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Chemical and Biological Investigation of Cyclopropyl Containing Diaryl-pyrazole-3-carboxamides as Novel and Potent Cannabinoid Type 1 Receptor Antagonists

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Obesity is a major clinical problem in the western world, and many molecular targets have been explored in the search for effective therapeutic agents. One of these, antagonism of the cannabinoid 1 (CB1) receptor, rose to prominence following reports demonstrating the positive modulation of food intake by the CB1 antagonist, rimonabant (**3**) (SR141716A). In the present study, various diaryl-pyrazole derivatives containing cycloalkyl building blocks were synthesized and tested for CB1 receptor binding affinities. Thorough structure−activity relationship (SAR) studies to optimize the pyrazole substituents led to several novel CB1 antagonists with $K_i \leq 5$ nM and with acceptable metabolic stability with human liver microsomes. Among these analogues, we identified 5-(4-cyclopropylphenyl)-1-(2,4-dichlorophenyl)-4-ethyl-*N*-pyrrolidin-1-yl-1*H*-pyrazole-3-carboxamide (**11r**), which exhibited a favorable pharmacological profile with outstanding efficacy in reducing serum lipid parameters of metabolic syndrome compared to clinical references.

Introduction

According to the World Health Organization (WHO[a]) Global InfoBase, 78% of the population of United States and 73% of the United Kingdom is classified as obese or overweight. Moreover, it is not only western society that is affected, as the prevalence of obesity has increased worldwide by 75% since 1980 and the WHO have consequently defined it as a global epidemic.[1] The importance of the obesity epidemic is emphasized by the fact that excessive bodyweight is now recognized as one of the most important risk factors associated with the metabolic syndrome.[2] Metabolic syndrome is a dangerous combination of risk factors: abdominal obesity, glucose intolerance, hypertension, and dyslipidemia (low high-density lipoprotein cholesterol (HDLc) but high low-density lipoprotein cholesterol (LDLc) and triglyceride levels),[3] which are responsible for increased prevalence of cardiovascular diseases, diabetes, and some cancers, so causing more than 1 million deaths and 12 million life years of ill health each year in Europe alone.[4]

In spite of the growing awareness of the medical problems that accompany obesity, current treatment strategies (dietary modifications, lifestyle change, and drug therapy) cannot be considered to be optimal and sustained weight loss is often difficult to achieve.

Besides the highly abusable norepinephrine stimulants, there are only two antiobesity pharmaceuticals on the market: the monaminergic reuptake inhibitor sibutramine **1** and the lipidase inhibitor orlistat **2** (Figure 1).[5]

Both compounds have only modest efficacy and are accompanied by severe adverse effects.

The main side effect of **1** is elevation of blood pressure, which is highly undesirable in obese patients, with current hypertension and/or dyslipidemia.

Orlistat (**2**), a gastrointestinal lipase inhibitor, has a rather inconvenient side effect profile characterized by steatorrhea (lipid evacuation) and fecal incontinence, the prevalence of which can be up to 30% among patients.

Numerous attempts have been made to identify new potential targets and thus create novel types of antiobesity drugs. One of these, the discovery of the endocannabinoid system, in the 1990s, has provided one opportunity to develop and introduce efficient pharmaceuticals for the treatment of obesity. In general, cannabinoids exert their effects through two known receptors: CB1, a $G_{i/o}$ protein coupled receptor that inhibits neurotransmitter release on axon terminals in the central nervous system (CNS) but also can be found in peripheral organs, (e.g., gut, liver, and also on cells of adipose tissue), and cannabinoid 2 (CB2), which suppresses immounocytes and exerts little if any effects on the CNS.[6]

The endocannabinoid system, and the CB1 receptor (cloned in 1990)[7−9] in particular, plays a special role in energy homeostasis. Blockade of CB1 receptors decreases food intake, leading to a reduction in body weight. Therefore, it was hoped that CB1 receptor antagonists/inverse agonists could provide effective therapies for the treatment of obesity.

Indeed, in phase III clinical studies, Rimonabant[10] (**3**) (SR141716A), the first potent and selective CB1 receptor inverse agonist, induced modest weight loss and had preferential effects in many parameters of dyslipidemia

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[a] Abbreviations: BMI, body mass index; WHO, World Health Organization; CB1, cannabinoid 1; CB2, cannabinoid 2; CL_{int}, intrinsic clearance; CNS, central nervous system; SAR, structure−activity relationship; DIO, diet induced obesity; LDLc, low-density lipoprotein cholesterol; HDLc, high-density lipoprotein cholesterol; EMEA, European Medicines Agency.

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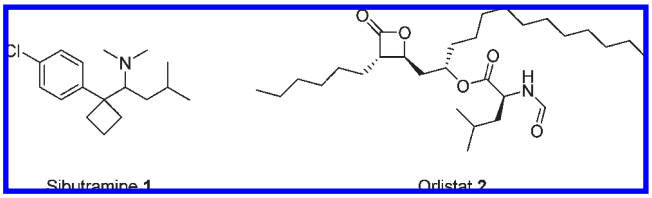


Figure 1. Structures of sibutramine and orlistat.

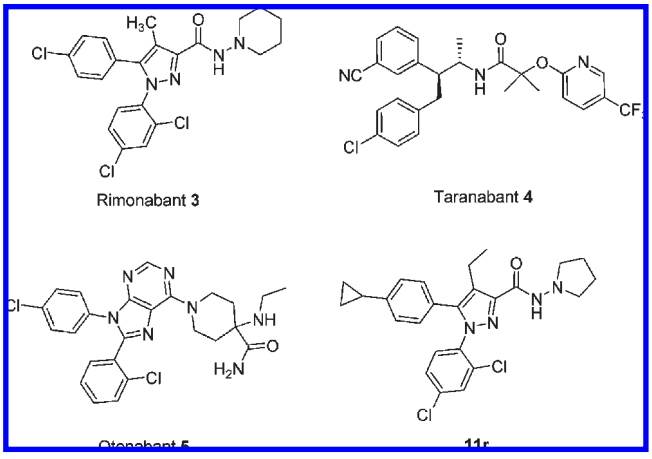


Figure 2. Structures of CB1R antagonists/inverse agonists.

(it increased HDLc and adiponectin, decreased triglyceride levels, but did not change total cholesterol, LDLc, and fasting insulin levels).[11] However, one year after its launch in Europe, its marketing has been discontinued by the European Medicines Agency (EMEA) because "benefits of Acomplia no longer outweigh its risks"—such as depression and anxiety.[12,13] Other CB1 antagonists/inverse agonists were also withdrawn from clinical development including taranabant[14] (**4**) (MK-0364) and otenabant[15,16] (**5**) (CP-945,598) (Figure 2).

Herein, we describe the design strategies and SAR studies that led to the identification of a series of cyclopropyl containing diaryl-pyrazole-3-carboxamide derivatives[17,18] with significant antiobesity effects in the applied animal model. In addition, in view of the clinical evidence that obesity is often associated with lipoprotein abnormalities,[3] we have investigated the effect of **3** and our best compounds on serum lipids, i.e., LDLc and HDLc levels, that resulted in the discovery of **11r** (Figure 2), a novel, potent CB1 antagonist with a greater preferential effect on the lipid profile parameters as compared to known CB1 antagonists.

