Available online at www.sciencedirect.com
SCIENCE DIRECT®
Bioorganic & Medicinal Chemistry Letters
Bioorganic & Medicinal Chemistry Letters 16 (2006) 2302–2305

Identification and structure–activity relationships of a new series of Melanocortin-4 receptor antagonists

Tricia J. Vos,* Suresh Balani, Christopher Blackburn, Ryan W. Chau, M. Diana Danca, Stacey V. Drabic, Cheryl A. Farrer, Michael A. Patane, Stephen G. Stroud, David L. Yowe and Christopher F. Claiborne

Millennium Pharmaceuticals, Inc. 40 Landsdowne St. Cambridge, MA 02139, USA

Received 9 November 2005; accepted 6 January 2006
Available online 3 February 2006

Abstract—The identification and optimization of a series of acylguanidine-based melanocortin-4 receptor antagonists is discussed.

The melanocortins are a family of five G-protein coupled receptors that play important physiological roles including energy homeostasis, body weight regulation, sexual behavior, anxiety, and pain.[1] The melanocortin-4 receptor is an important therapeutic target for the treatment of a variety of disorders.[2] Many peptidic modulators of the melancortin receptors have been discovered, but only in recent years have non-peptidic small molecule agonists and antagonists been reported.[3]

We recently reported a series of amidine-based MC4R antagonists (e.g., **1** and **2**).[3c] During the course of investigations leading to the discovery of **1**, acylguanidine **3** was synthesized and found to be an active MC4R antagonist (K_i = 0.70 μM, cAMP IC_{50} = 2.58 μM) which had reduced hERG binding (K_i = 3.15 μM for **3** vs 0.84 μM for **2**). We describe herein the optimization and structure–activity relationships of analogs of compound **3** (see Chart 1).

Analogs of **3** were prepared from the corresponding carboxylic acids[4] as shown in Scheme 1. Acylguanidines with substitution on the terminal nitrogen were prepared by treatment of the appropriate carboxylic acid **4** with fluoro-*N*,*N*,*N*′-tetramethylformamidinium hexafluorophosphate (TFFH)[5] followed by 2-methyl-2-thiopseudourea sulfate to give the acylthioguanidine **5**. Displacement of the thiomethyl group with primary or secondary amines gave the acylguanidines **6**. Alternatively, *N*,*N*′-disubstituted acylguanidines **8** were prepared by conversion of carboxylic acids **4** to amides **7** and then sequential treatment of the amide with sodium

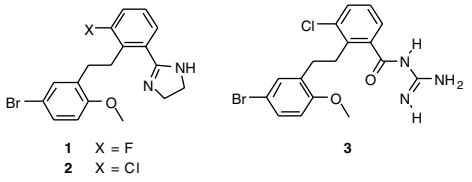
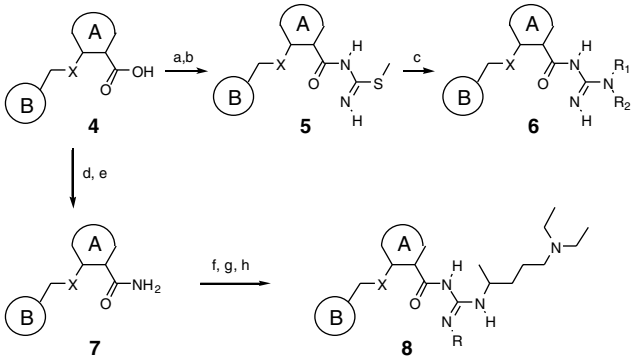


Chart 1. First- and second-generation small molecule MC4-R antagonists.



Scheme 1. Reagents and conditions: (a) $SOCl_2$, reflux, 1 h; (b) 2-methyl-2-thiopseudourea sulfate, 1 N NaOH, 0 °C, 3.5 h; (c) HNR_1R_2, Et_3N, *o*-xylene, 145 °C, 4 h; (d) DIPEA, TFFH, DMF, rt, 1.5 h; (e) $NH_{3(g)}$, 5 min; (f) NaH, DMF, rt, 5 min; (g) RNCS, 60 °C, 0.5 h; (h) 2-amino-5-diethylaminopentane, $HgCl_2$, rt, 10 min.

