in good yield (81%), but **16** could not be dehydrogenated to the corresponding carbazole.

Acceptable yields of an appropriately *N*-substituted carbazole were finally obtained employing a benzoyl group. Treatment of tetrahydrocarbazole **8** with ethylmagnesium bromide, followed by reaction with benzoyl chloride, afforded amide **17** in modest but acceptable (54%) yield. Dehydrogenation with chloranil proceeded smoothly to give carbazole **18** in 88% yield, bromination of which gave 1-benzoyl-3-bromo-2,4-dimethoxycarbazole (**19**) in 95% yield. Conversion of carbazole **19** to 1-pentyl-3-bromo-2,4-dimethoxycarbazole (**20**) was accomplished by basic hydrolysis of the amide (LiOH/THF/MeOH) to 3-bromo-2,4-dimethoxycarbazole, followed by alkylation with 1-bromopentane using LiOH in DMSO (Scheme 3). Attempted halogen–metal interconversion of **20** using butyllithium gave only recovered starting material. It appears probable that the failure of this halogen–metal interconversion and the failure of carbazole (**10**) to undergo directed metalation are the result of the strongly electron donating effects of the indole nitrogen combined with those of the two methoxy groups. These electronic effects apparently increase the basicity of a carbanion at C-3 to the extent that it would not be possible to generate the carbanion using organolithium reagents.

In contrast to the failure of carbazole **10** to provide the corresponding resorcinol analogue, *N*-benzoylcarbazole **18** provided bis-phenol **21** in 92% upon reaction with boron tribromide (Scheme 3). Acid catalysed condensation with *trans*-*p*-menthadienol then afforded hybrid cannabinoid **22** in modest yield (40%). The Petrzilka synthesis of cannabinoids usually employs symmetrical 3-alkyl resorcinols which afford only the desired cannabinoid and an isomer resulting from condensation adjacent to the alkyl group (isocannabinoid).[17] However, resorcinol **21** is unsymmetrical, and can afford not only the desired product (**22**) and an isocannabinoid, but a third isomer in which the initial condensation



Scheme 3. (a) BBr_3/CH_2Cl_2, 25 °C; (b) *trans*-*p*-methadienol/HOTS/benzene, reflux; (c) KOH/DMSO then *n*-$C_5H_{11}Br$, 25 °C; (d) NaSPr/DMF, 120 °C.

occurs between the hydroxyl groups, and ether formation takes place in an alternative fashion to provide isomer **23**.[23]

Although ^{1}H and ^{13}C NMR data could be interpreted in terms of any of these structures, the structure of **22** was initially assigned by difference NOE measurements which indicated no NOE between the aromatic singlet at δ 6.67 and the hydroxyl proton. Both structure **23** and the isocannabinoid have an aromatic proton *ortho* to the phenolic hydroxyl, and would be expected to exhibit an NOE between the aromatic and phenolic protons. However, NOE experiments involving protons bonded to oxygen are not entirely reliable, and the structure was ultimately confirmed by using the paramagnetic relaxation reagent $Cr(acac)_3$.[24] Substrates with hydroxyl groups form hydrogen bonds with $Cr(acac)_3$, and in outer-sphere adducts formed by diamagnetic substrates with paramagnetic $Cr(acac)_3$, the nuclei of the substrates will experience fast paramagnetic relaxation with a relaxation rate proportional to $\mathbf{r}^{-6}$ where **r** is the distance between the observed nuclei and paramagnetic center (Cr^{3+}). The difference between the paramagnetic and diamagnetic relaxation rates ($R_{1m} = 1/T_{1p} - 1/T_{1d}$) reflects the contribution from outer-sphere adducts in which nuclei of the substrate experience fast paramagnetic relaxation. Protons which are proximate to the hydroxyl group of the substrate (and are consequently relatively close to the paramagnetic center of outer-sphere adducts with $Cr(acac)_3$) will have larger paramagnetic relaxation rates R_{1m} compared to protons located further away from the hydroxyl group.

This approach has been employed to differentiate between isomeric structures **22** and **23**. In structure **23**, an aromatic proton is located *ortho* to the hydroxyl group which should exhibit a paramagnetic relaxation rate which is much faster than the other aromatic protons. In structure **22**, H-7 (numbering indicated in Scheme 4) is remote from the hydroxyl group and should exhibit relatively slow paramagnetic relaxation. Proton relaxation times (T_1) for the reaction product were measured in diamagnetic chloroform solution (T_{1d}) and in a paramagnetic solution containing 2 mM $Cr(acac)_3$ (T_{1p}). The paramagnetic rates (R_{1m}) for the aromatic protons were 1.1 Hz (H-7), 0.75 Hz (H-9), 1.1 Hz (H-10), 2.3 Hz (H-11) and 6.2 Hz (H-12). As expected, the paramagnetic relaxation for the hydroxyl proton was the fastest among all the protons ($R_{1m} = 21.0$ Hz). These data are consistent with structure **22**, but are inconsistent with structure **23**.[25]

Conversion of **22** to the target hybrid cannabinoid (**4**) was straightforward, and proceeded via basic hydrolysis of the amide. The hydrolysis product was not isolated, and treatment of the reaction mixture with *n*-pentyl bromide provided the product of both *N*- and *O*-alkylation. Treatment of this product with sodium thiopropoxide gave hybrid cannabinoid **4**.

