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Discovery of 2-[5-(4-Chloro-phenyl)-1-(2,4-dichloro-phenyl)-4-ethyl-1*H*-pyrazol-3-yl]-1,5,5-trimethyl-1,5-dihydro-imidazol-4-thione (BPR-890) via an Active Metabolite. A Novel, Potent and Selective Cannabinoid-1 Receptor Inverse Agonist with High Antiobesity Efficacy in DIO Mice

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By using the active metabolite **5** as an initial template, further structural modifications led to the identification of the titled compound **24** (BPR-890) as a highly potent CB1 inverse agonist possessing an excellent CB2/1 selectivity and remarkable in vivo efficacy in diet-induced obese mice with a minimum effective dose as low as 0.03 mg/kg (po qd) at the end of the 30-day chronic study. Current SAR studies along with those of many existing rimonabant-mimicking molecules imply that around the pyrazole C3-position, a rigid and deep binding pocket should exist for CB1 receptor. In addition, relative to the conventional carboxamide carbonyl, serving as a key hydrogen-bond acceptor during ligand−CB1 receptor interaction, the corresponding polarizable thione carbonyl might play a more critical role in stabilizing the Asp366-Lys192 salt bridge in the proposed CB1-receptor homology model and inducing significant selectivity for CB1R over CB2R.

Introduction

The endocannabinoid system (ECS[a]), consisting, to date, of endocannabinoids such as anandamide and 2-arachidonoyl glycerol (2-AG), two cannabinoid receptors type 1 (CB1) and type 2 (CB2), and enzymes responsible for endogenous ligand synthesis (phospholipase D) and degradation (fatty acid amide hydrolase (FAAH)), is a complicate physiological system involved in metabolic homeostasis such as modulating energy and glucose balance, etc.[1−4] The CB1 receptor is predominantly expressed in several brain areas and peripheral tissues; in contrast, the CB2 receptor is expressed almost exclusively in peripheral cells of the immune system related to immune regulation and neurodegeneration.[5] Studies on the ECS along the CB1-cannabinoid axis have disclosed and validated that blocking CB1 receptor activity could lead to weight loss through reduction of food intake and increased energy expenditure. Therefore, CB1 receptor antagonists were highly anticipated in the past decade to become a new therapeutic approach to treat obesity, a typical disease resulting from a long-term imbalance of the energy intake and expenditure, and widely recognized as one of major health concerns in the modern society, particularly given that currently only two antiobesity agents orlistat,[6] a gastrointestinal lipase inhibitor, and sibutramine,[7] a serotonin reuptake inhibitor, are available, but both meet with moderate success owing to their limited weight-loss efficacy and significant accompanying adverse effects. However, substantial clinical evidence revealed that CB1 antagonists might result in risks of severe psychiatric problems, including depression, anxiety, and stress disorders; these findings, indeed, have made rimonabant **1** (SR141716A),[8] the first CB1 inverse agonist approved and launched in Europe in 2006, withdrawn from the market in 2008, and thereof, several CB1 target-related candidates including taranabant **2** (MK-0364)[9] and otenabant **3** (CP-945598)[10] were suspended at the late clinical development stage (phase III) (Figure 1). In the meanwhile, increased evidence indicate that CB1 receptors present in the peripheral tissues, including fat and liver, might regulate food intake and energy balance as effectively as those appearing in the central nervous system (CNS).[11] It is widely accepted that adverse effects would be significantly attenuated when compounds act solely on receptors or enzymes located in the peripheral system rather than CNS. As such, instead of the conventional brain-penetrant CB1 antagonists, an alternative to develop peripherally restricted CB1 antagonists without penetrating blood−brain barrier (BBB) was then adopted. Recently, this strategy was found to meet with a certain degree of success in that less CNS toxic profile and sufficient weight-reduction efficacy have been observed with rimonabant-mimicking analogues acting exclusively on peripheral CB1 receptor as reported by Piomelli, et al.[12] and Jenrin Discovery.[13] Nevertheless, it is believed that more extensive safety evidence should be provided to validate the aforementioned concept.

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[a] Abbreviations: ECS, endocannabinoid system; CB, cannabinoid; BBB, blood−brain barrier; DIO, diet-induced obese; NADPH, β-nicotinamide adenine dinucleotide phosphate; SAR, structure−activity relationships; LHMDS, lithium bis(trimethylsily)amide; NBS, *N*-bromosuccinimde; DMF, *N*,*N*-dimethylformamide; Eu−GTP, europium guanosine 5′-triphosphate; IA, inverse agonist; FAAH, fatty acid amide hydrolase; CNS, central nervous system; ESMS, electrospray mass spectra.

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Chart 1. Proposed Mechanism of the Metabolite **5** Derived from Imide **4**

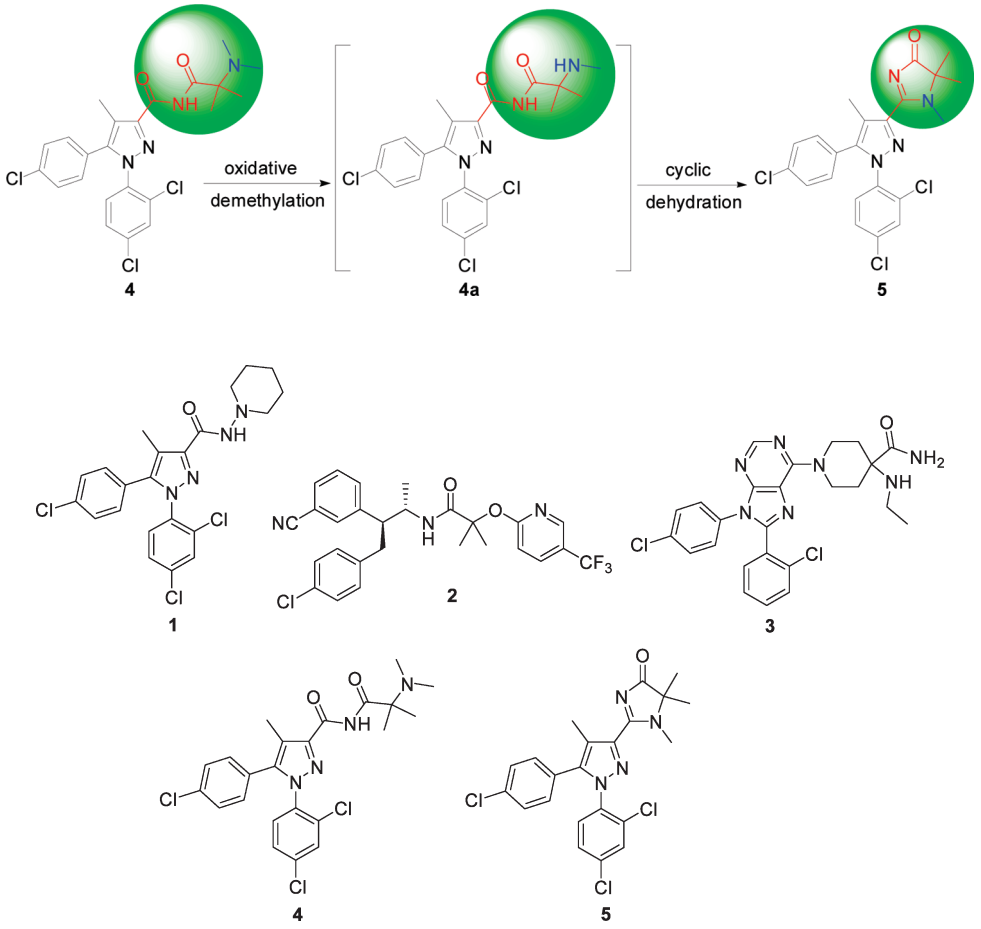


Figure 1. Chemical structure of compounds **1**−**5**.

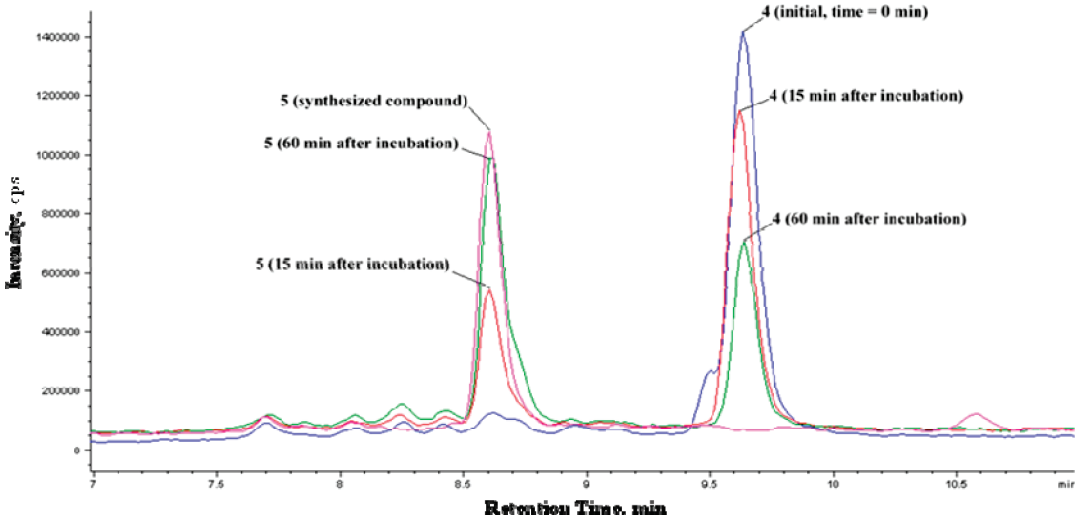
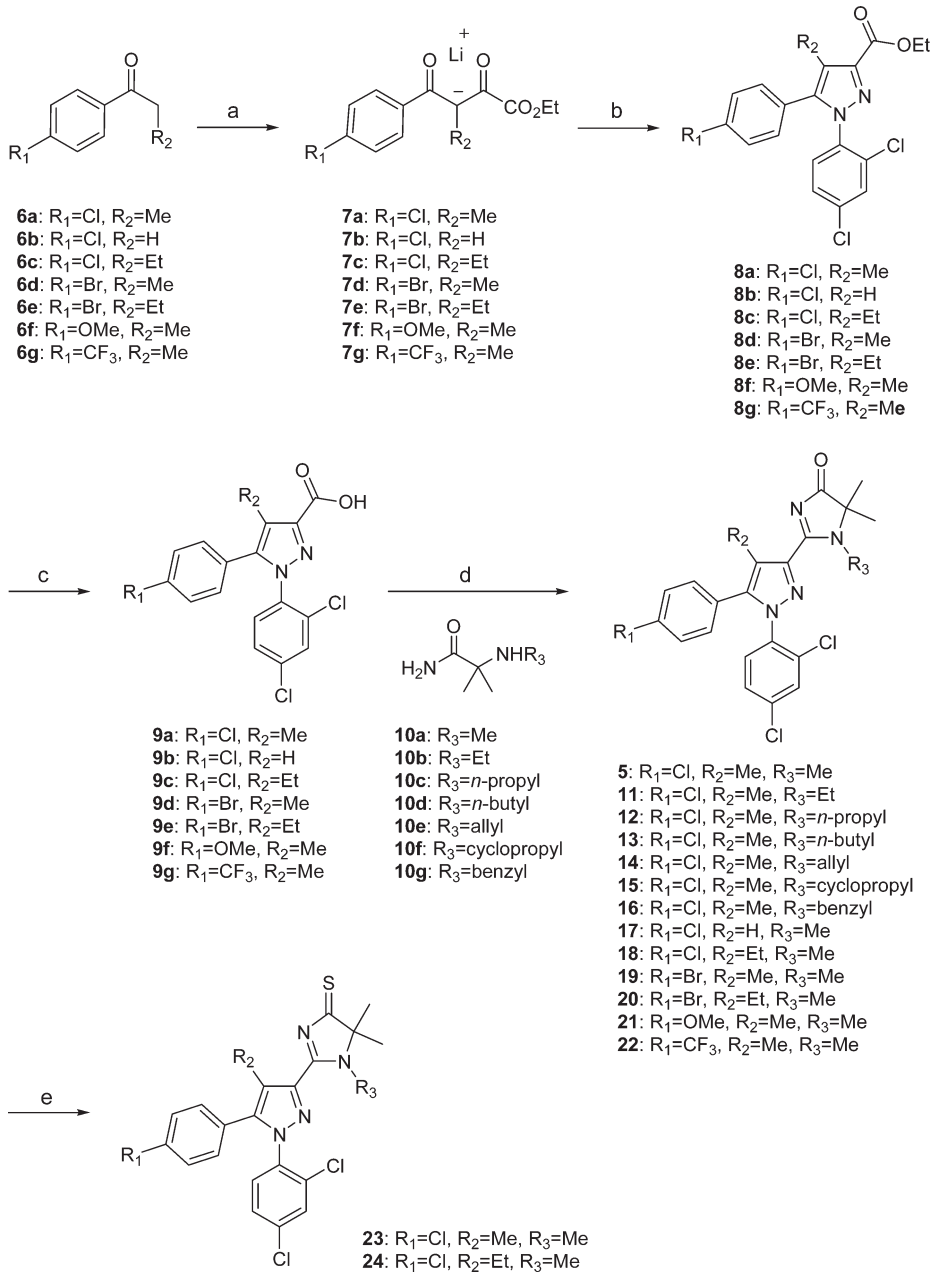


Figure 2. Compound **4** was incubated in rat liver microsomes with NADPH; the blue peak stands for the initial compound **4** with a retention time of 9.64 min; the red and green peaks stand for the growth of metabolite **5** at the expense of **4** after incubation in 15 and 60 min, respectively; the pink peak stands for the synthetic compound **5**, being identical to metabolite **5**, with a retention time of 8.61 min. Details of incubation and analytical method are described in the Experimental Section B1.

