Substituted 5,5′-Diphenyl-2-thioxoimidazolidin-4-one as CB_1 Cannabinoid Receptor Ligands: Synthesis and Pharmacological Evaluation

Giulio G. Muccioli,[†] Diana Martin,[†] Gerhard K. E. Scriba,[‡] Wolfgang Poppitz,[§] Jacques H. Poupaert,[†] Johan Wouters,[∥] and Didier M. Lambert*,[†]

Unité de Chimie Pharmaceutique et de Radiopharmacie, Ecole de Pharmacie, Faculté de Médecine, Université catholique de Louvain, Avenue E. Mounier 73, UCL-CMFA 7340, B-1200 Bruxelles, Belgium; Department of Pharmaceutical Chemistry, University of Jena, Philosophenweg 14, D-07743 Jena, Germany; Department of Inorganic and Analytical Chemistry, University of Jena, August-Bebel-Strasse 2, D-07743 Jena, Germany; and Laboratoire de Chimie Biologique Structurale, Faculté des Sciences, Facultés Universitaires Notre Dame de la Paix, Rue de Bruxelles 61, 5000 Namur, Belgium

Received September 10, 2004

A set of 30 substituted 5,5′-diphenyl-2-thioxoimidazolidin-4-one (thiohydantoins) derivatives was synthesized, and their affinity for the human CB_1 cannabinoid receptor has been evaluated. These compounds are derived from the previously described cannabinoid ligands 5,5′-diphenylimidazolidine-2,4-dione (hydantoins). The replacement of the oxygen by a sulfur leads to an increase of the affinity while the function—i.e., inverse agonism—determined by [^{35}S]-GTPγS experiments remains unaffected. Finally, to evaluate the molecular parameters that could influence the affinity of the thiohydantoins, molecular electrostatic potential as well as lipophilicity calculations were undertaken on representative thiohydantoins and hydantoins derivatives. In conclusion, 5,5′-bis-(4-iodophenyl)-3-butyl-2-thioxoimidazolidin-4-one (**31**) and 3-allyl-5,5′-bis(4-bromophenyl)-2-thioxoimidazolidin-4-one (**32**) possess the highest affinity for the CB_1 cannabinoid receptor described to date for the hydantoin and thiohydantoins series when compared in a same bioassay.

Introduction

Cannabinoids, either plant-derived or of synthetic origin, mainly exert their properties by binding to two G-protein-coupled receptors, the CB_1 and the CB_2 cannabinoid receptors. The cloning and pharmacological characterization of these receptors,[1−3] as well as the discovery of their endogenous ligands[4,5] along with the enzymes responsible for their inactivation,[6,7] have permitted a better understanding of the so-called endocannabinoid system.[8]

The CB_1 cannabinoid receptor acts upon activation by coupling primarily to a $G_{i/o}$ G-protein. G_s coupling has been described under certain conditions by Calandra et al.[9] The highest density of the receptor is found in the cerebellum, the basal ganglia, the substantia nigra pars compacta, and in some regions of the globus pallidus. It is also present in peripheral organs such as the adrenal glands, bone marrow, lungs, testis, and uterus.[10] In contrast to the CB_1 cannabinoid receptor, the CB_2 cannabinoid receptor is limited essentially to cells associated with the immune system, like leukocytes, spleen, thymus, and tonsils.[8] In addition, it was recently reported that some specific human cerebellum microglial cells do express the CB_2 cannabinoid receptor.[11]

The knowledge of the endocannabinoid system has led to considerable interest in its therapeutic potential.[12] Notably, the control of the motor activity by this system suggests that compounds targeting the cannabinoid system could be useful for the treatment of motor disorders, such as Parkinson's disease,[13] Tourette's syndrome,[14] or choreas.[15] The involvement of cannabimimetics in airway dilatation,[16] intraocular pressure,[17] and intestinal motility[18] represents further potential therapeutic applications for compounds targeting the cannabinoid system. Antagonists of the CB_1 receptor also possess very useful applications. For instance, CB_1 antagonists such as rimonabant (SR141716A, Acomplia)[19,20] could be of particular interest for treating obesity[21,22] and may be a helpful tool in smoking cessation.[23] These therapeutic goals have triggered the synthesis of new compounds able to modulate the activity of cannabinoid receptors. Several pharmaceutical companies have developed their own CB_1 receptor antagonist scaffolds, among them the diarylpyrazole derivatives, such as SR141716A or the recently described SR147778[24] by Sanofi, substituted benzofurane derivatives[25] described by Eli Lilly (LY-320135), or 4,5-dihydro-1*H*-pyrazole derivatives[26,27] developed by Solvay (SLV326) (Figure 1). Other derivatives such as imidazoles[28] and triazoles[29] have also been recently described.

We previously reported the synthesis and pharmacological characterization of several 3-substituted 5,5′-diphenylimidazolidinedione derivatives, also known as 3-substituted 5,5′-diphenylhydantoins, as cannabinoid ligands.[30] These compounds exhibit moderate affinity for the CB_1 cannabinoid receptor and act as antagonists. We recently demonstrated that they act as neutral antagonists on rat brain membrane preparations and as inverse agonists on human CB_1 cannabinoid receptors expressed in CHO cells, independently of the

* Corresponding author. Phone and Fax: +32 2 7647347. E-mail: lambert@cmfa.ucl.ac.be.
[†] Université Catholique de Louvain.
[‡] Department of Pharmaceutical Chemistry, University of Jena.
[§] Department of Inorganic and Analytical Chemistry, University of Jena.
[∥] Facultés Universitaires Notre Dame de la Paix.

10.1021/jm049263k CCC: $30.25
Published on Web 02/25/2005

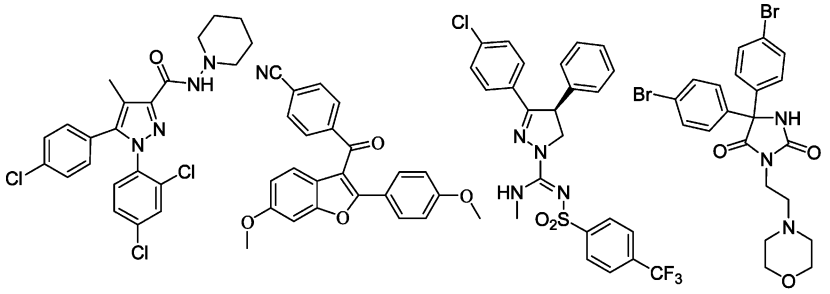


Figure 1. Structures of SR141716A, LY-320135, SLV326, and DML20, four CB_1 cannabinoid receptor antagonists.

receptor density at the cell surface.[31] Despite their modest affinity, the 5,5′-diphenylhydantoins represent an original structure for cannabinoid receptor recognition. Preliminary structure−affinity relationships revealed that introduction of a para substituent on the phenyl rings increases the affinity of the 3-alkyl-5,5′-diphenylhydantoins for the CB_1 receptor in the order H < Me < F < OMe < Br.[32] In addition, substitution of the nitrogen in position 3 is mandatory for the affinity towards the CB_1 cannabinoid receptor.

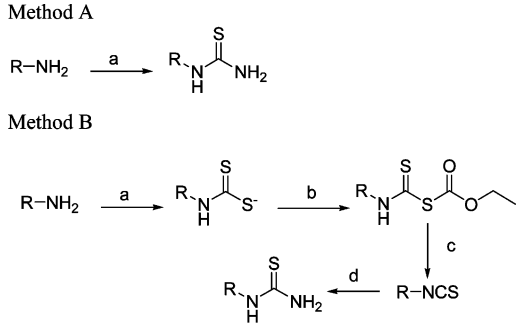
In the present study, this class of ligands was further evaluated by replacement of the oxygen in position 2 of the hydantoin ring by a sulfur atom, leading to 3-substituted 5,5′-diphenyl-2-thioxoimidazolidin-4-one derivatives.[33] These compounds can be prepared by reaction of benzil with a substituted thiourea derivative.[34] This reaction was optimized by using the same microwave-enhanced method we applied previously to the synthesis of 3-substituted 5,5′-diphenylhydantoin derivatives.[35] The pharmacological activity of the thiohydantoin derivatives at the CB_1 cannabinoid receptor was determined, and structure−activity relationships were established.

Results and Discussion

Chemistry. Benzoin condensation[36] was used to synthesize the dibromo- and dichlorobenzils. Despite the moderate yields obtained, this route proved to be the easiest for the benzil derivatives.

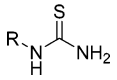
The substituted thioureas were synthesized by two methods, both starting from the corresponding amine. The first method (Scheme 1, method A) was used for the preparation of thiourea derivatives **2e**, **2f**, and **2k** from amines with a high boiling point due to the high temperatures applied during the reaction of the amine with ammonium isothiocyanate in bromobenzene at reflux. The second method, as illustrated in Scheme 1 (method B), is more general, although it requires two steps. The isothiocyanate derivative of the corresponding amine was first synthesized by following the procedure described by Moore.[37] The amine was heated in the presence of carbon disulfide and sodium hydroxide with subsequent addition of ethyl chlorocarbonate. After completion of the reaction, the isothiocyanate derivative, which separates on the top of the solution, was collected and further purified by distillation under reduced pressure, resulting in an approximately 90% pure product which was used in the second step. The substituted thioureas **2a**−**d**,**g**−**j**,**l** were obtained by reaction of the respective isothiocyanate derivatives with ammonia. Comparable yields were achieved by the two methods (A or B) as listed in Table 1.

Scheme 1. Synthesis of the Alkylthiourea Derivatives (**2a**−**2l**)[a]



[a] Method A reagents and conditions: (a) NH_4SCN, bromobenzene, reflux under nitrogen stream, 90 min. After cooling, the product is precipitated in water. Method B reagents and conditions: (a) CS_2, NaOH, reflux, 2 h; (b) $ClCOOC_2H_5$, rt, 1.5 h. The isothiocyanate derivative separates on cooling; (c) isothiocyanate derivative distilled under reduced pressure; (d) NH_3, rt.