Standard cannabinoid protocols were employed to evaluate the pharmacology of hybrid cannabinoid **4**, both in vitro and in vivo. The in vitro affinity for the cannabinoid brain (CB_1) receptor was determined by measuring the ability of the ligand. to displace the very potent cannabinoid, [^{3}H] CP-55,940, from its binding site in a membrane preparation.[26] The pharmacology was evaluated in vivo using the mouse model of cannabimimetic activity which measures spontaneous activity (SA), antinociception (as tail flick, TF) and rectal temperature (RT).[27,28] The data for hybrid cannabinoid **4** are summarized in Table 1, along with the previously published data for WIN-55,212-2 (**1**), Δ^9-THC (**2**) and a non-aminoalkyl cannabimimetic indole, JWH-007 (**3**, R = *n*-C_5H_{11}, R′ = CH_3).[10,11] Since **4** is a Δ^8-THC analogue, the pharmacology of Δ^8-THC is also included in Table 1.

The data summarized in Table 1 indicate that hybrid cannabinoid **4** has affinity for the CB_1 receptor similar to that of not only Δ^8-THC but also Δ^9-THC (**2**), WIN-55,212-2 (**1**) and a potent cannabimimetic indole which lacks the 1-aminoalkyl group (**3**, R = *n*-C_5H_{11}, R′ = CH_3). Although the hybrid cannabinoid is comparable in potency to Δ^8- and Δ^9-THC in the mouse model, it is somewhat less potent than WIN-55,212-2 and JWH-007.

The cannabimimetic activity of **4** is consistent with the model described above which we have suggested previously for the structural correlation of traditional cannabinoids and cannabimimetic indoles.[10–12] The molecular modeling program PCModel was employed to effect a comparison of the structures of hybrid cannabinoid (**4**) and Δ^8-THC.[29] This compari-son was carried out by minimizing the structures of **4** and Δ^8-THC, then aligning the aromatic ring of THC with the phenolic ring of **4**. As expected, the tricyclic nucleus of THC aligned almost exactly with the corresponding three rings of **4**. The carbazole nitrogen aligned nearly exactly with C-1′ of THC and the *N*-methylene group corresponded to C-2′ of the traditional cannabinoid. Given the flexibility of the remaining side-chain carbon–carbon bonds of both, many conformations of the side chains of each molecule will align closely. This alignment, combined with the pharmacology of **4** provides support for the alignment of traditional cannabinoids and cannabimimetic indoles which we have suggested previously.[10–12]

However, the work by Song and Bonner[13] and from Kendall's laboratory[14] using mutant CB_1 receptors

Table 1. In vitro and in vivo pharmacology of hybrid cannabinoid (**4**), WIN-55,212-2 (**1**), Δ^9-THC (**2**), and JWH-007 (**3**, R = *n*-C_5H_{11}, R′ = CH_3) and Δ^8-THC

Compound	K_i (nM)	SA (μmol/kg)	ED_{50} TF (μmol/kg)	RT (μmol/kg)
4	19 ± 3	2.7	6.2	3.0
1	24[a]	0.19[a]	1.4[a]	1.5[a]
Δ^8-THC	44 ± 12[b]	3.2[b]	4.5[b]	4.5[b]
2	41 ± 2[b]	3.2[b]	4.5[b]	4.5[b]
3	9.5 ± 4.5[a]	0.70[a]	0.25[a]	4.3[a]

[a]Ref 11.
[b]Martin, B. R.; Compton, D. R.; Semus, S. F.; Lin, S.; Marciniak, G.; Grzybowska, J.; Charalambous, A.; Makriyannis, A. *Pharmacol. Biochem. Behav.* **1993**, *46*, 205.

suggests that aminoalkyl-indoles similar to WIN-55,212-2 (**1**) interact with the receptor at a somewhat different site than traditional cannabinoids such as THC. This suggestion is supported by the modeling studies carried out by Reggio's group which employed docking studies using a three dimensional model of the human CB_1 receptor.[15,16] At present, however, the only indole based cannabinoid which has been evaluated using a mutant CB_1 in which a lysine on helix 3 of the receptor is replaced by amino acids which are incapable of hydrogen bonding to the ligand is WIN-55,212-2.[13,14] There is no assurance that those cannabimimetic indoles which lack an aminoalkyl group interact with the receptor in the same manner as the aminoalkyl indoles. The question of the manner in which various types of cannabinoid ligands interact with the CB_1 receptor cannot be answered with certainty given the present state of knowledge of the structure of this receptor. However, hybrid cannabinoid (**4**) represents a unique probe for the investigation of the interactions of various classes of cannabinoids with the CB_1 receptor.

