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Synthesis and SAR study of pyrrolo[3,4-*b*]pyridin-7(6*H*)-one derivatives as melanin concentrating hormone receptor 1 (MCH-R1) antagonists

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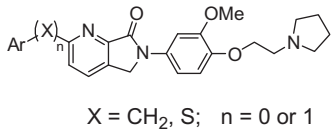
ABSTRACT

The discovery and optimization of novel pyrrolo[3,4-*b*]pyridin-7(6*H*)-one MCH-R1 antagonists are described. A systematic SAR study probing the effects of aryl-, benzyl- and arylthio-substituents at the 2-position of the pyrrolo[3,4-*b*]pyridin-7(6*H*)-ones led to identification of the 2-[(4-fluorophenyl)thio] derivative **7b** as a highly potent MCH-R1 antagonist. This compound also has favorable pharmacokinetic properties along with a high metabolic stability and a minimal impact on CYP isoforms and hERG.

The prevalence of obesity has grown and it now has reached global epidemic levels with more than one billion adults in world being overweight and at least 200 million being classified as obese.[1] In addition, obesity is a major risk factor for many other diseases including type 2 diabetes, dyslipidemia, coronary heart disease, stroke and certain cancers.[2] Unfortunately, no efficacious and safe anti-obesity drugs are currently available.[3] Among many centrally acting neuropeptides, the melanin concentrating hormone (MCH) has received recent attention as a target for obesity treatment. MCH, a cyclic 19-amino acid polypeptide, is primarily expressed in the lateral hypothalamus and zona incerta areas of the brain.[4] This peptide, which is known to play a physiological role in both the regulation of feeding and energy homeostasis, is mediated by two types of G protein-coupled receptors called MCH receptor 1 and 2 (MCH-R1 and -R2).[5] While the exact biological functions of MCH-R2 are still unknown, previous genetic and pharmacological studies have demonstrated that MCH-R1 plays an essential role in the control of food intake and body weight.[6] Therefore, MCH-R1 is considered to be one of the most promising targets for treating obesity. Indeed, numerous MCH-R1 antagonists have been found to have anti-obesity efficacy in diet-induced obesity (DIO) animal models.[7]

In spite of the fact that a variety of substances have been explored as MCH-R1 antagonists in the pharmaceutical industry, few candidates have progressed to the phase 1 clinical stage owing to their unsuitable PK profiles and safety concerns.[8] In particular, substances possessing diverse heteroaryl fused bicyclic ring systems, such as thiazolopyridinones, thienopyridazinones, and imidazopyrimidinones, based on the structure of GW856464 containing 3-methoxy-4-[2-(pyrrolidin-1-yl)ethoxy]aniline moiety have been reported to serve as MCH-R1 antagonists.[9] In continuing efforts aimed at the development of novel and potent MCH-R1 antagonists as anti-obesity agents,[10] we recently identified several pyrrolo[3,4-*b*]pyridin-7(6*H*)-ones that have highly potent binding affinities to MCH-R1 (Fig. 1).[11] Herein, we describe the results of an effort involving the synthesis, biological evaluation, and structure–activity relationships of several 2-substituted pyrrolo[3,4-*b*]pyridin-7(6*H*)-one derivatives.

The general synthetic route employed for the preparation of 2-substituted pyrrolo[3,4-*b*]pyridin-7(6*H*)-one derivatives **5**, **6** and **7** is outlined in Scheme 1. Methyl 3-methyl-2-picolinate was reacted with *m*-CPBA to give the corresponding *N*-oxide **1**, which upon



X = CH_2, S; n = 0 or 1

Figure 1. 2-Substituted pyrrolo[3,4-*b*]pyridin-7(6*H*)-one derivatives.

