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Bioorganic & Medicinal Chemistry Letters 14 (2004) 4883–4886
Bioorganic & Medicinal Chemistry Letters

Synthesis and evaluation of 2-amino-8-alkoxy quinolines as MCHr1 antagonists. Part 3

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Received 2 July 2004; revised 15 July 2004; accepted 17 July 2004
Available online 5 August 2004

Abstract—Prior SAR studies on 2-amino-8-alkoxyquinoline MCHr1 antagonists demonstrated that compounds with acyclic amide-containing sidechains displayed exceptional binding and functional potency, but negligible CNS penetration. Related analogs with acyclic benzylamine-containing sidechains showed greatly improved CNS exposure, but suffered in functional potency. In this report, we demonstrate that cyclization of these benzylic amine sidechains affords compounds that combine the best elements of potency and CNS penetration among this class of antagonists. This is exemplified by compound **21**, which has sub-nanomolar MCHr1 binding affinity, good functional potency, and excellent CNS exposure over 24 h.

Melanin-concentrating hormone (MCH) is a cyclic 19-amino acid neuropeptide that serves as an important mediator in the regulation of energy balance and food intake in rodents.[1,2] A single injection of MCH into the CNS stimulates food intake in rodents,[3] and chronic administration leads to increased body weight.[4] Similarly, transgenic mice overexpressing the MCH gene are susceptible to insulin resistance and obesity.[5] In contrast, mice lacking the gene encoding MCH are hypophagic, lean, and maintain elevated metabolic rates.[6] Consistent with this phenotype, genetically altered animals that lack the gene encoding the MCH receptor maintain elevated metabolic rates and remain lean despite hyperphagia on a normal diet.[7,8] These lines of evidence suggest that antagonism of MCH signaling could be an effective therapy for obesity, and there has recently been intense interest in the development of small molecule antagonists of MCHr1.[9]

Proceeding reports from these laboratories described our efforts to optimize the MCHr1 antagonist A-224940 (**1**, Fig. 1), which was identified via high-throughput screening.[10,11] An investigation into aminated 8-alkoxy sidechains afforded a series of compounds typified by amide **2** and benzylamine **3**. The amide subclass represented by **2** had excellent MCHr1 binding and functional antagonism of MCH-mediated Ca^{2+} release, but negligible central nervous system (CNS) penetration in diet-induced obese (DIO) mice.[10] Conversely, the benzylamine derivatives exemplified by **3** showed high levels of brain exposure but exhibited disappointing functional potency.[11] In this manuscript we describe the synthesis and identification of a series of compounds with the best combination of potency and CNS penetration for this general class of MCHr1 antagonists. This was accomplished by constraining the aminated sidechains present in analogs such as **3** within a pyrolidine ring.

As demonstrated in Scheme 1, 2-amino-8-hydroxyquinoline **4** was alkylated via Mitsunobu reaction to afford the corresponding Boc-protected pyrolidine intermediate **5**. After TFA-mediated deprotection, regioselective functionalization of the secondary pyrolidinyl-amine afforded the final analogs.

The initial set of *N*-benzyl analogs was assayed for MCHr1 affinity and functional antagonism (representative analogs shown in Table 1). The data revealed a preference for the (*S*) configuration with respect to the secondary carbinol, as benzaldehyde derivative **7** was almost fivefold more potent in binding than the opposite

