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Novel aminobenzimidazoles as selective MCH-R1 antagonists for the treatment of metabolic diseases

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Abstract—A series of novel aminobenzimidazoles was prepared and evaluated for h-MCH-R1 antagonist properties. Most of the compounds showed excellent h-MCH-R1 binding affinity as well as mouse ex vivo binding. Compounds **9** and **18** were active in mouse DIO studies at 30 mpk.

Melanin-concentrating hormone (MCH) is a 19-membered neuropeptide that is found in the lateral hypothalamus and regulates food intake.[1,2] There is evidence for involvement of MCH in feeding and obesity. Hypothalamic MCH peptide levels increase during fasting in ob/ob and WT mice.[3] ICV administration of MCH or analogs stimulates feeding in rodents and MCH−/− mice, while otherwise healthy, are hypophagic and leaner than WT mice.[4] MCH receptor knock-out mice are lean, hypophagic, hyperactive, have reduced fat mass, have increased metabolic rate, and they are resistant to diet-induced obesity (DIO).[5] Evidence from knock-outs suggests an MCH receptor antagonist should be beneficial for treatment of obesity and related disorders.[6,7] Several classes of small molecule MCH-R1 antagonists have recently been disclosed.[8–10]

Recent publications from our laboratories have demonstrated that compounds such as **1** and **2** are very selective MCH-R1 antagonists useful for the treatment of obesity and related disorders.[11–16] The potential Ames liability associated with the embedded biarylamine moiety present in **1** was addressed by the use of novel phenyl isosteres such as bicyclo[4.1.0]heptane and bicyclo[3.1.0]hexane units.[15,16] Compounds of this urea series had been hampered by moderate pharmacological properties ascribed primarily to urea hydrolysis. In order to minimize these issues, we investigated the use of urea isosteres such as aminobenzimidazoles **3** which share key pharmacophores (Fig. 1).

Structure–activity relationship (SAR) studies reported herein focus on all four regions of the inhibitor: aminobenzimidazoles, *N*-alkylamino sidechains, substitution of the pendant aromatic ring, and modifications of the central core structure.

A general synthesis of aminobenzimidazoles is shown in Scheme 1. Reductive amination of bicyclo[4.1.0] heptyl

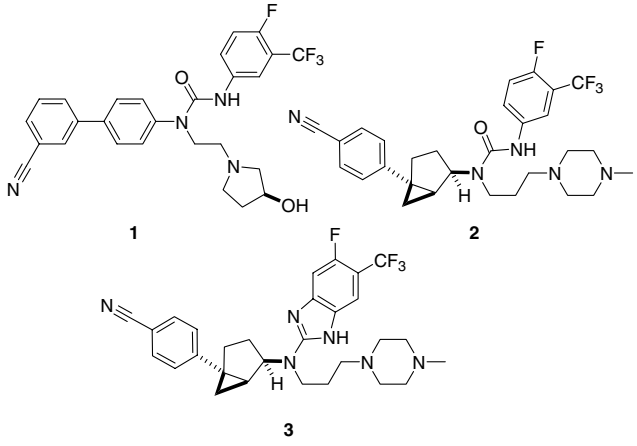

Figure 1. Evolution of aminobenzimidazole h-MCH-R1 antagonists.

Keywords: Melanin-concentrating hormone; Aminobenzimidazoles; Metabolic diseases.
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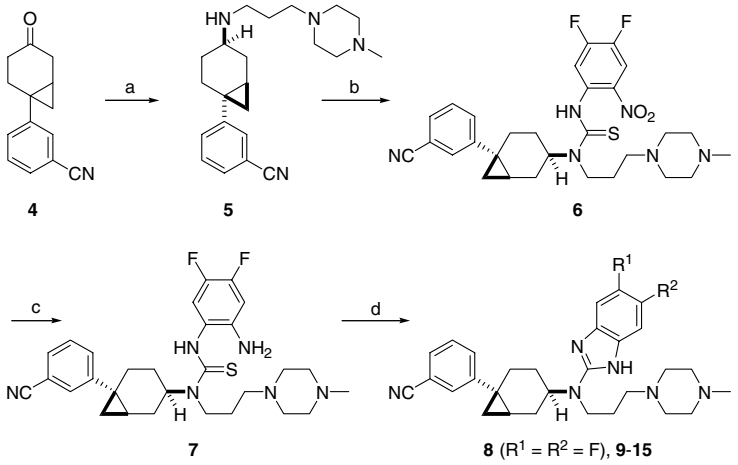


Scheme 1. Reagents and conditions: (a) 1-(3-aminopropyl)-4-methyl-piperazine, $Ti(OiPr)_4$, then MeOH, $NaBH_4$, 85%; (b) arylisothiocyanate, CH_2Cl_2, rt, 70%; (c) $SnCl_2 \cdot H_2O$, EtOAc, rt, 68%; (d) DIC, EtOAc, rt, 33%.