Chemistry. A series of new compounds **11a**−**r** based on the structural similarities with **3** were synthesized as shown in Scheme 1. Reaction of cycloalkyl-benzenes **6a**−**d** with the appropriate acyl-chloride in trichloroethylene provided phenones **7a**−**g**. Claisen condensation of **7a**−**g** and imidazol-1-yl-*oxo*-acetic acid ethyl ester[19] then gave diketone esters **8a**−**g** in good yields. The synthesis of acids **10a**−**g** involved basic hydrolysis of the corresponding esters **9a**−**g**, which in turn were prepared by condensing diketone esters **8a**−**g** with suitably substituted phenyl hydrazines. This reaction is a regioselective transformation and the 1,5-diarylpyrazoles could be generated almost exclusively by carrying out the condensation in the presence of the hydrochloride salt of the phenyl-hydrazines.[20] The intermediates **10a**−**g** were then converted into their acid chlorides with thionyl chloride in refluxing toluene. Reaction of these intermediates with commercially available 1-aminopiperidine or 1-aminopyrrolidine in dichloromethane at room temperature provided the target compounds **11a**−**r**.

1-(4-Cyclopropylphenyl)-2-methoxyethanone (**7f**) cannot be prepared by a direct Friedel−Crafts reaction as described in Scheme 1 because of the chloromethylation property of methoxyacetyl chloride and the formation of diarylmethane.[21] **7f** was synthesized from 2-methoxy-1,1-bis(trimethylsilyloxy) ethene (**14**0 and 4-cyclopropylbenzenecarboxylic acid chloride (**13**) by the method of Wissner (Scheme 2).[22]

Results and Discussion

The present synthetic design was based on the principles of analogue based drug discovery described by Fischer et al.[23] Using this approach, we synthesized several diaryl-pyrazoles **11a**−**r**. Our strategy in evaluating our newly synthesized compounds was first to determine their in vitro binding affinities and then their metabolic stabilities characterized by microsomal intrinsic clearance. Considerable information is available on the mechanisms of action of diaryl-pyrazoles, but their pharmacokinetic properties are poorly understood. Since only one reference has been published on the metabolism of diaryl-pyrazoles,[24] we considered that it was necessary to study the in vitro metabolism of **3** in detail. Our results showed that in human and mouse liver microsomes **3** has weak/moderate metabolic stability (for details, see Table 1). We therefore believed that potent and in vivo effective, metabolically stable diaryl-pyrazole analogues might achieve a remarkable improvement in the effectiveness of these compounds.

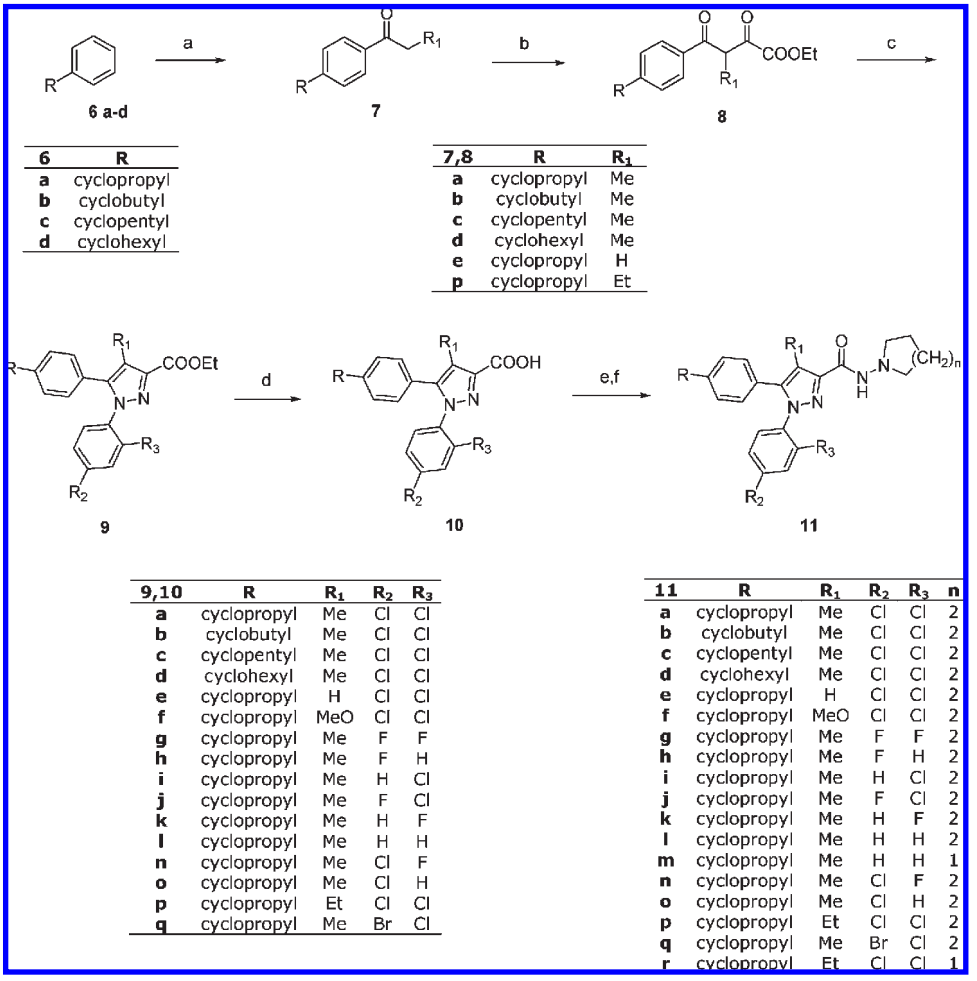
First, by replacing the chloro-substituent of **3** at position 5 by a cyclopropyl group, we synthesized its direct analogue **11a** with good affinity ($K_i = 3$ nM). Unfortunately, this had similar metabolic instability to **3**. Subsequently, we found that compounds containing a cyclobutyl **11b**, cyclopentyl **11c**, or cyclohexyl **11d** moiety instead of the cyclopropyl group showed both a significant in vitro CB1 affinity and high metabolic stability. Nevertheless, they were not effective per os (po) in the WIN 55,212-2 induced hypothermia test (**11b**, $ED_{50} = 4$ mg/kg, **11c**, $ED_{50} = \gg 3$ mg/kg, **11c**, $ED_{50} = > 3$ mg/kg) (for details, see Experimental Section). This unfavorable result is believed to be due to the poor in vivo absorption of these compounds, possibly arising from their high lipophilicity (**11b**, clogP = 7.25, **11c**, clogP = 7.81, **11d**, clogP = 8.37).

The best compound **11a** from the cycloalkyl series was further optimized by changing the substituents R2 and R3 at position 1 and the R1 substituent at position 4 (Table 1). Removal of the 2-chlorine and both the chlorine atoms from position 1 resulted in a drastic drop in efficacy for compound **11o** and **11m** (Table 1). However, by replacing the 4-chlorine atom by a bromine atom at position 1, **11q** enhanced metabolic stability.

We made some changes at position 4 on the pyrazole ring such as 4-ethyl-derivative **11p** and replacement of the piperidine ring at position 3 of **11p** with a pyrrolidine moiety **11r**. These changes gave compounds whose efficacies and metabolic stabilities were further improved. On the basis of their favorable in vitro binding and metabolic stability properties, **11p**, **11q**, and **11r** were selected for further in vivo evaluation.

