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Optimization of triaryl bis-sulfones as cannabinoid-2 receptor ligands

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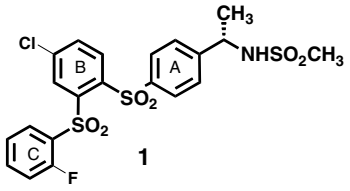
Abstract—Structure–activity relationship on our recently reported triaryl bis-sulfone class of cannabinoid-2 (CB2) receptor selective inverse agonists was explored. Modifications to the methane sulfonamide, substitutions to B and C phenyl rings, and replacements of the C-ring were investigated. A compound with excellent CB2 activity, selectivity for CB2 over CB1, and in vivo plasma levels was identified.

The CB2 receptor is a G-protein coupled receptor which is located primarily in the spleen and other immune-related tissues.[1] It is 44% homologous with CB1, and its difference in homology with CB1 offers the possibility to uncouple the immune-related effects of cannabinoids from the psychoactive effects typically associated with CB1.[2] To support this possibility, CB2 activity has been associated with modulation of B-cell differentiation,[3] altered immune cell migration[4] or chemotaxis, and altered antigen processing in macrophages.[5] Also, cannabinoid ligands are reported to be active in animal models of rheumatoid arthritis,[6,7] multiple sclerosis,[8] and inflammatory pain[9] reinforcing the idea that they possess anti-inflammatory properties.



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We previously reported identification of potent CB2 selective compounds[10] and their pharmacology.[11,12] The compound with the best combination of potency, selectivity, and rat exposure was **1**.[13] However, we felt the plasma levels of **1** after oral dosing were not high enough for further development (6 h AUC after oral dosing at 10 mpk = 6331 nM h, and the plasma levels decayed rapidly). Therefore, we selected **1** as a lead for further optimization. We hoped to try and find a compound with better plasma levels in vivo while maintaining excellent CB2 affinity, and selectivity for CB2 over CB1. Herein we describe SAR studies, on the fluorophenyl ring, methanesulfonyl, and B-ring substituent.

We pursued the synthetic strategy of assembling the A–B ring system first, and then installing the C-ring group, as shown in Scheme 1. Biarylsulfone **3** was prepared from **2** by metalation with *n*-BuLi and trapping with either a sulfonyl fluoride or disulfide. If a disulfide is used, then in a second step the sulfur was oxidized with *m*-chloroperoxy benzoic acid. Compound **3** was selectively *ortho*-lithiated on the B-ring using two equivalents of *n*-BuLi. Trapping of the anion with sulfur dioxide gas and conversion to the sulfonyl chloride with *N*-chlorosuccinimide[14] gave compound **4**. Treatment of the sulfonyl chloride **4** with various amines produced the

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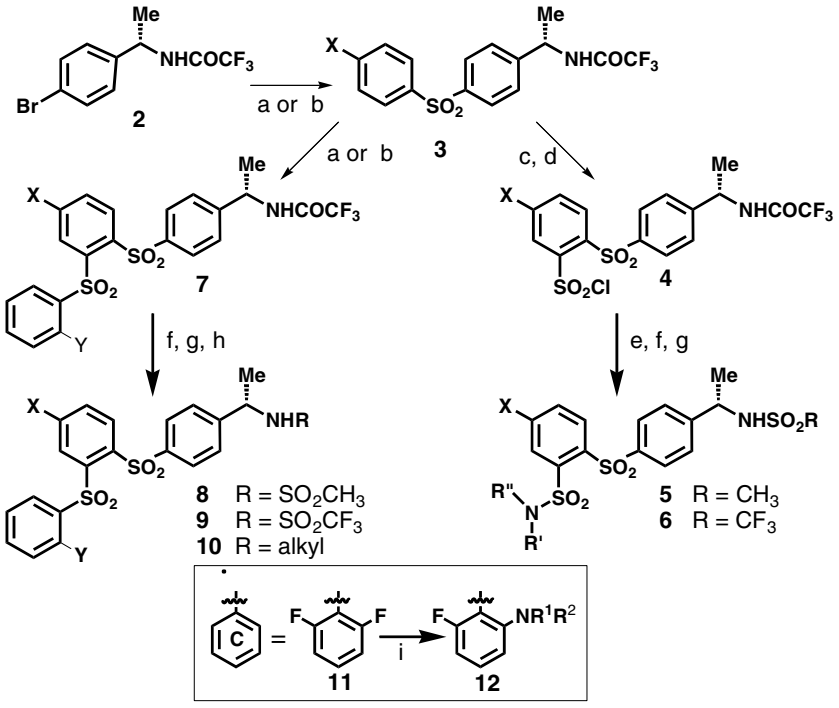


