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Synthesis and structure–activity relationship of substitutions at the C-1 position of Δ9-tetrahydrocannabinol

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ABSTRACT

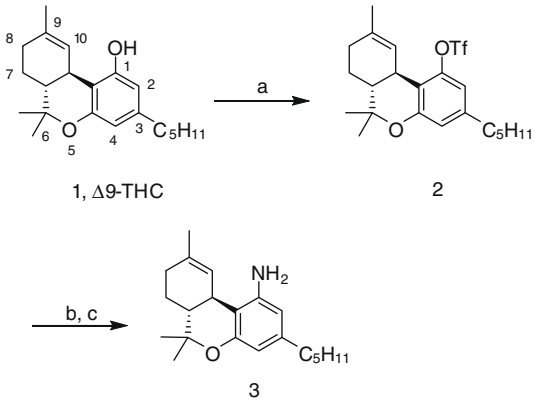
A novel series of Δ9-tetrahydrocannabinol (Δ9-THC) analogues were synthesized to determine their potential as cannabinoid receptor modulators. Chemistry focused on conversion of the phenol of Δ9-THC to other functionality through palladium catalyzed reactions with an intermediate triflate **2**. Two analogues with sub 100 nM affinity for the CB_1 and CB_2 receptors were identified.

Cannabinoid receptor type 1 (CB_1) and cannabinoid receptor type 2 (CB_2) are G-protein coupled receptors. The CB_1 receptors are found primarily on central and peripheral neurons while CB_2 receptors are located in the periphery.[1] There is much interest in cannabinoids for their therapeutic potential. CB_1 agonists have the potential to treat pain, neurodegenerative disease, and glaucoma.[2] Also of interest are CB_2 agonists which have the potential to treat neuropathic pain, asthma, allergies, rheumatoid arthritis, atherosclerosis, and autoimmune diseases.[2] Therapeutic interest of CB_1 antagonists includes use for the treatment of obesity, smoking cessation, and psychosis.[2] Currently, Dronabinol (Δ9-THC) and Nabilone are marketed for nausea and vomiting and Nabilone is undergoing clinical trials for neuropathic pain.

Our goal was to discover selective CB_2 agonists for the treatment of neuropathic pain by modifying Δ9-THC (**1**) at the C-1 position. Substitution has been explored at the C-1 position of some cannabinoids.[3] We focused on examining amino, amide, thiol, and aminomethyl analogues of Δ9-THC which have not been reported in the literature. Analogues were designed to be relatively small and/or to decrease lipophilicity. Since Δ9-THC (**1**) is very lipophilic, it was desired to synthesize analogues with polar groups or heterocycles to increase water solubility and potentially reduce brain exposure. Compounds that are selective for CB_2 and with reduced brain penetration would provide separation from potential CNS side effects due to CB_1 agonism.

The synthesis of amine **3** is illustrated in Scheme 1. Δ9-Tetrahydrocannabinol[4] (**1**) was converted to trifluoromethanesulfonate intermediate **2**. Cross-coupling of **2** with benzophenone imine catalyzed with $Pd(OAc)_2$/(*R*)-BINAP followed by hydrolysis gave amine **3**.[5]

As shown in Scheme 2, trifluoromethanesulfonate intermediate **2** was converted to nitrile **4** with zinc cyanide and $Pd(PPh_3)_4$.[6] Nitrile **4** was reduced with $LiAlH_4$ to provide amine **6**. Palladium catalyzed CO insertion with $Pd(OAc)_2$/Xantphos in DMSO with *N*-hydroxysuccinimide present gave *N*-hydroxysuccinimide ester **5**.[7] Couplings of ester **5** with amines failed to give desired amides or were low yielding (amides **7e** and **7f** were obtained by this route in 17% and 18% yields, respectively). The low yields were due to competitive addition at the succinimide carbonyls. To obtain additional amide analogues in greater yields ester **5** was converted to carboxylic acid **7a** and couplings were achieved with EDCI/HOBT in 59–62% yields.



