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Novel pyrazole-3-carboxamide derivatives as cannabinoid-1 (CB1) antagonists: Journey from non-polar to polar amides ☆

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ABSTRACT

The synthesis and biological evaluation of novel pyrazole-3-carboxamide derivatives as CB1 antagonists are described. As a part of eastern amide SAR, various chemically diverse motifs were introduced. In general, a range of modifications were well tolerated. Several molecules with high polar surface area were also indentified as potent CB1 receptor antagonists. The in vivo proof of principle for weight loss is exemplified with a lead compound from this series.

The prevalence of obesity is rapidly increasing globally. Obesity has reached epidemic proportions in both developed and developing countries. Although obesity is associated with the pathogenesis of major diseases including diabetes or cardiovascular diseases, no satisfactorily safe and effective obesity drugs are available at the moment. Thus, there is a tremendous unmet need to treat obesity and make a significant impact on the lives of the obese.

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.

Unfortunately, due to various psychiatric events in human trials and regulatory hurdles several CB1 receptor inverse agonists/antagonists were recently withdrawn from clinical development including rimonabant (**1**)[20] (Fig. 1), taranabant (**2**),[21] otenabant (**3**),[22] and ibipinabant (**4**).[23] However, despite consecutive failures of leading CB1 receptor antagonists, works continue to identify novel peripherally restricted CB1 antagonists[24] that limit BBB penetration so that they do not induce serious psychiatric disorders. One possibility to achieve this would be by making compounds having considerably higher polar surface area (PSA) and lower lipophilicity. In considering options for designing agents that would potentially have an improved profile relative to **1**, one of the elements we chose to replace was the hydrazide functionality with an amide. Subsequently, polar motifs were introduced to reduce CNS exposure. We described herein our efforts to develop proprietary series with desirable physicochemical properties by focusing SAR of eastern amide zone and subsequent modification in other parts to identify lead compounds.

The target compounds (Tables 1–5) were synthesized as outlined in Schemes 1–8. The synthesis of the core acids **IV** were

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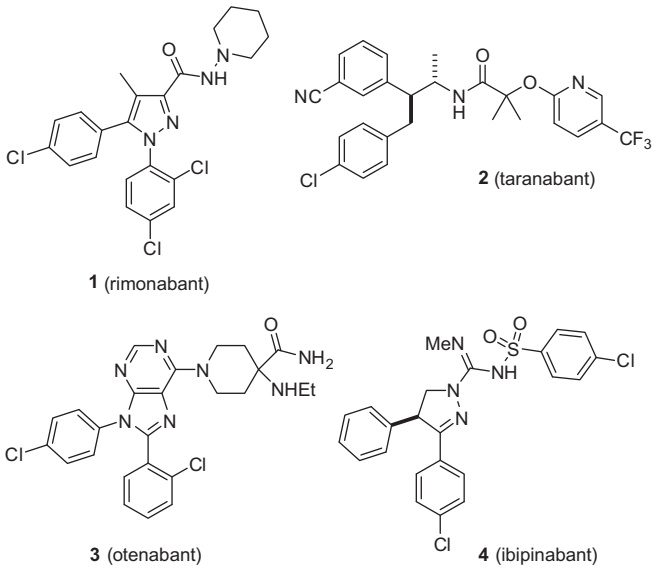
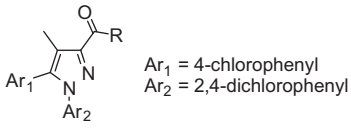
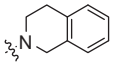
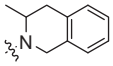
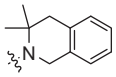
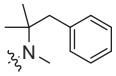
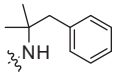
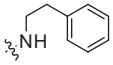
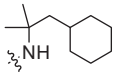
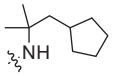


Figure 1. Structures of CB1 antagonists.

