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Design and synthesis of 3-arylpyrrolidine-2-carboxamide derivatives as melanocortin-4 receptor ligands

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Abstract—Based on 3-phenylpropionamides, a series of 3-arylpyrrolidine-2-carboxamide derivatives was designed and synthesized to study the effect of cyclizations as melanocortin-4 receptor ligands. It was found that the 2*R*,3*R*-pyrrolidine isomer possessed the most potent affinity among the four stereoisomers.

The melanocortin-4 receptor (MC4R) is a member of the G-protein-coupled receptor (GPCR) superfamily and plays an important role in regulating feeding behavior.[1] While MC4R agonists are pursued for reducing body weight,[2] MC4R antagonists have been shown to reverse both lean body mass loss and food intake reduction in animal models, suggesting their potential to be used for the treatment of cancer cachexia.[3,4] In addition, recent studies have shown that selective MC4R antagonists may also be useful in the treatment of anxiety and depression.[5]

We have previously identified a series of α-benzylpropionylpiperazines, such as **2a** (K_i = 26 nM, Fig. 1), as MC4R antagonists.[6] Compound **2a** is more potent than the 3-phenylpropionyl analog **1** (K_i = 74 nM)[7] but similar to the phenylalanine **2b**, suggesting a small role of the methyl group in **2a** or the amino moiety in **2b**. In contrast, the α,α-dimethyl analog **3** (K_i = 810 nM) displayed a much lower binding affinity than its monomethyl analog **2c** (K_i = 31 nM), indicating a strong steric effect caused by the additional α-methyl moiety on the 3-phenylpropionyl group. Therefore, we can conclude that the position and orientation of the substituted phenyl ring in a low-energy conformation is critical for high potency. When a nitrogen-containing moiety is used to replace the α-methyl group of **2a**, binding affinity is further improved.[8] For example, the acetamido **4** (K_i = 1.9 nM) is significantly more potent than **2a**. However, this improvement could result from the direct interaction of the acetyl group with the receptor. Since a small change in this region of the molecule has a large impact on its biological activity, we decided to synthesize constrained derivatives of **4** by cyclizing the acetamide moiety to lock the location of the important 4-chlorophenyl group as shown in Figure 2. Here we report the design, synthesis and structure–activity relationship study of these compounds.

2-Oxo-4-(4-chlorophenyl)methyloxazolidine-4-carboxylic acid **13** was synthesized using a procedure similar to that described by Qi et al. from 4-chlorophenylalanine **8**.[9] This was converted to the corresponding acid chloride **14**, which was coupled with the phenylpiperazine **15a**[10] to afford the desired product **6** after deprotection with HCl in methanol (Scheme 1).

Ethyl 5-oxo-3-(4-chlorophenyl)pyrrolidine-2-carboxylate **18** was synthesized using a procedure similar to that

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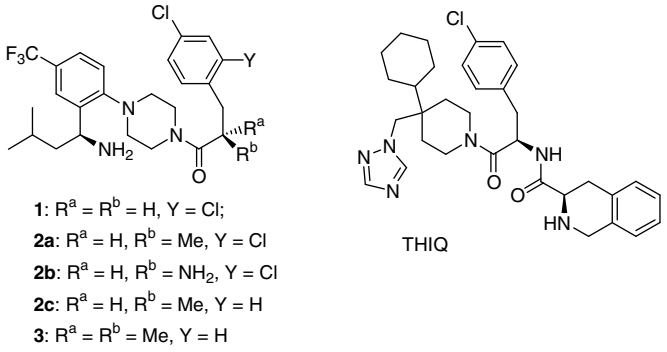


Figure 1. Chemical structures of previously reported MC4R antagonists **1**–**3** and agonist THIQ.