To determine the in vivo CB1 antagonist efficacy, we used the CB1 agonist induced hypothermia model as described by Fox et al.[25] In this model, **3** inhibited WIN 55,212-2 induced

Scheme 1. Synthesis of Target Compounds[a]



6	R
a	cyclopropyl
b	cyclobutyl
c	cyclopentyl
d	cyclohexyl

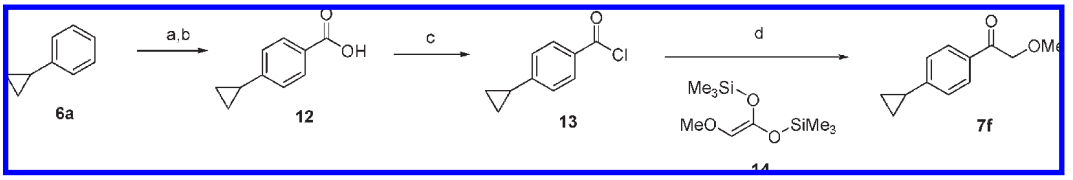
7,8	R	R_1
a	cyclopropyl	Me
b	cyclobutyl	Me
c	cyclopentyl	Me
d	cyclohexyl	Me
e	cyclopropyl	H
p	cyclopropyl	Et

9,10	R	R_1	R_2	R_3
a	cyclopropyl	Me	Cl	Cl
b	cyclobutyl	Me	Cl	Cl
c	cyclopentyl	Me	Cl	Cl
d	cyclohexyl	Me	Cl	Cl
e	cyclopropyl	H	Cl	Cl
f	cyclopropyl	MeO	Cl	Cl
g	cyclopropyl	Me	F	F
h	cyclopropyl	Me	F	H
i	cyclopropyl	Me	H	Cl
j	cyclopropyl	Me	F	Cl
k	cyclopropyl	Me	H	F
l	cyclopropyl	Me	H	H
n	cyclopropyl	Me	Cl	F
o	cyclopropyl	Me	Cl	H
p	cyclopropyl	Et	Cl	Cl
q	cyclopropyl	Me	Br	Cl

11	R	R_1	R_2	R_3	n
a	cyclopropyl	Me	Cl	Cl	2
b	cyclobutyl	Me	Cl	Cl	2
c	cyclopentyl	Me	Cl	Cl	2
d	cyclohexyl	Me	Cl	Cl	2
e	cyclopropyl	H	Cl	Cl	2
f	cyclopropyl	MeO	Cl	Cl	2
g	cyclopropyl	Me	F	F	2
h	cyclopropyl	Me	F	H	2
i	cyclopropyl	Me	H	Cl	2
j	cyclopropyl	Me	F	Cl	2
k	cyclopropyl	Me	H	F	2
l	cyclopropyl	Me	H	H	2
m	cyclopropyl	Me	H	H	1
n	cyclopropyl	Me	Cl	F	2
o	cyclopropyl	Me	Cl	H	2
p	cyclopropyl	Et	Cl	Cl	2
q	cyclopropyl	Me	Br	Cl	2
r	cyclopropyl	Et	Cl	Cl	1

[a] Reagents and conditions: (a) R_1CH_2COCl, $AlCl_3$, trichloroethylene, −50°C; (b) LiHMDS, THF, Imidazol-1-yl-*oxo*-acetic acid ethyl ester, −70°C → rt, 1 N HCl; (c) For **9a**−**f**, **9p**, and **9r** 2,4-dichlorophenylhydrazine hydrochloride, **9g** 2,4-difluorophenylhydrazine hydrochloride, **9h** 4-fluorophenylhydrazine hydrochloride, **9i** 2-chlorophenylhydrazine hydrochloride, **9j** 4-fluorophenylhydrazine hydrochloride, 4-bromo-2-chlorophenylhydrazine hydrochloride, **9k** 2-fluorophenylhydrazine hydrochloride, **9l** phenylhydrazine hydrochloride, **9n** 4-chloro-2-fluorophenylhydrazine hydrochloride, **9o** 4-chlorophenylhydrazine hydrochloride, **9q** 4-bromo-2-chlorophenylhydrazine hydrochloride, EtOH, reflux; (d) 2.5 N KOH, MeOH, reflux; (e) $(COCl)_2$, DMF, CH_2Cl_2 rt; (f) for **11a**−**l**, **11n**−**q**, 1-aminopiperidine, for **11m**, **11r**, 1-aminopyrrolidine, CH_2Cl_2, rt.

Scheme 2. Synthesis of Intermediate **7f**[a]



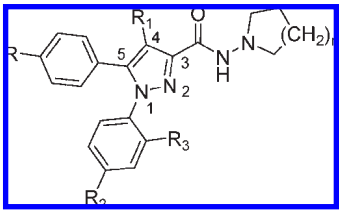
[a] Reagents and conditions: (a) CH_3COCl, $AlCl_3$, trichloroethylene, −50 to (−25 °C); (b) Br_2, NaOH, dioxan, reflux; (c) $SOCl_2$, DMF, toluene, 80°C; (d) $SnCl_4$, rt.

hypothermia with an ED_{50} value of 0.41 mg/kg per os. Compounds **11p**, **11r**, and **11q** also attenuated the hypothermia with an ED_{50} values of 0.84, 0.84, and 0.22 mg/kg, respectively, confirming that all are potent CB1 antagonists in vivo (Figure 3).

As decreased food intake is one of the most important elements of CB1 antagonist induced weight loss,[26] we tested our compounds for appetite suppressive efficacy in the fasting induced palatable chow intake test.[27] All compounds decreased food intake at the 10 mg/kg screen dose (**11p** = 47%; **11r** = 49%; **11q** = 54%) with efficacy comparable to that of **3** (50%) (Table 2).

The diet-induced obesity (DIO) model is known to be a pharmacologically relevant model of human obesity.[28,29] In good agreement with the earlier findings of Ravinet-Trillou,[27] we have shown that **3** can decrease DIO (Figure 4). Using this assay, we assessed the weight decreasing efficacy of our compounds at three doses. All compounds dose dependently decreased body weight with similar efficacy to **3** (Table 3). In spite of the lack of differences in weight loss data, we found

Table 1. Entries, Binding Affinities,[a] and Metabolic Stabilities[b] of Compounds **11a**−**r**



entry	R	R_1	R_2	R_3	*n*	CB1R affinity $K_i \pm$ SEM (nM)	intrinsic clearance CL_{int} (mL × min^{-1} × g $liver^{-1}$)	
							mouse	human
3	Cl	Me	Cl	Cl	2	6 ± 0.8	3.22	1.09
11a	cyclopropyl	Me	Cl	Cl	2	3 ± 0.4	3.28	0.87
11b	cyclobutyl	Me	Cl	Cl	2	7 ± 0.9	0.41	0.26
11c	cyclopentyl	Me	Cl	Cl	2	15 ± 4	0.68	0.16
11d	cyclohexyl	Me	Cl	Cl	2	13 ± 2	0.01	0.01
11e	cyclopropyl	H	Cl	Cl	2	16 ± 0.7	11.60	0.20
11f	cyclopropyl	MeO	Cl	Cl	2	3 ± 0.2	11.60	0.60
11g	cyclopropyl	Me	F	F	2	34 ± 3	0.90	0.41
11h	cyclopropyl	Me	F	H	2	190 ± 36	ND[c]	ND
11i	cyclopropyl	Me	H	Cl	2	4 ± 0.4	9.71	0.60
11j	cyclopropyl	Me	F	Cl	2	8 ± 0.8	3.20	0.41
11k	cyclopropyl	Me	H	F	2	11 ± 0.8	3.81	0.20
11 L	cyclopropyl	Me	H	H	2	66 ± 4	1.82	0.20
11m	cyclopropyl	Me	H	H	1	121 ± 13	ND	ND
11n	cyclopropyl	Me	Cl	F	2	14 ± 0.5	3.40	0.21
11o	cyclopropyl	Me	Cl	H	2	79 ± 1	ND	ND
11p	cyclopropyl	Et	Cl	Cl	2	4 ± 0.7	1.10	0.60
11q	cyclopropyl	Me	Br	Cl	2	3 ± 0.6	0.80	0.01
11r	cyclopropyl	Et	Cl	Cl	1	4 ± 0.2	1.50	1.04

