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Melanocortin subtype-4 receptor agonists containing a piperazine core with substituted aryl sulfonamides

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Abstract—The biological activity for a set of melanocortin-4 receptor (MC4R) agonists containing a piperazine core with an *ortho*-substituted aryl sulfonamide is described. Compounds from this set had binding and functional activities at MC4R less than 30 nM. The most selective compound in this series was >25,000-fold more potent at MC4R than MC3R, and 490-fold more potent at MC4R than MC5R. This compound also reduced food intake after oral dosing at 25, 50, and 100 mg kg^{-1} in fasted mice.

The melanocortin-4 receptor (MC4R) is a G-protein coupled receptor expressed in the hypothalamus, which has been shown to regulate feeding behavior.[1,2] Agonists to the receptor have been shown to decrease feeding in rodents.[3] Conversely, feeding increased when rodents were treated with MC4R antagonists.[4,5] In addition, mice lacking the gene encoding MC4R are obese and hyperphagic.[2] In humans, MC4R polymorphisms that impair receptor function have been linked to obesity.[6] More recently, experiments have been conducted that link MC4R to sexual arousal.[7,8] Agonists to MC4R cause an increase in the number of penile erection in rats.[7] In addition, administration of a potent melanocortin receptor peptide agonist increases the number of erections in men with erectile dysfunction (ED).[8] Because of the evidence supporting MC4R as a key mediator in two physiological functions, we set out to identify small molecule agonists for MC4R that might be used as therapies for either obesity or ED.

In the past few years, several patent applications[9] and articles in the literature[10] have appeared that contain MC4R agonists with either the piperidine or piperazine core (see Fig. 1). In many of the published structures, the piperidine or piperazine is appended with two amino acids: *para*-chloro-D-phenylalanine (pCl-D-Phe) and D-1,2,3,4-tetrahydro-3-isoquinoline (D-Tic). In 2002, a research group at Merck published agonists that contained this dipeptide appended onto a piperidine core.[10a] Compound **1** from this report was a low-nanomolar functional agonist and was several fold more selective for MC4R over two other receptor subtypes, MC3R and MC5R. In addition, compound **1** showed both anti-feeding effects and increased the number of erections in rats. Scientists at Lilly[10b] and Neurocrine Biosciences[10c–e] also independently identified potent and selective MC4R agonists that contained a piperazine appended to the pCl-D-Phe, D-Tic dipeptide. In our own studies, we identified MC4R agonists that contained the piperazine core with the pCl-D-Phe, and L-Tic dipeptide (compound **2**). The piperazine on **2** is appended with a *ortho*-substituted aryl sulfonamide group. Compound **2** was potent at MC4R and selective over MC3R, but **2** was only 21-fold selectivity for MC4R over MC5R. We wanted to further explore the

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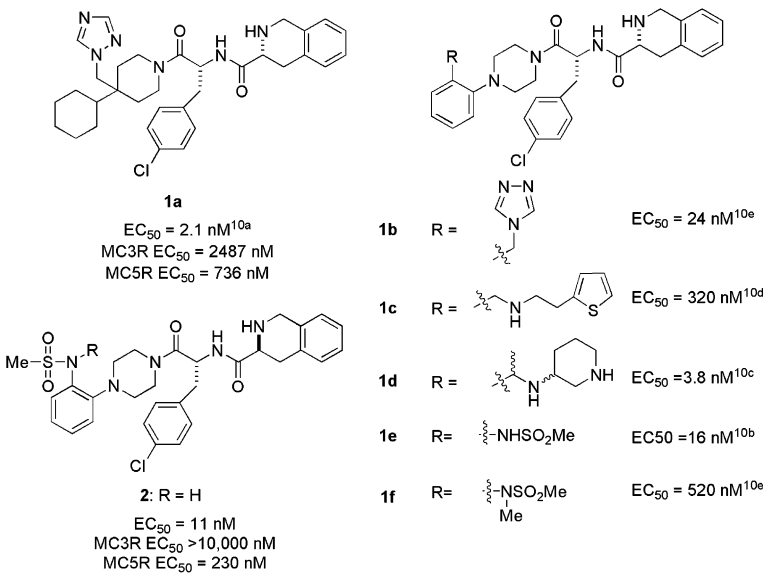


