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SYNTHESIS OF BENZO[*de*]CHROMENE ANALOGUE OF EFAROXAN

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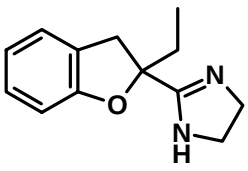
Abstract - 2-(2-Ethyl-2,3-dihydro-benzo[*de*]chromen-2-yl)-4,5-dihydro-1*H*-imidazole (**2**) was synthesized in seven steps starting from 3-methylanthranilic acid (**3**). The key intermediate 8-bromomethyl-4-bromonaphthoxybutyrate (**8**) was obtained starting from 8-methyl-1-naphthol (**5b**). The target molecule is a benzo[*de*]chromene analogue of efaroxan (**1**), a potent and selective antagonist of α_2-adrenoceptors.

Efaroxan, a 2,3-dihydrobenzofuran-2-imidazoline derivative (**1**) is a compound displaying high affinity and selectivity at α_2-adrenoreceptors.[1] The dextrorotatory isomer, dexefaroxan was studied for its potential activity in the treatment of neurodegenerative diseases such as Parkinson's or Alzheimer's diseases. The interest of the preclinical results focused on the investigation of related chemical structures.



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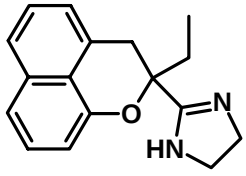

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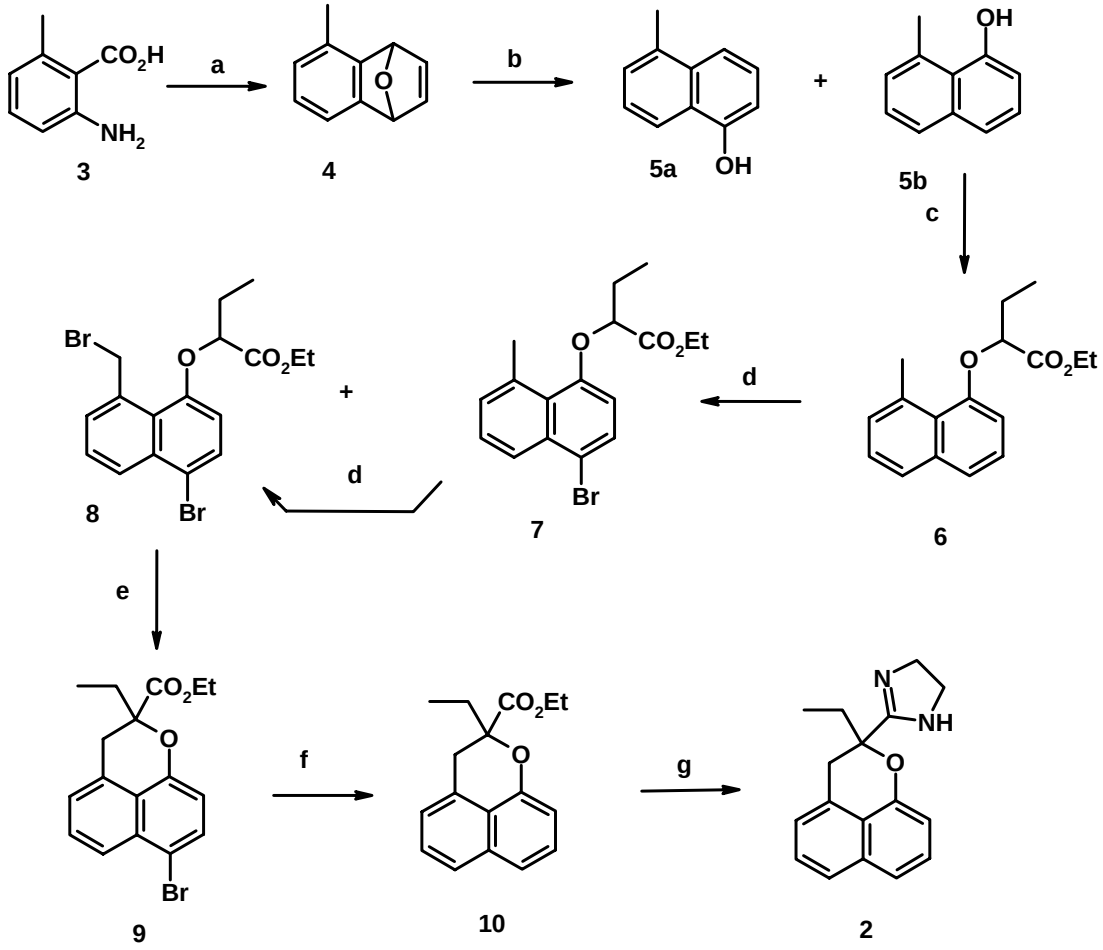
Our continuing efforts in the evaluation of new heterocyclic analogues of efaroxan [2] led us to study a synthetic approach to a 2,3-dihydrobenzo[*de*]chromene derivative (**2**).