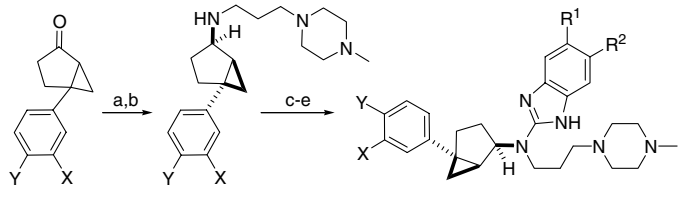
ketone[17] **4** with aminopropyl-*N*-methylpiperazine afforded compound **5**. The *trans*/*cis* selectivity of the reductive amination was highest at 9:1 using sodium borohydride in methanol solution.

The relative stereochemistry was assigned based on the 2D-NOESY analysis and X-ray crystallography of the fully elaborated urea analogs.[15,16] Compound **5** was treated with aryl isothiocyanate followed by $SnCl_2$ reduction of the nitro group to afford the aminothiourea **7** in moderate yields. The final cyclization to the aminobenzimidazoles proved difficult in most cases, however, best results were obtained when aminothiourea **7** was treated with diisopropyl carbodiimide at room temperature to afford compound **8**. Compounds **9**–**15** were similarly synthesized.

Analogous chemistry was employed to synthesize the bicyclo[3.1.0]hexane aminobenzimidazole series, as shown in Scheme 2. Reductive amination of 3-bromophenyl bicyclohexane-1-one[18] **16** followed by cyanation[19] provided compound **17**. Further derivatization as above afforded the final target molecules **18**–**20**. Aminobenzimidazoles **3**, **21**, and **22** were similarly synthesized according to Scheme 2 starting from 4-cyanophenyl bicyclohexanone **16a**.

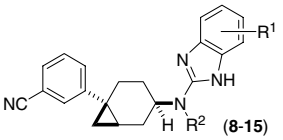
Receptor affinities for the compounds described have been determined in binding assays for the human MCH-R1 receptor.[20] The MCH-R1 inhibitory potency of the newly synthesized aminobenzimidazole compounds in the bicyclo[4.1.0]heptane series is summarized in Table 1. Initially, we focused on studying the SAR of the side chain portion of the molecule. Compounds bearing an aminopropyl-*N*-methylpiperazine sidechain exhibited excellent MCH-R1 binding affinities. Compound **8** with a 5,6-difluoro benzimidazole moiety showed a K_i of 8.4 nM, whereas compound **9** with 5,6-dichloro substitution on the benzimidazole ring showed a K_i of 2.2 nM. 6-Cl, 5-F substitution on the benzimidazole moiety was also well tolerated (**10**, K_i = 6.2 nM).

Next, we turned our attention to the aminomethyl piperidine sidechain as a replacement for the aminopropyl-*N*-methylpiperazine unit. The synthesis of molecule **12** was carried out using similar chemistry described in Scheme 1 starting with ketone **4** or **16** and 1-aminomethyl-*N*-Boc piperidine. The *N*-Boc-protected aminomethylpiperidine compound **11** showed only micromolar activity in the MCH-R1 assay, whereas the deprotected piperidine compound **12** showed excellent potency (K_i = 2.5 nM). The introduction of a methane sulfonyl group on the piperidine nitrogen of **12** produced an extremely potent compound **13** with a MCH-R1 K_i of 1.5 nM. Other methane sulfonamides such as **14** and **15** also showed good MCH-R1 potency (Table 1).



