A Convenient 3-Step Synthesis of 3-Acetamido-6-arylpyridazines Directed to Novel Y_5 Receptor Antagonist

Sébastien GUÉRY,[a] Yveline RIVAL,*[,a] Camille-Georges WERMUTH,[a] Pierre RENARD,[b] and Jean-Albert BOUTIN[c]

[a] *Laboratoire de Pharmacochimie de la Communication Cellulaire, UMR 7081 CNRS/ULP, Université Louis Pasteur, Faculté de Pharmacie; 74, route du Rhin 67401 ILLKIRCH cedex, France:* [b] *A.D.I.R., 1, rue Carle Hébert; 92415 Courbevoie cedex, France: and* [c] *Institut de Recherche Servier; 125 Chemin de Ronde, 78290 Croissy/Seine, France.*
Received December 26, 2001; accepted February 25, 2002

A 3-step synthesis of 3-acetamido-6-arylpyridazines as potential NPY_5 antagonists.

Key words NPY_5 receptor antagonist; obesity; palladium(0); Suzuki cross-coupling; 3-amino-6-chloropyridazine; coupling reaction

Obesity is a common disorder in the industrialized world. The major environmental factor associated with the rising prevalence of obesity is an increasingly sedentary lifestyle, compounded by greater levels of caloric intake. Recent studies[1—12] have shown that in the central nervous system (CNS), neuropeptide Y (NPY) has been implicated in obesity and feeding, anxiety and depression, endocrine function and metabolism.[1] More particularly it was observed that food intake was inhibited by antisense oligodeoxynucleotides to the NPY_5 receptors.[4]

Therefore there is a great interest in the synthesis of NPY receptor antagonists acting as antagonists on NPY_5 receptors. Some potent and selective NPY_5 receptor antagonists have been described in the literature[13—18] and their affinities were assessed through *in vitro* data over transfected CHO cells. However for most of them no *in vivo* data were published,[19] this is the case for compound **1** (Fig. 1) which is active *in vitro* (IC_{50}=8.3 nM) but inactive *in vivo*. We hypothetized that the exchange of the pyrazole ring by a pyridazine ring, in abolishing an intramolecular hydrogen bond between oxygen from amide function and the heterocyclic nitrogen, could lead a better central biodisponibility: in addition, pyridazines are known to have a good central bioavailability.[20] Hereafter we report the synthesis and biological evaluation of a series of pyridazine analogues of compound **1** (Fig. 1).

To acceed to these compounds, we propose a 3-step synthesis of a series of 3-acetamido-6-arylpyridazines **5a**—**k**.

The first strategy we envisaged for the synthesis of 3-*N*-(2-naphtylacetamido)-6-phenylpyridazine **5b** was based on a the sequence shown in route a (Chart 1): treatment of commercially available 3,6-dichloropyridazine **2** with aqueous ammonia[21] to yield the 3-amino-6-chloropyridazine **3**, coupling reaction between 3-amino-6-chloropyridazine **3** and 2-naphtylacetic acid in the presence of benzotriazol-1-yloxytris-(dimethylamino)phosphonium hexafluorophosphate (BOP)[22] produced the 3-*N*-(2-naphtylacetamido)-3-chloropyridazine **4**. Finally we proceeded to a palladium-catalyzed Suzuki cross-coupling reaction between acetamidopyridazine derivative **4** and a commercially available arylboronic acid. However, none of the several literature conditions[23,24] allowed us to obtain **5b** with satisfying yields (see Table 1).

