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Substituted acyclic sulfonamides as human cannabinoid-1 receptor inverse agonists

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Abstract—Sulfonamide analogues of the potent CB1R inverse agonist taranabant were prepared and optimized for potency and selectivity for CB1R. They were variably more potent than the corresponding amide analogues. The most potent representative **22** had good pharmacokinetic and brain levels, but was modestly active in blocking CB1R agonist-mediated hypothermia.

The steady increase in excessive body weight throughout the world over the last 50 years is associated with an increase in co-morbidities, such as diabetes, hypertension, cardiovascular disease, cancer, and arthritis and in an increase in healthcare costs.[1] Only two therapeutic agents with modest efficacy are currently approved for chronic use. The involvement of the cannabinoid receptor system in regulating feeding behavior and resultant weight loss has been demonstrated in both animal and clinical studies. Endogenous and exogenous cannabinoids have been shown to be cannabinoid receptor-1 (CB1R) agonists that enhance food intake and body weight. CB1R antagonists/inverse agonists have shown to be useful in the suppression of food intake and the reduction of body weight.[2] Furthermore, rimonabant **1**, a selective CB1R inverse agonist, is efficacious in the treatment of obesity in humans (Fig. 1).[3]

Recently, we described the discovery of a series of acyclic diphenylamides that are potent, selective CB1 receptor inverse agonists with good pharmacokinetic and pharmacological properties.[4] A key element in the optimization of that series was appropriate substitution on the three aryl rings. Most modifications of the acyclic scaffold of those diphenylamides resulted in compounds that were less potent inhibitors of CB1R. The result of that effort afforded a compound **2** (MK-0364; taranabant) that was a suitable candidate for advancement into clinical studies in the treatment of obesity. Herein, we describe the preparation and evaluation of a series of substituted sulfonamides as CB1R inverse agonists employing the optimized diphenylamine found in **2**.

The synthesis of the anti-diastereomer **3** of the substituted diphenylamine in **2** was reported.[4] The preparation of the individual enantiomers was also described. The sulfonamides were simply prepared by reaction of amine **3** with a substituted sulfonyl halide in the presence of an amine base (Scheme 1).[5] Likewise, the amides reported in Table 2 were prepared from amine **3** and the corresponding acid chlorides.

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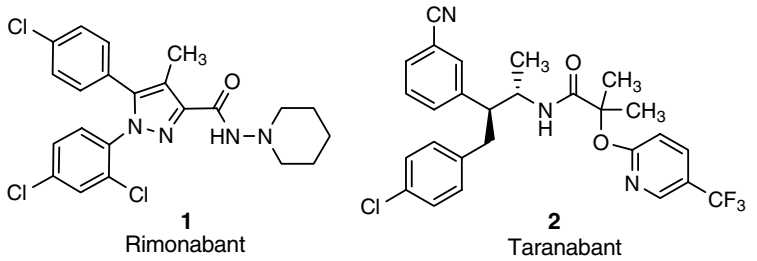
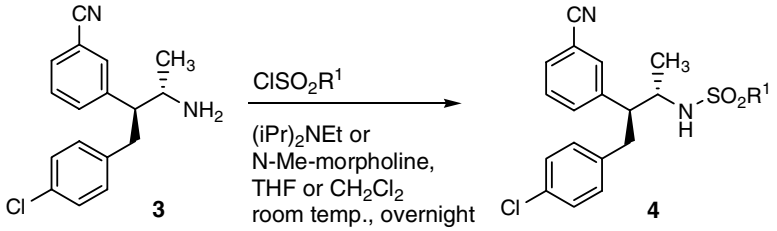


Figure 1. Structures of CB1R inverse agonists in clinical development.



Scheme 1. Preparation of substituted acyclic sulfonamides **4**.

The inhibition of the human CB1 and CB2 receptors by sulfonamides **4** is reported in Table 1.[6] The simple alkyl sulfonamides **5**–**8** have generally poor to modest affinity for the two receptors. The phenyl sulfonamide **9** suggests that an aryl substituent may afford both potency enhancement as well as selectivity for CB1R. All of the sulfonamides that had reasonable potency for the CB1 receptor were generally selective with respect to the CB2 receptor. Various substitution patterns on the aromatic ring (**10**–**25**) did little to enhance potency for CB1R much beyond the unsubstituted phenyl. In addition, methyl substitution on the sulfonamide nitrogen (**6** and **18**) gave relatively inactive compounds. All of the more potent compounds were determined to act as potent inverse agonists at CB1R (e.g., sulfonamide **22** had an $EC_{50} = 4$ nM [−172% maximum activation] in cyclic AMP production).[6]

A comparison of several sulfonamides with their analogous amides is presented in Table 2. The phenylsufonamide **9** is significantly more potent against CB1R than is the corresponding benzamide **32**. Likewise, the 3,5-dichlorophenylsulfonamide **17** retains greater potency and selectivity for CB1R than does the 3,5-dichlorobenzamide **33**. However, those differences are less apparent with the 2,6-dichlorophenyl derivatives (**16** and **34**), benzyl derivatives (**26** and **35**), and the phenylethyl derivatives (**30** and **36**). Clearly the positioning of the phenyl ring with respect to the amine portion of the molecule is important for efficient binding and not solely dependent upon the nature of the linking group (–SO_2NH– vs –CONH–).

