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Bioorganic & Medicinal Chemistry Letters 16 (2006) 3668–3673
Bioorganic & Medicinal Chemistry Letters

Synthesis and structure–activity relationships of piperidine-based melanin-concentrating hormone receptor 1 antagonists

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Received 9 March 2006; revised 21 April 2006; accepted 21 April 2006
Available online 11 May 2006

Abstract—Isosteric replacement of the urea group of lead compound **1** led to novel substituted piperidine phenylamide analogues. SAR on the electron-induced effects of various linkers as well as substituents on the phenyl rings and the piperidine nitrogen has been investigated. Many single-digit nanomolar MCH R1 antagonists have been identified from this series.

Melanin-concentrating hormone (MCH), a cyclic 19-amino-acid neuropeptide, is expressed exclusively within the lateral hypothalamus and has been regarded as an appetite-stimulating agent in the past decade.[1] The recent discovery of the G-protein-coupled MCH receptor 1 (MCH R1) has prompted much interest in developing MCH receptor antagonists for the treatment of obesity.[2,3] Several lines of pharmacologic evidence indicated the important role of MCH on food intake and body weight: injection of MCH into the lateral ventricles of rats resulted in increased food consumption;[4a] disruption of melanin-concentrating hormone receptor 1 expression leads to hyperphagia and resistance to diet-induced obesity;[4b] transgenic mice overexpressing the MCH gene are susceptible to insulin resistance and obesity;[4c] and mice lacking MCH hormone are hyperphagic and lean.[4d] A variety of small molecule MCH R1 antagonists have been disclosed in the literature.[5,6] Herein we would like to report the synthesis and SAR development of a series of piperidine-based phenylamide MCH R1 antagonists.

Urea compound **1** emerged as a lead compound for our MCH R1 antagonist program.[5d] In order to explore potential novel linkers and structural requirements, we substituted an amide group for the urea moiety (L = CH_2). Moreover, for convenience of synthesis, heteroatom linkers (L = N or O) were also inserted into the chain as shown in Figure 1.

The syntheses of the phenylamide analogues are depicted in Scheme 1. Compound **2** was converted to the ester **3** by the following steps: (i) reductive alkylation; (ii) reduction of the nitrile to an aldehyde; and (iii) Horner–Emmons elongation to give the α,β-unsaturated ester **3**. Hydrogenation of the olefin followed by bromination of the phenyl ring gave compound **4**. After installation of the 3-cyanophenyl moiety by Suzuki reaction, treat-

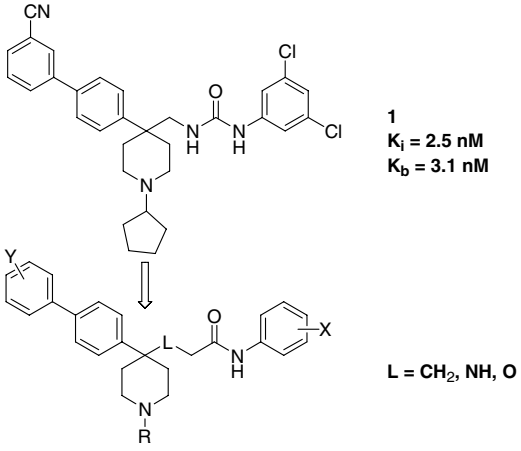

Figure 1. Lead compound and isosteric analogues.

Keywords: Structure–activity relationship; Melanin-concentrating hormone receptor 1; Antagonist.
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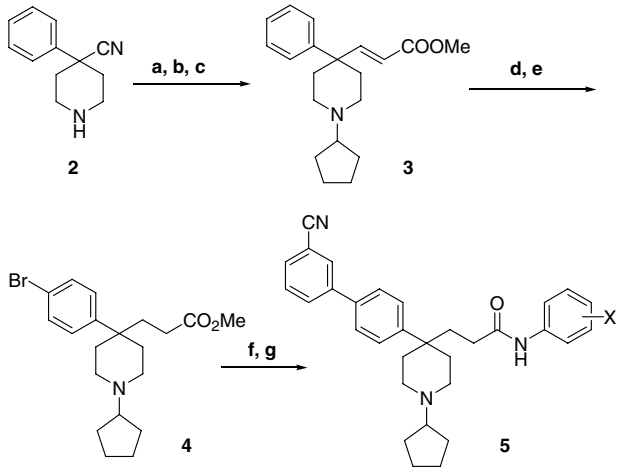
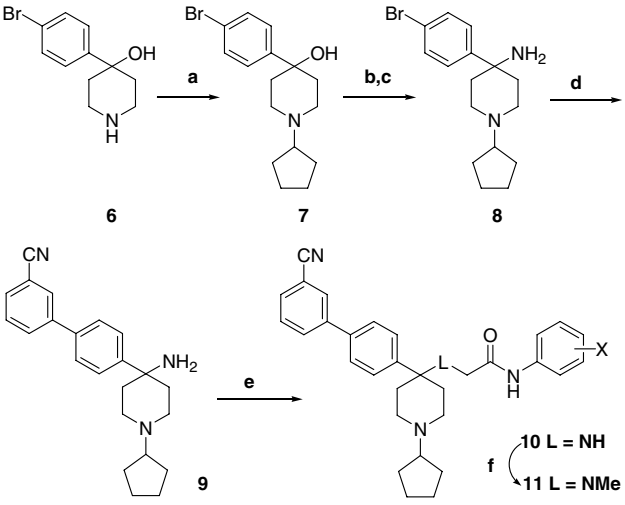
doi:10.1016/j.bmcl.2006.04.061