Table 1
Rat CB1 binding affinities of compounds **5**–**12**



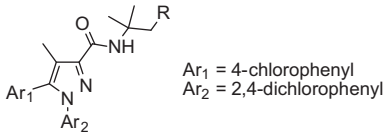
Compd	R	tPSA[a]	rCB1_IC$_{50}$[b] (nM)
5		35.9	18
6		35.9	20
7		35.9	1
8		35.9	96
9		44.7	0.6
10		44.7	10
11		44.7	26
12		44.7	21

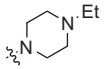
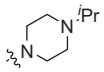
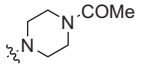
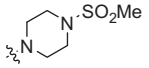
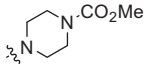
[a] tPSA: topological polar surface area.
[b] values are mean of at least two experiments.

achieved following Scheme 1 from the corresponding propiophenone or 1-phenylbutan-1-one derivatives **I**.

Compounds **5–22** were synthesized by coupling of 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxylic acid (**IVa**) with various primary and secondary amines under EDC/HOBt conditions (Scheme 2). The amide coupling of *tert*-butyl 4-(2-amino-2-methylpropyl)piperazine-1-carboxylate with the same acid produced intermediate **V**. Deprotection of the Boc group within **V** with TFA afforded compound **23** which after various

Table 2
Rat CB1 binding affinities of compounds **13**–**29**



Compd	R	tPSA[a]	rCB1_IC$_{50}$[b] (nM)
13		57.1	2
14		69.4	57
15		56.7	20
16		60.3	71
17		60.3	20
18		72.7	15
19		72.7	16
20		47.9	[c]
21		47.9	455
22		57.2	47
23		60.0	900
24		51.2	310
25		51.2	855
26		51.2	>1000[d]
27		68.3	633
28		68.3	980
29		77.5	29

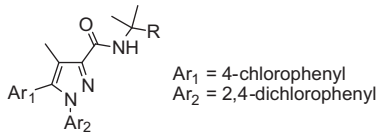
[a] and [b] as in Table 1.
[c] 50% binding at 1 μM.
[d] 34% binding at 1 μM.

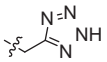
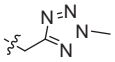
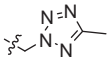
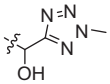
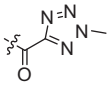
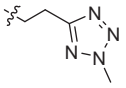
routine transformations furnished compounds **24–29** as outlined in Scheme 2.

The synthesis of compounds **30–36** is outlined in Scheme 3. The coupling of **IVa** with 3-amino-3-methylbutanenitrile produced intermediate amide **VI**. The cyano moiety was converted to various functional groups by standard protocols generating compounds **30**–**32** and the tetrazole **35** which after methylation under MeI/K_2CO_3 conditions in DMF afforded compounds **36** as the major product.[25] On the other hand coupling of **IVa** with 2-amino-2-methylpropan-1-ol and 3-amino-3-methylbutan-1-ol furnished compounds **33** and **34**, respectively.

Compound **37** was synthesized following Scheme 4. Ring opening of the sulfamate derivative **VII**[26] with 5-methyl-2*H*-tetrazole followed by debenzylation gave 2-methyl-1-(5-methyl-2*H*-tetra-

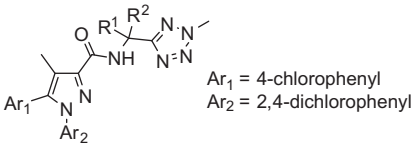
Table 3
Rat CB1 binding affinities of compounds **30–41**

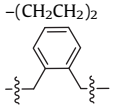


Compd	R	tPSA[a]	rCB1_IC$_{50}$[b] (nM)
30		71.0	17
31		82.0	>1000[c]
32		87.8	25
33		64.9	60
34		64.9	33
35		93.8	>1000[d]
36		85.0	71
37		85.0	18
38		105.3	74
39		102.1	6
40		85.0	11
41		85.0	88

[a] and [b] as in Table 1.
[c] 20% binding at 1 μM.
[d] 18% binding at 1 μM.

