Available online at www.sciencedirect.com
SCIENCE DIRECT®
European Journal of Medicinal Chemistry 39 (2004) 49–58
EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY
www.elsevier.com/locate/ejmech

Original article

Synthesis and evaluation of new arylsulfonamidomethylcyclohexyl derivatives as human neuropeptide Y Y_5 receptor antagonists for the treatment of obesity

Antonio Moreno, Silvia Pérez, Silvia Galiano, Laura Juanenea, Oihana Erviti, Carmen Frígola, Ignacio Aldana *, Antonio Monge

Unidad en Investigación y Desarrollo de Medicamentos, Centro de Investigación en Farmacobiología Aplicada (CIFA), Universidad de Navarra, c/Irunlarrea s/n, 31080 Pamplona, Spain

Received 26 June 2003; accepted 3 October 2003

Abstract

NPY is the most potent orexigenic peptide identified up to now. Stimulation of food intake is measured by the Y_1 and Y_5 receptor subtypes. In this study, the synthesis and evaluation of new arylsulfonamidomethylcyclohexyl derivatives are described as potential selective antagonists of the human NPY Y_5 receptor. The SAR of these series was examined and the amide derivatives were the compounds that showed the best activities. *trans-N*-{4-[(Quinolin-3-yl)aminocarbonyl]cyclohexylmethyl}-2,4-dichlorobenzenesulfonamide (**42**) bound to the human neuropeptide Y Y_5 receptor with a 2 nM IC_{50}.

Keywords: Arylsulfonamide; Obesity; NPY; H NPY Y_5 antagonists

1. Introduction

Obesity treatments will be a leading problem in the 21st century. Its prevalence is on the rise in all age groups and in all of the developed countries throughout the world. The exact etiology of obesity still remains unclear. It appears to be caused mainly by a combination of genetic factors, inappropriate eating and reduced activity. In addition, deregulation of various hypothalamic mechanisms controlling energy intake and energy expenditure has also been implicated in development and progression of obesity. In the past few years, advances made in the understanding of the body's weight regulating mechanisms have helped to define novel sites for targeting and intervention in order to reduce intake and enhance expenditure. Based on the aforementioned, many new antiobesity compounds have been described. Some of them are in the early stages of development, and the practically non-existence of efficient antiobesity drugs converts the search for pharmacological treatment into a target of notable interest [1,2].

Today the role of neuropeptide Y in food intake behavior is well recognized [3]. NPY is a protein made up of 36 amino acids with an amide in carboxyterminal position (pancreatic peptide family) found in abundance in the central and peripheral nervous system [4–7], whose alterations provoke eating disorders (obesity, bulimia and anorexia nervosa), emotional disorders (depression and anxiety), cardiovascular disorders (hypertension), diabetes and other diseases [8].

Physiological processes in both the CNS and PNS have been attributed to the activation of six receptor subtypes (Y_1, Y_2, Y_3, Y_4, Y_5 and Y_6), members of the superfamily of receptors linked to proteins G, with the Y_1 and Y_5 receptors being responsible for appetite stimulation [9–12]. Therefore, the enormous existing interest in the synthesis of new potent NPY Y_5 antagonists as antiobesity agents and the need to clarify the important role that this neuropeptide plays in the biology of food intake is more than justified.

This study proposes the search for new compounds that possess antagonistic activity on receptor Y_5 through the synthesis of new arylsulfonamidomethylcyclohexyl derivatives,

* Corresponding author.
E-mail address: ialdana@unav.es (I. Aldana).

doi:10.1016/j.ejmech.2003.10.001

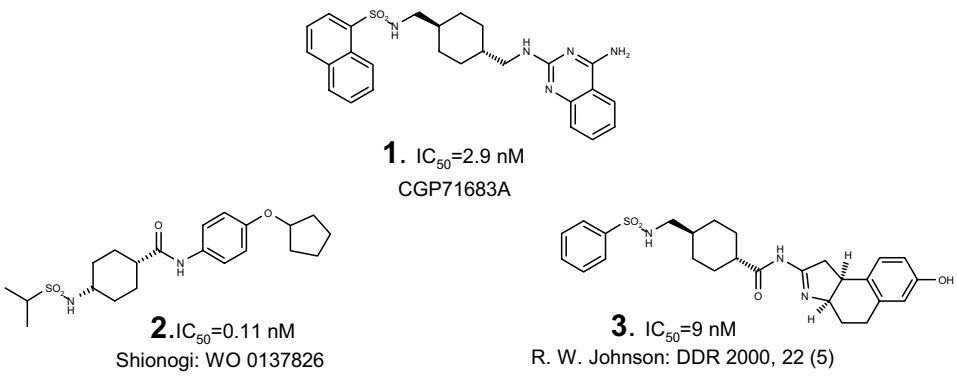
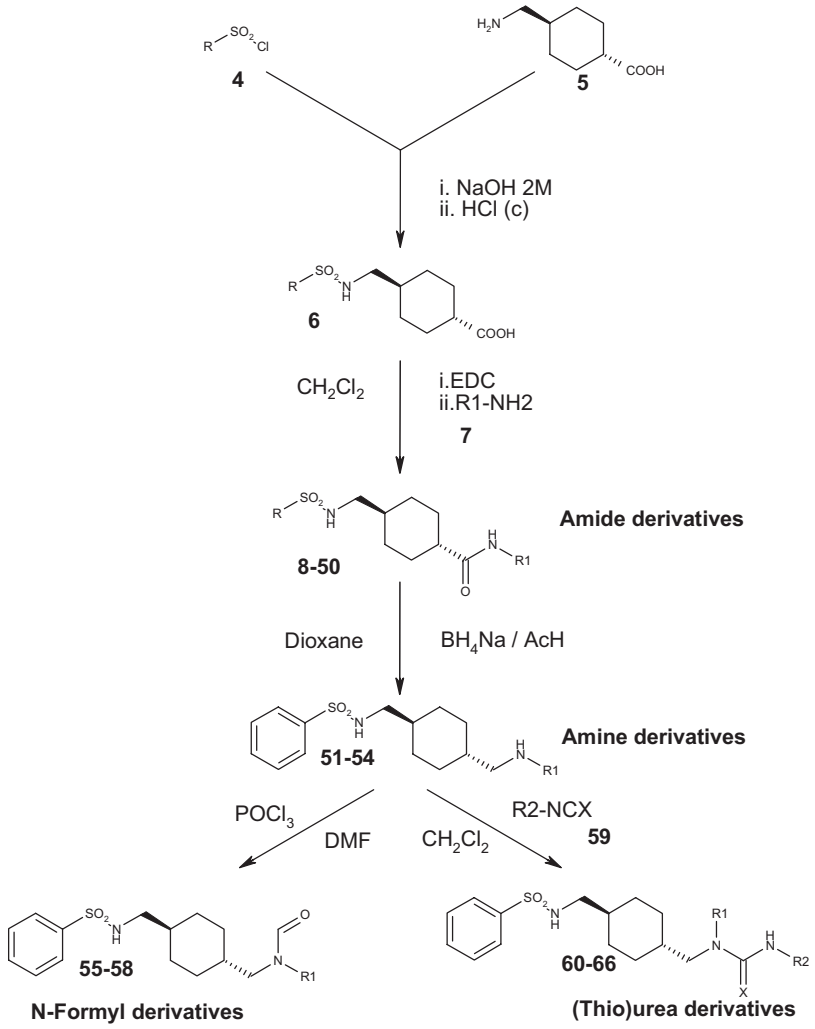