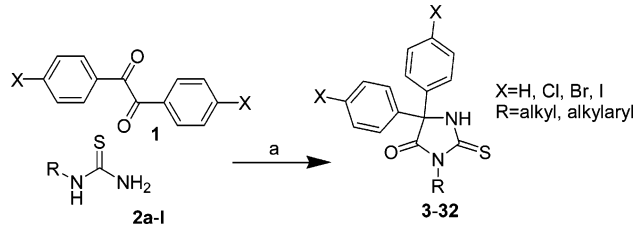
Table 1. Alkylthiourea Derivatives (**2a**−**2l**) Synthesized, Methods Used, and Synthetic Yields



compd	R	method	% yield
2a	C_2H_5	B	40
2b	i-C_3H_7	B	35
2c	n-C_4H_9	B	30
2d	i-C_4H_9	B	40
2e	C_7H_{15}	A	45
2f	C_8H_{17}	A	45
2g	C_6H_{11}	B	60
2h	$(CH_2)_3OCH_3$	B	40
2i	$CH_2CH{=}CH_2$	B	45
2j	$CH_2C_6H_5$	B	50
2k	$(CH_2)_2C_6H_5$	A	40
2l	furan-2-ylmethyl	B	35

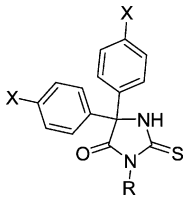
The target 5,5′-diphenyl-2-thioxoimidazolidin-4-one derivatives were obtained by reaction of the respective benzil and thiourea derivatives in moderate to good yields (Scheme 2, Table 2) following a microwave-enhanced method, previously described for the synthesis of several 3-alkyl-5,5′-diphenylhydantoin derivatives.[32] This procedure combines the advantages of a selective synthesis, since one of the thiourea nitrogens is already bearing the desired substituent, and an enhanced yield due to the microwaves applied during the reaction. Thus, compounds **3**−**32** selectively substituted at *N*-3 were obtained by reaction of benzil derivatives (X = H, Cl, Br, I), obtained from the corresponding benzalde-

Scheme 2. Synthesis of the 5,5′-Diphenyl-2-thioxoimidazolidin-4-one Derivatives (**3**−**32**)[a]



[a] Reagents and conditions: (a) DMSO/aq KOH, nine microwaves pulses.

Table 2. Synthetic Yield of the 5,5′-Diphenyl-2-thioxoimidazolidin-4-one Derivatives (**3**−**32**) and Percentages of Displacement of [^{3}H]SR141716A and [^{3}H]CP-55,940, Respectively, by Compounds **3**−**32** (10 μM) on hCB_1 and hCB_2 Cannabinoid Receptors[a]



				% of displacement	
compd	X	R	% yield	CB_1 receptor	CB_2 receptor
3	H	C_2H_5	70	40.0 ± 5.0	<10
4	H	i-C_3H_7	65	42.8 ± 4.2	<10
5	H	n-C_4H_9	80	42.8 ± 4.8	<10
6	H	i-C_4H_9	75	34.6 ± 3.4	<10
7	H	C_7H_{15}	77	28.8 ± 5.1	<10
8	H	C_8H_{17}	75	38.8 ± 4.3	<20
9	H	C_6H_{11}	85	38.5 ± 3.8	<10
10	H	$(CH_2)_3OCH3$	70	29.4 ± 3.8	<15
11	H	$(CH_2)_3OH$	65	20.8 ± 5.3	<10
12	H	$CH_2CH{=}CH_2$	65	40.0 ± 5.4	<15
13	H	CH_2C_6H5	70	44.7 ± 5.3	<10
14	H	$(CH_2)_2C_6H_5$	76	29.3 ± 5.5	<10
15	H	furan-2-ylmethyl	75	59.2 ± 4.5	<15
16	Cl	i-C_4H_9	45	76.1 ± 4.3	<20
17	Cl	C_7H_{15}	35	67.8 ± 4.5	<10
18	Cl	C_8H_{17}	37	36.6 ± 5.0	<10
19	Cl	$CH_2C_6H_5$	30	74.2 ± 2.5	<15
20	Cl	$(CH_2)_2C_6H_5$	35	79.4 ± 5.3	<15
21	Br	C_2H_5	30	90.9 ± 4.4	<20
22	Br	i-C_3H_7	25	91.7 ± 3.1	<15
23	Br	n-C_4H_9	35	73.8 ± 5.5	<15
24	Br	i-C_4H_9	30	76.3 ± 4.6	<20
25	Br	C_7H_{15}	35	34.2 ± 5.2	<10
26	Br	C_8H_{17}	50	23.4 ± 3.7	<10
27	Br	C_6H_{11}	32	45.5 ± 5.5	<10
28	Br	$CH_2CH{=}CH_2$	35	87.2 ± 5.6	<15
29	Br	$CH_2C_6H_5$	30	76.0 ± 4.7	<10
30	Br	$(CH_2)_2C_6H_5$	38	54.6 ± 4.1	<10
31	I	n-C_4H_9	35	77.4 ± 5.0	<20
32	I	$CH_2CH{=}CH_2$	34	94.2 ± 4.7	<20

[a] Mean ± SEM of at least four experiments performed in duplicate.

hydes, with substituted thioureas. The ORTEP diagram of compound **28** supporting the structure of these compounds is given in the Supporting Information.

Not surprisingly, yields tend to decrease when the size of the benzil substituent is enlarged (Table 2). Yields were up to 80% when an unsubstituted benzil was used in the reaction but fell to 30−35% when the benzil was substituted by chlorine, bromine, or iodine atoms. This is also the case in the 5,5′-diphenylimidazolidine-2,4-dione series,[32] either under classical reflux conditions or using microwave-enhanced conditions. The size of the substituent on the thiourea nitrogen does not seem to affect the reaction yield.

It should be noted that both methods described here (methods A and B) do not allow the synthesis of 3-hydroxypropylthiourea. Interestingly, previous attempts made to obtain the 3-hydroxypropylurea have also failed. Therefore, the *N*-hydroxypropyl thiohydantoin derivative (**11**) was synthesized starting from the respective *N*-methoxypropyl derivative (**10**) followed by demethylation with boron tribromide (BBr_3). The latter reaction is nearly quantitative and, therefore, only slightly reduces the overall yield for 3-(3-hydroxypropyl)-5,5′-diphenyl-2-thioxoimidazolidin-4-one (**11**).

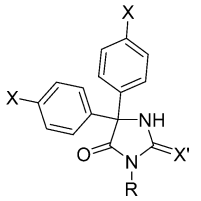
Pharmacology. The 5,5′-diphenyl-2-thioxoimidazolidin-4-one derivatives (**3**−**32**) were screened at 10 μM concentrations for their affinity and selectivity towards the human CB_1 and CB_2 (hCB_1 and hCB_2) cannabinoid receptors in a competitive binding experiment. Membranes from Chinese hamster ovarian (CHO) cells expressing either the hCB_1 or the hCB_2 cannabinoid receptor were used in these experiments. [^{3}H]SR141716A and [^{3}H]CP-55,940 at concentrations of 1 nM were used as radioligands for the hCB_1 and the hCB_2 cannabinoid receptor, respectively. The results expressed as the displacement percentages of the radioligand from its binding site are summarized in Table 2.

None of the compounds displayed significant affinity towards the hCB_2 receptor, as none of the tested compounds displaced more than 20% of [^{3}H]CP-55,940 bound to the receptor. However, good affinity was noted towards the hCB_1 receptor (Table 2). Substitution of the phenyl rings with chlorine, bromine, or iodine led to an increased affinity for the hCB_1 receptor. The radioactivity displacement is below 50% for the majority of the unsubstituted compounds (**3**−**15**), while higher displacement was observed for the respective *p*-halogenated compounds. This effect is well-illustrated by compounds **6**, **16**, and **24** or by compounds **13**, **19**, and **29**. Increasing the affinity for the hCB_1 receptor by para substitution with chlorine or bromine was previously shown for the hydantoins derivatives.[29]

To study structure−affinity relationships, 11 compounds (**16**, **19**−**24**, **28**, **29**, and **31**, **32**) were selected for the determination of the inhibition constant, K_i, by measuring the radioligand ([^{3}H]SR141716A, 1 nM) displaced by increasing concentrations of each compound (10^{-8}−10^{-5} M). Concentrations above 10^{-5} M could not be evaluated due to the poor aqueous solubility of the compounds. The results of the experiments are summarized in Table 3, and illustrated in Figure 2. The K_i values are expressed for a K_d of 1.13 nM and obtained from IC_{50} values following the Cheng and Prusoff method.[38]

A bromine substituent in the para position of the phenyl ring slightly increases the receptor affinity compared to chlorine substitution. Thus, K_i values of 2188 ± 101 and 993 ± 43 nM were determined for compounds **19** and **29**, respectively, differing only in the para phenyl substituent. Further, an iodine in the same position slightly enhanced the affinity for the cannabinoid receptor compared to the bromine substitution. K_i values of 1412 ± 65 and 724 ± 52 nM were obtained

Table 3. Affinities of Selected Derivatives (compounds **16**, **19**−**24**, **28**, **29**, **31**, **36**) and of SR141716A, WIN-55,212-2, and HU-210 at the hCB_1 Cannabinoid Receptor[a]



compd	X	X	R	K_i (nM)
			Thiohydantoins	
16	S	Cl	i-C_4H_9	2089 ± 96
19	S	Cl	$CH_2C_6H_5$	2188 ± 101
20	S	Cl	$(CH_2)_2C_6H_5$	3801 ± 175
21	S	Br	C_2H_5	2193 ± 98
22	S	Br	i-C_3H_7	3630 ± 167
23	S	Br	n-C_4H_9	1412 ± 65
24	S	Br	i-C_4H_9	1778 ± 82
28	S	Br	$CH_2CH{=}CH_2$	871 ± 40
29	S	Br	$CH_2C_6H_5$	993 ± 43
31	S	I	n-C_4H_9	724 ± 52
32	S	I	$CH_2CH{=}CH_2$	589 ± 49
			Hydantoins	
33	O	Br	n-C_4H_9	5495 ± 253
34	O	Br	$CH_2C_6H_5$	3467 ± 163
35	O	I	n-C_4H_9	1820 ± 251
36	O	I	$CH_2CH{=}CH_2$	1738 ± 82
			Reference Cannabinoids	
SR141716A				5.4 ± 0.2
WIN55,212-2				3802 ± 158
HU-210				18.6 ± 1.7

[a] The K_i values were obtained from nonlinear analysis of competition curves using [^{3}H]SR141716A as radioligand. Mean ± SEM of at least four experiments done in duplicate.

