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Diarylimidazolyl oxadiazole and thiadiazole derivatives as cannabinoid CB_1 receptor antagonists

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ABSTRACT

Since the CB1 receptor antagonist SR141716 (rimonabant) was reported to modulate food intake, CB1 antagonism has been considered as a new therapeutic target in the treatment of obesity. Several series of derivatives based on diarylimidazolyl oxadiazole and thiadiazole scaffolds were synthesized and tested for CB1 receptor binding affinity. SAR studies directed toward the optimization of imidazole scaffolds resulted in the discovery of **10s** which showed highest potency for CB1 receptor binding affinity (IC_{50} = 1.91 nM) prepared to date.

The CB1 cannabinoid receptor belongs to the G-protein-coupled receptor (GPCR) type and is coupled to inhibitory G proteins (G(i/o)) to inhibit certain adenylyl cyclase isozymes, leading to decreased cAMP production, decreased Ca^{2+} conductance, increased K^+ conductance, and increased mitogen-activated protein kinase activity.[1] The major physiological effect of cannabinoids is the modulation of neurotransmitter release via activation of presynaptic CB1 receptors located on distinct types of axon terminals throughout the brain.[2]

Δ^9-Tetrahydrocannabinol (Δ^9-THC) has been known as active ingredient of Marijuana which has ability to stimulate appetite by activating the cannabinoid receptor, CB1 in the brain.[3]

The CB1 receptor antagonists/inverse agonists have shown to be useful in the suppression of food intake and the reduction of body weight.[4] Food intake suppression mediated by the CB1 inverse agonists has been demonstrated in animal[5] and human studies.[6] The first published studies with rimonabant (SR141716) in both rodents[7] and primates[8] showed clear differentiation, that is, marked effects on sweet food intake vs. marginal effects on regular chow intake or water drinking.

The first specific cannabinoid CB1 receptor antagonist or inverse agonist, rimonabant, was discovered in a high-throughput screening program at Sanofi-Synthelabo in 1994.[9] Several CB1 receptor antagonists including rimonabant, SLV319 (ibipinabant),[10] CP-945,598 (otenabant)[11] and MK-0364 (taranabant)[12] have been reported to be late phase of clinical trials. A pharmacophore model for the binding of a low energy conformation of rimonabant in the CB1 receptor has been well-documented.[13,14] The crucial 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 in Figure 1.[15]

Bioisosteric replacement forms a rational medicinal chemistry approach for the discovery of new leads or series, based on existing key ligands. The three-dimensional structure of imidazole maintains a high similarity to that of the pyrazole. As a consequence, they can be regarded as isosteres thereof and have been applied in order to discover pyrazole bioisosteres.[16] Also, we demonstrated a successful replacement of the key carbonyl group of rimonabant with imine-type functionality, tetrazole group.[17] Among many heterocycles involving 'imine-type' functionality other than tetrazole, we were particularly interested in oxadiazole[23] or thiadiazole as a viable surrogate of amide, since modifying the key carbonyl group of rimonabant into oxadiazole or thiadiazole could furnish a favorable balance of potency and physicochemical properties to allow for further in vivo efficacy evaluation. Herein, we wish to disclose

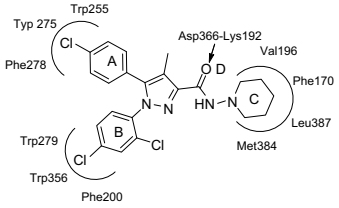

Figure 1. Rimonabant and its receptor–ligand interaction.

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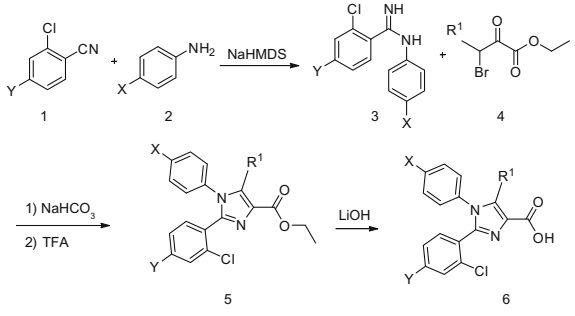
the synthesis and evaluation of the oxadiazole–diarylimidazole and thiadiazole–diarylimidazole as novel CB1 receptor antagonists.

