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Non-aromatic A-ring replacement in the triaryl bis-sulfone CB2 receptor inhibitors

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ABSTRACT

The triaryl bis-sulfone **1** was modified by converting the aryl A-ring to a piperidine ring. The piperidine ring was further elaborated to a spirocyclopropyl piperidine moiety. The effect on CB2 binding potency, rat calcium channel affinity, and CYP 2C9 inhibition is described.

The cannabinoid receptors CB1 and CB2 are G-protein coupled receptors that share 44% homology.[1] While the CB1 receptor is found primarily in the CNS, the CB2 receptor is highly expressed in the cells of the immune system.[2] Both CB1 and CB2 receptors have been the focus of much research since their discovery in 1990 and 1993, respectively.[3,4] For instance, CB1 and CB2 agonists have been pursued for the treatment of neuropathic and inflammatory pain.[5] The most active area of research has been with CB1 antagonists and inverse agonists. Work in this area is exemplified by Rimonabant (marketed as Acomplia® in Europe) for the treatment of obesity.[6,7]

Relative to these areas of cannabinoid receptor research, the CB2 antagonists and inverse agonists have received less attention. Due to the presence of CB2 receptors on immune cells, compounds that interact with this receptor hold promise for modulating the immune system.[8–10] We have reported that triaryl bis-sulfone **1** is a potent inhibitor of the CB2 receptor with good selectivity over the CB1 receptor.[11] Selectivity over the CB1 receptor is important in avoiding unwanted CNS side effects.

Herein we report on our efforts to find a structurally distinct backup series in which the A-ring of the triaryl bis-sulfone **1** has been replaced by a non-aromatic moiety. In addition to finding a structurally distinct chemotype, the backup program strove to (a) reduce the affinity for the rat calcium channel relative to **1** to avoid any potential issues with the preclinical toxicology species and, (b) to improve on the cytochrome P450 profile and in particular the 2C9 isozyme (Fig. 1).

Initial efforts focused on scanning replacements for the aryl A-ring of **1**. Our synthetic strategy involved reaction of a B,C-ring sulfonyl chloride with a mono-*N*-trifluoromethyl sulfonamido-diamine to provide the target molecules.

The B,C-ring sulfonyl chloride was prepared starting with Boc-protected 4-chloroaniline **3** (Scheme 1). Directed *ortho* metalation of **3** with *t*-BuLi and reaction with bis(2-fluorophenyl)disulfide provided a thioether that was oxidized with *m*-CPBA to yield sul-

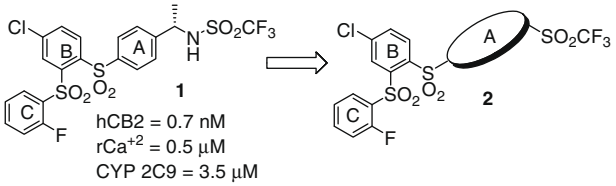

Figure 1. Converting the A-ring of **1** to a non-aryl moiety.

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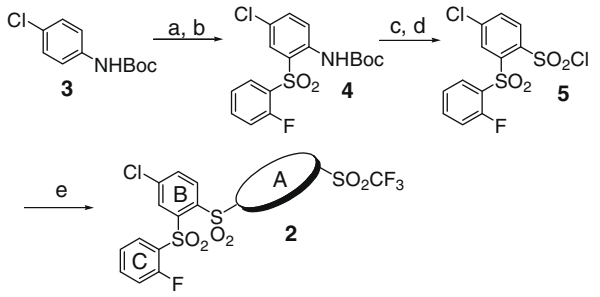


Scheme 1. Reagents and conditions: (a) (i) *t*-BuLi (2.4 equiv), THF, −78 °C; (ii) 1,2-bi-(2-fluorophenyl)disulfide, −20 °C to rt; (b) *m*-CPBA, dichloroethane, rt; (c) 4 M HCl in dioxane; (d) (i) $NaNO_2$, HCl(aq), AcOH, 0 °C, 1 h; (ii) CuCl, SO_2/AcOH, 0 °C, 2 h; (e) A-ring amine, TEA, CH_2Cl_2.

fone **4**. Compound **4** was then deprotected and converted to the diazonium salt. The diazonium salt was added to a saturated solution of sulfur dioxide in acetic acid containing copper chloride to afford sulfonyl chloride **5**.[12] Subsequent treatment of **5** with a mono-*N*-trifluoromethyl sulfamido-diamine yielded target molecule **2**.