The key difficulty in preparing compound **5b** lies in the cross-coupling reaction at last step. It can be explained by a stacking effect of the naphtyl ring with the pyridazine ring hindering the catalyst approach and by the electron withdrawing effect of amide function on pyridazine ring. To overcome this difficulty, the 3-*N*-(2-naphtylacetamido)-6-arylpyridazines **5a**—**k** (Table 2) were synthesized as outlined in route b of Chart 1. First a Suzuki cross-coupling reaction of available arylboronic acids with 3-amino-6-chloropyridazine **3** described previously[25] was used to prepare 3-amino-6-arylpyridazine **6** with 12—60% yields. The acetamidopyridazine derivatives **5a**—**k** were then prepared in 18—45% yields by coupling the activated 2-naphtylacetic acid with the 3-amino-6-arylpyridazine **6** using the diimidazolylcarbodiimide (DIC) procedure described by Honma *et al.*[26]

The derivatives **5** obtained above were evaluated for their affinity for the NPY_5 as well as the NPY_1 receptors. None of

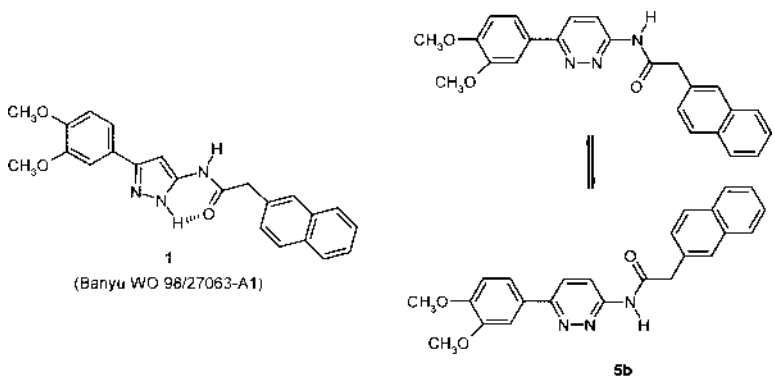
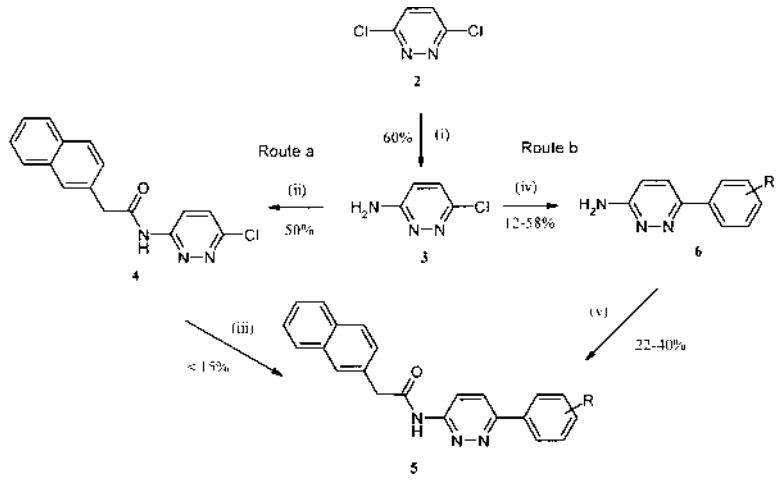


Fig. 1. Pyridazine Analogues of Compound **1**

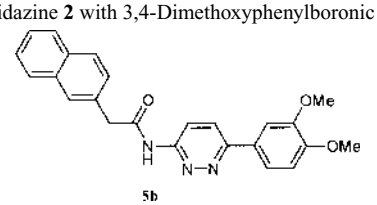
* To whom correspondence should be addressed. e-mail: rival@pharma.u-strasbg.fr



(i): 28% NH_4OH, 16 h, 105 °C; (ii): 2-naphtylacetic acid, BOP, DMAP cat, TEA, CH_3CN, 4 h, rt; (iii): arylboronic acid, $Pd(PPh_3)_4$, 2 M, Na_2CO_3, toluene/EtO; (iv): arylboronic acid, $Pd(PPh_3)_4$, 2 M Na_2CO_3, toluene/EtOH; (v): 2-naphtylacetic acid, DIC, anhydrous THF, anhydrous DMF.