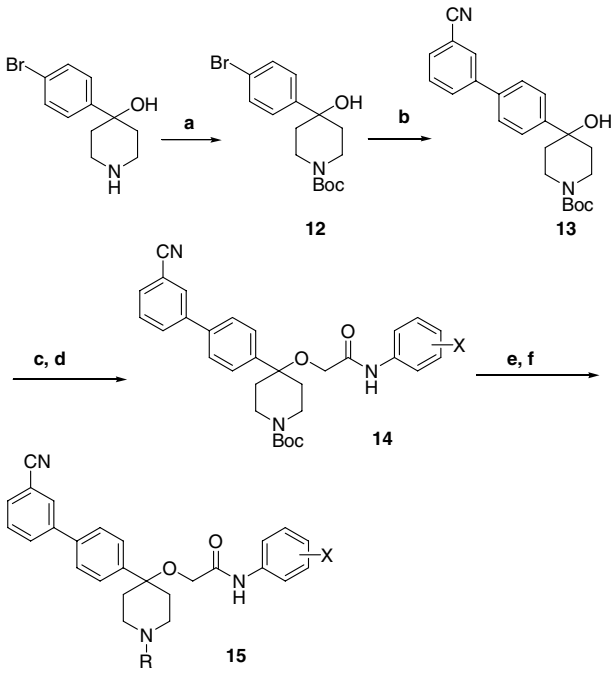
Scheme 1. Reagents and conditions: (a) cyclopentanone, $NaBH(OAc)_3$, DCM; (b) DIBAL, DCM, −78 °C to room temperature; (c) $(MeO)_2P(O)CH_2CO_2Me$, NaH, 50% in 3 steps; (d) $Pd(OH)_2/C$, HCO_2NH_4, MeOH, 96%; (e) 3,5-dibromohydantoin, $MeSO_3H$, DCM, 80%; (f) 3-cyanophenylboronic acid, $Pd(PPh_3)_4$, 2 N Na_2CO_3, toluene–MeOH (1:1), reflux, 91%; (g) anilines, 2 equiv *n*-BuLi, THF, 40–70%.

ment of the ester with various anilines in the presence of base gave the final analogues **5**.[7]

The corresponding N-linked amide analogues **10** and **11** were prepared according to Scheme 2. The piperidine alcohol **7**, derived from readily available **6**, was converted to the primary amine **8** in two steps.[8] The bromo substituent was exchanged to a 3-cyanophenyl group through Suzuki coupling; the amine **9** was then alkylated with a variety of 2-bromoacetamides, which are easily prepared by treatment of 2-bromoacetyl bromide with various anilines.[9] Finally, the N-Me-linked analogues **11** were obtained by reductive alkylation of **10** with formaldehyde.



Scheme 2. Reagents and conditions: (a) cyclopentanone, $NaBH(OAc)_3$, DCM, room temperature, 82%; (b) concd H_2SO_4, MeCN, 60%; (c) 2 N HCl, reflux, 98%; (d) 3-cyanophenylboronic acid, $Pd(PPh_3)_4$, 2 N Na_2CO_3, toluene–MeOH (1:1), reflux, 85%; (e) 2-bromoacetamides, K_2CO_3, MeCN, 60 °C, 30–50%; (f) 37% aqueous HCHO, $NaBH(OAc)_3$, DCM.

