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# Expansion of SAR studies on triaryl bis sulfone cannabinoid $CB_2$ receptor ligands

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ABSTRACT

We report further expansion of the structure activity relationship (SAR) on the triaryl bis sulfone class of compounds (**I**), which are potent $CB_2$ receptor ligands with excellent selectivity over the $CB_1$ receptor. This study was extended to B ring changes, followed by simultaneous optimization of the A-, B-, and C-rings. Compound **42** has excellent $CB_2$ potency, selectivity and rat exposure.

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There is an increasing appreciation of the therapeutic value of inverse agonists as drugs. β-Adrenoceptor inverse agonists may be useful in the chronic treatment of asthma, lacking the detrimental effects of chronic use of β2-adrenoceptor agonists.[1] $GABA_A$ receptor α5 subtype-selective inverse agonists may be valuable in the treatment of cognitive performance in disorders in Alzheimer's disease and schizophrenia.[2] Evidence for in vivo constitutive activity of the serotonin2A and 2C receptors suggest that inverse agonists will be valuable in the treatment of schizophrenia, anxiety, weight control and Parkinsonism.[3] Studies with cannabinoid $CB_1$ receptor-specific inverse agonists have shown clinical efficacy, though side effects proved unacceptable.[4]

Several class of compounds including pyrazoles, oxoquinolines and more recently imidazoles have been reported as highly receptor-specific ligands to cannabinoid $CB_2$ receptor.[5] We are developing chemistry around a class of triaryl bis sulfone ligands that behave as inverse agonists to the $CB_2$ receptor.[6] These ligands were shown to modulate antigen-induced lung eosinophilia,[7] antigen-induced bone loss and peptide-induced experimental autoimmune encephalomyelitis[8], and thus may be useful in several therapeutic indications.

Previously we described discovery of a novel triaryl bisulfone $CB_2$ selective inhibitor, and SAR studies optimizing this class of compounds.[6a,b] In these studies we optimized the benzylic methyl group and its stereochemistry (*R* preferred), nature of linkers ($SO_2$ was optimal), and variations to the **C** ring, (Fig. 1). These efforts led to **1**, a potent and selective compound with acceptable PK parameters.[6c] We recently reported SAR studies on **A** ring modifications.[9] In this communication, we report extension of the SAR studies to heterocyclic replacements of the B ring and analogs with simultaneous optimization of the A-, B-, C-rings, generic structure **I**. These efforts culminated in structurally novel ligands with very good potency, selectivity, and rat PK.

The two generic routes employed to access these compounds are shown in Schemes 1 and 2.

The first route required treating the lithiated heterocycle **II** (obtained by either extracting the most acidic proton or by halogen-metal exchange of brominated heterocycle) with sulfonyl fluoride **2**.[6c] The sulfone group in **III** then directed the next lithiation (with 2 equiv of *n*BuLi) to the *ortho* position of the B ring and the resulting lithio species was quenched with a disulfide or sulfonyl

