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Discovery of tetralin ureas as potent melanin concentrating hormone 1 receptor antagonists

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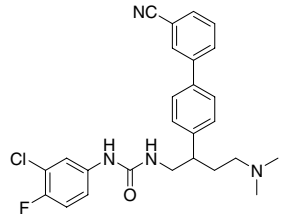
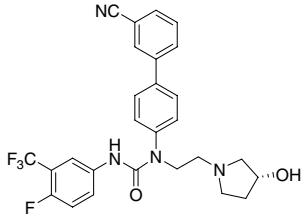
Abstract—Melanin concentrating hormone (MCH) plays an important role in the regulation of food intake and energy balance in mammals. MCH-1 receptor (MCH1R) deficient mice are lean and resistant to diet-induced obesity. As such, MCH1R antagonists are believed to have potential as possible treatments for obesity. The discovery of a novel class of tetralin ureas as potent MCH1R antagonists is described herein.

Melanin concentrating hormone (MCH) is a cyclic 19-amino-acid neuropeptide found in the brains of all vertebrates which has been demonstrated to play an important role in the regulation of food intake and energy homeostasis in mammals.[1a] Central administration of MCH in mice stimulates food intake while fasting results in an increase in MCH expression.[1b] Transgenic mice over-expressing MCH are susceptible to obesity and insulin resistance,[1c] whereas MCH knockout mice are hypophagic and leaner than wild-type mice but otherwise healthy.[1d] MCH binds and activates two distinct receptors in the brain, MCH1R and MCH2R.[2,3] MCH1R is present in all mammals, whereas MCH2R is found in ferrets, dogs, rhesus monkeys, and humans but not in rodents and lagomorphs. MCH1R knockout mice are lean, hyperphagic but hyperactive and resistant to diet-induced obesity, clearly establishing its critical role in the regulation of food intake and energy homeostasis.[4] In contrast, the physiological function of MCH2R has yet to be established.

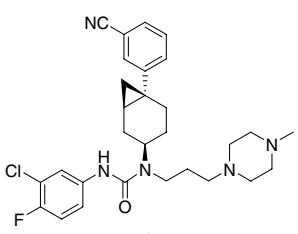
A wide variety of small molecule MCH1R antagonists has been reported as potential therapeutic agents for the treatment of obesity and a number of these antagonists have demonstrated in vivo efficacy in rodent models of obesity.[5] We recently disclosed the discovery of a series of biaryl-diaminobutane ureas (**1**) as potent MCH1R antagonists.[6a,b] Truncation of the carbon chain between the biaryl and the urea moieties led to the discovery of a series of biarylaniline ureas (**2**) which demonstrated oral efficacy in reducing food intake and body weight gain in rodent models of obesity.[6c] However, the biarylaniline unit in **2** was found to give highly positive results in the Ames test.[6c] Although compound **2** itself is not active in the Ames test, and no evidence suggests that the biarylaniline unit is generated in vivo, concerns about the highly mutagenic diarylaniline intermediate have prompted the design and synthesis of MCH1R antagonists devoid of biarylanilines. One



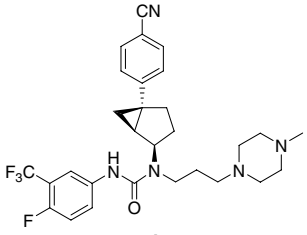
1
MCH1R K_i = 0.98 nM



2
MCH1R K_i = 8.9 nM



3
MCH1R K_i = 4.0 nM



4
MCH1R K_i = 2.7 nM

Keywords: MCH; MCH1R antagonists; Obesity.
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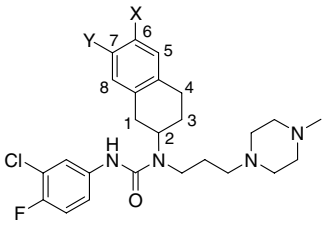
approach was to replace the biarylaniline unit of **2** with non-mutagenic bicyclo[4.1.0]heptyl (**3**)[6d] or bicyclo[3.1.0]hexyl (**4**) scaffolds.[6e,f,g] Compounds **3** and **4** have demonstrated excellent oral efficacy in rodent models of obesity.[6d,e–g] Alternatively, we envisaged that the biarylaniline unit could be replaced with a non-mutagenic tetralin scaffold. We report in this paper the discovery of a novel series of tetralin ureas as potent MCH1R antagonists.

Scheme 1 shows the general synthesis of tetralin ureas **7a**–**i**. Heating a neat mixture of 2-tetralones **5**, 1-(3-aminopropyl)-4-methylpiperazine, and titanium isopropoxide at 80 °C for 3 h (to generate imine intermediates), followed by reduction with $NaBH_4$ in MeOH at 0 °C to rt for 12 h, provided the secondary amine intermediate **6**. Treatment of **6** with 3-chloro-4-fluorophenyl isocyanate and Hunig base in dichloromethane afforded target compounds **7a**–**i**.

