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Discovery and activity of (1*R*,4*S*,6*R*)-*N*-[(1*R*)-2-[4-cyclohexyl-4-[[(1,1-dimethylethyl)amino]carbonyl]-1-piperidinyl]-1-[(4-fluorophenyl)methyl]-2-oxoethyl]-2-methyl-2-azabicyclo-[2.2.2]octane-6-carboxamide (3, RY764), a potent and selective melanocortin subtype-4 receptor agonist

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Abstract—A novel isoquinuclidine containing selective melanocortin subtype-4 receptor small molecule agonist, **3** (RY764), is reported. Its in vivo characterization revealed mechanism-based food intake reduction and erectile activity augmentation in rodents.

The worldwide prevalence of obesity is increasing at an alarming rate, with major adverse consequences for human health including increased risk for diabetes and cardiovascular disease. The search for an effective treatment for obesity is progressing on many fronts. Several physiological systems and pathways that regulate body weight in mammals have been identified in recent years.[1] Studies suggest that the centrally located melanocortin system may be a fundamental component in the regulation of appetite, body weight, and energy homeostasis.[2] All five known subtype melanocortin receptors (MC1R–MC5R) are activated by the endogenous agonists α-, β-, and γ-melanocyte-stimulating hormones (MSHs) and adrenocorticotropin (ACTH). These peptides are derived from pro-opiomelanocortin (POMC) and they mediate a diverse number of physiological functions such as inflammation, skin pigmentation, steroidogenesis, food intake, energy expenditure, sexual behavior, and exocrine gland secretion.[3] Highly expressed in the hypothalamus, and dorsal motor nucleus of the vagus in the caudal brainstem, the melanocortin-4 receptor (MC4R) has been linked to the control of feeding and sexual behaviors. The localization of the receptor correlates quite well with the brain sites displaying high sensitivity to melanocortin-regulated feeding responses to exogenously applied ligands.[4] Pharmacological evidence that modulation of melanocortin receptors might provide a mechanism for regulation of energy balance and erectile function has come from studies using MC4R agonist and antagonist peptides. Administration of agonists to rodents decreases food consumption and increases erectile responses, while antagonist administration produces the opposite effect suggesting that selec-

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tive MC4R agonists may prove useful for the treatment of obesity and impotency.[5]

Although peptides have been used extensively to characterize receptor systems, the development of peptides into pharmaceutical products is generally limited due to poor bioavailability. Thus, intensive efforts have gone into the identification of MC4R selective small molecule ligands for the treatment of obesity and sexual dysfunction.[6] We recently reported the discovery of potent and selective MC4R agonists **1** (THIQ)[6i] and **2** (MB243)[6a] (Fig. 1). Both compounds **1** and **2** displayed significant activities in the control of feeding behavior and in the stimulation of erectile response in our rodent models. However, undesirable properties such as covalent protein-binding activity in vitro prompted further optimization of compounds in this series.[7] In this study, we report the use of isoquinuclidines, in **3** (RY764), as a replacement for the piperazine residue of **2** to attenuate oxidative metabolism and subsequent binding to liver microsomal proteins. This modification enhanced in vivo efficacy of the series. The *tert*-butyl amide-privileged structure (**4**) and *p*-fluoro-(D)-phenylalanine residues were kept intact to maintain adequate functional potency.[8]

The synthesis of isoquinuclidines has been reported in the literature.[9] Preparation began with 1-carbobenzyloxy-1,2-dihydropyridine (**5**), which was obtained by the reaction of pyridine with sodium borohydride followed by the addition of benzylchloroformate (Scheme 1). The isoquinuclidine core was generated in a Diels–Alder reaction between dihydropyridine **5** and methyl acrylate. The separation of the resultant exo- and endomixture of **6** and **7** or their hydrogenated derivatives proved difficult. Hence, the mixture of **6** and **7** was hydrolyzed and treated with iodine. This resulted in conversion of the endoisomer into iodolactone **9**. After separation, compound **9** was incubated with zinc powder to regenerate the acid **10**. Hydrogenation of **8** and **10** followed by treatment with di-*tert*-butyl dicarbonate gave the protected isoquinuclidine acids **11** and **12**, respectively. Separation of enantiomers was achieved via coupling of compounds **11** and **12** with (*S*)-4-benzyl-2-oxazolidinone to produce, after hydrolysis of the separated diastereoisomers, the enantiomerically pure acids **13** and **14** (syn-isomers) and **15** and **16** (anti-isomers), respectively.[10] The absolute configurations were assigned according to literature[9b] and Mosher amide analysis.[11]

