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Synthesis and evaluation of 5,5-diphenylimidazolones as potent human neuropeptide Y5 receptor antagonists

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Abstract—A series of novel 5,5-diphenylimidazolones was synthesized and evaluated for activity against the human neuropeptide Y5 receptor. The 3-pyridyl analog **46** demonstrated an IC_{50} of 8.3 nM with a favorable pharmacokinetic profile in rats, but was ineffective in reducing food intake.
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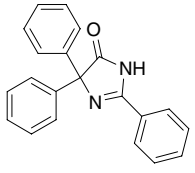
1. Introduction

Recently, there have been a number of publications discussing the potential of selective neuropeptide Y5 (NPY5) receptor antagonists as anorectic agents in a variety of in vivo feeding models.[1] The results of these studies have only led to increased speculation as to the function of the NPY5 receptor, given evidence both supporting and negating the hypothesis that the NPY5 receptor is indeed involved in the regulation of food intake in rodents. Much of the data published on small molecule, selective NPY5 antagonists to date has been compiled using compounds that suffer from a variety of pharmacokinetic issues such as poor brain penetration, or short in vivo half-lives which prevent definitive interpretation of the results. In an effort to further elucidate the potential of NPY5 receptor antagonism and how it relates to food intake, we set out to discover a novel compound lacking in the aforementioned pharmacokinetic liabilities. Herein we disclose results on the structure–activity and in vivo efficacy of a series of 5,5-diphenylimidazolone NPY5 selective antagonists.

2. Screening

High-throughput screening of the BMS compound collection for binding against the human NPY5 receptor identified a series of novel imidazolones as represented by **1** possessing sub-micromolar affinity. These imidazolones were attractive as a synthetic starting point based on their chemical tractability as well as possessing low affinity for the hNPY1 receptor. Particularly 5,5-diphenylimidazolone **1**[2] exhibited a >1000-fold selectivity for the NPY5 receptor versus the NPY1 receptor (IC_{50} = 6 nM NPY5 vs IC_{50} > 10 μM NPY1).



1

Although compound **1** possessed potent and selective binding affinity for the hNPY5 receptor, it suffered from poor aqueous solubility (4 μg/mL, pH 2.0) as well as negligible oral bioavailability, making it a poor candidate for either oral or parenteral formulations. In order to overcome these obstacles, we embarked on a synthetic campaign to enhance the aqueous solubility and oral

Keywords: Obesity; NPY5; Imidazolone; Orally bioavailable; Brain penetrant.
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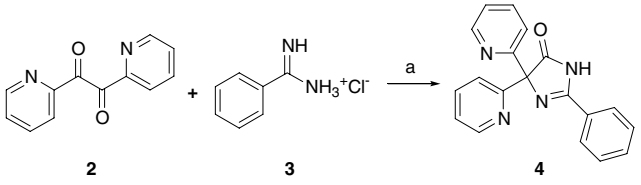
bioavailability within the imidazolone chemotype, while maintaining both potent binding affinity and selectivity for the NPY5 receptor.

3. Results and discussion

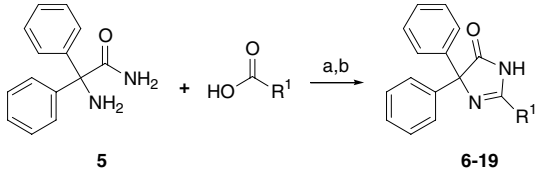
Initial synthetic efforts around the central imidazolone core focused on the removal of the lipophilic geminal diphenyl substitution at the 5-position. Replacement of the *gem*-diphenyl rings with 2-substituted pyridines was accomplished via a pinacol-like rearrangement arising from the reaction of 2,2′-pyridyl **2** and benzamidine/HCl **3** (Scheme 1).[3]

Despite possessing improved aqueous solubility (10 mg/mL in 0.1 N HCl) imidazolone **4** was completely devoid of any significant NPY5 binding affinity (IC_{50} > 1000 nM). Additional analogs directed at removing either one or both of the phenyl groups at the 5-position of the imidazolone core also exhibited poor or greatly reduced affinity at the hNPY5 receptor (data not shown).

Due to lack of tolerance for modification at the 5-position, synthetic efforts quickly shifted to modifying substituents at the 2-position on the imidazolone core. We developed an efficient two-step protocol starting from aminocarboxamide **5**[4] to construct a variety of diversely substituted analogs **6–19** (Scheme 2). Treatment of amine **5** with a polymer-supported carbodiimide reagent[5] in the presence of excess carboxylic acid afforded an intermediate α-amidoamide. These amides were isolated by simple filtration to remove the polymer-supported reagent as well as any unreacted carboxylic acid. Yields of the corresponding amides varied, but usually were low (10–50%) due to the hindered nature of the starting amine. The isolated α-amidoamides were cyclized to the desired imidazolones in ethanol with excess 1 N sodium hydroxide. All analogs were purified by reverse-phase chromatography and evaluated for their binding affinity against the human NPY5 receptor (Table 1).

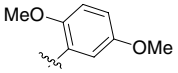
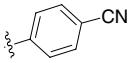
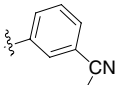
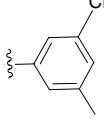
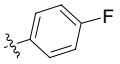
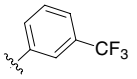
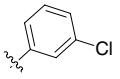
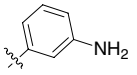
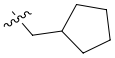
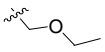
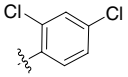


Scheme 1. 2-Phenyl-5,5-di-pyridin-2-yl-3,5-dihydro-imidazol-4-one synthesis. Reagents and conditions: (a) EtOH, NaOH, reflux, 2 h (**4**, 90%).



Scheme 2. Diphenylimidazolone synthesis. Reagents and conditions: (a) P-EDC resin, CH_2Cl_2, rt, 24 h; (b) NaOH, EtOH, rt, 2 h.

Table 1. Human NPY5 binding affinity for select 2-substituted imidazolone derivatives

Compound	R^1	hNPY5 IC_{50}[a] (nM)
6		6 (1)
7		434 ± 57 (2)
8		170 ± 6 (2)
9		0.66 ± 0.04 (2)
10		304 ± 40 (2)
11		108 ± 16 (2)
12		2.9 ± 0.2 (2)
13		0.59 ± 0.04 (2)
14		262 ± 2.7 (2)
15		>1000 (1)
16		>1000 (1)
17		102 ± 5.0 (2)
18		868 ± 9.5 (2)
19		>1000 (1)

[a] IC_{50} values are means ± SEM, number of results in parentheses.

