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Propionylpiperazines as human melanocortin-4 receptor ligands

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Abstract—A series of α-benzylpropionylpiperazines were synthesized and tested as antagonists of the melanocortin-4 receptor. In addition to its high potency and selectivity, *R*-**11a** had desirable pharmacokinetic properties including high brain penetration in mice.

We have previously identified a series of arylpropionylpiperazines such as **1b** as melanocortin-4 receptor (MC4R) antagonists from an initial lead **1a**. It has been found that introducing an amino acid group increases binding affinity.[1] Thus, the glycine derivative **2** has a K_i value 19 nM, which is about 4-fold better than **1b**. To further improve potency of this novel series, we have conducted an extensive survey on the 'right-hand' amide. Here, we report the discovery of potent and orally bioavailable MC4R antagonists (Fig. 1).

Compounds **4**–**14** were prepared from reactions of the key intermediate **3**[2] with various carboxylic acids under coupling conditions, or acid chlorides. α-Benzylpropionic acids for **8**–**12** were synthesized from the benzylation of methylmalonate, followed by hydrolysis and decarboxylation.[3] Chiral α-benzylpropionic acids were synthesized from alkylation of propionyl oxazolone as an Evan's chiral auxiliary.[4] Finally, 1,1-dimethyl-3-(4-chlorophenyl)propionic acid for **14** was synthesized from benzylation of the corresponding isobutyric acid.[5] These compounds were then tested for their binding affinity at the human MC4 receptor using [^{125}I]NDP-MSH as previously reported[6] (Fig. 2).

In comparison with 3-(2,4-dichlorophenyl)propionylpiperazine **1b** (K_i = 74 nM), the 2,4-dichlorophenylacetyl analog **4a** (K_i = 2.8 μM) was much less potent (Table 1). Other 4-chlorophenyl and cyclohexyl analogs (**4b**–**e**) were only weakly active. The 2,4-dichlorophenoxyacetamide **5a** had a K_i of 4.2 μM, which was much less potent than its carbon derivative **1b**. A broad survey of substituted phenoxy analogs only resulted in weakly potent compounds (**5b**–**n**) regardless of the substitution on the phenyl ring. Similarly, the 2,4-dichlorophenylthioacetamide **6a** (K_i = 1.5 μM) was weakly potent. Other amine-containing compounds (**7a**–**e**) displayed poor binding affinity. These results suggest that the 2,4-dichlorophenyl group of compounds **4a**, **5a** or **6a** is not able to mimic that of **1b**, possibly due to its unfavored conformation caused by the different connection (Table 1).

We then introduced a methyl group at the α-position of the phenylpropionyl group of **1** to reduce the flexibility of this side chain. Thus, the *R*-configured methyl analog of **1b** was found to have potency about 3-fold better than its parent (*R*-**8p**, K_i = 26 nM), while the *S*-antipode *S*-**8p** was approximately 2-fold less active than **1b**. It was also found by surveying the substitution at the phenyl ring of the racemic α-benzylpropionyl group that the

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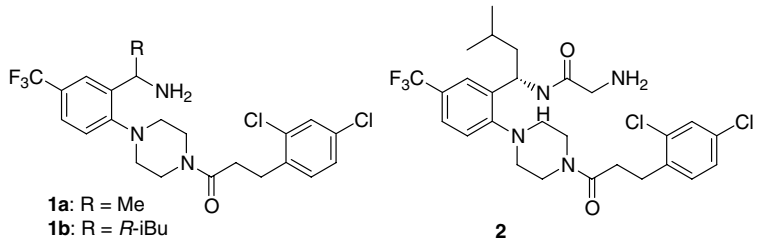


Figure 1. Phenylpropionylpiperazine MC4R antagonists.

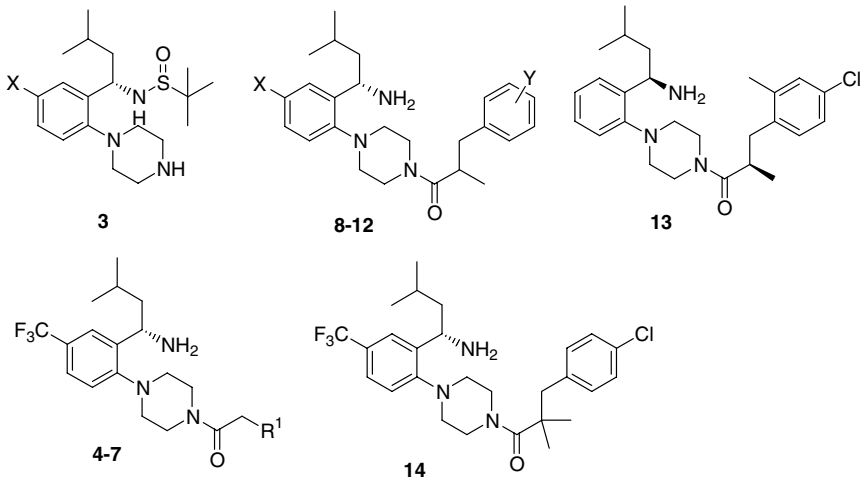


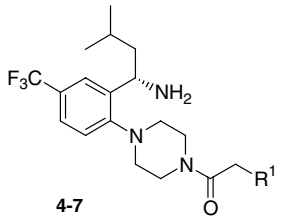
Figure 2. Compounds synthesized for this study.

