Bioorganic & Medicinal Chemistry Letters 18 (2008) 4817–4822

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Structure–activity relationship studies on a series of piperazinebenzylalcohols and their ketone and amine analogs as melanocortin-4 receptor ligands

Dragan Marinkovic [a], Fabio C. Tucci [a], Joe A. Tran [a], Beth A. Fleck [b], Jenny Wen [c], Chen Chen [a,*]

[a] Department of Medicinal Chemistry, Neurocrine Biosciences, Inc., 12790 El Camino Real, San Diego, CA 92121, USA
[b] Department of Pharmacology, Neurocrine Biosciences, Inc., San Diego, CA 92121, USA
[c] Department of Preclinical Development, Neurocrine Biosciences, Inc., San Diego, CA 92121, USA

ARTICLE INFO

Article history:
Received 1 July 2008
Revised 18 July 2008
Accepted 22 July 2008
Available online 25 July 2008

Keywords:
Melanocortin
Receptor
Ligand
Structure–activity relationship
Benzylalcohol
Ketone
Amine
Synthesis

ABSTRACT

A series of piperazinebenzylalcohols were prepared and studied to compare with their ketone and amine analogs as MC4R antagonists. Several benzylalcohols such as **14a** and **14g** displayed low nanomolar binding affinities (K_i < 10 nM), and high selectivities over other melanocortin receptor subtypes.

The melanocortin receptors, which consist of five subtypes MC1-5R and belong to the class A GPCR superfamily,[1] have been identified and cloned.[2] Among them, MC4R controls feeding behavior.[3] Therefore, MC4R agonists have been sought for the possible treatment of obesity.[4] Moreover, recent studies have also demonstrated that MC4R-selective antagonists might be useful in cachexia.[5]

The melanocyte-stimulating hormones (α-MSH, β-MSH and γ-MSH) and adrenocorticotropin (ACTH) are the endogenous agonists for the melanocortin receptors. All these peptides possess a His-Phe-Arg-Trp motif which is crucial for receptor binding and activation.[6] In addition, two endogenous antagonists, agouti-protein and agouti-related protein (AgRP) contain an Arg-Phe-Phe moiety located in a loop known to interact with the melanocortin receptors,[7] and are believed to be important for functional antagonism.[8] Mutagenesis and modeling studies have provided some information for understanding how a peptide ligand interacts with the receptor.[9] The requirement of a basic and an aromatic group for a MC4R ligand is also evidenced by many known non-peptide MC4R agonists and antagonists from several chemical classes.[10] For example, studies have shown that the dipeptide D-Tic-D-(4-Cl)Phe attaching to a piperazinebenzene that bears a polar functionality at the *ortho*-position is a potent MC4R agonist with high binding affinity.[11–13] Thus, Dyck et al. reported a K_i value of 270 nM for the weakly basic triazole **1a** (Fig. 1). In comparison to **1a**, the basic benzylamine **1b** possessed a similar K_i value of 380 nM, while its 2-thienylethyl derivative **1c** (K_i = 11 nM) displayed a substantially increased binding affinity, indicating that a basic nitrogen in combination with a small lipophilic group significantly contributes to receptor binding.[14] Compounds **1a–c** are full agonists, suggesting an important role of the Tic (1,2,3,4-tetrahydro-isoquinolinecarbonyl) group in the receptor binding and activation. In contrast, the β-Ala-D-(2,4-Cl)Phe analog of **2** (K_i = 1.8 nM) is a highly potent MC4R antagonist.[14]

Based on receptor modeling studies, the basic amine of the Tic group of **1** possibly interacts with an aspartic residue (Asp-126) at the top of the transmembrane domain-3 (TM-3) of the human MC4 receptor (*h*MC4R), while another acidic Asp-122 may contact with the polar triazole of **1a** via a hydrogen-bond, or the amine of **1b** and **1c** via a charge–charge interaction.[15–17]

We have shown that the binding affinity of benzylamine **3** (K_i = 490 nM) is improved when a small isobutyl group is incorporated (**4**, K_i = 74 nM).[18] In addition, β-Ala-D-(2,4-Cl)Phe-piperazines bearing a cyclohexyl-carboxylate such as **5** are potent MC4R antagonists,[19] indicating a basic amine in **4** might not be crucial for receptor binding. To further explore the structure–activity rela-

* Corresponding author. Tel.: +1 858 617 7600; fax: +1 858 617 7967.
E-mail address: cchen@neurocrine.com (C. Chen).