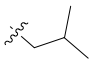
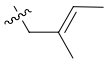
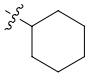
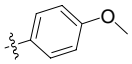
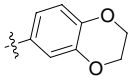
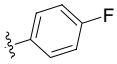
Initial structure–activity studies around the 2-position on the imidazolone core revealed a strong preference for small, electron-withdrawing, *meta*-substituted phenyl rings. For example, both analogs **9** and **13** displayed sub-nanomolar binding affinity to hNPY5, while **10** and **14** demonstrated considerably reduced affinity. Both *ortho* and *para* substitution or combinations thereof greatly diminished binding at the hNPY5 receptor. Additionally, alkyl substitution either straight chain, branched, or cyclic at the 2-position eliminated any significant binding affinity for the hNPY5 receptor.

We next turned our attention to aniline **14**, which served as a linchpin for further SAR studies. A variety of mono-benzyl and alkyl substituted analogs generated

from a reductive amination reaction with the corresponding aldehyde (Scheme 3) were prepared. In our hands we found that with aniline **14**, the procedure described by Abdel-Magid et al.[6] gave the highest product yields when using alkyl, electron-rich, or electron-deficient substituted aryl aldehydes. From the substituted aniline analogs synthesized and evaluated for binding affinity, we found that in all cases, alkyl substitution on the aniline nitrogen greatly decreased affinity for the hNPY5 receptor. Interestingly, many of the benzyl substituted analogs displayed moderate affinity, showing a preference for extended substitution at the *para* position on the nascent phenyl ring. Of all the aniline analogs we synthesized where substitution on the nitrogen varied, we did not see any increase in affinity for the hNPY5 receptor over the starting unsubstituted aniline **14** (see Table 2).

Structure–activity data generated from these 'early' analogs indicated that there was tolerability for expansion out from the 3-position of the phenyl ring, since sterically bulky aryl groups did not completely abolish binding affinity for the hNPY5 receptor. With this in mind we chose nitrile **9** as a versatile synthetic precursor for further structural elaboration at the 3-phenyl position. Nitrile **9** was initially hydrolyzed by hydrogen peroxide/sodium hydroxide[7] affording primary carboxamide **28** (hNPY5, IC_{50} = 13 nM) (see Scheme 4). Reduction of **9** with Raney nickel in methanolic ammonia[8] furnished amine **29**. Compound **29** provided us an additional branching point in which to expand our structure–activity studies. Initial attempts to selectively mono-alkylate amine **29** were unsuccessful using stoichiometric methyl iodide and potassium carbonate in acetonitrile. Unfortunately, we obtained the mono-methyl (**32**, Table 3) and di-methyl derivatives (**37**, Table 4) in equal amounts from the reaction mixture. The lack of product selectivity in the conversion of **29** to **32** precluded us from efficiently synthesizing large numbers of analogs via this procedure. To circumvent this problem, an alternative synthetic strategy was developed to prepare both mono- and di-alkylated 3-methylamino analogs independently. This was accomplished through the use of *meta*-benzyl-chloride intermediate **31**. In the case where secondary 3-methylamino derivatives **32**–**36** were desired, we added excess primary amine to the starting benzyl chloride **31** in the absence of base. Heating the mixture overnight in acetonitrile at 60 °C afforded the desired secondary benzylamine as the major product. These conditions significantly reduced the amount of dimerized product that formed in the presence of the reacting amine with potassium carbonate. Tertiary 3-methylamino analogs **37**–**43** were synthesized starting with an excess amount of the desired secondary amine in the presence of potassium carbonate. As before, heating the reaction mixture overnight at 60 °C in acetonitrile was necessary for the reaction to proceed to completion (Scheme 4).

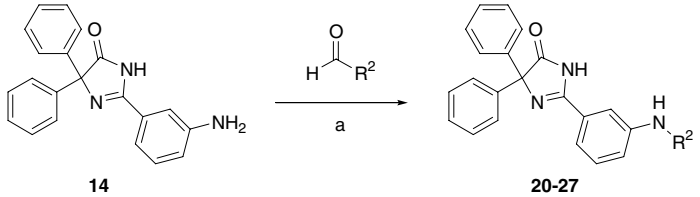
Table 2. Human NPY5 binding affinity for select *meta*-substituted aniline derivatives

Compound	R^2	hNPY5 IC_{50}[a] (nM)	Yield (%)
20		>1000 (1)	30
21		299 ± 45 (2)	70
22		>1000 (1)	19
23		248 ± 1.5 (2)	44
24		399 ± 135 (2)	50
25		134 ± 12 (2)	12
26		735 ± 2.8 (2)	47
27		293 ± 63 (2)	46

[a] IC_{50} values are means ± SEM, number of results in parentheses.

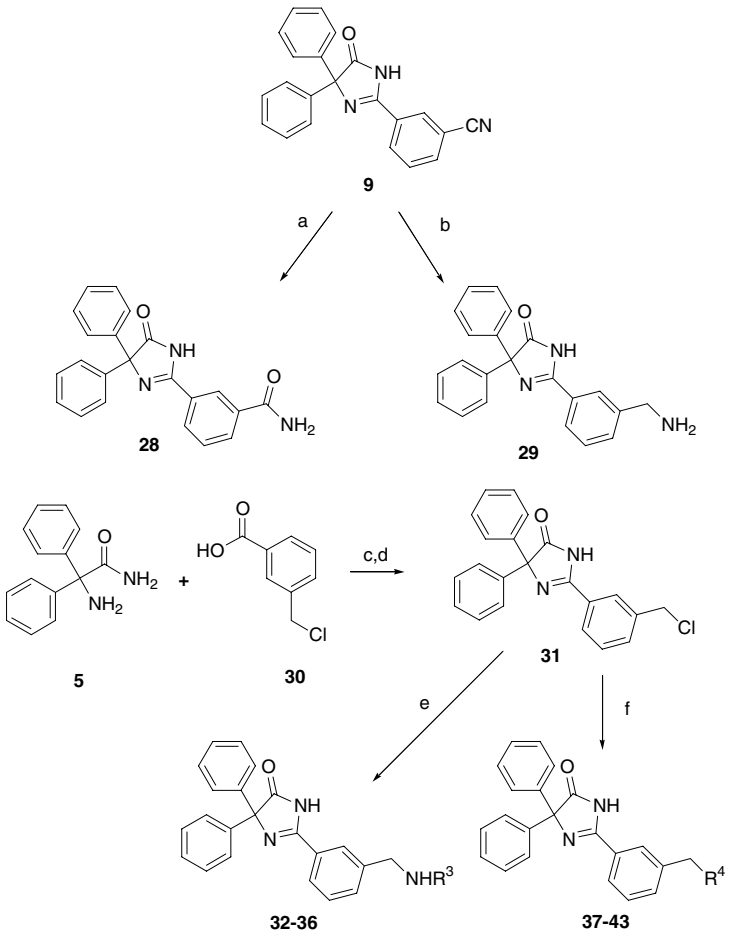
Structure–activity data generated from the secondary 3-methylamino series mirrored that found in the *meta*-substituted reductive amination studies (see Table 3). There was a clear preference for *para*-substituted aryl rings over straight chain and branched alkyl substituents for the hNPY5 receptor. In the case of the tertiary 3-methylamino series, cyclic substituted amines showed enhanced binding affinity, producing several analogs that exhibited binding affinities close to the lead compound **1** (see Table 4). Although compounds **36** and **42** possessed potent binding affinity for the hNPY5 receptor, they offered no significant improvement in physical properties when compared to imidazolone **1**.

