Biarylpyrazolyl Oxadiazole as Potent, Selective, Orally Bioavailable Cannabinoid-1 Receptor Antagonists for the Treatment of Obesity

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Since the CB1 cannabinoid receptor antagonist **1** (SR141716, rimonabant) was previously reported to modulate food intake, CB1 antagonism has been considered as a new therapeutic target for the treatment of obesity. In the present study, biarylpyrazole analogues based on a pyrazole core coupled with 1,3,4-oxadiazole were synthesized and tested for CB1 receptor binding affinity. Thorough SAR studies to optimize pyrazole substituents as well as 1,3,4-oxadiazole ring led to several novel CB1 antagonists with $IC_{50} \sim 1$ nM for the CB1 receptor binding. Among these analogues, we identified 2-(4-((1*H*-1,2,4-triazol-1-yl)methyl)-5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazol-3-yl)-5-(1-(trifluoromethyl)cyclopropyl)-1,3,4-oxadiazole **43c** as a promising precandidate for the development as an antiobesity agent.

Introduction

The prevalence of obesity has rapidly increased over the past decade. Obesity is not a simply cosmetic concern but a serious health problem. Thus, the World Health Organization (WHO) recently declared that obesity has become a global epidemic.[1,2] Obesity is characterized by excess of body fat and includes a pro-inflammatory state eventually resulting in type 2 diabetes, coronary heart disease, and hypertension. Furthermore, obesity elevates the relative risk of mortality owing to cardiovascular disease,[3] and obesity now ranks as the second leading cause of preventable death after smoking in the United States.[4] Treatment of obesity involves a combination of diet, exercise, and pharmacotherapy. However, there is growing evidence that short-term dietary changes or exercise alone cannot adequately address obesity as a chronic disease. Only two drugs are currently approved for chronic weight loss treatment: orlistat (1-(3-hexyl-4-oxo-oxetan-2-yl)tridecan-2-yl 2-formylamino-4-methyl-pentanoate) and sibutramine (1-(4-chlorophenyl)-*N*,*N*-dimethyl-*a*-(2-methylpropyl)-cyclobutanemethanamine). However, both of these agents have different adverse event profiles that limit more widespread use.[5]

Numerous studies on causes of obesity have been made to identify new potential targets that could be exploited to create novel types of antiobesity drugs. Eventually, the discovery was made that modulation of the endocannabinoid system by specifically blocking the cannabinoid receptor 1 (CB1)[a] in both the brain and periphery can provide a novel target for the treatment of obesity.[6a] The endocannabinoid system includes endogenous ligands (such as anandamide and 2-AG)[6b] and two cannabinoid receptor subtypes (CB1 and CB2). These receptors

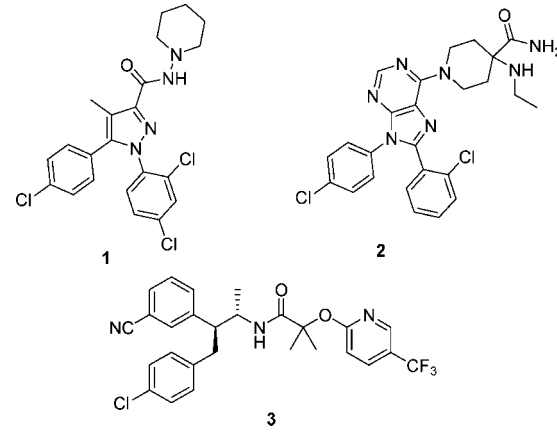

Figure 1. Structures of CB1R antagonists or inverse agonists.

(CB1 and CB2) belong to the G-protein coupled receptor superfamily and were first cloned in 1990 and 1993, respectively.[7−9] The CB1 receptors are mainly expressed in several brain areas including the limbic system (amygdala, hippocampus), hypothalamus, cerebral cortex, cerebellum, and basal ganglia. It has been known that CB1 receptors, especially in the limbic system−hypothalamus axis cannabinoids, have an important role in the control of appetite. In contrast, CB2 receptors are almost exclusively expressed in cells of the immune system.[10,11] The physiological role of both CB receptors is not yet completely understood, although they seem to be involved in certain pathophysiological processes. In particular, the physiological role of CB1 receptors has been of interest since the clinical results of **1** (SR141716, rimonabant, Figure 1),[15a] the first commercial CB1 antagonist, were reported for the treatment of obesity and metabolic disorders in 2001. Since then, antagonism of CB1 receptors has been pursued as a highly promising strategy for the treatment of obesity. Considering the important impact of obesity on public health, the increasing incidence of its worldwide prevalence, and the lack of highly efficient and well-tolerated drugs for treatment, it is not surprising that CB1 antagonism or inverse agonism is the subject of considerable interest.[12] Although **1** is currently marketed by Sanofi-Aventis

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[a] Abbreviations: CB1, cannabinoid-1; CB2, cannabinoid-2; 2-AG, 2-arachidonoylglycerol; DAST, diethylaminosulfur trifluoride; SAR, structure−activity relationships; NBS, *N*-bromosuccinimide; AIBN, azobisisobutyronitrile; CHO cells, Chinese hamster ovary cells; DIO mice, Diet-induced obese mice; DMSO, dimethyl sulfoxide.

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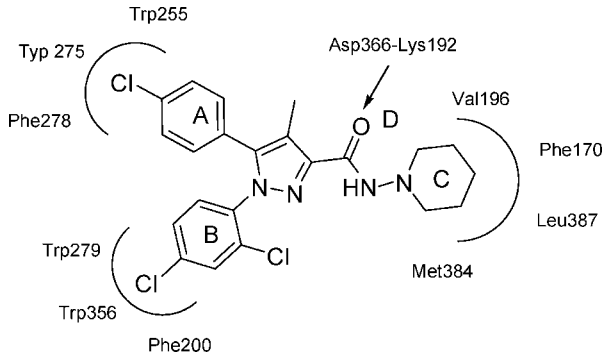


Figure 2. **1** and its receptor−ligand interaction.

in the European Union, many research groups, including major pharmaceutical companies, are still searching for novel CB1 antagonists with improved physicochemical properties and decreased adverse effects, such as depression or anxiety.[13,14]

Several CB1 receptor antagonists (Figure 1), including **1**, **2** (CP-945,598, otenabant),[15b] and **3** (MK-0364, taranabant),[16,17] have been reported to be in various phase of clinical trials. Several reviews describe recent medicinal chemistry research around pyrazolyl derivatives and other new chemotypes as CB1 receptor antagonists.[3,11] However, on the basis of recent literature and patent application reports, **1** appears to be widely used as a lead template for the design of new compounds.

A pharmacophore model for the binding of a low energy conformation of **1** in the CB1 receptor has been well-documented.[11,18] The key receptor−ligand interaction is known to be a hydrogen bond between the carbonyl group of **1** and the Lys192-Asp366 residue of the CB1 receptor, thereby exerting a stabilizing effect on the Lys192-Asp366 salt bridge as shown in Figure 2.[11]

To date, various analogues of **1** have been designed for the purpose of enhancing binding affinity and selectivity for the CB1 receptor, employing strategies such as conformational constraint or scaffold hopping.[11] In general, replacement of the pyrazole core with 5- or 6-membered ring scaffolds has been an active area of research. We envisioned that the key carbonyl group of **1** might be replaced to the corresponding imine-type moiety or "imine"-containing heterocycle. Among many heterocycles involving "imine-type" functionality, we were particularly interested in the 1,3,4-oxadiazole heterocycle as a viable amide surrogate. We speculated that replacement of the amide moiety into a 1,3,4-oxadiazole ring could impart a favorable balance of potency and physicochemical properties to allow for further in vivo efficacy evaluation. We note that similar approaches have already been successfully demonstrated with imidazoles[19a,b] and tetrazoles.[20] Subsequently, we also discovered that the 1,3,4-oxadiazole[21,22] scaffold has also been employed for this purpose, although there are clear differences evident between the current work and these prior examples. Herein, we describe the design, synthesis, and biological evaluation of biarylpyrazolyl oxadiazole analogues as novel CB1 receptor antagonists. Through a process of lead optimization, we successfully identified 2-(4-((1*H*-1,2,4-triazol-1-yl)methyl)-5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazol-3-yl)-5-(1-(trifluoromethyl)cyclopropyl)-1,3,4-oxadiazole (**43c**) as a promising precandidate for development as an antiobesity agent.

Chemistry. The synthesis of the biarylpyrazolyl oxadiazole analogues commenced with the generic acid A.[23] Compounds of general structure **4** were prepared by (i) reacting a carboxylic acid A with a hydrazide compound B in the presence of coupling reagent, e.g., EDCI, DMAP, and (ii) cyclizing the resulting product C using a dehydrating agent (i.e., Burgess reagent)[24] to obtain a 1,3,4-oxadiazole **4**. Alternatively, the acylhydrazide intermediate C was also available through the coupling of the hydrazide **6** with a corresponding acid **7** mediated by coupling reagents such as DMAP, EDCI or EDCI, HOBt, and NMM. For this sequence, the requisite hydrazide **6** was prepared by treating the known ester **5** with hydrazine in refluxing EtOH as shown in Scheme 1.

Further functionalization was initiated with the activated 4-pyrazole intermediate **8**, which was prepared from **4h** via a benzylic bromination-type reaction[25] as illustrated in Scheme 2. The alcohol functionality of **10** was then introduced by treating bromide **8** with sodium acetate, followed by basic hydrolysis of the resulting acetate.

As shown in Scheme 3, alcohol **10** could be alkylated with an alkyl iodide or an alkyl bromide in the presence of sodium hydride (Williamson ether synthesis conditions) to furnish the corresponding ether **12**. Aternatively, alcohol **10** could be converted into the corresponding fluoride **13** through the use of a fluorinating agent such as diethylaminosulfur trifluoride (DAST).[26] In another variation, the Burgess reagent could be employed to transform alcohol **10** to the corresponding carbamate **14**.[27] Ultimately, however, oxidation of the alcohol **10** to aldehyde **11** was achieved through the use of Dess−Martin periodinane[28] as described in Scheme 2.

Aldehyde **11** (Scheme 2) proved to be a versatile intermediate. This compound could be treated with DAST to provide the corresponding difluoromethylpyrazole **15**. Alternatively, aldehyde **11** could be further oxidized to acid **16** by use of sodium chlorite and monobasic potassium phosphate in aqueous *t*-BuOH. Aldehyde **11** could also be treated with a Grignard reagent such as methylmagnesium bromide to afford the corresponding alcohol **17.** Analogous to the transformations depicted in Scheme 3, alcohol **17** was also transformed into ether **18**, fluoride **19**, and ketone **20**, respectively. Interestingly, treatment of **17** with Burgess reagent produced carbamate **22** along with olefin **21** as described in Scheme 4.

As shown in Scheme 5, ketone **20** could be further treated with a Grignard reagent to provide alcohol **23**, which was then treated with Burgess reagent to afford olefin **24**.

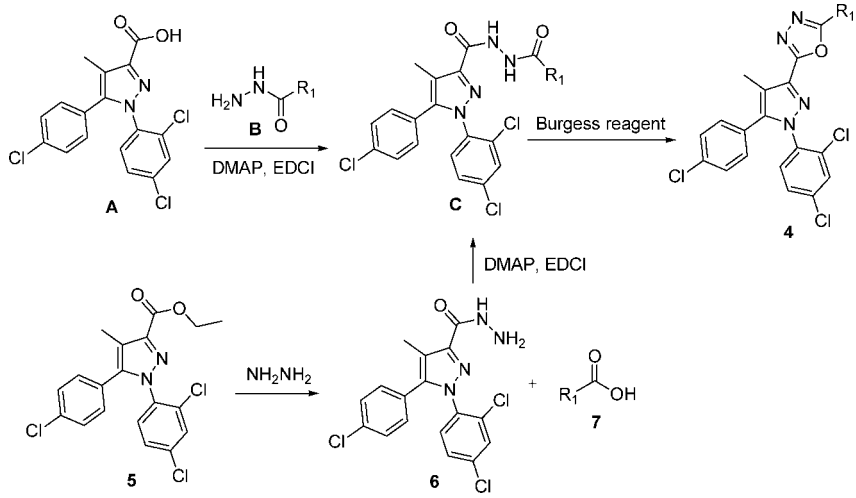
For SAR investigations, bromide **8** was key to the synthesis of substituted pyrazole derivatives as shown in Scheme 6. Thus, acetate **9**, thioacetate **25**, cyanide **26**, aryl ether **27**, various secondary or tertiary amine **28**, pyrrolidin-2-one **29**, succinimide **30**, and 2-oxazolidinone **31** could all be smoothly prepared.

Additionally, bromide **8** could be reacted with pyrrole and various azoles including pyrazole, imidazole, 1,2,4-triazole, 1,2,3-triazole, and tetrazole in the presence of a base to provide substituted pyrazole derivatives **32a**−**g** as shown in Scheme 7.

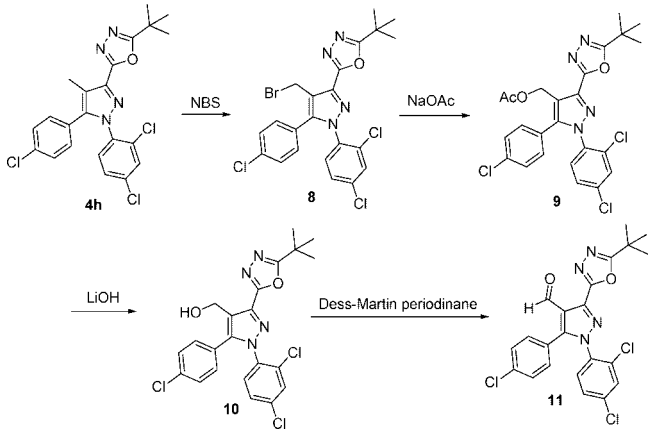
The compounds containing 1,2,4-triazole could also be obtained by a reaction sequence involving key intermediate bromide **33**. Thus, bromide **33**, obtained by reaction of pyrazole **5** with NBS in the presence of catalytic AIBN, was reacted with 1,2,4-triazole in the presence of cesium carbonate to provide **34**. Hydrolysis of ester **34**, activation of acid **35**, followed by coupling with a hydrazide in the presence of triethylamine, then afforded acylhydrazide **36**. Alternatively, hydrazynolysis of ester **34** produced the corresponding hydrazide, which could then be coupled with an acid to give acylhydrazide **36**. Cyclization was then performed using the Burgess reagent under microwave irradiation to give oxadiazole **32d** as illustrated in Scheme 8.

The 4-cyclopropyl pyrazole compound **41** was prepared as shown in Scheme 9. In the event, 4-bromo-pyrazole of structure **38**, prepared by following a generic procedure,[41] was coupled

Scheme 1



Scheme 2



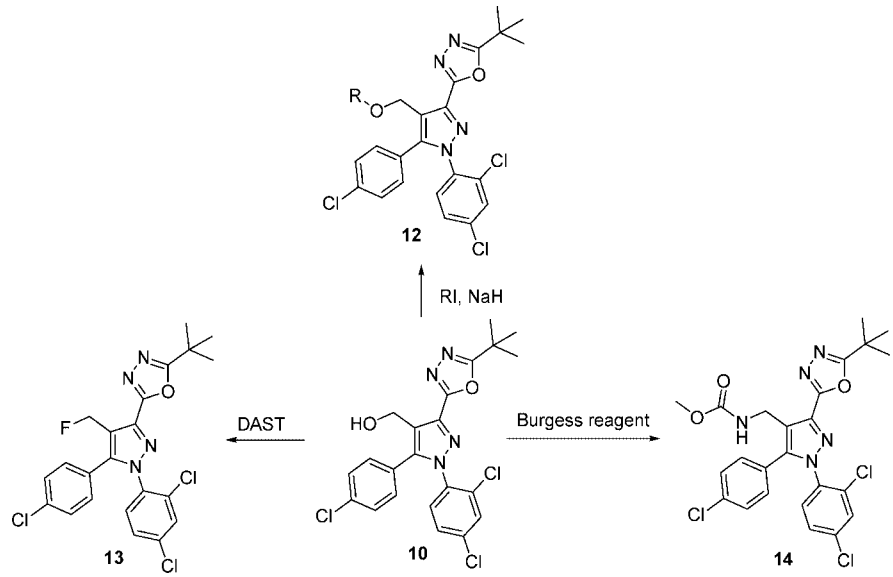
with a cyclopropylboronic acid under Suzuki−Miyaura coupling reaction conditions[29] to afford a 4-cyclopyrazole **39**. The ester **39** then underwent a series of reactions as previously described to generate oxadiazole **41**.

