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Discovery of novel, orally available benzimidazoles as melanin concentrating hormone receptor 1 (MCHR1) antagonists ☆

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ABSTRACT

Melanin concentrating hormone (MCH) is an important mediator of energy homeostasis and plays role in several disorders such as obesity, stress, depression and anxiety. The synthesis and biological evaluation of novel benzimidazole derivatives as MCHR1 antagonists are described. The in vivo proof of principle for weight loss with a lead compound from this series is exemplified.

Obesity, a chronic disorder associated with an imbalance between energy intake and expenditure,[1] is progressively developing into a global pandemic affecting the lives of more than a billion people worldwide.[2] It is emerging as a lead cause of morbidity and associated risk factors such as dyslipidemia, type 2 diabetes, stroke, cardiovascular disease, certain forms of cancer, osteoarthritis, and sleep apnea.[3]

Many biological targets for treating obesity, including centrally modulated satiety and hunger regulating systems, have been evaluated in the literature.[4] Among centrally acting targets, melanin concentrating hormone (MCH) and its receptor have been studied extensively. The hormone MCH is a 19-amino acid cyclic neuropeptide expressed predominantly in the lateral hypothalamus and zona incerta,[5] though some levels are also found throughout the central nervous system (CNS). Accumulated evidence has demonstrated that MCH is an important mediator of energy homeostasis.[6] The antagonists of MCH receptor (MCHR-1) have also demonstrated efficacy in rat models of urinary incontinence.[7] It is reported that a single injection of MCH into the CNS stimulates food intake in rats[8] and the chronic administration leads to increased body weight.[9] Transgenic mice over expressing MCH gene are susceptible to insulin resistance and obesity.[10] The obese rodents, such as *ob/ob*, *db/db*, and Ay/a mice show over expression of MCH mRNA,[11] whereas mice lacking the gene encoding MCH are hypophagic, lean, and tend to maintain elevated metabolic rates.[12] Consistent with this phenotype, genetically altered mice that lack the gene encoding MCH receptor maintain elevated metabolic rates and remain lean despite hyperphagia on a normal diet.[13] The accumulated data supports the therapeutic utility of MCHR1 antagonists in treatment of obesity. MCH also plays important role in other CNS disorders and MCHR1 antagonists may be useful in treatment of diseases such as depression and anxiety.[6]

Since the pioneering discovery of non-peptide MCHR1 antagonists SNAP-7941 (**1**, Fig. 1)[14] and T-226296 (**2**)[15] there have been significant efforts to develop MCHR1 antagonists[16] as anti-obesity agents. More recently, GW856464[17] (**3**), AMG-076[18] (**4**), and NGD-4715 (structure undisclosed)[19] have been reported to enter phase I clinical trials. One of our laboratories has previously reported selective and potent MCHR1 antagonists derived from chemogenomics approaches.[20] In our efforts to seek novel MCHR1 antagonists with optimal in vitro and in vivo profile, we have identified and developed benzimidazole derived series of compounds. Using

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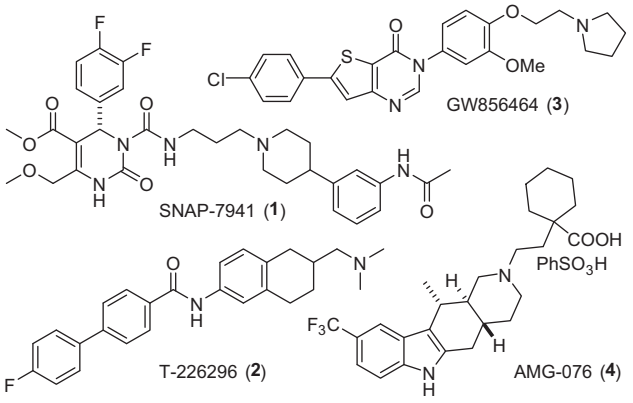


Figure 1. Potent MCHR1 antagonists.

SNAP-7941 as initial lead, systematic medicinal chemistry and computational approaches were used to develop proprietary series with desirable physicochemical properties. This Letter describes the synthesis and structure–activity studies in generation of lead molecule with good efficacy in obesity model.

