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Novel Adamantyl Cannabinoids as CB1 Receptor Probes

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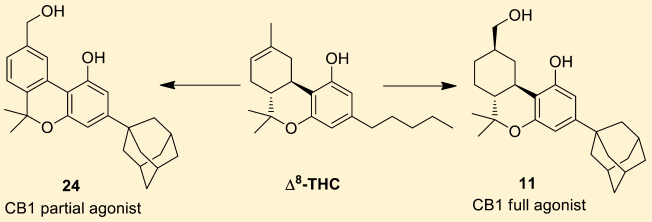
Supporting Information

ABSTRACT: In previous studies, compound **1** (AM411), a 3-(1-adamantyl) analogue of the phytocannabinoid (−)-Δ^8-tetrahydrocannabinol (Δ^8-THC), was shown to have improved affinity and selectivity for the CB1 receptor. In this work, we further explored the role of the 1-adamantyl group at the C-3 position in a series of tricyclic cannabinoid analogues modified at the 9-northern aliphatic hydroxyl (NAH) position. Of these, 9-hydroxymethyl hexahydrocannabinol **11** (AM4054) exhibited high CB1 affinity and full agonist profile. In the cAMP assay, the 9-hydroxymethyl cannabinol analogue **24** (AM4089) had a partial agonist profile, with high affinity and moderate selectivity for rCB1 over hCB2. In vivo results in rat models of hypothermia and analgesia were congruent with in vitro data. Our in vivo data indicate that 3-(1-adamantyl) substitution, within NAH cannabinergics, imparts improved pharmacological profiles when compared to the corresponding, traditionally used 3-dimethylheptyl analogues and identifies **11** and **24** as potentially useful in vivo CB1 cannabinergic probes.



INTRODUCTION

G-protein-coupled receptors (GPCRs) are the most abundant class of central nervous system (CNS) receptors in mammals and are targets of many therapeutic medications.[1] (−)-Δ^9-Tetrahydrocannabinol (Δ^9-THC), the main psychoactive ingredient of cannabis,[2] produces its biochemical and pharmacological effects by interacting with two well-characterized GPCRs, CB1 and CB2. CB1 is localized primarily in brain[3] and in various tissues in the periphery,[4−6] whereas CB2 is primarily associated with the immune system[6,7] and under homeostatic conditions is found to a much lesser extent in CNS.[8,9] The subsequent discovery of the endocannabinoids, represented by arachidonoylethanolamine (anandamide)[10,11] and 2-arachidonoylglycerol (2-AG)[12,13] has led to a better understanding of the physiological and biochemical roles of the endocannabinoid system.[14] During the past decade, numerous ligands with high affinities and subtype selectivities for both receptors encompassing several chemotypes were synthesized and their SAR was explored.[15−18] Δ^9-THC exhibits no receptor subtype CB1/CB2 selectivity. Also, SAR studies with a number of synthetic cannabinoids structurally related to Δ^9-THC have identified some key pharmacophores associated with cannabimimetic activity including (a) a phenolic hydroxyl group (PH) at C-1, (b) a C-3 side chain (SC), (c) 9-OH or 11-OH northern aliphatic hydroxyl group (NAH) functionalities, and (d) a southern aliphatic hydroxyl group (SAH) at C-6 (Figure 1).[17,19]

Modifying the phenolic hydroxyl in cannabinoids into a methoxy group or removing it leads to analogues with severely reduced CB1 affinities. However, such modifications produce only marginal effects on the compounds' affinities for CB2.[20] Additionally, analogues in which the C-1 phenolic OH group is absent have been shown to exhibit CB2 selectivity, and this observation has served as the basis for the synthesis of CB2 selective cannabinoids.[21,22] The C-3 aliphatic side chain is the most studied pharmacophore within the tricyclic cannabinoid template and was shown to have the most drastic effects on CB1/CB2 affinity and selectivity.[15,17] For example, compounds with a shorter side chain such as those carrying a C-3 butyl group exhibited enhanced CB2 selectivity,[23] whereas, analogues with longer seven- or eight-carbon side chains were shown to

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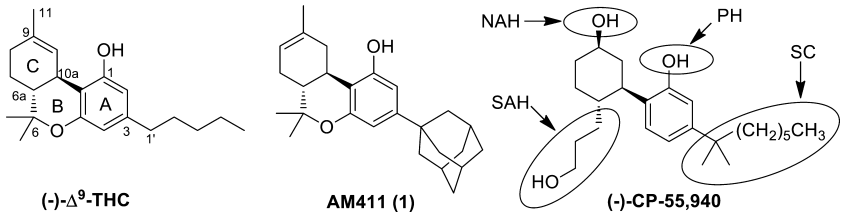
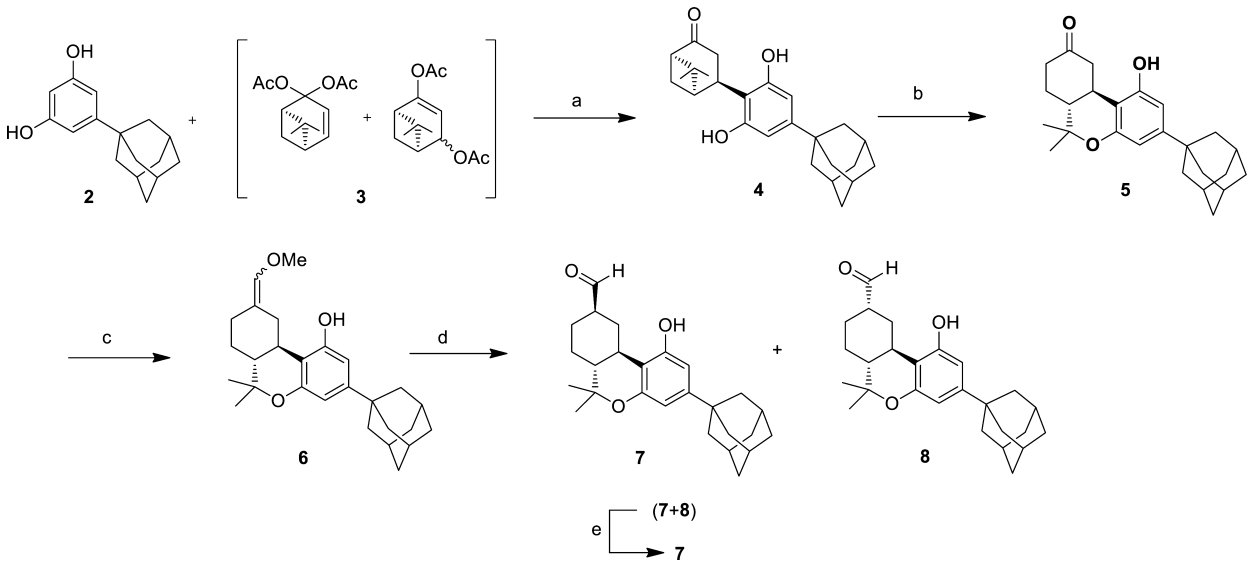


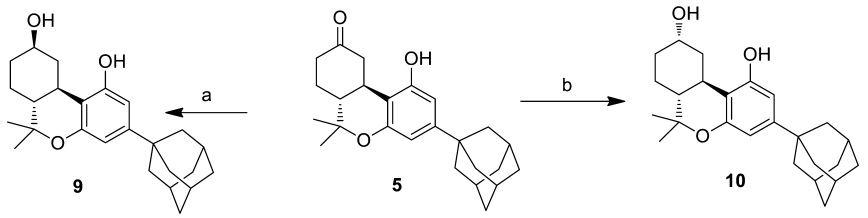
Figure 1. Structures of representative classical and nonclassical cannabinoids.

Scheme 1[a]



[a]Reagents and conditions: (a) *p*-TSA.H_2O, $CHCl_3$, rt, 3.5 days, 80.5%; (b) TMSOTf, CH_2Cl_2/CH_3NO_2 (3:1), 0 °C → 10 °C, 8 h, 61%; (c) $Ph_3PCH_2OMe^+Cl^-$, nBuLi, THF, −30 °C → 0 °C, 30 min, 96.4%; (d) CCl_3COOH, H_2O, CH_2Cl_2, rt, 45 min, 98%; (e) K_2CO_3, MeOH, rt, 4 h, 78%.

Scheme 2[a]



[a]Reagents and conditions: (a) $NaBH_4$, MeOH, 30 min, 92%; (b) K-selectride, THF, −78 °C, 3 h, 64%.

prefer CB1.[24−26] Optimal activity is obtained with the 1′,1′-dimethylheptyl chain which imparts a 100-fold increase in potency compared to the *n*-pentyl side chain of Δ^9-THC.[27] Cannabivarin, a 3-propyl Δ^9-THC analogue, exhibits poor binding to both CB receptors but behaves as a functional CB1 antagonist in tissue preparations.[28] Incorporation of cyclic or aryl moieties at the 3-position is well tolerated.[26,29−33] In previous work, we have shown that an analogue of (−)-Δ^8-THC, an equiactive isomer of the Δ^9-prototype, carrying a 1-adamantyl side chain exhibits substantial CB1 affinity, selectivity, and potency, whereas the 2-adamantyl analogue shows preference for CB2.[30,34] We have also explored other cyclic side chains such as 3-bornyl and 3-isobornyl,[35] aromatic groups,[33] and cycloalkyl chain or chains incorporating cycloalkyl groups.[31,32,36] The other two NAH and SAH pharmacophores also appear to play substantial roles in modulating CB1 and CB2 affinities and selectivities.[37−41]

We have now explored the SAR of 3-(1-adamantyl)-substituted cannabinoids with appropriately modified NAH substituents and obtained novel analogues with improved pharmacological profiles. This study has identified some key cannabinergic probes which can be employed as potent high efficacy agonists. Additionally, it has led to the identification of two low efficacy cannabinergic compounds which show promise as CB1 partial agonists.

CHEMISTRY

Adamantyl resorcinol **2** was synthesized from 2,6-dimethoxyphenol in four steps following a previously reported procedure.[30,42] The mixture of chiral terpene diacetates **3**, which was used previously in the stereospecific synthesis of 9-oxo-cannabinoids with a 6a*R*,10a*R* absolute configuration, was obtained from commercially available (+)-(1*R*)-nopinone, utilizing our earlier reported reaction conditions.[31,38,43,44]

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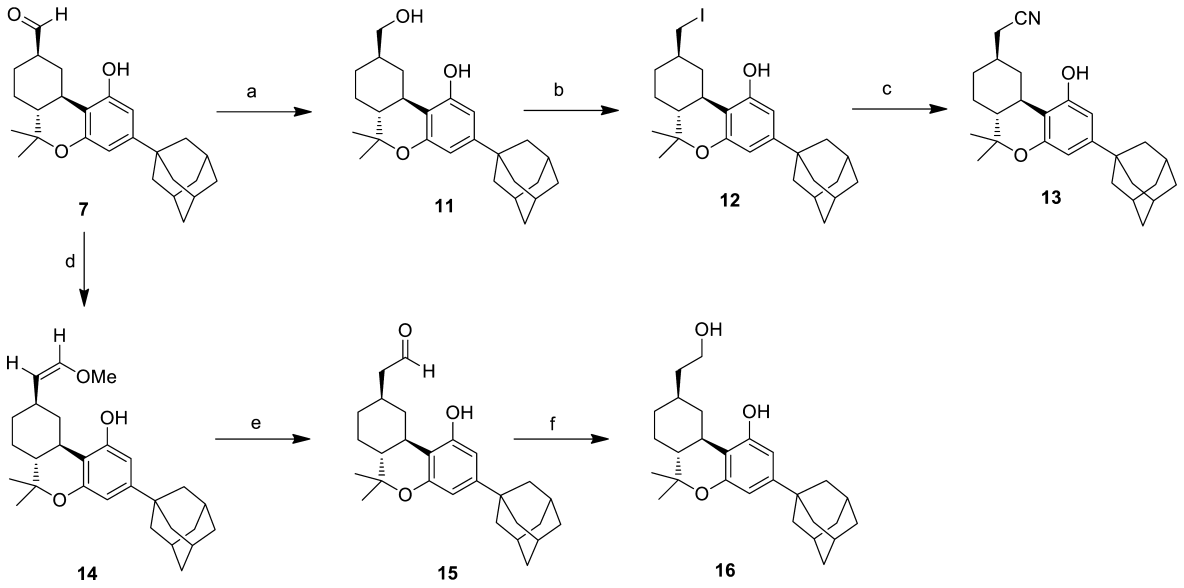
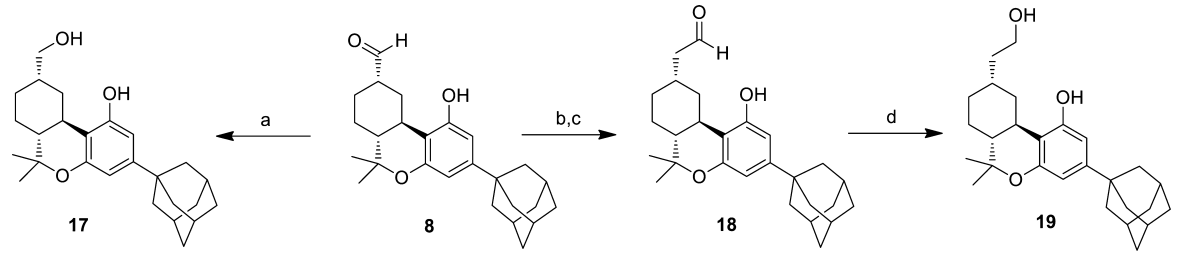
Scheme 3[a]



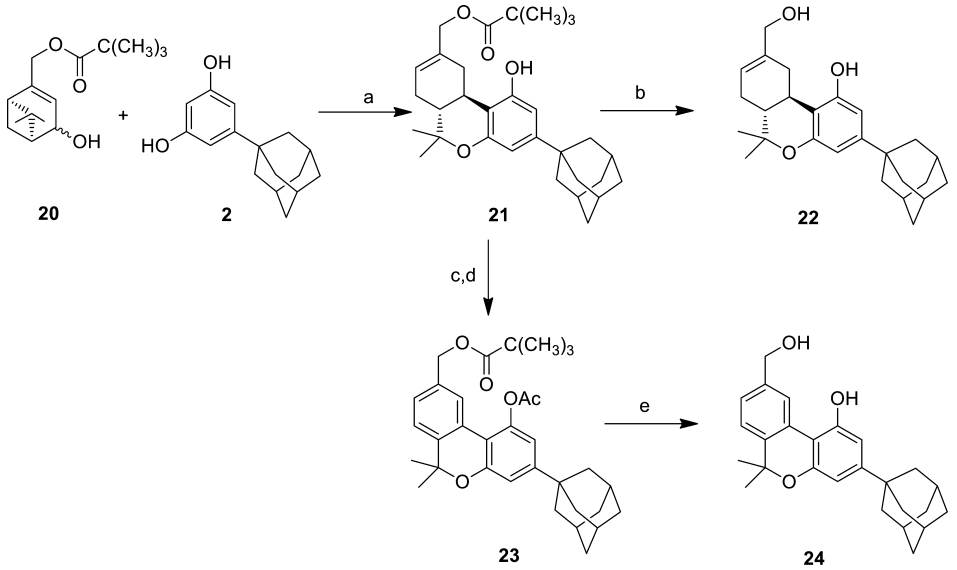
[a]Reagents and conditions: (a) $NaBH_4$, MeOH, rt, 30 min, 93%; (b) I_2, Ph_3P, imidazole, PhH, reflux, 1 h, 76%; (c) NaCN, DMSO, rt, 24 h, 72%; (d) $Ph_3PCH_2OMe^+Cl^-$, nBuLi, THF, −30 °C → 0 °C, 30 min, 86%; (e) CCl_3COOH, H_2O, CH_2Cl_2, rt, 45 min, 96%; (f) $NaBH_4$, MeOH, rt, 30 min, 98%.

