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Novel 1′,1′-Chain Substituted Δ^8-Tetrahydrocannabinols

Demetris P. Papahatjis,[a,*] Spyros P. Nikas,[a] Thanos Andreou[a] and Alexandros Makriyannis[b,*]

[a]*Institute of Organic and Pharmaceutical Chemistry, National Hellenic Research Foundation, 48 Vass. Constantinou, Athens 116-35, Greece*

[b]*Departments of Pharmaceutical Sciences and Molecular and Cell Biology and the Center for Drug Discovery, University of Connecticut, 372 Fairfield Road, Storrs, CT 06269, USA*

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Abstract—1′,1′-Cyclopropyl side chain substituents enhance the affinities of Δ^8-tetrahydrocannabinol and respective cannabidiol analogues for the CB1 and CB2 cannabinoid receptors. The results support the hypothesis for a subsite within CB1 and CB2 binding domain at the level of the benzylic side chain carbon in the tetrahydrocannabinol and cannabidiol series. Efficient procedures for the synthesis of 1′,1′-cyclopropyl analogues are described.

The discovery of CB1 and CB2 the two known cannabinoid receptors[1–3] and the availability of suitable biochemical test systems has opened the door for developing detailed information on the structural features of their respective binding site(s). A review[4] of the existing literature recognized four pharmacophores on the cannabinoid structure associated with cannabinergic activity. Of these, the aliphatic side chain was shown to play a pivotal role in determining receptor binding affinity and pharmacological activity, as was first demonstrated by Adams.[5a] His studies showed that substituting the *n*-pentyl chain of (−)-Δ^8-tetrahydrocannabinol ((−)-Δ^8-THC) **1a** (Fig. 1) with a 1′,1′-dimethylheptyl chain **1b** led to a 100-fold increase in potency. Since then, a considerable number of structure–activity correlations have dealt with the cannabinoid side chain and most of them have focused on its length, branching and spatial orientation as well as on the introduction of multiple bonds and heterogroups.[5] Earlier work from our own laboratories[6] demonstrated that structural modifications at the benzylic position of the side chain prototype **1b** led to profound effects on the affinities of the respective ligands for both CB1 and CB2 as exemplified by the 1′,1′-dithiolane derivative **1c**. This increase in affinity was attributed to a hydrophobic subsite within each of the CB1 and CB2 binding sites at the level of the benzylic side chain carbon, and suggested the significance of the side chain's orientation and conformation in determining cannabinergic activity.

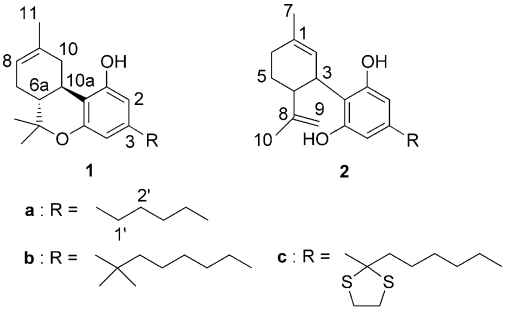

Figure 1.

We have now sought to further refine our understanding on the structural requirements for ligand interaction with this putative CB1/CB2 subsite through the further elaboration of the C-1′,1′-substituents. Earlier work had demonstrated that the presence of two benzylic methyl groups enhances a ligand's affinity for both cannabinoid receptors. It is also well established that the Δ^9- and Δ^8-isomers in the tetrahydrocannabinol series and their respective cannabidiols have very similar SAR profiles. In the present study we have substituted the 1′,1′-*gem*-dimethyl group with a sterically more confined cyclopropyl group. Furthermore, by introducing *gem*-dihalo substitution at the C-2″

*Corresponding authors. Tel.: +30-10-7273885; fax: +30-10-7273831; e-mail: dpapah@eie.gr, (D.P. Papahatjis); tel.: +1-860-486-2133; fax: +1-860-486-3089; e-mail: makriyan@uconnvm.uconn.edu (A. Makriyannis).

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position of the cyclopropyl ring (Scheme 1) we sought to probe the stereochemical limits of this novel pharmacophore. As with earlier work, the design of our analogues has included a seven-carbon side chain as the optimal length for cannabinergic activity.[4c] We have also extended our SAR to include the bicyclic synthetic intermediates **4a–4c** which represent modifications of cannabidiol **2a**, a significant constituent of cannabis that has been shown to bind weakly to both CB1 and CB2.

