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Pentacycle derivatives 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 pentacycle derivatives. Five of the new compounds which displayed high in vitro rCB1 binding affinities were assayed for binding to hCB2 receptor. Noticeably, 2-(5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-4-(5-methyl-1,3,4-thiadiazol-2-yl)-1*H*-pyrazol-3-yl)-5-(1-(trifluoromethyl)cyclopropyl)-1,3,4-oxadiazole (**16l**) demonstrated good binding affinity and decent selectivity for rCB1 receptor (IC_{50} = 1.72 nM, hCB2/rCB1 = 142).

The prevalence of obesity is rapidly increasing globally. Obesity has reached epidemic proportions especially in developed countries. Although obesity is associated with the pathogenesis of major diseases including diabetes or cardiovascular diseases, no satisfactorily safe and effective obesity drugs are available at the moment. Thus, there is a tremendous opportunity to make a significant impact on the lives of the obese through the discovery and development of additional pharmacotherapeutic options. Recently, we reviewed new trends in medicinal chemistry approaches used to develop drugs for treating obesity.[1] 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.[2,3] 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.[4] Another cannabinoid receptor, CB2 is related to immune regulation and neurodegeneration.[5] Therefore, the CB2/CB1 selectivity should be taken into consideration for new drug development of antiobesity agent.

The first specific cannabinoid CB1 receptor antagonist, rimonabant was discovered in a high throughput screening program at Sanofi-Synthélabo in 1994.[6] Several CB1 receptor antagonists including SR141716 (rimonabant), SLV319 (ibipinabant),[7a] CP-945,598 (otenabant)[7b] and MK-0364 (taranabant)[8] had been reported to be in various phase of clinical trials.[9,10,15d,24] However, rimonabant was withdrawn from the market in 2008 due to risks of severe psychiatric problems, including depression, anxiety, and suicidality. Subsequently, taranabant and otenabant were discontinued from developments at phase III, respectively. However, despite consecutive failures of leading CB1 receptor antagonists, works continue to identify novel peripherally restricted CB1 antagonists that are non-brain penetrant and do not induce serious psychiatric disorders.

A pharmacophore model for the binding of a low energy conformation of rimonabant in the CB1 receptor has been well-documented.[10,11] The key receptor–ligand interaction is reported 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.[2,25]

To date, various analogs of rimonabant by replacing the key carbonyl group have been designed for the purpose of enhancing

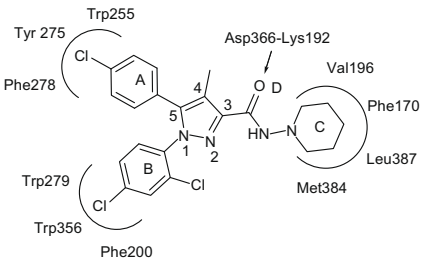

Figure 1. Rimonabant and its receptor–ligand interaction.

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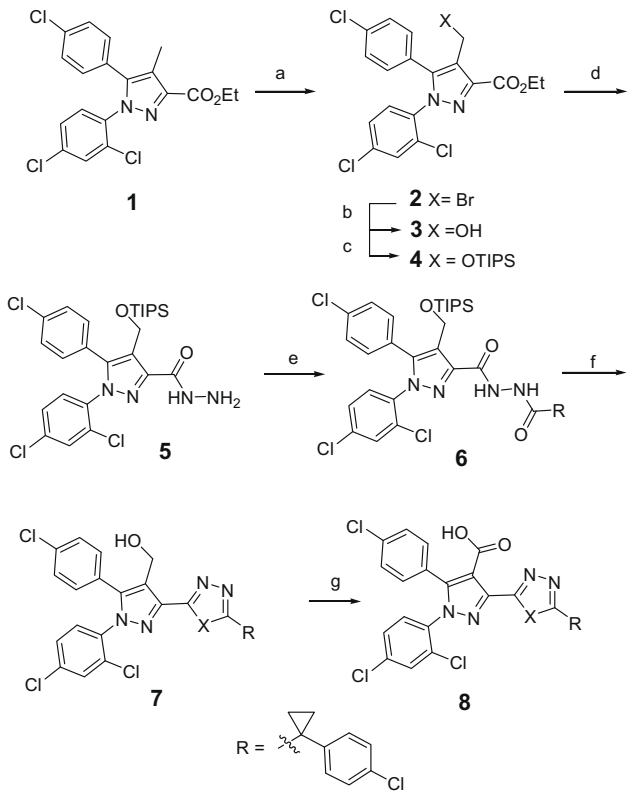
binding affinity and selectivity for the CB1 receptor. We note that such approaches were already demonstrated successfully with imidazole,[12] tetrazole.[13] Subsequently, we also discovered that the oxadiazole scaffold[14a,b] has also been employed for this purpose, even though there are clear differences evident between our previous works[15] and these prior examples.

