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Hair growth stimulator property of thienyl substituted pyrazole carboxamide derivatives as a cb1 receptor antagonist with in vivo antiobesity effect ☆

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ABSTRACT

A few thienyl substituted pyrazole derivatives were synthesized to aid in the characterization of the cannabinoid receptor antagonist and also to serve as potentially useful antiobesity agent. Structural requirements for selective CB1 receptor antagonistic activity of 5-thienyl pyrazole derivatives included the structural similarity with potent, specific antagonist rimonabant **1**. Compound **3** has been identified as a hair growth stimulator and an antiobesity agent in animal models.

Cannabinoid receptors present in the central nervous system have been implicated in the control of appetite, cognition, mood and drug dependency, thus indicating a promising new approach for reducing body weight and decreasing co-morbidities.[1] A large number of CB1 receptor antagonists and their pharmacological effects have been recently reviewed.[2–4] Selective CB1 receptor antagonists are under development for treatment of obesity.[5,6] CB1 receptors are found primarily in the brain, whereas CB2 receptors are found predominantly in the immune cells and tissues.[7–9] CB1 receptors are also found in human epidermal keratinocytes[10,11] and known to modify the proliferation and differentiation of the transformed keratinocytes.[12,13]

Rimonabant **1** (Fig. 1) is a potent CB1 receptor antagonist and has been approved in Europe as antiobesity drug.[14] However; no report has been yet published for the role of compound **1** as a hair growth stimulator. Interestingly, in a report it has been demonstrated that the endocannabinoid *N*-arachidonoylethanolamide as well as exocannabinoid Δ^9-tetrahydrocannabinol dose dependently inhibited hair shaft elongation and these effects were inhibited by a selective CB1 receptor antagonist.[15]

Thus, CB1 receptor antagonists could prove to be an interesting therapeutic tool to counteract hair loss and clinically manage unwanted hair loss as a life style drug. In continuation of our cannabinoid research,[16] we synthesized few thienyl substituted pyrazole-

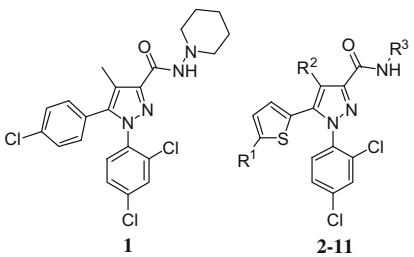

Figure 1.

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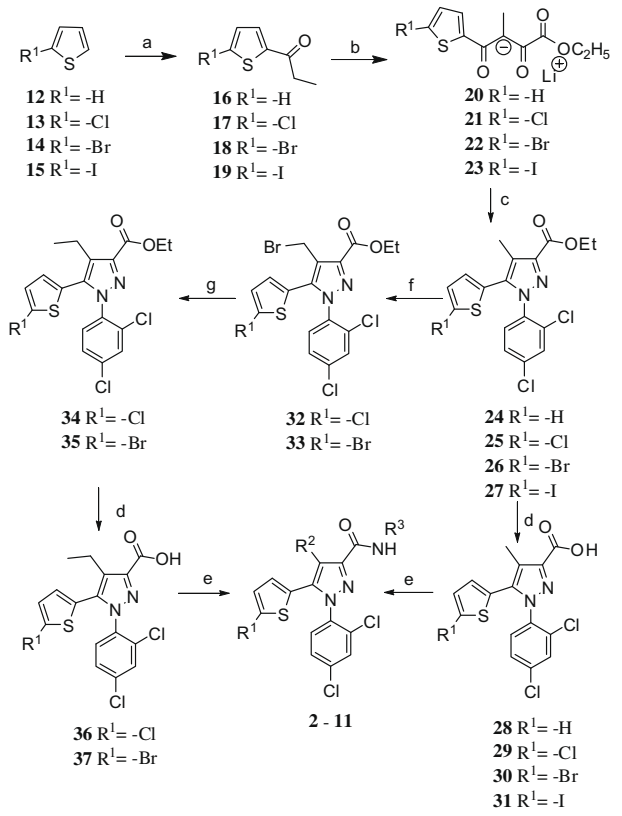


Scheme 1. Reagents and conditions: (a) $(CH_3CH_2CO)_2O$, $BF_3{\cdot}Et_2O$, 118–120 °C, 30 min, 62–78%; (b) $C_6H_{10}O_4$, LHMDS (1.06 M soln. in THF), Et_2O, −78 °C, 20–22 h, 56–64%; (c) 2,4-$Cl_2C_6H_4NHNH_2{\cdot}HCl$, C_2H_5OH, 0–5 °C, 1 h, IPA·HCl, 75–78 °C, 20–22 h: (d) KOH aq, CH_3OH, H_2O, 65–67 °C, 2 h; (e) R_3NH_2, EDC·HCl, HOBt·H2O, TEA, dry CH_2Cl_2, 30–45 min; (f) NBS, $(C_6H_5CO)_2O_2$, CCl_4, 72–74 °C, 4 h; (g) CuBr, CH_3Li (1.6 M soln. in diethylether), Et_2O, −78 °C, 2 h.