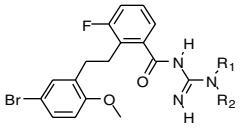
Keywords: Melanocortin; Antagonist; Non-peptide; Small molecule.
* Corresponding author. Tel.: +1 617 551 8692; e-mail: tricia.vos@mpi.com

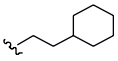
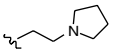
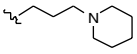
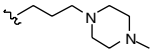
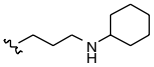
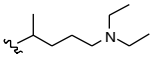
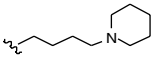
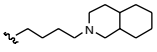
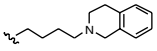
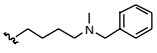
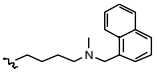
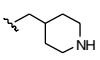
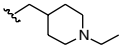
0960-894X/$ - see front matter
doi:10.1016/j.bmcl.2006.01.016

hydride, an isothiocyanate, and an amine in the presence of mercury (II) chloride.[6]

Initial optimization of **3** focused on exploring the effects of substituents on the terminal nitrogen atom (Table 1). Small linear, branched, or cyclic alkyl substitutents (**9**, **10**, and **11**) had little effect on activity. An enhancement of MC4R binding affinity was seen when a basic group was included in the acylguanidine substituent (**12**). Additional analogs were prepared in order to further investigate the effects of a distal basic group on MC4R activity. Increasing the length of the tether between the acylguanidine and the basic center from 2 to 3 methylene units significantly increased MC4R binding and function (**13**). Installation of an additional basic center (**14**) or the presence of a secondary rather than tertiary amine as the basic group (**15**) did not further enhance potency. An additional increase in tether length from 3

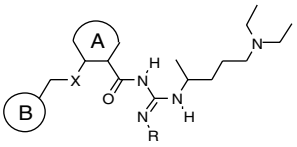
Table 1. SAR of terminal substituted acylguanidine analogs

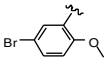
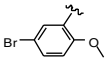
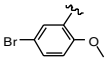
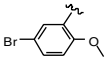
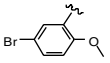
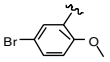
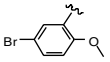
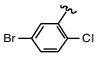


Compound	R_1	R_2	MC4-R binding affinity (K_i, μM)[a]	MC4-R antagonism (IC_{50}, μM)[b]
9		H	0.92	ND
10		H	0.77	8.5
11		H	2.6	ND
12		H	0.19	4.5
13		H	0.0032	0.33
14		H	0.064	0.67
15		H	0.080	5.7
16		H	0.0043	0.13
17		H	0.00058	0.070
18		H	0.021	0.39
19		H	0.026	0.65
20		H	0.0051	0.18
21		H	0.057	1.2
22		H	0.013	0.031
23		H	0.0028	0.097

[a] Values are means of at least three experiments (ND, not determined); results obtained in MC4-R membrane filtration assay.
[b] Values are means of at least three experiments (ND, not determined); results obtained in cAMP functional assay.

Table 2. *N*,*N*′-Disubstituted acylguanidine SAR



Compound	Ring A	X	R	Ring B	MC4-R binding affinity (K_i, μM)[a]	MC4-R antagonism (IC_{50}, μM)[a]
16		CH_2	H		0.0043	0.13
24		CH_2	H		0.00083	0.26
25		CH_2	H		0.011	0.26
26		O	H		0.90	0.53
27		CH_2	*i*-Pr		2.5	17
28		CH_2	Ph		4.1	ND
29		CH_2	Me		6.3	ND
30		CH_2	H		0.11	0.66
32		CH_2	H		26	>33
33		CH_2	H		0.014	0.17
34		CH_2	H		0.089	1.5
35		CH_2	H		0.69	1.8

[a] Values are averages of at least two determinations.

to 4 methylene units provided a boost in not only MC4R binding but also functional activity (**16**, **17**) Increasing lipophilicity in the distal region provided analogs (**18**, **18**, **20**, and **21**) which were less active than **M**. Binding and functional activity were further enhanced when the tether was constrained (**22**). A distal NH appears to be important (**23**).

Using compound **16** as a starting point, SAR about the remaining portions of the molecule were investigated (Table 2). Changes to Ring A (**24**, **25**) did not significantly affect MC4R activity. Substitution of one methylene unit by oxygen in the linker between the A and B rings resulted in a moderate decrease in activity (**26**). *N*,*N*′-disubstituted analogs (**27**–**29**) were very poor MC4R binders. B-ring analog **30** was slightly less active than **16**, while **32** was inactive in the antagonist assay. Other B-ring analogs (**33**–**35**) displayed varying levels of MC4R activity, but none had activity superior to that of **16**.

Pharmacokinetic profiles of compounds **13** and **22** were compared head to head with **1**. When dosed in rats, the oral bioavailability of **1** and **13** are similar (4.6% F and 6.3% F, respectively) however their plasma half-lives after iv dosing are extremely disparate (1 h for **1** vs 31 h for **13**). Compounds in this series also have longer brain half-lives than **1** as exemplified by comparison with **22** (Fig. 1).

In summary, we have identified a new series of small molecule melanocortin-4 antagonists-based on an acylguanidine scaffold. These compounds have improved pharmacokinetic profiles relative to previously reported amidine-based antagonists.