Scheme 2. Reagents and conditions: (a) 1-(3-aminopropyl)-4-methyl-piperazine, $Ti(OiPr)_4$, then MeOH, $NaBH_4$, 87%; (b) $Zn(CN)_2$, $Pd_2(dba)_3$, dppf, DMF, H_2O, 120 °C, 94%; (c) arylisothiocyanate, CH_2Cl_2, rt, 63%; (d) $SnCl_2 \cdot H_2O$, EtOAc, rt, 85%; (e) DIC, EtOAc, rt, 32%.

Table 1. MCH receptor binding for compounds **8**–**15**



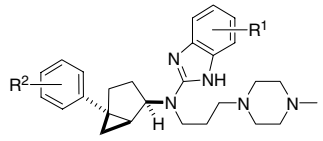
(**8-15**)

Compound	R^1	R^2	h-MCH-R1 K_i[a] (nM)
8	5, 6-Di-F	$(CH_2)_3$(4-methyl-1-piperazinyl)	8.4
9	5, 6-Di-Cl	$(CH_2)_3$(4-methyl-1-piperazinyl)	2.2
10	6-Cl, 5-F	$(CH_2)_3$(4-methyl-1-piperazinyl)	6.2
11	5, 6-Di-Cl	(CH_2)(4-Boc-piperidinyl)	1145
12	5, 6-Di-Cl	(CH_2)(4-*H*-piperidinyl)	2.5
13	5, 6-Di-Cl	(CH_2)(4-methylsulfonylpiperidinyl)	1.5
14	5, 6-Di-F	(CH_2)(4-methylsulfonylpiperidinyl)	27
15	6-Cl, 5-F	(CH_2)(4-methylsulfonylpiperidinyl)	6.7

[a] Values are means of three experiments. h-MCH-R2 $K_i > 3$ μM.

The MCH-R1 inhibitory potency of the amino benzimidazole compounds in the bicyclo [3.1.0]hexane series is summarized in Table 2. Compounds in bicyclohexane series are very well tolerated for both 3- and 4-cyano substitution on the phenyl ring. Compound **3** showed a MCH-R1 K_i of 8.6 nM. The most potent compound in this series was **22** with MCH-R1 K_i of 4.9 nM. Bicyclo[3.1.0]hexane aminobenzimidazoles **18** and **19** exhibited high affinity at the MCH-R1 receptor with K_i values of 5.6 and 6.8 nM, respectively. The most active compounds in the binding assay were evaluated for functional antagonism in a FLIPR™ assay. The K_b values were generally 2- to 5-fold higher than the corresponding K_i values. It should also be noted that all new aminobenzimidazole compounds were inactive in a similar MCH-R2 binding assay, suggesting high subtype selectivity.

Table 2. MCH receptor binding for compounds **3**, **18**–**22**

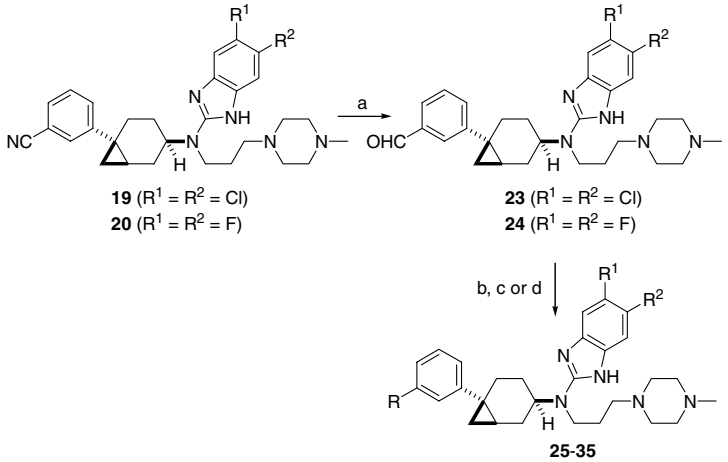


(**3**, **18-22**)

Compound	R^1	R^2	h-MCH-R1 K_i[a] (nM)	h-MCH-R1 K_b (nM)[b]
3	5-F, 6-CF_3	4-CN	8.6	43
18	6-Cl, 5-F	3-CN	5.6	10
19	5, 6-Di-Cl	3-CN	6.8	20
20	5, 6-Di-F	3-CN	20.7	
21	5, 6-Di-Cl	4-CN	11.4	
22	6-Cl, 5-F	4-CN	4.9	

[a] Values are means of three experiments. h-MCH-R2 $K_i > 3$ μM.
[b] Inhibition of MCH-mediated Ca^{2+} influx into cells expressing h-MCH-R1 via FLIPR assay.

