Bioorganic & Medicinal Chemistry Letters 19 (2009) 309–313

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

CB_2 selective sulfamoyl benzamides: Optimization of the amide functionality

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ARTICLE INFO

Article history:
Received 7 October 2008
Revised 21 November 2008
Accepted 24 November 2008
Available online 27 November 2008

Keywords:
Cannabinoid
CB1
CB2
Sulfamoyl benzamides
Antiallodynia

ABSTRACT

Previous research within our laboratories identified sulfamoyl benzamides as novel cannabinoid receptor ligands. Optimization of the amide linkage led to the reverse amide **40**. The compound exhibited robust antiallodynic activity in a rodent pain model when administered intraperitoneally. Efficacy after oral administration was observed only when ABT, a cytochrome P450 suicide inhibitor, was coadministered.

Activation of the endogenous cannabinoid receptors by compounds such as Δ^9-tetrahydrocannbinol (THC) (**1**) (Fig. 1), the active component of *Cannabis sativa*, has long been used in a variety of medical applications. These include appetite stimulation as well as treatments for emesis, cramps, fever, rheumatism and pain.[1] Two cannabinoid receptors, designated CB_1 and CB_2, have been characterized from the superfamily of G protein-coupled receptors (GPCRs). Sharing approximately 44% amino acid sequence homology, the two receptors differ in anatomical distribution with CB_1 receptors found mainly in the CNS, while CB_2 receptor expression occurs primarily in peripheral tissues associated with immune functions, including B and T cells and macrophages.[2] CB_2 receptors have also been isolated from peripheral nerve endings and mast cells.[3]

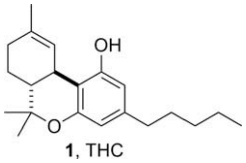
The clinically undesired effects associated with cannabis use, such as euphoria, are believed to be predominantly centrally mediated through activation of the CB_1 receptors. The use of CB_2 selective agonists is, therefore, one approach that could be adopted for the use of cannabinoid receptor activation in the treatment of pain.

The antihyperalgesia produced by the selective CB_2 agonist AM1241 (**2**) in the rat carrageenan induced inflammatory thermal hyperalgesia assay was reversed by pretreatment with a CB_2 selective antagonist, but not by a CB_1 selective antagonist, thus demonstrating a CB_2 receptor mediated effect.[4] Additionally, GW405833 (**3**) exhibited antihyperalgesic activity in rodent models of incisional, neuropathic and chronic inflammatory pain, but was devoid of significant activity in similar models in CB_2 knock-out mice.[5]

It is perhaps not surprising then that development of CB_2 selective agonists for the treatment of chronic and inflammatory pain has recently received a large amount of interest. From this research several structurally diverse classes of compounds have been identified. These include indoles (**2, 3**),[4,5] benzimidazoles (**4**),[6] iminopyrazoles (**5**),[7] oxadiazoles (**6**)[8] and aryl sulfonamides (**7**) (Fig. 2).[9]

Independently, through high-throughput screening, research within our organization identified the sulfamoyl benzamide **8** displaying weak affinity for the CB_2 receptor (Fig. 3).[10]

Optimization of the scaffold led to compound **9** which exhibited vastly improved affinity and selectivity for the CB_2 receptor. To further explore the SAR around the phenylsulfonamide core we first



1, THC

Figure 1. Structure of THC.

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doi:10.1016/j.bmcl.2008.11.091

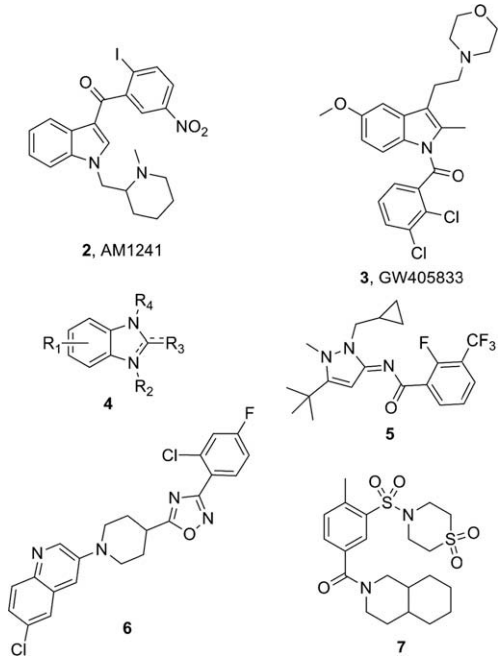


Figure 2. Structures of CB_2 selective agonists.