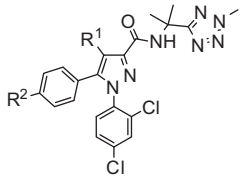
Table 4
Rat CB1 binding affinities of compounds **41–50**



Compd	R^1	R^2	tPSA[a]	rCB1_IC$_{50}$[b] (nM)
41	Me	Me	85.0	88
42	H	H	85.0	100
43	$-CH_2CH_2-$		85.0	61
44	Et	Et	85.0	35
45	$-CH_2CH_2CH_2-$		85.0	10
46	Me	Et	85.0	18
47	Me	$-CH_2OH$	105.3	77
48	$-(CH_2CH_2)_2$		85.0	16
49			85.0	14
50	$-(CH_2CH_2)_2NH$		97.1	[c]

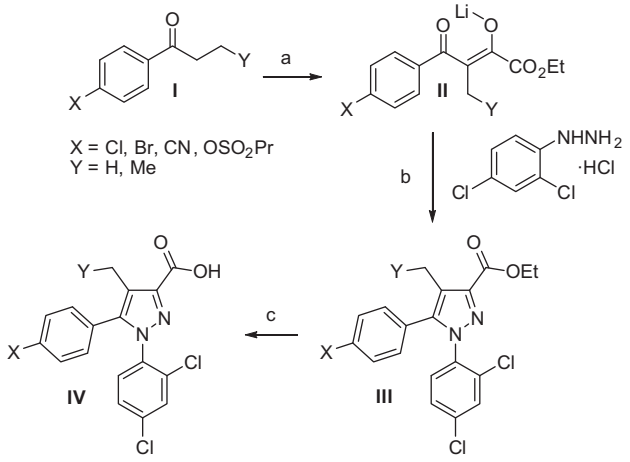
[a] and [b] as in Table 1.
[c] 50% binding at 1 μM.

Table 5
Rat CB1 binding affinities of compounds **51–60**

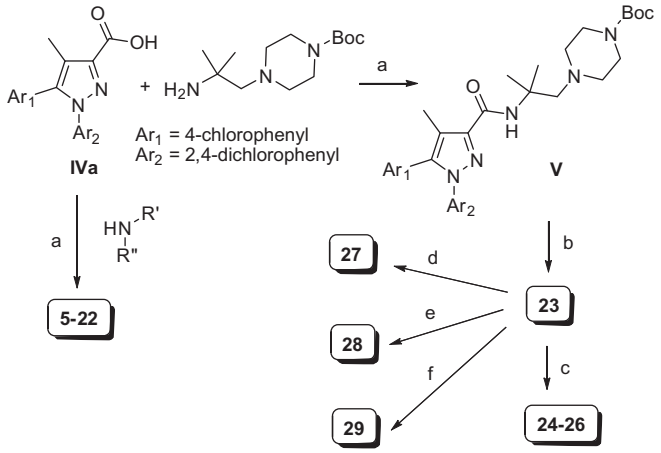


Compd	R	R^2	tPSA[a]	rCB1_IC$_{50}$[b] (nM)
51	Et	Cl	85.0	39
52	Et	Br	85.0	4
53	Me	OSO_2Pr	128.4	7
54	Me	CN	108.8	31
55	Et	CN	108.8	34
56	CH_2OH	Cl	105.3	8
57	CH_2F	Cl	85.0	3
58	CO_2H	Cl	122.3	>1000[c]
59	CO_2Et	Cl	111.3	1
60	CH_2OH	OSO_2Pr	148.6	0.5

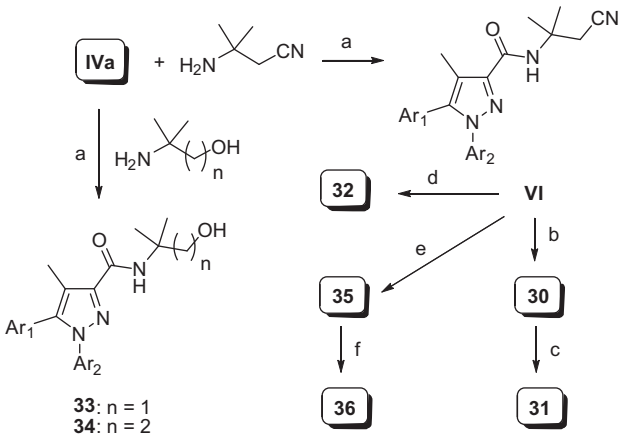
[a] and [b] as in Table 1.
[c] 45% binding at 1 μM.