Experimental

General

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

5,7-Dimethoxy-1,2,3,4-tetrahydrocarbazole (8). A mixture of 1.60 g (10.4 mmol) of 3,5-dimethoxyaniline and 0.66 g (5.2 mmol) of 2-chlorocyclohexanone was heated at 42 °C for 18 h. The resulting solid was taken up in ether; the ether solution was washed with water and brine, dried ($MgSO_4$), and the solvent was removed at reduced pressure. The resulting oil was purified by chromatography (petroleum ether:ether, 3:1) to give 0.60 g (51%) of pure **8** as needles: mp 150–151 °C (lit mp 146–147 °C[20]); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.78–1.86 (m, 4H), 2.63 (t, J = 5.8 Hz, 2H), 2.89 (t, J = 5.7 Hz, 2H), 3.80 (s, 3H), 3.84 (s, 3H), 6.15 (d, J = 1.8 Hz, 1H), 6.37 (d, J = 1.8 Hz, 1H), 7.52 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 23.0, 23.1, 23.6, 55.2, 55.7, 86.9, 91.1, 109.8, 112.5, 130.6, 136.9, 154.5, 156.7; MS (EI) m/z 231 (100), 216 (70), 204 (20), 174 (10). Anal. calcd for $C_{14}H_{17}NO_2$: C, 78.48; H, 7.20; N, 4.36; found: C, 78.43; H, 7.20; N, 4.16.

5,7-Dimethoxy-9-pentyl-1,2,3,4-tetrahydrocarbazole (9). To a solution of 0.57 g (2.48 mmol) of tetrahydrocarbazole **8** in 5 mL of DMSO was added 1.4 g of powdered KOH. The mixture was stirred at ambient temperature for 30 min, and 1.5 mL (12.4 mmol) of 1-bromopentane was added. The mixture was heated at 70 °C for 18 h, diluted with brine and extracted with ethyl acetate. The ethyl acetate solution was washed with brine, dried ($MgSO_4$), and the solvent was removed in vacuo to give a pale-yellow oil. Chromatography (petroleum ether:ethyl acetate, 20:1) gave 0.59 g (80%) of pure **9** as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, J = 6.8 Hz, 3H), 1.26–1.34 (m, 4H), 1.64–1.92 (m, 6H), 2.63 (t, J = 6.0 Hz, 2H), 2.90 (t, J = 5.9 Hz, 2H), 3.85 (s, 6H), 3.88 (t, J = 7.3 Hz, 2H), 6.15 (d, J = 1.8 Hz, 1H), 6.33 (d, J = 1.8 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0, 22.2, 22.4, 23.2, 23.5, 29.1, 29.8, 42.9, 55.2, 55.8, 85.7, 90.4, 108.9, 111.5, 131.9, 137.2, 154.6, 156.3; MS (EI) m/z 301 (100), 286 (50), 244 (15).

2,4-Dimethoxy-9-pentylearbazole (10). A solution of 0.51 g (1.7 mmol) of **9** and 1.00 g of chloranil in 14 mL of benzene was heated at reflux for 4 h, cooled, filtered and the solid residue was washed with ether. The solvent was evaporated in vacuo and the residue was chromatographed (petroleum ether:ethyl acetate, 12:1) to give 0.36 g (72%) of pure carbazole **10**: mp 59–61 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, J = 7.1 Hz, 3H), 1.33–1.35 (m, 4H), 1.81–1.86 (m, 2H), 3.92 (s, 3H), 4.03 (s, 3H), 4.20 (t, J = 7.2 Hz, 2H), 6.32 (d, J = 1.8 Hz, 1H), 6.46 (d, J = 1.8 Hz, 1H), 7.16–7.21 (m, 1H), 7.30–7.37 (m, 2H), 8.21 (d, J = 7.4 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.9, 22.4, 28.5, 29.3, 43.1, 55.4, 55.7, 85.3, 90.3, 106.1, 107.8, 119.0, 121.9, 122.4, 123.3, 139.6, 142.4, 156.7, 160. 1; MS (EI) m/z 297 (100), 240 (93), 182 (8), 120 (6). Anal. calcd for $C_{19}H_{23}NO_2$: C, 76.74; H, 7.80; N, 4.71; found: C, 76.84; H, 7.87; N, 4.74.

