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Bioorganic & Medicinal Chemistry Letters
Bioorganic & Medicinal Chemistry Letters 16 (2006) 5270–5274

2-Aminoquinoline melanin-concentrating hormone (MCH)1R antagonists

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Received 15 May 2006; revised 31 July 2006; accepted 1 August 2006
Available online 17 August 2006

Abstract—A series of 2-aminoquinoline compounds was prepared and evaluated in MCH1R binding and functional antagonist assays. Small dialkyl, methylalkyl, methylcycloalkyl, and cyclic amines were tolerated at the quinoline 2-position. The in vivo efficacy of compound **12** was explored and compared to that of a related inactive analog to determine their effects on food intake and body weight in rodents.

Melanin-concentrating hormone (MCH) is a cyclic peptide present in the lateral hypothalamus that is believed to be involved in energy homeostasis and feeding behavior.[1] The phenotypes of MCH KO[2] and MCH1R KO[3] mice along with rodent pharmacological studies in vivo using MCH1R agonists[4] and antagonists[5] have increased interest in MCH1R as an important central nervous system G-protein coupled receptor (GPCR) drug target. These biology and pharmacology results generated great interest in the development of MCH1R antagonists for the possible treatment of obesity[6] and depression or anxiety.[7] Many non-peptidyl MCH1R antagonists have appeared in the patent literature in recent years[8] in an effort to obtain compounds viable for clinical validation of MCH1R antagonism as a therapeutic target for human health.

In the previous letter, we described our initial work in the area of 4-aminoquinoline MCH1R antagonists.[9] Significant improvements of the original lead were made by modifications of the quinoline 2- and 6-positions to identify MCH1R antagonists exemplified by compound **1** (Fig. 1). However, we were unable to obtain further improvements on the series by modification of the 4-amino group. We subsequently proposed transposing the 4-amino group to the isoelectronic 2-amino position in the hope that modifications of the amino group at 2-position would be better tolerated for MCH1R antagonist activity. To our delight, the 2-dimethylaminoquinoline compound **2** was found to have equal MCH1R binding affinity as the related 4-aminoquinoline compound **1**.

This letter will describe the structure–activity relationships (SAR) of the isoelectronic 2-aminoquinoline-6-carboxamide MCH1R antagonists and in vivo rodent pharmacology of an optimized compound from this lead class. After the initial publication of 4-aminoquinoline[10]

Keywords: GPCR; Antagonist; Obesity; Quinoline; Melanin-concentrating hormone.
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doi:10.1016/j.bmcl.2006.08.006

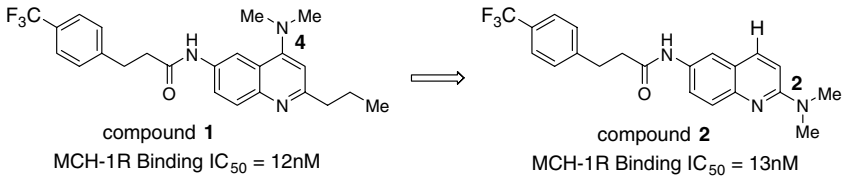


Figure 1. 4-Aminoquinoline (compound 1) and 2-aminoquinoline (compound **2**) MCH1R antagonists.

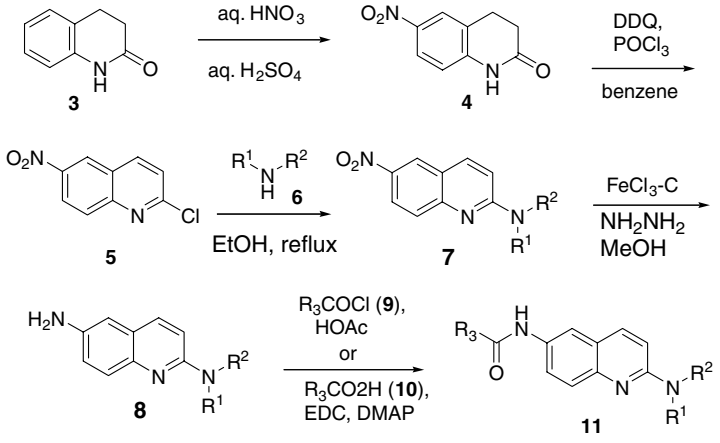
and 2-aminoquinoline[11] MCH antagonist patent applications from these laboratories, related aminoquinoline MCH1R antagonists have been reported by other laboratories.[12]

