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Discovery of pyrazine carboxamide CB1 antagonists: The introduction of a hydroxyl group improves the pharmaceutical properties and in vivo efficacy of the series

Bruce A. Ellsworth,* Ying Wang, Yeheng Zhu, Annapurna Pendri, Samuel W. Gerritz, Chongqing Sun, Kenneth E. Carlson, Liya Kang, Rose A. Baska, Yifan Yang, Qi Huang, Neil T. Burford, Mary Jane Cullen, Susan Johnghar, Kamelia Behnia, Mary Ann Pelleymounter, William N. Washburn and William R. Ewing

Pharmaceutical Research Institute, Bristol Myers Squibb Co., PO Box 5400 Princeton, NJ 08543, USA

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Abstract—Structure–activity relationships for a series of pyrazine carboxamide CB1 antagonists are reported. Pharmaceutical properties of the series are improved via inclusion of hydroxyl-containing sidechains. This structural modification sufficiently improved ADME properties of an orally inactive series such that food intake reduction was achieved in rat feeding models. Compound **35** elicits a 46% reduction in food intake in ad libidum fed rats 4-h post-dose.

Overweight and obese individuals, as characterized by BMI > 25 and 30 kg/M^2, respectively, constitute over 60% of the US population, and this fraction of the population has significantly increased over the last 20 years.[1,2] Obesity is caused by an imbalance between nutrient intake and energy expenditure,[3] is a significant risk factor for cardiovascular disease and diabetes, and is associated with significantly reduced longevity.[4] Feeding behavior is known to be modulated through the cannabinoid receptor 1 (CB1); increased feeding activity results upon activation of the receptor by its endogenous agonists, the endocannabinoids.[5] CB1 knockout mice are lean, hypophagic, and resistant to diet-induced obesity, demonstrating the receptor's role in energy homeostasis.[6]

Pharmacological intervention to inhibit the actions of the endocannabinoid-cannabinoid receptor system leads to a reduction in food intake in vivo. The most clinically advanced CB1 antagonist, SR141716 (Fig. 1), binds to the human CB1 receptor with nanomolar affinity and blocks signaling of the receptor.[7] In libidum-fed rats, SR141716 administered at 10 mg/kg i.p. produces a 50% reduction in food intake upon acute administration versus saline-treated control animals.[8] Upon chronic administration, animals initially display a fairly dramatic reduction in food intake which, over several days, returns to levels that are only slightly less than those of vehicle controls, resulting in an overall body weight reduction.[9] In the RIO clinical trials in North America and Europe, 20 mg q.d. of SR141716 (rimonabant) was shown to reduce the body weight of obese subjects by ~4.7% over placebo during the first year of treatment. This weight loss was maintained over the second year of treatment.[10]

The structures of many small molecule CB1 antagonists have been recently reviewed.[1,11] In general, the properties of the lead compounds do not deviate from a recent analysis of GPCR ligands. In this analysis of lipid-binding GPCRs, a class that includes CB1, the authors find that drugs developed to bind these receptors have a mean calculated log P (c log P) of 5.5.[12] A few published medicinal chemistry reports focus on efforts to reduce the log P of CB1 antagonists to improve pharmaceutical properties. For example, Lange et al. describe an effort to reduce the log P of clinical candidate SLV-319 through modifications of peripheral groups including

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* Corresponding author. Tel.:+1 609 818 4965; fax: +1 609 818 3550; e-mail: Bruce.Ellsworth@bms.com

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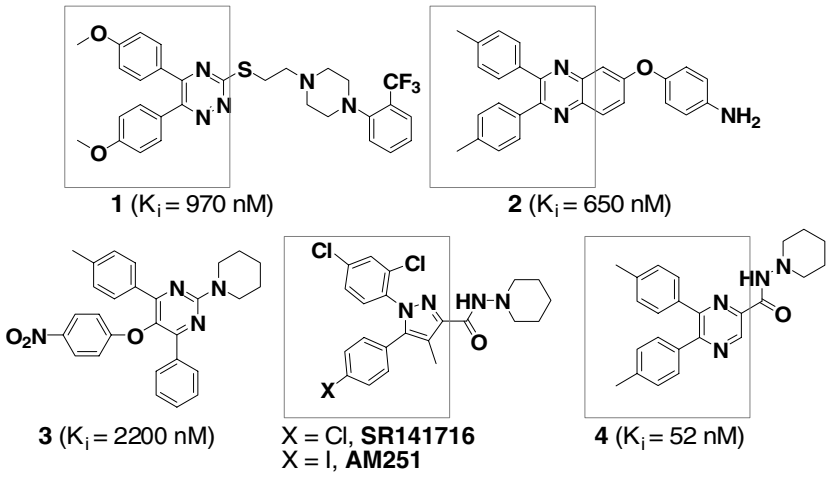


