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Novel benzimidazole-based MCH R1 antagonists

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Abstract—The identification of an MCH R1 antagonist screening hit led to the optimization of a class of benzimidazole-based MCH R1 antagonists. Structure–activity relationships and efforts to optimize pharmacokinetic properties are detailed along with the demonstration of the effectiveness of an MCH R1 antagonist in an animal model of obesity.

Obesity, characterized by excess body fat, is a chronic disease that has dramatically increased in prevalence over the past 30 years. The co-morbidities strongly associated with obesity are numerous—diabetes, coronary heart disease, hypertension, certain cancers, osteoarthritis, and others—thus, obesity remains an increasingly important medical and public health issue.[1]

Investigations into the factors that affect body weight have led to the identification of a group of central targets for the potential treatment of obesity.[2] Melanin-concentrating hormone (MCH) is a 19-amino acid peptide that signals through MCH R1 found in the CNS and stimulates food intake in mammals.[3] MCH peptide knock-out animals are hypophagic and lean, while MCH over-expressing animals are hyperphagic and obese.[4] Transgenic animals devoid of MCH R1 are resistant to diet-induced obesity and weigh less than their wild type counterparts.[5] These, and other data, are supportive of MCH as a key mediator in the regulation of energy balance and body weight.[6] Our efforts to identify antagonists of MCH R1 led to the discovery of a series of thienopyrimidinones that are selective, orally active compounds.[7] This letter describes the extension of the structure–activity relationships (SAR) to include compounds containing a benzimidazole moiety.

Concomitant to the SAR exploration of the thienopyrimidinone series, a screening hit was identified that contained structural features (*p*-biphenyl amide) related to the original hit (SB-282254). SB-282254 was the progenitor of the thienopyrimidinones, represented by GW 803430.[7,8] A boost in potency had been realized when the *p*-biphenyl amide group was replaced with the chlorophenylthienopyrimidinone; therefore, it was reasoned that a similar change in the new hit might produce more potent compounds as well (Fig. 1).

A general synthetic scheme for the preparation of thienopyrimidinone derivatives is outlined in Scheme 1. Amidine **2** was prepared by condensation of the commercially available thiophene derivative **1** with dimethylformamide dimethylacetal in EtOH at reflux followed by concentration and recrystallization of the sample. The reaction of amidine **2** with a variety of 5-amino-1*H*-benzimidazoles **3** (or corresponding 6-amino-1*H*-benzimidazoles) in refluxing ethanol under an atmosphere of nitrogen provided thienopyrimidinones **4**.[9] An improvement in reproducibility of the condensation reaction involved rapidly heating the reactants in phenol at 110–130 °C over 5–60 min.[9b]