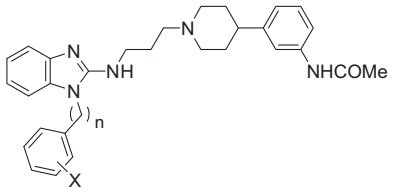
The target compounds (Tables 1–4) were synthesized as outlined in Schemes 1–10. For the synthesis of compounds **22a–g**, **23a–g** and **24a–b**, the benzimidazole part was made following Scheme 1. The S_N2Ar substitution on 2-fluoronitrobenzene with various amines followed by reduction yielded diamines **5a–r**. Heating with urea led to formation of cyclic compounds **6a–r** which were subsequently converted to 2-chlorobenzimidazoles **7a–r** by treatment with $POCl_3$.[21] Compound **8** was prepared by oxidation of **7h** with oxone.

Synthesis of the coupling partners **12a–d** and **13a–c** was accomplished as outlined in Scheme 2. Compound **9** (prepared by the N-alkylation of 4-piperidinone with 2-(3-bromopropyl)isoindoline-1,3-dione) was converted to enol triflate **10** and coupled with various boronic acids to yield **11**. Selective manipulation and removal of the phthalimide moiety[22] with hydrazine furnished the corresponding amines **12** and **13**.

The *N*-methylacetamide **16** was prepared from **14**[23] as illustrated in Scheme 3. Similarly synthesis of corresponding piperazine derivative **21** was achieved from *N*-aryl piperazine **18**[24] by alkylation with **19** followed by the typical transformations protocol as summarized in Scheme 4.

The coupling of the 2-chlorobenzimidazoles with various amines was accomplished in base mediated heating to the desired compounds (**22–24**) as outlined in Scheme 5.

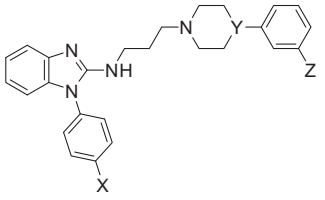
Table 1
Human MCHR1 binding and functional activity of compounds **22a–r**



Compd	*n*	X	hMCHRI[a] (IC_{50})	
			SPA[b] (nM)	IP3[b] (nM)
22a	0	*p*-Cl	11	49
22b	0	*m*-Cl	45	110
22c	0	H	21	153
22d	0	*p*-OMe	68	110
22e	0	*p*-CN	24	71
22f	0	*p*-Me	35	85
22g	0	*p*-F	2	18
22h	0	*p*-SO_2Me	269	798
22i	1	*p*-Cl	8	65
22j	1	*p*-F	22	45
22k	1	*p*-^{t}Bu	320	600
221	1	*p*-OCF_3	35	85
22m	1	*m*-OMe	180	54
22n	1	*m*-OCF_3	110	88
22o	1	*m*-CF_3	150	93
22p	1	*p*-CN	38	nd
22q	1	*m*-CN	140	nd
22r	1	*m*-Cl	29	nd

nd—not determined.
[a] Values are mean of at least two experiments.
[b] See Refs. 33 and 34 for the protocol.

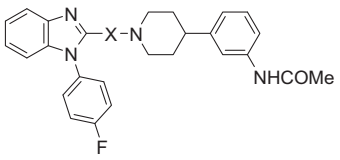
Table 2
Human MCHR1 binding and functional activity of compounds **23a–g** and **24a–b**

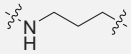
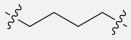
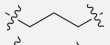
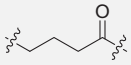
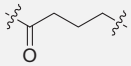
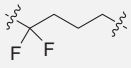
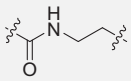


Compd	X	Y	Z	hMCHRI[a] (IC_{50})	
				SPA (nM)	IP3 (nM)
22a	Cl	CH	NHCOMe	11	49
22g	F	CH	NHCOMe	2	18
23a	Cl	CH	F	261	6320
23b	Cl	CH	OH	110	1435
23c	Cl	CH	OCF_3	528	7579
23d	Cl	CH	N(Me)COMe	1620	>10,000
23e	F	CH	NHEt	87	970
23f	F	CH	NHCO^{c}Pr	10	96
23g	F	CH	NHCO^{i}Pr	15	183
24a	Cl	N	NHCOMe	112	648
24b	F	N	NHCOMe	646	3002

[a] Footnotes as in Table 1.

