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Oxadiazole-diarylpyrazole 4-carboxamides as cannabinoid CB1 receptor ligands

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ABSTRACT

Cannabinoid CB-1 receptors have been the focus of extensive studies since the first clinical results of rimonabant (SR141716) for the treatment of obesity and obesity-related metabolic disorders were reported in 2001. To further evaluate the properties of CB receptors, we have designed and efficiently prepared a series of oxadiazole-diarylpyrazole 4-carboxamides. Six of the new compounds which displayed high in vitro CB1 binding affinities were assayed for binding to CB2 receptor. Noticeably, 5-(4-bromophenyl)-3-(5-*tert*-butyl-1,3,4-oxadiazol-2-yl)-1-(2,4-dichlorophenyl)-*N*-phenyl-1*H*-pyrazole-4-carboxamide (**12q**) and 5-(4-bromophenyl)-3-(5-*tert*-butyl-1,3,4-oxadiazol-2-yl)-1-(2,4-dichlorophenyl)-*N*-(pyridin-2-yl)-1*H*-pyrazole-4-carboxamide (**12r**) demonstrated good binding affinity and decent selectivity for CB1 receptor (IC_{50} = 1.35 nM, CB2/CB1 = 286 for **12q**; IC_{50} = 1.46 nM, CB2/CB1 = 256 for **12r**).

Recent development of obesity drugs reveals that it is possible to control appetite and reduce weight by blocking cannabinoid receptors in the brain, liver or muscle, via cannabinoid (CB1) receptor antagonists or CB1 receptor inverse agonists.[1,2] A cannabinoid CB1 receptor antagonist is designed to block the effects of endogenous cannabinoids. This type of drug is particularly interesting since it not only causes weight loss but also reverses the metabolic effects of obesity such as insulin resistance and hyperlipidemia.[3] The other cannabinoid receptor, CB2 is related to immune regulation and neurodegeneration.[4] Therefore, the CB2/CB1 selectivity should be taken into consideration for new drug development of anti-obesity agent.

The first specific cannabinoid CB1 receptor antagonist, rimonabant was discovered in a high throughput screening program at Sanofi-Synthélabo in 1994.[5] Several CB1 receptor antagonists including SR141716 (rimonabant), SLV319 (ibipinabant),[6] CP-945,598 (otenabant) and MK-0364 (taranabant)[7] have been reported to be in various phase of clinical trials.[8,9,23] A pharmacophore model for the binding of a low energy conformation of rimonabant in the CB1 receptor has been well-documented.[9,10] The key receptor–ligand interaction is known to be a hydrogen bond between the carbonyl group of rimonabant and the Lys192-Asp366 residue of the CB1 receptor, thereby exerting a stabilizing effect on the Lys192-Asp366 salt bridge as shown in Figure 1.[1]

To date, various analogs of rimonabant by replacing the key carbonyl group have been designed for the purpose of enhancing binding affinity and selectivity for the CB1 receptor. We note that

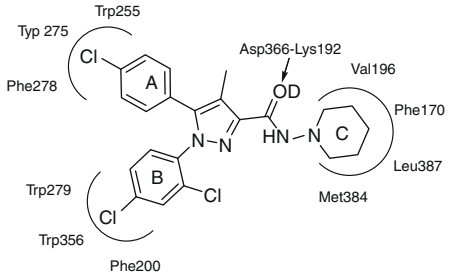

Figure 1. Rimonabant and its receptor–ligand interaction.

such approaches were already demonstrated successfully with imidazole,[11] tetrazole.[12] Subsequently, we also discovered that the oxadiazole[13] scaffold has also been employed for this purpose, even though there are clear differences evident between our previous works[14] and these prior examples.

With our efforts to discover and develop a new medicine for the treatment of obesity, we have recently reported the diarylpyrazolyl oxadiazole derivatives as potent, selective, orally bioavailable cannabinoid-1 receptor antagonists for the treatment of obesity.[14a] Therein, we demonstrated that incorporation of a 1,2,4-triazole ring onto the C-4 region of pyrazole scaffold via a methylene linker improved in vitro binding affinity, in turn leading to excellent in vivo efficacy on animal model.[15] We envisioned that the polar amide groups in the C-4 region of pyrazole scaffold can be accommodated based on the observation that this region is capable of embracing substituents of varying functionality, size, and polarity.