Scheme 1. Reagents and conditions: (a) i—*n*-BuLi (2 equiv), THF, −78 °C; ii—sulfonyl fluoride (55–65%); (b) i—*n*-BuLi (2 equiv), THF, −78 °C; ii—disulfide; iii—*m*-chloroperoxy benzoic acid, CH_2Cl_2, rt (30–50%); (c) *n*-BuLi (2 equiv), THF, −78 °C; ii—SO_2 gas; (d) *N*-chlorosuccinimide (40% over two steps); (e) $(C_2H_5)_3N$, R′NHR″, CH_2Cl_2 (25–75%); (f) LiOH, dioxane (70–90%); (g) $(C_2H_5)_3N$, CH_3SO_2Cl or $(CF_3SO_2)_2^{\circ}$ (57–88%); (h) R-OTf, Et_3N (47–62%); (i) NHR^1R^2, CH_3CN, Δ 31–87%).

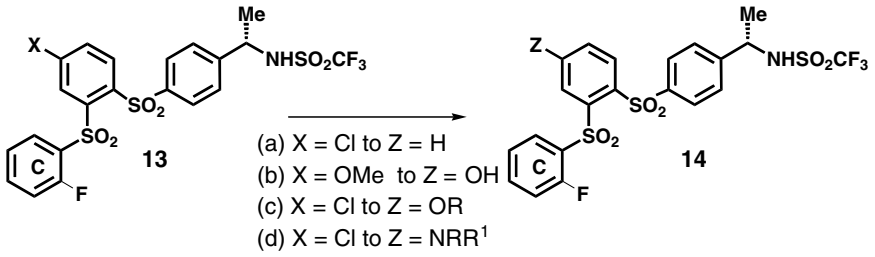
corresponding sulfonamides. The trifluoroacetamide group was removed by aqueous LiOH hydrolysis, followed by sulfonylation of the amine to provide analogs **5** and **6**.

The anion of compound **3**, formed from selective lithiation of the B-ring, was also trapped with either an arylsulfonyl fluoride, or disulfide. When disulfides were used, the newly formed sulfide linker between the B and C rings was oxidized to sulfone with *m*-chloroperoxy benzoic acid to produce **7**. Removal of the trifluoroacetamide group (aqueous LiOH) and sulfonylation of the amine provided **8** or **9**. With compound **17** an additional oxidation step was required to form the N-oxide. In compound **11**, one of the two fluorines could be displaced by heating the compound with an amine in acetonitrile to produce **12**. The cyclopropyl analog **38** was made from **3**, where X is cyclopropyl and 4-cyclopropylbenzenesulfonyl fluoride was prepared from cyclopropylbenzene.[16]

Scheme 2 describes the preparation of analogs shown in Table 3. The conversion of compounds **13**–**14** involves either hydrogenation of the chlorine (analog **31**), O-demethylation of a methoxy group (analog **32**), replacement of chlorine with alkoxy (analogs **34**, **35**), or replacement of chlorine with alkylamino (analogs **39**–**41**).

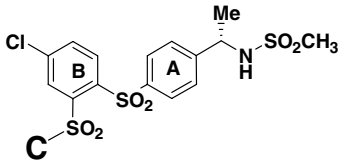
Table 1 shows the outcome of modifying or replacing the C-ring of compound **1**.[17] Simple alkyl and cycloalkyl analogs **15** and **20** lost affinity relative to **1**. Amino and sulfonamide analogs **21**–**23** also lost CB2 affinity. Among the heterocyclic analogs **16**–**19**, the 2-pyridyl analog **16** showed CB2 affinity and selectivity similar to **1**, however, it did not offer a clear advantage over the 2-F-phenyl. Hence, the 2-F-phenyl was maintained for further SAR modification.

