Bioorganic & Medicinal Chemistry Letters 20 (2010) 4399–4405

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Spiroindane based amides as potent and selective MC4R agonists for the treatment of obesity

Shuwen He [a,*], Zhixiong Ye [a], Peter H. Dobbelaar [a], Iyassu K. Sebhat [a], Liangqin Guo [a], Jian Liu [a], Tianying Jian [a], Yingjie Lai [a], Christopher L. Franklin [a], Raman K. Bakshi [a], James P. Dellureficio [a], Qingmei Hong [a], David H. Weinberg [b], Tanya MacNeil [b], Rui Tang [b], Alison M. Strack [c], Constantin Tamvakopoulos [d], Qianping Peng [d], Randy R. Miller [d], Ralph A. Stearns [d], Howard Y. Chen [b], Airu S. Chen [b], Tung M. Fong [b], Matthew J. Wyvratt Jr. [a], Ravi P. Nargund [a]

[a] Department of Medicinal Chemistry, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065, USA
[b] Department of Metabolic Disorders, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065, USA
[c] Department of Pharmacology, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065, USA
[d] Department of Drug Metabolism, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065, USA

ARTICLE INFO

Article history:
Received 1 May 2010
Revised 5 June 2010
Accepted 10 June 2010
Available online 15 June 2010

Keywords:
Spiroindane
Amide
Privileged structure
Melanocortin subtype-4 receptor
MC4R
Agonist
MK-0489
Obesity

ABSTRACT

We report a series of potent and selective MC4R agonists based on spiroindane amide privileged structures for potential treatments of obesity. Among the synthetic methods used, Method C allows rapid synthesis of the analogs. The series of compounds can afford high potency on MC4R as well as good rodent pharmacokinetic profiles. Compound **1r** (MK-0489) demonstrates MC4R mediated reduction of food intake and body weight in mouse models. Compound **1r** is efficacious in 14-day diet-induced obese (DIO) rat models.

Obesity has become a major health problem throughout the world, especially in urbanized societies. The associated morbidities, such as type 2 diabetes, cardiovascular diseases, hypertension, and certain types of cancers, further exacerbate the problem.[1] Finally, the World Health Organization (WHO) officially declared obesity a disease in 1998.[2] This means that obesity is no longer considered as a cosmetic issue, but rather a disease condition requiring medical interventions. The drugs currently available to patients suffer from variable efficacy and undesirable side effects. Therefore, there are significant unmet medical needs for the treatment of obesity.[3]

The melanocortin receptors with five subtypes (MC1R–MC5R) are a family of seven-transmembrane G-protein coupled receptors (GPCR's). The endogenous peptides derived from tissue-specific post-translational processing of proopiomelanocortin (POMC) interact with the melanocortin receptors to regulate a wide range of biological effects, including feeding behavior and body weight homeostasis, skin pigmentation, steroid production, sexual behaviors, and exocrine gland secretion.[4]

The melanocortin subtype-4 receptor (MC4R) is primarily expressed in the brain. The evidence on its involvement in energy balance and feeding behaviors is compelling. In human and mice, loss-of-function mutations of *MC4R* genes are associated with hyperphagia, obesity and metabolic defects.[5] Some studies suggest that MC4R is also involved in regulating reproductive function.[6] With these strong validations, MC4R has emerged as an attractive target against obesity as well as sexual dysfunction.

There have been intense efforts from our laboratories and other research groups to identify selective small molecule MC4R agonists.[7,8] Recently, we disclosed spiroindane based acetyl amide compounds **1r** and **1s** (Fig. 1).[7h,9] **1r** (also known as MK-0489) is a potent and selective MC4R agonist with excellent pharmacokinetics profiles in pre-clinical species. It shows excellent pro-erectile activity in a mouse model. In this letter, we will discuss our continued explorations in this spiroindane amide privileged structure series, focusing on obesity as a possible indication.

* Corresponding author. Tel.: +1 732 594 0881; fax: +1 732 594 3007.
E-mail address: shuwen_he@merck.com (S. He).

0960-894X/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2010.06.062

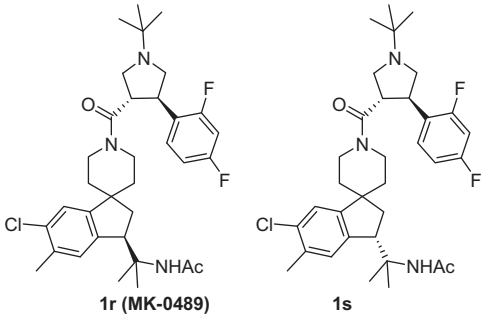


Figure 1. Structures of MK-0489 and its diastereomer **1s**.

