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# Biaryl diamides as potent melanin concentrating hormone receptor 1 antagonists

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**Abstract**—Herein, we report the discovery of the potent and selective biaryl diamide derived MCH-R1 receptor antagonist **1**, which was identified upon modification of a previously disclosed biaryl urea series. This paper describes one of the strategies incorporated to remove the highly mutagenic biarylaniline present in an otherwise promising biaryl urea series.


Melanin concentrating hormone (MCH) is a 19-amino acid cyclic peptide found in the brains of all vertebrate species which serves as an important mediator in the regulation of food intake and energy balance.[1,2] An icv injection of MCH in rats stimulates food intake,[3] and chronic administration leads to increased body weight.[4] Mice overexpressing the MCH gene are hyperphagic, mildly obese, hyperglycemic, and insulin resistant.[5] In contrast, mice that lack the gene encoding MCH are lean and hypophagic.[6] These observations suggest that MCH antagonists could be useful for the treatment of obesity. Several companies have published their efforts in identification of small molecule MCH receptor antagonists.[7–9]

We recently reported the MCH-R1 antagonist **2**,[10] which showed excellent in vitro and moderate in vivo activity; however, further studies with this compound were discontinued due to the presence of a highly mutagenic, Ames positive biarylaniline subunit.[11] Although **2** is non-mutagenic, and there is no evidence to suggest that the biarylaniline is generated in vivo, the risk of possible exposure to this highly mutagenic intermediate at any stage in the development of the series was considered unacceptable. Therefore, we turned our attention to identify an MCH-R1 antagonist lacking the mutagenic biarylaniline. One strategy that we followed was to replace the central phenyl ring of biaryl aniline with a bicycloalkyl group. This study resulted in discovery of the novel, orally active MCH-R1 antagonist **3** (Fig. 1).[12] We report herein a different approach to modifying the biaryl aniline portion of **2**, which resulted in discovery of biaryl diamide **1**, a potent and selective MCH-R1 receptor antagonist.

The synthesis of biaryl methylene ureas is outlined in Scheme 1. Suzuki coupling between *p*-bromobenzaldehyde and 3-cyanophenyl boronic acid followed by reductive amination with aminoethyl pyrrolidine or aminopropyl pyrrolidine afforded compound **4**. Treatment of resulting amines with aryl isocyanates afforded the desired products **7**–**12**.

The synthesis of biaryl methylene diamides and biaryl ethylene diamides proceeded via Scheme 2. Suzuki coupling between amine **5** and 3-cyanophenyl boronic acid followed by treatment of resulting biaryl amine with α-bromophenyl acetylamide afforded compound **6**. Acylation of **6** with chloroacetyl chloride followed by nucleophilic substitution with various amines afforded compounds **1**, **13**–**18**, and **23**–**24**. The compound **6** was then coupled with chloropropionic acid, followed by subsequent reaction with various amines to give compounds **19**–**22** and **25**–**28**.

To eliminate any possibility that 4-aminobiphenyl could be generated in vivo, we replaced the biarylaniline with a biarylmethylene amine. Table 1 shows the MCH-R1

