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Tetrahydroisoquinolines as MCH-R1 antagonists

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Abstract—A series of potent and selective inhibitors of h-MCH-R1 has been developed based on the piperidine glycineamide compounds **I** and **II**. These structurally more rigid tetrahydroisoquinolines (**III** and **IV**) showed better pharmacokinetics. The highly potent compounds **12d** and **12g** displayed excellent rat pk.

Melanin concentrating hormone (MCH) is a 19-membered neuropeptide that is found in the lateral hypothalamus and regulates food intake.[1,2] There is evidence for involvement of MCH in feeding and obesity.[3] One of the major findings is that hypothalamic MCH peptide levels increase during fasting in ob/ob and WT mice. ICV administration of MCH or analogs stimulates feeding in rodents and MCH−/− mice are hypophagic and leaner than WT mice but otherwise healthy.[4] MCH receptor knock-out mice are lean, hypophagic, hyperactive, have reduced fat mass, have increased metabolic rate, and they are resistant to diet-induced obesity (DIO). Evidence from knock-outs suggests an MCH receptor antagonist should be beneficial for treatment of obesity and related disorders.[5,6] Several classes of small molecule MCH-R1 antagonists have recently been disclosed.[7–12]

Recently we found compounds of the types **I** and **II** are potent and selective MCH-R1 antagonists useful for the treatment of metabolic diseases.[13] Compounds of this piperidine glycineamide series had been hindered by moderate pharmacological properties primarily due to the amide hydrolysis. In order to minimize these issues, we designed constrained analogs **III** and **IV** as shown in Figure 1. This restriction would better define the active binding conformations and mask the glycineamide structure. Since the free basic N–H is tied back to the aromatic ring, we anticipated less metabolism among these tetrahydroisoquinoline (THQ) structures (**III** and **IV**).

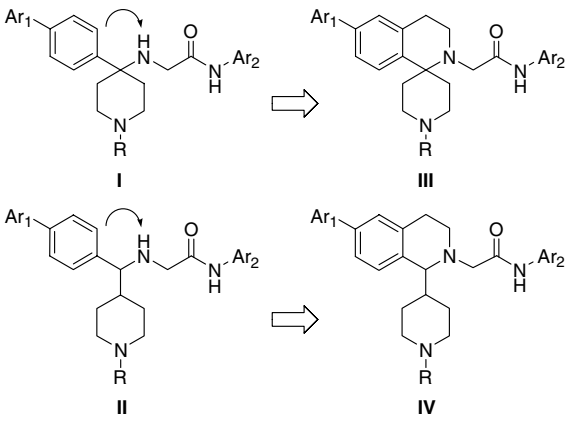

Figure 1. Design of tetrahydroisoquinoline MCH antagonists **III** and **IV**.

The synthesis of various spirocyclic as well as 2-substituted tetrahydroisoquinoline structures and structure–activity relationships (SARs) are described in this paper.

The spirocyclic tetrahydroisoquinoline compound **2** was synthesized from 3-methoxyphenethylamine **1** by Pictet–Spengler cyclization.[14] During this reaction, the *tert*-butoxy carbonyl group was hydrolyzed. The methyl group was removed by the reaction of BBr_3 and the Boc group was re-introduced in good yield. The phenol was converted to the triflate and Suzuki coupling reaction on this intermediate afforded the biaryl compound **3**.[15] N-Alkylation using methylbromoacetate gave compound **4**. Sodium hydride or trimethylaluminum mediated displacement of methyl ester with aromatic anilines afforded the corresponding amides in moderate

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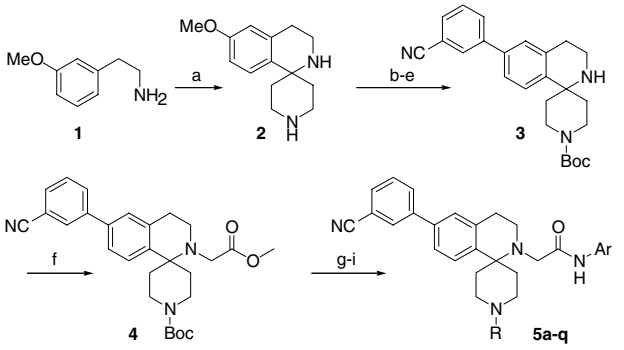
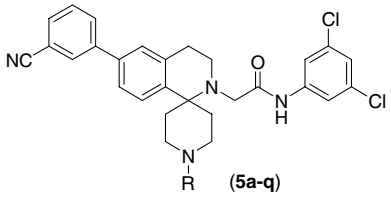
yields.[16] The Boc deprotection was achieved by trifluoroacetic acid and the reductive alkylation using a wide variety of aldehydes and ketones under standard reaction conditions furnished the final target compounds **5a**–**q** in good yields (Scheme 1).

