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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.

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

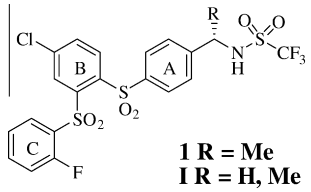

Figure 1.

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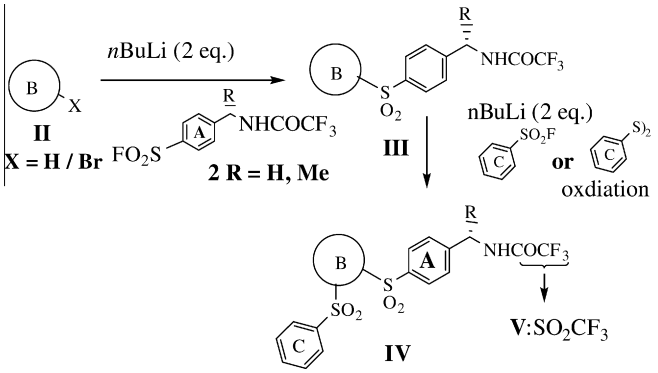
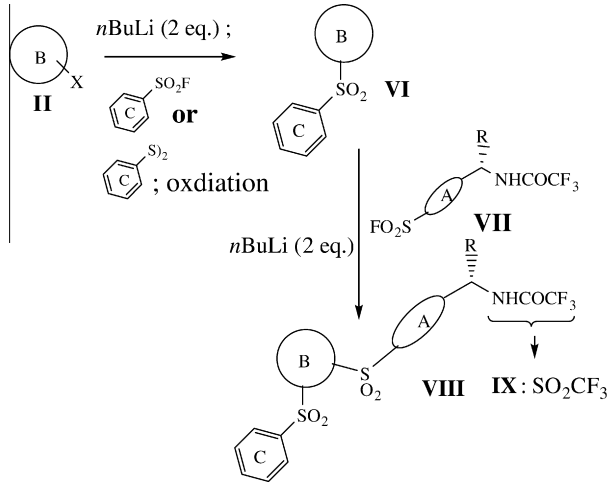
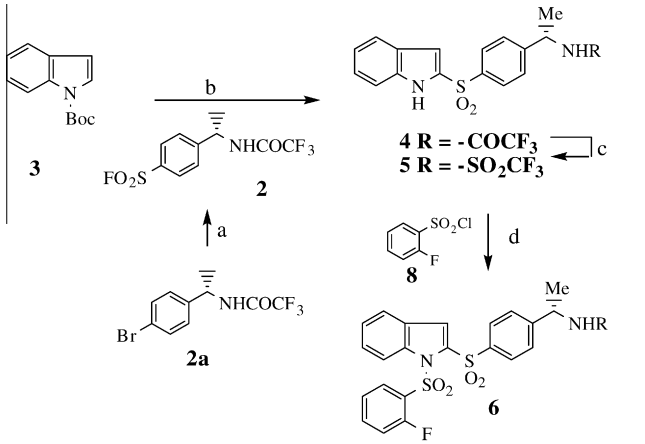


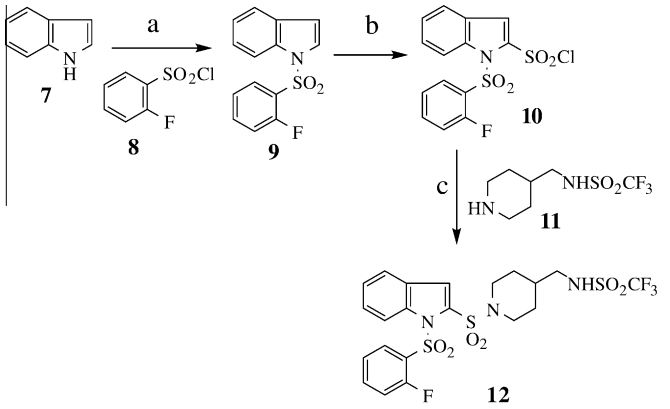
Scheme 1.