Chart 1

Table 1. Reaction Conditions for the Pd(0)-Catalyzed Cross-coupling of 3,6-Dichloropyridazine **2** with 3,4-Dimethoxyphenylboronic Acid

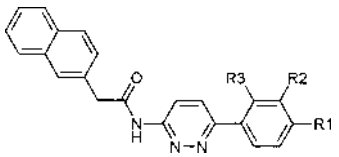


5b

Catalyst	Reaction conditions		Temp (°C)	Yield[a] (%)
	Base	Solvent		
$Pd(PPh_3)_4$	Na_2CO_3	Toluene/EtOH	110	<15
$Pd(PPh_3)_4$	Cs_2CO_3	Toluene/EtOH	110	—[b]
$Pd(PPh_3)_4$	K_3PO_4	DME	85	0
$Pd(PPh_3)_4$	$Ba(OH)_2$	DME	85	—
$Pd_2(dba)_3$/Pt-Bu_3	Cs_2CO_3	Dioxane	80	—

a) Yield of isolated pure product. *b*) —, traces.

Table 2. Synthesis of 3-*N*-(2-Naphtylacetamido)-6-arylpyridazines **5a**—**k**



Entry No.	R_1	R_2	R_3	Yield (%)	Y_5 IC_{50} (M)	Y_1 IC_{50} (M)
5a	H	H	H	32	$>10^{-5}$	$>10^{-5}$
5b	OMe	OMe	H	33	$>10^{-5}$	$>10^{-5}$
5c	–O–CH_2–O–		H	18	$>10^{-5}$	$>10^{-5}$
5d	OMe	H	H	38	$>10^{-5}$	$>10^{-5}$
5e	H	OMe	H	40	$>10^{-5}$	$>10^{-5}$
5f	H	H	OMe	22	$>10^{-5}$	$>10^{-5}$
5g	H	Cl	H	31	$>10^{-5}$	$>10^{-5}$
5h	H	H	Cl	25	$>10^{-5}$	$>10^{-5}$
5i	CH_3	H	H	45	$>10^{-5}$	$>10^{-5}$
5j	H	CH_3	H	40	$>10^{-5}$	$>10^{-5}$
5k	H	H	CH_3	38	$>10^{-5}$	$>10^{-5}$

the prepared compounds exhibited significant affinity (Table 2). This finding suggests that the intramolecular hydrogen bond of compound **1** stabilizes a locked conformation in which the orientation of the carbonyl function locates the oxygen atom close to the N1 nitrogen of the pyrazole ring whereas an opposite situation is preferred for compound **5b** and its analogues, the C=N and the C=O dipoles being located in a trans antiparallel arrangement.

In summary, a 3-step synthesis of 3-*N*-(2-naphtylacetamido)-6-arylpyridazines has been described as analogues of the pyrazole derivative **1** but behind the dramatically poor biological results, the working hypotheses must not be confirmed.

Experimental

All experiments were carried out under an argon atmosphere. Toluene, 1,2-dimethoxyethane (DME), tetrahydrofuran (THF) were distilled from benzophenone ketyl. Tetrakis(triphenylphosphine)palladium(0), 3,6-dichloropyridazine and arylboronic acids were purchased from Lancaster Synthesis. Melting points were determined with a Mettler FP62 apparatus and are uncorrected. All ^{1}H-NMR spectra were recorded on a Bruker AC 200 (200 MHz) or on a Bruker AC 300 (300 MHz) instruments, and chemical shifts are reported in parts per million (δ) relative to Me_4Si for $CDCl_3$ and Me_2SO-d_6 solutions (DMSO-d_6). Signals are quoted as s (singlet), d (doublet), t (triplet), q (quartet), or m (multiplet). Flash chromatography was carried out on silica gel (70—230 mesh ASTM). Elemental analyses were performed by CNRS (Vernaison) and are indicated only by the symbols of the elements; analytical results were within ±0.4% of the theoretical values.