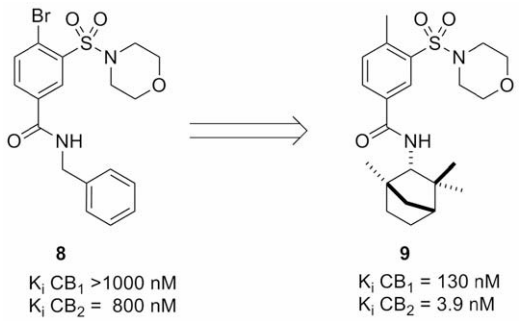
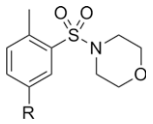
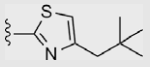
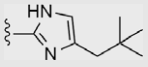
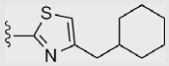
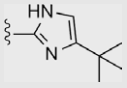
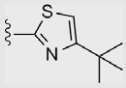
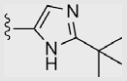
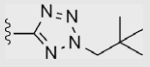
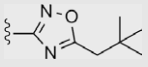
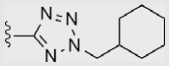
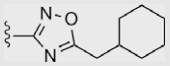
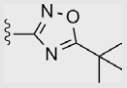
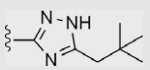
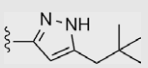
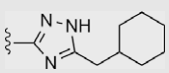
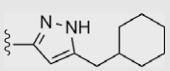
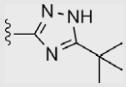
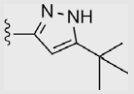


Figure 3. Optimization of high-throughput screening hit.

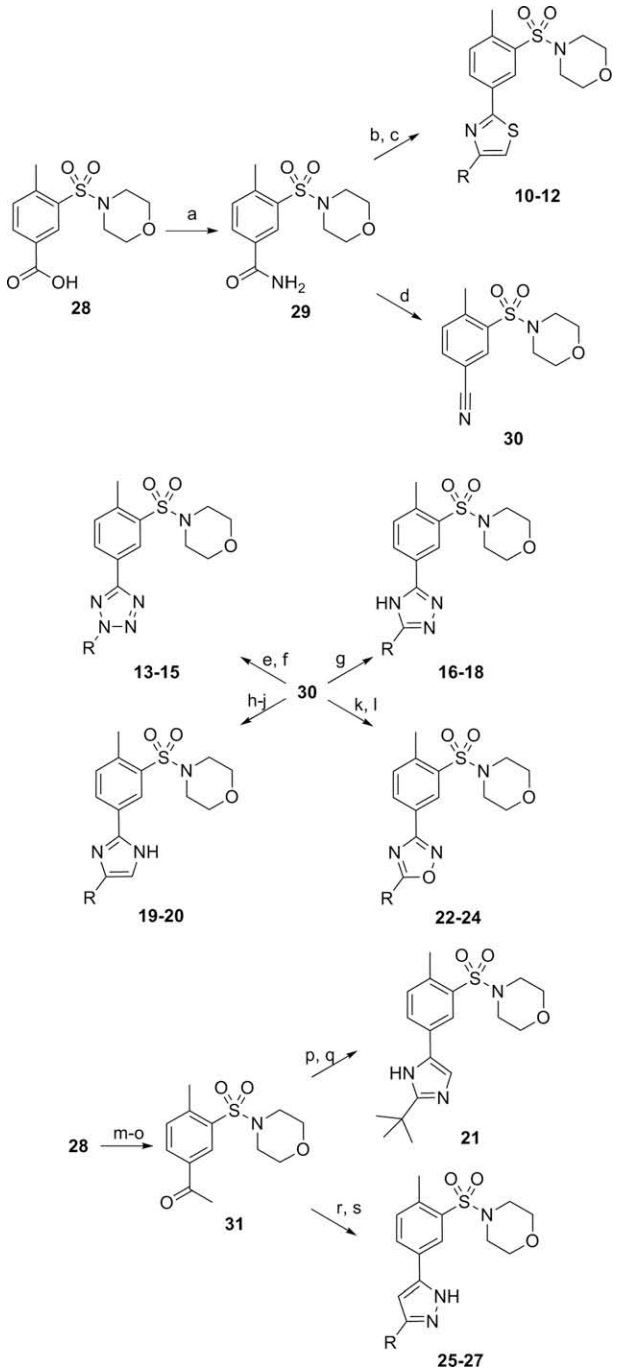
looked at the isosteric replacement of the amide functionality of **9** with various heterocycles.[11] These included thiazoles, oxadiazoles, pyrazoles, imidazoles, triazoles and tetrazoles. Examples are shown in Table 1.[12] Synthesis of compounds **10**–**27** is described in Scheme 1. Coupling of the previously described sulfonamide benzoic acid **28**[10] with ammonium chloride gave the primary amide **29**. Thiazoles **10**–**12** were then prepared from **29** in a two step process, that is, thioamide formation using Lawesson's reagent followed by cyclization with the respective bromoacetate. Dehydration of intermediate **29** with phosphorus oxychloride gave the nitrile **30** which was then used as a common intermediate for the synthesis of the tetrazoles **13**–**15**, the triazoles **16**–**18**, the

