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Discovery of highly potent and efficacious MC4R agonists with spiroindane *N*-Me-1,2,4-triazole privileged structures for the treatment of obesity

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ABSTRACT

We report an SAR study of MC4R analogs containing spiroindane heterocyclic privileged structures. Compound **26** with *N*-Me-1,2,4-triazole moiety possesses exceptional potency at MC4R and potent anti-obesity efficacy in a mouse model. However, the efficacy is not completely mediated through MC4R. Additional SAR studies led to the discovery of compound **32**, which is more potent at MC4R. Compound **32** demonstrates MC4R mediated anti-obesity efficacy in rodent models.

The melanocortin receptors are a family of seven-transmembrane G-protein coupled receptors (GPCR's) with five subtypes (MC1R–MC5R). The endogenous peptides (melanocortins), derived from common precursor proopiomelanocortin (POMC), interact with the melanocortin receptors to regulate many important physiological functions, including energy homeostasis, skin pigmentation, steroidogenesis, sexual functions, and exocrine gland secretion.[1]

The evidence linking MC4R with energy balance and feeding behaviors is compelling.[2] The agouti mouse which expresses an antagonist of MC1R, MC3R, and MC4R is obese, indicating that blocking the actions of these receptors can lead to obesity. MC4R knockout mice recapitulate the phenotype of the agouti mice, they are hyperphagic and obese. Most convincingly, both non-sense and frame shift variants in *MC4R* gene in humans lead to inherited obesity.

There have been intense efforts from our laboratories and other research groups to identify selective small molecule MC4R agonists.[3,4] Recently, we disclosed the analogs based on spiroindane amide privileged structures as potent and selective MC4R agonists

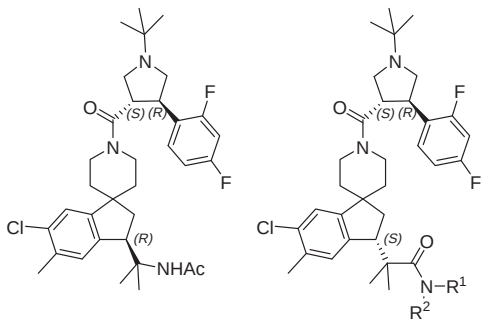

Figure 1. Structures of MK-0489 and the reverse amide analogs.

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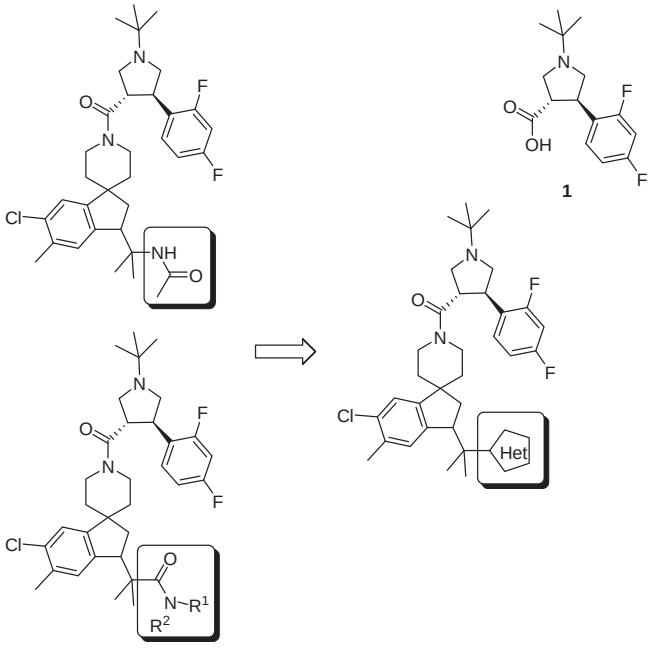


Figure 2. Design of spiroindane heterocyclic privileged structure.

(Fig. 1).[3h,3i] In particular, MK-0489 has excellent pharmacokinetics profiles in pre-clinical species. It shows excellent pro-erectile activity in a mouse model and good efficacy in rodent obesity models. Furthermore, in the reverse amide series, analogs with *S* configuration significantly improve the potency on MC4R. Herein, we describe the replacements of the amide with heterocycles (Fig. 2) and the effects on MC4R activity.