Scheme 4[a]



[a]Reagents and conditions: (a) $NaBH_4$, MeOH, rt, 30 min, 95%; (b) $Ph_3PCH_2OMe^+Cl^-$, nBuLi, THF, −30 °C → 0 °C, 30 min; (c) CCl_3COOH, H_2O, CH_2Cl_2, rt, 45 min, 82% (two steps); (d) $NaBH_4$, MeOH, rt, 30 min, 92%.

Scheme 5[a]



[a]Reagents and conditions: (a) BF_3. Et_2O, CH_2Cl_2, −20 °C → rt, 2 h, 32%; (b) $LiAlH_4$, THF, 0 °C → rt, 2 h, 85%; (c) pyridine, acetic anhydride, rt, overnight; (d) sulfur, 250 °C, 2 h, 34% (two steps); (e) $LiAlH_4$, THF, 0 °C → rt, 2 h, 91%.

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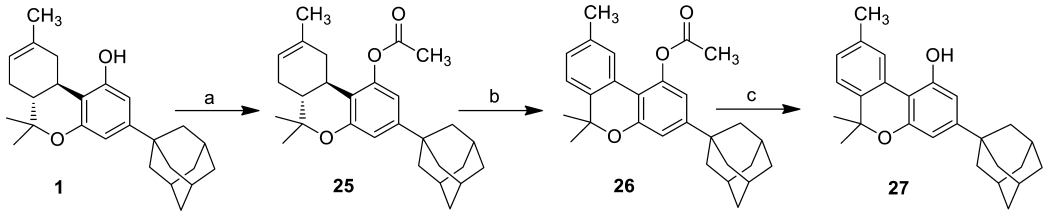
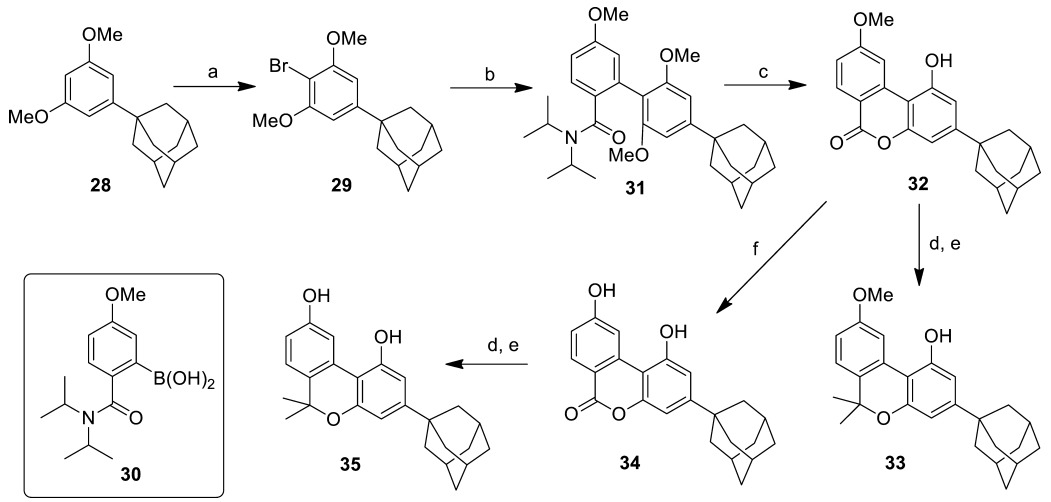
Scheme 6[a]



[a]Reagents and conditions: (a) pyridine, acetic anhydride, rt, overnight, 88%; (b) sulfur, 250 °C, 2 h, 37% ; (c) KOH, EtOH, rt, 30 min, 97%.

Scheme 7[a]



[a]Reagents and conditions: (a) Br_2, 18-crown-6, CH_2Cl_2, 0 °C, 30 min, quantitative; (b) **30**, $Pd(PPh_3)_4$, $Ba(OH)_2$, DME, H_2O, μW, 25 min, 71.9%; (c) 9-iodo-9-BBN, CH_2Cl_2, 0 °C, 4 h, then acetic acid, reflux, 5 h, 68.8%; (d) CH_3MgI, THF, rt → reflux, 2 h; (e) *p*-TSA·H_2O, $CHCl_3$, rt, 6 h, 72.5% for **33** and 56% for **35** (two steps); (f) BBr_3, CH_2Cl_2, reflux, 24 h, 85%.

Coupling of resorcinol **2** with **3** in the presence of catalytic *p*-toluenesulfonic acid led to norpinanone **4** (Scheme 1) in 81% yield, which was followed by TMSOTf promoted rearrangement−cyclization to give **5** in 61% yield. Introduction of the C-9 aldehyde group was accomplished by exposing **5** to (methoxymethylene)triphenylphosphorane followed by hydrolysis of the resulting enol ether **6** (Scheme 1).[39] Unlike our previous report, we found that this reaction did not require the previous protection of the phenolic OH groups.[39] The 9-formyl diastereomeric aldehydes **7** and **8** were obtained in 98% yield as a 2:1 (β versus α) mixture from **6**, the precursor vinyl ether (1:4 mixture of isomers). Epimerization of the diasteromeric mixture of aldehydes allowed us to obtain the β-equatorial isomer **7** in 78% isolated yield.[39]

Aiming for both 9β- and 9α-OH analogues, we used two different routes starting from the 9-keto analogue **5**. Reduction of **5** with sodium borohydride in methanol gave the C-9β (equatorial; **9**) and C-9α (axial; **10**) diasteromers as a 96:4 mixture, respectively (Scheme 2). Silica gel flash chromatographic separation provided the pure 9β-isomer **9** in 92% yield. Reduction of **5** with K-selectride at −78 °C led to axial alcohol **10**, exclusively in 64% yield. The stereochemistry of the 9-hydroxyl group of **9** and **10** was assigned on the basis of ^{1}H NMR spectral data.[39]

The NAH-functionalized 9β and 9α analogues were synthesized as shown in Schemes 3 and 4, respectively. Reduction of **7** with $NaBH_4$ in methanol at room temperature produced alcohol **11** in 93% yield. The 9β-hydroxylmethyl group was then converted to the corresponding iodomethyl analogue **12** in 76% yield by treatment with iodine, triphenylphosphine, and imidazole.[45] Treatment of iodide **12** with sodium cyanide in DMSO produced the corresponding cyano analogue **13** in 72% yield. Homologation with (methoxymethylene)triphenylphosphorane produced almost exclusively the *Z*-enol ether **14** (86% yield) as confirmed by ^{1}H NMR (see Experimental Section). Hydrolysis of **14** with wet trichloroacetic acid led to aldehyde **15** (96% yield) which upon reduction with $NaBH_4$ in methanol produced the 9β-hydroxyethyl analogue **16** (98% yield).

Reduction of **8** with $NaBH_4$ produced the 9α-hydroxymethyl analogue **17** in 95% yield (Scheme 4). Homologation of **8** with (methoxymethylene)triphenylphosphorane produced the enol ether which was hydrolyzed to produce aldehyde **18** in 82% overall yield. Reduction of **18** with $NaBH_4$ in methanol led to the 9α-hydroxyethyl analogue **19** in 92% yield.

Analog **22** with a 6a*R*,10a*R* absolute stereochemistry was synthesized from 4-hydroxy myrtenol pivalate (**20**) (Scheme 5) which was in turn prepared from (1*R*,5*S*)-myrtenol (>98% ee) by utilizing the modified procedure reported by Liddle et al.[46] Condensation of alcohol **20** with resorcinol **2** in anhydrous dichloromethane at −20 °C in presence of a Lewis acid led to the desired cannabinoid ester **21** in 32% yield which, upon reduction with $LiAlH_4$ in THF, afforded tetrahydrocannabinol **22** in 85% isolated yield. To obtain cannabinol analogue **24**, the phenolic pivaloyl intermediate **21** was first acetylated by treatment with pyridine/acetic anhydride and then dehydrogenated by heating with sulfur at 250 °C to provide the mixed

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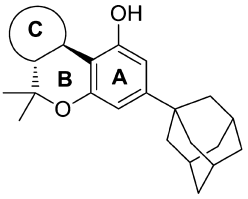
Table 1. Ligand Affinities (K_i) of Adamantyl Cannabinoids for rCB1, mCB2, and hCB2



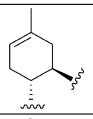
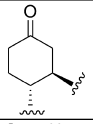
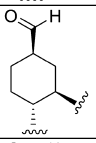
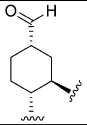
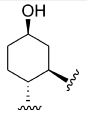
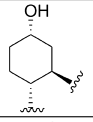
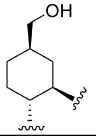
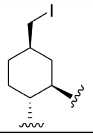
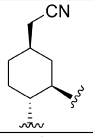
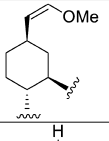
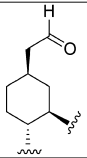
Compound No.	C-ring variation	Ki (nM)[a]			Selectivity	
		rCB1	mCB2	hCB2	mCB2/ rCB1	hCB2/ rCB1
1[b]		6.8	52	NA	7.6	NA
5		175.6	249.5	338	1.4	1.9
7		52.9	25.7	5.5	0.5	0.1
8		48.2	20.1	9	0.4	0.2
9		23.9	39.4	40.5	1.6	1.7
10		146.3	255	671.8	1.7	4.6
11		4.9	12.1	11.3	2.5	2.3
12		241	345.8	261.7	1.4	1.1
13		48.7	87	100.3	1.8	2.1
14		31	90.3	67.2	2.9	2.2
15		13.2	34.3	11.2	2.6	0.8

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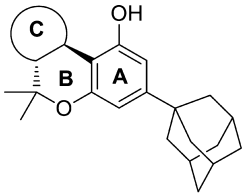
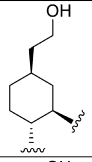
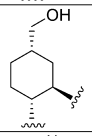
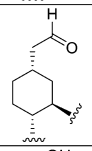
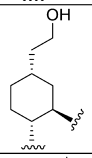
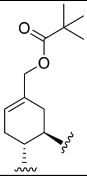
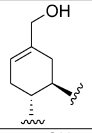
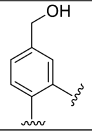
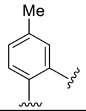
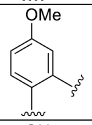
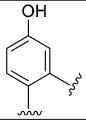
Table 1. continued



Compound No.	C-ring variation	Ki (nM)[a]			Selectivity	
		rCB1	mCB2	hCB2	mCB2/ rCB1	hCB2/ rCB1
16		8.6	38.4	33.3	4.5	3.9
17		30.1	65.1	121.2	2.2	4.0
18		17.5	8.1	7.8	0.5	0.4
19		40.9	21	365.3	0.5	8.9
21		16.5	126	49.2	7.6	3.0
22		7.2	10.6	14	1.5	1.9
24		2.1	32.3	46.7	15.4	22.2
27		62	42.2	63.5	0.7	1.0
33		507	950	338	1.9	0.7
35		88.6	251	551	2.8	6.2

[a]Affinities for rCB1, mCB2, and hCB2 were determined using rat brain (CB1), mouse spleen (CB2) membranes, or HEK293 cell membranes expressing hCB2 and [^{3}H]CP-55,940 as the radioligand (see Experimental Section). Data were analyzed using nonlinear regression analysis. K_i values were obtained from three independent experiments run in duplicate and are expressed as the mean of the three values (SD < ±20%). [b]Reported previously.[30]

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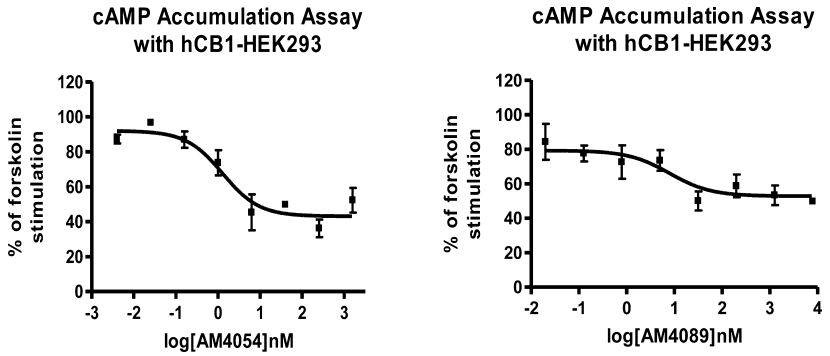

Figure 2. cAMP data of AM4054 (**11**, agonist, EC_{50} = 1.29 nM) and AM4089 (**24**, partial agonist, EC_{50} = 7.97 nM).

ester **23** in a 34% combined yield. Reduction of ester **23** with $LiAlH_4$ in THF produced alcohol **24** in 91% yield.

The C9-methyl cannabinol analogue **27** was prepared starting from **1**, using a previously reported synthetic approach.[47] The phenolic group of **1** was first protected as the acetate ester **25**. Dehydrogenation of **25** by treatment with sulfur at 250 °C to give **26** (37% yield) was followed by deprotection to give the phenol **27** in 97% isolated yield (Scheme 6).

