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Bioorganic & Medicinal Chemistry Letters 17 (2007) 3652–3656
Bioorganic & Medicinal Chemistry Letters

Biaryl cannabinoid mimetics—Synthesis and structure–activity relationship

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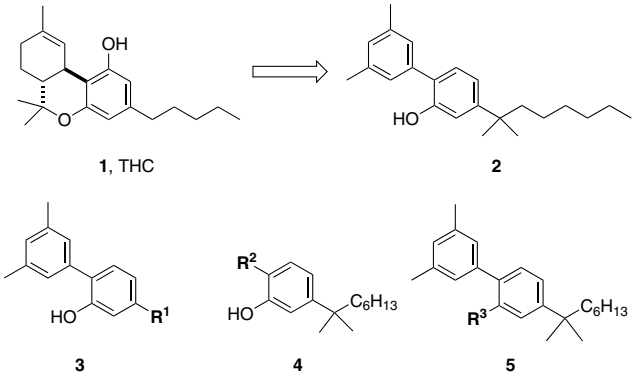
Received 2 March 2007; revised 10 April 2007; accepted 16 April 2007
Available online 25 April 2007

Abstract—Synthesis, in vitro biological evaluation, and structure–activity relationships of a biaryl cannabinoid mimetic **2** are reported. Variations in the substitution pattern yielded a number of agonists with low nanomolar affinity. Replacing the phenol group by a methyl morpholino acetate group led to compound **28**, a 500-fold selective CB_2 receptor agonist.

Δ^9-Tetrahydrocannabinol (THC, **1**) and other classical cannabinoids display a wide range of physiological effects including analgesic, anti-inflammatory, anticonvulsive, and immunosuppressive activities.[1] Two cannabinoid receptors have been cloned. The CB_1 receptor is mainly expressed in the CNS and the CB_2 receptor is localized mainly in peripheral tissues.[2] A number of SAR studies have explored the lipophilic side chain through variations in length, branching, spatial orientation or introduction of heteroatoms.[3] It has been shown that introducing a 1′,1′-dimethylheptyl- or 1′,1′-cyclopropylheptyl chain leads to enhanced affinity for both cannabinoid receptors.[4] Also it has been found that the tricyclic moiety in **1** is not essential for high cannabinoid receptor affinity as demonstrated by the biaryl phenol **2**, a cannabinoid mimetic originally described by researchers at Merck Frosst.[5]

To fully evaluate the potential of this underexplored but synthetically more accessible non-classical cannabinoid lead structure, we investigated modifications to the side-chain R^1 (**3**), top aryl group R^2 (**4**), and phenol replacements R^3 (**5**).



Previously **2** was synthesized in nine steps starting from 1,3-dimethoxy-5-(2-methyloctan-2-yl)benzene. This synthesis included a low yielding monophosphonation step (16%) resulting in a 4% yield overall.[5] Scheme 1 illustrates our shortened synthesis resulting in a 42% yield over six steps by adapting a procedure recently described by Papahatjis[4b] starting from commercially available (3-benzyloxyphenyl)acetonitrile **6**. After dialkylation with methylbromide gas in 50% aq NaOH, the nitrile intermediate was converted to aldehyde **7** with DIBAL-H. Wittig reaction with pentyltriphenylphosphonium bromide and NaH in DMSO and subsequent hydrogenation, followed by bromination, led to advanced intermediate **8** in good overall yield. The final step consisted of a Suzuki reaction with 3,5-

Keywords: Cannabinoid CB_1 receptors; Cannabinoid CB_2 receptors; Structure–activity relationships.
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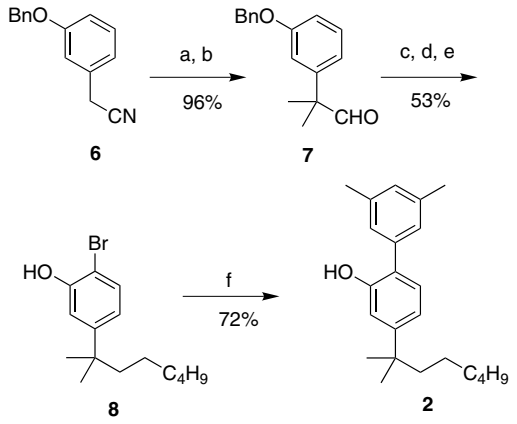
doi:10.1016/j.bmcl.2007.04.059

