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Synthesis and SAR investigations of novel 2-arylbenzimidazole derivatives as melanin-concentrating hormone receptor 1 (MCH-R1) antagonists

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ABSTRACT

Compounds containing 2-arybenzimidazole ring systems linked to arylpiperidines were synthesized and evaluated as MCH-R1 antagonists. The results of structure–activity relationship studies led to the identification of compound **4c** as a potent MCH-R1 antagonist (IC_{50} = 1 nM). This compound also has good metabolic stability, and favorable pharmacokinetic and brain penetration properties. However **4c** was found to be potent inhibitor of the hERG potassium channel.

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The melanin-concentrating hormone (MCH) is a cyclic 19-amino acid polypeptide that is expressed predominantly in the lateral hypothalamus and zona incerta of the central nervous system.[1] MCH is known to be involved in the regulation of feeding behavior and energy homeostasis that are mediated by two types of G protein-coupled receptors, MCH receptor 1 and 2 (MCH-R1 and R2).[2,3] Nearly homologous forms of MCH-R1 are present in both humans and rodents and their pharmacological effects on MCH are not significantly different. Owing to the observation that intracerebroventricular (ICV) injection of MCH into rat stimulates food intake and chronic administration, it can be argued that MCH is associated with obesity and hyperphagia.[4,5] Furthermore, it has been reported that the steady-state levels of MCH mRNA are high in obese rodents, such as ob/ob, db/db, Ay/a mice.[6] Additionally, a transgenic MCH-R1 knockout in mice led to reduced food intake and elevated metabolic rates, resulting in a lean phenotype.[7] In contrast, overexpression of MCH mRNA caused mice to have increased fat and body weight associated with an obese phenotype.[8] Indeed, numerous MCH-R1 antagonists have shown anti-obesity efficacy in diet-induced obesity (DIO) animal models.[9]

Since the time that T-226296[10] and SNAP-7941[11] were shown to be the first small molecule MCH-R1 antagonists, a number of pharmaceutical companies have undertaken large efforts to develop a variety of pharmacophore structures of MCH-R1 antagonists that might behave as anti-obesity agents. Despite good in vivo efficacy in rodents, a number of chemical series are unable to progress to clinical development due to unsuitable PK profile and hERG binding activity.[12] To date, GW856464,[13] AMG-076,[14] NGD-4715,[15] and ALB-127158 (structure undisclosed)[16] have advanced to the phase 1 trial stage (Fig. 1). Recently, benzimidazole based MCH-R1 antagonists have been described by several research groups.[17] In continuing efforts to uncover novel and potent MCH-R1 antagonists, we found that 2-aryl substituted benzimidazole derivatives, containing the piperidinylphenyl acetamide group at the 1-position, display highly potent binding affinities to MCH-R1.[18] We describe the synthesis, biological evaluation, and structure–activity relationships of several 2-arylbenzimidazole derivatives.

The general synthetic routes used to prepare the new 2-arylbenzimidazole derivatives **3–6** are outlined in Scheme 1. The aryl substituted benzimidazoles **1**, employed in these sequences are either commercially available or readily prepared by reaction of 1,2-phenylenediamine with benzoic acid derivatives using polyphosphoric acid (PPA). The methanesulfonate ester **9** of *N*-[3-[1-(3-hydroxypropyl)-4-piperidinyl]phenyl]acetamide, used as one coupling partner, was prepared from the known *N*-[3-(4-piperidinyl)phenyl]acetamide **7**.[19] The route employed alkylation of **7** with 3-bromopropan-1-ol in the presence of potassium carbonate in DMF to give *N*-[3-[1-(3-hydroxypropyl)-4-piperidinyl]phenyl]acetamide **8**. Treatment of **8** with methanesulfonyl chloride and triethylamine in dichloromethane provided **9**, which was directly used in the next step without further purification.

