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Structural modifications of the cannabinoid side chain towards C3-aryl and 1′,1′-cycloalkyl-1′-cyano cannabinoids

Demetris P. Papahatjis,[a,*] Victoria R. Nahmias,[a] Thanos Andreou,[a] Pusheng Fan[b] and Alexandros Makriyannis[b]

[a]*Institute of Organic and Pharmaceutical Chemistry, National Hellenic Research Foundation, 48 Vass. Constantinou, Athens 116-35, Greece*
[b]*Center for Drug Discovery, Northeastern University, 360 Huntington Avenue, 116 Mugar Life Sciences Building, Boston, MA 02115, USA*

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Abstract—The compounds reported in this study are Δ^8-THC analogues in which the C3 five-carbon linear side chain of Δ^8-THC was replaced with aryl and 1′,1′-cycloalkyl substituents. Of the compounds described here analogues **2d** (CB_1, K_i = 11.7 nM. CB_2, K_i = 9.39 nM) and **2f** (CB_1, K_i = 8.26 nM. CB_2, K_i = 3.86 nM) exhibited enhanced binding affinities for CB_1 and CB_2, exceeding that of Δ^8-THC. Efficient procedures for the synthesis of these novel cannabinoid analogues are described.

In the quest for cannabinoid receptor binding affinity and selectivity, pharmacophoric requirements of classical cannabinoids have been extensively examined, though recurrently revised. During the last decade, numerous selective ligands for each of the cannabinergic proteins were designed and synthesized.[1] Many of these agents serve as important molecular probes, providing structural information about receptor binding sites. Structure–activity relationship (SAR) studies have indicated four pharmacophores within the cannabinoid structure:[2] the phenolic hydroxyl, the lipophilic alkyl side chain, the northern aliphatic hydroxyl and the southern aliphatic hydroxyl. Among these, the cannabinoid side chain has been the object of extensive research for more than half a century. Structural variations within this pharmacophore can result in analogues varying by up to three orders of magnitude in receptor affinity and pharmacological potency. The spatial orientation of the side chain seems to play a pivotal role in cannabinergic activity. Introduction of a triple bond in the benzylic position of the *n*-heptyl-Δ^8-THC analogue led to the classical cannabinoid **1a** with high CB_1 affinity,[3] originally synthesized in our laboratory. Thus, several efforts towards chain orientation with regard to the tricyclic cannabinoid moiety were instigated.[4] Tetracyclic analogues synthesized a year later,[5] also aimed at restricting the cannabinoid side chain, exhibited decreased affinity for the CB_1 receptor, probably due to unfavourable interaction between the fourth ring and the receptor. On the other hand, the remarkable binding affinity and CB_1 selectivity exhibited by the bulky adamantyl-Δ^8-THC[6] analogue **1b**, indicated greater tolerance for steric bulk in the receptor subsite. Quite recently, it has been shown that variations in the adamantyl substituents can lead to cannabinoid analogues possessing higher affinities and selectivities for each of the two receptors depending on the relative orientation of the adamantyl group with respect to the tricyclic cannabinoid structure[7] (Fig. 1).

Taking these results into consideration, we were prompted to seek novel substituents for the cannabinoid side chain, which would introduce bulk close to the phenolic ring of Δ^8-THC and, at the same time, could constrain the orientation of the alkyl side chain, since the chain is flexible and can achieve any one of a number of conformations. Here we describe the synthesis of a carefully designed series of analogues, in which a variety of aryl substituents were introduced at the C3 position of the phenolic A ring of Δ^8-THC, as depicted in Figure 2.