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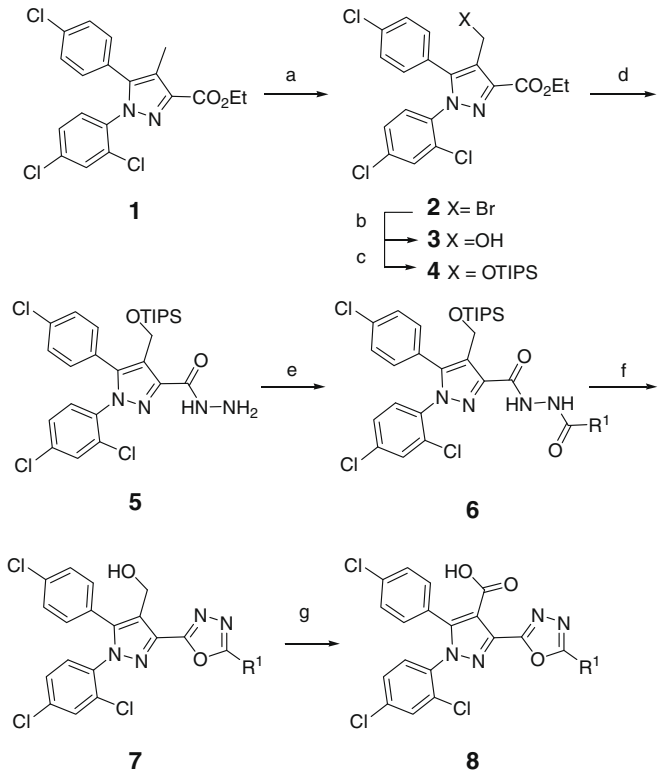
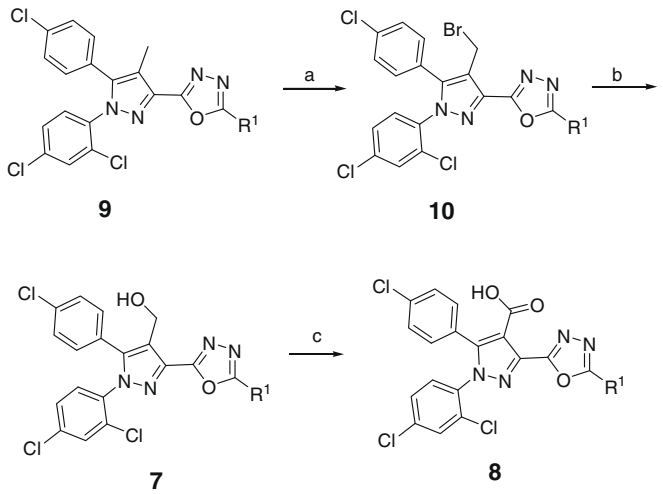


Scheme 1. Reagents and conditions: (a) NBS, AIBN, CCl_4, reflux, 55% (b) $AgNO_3$, acetone–H_2O, rt, 96%; (c) TIPSCl, imidazole, DMF, rt; (d) NH_2NH_2, EtOH, 90 °C, 97% (2 steps); (e) R^1CO_2H, EDC, HOBt, DMF, rt, 71%; (f) (i) Burgess reagent, THF, reflux, 76%; (ii) TBAF, THF, rt, 95%; (g) (i) Dess–Martin periodinane, CH_2Cl_2, rt, 78%; (ii) $NaClO_2$, KH_2PO_4, 2-methylbut-2-ene, *t*-BuOH–H_2O, rt, 95%.



Scheme 2. Reagents and conditions: (a) NBS, AIBN, CCl_4, reflux, 78%; (b) (i) NaOAc, THF–H_2O, rt, 63%; (ii) LiOH, THF–H_2O, rt, 95%; (c) (i) Dess–Martin periodinane, CH_2Cl_2, rt, 78%; (ii) $NaClO_2$, KH_2PO_4, 2-methylbut-2-ene, *t*-BuOH–H_2O, rt, 95%.

