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Discovery of potent, selective, and orally bioavailable 3*H*-spiro[isobenzofuran-1,4′-piperidine] based melanocortin subtype-4 receptor agonists

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ABSTRACT

Design, synthesis, and SAR of a series of 3*H*-spiro[isobenzofuran-1,4′-piperidine] based compounds as potent, selective and orally bioavailable melanocortin subtype-4 receptor (MC4R) agonists are disclosed.

Over the past 20 years, obesity has become one of the fastest growing diseases in the world. The medical problems associated with obesity include increased mortality, hypertension, diabetes, heart disease, and other substantial health risks. The current prescription drug market for anti-obesity agents is small compared to overall disease prevalence, so the unmet demand for more effective anti-obesity agents has prompted many pharmaceutical companies and research groups to conduct research in this area.

The melanocortin receptors are a family of seven-transmembrane G-protein-coupled receptors. All the five known subtype melanocortin receptors are activated by their endogenous ligands (the corticotropins and melanocortins) to mediate a variety of physiological functions, such as feeding behavior, sexual function, skin pigmentation, steroidogenesis, and exocrine gland secretion. The melanocortin subtype-4 receptor (MC4R), highly expressed in the hypothalamus and brainstem, has been clearly linked to the regulation of appetite, body weight, and energy homeostasis.[1] Both rodent and human genomic studies indicate that inactivation of MC4R results in obesity. In the past decade, considerable efforts have been devoted in drug discovery to develop potent and selective non-peptide MC4R agonists for the potential treatment of human obesity.[2] Previously, we disclosed the discovery of *t*-butyl pyrrolidine derived, potent and orally bioavailable MC4R modulators by modifying the 2,4-difluorophenyl in **1**.[3] Herein, we report our continued effort in this area, which has led to the discovery of a series of potent and orally bioavailable MC4R agonists containing a 3*H*-spiro[isobenzofuran-1,4′-piperidine] moiety (Fig. 1). The lead compound **2** is a potent, selective, orally bioavailable, and brain penetrable MC4R agonist with good efficacy in lowering food intake and body weight in rodents.

Our earlier efforts in modifying the piperidine part-structure to enhance MC4R potency and oral bioavailability revealed a 4,4-disubstituted piperidine bearing a *gem*-dimethyl acetamide moiety, exemplified by compound **3** (Fig. 2a).[4a] Aiming to further

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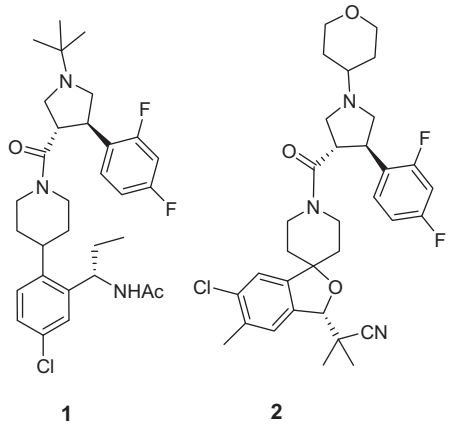


Figure 1. MC4R selective agonists.

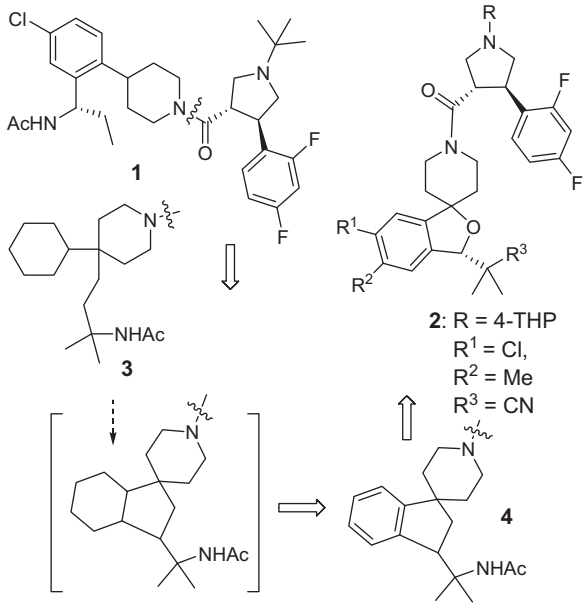


Figure 2a. Design of spiro isobenzofuran piperidine based MC4R selective agonists.