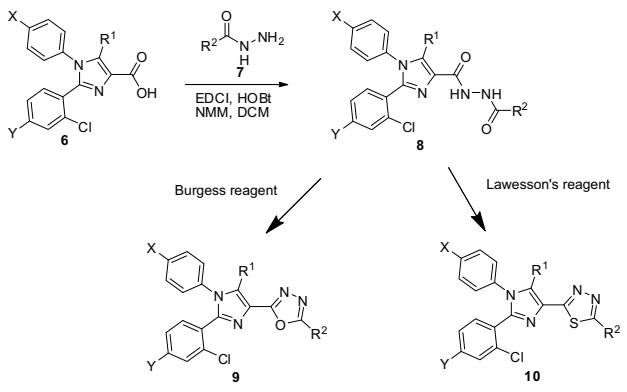
The carboxylic acid derivative **6** was prepared by a conventional method, for example, by reacting a benzonitrile **1** with an aniline derivative **2** using sodium bis(trimethylsilyl)amide (NaHMDS) to produce a corresponding arylbenzamidine **3**. Subsequent reaction of the resulting arylbenzamidine **3** with α-bromoketone **4** gave an intermediate ethyl 1,2-diaryl-5-alkyl-1*H*-imidazole-4-carboxylate **5**. An acid form **6** was transformed from the intermediate **5** using lithium hydroxide, followed by acidification, as shown in Scheme 1.[16]

The target compounds **9** and **10** were prepared by reaction of a carboxylic acid derivative **6** with hydrazide compound **7** in the presence of EDCI and HOBt in DCM, and cyclization of the resulting acyl hydrazide compound **8** using Burgess reagent[18] to provide an 1,3,4-oxadiazole compound **9**, or Lawesson's reagent[19] to yield a 1,3,4-thiadiazole compound **10** as shown in Scheme 2. The hydrazide derivative **7** was prepared by treating an ester or a carboxylic acid with hydrazine.

The target compounds of structures **9** and **10** were evaluated in vitro in a rat CB1 binding assay.[20,24] The results are shown in Table 1. Since there are a number of literature precedents describing the importance of lipophilic groups at the C domain of rimonabant as shown in Figure 1, various lipophilic groups have been focused for investigation. These data demonstrate that the size of carbocycle appears to affect binding affinity. Thus, 7-membered ring (**9d**) is slightly better than the 4- or 5-membered ring, suggesting that there might be a size requirement for the oxadiazole alkyl region to attain good binding to CB1 receptor. In the case of thiadiazole, 5-membered ring (**10b**) is more active in 2- to 4-fold than the corresponding oxadiazole (**9b**). Longer branched aliphatic chains are usually better, showing IC_{50} = 12.9 nM for **9j**. Introduction of additional methyl group at the branch such as *t*-butyl **9g** elevated CB1 binding affinity of *i*-propyl **9e** in 2-fold. Instead of gem-dimethyl group, cyclopropyl at the position can be replaced without impeding in vitro CB1 receptor binding affinity, displaying similar level of binding affinity (**9m**, **9n**). Interestingly, altering oxadiazoles to the corresponding thiadiazoles improved CB1 receptor binding affinity in approximately 2-fold, showing IC_{50} = 9.66 nM for **10m** and IC_{50} = 9.41 nM for **10n**, respectively. It was encouraging to notice that a considerable CB1 receptor binding affinity was already observed in a number of compounds. At this juncture, we decided to proceed to explore R^1, X and Y substituents of the imidazole core by using *t*-butyl oxadiazole as a tentative lead scaffold, since (i) our previous research[23c] on diarylimidazolyl oxadiazoles as the CB1R antagonists showed that the *t*-butyl group is beneficial for the moiety. (ii) The *t*-butyl group

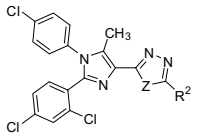


Scheme 1.



Scheme 2.