Results and Discussion

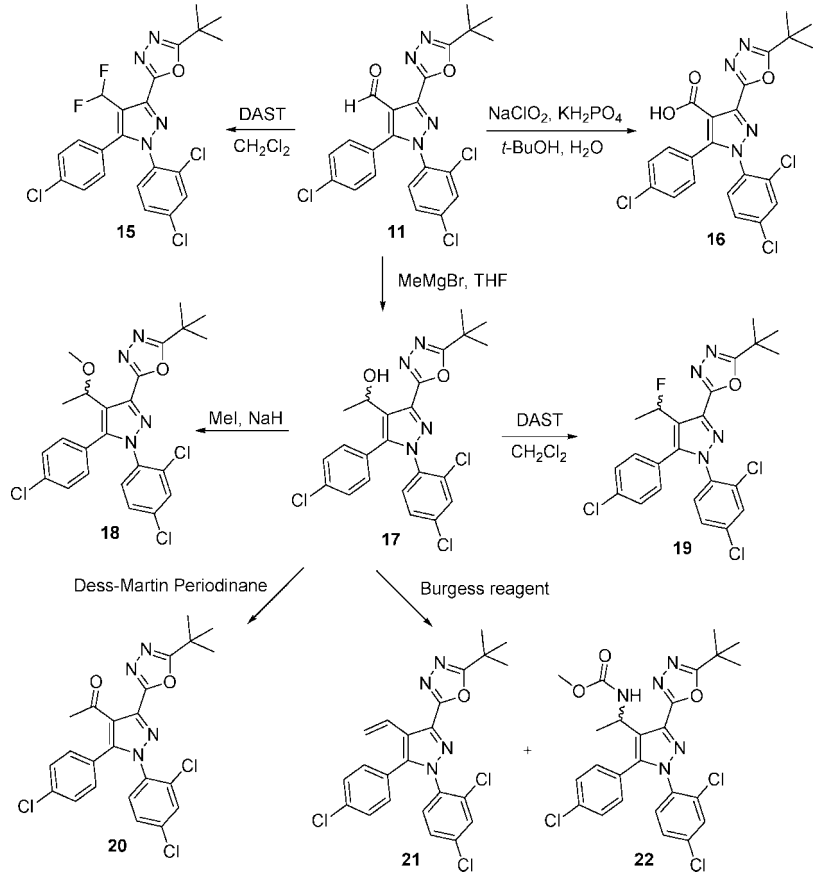
The target analogues were evaluated in vitro at a rat CB1 binding assay,[30] and the results are shown in Table 1. The results demonstrate that as the size of the carbon chain is increased, an increase in binding affinity is observed up to the C-4 or C-5 chain. Branched aliphatic chains are usually more potent than the corresponding counterparts as shown in entries 1 vs 5, or entries 4 vs 6. For cyclic analogues, the size of the carbocycle appears to affect binding affinity. Thus, four-or six-membered rings (entries 12 and 13) are slightly more potent than the corresponding seven-membered carbocycle (entry 14), suggesting that there might be a size requirement for the oxadiazole alkyl region to bind with high affinity to the CB1 receptor. As shown in oxadiazole **4k**, the (trifluoromethyl)cyclopropyl moiety appears to augment CB1 binding affinity, indicating that the fluorine substituents might be involved in a hydrogen bond interaction with the receptor that fosters high affinity. A aryl moiety (entry 16) does not appear to be tolerated because **4p** shows dramatic decrease in binding affinity to $IC_{50} = 281$ nM. In contrast, a benzyl substituent (entry 17) improved binding affinity approximately 15-fold. Importantly, addition of methyl groups alpha to the oxadiazole ring improved CB1 binding affinity, showing an approximately 2-fold increase in CB1 binding affinity of **4r** ($IC_{50} = 10.9$ nM) and **4s** ($IC_{50} = 8.42$ nM). Cyclization of the *gem*-dimethyl group at the benzylic position to generate a cyclopropane is also tolerated without detriment to in vitro CB1 binding affinity (entry 20). Chlorine substitution on the phenyl ring also maintained similar levels of CB1 receptor binding affinity, indicating that a halogen atom appears to be well tolerated at this position. The same is true for (4-chlorophenyl)cyclopropyl **4v**, which displays virtually identical binding affinity ($IC_{50} = 8.61$ nM), suggesting the importance of a nonpolar moiety in order to optimally bind to a hydrophobic area of the CB1 receptor. Furan and thiophene groups showed only modest CB1 receptor binding affinity, indicating that biaryls at this domain decrease binding affinity compared with aliphatic chains or carbocycles at this domain. Neither pyridine (entry 25) nor pyrazine (entry 26) improve CB1 binding affinity, although an interesting exception to this observation is pyridin-2-ylmethyl oxadiazole **4aa** (entry 27). Insertion of a methylene unit at the pyridine ring resulted in a dramatic improvement in binding affinity, and this compound almost regains the potency of benzyl oxadiazole **4q**.

It was encouraging to note that considerable CB1 receptor binding affinity was already evident in lead compound **4h**.[38] At this juncture, we proceeded to explore C-4 region of pyrazole core by using *t*-butyl oxadiazole as a lead scaffold.[39] The binding affinity data of selected key biarylpyrazolyl oxadiazoles for the CB1 receptor is shown in Table 2. Homologation of the methyl substituent to give **4ha** resulted in a slight improvement in binding potency as compared to **4h**. However, as the size of carbon chain is increased, binding affinity decreases 3- to 5-fold (see Table 2: **4hb**, **4hc**, and **41**). Surprisingly, various functional groups such as hydroxyl (**10**, **17**, and **23**), fluoro (**13**, **15**, and **19**), vinyl groups (**21**, **24**), carbamate (**14**, **22**), ether (**12**, **27**), acetate **9**, ethanethiolate **25**, and nitrile **26** appeared to be tolerated. Thus, the methyl group of the pyrazole ring can be extensively modified. However, substitution with amines (**28**) as well as 2-pyrrolidinone **29**, succinimide **30**, and 2-oxazolidinone **31** resulted in decreased potency relative to the simple methyl **4h** or ethyl group **4ha**. Moreover, carboxylic acid **16** demonstrated a complete loss of activity, implying that acidic functionality in the region is not tolerated. Additionally, substitution with pyrrole **32a**, pyrazole **32b**, and imidazole **32c** could be performed. These analogues showed moderate CB1 binding affinity, but none improved potency relative to the simple methyl group analogue **4h**. Five-membered ring hetero-

Scheme 3



Scheme 4

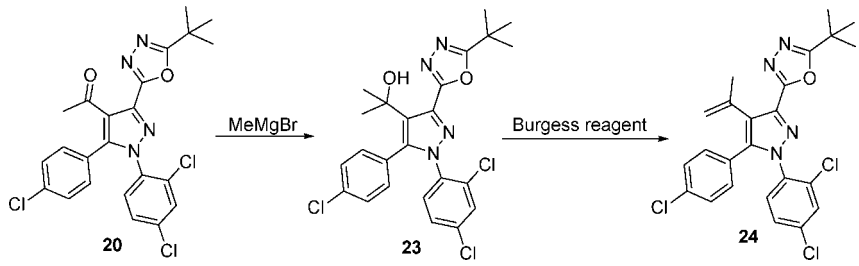


cycles with three or more heteroatoms proved to be more potent CB1 receptor ligands as shown in Table 2 (entries 37−40). Among the tested compounds in Table 2, 1,2,4-triazole **32d** demonstrated the superior CB1 receptor binding affinity (IC_{50} = 2.36 nM), implying that one of nitrogen in triazole ring might be involved in hydrogen bond formation with the backbone of the receptor, thereby promoting higher affinity.[31]

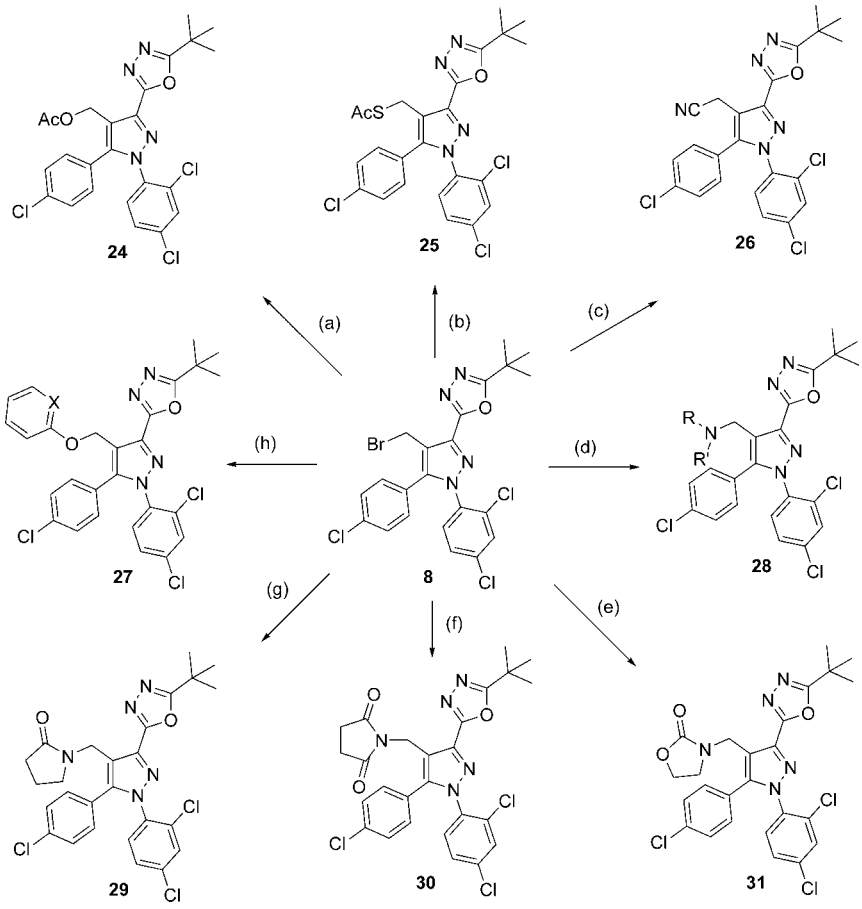
Binding affinity was also measured for the CB2 receptor expressed in CHO cells, employing [**3H**]**44** ([^{3}H]WIN55,212-2, [^{3}H] (*R*)-(+)-[2,3-dihydro-5-methyl-3-(4-morpholinylmethyl)pyrrolo[1,2,3-*de*)-1,4-benzoxazin-6-yl]-1-napthalenylmethanone])[32] as a radio ligand. Virtually all of our pyrazole-based compounds were devoid of activity in this CB2 binding assay, indicating high selectivity for CB1 over CB2 for these analogues. Selected examples of the above analogues are summarized in Table 2.

Because the addition of a hydrophilic 1,2,4-triazole substituent resulted in increased CB1 receptor binding affinity in the biarylpyrazolyl oxadiazole series, 1,2,4-triazole substituted derivatives of **32d** were prepared and tested (Table 3). A

Scheme 5



Scheme 6[a]

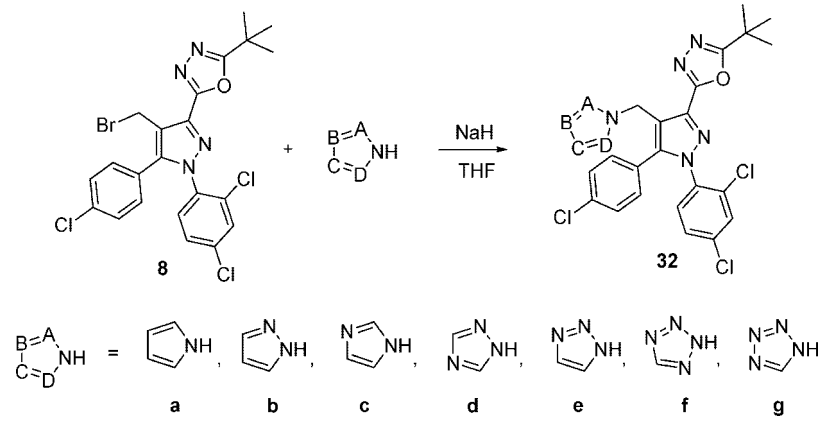


[a] Reagents: (a) NaOAc; (b) KSAc, DMF, rt; (c) NaCN, DMF; (d) RR′NH, DIPEA, CH_2Cl_2; (e) 2-oxazolidinone, K_2CO_3, DMF; (f) succimide, K_2CO_3, DMF; (g) 2-pyrrolidinone, K_2CO_3, DMF; (h) phenol or 2-hydroxypyridine, Cs_2CO_3.

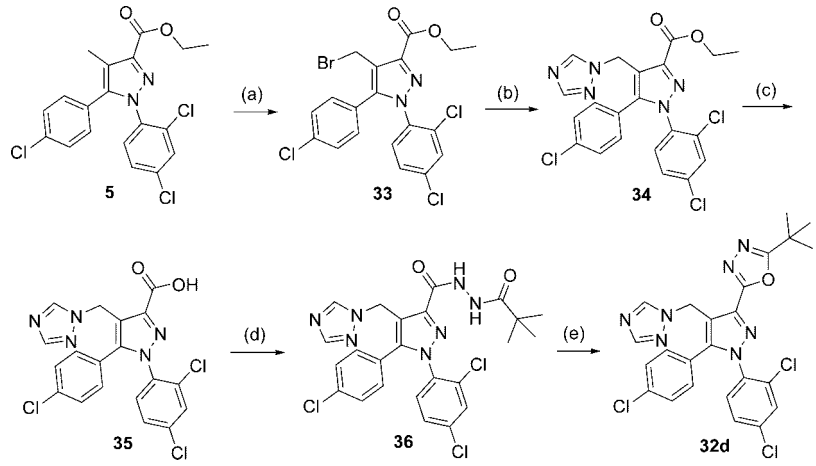
methylcyclopropyl substituent (**42b)** was selected for the direct comparison with *t*-butyl-oxadiazole **32d**. Indeed, **42b** showed the similar levels of CB1 receptor binding affinity, indicating that the cyclopropyl group is interchangeable with the corresponding *gem*-dimethyl group and possibly acts as a *gem*-dimethyl surrogate.[40] Next, trifluoromethylcyclopropyl **42c**, which should confer lower lipophilicity and possibly enhanced water solubility, was selected for bioassay. As shown for oxadiazole **4k** (Table 1), the (trifluoromethyl)cyclopropyl group appears to augment CB1 receptor binding affinity. To our delight, compounds with the (trifluoromethyl)cyclopropyl group also showed more than 1000-fold CB2/CB1 receptor selectivity as demonstrated by **42c** and **43c** in Table 3. In addition, *p*-tolylcyclopropyl oxadiazole **42e** displayed outstanding binding affinity, implying that increased lipophilicity can improve in vitro activity. When chlorine (entries 3−8) was exchanged for bromine (entries 9−14) as shown in Table 3, several compounds reached subnanomolar CB1 receptor binding affinity. Of note is that 4-bromophenylcyclopropyl oxadiazole **43f** was shown to be the most potent in vitro CB1 biarylpyrazolyl oxadiazole receptor ligand (IC_{50} = 0.57 nM) prepared to date. Compound **43f** also showed the highest CB2/CB1 receptor selectivity (∼1842) as demonstrated in Table 3. Some selected promising compounds have been tested on animal models for in vivo efficacy.

In vivo efficacy was evaluated on DIO mice.[37] Male C57BL/6J mice weighing over 38 g were housed 1 per cage on a 12 h/12 h light/dark cycle, had free access to food (rodent sterilized diet), and water and were experimentally native before testing. Mice were allowed at least 7 days to habituate to the experimental room prior to testing, and testing was conducted during the light period. Mice were maintained and experiments were conducted in accordance with Institutional Animal Care. The reference (**1**) and the inventive compounds of compounds **42c** and **43c** were prepared fresh daily by dissolving them in deionized water containing 10%

Scheme 7

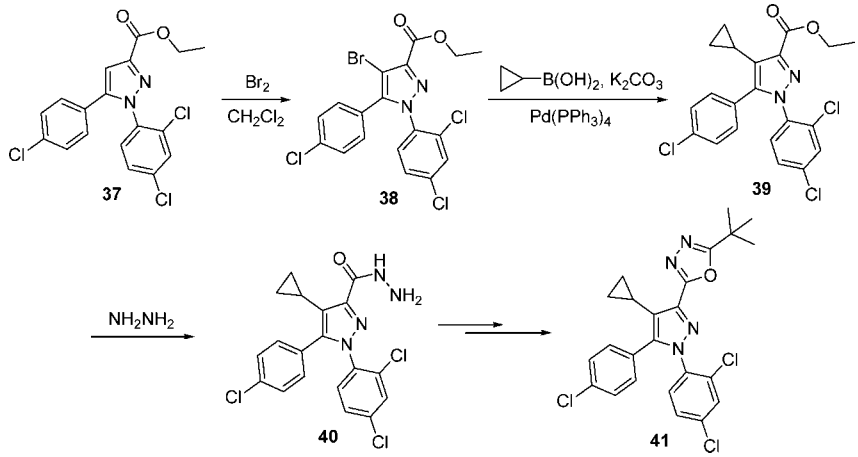


Scheme 8[a]



[a] Reagents: (a) NBS, AIBN, CCl_4; (b) 1,2,4-triazole, Cs_2CO_3, DMF; (c) LiOH, THF-H_2O; (d) (i) $(COCl)_2$, (ii) NH_2NH (CO)*t*-Bu, Et_3N, CH2Cl2; (e) Burgess reagent, THF, reflux or microwave.

