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Triaryl bis-sulfones as cannabinoid-2 receptor ligands: SAR studies

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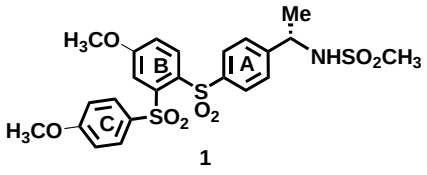
Abstract—We recently reported that compound **1** is a potent inhibitor of the CB2 receptor with high selectivity over CB1. This paper describes the SAR development for this class of compounds. Variation of the substitution pattern on the aromatic rings, as well as the groups linking them together, led to sub-nanomolar inhibitors of the CB2 receptor, with high selectivity over CB1.

1. Introduction

The CB2 receptor is a G-protein coupled receptor that was identified in 1993.[1] It is located primarily in the spleen and other immune-related tissues and is 44% homologous with CB1. The discovery of CB2 offered the possibility that immune-related biological effects of cannabinoid compounds could be obtained without the psychoactive effects typical of cannabinoid ligands that inhibit the CB1 receptor and enter the CNS, such as Δ9-THC.[2] Reported functions of CB2 include modulation of B-cell differentiation,[3] altered migration,[4] altered antigen processing[5] in macrophages, and altered cannabinoid-mediated anti-tumor activity.[6] Cannabinoid ligands have shown in vivo efficacy in rodent models of pain,[7–9] rheumatoid arthritis,[10,11] and multiple sclerosis[12], providing support to the idea that CB2 inhibitors might be useful as a new class of drugs to modulate the immune system.[13]

We recently disclosed compound **1**, a novel CB2-selective triaryl bis-sulfone.[14] Here, we describe SAR studies on **1**, where the impact of varying the nature of benzylic methyl, alternates for the sulfone linkers, and the substitution pattern on the aromatic rings are described.



1

2. Chemistry

Changes to the benzylic carbon were made by starting with the appropriate benzylamine and applying the chemistry previously reported.[14] Sulfone modifications were effected by chemistry shown in Schemes 1 and 2. Scheme 1 starts with the assembly of the B and C phenyl rings by ortholithiation of a 4-substituted benzaldehyde,[15] and quenching with a substituted phenyl disulfide, to provide **3**.[16] Halogen metal exchange on **4**, followed by reaction with **3**, led to **5**. Reduction of **5**, oxidation of the B, C-linker to sulfone, amine deprotection, followed by sulfonylation with methanesulfonyl chloride, resulted in **6**. Alternately, PCC oxidation of **5,** followed by oxidation of B, C-linker to sulfone, hydrolysis of the TFA group, and sulfonylation, led to compound **7**. Conversion of **7** to **8** was carried out via the Wittig procedure. Compound **7** was also converted to oxime **9** (1:1 *E* and *Z* mixture) with methoxylamine.

Keywords: CB2–CB1 receptor ligands; Inverse agonists; Cannabinoid receptors; Immunomodulatory; Anti-inflammatory.
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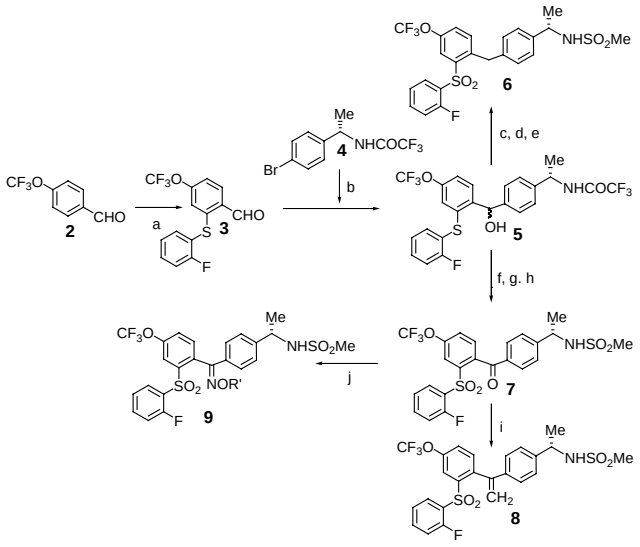
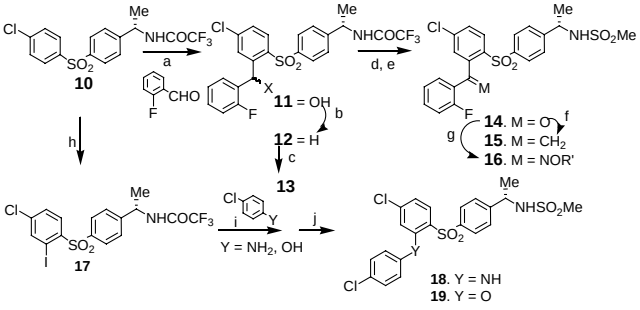