3-carboxamide derivatives **2**–**11** where the 5th aryl group of rimonabant has been bioisosterically replaced by thienyl group (Fig. 1) and evaluated them for their cannabinoid receptor selectivity, anti-obesity effect and selected compound for hair growth stimulator property in rodent models.[16j]

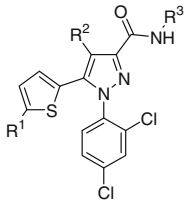
The preparation of thienyl pyrazole-3-carboxamides **2**–**11** are outlined in the Scheme 1 and were synthesized in a conventional method as reported in literature.[17–19] The thienyl derivatives **12**–**15** were procured from Sigma Aldrich and ketones **16**–**19** were synthesized as per the literature procedure.[20] The ketones were reacted with diethyl oxalate in the presence of lithium bis (trimethylsilyl) amide to afford corresponding lithium salts **20**–**23**. These lithium salts were reacted with 2,4-dichlorophenylhydrazine hydrochloride under acidic conditions to give thienyl substituted 1H-pyrazole-3-carboxylic acid ethyl esters **24**–**27**. The synthesis of acids **28**–**31**, **36** and **37** involved usual basic hydrolysis of corresponding ester **24**–**27**, **34** and **35**.

The thienyl pyrazole-3-carboxamide analogs **2**–**11** were prepared[21] by condensing the corresponding acids **28**–**31**, **36** and **37** with cyclic amines R^3–NH_2 under usual peptide bond formation chemistry using [1-(3-dimethylaminopropyl)-3-ethyl carbodiimide] hydrochloride and 1-hydroxybenzotriazole hydrate. The synthesis of 4-bromomethyl ester analog **32** and **33** involved the bromination using *N*-bromosuccinamide of ester **25** and **26**. The methylation of **32** and **33** was achieved using methyllithium catalyzed by cuprous bromide as per the reported procedure[21] to give **34** and **35**.

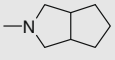
The target compounds **2**–**11** were screened in vitro in CHOK1 cells stably expressing human CB1 receptor using cAMP functional assay and functional activity determined which was expressed as EC_{50}. The in vitro CB1 receptor data (Table 1) revealed that the unsubstituted thienyl derivative **2** had 5.5-fold less CB1 activity than rimonabant **1**. The chloro thienyl derivative **3** was observed to be 2.4-fold less active in CB1 receptor activity when compared to compound **1**.

The bromo thienyl derivative **4** and iodo thienyl derivative **5** exhibited 1.6-and 1.3-fold less CB1 activity respectively when compared to compound **1**. Replacement of the piperidinyl group of **3** by pyrrolidinyl in **6** elicited decreased activity. Further substitution of homopiperidinyl **7** showed even lower CB1

Table 1
In vitro hCB1 and hCB2 functional assay for assessing cAMP activity for 5-thienyl pyrazole-3-carboxamide derivatives **2**–**11**



2-11

Compd	R^1	R^2	R^3	hCB1 (cAMP)[a,b] EC_{50} (μM)	hCB2 (cAMP)[a,c] EC_{50} (μM)
3	–Cl	–Me		0.58 ± 0.10	23.67 ± 1.00
4	–Br	–Me		0.40 ± 0.01	23.21 ± 2.30
5	–I	–Me		0.32 ± 0.05	29.44 ± 2.55
6	–Cl	–Me		1.00 ± 0.10	20.92 ± 1.85
7	–Cl	–Me		1.10 ± 0.09	12.81 ± 1.50
8	–Cl	–Me		0.69 ± 0.09	7.43 ± 0.55
9	–Cl	–Me		0.80 ± 0.05	15.66 ± 2.38
10	–Cl	–Et		0.54 ± 0.03	25.93 ± 3.55
11	–Br	–Et		0.51 ± 0.05	19.54 ± 1.25
2	H	–Me		1.33 ± 0.50	7.55 ± 0.3
1				0.24 ± 0.01	31.21 ± 3.21