Herein, we wish to describe the chemical synthesis, biological evaluation of oxadiazole-diarylpyrazole 4-carboxamide analogs as our additional research efforts toward discovery of a promising antiobesity agent.

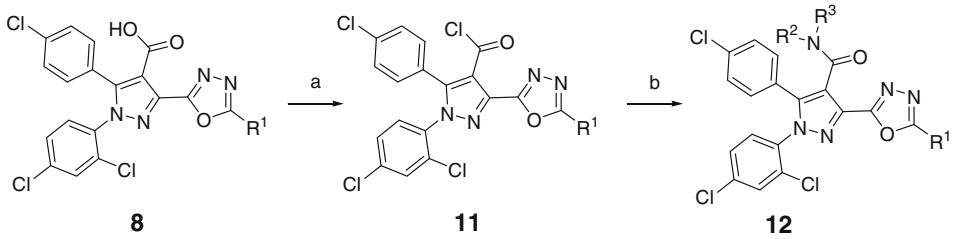
Synthesis of oxadiazole-biarylpyrazoles commenced with the generic carboxylate **1**.[16] he carboxylate **1** was converted to the bromide **2** using NBS in the presence of a catalytic amount of AIBN,[8] and this intermediate was then treated with silver nitrate in aqueous acetone[17] to afford the corresponding alcohol **3**. Subsequently, alcohol **3** was protected with TIPSCl (triisopropylsilyl chloride) in the presence of a suitable base such as imidazole to provide **4**. Treatment of the ester **4** with hydrazine efficiently gave rise to hydrazide **5** which was used to couple with an acid in the presence of appropriate coupling reagents such as EDC and HOBt to provide acyl hydrazide **6**. Cyclization was then performed using the Burgess reagent[18] under heating conditions, and subsequent TIPS deprotection with TBAF was conducted to afford alcohol **7.** Oxidation of the alcohol **7** to the corresponding aldehyde was achieved through the use of Dess–Martin periodinane.[19] Aldehyde was further oxidized to acid **8** by use of sodium chlorite and monobasic potassium phosphate in aqueous *t*-BuOH as shown in Scheme 1.[14a]

Alternatively, acid **8** can be prepared by benzylic bromination-type reaction on pyrazole **9** as illustrated in Scheme 2.[24] The alcohol functionality was then introduced by treating bromide **10** with sodium acetate, followed by basic hydrolysis of the resulting acetate. Subsequent two-step oxidation of alcohol **7** to acid **8** was conducted in the same way as described previously.[14a]

With requisite acid **8** in hand, the preparation of various amides was conducted as shown in Scheme 3. The first approach toward **12** using coupling reagents such as EDC, HOBt in the suitable base was unable to effect the requisite coupling reaction in a satisfactory manner. Subsequently, we found out that the two-step sequence via acyl chloride **11** proved to be more efficient in producing amides **12** in reasonable yields.

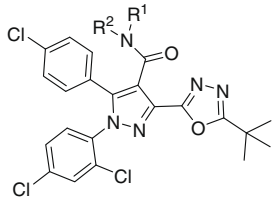
The target analogs were evaluated in vitro at a rat CB1 binding assay,[20,22] and the results are shown in Table 1.[25] Unsubstituted carboxamide **12a** had modest in vitro activity for rat CB1 receptor (IC_{50} = 23.8 nM). As the size of the carbon chain on carboxamide increases, increase in the binding affinity for rat CB1 receptor is observed up to C-3 chain. Thus, *N*-methyl **12b**, *N*-ethyl **12c**, and *N*-propyl **12d** showed rat binding affinity for CB1 receptor IC_{50} = 18.3, 12.7, 5.72 nM, respectively. The binding affinity for CB1 was decreased when the alkyl chain became more prolongated (**12g**, IC_{50} = 17.8 nM).