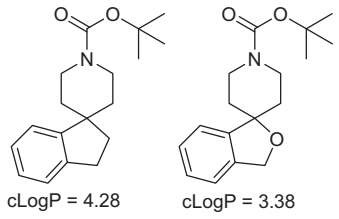
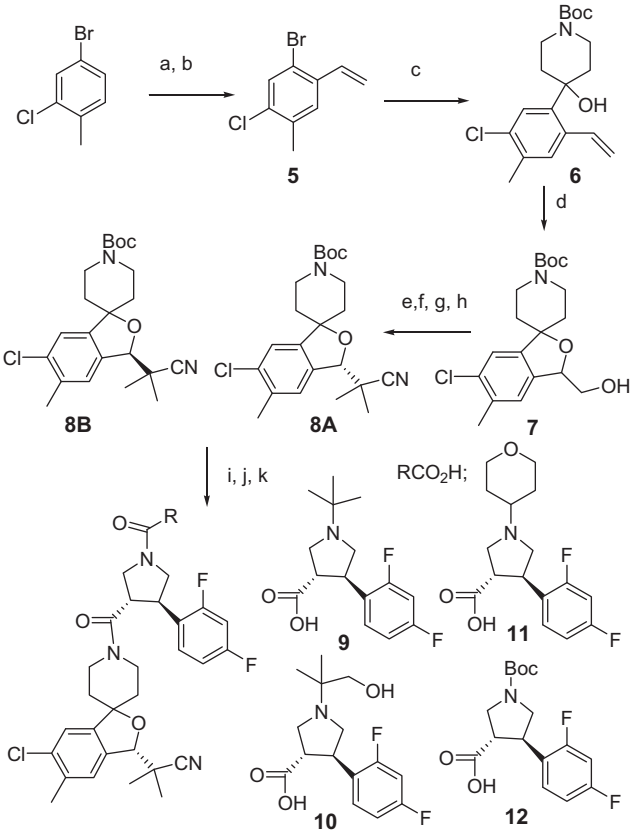


Figure 2b. Calculated Log *P*.

improve pharmacokinetic properties, this was coupled with piperidine design in **1**, leading to the cyclized analog **4**.[4] Attempts to lower the Log *P* of the molecules in hope of attenuating plasma protein binding and ultimately improving in vivo efficacy inspired us to design the oxygen tethered spiro indane or spiro isobenzofuran piperidine moiety (Fig. 2b), which in turn yielded a series of interesting MC-4 agonists with good MC4R in vitro potency and in vivo efficacy.

The general synthetic procedure for synthesizing 3*H*-spiro[isobenzofuran-1,4′-piperidine] containing structures bearing a nitrile



Scheme 1. Reagents and conditions: (a) NIS, TFA, RT, 2 h, 50 °C, 1 h; (b) $Bu_3Sn(CH{=}CH_2)$, $Pd(dppf)_2Cl_2$,LiCl, DMF, rt, 48 h; (c) *n*BuLi, *N*-Boc-4-oxopiperidine, THF–ether, −78 °C to rt; (d) MCPBA, DCM, rt-reflux, O/N; (e) TsCl, DIEA, DMAP, rt, overnight; (f) KCN, KI, DMSO, 110 °C, O/N; (g) NaHMDS, MeI, −78 °C to rt; (h) chiral HPLC resolution: ChiralCel OD column; mobile phase = 0.5% IPA/heptane; flow rate = 9 ml/min; (i) 4 N HCl, dioxane, rt, 1 h; (j) RCO_2H (9–12), DIEA, HOAt, HATU, DCM; (k) for RCO_2H = 12: (i) 4 N HCl, dioxane, rt, 1 h; (ii) DIEA, molecular sieve, aldehyde or ketone, $Na(OAc)_3BH$, DCM, rt.

moiety is summarized in Scheme 1. Iodination of 4-bromo-2-chloro-toluene, followed by a Stille coupling reaction, gave vinyl intermediate **5**. Trans metalation of **5** and addition to *N*-Boc-4-oxopiperidine yielded tertiary alcohol **6**, which, upon treatment with MCPBA, furnished the spiro isobenzofuran alcohol **7** via epoxide formation and subsequent intramolecular substitution. Tosylation of **7**, followed by substitution with cyanide and then methylation afforded a racemic *gem*-dimethyl nitrile, which underwent chiral HPLC resolution to give the separated enantiomers **8A** and **8B**.

The absolute stereochemistry of the faster eluting isomer **8A** was determined as 'S' by single-crystal X-ray diffraction analysis (Fig. 3).[5] Following deprotection, **8A** was coupled to pyrrolidine acids **9–11** to generate MC4R agonists **2**, **20** and **23**. Coupling to **12**, followed by removal of Boc and reductive amination, afforded a further series of MC4R agonists variously substituted on the pyrrolidine ring (Scheme 1).

