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Discovery and SAR of biaryl piperidine MCH1 receptor antagonists through solid-phase encoded combinatorial synthesis

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Abstract—An encoded combinatorial library based on aryl and biaryl piperidine scaffolds was designed and synthesized. Screening of this library resulted in the discovery of high-nanomolar biaryl piperidine-based MCH1 receptor antagonists. Follow-up optimization using a parallel synthesis provided potent, single digit nanomolar antagonists.

Melanin-concentrating hormone (MCH), a cyclic 19-amino-acid neuropeptide expressed in the brains of all mammals, plays an important role in the regulation of food intake and energy homeostasis.[1] It has been demonstrated that 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] On the contrary, transgenic mice over-expressing MCH are susceptible to obesity and insulin resistance.[1d] MCH interacts with two distinct G protein-coupled receptors (GPCRs) in the brain: MCH1R and MCH2R. MCH1R is present in all mammals and is strongly implicated in the regulation of food intake and energy homeostasis based on knockout experiments with *mch1r*$^{-/-}$ mice.[2] In contrast, MCH2R is expressed only in ferrets, dogs, rhesus monkeys, and humans but not in rodents and lagomorphs, and its physiological function has yet to be established.[3]

These findings have prompted significant efforts from a number of pharmaceutical companies in the discovery of MCH1R antagonists as potential treatments for obesity.[4] A crescendo of publications have appeared recently describing structurally diverse small molecule MCH1R antagonists,[5] several series of which have demonstrated in vivo efficacy in rodent obesity models.[5a,b,m,n] In this paper, we report the discovery of a novel series of biaryl piperidine MCH1R antagonists by using solid-phase combinatorial chemistry.

Combinatorial chemistry has become an integral component of today's drug discovery process. Among the various combinatorial techniques, the encoded combinatorial libraries on polymeric support (ECLiPS^{TM}) technology have proved to be a powerful tool for the discovery of new leads against a wide variety of biological targets.[6] As part of our efforts to synthesize ECLiPS^{TM} combinatorial libraries targeting GPCRs, an aryl and biaryl piperidine-based library **8** (Scheme 1) was designed and synthesized. As shown in Scheme 1A, the requisite aryl/biaryl piperidine scaffold **3** was first synthesized via treatment of various aryl/biaryl acetonitrile **1** with Boc-protected bis-(chloroethyl)-amine **2** in the presence of sodium amide, followed by reduction with $LiAlH_4$. Overall, 15 such scaffolds, including, for example R^1 = phenyl, pyridylphenyl, were prepared. Next, the reaction of scaffold **3** with a resin-bound photolabile linker **4**[7] under reductive alkylation conditions gave a resin-bound secondary amine **5**. Intermediate **5** was treated with a variety of R^2 reagents including aldehydes, acid chlorides, sulfonyl chlorides, isocyanates, and chloroformates under respective reductive alkylation or acylation conditions to yield **6** as tertiary amines, amides, sulfonamides, ureas, and carbamates, respectively. One portion of **6** was treated

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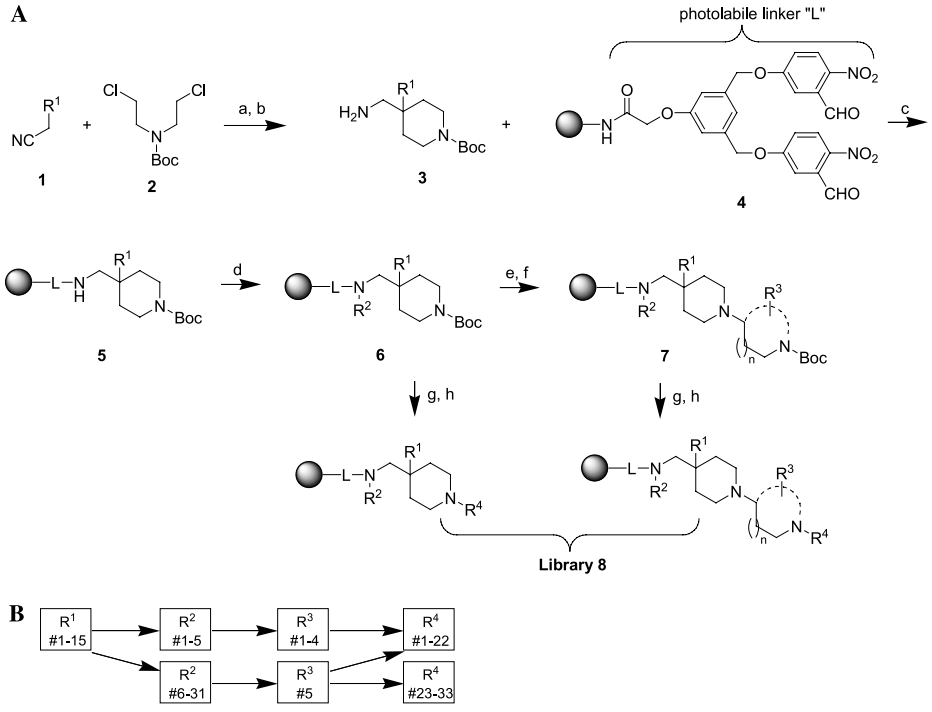