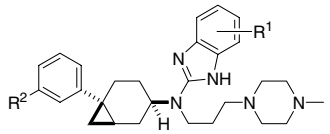
We briefly investigated the effect of aromatic substitution on the phenyl ring attached to the bicycloheptane system. Reduction of the cyano group of compound **19** with DIBAL afforded the aldehyde **23**. Reductive amination using various secondary amines gave a range of 3-substituted aminomethyl derivatives **27**–**35** as shown in Scheme 3. Similar chemistry was also performed on the difluoro analog **20**. Replacement of the 3-cyano group with formyl **23**, *O*-methyloxime **25**,



19 ($R^1 = R^2 = Cl$)
20 ($R^1 = R^2 = F$)
23 ($R^1 = R^2 = Cl$)
24 ($R^1 = R^2 = F$)

Scheme 3. Reagents and conditions: (a) DIBAL-H, CH_2Cl_2, −78 °C rt, 60%; (b) $MeONH_2$, CH_2Cl_2, 40%; (c) $NaBH_4$, MeOH, 55%; (d) amine, $NaBH(OAc)_3$, MeOH, 50–82%.

Table 3. MCH receptor binding for compounds **23–35**



(**23-35**)

Compound	R^1	R^2	h-MCH-R1 K_i[a] (nM)
23	5, 6-Di-Cl	–CHO	13.7
24	5, 6-Di-F	–CHO	16.3
25	5, 6-Di-F	–C=N–OMe	28.2
26	5, 6-Di-F	$–CH_2–OH$	70.8
27	5, 6-Di-Cl	Dimethylaminomethyl	4.9
28	5, 6-Di-F	Dimethylaminomethyl	327.6
29	5, 6-Di-F	Pyrrolidinylmethyl	25.7
30	5, 6-Di-F	(*S*)-3-OH-Pyrrolidinylmethyl	441
31	5, 6-Di-F	(*S*)-2-Hydroxymethyl-pyrrolidinylmethyl	3000
32	5, 6-Di-F	Piperidinylmethyl	405
33	5, 6-Di-Cl	Morpholinylmethyl	14.2
34	5, 6-Di-F	Morpholinylmethyl	21.3
35	5, 6-Di-F	4-Methylpiperazinylmethyl	321

[a] Values are means of three experiments. h-MCH-R2 $K_i > 3$ μM.

pyrrolidinomethyl **29**, and morpholinomethyl **33** and **34** resulted in a moderate retention of the MCH-R1 binding affinity. However, dimethyl aminomethyl compound **27** showed excellent binding affinity ($K_i = 4.9$ nM) (Table 3). Overall, the tolerance for substitution on the phenyl ring was very limited and 3-cyanophenyl was optimal for in vitro and in vivo activity.

Additionally, the receptor tolerance for N-alkylation of benzimidazole nitrogen of **18** was also explored. The N-methylated compound **36**[21] is substantially less potent than compound **18** indicating that the benzimidazole NH plays a key role in inhibitor binding to the MCH-R1 receptor (Fig. 2).

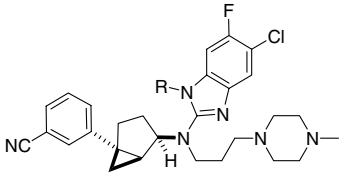
Having achieved excellent potency against MCH-R1 receptors, we shifted our attention toward measuring the mouse ex vivo binding[22,23] and pharmacokinetics.[24] The ex vivo binding and rapid rat analysis of some of the aminobenzimidazole derivatives are summarized in Table 4. The aminoalkyl sidechains play an important role in pharmacokinetics. Compounds **12**, **13**, and **14** bearing a methyl piperidine-based sidechain showed little or no ex vivo binding as well as low exposure in the rat pk. However, compounds with an aminopropyl *N*-methylpiperazine sidechain showed excellent ex vivo binding and rat pk. Examples are compounds **3**, **9**, **18**, and **20**. Typically, compounds displaying ex vivo binding >60% were active in the mouse DIO model. Compounds **9** and **18** were active in the DIO model at 30 mpk inhibiting food intake as seen in Table 5.[25]