1, Δ9-THC 2 3

Scheme 1. Reagents: (a) $(Tf)_2O$, DIPEA, CH_2Cl_2; (b) $Ph_2C{=}NH$, $Pd(OAc)_2$, (*R*)-BINAP, Cs_2CO_3, THF; (c) THF, H_2O, HCl.

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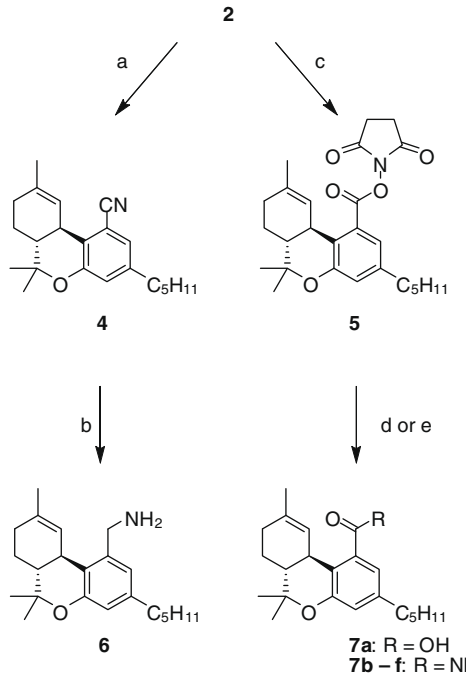
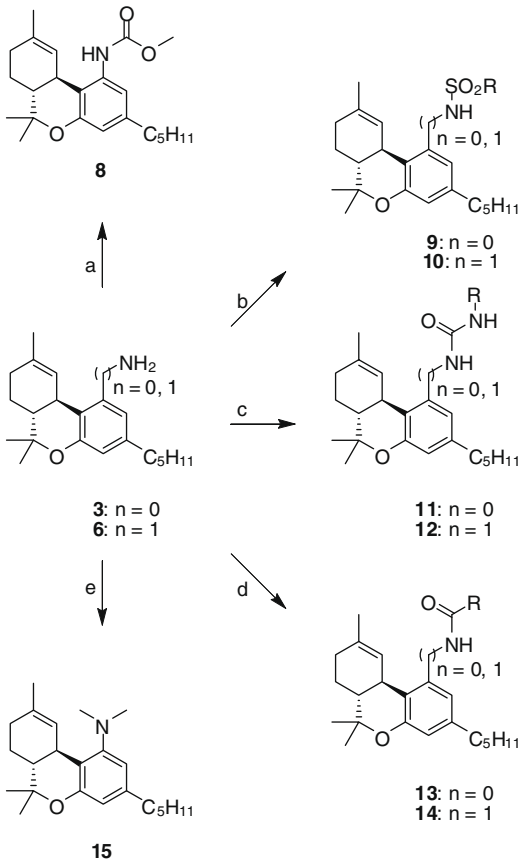
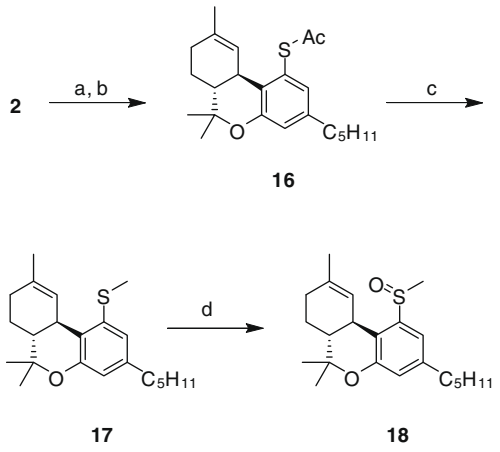


Scheme 2. Reagents and conditions: (a) $Zn(CN)_2$, $Pd(PPh_3)_4$, DMF, 100 °C; (b) $LiAlH_4$, THF; (c) CO, *N*-hydroxysuccinimide, Xantphos, $Pd(OAc)_2$, DIPEA, DMSO, 70 °C; (d) amine, THF, reflux; (e) THF, H_2O, Et_3N, reflux then amine, EDCI, HOBT, DIPEA, DMF.