6-Bromo-2,4-dimethoxy-9-pentylearbazole (11). To a solution of 0.15 g (0.5 mmol) of carbazole **10** in 1 mL, of acetic acid was added dropwise a solution of 0.025 mL, of bromine in 0.8 mL, of acetic acid. The reaction was stirred at ambient temperature for 3 h, poured into water and extracted with ether. The extracts were washed with saturated aqueous $NaHCO_3$, 5% aqueous NaOH, and brine, dried ($MgSO_4$) and the solvent was removed at reduced pressure. The residue was purified by chromatography (petroleum ether:ethyl acetate, 24:1) to give 0.085 g (43%) of **11** as colorless crystals: mp, 108–110 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, J = 6.6 Hz, 3H), 1.30–1.35 (m, 4H), 1.78–1.83 (m, 2H), 3.93 (s, 3H), 4.02 (s, 3H), 4.16 (t, J = 7.2 Hz, 2H), 6.31 (d, J = 1.7 Hz, 1H), 6.43 (d, J = 1.7 Hz, 1H), 7.16 (d, J = 8.4 Hz, 1H), 7.40 (dd, J = 8.5 Hz, J = 1.9 Hz, 1H), 8.31 (d, J = 1.9 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.9, 22.4, 28.5, 29.3, 43.2, 55.4, 55.7, 85.3, 90.6, 105.4, 109.2, 111.9, 124.1, 124.4, 125.8, 138.3, 142.8, 156.8, 160.7; MS (EI) m/z 377 (95), 375 (100), 320 (99), 260 (10), 239 (10), 181 (15). Anal. calcd for $C_{19}H_{22}NO_2Br$: C, 60.65; H, 5.89; N, 3.72; found: C, 60.38; H, 5.75; N, 3.63.

5,7-Dimethoxy-9-benzenesuifonyl-1,2,3,4-tetrahydrocarbazole (12). A solution of 0.44 g (1.93 mmol) of tetrahydrocarbazole **8** in 5 mL of dry DMSO was added dropwise at 0 °C to 0.064 g of NaH. The mixture was stirred at 0 °C for 0.5 h, and 0.4 mL, of benzenesulfonyl chloride was added. The reaction mixture was allowed to warm to ambient temperature and stirred for 18 h,

poured into water and extracted with ethyl acetate. The extracts were washed with brine, dried ($MgSO_4$), and the solvent was removed at reduced pressure. The crude product was purified by chromatography (petroleum ether:ethyl acetate, 9:1) to give 0.063 g (9%) of **12**: mp 138–139 °C; ^{1}H NMR (300 MHz, $CDC1_3$) δ 1.66–1.82 (m, 4H), 2.77 (t, J = 6.0 Hz, 2H), 2.89–2.93 (m, 2H), 3.78 (s, 3H), 3.86 (s, 3H), 6.28 (d, J = 1.9 Hz, 1 H), 7.34–7.41 (m, 3H), 7.46–7.52 (m 1), 7.18 (dd, J = 7.5, 1.6 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.4, 23.0, 23.5, 24.8, 55.2, 55.8, 91.2, 94.8, 114.1, 118.6, 126.1, 129.1, 131.9, 133.3, 137.9, 139.2, 154.1, 158.2; MS (EI) m/z 371 (25), 230 (100), 215 (15), 172 (8).

2,4-Dimethoxy-9-benzenesulfonylearbazole (13). The dehydrogenation was carried out as described above for the preparation of **10**, however the reaction was carried out for 72 h. From 0.62 g (1.67 mmol) of tetrahydrocarbazole **12** there was obtained 0.47 g (77%) of pure **13** after chromatography (petroleum ether:ethyl acetate, 9:l): mp 176–178 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.94 (s, 6H), 6.43 (s, 1H), 7.24–7.44 (m, 5H), 7.51 (d, J = 1.3 Hz, 1H), 7.79 (d, J = 7.5 Hz, 2H), 8.07 (d, J = 7.2 Hz, 1H), 8.24 (d, J = 7.6 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 55.5, 55.9, 91.6, 95.1, 109.5, 114.4, 122.0, 124.0, 125.1, 125.9, 126.4, 129.0, 133.7, 137.5, 137.9, 140.4, 156.0, 160.8; MS (EI) m/z 367 (50), 226 (100), 183 (15), 140 (16). Anal. calcd for $C_{20}H_{17}SO_4$: C, 65.38; H, 4.66; N, 3.81; found: C, 65.36; H, 4.64; N, 3.76.

