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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**).

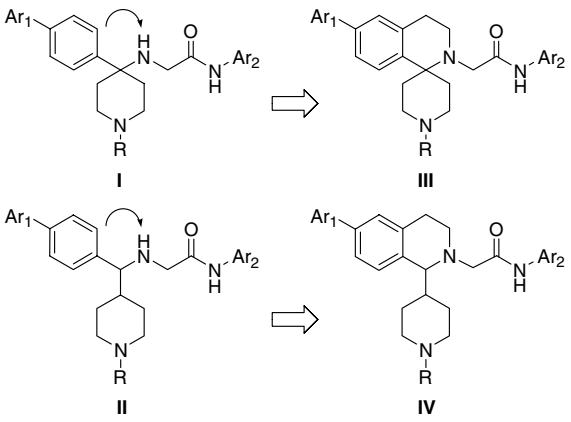

Figure 1. Design of tetrahydroisoquinoline MCH antagonists **III** and **IV**.

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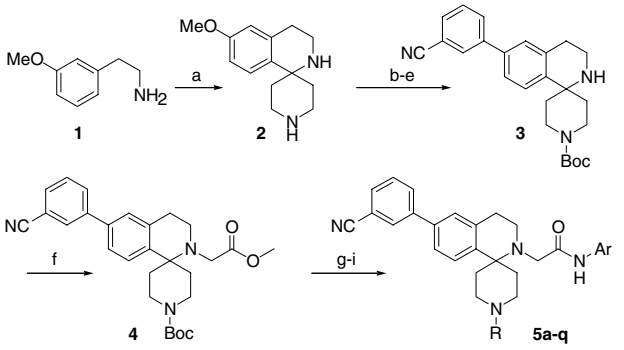
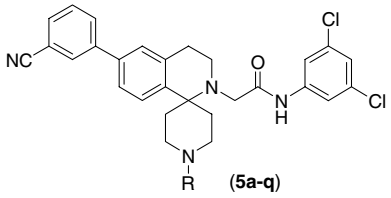
yields.[16] The Boc deprotection was achieved by trifluoroacetic acid and the reductive alkylation using a wide variety of aldehydes and ketones under standard reaction conditions furnished the final target compounds **5a**–**q** in good yields (Scheme 1).

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**)

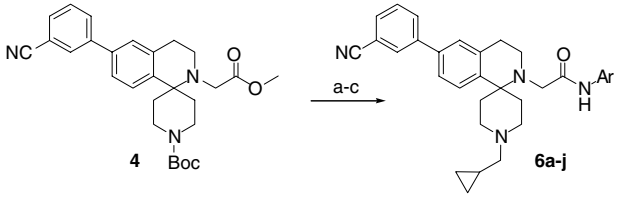


Compound	R	h-MCH-R1 K_i[a] (nM)
5a	Boc	>1000
5b	H	59
5c	Methyl	38
5d	Ethyl	38
5e	Isopropyl	29
5f	Cyclopropylmethyl	15
5g	Cyclopentyl	16
5h	1-Hydroxyethyl	41
5i	Cyclobutyl	13
5j	Cycloheptyl	11
5k	1-Tetrahydro-3-thienyl	34
5l	1-Tetrahydropyran-4-yl	16
5m	3-Furanylmethyl	36
5n	Acetyl	823
5o	Methylsulfonyl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

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

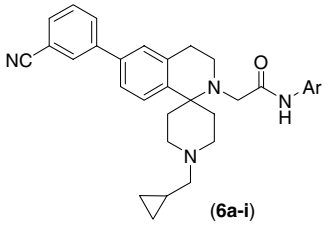
Next, we turned our attention to the alterations of the aromatic amide group in order to optimize the right-hand side of the molecule. Deprotection of **4** followed by reductive alkylation and subsequent amidation using various anilines furnished compounds **6a**–**j** (Scheme 2). As seen from Table 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).