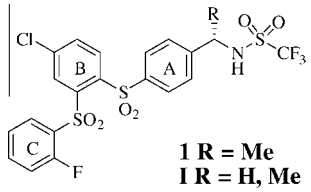


**Figure 1.**

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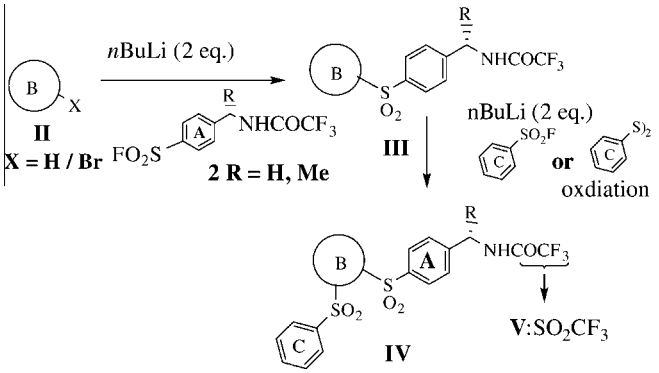
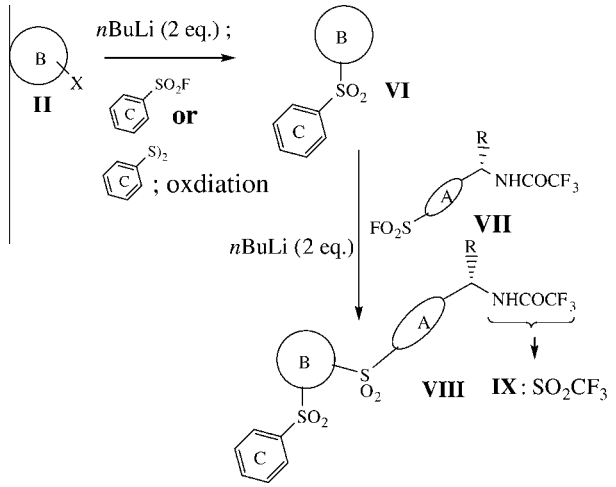
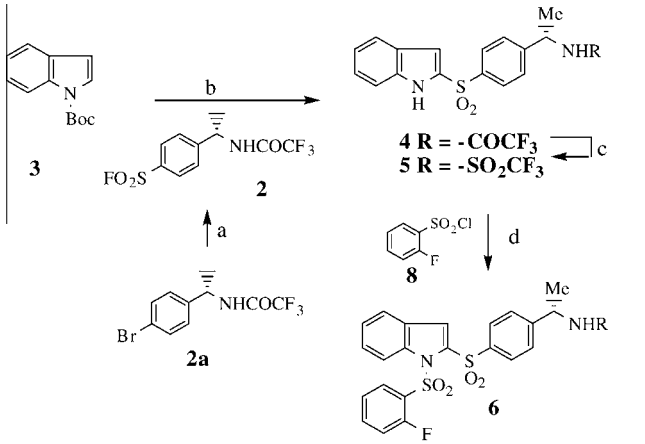


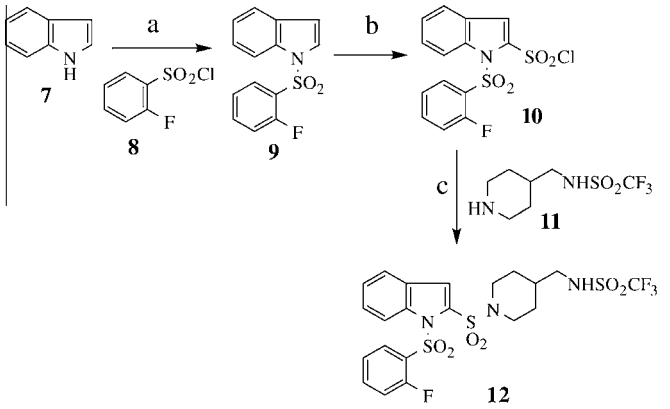

Scheme 1.




Scheme 2.




**Scheme 3.** Reagents and conditions: (a) (i) *n*BuLi, THF, −78 °C, $SO_2$; (ii) NCS, $CH_2Cl_2$, rt; (iii) KF, acetone/$H_2O$, rt; (b) *n*BuLi, THF, −78 °C, **2** (55%); (c) (i) LiOH, dioxane; (ii) $(C_2H_5)_3N$, $(CF_3SO_2)_2O$, −78 °C; (d) NaOH (aq 1 N), $CH_2Cl_2$, tetrabutylammonium hydrogensulfate (cat.), rt (35%).




**Scheme 4.** Reagents and conditions: (a) NaOH (aq 1 N), toluene, tetrabutylammonium hydrogensulfate (cat.), rt; (b) (i) *n*BuLi, THF, −78 °C, $SO_2$; (ii) NCS, $CH_2Cl_2$, rt; (45%); (c) $(C_2H_5)_3N$, $CH_2Cl_2$, rt.

fluoride to provide **IV**. With the disulfide quench, an additional oxidation step to sulfone was required. Base hydrolysis followed by derivatization with trifluoromethanesulfonic anyhdride provided **V**.