Scheme 3. Reagents: (a) methyl chloroformate, Et_3N, CH_2Cl_2; (b) sulfonyl chloride, pyridine, CH_2Cl_2; (c) isocyanate, DMF or THF, heat; (d) acid chloride, Et_3N, CH_2Cl_2; (e) MeI, K_2CO_3, CH_3CN.



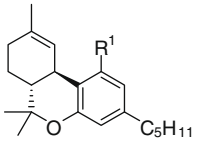
Scheme 4. Reagents and conditions: (a) $Pd(OAc)_2$, PPh_3, Cs_2CO_3, TIPS-SH, toluene, 100 °C; (b) Ac_2O, TBAF, THF; (c) KOH in MeOH, MeI, EtOH; (d) *m*-CPBA, CH_2Cl_2, −10 °C.

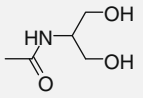
Amines **3** and **6** were elaborated as shown in Scheme 3. A diverse set of compounds including carbamates, sulfonamides, ureas, amides, and substituted amines were synthesized. Carbamate **8** was obtained by treatment of compound **3** with methyl chloroformate. Sulfonamides **9** and **10** were prepared from reaction of **3** or **6** with the desired sulfonyl chloride. Urea **11b** was synthesized from reaction of amine **3** with methylisocyanate. The unsubstituted ureas **11a** and **12** were arrived at from treatment of amine **3** or **6** with trimethylsilylisocyanate.[8] A series of amides **13a–c** and **14** were prepared from reaction of the desired acid chloride with **3** or **6**. Alkylation of amine **3** with methyl iodide provided the di-methylated product **15**.

Synthesis of the sulfur analogues is outlined in Scheme 4. Triflate **2** was treated with triisopropylsilanethiol using $Pd(OAc)_2$/PPh_3 to provide the TIPS protected thiol.[9] Treatment of the protected thiol with acetic anhydride followed by a solution of TBAF in THF provided thioacetate **16**.[10] The thioacetate was treated with KOH and methyl iodide to provide **17** and oxidized with *m*-CPBA to afford diastereomers **18a–b** which were separated by silica gel chromatography.

The carboxylic acid and the amide analogues shown in Table 1 were tested in both CB_1 and CB_2 in vitro binding assays.[11,12] These derivatives were all found to give greater than 3 μM affinities for the CB_1 receptor. Acid **7a** and bis-amide **7e** are not tolerated while

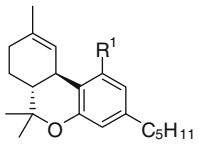
Table 1
Acid and amide analogues

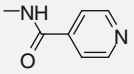


Compound	R^1	CB_1 K_i (nM)	CB_2 K_i (nM)
1	–OH	40[a]	36[a]
7a	$-CO_2H$	>3000	>3000
7b	$-CONH_2$	>3000	2190
7c	$-CONHCH_3$	>3000	1260
7d	$-CON(CH_3)_2$	>3000	1210
7e	$-CONHCH_2CONH_2$	>3000	>3000
7f		>3000	2000

[a] See Ref. 13.

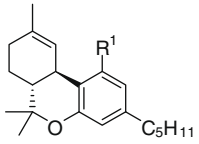
Table 2
Amino and aminomethyl analogues



Compound	R^1	CB_1 K_i (nM)	CB_2 K_i (nM)
3	$-NH_2$	616[a]	215[a]
4	–CN	1720[a]	387[a]
8	$-NHCO_2CH_3$	>3000	1400
9	$-NHSO_2CH_3$	>3000	1720
11a	$-NHCONH_2$	>3000	>3000
11b	$-NHCONHCH_3$	>3000	2050
13a	$-NHCOCH_3$	>3000	1400
13b	$-NHCOCH_2N(CH_3)_2$	>3000	>3000
13c		>3000	1770
15	$-N(CH_3)_2$	>3000	>3000
6	$-CH_2NH_2$	>3000	>3000
10	$-CH_2NHSO_2CH_3$	>3000	>3000
12	$-CH_2NHCONH_2$	>3000	782
14	$-CH_2NHCOCH_3$	>3000	1500

[a] $n = 2$.

