Acta Chim. Slov. **1998**, *45*(4), pp. 475—486.

THE SYNTHESES OF 1-(2-NAPHTHYL)PIPERAZINE DERIVATIVES. NOVEL SPIPERONE-CONTAINING PROBES†

Andrej Petrič*
Faculty of Chemistry and Chemical Technology, University of Ljubljana, SI-1000 Ljubljana, Slovenia

Jorge R. Barrio
Department of Molecular and Medical Pharmacology and the Laboratory of Structural Biology and Molecular Medicine, UCLA, School of Medicine, Los Angeles, California 90095, USA

Abstract

The synthesis of 1-(6-piperazino-2-naphthyl)-1-ethanone, a reactive fluorescent dye, is described. To this dye spiperone, a highly potent dopaminergic D_2 receptor ligand, was conjugated giving a new fluorescent probe. By the Knoevenagel reaction with malononitrile and subsequent deprotection, Vis range fluorescent probe was formed.

Introduction

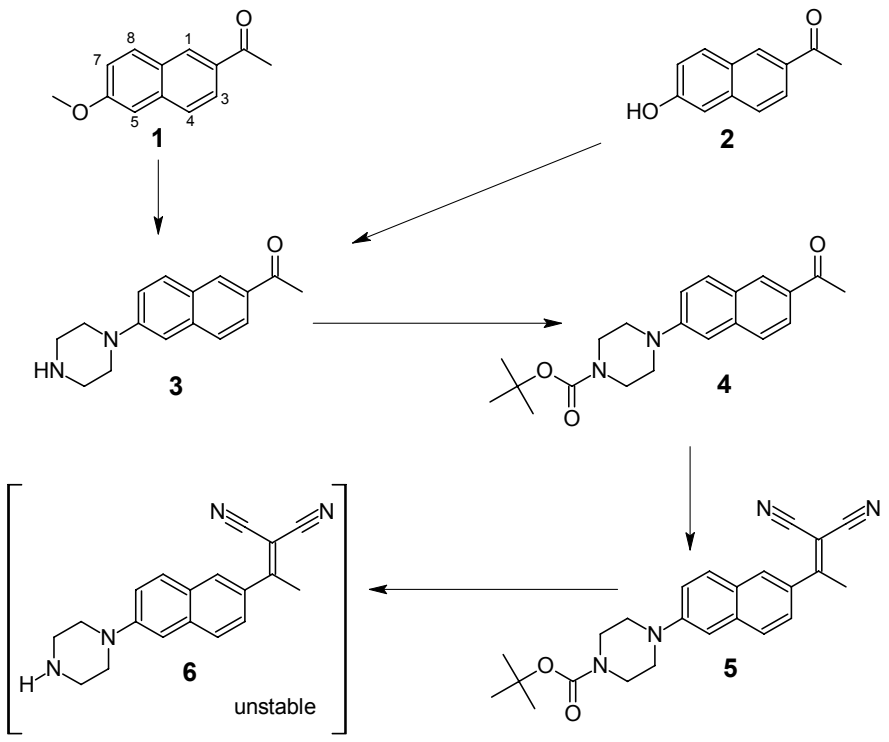
The discovery of 2-(1,1-dicyanopropenyl-2)-6-dimethylaminonaphthalene [1] prompted us to explore the possibility of incorporating the favorable optical properties of this compound into biological probes for use with fluorescence microscopy. We initially envisaged structural modification of the compound by formal replacement of the dimethylamino group by an amine bearing a reactive functional group. Such a functional group would be utilized for attachment of a ligand, which would introduce specificity in the molecule towards enzymes or receptors maintaining, at the same time, fluorescent properties. We have already reported on a application of this approach with 4-piperidine-

† Dedicated to the memory of Prof. Dr. Anton Šebenik

methanol or 2-ethylaminoethanol as the dimethylamino group replacement, and using spiperone, a highly potent dopaminergic D_2 receptor ligand, as the specific ligand [2]. We have proven that in this way new pharmacological probes which possess very similar optical properties to those of the parent fluorophore can be prepared. Similar optical properties were also found in compounds in which the 4-ethylpiperazine moiety linked the spiperone and naphthalene moieties [3]. *In vitro* binding assays of such a compound against ^{3}H-spiperone revealed high affinity for dopaminergic D_2 receptors. In this work we describe in detail synthetic procedures for the preparation of a series of piperazine-containing fluorescent compounds.