Scheme 9

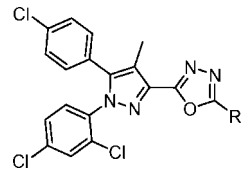


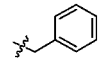
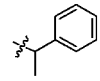
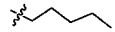
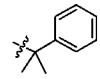
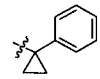
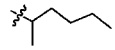
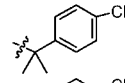
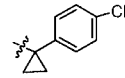
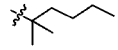
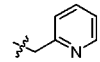
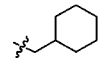
DMSO. By oral administration, animals received at a volume of 10 mL/kg for 14 days. All control animals received 10% DMSO dissolved in deionized water. The vehicles 10% DMSO-treated groups comprised five mice in oral test. There were six mice in each of the other experimental groups (n = 6 in each group). By oral administration, the losing weight was checked every day for the drug treated group and the control group.

Figure 3 shows chronic effects of compounds **4k**, **42c**, **43c**, and **1** in DIO mice. Body weight change from day 0 was observed on all days at 10 mg/kg of example **4k** compound, at 10 mg/kg of example **42c** compound, at 10 mg/kg of example **43c** compound, and at 10 mg/kg of **1**. Each value is the mean ± SEM of 5 mice. $*P < 0.05$, $**P < 0.01$ vs corresponding vehicle (ANOVA with Dunnett's test).

Figure 3 shows that compounds **42c** and **43c** are substantially more efficacious than **1** in in vivo efficacy study on the DIO mice model (29.5 ± 1.9% and 29.3 ± 0.5% reduction in body weight after 14 days, respectively), while **4k** reduces body weight moderately (22.8 ± 2.4%). Substitution of methyl with

Table 1. Structures and Binding Affinities of Selected Ligands for Rat CB1 Receptors[a]



entry	R	compound	rCB1 IC_{50}	entry	R	compound	rCB1 IC_{50}
1		**4a**	160	16		**4p**	281
2		**4b**	25	17		**4q**	19.2
3		**4c**	35	18		**4r**	10.9
4		**4d**	71.8	19		**4s**	8.42
5		**4e**	10.4	20		**4t**	11.0
6		**4f**	15.1	21		**4u**	4.78
7		**4g**	31.7	22		**4v**	8.61
8		**4h**	7.59	23		**4w**	112
9		**4i**	10.4	24		**4x**	96.6
10		**4j**	14.7	25		**4y**	563
11		**4k**	8.53	26		**4z**	196
12		**4l**	13.1	27		**4aa**	51.9
13		**4m**	12				
14		**4n**	26.5				
15		**4o**	22.7				

[a] rCB1 receptor was collected from brain tissue of SD rat. These data were obtained by single determinations. **1** is estimated to have CB1 binding affinity (IC_{50} = 5.0 nm) via in-house assay. Units: nM.

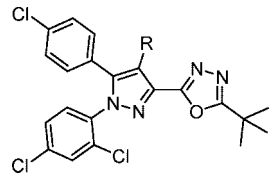
triazolylmethyl group on C-4 pyrazole ring improved in vitro binding affinity, in turn leading to excellent in vivo efficacy on DIO mouse model.[33]

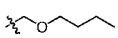
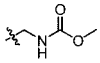
The identity of compound **43c** was further secured through single-crystal X-ray analysis, as demonstrated in Figure 4. Crystallographic data (excluding structure factors) for the structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC694371.

To explain the potent, selective CB1 binding affinity of **43c**, we built a docking model of CB1:**43c** complex using our homology model of the inactive state of human CB1. We initially constructed a **1**-CB1 binding model by taking into account the interactions between **1** and the active site of CB1 obtained from the published molecular modelings and mutagenesis studies.[34] Compound **43c** was docked into CB1 by defining the bound **1** as a reference. As demonstrated in Figure 5 and 6, **43c** is well superimposed over the docked pose of **1** occupying hydrophobic pocket of CB1. All the substituents attached to the central pyrazole ring of **43c** form various interactions with amino acid residues in the active site, facilitating the ligand bind deeper into binding pockets.

Two aryl groups of **43c**, commonly existent in CB1 antagonists analogous to **1**, are in close contacts with aromatic amino acid residues (Phe 200, Tyr 275, Trp 279, and Trp 356), forming π-stacking and hydrophobic interactions. In accord with the results of published modeling studies, Lys 192 is involved in a salt bridge with Asp 366, stabilizing the inactive state of hCB1.[16c,34c] In the case of **1**, the carboxamide oxygen formed a hydrogen bond (H-bond) with Lys 192, which should be responsible for the high affinity to the inactive state of receptor. In our model, the 1,3,4-oxadiazole ring of **43c**, a bioisostere of amide, forms a bidentate H-bond with Lys 192, and this may contribute to increase the binding selectivity toward the active site. The fluorine atom of trifluoromethyl group of **43c** plays a role in H-bond acceptor and is involved in H-bond with OH of Ser 383. The significance of the interaction with Ser 383 was revealed in previous combined mutagenesis and modeling studies on **3**.[16c] It is noticeable that the ((trifluoromethyl)cyclopropyl) oxadiazole substituent in **43c** can form H-bonds observed in the binding model of both **1** and **3**. In addition, the

Table 2. Structures and Binding Affinities of Selected Ligands to Rat CB1 and Human CB2 Receptors, and CB2/CB1 Selectivity of the Ligands[a]



entry	R	compound	receptor affinity (IC_{50}, nM)		CB2/CB1 selectivity	entry	R	compound	receptor affinity (IC_{50}, nM)		CB2/CB1 selectivity
			rCB1	hCB2					rCB1	hCB2	
1	Me	**4h**	7.59	1410	186	22		**9**	22.4	1300	58
2	Et	**4ha**	6.57	2330	355	23		**25**	20.7	1480	71
3	*n*-Pr	**4hb**	33.5	>10000	> 299	24		**26**	6.12	539	88
4	*i*-Pr	**4hc**	18.0	2820	157	25		**27a**	28.9	5910	204
5		**41**	30.3	3320	110	26		**27b**	24.4	2040	84
6		**10**	14.6	1810	124						
7		**12a**	113	-	-	27		**28a**	45.7	-	-
8		**12b**	15.4	375	24	28		**28b**	227	-	-
9		**13**	14.7	1120	76	29		**28c**	135	-	-
10		**14**	15.6	1670	107	30		**28d**	41.5	-	-
11		**11**	36.2	-	-	31		**29**	93.9	-	-
12		**15**	36.1	-	-	32		**30**	287	-	-
13		**16**	>10uM	-	-	33		**31**	125	-	-
14		**17**	10.1	1890	187	34		**32a**	38.4	-	-
15		**18**	62.7	-	-	35		**32b**	20.5	979	48
16		**19**	14.1	924	66	36		**32c**	18.7	376	20
17		**20**	49.4	-	-	37		**32d**	2.36	804	341
18		**21**	16.9	1050	62	38		**32e**	12.8	1120	88
19		**22**	9.0	>10000	> 1111	39		**32f**	3.37	680	202
20		**23**	22.6	1670	74	40		**32g**	7.64	736	96
21		**24**	4.83	1730	358						

[a] These data were obtained by single determinations. **1** is estimated to have CB1 binding affinity (IC_{50} = 5.0 nM) via in-house assay.

N2 of triazole substituent forms a bidentate H-bond with side chain OH and backbone NH of Thr 197, which is an exclusive interaction observed in the binding model of **43c**.

Significantly, the binding mode of **43c** generated by docking analysis conclusively reveals that the structure of the ligand binds with high potency to hCB1 by forming additional interactions than **1** and **3** and provides further insight into the design of more potent and selective hCB1 antagonists.

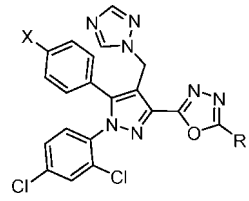
Conclusion

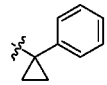
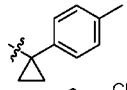
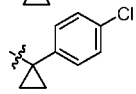
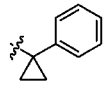
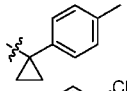
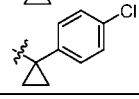
In the present study, we investigated a series of biarylpyrazolyl oxadiazole derivatives as antagonists to the cannabinoid CB1 and CB2 receptors. Several of the compounds in this series exceeded the potency of known CB1 antagonists, validating the hypothesis that a 1,3,4-oxadiazole could act as a bioisostere of the amide moiety in **1**. A subsequently conducted modeling study also suggested that the 1,3,4-oxadiazole ring participates in a bidentate H-bond interaction with Lys 192. This interaction is predicted to be stronger than the analogous monodentate H-bond interaction formed by the amide carbonyl oxygen of **1** that is hydrogen-bonded to Lys 192. In addition, we have demonstrated that incorporation of a 1,2,4-triazole ring onto the pyrazole scaffold via a methylene linker leads to a potent CB1 receptor antagonist with a significant antiobesity effect in the animal model. Importantly, these analogues also display good selectivity for CB1R over CB2R. Thus, the biarylpyrazolyl oxadiazole class of compounds bearing a methyl-triazole as the optimal side chain possesses a promising therapeutic potential as a CB1 receptor antagonist for the treatment of obesity.

Experimental Section

All references to ether are to diethyl ether; brine refers to a saturated aqueous solution of NaCl. Unless otherwise indicated,

Table 3. Structures and Binding Affinities of Selected Ligands to Rat CB1 and human CB2 Receptors and CB2/CB1 Selectivity of the Ligands[a]



entry	X	R	compound	receptor affinity (IC_{50}, nM)		CB2/CB1 selectivity
				rCB1	hCB2	
1			**1**	4.53	1760	389
2			**3**	0.86	1170	1360
3	Cl	t-Bu	**32d**	2.36	804	341
4	Cl		**42b**	1.98	954	482
5	Cl		**42c**	1.51	1750	1159
6	Cl		**42d**	insoluble	1130	-
7	Cl		**42e**	1.09	1240	1138
8	Cl		**42f**	2.21	1480	670
9	Br	t-Bu	**43a**	2.75	513	187
10	Br		**43b**	2.81	407	145
11	Br		**43c**	0.93	948	1019
12	Br		**43d**	0.96	242	252
13	Br		**43e**	1.34	579	432
14	Br		**43f**	0.57	1050	1842

[a] These data were obtained by single determinations. **1** and **3** were estimated to have CB1 binding affinity via in-house assay.

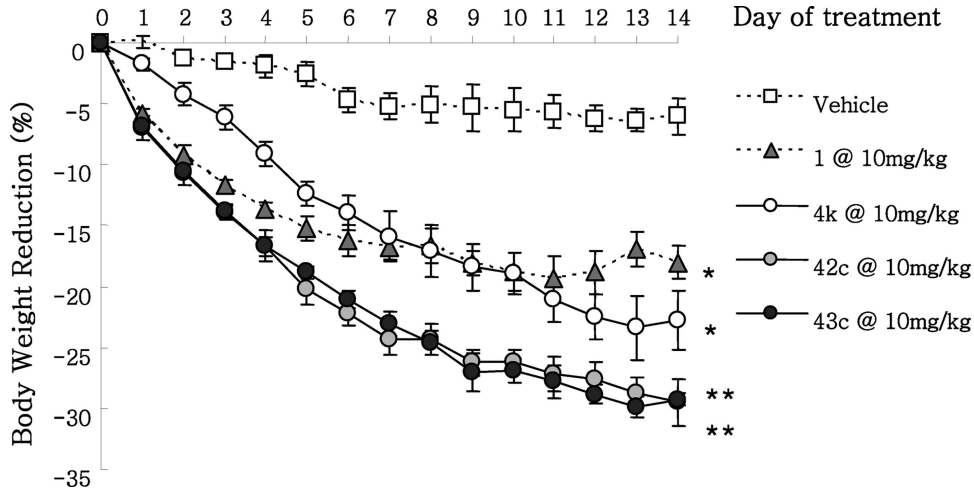


Figure 3. In vivo efficacy study of compounds **4k**, **42c**, **43c** and **1** in DIO mouse.

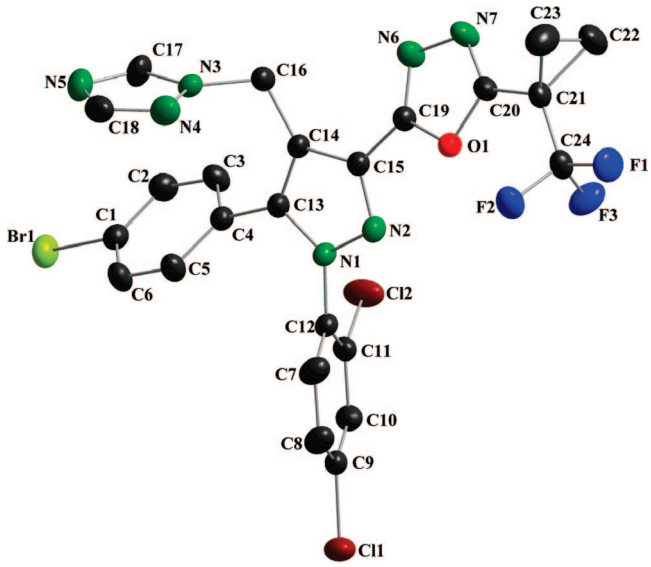


Figure 4. X-ray structure of compound **43c**.

all temperatures are expressed in °C (degrees centigrade). All reactions are conducted under an inert atmosphere at room temperature unless otherwise noted, and all solvents are of the highest available purity unless otherwise indicated. Microwave reaction was conducted with a Biotage microwave reactor. ^{1}H NMR spectra were recorded on either a Jeol ECX-400 or a Jeol JNM-LA300 spectrometer. Chemical shifts were expressed in parts per million (ppm, δ units). Coupling constants are in units of hertz (Hz). Splitting patterns describe apparent multiplicities and are designated as s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet), br (broad). Mass spectra were obtained with either a Micromass, Quattro LC triple quadruple tandem mass spectometer ESI or Agilent 1200LC/MSD ESI, and high resolution mass spectra were determined by Jeol, JMS-700 Mstation. For preparative HPLC, ca. 100 mg of a product was injected in 1 mL of DMSO onto a SunFire Prep C18 OBD 5 μm 19 mm × 100 mm column with a 10 min gradient from 10% CH_3CN to 90% CH_3CN in a H_2O Biotage SP1 Flash purification system was used for normal phase column chromatography with ethyl acetate and hexane. Flash chromatography was carried using Merck silica gel 60 (230−400 mesh). Most of the reactions were monitored by thin-layer chromatography on 0.25 mm E. Merck silica gel plates (60F-254), visualized with UV light using a 5% ethanolic phosphomolybdic acid or *p*-anisaldehyde solution.

***N*-Butanoyl-*N*′-[5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carbonyl]-hydrazine (C).** Added to a solution of 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)- 4-methyl-1*H*-pyrazole-3-carboxylic acid (**A**) (0.40 g, 1.05 mmol), *N*-butanoyl-hydrazine (**B**) (0.11 g, 1.05 mmol), and EDCI (0.24 g, 1.26 mmol) dissolved in DCM (11 mL) was DMAP (0.15 g, 1.26 mmol) in one portion at room temperature. The reaction mixture was stirred at room temperature for 6 h and then treated with 10% aq HCl. The organic layer was collected and evaporated under a vacuum. The crude mixture was further purified by preparative HPLC to obtain 0.38 g (0.81 mmol, 77%) of the title compound as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (br s, 1H), 7.31−7.27 (m, 4H), 7.08−7.03 (m, 2H), 2.33 (s, 3H), 2.31 (t, J = 7.8 Hz, 2H), 1.72 (m, 2H), 0.97 (t, J = 7.3 Hz, 3H). MH+ 463.

2-(5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazol-3-yl)-5-propyl-1,3,4-oxadiazole (4a). *N*-Butanoyl-*N*′-[5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carbonyl]-hydrazine (**C**) (0.35 g, 0.75 mmol) was added to a microwave reactor containing Burgess reagent (0.45 g, 1.88 mmol) in THF (2 mL). The capped reactor was placed in a microwave reactor, and the mixture was irradiated at 140 °C for 15 min. The reaction product was purified by preparative HPLC to provide the title compound (0.21 g, 0.46 mmol, 61%) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 2.3 Hz, 1H), 7.34−7.28 (m, 4H), 7.09−7.13 (m, 2H), 2.90 (t, J = 7.6 Hz, 2H), 2.45 (s, 3H), 1.88 (m, 2H), 1.03 (t, J = 7.6 Hz, 3H). MH+ 447.

2-(5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazol-3-yl)-5-isopropyl-1,3,4-oxadiazole (4b). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 2.28 Hz, 1H), 7.38−7.29 (m, 4H), 7.13−7.09 (m, 2H), 3.28 (m, 1H), 2.44 (s, 3H), 1.46 (d, J = 6.88 Hz, 6H). MH+ 447.

2-Butyl-5-(5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazol-3-yl)-1,3,4-oxadiazole (4c). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J = 1.84 Hz, 1H), 7.37−7.29 (m, 4H), 7.12 (dt, J = 2.28, 8.24 Hz, 2H), 2.94 (t, J = 7.56 Hz, 2H), 2.46 (s, 3H), 1.85 (m, 2H), 1.45 (m, 2H), 0.96 (t, J = 7.36 Hz, 3H). MH+ 461.

