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Structure–activity relationships of a novel series of melanin-concentrating hormone (MCH) receptor antagonists

Rosa Arienzo, David E. Clark, Sue Cramp, Stephen Daly, Hazel J. Dyke,* Peter Lockey, Dennis Norman, Alan G. Roach, Keith Stuttle, Maxine Tomlinson, Melanie Wong and Stephen P. Wren

Argenta Discovery Limited, 8/9 Spire Green Centre, Flex Meadow, Harlow, Essex CM19 5TR, UK

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Abstract—A new series of 2-aminoquinolines has been identified as antagonists of the melanin concentrating hormone receptor (MCH-1R). Syntheses and structure–activity relationships are described leading to a compound having low nanomolar activity against the receptor and demonstrating functional antagonism. Studies also showed that some of the compounds were selective against a range of other G protein-coupled receptors.

Obesity has reached epidemic proportions in the US and Western Europe, and it is currently estimated that over 30% of Americans are obese.[1] The incidence of obesity in children and adolescents is also increasing. Obesity has been linked to a number of co-morbidities such as stroke, heart disease, diabetes, hypertension, osteoarthritis and certain cancers. There exists a clear need for novel, safe and effective treatments for obesity, and the rapid expansion in incidence of this disease provides a clear incentive for the development of a suitable therapeutic agent. Although it is known that obesity is due to an imbalance between energy expenditure and food intake, the reasons for this imbalance in any given individual are not fully understood.

Melanin-concentrating hormone (MCH) is a cyclic 19-amino acid peptide, which is produced predominantly by neurons in the lateral hypothalamus and zona incerta, which project throughout the brain. The important role played by MCH in the regulation of energy balance and body weight has been demonstrated in several ways. Central administration of MCH in rats stimulates food consumption,[2] whilst fasting results in an increase in MCH expression. Mice lacking MCH are lean, hypophagic and maintain elevated metabolic rates.[3] Conversely, mice over-expressing MCH are susceptible to obesity and insulin resistance.[4]

The effects of MCH are mediated through two distinct receptors, MCH-1R and MCH-2R, both of which are members of the G protein-coupled receptor (GPCR) superfamily. MCH-1R has been identified in mammals and rodents, whereas functional MCH-2R receptors have not been found in rodents. The sequence identity between the two receptor types is only about 36%. The localisation of MCH-1R in the brain is in good agreement with the distribution of MCH itself.[5] The effects of small molecule MCH-1R antagonists in rodent feeding models have been described by two groups,[6,7] and the results support the hypothesis that MCH-1R antagonists should provide a novel treatment for obesity.

The identification of a potent hit compound (**1**) by virtual screening has been reported by us separately.[8] This communication describes the synthesis and structure–activity relationships of a series of novel, potent and selective MCH-1R antagonists based on (**1**) (Fig. 1).

The synthetic routes used to prepare analogues of the hit compound (**1**) were devised in order to maximise the possible variations at each end of the molecule. Scheme 1 depicts the synthetic route used to vary the amide at the final stage. Reaction of 2-chloro-4-methylquinoline with 1-methyl-piperazine followed by nitration gave the

* Corresponding author. Tel.: +44-(0)1279-645650; fax: +44-(0)1279-645646; e-mail: hazel.hunt@argentadiscovery.com

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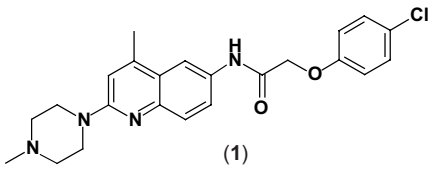


(1)

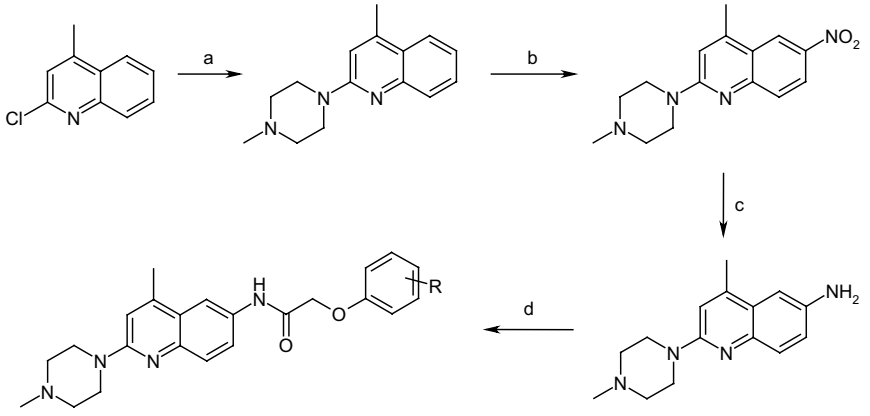
Figure 1. Hit compound identified by virtual screening.

desired 6-nitro derivative.[9] Subsequent reduction of the nitro group and coupling of the resultant amine with a range of carboxylic acids gave the target compounds.