[a] Values indicate mean ± SD of at least three independent experiments performed in duplicate.
[b,c] cAMP assay was carried out in Chinese Hamster Ovarian cells stably expressing human hCB1 and hCB2 receptor, respectively.

activity than **3** and **6**. Morpholine derivative **8** exhibited mediocre CB1 receptor activity. The presence of more bulky bicyclic amine **9** revived the CB1 activity up to some extent as compared to compounds **6** and **7**. Interestingly the chloro thienyl derivative with ethyl side chain **10** showed better CB1 receptor activity.

However, bromo thienyl derivative with ethyl chain on the position 4 of the pyrazole **11** exhibited nearly similar activity as that exhibited by compound **3**. The same set of compounds was also evaluated for their hCB2 functional activity (Table 1). It is clear that compounds **2**–**11** behave as weaker CB2R antagonist in cAMP assay. The CB1R agonists are reported to promote the sucrose consumption in rodents[22] and the selective CB1R antagonists reduce sucrose feeding and drinking in rodents.[23] Compounds **2**–**11** were further evaluated for their consumption of 5% sucrose solution in obese Zucker rats, which have elevated hypothalamic levels of the endocannabinoid as compared to lean rats.[24,25]

The thienyl derivative **2**, moderately inhibited the consumption of sucrose solution as compared to compound **1** (Table 2). The chloro thienyl derivative **3**, which structurally mimics to rimonabant, exhibited inhibition of sucrose solution comparable to compound **1**. The bromo thienyl derivative **4** and iodo thienyl derivative **5** exhibited lower suppression of sucrose solution consumption as compared to compound **3**, however, the iodo thienyl derivative **5** was found to be slightly superior to **1** in the sucrose solution intake assay. Pyrrolidinyl derivative **6**, homopiperidinyl derivative **7**, morpholinyl derivative **8** and bicyclic derivative **9**, all showed lesser efficacy as compared to compound **3** as well as compound **1** against sucrose solution consumption (Table 2). The bromo thienyl substituted with ethyl

Table 2
In vivo efficacy of 5-thienyl pyrazole-3-carboxamide derivatives **2**–**11** in 5% sucrose solution intake model at single dose of 10 mg/kg in female Zucker fa/fa rats

Compd	5% Sucrose solution intake in 4 h in gram[a]	% Inhibition versus control
Control	41.8 ± 3.6	
2	36.6 ± 4.1	12.4 ± 3.1
3	21.7 ± 3.6	48.0 ± 1.2
4	26.0 ± 4.8	37.8 ± 4.1*
5	24.2 ± 1.5	42.10 ± 0.6
6	27.4 ± 2.8	34.3 ± 1.3
7	33.4 ± 3.1	20.1 ± 1.7
8	28.6 ± 2.4	31.5 ± 1.2
9	30.8 ± 1.8	26.3 ± 0.9
10	28.7 ± 1.2	31.3 ± 0.8
11	25.4 ± 0.9	39.2 ± 0.6*
1	25.0* ± 4.3	40.1 ± 10.2

[a] Values indicate mean ± SEM for $n = 6$ rats in 4 h.
* p <0.05, when compared with the control group, one way ANOVA followed by Dunnett's multiple comparison test.

Table 3
Effect of compound **3** on CB1 agonist WIN-55212-2 (1 mg/kg, iv) induced mouse tetrad model[a]

Compd **3** (mg/kg, po)	Change in body temp. (°C)	Analgesic effect[b] (% MPE)	Catalepsy[c] (% immobility on ring for 300 s)	Locomotor activity[d] (No. of square crossed in 300 s)
0 (Control)	4.79 ± 0.27	88.75 ± 2.42	95.53 ± 7.86	20.67 ± 3.38
1	2.56 ± 0.40*	34.84 ± 13.03*	80.73 ± 2.35	69.8 ± 5.40*
3	1.92 ± 0.24*	12.28 ± 3.87*	73.13 ± 5.50	109.2 ± 6.23*
5	0.23 ± 0.09*	4.12 ± 1.52*	58.13 ± 4.33*	126.5 ± 8.37*
10	0.23 ± 0.07*	4.35 ± 1.35*	41.80 ± 3.31*	171.4 ± 6.38*

[a] Values indicate mean ± SEM for $n = 6$.
[b] % MPE on hot plate.
[c] % immobility.
[d] No of squares crossed in 5 min.
* P <0.05, significant differences with WIN 55212-2-treated control group.