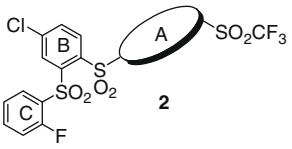
The effect of exchanging the aryl A-ring of **1** with various non-aromatic amines is shown in Table 1. In general, the linker length between the amines of the A-ring was important (**10** vs **6** and **9**) with a 4-atom linker being optimal (**10**). In addition, the manner in which the amines of the A-ring were conformationally constrained impacted the binding affinity (**7** vs **8**). Piperidine analogs such as **10**, **14**, and **18** showed the most promise as non-aromatic A-ring replacements. Based on these results, we embarked on a study to investigate the effect of other substituents in the 4-position of the aminomethyl piperidine A-ring and to fully explore targets containing a spirocyclopropyl piperidine A-ring.

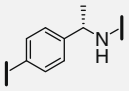
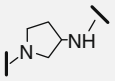
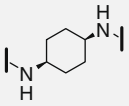
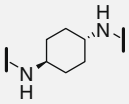
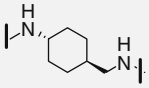
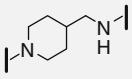
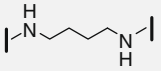
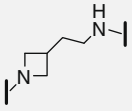
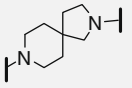
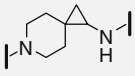
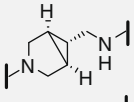
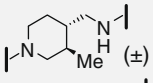
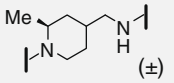
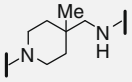
The 4-substituted piperidine intermediates were readily prepared from commercially available cyanopiperidine **19** (Scheme 2). Alkyl substituted piperidine intermediates were prepared by treating **19** with LDA and subsequent addition of an alkyl halide. The cyano group was reduced with Raney Nickel and capped as the trifluoromethyl sulfonamide. Removal of the Boc group provided piperidine intermediates **20–23**. Quenching the anion of **19** with acetaldehyde or paraformaldehyde provided access to **24** and **26**, respectively. Hydroxymethyl-substituted **25** was then converted to the tosylate which was displaced with sodium azide. The azide functionality was reduced with Pd/C and the resulting amine was converted to the trifluoromethyl sulfonamide **27**. Removal of the Boc group provided piperidine **28**. Cyano-substituted **27** was further elaborated by hydrogenating the cyano group. The primary amine was protected as the allyl carbamate and Boc removal provided **29**.

The effect of the A-ring piperidine on CB2 binding and CYP 2C9 inhibition is shown in Table 2. In general, alkyl and fluoro substitution was well tolerated (**18**, **30–32**, and **35**) as was hydroxyalkyl substitution (**33** and **34**). Cyano substitution resulted in a loss of CB2 receptor affinity (**36**) as did phenyl substitution (**39**). The Alloc protected amine **37** had much diminished CB2 binding potency. Removal of the Alloc group provided **38** which regained some binding potency relative to **37**. CYP 2C9 inhibition was improved relative to **1** with unsubstituted piperidine **10**. However, substitution that maintained or improved binding potency in general led to a worsening of the CYP 2C9 profile.

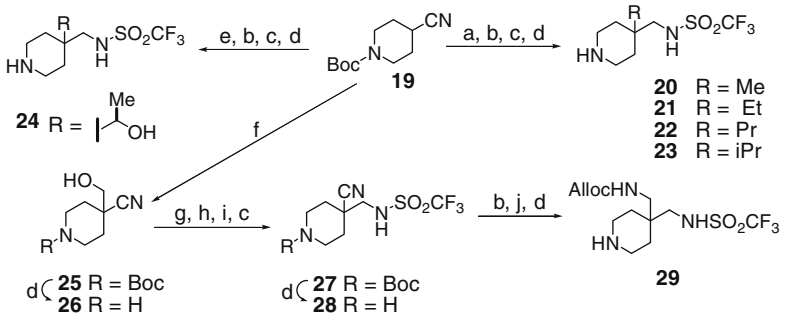
Synthesis of spirocyclopropyl piperidine began with *N*-Boc-piperidone **40** (Scheme 3).[16] Wittig olefination followed by cyclopropanation provided the ester that was saponified to yield carboxylic acid **41**. The acid was then converted to an acyl azide which underwent a Curtius rearrangement in the presence of trichloroethanol to produce the amine protected as the trichloroethyl carbamate (Troc). Removal of the Boc group yielded amine **42**. Treatment of the amine with 4-chlorophenylsulfonyl chloride and removal of the Troc group provided a racemic amine which was separated into pure enantiomers **43** and **44** by chiral HPLC. The two enantiomers

Table 1
Scanning A-ring replacements of **1**



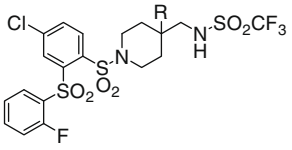
Compound	A	K_i[a] (CB2, nM)[11]	K_i[a] (CB1, nM)[11]
1		0.7	1600
6[b]		2950	9900
7[b]		1290	6900
8[b]		234	1615
9[b]		43	>10, 000
10[b]		5.5	>5000
11[b]		180	900
12[b]		92	2500
13[b]		750	>10,000
14		1.7	2500
15[c]		1.5	2200
16[d]		7.0	2500
17[e]		8.0	560
18		0.39	4100

[a] Individual data points for K_i determination were carried out in triplicate, in two separate assays.
[b] Mono *N*-Boc diamine commercially available.
[c] See Ref. 13 for synthesis of piperidine A-ring.
[d] See Ref. 14 for synthesis of piperidine A-ring.
[e] See Ref. 15 for synthesis of piperidine A-ring.



