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Design and synthesis of orally efficacious benzimidazoles as melanin-concentrating hormone receptor 1 antagonists

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Abstract—Biaryl urea lead compound **1** was discovered earlier in our MCH antagonist program. Novel benzimidazole analogues with increased chemical stability, devoid of the potential carcinogenic liability associated with a biarylamine moiety, were synthesized and evaluated to be potent MCH R1 antagonists. Two compounds in this series have demonstrated in vivo efficacy in a rodent obesity model.

Melanin-concentrating hormone (MCH), a cyclic 19-amino-acid peptide, was first identified in teleost fish where it appears to regulate color change.[1] The MCH R1 receptor was discovered in 1999.[2] More recently, the MCH R1 receptor has been investigated thoroughly for its possible role in regulating eating behavior in mammals. MCH-deficient mice have reduced body weight and are lean due to hypophagia;[3a] MCH mRNA levels are increased in ob/ob mice and in fasted mice;[3b] transgenic mice overexpressing the MCH gene are susceptible to insulin resistance and obesity;[3c] and disruption of MCH receptor 1 expression resulted in resistance to diet-induced obesity despite hyperphagia.[3d] All these findings suggest that MCH receptor antagonists could be useful for the treatment of obesity. A variety of small molecule MCH R1 antagonists have appeared in the literature.[4,5] Herein, we would like to report the design and synthesis of a series of novel orally efficacious MCH R1 antagonists.

The urea lead **1** was identified earlier in our MCH antagonist program;[6] however, it contains a biarylaniline moiety which was found to be highly mutagenic in the Ames test.[7] In order to circumvent this potential liability, one strategy is to modify the biaryl part.[4c] We reasoned that the biarylaniline N atom is sp^2-like and might be replaced with a vinyl carbon atom. Furthermore, the phenylamide moiety would be substituted with an isosteric benzimidazole skeleton based on our earlier findings.[8] Thus, our design involves two distinctly new elements and is depicted in Figure 1.

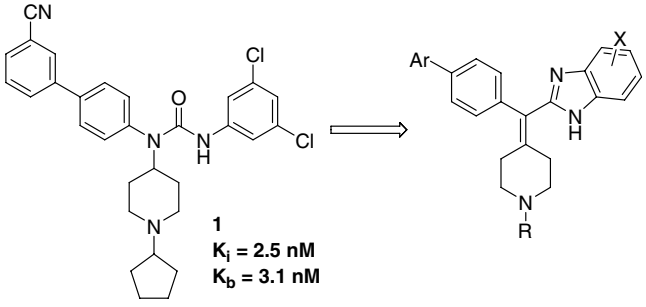

Figure 1. Lead compound and the design of benzimidazole analogues.

The first-generation synthetic route started with substituted phenylenediamines (Scheme 1). The SEM-protected benzimidazole **2**, obtained in two steps from commercially available diamines, was coupled with the known ketone **3**[9] to give the tertiary alcohol **4**. Chlorination of **4** followed by elimination with pyridine afforded the desired tetrasubstituted alkene **5** as the major product and some endo-alkene isomer, which can be partially

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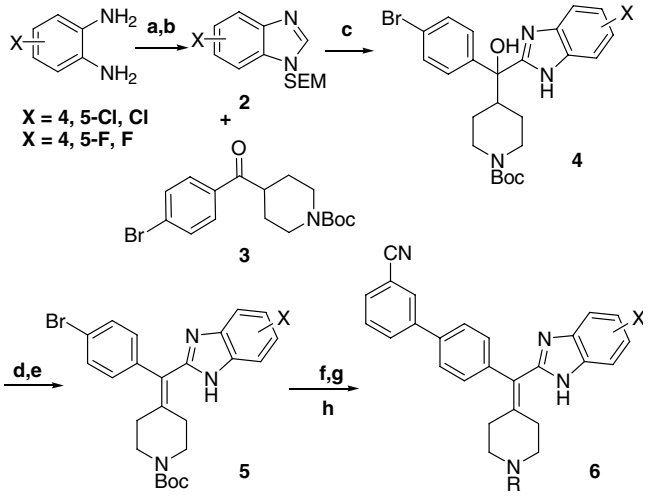


Scheme 1. Reagents and conditions: (a) HCO_2H, HCl, reflux, 97% (X = 4,5-Cl,Cl); (b) NaH, $Me_3SiCH_2CH_2OCH_2Cl$, DMF, rt, 62%; (c) *n*-BuLi, THF, ketone, 93%; (d) $SOCl_2$, pyridine, 94%; (e) pyridine, 150 °C, 43%; (f) TFA–DCM (1:1), rt, 100%; (g) 3-cyanophenylboronic acid, $Pd(PPh_3)_4$, 2N Na_2CO_3, toluene–MeOH (1:1), 58%; (h) aldehyde or ketone, $NaBH(OAc)_3$, DCM or Ac_2O–TEA.