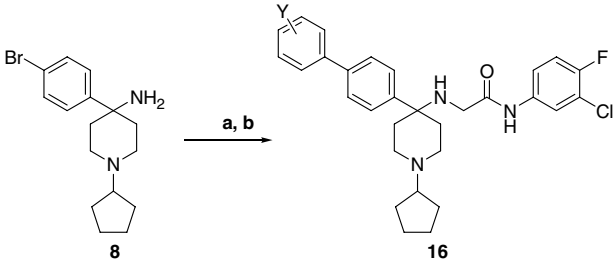


Scheme 3. Reagents and conditions: (a) $(Boc)_2O$, MeOH, 100%; (b) 3-cyanophenylboronic acid, $Pd(PPh_3)_4$, 2 N Na_2CO_3, toluene–MeOH (1:1), reflux, 56%; (c) KH, $BrCH_2COOH$, 92%; (d) anilines, DCC, DMAP, THF, 50–80%; (e) TFA–DCM (1:1), 53–85%; (f) aldehydes or ketones, $NaBH(OAc)_3$, DCM.

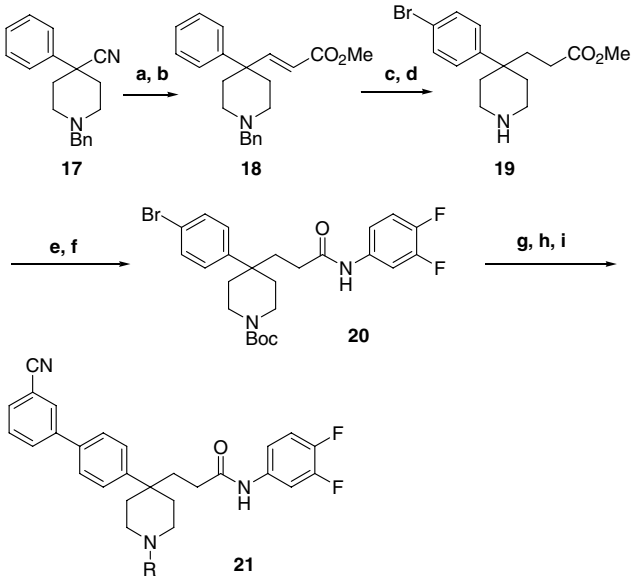
Scheme 3 shows the synthesis of the O-linked analogues **15**. Commercially available 4-(4-bromophenyl)-4-piperidinol was converted to **13** by treatment with Boc_2O and subsequent Suzuki coupling with 3-cyanophenylboronic acid. Treatment of **13** with potassium hydride followed by 2-bromoacetic acid gave an acid intermediate,[10] which in turn was coupled with various anilines in the presence of DCC to afford the O-linked amides **14**. Deprotection of *N*-Boc followed by conventional derivatization of the piperidine NH gave final targets **15**.

In conjunction with the SAR of the right side amides, a series of biaryls of the left side was explored by parallel synthesis utilizing intermediate **8** (Scheme 4).

Finally, by altering the sequence of reactions used previously, we could explore the SAR of the piperidine N-substituent as shown in **21** (Scheme 5).



Scheme 4. Reagents and conditions: (a) 3-chloro-4-fluorophenyl 2-bromoacetamide, K_2CO_3, 31%; (b) appropriate boronic acids, $Pd(PPh_3)_4$, 2 N Na_2CO_3, toluene–MeOH (1:1), reflux.



Scheme 5. Reagents and conditions: (a) DIBAL, DCM, 0 °C to room temperature, 48%; (b) $(MeO)_2P(O)CH_2CO_2Me$, NaH, THF, 85%; (c) $Pd(OH)_2/C$, HCO_2NH_4, MeOH, 60 °C, 97%; (d) 3,5-dibromohydantoin, $MeSO_3H$, DCM, 54%; (e) $(Boc)_2O$, MeOH, 70%; (f) anilines, 2 equiv *n*-BuLi, THF; (g) 3-cyanophenylboronic acid, $Pd(PPh_3)_4$, 2 N Na_2CO_3, toluene–MeOH (1:1), reflux, 60%; (h) TFA–DCM (1:1); (i) reductive alkylation or other derivatization.