2-(5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazol-3-yl)-5-pentyl-1,3,4-oxadiazole (4d). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.42 (m, 1H), 7.37−7.30 (m, 4H), 7.13−7.10 (m, 2H), 2.93 (t, J = 7.8 Hz, 2H), 2.46 (s, 3H), 1.90−1.83 (m, 2H), 1.45−1.32 (m, 4H), 0.91 (t, J = 7.3 Hz, 3H). MH+ 475.

2-*sec*-Butyl-5-(5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazol-3-yl)-1,3,4-oxadiazole (4e). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.41 (m, 1H), 7.36 (d, J = 8.2 Hz, 1H), 7.34−7.30 (m, 3H), 7.13−7.09 (m, 2H), 3.16−3.07 (m, 1H), 2.45 (s, 3H), 2.00−1.89 (m, 1H), 1.80−1.70 (m, 1H), 1.43 (d, J = 6.9 Hz, 3H), 0.97 (t, J = 7.4 Hz, 3H). MH+ 461.

2-(5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazol-3-yl)-5-(hexan-2-yl)-1,3,4-oxadiazole (4f). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.41 (m, 1H), 7.38−7.30 (m, 4H), 7.13−7.09 (m, 2H), 3.22−3.13 (m, 1H), 2.45 (s, 3H), 1.95−1.89 (m, 1H), 1.73−1.64 (m, 1H), 1.42 (d, J = 6.9 Hz, 3H), 1.38−1.25 (m, 4H), 0.91−1.87 (m, 3H). MH+ 489.

2-(5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazol-3-yl)-5-(pentan-3-yl)-1,3,4-oxadiazole (4g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 2.28 Hz, 1H), 7.38−7.30 (m, 4H), 7.13−7.10 (m, 2H), 2.96 (m, 1H), 2.46 (s, 3H), 1.93−1.79 (m, 2H), 0.94 (t, J = 7.32 Hz, 3H). MH+ 475.

2-*tert*-Butyl-5-(5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazol-3-yl)-1,3,4-oxadiazole (4h). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.41 (m, 1H), 7.38 (d, J = 8.2 Hz, 1H), 7.34−7.30 (m, 3H), 7.12−7.09 (m, 2H), 2.45 (s, 3H), 1.52 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 160.3, 143.2, 138.6, 136.4, 136.1, 135.3, 133.3, 131.1, 131.0, 130.5, 129.2, 128.2, 127.2, 117.4, 32.7, 28.5, 10.0. MH+ 461.

2-*tert*-Butyl-5-(5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-ethyl-1*H*-pyrazol-3-yl)-1,3,4-oxadiazole (4ha). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42−7.40 (m, 1H), 7.37−7.28 (m, 4H), 7.15−7.11 (m, 2H), 2.89−2.82 (m, 2H), 1.50 (s, 9H), 1.23 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 160.1, 143.1, 138.0, 136.4, 136.0, 135.5, 133.4, 131.1, 131.0, 130.5, 129.2, 128.1, 127.3, 124.0, 32.7, 28.5, 17.4, 15.5. MH+ 475.

2-*tert*-Butyl-5-(5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-propyl-1*H*-pyrazol-3-yl)-1,3,4-oxadiazole (4hb). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J = 2.4 Hz, 1H), 7.37−7.27 (m, 4H), 7.11 (d, J = 8.4 Hz, 2H), 2.81−2.77 (m, 2H), 1.66−1.57 (m, 2H), 1.49 (s, 9H), 0.88 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 160.2, 143.3, 138.2, 136.3, 136.0, 135.4, 133.4, 131.2, 131.0, 130.4, 129.2, 128.1, 127.4, 122.5, 32.7, 28.5, 25.9, 24.1, 14.3. MH+ 489.

2-*tert*-Butyl-5-(5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-isopropyl-1*H*-pyrazol-3-yl)-1,3,4-oxadiazole (4hc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, J = 2.0 Hz, 1H), 7.31−7.24 (m, 4H), 7.14 (d, J = 8.8 Hz, 2H), 3.48−3.43 (m, 1H), 1.49 (s, 9H), 1.26 (d, J = 7.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 160.3, 142.6, 137.2, 136.4, 135.8, 135.6, 133.6, 131.9, 131.1, 130.4, 128.9, 128.2, 128.0, 127.9, 32.7, 28.5, 24.9, 22.6. MH+ 489.

2-(5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazol-3-yl)-5-*tert*-pentyl-1,3,4-oxadiazole (4i). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.31 (m, 5H), 7.12−7.10 (m, 2H), 2.44 (s, 3H), 1.83 (q, J = 7.6 Hz, 2H), 1.47 (s, 6H), 0.87 (t, J = 7.6 Hz, 3H). MH+ 475.

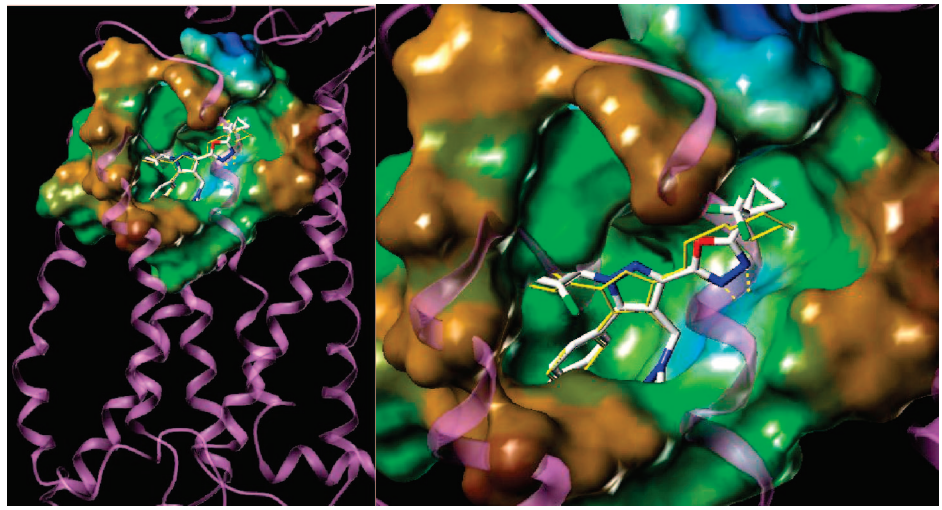


Figure 5. Docked pose of **43c** in the hCB1 homology model, in comparison with that of **1** (yellow). Solvent-accessible protein surfaces are colored by lipophilicity potential. Lipophilicity increases from blue (hydrophilic) to brown (lipophilic).

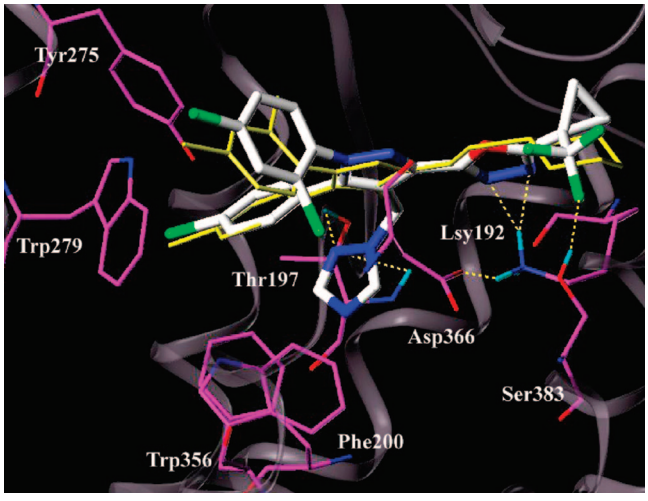


Figure 6. Binding pose of **43c** in the active site cavity of hCB1 overlaid over **1** (yellow). Key amino acid residues within the binding site are rendered in line form (magenta). Yellow dotted lines are hydrogen bonding interactions (<2.5 Å).

2-(5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazol-3-yl)-5-(2-methylhexan-2-yl)-1,3,4-oxadiazole (4j). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.38 (m, 2H), 7.34−7.30 (m, 3H), 7.15−7.09 (m, 2H), 2.44 (s, 3H), 1.78 (m, 2H), 1.47 (s, 6H), 1.25 (m, 4H), 0.87 (t, J = 7.0 Hz, 3H). MH+ 503.

2-(5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazol-3-yl)-5-(1-(trifluoromethyl)cyclopropyl)-1,3,4-oxadiazole (4k). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (br d, J = 2.0 Hz, 1H), 7.38−7.30 (m, 4H), 7.10 (m, 2H), 2.42 (s, 3H), 1.63 (m, 2H), 1.61 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6, 161.1, 143.4, 137.9, 136.5, 136.0, 135.5, 133.2, 131.0, 130.9, 130.5, 129.2, 128.2, 127.0, 124.5 (d, J = 272 Hz), 117.6, 21.2 (q, J = 37 Hz), 12.4, 9.9. MH+ 513.

2-(5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazol-3-yl)-5-cyclobutyl-1,3,4-oxadiazole (4l). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J = 2.3 Hz, 1H), 7.34−7.28 (m, 4H), 7.13−7.09 (m, 2H), 4.01 (m, 1H), 2.62−2.52 (m, 2H), 2.49 (s, 3H), 2.47−2.39 (m, 2H), 2.20−2.00 (m, 2H). MH+ 459.

2-(5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazol-3-yl)-5-cyclohexyl-1,3,4-oxadiazole (4m). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 1.84 Hz, 1H), 7.37−7.29 (m, 4H), 7.11 (dt, J = 2.28, 8.24 Hz, 2H), 3.00 (m, 1H), 2.44 (s, 3H), 2.16−2.12 (m, 2H), 1.87−1.81 (m, 2H), 1.78−1.65 (m, 3H), 1.44−1.28 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 160.0, 143.2, 138.6, 136.4, 136.1, 135.3, 133.3, 131.0, 130.9, 130.5, 129.1, 128.1, 127.1, 117.3, 35.4, 30.4, 25.8, 25.6, 10.0. MH+ 487.

2-(5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazol-3-yl)-5-cycloheptyl-1,3,4-oxadiazole (4n). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.41 (m, 1H), 7.37−7.29 (m, 4H), 7.13−7.10 (m, 2H), 3.23−3.16 (m, 1H), 2.45 (s, 3H), 2.21−2.14 (m, 4H), 1.98−1.89 (m, 2H), 1.85−1.79 (m, 2H), 1.68−1.53 (m, 4H). MH+ 501.

2-(5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazol-3-yl)-5-(cyclohexylmethyl)-1,3,4-oxadiazole (4o). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.42 (m, 1H), 7.37−7.29 (m, 4H), 7.13−7.10 (m, 2H), 2.82 (d, J = 7.3 Hz, 2H), 2.46 (s, 3H), 1.98−1.87 (m, 1H), 1.79−1.63 (m, 4H), 1.31−1.03 (m, 6H). MH+ 501.

2-(5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazol-3-yl)-5-phenyl-1,3,4-oxadiazole (4p). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22−8.18 (m, 2H), 7.57−7.49 (m, 3H), 7.45−7.44 (m, 1H), 7.41−7.32 (m, 4H), 7.16−7.12 (m, 2H), 2.51 (s, 3H). MH+ 483.

2-Benzyl-5-(5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazol-3-yl)-1,3,4-oxadiazole (4q). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 1.84 Hz, 1H), 7.38−7.27 (m, 9H), 7.12−7.08 (m, 2H), 4.29 (s, 2H), 2.43 (s, 3H). MH+ 495.

2-(5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazol-3-yl)-5-(1-phenylethyl)-1,3,4-oxadiazole (4r). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J = 2.3 Hz, 1H), 7.37−7.23 (m, 9H), 7.12−7.09 (m, 2H), 4.45 (m, 1H), 2.42 (s, 3H), 1.82 (d, J = 7.3 Hz, 3H). (M + Na)+ 531.

2-(5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazol-3-yl)-5-(2-phenylpropan-2-yl)-1,3,4-oxadiazole (4s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.38 (d, J = 2 Hz, 1H), 7.36−7.27 (m, 7H), 7.26−7.21 (m, 1H), 7.10−7.07 (m, 2H), 2.42 (s, 3H), 1.90 (s, 6H). MH+ 523.

2-(5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazol-3-yl)-5-(1-phenylcyclopropyl)-1,3,4-oxadiazole (4t). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49−7.46 (m, 2H), 7.41−7.27 (m, 8H), 7.15−7.08 (m, 2H), 2.38 (s, 3H), 1.78 (dd, J = 7.0, 5.0 Hz, 2H), 1.48 (dd, J = 7.0, 5.0 Hz, 2H). MH+ 521.

2-(5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazol-3-yl)-5-(2-(4-chlorophenyl)propan-2-yl)-1,3,4-oxadiazole (4u). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.38 (m, 1H), 7.35−7.27 (m, 6H), 7.26−7.21 (m, 1H), 7.10−7.07 (m, 2H), 2.42 (s, 3H), 1.88 (s, 6H). MH+ 559.

2-(5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazol-3-yl)-5-(1-(4-chlorophenyl)cyclopropyl)-1,3,4-oxadiazole (4v). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.39 (m, 3H), 7.35−7.29 (m, 6H), 7.08 (m, 2H), 2.38 (s, 3H), 1.79 (dd, J = 7.1, 4.6 Hz, 2H), 1.45 (dd, J = 7.1, 4.6 Hz, 2H). ^{13}C NMR (100 MHz,

$CDCl_3$) δ 168.9, 160.3, 143.2, 138.3, 137.6, 136.4, 136.0, 135.4, 133.8, 133.3, 131.2, 131.0, 130.9, 130.5, 129.2, 129.0, 128.1, 127.1, 117.4, 22.1, 16.3, 9.9. MH+ 555.

2-(5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazol-3-yl)-5-(furan-2-yl)-1,3,4-oxadiazole (4w). MH+ 471.

2-(5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazol-3-yl)-5-(thiophen-2-yl)-1,3,4-oxadiazole (4x). MH+ 487.

2-(5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazol-3-yl)-5-(pyridin-4-yl)-1,3,4-oxadiazole (4y). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (d, J = 7.43 Hz, 1H), 8.01 (d, J = 5.04 Hz, 1H), 7.41 (d, J = 1.84 Hz, 1H), 7.37−7.29 (m, 4H), 7.11 (d, J = 8.72 Hz, 2H), 2.48 (s, 3H). MH+ 482.

2-(5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazol-3-yl)-5-(pyrazin-2-yl)-1,3,4-oxadiazole (4z). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.53 (s, 1H), 8.76 (m, 1H), 7.43 (d, J = 1.84 Hz, 1H), 7.39 (d, J = 8.68 Hz, 1H), 7.36−7.30 (m, 4H), 7.15 (d, J = 8.24 Hz, 2H), 2.55 (s, 3H). MH+ 483.

2-(5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazol-3-yl)-5-(pyridin-2-ylmethyl)-1,3,4-oxadiazole (4aa). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, J = 4.12 Hz, 1H), 7.66 (dt, J = 1.84, 7.80 Hz, 1H), 7.41 (d, J = 1.84 Hz, 1H), 7.35−7.29 (m, 5H), 7.20 (dd, J = 5.04, 7.32 Hz, 1H), 7.13−7.09 (m, 2H), 4.52 (s, 2H), 2.45 (s, 3H). MH+ 496.

2-(4-(Bromomethyl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazol-3-yl)-5-*tert*-butyl-1,3,4-oxadiazole (8). To the solution of methyl pyrazole (**4h**) (18.7 g, 40.5 mmol) in CCl_4 (400 mL) was added *N*-bromosuccinimide (9.3 g, 52.6 mmol) and AIBN (340 mg, 2.0 mmol). The reaction mixture was heated for 12 h at 80 °C. Reaction mixture was filtered. Filtrate was washed with H_2O and brine. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to provide 17 g (yield: 78%) of desired bromide as a solid. The obtained bromide was used without further purification.

(3-(5-*tert*-butyl-1,3,4-oxadiazol-2-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazol-4-yl)methyl acetate (9). To the solution of bromide (**8**) (2.86 g, 5.29 mmol) in DMF (15 mL) was added sodium acetate (1.30 g, 15.87 mmol). The reaction mixture was stirred for 12 h at room temperature. The reaction mixture was diluted with EtOAc and washed with brine. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by silica gel column chromatography (eluent: hexane/EtOAc = 3/1) provided 1.75 g (63%) of desired acetate as solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.43 (m, 1H), 7.40−7.38 (m, 2H), 7.35−7.32 (m, 3H), 7.17−7.13 (m, 2H), 5.31 (s, 2H), 2.03 (s, 3H), 1.50 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 170.8, 159.4, 145.8, 139.0, 136.8, 136.2, 135.5, 133.3, 131.1, 130.9, 130.6, 129.4, 128.3, 125.9, 115.7, 56.6, 32.7, 28.4, 21.1. MH+ 519.