[a] Affinity of compounds for the CB1 receptor was evaluated using rat cerebellum membrane preparation and [^{3}H]SR141716A. K_i values were obtained from three independent experiments. [b] Intrinsic clearance (CL_{int}) was determined as a rate of compound consumption under first-order kinetic conditions using mouse and human liver microsomes. [c] Not determined

that our compounds were surprisingly able to lower the obesity-induced elevation of serum cholesterol levels, while **3**, in line with the literature data in mouse tests,[27,30] was ineffective on this variable ($p = 0.99$ vs fat control). **11r** was even more effective in this regard as it decreased serum cholesterol values to the level of the lean control ($p = 0.49$ vs lean control). For details, see Table 4.

To investigate the importance of the preferential effects of compound **11r** on the lipid profile parameters, we compared it face to face with three CB1 antagonists **3**, **4**, and **5**, known to have reached phase III clinical trials (Table 5). Doses were selected to favor a similar weight loss efficacy. Indeed, all four compounds induced a similar weight loss compared to fat control, but there was no statistical difference between them. DIO was accompanied by a highly significant elevation in serum glucose, triglyceride, cholesterol, HDLc, and LDLc levels. Decrease in fasting glucose and triglyceride levels were nonsignificant. **11r** was the only compound that could decrease cholesterol ($p = 0.037$) and LDLc levels ($p = 0.006$). None of the drugs changed HDLc levels significantly.

Conclusion

In the present study, we investigated a series of cyclopropyl containing diaryl-pyrazole-3-carboxamide derivatives as antagonists of the CB1 receptor. Several compounds in this series exceeded the potency of **3**. In addition, **11p**, **11q**, and **11r** achieved good metabolic stability. Further evaluation of these compounds identified potent CB1 receptor antagonists with significant antiobesity effects in the applied animal model. All the three compounds had remarkable cholesterol-decreasing efficacy and, importantly, **11r** displayed improved effects on lipid profile parameters compared to the known, clinically relevant CB1 receptor antagonist/inverse agonist compounds.

Experimental Section

Chemistry. Research chemicals were either purchased from Aldrich Co. or Fluka and used without further purification in the reactions or were prepared according to the procedure described in the literature. Reactions were monitored by thin-layer chromatography (TLC) on silica gel plates (60 F_{254}; Merck), visualizing with ultraviolet light or iodine. Column chromatography was performed on Silica Gel 60 (0.043−0.060 mm), Merck. The main reference compounds were prepared according to the literature procedures.[10,14−16] The yields of the products reported here are unoptimized. Melting points were determined with a Buchi 535 apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian INOVA-500 spectrometer, operating at 500 MHz. Chemical shifts (δ) are reported in parts per million downfield from tetramethylsilane. Mass spectra were scanned on a Finnigan MAT 95SQ spectrometer. Purity was verified using a Merck−Hitachi Lachrom Elite HPLC system. A linear gradient using water and 0.1% TFA (solvent A) and acetonitrile and 0.1% TFA (solvent B); $t = 0$ min, 10% B, $t = 18$ min, 64% B, $t = 20$ min, 64% B, $t =$ 22 min, 72% B (25 min) was employed on Chromolith RP18e (4.6 mm × 100 mm) column. Flow rate was 2 mL/min, and UV detection (diode array detector: Merck−Hitachi Lachrom Elite L-2450) was set to 254 nM. The LC column was maintained at 40 °C temperature. The purity of the compounds showed ≥95% purity for all the synthesized compounds.

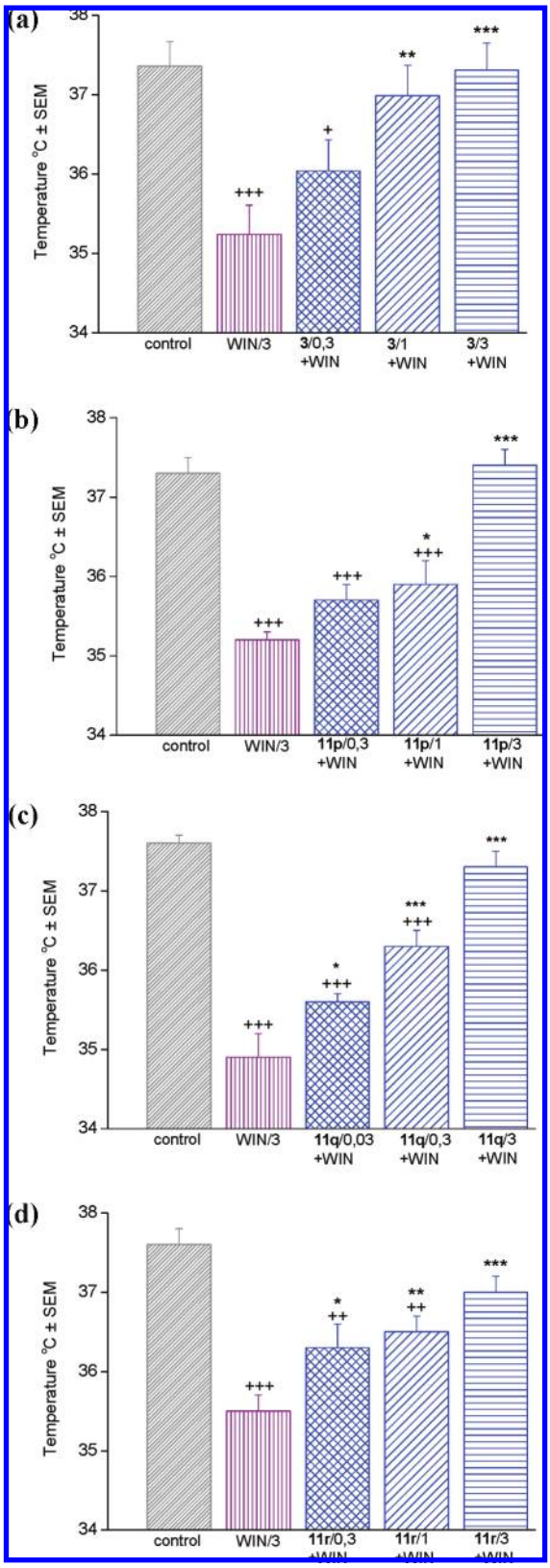


Figure 3. Effect of **3**, **11p**, **11q**, and **11r** on WIN 55,2121-2 (3 mg/kg ip) induced hypothermia test in mice ($n = 8$/group). * = difference from VEH/WIN treated and+= difference from VEH/VEH treated control. ***/+++ $p < 0.001$ **/++ $p < 0.01$; */+ $p < 0.05$.