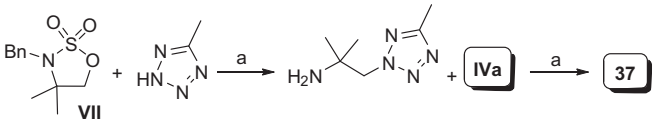
Scheme 1. Reagents and conditions: (a) LiHMDS, ether, −78 °C, $(CO_2Et)_2$, rt, 14 h (for Y = H); LiHMDS, ^{t}BuOMe, −20 °C, $ImCOCO_2Et$, rt, 14 h (for Y = Me); (b) (i) EtOH, reflux, 16 h; (ii) HOAc, reflux, 12 h; (c) LiOH, EtOH–H_2O, 1–6 h.



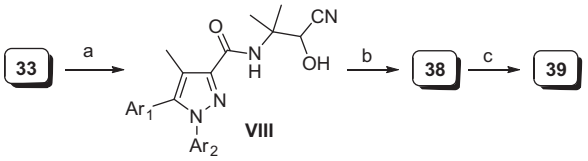
Scheme 2. Reagents and conditions: (a) amines, EDC, HOBt, Et_3N, CH_2Cl_2, rt, 4–10 h; (b) TFA, CH_2Cl_2, rt, 1 h; (c) NaH, DMF, alkyl iodide, 0 °C, 1 h; (d) AcCl, Et_3N, CH_2Cl_2, 0 °C to rt, 1 h; (e) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 30 min; (f) $ClCO_2Me$, Na_2CO_3, THF, rt, 16 h.



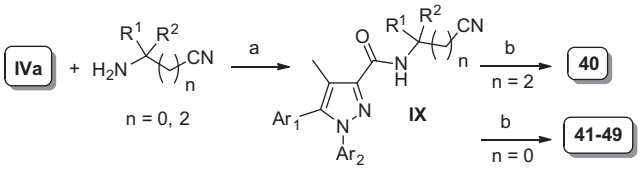
Scheme 3. Reagents and conditions: (a) EDC, HOBt, Et_3N, CH_2Cl_2, rt, 10 h; (b) dry HCl, MeOH, rt, 24 h; (c) LiOH, MeOH/THF/H_2O, rt, 1 h; (d) TFA/H_2SO_4 (4:1), rt, 30 min; (e) NaN_3, DMF, NH_4Cl, 120 °C, 16 h; (f) MeI, K_2CO_3, acetone, rt, 14 h.



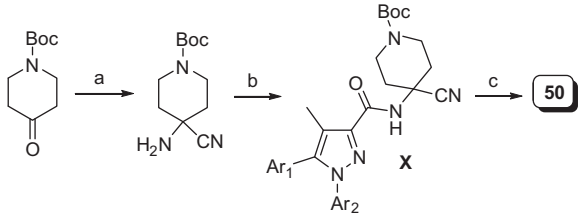
Scheme 4. Reagents and conditions: (a) (i) Cs_2CO_3, DMF, 60 °C, 3 h; (ii) 10% Pd/C, HCO_2NH_4, MeOH, reflux, 14 h; (b) EDC, HOBt, Et_3N, CH_2Cl_2, rt, 10 h.



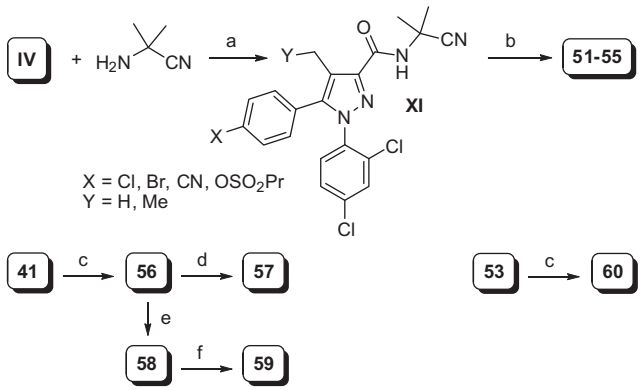
Scheme 5. Reagents and conditions: (a) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to rt, 2 h; (ii) KCN, THF/H_2O, rt, 1 h; (b) (i) Ac_2O, Py, CH_2Cl_2, 0 °C to rt, 16 h; (ii) NaN_3, DMF, NH_4Cl, 120 °C, 16 h; (iii) MeI, K_2CO_3, acetone, rt, 4 h; (iv) 1 M aqueous K_2CO_3, MeOH, rt, 16 h; (c) PCC, CH_2Cl_2, rt, 24 h.