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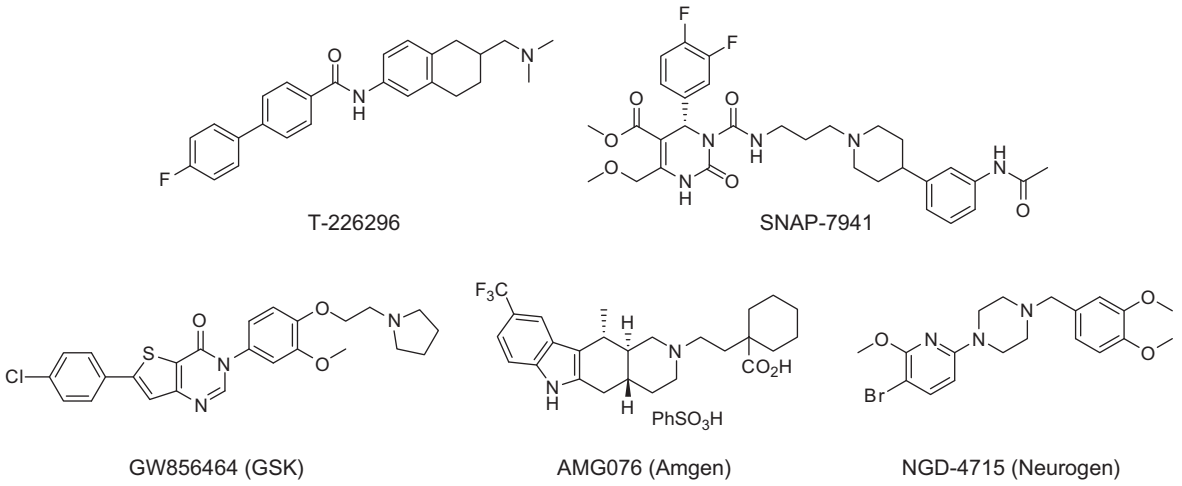
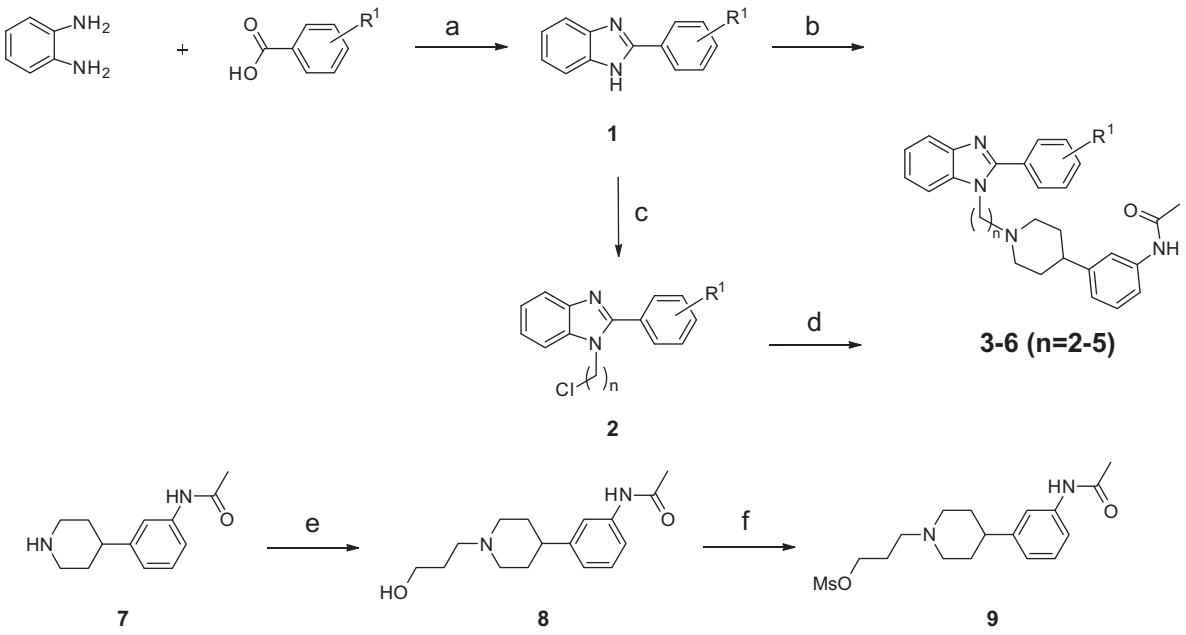


Figure 1. Representative structures of MCH-R1 antagonists.

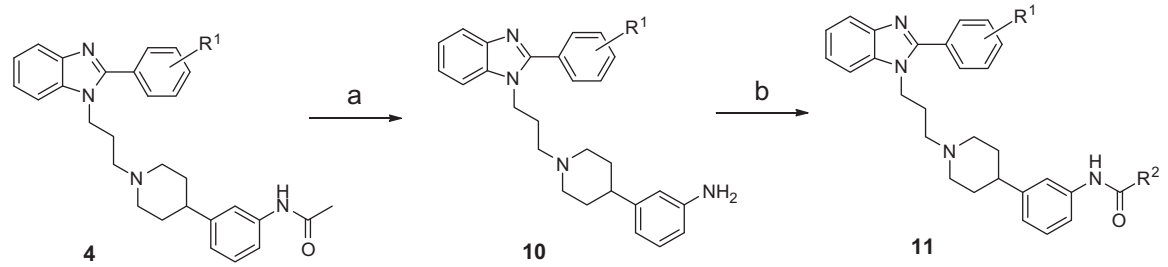


Scheme 1. Reagents and conditions: (a) PPA, reflux, 3 h; (b) **9**, K_2CO_3, DMF, 80 °C, 5 h; (c) 1-chloro-*n*-iodoalkane, K_2CO_3, DMF, rt, 10 h; (d) **7**, K_2CO_3, KI, DMF, 100 °C, 5 h; (e) 1-bromopropanol, K_2CO_3, DMF, 60 °C, 5 h; (f) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 3 h.