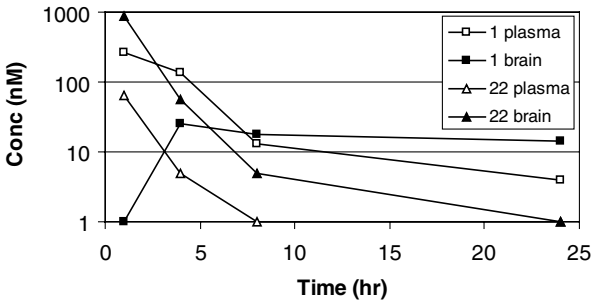


Figure 1. Concentration vs. time profiles in brain and plasma for compounds **1** and **22** after a 20 mg/kg po dose in mice. Each time point represents the average of three animals.

References and notes

1. (a) Cone, R. D.. In Lennarz, W. J., Lane, D. M., Eds.; Encyclopedia of Biological Chemistry; Elsevier: Oxford, 2004; Vol. 2, p 617–620; (b) Wikberg, J. E. S. *Exp. Opin. Ther. Patents* **2001**, *11*, 61.
2. (a) Chaki, S.; Nakazato, A. *Drugs Future* **2004**, *29*, 1065; (b) Sebhat, I.; Ye, Z.; Dednarek, M.; Weinberg, D.; Nargund, R.; Fong, T. M. *Ann. Rep. Med. Chem.* **2003**, *38*, 31.
3. (a) Arasasingham, P. N.; Fotsch, C.; Ouyang, X.; Norman, M. H.; Kelly, M. G.; Stark, K. L.; Karbon, B.; Hale, C.; Baumgartner, J. W.; Zambrano, J. C.; Tamayo, N. A. *J. Med. Chem.* **2003**, *46*, 9; (b) Chaki, S.; Hirota, S.; Funakoshi, T.; Suzuki, Y.; Suetake, S.; Okubo, T.; Ishii, T.; Nakazato, A.; Okuyama, S. *J. Pharm. Exp. Therap.* **2003**, *304*, 818; (c) Vos, T. J.; Caracoti, A.; Che, J. L.; Dai, M.; Farrer, C. A.; Forsyth, N. E.; Drabic, S. V.; Horlick, R. A.; Lamppu, D.; Yowe, D. L.; Balani, S.; Li, P.; Zeng, H.; Joseph, I. B. J. K.; Rodriguez, L. E.; Maguire, M. P.; Patane, M. A.; Claiborne, C. F. *J. Med. Chem.* **2004**, *47*, 1602; (d) Xi, N.; Hale, C.; Kelly, M. G.; Norman, M. H.; Stec, M.; Xu, S.; Baumgartner, J. W.; Fotsch, C. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 377; (e) Marsilje, T. H.; Roses, J. B.; Calderwood, E. F.; Stroud, S. G.; Forsyth, N. E.; Blackburn, C.; Yowe, D. L.; Miao, W.; Drabic, S. V.; Bohane, M. D.; Daniels, J. S.; Li, P.; Wu, L.; Patane, M. A.; Claiborne, C. F. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3721; (f) Pontillo, J.; Tran, J. A.; Fleck, B. A.; Marinkovic, D.; Arellano, M.; Tucci, F. C.; Lanier, M.; Nelson, J.; Parker, J.; Saunders, J.; Murphy, B.; Foster, A. C.; Chen, C. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5605; (g) Chen, C.; Pontillo, J.; Fleck, B. A.; Gao, Y.; Wen, J.; Tran, J. A.; Tucci, F. C.; Marinkovic, D.; Foster, A. C.; Saunders, J. *J. Med. Chem.* **2004**, *47*, 6821; (h) Tran, J. A.; Pontillo, J.; Arellano, M.; White, N. S.; Fleck, B. A.; Marinkovic, D.; Tucci, F. C.; Lanier, M.; Nelson, J.; Saunders, J.; Foster, A. C.; Chen, C. *Bioorg. Med. Chem. Lett.* **2005**, 833; (i) Pontillo, J.; Tran, J. A.; Markison, S.; Joppa, M.; Fleck, B. A.; Marinkovic, D.; Arellano, M.; Tucci, F. C.; Lanier, M.; Nelson, J.; Saunders, J.; Hoare, S. R. J.; Foster, A. C.; Chen, C. *Bioorg. Med. Chem. Lett.* **2005**, 2541.
4. Poirier, M.; Chen, F.; Bernard, C.; Wong, Y.-S.; Wu, G. G. *Org. Lett.* **2001**, *3*, 3795.
5. Carpino, L. A.; El-Faham, A. *J. Am. Chem. Soc.* **1995**, *117*, 5401.
6. Zhang, J.; Shi, Y.; Stein, P.; Atwal, K.; Li, C. *Tetrahedron Lett.* **2002**, *43*, 57.