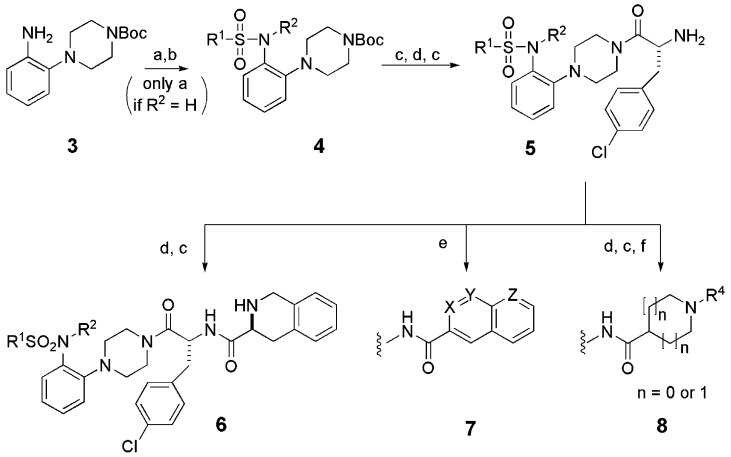
Figure 1. MC4R agonists containing a piperidine or a piperazine core (see Ref. 10).

structure–activity relationship of this compound by substituting the sulfonamide and replacing the Tic group to see if potency and selectivity could be improved. In addition, once we obtained a more potent and selective compound, we wanted to study its in vivo activity in rodent behavioral models that measured feeding.

Compounds for the SAR studies were derived from aminophenyl piperazine **3** (Scheme 1). Sulfonylation of compound **3**[11] followed by an *N*-alkylation of the sulfonamide gave compound **4**. Deprotection of **4**, followed by amino acid coupling with pCl-D-Phe, and then a second deprotection gave the key intermediate **5**. Compounds **6**, **7**, and **8** were all derived from intermediate **5** as outlined in the Scheme 1.

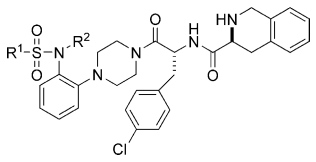
Compounds were tested in a competition binding assay with ^{125}I-NDP-melanocyte stimulation hormone (^{125}I-NDP-MSH). They were also tested in a whole cell functional assay where intracellular levels of adenosine 3′,5′-cyclic phosphate (cAMP) were measured.[12] The level of cAMP for the compounds tested was 90–100% of the level achieved with the endogenous ligand, α-melanocyte stimulation hormone (α-MSH), unless stated otherwise. The values in Tables 1–4 are the average of at least two separate experiments reported with the standard error of the mean. The pCl-D-Phe group was retained in all compounds since we had found that this group was preferred for MC4R binding and functional activity for this series of compounds.

We first examined the effects of substituting the sulfonamide group by increasing the size of R^1 and R^2 (see Table 1). Larger groups at R^1, like the benzyl analog **6a** and phenyl analog **6b**, did not improve activity. However, if substituents were added to the nitrogen of the



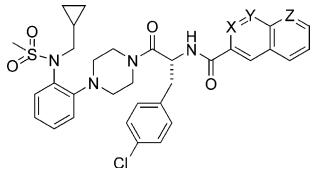
Scheme 1. Reagents and conditions: (a) R^1SO_2Cl, *i*-Pr_2NEt, $ClCH_2CH_2Cl$ (DCE); (b) NaH, R^2–I, DMF; (c) trifluoroacetic acid/CH_2Cl_2 or HCl in EtOAc; (d) Boc protected amino acid, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide HCl (EDC), 1-hydroxybenzotriazole (HOBT), DCE and/or DMF; (e) (hetero)aryl carboxylic acid, EDC, HOBT, DCE, and/or DMF; (f) ketone or aldehyde, $NaBH(OAc)_3$, DCE.

Table 1.



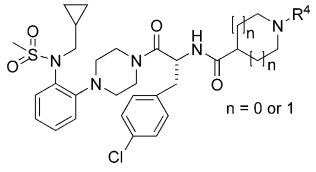
#	R^1	R^2	hMC4 receptor IC_{50} (nM)	hMC4R functional EC_{50} (nM)
2	CH_3	H	340 ± 30	11 ± 3
6a	Bn	H	720 ± 160	65 ± 23
6b	Ph	H	730 ± 60	120 ± 50
6c	CH_3	CH_3	210 ± 70	4 ± 4
6d	CH_3	CH_2(cyclopropyl)	61 ± 8	0.58 ± 0.15
6e[13]	CH_3	$(CH_2)_2NH_2$	35 ± 7	<0.1
6f	CH_3	$(CH_2)_2CH_3$	25 ± 3	0.44 ± 0.21

Table 2.



#	X	Y	Z	hMC4R receptor IC_{50} (nM)	hMC4R functional EC_{50} (nM)
7a	N	CH_2	CH_2	410 ± 37	18 ± 3
7b	CH_2	CH_2	CH_2	280 ± 100	63 ± 30
7c	CH_2	N	CH_2	94 ± 24	60 ± 16
7d	CH_2	CH_2	N	29 ± 8	27 ± 10 (50%)

Table 3.