5-(4-Cyclopropylphenyl)-1-(2,4-dichlorophenyl)-4-methyl-*N*-piperidin-1-yl-1-*H*-pyrazole-3-carboxamide (11a). To a stirred suspension of **10a** (8.9 g, 0.021 mol) and DMF (0.36 mL) in dichloromethane (278 mL), oxalyl chloride (3.8 mL, 0.043 mol) was added dropwise with cooling. The mixture was stirred for 2 h at room temperature and then evaporated in vacuo and dissolved in dichloromethane (80 mL). The so-obtained solution was added dropwise to a stirred mixture of *N*-aminopiperidine (3.4 mL, 0.032 mol) and triethyl amine (4.5 mL, 0.032 mol) in dichloromethane (150 mL) at 0−5 °C. The resulting mixture was allowed to warm to ambient temperature and stirred for 14−16 h then evaporated in vacuo. The residue was purified by column chromatography using dichloromethane/ethyl acetate as eluent. Yield: 8.6 g (80%); 95.7% purity by HPLC. ^{1}H NMR (300 MHz, DMSO-d_6): 0.62−0.66 m (2H), 0.92−1.02 m (2H), 1.31−1.41 m (2H), 1.54−1.64 m (4H), 1.86−1.96 m (1H), 2.20 s (3H), 2.76−2.83 m (4H), 7.06 s (4H), 7.54 dd ($J = 8.6$, 2.3 Hz, 1H), 7.71 d ($J = 8.6$ Hz, 1H), 7.78 d ($J = 2.3$ Hz, 1H), 9.01 s (1H). FIB-MS 468 $[M + H]^+$.

Table 2. Effect of **3**, **11p**, **11q**, and **11r** on the Food Intake in Fasted Mice ($n = 8-10$/group)

group	food intake (g ± SEM)	difference from control (%)
control	2.06 ± 0.21	
3 (10 mg/kg)	1.02 ± 0.12	50
control	1.91 ± 0.22	
11p (10 mg/kg)	0.97 ± 0.06	49
control	1.89 ± 0.17	
11r (10 mg/kg)	0.99 ± 0.13	48
control	2.19 ± 0.16	
11q (10 mg/kg)	1.00 ± 0.12	54

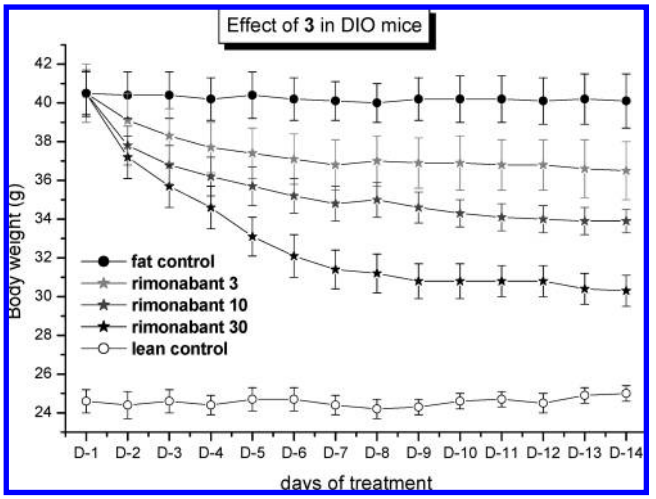


Figure 4. Body weight decreasing effect of **3** at 3−30 mg/kg po dose range in diet induced obesity model (DIO) in mice ($n = 8$/group).

5-(4-Cyclobutylphenyl)-1-(2,4-dichlorophenyl)-4-methyl-*N*-piperidin-1-yl-1-*H*-pyrazole-3-carboxamide hydrochloride (11b). This compound was synthesized according to the procedure described for **11a** using 4-cyclobutylbenzene in step "a", which can be prepared by a known method[31] starting from commercially available 2-phenyl-1,4-butanediol. Yield: 65%; 96.2% purity by HPLC. ^{1}H NMR (500 MHz, DMSO-d_6): 1.90−2.01 m (1H), 1.99−2.11 m (2H), 2.21−2.29 m (1H), 2.27 s (3H), 3.28−3.41 m (4H), 3.44−3.55 m (1H), 7.13−7.18 m (2H), 7.23−7.27 m (2H), 7.59 dd ($J = 8.5$, 2.3 Hz 1H), 7.77 d ($J = 8.5$ Hz, 1H), 7.79 d ($J = 2.3$ Hz, 1H). EI-MS 482 $[M + H]^+$.

5-(4-Cyclopentylphenyl)-1-(2,4-dichlorophenyl)-4-methyl-*N*-piperidin-1-yl-1-*H*-pyrazole-3-carboxamide (11c). This compound was synthesized according to the procedure described for **11a** using 4-cyclopentylbenzene in step "a", which can be prepared by a known method.[32] Yield: 72%; 97.5% purity by HPLC.

^{1}H NMR (500 MHz, DMSO-d_6): 1.44−1.56 m (4H), 1.57−1.67 m (2H), 1.70−1.79 m (2H), 1.84−1.92 m (4H), 1.95−2.04 m (2H), 2.30 s (3H), 2.89−3.01 m (1H), 3.39−3.51 m (4H), 7.13−7.18 m (2H), 7.26−7.30 m (2H), 7.59 dd (J = 8.6, 2.3 Hz, 1H), 7.78 d (J=8.6 Hz 1H), 7.79 d (J=2.3 Hz,1H), 11.60 br s (1H). EI-MS 496 $[M + H]^+$.

Table 3. Effect of **3**, **11p**, **11q**, and **11r** on the Body Weight of DIO Mice after 2 Weeks Treatment (n = 8/group)

group	body weight at day14 (g ± SEM)	difference from fat control (%)[a]
fat control	40.07 ± 1.41+++[b]	
3 (3 mg/kg)	36.46 ± 1.47+++	9
3 (10 mg/kg)	33.87 ± 0.63***;+++	15
3 (30 mg/kg)	30.28 ± 0.81***;+++	24
lean control	25.02 ± 0.42***	38
fat control	45.31 ± 0.89+++	
11p (3 mg/kg)	41.55 ± 1.56+++	8
11p (10 mg/kg)	38.47 ± 1.30***;+++	15
11p (30 mg/kg)	35.51 ± 0.85***;+++	22
lean control	28.16 ± 0.59***	38
fat control	44.00 ± 1.13+++	
11r (3 mg/kg)	40.48 ± 1.65+++	8
11r (10 mg/kg)	37.53 ± 0.76***;+++	15
11r (30 mg/kg)	34.57 ± 1.06***;+++	21
lean control	28.75 ± 0.62***	35
fat control	43.73 ± 0.83+++	
11q (3 mg/kg)	39.67 ± 1.28*;'+++	9
11q (10 mg/kg)	35.61 ± 1.09***;+++	19
11q (30 mg/kg)	32.38 ± 0.84***;+++	26
lean control	26.22 ± 0.51***	40

[a] Percent difference from control values were calculated as follows: % diff = 100 × (control − groupX)/control. [b] * = difference from fat and + = difference from lean control. ***/+++ $p < 0.001$ **/++ $p < 0.01$; */+ $p < 0.05$.