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**.

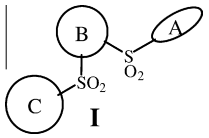
Specific chemistry to access indole derivative **6**, is described in Scheme 3. *N*-Boc indole was selectively lithiated at 2-position and treated with sulfonyl fluoride **2** to provide compound **4**. Base promoted hydrolysis of the trifluormethyl acetamide group followed by sulfonylation with trifluoromethylsulfonic 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]

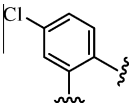
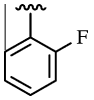
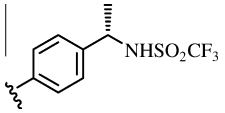
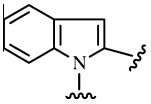
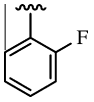
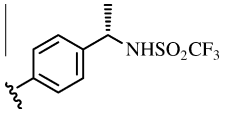
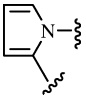
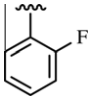
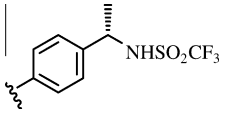
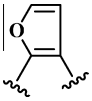
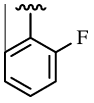
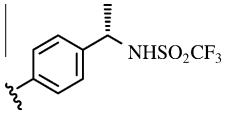
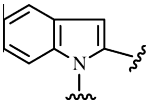
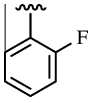
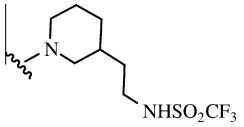
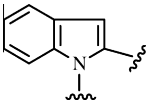
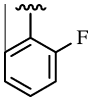
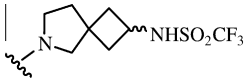
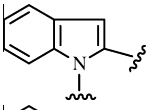
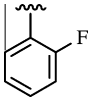
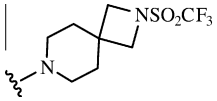
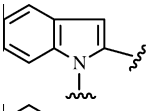
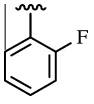
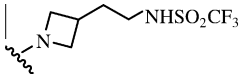
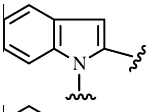
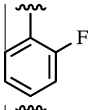
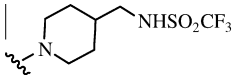
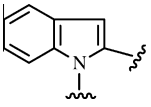
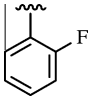
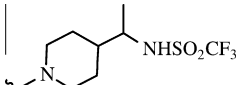
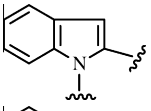
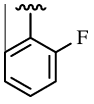
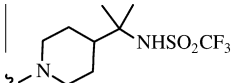
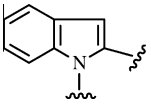
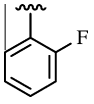
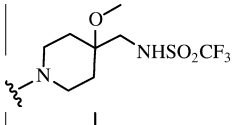
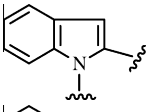
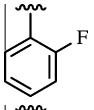
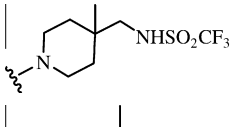
All the compounds shown in Table 1 were accessed by the chemistry exemplified above. SAR was developed to identify B ring alternates to the *p*-chloro-phenyl of **1** (entries: **6**, **13**, and **14**). All of them showed diminished activity compared to 1. Keeping the ease of synthesis in mind, and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

