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Sulfonamide derivatives as new potent and selective CB_2 cannabinoid receptor agonists

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Abstract—A novel series of sulfonamide derivatives **3**, the CB_2 receptor agonists, was synthesized and evaluated for activity against the human CB_2 receptor. We first identified sulfonamide **3a**, which was obtained by random screening of our in-house chemical library as a moderately active (CB_2 IC_{50} = 340 nM) CB_2 receptor agonist. We then attempted to test its analogues to identify compounds with a high affinity for the CB_2 receptor. One of these, compound **3f**, exhibited high affinity for the human CB_2 receptor (IC_{50} = 16 nM) and high selectivity for CB_2 over CB_1 (CB_1 IC_{50}/CB_2IC_{50} = 106), and behaved as a full CB_2 receptor agonist in the [^{35}S]GTPγS binding assay (CB_2 EC_{50} = 7.2 nM, E_{max} = 100%).

Cannabis sativa L. (marijuana) has been used for its psychoactive and medicinal properties since times immemorial, and delta^9-tetrahydrocannabinol (delta^9-THC) was isolated as its major psychoactive component in the 1960s.[1] THC and its analogues are classified as cannabinoids, and possess numerous biological properties, including analgesic, antiemetic, anti-inflammatory, anticonvulsive, and anticancer effects.[2] Significant advances have been made in the understanding of the manner in which cannabinoids interact with biological systems, after the discovery of the CB_1 and CB_2 receptors.[3,4] The CB_1 receptor is expressed primarily in the CNS and activates the psychotropic effects of marijuana. The CB_2 receptor is expressed in immune-related tissues and cells, such as the spleen, tonsils, and thymus, natural killer cells, T cells, and B cells.[5–7] It has been suggested that the immunomodulatory effects of the cannabinoid present in marijuana are mediated via the CB_2 receptor. Recent studies have indicated that the CB_2 receptor may be involved in the control of peripheral pain,[8,9] inflammation,[10] and cancer development.[11] The receptor has also been suggested to have an antifibrogenic role in the liver[12] and to act as a regulator of microglial cell migration in the brain.[13,14] It is considered that the development of a highly selective CB_2 receptor ligand is important for an understanding of the physiological effects of cannabinoids, such as their immunosuppressive, anti-inflammatory, and antinociceptive activities. However, there are a few compounds, such as aminopyrimidine[15] (GW842166X, CB_2 EC_{50} = 50 nM, CB_1 EC_{50} > 30,000 nM) and 3-carbonylindole[16] (A-0796260, CB_2 IC_{50} = 0.77 nM, CB_1 IC_{50} = 330 nM), that are selective for the CB_2 receptor (Fig. 1).

In this paper, we report the identification of novel, selective, and potent CB_2 receptor agonists. Sulfonamide **3a** was identified as one of the hits by our high-throughput screening and showed moderate binding affinity for the CB_2 receptor (IC_{50} = 340 nM). Compound **3a** was found to be an agonist of the CB_2 receptor as confirmed by the human [^{35}S]GTPγS binding assay (EC_{50} = 110 nM, E_{max} = 110%). This compound has attractive attributes, including a low molecular weight and various sites in the molecule that render themselves to structural modification for optimization. We, therefore, tried exploring its analogues to identify compounds with a high affinity for the CB_2 receptor.

Keywords: Cannabinoid; CB_2 receptor; Sulfonamide derivatives; SAR.
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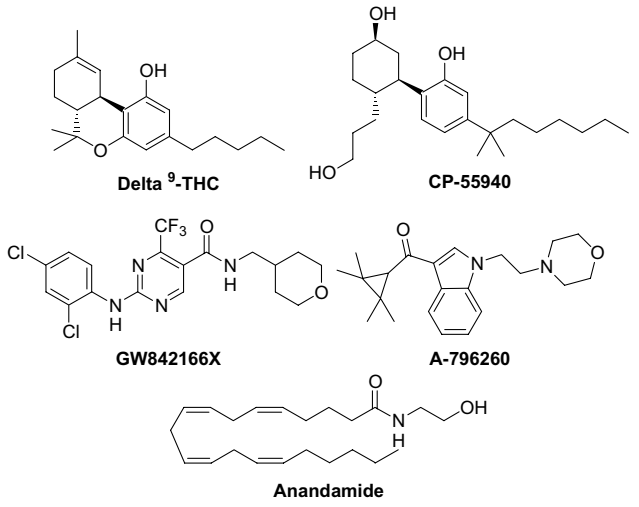