Scheme 6. Reagents and conditions: (a) EDC, HOBt, Et_3N, CH_2Cl_2, rt, 12 h; (b) (i) NaN_3, DMF, NH_4Cl, 120 °C, 16 h; (ii) MeI, K_2CO_3, acetone, rt, 4 h.



Scheme 7. Reagents and conditions: (a) NaCN, NH_4Cl, NH_4OH, rt, 24 h; (b) **IVa**, EDC, HOBt, Et_3N, CH_2Cl_2, rt, 14 h; (c) (i) NaN_3, DMF, NH_4Cl, 120 °C, 16 h; (ii) MeI, K_2CO_3, acetone, rt, 4 h; (iii) TFA, CH_2Cl_2, rt, 2 h.



Scheme 8. Reagents and conditions: (a) EDC, HOBt, Et_3N, CH_2Cl_2, rt, 4–10 h; (b) (i) NaN_3, DMF, NH_4Cl, 120 °C, 16 h; (ii) MeI, K_2CO_3, acetone, rt, 14 h; (c) (i) NBS, CCl_4, $(PhCO)_2O_2$, reflux, 16 h; (ii) $AgNO_3$, 70% aqueous acetone, reflux, 14 h; (d) DAST, CH_2Cl_2, rt, 16 h; (e) (i) PCC, CH_2Cl_2, rt, 14 h; (ii) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, ^tBuOH/THF/H_2O (4:2:1), rt, 1 h; (f) $SOCl_2$, $CHCl_3$, reflux, 1 h; (ii) EtOH, rt, 16 h.

zol-2-yl)propan-2-amine which after coupling with **IVa** afforded the desired compound.

Compounds **38** and **39** were synthesized following protocols as outlined in Scheme 5. The Swern oxidation of **33** followed by treatment of the resulting aldehyde with KCN furnished the cyanohydrin intermediate **VIII**. Further manipulation viz., (i) protection of the hydroxyl group as its acetate, (ii) tetrazole formation, (iii) N-methylation, and (iv) deacetylation furnished the desired compound **38**. PCC mediated oxidation of **38** afforded keto tetrazole derivative **39**.

The synthesis of compounds **40–49** were accomplished from **IVa** and various cyano amines by standard protocols as illustrated in Scheme 6. The synthesis of compound **50** is outlined in Scheme 7. The aminocyanation reaction on *tert*-butyl 4-oxopiperidine-1-carboxylate produced *tert*-butyl 4-amino-4-cyanopiperidine-1-carboxylate which was coupled with **IVa** to afford intermediate **X**. The cyano group was converted to the corresponding tetrazole which after N-methylation and deprotection of *N*-Boc furnished the piperidine appended tetrazole derivative **50**.

The coupling of 2-amino-2-methylpropanenitrile with various substituted core acids **IV** and subsequent manipulation produced compounds **51–55** as described in Scheme 8. Compounds **56** and **60** were synthesized from **41** and **53** respectively by photochemical bromination followed by $AgNO_3$ mediated hydrolysis. Reaction of DAST with **56** furnished the corresponding fluoromethyl analog **57**. The hydroxymethyl group within **56** was converted to the carboxylic acid functionality (**58**) by a two-step oxidation protocol (PCC and $NaClO_2$). A simple esterification led to the formation of compound **59**.

The target compounds were evaluated in vitro in a rat CB1 binding assay[27] and results are shown in Tables 1–5. Select compounds were then tested for hCB2 receptor affinity studies (Table 6).[27] Initially the hydrazide moiety of **1** was replaced with an amide of tetrahydroisoquinoline (compound **5** in Table 1) which showed good rCB1 binding affinity with IC_{50} 18 nM. To introduce novelty into this template mono and gem-dimethyl groups were introduced. As mentioned in Table 1, compound **7** with a gem-dimethyl group showed superior potency over **5** and **6**. Cleaving the tetrahydroisoquinoline ring system to compound **8** showed 96-fold loss in potency. The phentermine amide **9** showed gratifyingly very high potency of IC_{50} 0.6 nM. Both **7** and **9** showed good selectivity profile against hCB2 as well (Table 6). Pulling out gem-dimethyl group from **9** ended up with 16-fold loss in potency as mentioned for compound **10**. Replacing phenyl group (compound **11**) with a