Amides analogs were generated from the nitrile of **8A** via hydrolysis to the de-protected amino acid followed by a one-pot, two-step coupling procedure (Scheme 2a). Reversed amides and a *gem*-dimethyl acetamide moiety were generated from intermediate **13** via Curtis rearrangement to give an isocyanate intermediate and subsequent reaction with 2-(trimethylsilyl)ethanol affording the protected amine **14**. De-protection and acetylation gave acetamide **15**. Removal of Boc followed by coupling to **11** afforded **16** (Scheme 2b).

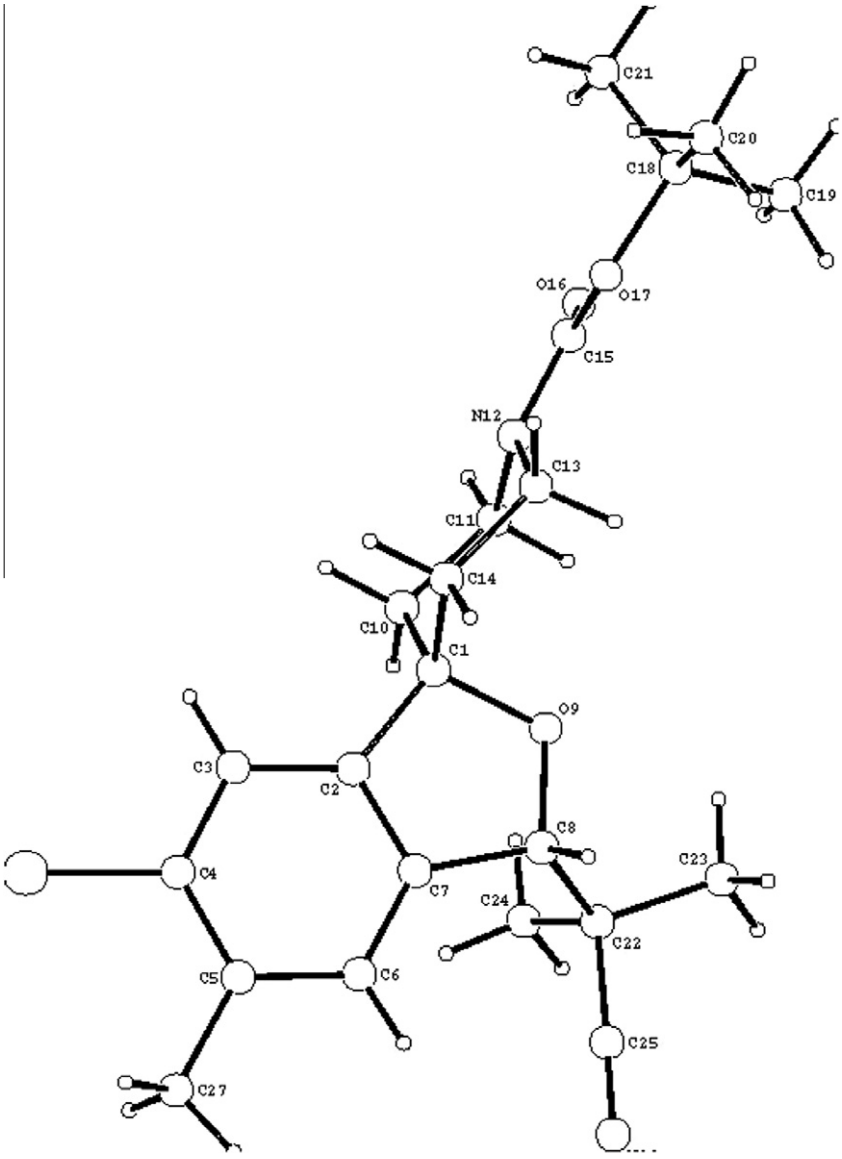
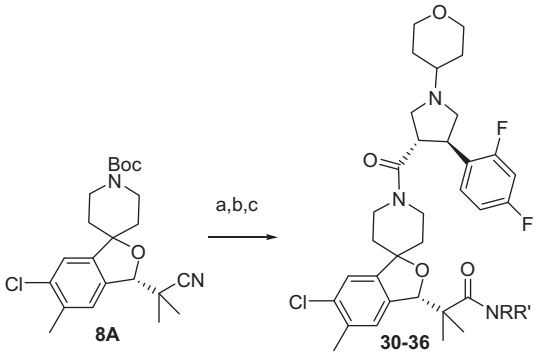


Figure 3. Structure of **8A** by single-crystal X-ray diffraction.