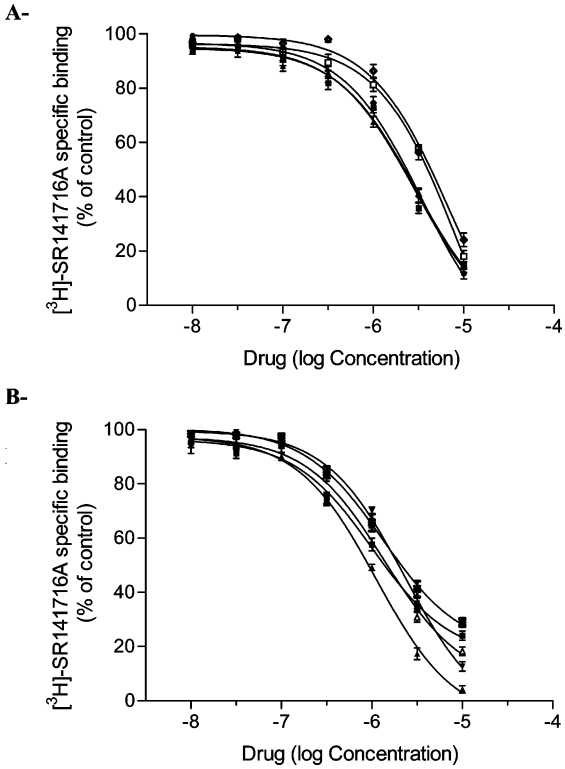


Figure 2. Effect of **16** (■), **19** (▲), **20** (◇), **21** (●), and **22** (□) on [^{3}H]SR141716A binding on hCB_1-CHO cells. Data are the mean of at least four experiments, and vertical lines show the SEM. Effect of **23** (△), **24** (▼), **28** (▲), **29** (■), **31** (◇), and **32** (×) on [^{3}H]SR141716A binding on hCB_1-CHO cells. Data are the mean of at least four experiments, and vertical lines show the SEM.

for compounds **23** and **31**, respectively, substituted with a butyl in position 3 and differing only in the halogen substituent of the phenyl ring. With respect to N_3-alkyl substitution, increasing the chain length over six carbon atoms caused a significant loss of affinity, as the displacement of the radioligand dropped below 40% for compounds **25** and **26**. An alkylaryl substituent like benzyl (**19** or **29**) increased the affinity of these compounds for the hCB_1 receptor, while the additional methylene group of the ethylphenyl substituent decreased the affinity as illustrated by compounds **19** and **20** (K_i values of 2188 ± 101 and 3801 ± 175 nM, respectively) or by compounds **29** and **30** (K_i values 993 ± 43 and >10 000 nM, respectively). Finally, a short unsaturated alkyl chain such as the allyl group in **28** and **32** appears to be favorable for the affinity of this series of compounds.

The effect of the sulfur−oxygen exchange in position 2 of the hydantoin nucleus, leading to the thiohydantoin derivatives, may be estimated from a comparison of the 5,5′-bis(4-bromophenyl)-3-butylimidazolidine-2,4-dione (**33**), 3-benzyl-5,5′-bis(4-bromophenyl)imidazolidine-2,4-dione (**34**), 3-butyl-5,5′-bis(4-iodophenyl)imidazolidine-2,4-dione (**35**), and 3-allyl-5,5′-bis(4-iodophenyl)-imidazolidine-2,4-dione (**36**) with the respective thiohydantoins **23**, **29**, **31**, and **32**. The K_i values for derivatives **33** to **36** are approximately 2−4 times higher than the K_i values of the corresponding thiohydantoin derivatives (Table 3). For instance, compound **29** has a K_i value of 993 ± 43 nM compared to 3467 ± 163 nM for the corresponding hydantoin **34**. Thus, replacement of the oxygen in position 2 of the hydantoin ring by a sulfur atom resulted in an increase of affinity for the hCB_1 receptor.

The question whether the thiohydantoin derivatives possess the same functionality compared to the hydantoin derivatives was also investigated by using a [^{35}S]-GTPγS assay.[39] This assay constitutes a functional measure of the interaction of the receptor and the G-protein, the first step in activation of the G-protein-coupled receptors. It is a useful tool to distinguish between agonists (increasing the nucleotide binding), inverse agonists (decreasing the nucleotide binding), and neutral antagonists (not affecting the nucleotide binding). The known cannabinoid agonist HU-210, the inverse agonist SR141716A, and thiohydantoins **16**, **19**−**24**, **28**, **29**, **31**, and **32** showing higher affinity for the receptor, as well as the four hydantoins **33**−**36** were screened at a concentration of 10 μM in this assay. As expected, 10 μM HU-210 induced an increase in the [^{35}S]-GTPγS binding (130% compared to basal level), while SR141716A at the same concentration decreased [^{35}S]-GTPγS binding (−85% compared to basal level). The test compounds induced a significant decrease in the [^{35}S]-GTPγS binding, ranging from −52% to −74% compared to the basal level at a concentration of 10 μM, revealing inverse agonist properties at the hCB_1 cannabinoid receptor (Figure 3). Thus, the 5,5′-diphenylthiohydantoins derivatives, like the 5,5′-diphenylhydantoins derivatives, possess inverse agonist properties at the human CB_1 cannabinoid receptor. The substitution of the oxygen atom by a sulfur atom does not affect the

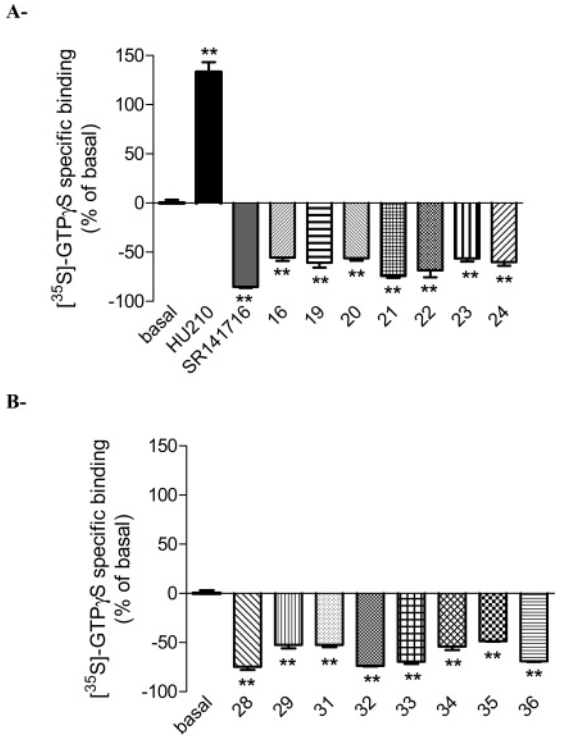


Figure 3. Influence of 10 μM HU-210, SR141716A, and **16**, **19**, **20**, **21**, **22**, **23**, and **24** on [^{35}S]GTPγS binding on hCB_1-CHO cells membranes. Data are the mean ± SEM of three experiments performed in duplicate, with one-way ANOVA followed by a Dunett post-test (**P < 0.01). Influence of 10 μM **28**, **29**, **31**, **32**, **33**, **34**, **35**, and **36** on [^{35}S]GTPγS binding on hCB_1-CHO cells membranes. Data are the mean ± SEM of three experiments performed in duplicate, with one-way ANOVA followed by a Dunett post-test (**P < 0.01).

functionality of the compounds. Moreover, an EC_{50} value of 282 ± 35 nM was obtained for the inhibition of [^{35}S]-GTPγS binding by derivative **32**. This value is in good accordance with the K_i value of the compound (K_i = 589 ± 49 nM).

To estimate the molecular parameters that could influence the affinity of thiohydantoins, the electrostatic and lipophilic properties of both series, the thiohydantoin and hydantoin derivatives, were calculated.

The MIDI basis set developed by Truhlar et al. used for the molecular electrostatic potential calculations applies to H, C, F, S, Cl, Br, and I, and includes polarization functions.[40] Therefore, in contrast to many other classical basis sets, MIDI is well-suited to study the electronic properties of the selected bromo- and iodohydantoins and thiohydantoins. Molecular electrostatic potential maps calculated for **28**, **32**, and **36** show distinct patterns of attractive potentials generated by the sulfur or oxygen atom of the (thio)hydantoin ring (Figure 4). In particular, the thiocarbonyl appears less prone to interact via hydrogen bonds compared to the carbonyl of the hydantoin. This may suggest that hydantoin and thiohydantoin derivatives bind in a slightly different way to the receptor. However, in contrast to the biological data, there is no significant influence of the halogen substituent of the phenyl moiety (bromo or iodo) on the molecular electrostatic potential and atomic charges on the sulfur and/or oxygen atoms of the (thio)hydantoin analogues.

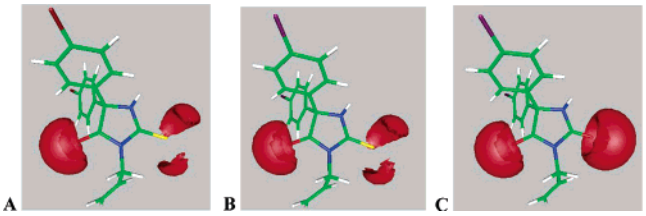


Figure 4. Attractive electrostatic potential zones (isocontour of −0.3 e/Å^3) of the molecular electrostatic potential calculated for compounds **28** (A), **32** (B), and **36** (C). The ab initio calculated MEP isocontour was plotted using the GopenMol graphical interface.

The lipophilicity of the compounds was calculated using the CLOGP program. The CLOGP values obtained for the thiohydantoins derivatives **23** and **29** (5.86 and 6.04, respectively) were slightly higher than those obtained for the corresponding hydantoin derivatives **33** and **34** (5.56 and 5.64, respectively). However, the thiohydantoin **28** having a CLOGP value of 5.05 possesses an affinity for the hCB_1 cannabinoid receptor comparable to the affinity of the thiohydantoin **29**. In contrast, the hydantoin **34**, characterized by a higher CLOGP value compared to the thiohydantoin **28**, possesses a lower affinity for the hCB_1 receptor. Consequently, although an enhanced overall lipophilicity (CLOGP value) is not solely responsible for the better affinity of the thiohydantoin derivatives, a local increase in lipophilicity around carbon 2 compared to the hydantoins could be a favorable parameter for binding of the ligands to the receptor.

In conclusion, the 5,5′-diphenyl-2-thioxoimidazolidin-4-one derivatives bind to the hCB_1 cannabinoid receptor with good selectivity. The most active compounds possess an iodine atom in para position of the phenyl rings as well as an alkyl chain on *N*-3 having less than six carbon atoms. Preferably, the alkyl chain is unsaturated. The bioisosteric replacement of the oxygen in the hydantoin nucleus by a sulfur atom resulting in thiohydantoins led to an increase in the affinity of the compounds without affecting their functional characteristics. Finally, compounds 5,5′-bis(4-iodophenyl)-3-butyl-2-thioxoimidazolidin-4-one (**31**) and 3-allyl-5,5′-bis(4-bromophenyl)-2-thioxoimidazolidin-4-one (**32**) possess the highest affinity for the CB_1 cannabinoid receptor described to date for the hydantoin and thiohydantoins series when compared in the same bioassay.