We adopted an alternative approach for the synthesis of the cannabinol analogues carrying 9-OCH_3 (**33**) or 9-OH groups (**35**) (Scheme 7).[48] Dimethoxy resorcinol **28** was monobrominated to provide 2-bromo-5-(1-adamantyl)-1,3-dimethoxybenzene **29** in quantitative yields using bromine and 18-crown-6.[49] Biphenyl **31** was prepared by coupling 2-diisopropyl carbamoyl-5-methoxyphenyl boronic acid **30** with **29** under our microwave-accelerated Suzuki reaction conditions.[48] Selective demethylation of biphenyl **31** with 9-I-9-BBN, followed by acetic acid-catalyzed intramolecular cyclization gave cannabilactone **32** in a combined 69% isolated yield. Compound **32** was then converted to its 6,6-dimethyl analogue **33** by treating first with methyl magnesium iodide followed by cyclization in the presence of *p*-toluenesulfonic acid in a combined 72% yield.[48]

Our attempt to remove the methyl ether group of **33** under BBr_3 conditions did not proceed smoothly and gave **35** in only modest yields. As an alternative route, cannabilactone **32** was demethylated to obtain the bisphenolic lactone **34** (85% yield) which was then converted to the desired 6,6-dimethyl analogue **35** by treatment with excess methyl magnesium iodide followed by cyclization in the presence of *p*-toluenesulfonic acid in a 56% combined yield.

RESULTS AND DISCUSSION

Receptor Binding Studies. The SAR of the novel adamantyl cannabinoids was examined by measuring their affinities for the CB1 and CB2 receptors (Table 1). Our receptor affinity assays included CB2 measurements for both mouse and human receptors because of species variations observed in our previous work.[31,48] Conversely, CB1 affinities were measured using only native rCB1 preparations because no significant variations in CB1 between rodent and human receptors have been observed. The 1-adamantyl cannabinergic analogues included in this study exhibited binding properties that were distinct from those of their Δ^8- and/or C-3 alkyl counterparts. Modification of the Δ^8-analogues to their 9-keto and 9-OH counterparts was aimed at obtaining more polar analogues with improved pharmacokinetic and pharmacological properties. However, the 9-keto analogue **5** had substantially reduced affinities for the rCB1, hCB2, and mCB2 receptors. Similarly, the hexahydro 9α-OH analogue (**10**) exhibited a relatively low affinity profile for all three receptors, while the 9β-OH isomer (**9**) showed improved CB1 and CB2 affinities compared to the 9α-isomer but still lower than its Δ^8-analogue **1**. Also, unlike **1**, compound **9** exhibited no CB1/CB2 selectivity. Aromatization of the rings C to give the respective 9-methyl (**27**), 9-OCH_3 (**33**), and 9-OH (**35**) analogues resulted in compounds with moderate or low affinities for both CB receptors.

One-carbon homologation at the 9-position led to compounds with overall improved CB1/CB2 affinities. The β-formyl hexahydro analogue **7** had a very similar binding profile as its α-formyl counterpart **8** both exhibiting moderate binding profiles with modest selectivity for hCB2 (Table 1). Its cyanomethyl analogue **13** had no observable change in CB1/CB2 binding profile. Conversely, the corresponding iodomethyl analogue **12** had severely reduced CB1/CB2 affinities, possibly reflecting unfavorable steroelectronic interactions at CB1 and CB2 subsites.

The most interesting compounds in the one carbon homologation series were the hydroxymethyl analogues (Table 1). The β-hydroxymethyl hexahydro analogue **11** had the most favorable binding profile while its α-hydroxymethyl isomer **17** had 6- to 11-fold lower affinities. The corresponding 11-OH tetrahydrocannabinol analogue **22** had a high affinity binding profile very similar to the hexahydro analogue **11**, with both compounds exhibiting no significant CB1/CB2 selectivities. Finally, **24** the 9-hydroxymethyl analogue with an aromatized C-ring had the highest CB1 affinity (K_i = 2.1 nM) of the compounds included in this study. It also exhibited a 22- and 15-fold CB1 selectivity over hCB2 and mCB2, respectively. Interestingly, compound **21** containing the bulky pivalate ester at NAH maintains significant affinity for CB1 while its CB2 affinity is severely reduced.

Our effort to determine the SAR of 1-adamantyl 9-substituted cannabinoids was extended to include the 2-carbon NAH homologues, 9β- (**16**) and 9α-hydroxyethyl (**19**), as well as the 9β- (**15**) and 9α-formylmethyl (**18**) and 9β-vinylmethyl ether (**14**) analogues. All of these analogues exhibited relatively unremarkable CB1/CB2 binding profiles with intermediate CB1 and CB2 K_i values. Interestingly, only compound **19** exhibited significant (17-fold) species selectivity for mCB2 over hCB2. Among the 2-carbon NAH analogues, the most interesting was the 9β-hydroxyethyl analogue **16** with a K_i value of 8.6 nM for CB1 and modest (~ 4-fold) CB1 over hCB2 and mCB2 selectivities. Interestingly, all analogues

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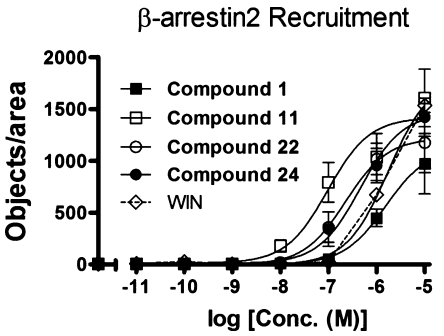

Compd.	Functional Data (β-arrestin2)	
	hCB1	
	efficacy	EC_{50} (μM)
1	0.62	1.53
11	0.78	0.096
22	0.67	0.23
24	0.81	0.45
WIN55,212-2	1	1.76

Figure 3. Dose−response of compounds on U2OS cell lines permanently expressing β-arrestin2-GFP and CB1 receptors. Efficacy of translocation is a measure of the ability of compounds to form membrane or cytosolic clusters of cannabinoid receptor complexes in CB1-E /β-arrestin2-GFP upon exposure to ligand. Note the CB1-E is the CB1 receptor substituted with the human neurokinin-1 receptor tail to enhance arrestin binding.[58,59] Efficacy data were normalized to the β-arrestin2 response of WIN55212-2 (WIN) which is set to 1. Mean efficacy and potency data are presented in the table. Corresponding 95% confidence intervals for compounds **1**, **11**, **22**, and **24** are respectively (compound, efficacy, potency); (**1**; 0.43−0.81, 0.51−4.6 μM), (**11**; 0.65−0.92, 0.037−0.25 μM), (**22**; 0.54−0.80, 0.083−0.62 μM), and (**24**; 0.68−0.94, 0.21−0.98 μM). Data were analyzed by nonlinear regression, $N = 3$.

containing an aldehyde group at the northern site (**7**, **8**, **15**, and **18**) exhibited moderate to high binding affinities for hCB2 with some selectivity over rCB1.

Functional Characterization Using cAMP and β-Arrestin Assays. The key high affinity adamantyl ligands were further tested for their functional potencies which were obtained by measuring the decrease in forskolin-stimulated cAMP (compounds **11** and **24**) and by their β-arrestin recruitment assays (compounds **1**, **11**, **22**, and **24**) for CB1 receptors. Although all four compounds have similar binding affinities, their functional profiles for CB1 are significantly different. In the cAMP assay, **11** was a potent CB1 agonist (EC_{50} = 1.29 nM), while **24** had good potency (EC_{50} = 7.97 nM) but reduced efficacy, thus qualifying as a CB1 partial agonist (Figure 2). These results are congruent with their β-arrestin recruitment data (Figure 3) with compound **1** having the lowest potency and efficacy of the four and **11** being the most potent and efficacious. Compounds **22** and **24** exhibited intermediate potencies. The above functional data are supported by our in vivo results.

Computational and X-ray Crystallographic Studies. To establish a structural basis for explaining the affinity and functional properties of our new analogues while focusing on CB1 receptor SAR, we sought to obtain the crystal structure of a representative analogue, as well as computationally derived 3-D information on our most successful ligands. Of all the novel cannabinoids studied here, only compound **5**, the 9-tetrahydro analogue, provided crystals suitable for X-rays studies. X-ray analysis (Figure 4) allowed us to obtain an overall understanding of the 3D structures of the novel 9-substituted 3-adamantyl series. As with our previously reported **1**, the (−)-Δ^8-THC analogue, the adamantyl moiety occupies a distinct computational space relative to the tricyclic ring system.[30] Rotation around the C3−1-adamantyl bond encompasses a spherical space that is symmetrically aligned with the tricyclic cannabinoid component and suggests a distinctive pharmacophoric subsite within the CB1 receptor. To further explore 3D differences between the key compounds discussed above (**5**, **9**, **11**, **22**, **24**), we compared their computationally derived structures (Figures 5 and 6). All of the above four compounds, when properly aligned, exhibit virtually overlapping phenolic (A ring) and adamantyl rings. While assuming that the sites of interaction of the above two moieties are similar for all compounds, we focused our comparisons on the B and C rings of the tricyclic component.

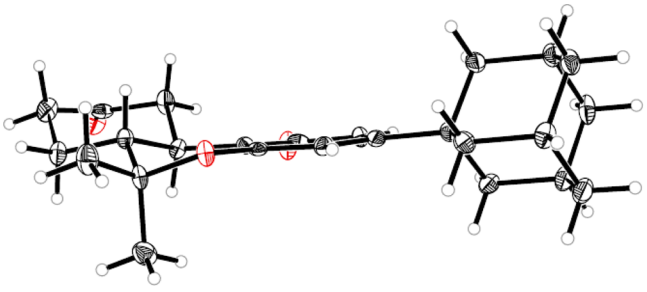

Figure 4. Thermal ellipsoid plot of compound **5** is shown with the aromatic A ring perpendicular to the paper.

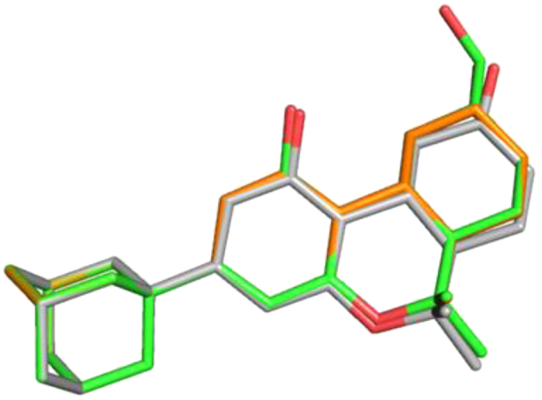

Figure 5. Top view of an overlay of **5** (gray carbons), **9** (orange carbons), and **11** (green carbons). The overlay was performed with the flexible ligand alignment tool in Maestro, version 9.3 (Schrödinger, LLC, New York, NY, 2012).

Our molecular modeling suggests that both the hexahydro- (**11**) and tetrahydro- (**22**) hydroxymethyl analogues have effectively overlapping B and C rings with their respective hydroxyl groups capable of engaging in hydrogen-bonding interactions with a putative corresponding subsite on the receptor. Conversely, in the 9-keto (**5**) and 9β-OH (**9**) analogues, the respective keto and hydroxyl groups are situated

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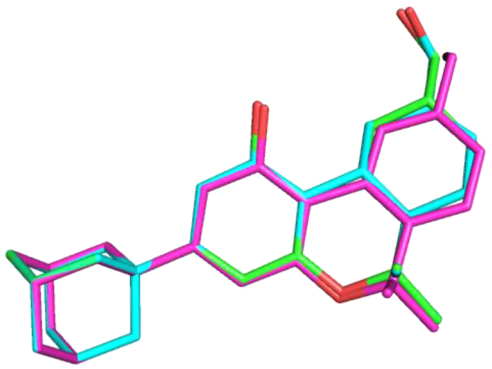

Figure 6. Side view of an overlay of **11** (green carbons), **22** (cyan carbons), and **24** (magenta carbons). The overlay was performed with the flexible ligand alignment tool in Maestro, version 9.3 (Schrödinger, LLC, New York, NY, 2012).

in a relative space different from that of **11** (Figure 5). It can be argued that the 11-hydroxymethyl groups in **11** and **22** position the respective hydroxyl groups in a favorable site within the receptor, resulting in optimized binding affinities and functional potencies. This interaction is not available for the 9-keto (**5**) and 9β-OH (**9**) analogues where the position of the keto and β-OH group does not allow for optimal ligand−receptor (CB1) interaction, thus explaining their lower CB1 affinities.

In the partial agonist **24** the C-ring is aromatic and has the hydroxymethyl group oriented in a distinct pharmacophoric space which allows it to interact favorably with the same CB1 subsite. However, this interaction involves a slightly different but distinct orientation compared to its other two high efficacy agonist hydroxymethyl congeners, **11** and **22** (Figure 6). To explain the observed functional differences, we propose that the hydrogen bonding interaction of high efficacy agonists **11** and **22** with the activated form of CB1 is significantly more favorable than that of the partial agonist **24**.

Earlier work from our laboratory based on mutational data with an 9-hydroxymethyl analogue, (−)-9β-hydroxymethyl-3-(1′,1′-dimethylheptyl)-hexahydrocannabinol (AM4056) had identified Ser7.39 (383) in helix-7 as the site of interaction of this very potent high efficacy agonist.[50] On the basis of the work presented here, we can postulate that this Ser7.39 (383) is the putative site for interaction with the hydroxyl groups in **11** and **22**. Conversely, compounds **5** and **9** are unable to access this favorable interaction while **24** can do this, however, with a reduced H-bonding strength.