Organic extracts were dried over Na_2SO_4.

Preparation of 3-Amino-6-arylpyridazines (6a—k) The 3-amino-6-arylpyridazines **6a**—**k** necessary for the synthesis of compounds **5a**—**k** were synthesized by using the Suzuki procedure described in our previous paper [25] where the 3-amino-6-arylpyridazines were already prepared. Aryl boronic acids were commercially available.

General Procedure for the Preparation of 3-*N*-(2-Naphtyl)acetamido-6-phenylpyridazine (5a—k) Diimidazolylcarbodiimide (DIC) (1.53 mmol; 248 mg; 1.05 eq) was added to a solution of 2-naphtylacetic acid (1.46 mmol; 272 mg; 1 eq.) in THF (3.52 ml) and *N*,*N*-dimethylformamide (DMF) (1.75 ml). The mixture was stirred at room temperature over 2 h and then aminopyridazine (**3**) (1.46 mmol; 1 eq) was added. The solution was stirred and allowed to warm to 70 °C over 4 h.

The solvents were removed by evaporation under reduce pression and the residue was diluted with AcOEt. The organic layer was washed with 1 N HCl and then with 1 N NaOH and then dried over Na_2SO_4. After removing the solvent by evaporation, the free base was purified by flash chromatography (AcOEt–Heptane, 2.5 : 7.5).

3-*N*-(2-Naphtyl)acetamido-6-phenylpyridazine (**5a**): White needles; mp 250 °C; *Rf* 0.15 (AcOEt 2.5/Heptane 7.5) ^{1}H-NMR (DMSO-d_6, 200 MHz) δ: 4.03 (s, 2H), 7.54—7.58 (m, 5H), 7.89—7.94 (m, 5H), 8.10—8.26 (m, 3H), 8.40 (d, J=9.3 Hz, 1H), 11.54 (s, 1H); ^{13}C-NMR (DMSO-d_6, 300 MHz) δ:

43.62, 119.24, 126.31, 126.58, 126.79, 126.97, 128.12, 128.38, 128.39, 129.58, 130.18, 132.55, 133.72, 136.46, 155.29, 156.0, 171.50; *Anal.* Calcd for $C_{22}H_{17}N_3O$, $0.25H_2O$: C, 76.83; H, 5.13; N, 12.22. Found: C, 76.52; H, 4.92; N, 12.27.

3-*N*-(2-Naphtyl)acetamido-6-(3,4-dimethoxyphenyl)pyridazine (**5b**): White needles; mp 240 °C; *Rf* 0.15 (AcOEt 2.5/Heptane 7.5) ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 3.88 (s, 3H), 3.94 (s, 3H), 4.10 (s, 2H), 6.95 (d, J=8.8 Hz, 1H), 7.43—7.54 (m, 4H), 7.74—7.92 (m, 6H), 8.54 (d, J=9.5 Hz, 1H), 8.90 (m, 1H); ^{13}C-NMR (DMSO-d_6, 200 MHz) δ: 45.12, 55.90, 110.6, 115.47, 125.0, 125.40, 126.0, 127.5, 128.3, 128.6, 128.7, 130.1, 133.2, 135.1, 139.4, 156.7, 158.8, 161.4, 172.0; *Anal.* Calcd for $C_{24}H_{21}N_3O_3$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.47; H, 5.16; N, 10.77.

3-*N*-(2-Naphtyl)acetamido-6-(3,4-methylenedioxyphenyl)pyridazine (**5c**): White needles; mp 250 °C.; *Rf* 0.15 (AcOEt 2.5/Heptane 7.5) ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 4.08 (s, 2H), 6.02 (s, 2H), 6.90 (d, J=8.3 Hz, 1H), 7.43—7.57 (m, 5H), 7.76—7.92 (m, 5H), 8.53 (d, J=8.8 Hz, 1H), 8.92 (m, 1H); ^{13}C-NMR (DMSO-d_6, 300 MHz) δ: 45.2, 101.6, 107.2, 108.9, 119.2, 121.0, 125.6, 126.4, 126.7, 127.3, 128.0, 128.7, 129.3, 131.2, 132.9, 148.7, 149.4, 153.7, 156.4, 170.6; *Anal.* Calcd for $C_{23}H_{19}N_3O_3$, 1.75 H_2O: C, 66.58; H, 4.98; N, 10.13. Found: C, 66.44; H, 4.69 N, 10.27.

