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Discovery and SAR of 4-amino-2-biarylbutylurea MCH 1 receptor antagonists through solid-phase parallel synthesis

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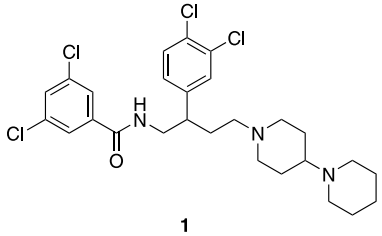
Abstract—-4-Amino-2-arylbutylbenzamides such as **1** were identified as micromolar MCH 1 receptor (MCH1R) antagonists via screening using a scintillation proximity assay based on [^{125}I]-MCH binding to recombinant, human MCH1R. Subsequent lead optimization efforts using solid-phase parallel synthesis resulted in the defined structure–activity relationships and the identification of 4-amino-2-biarylbutylureas, such as **11g**, as potent single digit nanomolar MCH1R antagonists.

Melanin-concentrating hormone (MCH) is a cyclic 19-amino-acid neuropeptide expressed broadly throughout the brain, with the highest concentration located in the lateral hypothalamus and zona incerta regions.[1a] It has been demonstrated that MCH plays an important role in the central regulation of food intake and energy homeostasis through the following studies: central administration of MCH in mice stimulates food intake while fasting results in an increase in MCH expression;[1b] MCH knockout mice are hypophagic and leaner than wild-type mice but otherwise healthy;[1c] and transgenic mice over-expressing MCH are susceptible to obesity and insulin resistance.[1d]

MCH binds and activates two distinct receptors in the brain, MCH1R and MCH2R, both of which belong to the rhodopsin superfamily of G-protein-coupled receptors (GPCRs), but which have low (38%) sequence homology to one another.[2,3] MCH1R is present in all mammals whereas MCH2R is found only in ferrets, dogs, rhesus monkeys, and humans but not in rodents and lagomorphs. More recently, it has been demonstrated that MCH1R knockout mice are lean, hyperphagic but hyperactive and resistant to diet-induced obesity, strongly implicating MCH1R in playing a critical role in the regulation of food intake and energy homeostasis.[4] However, the physiological function of MCH2R has not been established.

Based on the evidence implicating MCH1R in the control of feeding behavior and energy expenditure, the development of potent and selective MCH1R antagonists as new therapeutics for the treatment of obesity has become an attractive field of research. A number of structurally diverse and small molecule MCH1R antagonists have emerged over the past few years.[5,6] Some of these antagonists have been further demonstrated to show in vivo efficacy in several animal models of body weight regulation and feeding behavior.[6a,6b,6m,6n] In this article, we describe our efforts in the discovery of novel 4-amino-2-biarylbutylureas as highly potent MCH1R antagonists by using solid-phase parallel synthesis.

Initial screening for MCH1R antagonists, using a scintillation proximity assay (SPA) that is based on