Along this line, a novel series of imide derivatives, originally intended to reduce the ability in blood−brain penetration,[14−16] was then designed and experimentally realized in our laboratories.[17] Unfortunately, it was found that during pharmacokinetic studies in rats, many of these imide CB1 antagonists disappeared in approximately 50 and 15 min following oral administration and iv injection, respectively. Instead, a primary metabolite, which proved to be an active metabolite later, was significantly formed in each case examined. Similar metabolic profiles were observed and verified

Scheme 1. Synthesis of Imidazol-4-one/thione Compounds **5** and **11**−**24**[a]

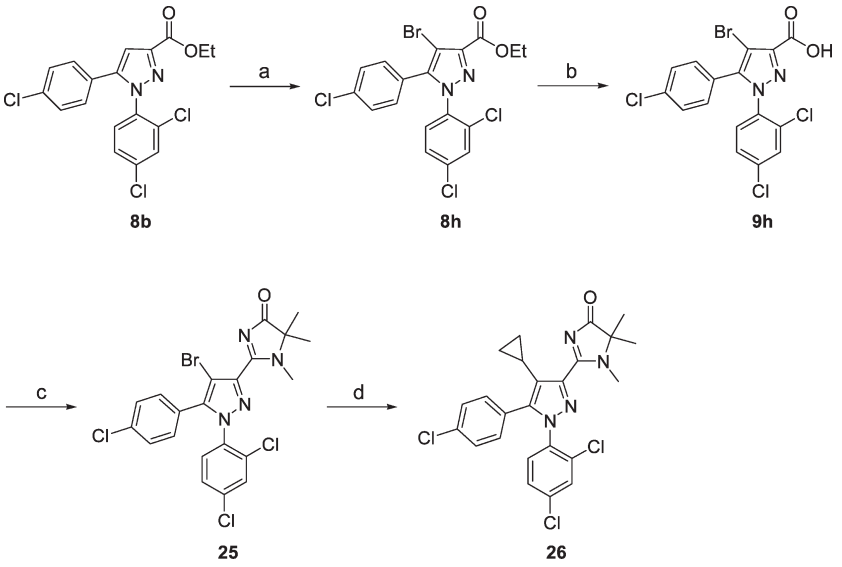


[a] Reagents and conditions: (a) diethyl oxalate, LHMDS, −78 °C to room temp, 16 h, 65−80%; (b) 2,4-dichlorophenylhydrazine hydrochloride, EtOH, room temp, 20 h, then AcOH, reflux, 24 h, 36−50% over two steps; (c) KOH, MeOH, 60 °C, 4 h, 84−94%; (d) oxalyl chloride, DMF (cat), toluene, 1 h; **10a**−**10g**, NEt_3, THF, 0 °C to room temp, 15 h, then NaOMe, MeOH, 60 °C, 4 h, 30−60% over two steps; (e) Lawesson's reagent, toluene, 60 °C, 4 h, 58−77%.

in parallel by incubating them in vitro in the rodent or human liver microsomes in the presence of β-nicotinamide adenine dinucleotide phosphate (NADPH). As typified by imide **4** (IC_{50} = 82.9 nM; CB2/1 = 35) incubated in the rat microsomes (Figure 2), an active metabolite **5** (IC_{50} = 54.7 nM; CB2/1 = 9), unambiguously identified through comparison with the synthetic molecule illustrated in Scheme 1, appeared within 15 min and steadily grew at the expense of **4** during the progress of reaction. A mechanistic rationale is depicted in Chart 1. It is conceivable that the metabolic demethylation occurred initially to convert **4** into the metastable amine **4a**, which underwent intramolecular cyclization rapidly via an enzyme-mediated dehydration process to generate the final metabolite **5**. On the basis of these findings, herein, we wish to report that using **5** as an initial model, further structural modifications led to the identification of compounds **24** (BPR-890) (IC_{50} = 12.0 nM; CB2/1 = 396) and **28** (IC_{50} = 32.6 nM; CB2/1 = 314) as highly potent and selective CB1 inverse agonists with a significant increase in weight-reduction efficacy in diet-induced obese (DIO) mice by 33-fold and 10-fold, respectively, as compared to agent **1** (IC_{50} = 13.2 nM; CB2/1 = 124). Detailed description of the design, synthesis, and structure−activity relationships (SAR) of the newly developed imidazol-4-ones (thiones) as well as the long-term efficacy study on weight loss in DIO mice for potential compounds will be presented as follows.

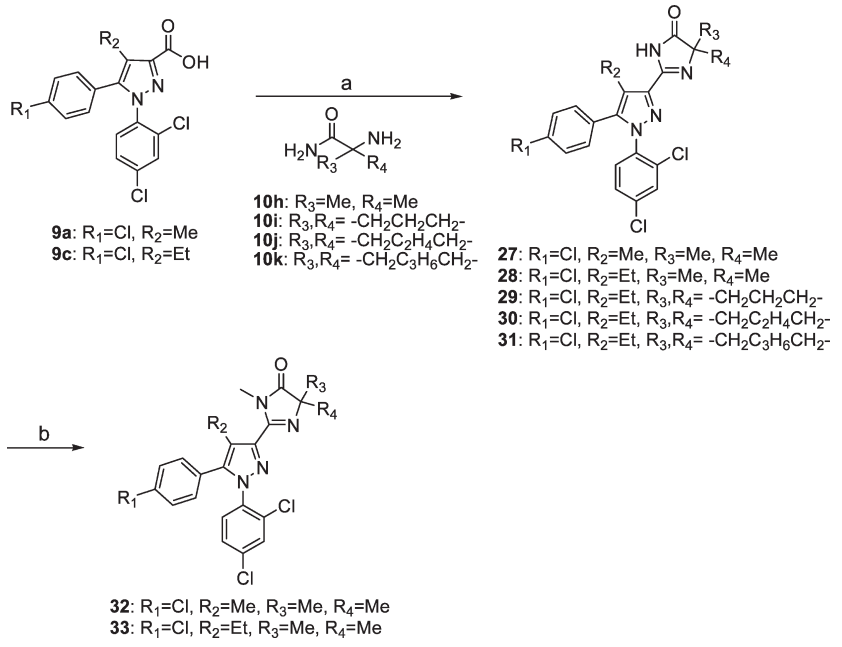
Chemistry. Compounds **5** and **11**−**24** were prepared according to a general synthetic method shown in Scheme 1

Scheme 2. Synthesis of Imidazol-4-ones **25** and **26**[a]



[a] Reagents and conditions: (a) NBS, THF, room temp, 72 h, 59%; (b) KOH, MeOH, 60 °C, 4 h, 87%; (c) oxalyl chloride, DMF (cat), toluene, 1 h; **10a**, NEt_3, THF, 0 °C to room temp, 15 h, then NaOMe, MeOH, 60 °C, 4 h, 51% over two steps; (d) $C_3H_5B(OH)_2$, K_2CO_3, $Pd(PPh_3)_4$, toluene, microwave, 80 °C, 2 h, 35%.

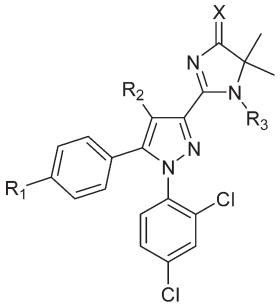
Scheme 3. Synthesis of Imidazol-4-ones **27**−**33**[a]



[a] Reagents and conditions: (a) oxalyl chloride, DMF (cat), toluene, 1 h; **10h**−**10k**, NEt_3, THF, 0 °C to room temp, 15 h, then $POCl_3$, 1,2-dichloroethane, 80 °C, 4 h, 47−52%; (b) NaH, MeI, DMF, room temp, 2 h, 68−69%.

using compound **5** and its corresponding thioketone **23**, respectively, as a typical example. Treatment of 1-(4-chlorophenyl)-propan-1-one (**6a**) with diethyl oxalate in the presence of LHMDS as a base gave rise to lithium salt **7a** in 80% yield, which in turn, without purification, was coupled with 2,4-dichlorophenylhydrazine hydrochloride in ethanol followed by intramolecular cyclization in acetic acid under refluxing conditions to provide ester **8a** in 49% yield over two steps. Compound **8a** thus obtained was subjected to basic hydrolysis under standard conditions to afford carboxylic acid **9a** in 94% yield. The carboxylic group of **9a** was then activated with oxalyl chloride in the presence of DMF as a catalyst to form the corresponding acyl chloride, which was allowed to couple with 2-methyl-2-methylamino-propionamide (**10a**) to afford an amide intermediate. This intermediate, without purification, could undergo intramolecular cyclization effectively under treatment with sodium methoxide in methanol, giving rise to the desired product **5** in 55% yield over two steps. Compound **5** was smoothly transformed into the corresponding thioketone **23** with Lawesson's reagent[18] in toluene in 77% yield. On the other hand, compounds **25** and **26** were provided according to a synthetic sequence illustrated in Scheme 2 using intermediate **8b** as the starting material. Selective bromination

Table 1. Biological Evaluation of Novel 2-pyrazolyl Imidazol-4-one/thione Derivatives on hCB1 and hCB2 Receptors



					IC_{50} (nM)[a,b]		selectivity
compd	R_1	R_2	R_3	X	hCB1	hCB2	CB2/CB1
5	Cl	Me	Me	O	54.7 ± 6.9	486.9 ± 129.8	9
11	Cl	Me	Et	O	107.0 ± 17.9	1173.7 ± 235.1	11
12	Cl	Me	*n*-Pr	O	853.6 ± 135.0	5510.1 ± 318.3	7
13	Cl	Me	*n*-Bu	O	1110.8 ± 52.0	4763.3 ± 349.7	4
14	Cl	Me	allyl	O	248.9 ± 75.9	2881.5 ± 252.3	12
15	Cl	Me	cyclo-propyl	O	95.2 ± 28.1	1950.4 ± 151.1	21
16	Cl	Me	Bn	O	197.0 ± 37.3	5126.9 ± 160.1	26
17	Cl	H	Me	O	325.1 ± 20.2	7946.1 ± 658.9	24
18	Cl	Et	Me	O	12.9 ± 3.9	2736.6 ± 374.3	213
19	Br	Me	Me	O	47.4 ± 18.9	1095.5 ± 358.1	23
20	Br	Et	Me	O	16.3 ± 1.2	768.4 ± 130.9	47
21	OMe	Me	Me	O	211.8 ± 93.1	1058.5 ± 38.6	5
22	CF_3	Me	Me	O	15.9 ± 3.5	3968.0 ± 116.7	250
23	Cl	Me	Me	S	6.3 ± 2.7	901.4 ± 189.5	143
24	Cl	Et	Me	S	12.0 ± 4.1	4746.0 ± 481.5	396
25	Cl	Br	Me	O	42.5 ± 21.2	1570.6 ± 503.9	37
26	Cl	cyclo-propyl	Me	O	43.9 ± 9.2	822.0 ± 76.0	19
1					13.2 ± 2.3	1631.1 ± 208.5	124

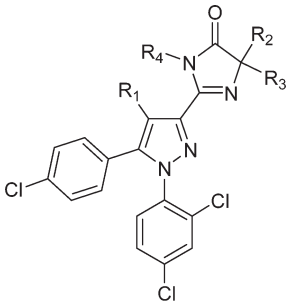
[a] Binding affinity determined by inhibition of [^{3}H] CP-55,940 ([^{3}H] **34**) binding to hCB1 or hCB2-transfected HEK 293 membrane is expressed as IC_{50}. [b] Data are expressed as the mean ± SD of at least three independent experiments.

was effected with NBS in THF to afford **8h** in 57% yield, which in turn was hydrolyzed under basic conditions to give carboxylic acid **9h** in high yield (87%). Compound **9h** thus obtained was reacted with oxalyl chloride and DMF (cat.) to form the corresponding acyl chloride, which was then condensed with **10a** to give the amide intermediate. This intermediate, without purification, could undergo intramolecular cyclization in the presence of sodium methoxide in methanol at 60 °C to afford product **25** in 51% yield over two steps. Compound **25** was successfully coupled with cyclopropylboronic acid under Suzuki−Miyaura coupling conditions[19] to furnish the desired 4-cyclopropyl pyrazole **26** in 35% yield. Similarly, compounds **27**−**33** were readily prepared following a general synthetic approach depicted in Scheme 3 using compound **27** and its methylated derivative **32**, respectively, as a typical example. Carboxylic acid **9a** was treated with oxalyl chloride in toluene to form acyl chloride, which was coupled with 2-amino-2-methyl-propionamide (**10h**) to provide the corresponding amide. The crude amide, without purification, was then treated with $POCl_3$ in 1,2-dichloroethane at elevated temperature to undergo intramolecular cyclization, affording product **27** in 52% yield over two steps. Interestingly, it is noteworthy that the cyclization process for compounds **27**−**33** must be carried out under acidic conditions with $POCl_3$ instead of previous basic conditions with NaOMe as employed in Schemes 1 and 2 for compounds **5** and **11**−**26**. Further alkylation of **27** with methyl iodide in DMF resulted in the corresponding methylated **32** in 69% yield. All tested compounds mentioned above exhibited more than 95% purity, as evidenced by elemental analysis outlined in Supporting Information, prior to submission for biological assays and animal studies.