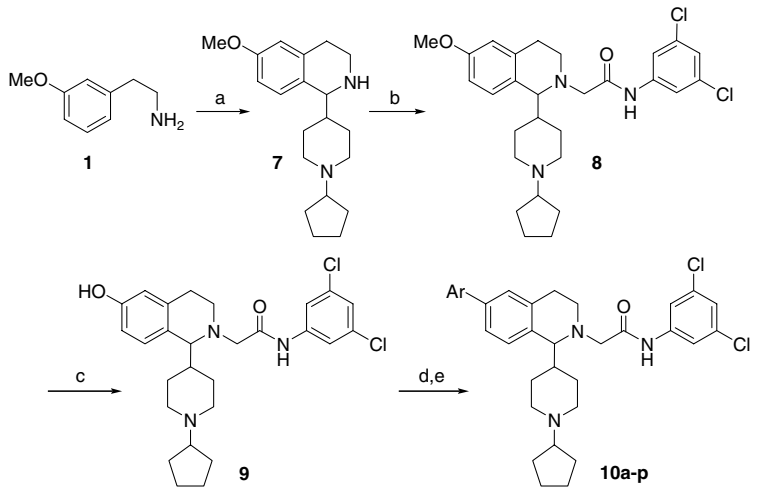
Scheme 2. Reagents and conditions: (a) TFA, CH_2Cl_2; (b) RCHO, $NaBH(OAc)_3$, CH_2Cl_2; (c) Ar-NH_2, NaH, THF.

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



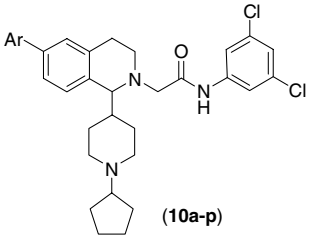
Compound	Ar	h-MCH-R1 K_i[a] (nM)
5f	3,5-Dichlorophenyl	15
6a	3,5-Difluorophenyl	63
6b	3,4-Dichlorophenyl	138
6c	3-CF_3-4-Cl-phenyl	119
6d	3-Cl-4-F-phenyl	24
6e	4-Cl-phenyl	138
6f	3-Cl-phenyl	45
6g	3,4-Difluorophenyl	35
6h	3-CF_3-4-F-phenyl	25
6i	3-CF_3-5-F-phenyl	54

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



Scheme 3. Reagents and conditions: (a) *N*-cyclopentylpiperidine-4-carboxaldehyde, TFA, reflux; (b) $BrCH_2CONHAr$, K_2CO_3, CH_3CN; (c) BBr_3, CH_2Cl_2; (d) $PhNTf_2$, CH_2Cl_2; (e) $ArB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, Tol/MeOH.

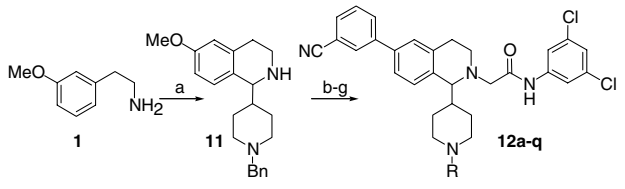
Table 3. MCH-R1 binding affinities of THQs (**10a–p**)



(**10a-p**)

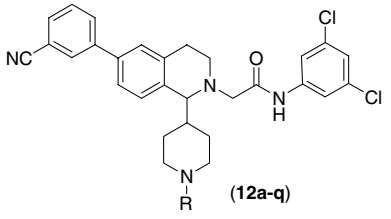
Compound	Ar	h-MCH-R1 K_i[a] (nM)
10a	3-CN-phenyl	11
10b	Phenyl	168
10c	4-CN-phenyl	108
10d	3-F-phenyl	73
10e	3-Cl-phenyl	43
10f	3-MeO-phenyl	95
10g	3-CF_3-phenyl	191
10h	3-CF_3O-phenyl	77
10i	3-CHO-phenyl	77
10j	3,6-Di-Cl-phenyl	87
10k	8-Quinolinyl	799
10l	4-Pyridyl	24
10m	3-Pyridyl	23
10n	3-(1*H*-Imidazol-2-yl)phenyl	46
10o	1*H*-Pyrrol-2-yl	455
10p	3-Thienyl	115

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



Scheme 4. Reagents and conditions: (a) *N*-benzylpiperidine-4-carboxaldehyde, TFA, reflux; (b) $BrCH_2CONHAr$, K_2CO_3, CH_3CN; (c) BBr_3, CH_2Cl_2; (d) $PhNTf_2$, CH_2Cl_2; (e) $ArB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, Tol/MeOH; (f) chloroethylchloroformate, CH_2Cl_2; (g) RCHO, $NaBH(OAc)_3$, CH_2Cl_2.