Keywords: Cannabinoid analogues; Suzuki coupling; Biaryls.
* Corresponding author. Tel.: +30 10 7273885; fax: +30 10 7273831; e-mail: dpapah@eie.gr

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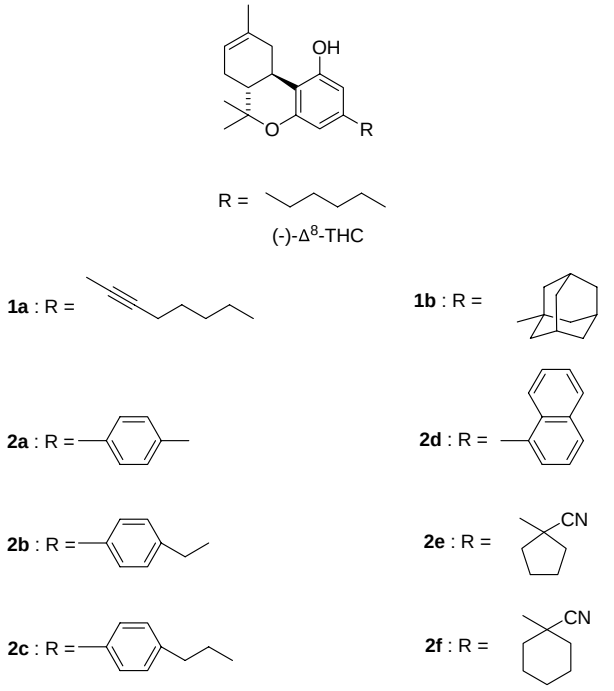


Figure 1.

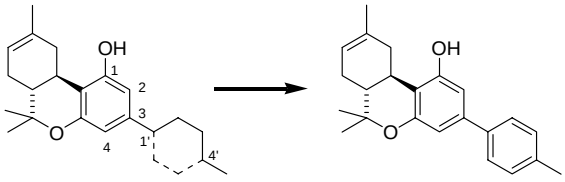


Figure 2. Structural modification of the side chain towards C3-aryl cannabinoids.

The presence of the biaryl unit in a great number of pharmaceutical compounds has also been a significant motivation to us, in designing biaryl cannabinoids. The biphenyl framework is without doubt a privileged substructure. This motif has shown activity across a wide range of therapeutic classes, which include antifungal, anti-inflammatory, antirheumatic, antitumor, antihypertensive and antiatherosclerotic agents.[8] The protein binding of drugs that contain aromatic substituents is dominated by interactions with aromatic and hydrophobic residues. In addition, aromatics have been shown to form favourable interactions with polar substituents, such as amides or hydroxyl groups, and even positively charged moieties.[9] This diversity in receptor selectivity is not overly surprising when one considers that aromatic moieties have long been considered as major players in molecular recognition.[8] Thus, we have sought to enrich our library of cannabinoid analogues with the synthesis of biaryl-containing compounds, in an effort to obtain high-affinity ligands for the two cannabinoid receptors (Figs. 1 and 2).

Additionally, in order to further explore the pharmacophoric requirements of the cannabinoid side chain within the classical tetrahydrocannabinol template, we have extended our studies to include the synthesis of 1′,1′-

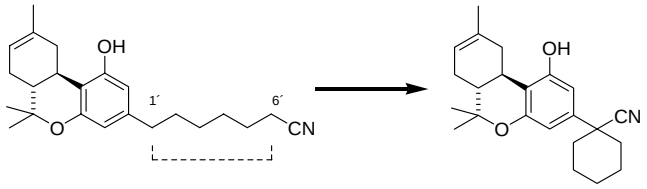


Figure 3. Structural modification of the side chain towards bulky, cyano functionalized cannabinoids.

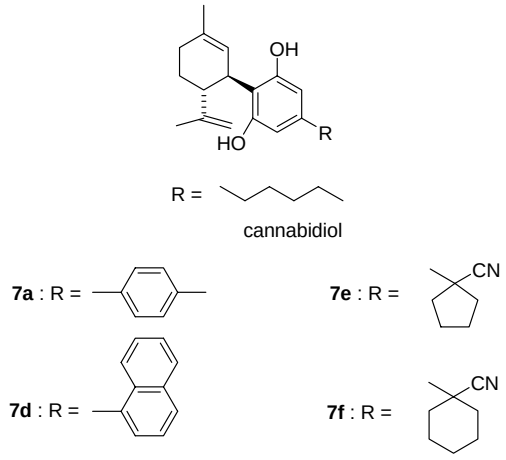


Figure 4.