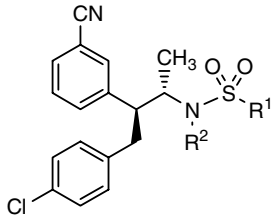
The conformations of sulfonamides **9** and **26** were overlayed with their respective amides **32** and **35** and are shown in Figure 2. The amine portion of the molecules was assumed to be similar in each molecule. The benzyl analogs **26** and **35** are more closely aligned in space than are those of the phenyl analogues **9** and **32**. In addition, the calculated conformations of **26** and **35** more closely resemble that of MK-0364 (Fig. 3).[7]

Given its improved CB1 activity, the 3-biphenyl derivative **22** was chosen for further in vivo characterization (rat CB1R $IC_{50} = 2.3$ nM). Its rat pharmacokinetic profile and brain penetration are shown in Table 3. The compound is well absorbed with low clearance and good distribution. At an oral dose of 2 mg/kg, it afforded a plasma C_{max} of 343 nM. Access to the brain compartment was good, with a brain/plasma ratio of ~1–2.

It is reported that CB1R agonists will elicit a significant hypothermia response in rodents.[8] The tetrahydro-cannabinol derivative CP-55940, when dosed by intravenous administration, causes a 3–5 °C drop in body temperature in rats. The blockade of this agonist-induced temperature drop by another CB1 ligand is considered to be a measure of the intrinsic receptor antagonist activity of that compound as well as its access to the CB1R in the CNS. We used the blockade of the agonist-induced hypothermia effect to assess the relative in vivo potency of CB1R ligands. As shown in Table 4, both rimonabant **1** and MK-0364 **2** when administered by iv dosing completely blocked the hypothermic effects of CP-55940. On the other hand, sulfonamide **22** was considerably less active in this model. This hypothermia model was generally useful for assessing the ability of compounds to access the CB1 receptor in the brain and, at least for the acyclic amide class, was predictive of potent activity in other CB1R-mediated models, such as inhibition of food intake and body weight reduction. Therefore, compound **22** was not evaluated further in other CB1R-mediated models.

The relatively poorer activity of **22** in the hypothermia inhibition model is not likely associated with poor systemic plasma exposure. The pharmacokinetic profile outlined in Table 3 suggests that the compound was well

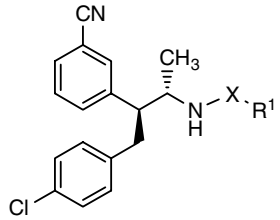
Table 1. Inhibition of hCB1R and hCB2R by substituted diphenylsulfonamides **4**



Compound [a]	R^1	R^2	CB1 IC_{50} (nM)[b]	CB2 IC_{50} (nM)[b]
1	Rimonabant		6.1	603.3
2	Taranabant		0.3	284.7
5	CH_3	H	>2000	>2000
6	CH_3	CH_3	>2000	>2000
7	*n*-C_4H_9	H	75.2	1441
8	*t*-C_4H_9	H	1677	>2000
9	Ph	H	9.7	1488
10	Ph-2-Cl	H	12.3	668.2
11	Ph-3-Cl	H	13.9	807.7
12	Ph-4-Cl	H	21.7	454.2
13 (S,S)	Ph-2,3-Cl_2	H	10.7	201.7
14 (S,S)	Ph-2,4-Cl_2	H	7.1	300.8
15 (S,S)	Ph-2,5-Cl_2	H	7.4	498.2
16 (S,S)	Ph-2,6-Cl_2	H	29.8	283.5
17 (S,S)	Ph-3,5-Cl_2	H	11.4	997.8
18 (S,S)	Ph-3,5-Cl_2	CH_3	>2000	>2000
19 (S,S)	Ph-2,4,5-Cl_3	H	16	622
20 (S,S)	Ph-3,5-$(CF_3)_2$	H	3.2	1755
21 (S,S)	Ph-3,5-F_2	H	5.1	1079
22 (S,S)	Ph-3-Ph	H	2.8	394.4
23 (S,S)	Ph-4-Ph	H	23.0	406
24	1-Naphthyl	H	21.1	1117
25	2-Naphthyl	H	15	1092
26	CH_2Ph	H	20.9	>2000
27 (S,S)	CH_2Ph-2-Cl	H	16.0	1918
28 (S,S)	CH_2Ph-3-Cl	H	53.5	>2000
29 (S,S)	CH_2Ph-4-Cl	H	15.4	1757
30	CH_2CH_2Ph	H	19.3	904
31 (S,S)	*t*-CH=CHPh	H	41.8	1077

