Bioorganic & Medicinal Chemistry Letters 21 (2011) 4913–4918

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Structure–activity relationship studies of novel pyrazole and imidazole carboxamides as cannabinoid-1 (CB1) antagonists ☆

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ARTICLE INFO

Article history:
Received 22 February 2011
Revised 27 May 2011
Accepted 6 June 2011
Available online 7 July 2011

Keywords:
Cannabinoid 1 (CB1) receptor
CB1 antagonists
Pyrazole and imidazole carboxamides
Obesity
DIO mice model

ABSTRACT

The synthesis and biological evaluation of novel pyrazole and imidazole carboxamides as CB1 antagonists are described. As a part of eastern amide SAR, various chemically diverse motifs were introduced on rimonabant template. The central pyrazole core was also replaced with its conformationally constrained motif and imidazole moieties. In general, a range of modifications were well tolerated. Several molecules with low- and sub-nanomolar potencies were identified as potent CB1 receptor antagonists. The in vivo proof of principle for weight loss is demonstrated with a lead compound in DIO mice model.

The prevalence of obesity is rapidly increasing globally and no satisfactorily safe and effective obesity drugs are available at the moment. Recent studies have shown that impaired handling of cellular energy homeostasis is closely associated with metabolic syndrome including obesity, type 2 diabetes and related diseases. The endocannabinoid system (ECS), and specifically the cannabinoid type 1 (CB1) receptor, plays a pivotal role in energy homeostasis.[1–3] As such, stimulation of the ECS promotes food intake and energy storage and may be chronically overactive in obese subjects.[4–7] CB1 receptor-deficient mice are resistant to diet-induced obesity even though their total caloric intake is similar to that of wild-type littermates.[8] In contrast, blockade of the CB1 receptor in the central nervous system decreases food intake and increases energy expenditure, leading to a reduction in body weight.[9–12] Such an approach is particularly interesting since it not only causes weight loss but also reverses the metabolic effects of obesity such as insulin resistance and hyperlipidemia.[13] Besides obesity, blocking CB1 receptor may have potential in the treatment of a number of diseases such as neuroinflammatory disorders,[14] cognitive disorders,[15] septic shock,[15] psychosis,[15,16] addiction,[17] and gastrointestinal disorders.[18] Another cannabinoid receptor, CB2 is related to immune regulation and neurodegeneration.[19] Therefore, the CB2/CB1 selectivity should be taken into consideration for new drug development of antiobesity agent. Significant efforts around the globe led to the identification of several potent and selective CB1 antagonists which were tested in clinical trials. Amongst these rimonabant (**1**)[20] (Fig. 1) was initially approved by EMEA for the treatment of obesity but unfortunately this was withdrawn from

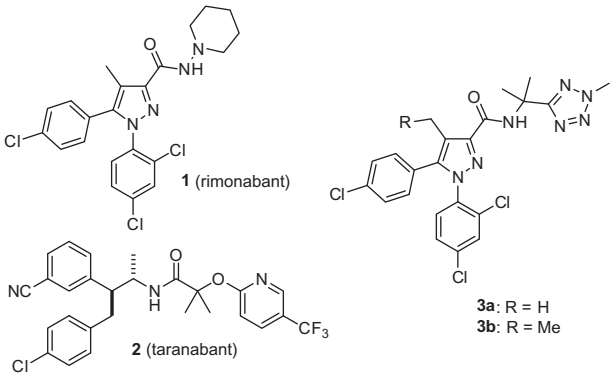

Figure 1. Structures of CB1 antagonists.

☆ DRL Publication No. 728.

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doi:10.1016/j.bmcl.2011.06.017

the market due to various psychiatric events. For the similar reason, the development of another CB1 antagonist taranabant (**2**)[21] was suspended from clinical trial.

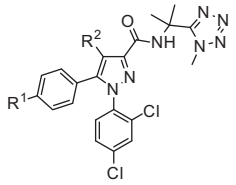
However, despite consecutive failures of leading CB1 receptor antagonists, works continue to identify novel peripherally restricted CB1 antagonists[22] that limit BBB penetration so that they do not induce serious psychiatric disorders. To test this hypothesis, recently 7TM Pharma is evaluating their peripherally restricted CB1 antagonist TM-38837[23] (structure undisclosed) in human. In our previous communication,[24] we disclosed N2-methylated tetrazole derivatives including compounds **3a** and **3b** as potent CB1 antagonists. We report herein SAR studies on novel eastern amides along with the central pyrazole core modifications to imidazoles and conformationally constrained tricyclic pyrazoles to identify lead compounds.