We carried out an SAR study varying heterocycles on the spiroindane privileged structure (Fig. 2), while keeping acid **1** top piece intact.[3f] These heterocyclic privileged structures were synthesized from the corresponding acid or acid equivalents.[3i]

First we prepared the 1,3,4-oxadiazole analogs (Scheme 1). The racemic acid **2** was converted to the acyl hydrazine **3**, which was then cyclized to form 1,3,4-oxadiazole privileged structure **4**. This racemic material was resolved by chiral HPLC to give two enantiomers **4e1** (first peak) and **4e2** (second peak). Boc group on each enantiomer was removed.[5] The resulting amines were coupled with acid **1** to give single compounds **5d1** and **5d2**.[6]

We then synthesized analog **8** with methyl substituted 1,3,4-oxadiazole (Scheme 2). The synthesis began with enantiomerically pure acid **2a** with *S* configuration since previously we showed that reversed amide analogs (Fig. 1) with *S* configuration were much more potent than their *R* isomers.[3i] Acid **2a** was converted to amide **6** tethered with acetyl amide group, which cyclized to give a methyl-1,3,4-oxadiazole intermediate, which was Boc protected

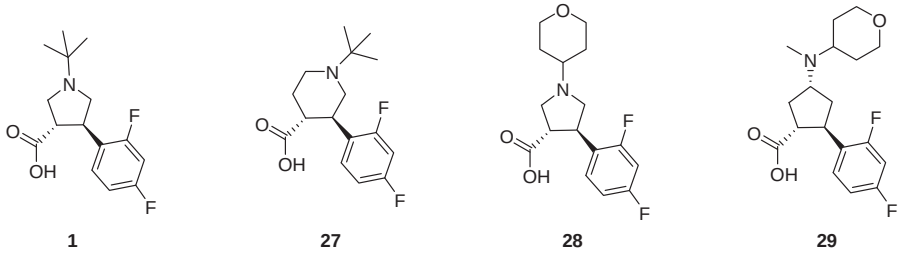
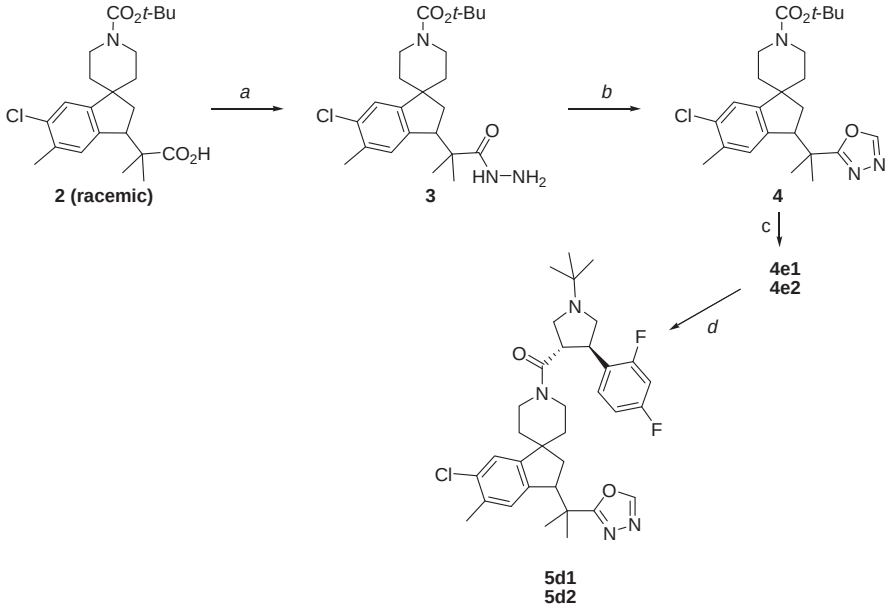
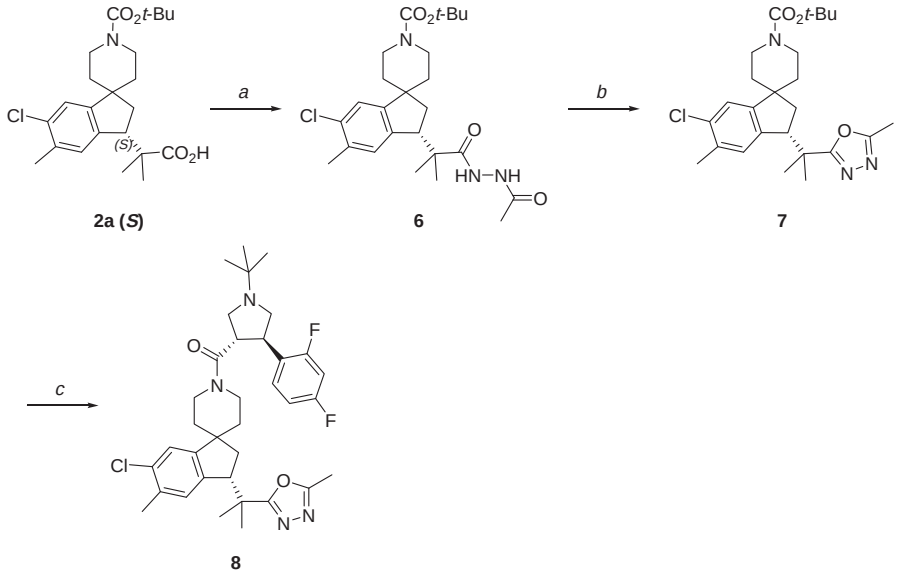


