Available online at www.sciencedirect.com
SCIENCE DIRECT®
Bioorganic & Medicinal Chemistry Letters 14 (2004) 4879–4882
Bioorganic & Medicinal Chemistry Letters

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

Anil Vasudevan,* Dariusz Wodka, Mary K. Verzal, Andrew J. Souers, Ju Gao, Sevan Brodjian, Dennis Fry, Brian Dayton, Kennan C. Marsh, Lisa E. Hernandez, Christopher A. Ogiela, Christine A. Collins and Philip R. Kym

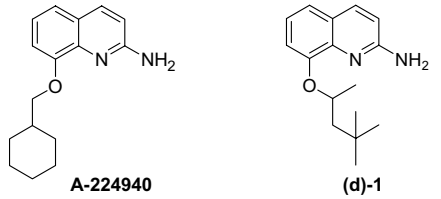
Metabolic Diseases Research, Global Pharmaceutical Research and Development, Abbott Laboratories, Abbott Park, IL 60064, USA

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

Abstract—The continued SAR investigation of 2-amino-8-alkoxy quinolines as melanin concentrating hormone receptor-1 (MCHr1) antagonists is reported. Prior hit-to-lead efforts resulted in the identification of **1** as a robust MCHr1 antagonist. Further delineation of the structural parameters essential for MCHr1-binding affinity of this class of nontraditional GPCR ligands resulted in the identification of compounds such as **33**, **34** and **37**, which demonstrate single digit nanomolar antagonism of MCHr1-mediated Ca^{2+} release. The synthesis and biological evaluation of these compounds are reported.

Melanin concentrating hormone (MCH) is a cyclic neuropeptide that regulates feeding behavior and energy balance in mammals.[1] MCH is expressed throughout the brain with the highest levels in the lateral hypothalamus and zona incerta areas.[2] The hypothalamic MCH mRNA level is up-regulated in leptin-deficient (*ob*/*ob*) mice, and further increased by fasting.[3] MCH deficient mice are hypophagic and hypermetabolic with decreased body weight and increased leanness,[4] while over expression of MCH peptide in mice leads to obesity and insulin resistance.[5] The pharmacological validation from these studies suggest that MCHr1 antagonists may provide a novel therapy for obesity.[6]

High throughput screening of the Abbott compound collection resulted in the identification of A-224940. Subsequent modifications of the alkoxy substituent pattern using a focused collection of building blocks resulted in the identification of **1**.[7] Even though this analog afforded an eightfold improvement compared to A-224940 in inhibiting the MCHr1-mediated Ca^{2+} release in IMR-32 cells, it demonstrated sub-optimal functional potency. We report in this article, our continuing efforts at transforming A-224940 into a potent, orally active MCHr1 antagonist, via continued exploration of the 8-alkoxy substitution.



A-224940
MCHr1 IC_{50} = 0.091 μM
MCHr1FLIPR IC_{50} = 1.68 μM

(d)-1
MCHr1 IC_{50} = 0.02 μM
MCHr1FLIPR IC_{50} = 0.098 μM

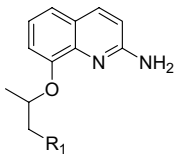
The hit-to-lead progression from A-224940 to **1** was primarily geared toward optimizing hydrophobic interactions made by the 8-alkoxy substituent of A-224940.[8] In an attempt to improve the MCHr1 binding affinity as well as functional potency, we were interested in exploring the effect of heteroatoms in the tether at the 8-position of this class of nontraditional G-protein coupled receptor (GPCR) ligands.[9]

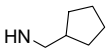
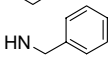
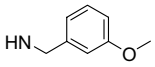
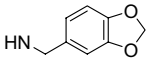
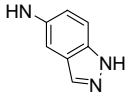
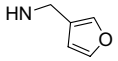
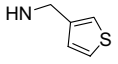
Alkylation of 2-amino-8-hydroxy quinoline **2** with 2-chloro-1,1-dimethoxypropane afforded **3a** (Scheme 1). Similar alkylation with 2-chloro-1,1-dimethoxy ethane afforded **3b**. Deprotection with 4 N HCl/dioxane afforded the desired intermediates **4a** and **4b**, respectively.