Scheme 1. Solid-phase synthesis of a piperidine-based 19,470-member ECLiPS^{TM} encoded combinatorial library. (A) Synthetic scheme: (a) $NaNH_2$, DMSO; (b) $LiAlH_4$, H_2SO_4, THF; (c) $Na(OAc)_3BH$, $ClCH_2CH_2Cl$; (d) acylation with R_2COCl, R_2NCO, R_2OCOCl, R_2SO_2Cl (pyridine, CH_2Cl_2), or reductive alkylation with R_2CHO ($Na(OAc)_3BH$, $ClCH_2CH_2Cl$); (e) TFA, CH_2Cl_2; (f) acylation or reductive alkylation with R^3 reagents; (g) TFA, CH_2Cl_2; (h) R^4 derivatization. (B) Split–pool scheme: to balance diversity with drug-likeness, certain synthon combinations were removed from the final library synthesis.

with TFA to remove the Boc-group and then reductively alkylated with Boc-protected aminoaldehydes or ketones (R^3 pieces) to generate intermediate **7**. Intermediate **7** was first treated with TFA to remove Boc and then reacted with a diverse set of R^4 reagents including aldehydes, acid chlorides, sulfonyl chlorides, isocyanates, and chloroformates under reductive alkylation or acylation conditions to yield the first part of library **8**. The other portion of **6**, after Boc removal with TFA, was reacted directly with the R^4 reagents to generate the second part of library **8**.

Overall, 15 R^1, 31 R^2, 4 R^3, and 33 R^4 synthons were employed. To balance the size and diversity of the library against drug-like properties, only certain combinations of the synthons were prepared. Thus, as shown in Scheme 1B, a pool and split strategy yielding a library of 19,470-members with optimal diversity and "drug-like" properties was used in the library synthesis. The plot of C log *P* (calculated log *P*) versus PSA (polar surface area) for the 19,470 compounds in library **8** is shown in Figure 1. Based on the computational model of passive absorption by Egan and co-workers,[8] a majority of the piperidine library compounds (95%, green dots within the blue ellipse) were predicted to have characteristics compatible with good oral absorption (>90% absorbed), a small number of compounds (4%, blue dots between the blue and red ellipses) were predicted to be moderately absorbed (30–90% absorbed), whereas only a tiny portion (1%, red dots outside the red ellipse) was predicted to be poorly absorbed (<30% absorbed).

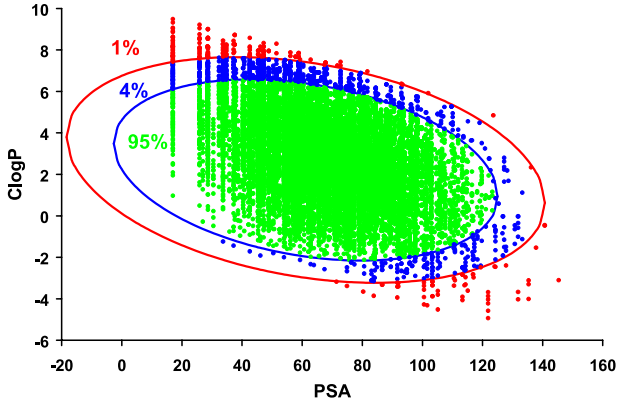


Figure 1. C log *P* versus PSA plot of the piperidine library for oral absorption prediction:[8] well-absorbed (green), moderately absorbed (blue), and poorly absorbed (red) compounds.

