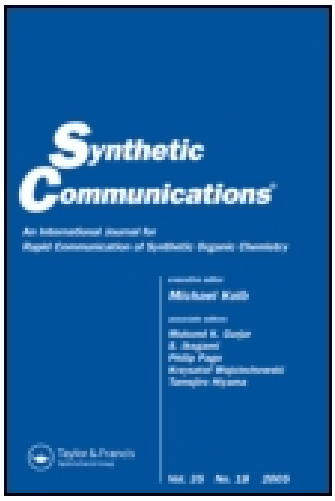

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EFFICIENT SYNTHESIS OF A SELECTIVE Y5 RECEPTOR ANTAGONIST

Sébastien Guery [a] , Yveline Rival [a] & Camille G. Wermuth [a]

[a] Faculté de Pharmacie , Laboratoire de Pharmacochimie de la Communication Cellulaire , UMR 7081 CNRS/ULP , Université Louis Pasteur , 74 Route du Rhin, Illkirch, Cedex 67401, France

[b] Université Louis Pasteur , Laboratoire de Pharmacochimie de la Communication Cellulaire, UMR 7081 CNRS/ULP, Faculté de pharmacie, 74 Route du Rhin, Illkirch Cedex, 67401, France

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EFFICIENT SYNTHESIS OF A SELECTIVE Y5 RECEPTOR ANTAGONIST

Sébastien Guery, Yveline Rival,* and Camille G. Wermuth

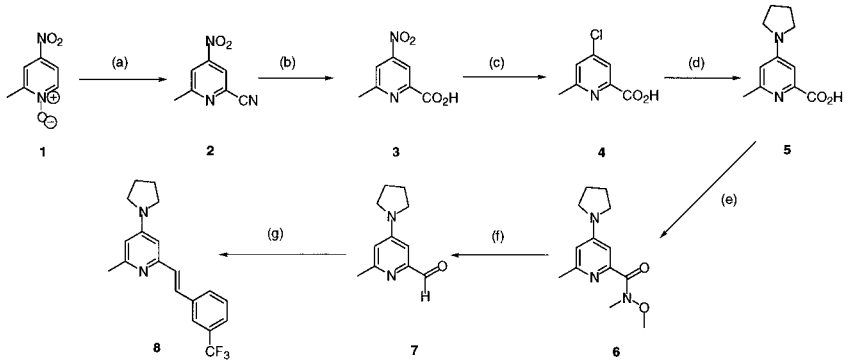
Laboratoire de Pharmacochimie de la Communication Cellulaire, UMR 7081 CNRS/ULP, Université Louis Pasteur, Faculté de pharmacie, 74 Route du Rhin, 67401 Illkirch Cedex, France

ABSTRACT

A selective Y_5 receptor antagonist, the hydrochloride of 2-methyl-4-pyrrolidinyl-6-[(E)-2-(3-trifluoromethylphenyl)-vinyl]pyridine, can be prepared in a 7-step synthesis.

Neuropeptide Y(NPY) is a 36 amino-acid peptide, which binds to 5 subtypes of receptors called Y_1, Y_2, Y_4, Y_5 and Y_6,[1,2] and it seems to be implicated in the physiological regulation of food intakes via the Y_1 and Y_5 receptors.[3–9] Particularly selective antagonists of these latter receptors may lead structures for the design of anti-obesity drugs.[10] Some Y_5 antagonists have been reported in the literature[10,11] but most of them are inactive in vivo.[11] An exception is represented by the compound **8**, described in a patent from the Banyu Pharmaceutical Co.[10] (Scheme 1).

*Corresponding author. E-mail: Rival@pharma.u-strasbg.fr



Reagents and conditions: (a) 1-$(CH_3)_2SO_4$, 2-KCN, −8°C (50%); (b) 90% H_2SO_4, $NaNO_2$, 91%; (c) 37% HCl, 100°C, 2 h (80%); (d) Pyrrolidine, NH_4Cl, 140°C, 2 h; (e) 1-$SOCl_2$, 60°C, 3 h; 2-Pyridine, CH_2Cl_2, $H_3C–NH–O–CH_3$, HCl (50%); (f) DiBALH, THF, −78°C (93%); (g) Trifluoromethylbenzylphosphonate, CH_3ONa, DMF, 7 h, r.t. (23%).

Scheme 1.

This compound is claimed to be active in vivo[10] and we wanted to use it as a reference for the biologic testing of our own compounds. The description of the synthesis of the reference compound **8** in the Banyu patent is limited to the last step, a Wittig-Horner reaction between 6-methyl-4-pyrrolidinylpyridine-2-carboxaldehyde **7** and 3-trifluoromethylbenzyldiethylphosphonate.