In Vivo Evaluation. In vivo evaluation aimed at comparing the CB1 potencies and efficacies of the novel CB1 high efficacy and potent agonist **11** with its partial agonist counterpart **24** and the previously reported parent 1-adamantyl cannabinoid **1**. The work included measurement of ligand-induced hypothermia and analgesia in rats. Body temperature was measured in isolated rats over a 6 h period following drug injection. Compound **11** decreased core body temperature in a dose-dependent manner, with a dose of 1.0 mg/kg reducing body temperature up to 6.4 ± 0.4 °C from an average baseline of 38.02 ± 0.18 °C (Figure 7). At this dose, the onset of drug effects occurred within 60−90 min after injection, although peak effects were obtained at 240−360 min after injection. Compound **1** did not have hypothermic effects up to a dose of 10.0 mg/kg, and a 10.0 mg/kg dose of compound **24** decreased colonic temperature by 4.1 ± 0.1 °C. Antinociception was measured using a tail-flick procedure over a 6 h period

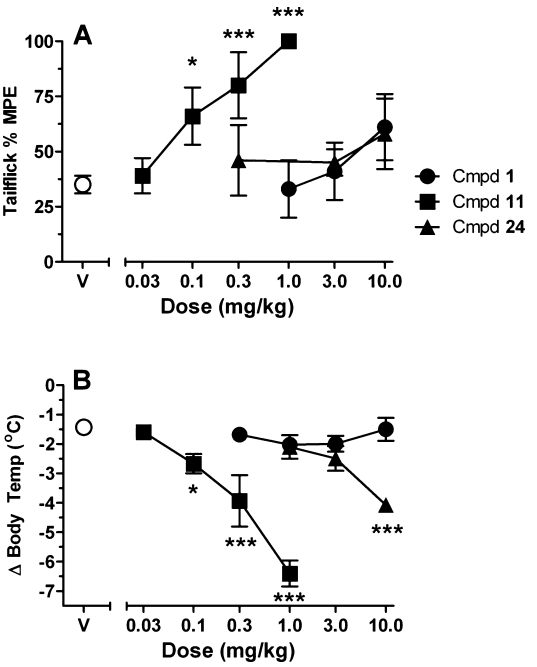

Figure 7. Effects of **1** (●), **11** (■), and **24** (▲) on antinociception (top graph; A) and body temperature (bottom graph; B). Symbols represent the group mean ± SEM (n = 5−7 rats), and the open circles to the left indicate the effects of vehicle pretreatment. Abscissa: dose, in mg/kg; ordinate: (A) Percentage of the maximum possible antinociceptive effect, (B) change in body temperature. Asterisks indicate effects that are significantly different from vehicle, *p < 0.05, *** p < 0.001.

following drug injection. Prior to drug administration, the average baseline tail-flick latency for individual groups was 2.3 s; with a range from 1.8 to 2.6 s. Compound **11** increased tail-flick latency over the same dose range as that for hypothermic effects and with a similar time course. Doses of 0.1−1.0 mg/kg compound **1** had significant antinociceptive effects, with a mean (±95% cx CL) ED_{50} value of 0.05 mg/kg (0.01, 0.1). The onset of the antinociceptive effects occurred between 60 and 120 min after injection, and these effects generally increased over the 6 h test period. In comparison, although both **1** and **24** tended to increase tail-flick latency, neither had significant antinociceptive effects up to doses of 10.0 mg/kg. The results obtained with **1** seemingly contradict previous reports of the effects of this drug in rats; however, this likely reflects slight differences in procedures, as the absolute magnitude of hypothermic effects reported here are similar to those reported earlier.[51,52]

■ CONCLUSION

We have sought to further probe the SAR of 3-(1-adamantyl) cannabinoids and supplement previous work involving the 3-(1-adamantyl) Δ^8-THC analogue **1** to develop novel ligands as useful CB1 pharmacological tools with improved pharmacological profiles. Of the new analogues synthesized, the most interesting were those carrying a hydroxymethyl group at the 9-position. In vitro functional characterization assays found both compound **11** and **22** to be high efficacy CB1 agonists while **24** exhibited the profile of a partial CB1 agonist in cAMP assay. Initial in vivo characterization showed that compound **11** dose-dependently produced hypothermia and antinociception, two effects often associated with cannabinoid agonist activity (Figure 8). In comparison, compound **1** had reduced behavioral

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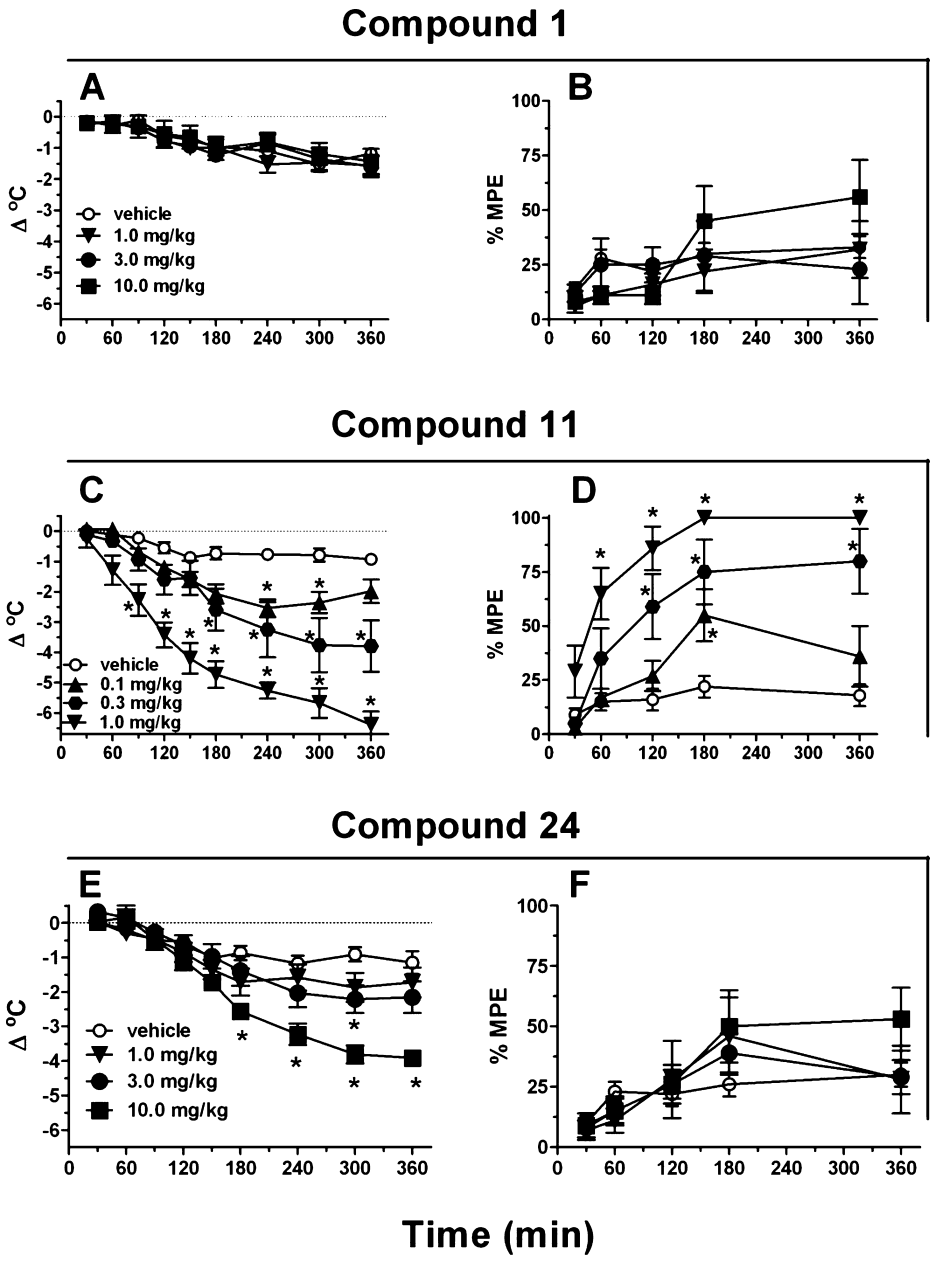

Figure 8. Effects of compounds **1**, **11**, and **24** at different times after injection on body temperature (left panels, A, C, and E) and antinociception (right panels, B, D, and F). Abscissae: time (in minutes) after injection; left ordinates: change in body temperature; right ordinates: percentage of the maximum possible antinociceptive effect. Asterisks indicate effects that are significantly different from vehicle, $*p < 0.05$.

effects, and **24** produced only hypothermia up to a dose of 10 mg/kg (Figure 7). Due to its improved pharmacological profiles when compared to the highly long acting side chain counterparts, **11** should prove to be a very useful CB1 in vivo probe. Additionally, in view of the paucity of available CB1 partial agonists, **24** will be of value as such a ligand in cannabinoid research.

EXPERIMENTAL SECTION

Chemistry. All commercial chemicals and solvents were purchased from Aldrich Chemicals and Co., unless otherwise specified, and were used without further purification. All moisture-sensitive reactions were performed under a static atmosphere of nitrogen or argon in oven-dried or flame-dried glasswares. The progress of the reaction was monitored by thin layer chromatography (TLC) using commercially prepared silica gel 60 F_{254} glass-backed plates. All compounds were visualized under ultraviolet (UV) light by phosphomolybdic acid staining or by anisaldehyde reagent staining. Flash column chromatography employed silica gel 60 (230−400 mesh). Melting points were determined on a micromelting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded in $CDCl_3$, unless otherwise stated, on a Varian 500 MHz. Chemical shifts are recorded in parts per million (δ) relative to internal TMS. Multiplicities are indicated as br (broadened), s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sept (septet), or m (multiplet). Coupling constants (J) are reported in hertz (Hz). Low and high resolution mass spectra were performed in School of Chemical Sciences, University of Illinois at Urbana-Champaign. Mass spectral data are reported in the form of m/z (intensity relative to base = 100). Purity of all material was determined to be at least 95% from HPLC.

(4*R*)-4-[4-(1-Adamantyl)-2,6-dihydroxyphenyl]-6,6-dimethyl-2-norpinanone (4). To a degassed solution of **2** (6.50 g, 26.60 mmol) and diacetates **3** (8.86 g, 37.20 mmol; 10.19 g, 87% pure diacetates **3** were used) in $CHCl_3$ (267 mL) at 0 °C under an argon

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atmosphere was added *p*-toluenesulfonic acid monohydrate (7.085 g, 37.25 mmol). The reaction mixture was warmed to room temperature and stirred for 3.5 days. The reaction mixture was diluted with ether and washed sequentially with water, saturated aqueous $NaHCO_3$, and brine. The organic phase was dried ($MgSO_4$), and the solvent was removed under reduced pressure to give crude product as a brown oil. Recrystallization from CH_2Cl_2 and hexane (2:3) gave **4** as a white crystalline solid (7.95 g, 80.5% yield): mp = 284−286 °C. R_f = 0.4 (EtOAc/hexane = 30/70) ^{1}H NMR (500 MHz, $CDCl_3$ + 1 drop DMSO) δ: 6.50 (br s, 2H, ArOH), 6.38 (s, 2H, 3-H and 5-H, ArH), 4.00 (t, J = 8.0 Hz, 1H, 4-H), 3.63 (dd, J = 19.0 Hz, J = 8.0 Hz, 1H, 3α-H), 2.60−2.52 (m, 3H, especially 2.56, dd, J = 17.0 Hz, J = 8.5 Hz, 1H, 3β-H), 2.50−2.44 (m, 1H), 2.28 (t, J = 5.0 Hz, 1H, 5-H), 2.06 (br s, 3H, Ad-H), 1.82 (br s, 6H, Ad-H), 1.77 (br d, J = 12.5 Hz, 3H, Ad-H), 1.70 (br d, J = 12.5 Hz, 3H, Ad-H), 1.35 (s, 3H, 6-CH_3), 0.99 (s, 3H, 6-CH_3). HRMS (ESI) calculated for $C_{25}H_{33}O_3$: calculated 381.2430; found 381.2433.

(6a*R*,10a*R*)-3-(1-Adamantyl)-6,6a,7,8,10,10a-hexahydro-1-hydroxy-6,6-dimethyl-9*H*-dibenzo[*b*,*d*]pyran-9-one (5). To a solution of **4** (3.95 g, 10.38 mmol) in anhydrous CH_2Cl_2/CH_3NO_2 (3:1, 260 mL) at 0 °C under an argon atmosphere was added trimethylsilyl trifluoromethanesulfonate (13.84 mL, 0.3 M solution in CH_3NO_2, 4.152 mmol), and the resulted mixture was stirred at 10 °C for 8 h. The reaction was quenched with saturated aqueous $NaHCO_3$/brine (1:1), and diethyl ether was added. The organic phase was separated, the aqueous phase was extracted with diethyl ether, and the combined organic phase was washed with brine and dried over $MgSO_4$. Solvent evaporation and purification by flash column chromatography on silica gel (acetone/hexane = 20/80) afforded **5** as white crystalline solid (2.41 g, 61% yield): mp = 263−264 °C. R_f = 0.55 (ethylacetate/hexane = 40/60). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.74 (br s, 1H, ArOH), 6.41 (d, J = 2.0 Hz, 1H, ArH), 6.37 (d, J = 2.0 Hz, 1H, ArH), 4.07 (ddd, J = 15.0 Hz, J = 3.5 Hz, J = 2.5 Hz, 1H, 10eq-H), 2.90 (ddd, J = 13.5 Hz, J = 12.5 Hz, J = 4.0 Hz, 1H, 10a-H), 2.66−2.59 (m, 1H, 8eq-H), 2.47 (ddd, J = 15.0 Hz, J = 13.0 Hz, J = 7.0 Hz, 1H, 8ax-H), 2.20−2.12 (m, 2H, 10ax-H, 7eq-H), 2.05 (br s, 3H, Ad-H), 1.97 (td, J = 12.0 Hz, J = 2.5 Hz, 1H, 6a-H), 1.85 (br s, 6H, Ad-H), 1.76 (d, J = 12.5 Hz, 3H, Ad-H), 1.71 (d, J = 12.5 Hz, 3H, Ad-H), 1.53 (dddd, J = 15.0 Hz, J = 13.0 Hz, J = 12.5 Hz, J = 5.0 Hz, 1H, 7ax-H), 1.47 (s, 3H, 6-CH_3), 1.13 (s, 3H, 6-CH_3); HRMS (ESI) calculated for $C_{25}H_{33}O_3$: calculated 381.2430; found 381.2433.

Tricyclic Methyl Enol Ether (6). To a suspension of (methoxymethyl)triphenylphosphonium chloride (8.12 g, 23.7 mmol) in 90 mL of anhydrous THF at −30 °C was added a solution of *n*-BuLi in THF (9.21 mL, 23.02 mmol, 2.5 M in hexane). The resulting blood red colored solution was warmed to 0 °C over a period of 15 min. A solution of ketone **5** (1.288 g, 3.38 mmol) in anhydrous THF (60 mL) was then added through cannula, keeping the reaction temperature at 0 °C. The resulting solution was stirred for 15 min and then quenched by addition of water and stirred for 30 min till the solution turns colorless. The reaction mixture was diluted with ether, organic phase separated, and the aqueous phase extracted with ether (2×). Combined organic extracts was washed with brine and dried ($MgSO_4$). Purification by flash chromatography on silica gel (EtOAc/hexane = 2/98 → 15/85) gave **6** as a white foam (1.33 g, 96.4%, 1:4 mixture of geometric isomers). R_f = 0.50 (EtOAc/hexane = 20/80). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.41 (d, J = 2.0 Hz, 1H, ArH), 6.40 (d, J = 2.0 Hz, 1H, ArH), 6.26 (d, J = 2.0 Hz, 1H, ArH), 6.24 (d, J = 2.0 Hz, 1H, ArH), 5.93 (t as br s, 1H),5.85 (t as br s, 1H), 4.79 (s, 1H ArOH), 4.65 (s, 1H, ArOH), 4.18−4.12 (m, 1H), 3.59 (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3), 3.47−3.40 (m), 2.92 (br d, J = 11.5 Hz, 1H), 2.41 (td, J = 12.0 Hz, J = 3.5 Hz, 2H),, 2.08−2.02 (m, 6H, Ad-H, both isomers), 1.93−1.86 (m, 2H), 1.85 (br s, 12H, Ad-H, both isomers), 1.76 (d, J = 12.5 Hz, 6H, Ad-H, both isomers) 1.70 (d, J = 12.0 Hz, 6H, Ad-H, both isomers) 1.65−1.58 (m, 2H), 1.39 (s, 3H, 6β-CH_3), 1.38 (s, 3H, 6β-CH_3), 1.06 (s, 6H, 6α-CH_3 of both isomers). HRMS (ESI) calculated for $C_{27}H_{37}O_3$: calculated 409.2743; found 409.2735.