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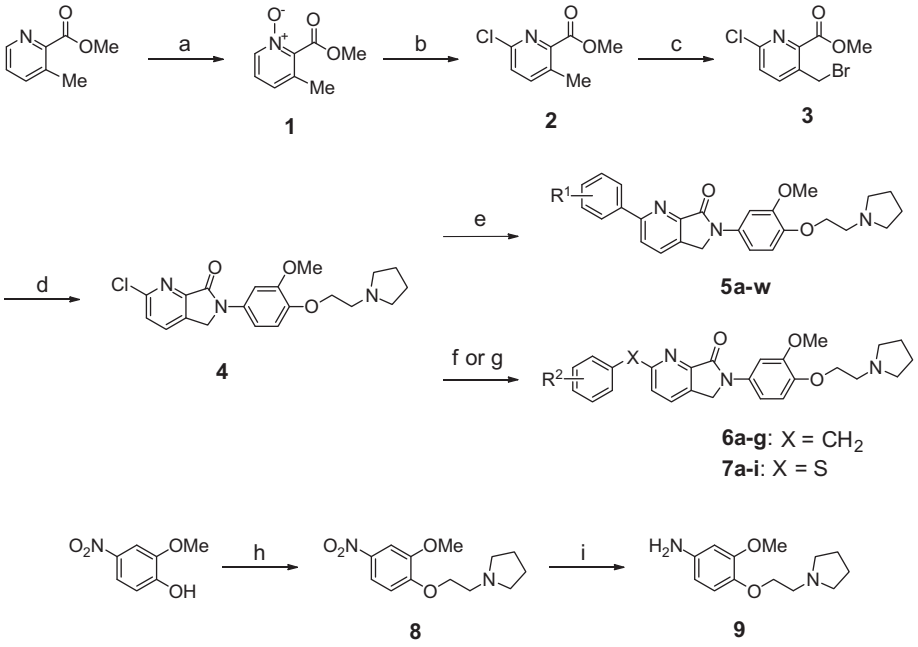
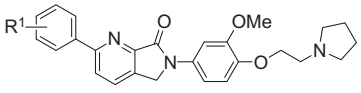


Scheme 1. Reagents and conditions: (a) *m*-CPBA, dichloromethane, rt; (b) $POCl_3$, $ClCH_2CH_2Cl$, reflux; (c) *N*-bromosuccinimide, benzoyl peroxide, CCl_4, reflux; (d) **9**, acetic acid, reflux; (e) arylboronic acid, $Pd(PPh_3)_4$, 2 M Na_2CO_3, MeOH and toluene (1:4), reflux; (f) benzylboronic acid pinacol ester, $Pd(PPh_3)_4$, $Ba(OH)_2$, 1,4-dioxane, reflux; (g) aryl thiol, Et_3N, DMF, 130 °C; (h) 1-(2-chloroethyl)pyrrolidine hydrochloride, K_2CO_3, DME and H_2O (10:1), reflux; (i) 10% Pd/C, H_2(g), MeOH.

treatment with excess phosphorus oxychloride provided a mixture of *ortho*- and *para*-chloro regioisomeric products. Separation by using silica gel column chromatography gave the desired *ortho*-chloropyridine **2**.[12] Reaction of **2** with NBS in the presence of benzoyl peroxide in CCl_4 at reflux afforded the benzyl bromide derivative **3**. In a parallel sequence, 3-methoxy-4-[2-(pyrrolidin-1-yl)ethoxy]aniline **9** was prepared starting by treatment of 2-methxoy-4-nitrophenol[13] with 1-(2-chloroethyl)pyrrolidine, using sodium carbonate as a base, to generate the ether **8**. Reduction of the nitro group in **8** utilizing catalytic hydrogenation provided the corresponding aniline derivative **9**. In initial studies, we observed that reaction of **3** with aniline **9** using several bases did not produce the desired 2-chloro-pyrrolo[3,4-*b*]pyridin-7(6*H*)-one **4**. However, when this reaction was carried out in acetic acid, condensation product **4** was generated in high yield. Finally, the target 2-substituted pyrrolo[3,4-*b*]pyridin-7(6*H*)-ones **5** and **6** were obtained by reaction of **4** with selected arylboronic acids or benzylboronic acid pinacol esters under standard Suzuki coupling conditions. In addition, the 2-arylthio derivatives **7** were synthesized by using simple nucleophilic substitution reactions of **4** with aryl thiols with triethylamine as a base.