3-*N*-(2-Naphtyl)acetamido-6-(4-methoxyphenyl)pyridazine (**5d**): White needles; mp dec.; *Rf* 0.15 (AcOEt 2.5/Heptane 7.5) ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 3.86 (s, 3H), 4.10 (s, 2H), 6.99 (d, J=8.7 Hz, 2H), 7.49—7.53 (m, 3H), 7.77—8.01 (m, 7H), 8.54 (d, J=9.3 Hz, 1H), 9.01 (m, 1H); ^{13}C-NMR (DMSO-d_6, 300 MHz) δ: 43.6, 55.8, 115.0, 119.3, 125.9, 126.3, 126.8, 128.1, 128.3, 128.4, 128.9, 132.5, 133.6, 133.7, 154.8, 155.7, 161.3, 171.4; *Anal.* Calcd for $C_{23}H_{19}N_3O_2$: C, 74.78; H, 5.18; N, 11.38. Found: C, 74.53; H, 5.16; N, 11.30.

3-*N*-(2-Naphtyl)acetamido-6-(3-methoxyphenyl)pyridazine (**5e**): White needles; mp 225 °C; *Rf* 0.15 (AcOEt 2.5/Heptane 7.5) ^{1}H-NMR (DMSO-d_6, 200 MHz) δ: 3.87 (s, 3H), 4.03 (s, 2H), 7.08 (dd, J=8.56 Hz, 1H), 7.43—7.70 (m, 6H), 7.89—7.94 (m, 4H), 8.24 (d, J=9.54 Hz, 1H), 8.39 (d, J=9.28 Hz, 1H), 11.52 (s, 1H); ^{13}C-NMR (DMSO-d_6, 300 MHz) δ: 43.6, 55.9, 112.1, 116.0, 119.2, 119.3, 126.3, 126.8, 128.1, 128.12, 128.3, 128.4, 130.7, 132.5, 133.6, 137.9, 155.4, 155.8, 160.0, 171.4; *Anal.* Calcd for $C_{23}H_{19}N_3O_2$: C, 72.14; H, 5.40; N, 10.98. Found: C, 71.95; H, 4.99; N, 11.00.

3-*N*-(2-Naphtyl)acetamido-6-(2-methoxyphenyl)pyridazine (**5f**): White needles; mp 163 °C; *Rf* 0.15 (AcOEt 2.5/Heptane 7.5) ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 3.86 (s, 3H), 4.25 (s, 2H), 6.99—7.06 (m, 2H), 7.37—7.88 (m, 10H), 8.58 (d, J=9.3 Hz, 1H), 10.53 (s, 1H); ^{13}C-NMR (DMSO-d_6, 300 MHz) δ: 45.1, 55.7, 110.5, 118.0, 121.5, 126.1, 126.7, 127.4, 127.8, 128.5, 129.2, 130.6, 130.9, 131.1, 131.6, 133.0, 133.7, 153.8, 156.1, 157.3, 170.9; *Anal.* Calcd for $C_{23}H_{19}N_3O_2$, 0.25 H_2O: C, 73.88; H, 5.26; N, 11.24. Found: C, 74.08; H, 5.24; N, 11.26.