Parallel to SAR studies on maximizing the binding affinity in our '*meta*' 2-phenylimidazolone series, we



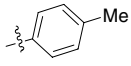
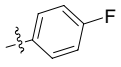
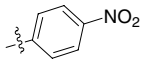
14 **20-27**

Scheme 3. 3-Substituted aniline synthesis. Reagents and conditions: (a) aldehyde, $NaBH(OAc)_3$, $C_2H_4Cl_2$, AcOH, rt, 96 h.



Scheme 4. Expanded 3-substituted analog synthesis. Reagents and conditions: (a) NaOH, 30% H_2O_2, EtOH, reflux, 3 h, 63%; (b) Raney Ni, H_2, NH_4OH/MeOH, rt, 24 h, 64%; (c) EDC, HOBt, DMF, rt, 24 h, 30%; (d) NaOH, EtOH, rt, 1 h, 84%; (e) amine, CH_3CN, 60 °C, 24 h; (f) amine, excess K_2CO_3, CH_3CN, 60 °C, 24 h.

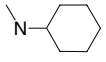
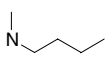
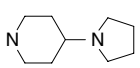
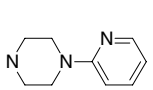
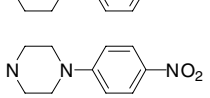
Table 3. Human NPY5 binding affinity for secondary 3-substituted aryl- and akyl-methylamino derivatives

Compound	R^3	hNPY5 IC_{50}[a] (nM)
29	H	48 ± 3.6 (2)
32	Me	>1000 (1)
33		>1000 (1)
34		31 ± 3.5 (2)
35		62 ± 11 (2)
36		55 ± 0.4 (2)

[a] IC_{50} values are means ± SEM, number of results in parentheses.

examined replacing the phenyl ring at the 2-position on the imidazolone ring with a variety of aromatic heterocycles. Through the incorporation of heteroatoms, specifically nitrogen on the aryl ring in the 2-position, it was postulated that we could lower the clog*P* values

Table 4. Human NPY5 binding affinity for tertiary 3-substituted methylamino derivatives

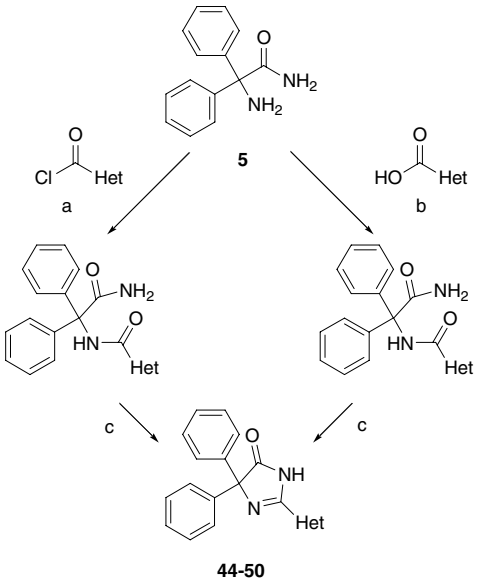
Compound	R^4	hNPY5 IC_{50}[a] (nM)
37		>1000 (1)
38		395 ± 70 (2)
39		326 ± 112 (2)
40		35 ± 2.6 (2)
41		15.4 ± 6.3 (2)
42		8.6 ± 1 (2)
43		70 ± 6.2 (2)

[a] IC_{50} values are means ± SEM, number of results in parentheses.

in the imidazolone series, and thereby increase the aqueous solubility of these analogs. The synthesis of heterocyclic analogs **44**–**50** was accomplished using either the corresponding acid or acyl chloride based on commercial availability. We found that on average the overall yields from amine **5** to the desired imidazolone were better using an acyl chloride to form the intermediate α-amidoamide (Scheme 5). In the synthesis of imidazolone **47** (see Table 5) the starting pyrimidine-5-carboxylic acid was not commercially available, and therefore was prepared following the procedure described by Kress.[9] In the case of the heterocyclic imidazolone series, the yield of the initial amide bond formation dictated the overall imidazolone yield, since the base-induced cyclization step proceeded cleanly, and on average in >80% yield for all analogs.

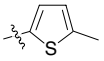
Analogs synthesized in the 2-heterocyclic imidazolone series were screened for binding affinity at both the hNPY5 and hNPY1 receptor. Fortunately, a number of analogs in the 2-heterocyclic imidazolone series displayed excellent affinity for the hNPY5 receptor while maintaining exquisite selectivity over the hNPY1 receptor (see Table 5). Pyridines **44** and **45**, although modestly active, were eclipsed by **46**, their 3-substituted homolog, further supporting the preference for *meta* substitution in the 2-aryl imidazolone series. Interestingly, pyrimidine **47** possessed significantly less binding affinity for the hNPY5 receptor compared to pyridine **46**. This suggests that there is an additional preference for specific electrostatic interactions in the heteroaryl ring binding pocket on the hNPY5 receptor. Similar to pyrimidine **47**, both thiophene **50** and furan analog **49** demonstrated only moderate affinity at the hNPY5 receptor.