(6a*R*,10a*R*)-3-(Adamantan-1-yl)-1-hydroxy-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[*c*]chromene-9-carbaldehyde (7 and 8). To a solution of enol ether **6** (1.21 g, 2.96 mmol) in 70 mL of CH_2Cl_2 at room temperature was added wet trichloroacetic acid (4.84 g, 29.6 mmol in 5 mL of water). The resulting solution was stirred at room temperature for 45 min, quenched with saturated $NaHCO_3$, and diluted with water. The organic layer separated, and the aqueous phase was extracted with CH_2Cl_2 (2×). The combined organic layer was washed with water, brine (1×), dried ($MgSO_4$), and concentrated to give crude aldehyde. Purification by flash chromatography on silica gel (EtOAc/hexane = 7/93 → 15/85) gave a aldehyde mixture as a white foam (1.15 g, 98% yield; ratio of α:β epimers = 1:2). ***β*-isomer (7)**: R_f = 0.49 (EtOAc/hexane = 30/70). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.65 (s, 1H, CHO), 6.40 (d, J = 1.5 Hz, 1H, ArH), 6.26 (d, J = 1.5 Hz, 1H, ArH), 5.55 (br s, 1H, ArOH), 3.52 (d, J = 13.0 Hz, 1H), 2.56−2.45 (m, 2H), 2.15−2.08 (m, 1H), 2.06−1.96 (m, 4H, especially 2.03, br s, 3H), 1.81 (br s, 6H), 1.74 (d, J = 12.5 Hz, 3H), 1. 68 (d, J = 11.5 Hz, 3H), 1.52−1.35 (m, 5H, especially 1.39, s, 3H, 6β-CH_3), 1.16 (qd, J = 13.0 Hz, J = 4.0 Hz, 1H), 1.09 (s, 3H, 6α-CH_3), 1.06 (q, J = 12.0 Hz, 1H); HRMS (ESI) calculated for $C_{26}H_{35}O_3$: calculated 395.2586; found 395.2582. ***α*-isomer (8)**: R_f = 0.35 (EtOAc/hexane = 20/80) ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.86 (s, 1H, CHO), 6.40 (d, J = 2.0 Hz, 1H, ArH), 6.31 (d, J = 2.0 Hz, 1H, ArH), 4.95 (s, 1H, ArOH), 3.56 (m as dd, J = 14.0 Hz, J = 2.5 Hz, 1H), 2.64 (m as br s, 1H), 2.41 (m as dd, J = 14.0 Hz, J = 2.0 Hz, 1H), 2.31 (td, J = 11.5 Hz, J = 3.0 Hz, 1H), 2.05 (br s, 3H, Ad-H), 1.84 (br s, 6H, Ad-H), 1.82−1.64 (m, 8H), 1.52 (td, J = 11.5 Hz, J = 2.5 Hz, 1H),, 1.41 (ddd, J = 13.5 Hz, J = 11.5 Hz, J = 5.0 Hz, 1H), 1.36 (s, 3H, 6β-CH_3), 1.08 (qd, J = 13.0 Hz, J = 4.0 Hz, 1H), 0.99 (s, 3H, 6α-CH_3). HRMS (ESI) calculated for $C_{26}H_{35}O_3$: calculated 395.2586; found 395.2585.

(6a*R*,9*R*,10a*R*)-3-(Adamantan-1-yl)-1-hydroxy-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[*c*]chromene-9-carbaldehyde (7). The aldehyde mixture (1.0 g, 2.53 mmol) was dissolved in 70 mL of methanol and added via cannula to powdered K_2CO_3 (1.75 g, 12.67 mmol). After the reaction mixture was stirred for 4 h at room temperature, methanol was removed under reduced pressure, diluted with water, and extracted with ethyl acetate (3×). Combined organic extracts washed with brine and dried ($MgSO_4$). Evaporation of volatiles under reduced pressure gave a crude product that was purified by column chromatography (EtOAc/hexane = 7/93 → 15/85) to give pure β-aldehyde **7** (0.78 g, 78% yield) as a white foam.

(6a*R*,9*R*,10a*R*)-3-(Adamantan-1-yl)-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[*c*]chromene-1,9-diol (9). To a solution of ketone **5** (500 mg, 1.31 mmol) in 15 mL of methanol at room temperature was added $NaBH_4$ (198 mg, 5.25 mmol) portionwise. The reaction mixture was stirred for 30 min and quenched with 10% acetic acid, and the mixture diluted with ethyl acetate. The aqueous phase was extracted twice with ethyl acetate, and the combined organic extract was washed with brine and dried ($MgSO_4$). The solvent was evaporated, and the crude product was chromatographed (EtOAc/hexane = 40/60 → 50/50) to produce pure β-alcohol **9** as a white solid (463 mg, 92%). R_f = 0.30 (EtOAc/hexane = 70/30). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.39 (d, J = 2.0 Hz, 1H), 6.23 (d, J = 2.0 Hz, 1H), 5.40 (s, 1H, OH), 3.90−3.82 (m, 1H, 9ax-H, peak half-width =21 Hz), 3.49 (m as br d, J = 14.0 Hz, 1H, 10eq-H), 2.48 (ddd, J = 12.0 Hz, J = 11.5 Hz, J = 3.0 Hz, 1H, 10a-H), 2.17 (m as br d, J = 11.0 Hz, 1H, 8eq-H), 2.05 (br s, 3H, Ad-H), 1.88 (dq, J = 13.5 Hz, J = 3.5 Hz, 1H, 7eq-H), 1.83 (br s, 6H, Ad-H), 1.75 (d, J = 12.5 Hz, 3H, Ad-H), 1.70 (d, J = 12.5 Hz, 3H, Ad-H), 1.64 (br s, 1H, OH), 1.49 (ddd, J = 12.0 Hz, J = 11.5 Hz, J = 2.5 Hz, 1H, 6a-H), 1.45−1.34 (m and s overlapping, 4H, 8ax-H, 6β-CH_3 especially 1.38, s, 3H, 6β-CH_3), 1.20−1.08 (m, 2H, 7ax-H and 10ax-H), 1.07 (s, 3H, 6α-CH_3). HRMS (ESI) calculated for $C_{25}H_{35}O_3$: calculated 383.2586; found 383.2590.

(6a*R*,9*S*,10a*R*)-3-(Adamantan-1-yl)-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[*c*]chromene-1,9-diol (10). To a solution of ketone **5** (400 mg, 1.05 mmol) in anhydrous THF (21 mL) at −78 °C under argon was added K-selectride (7.35 mL, 1.0 M solution in THF) over a period of 10 min, and the resulting solution was stirred at the same temperature for 3 h. The reaction was quenched by addition of water, warmed to room temperature, and diluted with ether. The organic layer separated, washed with 1 M HCl,

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water, and brine, and dried ($MgSO_4$). Evaporation of volatiles gave crude product that was purified by column chromatography (ethyl acetate/hexane = 40/60 → 50/50) to give **10** as a white foam (257 mg, 64% yield). R_f = 0.35 (diethyl ether/hexane = 70/30). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.67 (br s, 1H, OH), 6.39 (d, J = 2.0 Hz, 1H, ArH), 6.36 (d, J = 2.0 Hz, 1H, ArH), 4.29 (s, 1H, 9eq-H; peak half-width =10 Hz), 3.25 (m as dd, J = 14.5 Hz, J = 2.5 Hz, 1H, 10eq-H), 2.95 (m as t, J = 10.5 Hz, 1H), 2.71 (br s, 1H, OH), 2.06−1.94 (m and br s overlapping, 4H, especially 2.01, br s, 3H, Ad-H), 1.81 (br s, 6H), 1.78−1.60 (m and doublets overlapping, 8H, especially 1.73, d, J = 12.0 Hz, 3H, Ad-H and 1.67, d, J = 11.5 Hz, 3H, Ad-H), 1.55−1.47 (m, 2H), 1.39−1.32 (m, 4H especially 1.37, s, 3H, 6β-CH_3), 1.03 (s, 3H, 6α-CH_3). HRMS (ESI) calculated for $C_{25}H_{35}O_3$: calculated 383.2586; found 383.2580.

(6a*R*,9*R*,10a*R*)-3-(Adamantan-1-yl)-9-(hydroxymethyl)-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[*c*]chromen-1-ol (11). To a solution of aldehyde **7** (1.50 g, 3.80 mmol) in 45 mL of methanol at room temperature was added $NaBH_4$ (0.575 g, 15.21 mmol) portionwise. The reaction mixture was stirred for 30 min and quenched with 10% acetic acid, and the mixture was diluted with ether. The aqueous phase was extracted twice with ethyl acetate, and the combined organic extract was washed with brine and dried ($MgSO_4$). The solvent was evaporated, and the crude was chromatographed (EtOAc/hexane = 40/60 → 50/50) to produce pure β-alcohol **11** as a white solid (1.41 g, 93% yield). R_f = 0.42 (EtOAc/hexane = 50/50). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.40 (d, J = 2.0 Hz, 1H, ArH), 6.24 (d, J = 2.0 Hz, 1H, ArH), 4.78 (s, 1H, ArOH), 3.57−3.46 (m, 2H), 3.24−3.16 (m as br d, J = 12.5 Hz, 1H), 2.48 (ddd as dt, J = 11.0 Hz, J = 2.5 Hz, 1H, 10a-H), 2.05 (br s, 3H, Ad-H), 2.00−1.89 (m, 2H), 1.84 (br s, 6H, Ad-H), 1.80−1.67 (m, 7H, especially 1.75, d, J = 12.5 Hz, 3H, Ad-H and 1.70, d, J = 12.5 Hz, 3H, Ad-H), 1.48 (td, J = 11.0 Hz, J = 2.5 Hz, 1H, 6a-H), 1.38 (s, 3H, 6β-CH_3), 1.36 (br s, 1H, OH), 1.18−1.10 (m, 2H), 1.08 (s, 3H, 6α-CH_3), 0.82 (q, J = 12.0 Hz, 1H, 9ax-H). HRMS (ESI) calculated for $C_{26}H_{37}O_3$: calculated 397.2743; found 397.2736.

(6a*R*,9*R*,10a*R*)-3-(Adamantan-1-yl)-9-(iodomethyl)-6, 6-dimethyl-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[*c*]chromen-1-ol (12). To a solution of **11** (250 mg, 0.63 mmol) in 10 mL anhydrous benzene under argon was added triphenylphosphine (331 mg, 1.26 mmol), imidazole (258 mg, 3.78 mmol) and iodine (320 mg, 1.26 mmol), and the resulting solution was refluxed for 1 h. The mixture was cooled to room temperature, diluted with ether, washed with water, aqueous sodium thiosulfate, and brine, dried ($MgSO_4$), and evaporated under reduced pressure. Purification by flash chromatography (EtOAc/hexane = 2/98 → 10/90) gave **12** as white solid (243 mg, 76%). R_f = 0.41 (EtOAc/hexane = 5/95). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.40 (d, J = 2.0 Hz, 1H, ArH), 6.23 (d, J = 2.0 Hz, 1H, ArH), 4.71 (s, 1H, ArOH), 3.28 (m as dd, J = 13.0 Hz, J = 2.0 Hz, 1H, 10eq-H), 3.22 (dd, J = 9.0 Hz, J = 6.0 Hz, 1H, −CH_2I), 3.14 (dd, J = 9.0 Hz, J = 7.0 Hz, 1H, −CH_2I), 2.49 (ddd as dt, J = 11.0 Hz, J = 2.5 Hz, 1H, 10a-H), 2.10−2.02 (m and br s overlapping, 4H, especially 2.05, br s, 3H, Ad-H), 1.94−1.88 (m, 1H), 1.83 (br s, 6H, Ad-H), 1.79−1.64 (m, 7H, especially 1.75, d, J = 12.5 Hz, 3H, Ad-H and 1.70, d, J = 11.5 Hz, 3H, Ad-H), 1.46 (td, J = 11.0 Hz, J = 2.5 Hz, 1H, 6a-H), 1.38 (s, 3H, 6β-CH_3), 1.19−1.10 (m, 2H), 1.07 (s, 3H, 6α-CH_3), 0.88 (q, J = 12.0 Hz, 1H, 9ax-H). HRMS (ESI) calculated for $C_{26}H_{36}O_2I$: calculated 507.1760; found 507.1761.

2-((6a*R*,9*R*,10a*R*)-3-(Adamantan-1-yl)-1-hydroxy-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[*c*]chromen-9-yl)-acetonitrile (13). To a solution of **12** (70 mg, 0.138 mmol) in DMSO (4 mL) at room temperature under an argon atmosphere was added NaCN (34 mg, 0.691 mmol). After being stirred at the same temperature for 24 h, the reaction mixture was cooled to 0 °C and diluted with water and ethyl acetate. The organic layer separated and the aqueous layer extracted with EtOAc (3×). Combined organic layer was washed with water and brine, dried ($MgSO_4$), and evaporated under reduced pressure. Purification by flash chromatography on silica gel (EtOAc/hexane = 20/80 → 50/50) gave **13** as a white foam (40.5 mg, 72%)). R_f = 0.49 (EtOAc/hexane = 30/70). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.40 (d, J = 2.0 Hz, 1H, ArH), 6.23 (d, J = 2.0 Hz, 1H, ArH), 4.81 (s, 1H, ArOH), 3.31 (m as dd, J = 12.5 Hz, J = 2.0 Hz, 1H, 10eq-H), 2.50 (ddd as dt, J = 11.5 Hz, J = 2.5 Hz, 1H, 10a-H), 2.35 (dd, J = 17.0 Hz, J = 6.0 Hz, 1H, −CH_2CN), 2.29 (dd, J = 17.0 Hz, J = 7.0 Hz, 1H, −CH_2CN), 2.09−2.02 (m, 4H, especially 2.05, br s, 3H, Ad-H), 2.00−1.90 (m, 2H), 1.83 (br s, 6H, Ad-H), 1.75 (d, J = 12.5 Hz, 3H, Ad-H), 1.70 (d, J = 11.5 Hz, 3H, Ad-H), 1.49 (td, J = 12.0 Hz, J = 2.5 Hz, 1H, 6a-H), 1.38 (s, 3H, 6β-CH_3), 1.32−1.11 (m, 2H), 1.08 (s, 3H, 6α-CH_3), 0.95 (q, J = 12.5 Hz, 1H, 9ax-H). HRMS (ESI) calculated for $C_{27}H_{36}NO_2$: calculated 406.2746; found 406.2747.