Alternatively, B and C rings were assembled first, employing lithiation followed by sulfonylhalide quench as described above. The biaryl sulfone **VI** was lithiated directly with *n*-BuLi and the resulting lithio species reacted with sulfonyl fluoride **VII**, providing **VIII** which can then be processed as described above (**III** to **IV**) to provide **IX**.

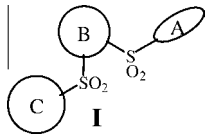
Specific chemistry to access indole derivative **6**, is described in Scheme 3. *N*-Boc indole was selectively lithiated at 2-position and treated with sulfonyl fluoride **2** to provide compound **4**. Base promoted hydrolysis of the trifluormethyl acetamide group followed by sulfonylation with trifluoromethylsulfonic anhydride in the presence of a base at −78 °C provided selectively derivatized **5**. The C ring was installed by treating **5** with 2-fluorophenylsulfonyl chloride under phase transfer conditions, providing **6**.

Chemistry to access analogs such as **12** where the **A** ring is piperidine and **B** ring is indole, is shown in Scheme 4. The indole NH was sulfonylated with aryl sulfonyl chloride **8**, under phase transfer conditions using aqueous base, to provide **9**. Regioselective lithiation at the 2-position of indole **9** followed by $SO_2$ quench and chlorination with *N*-chlorosuccinimde of the resulting sulfonic acid resulted in the sulfonyl chloride **10**. This reagent reacted with piperidine derivative **11**,[9] in the presence of a base to provide the target **12**.[11]

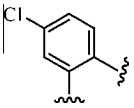
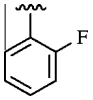
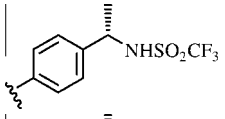
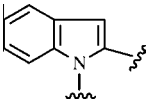
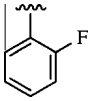
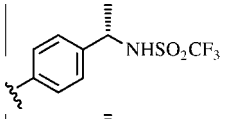
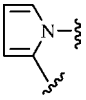
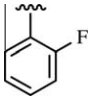
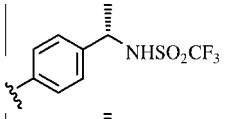
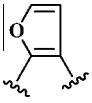
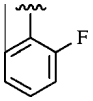
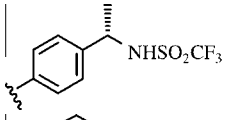
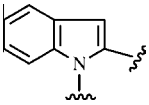
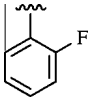
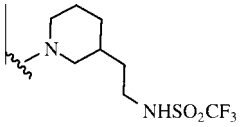
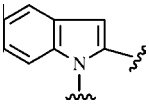
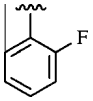
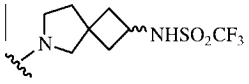
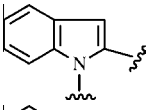
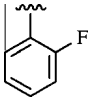
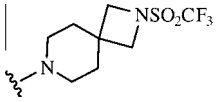
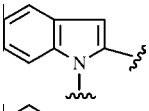
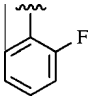
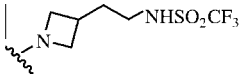
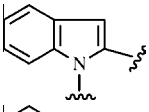
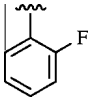
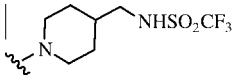
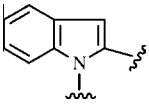
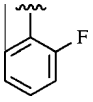
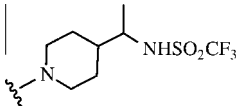
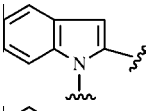
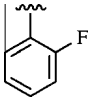
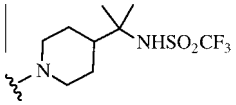
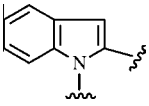
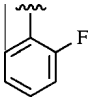
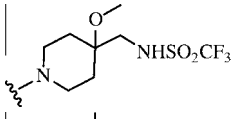
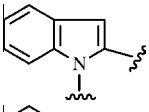
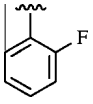
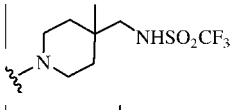
All the compounds shown in Table 1 were accessed by the chemistry exemplified above. SAR was developed to identify B ring alternates to the *p*-chloro-phenyl of **1** (entries: **6**, **13**, and **14**). All of them showed diminished activity compared to 1. Keeping the ease of synthesis in mind, and the desire to change the B-ring, the indole ring was selected for further investigation.

