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4-Aminoquinoline melanin-concentrating hormone 1-receptor (MCH1R) antagonists

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Abstract—Structure–activity relationships of a 4-aminoquinoline MCH1R antagonist lead series were explored by synthesis of analogs with modifications at the 2-, 4-, and 6-positions of the original HTS hit. Improvements to the original screening lead included lipophilic groups at the 2-position and biphenyl, cyclohexyl phenyl, and hydrocinnamyl carboxamides at the 6-position. Modifications of the 4-amino group were not well tolerated.

Melanin-concentrating hormone (MCH) is a cyclic peptide present in the lateral hypothalamus that is believed to be involved in energy homeostasis, feeding behavior as well as other potential functions.[1] Pre-prohormone MCH KO mice were shown to have reduced food intake.[2] In addition, MCH has been shown to stimulate feeding in rodents,[3] while MCH1R KO mice are hyperphagic and lean.[4] Development of MCH1R antagonists has been of interest for the possible treatment of obesity[5] and depression or anxiety.[6] To that end, peptidyl MCH1R antagonists have been identified by modification of MCH[7a] and chronic infusion of peptidyl agonists or antagonists altered appetite, body weight, and adiposity in rats.[7b] Many non-peptidyl MCH1R antagonists have appeared in the literature in recent years[8] but human clinical data to validate MCH1R antagonists as viable therapeutic agents for the treatment of human disease remain elusive.

In this letter, we describe our initial work in the area of aminoquinoline MCH 1R antagonists.[9,10a] This letter will focus on our early high-throughput screening hit from the 4-aminoquinoline MCH antagonist class, while the subsequent letter[10b] will describe the isoelectronic 2-aminoquinoline series. Related aminoquinoline MCH1R antagonists have been reported by other laboratories after the initial publication of patent applications from these laboratories.[11]

Our initial high-throughput screening hit was a 4-aminoquinoline derived from an earlier medicinal chemistry program (see entry 1, Table 1).[12] Early analog synthesis to optimize the 2-substituent, as well as to prepare 2-propyl substituted intermediates for optimization of the 6-amino substituent closely followed the literature synthesis. Treatment of 4-acetylaminoaniline (**1**) with the appropriately substituted ketonylacetates **2** in the presence of catalytic acid provided the vinylogous urethane intermediates **3**. Alternatively, alkyl substituted acetylene carboxylates **4** were also used to prepare the vinylogous urethane quinoline precursors **3** from aniline

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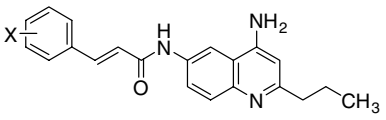
Table 1. In vitro biological activity of substituted cinnamyl carboxamides[a]

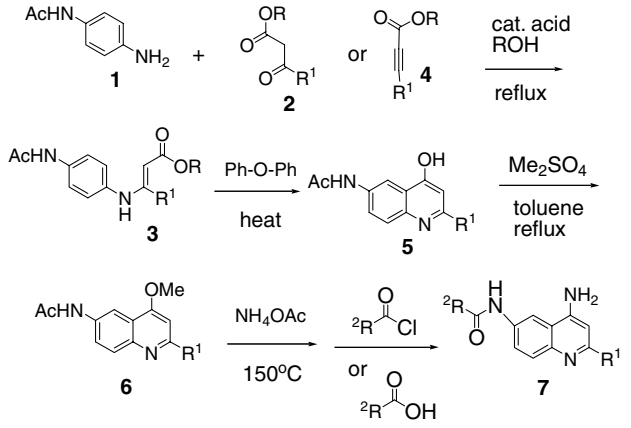


Entry	X	Binding IC_{50}	Aeq. EC_{50}
1	2-Ci	120	500
2	H	1000	nd
3	3-Ci	1100	nd
4	4-Ci	6	96
5	4-F	130	200
6	4-Br	4	93
7	4-I	2.3	280
8	4-Me	9	71
9	4-CF_3	1.3	61
10	4-Et	1.4	160
11	4-*n*-Pr	4	3600
12	4-*n*-Bu	45	740
13	4-*i*-Pr	2.9	520
14	4-*t*-Bu	22	910
15	4-SMe	9	71
16	4-Ph	1.1	118
17	2,4-DiCi	6.6	904
18	3,4-DiCi	60	990
19	4-NO_2	20	310
20	4-NH_2	790	nd
21	4-OAc	95	630
22	4-OH	1100	nd