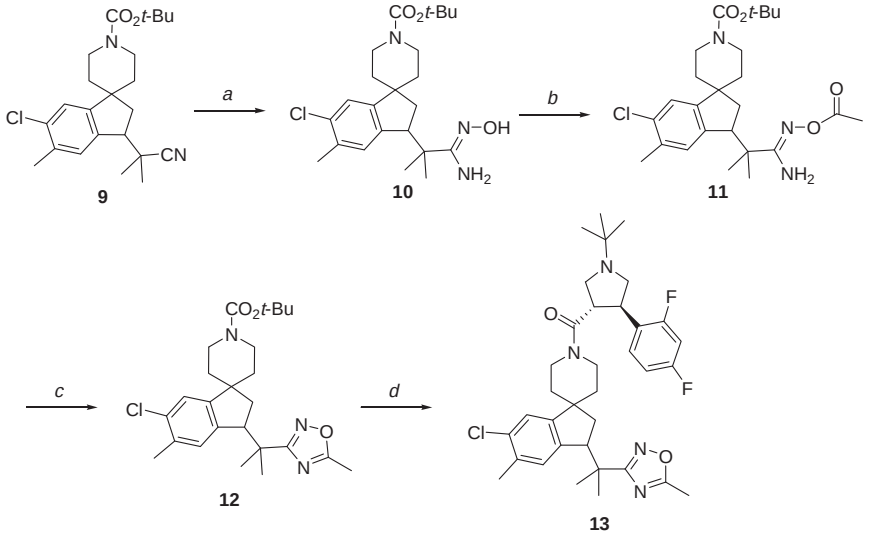
Figure 3. Acid top pieces.



Scheme 1. Preparation of 1,3,4-oxadiazole analog **5d1** and **5d2**. Reagents and conditions: (a) (1) HOAt, EDC, DMF; (2) hydrazine monohydrate; (b) triethyl orthoformate, 155 °C; (c) chiral AS column, 9% 2-propanol in heptane; (d) (1) CAN, MeCN, 100 °C; (2) acid **1**, HATU, HOAt, NMM, CH_2Cl_2.



Scheme 2. Preparation of 1,3,4-oxadiazole analog **8**. Reagents and conditions: (a) (1) HOAt, EDC, DMF; (2) acetylhydrazine; (b) (1) $POCl_3$, 100 °C; (2) NaOH (2 M, aqueous), dioxane, Boc_2O; (c) (1) 4 M HCl in dioxane; (2) acid **1**, HATU, HOAt, NMM, CH_2Cl_2.



Scheme 3. Preparation of 1,2,4-oxadiazole analog **13**. Reagents and conditions: (a) NH_2OH HCl salt, NaOH (5 N, aqueous), EtOH, reflux; (b) acetic acid, diisopropylcarbodiimide, HOBt; (c) TBAF, THF; (d) (1) 4 M HCl in dioxane; (2) acid **1**, HATU, HOAt, NMM, CH_2Cl_2.

to give **7** for the purpose of isolation since the Boc group is unstable under $POCl_3$ cyclization conditions. The privileged structure **7** was then coupled with the acid **1** top piece to give analog **8**.

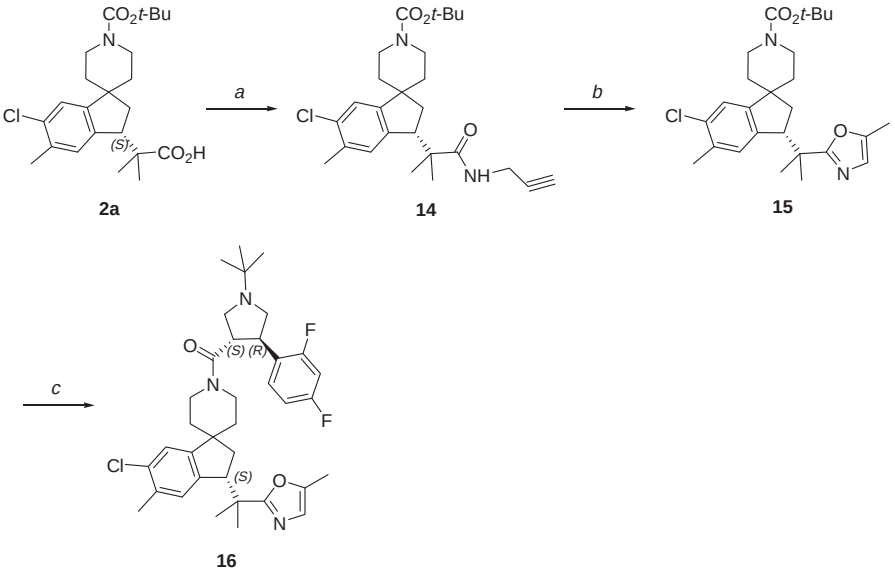
We also prepared analog **13** with 1,2,4-oxadiazole (Scheme 3). Racemic nitrile **9** was converted to amide oxime **10**, which was then acetylated to give intermediate **11**. Upon treating with TBAF, **11** cyclized to give racemic privileged structure **12** with 1,2,4-oxadiazole, which was coupled with acid **1** to analog **13** containing two diastereomeric isomers.