With our efforts to discover and develop a new medicine for the treatment of obesity, we have reported the diarylpyrazolyl oxadiazole derivatives as potent, selective, orally bioavailable cannabinoid-1 receptor antagonists for the treatment of obesity.[15a] 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.[16] We also reported 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.[15b] Along this line, we envisioned that a bioisostere of polar amide groups in the C-4 region of pyrazole can provide a novel series of pentacycle derivatives which act as cannabinoid CB1 receptor antagonists for the treatment of obesity.

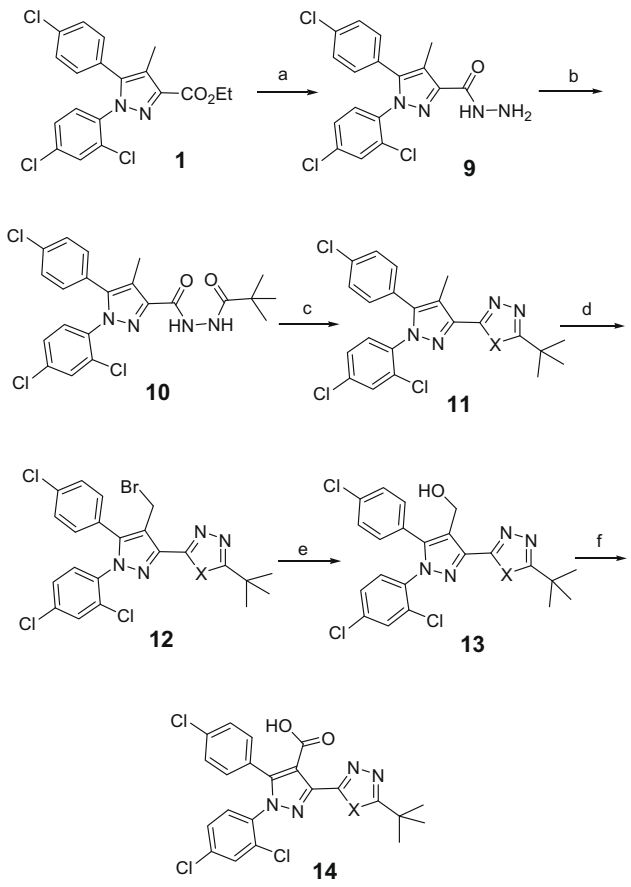
Herein, we wish to describe the chemical synthesis, biological evaluation of a novel series of pentacycle analogues as our additional research efforts toward discovery of a promising antiobesity agent.

Synthesis of pentacycle derivatives began with the generic carboxylate **1** as shown in Scheme 1.[17] This reaction sequence was developed and reported previously by our laboratory. We were able to modify and refine some of the previous procedure to provide the required carboxylic acid **8** in 'tens of grams' amount. Thus, the carboxylate **1** was converted to the bromide **2** in 55% yield using NBS (*N*-bromosuccinimide) in the presence of a catalytic amount of AIBN [2,2′-azobis(2-methylpropionitrile)],[8] and this intermediate was then treated with silver nitrate in aqueous acetone[18] to afford the corresponding alcohol **3** in 96% yield. 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** in 97% yield for the two steps which was used to couple with an acid in the presence of appropriate coupling reagents such as EDC {1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide} and HOBt (1-hydroxybenzotriazole) to provide acylhydrazide **6** in 75% yield. Cyclization was then performed smoothly using either Burgess reagent[19a,b] or Lawesson's reagent[19c] under reflux conditions. These reactions can be carried out under microwave irradiation as well. Subsequent removal of triisopropylsilyl group with TBAF (tetrabutylammonium fluoride) was conducted to afford alcohols **7** in high yields. Oxidation of the alcohols **7** to the corresponding aldehydes was achieved through the use of Dess–Martin periodinane (80% yield).[20] Aldehydes were further oxidized to acids **8** in high yields by use of sodium chlorite and monobasic potassium phosphate in aqueous *t*-BuOH as shown in Scheme 1.[15a,b]

Alternatively, acids **14** can be prepared by benzylic bromination-type reaction on pyrazoles **11** as illustrated in Scheme 2.