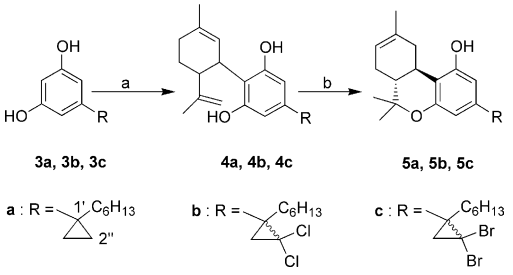
Available procedures for the synthesis of (−)-Δ^8-THC analogues generally involve the condensation of a suitable chiral terpene with 5-substituted resorcinols.[6–8] Thus, terpenylation of the resorcinol derivatives **3a**, **3b**, and **3c** (Scheme 1) with (+)-*cis*/*trans*-*p*-mentha-2,8-dien-1-ol[9] in the presence of catalytic amounts of *p*-toluenesulfonic acid afforded cannabidiols **4a**, **4b**, and **4c**, respectively.[10] The presence of the cyclopropyl and di-halocyclopropyl substituents evidently enhances the regioselectivity of the reaction with yields greater than 75%. Treatment of cannabidiols **4a–4c** with catalytic amounts of boron trifluoride etherate resulted in a clean cyclization reaction to produce the respective tricyclic tetrahydrocannabinols[10] **5a–5c** in 87–90% yields in which the initially formed Δ^9-THCs that should be isolatable under controlled conditions were converted to the respective thermodynamically more stable Δ^8-isomers.

5-(1-Hexyl-cyclopropyl)resorcinol **3a** was synthesized from the corresponding 1-(3,5-dimethoxyphenyl)cyclopropanecarboxaldehyde **6** (Scheme 2), which was in turn obtained from commercially available 3,5-dimethoxybenzaldehyde in five steps by a methodology recently developed in our laboratories.[11] Freshly prepared (butylmethylene)triphenylphosphorane was coupled with aldehyde **6** affording the intermediate alkene **7** in excellent yield (96%). However, reduction of the double bond of **7** using palladium on active carbon was found to be complicated by the susceptibility of the cyclopropyl ring to rapid degradation under catalytic hydrogenation conditions. The problem was solved by using a diimide based reduction[12] of alkene **7** to give 1,3-dimethoxy-5-(1-hexyl-cyclopropyl)benzene **8** in 96% yield after purification. Treatment of **8** with 9-iodo-9-BBN in hexane[13] produced resorcinol **3a** in 95% yield.

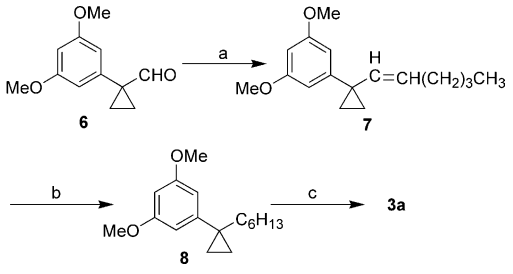
We have recently described[6] the efficient synthesis of 1-(dimethoxyphenyl)-1-heptan-1-one **9**. This compound has served as the starting point for the synthesis of requisite resorcinols **3b** and **3c** by a reaction sequence depicted in Scheme 3.

Thus, the labile (methylene)triphenylphosphorane was prepared from commercially available methyl triphenylphosphonium iodide and immediately treated with phenone **9** in a Wittig olefination reaction affording alkene **10** in 93% yield after purification. Exposure of **10** to dichloro and dibromo carbene, prepared in situ[14] under basic conditions, provided the dichloro and dibromo cyclopropyl derivatives **11b** and **11c**. Cleavage of the two phenolic methyl ether groups was accomplished by exposure to boron tribromide[15] in methylene chloride for 3 days affording resorcinols **3b** and **3c** in 63–86% yields. It should be pointed out that analogues **4b**, **4c**, **5b**, and **5c** were obtained as 1:1 diastereomeric mixtures as indicated by their respective ^{1}H NMR spectra. The abilities of cannabinoids **4a**, **5a** and the diastereomeric mixtures **4b**, **4c**, **5b**, and **5c** to displace radiolabeled CP-55,940 from purified rat forbrain synaptosomes and mouse spleen synaptosomes were determined as described elsewhere.[6] K_i values calculated from the respective displacement curves are listed in Table 1 and serve as indicators for the affinities of these cannabinoid analogues for the CB1 and CB2 receptors.