3-Bromo-2,4-dimethoxy-9-benzenesulfonylearbazole (14). The bromination was carried out as described above for the preparation of **11**. From 0.47 g (1.3 mmol) of carbazole **13** there was obtained 0.30 g (95%) of pure **14** as a colorless solid after chromatography (petroleum ether:ethyl acetate, 92:8): mp 212–213 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 3 3.98 (s, 3H), 4.07 (s, 3H), 7.33–7.52 (m, 5H), 7.77–7.80 (m, 3H), 8.03 (d, J = 7.8 Hz, 1H), 8.27 (d, J = 8.1 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 57.0, 60.4, 92.2, 95.2, 103.2, 114.4, 114.8, 121.9, 124.5, 124.6, 126.4, 129.2, 134.1, 137.6, 137.8, 139.2, 153.0, 156.5; MS (EI) m/z 447 (80), 445 (80), 306 (100), 263 (12), 246 (10), 167 (10).

5,7-Dimethoxy-9-trifluoroacetyl-1,2,3,4-tetrahydrocarbazole (15) and 5,7-dimethoxy-l-trifluoroacetyl-1,2,3,4-tetrahydrocarbazole. To a solution of 0.25 g (1.08 mmol) of tetrhaydrocarbazole **8** and 0.0066 g of DMAP in a mixture of 2 mL of acetonitrile and 1.5 mL of CH_2Cl_2 at ambient temperature was added dropwise 0.16 mL (1.13 mmol) of trifluoroacetic anhydride. The reaction mixture was stirred for 8 h, diluted with ethyl acetate, washed with water and brine, dried ($MgSO_4$) and the solvent removed at reduced pressure. Chromatography (petroleum ether:ethyl acetate, 85:15) provided 0.037 g (11%) of amide as pale-yellow crystals: mp 78–80 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.78–1.80 (m, 4H), 2.82–2.85 (m, 4H), 3.84 (s, 6H), 6.37 (d, J = 1.9 Hz, 1H), 7.29 (d, J = 1.9 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCL_3$) δ 22.0, 23.2, 23.8, 24.5, 55.3, 55.7, 92.7, 96.0, 114.1, 117.4, 121.3, 138.1, 154.2, 155.9, 159.0; MS (M) m/z 327 (100), 312 (12), 284 (10), 230 (60). Further elution with the same solvent pair gave 0.24 g (67%) of 5,7-dimethoxy-l-trifluoroacetyl-1,2,3,4-tetrahydrocarbazole as pale-brown needles: mp 156–157 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.78–1.87 (m, 4H), 2.67 (t, J = 6.0 Hz, 2H), 2.82 (t, J = 6.0 Hz, 2H), 3.95 (s, 3H), 3.98 (s, 3H), 6.09 (s, 1H), 9.98 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.7, 22.8, 22.9, 23.3, 55.5, 56.5, 86.8, 100.6, 110.6, 112.5, 119.5, 132.1, 138.1, 161.4, 161.9; MS (EI) m/z 327 (100), 298 (15), 25 8 (80), 200 (12).

5,7-Dimethoxy-9-*tert*-butoxycarbonyl-1,2,3,4-tetrahydrocarbazole (16). To a solution of 0.25 g (1.08 mmol) of tetrahydrocarbazole **8** and 0.0066 g of DMAP in a mixture of 2 mL of acetonitrile and 1.5 mL of CH_2Cl_2 at ambient temperature was added 0.25 g (1.20 mmol) of di-*tert*-butyl dicarbonate. The reaction mixture was stirred at ambient temperature for 8 h, diluted with ethyl acetate, washed with water and brine, dried ($MgSO_4$) and the solvent was removed at reduced pressure. The residue was chromatographed (petroleum ether:ethyl acetate, 85:15) to give 0.30 g (81%) of product as a pale-yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.57 (s, 9H), 1.64–1.81 (m, 4H), 2.84–2.91 (m, 4H), 3.82 (s, 3H), 3.84 (s, 3H), 6.29 (d, J = 1.8 Hz, 1H), 7.39 (d, J = 1.9 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.6, 23.4, 23.6, 55.2, 55.6, 82.9, 92.2, 94.1, 113.4, 116.4, 132.0, 137.4, 150.8, 153.9, 157.8; MS (EI) m/z 231 (100), 217 (80), 188 (30), 145 (10).