The target compounds (Tables 1–4) were synthesized as outlined in Schemes 1–6. The synthesis of 2-(1-methyl-1*H*-tetrazol-5-yl)propan-2-amine (**III**) was commenced with 2-amino-2-methylpropanenitrile (Scheme 1). The alkylation of tetrazole **I**[25] led to the formation of both **II** and **IIa**.[26] Hydrogenolysis of **II** gave the crucial intermediate **III**, coupling of which with various pyrazole acids **IV**[24,27] furnished compounds **4–14**.

The constrained analogs **15** and **16** were synthesized following Scheme 2. The tetrahydrobenzoannulenone derivatives **V** were first converted to tetrahydrobenzocycloheptapyrazole carboxylic acid derivatives **VI** which after subsequent coupling with **III** afforded the desired compounds. Synthesis of compounds **17–21** is mentioned in Scheme 3. The coupling of 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxylic acid (**IVa**) with aminonitrile under EDC/HOBt conditions furnished intermediate **VII** which was subsequently converted to thioamide **VIII**. Treatment of **VIII** with various haloketones afforded targets **17–20**. Hydrolysis of **20** produced **21**. Compounds **22–26** were synthesized following routes as outlined in Scheme 4. The pyrazole acid was first converted to amide **IX** which after four steps protocol viz., hydrolysis of ester, Weinreb amide formation, Grignard reaction and bromination produced bromo ketone **X**. Coupling of **X** with various partners afforded the target compounds **22–26**.

The synthesis of oxadiazole compounds **27–37** is outlined in Scheme 5. Upon treatment with hydroxylamine, the cyano intermediates **VII** were converted to N-hydroxyamidines **XI** which after reaction with acetic anhydride furnished 5-methyl-1,2,4-oxadiazole derivative **27**. The corresponding trifluoromethyl analogs **28** and **30–32** were prepared by the treatment of **XI** with trifluoroacetic anhydride under refluxing conditions. The isomeric 1,3,4-oxadiazole derivative **29** was synthesized from **VII** via two steps protocols viz., tetrazole formation from cyano compound followed by treatment of **XII** with trifluoroacetic anhydride. Compounds **33** and **35** were synthesized from **28** and **31** respectively by NBS mediated bromination followed by $AgNO_3$ mediated hydrolysis.

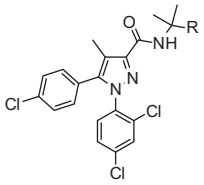
Table 1
Rat CB1 binding affinities of compounds **1**–**16**

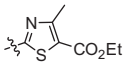
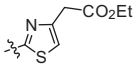
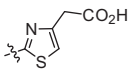
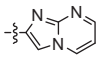
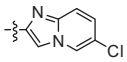
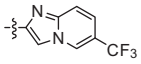
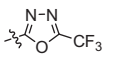


Compound	R^1	R^2	rCB1_IC$_{50}$[a] (nM)
1			18[b]
2			0.3[b]
3a			88
3b			39
4	Cl	Me	145
5	Cl	Et	0.5
6	Br	Et	0.1
7	$OSO_2{}^nPr$	Me	1.1
8	CN	Et	22
9	OMe	Et	5
10	CO_2Et	Et	17
11	CO_2H	Et	[c]
12	OH	Et	[d]
13	OCH_2COOEt	Et	[e]
14	OCH_2COOH	Et	>1000[f]
15			31
16			[g]

[a] Data are reported as the mean for $n = 2$ measurements and SD is generally within ±20% of the average.
[b] See Ref. 30 for comparison with literature.
[c] 50% binding at 1 μM.
[d] 23% binding at 100 nM.
[e] 32% binding at 100 nM.
[f] 25% binding at 1 μM
[g] 38% binding at 100 nM.