Results and Discussion

Compounds described above were subjected to in vitro biological evaluation toward CB1 and CB2 receptors, results of which are compiled in Tables 1−3, and related SAR studies are discussed in the following. Using the active metabolite **5** (IC_{50} = 54.7 nM; CB2/1 = 9) as a novel template, a series of structurally related imidazol-4-ones/thiones were thus synthesized according to Schemes 1 and 2. As illustrated in Table 1, when the methyl substituent of **5** at R_3 was replaced with a linear alkyl group, the resulting compounds **11**−**13** exhibited a significant decrease in binding affinity for both CB1 and CB2 receptor in chain length-ascending order: methyl > ethyl > *n*-propyl > *n*-butyl. In addition, there was no improvement in CB2/1 selectivity (CB2/1 = 4−11) by above linker-elongation modifications as compared to **5** (CB2/1 = 9). Similar results in poor CB1 binding affinity and selectivity were also observed for compounds **14**−**16**, wherein R_3 was individually equipped with an aliphatic group in various dimensions, indicating that a hydrocarbon moiety bulkier than methyl group seems not to be tolerated at this position. As such, using the methyl motif as a fixed theme for R_3, further structural modifications were extended to explore R_2 substitution. Encouragingly, it was found that when the methyl group of R_2 in **5** (IC_{50} = 54.7 nM; CB2/1 = 9) was replaced with an ethyl unit, the resulting compound **18** (IC_{50} = 12.9 nM; CB2/1 = 213) showed not only a substantial increase in CB1 binding affinity but also an excellent selectivity for CB1R over CB2R. In contrast, when the methyl group switched to a smaller hydrogen atom, compound **17** (IC_{50} = 325.1 nM) thus obtained resulted in a 6-fold decrease in CB1 activity along with a slight improvement in selectivity (CB2/1 = 24). However, once a larger group, such as a cyclopropyl ring or a bromine atom, was installed instead of the hydrogen, the CB1 activity was recovered as indicated by compounds **25** (IC_{50} = 42.5 nM) and **26** (IC_{50} = 43.9 nM), respectively, relative to the initial model **5** (IC_{50} = 54.7 nM). Although a variety of functional groups could be established for R_2 substitution from synthetic point of view,[20] both methyl and ethyl units were found to be extremely successful for rimonabant-mimicking molecules in many historical cases.[2] Similar conclusions could also be derived based on an array of examples outlined in Table 1. Accordingly, R_2 was then restricted to the methyl or ethyl functionality for further structural exploration with particular emphasis on the latter in light of metabolic stability.[2] As for R_1 substitution, as expected, bromine atom is an excellent bioisosteric surrogate for the chlorine atom as highlighted by compounds **19** (IC_{50} = 47.4 nM) and **20** (IC_{50} = 16.3 nM) in comparison with their chlorine counterparts **5** (IC_{50} = 54.7 nM) and **18** (IC_{50} = 12.9 nM), respectively. Also noted was the finding that compounds containing an electron-withdrawing group at R_1 appeared superior to the corresponding compounds with an electron-donating group in bestowing CB1 binding affinity and selectivity as typified by **22** (R_1 = CF_3; IC_{50} = 15.9 nM; CB2/1 = 250) and its counterpart **21** (R_1 = OCH_3;

Table 2. Biological Evaluation of Novel 2-Pyrazolyl Imidazol-4-one Derivatives on hCB1 and hCB2 Receptors



					IC_{50} (nM)[a,b]		Selectivity
compd	R_1	R_2	R_3	R_4	hCB1	hCB2	CB2/CB1
27	Me	Me	Me	H	53.4 ± 14.2	3500.6 ± 831.1	66
28	Et	Me	Me	H	32.6 ± 4.7	10260.0 ± 579.1	314
29	Et	$-CH_2CH_2CH_2-$		H	22.8 ± 4.3	3177.2 ± 441.3	139
30	Et	$-CH_2C_2H_4CH_2-$		H	14.6 ± 5.2	1372.2 ± 317.3	94
31	Et	$-CH_2C_3H_6CH_2-$		H	12.3 ± 2.2	496.7 ± 149.4	40
32	Me	Me	Me	Me	33.6 ± 5.1	3249.2 ± 122.8	97
33	Et	Me	Me	Me	33.8 ± 4.7	4326.9 ± 264.2	128
1					13.2 ± 2.3	1631.1 ± 208.5	124

[a] Binding affinity determined by inhibition of [^{3}H] **34** binding to hCB1 or hCB2-transfected HEK 293 membrane is expressed as IC_{50}. [b] Data are expressed as the mean ± SD of at least three independent experiments.

IC_{50} = 211.8 nM; CB2/1 = 5). More encouragingly, when the oxygen atom of the imidazol-4-one moiety at pyrazole C3-position was replaced with the sulfur atom, the corresponding thioketone **23** (IC_{50} = 6.3 nM; CB2/1 = 143) exhibited a substantial improvement in both potency and selectivity for CB1 receptor by approximately 10-fold relative to **5**. Similar structural modifications were also extended to compound **18** (IC_{50} = 12.9 nM; EC_{50} = 9.8 nM; CB2/1 = 213), leading to the identification of thioketone **24** (IC_{50} = 12.0 nM; EC_{50} = 5.1 nM; CB2/1 = 396) with a modest enhancement on selectivity and functional activity for CB1 receptor, presumably due to the presence of a polarizable thioketone group resulting in an unusual stabilizing effect on the Asp366-Lys192 salt bridge as highlighted in the proposed CB1-receptor homology model in Figure 3, where the conventional carboxamide carbonyl is believed to serve as a key hydrogen-bond acceptor.[2]

On the basis of these promising results, several structurally closely related analogues **27**−**33** (Table 2) were further prepared for biological evaluation following a synthetic sequence in Scheme 3. It was observed that when R_1 was fixed with the ethyl group, compounds **28** (IC_{50} = 32.6 nM; CB2/1 = 314) and **33** (IC_{50} = 33.8 nM; CB2/1 = 128) exhibited significant CB2/1 selectivity compared to their R_1-methyl counterparts **27** (IC_{50} = 53.4 nM; CB2/1 = 66) and **32** (IC_{50} = 33.6 nM; CB2/1 = 97), respectively; however, the corresponding CB1 binding activities (IC_{50} values) are comparable, indicating that for this new series the presence of the ethyl moiety mainly weakens CB2-binding ability. Along this line, an array of compounds appended with different cyclic rings α to the carbonyl were also explored. The results disclosed that the binding affinity toward both CB1 and CB2 increased with the enlargement of the ring size as demonstrated by compounds **29** (IC_{50} = 22.8 nM; CB2/1 = 139; with a four-membered ring), **30** (IC_{50} = 14.6 nM; CB2/1 = 94; with a five-membered ring), and **31** (IC_{50} = 12.3 nM; CB2/1 = 40; with a six-membered ring), indicating that the increase of lipophilicity at the α position might enhance dual CB1/2 binding affinity with a preference for CB2 receptor as reflected by a sharp drop in CB2/1 selectivity for compounds **28**−**31**. In general, as exemplified by compounds **32** and **33** (Table 2) and their corresponding regioisomers **5** and **18** (Table 1), these two series exhibit very similar CB1/2 receptor−ligand interaction behaviors in terms of binding affinity and selectivity. As well, the rimonabant-mimicking molecules developed above along with many other documented mimetics, wherein a variety of functionalities at the pyrazole C3-position, including 1,3,4-oxadiazole ring,[20,21] 1,2,4-oxadiazole ring,[22] imide,[17,23] and sulfonamide group,[23] have been installed and proven to be effective bioisosteres to the conventional carboxamide moiety, one might come to a conclusion that a rigid and deep cavity should exist around the CB1-receptor pocket surrounded by a series of lipophilic residues (Val196/Phe170/Leu387/Met384) as illustrated in Figure 3.

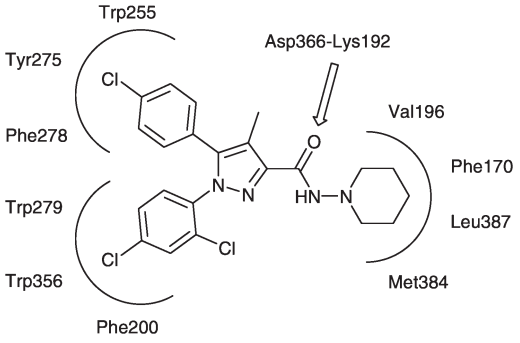


Figure 3. Binding mode of compound **1** in the proposed CB1-receptor homology model.

Compounds with excellent CB1 binding affinity and selectivity were selected for further studies on their functional activity (EC_{50}) and intrinsic property as detailed in the Experimental Section B4 As indicated in Table 3, all promising compounds were evaluated and determined to be inverse agonists as they exhibited a significant decrease in the induced Eu−GTP binding intensity relative to the basal

Table 3. Functional Activity of Compounds **18**, **22**, **23**, **24**, **28**, **29**, and **33** with High CB1 Binding Affinity and CB1/2 Selectivity

compd	EC_{50} (nM)[a,c]	IC_{50} (nM)[b,c]	selectivity CB2/CB1	intrinsic property[d]
18	9.8 ± 2.0	12.9 ± 3.9	213	IA[e]
22	81.0 ± 22.1	15.9 ± 3.5	250	IA
23	8.5 ± 1.6	6.3 ± 2.7	143	IA
24	5.1 ± 1.0	12.0 ± 4.1	396	IA
28	20.2 ± 5.2	32.6 ± 4.7	314	IA
29	12.3 ± 2.2	22.8 ± 4.3	139	IA
33	65.5 ± 31.6	33.8 ± 4.7	128	IA
1	15.7 ± 4.6	13.2 ± 2.3	124	IA

[a] Functional activity determined by inhibition of Eu−GTP binding to hCB1-transfected HEK 293 membrane is expressed as EC50. [b] Binding affinity determined by inhibition of [^{3}H] **34** binding to hCB1or hCB2-transfected HEK 293 membrane as indicated in Tables 1 and 2 is expressed as IC50. [c] Data are expressed as the mean ± SD of the least three independent experiments. [d] The intrinsic property was assessed by the use of Eu−GTP binding to hCB1-transfected HEK 293 membrane at a concentration of 10 μM as indicated in Figure 3.[28,29] [e] Inverse agonist.

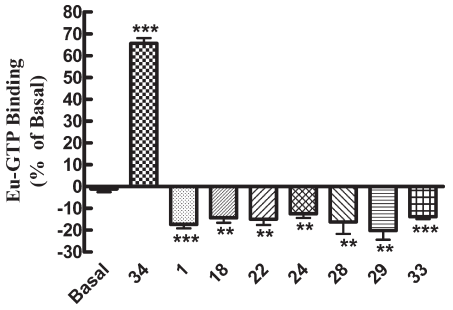


Figure 4. Eu−GTP binding assay of selected 2-pyrazolylimidazol-4-one/thione **18**, **22**, **24**, **28**, **29**, and **33**, as well as reference compounds **1** and **34** at a concentration of 10 μM on the hCB1 cannabinoid receptor, was conducted.[27−29] Data are expressed as the mean ± SD of at least three experiments performed in duplicate. Statistical significance is assessed by unpaired two-tailed *t* test using the GraphPad Prism program (GraphPad Software, San Diego, CA). $P < 0.05$ (*) was considered significant. Compounds with the induced Eu−GTP binding intensity around the basal level are defined as neutral antagonists (NA); compounds with a significant increase in the intensity relative to the basal level are agonists (A) such as **34**; compounds with a significant decrease in the binding intensity are inverse agonists (IA) such as reference **1**. The experimental protocol is detailed in section B4.

level at a concentration of 10 μM (Figure 4). Compounds **24** (EC_{50} = 5.1 nM; IC_{50} = 12.0 nM; CB2/1 = 396; inverse agonist) and **28** (EC_{50} = 20.2 nM; IC_{50} = 32.6 nM; CB2/1 = 314; inverse agonist), each serving as a representative of two different series in the current studies, possessed satisfactory biological profiles in all aspects and thus were elected as potential candidates for further in vivo efficacy studies. As depicted in Figure 5, it was found that as compared to reference **1** (10 mg/kg), compounds **24** and **28** are orally active and able to suppress food intake effectively in nondeprived rats at a dose as low as 0.3 and 3 mg/kg, respectively, indicating that both are well qualified for the further long-term disease animal studies. As a result, chronic treatment of diet-induced obese (DIO) mice with compounds **24** and **28** for 29 days led to significant weight loss with an impressively minimum effective dose of 0.03 and 0.1 mg/kg (po qd), respectively. As demonstrated in Figure 6A, the food intake was substantially reduced at all doses with **24** and appeared to be restored to the level of vehicle-treated mice approximately after six days;

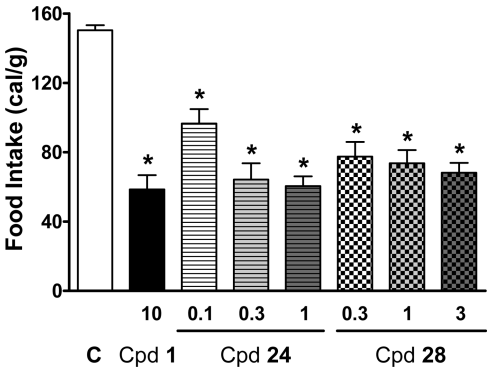


Figure 5. Six-hour culmulative food intake of compounds **24** (0.1, 0.3, and 1 mg/kg) and **28** (0.3, 1, and 3 mg/kg) was examined in rat spontaneous feeding model relative to reference **1** at an oral dose of 10 mg/kg and vehicle C. Data are presented as mean of calorie ingestion normalized by body weight ± standard error (n = 6/group). Statistical analysis was performed by *t* test. $P < 0.05$ (*) was considered significant. The experimental protocol is detailed in section B5.