9-Benzoyl-5,7-dimethoxy-1,2,3,4-tetrahydrocarbazole (17). To a solution of 1.05 g (4.5 mmol) of 2,4-dimethoxy-5,6,7,8-tetrahydrocarbazole **8** in 50 mL of ether at ambient temperature was added dropwise 1.67 mL of 3.0 M ethylinagnesium bromide. The mixture was stirred for 0.5 h and 0.9 mL of benzoyl chloride was added dropwise. Stirring was continued for 8 h and the reaction mixture was poured into water and extracted with ether. The ether extracts were washed with brine, dried ($MgSO_4$), and the solvent was removed in vacuo. The crude product was purified by chromatography (petroleum ether:ether, 3:1) to give 0.84 g (54%) of **17** as yellow needles: mp 125–127 °C; ^{1}H NMR (3 00 MHz, $CDCl_3$) δ 1.66–1.78 (m, 4H), 2.40 (t, J = 6.0 Hz, 2H), 2.88 (t, J = 6.0 Hz, 2H), 3.63 (s, 3H), 3.84 (s, 3H), 6.27 (d, J = 1.8 Hz, 1H), 6.59 (d, J = 1.9 Hz, 1H), 7.47 (t, J = 7.2 Hz, 2H), 7.55–7.60 (m, 1H), 7.63–7.69 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.6, 23.3, 23.5, 26.4, 55.3, 55.4, 91.8, 94.4, 113.7, 117.6, 128.5, 129.4, 130.2, 132.2, 136.2, 138.2, 154.1, 157.8, 169.6; MS (EI) m/z 335 (100), 230 (70), 216 (12), 172 (6). Anal. calcd for $C_{21}H_{21}NO_3$: C, 75.20; H, 6.31; N, 4.18; found: C, 75.02; H, 6.34; N, 4.14.

9-Benzoyl-2,4-dimethoxycarbazole (18). The dehydrogenation was effected as described above for the preparation of **10**, however, the reaction was carried out for 18 h. From 0.19 g (0.59 mmol) of tetrahydrocarbazole there was obtained 0.17 g (88%) of pure **18** after chromatography (petroleum ether:ethyl acetate, 88:12): mp 115–116 °C; ^{1}H NMR (3 00 MHz, $CDCl_3$) δ 3.69 (s, 3 H), 4.01 (s, 3 H), 6.43 (d, J = 1.8 Hz, 1H), 6.76 (1.8, 1H), 7.16 (t, J = 7.2 Hz, 1H), 7.24–7.32 (m, 2H), 7.51 (t, J = 7.2 Hz, 2H), 7.62 (t, J = 7.5 Hz, 1H), 7.70 (t,

$J = 7.5$ Hz, 2H), 8.18 (d, $J = 7.5$ Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 55.5, 55.6, 92.3, 94.8, 109.2, 114.9, 119.8, 122.0, 123.4, 124.4, 125.5, 128.8, 129.1, 132.3, 136.2, 138.2, 141.1, 156.0, 160.2; MS (EI) *m*/*z* 331 (90), 226 (10), 140 (12), 105 (100). Anal. calcd for $C_{21}H_{17}NO_3$: C, 76.12; H, 5.17; N, 4.23; found: C, 76.23; H, 5.07; N, 4.15.

9-Benzoyl-3-bromo-2,4-dimethoxycarbazole (19). The bromination was carried out as described above for the preparation of **11**, however, the reaction was stirred at ambient temperature for 8 h. From 0.24 g (0.72 mmol) of carbazole **18** there was obtained, after chromatography (petroleum ether:ethyl acetate, 92:8), 0.28 g (95%) of **19** as a colorless solid: mp 158–159 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.75 (s, 3H), 4.06 (s, 3H), 6.84 (s, 1H), 7.12–7.33 (m, 2H), 7.35–7.38 (m, 1H), 7.54 (t, $J = 7.3$ Hz, 2H), 7.64–7.73 (m, 3H), 8.14 (d, $J = 7.5$ Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 56.5, 60.4, 96.1, 102.4, 113.8, 115.3, 121.8, 123.9, 124.1, 125.6, 129.0, 129.1, 132.6, 135.4, 138.6, 139.9, 155.9, 169.5; MS (EI) *m*/*z* 4H (17), 409 (18), 105 (100). Anal. calcd for $C_{21}H_{16}NO_3Br$: C, 61.48; H, 3.93; N, 3.41; found: C, 61.38; H, 3.89; N, 3.46.

3-Bromo-2,4-dimethoxycarbazole. A solution of 0.70 g (1.7 mmol) of **19** and 0.70 g of $LiOH{\cdot}H_2O$ in 10 mL of THF and 0.5 mL, of methanol was heated at reflux for 5 h. After cooling the reaction mixture was poured into water and extracted with ethyl acetate. The extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and the solvent was removed at reduced pressure. The residue was chromatographed (petroleum ether:ethyl acetate, 7:3) to give 0.45 g (72%) of bromocarbazole as colorless crystals: mp 155–157 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.92 (s, 3H), 4.08 (s, 3H), 6.71 (s, 1H), 7.23–7.29 (m, 1H), 7.37 (d, $J = 3.9$ Hz, 2H), 8.06 (s, 1H), 8.14 (d, $J = 8.1$ Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 55.7, 60.3, 90.4, 98.2, 110.2, 111.1, 120.3, 121.5, 121.8, 124.9, 139.0, 140.3, 153.2, 155.7; MS (EI) *m*/*z* 307 (100), 305 (95), 264 (25), 262 (25), 211 (35). Anal. calcd for $C_{14}H_{12}BrNO_2$: C, 54.92; H, 3.95; N, 4.57; found: C, 55.10; H, 4.04; N, 4.54.