The MCH-R1 affinities of several representative spirocyclic glycineamide compounds containing modifications on the piperidine nitrogen are shown in Table 1. A wide range of alkyl substitutions on the piperidine nitrogen is tolerated. The cyclopropylmethyl **5f**, cyclopentyl **5g**, cyclobutyl **5i**, and cycloheptyl **5j** were the best among the several other compounds prepared. Acylations and sulfonylations of the piperidine nitrogen completely eliminate the MCH-R1 binding affinity (**5n**–**q**).



Scheme 1. Reagents and conditions: (a) *N*-Boc-piperidone, H_3PO_4, 90 °C; (b) BBr_3, CH_2Cl_2; (c) Boc_2O; (d) $PhNTf_2$, CH_2Cl_2; (e) 3-CN-phenylboronic acid, $Pd(PPh_3)_4$, Na_2CO_3, Tol/MeOH, 90 °C; (f) $BrCH_2COOMe$, K_2CO_3, CH_3CN; (g) 3,5-di-Cl-aniline, NaH, THF; (h) TFA, CH_2Cl_2; (i) RCHO, $NaBH(OAc)_3$, CH_2Cl_2.

Table 1. MCH-R1 binding affinities of spirocyclic THQs (**5a**–**q**)

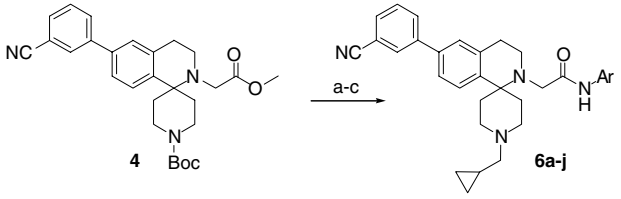


Compound	R	h-MCH-R1 K_i[a] (nM)
5a	Boc	>1000
5b	H	59
5c	Methyl	38
5d	Ethyl	38
5e	Isopropyl	29
5f	Cyclopropylmethyl	15
5g	Cyclopentyl	16
5h	1-Hydroxyethyl	41
5i	Cyclobutyl	13
5j	Cycloheptyl	11
5k	1-Tetrahydro-3-thienyl	34
5l	1-Tetrahydropyran-4-yl	16
5m	3-Furanylmethyl	36
5n	Acetyl	823
5o	Methylsulfonyl	>1000
5p	1-Dimethylaminosulfonyl	>1000
5q	1-Ethylaminosulfonyl	>1000

[a] Values are means of three experiments. Variability around the mean value was <5%.

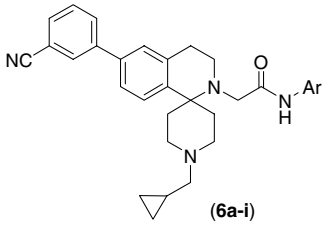
Next, we turned our attention to the alterations of the aromatic amide group in order to optimize the right-hand side of the molecule. Deprotection of **4** followed by reductive alkylation and subsequent amidation using various anilines furnished compounds **6a**–**j** (Scheme 2). As seen from Table 2, 3,5-dichlorophenyl glycineamide compound **5f** still has the best MCH-R1 binding affinity (K_i = 15 nM). Other aromatic amides such as 3-Cl-4-F-phenyl **6d** and 3-CF_3-4-F-phenyl **6h** also showed a similar binding profile. We decided to keep the 3,5-dichlorophenyl group as a constant in the further development of SAR in the THQ series.

After having examined the binding affinity of spirocyclic compounds, we began looking into the homologated tetrahydroisoquinoline structures represented by **IV** (Fig. 1). Compound of this type was prepared according to Scheme 3. At first we decided to study the biaryl SAR in detail. Pictet–Spengler cyclization of **1** with *N*-cyclopentylpiperidine-4-carboxaldehyde afforded compound **7**. Initial trials of this cyclization reaction using phosphoric acid gave mixture of products. However, cyclization reaction in boiling TFA gave **7** in 60% yield. Further modifications of **7** according to Scheme 3 afforded compounds **10a**–**p** (Table 3).



Scheme 2. Reagents and conditions: (a) TFA, CH_2Cl_2; (b) RCHO, $NaBH(OAc)_3$, CH_2Cl_2; (c) Ar-NH_2, NaH, THF.

Table 2. MCH-R1 binding affinities of spirocyclic THQs (**6a**–**i**)



Compound	Ar	h-MCH-R1 K_i[a] (nM)
5f	3,5-Dichlorophenyl	15
6a	3,5-Difluorophenyl	63
6b	3,4-Dichlorophenyl	138
6c	3-CF_3-4-Cl-phenyl	119
6d	3-Cl-4-F-phenyl	24
6e	4-Cl-phenyl	138
6f	3-Cl-phenyl	45
6g	3,4-Difluorophenyl	35
6h	3-CF_3-4-F-phenyl	25
6i	3-CF_3-5-F-phenyl	54

[a] Values are means of three experiments. Variability around the mean value was <5%.