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# 6-Acylamino-2-amino-4-methylquinolines as potent melanin-concentrating hormone 1 receptor antagonists: Structure–activity exploration of eastern and western parts

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**Abstract**—SAR explorations of the eastern and western parts of recently disclosed 2-aminoquinoline MCH1R-antagonists are reported. Eastern part investigations confirmed a high degree of structural freedom, and a number of additional single digit nanomolar antagonists were identified. Investigations of the western part also confirmed the initial SAR analysis, requiring a *para*-substituted phenyl ring spaced from the 6-amide by two connecting atoms. The exploration led to the discovery of a novel sub-series with a 4-biphenylcarboxamide western part, also exhibiting single digit nanomolar affinity.


Obesity has become a global epidemic and is no longer regarded as a cosmetic problem but a major contributor to the development of diseases including type 2 diabetes mellitus, coronary heart disease, certain forms of cancer, osteoarthritis, and sleep apnoea.[1] The increasing understanding of central control mechanisms, especially hypothalamic neuropeptide pathways, has provided novel targets for potential anti-obesity agents.[2,3]

Melanin-concentrating hormone (MCH) is a neuropeptide found in rat and human brain, and the evidence for involvement of MCH in feeding and body weight regulation is abundant.[4] Two seven transmembrane (7TM) G protein-coupled receptors, MCH1R (SLC-1) and MCH2R (SLT), have been identified for MCH.[4] The former is recognized as an interesting target for treatment of obesity and has triggered substantial drug discovery efforts.[5–10]

We[7] and others[8,9] have recently reported a series of 6-acylamino-2-aminoquinoline MCH1R antagonists (Fig. 1). We identified this series by in silico screening of commercial compound libraries using 3D pharmacophore models which were based on a series of benzamide MCH1R antagonists from our laboratories (Fig. 2).[10] During a scaffold-based search, we found equipotent compounds lacking the aliphatic terminal nitrogen (e.g., **B**), which led us to revise our receptor binding hypothesis for this class of compounds.[7a] However,

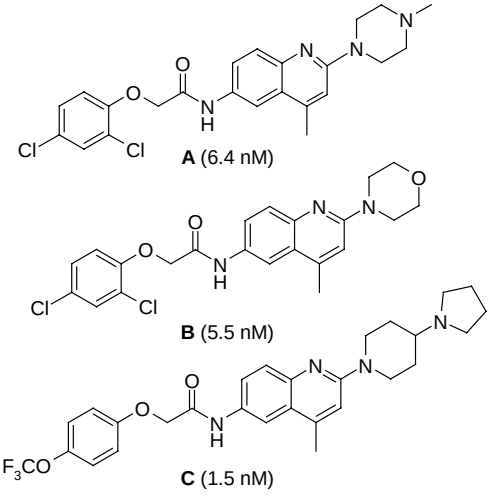


**Figure 1.** 2-Aminoquinoline MCH1R antagonists ($IC_{50}$, whole cell binding).[7a]

*Keywords*: Melanin-concentrating hormone; MCH1R antagonists; Obesity.
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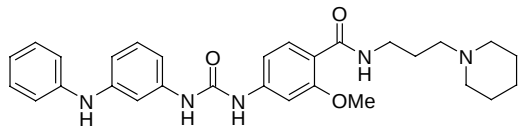



**D** (8.1 nM)

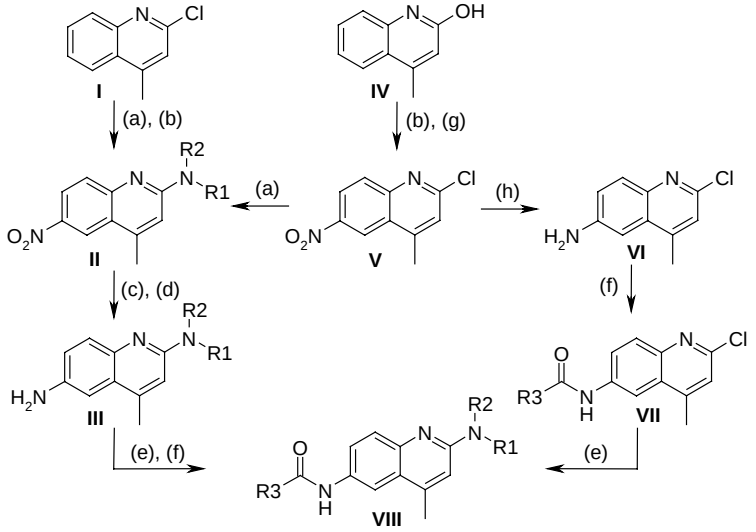
**Figure 2.** Benzamide MCH1R antagonist ($IC_{50}$, whole cell binding).[10]

the solubility properties of these compounds were poor and after structural exploration the 4-trifluoromethoxyphenoxyacetamide western appendage (e.g., **C**) was found to possess an optimal combination of potency and solubility properties (Fig. 1). Herein, we present the results from studies further exploring the structure–activity relationships (SAR) of the eastern part of the compounds carrying the preferred 4-trifluoromethoxyphenoxyacetamide and from further SAR-studies of the western appendage containing a flexible and basic dimethylaminoethylamine side chain providing favorable solubility properties.