Pyridine **46** was selected for further pharmacologic characterization and found to be equipotent compared to compound **1** at the hNPY5 receptor while devoid of any hNPY1 binding affinity. Both equilibrium binding by Scatchard analysis and functional activity based on cAMP accumulation of **46** indicated that the compound was a competitive antagonist against the hNPY5 receptor with an app. K_b = 7.1 nM, which is in good agreement with its binding affinity. Additionally, compound **46** displaced ^{125}I-PYY in rat brain homogenates with a measured IC_{50} = 6.5 ± 3.5 nM.



Scheme 5. 2-Heterocyclic-5,5-diphenylimidazolone analog synthesis. Reagents and conditions: (a) Et_3N, 4-DMAP, CH_2Cl_2, rt, 24 h; (b) EDC, HOBt, CH_2Cl_2, rt, 24 h; (c) NaOH, EtOH, rt, 1 h.

Table 5. Human NPY5 and NPY1 binding affinity for select 2-heterocyclic-5,5-diphenylimidazolone derivatives

Compound	Het	Yield (%)	hNPY5 IC_{50}[c] (nM)	hNPY1 IC_{50} (nM)
44		65[a]	50 (1)	>1000 (1)
45		45[a]	45 (1)	>1000 (1)
46		48[a]	8.3 ± 0.7 (6)	>1000 (1)
47		8[b]	76 ± 28 (2)	>1000 (1)
48		20[b]	9.4 ± 0.3 (2)	>1000 (1)
49		19[b]	109 ± 0.8 (2)	[d]
50		5[b]	171 ± 19 (2)	[d]

[a] Synthesized starting with the corresponding acyl chloride.
[b] Synthesized starting with the corresponding carboxylic acid.
[c] IC_{50} values are means ± SEM, number of results in parentheses.
[d] hNPY1 binding data were not measured.

The measured aqueous solubility of pyridine **46** was 33 μg/mL (pH 2.0) an approximate 10-fold improvement over starting imidazolone **1**. Encouraged by this increase in aqueous solubility, **46** was dosed in rats by both intraperitoneal (ip) and oral (po) administration. The absolute brain levels as well as bioavailability were measured. The pharmacokinetic data compiled on imidazolone **46** demonstrated that this compound was far superior to our lead imidazolone **1** in many respects. The measured bioavailability of **46** dosed in rats by both po and ip routes of administration was >90% (data not shown). Imidazolone **46** demonstrated a relatively high level of free drug concentration when measured in rat serum (18.9%). The brain/plasma ratio at 120 min was 1.2 (see Table 6) with peak absolute brain levels of **46** achieving a concentration ~500-fold over the experimental K_b value of 7.1 nM out to 6 h. Oral dosing [(25 mg/kg) 10:10:80 Cremophor EL™/ethanol/water] of **46** demonstrated that the compound was rapidly absorbed, achieving peak plasma levels of 10 μM at 70 min. The measured half-life (1.1 h) indicated the com-

Table 6. Absolute brain and plasma levels for **46** dosed ip (15 mg/kg)[a] in Sprague–Dawley rats

Time (min)	Plasma concn[b] (nM/L)	Whole brain concn[a] (nM/L)	Free plasma concn[c] (nM/L)	Brain/plasma ratio
10	13,617	16,022	2574	1.2
120	6585	7396	1244	1.2
360	2661	4006	503	1.4

[a] Dosing vehicle, 2.0 mg/mL, 10:10:80 Cremophor EL™/ethanol/water.
[b] Absolute concentration values are means of two measurements.
[c] Plasma-free fraction values calculated based on a serum-free fraction of 18.9%.

pound exhibited a modest rate of clearance (39 mL/min/kg). When dosed either 25 mg/kg po or 15 mg/kg ip, absolute brain levels were maintained at concentrations >10-fold over the measured K_b as well as the protein adjusted IC_{50} value (prot. adj. IC_{50} = 44 nM) for extended periods. Given the favorable pharmacokinetic data for imidazolone **46**, the compound was evaluated in in vivo feeding studies in several accepted rodent models of obesity (see Table 7).

We initially evaluated the effect of **46** on reversing NPY-induced feeding in Sprague–Dawley rats via two routes of administration. Food intake was increased by administration of NPY^{1-36} (1 nmol) into the cerebral ventricle of rats.[10] Compound **46** was either administered into the paraventricular nucleus of the hypothalamus (30 nmol, **46**), or orally (60 mg/kg **46**). In both cases there was no statistically significant reduction in food intake between the **46** treated and vehicle control animals as compared to the NPY treated groups.

We additionally looked at the effect of **46** when dosed at either 60 or 100 mg/kg po on spontaneous overnight food intake in a 24 h light/dark free-feeding model with Sprague–Dawley rats (see Fig. 1). As in the NPY-induced feeding study, there was no significant reduction in total food intake in the treated animals when compared to the vehicle dosed control group in either the 60 or 100 mg/kg dosed animals.

Last, we looked extensively at the effect of **46** using a broad range of ip doses (0.001–15 mg/kg) in a time dependent, diet-induced model of obesity in Sprague–Dawley rats. This study has the potential advantage of depicting any time dependent differences of food intake that arise during a normal 12 h light/dark feeding regimen.

Similar to previous feeding studies, no statistical difference between the compound **46** and vehicle dosed

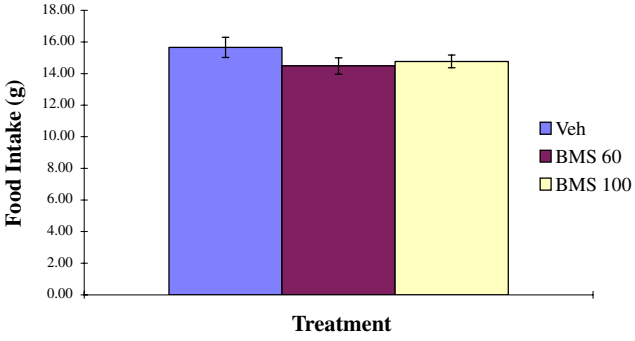


Figure 1. Total nocturnal food intake following oral dosing (60 and 100 mg/kg) of compound **46** in rats (n = 12 animals/group). Vehicle: 20% DMSO/40% PEG400/40% Trappsol™.

groups was observed. The results of the study, depicted below (Fig. 2) are representative of all doses evaluated (0.001–15.0 mg/kg ip) in this model.