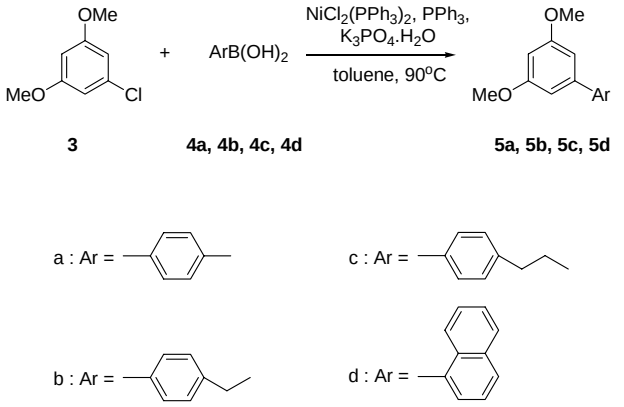
cycloalkyl-1′-cyano-substituted cannabinoids, as depicted in Figure 3. Conformational restriction within the chain was achieved through the incorporation of the side chain carbons into five- and six-membered rings. The C1′ cyano functionalization served to ensure enhanced receptor binding affinities.[10]

We have also included in our SAR studies the synthetic bicyclic intermediates **7a**, **7d**, **7e** and **7f** which represent modifications of cannabindiol (Fig. 4), a significant cannabis constituent, which has been shown to exhibit weak binding affinity for the cannabinoid receptors.

The key step in the C3-aryl cannabinoid synthetic pathway was the formation of 5-aryl resorcinols, through the application of the Suzuki–Mijaura reaction.[11] The commercially available nickel catalyst $NiCl_2(PPh_3)_2$, reduced in situ to the active Ni(0) species, was used over 3,5-dimethoxychloride with various arylboronic substrates (Scheme 1).

4-Alkyl-phenylboronic acids were employed to achieve varying chain lengths, whereas the naphthyl substrate provided further bulk at the C1′ position. The resulting 4-alkyl biaryls were obtained in increasing yields as the chain length decreased. However, the Suzuki–Mijaura procedure did not prove to be as efficient on the naphthyl-boronic substrate, which exhibited the lowest reaction yield (Table 1).

Compounds **5a**–**5d** were efficiently deprotected using highly selective *B*-I-9BBN reagent to afford the respective



Scheme 1. Application of the Suzuki–Mijaura reaction on various aryl-boronic acids.

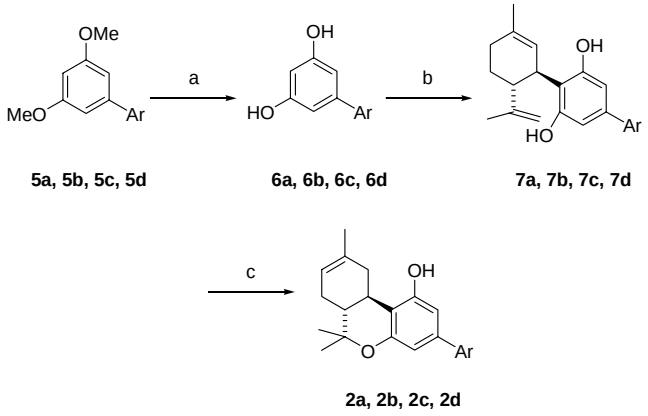
Table 1. Reaction yields of the Suzuki–Mijaura coupling

Compound	Yield (%)	Reaction time (h)
5a	73	12
5b	50	14
5c	44	14
5d	35	12

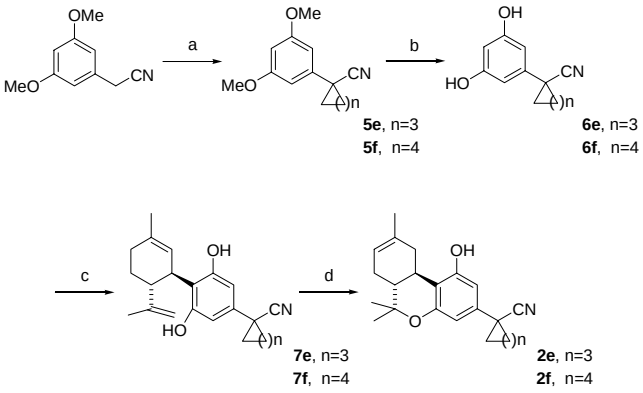
resorcinols.[12] (+)-*cis*/*trans*-*p*-Mentha-2,8-dien-1-ol[13] was then introduced, in the presence of catalytic amount of *p*-TSA, followed by ring closure through treatment with $BF_3{\cdot}Et_2O$ in dry CH_2Cl_2[3], leading to biaryl cannabinoids **2a**, **2b**, **2c** and **2d**[14] (Scheme 2).