(3-(5-*tert*-Butyl-1,3,4-oxadiazol-2-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazol-4-yl)methanol (10). To the solution of acetate (**9**) (1.57 g, 3.020 mmol) in THF (9 mL)/MeOH (9 mL)/H_2O (2 mL) was added LiOH monohydrate (380 mg, 9.060 mmol). The reaction mixture was stirred for 12 h at room temperature. The reaction mixture was diluted with EtOAc and washed with brine. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to provide 1.37 g (95%) of desired alcohol (**10**) as a solid. The obtained alcohol was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45−7.44 (m, 1H), 7.34−7.32 (m, 4H), 7.16−7.14 (m, 2H), 4.82−4.78 (m, 1H), 4.72−4.70 (m, 2H), 1.51 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 160.5, 143.7, 138.4, 136.7, 136.0, 135.6, 133.4, 131.3, 130.9, 130.6, 129.3, 128.3, 126.0, 122.0, 54.6, 32.8, 28.4. MH+ 478.

3-(5-*tert*-Butyl-1,3,4-oxadiazol-2-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazole-4-carbaldehyde (11). To the solution of alcohol (**10**) (100 mg, 0.209 mmol) and Dess−Martin periodinane (132 mg, 0.313 mmol) in CH_2Cl_2 (5 mL) was stirred at room temperature. The reaction mixture was filtered off the white solid and then diluted with CH_2Cl_2 (50 mL) and washed with brine. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by silica gel column chromatography (eluent: hexane/EtOAc = 3/1) provided 78 mg (78%) of desired aldehyde (**11**) as a solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.65 (s, 1H), 7.46−7.45 (m, 1H), 7.38−7.31 (m, 4H), 7.36−7.23 (m, 2H), 1.52 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.8, 174.1, 158.8, 147.7, 140.5, 137.4, 136.9, 134.6, 133.2, 131.6, 130.8, 130.7, 129.0, 128.4, 124.9, 119.7, 32.9, 28.5. MH+ 475.

2-*tert*-Butyl-5-(5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methoxymethyl-1*H*-pyrazol-3-yl)-1,3,4-oxadiazole (12b). To the suspension of alcohol (**10**) (120 mg, 0.251 mmol), NaH (20 mg, 60% dispersion in mineral oil) in DMF (5 mL) was stirred at room temperature. After 1 h, the reaction mixture was added MeI (40 μL, 0.33 mmol) and stirred for 12 h. The reaction mixture was filtered off the white solid and then extracted with EtOAc (50 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by silica gel column chromatography (eluent: hexane/EtOAc = 4/1) provided 103 mg (84%) of desired ether (**12b**) as a solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45−7.44 (m, 1H), 7.36−7.31 (m, 4H), 7.26−7.23 (m, 2H), 4.66 (s, 2H), 3.48 (s, 3H), 1.50 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 159.8, 145.7, 139.0, 136.6, 135.9, 135.8, 133.4, 131.1, 130.9, 130.6, 129.2, 128.2, 126.4, 118.0, 63.6, 58.7, 32.7, 28.5. MH+ 491.

2-(4-(Butoxymethyl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazol-3-yl)-5-*tert*-butyl-1,3,4-oxadiazole (12a). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45−7.36 (m, 1H), 7.34−7.31 (m, 4H), 7.28−7.26 (m, 2H), 4.70 (s, 2H), 3.60 (t, J = 6.4 Hz, 2H), 1.66−1.57 (m, 2H), 1.50 (s, 9H), 1.41−1.26 (m, 2H), 0.91 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 159.8, 145.6, 138.9, 136.5, 135.9, 135.8, 133.3, 131.1, 130.9, 130.6, 129.1, 128.2, 126.5, 118.3, 70.8, 62.0, 32.7, 31.9, 28.5, 19.6, 14.1. MH+ 533.

2-*tert*-Butyl-5-(5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-(fluoromethyl)-1*H*-pyrazol-3-yl)-1,3,4-oxadiazole (13). To the solution of alcohol (**10**) (200 mg, 0.418 mmol) in CH_2Cl_2(5 mL) in Falcon tube was added (diethylamino)sulfur trifluoride (DAST, 110 μL, 0.836 mmol). The reaction mixture was stirred for 2 h at room temperature. Saturated $NaHCO_3$ (30 mL) was added to the reaction mixture. After 1 h, the organic extract was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by silica gel column chromatography (eluent: hexane/EtOAc = 4/1) provided 106 mg (53%) of desired fluoride (**13**) as a solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47−7.46 (m, 1H), 7.38−7.32 (m, 4H), 7.24−7.20 (m, 2H), 5.67 (d, J = 48.8 Hz, 2H), 1.50 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 159.3, 146.8, 139.1, 136.9, 136.4, 135.5, 133.3, 131.1, 130.9, 130.7, 129.4, 128.3, 125.6, 116.0 (d, J = 20 Hz), 74.2 (d, J = 162 Hz), 32.8, 28.5. MH+ 479.

Methyl (3-(5-*tert*-Butyl-1,3,4-oxadiazol-2-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazol-4-yl)methylcarbamate (14). To the solution of alcohol (**10**) (100 mg, 0.209 mmol) and Burgess reagent (55 mg, 0.230 mmol) in THF (5 mL) was irradiated in a microwave reactor (Biotage) for 60 min at 120 °C. The organic extract was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by Prep-LC (Gilson) provided 45 mg (40%) as a solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.41 (m, 1H), 7.38−7.27 (m, 6H), 6.86−6.78 (m, 1H), 4.41 (d, J = 6.8 Hz, 2H), 3.60 (s, 3H), 1.50 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 160.3, 157.2, 144.0, 138.3, 136.6, 136.0, 135.7, 133.4, 131.6, 130.9, 130.6, 129.3, 128.2, 125.9, 119.1, 52.2, 34.8, 32.8, 28.4. MH+ 534.

2-*tert*-Butyl-5-(5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-(difluoromethyl)-1*H*-pyrazol-3-yl)-1,3,4-oxadiazole (15). To the solution of aldehyde (**11**) (50 mg, 0.105 mmol) in CH_2Cl_2(5 mL) in Falcon tube was added (diethylamino)sulfur trifluoride (DAST, 30 μL, 0.210 mmol). The reaction mixture was stirred for 2 h at room temperature. Saturated $NaHCO_3$ (30 mL) was added to the reaction mixture. After 1 h, the organic extract was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by silica gel column chromatography (eluent: hexane/EtOAc = 4/1) provided 25 mg (48%) of desired difluoride (**15**) as a solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 53.6 Hz, 1H), 7.45−7.44 (m, 1H), 7.37−7.30 (m, 4H), 7.27−7.24 (m, 2H), 1.50 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 158.9, 145.6, 137.4, 137.2, 136.6, 134.9, 133.4, 131.4, 130.9, 130.7, 129.1, 128.3, 125.6, 115.4 (t, J = 26 Hz), 110.4 (t, J = 232 Hz), 32.8, 28.4. MH+ 497.

3-(5-*tert*-Butyl-1,3,4-oxadiazol-2-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazole-4-carboxylic acid (16). To the solution of aldehyde (**11**) (1.0 g, 2.10 mmol) in *t*-BuOH (60 mL) was added 2-methyl-2-butene (12.0 mL, 99.0 mmol), KH_2PO_4 (2.2 g, 14.7 mmol), and $NaClO_2$ (2.4 g, 18.9 mmol in H_2O (35 mL)). The reaction mixture was stirred for 12 h at rt. The reaction mixture was acidified with AcOH and extracted with EtOAc. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to provide 981 mg (95%) of desired acid as a solid. The obtained acid was used without further purification. MH+ 491.

1-(3-(5-*tert*-Butyl-1,3,4-oxadiazol-2-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazol-4-yl)ethanol (17). To the solution of aldehyde (**11**) (100 mg, 0.210 mmol) in THF (5 mL) was added methyl magnesium bromide (200 μL, 3.0 M solution in diethylether). The reaction mixture was stirred for 12 h at room temperature. H_2O (20 mL) was added to the reaction mixture and then extracted with CH_2Cl_2 (50 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by silica gel column chromatography (eluent: hexane/EtOAc = 2/1) provided 83 mg (80%) of desired secondary alcohol (**17**) as a solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.41 (m, 1H), 7.34−7.29 (m, 4H), 7.13−7.10 (m, 2H), 5.72 (d, J = 11.6 Hz, 1H), 4.86−4.78 (m, 1H), 1.61 (d, J = 7.2 Hz, 3H), 1.51 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 161.0, 142.3, 136.7, 136.3, 136.0, 135.5, 133.4, 131.4, 130.9, 130.6. 129.3, 128.2, 126.5, 126.4, 62.6, 32.8, 28.4, 24.4. MH+ 491.

2-*tert*-Butyl-5-(5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-(1-methoxyethyl)-1*H*-pyrazol-3-yl)-1,3,4-oxadiazole (18). To the suspension of secondary alcohol (**17**) (50 mg, 0.101 mmol), NaH (25 mg, 60% dispersion in mineral oil) in DMF (5 mL) was stirred at room temperature. After 1 h, the reaction mixture was added MeI (20 μL, 0.33 mmol) and stirred for 12 h. The reaction mixture was filtered off the white solid and then extracted with EtOAc (50 mL). The organic extract was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by silica gel column chromatography (eluent: hexane/EtOAc = 2/1) provided 42 mg (82%) of desired product (**18**) as a solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.40 (m, 1H), 7.30−7.22 (m, 6H), 5.27 (q, J = 6.4 Hz, 1H), 3.27 (s, 3H), 1.50 (s, 9H), 1.39 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 160.0, 143.9, 137.9, 136.6, 135.7, 135.6, 133.5, 131.8, 131.0, 130.5, 128.7, 128.1, 127.5, 123.1, 71.0, 56.6, 32.7, 28.5, 21.5. MH+ 505.

2-*tert*-Butyl-5-(5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-(1-fluoroethyl)-1*H*-pyrazol-3-yl)-1,3,4-oxadiazole (19). To the solution of secondary alcohol (**17**) (50 mg, 0.101 mmol) in CH_2Cl_2 (3 mL) in Falcon tube was added DAST (27 μL, 0.202 mmol). The reaction mixture was stirred for 2 h at room temperature. Saturated $NaHCO_3$ (30 mL) was added to the reaction mixture. After 1 h, the organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by silica gel column chromatography (eluent: hexane/EtOAc = 2/1) provided 40 mg (80%) of desired product (**19**) as a solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (bs, 1H), 7.32−7.29 (m, 4H), 7.25−7.22 (m, 2H), 6.49 (q, J = 6.8 Hz, 1H), 1.61 (d, J = 6.4 Hz, 3H), 1.50 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 159.5, 144.3, 136.9, 136.8, 136.1, 135.4, 133.5, 131.8, 131.0, 130.5, 128.9, 128.1, 126.8, 121.5 (d, J = 23 Hz), 84.0 (d, J = 164 Hz), 32.7, 28.5, 21.7 (d, J = 26 Hz). MH+ 493.

1-(3-(5-*tert*-Butyl-1,3,4-oxadiazol-2-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazol-4-yl)ethanone (20). To the solution of secondary alcohol (**17**) (150 mg, 0.305 mmol) and Dess−Martin periodinane (155 mg, 0.366 mmol) in CH_2Cl_2 (5 mL) was stirred at room temperature. The reaction mixture was filtered off the white solid and then diluted with CH_2Cl_2 (50 mL) and washed with brine. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by silica gel column chromatography (eluent: hexane/EtOAc = 2/1) provided 117 mg (78%) of desired ketone (**20**) as a solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.43 (m, 1H), 7.35−7.30 (m, 4H), 7.23−7.19 (m, 2H), 2.40 (s, 3H), 1.50 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.7, 174.1, 158.9, 146.0, 137.6, 137.2, 136.7, 134.9, 133.3, 131.5, 130.9, 130.6, 129.2, 128.3, 125.9, 123.1, 32.8, 31.4, 28.5. MH+ 489.

2-*tert*-Butyl-5-(5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-vinyl-1*H*-pyrazol-3-yl)-1,3,4-oxadiazole (21). To the solution of secondary alcohol (**17**) (200 mg, 0.41 mmol) and Burgess reagent (193 mg, 0.81 mmol) in THF (5 mL) was irradiated in a microwave reactor (Biotage) for 10 min at 150°. The organic extract was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by silica gel column chromatography (eluent: hexane/EtOAc = 4/1) provided 50 mg (**21**, 26%) and 100 mg (**22**, 44%) as a solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.41 (m, 1H), 7.34−7.28 (m, 4H), 7.20−7.18 (m, 2H), 7.12−7.04 (m, 1H), 5.41 (dd, J = 18.0, 1.2 Hz, 1H), 5.25 (dd, J = 11.6, 1.2 Hz, 1H), 1.50 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 160.0, 142.6, 137.2, 136.7, 135.8, 135.5, 133.6, 131.5, 131.0, 130.5, 129.4, 128.1, 127.2, 125.5, 119.6, 118.7, 32.7, 28.5. MH+ 473.

Methyl 1-(3-(5-*tert*-Butyl-1,3,4-oxadiazol-2-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazol-4-yl)ethylcarbamate (22). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52−7.49 (m, 2H), 7.42−7.30 (m, 6H), 5.05−5.00 (m, 1H), 3.63 (s, 3H), 1.52−1.48 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 160.7, 156.8, 143.1, 136.6, 136.5, 136.0, 135.6, 133.4, 131.6, 130.9, 130.6, 129.4, 128.1, 126.1, 124.1, 52.1, 42.4, 32.8, 28.4, 21.6. MH+ 473.

2-(3-(5-*tert*-Butyl-1,3,4-oxadiazol-2-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazol-4-yl)propan-2-ol (23). To the solution of ketone (**20**) (40 mg, 0.082 mmol) in THF (5 mL) was added methyl magnesiumbromide (100 μL, 3.0 M solution in diethylether). The reaction mixture was stirred for 12 h at room temperature. H_2O (20 mL) was added to the reaction mixture and then extracted with CH_2Cl_2 (50 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by silica gel column chromatography (eluent: hexane/EtOAc = 2/1) provided 33 mg (80%) of desired tertiary alcohol (**23**) as a solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.38 (m, 1H), 7.29−7.17 (m, 6H), 6.77 (s, 1H), 1.51 (s, 9H), 1.42 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 161.5, 141.2, 136.8, 136.2, 136.1, 135.5, 134.0, 132.1, 131.1, 130.4, 130.3, 128.9, 128.7, 127.9, 68.4, 32.8, 31.4, 28.4. MH+ 505.

2-*tert*-Butyl-5-(5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-(prop-1-en-2-yl)-1*H*-pyrazol-3-yl)-1,3,4-oxadiazole (24). To the solution of tertiary alcohol (**23**) (52 mg, 0.103 mmol) and Burgess reagent (50 mg, 0.206 mmol) in THF (5 mL) was irradiated in a microwave reactor (Biotage) for 10 min at 150°. The organic layer was washed with brine and dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by silica gel column chromatography (eluent: hexane/EtOAc = 4/1) provided 49 mg (98%) of desired product (**24**) as a solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 2.4 Hz, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.32 (dd, J = 8.4, 2.4 Hz, 1H), 7.28−7.26 (m, 2H), 7.14−7.10 (m, 2H), 5.28−5.27 (m, 1H), 4.99−4.98 (m, 1H), 2.02 (s, 3H), 1.48 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 159.7, 142.4, 137.1, 136.5, 135.9, 135.5, 135.2, 133.3, 131.0, 130.9, 130.5, 129.0, 128.1, 127.1, 124.5, 119.7, 32.7, 28.5, 24.2. MH+ 487.

***S*-(3-(5-*tert*-Butyl-1,3,4-oxadiazol-2-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazol-4-yl)methyl ethanethioate (25).** To the solution of bromide (**8**) (150 mg, 0.28 mmol) in DMF (3 mL) was added KSAc (48 mg, 0.42 mmol). The reaction mixture was refluxed for 12 h at room temperature. The reaction mixture was diluted with EtOAc (25 mL) and washed with brine. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by Prep-LC (Gilson) provided 45 mg (30%) of desired thioacetate as a solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J = 2.4 Hz, 1H), 7.38−7.26 (m, 5H), 7.16−7.12 (m, 2H), 4.40 (s, 2H), 2.26 (s, 3H), 1.49 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.1, 173.3, 159.6, 144.4, 138.4, 136.7, 136.0, 135.6, 133.3, 131.2, 130.9, 130.5, 129.3, 128.2, 126.2, 116.7, 32.7, 30.4, 28.5, 23.4. MH+ 535.

2-(3-(5-*tert*-Butyl-1,3,4-oxadiazol-2-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazol-4-yl)acetonitrile (26). To the solution of bromide (**8**) (1.0 g, 1.85 mmol) in CH_3CN (20 mL)

was added KCN (0.24 g, 3.70 mmol) and 18-crown-6 (0.20 g, 0.74 mmol). The reaction mixture was refluxed for 12 h. The reaction mixture was cooled to room temperature and diluted with brine. The aqueous layer was extracted with EtOAc. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by normal phase column chromatography (Biotage) provided 0.66 g (74%) of desired cyanide as a solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45−7.32 (m, 5H), 7.21−7.18 (m, 2H), 4.05 (s, 2H), 1.51 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 159.3, 144.8, 138.0, 137.1, 136.7, 135.2, 133.3, 131.0, 130.9, 130.7, 129.8, 128.4, 125.3, 117.3, 110.5, 32.8, 28.5, 13.8. MH+ 488.