The compounds were conveniently obtained by either of the two synthetic routes outlined in Scheme 1, as described previously.[7a]

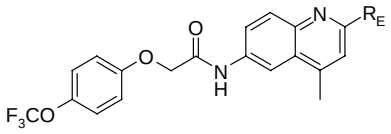
In the initial SAR exploration, we found that various structural changes in the eastern part of the compounds were congruent with high affinity, and the eastern amine originally presumed to be required for activity turned out not to contribute to the affinity of the compounds, since we later provided support for an interaction of the quinoline core nitrogen with Asp123 in the third TM domain of the MCH1R.[7a] The 4-trifluoromethoxyphenoxyacetamide western part was found to possess the optimal combination of activity and solubility properties, and compound **1** was chosen as the starting point for the further exploration of the eastern part (Table 1). The compounds were tested in the SPA binding assay, and selected compounds were also tested in the whole cell binding assay and for antagonistic activity in an inositol phosphate assay.[11] Various changes, like removal of the methyl group on the adjoining amine (**2**), extension of the substituents on the terminal amine to ethyl (**3**) or isopropyl (**4**), ring closure to form a terminal morpholine (**5**) or piperidine (**6**), constrainment to form dimethylaminopyrrolidine (**7**), insertion of a bulky dimethylmethylene group (**8**), a large *N*-benzyl-4-piperidinyl (**9**), and piperazines with methyl groups in various positions (**10**–**12**) all resulted in compounds with high affinity. The only modification that resulted in lower affinity was introduction of 3,5-dimethylpiperazine (**13**), whereas 2,5-dimethylpiperazine (**14**) produced a compound with high affinity, as did homopiperazines (**15** and **16**) and in particular *N*-hydroxyethylpiperazine (**17**). Clearly, a high degree of structural freedom was found in these basic side chains which convey appreciable physicochemical features and solubility as detailed earlier.[7a]

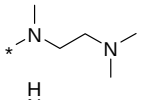
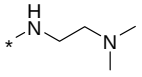
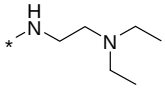
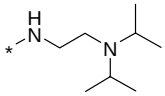
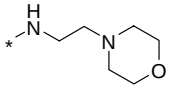
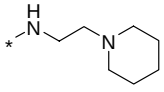
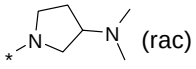
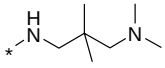
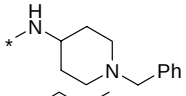
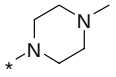
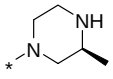
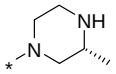
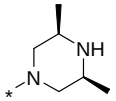
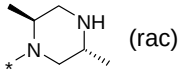
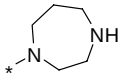
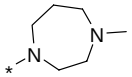
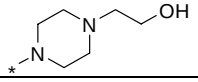
In our initial SAR analysis, based on commercial 2-aminoquinolines, the preferred western part was an amide in the 6-position of the quinoline connected by a two-atom linker, preferably methyleneoxy or *trans*-ethene, to a *para*-substituted phenyl ring. The phenyl ring could also carry a small *ortho*-, but not *meta*-substituent. To further explore the SAR of this region we synthesized the library presented in Table 2. We reasoned that a more flexible eastern part would better accommodate variation in the western part, thus, 2-(2-dimethylaminoethyl)methylamine was chosen. The analogs having *para*-substituted western phenyl rings, like chloro (**18**), methyl (**19**), and in particular trifluoromethoxy (**1**, **20**, and **21**), exhibited high affinity, whereas compounds lacking the *para*-substituent (**22**–**26**) all exhibited low or no affinity. Introduction of *ortho*-chloro (**27**) or constrainment to form benzothiophene (**28**) appears to induce a slight increase in affinity. Removing the two-carbon linker while keeping the 4-trifluoromethoxy substituent (**29**) also dramatically decreased affinity.