The MCH1R binding data for tetralin ureas **7a**–**i** are shown in Table 1. These compounds all contain the 3-chloro-4-fluoro-phenylurea on the left hand side and the 1-(3-aminopropyl)-4-methylpiperazine on the right hand side, both of which have been shown to be among the optimal side chains for MCH1R activity.[6a,b–g] As shown in Table 1, the unsubstituted tetralin compound **7a** displayed modest potency (K_i value of 380 nM). Mono-substitution at the tetralin C-6 position with either electron withdrawing groups (**7b**: 6-Br, **7c**: 6-CN) or electron donating groups (**7d**: 6-methoxy) caused little change in potency relative to the unsubstituted compound **7a**. However, mono-substitution at the tetralin C-7 position resulted in pronounced potency changes. As can be seen, C-7 substitution with a methoxy group (**7e**) increased the potency by 4-fold relative to **7a**, whereas C-7 substitutions with sulfonyl or sulfonamido groups (**7f**–**h**) decreased the potency by 3- to 7-fold relative to **7a**. Most interestingly, introduction of a C-7 nitro group (**7i**: K_i = 11 nM) enhanced the potency by 35-fold relative to **7a**.

To further explore C-7 substituents, conversion of the nitro group **7i** into amino (**7j**), amido (**7k**–**l**), ureido (**7m**), sulfonamido (**7n**), and cyano (**7o**) groups was next carried out. Thus, as shown in Scheme 2, hydrogenation of **7i** provided **7j**, which, upon acylation, generated **7k**–**n**. Diazotization of **7j** followed by treatment with NaCN/CuCN provided **7o**.

Table 1. MCH1R binding data

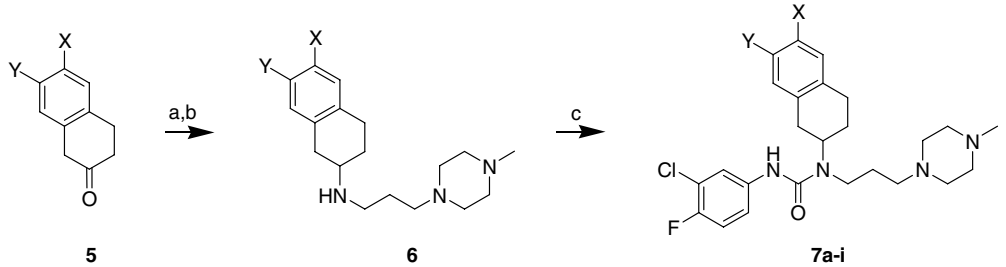


Compound	X	Y	h-MCH1R K^a_i (nM)
7a	H	H	380
7b	Br	H	180
7c	CN	H	340
7d	OMe	H	190
7e	H	OMe	92
7f	H	SO_2Me	1300
7g	H	SO_2NHMe	3000
7h	H	SO_2NMe_2	3000
7i	H	NO_2	11
7j	H	NH_2	260
7k	H	NHCOMe	6.0
7l	H	NHCO-*i*-Pr	61
7m	H	NHCONHEt	160
7n	H	$NHSO_2Me$	96
7o	H	CN	8.5

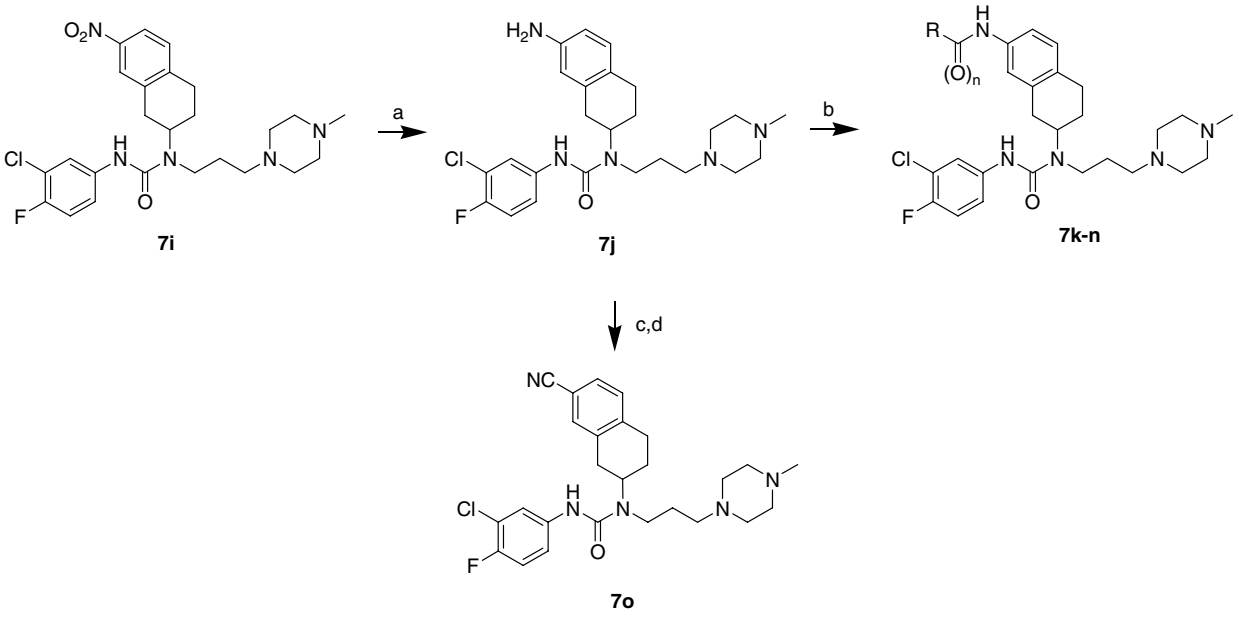
[a] K_is are mean values of two or more determinations with the standard deviations no greater than 50% from the mean.[7]