Figure 1. A comparison of SR141716[7] and AM251[16] with BMS HTS screening hits. *h*CB1 binding K_is are reported in parentheses.[17]

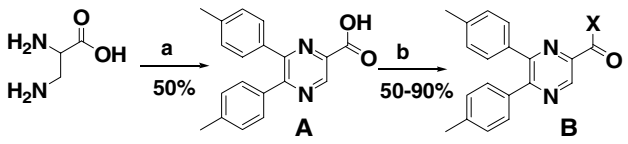
the sulfonamido-sidechain.[13] Most of the CB1 antagonists in this report have a lower log *P*, however they sacrifice some in vitro and in vivo potency relative to the starting point. To address a lead compound's poor PK properties, Debenhem et al. sought to modify the central core to effect reductions in log *P*.[14] As a consequence, the in vivo efficacy of the lead compound improved due to increases in plasma and brain exposure as well as oral bioavailability despite a fivefold reduction in CB1 binding affinity. A similar effort to improve pharmaceutical properties of a lead compound is described herein.

High-throughput screening of the Bristol Myers Squibb chemical collection for binding to the CB1 receptor resulted in many compounds of interest, including compounds **1**–**3**, that were suggestive of known ligands for type-1 GPCRs. The diaryl-substituted cores of these leads (Fig. 1, boxed moieties) are similar to the diaryl-substituted pyrazole of the known CB1 inverse agonist, SR141716, a moiety proposed to be important in aromatic stacking interactions that stabilize the inactive form of the receptor.[15] Structural overlays of these hits with SR141716 suggested that the 6-membered core ring of compounds **1** and **3** may be preferable to a linear 6,6-fused structure of compound **2**. The inclusion of a carboxamide may be important vis-à-vis published reports of the importance of an H-bond acceptor with Lys192 for the inverse-agonist activity of SR141716.[15]

Combining design elements from compounds **1** to **3** with those from known literature compounds rapidly led to the synthesis of pyrazine carboxamide **4**[18] (Fig. 1). The SAR of the carboxamide sidechain was elucidated by preparing a library of alkyl carboxamides derived from carboxylic acid **A** which was readily obtained by condensation of 2,3-diaminopropionic acid and 4,4′-dimethylbenzil.[19] Following treatment of carboxylic acid **A** with oxalyl chloride, the resulting acid chloride **B** (X=Cl) (Scheme 1) was isolated and distributed into reactor tubes containing PS-DIEA in methylene chloride, followed by addition of the amines. Final compounds were purified via preparative RP-HPLC. CB1 binding results for a series of alkyl pyrazine carboxamides are shown in Table 1. While short-chain alkyl groups demonstrated sub-micromolar potency, the inclusion of an aromatic group with a 3-carbon linker (entries **13** and **15**) gave rise to greater binding potency versus recombinant CB1. An ether linkage in **14** is detrimental to CB1 binding versus compound **13**, but a tertiary amine is well tolerated in the linker (entry **16**). Compound **13**, with a K_i value of 18 nM and full-functional CB1 antagonism in a GTP-γS assay,[20] was chosen for evaluation in our in vivo rat food intake model.

Compound **13** did not induce any reduction in food intake when administered orally at 30 mg/kg in food-deprived rats.[21] In an oral PK study, this compound exhibited low plasma and brain exposure, and slow absorption (Table 3) when administered at 30 mg/kg as a suspension in 0.5% Methocel and 1% Tween 80 to male Sprague–Dawley rats. The plasma and brain concentrations observed are likely too low to elicit a robust effect on food intake via CB1 inhibition.

In an attempt to simultaneously improve efficacy and oral exposure, we sought to lower *c* log *P* guided by both the 'Rule of 5'[22] concepts and prior CB1 literature reports (vide supra). Incorporation of polar amines such as 3-aminopyrrolidin-2-one and piperizin-2-one yielded analogs **33** and **34** which exhibited significantly reduced *c* log *P* and CB1 affinity (Table 2). The reported finding from a SAR study of the SR141716 pyrazole chemotype suggested that hydroxylation may offer a more conser-



Scheme 1. Synthesis of pyrazine carboxamides **B** (X=NHR). Reagents: (a) i—HCl (gas), MeOH; ii—4,4′-dimethylbenzil, KOH, MeOH; iii—LiOH, H_2O/THF/CH_3CN; (b) i—$(COCl)_2$, DMF, CH_2Cl_2; ii—RNH_2, PS-DIEA, CH_2Cl_2.