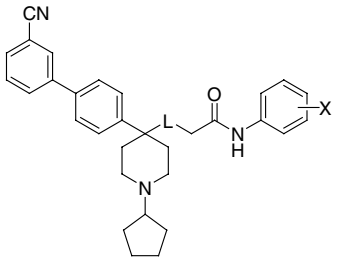
The compounds described above were evaluated in a radioligand binding assay.[11] As revealed in Table 1, within each series of same linker (L), electron-withdrawing groups (either 3,4- or 3,5-disubstituents) on the amide phenyl ring showed more or less similar potency. In terms of the effect of various linkers, the order is as follows: O > NH = NMe > CH_2 (based on our full data set), reflecting their decreased electronegativity and therefore lower acidity of the attached amide N–H moiety. These results indicated that the amide N–H moiety serves as a hydrogen-bond donor when binding to the MCH R1 receptor.[12]

In terms of the SAR of the biaryl part, more than 50 compounds were prepared, and selected data are reported in Table 2. It is clear that analogues with 3-substituents are more active than those bearing 2- or 4-substituents. Within the 3-substituted series, the 3-cyano group remained the best, consistent with earlier findings for the related urea series as for compound **5c** (K_i = 30 nM).[5d]

The piperidine N-substituent effects can be seen in Table 3, exemplified by the C-linked amide analogues. Small alkyl groups are well tolerated, although cyclopropylmethyl is the best (**21c**). Interestingly, some analogues bearing a nonbasic piperidine moiety are also quite potent (**21f** and **21i**).

In order to further improve the potency, a homologated series was prepared (Scheme 6). Condensation of 4-bromophenylacetonitrile with 4-piperidinone gave compound **22**. Sequential reduction of the olefin and then the nitrile group using DIBAL afforded an aldehyde

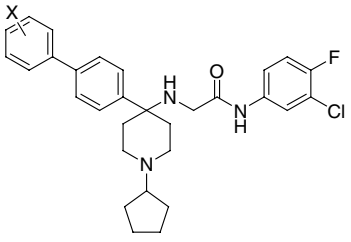
Table 1. SAR of substituents on the amide phenyl ring[a,b]



Compound	L	X	MCH K_i (nM)
5a	CH_2	3,5-Cl_2	42
5b	CH_2	3-CF_3-4-Cl	128
5c	CH_2	3-Cl-4-F	30
5d	CH_2	3-5-F_2	40
5e	CH_2	3,4-F_2	13
10a	NH	3,5-Cl_2	3
10b	NH	3-CF_3-4-Cl	23
10c	NH	3-CF_3-4-F	16
10e	NH	3-Cl-4-F	3
10f	NH	3-5-F_2	3
11a	NMe	3,5-Cl_2	9
11b	NMe	3-CF_3-4-Cl	16
11c	NMe	3-CF_3-4-F	18
11d	NMe	3-Cl-4-F	4
11e	NMe	3-5-F_2	6
15a	O	3,5-Cl_2	2
15b	O	3-CF_3-4-Cl	49

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

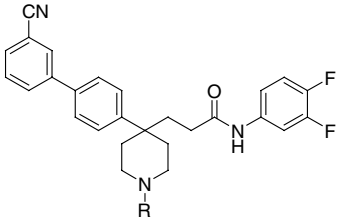
Table 2. SAR of substituents on the biaryl phenyl ring[a]



Compound	X	MCH K_i (nM)
16a	H	241
16b	4-CN	523
16c	4-CF_3	3247
16d	4-Cl	1428
16e	4-F	180
16f	3-CF_3	281
16g	3-Cl	63
16h	3-OCF_3	76
16i	3-OMe	77
16j	3-F	99
16k	3-CHO	21
16l	2-Cl	690
16m	2-F	178
16n	3,4-Cl_2	2162
16o	3,5-Cl_2	786
16p	3-5-F_2	141
16q	2,5-Cl_2	52
16r	2,6-Cl_2	1667

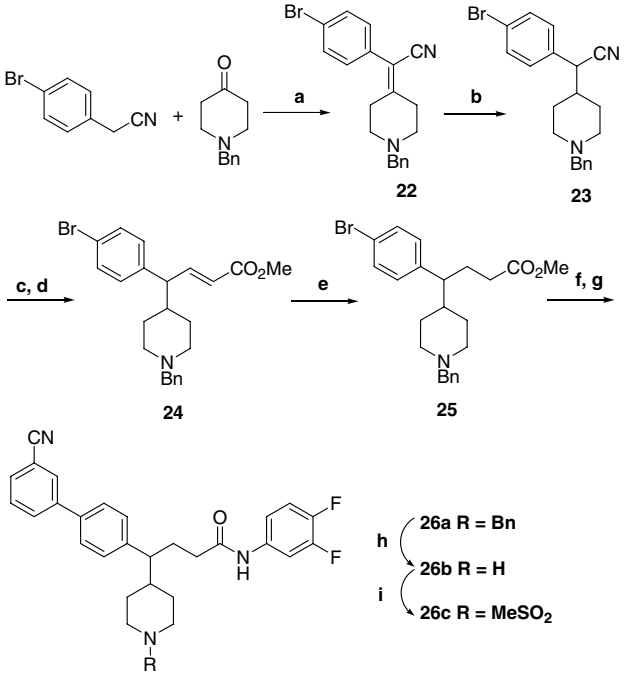
[a] See Table 1 notes.