more encouragingly, reduction of body weight (Figure 6B) was found to proceed in a dose-dependent manner throughout the 30-day period with a relative weight-loss rate of 14.7%, 19.4%, and 25.4% for 0.03, 0.1, and 0.3 mg/kg groups, respectively, indicating that this compound is more efficacious than reference **1** (10 mg/kg, po qd; 23.8% weight reduction) by more than 33-fold in antiobesity efficacy. Similar in vivo responses including food intake suppression (Figure 7A) and body weight loss (Figure 7B) were also observed with compound **28**. As compared to **1** (10 mg/kg) with a 23.7% weight reduction, compound **28** displayed a comparable 27.4% reduction at a dose as low as 1 mg/kg (Figure 7B) and was determined to be more efficacious than **1** by at least 1 order of magnitude. Although compounds **24** and **28** have comparable in vitro activities to **1**, they displayed much more potent in vivo efficacy than **1**. These unexpected outcomes might be attributed to their higher concentration found in the several areas of the brain including hypothalamus, where CB1 receptors are predominantly expressed. As indicated by pharmacokinetic analysis, the brain concentration of **24**, **28**, and **1** was found to be 243 ± 47, 1118 ± 204, and 113 ± 14 ng/g at an oral dose of 0.3, 1, and 10 mg/kg, respectively, suggesting that the distribution of **24** and **28** into the brain is much higher than **1**. These data appear to lend support to the remarkable efficacies for **24** and **28** in DIO mouse studies. As well, for comparison purposes, chronic treatment of DIO rats with compound **24** was also carried out, and preliminary results revealed that when dosed orally once a day for 29 days, the relative weight loss compared with vehicle was 5.1% (vs 19.4% in DIO mice) and 9.5% (vs 25.4% in DIO mice) for the 0.1 and 0.3 mg/kg groups (po qd), respectively.[24] Accordingly, compound **24** is considered to be as effective as agent **2** in terms of the corresponding efficacy data observed with DIO rats in the literature.[25]

In summary, using the active metabolite **5** as an initial template, further structural modifications led to the identification of compound **24** as a highly potent CB1 inverse agonist with an excellent CB2/1 selectivity and a remarkable antiobesity efficacy. As indicated above, in the 30-day chronic study, compound **24** showed an astounding effect on weight reduction in DIO mouse model with a minimum effective dose as low as 0.03 mg/kg and was comparable to agent **1** (10 mg/kg) at a dose of 0.3 mg/kg, indicating that it could be more potent than **1** by at least 33-fold. Current SAR studies in conjunction

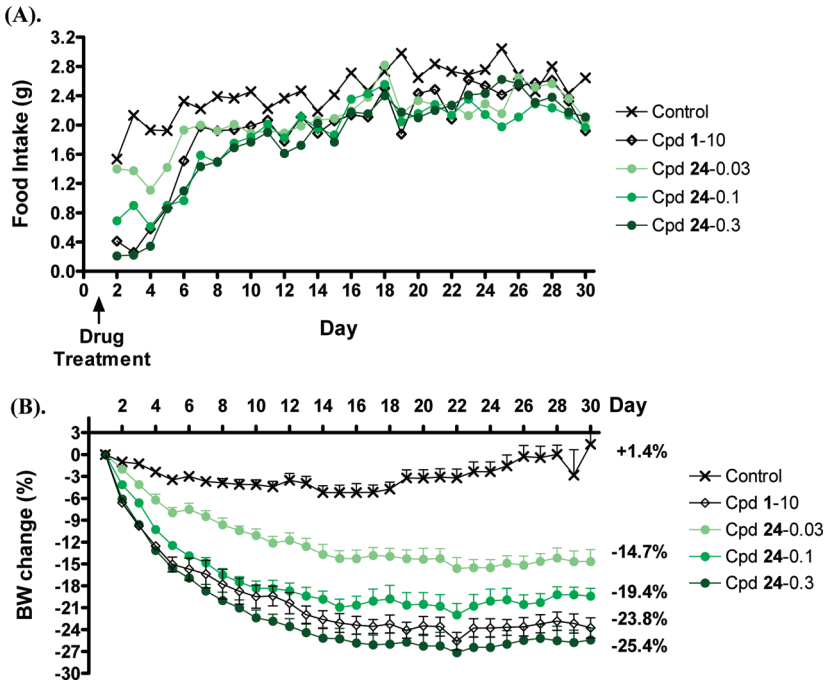


Figure 6. Antiobesity efficacy in DIO mouse model following oral administration of compound **24** (0.03, 0.1, and 0.3 mg/kg, po qd) compared to reference **1** (10 mg/kg, po qd) in the 30-day chronic study (n = 8/group). (A) daily food intake; (B) cumulative percentage of body weight (BW) change. Data are presented as mean ± standard error. The experimental protocol is detailed in section B6.

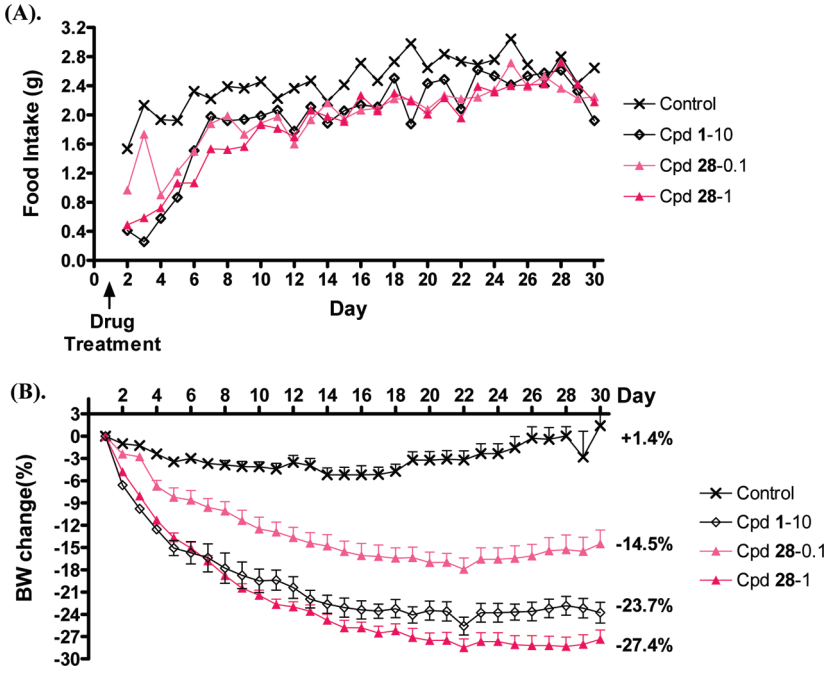


Figure 7. Antiobesity efficacy in DIO mouse model following oral administration of compound **28** (0.1 and 1 mg/kg, po qd) compared to reference **1** (10 mg/kg, po qd) in the 30-day chronic study (n = 8/group). (A) daily food intake; (B) cumulative percentage of body weight (BW) change. Data are presented as mean ± standard error. The experimental protocol is detailed in section B6.

with those of many other rimonabant-mimicking analogues might imply that around the pyrazole C3-position, a rigid and deep binding pocket should exist for CB1 receptor. In addition, as compared to the conventional carboxamide carbonyl, serving as a key hydrogen-bond acceptor during ligand−CB1 receptor interaction, the corresponding thione carbonyl might play a more critical role in stabilizing the putative Asp366−Lys192 salt bridge and inducing significant selectivity for CB1R over CB2R. Further efficacy and pharmacokinetic studies, including central nervous system toxicity, behavioral effects, and blood−brain penetration ability for aforementioned promising antiobesity agents are under active investigation, and results will be reported elsewhere in due course.

Experimental Section

A. Chemistry. Unless otherwise stated, all materials used were commercially available and used as supplied. Reactions requiring

anhydrous conditions were performed in flame-dried glassware and cooled under an argon or nitrogen atmosphere. Unless otherwise stated, reactions were carried out under argon or nitrogen and monitored by analytical thin-layer chromatography performed on glass-backed plates (5 cm × 10 cm) precoated with silica gel 60 F_{254} as supplied by Merck. Visualization of the resulting chromatograms was done by looking under an ultraviolet lamp ($\lambda = 254$ nm), followed by dipping in an ethanol solution of vanillin (5% w/v) containing sulfuric acid (3% v/v) or phosphomolybdic acid (2.5% w/v) and charring by heat gun. Solvents for reactions were dried and distilled under an argon or nitrogen atmosphere prior to use as follows: THF, diethyl ether (ether), and DMF from a dark-blue solution of sodium benzophenone ketyl; toluene, dichromethane, and pyridine from calcium hydride. Flash chromatography was used routinely for purification and separation of product mixtures using silica gel 60 of 230−400 mesh size as supplied by Merck. Eluent systems are given in volume/volume concentrations. ^{1}H and ^{13}C NMR spectra were recorded on Varian Mercury-300 (300 MHz), Varian Mercury-400 (400 MHz), or Varian Mercury-600 (600 MHz). Chloroform-*d* or dimethyl sulfoxide-d_6 was used as the solvent and TMS (δ 0.00 ppm) as an internal standard. Chemical shift values are reported in ppm relative to the TMS in delta (δ) units. Multiplicities are recorded as s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublet), dt (doublet of triplet), m (multiplet). Coupling constants (*J*) are expressed in Hz. Electrospray mass spectra (ESMS) were recorded using an agilent 1100 MSD mass spectrometer. Spectral data were recorded as *m*/*z* values. Combustion elemental analyses were performed by the microanalytical laboratory at National Chung Hsing University, Taiwan, ROC. As required, all tested compounds compiled in Tables 1−3 possessed a purity of higher than 95%, as evidenced by elemental analysis data (Supporting Information) for each compound with an accuracy of elements C, H, and N within ±0.4% with the exception of compound **24**, possessing a variation within ± 0.46% for elements C and N, prior to submitting for functional assay (Eu−GTP), binding affinity assay, and animal studies.

General Procedure for the Synthesis of Compounds 7a−7g. The general procedure is illustrated immediately below with compound **7a** as a specific example.

Lithium Salt of 4-(4-Chloro-phenyl)-3-methyl-2,4-dioxo-butyric Acid Ethyl Ester (7a). To a magnetically stirred solution of lithium *bis*-(trimethylsilyl)amide (16.0 mL, 1.0 M in THF, 16 mmol) in diethyl ether (45 mL) at −78 °C was added a solution of 1-(4-chloro-phenyl)-propan-1-one (**6a**) (2.02 g, 11.98 mmol) in diethyl ether (15 mL) dropwise under an argon atmosphere. After the mixture was stirred at the same temperature for an additional period of 45 min, diethyl oxalate (2.03 g, 13.89 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for another 16 h. The precipitate formed was collected by filtration, washed with diethyl ether, and dried under vacuum to afford the crude lithium salt **7a** (2.60 g, 79%) as a yellowish solid.

General Procedure for the Synthesis of Compounds 8a−8g. The general procedure is illustrated immediately below with compound **8a** as a specific example.

5-(4-Chloro-phenyl)-1-(2,4-dichloro-phenyl)-4-methyl-1*H*-pyrazole-3-carboxylic Acid Ethyl Ester (8a). To a solution of the lithium salt **7a** (2.60 g, 9.47 mmol) in ethanol (35 mL) was added 2,4-dichlorophenylhydrazine hydrochloride (1.82 g, 8.52 mmol) in one portion at room temperature. The resulting mixture was stirred at the same temperature for 20 h. After the reaction was complete, the precipitate was collected by filtration, washed with ethanol and diethyl ether, and dried under vacuum to give a light-yellow solid. This crude solid, without purification, was dissolved in acetic acid (30 mL) and heated to reflux for 24 h. The reaction mixture was poured into ice water, and the resulting mixture was extracted with ethyl acetate (2 × 30 mL). The combined extracts were washed with water, saturated aqueous sodium bicarbonate, brine, dried over anhydrous sodium sulfate, filtered, and concentrated. Purification of the crude residue by flash chromatography on silica gel with *n*-hexane/ethyl acetate (9:1) gave the ester **8a** (1.89 g, 49%) as a white solid: mp 120−121 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, $J = 2.0$ Hz, 1H), 7.27 (d, $J = 8.4$ Hz, 1H), 7.22−7.20 (m, 3H), 6.99 (d, $J = 8.4$ Hz, 2H), 4.36 (q, $J = 6.8$ Hz, 2H), 2.25 (s, 3H), 1.33 (t, $J = 6.8$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8, 143.1, 143.0, 136.1, 136.0, 135.1, 133.2, 131.0 (×2), 130.9, 130.2, 129.0 (×2), 127.9, 127.2, 119.2, 61.1, 14.6, 9.8. ESMS *m*/*z*: 409.1 (M + 1).