**Scheme 1.** Reagents and conditions: (a) amine (HNR1R2) (2–50 equiv), neat or in EtOH or DMF, Δ; (b) >90% $HNO_3$, 0 °C, 1 h; (c) If R2 = H: $Boc_2O$, $Et_3N$; (d) $H_2$, Pd/C, THF; (e) acid chloride (R3COCl), $CH_2Cl_2$, rt, 3 h; (f) if R2 = Boc: TFA, $CH_2Cl_2$; (g) $POCl_3$, 150 °C (microwaves), 5 min (97%); (h) $H_2$, 5% Pt/C, MeOH, rt, 2 h (82%) or $SnCl_2{\cdot}2H_2O$, HCl (concd), AcOH.

**Table 1.** Binding and antagonistic activity on MCH1R of aminoquinolines with diverse eastern appendages



| Compound | $R_E$ | MCH1 | | |
|---|---|---|---|---|
| | | $IC_{50}$ WC (nM)[a] | $IC_{50}$ SPA (nM)[b] | $IC_{50}$ IP3 (nM)[c] |
| **1** |  | 2.3 | 18 ± 1.3 | 31 |
| **2** |  | 5.3 | 18 | |
| **3** |  | 3.2 | 15 | |
| **4** |  | 7.1 | 22 | |
| **5** |  | 1.3 | 9.6 | 16 |
| **6** |  | 0.91 ± 0.30 | 5.3 ± 3.7 | 33 |
| **7** |  (rac) | 2.4 | 6.2 | 82 |
| **8** |  | 4.7 | 16 ± 6.9 | 192 |
| **9** |  | 13 | 40 | 91 |
| **10** |  | 2.3 | 29 | 25 |
| **11** |  | 3.7 | 13 | |
| **12** |  | 4.1 ± 0.87 | 18 | 100 |
| **13** |  | 44 | 87 | |
| **14** |  (rac) | 3.4 | 20 | |
| **15** |  | 2.0 | 12 ± 6.8 | 71 |
| **16** |  | 3.7 | 20 | 244 |
| **17** |  | 1.7 | 5.0 | 23 |

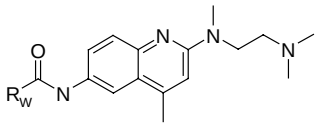
Single determinations unless indicated as range for $n = 2$.

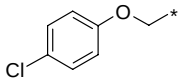
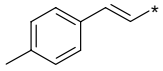
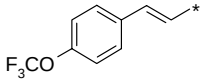
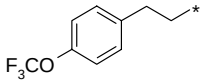
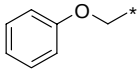
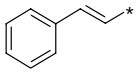
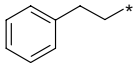
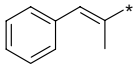
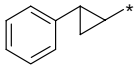
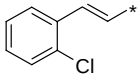
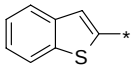
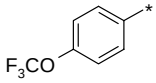
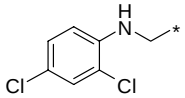
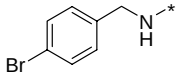
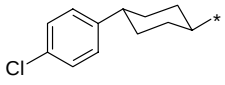
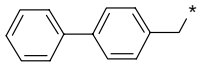
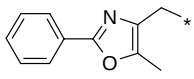
[a] Binding (CHO-whole cells).[7,11]

[b] Binding (membranes).[7,11]

[c] Inhibition of MCH-included phosphatidylinositol accumulation (CHO-whole cells).[7,11]

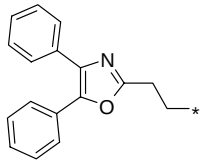
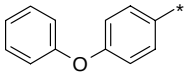
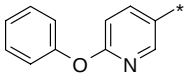
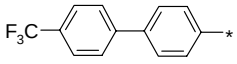
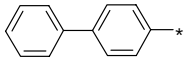
**Table 2.** Binding and antagonistic activity on MCH1R of aminoquinolines with diverse western appendages



| Compound | $R_W$ | MCH1 | | |
|---|---|---|---|---|
| | | $IC_{50}$ WC (nM)[a] | $IC_{50}$ SPA (nM)[b] | $IC_{50}$ IP3 (nM)[c] |
| **18** |  | 33 | 83 | 807 |
| **19** |  | 17 | 48 | 478 |
| **20** |  | 16 | 19 | 144 |
| **21** |  | 14 | 40 ± 3.2 | 724 |
| **22** |  | | >10,000 | |
| **23** |  | | 6970 | |
| **24** |  | | >10,000 | |
| **25** |  | | 9460 | |
| **26** |  (rac) | | >10,000 | |
| **27** |  | | 2540 | |
| **28** |  | | 2100 | |
| **29** |  | | 2760 | |
| **30** |  | | 125 | |
| **31** |  | | 271 | |
| **32** |  | 23 | 423 | 393 |
| **33** |  | | 3280 | |
| **34** |  | | 568 | |