#	*n*	R^4	hMC4R receptor IC_{50} (nM)	hMC4R functional EC_{50} (nM)
8a	1	Methyl	120 ± 40	12 ± 1
8b	1	Ethyl	110 ± 30	8.6 ± 1.5
8c	0	*tert*-Amyl	83 ± 30	49 ± 13
8d	0	Cyclohexyl	67 ± 10	1.8 ± 1.7

sulfonamide, activity improved (see **6d–f**). Interestingly, compound **6e** and **6f** have very different functionalities at R^2, an ethyl amino group, and a propyl group, respectively, but their binding and functional activities were similar (IC_{50}s <40 nM and EC_{50}s <1–4 nM). Compound **6d** containing a methylene cyclopropyl group on R^2 was slightly less potent that **6f** in the binding assay (IC_{50} = 61 vs 25 nM), but functional activity was nearly the same (EC_{50} = 0.58 vs 0.44 nM).

While investigating the SAR at the Tic position, we kept the left side of the molecule constant with a one of our more potent sulfonamides, the methylene cyclopropyl group (see Tables 2 and 3). Compounds that were studied in Table 2 contained two fused 6-membered rings, which we thought might be good surrogates for Tic ring system. Compound **7a**, with the isoquinoline group, was ca. 7-fold less potent in the binding assay than the corresponding Tic analog, compound **6d**. The naphthyl derivative **7b** had a similar binding affinity to **7a**, and the 3-quinoline and 6-quinoline derivatives, **7c** and **7d**, were 4–5-fold more potent than **7a**. The trend for receptor binding and functional activity diverged in this group of compounds, however. In this set, compound **7a** was the least potent in the binding assay, but it was the most potent in the functional assay. Compounds **7b** and **7c** differed in potency by ca. 3-fold (IC_{50} = 280 vs 94 nM), but their functional activities were similar (EC_{50} ca. 60 nM). The functional activity for compound **7d** was nearly identical to its binding affinity (IC_{50} and EC_{50} both ca. 30 nM), but **7d** could only produce 50% of the total response. None of the compounds in Table 2 were functionally as potent as **6d**, so these analogs were not further pursued.

We then looked at a set of piperidines and azetidines as replacements for the Tic group. A disparity between the trends in binding and functional activities was observed for this set of compounds too (see Table 3). In the binding assay, the rank order for potency was **8d > 8c > 8b > 8a**. Compound **8d,** with the *N*-cyclohexylazetidine group, had the best binding and functional activity for this set of compounds (IC_{50} = 67 nM, EC_{50} = 1.8 nM). However, the rank order potency in the functional assay for the remaining compounds was **8b > 8a > 8c**. Apparently, the factors responsible for functional activity are subtly different from those elements that affect binding to the receptor for this region of the molecule.[14] Since we were interested in agonists for MC4R, we chose compounds with the best functional activity for further profiling.

Table 4. Selectivity at human melanocortin receptors

#	hMC4R IC_{50} (nM)	hMC4R EC_{50} (nM)	hMC3R EC_{50} (nM)	hMC5R EC_{50} (nM)	MC5R/MC4R
MTII	1.48 ± 0.23	<0.01	<0.01	0.01 ± 0.006	
2	340 ± 30	11 ± 3	>10,000	230 ± 50	21
6d	61 ± 9	0.6 ± 0.2	7000	170 ± 20 (50%)	280
6e	35 ± 7	<0.1	>10,000	79 ± 50 (60%)	~79
6f	25 ± 3	0.4 ± 0.2	>10,000	210 ± 10	490

Table 5. In vitro potency and pharmacokinetics of compound **6f** in mice[a]

MC4R IC_{50} (nM)	MC4R EC_{50} (nM)	Cl/F (mL min^{-1} kg^{-1})	V_z/F (L kg^{-1})	T_{max} (h)	C_{max} (ng mL^{-1})	$t_{1/2}$ (h)	%F	C_{brain} (ng g^{-1}) at T_{max}
0.1	0.1	30	19	0.25	1400	0.44	20%	130

[a] Compound formulated in PBS with 1% HMBC; 1% Tween 80. Dosed in fed male CD-1 mice at 50 mg kg^{-1} (p.o.).