Keywords: Melanin-concentrating hormone; Obesity.
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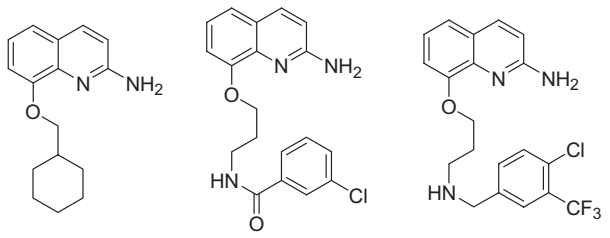
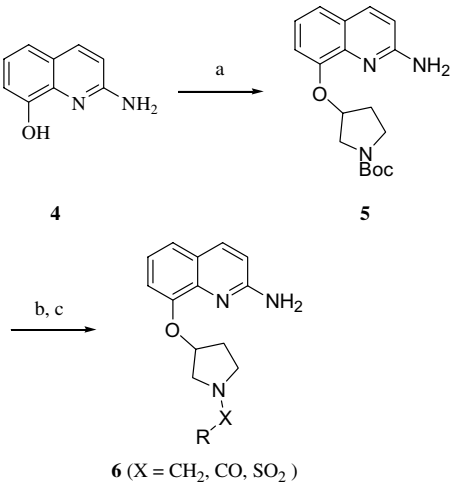
doi:10.1016/j.bmcl.2004.07.035



1 (A-224940) **2** **3**

Compound	1	2	3
MCHr1 IC_{50} (μM)	0.091	0.003	0.005
MCHr1 Functional IC_{50} (μM)	1.68	0.007	0.22
Brain/Plasma (DIO mice)	NT	0.03	0.96
Brain AUC (ng,hr/ml)	NT	11	9521

Figure 1. MCHr1 antagonists.



4 **5**

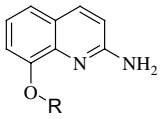
6 (X = CH_2, CO, SO_2)

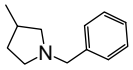
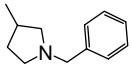
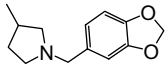
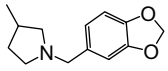
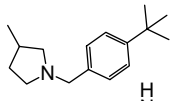
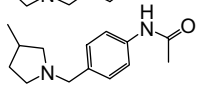
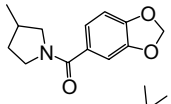
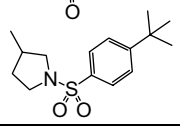
Scheme 1. Reagents and conditions: (a) ROH, DBAD, PS-PPh_3, THF; (b) TFA; (c) RCHO, 1:1 DCE/MeOH (1% AcOH), MP-$CNBH_3$,[12] 55 °C; or RCO_2H, PS-DCC, HOBt, DMF; or RSO_2Cl, PS-*N*-Me-piperazine, CH_2Cl_2.

enantiomer **8**. This was further demonstrated by the considerable potency of compound **9**, which was over 20-fold more active in binding and 45-fold more functionally potent than its enantiomer **10**. Analysis of the additional reductive amination products revealed a strong preference for *para* and *meta–para* disubstituted benzylamine derivatives with hydrophobic substituents as exemplified by the considerable potency of compound **11**. In contrast, analogs containing terminal polar functionality such as amide **12** were consistently less active.

Various tertiary amides and sulfonamides were also synthesized to explore the tolerance of the receptor for alternative linkages at this position. In contrast to the analogs described in the proceeding paper,[11] amide linked compounds such as **13** were significantly less active than the corresponding tertiary amine derivatives. Compound **13** was nearly 100-fold less potent in the binding assay than amine **9** and almost 250-fold less active in the functional assay. The presence of a sulfonamide at this position also proved deleterious to activity, with analog **14** dropping nearly 200-fold in binding potency relative to amine **11**.

Table 1. Binding and functional potency of MCHr1 antagonists



Entry	R	Config.	IMR32 binding IC_{50} (μM)[a]	IMR32 FLIPR™ IC_{50} (μM)[a]
7		(*S*)	0.124	1.69
8		(*R*)	0.58	>10.0
9		(*S*)	0.079	0.037
10		(*R*)	0.076	1.60
11		(*S*)	0.001	0.038
12		(*S*)	0.095	1.26
13		(*S*)	0.737	9.14
14		(*S*)	0.219	1.14