Table 4. MCH receptor ex vivo binding and rat PK

Compound	h-MCH-R1 K_i[a] (nM)	Mouse ex vivo[b] binding		rat PK, (10 mpk), AUC (ng h/mL)[c]
		6 h (%)	24 h (%)	
3	8.6	100	94	2796
8	8.4	37	17	293
9	2.2	81	97	965
12	2.5	0	0	114
13	1.5	12	0	0
14	27	0	0	350
18	5.6	92	77	1925
19	6.8	97	51	na
20	20.7	75	33	1487
22	4.9	100	81	na

[a] Values are means of three experiments.
[b] Expressed as a percentage inhibition of MCH-ADO binding relative to vehicle control ± SEM ($n = 3$, dosed at 30 mpk, po).
[c] Data from pooled samples, dosed at 10 mpk, po. See Ref. 24 for procedure. na, not available.

In summary, a series of new aminobenzimidazole derivatives were prepared and found to be potent and selec-



18, R = H, MCH-R1 K_i = 5.6 nM
36, R = Me, MCH-R1 K_i = 1186 nM

Figure 2. Effect of N-methylation of benzimidazole on MCH-R1 K_i.

Table 5. In vivo efficacy in DIO mice[a]

Compound	% Inhibition at indicated time			
	2 h	4 h	6 h	24 h
9	12 ± 8	19 ± 6	18 ± 6	9 ± 4
18	13 ± 4	19 ± 4	21 ± 4	5 ± 4

[a] All values are significantly different ($p < 0.05$) from vehicle control animals and represent the % inhibition of cumulative food intake at the indicated times in fasted DIO mice. There are 15 mice per group.

tive antagonists of the h-MCH-R1 receptors. Their in vitro activities were comparable with those of the corresponding urea compounds, while some representatives of the benzimidazole class showed outstanding activity in vivo. Compounds with greater than 80% receptor occupancy in mouse at 6 h and some with greater than 50% receptor occupancy after 24 h have been identified (compounds **3**, **9**, **18**, **19**, and **22**). Activity in DIO mouse is predicted by receptor occupancy as seen for the efficacious analogs **9** and **18**.

Acknowledgments

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20. Membranes from CHO cells expressing MCH-R1 (0.1 mg/mL) were incubated with SPA beads (1 mg/mL) in a binding buffer (25 mM HEPES, 10 mM $MgCl_2$, 5 mM $MnCl_2$, and 0.1% BSA, pH 7.4) for 5 min on ice forming a bead/membrane mixture. The bead/membrane mixture was centrifuged (4 min at 300*g*) and resuspended in the binding buffer. The bead/membrane mixture was then pelleted again (4 min at 300*g*), resuspended in the binding buffer, and set aside. Binding buffer (50 μL/well) containing vehicle alone (2% DMSO), various compound concentrations, or 4 μM MCH (for nonspecific binding) was added to a 96-well plate. Subsequently, 50 μL of binding buffer containing 0.5 nM [^{125}I]MCH was added to each well of the 96-well plate. Finally, 100 μL of the bead/membrane mixture was added to each well of the 96-well plate. The binding reaction mixtures were incubated for 2–4 h at room temperature. Binding of [^{125}I]MCH to the bead/membrane mixture was detected using a TOPCOUNT (Packard). K_i values were determined using nonlinear regression analysis and represent the average of at least three determinations. The standard deviations were no greater than 5% from the mean.
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23. Animals were administered compound (30 mpk) via oral gavage. At subsequent time points, brains were harvested and frozen. Brain sections from the caudate were placed on slides and allowed to bind to radiolabeled MCH-ADO ([^{125}I]-S36057, NEN) [22] for 30 min. The sections were then rinsed with binding buffer and dried. The amount of radiolabeled MCH-ADO that remained bound to the brain section following washing was specific to MCH binding sites. Addition of nonlabeled MCH to the binding reaction completely abolished radiolabeled MCH-ADO binding to the brain section. Radioactivity bound to the section was quantified using a Storm 860 phosphorimager as described in Ref. 22.
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25. In vivo efficacy was determined by incorporation of a fasted, diet-induced obese (DIO) mouse model. Mice were fasted for 24 h and dosed orally 1 h prior to dark onset. Food was returned at dark onset and intake was measured at 2, 4, 6, and 24 h after food presentation.