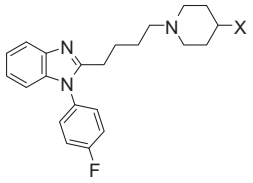
Table 3
Human MCHR1 binding and functional activity of compounds generated by linker modification

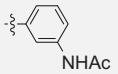
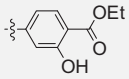
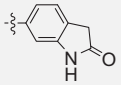
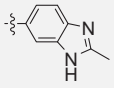


Compd	X	hMCHRI[a] (IC_{50})	
		SPA (nM)	IP3 (nM)
22g		2	18
27a		0.6	3
27b		88	280
27c		336	1467
29		1450	>10,000
33		13	112
34		4	37
37		678	973

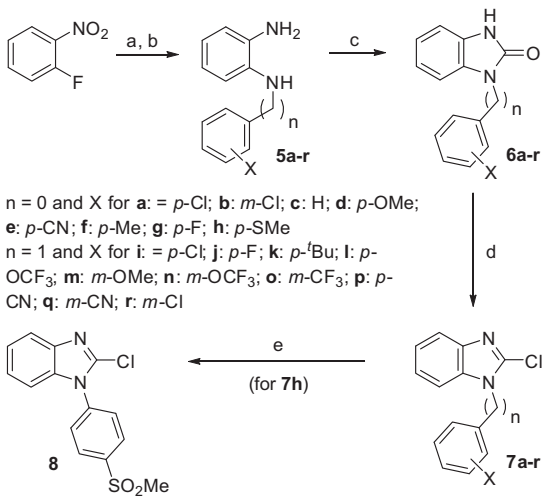
[a] Footnotes as in Table 1.

Table 4
Human MCHR1 binding and functional activity of compounds **44a–c**



Compd	X	hMCHRI[a] (IC_{50})	
		SPA (nM)	IP3 (nM)
27a		0.6	3
44a		456	566
44b		1	9
44c		23	106

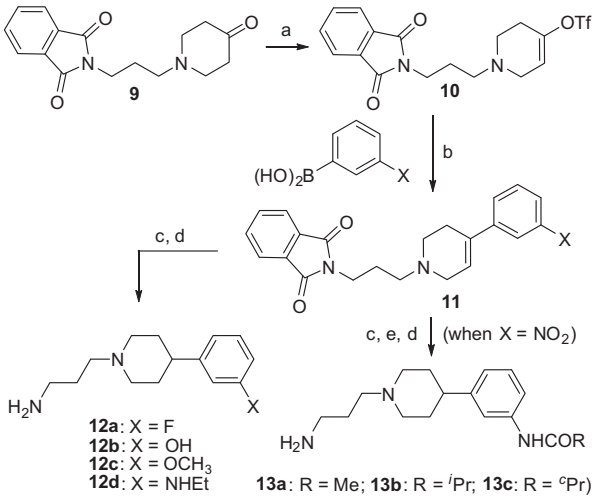
[a] Footnotes as in Table 1.



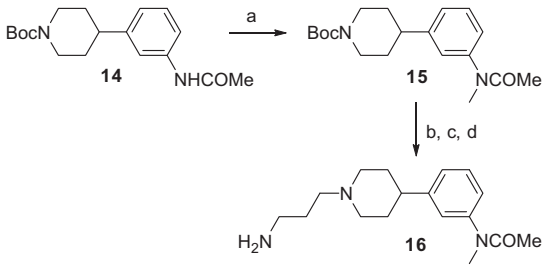
Scheme 1. Reagents and conditions: (a) K_2CO_3, neat, 160 °C, 14 h; (b) $NiCl_2{\cdot}6H_2O$, $NaBH_4$, MeOH, 0 °C to rt, 30 min or $SnCl_2{\cdot}2H_2O$, EtOH, reflux, 4 h (for R = *p*-$SMeC_6H_4$); (c) urea, DMF, 160 °C, 5 h; (d) $POCl_3$, 110 °C, 3–5 h; (e) oxone, acetone/H_2O, rt, 2 h.