(6a*R*,9*R*,10a*R*)-3-(Adamantan-1-yl)-9-((*Z*)-2-methoxyvinyl)-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[*c*]-chromen-1-ol (14). To a suspension of (methoxymethyl)-triphenylphosphonium chloride (5.21 g, 15.21 mmol) in 90 mL of anhydrous THF at −30 °C was added a solution of *n*-BuLi in THF (5.88 mL, 14.70 mmol, 2.5 M in hexane). The resulting blood red colored solution was warmed to 0 °C over a period of 15 min. A solution of aldehyde **7** (1.0 g, 2.53 mmol) in anhydrous THF (30 mL) was then added through cannula, keeping the reaction temperature at 0 °C. The resulting solution was stirred for 15 min and then quenched by addition of water and stirred for 30 min till the solution turned colorless. The reaction mixture was diluted with diethyl ether, the organic phase separated, and the aqueous phase extracted with ether (2×). Combined organic extracts was washed with brine and then dried ($MgSO_4$). Purification by flash chromatography on silica gel (EtOAc/hexane = 5/95 → 20/80) gave **14** as a white foam (0.92 g, 86% yield). R_f = 0.47 (EtOAc/hexane = 20/80). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.39 (d, J = 2.0 Hz, 1H, ArH), 6.24 (d, J = 2.0 Hz, 1H, ArH), 5.82 (d, J = 6.5 Hz, 1H, CH═C*H*-OMe), 4.78 (s, 1H, ArOH), 4.22 (dd, J = 9.0 Hz, J = 6.5 Hz, 1H, C*H*═CH−OMe), 3.60 (s, 3H, OCH_3), 3.05 (m as br d, J = 12.5 Hz, 1H, 10eq-H), 2.72−2.62 (m, 1H), 2.51 (td, J = 12.0 Hz, J = 2.5 Hz, 1H), 2.04 (br s, 3H, Ad-H), 1.92−1.80 (m, 8H, especially 1.84, s, 6H, Ad-H), 1.78−1.66 (m, 7H, especially 1.75, d, J = 12.5 Hz, 3H, Ad-H and 1.69, d, J = 11.5 Hz, 3H, Ad-H), 1.48 (t, J = 11.0 H, 1H, 6aH), 1.37 (s, 3H, 6β-CH_3), 1.22−1.11 (m, 1H), 1.07 (s, 3H, 6α-CH_3), 0.88−0.83 (m, 1H). HRMS (ESI) calculated for $C_{28}H_{39}O_3$: calculated 423.2899 found 423.2896.

2-((6a*R*,9*R*,10a*R*)-3-(Adamantan-1-yl)-1-hydroxy-6,6-dimethyl-6a,7,8, 9,10,10a-hexahydro-6*H*-benzo[*c*]chromen-9-yl)-acetaldehyde (15). To a solution of enol ether **14** (800 mg, 1.893 mmol) in 40 mL of CH_2Cl_2 at room temperature was added wet trichloroacetic acid (1.546 g, 9.47 mmol in 5 mL of water). The resulting solution was stirred at room temperature for 45 min, quenched with saturated $NaHCO_3$, and diluted with water. The aqueous phase was extracted with CH_2Cl_2 (2×), and the combined organic extracts were washed with water and brine (1×), dried ($MgSO_4$), and concentrated to give crude aldehyde. Purification by flash chromatography on silica gel (EtOAc/hexane = 15/85 → 40/60) gave **15** as a white foam (743 mg, 96% yield). R_f = 0.24 (EtOAc/hexane = 20/80). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.79 (s, 1H, CHO), 6.40 (d, J = 1.5 Hz, 1H, ArH), 6.24 (d, J = 1.5 Hz, 1H, ArH), 4.64 (br s, 1H, ArOH), 3.18 (m as br d, J = 12.5 Hz, 1H, 10eq-H), 2.52 (ddd as td, J = 11.5 Hz, J = 3.0 Hz, 1H, 10a-H), 2.44−2.32 (m, 2H), 2.22−1.92 (m, 1H), 2.04 (br s, 3H, Ad-H), 1.97−1.86 (m, 2H), 1.82 (br s, J = 2.5 Hz, 6H, Ad-H), 1.78−1.64 (m, 7H, especially 1.75, d, J = 12.0 Hz, 3H, Ad-H and 1.69, d, J = 12.0 Hz, 3H, Ad-H), 1.48 (td, J = 11.5 Hz, J = 2.5 Hz, 1H, 6a-H), 1.37 (s, 3H, 6β-CH_3), 1.29−124 (m, 1H), 1.17 (br t, J = 10.0 Hz, 1H), 1.08 (s, 3H, 6α-CH_3). HRMS (ESI) calculated for $C_{27}H_{37}O_3$: calculated 409.2743; found 409.2740

(6a*R*,9*R*,10a*R*)-3-(Adamantan-1-yl)-9-(2-hydroxyethyl)-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[*c*]chromen-1-ol (16). To a solution of aldehyde **15** (100 mg, 0.245 mmol) in 10 mL of methanol at room temperature was added $NaBH_4$ (46.3 mg, 1.224 mmol) portionwise. The reaction mixture was stirred for 30 min and quenched with 10% acetic acid, and the mixture was diluted with ether. The aqueous phase was extracted twice with ethyl acetate, and the combined organic extract was washed with brine and dried ($MgSO_4$). The solvent was evaporated, and the crude was chromatographed (EtOAc/hexane = 30/70 → 70/30) to produce pure β-alcohol **16** as a white solid (98 mg, 98%). R_f = 0.41 (EtOAc/hexane = 50/50). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.43 (d, J = 2.0 Hz, 1H, ArH), 6.27 (d, J

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= 2.0 Hz, 1H, ArH), 4.92 (s, 1H, ArOH), 3.82−3.70 (m, 2H), 3.17 (m as br d, J = 13.5 Hz, 1H, 10eq-H), 2.46 (ddd as td, J = 11.5 Hz, J = 2.5 Hz, 1H, 10a-H), 2.05 (br s, 3H, Ad-H), 1.96−1.82 (m, 8H especially 1.83, br s, 6H, Ad-H), 1.79−1.66 (m, 7H, especially 1.75, d, J = 12.5 Hz, 3H, Ad-H and 1.70, d, J = 11.5 Hz, 3H, Ad-H), 1.58−1.51 (m, 2H), 1.48 (td, J = 11.5 Hz, J = 2.5 Hz, 1H, 6a-H), 1.37 (s, 3H, 6β-CH_3)1.25 (br s, 1H, OH), 1.16−1.05 (m and s overlapping, 5H, especially 1.07, s, 3H, 6α-CH_3), 0.82 (q, J = 12.5 Hz, 1H). HRMS (ESI) calculated for $C_{27}H_{39}O_3$: calculated 411.2899; found 411.2904.

(6a*R*,9*S*,10a*R*)-3-(Adamantan-1-yl)-9-(hydroxymethyl)-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[*c*]chromen-1-ol (17). To a solution of aldehyde **8** (200 mg, 0.507 mmol) in 15 mL of methanol at room temperature was added $NaBH_4$ (96 mg, 2.53 mmol) portionwise. The reaction mixture was stirred for 30 min and quenched with 10% acetic acid, and the mixture was diluted with ethyl acetate. The aqueous phase was extracted twice with ethyl acetate, and the combined organic extract was washed with brine and dried ($MgSO_4$). The solvent was evaporated and the crude was chromatographed (EtOAc/hexane = 30/70 → 60/40) to produce pure alcohol **17** (191 mg, 95% yield). R_f = 0.41 (EtOAc/hexane = 50/50). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.38 (d, J = 2.0 Hz, 1H, ArH), 6.31 (d, J = 2.0 Hz, 1H, ArH), 6.09 (s, 1H, ArOH), 3.90 (dd as br t, J = 10.5 Hz, 1H, CH_2OH), 3.74 (dd, J = 10.5 Hz, J = 7.0 Hz, 1H, CH_2OH), 3.17 (m as dd, J = 14.0 Hz, J = 1.5 Hz, 1H, 10eq-H), 2.51−2.45 (m, 2H), 2.11 (br s, 1H), 2.05 (br s, 3H, Ad-H), 1.83 (br s, 6H, Ad-H), 1.78−1.60 (m, 9H, especially 1.75, d, J = 12.0 Hz, 3H, Ad-H and 1.70, d, J = 12.0 Hz, 3H, Ad-H), 1.51 (td, J = 11.5 Hz, J = 2.5 Hz, 1H, 6a-H), 1.33 (s, 3H, 6β-CH_3), 1.29−1.08 (m, 2H), 0.93 (s, 3H, 6α-CH_3); HRMS (ESI) calculated for $C_{26}H_{37}O_3$: calculated 397.2743; found 397.2751.

2-((6a*R*,9*S*,10a*R*)-3-(Adamantan-1-yl)-1-hydroxy-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[*c*]chromen-9-yl)-acetaldehyde (18). To a suspension of (methoxymethyl)-triphenylphosphonium chloride (4.17 g, 12.17 mmol) in 80 mL of anhydrous THF at −30 °C was added a solution of *n*-BuLi in THF (4.70 mL, 11.76 mmol, 2.5 M in hexane). The resulting blood red colored solution was warmed to 0 °C over a period of 15 min. A solution of aldehyde **8** (0.8 g, 2.03 mmol) in anhydrous THF (20 mL) was then added through a cannula, keeping the reaction temperature at 0 °C. The resulting solution was stirred for 30 min and then quenched by addition of water and stirred for 30 min till the solution turned colorless. The reaction mixture was diluted with diethyl ether, the organic phase separated, and the aqueous phase extracted with ether (2×). Combined organic extracts was washed with brine and then dried ($MgSO_4$). The residue was dissolved in 20 mL of CH_2Cl_2, wet trichloroacetic acid (1.66 g, 10.15 mmol in 7 mL of water) was added, and the resulting solution was stirred at room temperature for 45 min. The reaction was quenched with saturated $NaHCO_3$. The organic layer separated and aqueous phase was extracted with CH_2Cl_2 (2×), and the combined organic extracts were washed with water and brine (1×), dried ($MgSO_4$), and concentrated to give crude aldehyde. Purification by flash chromatography on silica gel (EtOAc/hexane = 20/80 → 40/60) gave aldehyde **18** as a white foam (657 mg, 82% overall yield). R_f = 0.24 (EtOAc/hexane = 20/80). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.84 (d, J = 2 Hz, 1H, CHO), 6.39 (d, J = 2.0 Hz, 1H, ArH), 6.24 (d, J = 2.0 Hz, 1H, ArH), 4.97 (br s, 1H, ArOH), 3.00 (m as br dd, J = 14.0 Hz, J = 1.5 Hz 1H, 10eq-H), 2.76 −2.66 (m, 1H), 2.64−2.52 (m, 3H), 2.04 (br s, 3H, Ad-H), 1.83 (br s, 6H, Ad-H), 1.80−1.64 (m, 8H, especially 1.75, d, J = 13.0 Hz, 3H, Ad-H and 1. 69, d, J = 10.5 Hz, 3H, Ad-H), 1.52 (td, J = 12.0 Hz, J = 2.5 Hz, 1H, 6a-H), 1.44−1.32 (m and s overlapping, 4H, especially 1.37, s, 3H, 6β-CH_3), 1.30−1.18 (m, 2H), 1.08 (s, 3H, 6α-CH_3); HRMS (ESI) calculated for $C_{27}H_{37}O_3$: calculated 409.2743; found 409.2742.

(6a*R*,9*S*,10a*R*)-3-(Adamantan-1-yl)-9-(2-hydroxyethyl)-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[*c*]chromen-1-ol (19). To a solution of aldehyde **18** (100 mg, 0.245 mmol) in 10 mL of methanol at room temperature was added $NaBH_4$ (46.3 mg, 1.224 mmol) portionwise. The reaction mixture was stirred for 30 min and quenched with 10% acetic acid, and the mixture diluted with ether. The aqueous phase was extracted twice with ethyl acetate, and the combined organic extract was washed with brine and dried ($MgSO_4$). The solvent was evaporated, and the crude was chromatographed (EtOAc/hexane = 30/70 → 70/30) to produce pure β-alcohol **19** (92 mg, 92% yield). R_f = 0.40 (EtOAc/hexane = 50/50). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.88 (br s, 1H, ArOH), 6.38 (d, J = 1.5 Hz, 1H, ArH), 6.34 (d, J = 1.5 Hz, 1H, ArH), 4.02−3.92 (m, 1H, CH_2OH), 3.90−3.80 (m, 1H, CH_2OH), 2.96 (br d, J = 13.5 Hz, 1H, 10eq-H), 2.71 (br t, J = 10.5 Hz, 1H, 10a-H), 2.45 (br s, 1H, OH), 2.10−1.96 (m, 4H, especially 2.04, br s, 3H, Ad-H), 1.85 (br s, 6H, Ad-H), 1.78−1.52 (m, 11H, especially 1.74, d, J = 12.0 Hz, 3H, Ad-H and 1.69, d, J = 13.0 Hz, 3H, Ad-H), 1.42−1.20 (m and s overlapping 5H, especially 1.36, s, 3H, 6β-CH_3), 1.08 (s, 3H, 6α-CH_3), 0.92−0.82 (m, 1H). HRMS (ESI) calculated for $C_{27}H_{39}O_3$: calculated 411.2899; found 411.2903.

((6a*R*,10a*R*)-3-(Adamantan-1-yl)-1-hydroxy-6,6-dimethyl-6a,7,10,10a-tetrahydro-6*H*-benzo[*c*]chromen-9-yl)methyl Pivalate (21). To a solution of resorcinol **2** and pivalate ester **20** (0.413 g, 1.64 mmol) in anhydrous dichloromethane (40 mL) at −20 °C under argon atmosphere was added boron trifluoride etherate (1.03 mL, 8.18 mmol). The mixture was allowed to warm up to room temperature and then stirred for further 2 h. The mixture was washed with brine and dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. The crude product was then purified by flash chromatography on silica gel (EtOAc/hexane = 5/95 → 15/85) to give the cannabinoid ester **21** as a white foam (0.25 g, 32% yield); R_f = 0.38 (EtOAc/hexane = 15/85). ^{1}H NMR (500 MHz, $CDCl_3$): δ: 6.43 (d, J = 2.0 Hz, 1H, ArH), 6.27 (d, J = 2.0 Hz, 1H, ArH), 5.75 (d, J = 4.5 Hz, 1H, −CH═C<), 4.75 (s, 1H, ArOH), 4.50 (s, 2H), 3.35 (dd, J = 16.0 Hz, J = 4.5 Hz, 1H), 2.71 (td, J = 11.0 Hz, J = 4.5 Hz, 1H), 2.28−2.20 (m, 1H), 2.05 (br s, 3H, Ad-H), 1.92−1.80 (m, 8H, especially 1.84, br s, 6H, Ad-H), 1.79−1.68 (m, 7H, especially 1.75, d, J = 12.0 Hz, 3H, Ad-H and 1.70, d, J = 11.5 Hz, 3H, Ad-H), 1.39 (s, 3H, 6β-CH_3), 1.21 (s, 9H), 1.12 (s, 3H, 6α-CH_3). HRMS (ESI) calculated for $C_{31}H_{43}O_4$: calculated 479.3161; found 479.3156.