Table 1
Bioisosteric replacement of amide functionality—in vitro results[a,b,c,d]



Compound	R	CB_1K_i[a,b] (nM)	CB_2K_i[a,b] (nM)	Ratio CB_1/CB_2	CB_2EC_{50}[a,c] (nM)	Compound	R	CB_1K_i[a,b] (nM)	CB_1K_i[a,b] (nM)	Ratio CB_1/CB_2	CB_2EC_{50}[a,c]
10		200	5.2	38	23	**19**		1100	36	31	47
11		390	23	17	120	**20**		1100	23	48	58
12		260	5.7	47	21	**21**		770	81	9.4	130
13		130	17	7.6	49	**22**		270	59	4.5	70
14		560	82	6.9	78	**23**		740	130	5.9	110
15		>5000	>5000	n.d.[d]	n.d.[d]	**24**		510	75	6.8	77
16		140	85	1.6	64	**25**		750	75	10	120
17		310	27	11	57	**26**		1400	87	16	190
18		530	100	5.3	130	**27**		6990	160	6.1	130

[a] Values are the geometric means computed from at least three separate determinations.
[b] For assay description see Ref. 13a.
[c] EC_{50} values determined through [^{35}S]GTPγS stimulation. For assay description see Ref. 13b.
[d] Not determined.



Scheme 1. Reagents and conditions[12]: (a) NH_4Cl, TBTU, DIEA, CH_3CN, 89%; (b) Lawesson's Reagent, toluene, 66%; (c) $RCOCH_2Br$, DBU, EtOH, 11–70%; (d) $POCl_3$, DMF, 75%; (e) NaN_3, ZnBr, H_2O, 52%; (f) RX, Et_3N, DMF, 51–81%; (g) $RCONHNH_2$, K_2CO_3, $CH_3(CH_2)_3OH$, 10–74%; (h) $NH_2OH{\cdot}HCl$, K_2CO_3, EtOH, 32–65%; (i) Raney Nickel, CH_3COOH, MeOH, H2, 28–91%; (j) $RCOCH_2Br$, DBU, EtOH, 11–14%; (k) $NH_2OH{\cdot}HCl$, K_2CO_3, EtOH, 32%; (l) RCOCl, pyridine, 2–22%; (m) $SOCl_2$, DMF, 94%; (n) CH_3NHOCH_3, Et_3N, CH_2Cl_2, 76%; (o) CH_3MgBr, Et_2O, THF, 92%; (p) $C_6H_5CH_2N(CH_3)_3{}^+Br_3{}^-$, CH_2Cl_2, MeOH, 47%; (q) $(CH_3)_3CC{=}(NH)NH_2{\cdot}HCl$, K_2CO_3, DMF, 83%; (r) CDI, RCOOH, LAH, THF, 56–89%; (s) NH_2NH_2 H_2O, EtOH, 8–21%.

imidazoles **19**–**20** and the oxadiazoles **22**–**24**. Compounds **21** and **25**–**27** were generated from the ketone intermediate **31**. Compound **31** was prepared in a three step procedure from the acid **28**, i.e. acid chloride formation using thionyl chloride, Weinreb amide synthesis followed by reaction with methylmagnesium bromide.