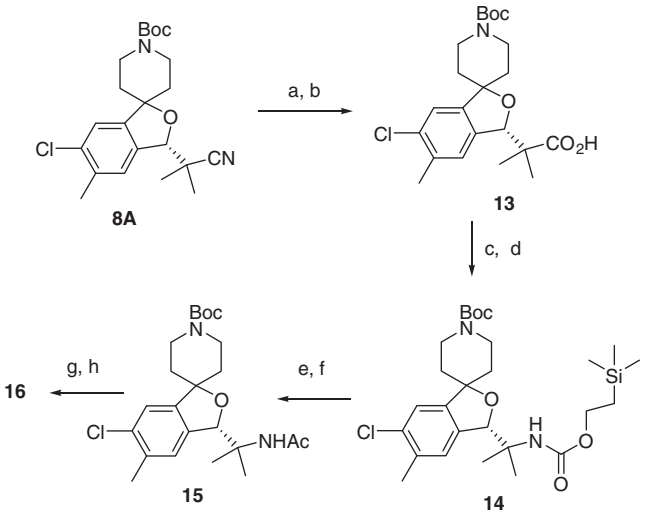


Scheme 2a. Reagents and conditions: (a) concd HCl, reflux; (b) **11**, DIEA, HOAt, HATU, DMF; (c) RR′NH.

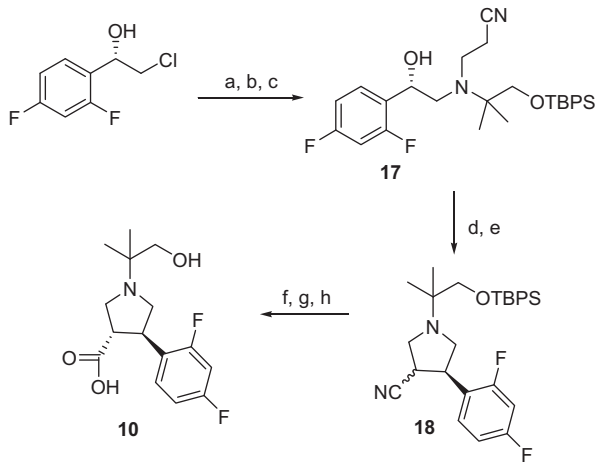
Compound **10** was synthesized using a modified literature procedure (Scheme 3).[6a] Substitution of the chloride in (*1S*)-2-chloro-1-(2,4-diflurophenyl)ethanol with the amine of 2-amino-2-methyl-1-propanol resulted in a hydroxylamine intermediate, which was converted to the nitrile **17** via Michael addition using acrylonitrile followed by selective protection of the primary alcohol using *tert*-butyl chlorodiphenylsilane. Activation of the benzyl alcohol using diethyl phosphoryl chloride followed by treatment with LiHMDS effected the intramolecular SN_2 reaction to construct the pyrrolidine ring (**18**) with inversion of the benzyl stereo center from '*S*' to '*R*'. Refluxing **18** under basic conditions epimerized the stereo center at the α-position of the nitrile group to 'S' favoring the more stable *trans* conformation, and hydrolyzed the nitrile to the carboxylic acid. The TBPS protecting group was also removed in this step to afford **10**.

Compound **11** was synthesized from **12**[6b] via esterification, deprotection, reductive amidation, and hydrolysis (Scheme 4).

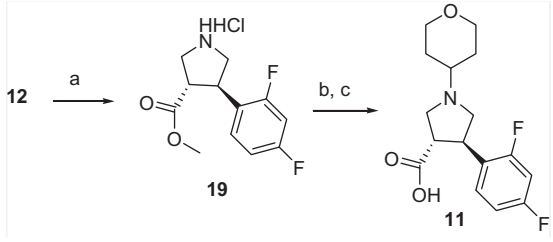
All final compounds were evaluated in MCR binding and functional assays for initial SAR studies.[7] Selected compounds were also evaluated in pharmacokinetic studies in rats. As shown in Table 1, compound **20A**, derived from intermediate **8A**, is significantly more potent than **20B**, derived from intermediate **8B**, indicating that '*S*' configuration in the 3-position of the spiro isobenzofuran is preferred for MC4R binding affinity and functional activity.



Scheme 2b. Reagents and conditions: (a) concd HCl, reflux; (b) $(Boc)_2O$, NaOH, dioxane–H_2O; (c) DPPA, Et_3N, toluene, reflux; (d) $HO(CH_2)_2TMS$, reflux; (e) TBAF, THF, rt, O/N; (f) Ac_2O, pyridine, CH_2Cl_2, rt, overnight; (g) HCl in dioxane, rt, 1 h; (h) **11**, DIEA, HOAt, HATU, DCM.