4-chloro (**8a**) and the 2,4-dichloro compound **8p** (by comparing the *R*-isomers) possessed similar binding affinity, while the 4-methoxy analog (**8b**) was less potent. The 3-substitution was detrimental for potency, thus, compounds **8c–j** were low to moderately active. For the 2,4-di-substitution (**8k–o**), 2-methoxy-4-chlorophenyl gave a compound with the best binding affinity (**8o**, $K_i = 14$ nM). The *R*-isomer of **8o** (*R*-**8o**, $K_i = 6.5$ nM) was about 5-fold better than its *S*-isomer, which agreed with the results from compounds *R*-**8p** and *S*-**8p** (Table 2).

For substitution at the 'left-hand' phenyl ring, a chloro-group almost matched with the trifluoromethyl moiety for binding affinity (**9a–c**), while a less lipophilic fluorine decreased potency (**10a**, $K_i = 390$ nM). The *R*-configured 4-methyl analogs (*R*-**11a–d**) were comparatively active to **9**, while the unsubstituted compounds (*R*-**12a–d**) displayed about 2- to 3-fold reduction in binding affinity, suggesting the 4-trifluoromethyl group from the initial lead was not critical for potency, although its strong electron-withdrawing property might reduce the potential metabolic oxidation of the electron-rich aniline group.[7] Finally, the *R*-benzylamine **13** ($K_i = 1.7$ μM) exhibited much lower binding affinity than its *S*-isomer (*R*-**12d**, $K_i = 12$ nM), demonstrating stereo-preference of this α-alkyl benzylamine group (Table 2).

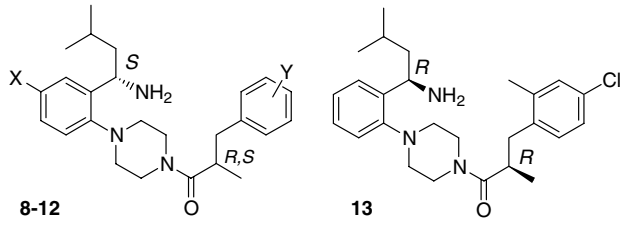
Interestingly, the α,α-dimethyl phenylpropionyl compound **14** exhibited a K_i of 810 nM, which was over 10-fold less potent than **1b**. All these results seem to suggest that the *R*-methyl group of **8–12** locks the phenyl ring at the propionyl group into a favored conformation

Table 1. SAR of substituted acetamides at the human MC4R



Compound	R^1	K_i (nM)
4a	2,4-ClPh	2800
4b	4-ClPhCOCH$_2$	820
4c	4-ClPhCOCH(Me)	1100
4d	*c*-HexCH$_2$	5700
4e	*c*-HexCH$_2$CH$_2$	4100
5a	2,4-ClPhO	4200
5b	PhO	>10,000
5c	4-ClPhO	2900
5d	4-MePhO	4400
5e	4-MeOPhO	3800
5f	4-HOPhO	4600
5g	4-NO$_2$PhO	3100
5h	3-ClPhO	2600
5i	2-ClPhO	4500
5j	2,4-MePhO	4000
5k	3,4-ClPhO	2500
5l	2,3-ClPhO	2500
5m	1-Naphthyl-O	2600
5n	2-Naphthyl-O	2000
6a	2,4-ClPhS	1500
7a	PhNH	3600
7b	1-Benzimidazolyl	2100
7c	*c*-HexNHCH$_2$	4800
7d	NH$_2$COCH$_2$	>10,000
7e	Me$_2$NCOCH$_2$	>10,000