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



Compound	R	MCH K_i (nM)
21a	Boc	51
21b	H	25
21c	Cyclopropylmethyl	8
21d	Cyclobutyl	19
21e	Cyclopentyl	13
21f	MeCO	61
21g	$MeSO_2$	190
21h	EtOCO	249
21i	Et_2NCO	45
21j	Et_2NSO_2	193

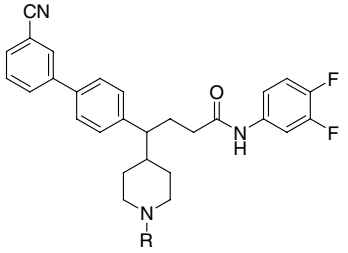
[a] See Table 1 notes.



Scheme 6. Reagents and conditions: (a) EtONa, EtOH, reflux, 56%; (b) 1.2 equiv DIBAL, DCM, −78 °C, 65%; (c) 1.5 equiv DIBAL, DCM, −50 °C to room temperature, 85%; (d) $(MeO)_2P(O)CH_2CO_2Me$, NaH, THF, 50%; (e) H_2, Rh/Al_2O_3, room temperature, 95%; (f) $Pd(PPh_3)_4$, 3-cyanophenylboronic acid, 2 N Na_2CO_3, toluene–MeOH (1:1), reflux, 65%; (g) 3,4-difluorophenylaniline, Me_3Al, toluene, reflux, 55%; (h) 1—$ClCO_2C(Cl)HMe$, DCE, reflux; 2—MeOH, reflux; (i) $MeSO_2Cl$, TEA, DCM.

intermediate.[13] Horner–Emmons elongation followed by selective hydrogenation provided the ester intermediate **25**, which was coupled with 3-cyanophenyl boronic acid under Suzuki conditions to give compound **26a**. Deprotection revealed the piperidine NH, and sulfonylation gave compound **26c**.

Table 4. SAR of homologous amide analogues[a]



Compound	R	MCH K_i (nM)
26a	Bn	1
26b	H	1.2
26c	$MeSO_2$	26

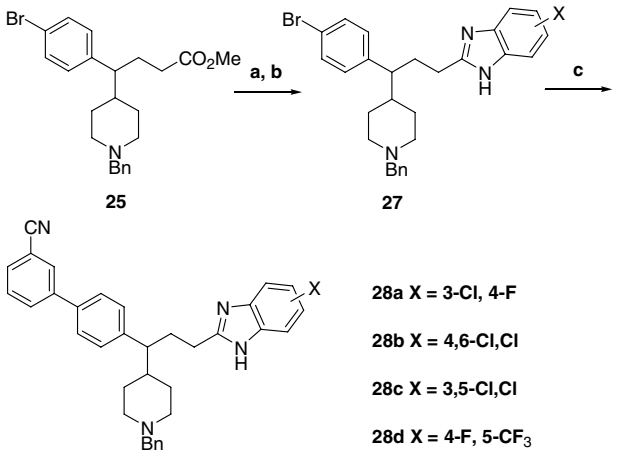
[a] See Table 1 notes.

As shown in Table 4, the homologated compounds are more potent than the 4,4-disubstituted analogues.