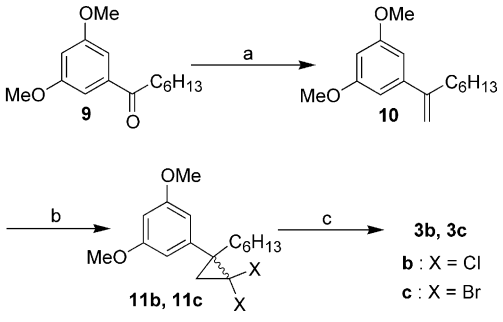
The present results indicate that the presence of a 1′,1′-cyclopropyl group leads to analogues with enhanced affinities for both CB1 and CB2 and support the hypothesis of respective subsites within the two receptors' binding domains. This subsite is capable of accommodating a hydrophobic cyclopropyl group as



Scheme 1. Reagents and conditions: (a) (+)-*cis*/*trans*-*p*-mentha-2,8-dien-1-ol, *p*-TSA, C_6H_6, 10 °C to rt, 2–3 h, 75–84%; (b) $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C to rt, 4 h, 87–90%.



Scheme 2. Reagents and conditions: (a) Br^- Ph_3P^+-$(CH_2)_4CH_3$, $(Me_3Si)_2N^-K^+$, THF, rt, 2 h, 96%; (b) $TsNHNH_2$, CH_3COONa, DME, H_2O, reflux, 5 h, 96%; (c) 9-I-9-BBN, hexane, −78 °C to 0 °C, 3 h, 95%.



Scheme 3. Reagents and conditions: (a) I^- Ph_3P^+-CH_3, $(Me_3Si)_2N^-K^+$, THF, rt, 1.5 h, 93%; (b) $Me_3CO^-K^+$, CHX_3, hexane, −10 °C to rt, 2–2.5 h, 56–89%; (c) BBr_3, CH_2Cl_2, −78 °C to −20 °C, 3 days, 63–86%.

Table 1. Affinities (K_i) of cannabinoid analogues **4a**, **4b**, **4c** and **5a**, **5b**, **5c** for the CB1 and CB2 receptors

Compd	CB1 (K_i, nM)[a]	CB2 (K_i, nM)[a]
1a[5c]	47.6	39.3
1b[4c]	0.83	0.49
1c[6]	0.32	0.52
2a[16]	1265	230
2c[6]	136	50
4a	59 (±7)	99 (±15)
4b	665 (±161)	33 (±9)
4c	189 (±29)	63 (±16)
5a	0.44 (±0.07)	0.86 (±0.16)
5b	1.27 (±0.27)	0.29 (±0.06)
5c	0.71 (±0.21)	1.0 (±0.36)

[a]K_i values of the cannabinoid analogues were obtained from three independent experiments run in duplicate and are expressed as the mean of three values, standard deviation is given in parentheses.

well as the significantly bulkier C-2″,2″-dichloro and dibromo groups. Our data show that the cyclopropyl analogue **5a** exhibits similar affinities for CB1 and CB2 as its *gem*-dimethyl prototype **1b**, although the presence of the cyclopropyl group appears to lead to slightly enhanced selectivity for CB1. This preference is reversed with the introduction of *gem*-dichloro substitution in the cyclopropyl ring (**5b**). Conversely, the bulkier *gem*-dibromocyclopropyl analogue (**5c**) has almost equal affinities for both receptors. As expected, the cannabidiol analogues **2a**,[16] **2c**, and **4a**–**4c** have affinities for CB1 and CB2 over two orders of magnitude weaker than the respective tetrahydrocannabinols. However, the two series appear to exhibit similar SAR trends. This suggests similar binding motifs for the benzylic chain substituents at CB1 and CB2 for tetrahydrocannabinol and cannabidiol analogues. We conclude that this study adds to earlier work pointing to the presence of a CB1/CB2 subsite at the level of the benzylic side chain carbon in the tetrahydrocannabinol and cannabidiol series. We have also observed some preference for CB1 or CB2 based on the different benzylic substituents. However, these selectivities are relatively modest and do not allow us to identify any specific trends. These will have to await the development of additional side chain substituted ligands aimed at probing the stereochemical features of this intriguing putative subsite.