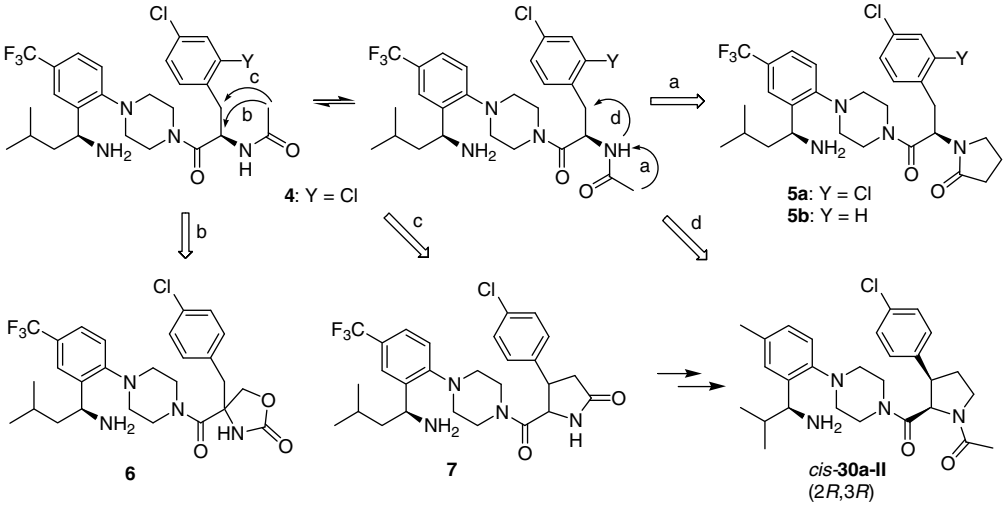
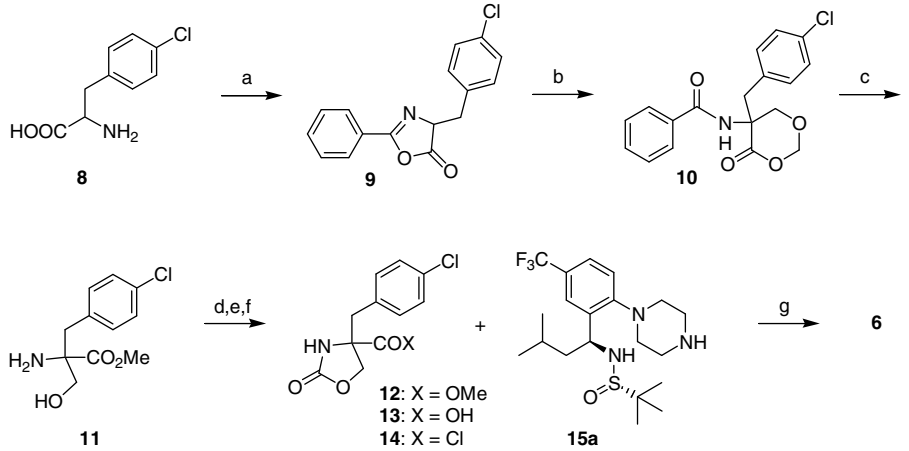


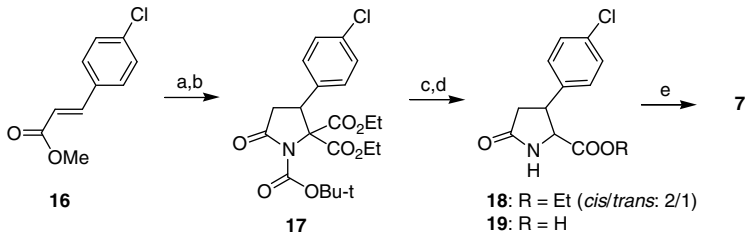
Figure 2. Strategy for constrained analogs of MC4R antagonists **4**.



Scheme 1. Reagents and conditions: (a) i—PhCOCl/NaOH/acetone/H_2O/rt, 2 h; ii—Ac_2O/80 °C, 20 min, 63%; (b) CH_2O/Py/H_2O/rt, 16 h, 63%; (c) i—5 N HCl/reflux, 3 h; ii—H_2SO_4/MeOH/rt, 8 h; (d) $COCl_2$/DMAP/DCM/0 °C to rt, 1.5 h, 60%, three steps; (e) LiOH/dioxane/65 °C, 8 h, 46%; (f) $(COCl)_2$/DMF(cat.)/DMC/rt, 1 h; (g) i—Et_3N/DCM/rt, 8 h; ii—HCl/MeOH/rt, 1 h, 4% for 3 steps.

described by Soloshonok.[11] This was then converted to compound **7** as shown in Scheme 2.

2*E*-3-Arylpropenals **20** were prepared from 4-iodobenzenes as described by Haemers et al.[12] Cyclization of **20** with acetamidomelonate gave the intermediate **21**, which was hydrolyzed, followed by decarboxylation and Boc-protection to afford 1-*tert*-butoxycarbony-3-(4-chlorophenyl)pyrrolidine-2-carboxylic acid **22** and **23a**.[13] Coupling reactions of **22** and **23a** with phenyl-



Scheme 2. Reagents and conditions: (a) $AcNHCH(COOEt)_2$/NaOEt/EtOH/reflux, 24 h, 53%; (b) $(Boc)_2O/Et_3N$/DMAP/THF/rt, 16 h, 91%; (c) NaCl/DMSO/150 °C, 40 h, ~100%; (d) NaOH/EtOH/H_2O/rt, 3 h, 78%; (e) i—**15a**/EDC/HOBt/DMF/DCM/rt, 16 h; ii—HCl/MeOH/rt, 1 h, 53%.

piperaines **15a–d** gave the desired products **24a–c** after a double deprotection with TFA followed by HCl in methanol (Scheme 3).