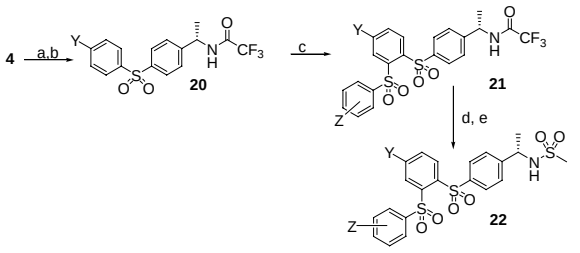
Scheme 1. Reagents and conditions: (a) i. *N*,*N*,*N*-Trimethylethylenediamine, *n*-BuLi, THF, −20 °C; ii. 4-trifluoromethoxybenzaldehyde; iii. *n*-BuLi (3 equiv), bis(2-fluorophenyl)disulfide (2 equiv), THF, −40 °C; (b) **4**, CH_3Li, *n*-BuLi, THF, −78 °C; (c) $(C_2H_5)_3SiH$, $BF_3{\cdot}(OEt)_2$, CH_2Cl_2, rt; (d) *m*-chloroperoxybenzoic acid (5 equiv), CH_2Cl_2, rt; (e) i. LiOH (3 equiv), dioxane; ii. $(C_2H_5)_3N$ (5 equiv), CH_3SO_2Cl (2 equiv); (f) PCC, CH_2Cl_2, rt; (g) *m*-chloroperoxybenzoic acid (5 equiv), CH_2Cl_2, rt; (h) i. LiOH (3 equiv), dioxane; ii. pyridine (10 equiv), CH_3SO_2Cl (4 equiv); (i) $LiN(Si(CH_3)_3)_2$ (3 equiv), $CH_3P(Ph)_3Br$ (2 equiv), THF, 0 °C; (j) $R'ONH_2{\cdot}HCl$ (20 equiv), pyridine, 80 °C.



Scheme 2. Reagents and conditions: (a) *n*-BuLi, THF, −78 °C; 2-fluorobenzaldehyde; (b) $(C_2H_5)_3SiH$, $BF_3{\cdot}(OEt)_2$, CH_2Cl_2, rt; (c) i. LiOH, dioxane; ii. $(C_2H_5)_3N$, CH_3SO_2Cl; (d) PCC, CH_2Cl_2, rt; (e) i. LiOH, dioxane; ii. $(C_2H_5)_3N$, CH_3SO_2Cl; (f) $LiN(Si(CH_3)_3)_2$, $CH_3P(Ph)_3Br$, THF, 0 °C; (g) $R'ONH_2{\cdot}HCl$, pyridine, 80 °C; (h) *n*-BuLi, , I_2, THF, −78 °C; (i) i. $Pd(OAc)_2$, P^tBu_3, $NaOBu^t$, 4-chloroaniline, toluene, 120 °C (sealed tube); ii. NaH, $CuBr{\cdot}(CH_3)_2S$, 4-chlorophenol, toluene, 120 °C (sealed tube); (j) i. LiOH, dioxane; ii. $(C_2H_5)_3N$, CH_3SO_2Cl.

Scheme 2 utilizes preassembled[17] **10**. Ortholithiation of **10** followed by treatment with 2-fluorobenzaldehyde, provided **11**, which was transformed to analogs **14**, **15**, and **16**, as described in Scheme 1. The nitrogen- and oxygen-linked compounds **18** and **19** were accessed by palladium- and copper-mediated[18] coupling of 2-iodo derivative **17**, which itself was obtained from **10** by ortholithiation and iodide quenching.

Scheme 3 describes compounds that were prepared in which one or both of the methoxy groups were replaced



Scheme 3. (a) 2.1 equiv *n*-BuLi, THF–hexanes, −78 °C, (b) Y-phenylsulfonyl fluoride, (c) 2.1 equiv *n*-BuLi, THF–hexanes, −78 °C, then *Z*-aryl sulfonyl fluoride, −78 °C to rt overnight, (d) 1.0 M aq LiOH, dioxane, and (e) methanesulfonyl chloride, Et_3N, CH_2Cl_2.

by halogen or other moieties.[19] (Table 3). Halogen metal exchange of **4** with *n*-butyl lithium, followed by trapping with an aryl sulfonyl fluoride, afforded **20**.