Preferable in vitro binding affinity displayed for the carbocycle (*N*-cyclopropyl, **12f**, IC_{50} = 3.27 nM) than straight chain (*N*-propyl, **12d**, IC_{50} = 5.72 nM) or branched chain (*N*-isopropyl, **12e**, IC_{50} = 9.31 nM) if the same number of carbons are counted. As the size of carbocycle increases, the binding affinity for CB1 receptor decreases. For example, *N*-cyclopentyl, **12h** showed the slightly weaker binding affinity for CB1 receptor (IC_{50} = 7.25 nM), whereas *N*-cyclopropyl, **12f** showed the superior binding affinity for CB1 receptor (IC_{50} = 3.27 nM). N,N-disubstitution on carboxamide such as *N*,*N*-dimethyl **12m**, *N*-ethyl-*N*-methyl **12n** appeared to be toler-



Scheme 3. Reagents and conditions: (a) oxalyl chloride, cat. DMF, CH_2Cl_2, rt (b) NHR^2R^3, THF, rt, 60–70% (2 steps).

Table 1
Binding affinity of 4-carboxamide diarylpyrazoles to rCB1 receptor[a]



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R^1	R^2	Compound	rCB1 IC_{50}[b]
Rimonabant			5.0 ± 1.0[c]
H	H	**12a**	23.8
Me	H	**12b**	18.3
Et	H	**12c**	12.7
n-Propyl	H	**12d**	5.72
i-Propyl	H	**12e**	9.31
c-Propyl	H	**12f**	3.27
n-Butyl	H	**12g**	17.8
c-Pentyl	H	**12h**	7.25
N-Piperidinyl	H	**12i**	17.2
Ph	H	**12j**	1.66
2-Pyridinyl	H	**12k**	1.47
$CH_2(CO)CH_3$	H	**12l**	3.51
Me	Me	**12m**	13.4
Et	Me	**12n**	11.5
Et	Et	**12o**	62.1
CH_2CH_2 CH_2CH_2		**12p**	93.4

[a] CB1 receptor was collected from brain tissue of SD rat.
[b] These data were obtained by single determinations.
[c] The CB1R binding affinity for rimonabant has showed a certain number in the close range (IC_{50} = 5.0 ± 1.0 nM) in each different assay (>1500 compounds tested).

ated for the replacement to a degree, but as the size of substituted chains become bigger (**12o, 12p**), none appeared more potent than the monosubstituted carboxamide (**12c**). As shown in *N*-(2-oxopropyl)-1*H*-pyrazole-4-carboxamide **12l**, polar carbonyl group appears to be tolerated, indicating that there might be some SAR potential for other carbocycles. Among the various rings, or chains tested on carboxamide, the best result was obtained when nitrogen on carboxamide has simple phenyl (**12j**) or 2-pyridinyl (**12k**). They showed excellent binding affinity for rat CB1R (IC_{50} = 1.66 nM for **12j**, 1.47 nM for **12k**, respectively).

In order to improve the binding affinity levels for the CB1 receptor, a structural replacement of 4-chlorophenyl moiety to 4-bromophenyl was undertaken.

In addition, the surrogate effect of the cyclopropyl group for a gem-dimethyl group was also studied. A structurally related series of oxadiazole-diarylpyrazole 4-carboxamide derivatives was prepared in an analogous fashion previously described. The binding affinity data of these oxadiazole-diarylpyrazole 4-carboxamide analogs are shown in Table 2. The interesting compounds were further evaluated with observation of the CB2 receptor binding affinity. The IC_{50} values were measured for the recombinant human CB2 receptor expressed in CHO cells and employing [3H]WIN-55,212-2 as a radio-ligand.[21] Replacement of 5-(4-chlorophenyl) **12j** (IC_{50} = 1.66 nM) with 5-(4-bromophenyl) **12q** (IC_{50} = 1.35 nM) slightly improved CB1 receptor binding affinity. However, this phenomenon is not clearly demonstrated by replacement of **12k** (IC_{50} = 1.47 nM) with **12r** (IC_{50} = 1.46 nM). Regarding the CB2/CB1 selectivity, there appeared to deteriorate as chlorines were switched to the corresponding bromides, as exemplified by two pairs of compounds involving **12j** (CB2/CB1 selectivity = 445) to **12q**(CB2/CB1 selectivity = 286) and **12k**(CB2/CB1 selectivity = 433) to **12r** (CB2/CB1 selectivity = 256). As far as the CB2 receptor activity is concerned, the best result was obtained when R^2 is substituted with bulky (4-chlorophenyl)cyclopropyl (**12s**, IC_{50} = >10 μM for CB2R), indicating the importance of massive groups for the region for improvement of the CB2/CB1 selectivity.[26]