Initially, we prepared **4r** and **4s**, *N*-methyl analogs of **1r** and **1s**, from known **2r** and **2s** (Scheme 1).[7h] Both **4r** and **4s** maintained the potency on MC4R in the binding and functional assays (Table 1).[10] They have comparable selectivity against MC1bR, which is an isoform of MC1R involved in regulating skin and hair color. Agonism of MC1bR can lead to undesirable darkness of skin.[11] Furthermore, we were encouraged to find that **4r** had good pharmacokinetic profiles in rat, with a half life of 15.1 h and good oral bioavailability (22%) (Table 2).

To improve the potency on MC4R, we further explored a series with reverse amide privileged structures (Fig. 2). The first few analogs in this series were prepared from racemic acid **7**, available from the selective chlorination of known acid **6**,[7h] exemplified by the preparation of di-methyl amide analogs (Method A, Scheme 2). The racemic amide **8** was resolved by chiral HPLC to give enantiomers **8r** and **8s**. Each enantiomer was then coupled with the acid **5** to give the analogs **9r** and **9s**.[12] With Method A, each privileged structure required a chiral resolution in order to prepare a pair of final analogs.

The reverse amide analog **9s** had subnanomolar activity on MC4R and good selectivity against MC1bR, while its diasteromer **9r** was much less potent on MC4R (Table 3). In contrast, in the original acetyl amide series, **1r** and **4r** were as potent as their corresponding diastereomers **1s** and **4s** (Table 1).

To avoid resolving each privileged structure, we synthesized the enantiomeric pure acids **7r** and **7s** (Scheme 3). The corresponding racemic methyl ester **10** was resolved by chiral HPLC. Each enantiomerically pure ester was then hydrolyzed to provide the acids **7r** and **7s**. To establish their stereochemistry, we correlated the acid with the acetyl amide, whose stereochemistry was determined

Table 1
In vitro activities of **4r** and **4s** compared with **1r** and **1s**[a]

	Human MC4R binding IC_{50} (nM)	Human MC4R functional EC_{50} (nM) (% activation)	Human MC1bR functional EC_{50} (nM) (% activation)
1r	13	4.6 (109%)	1020 (25%)
1s	4.5	3.3 (90%)	260 (43%)
4r	8.5	2.1 (112%)	494 (35%)
4s	2.5	4.3 (83%)	270 (41%)

[a]Data are averages of at least three repeated measurements

Table 2
Rat pharmacokinetic data for **4r**[a]

PK parameter	Rat[a]
F (%)	22
Cl (mL min^{-1} kg^{-1})	9.1
V_{dss} (L kg^{-1})	10.4
$t_{1/2}$ (h)	15.1
AUCn (μM h/mpk)	0.83

[a] Compound dosed in Sprague–Dawley rats as a solution in EtOH/PEG400/water (10:40:50) at 1 mg/kg, iv and 4 mg/kg, po.

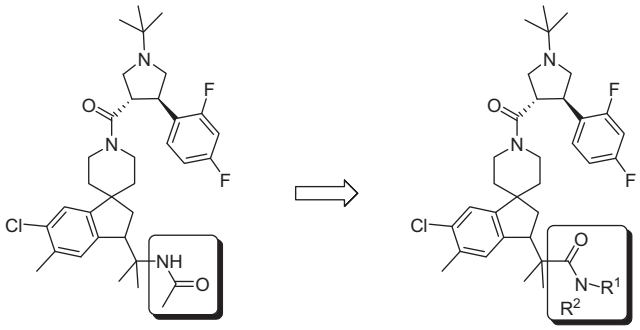
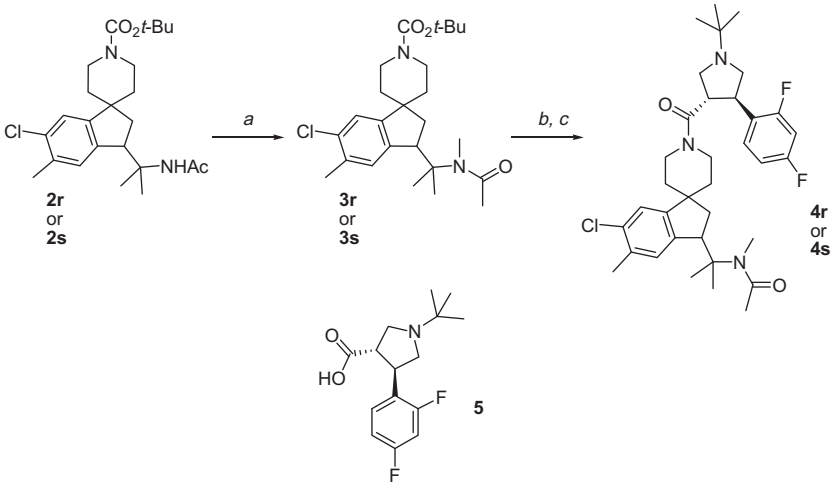


Figure 2. Reverse amide design.