Fig. 1. Antecedents.

due to the fact that the sulfonamide group and the cyclohexyl linker were found to be essential in the concession of biological activity [13]. Recently, new derivatives, which antagonize the NPY Y5 receptor, have been published; all of them were considered to be potential antiobesity agents due to their notable in vitro activity (Fig. 1). Compound **1**, CGP71683A, reduces food intake in ob/ob rats and Zucker obese models [14,15].

2. Chemistry

Synthesis has been carried out on a series of compounds with a common nucleus, arylsulfonamidomethylcyclohexyl, following the synthetic route shown in Scheme 1. The said scheme presents both amide and amine derivatives as well as *N*-formyl and (thio)urea derivatives for the optimization and



Scheme 1. Synthesis of amide, amine, N-formyl and (thio)urea derivatives

identification of compounds with high affinity to the human Y_5 receptor.

Amide derivatives **8–50** are first obtained by the formation reaction of the primary sulfonamide intermediate **6**, which consists of a nucleophilic attack of amine **5** against sulfonyl chloride **4** [16]. Finally, the acylation of the different amine derivatives **7** required previous activation of the carboxylic group **6** with 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide·HCl (EDC) [17].

The amine derivatives **51–54** are obtained from the starting amides using the reaction medium BH_4Na/AcH, which yields the reducing agent sodium monoacetyloxy borohydride, capable of reducing the amide group by means of a transfer mechanism of hydrides [18]. Other reducing agents (B_2H_6, $BH_3{\cdot}Me_2S$, DIBAL, BH_4Na/CH_3SO_3H, H_4LiAl) were used without success.

The *N*-formyl derivatives **55–58** are prepared from the corresponding amine derivatives, using the Vilsmeier reagent as the formylating agent ($POCl_3$/DMF).

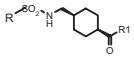
The (thio)urea derivatives **60–66** are obtained by reacting the corresponding amine derivatives with iso(thio)cyanates **59**.

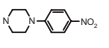
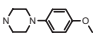
All of the compounds were chemically characterized by thin layer chromatography (TLC), melting point, infrared, nuclear magnetic resonance (^{1}H NMR), elemental microanalysis and HPLC.

3. Pharmacology

Binding assays for both receptors NPY Y_1 and NPY Y_5 were carried out following the method described by Duhault et al. [19]. 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 per 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 [^{125}I]PYY in 50 μl, 400 μl of membrane suspension (0.15 mg ml^{-1}) and competitor dilutions in 50 μl, at 30 °C for 2 h. The reaction was stopped by filtration through GF/C filters (Whatman). The results in both assays are expressed in IC_{50} (Tables 1–4).

Table 1
IC_{50} (NPY Y_5) results of the amide derivatives

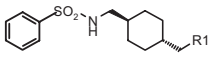


C.	R	R1	IC_{50} (nM)	C.	R	R1	IC_{50} (nM)
8			>10^4	9			>10^4
10			>10^4	11			>10^4
12			>10^4	13			>10^4
14			>10^4	15			>10^4
16			>10^4	17			>10^4
18			9240	19			748
20			>10^4	21			>10^4
22			>10^4	23			>10^4
24			425	25			138
26			416	27			179
28			19.2	29			>10^4
30			335	31			>10^4
32			>10^4	33			573
34			885	35			>10^4
36			1910	37			106
38			38.9	39			34.6
40			30.4	41			17.3
42			2.12	43			>10^4
44			>10^4	45			4220
46			>10^4	47			2840
48			79.9	49			79.9
50			4.16				

4. Results and discussion

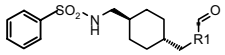
Fifty-eight new compounds, derivatives of the arylsulfonamidomethylcyclohexyl nucleus, have been synthesized; their affinities on the NPY Y_1 and Y_5 receptors have been evaluated in vitro. The compounds presented show no an-

Table 2
IC_{50} (NPY Y_5) results of the amine derivatives



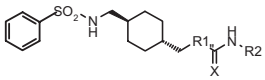
Comp.	R1	IC_{50} (nM)	Comp.	R1	IC_{50} (nM)
51		$>10^4$	**52**		$>10^4$
53		$>10^4$	**54**		113

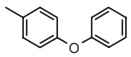
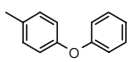
Table 3
IC_{50} (NPY Y_5) results of the N-formyl derivatives



Comp	R1	IC_{50} nM	Comp.	R1	IC_{50} nM
55		$>10^4$	**56**		$>10^4$
57		$>10^4$	**58**		n.d.

Table 4
IC_{50} (NPY Y_5) results of the (thio)urea derivatives



Comp.	R1	R2	X	IC_{50} (nM)
60			O	10200
61			O	$>10^5$
62			O	$>10^5$
63			S	$>10^5$
64			O	$>10^5$
65			O	$>10^5$
66			O	$>10^5$

tagonistic activity on the Y_1 receptor because their IC_{50} values are greater than 10^4 nM. The antagonistic activity of the molecules on the NPY Y_5 receptor, shown in Tables 1–4, will now be discussed.