Figure 1. Structure of delta^9-THC, CP-55940, GW842166X, A-796260, and anandamide.

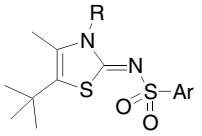
The synthetic chemistry for the preparation of **3a**–**g** is outlined in Scheme 1. Sulfonamides **3a**–**g** were synthesized from 2-aminothiazole (**1**), a commercially available compound (Fluorochem Ltd). Compound **1** was treated with aryl sulfonyl chlorides under basic conditions, followed by treatment with alkyl halides in the presence of sodium hydride, to obtain sulfonamides **3a**–**g** (the procedure for synthesis of compound **3f** is described in detail in the note).[17]

Compound **3a**, which was identified by our high-throughput screening, exhibited moderate affinity for the CB_2 receptor (IC_{50} = 340 nM) and no affinity for the CB_1 receptor (IC_{50} > 50,000 nM). These findings encouraged us to use sulfonamide **3a** to seek a new type of selective CB_2 receptor ligand (Table 1). First, we modified the methyl group at the position-3 of the thiazole ring to clarify the effects of substituents on the CB_2 receptor activity. We designed **3b** with an allyl group based on the presence of the double bond of anandamide,[18] an endogenous ligand of the cannabinoid receptor. Replacing the methyl group at **3a** with an allyl group markedly increased the binding affinity of the compound for the CB_2 receptor (**3a** vs **3b**), therefore, we investigated its analogues (**3c**–**e**). Substitution with bulky alkenyl groups, such as the prenyl group, resulted in a lowering of the affinity for the CB_2 receptor as compared with that of the straight-chain alkenyl compound (**3c** vs **3b**). Compound **3e** (**R** = propargyl) exhibited about threefold lower affinity for the CB_2 receptor than compound **3b** (**R** = allyl). The results of structural transformations indicated that the most suitable group for this site was a cyclopropylmethyl group (**3d**), which was used as an alternative to the allyl group. Compound **3d** demonstrated a significant increase, by about fivefold, of the affinity for the CB_2 receptor over that of **3a**. These findings suggest that the improved affinity associated with the introduction of the allyl and cyclopropylmethyl groups may depend on the donor–acceptor interaction with the π electron between these functional groups and the CB_2 receptor, and that the sterically acceptable space on **R** for interaction with the CB_2 receptor is narrow.

Next, modification focused on the phenyl group in **3d**. Substitution of the phenyl group of **3d** with a 2-naphthyl group (**3g**) decreased the affinity for the CB_2 receptor by about sevenfold. However, replacement of the phenyl group of **3d** with a 1-naphthyl group (**3f**) resulted in a significant increase in the affinity for the CB_2 receptor (**3f** vs **3d**). These results suggest that the conformation of the aromatic ring is important to obtain a high affinity for the CB_2 receptor. Furthermore, **3f** exhibited a high selectivity for the CB_2 receptor (CB_1 IC_{50}/CB_2 IC_{50} = 106) and was found to be a full CB_2 receptor agonist (CB_2 EC_{50} = 7.2 nM, E_{max} = 100%).