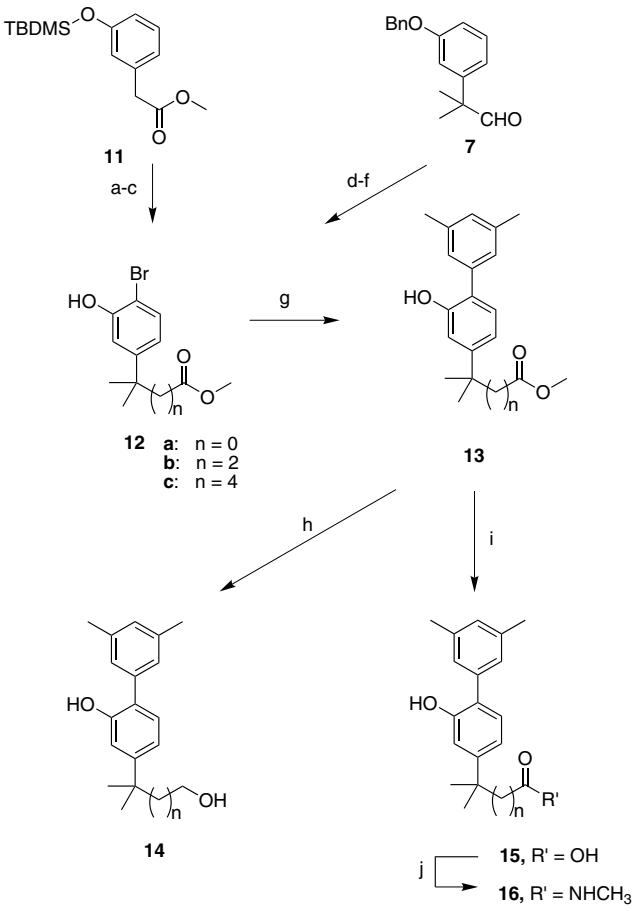


Scheme 1. Reagents and condition: (a) 50% aq NaOH, CH_3Br; (b) DIBAL-H, aq H_2SO_4; (c) NaH, DMSO, $PPh_3C_5H_{11}Br$; (d) H_2, 10% Pd/C; (e) Br_2, $CC1_4$; (f) 3,5-dimethylphenylboronic acid **9**, $Pd(PPh_3)_4$ cat., Cs_2CO_3, DMF, 90 °C.

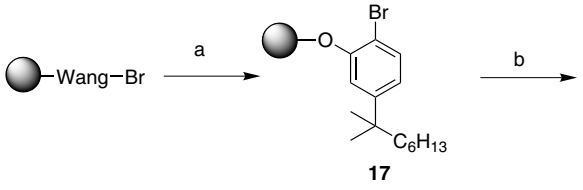
dimethylphenylboronic acid **9**, tetrakis-triphenylphosphine palladium, and cesium carbonate in DMF.

