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Identification of novel and orally active spiroindoline NPY Y5 receptor antagonists

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ABSTRACT

A series of spiroindoline-3,4′-piperidine derivatives were synthesized and evaluated for their binding affinities and antagonistic activities at Y5 receptors. Potent Y5 antagonists were tested for their oral bioavailabilities and brain penetration in rats. Some of the antagonists showed good oral bioavailability and/or good brain penetration. In particular, compound **6e** was orally bioavailable and brain penetrant, and oral administration of **6e** inhibited bPP-induced food intake in rats with a minimum effective dose of 10 mg/kg.

Neuropeptide Y (NPY) is a highly conserved C-terminus amidated peptide consisting of 36 amino acid residues which has been shown to have potent, centrally-mediated orexigenic effects.[1–4] NPY is abundant in the central nervous system throughout the cerebral cortex, forebrain, hypothalamus, brain stem and spinal cord. In the periphery, NPY is present in most sympathetic nerve fibers, especially around blood vessels. Reports of NPY activity demonstrate a wide range of potential effects at both central and peripheral targets, acting either alone or in combination with other neurotransmitters such as norepinephrine and glutamate. The effects of the NPY family of peptides are mediated via a family of GPCRs, providing opportunities for subtype selective therapeutics. At least six receptor subtypes of the NPY family have been characterized based on cloning and/or their pharmacological properties.[5–19] Various pharmacological studies, employing receptor deficient mice and/or subtype-selective agonists and antagonists, have suggested that the Y1 and Y5 receptors are involved in body weight regulation.[15,18,20–32] Thus, the antagonism of the Y1 and/or Y5 receptors may have considerable therapeutic benefits for the treatment of obesity.

Various structurally diverse NPY Y5 receptor antagonists have been reported by a variety of research groups including ours.[33–60] We previously reported discovery of potent phenylpiperazine derivatives Y5 antagonists such as **2** by derivatization of an arylpyrazole lead (**1**),[50,59] which was identified by screening of the MRL chemical collection. Further screening efforts identified highly potent spiroindoline leads, exemplified by **3**. The spiroindoline-3,4′-piperidine structure in **3** can be recognized as an isostere of the phenylpiperazine structure in **2**, and this assumption prompted us to undertake further exploration of this moiety. In addition, the potent Y5 binding activity of **3** suggested that the arylpyrazole structure in **2** was not necessary for the Y5 binding activity, which provided further opportunity to adjust DMPK and brain penetration profiles which are usually very important for drug development (see Fig. 1).

Initial SAR exploration of the human NPY Y5 binding affinity[61] was performed using a series of spiroindolines identified as related structures by similarity searching of the MRL compound collection. Subsequently, a small library was made by reaction of amines **4a–r** and isocyanates **5a–t** listed in Figure 2. This effort resulted in additional potent compounds described in Figure 3, suggesting that the spiroindoline is an extremely useful scaffold for Y5 antagonists. Of the compounds, **3e** was particularly attractive since it had good brain penetration and chemical tractability, although it was not

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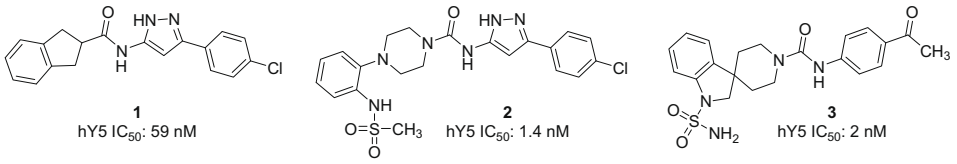


Figure 1. Y5 leads (in vitro data are the average of at least two experiments).

