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Bioorganic & Medicinal Chemistry Letters 15 (2005) 3853–3856
Bioorganic & Medicinal Chemistry Letters

Lead optimization of 4-(dimethylamino)quinazolines, potent and selective antagonists for the melanin-concentrating hormone receptor 1

Kosuke Kanuma,[a] Katsunori Omodera,[a] Mariko Nishiguchi,[a] Takeo Funakoshi,[a] Shigeyuki Chaki,[a] Graeme Semple,[b] Thuy-Anh Tran,[b] Bryan Kramer,[b] Debbie Hsu,[b] Martin Casper,[b] Bill Thomsen[b] and Yoshinori Sekiguchi[a,*]

[a]*Medicinal Research Laboratories, Taisho Pharmaceutical Co. Ltd., 1-403 Yoshino-cho, Kita-ku, Saitama, Saitama 331-9530, Japan*
[b]*Arena Pharmaceuticals Inc., 6166 Nancy Ridge Drive, San Diego, CA 92121, USA*

Received 16 March 2005; revised 23 May 2005; accepted 30 May 2005
Available online 5 July 2005

Abstract—The optimization of a series of 4-(dimethylamino)quinazoline antagonists of the melanin-concentrating hormone receptor 1 (MCH-R1) is described. The combination of the elaboration of both the linker portion and the terminal phenyl ring provided *N*-(*cis*-4-{[4-(dimethylamino)quinazolin-2-yl]amino}cyclohexyl)-3,4-difluorobenzamide hydrochloride **28** (ATC0175), which showed excellent antagonist activity at the MCH-R1 (IC_{50} = 3.4 nM) as well as good selectivity over the Y5 and the α_{2A} receptors.

Melanin-concentrating hormone (MCH) is a cyclic 19 amino acid peptide expressed in the lateral hypothalamic area (LHA) and the rostromedial zona incerta.[1,2] The intracerebroventricular (icv) injection of MCH in rats results in increased food intake.[3,4] In contrast, prepro-MCH-knockout mice were found to be hypophagic and have reduced body weight and increased leanness relative to their wild type counterparts.[5] T-226296, a selective MCH-R1 antagonist, has been reported to attenuate MCH-induced hyperphagia, suggesting implication of MCH-R1 in the actions of MCH on food intake.[6] Thus, it can be inferred that a centrally acting MCH-R1 antagonist may be effective in treating obesity. In addition, MCH has been reported to induce an anxiogenic effect when injected into the medial preoptic area in rats,[7] while icv injection of MCH exhibited anxiolytic-like effect in the elevated plus-maze test,[8] suggesting that MCH may also be implicated in the modulation of emotional states. This hypothesis is supported by the recent finding that SNAP-7941, a selective antagonist for the MCH-R1, exhibits anxiolytic- and antidepressant-like effects in rodent models.[9]

As previously reported, high throughput screening of our in-house GPCR-directed library resulted in the identification of our lead compound, AR129330 (Table 1).[10] In our initial modifications, we identified that both 4-amino-substitution of the quinazoline and the terminal phenyl group are crucial for MCH-R1 activity. Subsequent optimization of the spacer portion between the quinazoline ring and the sulfonamide linker resulted in the identification of compounds **1**–**3**. Although these initial hits showed lower receptor selectivity, in particular, for the α_{2A} adrenergic receptor, we considered compounds AR129330, **1**, **2**, and **3** to be of sufficient potency and diversity, as well as having promise for improving MCH-R1 potency and selectivity over the Y5 and α_{2A} receptors, to merit further optimization. We herein describe our efforts to investigate structure–activity relationships (SAR) at the MCH-R1 based on the 4-(dimethylamino)quinazoline series and to improve selectivity leading to the identification of ATC0175, a potent and selective antagonist of MCH-R1.

Preparation of the quinazoline derivatives with the *cis*-cyclohexane-1,4-diamine is summarized in Scheme 1. The quinazoline core **6** was synthesized in two steps

Keywords: Melanin-concentrating hormone receptor 1 antagonists; MCH-R1 antagonists; ATC0175.
* Corresponding author. Tel.: +81 48 669 3064; fax: +81 48 652 7254; e-mail: yoshi.sekiguchi@po.rd.taisho.co.jp