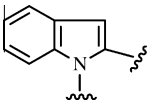
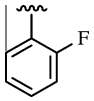
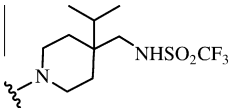
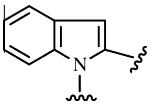
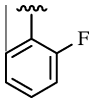
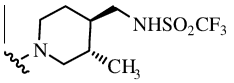
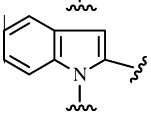
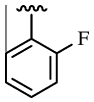
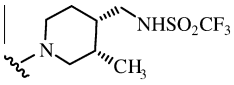
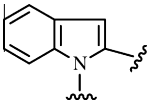
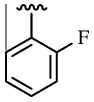
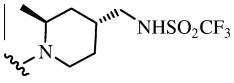
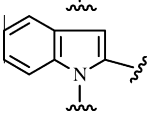
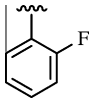
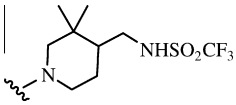
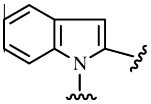
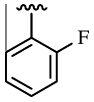
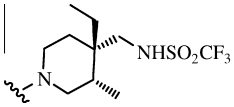
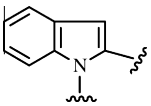
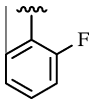
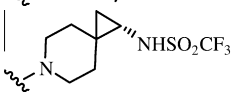
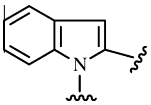
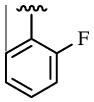
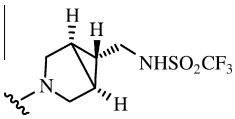
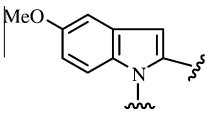
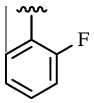
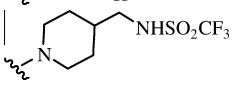
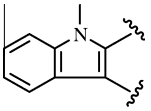
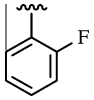
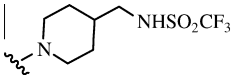
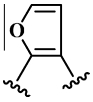
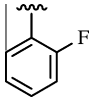
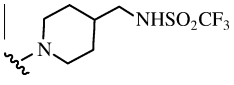
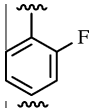
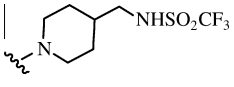
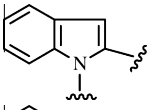
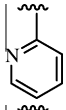
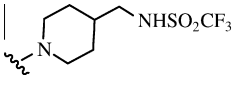
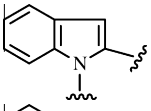
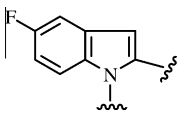
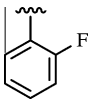
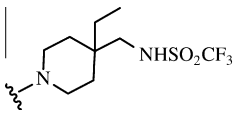
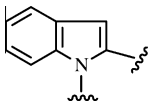
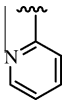
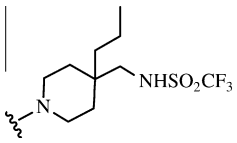
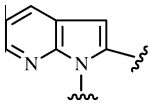
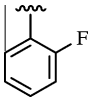
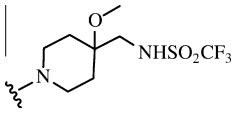
Compound	Synthesis scheme	B ring	C ring	A ring	K_i[a,15] CB_2 (nM)	Selectivity K_iCB_1/K_iCB_2
24	4				78	24
25	4				0.5	2256
26	4				1.5	6666
27	4				16	334
28	4				4.2	245
29	4				3.1	630
30	4				1	413
31	4				9	279
32	4				0.8	5161
34	4				70	364
35	1				1.4	4524
36	1				790	126
37	4				0.9	9177
38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

Acknowledgement

We thank Dr. J. Palamanda for pharmacokinetic evaluations.

References and notes

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11. *Compound* **12**: ^{1}H NMR ($CDCl_3$) δ 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 ($CDCl_3$) δ 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 ($CDCl_3$) δ 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 ($CDCl_3$) δ 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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