We next explored the possibility of replacing the methanesulfonyl by other groups. The results are shown in



Scheme 2. Reagents and conditions: (a) H_2/Pd(C) 91%; (b) BBr_3, CH_2Cl_2; 9% (c) NaOH, ROH (70–89%); (d) NRR′, Pd, Ref. 15 (22–40%).

Table 1. SAR: changes to the C-ring of **1**

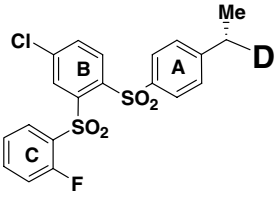


Compound	C	K_i (CB2, nM)	Selectivity (CB1 K_i/CB2 K_i)
1		1.3	4387
15	$-CH_2CH_2CH_3$	308	57
16		2.9	4403
17		119	840
18		129	538
19		204	31
20		8.9	345
21	$-NHCH_3$	1251	64
22	$-N(CH_3)_2$	1273	58
23	$-NHSO_2CH_3$	2749	36

Table 2 where an amide, sulfonamide, urea, or amine was prepared. Alkylated amines **29** and **30** showed good CB2 affinity, but it was the trifluoromethanesulfonamide **24** that showed the best combination of CB2 affinity and selectivity.

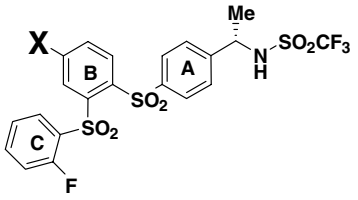
Table 3 shows results where the chlorine group on **24** was replaced. Although analogs **34**, **37**, and **38** showed good CB2 affinity and selectivity, none had a profile significantly better than **24**.

Table 2. SAR: changes to the methanesulfonate of **1**



Compound	D	K_i (CB2, nM)	Selectivity (CB1 K_i/CB2 K_i)
24	$-NH-SO_2CF_3$	2	3393
25	$-NHCOCH_3$	60.7	250
26	$-NHCOCF_3$	3.7	784
27	–NHCONHEt	>10,000	—
28	$-NH_2$	3953	14
29	$-NCH_2CF_3$	7	325
30	$-NCH_2CH_2CF_3$	17	105

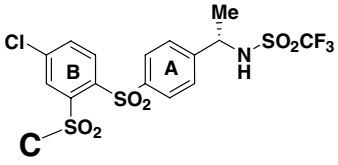
Table 3. SAR: changes to the B-ring of **24**

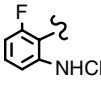
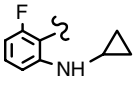
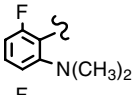
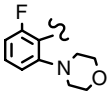


Compound	X	K_i (CB2, nM)	Selectivity (CB1 K_i/CB2 K_i)
31	H	25	426
32	–OH	1.3	1571
33	$-OCF_3$	5	525
34	$-OCH_2CH_3$	0.9	1964
35	$-OCH_2CH_2OCH_3$	2.5	1602
36	$-CF_3$	2.5	2080
37	$-CH_3$	1.1	2287
38	–Cyclopropyl	1.4	2239
39	$-NH_2$	10	170
40	–NH-cyclopropyl	4.9	66
41	–*N*-Piperazine	1099	31

Now by fixing the B-ring group as chlorine and the amine substitution as trifluoromethanesulfonyl, we revisited C-ring modifications to identify the best combi-

Table 4. SAR: changes to the C-ring of **24**



Compound	C	K_i (CB2, nM)	Selectivity (CB1 K_i/CB2 K_i)
11	2,6-Difluorophenyl	5.8	642
42		3.6	1152
43		21	859
44		4.1	1191
45		22	212
46		14.4	688
47		115	60
48		140	18
49	–NH–*t*-Bu	136	123
50	–*N*-Piperidine	58	231
51	–*N*-Morpholine	192	99

nation, shown in Table 4. The 2-pyridyl analog **42** maintained reasonable CB2 affinity and selectivity, but we found that none of the changes in the C-ring improved CB2 affinity or selectivity over **24**.