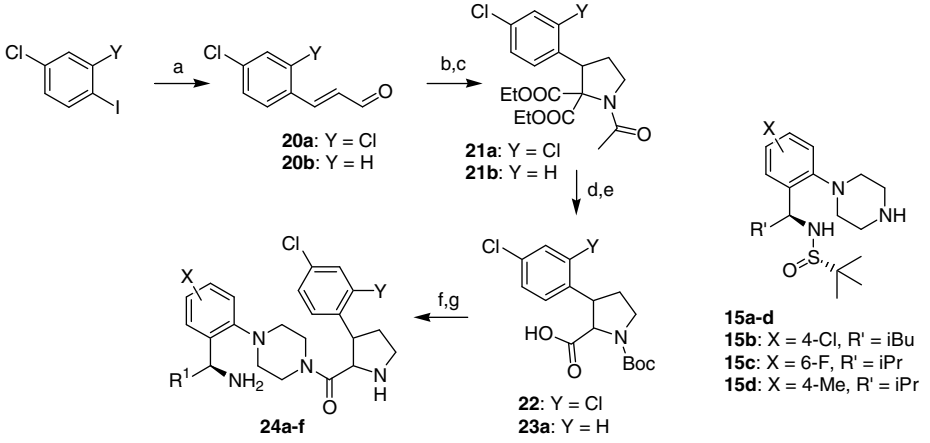
Alternatively, 1-acetylpyrrolidine-2-carboxylic acids **26a** were synthesized from **21b** using a procedure described in Scheme 4. When the ester **25**, as a mixture of about 1:1, was subjected to basic conditions in aqueous solution (1 N NaOH/EtOH/rt, 20 h), the *trans*-isomer (*trans*-**25**) was hydrolyzed much faster than the *cis*-isomer, resulting in a mixture of *cis*-ester (*cis*-**25**) and a *trans*-acid (*trans*-**26a**), which were easily separated by chromatography. Coupling reaction of the acid *trans*-**26a** with (*R*)-4-benzyl-2-oxazolidinone resulted in a pair of diastereoisomers, which were separated by chromatography to give the amides *trans*-**27**-I and *trans*-**27**-II. The crystal structure of *trans*-**27**-I was resolved (Fig. 3, left), and its stereochemistry was therefore established.

The ester *cis*-**25** was then subjected to an acidic hydrolysis (6 N HCl/AcOH/reflux, 8 h). Under these conditions, the acetyl group was also removed, therefore, treatment with acetic anhydride was required before purification which provided the desired acid *cis*-**26a**. Alternatively, treatment of the intermediate with $(Boc)_2O$ provided *cis*-**23a**. The single diastereoisomers *cis*-**26a-I** and *cis*-**26a-II** were obtained through the oxazolidinones *cis*-**27-I** and *cis*-**27-II**. The crystal structure of *cis*-**27-II** was also resolved to establish the stereochemistry (Fig. 3, right).[14]

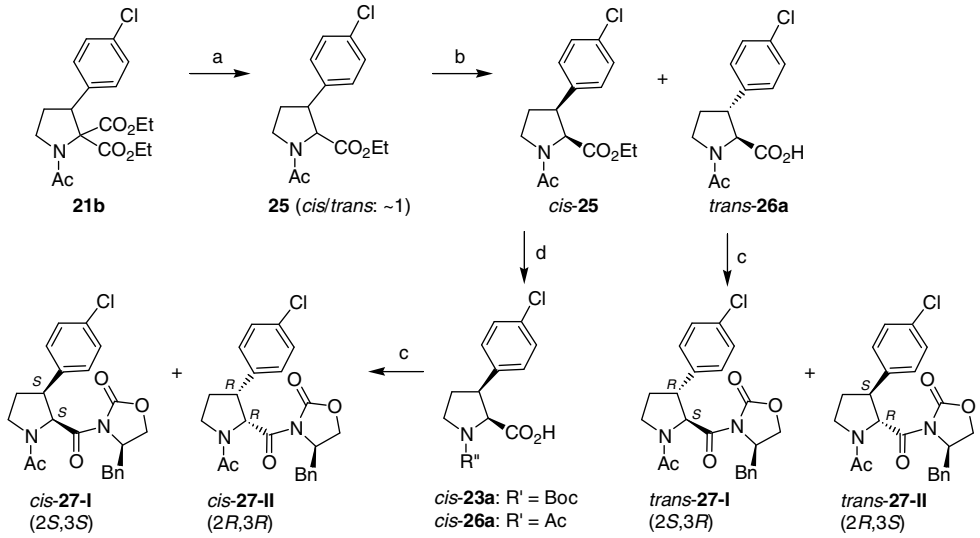
Coupling reactions of the acids *cis*-**23a** with phenylpiperazines **15d–g** provided the amides *cis*-**28** after TFA treatment. Deprotection of *cis*-**28a** with HCl/MeOH gave the diamine *cis*-**24f**. Reductive alkylations of *cis*-**28a** afforded the tertiary amines *cis*-**29** after HCl/MeOH treatment. Similarly, coupling reactions of *cis*-**28a** with several carboxylic acids gave the amides *cis*-**30a–d**; reactions of *cis*-**28a–d** with chloro alkylformates afforded the carbamates *cis*-**31a–f**. The urea *cis*-**32** was obtained from *cis*-**28a** and ethyl isocyanate, and the sulfonamide *cis*-**33** was obtained from methanesulfonyl chloride (Scheme 5).