Keywords: Melanin concentrating hormone; Obesity.
* Corresponding author. Tel.: +1-847-938-6594; fax: +1-847-935-0310; e-mail: anil.vasudevan@abbott.com

0960-894X/$ - see front matter © 2004 Published by Elsevier Ltd.
doi:10.1016/j.bmcl.2004.07.034

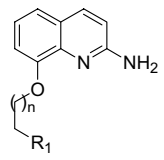
Table 1. MCHr1 binding affinity and functional activity of analogs[a]

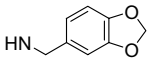
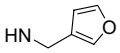
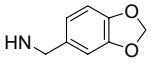
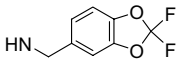
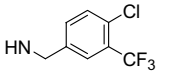
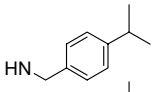
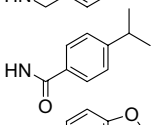
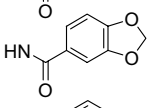
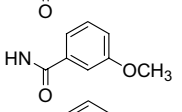
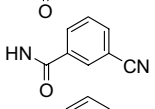
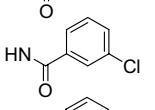
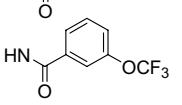
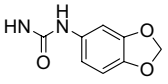
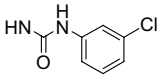


Compd	R_1	IMR32 binding IC_{50} (μM)	IMR32 FLIPR™ IC_{50} (μM)
6		0.089	0.46
7		0.107	0.98
8		0.059	0.58
9		0.038	0.30
10		0.214	2.17
11		0.079	0.36
12		0.04	0.29
13		0.083	0.19
14		0.102	0.34
15		0.001	0.60
16		0.030	0.13
17		0.53	8.18
18		0.016	0.1
19		0.014	0.15
1	*tert*-Butyl	0.055	0.21

[a] Values are means of three experiments.

Table 2. MCHr1 binding affinity and functional activity of analogs[a]

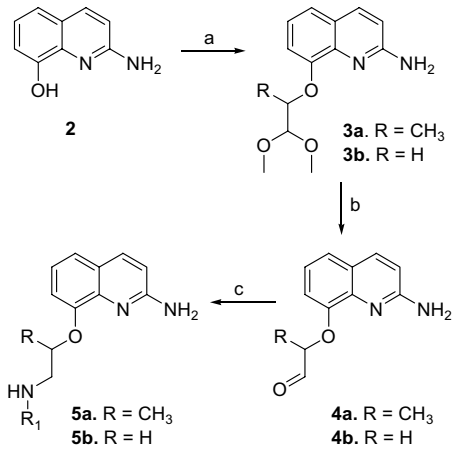


Compd	*n*	R_1	IMR32 binding IC_{50} (μM)[a]	IMR32 FLIPR™ IC_{50} (μM)[a]
24	1		0.52	8.96
25	1		0.66	>10
26	2		0.014	0.27
27	2		0.001	0.10
28	2		0.005	0.22
29	2		0.010	0.63
30	2		0.066	0.14
31	2		0.007	0.07
32	2		0.002	0.03
33	2		0.003	0.007
34	2		0.0004	0.003
35	2		0.006	0.024
36	2		0.005	0.11
37	2		0.0009	0.008

[a] Values are means of three experiments.