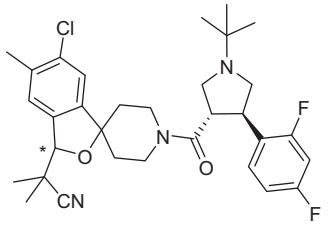


Scheme 3. Reagents and conditions: (a) 2-amino-2-methylpropan-1-ol, NaOH, MeOH; (b) acrylonitrile, 80 °C, overnight; (c) DIEA, DMAP, $Me_3Si(Ph)_2Cl$; (d) $(EtO)_2P(O)Cl$; (e) LiHMDS; (f) NaOH, EtOH–H_2O, reflux; (g) $SOCl_2$, MeOH, reflux, 1 h; (h) NaOH, THF–H_2O, rt



Scheme 4. Reagents and conditions: (a) $SOCl_2$, MeOH, reflux, 2 h; (b) tetrahydro-4*H*-pyran-4-one, DIEA, 4 Å molecular sieve, CH_2Cl_2, rt, O/N; (c) NaOH, THF–H_2O, rt, 4 h.

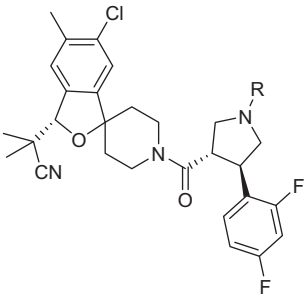
Table 1
Effects of chirality of spiro isobenzofuran on binding affinity and functional activity at the human MC4R[7]



Compd	*	MC4R binding IC_{50} (nM)	MC4R cAMP EC_{50} (nM) [%Max][a]
20A	'S'	0.9	1.1 [122]
20B	'R'	31.4	195.6 [127]

[a] Percentage of cAMP accumulation at 10 μM relative to α-MSH.

Table 2
Effects of N-substitutions of pyrrolidine part in MC-4 agonists on oral bioavailability, MC4R activity and selectivity at the human melanocortin receptors[7]

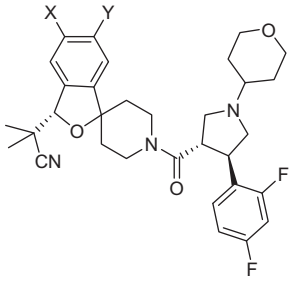


Compd	R	MC4R binding IC_{50} (nM)	EC_{50} (nM) [%Max]		*F*%[a]
			MC4R	MC1b	
21	Boc	479.2	1006.0 [68%]	— [3]	nd[b]
22	H	15.0	78.1 [99%]	2100 [36]	nd
20A		0.9	1.1 [122%]	115 [50%]	32
23		2.8	2.6 [112%]	342.9 [77]	44
2		2.0	2.7 [106%]	1697 [44]	64
24		52.5	95.9 [66%]	735.0 [38]	nd
25		6.6	9.8 [105]	295.0 [55]	nd
26		11.9	33.6 [115]	465 [63]	nd
27		44.3	73.2 [95]	615 [36]	nd

[a] Compounds were dosed in Sprague-Dawley rats as a solution in EtOH/PEG/saline (1:4:5) at 1 mg/kg, iv ($n = 2$) and 4 mg/kg, po ($n = 3$).
[b] nd = not determined.

Compound **20a** showed potent MC4R binding and functional activity and good oral bioavailability in rats ($F = 32\%$), however, it had modest MC4R selectivity against MC1b (~100-fold). The effects of modifications to the *N*-substitution of the pyrrolidine of **20A** are highlighted in Table 2. Compound **2**, containing an *N*-THP pyrrolidine was revealed as a potent MC4R full agonist with much improved selectivity against MC1b (>600-fold) and good PK profiles in rats ($F = 64\%$, AUCN = 0.44 μM h, CLp = 42.9 ml/min/

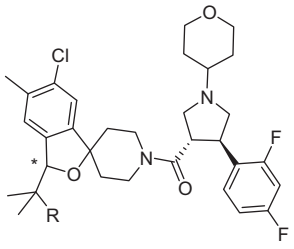
Table 3
Effects of substitutions at benzene ring of benzofuran on oral bioavailability and binding affinity and functional activity at the human MC4R[7]

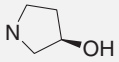
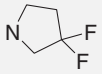


Compd	X, Y	MC4R binding IC_{50} (nM)	MC4R cAMP EC_{50} (nM) [%Max]	F%[a]	cLog *P*
2	Me, Cl	2.0	2.7 [106]	64	6.9
28	F, F	7.6	8.4 [99]	7	5.9
29	Cl, F	7.3	17.1 [109]	23	6.6

[a] Compounds were dosed in Sprague-Dawley rats as a solution in EtOH/PEG/saline (1:4:5) at 1 mg/kg, iv ($n = 2$) and 4 mg/kg, po ($n = 3$).