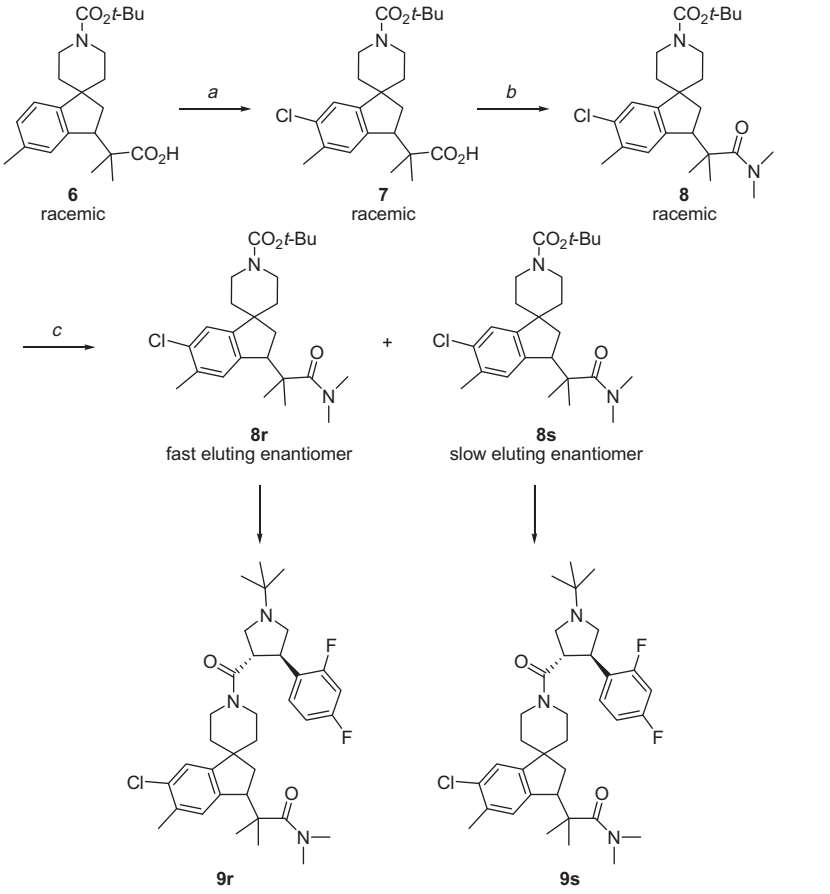
Table 3
In vitro activities of **9r** and **9s**[a]

	Human MC4R binding IC_{50} (nM)	Human MC4R functional EC_{50} (nM) (% activation)	Human MC1bR functional EC_{50} (nM) (% activation)
9r	59	53 (80%)	5000 (17%)
9s	0.71	0.87 (108%)	255 (92%)

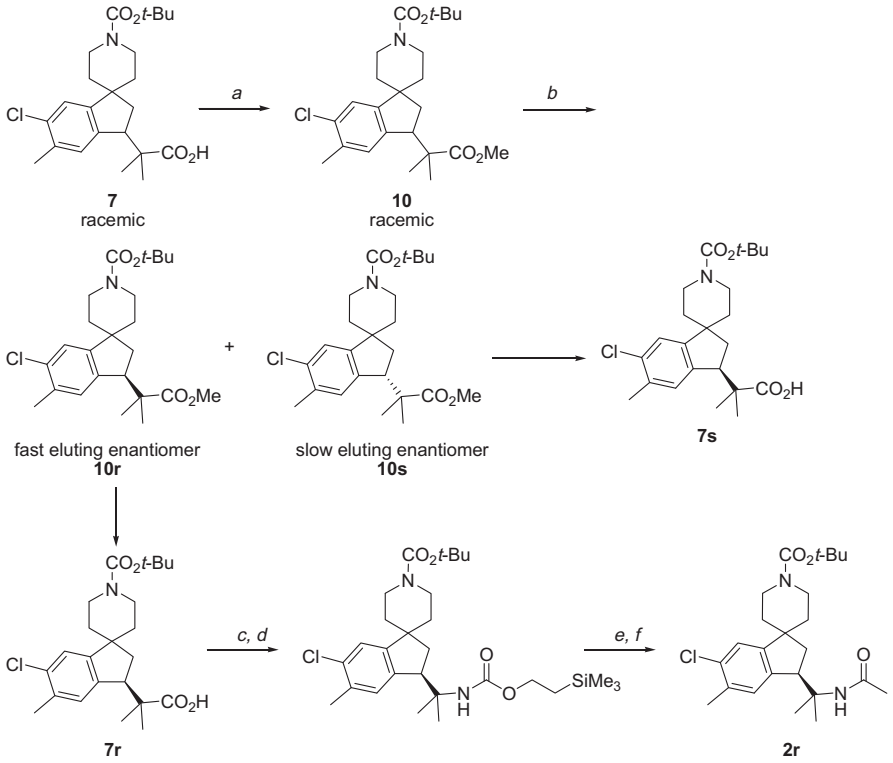
[a] Data are averages of at least three repeated measurements.