(*continued on next page*)

**Table 2** (*continued*)

| Compound | $R_W$ | MCH1 | | |
|---|---|---|---|---|
| | | $IC_{50}$ WC (nM)[a] | $IC_{50}$ SPA (nM)[b] | $IC_{50}$ IP3 (nM)[c] |
| **35** |  | | 162 | |
| **36** |  | | 210 ± 21 | |
| **37** |  | | 105 | |
| **38** |  | 10 | 63 | 474 |
| **39** |  | 5.7 | 42 ± 28 | 25 |

Single determinations unless indicated as range for $n = 2$.
[a] Binding (Binding (CHO-whole cells).[7,11]
[b] Binding (membranes).[7,11]
[c] Inhibition of MCH-included phosphatidylinositol accumulation (CHO-whole cells).[7,11]

These observations all corroborated our initial SAR analysis.

Replacement of the oxygen atom in the methyleneoxy linker with a nitrogen atom (**30**) gave a lower but nevertheless acceptable affinity. Turning this methyleneaza linker around, and thus forming a urea (**31**), resulted in a further loss of affinity. Notably, replacement of the two-carbon linker with a *trans*-1,4-cyclohexylene linker produced a compound (**32**) with respectable affinity and functional activity. Several bi- and tri-aryl systems were also investigated. Whereas the 4-biphenylmethyl (**33**) and the 2-phenyl-4-methyloxazol-3-ylmethyl (**34**) did not produce interesting affinity, the bulky 4,5-diphenyloxazole **35** exhibited higher affinity than expected, considering the strict requirements observed in this part of the compound. The initial commercial compound selection contained a number of compounds with western aromatic rings connected directly to the amide.[7a] None of these displayed significant affinity, the only exception being a 4-butylbenzamide analog. Introducing a second aromatic ring in the 4-position, like 4-phenoxy (**36**) also produced compounds with moderate affinity, and introduction of a nitrogen to form pyridyl (**37**) represented an improvement. Attaching the phenyl ring directly to produce biphenyl compounds **38** and **39** resulted in surprisingly active compounds, especially the unsubstituted **39** displaying both single digit nanomolar affinity and high functional activity. This observation is of high importance for two reasons. First, the structure–activity relationships in the western part demanding a *para*-substituted phenyl ring attached via two atoms to the amide have been very clear through a large number of analogs. This is the only example of high affinity compounds violating this pattern in the aminoquinoline series. Second, the 4-biphenylcarboxamide pattern has also been observed in previously disclosed compound series, like the aminotetralin series exemplified by T-226296,[6a] and a recently disclosed series of 1-(4-amino-phenyl)-pyrrolidin-3-yl-amines.[6h] Thus, the biphenyl moiety may serve as an anchor in the alignment of these compound series. An alternative anchor to the positively charged amine is of particular value in light of its variable position resulting from the multiple rotamer states of the Asp123, as discussed in detail previously.[7a]

In summary, the structure–activity relationships of a series of 6-acylamino-2-aminoquinolines identified by in silico screening have been further investigated by synthesis and in vitro testing of two directed libraries addressing the western and eastern parts of the molecule, respectively. The eastern part accommodated for a wide variety of modifications, and numerous additional single digit antagonists were identified. The previously established SAR analysis for the western part was confirmed, and in addition several alternative structures with interesting affinities were observed. Most notably, the original western appendage from the commercial compounds could be replaced by a 4-biphenylcarboxamide to produce a new sub-class of aminoquinolines with single digit nanomolar affinity.

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## References and notes


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11. Radioligand binding assay was conducted with stably transfected CHO cells, expressing human MCH1 receptor, by competition binding using [$^{125}$I]-MCH. Alternatively, binding was conducted as scintillation proximity assay (SPA) by incubating membranes from Euroscreen (ES-370-M) and PEI-treated WGA-coupled PVT SPA beads, type B from Amersham Pharmacia Biotech, with tracer in the presence of various concentrations of test compounds. Nonspecific binding was determined as the binding in the presence of 1 μM MCH. In the phosphatidylinositol assay, the cells were incubated with 5 μCi of [$^{3}$H]-myo-inositol in inositol-free culture medium. Phosphatidylinositol turnover was stimulated by submaximal concentrations of MCH in the presence of increasing amounts of ligand and the generated [$^{3}$H]-inositol phosphates were purified on Bio-Rad AG 1-X8 anion-exchange resin. Data were analyzed and $IC_{50}$ values were determined by nonlinear regression. For details, see Ref. 7.