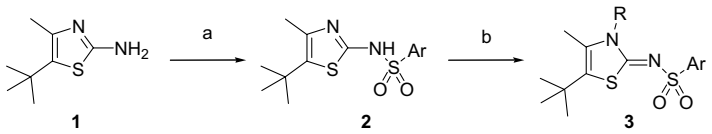
In this paper, we have reported the synthesis and SAR of novel CB_2 receptor ligands. The SAR study showed

Table 1. Pharmacological profile of sulfonamide derivatives



Compound	Ar	R	Binding affinity IC_{50}[a] (nM)		Agonist activity	
			CB_2	CB_1	CB_2 EC_{50}[b] (nM)	E_{max}[c] (%)
3a	Ph	Me	340	>50,000	110	110
3b	Ph	CH_2–CH=CH_2	75	—	—	—
3c	Ph	CH_2–CH=CMe_2	170	—	—	—
3d	Ph	CH_2–(Cyclopropyl)	65	—	—	—
3e	Ph	CH_2–CCH	210	—	—	—
3f	1-Nap	CH_2–(Cyclopropyl)	16	1700	7.2	100
3g	2-Nap	CH_2–(Cyclopropyl)	490	—	—	—
CP-55,940 Ref. 19			0.82	2.1	0.86	100

[a] Evaluated on the basis of [^{3}H]-CP-55,940 binding to membranes of Chinese hamster ovary (CHO) cells expressing the human CB_2 or CB_1 receptor.
[b] Evaluated by using a functional assay based on [^{35}S]GTPγS binding to membranes of CHO cells expressing the human CB_2 receptor.
[c] Compared to the maximal response to CP-55,940, a full agonist of the human CB_2 receptor.



Scheme 1. Reagents and conditions: (a) $ArSO_2Cl$, cat. DMAP, pyridine, rt; (b) RX, cat. NaI, NaH, DMF, rt.

that the functional group at position-3 of the thiazole ring and the Ar group of sulfonamide greatly affected the CB_2 receptor affinity. These studies led to compound **3f**, which combines good potency with a high selectivity for the CB_2 receptor. We believe that SAR studies will provide new opportunities to explore newer CB_2 receptor ligands with improved features.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2007.07.005.

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17. Typical procedure; synthesis of *N*-[5-*tert*-butyl-3-(cyclopropylmethyl)-4-methyl-1,3-thiazol-2(3*H*)-ylidene]naphthalene-1-sulfonamide (**3f**). To a mixture of **1** (0.12 g, 0.70 mmol), 4-dimethylaminopyridine (0.010 g, 0.082 mmol), and pyridine (1.5 ml) was added 1-naphthalenesulfonylchloride (0.19 g), and the mixture was stirred overnight. To the reaction mixture was added water. The precipitate was filtered and recrystallized from chloroform/hexane to give 0.22 g (yield; 88%) of **2f** as a pale pink powder. To a mixture of **2f** (0.20 g, 0.55 mmol) and sodium iodide (0.010 g 0.068 mmol) in DMF (1.5 ml) was added sodium hydride (0.024 g, 0.67 mmol), and the mixture was stirred for 15 min. To the reaction mixture was added (bromomethyl)cyclopropane (0.11 g, 0.83 mmol), and the reaction mixture was stirred overnight. To the reaction mixture was added 3 M HCl, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, evaporated in vacuo, and purified by silica gel column chromatography (eluent: hexane/ethyl acetate = 4:1) to give a colorless solid. The solid was recrystallized from chloroform/hexane to give 0.12 g (yield; 53%) of **3f** as colorless powder: mp 178.5–180.5 °C; ^{1}H NMR (200 MHz, chloroform-*d*) δ ppm 0.20–0.44 (m, 4H), 0.85–1.08 (m, 1H), 1.33 (s, 9H), 2.24 (s, 3H), 3.80 (d, J = 7.0 Hz, 2H), 7.42–7.69 (m, 3H), 7.82–8.03 (m, 2H), 8.29–8.40 (m, 1H), 8.86–8.97 (m, 1H); MS(ESI) *m/z* 415(M+H); Anal. Calcd for $C_{22}H_{26}N_2O_2S_2$: C, 63.74; H, 6.32; N, 6.76. Found: C, 63.71; H, 6.35; N, 6.73.
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