Experimental Section

General Procedures. All reagents were purchased from commercial sources (Sigma-Aldrich or Acros) and were used without further purification. Solvents were of analytical grade. The microwave oven used was a commercial household microwave oven (frequency 2450 MHz).

Melting points (mp) were determined in open capillaries using a Electrothermal 9100 apparatus and are reported uncorrected. Infrared (IR) spectra were recorded using a Perkin-Elmer FT-IR 286 spectrometer, and values are reported as ν in cm^{-1} (see the Supporting Information). Nuclear magnetic resonance (^{1}H NMR, ^{13}C NMR) spectra were recorded on a Bruker AM-300 spectrometer at room temperature and analyzed using the WIN NMR software package. Chemical shifts (δ) are reported relative to tetramethylsilane peak set at 0.00 ppm. In the case of multiplets, the signals are reported as intervals. Signals were abbreviated as s, singlet; d, doublet; t, triplet; and m, multiplet. Coupling constants are expressed in hertz. Mass spectra were recorded on a Finnigan MAT 44S,

with an ionization voltage of 70 eV. Elemental analyses were performed on a Carlo Erba EA 1108 Analyzer (Carlo Erba, Milano, Italy) and are within ±0.4% of the theoretical values.

Synthesis. General Procedure for the Synthesis of Substituted Thiourea Derivatives. Method A. The amine hydrochloride (0.1 mol) and ammonium isothiocyanate (0.1 mol) were refluxed in bromobenzene (25 mL) under nitrogen for 90 min. Upon cooling to 5 °C the precipitate was placed in 300 mL of water with shaking. The resulting powder was filtered and used without further purification.

Method B. Carbon disulfide (12.2 mL, 0.2 mol) and sodium hydroxide (0.2 mole) were shaken at 4 °C before addition of the amine (0.2 mol). Subsequently, the solution was refluxed for 2 h. After cooling to room temperature, ethyl chloroformate (0.2 mol) was added and the resulting mixture was stirred for an additional 30 min. The isothiocyanate derivative floating on the top of the solution was separated and dried over $MgSO_4$. Further purification was performed by distillation under reduced pressure. The isothiocyanate was reacted with an excess of ammonia at room temperature to afford the thiourea derivative. The excess of ammonia was removed under reduced pressure and the solid washed twice with water.

General Procedure for the Synthesis of the 2-Thioxoimidazolidin-4-one Compounds (Except Compound 11). The synthesis was performed as described for hydantoin derivatives.[34] Briefly, to a solution of benzil (9.9 mmol) and a substituted thiourea (19.9 mmol) in 25 mL of DMSO was added 15 mL of a 1.2 M KOH solution with stirring. Following an initial 90-s microwave irradiation (750 W), the mixture was stirred for 5 min. Eight 30-s microwaves pulses were applied at the time points of 6, 9, 12, 15, 18, 21, 24, and 30 min. The mixture was stirred between pulses. At the end of the sequence the mixture was poured onto crushed ice and the precipitate filtered off. The residue was subsequently crystallized.

3-Ethyl-5,5′-diphenyl-2-thioxoimidazolidin-4-one (3). Mp: 188.3−189.4 °C. MS (EI): 296 $[M]^+$. ^1H NMR (300 MHz): δ 1.13 (t, J = 7.35, 3H), 3.78 (q, J = 7.35, 2H), 7.30−7.43 (m, 10H), 10.98 (s, 1H). ^{13}C NMR (300 MHz): δ 13.23 (CH_3), 36.14 (CH_2), 71.05 (C), 126.98 (CH_{arom}), 128.92 (CH_{arom}), 129.24 (CH_{arom}), 138.56 (C_{arom}), 173.69 (C=O), 181.39 (C=S). Anal. Calcd for $C_{17}H_{16}N_2OS$: C, H, N.

3-Isopropyl-5,5′-diphenyl-2-thioxoimidazolidin-4-one (4). Mp: 215.9−216.5 °C. MS (EI): 310 $[M]^+$. ^1H NMR (300 MHz): δ 1.36 (m, 6H), 4.83−4.92 (m, 1H), 7.28−7.45 (m, 10H), 11.74 (s, 1H). ^{13}C NMR (300 MHz): δ 26.86 (2 × CH_3), 54.55 (CH), 78.29 (C), 134.78 (CH_{arom}), 136.59 (CH_{arom}), 136.91 (CH_{arom}), 146.49 (C_{arom}), 181.75 (C=O), 189.58 (C=S). Anal. Calcd for $C_{18}H_{18}N_2OS$: C, H, N.

3-Butyl-5,5′-diphenyl-2-thioxoimidazolidin-4-one (5). Mp: 132.5−133.5 °C. MS (EI): 324 $[M]^+$. ^1H NMR (300 MHz): δ 0.85 (t, J = 7.35, 3H), 1.17−1.29 (m, 2H), 1.52−1.62 (m, 2H), 3.77 (t, J = 7.35, 2H), 7.32−7.45 (m, 10H), 11.68 (s, 1H). ^{13}C NMR (300 MHz): δ 13.45 (CH_3), 19.21 (CH_2), 29.24 (CH_2), 37.75 (CH_2), 71.10 (C), 126.55 (CH_{arom}), 128.42 (CH_{arom}), 128.68 (CH_{arom}), 138.19 (C_{arom}), 173.46 (C=O), 181.22 (C=S). Anal. Calcd for $C_{19}H_{20}N_2OS$: C, H, N.

3-Isobutyl-5,5′-diphenyl-2-thioxoimidazolidin-4-one (6). Mp: 173.6−174.3 °C. MS (EI): 324 $[M]^+$. ^1H NMR (300 MHz): δ 0.78−0.80 (m, 6H), 2.09−2.23 (m, 1H), 3.58−3.60 (d, J = 7.35, 2H), 7.25−7.50 (m, 10H), 11.68 (s, 1H). ^{13}C NMR (300 MHz): δ 19.60 (2 × CH_3), 26.52 (CH), 47.42 (CH_2), 71.04 (C), 126.48 (CH_{arom}), 128.36 (CH_{arom}), 128.68 (CH_{arom}), 138.13 (C_{arom}), 173.65 (C=O), 181.54 (C=S). Anal. Calcd for $C_{19}H_{20}N_2OS$: C, H, N.

3-Heptyl-5,5′-diphenyl-2-thioxoimidazolidin-4-one (7). Mp: 110−110.8 °C. MS (EI): 367 $[M + H]^+$. ^1H NMR (300 MHz): δ 0.81 (t, J = 7.35, 3H), 1.18 (m, 8H), 1.57−1.61 (m, 2H), 3.76 (t, J = 7.35, 2H), 7.31−7.45 (m, 10H), 11.65 (s, 1H). ^{13}C NMR (300 MHz): δ 13.78 (CH_3), 21.80 (CH_2), 25.75 (CH_2), 26.98 (CH_2), 28.01 (CH_2), 30.99 (CH_2), 38.10 (CH_2), 71.10 (C), 126.55 (CH_{arom}), 128.42 (CH_{arom}), 128.68 (CH_{arom}), 138.19 (C_{arom}), 173.52 (C=O), 181.12 (C=S). Anal. Calcd for $C_{22}H_{26}N_2OS$: C, H, N.

3-Octyl-5,5′-diphenyl-2-thioxoimidazolidin-4-one (8). Mp: 96.6−97.4 °C. MS (EI): 381 $[M + H]^+$. ^1H NMR (300 MHz): δ 0.83 (t, J = 7.35, 3H), 1.76 (m, 10H), 1.58−1.60 (m, 2H), 3.75 (t, J = 7.35, 2H), 7.30−7.45 (m, 10H), 11.65 (s, 1H). ^{13}C NMR (300 MHz): δ 13.84 (CH_3), 21.93 (CH_2), 25.81 (CH_2), 26.97 (CH_2), 28.40 (CH_2), 30.99 (CH_2), 38.44 (CH_2), 40.38 (CH_2), 71.10 (C), 126.55 (CH_{arom}), 128.49 (CH_{arom}), 128.68 (CH_{arom}), 138.13 (C_{arom}), 173.52 (C=O), 181.28 (C=S). Anal. Calcd for $C_{23}H_{28}N_2OS$: C, H, N.

3-Cyclohexyl-5,5′-diphenyl-2-thioxoimidazolidin-4-one (9). Mp: 237.5−238.3 °C. MS (EI): 350 $[M]^+$. ^1H NMR (300 MHz): δ 1.08−1.32 (m, 3H), 1.58−1.61 (m, 3H), 1.76−1.80 (m, 2H), 2.06−2.13 (m, 2H), 4.47−4.55 (m, 1H), 7.21−7.45 (m, 10H), 11.59 (s, 1H). ^{13}C NMR (300 MHz): δ 24.71 (CH_2), 25.36 (CH_2), 28.08 (CH_2), 54.09 (CH), 70.07 (C), 126.55 (CH_{arom}), 128.42 (CH_{arom}), 128.68 (CH_{arom}), 138.32 (C_{arom}), 173.59 (C=O), 181.54 (C=S). Anal. Calcd for $C_{21}H_{22}N_2OS$: C, H, N.

3-(3-Methoxypropyl)-5,5′-diphenyl-2-thioxoimidazolidin-4-one (10). Mp: 145.5−146.3 °C. MS (EI): 340 $[M]^+$. ^1H NMR (300 MHz): δ 1.81 (m, 2H), 3.08 (s, 3H), 3.28 (t, J = 7.35, 2H), 3.82 (t, J = 7.35, 2H), 7.30−7.43 (m, 10H), 11.03 (s, 1H). ^{13}C NMR (300 MHz): δ 28.65 (CH_2), 41.98 (CH_2), 57.88 (CH_3), 69.97 (CH_2), 71.05 (C), 126.08 (CH_{arom}), 128.45 (CH_{arom}), 129.02 (CH_{arom}), 138.71 (C_{arom}), 170.95 (C=O), 181.35 (C=S). Anal. Calcd for $C_{19}H_{20}N_2O_2S$: C, H, N.