The synthesis of 1′,1′-cycloalkyl-1′-cyano cannabinoid analogues involves cyclobisalkylation of 3,5-dimethoxyphenylacetonitrile with the appropriate α,ω-dibromoalkane,[15] followed by demethylation through the use of boron tribromide.[4b] Terpene coupling and ring closure, as mentioned above, afforded cannabinoid analogues **2e** and **2f**[14] (Scheme 3).

The abilities of **2a**–**2f** and cannabidiol (**7a**, **7d**, **7e** and **7f**) analogues to displace radiolabelled CP-55,940 from



Scheme 2. Reagents and conditions: (a) *B*-I-9-BBN, hexanes, rt; (b) (+)-*cis*/*trans*-*p*-mentha-2,8-dien-1-ol, *p*-TSA, dry benzene, 5 °C; (c) $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C.



Scheme 3. Reagents and conditions: (a) $Br(CH_2)_3CH_2Br$ for **5e** and $Br(CH_2)_4CH_2Br$ for **5f**, KHMDS, dry THF, 0 °C; (b) BBr_3, CH_2Cl_2, −78 °C; (c) (+)-*cis*/*trans*-*p*-mentha-2,8-dien-1-ol, *p*-TSA, dry benzene, 5 °C, (d) $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C.

Table 2. Affinities (K_i) of tetrahydrocannabinol and cannabidiol analogues for cannabinoid receptors CB_1 and CB_2

Compound	K_i[a] (nM)		Ratio CB_1/CB_2
	CB_1	CB_2	
Δ^8-THC	47.6	39.3	1.2
1a	0.65	3.1	0.2
1b	6.80	52	0.1
2a	95.49 (±16.67)	71.81 (±12.17)	1.3
2b	119 (±30.04)	51.7 (±12.79)	2.3
2c	57.77 (±7.17)	107.8 (±18.45)	0.5
2d	11.73 (±1.62)	9.39 (±1.54)	1.2
2e	27.9 (±5.06)	25.2 (±4.79)	1.1
2f	8.26 (±0.96)	3.86 (±0.47)	2.1
7a	638.1 (±106.4)	374.4 (±60.55)	1.7
7d	753.5 (±178.1)	221.6 (±36.75)	3.4
7e	255.4 (±45.2)	105 (±26.1)	2.4
7f	319 (±67.55)	110.7 (±22.68)	2.9

[a] Affinities for CB_1 and CB_2 were determined using rat brain (CB_1) or mouse spleen (CB_2) membranes and [^{3}H]CP-55,940 as the radioligand following previously described procedures.[4,16] K_i values were obtained from three independent experiments run in duplicate and are expressed as means of three values.

purified rat forebrain synaptosomes and mouse spleen synaptosomes were determined as described elsewhere.[4,16] K_i values calculated from the respective displacement curves are listed in Table 2 and serve as indicators for the affinities of these Δ^8-THC analogues for the CB_1 and CB_2 receptors.