0960-894X/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2008.07.076

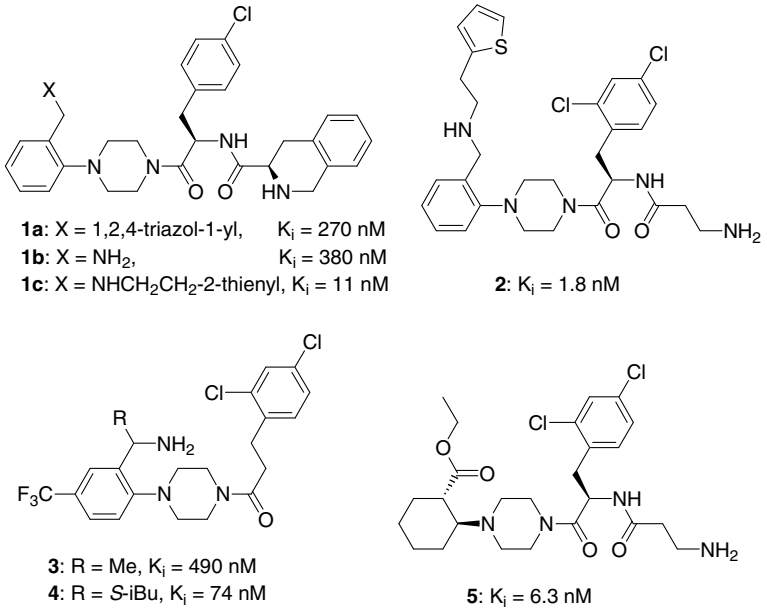
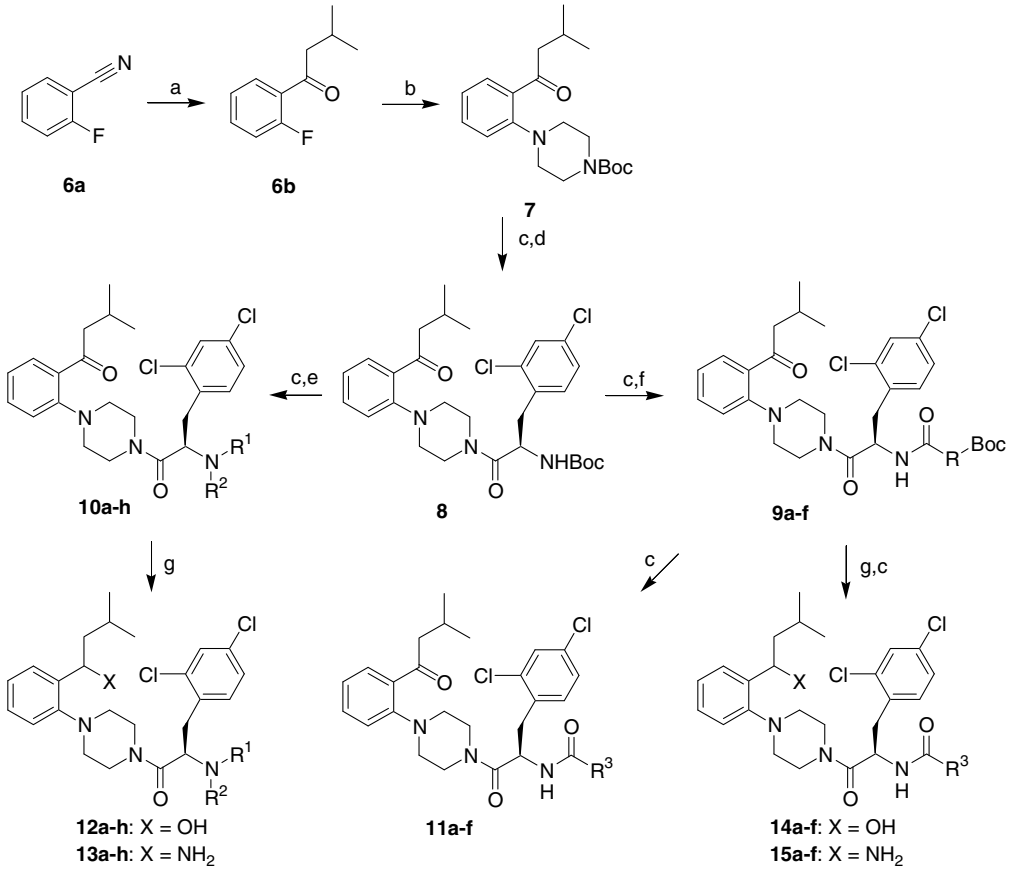


Figure 1. Chemical structures of some non-peptide MC4R ligands.

tionship and understand the ligand–receptor interactions, we synthesize a series of alcohols, as well as their amines and ketone analogs, to study their binding affinities at MC4R and the role of these functional groups in receptor binding.