Compound **20** was treated with two equivalents of *n*-butyl lithium and then trapped with an aryl sulfonyl fluoride to give intermediate **21**. Deprotection and sulfonylation of the benzylic amine gave **22**.

3. Results and discussion

Table 1 shows the outcome of altering the stereochemistry and the substitution on the benzylic carbon. The antipode of **1** was less active and less selective. Introduction of an additional methyl group (**1b**), rendering the benzylic carbon achiral, decreased affinity and selectivity. Removal of the methyl group provided the equipotent and more selective compound **1c**. However, the potential increase in metabolic activity at this less hindered benzylic site was not desirable, and the original substitution and stereochemistry were retained. Transforming L_1 from SO_2 to CH_2 provided compounds with good affinity for CB2, but with varying selectivity. Compounds **25** vs. **28** show comparable activity for substitution at the 2-position over the 3-position of the C-ring. However, compounds **23** and **24** showed the best profile with respect to CB2 affinity and selectivity, and both of them retained an oxygen at the 4-position of the B-ring. Aiming to optimize substitution at L_1, additional linkers were investigated (**9**, **33**, and **34**). Sulfone- and methylene-linked (L_1) analogs were preferred, as presented in Table 2.

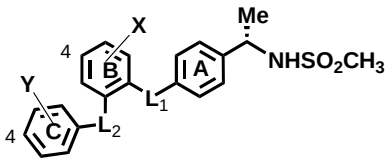
L_2 SAR was investigated, and a similar strategy of screening different functional groups was initiated. The L_2-linkers examined were significantly less active compared to the original sulfone.

Table 1. Benzylic carbon variant of **1**

Compounds	Benzyl carbon	K_i[a] (CB2 nM)	Selectivity (CB1 K_i/CB2 K_i)
1	$CHCH_3$ (*S*)	0.4	2262
1a	$CHCH_3$ (*R*)	30	105
1b	$C(CH_3)_2$	6	282
1c	CH_2	1.3	2168

[a] Individual data points for determinations of K_i for CB1 and CB2 were carried out in triplicate, in two separate assays.

Table 2. Linker (L_1; L_2) and substitution (X; Y) variants of **1**



Compound	L_1	L_2	X	Y	K_i[a] (CB2 nM)	Selectivity (CB1 K_i/CB2 K_i)
23	CH_2	SO_2	4-OCH_3	4-OCH_3	0.6	1300
8	CH_2	SO_2	4-Cl	4-Cl	6.7	188
24	CH_2	SO_2	4-OCF_3	2-F	0.4	1178
25	CH_2	SO_2	4-CF_3	2-F	1	674
26	CH_2	SO_2	4-CF_3	2, 6-Di F	1.8	584
27	CH_2	SO_2	4-OCF_3	2-OCF_3	16	60
28	CH_2	SO_2	4-CF_3	3-F	3.5	438
29	CH_3	SO_2	4-OCF_3	3-CF_3	35	27
30	CO	SO_2	4-OCH_3	4-OCH_3	44	108
31	CO	SO_2	4-OCF_3	2-F	179	28
32	CO	SO_2	4-Cl	4-Cl	410	16
33	$C(CH_3)_2$	SO_2	4-Cl	4-Cl	76	48
9	$C{:}CH_2$	SO_2	4-OCF_3	2-F	86	19
34	$C{:}NOCH_3$	SO_2	4-Cl	4-Cl	406	5
35	SO_2	CH_2	4-Cl	4-Cl	164	11
36	SO_2	CO	4-Cl	4-Cl	192	284
15	SO_2	$C{:}CH_2$	4-Cl	2-F	247	17
37	SO_2	$C(CH_3)(OH)$	4-Cl	2-F	77	111
38	SO_2	$C(CH_3)(OH)$	4-Cl	4-Cl	230	25
18	SO_2	NH	4-Cl	4-Cl	278	5
19	SO_2	O	4-Cl	4-Cl	983	3

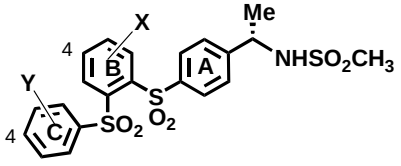
[a] Individual data points for determinations of K_i for CB1 and CB2 were carried out in triplicate, in two separate assays.

After ascertaining that sulfone offered the best in vitro profile for L_1 and L_2, with the least metabolic risk, we revisited substitution on the aromatic rings. A series of compounds were prepared in which one or both of the methoxy groups of compound **1** were replaced with other moieties (Table 3).