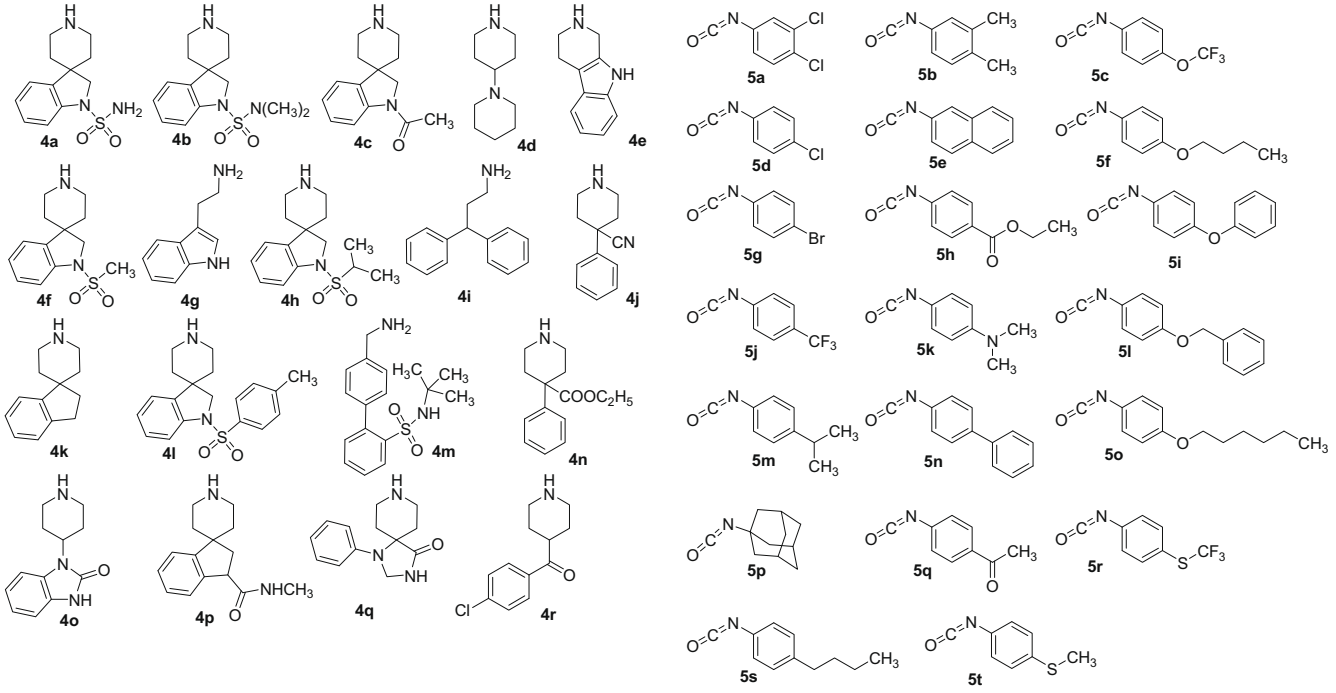


Figure 2. Amines and isocyanates used for the combinatorial library.

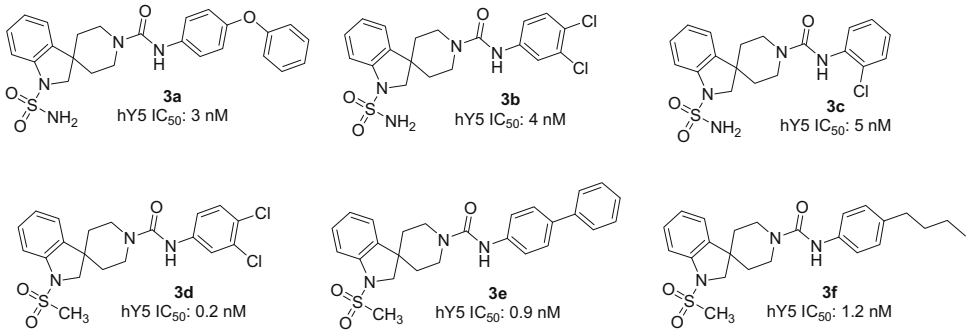
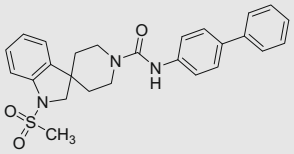
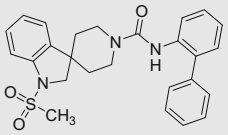
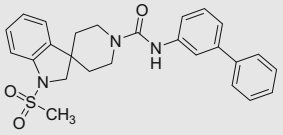
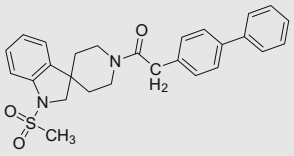
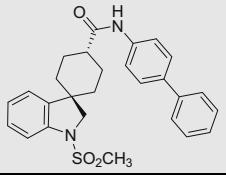