The ketones **10** and **11** were synthesized from 2-fluorobenzonitrile **6a** as described in Scheme 1. Reaction of **6a** with isobutylmagnesium bromide gave the corresponding ketone **6b** in 74% yield, which was condensed with Boc-protected piperazine to give **7** in



Scheme 1. Reagents and conditions: (a) ^{t}BuMgBr/THF/rt, 2 h, 74%; (b) *N*-Boc-piperazine/K_2CO_3/DMF/130 °C, 10 h, 62%; (c) TFA/DCM/rt, 0.5 h; (d) D-*N*-Boc-(2,4-Cl)Phe-OH/-HBTU/DMF/40 °C, 10 h, 59%; (e) i—$(iPr)_2$NEt/DCM; ii—aldehyde/$NaBH(OAc)_3$/THF/rt, 8 h; (f) *N*-Boc-amino acid/HBTU/$(iPr)_2$NEt/DMF/40 °C, 10 h; (g) NH_4OAc/$NaB(CN)H_3$/-^{i}PrOH/70 °C, 6 h.

62% yield. Deprotection of **7** with TFA, followed by a coupling reaction with D-*N*-Boc-(2,4-Cl)Phe-OH under standard amide coupling conditions gave the amide **8** (59%). After deprotection with TFA, **8** was subjected to reductive alkylations with several aldehydes to afford the ketones **10a–h**. Alternatively, coupling reactions of the deprotected **8** with Boc-protected amino acids gave the intermediates **9**, which were deprotected with TFA to provide the dipeptides **11a–f**.

Reactions of **10** with sodium cyanoborohydride in the presence of ammonium acetate gave a mixture of the corresponding alcohols **12a–h** and the amines **13a–h**, which were separated using a HPLC system. The alcohols **14a–f** and the amines **15a–f** were obtained from **9** using the same procedure as **12** and **13**, followed by a TFA-deprotection.

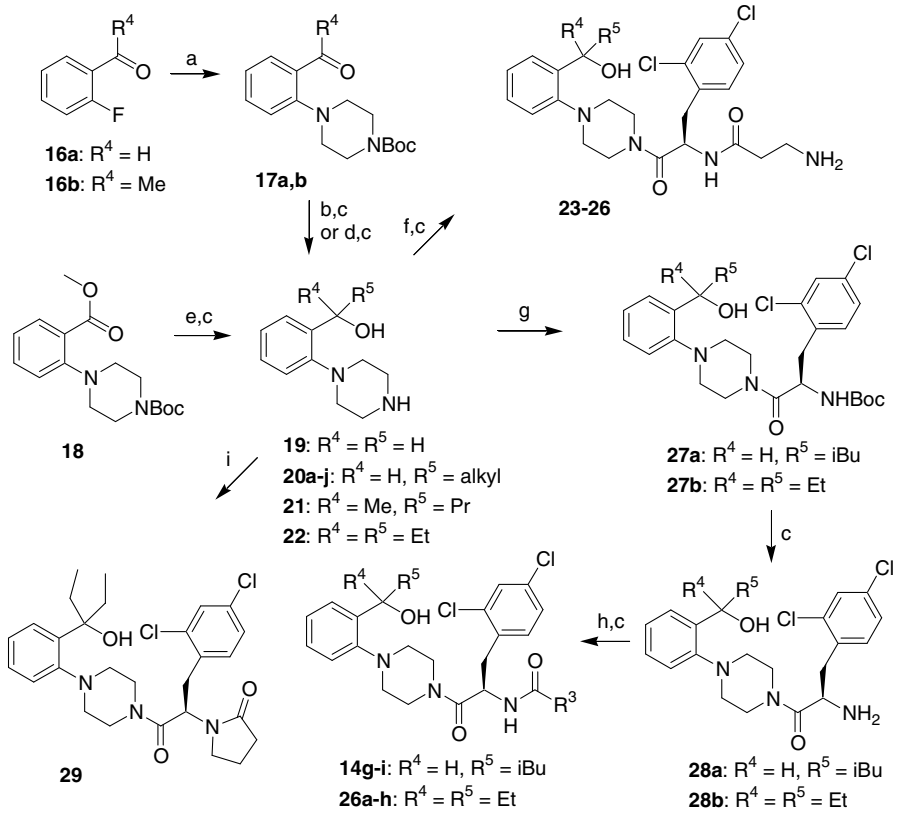
The Boc-protected piperazine-benzaldehyde **17a** and piperazine-acetophenone **17b** were prepared from the fluorobenzenes **16** and Boc-piperazine (Scheme 2). Reduction of **17a** with sodium borohydride gave the benzyl alcohol **19** after Boc-deprotection. Reactions of **17a** with various alkyl Grignard reagents afforded the secondary alcohols **20a–j**. The tertiary alcohol **21** was obtained from **17b** and propylmagnesium bromide. Alternatively, the ester **18** was converted to **22** with ethylmagnesium bromide. Coupling reactions of **19–22** with *N*-Boc-β-Ala-D-(2,4-Cl)Phe-OH provided the dipeptide derivatives **23–26** after deprotection. Alternatively, coupling reactions of **20e** (R^4 = H, R^5 = *i*Bu) and **22** with *N*-Boc-D-(2,4-Cl)Phe-OH afforded the amides **28a–b**, respectively, after deprotection. Coupling reactions of **27** and **28** with various *N*-Boc amino acids gave the dipeptides **14g–i** and **26a–h** after deprotection. Finally, a coupling reaction of **22** with (2*R*)-(2-oxopyrrolidin-1-yl)-3-(2, 4-dichlorophenyl)-propionic acid gave the amide **29**.