(6a*R*,10a*R*)-3-(Adamantan-1-yl)-9-(hydroxymethyl)-6, 6-dimethyl-6a,7,10,10a-tetrahydro-6*H*-benzo[*c*]chromen-1-ol (22). To a solution of pivalate ester **21** (125 mg, 0.261 mmol) in anhydrous THF (20 mL) at 0 °C under argon was added a solution of $LiAlH_4$ in THF (1.05 mL, 1.045 mmol, 1.0 M in THF), and the resulting mixture was stirred at same temperature for 2 h. The reaction was quenched by addition of water and extracted with ethyl acetate (3×). Combined organic layer was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Purification of the crude by flash chromatography on silica gel (EtOAc/hexane = 30/70 → 70/30) gave allylic alcohol **22** as a white solid (88 mg, 85% yield). R_f = 0.50 (EtOAc/hexane = 50/50). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.40 (d, J = 1.5 Hz, 1H, ArH), 6.28 (d, J = 1.5 Hz, 1H, ArH), 6.12 (s, 1H, ArOH), 5.73 (d, J = 4.5 Hz, 1H, −CH═C<), 3.53−3.42 (m, 2H), 2.68 (td, J = 11.0 Hz, J = 4.5 Hz, 1H), 2.29 (br s, 1H), 2.25−2.15 (m, 1H), 2.03 (br s, 3H, Ad-H), 1.90−1.76 (m, 10H, especially 1.81, br s, 6H, Ad-H), 1.75 (d, J = 12.5 Hz, 3H, Ad-H), 1.69 (d, J = 11.5 Hz, 3H, Ad-H), 1.37 (s, 3H, 6β-CH_3), 1.05 (s, 3H, 6α-CH_3). HRMS (ESI) calculated for $C_{26}H_{35}O_3$: calculated 395.2586; found 395.2583.

(1-Acetoxy-3-(adamantan-1-yl)-6,6-dimethyl-6*H*-benzo[*c*]-chromen-9-yl)methyl Pivalate (23). To a solution of **21** (1.0 g, 2.089 mmol) in dry pyridine (5 mL) at 0 °C was added acetic anhydride (0.97 mL, 10.45 mmol), the resulting solution was warmed to room temperature and stirred overnight. The reaction was cooled to 0 °C, quenched by addition of water, and diluted with ether. The organic layer was separated and the aqueous layer extracted with ether (3×). Combined organic layer was washed with water (2×), aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), and evaporated in vacuo. The crude was mixed with sulfur (0.67 g, 20.89 mmol), and the resulting solid mixture was heated to 250 °C for 2 h. The reaction mixture was cooled to room temperature, dissolved in ethyl acetate, filtered, and washed with water and brine, dried ($MgSO_4$), and concentrated. Purification of crude by flash chromatography on silica gel (EtOAc/hexane = 5/95 → 20/80) yielded **23** as a white solid (0.37 g, 34% overall yield). R_f = 0.50 (EtOAc/hexane = 15/85). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.96 (s, 1H, ArH), 7.25 (br s, 2H, ArH), 6.89 (d, J = 2.0 Hz, 1H, ArH), 6.73 (d, J = 2.0 Hz, 1H, ArH), 5.10 (s, 2H, CH_2O-

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Piv), 2.35 (s, 3H, CH_3COO), 2.09 (s, 3H, Ad-H), 1.90 (br s, 6H, Ad-H), 1.78 (d, J = 12.0 Hz, 3H, Ad-H), 1.73 (d, J = 11.5 Hz, 3H, Ad-H), 1.62 (s, 6H), 1.23 (s, 9H). HRMS (ESI) calculated for $C_{33}H_{41}O_5$: calculated 517.2954; found 517.2958.

3-(Adamantan-1-yl)-9-(hydroxymethyl)-6,6-dimethyl-6*H*-benzo[*c*]chromen-1-yl Acetate (24). To a solution of ester **23** (150 mg, 0.29 mmol) in anhydrous THF (20 mL) at 0 °C under argon was added a solution of $LiAlH_4$ in THF (0.32 mL, 0. 32 mmol, 1.0 M in THF), and the resulting mixture was stirred at same temperature for 2 h. The reaction was quenched by addition of water and extracted with ethyl acetate (3×). Combined organic layer was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Purification of the crude by flash chromatography on silica gel (EtOAc/hexane = 5/95 → 15/85) gave alcohol **24** as a white solid (103 mg, 91% yield). M. P. = 134−135 °C. R_f = 0.48 (EtOAc/hexane = 50/50). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.42 (s, 1H, ArH), 7.32−7.20 (m, 2H, ArH), 6.60 (d, J = 1.5 Hz, 1H, ArH), 6.45 (d, J = 1.5 Hz, 1H, Ar−H), 5.53 (s, 1H, ArOH), 4.73 (br s, 2H, CH_2OH), 2.08 (br s, 3H, Ad-H), 1.88 (br s, 6H, Ad-H), 1.78 (d, J = 12.5 Hz, 3H, Ad-H), 1.73 (d, J = 11.5 Hz, 3H, Ad-H), 1.61 (s, 6H, 2xCH_3), 1.26 (br s, 1H, OH). HRMS (ESI) calculated for $C_{26}H_{31}O_3$: calculated 391.2273; found 391.2268.

(6a*R*,10a*R*)-3-(Adamantan-1-yl)-6,6,9-trimethyl-6a,7,10,10a-tetrahydro-6*H*-benzo [*c*]chromen-1-yl Acetate (25). To a solution of **1** (800 mg, 2.113 mmol) in dry pyridine (5 mL) at 0 °C was added acetic anhydride (1.0 mL, 10.57 mmol), and the resulting solution was warmed to room temperature and stirred overnight. The reaction was cooled to 0 °C, quenched by addition of water, and diluted with ether. The organic layer was separated and the aqueous layer extracted with ether (3×). Combined organic layer was washed with water (2×), aqueous $NaHCO_3$, and brine, dried, ($MgSO_4$) and evaporated in vacuo. Purification of the crude by flash chromatography on silica gel (EtOAc/hexane = 5/95 → 15/85) gave acetoxy **25** as a white foam (782 mg, 88% yield). R_f = 0.47 (EtOAc/hexane = 10/90). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.71 (d, J = 2.0 Hz, 1H, ArH), 6.56 (d, J = 2.0 Hz, 1H, ArH), 5.43 (br d, J = 4.5 Hz, 1H, C*H*═C<), 2.72 (dd, J = 17.0 Hz, J = 5.0 Hz, 1H), 2.61 (td, J = 11.0 Hz, J = 4.5 Hz, 1H), 2.29 (s, 3H, CH_3CO), 2.17−2.09 (m, 1H), 2.06 (br s, 3H, Ad-H), 1.96−1.84 (m, 7H, especially 1.86, br s, 6H, Ad-H), 1.83−1.64 (m, 11H), 1.38 (s, 3H, 6β-CH_3), 1.11 (s, 3H, 6α-CH_3). HRMS (ESI) calculated for $C_{28}H_{37}O_3$: calculated 421.2743; found 421.2739.

3-(Adamantan-1-yl)-6,6,9-trimethyl-6*H*-benzo[*c*]chromen-1-yl Acetate (26). Compound **25** (600 mg, 1.427 mmol) was mixed with sulfur (457 mg, 14.27 mmol), and the resulting solid mixture was heated at 250 °C for 2 h. The reaction mixture was cooled to room temperature, dissolved in ethyl acetate, filtered, and washed with water and brine, dried ($MgSO_4$), and concentrated. Purification of the crude by flash chromatography on silica gel (EtOAc/hexane = 5/95 → 15/85) gave **26** as a white solid (220 mg, 37% yield). R_f = 0.40 (EtOAc/hexane = 10/90). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.80 (s, 1H, ArH), 7.13 (d, J = 8.0 Hz, 1H, ArH), 7.08 (dd, J = 8.0 Hz, J = 1.0 Hz, 1H, ArH), 6.88 (d, J = 2.0 Hz, 1H, ArH), 6.71 (d, J = 2.0 Hz, 1H, ArH), 2.36 (s, 3H), 2.32 (s, 3H), 2.09 (br s, 3H, Ad-H), 1.90 (br s, 6H, Ad-H), 1.78 (d, J = 12.0 Hz, 3H, Ad-H), 1.73 (d, J = 11.5 Hz, 3H, Ad-H), 1.60 (s, 6H, 2xCH_3). HRMS (ESI) calculated for $C_{28}H_{33}O_3$: calculated 417.2430; found 417.2424.

3-(-Adamantan-1-yl)-6,6,9-trimethyl-6*H*-benzo[*c*]chromen-1-ol (27). To a stirred solution of **26** (110 mg, 0.264 mmol) in 10 mL of EtOH at room temperature was added an aqueous solution of KOH (59.3 mg, 1.06 mmol, in 3 mL of water), and the resulting solution was stirred at room temperature for 30 min. The reaction mixture was neutralized by addition of 1 N HCl solution and extracted with ethyl acetate (3×). The combined organic layer was washed with water and brine, dried ($MgSO_4$), and concentrated. Purification by flash chromatography on silica gel (EtOAc/hexane = 5/95 → 20/80) gave **27** as a white solid (96 mg, 97% yield). R_f = 0.50 (EtOAc/hexane = 20/80). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.15 (s, 1H, ArH), 7.14 (d, J = 8.0 Hz, 1H, ArH), 7.07 (dd, J = 8.0 Hz, J = 1.0 Hz, 1H, ArH), 6.60 (d, J = 2.0 Hz, 1H, ArH), 6.44 (d, J = 2.0 Hz, 1H, ArH), 5.11 (s, 1H, ArOH), 2.38 (s, 3H), 2.08 (br s, 3H), 1.89 (br s, 6H, Ad-H), 1.78 (d, J = 12.0 Hz, 3H, Ad-H), 1.73 (d, J = 11.5 Hz, 3H, Ad-H), 1.60 (s, 6H, 2 × CH_3). HRMS (ESI) calculated for $C_{26}H_{31}O_2$: calculated 375.2324; found 375.2318.

5-(1-Adamantyl)-2-bromo-1,3-dimethoxybenzene (29). Bromine (0.38 mL, 7.34 mmol) was added dropwise to a stirred solution of **28** (5-(1-adamantyl)-1,3-dimethoxybenzene)[30] (2.0 g, 7.34 mmol) and 18-crown-6 (0.194 g, 0.734 mmol) in 74 mL of anhydrous CH_2Cl_2 at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and quenched by addition of saturated aqueous sodium bisulfite solution. The organic layer separated, washed with water and brine, and then dried ($MgSO_4$). Evaporation of volatiles under reduced pressure gave **29** as white solid (2.58 g, quantitative) which was >98% pure by NMR and used for the next reaction without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.59 (s, 2H, ArH), 3.91 (s, 6H, 2 x OCH_3), 2.11 (br s, 3H, Ad-H), 1.91 (br s, 6H, Ad-H), 1.81 (d, J = 12.5 Hz, 3H, Ad-H), 1.76 (d, J = 12.0 Hz, 3H, Ad-H). HRMS (ESI) for $C_{18}H_{24}BrO_2$: calculated 351.0960; found, 351.0959.

4′-(Adamantan-1-yl)-*N*,*N*-diisopropyl-2′,5,6′-trimethoxy-[1,1′-biphenyl]-2-carboxamide (31). Argon was bubbled through a mixture of boronic acid **30** (0.715 g, 2.562 mmol),[48] **29** (0.75 g, 2.135 mmol), $Ba(OH)_2.8H_2O$ (1.01 g, 3.203 mmol), 2.5 mL of water, and 16 mL of dimethoxyethane for 10 min. The $Pd(PPh_3)_4$ (0.247 g, 0.213 mmol) catalyst was added to the mixture while argon bubbling was maintained through the mixture, and degassing was continued for an additional 5 min. The reaction mixture was microwaved for 25 min at 160 °C in a CEM Discover apparatus. Then the mixture was cooled to room temperature and filtered through a short Celite pad. The filtrate was concentrated, and Et_2O was added. The ether layer was washed with water and brine and dried ($MgSO_4$). Evaporation of solvent under reduced pressure gave a crude product which was purified by flash chromatography (EtOAc/hexane: 30/70 → 40/60) on silica gel to afford biphenyl **31** as a white solid (0.776 g, 71.9% yield). R_f = 0.50 (EtOAc/hexane = 20/80). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.25 (d, J = 9.0 Hz, 1H, ArH), 6.86 (dd, J = 9.0 Hz, J = 3.0 Hz, 1H, ArH), 6.80 (d, J = 3.0 Hz, 1H, ArH), 6.58 (s, 1H, ArH), 6.56 (s, 1H, ArH), 3.80 (s, 3H, OMe), 3.73 (s, 3H, OMe), 3.72 (s, 3H, OMe), 3.68 (sept, J = 6.5 Hz, 1H, $(CH_3)_2CH$), 3.17 (sept, J = 6.5 Hz, 1H, $(CH_3)_2CH$), 2.12 (br s, 3H, Ad-H), 1.94 (br s, 6H, Ad-H), 1.84−1.74 (m, 6H, Ad-H), 1.45 (d, J = 6.5 Hz, 3H, $(CH_3)_2CH$), 1.07 (d, J = 6.5 Hz, 3H, $(CH_3)_2CH$), 0.91 (d, J = 6.5 Hz, 3H, $(CH_3)_2CH$), 0.55 (d, J = 6.5 Hz, 3H, $(CH_3)_2CH$), HRMS (ESI) for $C_{32}H_{44}NO_4$: calculated 506.3270; found 506.3268.

