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Bioorganic & Medicinal Chemistry Letters 17 (2007) 6825–6831
Bioorganic & Medicinal Chemistry Letters

Synthesis and characterization of *trans*-4-(4-chlorophenyl) pyrrolidine-3-carboxamides of piperazinecyclohexanes as ligands for the melanocortin-4 receptor

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Received 25 July 2007; revised 5 October 2007; accepted 8 October 2007
Available online 17 October 2007

Abstract—A series of *trans*-*N*-alkyl-4-(4-chlorophenyl)pyrrolidine-3-carboxamides of piperazinecyclohexanemethylamines was synthesized and characterized for binding and function at the melanocortin-4 receptor (MC4R), and several potent benzylamine derivatives were identified. Compound **18v** was found to bind MC4R with potent affinity (K_i = 0.5 nM) and high selectivity over the other melanocortin subtypes and behaved as a functional antagonist (IC_{50} = 48 nM).

The melanocortin-4 receptor (MC4R) is a member of the G-protein-coupled receptor superfamily and plays an important role in biological functions, including regulation of feeding behavior.[1] MC4R agonists have been extensively studied in an effort to discover small molecules for the treatment of obesity,[2] and several small molecule MC4R agonists from different chemical classes have been reported.[3] MC4R antagonists, on the other hand, have been shown to reverse lean body mass loss and increase food intake in animal models of cachexia, suggesting potential in cancer cachexia treatment.[4,5]

Pyrrolidine derivatives were first reported by Ujjainwalla as potent and selective MC4R agonists.[6] An example of this chemical class is compound **1b**, which has a binding IC_{50} of 14 nM and a functional EC_{50} of 2 nM (Fig. 1). This functional activity is similar to that reported for THIQ **1a**.[7] One advantage of compound **1b** is its pyrrolidine structure. This structure is much different than many reported small molecule MC4R agonists, such as **1a**, in which a Tic-(4-Cl)Phe dipeptide is required as an 'address element'.[2] We have recently shown that by combining the *trans*-4-arylpyrrolidine-3-carbonyl moiety of **1b** with the piperazinebenzylamine *N*,*N*-dimethylaminopropionamide of the antagonist **2**, potent MC4R agonists have been identified from the resulting compounds. For example, **3** (K_i = 4.7 nM) possesses an EC_{50} value of 16 nM with intrinsic activity (IA) of 102% relative to the endogenous ligand α-MSH.[8] We have also previously reported that the piperazinecyclohexanes with the Tic-(4-Cl)Phe dipeptide are MC4 agonists and can be converted into functional antagonists by replacing the dipeptide. Thus, **4** is a potent agonist (K_i = 16 nM, EC_{50} = 33 nM, IA = 96%),[9] while the β-Ala-(2,4-Cl)Phe analog **5a** is a functional antagonist (K_i = 8.8 nM, IC_{50} = 260 nM).[10] Like the amide **5a**, the benzylamine **5b** (K_i = 18 nM) also possesses potent binding affinity.

Because of the success in converting antagonist **2** into agonist **3**, we were interested in the pharmacological properties of compounds derived from the combination of the left-side of compound **4** with the pyrrolidine moiety of **1b**. Here we report the synthesis and characterization of *trans*-4-(4-chlorophenyl)pyrrolidine-3-carboxamides of 1-(1-piperazine)cyclohexanemethylamine derivatives **7**–**22** as MC4R ligands.

Keywords: Synthesis; Pyrrolidine; Melanocortin-4 receptor; Agonist; Antagonist; Structure–activity relationship.
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doi:10.1016/j.bmcl.2007.10.032