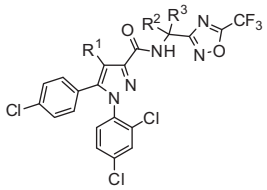
Table 2
Rat CB1 binding affinities of compounds **17**–**29**



Compound	R	rCB1_IC$_{50}$[a] (nM)
17		15
18		2
19		22
20		10
21		[b]
22		12
23		121
24		11
25		88
26		63
27		33
28		3
29		6

[a] As in Table 1.
[b] 50% binding at 1 μM.

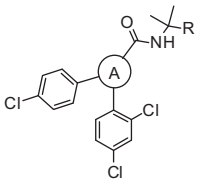
Table 3
Rat CB1 binding affinities of compounds **30–37**

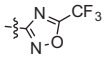
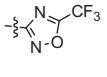
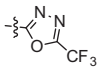


Compound	R^1	R^2	R^3	rCB1_IC_{50}[a] (nM)
28	Me	Me	Me	3
30	Me	Et	Me	6
31	Me	$-CH_2CH_2-$		0.1
32	Me	$-CH_2CH_2CH_2-$		0.8
33	CH_2OH	Me	Me	0.4
34	CH_2OMe	Me	Me	4
35	CH_2OH	$-CH_2CH_2-$		0.1
36	CO_2H	$-CH_2CH_2-$		[b]
37	CO_2Et	$-CH_2CH_2-$		1

[a] As in Table 1.
[b] 44% and 66% binding at 100 nM and 1 μM, respectively.

Table 4
Rat CB1 binding affinities of compounds **38–42**



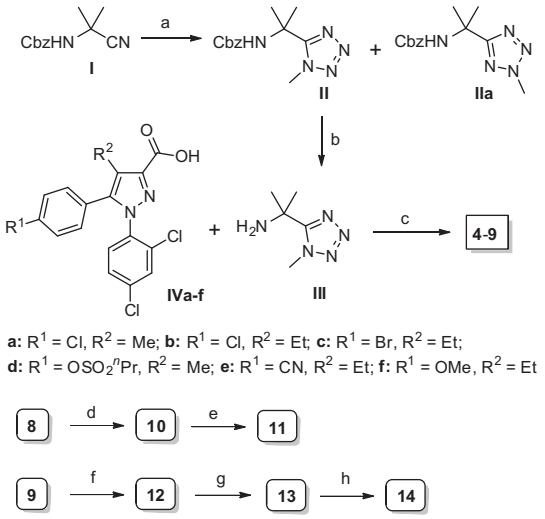
Compound	A	R	rCB1_IC_{50}[a] (nM)
38			[b]
39			36
40			3
41			30
42			13

[a] As in Table 1.
[b] 42% binding at 100 nM.

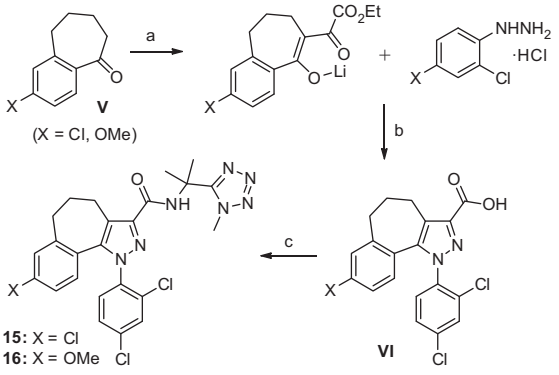
Compound **34** was made by the treatment of methanol on bromo intermediate derived from **28**. The $RuCl_3$–$NaIO_4$ mediated oxidation of **35** led to the corresponding carboxylic acid **36** which was converted to ester **37**.

The synthesis of compounds **38–42** were accomplished from imidazole carboxylic acids **XIII**[28] and **XIV**[29] by standard protocols as illustrated in Scheme 6.