Figure 3. Additional potent Y5 antagonists (in vitro data are the average of at least two experiments).

orally bioavailable (Table 2). To improve the lead **3e**, the next approach focused on replacement of the biphenyl urea portion.

Urea analogs **6a–n** were prepared by reaction of the spiroindoline **4f** with phenylcarbamates derived from the corresponding amines in the presence of triethylamine (Scheme 1). Replacement of the urea linkage with amide surrogate was performed as shown in Scheme 2. Spiroindoline **4f** was reacted with 4-biphenylacetic acid in the presence of water soluble carbodiimide hydrochloride (WSC·HCl) in pyridine to produce 4-biphenylacetamide **7**. Two diastereoisomers of spiro(indoline-3,4′-cyclohexane)-1′-carboxamide, **14a** and **14b**, were prepared as follows. Terephthalic acid monomethyl ester **8** was hydrogenated (50 atm) over 5% Rh/C to afford a cyclohexane derivative **9** as a *cis* and *trans* mixture. The carboxyl group in **9** was reduced by $Me_2S{\cdot}BH_3$ to produce an alcohol **10**, which was subsequently oxidized by PCC to give an aldehyde **11**. The aldehyde **11** was reacted with phenylhydrazine, followed by $NaBH_4$ to give a spiroindoline derivative **12** as a mixture of *cis* and *trans* isomers. Compound **12** was reacted with methylsulfonyl chloride in the presence of Et_3N, followed by separation on silica gel to afford the corresponding *cis* and *trans* isomers **13a** and **13b**. Alkaline hydrolysis of the methyl ester in **13a** and **13b**, followed by condensation with biphenylamine in the presence of WSC·HCl to produce the *cis* and *trans* isomers of spiro(indoline-3,4′-cyclohexane)-1′-carboxamide, **14a** and **14b**.[62]

Table 1
Y5 binding affinities[a]

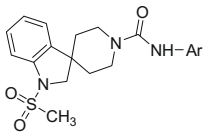
Compounds	Structure	hY5 binding IC_{50} (nM)
3e		0.85
6a		430
6b		1.3
7		180
14a		200
14b		1.5

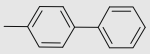
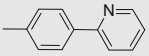
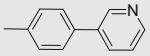
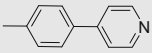
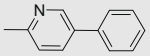
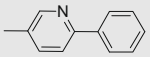
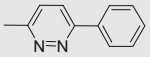
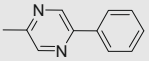
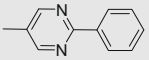
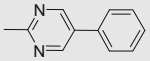
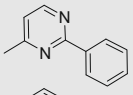
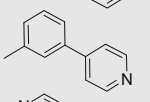
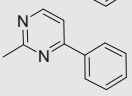
[a] In vitro data in nM are the average of at least two experiments.

Compounds **6a** and **6b** are biphenylamine regioisomers. The *o*-biphenyl urea analog **6a** showed very weak Y5 binding affinity while the *m*-isomer **6b** was as potent as the *p*-isomer **3e**. With regard to the amide analogs, a *trans* isomer of spiro(indoline-3,4′-cyclohexane)-1′-carboxamide **14b** retained Y5 binding affinity while the corresponding *cis* isomer **14a** and 4-biphenylacetamide **7** lost Y5 binding activity (Table 1). Compounds **6b** and **14b** were tested for their bioavailability in rats; however, it turned out they were not orally bioavailable.