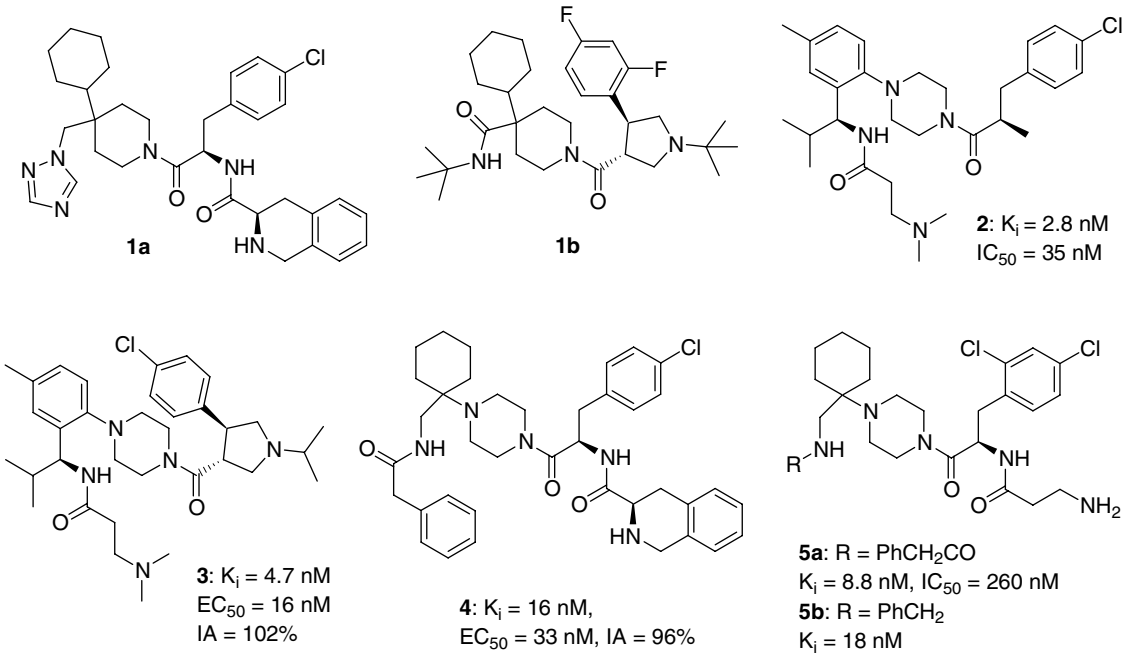


Figure 1. Chemical structures of some MC4R agonists and antagonists related to this study.

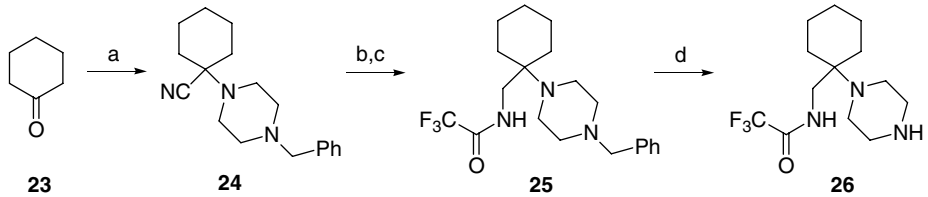
The core structure of 1-trifluoroacetamidomethyl-1-(1-piperazine)cyclohexane **26** was synthesized as shown in Scheme 1. A Strecker reaction of cyclohexanone **23** with 1-benzylpiperazine afforded the intermediate **24**, which was reduced with lithium aluminumhydride, followed by a treatment with trifluoroacetic anhydride to provide the protected diamine **25**. Debenzylation of **25** catalyzed by palladium gave the desired amine **26** in a good overall yield.

The *trans*-*N*-isopropyl-4-(4-chlorophenyl)pyrrolidine-3-carboxylic acid **28a** was synthesized from the cyclization of *N*-(methoxylmethyl)-*N*-(trimethylsilylmethyl)isopropylamine **27a** with methyl *trans*-4-chlorocinnamate mediated by trifluoroacetic acid, followed by hydrolysis with lithium hydroxide. Compound **28a** was coupled with the amine **26** to provide the amide **29a**, which was deprotected under basic conditions to give the primary amine **6a** (Scheme 2).