Keywords: Melanin-concentrating hormone; MCH; MCH R1; MCH R1 antagonists; Obesity.
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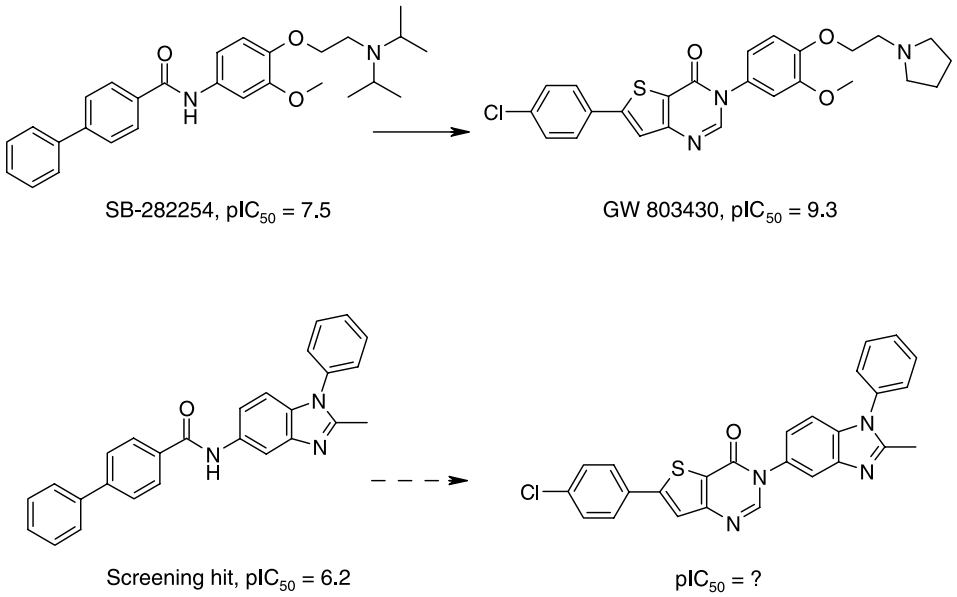
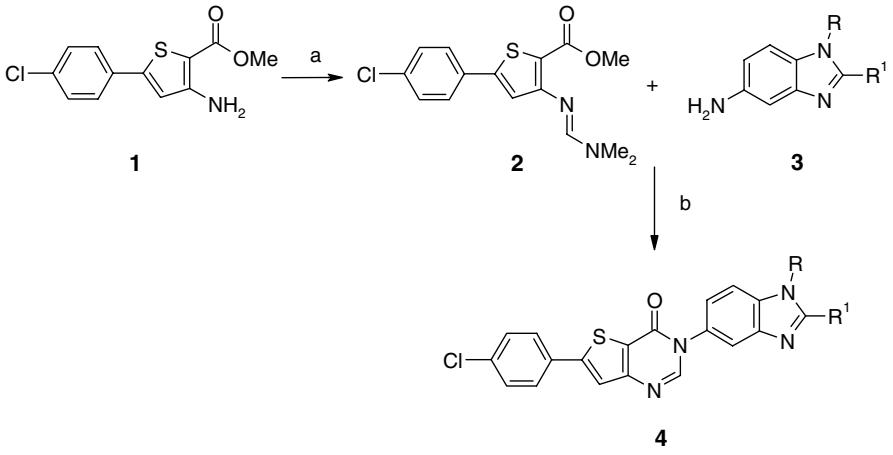


Figure 1. Structural similarity between the progenitor of the thienopyrimidinone series and the screening hit.



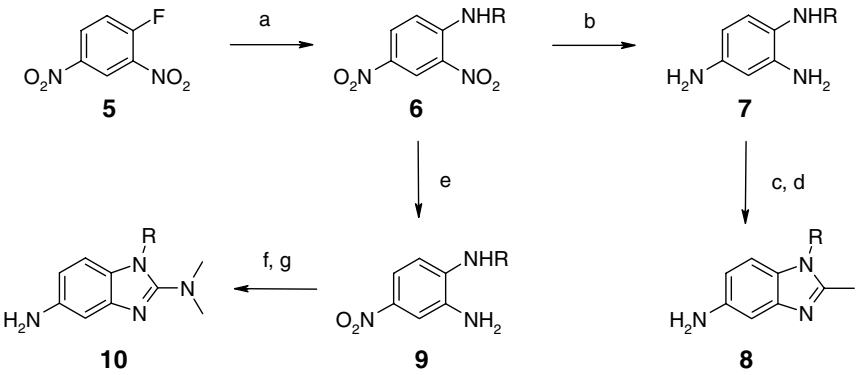
Scheme 1. Reagents and conditions: (a) DMF–DMA, EtOH, reflux; (b) EtOH, reflux or PhOH, 110–130 °C.