The target compounds **4** ($n = 3$) were obtained by reaction of benzimidazoles **1** with **9** in the presence of potassium carbonate in DMF. Alternatively, compounds **3–6** can be generated from **1** by alkylation with the appropriate 1-chloro-*n*-iodoalkanes followed by reaction with **7**.

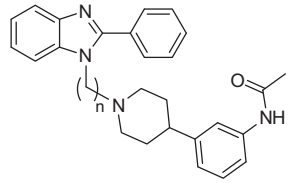
As shown in Scheme 2, the routes for preparation of anilide derivatives **11** utilized simple synthetic manipulations starting with acetamide **4**. Hydrolysis of **4** by treatment with 5 N HCl in methanol afforded the free amine **10**, which was then reacted with an appropriate acid chloride in the presence of triethylamine in dichloromethane to afford the corresponding amides **11**.

The 2-arylbenzimidazole derivatives were evaluated for their binding affinities to the membranes of CHO cells expressing human MCH-R1. These measurements were performed by using a



Scheme 2. Reagents and conditions: (a) 5 N HCl, MeOH, 50 °C, 3 h; (b) R^2COCl, Et_3N, CH_2Cl_2, 0 °C to rt, 1 h.

Table 1
Effects of chain length on MCH-R1 binding affinity



Compound	*n*	MCH-R1 IC_{50}[a,b] (nM)
3	2	10,000
4	3	2
5	4	29
6	5	74

[a] Binding affinities of compounds for MCH-R1 were determined by using competitive binding with Eu-MCH and a TRF assay.
[b] Values are means of at least two measurements.

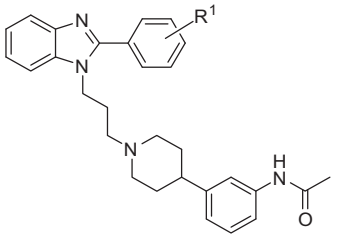
competition binding assay with Eu-labeled MCH and a time-resolved fluorometric (TRF) assay (Table 1).[20] The initial SAR study was aimed at determining the distance between the benzimidazole and arylpiperidine moieties that leads to optimal binding to MCH-R1. Among those tested (**3–6**), compound **4** containing a three-carbon linker showed the most potent MCH-R1 binding activity. When the length of the linker is increased from C-3 (**4**) to C-4 (**5**) and C-5 (**6**), a large decrease in MCH-R1 binding affinity was observed. Interestingly, the C2-linked compound **3** does not bind to MCH-R1. These results indicate that the length of the linker between the benzimidazole and arylpiperidine groups plays a significant role in binding to MCH-R1.

With the optimal linker length determined ($n = 3$), the effects of various substituents on the aryl group at the 2-position of the benzimidazole moiety were investigated. As the results displayed in Table 2 show, introduction of a chlorine group at the *para*-aryl position (**4c**) gives an improved affinity for MCH-R1 ($IC_{50} = 1$ nM) as compared to **4**. However the *ortho*- and *meta*-analogs **4a** and **4b**, have 10- and 5-fold reduced binding affinities, respectively. Independent of their different electronic properties, the trifluoromethyl (**4d**–**4f**) and methoxy (**4g**–**4i**) derivatives display similar structure–activity relationships.

A further exploration of the effects of substituents at the *para* position of aryl group demonstrated that the bromo and phenyl substituted substances, **4k** and **4n**, have high MCH-R1 binding affinities. In contrast, other *para*-substituents such as fluoro **4j**, ethyl **4l**, *i*-propyl **4m**, phenoxy **4o**, and nitrile **4p** have detrimental effects on binding. The effects of disubstitution on the aryl group were investigated next. Incorporation of 2-F and 4-Cl groups (**4s**) resulted in a potency that is comparable to both the unsubstituted compound **4** and the 4-chloro derivative **4c**. Except for 3,4-di-Cl **4r**, disubstituted substrates such as 2,4-di-Cl **4q**, 3,4-di-F **4t**, and 2-Cl-4-F **4u** had low IC_{50} values in the range of 1–4 nM.