The amide derivative results are shown in Table 1. Optimization of this series led to the identification of compounds with high affinity for the human Y_5 receptor subtype. Three lead compounds are obtained and referred to as **28, 42** and **50**. The incorporation of more than one nitrogen atom in the amine substituent R1 (**16–28** and **35–50**) of the amide derivatives favors the appearance of antagonistic activity of these compounds in comparison to other compounds that lack this

heteroatom in their chains (**8–15** and **29–34**). In addition, the said incorporation provides the molecule with the ability to accept hydrogen bonds and with basicity related to the permeability of the hematoencephalic barrier.

The arylsulfonamide substituents R favor activity in the cases of substitution in the *ortho* position on the benzene ring (**19, 22** vs. **24, 25; 29** vs. **30; 37, 39** vs. **40, 41**), even more so in cases of disubstitution *ortho–para* (**42**), or with condensation of the ring with another benzene, giving rigidness to the molecule (**19** vs. **26, 28**). Substitution effects on R1 are observed; they cause the chain to lengthen and become rigid, thereby giving better antagonistic activity to the molecule (**31** vs. **33; 35** vs. **37**). In conclusion, compounds that contain rigid groups with basic moieties give greater affinity to the antagonist.

The preliminary results show that the amine derivatives **51–54** (Table 2), *N*-formyl derivatives **55–58** (Table 3) and urea and thiourea derivatives **60–66** (Table 4) do not improve the results of the amide derivatives to a significant degree.

5. Conclusion

This study shows new arylsulfonamidomethylcyclohexyl derivatives as antagonistic agents of the NPY Y_5 receptor. The compounds are characterized by their selectivity on the Y_5 receptor as they show no affinity on the receptor Y_1.

The amide derivatives possess good results of IC_{50}, with activities that reach a nanomolar level (compounds **28, 42** and **50** stand out). They are characterized by possessing rigid moieties and basic centers capable of accepting hydrogen bonds, containing an amide group, and having electron-withdrawing substituents on the benzene ring of the arylsulfonamide group. These factors could orientate the arylsulfonamide, the linker cyclohexane, and the amine group correctly in the Y_5 receptor binding pockets.

The amine, *N*-formyl and (thio)urea derivatives do not present activity, or in the cases in which they do, the results are not within the range of nanomolar activity that our group is interested in (<75 nM).

6. Experimental protocols

6.1. General

Melting points were determined with a Mettler FP82 + FP80 apparatus (Greifense, Switzerland) and have not been corrected. The ^{1}H NMR spectra were recorded on a Bruker 400 Ultrashield™, using TMS as the internal standard and with DMSO-d_6 as the solvent; the chemical shifts are reported in ppm (δ) and coupling constants (J) values are given in Hertz (Hz). Signal multiplicities are represented by: s (singlet), ws (wide singlet), d (doublet), dd (double doublet), t (triplet), m (multiplet) and the IR spectra were performed on a Perkin Elmer 1600 FTIR (Norwalk, CT, USA) in KBr pellets; the frequencies are expressed in cm^{-1}. Signal intensities are expressed by: s (strong), m (medium) and w (weak). Elemental microanalyses were obtained on an Elemental Analyzer (Carlo Erba 1106, Milan, Italy) from vacuum-dried samples. The analytical results for C, H, and N, were within ±0.4 of the theoretical values.

Alugram® SIL G/UV_{254} (Layer: 0.2 mm) (Macherey-Nagel GmbH & Co., KG, Postfach 101352, D-52313 Düren, Germany) was used for TLC and Silica gel 60 (0.040–0.063 mm) for Column Chromatography (Merck). HPLC conditions: Column Lichrospher 100 RP18 E.C. 5 μm (20 × 0.46), Ref. TR011567, NS N23892; mobile phase: MeOH/H_2O 60/40; flux: 1 ml min^{-1}.

Chemicals were purchased from E. Merck (Darmstadt, Germany), Scharlau (F.E.R.O.S.A., Barcelona, Spain), Panreac Química S.A. (Montcada i Reixac, Barcelona, Spain), Sigma-Aldrich Química, S.A., (Alcobendas, Madrid), Acros Organics (Janssen Pharmaceuticalaan 3a, 2440 Geel, België) and Lancaster (Bischheim-Strasbourg, France).

6.2. General procedure for the synthesis of trans-4-(R-sulfonylaminomethyl)cyclohexanecarboxylic acid (6)

A solution of R-sulfonyl chloride (47.70 mmol) in the minimum amount of $CHCl_3$ was added, alternately and portionwise, to a solution of *trans*-4-(aminomethyl)-cyclohexanecarboxylic acid (5.0 g, 31.80 mmol) in NaOH 2 M (150 ml), with stirring for 30 min. After the addition, the mixture was stirred at room temperature for 48 h. The aqueous layer was acidified with HCl (c) to pH 1–2. The residue obtained was filtered and washed with H_2O (5 × 20 ml) and *n*-hexane (5 × 20 ml) in order to obtain sulfonamides **6**.

6.2.1. Synthesis of trans-4-(benzenesulfonylaminomethyl) cyclohexanecarboxylic acid

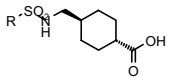
From benzenesulfonyl chloride (6.11 ml, 47.70 mmol) to obtain the compound as a white solid (3.46 g, 24%); m.p. 160–162 °C; IR (KBr): ν 1698 (s, carboxylic acid C=O), 1326 and 1162 (s, SO_2–N) $cm^{-1;}$ ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 0.80–0.84 (m, 2H, $\mathbf{H_a}$ of CH–C$\mathbf{H}_2$–CH_2–CH–CO); 1.09–1.27 (m, 3H, $\mathbf{H_a}$ of C$\mathbf{H}$–CH_2–C$\mathbf{H}_2$–CH–CO); 1.69 (d, 2H, $\mathbf{H_e}$ of CH–C$\mathbf{H}_2$–CH_2–CH–CO, J_{He} = 12.2 Hz); 1.84 (d, 2H, $\mathbf{H_e}$ of CH–CH_2–C$\mathbf{H}_2$–CH–CO, J_{He} = 12.2 Hz); 2.06 (t, 1H, CH–CH_2–CH_2–C$\mathbf{H}$–CO, J = 11.8 Hz); 2.56 (d, 2H, SO_2–NH–C$\mathbf{H}_2$, $J_{CH2–NH}$ = 6.3 Hz); 7.58–7.61 (m, 4H, $\mathbf{H}_3$, $\mathbf{H}_4$ and $\mathbf{H}_5$ of $C_6\mathbf{H}_5$ and SO_2–N$\mathbf{H}$); 7.78 (d, 2H, $\mathbf{H}_2$ and $\mathbf{H}_6$ of $C_6\mathbf{H}_5$, $J_{2.6–3.5}$ = 8.0 Hz); 12.00 (s, 1H, COO$\mathbf{H}$). Anal. $C_{14}H_{19}NO_4S$ (C, H, N); M_r 297.