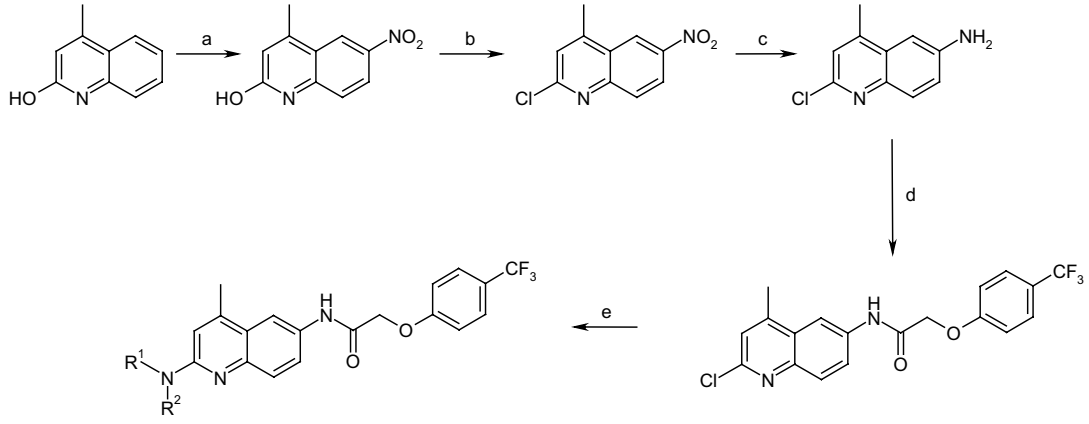
Scheme 2 shows the synthetic route used to prepare compounds in which the amine was varied. In this case nitration of 2-hydroxy-4-methylquinoline gave the desired 6-nitro isomer.[10] Conversion of the hydroxyl substituent to a chloro substituent provided a key functionality for later variation. Reduction of the nitro group gave the corresponding amine, which was coupled with the appropriate carboxylic acid to give the intermediate chloro derivative ready for derivatisation at the 2-position. Reaction of the 2-chloro compound with a range of secondary amines could be achieved in the microwave[11] at 180 °C for 20 min, although more vigorous conditions were required for reaction with primary amines (225 °C for 60 min).

Compounds were screened in a scintillation proximity assay in competition with ^{125}I-[Phe^{13},Tyr^{19}]-MCH binding to MCH-1R membranes.

Our first objective was the exploration of the SAR of the substitution on the phenyl ring. We initially investigated a range of substituents in the 4-position, and the results are provided in Table 1. Electron-withdrawing substituents such as chloro, trifluoromethyl and trifluoromethoxy provided the most potent compounds (compounds **A**, **C** and **E**). The lack of potency of the 4-fluoro compound (**G**) and the 4-cyano compound (**F**) suggested that there was also a steric requirement at the 4-position. A comparison between 4-, 3- and 2-chloro compounds suggested that substitution in the 4-position was favoured over substitution in either the 2- or 3-position. This conclusion was confirmed by the lack of potency of the 2-methyl, 2-methoxy and 3-methoxy analogues (compounds **J**, **K** and **M**). The absence of a substituent in any position (compound **H**) was clearly detrimental. The potency of the 2,4-dichloro compound suggested that incorporation of a suitable substituent at

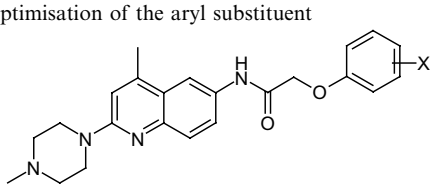


Scheme 1. Synthesis of compounds with variation of the amide. Reagents and conditions: (a) 1-methylpiperazine, toluene, reflux; (b) HNO_3, H_2SO_4, <0 °C; (c) H_2, 10% Pd/C, EtOH; (d) $ArOCH_2CO_2H$, EDCI, HOBt, DMF.



Scheme 2. Synthesis of compounds with variations of the amine. Reagents and conditions: (a) fuming HNO_3, H_2SO_4, <10 °C; (b) $POCl_3$, reflux; (c) Fe, HCl, EtOH, reflux; (d) $ArOCH_2CO_2H$, HATU, (*iso*-Pr)$_2$EtN, DMF; (e) R^1R^2NH, NMP, microwave, 180 °C for 20 min or 225 °C for 60 min.

Table 1. Optimisation of the aryl substituent

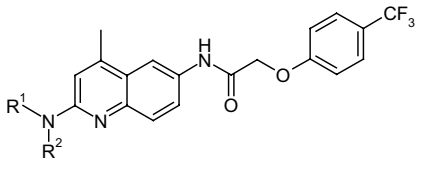


Compound	X	IC_{50} (nM) or % @ 1 μM
A	4-Cl	55
B	4-CH_3	80
C	4-CF_3	14
D	4-OCH_3	152
E	4-OCF_3	36
F	4-CN	370
G	4-F	1682
H	H	2%
I	2-Cl	470
J	2-CH_3	1050
K	2-OCH_3	0%
L	3-Cl	19%
M	3-OCH_3	9%
N	2,4-Di-Cl	24

the 2-position in addition to substitution at the 4-position was beneficial (compare compound **N** with compound **A**).