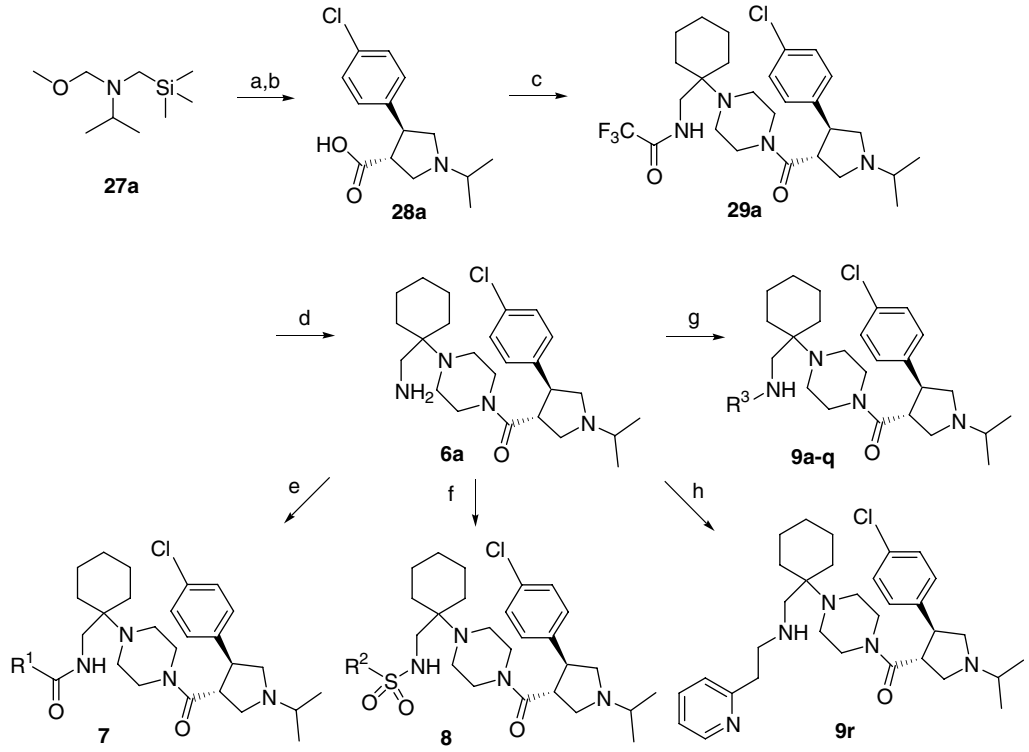
Coupling reactions of **6a** with various carboxylic acids afforded the amides **7**. Similarly, reactions of **6a** with several sulfonyl chlorides gave the sulfonamides **8**. Alternatively, reductive alkylations of **6a** with a variety of aldehydes provided the secondary amines **9**. A reaction of **6a** with 2-vinylpyridine in the presence of acetic acid in ethanol gave the 2-pyridinylethylamine **9r**.

The key intermediate **6b** was synthesized from *N*-(methoxylmethyl)-*N*-(trimethylsilylmethyl)benzylamine **27b** using a procedure similar to that for **6a**. Reductive alkylations of **6b** with benzaldehyde and 4-pyridylcarboxaldehyde afforded the corresponding secondary amines **10a** and **10b**, respectively. Debenzylation of **10a** or **10b** was accomplished using 1-chloroethyl chloroformate to provide the secondary amine **11a** or **11b**. Reductive alkylations of **11a** with several ketones gave the tertiary amines **12** after purification. Reactions of **11a**–**b** with acyl chlorides in the presence of triethylamine resulted in the amides **13** and **15**, respectively. Alternatively, coupling reactions of **11a** with *N*-Boc-amino acids, followed by TFA-treatment, gave the amides **14**. The urea **16** was obtained by a reaction of **11b** with ethylisocyanate, and the sulfonamide **17** was synthesized from methylsulfonyl chloride and **11b** (Scheme 3).