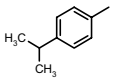
The rest of the sulfonamides were prepared similarly (Table 5).

6.3. General procedure for the synthesis of trans-N-[4-(R1-ylaminocarbonyl) cyclohexylmethyl]-R-sulfonamide (8–50)

Sulfonamides **6** (1 equiv.) in dry CH_2Cl_2 (150 ml) at 0 °C, under N_2 atmosphere, were treated with EDC (1.13 equiv.).

Table 5
Sulfonamide compounds



Comp.	R	Com	p.	R	Comp.	R
6.a			**6.b**		**6.c**	
6.d			**6.e**		**6.f**	
6.g			**6.h**		**6.i**	
6.j			**6.k**		**6.l**	
6.m			**6.n**			

After 1 h at 0 °C, the corresponding amine **7** (1.13 equiv.) was added. The reaction was stirred at room temperature for 24 h. The solvent was evaporated and the residue was taken up with H_2O (20 ml) and diethyl ether (5 ml). The obtained precipitate was filtered and washed with H_2O (5 × 20 ml) and diethyl ether (1 × 10 ml) in order to obtain compounds **8–50**. When necessary, the compounds were purified by means of recrystallization with *i*-PrOH:H_2O or by column chromatography (CH_2Cl_2 to CH_2Cl_2/MetOH).

6.3.1. Synthesis of trans*-N-[4-(phenylaminocarbonyl) cyclohexylmethyl]benzene sulfonamide (**31**)*

From *trans*-4-(benzenesulfonylaminomethyl)cyclohexanecarboxylic acid (5.05 mmol, 1.50 g), EDC (5.71 mmol, 1.09 g) and aniline (5.71 mmol, 0.53 g) to obtain **31** as a white solid (1.00 g, 53%). m.p. 230–231 °C. IR (KBr): *v* 1666 (s, amide C=O); 1311 and 1156 (s, SO_2–N). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 0.83–0.94 (m, 2H, $\mathbf{H_a}$ of CH–C$\mathbf{H}_2$–CH_2–CH–CO); 1.31–1.42 (m, 3H, $\mathbf{H_a}$ of C$\mathbf{H}$–CH_2–C$\mathbf{H}_2$–CH–CO); 1.62–1.90 (m, 4H, $\mathbf{H_e}$ of CH–C$\mathbf{H}_2$–C$\mathbf{H}_2$–CH–CO); 2.17–2.22 (m, 1H, CH–CH_2–CH_2–C$\mathbf{H}$–CO); 2.60 (t, 2H, SO_2–NH–C$\mathbf{H}_2$, $J_{CH2–NH}$ = 5.9 Hz); 7.00 (t, 1H, $\mathbf{H}_4$ of NH–$C_6\mathbf{H}_5$, $J_{H4–H3,5}$ = 7.3 Hz); 7.26 (t, 2H, $\mathbf{H}_3$ and $\mathbf{H}_5$ of NH–$C_6\mathbf{H}_5$, $J_{H3,5–H4}$ = 7.3 Hz); 7.56–7.62 (m, 6H, $\mathbf{H}_3$, $\mathbf{H}_4$, and $\mathbf{H}_5$ of $C_6\mathbf{H}_5$, $\mathbf{H}_2$ and $\mathbf{H}_6$ of NH–$C_6\mathbf{H}_5$ and SO_2–N**H**); 7.78–7.82 (m, 2H, $\mathbf{H}_2$ and $\mathbf{H}_6$ of $C_6\mathbf{H}_5$); 9.78 (s, 1H, N**H**–CO) ppm. Anal. $C_{20}H_{24}N_2O_3S$ (C, H, N); M_r 372.

The rest of the amide derivatives were prepared similarly.

6.4. General procedure for the synthesis of trans*-N-[4-(R1-ylaminomethyl)cyclohexylmethyl]benzenesulfonamide (**51–54**)*

Compounds **8, 12, 31, 33** (1 equiv., 0.75 g) in dry dioxane (30 ml) under anhydrous conditions were mixed with BH_4Na (5 equiv.) at 0 °C. A mixture of dioxane (10 ml) and glacial acetic acid (5 equiv.) was added over a period of 10 min at 10 °C. The resulting mixture was stirred under reflux for 5 h and concentrated to dryness in vacuo. The excess reagent was decomposed with water and extracted with chloroform. The extract was evaporated in vacuo and the residue was collected with *n*-hexane. The precipitate obtained was filtered in order to obtain compounds **51–54**.