The binding affinities of the 2-substituted pyrrolo[3,4-*b*]pyridin-7(6*H*)-one derivatives **5**, **6** and **7** to membranes of CHO cells expressing human MCH-R1 were determined by using a competitive binding assay with Eu-labeled MCH and a time-resolved fluorometric (TRF) assay.[14] The initial SAR study focused on exploring the effects of various substitutents on the 2-phenyl group of the pyrrolo[3,4-*b*]pyridin-7(6*H*)-ones. As the results summarized in Table 1 show, while the substance having a methoxy group at the *para*-position (**5d**) exhibits moderate binding affinity for MCH-R1, those in which this group is either removed (**5a**, R^1 = H) or repositioned from the *para* to *ortho* (**5b**) or *meta* (**5c**) positions have significantly decreased binding affinities. In addition, binding of the chloro (**5e–g**), fluoro (**5h–i**), methyl (**5l–m**) and ethyl (**5n–o**)-substituted derivatives also displays similar trends. A further exploration of the effects of substitutents at the *para* position of aryl group demonstrated that substances containing fluoro (**5i**), trifluoromethyl (**5j**) and nitrile (**5k**) moieties at this position all have low binding affinities. In contrast, introduction of a methyl group at the *para*-position (**5m**) was found to result in a high

Table 1
Effects of substituents on the 2-phenyl group of pyrrolo[3,4-*b*]pyridin-7(6*H*)-one derivatives on MCH-R1 binding affinity

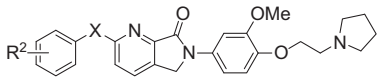


5

Compound	R^1	MCH-R1 IC_{50}[a,b] (nM)
5a	H	10,000
5b	2-OMe	7110
5c	3-OMe	2010
5d	4-OMe	340
5e	2-Cl	510
5f	3-Cl	5650
5g	4-Cl	440
5h	2-F	4130
5i	4-F	3100
5j	4-CF_3	540
5k	4-CN	10,000
5l	2-Me	1040
5m	4-Me	80
5n	2-Et	2000
5o	4-Et	50
5p	4-*n*-Pr	210
5q	4-*n*-Bu	2780
5r	4-*i*-Pr	90
5s	4-Vinyl	130
5t	4-*t*-Bu	320
5u	2,3-Di-Me	190
5v	2,5-Di-Me	300
5w	3,4-Di-Me	180

[a] Binding affinities of compounds for MCH-R1 were determined by using a competitive binding with Eu-MCH and a TRF assay.
[b] Values are means of at least two measurements.

Table 2
Effects of substituents on the 2-benzyl and 2-arylthio groups of pyrrolo[3,4-*b*]pyridin-7(6*H*)-one derivatives on MCH-R1 binding affinity



6, X = CH_2; **7**, X = S

Compound	X	R^2	MCH-R1 IC_{50}[a,b] (nM)
6a	CH_2	H	70
6b	CH_2	2-Me	720
6c	CH_2	3-F	410
6d	CH_2	4-F	80
6e	CH_2	4-Cl	120
6f	CH_2	4-Me	160
6g	CH_2	4-*t*-Bu	1910
7a	S	H	20
7b	S	4-F	30
7c	S	4-Cl	40
7d	S	4-Me	60
7e	S	4-OMe	100
7f	S	2,4-Di-F	60
7g	S	3,4-Di-F	50
7h	S	2-Cl-4-F	80
7i	S	3-Cl-4-F	50

[a] Binding affinities of compounds for MCH-R1 were determined by using a competitive binding with Eu-MCH and a TRF assay.
[b] Values are means of at least two measurements.

MCH-R1 binding activity (IC_{50} = 80 nM). Moreover, the ethyl derivative **5o** was found to have a 1.6-fold more potent binding affinity (IC_{50} = 50 nM) than the *p*-methyl analog **5m**. When the size of the alkyl group was increased from ethyl (**5o**) to *n*-propyl (**5p**) and *n*-butyl (**5q**), a large decrease in MCH-R1 binding activity took place. Other analogs having similar two carbon units such as *i*-propyl (**5r**), vinyl (**5s**) and *t*-butyl (**5t**) displayed comparatively lower binding affinities. The effects of disubstitution on the phenyl group were also investigated. Incorporation of two methyl groups at the 2,3- (**5u**), 2,5- (**5v**) and 3,4- (**5w**) positions led to reduced binding affinities compared to the 4-methyl analog **5m**. The SAR results described above indicate that the properties of substitutents on phenyl group at the 2-position of the pyrrolo[3,4-*b*]pyridin-7(6*H*)-one ring system play significant roles in determining binding to MCH-R1.