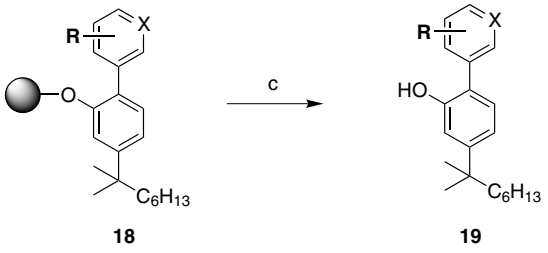
Scheme 2 describes utilizing this shortened approach to substitute the 1′,1′-dimethyl group in **2** with carbocycles of various ring sizes **10** to probe the steric limits of this system. Using the same starting material **6**, alkylations and ring closures were accomplished using 1,2-dichloroethane, 1,4-dibromobutane, and 1,5-dibromopentane, respectively, followed by the chemistry described for the synthesis of **2**.[6] Scheme 3 outlines the synthesis of analogs **3** with modifications of the hydrocarbon tail by varying length and substitution pattern which were investigated next. Three different ester core structures **12a–c** were prepared and converted to alcohols **14**, acids **15**, and amides **16**. The solid phase synthesis approach shown in Scheme 4 and the commercial availability of a diverse set of aryl boronic acids allowed access to a large number of analogs **4**. Coupling of **8** to solid support followed by Suzuki coupling and cleavage from resin yielded aryl- and heteroaryl-substituted analogs **19**.[7]

The phenol group in **2** seemed to be essential for the cannabinoid binding affinity of this biaryl system, since replacing it with hydrogen led to a striking loss of binding.[5] In order to further evaluate the effectiveness of the phenol functionality as a H-bond donor, it was replaced with a wide range of substituents displaying various

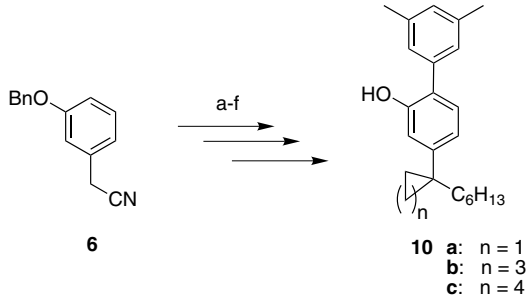


Scheme 3. Reagents and conditions: (a) MeI, DCM; (b) TBAF, THF; (c) Br_2, $CC1_4$; (d) NaH, DMSO, trimethyl phosphonoacetate or 4-(dimethoxyphosphoryl)but-2-enoic acid methyl ester; (e) H_2, 10% Pd/C; (f) Br_2, $CC1_4$; (g) 3,5-dimethyl-phenylboronic acid, $Pd(PPh_3)_4$ cat., Cs_2CO_3, DMF, 90 °C; (h) $NaBH_4$; (i) LiOH; (j) CH_3NH_2, TBTU, DIEA, acetonitrile, 25 °C.

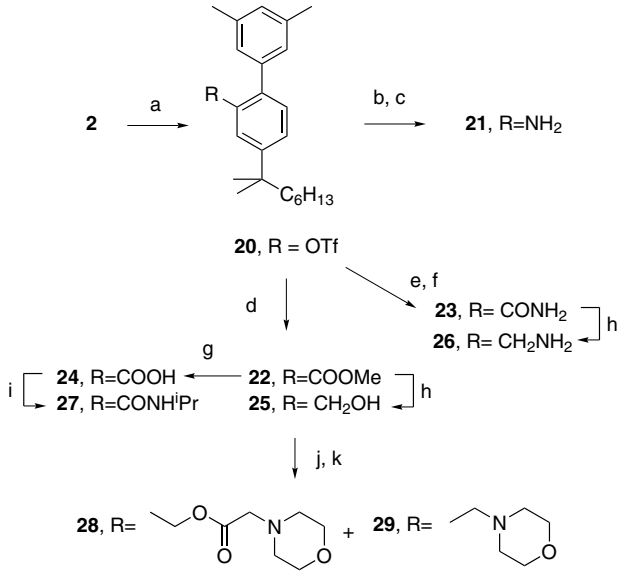




Scheme 4. Reagents and conditions: (a) Compound **8**, K_2CO_3, DMF, 80 °C; (b) boronic acids, $Pd(PPh_3)_4$ cat., Cs_2CO_3, DMF, 90 °C; (c) TFA/DCM (1:1).



