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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-

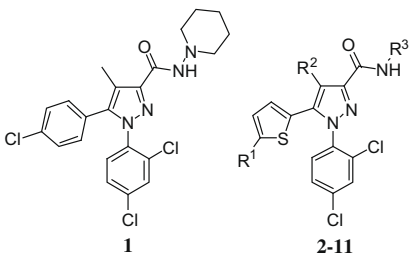

Figure 1.

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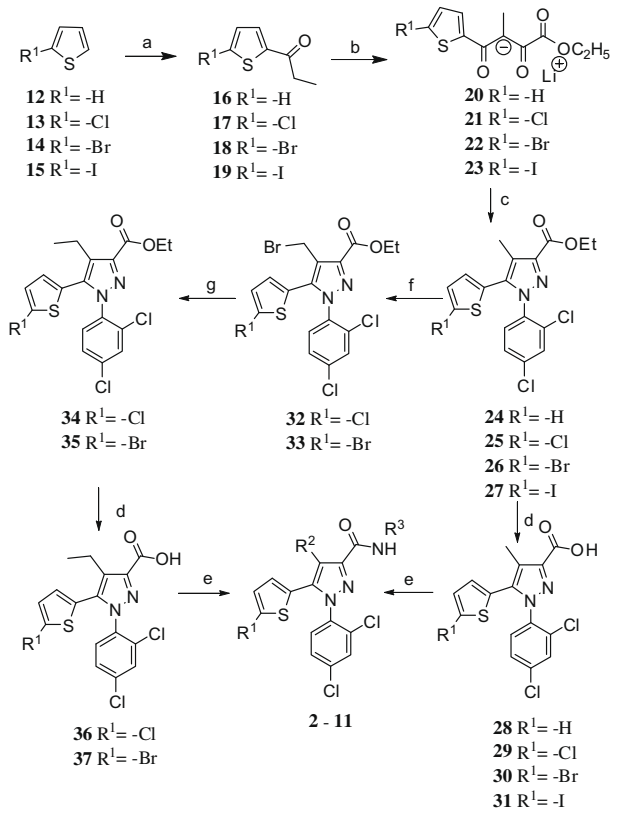


Scheme 1. Reagents and conditions: (a) $(CH_3CH_2CO)_2O$, $BF_3{\cdot}Et_2O$, 118–120 °C, 30 min, 62–78%; (b) $C_6H_{10}O_4$, LHMDS (1.06 M soln. in THF), Et_2O, −78 °C, 20–22 h, 56–64%; (c) 2,4-$Cl_2C_6H_4NHNH_2{\cdot}HCl$, C_2H_5OH, 0–5 °C, 1 h, IPA·HCl, 75–78 °C, 20–22 h: (d) KOH aq, CH_3OH, H_2O, 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]

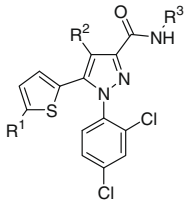
The preparation of thienyl pyrazole-3-carboxamides **2**–**11** are outlined in the Scheme 1 and were synthesized in a conventional method as reported in literature.[17–19] The thienyl derivatives **12**–**15** were procured from Sigma Aldrich and ketones **16**–**19** were synthesized as per the literature 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**.

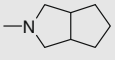
The target compounds **2**–**11** were screened in vitro in CHOK1 cells stably expressing human CB1 receptor using cAMP functional assay and functional activity determined which was expressed as EC_{50}. The in vitro CB1 receptor data (Table 1) revealed that the unsubstituted thienyl derivative **2** 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.