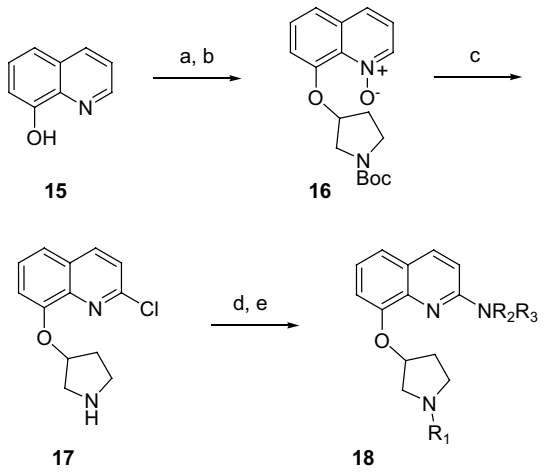
[a] Values are means of three experiments.

The potent compound **9** was dosed orally at 10 mg/kg in DIO mice to assess the CNS penetration and plasma exposure. As shown in Table 2, the brain/plasma ratio for compound **9** was greater than one, indicating efficient CNS penetration. In addition, the absolute brain exposure was greater than 1000 ng h/g over 24 h.

Encouraged by the potent binding and improved functional antagonism of the benzylamine derivatives such as **9** and **11** relative to lead **3**, in addition to the significant CNS exposure of **9** observed in DIO mice, we further explored the SAR surrounding the benzyl portion of the 3-alkoxy pyrolidine sidechain. A survey of benzaldehyde derivatives that were biased toward hydrophobic substituents and *para* or *meta*/*para* disubstitution was

Table 2. Selected PK parameters of **9** in DIO mice (10 mg/kg dose po)

	C_{max} (ng/mL or ng/g)	$T_{1/2}$ (h)	AUC (ng h/ml or ng h/g)
Plasma	543	6.5	1350
Brain	183	8.3	1711



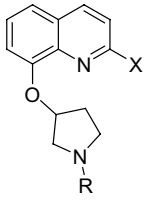
Scheme 2. Reagents and conditions: (a) 3-hydroxy-*N*-Boc-pyrolidine, DBAD, PS-PPh_3, THF; (b) *m*-CPBA, CH_2Cl_2; (c) $POCl_3$, reflux; (d) R_1CHO, 1:1 DCE/MeOH (1% AcOH), MP-$CNBH_3$, 55 °C; (e) R_2R_3NH, NMP, 220 °C.

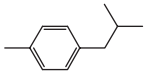
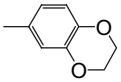
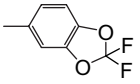
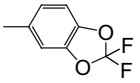
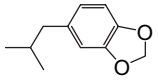
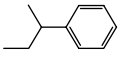
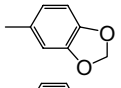
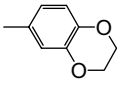
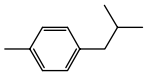
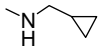
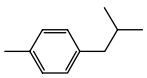
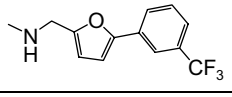
readily performed (see Scheme 1), along with a set of homobenzylic derivatives.

Additionally, as demonstrated in Scheme 2, the receptor tolerance for 2-*N*-alkylation was explored. The synthesis of the 2-alkylamino analogs was initiated by reacting 8-hydroxyquinoline with *N*-Boc-3-hydroxypyrolidine under Mitsunobu conditions followed by *N*-oxidation with *m*-CPBA to afford the *N*-oxide **16**. Refluxing **16** in $POCl_3$ effected the installation of the 2-chloro moiety with concomitant deprotection of the *N*-Boc group to afford free pyrolidine **17**. Finally, reductive amination on the pyrolidine nitrogen followed by S_NAr with amines under microwave heating conditions afforded the 2-*N*-alkylated compounds **18**.