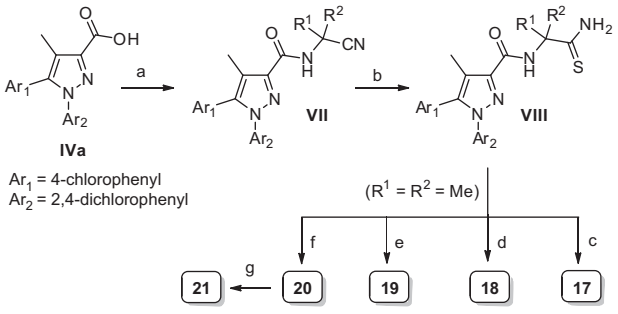
The target compounds were evaluated in vitro in a rat CB1 binding assay[24] and results are shown in Tables 1–4. Initially, the N2-methylated tetrazoles of **3a** and **3b** were replaced with N1-methylated tetrazoles. As mentioned in Table 1, compound **4** showed little reduction in rCB1 potency compared to **3a** whereas



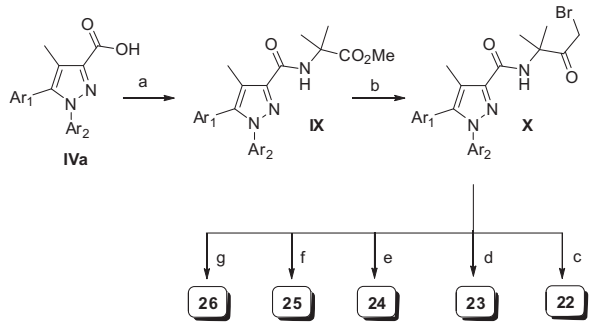
Scheme 1. Reagents and conditions: (a) (i) NaN_3, DMF, NH_4Cl, 120 °C, 16 h; (ii) MeI, K_2CO_3, DMF, rt, 2 h, 26% for **II** and 36% for **IIa** over two steps; (b) $Pd(OH)_2$/C, EtOAc, H_2 (balloon), rt, 14 h, 92%; (c) EDC·HCl, HOBt, Et_3N, CH_2Cl_2, rt, 10 h, 68–83%; (d) HCl (g), EtOH, 0 °C, 1 h then rt, 40 h, 43%; (e) LiOH, EtOH/THF/H_2O (1:1:1), rt, 4 h, 79%; (f) BBr_3, CH_2Cl_2, 0 °C to rt, 30 min, 63%; (g) K_2CO_3, DMF, bromoethyl acetate, 60 °C, 3 h, 42%; (h) LiOH, THF/H_2O (1:1), rt, 4 h, 74%.



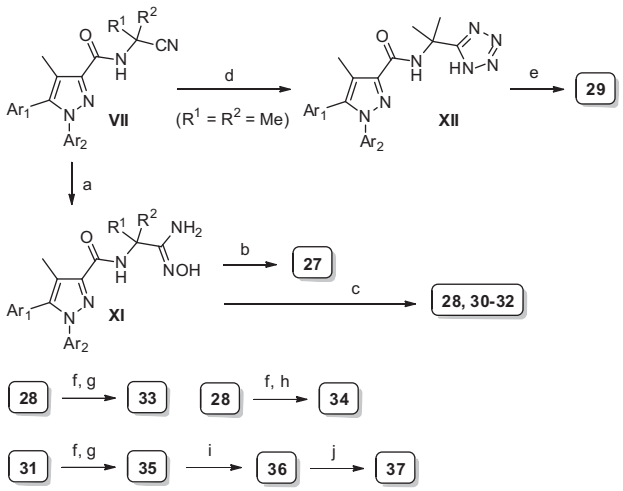
Scheme 2. Reagents and conditions: (a) LiHMDS, ether, −78 °C, $(CO_2Et)_2$, rt, 14 h, 95%; (b) (i) EtOH, reflux, 16 h; (ii) HOAc, reflux, 12 h; (iii) KOH, MeOH, reflux, 3 h, 28% over three steps; (c) **III**, EDC·HCl, HOBt, Et_3N, CH_2Cl_2, rt, 10 h, 62–69%.



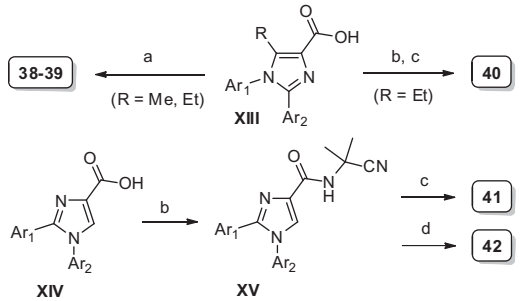
Scheme 3. Reagents and conditions: (a) aminonitrile, EDC·HCl, HOBt, Et_3N, CH_2Cl_2, rt, 10 h, 73–88%; (b) H_2S, EtOH, NH_4OH, −10 °C to rt, 10 h, 80%; (c) chloroacetone, EtOH, reflux, 16 h, 74%; (d) (i) 3-bromo-1,1,1-trifluoropropan-2-one, EtOH, reflux, 16 h; (ii) PTSA, benzene, reflux, 30 min, 35% (two steps); (e) ethyl 2-chloro-3-oxobutanoate, EtOH, reflux, 16 h, 46%; (f) ethyl 4-chloro-3-oxobutanoate, EtOH, reflux, 16 h, 41%; (g) LiOH, THF/H_2O (1:1), rt, 16 h, 95%.