3-(1-Adamantyl)-1-hydroxy-9-methoxy-6*H*-benzo[*c*]-chromen-6-one (32). A solution of **31** (1.20 g, 2.37 mmol) in 25 mL of anhydrous CH_2Cl_2 was cooled to 0 °C, and 9-iodo-9-BBN (9.50 mL, 1.0 M solution in hexane) was added dropwise. The reaction mixture was stirred at 0 °C for 4 h. It was then warmed to rt and concentrated under reduced pressure, and the residue was dissolved in anhydrous diethyl ether (50 mL). To this mixture was added 10 mL of ethanolamine solution (1.0 M in ether). The reaction mixture was stirred for 40 min and then filtered through a short Celite column. The filtrate was concentrated and dissolved in 10 mL of glacial acetic acid. The reaction mixture was refluxed for 5 h and then cooled to room temperature, and water was added cautiously to the mixture at 0 °C followed by addition of ether (50 mL). The organic layer separated,s washed with water, 15% aqueous $NaHCO_3$, water, and brine, and then dried over $MgSO_4$. Evaporation of volatiles under reduced pressure gave crude product that was chromatographed (EtOAc/hexane, 10/90 → 40/60) on silica gel to give **32** as a white solid (0.615 g, 68.8% yield). R_f = 0.42 (EtOAc/hexane = 30/70); ^{1}H NMR ($CDCl_3$) δ: 8.57 (d, J = 2.5 Hz, 1H, ArH), 8.34 (d, J = 8.5 Hz, 1H, ArH), 7.55 (s, 1H, ArOH), 7.05 (dd, J = 9.0 Hz, J = 2.5 Hz, 1H, ArH), 6.94 (d, J = 2.0 Hz, 1H, ArH), 6.80 (d, J = 2.0 Hz, 1H, ArH), 3.96 (s, 3H, OCH_3), 2.12 (br s, 3H, Ad-H), 1.90 (br s, 6H, Ad-H), 1.81 (d, J = 12.5 Hz, 3H, Ad-H), 1.75 (d, J = 12.5 Hz, 3H, Ad-H). HRMS (ESI) for $C_{24}H_{25}O_4$: calculated 377.1753; found 377.1751.

3-(1-Adamantyl)-9-methoxy-6,6-dimethyl-6*H*-benzo[*c*]-chromen-1-ol (33). To a solution of **32** (0.4 g, 1.06 mmol) in anhydrous THF (22 mL) was added methylmagnesium iodide (1.77 mL, 3.0 M solution in ether, 5.30 mmol) at room temperature under

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an argon atmosphere. The reaction mixture was stirred at room temperature for 30 min and then refluxed for 2 h. The reaction was cooled to room temperature and quenched by addition by saturated aqueous NH_4Cl (30 mL). THF was removed, and the residue was dissolved in diethyl ether (50 mL). The organic phase separated, washed with water and brine, and dried ($MgSO_4$). Evaporation of volatiles under reduced pressure gave the crude intermediate that was used without further purification in the subsequent cyclization reaction. The crude was dissolved in $CHCl_3$ (15 mL), and *p*-toluenesulfonic acid monohydrate (50 mg; 0.262 mmol) was added under argon atmosphere. The reaction was stirred at room temperature for 6 h and then treated with 10 mL of water. The organic phase was separated, washed with saturated aqueous $NaHCO_3$, water, and brine, and then dried ($MgSO_4$). Solvent removal under reduced pressure gave the crude product that was chromatographed (EtOAc/hexane = 10/90 → 20/80) to give **33** as a white crystalline solid (0.3g mg, 72.5% overall yield). R_f = 0.39 (EtOAc/hexane = 20/80).^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.99 (d, J = 3.0 Hz, 1H), 7.16 (d, J = 9.0 Hz, 1H), 6.79 (dd, J = 9.0 Hz, J = 3.0 Hz, 1H), 6.60 (d, J = 2.0 Hz, 1H), 6.43 (d, J = 2.0 Hz, 1H), 5.18 (br s, 1H, ArOH), 3.84 (s, 3H, OCH_3), 2.08 (br s, 3H, Ad-H), 1.88 (br d, J = 2.5 Hz, 6H, Ad-H), 1.78 (d, J = 12.0 Hz, 3H, Ad-H), 1.73 (d, J = 12.0 Hz, 3H, Ad-H), 1.60 (s, 6H, 2 × CH_3). HRMS (ESI) for $C_{26}H_{31}O_3$: calculated 391.2273; found 391.2279.

3-(1-Adamantyl)-1,9-dihydroxy-6*H*-benzo[*c*]chromen-6-one (34). To a suspension of **32** (105 mg, 0.279 mmol) in anhydrous CH_2Cl_2 (15 mL) was added a solution of boron tribromide (0.56 mL, 1.0 M in CH_2Cl_2) at room temperature under an argon atmosphere. The reaction mixture was stirred at the same temperature for 30 min and then refluxed for 24 h. The reaction was then cooled and quenched by addition of ice−water and diluted with ethyl acetate. The aqueous layer was extracted with ethyl acetate (2×), and the combined organic layer was washed with 15% aq $NaHCO_3$, water, and brine and then dried ($MgSO_4$). Evaporation of volatiles under reduced pressure gave a crude product that was chromatographed (EtOAc/hexane = 30/70 → 80/20) to give **34** as a white solid (86 mg, 85% yield). R_f = 0.45 (EtOAc/hexane = 50/50). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 10.76 (br s, 2H, ArOH), 8.49 (d, J = 2.0 Hz), 8.10 (d, J = 9.0 Hz, 1H), 6.97 (dd, J = 9.0 Hz, J = 2.5 Hz, 1H), 6.88 (d, J = 2.0 Hz, 1H), 6.80 (d, J = 2.0 Hz, 1H), 2.07 (br s, 3H), 1.86 (br s, 6H), 1.80−1.70 (m, 6H). HRMS (ESI) for $C_{23}H_{23}O_4$: calculated 363.1596; found 363.1598.

3-(1-Adamantyl)-6,6-dimethyl-6*H*-benzo[*c*]chromene-1,9-diol (35). This compound was prepared analogously to **33**, starting from **34** (0.30 g, 0.828 mmol) in THF (16 mL), methylmagnesium iodide (1.38 mL, 3.0 M solution in ether, 4.14 mmol), and cyclization using *p*-TSA·H_2O (50 mg, 0.262 mmol). Purification of crude by flash chromatography on silica gel (EtOAc/hexane = 10/90 → 20/80) gave **35** as a white crystalline solid (180 mg, 56% overall yield). R_f = 0.42 (EtOAc/hexane = 30/70).^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.92 (d, J = 2.5 Hz, 1H), 7.09 (d, J = 9.0 Hz, 1H), 6.73 (dd, J = 9.0 Hz, J = 2.5 Hz, 1H), 6.58 (d, J = 1.5 Hz, 1H), 6.40 (d, J = 1.5 Hz, 1H), 5.58 (br s, 1H, ArOH), 5.30 (br s, 1H, ArOH), 2.05 (br s, 3H, Ad-H), 1.84 (br d, J = 2.0 Hz, 6H, Ad-H), 1.76 (d, J = 12.5 Hz, 3H, Ad-H), 1.70 (d, J = 12.5 Hz, 3H, Ad-H), 1.58 (s, 6H, 2 × CH_3). HRMS (ESI) for $C_{25}H_{29}O_3$: calculated 377.2117; found 377.2114.

Radioligand Binding Assays: rCB1, hCB2, and mCB2. All compounds synthesized were tested for their ability to bind to CB1 and CB2 receptors using rat brain or HEK293 cell membranes expressing hCB2 membrane preparations, respectively, as previously described via competition-equilibrium binding using [^{3}H]CP-55,940.[53−55] The results were analyzed using nonlinear regression to determine the actual IC_{50} of the ligand by GraphPad Prism 5.0 Software (GraphPad, San Diego, CA), and the K_i values were calculated from the IC_{50}.[56]

cAMP Assay. HEK-293 cells transfected with rCB1, mCB2, or hCB2 receptor were used with the PerkinElmer Lance ultra cAMP kit following the protocol of the manufacturer. Briefly, the assays were carried out in 384-well format using 1000 cells/well. Test compounds were added to wells containing stimulation buffer and 2 μM forskolin followed by cell suspension. After 30 min stimulation, the Eu-cAMP tracer and Ulight-anti-cAMP were added to the plate and incubated at room temperature for 1 h prior to detection via PerkinElmer Envision; data were analyzed using GraphPad Prism 5.0 software.[31]

***β*-Arrestin2 Translocation Assay.** U2OS cells stably expressing the CB1-E cannabinoid receptors and *β*-arrestin2-GFP were split into glass-bottom 384 well plates (MGB101-1-2-LG, MatriCal, Spokane, WA) at a density of 8000 cells/30 μL media/well using a Multidrop 384 dispenser (Thermo Fisher Scientific, Waltham, MA). The plates were incubated overnight at 37 °C in 5% CO_2. The following day, culture medium was changed to 30 μL/well of clear minimum Eagle's medium (MEM) with 10 mM HEPES, and then the cells were treated with a serial concentration of test compounds with WIN55212-2 as a positive control. A set of serial diluted 4× concentration of each compound (10 mM in DMSO) was prepared in the same medium and applied to cells at a volume of 10 μL (final DMSO concentration <1%). The cells were incubated with compound for 40 min at 37 °C prior to fixation with an equal volume of PBS containing 2% paraformaldehyde (Sigma, St. Louis, MO). Plates were stored at 4 °C until analysis. *β*-arrestin2-GFP aggregates were identified as described.[57] Dose response curves were analyzed by nonlinear regression techniques using GraphPad Prism version 5.0 (GraphPad Software, La Jolla, CA), and data were fitted to sigmoidal dose−response curves to obtain EC_{50} and efficacy values.

Single-Crystal X-ray Diffraction Analysis of 5. A clear rod of dimensions 0.33 × 0.07 × 0.06 mm^2 was mounted on a MiteGen MicroMesh using a small amount of Cargille Immersion Oil. Data were collected on a Bruker three-circle platform diffractometer equipped with a SMART APEX II/Platinum 135 CCD detector. The crystals were irradiated using graphite monochromated Mo K_α radiation (λ = 0.71073). An Oxford Cobra low temperature device was used to keep the crystals at a constant 113(2) K during data collection. Data collection was performed, and the unit cell was initially refined using *APEX2* [v2010.3-0].[60] Data reduction was performed using *SAINT* [v7.68A][61] and *XPREP* [v2008/2].[62] Corrections were applied for Lorentz, polarization, and absorption effects using *SADABS* [v2008/1].[63] The structure was solved and refined with the aid of the programs in the *SHELXTL-plus* [v2008/4] system of programs.[64] The full-matrix least-squares refinement on F^2 included atomic coordinates and anisotropic thermal parameters for all non-H atoms. The H atoms were included using a riding model.

$C_{28}H_{38}O_4$, FW = 438.58, hexagonal, $P3_1$, a = 12.9968(13) Å, b= 12.9968(13) Å, c = 49.145(10) Å, α = 90°, β = 90°, γ = 120°, V = 7189.2(18) Å^3, Z = 12, ρ_{calc} = 1.216 mg/m^3, μ = 0.079 mm^{-1}, F(000) = 2472, R_1 = 0.0644 for 12705 observed ($I > 2\sigma I$) reflections and 0.1018 for all 18166 reflections, goodness-of-fit = 1.054, 1165 parameters.

In Vivo Studies. *Subjects.* Female Sprague−Dawley rats (n = 5−7/group), weighing between 235 and 350 g (Charles River, Wilmington, MA). Rats were tested repeatedly with at least seven days intervening between drug sessions. Outside of experimental sessions, rats were group housed (2/cage) in a climate-controlled vivarium with unrestricted access to food and water.

Procedure. The temperature was recorded using a thermistor probe (Model 401, Measurement Specialties, Inc., Dayton, OH) inserted to a depth of 7 cm and secured to the tail with micropore tape. Rats were minimally restrained and isolated in 38 × 50 × 10 cm plastic stalls. The temperature was read to the nearest 0.01 °C using a thermometer (Model 4000A, Measurement Specialties, Inc.). Two baseline temperature measurements were recorded at 15 min intervals, and drugs were injected immediately after the second baseline was recorded. After injection, temperature was recorded every 30 min for 3 h and every 1 h thereafter for a total of 6 h. The change in temperature was determined for each rat by subtracting temperature readings from the average of the two baseline measures.

Antinociception was measured using a modified version of the tail-flick procedure of D'Amour and Smith.[65] Radiant heat from a halogen lamp was focused on the tail using a commercial tail-flick apparatus (model no. LE7106, Harvard Apparatus, Holliston, MA); movement of the tail activated a photocell, tuning off the lamp and a reaction timer. The lamp intensity was adjusted to yield baseline values of 2−3

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s, and a maximum latency of 6.0 s was imposed to avoid damage to the tail. Two baseline tail-flick latencies were obtained in each rat at 10 min intervals, and drugs were injected immediately after the second baseline was recorded. Tail-flick responses were recorded at 30, 60, 120, 180, and 360 min after injection.

Drugs. All compounds were initially dissolved in a solution of 20% ethanol, 20% emulphor, and 60% saline and were further diluted with saline. Injections were administered sc in a volume of 1.0 mL/kg.

Data Analysis. For each rat, the two baseline values recorded prior to drug injection were averaged to obtain a single baseline value. Temperatures recorded after drug injection are expressed as a change from baseline, calculated for each animal by subtracting the baseline temperature from the temperatures recorded postinjection. Tail-flick responses are expressed as a percentage of the maximum possible effect (%MPE) calculated according to the equation: 100 × (test latency − baseline latency)/(6 − baseline latency); where 6 represents the cutoff latency. Dose−effect functions were constructed using the maximum effect recorded in each rat at a given dose of drug. Group means and SEM were calculated, and time−effect functions were analyzed using two-way repeated measures ANOVA procedures followed by Bonferroni's posthoc test. Dose−effect functions were analyzed using one-way repeated measures ANOVA procedures followed by Dunnett's multiple comparison t test; p was set at <0.05, and statistical analyses were performed using GraphPad Prism 5.03 (GraphPad Software, San Diego, CA).

■ ASSOCIATED CONTENT

Supporting Information

Crystal data and structure refinement, atomic coordinates and equivalent isotropic displacement parameters, bond lengths and angles, anisotropic displacement parameters, hydrogen coordinates and isotropic displacement parameters, and torsion angles for compound **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS USED

CB1, cannabinoid receptor 1; CB2, cannabinoid receptor 2; hCB1 human cannabinoid 1; Δ^8-THC, (−)-Δ^8-tetrahydrocannabinol; GPCRs, G-protein-coupled receptors; 2-AG, 2-arachidonoylglycerol; SAR, structure−activity relationship; NAH, northern aliphatic hydroxyl; SAH, southern aliphatic hydroxyl; TMSOTf, trimethylsilyl trifluoromethanesulfonate; cAMP, cyclic adenosine monophosphate; HEPES, (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid; MPE, maximum possible effect

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