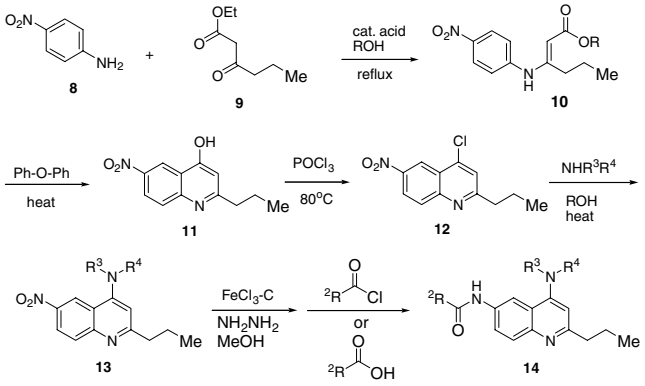
nd, not determined.

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

1 in good yields. Heating the intermediates **3** at high temperature in diphenyl ether resulted in the smooth cyclization to 2-alkyl-4-hydroxy-6-acetamido quinoline intermediates **5**. Subsequent alkylation with dimethyl sulfate provided ether intermediates **6**. Heating with ammonium acetate at 150 °C followed by hydrolysis of the acetamide provided the 4,6-diaminoquinolines. Selective derivatization at the more reactive 6-position using standard reaction protocols to execute, for example, amide bond formation, provided the 2-alkyl-4-aminoquinoline-6-aminocarboxamide analogs **7** Scheme 1.



Scheme 1. Standard synthesis of 2-alkyl-4-amino quinoline MCH1R antagonist analogs. For full experimental details, see Ref. 9.



Scheme 2. Standard synthesis of 2-propyl-4-substituted aminoquinoline MCH1R antagonist analogs. For full experimental details, see Ref. 9.

A more versatile intermediate, from which selective reactions at the 4- and 6-positions could be achieved, was prepared as outlined in Scheme 2. Condensation of 4-nitroaniline (**8**) with ethyl 3-oxohexanoate (**9**) provided the intermediate vinylogous urethanes **10**, which upon heating in diphenyl ether gave 2-propyl-4-hydroxy-6-nitroquinoline (**11**). Treatment with $POCl_3$ at 80 °C provided 4-chloroquinoline intermediate **12**, suitable for selective amination of the 4-position. Treatment with a variety of amines provided analogs to explore the 4-position structure–activity relationships for MCH1R binding affinity. Later, clean reduction of the 6-nitro group with $FeCl_3$-hydrazine system,[13] followed by derivatization of the intermediate 6-amino group, afforded the 6-acylamino quinoline analogs **14** with alkyl substituents on the 4-amino group.

Compounds were evaluated for their binding affinity to cloned human MCH1R in a competition binding assay with [^{125}I]-[Phe13,Tyr19]-hMCH as the radioligand (binding in Tables).[7a] Functional activation of MCH1R was also assessed by stimulation of IP3-coupled mobilization of intracellular calcium in human HEK-293 cells expressing MCH1R (Aeq. In Tables).[7a] This series of compounds had good selectivity over MCH2R; most compounds had less than 50% inhibition at a screening dose of 2 μM.

The HTS hit, from a C5a-receptor antagonist program, the 2-chlorocinnamide shown in Table 1, entry 1, had MCH1R binding affinity of 120 nM. We initially explored the structure–activity relationships of the cinnamide group and rapidly found that substitution at the 4-position was preferred. No 4-substituent, entry 2 or 3-Cl substituted analog, entry 3, provided compounds with 10-fold decreased binding affinity, while the 4-Cl analog, entry 4, showed 19-fold improved binding affinity and functional activity of 96 nM as compared to the 2-Cl HTS hit. We rapidly expanded the SAR and found that a wide variety of lipophilic 4-substituents including bromide, iodide, alkyl, trifluoroalkyl, and phenyl groups provided compounds with binding affinities less than 10 nM with good functional antagonist activity. 4-Fluoro substituent, disubstituted phenyl, and more polar

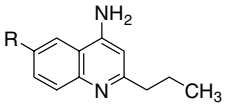
4-substituents such as nitro, amino, acetoxy, and hydroxy were deleterious to MCH1R binding affinity and functional activity. The trifluoromethyl group (entry 9) was selected for future analog work due to its excellent binding and functional activity, presumed metabolic stability, and lipophilicity which might positively impact access to MCH1R in the brain.