The *R*- or *S*-benzylalcohols (*R*-**14b** and *S*-**14b**) was synthesized from the ketone **8** by a stereo-selective reduction using *S*- or *R*-diphenylprolinol chiral auxiliary as show in Scheme 3. Thus, treatment of **8** using a Corey protocol gave the corresponding *R*- or *S*-benzylalcohol **31** (the stereochemistry was assigned based on mechanism),[20] which was converted to the targeted *R*-**14b** or *S*-**14b**. Their ee values were determined to be >93% based on chiral HPLC analyses.

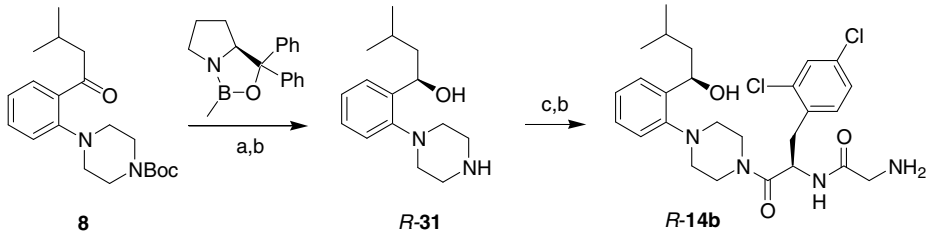
Compounds **10–15, 23–26, 27**, and **29** were measured for their abilities to inhibit [^{125}I]-NDP-MSH binding to *h*MC4R stably transfected in HEK293 cells in a binding assay,[21] and the results are summarized in Tables 1–3.

In comparison to the amines **13**, the alcohols **12** were significant less potent (6- to 15-fold). The binding affinity of the pyridine derivative **12h** (K_i = 83 nM) was over 40-fold lower than that of the corresponding amine **13h** (K_i = 2.0 nM). The ketones **10** exhibited similar binding affinities to the alcohols **12** (Table 1). These results indicate an important role of the basic benzylamine in **13**. For the dipeptides **11**, **14** and **15**, the amines **15** were still more potent than the alcohols **14** and the ketones **11**. For example, the binding affinity of the alcohol **14a** (K_i = 8.1 nM) was about 3-fold lower than that of the amine **15a** (K_i = 3.2 nM). However, the difference between **15** and **14** was small (⩽6-fold). In contrast, the binding affinities between the ketones **11** and the alcohols were relatively large (up to 8-fold).