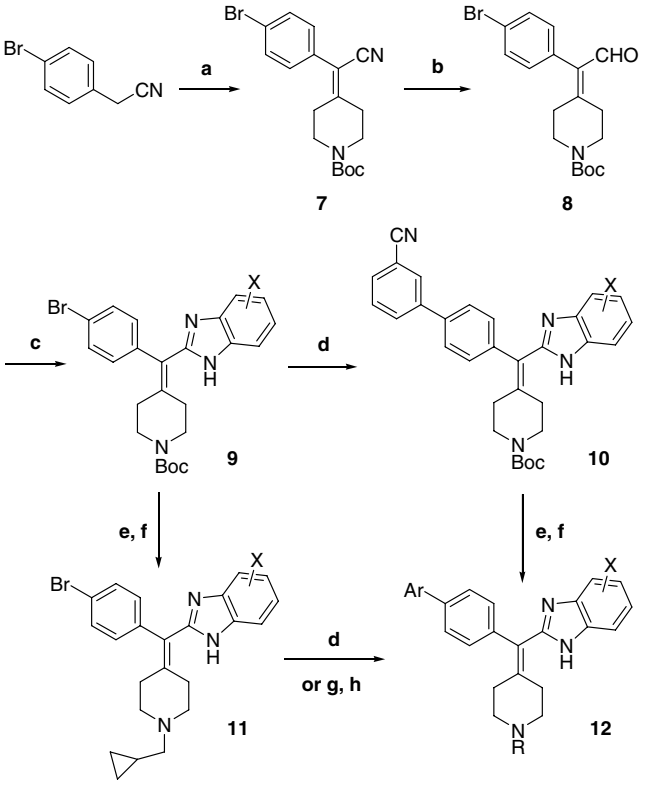
converted to **5** under basic conditions.[10] Suzuki coupling installed the required 3-cyanophenyl moiety. Deprotection of the *N*-Boc group and subsequent derivatization of the revealed NH by conventional methods provided the N-substituted piperidine analogues **6a**–**c**.

A more efficient synthesis is depicted in Scheme 2. Condensation of 4-bromobenzonitrile with 1-Boc-4-piperidone gave compound **7**. Selective reduction with DIBAL afforded aldehyde **8**,[11] which was treated with diamines in the presence of sodium bisulfite to give benzimidazole **9**.[12] From this advanced intermediate, a reaction sequence (d-e-f), namely: (i) Suzuki coupling, (ii) deprotection of the *N*-Boc, and (iii) N-substitution via parallel synthesis (reductive amination or acylation), provided the final targets **12**. Alternatively, removal of the *N*-Boc group first, followed by reductive alkylation, gave the bromo-compound **11**, which set the stage for another parallel synthesis to explore the SAR of the biaryl moiety (e-f-d). Suzuki coupling of **11** with various phenylboronic acids furnished the targets **12**. In cases where the boronic acids were not easily available, compound **11** was converted to its pinacolboronic ester[13] and then coupled with appropriate aryl bromides to give the final analogues (**12d**, **12e**). Through these flexible reaction sequences, we developed SAR in both directions handily.

The analogues mentioned above were evaluated in a radioligand binding assay as described in the preceding article[8] and the results are shown in Table 1.

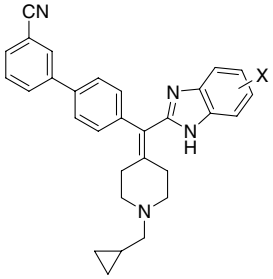
As shown in Table 1, compound **12c** displayed single-digit nanomolar affinity to the MCH R1 receptor. These initial results prompted us to focus on the 5-F–6-CF_3 substituents on the benzimidazole and explore the SAR of the biaryl part. As revealed in Table 2, 3-cyanophenyl remained optimal for MCH R1 binding, consistent with our earlier findings.[8] Small changes such as those in compounds **12d** and **12e** were also tolerated. Other substituted analogues were less potent.

The SAR of the piperidine N-substituent is summarized in Table 3. The N–H analogue **12a** was equally potent as



Scheme 2. Reagents and conditions: (a) 1-Boc-4-piperidinone, EtONa, EtOH, reflux, 87%; (b) DIBAL, DCM, −78 °C, 38%; (c) substituted 1,2-diphenylamines, 40% $NaHSO_3$, EtOH, 27–40%; (d) 3-cyanophenylboronic acid, $Pd(PPh_3)_4$, 2N Na_2CO_3, toluene–MeOH (1:1), reflux, 90%; (e) TFA–DCM (1:1), 100%; (f) aldehyde or ketone, $NaBH(OAc)_3$, DCM or Ac_2O–TEA; (g) bispinacolatodiboron, KOAc, $PdCl_2(dppf)_2$, DMSO, 100 °C, 47%; (h) ArBr, $Pd(PPh_3)_4$, 2N Na_2CO_3, toluene–MeOH (1:1), 120 °C, 10 min (microwave).