6.4.1. Synthesis of trans*-N-[4-(phenylaminomethyl)cyclohexylmethyl]benzenesulfonamide (**53**)*

From **31** (2.02 mmol, 0.75 g), BH_4Na (15.9 mmol, 0.60 g) and a mix of dioxane (10 ml) and glacial acetic acid (0.6 ml) to obtain **53** as a white solid (0.50 g, 69%). m.p. 123–125 °C; IR (KBr): *v* 1315 and 1152 (s, SO_2–N); ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 0.74–0.94 (m, 4H, $\mathbf{H_a}$ of CH–C$\mathbf{H}_2$–C$\mathbf{H}_2$–CH–CH_2–N); 1.29 (s, 1H, C$\mathbf{H}$–CH_2–CH_2–CH–CH_2–N); 1.43 (s, 1H, CH–CH_2–CH_2–C$\mathbf{H}$–CH_2–N); 1.70 (d, 2H, $\mathbf{H_e}$ of CH–C$\mathbf{H}_2$–CH_2–CH–CH_2–N, J_{He} = 11.1 Hz); 1.80 (d, 2H, $\mathbf{H_e}$ of CH–CH_2–C$\mathbf{H}_2$–CH–CH_2–N, J_{He} = 11.1 Hz); 2.57 (t, 2H, SO_2–NH–C$\mathbf{H}_2$, $J_{CH2–NH}$ = 6.4 Hz); 2.80 (t, 2H, CH–CH_2–CH_2–CH–C$\mathbf{H}_2$–N, $J_{CH2–NH}$ = 5.7 Hz); 5.53 (t, 1H, N**H**–C_6H_5, $J_{NH–CH2}$ = 5.7 Hz); 6.45–6.53 (m, 3H, $\mathbf{H}_2$, $\mathbf{H}_4$ and $\mathbf{H}_6$ of NH–$C_6\mathbf{H}_5$); 7.03 (t, 2H, $\mathbf{H}_3$ and $\mathbf{H}_5$ of NH–$C_6\mathbf{H}_5$, *J* = 7.8 Hz); 7.57–7.64 (m, 4H, $\mathbf{H}_3$, $\mathbf{H}_4$ and $\mathbf{H}_5$ of $C_6\mathbf{H}_5$ and

SO_2–N**H**); 7.78–7.80 (m, 2H, $\mathbf{H}_2$ and $\mathbf{H}_6$ of $C_6\mathbf{H}_5$) ppm. Anal. $C_{20}H_{26}N_2O_2S$ (C, H, N); M_r 358.

The rest of the amine derivatives were prepared similarly.

6.5. General procedure for the synthesis of trans-N-*{4-[(*N′*formyl-*N′*R1-ylamino)methyl]cyclohexylmethyl}benzenesulfonamide (**55–58**)*

Ten milliliters of dry $POCl_3$ was added dropwise to a 100 ml round-bottomed flask with 30 ml of dry *N,N*-DMF, provided with a magnetic stirring bar and a $CaCl_2$ tube. This addition was carried out for 30 min at 0 °C. Next, the system was stirred at room temperature for 20 min and a mixture of **51–54** (1.00 g) in *N,N*-DMF (5 ml) was added dropwise during 20 min at 0–10 °C. The reaction was then heated to 40 °C during 2 h. At 0 °C, the mixture was hydrolyzed with ice. NaOH 10% was added to pH 8 and the mixture was heated until boiling. The mixture was left overnight at 0 °C and a precipitate was formed. The precipitate was purified by flash chromatography (CH_2Cl_2 to CH_2Cl_2/MetOH) in order to obtain compounds **55–58**.

6.5.1. Synthesis of trans-N-*{4-[(*N-*formyl*-N-*phenylamino)methyl]cyclohexylmethyl}benzene sulfonamide (**57**)*

From **53** (2.80 mmol, 1.00 g) and after purification by flash chromatography (CH_2Cl_2/MetOH 97/3) in order to obtain **57** as a white solid (0.22 g, 20%). m.p. 83–85 °C. IR (KBr): *ν* 1653 (s, formyl C=O); 1327 and 1161 (s, SO_2–N); ^{1}H NMR (DMSO-d_6, 400 MHz) *δ*: 0.60–0.71 (m, 2H, $\mathbf{H_a}$ of CH–C**H**$_2$–CH_2–CH–CH_2–N); 0.75–0.91 (m, 2H, $\mathbf{H_a}$ of CH–CH_2–C**H**$_2$–CH–CH_2–N); 1.20–1.39 (m, 2H, C**H**–CH_2–CH_2–C**H**–CH_2–N); 1.60 (t, 4H, $\mathbf{H_e}$ of CH–C**H**$_2$–C**H**$_2$–CH–CH_2–N, J_{He} = 11.2 Hz); 2.49–2.53 (m, 2H, SO_2–NH–C**H**$_2$); 3.65 (d, 2H, CH–CH_2–CH_2–CH–C**H**$_2$–N, $J_{CH2–CH}$ = 7.2 Hz); 7.23–7.30 (m, 1H, $\mathbf{H}_4$ of N–$C_6\mathbf{H}_5$); 7.34 (d, 2H, $\mathbf{H}_2$ and $\mathbf{H}_6$ of N–$C_6\mathbf{H}_5$, $J_{H2,6–H3,5}$ = 7.4 Hz); 7.42 (t, 2H, $\mathbf{H}_3$ and $\mathbf{H}_5$ of N–$C_6\mathbf{H}_5$); 7.51–7.65 (m, 4H, $\mathbf{H}_3$, $\mathbf{H}_4$ and $\mathbf{H}_5$ of $C_6\mathbf{H}_5$ and SO_2–N**H**); 7.75 (t, 2H, $\mathbf{H}_2$ and $\mathbf{H}_6$ of $C_6\mathbf{H}_5$); 8.26 and 8.40 (2s, 1H, C**H**O) ppm. Anal. $C_{21}H_{26}N_2O_3S{\cdot}1/2H_2O$ (C, H, N); M_r 395.

The rest of the *N*-formyl derivatives were prepared similarly.

6.6. General procedure for the synthesis of trans-N-*[4-(3-R2-yl-1-R1-ylureidomethyl)cyclohexylmethyl}benzenesulfonamide*

Compounds **51–53** (0.50 g, 1 equiv.) and 30 ml of dry CH_2Cl_2 were added to a 100 ml round-bottomed flask equipped with a magnetic stirring bar and a $CaCl_2$ tube. The corresponding isocyanate **59** (1.10 equiv.) was added using a syringe and the reaction mixture was stirred for 5 h at room temperature. *n*-Hexane was added until a white precipitate was obtained. The precipitate was filtered and washed with *n*-hexane (2 × 10 ml) and then recrystallized from *i*-PrOH:H_2O (3:1) in order to obtain urea derivatives (**60–62, 64–66**).