Table 4. MCH-R1 binding affinities of THQs (**12a–q**)



(**12a-q**)

Compound	R	h-MCH-R1 K_i[a] (nM)
12a	H	26
12b	Methyl	22
12c	Phenylmethyl	24
12d	5-(OH)-1-pentyl	6.8
12e	Cycloheptyl	9.7
12f	N-Methylpiperidinyl	68
12g	1-Tetrahydropyran-4-yl	6.4
12h	1-Tetrahydro-3-thienyl	7.0
12i	3-Furanylmethyl	14
12j	2-MeO-phenylmethyl	16
12k	Cyclopropylmethyl	9.3
12l	Cyclobutyl	15
12m	Phenylpropyl	69
12n	Isopropyl	35
12o	Cyclohexyl	10
12p	Acetyl	927
12q	Methanesulfonyl	718

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

As evidenced from Table 3, the biaryl portion of the molecule is less tolerant of substitutions. 3-Cyanophenyl moiety is still the best substitution in the biaryl region of the molecule. Groups like 3- and 4-pyridyls are tolerated to some extent (**10l** and **10m**). Heterocyclic substitutions such as 2-pyrrolyl **10o** and quinolyl **10k** reduce the binding affinity by 40- to 70-fold. 3-Chlorophenyl substitution **10e** afforded a 4-fold decrease in potency relative to 3-cyanophenyl.

The piperidine nitrogen SAR was studied according to Scheme 4. Pictet–Spengler cyclization of **1** with

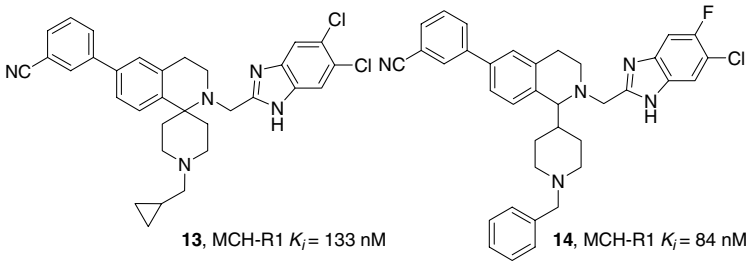


Figure 2. Benzimidazole compounds **13** and **14**.

Table 5. PK data for selected compounds

Compound	h-MCH-R1 K_i[a] (nM)	Rat PK (10 mpk, po)[b] AUC (ng h/mL)
5g	16	332
10a	11	910
12d	6.8	1636
12g	6.4	1244
12h	7	499

[a] Values are means of three experiments. Variability around the mean value was <5%.
[b] See Ref. 17 for procedure.

N-benzylpiperidine-4-carboxaldehyde afforded compound **11**. N-Alkylation of **11** followed by demethylation, triflation, and Suzuki coupling produced the biaryl compound, and subsequent debenzylation and reductive alkylations using various aldehydes and ketones gave compounds **12a**–**q** (Scheme 4).

The SAR of the MCH-R1 binding of several tetrahydroisoquinoline structures with substitutions on the piperidine nitrogen is summarized in Table 4. Generally reductive alkylation products showed excellent MCH-R1 binding affinity. Compounds such as hydroxypentyl **12d** (K_i 6.8 nM), tetrahydropyranyl **12g** (K_i = 6.4 nM), tetrahydrothienyl **12h** (K_i = 7.0 nM), and cyclopropyl methyl **12k** (K_i = 9.3 nM) are some of the very active compounds in this series. Other modifications to the piperidine nitrogen, including acylation, sulfonylation, and urea formation, resulted in inactive compounds. These results indicate that the basic nitrogens both in chemotypes **III** and **IV** are very important for MCH-R1 binding affinity. In most of the cases, the MCH-R1 SAR for chemotypes **IV** parallels that for chemotype **III**.

We briefly attempted to change the amide portion of the THQ core by introducing amide isosteres such as benzimidazoles and oxazoles. These attempts did not provide any superior MCH-R1 compounds compared to the amide derivatives. Some examples are given in Figure 2. Benzimidazole derivatives **13** and **14** showed moderate MCH-R1 binding affinity (Fig. 2).

Compounds with good MCH-R1 affinity were selected for PK studies (Table 5). Compounds like **12d** and **12g** showed remarkable improvement in pharmacokinetics. The corresponding uncyclized piperidine glycineamides showed zero or negligible rat AUC under similar experimental conditions.[17] These results indicate that conformationally restricted analogs are better MCH-R1 antagonists with improved pharmacokinetic profiles. Further in vivo results will be reported in due course.

In summary, we have undertaken a three-point modification of our tetrahydroisoquinoline (THQ) core structures and generated a number of selective MCH-R1 antagonists. Both spirocyclic as well as homologated tetrahydroisquinolines followed a similar SAR trend. We have shown that the basic nitrogen of the piperidine moiety is very important for high affinity binding. Pharmacokinetic studies confirmed an enhanced profile relative to non-THQ analogs.

Acknowledgment

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