Scheme 1. Reagents: (a) KHMDS, MeI, THF; (b) 4 M HCl in dioxane; (c) acid **5**, HATU, HOAt, NMM, CH_2Cl_2.

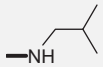
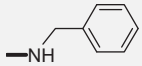
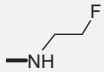
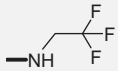
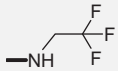
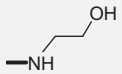
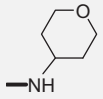
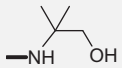


Scheme 2. Preparation of amide analogs: Method A (exemplified by the preparation of **9r** and **9s**). Reagents and conditions: (a) *N*-chlorosuccinimide, DMF, 50 °C; (b) $(COCl)_2$, DMF (cat.), CH_2Cl_2, 0 °C; (c) $NHMe_2$ (2 M in THF), 0 °C to rt; (d) chiral AD column, EtOH–heptane; (e) acid **5**, HATU, HOAt, NMM, CH_2Cl_2.



Scheme 3. Preparation of enantiomerically pure acid **7r** and **7s** and determination of their configurations. Reagents and conditions: (a) $TMSCHN_2$, MeOH; (b) chiral AD column, EtOH–heptane; (c) DPPA, Et_3N, toluene, reflux; (d) $HOCH_2CH_2SiMe_3$, reflux; (e) TBAF, THF, 50 °C; (f) CH_3COCl, Et_3N, CH_2Cl_2.

Table 4
Potency of secondary amide analogs on human MC4R and MC1bR

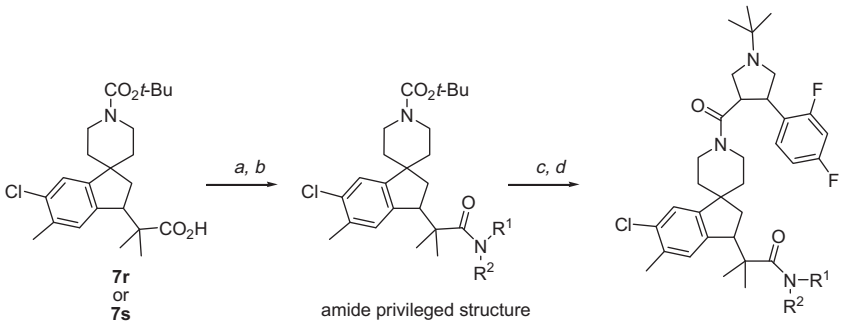
Compound	NHR	Preparation method	hMC4R binding IC_{50}, nM[a]	hMC4R agonism EC_{50}, nM (% activation)[a]	hMC1bR agonism EC_{50}, nM (% activation)[a]
13r		A	47	12 (86%)	1375 (38%)
13s		A	2.6	0.91 (94%)	323 (60%)
14r		A	53	32 (96%)	1417 (26%)
14s		A	3.1	1.4 (100%)	295 (50%)
15r		B	55	28 (95%)	1115 (20%)
15s		B	2.2	0.80 (95%)	243 (50%)
16s		C	5.9	2.9 (92%)	435 (45%)
17s		C	12	9.9 (76%)	1033 (47%)
18s		C	6.6	27(92%)	2050 (45%)
19s		C	12	42 (79%)	935(29%)
20s		C	2.6	1.1 (84%)	260 (48%)
21r		B	93	307 (78%)	ND[b] (5%)
21s		B	5.4	4.2 (89%)	838 (30%)
22s		C	2.6	1.3 (100%)	83 (56%)
23s		C	2.5	2.3 (92%)	260 (74%)
24s		C	3.9	1.9 (89%)	218 (53%)

[a] The reported data are the average of at least three repeated experiments.
[b] Not determined.

previously.[7h] Curtis rearrangement of acid **7r** gave an isocyanate intermediate, which was trapped with trimethylsilyl ethanol. The Teoc protecting group was removed to give the amine, which was acylated to give the acetyl amide. This sample had a chiral HPLC retention time identical to that of the enantiomerically pure amide **2r**, but different from that of amide **2s**. Therefore, **7r** and **2r** had the same configuration, so did **7s** and **2s**. Through this effort, enantiomerically pure acids **7r** and **7s** were obtained with the stereochemistry firmly established.

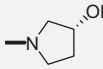
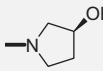
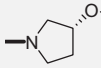
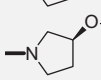
To determine the stereochemistry of the analogs prepared by Method A (Scheme 2), we repeated the synthesis of the amide privileged structures from the enantiomerically pure **7r** and/or **7s**. By comparing the amides with the amides previously prepared from racemic acid by chiral HPLC, we established the stereochemistry of all analogs prepared by Method A.