3-Bromo-2,4-dimethoxy-9-pentylearbazole (20). To a solution of 0.45 g (1.46 mmol) of bromocarbazole in 9 mL of DMSO was added 0.74 g of $LiOH.H_2O$; the mixture was stirred at 65 °C for 0.5 h and 0.19 mL of 1-bromopentane was added dropwise. The reaction mixture was stirred at 65 °C for 18 h, poured into 5% aqueous HCl and extracted with ethyl acetate. The extracts were washed with saturated brine, dried ($MgSO_4$) and the solvent was removed in vacuo. Chromatography (petroleum ether:ethyl acetate, 93:7) provided 0.50 g (95%) of **20** as colorless crystals: mp 159–160 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, $J = 7.9$ Hz, 3H), 1.25–1.43 (m, 4H), 1.82 (t, $J = 6.9$ Hz, 2H), 3.98 (s, 3H), 4.07 (s, 3H), 4.20 (t, $J = 7.4$ Hz, 2H), 6.64 (s, 1H), 7.23 (t, $J = 7.4$ Hz, 1H), 7.33 (d, $J = 7.5$ Hz, 1H), 7.40 (t, $J = 7.3$ Hz, 1H), 8.17 (d, $J = 7.5$ Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.9, 22.4, 28.4, 29.3, 43.1, 56.7, 60.2, 86.5, 97.5, 108.4, 110.6, 119.6, 120.9, 121.8, 124.6, 139.9, 141.2, 153.2, 155.5; MS (EI) *m*/*z* 377 (85), 375 (88), 320 (100), 262 (10), 240 (20). Anal. calcd for $C_{19}H_{22}NO_2Br$: C, 60.65; H, 5.89; N, 3.72; found: C 60.38; H, 5.75; N, 3.63.

(1a*R*,5a*R*)-13-hydroxy-2,5,5-trimethyl-8-benzoyl-indolo-[3,2-*b*]-l,la,4,5a-tetrahydro-5*H*-dibenzo[*h*, *j*]pyran (22). To solution of 0.105 g (0.31 mmol) of 9-benzoyl-2,4-dimethoxycarbazole in 2 mL, of CH_2Cl_2 at 0 °C was added 0.72 mL, of BBr_3 (1.0 M in CH_2Cl_2). The mixture was allowed to warm to ambient temperature, and stirred for 18 h. The reaction mixture was diluted with then, washed with water and brine, dried ($MgSO_4$) and the solvent removed in vacuo, to give 0.095 g (94%) of dihydroxycarbazole **21** which was used in the subsequent step without purification: ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.32 (d, $J = 1.8$ Hz, 1H), 6.37 (d, $J = 1.7$ Hz, 1H), 7.08–7.17 (m, 2H), 7.19–7.27 (m, 1H), 7.55–7.82 (m, 5H), 8.06 (d, $J = 7.4$ Hz, 1H), 9.62 (s, 1H), 10.47 (s, 1H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 94.1, 98.6, 106.3, 114.7, 121.3, 123.6, 123.9, 125.9, 128.7, 129.3, 132.6, 135.6, 137.7, 141.3, 154.1, 158.1, 169.5.

A mixture of 0.14 g (0.46 mmol) of 9-benzoyl-2,4,-dihydroxycarbazole, 0.15 g (1.0 mmol) of *trans*-*p*-menthadienol and 0.020 g of *p*-toluenesulfonic acid in 20 mL of benzene was heated at reflux for 20 h. The solvent was removed in vacuo and the residue was purified by chromatography (petroleum ether:ether, 3:1) to give 0.092 g (40%) of **22** as a yellow gum: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.04 (s, 3H), 1.18–1.26 (m, 1H), 1.35 (s, 3H), 1.72 (s, 3H), 1.82 (d, $J = 7.8$ Hz, 2H), 2.00–2.05 (m, 1H), 2.83–2.85 (m, 1H), 3.06 (dd, $J = 8.1$, 1.9 Hz, 1H), 5.46 (s, 1H), 5.59 (s, 1H), 6.67 (s, 1H), 7.15 (t, $J = 7.5$ Hz, 1H), 7.27 (t, $J = 7.2$ Hz, 1H), 7.36 (d, 8.1H), 7.46 (t, $J = 7.2$ Hz, 2H), 7.61 (t, $J = 7.2$ Hz, 1H), 7.69 (d, $J = 7.2$ Hz, 2H), 8.07 (d, 7.5, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 18.3, 23.4, 27.4, 27.9, 31.5, 36.6, 45.2, 98.1, 108.1, 108.9, 115.2, 120.1, 120.8, 123.4, 124.5, 125.5, 128.8, 129.1, 132.3, 133.9, 135.6, 138.5, 139.7, 150.7, 154.4, 169.7; MS (EI) *m*/*z* 437 (10), 354 (11), 105 (100); HRMS calcd for $C_{29}H_{27}NO_3$: 437.1994, found 437.19941.