The synthesis of the various 5- and 6-amino-1*H*-benzimidazole derivatives[10] was achieved through several complementary methods, some achieving regioselective access to N1-versus N3-substitution (yielding 5-amino-1*H*-benzimidazoles and 6-amino-1*H*-benzimidazoles, respectively), while others simply gave mixtures that required separation.[11]

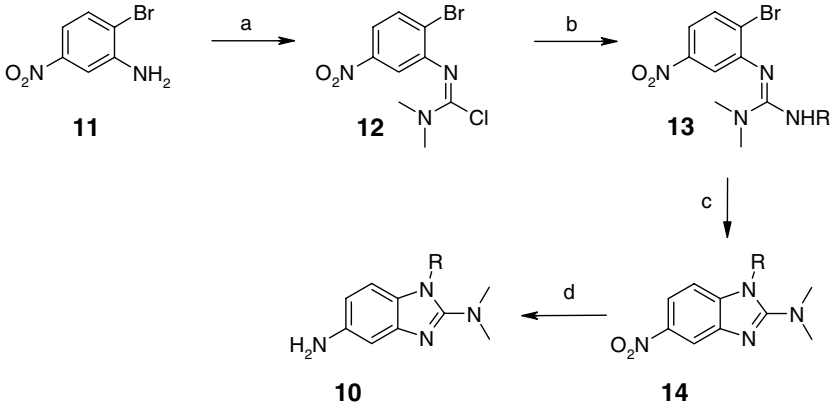
Selective introduction of an N1-aryl group was achieved by treating 2,4-dinitrofluorobenzene (**5**) with the appropriate aniline (Scheme 2). Reduction of the nitro groups with palladium on carbon under an atmosphere of hydrogen generated the unstable diamino derivative **7** that was immediately treated with acetyl chloride and Et_3N in DMF. Acid catalyzed cyclization to the benzimidazole with concomitant deacylation provided the 5-amino-1-aryl-1*H*-benzimidazole coupling partner **8**. The same protocol was also used to introduce alkyl substitution at the N1-position by treating 2,4-dinitrofluorobenzene with alkyl amines.

The exploration of the benzimidazole-based antagonists also focused on appending solubilizing groups at the N1-, N3-, or C2-positions. To this end, 2-dimethylamino analogs were also prepared from the dinitro intermediate (Scheme 2). After introduction of the requisite aniline, a moderately selective reduction with sodium dithionite was performed (purification required) and the resultant 2-amino-1-anilino-4-nitrobenzene derivative **9** was treated with phosgene iminium chloride to directly provide the 2-dimethylamino-1*H*-benzimidazole. Nitro reduction as before completed the synthesis of this fragment.

An alternative route to the 2-dimethylamino-1*H*-benzimidazoles **10**, which provided the 5-amino-N1-substituted benzimidazole regioisomer, employed a modification of the palladium-mediated intramolecular cyclization as reported by Brain and Brunton.[12] As depicted in Scheme 3, commercially available 2-bromo-5-nitroaniline (**11**) was treated with phosgene iminium



Scheme 2. Reagents and conditions: (a) $ArNH_2$ or RNH_2, K_2CO_3, DMF, 80 °C; (b) Pd/C, H_2, EtOAc; (c) AcCl, Et_3N, DMF; (d) concentrated HCl, 100 °C; (e) $Na_2S_2O_4$; (f) phosgene iminium chloride, DCM; (g) Pd/C, H_2, EtOH.



Scheme 3. Reagents and conditions: (a) phosgene iminium chloride, DCM, reflux; (b) RNH_2, Et_3N, THF, reflux; (c) $Pd(OAc)_2$, BINAP, Cs_2CO_3, THF, reflux; (d) Pd/C, H_2, EtOH.

chloride and the resultant dimethylcarbamimidic chloride intermediate **12** was then treated with a variety of primary amines to afford the guanidinyl derivatives **13**. Palladium-mediated cyclization in the presence of BINAP afforded the 5-nitrobenzimidazole derivatives **14**. Nitro reduction completed the synthesis of these fragments.