The synthesis of 2-aminoquinoline-6-carboxamide derivatives[11] is outlined in Scheme 1. Dihydroquinolinone **3** was converted according to literature procedures to the 6-nitro compound **4** under standard conditions followed by treatment with $POCl_3$ to provide 2-chloro-6-nitroquinoline **5**.[13] A variety of amines **6** could be added to the 2-position of the quinoline by refluxing with an excess of the amine in ethanol. The resulting 2-amino derivatives **7** were subsequently converted to 6-amino derivatives **8** by reduction of the 6-nitro group using $FeCl_3$–NH_2NH_2 system.[14] Simple carboxamide formation using acid chlorides **9** or carboxylic acids **10** provided the desired 2-aminoquinoline-6-carboxamide derivatives **11**.

Compounds were evaluated for their binding affinity to cloned human MCH1R in a competition binding assay with [125I]-[Phe13,Tyr19]-hMCH as the radioligand (Binding in Tables).[15] Functional activation of rat MCH1R was also assessed by stimulation of IP3-coupled mobilization of intracellular calcium in human HEK-293 cells expressing rat MCH1R (rAeq in Tables).[15] Compounds from the 2-aminoquinoline class were also screened on MCH2R and found to exhibit less than 50% inhibition at a screening dose of 4 μM, showing good selectivity for MCH1R over MCH2R.[16]

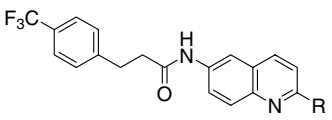
The MCH1R binding affinities and functional activities for analogs with a variety of amine substituents are shown in Table 1. The primary amine (entry 1) is much less active than the mono- and dimethyl amine analogs; results which are in contrast to those of the 4-aminoquinoline designs, where the more active analogs contained the primary amino group. This result allowed for further elaboration of the structure–activity relationships of the 2-aminoquinoline series. A series of dialkyl amine analogs showed that smaller dialkyl groups were preferred, for example, dimethylamino compound (entry 3) had superior binding affinity as compared to the diethyl and di-*n*-propyl analogs (entries 6 and 7). However, the unsymmetrical combination of a larger alkyl group with a methyl group on the amine afforded compounds with excellent binding affinity and functional antagonist activity. *N*-Propyl-*N*-methylamino (entry 4), *N*-*i*-propyl-*N*-methylamino (entry 5) groups were particularly active analogs. Cycloalkyl groups were also tolerated such as *N*-methylcyclopentyl amine and *N*-methylcyclohexyl amine, while the *N*-methyl-*N*-phenyl amino compound (entry 10) had significantly reduced MCH1R binding affinity. A series of cyclic amines were evaluated to complete the simple amino group SAR. Analogs containing small cyclic amines such as azetidine, pyrrolidine and piperidine rings (entries 11–13) were superior to the analog possessing the larger azepine ring (entry 14). In addition, the bridged bicyclic amino analog (entry 15) had comparable MCH1R binding affinity and functional activity as compared to the small ring analogs. These results allowed for the exploration of substituents on the cyclic amine analogs in order to find functional groups that might modulate the physical–chemical properties of the 2-aminoquinoline series of MCH1R antagonists.

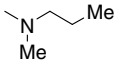
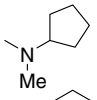
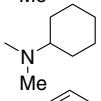
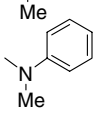
The pyrrolidine ring was chosen for further functionalization with the subset of analogs prepared shown in Table 2. Simple methyl substitution of the pyrrolidine 2- or



Scheme 1. Standard synthesis of 2-aminoquinoline-6-carboxamide MCH1R antagonist analogs. For full experimental details, see Ref. 11.