Our attention next turned to an exploration of the effects of substituents on the aromatic ring of the 2-benzyl group. In a manner that is similar to the results of the SAR performed on members of the 2-phenyl-pyrrolo[3,4-*b*]pyridin-7(6*H*)-one family, the binding affinities of simple benzyl (**6a**), *o*-methyl (**6b**) and *m*-fluoro (**6c**) analogs were lower than that of the *p*-ethylphenyl analog **5o** (Table 2). In addition, other benzyl-substrates possessing *p*-fluoro (**6d**), *p*-chloro (**6e**), *p*-methyl (**6f**) and *p*-*t*-butyl (**6g**) substituents were found to display comparatively lower binding affinities than that of **6a**.

The effect of replacement of the benzyl group with an arylthio group at the 2-position of the pyrrolo[3,4-*b*]pyridin-7(6*H*)-ones was evaluated. The results, summarized in Table 2, show that, in general, the arylthio compounds **7** have higher binding affinities than the corresponding aryl (**5**) and benzyl (**6**) derivatives. The phenylthio-analog **7a** was observed to have the most potent MCH-R1 binding activity among all substances tested (IC_{50} = 20 nM). The *p*-fluoro (**7b**) and *p*-chloro (**7c**) arylthio analogs bind slightly less tightly with IC_{50} values of 30 and 40 nM, respectively, while other substrate such as those containing 4-methyl (**7d**) and 4-methoxy (**7e**) substituents have reduced binding activities. Additionally, disubstitued substrates, such as the 2,4-difluoro (**7f**), 3,4-difluoro (**7g**), 2-chloro-4-fluoro (**7h**) and 3-chloro-4-fluoro (**7i**) derivatives, also exhibited high binding activities. Interestingly, replacement of the arylthio group (R^2PhS) with an arylsulfonyl group (R^2PhSO_2) led to complete loss of MCH-R1 binding activity (data not shown).

Table 3
In vivo pharmacokinetic profiles of **7a** and **7b** in rats

Parameter[a]	7a	7b
$t_{1/2}$ (h)	2.8	3.4
Oral AUC (μg h/mL)	0.32	5.7
iv CL (mL/kg min)	25.7	1.6
*V*dss (L/kg)	22.7	8.3
F (%)	35	92

[a] Determined in rats by administration of 10 mg/kg, iv and po (n = 3).

The 2-phenylthio- (**7a**) and 2-[(4-fluorophenyl)thio]- (**7b**) pyrrolo[3,4-*b*]pyridin-7(6*H*)-ones that display the most potent MCH-R1 binding affinity were subjected to further studies. The pharmacokinetic properties of the two derivatives, determined employing an iv/po pharmacokinetic study (10 mg/kg) in rats, are shown in Table 3. While both compounds showed acceptable half-lives and clearances, **7b** has a relatively better plasma level and volume of distribution than **7a**. In addition, **7b** displayed excellent oral bioavailability (F = 92%) and it exhibits good metabolic stability in human and rat liver microsomes (97% and 79% for 30 min, respectively), moderate permeability (1.9×10^{-6} cm/s, PAMPA) and high aqueous solubility (104 μg/mL). Finally, **7b** does not inhibit the cytochrome P450 enzymes 2D6 and 3A4 (<10% at 10 μM) and it has a low hERG binding activity (IC_{50} = 25 μM).

In summary, the studies described above have led to the discovery of pyrrolo[3,4-*b*]pyridin-7(6*H*)-one derivatives that act as MCH-R1 antagonists. An extensive, systematic SAR investigation probing the effects of substituents on the 2-aryl, 2-benzyl and 2-arylthio groups on the pyrrolo[3,4-*b*]pyridin-7(6*H*)-one ring system resulted in the identification of the 2-[(4-fluorophenyl)thio]-pyrrolo[3,4-*b*]pyridin-7(6*H*)-one **7b** as a highly potent MCH-R1 antagonist. This compound was observed to have good pharmacokinetic properties, metabolic stability and minimal impact on CYP isoforms and hERG. Further investigations aimed at evaluating the in vivo efficacy of **7b** in animal models are underway.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2013.01.053.

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