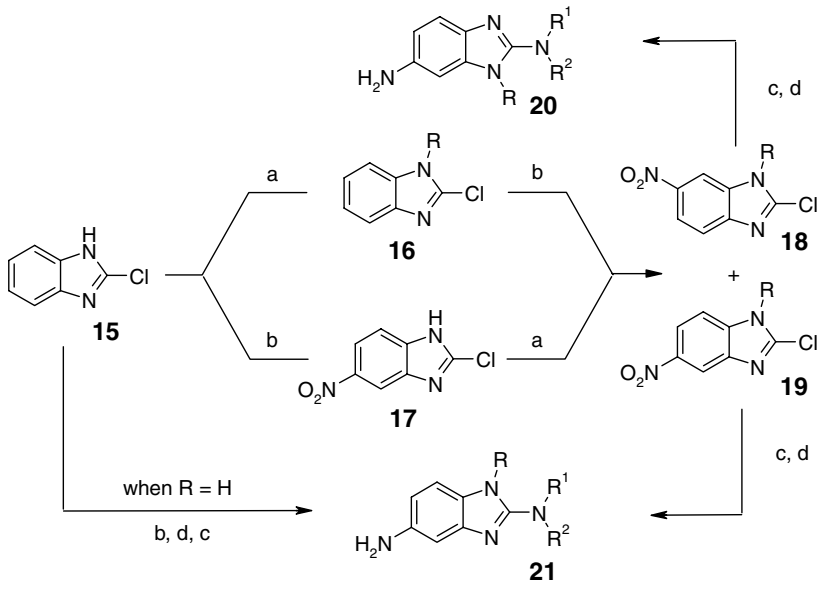
The preparation of other 2-dialkylamino-1*H*-benzimidazoles **20** and **21** could be performed by either starting with the alkylation of 2-chlorobenzimidazole (**15**) followed by a non-selective nitration of the 6-membered ring with HNO_3 and H_2SO_4, or switching the order of the sequence, depending on the nature of the R group. After separation of the regioisomers, introduction of an amine via thermally induced nucleophilic aromatic substitution followed by nitro reduction completed the synthesis of this coupling partner (Scheme 4). In this divergent synthesis, a variety of nucleophilic secondary amines could be introduced by treating the chloro derivative with an amine in an alcohol solvent in a sealed tube.

The *N*-unsubstituted 2-dialkylamino-1*H*-benzimidazoles could be prepared by foregoing the alkylation step, nitrating, reducing the nitro group, and then introducing the dialkylamino group in a similar fashion (steps b and c).

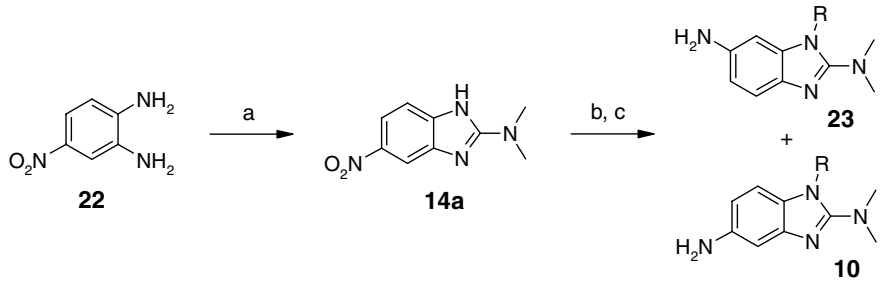
The 2-dimethylamino-1*H*-benzimidazole analogs could also be conveniently prepared by a three-step sequence starting with commercially available 3,4-diaminonitrobenzene (**22**) (Scheme 5). Treatment of the diamine with phosgene iminium chloride followed by non-selective alkylation provided a mixture of 1-substituted benzimidazoles that were separated and carried into the nitro reduction step.

Gratifyingly, our initial foray into the series of thienopyrimidinones containing a 1-aryl-1*H*-benzimidazole moiety produced antagonists with improved potency[13] over the screening hit. The potency was improved with selected substitution at the para position on the aryl ring; for example, H versus ethoxy (compounds **24** and **27**, respectively) produced a full log improvement in potency. Unfortunately, these analogs suffered from poor solubility, and one representative compound, **26** (Table 1), showed undesirable bioavailability[14] in rats.