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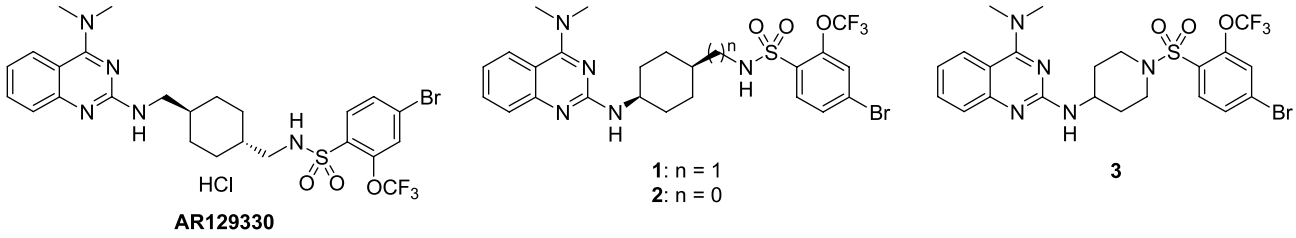
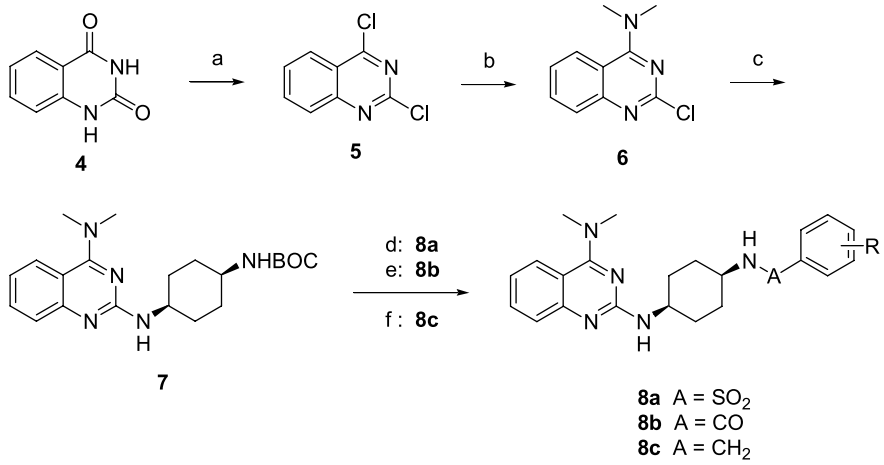
doi:10.1016/j.bmcl.2005.05.121

Table 1. Quinazoline derivatives as MCH-R1 antagonists



Compound	IC_{50} (nM)[a]		
	MCH-R1	Y5	α_{2A}
AR129330	160	2.7	7.7
1	140	120	130
2	83	880	57
3	250	8900	170

[a] Compounds were evaluated for their ability to compete with [^{125}I](Phe^{13}, Tyr^{19})MCH, [^{125}I]PYY, or [^{3}H]MK912 at a human CA-MCH-R1 stably expressed in HEK293 cells or a human Y5 or α_{2A} transiently expressed in COS-1 cells. Data represent the mean of 1–3 separate experiments performed from five concentrations and in duplicate.

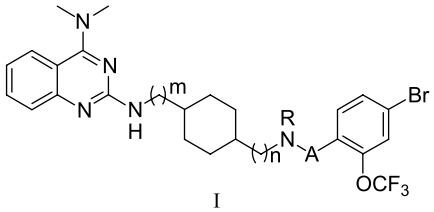


Scheme 1. Representative synthetic route of quinazolines. Reagents and conditions: (a) $POCl_3$, *N*,*N*-dimethylaniline, reflux, 7 h, 86%; (b) aq 50% Me_2NH, THF, room temperature, 80 min, 94%; (c) *tert*-butyl (*cis*-4-aminocyclohexyl)carbamate, isopropanol, reflux, 24 days, 93%; (d) (i) 4 M HCl in EtOAc, EtOAc, room temperature, 70 min, (ii) RSO_2Cl, iso-Pr_2NEt, CH_2Cl_2, 4 °C; (e) (i) 4 M HCl in EtOAc, EtOAc, room temperature, 70 min, (ii) RCOCl, iso-Pr_2NEt or Et_3N, CH_2Cl_2, room temperature; (f) (i) 4 M HCl in EtOAc, EtOAc, room temperature, 70 min, (ii) RCHO, $NaBH(OAc)_3$, AcOH, CH_2Cl_2, room temperature.

from commercially available 1*H*,3*H*-quinazoline-2,4-dione **4**. The starting material was reacted with phosphorous oxychloride ($POCl_3$) under reflux in the presence of *N*,*N*-dimethylaniline to provide 2,4-dichloro-quinazoline **5**. Selective substitution of the chlorine at the 4-position with 50% aqueous dimethylamine gave the corresponding 4-dimethylamino-2-chloro-quinazoline **6**. Coupling of **6** with *tert*-butyl (*cis*-4-aminocyclohexyl)carbamate was accomplished upon reflux in isopropanol to afford coupling product **7**. Deprotection of the Boc-group was achieved with hydrogen chloride to provide the amine as a precursor for target quinazoline derivatives **8a**–**c**. The amine was coupled with a sulfonyl chloride or an acid chloride to afford the desired quinazoline sulfonamide **8a** or quinazoline carboxylic amide **8b**, respectively. The quinazoline amine **8c** was obtained by reductive amination with the appropriate aldehyde.