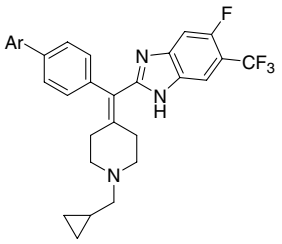
Table 1. SAR of substituents at the benzimidazole phenyl ring[a]

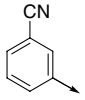
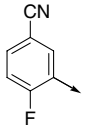
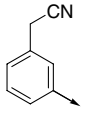
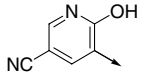
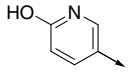
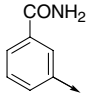
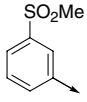
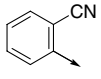


Compound	X	MCH K_i (nM)
6a	5,6-Cl_2	15
6b	5,6-F_2	52
6c	4,6-Cl_2	87
12b	5-CN	133
12c	5-F, 6-CF_3	3.5

[a] Mean values (n = 3). h-MCH R1.

Table 2. SAR of modification of biaryls[a]



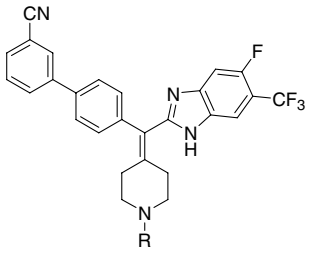
Compound	Ar	MCH K_i (nM)
12c		3.5
12d		3.9
12e		10.3
12f		26
12g		99
12h		174
12i		95
12j		77
12k		132
12l		464

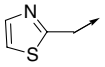
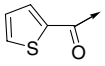
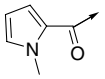
[a] Mean values ($n = 3$). h-MCH R1.

the cyclopropylmethyl analogue **12c**. Polar substituents as in **12e** and **12f** were also tolerated, although slightly less potent. It is noteworthy that some non-basic piperidine analogues such as amides, ureas, and sulfonamides retained quite good activity (**12p–x**).

Considering the potential metabolic instability of the alkene moiety, we replaced it with a cyclopropane isostere to generate cyclopropyl benzimidazole analogues as depicted in Scheme 3.[14] To this end, the α,β-unsaturated nitrile **7** was treated with trimethylsulfoxonium iodide in the presence of base to give compound **13** in excellent yield.[15] Following similar reaction steps as per Scheme 2 led to compounds **15a–i**.

Table 3. SAR of substituents at the piperidine nitrogen[a]



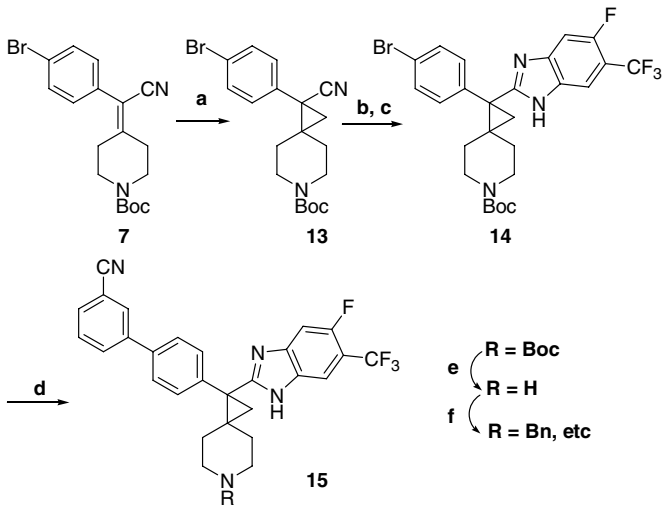
Compound	R	MCH K_i (nM)
12a	H	3.6
12c	Cyclopropylmethyl	3.5
12m	$HOCH_2CH_2$	7.2
12n	NH_2COCH_2	15.5
12o		45
12p	MeCO	31
12q		21
12r		20
12s		10.1
12t	Me_2NCO	37
12u	Et_2NCO	22
12v	$MeSO_2$	71.4
12w	*i*-$PrSO_2$	129
12x	Me_2NSO_2	64

[a] Mean values ($n = 3$). h-MCH R1.

As shown in Table 4, the cyclopropyl benzimidazole analogues (racemic) were very potent MCH R1 ligands, and followed a similar SAR trend as corresponding alkene-linked countparts, confirming the isosteric equivalence of cyclopropyl and ethylene groups in this series.