Table 4
Mean pharmacokinetic parameter of **3** and **1** in fasted female Zucker fa/fa rats after oral dose of 30 mg/kg[a]

Compd	T_{max} (h)	C_{max} (μg/mL)	$T_{1/2}$ (h)	AUC(0–∞) (h μg/mL)
3	1.4 ± 0.7	0.52 ± 0.07	20.78 ± 1.07	12.41 ± 4.54
1	2.6 ± 1.3	1.92 ± 0.31	26.55 ± 7.23	41.20 ± 3.65

[a] Values indicate mean ± SD for $n = 6$ rats.

Table 5
Tissue and plasma distribution of compounds **3** and **1** in fasted female Zucker fa/fa rat at 3 h after oral dose of 30 mg/kg[a]

Compd	Drug concentration				
	Brain		White adipose tissue		Plasma
	μg/mL	μg/g	μg/mL	μg/g	μg/mL
3	0.21 ± 0.18	0.64 ± 0.55	0.98 ± 0.40	2.97 ± 1.19	0.85 ± 0.06
1	0.15 ± 0.01	0.45 ± 0.03	1.40 ± 0.22	4.25 ± 0.66	0.40 ± 0.04

[a] Values indicate mean ± SEM for $n = 6$ rats.

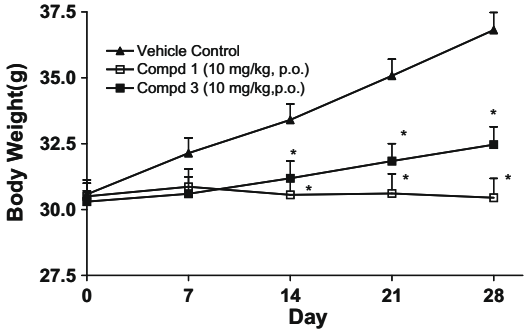


Figure 2. The effect of compounds **1** and **3** on bodyweight in high fat diet-induced obese C57BL/6J mice. * P <0.05 when compared with the vehicle-treated control group, repeat measure ANOVA followed by Dunnett's test. Mean ± SEM for $n = 8$ rats.

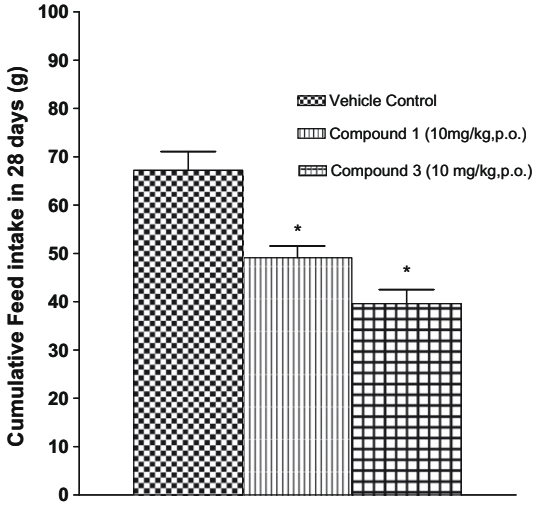


Figure 3. The effect of compounds **1** and **3** on food intake in high fat diet-induced obese C57BL/6J mice. * P <0.05 when compared with the vehicle-treated control group, One way ANOVA followed by Dunnett's test. Mean ± SEM for $n = 8$ rats.

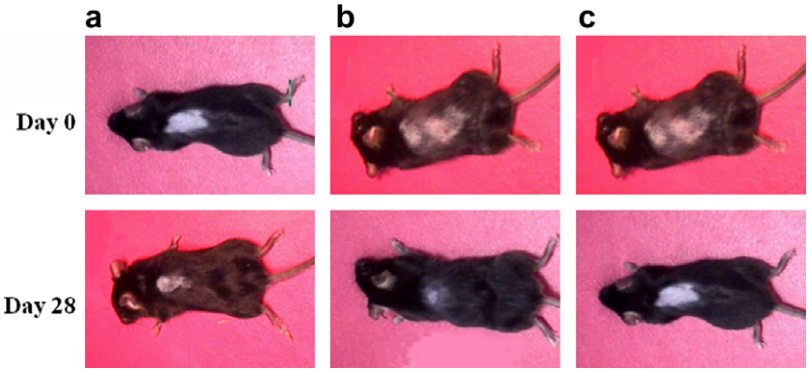


Figure 4. The long term (28 days) effect of control, compounds **3** and **1** (10 mg/kg) on hair growth in C57BL/6J mice: (a) high fat fed mouse as control; (b) compound **3** (10 mg/kg) repeat dose treatment in high fat fed mouse; (c) compound **1** (10 mg/kg) repeat dose treatment in high fat fed mouse.