Scheme 2. Reagents and conditions: (a) (i) LDA, THF, −78 °C, 1 h; (ii) RX, −78 °C to rt, 18 h, 80–100%; (b) Raney Ni, $H_{2(g)}$ (50 psi), EtOH/(NH_3/MeOH), 48 h, 86–100%; (c) trifluoromethanesulfonic anhydride, TEA, CH_2Cl_2, −78 °C, 27–96%; (d) 2 N HCl/ether, rt, 12 h; (e) (i) LDA, THF, −78 °C, 1 h; (ii) acetaldehyde, −78 °C to rt, 18 h, 81%; (f) (i) LDA, THF, −78 °C, 1 h; (ii) paraformaldehyde, −78 °C to rt, 18 h, 38%; (g) *p*-toluenesulfonyl chloride, TEA, CH_2Cl_2, 74%; (h) sodium azide, DMSO, 100 °C, 18 h, 86%; (i) H_2 (45 psi), Pd/C, EtOH, 99%; (j) allyl chloroformate, TEA, DCE, 78%.

Table 2
4-Substituted piperidine analogs of **10**



Compound	R	K_i[a] (CB2, nM)[11]	CYP 2C9 IC_{50} (μM)[17]
10	H	5.5	14
18	–Me	0.39	2
30	–Et	0.20	2
31	–Pr	5.4	2
32	–*i*Pr	21	2
33	$-CH_2OH$	3	1
34		5.1	1
35[b]	–F	7.6	7
36	–CN	37.5	1
37	$-CH_2NH$–Alloc	2460	13
38	$-CH_2NH_2$	202.5	23
39[c]	–Ph	350	0.3

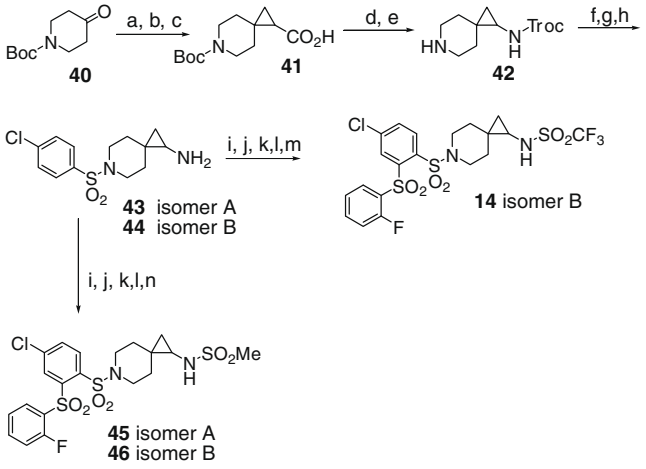
[a] Individual data points for K_i determination were carried out in triplicate, in two separate assays.
[b] See Ref. 18 for the synthesis of piperidine A-ring.
[c] See Ref. 19 for the synthesis of piperidine A-ring.

were carried on separately to methyl sulfonamide targets **45** and **46**.

Comparing the binding potencies of the two isomers (**45** and **46**, Table 3) establishes that isomer B is the more active isomer. Having determined this, trifluoromethanesulfonamide **14** (Scheme 3) was prepared from **44**. The remaining entries in Table 3 are analogs of the active piperidine isomer and reveal how substitution on the B and C rings affects the CYP 2C9 profile and CB2 binding potency.

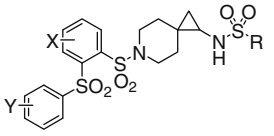
Overall, compounds with a spirocyclopropylpiperidine A-ring had good to excellent binding potency (Table 3). The CYP 2C9 inhibition did vary however based on the substitution pattern. A 2-pyridyl C-ring seemed to improve the CYP 2C9 profile (**47**, **48**, and **53**) although it was not always sufficient (**51**). Compounds **46**, **48**, and **53** possessed the best combination of CYP 2C9 profile and binding potency.