Table 2. SAR of 2-methyl-3-arylpropionyl amides at human MC4R



Compound	X	Y	K_i (nM)
8a	CF_3	4-Cl	47
R-**8a**	CF_3	4-Cl	31
8b	CF_3	4-MeO	120
8c	CF_3	3-Cl	920
8d	CF_3	3-MeO	3100
8e	CF_3	3-EtO	2200
8f	CF_3	3-Me,4-Cl	71
8g	CF_3	3,4-Me	240
8h	CF_3	3-F,4-MeO	200
8i	CF_3	3-MeO,4-Cl	230
8j	CF_3	3,4-Cl	120
8k	CF_3	2,4-Me	92
8l	CF_3	2-F,4-Cl	60
8m	CF_3	2-Me,4-Cl	38
8n	CF_3	2-HO,4-Cl	36
8o	CF_3	2-MeO,4-Cl	14
R-**8o**	CF_3	2-MeO,4-Cl	6.5
S-**8o**	CF_3	2-MeO,4-Cl	31
R-**8p**	CF_3	2,4-Cl	26
S-**8p**	CF_3	2,4-Cl	140
8r	CF_3	2-MeO,2,4-Cl	230
8q	CF_3	3,4-Cl	1600
9a	Cl	4-Cl	67
9b	Cl	4-MeO	160
9c	Cl	2-MeO,4-Cl	9.1
10a	F	4-Cl	390
R-**11a**	Me	4-Cl	25
R-**11b**	Me	2-Me,4-Cl	5.9
R-**11c**	Me	2-F,4-Cl	20
R-**11d**	Me	2-MeO,4-Cl	8.1
R-**11e**	Me	2,4-Cl	8.8
R-**12a**	H	4-Cl	80
R-**12b**	H	2-F,4-Cl	67
R-**12c**	H	2,4-Cl	16
R-**12d**	H	2-Me,4-Cl	12
13			1700

for its interaction with the receptor.[8,9] The 'Y' shape conformation for the Tic-D(4-Cl)Phe piperazine of the THIQ MC4R agonist has been demonstrated by its X-ray structure.[10]

Selected compounds were further tested for their selectivity over the other melanocortin receptor subtypes. Thus, **8o** displayed low affinity at the MC1 and MC3 receptors, while it still had moderate binding affinity at the MC5 receptor (K_i = 80 nM, Table 3). In contrast, *R*-**11a** exhibited high selectivity. None of the compounds exhibited significant stimulation of cAMP release in cells expressing the MC4 receptor, demonstrating that they were not functional agonists. Instead, **8o** and *R*-**11a** showed dose-dependent inhibition of α-MSH-stimulated cAMP production with IC_{50} values of 1.7 and 0.56 μM, respectively.

Table 3. Selectivity profiles of **8o** and *R*-**11a**[a]

Compound	K_i (nM)			
	MC1R	MC3R	MC4R	MC5R
8o	(23%)	320	14	86
R-**11a**	3100	1300	25	1000

[a] Binding affinity at the human melanocortin receptors stably expressed in HEK 283 cells using [^{125}I]NDP-MSH as radiolabeled ligand.

Table 4. Pharmacokinetic parameters of compounds **8o** and *R*-**11a** in mice[a]

Compound	**8o**	*R*-**11a**
iv dose (mg/kg)	5	5
CL (mL/min kg)	62.3	33.3
V_d (L/kg)	10.3	10.2
$t_{1/2}$ (h)	1.9	3.5
AUC (ng/mL h)	1452	2558
C_{brain} (ng/g)@1, 4 h	735, 122	940, 330
C_{brain}/C_{plasma}	2.3, 1.9	2.9, 1.4
po dose (mg/kg)	10	10
C_{max} (ng/mL)	99	267
T_{max} (h)	0.25	0.5
AUC (ng/mL h)	249	1762
F (%)	8.6	34.4

[a] Average of three animals.

Due to the desirable in vitro properties, **8o** and *R*-**11a** were profiled for their pharmacokinetic properties in mice. After an intravenous injection at 5 mg/kg, **8o** exhibited a plasma clearance (CL) of 62.3 mL/min kg, and volume of distribution (V_d) of 10.3 L/kg, resulting in a half-life ($t_{1/2}$) of 1.9 h in this species. At 1 and 4 h postdosing, the whole brain concentrations were 735 and 122 ng/g, which gave brain/plasma ratio of 2.3 and 1.9, respectively. After an oral dose of 10 mg/kg, **8o** reached a maximal concentration of 99 ng/mL at 0.25 h, suggesting a very fast absorption. Its area under curve (AUC) was 249 ng/mL h, which resulted in an absolute bioavailability of 8.6%. The low bioavailability could be caused by its high clearance associated with its high lipophilicity (measured log D was > 4).[11,12] In comparison, the less lipophilic *R*-**11a** (measured log D of 3) had a CL value of 33.3 mL/min kg, a V_d of 10.2 L/kg, and a $t_{1/2}$ of 3.5 h. In addition to its high brain penetration (b/p ratio was 2.9 and 1.4 at 1 and 4 h postdosing, respectively), *R*-**11a** had an oral bioavailability of 34.4% (Table 4).

In conclusion, a series of α-benzylpropionylpiperazines were synthesized and tested as antagonists of the melanocortin-4 receptor. Potent and selective derivatives were discovered from this series. In addition, *R*-**11a** had good pharmacokinetic profile, including high brain penetration.

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