Compounds *trans*-**30** and *trans*-**31** were synthesized from *trans*-**26a** using a procedure similar to that for the corresponding *cis*-isomers.

Compounds *cis*-**34–38** with various 4-substituted phenyl group were synthesized as described in Scheme 6. Cyclization of the di-ester **40** under basic conditions gave 3-oxo-1,2-pyrrolidinedicarboxylic acid 1-(*tert*-butyl)-2-ethyl ester **41**,[15] which was converted to the corresponding triflate **42** in a moderate yield. Coupling reactions of **42** with various 4-substituted phenylboronic acids provided the unsaturated intermediates **43a–f**,[16] which



Scheme 3. Reagents and conditions: (a) CH_2 = $CHCH(OEt)_2/Pd(OAc)_2/nBu_4NOAc/K_2CO_3$/KCl/rt, 87% for **20a** (Y = Cl); (b) $AcNHCH(COOEt)_2$/Na/EtOH/rt, 8 h, 70% from **20a**; (c) Et_3SiH/TFA/$CHCl_3$/rt, 4 h, 90% for **21a**; (d) i—NaOH/H_2O/rt, 20 h; ii—toluene/75 °C, 1 h; (e) $(Boc)_2O$/$NaHCO_3$/THF/H_2O, rt, 16 h; (f) **15a–d**/EDC/HOBt/Et_3N/DCM/rt, 18 h; (g) i—TFA/DCM/rt, 1 h; ii—HCl/MeOH/rt, 1 h.



Scheme 4. Reagents and conditions: (a) i—NaOH/H_2O/rt, 20 h; ii—toluene/75 °C, 1 h, 97%; (b) i—NaOEt/EtOH/rt, 8 h; ii—1 N NaOH/EtOH/rt, 20 h, then separation, 41% for *cis*-**25** and 38% for *trans*-**26a**; (c) i—Me_3CCOCl/Et_3N/THF/−20 °C, 20 h; ii—(*R*)-4-benzyl-2-oxazolidinone/LiCl/THF/rt, 8 h, iii—chromatography separation, 20–30%; (d) i—6 N HCl/AcOH/reflux, 8 h; ii—Ac_2O/Et_3N/DCM/rt, 4 h; or $(Boc)_2O/NaHCO_3$/THF/H_2O, rt, 16 h, ~100%.