In conclusion, we investigated a series of oxadiazole-diarylpyrazole 4-carboxamide derivatives for their binding affinity for cannabinoid CB1 and CB2 receptors. We have identified a novel series of small molecule cannabinoid CB1 ligands that shows binding affinity superior to that of known CB1 antagonists. Several compounds in this series exhibited potent CB1 receptor binding affinities, validating the hypothesis that the polar amide groups in the C-4 region of pyrazole scaffold can be accommodated. Importantly, these analogs also display good selectivity for CB1R over CB2R. Additional PK and in vivo efficacy studies in addition to further SAR studies of the oxadiazole-diarylpyrazole 4-carboxamide derivatives will be the subject of future investigations.

Acknowledgements

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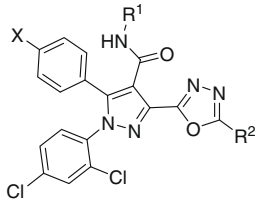
Table 2
Binding affinity of 4-carboxamide diarylpyrazoles to rCB1 and hCB2 receptors[a,b]



12

R^1	R^2	X	Compound	rCB1 IC_{50}[c]	hCB2 IC_{50}[c]	CB2/CB1 selectivity
Rimonabant				5.0 ± 1.0[d]	1760[c]	~352
Ph	*t*-Butyl	Cl	**12j**	1.66	738	445
2-Pyridinyl	*t*-Butyl	Cl	**12k**	1.47	636	433
Ph	*t*-Butyl	Br	**12q**	1.35	386	286
2-Pyridinyl	*t*-Butyl	Br	**12r**	1.46	374	256
Ph	(4-Chlorophenyl)cyclopropyl	Br	**12s**	1.96	>10,000	>5102
2-Pyrininyl	trifluoromethylcyclopropyl	Cl	**12t**	1.94	488	252

[a] CB1 receptor was collected from brain tissue of SD rat.
[b] CB2 receptor was recombinant human receptor expressed in CHO cell.
[c] These data were obtained by single determinations.
[d] This data was obtained by multiple determinations.

discussions throughout small molecule programs at GCC. Also we are grateful to Dr. Eun Chul Huh, Mr. Jung Ho Kim and Ms. Jae-Young Jang at GCC Office of R& D planning and coordination for their supports and services.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2009.02.063.