6.6.1. Synthesis of trans-N-*[4-(3-benzyl-1-phenylureidomethyl)cyclohexylmethyl}benzenesulfonamide (**65**)*

From **53** (1.40 mmol, 0.50 g) and benzylisocyanate (1.54 mmol, 0.20 g) to obtain **65** as a white solid (0.40 g, 58%). m.p. 162–164 °C; IR (KBr): *ν* 1637 (s, urea C=O); 1327 and 1161 (s, SO_2–N); ^{1}H NMR (DMSO-d_6, 400 MHz) *δ*: 0.61–0.85 (m, 4H, $\mathbf{H_a}$ of CH–C**H**$_2$–C**H**$_2$–CH–CH_2–N); 1.24 (s, 2H, C**H**–CH_2–CH_2–C**H**–CH_2–N); 1.64 (d, 4H, $\mathbf{H_e}$ of CH–CH_2–C**H**$_2$–CH–CH_2–N, J_{He} = 10.4 Hz); 2.54 (m, 2H, SO_2–NH–C**H**$_2$, $J_{CH2–NH}$ = 6.3 Hz); 3.45 (d, 2H, CH–CH_2–CH_2–CH–C**H**$_2$–N, $J_{CH2–CH}$ = 7.1 Hz); 4.18 (d, 2H, C**H**$_2$–C_6H_5, $J_{CH2–NH}$ = 5.9 Hz); 6.10 (t, 1H, CO–N**H**, $J_{NH–CH2}$ = 5.9 Hz); 7.19 (d, 3H, $\mathbf{H}_2$, $\mathbf{H}_4$ and $\mathbf{H}_6$ of CH_2–$C_6\mathbf{H}_5$, *J* = 7.3 Hz); 7.24–7.31 (m, 5H, $\mathbf{H}_2$, $\mathbf{H}_4$ and $\mathbf{H}_6$ of N–$C_6\mathbf{H}_5$ and $\mathbf{H}_3$ and $\mathbf{H}_5$ of CH_2–$C_6\mathbf{H}_5$); 7.42 (t, 2H, $\mathbf{H}_3$ and $\mathbf{H}_5$ of N–$C_6\mathbf{H}_5$, *J* = 7.6 Hz); 7.51–7.62 (m, 4H, $\mathbf{H}_3$, $\mathbf{H}_4$ and $\mathbf{H}_5$ of $C_6\mathbf{H}_5$ and SO_2–N**H**); 7.78 (d, 2H, $\mathbf{H}_2$ and $\mathbf{H}_6$ of $C_6\mathbf{H}_5$, $J_{H2,6–H3,5}$ = 6.8 Hz) ppm. Anal. $C_{28}H_{33}N_3O_3S{\cdot}1/2H_2O$ (C, H, N); M_r 500.

The rest of the urea derivatives were prepared similarly.

6.6.2. Synthesis of trans-N-*[4-(1-isopropyl-3-phenylthioureidomethyl)cyclohexylmethyl]benzenesulfonamide (**63**)*

Compound **51** (1.54 mmol, 0.50 g) and 30 ml of dry CH_2Cl_2 were added to a 100 ml round-bottomed flask equipped with a magnetic stirring bar and a $CaCl_2$ tube. Phenylisothiocyanate (3.34 mmol, 0.45 g) was added using a syringe and the reaction mixture was stirred for 5 h at room temperature. *n*-Hexane was added until a white precipitate was obtained. The precipitate was filtered and washed with *n*-hexane (2 × 10 ml) and then recrystallized from *i*-PrOH:H_2O (3:1) in order to obtain **63** as a white solid (0.20 g, 28%). m.p. 130–132 °C; IR (KBr): *ν* 1337 and 1155 (s, SO_2–N); ^{1}H NMR (DMSO-d_6, 400 MHz) *δ*: 0.70–0.78 (m, 2H, $\mathbf{H_a}$ of CH–C**H**$_2$–CH_2–CH–CH_2–N); 0.83–0.94 (m, 2H, $\mathbf{H_a}$ of CH–CH_2–C**H**$_2$–CH–CH_2–N); 1.13 (d, 6H, CH–(C**H**$_3$)$_2$, $J_{CH3–CH}$ = 6.8 Hz); 1.27 (ws, 1H, C**H**–CH_2–CH_2–CH–CH_2–N); 1.61–1.80 (m, 5H, $\mathbf{H_e}$ of CH–C**H**$_2$–C**H**$_2$–CH–CH_2–N and CH–CH_2–CH_2–C**H**–CH_2–N); 2.56 (t, 2H, SO_2–NH–C**H**$_2$, $J_{CH2–NH}$ = 6.3 Hz); 3.31–3.39 (m, 2H, CH–CH_2–CH_2–CH–C**H**$_2$–N); 5.34 (ws, 1H, C**H**–$(CH_3)_2$); 7.10 (t, 1H, $\mathbf{H}_4$ of NH–$C_6\mathbf{H}_5$); 7.18 (d, 2H, $\mathbf{H}_2$ and $\mathbf{H}_6$ of NH–$C_6\mathbf{H}_5$, $J_{H2,6–H3,5}$ = 7.8 Hz); 7.29 (t, 2H, $\mathbf{H}_3$ and $\mathbf{H}_5$ of NH–$C_6\mathbf{H}_5$, $J_{H3,5–H2,6}$ = 7.8 Hz); 7.57–7.63 (m, 4H, $\mathbf{H}_3$, $\mathbf{H}_4$ and $\mathbf{H}_5$ of $C_6\mathbf{H}_5$ and SO_2–N**H**); 7.72 (d, 2H, $\mathbf{H}_2$ and $\mathbf{H}_6$ of $C_6\mathbf{H}_5$, $J_{H6–H3,5}$ = 6.6 Hz); 8.89 (s, 1H, N**H**–CS) ppm. Anal. $C_{24}H_{33}N_3O_2S_2{\cdot}1/2H_2O$ (C, H, N); M_r 468.

Acknowledgements

This group of authors wishes to thank Carmen Elizalde and Lara Orús for their collaboration. We wish to thank the Asociación de Amigos de la Universidad de Navarra for grants given to A. Moreno.