Compound **24** was dosed orally at 10 mpk in the rapid rat assay[18] and showed a 6 h AUC of 3581 nM h, which was worse than the 6331 nM h observed for compound **1**. However, we observed that the compound was a suspension in the methylcellulose dosing solution and suspected that poor solubility might be a factor in the lower plasma levels. Taking advantage of the increased acidity of the NH of $NHSO_2CF_3$, over the NH of $NHSO_2CH_3$ (pK_a approximately 6.5 vs ~12) we prepared and dosed several salt forms of compound **24**. In the same rapid rat paradigm, we found the potassium (5405 nM h), and calcium (5075 nM h) salts gave AUCs comparable to the neutral compound, and the zinc (297 nM h) salt was lower. However, the sodium salt AUC (21,022 nM h) was significantly improved over the neutral compound.

Because of its potency, selectivity, and improved plasma levels in the rapid rat screening assay, the DMPK profile of the sodium salt of compound **24** was investigated further. In rats, the bioavailability of **24** was 25%, the $t_{1/2}$ was 1.6 h, the clearance was 11.4 mL/min/kg, and the volume of distribution was 0.7 L/kg. When dosed orally in cynomolgus monkeys at 10 mpk, it had a 0–24 h AUC of 45,400 nM h, bioavailability of 50%, a $t_{1/2}$ of 3.7 h, clearance of 8.1 mL/min/kg, and a volume of distribution of 1.3 L/kg. In dogs, the 0–24 h AUC was 173,800 nM h after dosing at 10 mpk orally. The bioavailability was 66%, the clearance was 1.2 mL/min/kg, and the V_d was 1.1 L/kg.

In an effort to optimize the profile of compound **1**, we expanded the SAR, by making structural changes to several points of the molecule. These changes included the addition of polar groups to the 2-fluorophenyl ring, replacement of the fluorophenyl ring with heterocycles and other groups, and changing the $NHSO_2CH_3$ group into a $NHSO_2CF_3$ thereby allowing the formation of salts to improve solubility. Compound **24** was found to have the best overall profile as a sodium salt and was selected for further progression.

Supplementary data

Experimental details of the determination of K_i values, the synthesis of cyclopropyl benzene sulfonyl fluoride, and the preparation of compound **24** can be found in the online version at doi:10.1016/j.bmcl.2007.04.028.