Scheme 4. Reagents and conditions: (a) (i) $SOCl_2$, EtOH, reflux, 2 h; (ii) methyl 2-amino-2-methylpropanoate hydrochloride, Et_3N, CH_2Cl_2, 0 °C to rt, 14 h, 95% over two steps; (b) (i) LiOH, THF/H_2O (1:1), rt, 16 h, 93%; (ii) *N,O*-dimethylhydroxylamine hydrochloride, Et_3N, BOP, CH_2Cl_2, rt, 16 h, 40%; (iii) MeMgCl (3 M in THF), THF, −78 °C, 2 h, then warming to rt, 2 h, 53%; (iv) Br_2, $CHCl_3$, 0 °C to rt, 14 h, 60%; (c) thioacetamide, EtOH, reflux, 16 h, 46%; (d) 2-aminopyrimidine, EtOH, reflux, 16 h, 31%; (e) 2-aminothiazole, EtOH, reflux, 16 h, 35%; (f) 5-chloropyridin-2-amine, EtOH, reflux, 16 h, 38%; (g) 5-(trifluoromethyl)pyridin-2-amine, EtOH, reflux, 16 h, 32%.



Scheme 5. Reagents and conditions: (a) hydroxylamine hydrochloride, K_2CO_3, EtOH, reflux, 5 h, 60–75%; (b) acetic anhydride, 120 °C, 4 h, 58%; (c) trifluoroacetic anhydride, reflux, 6 h, 48%; (d) NaN_3, DMF, NH_4Cl, 120 °C, 16 h, 90%; (e) trifluoroacetic anhydride, rt, 48 h, 21%; (f) NBS, benzoyl peroxide, CCl_4, reflux, 5 h, 80%; (g) $AgNO_3$, acetone/H_2O (7:3), 60 °C, 16 h, 53%; (h) MeOH, rt, 16 h, 63%; (i) $RuCl_3$, $NaIO_4$, CCl_4/MeCN/H_2O (1:1:1); 0 °C to rt, 4 h, 36%; (j) (i) $SOCl_2$, $CHCl_3$, reflux, 1 h; (ii) EtOH, rt, 1 h, 77% over two steps.



Scheme 6. Reagents and conditions: (a) **III**, EDC·HCl, HOBt, Et_3N, CH_2Cl_2, rt, 10 h, 60–67%; (b) 2-amino-2-methylpropanenitrile, EDC·HCl, HOBt, Et_3N, CH_2Cl_2, rt, 10 h, 75–86%; (c) (i) hydroxylamine hydrochloride, K_2CO_3, EtOH, reflux, 5 h, 60–68%; (ii) trifluoroacetic anhydride, reflux, 6 h, 49–53%; (d) (i) NaN_3, DMF, NH_4Cl, 120 °C, 16 h, 98%; (ii) trifluoroacetic anhydride, rt, 48 h, 30%.

compound **5** showed very good rCB1 binding affinity with IC_{50} 0.5 nM compare to the potency of **3b**. In general, the replacement of *p*-Cl with other functionalities (Br, CN, OSO_2Pr, OMe and CO_2Et) is well tolerated with the most potency of IC_{50} 0.1 nM displayed by bromo anlog **6** whereas the hydrogen bond donors (COOH and OH) are detrimental to potency. The phenoxyacetate derivative **13** has shown reduction in potency whereas the corresponding acid **14** has lost all its potency. Extending the pyrazole ethyl group to its constrained counterpart tetrahydrobenzocycloheptapyrazole has shown reduction in potency (**5** vs **15**) and further loss in potency was observed when chloro was replaced with methoxy group (**5** vs **9** and **15** vs **16**).