Table 3
Thiol analogues



Compound	R^1	CB_1 K_i (nM)	CB_2 K_i (nM)
17	$-SCH_3$	955	469
18a	$-SOCH_3$ diast A	>3000	1930
18b	$-SOCH_3$ diast B	>3000	>3000

other amides (**7b–d** and **7f**) maintain low micromolar affinity at the CB_2 receptor.

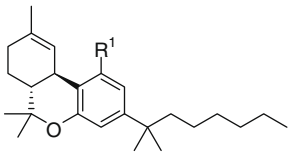
The in vitro results for the amino and aminomethyl analogues are presented in Table 2.[11,12] The primary amine **3** and nitrile **4** showed affinity for both receptors with a 3–4-fold selectivity for the CB_2 receptor. Conversion of **3** into carbamates, sulfonamides, ureas, or amides resulted in a sixfold or greater loss in activity for both the CB_1 and CB_2 receptors. Insertion of a methylene spacer generally resulted in loss of potency (**3** vs **6**; **9** vs **10**), however urea **12** did show improved CB_2 affinity compared to **11a**. The data indicates that small polar groups are well tolerated with regard to activity and selectivity.

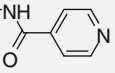
Table 3 provides the results for the thiol analogues.[11,12] The thiomethyl ether analogue **17** demonstrated affinity for both receptors with a twofold selectivity for CB_2 over the CB_1 receptor. Oxidation of **17** to the corresponding sulfoxide resulted in loss of activity in both diastereomers **18a–b**.

The 1,1-dimethylheptyl (DMH) sidechain commonly increases potency of Δ9-THC analogues by 100–200-fold.[14] Consequently, analogues where the *n*-pentyl side chain of Δ9-THC was replaced with a DMH sidechain were also explored.[11] The binding results of this series are shown in Table 4.[12] The binding affinities for Δ9-THC–DMH, **19**, are shown in the table for comparison.

In general the functionalized DMH analogues demonstrated an increased affinity for both CB_1 and CB_2. As expected from our previous results small groups provide both affinity and selectivity. Compounds **20** and **21** demonstrate comparable affinities for both the CB_1 and CB_2 receptors as Δ9-THC (**1**). Also, nitrile **20** shows a 13-fold selectivity for CB_2 over the CB_1 receptor, representing a significant improvement over Δ9-THC.

Table 4
1,1-Dimethylheptyl analogues



Compound	R^1	CB_1 K_i (nM)	CB_2 K_i (nM)	CB_1/CB_2 Ratio
19	–OH	0.24[a]	0.20[a]	1
20	–CN	67.8[b]	5.3[b]	13
21	$-NH_2$	11.7[b]	2.9[b]	4
22	$-NHCOCH_3$	1340	216	6
23	$-NHCONHCH_3$	333	257	1
24		>3000	1090	>3
25	$-NHSO_2CH_3$	1840	255	7

[a] See Ref. 14a.
[b] $n = 2$.

In summary, a series of novel Δ9-THC analogues were synthesized. The synthetic strategy to convert the phenol of Δ9-THC to other functionalities via the aryl triflate was successful. From these efforts two hits with approximately 300 nM affinity for the CB_2 receptor were discovered. Conversion of the *n*-pentyl sidechain to the DMH sidechain increased potency of the hits to <10 nM. This data indicates that potent and selective compounds for the CB_2 receptor can be achieved by modification of Δ9-THC.

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