5-(4-Chloro-phenyl)-1-(2,4-dichloro-phenyl)-1*H*-pyrazole-3-carboxylic Acid Ethyl Ester (8b). Treatment of **7b** (2.29 g, 8.79 mmol) with 2,4-dichlorophenylhydrazine hydrochloride (1.68 g, 7.5 mmol) and acetic acid (30 mL) gave compound **8b** (1.73 g, 50%) as a white solid: mp 104−106 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, $J = 2.0$ Hz, 1H), 7.41 (d, $J = 8.4$ Hz, 1H), 7.35 (dd, $J = 8.4$, 2.0 Hz, 1H), 7.27(d, $J = 8.4$ Hz, 2H), 7.11 (d, $J = 8.4$ Hz, 2H), 7.06 (s, 1H), 4.45 (q, $J = 6.8$ Hz, 2H), 1.42 (t, $J = 6.8$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 145.6, 145.2, 136.6, 136.1, 136.0, 133.3, 130.8, 130.6, 129.4 (×2), 129.3 (×2), 128.3, 127.6, 109.1, 61.6, 14.6. ESMS *m*/*z*: 395.1 (M + 1).

5-(4-Chloro-phenyl)-1-(2,4-dichloro-phenyl)-4-ethyl-1*H*-pyrazole-3-carboxylic Acid Ethyl Ester (8c). Treatment of **7c** (2.13 g, 7.38 mmol) with 2,4-dichlorophenylhydrazine hydrochloride (1.41 g, 6.60 mmol) and acetic acid (30 mL) gave compound **8c** (1.41 g, 45%) as a white solid: mp 95−96 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, $J = 2.0$ Hz, 1H), 7.33 (d, $J = 8.4$ Hz, 1H), 7.29 (d, $J = 8.4$ Hz, 2H), 7.26 (dd, $J = 8.4$, 2.0 Hz, 1H), 7.07 (d, $J = 8.4$ Hz, 2H), 4.45 (q, $J = 6.8$ Hz, 2H), 2.73 (q, $J = 7.2$ Hz, 2H), 1.42 (t, $J = 6.8$ Hz, 3H), 1.18 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8, 142.9, 142.7, 136.3, 136.1, 135.4, 133.4, 131.2 (×2), 130.9, 130.3, 129.1 (×2), 127.9, 127.4, 126.0, 61.2, 17.4, 15.9, 14.6. ESMS *m*/*z*: 423.1 (M + 1).

5-(4-Bromo-phenyl)-1-(2,4-dichloro-phenyl)-4-methyl-1*H*-pyrazole-3-carboxylic Acid Ethyl Ester (8d). Treatment of **7d** (2.20 g, 6.89 mmol) with 2,4-dichlorophenylhydrazine hydrochloride (1.35 g, 6.34 mmol) and acetic acid (30 mL) gave compound **8d** (1.51 g, 48%) as a white solid: mp 140−141 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, $J = 8.4$ Hz, 2H), 7.38 (d, $J = 2.0$ Hz, 1H), 7.34 (d, $J = 8.4$ Hz, 1H), 7.28 (dd, $J = 8.4$, 2.0 Hz, 1H), 7.00 (d, $J = 8.4$ Hz, 2H), 4.45 (q, $J = 6.8$ Hz, 2H), 2.33 (s, 3H), 1.43 (t, $J = 6.8$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8, 142.9, 142.7, 136.3, 136.2, 133.4, 132.1 (×2), 131.4 (×2), 131.0, 130.4, 128.0, 127.7, 123.7, 119.9, 61.2, 14.7, 9.9. ESMS *m*/*z*: 453.0 (M + 1).

5-(4-Bromo-phenyl)-1-(2,4-dichloro-phenyl)-4-ethyl-1*H*-pyrazole-3-carboxylic Acid Ethyl Ester (8e). Treatment of **7e** (1.91 g, 5.73 mmol) with 2,4-dichlorophenylhydrazine hydrochloride (1.11 g, 5.22 mmol) and acetic acid (30 mL) gave compound **8e** (1.35 g, 50%) as a white solid: mp 103−104 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, $J = 8.4$ Hz, 2H), 7.37 (d, $J = 2.0$ Hz, 1H), 7.33 (d, $J = 8.4$ Hz, 1H), 7.26 (dd, $J = 8.4$, 2.0 Hz, 1H), 7.01 (d, $J = 8.4$ Hz, 2H), 4.45 (q, $J = 6.8$ Hz, 2H), 2.73 (q, $J = 7.2$ Hz, 2H), 1.41 (t, $J = 6.8$ Hz, 3H), 1.18 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 142.9, 142.7, 136.3, 136.1, 133.4, 132.1 (×2), 131.4 (×2), 130.9, 130.3, 127.9, 127.8, 126.0, 123.6, 61.2, 17.4, 15.9, 14.6. ESMS *m*/*z*: 467.0 (M + 1).

1-(2,4-Dichloro-phenyl)-5-(4-methoxy-phenyl)-4-methyl-1*H*-pyrazole-3-carboxylic Acid Ethyl Ester (8f). Treatment of **7f** (2.60 g, 9.62 mmol) with 2,4-dichlorophenylhydrazine hydrochloride (1.81 g, 8.47 mmol) and acetic acid (30 mL) gave compound **8f** (1.63 g, 42%) as a white solid: mp 96−97 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, $J = 2.0$ Hz, 1H), 7.32 (d, $J = 8.4$ Hz, 1H), 7.25 (dd, $J = 8.4$, 2.0 Hz, 1H), 7.04 (d, $J = 8.7$ Hz, 2H), 6.82 (d, $J = 8.7$ Hz, 2H), 4.44 (q, $J = 6.8$ Hz, 2H), 3.78 (s, 3H), 2.32 (s, 3H), 1.41 (t, $J = 6.8$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2, 159.9, 144.2, 143.0, 136.5, 135.9, 133.4, 131.1 (×2), 131.0, 130.2, 127.8, 120.9, 118.8, 114.2 (×2), 61.1, 55.4, 14.7, 9.9. ESMS *m*/*z*: 405.1 (M + 1).

1-(2,4-Dichloro-phenyl)-5-(4-trifluoromethyl-phenyl)-4-methyl-1*H*-pyrazole-3-carboxylic Acid Ethyl Ester (8g). Treatment of **7g** (2.42 g, 7.85 mmol) with 2,4-dichlorophenylhydrazine hydrochloride (1.56 g, 7.31 mmol) and acetic acid (30 mL) gave compound **8g** (1.50 g, 43%) as a white solid: mp 128−129 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 1.8 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.29 (dd, J = 8.0, 1.8 Hz, 1H), 7.26 (d, J = 8.4 Hz, 2H), 4.45 (q, J = 6.8 Hz, 2H), 2.35 (s, 3H), 1.41 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 143.3, 142.7, 136.4, 136.0, 133.2, 132.5, 130.9, 130.4, 130.2 (×2), 128.1, 125.8, 125.7, 125.2, 122.7, 119.8, 61.2, 14.6, 9.9. ESMS m/z: 443.1 (M + 1).

4-Bromo-5-(4-chloro-phenyl)-1-(2,4-dichloro-phenyl)-1*H*-pyrazole-3-carboxylic Acid Ethyl Ester (8h). To a solution of **8b** (2.22 g, 5.61 mmol) in THF (70 mL) was added NBS (2.21 g, 12.41 mmol) in one portion at room temperature. The resulting mixture was stirred at the same temperature for 72 h. The reaction mixture was filtered, and the filtrate was concentrated. The residue was purified by flash chromatography on silica gel with *n*-hexane/ethyl acetate (9:1) to give **8h** (1.56 g, 59%) as a white solid: mp 107−108 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, J = 2.0 Hz, 1H), 7.36 (d, J = 8.4 Hz, 1H), 7.33−7.30 (m, 3H), 7.19 (d, J = 8.4 Hz, 2H), 4.47 (q, J = 6.8 Hz, 2H), 1.43 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0, 144.1, 142.4, 136.9, 136.1, 135.7, 133.1, 131.2 (×2), 130.7, 130.5, 129.2 (×2), 128.2, 125.7, 97.5, 61.8, 14.5. ESMS m/z: 473.0 (M + 1).

General Procedure for the Synthesis of Compounds 9a−9h. The general procedure is illustrated immediately below with compound **9a** as a specific example.

5-(4-Chloro-phenyl)-1-(2,4-dichloro-phenyl)-4-methyl-1*H*-pyrazole-3-carboxylic Acid (9a). To a solution of the ester **8a** (1.00 g, 2.44 mmol) in methanol (25 mL) was added potassium hydroxide (1.02 g, 18.21 mmol) in one portion. The resulting mixture was heated at 60 °C for 4 h. The reaction mixture was then poured into ice water and acidified with 10% hydrochloric acid. The precipitate thus formed was collected by filtration, washed with water, and dried under vacuum to give carboxylic acid **9a** (0.88 g, 94%) as a white solid: mp 202−203 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, J = 2.0 Hz, 1H), 7.31 (d, J = 8.4 Hz, 1H), 7.29−7.26 (m, 3H), 7.05 (d, J = 8.4 Hz, 2H), 2.31 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 143.5, 142.4, 136.4, 135.9, 135.4, 133.1, 131.1 (×2), 130.8, 130.4, 129.2 (×2), 128.1, 127.0, 119.9, 9.8. ESMS m/z: 381.0 (M + 1).

5-(4-Chloro-phenyl)-1-(2,4-dichloro-phenyl)-1*H*-pyrazole-3-carboxylic Acid (9b). Treatment of **8b** (0.97 g, 2.45 mmol) with potassium hydroxide (1.03 g, 18.39 mmol) in methanol (25 mL) gave compound **9b** (0.84 g, 93%) as a white solid: mp 114−115 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 2.0 Hz, 1H), 7.43 (d, J = 8.2 Hz, 1H), 7.37 (dd, J = 8.2, 2.0 Hz, 1H), 7.29 (d, J = 8.3 Hz, 2H), 7.13 (d, J = 8.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 146.1, 144.6, 136.8, 136.0, 135.6, 133.1, 130.7, 130.6, 129.5 (×2), 129.3 (×2), 128.3, 127.4, 109.4. ESMS m/z: 367.0 (M + 1).

5-(4-Chloro-phenyl)-1-(2,4-dichloro-phenyl)-4-ethyl-1*H*-pyrazole-3-carboxylic Acid (9c). Treatment of **8c** (1.02 g, 2.41 mmol) with potassium hydroxide (1.02 g, 18.21 mmol) in methanol (25 mL) gave compound **9c** (0.85 g, 89%) as a white solid: mp 215−216 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, J = 8.4 Hz, 1H), 7.33 (d, J = 2.0 Hz, 1H), 7.28 (d, J = 8.4 Hz, 2H), 7.25 (dd, J = 8.4, 2.0 Hz, 1H), 7.05 (d, J = 8.4 Hz, 2H), 2.66 (q, J = 7.2 Hz, 2H), 1.12 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 143.2, 136.2, 135.9, 135.4, 133.5, 132.9, 131.1 (×2), 131.0, 130.2, 129.1 (×2), 128.1, 127.4, 125.9, 17.3, 15.9. ESMS m/z: 395.1 (M + 1).

5-(4-Bromo-phenyl)-1-(2,4-dichloro-phenyl)-4-methyl-1*H*-pyrazole-3-carboxylic Acid (9d). Treatment of **8d** (1.02 g, 2.25 mmol) with potassium hydroxide (1.04 g, 18.57 mmol) in methanol (25 mL) gave compound **9d** (0.81 g, 85%) as a white solid: mp 182−183 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 8.4 Hz, 2H), 7.40 (d, J = 2.0 Hz, 1H), 7.34 (d, J = 8.4 Hz, 1H), 7.30 (dd, J = 8.4, 2.0 Hz, 1H), 7.01 (d, J = 8.4 Hz, 2H), 2.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 143.6, 142.3, 136.5, 135.9, 133.1, 132.1 (×2), 131.3 (×2), 130.7, 130.4, 128.1, 127.4, 123.7, 119.9, 9.8. ESMS m/z: 425.0 (M + 1).

5-(4-Bromo-phenyl)-1-(2,4-dichloro-phenyl)-4-ethyl-1*H*-pyrazole-3-carboxylic Acid (9e). Treatment of **8e** (0.94 g, 2.01 mmol) with potassium hydroxide (0.91 g, 16.25 mmol) in methanol (25 mL) gave compound **9e** (0.78 g, 88%) as a white solid: mp 214−215 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 8.4 Hz, 2H), 7.40 (d, J = 2.0 Hz, 1H), 7.33 (d, J = 8.4 Hz, 1H), 7.29 (dd, J = 8.4, 2.0 Hz, 1H),7.03 (d, J = 8.4 Hz, 2H), 2.75 (q, J = 7.2 Hz, 2H), 1.21 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 143.5, 141.7, 136.5, 135.8, 133.2, 132.2 (×2), 131.4(×2), 130.7, 130.5, 128.0, 127.6, 126.5, 123.9, 17.4, 15.8. ESMS m/z: 439.0 (M + 1).

1-(2,4-Dichloro-phenyl)-5-(4-methoxy-phenyl)-4-methyl-1*H*-pyrazole-3-carboxylic Acid (9f). Treatment of **8f** (1.01 g, 2.49 mmol) with potassium hydroxide (1.06 g, 18.93 mmol) in methanol (25 mL) gave compound **9f** (0.79 g, 84%) as a white solid: mp 185−186 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, J = 2.0 Hz, 1H), 7.31 (d, J = 8.4 Hz, 1H), 7.26 (dd, J = 8.4, 2.0 Hz, 1H), 7.06 (d, J = 8.4 Hz, 2H), 6.83 (d, J = 8.4 Hz, 2H), 3.80 (s, 3H), 2.36 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 160.1, 144.7, 142.2, 136.3, 136.1, 133.3, 131.1 (×2), 130.9, 130.3, 127.9, 120.7, 119.3, 114.3 (×2), 55.4, 9.8. ESMS m/z: 377.1 (M + 1).