Table 1. SAR of pyrazine carboxamides **B**[17]

Compound	X = NHR	*h*CB1 K_i (nM)	SD (nM)	*c* log *P*
AM251	(see Fig. 1)	3	0.5	6.9
4	1-Aminopiperidine	53	13	5.5
5	Methylamine	3848	2636	4.3
6	Ethylamine	2381	397	4.8
7	*i*-Propylamine	656	86	5.1
8	*i*-Amylamine	195	21	6.3
9	Aniline	509	36	6.1
10	*N*-Methylbenzylamine	110	20	5.3
11	Cyclohexylmethylamine	59	11	6.9
12	Cyclopropylmethylamine	178	31	5.2
13	3-Phenylpropylamine	18	6	6.8
14	2-Phenoxyethylamine	631	322	6.3
15	4-Phenylbutyl-2-amine	5	2	7.1
16	3-(*N*-methyl-*N*-phenylamino)propylamine	25	10	7.0
17	3-(2,6-Dimethylphenoxy)-propyl-2-amine	39	5	7.6
18	1-Benzyloxybutyl-2-amine	203	49	7.0

Table 2. SAR of pyrazine carboxamides **B** (Scheme 1) with H-bond donor sidechains

Compound	X = amine	hCB1 K_i (nM)	SD (nM)	*c* log *P*
19	Ethanolamine	8430	2339	3.7
6	Ethylamine	2381	397	4.8
20	2-Aminoindan-3-ol	33	3	5.9
21	S-Leucinol	45	49	5.5
8	*i*-Amylamine	178	4	6.3
22	*R*-Leucinol	460	278	5.5
23	*S*-Valinol	237	65	4.9
24	*R*-Valinol	316	35	4.9
25	(±)-2-aminopentan-1-ol	158	66	5.1
26	2R-aminocyclohexan-1S-ol	300	15	5.1
27	*trans*-Aminocyclohexan-4-ol	(54%)[a]		4.2
28	Piperdin-4-ol	(38%)[a]		2.3
29	*trans*-Aminocyclohexan-2-methanol	167	39	5.5
30	*cis*-Aminocyclohexan-2-methanol	50	19	5.5
31	L-Leucinamide	105	62	4.9
32	D-Phenylglycinamide	238	69	4.8
33	3-Aminopyrrolidin-2-one	(46%)[a]		3.4
34	4-Piperazin-2-one	(29%)[a]		3.1
35	(see Figure. 3 for structure)	14	4	5.9

Key comparator compounds are boxed.[17]
[a] Percent inhibition at 13 μM.

vative means to increase polarity of the alkyl pyrazine carboxamides.[23] We hoped that the reduced log *P* of hydroxylated pyrazine carboxamides might improve pharmaceutical properties to produce compounds that would display in vivo efficacy in the CB1 feeding behavior study.

Ethanolamine carboxamide **19** (Table 2) exhibited reduced binding affinity as compared to the *des*-hydroxyl derivative **6**, though the 4-fold loss in affinity was moderate given the difference in polarity (Δc log *P* = 0.9). The hydroxyl group in aminocyclohexan-4-ol **27** and piperidin-4-ol **28**, however, resulted in compounds with significantly reduced CB1 binding affinity. Upon recognition that intramolecular hydrogen bonding (Fig. 2) of the hydroxyl group in compound **19** may minimize the impact of the polar group within the hydrophobic CB1 binding pocket, we focused on substituted ethanolamines.

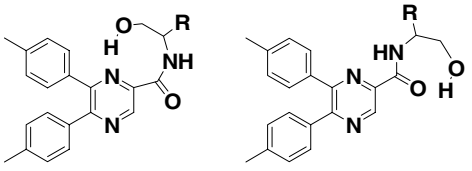


Figure 2. Proposed conformations for intramolecular H-bonded pyrazine carboxamides.

CB1 binding affinity in pyrazine carboxamides is dependent on the stereochemical configuration of the alkyl sidechain as demonstrated by the ten-fold affinity difference for the enantiomeric pair **21** and **22**. One isomer, compound **21**, is ~fourfold more potent than its *des*-hydroxymethyl counterpart **8**. In contrast, hydroxylation of SR141716 analogs substantially reduced CB1 binding affinity with no stereochemical preference for

the functionalized alkyl sidechain.[23] Benefits of an internal hydrogen bond were not limited to alcohols. The hydroxymethyl group of compound **21** was replaced with a primary carboxamide to give compound **31**. Intramolecular H-bonding of **31** to minimize unfavorable hydrophobic receptor interactions would account for the twofold greater binding potency than that of the alkyl derivative **8** despite a reduced *c* log*P* (Δc log*P* = 1.4).