From **7r** and **7s**, we prepared more analogs according to Method B (Scheme 4). This method required isolation of the amide privileged structure prior to coupling with acid **5**. The

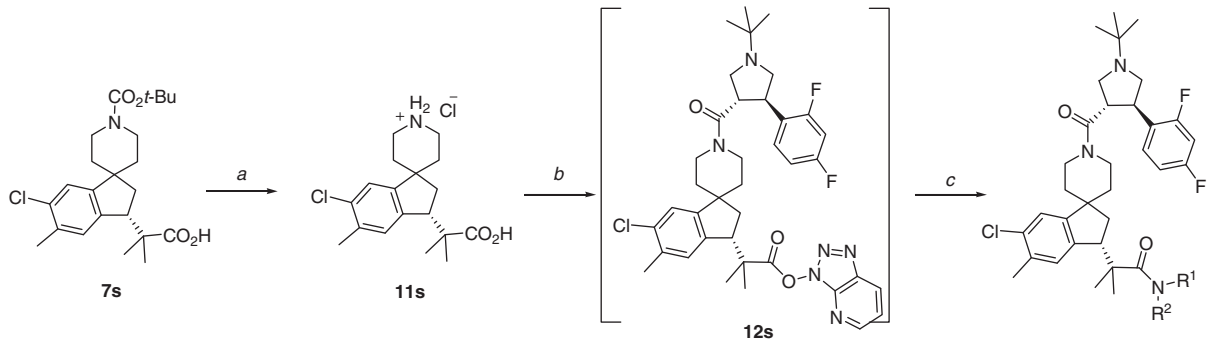


Scheme 4. Preparation of amide analogs: Method B. Reagents and conditions: (a) $(COCl)_2$, DMF (cat.), CH_2Cl_2, 0 °C; (b) NHR^1R^2, 0 °C to rt; (c) 4 M HCl in dioxane; (d) acid **5**, HATU, HOAt, NMM, CH_2Cl_2.

Table 5
The potency of tertiary amide analogs on human MC4R and MC1bR

Compound	NR^1R^2	Synthetic method	hMC4R binding IC_{50}, nM[a]	hMC4R agonism EC_{50}, nM (% activation)[a]	hMC1bR agonism EC_{50}, nM (% activation)[a]
9r		A	59	53 (80%)	5000 (17%)
9s		A	0.71	0.87 (108%)	255 (92%)
25s		C	2.1	1.6 (103%)	355 (69%)
26s		C	2.6	1.7(81%)	168 (67%)
27s		C	1.1	0.59 (88%)	238 (72%)
28s		C	1.8	4.3 (78%)	430 (46%)
29s		C	0.85	0.38 (94%)	84 (66%)
30s		C	1.6	0.76(96%)	69 (72%)
31s		C	1.8	1.0 (73%)	223 (60%)
32s		C	1.6	1.1 (87%)	122 (69%)
33s		C	1.4	0.98 (106%)	203 (68%)
34s		C	2.0	3.8 (96%)	285 (54%)
35s		C	0.53	0.25 (98%)	33 (71%)
36s		C	0.89	0.37 (88%)	29 (93%)
37s		C	1.4	0.69 (111%)	103 (67%)
38s		C	2.3	1.2 (112%)	102 (71%)

[a] The reported data are the average of at least three repeated experiments.



Scheme 5. Preparation of amides analog: Method C. Reagents: (a) 4 M HCl in dioxane; (b) acid **5**, HATU, HOAt, NMM, DMF; (c) amine HNR^1R^2.

Table 6
Pharmacokinetic data for **9s** and **28s**[a]

PK parameter	9s	28s
F (%)	24	29
Cl (mL min^{-1} kg^{-1})	17.2	21.8
V_{dss} (L kg^{-1})	6.95	8.88
$t_{1/2}$ (h)	5.14	7.3
AUCn (μM h/mpk)	0.39	0.35

[a]Compound dosed in Sprague–Dawley rats as a solution in EtOH/PEG400/water (10:40:50) at 1 mg/kg, iv and 4 mg/kg, po.

data of the analogs made by this method will be summarized in Tables 4 and 5.

Finally, we developed a unique and convenient method to prepare a library of analogs efficiently (Scheme 5, Method C). In contrast to Methods A and B, Method C was a one-pot procedure from the acid to the final analog without isolation of any intermediate.[13] Routine de-Boc with HCl gave the corresponding HCl salt **11s**, which was then treated with acid **5**, HOAt (3 equiv) and HATU. Flanked by the *gem*-dimethyl groups, the acid group in **11s** was much more hindered sterically than the acid group in compound **5**. With no dimerization of **11s** observed, piperidine nitrogen in **11s** was acylated by acid **5** to give intermediate **12s**, where the *gem*-dimethyl acid group was terminated by formation of HOAt ester. This activated ester, upon treatment of an amine, formed the amide bond to give the analog.[13] Using Method C, we prepared the library rapidly. The analogs are listed together with others prepared by Methods A and B.