Acknowledgements

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9. (+)-*cis*/*trans*-*p*-Mentha-2,8-dien-1-ol was supplied by Firmenich Inc., Princeton, NJ.
10. All new compounds (**3a**, **3b**, **3c**, **4a**, **4b**, **4c**, **5a**, **5b**, **5c**, **7**, **8**, **10**, **11b**, and **11c**) were fully characterized by NMR, MS, and HRMS spectra. Selected data of final cannabinoids:

4a. ^{1}H NMR ($CDCl_3$) δ 6.30 (brs, 2H), 5.95 (brs, 1H, –OH), 5.57 (s, 1H, 2-H), 4.66 (s, 1H), 4.60 (brs, 1H, –OH), 4.55 (s, 1H), 3.83 (m, 1H, 3-H), 2.37 (td, $J_1 = 10.4$ Hz, $J_2 = 4.3$ Hz, 1H, 4-H), 2.26–2.06 (m, 2H, 5-H, 6-H), 1.79 (brs, 5H, 5-H, 6-H, 7-CH_3), 1.63 (s, 3H, 10-CH_3), 1.47 (m, 2H, 2′−CH_2−), 1.19 (m, 8H), 0.84 (t, $J = 6.1$ Hz, 3H, 7′-CH_3), 0.71 (m, 2H, cyclopropyl), 0.56 (m, 2H, cyclopropyl); MS *m*/*z* (rel intensity) 368 (M^+, 43), 300 (77), 285 (100), 247 (38), 229 (37), 121 (19). Exact mass calcd for $C_{25}H_{36}O_2$, 368.2715; found, 368.2710.

4b. ^{1}H NMR ($CDCl_3$) δ 6.31 (m, 1H), 6.23 (m, 1H), 6.12 (brs, 1H, –OH), 5.60 (m, 1H, 2-H), 4.79 (brs, 1H, –OH), 4.63 (s, 1H), 4.48 (s, 1H), 3.84 (m, 1H, 3-H), 2.33 (m, 1H, 4-H), 2.21–2.10 (m, 2H, 5-H, 6-H), 2.06 (m, 1H, 2′-H), 1.80 (m, 6H, 7-CH_3, 5-H, 6-H, –$CHCCl_2$), 1.60 (m, 4H, 10-CH_3, 2′-H), 1.45 (d, $J = 7.3$ Hz, 1H, –$CHCCl_2$), 1.18 (m, 8H), 0.82 (t, $J = 6.7$ Hz, 3H, 7′-CH_3); MS *m*/*z* (rel intensity) 436 (M^+, 100), 401 (56), 365 (52), 329 (44), 317 (92), 261 (58). Exact mass calcd for $C_{25}H_{34}Cl_2O_2$, 436.1936; found, 436.1932.

4c. ^{1}H NMR ($CDCl_3$) δ 6.28 (m, 2H), 6.10 (brs, 1H, −OH), 5.61 (m, 1H, 2-H), 4.70 (brs, 1H, –OH), 4.62 (s, 1H), 4.47 (s, 1H), 3.83 (m, 1H, 3-H), 2.35 (m, 1H, 4-H), 2.21–2.05 (m, 2H, 5-H, 6-H), 2.01 (m, 1H, 2′-H), 1.99 (d, $J = 7.3$ Hz, 1H, –$CHCBr_2$), 1.80 (m, 5H, 7-CH_3, 5-H, 6-H), 1.60 (m, 5H, 10-CH_3, 2′-H, –$CHCBr_2$), 1.17 (m, 8H), 0.82 (2t, overlapping, 3H, 7′-CH_3, mixture of diastereomers); MS *m*/*z* (rel intensity) 526 (M^+, 40), 447 (26), 446 (28), 445 (25), 363 (34), 361 (35), 298 (40), 283 (89), 213 (100), 135 (34). Exact mass calcd for $C_{25}H_{34}Br_2O_2$, 524.0926; found, 524.0920.