Scheme 2. Reagents and condition: (a) LHMDS, HMPA, 1,2-dichloroethane, 1,4-dibromobutane, 1,5-dibromopentane; (b) DIBAL-H, aq H_2SO_4; (c) NaH, DMSO, $PPh_3C_5H_{11}Br$; (d) H_2, 10% Pd/C; (e) Br_2, $CC1_4$; (f) 3,5-dimethylphenyl boronic acid, $Pd(PPh_3)_4$ cat., Cs_2CO_3, DMF, 90 °C.

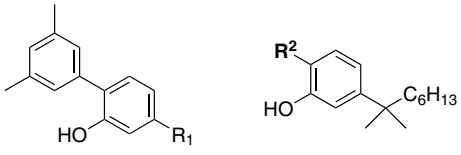


Scheme 5. Reagents and conditions: (a) $(Tf)_2O$/pyridine, DCM; (b) Ph_2CNH, $Pd_2(dba)_3$/dppf, NaO^tBu, toluene, 80 °C, 16 h; (c) H_2NOH-HCl, KOAc, MeOH, 25 °C, 1.5 h; (d) CO/$Pd(OAc)_2$/dppf, TEA, MeOH/DMSO; (e) $PdCl_2(PPh_3)_2$, HMDS, DMF, CO, 95 °C, 16 h; (f) 2 N aq H_2SO_4; (g) LiOH/H_2O/MeOH, rt; (h) LAH/THF, 0–25 °C; (i) TBTU, DIEA, $(CH_3)2CHNH_2$, 0–25 °C; (j) 2-bromoacetyl chloride, DCM; (k) morpholine.

H-bond strengths, H-bond orientations/conformations, and charge distributions. The synthesis is summarized in Scheme 5. The phenol replacement analogs **5** were prepared from **2** through the trifluoromethanesulfonate intermediate **20**. Cross-coupling with benzophenone imine catalyzed by $Pd_2(dba)_3$/dppf with NaO^tBu as base followed by hydrolysis gave the aniline **21**. Pd-catalyzed CO insertion with hexamethyldisilazane yielded analog **23**, which was then reduced by $LiAlH_4$ to generate compound **26**. A similar CO insertion catalyzed by $Pd(OAc)_2$ in MeOH/DMSO gave the methyl ester analog **22**, which was in turn reduced to a benzylic alcohol **25**. Analog **22** was also hydrolyzed to a carboxylic acid **24**, which was then coupled with isopropyl amine with assistance of TBTU to give amide **27**. Esterification of **25** with 2-bromoacetyl chloride followed by amination with morpholine generated not only the desired product **28**, but also a side product **29**.[8]

All the compounds[9] were evaluated in CB_1 and CB_2 binding studies.[10a] Active compounds were tested in [^{35}S]GTPγS binding and behaved as full agonists relative to the maximal effect of WIN55212-2.[10b] The results of the in vitro binding assays for side-chain analogs **3** and aryl modifications **4** are presented in Table 1. Connecting the two methyl groups into a cyclopropyl ring leads to some loss of activity, in contrast to what was

Table 1. Side chain and top modifications[a,b]



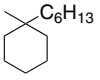
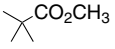
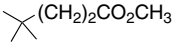
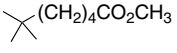
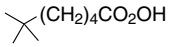
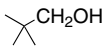
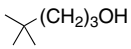
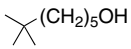
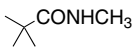
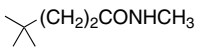
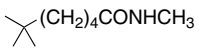
Compound	R^1	K_iCB_1 (nM)	K_iCB_2 (nM)	Ratio CB_1/CB_2	Compound	R^2	K_iCB_1 (nM)	K_iCB_2 (nM)	Ratio CB_1/CB_2
2		2.7	2.3	1	**18a**	2,6-Dimethylphenyl	1.7	18	0.1
10a		13	55	0.2	**18b**	2,5-Dimethylphenyl	4.6	6.6	0.7
10b		2.9	5.5	0.5	**18c**	2,3-Dimethylphenyl	49	20	2
10c		1.8	1.7	1	**18d**	3,4-Dimethylphenyl	600	830	0.7
13a		160	16	10	**18e**	2-Methoxyphenyl	1.7	1.0	2
13b		120	5.6	20	**18f**	2,3-Dimethoxyphenyl	34	7.8	4
13c		24	14	2	**18g**	3-Methoxyphenyl	91	580	0.2
15a		>1000	>1000	n.d.	**18h**	3,4-Dimethoxyphenyl	1400	1700	0.8