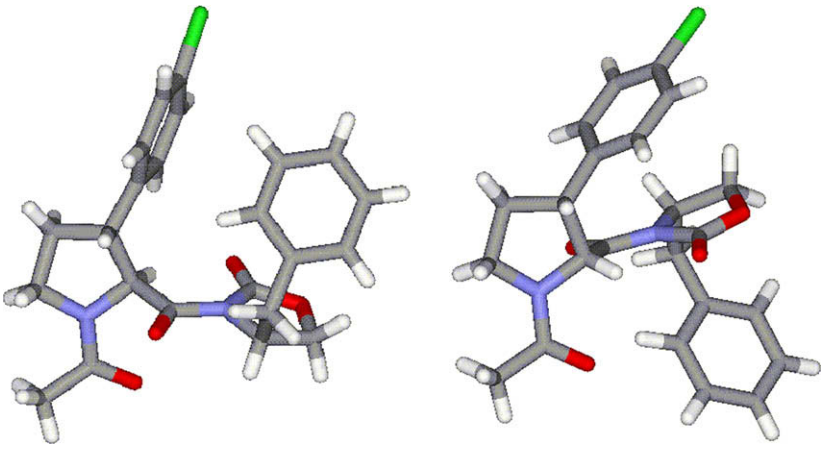


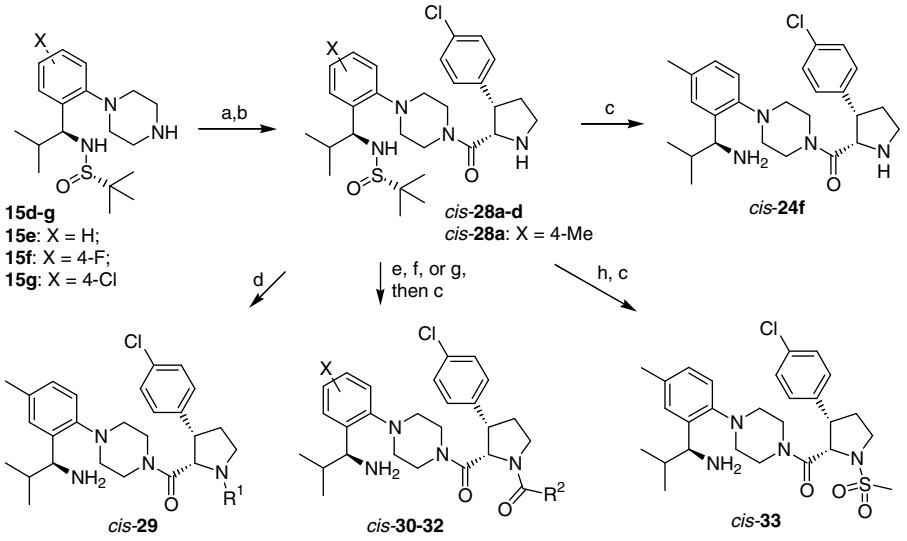
Figure 3. X-ray crystal structures of (*R*)-3-[(2*S*,3*R*)-1-acetyl-3-(4-chlorophenyl)-pyrrolidine-2-carbonyl]-4-benzyl-oxazolidin-2-one (*trans*-**27-I**, left) and (*R*)-3-[(2*R*,3*R*)-1-acetyl-3-(4-chlorophenyl)-pyrrolidine-2-carbonyl]-4-benzyl-oxazolidin-2-one (*cis*-**27-II**, right).

were hydrogenated to give the pyrrolidines *cis*-**44**.[17] Hydrolysis of *cis*-**44** using LiOH gave the corresponding acids *cis*-**23**, which were deprotected, followed by acetylation to afford *cis*-**26**. Coupling reactions of *cis*-**26** with the phenylpiperazine **15d** provided the *cis*-**34**–**38** after deprotection.

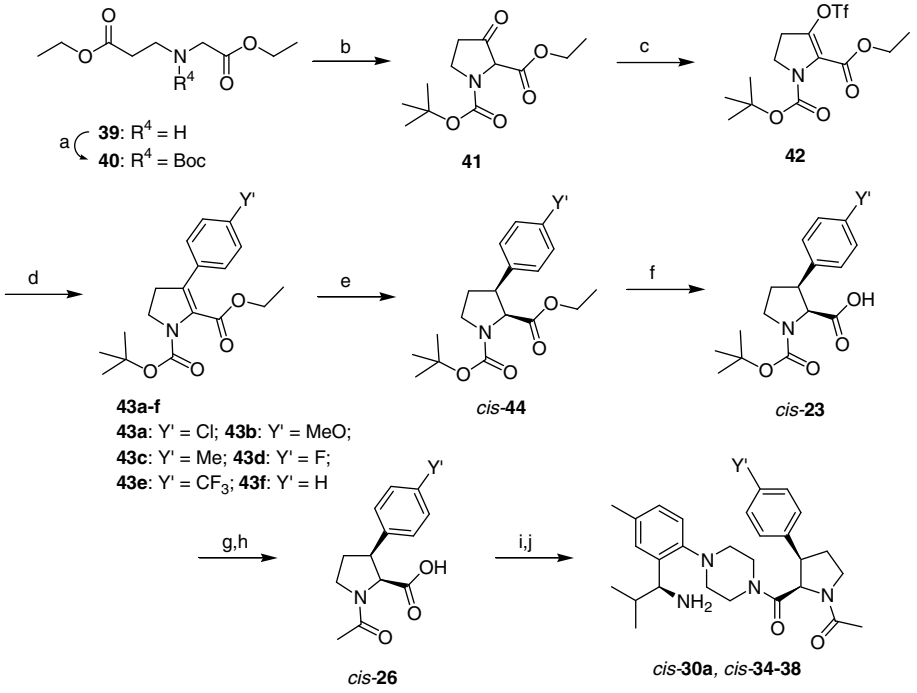
These compounds were then tested for their binding affinity at the human MC4 receptor stably expressed in HEK293 cells using [^{125}I]-NDP-MSH as previously reported.[18]

While the acetamido **4** (K_i = 1.9 nM) was about 40-fold more potent than the early lead compound **1** (K_i = 74 nM), the cyclic pyrrolidinone **5a** (K_i = 4.5 nM)[8] was only slightly less active than **4**, demonstrating the amide proton is not critical for ligand-receptor interaction. The pyrrolidinone **5b** with a 4-chlorophenylpropionyl group displayed a K_i of 11 nM, indicative of a minor role of the 2-chloro group of **5a**. The oxazolinone **6** as a 1:1 mixture of two diastereoisomers, which contains a CONH functionality, only exhibited weak binding affinity (K_i = 550 nM) which is quite similar to the α,α-dimethyl compound **3** (K_i = 810 nM). These results strongly suggest that the substituent at the α-position of the phenylpropionyl group of these compounds contributes to the structural conformation instead of direct interactions with the receptor.