In this paper, we describe the complete synthetic sequence leading to compound **8** which may be useful to the pharmacologists working in the field of NPY.

Our synthesis starts with the pyridinium *N*-oxide **1** which was condensed with potassium cyanide in a Reissert-Kaufmann reaction[12] to yield the nitrile **2**[16] which was hydrolyzed to the carboxylic acid **3**.[12,17] (Scheme 1). The *N*-pyrrolydinyl picolinic acid **5** was prepared starting from 2-methyl-4-nitropicolinic acid **3** by means of two successive aromatic nucleophilic substitutions.[13,18,19] The transformation of compound **5** in a Weinreb amide **6**, followed by reduction by means of DiBALH gave compound **7**.[13,20] The last step was a Wittig-Horner reaction between **7** and 3-trifluoromethylbenzyldiethylphosphonate; we performed it according to the procedure in the Banyu patent.[10,14,21]

Despite the moderate yield of the last step, the present procedure allows an efficient access to 2-methyl-4-pyrrolidinyl-6-[(*E*)-2-(3-trifluoromethylphenyl) vinyl] pyridine **8**.

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15. 2-Methyl-4-pyrrolidinyl-6-[(E)-2-(3-trifluoromethylphenyl)vinyl]pyridine **8**. The mixture of 3-trifluoromethylbenzylphosphonate (1.57 g, 5.3 mmol, 1.2 eq.) and aldehyde **7** (840 mg, 4.42 mmol, 1 eq.) was added dropwise to a ice-cooled solution of sodium methylate (3.43 mg, 6.37 mmol, 1.44 eq.) in dry DMF (1.53 ml) and the mixture was stirred for 9 h at room temperature. H_2O (15 ml) was added and the aqueous layer was extracted with Et_2O (3 × 5 ml). The organic layer was washed with a 10% citric acid solution and the combined aqueous phases were rendered alkaline with K_2CO_3 and then extracted with Et_2O. After drying over Na_2SO_4, the organic layer was evaporated under reduced pressure and the obtained crude compound was purified by flash chromatography using EtOAc–MeOH: 9 : 1 with 2%(v/v) triethylamine and 340 mg of **8** were obtained. The corresponding hydrochloride was prepared by treating the free base dissolved in Et_2O with gaseous hydrogen chloride. The collected solid (180 mg) was recrystallized in i-PrOH with Et_2O. The global yield starting

from compound **7** is 23%. M.p. 220°C (hydrochloride). Rf. 0.50 (AcOEt/MeOH 9 : 1). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.08 (quint, $J = 3.30$ Hz, 4H), 2.55(s, 3H), 3.39 (t, $J = 6.6$ Hz, 4H), 6.22 (d, $J = 1.9$ Hz, 1H), 6.44 (d, $J = 1.9$ Hz, 1H), 7.22 (d, $J = 16$ Hz, 1H), 7.45–7.85 (m, 5H). ^{13}C-RMN ($CDCl_3$, 300 MHz): $\delta = 157.5$, 153.5, 153.12, 137.94, 130.39, 129.26, 124.52, 123.61, 105.34, 103.68, 47.30, 25.45, 24.52. Anal. calcd for $C_{19}H_{19}F_3N_2$. HCl. 3 H_2O: C, 59.69; H, 5.67, N, 7.33. Found: C, 59.73; H, 6.10; N, 7.26.