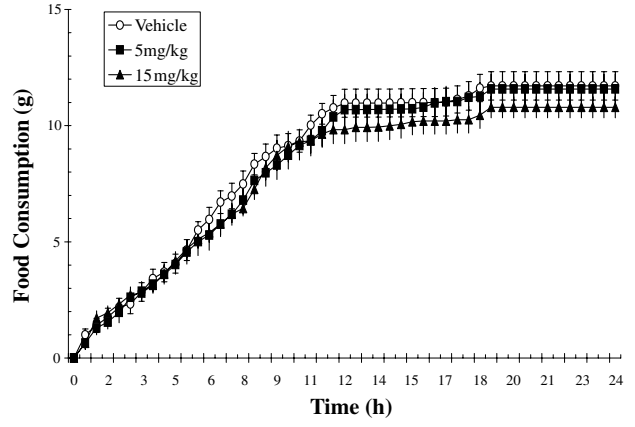


Figure 2. Cumulative food consumption in diet-induced obese rats following compound **46** (5 and 15 mg/kg, ip) injections before onset of dark cycle (n = 11–12 animals/group). Vehicle: 20% NMP/30% PEG400/50% (5% Tween 80™) in water.

Table 7. In Vivo feeding studies with imidazolone **46**

Animal model	Route of administration	Dose	Significant effect
NPY-induced food intake in SD[a] rats	NPY (1 nmol) icv, **46** po	60 mg/kg	None
NPY-induced food intake in SD[a] rats	NPY (1 nmol) icv, **46** PVN[b]	30 nmol	None
Spontaneous overnight food intake in SD[a] rats	**46** po	60 and 100 mg/kg	None
Diet-induced obese model in SD[a] rats	**46** ip	5 and 15 mg/kg	None

[a] Sprague–Dawley.
[b] Paraventricular nucleus.

4. Conclusion

Imidazolone **46** is a potent and selective hNPY5 receptor antagonist with excellent pharmacokinetic properties. The compound exhibits high oral bioavailability (>90%) and brain penetration, achieving sufficient brain concentrations compared to the protein adjusted IC_{50} = 44 nM of the compound (IC_{50}/plasma-free fraction) after both ip and po administration. In spite of its pharmacokinetic profile, **46** demonstrated no effect on appetite control in a variety of animal models, including the diet-induced animal model that is believed to mimic human obesity. Multiple pharmacological, molecular, and physiological studies[1] suggest the involvement of the NPY5 receptor in the reduction of food intake and body weight. Imidazolone **46** possesses many favorable pharmacokinetic properties including a high plasma-free fraction, good brain penetration, as well as in vivo half-life. Dosed both orally and ip, **46** achieved free drug concentrations in plasma along with sufficient whole brain concentrations to cover the protein adjusted IC_{50} for the NPY5 receptor. Despite this, in our hands imidazolone **46** was ineffective in reducing appetite, food intake or body weight in a variety of accepted feeding models. Based on these data we suggest that the NPY5 receptor in and of itself is not solely responsible for the modulation of food intake in rats. Further studies may be necessary to conclude unequivocally the role of selective NPY5 antagonists and their ability to modulate food intake.

5. Experimental

5.1. Chemistry

Melting points were determined using a Thomas–Hoover capillary melting apparatus and are uncorrected. Elemental analyses were performed at Robertson Microlabs, Madison, NJ, USA, and are within 0.4% of theoretical C, H, and N values. ^{1}H NMR spectra were recorded in $CDCl_3$ (unless otherwise noted) with the solvent resonance of $CDCl_3$ (7.27 ppm) as the internal standard on a Bruker AC 300 MHz spectrometer. Electrospray mass spectra (MS) were recorded on a Finnigan SSQ-7000 mass spectrometer. Reagents and solvents were used as obtained from commercial suppliers without further purification. Column chromatography was performed using silica gel and the flash technique. Representative procedures and physical properties for selected compounds are described.

5.1.1. 2,5,5-Triphenyl-3,5-dihydro-imidazol-4-one (1). Compound **1** was prepared by standard procedure as referenced in the literature.[2] All spectroscopic data were consistent with that as indicated by structure **1**: white solid (mp 238–239 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.98 (d, 2H, J = 6.0 Hz), 7.51 (d, 4H, J = 6.0 Hz), 7.41 (m, 3H), 7.26 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 188.36, 140.34, 132.54, 129.21, 128.75, 128.31, 128.13, 127.61, 127.56; LRMS m/z (ESI) 311 $(M-H)^-$; Anal. Calcd for $C_{21}H_{16}N_2O$: C, 80.75; H, 5.16; N, 8.97. Found: C, 80.47; H, 5.06; N, 8.94.

5.1.2. General procedure for the preparation of imidazolones (7–19). α-Amino-α,α-diphenylacetamide **5** (0.050 g, 0.22 mmol) was added to a solution of the corresponding carboxylic acid (0.44 mmol), 0.690 g of P-EDC[5] resin (1.4 meq/g, 0.88 mmol) in 5 mL of dry CH_2Cl_2. The reaction mixture was shaken for 36 h at rt, then the crude reaction mixture was filtered and the filter cake was washed with excess CH_2Cl_2. The resulting filtrate was evaporated in vacuo to yield a crude solid. This solid was dissolved in 3 mL EtOH and 0.5 mL of 1 N NaOH (aq). The resulting solution was stirred for 16 h then neutralized with 1 N HCl (aq). The solvent was evaporated in vacuo and the crude solid was purified by reverse-phase chromatography YMC Inc., 20 × 100 mm, 5 μm particle size, 120 Å pore size C_{18} stationary phase ODS-A fast elution: 50–100% B A = (10% MeOH/90% H_2O–0.1% TFA), B = (90% MeOH/10% H_2O–0.1% TFA) providing the desired pure imidazolones **7**–**19** in yields ranging from 2% to 42% (hNPY5 binding data-summarized in Table 1).

5.1.3. 2-(3-Aminophenyl)-5,5-diphenyl-3,5-dihydro-imidazol-4-one (14). To a 250-mL flask were added α-amino-α,α-diphenylacetamide **5** (1.0 g, 4.42 mmol) and 3-nitrobenzoic acid (1.11 g, 6.64 mmol). The solids were dissolved in 40 mL of dry CH_2Cl_2 and the reaction mixture was stirred until homogeneous. After cooling to 0 °C, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) (1.74 g, 7.07 mmol) was added in one portion and the reaction was allowed to warm slowly to rt overnight. The organic layer was washed with 0.5 N HCl, dried (Na_2SO_4), and evaporated in vacuo to yield a crude solid. Treatment of the solid with 4.0 mL of 1 N NaOH in 20 mL EtOH for 16 h followed by neutralization with 1 N HCl and evaporation of the solvent produced a crude yellow oil. The oil was chromatographed with silica gel (3:1 hexane/acetone) affording 2-(3-nitrophenyl)-5,5-diphenyl-3,5-dihydro-imidazol-4-one (0.744 g, 69%) as a light yellow solid: LRMS m/z (ESI) 358.3 $(M+H)^+$; ^{1}H NMR (DMSO-d_6, 300 MHz) δ = 12.17 (br s, 1H), 8.93 (s, 1H), 8.52 (d, 1H, J = 6.0 Hz), 8.47 (d, 1H, J = 6.0 Hz), 7.88 (t, 1H, J = 6.0 Hz), 7.48 (m, 4H), 7.35 (m, 6H); Anal. Calcd for $C_{21}H_{15}N_3O_3$: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.29; H, 4.39; N, 11.49.