Compounds **27a–c** were prepared following Scheme 6. Coupling of diamine (**5g**) with ω-chloro acid chloride afforded the corresponding 2-(ω-chloroalkyl)benzimidazoles **25** which after N-alkylation with piperidinylphenyl acetamide **26**[23] (generated from **14**) furnished the targeted molecules **27a–c**.[25] In a similar fashion, diamine **5g** after treatment with methyl 5-chloro-5-oxopentanoate followed by hydrolysis and coupling with **26** afforded the corresponding amide **29** as illustrated in Scheme 7.

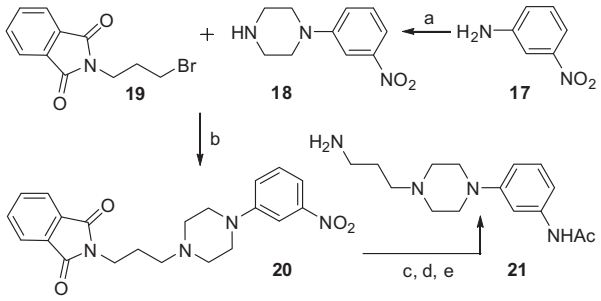
Synthesis of keto analog **33** (Scheme 8) commenced with compound **30** which was prepared by copper-catalyzed N-arylation of benzimidazole following Buchwald's protocol.[26] The treatment of **30** with LDA followed by acylation with Weinreb amide (4-chloro-*N*-methoxy-*N*-methylbutanamide) afforded intermediate **31** which upon coupling with **26** produced **33**. Compound **31** was treated with DAST to give **32** which was then converted to the corresponding difluoro analog **34**.



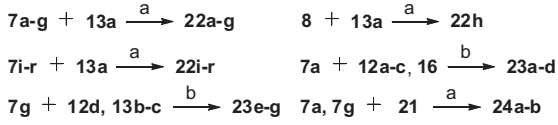
Scheme 2. Reagents and conditions: (a) $PhNTf_2$, NaHMDS, THF, −78 °C to rt, 4 h; (b) $ArB(OH)_2$, $(PPh_3)_2PdCl_2$, 2 M Na_2CO_3, THF, 400 °C, 30 min; (c) 10% Pd/C, H_2, MeOH, 4–10 h; (d) hydrazine hydrate, MeOH, reflux, 1 h; (e) RCOCl, Et_3N, CH_2Cl_2, 0 °C to rt, 30 min.



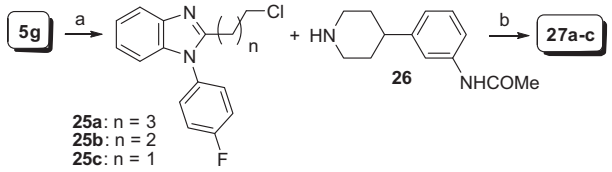
Scheme 3. Reagents and conditions: (a) NaH, THF, MeI, rt, 6 h; (b) TFA, CH_2Cl_2, rt, 1 h; (c) acrylonitrile, $NaHCO_3$, MeOH, rt, 2 h; (d) RaNi, MeOH saturated with NH_3 (gas), rt, 24 h.



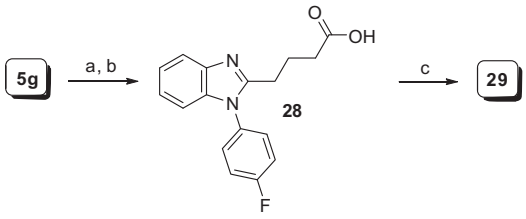
Scheme 4. Reagents and conditions: (a) bis(2-chloroethyl)amine hydrochloride, diethylene glycol monomethyl ether, 150 °C, 12 h; (b) K_2CO_3, MeCN, reflux, 3 h; (c) 10% Pd/C, H_2, MeOH, 5 h; (d) Ac_2O, CH_2Cl_2, rt, 16 h; (e) hydrazine hydrate, MeOH, reflux, 3 h.