3-(3-Hydroxypropyl)-5,5′-diphenyl-2-thioxoimidazolidin-4-one (11). To a solution of **10** in dry CH_2Cl_2 (1 mM) kept in an ice bath was added boron tribromide (1.2 mM) under stirring. The solution was then allowed to reach room temperature and stirred overnight. The resulting solution was evaporated to dryness under reduced pressure and the resulting solid washed with water. After filtration, the compound was crystallized from ethanol. Mp: 227.2−227.8 °C. MS (EI): 326 $[M]^+$. ^1H NMR (300 MHz): δ 2.12 (m, 2H), 3.18 (m, 2H), 3.57−3.62 (m, 2H), 7.27−7.38 (m, 10H), 11.59 (s, 1H), 11.67 (s, 1H). ^{13}C NMR (300 MHz): δ 27.15 (CH_2), 40.66 (CH_2), 55.72 (CH_2), 71.96 (C), 127.06 (C_{arom}), 128.45 (CH_{arom}), 128.98 (CH_{arom}), 139.23 (C_{arom}), 170.96 (C=O), 181.36 (C=S). Anal. Calcd for $C_{18}H_{18}N_2O_2S$: C, H, N.

3-Allyl-5,5′-diphenyl-2-thioxoimidazolidin-4-one (12). Mp: 178.7−179.2 °C. MS (EI): 308 $[M]^+$. ^1H NMR (300 MHz): δ 4.39−4.40 (d, J = 4.41, 2H), 4.94−5.00 (d, J = 17.64, 1H), 5.08−5.12 (d, J = 10.29, 1H), 5.76−5.89 (m, 1H), 7.32−7.46 (m, 10H), 11.75 (s, 1H). ^{13}C NMR (300 MHz): δ 42.37 (CH_2), 71.23 (C), 116.71 (CH_2), 126.48 (CH_{arom}), 128.42 (CH_{arom}), 128.68 (CH_{arom}), 131.34 (C_{arom}), 138.13 (CH), 173.00 (C=O), 180.90 (C=S). Anal. Calcd for $C_{18}H_{16}N_2OS$: C, H, N.

3-Benzyl-5,5′-diphenyl-2-thioxoimidazolidin-4-one (13). Mp: 155.1−156.0 °C. MS (EI): 358 $[M]^+$. ^1H NMR (300 MHz): δ 5.00 (s, 2H), 7.23−7.43 (m, 15H), 11.77 (s, 1H). ^{13}C NMR (300 MHz): δ 43.90 (CH_2), 71.40 (C), 126.65 (CH_{arom}), 127.36 (CH_{arom}), 127.56 (CH_{arom}), 128.53(CH_{arom}), 128.66 (CH_{arom}), 128.85 (CH_{arom}), 136.16 (C_{arom}), 138.17 (C_{arom}), 173.49 (C=O), 181.32 (C=S). Anal. Calcd for $C_{22}H_{18}N_2OS$: C, H, N.

3-Phenethyl-5,5′-diphenyl-2-thioxoimidazolidin-4-one (14). Mp: 175.2−176.1 °C. MS (EI): 372 $[M]^+$. ^1H NMR (300 MHz): δ 2.97 (t, J = 7.35, 2H), 4.01 (t, J = 7.35, 2H), 7.19−7.38 (m, 15H), 11.02 (s, 1H). ^{13}C NMR (300 MHz): δ 32.73 (CH_2), 41.53 (CH_2), 71.10 (C), 126.03 (CH_{arom}), 126.29 (CH_{arom}), 126.55 (CH_{arom}), 127.13 (CH_{arom}), 128.30 (CH_{arom}), 128.75 (CH_{arom}), 137.48 (C_{arom}), 138.07 (C_{arom}), 173.20 (C=O), 180.83 (C=S). Anal. Calcd for $C_{23}H_{20}N_2OS$: C, H, N.

3-(Furan-2-ylmethyl)-5,5′-diphenyl-2-thioxoimidazolidin-4-one (15). Mp: 178.2−179.1 °C. MS (EI): 348 $[M]^+$. ^1H NMR (300 MHz): δ 5.01 (s, 2H), 6.20−6.39 (m, 3H), 7.31−7.56 (m, 10H), 11.79 (s, 1H). ^{13}C NMR (300 MHz): δ 37.33 (CH_2), 71.23 (C_5), 108.11 (CH), 110.50 (CH), 126.55 (CH_{arom}), 128.42 (CH_{arom}), 128.68 (CH_{arom}), 137.93 (C_{arom}), 142.46 (C), 148.80 (CH), 172.87 (C=O), 180.44 (C=S). Anal. Calcd for $C_{20}H_{16}N_2OS$: C, H, N.

5,5′-Bis(4-chlorophenyl)-3-isobutyl-2-thioxoimidazolidin-4-one (16). Mp: 187.6−188.4 °C. MS (EI): 392 $[M]^+$. ^1H NMR (300 MHz): δ 0.78 (m, 6H), 2.09−2.19 (m, 1H), 3.59 (d,

J = 7.35, 2H), 7.31−7.34 (d, J = 8.82, 4H), 7.52−7.55 (d, J = 8.82, 4H), 11.73 (s, 1H). ^{13}C NMR (300 MHz): δ 19.60 (2 × CH_3), 26.52 (CH), 47.61 (CH_2), 70.07 (C), 128.36 (C_{arom}), 128.94 (CH_{arom}), 133.54 (CH_{arom}), 136.77 (C_{arom}), 173.20 (C=O), 181.74 (C=S). Anal. Calcd for $C_{19}H_{18}Cl_2N_2OS$: C, H, N.

5,5′-Bis(4-chlorophenyl)-3-heptyl-2-thioxoimidazolidin-4-one (17). Mp: 159.5−160.0 °C. MS (EI): 434 $[M]^+$. ^{1}H NMR (300 MHz): δ 0.81 (t, J = 7.35, 3H), 1.16 (m, 8H), 1.56−1.61 (m, 2H), 3.76 (t, J = 7.35, 2H), 7.32−7.35 (d, J = 8.82, 4H), 7.51−7.54 (d, J = 8.82, 4H), 11.72 (s, 1H). ^{13}C NMR (300 MHz): δ 13.23 (CH_3), 22.03 (CH_2), 25.91 (CH_2), 27.14 (CH_2), 28.31 (CH_2), 31.22 (CH_2), 38.44 (CH_2), 70.23 (C), 127.49 (C_{arom}), 129.76 (CH_{arom}), 133.77 (CH_{arom}), 136.94 (C_{arom}), 173.17 (C=O), 181.52 (C=S). Anal. Calcd for $C_{19}H_{18}Cl_2N_2OS \cdot 1/3H_2O$: C, H, N.

5,5′-Bis(4-chlorophenyl)-3-octyl-2-thioxoimidazolidin-4-one (18). Mp: 133.0−133.8 °C. MS (EI): 449 $[M + H]^+$. ^{1}H NMR (300 MHz): δ 0.83 (m, 3H), 1.16 (m, 10H), 1.57 (m, 2H), 3.75 (m, 2H), 7.30−7.33 (d, J = 8.82, 4H), 7.52−7.54 (d, J = 8.82, 4H), 11.71 (s, 1H). ^{13}C NMR (300 MHz): δ 13.78 (CH_3), 21.93 (CH_2), 25.75 (CH_2), 26.85 (CH_2), 28.33 (CH_2), 30.92 (CH_2), 38.69 (CH_2), 40.54 (CH_2), 70.07 (C), 128.36 (C_{arom}), 128.88 (CH_{arom}), 133.54 (CH_{arom}), 136.71 (C_{arom}), 173.00 (C=O), 181.35 (C=S). Anal. Calcd for $C_{23}H_{26}Cl_2N_2OS$: C, H, N.

3-Benzyl-5,5′-bis(4-chlorophenyl)-2-thioxoimidazolidin-4-one (19). Mp: 182.3−182.8 °C. MS (EI): 426 $[M]^+$. ^{1}H NMR (300 MHz): δ 4.98 (s, 1H), 7.21−7.61 (m, 13H), 11.86 (s, 1H). ^{13}C NMR (300 MHz): δ 43.86 (CH_2), 70.26 (C), 127.19 (C_{arom}), 127.45 (CH_{arom}), 128.42 (CH_{arom}), 128.94 (CH_{arom}), 133.42 (CH_{arom}), 133.60 (CH_{arom}), 135.86 (C_{arom}), 136.64 (C_{arom}), 172.84 (C=O), 181.28 (C=S). Anal. Calcd for $C_{22}H_{16}Cl_2N_2OS$: C, H, N.

5,5′-Bis(4-chlorophenyl)-3-phenethyl-2-thioxoimidazolidin-4-one (20). Mp: 203.4−204.2 °C. MS (EI): 440 $[M]^+$. ^{1}H NMR (300 MHz): δ 2.96 (t, J = 7.35, 2H), 3.99 (t, J = 7.35, 2H), 7.12−7.48 (m, 13H), 11.63 (s, 1H). ^{13}C NMR (300 MHz): δ 32.60 (CH_2), 41.60 (CH_2), 70.07 (C), 126.35 (C_{arom}), 128.23 (C_{arom}), 128.49 (CH_{arom}), 128.75 (CH_{arom}), 129.23 (CH_{arom}), 133.47 (CH_{arom}), 136.64 (C_{arom}), 137.42 (C_{arom}), 172.68 (C=O), 181.02 (C=S). Anal. Calcd for $C_{23}H_{18}Cl_2N_2OS$: C, H, N.

5,5′-Bis(4-bromophenyl)-3-ethyl-2-thioxoimidazolidin-4-one (21). Mp: 203.9−204.5 °C. MS (EI): 454 $[M]^+$. ^{1}H NMR (300 MHz): δ 1.12 (t, J = 7.35, 3H), 3.79 (q, J = 7.35, 2H), 7.23−7.25 (d, J = 8.82, 4H), 7.64−7.67 (d, J = 8.82, 4H), 11.70 (s, 1H). ^{13}C NMR (300 MHz): δ 12.68 (CH_3), 35.84 (CH_2), 70.19 (C), 122.21 (C_{arom}), 128.68 (CH_{arom}), 131.85 (CH_{arom}), 137.03 (C_{arom}), 172.55 (C=O), 181.02 (C=S). Anal. Calcd for $C_{17}H_{14}Br_2N_2OS$: C, H, N.

5,5′-Bis(4-bromophenyl)-3-isopropyl-2-thioxoimidazolidin-4-one (22). Mp: 214.0−214.8 °C. MS (EI): 468 $[M]^+$. ^{1}H NMR (300 MHz): δ 1.36 (m, 6H), 4.81−4.90 (m, 1H), 7.20−7.23 (d, J = 8.82, 4H), 7.64−7.67 (d, J = 8.82, 4H), 11.69 (s, 1H). ^{13}C NMR (300 MHz): δ 25.98 (2 × CH_3), 53.85 (CH), 77.89 (C), 122.98 (C_{arom}), 129.41 (CH_{arom}), 132.78 (CH_{arom}), 137.70 (C_{arom}), 173.49 (C=O), 182.10 (C=S). Anal. Calcd for $C_{18}H_{16}Br_2N_2OS$: C, H, N.

