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Sulfamoyl benzamides as novel CB_2 cannabinoid receptor ligands

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Abstract—Sulfamoyl benzamides were identified as a novel series of cannabinoid receptor ligands. Starting from a screening hit **8** that had modest affinity for the cannabinoid CB_2 receptor, a parallel synthesis approach and initial SAR are described, leading to compound **27** with 120-fold functional selectivity for the CB_2 receptor. This compound produced robust antiallodynic activity in rodent models of postoperative pain and neuropathic pain without traditional cannabinergic side effects.

Two cannabinoid receptors, CB_1 and CB_2, have been identified and subsequently cloned. They belong to the family of G-protein coupled receptors and share 44% amino acid sequence homology but differ in anatomical distribution. The CB_1 receptor is expressed mainly in the CNS and to a lesser extent in other tissues. The CB_2 receptor is primarily expressed in peripheral tissues associated with immune functions, including macrophages, B and T cells, as well as in peripheral nerve terminals and on mast cells.[1] Δ^9-Tetrahydrocannabinol (THC, **1**), the main active component of *Cannabis sativa*, and other classical cannabinoids display a wide range of physiological effects including analgesic, anti-inflammatory, anti-convulsive and immunosuppressive activities.[2] Cannabinoid receptor agonists also induce a number of unwanted CNS effects, which are believed to be mediated predominantly by the central distribution pattern of CB_1 receptors.[3]

A separation between therapeutic effects and undesirable CNS side effects could be accomplished either by preventing the cannabinoid from crossing the blood–brain barrier[4] or by increasing the selectivity for the CB_2 receptor over the CB_1 receptor.[5] Several structural classes have displayed selectivity for the CB_2 receptor (Fig. 1).[6] Compound **4** (GW405833) was shown to be antihyperalgesic in rodent models of neuropathic, incisional and chronic inflammatory pain, but had no significant effect in CB_2 knockout mice in the same assays.[7] Compound **5** (AM1241) was reported to reverse carrageenan-induced inflammatory thermal hyperalgesia in rats. This effect was attenuated by a CB_2 selective antagonist, but not a CB_1 selective antagonist.[8] Thus, there is considerable interest in developing new cannabimimetic compounds possessing preferentially high affinity for the CB_2 receptor, which could lead to novel therapeutics for the treatment of inflammation and chronic pain.[9]

During a high-throughput screening campaign[10a] we identified **8** as a compound with modest affinity for the CB_2 receptor (Fig. 2). Initially, SAR was explored via a parallel approach shown in Scheme 1 and Figure 3. Starting from commercially available 4-bromo-3-(chlorosulfonyl)benzoic acid **10a** and amines **11a–h**, we prepared eight 4-bromo-3-sulfamoyl-benzoic acids **12a–h**. A diverse set of 10 amines **13a–j** was attached to aldehyde-based polystyrene resin via reductive amination using sodium triacetoxyborohydride as the reducing agent.[11] The resulting resin-bound amines **14a–j** were then reacted with the sulfamoyl-benzoic acids **12a–h** previously obtained using the coupling reagent bromo-*tris*-pyrrolidinophosphonium hexafluorophosphate (PyBrop) and diisopropylethylamine. After cleavage from solid support with trifluoroacetic acid in

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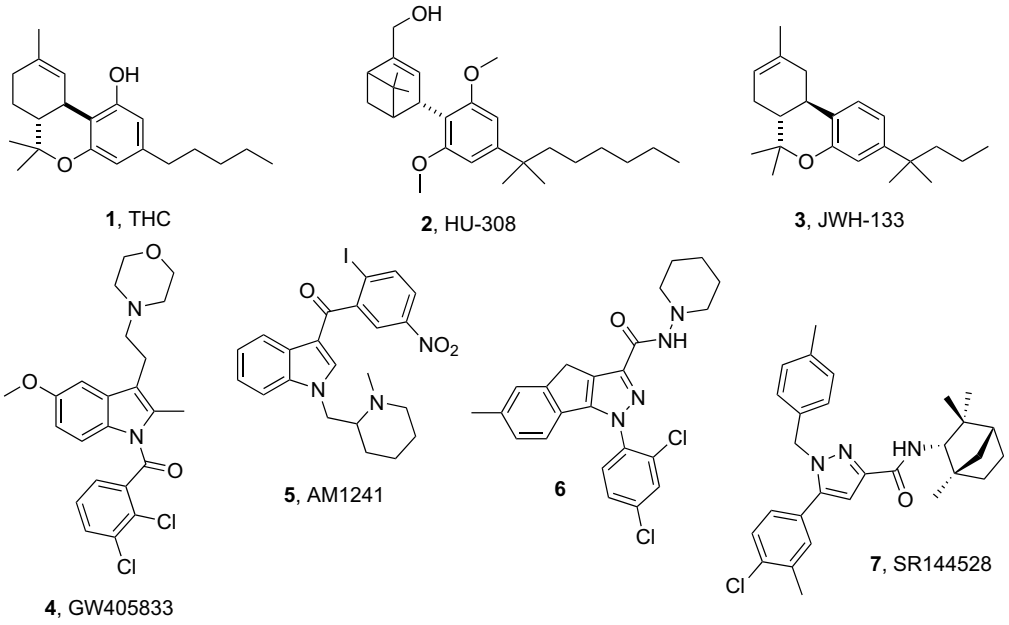