We then synthesized analog **16** with a privileged structure containing oxazole (Scheme 4). Acid **2a** was converted to amide **14**, which underwent $AuCl_3$ catalyzed cyclization to give privileged structure **15**.[7] A routine coupling with acid **1** afforded analog **16**.

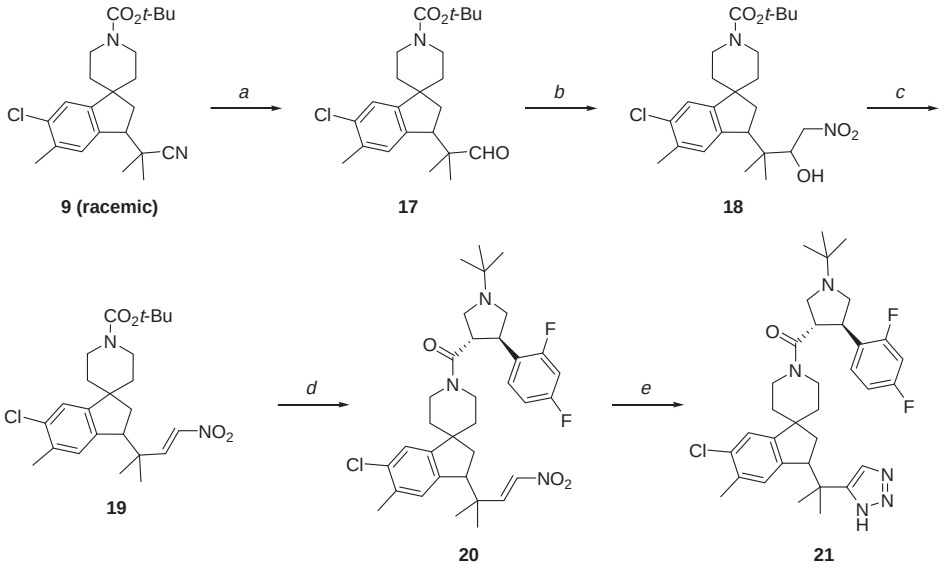
Analog **21** with 1,2,3-triazole was prepared from aldehyde **17** (Scheme 5), which was available from racemic nitrile **9** by DIBAL reduction. Henry reaction of aldehyde **17** with nitromethane followed by dehydration afforded nitroalkene **19**, which was then coupled with acid **1** to give **20**. The nitroalkene moiety was then transformed to 1,2,3,-triazole by treating with sodium azide. Since the starting material nitrile **9** was racemic, analog **21** was a mixture of two diastereomers.

Finally, we prepared analog **26** with *N*-Me-1,2,4-triazole (Scheme 6). Primary amide **22** prepared from acid **2a**, was condensed with *N*,*N*-dimethylformamide dimethyl acetal to give intermediate **23**, which upon treatment of methyl hydrazine give the privileged structure **24**.[8] The other possible regioisomer **25** was formed in negligible amount and was not isolated. Routine coupling of **24** with the acid **1** afforded analog **26**.

The in vitro potency of these analogs on human MC4R versus MC1bR are summarized in Table 1.[9] Agonism of MC1bR, an isoform of MC1R involved in regulating skin and hair color, can lead to undesirable skin darkening.[9d] To our excitement, analog **26** is



Scheme 4. Preparation of oxazole analog **16**. Reagents and conditions: (a) (1) HOAt, EDC, DMF; (2) propargylamine hydrochloride, NMM; (b) $AuCl_3$ (cat.), CH_2Cl_2; (c) (1) 4 M HCl in dioxane; (2) acid **1**, HATU, HOAt, NMM, CH_2Cl_2.