The hypothesis that the *N*-aryl substituent was primarily responsible for diminished oral absorption was tested by replacing the aryl groups with hydrogen, alkyl or substituted alkyl groups (Table 2). Completely removing the aryl group did result in a slight loss of potency, but replacing the aryl group with the cyclohexyl retained almost all activity. While the fully saturated cyclohexyl

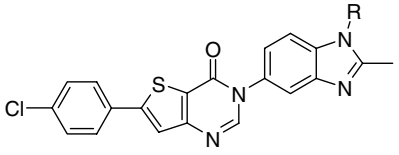


Scheme 4. Reagents and conditions: (a) RX, K_2CO_3, DMF, 60 °C; (b) HNO_3, H_2SO_4; (c) R^1R^2NH, sealed tube, reflux; (d) Pd/C, H_2, EtOH.



Scheme 5. Reagents and conditions: (a) phosgene iminium chloride, DCM, reflux; (b) RX, K_2CO_3, DMF, 60 °C; (c) Pd/C, H_2, EtOH; (**14a** = **14**, R = H).

Table 1. SAR and bioavailability of 2-methyl-1-aryl-1*H*-benzimidazoles (compounds **24**–**29**)



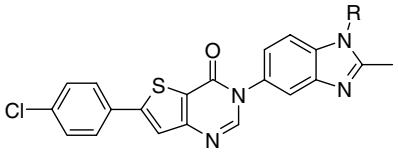
Compound	R	pIC_{50}[a]	% *F*[b]
24	Ph	7.5	nd
25	4-Toluyl	7.7	nd
26	4-Methoxyphenyl	8.3	3
27	4-Ethoxyphenyl	8.5	nd
28	4-Isopropoxyphenyl	8.1	nd
29	4-Dimethylaminophenyl	8.3	nd

[a] Values are means of greater than three experiments; $pIC_{50} = -\log(IC_{50})$.
[b] Bioavailability (nd, not determined).

was clearly not an improvement with respect to oral bioavailability, introduction of the aminoethyl substituents produced compounds with improved bioavailabilities (compounds **32** and **33**) while retaining potency. In the 2-methyl-1*H*-benzimidazole series, the best improvements in bioavailability were found with alkoxy- and hydroxypropyl substituents (compounds **34** and **35**).

Encouraged by the improvements in oral bioavailability by the incorporation of tethered amino functionality, a series of 2-amino-1*H*-benzimidazoles was investigated (Table 3). In general, this series exhibited acceptable potency. Increasing the bulk on the exocyclic nitrogen appeared to have a beneficial effect (compounds **36** vs. **37**, **38** and **42**). The limit appeared to be reached with

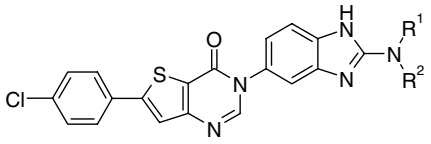
Table 2. SAR and bioavailability of 2-methyl-1-substituted-1*H*-benzimidazoles (compounds **26**, **30**–**35**)



Compound	R	pIC_{50}[a]	% F[b]
26	4-Methoxyphenyl	8.3	3
30	H	7.6	nd
31	Cyclohexyl	8.2	0
32	2-(4-Morpholinyl)ethyl	8.2	24
33	2-(1-Pyrrolidinyl)ethyl	8.7	31
34	3-Methoxypropyl	8.3	40
35	3-Hydroxypropyl	8.8	$\geqslant$100[14b]

[a] Values are means of greater than 3 experiments; $pIC_{50} = -\log(IC_{50})$.
[b] Bioavailability (nd, not determined).