With the B ring fixed as an indole and C ring as 2-fluorophenyl, we explored the SAR around the A ring to restore potency for $CB_2$. A variety of cyclic amines were examined (**12**, **15**, **16**, **17**, and **18**). A 4-substituted piperidine ring was well tolerated, that is, **12**. Next, a variety of piperidine analogs which maintained a substituent in the 4-position of the piperidine were investigated (entries **19**–**31**). Additional substitutions at 3- and 4-positions were often tolerated, with marginal decrease in selectivity (entries **21**–**26**). Other substitution patterns led to diminished potency and selectivity (entries **27**–**31**). Now, selecting the A ring as unsubstituted 4-piperidinyl methyl while keeping the C ring as 2 F-phenyl, we revisited the B ring SAR. Substituted indole, aza indole, reverse indole, furan and pyridyl ring were synthesized and evaluated (entries **32**–**36**). Besides the substituted indole, aza indole and furan ring were tolerated. However, none of them were superior to the simple indole ring (compound **12**). Based on our earlier work in the triphenyl sulfone series,[6b] we found 2-pyridyl to be well tolerated. Several pyridyl isomers were explored here (entries **37**–**39**) with the 2-pyridyl preferred. Finally, three point changes by incorporating optimized A, B, and C rings provided us with very potent and selective compounds (entries **40**–**43**).

**Table 1**




**I**

| Compound | Synthesis scheme | B ring | C ring | A ring | $K_i$[a,15] $CB_2$ (nM) | Selectivity $K_iCB_1/K_iCB_2$ |
|---|---|---|---|---|---|---|
| **1** | 1 |  |  |  | 0.7 | 2273 |
| **6** | 3 |  |  |  | 7.5 | 1338 |
| **13** | 1 |  |  |  | 8.4 | 962 |
| **14** | 1 |  |  |  | 4.4 | 2686 |
| **15** | 4 |  |  |  | 258 | 3 |
| **16** | 4 |  |  |  | 452 | 117 |
| **17** | 4 |  |  |  | 8430 | 12 |
| **18** | 4 |  |  |  | 249 | 11 |
| **12** | 4 |  |  |  | 0.38 | 9250 |
| **19** | 4 |  |  |  | 0.4 | 2077 |
| **20** | 4 |  |  |  | 171 | 64 |
| **21** | 4 |  |  |  | 0.2 | 4375 |
| **22** | 4 |  |  |  | 0.35 | 6720 |
| **23** | 4 |  |  |  | 1.8 | 2525 |

(*continued on next page*)