Table 4. Effect of **3**, **11p**, **11q**, and **11r** on the Serum Cholesterol Level of DIO Mice after 2 Weeks Treatment (n = 5−6/group)

group	serum cholesterol (mmol/mL ± SEM)	difference from fat control (%)
fat control	4.47 ± 0.19+++[a]	
3 (30 mg/kg)	4.47 ± 0.18+++	0
lean control	2.70 ± 0.17***	40
fat control	5.49 ± 0.10+++	
11p (30 mg/kg)	4.46 ± 0.33*;+++	19
lean control	2.44 ± 0.10***	56
fat control	5.12 ± 0.17+++	
11r (30 mg/kg)	3.27 ± 0.30***	36
lean control	2.90 ± 0.19***	43
fat control	5.56 ± 0.24+++	
11q (30 mg/kg)	4.66 ± 0.14*;+++	16
lean control	2.87 ± 0.24***	48

[a] * = difference from fat and + = difference from lean control. ***/+++ $p < 0.001$ **/++ $p < 0.01$; */+ $p < 0.05$

5-(4-Cyclohexylphenyl)-1-(2,4-dichlorophenyl)-4-methyl-*N*-piperidin-1-yl-1-*H*-pyrazole-3-carboxamide (11d). This compound was synthesized according to the procedure described for **11a** using commercially available 4-cyclohexylbenzene in step "a". Yield: 80%; 96.4% purity by HPLC; ^{1}H NMR (500 MHz, DMSO-d_6): 1.16−1.26 m (1H), 1.29−1.41 m (4H), 1.46−1.56 m (2H), 1.64−1.73 m (1H), 1.73−1.81 m (4H), 1.82−1.88 m (4H), 2.28 s (3H), 2.43−2.50 m (1H), 3.34−3.48 m (4H), 7.12−7.17 m (2H), 7.21−7.28 m (2H), 7.58 dd (J = 8.6, 2.3 Hz, 1H), 7.76 d (J = 8.6 Hz, 1H), 7.79 d (J = 2.3 Hz, 1H), 11.38 br s (1H). EI-MS 510 $[M + H]^+$.

5-(4-Cyclopropylphenyl)-1-(2,4-dichlorophenyl)-*N*-piperidin-1-yl-1-*H*-pyrazole-3-carboxamide Hydrochloride (11e). This compound was synthesized according to the procedure described for **11a** using acetyl chloride in step "a". Yield: 56%; 96.7% purity by HPLC. ^{1}H NMR (500 MHz, DMSO-d_6): 0.64−0.69 m (2H), 0.91−0.98 m (2H), 1.42−1.51 m (2H), 1.76−1.83 m (4H), 1.84−1.92 m (1H), 3.25−3.35 m (4H), 7.03−7.08 m (2H), 7.10−7.15 m (2H), 7.24 s (1H), 7.65 dd (J=8.6, 2.3 Hz, 1H), 7.81 d (J=8.6 Hz, 1H), 7.87 d (J= 2.3 Hz, 1H), 11.21 s (1H). EI-MS 454 $[M + H]^+$.

5-(4-Cyclopropylphenyl)-1-(2,4-dichlorophenyl)-4-methoxy-*N*-piperidin-1-yl-1-*H*-pyrazole-3-carboxamide (11f). This compound was synthesized according to the procedure described for **11a** starting from 7f in step "b". Yield: 32%; 96.5% purity by HPLC. ^{1}H NMR (500 MHz, DMSO-d_6) 0.70−0.63 (m, 2H), 0.97−0.90 (m, 2H), 1.39−1.29 (m, 2H), 1.63−1.52 (m, 4H), 1.91−1.82 (m, 1H), 2.84−2.73 (m, 4H), 3.75 (s, 3H), 7.13−7.02 (m, 4H), 7.59 (dd, J = 8.5, 2.3 Hz, 1H), 7.75 (d, J = 8.5 Hz, 7.78 (d, J = 2.3 Hz, 1H), 9.03 (s, 1H). EI-MS 484 $[M + H]^+$.

5-(4-Cyclopropylphenyl)-1-(2,4-difluorophenyl)-4-methyl-*N*-piperidin-1-yl-1*H*-pyrazole-3-carboxamide (11g). This compound was synthesized according to the procedure described for **11a** using commercially available 2,4-difluoro-phenylhydrazine hydrochloride in step "c". Yield: 77%; 98.7% purity by HPLC. ^{1}H NMR (500 MHz, DMSO-d_6): 0.65−0.70 m (2H), 0.91−0.98 m (2H), 1.28−1.37 m (2H), 1.54−1.63 m (4H), 1.84−1.92 m (1H), 2.19 s (3H), 2.72−2.82 m (4H), 7.03−7.08 m (4H), 7.19−7.25 m (1H), 7.35−7.42 m (1H), 7.66−7.73 m (1H), 9.02 s (1H). EI-MS 436 $[M + H]^+$.

5-(4-Cyclopropylphenyl)-1-(4-fluorophenyl)-4-methyl-*N*-piperidin-1-yl-1*H*-pyrazole-3-carboxamide (11h). This compound was synthesized according to the procedure described for **11a** using commercially available 4-fluoro-phenylhydrazine hydrochloride in step "c". Yield: 80%; 96.1% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$): 0.68−0.74 m (2H), 0.97−1.04 m (2H), 1.40−1.50 m (2H), 1.74−1.83 m (4H), 1.83−1.93 m (1H), 2.33 s (3H), 2.91−3.01 m (4H), 6.95−7.09 m (6H), 7.16−7.23 m (2H), 7.83 br s (1H). EI-MS 418 $[M + H]^+$.

5-(4-Cyclopropylphenyl)-1-(2-chlorophenyl)-4-methyl-*N*-piperidin-1-yl-1*H*-pyrazole-3-carboxamide (11i). This compound was synthesized according to the procedure described for **11a** using commercially available 2-chloro-phenylhydrazine hydrochloride in step "c". Yield: 81%; 98.8% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$): 0.64−0.69 m (2H), 0.92−0.99 m (2H), 1.38−1.47 m (2H), 1.71−1.79 m (4H), 1.79−1.87 m (1H), 2.37 s (3H),

Table 5. Effect of **3**, **4**, **5**, and **11r** on the Body Weight, Serum Glucose, and Lipid Levels of DIO Mice after 2 Weeks Treatment (n = 8/group)

		serum levels (mmol/mL)				
group	body weights at ay 14 (g ± SEM)	glucose	cholesterol	triglyceride	HDLc	LDLc
fat control	41.90 ± 1.30+++[a]	9.52 ± 0.38+++	5.35 ± 0.12+++	1.42 ± 0.04++	4.42 ± 0.08+++	0.84 ± 0.03+++
3 (10 mg/kg)	35.60 ± 1.10***+++	8.84 ± 0.65++	5.35 ± 0.32+++	1.18 ± 0.06	4.4 ± 0.25+++	0.82 ± 0.05+++
4 (3 mg/kg)	33.70 ± 0.70***+++	9.11 ± 0.49++	5.01 ± 0.13+++	1.44 ± 0.05+++	4.16 ± 0.10+++	0.82 ± 0.03+++
5 (30 mg/kg)	36.60 ± 1.10***+++	9.45 ± 0.71++	5.34 ± 0.13+++	1.32 ± 0.04+	4.40 ± 0.11+++	0.85 ± 0.06+++
11r (10 mg/kg)	35.60 ± 0.90***+++	8.79 ± 0.51+	4.56 ± 0.20 +++	1.30 ± 0.09	3.90 ± 0.16+++	0.68 ± 0.04** +++
lean control	26.10 ± 0.90***	6.08 ± 0.42***	2.75 ± 0.08***	1.03 ± 0.07***	2.34 ± 0.07***	0.42 ± 0.02***

[a] * = difference from fat and + = difference from lean control. ***/+++ $p < 0.001$ **/++ $p < 0.01$; */+ $p < 0.05$.