Results and discussion

The synthetic route to the title derivatives started with the preparation of 1-(6-piperazino-2-naphthyl)-1-ethanone (**3**). Thoroughly dried piperazine was treated with lithium metal in a mixture of anhydrous toluene and hexamethylphosphoric triamide (HMPT) to yield the lithium salt. The latter reacted with 1-(6-methoxy-2-naphthyl)-1-ethanone **1** to give compound **3** (**Scheme 1**).



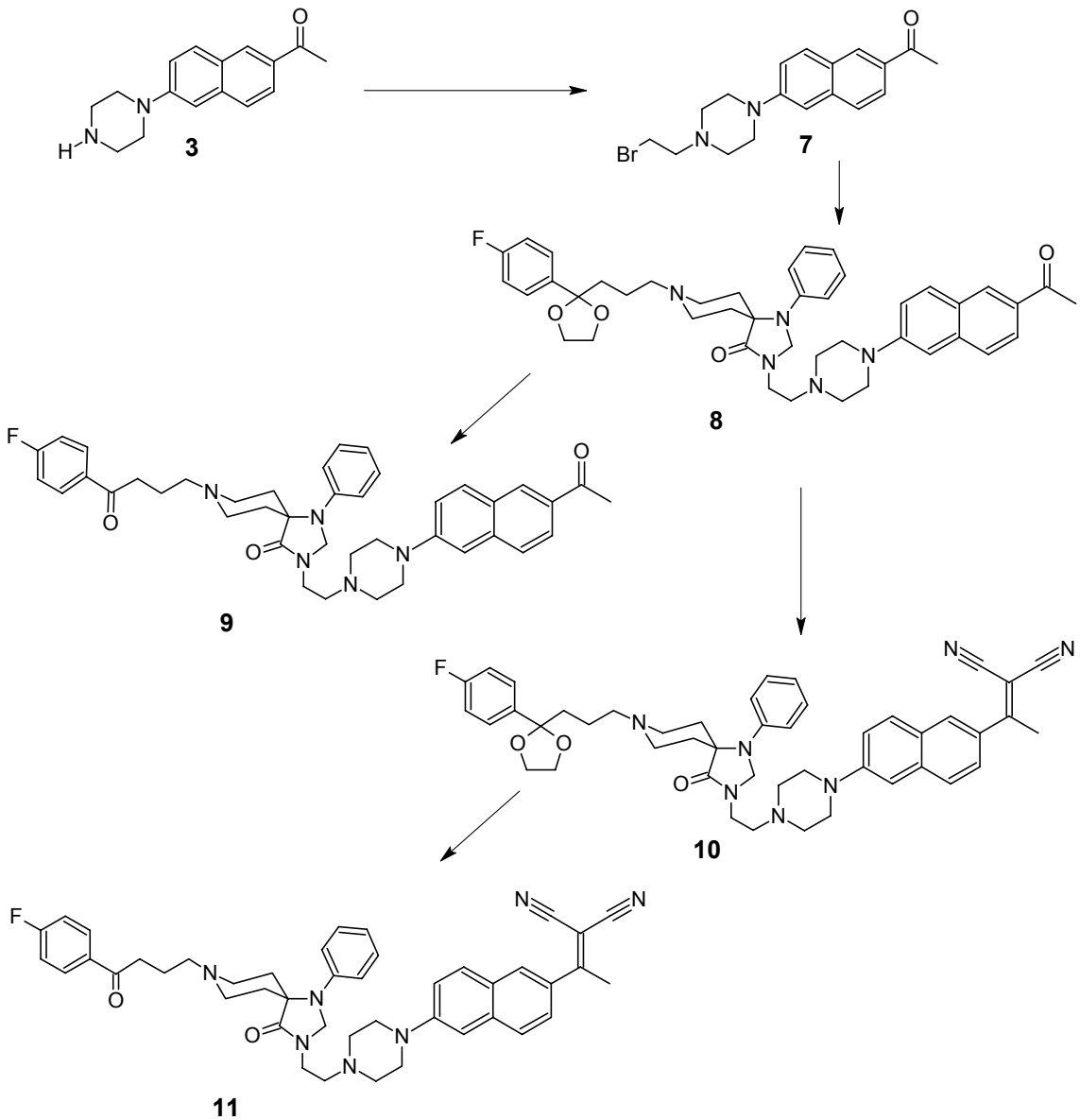
Scheme 1

Compound **3** was purified by column chromatography to remove 1-(6-dimethylamino-2-naphthyl)-1-ethanone, which was formed in a competing reaction of **1** with dimethylamine. It has been earlier described that HMPT decomposed under the reaction conditions releasing dimethylamine [4]. The Bucherer reaction [5] of 6-acetyl-2-naphthol with piperazine in the presence of sodium bisulfite gave a better yield of compound **3**, but due to the presence of the unreacted starting naphthol **2**, the chromatographic purification step could not be avoided.

An attempt to transform 1-(6-piperazino-2-naphthyl)-1-ethanone (**3**) into compound **6** resulted in a very low yield. We assumed that the free NH group in the piperazine ring catalyzed the decomposition of **6**. When we protected the free NH group in **3** with a *tert*-butyloxycarbonyl group, we obtained compound **4**. The transformation of **4** with malononitrile proceeded smoothly to give compound **5** in good yield. In the last step, the protective group was removed by treatment with trifluoroacetic acid (TFA) at room temperature. The product exhibited a ^{1}H NMR spectrum consistent with structure **6**, but was found to be unstable. This proved our initial assumption that the basic NH group can promote the decomposition of **6**, thus rendering this compound inappropriate starting material for further transformations.

The above observation led to the redesign of our synthetic approach as presented in **Scheme 2**. First, compound **3** was treated with an excess of 1,2-dibromoethane under phase transfer conditions to yield slightly unstable compound **7**, which was let to react with ketal protected spiperone in the next step and compound **8** was obtained. It served as a