The MCH1R binding data for **7j**–**o** are also listed in Table 1. Conversion of 7-nitro (**7i**) into 7-amino (**7j**) caused a 25-fold decrease in potency. But interestingly, acetylation of the amino group brought the potency level into the single digit nanomolar range (**7k**: K_i = 6.0 nM). Replacement of the acetamido group (**7k**) with isopropionamido (**7l**), ethylureido (**7m**) or methylsulfonamido (**7n**) groups, all resulted in potency decreases of 10-fold or more relative to **7k**. However, the 7-cyano compound **7o** displayed potent, single digit nanomolar activity (K_i = 8.5 nM), similar to **7k**.

Compounds **7k** and **7o** were further evaluated in rapid rat AUC[8] and mouse ex vivo binding[9] studies (Table 2). The acetamido compound **7k** displayed poor rapid rat AUC (195 ng h/mL, 10 mg/kg, po) and poor brain receptor ex vivo binding (23% I, 30 mg/kg, po, 6 h), whereas **7o** exhibited modest AUC (642 ng h/mL, 10 mg/kg, po) and significant ex vivo binding (84%, 30 mg/kg, po, 6 h), indicating that the cyano compound



Scheme 1. Preparation of tetralin ureas **7a**–**i**. Reagents and conditions (yields for **7a**): (a) 1-(3-aminopropyl)-4-methylpiperazine, Ti(O-*i*-Pr)$_4$, 80 °C, 3 h; (b) $NaBH_4$, MeOH, 0 °C to rt, 12 h, 67% (two steps); (c) 3-chloro-4-fluorophenyl isocyanate, *i*-Pr_2NEt, CH_2Cl_2, 48%.



Scheme 2. Preparation of tetralin ureas **7j–o**. Reagents and conditions: (a) Raney Ni, H_2 (50 psi), EtOH, rt, 2 h, 75%; (b) acylating agent, *i*-Pr_2NEt, CH_2Cl_2, rt, 16 h, 83–92%; (c) $NaNO_2$, HCl (aq), 0 °C, 30 min; (d) Na_2CO_3, NaCN, CuCN, H_2O, 50 °C, 30 min, 24% (two steps).

Table 2. Rapid rat PK and mouse ex vivo binding data

Compound	Rapid rat AUC_{0-6h}[a] (10 mg/kg, po, ng h/mL)	Mouse MCH1R ex vivo binding[b] (30 mg/kg, po, 6 h, % I)
7k	195	23
7o	642	84

[a] Data represent the pooled samples from two rats in cassette-accelerated rapid rat protocol as described in Ref. 8.

[b] Data are expressed as a percent inhibition of MCH–ADO binding relative to vehicle control (mean values, $n = 3$).[9]

7o has superior in vivo properties as compared to the acetamido compound **7k**.

In summary, a novel class of tetralin ureas has been discovered as potent MCH1R antagonists. Compound **7o** has demonstrated excellent in vitro activity, modest oral bioavailability, and good ex vivo MCH1R receptor binding, making it suitable for further in vivo studies.

Acknowledgments

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7. MCH1R K_i determination: Membranes prepared from CHO cells that express human MCH1R (0.05 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 $MnCl_2$, and 0.1% BSA, pH 7.4) for 5 min on ice and subsequently washed two times in assay buffer. Test compound (20 μL) prepared in 7.5% DMSO, 7.5% DMSO (vehicle) or MCH (1.0 μM final – used to quantify the non-specific signal) was mixed with 45 μL assay buffer in 96-well assay plates (Corning #3604). 20 μL of the bead/membrane mixture was added to the compounds followed by 10 μL of [^{125}I]-MCH (0.125 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). K_i values were calculated using the Cheng–Prusoff equation with a K_d of 1 nM. All K_is represent the average of two or more determinations. The standard deviations were not greater than 50% from the mean.
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9. Mouse MCH1R ex vivo binding assay: Animals were administered compound (30 mg/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)[10] 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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