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22. CB1 and CB2 Receptor Binding Assay. For the CB1 receptor binding studies, rat cerebellar membranes were prepared aspreviously described by the methods of Kuster et al.[20] MaleSprague–Dawley rats (200–300 g) were sacrificed by decapitation and the cerebella rapidly removed. The tissue was homogenized in 30 volumes of TME buffer (50 mM Tris–HCl, 1 mM EDTA, 3 mM $MgCl_2$, pH = 7.4) using a Dounce homogenizer. The crude homogenates were immediately centrifuged (48,000*g*) for 30 min at 4 °C. The resultant pellets were resuspended in 30 volumes of TME buffer, and protein concentration was determined by the method of Bradford and stored at −70 °C until use. For the CB2 receptor binding studies, CHO K-1 cells were transfected with the human CB2 receptor as previously described, and cell membranes were prepared as described above.[21] Competitive binding assays were performed as described. Briefly, approximately 10 μg of rat cerebella membranes (containing CB1 receptor) or cell membranes (containing CB2 receptor) were incubated in 96-well plate with TME buffer containing 0.5% essentially fatty acid free bovine serum albumin (BSA), 3 nM [3*H*]WIN55,212-2 (for CB2 receptor, NEN; specific activity 50–80 Ci/mmol) or 3 nM ([3*H*]CP55,940, [3*H*]2-[(1*S*,2*R*,5*S*)-5-hydroxy-2-(3-hydroxypropyl) cyclohexyl]-5-(2-methyloctan-2-yl)phenol, for CB1 receptor, NEN; specific activity 120–190 Ci/mmol) and various concentrations of the synthesized cannabinoid ligands in a final volume of 200 μL. The assays were incubated for 1 h at 30 °C and then immediately filtered over GF/B glass fiber fiber filter (PerkinElmer Life and Analytical Sciences, Boston, MA) that had been soaked in 0.1% PEI for 1 h by a cell harvester (PerkinElmer Life and Analytical Sciences, Boston, MA). Filters were washed five times with ice-cold TBE buffer containing 0.1% essentially fatty acid free BSA, followed by oven-dried for 60 min and then placed in 5 mL of scintillation fluid (Ultima Gold XR; PerkinElmer Life and Analytical Sciences, Boston, MA), and radioactivity was quantitated by liquid scintillation spectrometry. In CB1 and CB2 receptor competitive binding assay, nonspecific binding was assessed using 1 μM rimonabant and 1 μM WIN55,212-2, respectively. Specific binding was defined as the difference between the binding that occurred in the presence and absence of 1 μM concentrations of rimonabant or WIN55,212-2 and was 70–80% of the total binding. IC50 was determined by nonlinear regression analysis using Graph–Pad PRISM. All data were collected in triplicate and IC50 was determined from three independent experiments.
23. As of November 5, 2008, Sanofi-Aventis, Merck, and Pfizer announced that they have decided to discontinue their ongoing clinical development programs about rimonabant (SR141716), taranabant (MK-0364), and otenabant (CP-945,598), respectively based on changing regulatory perspectives on the risk/benefit profile of the CB1 class and likely new regulatory requirements for approval.
24.

Comparison of alternative routes to key intermediates 8[1,b]

	Scheme 1	Scheme 2
R^1	4-(Chlorophenyl) cyclopropyl	*t*-Butyl
Overall yield (%)	19 (8-steps)	15 (8-steps)
Retention time (min)	8.119	4.835
Purity (%)	99	99

[b] Compound 9 was prepared from compound 1 as described in [14a].

[1] HPLC Purity was determined by Agilent 1200 series high performance liquid chromatography with UV detection at 254 nm (Xterra® MS C18 3.5 μm, 2.1 × 50 mm, 12 min, 0.3 mL/min flow rate, 50–100% 0.05% TFA in CH_3CN/ 100–50% 0.05% TFA in H_2O).

25.

Table of HPLC retention time and Purity of final compounds[a]

Compound	Retention time (min)	Purity (%)
12a	3.717	>99
12b	4.279	>99
12c	5.483	>99
12d	6.831	99
12e	6.601	99
12f	5.705	>99
12g	7.988	>99
12h	8.201	>99
12i	2.953	>99
12j	9.540	99
12k	6.280	>99
12l	4.703	>99
12m	4.513	>99
12n	5.551	>99
12o	6.594	99
12p	5.338	>99
12q	9.850	>99
12r	6.597	>99
12s	11.795	99
12t	6.661	>99

[a] HPLC Retention time and Purity were determined by Agilent 1200 series high performance liquid chromatography with UV detection at 254 nm (Xterra® MS C18 3.5 μm, 2.1 × 50 mm, 12 min, 0.3 mL/min flow rate, 50–100% 0.05% TFA in CH_3CN/ 100–50% 0.05% TFA in H_2O).

26. As pointed out by a reviewer, compound **12s** represents the best diarylpyrazole-oxadiazole to date, and the selectivity is impressive. A bulky group such as (4-chlorophenyl)cyclopropyl in compound 12 appears to deactivate CB2 receptor binding affinity while maintaining its activity for CB1 receptor, thereby improving CB2/CB1 selectivity.