precursor for the preparation of a fluorescent probe **9**, with the excitation maximum in the UV range at approximately 340 nm. The transformation of **8** into **9** was reflected in expected changes in the ^{1}H NMR spectrum [6]. The lack of the two multiplets at approximately 3.75 and 4.00 ppm, corresponding to the ethylene protons of the ketal protecting group, and the downfield shift of the signals for protons 2 and 6 in the 4-fluorophenyl group supported the structure. Compound **8** also served as a precursor for the preparation of a fluorescent probe, with the excitation maximum in the visible range.

In the Knoevenagel reaction with malononitrile in pyridine, the acetyl group in **8** was transformed into the 1,1-dicyanopropenyl group, resulting in the yellow orange compound **10**. The target fluorescent probe for *in-vivo* probing of the dopaminergic D_2 receptors, which can be excited in the Vis range (approximately at 400 nm), was obtained upon mild, acid catalyzed, ketal protection removal from the spiperone moiety. It was found that compound **11** underwent slow decomposition at room temperature in a dichloromethane solution. The decomposition was prevented by the addition of 1 to 5% methanol and storage in a freezer.



Scheme 2

Conclusions

A novel fluorescent reactive dye 1-(6-piperazino-2-naphthyl)-1-ethanone was prepared from 1-(6-methoxy-2-naphthyl)-1-ethanone or 6-acetyl-2-naphthol. It contains a free NH group available for the attachment of a ligand of choice. If such a ligand contains an electrophilic reactive center, novel fluorescent probes become available. If the intended ligand contains a nucleophilic center, which can be alkylated without significant deterioration of the binding properties, 1-6-[4-(2-bromoethyl)piperazino]-2-naphthyl-1-ethanone can be used instead. The optical properties of these compounds can be modified by the Knoevenagel reaction with malononitrile in which the acetyl group is transformed into a 1,1-dicyanopropenyl. This structural change induces the shift of the fluorescence excitation and emission maxima into the Vis range. Using spiperone, a highly potent ligand for the dopamine D_2 receptors, this approach was successfully tested.