1
MCH1R K_i = 4.1 μM

Keywords: MCH; MCH1R antagonists; Obesity; Solid-phase parallel synthesis.
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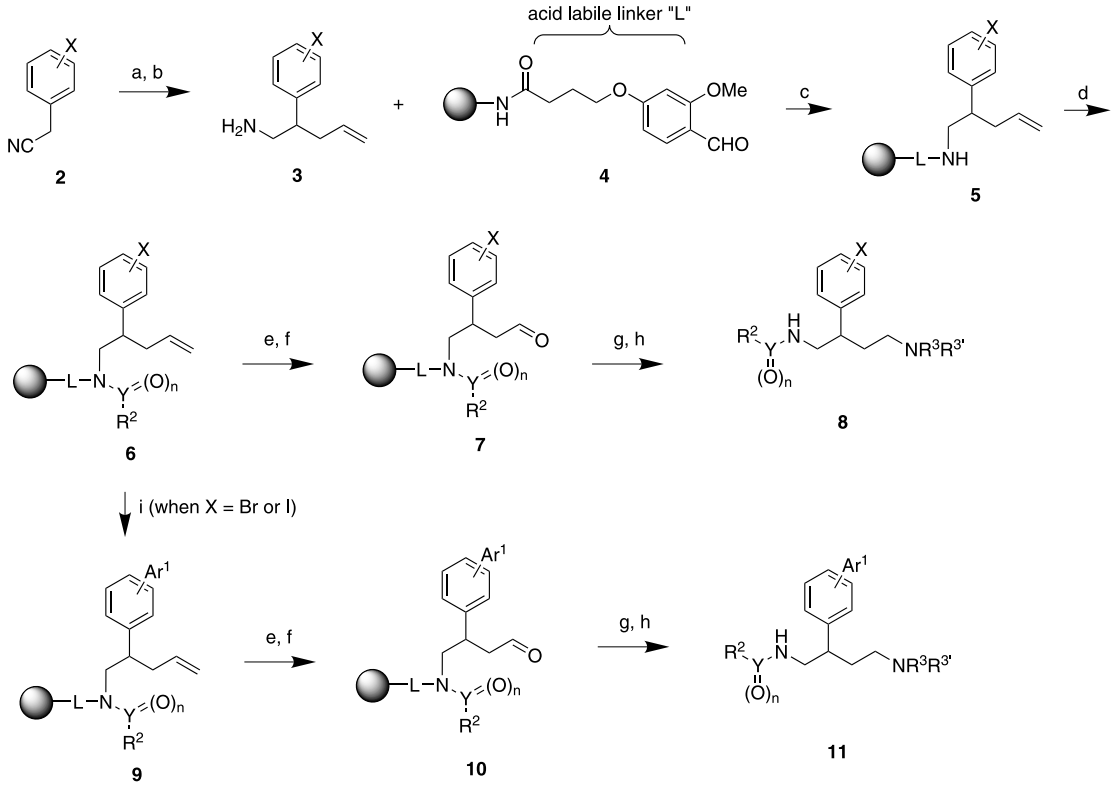


Scheme 1. Solid-phase synthesis of parallel optimization libraries **8** and **11**. Reagents and conditions: (a) LDA, allyliodide, THF, −78 °C; (b) $LiAlH_4$, H_2SO_4, THF; (c) $Na(OAc)_3BH$, $ClCH_2CH_2Cl$; (d) R^2COCl (or R^2NCO, R^2OCOCl, R^2SO_2Cl), pyridine, CH_2Cl_2; (e) OsO_4, NMMO, acetone, H_2O; (f) $NaIO_4$, acetone, H_2O; (g) $R^3R^{3'}NH$, $Na(OAc)_3BH$, $ClCH_2CH_2Cl$; (h) TFA, CH_2Cl_2; (i) $Ar^1B(OH)_2$, $Pd(PPh_3)_4$, K_2CO_3, DMF, 70 °C.

[^{125}I]-MCH binding to membranes prepared from CHO cells that express human MCH1R, resulted in the identification of a series of 4-amino-2-(3,4-dichlorophenyl)-butylbenzamides such as **1** (MCH1R, K_i = 4.1 μM) with potencies in the micromolar range.

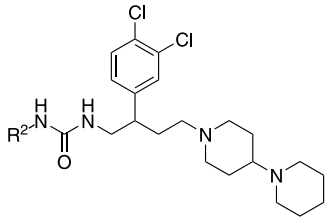
To explore the SAR around compound **1** and to optimize its potency, parallel libraries **8** and **11** (Scheme 1) were designed to allow systematic variations of the three regions of compound **1**: variation of the 3,4-dichlorophenyl group in the center with various aryl and biaryl groups; variation of the 3,5-dichlorobenzamide substituent on the left-hand side with diverse amides, sulfonamides, ureas, and carbamates; and variation of the 4-piperidylpiperidyl unit on the right-hand side with various secondary and tertiary amines.