Table 3. SAR and bioavailability of *N*-unsubstituted 2-aminobenzimidazoles (compounds **36**–**47**)



Compound	R^1	R^2	pIC_{50}[a]	% F[b]
36	H	H	7.5	nd
37	H	Me	8.4	0
38	Me	Me	8.6	4
39	H	*i*-Pr	8.1	nd
40	H	*c*-Pr	7.8	nd
41	$CH_2CH_2CH_2CH_2$		8.5	76
42	$CH_2CH_2CH_2CH_2CH_2$		8.3	31
43	$CH_2CH_2OCH_2CH_2$		7.8	nd
44	$CH_2CH_2N(CH_3)CH_2CH_2$		7.0	nd
45	H	2-Methoxyethyl	7.5	nd
46	H	2-(1-Pyrrolidinyl)ethyl	8.2	0
47	Me	2-(1-Pyrrolidinyl)ethyl	8.3	0

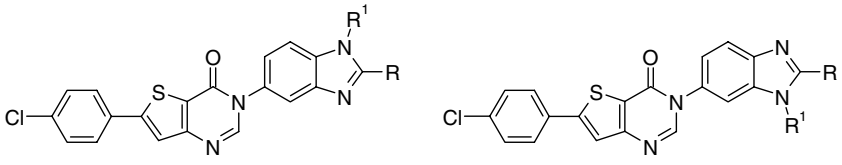
[a] Values are means of greater than three experiments; $pIC_{50} = -\log(IC_{50})$.
[b] Bioavailability (nd, not determined).

the cyclic constrained *N*-methyl piperazine analog (compound **44**), although the flexible N–H and N–Me pyrrolidinoethyl groups were well tolerated (compounds **46** and **47**). Unfortunately, with the notable exception of the 2-pyrrolidino- and 2-piperidino-1*H*-benzimidazole derivatives (compounds **41** and **42** at 76% and 31%, respectively), the unsubstituted analogs exhibited unfavorable bioavailabilities (<5%).

Thus, a series of 1-*substituted*-2-dialkylamino-1*H*-benzimidazoles was prepared to potentially elicit improved bioavailabilities (Table 4). One curious aspect of this exploration was how regioisomeric substitution on the benzimidazole ring would affect both potency and bioavailability. A few general conclusions could be made regarding this series. First, as exemplified in compound **48**, analogs with dialkylamino functionality at the 2-position typically had increased plasma exposure over the 2-methyl-1*H*-benzimidazoles. Second, there did not appear to be a substantial effect on potency from N-substitution of the benzimidazoles, with the glaring exception being the 4-methoxybenzyl derivative where the substitution is proximal to the thienopyrimidinone core (series II, compound **54**). Third, and most importantly, this series produced a number of compounds that showed promising bioavailabilities necessary for progression, most notably compound **50**, which possesses a favorable mix of potency and high oral bioavailability.

Efforts to establish the utility of an MCH R1 antagonist in an animal model of obesity led to the examination of compound **50** in a semi-chronic study. The compound exhibited good pharmacokinetic properties in mouse (bioavailability[15] >90%, $t_{1/2}$ = 6 h) with good brain penetration (brain:plasma ratio = 2.6). Importantly, compound **50** was found to be selective (>100×) over a

Table 4. SAR and bioavailability of regioisomeric 2-amino-1*H*-benzimidazoles (compounds **48**–**58**)



I II

Compound	Series	R	R^1	pIC_{50}[a]	% F[b]
26	I	Me	4-Methoxyphenyl	8.3	3
48	I	NMe_2	4-Methoxyphenyl	8.0	16
49	I	NMe_2	Me	8.2	nd
50	II	NMe_2	Me	8.8	$\geqslant 100$[14b]
51	I	NMe_2	*n*-Pr	8.3	30
52	II	NMe_2	*n*-Pr	8.3	21
53	I	NMe_2	4-Methoxybenzyl	7.9	nd
54	II	NMe_2	4-Methoxybenzyl	5.6	nd
55	I	NMe_2	2-Hydroxyethyl	8.0	59
56	II	NMe_2	2-Hydroxyethyl	7.9	55
57	I	NC_4H_8	Me	7.6	nd
58	II	NC_4H_8	Me	8.2	$\geqslant 100$[14b]

[a] Values are means of greater than three experiments; $pIC_{50} = -\log(IC_{50})$.
[b] Bioavailability (nd, not determined).

battery of G-protein coupled receptors, ion channels, and enzymes. Its efficacy in inducing weight loss was evaluated in high fat (58% kcal of fat, Research Diets #D12331) diet-induced obese AKR/J mice.