2.83−2.89 m (4H), 6.93−7.02 m (4H), 7.25−7.35 m (3H), 7.37−7.7.43 m (1H), 7.68 s (1H). EI-MS 434 $[M + H]^+$.

5-(4-Cyclopropylphenyl)-1-(2-chloro-4-fluorophenyl)-4-methyl-*N*-piperidin-1-yl-1*H*-pyrazole-3-carboxamide (11j). This compound was synthesized according to the procedure described for **11a** using commercially available 4-fluoro-2-chloro-phenylhydrazine hydrochloride in step "c". Yield: 76%; 96.1% purity by HPLC. ^{1}H NMR (500 MHz, DMSO-d_6): 0.64−0.72 m (2H), 0.90−0.98 m (2H), 1.29−1.38 m (2H), 1.52−1.62 m (4H), 1.84−1.90 m (1H), 2.20 s (3H), 2.74−2.81 m (4H), 7.03−7.09 m (4H), 7.35 ddd (J = 8.8, 8.3, 2.8 Hz, 1H), 7.57 dd (J = 8.5, 2.8 Hz, 1H), 7.75 dd (J = 8.8, 5.6 Hz, 1H), 8.99 s (1H). EI-MS 452 $[M + H]^+$.

5-(4-Cyclopropylphenyl)-1-(2-fluorophenyl)-4-methyl-*N*-piperidin-1-yl-1*H*-pyrazole-3-carboxamide (11k). This compound was synthesized according to the procedure described for **11a** using commercially available 2-fluoro-phenylhydrazine hydrochloride in step "c". Yield: 66%; 94.8% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$): 0.65−0.71 m (2H), 0.93−1.00 m (2H), 1.38−1.48 m (2H), 1.71−1.79 m (4H), 1.80−1.89 m (1H), 2.36 s (3H), 2.83−2.90 m (4H), 6.95−7.02 m (4H), 7.02−7.08 m(1H), 7.14−7.20 m (1H), 7.30−7.40 m (2H), 7.68 br s (1H). EI-MS 418 $[M + H]^+$.

5-(4-Cyclopropylphenyl)-1-phenyl-4-methyl-*N*-piperidin-1-yl-1*H*-pyrazole-3-carboxamide (11l). This compound was synthesized according to the procedure described for **11a** using commercially available phenylhydrazine hydrochloride in step "c". Yield: 91%; 98.1% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$): 0.67−0.74 m (2H), 0.95−1.03 m (2H), 1.41−1.50 m (2H), 1.74−1.84 m (4H), 1.84−1.92 m (1H), 2.34 s (3H), 2.91−3.04 m (4H), 6.98−7.04 m (4H), 7.19−7.25 m (2H), 7.25−7.34 m (3H), 7.91 br s (1H). EI-MS 400 $[M + H]^+$.

5-(4-Cyclopropylphenyl)-1-phenyl-4-methyl-*N*-pirrolidin-1-yl-1*H*-pyrazole-3-carboxamide (11m). This compound was synthesized according to the procedure described for **11a** using commercially available 1-aminopyrrolidine in step "e". Yield: 87%; 97.2% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$): 0.67−0.74 m (2H), 0.95−1.03 m (2H), 1.83−1.91 m (1H), 1.91−1.98 m (4H), 2.35 s (3H), 3.03−3.16 m (4H), 6.98−7.05 m (4H), 7.20−7.25 m (2H), 7.25−7.34 m (3H), 7.86 br s (1H). EI-MS 386 $[M + H]^+$.

5-(4-Cyclopropylphenyl)-1-(2-fluoro-4-chlorophenyl)-4-methyl-*N*-piperidin-1-yl-1*H*-pyrazole-3-carboxamide (11n). This compound was synthesized according to the procedure described for **11a** using commercially available 2-fluoro-4-chloro-phenylhydrazine hydrochloride in step "c". Yield: 84%; 95.4% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$): 0.63−0.73 m (2H), 0.95−1.03 m (2H), 1.39−1.46 m (2H), 1.72−1.79 m (4H), 1.80−1.88 m (1H), 2.35 s (3H), 2.82−2.91 m (4H), 6.96−7.03 m (4H), 7.08 dd (J = 9.6, 2.2 Hz, 1H), 7.17 ddd (J = 8.7, 2.2, 1.3 Hz, 1H), 7.31 dd (J = 8.7, 8.3 Hz, 1H), 7.65 s (1H). EI-MS 452 $[M + H]^+$.

5-(4-Cyclopropylphenyl)-1-(4-chlorophenyl)-4-methyl-*N*-piperidin-1-yl-1*H*-pyrazole-3-carboxamide (11o). This compound was synthesized according to the procedure described for **11a** using commercially available 4-chloro-phenylhydrazine hydrochloride in step "c". Yield: 79%; 96.4% purity by HPLC. ^{1}H NMR (500 MHz, DMSO-d_6): 0.67−0.73 m (2H), 0.94−1.04 m (2H), 1.31−1.41 m (2H), 1.54−1.64 m (4H), 1.88−1.97 m (1H), 2.16 s (3H), 2.75−2.84 m (4H), 7.05−7.14 m (4H), 7.25−7.31 m (2H), 7.42−7.48 m (2H), 9.02 s (1H). EI-MS 434 $[M + H]^+$.

5-(4-Cyclopropylphenyl)-1-(2,4-dichlorophenyl)-4-ethyl-*N*-piperidin-1-yl-1-*H*-pyrazole-3-carboxamide (11p). This compound was synthesized according to the procedure described for **11a** using butyryl chloride in step "a". Yield: 68%; 95.3% purity by HPLC. ^{1}H NMR (400 MHz, DMSO-d_6): 0.64−0.69 m (2H), 0.91−0.97 m (2H), 1.07 t (J = 7.3 Hz, 3H), 1.30−1.38 m (2H), 1.52−1.65 m (4H), 1.82−1.92 m (1H), 2.62 q (J = 7.3 Hz, 2H), 2.74−2.81 m (4H), 7.03−7.09 m (4H), 7.51 dd (J = 8.6, 2.3 Hz, 1H), 7.71 d (J = 8.6 Hz, 1H), 7.73 d (J = 2.3 Hz, 1H), 9.01 s (1H). FIB-MS 482 $[M + H]^+$.

5-(4-Cyclopropylphenyl)-1-(2-chloro-4-bromophenyl)-4-methyl-*N*-piperidin-1-yl-1*H*-pyrazole-3-carboxamide (11q). This compound was synthesized according to the procedure described for **11a** using commercially available 4-bromo-2-chloro-phenylhydrazine hydrochloride in step "c". Yield: 81%; 99.1% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$): 0.65−0.73 m (2H), 0.93−1.01 m (2H), 1.39−1.46 m (2H), 1.70−1.78 m (4H), 1.79−1.87 m (1H), 2.35 s (3H), 2.81−2.91 m (4H), 6.99 m (4H), 7.18 d (J = 8.5 Hz, 1H), 7.41 dd (J = 8.5, 2.2 Hz, 1H), 7.57 d (J = 2.2 Hz, 1H), 7.63 s (1H). EI-MS 512 $[M + H]^+$.