Tables 4 and 5 summarize MC4R and MC1bR activities of the analogs with this reverse amide design. Table 4 includes the compounds with secondary amides, while Table 5 covers the tertiary amides. Consistent with the data for **9s** and **9r** described earlier (Table 3), each analog with S configuration is more potent than its R diastereomer on MC4R. In the secondary amide S configuration series (Table 4), bulkier amides (*tert*-butyl and benzyl in **17s** and **19s**) reduce MC4R potency while incorporation of oxygen atom (**23s** and **24s**) tends to restore the potency. The tertiary amide analogs (Table 5) are generally more potent that the secondary amide analogs on MC4R. Small alkyl amides offer good potency (**9s**, **25s**, **26s**, and **27s**). For the pyrrolidine amide analogs, mono fluoro (**32s**) has indistinguishable MC4R potency compared with the parent (**31s**) while incorporation of di-fluoro (**34s**) has reduced potency. Substitution by an oxygen atom is well tolerated (e.g., **29s** and **30s**). Two pyrrolidinol analogs (**35s** and **36s**) are equally potent. Methylation of the alcohol slightly reduces the potency (**37s** and **38s**). Many analogs are extremely potent on MC4R with subnanomolar potency. However, their activities on MC1bR also increase although most of them maintain an EC_{50} ratio of v.s. MC4R greater than 100.

Two additional compounds (**9s** and **28s**) were also tested in rat PK. Both compounds had good oral bioavailability and reasonable half life in rat (Table 6).

Finally, **1r** (MK-0489) was evaluated in rodent obesity efficacy models. It was first tested in wild type (WT) v.s. MC4R/3R knock-out (KO) mouse for food intake and body weight change (Fig. 3).[14] Compared with vehicle, after oral dosing of **1r** at 10 mg/kg, significant reduction of food intake and body weight was observed in WT mice but not in KO mice. Since **1r** was much less active on MC3R than MC4R,[7h,15] we concluded that the observed efficacy was mediated through MC4R. Compound **1r** was also tested in a 14-day diet-induced obese rat model (Fig. 4). In this study, **1r** was dosed orally to rats at 2, 6, 20 mpk twice a day. **Control 1** (10 mpk, twice a day)[16] and **control 2** (dexfenfluramine, 3 mpk once a day) were dosed orally as positive controls. The body weight of the rat was recorded daily. Compound **1r** dosed at 6 mpk had

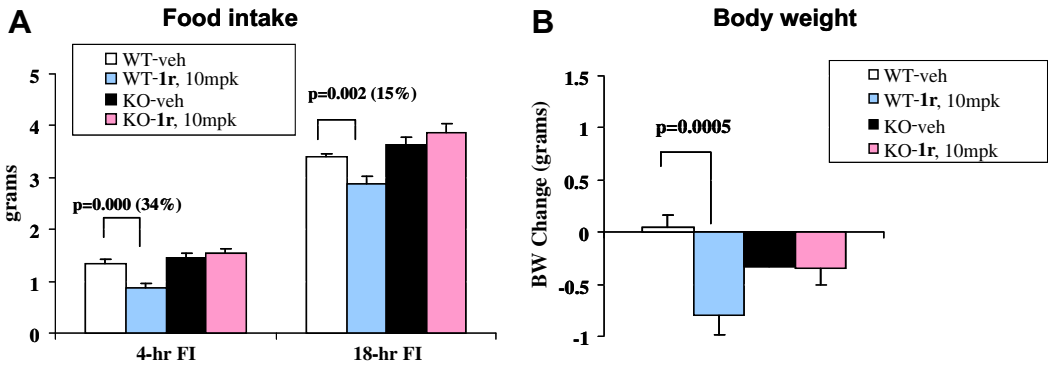


Figure 3. Food intake (FI) and body weight (BW) in wild type mouse and MC4R/3R knock-out mouse after oral dosing of **1r**.

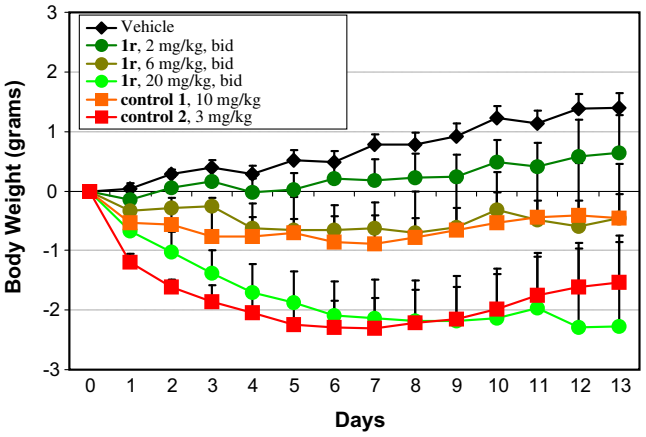


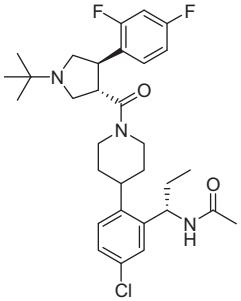
Figure 4. Body weight effect of orally dosed **1r** in diet-induced obese rats.

efficacy similar to **control 1** dosed at 10 mpk. When dosed at 20 mpk twice a day, **1r** afforded efficacy comparable to that of **control 2** dosed at 3 mpk once a day.