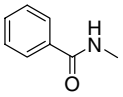
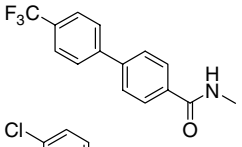
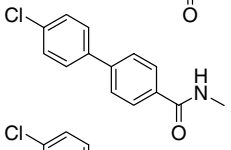
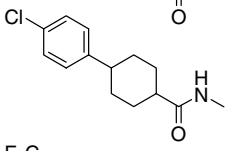
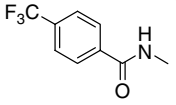
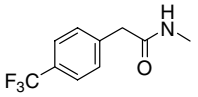
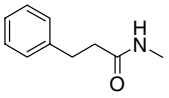
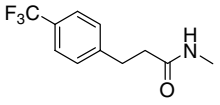
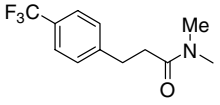
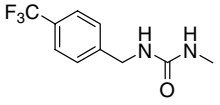
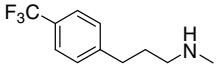
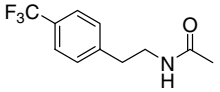
We were interested in removing the cinnamide group due to its potential reactivity with nucleophiles at the β-position of the olefin. Table 2 shows analogs in which the cinnamide has been replaced with other carboxamides. A simple benzamide leads to an inactive analog (entry 1). Incorporation of the biphenyl scaffold significantly improves MCH1R activity (see Table 1, entry 16). The 4′-trifluoromethyl biphenyl carboxamide (entry 2) had comparable binding affinity but reduced functional activity as compared to the unsubstituted biphenyl analog. The 4′-chloro-biphenyl carboxamide (entry 3) had subnanomolar binding affinity and improved functional activity, while the 4-chlorophenyl-4-cyclohexyl analog had somewhat reduced binding affinity. The 4-trifluoromethyl substituted benzamide and phenylacetamide (entries 5, 6) were also much less active. The hydrocinnamide entry 7 had improved binding affinity, however, incorporation of the 4-CF_3 group (entry 8) provided a compound with binding affinity of 13 nM and functional activity of 110 nM. Other functional groups were explored as a linkage from the quinoline 6-position to the preferred 4-trifluoromethylated phenyl pharmacophore. For example, N-methylated carboxamide, trifluoromethyl benzyl urea, 4-trifluoromethylphenylpropylamine (removal of the carboxamide carbonyl), and the 'reversed' carboxamide groups (entries 9–12, respectively) were modifications that provided less active MCH1R antagonist analogs. These structure–activity relationships demonstrate that rigid scaffolds such as a *trans*-olefin, 4-4′-biphenyl, cyclohexylphenyl or the proper alkyl chain length to the phenyl substituent, linked to the quinoline 6-position, are desired for improved MCH1R binding affinity and functional antagonist activity.

The analogs with modifications of the quinoline 2-substituent are shown in Table 3. Straight-chain and branched alkyl groups are well tolerated and lead to compounds with high binding affinities and less than 100 nM functional antagonist activities. Optimal analogs included substituents such as the *n*-propyl (of the original lead, entry 3), isobutyl (entry 7), and cyclopentyl (entry 11) groups. The cyclohexyl group was also well tolerated; however installation of a phenyl ring (entry 13) provided a compound with reduced binding affinity and minimal functional antagonist activity (albeit from the 4-chlorocinnamide series—compare entries 3 and 9 from Table 1).

The last area of structure modification to be explored was the 4-position of the quinoline. The amine of the original lead series was important for MCH1R binding affinity as shown by lack of activity for the 4-hydroxy analog (entry 2). The methyl ether analog (entry 3) was much improved over the hydroxyl analog but still possessed reduced binding affinity and functional activity as compared to the isosteric but basic *N*-methylamine analog entry 4. Incorporation of larger monoalkyl groups and dialkyl substituted amines led to analogs with much reduced binding affinity and functional activ-

Table 2. In vitro biological activity of 6-substituted-4-aminoquinolines[a]

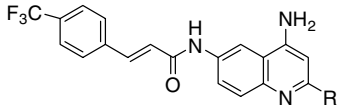


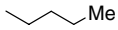
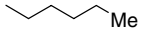
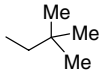
Entry	R	Binding IC_{50}	Aeq. EC_{50}
1		na	nd
2		4.5	310
3		0.7	75
4		4.4	370
5		10,000	nd
6		4000	nd
7		8300	nd
8		13	120
9		1700	nd
10		38	380
11		180	1000
12		2700	nd

na, not active; <50%I at 10 μM. nd, not determined. Synthesis of entries 10–12 described in Ref. 9.