We first examined the importance of the linker between the spacer portion and the terminal phenyl ring for MCH-R1 potency and selectivity over the Y5 and α_{2A} receptors (Table 2). In a series of *trans*-1,4-cyclohexylmethyldiamine compounds, replacement of the sulfonamide group with an amide **10** or an amine **11** showed a modest loss of affinity for the MCH-R1. The *N*-methylated sulfonamide analogue **9**, however resulted in a more drastic decrease in affinity. Likewise, *N*-methylation of the amine **11** provided compound **12**, which was less active at both the MCH-R1 and the Y5 receptors and revealed that the N–H, presumably active as a hydrogen bond donor, was crucial for MCH-R1 activity. In the series of 4-aminomethyl-*cis*-cyclohexylamine analogues **1**, **13**, and **14**, the amide analogue **13** was around 2-fold more potent at MCH-R1 than the corresponding sulfonamide **1**. Interestingly, the affinity for the Y5 and the α_{2A} receptors decreased markedly (IC_{50}

Table 2. In vitro data of quinazolines with linker modifications



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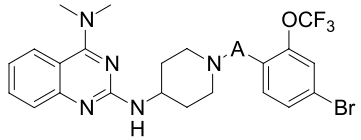


II

Compound	Structure	Conformation	*m*	*n*	A	R	IC_{50} (nM)[a]		
							MCH-R1	Y5	α_{2A}
AR129330	I	trans	1	1	SO_2	H	160	2.7	7.7
9	I	trans	1	1	SO_2	Me	5800	460	34
10	I	trans	1	1	CO	H	1500	470	9.9
11	I	trans	1	1	CH_2	H	960	560	31
12	I	trans	1	1	CH_2	Me	5600	>1000	44
1	I	cis	0	1	SO_2	H	140	120	130
13	I	cis	0	1	CO	H	79	1800	570
14	I	cis	0	1	CH_2	H	4.9	2400	360
2	I	cis	0	0	SO_2	H	83	880	57
15	I	cis	0	0	CO	H	160	>1000	390
16	I	cis	0	0	CH_2	H	35	>1000	170
3	II	—	—	—	SO_2	—	250	8900	170
17	II	—	—	—	CO	—	1200	NE[b]	NE
18	II	—	—	—	CH_2	—	320	>1000	520

[a] Compounds were evaluated for their ability to compete with [^{125}I](Phe^{13}, Tyr^{19})MCH, [^{125}I]PYY, or [^{3}H]MK912 at a human CA-MCH-R1 stably expressed in HEK293 cells or a human Y5 or α_{2A} transiently expressed in COS-1 cells. Data represent the mean of 1–3 separate experiments performed from five concentrations and in duplicate.

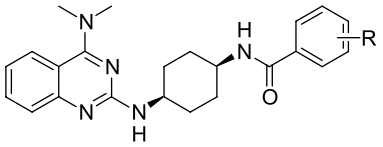
[b] Not evaluated.

for Y5 = 1800 nM). Replacement of the sulfonamide with a simple amine provided compound **14**, which was highly potent at the MCH-R1 (IC_{50} = 4.9 nM) and much less active at the Y5 receptor than our lead compound. This combination of effects provided selectivity for the MCH-R1 over the Y5 and α_{2A} receptors of 490-fold and 75-fold, respectively. In a similar series of *cis*-1,4-cyclohexane-diamine derivatives, the conversion of the sulfonamide **2** to the corresponding amide **15** led to a 2-fold decrease in affinity for the MCH-R1. In contrast, the amine analogue **16** exhibited a 2-fold higher affinity. Within the piperidine derivative series, the conversion from the sulfonamide **3** to an amide **17** resulted in a significantly reduced affinity for the MCH-R1. However, the amine analogue **18** provided comparable potency to the sulfonamide **3**, showing that the SAR trends were different between this and the two *cis*-1,4-cyclohexane series **1** and **2**. Based on the data, we concluded that *cis*-1,4-cyclohexanes **1** and **2** provided the most interesting spacer groups for further study, providing as they did, improved activity for the MCH-R1 and a significant degree of selectivity over the Y5 and the α_{2A} receptors. During the course of our investigations, we had been routinely monitoring the in vitro metabolic profile of selected active compounds. It became clear that sulfonamide derivatives in general had a tendency to be less metabolically stable than the amide and the amine derivatives in rat and human liver microsome preparations.