5,5′-Bis(4-bromophenyl)-3-butyl-2-thioxoimidazolidin-4-one (23). Mp: 177.7−178.3 °C. MS (EI): 482 $[M]^+$. ^{1}H NMR (300 MHz): δ 0.85 (t, J = 7.35, 3H), 1.16−1.28 (m, 2H), 1.51−1.61 (m, 2H), 3.76 (t, J = 7.35, 2H), 7.24−7.27 (d, J = 8.82, 4H), 7.64−7.67 (d, J = 8.82, 4H), 11.67 (s, 1H). ^{13}C NMR (300 MHz): δ 14.07 (CH_3), 19.90 (CH_2), 29.80 (CH_2), 38.44 (CH_2), 70.88 (C), 122.90 (C_{arom}), 129.37 (CH_{arom}), 132.54 (CH_{arom}), 137.78 (C_{arom}), 173.49 (C=O), 182.10 (C=S). Anal. Calcd for $C_{19}H_{18}Br_2N_2OS$: C, H, N.

5,5′-Bis(4-bromophenyl)-3-isobutyl-2-thioxoimidazolidin-4-one (24). Mp: 210.6−211.0 °C. MS (EI): 382 $[M]^+$. ^{1}H NMR (300 MHz): δ 0.76−0.79 (m, 6H), 2.09−2.18 (m, 1H), 3.57−3.59 (d, J = 7.35, 2H), 7.24−7.27 (d, J = 8.82, 4H), 7.65−7.68 (d, J = 8.82, 4H), 11.74 (s, 1H). ^{13}C NMR (300 MHz): δ 19.53 (CH_3), 26.52 (CH), 47.55 (CH_2), 70.13 (C), 122.15 (C_{arom}), 128.62 (CH_{arom}), 131.79 (CH_{arom}), 137.09 (C_{arom}), 173.07 (C=O), 181.67 (C=S). Anal. Calcd for $C_{19}H_{18}Br_2N_2OS$: C, H, N.

5,5′-Bis(4-bromophenyl)-3-heptyl-2-thioxoimidazolidin-4-one (25). Mp: 161.8−162.4 °C. MS (EI): 525 $[M + H]^+$. ^{1}H NMR (300 MHz), δ 0.81 (t, J = 7.35, 3H), 1.15 (m, 8H), 1.58 (m, 2H), 3.75 (t, J = 7.35, 2H), 7.24−7.27 (d, J = 8.82, 4H), 7.64−7.67 (d, J = 8.82, 4H), 11.71 (s, 1H). ^{13}C NMR (300 MHz): δ 13.78 (CH_3), 21.80 (CH_2), 25.75 (CH_2), 26.85 (CH_2), 28.01 (CH_2), 30.99 (CH_2), 38.44 (CH_2), 70.19 (C), 122.15 (C_{arom}), 128.68 (CH_{arom}), 131.85 (CH_{arom}), 137.09 (C_{arom}), 172.87 (C=O), 181.35 (C=S). Anal. Calcd for $C_{22}H_{24}Br_2N_2OS$: C, H, N.

5,5′-Bis(4-bromophenyl)-3-octyl-2-thioxoimidazolidin-4-one (26). Mp: 147.8−148.3 °C. MS (EI): 538 $[M]^+$. ^{1}H NMR (300 MHz): δ 0.82 (t, J = 7.35, 3H), 1.15 (m, 10H), 1.55 (m, 2H), 3.75 (t, J = 7.35, 2H), 7.24−7.27 (d, J = 8.82, 4H), 7.64−7.67 (d, J = 8.82, 4H), 11.70 (s, 1H). ^{13}C NMR (300 MHz): δ 13.78 (CH_3), 21.93 (CH_2), 25.75 (CH_2), 26.85 (CH_2), 28.33 (CH_2), 30.92 (CH_2), 38.43 (CH_2), 40.37 (CH_2), 70.19 (C), 122.15 (C_{arom}), 128.68 (CH_{arom}), 131.79 (CH_{arom}), 137.09 (C_{arom}), 172.87 (C=O), 181.35 (C=S). Anal. Calcd for $C_{23}H_{26}Br_2N_2OS$: C, H, N.

5,5′-Bis(4-bromophenyl)-3-cyclohexyl-2-thioxoimidazolidin-4-one (27). Mp: 227.1−228.0 °C. MS (EI): 508 $[M]^+$. ^{1}H NMR (300 MHz): δ 1.24 (m, 3H), 1.59 (m, 3H), 1.75 (m, 2H), 2.08 (m, 2H), 4.49 (m, 1H), 7.20−7.23 (d, J = 8.82, 4H), 7.64−7.66 (d, J = 8.82, 4H), 11.70 (s, 1H). ^{13}C NMR (300 MHz): δ 24.71 (CH_2), 25.29 (CH_2), 28.01 (CH_2), 54.15 (CH), 69.16 (C), 122.15 (C_{arom}), 128.68 (CH_{arom}), 131.85 (CH_{arom}), 137.22 (C_{arom}), 172.87 (C=O), 181.61 (C=S). Anal. Calcd for $C_{21}H_{20}Br_2N_2OS$: C, H, N.

3-Allyl-5,5′-bis(4-bromophenyl)-2-thioxoimidazolidin-4-one (28). Mp: 181.3−181.9 °C. MS (EI): 466 $[M]^+$. ^{1}H NMR (300 MHz), δ 4.38 (d, J = 4.40, 2H), 4.91−4.97 (d, J = 17.62, 1H), 5.08−5.12 (d, J = 10.29, 1H), 5.75−5.86 (m, 1H), 7.24−7.27 (d, J = 8.82, 4H), 7.65−7.68 (d, J = 8.82, 4H), 11.78 (s, 1H). ^{13}C NMR (300 MHz): δ 42.57 (CH_2), 70.32 (C), 116.84 (CH_2), 122.71 (C_{arom}), 128.68 (CH_{arom}), 131.21 (CH), 131.85 (CH_{arom}), 137.03 (C_{arom}), 172.42 (C=O), 181.03 (C=S). Anal. Calcd for $C_{18}H_{14}Br_2N_2OS$: C, H, N.

3-Benzyl-5,5′-bis(4-bromophenyl)-2-thioxoimidazolidin-4-one (29). Mp: 162.1−162.8 °C. MS (EI): 516 $[M]^+$. ^{1}H NMR (300 MHz): δ 4.98 (s, 2H), 7.23−7.67 (m, 13H), 11.85 (s, 1H). ^{13}C NMR (300 MHz): δ 43.86 (CH_2), 70.32 (C), 122.21 (C_{arom}), 127.13 (CH_{arom}), 127.39 (CH_{arom}), 128.36 (CH_{arom}), 128.62 (CH_{arom}), 131.85 (CH_{arom}), 135.80 (C_{arom}), 136.96 (C_{arom}), 172.68 (C=O), 181.28 (C=S).

5,5′-Bis(4-bromophenyl)-3-phenethyl-2-thioxoimidazolidin-4-one (30). Mp: 189.1−190.0 °C. MS (EI): 530 $[M]^+$. ^{1}H NMR (300 MHz): δ 2.95 (t, J = 7.35, 2H), 3.99 (t, J = 7.35, 2H), 7.06−7.62 (m, 13H), 11.63 (s, 1H). ^{13}C NMR (300 MHz): δ 33.10 (CH_2), 42.09 (CH_2), 70.62 (C), 122.51 (C_{arom}), 126.78 (CH_{arom}), 128.66 (CH_{arom}), 129.17 (CH_{arom}), 131.99 (CH_{arom}), 132.15(CH_{arom}), 137.46 (C_{arom}), 137.91 (C_{arom}), 173.04 (C=O), 181.03 (C=S). Anal. Calcd for $C_{23}H_{18}Br_2N_2OS$: C, H, N.

5,5′-Bis(4-iodophenyl)-3-butyl-2-thioxoimidazolidin-4-one (31). Mp: 163.6−165.3 °C. MS (EI): 576 $[M]^+$. ^{1}H NMR (300 MHz): δ 0.85 (t, J = 7.35, 3H), 1.14−1.26 (m, 2H), 1.49−1.59 (m, 2H), 3.73 (t, J = 7.35, 2H), 7.05−7.82 (m, 8H), 11.66 (s, 1H). ^{13}C NMR (300 MHz): δ 13.61 (CH_3), 19.38 (CH_2), 29.28 (CH_2), 38.25 (CH_2), 70.62 (C), 95.60 (C_{arom}), 128.85 (C_{arom}), 137.65 (CH_{arom}), 137.85 (CH_{arom}), 172.98 (C=O), 181.46 (C=S). Anal. Calcd for $C_{19}H_{18}I_2N_2OS$: C, H, N.

3-Allyl-5,5′-bis(4-iodophenyl)-2-thioxoimidazolidin-4-one (32). Mp: 223.6−224.3 °C. MS (EI): 560 $[M]^+$. ^{1}H NMR (300 MHz), δ 4.37 (m, 2H), 4.91−4.97 (d, J = 17.62, 1H), 5.07−5.11 (d, J = 10.29, 1H), 5.75−5.84 (m, 1H), 7.08−7.68 (m, 8H), 11.70 (s, 1H). ^{13}C NMR (300 MHz): δ 42.99 (CH_2), 71.01 (C), 95.92 (C_{arom}), 117.27 (CH_2), 129.11 (C_{arom}), 131.70 (CH), 137.91 (CH_{arom}), 138.17 (C_{arom}), 172.78 (C=O), 181.46 (C=S). Anal. Calcd for $C_{18}H_{14}I_2N_2OS$: C, H, N.

5,5′-Bis(4-bromophenyl)-3-butylimidazolidine-2,4-dione (33). The synthesis of this compound was previously described by us.[34] Mp: 151.0−152.2 °C. MS DCI (H_2O): 467 $[M + H]^+$. ^{1}H NMR (300 MHz): δ 0.8183−0.8673 (m, 3H), 1.1565−1.2300 (m, 2H), 1.4701−1.5191 (m, 2H), 3.4106−3.4596 (m, 2H), 7.2719 (d, J = 8.82 Hz, 4H), 7.6345 (d, J = 8.82 Hz, 4H), 9.6975 (s, 1H). ^{13}C NMR (300 MHz): δ 13.2320

(CH_3), 19.0549 (CH_2), 29.3422 (CH_2), 37.7531 (CH_2), 68.1619 (C), 121.6685 (C_{arom}), 128.6560 (CH_{arom}), 131.5028 (CH_{arom}), 138.6198 (C_{arom}), 155.1182 (C=O), 172.4576 (C=O). Anal. Calcd for: $C_{19}H_{18}Br_2N_2O_2$: C, H,N.