5a. ^{1}H NMR ($CDCl_3$) δ 6.34 (d, $J = 1.2$ Hz, 1H), 6.19 (d, $J = 1.2$ Hz, 1H), 5.42 (m, 1H, 8-H), 4.62 (s, 1H, –OH), 3.18 (dd, $J_1 = 16.5$ Hz, $J_2 = 4.3$ Hz, 1H, 10α-H), 2.68 (m, 1H, 10a-H), 2.14 (m, 1H), 1.90–1.77 (m, 3H), 1.69 (s, 3H, 9-CH_3), 1.46 (m, 2H, 2′−CH_2–), 1.37 (s, 3H, 6-CH_3), 1.21 (m, 8H), 1.09 (s, 3H, 6-CH_3), 0.84 (t, $J = 6.7$ Hz, 3H, 7′-CH_3), 0.73 (m, 2H, cyclopropyl), 0.57 (m, 2H, cyclopropyl); MS *m*/*z* (rel intensity) 368 (M^+, 100), 353 (6), 325 (15), 297 (37), 285 (39), 246 (15). Exact mass calcd for $C_{25}H_{36}O_2$, 368.2715; found, 368.2708.

5b. ^{1}H NMR ($CDCl_3$) δ 6.30 and 6.26 (d, $J = 1.4$ Hz, 0.5H each, mixture of diastereomers), 6.20 and 6.17 (d, $J = 1.4$ Hz, 0.5H each, mixture of diastereomers), 5.42 (m, 1H, 8-H), 4.90

(s, 1H, –OH), 3.19 (dd, $J_1 = 17.2$ Hz, $J_2 = 3.9$ Hz, 1H, 10α-H), 2.69 (td, $J_1 = 10.7$ Hz, $J_2 = 4.5$ Hz, 1H, 10a-H), 2.13 (m, 1H), 1.99 (m, 3H), 1.79 (m, 2H, 2′-H and $-CHCCl_2$), 1.69 (s, 3H, 9-CH_3), 1.46 (m, 2H, 2′-H and $-CHCCl_2$), 1.37 (s, 3H, 6-CH_3), 1.19 (m, 8H, $-CH_2-$), 1.10 and 1.09 (2s, 1.5H each, 6-CH_3, mixture of diastereomers), 0.83 (t, $J = 6.2$ Hz, 3H, 7′$-CH_3$); MS *m*/*z* (rel intensity) 436 (M^+, 35), 401 (20), 365 (19), 329 (13), 104 (37), 73 (100). Exact mass calcd for $C_{25}H_{34}Cl_2O_2$, 436.1936; found, 436.1941.

5c. ^{1}H NMR ($CDCl_3$) δ 6.30 and 6.26 (d, $J = 1.7$ Hz, 0.5H each, mixture of diastereomers), 6.20 and 6.17 (d, $J = 1.7$ Hz, 0.5H each, mixture of diastereomers), 5.42 (m, 1H, 8-H), 4.90 (s, 1H, –OH), 3.20 (m, 1H, 10α-H), 2.69 (td, $J_1 = 10.6$ Hz, $J_2 = 4.5$ Hz, 1H, 10a-H), 2.10 (m, 2H, 7-H, 2′-H), 1.99 (m, 1H, $-CHCBr_2$), 1.96–1.79 (m, 3H), 1.69 (s, 3H, 9-CH_3), 1.62 (m, 2H, 2′-H,$-CHCBr_2$), 1.38 (s, 3H, 6-CH_3), 1.19 (m, 8H, $-CH_2-$), 1.09 and 1.08 (2s, 1.5H each, 6-CH_3, mixture of diastereomers), 0.84 and 0.83 (2t, 1.5H each, $J = 6.2$ Hz, 3H, 7′$-CH_3$, mixture of diastereomers); MS *m*/*z* (rel intensity) 526 (M^+, 100), 447 (46), 445 (45), 366 (67), 365 (71), 296 (57), 283 (68), 213 (55), 135 (54). Exact mass calcd for $C_{25}H_{34}Br_2O_2$, 524.0926; found, 524.0927.

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