2-*tert*-Butyl-5-(5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-(phenoxymethyl)-1*H*-pyrazol-3-yl)-1,3,4-oxadiazole (27a). To the solution of bromide (**8**) (150 mg, 0.277 mmol) in DMF (5 mL) was added phenol (40 mg, 0.415 mmol) and Cs_2CO_3 (202 mg, 0.622 mmol). The reaction mixture was refluxed for 12 h at room temperature. Reaction mixture was filtered off the white solid and then extracted with EtOAc (50 mL). The organic extract was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by silica gel column chromatography (eluent: hexane/EtOAc = 5/1) provided 86 mg (56%) of desired ether (**27a**) as a solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J = 2.0 Hz, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.33 (dd, J = 8.4, 2.0 Hz, 1H), 7.30−7.22 (m, 6H), 6.97−6.95 (m, 3H), 5.27 (s, 2H), 1.44 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 159.6, 158.7, 146.0, 138.9, 136.7, 136.0, 135.7, 133.4, 131.1, 131.0, 130.6, 129.7, 129.3, 128.3, 126.2, 121.5, 116.7, 115.4, 60.3, 32.7, 28.4. MH+ 553.

2-*tert*-Butyl-5-(5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-((pyridin-2-yloxy)methyl)-1*H*-pyrazol-3-yl)-1,3,4-oxadiazole (27b). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11−8.09 (m, 1H), 7.56−7.53 (m, 1H), 7.44−7.41 (m, 2H), 7.34−7.32 (m, 1H), 7.28−7.19 (m, 4H), 6.88−6.86 (m, 1H), 6.73−6.71 (m, 1H), 5.52 (s, 2H), 1.52 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 163.5, 159.6, 147.0, 145.9, 139.2, 138.8, 136.7, 135.9, 135.7, 133.3, 131.1, 131.0, 130.6, 129.2, 128.2, 126.3, 117.2, 116.9, 111.2, 57.9, 32.7, 28.4. MH+ 554.

***N*-((3-(5-*tert*-Butyl-1,3,4-oxadiazol-2-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazol-4-yl)methyl)-*N*-methylethanamine (28b).** To the suspension of bromide (**8**) (150 mg, 0.28 mmol) in CH_2Cl_2 (5 mL) was added *N*-ethylmethylamine (30 μL, 0.33 mmol) and DIPEA (63 μL, 0.36 mmol). The reaction mixture was stirred for 12 h at room temperature. H_2O (25 mL) was added to the reaction mixture and then extracted with EtOAc (50 mL). The organic extract was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by Prep-LC (Gilson) provided 83 mg (58%) of desired amine as a solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.27 (m, 7H), 3.78 (s, 2H), 2.51−2.43 (m, 2H), 2.13 (s, 3H), 1.51 (s, 9H), 0.99 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 160.1, 145.1, 139.3, 136.4, 136.1, 135.5, 133.3, 131.6, 131.0, 130.5, 128.9, 128.1, 127.2, 119.2, 51.5, 49.5, 40.9, 32.7, 28.5, 12.5. MH+ 518.

2-*tert*-Butyl-5-(5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-(piperidin-1-ylmethyl)-1*H*-pyrazol-3-yl)-1,3,4-oxadiazole (28a). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.26 (m, 7H), 3.58 (s, 2H), 2.38 (br s, 4H), 1.60−1.45 (m, 15H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 160.2, 145.1, 139.3, 136.4, 136.1, 135.4, 133.3, 131.6, 130.9, 130.5, 128.8, 128.1, 127.3, 118.9, 54.0, 51.1, 32.7, 28.5, 26.3, 24.5. MH+ 546.

4-((3-(5-*tert*-Butyl-1,3,4-oxadiazol-2-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazol-4-yl)methyl)morpholine (28c). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.41 (m, 1H), 7.38−7.27 (m, 4H), 6.98−6.81 (m, 2H), 4.92 (s, 2H), 3.77−3.51 (m, 8H), 2.51−2.39 (m, 8H), 1.50 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 160.0, 145.2, 139.2, 136.5, 135.9, 135.6, 133.3, 131.4, 130.9, 130.5, 128.9, 128.2, 127.1, 117.9, 67.3, 53.1, 50.8, 32.7, 28.5. MH+ 548.

***N*-((3-(5-*tert*-Butyl-1,3,4-oxadiazol-2-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazol-4-yl)methyl)propan-2-amine (28d).** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.31 (m, 7H), 3.95 (s, 2H), 3.20−3.07 (m, 1H), 1.51 (s, 9H), 1.05 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 160.2, 144.6, 138.3, 136.6, 135.9, 135.8, 133.4, 131.4, 131.0, 130.5, 130.4, 129.2, 128.2, 126.4, 49.0, 40.4, 32.8, 28.4, 22.4. MH+ 518.

1-((3-(5-*tert*-Butyl-1,3,4-oxadiazol-2-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazol-4-yl)methyl)pyrrolidine-2,5-dione (30). To the suspension of bromide (**8**) (150 mg, 0.28 mmol) in acetone (10 mL) was added succinimide (35 mg, 0.33 mmol) and K_2CO_3 (60 mg, 0.42 mmol). The reaction mixture was refluxed for 12 h and cooled to room temperature. H_2O (25 mL) was added to the reaction mixture and then extracted with EtOAc (50 mL). The organic extract was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by Prep-LC (Gilson) provided 99 mg (64%) of desired product as a solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.16 (m, 7H), 4.99 (s, 2H), 2.33 (s, 4H), 1.47 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8, 173.3, 159.6, 143.2, 137.5, 136.8, 136.1, 135.3, 133.6, 131.6, 131.1, 130.4, 129.0, 128.0, 126.4, 115.1, 34.2, 32.7, 28.5, 28.2. MH+ 560.

1-((3-(5-*tert*-Butyl-1,3,4-oxadiazol-2-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazol-4-yl)methyl)pyrrolidin-2-one (29). Similar procedure with preparation of **30** proceeded with 2-pyrrolidinone, instead of succinimide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 2.0 Hz, 1H), 7.36−7.27 (m, 4H), 7.13−7.09 (m, 2H), 4.87 (s, 2H), 3.26 (t, J = 6.8 Hz, 2H), 2.12 (t, J = 8.0 Hz, 2H), 1.68−1.65 (m, 2H), 1.50 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 173.4, 159.8, 144.5, 138.6, 136.7, 136.0, 135.6, 133.4, 131.1, 130.9, 130.5, 129.0, 128.2, 126.1, 116.2, 46.8, 36.6, 32.7, 30.9, 28.5, 17.8. MH+ 544.

3-((3-(5-*tert*-Butyl-1,3,4-oxadiazol-2-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazol-4-yl)methyl)oxazolidin-2-one (31). Similar procedure with preparation of **30** proceeded with 2-oxazolidinone, instead of succinimide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45−7.41 (m, 1H), 7.37−7.28 (m, 4H), 7.18−7.15 (m, 2H), 4.75 (s, 2H), 4.13 (t, J = 8.0 Hz, 2H), 3.62 (t, J = 8.0 Hz, 2H), 1.50 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 159.8, 158.1, 145.4, 138.5, 136.8, 136.3, 135.6, 133.4, 131.2, 130.9, 130.6, 129.3, 128.2, 125.8, 115.8, 62.1, 45.1, 38.2, 32.8, 28.5. MH+ 546.

Ethyl 4-(Bromomethyl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazole-3-carboxylate (33). To the solution of ester (**5**) (29.5 g, 72.0 mmol) in CCl_4 (500 mL) was added *N*-bromosuccinimide (15.3 g, 86.4 mmol) and AIBN (0.6 g, 3.6 mmol). The reaction mixture was heated for 12 h at 80 °C. Reaction mixture was filtered. Filtrate was washed with H_2O and brine. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to provide 31.8 g (yield: 90%) of desired bromide as a solid. The obtained bromide was used without further purification.

Ethyl 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazole-3-carboxylate (34). NaH (0.37 g, 9.21 mmol, 60% dispersion in mineral oil) was added to the solution of 1,2,4-triazole (0.51 g, 7.37 mmol) in THF (30 mL) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C. The solution of bromide (**33**) (3 g, 6.14 mmol) in THF (15 mL) was added to the reaction mixture. The reaction mixture was warmed up to room temperature, stirred for 1 h at room temperature and for 12 h at 45 °C. The reaction mixture was cooled to room temperature. H_2O (100 mL) was added to the reaction mixture and then extracted with EtOAc (150 mL). The organic extract was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by silica gel column chromatography (Biotage, eluent: 12% EtOAc/hexane → EtOAc (gradient)) provided 1.35 g (46%) of desired triazole (**34**) as a solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (s, 1H), 8.09 (s, 1H), 7.41−7.27 (m, 7H), 5.48 (s, 2H), 4.44 (quartet, J = 7.2 Hz, 2H), 1.398 (t, J = 7.2 Hz, 3H). MH+ 478.

4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazole-3-carboxylic acid (35). To the solution of ester (**34**) (500 mg, 1.05 mmol) in THF (5 mL)/H_2O (15 mL) was added LiOH monohydrate (132 mg, 3.15 mmol). The reaction mixture was refluxed for 2 h and cooled to room temperature. The reaction mixture was acidified with aq 1N HCl solution and extracted with 30% MeOH/$CHCl_3$. The organic extract

was dried over anhydrous $MgSO_4$, filtered, concentrated and dried in vacuo to provide 470 mg (100%) of desired acid (**35**) as a solid. The obtained acid was used without further purification.

4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-*N*′-pivaloyl-1*H*-pyrazole-3-carbohydrazide (36). To the solution of acid (**35**) (330 mg, 0.74 mmol) in CH_2Cl_2 (10 mL) was added oxalyl chloride (77 μL, 0.88 mmol) and the catalytic amount of DMF. The reaction mixture was stirred for 1 h and concentrated in vacuo. The residue (crude acyl chloride) was diluted with CH_2Cl_2 (10 mL) and pivalohydrazide (128 mg, 1.10 mmol), and triethylamine (0.31 mL, 2.21 mmol) was added. The reaction mixture was stirred for 2 h at room temperature. The reaction mixture was concentrated in vacuo and diluted with EtOAc (50 mL). The organic layer was washed with aq 1N HCl and aq sat $NaHCO_3$ solution, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by Prep-LC (Gilson) provided 244 mg (61%) of desired diamide to target compound.

2-(4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazol-3-yl)-5-*tert*-butyl-1,3,4-oxadiazole (32d). NaH (15 mg, 0.36 mmol, 60% dispersion in mineral oil) was added to the solution of 1,2,4-triazole (23 mg, 0.33 mmol) in THF (5 mL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C. The solution of bromide (**8**) (150 mg, 0.28 mmol) in THF (5 mL) was added to the reaction mixture. The reaction mixture was warmed up to room temperature and stirred for 12 h at room temperature. H_2O (25 mL) was added to the reaction mixture and then extracted with EtOAc (50 mL). The organic extract was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by Prep-LC (Gilson) provided 70 mg (47%) of desired product as a solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (s, 1H), 7.99 (s, 1H), 7.49−7.44 (m, 3H), 7.49−7.29 (m, 4H), 5.59 (s, 2H), 1.48 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 159.4, 151.9, 146.2, 144.8, 138.2, 136.9, 136.5, 135.4, 133.4, 131.7, 130.9, 130.7, 129.4, 128.3, 125.4, 115.1, 43.0, 32.8, 28.4. ESI-MS *m*/*z*: 528 $[M + H]^+$; positive HR-FAB-MS *m*/*z*: 528.0884 $[M + H]^+$ (calcd for $C_{24}H_{20}Cl_3N_7O$: 528.0873).

2-(4-((1*H*-Pyrrol-1-yl)methyl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazol-3-yl)-5-*tert*-butyl-1,3,4-oxadiazole (32a). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45−7.27 (m, 7H), 6.45−6.39 (m, 2H), 5.92−5.85 (m, 2H), 5.53 (s, 2H), 1.51 (s, 9H). MH+ 528.

2-(4-((1*H*-Pyrazol-1-yl)methyl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazol-3-yl)-5-*tert*-butyl-1,3,4-oxadiazole (32b). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 2.0 Hz, 1H), 7.49−7.47 (m, 1H), 7.42−7.28 (m, 7H), 6.18 (t, J = 2.0 Hz, 1H), 5.54 (s, 2H), 1.47 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 159.6, 145.9, 139.5, 138.4, 136.7, 136.2, 135.7, 133.4, 131.7, 130.9, 130.8, 130.6, 129.2, 128.2, 125.8, 116.4, 105.3, 45.1, 32.7, 28.4. MH+ 527.

2-(4-((1*H*-Imidazol-1-yl)methyl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazol-3-yl)-5-*tert*-butyl-1,3,4-oxadiazole (32c). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.43−7.33 (m, 5H), 7.10−7.05 (m, 2H), 7.01 (t, J = 6.8 Hz, 1H), 6.92 (t, J = 1.2 Hz, 1H), 5.47 (s, 2H), 1.49 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 159.4, 145.6, 138.2, 137.2, 137.0, 136.7, 135.2, 133.3, 131.1, 130.8, 130.6, 129.7, 129.4, 128.3, 125.6, 119.2, 116.5, 39.8, 32.8, 28.4. MH+ 527.

2-(4-((1*H*-1,2,3-Triazol-1-yl)methyl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazol-3-yl)-5-*tert*-butyl-1,3,4-oxadiazole (32e). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, J = 1.2 Hz, 1H), 7.66 (d, J = 0.8 Hz, 1H), 7.44 (dd, J = 1.6 Hz, 0.8 Hz, 1H), 7.42−7.29 (m, 6H), 5.76 (s, 2H), 1.48 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 159.5, 146.3, 138.1, 136.9, 136.6, 135.4, 133.5, 133.4, 131.7, 130.8, 130.7, 129.5, 128.3, 125.6, 125.3, 115.1, 43.5, 32.8, 28.4. MH+ 530.

2-(4-((2*H*-tetrazol-2-yl)methyl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazol-3-yl)-5-*tert*-butyl-1,3,4-oxadiazole (32f). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.44−7.43 (m, 1H), 7.36 (d, J = 0.4 Hz, 1H), 7.33 (d, J = 2.4 Hz, 1H), 7.31−7.27 (m, 2H), 7.16−7.13 (m, 2H), 6.07 (s, 2H), 1.47 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 159.2, 153.0, 146.3, 138.8, 137.0, 136.7, 135.3, 133.4, 131.1, 130.9, 130.6, 129.5, 128.3, 125.2, 112.7, 47.0, 32.7, 28.4. MH+ 531.

2-(4-((1*H*-Tetrazol-1-yl)methyl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazol-3-yl)-5-*tert*-butyl-1,3,4-oxadiazole (32g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.26 (s, 1H), 7.46−7.29 (m, 7H), 5.78 (s, 2H), 1.49 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 159.4, 146.6, 144.2, 138.0, 137.1, 136.9, 135.2, 133.3, 131.7, 130.8, 130.7, 129.7, 128.4, 124.9, 113.9, 41.9, 32.8, 28.4. MH+ 531.

Ethyl 4-Bromo-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazole-3-carboxylate (38). To a solution of ethyl 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazole-3-carboxylate (**37**) (1 g, 2.4 mmol) in methylene chloride (30 mL) at room temperature was added bromine (4.9 mL, prepared 1.0 M solution in methylene chloride, 4.9 mmol) dropwise. The reaction mixture was stirred at room temperature for 1 h, and the resulting solution was diluted with ethyl ether (50 mL). The reaction mixture was quenched with saturated sodium bicarbonate solution (30 mL) and extracted with ethyl ether (50 mL twice). The organic solution was evaporated under reduced pressure, and crude residue was purified with silica gel column (hexane/ethyl acetate = 5/1) to recover starting material (**37**) (401 mg, 40%) and produce the title compound (**38**) (520 mg, 45% yield) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 2.0 Hz, 1H), 7.37 (d, J = 8.4, 2H), 7.35−7.31 (m, 3H), 7.21−7.19 (m, 2H), 4.50 (q, J = 7.2 Hz, 2H), 1.44 (t, J = 7.2 Hz, 3H). MH+ 473.

Ethyl 5-(4-Chlorophenyl)-4-cyclopropyl-1-(2,4-dichlorophenyl)-1*H*-pyrazole-3-carboxylate (39). To a solution of ethyl 4-bromo-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazole-3-carboxylate (**38**) (500 mg, 1.1 mmol) in aqueous toluene, tetrakis(triphenylphsophine)palladium (122 mg, 0.11 mmol) and potassium carbonate (510 mg, 3.9 mmol) were added. The reaction mixture was placed under microwave irradiation with the temperature set to 140 °C. The resulting solution was filtered with syringe filter, and then the solvent was evaporated under reduced pressure. The residue was purified with silica gel column chromatography to obtain the title compound (283 mg, 44%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46−7.43 (m, 1H), 7.38−7.35 (m, 4H), 7.13−7.11 (m, 2H), 4.48 (q, J = 7.1 Hz, 2H), 2.02−1.98 (m, 1H), 1.44 (t, J = 7.1, 3H), 1.26−1.23 (m, 1H), 0.89−0.86 (m, 1H). MH+ 436.