3-Benzyl-5,5′-bis(4-bromophenyl)imidazolidine-2,4-dione (34). The synthesis of this compound was previously described by us elsewhere.[41] Mp: 181.1−182.2. MS DCI: 500 $[M + H]^+$. ^{1}H NMR (300 MHz): δ 4.63 (s, 2H), 7.18−7.64 (m,-13H), 9.84 (s, 1H).^{13}C NMR (300 MHz): δ 41.76 (CH_2), 68.55 (C), 121.99, 127.36, 127.69, 128.72, 128.85, 131.83, 136.42, 138.62, 155.12 (C=O), 172.46 (C=O). Anal. Calcd for $C_{22}H_{16}Br_2N_2O_2$: C, H, N.

3-Butyl-5,5′-bis(4-iodophenyl)imidazolidine-2,4-dione (35). This compound was synthesized with the same microwave-enhanced procedure described previously.[34] Mp: 147.3−148.3 °C. MS (EI): 560 $[M]^+$. ^{1}H NMR (300 MHz): δ 0.83 (t, J = 7.35, 3H), 1.14−1.21 (m, 2H), 1.46−1.50 (m, 2H), 3.39−3.77 (m, 2H), 7.1−7.79 (m, 8H), 9.66 (s, 1H). ^{13}C NMR (300 MHz): δ 13.08 (CH_3), 19.64 (CH_2), 29.86 (CH_2), 38.28 (CH_2), 68.88 (C), 95.47 (C_{arom}), 129.24 (CH_{arom}), 137.91 (CH_{arom}), 139.46 (C_{arom}), 155.64 (C=O), 172.91 (C=O). Anal. Calcd for $C_{19}H_{18}I_2N_2O_2$: C, H, N.

3-Allyl-5,5′-bis(4-iodophenyl)imidazolidine-2,4-dione (36). This compound was synthesized with the same microwave-enhanced procedure described previously.[34] Mp: 187.0−189 °C. MS (EI): 544 $[M]^+$. ^{1}H NMR (300 MHz), δ 4.04 (m, 2H), 4.92−4.98 (d, J = 17.64, 1H), 5.07−5.10 (d, J = 10.29, 1H), 5.73−5.84 (m, 1H), 7.12−7.81 (m, 8H), 9.71 (s, 1H). ^{13}C NMR (300 MHz): δ 40.51 (CH_2), 68.75 (C), 95.14 (C_{arom}), 116.56 (CH_2), 128.92 (C_{arom}), 132.03 (CH), 137.65 (CH_{arom}), 139.08 (C_{arom}), 154.87 (C=O), 172.27 (C=O). Anal. Calcd for $C_{18}H_{14}I_2N_2O_2$: C, H, N.

Cell Culture and Preparation of hCB_1- or hCB_2-Transfected CHO Cell Membranes. CHO cells stably transfected with the cDNA sequences encoding either the human CB_1 or the human CB_2 cannabinoid receptors were kindly donated by Dr. M. Detheux and Dr. P. Nokin, respectively (Euroscreen s.a., Gosselies, Belgium). Cells were grown in Ham's F12 nutrient mixture supplemented with 10% FBS, 2.5 μL/mL fungizone, 100 U/mL penicillin, 100 μg/mL streptomycin, and 400 μg/mL G418. Once at confluence, the cells were trypsinized and collected by centrifugation at 100g for 10 min. The following steps were performed in ice. The pellet was lysed in ice-cold 50 mM Tris-HCl, pH 7.4, and the homogenate was centrifuged at 15 000g for 10 min. The resulting pellet (membranes) was washed twice with the same solution under identical conditions. The protein content was determined as described by Bradford[42] using Coomasie Blue (Biorad, Belgium) with bovine serum albumin as standard.

Competition Binding Assay. [^{3}H]SR141716A (52 Ci/mol) was from Amersham (Roosendaal, The Netherlands), [^{3}H]CP-55,940 (101 Ci/mol) was from NEN Life Science (Zaventem, Belgium), and HU-210 was from Tocris (Bristol, UK). Glass fiber filters were purchased from Whatman (Maidstone, UK), while Aqualuma was from PerkinElmer (Schaesberg, The Netherlands). Stock solutions of the compounds were prepared in DMSO and further diluted (100×) with the binding buffer to the desired concentration. Final DMSO concentrations in the assay were less than 0.1%.

Under these conditions, using [^{3}H]SR141716A, the B_{max} value was 57 pmol/mg of protein and the K_d value was 1.13 ± 0.13 nM for the hCB_1 cannabinoid receptor.

The competitive binding experiments were performed using [^{3}H]SR141716A (1 nM) or [^{3}H]CP-55940 (1 nM) as radioligands for the hCB_1 and the hCB_2 cannabinoid receptor, respectively, at 30 °C in plastic tubes, and 40 μg of membranes per tube was resuspended in 0.5 mL (final volume) binding buffer (50 mM Tris-HCl, 3 mM $MgCl_2$, 1 mM EDTA, 0.5% bovine serum albumine, pH 7.4). The test compounds were present at varying concentrations and the nonspecific binding was determined in the presence of 10 μM HU-210. After 1 h the incubation was stopped, solutions were rapidly filtered through 0.5% PEI pretreated GF/B glass fiber filters on a M-48T Brandell cell harvester and washed twice with 5 mL ice-cold binding buffer without serum albumin. The radioactivity on the filters was measured in a Pharmacia Wallac 1410 β-counter using 10 mL of Aqualuma, after 10 s of shaking and 3 h of resting. Assays were performed at least in triplicate.

[^{35}S]GTPγS Assay. [^{35}S]GTPγS (1173 Ci/mmol) was from Amersham (Roosendaal, The Netherlands). The binding experiments were performed at 30 °C in plastic tubes containing 40 μg of protein in 0.5 mL (final volume) of binding buffer (50 mM Tris-HCl, 3 mM $MgCl_2$, 1 mM EDTA, 100 mM NaCl, 0.1% bovine serum albumin, pH 7.4) supplemented with 20 μM GDP and 10 μM of the test compounds. The assay was initiated by the addition of [^{35}S]GTPγS (0.05 nM, final concentration). The tubes were incubated for 1 h. The incubations were terminated by the addition of 5 mL of ice-cold washing buffer (50 mM Tris-HCl, 3 mM $MgCl_2$, 1 mM EDTA, 100 mM NaCl). The suspension was immediately filtered through GF/B filters using a 48-well Brandell cell harvester and washed twice with the same ice-cold buffer. The radioactivity on the filters was counted as mentioned above. Nonspecific binding was measured in the presence of 100 μM Gpp(NH)p. Assays were performed in triplicate.

Data Analysis. IC_{50} values were determined by nonlinear regression analysis performed using the GraphPad prism 4.0 program (GraphPad Software, San Diego). The K_i values were calculated based on the Cheng−Prusoff equation: $K_i = IC_{50}/(1 + L/K_d)$. The statistical significance of [^{35}S]GTPγS assay results was assessed using an one-way ANOVA followed by a Dunett post-test.

Molecular Electrostatic Potential and CLOGP Calculations. The crystal structure of **28** served as starting point for the geometry optimization of compounds **28**, **32**, and **36** using molecular mechanics (Discover program). The internal coordinates served as input for ab initio calculation of the electronic properties (Gaussian94 program). The molecular electrostatic potential isocontour was plotted using the GopenMol graphical interface.[43]

Values of lipophilicity were calculated using the CLogP program implemented in the ChemDraw Ultra 8.0 package (CambridgeSoft).

Acknowledgment. The authors acknowledge Bernadette Norberg for the X-ray analysis. One of us (G.G.M.) is very indebted to "Fonds pour la formation à la Recherche dans l'Industrie et l'Agriculture (FRIA)" for the award of a research fellowship. This work was partially funded by a FRSM grant from the Belgian National Fund for Scientific Research and a FSR grant from the Université catholique de Louvain.

Supporting Information Available: General procedure for the synthesis of benzil derivatives, characteristic IR peaks of the alkylthiourea derivatives, X-ray crystallographic data of compound **28**, characteristic IR peaks, and elemental analysis of compounds **3**−**36**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Matsuda, L. A.; Lolait, S. J.; Brownstein, M. J.; Young, A. C.; Bonner, T. I. Structure of a cannabinoid receptor and functional expression of the cloned cDNA. *Nature* **1990**, *346*, 561−564.
(2) Gérard, C. M.; Mollereau, C.; Vassart, G.; Parmentier, M. Molecular cloning of a human cannabinoid receptor which is also expressed in testis. *Biochem. J.* **1991**, *279*, 129−134.
(3) Munro, S.; Thomas, K. L.; Abu-Shaar, M. Molecular characterization of a peripheral receptor for cannabinoids. *Nature* **1993**, *365*, 61−65.
(4) Devane, W. A.; Hanus, L.; Breuer, A.; Pertwee, R. G.; Stevenson, L. A.; Griffin, G.; Gibson, D.; Mandelbaum, A.; Etinger, A.; Mechoulam, R. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. *Science* **1992**, *258*, 1946−1949.
(5) Sugiura, T.; Kondo, S.; Sukagawa, A.; Nakane, S.; Shinoda, A.; Itoh, K.; Yamashita, A.; Waku, K. 2-Arachidonoylglycerol: A possible endogenous cannabinoid receptor ligand in brain. *Biochem. Biophys. Res. Commun.* **1995**, *215*, 89−97.