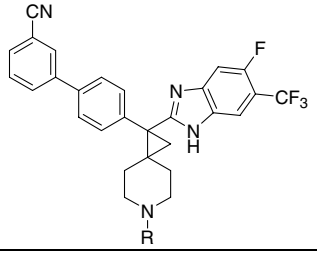
Several potent compounds were selected for pharmacokinetic investigation in rats[16] and a mouse ex vivo binding assay.[17,18] The profiles are reported in Table 5. The alkene analogues (**6a**, **12c**, **12d**, **12p**, and **12t**) exhibited very good exposure in rats, indicating the tetra-substituted olefin bonds are metabolically quite stable. The lower AUC of cyclopropyl analogue **15b** compared to compound **6a** was a surprise and may be a result of poorer absorption relative to the olefinic analogue. All the compounds showed good to excellent ex vivo binding in mice.

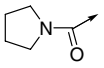
Compounds **6a** and **12c** have been demonstrated to be full MCH R1 antagonists in a functional assay (with K_b values of 70 and 25 nM, respectively).[19] More importantly, compounds **6a** and **12c** were chosen for further in vivo study and, as seen in Table 6 both compounds produced a robust reduction of food intake after oral dosing at 30 mg/kg in a fasted DIO mouse model[20,21].



Scheme 3. Reagents and conditions: (a) $Me_3S(O)^+I^-$, *t*-BuOK, DMSO, 97%; (b) DIBAL, DCM, −78 °C, 27%; (c) 1,2-diamino-4-fluoro-5-trifluoromethylbenzene, 40% $NaHSO_3$, EtOH, 94%; (d) $Pd(PPh_3)_4$, 2N Na_2CO_3, 3-cyanophenylboronic acid, toluene–MeOH (1:1), 110 °C (microwave, 18 min), 73%; (e) HCl in ether, 87%; (f) aldehyde or ketone, $NaBH(OAc)_3$, DCM or Ac_2O–TEA.

Table 4. SAR of cyclopropane-linked benzimidazole analogues[a]



Compound	R	MCH K_i (nM)
15a	H	1.7
15b	Cyclopropylmethyl	4.8
15c	Bn	10.3
15d	$Et_2NCH_2CH_2$	15
15e	$HOOCCH_2$	41
15f	Me_2NCO	32
15g	Et_2NCO	221
15h		44
15i	*i*-$PrSO_2$	67

[a] Mean values ($n = 3$). h-MCH R1.

Table 5. Rat Pharmacokinetics and mouse MCH receptor ex vivo binding of selected compounds[a,b]

Compound	$AUC_{0-6\ h}$[a] (ng/mL h)	Ex vivo binding[b]	
		6 h	24 h
6a	6637	68 ± 16	54 ± 13
12c	2882	96 ± 23	84 ± 20
12d	3001	92 ± 22	80 ± 18
12p	5252	48 ± 11	NT
12t	1292	50 ± 12	NT
15b	1032	74 ± 18	NT

[a] Data are from pooled samples from two mice ($n = 2$; dosed at 10 mg/kg, po) in cassette-accelerated rapid rat protocol as described in Ref. 16.

[b] Expressed as a percent of inhibition of MCH-ADO binding relative to vehicle control ± SEM ($n = 3$; dosed at 30 mg/kg, po).

Table 6. In vivo efficacy in DIO mice[a]

Compound	% Inhibition at indicated time		
	2 h	6 h	24 h
6a	37.4 ± 6.5	41.8 ± 5.6	26.8 ± 7.2
12c	31.0 ± 5.6	32.6 ± 5.4	18.6 ± 5.5

[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.

In summary, we have designed and synthesized potent novel benzimidazole MCH R1 antagonists. Among them, compounds **6a** and **12c** demonstrated good pharmacokinetics in rats and oral efficacy in a DIO mouse model for weight loss.

Acknowledgments

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17. Animals were administered compound (30 mk/kg) 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)[18] 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. Hawes, B. E.; Green, B.; O'Neill, K.; Fried, S.; Graziano, M. P. *Endocrinology* **2000**, *141*, 4524.
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19. Inhibition of MCH-mediated Ca^{2+} influx into cells expressing hMCH-R1 via FLIPR assay. Affinity at h-MCH-R_2 > 3 μM for all compounds.
20. 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, 6, and 24 h after food presentation.
21. Data from our ex vivo binding studies were used to prioritize compounds for in vivo evaluation. Receptor occupancies $\sim \geqslant 60\%$ were predictive of activity in the DIO mouse model. Furthermore, receptor occupancy at 24 h suggested a significant potential for duration of action. Further correlation of receptor occupancy and in vivo efficacy was not rigorously established.