(1a*R*,5a*R*)-13-pentoxy-2,5,5-trimethyl-8-pentyl-indolo-[3,2-*b*]-1,1a,4,5a-tetrahydro-5*H*-dibenzo[*h*, *j*]pyran. To a solution of 0.18 g (0.42 mmol) of **22** in 4 mL of DMSO at ambient temperature was added 0.15 g of powdered KOH. After stirring for 0.5 h, 0.4 mL of 1-bromopentane was added and the reaction was stirred for an additional 18 h. The reaction mixture was poured into saturated brine and extracted with ethyl acetate. The extracts were washed with brine, dried ($MgSO_4$) and the solvent removed in vacuo. The crude product was purified by chromatography (petroleum ether:ether, 60:1) to give 0.16 g (80%) of product as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, $J = 6.9$ Hz, 3H), 0.97 (t, $J = 7.2$ Hz, 3H), 1.34 (s, 3H), 1.39–1.59 (m, 12H), 1.75–2.00 (m, 9H), 2.19–2.31 (m, 1H), 2.87–2.89 (m, 1H), 3.38–3.45 (m, 1H), 3.94–4.01 (m, 1H), 4.09–4.15 (m, 3H), 5.45 (s, 1H), 6.62 (s, 1H), 7.17 (t, $J = 6.9$ Hz, 1H), 7.19–7.48 (m, 2H), 8.12 (d, $J = 7.8$ Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.9, 14.0, 18.5, 22.5, 22.7, 23.5, 27.6, 28.1, 28.4, 28.5, 29.4, 30.4, 32.6, 36.9, 43.2, 45.1, 72.7, 76.8, 92.6, 107.8, 110.5, 111.1, 118.8, 119.0,

121.7, 121.8, 123.9, 135.2, 140.3, 141.6, 153.9, 154.4; MS (EI) *m*/*z* 473 (100), 402 (15), 390 (26), 320 (30), 282 (11); HRMS calcd for $C_{32}H_{43}NO_2$: 473.3301, found 473.3294.

(1a*R*,5a*R*)-13-Hydroxy-2,5,5-trimethyl-8-pentyl-indolo-[3,2-*b*]-1,la,4,5a-tetrahydro-5*H*-dibenzo[*h*, *j*]pyran (4). A mixture of 0.38 g of NaH (80% in mineral oil, washed thoroughly with dry ether), 1.14 mL, of 1-propanethiol and 0.42 g (0.89 mmol) of the above *N*-pentyl, *O*-pentyl compound in 4 mL, of DMF was heated at 120 °C for 18 h. After cooling the reaction mixture was poured into 5% aqueous HCl and extracted with ether. The ether extracts were washed with water and brine, dried ($MgSO_4$) and the solvent was removed in vacuo. Chromatography (petroleum ether:ethyl acetate, 4:1) gave 0.21 g (60%) of **4** as an air-sensitive yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, J = 7.2 Hz, 3H), 1.14 (s, 3H), 1.25 (s, 1H), 1.33–1.44 (m, 5H), 1.44 (s, 3H), 1.63–1.95 (m, 3H), 1.72 (s, 3H), 1.95–2.04 (m, 1H), 2.10 (m, 1H), 2.91–2.93 (m, 1H), 3.21 (dd, J = 14.4 Hz, 1H), 4.12 (t, J = 7.5 Hz, 2H), 5.43 (s, 1H), 5.48 (s, 1H), 7.17 (t, J = 8.2 Hz, 1H), 7.28–7.36 (m, 2H), 7.99 (d, J = 7.5 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.8, 18.3, 22.3, 23.4, 27.5, 27.9, 28.3, 29.2, 31.6, 36.8, 43.0, 45.2, 89.8, 104.6, 105.3, 107.9, 118.6, 119.6, 120.0, 121.8, 123.4, 134.3, 140.0, 141.2, 150.7, 151.9; M S (EI) *m*/*z* 403 (100), 360 (4), 335 (18), 320 (77), 282 (17); HRMS calcd for $C_{27}H_{33}NO_2$: 403.2506, Found 403.2511.

Receptor binding assays

[^{3}H]CP-55,940 (K_D = 690 nM) binding to P_2 membranes was conducted as described elsewhere,[30] except whole brain (rather than cortex only) was used. Displacement curves were generated by incubating drugs with 1 nM of [^{3}H]CP-55,940. The assays were performed in triplicate, and the results represent the combined data from three individual experiments.

Pharmacology

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

Spontaneous activity

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

Tail-flick latency

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

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

Core temperature

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

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