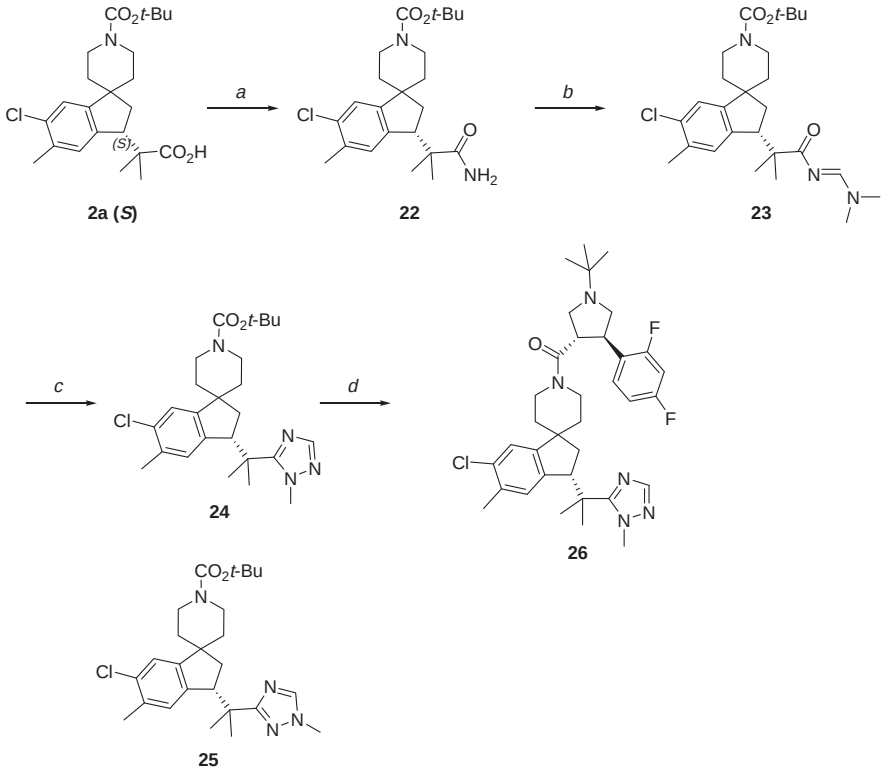


Scheme 5. Preparation of 1,2,3-triazole analog **21**. Reagents and conditions: (a) DIBAL, −78 °C; (b) $MeNO_2$, NaOH (aq, 10 N, 1.5 equiv), EtOH; (c) Et_3N, MsCl, EtOAc; (d) (1) 4 M HCl in dioxane; (2) acid **1**, HATU, HOAt, NMM, CH_2Cl_2; (e) NaN_3, DMSO.

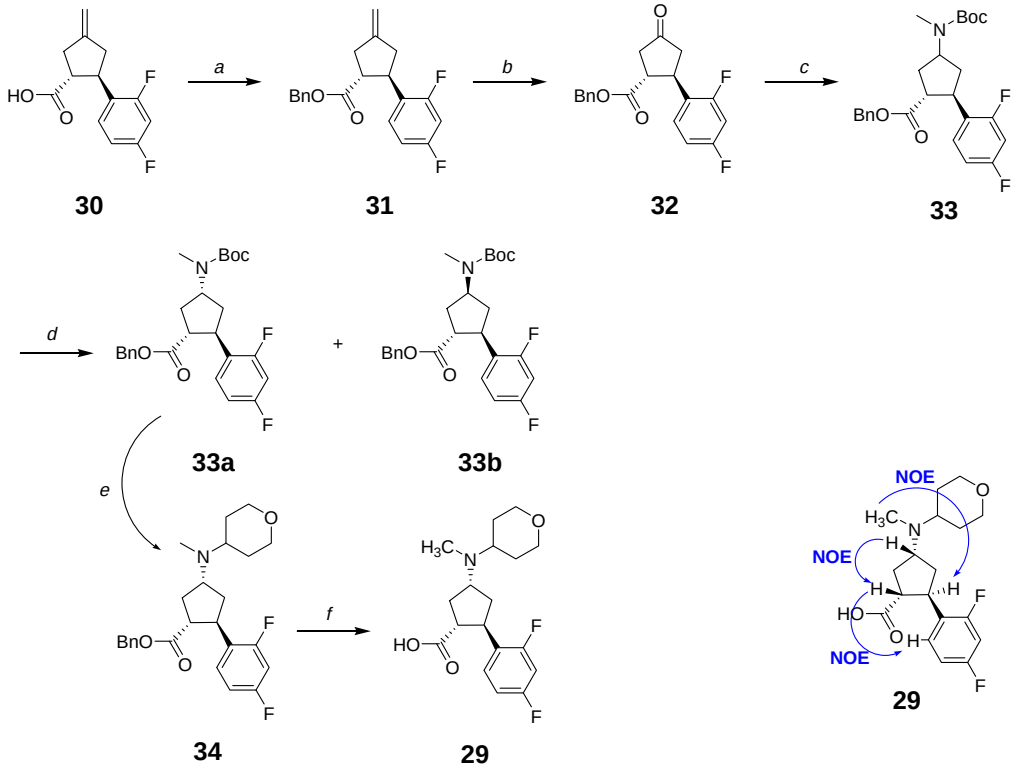
exceptional in that it is more than a magnitude more potent than other analogs! Its rat pharmacokinetics profile is excellent, with a half life of 9.4 h as well as excellent exposure (Table 2). It is also highly efficacious in diet induced obese mouse obesity model. Unfortunately, **26** also lowers food intake and body weight in MC4R/3R double knockout mouse[10] (see Supplementary data). These results indicate that the efficacy observed is not solely mediated through MC4R.