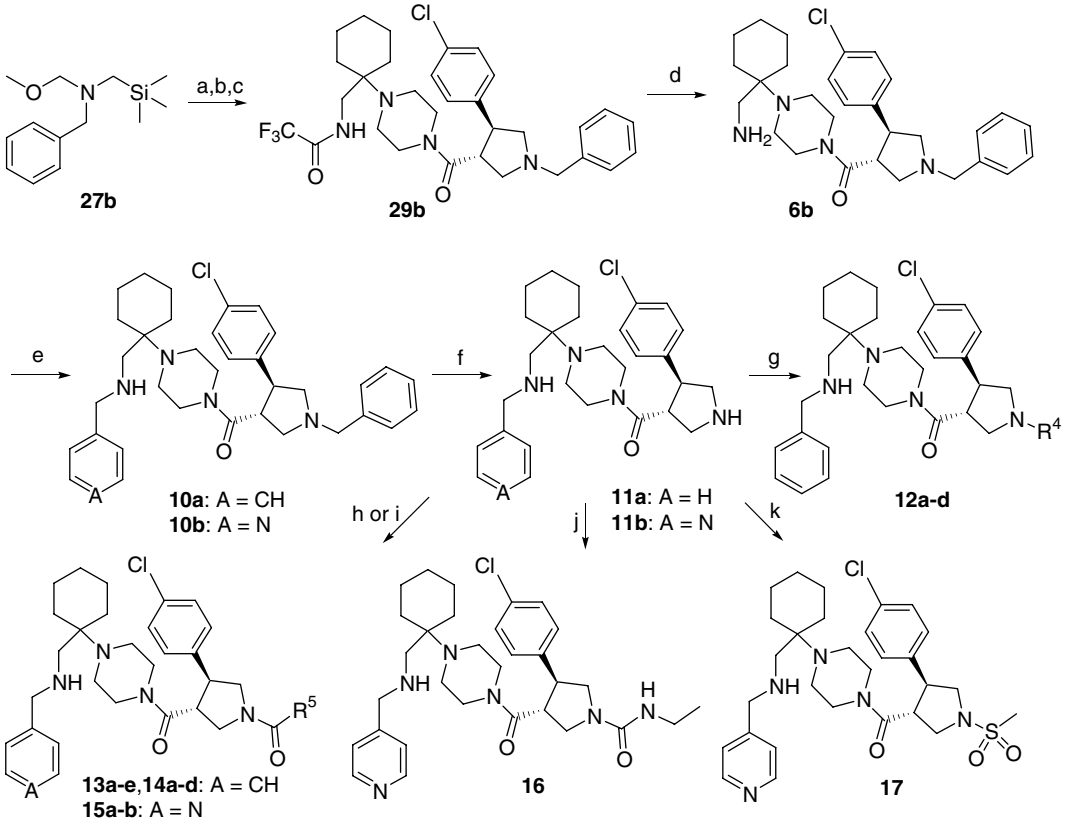
Reductive alkylations of **6a** with various substituted benzaldehydes gave the corresponding benzylamines **18**. The secondary amines **9p** and **18j** were further con-



Scheme 1. Reagents and conditions: (a) 1-Benzylpiperazine/KCN/$Na_2S_2O_5$/H_2O/rt, 18 h, 81%; (b) $LiAlH_4$/Et_2O/rt, 16 h, 93%; (c) $(CF_3CO)_2O$/TEA/DCM/rt, 2 h, 100%; (d) Pd–C/HCO_2NH_4/MeOH, ~100%.



Scheme 2. Reagents and conditions: (a) *trans*-4-ClPhCH=CHCOOMe/TFA/DCM/rt, 6 h, 80%; (b) LiOH/THF/H_2O/rt, 3 h, 99%; (c) **26**/HBTU/DIEA/DMF/rt, 16 h, 85%; (d) K_2CO_3/MeOH/H_2O/65 °C, 16 h, 92%; (e) R^1COOH/EDC/HOBt/TEA/DCM/rt, 16 h; (f) R^2SO_2Cl/TEA/rt, 2 h; (g) aldehyde/$NaBH(OAc)_3$/DCE/rt, 16 h; (h) 2-PyCH=CH_2/AcOH/EtOH/90 °C, 4 h, 30%.



Scheme 3. Reagents and conditions: (a) TFA/DCM/rt, 16 h, 57%; (b) LiOH/THF/H_2O/rt, 3 h, quantitative; (c) **26**/HBTU/DIEA/DMF/rt, 16 h, 9 4%; (d) K_2CO_3/MeOH/H_2O/65 °C, 16 h, 76%; (e) ArCHO/$NaBH(OAc)_3$/DCE/rt, 16 h, ~40%; (f) MeCH(Cl)OCOCl/DCE/reflux, 4 h, then MeOH/reflux, 2 h; (g) carbonyl compound/$NaBH(OAc)_3$/DCE/rt, 16 h; (h) R^5COCl/TEA/DCM/rt, 2 h; (i) *N*-Boc-amino acid/EDC/HOBt/DIEA/DCM/rt, 16 h, then TFA/DCM/rt, 1 h; (j) EtNCO/TEA/DCM/rt, 1 h; (k) $MeSO_2Cl$/TEA/DCM/rt, 2 h.

verted to the tertiary amines **19** and **20** and acetamides **21** and **22** as shown in Scheme 4.

The synthesized compounds were tested in a competition binding assay using HEK293 cells expressing the human melanocortin-4 receptor and [^{125}I]-NDP-MSH as the radiolabeled ligand.[11] Compounds with potent binding affinities were also tested in a functional agonist assay measuring the stimulation of cAMP release. Selected compounds were studied in a functional antagonist assay to determine the inhibition of α-MSH-stimulated cAMP release. Results are shown in Tables 1–4.