3-*N*-(2-Naphtyl)acetamido-6-(3-chlorophenyl)pyridazine (**5g**): Yellow needles; mp 238 °C; *Rf* 0.13 (AcOEt 2.5/Heptane 7.5) ^{1}H-NMR (DMSO-d_6, 200 MHz) δ: 4.03 (s, 2H), 7.49—7.60 (m, 5H), 7.89—8.17 (m, 6H), 8.30 (d, J=9.5 Hz, 1H), 8.41 (d, J=9.5 Hz 1H), 8.41 (d, J=9.5 Hz 1H), 11.50 (m, 1H); ^{13}C-NMR (DMSO-d_6, 300 MHz) δ: 43.7, 79.8, 119.2, 125.6, 126.3, 126.6, 126.8, 126.9, 128.08, 128.1, 128.3, 128.4, 130.0, 131.5, 132.5, 133.6, 134.5, 138.7, 154.5, 155.5, 171.6; *Anal.* Calcd for $C_{22}H_{16}N_3OCl$, 0.75 H_2O: C, 68.22; H, 4.55; N, 10.85. Found: C, 68.50; H, 4.32; N, 11.02.

3-*N*-(2-Naphtyl)acetamido-6-(2-chlorophenyl)pyridazine (**5h**): Yellow needles; mp 179 °C; *Rf* 0.15 (AcOEt 2.5/Heptane 7.5) ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 4.15 (s, 2H), 7.34—7.92 (m, 13H), 8.63 (d, J=9.3 Hz 1H), 9.81 (m, 1H); ^{13}C-NMR ($CDCl_3$, 300 MHz) δ: 44.9, 118.3, 126.2, 126.5, 127.4, 127.5, 127.9, 128.5, 129.0, 130.4, 130.5, 130.7, 131.7, 132.9, 133.8, 135.8, 154.6, 156.8, 171.0; *Anal.* Calcd for $C_{22}H_{16}N_3OCl$, 0.75 H_2O: C, 68.22; H, 4.55; N, 10.85. Found: C, 68.51; H, 4.31; N, 10.91.

3-*N*-(2-Naphtyl)acetamido-6-(4-methylphenyl)pyridazine (**5i**): Yellow needles; mp 256 °C; *Rf* 0.16 (AcOEt 2.5/Heptane 7.5) ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 2.40 (s, 3H), 4.15 (s, 2H), 7.19—7.28 (m, 1H), 7.47—7.54 (m, 4H), 7.79—792 (m, 7H), 8.58 (d, J=9.3 Hz, 1H), 9.49 (m, 1H); ^{13}C-NMR ($CDCl_3$, 200 MHz) δ: 15.7, 40.8, 119.15, 126.1, 126.6, 127.0, 128.3, 129.5, 130.4, 132.0, 133.5, 134.0, 141.2, 152.0, 170.1; *Anal.* Calcd for $C_{23}H_{19}N_3O$: C, 78.16; H, 5.42; N, 11.89. Found: C, 78.20; H, 5.33; N, 12.01.

3-*N*-(2-Naphtyl)acetamido-6-(3-methylphenyl)pyridazine (**5j**): White needles; mp 255 °C; *Rf* 0.15 (AcOEt 2.5/Heptane 7.5) ^{1}H-NMR (DMSO-d_6, 200 MHz) δ: 2.43 (s, 3H), 4.03 (s, 2H), 7.31—7.58 (m, 5H), 7.90—7.94 (m, 6H), 8.21 (d, J=10.3 Hz, 1H), 8.39 (d, J=8.8 Hz, 1H), 11.51 (m, 1H); ^{13}C-NMR (DMSO-d_6, 300 MHz) δ: 21.7, 43.7, 119.2, 124.2, 126.4, 126.6, 126.8, 127.5, 128.1, 128.4, 129.5, 130.9, 132.6, 133.7, 136.5, 138.8, 155.3, 156.0, 171.7; *Anal.* Calcd for $C_{23}H_{19}N_3O$: C, 78.16; H, 5.42; N, 11.89. Found: C, 78.27; H, 5.39; N, 11.99.