To address this problem, we continued with the SAR study keeping *N*-Me-1,2,4-triazole privileged structure while changing the acid top piece. The structures of the top acid pieces are listed in Figure 3. Acid **27** was previously incorporated in the structure of RY-767, a potent MC4R agonist.[11,12] Acid **28** was independently discovered by us and a Neurocrine group.[13,4e] Acid **29** was originally identified in our laboratories as a MC4R potency enhancing moiety exemplified in some analogs, which nevertheless were diastereomeric mixtures at the stereogenic carbon next to the nitrogen atom on the cyclopentyl ring.[13]

We synthesized the top piece **29** in its pure form from enantiomerically pure alkene acid **30** (Scheme 7). First, alkene acid **30** was protected as the benzyl ester **31**.[14] Then the double bond was cleaved oxidatively to give ketone **32**. Reduction amination with methyl amine followed Boc protection gave intermediate **33** as a 2:1 mixture of two diastereomers, which were separated by chiral HPLC. Deprotection of the major isomer **33a** (also the first peak from chiral HPLC) followed by reductive amination with tetrahydro-4*H*-pyran-4-one installed the tetrahydropyran group. Removal of the Bn group by hydrogenolysis afforded the acid top piece **29** as a homogenous material. The configuration of the newly created stereogenic carbon was determined by NOE studies.

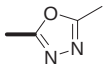
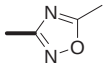
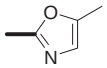


Scheme 6. Preparation of *N*-Me 1,2,4-triazole analog **26**. Reagents and conditions: (a) (1) HOAt, EDC, DMF; (2) concd NH_3 in H_2O; (b) *N*,*N*-dimethylformamide dimethyl acetal, 120 °C; (c) methylhydrazine, HOAc, 90 °C; (d) (1) 4 M HCl in dioxane; (2) acid **1**, HATU, HOAt, NMM, CH_2Cl_2.



Scheme 7. Preparation of acid top piece **29**. Reagents and conditions: (a) BnOCOCl, Et_3N, DAMP (cat.), CH_2Cl_2; (b) $NaIO_4$, OsO_4 (cat.), *t*-BuOH–H_2O; (c) (1) $MeNH_2$ HCl salt, $NaBH(OAc)_3$, Et_3N, molecular sieves, CH_2Cl_2; (2) Boc_2O, Et_3N, NaOH (2 N, aqueous), CH_2Cl_2; (d) chiral OJ column, eluted with 20% 2-propanol in heptane; (e) (1) 4 M HCl in dioxane; (2) tetrahydro-4*H*-pyran-4-one, $NaBH(OAc)_3$, Et_3N, molecular sieves, CH_2Cl_2; (f) Pd/C (cat.), HCl (1 M, aqueous), 2-propanol.

Table 1
Analogs with spiroindane heterocyclic privileged structures: in vitro potency on human MC4R and MC1bR

Compound	Het	hMC4R binding IC_{50}[a] (nM)	hMC4R agonism EC_{50}[a] (nM) (% activation)	hMC1bR agonism EC_{50}[a] (nM) (% activation)
5d1		49	211 (117%)	ND[b] (10%)
5d2		1.3	2.2 (92%)	138 (57%)
8		1.9	2.3 (97%)	1145 (88%)
13[c]		5.7	14 (71%)	855 (46%)
16		9.7	48 (99%)	1650 (57%)
21[c]		16	4.2 (82%)	1040 (31%)
26		0.41	0.23 (106%)	125 (80%)

[a] The reported data are the average of at least three repeated experiments.
[b] Not determined.
[c] A mixture of two diastereomers.

Table 2
Rat pharmacokinetic data for **26**[a]

PK parameter	**26**
F (%)	26
Cl (mL min^{-1} kg^{-1})	6.7
V_{dss} (L kg^{-1})	5.0
$t_{1/2}$ (h)	9.4
AUC_n (μM h/mpk)	1.1

[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.

From acids **27**, **28**, and **29**, we synthesized analogs **30**, **31**, and **32**. Their structures and potency data are listed in Table 3 together with data of analog **26** as a comparison. Compared with analog **26**, piperidine analog **30** is about 5–10-folds less potent on MC4R. Analog **31** has slight loss of MC4R potency. However, analog **32** is more potent than **26** on MC4R while its off-target activity on MC1bR is also diminished.