Reductive amination with aliphatic and heterocyclic amines afforded the compounds shown in Tables 1 and 2. These compounds were assayed for their MCHr1 binding affinity as well as functional antagonism in IMR-32 cells as described in the preceding paper.[7]

The effect of introducing a nitrogen atom in the side chain of these analogs was investigated via affixing aliphatic and aromatic hydrophobic substituents as well as heteroaromatic moieties. Analogs **6**–**9** suggest that extending the aliphatic hydrophobic substituent by a one-carbon tether is slightly detrimental to MCHr1 binding affinity. Introduction of secondary amines such as pyrrolidine, piperidine and morpholine is well tolerated by the receptor, with the piperidine containing compound **12** being the most potent amongst this set of analogs in the MCHr1 binding assay. Analogs **14**–**19** were synthesized to evaluate the effect of introducing aryl substituents at the end of a heteroatom-containing tether. While the *N*-benzyl analog **14** was equipotent with a similar aliphatic analog **7**, introduction of a methoxy group at the *meta* position to afford **15** resulted in a 100-fold improvement in MCHr1 binding affinity, though its functional activity was not improved. The piperonyl substituted compound **16** afforded a better combination of MCHr1 binding affinity and functional

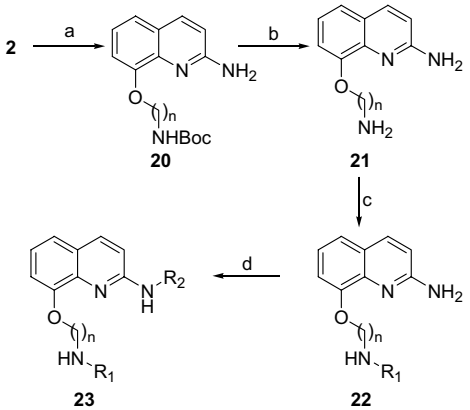


Scheme 1. (a) $ClCH(CH_3)CH(OCH_3)_2$, DMF, Cs_2CO_3, 87% for **3a**; $ClCH_2C(OCH_3)_2$, DMF, Cs_2CO_3, 85% for **3b**; (b) 4 N HCl/dioxane; (c) R_1NH_2, 1:1 $ClCH_2CH_2Cl$–CH_3OH, MP-$CNBH_3$,[10] 1% CH_3COOH, 50 °C, 4 h.

antagonism compared to **14** and **15**, whereas *N*-arylated compounds such as **17** were less potent than the *N*-benzyl analogs. Replacement of the piperonyl moiety in compound **16** with heterocylic substituents such as a furan or thiophene afforded compounds with comparable binding affinity and functional antagonism.

The synthesis of one-carbon homologated analogs lacking the α-methyl group was accomplished as shown in Scheme 2. Nucleophilic displacement of methanesulfonic acid 3-*tert*-butoxycarbonylamino propyl ester with **2** followed by deprotection, afforded the desired intermediate. Reductive amination with various aldehydes afforded regioselective coupling at the pendant amino moiety. The 2-amino group could also be functionalized via reductive amination at higher temperatures with longer reaction times to afford analogs **38**–**42**.

Consistent with previous results,[7] removal of the α-methyl moiety to afford 2-amino quinolin-8-yloxyethylamino-substituted compounds such as **24** and **25**,



Scheme 2. (a) $MsO(CH_2)_3NHBoc$, DMF, 100 °C, Cs_2CO_3, 85%; (b) 4 N HCl/dioxane, 53%; (c) R_1CHO, 1:1 $ClCH_2CH_2Cl$–CH_3OH 50 °C, 4 h; (d) 2 equiv. ArCHO, MP-$CNBH_3$,[10] 1:1 $ClCH_2CH_2Cl$–CH_3OH 65 °C, 6 h.