We next chose to examine the selectivity of our most potent compounds at receptor subtypes MC3R and MC5R (see Table 4).[12] For reference purposes, we also included the activity of MT-II, a known potent peptide agonist for the melanocortin receptors.[15] Our lead compound **2** and three of our most potent analogs, **6d–f**, all had IC_{50}s over 10 μM in the human MC3R functional assay. At the human MC5 receptor, our lead compound **2** was only modestly selectivity for MC4R over MC5R (20-fold). On the other hand, compounds **6d**, **6e**, and **6f** were, respectively, 280, ~79, and 490-fold more selective for MC4R versus MC5R. Only partial activation of MC5R (50–60%) was seen for compound **6d** and **6e**. Compound **6f** was chosen for additional in vivo pharmacology experiments since it was the most selective and did not show partial agonism for MC5R.

Compound **6f** was then run in a pharmacology model that measured acute feeding behavior in mice. Prior to this study, however, we tested **6f** for in vitro potency and determined the pharmacokinetic profile in mice. Compound **6f** was very potent at the mouse receptor (IC_{50} and EC_{50} below 1 nM, see Table 5). In the PK experiments, we dosed compound **6f** orally at 50 mg kg^{-1}. The concentration of **6f** in the brain was measured since we were looking for exposure in the tissue where MC4R presumably affects feeding. While the T_{max} was under an hour, compound **6f** had plasma and brain concentrations well above the IC_{50} and EC_{50} of the receptor, so we felt that this compound would be useful in evaluating the effects of MC4R agonism in mice.

To examine the feeding behavior in mice, we measured the amount of food consumed in animals that were fasted for 24 h. Since rodents normally eat during the night, mice were acclimated to a reversed light-cycle (lights on at night, lights off during the day) so their feeding behavior could be measured during normal working hours. Mice were given compound **6f**, by oral gavage, and then given a pre-weighed amount of chow. Efficacy was measured by comparing the amount of food consumed in mice treated with compound to those animals treated only with the vehicle. Compound **6f** showed a dose dependent decrease in food intake at 25, 50, and 100 mg kg^{-1} after 1 h (Fig. 2). Animals treated at 50 mg kg^{-1} showed a significant reduction in food intake that extended for 4 h, and the 100 mg kg^{-1} group showed a significant reduction in feeding that lasted 6 h. After 24 h, however, cumulative food intake in all dose groups returned to levels observed in the control animals.

We next ran experiments to address whether the inhibition of food intake with **6f** was a result of non-specific or toxic side effects. Compound **6f** was screened against two other receptors that are implicated in regulating feeding behavior: the neuropeptide Y5 and melanocyte stimulating hormone receptors. In both cases, compound **6f** had IC_{50}s > 10,000 nM in a receptor binding assay for these two receptors. In addition, no overt motor deficiencies were observed in any of the animals that showed a reduction in feeding, indicating that the feeding effects of compound **6f** were not caused by a decrease in locomotor activity. Our experience is that overtly toxic agents will produce decreases in locomotor activity. Feeding inhibition through a mechanism other than MC4R agonism still cannot be completely ruled out. However, the evidence shown here, and the fact that **6f** is a potent MC4R agonist that accesses the target tissue, suggests that the feeding effects are mediated through the MC4R.

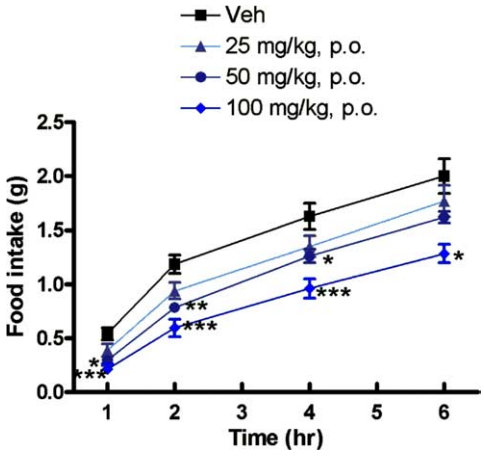


Figure 2. Effects of oral administration of **6f** on cumulative food intake in fasted male C57BL/6 mice. Values represent mean ± SEM (n = 10/group); significantly different from vehicle; $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$ based on ANOVA followed by Fishers protected least significant difference test where appropriate.

By preparing analogs at the sulfonamide and Tic positions we were able to identify compounds that were more potent at MC4R than our lead compound **2**. Analogs with larger groups on the sulfonamide nitrogen, for example, **6d–f**, were also more selective than the lead. We were able to show that one of these compounds, **6f**, achieved brain levels above its EC_{50}, and reduced food consumption in fasted mice. These effects are consistent with the observations that MC4R agonism reduces feeding. Additional in vivo pharmacology experiments with **6f** that study the erections in rodents are being conducted and will be reported in a future publication.

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11. Compound **3** was prepared according to the procedure found in Ref. 9h.
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