Experimental

NMR spectra were obtained on Bruker AM 360 WB or DPX 300 Spectrometers. ^1H chemical shifts are reported in ppm downfield from TMS as internal standard. ^{19}F chemical shifts are reported relative to external fluorotrichloromethane. Deuteriochloroform was used as the solvent unless stated otherwise. Naphthalene ring atom numbering as specified for structure **1** in **Scheme 1** was used in reporting the spectral assignments, although the numbering according to the IUPAC Nomenclature rules differs [7]. Melting points were determined on a Electrothermal Melting Point Apparatus and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN and Ms. Metka Kastelic at the Faculty of Chemistry and Chemical Technology, University of Ljubljana. Radial chromatography was performed on Chromatotron (Harrison Research, 840 Moana Court, Palo Alto, CA 94306). The rotors were prepared as recommended by Harrison Research using E. Merck Silica Gel (Cat. No. 7749-3). HPLC was performed on an Alltech Econosil C18

5 μm 4.6×250 mm column using water : acetonitrile : triethylamine = 40 : 60 : 2 as the solvent. UV detection at 254 nm was used. Solvents and reagents were purchased from Fisher, Aldrich or Fluka and were used as received unless noted otherwise.

1-(6-Piperazino-2-naphthyl)-1-ethanone (3). Method a: Anhydrous piperazine (7 g, 81.3 mmol; dried in a vacuum dessicator over KOH-drierite mixture for 3 days) was dissolved in a mixture of dry, freshly distilled toluene and hexamethyl phosphoric triamide (HMPT), 25 mL each. To the solution, 556 mg (80.1 mmol) of lithium rod, cut in small pieces under argon atmosphere, was added and the mixture was stirred under argon for 24 hours during which time all lithium has dissolved. Vacuum-dried **1** [8] (3.5g, 17.5 mmol) was added and stirring was continued for additional 65 hours. After quenching with 300 mL of water, extraction with dichloromethane (3×300 mL), drying with anhydrous magnesium sulfate, and evaporation, a mixture of white and yellow solids was obtained. Extraction with 300 mL of hot methanol gave raw material that was purified by column chromatography (70-230 mesh silica, 25×120 mm, 5% methanol in dichloromethane) to yield 1.54 g (35 %) of **3**. After recrystallization from ethyl acetate the sample melted at 170.5-172 ^{o}C. **Method b:** Compound **2** [2] (441 mg, 2.36 mmol) was heated at 140-150 ^{o}C with 6 g piperazine hydrate (30.9 mmol) and $NaHSO_3$ (244 mg, 2.35 mmol) for 24 hours when additional 2 g (19.2 mmol) of sodium bisulfite was added and heating was continued. After additional 24 hours more bisulfite (1 g) was added and heating was continued to the total reaction time of 72 hours. After cooling the mixture was extracted with methanol (2×50 mL). After evaporation of methanol the residue was suspended in water (50 mL) and extracted with ethyl acetate (5×80 mL). Combined extracts were dried (magnesium sulfate) and evaporated to give 430 mg of yellow solid. Radial chromatography (4 mm silica, methanol) gave 83 mg (19 %) of starting naphthol **2** and 276 mg (46 %; 56 %, based on unrecovered starting material) of product **3**. The product was in all respects identical to the compound obtained as described under **method a**. *Anal*. Calculated for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N, 11.01. Found: C, 75.82; H, 7.27; N, 10.92. ^{1}H NMR: δ 2.68 (s, 3H, CH_3), 3.09 and 3.35 (t, J= 4.95 Hz, 8H, piperazine), 7.10 (d, 1H, 5-H), 7.31 (dd, 1H, 7-H), 7.69 (d, 1H, 4-H),

7.83 (d, 1H, 8-H), 7.95 (d, 1H, 3-H), 8.34 (s, 1H, 1-H); $J_{5,7}$= 2 Hz, $J_{7,8}$= 8.4 Hz, $J_{1,3}$= 2 Hz, $J_{3,4}$= 8.4 Hz.