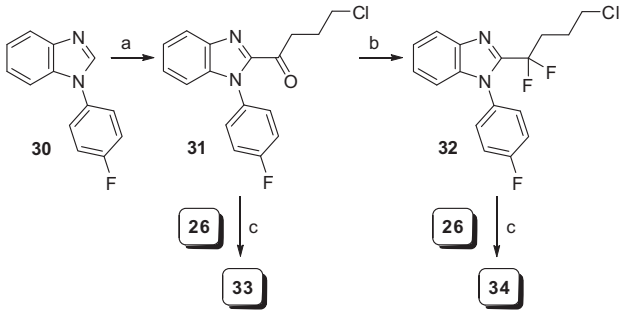
Scheme 5. Reagents and conditions: (a) DBU, 150 °C, 1–4 h; (b) ^{n}BuOH/pyridine (1:1), 120 °C, 1–4 h.



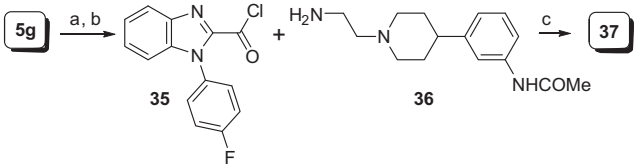
Scheme 6. Reagents and conditions: (a) (i) ω-chloro acid chloride, Et_3N, CH_2Cl_2, rt, 1 h; (ii) AcOH, 65 °C, 16 h; (b) DMF, 60 °C, 2–6 h.



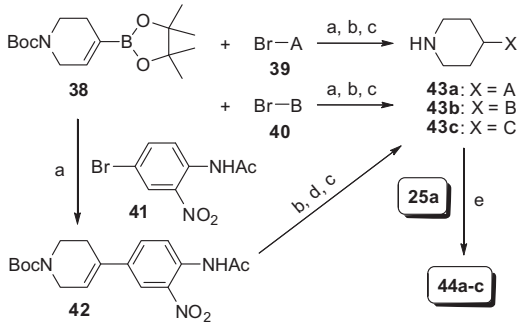
Scheme 7. Reagents and conditions: (a) (i) methyl 5-chloro-5-oxopentanoate, Et_3N, CH_2Cl_2, rt, 2 h; (ii) AcOH, 65 °C, 16 h; (b) LiOH, THF/H_2O (4:1), rt, 4 h; (c) **26**, EDC·HCl, HOBt, DMF, rt, 6 h.



Scheme 8. Reagents and conditions: (a) LDA, 4-chloro-*N*-methoxy-*N*-methylbutanamide, THF, −78 °C to rt, 2 h; (b) DAST, CH_2Cl_2, rt, 16 h; (c) DMF, 60 °C, 4–6 h.



Scheme 9. Reagents and conditions: (a) ethyl 2,2,2-triethoxyacetate, neat, 100 °C, 18 h; (b) $SOCl_2$, DMF, $CHCl_3$, 40 °C, 16 h; (c) Et_3N, CH_2Cl_2, rt, 16 h.



Scheme 10. Reagents and conditions: (a) $PdCl_2$(dppf), K_2CO_3, DMF, 80 °C, 4 h; (b) 10% Pd/C, H_2, MeOH, rt, 16 h; (c) (i) dioxane saturated with HCl (gas), CH_2Cl_2, rt, 16 h; (ii) CH_2Cl_2, NH_3 (gas); (d) HOAc, 80 °C, 16 h; (e) DMF, 70 °C, 4 h.

The synthesis of amide **37** is outlined in Scheme 9. The diamine (**5g**) was treated with ethyl 2,2,2-triethoxyacetate[27] to afford benzimidazole-2-carboxylic acid which was converted to the corresponding acid chloride **35** and subsequently treated with amine **36**[28] to furnish **37**.

The compounds **44a–c**, carrying acetanilide mimetics (viz., A, B and C, Fig. 2), were synthesized following Scheme 10. The dioxaborolane derivative **38**[29] was subjected to Suzuki coupling of with coupling partners **39**,[30] **40**[31] and **41**[32] in the presence of $PdCl_2$(dppf). The synthetic manipulations discussed earlier furnished the crucial arylpiperidine derivatives **43a–c**, which were N-alkylated with **25a** to afford **44**.