1-(2,4-Dichloro-phenyl)-4-methyl-5-(4-trifluoromethyl-phenyl)-1*H*-pyrazole-3-carboxylic Acid (9g). Treatment of **8g** (0.98 g, 2.21 mmol) with potassium hydroxide (0.95 g, 16.96 mmol) in methanol (25 mL) gave compound **9g** (0.84 g, 91%) as a white solid: mp 163−164 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 2.0 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.30 (dd, J = 8.0, 2.0 Hz, 1H), 7.27 (d, J = 8.4 Hz, 2H), 2.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 143.2, 142.8, 136.6, 135.8, 132.9, 132.3, 130.8, 130.5, 130.2 (×2), 128.2, 125.9, 125.8, 125.3, 122.8, 120.2, 9.8. ESMS m/z: 415.1 (M + 1).

4-Bromo-5-(4-chloro-phenyl)-1-(2,4-dichloro-phenyl)-1*H*-pyrazole-3-carboxylic Acid (9h). Treatment of **8h** (1.07 g, 2.25 mmol) with potassium hydroxide (1.02 g, 18.21 mmol) in methanol (25 mL) gave compound **9h** (0.88 g, 87%) as a white solid: mp 223−224 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J = 2.0 Hz, 1H), 7.37 (d, J = 8.4 Hz, 1H), 7.32−7.31 (m, 3H), 7.20 (d, J = 8.4 Hz, 2H), 6.78 (br s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0, 144.4, 141.8, 137.0, 136.2, 135.5, 133.0, 131.2 (×2), 130.6, 130.5, 129.2 (×2), 128.2, 125.5, 97.9. ESMS m/z: 446.7 (M + 1).

2-[5-(4-Chloro-phenyl)-1-(2,4-dichloro-phenyl)-4-methyl-1*H*-pyrazol-3-yl]-1,5,5-trimethyl-1,5-dihydro-imidazol-4-one (5). To a solution of **9a** (1.01 g, 2.65 mmol) in toluene (30 mL) at 0 °C was sequentially added DMF (0.2 mL) and oxalyl chloride (1.48 g, 11.66 mmol) dropwise. The resulting mixture was allowed to warm to room temperature for 1 h, at which time toluene was removed under reduced pressure and the crude residue was dissolved in THF (10 mL) and transferred slowly to a mixture of **10a** (0.50 g, 4.30 mmol) and triethylamine (0.42 g, 4.16 mmol) in THF (25 mL) at 0 °C. After the mixture was warmed and stirred at room temperature for 15 h, the reaction was quenched with water and extracted with ethyl acetate (2 × 30 mL). The combined extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated to give the crude residue (1.22 g), which without purification underwent intramolecular cyclization by treatment with sodium methoxide (270 mg, 5.00 mmol) in methanol (30 mL) at 60 °C for 4 h. After the reaction was completed, the solution was concentrated, poured into ice water, and extracted with ethyl acetate (2×30 mL). The combined extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by flash chromatography on silica gel with *n*-hexane/ethyl acetate (1:1) to afford the desired product **5** (0.67 g, 55%) as a white solid: mp 123−124 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 2.1 Hz, 1H), 7.25 (d, J = 8.4 Hz, 2H), 7.22 (dd, J = 8.4, 2.1 Hz, 1H), 7.12 (d, J = 8.4 Hz, 1H), 7.01

(d, J = 8.4 Hz, 2H), 3.42 (s, 3H), 2.35 (s, 3H), 1.37 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.1, 170.1, 142.9, 142.1, 136.4, 136.0, 135.5, 133.1, 131.1 (×2), 130.7, 130.5, 129.3 (×2), 128.2, 127.1, 121.1, 65.2, 30.8, 22.4 (×2), 10.8. ESMS m/z: 461.1 (M + 1). Anal. ($C_{22}H_{19}Cl_3N_4O$) C, H, N.

2-[5-(4-Chloro-phenyl)-1-(2,4-dichloro-phenyl)-4-methyl-1*H*-pyrazol-3-yl]-1-ethyl-5,5-dimethyl-1,5-dihydro-imidazol-4-one (11). Compound **11** was synthesized from **9a** (251 mg, 0.66 mmol) and **10b** (140 mg, 1.08 mmol) following a similar synthetic procedure for **5**, and obtained as a white solid (110 mg, 35%): mp 213-214 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J = 2.1 Hz, 1H), 7.27 (d, J = 8.4 Hz, 2H), 7.25 (dd, J = 8.4, 2.1 Hz, 1H), 7.14 (d, J = 8.4 Hz, 1H), 7.05 (d, J = 8.4 Hz, 2H), 3.90 (q, J = 6.8 Hz, 2H), 2.37 (s, 3H), 1.41 (s, 6H), 1.27 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.6, 169.8, 142.4, 141.5, 135.9, 135.7, 134.9, 132.6, 130.7 (×2), 130.3, 130.1, 128.8 (×2), 127.8, 126.7, 120.6, 65.3, 38.9, 23.0 (×2), 15.9, 10.5. ESMS m/z: 475.0 (M + 1). Anal. ($C_{23}H_{21}Cl_3N_4O$) C, H, N.

2-[5-(4-Chloro-phenyl)-1-(2,4-dichloro-phenyl)-4-methyl-1*H*-pyrazol-3-yl]-5,5-dimethyl-1-propyl-1,5-dihydro-imidazol-4-one (12). Compound **12** was synthesized from **9a** (250 mg, 0.66 mmol) and **10c** (150 mg, 1.04 mmol) following a similar synthetic procedure for **5**, and obtained as a white solid (97 mg, 30%): mp 200−201 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45 (d, J = 2.2 Hz, 1H), 7.28 (d, J = 8.4 Hz, 2H), 7.24 (dd, J = 8.4, 2.2 Hz, 1H), 7.11 (d, J = 8.4 Hz, 1H), 7.05 (d, J = 8.4 Hz, 2H), 3.76−3.74 (m, 2H), 2.37 (s, 3H), 1.72−1.68 (m, 2H), 1.41 (s, 6H), 0.81 (t, J = 7.3 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 194.5, 169.8, 142.4, 141.7, 135.9, 135.7, 135.0, 132.6, 130.7 (×2), 130.3, 130.0, 128.8, 128.7, 127.8, 126.7, 120.6, 65.3, 41.8, 23.1 (×2), 22.5, 13.6, 10.7. ESMS m/z: 489.1 (M + 1). Anal. ($C_{24}H_{23}Cl_3N_4O$) C, H, N.

1-Butyl-2-[5-(4-chloro-phenyl)-1-(2,4-dichloro-phenyl)-4-methyl-1*H*-pyrazol-3-yl]-5,5-dimethyl-1,5-dihydro-imidazol-4one (13). Compound **13** was synthesized from **9a** (252 mg, 0.66 mmol) and **10d** (161 mg, 1.02 mmol) following a similar synthetic procedure for **5** and obtained as a white solid (141 mg, 42%): mp 217−218 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45 (d, J = 2.2 Hz, 1H), 7.28 (d, J = 8.4 Hz, 2H), 7.24 (dd, ;J = 8.4, 2.2 Hz, 1H), 7.09 (d, J = 8.4 Hz, 1H), 7.05 (d, J = 8.4 Hz, 2H), 3.81−3.79 (m, 2H), 2.39 (s, 3H), 1.69−1.64 (m, 2H), 1.42 (s, 6H), 1.26−1.24 (m, 2H), 0.82 (t, J = 7.3 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 194.8, 170.0, 142.6, 141.8, 136.1, 135.8, 135.1, 132.7, 130.8 (×2), 130.3, 130.2, 129.0 (×2), 127.9, 126.8, 120.8, 65.4, 44.2, 32.6, 23.2 (×2), 20.1, 13.6, 10.7. ESMS m/z: 503.0 (M + 1). Anal. ($C_{25}H_{25}Cl_3N_4O$) C, H, N.

1-Allyl-2-[5-(4-chloro-phenyl)-1-(2,4-dichloro-phenyl)-4-methyl-1*H*-pyrazol-3-yl]-5,5-dimethyl-1,5-dihydro-imidazol-4-one (14). Compound **14** was synthesized from **9a** (253 mg, 0.66 mmol) and **10e** (148 mg, 1.04 mmol) following a similar synthetic procedure for **5** and obtained as a white solid (171 mg, 53%): mp 203−204 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 (d, J = 2.2 Hz, 1H), 7.25 (d, J = 8.4 Hz, 2H), 7.23 (dd, J = 8.4, 2.2 Hz, 1H), 7.13 (d, J = 8.4 Hz, 1H), 7.03 (d, J = 8.4 Hz, 2H), 5.92−5.88 (m, 1H), 5.14−5.07 (m, 2H), 4.54 (d, J = 6.0 Hz, 2H), 2.37 (s, 3H), 1.40 (s, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 194.8, 170.1, 142.5, 141.6, 136.0, 135.7, 135.1, 134.4, 132.6, 130.8 (×2), 130.4, 130.1, 128.9 (×2), 127.9, 126.7, 120.7, 117.5, 65.5, 46.9, 23.2 (×2), 10.5. ESMS m/z: 487.0 (M + 1). Anal. ($C_{24}H_{21}Cl_3N_4O$) C, H, N.

2-[5-(4-Chloro-phenyl)-1-(2,4-dichloro-phenyl)-4-methyl-1*H*-pyrazol-3-yl]-1-cyclopropyl-5,5-dimethyl-1,5-dihydro-imidazol-4-one (15). Compound **15** was synthesized from **9a** (248 mg, 0.65 mmol) and **10f** (148 mg, 1.04 mmol) following a similar synthetic procedure for **5** and obtained as a white solid (122 mg, 38%): mp 206−207 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 (d, J = 2.2 Hz, 1H), 7.28−7.26 (m, 3H), 7.21 (d, J = 8.4 Hz, 1H), 7.07 (d, J = 8.4 Hz, 2H), 2.92−2.90 (m, 1H), 2.29 (s, 3H), 1.49 (s, 6H), 0.89−0.87 (m, 2H), 0.79−0.77 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 194.3, 172.9, 142.3, 142.2, 136.1, 135.9, 135.1, 132.9, 130.7 (×2), 130.5, 130.3, 128.9 (×2), 128.0, 126.9, 119.1, 66.9, 26.3, 23.9 (×2), 10.0, 7.8 (×2). ESMS m/z: 487.0 (M + 1). Anal. ($C_{24}H_{21}Cl_3N_4O$) C, H, N.

1-Benzyl-2-[5-(4-chloro-phenyl)-1-(2,4-dichloro-phenyl)-4-methyl-1*H*-pyrazol-3-yl]-5,5-dimethyl-1,5-dihydro-imidazol-4-one (16). Compound **16** was synthesized from **9a** (250 mg, 0.66 mmol) and **10g** (189 mg, 0.99 mmol) following a similar synthetic procedure for **5** and obtained as a white solid (155 mg, 44%): mp 99−100 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, J = 2.2 Hz, 1H), 7.31 (d, J = 8.4 Hz, 2H), 7.26 (m, 5H), 7.20 (dd, J = 8.4, 2.2 Hz, 1H), 7.04 (d, J = 8.4 Hz, 2H), 7.01 (d, J = 8.4 Hz, 1H), 5.29 (s, 2H), 2.45 (s, 3H), 1.31 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.0, 170.6, 142.8, 141.8, 137.5, 136.1, 135.8, 135.3, 132.8, 131.0 (×2), 130.5, 130.3, 129.1 (×2), 128.6 (×2), 128.0, 127.6, 127.5 (×2), 127.0, 121.0, 65.7, 48.1, 23.5 (×2), 10.8. ESMS m/z: 537.0 (M + 1). Anal. ($C_{28}H_{23}Cl_3N_4O$) C, H, N.

2-[5-(4-Chloro-phenyl)-1-(2,4-dichloro-phenyl)-1*H*-pyrazol-3-yl]-1,5,5-trimethyl-1,5-dihydro-imidazol-4-one (17). Compound **17** was synthesized from **9b** (249 mg, 0.68 mmol) and **10a** (125 mg, 1.08 mmol) following a similar synthetic procedure for **5** and obtained as a white solid (152 mg, 50%): mp 191−192 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (br s, 1H), 7.30−7.28 (m, 3H), 7.21 (d, J = 8.0 Hz, 2H), 7.04 (d, J = 8.0 Hz, 2H), 3.48 (s, 3H), 1.36 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.5, 168.8, 145.2, 144.5, 136.7, 135.9, 135.6, 132.9, 130.8, 130.4, 129.5 (×2), 129.3 (×2), 128.4, 127.1, 111.7, 66.5, 30.6, 22.2 (×2). ESMS m/z: 447.0 (M + 1). Anal. ($C_{21}H_{17}Cl_3N_4O$) C, H, N.