It should be noted that according to the ECLiPS^{TM} synthesis protocol,[6] the 15 R^1, 31 R^2, and 4 R^3 synthons were encoded, prior to each pool and split step, by haloaromatic alcohol tags that can be detached via oxidative cleavage and analyzed by electron capture gas chromatography, whereas, the 33 R^4 synthons were not encoded, and instead, the final library compounds **8** were kept as 33 separate sub-libraries, where 1–22 contained 690 compounds per sub-library and 23–33 contained 390 compounds per sub-library. It should also be noted that based on the ECLiPS^{TM} synthesis protocol,[6] extensive synthon profiling, careful solid-phase

reaction optimization, and rigorous analysis of library quality control compounds were performed to ensure the fidelity of the library.

Screening of the 19,470-member library in a high-throughput scintillation proximity assay (SPA), based on [^{125}I]-MCH binding to membranes prepared from CHO cells that express human MCH1R[9], was carried out in two stages. First, a survey screen was performed, in which one copy of each sub-library was arrayed in a 96-well plate as a mixture of ~10 compounds per well (~10 μM per compound through photolytic cleavage of the compound from the resin bead) and screened for the purpose of identifying active sub-libraries. Next, active sub-libraries were selected for a follow-up screen, in which three copies of each sub-library were arrayed in 96-well plates in a single compound per well format (~10 μM per compound through photolytic cleavage of the compound from the resin bead), with the aim of identifying active, individual compounds. Once a well was determined to contain an active compound (⩾50% inhibition at 10 μM screening concentration) in the screen, the structures of the active compounds were determined by analyzing the haloaromatic tags via oxidative cleavage from the source resin bead.[6]

Overall, 84 active structures were identified from eight sub-libraries, with many of these structures found multiple times indicative of a specific interaction with the biological target. Figure 2 depicts the frequency of synthons that appeared for all the decoded structures. As can be seen from Figure 2, the majority of the active compounds were found in three sub-libraries: 3 (R^4 = benzenesulfonyl), 24 (R^4 = phenylpropyl), and 31 (R^4 = 1*N*-methylbenzimidazol-2-ylmethyl). Also, there were pronounced preferences for R^3 = 5 (bond) and R^1 = 11 (4-(3-pyridyl)phenyl)) in the active structures. In contrast, the synthon preference for R^2 was less pronounced. However, the ureas (R^2 = 21: 2-fluorophenylurea, 22: 4-methylthiophenylurea, 23 (3-methoxyphenylurea, and 24: cyclohexylurea) were more preferred over others. One may argue that such a striking combinatorial SAR could not be obtained as readily through the traditional one-variation-at-a-time approach. It should be noted that these compounds were found to be selective for MCH1R,

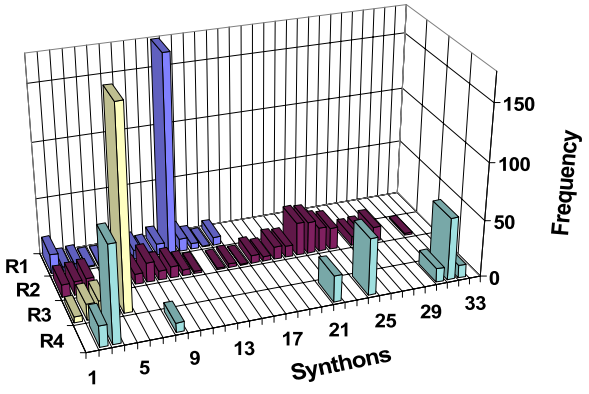
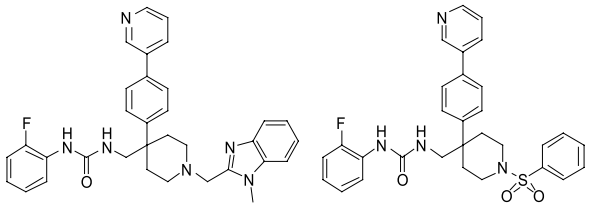


Figure 2. The distribution frequency of synthons for active compounds discovered from screening the encoded combinatorial library.