Compound **21**[24] exhibited reduced lipophilicity (Δc log*P* = 1.3) and similar CB1 affinity to the lead *in vivo* candidate, **13**.[25] In contrast to compound **13**, compound **21** displayed improved exposure, and a more favorable brain/plasma ratio at 4 h when administered to rats at 10 mg/kg (Table 3). In addition, when administered orally at 10 mg/kg in the food deprived rat feeding model,[21] compound **21** reduced feeding by 37% 2 h after administration, by 32% 4 h after administration, and by 16% 24 h after administration (with no change in locomotor activity versus vehicle-treated animals). Using a model of ad libidum fed rats that are trained to operate a lever to obtain food, a 10 mg/kg dose of compound **21** did not produce a statistically significant change in food intake, however a 30 mg/kg dose induced a 34% ($p < 0.05$) cumulative reduction in food intake at 4 h versus vehicle-treated control animals.[26,27] These results suggested that hydroxyl-containing pyrazine carboxamides provided the improvement in physicochemical properties needed to drive in vivo efficacy.

A limited exploration of SARs at the diaryl portion of the pyrazine carboxamide core revealed that CB1 binding affinity was enhanced by substituting chlorine for methyl substituents.[18] A priori, the bis-(4-chlorophenyl) series would be expected to be too lipophilic to exhibit good PK properties; however, hydroxylation of the sidechain to generate **35**[28] (Fig. 3) was anticipated to ameliorate this matter. The expected enhancement in affinity of **35** relative to **21** was maintained; CB1 K_i values of 14 and 45 nM, respectively. Moreover, the two compounds display very similar PK properties (Table 3) despite *c* log*P* of the dichloro analog **35** being ~0.4 U higher than

Table 3. Measured PK parameters for pyrazine carboxamides[a]

Compound p.o. dose	**13**[b] 30 mg/kg (nM)	**21**[c] 10 mg/kg (nM)	**35**[c] 10 mg/kg (nM)
Time (h)			
0.5	23	74	218
1	35	245	257
2	89	148	187
4	84	105	157
Avg. T_{max} (h)	2	1	1
AUC_{0-4h} (nM h)	256	541	736
Brain concd 4 h (nM)	34	306	491
Brain/plasma at 4 h	0.4	3	3.1

[a] Tabular values are averages from $n = 2$ male Sprague–Dawley rats.
[b] Administered as a suspension in 0.5% Methocel/1% Tween 80/water; compound **13** is insoluble in 10%EtOH/10% Cremaphor/water.
[c] Administered as a solution in 10% EtOH/10% Cremaphor/water.

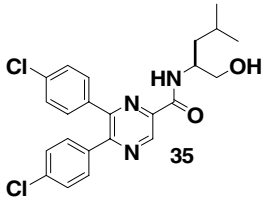


Figure 3. Bis-(4-chlorophenyl)pyrazine carboxamide (**35**).

that of the dimethyl analog **21**. When administered at 10 mg/kg to rats trained to operate a lever to obtain food, compound **35** demonstrated a 46% cumulative reduction of food intake at 4 h versus vehicle-treated control animals. Inclusion of a hydroxylic sidechain potentially provides a means to further enhance solubility and oral bioavailability by incorporation of a prodrug moiety.[29,30]

We report a series of pyrazine carboxamides as CB1 receptor antagonists that were developed from high-throughput screening lead structures. The incorporation of a hydroxyl moiety provides physicochemical benefits, including lowered *c* log*P*, that results in compounds with enhanced oral exposures and in vivo efficacy in a food intake model in rats. The hydroxyl group also provides an opportunity for prodrug strategies that provide further improvements in physicochemical characteristics such as aqueous solubility. Our efforts to increase the in vitro and in vivo potency of this series while maintaining low log*P* will be the subject of future communications.

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28. Compound **35**: ^{1}H NMR δ 9.38 (s, 1H), 7.85 (d, 1H, J = 8.4 Hz), 7.61–7.31 (m, 8H), 4.33–4.28 (m, 1H), 3.83 (dd, 1H, J = 3.6, 11.1), 3.69 (dd, 1H, J = 4.7, 11.1), 1.75–1.64 (m, 1H), 1.62–1.46 (m, 2H), 0.98 (dd, 6H, 2.0, 6.5 Hz) ^{13}C NMR ($CDCl_3$) δ 163.5, 151.2, 149.4, 141.7, 141.0, 136.0, 135.9, 131.1, 131.0, 129.0, 128.9, 66.1, 50.4, 40.2, 25.1, 23.1, 22.3. HRMS anal. calcd for $C_{23}H_{23}Cl_2N_3O_2$ 443.11673 found [M+H] 444.1257.
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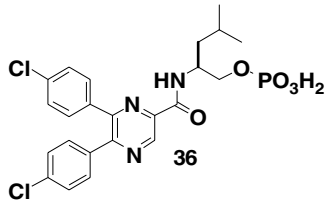
30. Compound 35 was converted to a phosphate ester via reaction with $POCl_3$ in THF at 0 °C, followed by workup with aqueous HCl to give phosphate **36** that exhibited 0.43 mg/mL aqueous solubility at pH 6.5.



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