Scheme 1 shows the synthesis of libraries **8** and **11**. First, the requisite 2-aryl-pent-4-enylamine scaffold **3** was prepared via treatment of various commercially available arylacetonitriles **2** with LDA and allyliodide followed by reduction using $LiAlH_4$. Overall, 15 scaffolds were prepared including, for example, 2-(3,4-dichlorophenyl)-pent-4-eneamine and 2-(4-iodophenyl)-pent-4-eneamine. Next, reductive alkylation of resin-bound aldehyde linker **4** (which was readily prepared via coupling of the acid labile linker 4-(4-formyl-3-methoxy-phenoxy)-butyric acid with the amine resin Argo-Gel-NH_2 using DIC and HOBt) with scaffold **3** generated secondary amine **5**. Treatment of **5** with various reagents such as acid chlorides, sulfonyl chlorides, isocyanates, and chloroformates produced **6** as amides, sulfonamides, ureas, and carbamates, respectively. Finally, olefin **6** was treated with OsO_4 and NMMO followed by $NaIO_4$ to generate aldehyde **7**, which was reductively alkylated with various primary and secondary amines to provide the aryl library **8** after TFA-mediated cleavage from the resin. When X = Br or I, treatment of **6** with various arylboronic acids under standard Suzuki coupling conditions provided biaryl olefin **9**. Subsequently, olefin **9** was treated with OsO_4 and NMMO followed by $NaIO_4$ to generate aldehyde **10**, which was reductively alkylated with various primary and secondary amines to provide the biaryl library **11** after TFA-mediated cleavage from the resin.

Overall, more than 500 compounds were prepared. Each compound (≈5 mg) was purified by HPLC prior to biological evaluation.[7]

Table 1 highlights the SAR from library **8**. First, there is a dramatic enhancement in potency (>10-fold) when the 3,5-dichlorobenzamide group in **1** is replaced with various dihalo substituted phenylureas. As can be seen, 3,5-dichlorophenylurea (**8a**), 3,4-dichlorophenylurea (**8b**), 3,4-difluorophenylurea (**8c**), and 3-chloro-4-fluoro-phenylurea (**8d**) display MCH1R K_is ranging from 100 to 300 nM. However, the unsubstituted phenylurea (**8e**)

Table 1. Key SAR from parallel library **8**

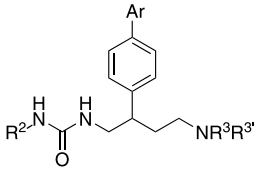


Compound	R^2	MCH1R, K_i (nM)[7]
8a	3,5-$Cl_2C_6H_3$	135
8b	3,4-$Cl_2C_6H_3$	300
8c	3,4-$F_2C_6H_3$	240
8d	3-Cl-4-FC_6H_3	100
8e	C_6H_5	18,500
8f	3-$MeOC_6H_4$	11,000
8g	3-MeC_6H_4	6800
8h	3-ClC_6H_4	1641
8i	3-$CF_3C_6H_4$	205
8j	4-$CF_3C_6H_4$	1080
8k	2-$CF_3C_6H_4$	22,500
8l	3,5-$(CF_3)_2C_6H_3$	1223

has a 4-fold drop in potency (K_i = 18,500 nM) relative to **1**. Second, phenylureas appended with some electron withdrawing groups are more potent than with electron donating groups. For example, 3-methoxyphenylurea (**8f**) and 3-toluylurea (**8g**) are 7-fold and 4-fold less potent, respectively, than the 3-chlorophenylurea (**8h**). Also, *meta*-substituents are preferred over para-substituents, and *ortho* substitution is detrimental. For example, in the mono-CF_3-substituted series, the potency rank is as follows: *meta* (**8i**) > *para* (**8j**) > *ortho* (**8k**). However, the 3,5-di-CF_3-substituted analog **8** is 6-fold less active than **8i**. Finally, aromatic carbamates and sulfonamides did not show any potency enhancement as compared to amide **1** (data not shown).

Table 2 summarizes the SAR from parallel library **11**. Only para-substituted biaryl analogs from library **11** are listed in the table since *meta*- or *ortho*-linked biraryl analogs were all >10-fold less active than the corresponding para-biaryl compounds (data not shown). As is evident from Table 2, installing an aryl group at the para-position can further enhance the potency, in many cases yielding potent low nanomolar compounds. Compounds **11a**–**j** highlight the SAR at the Ar position in this series. Substitution at the 3-position of the distal phenyl ring with a chloro group increased the potency by 2-fold (**11b**, K_i = 26 nM) relative to the unsubstituted compound (**11a**, K_i = 50 nM). Substitution at the 2-position (**11c**) or the 4-position (**11d**) both resulted in a decrease in potency relative to **11a**. Similar to the 3-chloro compound, the 3-fluoro analog **11e**, and the