In summary, we have described our discovery of potent and selective MC4R agonists in the spiroindane amide privileged structure series. Many potent analogs with *S* stereochemistry on the spiroindane possess subnanomolar in vitro potency on MC4R. Several compounds also show good rodent pharmacokinetics profile. Furthermore, **1r** (MK-0489) demonstrates MC4R mediated efficacy in an acute mouse model of obesity as well as good efficacy in a 14-day DIO rat model. Further interrogation of the SAR of this series is the subject of the following communication.

References and notes

1. Haslam, D. W.; James, W. P. *Lancet* **2005**, *366*, 1197.
2. Obesity: Preventing and Managing the Global Epidemic, Report of a WHO Consultation, World Health Organization, Geneva, 2004.
3. Bays, H. E. *Obes. Res.* **2004**, *12*, 1197.
4. (a) Cone, R. D. *Endocr. Rev.* **2006**, *27*, 736; (b) Gantz, I.; Fong, T. M. *Am. J. Physiol. Endocrinol. Metab.* **2003**, *284*, E468; (c) Yang, Y. K.; Harmon, C. M. *Obes. Rev.* **2003**, *4*, 239.
5. (a) 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; (b) Vaisse, C.; Clement, K.; Guy-Grand, B.; Froguel, P. *Nat. Genet.* **1998**, *20*, 113; (c) Yeo, G. S.; Farooqi, I. S.; Aminian, S.; Halsall, D. J.; Stanhope, R. G.; O'Rahilly, S. *Nat. Genet.* **1998**, *20*, 111.
6. (a) Van der Ploeg, L. H. T.; Martin, W. J.; Howard, A. D.; Nargund, R. P.; Austin, C. P.; Guan, X.; Drisko, J.; Cashen, D.; Sebhat, I.; Patchett, A. A.; Figueroa, D. J.; DiLella, A. G.; Connolly, B. M.; Weinberg, D. H.; Tan, C. P.; Palyha, O. C.; Pong, S.-S.; MacNeil, T.; Rosenblum, C.; Vongs, A.; Tang, R.; Yu, H.; Sailer, A. W.; Fong, T. M.; Huang, C.; Tota, M. R.; Chang, R. S.; Stearns, R.; Tamvakopoulos, C.; Christ, G.; Drazen, D. L.; Spar, B. D.; Nelson, R. J.; MacIntyre, D. E. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 11381; (b) Hadley, M. E. *Peptides* **2005**, *26*, 1687.
7. (a) Nargund, R. P.; Strack, A. M.; Fong, T. M. *J. Med. Chem.* **2006**, *49*, 4035; (b) Ujjainwalla, F.; Sebhat, I. K. *Curr. Top. Med. Chem.* **2007**, *7*, 1068; (c) 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.; Stearns, R. A.; Miller, R. R.; Tamvakopoulos, C.; Strack, A. M.; 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. P. *J. Med. Chem.* **2002**, *45*, 4589; (d) Palucki, B. L.; Park, M. K.; Nargund, R. P.; Ye, Z.; Sebhat, I. K.; Pollard, P. G.; Kalyani, R. N.; Tang, R.; MacNeil, T.; Weinberg, D. H.; Vongs, A.; Rosenblum, C. I.; Doss, G. A.; Miller, R. R.; Stearns, R. A.; Peng, Q.; Tamvakopoulos, C.; McGowan, E.; Martin, W. J.; Metzger, J. M.; Shepherd, C. A.; Strack, A. M.; MacIntyre, D. E.; Van der Ploeg, L. H. T.; Patchett, A. A. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 171; (e) Ujjainwalla, F.; Warner, D.; Snedden, C.; Grisson, R. D.; Walsh, T. F.; Wyvratt, M. J.; Kalyani, R. N.; MacNeil, T.; Tang, R.; Weinberg, D. H.; van der Ploeg, L. H. T.; Goulet, M. T. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4023; (f) Ujjainwalla, F. *Abstracts of Papers*, Presentation (MEDI-275), 230th ACS National Meeting, Washington, DC, August 28–September 1, 2005.; (g) Guo, L.; Ye, Z.; Ujjainwalla, F.; Sings, H.; Sebhat, I. K.; Huber, J.; Weinberg, D. H.; Tang, R.; McNeil, 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; (h) He, S.; Ye, Z.; Dobbelaar, P. H.; Sebhat, I. K.; Guo, L.; Liu, J.; Jian, T.; Lai, Y.; Franklin, C. L.; Bakshi, R. K.; Dellureficio, J. P.; Hong, Q.; Tsou, N. N.; Ball, R. G.; Cashen, D. E.; Martin, W. J.; Weinberg, D. H.; MacNeil, T.; Tang, R.; 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.