(6) Cravatt, B. F.; Giang, D. K.; Mayfield, S. P.; Boger, D. L.; Lerner, R. A.; Gilula, N. B. Molecular characterization of an enzyme that degrades neuromodulatory fatty-acid amides. *Nature* **1996**, *384*, 83−87.
(7) Ueda, N.; Yamanaka, K.; Yamamoto, S. Purification and characterization of an acid amidase selective for *N*-palmitoylethanolamine, a putative endogenous antiinflammatory substance. *J. Biol. Chem*. **2001**, *276*, 35552−35557.
(8) Piomelli, D. The molecular logic of endocannabinoid signaling. *Nat. Rev. Neurosci*. **2003**, *4*, 873−84.
(9) Calandra, B.; Portier, M.; Kerneis, A.; Delpech, M.; Carillon, C.; Le Fur, G.; Ferrara, P.; Shire, D. Dual intracellular signaling pathways mediated by the human cannabinoid CB1 receptor. *Eur. J. Pharmacol.* **1999**, *374*, 445−455.
(10) Howlett, A. C.; Barth, F.; Bonner, T. I.; Cabral, G.; Casellas, P.; Devane, W. A.; Felder, C. C.; Herkenham, M.; Mackie, K.; Martin, B. R.; Mechoulam, R. Pertwee, R. G. International Union of Pharmacology. XXVII. Classification of cannabinoid receptors. *Pharmacol. Rev*. **2002**, *54*, 161−202.
(11) Nunez, E.; Benito, C.; Pazos, M. R.; Barbachano, A.; Fajardo, O.; Tolon, R. M.; Romero, J. Cannabinoid CB_2 receptors are expressed by perivascular microglial cells in the human brain: An immunohistochemical study. *Synapse* **2004**, *53*, 208−213.
(12) Goutopoulos, A. and Makriyannis, A. From cannabis to cannabinergics: New therapeutic opportunities. *Pharmacol. Ther.* **2002**, *95*, 103−117.
(13) Brotchie, J. M. CB_1 cannabinoid receptor signaling in Parkinson's disease. *Curr. Opin. Pharmacol*. **2003**, *3*, 54−61.
(14) Muller-Vahl, K. R. Cannabinoids reduce symptoms of Tourette's syndrome. *Expert. Opin. Pharmacother*. **2003**, *4*, 1717−1725.
(15) Lastres-Becker, I.; de Miguel, R.; De Petrocellis, L.; Makriyannis, A.; Di Marzo, V.; Fernandez-Ruiz, J. Compounds acting at the endocannabinoid and/or endovanilloid systems reduce hyperkinesia in a rat model of Huntington's disease. *J. Neurochem.* **2003**, *84*, 1097−1109.
(16) Calignano, A.; Katona, I.; Desarnaud, F.; Giuffrida, A.; La Rana, G.; Mackie, K.; Freund, T. F.; Piomelli, D. Bidirectional control of airway responsiveness by endogenous cannabinoids. *Nature* **2000**, *408*, 96−101.
(17) Song, Z. H.; Slowey, C. A. Involvement of cannabinoid receptors in the intraocular pressure-lowering effects of WIN55212-2. *J. Pharmacol. Exp. Ther.* **2000**, *292*, 136−139.
(18) Pinto, L.; Izzo, A. A.; Cascio, M. G.; Bisogno, T.; Hospodar-Scott, K.; Brown, D. R.; Mascolo, N.; Di Marzo, V.; Capasso, F. Endocannabinoids as physiological regulators of colonic propulsion in mice. *Gastroenterology* **2002**, *123*, 227−234.
(19) Rinaldi-Carmona, M.; Barth, F.; Heaulme, M.; Shire, D.; Calandra, B.; Congy, C.; Martinez, S.; Maruani, J.; Neliat, G.; Caput, D. SR141716A, a potent and selective antagonist of the brain cannabinoid receptor. *FEBS Lett.* **1994**, *350*, 240−244.
(20) Rinaldi-Carmona, M.; Barth, F.; Heaulme, M.; Alonso, R.; Shire, D.; Congy, C.; Soubrie, P.; Breliere, J. C.; Le Fur, G. Biochemical and pharmacological characterisation of SR141716A, the first potent and selective brain cannabinoid receptor antagonist. *Life Sci.* **1995**, *56*, 1941−1947.
(21) Ravinet Trillou, C.; Arnone, M.; Delgorge, C.; Gonalons, N.; Keane, P.; Maffrand, J. P.; Soubrie, P. Anti-obesity effect of SR141716, a CB_1 receptor antagonist, in diet-induced obese mice. *Am. J. Physiol.* **2003**, *284*, R345−353.
(22) Colombo, G.; Agabio, R.; Diaz, G.; Lobina, C.; Reali, R.; Gessa, G. L. Appetite suppression and weight loss after the cannabinoid antagonist SR 141716. *Life Sci*. **1998**, *63*, PL113−117.
(23) Cohen, C.; Perrault, G.; Voltz, C.; Steinberg, R.; Soubrie, P. SR141716, a central cannabinoid (CB_1) receptor antagonist, blocks the motivational and dopamine-releasing effects of nicotine in rats. *Behav Pharmacol.* **2002**, *13*, 451−63.
(24) Rinaldi-Carmona, M.; Barth, F.; Congy, C.; Martinez, S.; Oustric, D.; Pério, A.; Poncelet, M.; Maruani, J.; Arnone, M.; Finance, O.; Soubrié P.; Le Fur, G. SR147778 [5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-4-ethyl-*N*-(1-piperidinyl)-1*H*-pyrazole-3-carboxamide], a new potent and selective antagonist of the CB_1 cannabinoid receptor. Biochemical and pharmacological characterization. *J. Pharmacol. Exp. Ther.* **2004**, *310*, 905−914.
(25) Felder, C. C.; Joyce, K. E.; Briley, E. M.; Glass, M.; Mackie, K. P.; Fahey, K. J.; Cullinan, G. J.; Hunden, D. C.; Johnson, D. W.; Chaney, M. O.; Koppel, G. A.; Brownstein, M. LY320135, a novel cannabinoid CB1 receptor antagonist, unmasks coupling of the CB_1 receptor to stimulation of cAMP accumulation. *J. Pharmacol. Exp. Ther*. **1998**, *284*, 291−297.
(26) Lange, J. H.; Kruse, C. G.; Tipker, J.; Tulp, M. T.; Van Vliet, B. J. 4,5-Dihydro-1*H*-pyrazole derivatives having CB_1-antagonistic properties. World Patent Organization WO0170700, 2001.
(27) Lange, J. H.; Coolen, H. K.; van Stuivenberg, H. H.; Dijksman, J. A.; Herremans, A. H.; Ronken, E.; Keizer, H. G.; Tipker, K.; McCreary, A. C.; Veerman, W.; Wals, H. C.; Stork, B.; Verveer, P. C.; den Hartog, A. P.; de Jong, N. M.; Adolfs, T. J.; Hoogendoorn, J.; Kruse, C. G. Synthesis, biological properties, and molecular modeling investigations of novel 3,4-diarylpyrazolines as potent and selective CB_1 cannabinoid receptor antagonists. *J. Med. Chem.* **2004**, *47*, 627−643.
(28) Dyck, B.; Goodfellow, V. S.; Phillips, T.; Grey, J.; Haddach, M.; Rowbottom, M.; Naeve, G. S.; Brown, B.; Saunders, J. Potent imidazole and triazole CB_1 receptor antagonists related to SR141716. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1151−1154.
(29) Jagerovic, N.; Hernandez-Folgado, L.; Alkorta, I.; Goya, P.; Navarro, M.; Serrano, A.; Rodriguez de Fonseca, F.; Dannert, M. T.; Alsasua, A.; Suardiaz, M.; Pascual, D.; Martin, M. I. Discovery of 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-3-hexyl-1*H*-1,2,4-triazole, a novel in vivo cannabinoid antagonist containing a 1,2,4-triazole motif. *J. Med. Chem.* **2004**, *47*, 2939−2942.
(30) Kanyonyo, M.; Govaerts, S. G.; Hermans, E.; Poupaert, J. H.; Lambert, D. M. 3-Alkyl-(5,5′-diphenyl)imidazolidinediones as new cannabinoid receptor ligands. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2233−2236.
(31) Govaerts, S. J.; Muccioli, G. G.; Hermans, E.; Lambert, D. M. Characterization of the pharmacology of imidazolinedione derivatives at cannabinoid CB_1 and CB_2 receptors. *Eur. J. Pharmacol.* **2004**, *495*, 43−53.
(32) Ooms, F.; Wouters, J.; Oscari, O.; Happaerts, T.; Bouchard, G.; Carrupt, P. A., Testa, B.; Lambert, D. M. Exploration of the pharmacophore of 3-alkyl-5-arylimidazolidinediones as new CB_1 cannabinoid receptor ligands and potential antagonists: Synthesis, lipophilicity, affinity, and molecular modeling. *J. Med. Chem.* **2002**, *45*, 1748−1756. Erratum published in *J. Med. Chem.* **2002**, *45*, 4799.
(33) The 2-thioxoimidazolidin-4-one ring is also called thiohydantoin.
(34) Ellsworth, T. J. 5,5-Diaryl-2-thiohydantoins and 5,5-diaryl *N*3-substituted 2-thiohydantoins as potential hypolipidemic agents. *J. Med. Chem.* **1986**, *29*, 855−859.
(35) Muccioli, G. G.; Poupaert, J. H.; Wouters, J.; Norberg, B.; Poppitz, W.; Scriba, G. K. E.; Lambert, D. M. A rapid and efficient microwave-assisted synthesis of hydantoins and thiohydantoins. *Tetrahedron* **2003**, *59*, 1301−1307.
(36) Kuebrich, J. P.; Schowen, R. L.; Wang, M.; Lupes, M. E. Mechanism of the benzoin condensation. *J. Am. Chem. Soc*. **1971**, *93*, 1214−1220.
(37) Moore, M. L.; Crossley F. S. *Organic Synthesis*; Wiley: New York, 1963; Collect. Vol. III, pp 599−601.
(38) Cheng, Y. C. and Prusoff, W. H. Relationship between the inhibition constant (K1) and the concentration of inhibitor which causes 50% inhibition (IC_{50}) of an enzymatic reaction. *Biochem. Pharmacol.* **1973**, *22*, 3099−3108.
(39) Harrison, C. and Traynor, J. R. The [^{35}S]GTPgammaS binding assay: Approaches and applications in pharmacology. *Life Sci.* **2003**, *74*, 489−508.
(40) Easton, R. E.; Giesen, D. J.; Welch, A.; Cramer, C. J.; Truhlar, D. G. The MIDI! basis set for quantum mechanical calculations of molecular geometries and partial charges. *Theor. Chim. Acta* **1996**, *93*, 281−301.
(41) Muccioli, G. G.; Wouters, J.; Poupaert, J. H.; Norberg, B.; Poppitz, W.; Scriba, G. K.; Lambert, D. M. Versatile access to benzhydryl-phenylureas through an unexpected rearrangement during microwave-enhanced synthesis of hydantoins. *Org. Lett.* **2003**, *5*, 3599−3602.
(42) Bradford, M. M. A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding. *Anal. Biochem.* **1976**, *72*, 248−254.
(43) Bergman, D. L.; Laaksonen, L.; Laaksonen, A. Visualization of solvation structures in liquid mixtures. *J. Mol. Graph. Model.* **1997**, *15*, 301−306.

JM049263K