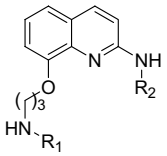
resulted in a significant reduction in MCHr1 binding affinity as well as functional potency. Compound **24** was 17-fold less potent than the corresponding α-methyl substituted compound **16**, whereas **25** was 55-fold less potent than **18**. However, one-carbon homologation of **24** afforded **26**, which demonstrated a 37-fold boost in MCHr1 binding affinity and was more potent than the α-methyl substituted analog **16**. Given this significant improvement in potency achieved via homologation, further structural manipulations of the pendant amino moiety were pursued. Introduction of a series of aryl (**27**–**29**) and heteroaryl moieties (data not shown) afforded very potent MCHr1 binding antagonists, though their potency in the FLIPR™ assay was sub-optimal. Acylation of the pendant amine with aryl moieties afforded a further boost in functional MCHr1 antagonism, with **31** being twofold more potent than **24** in terms of MCHr1 binding affinity, but fourfold better in the FLIPR™ assay. Consistent with previous results, incorporation of functional groups at the *meta* position of the benzoyl moiety afforded several potent MCHr1 antagonists **32**–**35**, with **34** demonstrating an IC_{50} for the MCHr1 receptor of 400 pM and functional antagonism of 3 nM. Comparisons with the known MCHr1 antagonists T-226296[6a] (IMR32 binding IC_{50} = 85 nM, IMR FLIPR™ IC_{50} = 872 nM) and SNAP-7931[6b] (IMR32 binding IC_{50} = 3 nM, IMR FLIPR™ IC_{50} = 15 nM) reveal that the 2-aminoquinoline **34** is one of the most potent MCHr1 antagonists reported to date. The corresponding urea-substituted compounds **36** and **37** were also extremely potent MCHr1 antagonists.

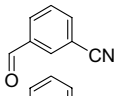
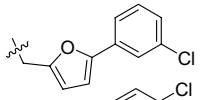
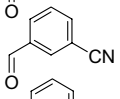
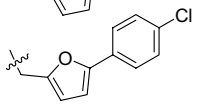
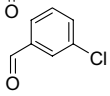
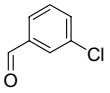
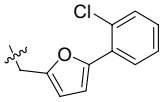
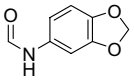
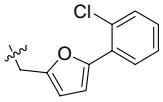
Functionalization of the 2-amino moiety of **33** with aryl groups such as the 2-chlorophenyl-5-furanyl moiety afforded compounds **38** and **39** with comparable MCHr1 binding affinity, though the MCHr1 functional activity of **39** was reduced about fivefold compared to **33** (Table 3). Reductive alkylation of the 2-amino group of **34** with aliphatic moieties such as a propyl functionality resulted in a 33-fold reduction in MCHr1 potency, but a 1000-fold drop in functional activity. The 2-phenyl-5-furanyl moiety in **41** is significantly better tolerated compared to the propyl substituent. Acylation of the 2-amino group of **36** was detrimental to both binding affinity as well as functional activity.

Compounds **33** and **35** were dosed at 10 mg/kg in diet-induced obese (DIO) mice to evaluate their brain penetration using methods described in the preceding publication,[7] and summary data are shown in Table 4.

While introduction of heteroatoms in the tether at the 8-position of these 2-aminoquinolines afforded several compounds with exceptional MCHr1 binding affinity as well as functional antagonism of the MCHr1 receptor mediated Ca^{2+} release, preferential brain penetration was significantly compromised. In an attempt to investigate the effect of retention of the basic nitrogen on the half-life and brain penetration, compound **28** was also dosed at 10 mg/kg in DIO mice, and the results are included in Table 4. Despite its reduced MCHr1 functional activity, **28** had a longer half-life and better exposure in the brain and plasma compared to **33** and

Table 3. MCHr1 binding affinity and functional activity of analogs[a]



Compd	R_1	R_2	IMR32 binding IC_{50} (μM)[a]	IMR32 FLIPR™ IC_{50} (μM)[a]
38			0.005	0.01
39			0.002	0.04
40		$-CH_2CH_2CH_3$	0.012	1.12
41			0.001	0.02
42			0.058	3.11

[a] Values are means of three experiments.

Table 4. Plasma and brain exposure of **28**, **33** and **35** in DIO mice after a 10 mg/kg oral dose

	28	**33**	**35**
Plasma AUC (ng/h/mL)	9965	328	424
Plasma $T_{1/2}$ (h)	8.9	1.4	1.2
Brain AUC (ng/hr/g)	9521	11	68
Brain $T_{1/2}$ (h)	—	1.6	0.6
Brain/plasma	0.96	0.03	0.2

35, suggesting the importance of the basic nitrogen in the tether at the 8-position for achieving the desired brain:plasma distribution.