2-*tert*-Butyl-5-(5-(4-chlorophenyl)-4-cyclopropyl-1-(2,4-dichlorophenyl)-1*H*-pyrazol-3-yl)-1,3,4-oxadiazole (41). Similar procedure with preparation of **4h** proceeded with **39**, instead of **5**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55−7.50 (m, 2H), 7.37−7.31 (m, 2H), 7.22−7.20 (m, 1H), 7.15−7.10 (m, 2H), 1.45 (m, 1H), 1.34 (s, 9H), 0.62−0.59 (m, 2H), 0.38−0.34 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 160.0, 139.7, 136.4, 136.0, 135.3, 133.4, 131.4, 131.1, 130.5, 129.3, 128.8, 128.1, 127.3, 122.7, 32.7, 28.5, 7.8, 5.7. MH+ 489.

2-(4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazol-3-yl)-5-(1-methylcyclopropyl)-1,3,4-oxadiazole (42b). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.41 (s, 1H), 7.89 (s, 1H), 7.83 (d, J = 8.8 Hz, 1H), 7.60 (d, J = 2.4 Hz, 1H), 7.59 (dd, J = 8.8 Hz, 2.4 Hz, 1H), 7.50−7.76 (m, 4H), 5.50 (s, 2H), 1.50 (s, 3H), 1.26−1.19 (m, 2H), 1.05−0.99 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 158.8, 151.9, 146.1, 144.8, 138.1, 136.9, 136.5, 135.4, 133.4, 131.7, 130.8, 130.7, 129.4, 128.3, 125.4, 114.9, 43.0, 20.5, 17.0, 13.1. ESI-MS *m*/*z*: 526 $[M + H]^+$. Positive HR-FAB-MS *m*/*z*: 526.0731 $[M + H]^+$ (calcd for $C_{24}H_{18}Cl_3N_7O$: 526.0717).

2-(4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazol-3-yl)-5-(1-(trifluoromethyl)cyclopropyl)-1,3,4-oxadiazole (42c). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (s, 1H), 8.14 (s, 1H), 7.45−7.32 (m, 7H), 5.62 (s, 2H), 1.64 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0, 160.0, 152.0, 146.3, 144.7, 137.4, 137.0, 136.6, 135.3, 133.3, 131.7, 130.8, 130.6, 129.4, 128.3, 125.3, 124.3 (d, J = 272 Hz), 115.2, 42.9, 21.2 (q, J = 37 Hz), 12.7. ESI-MS *m*/*z*: 580 $[M + H]^+$; Positive HR-FAB-MS *m*/*z*: 580.0435 $[M + H]^+$ (Calcd for $C_{24}H_{15}Cl_3F_3N_7O$: 580.0434).

2-(4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazol-3-yl)-5-(1-phenylcyclopropyl)-1,3,4-oxadiazole (42d). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 (s, 1H), 7.94 (s, 1H), 7.89−7.78 (m, 2H), 7.60−7.55 (m, 1H), 7.48−7.26 (m, 8H), 5.52 (s, 2H), 1.69−1.64 (m, 2H), 1.55−1.47 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 159.2, 151.9, 146.1, 144.8, 138.6, 138.0, 136.9, 136.5, 135.4, 133.3, 131.7, 130.8, 130.6, 130.0, 129.4, 128.9, 128.3, 128.1, 125.4, 115.0, 42.9, 22.7, 16.5. ESI-MS *m/z*: 588 $[M + H]^+$. positive HR-FAB-MS *m/z*: 588.0896 $[M + H]^+$ (calcd for $C_{29}H_{20}Cl_3N_7O$: 588.0873).

2-(4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazol-3-yl)-5-(1-*p*-tolylcyclopropyl)-1,3,4-oxadiazole (42e). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.37 (s, 1H), 7.88 (s, 1H), 7.84−7.76 (m, 2H), 7.57 (dd, J = 8.4 Hz, 2.4 Hz, 1H), 7.48−7.43 (m, 2H), 7.43−7.36 (m, 8H), 7.30−7.24 (m, 2H), 7.18−7.12 (m, 2H), 5.52 (s, 2H), 2.26 (s, 3H), 1.65−1.59 (m, 2H), 1.48−1.41 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 159.1, 151.9, 146.1, 144.8, 138.0, 137.9, 136.9, 136.5, 135.7, 135.4, 133.3, 131.7, 130.8, 130.6, 129.9, 129.6, 128.3, 125.4, 115.0, 42.9, 22.4, 21.4, 16.5. ESI-MS *m/z*: 602 $[M + H]^+$. Positive HR-FAB-MS *m/z*: 602.1028 $[M + H]^+$ (calcd for $C_{30}H_{22}Cl_3N_7O$: 602.1030).

2-(4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazol-3-yl)-5-(1-(4-chlorophenyl)cyclopropyl)-1,3,4-oxadiazole (42f). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (s, 1H), 7.99 (s, 1H), 7.46−7.28 (m, 11H), 5.54 (s, 2H), 1.78 (m, 2H), 1.47 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 159.3, 152.0, 146.2, 144.8, 137.9, 137.1, 136.9, 136.5, 135.4, 134.0, 133.3, 131.7, 131.4, 130.8, 130.7, 129.4, 129.1, 128.3, 125.4, 115.0, 42.9, 22.2, 16.6. ESI-MS *m/z*: 622 $[M + H]^+$. Positive HR-FAB-MS *m/z*: 622.0491 $[M + H]^+$ (Calcd for $C_{29}H_{19}Cl_4N_7O$: 622.0483).

2-(4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazol-3-yl)-5-*tert*-butyl-1,3,4-oxadiazole (43a). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (s, 1H), 7.91 (s, 1H), 7.55−7.53 (m, 2H), 7.47−7.43 (m, 3H), 7.38−7.32 (m, 2H), 5.57 (s, 2H), 1.50 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 159.4, 151.9, 146.1, 144.8, 138.2, 136.9, 135.4, 133.4, 132.4, 131.9, 130.8, 130.7, 128.3, 125.9, 124.9, 115.1, 43.0, 32.8, 28.4. ESI-MS *m/z*: 572 $[M + H]^+$. Positive HR-FAB-MS *m/z*: 572.0375 $[M + H]^+$ (calcd for $C_{24}H_{20}BrCl_2N_7O$: 572.0368).

2-(4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazol-3-yl)-5-(1-methylcyclopropyl)-1,3,4-oxadiazole (43b). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1H), 7.89 (s, 1H), 7.54−7.52 (m, 2H), 7.45−7.41 (m, 3H), 7.35−7.30 (m, 2H), 5.55 (s, 2H), 1.61 (s, 3H), 1.42−1.39 (m, 2H), 1.00−0.97 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 158.8, 151.9, 146.1, 144.8, 138.1, 136.9, 135.4, 133.4, 132.4, 131.9, 130.8, 130.7, 128.3, 125.9, 124.9, 114.9, 43.0, 20.5, 17.0, 13.1. ESI-MS *m/z*: 570 $[M + H]^+$. Positive HR-FAB-MS *m/z*: 570.0220 $[M + H]^+$ (calcd for $C_{24}H_{18}BrCl_2N_7O$: 570.0211).

2-(4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazol-3-yl)-5-(1-(trifluoromethyl)cyclopropyl)-1,3,4-oxadiazole (43c). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.43 (s, 1H), 7.89 (s, 1H), 7.85 (d, J = 8.8 Hz, 1H), 7.80 (d, J = 2.4 Hz, 1H), 7.63−7.55 (m, 3H), 7.38−7.30 (m, 2H), 5.52 (s, 2H), 1.73 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0, 160.0, 152.0, 146.4, 144.7, 137.5, 137.0, 135.3, 133.3, 132.4, 131.9, 130.8, 130.7, 128.3, 125.7, 125.0, 124.3 (d, J = 272 Hz), 42.9, 21.2 (q, J = 37 Hz), 12.7. ESI-MS *m/z*: 624 $[M + H]^+$. Positive HR-FAB-MS *m/z*: 623.9928 $[M + H]^+$ (calcd for $C_{24}H_{15}BrCl_2F_3N_7O$: 623.9929).

2-(4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazol-3-yl)-5-(1-phenylcyclopropyl)-1,3,4-oxadiazole (43d). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 1H), 7.88 (s, 1H), 7.53−7.51 (m, 2H), 7.48−7.29 (m, 10H), 5.50 (s, 2H), 1.79−1.76 (m, 2H), 1.52−1.49 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 159.2, 151.9, 146.1, 144.8, 138.6, 138.0, 136.9, 135.4, 133.3, 132.4, 131.9, 130.8, 130.7, 130.0, 129.0, 128.3, 128.1, 125.9, 124.9, 115.0, 42.9, 22.7, 16.5. ESI-MS *m/z*: 632 $[M + H]^+$. Positive HR-FAB-MS *m/z*: 632.0361 $[M + H]^+$ (calcd for $C_{29}H_{20}BrCl_2N_7O$: 632.0368).

2-(4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazol-3-yl)-5-(1-*p*-tolylcyclopropyl)-1,3,4-oxadiazole (43e). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1H), 7.89 (s, 1H), 7.54−7.52 (m, 2H), 7.45−7.41 (m, 3H), 7.38−7.30 (m, 4H), 7.19−7.17 (m, 2H), 5.50 (s, 2H), 2.35 (s, 3H), 1.77−1.74 (m, 2H), 1.49−1.46 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 159.1, 151.9, 146.1, 144.8, 138.1, 137.9, 136.9, 135.7, 135.4, 133.3, 132.4, 131.9, 130.8, 130.7, 129.9, 129.6, 128.3, 125.9, 124.9, 115.0, 42.9, 22.4, 21.4, 16.5. ESI-MS *m/z*: 646 $[M + H]^+$. Positive HR-FAB-MS *m/z*: 646.0522 $[M + H]^+$ (calcd for $C_{30}H_{22}BrCl_2N_7O$: 646.0525).

2-(4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazol-3-yl)-5-(1-(4-chlorophenyl)cyclopropyl)-1,3,4-oxadiazole (43f). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (s, 1H), 7.89 (s, 1H), 7.54−7.52 (m, 2H), 7.45−7.40 (m, 5H), 7.36−7.30 (m, 4H), 5.52 (s, 2H), 1.81−1.78 (m, 2H), 1.50−1.47 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 159.3, 152.0, 146.2, 144.8, 137.9, 137.1, 137.0, 135.4, 134.0, 133.3, 132.4, 131.9, 131.4, 130.8, 130.7, 129.1, 128.3, 125.8, 124.9, 115.0, 42.9, 22.2, 16.6. ESI-MS *m/z*: 666 $[M + H]^+$. Positive HR-FAB-MS *m/z*: 665.9971 $[M + H]^+$ (calcd for $C_{29}H_{19}BrCl_3N_7O$: 665.9978).

HPLC Analysis Data. All final compounds were determined by Agilent 1200 series high performance liquid chromatography with UV detection at 254 nm (Xterra MS C18 3.5 μm, 2.1 ± 50 mm, 12 min, 0.3 mL/min flow rate, 50−100% 0.05% TFA in CH_3CN/100−50% 0.05% TFA in H_2O) (Table 4).

Table 4. HPLC Analysis Data

entry	compd	HPLC: retention time (min)	entry	compd	HPLC: retention time (min)
1	**4h**	8.013	27	**28a**	1.442
2	**4ha**	9.038	28	**28b**	1.248
3	**4hb**	10.012	29	**28c**	1.103
4	**4hc**	9.770	30	**28d**	1.265
5	**4k**	8.571	31	**29**	4.293
6	**9**	7.067	32	**30**	4.416
7	**10**	5.103	33	**31**	4.255
8	**11**	6.550	34	**32a**	8.660
9	**12a**	10.555	35	**32b**	6.861
10	**12b**	7.307	36	**32c**	1.354
11	**13**	7.577	37	**32d**	4.220
12	**14**	6.164	38	**32e**	4.327
13	**15**	8.212	39	**32f**	5.915
14	**16**	3.866	40	**32g**	5.096
15	**17**	6.264	41	**41**	8.696
16	**18**	7.767	42	**42b**	3.559
17	**19**	8.209	43	**42c**	4.714
18	**20**	6.216	44	**42d**	5.976
19	**21**	8.786	45	**42e**	7.106
20	**22**	7.633	46	**42f**	7.259
21	**23**	6.902	47	**43a**	4.598
22	**24**	8.881	48	**43b**	3.927
23	**25**	8.294	49	**43c**	4.712
24	**26**	6.508	50	**43d**	6.299
25	**27a**	9.990	51	**43e**	7.395
26	**27b**	8.190	52	**43f**	7.548

CB1 and CB2 Receptor Binding Assay. For CB1 receptor binding studies, rat cerebellar membranes were prepared as previously described by the methods of Kuster et al.[30] Male Sprague−Dawley rats (200−300 g) were sacrificed by decapitation and the cerebella rapidly removed. The tissue was homogenized in 30 volumes of TME buffer (50 mM Tris-HCl, 1 mM EDTA, 3 mM $MgCl_2$, pH = 7.4) using a Dounce homogenizer. The crude homogenates were immediately centrifuged (48000*g*) for 30 min at 4 °C. The resultant pellets were resuspended in 30 volumes of TME buffer, and protein concentration was determined by the method of Bradford and stored at −70 °C until use.[31]

For CB2 receptor binding studies, CHO K-1 cells were transfected with human CB2 receptor as previously described, and cell membranes were prepared as described above.[32]

Competitive binding assays were performed as described.[33] Briefly, approximately 10 μg of rat cerebella membranes (containing

CB1 receptor) or cell membranes (containing CB2 receptor) were incubated in 96-well plate with TME buffer containing 0.5% essentially fatty acid free bovine serum albumin (BSA),

Three nM [**3H**]**44** (for CB2 receptor, NEN; specific activity 50−80 Ci/mmol) or 3 nM **45** ([^{3}H]CP55,940, [^{3}H]2-[(1*S*,2*R*,5*S*)-5-hydroxy-2-(3-hydroxypropyl) cyclohexyl]-5-(2-methyloctan-2-yl)phenol, for CB1 receptor, NEN; specific activity 120−190 Ci/mmol) and various concentrations of the synthesized cannabinoid ligands in a final volume of 200 μL. The assays were incubated for 1 h at 30 °C and then immediately filtered over GF/B glass fiber fiber filter (PerkinElmer Life and Analytical Sciences, Boston, MA) that had been soaked in 0.1% PEI for 1 h by a cell harvester (PerkinElmer Life and Analytical Sciences, Boston, MA). Filters were washed five times with ice-cold TBE buffer containing 0.1% essentially fatty acid free BSA, followed by oven-dried for 60 min and then placed in 5 mL of scintillation fluid (Ultima Gold XR; PerkinElmer Life and Analytical Sciences, Boston, MA), and radioactivity was quantitated by liquid scintillation spectrometry. In CB1 and CB2 receptor competitive binding assay, nonspecific binding was assessed using 1 μM **1** and 1 μM **44** (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 **1** or **44** and was 70−80% of the total binding. IC_{50} was determined by nonlinear regression analysis using GraphPad PRISM. All data were collected in triplicate and IC_{50} was determined from three independent experiments.

Measurements of in Vivo Activity Analysis. Male C57BL/6J mice weighing over 38 g were housed 1 per cage on a 12 h/12 h light/dark cycle, had free access to food (rodent sterilizable diet) and water, and were experimentally native before testing. Mice were allowed at least 7 days to habituate to the experimental room prior to testing, and testing was conducted during the light period. Mice were maintained and experiments were conducted in accordance with Institutional Animal Care. The reference (**1**) and the compounds **4k**, **42c**, and **43c** were prepared daily by dissolving it in deionized water containing 10% DMSO. By oral administration, animals received at a volume of 10 mL/kg for 14 days. All control animals received 10% DMSO dissolved in deionized water. The vehicles 10% DMSO treated group were comprised of five mice in oral test. There were six mice in each of the other experimental groups ($n = 6$ in each group). By oral administration, the losing weight was checked everyday for the drug treated group and the control group.

Protein modeling and docking experiments have been performed with the Sybyl 7.3 software package (Tripos, Inc., St. Louis, MO)[35] based on Linux CentOS 4.0.

Homology Modeling of hCB1 Receptor. The sequence of human CB1 receptor was taken from the Swiss-Prot Database (entry P21554; http://us.expasy.org/sprot/). The crystal structure of bovine rhodopsin at 2.80 Å resolution (PDB entry 1F88) from the HOMSTRAD, a database containing thousands of 3D protein structures clustered into related families, was used as a template. The first alignment is based on an automatic alignment created in FUGUE, structural homologues of hCB1 were identified by sequence−structure comparison using protein database. Additional manual adjustments were performed to eliminate unwanted gaps in the produced alignment for hCB1. Using the ORCHESTRAR, aligned sequence of hCB1 was built using structure of bovine rhodopsin. Loops were then modeled by knowledge-based or ab initio approaches, and side chains were added.