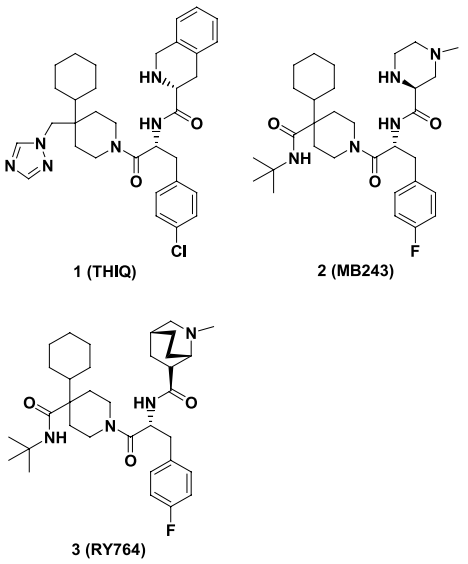
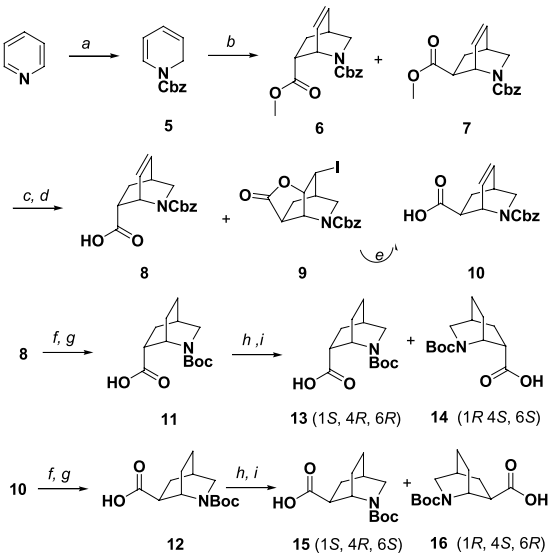


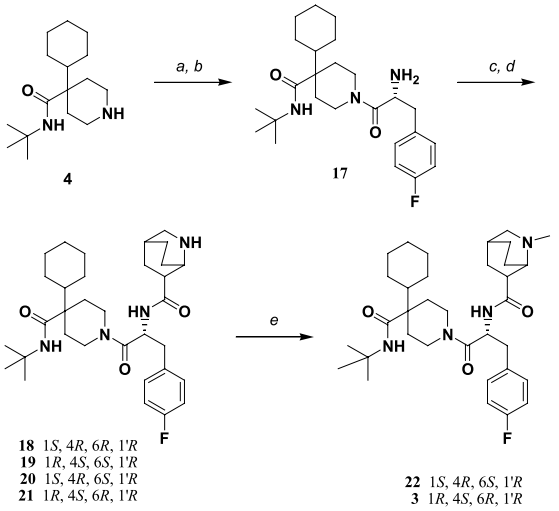
Figure 1. Structures of compounds **1**, **2**, and **3**.



Scheme 1. Reagents and conditions: (a) $NaBH_4$, $PhCH_2OCOCl$, MeOH, −70 °C; (b) methyl acrylate, hydroquinone, 85 °C; (c) NaOH, H_2O–MeOH; (d) I_2, KI, $NaHCO_3$, H_2O; (e) Zn, HOAc; (f) H_2, Pd/C, MeOH; (g) $(Boc)_2O$, NaOH, dioxane; (h) (*S*)-4-benzyl-2-oxazolidinone, pivaloyl chloride, LiCl, Et_3N, THF; (i) LiOH, H_2O_2, THF–H_2O.