In summary, introduction of a nitrogen atom in the tether at the 8-postion of **1**, followed by functionalization resulted in several exceptionally potent MCHr1 antagonists. Compounds that retained the basic nitrogen in the side chain were found to have more efficient brain penetration and half-life parameters compared to analogs that were acylated, and subsequent efforts were focused on improving the functional potency of compounds such as **27** and **28**.

References and notes

1. Saito, Y.; Nothacker, H.-P.; Civelli, O. *Trends Endocrinol. Metab.* **2000**, *11*, 299–303.
2. Bittencourt, J. C.; Presse, F.; Arias, C.; Peto, C.; Vaughan, J.; Nahon, J. L.; Vale, W.; Sawchenko, P. E. *J. Comp. Neurol.* **1992**, *319*, 218–245.
3. Kokkotou, E. G.; Tritos, N. A.; Mastaitis, J. W.; Slieker, L.; Maratos-Flier, E. *Endocrinology* **2001**, *12*, 680–686.
4. (a) Shimada, M.; Tritos, N. A.; Lowell, B. B.; Flier, J. S.; Maratos-Flier, E. *Nature* **1998**, *396*, 670–674; (b) Chen, Y.; Hu, C.; Hsu, C. K.; Zhang, O.; Bi, C.; Asnicar, M.; Hsiung, H. M.; Fox, N.; Slieker, L. J.; Yang, D. D.; Heiman, M. L.; Shi, Y. *Endocrinology* **2002**, *143*, 2469–2477.
5. Ludwig, D. S.; Tritos, N. A.; Mastaitis, J. W.; Kulkarni, R.; Kokkotou, E.; Elmquist, J.; Lowell, B.; Flier, J. S.; Maratos-Flier, E. *J. Clin. Invest.* **2001**, *107*, 379–386.
6. (a) Takekawa, S.; Asami, A.; Ishihara, Y.; Terauchi, J.; Kato, K.; Shimomura, Y.; Mori, M.; Murakoshi, H.; Kato, K.; Suzuki, N.; Nishimura, O.; Fujino, M. *Eur. J. Pharmacol.* **2002**, *438*, 129–135; (b) Borowsky, B.; Durkin, M. M.; Ogozalek, K.; Marzabadi, M. R.; DeLeon, J.; Lagu, B.; Heurich, R.; Lichtblau, H.; Shaposhnik, Z.; Daniewska, I.; Blackburn, T. P.; Branchek, T. A.; Gerald, C.; Vaysse, P. J.; Forray, C. *Nature Med.* **2002**, *8*, 779–781; (c) Collins, C. A.; Kym, P. R. *Curr. Opin. Invest. Drugs* **2003**, *4*, 386–394; (d) Browning, A. *Expert Opinion Ther. Patents* **2004**, *14*, 313–325; (e) Carpenter, A. J.; Hertzog, D. L. *Expert Opinion Ther. Patents* **2002**, *12*, 1639–1646.
7. 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*, preceding publication. doi:10.1016/j.bmcl.2004.07.032.
8. Gentles, R. G.; Wodka, D.; Park, D. C.; Vasudevan, A. *J. Comb. Chem.* **2002**, *4*, 442–456.
9. (a) Devita, R. J.; Chang, L.; Chaung, D.; Hoang, M.; Jiang, J.; Lin, P.; Sailer, A. W.; Young, J. R. WO2003045313; (b) Collins, C. A.; Gao, J.; Kym, P. R.; Lewis, J. C.; Souers, A. J.; Vasudevan, A.; Wodka, D. WO 2003105850.
10. Macroporous cyanoborohydride (MP-$CNBH_3$) was purchased from Argonaut Technologies (www.argotech.com).