Several analogs with improved binding and functional potency relative to **3** were identified (Table 3). Consistent with the initial set of analogs described in Table 1, terminally branched benzylamine **19** exhibited excellent

Table 3. SAR of pyrolidine-linked MCHr1 antagonists



Entry	R	X	IMR32 binding IC_{50} (nM)[a]	IMR32 FLIPR™ IC_{50} (nM)[a]
19		$-NH_2$	1.20	53.3
20		$-NH_2$	2.70	51.0
21		$-NH_2$	0.90	22.4
22[b]		$-NH_2$	38.6	531
23		$-NH_2$	2.20	79.2
24		$-NH_2$	20.5	224
25			>2000	>10,000
26			25.6	244
27			149	>10,000
28			41.0	41.0

[a] Values are means of three experiments.
[b] (*R*)-Configuration.

potency in the binding assay, although the functional antagonism dropped nearly 50-fold. The benzodioxane and difluoromethylenedioxyphenyl substituents present in analogs **20** and **21** proved to be potent bioisosteres of the methylenedioxyphenyl group present in analog **9**. In particular, compound **21** had a sub-nanomolar binding IC_{50}, making it the most potent analog in this class of pyrolidine-containing compounds. The receptor preference for the (*S*)-configuration was evident as compound **21** was over 40-fold more potent in binding than (*R*)-enantiomer **22**. The branched homobenzylic compounds **23** and **24** were also potent analogs, extending the flexibility of groups that could be used to modify the pyrolidine ring.

As observed with the open chain analogs described previously, 2-*N*-alkylation typically produced compounds with lower binding and functional potencies. Tertiary amines such as **25** were inactive, while secondary amines exemplified by **26** and **27** were tolerated but consistently less active than their primary amine counterparts. An interesting exception was compound **28**. This 2-*N*-(5-phenylfurfural) substituted analog was nearly 40-fold less active than the parent compound **19** in the binding assay, but was comparable in functional antagonism.

The highly potent compound **21** was chosen for evaluation in DIO mice. As shown in Table 4, the CNS penetration was excellent (>20 times plasma AUC), with an AUC over 17,000 ng h/g following an oral dose of 10 mg/kg. The sustained exposure over 24 h (Fig. 2) bodes well for once-a-day dosing in an efficacy model for weight loss using DIO mice.

Table 4. Selected PK parameters of **21** in DIO mice (10 mg/kg po)

	C_{max} (ng/mL or ng/g)	$T_{1/2}$ (h)	AUC (ng h/mL or ng h/g)
Plasma	331	4.6	801
Brain	2865	5.1	17,711

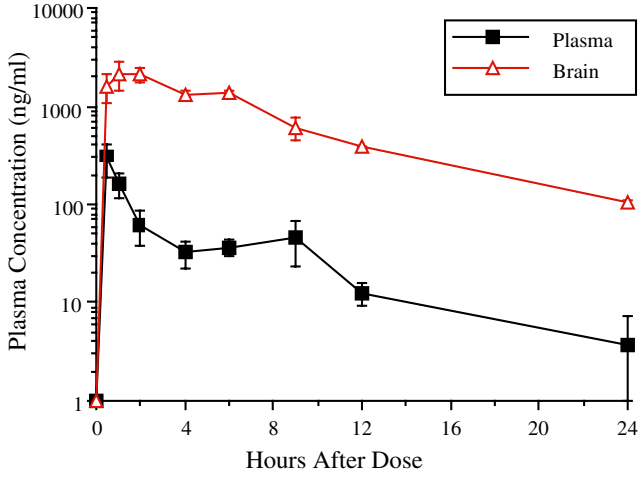


Figure 2. DIO mouse PK profile of MCHr1 antagonist **21** over 24 h.

In summary, constraining the acyclic sidechain of compounds represented by **3** into pyrolidine-linked benzylamines resulted in analogs with dramatically improved in vitro and in vivo parameters. Specifically, **21** presents the best combination of MCHr1 binding potency, functional antagonism, and CNS penetration in this class of 2-amino-8-alkoxyquinoline MCHr1 antagonists. The evaluation of this compound and related analogs in a DIO mouse model for weight loss will be fully described elsewhere.

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