as evidenced by the fact that the MCH1R hits from library **8** were not decoded for 30 additional GPCR screens in the Pharmacopeia repertoire. The active compounds were resynthesized in greater quantities (>5 mg) for MCH1R K_i determination,[9] and two of the most potent compounds, **8a** (from sub-library 31) and **8b** (from sub-library 3), are shown below. Both compounds are predicted to have good oral absorption (within the blue ellipse in the absorption chart in Fig. 1).[8]



8a
MCH1R K_i = 98 nM
(MW = 548.7, ClogP = 5.0, PSA = 74.1)

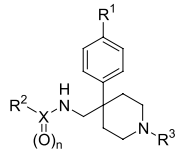
8b
MCH1R K_i = 460 nM
(MW = 544.6, ClogP = 4.1, PSA = 92.1)

To enhance the potency of these screening hits and to expand the SAR further, solid-phase parallel synthesis of a small number of close analogs of **8a**–**b** was carried out by adopting the same solid-phase reactions prescribed for the preparation library **8**. Briefly, 130 compounds were prepared using the FlexChem® reaction block system (Robbins Scientific), and each compound (~5 mg) was purified by reverse-phase HPLC (>95% pure) prior to K_i determination.[9] The SAR of selected compounds are listed in Table 1.

As shown in Table 1, a dramatic increase in potency was achieved by replacing the 2-fluorophenylureido group in the screening hits **8a**–**b** with a 3,5-dichlorophenylureido group at the R^2 position (**8c**–**e**), a preferred moiety found in the 4-amino-2-biaryl-butylurea series of MCH1R antagonists from our laboratories.[10] Specifically, the 3-pyridyl compound **8c**, without any substituent at the piperidine nitrogen (R^3 = H) exhibited a K_i of 39 nM. Substitution of the piperidine nitrogen with either a methylsulfonyl group (**8d**, R^3 = $MeSO_2$, K_i = 2.2 nM) or a methyl group (**8e**, R^3 = Me, K_i = 3.1 nM) resulted in >10-fold increases in potency, relative to **8c**. In contrast, substitution of the piperidine nitrogen with a dimethylsulfamyl group reduced the potency by 2-fold (**8f**, R^3 = Me_2NSO_2, K_i = 84 nM), relative to **8c**. Replacement of the 3-pyridyl group at R^1 with either an alkyl group, such as methyl (**8g**), or a fused heterobicycle, such as 5-indolyl (**8h**), caused potency decreases of 100-fold or more, relative to **8e**. However, replacing the 3-pyridyl at R^1 with 3-substituted phenyl groups, such as 3-Cl-, AcHN-, OHC-, or NC-phenyl gave compounds with potency (**8i**–**l**, K_i = 1.4–5.5 nM) similar to that of **8e**.

Next, with R^1 and R^2 fixed as 3-cyanophenyl and 3,5-dichlorophenylureido groups, respectively, further variation of the R^3 substituents on the piperidine nitrogen was carried out (**8m**–**v**) and the following interesting SAR were obtained: *n*-propyl (**8n**), *iso*-propyl (**8q**), *cyclo*-propylmethyl (**8s**), and *cyclo*-pentyl (**8u**) substitution gave rise to subnanomolar compounds; *n*-butyl (**8o**), *sec*-butyl (**8r**), and *cyclo*-butyl (**8t**) substitution produced less