As a part of SAR studies on eastern amide part, the tetrazole moiety was replaced with various monocyclic and bicyclic heretocycles and the results are displayed in Table 2. In general the wide range of variations is accepted in this region though the hydrogen bond donor as in **21** is not tolerated. The replacement of methyl group with more lipophilic trifluoromethyl group has shown to boost potency (**17** vs **18** and **27** vs **28**). The 1,3,4-oxadiazole derivative **29** has shown twofold loss in potency compared to its isomeric 1,2,4-oxadiazole derivative **28**.

Considering various properties (*c* Log *P*, tPSA, solubility, etc.), oxadiazoles were preferred over thiazoles for additional SAR in the eastern part of this scaffold. Further SAR was focused on compound **28** by replacing *gem*-dimethyl group with ethyl-methyl, cyclopropyl and cyclobutyl groups and the results are disclosed in Table 3. The cyclopropyl analog **31** has shown very high rCB1 affinity with IC_{50} of 0.1 nM. Replacement of the 4-methyl group of pyrazole with more polar hydroxymethyl functionality as in compound **33** and **35** displayed also low-nanomolar potency of IC_{50} 0.4 and 0.1 nM, respectively. The corresponding carboxylic acid of **35** as in **36** was completely detrimental to CB1 whereas the carbethoxy group as in **37** displayed potency of 1 nM.

The effect of replacing the pyrazole core with imidazole is presented in Table 4. The combination of imidazole core with eastern tetrazole has shown significant reduction in rCB1 potency (**39** vs **5**) though as observed before the switching methyl to ethyl at C5 of imidazole has displayed significant improvement in potency (**38** vs **39**). Compared to tetrazole counterpart **39**, as expected the oxadiazole derivative **40** has shown 12-fold improvement in potency displaying rCB1 IC_{50} of 3 nM. The isomeric imidazole core as in **41** and **42** has shown to be non-optimal in this scenario.

As discussed above a number of compounds with low nanomolar binding affinity for CB1 have been identified. Select compounds were tested for hCB2 receptor affinity studies and also assessed for its central pharmacodynamic effect in the hypothermia model[31]

Table 5
Profile of select CB1 antagonist

Compound	hCB2 affinity (% binding at 1 μM)	% Inhibition of hypothermia[a]	hERG_IC_{50} (μM)
1	34[b]	99[c]	2.79[d]
5	16	96	[e]
6	27	83	22.7
29	64	97	nd[f]
31	49	97	>30 μM[g]
33	34	97	>30 μM[h]
35	18	99	nd

[a] % Inhibition of WIN-55212 induced hypothermia at 30 min in SAM after compound administration (10 mg/kg po).
[b] hCB2_IC_{50} 1.98 μM.
[c] Dose 3 mg/kg po.
[d] Reported value, see Ref. 33.
[e] 59.7% inhibition at 10 μM and precipitation at higher concentration.
[f] Not determined.
[g] 7.2% inhibition at 30 μM.
[h] 38.9% inhibition at 30 μM.

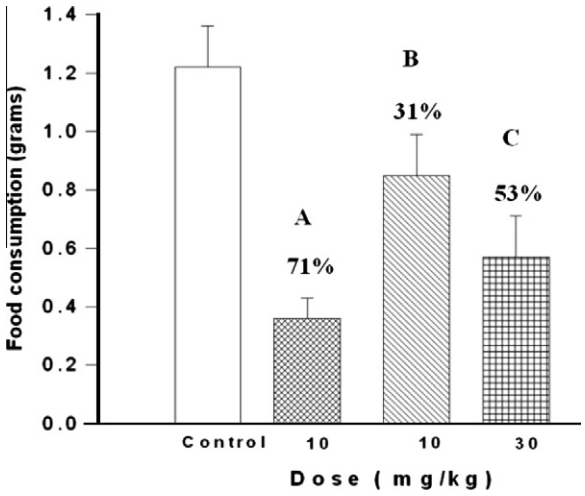


Figure 2. Effect on acute food intake after single dose oral administration of rimonabant (A: 10 mg/kg dose) and **31** (B: 10 mg/kg dose and C: 30 mg/kg dose) to SAM versus vehicle control animals.

and the results are summarized in Table 5. All of these compounds have shown decent selectivity over hCB2 and very good inhibition of CB1 agonist (WIN-55212) induced hypothermia in Swiss Albino Mice (SAM) model. Few of them were also tested in patch clamp assay[32] to measure their potential to block hERG potassium channel. Amongst these compound **31** was found to be highly selective over hERG (Table 5).