Next, we surveyed a series of alcohols **23–26a** (Table 2). The primary alcohol **23** (K_i = 870 nM) was only weakly active in the binding assay. Addition of a propyl group to **23** significantly increased its binding affinity by almost 35-fold (**24a**, K_i= 26 nM). This result is parallel to that of the benzylamines **3** and **4**.[14] While the isopropyl, 1-vinylethyl and sec-butyl (**24b–d**) were minimally effective,



Scheme 2. Reagents and conditions: (a) *N*-Boc-piperazine/DMF/160 °C, 10 h; (b) $NaBH_4$/MeOH/rt, 0.5 h; (c) TFA/DCM/rt, 0.5 h; (d) R^5MgBr/THF/−78 °C, 0.5 h, then rt, 1–4 h; (e) 2EtMgBr/THF/Et_2O/rt, 4 h, 69%; (f) *N*-Boc-Ala-D-(2,4-Cl)Phe-OH/HBTU/$(iPr)_2NEt$/DMF/30 °C, 16 h; (g) D-*N*-Boc-(2,4-Cl)Phe-OH/HBTU/$(iPr)_2NEt$/DMF/rt, 1 h; (h) *N*-Boc-amino acid/HBTU/DMF/rt, 16 h; (i) (2*R*)-(2-oxopyrrolidin-1-yl)-3-(2,4-dichlorophenyl)propionic acid/HBTU/DMF/rt, 8 h.



Scheme 3. Reagents and conditions: (a) BH_3/THF/rt, 1 h, 17%, 88% e.e.; (b) TFA/DCM/rt, 0.5 h; (c) D-*N*-Boc-Gly-(2,4-Cl)Phe-OH/HBTU/$(iPr)_2$NEt/DMF/rt, 16 h, 30%.

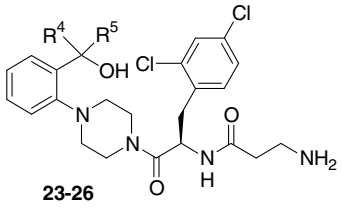
the isobutyl **14a** (K_i = 8.1 nM) was 3-fold better than **24a**. The other secondary alcohols **24e–i** were not better than **14a**. The two tertiary alcohols **25** and **26a** were also potent (K_i = 11 nM).

Studies on several amides **26a–h** showed that a small variation at this site had no significant effect (Table 3), similar to some benzylamine analogs.[14] The amino group at this side-chain played a small role since the *R*-configured alanine derivative **26f** was over 3-fold less potent than its *S*-analog **26e**. The intermediate **27b** (K_i = 390 nM) was significantly less active than **26a–h**. The non-basic lactam **29** (K_i = 110 nM) was 10-fold less active than the β-alanine **26a**.

The binding affinities of the two stereoisomers of **14b** were only marginally different and the *R*-isomer (*R*-**14b**, K_i = 9 nM) was slightly more potent than its *S*-isomer (*S*-**14b**, K_i = 28 nM). This is somewhat surprised since we have shown that an *S*-benzylamine was more potent than its *R*-isomer.[22] It is worth noting that the stereochemistry of these two isomeric alcohols was assigned based on the reported mechanism only.[16] The amide **14b** was 20-fold more active than its precursor amine **28a** (K_i = 280 nM). In comparison, the cyclic amine **14h** was 6-fold less active than the β-analine **14a**. These results further prove that the amino group at the amide side-chain plays a role in receptor interactions.

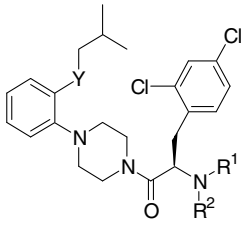
Results from this study showed that the SAR of benzylalcohols was quite similar to that of some benzylamines reported earlier,[14]

Table 2
SAR of alcohols **23–26** at *h*MC4R

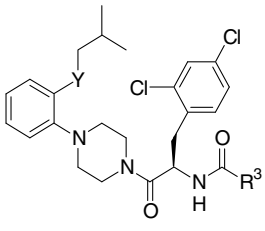


Compound	R^4	R^5	K_i (nM)
23	H	H	870
24a	H	$CH_2CH_2CH_3$	26
24b	H	$CHMe_2$	110
24c	H	$CH(CH{=}CH_2)CH_3$	29
24d	H	$CH(CH_2CH_3)CH_3$	47
14a	H	$CH_2CH(CH_3)_2$	8.1
24e	H	$CH_2C_6H_5$	54
24f	H	$CH_2C_6H_4(OCH_3)$-2	66
24g	H	$CH_2C_6H_4(OCH_3)$-3	66
24h	H	$CH_2CH_2C_6H_5$	32
24i	H	$CH_2CH_2C_6H_4(OCH_3)$-4	23
25	Me	$CH_2CH_2CH_3$	11
26a	CH_2CH_3	CH_2CH_3	11

Table 1
Comparison of ketones (**10**, **11**), alcohols (**12**, **14**), and amines (**13**, **15**) at *h*MC4R (K_i, nM)