Compound **3e** displayed very poor solubility and high lipophilicity (<0.01 μg/mL at pH 1, 3, 5 and 7; log*D* at pH 7.4 > 4). We hypothesized that the high lipophilicity produced poor metabolic stability, and the poor solubility afforded inadequate or slow absorption from GI tract, resulting in poor bioavailability. This hypothesis prompted us to incorporate N atom(s) into the biphenyl region. The analogs were initially tested for their Y5 binding affinities, and potent compounds subsequently were evaluated for their oral bioavailability and/or brain penetrations in rats (Table 2). Introduction of nitrogen atoms into the outer phenyl ring produced *o*-, *m*- and *p*-isomers of pyridyl analogs **6c–e**. While these modifications resulted in a modest decrease in Y5 binding affinities, they were still in the class of potent, low nM Y5 antagonists. Introduction of nitrogen atoms into the inner phenyl ring produced **6f** and **6g** with retention in Y5 binding activities. Since incorporation of a nitrogen atom into inner phenyl ring looked more tolerable in terms of Y5 potency, heteroaromatic rings bearing two nitrogen

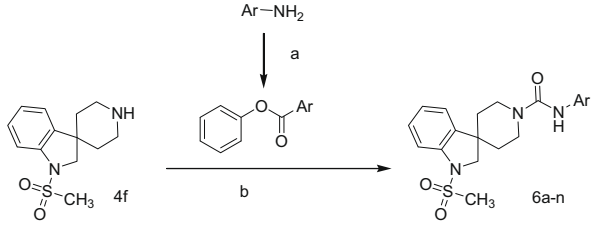
Table 2
Y5 binding affinities and their oral bioavailability/brain penetration data in rats



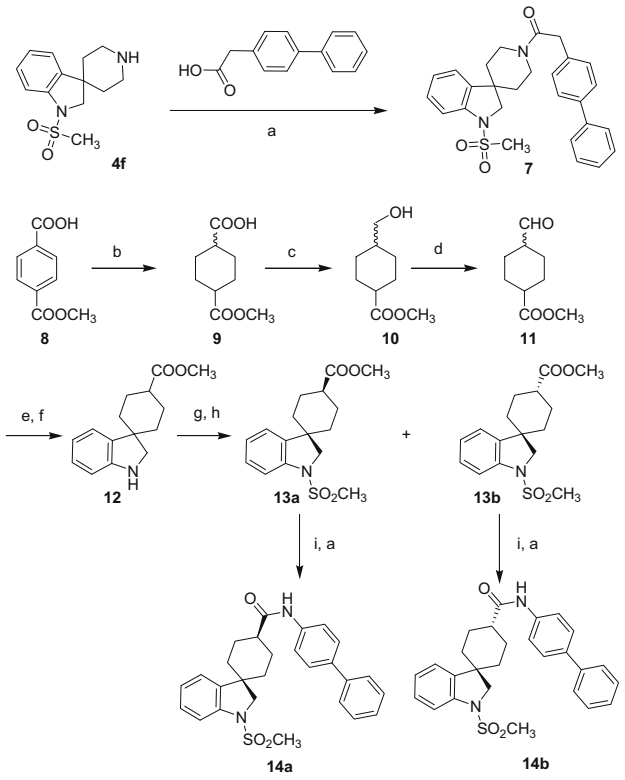
Compounds	Ar	IC50, nM[a]	Rat F[b], %	Brain/plasma ratio, rat, iv[c]	
				10 min	60 min
3e		0.85	0	1.30	1.93
6c		3.0	12	0.23	0.24
6d		2.1	47	0.13	0.11
6e		4.1	53	0.12	0.12
6f		0.96	0	NT	NT
6g		0.82	0	NT	NT
6h		3.0	20	0.42	0.32
6i		0.97	0	NT	NT
6j		0.86	0	NT	NT
6k		0.57	24	0.14	0.07
6l		7.5	NT	NT	NT
6m		23	NT	NT	NT
6n		9.8	NT	NT	NT

NT, not tested.
[a] In vitro data in nM are the average of at least two experiments.
[b] 3 mg/kg iv ($n = 2$) versus 10 mg/kg po ($n = 2$).
[c] $n = 2$.

atoms, such as pyridazine, pyrazine and pyrimidine, were incorporated, and those analogs were also potent Y5 antagonists. Compounds **6l–n** were heteroaromatic versions of the *m*-biphenyl



Scheme 1. Synthesis of urea analogs **6a**–**n**. (a) PhOCOCl, pyridine, room temperature; (b) Et_3N, $CHCl_3$, reflux.