2-[5-(4-Chloro-phenyl)-1-(2,4-dichloro-phenyl)-4-ethyl-1*H*-pyrazol-3-yl]-1,5,5-trimethyl-1,5-dihydro-imidazol-4-one (18). Compound **18** was synthesized from **9c** (252 mg, 0.64 mmol) and **10a** (125 mg, 1.08 mmol) following a similar synthetic procedure for **5** and obtained as a white solid (158 mg, 52%): mp 154−155 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J = 2.1 Hz, 1H), 7.31 (d, J = 8.4 Hz, 2H), 7.28 (dd, J = 8.4, 2.1 Hz, 1H), 7.20 (d, J = 8.4 Hz, 1H), 7.10 (d, J = 8.4 Hz, 2H), 3.46 (s, 3H), 2.88 (q, J = 7.0 Hz, 2H), 1.44 (s, 6H), 1.12 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.2, 170.2, 142.5, 141.2, 136.2, 135.8, 135.4, 133.0, 131.1 (×2), 130.5 (×2), 129.1 (×2), 128.0, 127.2, 127.1, 65.0, 30.6, 22.2 (×2), 17.3, 16.0. ESMS m/z: 475.1 (M + 1). Anal. ($C_{23}H_{21}Cl_3N_4O$) C, H, N.

2-[5-(4-Bromo-phenyl)-1-(2,4-dichloro-phenyl)-4-methyl-1*H*-pyrazol-3-yl]-1,5,5-trimethyl-1,5-dihydro-imidazol-4-one (19). Compound **19** was synthesized from **9d** (251 mg, 0.59 mmol) and **10a** (125 mg, 1.08 mmol) following a similar synthetic procedure for **5**, and obtained as a white solid (170 mg, 57%): mp 220−221 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48−7.46 (m, 3H), 7.29 (dd, J = 8.4, 2.2 Hz, 1H), 7.19 (d, J = 8.4 Hz, 1H), 7.01 (d, J = 8.4 Hz, 2H), 3.49 (s, 3H), 2.41 (s, 3H), 1.43 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.0, 170.1, 142.8, 142.1, 136.4, 135.9, 133.0, 132.2 (×2), 131.3 (×2), 130.6, 130.4, 128.1, 127.5, 123.7, 121.0, 65.1, 30.7, 22.3 (×2), 10.8. ESMS m/z: 505.0 (M + 1). Anal. ($C_{22}H_{19}BrCl_2N_4O$) C, H, N.

2-[5-(4-Bromo-phenyl)-1-(2,4-dichloro-phenyl)-4-ethyl-1*H*-pyrazol-3-yl]-1,5,5-trimethyl-1,5-dihydro-imidazol-4-one (20). Compound **20** was synthesized from **9e** (250 mg, 0.57 mmol) and **10a** (125 mg, 1.08 mmol) following a similar synthetic procedure for **5** and obtained as a white solid (160 mg, 54%): mp 161−162 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45−7.43 (m, 3H), 7.27 (dd, J = 8.4, 2.2 Hz, 1H), 7.20 (d, J = 8.4 Hz, 1H), 7.01 (d, J = 8.4 Hz, 2H), 3.44 (s, 3H), 2.84 (q, J = 7.3 Hz, 2H), 1.41 (s, 6H), 1.09 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.2, 170.2, 142.6, 141.3, 136.3, 135.8, 133.0, 132.1 (×2), 131.3 (×2), 130.5, 130.4, 128.0, 127.6, 127.2, 123.7, 65.1, 30.6, 22.2 (×2), 17.3, 16.0. ESMS m/z: 519.1 (M + 1). Anal. ($C_{23}H_{21}BrCl_2N_4O$) C, H, N.

2-[1-(2,4-Dichloro-phenyl)-5-(4-methoxy-phenyl)-4-methyl-1*H*-pyrazol-3-yl]-1,5,5-trimethyl-1,5-dihydro-imidazol-4-one (21). Compound **21** was synthesized from **9f** (249 mg, 0.66 mmol) and **10a** (125 mg, 1.08 mmol) following a similar synthetic procedure

for **5** and obtained as a white solid (143 mg, 47%): mp 207−208 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 2.2 Hz, 1H), 7.25 (dd, J = 8.4, 2.2 Hz, 1H), 7.16 (d, J = 8.4 Hz, 1H), 7.06 (d, J = 8.4 Hz, 2H), 6.84 (d, J = 8.4 Hz, 2H), 3.79 (s, 3H), 3.49 (s, 3H), 2.40 (s, 3H), 1.43 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.2, 170.3, 160.1, 143.8, 141.8, 136.4, 136.0, 133.2, 131.2 (×2), 130.6 (×2), 128.0, 120.7, 120.5, 114.3 (×2), 65.1, 55.5, 30.8, 22.4 (×2), 10.9. ESMS m/z: 457.0 (M + 1). Anal. ($C_{23}H_{22}Cl_2N_4O_2$) C, H, N.

2-[1-(2,4-Dichloro-phenyl)-4-methyl-5-(4-trifluoromethyl-phenyl)-1*H*-pyrazol-3-yl]-1,5,5-trimethyl-1,5-dihydro-imidazol-4-one (22). Compound **22** was synthesized from **9g** (251 mg, 0.60 mmol) and **10a** (126 mg, 1.08 mmol) following a similar synthetic procedure for **5** and obtained as a white solid (176 mg, 60%): mp 188−189 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 8.0 Hz, 2H), 7.46 (d, J = 2.1 Hz, 1H), 7.30−7.27 (m, 3H), 7.22 (d, J = 8.0 Hz, 1H), 3.49 (s, 3H), 2.42 (s, 3H), 1.42 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.4, 169.6, 153.9, 142.3, 141.7, 136.3, 135.5, 132.7, 132.0, 130.4, 130.2, 129.9 (×2), 128.0, 125.6, 125.5, 121.2, 112.9, 65.0, 30.6, 22.0 (×2), 10.5. ESMS m/z: 495.1 (M + 1). Anal. ($C_{23}H_{19}Cl_2F_3N_4O$) C, H, N.

2-[5-(4-Chloro-phenyl)-1-(2,4-dichloro-phenyl)-4-methyl-1*H*-pyrazol-3-yl]-1,5,5-trimethyl-1,5-dihydro-imidazole-4-thione (23). To a solution of compound **5** (98 mg, 0.21 mmol) in toluene (5 mL) was added Lawesson's reagent (150 mg, 0.37 mmol) in one portion. The resulting mixture was heated at 60 °C for 4 h, cooled to room temperature, and then poured into ice water. The resulting mixture was extracted with ethyl acetate (2×30 mL). The combined extracts were washed with water, saturated aqueous sodium bicarbonate, and brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by flash chromatography on silica gel with *n*-hexane/ethyl acetate (7:3) to give the desired thioketone **23** (78 mg, 77%) as a yellow solid: mp 177−178 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (d, J = 2.1 Hz, 1H), 7.32 (d, J = 8.4 Hz, 2H), 7.28 (dd, J = 8.4, 2.1 Hz, 1H), 7.22 (d, J = 8.4 Hz, 1H), 7.08 (d, J = 8.4 Hz, 2H), 3.62 (s, 3H), 2.48 (s, 3H), 1.55 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 230.2, 166.5, 143.1, 141.2, 136.5, 135.9, 135.5, 133.0, 131.2 (×2), 130.7, 130.5, 129.3 (×2), 128.2, 126.9, 121.5, 79.3, 32.6, 26.8 (×2), 11.0. ESMS m/z: 477.0 (M + 1). Anal. ($C_{22}H_{19}Cl_3N_4S$) C, H, N.

2-[5-(4-Chloro-phenyl)-1-(2,4-dichloro-phenyl)-4-ethyl-1*H*-pyrazol-3-yl]-1,5,5-trimethyl-1,5-dihydro-imidazol-4-thione (24). Compound **24** was synthesized from **18** (100 mg, 0.21 mmol) following a similar synthetic procedure for **23**, and obtained as a yellow solid (62 mg, 58%): mp 138−139 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, J = 1.8 Hz, 1H), 7.31 (d, J = 8.1 Hz, 2H), 7.26−7.23 (m, 2H), 7.09 (d, J = 8.1 Hz, 2H), 3.58 (s, 3H), 2.91 (q, J = 7.2 Hz, 2H), 1.51 (s, 6H), 1.09 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 230.6, 166.7, 142.9, 140.7, 136.5, 135.9, 135.6, 133.1, 131.2 (×2), 130.6, 130.5, 129.3 (×2), 128.2, 127.9, 127.1, 79.3, 32.6, 26.8 (×2), 17.6, 16.2. ESMS m/z: 491.0 (M + 1). Anal. ($C_{23}H_{21}Cl_3N_4S$) calcd: C 56.16, H 4.30, N 11.39; found: C 56.62, H 4.43, N 10.97.

2-[4-Bromo-5-(4-chloro-phenyl)-1-(2,4-dichloro-phenyl)-1*H*-pyrazol-3-yl]-1,5,5-trimethyl-1,5-dihydro-imidazol-4-one (25). Compound **25** was synthesized from **9h** (251 mg, 0.56 mmol) following a similar synthetic procedure for **5** and obtained as a yellow solid (152 mg, 51%): mp 111−112 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J = 2.0 Hz, 1H), 7.46 (d, J = 8.4 Hz, 2H), 7.30 (dd, J = 8.4, 2.0 Hz, 1H), 7.27 (d, J = 8.4 Hz, 1H), 7.21 (d, J = 8.4 Hz, 2H), 3.40 (s, 3H), 1.45 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.4, 168.9, 143.9, 141.4, 137.0, 136.3, 135.5, 132.9, 131.1 (×2), 130.7, 130.4, 129.2 (×2), 128.4, 125.4, 98.4, 65.2, 30.4, 22.2 (×2). ESMS m/z: 526.0 (M + 1). Anal. ($C_{21}H_{16}BrCl_3N_4O$) C, H, N.

2-[5-(4-Chloro-phenyl)-4-cyclopropyl-1-(2,4-dichloro-phenyl)-1*H*-pyrazol-3-yl]-1,5,5-trimethyl-1,5-dihydro-imidazol-4-one (26). A mixture of compound **25** (50 mg, 0.09 mmol), cyclopropylboronic acid (10 mg, 0.12 mmol), tetrakis(triphenylphosphine) palladium (10 mg, 0.01 mmol), and potassium carbonate (30 mg, 0.22 mmol) in toluene (3 mL) was heated at 80 °C for 2 h under microwave irradiation. After the reaction was complete, the precipitate was filtered and the resulting solution was concentrated under reduced pressure. The residue thus obtained was further purified by flash chromatography with *n*-hexane/ethyl acetate (9:1) to give compound **26** (16 mg, 35%) as a liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 2.4 Hz, 1H), 7.29 (d, J = 8.4 Hz, 2H), 7.26 (dd, J = 8.4, 2.4 Hz, 1H), 7.14 (d, J = 8.4 Hz, 1H), 7.13 (d, J = 8.4 Hz, 2H), 3.41 (s, 3H), 2.19−2.16 (m, 1H), 1.45 (s, 6H), 0.79−0.76 (m. 2H), 0.20−0.18 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.6, 170.0, 143.0, 142.4, 136.2, 135.5, 135.2, 132.9, 130.6 (×2), 130.4, 130.3, 128.7 (×2), 127.9, 126.7, 125.2, 65.1, 53.4, 30.1, 22.0 (×2), 7.3, 5.7. ESMS m/z: 487.1 (M + 1). Anal. ($C_{24}H_{21}Cl_3N_4O$) C, H, N.

2-[5-(4-Chloro-phenyl)-1-(2,4-dichloro-phenyl)-4-methyl-1*H*-pyrazol-3-yl]-5,5-dimethyl-3,5-dihydro-imidazol-4-one (27). To a solution of **9a** (1.01 g, 2.65 mmol) in toluene (30 mL) at 0 °C were sequentially added DMF (0.2 mL) and oxalyl chloride (1.48 g, 11.66 mmol) dropwise. The mixture was allowed to warm to room temperature and stirred for 2 h, which was then transferred slowly to a mixture of **10h** (0.56 g, 4.07 mmol) and triethylamine (0.42 g, 4.20 mmol) in THF (120 mL) at 0 °C. After the mixture was warmed and stirred at room temperature for 15 h, water was added to quench the reaction. The aqueous layer was separated and extracted with ethyl acetate (2×30 mL). The combined extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated to give the crude amide (1.02 g), which was further treated with $POCl_3$ (1.25 g, 8.15 mmol) in 1,2-dichloroethane (25 mL) at 80 °C for 4 h. The mixture was cooled to room temperature and poured into ice water followed by extraction with ethyl acetate (2 × 50 mL). The combined extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated to give the crude residue, which was purified by flash chromatography on silica gel with *n*-hexane/ethyl acetate (7:3) to afford **27** (0.62 g, 52%) as a white solid: mp 185−186 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (br s, 1H), 7.32−7.27 (m, 4H), 7.05 (d, J = 8.0 Hz, 2H), 7.00 (br s, 1H), 2.38 (s, 3H), 1.81 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 144.0, 143.7, 136.5, 136.0, 135.4, 133.2, 131.0 (×2), 130.7, 130.6, 129.2 (×2), 128.2, 127.1, 121.1, 118.5, 46.4, 27.7 (×2), 9.6. ESMS m/z: 447.0 (M + 1). Anal. ($C_{21}H_{17}Cl_3N_4O$) C, H, N.

2-[5-(4-Chloro-phenyl)-1-(2,4-dichloro-phenyl)-4-ethyl-1*H*-pyrazol-3-yl]-5,5-dimethyl-3,5-dihydro-imidazol-4-one (28). Compound **28** was synthesized from **9c** (1.02 g, 2.58 mmol) and **10h** (0.56 g, 4.07 mmol) following a similar synthetic procedure for **27** and obtained as a white solid (0.58 g, 49%): mp 164−165 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J = 2.0 Hz, 1H), 7.30 (d, J = 8.0 Hz, 2H), 7.29−7.25 (m, 2H), 7.05 (d, J = 8.0 Hz, 2H), 7.01 (br s, 1H), 2.79 (q, J = 7.4 Hz, 2H), 1.81 (s, 6H), 1.21 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6, 143.6, 143.2, 136.2, 135.7, 135.3, 133.1, 130.9 (×2), 130.5, 130.4, 129.0 (×2), 127.9, 127.1, 125.0, 120.9, 46.2, 27.5 (×2), 17.0, 15.7. ESMS m/z: 461.0 (M+1). Anal. ($C_{22}H_{19}Cl_3N_4O$) C, H, N.