Analogs **30**, **31**, and **32** were further evaluated in rat pharmacokinetics (Table 4). Analogs **31** and **32** had good pharmacokinetic profiles while analog **30** was outstanding with a long half life (11 h) and excellent bioavailability (86%).

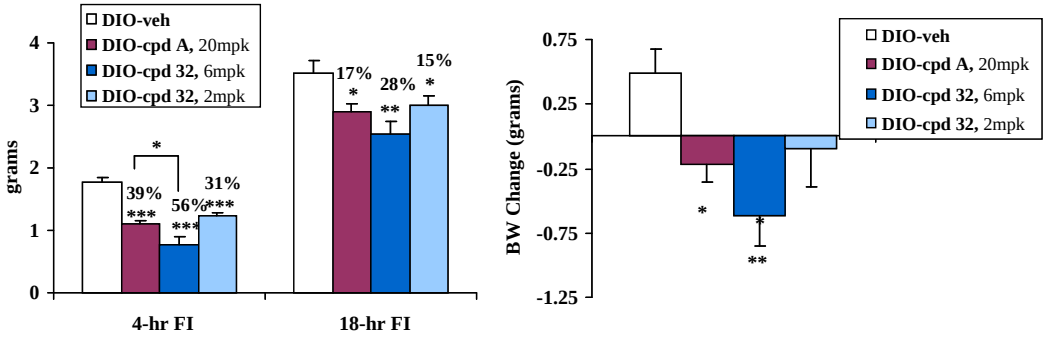


Figure 4. Food intake (FI) and body weight (BW) in DIO mouse after oral dosing of analog **32** (*P <0.05; **P <0.01).

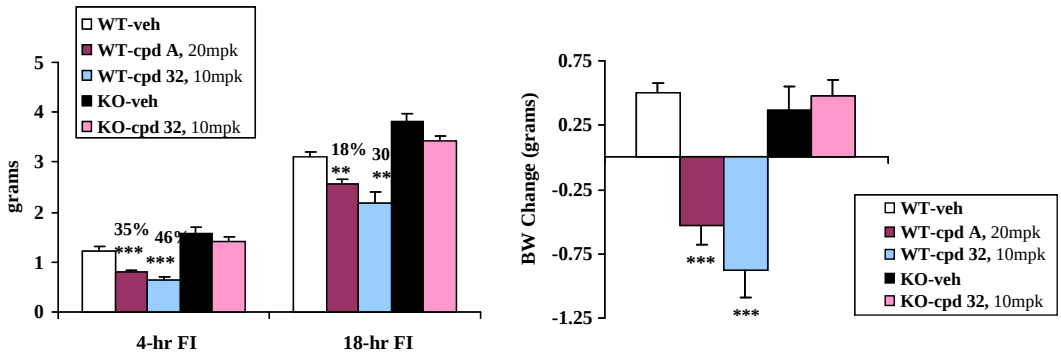


Figure 5. Food intake (FI) and body weight (BW) in wild type (WT) mouse and MC4R/3R knockout (KO) mouse after oral dosing of analog **32** (*P <0.05; **P <0.01).

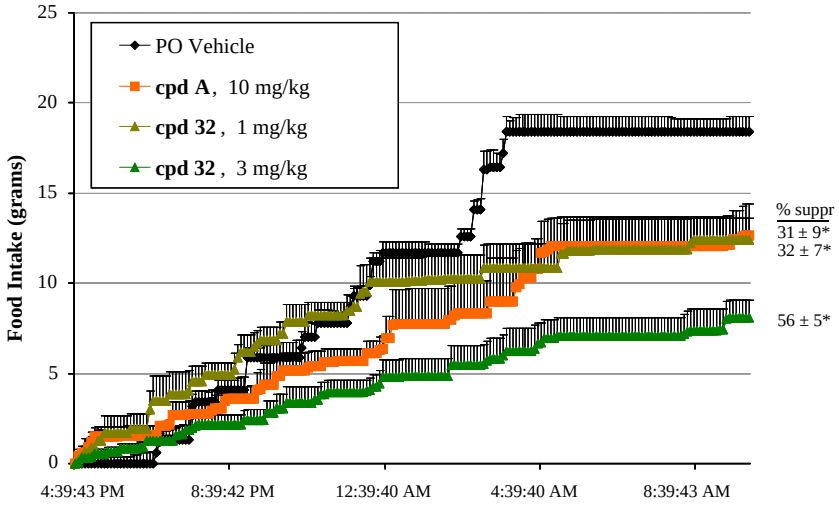


Figure 6. Food intake (FI) in diet induced obese (DIO) rats after oral dosing of analog **32**.