To a 100-mL flask were added 2-(3-nitrophenyl)-5,5-diphenyl-3,5-dihydro-imidazol-4-one (0.614 g, 1.72 mmol) and 0.092 g of platinum(IV) oxide in 20 mL of a 8:1 EtOH/THF solution. The reaction vessel was charged with 5 psi hydrogen and stirred overnight. Upon completion the reaction was filtered through Celite and the solvent was evaporated in vacuo. The crude solid was chromatographed with silica gel (4:1 hexane/acetone) affording (0.480 g, 85%) of the desired amine **14** as a white solid: LRMS m/z (ESI) 328.3 $(M+H)^+$; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.60 (d, 4H, J = 6.0 Hz), 7.41 (s, 1H), 7.35 (m, 6H), 7.19 (m, 1H), 6.85 (m, 1H), 6.41 (d, 1H, J = 6.0 Hz).

5.1.4. General procedure for the preparation of imidazolones (20–27). Aniline **14** (0.025 g, 0.076 mmol) was added to a solution of the corresponding aldehyde

(0.11 mmol), acetic acid (0.10 mL, 0.11 mmol), and sodium triacetoxyborohydride (0.097 g, 0.46 mmol) in 5 mL of dry CH_2Cl_2. The reaction mixture was stirred for 96 h at rt, then the crude reaction mixture was loaded onto an SCX cartridge pretreated with CH_2Cl_2. The cartridge was washed with 5 mL CH_2Cl_2 followed by 5 mL CH_3OH. The product was eluted with 2% NH_4OH in CH_3OH. The filtrate was evaporated in vacuo and the crude solid was purified by reverse phase chromatography YMC Inc., 20 × 100 mm, 5 μm particle size, 120 Å pore size C_{18} stationary phase ODS-A fast elution: 50–100% B A = (10% MeOH/90% H_2O–0.1% TFA) B = (90% MeOH/10% H_2O–0.1% TFA) providing the desired pure imidazolones **20**–**27** in yields ranging from 12% to 70% (hNPY5 binding data are summarized in Table 2).

5.1.5. 3-(5-Oxo-4,4-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-benzamide (28). To a 50-mL flask were added imidazolone **9** (0.30 g, 0.889 mmol) and 6 mL of 95% EtOH. The solution was stirred until homogeneous and then 1 mL of 6 N NaOH and 1 mL of 30% hydrogen peroxide were added and the solution was heated to reflux for 3 h. The reaction was cooled to rt and neutralized with concd HCl. The solvent was evaporated in vacuo, and the crude residue was chromatographed with silica gel (4:1 hexane/acetone) producing (0.20 g, 63%) of the desired amide **28** as a white solid: LRMS *m*/*z* (ESI) 356.2 $(M+H)^+$; ^1H NMR (DMSO-d_6, 300 MHz) δ = 8.74 (s, 1H), 8.32 (d, 1H, *J* = 6.0 Hz), 8.10 (d, 1H, *J* = 6.0 Hz), 7.66 (t, 1H, *J* = 6.0 Hz), 7.48 (d, 4H, *J* = 6.0 Hz), 7.33 (m, 6H).

5.1.6. 2-[3-(Aminomethyl)-phenyl]-5,5-diphenyl-3,5-dihydro-imidazol-4-one (29). To a Parr hydrogenator were added **9** (0.100 g, 0.297 mmol) and 0.010 g of freshly washed Raney nickel in 6 mL of a 5:1 MeOH/NH_4OH (concd) solution. The reaction vessel was charged with 50 psi hydrogen and shaken overnight. The reaction was filtered through Celite and the solvent was evaporated in vacuo. The crude solid was chromatographed with silica gel (2:1 hexane/acetone) affording (0.065 g, 64%) of the desired amine **29** as an off-white solid: LRMS *m*/*z* (ESI) 342.3 $(M+H)^+$; ^1H NMR ($CDCl_3$, 300 MHz) δ = 8.02 (s, 1H), 7.90 (m, 2H), 7.59–7.56 (m, 4H), 7.47–7.40 (m, 2H), 7.35–7.24 (m, 5H), 3.93 (s, 2H), 2.18 (s, 2H).

5.1.7. 2-[3-(Chloromethyl)-phenyl]-5,5-diphenyl-3,5-dihydro-imidazol-4-one (31). To a 500 mL flask were added α-amino-α,α-diphenylacetamide **5** (5.0 g, 22.1 mmol) and 3-(chloromethyl)benzoic acid **30** (4.15 g, 24.3 mmol). The solids were dissolved in 100 mL of dry DMF and the reaction mixture was stirred until homogeneous and then cooled to 0 °C. 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) (4.65, 24.3 mmol) and 1-hydroxybenzotriazole hydrate (HOBt) (3.28 g, 24.3 mmol) were added in one portion and the reaction was allowed to warm slowly to rt and stirred overnight. After concentrating in vacuo, the crude residue was dissolved in 250 mL CH_2Cl_2 and washed with 0.5 N HCl. The organic layer was separated, dried (Na_2SO_4), and evaporated in vacuo to yield a crude solid. The solid was purified by chromatography with silica gel (4:1 hexane/acetone) affording (2.5 g, 30%) of the desired amide intermediate as a white solid. Treatment of the purified amide with 10.0 mL of 1 N NaOH in 50 mL EtOH for 1 h followed by neutralization with 1 N HCl and evaporation of the solvent produced a crude solid which was chromatographed with silica gel (4:1 hexane/acetone) affording (2.0 g, 84%) of the desired imidazolone **31** as a white solid: LRMS *m*/*z* (ESI) 361.2 $(M+H)^+$; ^1H NMR ($CDCl_3$, 300 MHz) δ = 8.10 (s, 1H), 7.91 (d, 1H, *J* = 6.0 Hz), 7.65–7.51 (m, 6H), 7.40–7.30 (m, 6H), 4.65 (s, 2H).