As shown in Figure 2, during a 15-day treatment, oral administration of compound **50** at 0.3, 1, 3, and 10 mg/kg once daily caused a sustained dose-dependent change in body weight of −1.6%, −2.1%, −5.1%, and −10%, respectively, relative to vehicle controls.[16]

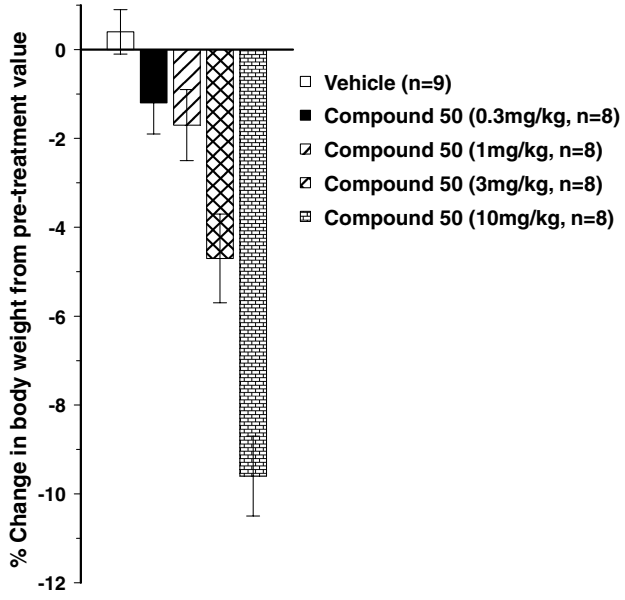


Figure 2. Effect of compound **50** at 0.3, 1, 3, and 10 mg/kg (orally, qd) on body weight loss in high fat diet-induced obese AKR/J mice. Weight loss is expressed as percentage weight change from pre-treatment value for each treatment group (average pre-treatment body weight value was 49.6 ± 0.6 g, $n = 41$). Values are means ± SEM; *n*, number of mice per group.

In conclusion, a series of benzimidazole-containing thienopyrimidinones was synthesized based upon a screening hit and assessed for their potency as antagonists of MCH. SAR analysis showed that most compounds were potent antagonists, with activities below 100 nM. There also was a wide tolerance for a variety of sterically demanding functional groups at ring-nitrogen substitution (positions 1 and 3) or at position 2 of the benzimidazole. Improvements in the bioavailability of these antagonists were also made and one such analog, compound **50**, was progressed into an animal model of obesity and produced weight loss over the 15-day treatment period.

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13. The compounds were evaluated in a functional assay for MCH R1 activity utilizing luciferase activity as a readout as described in WO 2004/092181 A1 (corrected version), pages 215–216. CHO cells expressing an elkgal4-luc^{+} reporter gene (host) were transfected with human MCH R1. The ability of the antagonists to inhibit an EC_{80} response of MCH was assessed via a TopCount microplate scintillation counter (Packard) and the specificity of the MCH R1 response was determined by measuring the ability of the antagonists to inhibit an EC_{80} thrombin response in the host cells. All compounds were assayed with $n \geqslant 4$.
14. (a) Bioavailabilities (% *F*) were determined in rats using an i.v. (~3 mg/kg) and oral (~5–10 mg/kg) arm of dosing ($n = 1$ each) and were used primarily as a screening filter.; (b) A value greater than 100% is achieved due to variability amongst the individual animals or due to saturation of clearance mechanisms when comparing the intravenous and oral dosings.
15. This oral bioavailability (% *F*) value was determined in mice using an i.v. (1.6 mg/kg) and oral (5.2 mg/kg) arm of dosing ($n \geqslant 2$ each).
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