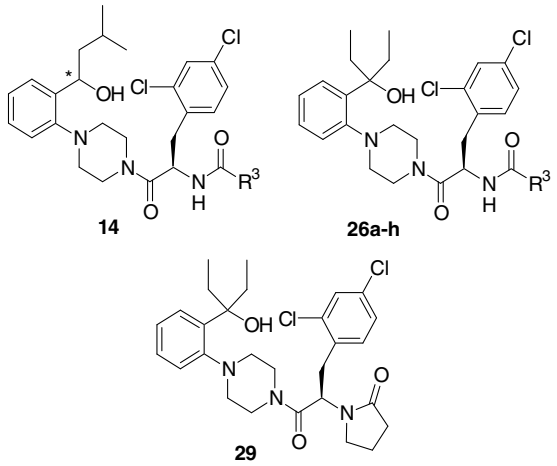
10: Y = CO
12: Y = CHOH
13: Y = $CHNH_2$



11: Y = CO
14: Y = CHOH
15: Y = $CHNH_2$

Compound	R^1 NR^2	**10**	**12**	**13**
a	$NHCHMe_2$	560	380	53
b	$NH(CH_2)_3SMe$	230	330	21
c	$NHCH_2$-3-THF	150	89	15
d	$N[(CH_2)_3Me]_2$	1700	1400	120
e	$N[(CH_2)_4Me]_2$	5800	3200	350
f	$NH(CH_2CHMe_2)_2$	>10,000	>10,000	1200
g	$N(CH_2$-c-Pr)2	>10,000	>10,000	350
h	$N(CH_2$-2-Py$)_2$	110	83	2.0
	$NHCOR^3$	**11**	**14**	**15**
a	$NHCOCH_2CH_2NH_2$	24	8.1	3.2
b	$NHCOCH_2NH_2$	33	13	2.0
c	$NHCOCH_2NHMe$	31	8.3	1.7
d	*S*-$NHCOCH(NH_2)Me$	26	16	4.2
e	$NHCOC(NH_2)Me_2$	110	46	7.7
f	$NHCOC(NHMe)Me_2$	91	21	4.7

Table 3
SAR of acyl substituents at *h*MC4R



Compound	R^3	K_i (nM)
28a		280
14b	CH_2NH_2	13
R-**14b**	CH_2NH_2	9
S-**14b**	CH_2NH_2	28
14g	$CH_2N(CH_3)_2$	9.6
14h	3-Piperidine	49
26a	$CH_2CH_2NH_2$	11
26b	CH_2NH_2	26
26c	CH_2NHCH_3	13
26d	$CH_2N(CH_3)_2$	9.4
26e	*S*-$CH(NH_2)CH_3$	18
26f	*R*-$CH(NH_2)CH_3$	65
26g	$C(CH_3)_2NH_2$	38
26h	1-Amino-cyclopropyl	42
27b	$OC(CH_3)_3$	390
29		110

indicating that the hydroxyl group of **14** might directly mimic the amino moiety of **15** in the receptor with lower intensity, possibly via hydrogen bonding with the receptor.

Since the Asp-122 at the top of TM-3 of *h*MC4R has been determined to play an important role in ligand interactions,[9,15] we tested if the hydroxyl group of **14** might have a contact with this residue. The binding affinities of **11c**, **14c**, and **15c** were determined at the Asp122Ala mutant receptor as well as the wild-type MC4R (Table 4).

The results showed that the alcohol **14c** at the mutant receptor was 60-fold lower than that at the wild-type. Its fold of reduction was similar to that of the amine **15c** (58-fold), indicating that the Asp-122 residue may have a specific interaction with the hydroxyl or amino group of compound **14c** or **15c**. However, it is worth noting that the endogenous α-MSH reduced its binding affinity by 28-fold from the wild-typ (K_i = 45 nM) to the Asp122Ala MC4R mutant (K_i = 1250 nM). It is also interesting that reduction in binding affinity for the ketone **11c** was less significant compared to **14c** and **15c**.

Table 4
Binding affinities of compound **11c**, **14c** and **15c** at the Asp122Ala mutant in comparison with those at the wild-type MC4R (K_i, nM)

Compound	Wild-type	Asp122Ala[a]	Fold
11c	31	290	9
14c	8.3	500	60
15c	1.7	99	58

[a] At Asp122Ala MC4R mutant.