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% (two steps); (e) 1-(4-chlorophenyl)cyclopropanecarboxylic acid, EDC, HOBt, NMM, DMF, rt, 75%; (f) (i) Burgess reagent (X = O) or Lawesson's reagent (X = S), THF, reflux, 84% (X = O), 79% (X = S), (ii) TBAF, THF, rt, 96% (X = O), 93% (X = S); (g) (i) Dess–Martin periodinane, CH_2Cl_2, rt, 78% (X = O), 81% (X = S), (ii) $NaClO_2$, KH_2PO_4, 2-methylbut-2-ene, *t*-BuOH–H_2O, rt, 92% (X = O), 95% (X = S).



Scheme 2. Reagents and conditions: (a) NH_2NH_2, EtOH, 90 °C, 95%; (b) pivalic acid, EDC, HOBt, NMM, DMF, rt, 87%; (c) Burgess reagent (X = O) or Lawesson's reagent (X = S), THF, reflux, 81% (X = O), 83% (X = S); (d) NBS, AIBN, CCl_4, reflux, 87% (X = O), 79% (X = S) (e) (i) NaOAc, THF–H_2O, rt, 91% (X = O), 88% (X = S), (ii) LiOH, THF–H_2O, rt, 92% (X = O), 93% (X = S); (f) (i) Dess–Martin periodinane, CH_2Cl_2, rt, 85% (X = O), 79% (X = S), (ii) $NaClO_2$, KH_2PO_4, 2-methylbut-2-ene, *t*-BuOH–H_2O, rt, 91% (X = O), 96% (X = S).

The alcohol functionality was then introduced by treating bromides **12** with sodium acetate, and subsequent basic hydrolysis of the resulting acetates. Next, two-step oxidation reactions of alcohols **13** to acids **14** were conducted in the same way as described previously.[15a,b]

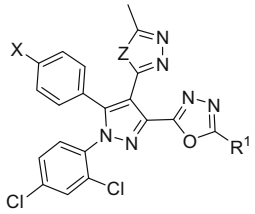
With requisite acids **8** or **14** in hand, preparation of pentacycle derivatives was conducted as shown in Scheme 3. Thus, acids **14** were coupled with a hydrazide such as acetohydrazide in the presence of suitable coupling reagents such as EDC {1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide}, HOBt (1-hydroxybenzotriazole), NMM (4-methylmorpholine) in DMF (*N*,*N*-dimethylformamide) to provide acylhydrazide **15** in 71–87% yields. Cyclization was then performed using either Burgess reagent[19a,b] or Lawesson's reagent[19c] under reflux conditions to generate the target pentacycle derivatives **16** in 67–88% yields as shown in Scheme 3.

The target oxadiazole analogues were evaluated in vitro at a rat CB1 binding assay,[21,23] and the results are shown in Table 1. We focused on *t*-butyl, 1-(trifluoromethyl)cyclopropyl, and (4-chlorophenyl)cyclopropyl group connected to the oxadiazole, since our previous findings[15a] indicate that these lipophilic or fluorine-containing substituents with *gem*-dimethyl or the corresponding cyclopropyl groups demonstrated the favorable biological activity of the examined diarylpyrazolyl oxadiazoles. Bisoxadiazole **16a**, **16b** showed reasonably good binding affinity (**16a**, IC_{50} = 6.47 nM; **16b**, IC_{50} = 3.93 nM) compared with rimonabant (IC_{50} = 5.0 ± 1.0 nM), while 1-(trifluoromethyl)cyclopropyl **16c** showed rather low binding affinity for rCB1 receptor (IC_{50} = 14.7 nM). From the beginning, it was encouraging to find out that this type of pentacycles acts as a good rCB1 receptor ligand despite crowded appearances.

Next, in order to test the effect of oxadiazole ring at C-4 on pyrazole against cannabinoid receptor binding affinities, the oxadiazole moiety was replaced with its isosteric thiadiazole ring. Unlike oxadiazole analogues, increase of rCB1 receptor binding affinity was observed for the *t*-butyl derivative **16d** (IC_{50} = 2.83 nM) by replacement of oxadiazole **16a** (IC_{50} = 6.47 nM). This phenomenon was even more pronounced with 1-(trifluoromethyl)cyclopropyl (**16f**, IC_{50} = 4.14 nM vs **16c**, IC_{50} = 14.7 nM). In order to test the effect of substituents of diphenylpyrazole, a chlorine atom (X = Cl) was replaced with a bromine atom (X = Br). Chlorine at X on 5-phenyl can be displaced by bromine without exacerbating rCB1 receptor binding affinity. Rather, binding affinities for rCB1 receptor were improved up to fivefold as exemplified by a pair of compounds involving (4-chlorophenyl)cyclopropyl **16e** (IC_{50} = 10.3 nM) and **16k** (IC_{50} = 2.13 nM). Up to date, the best rCB1 receptor binding affinity in the pentacycle series was obtained when X = bromine, Z = S, and R^1 = 1-(trifluoromethyl)cyclopropyl group were introduced as in **16l** (IC_{50} = 1.72 nM). The analogue **16l** was also shown to be potent in the CHO-hCB1R-Luciferase assay,[26,27] with IC_{50} value being 38.5 nM (for comparison, IC_{50} = 92.5 nM for rimonabant), thus demonstrating inverse agonism activity of this series.