**Table 1** (*continued*)

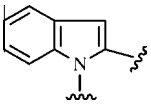
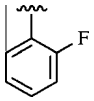
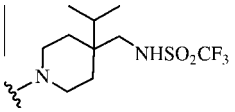
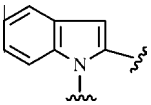
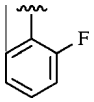
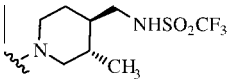
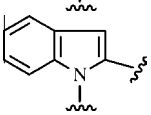
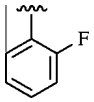
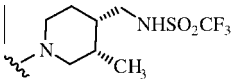
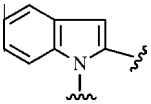
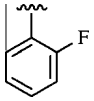
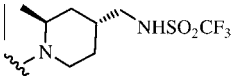
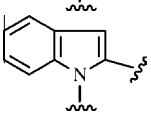
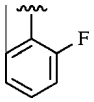
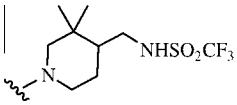
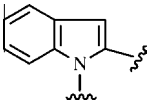
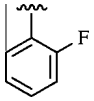
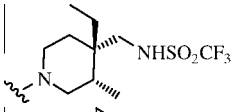
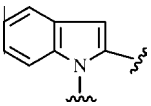
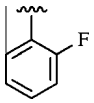
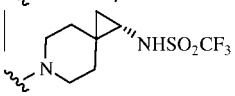
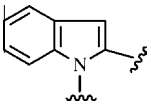
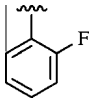
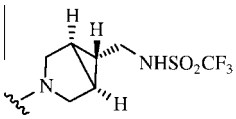
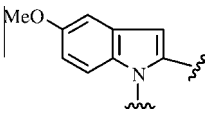
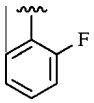
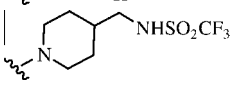
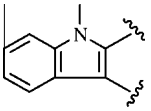
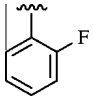
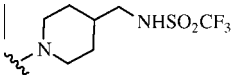
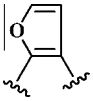
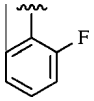
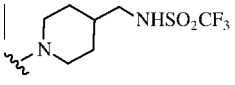
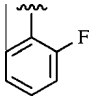
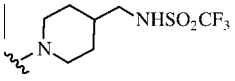
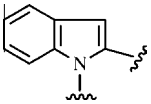
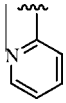
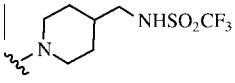
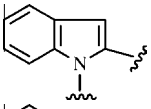
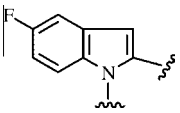
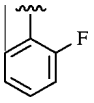
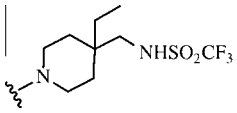
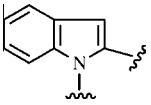
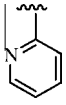
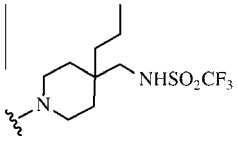
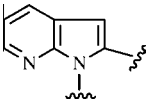
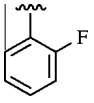
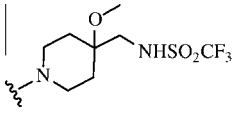
| Compound | Synthesis scheme | B ring | C ring | A ring | $K_i$[a,15] $CB_2$ (nM) | Selectivity $K_iCB_1/K_iCB_2$ |
|---|---|---|---|---|---|---|
| **24** | 4 |  |  |  | 78 | 24 |
| **25** | 4 |  |  |  | 0.5 | 2256 |
| **26** | 4 |  |  |  | 1.5 | 6666 |
| **27** | 4 |  |  |  | 16 | 334 |
| **28** | 4 |  |  |  | 4.2 | 245 |
| **29** | 4 |  |  |  | 3.1 | 630 |
| **30** | 4 |  |  |  | 1 | 413 |
| **31** | 4 |  |  |  | 9 | 279 |
| **32** | 4 |  |  |  | 0.8 | 5161 |
| **34** | 4 |  |  |  | 70 | 364 |
| **35** | 1 |  |  |  | 1.4 | 4524 |
| **36** | 1 |  |  |  | 790 | 126 |
| **37** | 4 |  |  |  | 0.9 | 9177 |
| **38** | 4 |  |  |  | 41 | 139 |
| **39** | 4 |  |  |  | 23 | 126 |
| **40** | 4 |  |  |  | 0.4 | 3500 |

**Table 1** (*continued*)

| Compound | Synthesis scheme | B ring | C ring | A ring | $K_i$[a,15] $CB_2$ (nM) | Selectivity $K_iCB_1/K_iCB_2$ |
|---|---|---|---|---|---|---|
| **41**[12] | 4 |  |  |  | 0.4 | 2797 |
| **42**[13] | 4 |  |  |  | 1.6 | 26,378 |
| **43**[14] | 4 |  |  |  | 2.5 | 3199 |

[a] Individual data points for determinations of $K_i$ for $CB_1$ and $CB_2$ were carried out in triplicate, in two separate assays.