The privileged structure, *N*-(*tert*-butyl)-4-cyclohexylpiperidine-4-carboxamide (**4**), was synthesized as described earlier.[6a] A sequential coupling of compound **4** with *p*-fluoro-(D)-phenylalanine and the isoquinuclidine acids **13–16** in the presence of *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide followed by deprotection afforded **18**, **19**, **20**, and **21**, respectively (Scheme 2). Reductive amination of the amines **20** and **21** with formaldehyde furnished **22** and **3**.

Binding affinities and functional activities at the human melanocortin receptors were evaluated in competitive binding assays using radiolabeled ligand [^{125}I]-NDP-α-MSH and in cAMP assays employing CHO cells expressing the receptors.[12] The in vitro data for compounds **3** and **18–22** are summarized in Tables 1 and 2. Compounds **20** and **21**, bearing an *anti*-isoquinuclidine, were more potent than **18** and **19**, bearing a *syn*-isoquinuclidine, in both binding affinity and functional activity at the human MC4 receptor. Among the anti-isomers, the two were equipotent in binding but (1*R*,4*S*,6*R*)-isoquinuclidine analog **21** possessed a slight edge in functional activity at the human MC4 receptor. However, no bioavailability was observed for **21** in pharmacokinetic studies in rats. Methylation of the isoquinuclidine amine of **20** and **21** afforded **22** and **3**. The latter exhibited an approximately 2-fold increase in binding affinity and a 2-fold improvement in functional activity at the human MC4 receptor.



Scheme 2. Reagents and conditions: (a) *N*-Boc-*p*-fluoro-(D)-Phe, EDC, HOBt, DIEA, CH_2Cl_2; (b) TFA, CH_2Cl_2; (c) **13**–**16**, EDC, HOBt, DIEA, CH_2Cl_2; (d) HCl, dioxane; (e) HCHO, $NaBH_3CN$, NaOAc, MeOH.

Table 1. Binding affinity of compounds at the human melanocortin receptors[a]

Compounds	IC_{50}[b] (nM)		
	MC4R	MC3R	MC5R
α-MSH	19 ± 2	19 ± 2	118 ± 19
3	8 ± 1	942 ± 42	945 ± 44
18	28 ± 8	1350 ± 170	6460 ± 1150
19	41 ± 8	2060 ± 320	9870 ± 880
20	14 ± 2	620 ± 160	1020 ± 290
21	16 ± 6	690 ± 240	940 ± 150
22	6 ± 1	410 ± 120	1080 ± 340

[a] Values are represented as means ± standard error. All data represent at least three determinations.
[b] Displacement of [^{125}I]-NDP-α-MSH from the human receptors expressed in CHO cells.

Table 2. Functional activity of compounds at human melanocortin receptors[a]

Compounds	EC_{50}[b] (nM) [% max][c]		
	MC4R	MC3R	MC5R
α-MSH	1.9 ± 0.1 [100]	1.1 ± 0.1 [102]	17 ± 1 [113]
3	11 ± 1 [81]	[8 ± 4]	850 ± 130 [33]
18	165 ± 31 [22]	[5 ± 1]	[14 ± 3]
19	238 ± 59 [59]	[10 ± 3]	1980 ± 230 [26]
20	52 ± 3 [57]	[3 ± 4]	[3 ± 4]
21	20 ± 5 [90]	[4 ± 3]	[11 ± 7]
22	34 ± 10 [58]	[4 ± 4]	[5 ± 5]

[a] Values are represented as means ± standard error except for where indicated. All data represent at least three determinations.
[b] Concentration of compound at 50% maximum cAMP accumulation.
[c] Percentage of cAMP accumulation at 10 μM compound relative to α-MSH and values represent means ± standard deviation.

Overall, compound **3** was the most promising compound in the series. It exhibited excellent binding affinity (IC_{50} of 8 nM) and agonist potency (EC_{50} of 11 nM with 81% activation) at the human MC4 receptor and acceptable melanocortin receptor subtype selectivity. It was further evaluated in vitro on rat, mouse, and dog melanocortin receptors. Data are listed in Table 3. The compound showed slightly higher potency in rat and mouse cells than in dog and human cells. On the basis of its good potency at hMC4 receptors in all cell lines and acceptable subtype selectivity at the human receptors, the compound was subjected to further in vivo characterization.