Table 1. SAR of aryl and biaryl piperidine analogs



Compound	R^1	$R^2X(O)_n$	R^3	MCH1R K_i (nM)[9]
8c	3-Pyridyl	3,5-$Cl_2C_6H_3NHCO$	H	39
8d	3-Pyridyl	3,5-$Cl_2C_6H_3NHCO$	$MeSO_2$	2.2
8e	3-Pyridyl	3,5-$Cl_2C_6H_3NHCO$	Me	3.1
8f	3-Pyridyl	3,5-$Cl_2C_6H_3NHCO$	Me_2NSO_2	84
8g	Me	3,5-$Cl_2C_6H_3NHCO$	Me	300
8h	5-Indolyl	3,5-$Cl_2C_6H_3NHCO$	Me	1188
8i	3-Cl–C_6H_4	3,5-$Cl_2C_6H_3NHCO$	Me	2.6
8j	3-AcHN–C_6H_4	3,5-$Cl_2C_6H_3NHCO$	Me	2.1
8k	3-OHC–C_6H_4	3,5-$Cl_2C_6H_3NHCO$	Me	5.5
8l	3-NC–C_6H_4	3,5-$Cl_2C_6H_3NHCO$	Me	1.4
8m	3-NC–C_6H_4	3,5-$Cl_2C_6H_3NHCO$	Et	2.6
8n	3-NC–C_6H_4	3,5-$Cl_2C_6H_3NHCO$	*n*-Pr	0.31
8o	3-NC–C_6H_4	3,5-$Cl_2C_6H_3NHCO$	*n*-Bu	11
8p	3-NC–C_6H_4	3,5-$Cl_2C_6H_3NHCO$	$MeOCH_2CH_2$	0.41
8q	3-NC–C_6H_4	3,5-$Cl_2C_6H_3NHCO$	*i*-Pr	0.45
8r	3-NC–C_6H_4	3,5-$Cl_2C_6H_3NHCO$	*sec*-Bu	13
8s	3-NC–C_6H_4	3,5-$Cl_2C_6H_3NHCO$	*cyclo*-Propylmethyl	0.17
8t	3-NC–C_6H_4	3,5-$Cl_2C_6H_3NHCO$	*cyclo*-Butyl	11
8u	3-NC–C_6H_4	3,5-$Cl_2C_6H_3NHCO$	*cyclo*-Pentyl	0.63
8v	3-NC–C_6H_4	3,5-$Cl_2C_6H_3NHCO$	*cyclo*-Hexyl	1.2
8w	3-NC–C_6H_4	C_6H_5NHCO	Me	2.2
8x	3-NC–C_6H_4	3-CF_3-4–ClC_6H_3NHCO	Me	0.98
8y	3-NC–C_6H_4	3,4-$F_2C_6H_3NHCO$	Me	1.4
8z	3-NC–C_6H_4	3-NCC_6H_4NHCO	Me	1.5
8a′	3-NC–C_6H_4	2,5-$Cl_2C_6H_3NHCO$	Me	140
8b′	3-NC–C_6H_4	3,5-$Cl_2C_6H_3CH_2CO$	Me	164
8c′	3-NC–C_6H_4	3,5-$Cl_2C_6H_3CO$	Me	155
8d′	3-NC–C_6H_4	3,5-$Cl_2C_6H_3SO_2$	Me	281

potent compounds ($K_i \sim 11$ nM); both the ethyl (**8m**) and the *cyclo*-hexyl (**8v**) analogs showed an activity similar to that of the methyl analog (**8l**); and the methoxyethyl compound (**8p**) had subnanomolar activity.

Finally, with R^1 and R^3 fixed as 3-cyanophenyl and methyl groups, respectively, variations at the R^2 position (**8w**–**d′**) revealed the following interesting SAR: unsubstituted phenylurea (**8w**), 3-CF_3-4-Cl-phenylurea (**8x**), 3,4-difluorophenylurea (**8y**), and 3-cyanophenylurea (**8z**) all exhibited similar potency ($K_i = 0.98$–2.2 nM), relative to the 3,5-dichlorophenylurea analog **8e** ($K_i = 3.1$ nM); however, *ortho*-substitution on the urea phenyl group is not as well-tolerated, for example, the 2,5-dichlorophenylurea analog **8a′** ($K_i = 140$ nM) is >40-fold less active than **8e**; and replacement of the 3,5-dichlorophenylurea moiety in **8e** with amides (such as **8b′**–**c′**) or sulfonamides (such as **8d′**) all resulted in large potency decreases (>50-fold).

It should be noted that good functional activity and oral absorption were also observed with these compounds, consistent with the design of these compounds and the prediction of favorable drug-like properties. For example, compound **8e** ($K_i = 3.1$ nM, MW = 469.4, C log $P = 4.6$, PSA = 57.5) displayed functional antagonism in a Ca^{2+} flux FLIPR® assay[11] ($K_b = 0.4$ nM) and showed good oral absorption (rapid rat $AUC_{0-6h} = 1.4\ \mu M \cdot h$ and $C_{6h} = 0.30\ \mu M$ at 10 mg/kg, p.o.).

In summary, we have described the design and synthesis of an aryl and biaryl piperidine-based ECLiPS™ combinatorial library and the subsequent discovery of potent biaryl piperidine MCH1R antagonists. Further study of these compounds will be reported in due course.

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