The phenylacetamide **7a** ($R^1 = PhCH_2$, $K_i = 510$ nM, Table 1) only showed moderate binding affinity and was 30-fold less potent than the Tic-(4-Cl)Phe dipeptide **4** ($K_i = 16$ nM). All the arylacetamides **7** (16 compounds) showed similar binding affinity ($K_i = 260$–820 nM, data not shown) and were only slightly more potent than the parent primary amine **6a** ($K_i = 1200$ nM). These results are very different than the SAR in the dipeptide series **5** where an amide side chain increases the binding affinity as much as 30-fold.[8,9]

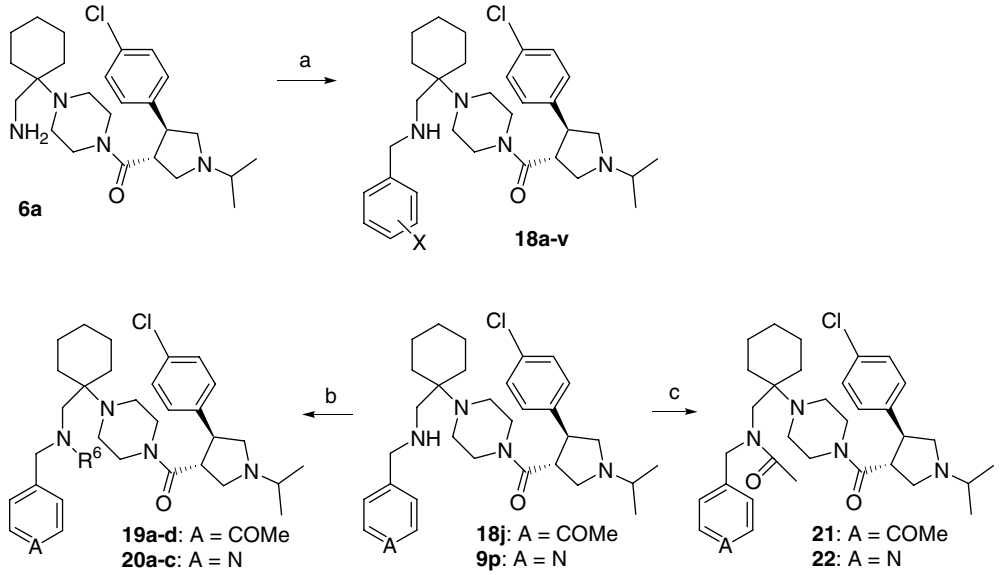
We also tested several sulfonamides, since this functional group has been used in other small molecule MC4R agonists.[12,13] Like amides **7**, the sulfonamides **8** (6 compounds) displayed moderate binding affinity ($K_i = 330$–550 nM). For example, the benzyl- and phenylsulfonamides **8a** and **8b** displayed K_i values of 340 and 330 nM, respectively.

A series of secondary amines **9a**–**r** were then examined (Table 3). While the two alkylamines **9a** and **9b** only exhibited 4-fold improvement in binding affinity over the primary amine **6a**, the benzylamine **9c** displayed a K_i value of 26 nM, which was over 10-fold better than the cyclohexanemethyl analog **9b** ($K_i = 300$ nM). These results, in combination with those from the amides **7**, suggest that a basic amine as well as an aromatic ring on the side chain is important for high affinity binding. In the dipeptide series **5**, the basicity of the amine is unnecessary since both the amide **5a** ($K_i = 8.8$ nM) and the amine **5b** ($K_i = 18$ nM) possess good binding affinity. While its binding affinity was similar to that of the Tic-(4-Cl)Phe dipeptide agonist **4** ($K_i = 16$ nM), **9c** had poor potency and low efficacy in the functional agonist assay ($EC_{50} = 1100$ nM, IA = 31%). These results clearly indicate that the current series is much different from the dipeptides such as **4**.

The furan and thiophene derivatives **9d**–**g** exhibited binding affinities similar to **9c**, while the electron-deficient aromatic thiazole and imidazole analogs **9h**–**k** were less potent. The 1,5-dimethylpyrazolemethylamine **9l** ($K_i = 11$ nM) exhibited the best binding affinity in this group. The pyrimidine **9m** had a K_i value of 220 nM, while the pyridine analogs **9n**–**p** were more potent than **9m**, especially the 4-pyridine **9p** ($K_i = 27$ nM), which was equal to **9c** in binding affinity. In comparison to **9c**, the indole derivative **9q** and the pyridylethylamine **9r** were significantly less potent.