Table 2. Key SAR from parallel library **11**



Compound	Ar	R^2	$NR^3R^{3'}$	MCH1R K_i (nM)[7]
11a	C_6H_5	3,5-$Cl_2C_6H_3$	*cyclo*-Pentylamino	50
11b	3-ClC_6H_4	3,5-$Cl_2C_6H_3$	*cyclo*-Pentylamino	26
11c	2-ClC_6H_4	3,5-$Cl_2C_6H_3$	*cyclo*-Pentylamino	130
11d	4-ClC_6H_4	3,5-$Cl_2C_6H_3$	*cyclo*-Pentylamino	280
11e	3-FC_6H_4	3,5-$Cl_2C_6H_3$	*cyclo*-Pentylamino	37
11f	3-$CF_3OC_6H_4$	3,5-$Cl_2C_6H_3$	*cyclo*-Pentylamino	20
11g	3-NCC_6H_4	3,5-$Cl_2C_6H_3$	*cyclo*-Pentylamino	3.0
(+)-**11g**	3-NCC_6H_4	3,5-$Cl_2C_6H_3$	*cyclo*-Pentylamino	3.0
(−)-**11g**	3-NCC_6H_4	3,5-$Cl_2C_6H_3$	*cyclo*-Pentylamino	4.0
11h	4-NCC_6H_4	3,5-$Cl_2C_6H_3$	*cyclo*-Pentylamino	46
11i	3-pyridyl	3,5-$Cl_2C_6H_3$	*cyclo*-Pentylamino	24
11j	4-pyridyl	3,5-$Cl_2C_6H_3$	*cyclo*-Pentylamino	122
11k	3-NCC_6H_4	3,5-$Cl_2C_6H_3$	Methylamino	2.6
11l	3-NCC_6H_4	3,5-$Cl_2C_6H_3$	Dimethylamino	4.7
11m	3-NCC_6H_4	3,5-$Cl_2C_6H_3$	Ethylamino	4.3
11n	3-NCC_6H_4	3,5-$Cl_2C_6H_3$	Isopropylamino	5.6
11o	3-NCC_6H_4	3,5-$Cl_2C_6H_3$	Piperidin-1-yl	5.4
11p	3-NCC_6H_4	C_6H_5	Dimethylamino	2.4
11q	3-NCC_6H_4	3-ClC_6H_4	Dimethylamino	1.1
11r	3-NCC_6H_4	4-ClC_6H_4	Dimethylamino	9.2
11s	3-NCC_6H_4	3-FC_6H_4	Dimethylamino	1.2
11t	3-NCC_6H_4	4-FC_6H_4	Dimethylamino	7.4
11u	3-NCC_6H_4	3-Cl-4-FC_6H_3	Dimethylamino	0.98
11v	3-NCC_6H_4	3,4-$F_2C_6H_3$	Dimethylamino	0.84
11w	3-NCC_6H_4	3,5-$F_2C_6H_3$	Dimethylamino	0.88

3-trifluoromethoxy analog **11f** were more potent than **11a**. To our delight, when a cyano group is introduced at the 3-position (**11g**, K_i = 3.0 nM), a dramatic 17-fold increase in potency relative to that of **11a** was achieved. However, the 4-cyano analog (**11h**) showed no improvement in potency as compared to **11a**. Furthermore, the 3-pyridyl compound **11i** is 2-fold more potent than the benzene analog **11a**, while the 4-pyridyl compound **11j** is 2-fold less potent than **11a**.

Compounds **11k**–**o** illustrate the SAR at the R3R3′N position. A wide variety of acyclic and cyclic amines are explored—methylamino, dimethylamino, ethyl amino, isopropylamino, and piperidin-1-yl—all of which showed similar activity (K_i = 2.6–5.6 nM), suggesting greater latitude at this position.