**Table 2**

| Compound | Rat AUC nM h (10 mpk) |
|---|---|
| **12** | 3900 |
| **40** | 4559 |
| **41** | 3767 |
| **42** | 17,555 |
| **43** | 3191 |

Selected compounds were dosed in rats for pharmacokinetic evaluations.[16] The exposure levels attained for compounds **12**, **40**–**43** at 10 mg/kg dose in 20% (w/v) hydroxypropyl β cyclodextrin, are shown in Table 2.

In conclusion, we expanded the SAR of compound **1** by selecting the indole ring as a B-ring surrogate, and second by optimizing the SAR in an iterative fashion through A- and C-ring changes. These efforts culminated in identification of compounds (Table 2) which are structurally very different than **1**, which have comparable potency and selectivity for $CB_2$, and are currently under going further evaluation.

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11. *Compound* **12**: $^1$H NMR ($CDCl_3$) $\delta$ 8.25 (d, $J$ = 9.3 Hz, 1H), 8.03 (dt, $J$ = 1.6 Hz, 7.0 Hz, 1H), 7.64 (d, $J$ = 8 Hz, 1H), 7.51–7.60 (m, 2H), 7.47 (b, 1H), 7.37 (t, $J$ = 7.7 Hz, 1H), 7.28 (t, $J$ = 7.7 Hz, 1H), 7.05 (t, $J$ = 9.6 Hz, 1H), 5.6 (b, 1H), 3.95 (d, $J$ = 13 Hz, 2H), 3.19 (d, $J$ = 6.6 Hz, 2H), 2.84 (t, $J$ = 11.5 Hz, 2H), 1.81 (d, $J$ = 13.3 Hz, 2H), 1.70 (m, 1H), 1.35 (dt, $J$ = 4.0 Hz, 11.6 Hz, 2H).
12. *Compound* **41**: $^1$H NMR ($CDCl_3$) $\delta$ 8.23 (m, 1H), 8.02 (m, 1H), 7.58 (m, 1H), 7.42 (s, 1H), 7.25 (m, 3H), 7.04 (m, 1H), 5.17 (t, $J$ = 6.6 Hz, 1H), 3.42 (m, 2H), 3.33 (m, 2H), 3.19 (d, $J$ = 6.6 Hz, 2H), 1.54 (m, 4H), 1.42 (q, $J$ = 7.0 Hz, 2H), 0.83 (t, $J$ = 7.0 Hz, 3H).
13. *Compound* **42**: $^1$H NMR ($CDCl_3$) $\delta$ 8.5 (d, $J$ = 4 Hz, 1H), 8.4 (d, $J$ = 6 Hz, 1H), 8.2 (d, $J$ = 6 Hz, 1H), 7.9 (m, 1H), 7.62 (d, 1H), 7.4–7.6 (m, 3H), 7.36 (m, 1H), 3.5 (m, 2H), 3.38 (m, 2H), 3.19 (d, $J$ = 6.6 Hz, 2H), 1.58 (m, 4H), 1.38 (m, 2H), 1.2 (m, 4H).
14. *Compound* **43**: $^1$H NMR ($CDCl_3$) $\delta$ 8.40 (d, $J$ = 7.0 Hz, 1H), 8.23 (m, 1H), 7.97 (d, $J$ = 10 Hz, 1H), 7.58 (m, 1H), 7.30 (m, 1H), 7.22 (m, 1H), 7.02 (m, 1H), 5.40 (b, 1H), 3.70 (d, $J$ = 15 Hz, 2H), 3.25 (m, 4H), 3.20 (s, 3H), 1.96 (d, $J$ = 15 Hz, 2H), 1.66 (m, 2H).
15. Compounds **1**, **6**, **12** and **42** were tested for the ability to modulate interaction between a recombinant cannabinoid $CB_2$ receptor and β-arrestin, using the PathHunter™ protein complementation assay (DiscoveRx Corporation). Previous studies showed that this system correctly predicts the pharmacology of a number of cannabinoid $CB_2$ agonists and inverse agonists.[10] Test compounds behaved as inverse agonists in a manner similar to compound **1**, decreasing the constitutive ability of the cannabinoid $CB_2$ receptor to interact with β-arrestin. As expected, the agonist WIN55212-2 increases this interaction.
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