Table 4
Effect of substitution at benzene ring of isobenzofuran on binding affinity and functional activity at the human MC4R[7]



Compd[a]	R	MC4R binding IC_{50} (nM)	MC4R cAMP EC_{50} (nM) [%Max]	F%
16A	NHAc	6.2	7.4 [99]	26
16B[b]	NHAc	150.7	351.7 [92]	nd
30	NMe_2	2.4	1.5 [101]	nd
31	NHMe	3.6	3.8 [101]	46
32	NHEt	2.3	3.3 [100]	nd
33		1.0	0.6 [107]	nd
34		1.6	3.1 [109]	nd
35		1.4	0.8 [107]	nd
36		2.4	2.9 [100]	nd

[a] All the compounds, except **16B**, were derived from intermediate **8A**, and hold '*S*' configuration.
[b] Compound **16B**, derived from **8B**, holds '*R*' configuration.

Table 5
MCR activity profiles of **2**

Receptor	Binding IC_{50} (nM)	cAMP EC_{50} (nM)	% Acti. at 10 μM[a]
hMC1b	1523	1697	37
hMC3	482.7	766.7	82
hMC4	2.0	2.7	106
hMC5	122.7	—	1
rMC4	nd	1.1	101
f MC4	nd	3.1	105
mMC4	nd	3.4	100

[a] Percentage of cAMP accumulation at 10 μM relative to α-MSH.

Table 6
Brain penetration study of **2**

Time point	Plasma (μM)	Brain (μM)	b/p ratio
15 min	0.425	1.212	2.848
1 h	0.352	0.666	1.890
4 h	0.139	0.299	2.151

kg, $t_{1/2} = 5.4$ h). Another interesting finding from this study was that, incorporating *N-tert*-butyl hydroxyl pyrrolidine (**23**), maintained similar MC4R potency and rat PK profile to **20A**. Incorporation of the hydroxyl functionality affords a number of benefits: lipophilicity is lowered; and the structure holds potential in addressing a metabolism issue associated with other compounds bearing an *N-tert*-butyl substituent.[8]

Attempts were also made to vary the substituents on the isobenzofuran benzene ring with a goal of further lowering the polar-

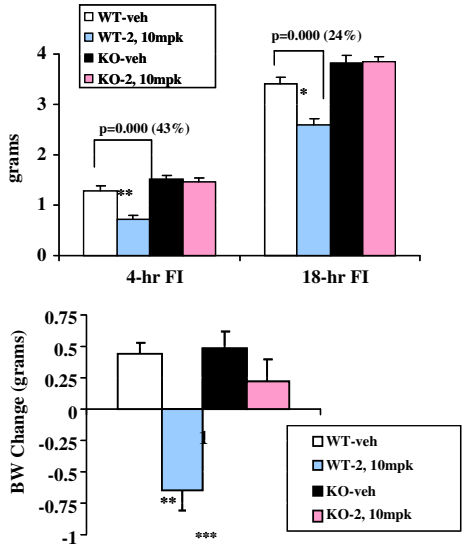


Figure 4. Effects of **2** on FI and BW in MC3/4R KO and WT DIO mice.

ity (lower calculated Log *P*) and/or increasing the metabolic stability of the compounds. However, this approach resulted in less potent and less orally bioavailable MC4R agonists (Table 3).

Another approach to further optimize lead compound **2** focused on replacing the nitrile group. As shown in Table 4, a number of functional groups were well tolerated, including the hydroxyl amine (**35**). In addition, most amide analogs of **2** showed comparable potency to **2**. Methyl amide **31** also exhibited very promising rat pharmacokinetics profile with higher drug level and lower clearance compared to **2** (*F*% = 46, AUCN = 1.0 μM h kg/mg, Cl = 12.1 ml/min/kg, Vdss = 1.5 L/kg). However, **29A** bearing a *gem*-dimethyl acetamide exhibited decreased MC4R potency and modest oral bioavailability. Compound **29B**, the diastereomer of **29A**, was less potent than **29A**, suggesting that the *S* stereo configuration at the 3-position of the spiro isobenzofuran is preferred for MC4R activity regardless of substitution.

Compound **2** was the most promising lead in this series. Potent functional activity and selectivity was maintained at melanocortin-4 receptors across a number of species (ferret, rat, and mouse) (Table 5).

The compound also exhibited high exposure in the brain of Sprague-Dawley rats (brain/plasma ratio >2 @ 4 h time point following 1 mg/kg IV administration) (Table 6).