The target compounds were tested in a SPA based [^{125}I]MCH binding assay[33] using Chinese hamster ovary (CHO-K1) cell membranes expressing human recombinant MCH1R receptors for their MCHR1 potency. The functional antagonism was measured in an IP3 SPA-YSI assay.[34]

Table 1 shows a summary of results obtained by varying *N*-aryl and *N*-benzyl substituents in benzimidazole. In general, *para*-substituents showed somewhat better potency over *meta*-substituents. The compounds with small substituents (F, Cl) at *para*-position seem to furnish better potency. Adding larger functionality such as (SO_2Me, OMe) show dramatic loss in activity. Adding methylene spacer in **22a** and **22g** as in **22i** and **22j**, respectively, gave potent compounds although bulkier substituents at *para*- or *meta*-position continued to show drop in potency. The *para*-fluorophenyl derivative **22g** displayed the best potency in binding (IC_{50} 2 nM) and efficacy in the functional assay (IC_{50} 18 nM).

To understand the importance of acetamide group, compounds **23a–e** containing the preferred *para*-fluoro- or *para*-chlorophenyl moieties were tested (Table 2). The reduced potency of compounds **23d** and **23e** versus **22a** and **22g** supports the need for both hydrogen bond donor and acceptor interactions in this region. The branched *c*-propyl and *i*-propyl amides **23f** and **23g**, respectively, showed good binding affinity although reduced functional activity compared to **22g**.

When the piperidine system was replaced with piperazine as in **24a** and **24b**, dramatic loss in potency was observed (vs **22a** and **22g**; Table 2) This is also likely related to the reduced basicity of piperidine nitrogen that seems to be involved in important interaction with receptor.

Having explored western end, we turned attention to optimize linker chain (Table 3). The replacement of NH moiety in **22g** with a methylene unit gave **27a** with improved potency in both binding (IC_{50} 0.6 nM) and functional (IC_{50} 3 nM) assays. The length of the linker between eastern and western pharmacophoric motifs seems critical as molecules with reduced chain **27b** and **27c** showed >50-fold loss in potency. The N-acylated analog **29** showed >1000-fold drop in potency (binding or functional assay) versus *N*-alkyl analog **27a** (Table 3) further supporting importance of basic piperidine nitrogen as discussed above.

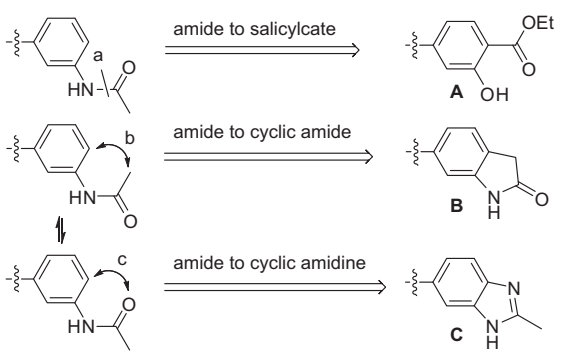


Figure 2. Bioisosteres of acetanilide.

Variation of connector chain (viz., **33**, **34** and **37**; Table 3) in close proximity to the benzimidazole was also investigated. The introduction of carbonyl functionality as in **33** gave good binding affinity although drop in potency in functional assay. Converting the carbonyl group to the corresponding CF_2 analog (**34**) improved both binding and functional potencies. On the other hand, carboxamide variation (**37** vs **33**) was detrimental to potency, possibly related to its conformational influence.

Additional, functional mimetics of acetamide were investigated (Table 4) with one of the most potent leads **27a**. Compound **27a** was docked into the main ligand binding pocket of the hMCHR1 receptor using a multi-conformational docking setup (described in Supplementary data). The top scoring docking poses of **27a** nicely fitted into a complementary binding pocket of the hMCHR1 receptor in a low energy conformation which qualitatively is in good agreement with the overall SAR. In this docking pose, the coplanar acetamide moiety makes hydrogen bond interactions with a polar subpocket containing three glutamine residues in III:12, V:08 and VI:20 shown in Figure 3.[35] In addition the positively charged piperidine nitrogen is forming an ionic interaction with aspartic acid III:08 and the 3-benzimidazole nitrogen forms a hydrogen bond with asparagines VII:02. The remaining scaffold makes good aromatic (edge to face and stacking) as well as hydrophobic interactions with a cluster of aromatic and hydrophobic residues between TM II, III and VII, that is, Ile II 21, Leu II:24, Met 25, Ile III:04, Tyr VII:02, Iso VII:06, Tyr VII:10 and aromatic residues in first extracellular loop.