The 3-phenyl-5-oxopyrrolidine-2-carboxamide **7**, which also contains the CONH moiety, displayed only moderate binding affinity (K_i = 340 nM) as a mixture of *cis*- and *trans*-isomers (~2:1). Removing the 5-oxo moiety of **7** resulted in a derivative with improved potency (**24a**, K_i = 98 nM). This structural change might slightly alter the conformation of the five-membered ring. As a



Scheme 5. Reagents and conditions: (a) *cis*-**23a**/EDC/HOBt/Et_3N/DMF/rt, 16 h; (b) TFA/DCM/rt, 1 h; (c) HCl/MeOH/rt, 1 h; (d) aldehyde/$NaBH(OAc)_3$/DCM/rt, 8 h; (e) R^2COOH/EDC/DCM/rt, 16 h; (TFA treatment for *cis*-**30c**); (f) ROCOCl/Et_3N/DCM/rt, 2 h; (g) EtNCO/DCM/rt, 0.5 h; (h) $MeSO_2Cl/Et_3N$/DCM/rt, 0.5 h.

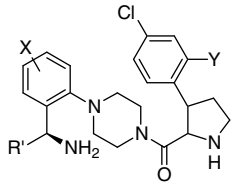


Scheme 6. Reagents and conditions: (a) $(Boc)_2O/NaOH/H_2O$/DCM/rt, 100%; (b) tBuOK/toluene/0 °C, 2 h, 45%; (c) KHMDS/THF/−78 °C, 0.5 h, then $(Tf)_2O$/rt, 2 h, 52%; (d) 4-Y′$C_6H_4B(OH)_2/PdCl_2$(dppf)/K_2CO_3/toluene/MeOH/reflux, 17 h, ~80%; (e) $NiCl_2/NaBH_4$/MeOH/0 °C, 1 h, 80% for **43a** (Y′ = Cl); or H_2 (1 atm)/PtO_2/EtOH/rt, 6 h; (f) LiOH/THF/H_2O/reflux, 20 h, ~85%; (g) TFA/DCM/rt, 1 h; (h) Ac_2O/Et_3N/DCM/0 °C, 1 h, ~70% for two steps; (i) **15 d**/HBTU/DIEA/DCM/rt, 8 h; (j) HCl/Et_2O/MeOH/rt, 1 h.

mixture of *cis*-/*trans*-isomers (~2:1), **24a** was only moderately less potent than the *R*-configured amine **2b** (K_i = 39 nM), indicating that using cyclization to provide a much more constrained molecule is worth for further exploration.

A quick survey on the left-side phenyl ring showed that the chloro analog **24b** had similar affinity to **24a** (Table 1), while the α-isopropylbenzylamine derivatives **24d** and **24f** possessed similar or better potency compared to the α-isobutyl **24a** and **24b**. Interestingly, the 2,4-dichlorophenyl **24c** as a 1:1 *cis*/*trans* mixture was less potent than the monochloro **24b**, implying that the *ortho*-chlorine at the phenyl group of **24c** hinders the rotation of this aromatic ring from adopting an optimal orientation for receptor interactions. Similar results were also obtained from **24d**/**24e**. Finally, for these diamines, the *cis*-isomer (*cis*-**24f**, K_i = 52 nM) displayed

Table 1. Summary of SAR of oxazolinone **6**, pyrrolidinone **7** and pyrrolidines **24a–f** at MC4R[a]

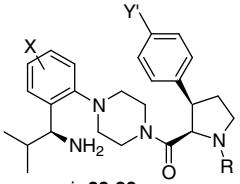


24a-f

Compound	X	R′	Y	K_i (nM)
6				550
7[b]				340
24a[c]	4-CF_3	*i*-Bu	H	98
24b[c]	4-Cl	*i*-Bu	H	96
24c[c]	4-Cl	*i*-Bu	Cl	190
24d[c]	6-F	*i*-Pr	H	110
24e[c]	6-F	*i*-Pr	Cl	560
24f[c]	4-Me	*i*-Pr	H	56
cis-**24f**	4-Me	*i*-Pr	H	52

[a] Data are average of two or more independent measurements.
[b] Ratio of *cis*-/*trans*-isomers was about 2:1.
[c] Ratio of *cis*-/*trans*-isomers was about 1.