Compounds **11p**–**w** were made to probe the SAR at the R2 position. As is shown, the potency for this series of compounds is relatively insensitive to changes in the R2 aryl group. Even the simple phenyl urea **11p** exhibited potency (K_i = 2.4 nM) as good as the substituted phenyl ureas (**11q**–**w**). However, in the mono-substituted cases, the 4-chloro analog **11q** and 4-fluoro analog **11s** exhibited 6- to 8-fold decreases in potency relative to the corresponding 3-chloro (**11r**) and 3-fluoro (**11t**) compounds. Interestingly, the 3,4-disubstituted analogs **11u**–**w** displayed slightly greater potency than the mono-substituted ones (**11p**–**r**).

It should be noted that all the compounds tested are racemic mixtures except that in the case of **11g**, its two enantiomers, (+)- and (−)-**11g**, resolved via chiral HPLC (Chiracel AD column), were also evaluated. Interestingly, both enantiomers showed almost identical activity in the MCH1R binding assay: (+)-**11g** K_i = 3.0 nM; and (−)-**11g** K_i = 4.0 nM. The two enantiomers were further tested in a Ca^{2+} mobilization FLIPR® assay[8] and both displayed identical and potent functional antagonism of MCH1R: (+)-**11g** K_b = 1.0 nM; and (−)-**11g** K_b = 1.0 nM.

In summary, starting from micromolar 4-amino-2-arylbutylbenzamide MCH1R receptor antagonists identified from screening, solid-phase parallel synthesis of optimization libraries resulted in the discovery of 4-amino-2-biarylbutylureas, such as **11g**, as potent single digit nanomolar MCH1R antagonists along with defined SAR.

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7. (a) MCH1R K_is were determined as follows: membranes prepared from CHO cells that express human MCH1R (0.1 mg/mL final) were incubated with wheatgerm-agglutinin (WGA) coated SPA beads (1 mg/mL final, Amersham Biosciences, Piscataway, NJ) in assay buffer (25 mM HEPES, 10 mM NaCl, 10 mM $MgCl_2$, 5 mM $MnCl_2$, 0.1% BSA, pH 7.4) for 5 min on ice and subsequently washed two times in assay buffer. The test compound (5 μl) prepared in DMSO, DMSO (vehicle, 5%) or MCH (2.5 μM final—used to quantify the non-specific signal) was mixed with 45 μl assay buffer in 96-well assay plates (Corning #3604). The bead/membrane mixture (100 μl) was added to the compounds followed by 50 μl of [^{125}I]-MCH (0.5 nM final, Perkin-Elmer, Boston, MA). The assay plates were shaken for 5 min on a plate shaker and then incubated for 2 h. Binding of [^{125}I]-MCH to the bead/membrane mixture was detected using a Microbeta Trilux™ scintillation counter (Perkin-Elmer). The data were fit to a one-site competition binding model for IC_{50} determination using the program GraphPad Prism (GraphPad Software, Inc., San Diego, CA) and K_i values were calculated using the Cheng–Prusoff equation. All K_is represent the average of two or more determinations. The standard deviations were no greater than 30% from the mean; (b) Cheng, Y.; Prusoff, W. H. *Biochem. Pharmacol.* **1973**, *22*, 3099.
8. Calcium mobilization assay: MCH1R/CHO cells were incubated with 4 μM Fluoro-3-AM/0.04% pluronic acid in assay buffer (Hanks' BSS, 0.1% BSA, 20 mM HEPES, 2.5 mM probencid) for 1 h at 37 °C. The cells were centrifuged for 7 min at 1000*g* and the pellet was resuspended in assay buffer to a density of 500 cells/μl. The cells (40 μl) were plated at 20,000 cells per well into 96-well BD Biocoat poly-D-lysine black/clear plates, centrifuged for 3 min at 1000*g* and incubated at room temperature for 30 min. Compounds or 2% DMSO (vehicle) were added to the cells and incubated for 10–15 min at room temperature. The cells were stimulated with 100 nM MCH and the calcium response was monitored for 1 min per well in a FLIPR® system from Molecular Devices (Sunnyvale, CA). K_b values were determined as described for K_i in Ref. 7a. All K_bS represent the average of two or more determinations, and the standard deviations were no greater than 30% from the mean.