Table 6
Selectivity profile of CB1 ligands against hCB2

Compd	rCB1_IC_{50} (nM)	hCB2 affinity IC_{50} (nM) or% binding @1 μM	IC_{50}'s ratio hCB2/rCB1
7	1	800	800
9	0.6	149	248
13	2	71%	–
17	20	5200	260
29	29	70%	–
31	25	790	32
36	71	2350	33
37	18	2500	139
38	74	2900	78
39	6	248	41
40	11	35%	–
41	88	338	3.8
45	10	55%	–
46	18	100	–
48	16	75%	–
49	14	67%	–
51	39	77%	–
52	4	165	41
53	7	1040	149
54	31	1020	33
56	8	5000	625
57	3	1010	337
59	1	30%	–
60	0.5	46%	–

cyclohexyl group showed loss in potency. The cyclopentyl counterpart displayed a similar result. But all of these compounds are sufficiently non-polar with lower PSA.[28]

After establishing good CB1 potency with proprietary amide motif within rimonabant template, attention was shifted to replace lipophilic eastern part with various heterocyclic groups and the results are summarized in Table 2. The 2-pyridyl analog (**13**) showed 2 nM potency whereas 2-pyrazinyl and 3-indolyl moieties (**14** and **15**) showed loss in potency. The compound with 1-imidazolyl moiety displayed significant loss in potency whereas the corresponding 4-methyl analog showed improvement in rCB1 potency (**16** vs **17**) as well as selectivity of 260-fold against hCB2. Both the isomeric triazoles **18** and **19** were tolerated displaying similar potencies. Replacement of five-membered hetero-aryls with pyrrolidine (**20**) was detrimental to CB1 potency whereas little improvement in potency was observed with piperidine moiety (**21**) though the corresponding morpholine analog (**22**) was well tolerated showing rCB1 binding affinity of 47 nM. The piperazine moiety was not tolerated whereas CB1 potency was improved with the corresponding *N*-methyl piperazine analog (**24**). These observations showed less tolerance for HBD in this region. Replacement of *N*-methyl with bulkier ethyl and iso-propyl groups (**24** vs **25** and **26**) were detrimental to CB1 potency.

Though the acetyl and mesylate analogs were not tolerated the corresponding carbamate (**29**) displayed good potency (IC_{50} 29 nM) in rCB1 binding assay. This observation encouraged us to explore the tolerance of carboxylate functionality in this region. When the methyl piperazine-1-carboxylate was replaced with a much shorter group, methyl carboxylate, compound **30** showed good potency of 17 nM in rCB1 binding assay though the carboxylic acid **32** was completely detrimental. More polar carboxamide derivative **31** was also equipotent to ester displaying IC_{50} of 25 nM. The hydroxyl functionality with one and two methylene units as in **33** and **34** also retained their potencies. The in vitro potency of **30** encouraged us to explore the bioisosteric and more polar tetrazole motif. The *N*-methyl tetrazole **36** having PSA of 85.0 showed acceptable potency whereas the N-unsubstituted tetrazole (**35**), like its carboxylic acid counterpart lost all its potency. The isomeric tetrazole **37** displayed fourfold increase in rCB1 potency.

At this juncture we observed that most of the potent compounds showed poor metabolic stability.[29] Metabolite identification work indicated that methylene group flanked between gem-dimethyl center and heterocycles is the hot spot. We adopted three strategies viz., (i) introduction of additional methylene unit, (ii) oxidation of the methylene center, and (iii) removal of the hot spot. The insertion of additional methylene as in compound **40** gave 11 nM binding potency against rCB1. The oxidation of methylene to its hydroxyl analog as in **38** showed equipotency to **36** whereas the corresponding carbonyl analog **39** with PSA of 102.1 displayed very good rCB1 potency of 6 nM. Removing the methylene unit as in **41** showed moderate potency.

Both **39** and **41** showed very good metabolic stability[30] but the selectivity against hCB2 was not high enough for these molecules. We next investigated the impact of replacing gem-dimethyl group with other moieties in CB1 potency and selectivity and the results are summarized in Table 4. In few occasion, potency was retained and moderate as in case of **41** whereas molecules like **45**, **46**, **48**, and **49** showed 5–8-fold improvement in CB1 potency but didn't impact much in terms of selectivity. The piperidine analog **50** completely lost its potency.