Having discovered that *p*-chloro is the optimal substituent on the 2-aryl ring of benzimidazoles, our attention next turned to the anilide moiety in the arylpiperidine part of these compounds. As the data in Table 3 indicate, while placement of an acetanilide group at the *meta*-position (**4c**) leads to excellent MCH-R1 binding affinity, introduction of this group at the *ortho* (**11a**) and *para* (**11b**) positions resulted in a loss of binding. In addition, introduction of a *i*-propyl-anilide moiety at the *meta*-position (**11c**) in place of acetanilide led to a slight reduction in activity. However, the presence of benzoyl anilides such as phenyl (**11d**), tolyl (**11e**), and *m*-chlorophenyl (**11f**) were detrimental to MCH-R1 binding. Additionally, replacement of the anilide group by small substituents such as

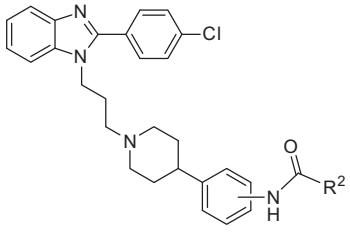
Table 2
Effects of substituents on the 2-aryl group of benzimidazole derivatives



Compound	R^1	MCH-R1 IC_{50}[a,b] (nM)
4	H	2
4a	2-Cl	10
4b	3-Cl	5
4c	4-Cl	1
4d	2-CF_3	50
4e	3-CF3	30
4f	4-CF3	3
4g	2-OMe	747
4h	3-OMe	7
4i	4-OMe	9
4j	4-F	56
4k	4-Br	5
41	4-Et	32
4m	4-*i*-Pr	60
4n	4-Ph	8
4o	4-OPh	42
4p	4-CN	16
4q	2,4-di-Cl	3
4r	3,4-di-Cl	24
4s	2-F-4-Cl	1
4t	3,4-di-F	4
4u	2-Cl-4-F	4

[a] Binding affinities of compounds for MCH-R1 were determined by using competitive binding with Eu-MCH and a TRF assay.
[b] Values are means of at least two measurements.

Table 3
Effects of the anilide group on the arylpiperidine moiety on MCH-R1 binding affinity.



Compound	Position	R^2	MCH-R1 IC_{50}[a,b] (nM)
4c	3-	Me	1
11a	2-	Me	>6000
11b	4-	Me	5380
11c	3-	*i*-Pr	5
11d	3-	Ph	19
11e	3-	4-Me-Ph	300
11f	3-	3-Cl-Ph	213

[a] Binding affinities of compounds for MCH-R1 were determined by using competitive binding with Eu-MCH and a TRF assay.
[b] Values are means of at least two measurements.

fluorine, methoxy, and methyl resulted in a drop in binding affinity (data not shown). These findings indicate that the position and size of the anilide group, which serves as both a H-bonding donor and acceptor, might be critical for binding to MCH-R1.

The metabolic stability of **4c**, which was shown to have the highest MCH-R1 binding affinity, was evaluated. This substance

Table 4
Pharmacokinetic profile of **4c** in rats

Parameter[a]	Value
$t_{1/2}$ (h)	4.3
Oral AUC (mg h/mL)	9.1
iv CL (mL/kg min)	28.3
V_{dss} (L/kg)	6.0
%*F*	99
$Plasma_{3h}$ (ng/mL)[b]	420
$Brain_{3h}$ (ng/g)[b]	160

[a] Determined in rats by administration of 10 mg/kg, iv and po ($n = 3$).
[b] The values are the means for $n = 3$ SD rats. The concentrations were determined at 3 h after 10 mg/kg oral dosing.

displayed good metabolic stability in human and rat liver microsomes (97% and 98% for 30 min, respectively). The pharmacokinetic properties of **4c** are displayed in Table 4. As can be seen by viewing these data, **4c** showed excellent oral bioavailability ($F = 99\%$) with an acceptable clearance (28.3 mL/kg min), half-life (4.3 h) and plasma level. Furthermore, **4c** exhibited moderate brain penetration in rats at 3 h after oral dosing of 10 mg/kg. The hERG affinity of compound **4c** was also determined by utilizing a patch clamp assay. Unfortunately, this compound was found to be a potent inhibitor of the hERG potassium channel ($IC_{50} = 0.003$ μM) and, as a result, it is unsuitable for further development.

In summary, the studies described above led to the discovery of several novel compounds, comprised of linked 2-arylbenzimidazoles and arylpiperidines, which serve as MCH-R1 antagonists. Extensive SAR studies probing substituents on both the aryl group at the 2-position of the benzimidazole and the anilide group, and the length of the chain linking the 2-arylbenzimidazole and arylpiperidine moieties led to the identification of compound **4c**, a substance that is a potent MCH-R1 antagonist with good metabolic stability and favorable pharmacokinetic properties. Further efforts aimed at overcoming the hERG binding problem associated with this compound are now in progress.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2011.02.099.

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