***tert*-Butyl 4-(6-acetyl-2-naphthyl)-1-piperazinecarboxylate (4).** Compound **3** (254 mg, 1 mmol) was added to a stirred mixture of NaOH (1 g), tetra-*n*-butylammonium hydrogensulfate (100 mg), water (2 mL) and toluene (6 mL), followed by a solution of di-*tert*-butyl dicarbonate (230 mg, 1.05 mmol) of. The course of the reaction was followed by TLC (silica, 5% methanol in dichloromethane). Every 10 minutes additional amount of the dicarbonate was added until all starting material has reacted. A total of approximately 1.5 equivalents were used. A mixture of water and dichloromethane (60 mL each) was added and after thorough shaking the layers were separated. The aqueous layer was extracted with an additional 30 mL of dichloromethane. The combined organic extracts were dried with anhydrous magnesium sulfate. During this procedure the color of the solution turned from pink to light yellow. Evaporation *in vacuo* gave 295 mg (83 %) of **4**, which on recrystallization from dichloromethane - petroleum ether mixture melted at 153-154 ^{o}C *Anal.* Calculated for $C_{21}H_{26}N_2O_3$: C, 71.16; H, 7.39; N, 7.90. Found: C, 71.27; H, 7.60; N, 7.86. ^{1}H NMR: δ 1.50 (s, 9H, -C(CH_3)$_3$), 2.68 (s, 3H, CH_3), 3.33 and 3.64 (t, J= 4.9 Hz, 8H, piperazine), 7.10 (d, 1H, 5-H), 7.31 (dd, 1H, 7-H), 7.70 (d, 1H, 4-H), 7.85 (d, 1H, 8-H), 7.97 (d, 1H, 3-H), 8.35 (d, 1H, 1-H); $J_{5,7}$= 2 Hz, $J_{7,8}$= 9 Hz, $J_{3,4}$= 8.7 Hz.

***tert*-Butyl 4-[6-(2,2-dicyano-1-methylvinyl)-2-naphthyl]-1-piperazinecarboxylate (5).** Compound **4** (177 mg, 0.5 mmol) was heated with 40 mg (0.6 mmol) of malononitrile in pyridine (4 mL) at 105-110 ^{o}C. After 5.5 hours additional 24 mg of malononitrile was added and heating was continued to a total of 13 hours. The mixture was cooled and evaporated *in vacuo*. Polar components of the mixture were removed by column chromatography (70-230 mesh silica, 20×120 mm, chloroform) and the product was finally purified by radial chromatography (silica, 2 mm, chloroform) to yield 155 mg (77%) of **5** that was recrystallized from dichloromethane - petroleum ether mixture,

M.p. 169-171 ^{o}C. *Anal.* Calculated for $C_{24}H_{26}N_4O_2$: C, 71.62; H, 6.51; N,13.92. Found: C, 71.62; H, 6.66; N, 13.87. ^{1}H NMR: δ 1.50 (s, 9H, -C(CH_3)$_3$), 2.72 (s, 3H, CH_3), 3.34 and 3.64 (t, J= 5.1 Hz, 8H, piperazine), 7.09 (d, 1H, 5-H), 7.33 (dd, 1H, 7-H), 7.58 (dd, 1H, 3-H), 7.74 (d, 1H, 4-H), 7.81 (d, 1H, 8-H), 8.02 (d, 1H, 1-H); $J_{5,7}$= 2 Hz, $J_{7,8}$= 9.1 Hz, $J_{1,3}$= 2 Hz, $J_{3,4}$= 9.1 Hz.

2-[1-(6-Piperazino-2-naphthyl)ethylidene]malononitrile (6). Compound **5** (10 mg) was treated with an excess of TFA (1 mL) at room temperature for 5 min followed by TFA was removal *in vacuo* at room temperature. TLC revealed the presence of a single compound. ^{1}H NMR: δ 2.72 (s, 3H, CH_3), 3.50 and 3.63 (broad, 8H, piperazine), 7.18 (broad s, 1H, 5-H), 7.29 (d, 1H, 7-H), 7.59 (d, 1H, 3-H), 7.79 (d, 1H, 4-H), 7.87 (d, 1H, 8-H), 8.04 (s, 1H, 1-H), 9.0 (broad, 1.5H, NH and acid); $J_{7,8}$= 8.8 Hz, $J_{3,4}$= 8.4 Hz. ^{19}F NMR: ? -76.2 (CF_3COO).