Figure 1. Cannabinoid receptor ligands.

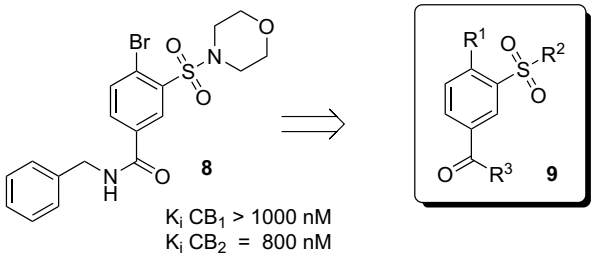
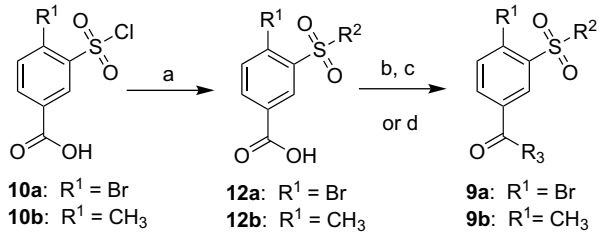


Figure 2. Screening hit.



Scheme 1. Reagents and conditions: (a) R^2-amine **11a**–**h** EtOAc; (b) resin-bound R^3-amine **14a**–**j**, *i*-Pr_2EtN, PyBrop, CH_2Cl_2; (c) TFA/CH_2Cl_2; (d) R^3-amine, TBTU, *i*-Pr_2EtN, ACN.

dichloromethane 80 final compounds, **9a**, were obtained. Almost half of these compounds retained or improved binding affinity for the CB_2 receptor compared to **8**, while the remaining compounds lost affinity for both CB receptors. Representative examples are shown in Table 1. Branched alkyl amines seemed to be preferred as both neopentyl and isobutyl amides yielded combinations with improved binding affinity (K_i CB_2 = 100–450 nM).

Since the selective CB_2 antagonist SR144528[6b] (**7**) also bears a highly branched amine substituent, we attempted to introduce this *S*-fenchyl residue into our system via the solid phase route just described. Due to steric hindrance the coupling of fenchyl amine to the polystyrene solid support failed. Therefore highly branched analogs **23**– **37** were synthesized in solution from respective sulfamoyl-benzoic acids **12a**–**d** utilizing *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetra-methyluronium tetrafluoroborate (TBTU) as the coupling reagent (Table 2).[12,13] All four sulfamoyl-benzoic acids **12a**–**d** yielded analogs with greatly improved binding affinity (**23**– **26**). Morpholine, pyrrolidine, and piperidine in R^2 showed similar profiles, with the morpholine analog **23** being slightly more selective. Methylbenzyl amine in R^2 led to the most selective analog **25** with a binding constant K_i CB_2 = 11 nM and $\geqslant$1000-fold lower binding to the CB_1 receptor (33% inhibition at 10 μM). Compounds **23**– **26** were then evaluated in the [^{35}S]GTPγS functional assay.[10b] Compounds **23**, **24**, and **26** were full agonists, but the most selective compound **25** behaved as an inverse agonist. To exclude possible reactivity with proteins in vivo the bromo substituent in **23** was replaced with a methyl group. Starting the synthesis from 3-(chlorosulfonyl)-4-methylbenzoic acid **10b** we obtained compound **27**, a 31-fold selective agonist with functional activities of EC_{50} CB_2 = 4.6 nM and EC_{50} CB_1 = 550 nM.

In an attempt to further improve selectivity and retain agonist activity, other commercially available branched amines were attached to **12b** (R^2 = morpholino, Table 2, **28**–**37**). Bicyclic amine substituents with branching in the 1 and/or 2 position seem to be preferred. Globular amines like 2-adamantyl, 1-(1-adamantyl)ethylamine, and bornyl amine yielded compounds with binding constants K_i CB_2 $\leqslant$ 10 nM. Analogs containing open chain and monocyclic amides, as well as analog **34** containing the *R*-isomer of fenchyl amine, lost