Compound **31** has shown dose dependant reduction in acute food intake (Fig. 2) when tested at 10 and 30 mg/kg po in SAM model. Rimonabant at a dose of 10 mg/kg po showed better effect compared to the highest tested dose of 30 mg/kg po of compound **31** suggesting that rimonabant might be having more pronounced central effect compared to more polar compound **31**.[34] Compound **31**, showing good oral PK profile,[35] was evaluated further in a diet-induced obesity (DIO) mouse model using C57BL/6J mice. On oral administration, compound **31** (10 mg/kg, q.d.)[36] showed steady loss of body weight culminating in a statistically significant weight loss of 11% on day 15 as shown in Figure 3.

In summary, we have explored novel chemically diverse motifs as a part of eastern amide SAR on rimonabant template. Few constrained analogs and central pyrazole core modification with pyrazoles were also tested for rCB1 receptor affinity. In general, a range of modifications were well tolerated. Several molecules were identified with low and sub-nanomolar potency as CB1 antagonists. The representative molecule **31** displaying excellent potency for rCB1 and high selectivity over both hCB2 and hERG showed significant anti-obesity effect in a DIO mice model after chronic treatment for 15 days. This effect of **31** might come from the peripheral mode of action along with some contribution of central effect. Besides obesity, the disclosed CB1 ligands might find their application in pharmacological intervention of other diseases involving CB1 signaling pathways.[37]

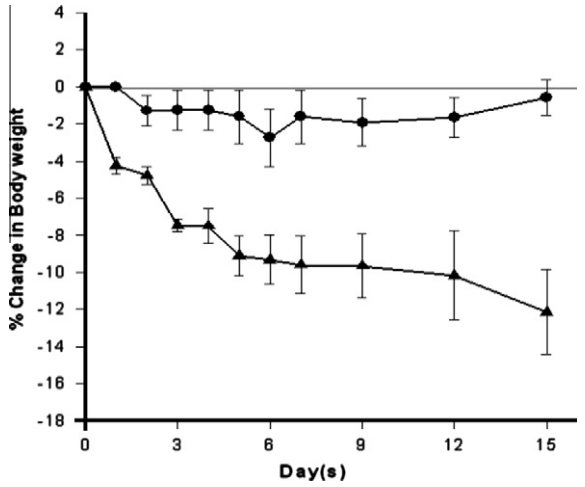


Figure 3. Effect on body weight after subchronic oral administration of **31** (▲ 10 mg/kg, q.d.) to DIO mice versus vehicle control animals (●) ($n = 9$).

Acknowledgments

We thank Professor Javed Iqbal and Dr. Ranjan Chakrabarti for their continuous support and encouragement. The support of the analytical department of Discovery Research is highly appreciated.

Supplementary data

Supplementary data (synthetic procedures and characterization data of all compounds **4–42**) associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2011.06.017.

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32. Assay protocol for hERG: HEK293 cells stably expressing hERG potassium channels were voltage clamped using automated PatchXpress 7000A (molecular devices) electrophysiology system. Whole cell hERG currents were elicited by a standard Voltage pulse protocol and peak hERG tail currents were recorded. Test items were dissolved in DMSO and diluted with HEPES buffered physiological saline (HB-PS). Cells were exposed to test concentration for 5 min at room temperature (22–25 °C). Each cell acted as its own control. E-4031 (0.5 μM) was used as an internal positive control to confirm the sensitivity of the test system to hERG inhibition. The extent of inhibition of channel was expressed as a percentage of the control response (minus the test compound).
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34. Brain to plasma ratio at a dose of 30 mg/kg po in SAM after 1 h for rimonabant and compound **31** is 3.64 and 0.21, respectively.
35. Plasma PK profile of **31** in SAM (30 mg/kg po): $AUC_{(0-24)}$: 4.30 μg h/mL, C_{max}: 0.35 μg/mL, $t_{1/2}$: 4.22 h.
36. q.d. stands for Latin word *quaque die* (every day).
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