To introduce additional polarity into the template of **41**, further modification was done in the 4-methyl position of pyrazole as well in the chlorophenyl region and the results are summarized in Table 5. Most of these modifications were well tolerated with improved selectivity profile. Compound **53** having propane sulfonate functionality with PSA of 128.4 displayed potency of 7 nM for CB1 and 149-fold selectivity against CB2 whereas the corresponding cyano analog **54** showed CB1 potency of 31 nM with moderate selectivity. Replacement of the methyl group with more polar hydroxymethyl functionality as in compound **56** with PSA of 105.3 displayed good rCB1 binding affinity (IC_{50} 8 nM) with 625-fold selectivity against hCB2. The corresponding fluoro analog **57** was also potent displaying 3 nM potency. Replacement of the methyl group with carbethoxy group as in **59** displayed 1 nM potency whereas the corresponding carboxylic acid **58** was completely detrimental to CB1. Combining the features of **53** and **56** led to the identification of very polar compound **60** (PSA 148.6) which displayed very high CB1 potency (IC_{50} 0.5 nM) with very high selectivity of >1000-fold. All these potent and selective CB1 ligands also showed good metabolic stabilities.[30]

As discussed above a number of compounds with low nanomolar binding affinity for CB1 with good selectivity profile against CB2 have been identified. Select compounds were initially assessed for its central pharmacodynamic effect in the hypothermia model[31,32] and the results are summarized in Table 7. All of these compounds have shown moderate to good inhibition of CB1 agonist (WIN-55212) induced hypothermia in SAM model. One of the lead compounds **56** has shown dose dependant reduction in acute food intake (Fig. 2)[33] when tested at 3, 10, and 30 mg/kg po in SAM model. The effect of rimonabant at 10 mg/kg po was comparable to the highest dose of 30 mg/kg po of compound **56** suggesting that rimonabant might be having more pronounced central effect

Table 7
Inhibition of CB1 agonist (WIN-55212) induced hypothermia in Swiss Albino Mice (SAM)

Compd	% Inhibition of WIN-55212 induced hypothermia at 30 min in SAM	
	3 mpk po	10 mpk po
31	–	84
39	94	–
41	–	70
52	54	–
53	89	–
56	–	95
60	–	48

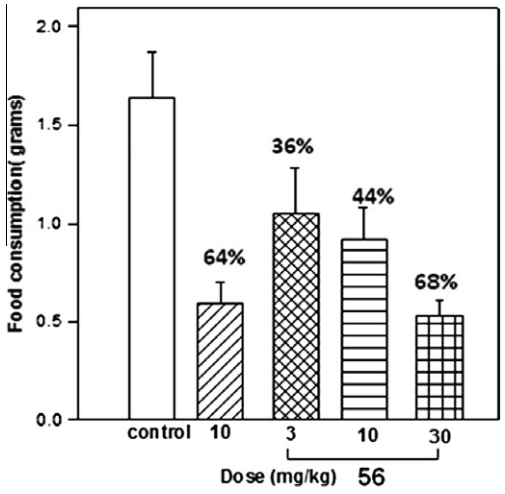


Figure 2. Effect on acute food intake after single dose oral administration of rimonabant (10 mg/kg dose) and **56** (3, 10 and 30 mg/kg dose) to SAM versus vehicle control animals.

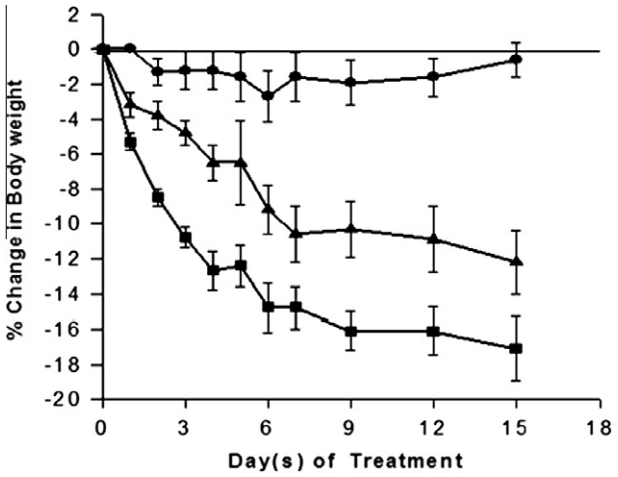


Figure 3. Effect on body weight after subchronic oral administration of **56** (▲ 10 mg/kg, q.d.) and rimonabant (■ 10 mg/kg, q.d.) to DIO mice versus vehicle control animals (●) ($n = 9$).