Elemental microanalysis

Compound	Calculated	Found	Compound	Calculated	Found
(I) IC_{50} (NPY Y_5) results of the amide derivatives					
6a	C: 56.56	C: 56.60	**6b**	C: 44.69	C: 44.71
	H: 6.40	H: 6.34		H: 4.82	H: 4.84
	N: 4.71	N: 4.57		N: 3.72	N: 3.66
6c	C: 44.69	C: 44.51	**6d**	C: 49.12	C: 49.01
	H: 4.82	H: 4.83		H: 5.26	H: 5.22
	N: 3.72	N: 3.58		N: 8.19	N: 7.96
6e	C: 60.18	C: 59.92	**6f**	C: 48.00	C: 47.78
	H: 7.37	H: 7.70		H: 5.60	H: 5.92
	N: 4.13	N: 4.52		N: 3.73	N: 3.64
6g·1/2H_2O	C: 60.67	C: 60.59	**6h**	C: 57.14	C: 57.29
	H: 6.17	H: 5.84		H: 5.60	H: 5.99
	N: 3.93	N: 3.79		N: 7.84	N: 7.85
6i	C: 58.62	C: 58.50	**6j**	C: 50.69	C: 50.71
	H: 5.75	H: 5.82		H: 5.43	H: 5.43
	N: 8.05	N: 7.95		N: 4.22	N: 4.20
6k	C: 62.25	C: 62.48	**6l**	C: 50.69	C: 50.63
	H: 6.04	H: 6.27		H: 5.43	H: 5.65
	N: 4.03	N: 4.02		N: 4.22	N: 4.24
6m·1/2H_2O	C: 51.87	C: 52.04	**6n**	C: 48.00	C: 48.31
	H: 5.86	H: 5.72		H: 4.86	H: 4.86
	N: 4.32	N: 4.24		N: 4.00	N: 4.10
8	C: 60.36	C: 59.97	**9**	C: 61.36	C: 61.06
	H: 7.69	H: 7.80		H: 7.95	H: 7.95
	N: 8.28	N: 8.10		N: 7.95	N: 7.85
10	C: 56.47	C: 56.07	**11**	C: 57.63	C: 57.59
	H: 7.05	H: 6.90		H: 7.34	H: 7.39
	N: 8.24	N: 8.27		N: 7.91	N: 7.60
12	C: 63.49	C: 63.45	**13**	C: 62.64	C: 62.33
	H: 7.94	H: 7.98		H: 7.69	H: 7.43
	N: 7.41	N: 7.25		N: 7.69	N: 7.48
14·1/2H_2O	C: 57.60	C: 57.91	**15**	C: 60.00	C: 59.84
	H: 6.93	H: 7.37		H: 7.37	H: 7.20
	N: 7.47	N: 7.41		N: 7.37	N: 7.51
16	C: 59.26	C: 59.01	**17**	C: 60.58	C: 60.50
	H: 6.17	H: 6.12		H: 6.31	H: 6.56
	N: 11.52	N: 11.47		N: 8.83	N: 8.68
18·1/2H_2O	C: 62.50	C: 62.22	**19**	C: 59.59	C: 59.49
	H: 7.08	H: 7.02		H: 6.54	H: 6.66
	N: 8.75	N: 9.14		N: 15.80	N: 15.62
20	C: 61.86	C: 61.87	**21**	C: 54.01	C: 53.62
	H: 7.22	H: 7.38		H: 5.48	H: 5.48
	N: 14.43	N: 14.44		N: 13.70	N: 13.50
22	C: 50.58	C: 50.28	**23**	C: 52.97	C: 52.57
	H: 5.36	H: 5.47		H: 5.95	H: 6.21
	N: 13.41	N: 13.01		N: 13.44	N: 13.29
24	C: 54.10	C: 53.93	**25**	C: 55.29	C: 54.90
	H: 5.73	H: 5.62		H: 5.86	H: 5.89
	N: 17.21	N: 17.17		N: 14.65	N: 14.77
26·1/2H_2O	C: 62.07	C: 62.35	**27**·1/2H_2O	C: 59.64	C: 59.32
	H: 6.36	H: 6.32		H: 5.96	H: 6.22
	N: 13.93	N: 13.86		N: 16.70	N: 16.41

(continued on next page)

Elemental microanalysis *(continued)*

Compound	Calculated	Found	Compound	Calculated	Found
28	C: 62.37	C: 61.99	**29**·1/2H_2O	C: 67.41	C: 67.01
	H: 6.44	H: 6.84		H: 6.51	H: 6.32
	N: 14.55	N: 14.25		N: 6.29	N: 6.01
30	C: 58.45	C: 58.77	**31**	C: 64.52	C: 64.16
	H: 5.84	H: 5.93		H: 6.45	H: 6.42
	N: 9.74	N: 9.74		N: 7.53	N: 7.56
32	C: 52.13	C: 52.26	**33**	C: 68.25	C: 68.01
	H: 5.00	H: 5.00		H: 6.16	H: 6.12
	N: 6.08	N: 6.29		N: 6.64	N: 6.25
34	C: 59.04	C: 58.48	**35**	C: 61.13	C: 60.78
	H: 5.65	H: 5.88		H: 6.17	H: 6.36
	N: 6.88	N: 7.10		N: 11.26	N: 11.34
36·1/2H_2O	C: 63.88	C: 63.78	**37**	C: 62.25	C: 64.94
	H: 5.79	H: 6.20		H: 5.91	H: 6.09
	N: 9.72	N: 9.75		N: 9.93	N: 9.61
38	C: 60.33	C: 60.24	**39**	C: 54.99	C: 55.04
	H: 5.25	H: 5.37		H: 4.78	H: 5.00
	N: 9.18	N: 9.23		N: 8.37	N: 8.26
40	C: 62.58	C: 62.21	**41**	C: 54.99	C: 54.67
	H: 5.44	H: 5.55		H: 4.78	H: 5.09
	N: 9.52	N: 9.31		N: 8.37	N: 8.05
42	C: 56.11	C: 55.79	**43**·1/2H_2O	C: 59.85	C: 60.15
	H: 4.68	H: 4.79		H: 5.70	H: 5.54
	N: 8.54	N: 8.41		N: 13.30	N: 13.24
44·1/2H_2O	C: 47.11	C: 47.22	**45**·1/2H_2O	C: 57.53	C: 57.37
	H: 4.62	H: 5.01		H: 5.25	H: 5.30
	N: 12.93	N: 12.69		N: 9.59	N: 9.90
46	C: 58.74	C: 58.61	**47**·1/2H_2O	C: 57.53	C: 57.80
	H: 5.36	H: 5.61		H: 5.25	H: 5.51
	N: 9.79	N: 9.43		N: 9.59	N: 9.72
48·1/2H_2O	C: 64.93	C: 64.90	**49**	C: 66.12	C: 65.84
	H: 6.01	H: 6.22		H: 6.12	H: 6.02
	N: 11.22	N: 11.43		N: 1.43	N: 11.37
50	C: 56.91	C: 56.54			
	H: 5.57	H: 5.48			
	N: 14.43	N: 14.09			
(II) IC_{50} (NPY Y_5) results of the amine derivatives					
51	C: 62.96	C: 62.83	**52**	C: 65.93	C: 65.90
	H: 8.64	H: 8.74		H: 8.79	H: 8.70
	N: 8.64	N: 8.28		N: 7.69	N: 7.58
53	C: 67.04	C: 66.91	**54**	C: 70.59	C: 70.19
	H: 7.26	H: 7.16		H: 6.89	H: 6.81
	N: 7.82	N: 7.68		N: 6.86	N: 6.52
(III) IC_{50} (NPY Y_5) results of the N-formyl derivatives					
55	C: 61.36	C: 61.62	**56**	C: 64.28	C: 64.04
	H: 7.95	H: 8.07		H: 8.16	H: 8.30
	N: 7.95	N: 7.69		N: 7.14	N: 7.17
57·1/2H_2O	C: 63.80	C: 63.95	**58**·1/2H_2O	C: 67.41	C: 67.41
	H: 6.83	H: 6.96		H: 6.52	H: 6.52
	N: 7.09	N: 6.77		N: 6.29	N: 6.26