[a] Racemic mixture of anti-diastereomers unless otherwise noted.
[b] Binding affinity determined by inhibition of binding of [^{3}H]CP-55940 to recombinant human CB1 or CB2 receptors expressed on Chinese Hamster Ovary (CHO) cells (n = 2).[6]

Table 2. Comparison of sulfonamides and amides in the inhibition of hCB1R and hCB2R



Compound [a]	R^1	X	CB1 IC_{50} (nM)[b]	CB2 IC_{50} (nM)[b]
9	Ph	SO_2	9.7	1488
32	Ph	C=O	845	1907
17	Ph-3,5-Cl_2	SO_2	5.5	1419
33	Ph-3,5-Cl_2	C=O	282.8	180.7
16 (S,S)	Ph-2,6-Cl_2	SO_2	29.8	283.5
34 (S,S)	Ph-2,6-Cl_2	C=O	37.2	945
26	CH_2Ph	SO_2	20.9	>2000
35	CH_2Ph	C=O	44.1	>2000
30	CH_2CH_2Ph	SO_2	19.3	904
36	CH_2CH_2Ph	C=O	38.3	1368

[a] Racemic mixture of anti-diastereomers unless otherwise noted.
[b] Binding affinity determined by inhibition of binding of [^{3}H]CP-55940 to recombinant human CB1 or CB2 receptors expressed on Chinese Hamster Ovary (CHO) cells (n = 2).[6]

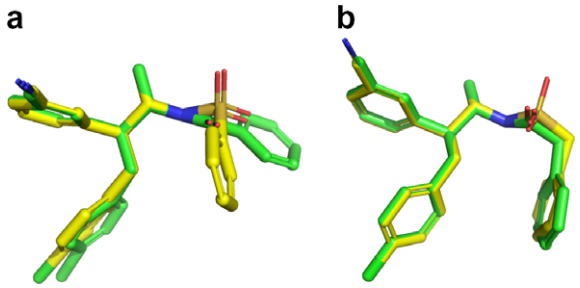


Figure 2. Overlay of (a) sulfonamide **9** (yellow) and amide **32** (green) and (b) sulfonamide **26** (yellow) and amide **35** (green).

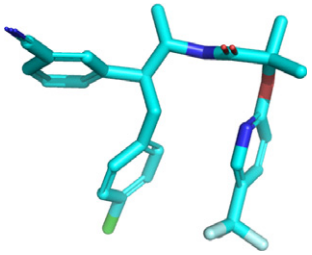


Figure 3. Conformation of MK-0364 as determined from X-ray analysis.[8]

absorbed and distributed. The levels of compound in the brain and the brain to plasma ratio also look reasonable and target engagement would be expected. However, high levels of compound in the brain do not in turn guarantee facile access to receptor targets. The highly hydrophobic nature of compounds such as **22** may limit their 'bioavailability' in the brain by binding to brain proteins and membranes. That said, the clog $D_{pH\ 7.4}$ of **22** (7.3) does not differ much from that of **2** (7.2). As with many CNS targets, assessment of in vivo receptor occupancy utilizing a CB1R PET ligand may be key to understanding the lack of activity of compounds such as **22**.[9]

In summary, sulfonamide analogues of the potent CB1R inverse agonist taranabant were prepared and optimized for potency and selectivity for CB1R. The sulfonamides were variably more potent than the corresponding amide analogues, depending upon substitution patterns. The most potent representative of the series **22** had good pharmacokinetic characteristics and good brain penetration. Despite these properties, compound **22** was considerably less active in blocking CB1 agonist-mediated hypothermia than other CB1R inverse agonists. Given the good levels of compound isolated from the brain,

Table 3. In vivo characterization of biphenylsulfonamide **22**

Rat pharmacokinetics (1 mg/kg iv, 2 mg/kg po)

F(%)	$t_{1/2}$ (h)	Cl_p (ml/min/kg)	Vd_{ss} (L/kg)	C_{max} (nM)
48%	8.4	10.6	6.9	343

Rat brain penetration (1 mg/kg iv)

Time (h)	Plasma concn (nM)	Brain concn (nM)	Ratio (b/pl)
0.25	220	146	0.66
1	113	92	0.82
2	54	54	1.00

Table 4. Inhibition of CB1R agonist-induced hypothermia

Compound	Inhibition (%)
Rimonabant **1**	97.9%
Taranabant **2**	109.6%
Sulfonamide **22**	48.9%

Rats ($n = 3$) were dosed with test compounds (3 mg/kg iv) 30 min before administration of CP-55940 (1 mg/kg ip). Rectal temperatures were measured at 75 min following the CP-55940 injection.

it may be that sulfonamides such as **22** are too hydrophobic to effectively access the CB1 receptor in the CNS.

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