Compounds with an improved CYP 2C9 profile from Tables 2 and 3 (**10**, **46**, **48**, and **53**) were profiled further (Table 4). All compounds showed good selectivity against CB1. The rat calcium channel affinity was modestly improved in **10** and greatly improved in the case of **46**, **48** and **53**. Rat PK was good for **48** and **53**, modest for **10**, and poor for **46**. In the end, compound **53** showed the desired improvement in CYP 2C9 inhibition and rat calcium channel



Scheme 3. Reagents and conditions: (a) methyl triphenylphosphoranylidene, toluene, reflux, 96%; (b) trimethylsulfoxonium iodide, KO*t*Bu, DMSO, rt, 85%; (c) LiOH, THF, rt, 92%; (d) (i) acetone, TEA, ethylchloroformate; (ii) NaN_3, H_2O (91% yield, two steps); (iii) toluene, trichloroethanol, reflux, 18 h, 56% (three steps); (e) CH_2Cl_2, HCl/ether, quant.; (f) 4-chlorophenylsulfonyl chloride, TEA, CH_2Cl_2, 71%; (g) Zn, AcOH, rt, 90%; (h) chiral HPLC (Chiralpak AD, 25% IPA/hexanes), **44** slower eluting; (i) trifluoroacetic anhydride, TEA, dichloroethane, rt, 92%; (j) (i) *n*-BuLi, THF, −78 °C, (ii) bis(2-fluorophenyl)disulfide, −78 °C to rt, 69%; (k) *m*-CPBA, dichloroethane, rt, 53%; (l) $LiOH_{(aq)}$, THF, rt, quant.; (m) trifluoromethanesulfonic anhydride, TEA, CH_2Cl_2, −78 °C to rt, 71%; (n) methanesulfonyl chloride, TEA, dichloroethane, rt, 50%.

Table 3
Effect of substitution on the B and C ring in the amino spirocyclopropyl piperidine series



Example	X	Y	R	K_i[a] (CB2, nM)[11]	CYP 2C9 IC_{50} (μM)[17]
45 isomer A	4-Cl	2-F	Me	122	12
46 isomer B	4-Cl	2-F	Me	1.1	13
14	4-Cl	2-F	CF_3	1.7	2
47	H	2-pyr	CF_3	11	30
48	4-Cl	2-pyr	CF_3	1.6	15
49	4-Cl	4-OMe	CF_3	0.65	1
50	4-CF_3	2-F	CF_3	2.0	1
51	4-CF_3	2-pyr	CF_3	5.0	1
52	4-OCF_3	2-F	CF_3	3.0	4
53	4-OCF_3	2-pyr	CF_3	0.90	30

[a] Individual data points for K_i determination were carried out in triplicate, in two separate assays.

Table 4
Comparison of rat calcium channel affinity, CYP 2C9 IC_{50}'s, and rat PK for **1**, **10**, **46**, **48**, and **53**

Example	CB2 K_i (nM)	Ratio CB1/CB2	Rat Ca^{+2} channel K_i (μM)	CYP 2C9 IC_{50} (μM)[17]	Rapid Rat[21] 0–6 h AUC (μM h)
1	0.7	>2000	0.5	3.5	27
10	5.5	>1000	2	14	1.9
46	1.1	>2000	56	13	0.2
48	1.7	>1000	28	15	6.1
53	0.9	>1000	8	30	7.3

affinity while maintaining CB2 binding potency, rat PK and selectivity versus CB1.

The pharmacology of **1** and **53** were profiled in the β-Arrestin functional receptor assay.[20] This assay has been shown to accurately characterize the pharmacology of cannabinoid CB2 ligands. In this assay, **1** and **53** were shown to be inverse agonists.

In conclusion, we have discovered a CB2 inverse agonist in **53** that is structurally distinct from **1** that has an improved profile with respect to CYP 2C9 inhibition and rat calcium channel affinity.[22]

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22. *The analytical data for compound **53** is as follows*: ^{1}H NMR (400 MHz,$CDCl_3$) δ = 8.55–8.51 (m, 1H), 8.51–8.48 (m, 1H), 8.21–8.15 (m, 1H), 8.08 (d, *J* = 8.8 Hz, 1H), 7.96 (dt, *J* = 1.6, 7.8 Hz, 1H), 7.65–7.55 (m, 1H), 7.47 (dd, *J* = 4.9, 7.1 Hz, 1H), 5.15 (s, 1H), 3.72–3.54 (m, 2H), 3.23–3.09 (m, 2H), 2.57 (br s, 1H), 1.87–1.77 (m, 1H), 1.73–1.61 (m, 1H), 1.55–1.49 (m, 1H), 1.30–1.19 (m, 1H), 0.96–0.85 (m, 1H), 0.84–0.75 (m, 1H); ESI-MS (M+H) 624.1; HRMS (FAB): calcd for (M+H) $C_{20}H_{20}F_6N_3O_7S_3$, 624.0368, found 624.0376.