(continued on next page)

Elemental microanalysis *(continued)*

Compound	Calculated	Found	Compound	Calculated	Found
(IV) IC_{50} (NPY Y_5) results of the (thio)urea derivatives					
60	C: 65.64	C: 65.38	**61**	C: 65.01	C: 64.91
	H: 7.66	H: 8.01		H: 7.45	H: 7.45
	N: 9.19	N: 8.80		N: 9.48	N: 9.36
62	C: 67.29	C: 66.94	**63**·1/2H_2O	C: 61.54	C: 61.62
	H: 6.92	H: 6.83		H: 7.56	H: 7.40
	N: 7.85	N: 7.91		N: 8.97	N: 9.15
64	C: 67.60	C: 67.50	**65**	C: 68.43	C: 68.30
	H: 7.85	H: 7.72		H: 6.72	H: 6.61
	N: 8.45	N: 8.31		N: 8.55	N: 8.51
66	C: 69.60	C: 69.02			
	H: 6.15	H: 6.08			
	N: 7.38	N: 7.15			

References

[1] P. Björntorp (Ed.), International Textbook of Obesity, Wiley, Chichester, 2001.

[2] second ed, in: J. Braguinsky (Ed.), Obesidad, El Ateneo, Buenos Aires, 1996.

[3] S.P. Kalra, P.S. Kalra, Curr. Opin. Endocrinol. Diabetes 3 (1996) 157–163.

[4] K. Tatemoto, M. Carlquist, V. Mutt, Nature 296 (1982) 659–660.

[5] T.S. Gray, J.E. Morley, Life Sci. 38 (1986) 389–401.

[6] T.L. O'Donohue, B.M. Chronwall, R.M. Pruss, E. Mezey, J.Z. Kiss, L.E. Eiden, J. Massari, E. Tessel, V.M. Pickel, D.A. DiMaggio, A.J. Hotchkiss, W.R. Crowly, Z. Zukowska-Grojec, Peptides 6 (1985) 755–768.

[7] K. Tatemoto, M.J. Mann, M. Shimizu, Proc. Natl. Acad. Sci. USA 89 (1992) 1174–1178.

[8] W.F. Colmers, C. Wahlestedt (Eds.), The Biology of Neuropeptide Y and Related Peptides, The Humana Press Inc., Totowa, NJ, 1993.

[9] C. Gerald, M.W. Walker, L. Criscione, E.L. Gustafson, C. Batzl-Hartmann, K.E. Smith, P. Vaysse, M.M. Durkin, T.M. Laz, D.L. Linemeyer, A.O. Schaffauser, S. Whitebread, K.G. Hofbauer, R.I. Taber, T.A. Brachek, R.B.L. Weinshank, Nature 382 (1996) 168–171.

[10] A. Inui, Trends Pharmacol. Sci. 20 (1999) 43–46.

[11] B.G. Stanley, W. Magdalin, A. Seirafi, M.M. Nguyen, S.F. Leibowitz, Peptides 13 (1992) 581–587.

[12] D.A. Kirby, S.C. Koerber, J.M. May, C. Hagaman, M.J. Cullen, M.A. Pellymounter, J.E. Rivier, J. Med. Chem. 38 (1995) 4579–4586.

[13] I. Islam, D. Dhanoa, J. Finn, P. Du, M.W. Walker, J.A. Salon, J. Zhang, C. Gluchowski, Bioorg. Med. Chem. Lett 12 (2002) 1767–1769.

[14] H. Rueger, T. Schmidlin, P. Rigollier, Y. Yamaguchi, M. Tintelnot-Blomley, W. Schilling, L. Criscione, R. Mah, PCT WO 97/20823.

[15] K.G. Hofbauer, A.O. Schaffhauser, C. Batel-Hartmann, A. Stricker-Krongrad, S. Whitebread, F. Cumin, P. Rigollier, Y. Yamaguchi, M. Chiesi, N. Levens, W. Schilling, M. Walker, C. Gerald, H. Rueger, L. Criscione, Fourth International NPY Conference 1997, Abstract in Regul. Pept, 71, 1997, p. 211.

[16] fifth ed, in: M.B. Smith, J. March (Eds.), March's Advanced Chemistry, Wiley-Interscience, New York, 2001, pp. 574–578.

[17] J. Rebek, D. Feitler, J. Am. Chem. Soc. 95 (1973) 4052–4053.

[18] G.W. Grible, Chem. Soc. Rev 27 (1998) 395–404.

[19] J. Duhault, M. Boulanger, S. Chamorro, J.A. Boutin, O. Della Zuana, E. Douillet, J.L. Fauchere, M. Feletou, M. Germain, B. Husson, P. Renard, F. Tisserand, Can. J. Biochem. Physiol. 78 (2000) 173–185.