3-*N*-(2-Naphtyl)acetamido-6-(2-methylphenyl)pyridazine (**5k**): Yellow needles; mp 175 °C; *Rf* 0.12 (AcOEt 2.5/Heptane 7.5) ^{1}H-NMR (DMSO-d_6, 200 MHz) δ: 2.33 (s, 3H), 4.03 (s, 2H), 7.33—7.59 (m, 7H), 7.82—7.94 (m, 5H), 8.39 (d, J=9.3 Hz, 1H), 11.55 (m, 1H); ^{13}C-NMR (DMSO-d_6, 300 MHz) δ: 43.7, 50.6, 118.6, 126.3, 126.7, 126.8, 128.1, 128.15, 128.3, 128.4, 129.5, 129.8, 130.2, 131.3, 132.5, 133.6, 133.7, 136.2, 137.6, 154.8, 158.7, 171.5; *Anal.* Calcd for $C_{23}H_{19}N_3O$, 0.25 H_2O: C, 77.18; H, 5.49; N, 11.74. Found: C, 77.27; H, 5.39; N, 11.98.

Binding Assays Binding assays for both receptors NPY_1 and NPY_5 were done as described by Duhault *et al.*[27] In brief, for the human Y_1 receptor binding assay, using iodinated Peptide YY (NEN), incubations were performed at 30 °C for 90 min with various competitors concentrations in Buffer A (Hepes/NaOH 20 mM, pH 7.4, NaCl 10 mM, KH_2PO_4 220 μM, $CaCl_2$ 1.26 mM, $MgSO_4$ 0.81 mM and bovine serum albumin 0.1%) with SK-N-MC cell membranes (50 μg of protein/ml of assay) in a total volume of 500 μl. Non-specific binding was determined in the presence of 1 μM NPY. The reaction was then stopped by filtration, the filters (GF/B, Whatman, precoated in 0.3% PEI) were extensively washed with buffer A, and counted in a gamma counter (Packard). For human Y_5 receptor binding assay, the binding was carried out with iodinated peptide YY (NEN) as follows: COS cells transfected with the human Y_5 NPY receptor were lysed and the membranes prepared by differential centrifugation. These membranes contained about 2 pmol per mg of protein of this receptor. Incubations were performed in 500 μl comprising, 20 pM final of [125I]PYY in 50 μl, 400 μl of membrane suspension (0.15 mg/ml) and competitor dilutions in 50 μl, at 30 °C for 2 h. The reaction was stopped by filtration through GF/C filters (Whatman).