compared to more polar compound **56**. Compound **56** was evaluated further in a diet-induced obesity (DIO) mouse model using C57BL/6 J mice. On oral administration **56** (10 mg/kg, q.d.), showed steady loss of body weight culminating in a statistically significant weight loss of 12% on day 15 as shown in Figure 3.[34]

In summary, we have explored various chemically diverse motifs as a part of eastern amide SAR on rimonabant template. In general, a range of modifications were well tolerated. Several molecules with high polar surface area were also indentified as potent CB1 antagonists. The representative molecule **56** showed significant anti-obesity effect in a DIO mice model after chronic treatment for 15 days. The most polar compound **60** displaying sub-nanomolar potency for CB1 requires additional experimentation to demonstrate its peripheral mode of action. Besides obesity, the disclosed CB1 ligands might find their application in pharmacological intervention of other diseases involving CB1 signaling pathways.[35]

Acknowledgments

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Supplementary data

Supplementary data (synthetic procedures and characterization data of all 56 compounds **5**–**60**) associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.10.055.

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25. A 2:1 mixture of N2- and N1-methylated products were formed which were easily separable by flash chromatography. In proton NMR, the CH_3 signal of N2-methylated product always appears in downfield compared to the CH_3 signal of N1-methylated product. The structure of **36** was also confirmed by NOE experiments.
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27. *Assay protocols for in vitro binding affinities against rCB1 and hCB2*: The molecules were tested for potential binding to CB1 receptor using rat brain extract and [^{3}H]-SR141716A. Briefly, membranes (~5 μg) were incubated at 30 °C with [^{3}H]-SR141716A (2 nM) in 0.25 ml of Tris based buffer, pH 7.4 for 1 h. A rapid filtration technique using Whatman GF/C filters [pretreated with

0.5% (v/v) Brij-35], and a 96-well filtration apparatus was used to harvest and rinse labeled membranes (six times with 0.5 ml of cold buffer containing 0.25% bovine serum albumin). The radioactivity bound to the filters was counted with biofluor liquid scintillant. Non specific binding was determined in presence of 10 μM of unlabeled ligand. A similar assay was conducted with membrane preparations derived from hCB2-CHO cells for analyzing binding to CB2 receptors using [^{3}H]-CP 55,940 as the input ligand.
28. tPSA was calculated using ChemBioDraw Ultra 11.0 software.
29. Metabolic stability <20% after 30 min when test compounds incubated in mice and rat liver microsomes.
30. Metabolic stability >60% after 30 min.
31. CB1 agonists induce a reduction in body temperature by acting on CB1 receptors in the hypothalamus, an effect that can be reversed by an antagonist
32. *Protocol for hypothermia studies*: animals were grouped based on body weight and basal rectal temperatures were measured. They were then dosed orally with either test compounds or vehicle and 1 h later the rectal temperatures were recorded again. 2 mg/kg of Win 55212-2 was then injected through the tail vein and the rectal temperatures were measured 0.5 h post injection.
33. *Protocol for acute food intake studies*: The acute effects of the drug on food consumption were analyzed in animals deprived of food for 24 h and habituated to handling. Prior to the start of the experiment, animals were subjected to two vehicle tests and grouped based on their food consumption in the second test. The vehicle tests were done to acclimatize the animals to experimental conditions. Twenty four hours after the second vehicle test, animals were kept for fasting for 24 h. On the day of the experiment, the animals were housed in individual cages and dosed with test compounds/vehicle. After the first hour, a measured amount of food was made available and the amount of food consumed within the first hour was recorded.
34. All animals (c57B/L6 mice) were maintained on 12 h light–dark cycle at 25 °C. They were given high fat diet (Research Diets, D12492, 60% kcal fat) for 3 months to develop obesity and randomized to control and treatment groups based on their body weight. Test compound(s) were administered through oral gavage to the animals, once daily. Control animals received vehicle (0.25% CMC) only. The animals were maintained on same high fat diet throughout the study. Body weight and food consumption were monitored daily for the first 7 days and subsequently every 3 days.
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