Table 3. Binding affinity and functional activity of compound **3** in human, rat, mouse, and dog melanocortin receptors[a]

Receptor	Binding[b] IC_{50} (nM) [% inh.]	cAMP[c] EC_{50} (nM) [% max]	Activation[d] at 10 μM (%)
hMC1R	750 ± 70	160 ± 30 [75]	
hMC2R	>10,000		2 ± 1
hMC3R	942 ± 42		8 ± 4
hMC4R	8 ± 1	11 ± 1 [81]	
hMC5R	945 ± 44	850 ± 130 [33]	
rMC4R	3 ± 1	5 ± 1 [80]	
mMC4R	3 ± 1	6 ± 1 [54]	
dMC4R	7 ± 2	11 ± 2 [65]	

[a] All data represent at least three determinations.
[b] Displacement of [^{125}I]-NDP-α-MSH receptors expressed in CHO cells. Values are represented as means ± standard error except for where indicated.
[c] Concentration of compound at 50% maximum cAMP accumulation. Values are represented as means ± standard error except for where indicated.
[d] Percentage of cAMP accumulation at 10 μM compound relative to α-MSH. Values are represented as means ± standard error except for where indicated.

In pharmacokinetic studies, compound **3** displayed moderate-to-good bioavailability (*F*) in rats, dogs, and monkeys. With good plasma drug exposure and relatively long duration in all species, compound **3** was chosen as a candidate for evaluating feeding effects in animal models (see Table 4).

Compound **3** was evaluated for its effects on food intake in vivo in Sprague–Dawley rats in a fasting induced refeeding paradigm. Twelve-week-old, male, Sprague–Dawley rats were fasted for 18 h. The compound was orally administered in a 0.5% methylcellulose vehicle at 2, 6, or 20 mg/kg. Food intake was measured at 2,

Table 4. Pharmacokinetic data for compound **3** in preclinical species

PK parameter	Rat[a]	Dog[b]	Monkey[c]
F (%)	32	50	16
Cl (mL/min/kg)	46.9	6.6	3.4
V_{dss} (L/kg)	9.6	2.3	0.8
$t_{1/2}$ (h)	3.2	4.9	4.6
T_{max} (h)	3	1.1	1.3
AUC_{norm} (μM h kg/mg)	0.196	2.7	1.3
C_{max} (μM)	0.87	0.91	0.85

[a] Compound dosed in Sprague–Dawley rats as a solution in water at 1 mg/kg, iv and 20 mg/kg, po.
[b] Compound dosed in beagles as a solution in water at 0.5 mg/kg, iv and 2.0 mg/kg, po.
[c] Compound dosed in rhesus as a solution in water at 0.5 mg/kg, iv and 2 mg/kg po.

8, and 18 h postdosing. Significant food intake reduction was observed at 8-h (−39%, $P < 0.05$) and 18-h (−37%, $P = 0.055$) timepoints. In an overnight food intake study in MC3/4R knockout (KO) and wild type (WT) mice, compound **3** displayed a significant food intake reduction in WT mice (−28%, $P = 0.004$) but not in KO mice (−8.6%, $P = 0.19$). The data suggested that the reductions of food intake observed in the rodents are a mechanism-based event mediated by the MC4 receptor (see Fig. 2).

Further in vivo studies were performed to evaluate the erectogenic activity of **3** using an established rodent model of erectile function.[3a,6j,k] Compound **3** augmented the magnitude and duration of electrically stimulated erectile activity following intravenous administration (1 mg/kg) in mice (Fig. 3). Administered at 1 mg/kg, compound **3** significantly augmented poststimulation AUC by 34% and 26% at 15 and 45 min, respectively. The effects were not sustained out to 60 min. At a suboptimal dose (0.1 mg/kg), compound **3** failed to augment electrically evoked changes in erectile activity. Administration of **3** did not elicit erectile activity in the absence of electrical stimulation.