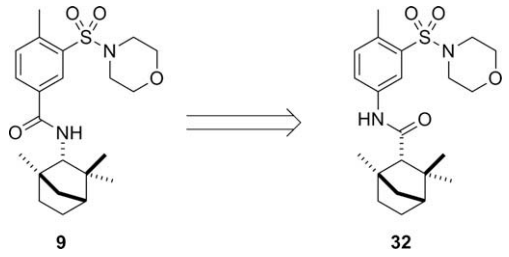
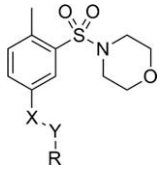
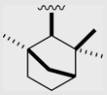
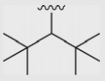


Figure 4. Reversal of amide linkage.

Table 2
In vitro binding of 'reverse amides' for select compounds[a,b,c]



Compound	R	X	Y	CB_1K_i[a,b] (nM)	CB_2K_i[a,b] (nM)	Ratio CB_1/CB_2	CB_2EC_{50}[a,c] (nM)
9		C=O	NH	130	3.9	31	4.6
32		NH	C=O	640	1.7	380	9.6
33		C–0	NH	540	48	11	25
34		NH	C=0	1200	9.4	130	49
35		C=0	NH	310	34	9.0	21
36		NH	C=O	1200	11	110	31

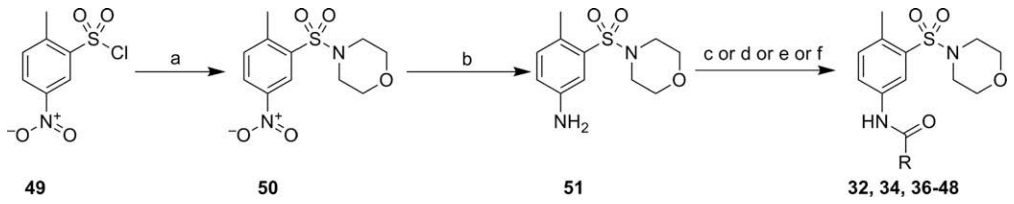
[a] Values are the geometric means computed from at least three separate determinations.
[b] For assay description see Ref. 13a.
[c] EC_{50} values determined through [^{35}S]GTPγS stimulation. For assay description see Ref. 13b.

From this research the thiazole substituted compounds (**10**, **12**) showed the best overall profile for the CB_2 receptor. However, as can be seen from Table 1, replacement of the amide moiety with various heterocycles did not significantly improve affinity or selectivity for the CB_2 receptor in comparison to the lead compound **9**. Continuing our focus on optimization of the amide moiety we then turned our attention to reversal of the amide linkage (Fig. 4).[14] Three compounds from our original study were initially selected for comparison and their reverse amide analogs prepared (Table 2).

Reversal of the amide linkage of compound **9,** to give **32,** led to a compound with superior selectivity over the CB_1 receptor (CB_1/CB_2 **9** = 30-fold; CB_1/CB_2 **32** = 380-fold) while retaining good affinity for CB_2. Similarly, compounds **34** and **36**, when compared to their respective analogs **33**, **35**, exhibited superior affinities and selectivities for the CB_2 receptor in in vitro testing. Following the identification of these novel and selective CB_2 agonists, we decided to extend the SAR around the amide functionality. Compounds **37**–**48** were prepared as shown in Scheme 2.

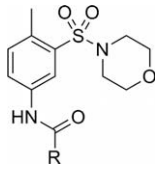
The synthesis of the morpholinosulfonamide intermediate **50** was achieved by addition of morpholine to the commercially available nitrophenylsulfonyl chloride **49**. After reduction of the nitro group to give **51**, the target compounds (**32, 34, 36**–**48**) were generated using a variety of coupling methods.

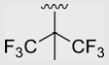
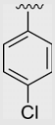
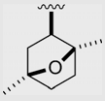
In vitro binding data for compounds **37**–**48** at the CB_1 and CB_2 receptors is shown in Table 3.



Scheme 2. Reagents and conditions:[12] (a) Morpholine, EtOAc, 100%; (b) Fe, NH_4Cl, EtOH, H_2O, 100%; (c) RCOOH, Bop-Cl, Et_3N, THF, 20–81%; (d) RCOOH, TBTU, DIEA, CH_3CN, 3–18%; (e) RCOOH, BEP, DIEA, CH_2Cl_2, 20%; (f) RCOCl, Et_3N, THF, 20–28%.