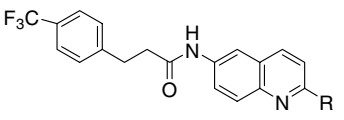
Table 1. In vitro biological activity of 2-amino substituents of 2-aminoquinoline-6-carboxamide MCH1R antagonists[a]

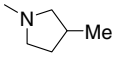
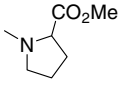
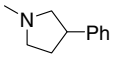
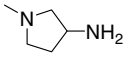
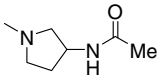
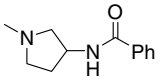
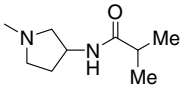
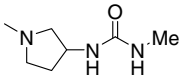
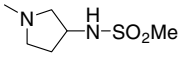
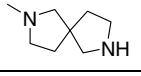


Entry	R	hBinding IC_{50}	rAeq. EC_{50}
1		240	720
2		20	330
3		13	110
4		10	140
5		2	140
6		88	830
7		490	nd
8		2	350
9		18	1200
10		3700	nd
11		4	56
12		3	320
13[b]		12	110
14		36	1800
15		3	190

[a] In vitro data in nM are the average of at least two experiments.
[b] Cinnamide analog.

Table 2. In vitro biological activity of pyrrolidine substitutents of 2-pyrrolidine quinoline-6-carboxamide MCH1R antagonists[a]



Entry	R	hBinding IC_{50}	rAeq. EC_{50}
1		3	320
2		5	270
3		2	400
4		800	580
5		25	1770
6		12	200
7		5	44
8		10	110
9		1	90
10		6	30
11		3	50
12		1	150
13		13	70
14		210	490
15		0.5	140

[a] In vitro data in nM are the average of at least two experiments.

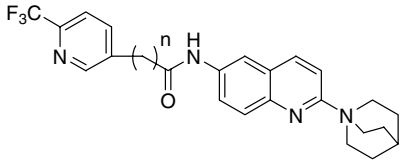
3-positions (entries 2 and 3) had minimal effect on MCH1R binding affinity and functional activity as compared to the unsubstituted pyrrolidine. The prolinate analog (entry 4), with a methyl carboxylate group at the 2-position, showed a significant decrease in binding affinity, while addition of the phenyl group to the 3-position was also deleterious to MCH1R antagonist activity. The addition of a 3-amino group (entry 6) was well tolerated and allowed for the further elaboration of the amino group into other functionalized analogs. For example, *N*-acetyl, *N*-benzoyl, and *N*-isobutyryl carbox-

amides (entries 7–9) possessed excellent binding affinities and functional MCH1R antagonist activity of near or below 100 nM. Other small functionalized amino groups such as the *N*-methyl urea (entry 10) and methanesulfonamide (entry 11) also showed low nanomolar MCH1R binding affinity and excellent functional antagonist activity. A series of bicyclic amine analogs (entries 11–15) was similarly active in the binding assay and demonstrated the variety of functionalized pyrrolidines that were useful in defining the SAR of the 2-aminoquinoline lead series.

The 2-aminoquinoline series had been sufficiently developed to provide many compounds with low nanomolar binding affinities and functional antagonist activity useful for proof-of-concept studies in vivo. The usefulness of peptidyl MCH antagonists for the reduction of food intake and body weight had been previously demonstrated[5] but the need to establish similar in vivo effects with the 2-aminoquinoline MCH antagonist series remained. Table 3 shows the profiles of two compounds chosen for intravenous infusion studies for the reduction of food intake and modulation of body weight in rats. Compound **12**, the 2-azabicyclo[2.2.2]quinoline MCH1R antagonist analog possessing the (2-trifluoromethylpyridin-5-yl)propionamide, was paired in a study with less active analog compound **13** containing a shortened (2-trifluoromethylpyridin-5-yl)carboxamide at the quinoline 6-position. Inclusion of the pyridyl group improved vehicle solubility for iv dosing as compared to the phenyl series of analogs.