NMR of the residue revealed clean hydrolysis of the *tert*-butyloxycarbonyl group. The NMR sample was diluted by dichloromethane (10 mL), the solution washed with saturated $NaHCO_3$ solution (to remove traces of TFA), dried, and evaporated *in vacuo*. A light yellow oil was obtained which, on standing at room temperature, turned dark red. TLC analysis showed color change due to decomposition of **6** into several products, the most intense spot being low-Rf red-orange. Selected ^{1}H NMR signals after neutralization: δ 2.72 (s, 3H, CH_3), 3.09 and 3.35 (t, J= 5 Hz, 8H, piperazine), 7.08 (s, 1H, 5-H), 8.02 (s, 1H, 1-H).

1-{6-[4-(2-Bromoethyl)piperazino]-2-naphthyl}-1-ethanone (7). To a solution of NaOH (1g) and tetra-*n*-butylammonium hydrogensulfate (50 mg, 0.15 mmol) in water (2 mL) compound **3** was added (255 mg, 1 mmol) and the mixture was stirred for 45 min at room temperature. After the adition of 1,2-dibromoethane (2 mL), stirring was continued for 4 hours. TLC (silica, 5% methanol in dichloromethane) had revealed that the starting material was still present in the reaction mixture. Additional 1 mL of 1,2-dibromoethane was added and stirring was continued for a total of 20 hours. Water and

dichloromethane (50 mL each) were added to the mixture, the organic layer washed with water, dried and evaporated *in vacuo* at 35 ^{o}C. The solid was chromatographed by radial chromatography (4 mm silica, dichloromethane) to give 180 mg (50%) of pure (as determined by NMR) bromoethyl product **7.** This compound decomposes upon handling or when left at room temperature in the air, as determined by TLC on silicagel. It was necessary to use purified **7** immediately in the next step. ^{1}H NMR: δ 2.69 (s, 3H, CH_3), 2.74 and 3.40 (t, 8H, J= 4.8 Hz, piperazine), 2.89 and 3.50 (t, J= 7.2 Hz, 4H, CH_2CH_2), 7.10 (d, 1H, 5-H), 7.31 (dd, 1H, 7-H), 7.69 (d, 1H, 4-H), 7.83 (d, 1H, 8-H), 7.96 (d, 1H, 3-H), 8.35 (s, 1H, 1-H); $J_{5,7}$= 2 Hz, $J_{7,8}$= 8.8 Hz, $J_{3,4}$= 8.6 Hz.

1-(6-{4-[2-(8-{3-[2-(4-Fluorophenyl)-1,3-dioxolan-2-yl]propyl}-1-oxo-4-phenyl-2,4,8-triazaspiro[4.5]dec-2-yl)ethyl]piperazino}-2-naphthyl)-1-ethanone (8). To the solution of NaOH (1 g) and tetra-*n*-butylammonium hydrogensulfate (100 mg) in 2 mL of water, 8-{3-[2-(4-fluorophenyl)-1,3-dioxolan-2-yl]propyl}-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one (spiperone ketal, 199 mg, 0.454 mmol)) [9,10] was added, followed by 1 mL of toluene. After stirring for 20 min, a solution of 180 mg (0.5 mmol) of **7** in toluene (9 mL) was added. The mixture was stirred at room temperature for 16 hours and, after addition of a mixture of ethyl acetate (100 mL) and water (50 mL), the organic layer was washed with 50 mL of brine. After drying with anhydrous magnesium sulfate and evaporation in vacuo, 387 mg of a yellow oil was obtained which was purified by chromatography (70-230 mesh silica, 21×120 mm, ethyl acetate) to give 258 mg (71%) of **8**. *HRMS* Calculated for $C_{43}H_{51}N_5O_4F$ (M+H): 720.3925. Found: 720.3941. ^{1}H NMR: δ 1.49-3.65 (m, 29H, CH_3, spiperone, piperazine and ethylene between the latter two), 3.75 and 4.00 (m, 4H, OCH_2CH_2O), 4.75 (s, 2H, NCH_2N), 6.79-7.03 (m, 5H, Ar), 7.08 (d, 1H, 5-H(naphth.)), 7.23-7.32 (m, 3H, Ar and 7-H(naphth.)), 7.41 (m, 2H, Ar), 7.68 (d, 1H, 4-H(naphth.)), 7.82 (d, 1H, 8-H(naphth.)), 7.95 (d, 1H, 3-H(naphth.)), 8.34 (s, 1H, 1-H(naphth.)); $J_{3,4}$= 8.6 Hz, $J_{7,8}$= 8.9 Hz.