8. (a) Tian, X.; Switzer, A. G.; Derose, S. A.; Mishra, R. K.; Solinsky, M. G.; Mumin, R. N.; Ebetino, F. H.; Jayasinghe, L. R.; Webster, M. E.; Colson, A.-O.; Crossdoersen, D.; Pinney, B. B.; Farmer, J. A.; Dowty, M. E.; Obringer, C. M.; Cruze, C. A.; Burklow, M. L.; Suchanek, P. M.; Dong, L.; Dirr, M. K.; Sheldon, R. J.; Wos, J. A. *J. Med. Chem.* **2008**, *51*, 6055; (b) Liu, X. W.; Ma, J.; Colson, A.-O.; Doersen, D. C.; Ebetino, F. H. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1223; (c) Chen, C. *Prog. Med. Chem.* **2007**, *45*, 111; (d) Chen, C.; Jiang, W.; Tran, J. A.; Tucci, F. C.; Fleck, B. A.; Markison, S.; Wen, J.; Madan, A.; Hoare, S. R.; Foster, A. C.; Marinkovic, D.; Chen, C. W.; Arellano, M.; Saunders, J. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 129; (e) Joseph, C. G.; Wilson, K. R.; Wood, M. S.; Sorenson, N. B.; Phan, D. V.; Xiang, Z.; Witek, R. M.; Haskell-Luevano, C. *J. Med. Chem.* **2008**, *51*, 1423; (f) Kuklish, S. L.; Backer, R. T.; Briner, K.; Doecke, C. W.; Husain, S.; Mullaney, J. T.; Ornstein, P. L.; Zgombick, J. M.; O'Brien, T. P.; Fisher, M. F. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3843.
9. In this communication, the lower case **r** or **s** in the compound number designates the *R* or *S* configuration at the stereogenic carbon of the spiroindane.
10. (a) All data are mean values for at least three separate experiments. For a detailed description of the assay protocols, see.; (b) 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; (c) Bednarek, M. A.; Siva, M. V.; Arison, B.; MacNeil, T.; Kalyani, R. N.; Huang, R.-R. C.; Weinberg, D. H. *Peptides* **1999**, *20*, 401.
11. Tan, C. P.; McKee, K. K.; Weinberg, D. H.; MacNeil, T.; Palyha, O. C.; Feighner, S. D.; Hreniuk, D. L.; Van Der Ploeg, L. H. T.; MacNeil, D. J.; Howard, A. D. *FEBS Lett.* **1999**, *451*, 137.
12. We were able to establish the *R*/*S* configuration analog **9r** and **9s** (see discussion later in the text).
13. Experimental details for Method C exemplified by the preparation of **28s**: acid **7s** (60 mg, 0.143 mmol) was dissolved in CH_2Cl_2 (0.5 mL) and treated with 4 M HCl in dioxane (2 mL) at rt. Upon completion of de-Boc, the mixture was concentrated in vacuo. The residue was dissolved in DMF (2 mL) and treated with *N*-methylmorpholine (NMM) (94 μL, 0.858 mmol), followed by HOAt (58 mg, 0.429 mmol), HATU (163 mg, 0.429 mmol) and acid **5** (49 mg, 0.172 mmol). The mixture was stirred overnight at rt. The mixture was then treated with 3,3-difluoroazetidine HCl salt (185 mg, 1.43 mmol) and NMM (314 μL, 2.86 mmol) at rt. Upon completion of reaction, the mixture was purified by reverse HPLC to give the analog **28s**.
14. For a discussion of MC4R/3R knock out mouse, see: Chen, A. S.; Marsh, D. J.; Trumbauer, M. E.; Frazier, E. G.; Guan, X.-M.; Yu, H.; Rosenblum, C. I.; Vongs, A.; Feng, Y.; Cao, L.; Metzger, J. M.; Strack, A. M.; Camacho, R. E.; Mellin, T. N.; Nunes, C. N.; Min, W.; Fisher, J.; Gopal-Truter, S.; MacIntyre, D. E.; Chen, H. Y.; Van der Ploeg, L. H. T. *Nat. Genet.* **2000**, *26*, 97.
15. Compound **1r** has in vitro functional activity of 22 nM (EC_{50}) on mouse MC4R and 1.7 μM (EC_{50}) on mouse MC3R.
16. **Control 1** was discovered previously in our laboratories. Ujjainwalla, F; Sings, H. L. unpublished results.



control 1
hMC4R binding IC_{50} 70 nM
agonism EC_{50} 18 nM
(97% act.)