Table 1 (*continued*)

Compound	R^1	K_iCB_1 (nM)	K_iCB_2 (nM)	Ratio CB_1/CB_2	Compound	R^2	K_iCB_1 (nM)	K_iCB_2 (nM)	Ratio CB_1/CB_2
15b		>1000	>1000	n.d.	**18i**	2-Aminophenyl	5.2	17	0.3
14a		2200	600	4	**18j**	3-Aminophenyl	15	44	0.3
14b		1100	56	20	**18k**	4-Aminophenyl	320	1000	0.3
14c		39	3.6	10	**18l**	3-Cyanophenyl	27	45	0.6
16a		>1000	>1000	n.d.	**18m**	4-Cyanophenyl	>1000	>1000	n.d.
16b		840	140	6	**18n**	Phenyl-3-carboxylic acid	>1000	>1000	n.d.
16c		96	39	2	**18o**	3-Pyridyl	23	20	1

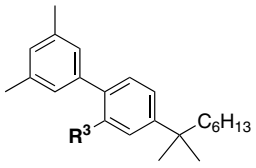
[a] Values are geometric means computed from at least three separate determinations.
[b] For assay description, see Ref. 10.

observed for THC analogs.[4b] Increasing the ring size restores affinity and substitutions up to a six-membered ring in **3** are well accepted, indicating some tolerance for steric bulk in the C1′-subsite. In general, longer side chains give better binding, as seen in THC analogs. Introduction of a carboxylic acid group results in loss of affinity for both receptors ($K_i > 1000$ nM). The CB_2 receptor seems more tolerant toward polar groups in R^1, accepting alcohol, ester, and amide functionalities. Ester **13b** and alcohol **14b** exhibit a 20-fold selectivity for the CB_2 receptor. In compound **4** activity is retained relative to compound **2** when the top aryl ring is substituted in the 2 and/or 3 positions, with the 2-position being preferred. Substitution in the 4-position reduces receptor affinities by about two orders of magnitude compared to substitution in the 2-position and again the introduction of a carboxylic acid group leads to a loss of affinity at both receptors. Aryl analogs **4** did not show significant selectivity for either receptor with the exception of **18a** with a modest 10-fold selectivity for the CB_1 receptor.

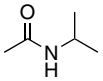
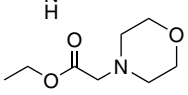
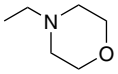
The results for analogs **5** are summarized in Table 2. Replacing the phenol group in **2** leads generally to a significant loss of potency at both receptors with the methoxy and amino compounds **30** and **21** retaining some binding affinity to CB_2. Introducing a methyl morpholino acetate considerably enhances the CB_2 binding affinity of the benzylic alcohol precursor **25** leading to the discovery of **28** with a selectivity for the CB_2 receptor of 500-fold.

Overall the side-chain SAR was comparable to that reported for THC analogs.[3,4] This general observation does not extend to the introduction of a cyclopropyl ring, which leads to an increase in affinity for THC analogs[4b] but to a loss of affinity in the biaryl system (**10a**). The high selectivity for the CB_2 receptor observed in **28**

Table 2. Phenol replacements[a,b]



5

Compound	R^3	K_iCB_1 (nM)	K_iCB_2 (nM)	Ratio CB_1/CB_2
22	–OH	2.7	2.3	1
30[11]	$-OCH_3$	320	34	9
31[5]	–H	>30000	2138	>10
21	$-NH_2$	80	51	2
22	$-COOCH_3$	230	110	2
23	$-CONH_2$	370	320	1
24	–COOH	>1000	>1000	n.d.
25	$-CH_2OH$	360	480	0.8
26	$-CH_2NH_2$	1500	380	4
27		>1000	>1000	n.d.
28		370	0.81	500
29		3900	660	6