5-(4-Cyclopropylphenyl)-1-(2,4-dichlorophenyl)-4-ethyl-*N*-pyrrolidin-1-yl-1-*H*-pyrazole-3-carboxamide (11r). This compound was synthesized according to the procedure described for **11a** using commercially available 1-aminopyrrolidine in step "e". Yield: 67%; 95.5% purity by HPLC. ^{1}H NMR (500 MHz, DMSO-d_6): 0.64−0.67 m (2H), 0.91−0.97 m (2H), 1.07 t (J = 7.4 Hz, 3H), 1.71−1.79 m (4H), 1.82−1.92 m (1H), 2.62 q (J = 7.4 Hz, 2H), 2.85−2.94 m (4H), 7.03−7.09 m (4H), 7.53 dd (J = 2.3 Hz, 1H), 7.70 d (J = 2.3 Hz, 1H), 7.73 d (J = 2.3 Hz, 1H), 9.03 s (1H). FIB-MS 468 $[M + H]^+$.

Preparation of 1-(4-Cyclopropylphenyl)-2-methoxyethanone (7f). 2-Methoxy-1,1-bis(trimethylsilyloxy)ethene 14 and 4-cyclopropylbenzenecarboxylic acid (**12**) were prepared as described in the literature.[22,33] To a suspension of 17.4 g (107 mmol) of **12** in 100 mL of anhydrous toluene, 15.6 mL (213 mmol) of thionyl chloride and a catalytic amount of DMF were added and the reaction mixture was stirred for 5 h at 80 °C. After the reaction completed, the solvent and the excess of thionyl chloride were evaporated and the residue was distillated under reduced pressure. The corresponding acid chloride **13** as a main fraction was collected between 42 and 48 °C at 0.032 mbar (15.9 g, 82%). then 15.9 g of **13** was added to 20.6 g (88.0 mmol) of **14** containing 3 drops of $SnCl_4$ in one portion and the mixture was stirred for 2 h and allowed to stand for overnight. The reaction mixture was poured into 150 mL of 0.5 M aqueous HCl and extacted with EtOAc. The organic phase was washed with saturated aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4, and the solvent was removed by evaporation. The oily residue was purified by flash chromatography, and the desired compound was obtained in a poor yield: 3.14 g (19%), as a yellowish, oily liquid. 95.8% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$): 0.81−0.75 (m, 2H), 1.10−1.03 (m, 2H), 1.98−1.90 (m, 1H), 3.50 (s, 3H), 4.67 (s, 2H), 7.12 (ca.d, J = 8.3, 2H), 7.82 (ca.d, J = 8.3, 2H). EI-MS 190 $[M + H]^+$.

Biological Methods. In Vitro [^{3}H]SR141716A Ligand Binding at CB1 Receptors. Rat cerebellum was removed and homogenized and a membrane preparation was made according to Thomas et al.[34] and Devane et al.[35] and then stored at −80 °C until use.

A solution of 0.4 nM [^{3}H]SR-141716A in 50 mM Tris-HCl buffer complemented with 5 mM $MgCl_2$, 1 mM EDTA, and containing 20% ethanol was prepared freshly each day from a stock solution (0.002 mCi/ml, in ethanol).

Incubation was performed in the above-mentioned buffer complemented with 1 mg/mL bovine serum albumin (BSA) and 1 mM dithiothreitol (DTT) for 60 min at 30 °C in a thermostatted shaker. Incubation mixture (total volume of 1 mL) contained 200 μg rat cerebellar membrane (thoroughly homogenized and kept vortexed under the whole preincubation procedure) while the final radioligand concentration was 0.04 nM. Assay mixture was then filtered through Whatman GF/C glass fiber filters (Brandel M48 harvester) and washed with 5 × 5 mL incubation buffer (without DTT). Filters were dried and placed in scintillation vials, and 3.5 mL HiSafe scintillation cocktail was added. Samples were left to stand overnight, and radioactivity was determined in a Wallac 1409 scintillation spectrometer. Nonspecific binding was determined in the presence of 1 μM unlabeled SR141716A.

IC_{50} values were determined from displacement curves using sigmoid fitting by Origin 6.0 software. K_i values were calculated by the Cheng−Prusoff equation.[36]

In Vitro Metabolic Stability. Metabolic stability was assessed in vitro using human, rat or mouse liver microsomes.

Test compounds at 2.5 μM were incubated for various lengths of time (0−40 min) with human (XenoTech, USA) or CD1 mouse (Richter) liver microsomes. CL_{int} were calculated from the rate of compound consumption.

WIN 55,212-2 Induced Hypothermia Test. CD1 mice, weighing 25−30 g, were kept in groups of 5. On the experimental day, subjects received the test compound (antagonist) or vehicle orally (WIN 55,212-2 was suspended in the mixture of 2% Tween 80 and saline. Test compounds were suspended in the mixture of 5% Tween 80 and distilled water).

After 15 min, the CB1 agonist WIN 55,212-2 or vehicle was administered intraperitoneally, and rectal temperature was measured 45 min later. Data were analyzed with One-Way ANOVA and Tukey post hoc test.

Acute Appetite Suppressant Assay: Food Intake Test. Test protocol has been derived from Wiley et al.[37] but modified in several ways in order to adapt to our in-house conditions.

CD1 mice weighing >25 g were kept isolated at least for 3 days before the test. Sixteen hours before measurement, chow was removed from home cages (overnight fasting). The next day, subjects were treated per os with vehicle (5% Tween 80 solution) in their home cages. One hour later (pretreatment time), preweighed palatable chow (Test Diet, no. 58 V8) was added to the feeding boxes of home cages. After one hour, chow was reweighed and consumption was calculated. Final results are expressed as the percentage differences from control mean consumption.

DIO Test. Test protocol has been derived from the literature[29] and modified for daily routine. C57Bl/6 mice initially weighing 22−25 g were fed with standard laboratory chow (lean control) or with Test Diets no. TBU8 high fat containing diet (60% caloric content is fat). After the TBU8 fed group reached ∼60% excess body weight over lean control group (it takes usually 6−8 weeks), subjects were isolated and assigned to treatment groups ($n = 8$) counterbalanced by body weight. After three-day habituation phase (daily treatment with tap water), mice were treated once daily with test compounds or vehicle (fat control) orally for 14 days. (Test compounds were suspended in the mixture of 5% Tween 80 and distilled water). Body weight and chow consumed were weighed daily. Data were analyzed with One-Way ANOVA and Tukey post hoc test.

Serum Lipid Profile Determination. On the 14th day of the diet induced obesity test, after the (last) oral treatment, chow was removed from the home cages. the next day, animals were deeply anesthetized and blood was collected through the aorta abdominalis or through plexus retroorbitalis. Immediately thereafter, mice were sacrificed. Blood samples were centrifugated in vacuo for 20 min at 4 °C on 3000U/min. Serum was collected and analyzed by "Olympus test package for lipid profile measurement". Data were analyzed with One-Way ANOVA and Tukey post hoc test.

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Supporting Information Available: General synthesis and experimental and spectroscopic (^{1}H NMR and MS) details for nonkey compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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