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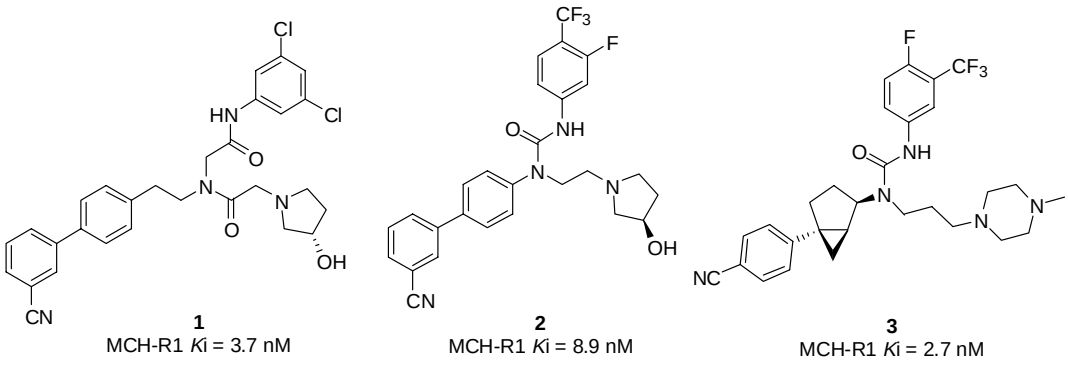
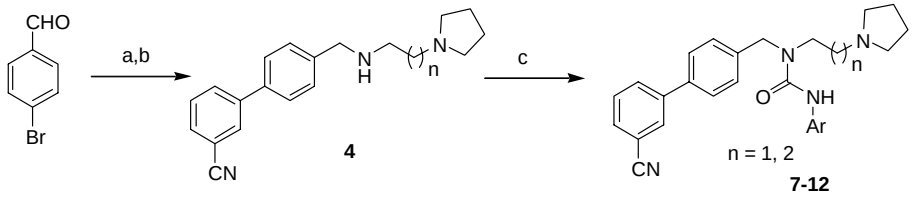
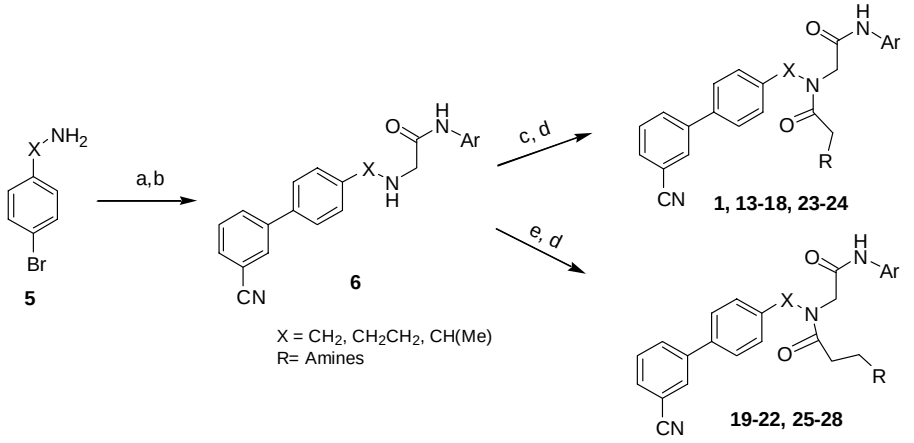



**Figure 1.** MCH-R1 antagonists.

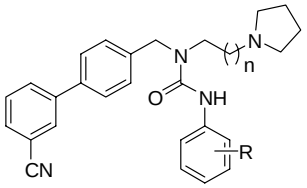



**Scheme 1.** Reagents: (a) 3-cyanophenyl boronic acid, $Na_2CO_3$, $Pd(PPh_3)_4$, toluene:EtOH:$H_2O$ or $PdCl_2(PPh_3)_2$, $K_3PO_4$, DME:$H_2O$, 50–80%; (b) 1-aminoethyl pyrrolidine or 1-aminopropyl pyrrolidine, $NaCNBH_3$, HCl, MeOH 60–90%; (c) ArNCO, $Et_3N$, $CH_2Cl_2$, 75–100%.




**Scheme 2.** Reagents: (a) 3-cyanophenyl boronic acid, $Na_2CO_3$, $Pd(PPh_3)_4$, toluene:EtOH:$H_2O$ or $PdCl_2(PPh_3)_2$, $K_3PO_4$, DME:$H_2O$, 50–80%; (b) $ArNHCOCH_2Br$, $CH_2Cl_2$, 90%; (c) chloroacetyl chloride $CH_2Cl_2$, 70%; (d) amine, $K_2CO_3$, NaI, $CH_3CN$, 75–100%; (e) chloropropionic acid, EDCl, $CH_2Cl_2$, 80%.

**Table 1.** MCH receptor binding for biaryl methylene ureas



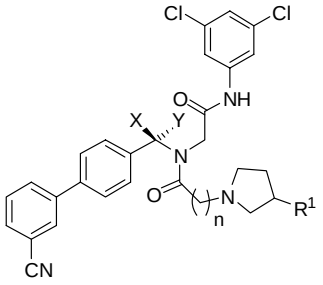
| Compound | *n* | R | h-MCH-R1[a] $K_i$ (nM) |
|---|---|---|---|
| **7** | 1 | 3,5-diCl | 151 ± 29 |
| **8** | 1 | 3-Cl, 4-F | 287 ± 4 |
| **9** | 1 | 4-F, 3-$CF_3$ | 159 ± 40 |
| **10** | 2 | 3,5-diCl | 48 ± 3 |
| **11** | 2 | 3-Cl, 4-F | 48 ± 2 |
| **12** | 2 | 4-F, 3-$CF_3$ | 70 ± 1 |

[a] Mean values ($n = 3$) ± SEM. h-MCH-R1 denotes human MCH-R1. Affinity at h-MCH-R2 > 3 μM for all compounds.

activities of several representative biaryl methylene ureas containing modifications at the urea phenyl. The propyl linker was preferred over the ethyl linker. The 3,5-dichloro and 3-chloro-4-fluorophenyl substitutions (**10** and **11**) were the best among the several disubstituted ureas prepared and tested. Note that the 4-fluoro-3-trifluoromethyl substitutions which was one of the best in the biaryl aniline series, showed 50-fold less MCH-R1 affinity in the biarylmethylene series. We speculated that this considerable loss of activity with biarylmethylene series could be due to changes in the orientation of the biaryl as well as the hydrogen bonding interaction provided by urea N–H with the receptor.