Table 2. SAR of *cis*-pyrrolidines *cis*-**29–38** at MC4R[a]

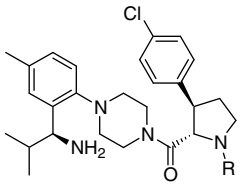


cis-**29-38**

Compound	X	Y′	R	K_i (nM)
cis-**29a**	4-Me	Cl	Me	160
cis-**29b**	4-Me	Cl	iPr	110
cis-**30a**	4-Me	Cl	Ac	24
cis-**30a-I** (2*S*,3*S*)				120
cis-**30a-II** (2*R*,3*R*)				11
cis-**30b**	4-Me	Cl	tBuCO	7.2
cis-**30c**	4-Me	Cl	Tic[b]	1.1[c]
cis-**31a**	4-Me	Cl	MeOCO	17
cis-**31a-I** (2*S*,3*S*)				53
cis-**31a-II** (2*R*,3*R*)				18
cis-**31b**	4-Me	Cl	EtOCO	16
cis-**31b-I** (2*S*,3*S*)				130
cis-**31b-II** (2*R*,3*R*)				11
cis-**31c**	4-Me	Cl	iPrOCO	12
cis-**31d**	H	Cl	EtOCO	94
cis-**31e**	4-F	Cl	EtOCO	74
cis-**31f**	4-Cl	Cl	EtOCO	18
cis-**32**	4-Me	Cl	Me_2NCO	7.4
cis-**32-I** (2*S*,3*S*)				190
cis-**32-II** (2*R*,3*R*)				6.5
cis-**33**	4-Me	Cl	$MeSO_2$	40
cis-**34**	4-Me	MeO	Ac	45
cis-**35**	4-Me	Me	Ac	97
cis-**36**	4-Me	F	Ac	330
cis-**37**	4-Me	CF_3	Ac	54
cis-**38**	4-Me	H	Ac	1800

[a] Data are average of two or more independent measurements.
[b] Tic: tetrahydroisoquinoline-3*R*-carbonyl.
[c] Functional partial agonist with an EC_{50} of 3.5 μM and E_{max} of 44%.

Table 3. Binding affinity of *trans*-pyrrolidines *trans*-**30–31** at MC4R[a]



trans-**30-31**

Compound	R	K_i (nM)
trans-**30a-I** (2*S*,3*R*)	Ac	78
trans-**30a-II** (2*R*,3*S*)	Ac	180
trans-**30b**	*t*-BuCO	79
trans-**30c**	Tic[b]	92[c]
trans-**30d**	EtCO	62
trans-**30e**	*n*-PrCO	52
trans-**30f**	*c*-BuCO	55
trans-**31a**	MeOCO	59
trans-**31b**	EtOCO	42
trans-**31c**	*i*-PrOCO	68

[a] Data are average of two or more independent measurements.
[b] Tic: 3*R*-tetrahydroisoquinolinyl-3*R*-carbonyl.
[c] Very weak functional agonist with an EC_{50} of 15 μM and E_{max} of 21%.

similar binding affinity to the mixture (**24f**, K_i = 56 nM), suggesting that the *cis*-isomer might be a preferred stereoisomer.

To examine the effect of a substituent at the pyrrolidine nitrogen, compounds **29–32** were studied for their binding affinity at MC4R (Tables 2 and 3). For *cis*-isomers, the tertiary amines *cis*-**29a–b** were slightly less potent than the secondary amine *cis*-**24f**. Acylation of *cis*-**24f** resulted in about 2-fold improvement (*cis*-**30a**, K_i = 24 nM). Between the two individual diastereoisomers of *cis*-**30a**, the 2*R*-configured *cis*-**30a-II** (K_i = 11 nM) was much more potent than the 2*S*-configured *cis*-**30a-I** (K_i = 120 nM), demonstrating the 2*R*-stereo is preferred. These results match the stereo preference for acyclic analogs such as **4**. The bulky isobutylcarbonyl compound *cis*-**30b** (K_i = 7.2 nM) showed similar binding affinity to the acetyl analog *cis*-**30a**, indicating an open space in this area. This is further confirmed by the Tic (tetrahydroisoquinoline-3*R*-carbonyl) compound *cis*-**30c**, which displayed a K_i value of 1.1 nM. While combining with 4-chlorophenylalanine, the Tic group has been used for many potent MC4R agonists such as THIQ (Fig. 1). However, *cis*-**30c** only exhibited weak agonist activity in a cAMP assay (EC_{50} = 3500 nM, E_{max} = 44%), suggesting the Tic group in this compound might not be at a preferred position for receptor activation.