Subsequently, the effect of oxadiazole ring at C-3 on pyrazole against cannabinoid receptor binding affinities was examined through replacement of oxadiazole ring with its isosteric thiadiazole ring. The binding affinity data of key diarylpyrazolyl thiadiazoles for the rCB1 receptor are shown in Table 2. Compared with the corresponding oxadiazoles, slight decreases of rCB1 receptor binding affinity were observed, especially for the 1-(trifluoromethyl)cyclopropyl thiadiazole derivatives (approximately twofold decrease).

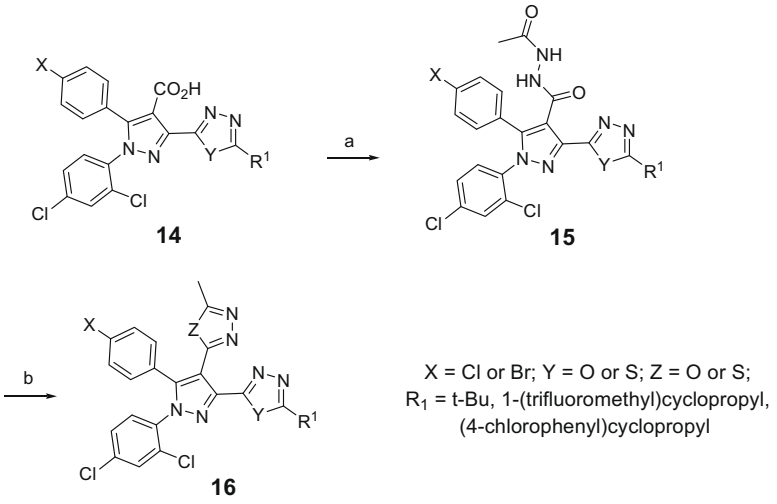
Table 1
Binding affinity of oxadiazoles to rCB1 receptor[a]



16

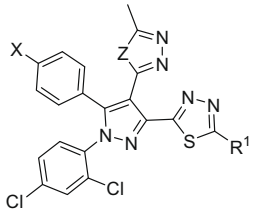
X	Z	R^1	Compound	rCB1 IC_{50}[b]
		Rimonabant		5.0 ± 1.0[c]
Cl	O	*t*-Bu	**16a**	6.47
Cl	O	(4-Chlorophenyl)cyclopropyl	**16b**	3.93
Cl	O	1-(Trifluoromethyl)cyclopropyl	**16c**	14.7
Cl	S	*t*-Bu	**16d**	2.83
Cl	S	(4-Chlorophenyl)cyclopropyl	**16e**	10.3
Cl	S	1-(Trifluoromethyl)cyclopropyl	**16f**	4.14
Br	O	*t*-Bu	**16g**	2.56
Br	O	(4-Chlorophenyl)cyclopropyl	**16h**	4.91
Br	O	1-(Trifluoromethyl)cyclopropyl	**16i**	4.70
Br	S	*t*-Bu	**16j**	3.69
Br	S	(4-Chlorophenyl)cyclopropyl	**16k**	2.13
Br	S	1-(Trifluoromethyl)cyclopropyl	**16l**	1.72

[a] rCB1 receptor was collected from brain tissue of SD rat.
[b] These data were obtained by single determinations.
[c] The rCB1R 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).



Scheme 3. Reagents and conditions: (a) acetohydrazide, EDC, HOBt, DMF, rt, 71–87%; (b) Burgess reagent or Lawesson's reagent, THF, reflux, 67–88%.

Table 2
Binding affinity of thiadiazoles to rCB1 receptor[a]



16

X	Z	R^1	Compound	rCB1 IC_{50}[b]
		Rimonabant		5.0 ± 1.0[c]
Cl	O	(4-Chlorophenyl)cyclopropyl	**16m**	3.23
Cl	O	1-(Trifluoromethyl)cyclopropyl	**16n**	26.9
Cl	S	(4-Chlorophenyl)cyclopropyl	**16o**	3.03
Cl	S	1-(Trifluoromethyl)cyclopropyl	**16p**	7.39
Br	O	*t*-Bu	**16q**	4.93
Br	O	(4-Chlorophenyl)cyclopropyl	**16r**	4.44
Br	O	1-(Trifluoromethyl)cyclopropyl	**16s**	4.86
Br	S	*t*-Bu	**16t**	2.56
Br	S	(4-Chlorophenyl)cyclopropyl	**16u**	3.70
Br	S	1-(Trifluoromethyl)cyclopropyl	**16v**	4.21

[a] rCB1 receptor was collected from brain tissue of SD rat.
[b] These data were obtained by single determinations.
[c] The rCB1 R 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).