The alcohols **14a**, **14c**, **14g**, and **26d** were further tested for their binding affinities to the other subtypes of the human melanocortin receptors to compare with the ketone **11a** and amine **15a**, and the results are summarized in Table 4. None of these compounds showed a significant interaction with MC1R (⩽42% inhibition at 10 μM concentration), and they possessed micromolar affinities at the MC3 and MC5 receptors, demonstrating high selectivities.

None of these alcohols had a significant stimulation of cAMP production in cells expressing the human MC4 receptor at a 10 μM concentration. In contrast, they dose-dependently inhibited α-MSH-stimulated cAMP accumulation, demonstrating functional antagonist activities. For example, compound **14a** exhibited an IC_{50} value of 260 nM in this assay (Table 5).

The measured log *D* values were 2.4, 2.2, and 0.15, respectively, for **11a**, **14a**, and **15a**. In an in vitro human liver microsomal assay, the lipophilic ketone **11a** exhibited much lower metabolic stability (systemic clearance CL_{sys} = 18.4 mL.min kg) than the hydrophilic amine **15a** (CL_{sys}3.6 mL/min kg), while the alcohol **14a** was moderately stable (CL_{sys} = 14.7 mL/min kg).

The pharmacokinetic parameters of **14a** and **15a** were compared in rats after an intravenous injection at a 5 mg/kg dose (Table 6). The alcohol **14a** displayed a high plasma clearance (CL_p = 64.5 mL/min kg) and a large volume of distribution (V_d = 42.3 L/kg), resulting in a very long elimination half-life ($t_{1/2}$ = 7.6 h). The brain concentration measured at 1 h after i.v. administration was moderate (C_{brain} = 117 ng/g), resulting in a brain/plasma ratio of 0.53. The plasma exposure of **14a** (AUC = 30 ng/mL.h) was very poor after an oral gavage at 10 mg/kg, resulting in an oral bioavailability of 1.2%. In comparison, the amine **15a** exhibited a very similar profile (CL_p = 68 mL/min kg, V_d = 41.5 L/kg, $t_{1/2}$ = 7.1 and *F* = 2.1%), although its brain penetration (C_{brain} = 245 ng/g, brain/plasma ratio = 1.8) was slightly better than that of **14a**.

In conclusion, a series of piperazinebenzylalcohols were synthesized and studied as MC4R antagonists, to compare with their ketone and amine analogs. While the alcohols **14a–f** were less active than the corresponding amines **15a–f** in general, potent compounds such as **14a**, **14c**, **14g**, and **26d** (K_i < 10 nM) were identified. Like their amine counterparts, these alcohols showed good selectivity over other melanocortin receptor subtypes. In addition, these

Table 5
Selectivity and antagonist activity of alcohols at melanocortin receptor subtypes (K_i, nM)

Compound	MC1R[a]	MC3R	MC4R	MC5R	IC_{50}[b,c] (nM)
15a	38%	870	3.2	540	250
11a	42%	2300	24	330	650
14a	24%	1700	8.1	970	260
14c	34%	2500	8.3	1800	420
14g	36%	3100	9.6	1300	250
26d	34%	3100	9.4	950	400

[a] Percentage of inhibition at 10 μM concentration.
[b] Dose-dependent inhibition of α-MSH-stimulated cAMP production in cells expressing *h*MC4R.
[c] At MC4R.

Table 6
Pharmacokinetic parameters of **14a** and **15a** in rats (*N* = 3)[a]

Compound	CL_p (mL/min kg)	V_d (L/kg)	$t_{1/2}$ (h)	C_{brain} (ng/g)[b]	*b*/*p* Ratio[b]	*F* (%)
14a	64.5	42.3	7.6	117	0.53	1.2
15a	68	41.5	7.1	245	1.8	2.1

[a] Intravenous dose at 5 mg/kg and oral gavage at 10 mg/kg.
[b] Determined 1-h postdosing.

alcohols were functional antagonists in a cAMP assay. These results might provide useful information for understanding the ligand–receptor interactions.