Because of multiple rotamers and their possible engagement in energetically acceptable binding modes with the glutamine residues, the prediction of preferred acetamide mimetics was a challenging computational work. The analogs with rigid conformation or potentially generating co-operative binding were explored. These compounds (viz., salicylate (**A**), lactam (**B**) and imidazole (**C**); Fig. 2) when docked into the model produced reasonable interactions with at least two of the three glutamine residues in TM III, V and VI. As indicated in Table 4, the salicylate analog **44a** was significantly less potent versus the acetamide **27a**. The 2-methylbenzimidazole (**44c**) compatible with an acetamide rotamer conformation showed moderate potency. It was gratifying to observe that the cyclic amide **44b** displayed hMCHR1 potency comparable to the lead acetamide derivative **27a** with a binding affinity of 1 nM and functional antagonism of 9 nM yielding a potentially useful isosteric replacement.

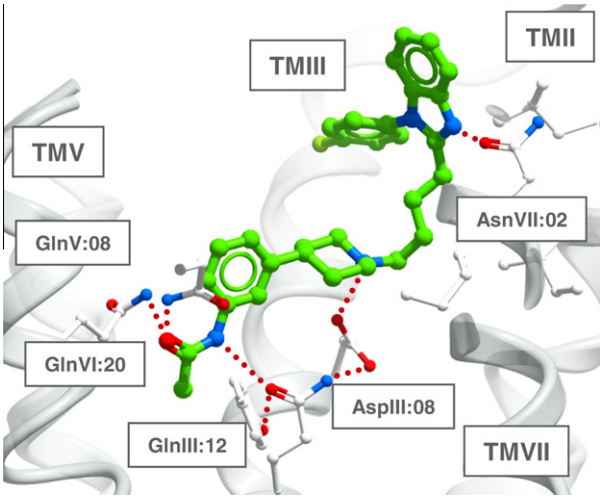


Figure 3. Docking of **27a** in homology model of hMCHR1 depicting crucial interactions with acetamide moiety, piperidine nitrogen and benzimidazole nitrogen.

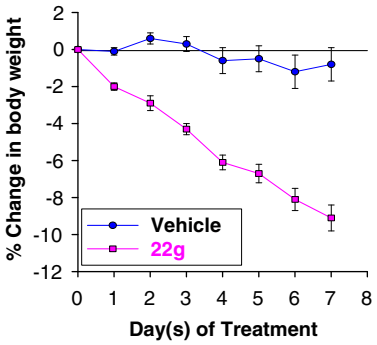


Figure 4. Effect of **22g** on the body weight of DIO C57BL/6J mice. Mice were orally administered either vehicle or the MCHR1 antagonist at doses of 30 mg/kg, b.i.d. for 7 days (n = 12).

As discussed above a number of highly potent MCHR1 antagonists (such as **22g**, **27a**, **34** and **44b**) with low nanomolar potency in both binding and functional assay have been identified. The lead compound **22g** was evaluated further to establish proof of concept in a diet induced obesity (DIO) mouse model using C57BL/6J mice. On oral administration **22g** (30 mg/kg, b.i.d.), showed steady loss of body weight culminating in a statistically significant weight loss of 8% on day 7 as shown in Figure 4.[36]

In summary, we have discovered a benzimidazole derived novel series of potent MCHR1 antagonists. Systematic structural activity studies helped identify key binding interaction and develop useful pharmacophore model. The representative molecule **22g** showed significant anti-obesity effect in a DIO mice model after subchronic treatment for 7 days. Efforts are ongoing to further profile **22g** and optimize series and details will be disclosed in due course.

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Supplementary data

Supplementary data (Details on hMCHR1 model construction and subsequent docking setup are available as supplementary material.) associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.07.086.

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34. Functional response of compounds was assessed using the IP3-SPA-YSI method. Briefly, CHO-K1 cells stably expressing hMCHR1 were incubated overnight with 0.5 μCi/well of 3H-myo-inositol to generate a pool of 3H-PIP2. After aspiration of labeling medium, the cells were incubated with test compounds followed by stimulation with 80 nM of agonist (MCH peptide). The resulting pool of 3H-IPs was extracted with formic acid and the amount of 3H-IPs generated in the cells was detected using the non-derivatized yttrium silicate SPA beads.
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