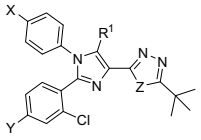
Table 1
Structures and binding affinities of selected ligands for rat CB1 receptors



Compound Z			IC50 (nM) for rCB1R[a,b] Z	
O	S	R^2	O	S
9a	**10a**	Cyclobutyl	38.7	42.3
9b	**10b**	Cyclopentyl	35.3	10.8
9c	**10c**	Cyclohexyl	115	46.0
9d	**10d**	Cycloheptyl	27.6	21.6
9e	**10e**	*i*-Pr	25.8	22.2
9f	**10f**	*i*-Bu	39.4	28.1
9g	**10g**	*t*-Bu	13.2	20.2
9h	**10h**	Pentan-2-yl	14.2	12.7
9i	**10i**	Pentan-3-yl	22.3	19.7
9j	**10j**	Hexan-2-yl	12.9	15.0
9k	**10k**	1-Phenylethyl	31.4	16.9
9l	**10l**	1-(Triflluoromethyl)cyclopropyl	55.1	33.5
9m	**10m**	1-(Triflluoromethyl)cyclobutyl	16.7	9.66
9n	**10n**	1-(4-Chlorophenyl)cyclopropyl	15.2	9.41
		Rimonabant	5.0 ± 1.0[c]	

[a] CB1 receptor was collected from brain tissue of SD rat.[24]
[b] These data were obtained by single determinations.[26]
[c] These data were obtained by in-house assay.

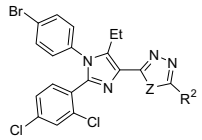
Table 2
Structures and binding affinities of selected ligands for rat CB1 receptors



Compound Z					IC50 (nM) for rCB1R[a,b] Z	
O	S	X	Y	R^1	O	S
9g	**10g**	Cl	Cl	Me	13.2	20.2
9o	**10o**	Cl	Cl	Et	18.1	15.8
9p	**10p**	Cl	Cl	*n*-Pr	18.9	7.94
9q	**10q**	Cl	Cl	Cyclopropyl	79.9	58.0
9r	**10r**	Br	Cl	Me	5.81	3.45
9s	**10s**	Br	Cl	Et	3.15	1.91
9t	**10t**	Br	Cl	*n*-Pr	71.5	13.5
9u	**10u**	Br	Cl	*i*-Pr	21.2	6.49
9v	**10v**	Cl	H	Me	5.29	12.7
9w	**10w**	Cl	H	Et	21.3	–[c]
9x	**10x**	Br	H	Me	31.7	10.7
9y	**10y**	Br	H	Et	14.7	–[c]
			Rimonabant		5.0 ± 1.0[c]	

[a] CB1 receptor was collected from brain tissue of SD rat.
[b] These data were obtained by single determinations.
[c] These data were obtained by in-house assay.

Table 3
Structures and binding affinities of selected ligands to rat CB1 and human CB2 receptors, and CB2/CB1 selectivity of the ligands



Compound	R^2	Z	IC_{50} (nM) for rCB1R[a,c]	IC_{50} (nM) for hCB2R[b,c]
9z	1-Phenylcyclopropyl	O	9.14	–
9aa	1-(4-Methoxyphenyl)cyclopropyl	O	18.6	–
9ab	1-(4-Methylphenyl)cyclopropyl	O	8.38	>10,000
9ac	1-(2,4-Dichlorophenyl)cyclopropyl	O	8.05	>10,000
9ad	1-(4-Chlorophenyl)cyclopropyl	O	9.05	–
9ae	1-(4-Chlorophenyl)cyclobutyl	O	13.6	>10,000
10z	1-Phenylcylcopropyl	S	8.29	>10,000
10aa	1-(4-Methoxyphenyl)cyclopropyl	S	9.21	>10,000
10ab	1-(4-Methylphenyl)cyclopropyl	S	5.72	>10,000
10ac	1-(2,4-Dichlorophenyl)cyclopropyl	S	6.57	>10,000
10ad	1-(4-Chlorophenyl)cyclopropyl	S	4.53	>10,000
10ae	1-(4-Chlorophenyl)cyclobutyl	S	4.79	>10,000
	Rimonabant		5.0 ± 1.0[d]	1760[d]

[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.

has played an outstanding role in the field of medicinal chemistry due to its unique properties.[21]

The binding affinity data of selected key diarylimidazolyl oxadiazoles and thiadiazoles for the CB1 receptor are shown in Table 2.