After the limited success with biarylmethylene compounds, we next explored alterations to the urea functionality by introducing diamides instead of changing the

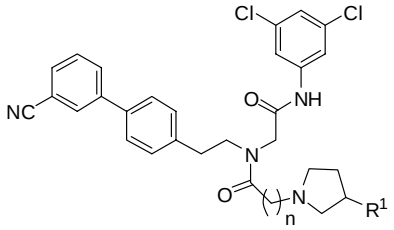
**Table 2.** MCH receptor binding for biarylmethylene diamides



| Compound | X,Y | *n* | $R^1$ | h-MCH-R1[a] $K_i$ (nM) |
|---|---|---|---|---|
| **13** | H, H | 1 | H | 35 ± 2 |
| **14** | H, H | 1 | (*R*)-OH | 61 ± 8 |
| **15** | H, H | 1 | (*S*)-OH | 27 ± 4 |
| **16** | Me, H | 1 | (*S*)-OH | 31 ± 0.5 |
| **17** | H, Me | 1 | (*S*)-OH | 16 ± 1 |
| **18** | Me, Me | 1 | H | 131 ± 2 |
| **19** | H,H | 2 | H | 21 ± 5 |
| **20** | Me, H | 2 | (*S*)-OH | 23 ± 0.5 |
| **21** | H, Me | 2 | (*S*)-OH | 18 ± 1 |
| **22** | Me, H | 3 | (*S*)-OH | 76 ± 5 |

[a] Mean values ($n = 3$) ± SEM. h-MCH-R1 denotes human MCH-R1. Affinity at h-MCH-R2 > 3 μM for all compounds.

**Table 3.** MCH receptor binding for biarylethylene diamides



| Compound | *n* | $R^1$ | h-MCH-R1[a] $K_i$ (nM) |
|---|---|---|---|
| **23** | 1 | H | 19 ± 5 |
| **24** | 1 | (*R*)-OH | 15 ± 1 |
| **1** | 1 | (*S*)-OH | 3.7 ± 0.1 |
| **25** | 1 | (*R*)-NHCOMe | 82 ± 9 |
| **26** | 2 | H | 10 ± 2 |
| **27** | 2 | (*R*)-OH | 12 ± 2 |
| **28** | 2 | (*S*)-OH | 7.2 ± 0.2 |

[a] Mean values ($n = 3$) ± SEM. h-MCH-R1 denotes human MCH-R1. Affinity at h-MCH-R2 > 3 μM for all compounds.

orientation of the biaryl unit and the interaction of the urea N–H with the receptor. Table 2 summarizes the SAR of the MCH-R1 binding of several biarylmethylene diamides with benzylic and pyrrolidine side-chain variations. The unsubstituted pyrrolidine **13**, which was the first compound prepared in this series, showed promising MCH-R1 activity. The SAR at the pyrrolidine side chain very much paralleled that observed in the biarylanilinourea series.[10] The (*S*)-OH pyrrolidine **15** showed MCH-R1activity of 3-fold better than enantiomer **14**. Benzylic methyl substitution gave slightly better MCH-R1 binding, with a preference observed for (*S*)-stereochemistry. In contrast to the urea series described in Table 1, the carbon chain extended compounds (**19**–**22**) did not provide any enhancement in MCH-R1 binding.

To further improve the MCH-R1 affinity, we studied the replacement of the biarylmethylene with a biarylethylene linker. Table 3 shows MCH-R1 binding of selected biarylethylene amides. The unsubstituted pyrrolidine **23** gave slightly better activity for MCH-R1 than the corresponding biarylmethyelene amide **13**. Again, similar to biarylmethylene diamide series, the (*S*)-OH pyrrolidines **1** and **28** showed better MCH-R1 affinity than (*R*)-OH isomer and unsubstituted compounds **23** or **26**. Compound **1** was identified as a potent and selective MCH-R1 antagonist, which was selected for followup studies.

In summary, a systematic SAR modification strategy of compound **2** resulted in the identification of several structurally novel, non-biarylaniline containing MCH-$R^1$ antagonists. Compound **1** showed excellent in vitro activity; further in vivo studies with this compound will be reported in due course.

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