3-{2-[4-(6-Acetyl-2-naphthyl)piperazino]ethyl}-8-[4-(4-fluorophenyl)-4-oxobutyl]-1-

phenyl-1,3,8-triazaspiro[4.5]decan-4-one (9). Ketal **8** (10 mg, 0.014 mmol) was treated with 2 mL of methanol and 1 drop of concentrated hydrochloric acid. After stirring at room temperature for 3 hours the mixture was diluted with dichloromethane (50 mL) and washed with saturated sodium bicarbonate solution (20 mL). After drying with anhydrous magnesium sulfate and removal of the solvent, 8 mg of off-white foam was obtained. It was purified by chromatography on two 10×20 cm silica plates (0.2 mm layer thickness), using 5% methanol in dichloromethane as the solvent. Final purification was achieved by radial chromatography (1 mm silica, 5% methanol in dichloromethane). Appropriate fractions were collected and evaporated to give 5 mg (53 %) of pure **9**. ^{1}H NMR: δ 1.5-3.7 (m, 29 H, CH_3, spiperone, piperazine and ethylene between the latter two), 4.77 (s, 2H, NCH_2N), 6.82-7.03 (m, 3H, Ar), 7.09 (d, 1H, 5-H(naphth.)), 7.12 (t, J=8.5 Hz, 2H, Ar), 7.30 (m, 3H, Ar and 7-H(naphth.)), 7.68 (d, 1H, 4-H(naphth.)), 7.82 (d, 1H, 8-H(naphth.)), 7.95 (d, 1H, 7-H(naphth.)), 8.02 (m, 2H, Ar), 8.33 (s, 1H, 1-H(naphth.)); $J_{5,7}$= 2 Hz, $J_{7,8}$= 9 Hz, $J_{3,4}$= 8.5 Hz.

2-[1-(6-{4-[2-(8-{3-[2-(4-Fluorophenyl)-1,3-dioxolan-2-yl]propyl}-1-oxo-4-phenyl-2,4,8-triazaspiro[4.5]dec-2-yl)ethyl]piperazino}-2-naphthyl)ethylidene]malono-nitrile (10). Acetyl compound **8** (220 mg, 0.31 mmol) was heated and stirred at 70-85 ^{o}C under argon with malononitrile (101 mg, 1.5 mmol) in pyridine (6 mL) for 17 hours. After evaporation of the solvent *in vacuo* at 40 ^{o}C an orange-red oil (233 mg) was obtained and chromatographed (70-230 mesh neutral alumina, 16×360 mm, chloroform) to give 167 mg (67 %) of **10** as an orange oil. *HRMS* calcd. for $C_{46}H_{51}N_7O_3F$ (M+H): 768.4037. Found: 768.3994. ^{1}H NMR: δ 1.48-3.65 (m, 29H, CH_3, spiperone, piperazine and ethylene between the latter two), 3.75 and 4.01 (t, J= 7 Hz, 4H, OCH_2CH_2O), 4.75 (s, 2H, NCH_2N), 6.80-7.03 (m, 5H, Ar), 7.07 (d, 1H, 5-H(naphth.)), 7.32-7.38 (m, 3H, Ar and 7-H(naphth.)), 7.41 (m, 2H, Ar), 7.58 (dd, 1H, 3-H(naphth.)), 7.72 (d, 1H, 4-H(naphth.)), 7.80 (d, 1H, 8-H(naphth.)), 8.01 (s, 1H, 1-H(naphth.)); $J_{5,7}$= 2.7 Hz, $J_{7,8}$= 9. Hz, $J_{1,3}$= 2.5 Hz, $J_{3,4}$= 9 Hz.