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

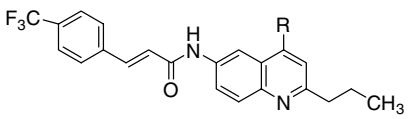
Table 3. In vitro biological activity of 2-substituted-4-aminoquinolines[a]



Entry	R	Binding IC_{50}	Aeq. EC_{50}
1		8	140
2		1.2	110
3		2	40
4		1.5	210
5		1.2	90
6		2.1	160
7		0.3	44
8		0.3	29
9		5.8	110
10		2.0	250
11		0.8	68
12		1.2	96
13[b]		18.5	6600

[a] In vitro data in nM are the average of at least two experiments.
[b] Entry 13, 4-chloro not 4-trifluoromethyl cinnamide.

Table 4. In vitro biological activity of 4-substituted quinolines[a]



Entry	R	Binding IC_{50}	Aeq. EC_{50}
1		1.3	60
2		na	nd
3		26	360
4		1.5	150
5		4.8	340
6		40	nd
7		18	2700
8		43	300
9		1100	nd
10		2.8	2500
11		17	2800
12		>4000	nd

na, not active; <50I at 10 μM; nd, not determined. Entry 7, MCH2R binding IC_{50} = 960 nM.
[a] In vitro data in nM are the average of at least two experiments.

ity. In addition, cyclic amines such as azetidine, pyrrolidine, and piperidine were not advantageous for MCH1R binding affinity. The analogs in Table 4 demonstrate minimal tolerance for modifications at the 4-position with optimal substituents limited to the unsubstituted amino group or small *N*-alkyl amines.

The structure–activity relationships of 4-aminoquinoline MCH1R antagonist lead series were explored by synthesis of analogs with modifications at the 2-, 4-, and 6-positions of the original HTS hit. Lipophilic groups were well tolerated at the 2-position, with *n*-propyl, *tert*-butyl, and cyclopentyl groups being optimal. 6-Aminocarboxamides of the original lead were moderately improved upon, but more importantly, replacements for the potentially reactive cinnamide moiety were identified such as biphenyl, cyclohexyl phenyl, and hydrocinnamyl carboxamides. Modifications of the 4-amino group were not well tolerated with the optimal substituent being the unsubstituted amine identified from the original lead.

The inability to substantially modify this initial amino quinoline MCH1R antagonist lead class, especially for physical chemical properties, led us to explore other permutations of the aminoquinoline substructure. Ultimately, this led to the design of the isoelectronic 2-aminoquinoline series of MCH1R antagonists. The development of this lead class is described in the subsequent paper.[10b]