Compound **12** possesses low nanomolar binding affinity on the human and rat MCH1R, and an EC_{50} of 25 nM in the rat functional assay. The related compound **13** has very poor binding affinity and functional activity making it a useful tool to determine if any impact on feeding is mechanism-based and not due to inherent toxicity of the structure class. The compounds were also matched with respect to rat pharmacokinetics, with similar half-lives and clearances, such that continuous iv infusion was determined as the optimal method of compound delivery.

Table 3. Biological profile of 2-azabicyclo[2.2.2]-quinoline-6-carboxamide MCH1R antagonist compounds **12** and **13**[a]



Compound	12 (n = 12)	13 (n = 0)
MCH1R binding	IC_{50}	IC_{50}
Human	5 nM	30%I at 5 μM
Rat	13 nM	20%I at 5 μM
MCH1R function	EC_{50}	EC_{50}
Rat	25 nM	>10 μM
Rat Pharmacokinetics		
Clp (mL/min/kg)	36	57
V_{dss} (L/kg)	1.0	3.92
$t_{1/2}$ (h)	0.6	1.1

[a] In vitro data in nM are the average of at least two experiments.

Male Sprague–Dawley rats were used to assess acute effects of an MCH1R antagonist on energy homeostasis. In order to obtain constant circulating levels of compound, lean male Sprague–Dawley rats were implanted with indwelling infusion pumps (Kent Scientific, Torrington, CT) and given an iv bolus of either compound,[5] followed by a continuous compound infusion (iv bolus 1.6 mg/kg followed by ip infusion of 1.33 mg/kg/h in 30% HPCD) for 18 h (overnight with lights out) with access to a palatable moderate high-fat diet (32% kcal fat). Compound **12** decreased overnight food intake by 26% ($p = 0.049$ vs. vehicle) with a non-significant reduction in body weight gain ($p = 0.065$) as compared to vehicle-treated controls. In a separate study, the related inactive analog, compound **13**, administered at a molar equivalent (iv bolus 5.8 mg/kg followed by ip infusion of 1.2 mg/kg/h in 30% HPCD) had no significant effects on food intake or body weight gain during the overnight study. These results indicate that the 2-aminoquinoline MCH1R antagonists, exemplified by compound **12**, reduce food intake in rodents. These feeding effects are most likely mechanism-based by antagonism of MCH1R and not due to structure-based toxicity, since the closely related inactive analog compound **13** had no effect on food intake in the parallel study.

We have described the structure–activity relationships of the 2-aminoquinoline series of MCH1R antagonists. A variety of 2-amino groups were explored with small dialkyl, methylalkyl, and methyl-cycloalkylamines providing MCH1R antagonists with high binding affinity. In addition, small cyclic, bridged, and spirocyclic amines were well tolerated at the quinoline 2-position. It was also found that aminoquinolines with 2-position pyrrolidines functionalized at the C-3 with amino, urea, carboxamide, and sulfonamide groups afforded compounds with exceptional binding and functional antagonist activity. In vivo efficacy studies showed that compound **12** from this class of MCH1R antagonists is useful for the inhibition of food intake but not body weight gain after iv bolus followed by continuous iv infusion. These effects were most likely mechanism-based since the control experiment with a closely related analog failed to have any effects on food in take and body weight thereby diminishing the possibility that non-mechanism-based toxicity or off-target activities accounted for these biological effects. These results indicate the potential of the 2-aminoquinoline class for the reduction of food intake in mammals and contribute to the ongoing validation of MCH1R as a potential target for obesity.

Acknowledgments

The authors thank Dr. A. Kanatani and Dr. M. Ito (MRL Tsukuba) for screening compounds on MCH2R.

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16. Compounds listed in Tables 1–3 were assayed for MCH2R binding affinity and found to have <50%I at the screening dose of 4 μM.