References and Notes

1) Zimanyi I. A., Fathi Z., Poindexter G. S., *Current Pharmaceutical Design*, **4**, 349—366 (1998).
2) Inui A., *TiPS*, **20**, 43—46 (1999).
3) O'Shea D., Morgan D. G. A., Meeran K., Edwards C. M. B., Turton M. D., Choi S. J., Heath M. M., Gunn I., Taylor G. M., Howard J. K., Bloom C. I., Small C. J., Haddo O., Ma J. J., Callinan W., Smith D. M., Ghatei M. A., Bloom S. R., *Endocrinology*, **138**, 196—202 (1997).
4) Schaffhauser A. O., Stricker-Krongrad A., Brunner L., Cumin F., Gerald C., Whitebread S., Criscione L., Hofbauer K. G., *Diabetes*, **46**, 1792—1798 (1997).
5) Hu Y., Blommqvist B. J., Cornfield L. J., Decarr L. B., Flores-Riveros J. R., Friedman L., Jiang P., Lewis-Higgins L., Sadlowski Y., Schaeffer J., Velazquez N., Mc Caleb M. L., *J. Biol. Chem.*, **271**, 26315—26319 (1996).
6) Marsh D. J., Hollopeter G., Kafer K. E., Palmiter R. D., *Nat. Med. Chem.*, **4**, 718—721 (1998).
7) Wyss P., Stricker-Krongrad A., Brunner L., Miller J., Crossthwaite A., Whitebread S., Criscione L., *Regulatory Peptides.*, **75**—**76**, 363—371 (1998).
8) Flynn M. C., Turrin N. P., Plata-Salaman C. R., French-Mullen J. M. H., *Physiology Behavior.*, **66**, 881—884 (1999).
9) Wyss P., Levens N., Stricker-Krongrad A., *Neuroreport*, **9**, 2675—2677 (1998).
10) Gerald C., Walker M. W., Criscione L., *Nature* (London), **382**, 168—171 (1996).
11) Bischoff A., Michel M. C., *TiPS.*, **20**, 104—106 (1999).
12) Haynes A. C., Arch J. R. S., Wilson S., Mc Clue S., Buckingham R. E., *Regulatory Peptides*, **75**—**76**, 355—361 (1998).
13) Rueger H., Yamaguchi Y., Tintelnot-Blomley M., Scilling W., "Quinazolin-2,4-diaziridines as NPY Receptor Antagonists," WO 97/20822.
14) Rueger H., Schmidlin T., Rigollier R., Yamagichi Y., "New Quinazoline Derivatives are NPY Y5 Receptor Antagonists," WO 97/20283.
15) Fukami T., Fukuroda T., Kanatani A., Ihara M., New Aminopyrazoles are Neuropeptide Y Antagonists. Useful for the Treatment of *e.g.* Bulimia, Obesity ans Diabetes.; WO 98/27063 A1.
16) Fukami T., Fukuroda T., Kanatani A., Ihara M., New Carbonylaminopyrazole Derivatives are Neuropeptide Y Antagonists. Useful for Treating *e.g.* Bulimia, Obesity and Diabetes.; WO 98/25907.
17) Fukami T., Okamoto O., Fukuroda T., Kanatani A., Ihara M., Use of Aminopyridine Derivatives as Neuroipeptide Y Receptor Antagonists-for the Treatment of Obesity, Bulimia and Diabetes, and for Prevention and Treatment of Hypertension, Kidney Diseases, Cardiac Diseases, Circulation Disorders, Dementia, Depression, Anxiety and Hormone Disorders.; WO 98/40356-A1.
18) Connell R. D., Lease T. G., Ladouceur G. H., Osterhout M. H., Use of

Amide Derivatives as Selective NPY Y5 Receptor Antagonists-for the Treatment of *e.g.* Obesity, Bulimia, Type II Diabetes, Hypertension, Pulmonary Disease, Memory Disorders, Epilepsy, Dyslipidemia and Depression.; WO 98/355957-A1.
19) Kordik C. P., Reitz A. B., *J. Med. Chem.*, **42**, 181—201 (1999).
20) Wermuth C. G., *J. Heterocyclic Chem.*, **35**, 1091—1100 (1998).
21) Boger D. L., Coleman R. S., *J. Org. Chem.*, **49**, 2240—2245 (1984).
22) Castro B., Dormoy J. R., Evin G., Selve C., *Tetrahedron Lett.*, **14**, 1219—1222 (1975).
23) Parrot I., Rival Y., Wermuth C. G., *Synthesis*, **7**, 1163—1168 (1999).
24) Littke A. F., Fu G. C., *Angew. Chem. Int. Ed.*, **37**, 3387—3388 (1998).
25) Guery S., Parrot I., Rival Y., Wermuth C. G., *Tetrahedron Lett.*, **42**, 2115—2117 (2001).
26) Honma Y., Hanamoto K., Hashiyama T., Sekine Y., Takeda M., Ona Y., Tsuzurahara K., *J. Med. Chem.*, **27**, 125—128 (1984).
27) Duhault J., Boulanger M., Chamorro S., Boutin J. A., Della Zuana O., Douillet E., Fauchere J. L., Feletou M., Germain M., Husson B., Renard P., Tisserand F., *Can. J. Biochem. Physiol.*, **78**, 173—185 (2000).