References and notes

1. Qu, D.; Ludwig, D. S.; Gammeltoft, S.; Piper, M.; Pelley-Mounter, M. A.; Cullen, M. J.; Mathes, W. F.; Przypek, R.; Kanarek, R.; Maratos-Flier, E. *Nature* **1996**, *380*, 243.
2. Shimada, M.; Tritos, N. A.; Lowell, B. B.; Flier, J. S.; Maratos-Flier, E. *Nature* **1998**, *396*, 670.
3. Rossi, M.; Choi, S. J.; O'Shea, D.; Miyoshi, T.; Ghatei, M. A.; Bloom, S. R. *Endocrinology* **1997**, *138*, 351.
4. (a) Chen, Y.; Hu, C.; Hsu, C. K.; Zhang, Q.; Bi, C.; Asnicar, M.; Hsiung, H. M.; Fox, N.; Slieker, L. J.; Yang, D. D.; Heiman, M. L.; Shi, Y. *Endocrinology* **2002**, *143*, 2469; (b) Marsh, D. J.; Weingarth, D. T.; Novi, D. E.; Chen, H. Y.; Trumbauer, M. E.; Chen, A. S.; Guan, X.-M.; Jiang, M. M.; Feng, Y.; Camacho, R. E.; Shen, Z.; Frazier, E. G.; Yu, H.; Metzger, J. M.; Kuca, S. J.; Shearman, L. P.; Gopal-Truter, S.; MacNeil, D. J.; Strack, A. M.; MacIntyre, D. E.; Van der Ploeg, L. H. T.; Qian, S. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 3240.
5. Kowalski, T. J.; McBriar, M. D. *Expert Opin. Investig. Drugs* **2004**, *13*, 2469.
6. (a) Chaki, S.; Yamaguchi, J.-I.; Yamada, H.; Kanuma, K.; Sekiguchi, Y. *Drug Dev. Res.* **2005**, *65*, 278; (b) Dyck, B. *Drug Dev. Res.* **2005**, *65*, 291.
7. (a) Bednarek, M. A.; Hreniuk, D. L.; Tan, C.; Palyha, O. C.; MacNeil, D. J.; Van der Ploeg, L. H. T.; Howard, A. D.; Feighner, S. D. *Biochemistry* **2002**, *41*, 6383; (b) Shearman, L. P.; Camacho, R. E.; Striblings, D. S.; Zhou, D.; Bednarik, M. A.; Hreniuk, D. L.; Feighner, S. D.; Tan, C.; Howard, A. D.; Van der Ploeg, L. H. T.; MacIntyre, D. E.; Hickey, G. J.; Strack, A. M. *Eur. J. Pharm.* **2003**, *475*, 37.
8. Dyke, H. J.; Ray, N. C. *Expert Opin. Ther. Patents* **2005**, *15*, 1303.
9. DeVita, R. J.; Chang, L.; Hoang, M.; Jiang, J.; Lin, P.; Sailer, A. W.; Young, J. R. WO 03045920, 2003, 4-Aminoquinoline MCH antagonists. All compounds characterized by LC–MS and/or ^{1}H NMR.
10. (a) DeVita, R. J.; Chang, L.; Hoang, M.; Jiang, J.; Lin, P.; Sailer, A.W.; Young, J.R. WO 03045313, 2003, 2-Aminoquinoline MCH Antagonists; (b) Jiang, J.; Hoang, M. T.; Lin, P.; Chang, L.; Tan, C.; Feighner, S. D.; Palyha, O. C.; Pan, J.; Sailer, A. W.; MacNeil, D. J.; Howard, A. D.; Van der Ploeg, L. H. Y.; Goulet, M. T.; DeVita, R. J. *Bioorg. Med. Chem. Lett.* **2006**, *16*. doi:10.1016/j.bmcl.2006. 08.006.
11. (a) Arienzo, R.; Clark, D. E.; Cramp, S.; Daly, S.; Dyke, H. J.; Lockey, P.; Norman, D.; Roach, A. G.; Stuttle, K.; Tomlinson, M.; Wong, M.; Wren, S. P. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4099; (b) Souers, A. J.; Wodka, D.; Gao, J.; Lewis, J. C.; Vasudevan, A.; Gentles, R.; Brodjian, S.; Dayton, B.; Ogiela, C. A.; Fry, D.; Hernandez, L. E.; Marsh, K. C.; Collins, C. A.; Kym, P. R. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4873; (c) Vasudevan, A.; Wodka, D.; Verzal, M. K.; Souers, A. J.; Gao, J.; Brodjian, S.; Fry, D.; Dayton, B.; Marsh, K. C.; Hernandez, L. E.; Ogiela, C. A.; Collins, C. A.; Kym, P. R. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4879; (d) Souers, A. J.; Wodka, D.; Gao, J.; Lewis, J. C.; Vasudevan, A.; Brodjian, S.; Dayton, B.; Ogiela, C. A.; Fry, D.; Hernandez, L. E.; Marsh, K. C.; Collins, C. A.; Kym, P. R. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4883; (e) Clark, D. E.; Higgs, C.; Wren, S. P.; Dyke, H. J.; Wong, M.; Norman, D.; Lockey, P.; Roach, A. G. *J. Med. Chem.* **2004**, *47*, 3962; (f) Ulven, T.; Frimurer, T. M.; Receveur, J.-M.; Little, P. B.; Rist, O.; Norregaard, P. K.; Hogberg, T. *J. Med. Chem.* **2005**, *48*, 5684; (g) Ulven, T.; Little, P. B.; Receveur, J.-M.; Frimurer, T. M.; Rist, O.; Norregaard, P. K.; Hogberg, T. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1070.
12. Lanza, T. J.; Durette, P. L.; Rollins, T.; Siciliano, S.; Cianciarulo, D. N.; Kobayashi, S. V.; Caldwell, C. G.; Springer, M. S.; Hagmann, W. K. *J. Med. Chem.* **1992**, *35*, 252.
13. Hirashima, T.; Manabe, O. *Chem. Lett.* **1975**, 259.