References and notes

1. Ballesteros, J.; Shi, L.; Javitch, J. A. *Mol. Pharmacol.* **2001**, *60*, 1.
2. Wikberg, J. E. S. *Eur. J. Pharmacol.* **1999**, *375*, 295.
3. Wikberg, J. E. S.; Muceniece, R.; Mandrika, I.; Prusis, P.; Post, C.; Skottner, A. *Pharmacol. Res.* **2000**, *42*, 393.
4. Yang, Y. K.; Harmon, C. M. *Obes. Rev.* **2003**, *4*, 239.
5. Marks, D. L.; Butler, A. A.; Turner, R.; Brookhart, G.; Cone, R. D. *Endocrinology* **2003**, *144*, 1513–1523.
6. Goodfellow, V.; Saunders, J. *Curr. Topic Med. Chem.* **2003**, *3*, 855.
7. Millhauser, G. L.; Mcnulty, J. C.; Jackson, P. J.; Thompson, D. A.; Barsh, G. S.; Gabtz, I. *Ann. N.Y. Acad. Sci.* **2003**, *994*, 27.
8. Kiefer, L. L.; Veal, J. M.; Mountjoy, K. G.; Wilkison, W. O. *Biochemistry* **1998**, *37*, 991.
9. Yang, Y. K.; Fong, T. M.; Dickinson, C. J.; Mao, C.; Li, J. Y.; Tota, M. R.; Mosley, R.; Van Der Ploeg, L. H.; Gantz, I. *Biochemistry* **2000**, *39*, 14900.
10. Chen, C. *Prog. Med. Chem.* **2007**, *45*, 111.
11. Dyck, B.; Parker, J.; Phillips, T.; Carter, L.; Murphy, B.; Summers, R.; Hermann, J.; Baker, T.; Cismowski, M.; Saunders, J.; Goodfellow, V. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3793.
12. Richardson, T. I.; Ornstein, P. L.; Briner, K.; Fisher, M. J.; Backer, R. T.; Biggers, C. K.; Clay, M. P.; Emmerson, P. J.; Hertel, L. W.; Hsiung, H. M.; Husain, S.; Kahl, S. D.; Lee, J. A.; Lindstrom, T. D.; Martinelli, M. J.; Mayer, J. P.; Mullaney, J. T.; O'Brien, T. P.; Pawlak, J. M.; Revell, K. D.; Shah, J.; Zgombick, J. M.; Herr, R. J.; Melekhov, A.; Sampson, P. B.; King, C. H. *J. Med. Chem.* **2004**, *47*, 744.
13. Fotsch, C.; Han, N.; Arasasingham, P.; Bo, Y.; Carmouche, M.; Chen, N.; Davis, J.; Goldberg, M. H.; Hale, C.; Hsieh, F. Y.; Kelly, M. G.; Liu, Q.; Norman, M. H.; Smith, D. M.; Stec, M.; Tamayo, N.; Xi, N.; Xu, S.; Bannon, A. W.; Baumgartner, J. W. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1623.
14. 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.
15. Fleck, B. A.; Chen, C.; Yang, W.; Huntley, R.; Markison, S.; Nickolls, S. A.; Foster, A. C.; Hoare, S. R. *Biochemistry* **2005**, *44*, 14494.
16. Pogozheva, I. D.; Chai, B. X.; Lomize, A. L.; Fong, T. M.; Weinberg, D. H.; Nargund, R. P.; Mulholland, M. W.; Gantz, I.; Mosberg, H. I. *Biochemistry* **2005**, *44*, 11329.
17. Hogan, K.; Peluso, S.; Gould, S.; Parsons, I.; Ryan, D.; Wu, L.; Visiers, I. *J. Med. Chem.* **2006**, *49*, 911.
18. Jiang, W.; Tucci, F. C.; Chen, C. W.; Arellano, M.; Tran, J. A.; White, N. S.; Marinkovic, D.; Pontillo, J.; Fleck, B. A.; Wen, J.; Saunders, J.; Madan, A.; Foster, A. C.; Chen, C. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4674.
19. Tucci, F. C.; White, N. S.; Markison, S.; Joppa, M.; Tran, J. A.; Fleck, B. A.; Madan, A.; Dyck, B. P.; Parker, J.; Pontillo, J.; Arellano, L. M.; Marinkovic, D.; Jiang, W.; Chen, C. W.; Gogas, K. R.; Goodfellow, V. S.; Saunders, J.; Foster, A. C.; Chen, C. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4389.
20. Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C. P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925.
21. Nickolls, S. A.; Cismowski, M. I.; Wang, X.; Wolff, M.; Conlon, P. J.; Maki, R. A. *J. Pharmacol. Exp. Ther.* **2003**, *304*, 1217.
22. Chen, C. W.; Tran, J. A.; Jiang, W.; Tucci, F. C.; Arellano, M.; Wen, J.; Fleck, B. A.; Marinkovic, D.; White, N. S.; Pontillo, J.; Saunders, J.; Madan, A.; Foster, A. F.; Chen, C. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4800.