6-[5-(4-Chloro-phenyl)-1-(2,4-dichloro-phenyl)-4-ethyl-1*H*-pyrazol-3-yl]-5,7-diaza-spiro[3.4]oct-5-en-8-one (29). Compound **29** was synthesized from **9c** (251 mg, 0.63 mmol) and **10i** (140 mg, 0.94 mmol) following a similar synthetic procedure for **27** and obtained as a white solid (141 mg, 47%): mp 193−194 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 2.2 Hz, 1H), 7.34 (s, 1H), 7.31−7.25 (m, 4H), 7.06 (d, J = 8.4 Hz, 2H), 2.87−2.82 (m, 2H), 2.75 (q, J = 7.4 Hz, 2H), 2.48 (dt, J = 17.9, 9.5 Hz, 2H), 2.24−2.21 (m, 1H), 2.14−2.10 (m, 1H), 1.19 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8, 143.5, 143.3, 136.4, 135.8, 135.4, 133.1, 131.0 (×2), 130.6, 130.5, 129.1 (×2), 128.1, 127.1, 125.1, 120.9, 47.6, 34.3 (×2), 17.1, 16.3, 15.8. ESMS m/z: 473.1 (M + 1). Anal. ($C_{23}H_{19}Cl_3N_4O$) C, H, N.

2-[5-(4-Chloro-phenyl)-1-(2,4-dichloro-phenyl)-4-ethyl-1*H*-pyrazol-3-yl]-1,3-diaza-spiro[4.4]non-1-en-4-one (30). Compound **30**

was synthesized from **9c** (253 mg, 0.64 mmol) and **10j** (142 mg, 0.86 mmol) following a similar synthetic procedure for **27** and obtained as a white solid (152 mg, 49%): mp 166−167 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, J = 1.3 Hz, 1H), 7.31−7.26 (m, 4H), 7.15 (s, 1H), 7.06 (d, J = 8.4 Hz, 2H), 2.76 (q, J = 7.4 Hz, 2H), 2.51−2.46 (m, 2H), 2.20−2.15 (m, 2H), 1.88−1.83 (m, 4H), 1.18 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 143.7, 143.3, 136.3, 135.8, 135.3, 133.1, 131.0 (×2), 130.7, 130.4, 129.1 (×2), 128.0, 127.2, 125.0, 121.1, 55.0, 39.4 (×2), 23.3 (×2), 17.1, 15.8. ESMS m/z: 487.1 (M+1). Anal. ($C_{24}H_{21}Cl_3N_4O$) C, H, N.

2-[5-(4-Chloro-phenyl)-1-(2,4-dichloro-phenyl)-4-ethyl-1*H*-pyrazol-3-yl]-1,3-diaza-spiro[4.5]dec-1-en-4-one (31). Compound **31** was synthesized from **9c** (249 mg, 0.63 mmol) and **10k** (142 mg, 0.79 mmol) following a similar synthetic procedure for **27** and obtained as a white solid (147 mg, 47%): mp 196−197 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 1.9 Hz, 1H), 7.31−7.26 (m, 4H), 7.07 (d, J = 8.4 Hz, 2H), 6.97 (s, 1H), 2.77 (q, J=7.4 Hz, 2H), 2.50 (m, 2H), 1.76−1.68 (m, 7H), 1.33−1.32 (m, 1H), 1.20 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6, 143.9, 143.3, 136.3, 135.9, 135.3, 133.2, 131.0 (×2), 130.7, 130.5, 129.1 (×2), 128.0, 127.3, 125.1, 119.9, 51.6, 35.8 (×2), 25.0, 22.3 (×2), 17.1, 15.9. ESMS m/z: 501.1 (M + 1). Anal. ($C_{25}H_{23}Cl_3N_4O$) C, H, N.

2-[5-(4-Chloro-phenyl)-1-(2,4-dichloro-phenyl)-4-methyl-1*H*-pyrazol-3-yl]-3,5,5-trimethyl-3,5-dihydro-imidazol-4-one (32). To a solution of sodium hydride (14.4 mg, 0.66 mol) in DMF (5 mL) at 0 °C was added compound **27** (100 mg, 0.22 mmol) in one portion. The mixture was allowed to warm to room temperature and stirred for 30 min, at which time methyl iodide (2.02 g, 14.08 mmol) was added dropwise. After the mixture was stirred for 2 h, water was added to quench the reaction followed by extraction with ethyl acetate (2×50 mL). The combined extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. Purification of the crude residue by flash chromatography on silica gel with *n*-hexane/ethyl acetate (1:1) gave the product **32** (70 mg, 68%) as a white solid: mp 113−114 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J = 2.2 Hz, 1H), 7.30 (d, J = 8.4 Hz, 2H), 7.26 (dd, J=8.4, 2.2 Hz, 1H), 7.18 (d, J=8.4 Hz, 1H), 7.07 (d, J=8.4 Hz, 2H), 3.28 (s, 3H), 2.24 (s, 3H), 1.87 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 146.3, 142.3, 135.9, 135.8, 135.0, 133.0, 130.7 (×2), 130.5, 130.3, 128.9 (×2), 127.9, 127.1, 121.0, 117.8, 52.3, 33.8, 25.7 (×2), 9.1. ESMS m/z: 461.1 (M+1). Anal. ($C_{22}H_{19}Cl_3N_4O$) C, H, N.

2-[5-(4-Chloro-phenyl)-1-(2,4-dichloro-phenyl)-4-ethyl-1*H*-pyrazol-3-yl]-3,5,5-trimethyl-3,5-dihydro-imidazol-4-one (33). Compound **33** was synthesized from compound **28** (101 mg, 0.22 mmol) and methyl iodide (2.02 g, 14.08 mmol) following a similar synthetic procedure for **32** and obtained as a white solid (72 mg, 69%): mp 124−125 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (br s, 1H), 7.28 (d, J = 7.2 Hz, 2H), 7.26−7.18 (m, 2H), 7.07 (d, J = 7.2 Hz, 2H), 3.21 (s, 3H), 2.62 (q, J = 6.9 Hz, 2H), 1.85 (s, 6H), 1.11 (t, J = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 146.2, 142.2, 136.1, 135.9, 135.3, 133.4, 131.0 (×2), 130.8, 130.4, 129.1 (×2), 128.0, 127.4, 124.1, 121.1, 52.5, 34.0, 25.8 (×2), 16.9, 15.8. ESMS m/z: 475.1 (M + 1). Anal. ($C_{23}H_{21}Cl_3N_4O$) C, H, N.

B. Biological Evaluation. The following methods were used to generate the data in Figure 2 and Figures 4−7 and Tables 1−3.

B1. Rat Microsome Incubation and LC/MS Analysis. The rat microsome incubation medium contained 1 mg of microsomal protein, 100 mM potassium phosphate (pH7.4) buffer, 10 mM $MgCl_2$, 3 mM NADPH, and 100 μM of compound **4**. Total volume of incubation was 500 μL. Incubation was performed aerobically at 37 °C with constant shaking in a test tube placed on a temperature-controlled heating block. After reaction mixture was preincubated without NADPH for 5 min at 37 °C, the reaction was initiated by addition of NADPH. At indicated time for 0, 15, and 60 min, the incubation mixture was mixed with 1 mL of acetonitrile to terminate the reaction. The sample was then transferred to a centrifuge tube and centrifuged at 3000*g* for 20 min at room temperature. The supernatant was transferred to a separate tube. Then 10 μL of supernatant was mixed with 40% acetonitrile and then analyzed by LC/MS. The chromatographic system consisted of an Agilent 1100 series LC system (Agilent Technologies, Palo Alto, CA) and equipped with an Agilent G1946C single quadrupole mass spectrometer with an ESI in the positive scanning mode. The HPLC analysis was performed on an Agilent Eclipse XDB-C_8 guard column (5 μm, 4.6 mm × 12.5 mm) and an Agilent ZORBAX Eclipse XDB-C_8 column (5 μm, 4.6 mm×150 mm). A gradient HPLC method was employed for separation. Mobile phase A consisted of acetonitrile, and mobile phase B consisted of 10 mM ammonium acetate aqueous solution containing 0.1% formic acid. The gradient system was from A:B (30%:70%) to A:B (95%:5%). The flow rate was set at 0.8 mL/min.

B2. Establishment of Human CB1 (hCB1) and CB2 (hCB2) Stable Cell Lines and Membrane Purification. The hCB1 cDNA tagged with Flag at the N terminus or hCB2 cDNA was subcloned into the pIRES2-EGFP vector (Clontech Laboratories, Inc., Mountain View, CA). After transfection to HEK 293 cells, clones stably expressed either hCB1 or hCB2 were selected by GFP and G418 sulfate and maintained in DMEM supplemented with 10% fetal bovine serum and 0.5 mg/mL G418 sulfate under 5% CO_2 at 37 °C. For membrane purification, cells were homogenized in ice-cold buffer A (50 mM Tris, 5 mM $MgCl_2$, 2.5 mM EDTA, pH 7.4, 10% sucrose) with 1 mM PMSF. The homogenate was centrifuged for 15 min at 2000*g* at 4 °C. The resulting supernatant was centrifuged for another 30 min at 43000*g* at 4 °C. The final pellet was resuspended in buffer A and stored at −80 °C.

B3. Radioligand Binding Assay.[26] The radioligand binding assay was performed according to Felder et al. with minor modification. An amount of 0.2−8 μg of the purified membrane was incubated with 0.75 nM [^{3}H] CP-55, 940 ([^{3}H] **34**), and compounds of interest in the incubation buffer (50 mM Tris-HCl, 5 mM $MgCl_2$, 1 mM EDTA, 0.3% BSA, pH 7.4). The nonspecific binding was defined in the presence of 1 μM of CP-55,940. The reactions were incubated for 1.5 h at 30 °C in Multiscreen microplates (Millipore Corp., Billerica, MA). The reactions were terminated by manifold filtration and washed with ice-cold wash buffer (50 mM Tris, pH 7.4, 0.25% BSA) for four times. The radioactivity bound to the filters was measured by Topcount (PerkinElmer Inc., Waltham, MA). IC_{50} was determined by the concentration of compounds required to inhibit 50% of the binding of [^{3}H] CP-55, 940 and calculated by nonlinear regression (GraphPad software, San Diego, CA).

B4. Eu−GTP Binding Assay.[27−29] The Eu−GTP binding assay was performed using the DELFIA Eu−GTP binding kit (Perkin-Elmer Inc., Waltham, MA) based on methods developed by Frang et al. with minor modifications as described in the following: 1−4 μg of purified membrane was incubated with compounds of interest and 20 nM of CP-55,940 in assay buffer (50 mM HEPES, pH 7.4, 100 mM NaCl, 100 μg/mL saponin, 5 mM $MgCl_2$, 2 μM GDP, 0.5% BSA) at 30 °C for 60 min in acroplates (Pall Life Sciences, Ann Arbor, Mich.). Following the addition of Eu−GTP and incubation of 30 min at 30 °C, the assay was terminated by washing four times in washing buffer provided in the kit. The fluorescence signal of Eu−GTP was determined by Victor 2 multilabel reader (Perkin-Elmer Inc., Waltham, MA). EC_{50} values were analyzed by increasing concentrations of test compounds after activation with 30 nM of CP-55,940 and were determined by nonlinear regression analysis using the GraphPad Prism program (GraphPad software, San Diego, CA). The intrinsic property was assessed by using test compounds alone in the absence of agonist CP-55,940; the percentage change of the induced Eu−GTP binding is defined as: [(Eu−GTP binding in the presence of test compound at 10 μM − basal Eu−GTP binding)/basal Eu−GTP binding]

×100%. Statistical analysis was performed by *t* test. A *P* value (*) less than 0.05 was considered significant.

B5. Spontaneously Feeding Model.[30] Male Wistar rats were individually housed under 12 h reverse light−dark cycle (light off at 10 a.m.) for more than a week and weighed 210−270 g at the start of the study. Drugs at defined dosage or vehicle (20% DMSO/10% Tween 80/70% H_2O) were orally gavaged before the light was off, and sufficient powder chow diet was supplied at 11 a.m. The unconsumed food was measured after 1, 2, 3, and 6 h. Food intake was expressed as calorie (cal) ingestion normalized by body weight (g). Statistical analysis was performed by *t* test. A *P* value (*) less than 0.05 was considered significant.

B6. DIO Mouse Model.[31] Six-week-old C57BL/6 mice were given high-fat diet of 4.73 kcal/g energy density (Research Diet D 12451; 45% fat, 20% protein, and 35% carbohydrate) for 16 weeks before the drug treatment. Mice weight matched were assigned to different groups and orally gavaged once daily with vehicle (10% DMSO/10% Tween 80/80% H_2O) or compounds at defined dosage for 29 days. The sum of food taken for each treatment and body weight was measured daily.

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Supporting Information Available: Combustion analysis data for compounds **5** and **11**−**33**. This material is available free of charge via the Internet at http://pubs.acs.org.

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