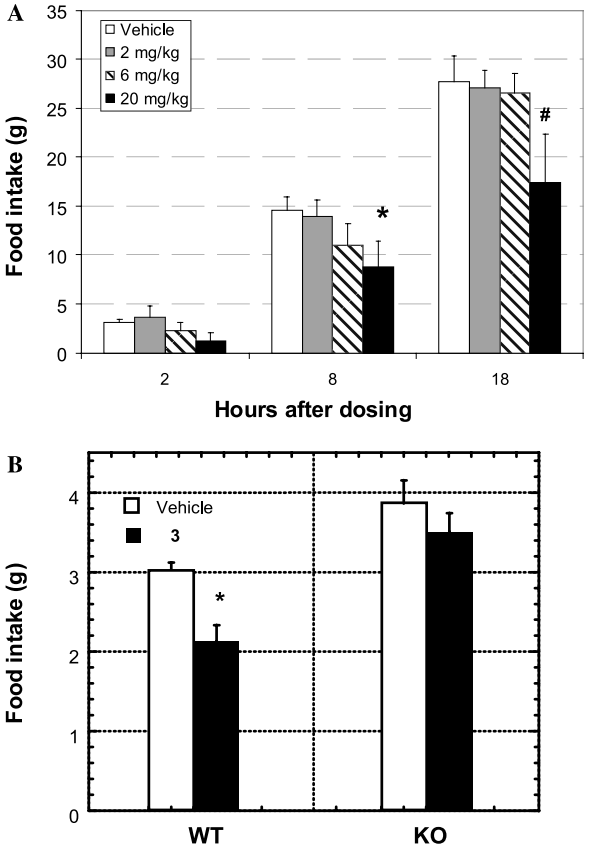


Figure 2. Effect of compound **3** on overnight food intake in (A) fasted DIO rats and (B) knockout (KO) and wild type (WT) mice. (A) Sprague–Dawley rats were fasted overnight and then refed at the time of dosing. Compound **3** was administered in a 0.5% methylcellulose oral vehicle. Feeding was measured at 2, 8, and 18 h postdosing. $^{*}P < 0.05$, $^{\#}P = 0.055$. (B) Effect of compound **3** on overnight food intake in KO and WT mice. Compound **3** was administered in a 0.5% methylcellulose oral vehicle at 20 mpk to MC3/4 KO and WT mice. Feeding was measured at 18 h postdosing. $^{*}P < 0.05$.

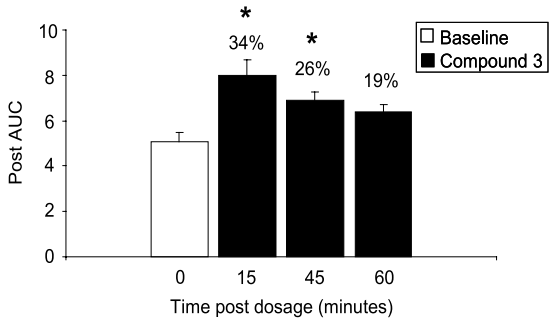


Figure 3. Proerectile effects of compound **3** in anesthetized male C57BL/6J mice. Compound **3** (1 mg/kg, iv) was administered in a PEG400–EtOH–water (4:1:5) vehicle in sodium pentobarbital anesthetized mice. Electrically evoked erectile activity was measured pre, 15, 45, and 60 min postdosage, depicted as AUC (30 s poststimulation) and percent change from baseline. Statistical significance is defined as $^{*}P < 0.05$.

Table 5. Irreversible protein binding of [^{3}H]-**3**

	Liver microsomes (pmol equiv/mg protein)		
	30′-NADPH	30′ + NADPH	30′ + NADPH + GSH
Rat	1	28	11
Human	2	26	17

With an eye to addressing concerns of covalent protein binding that were raised by studies of **2**,[7] tritium-labeled **3** was evaluated for irreversible protein binding in vitro. We were gratified to find that introduction of the isoquinuclidine has appreciably reduced the metabolic activation potential to relatively low levels following incubation with rat and human liver microsomes (Table 5). Irreversible protein binding was measured in vivo in rats dosed orally at 2 and 20 mpk and the study revealed protein binding in plasma and liver at 2, 6, and 24 h postdose was <1 pM equiv/mg of protein.

In conclusion, a new series of potent MC4R agonists having excellent in vitro and in vivo activities has been developed. Replacement of a piperazine ring with an isoquinuclidine ring attenuated covalent protein binding to acceptable levels. Furthermore, compound **3** (RY764) is efficacious in lowering food intake in both rats and mice and dose-dependently augments erectile activity in mice.

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