Table 3
In vitro binding results for reverse amides at the CB_1 and CB_2 receptors[a,b,c,d]



Compound	R	CB_1K_i[a,b] (nM)	CB_2K_i[a,b] (nM)	RatioCB_1/CB_2	CB_2EC_{50}[a,c] (nM)	Compound	R	CB_1K_i or % inh. @ 10 μM[a,b] (nM)	CB_2K_i[a,b] (nM)	RatioCB_1/CB_2	CB_2EC_{50}[a,c] (nM)
37		790	11	72	8400	**43**		4.7%	540	n.d.[d]	n.d.[d]
38		1800	14	130	42	**44**		270	120	2.3	220
39		470	23	20	29	**45**		1100	170	6.5	390
40		3400	23	150	11	**46**		25%	2900	n.d.[d]	n.d.[d]
41		1200	35	34	33	**47**		2900	660	4.4	n.d.[d]
42		1900	120	16	n.d.[d]	**48**		44%	2000	n.d.[d]	n.d.[d]

[a] Values are the geometric means computed from at least three separate determinations.
[b] For assay description see Ref. 13a.
[c] EC_{50} values determined through [^{35}S]GTPγS stimulation. For assay description see Ref. 13b.
[d] Not determined.

Attempts to replace the lipophilic amide group of **32** generally led to a decrease in affinity for the CB_2 receptor. For example, in the aryl chloride series of compounds, **44**–**46**, the affinity for the receptor was decreased by ~100- to 2000-fold compared to compound **32**. Likewise, incorporation of heteroatoms into the amide substituent (**47, 48**) was not tolerated, leading to substantial loss in receptor affinity. However, other lipophilic substituents (**37**–**41**) were well tolerated and retained good activity for the CB_2 receptor. From this subset of ligands, the tetramethylcyclopropyl compound (**40**) (EC_{50} = 11 nM, E_{max} = 84%) was determined to possess the best overall profile and was selected for in vivo evaluation in the rodent hindpaw incisional model (Fig. 5).[15]

As can be seen from Figure 5, compound **40** exhibited robust antiallodynic activity when administered at a dose of 30 mg/kg ip. However, the compound did not produce a significant antiallodynic effect following oral administration.

To determine whether this lack of efficacy after oral dosing was due to poor absorption or rapid metabolism, a second study was performed. In this study, rats were pretreated with the cytochrome P450 suicide inhibitor aminobenzotriazole (ABT) before administration of compound **40** (300 mg/kg po) (Fig. 6).

The robust activity of the ABT pretreated animals with compound **40** supported our assertion that the compound was rapidly metabolized. In vitro metabolism studies of compound **40** in the presence of human and rat liver microsomes confirmed these findings (RLM = 2%; HLM = 1% remaining at 30 min).[16]

In summary, the SAR of the phenylsulfonamide series of CB_2 ligands was expanded. Replacement of the amide substituent with various heterocycles offered no improvement in potency or selectivity for the CB_2 receptor over the CB_1 receptor. However, reversal of the amide linkage led to a series of sulfamoyl benzamides with improved affinity and selectivity for the CB_2 receptor. Optimization

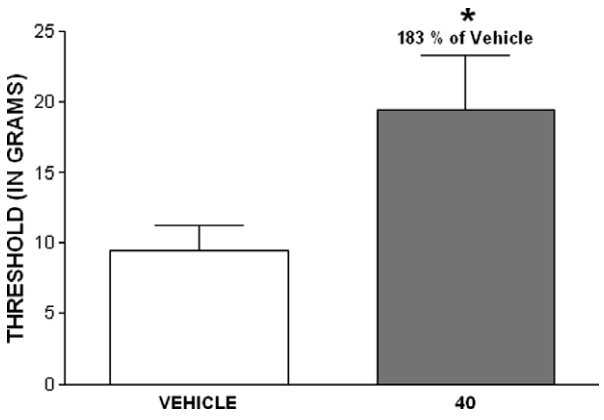


Figure 5. In vivo activity of compound **40** in the hindpaw incision model. Mechanical paw-withdrawal thresholds for the left hindpaw of the hindpaw incision group and compound **40** treated group. Data are plotted as the mean (±SEM) paw-withdrawal threshold of the left paw for each group. $^{*}p < 0.05$ compared to vehicle-treated group. $N = 8$/group. Vehicle response 9.4 g. Drugs were administered 30 min before testing.