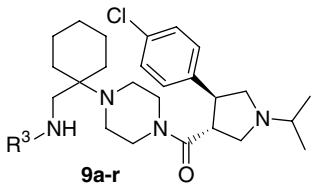
While **9c** was a weak partial agonist, several of its analogs exhibited partial agonism with moderate potency (Table 1). The most potent compound in this group was **9l** which had an EC_{50} of 50 nM with an intrinsic activity of 43% of α-MSH. The 4-pyridine **9p** displayed an EC_{50} of 780 nM with very low efficacy (IA = 27%) in the functional agonist assay. Additionally, **9c** behaved as a functional antagonist, dose-dependently inhibiting α-MSH-stimulated cAMP release with an IC_{50} of 410 nM.

The role of the *N*-group on pyrrolidine was also studied in this series of compounds, and the results are summarized in Table 2. For the benzylamines **10a** and **12**–**14**,



Scheme 4. Reagents and conditions: (a) ArCHO/MeOH/rt, 2 h, then $NaBH_4$; (b) aldehyde/$NaBH(OAc)_3$/DCE/rt, 16 h; (c) MeCOCl/TEA/DCM/rt, 2 h.

Table 1. SAR of secondary amines **9a–r** at MC4R

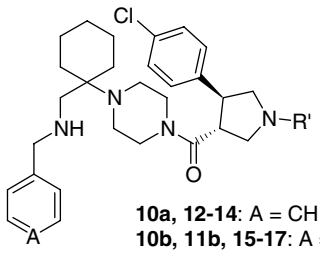


9a-r

Compound	R^1	K_i (nM)	EC_{50} (nM)[a]
6a	H	1200	
7a	$PhCH_2CO$	510	
8a	$PhCH_2SO_2$	340	(40%)
8b	$PhSO_2$	330	(20%)
9a	$MeOCH_2CH(Me)$	310	
9b	$CyclohexaneCH_2$	300	
9c	$PhCH_2$	26	1100 (31%)
9d	$2\text{-}FuranCH_2$	38	570 (32%)
9e	$3\text{-}FuranCH_2$	75	480 (53%)
9f	$2\text{-}ThiopheneCH_2$	37	590 (58%)
9g	$3\text{-}ThiopheneCH_2$	22	840 (31%)
9h	$2\text{-}ThiazoleCH_2$	130	740 (72%)
9i	$4\text{-}ImidazoleCH_2$	220	110 (49%)
9j	$2\text{-}ImidazoleCH_2$	560	230 (69%)
9k	$1\text{-}Me\text{-}2\text{-}imidazoleCH_2$	390	(31%)
9l	$1,5\text{-}(Me)_2\text{-}4\text{-}pyrazoleCH_2$	11	50 (43%)
9m	$5\text{-}PyrimidineCH_2$	220	220 (66%)
9n	$2\text{-}PyCH_2$	76	1200 (34%)
9o	$3\text{-}PyCH_2$	35	390 (72%)
9p	$4\text{-}PyCH_2$	27[b]	780 (27%)
9q	$1\text{-}Me\text{-}2\text{-}indoleCH_2$	1200	
9r	$2\text{-}PyCH_2CH_2$	690	

[a] Data are average of two or more independent measurements; intrinsic activity is indicated in parentheses.
[b] Compound **9p** dose-dependently inhibited α-MSH-stimulated cAMP release with an IC_{50} value of 410 nM.

Table 2. SAR of the *N*-group of pyrrolidines 10–17 at MC4R



10a, 12-14: A = CH
10b, 11b, 15-17: A = N

Compound	R′	K_i (nM)	EC_{50} (nM)
10a	$PhCH_2$	140	(1%)
9c	*i*-Pr	26	1100 (31%)
12a	$CH(Me)CH_2OMe$	100	(7%)
12b	Cyclopentyl	17	1800 (33%)
12c	Cyclohexyl	5.5[a]	1500 (16%)
12d	4-Tetrahydropyran	29	1000 (70%)
13a	MeCO	190	(13%)
13b	EtCO	210	(19%)
13c	*n*PrCO	190	(8%)
13d	*i*-PrCO	210	(47%)
13e	CyclopentaneCO	180	(26%)
14a	$MeNHCH_2CO$	100	(8%)
14b	$MeCH(NH_2)CO$	430	(3%)
14c	$NH_2CH_2CH_2CO$	110	(9%)
14d	$i\text{-}PrCH(NH_2)CO$	670	(0%)
10b	$PhCH_2$	200	
11b	H	2200	
15a	MeCO	3000	
15b	EtCO	3100	
16	EtNHCO	4600	
17	$MeSO_2$	3400	