References and notes

1. For general reviews of the cannabinoid field, see: (a) Mackie, K. *Annu. Rev. Pharmacol. Toxicol.* **2006**, *46*, 101; (b) Hertzog, D. L. *Expert. Opin. Ther. Patents* **2004**, *14*, 1430; (c) Pertwee, R. G. *Exp. Opin. Invest. Drugs* **2000**, *9*, 1553; (d) Huffman, J. W. *Curr. Pharm. Des.* **2000**, *6*, 1323; (e) Goya, P.; Jagerovic, N. *Exp. Opin. Ther. Patents* **2000**, *10*, 1529, and references cited therein.
2. For a review of cannabinoids and the immune system, see: Croxford, J. L.; Yamamura, T. *J. Neuroimmunol.* **2005**, *166*, 3.
3. Carayon, P.; Marchand, J.; Dussossoy, D.; Derocq, J. M.; Jbilo, O.; Bord, A.; Bouaboula, M.; Galiegue, S.; Mondiere, P.; Penarier, G.; Fur, G. L.; Defrance, T.; Casellas, P. *Blood* **1998**, *92*, 3605.
4. Sacerdote, P.; Massi, P.; Panerai, A. E.; Parolaro, D. *J. Neuroimmunol.* **2000**, *109*, 155.
5. McCoy, K. L.; Matveyeva, M.; Carlisle, S. J.; Cabral, G. A. *J. Pharmacol. Exp. Ther.* **1999**, *289*, 1620.
6. Zurier, R. B.; Rossetti, R. G.; Lane, J. H.; Goldberg, J. M.; Hunter, S. A.; Burstein, S. H. *Arthritis Rheum.* **1998**, *41*, 163.
7. Malfait, A. M.; Gallily, R.; Sumariwalla, P. F.; Malik, A. S.; Andreakos, E.; Mechoulam, R.; Feldman, M. *Proc. Natl. Acad. Sci.* **2000**, *97*, 9561.
8. Baker, D.; Pryce, G.; Croxford, J. L.; Brown, P.; Pertwee, R. G.; Huffman, J. W.; Layward, L. *Nature* **2000**, *404*, 84.
9. Quartilho, A.; Mata, H. P.; Ibrahim, M. M.; Vanderah, T. W.; Porreca, F.; Makriyannis, A.; Malan, T. P. *Anesthesiology* **2003**, *99*, 955.
10. Lavey, B. J.; Kozlowski, J. A.; Hipkin, R. W.; Gonsiorek, W.; Lundell, D. J.; Piwinski, J. J.; Narula, S.; Lunn, C. A. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 783.
11. Lunn, C. A.; Fine, J. S.; Rojas-Triana, A.; Jackson, J. V.; Fan, X.; Kung, T. T.; Gonsiorek, W.; Schwarz, M.; Lavey, B. J.; Kozlowski, J. A.; Narula, S. K.; Lundell, D. J.; Hipkin, R. W.; Bober, L. A. *J. Pharacol. Exp. Ther.* **2006**, *316*, 780.
12. Gonsiorek, W.; Hesk, D.; Kinsley, D.; Chen, S.-C.; Fine, J. S.; Jackson, J. V.; Bober, L. A.; Deno, G.; Lunn, C. A.; Kozlowski, J. A.; Lavey, B.; Piwinski, J.; Narula, S. K.; Lundell, D. J.; Hipkin, R. W. *J. Biol. Chem.* **2006**, *281*, 28143.
13. Shankar, Bandarpalle B.; Lavey, Brian J.; Zhou, Guowei; Spitler, James A.; Tong, Ling; Rizvi, Razia; Yang, De-Yi; Wolin, Ronald; Kozlowski, Joseph A.; Shih, Neng-Yang; Wu, Jie; Hipkin, R. William; Gonsiorek, Waldemar; Lunn, Charles A. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4417.
14. To a THF (40 mL) solution of compound **3**, X = Cl (6.5 mmol), at −78 °C, *n*-BuLi (2.0 M, 6.6 mL) was added drop wise. After stirring for 45 min at −78 °C, SO_2 gas was bubbled gently for 45 min. The reaction turned light yellow and then it was allowed to warm to room temperature. The reaction mixture was concentrated to dryness and redissolved in CH_2Cl_2 (5 mL). The resulting lithium sulfinate salt was precipitated by adding cold hexanes and collected by suction filtration. The salt was dissolved in CH_2Cl_2 (100 mL) and treated with *N*-chlorosuccinimide (1.05 g, 7.8 mmol) and the reaction mixture was stirred overnight at room temperature. The organic layer was washed with brine and water, dried over Na_2SO_4, filtered, and concentrated to provide crude **4**, which was purified by silica gel chromatography (10% EtOAc/Hexanes), resulting in 1 g of **4** (40%) as a solid.
15. For conditions to convert X = Cl to X = NRR′, see: Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158.
16. For the preparation of cyclopropylbenzene sulfonyl fluoride, see the supplementary material of this article.
17. In all cases, individual data points for determinations of K_i for CB1 and CB2 were carried out in triplicate, in two separate assays. For experimental details of the determination of K_i values, see the supplementary material. For additional details on the syntheses, see: Kozlowski, J. A.;

Shih, N.-Y.; Lavey, B. J.; Rizvi, R. K.; Shankar, B. P; Spitler, J. M.; Tong, L.; Wolin, R.; Wong, M. K. WO02062750, and Kozlowski, J. A. et. al. US2003232859. All CB2 inhibitors gave satisfactory analytical data as indicated by ^{1}H NMR and LC–MS.

18. For experimental details of the rapid rat assay, see: Korfmacher, W. A.; Cox, K. A.; Ng, K. J.; Veals, J.; Hsieh, Y.; Wainhaus, S.; Broske, L.; Prelusky, D.; Nomeir, A.; White, R. E. *Rapid Commun. Mass Spectrom.* **2001**, *15*, 335.