5.1.8. 2-[3-((Methylamino)methyl)-phenyl]-5,5-diphenyl-3,5-dihydro-imidazol-4-one (32). To a glass bomb were added benzylchloride **31** (0.107 g, 0.297 mmol) and excess anhydrous methylamine (4.0 mL of a 2.0 M solution in THF). The reaction vessel was sealed and stirred at rt overnight. The solvent was evaporated in vacuo producing an off-white solid. The crude solid was purified by reverse-phase chromatography YMC Inc., 20 × 100 mm, 5 μm particle size, 120 Å pore size C_{18} stationary phase ODS-A fast elution: 50–100% B A = (10% MeOH/90% H_2O–0.1% TFA) B = (90% MeOH/10% H_2O–0.1% TFA) producing (0.070 g, 67%) of the desired amine **32** as a white solid: LRMS *m*/*z* (ESI) 356.2 $(M+H)^+$; ^1H NMR (MeOH-d_4, 300 MHz) δ = 8.26 (s, 1H), 8.10 (d, 1H, *J* = 6.0 Hz), 7.79 (d, 1H, *J* = 6.0 Hz), 7.71 (t, 1H, *J* = 6.0 Hz), 7.49 (d, 4H, *J* = 6.0 Hz), 7.32 (m, 6H), 4.31 (s, 2H), 2.77 (s, 3H).

5.1.9. General procedure for the synthesis of secondary amino analogs 33–36. Benzylchloride **31** (0.015 g, 0.042 mmol) was added to a solution of the corresponding primary amine (0.083 mmol), in 2 mL of dry CH_3CN. The reaction vessel was sealed and gently heated to 60 °C with stirring for 16 h. The reaction mixture was reduced in vacuo and the crude oil was purified by reverse-phase chromatography (YMC Inc., 20 × 100 mm, 5 μm particle size, 120 Å pore size C_{18} stationary phase ODS-A fast elution: 50–100% (10% MeOH/90% H_2O–0.1% TFA): (90% MeOH/10% H_2O–0.1% TFA)) providing the desired pure secondary-aminoimidazolones **33**–**36** in yields ranging from 6% to 13% (hNPY5 binding data are summarized in Table 3).

5.1.10. General procedure for the synthesis of tertiary-amino analogs 37–43. Benzylchloride **31** (0.025 g, 0.069 mmol) was added to a solution of the corresponding primary amine (0.138 mmol) and K_2CO_3 (0.038 g, 0.277 mmol), in 2 mL of dry CH_3CN. The reaction vessel was sealed and gently heated to 60 °C with stirring for 16 h. The reaction mixture was reduced in vacuo and the crude oil was purified by reverse-phase chromatography YMC Inc., 20 × 100 mm, 5 μm particle size, 120 Å pore size C_{18} stationary phase ODS-A fast elution: 50–100% B A = (10% MeOH/90% H_2O–0.1% TFA) B = (90% MeOH/10% H_2O–0.1% TFA) providing the desired pure tertiary-aminoimidazolones **37**–**43** in yields ranging from 6% to 100% (hNPY5 binding data are summarized in Table 4).

5.1.11. General procedure for the synthesis of heterocyclic imidazolones 44 and 45 (procedure A). α-Amino-α,α-diphenylacetamide **5** (0.30 g, 1.24 mmol) was added to a solution of triethylamine (0.503 g, 4.98 mmol), 4-dimethylaminopyridine (4-DMAP) (0.015 g, 0.124 mmol), and 15 mL dry CH_2Cl_2. The solution was cooled to 0 °C and then the corresponding acid chloride (2.48 mmol) was added in one portion. The reaction mixture was stirred at 0 °C for 1 h then warmed to rt and stirred for an additional 16 h. The reaction was then quenched with 5% $NaHCO_3$ (aq) and the aqueous layer was extracted with CH_2Cl_2. The organic fractions were combined, dried with anhydrous Na_2SO_4, and evaporated in vacuo to yield a red oil. This oil was chromatographed with silica gel (4:1 hexane/acetone) affording the desired intermediate amide. The resulting amide was dissolved in 20 mL EtOH and 1 N NaOH (aq) (3.0 mL, 3.0 mmol) was added. The reaction mixture was stirred for 3 h at rt, then the reaction was neutralized with 1 N HCl (aq). The reaction solvent was evaporated in vacuo and the crude solid was dissolved in CH_2Cl_2 and washed with H_2O. The organic phase was dried with anhydrous Na_2SO_4 and the solvent was evaporated in vacuo. The resulting solid was chromatographed with silica gel (6:1 hexane/acetone) affording the desired imidazolones **44** and **45** in yields ranging from 46% to 65% (hNPY5 binding data are summarized in Table 5).

5.1.12. General procedure for the synthesis of heterocyclic imidazolones 48–50 (procedure B). To a 50 mL flask were added α-amino-α,α-diphenylacetamide **5** (0.33 g, 1.46 mmol) and the corresponding carboxylic acid (1.61 mmol). The solids were dissolved in 10 mL dry CH_2Cl_2 and the reaction mixture was stirred until homogeneous, then cooled to 0 °C. 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.31 g, 1.61 mmol) and 1-hydroxybenzotriazole hydrate (0.22 g, 1.61 mmol) were then added in one portion. The reaction was allowed to warm slowly to rt and stirred overnight. The reaction mixture was poured into a separatory funnel, diluted with 100 mL CH_2Cl_2, and washed with 0.5 N HCl. The organic layer was separated, dried (Na_2SO_4), and evaporated in vacuo to yield a crude solid which was chromatographed with silica gel (4:1 hexane/acetone) affording the desired amide intermediate. Treatment of the purified amide with 2.0 mL of 1 N NaOH in 10 mL EtOH for 4 h was followed by neutralization with 1 N HCl. Evaporation of the solvent produced a crude solid which was chromatographed with silica gel (4:1 hexane/acetone) affording the desired imidazolones **48–50** in yields ranging from 5% to 20% (hNPY5 binding data are summarized in Table 5).