[a] Values are geometric means computed from at least three separate determinations.
[b] For assay description, see Ref. 10.

was not paralleled in the tricyclic system, suggesting a divergence in the SAR and promising areas for future exploration. In summary, these synthetically more accessible biaryl cannabinoid mimetics may represent a valid starting point for the development of more selective ligands. The results of a combinatorial approach examining substitutions in the R^1, R^2, and R^3 positions conducted in our laboratories will be reported subsequently.

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8. Zhou, Q. J.; Worm, K.; Dolle, R. E.; Stabley, G.; DeHaven, R. N. *Abstracts of Papers*, 230th National Meeting of the American Chemical Society, Washington, DC; American Chemical Society: Washington, DC, 2005; MEDI 88.
9. New compounds were fully characterized by ^{1}H NMR and LC/MS.
10. Binding assays were performed by modification of the method of (a) Pinto, J. C.; Potie, F.; Rice, K. C.; Boring, D.; Johnson, M. R.; Evans, D. M.; Wilken, G. H.; Cantrell, C. H.; Howlett, A. *Mol. Pharmacol.* **1994**, *46*, 516, Receptor binding assays were performed by incubating 0.2–0.6 nM [^{3}H]CP55940 with membranes prepared from cells expressing cloned human CB_1 or CB_2 receptors in buffer consisting of 50 mM Tris–HCl, pH 7.0, 5.0 mM $MgCl_2$, 1.0 mM ethylene glycol-bis(2-aminoethylether)-*N*,*N*,*N*′,*N*′-tetraacetic acid (EGTA), and 1.0 mg/ml fatty acid-free bovine serum albumin. After incubation for 60 min at room temperature for CB_2 binding or 120 min at 30 °C for CB_1 binding, the assay mixtures were filtered through GF/C filters that had been pre-soaked overnight in 0.5% (w/v) poly(ethyleneimine) and 0.1% BSA in water. The filters were rinsed six times with 1 ml each of cold assay buffer, 30 μl of MicroScint 20 (Perkin-Elmer) was added to each filter, and the radioactivity on the filters was determined by scintillation spectroscopy in a TopCount (Perkin-Elmer). Nonspecific binding was determined in the presence of 10 μM WIN55212-2.; The [^{35}S]GTPγS binding method is a major modification of the method by (b) Selley, D. E.; Stark, S.; Sim, L. J.; Childers, S. R. *Life Sci.* **1996**, *59*, 659, CB_2-mediated stimulation of [^{35}S]GTPγS binding was measured in a mixture containing 100–150 pM [^{35}S]GTPγS, 150 mM NaCl, 45 mM $MgCl_2$, 3 μM GDP, 0.4 mM dithiothreitol, 1.0 mM EGTA, 1.0 mg/ml fatty acid-free bovine serum albumin, 25 μg of membrane protein, and agonist in a total volume of 250 μl of 50 mM Tris–HCl buffer, pH 7.0, in 96-well Basic FlashPlates (Perkin-Elmer). After incubation at room temperature for 6 h, the plates were centrifuged at 800*g* at 4 °C for 5 min and the radioactivity bound to the membranes was determined by scintillation spectrometry using a TopCount (Perkin-Elmer). The extent of stimulation over basal [^{35}S]GTPγS binding was calculated as a percentage of the stimulation by 10 μM WIN55212-2. Basal [^{35}S]GTPγS binding was determined in the absence of agonist. Generally, the stimulation by 10 μM WIN55212-2 was between 50% and 100% over basal binding. Full agonists stimulate binding to the same maximal extent as WIN55212-2.
11. Zhou, Q. J.; Worm, K.; Dolle, R. E. *J. Org. Chem.* **2004**, *69*, 5147.