Table 3
Potency of triazole analogs on human MC4R and MC1bR

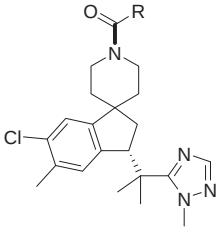
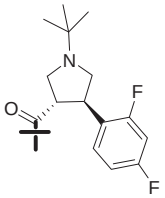
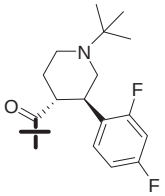
Compound		hMC4R binding IC_{50}[a] (nM)	hMC4R agonism EC_{50}[a] (nM) (% activation)	hMC1b-R agonism EC_{50}[a] nM (% activation)
				
26		0.41	0.23 (106%)	125 (80%)
30		1.7	2.4 (96%)	1050 (37%)

Table 3 (*continued*)

Compound	hMC4R binding IC_{50}[a] (nM)	hMC4R agonism EC_{50}[a] (nM) (% activation)	hMC1b-R agonism EC_{50}[a] nM (% activation)
31	0.84	0.90 (105%)	708 (54%)
32	0.43	0.11 (99%)	250 (49%)

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

Table 4
Rat pharmacokinetic data for **30**, **31**, and **32**[a]

PK parameter	**30**	**31**	**32**
F (%)	86	35	20
Cl (mL min^{-1} kg^{-1})	22	37	24
V_{dss} (L kg^{-1})	19	10	9.7
$t_{1/2}$ (h)	11	3.4	5.1
AUC_n (μM h/mpk)	1.1	0.24	0.20

[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.

These analogs were then tested in DIO mouse obesity model and MC4R/3R double knockout (KO) versus wild type (WT) mouse model. Similar to analog **26**, analog **30** showed excellent efficacy in DIO mice (see Supplementary data for data of analogs **30** and **31**). But it also reduced food intake and body weight in KO mice (see Supplementary data), indicative of non-MC4R mediated effects. Analog **31** had good efficacy in DIO mice. It slightly reduced food intake in MC4R/3R knockout mice by 20% at 4 h time point although the reduction was not statistically significant ($P = 0.056$). We were delighted to find that analog **32** was highly efficacious in the DIO mouse obesity model and that the efficacy was mediated through MC4R. In the DIO mouse study, when dosed orally at 6 mpk and 2 mpk, analog **32** reduced food intake by 56% and 31% at the 4 h time point, followed by 28% and 15% at 18 h time point (Fig. 4). It also lowered body weight significantly. The efficacy of **32** at 2 mpk was similar to that of compound A dosed at 20 mpk.[15] In a KO mouse versus WT mouse study, analog **32** reduced food intake at 4 and 18 h, as well as body weight in WT mice, but not in KO mice (Fig. 5). Therefore, analog **32** demonstrated M4R mediated efficacy in mouse obesity models, resolving the off-target issue associated with analog **26**.[16]

Analog **32** was further tested in a DIO rat obesity model for food intake during 18 h after oral dosing (Fig. 6). Analog **32** reduced food intake by 56% and 32% at 3 mpk and 1 mpk, respectively. The efficacy of analog **32** at 1 mpk was comparable to that of the positive control (compound A) at 10 mpk. Therefore, analog **32** showed potent efficacy in the DIO rat obesity model.

In summary, we have described our SAR study of MC4R agonists in the spiroindane heterocyclic privileged structure series. This work culminates in the identification of *N*-Me-1,2,4-triazole moiety which significantly enhances MC4R in vitro potency. This privileged structure, in combination with an appropriate acid top piece, results in MC4R agonists with excellent efficacy in rodent models of obesity.

Supplementary data

Supplementary data (NMR spectra of privileged structure **24** and efficacy data of analogs **26**, **30**, and **31** in DIO mouse as well as MC4R/3R KO vs WT mouse) associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.09.049.

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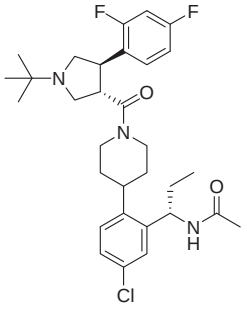

compound A
hMC4R binding IC_{50} 70 nM
agonism EC_{50} 18 nM
(97% act.)

16. Analog **32** is potent on MC3R (hMC3R EC_{50} 7.2 nM, 110% act.). It is highly potent on murine MC4R (mMC4R EC_{50} 0.052 nM, 117% act.). Its potency on murine MC3R was not determined. If we assume the potency is similar to the data on human MC3R, the possible involvement of MC3R in the efficacy observed can not be ruled out completely, although analog **32** is over 100-fold more potent on MC4R than MC3R.