Hence, we decided to further focus our efforts on the two *cis*-1,4-cyclohexanes **1** and **2** as suitable spacers, and amides and amines as acceptable linkers, providing an appropriate combination of MCH-R1 activity and metabolic stability in vitro. As a final elaboration, we synthesized approximately 2500 compounds using the plate formatted synthesis method.[11] After the survey of the compounds, we found that 4-[(dimethylamino-quinazolin-2-ylamino)-*cis*-cyclohexyl]-benzamide derivatives provided an extensive series of compounds with high affinity for the MCH-R1 and excellent selectivity over the α_{2A} receptor, a selection of which is shown in Table 3.

A direct comparison of the 2-fluoro substituted **19**, 3-fluoro substituted **20**, and 4-fluoro substituted **21** analogues revealed that **19** had significantly reduced affinity relative to the other two. In addition, the profiles of the more active **20** and **21** were very similar with respect to selectivity over the α_{2A} receptor. Other meta-halogenated analogues **22** (3-chloro) and **23** (3-bromo) exhibited a 2-fold higher affinity than **20** for both the MCH-R1 and the α_{2A} receptors and therefore did not provide improvement in selectivity for the α_{2A} receptor. The 3-methyl substituted compound **24** displayed essentially the comparable affinity as the halogenated analogues with a slight improvement in selectivity. Electron-withdrawing groups such as 3-trifluoromethyl substituted **25**, 3-cyano substituted **26**, and 3-nitro substituted **27** were also tolerated for the activity for the MCH-R1, indicating broad tolerability for substitution in this position. However, for **25** the selectivity over the α_{2A} receptor was significantly lower. 3,4-Difluoro substituted **28** (ATC0175) showed not only highly potent affinity at the MCH-R1 (IC_{50} = 3.4 nM) but also 76-fold selectivity for the MCH-R1 over the α_{2A} receptor. In addition, the selectivity over the Y5 receptor was increased to a factor of 800. ATC0175 inhib-

Table 3. In vitro data of quinazolines with R substituion modifications



Compound	R	IC_{50} (nM)			Selectivity α_{2A}/MCH
		MCH-RI[a]	α_{2A} [b]	Y5[b]	
15	4-Br-2-OCF_3	160	390	>1000	2.4
19	2-F	170	NE[c]	NE	—
20	3-F	9.5	130	NE	14
21	4-F	9.4	150	NE	16
22	3-Cl	4.5	76	NE	17
23	3-Br	5.9	63	NE	11
24	3-Me	4.6	110	NE	24
25	3-CF_3	15	60	NE	4.0
26	3-CN	10	150	NE	15
27	3-NO_2	6.8	97	NE	14
28 (ATC0175)	3,4-di F	3.4	260	2700	76
29	3,4-di Cl	5.0	47	NE	9.4
30	2,3,4-tri F	38	200	NE	5.3
31	3,5-di OMe	2.0	71	NE	36

[a] Compounds were evaluated for their ability to inhibit transient intracellular calcium-mobilization evoked by MCH agonist in HEK293 cells stably expressing CA-MCH-R1 receptor. Data represent the mean of 1-3 separate experiments performed from five concentrations and in duplicate.
[b] Compounds were evaluated for their ability to compete with [^{125}I]PYY or [^{3}H]MK912 at a human Y5 or α_{2A} transiently expressed in COS-1 cells. Data represent the mean of 1–3 separate experiments performed from five concentrations and in duplicate.
[c] Not evaluated.

ited [^{125}I](Phe^{13}, Tyr^{19})MCH binding to recombinant human MCH-R1 with an IC_{50} value of 7.23 ± 0.59 nM.[12] The activity for the MCH-R1 of 3,4-dichloro substituted **29** was essentially equal to that of ATC0175, but the selectivity over the α_{2A} receptor of **29** was reduced significantly. 2,3,4-Trifluoro substituted **30** displayed lower affinity for the MCH-R1. All of the compounds that had substituents incorporated in the 2-position (**15**, **19**, and **30**) showed only modest affinity for the MCH-R1 in comparison to the other analogues, suggesting that the binding site of the MCH-R1 is very sensitive to steric properties of substitution at the 2-position. 3,5-Dimethoxy substituted **31** demonstrated the most potent antagonist activity (IC_{50} = 2.0 nM) in this series, but the selectivity over the α_{2A} receptor of **31** was lower than that of ATC0175.

Through a systematic optimization of the spacer, linker, and right-hand side aromatic ring portion of our lead series, we succeeded in identifying a new class of potent and selective non-peptide antagonists for the MCH-R1, based around a core 4-(dimethylamino)quinazoline-*cis*-1,4-cyclohexane amide or amine structure. ATC0175 (**28**), in particular, displayed potent antagonist activity for the MCH-R1 (IC_{50} = 3.4 nM). Importantly, the selectivity of ATC0175 for the MCH-R1 over the Y5 and the α_{2A} receptors represented a significant improvement over that of initial *trans*-1,4-cyclohexane sulfonamide derivative.

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