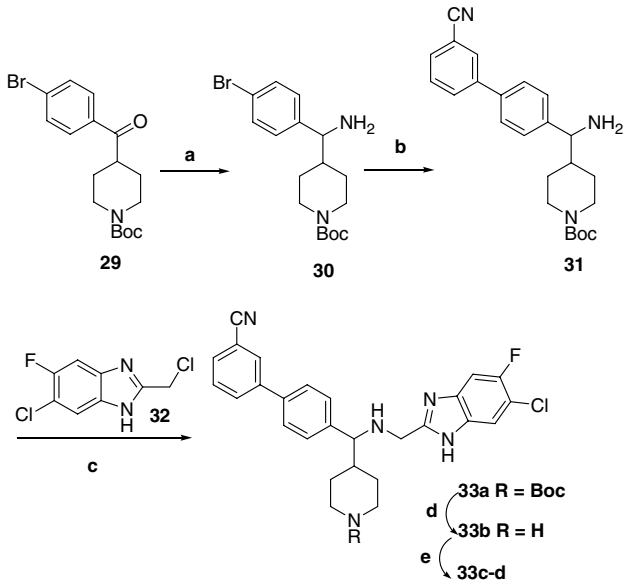
Imidazole and benzimidazole have been used as isosteric replacements for an amide moiety to circumvent the potential instability of amide bond.[14] Thus, several benzimidazole analogues were prepared (Scheme 7). The ester intermediate **25** was reduced to an aldehyde intermediate, which was treated with diamines to form benzimidazole compounds **27**.[15] Suzuki coupling gave compounds **28a**–**28d**.

The NH-linked benzimidazole analogues **33a**–**d** were synthesized according to Scheme 8. The known ketone **29**[16] was first converted to the amine **30** by reductive amination. After Suzuki reaction, the resulting amine was treated with the benzimidazole compound **32**[17] to give compound **33a**. Deprotection revealed the NH moiety, and further reductive alkylation gave compounds **33c** and **33d**.

As can be seen from Tables 5 and 6, the benzimidazole analogues showed quite good potency, although not as

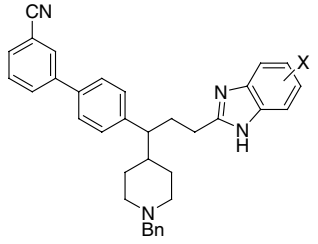


Scheme 7. Reagents and conditions: (a) DIBAL, DCM, −78 °C, 95%; (b) substituted 1,2-phenyldiamines, $Na_2S_2O_5$, DMA, 100 °C, 33%; (c) $Pd(PPh_3)_4$, 2 N Na_2CO_3, 3-cyanophenylboronic acid, toluene–MeOH (1:1), reflux, 61%.



Scheme 8. Reagents and condition: (a) NH_4OAc, $NaCNBH_3$, MeOH, room temperature, 90%; (b) 3-cyanophenylboronic acid, $Pd(PPh_3)_4$, 2 N Na_2CO_3, toluene–MeOH (1:1), reflux, 57%; (c) K_2CO_3, MeCN, room temperature, 60%; (d) TFA–DCM (1:1), 100%; (e) cyclopropylcarboxyaldehyde or cyclopentanone, $NaBH(OAc)_3$, DCM.

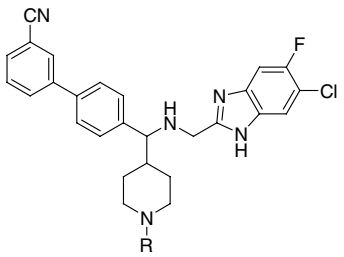
Table 5. SAR of benzimidazole analogues[a]



Compound	X	MCH K_i (nM)
28a	3-Cl, 4-F	46
28b	4,6-Cl,Cl	53
28c	3,5-Cl,Cl	26
28d	4-F,5-CF_3	92

[a] See Table 1 notes.

Table 6. SAR of benzimidazole analogues (Cont'd)[a]



Compound	R	MCH K_i (nM)
33a	Boc	48
33b	H	20
33c	Cyclopentyl	39
33d	Cyclopropylmethyl	14

[a] See Table 1 notes.

potent as their corresponding amide analogues. These results are very encouraging and will be exploited in future designs.[18]

In summary, we have successfully replaced the urea moiety of our lead structure, **1**, with isosteric amide and benzimidazole groups to generate novel MCH antagonists. Extensive SAR exploration with various linkers as well as the substituent effects led to the discovery of many potent and selective MCH-R1 antagonists, such as compounds **10a–f**, **11a–e**, and **26a–b**.

Acknowledgments

We thank Dr. Michael P. Graziano, Dr. Margaret Van Heek, and Dr. John W. Clader for their support and helpful discussions. We thank Dr. Briendra Pramanik's group and Dr. Tse-Ming Chan's group for analytical support.

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11. 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 reactions 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.
12. Simple alkylation of the amide nitrogen resulted in dramatic loss of potency. The corresponding amide N-Me derivatives of compounds **5a** and **10e** are inactive (K_i = 778 nM, 2038 nM, respectively). One N-Me derivative of benzimidazole analogue from closely related series is also inactive (K_i = 1186 nM).[19]
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