Scheme 2. Synthesis of amide analog **7** and two diastereoisomers of spiro(indoline-3,4′-cyclohexane)-1′-carboxamide, **14a** and **14b**. (a) WSC·HCl, pyridine, room temperature; (b) 5% Rh–C (wet), 50 atm H_2, 1,4-dioxane/MeOH (5/4); (c) $Me_2S{\cdot}BH_3$, THF, 0 °C→room temperature; (d) PCC, Celite, CH_2Cl_2, room temperature; (e) phenylhydrazine, TFA, toluene/acetonitrile (39/1), 0 °C→room temperature; (f) $NaBH_4$, MeOH, 0 °C; (g) $MeSO_2Cl$, Et_3N, THF, 0 °C; (h) separation on silica gel, hexane/ethyl acetate (3/1→4/3); (i) 4 N, NaOH, MeOH, room temperature.

analog, and these analogs tended to be less active compared to the heteroaromatic versions of the *p*-biphenyl analog.

Exploratory rat PK studies for compounds **6c–k** were conducted employing intravenous injection at 3 mg/kg ($n = 2$) and oral administration at 10 mg/kg ($n = 2$). Compounds **6d** and **6e** showed good oral bioavailability of 47% and 53%, respectively. Compounds **6c**, **6h** and **6k** showed moderate bioavailability of 12%, 20% and 24%, respectively, while the other compounds were not orally bioavailable. Compounds **6c–e**, **6h** and **6k** were also evaluated for their brain penetration after intravenous injection at 3 mg/kg in rats. These compounds were brain penetrable to some extent although they exhibited poorer brain penetration compared with **3e**. The compounds were also evaluated for their inhibitory effect on the Y5 agonist, bovine pancreatic polypeptide (bPP)-induced food intake in rats[63] at 30 mg/kg oral dosing. Of the compounds, **6e** most potently inhibited the food intake. Compound **6e** was dose titrated and showed minimum effective dose of 10 mg/kg (Fig. 4). Compound **6e** at 30 mg/kg po did not produce any abnormal behavior, such as sedation, suggesting that the food intake inhibitory effect was due to the Y5 receptor antagonism.

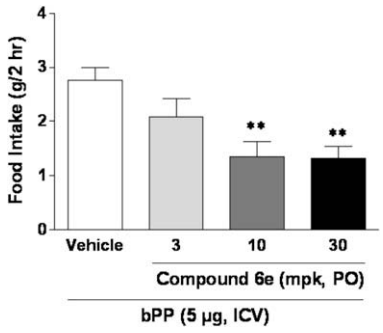


Figure 4. Inhibitory effect of compound **6e** on bPP induced food intake in rats ($^{**}P < 0.01$ vs vehicle treated group. $n = 13–16$).

In summary, we found potent spiroindoline derivative Y5 antagonists, exemplified by **3e**, by screening and an exploratory combinatorial approach. While **3e** itself was not orally bioavailable, subsequent derivatization employing introduction of nitrogen atom(s) produced some orally bioavailable Y5 antagonists. Of the compounds, **6e** was orally active and showed inhibitory effect on bPP-induced food intake in rats.

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63. See Ref. 64 for the protocol used for the in vivo feeding experiments described herein. Compounds were evaluated in groups of 13–16 animals which received injections of 5 μg of bPP (10 μL ICV, solved in 10 mM phosphate buffered saline containing 0.05% bovine serum albumin), and their food intake was monitored for 2 h. Oral dosing of compounds (5 mL/kg, suspended in 0.5% methylcellulose in distilled water) was done 1 h before ICV-agonist dosing.
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