Several carbamates *cis*-**31a–f** were also studied. The three close derivatives *cis*-**30a–c** were essentially equipotent, and for both *cis*-**31a** and *cis*-**31b**, the 2*R*-stereoisomers (*cis*-**31a-II** and *cis*-**31b-II**) possessed higher binding affinity than their 2*S*-counterparts (*cis*-**31a-I** and *cis*-**31b-I**). The urea *cis*-**32** had a K_i of 7.4 nM, which was substantially higher than the methylsulfonamide *cis*-**33** (K_i = 40 nM).

The effect of a substituent at the left-side phenyl group was examined using compounds *cis*-**31b** and *cis*-**31d–f**. The 4-fluoro compound *cis*-**31e** had a binding affinity similar to the phenyl analog *cis*-**30d**, while the more lipophilic chloro compound *cis*-**31f** increased affinity by 5-fold. For the substituent at the right-side phenyl group, the 4-chloro-compound *cis*-**30a** showed higher binding affinity than other compounds examined (*cis*-**34–38**). The 4-methoxy *cis*-**34** (K_i = 45 nM) displayed 40-fold improvement from the unsubstituted *cis*-**38** (K_i = 1800 nM). These data agree with our early findings from an acyclic series at this site,[19] indicating the significant contribution of the 4-chlorophenyl group to receptor-binding.

The *trans*-pyrrolidine derivatives *trans*-**30–31** were also studied in the binding assay, and the results are summarized in Table 3. Unlike their *cis*-isomers, these compounds showed flat SAR. For example, the 2*S*-configured *trans*-**30a-I** (K_i = 78 nM) was only slightly more potent than the 2*R*-isomer *trans*-**30a-II** (K_i = 180 nM), and both were less potent than the *cis*-**30a**. The Tic-analog *trans*-**30c** had a K_i of 92 nM, which was almost 90-fold less potent than *cis*-**30c**. These results indicate that the acyl group of *trans*-pyrrolidines is not at a place to interact with the receptor. In contrast, for a series of 4-arylpyrrolidine-3-carboxamide derivatives as MC4R agonists,[20] the *trans*-isomers have higher binding affinity than the *cis*-analogs. The 'Y' shape conformation for the MC4R agonist Tic-D(4-Cl)Phe piperazine THIQ has been observed in a solid structure[21] in which the 4-chlorophenyl group is almost parallel to the piperidine ring. Recently, we have also shown that a close analog of **2c** displays a similar relationship in a crystal structure.[22] The MC4R agonists and antagonists might have a similar conformation in binding to the receptor,[23,24] but the Tic or its replacement is required for receptor activation. Apparently in the current pyrrolidine series, the Tic group was not in the right position.

Selected compounds were further tested for their functional activity at MC4R and found to be antagonists (Table 4). None of the compounds listed in Table 4 exhibited significant stimulation of cAMP release at a 10 μM concentration (IA < 10%, data not shown) in cells expressing the MC4 receptor, demonstrating the lack of functional agonist activity of these compounds.

Table 4. Functional activity of pyrrolidines[a]

Compound	K_i (nM)	IC_{50} (nM)
cis-**24a**	98	2400
cis-**24c**	190	1500
cis-**24d**	110	960
cis-**24f**	56	310
cis-**30a-II**	11	520
cis-**31a**	17	720
cis-**31b**	16	640
cis-**32a**	7.4	190
cis-**32a-II**	6.5	93

[a] Dose-dependent inhibition of α-MSH-stimulated cAMP production. Data are average of two independent measurements.

Instead, all compounds showed dose-dependent inhibition of α-MSH-stimulated cAMP production. For example, *cis*-**30a-II** and *cis*-**32a-II** had IC_{50} values of 520 and 93 nM, respectively, in this functional assay.

Compound *cis*-**32a-II** was profiled for its pharmacokinetic properties in rats. After an intravenous injection at a 5 mg/kg dose, *cis*-**32a-II** exhibited a moderate plasma clearance of 20 ml/min kg and a high volume of distribution (V_d = 17.2 L/kg), resulting in a half-life of 4.3 h. After an oral dose of 10 mg/kg, *cis*-**32a-II** reached a maximal concentration of 35 ng/ml to give an area under the curve of 533 ng/ml h, resulting in an absolute bioavailability of 7.2%. The whole brain concentration reflected by area under the curve was 80% of the plasma.

In conclusion, a series of 3-phenylpyrrolidine-2-carboxamide derivatives were designed and synthesized to compare with their acyclic analogs as MC4R ligands. Optimization led to several potent compounds. It was determined that the *2R,3R*-pyrrolidine was the preferred stereoisomer for receptor-binding. These results provide further insights into the structure–activity relationship of the 3-phenylpropionyl derivatives and related compounds as MC4R ligands.

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