2-(1-{6-[4-(2-{8-[4-(4-Fluorophenyl)-4-oxobutyl]-1-oxo-4-phenyl-2,4,8-triaza-spiro[4.5]dec-2-yl}ethyl)piperazino]-2-naphthyl}ethylidene)malononitrile (11).

Compound **10** (71 mg, 0.098 mmol) was stirred with 5 drops of concentrated hydrochloric acid in 10 mL of methanol for 4 hours. A mixture of 150 mL of dichloromethane and 50 mL of saturated sodium bicarbonate solution was added and the organic layer was washed with 50 mL of water. After drying with magnesium sulfate and evaporation of the solvent of an orange oil (45 mg, 67 %) was obtained. NMR analysis demonstrated removal of the ketal group. The product was purified by preparative TLC (2 mm silica, 5% methanol in dichloromethane). *HRMS* Calculated for $C_{44}H_{47}N_7O_2F$ (M+H): 724.3775. Found: 724.3791. ^{1}H NMR: δ 1.63-3.65 (m, 29H, CH_3, spiperone, piperazine and ethylene between the latter two), 4.75 (s, 2H, NCH_2N), 6.83-6.93 (m, 3H, Ar), 7.05 (d, 1H, 5-H(naphth.)), 7.12 (t, J=8.5 Hz, Ar), 7.26 (t, J=9.7 Hz, 2H, Ar), 7.31 (dd, 1H, 7-H(naphth.)), 7.56 (m, 1H, 3-H(naphth.)), 7.71 (d, 1H, 4-H(naphth.)), 7.78 (d, 1H, 8-H(naphth.)), 7.98-8.04 (m, 3H, Ar and 1-H(naphth.)); $J_{5,7}$= 2.5 Hz, $J_{3,4}$= 10 Hz, $J_{7,8}$= 10 Hz.

Acknowledgments

This work was supported by the U.S. - Slovene Science and Technology Joint Fund in co-operation with the US Department of Energy and the Ministry of Science and Technology of the Republic of Slovenia (Project No. US-SLO 95/2-02), in part by US Department of Energy Grant DE-FC0387-ER60615, and in part by the Ministry of Science and Technology of the Republic of Slovenia.

References and Notes

[1] A. Jacobson, A. Petric, A. Sinur, J. R. Barrio, *J. Am. Chem. Soc*. **1996**, *118*, 5572-5579.
[2] A. Petrič, T. Špes, J. R. Barrio, *Monatsh. Chem.* **1998**, *129*, 777-786.

[3] A. Petrič**,** A. F. Jacobson**,** J. R. Barrio, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1455-1460.
[4] T. Cuvigny, H. Normant, *C.R. Acad. Sci. Paris* **1971,** *272*, 1425-1430.
[5] N. L. Drake, *Organic Reactions* **1942,** Vol I, 105-128.
[6] G. Ambrožič, S. Čeh, A. Petrič, *Magn. Reson. Chem.* **1998**, *36*, 873-877.
[7] Chemical names were generated by ACD Labs' Name software package, courtesy of Dr. D. Kikelj, Faculty of Pharmacy, University of Ljubljana.
[8] L. Arsenijević, V. Arsenijević, A. Horeau, J. Jacques, *Org. Synth. Coll. Vol*. **1988**, *6*, 34-36.
[9] W. G. Scharpf, (1974) U.S. Pat. 3,839,342; *Chem. Abstr.* **1975,** *82,* 43416.
[10] D. O. Kiesewetter, W. C. Eckelman, R. M. Cohen, R. D. Finn, S. M. Larson, *Appl. Radiat. Isot.* **1986**, *37*, 1181.

Povzetek

Opisana je sinteza 1-(6-piperazino-2-naftil)-1-etanona, reaktivnega fluorescentnega barvila, ki ga je moč vzbujati z UV svetlobo. V nadaljevanju so opisane pretvorbe te spojine s spiperonom, močnim in selektivnim ligandom za dopaminske D_2 receptorje. S Knoevenagel-ovo reakcijo z malononitrilom in sledečo odstranitvijo zaščitne skupine, smo pripravili novo fluorescentno probo, ki jo je moč vzbujati z vidno svetlobo.