The conserved disulfide bond between residues Cys257 and Cys264 in the middle of extracellular loop 2 was also created and kept as a constraint in the geometric optimization. The resultant structure of the hCB1 receptor was optimized using Powell methods with the following parameters: a distance-dependent dielectric constant of 1.0, nonbounded cutoff 8 Å, Powell and Kollman all-atom charges, and conjugate gradient minimization until the maximum derivative is less than 0.05 kcal/(mol·Å). The side chains of the resulting minimized structure underwent simulated annealing to relieve any steric clashes and correct unfavorable torsion angle. Stereochemical feature of the minimized structure was evaluated by inspection of the Ramachandran plots obtained from PROCHECK analysis.

Molecular Docking. Structures of **1** and **43c** were energy-minimized by the conjugated gradient method with Gasteiger−Hückel charge until a convergence value of 0.001 kcal/(Å·mol), using the Tripos force field. The model for **1** complex was generated by manual docking in the active site of the hCB1 homology model considering the key ligand−receptor interactions. The model was optimized using the FlexiDock utility in the Biopolymer module of Sybyl to determine the most energetically favorable binding conformation and orientation. After the hydrogen atoms were added to the hCB1 receptor, atomic charges were recalculated by Kollman all-atom for the protein and Gasteiger−Hückel for **1**. H-bond sites were marked for all residues in the binding pocket (6.5 Å cavity centered by **1**) and for ligands that were able to act as H-bond donors or acceptors. During the Flexi-Dock run, single bonds in the ligand and the residues of the binding pocket were defined as rotatable. Default FlexiDock parameters were set at 30000 generation for genetic algorithms. Finally, the complex structure was minimized by Powell method with a gradient of 0.05 kcal/(mol·Å).

Compound **43c** was docked into hCB1 with Surflex-Dock[36] after the active site region was defined by using protocol that reproduces the interactions made by **1** with hCB1. Subsequent scoring for Surflex-Dock solution was performed by a consensus scoring function (CScore[35]). The binding modes of conformers with high CScore value (3−5) were visually inspected. A conformer with the top D-score rank showed the most favorable binding mode in complex with hCB1, and it is displayed in Figures 5 and 6.

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Supporting Information Available: Elemental analyses data for compounds **42c**, **43c**; HRMS and HPLC purity data for compounds **32d**, **42b**−**42f**, **43a**−**43f**; ^{1}H NMR and ^{13}C NMR spectrum data for compounds **4k**, **32d**, **42b**−**42f**, **43a**−**43f**; HRMS and HPLC spectrum data for compounds **42c**, **43c**; single-crystal X-ray analysis data for **43c**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Bray, G. A. Obesity: the disease. *J. Med. Chem.* **2006**, *49*, 4001–4007.
(2) *Report of a WHO Consultation on Obesity: Obesity-Preventing and Managing a Global Epidemic*; World Health Organization: Geneva, 2000.
(3) Antel, J.; Gregory, P. C.; Nordheim, U. CB1 Cannabinoid receptor antagonists for treatment of obesity and prevention of comorbid metabolic disorders. *J. Med. Chem.* **2006**, *49*, 4008–4016.
(4) Mokdad, A. H.; Marks, J. S.; Stroup, D. F.; Gerberding, J. L. Actual causes of death in the United States. *J. Am. Med. Assoc.* **2004**, *291*, 1238–1245.
(5) Hepworth, D.; Carpino, P. A.; Black, S. C. Centrally acting anti-obesity agents. *Annu. Rep. Med. Chem.* **2006**, *41*, 77–97.
(6) (a) Pagotto, U.; Vicennati, V.; Pasquali, R. The endocannabinoid system and the treatment of obesity. *Ann. Med.* **2005**, *37*, 270. (b) Stella, N.; Schweitzer, P.; Piomelli, D. A second endogenous cannabinoid that modulates long-term potentiation. *Nature* **1997**, *388*, 773–778.
(7) Muineddu, G.; Ruiu, S.; Mussinu, J.-M.; Loriga, G.; Grella, G. E.; Carai, M. A. M.; Lazzari, P.; Pani, L.; Pinna, G. A. Tricyclic pyrazoles. Part 2: Synthesis and biological evaluation of novel 4,5-dihydro-1*H*-benzo[*g*]indazole-based ligands for cannabinoid receptors. *Bioorg. Med. Chem.* **2005**, *13*, 3309–3320.

(8) 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.
(9) Munro, S.; Thomas, K. L.; Abu-Shaar, M. Molecular characterization of a peripheral receptor for cannabinoids. *Nature* **1993**, *365*, 61–65.
(10) Lange, J. H. M.; Kruse, C. G. Recent advances in CB1 cannabinoid receptor antagonists. *Curr. Opin. Drug Discovery Dev.* **2004**, *7*, 498–506.
(11) Lange, J. H. M.; Kruse, C. G. Medicinal chemistry strategies to CB1 cannabinoid receptor antagonists. *Drug Discovery Today* **2005**, *10*, 693–702.
(12) Barth, F. *CB1 cannabinoid receptor antagonists. Annu. Rep. Med. Chem.* **2005**, *40*, 103–118.
(13) Bellocchio, L.; Mancini, G.; Vicennati, V.; Pasquali, R.; Pagotto, U. Cannabinoid receptors as therapeutic targets for obesity and metabolic diseases. *Curr. Opin. Pharmacol.* **2006**, *6*, 586–591.
(14) Boström, J.; Berggren, K.; Greasley, P.; Wilstermann, M. Scaffold hopping, synthesis and structure−activity relationships of 5,6-diarylpyrazine-2-amide derivatives: a novel series of CB1 receptor antagonists. *Bioorg. Med. Chem.* **2007**, *15*, 4077–4084.
(15) (a) Barth, F.; Casellas, P.; Congy, C.; Martinez, S.; Rinaldi, M. Pyrazole-3-carboxamide derivatives, process for their preparation and pharmaceutical compositions in which they are present. U.S. Patent 1995/5462960, 1995. (b) Ragan, J. Process for preparing purine compounds. PCT Patent WO 2006/043175 A2, 2006.
(16) (a) Lin, L. S.; Lanza, T. J.; Jewell, J. P.; Liu, P.; Shah, S. K.; Qi, H.; Tong, X.; Wang, J.; Xu, S.; Fong, T. M.; Shen, C.-P.; Lao, J.; Chen, J.; Shearman, L. P.; Stribling, D. S.; Rosko, K.; Strack, A.; Marsh, D. J.; Feng, Y.; Kumar, S.; Samuel, K.; Yin, W.; Van der Ploeg, L.; Goulet, M. T.; Hagmann, W. K. Discovery of *N*-[(1*S*,2*S*)-3-(4-chlorophenyl)-2-(3-cyanophenyl)-1-methylpropyl]-2-methyl-2-{[5-(trifluoromethyl) pyridin-2-yl]oxy}propanamide (MK-0364), a novel, acyclic cannabinoid-1 receptor inverse agonist for the treatment of obesity. *J. Med. Chem.* **2006**, *49*, 7584–7587. (b) Chen, C.-y.; Frey, L. F.; Shultz, S.; Wallace, D. J.; Marcantonio, K.; Payack, J. F.; Vazquez, E.; Springfield, S. A.; Zhou, G.; Liu, P.; Kieczykowski, G. R.; Chen, A. M.; Phenix, B. D.; Singh, U.; Strine, J.; Izzo, B.; Krska, S. W. Catalytic, enantioselective synthesis of taranabant, a novel, acyclic cannabinoid-1 receptor inverse agonist for the treatment of obesity. *Org. Process Res. Dev.* **2007**, *11*, 616–623. (c) Lin, L. S.; Ha, S.; Ball, R. G.; Tsou, N. N.; Castonguay, L. A.; Doss, G. A.; Fong, T. M.; Shen, C. P.; Xiao, J. C.; Goulet, M. T.; Hagmann, W. K. Conformational analysis and receptor docking of *N*-[(1*S*,2*S*)-3-(4-chlorophenyl)-2-(3-cyanophenyl)-1-methylpropyl]-2-methyl-2-{[5-(trifluoromethyl)pyridin-2-yl]oxy}propanamide (taranabant, MK-0364), a novel, acyclic cannabinoid-1 receptor inverse agonist. *J. Med. Chem.* **2008**, *51*, 2108–2114.
(17) Fong, T. M.; Guan, X.-M.; Marsh, D. J.; Shen, C.-P.; Stribling, D. S.; Rosko, K. M.; Lao, J.; Yu, H.; Feng, Y.; Xiao, J. C.; Van der Ploeg, L. H. T.; Goulet, M. T.; Hagmann, W. K.; Lin, L. S.; Lanza, T. J., Jr.; Jewell, J. P.; Liu, P.; Shah, S. K.; Qi, H.; Tong, X.; Wang, J.; Xu, S. S.; Francis, B.; Strack, A. M.; Macintyre, D. E.; Shearman, L. P. Antiobesity efficacy of a novel cannabinoid-1 receptor inverse agonist, *N*-[(1*S*,2*S*)-3-(4-chlorophenyl)-2-(3-cyanophenyl)-1-methylpropyl]-2-methyl-2-{[5-(trifluoromethyl)pyridin-2-yl]oxy}propanamide (MK-0364), in rodents. *J. Pharmacol. Exp. Ther.* **2007**, *321*, 1013–1022.
(18) Shim, J.-Y.; Welsh, W. J.; Cartier, E.; Edwards, J. L.; Howlett, A. C. Molecular Interaction of the Antagonist *N*-(Piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide with the CB_1 Cannabinoid Receptor. *J. Med. Chem.* **2002**, *45*, 1447–1459.
(19) (a) Dow, L. R. Cannabinoid receptor ligands and uses thereof. U.S. Patent 2004/0077650A1, 2004. (b) Coe, J. W. Purine compounds and uses thereof. U.S. Patent 2005/0043327 A1, 2005.
(20) Kang, S. Y.; Lee, S.-H.; Seo, H. J.; Jung, M. E.; Ahn, K.; Kim, J.; Lee, J. Tetrazole-biarylpyrazole derivatives as cannabinoid CB1 receptor antagonists. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2384–2388.
(21) Barth, F.; Congy, C.; Gueule, P.; Rinaldi-Carmona, M.; Van Brodeck, D. (1,5-Diphenyl-1*H*-pyrazol-3-yl)oxadiazole derivatives, preparation method thereof and use of same in therapeutics. PCT Patent WO 2006/087480 A1, 2006.
(22) Moritani, Y. Pyrazole compounds having cannabinoid receptor (CB1) antagonizing activity. PCT Patent WO 2007/046550 A1, 2007.
(23) (a) Barth, F.; Casellas, P.; Congy, C.; Martinez, S.; Ridaldi, M. Pyrazole-3-carboxamide derivatives, process for their preparation and pharmaceutical compositions in which they are present. U.S. Patent 5,462,960, 1995. (b) Lan, R.; Liu, Q.; Fan, P.; Lin, S.; Frnando, S. R.; McCallion, D.; Pertwee, R.; Makriyannis, A. Structure−activity relationships of pyrazole derivatives as cannabinoid receptor antagonists. *J. Med. Chem.* **1999**, *42*, 769–776. (c) Katoch-Rouse, R.; Pavlova, O. A.; Caulder, T.; Hoffman, A. F.; Mukhin, A. G.; Horti, A. G. Synthesis, structure−activity relationship, and evaluation of SR141716 analogues: development of central cannabinoid receptor ligands with lower lipophilicity. *J. Med. Chem.* **2003**, *46*, 642–645.
(24) (a) Brain, C. T.; Paul, J. M.; Loong, Y.; Oakely, P. J. Novel procedure for the synthesis of 1,3,4-oxadiazoles from 1,2-diacylhydrazines using polymer-supported Burgess reagent under microwave conditions. *Tetrahedron Lett.* **1999**, *40*, 3275–3278. (b) Brain, C. T.; Brunton, S. A. Synthesis of 1,3,4-oxadiazoles using polymer-supported reagents. *Synlett* **2001**, 382.
(25) (a) Barth, F.; Congy, C.; Martinez, S.; Rinaldi, M. Pyrazole derivatives, method for preparing same, and pharmaceutical compositions containing said derivatives. U.S. Patent 6,028,084, 2000. (b) Amengual, R.; Marsol, C.; Mayeux, E.; Sierra, M.; Wagner, P. Pyrazole derivatives as cannabinoid receptor modulators. PCT Patent WO 2006/133926 A1, 2006.
(26) Walba, D. M.; Razavi, H. A.; Clark, N. A.; Parmar, D. S. Design and synthesis of new ferroelectric liquid crystals. 5. Properties of some chiral fluorinated FLCs: a direct connection between macroscopic properties and absolute configuration in a fluid phase. *J. Am. Chem. Soc.* **1988**, *110*, 8686–8691.
(27) Wood, M. R.; Kim, J. Y.; Brooks, K. M. A novel one-step method for the conversion of primary alcohols into carbamate-protected amines. *Tetrahedron Lett.* **2002**, *43*, 3887–3890.
(28) Dess, D. B.; Martin, J. C. Readily accessible 12-I-5-oxidant for the conversion of primary and secondary alcohols to aldehydes and ketones. *J. Org. Chem.* **1983**, *48*, 4155–4156.
(29) (a) Miyaura, N.; Suzuki, A. Palladium-catalyzed cross-coupling reactions of organoboron compounds. *Chem. Rev.* **1995**, *95*, 2457–2483. (b) Wallace, D. J.; Chen, C.-y. Cyclopropylboronic acid: synthesis and Suzuki cross-coupling reactions. *Tetrahedron Lett.* **2002**, *43*, 6987–6990. (c) Lemhadri, M.; Doucet, H.; Santelli, M. Suzuki coupling of cyclopropylboronic acid with aryl halides catalyzed by a palladium-tetraphosphine complex. *Synth. Commun.* **2006**, *36*, 121–128.
(30) Kuster, J. E.; Stevenson, J. I.; Ward, S. J.; D'Ambra, T. E.; Haycock, D. A. Aminoalkylindole binding in rat cerebellum: selective displacement by natural and synthetic cannabinoids. *J. Pharmacol. Exp. Ther.* **1993**, *264*, 1352–1363.
(31) See homology modeling results in Figure 5.
(32) Murphy, J. W.; Kendall, D. A. Integrity of extracellular loop 1 of the human cannabinoid receptor 1 is critical for high-affinity binding of the ligand CP 55,940 but not SR 141716A. *Biochem. Pharmacol.* **2003**, *65*, 1623–1631.
(33) In contrast to compounds **42c** and **43c**, **43f** was observed to be less efficacious in the DIO mouse model ($16.7 \pm 1.6\%$ reduction in body weight after seven days).
(34) (a) McAllister, S. D.; Hurst, D.; Buehner, K.; Norris, J. B.; Reggio, P. H.; Abood, M. E. Aromatic residues in helixes 3-5-6 of CB1 provide specific interaction sites for WIN55,212-2 and SR141716A. *2002 Symposium on the Cannabinoids*; International Cannabinoid Research Society, Burlington, VT, 2002; p 76. (b) McAllister, S. D.; Rizvi, G.; Anavi-Goffer, S.; Hurst, D. P.; Barnett-Norris, J.; Lynch, D. L.; Reggio, P. H.; Abood, M. E. An aromatic microdomain at the cannabinoid CB(1) receptor constitutes an agonist/inverse agonist binding region. *J. Med. Chem.* **2003**, *46*, 5139–5152. (c) Salo, O. M. H.; Lahtela-Kakkonen, M.; Gynther, J.; Jarvinen, T.; Poso, A. Development of a 3D model for the human cannabinoid CB1 receptor. *J. Med. Chem.* **2004**, *47*, 3048–3057.
(35) *Sybyl*, 7.3 ed.; SYBYL molecular modeling software. Tripos Inc.: St. Louis, MO, 2007.
(36) Jain, A. N. Surflex: fully automatic flexible molecular docking using a molecular similarity-based search engine. *J. Med. Chem.* **2003**, *46*, 499–511.
(37) Hildebrandt, A. L.; Kelly-Sullivan, D. M.; Black, S. C. Antiobesity effects of chronic cannabinoid CB1 receptor antagonist treatment in diet-induced obese mice. *Eur. J. Pharmacol.* **2003**, *462* (1−3), 125–132.
(38) Although compound **4u** shows good in vitro activity, this compound did not provide acceptable in vivo efficacy. Therefore, we selected **4h** as our lead compound rather than **4u**.
(39) According to related publications, substitution around the C-4 region of the pyrazole scaffold has been relatively unexplored. Initially, we intended to investigate small changes in the C-4 region, and we were surprised to discover that this region is capable of accommodating substituents of varying functionality, size, and polarity.
(40) As pointed out by a reviewer, the surrogate effect of the cyclopropyl group for a gem-dimethyl group is observed in compounds **4u** and **4v**, but this effect appears to be more pronounced in compounds **32d** and **42b**.
(41) Katoch-Rouse, R.; Pavlova, O. A.; Caulder, T.; Hoffman, A. F.; Mukhin, A. G.; Horti, A. G. Synthesis, structure−activity relationship, and evaluation of SR141716 analogues: development of central cannabinoid receptor ligands with lower lipophilicity. *J. Med. Chem.* **2003**, *46*, 642–645.

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