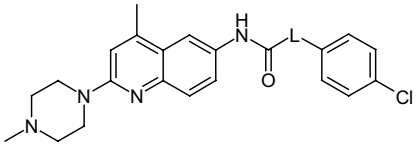
Our next objective was the investigation of the amino substituent at the 2-position of the quinoline, and the results are summarised in Table 2. Replacement of the *N*-methylpiperazine by morpholine resulted in only a small reduction in potency, indicating that the remote basic nitrogen was not essential for activity. The incorporation of piperidine resulted in a reduction in potency, but the smaller pyrrolidine provided a very potent compound (compare compounds **P** and **Q**). Small secondary amines were also well tolerated, with isopropylamine providing the most potent compound in this series (compound **S**). Incorporation of a remote basic nitrogen is also well tolerated (compound **U**). The lack

Table 2. Optimisation of the 2-amino substituent



Compound	NR^1R^2	IC_{50} (nM) or % @ 1 μM
C	*N*-Methylpiperazino	55
O	Morpholino	91
P	Piperidino	226
Q	Pyrrolidino	15
R	Cyclopentylamino	38
S	Isopropylamino	11
T	Dimethylamino	174
U	$(CH_3)_2NCH_2CH_2N(CH_3)$	22
V	$PhCH_2N(CH_3)$	40%

Table 3. Investigation of the linker



Compound	Linker L	IC_{50} (nM) or % @ 1 μM
A	CH_2O	55
W	CH_2CH_2	300
X	CH_2SCH_2	38%
Y	CH_2OCH_2	19%

of potency of the *N*-methyl-*N*-benzyl compound (compound **V**) suggests a steric limitation.

Removal of the methyl substituent in the 4-position of the quinoline was also detrimental. The 4-desmethyl analogue of compound **A** showed only 38% inhibition at 1 μM in the MCH-1 binding assay.

Finally, we investigated the linker between the quinoline and phenyl rings, and the results are summarised in Table 3. The originally discovered oxyacetamide linker was found to be optimal, but a propionamide linker also provided a compound with some activity (compound **W**). Either increasing or reducing the length of the linker was detrimental, and N-methylation of the amide abolished activity (data not shown).

MCH-1 induced Ca^{2+} release from CHO cells transfected with human MCH-1R was used to evaluate the functional antagonist potency of selected compounds. The compounds were pre-incubated with the cells for 5 min prior to addition of 0.1 μM MCH (a concentration producing 80% of maximal Ca^{2+} release). None of the compounds caused a release of Ca^{2+} from the cells and thus no MCH-1R agonist activity was noted. All the compounds tested showed functional antagonism in this assay, and selected results are included in Table 4.

In addition, the specificity of selected compounds for MCH-1R over several other GPCRs was determined, and these results are also provided in Table 4. Although the original hit compound (compound **A**) exhibited significant binding affinity for other receptors, in particular 5-HT_{2B} and 5-HT_{2C}, it was possible to identify compounds, such as compound **Q**, with a significantly improved profile. Thus, whereas compound **A** only exhibited sixfold selectivity for MCH-1R over 5-HT_{2B} receptors, compound **Q** was greater than 200-fold selective.

In conclusion, we have described the optimisation of a series of 2-aminoquinoline MCH-1R antagonists first identified using a virtual screening approach. Compounds in this series provided functional antagonism in a calcium flux assay, and no agonism was observed with any compound tested. In addition to improving binding affinity and functional activity, a significant improvement in specificity for MCH-1R over other GPCRs has

Table 4. Activity of selected compounds at MCH-1R and other human amine GPCRs. The selectivity ratios of compounds for MCH-1R versus 5-HT_{2B} receptors are shown

Compd	MCH-1R IC_{50} (nM)	Ca^{2+} release IC_{50} (nM)	5-HT_{2A} IC_{50} (nM) or % @ 1 μM	5-HT_{2B} IC_{50} (nM) or % @ 1 μM	5-HT_{2C} IC_{50} (nM) or % @ 1 μM	D2 % @ 1 μM	α_{1A} % @ 1 μM	Ratio 5-HT_{2B}:MCH-1
A	55	71	2180	349	970	35%[a]	84%[a]	6
C	14	63	27%	442	39%	41%[a]	85%[a]	32
N	24	NT	10%	201	33%	35%[a]	55%[a]	8
O	91	124	27%	19%	27%	43%	5%	>11
Q	15	10	11%	>3000	7%	7%	10%	>200
S	11	NT	18%	400	18%	2%	24%	36

NT = not tested.
[a] % inhibition @ 10 μM.

been achieved. Our efforts are continuing in this area, and will be reported in due course.

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