5.1.13. 2-(3-Pyridinyl)-3,5-dihydro-5,5-diphenyl-4*H*-imidazol-4-one (46). α-Amino-α,α-diphenylacetamide **5** (1.40 g, 6.19 mmol) was added to a solution of triethylamine (2.50 g, 24.8 mmol) and 30 mL dry CH_2Cl_2. The solution was cooled to 0 °C and then nicotinoyl chloride hydrochloride (1.43 g, 8.05 mmol) was added in one portion. The reaction mixture was stirred at 0 °C for 1 h then warmed to rt and stirred for a total of 16 h. The reaction was then quenched with 5% $NaHCO_3$ (aq) and the aqueous layer was extracted with CH_2Cl_2. The organic fractions were combined, dried with anhydrous Na_2SO_4, and evaporated in vacuo to yield a red oil. This oil was chromatographed with silica gel (4:1 hexane/acetone) affording the desired intermediate amide as a white solid (1.2 g, 58%). The resulting amide (1.2 g, 3.63 mmol) was dissolved in 30 mL EtOH and 1 N NaOH (aq) (4.0 mL, 4.0 mmol) was added. The reaction mixture was stirred for 2 h at rt and then neutralized with 1 N HCl (aq). The reaction solvent was evaporated in vacuo and the crude solid was dissolved in CH_2Cl_2 and subsequently washed with H_2O. The organic phase was dried with anhydrous Na_2SO_4 and the solvent was evaporated in vacuo. The resulting solid was chromatographed with silica gel (6:1 hexane/acetone) producing pure imidazolone **46** as a white solid (0.940 g, 83%): mp 205–206 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) $\delta = 9.40$ (br s, 1H), 8.83 (d, 1H, $J = 3$ Hz), 8.59 (d, 1H, $J = 9.0$ Hz), 7.56 (d, 4H, $J = 6.0$ Hz), 7.32 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz) $\delta = 193.19$, 186.16, 152.74, 148.31, 139.91, 135.04, 128.67, 128.09, 127.33, 124.77, 123.97; LRMS *m/z* (ESI) 314 $(M+H)^+$; Anal. Calcd for $C_{20}H_{15}N_3O$: C, 76.66; H, 4.82; N, 13.41. Found: C, 76.51; H, 4.83; N, 13.36.

6. Biological methods

6.1. Membrane harvest

Membranes were harvested from either Hi5 or CHO cells transfected with the human NPY5 receptor. Hi5 cells were pelleted and washed with phosphate-buffered saline (138 mM NaCl, 8.1 mM Na_2HPO_4, and 1.2 mM KH_2PO_4, pH 7.4). Adherent cells were washed twice with ice-cold (4 °C) phosphate-buffered saline. Cells were scraped in ice-cold hypotonic buffer (20 mM Tris and 5 mM EDTA, pH 7.7), lysed in a Dounce homogenizer, and membranes were pelleted by centrifugation (18,000 rpm, SS-34 rotor, 15 min, 4 °C). Both pellets were resuspended, homogenized in ice-cold hypotonic buffer, and again centrifuged. The final membrane pellet was resuspended through a 27 G needle into a small volume of ice-cold buffer (10 mM NaCl, 20 mM Hepes, 0.22 mM KH_2PO_4, 1.26 mM $CaCl_2$, and 0.81 mM $MgSO_4$, pH 7.4), approximately 100 μL per T175 flask (5–8 mg/mL protein concentration). Protein concentration was measured by the Bradford method (Bradford, 1976) using Bio-Rad reagent with a BSA standard curve. Membranes were held on ice for up to 2 h or flash-frozen in liquid nitrogen and stored at −80 °C.

6.2. Radioligand binding

Membrane solutions were diluted in binding buffer consisting of 50 mM Tris–HCl (pH 7.4), 10 mM NaCl, 5 mM $MgCl_2$, and 2.5 mM $CaCl_2$, supplemented with Aprotinin (10μg/μL), Leupeptin (10μg/μL), and 0.1% BSA. Compounds were diluted in 100% DMSO to a 10 mM stock concentration, then assayed at 1–10,000 nM. The assay was run in 96-deep well plates

containing 25 μL NSB, Total, Reference, or compound, and 25 μL of 0.5 nM [125I]PYY (0.05 nM final). Finally, 200 μL Hi 5 membrane preparation (5 μg total protein) was added to each well for a final DMSO concentration of 1%. The assay plates were incubated at 22 °C for 90 min. Incubation was terminated by filtration over Whatman GF/C filters (pre-soaked in 1% polyethyleneimine for at least 1 h), followed by four washes with ice-cold 50 mM Tris–HCl at pH 7.4 on the Brandel 96 Harvester. The filters were counted on the WALLAC Trilux 1450 microbeta counter. Non-specific binding was defined in the presence of 1 μM NPY. Binding data were analyzed by non-linear regression using the KaleidaGraph or the Ligand program.

6.3. cAMP assay

CHO cells expressing the human NPY5 receptor were seeded on 48-well cell culture plates (Polyfiltronics catalogue #PF-150-SCC9; ordered from VWR) at a density of 5×10^4 to 1×10^5 cells/mL, and they were incubated at 37 °C, 5% CO_2overnight. The medium was removed and displaced with fresh serum-free medium containing 20 mM Hepes, 100 μM IBMX, 10 μM forskolin, and various concentrations of NPY with or without various concentrations (100–1500 nM) of compound **46**. The cells were incubated for 10 min at 37 °C. The drug solution was aspirated from cells and the reaction was terminated by addition of 700 μL of 0.1 N HCl. Cells were incubated for at least 1 h at room temperature before starting radioimmunoassay to measure cyclic-AMP. Each data point was performed in duplicate. cAMP levels were determined using an RIA assay kit (BIOTRAK cAMP [^{125}I] Assay System; Amersham RPA 509 kit) according to the manufacturer's directions. cAMP levels were expressed in femtomoles based on a standard curve.

6.4. Feeding studies

All test subjects were male Sprague–Dawley rats (Harlan, USA). Rats were individually housed with free access to food and water in a temperature and humidity controlled environment (12 h light/12 h dark). Rats in nocturnal food intake and diet-induced obesity studies were dosed 45–60 min prior to the onset of darkness. NPY-Induced Feeding studies were performed during the daylight portion of the cycle. For the diet-induced obesity studies rats were fed a high fat diet (45% calories from fat) for 16 weeks. A control group was fed a low fat diet (10% calories from fat). After 16 weeks, the mean bodyweights were calculated. Animals in the high fat group with bodyweights exceeding means + 1 standard deviation of the control group were considered obesity prone and used in the diet-induced obesity studies. All protocols and procedures were approved by the Bristol-Myers Squibb Animal Care and Use Committee and conducted in a facility approved by the American Association for the Accreditation of Laboratory Animal Care (AAALAC).

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References and notes

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