This observation was made in two pairs of compounds **16n** (IC_{50} = 26.9 nM) and **16p** (IC_{50} = 7.39 nM) by replacement of oxadiazoles **16c** (IC_{50} = 14.7 nM) and **16f** (IC_{50} = 4.14 nM), respectively. This phenomenon was even more pronounced with bis-thiadiazole (**16v**, IC_{50} = 4.21 nM vs **16l**, IC_{50} = 1.72 nM), indicating bis-thiadiazole rings make the molecule somewhat bulkier overall, thereby slightly reducing binding potency against rCB1 receptor.

The interesting compounds were further evaluated with observation of the hCB2 receptor binding affinity. [22] 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] These results are shown in Table 3. The hCB2/rCB1 selectivity turned out to be modest, ranging from 142 to 167 among the compounds tested. However, compound with (4-chlorophenyl)cyclopropyl appears to deactivate hCB2 receptor binding affinity while maintaining their favorable binding affinity against rCB1 receptor, thereby improving hCB2/rCB1 selectivity. In order to further evaluate this series, pharmacokinetic (PK) properties of **16l** have been measured in rats. After oral administration of a 5-mg/kg dose of **16l** to rats, a C_{max} of 0.03 μg/mL was obtained at 1.3 h with a moderate systemic clearance rate of 12.6 mL/mg/Kg. The elimination half-life for **16l** following oral administration was 18.4 h in rats. **16l** showed relatively low oral bioavailability (F = 7.2%) in rats, implying its probable solubility-limited absorption.

Table 3
Binding affinity of selected pentacycles to rCB1 and hCB2 receptors[a,b]

Compound	rCB1 IC_{50}[c]	hCB2 IC_{50}[c]	hCB2/rCB1 selectivity
Rimonabant	5.0 ± 1.0[d]	1760[c]	352
16g	2.56	414	162
16l	1.72	245	142
16t	2.56	427	167
16u	3.70	>10,000	>2703

[a] rCB1 receptor was collected from brain tissue of SD rat.
[b] hCB2 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.

In conclusion, we investigated a series of pentacycle derivatives for their binding affinity for cannabinoid rCB1 and hCB2 receptors. We have identified a novel series of small molecule rCB1 ligands that demonstrate binding affinity superior to that of known rCB1 antagonists. Several compounds in this series showed potent rCB1 receptor binding affinities, validating the hypothesis that a bioisostere of polar amide groups in the C-4 region of pyrazole can provide a novel series of pentacycle derivatives which act as rCB1 receptor ligands. Of note is 2-(5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-4-(5-methyl-1,3,4-thiadiazol-2-yl)-1*H*-pyrazol-3-yl)-5-(1-(trifluoromethyl)cyclopropyl)-1,3,4-oxadiazole (**16l**) was shown to possess the highest binding affinity in this pentacycle series prepared to date. The analogue **16l** was also shown to be potent in the CHO-hCB1R-Luciferase assay, with IC_{50} value being 38.5 nM, thus demonstrating inverse agonism activity of this series. The information obtained from the SAR studies in this series might help to design more active CB1 antagonists or inverse agonists that are structurally related to this series.

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.2009.10.015.

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23. *CB1 and CB2 receptor binding assay*. For the rCB1 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 vol 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 vol of TME buffer, and protein concentration was determined by the method of Bradford and stored at −70 °C until use. For the hCB2 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 rCB1 receptor) or cell membranes (containing hCB2 receptor) were incubated in 96-well plate with TME buffer containing 0.5% essentially fatty acid free bovine serum albumin (BSA), 3 nM [3H]WIN55,212-2 (for CB2 receptor, NEN; specific activity 50-80 Ci/mmol) or 3 nM ([3H]CP55,940, [3H]2-[(1*S*,2*R*,5*S*)-5-hydroxy-2-(3-hydroxypropyl) cyclohexyl]-5-(2-methyloctan-2-yl)phenol, for rCB1 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 rCB1 and hCB2 receptor competitive binding assay, non-specific 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 non-linear regression analysis using Graph-Pad PRISM. All data were collected in triplicate and IC_{50} was determined from three independent experiments.
24. 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.
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