When methyl was replaced by ethyl **9o** or *n*-propyl **9p**, it showed similar level of CB1 receptor binding affinity, respectively, but binding potency for cyclopropyl **9q** deteriorated in 4-fold, indicating that even small ring such as cyclopropyl is not tolerated for the region. This is also observed in the thiadiazole **10q**. Replacement of 1-(4-chlorophenyl) **9g** (IC_{50} = 13.2 nM) with 1-(4-bromophenyl) **9r** (IC_{50} = 5.81 nM) improved CB1 receptor binding affinity in more than 2-fold. This phenomenon is clearly demonstrated by comparing **9o** (IC_{50} = 18.1 nM) versus **9s** (IC_{50} = 3.15 nM). However, this effect is not observed any longer as the number of carbon on imidazole core is increased beyond ethyl as shown in *n*-propyl **9t** (IC_{50} = 71.5 nM).

As observed previously, thiadiazoles turned out to be more active than the corresponding oxadiazoles. Of note is that among our compounds tested, 2-(1-(4-bromophenyl)-2-(2,4-dichlorophenyl)-5-ethyl-1*H*-imidazol-4-yl)-5-*t*-butyl-1,3,4-thiadiazole **10s** was shown to be most potent in vitro CB1 diarylimidazolyl heterocycle receptor ligand (IC_{50} = 1.91 nM) prepared to date.[27]

The binding affinity data of selected key 2-(1-(4-bromophenyl)-2-(2,4-dichlorophenyl)-5-ethyl-1*H*-imidazol-4-yl)-1,3,4-oxa(thia-)diazole for the CB1 receptor is shown in Table 3. Cyclopropanes or cyclobutanes at the benzylic position are also well tolerated without detriment to in vitro CB1 receptor binding affinity as displayed in Table 3. Chlorine or methoxy substitution on the phenyl ring also maintained similar receptor binding affinity, indicating that a halogen atom or methoxy group appears to be well tolerated at this position. Binding affinity was also measured for the CB2 receptor expressed in CHO cells, employing [^{3}H]WIN-55,212-2 as a radio-ligand.[22,24] Virtually all of our imidazole-based compounds were devoid of activity in this CB2 receptor binding assay, indicating high selectivity for CB1 over CB2 for these analogs. Selected examples of the above analogs are summarized in Table 3.

In conclusion, we investigated a series of diarylimidazolyl oxadiazole and thiadiazole derivatives as antagonists to the cannabinoid CB1 and CB2 receptors. Several of the compounds in these series exceeded or maintained the potency of known CB1 antagonists,[25] validating that (i) a 1,3,4-oxadiazole/thiadiazole ring could act as a bioisostere of the amide moiety and (ii) an imidazole ring is interchangeable with a pyrazole ring in rimonabant as shown in Refs. 15 and 16. Importantly, these analogs also display good selectivity for CB1R over CB2R. Thus, the diarylimidazolyl oxadiazole or thiadiazole class of compounds possesses promising therapeutic possibility as a CB1 receptor antagonist for the treatment of obesity.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2008.10.130.

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24. CB1 and CB2 receptor binding assay. For the CB1 receptor binding studies, rat cerebellar membranes were prepared as previously described by the methods of Kuster et al.[20] Male Sprague–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.[22] 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 filter (Perkin-Elmer Life and Analytical Sciences, Boston, MA) that had been soaked in 0.1% PEI for 1 h by a cell harvester (Perkin-Elmer 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; Perkin-Elmer 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. IC_{50} was determined by nonlinear regression analysis using Graph-Pad PRISM. All data were collected in triplicate and IC_{50} was determined from three independent experiments.
25. Several compounds in this series were highly efficacious in in vivo efficacy on the DIO mouse model. One of the compounds in the series showed 25 ± 1% reduction in body weight after 14 days at 10 mg/kg via po. That is a notable piece of information that this series of compounds are indeed CB1R antagonists or inverse agonists, unpublished results.
26. In this communication, CB1R data were obtained by single determinations. Whenever we use rimonabant as our reference in our in-house assay, 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). Therefore, we believe that all SAR discussions in the manuscript are scientifically meaningful.
27. The compound **10s** shows *c*Log*P* = 8.0, indicating the highly lipophilic character of **10s** just as many other known CB1R ligands are so.