chain **11**, showed significant suppression of sucrose solution as compared to corresponding chloro thienyl derivative **10** and compound **1**. Depending upon the in vitro hCB1 activity and pronounced in vivo efficacy shown by compound **3**, the effect of compound **3** was evaluated on CB1 agonist WIN-55212-2 induced hypothermia, analgesia, locomotor activity and catalepsy in male Swiss Albino mice to further confirm its CB1 antagonism (Table 3).[26,27] Compound **3** showed dose dependent CB1 antagonism in this model. The pharmacokinetics parameters of compound **3** were also evaluated in fasted female Zucker fa/fa rats and compared with compound **1** (Table 4). The AUC (0–∞) for compound **3** was found to be inferior to compound **1**. The tissue and plasma distribution of compound **3** (Table 5); when compared to compound **1**, revealed higher drug concentration in the brain (0.21 ± 0.18 μg/mL) for compound **3** as compared to compound **1**(0.15 ± 0.01 μg/mL). However, the concentration of compound **3** was found to be slightly less in white adipose tissues (0.98 ± 0.40 μg/mL) as compared to compound **1** (1.40 ± 0.22 μg/mL).

Since, the chloro thienyl derivative **3** exhibited a significant potency and efficacy it was subsequently taken for 28 days chronic oral study, once daily at the dose of 10 mg/kg in C57BL/6J mice of 6–8 weeks age with diet-induced obesity. The diet-induced obesity in C57BL/6J mice is a well-known model for obesity that resembles the clinical obesity in humans and the relative potency of CB1 receptor antagonists is also evaluated by various in vivo effects in C57BL/6J mice.[28] Thus, compounds **3** and **1** were studied in C57BL/6J mice. For all in vivo experiments, compounds were suspended with 0.01% Tween 80 plus 5% DMSO in saline (NaCl 0.9%) for intravenous administration (particularly for the CB1 agonist WIN-55212-2) or with 0.5% carboxymethylcellulose sodium salt in distilled water for oral route. The test compounds were administered at the dose of 10 mg/kg. All the compounds were administered by oral route in a volume of 2 mL/kg body weight for rats and 10 mL/kg body weight for mice. WIN-55212-2 was injected intravenous at a dose of 1 mg/kg in mice in a volume of 10 mL/kg body weight.

Compound **3** significantly reduced the body weight gain and food intake as compared to control (Figs. 2 and 3). The C57BL/6J mice when fed on high fat diet for eight weeks displayed significant alopecia (loss of hair on dorsal side, Fig. 4). These C57BL/6J mice were divided into three groups and each group was treated for a period of 28 days. Interestingly, compound **3** affected hair growth significantly and the bald area reduced to 0.011 cm^2 as compared to rimonabant, which showed bald area 0.156 cm^2 where hair growth has not appeared (Table 6, Fig. 4).

Table 6
The effect of compounds **1** and **3** on the hair growth on male C57BL/6J mice after 28th day of dosing (n = 8 mice)

Compd	Area (cm^2) (mean ± SEM)[a]	
	Treatment day 0	Treatment day 28
Control	0.297 ± 0.021	0.346 ± 0.079
3	0.292 ± 0.024	0.011 ± 0.023*
1	0.256 ± 0.074	0.156 ± 0.068

[a] The bald area where hair growth or pigmentation has not appeared.
* P <0.05, ANOVA followed by Dunnets multiple comparison test, when compared with the vehicle-treated control group.

Herein, we have described compound **3** with antiobesity effect through CB1 receptor antagonism, which structurally mimics the rimonabant **1**. Additionally, compound **3** was also efficacious in diet-induced obese (C57BL/6J) mice, showing reduction in overall body weight with interesting activity as a hair growth stimulator. However, no any such hair growth stimulation was observed after the topical application of either of compounds **3** and **1**. Notably, no report has been yet published for compound **1** as a hair growth stimulator. Thus, this class of compounds needs further attention as a hair growth stimulator.

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Supplementary data

Supplementary data (biological assays) associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2009.03.046.

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