16. 6-Methyl-4-nitropyridine-2-carbonitrile **2.** A mixture of 2-methyl-4-nitropyridine *N*-oxide **1** (5 g; 32.5 mmol; 1 eq.) and dimethyl sulfate (3.7 ml; 39 mmol; 1.2 eq.) was stirred at 70°C for 1 h. The reaction was allowed to cool to r.t. and after filtration, the mixture was concentrated under reduced pressure. The residue was diluted with H_2O (12.5 ml) and a solution of KCN (4.72 g) in H_2O (25 ml) was added dropwise at −8°C. The mixture was allowed to warm to 0°C. After standing overnight, filtration and recrystallization in $(i\text{-}Pr)_2O$ gave 2.64 g of crystalline **2**. Yield 50%. m.p. 76°C (lit. 76.5–77.5°C). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.80 (s, 3H), 8.12 (s, 1H), 8.24 (s, 1H).
17. 6-Methyl-4-nitropyridine-2-carboxylic acid **3.** A solution of 6-methyl-4-nitropyridine-2-carbonitrile **2** (2.92 g, 18 mmol, 1 eq.) in 90% H_2SO_4 (29.2 g) was heated for 2 h at 120°C. After cooling to room temperature, a solution of $NaNO_2$ (3.3 g) in H_2O (5.82 ml) was added and the reaction mixture was stirred for 1 h, heated at 80°C for 1 h, then poured over a mixture of H_2O/ice (20 ml). The precipitate was removed by filtration and 2.96 g of **3** were obtained as yellow crystals. Yield 91%. M.p. 127°C (lit. 129°C). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.83 (s, 3H), 8.18 (d, $J = 1.5$ Hz, 1H), 8.73 (d, $J = 1.5$ Hz, 1H).
18. 4-Chloro-6-methylpyridine-2-carboxylic acid **4.** A solution of 6-methyl-4-nitropyridine-2-carboxylic acid **3** (2.96 g, 16.3 mmol, 1 eq.) in 37% HCl (29.6 ml) was heated at 100°C for 2 h. After evaporation under reduced pressure, the residue was diluted with H_2O and the mixture was alkalinized with K_2CO_3 until pH = 2. The solid material was collected by filtration affording 2.2 g of compound **4**. Yield 80%. m.p. 123°C (lit. 123–124°C). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.63 (s, 3H), 4.51 (m, 1H), 7.45 (s, 1H), 8.04 (s, 1H).
19. *N*-methoxy-*N*,6-dimethyl-4-pyrrolidinylpyridin-2-carboxamide **5.** A mixture of 4-chloro-6-methylpyridine-2-carboxylic acid **4** (2 g, 11.7 mmol, 1 eq.), pyrrolidine (1.93 ml, 23.3 mmol, 2 eq.), ammonium chloride (11.7 mmol) in *n*-BuOH (42 ml) was refluxed for 16 h. The solvent was removed by evaporation. The crude product **5** was dissolved in $SOCl_2$ (60 ml) and the reaction mixture was heated at 60°C for 3 h. After cooling, $SOCl_2$ was removed by distillation under

reduced pressure giving a green oil. *N-O*-Dimethylhydroxylamine hydrochloride (1.2 g, 12.8 mmol, 1.1 eq.) was added dropwise to a stirred solution of the previous oil dissolved in CH_2Cl_2 (82 ml). The reaction mixture was then cooled to 0°C and pyridine (1.72 ml, 21.36 mmol, 2.2 eq.) was added. After stirring for 1 h, the solvent was removed by evaporation. The residue was dissolved in water (20 ml) and brine (10 ml) and extracted with EtOAc (3 × 5 ml). The organic layer dried over Na_2SO_4 was evaporated under reduced pressure. A yellow oil (1.5 g) of **6** was obtained after purification by flash chromatography (EtOAc–MeOH: 9 : 1 with 2% (v) triethylamine). Yield 50%. Rf. 0.23 (AcOEt/MeOH 9 : 1, TEA 2% v). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.01 (quint, $J = 3.35$ Hz, 4H), 2.45 (s, 3H), 3.29–3.37 (m, 7H), 3.79 (s, 3H), 6.26 (d, $J = 2.2$ Hz, 1H), 6.56 (m, 1H).

20. 6-Methyl-4-pyrrolidinylpyridin-2-carboxaldehyde **7.** Argon was passed for 20 min through a solution of **6** (1.2 g, 4.7 mmol, 1 eq.) in dry THF (47.2 ml), a solution of 1 M DiBALH in THF (14.2 ml, 14.2 mmol, 3 eq.) was added dropwise under stirring to the reaction mixture cooled until −78°C. After 2 h, a solution of 5% HCl in EtOH (14 ml) was added dropwise. The reaction mixture was allowed to warm to room temperature and the solvents were removed under reduced pressure. The residue was diluted with a saturated solution of K_2CO_3 and extracted with EtOAc (3 × 5 ml). The organic layer was washed with H_2O (3 × 5 ml), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel eluting with a 9 : 2 (v/v) mixture of EtOAc–Heptane: 840 mg of **6** (yellow oil) were obtained. Yield 93%. Rf 0.20 (AcOEt/Heptane 9 : 2). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.04 (quint, $J = 3.30$ Hz, 4H), 2.52 (s, 3H), 3.35 (t, $J = 4.5$ Hz, 4H), 6.40 (d, $J = 2.5$ Hz, 1H), 6.92 (d, $J = 2.5$ Hz, 1H), 9.95 (s, 1H).
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