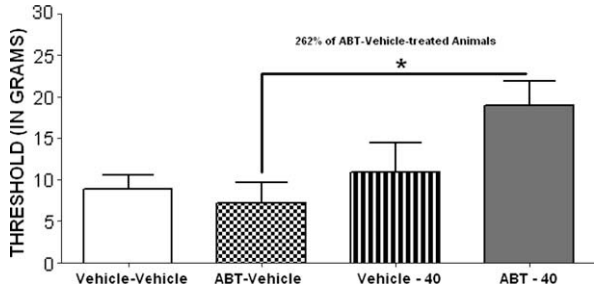


Figure 6. In vivo activity of orally administered compound **40** in the presence and absence of ABT in the hindpaw incision model. Mechanical paw-withdrawal thresholds for the left hindpaw of the hindpaw incision group, ABT, compound **40** and ABT/compound **40** treated groups. Data are plotted as the mean (±SEM) paw-withdrawal threshold of the left paw for each group. All statistical analyses were performed with one-way ANOVA followed by post-hoc comparisons (protected *t*-test) among groups. $^{*}p < 0.01$ compared to ABT-vehicle treated hindpaw incised animals. $N = 8$/group. Vehicle response 8.9 g. Drugs were administered 120 min before testing.

of this scaffold afforded compound **40**. In vivo efficacy of **40** was demonstrated in the rodent hindpaw incisional model after intraperitoneal administration. Lack of activity after oral dosing of **40** was attributable to the rapid metabolism of the compound. Attempts to improve the metabolic stability of these CB_2 selective compounds will be reported in due course.

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12. (a) *Abbreviations:* TBTU, *O*-(Benzotriazol-1-yl)-*N, N, N′, N′*-tetramethyluronium tetrafluoroborate; BEP, 2-Bromo-1-ethylpyridinium tetrafluoroborate; Bop-Cl, Bis(2-oxo-3-oxazolidinyl)phosphonic chloride; DIEA, diisopropylethylamine; DBU, 1, 8-diazabicyclo-[5.4.0]undec-7-ene; (b) compounds were fully characterized by ^{1}H NMR and LC/MS.
13. (a) Binding assays were performed by modification of the method of Pinto, J. C.; Potie, F.; Rice, K. C.; Boring, D.; Johnson, M. R.; Evans, D. M.; Wilken, G. H.; Cantrell, C. H.; Howlett A. *Mol. Pharmacol.* **1994**, *46*, 516–522: Receptor binding assays were performed by incubating 0.2–0.6 nM [^{3}H]CP55940 with membranes prepared from cells expressing cloned human CB_1 or CB_2 receptors in buffer consisting of 50 mM Tris–HCl, pH 7.0, 5.0 mM $MgCl_2$, 1.0 mM ethylene glycol-bis(2-aminoethylether)-*N,N,N′,N′*-tetraacetic acid (EGTA), and 1.0 mg/ml fatty acid free bovine serum albumin. After incubation for 60 min at room temperature for CB_2 binding or 120 min at 30 °C for CB_1 binding, the assay mixtures were filtered through GF/C filters that had been pre-soaked overnight in 0.5% (w/v) poly(ethyleneimine) and 0.1% BSA in water. The filters were rinsed 6 times with one mL each of cold assay buffer, 30 μL of MicroScint 20 (Perkin-Elmer) was added to each filter and the radioactivity on the filters was determined by scintillation spectroscopy in a TopCount (Perkin-Elmer). Nonspecific binding was determined in the presence of 10 μM WIN55212-2.(b) The [^{35}S]GTPγS binding method is a major modification of the method by Selley, D. E.; Stark, S.; Sim, L. J.; Childers, S. R. *Life Sci.* **1996**, *59*, 659–668: CB_2-mediated stimulation of [^{35}S]GTPγS binding was measured in a mixture containing 100–150 pM [^{35}S]GTPγS, 150 mM NaCl, 45 mM $MgCl_2$, 3 μM GDP, 0.4 mM dithiothreitol, 1.0 mM EGTA, 1.0 mg/mL fatty acid free bovine serum albumin, 25 μg of membrane protein, and agonist in a total volume of 250 μL of 50 mM Tris–HCl buffer, pH = 7.0 in 96-well Basic FlashPlates (PerkinElmer). After incubation at room temperature for 6 h, the plates were centrifuged at 800g at 4 °C for 5 min and the radioactivity bound to the membranes was determined by scintillation spectrometry using a TopCount (PerkinElmer). The extent of stimulation over basal [^{35}S]GTPγS binding was calculated as a percentage of the stimulation by 10 μM WIN55212-2. Basal [^{35}S]GTPγS binding was determined in the absence of agonist. Generally, the stimulation by 10 μM WIN55212-2 was between 50% and 100% over basal binding. Full agonists stimulate binding to the same maximal extent as WIN55212-2.
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