The compounds reported in this study are Δ^8-THC analogues in which the C3 five-carbon linear side chain of Δ^8-THC was replaced with aryl and 1′,1′-cycloalkyl substituents. Interestingly, replacing the side chain of Δ^8-THC with bulky groups did not abolish binding affinity. Both 3-(1-naphthyl)-Δ^8-tetrahydrocannabinol and 1′,1′-cyclohexyl-1′-cyano analogues, **2d** and **2f**, exhibited enhanced affinities for CB_1 and CB_2 exceeding that of Δ^8-THC. Conversely, the 4-alkyl-phenyl cannabinoids **2a**–**2c** exhibited modest binding affinity for both cannabinoid receptors. More specifically, the methyl-phenyl analogue **2a** exhibited comparable binding affinity for the two cannabinoid receptors, whereas the ethyl-phenyl

analogue **2b** and the propyl-phenyl analogue **2c** showed moderate receptor selectivity. Analogue **2b** exhibited 2-fold CB_2 selectivity, while analogue **2c** showed preference for the CB_1 cannabinoid receptor. 1′,1′-Cyclopentyl-1′-cyano analogue **2e** exhibited adequate K_i values for both receptors without any selectivity whatsoever.

Cannabidiol analogues **7a**, **7d**, **7e** and **7f** exhibited enhanced CB_2 receptor selectivity although their binding affinities are approximately one order of magnitude lower than the binding values of their respective Δ^8-tetrahydrocannabinol analogues.

In conclusion, the present study shows that bulky substituents on the C3 position of the cannabinoid moiety are well tolerated by both receptors, whereas some preference for CB_1 or CB_2 is observed based on different chain lengths of the 4-alkyl-phenyl analogues or upon ring size variation at the C1′-position in the case of C1′-cyano-substituted cannabinoid analogues. The above findings provide interesting additions to the currently available SAR for the cannabinoid side chain, while opening up a new field of research on cannabinoid analogues characterized by the privileged biaryl substructure.