In general, the B-ring methoxy replacements were well-tolerated, although there seems to be a preference for smaller substituents. Small alkoxy substituents are highly potent at CB2 and show good selectivity (compound **39**–**42**). When the *O*-alkyl group becomes too large however, the affinity at CB2 decreases (compound **42**). Small alkyl substitution (CF_3/CH_3) gave compounds with subnanomolar activity (compounds **45**, **46**). Compounds where X = H are less active than those with substitution at this position (compounds **44**, **47**).

While the in vitro profiles of compounds **39** and **45** are desirable, we favored **46** due to its putative metabolic stability. Exploring other putatively stable groups, we examined chlorine as an alternate to 4-CF_3 and varied substitution on the C-ring (compounds **16**–**28**). A preference for smaller groups was observed (compounds **48** and **52** vs. **53**). Fluorine substitution gave somewhat more potent compounds than hydrogen substitution (compounds **48** vs. **52**). The compound with the best combination of potency and CB2 selectivity was **52**, although **46** was similar. Compound **52** gave an AUC of 6331 nM h when dosed orally in rats,[20] indicating that the combination of chlorine and fluorine was effective at decreasing the oxidative metabolism observed for compound **1**. Like compound **1**, compound **52** is an inverse agonist at the CB2 receptor, as indicated by its effect on the binding of [^{35}S]GTPγS to the CB2 receptor[21] (Fig. 1).

Table 3. Substitution (X; Y) variants of **1**.



Compound	X	Y	K_i[a] (CB2 nM)	CB1 K_i/ CB2 K_i
1	4-OCH_3	4-OMe	0.4	2262
39	4-OCH_3	H	0.6	2482
40	4-OCH_3	4-Cl	0.9	1146
41	4-OH	4-Cl	13	2315
42	4-O-c-C_5H_9	4-Cl	232	11
43	4-CF_3	4-Cl	8	558
44	H	4-Cl	58	127
45	4-CH_3	2-F	0.5	1741
46	4-CF_3	2-F	0.9	3552
47	H	2-F	9	1449
48	4-Cl	H	2	1941
49	4-Cl	2-Cl	6	1778
50	4-Cl	3-Cl	23	238
51	4-Cl	4-Cl	10	687
52	4-Cl	2-F	1	4387
53	4-Cl	2-OCF_3	128	134

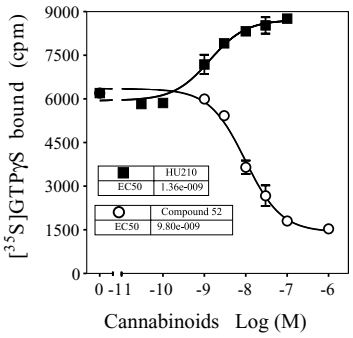


Figure 1. Effect of cannabinoids on [35S]GTPgS exchange in SF9 hCB2 membranes.

4. Conclusions

We have studied the SAR of the CB2 antagonist **1**, targeting the nature of the chiral benzylic carbon, substitution on the aromatic rings, and the linkers L_1 and L_2. Achiral benzylic analog **1c** maintained significant activity, while all other variations resulted in loss of activity. Changes at L_2 were not tolerated, and sulfone was judged to be the best overall for L_1 and L_2. Substitution on the phenyl rings showed a preference for a small group at the 2-position of the C-ring and a small alkyl or halogen at the 4-position of the B-ring.

Supplementary data

Characterization data and experimental procedures for the synthesis of **10** and **52** can be found in the online version at doi:10.1016/j.bmcl.2005.07.023.

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16. Preparation of intermediate **3**: to a solution of *N*,*N*,*N*-trimethylethylenediamine (1.2 mL, 8.6 mmol) in THF (8 mL) at −20 °C was added *n*-BuLi (1.6 M, 5.4 mL, 8.6 mmol) dropwise. After 15 min, 4-trifluoromethoxybenzaldehyde (1.5 g, 7.8 mmol) in THF (8 mL) was added. The mixture was stirred for 15 min and additional *n*-BuLi (1.6 M, 14.6 mL, and 23 mmol) was added. The reaction mixture was stirred at −20 °C for 1 h and then placed in a freezer at −20 °C for 20 h. The mixture was cooled to −40 °C, and a solution of bis(2-fluorophenyl)disulfide (4.0 g, 15.7 mmol) in 30 mL THF was added. The reaction mixture was stirred at −35 °C for 3 h, poured into 0.5 N HCl, and extracted with EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4, filtered, and concentrated to an oil. Purification by silica gel chromatography (3% EtOAc/hexanes) gave 1.55 g (62%) of compound **3**, as a solid.
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