Compound **2** was further evaluated in in vivo rodent obesity models. It demonstrated mechanism-based acute food-intake and body-weight reduction in DIO mice (Fig. 4), significantly lowering food intake (43% and 24% at 4 h and 18 h, respectively) and body weight in WT DIO mice with no appreciable effects these parameters in MC3R/4R knockout mice. Further, dose-dependent food-intake and body-weight reduction was observed in an 18-h acute food-intake study in DIO rats following orally administration of **2** (3 and 10 mpk). Compared to vehicle (0.5% methylcellulose), the compound lowered food intake by 63% at 18 h post-oral dosing at 10 mpk.[9]

In summary, we have described the design, synthesis, SAR, and evaluation of a series of MC4R selective agonists containing a spiro isobenzofuran core structure. This study led to the discovery of **2** as a potent, selective, orally bioavailable, and brain penetrable MC4R agonist with good efficacy of lowering food intake and body weight in DIO mice and rats.

References and notes

1. (a) Emmerson, P. J.; Fisher, M. J.; Yan, L. Z.; Mayer, J. P. *Curr. Top. Med. Chem.* **2007**, *7*, 1121; (b) Nargund, R. P.; Strack, A. M.; Fong, T. M. *J. Med. Chem.* **2006**, *49*, 4035; (c) Zimanyi, I. A.; Pelleymounter, M. A. *Curr. Pharm. Des.* **2003**, *9*, 627; (d) Van der Ploeg, L. H. T.; Howard, A. D.; Nargund, R. P.; Austin, C. P.; Guan, X.; Drisko, J.; Cashen, D.; Sebhat, I.; Pattchett, A. A.; Figueroa, D. J.; DiLella, A. G.; Connolly, D. H.; Weinberg, D. H.; Tan, C. T.; Palyha, O. C.; Pong, S.; MacNeil, T.; Rosenblum, C.; Vongs, A.; Tang, R.; Yu, H.; Sailer, A. W.; Fong, T. M.; Huang, C.; Tota, M.; Chang, R. S.; Sterns, R.; Tamvakopoulos, T.; Christ, G.; Drazen, D. L.; Spar, B. D.; Nelson, R. J.; MacIntyre, D. E. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 11381; (e) Eberle, A. N. In *The Melanocortin Receptors*; Cone, R. D., Ed.; Humana Press, 2000. p 3; (f) Gu, W.; Tu, Z.; Kleyn, P. W.; Kissebah, A.; Duprat, L.; Lee, J.; Chin, W.; Maruti, S.; Deng, N.; Fisher, S. L.; Franco, L. S.; Burn, P.; Yagaloff, K. A.; Nathan, J.; Heymsfield, S.; Albu, J.; Pi-Sunyer, F. X.; Allison, D. B. *Diabetes* **1999**, *48*, 635; (g) Hinney, A.; Schmidt, A.; Nottebom, K.; Heibult, O.; Becker, I.; Ziegler, A.; Gerber, G.; Sina, M.; Gorg, T.; Mayer, H.; Hebebrand, J. *J. Clin. Endocrinol. Metab.* **1999**, *84*, 1483; (h) Huszar, D.; Lynch, C. A.; Fairchild-Huntress, V.; Dunmore, J. H.; Fang, Q.; Berkemeier, L. R.; Gu, W.; Kesterson, R. A.; Boston, B. A.; Cone, R. D.; Smith, F. J.; Campfield, L. A.; Burn, P.; Lee, F. *Cell* **1997**, *88*, 131; (i) Fan, W.; Boston, B. A.; Kesterson, R. A.; Hruby, V. J.; Cone, R. D. *Nature* **1997**, *385*, 165.
2. (a) Ujjainwalla, F.; Sebhat, I. K. *Curr. Top. Med. Chem.* **2007**, *7*, 1068; (b) Sebhat, I. K.; Lai, Y.; Barakat, K.; Ye, Z.; Tang, R.; Kalyani, R. N.; Vongs, A.; MacNeil, T.; Weinberg, D. H.; Cabello, M. A.; Maroto, M.; Teran, A.; Fong, T. M.; Van der Ploeg, L. H. T.; Patchett, A. A.; Nargund, R. P. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5720; (c) Ye, Z.; Guo, L.; Barakat, K. J.; Pollard, P. G.; Palucki, B. L.; Sebhat, I. K.; Bakshi, R. K.; Tang, R.; Kalyani, R. N.; Vongs, A.; Chen, A. S.; Chen, H. Y.; Rosenblum, C. I.; MacNeil, T.; Weinberg, D. H.; Peng, Q.; Tamvakopoulos, C.; Miller, R. R.; Stearns, R. A.; Cashen, D. E.; Martin, W. J.; Metzger, J. M.; Strack, A. M.; MacIntyre, D. E.; Van der Ploeg, L. H. T.; Patchett, A. A.; Wyvratt, M. J.; Nargund, R. P. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3501; (d) Ujjainwalla, F.; Warner, D.; Snedden, C.; Grisson, R. D.; Walsh, T. F.; Wyvratt, M. J.; Kalyani, R. N.; Mac Neil, T.; Tang, R.; Weinberg, D. H.; Van der Ploeg, L.; Goulet, M. T. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4023; (e) Pan, K.; Scott, M. K.; Lee, D. H. S.; Fitzpatrick, L. J.; Crooke, J. J.; Rivero, R. A.; Rosenthal, D. I.; Vaidya, A. H.; Zhao, B.; Reitz, A. B. *Bioorg. Med. Chem.* **2003**, *11*, 185; (f) Sebhat, I. K.; Martin, W. J.; Ye, Z.; Barakat, K.; Mosley, R. T.; Johnston, D. B. R.; Bakshi, R.; Palucki, B.; Weinberg, D. H.; MacNeil, T.; Kalyani, R. N.; Tang, R.; Sterns, R. A.; Miller, R.; Tamvakopoulos, C.; Strack, A.; McGowan, E.; Cashen, D. E.; Drisko, J. E.; Hom, G. J.; Howard, A. D.; MacIntyre, D. E.; Van der Ploeg, L. H. T.; Patchett, A. A.; Nargund, R. A. *J. Med. Chem.* **2002**, *45*, 4589.
3. (a) Guo, L.; Ye, Z.; Ujjainwalla, F.; Sings, H. L.; Sebhat, I. K.; Huber, J.; Weinberg, D. H.; Tang, R.; MacNeil, T.; Tamvakopoulos, C.; Peng, Q.; MacIntyre, E.; van der Ploeg, L. H. T.; Goulet, M. T.; Wyvratt, M. J.; Nargund, R. P. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3242; (b) Ujjainwalla, F. Presented at the *230th National Meeting of American Chemical Society*, Washington, DC, August 2005; paper MEDI-275.
4. (a) Guo, L. et al. unpublished results.; (b) He, S.; Ye, Z.; Dobbelaar, P. H.; Sebhat, I. K.; Guo, L.; Liu, J.; Jian, T.; Lai, Y.; Franklin, C. L.; Bakshi, B. K.; Dellureficio, J. P.; Hong, Q.; Tsou, N. N.; Ball, R. G.; Sashen, E. E.; Martin, W. J.; Weinberg, D. H.; MacNeil, T.; Tang, T.; Tamvakopoulos, C.; Peng, Q.; Miller, R. R.; Stearns, R. A.; Chen, H. Y.; Chen, A. S.; Strack, A. M.; Fong, T. M.; MacIntyre, D. E.; Wyvratt, M. J.; Nargund, R. P. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2106.
5. The supplementary crystallographic data for compound **8A** has been deposited with The Cambridge Crystallographic Data Centre as CCDC 780119. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
6. (a) Chung, J. Y. L.; Cvetovich, R.; Amato, J.; McWilliams, J. C.; Reamer, R.; DiMichele, L. *J. Org. Chem.* **2005**, *70*, 3592; (b) Compound **12** was provided by Merck process research labs and synthesized in a similar way as shown in Scheme 3 and literature **6a**, in which benzyl amine was used in the first step, and hydrogenation and Boc formation were involved at the end of synthesis.
7. (a) MC4R binding IC_{50} was defined as the concentration of compound that can inhibit binding of [^{125}I]-NDP-α-MSH by 50% from membranes prepared from CHO cells expressing human MC4R. Agonist potency was determined in cAMP release assays using CHO cells expressing the relevant receptors. MC4R cAMP EC_{50} was defined as the inflection point of the cAMP dose–response curve for any given compounds. Maxi percentage activation [%Max] is the percentage of cAMP accumulation at 10 μM of compound relative to α-MSH; (b) for details about assay protocols see: (i) Bednarek, M. A.; MacNeil, T.; Kalyani, R. N.; Tang, R.; Van der Ploeg, L. H. T.; Weinberg, D. H. *J. Med. Chem.* **2001**, *44*, 3665; (ii) Bednarek, M. A.; Silva, M. V.; Arison, B.; MacNeil, T.; Kalyani, R. N.; Huang, R. R. C.; Weinberg, D. H. *Peptides* **1999**, *20*, 401.
8. Miller, R. R. et al., unpublished results.
9. Strack, A. et al., unpublished results.