Acknowledgments

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13. (+)-*cis*/*trans*-*p*-Mentha-2,8-dien-1-ol was supplied by Firmenich, Princeton, NJ.
14. All new compounds **2a**, **2b**, **2c**, **2d**, **2e**, **2f**, **7a**, **7d**, **7e** and **7f** were fully characterized by NMR, MS and HRMS spectra. Selected data of final cannabinoids.
Compound **2a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, J = 7.9 Hz, 2H), 7.19 (d, J = 7.9 Hz, 2H), 6.68 (d, J = 1.8 Hz, 1H, 4-H), 6.50 (d, J = 1.8 Hz, 1H, 2-H), 5.45 (br s, 1H, 8-H), 4.84 (s, 1H, OH), 3.23 (dd, J = 17.1 Hz, J = 4.3 Hz, 1H, 10α-H), 2.76 (ddd as td, J = 11.0 Hz, J = 4.3 Hz, 1H, 10a-H), 2.36 (s, 3H, CH_3), 2.17 (m, 1H, 7α-H), 1.95–1.82 (m, 3H, 10β-H, 7β-H, 6a-H), 1.71 (s, 3H, 9-CH_3), 1.40 (s, 3H, 6β-CH_3), 1.13 (s, 3H, 6α-CH_3); mass spectrum *m*/*z* (relative intensity) 334 (M^+, 100), 291 (30), 266 (22), 251 (95), 205 (25), 84 (93). Exact mass calculated for $C_{23}H_{26}O_2$, 334.1933. Found: 334.1931.
Compound **2b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, J = 7.9 Hz, 2H), 7.22 (d, J = 7.9 Hz, 2H), 6.69 (d, J = 1.8 Hz, 1H, 4-H), 6.50 (d, J = 1.8 Hz, 1H, 2-H), 5.45 (br s, 1H, 8-H), 4.86 (s, 1H, OH), 3.24 (dd, J = 17.7 Hz, J = 4.4 Hz, 1H, 10α-H), 2.79–2.63 (m, 3H, 10a-H, –CH_2–), 2.17 (m, 1H, 7α-H), 1.95–1.82 (m, 3H, 10β-H, 7β-H, 6a-H), 1.72 (s, 3H, 9-CH_3), 1.41 (s, 3H, 6β-CH_3), 1.26 (t, J = 7.3 Hz, 3H, –CH_3), 1.14 (s, 3H, 6α-CH_3). Exact mass calculated for $C_{24}H_{28}O_2$, 348.2089. Found: 348.2091.
Compound **2c**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, J = 7.9 Hz, 2H), 7.19 (d, J = 7.9 Hz, 2H), 6.68 (d, J = 1.7 Hz, 1H, 4-H), 6.50 (d, J = 1.7 Hz, 1H, 2-H), 5.45 (br s, 1H, 8-H), 4.87 (s, 1H, OH), 3.23 (dd, J = 16.5 Hz, J = 4.3 Hz, 1H, 10α-H), 2.77 (m, 1H, 10a-H), 2.60 (t, J = 7.3 Hz, 2H, –CH_2–), 2.16 (m, 1H, 7α-H), 1.95–1.82 (m, 3H, 10β-H, 7β-H, 6a-H), 1.72 (s, 3H, 9-CH_3), 1.65 (m, 2H, –CH_2–), 1.40 (s, 3H, 6β–CH_3), 1.14 (s, 3H, 6α-CH_3), 0.95 (t, J = 7.3 Hz, 3H, –CH_3); mass spectrum *m*/*z* (relative intensity) 362 (M^+, 100), 347 (13), 319 (26), 294 (18), 279 (54), 241 (15). Exact mass calculated for $C_{25}H_{30}O_2$, 362.246. Found: 362.2246.
Compound **2d**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, J = 7.9 Hz, 1H), 7.88 (d, J = 7.3 Hz, 1H), 7.80 (d, J = 7.9 Hz, 1H), 7.50–7.40 (m, 4H), 6.59 (d, J = 1.8 Hz, 1H, 4-H), 6.40 (d, J = 1.8 Hz, 1H, 2-H), 5.48 (br s, 1H, 8-H), 4.87 (s, 1H, OH), 3.29 (dd, J = 15.9 Hz, J = 4.3 Hz, 1H, 10α-H), 2.82 (m, 1H, 10a-H), 2.19 (m, 1H, 7α-H), 1.98–1.87 (m, 3H, 10β-H, 7β-H, 6a-H), 1.74 (s, 3H, 9-CH_3), 1.41 (s, 3H, 6β-CH_3), 1.18 (s, 3H, 6α-CH_3); mass spectrum *m*/*z* (relative intensity) 370 (M^+, 100), 327 (36), 287 (80), 205 (60), 149 (67). Exact mass calculated for $C_{26}H_{26}O_2$, 370.1933. Found: 370.1930.
Compound **2e**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.51 (d, J = 1.8 Hz, 1H), 6.39 (d, J = 1.8 Hz, 1H), 5.70 (s, 1H, OH), 5.42 (d, J = 3.7 Hz, 1H, 8-H), 3.21 (dd, J = 15.5 Hz, J = 4.3 Hz 1H, 10α-H), 2.70 (td, J = 11.0 Hz, J = 4.9 Hz, 1H, 10a-H), 2.37 (m, 2H, –CH_2–), 2.11–1.86 (m, 10H, 7α-H, 10β-H, 7β-H, 6a-H, 6H–CH_2–), 1.70 (s, 3H, 9-CH_3), 1.37 (s, 3H, 6β-CH_3), 1.09 (s, 3H, 6α-CH_3); mass spectrum *m*/*z* (relative intensity) 337 (60), 294 (47), 254 (100), 205 (65). Exact mass calculated for $C_{22}H_{27}NO_2$, 337.2042. Found: 337.2041.
Compound **2f**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.56 (d, J = 1.8 Hz, 1H), 6.41 (d, J = 1.8 Hz, 1H), 5.87 (s, 1H, OH), 5.42 (d, J = 3.6 Hz, 1H, 8-H), 3.23 (dd, J = 16.0 Hz, J = 4.3 Hz, 1H, 10α-H), 2.71 (ddd as td, J = 11.0 Hz, J = 4.3 Hz, 1H, 10a-H), 2.11 (m, 3H, 7α-H, 2H–CH_2–),

1.81–1.64 (m, 14H, 10β-H, 7β-H, 6a-H, 9-CH_3, 8H –CH_2–), 1.37 (s, 3H, 6β-CH_3), 1.09 (s, 3H, 6α-CH_3); mass spectrum *m/z* (relative intensity) 351 (85), 308 (52), 268 (93), 205 (100). Exact mass calculated for $C_{23}H_{29}NO_2$, 351.2198. Found: 351.2198.

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