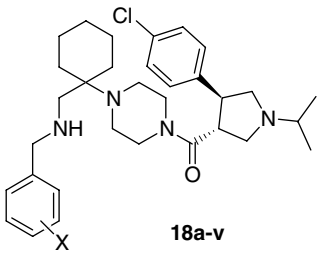
[a] Compound **12c** dose-dependently inhibited α-MSH-stimulated cAMP release with an IC_{50} value of 130 nM.

the *N*-benzyl intermediate **10a** (K_i = 140 nM) was 5-fold less potent in binding affinity than the *N*-isopropyl analog **9c**. Incorporating a methoxyl group into the isopropane in **9c** reduced its affinity by 4-fold (**12a**, K_i = 100 nM). While the cyclopentane **12b** was not much different from **9c**, the cyclohexane **12c** (K_i = 5.5 nM) was significantly more potent in binding affinity than **9c**. Functionally, **12c** behaved as an antagonist with an IC_{50} of 130 nM. The amides **13a–e** and **14a–d** had lower binding affinity than the isopropyl **9c**. Similarly, urea **16** and sulfonamide **17** exhibited poor binding affinity (Table 2). These results suggest that the basic nitrogen and a small lipophilic group such as isopropyl are important for high binding affinity of these compounds.

Because the benzyl side chain (**9c**) on the core structure **6a** provided great improvement in binding affinity, a more detailed survey was conducted using various benzaldehydes via reductive alkylations, and the results are depicted in Table 3. For the 2-substituted phenyl derivatives **18a–e**, the small fluorine (**18a**, K_i = 12 nM) slightly increased potency compared to the unsubstituted parent **9c**, while the affinity of the chloro-derivative **18b** remained unchanged. The other analogs (**18c–e**) displayed less potent affinity compared to **9c**, suggesting a bulky group is unfavored at this position. The electron-withdrawing fluorine (**18f**) and electron-donating methoxy group (**18g**) alone at the 3-position of the phenyl ring had no effect on the potency compared to **9c**, while substitution at the 4-position of **9c** altered the binding affinity (compounds **18h–q**). For example, the 4-methoxy compound **18j** (3.6 nM) displayed a K_i value 7-fold more potent than **9c**, while the 4-trifluoromethyl analog **18k** (130 nM) was 5-fold less potent. The 4-isopropoxy **18q** (K_i = 2.1 nM) was over 10-fold more potent than **9c**. These results indicate a hydrogen-bond donor at this position increases binding affinity. For the disubstituted phenyl derivatives **18r–v**, the 2-fluoro-4-methoxy **18t** (K_i = 1.8 nM) improved the affinity over 6-fold from the 2-fluoro **18a**, while the 3-fluoro-4-methoxy analog **18v** (K_i = 0.5 nM) exhibited the best binding affinity among these compounds.

Functionally, none of these substituted benzylamines **18a–v** tested in the agonist assay showed high potency or high efficacy. For example, compound **18a** exhibited an EC_{50} of 580 nM with an IA of 48%, indicative of a moderately active partial agonist. Compound **18v** had an IA value of only 10% and functioned as a potent antagonist with an IC_{50} value of 48 nM. The

Table 3. SAR of substituted benzylamines **18a–v** at MC4R

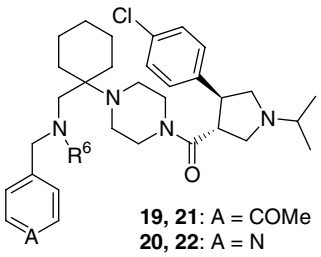


18a-v

Compound	X	K_i (nM)	EC_{50} (nM)[a]
9c	H	26	1100 (31%)
18a	2-F	12	580 (48%)
18b	2-Cl	25	1300 (75%)
18c	2-MeO	62	1000 (48%)
18d	2-CF_3	140	
18e	2-CF_3O	110	
18f	3-F	24	(23%)
18g	3-MeO	30	1200 (39%)
18h	4-F	44	6600 (61%)
18i	4-Cl	90	4200 (29%)
18j	4-MeO	3.6	(17%)
18k	4-CF_3	130	(16%)
18l	4-NO_2	52	
18m	4-AcNH	29	190 (27%)
18n	4-Me_2N	65	1100 (16%)
18o	4-COOMe	32	(21%)
18p	4-MeS	27	
18q	4-*i*-PrO	2.1	(6%)
18r	2,4-F	11	1300 (27%)
18s	2,4-MeO	16	(29%)
18t	2-F,4-MeO	1.8	1600 (26%)
18u	3,4-OCH_2O	8.3	(7%)
18v	3-F,4-MeO	0.5[b]	170 (10%)

[a] Data are average of two or more independent measurements; intrinsic activity is indicated in parentheses.
[b] Compound **18v** dose-dependently inhibited α-MSH-stimulated cAMP release with an IC_{50} value of 48 nM.

Table 4. SAR of tertiary amines **19–20** and amides **21–22** at MC4R



19, 21: A = COMe
20, 22: A = N

Compound	R^6	K_i (nM)
18j	H	3.6
19a	Me	110
19b	Et	190
19c	*i*-Bu	1800
19d	4-$MeOC_6H_4CH_2$	2800
21	MeCO	1300
9p	H	27
20a	Me	750
20b	Et	1300
20c	*i*-Bu	2700
22	MeCO	1500

discrepancy between the binding affinity and functional activity of **18v** is probably due to different assay conditions.

Compounds **18j** and **9p** were further derivatized to the tertiary amines **19** and **20**, respectively. A simple methylation of **18j** reduced its affinity by 30-fold (**19a**, K_i = 110 nM), while larger alkyl groups (**19b–d**) displayed further reduced affinity, suggesting the secondary amine is optimal. Acetylation of **18j** resulted in compound **21** (K_i = 1300 nM) with poor binding affinity, indicating the importance of the basic nitrogen of **18**. Similar results were also obtained for the pyridine analogs of **9p** (Table 4).

Compound **18v** was tested for affinity at the other melanocortin receptor subtypes and was found to be highly selective for MC4R. Thus, **18v** bound to the MC1R, MC3R, and MC5R with K_i values of 3,900, 760, and 540 nM, respectively, demonstrating 1000-fold selectivity at the melanocortin-4 receptor. Compound **18v** also bound to the mouse MC4R with a K_i of 0.6 nM, indicating no species difference for this compound.

Compared to the dipeptide **1a**, the pyrrolidine **1b** is a more compact molecule with fewer peptide features yet still possesses potent MC4R agonist activity. We have successfully converted the benzylamine antagonists such as **2** into potent MC4R agonists such as **3** by incorporating the *N*-alkylpyrrolidine moiety. Compound **4** is a functional agonist, but replacing its Tic-(4-Cl)Phe with 1-isopropyl-4-(chlorophenyl)pyrrolidine-3-carbonyl moiety results in a compound (**7a**) with low binding affinity. The basic amine on the left-side was required for the current series to have high binding affinity, contrary to the SAR in the β-Ala-(2,4-Cl)Phe dipeptides **5**. In addition, functional antagonists were identified. These results demonstrate that the current series of compounds has unique SAR. Previous studies indicated that the basic nitrogen of the Tic-group might interact with the Asp-126 residue of the human MC4 receptor,[14] which is believed to be important for receptor activation.[15] The requirement of the basic amine at the left-side of current compounds might suggest that it interacts with this residue, resulting in a binding mode that is different from other series such as **1b** and **3**.

In conclusion, a series of *trans*-*N*-alkyl-4-(4-chlorophenyl)pyrrolidine-3-carboxamides of piperazinecyclohexanemethylamines were synthesized and characterized at the melanocortin-4 receptor. While the *trans*-4-arylpyrrolidine-carbonyl group has been successfully used in other templates to replace the Tic-(4-Cl)Phe dipeptide for small molecule agonists such as **1b** and **3**, no potent agonists were discovered in this study. It was found that the basicity of the cyclohexanemethylamine was essential for potent binding affinity, and several potent benzylamine derivatives were identified with single digit K_i values. Compound **18v** was found to bind MC4R with potent affinity (K_i = 0.5 nM) and high selectivity

over the other melanocortin subtypes and behaved as a functional antagonist (IC_{50} = 48 nM).

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