An overview of the literature revealed only limited information on this kind of heterocycle. It has reportedly been obtained by rearrangement of 1-hydroperoxy-1,2-dihydroacenaphtylene,[3] hydrogenation of benzo[*de*]chromene compounds,[4] addition of acrylic acid derivative to anthraquinonediazonium salts,[5] or cyclisation of a properly substituted naphthol derivative.[6,7] We

have based our current strategy on a cyclisation of a 8-bromomethylnaphthoxybutyrate (**8**) as the key step (Scheme 1). The first step of this synthesis was the preparation of 8-methyl-1-naphthol (**5b**) following the described procedure.[8] Treatment of the 6-methylanthranilic acid (**3**) with isoamyl nitrite gave rise to a benzyne intermediate which reacted *in situ* with furan in refluxing dimethoxyethane. The bridged oxatricyclo adduct (**4**) was subjected to acidic hydrolysis in methanol to afford both regioisomers (**5a**) and (**5b**), which were separated by column chromatography, in 34 and 32 % yields respectively. Alkylation of the 8-methyl isomer (**5b**) with ethyl 2-bromobutyrate and potassium carbonate in refluxing acetonitrile gave the naphthoxybutyrate (**6**) in 80 % yield.



a) furan/isoamyl nitrite/DME/reflux; b) conc. HCl /MeOH/reflux;
c) ethyl 2-bromobutyrate/MeCN/K_2CO_3; d) NBS/CCl_4/reflux, see text; e) *tert*-BuOK/dioxane/rt
f) H_2/10% Pd/C/EtOH; g) ethylenediamine/$AlMe_3$/toluene

Scheme 1

Selective bromination of the methyl group appeared to be problematic. Indeed, when the reaction was performed in the presence of one molar equivalent of *N*-bromosuccinimide, a mixture of the 4-bromonaphtho derivative (**7**) and the dibrominated derivative (**8**) was obtained, along with unreacted starting material. However, reaction of one equivalent of *N*-bromosuccinimide with the 4-bromo-8-

methyl-1-naphthol derivative (**7**) afforded also the dibrominated compound (**8**) in 70 % yield. Consequently, by the action of two molar equivalents of *N*-bromosuccinimide on the naphthoxybutyrate (**6**), the 4-bromo-8-bromomethyl compound (**8**) was obtained as the sole product in 95 % yield. The presence of the bromine atom in position 4 of the naphthyl moiety of compound (**8**) was determined by an 2D ^{1}H NMR study. This aromatic bromo substitution was not problematic as its cleavage could be easily obtained by hydrogenolysis in a later step. The key cyclisation step was achieved at room temperature using potassium *tert*-butoxide in dry dioxane, and so avoided the saponification of the ester function. The benzo[*de*]chromene-2-carboxylate (**9**) was then obtained in 74 % yield. Removal of the bromine atom in position 4 was achieved by a catalytic hydrogenation with Pd/C in ethanol. The final conversion in one step of the ester function into an imidazoline group was readily achieved in 20 % unoptimized yield, by using the ethylenediamine/trimethylaluminum procedure.[9]

We took advantage of the synthetic approach to 8-methyl-1-naphthol to efficiently prepare a benzo[*de*]chromene analogue of efaroxan. Biological evaluation of compound (**2**) showed a loss of α_2-adrenoreceptor binding affinity compared to efaroxan.

EXPERIMENTAL

General notes :

All solvents and reagents used were commercially available in 'pure for synthesis' grade, and used without further purification unless otherwise indicated. The reaction progress was monitored by TLC on silica gel plates 60F-254 (Merck art. 1.05554). Flash chromatography was run on silica gel 60-chromagel, 35-70 μ. Melting points were obtained with a Electrothermal IA9300 melting point apparatus and are uncorrected. NMR spectra were measured on a BRUCKER DPX400 (^{1}H, 400 MHz) spectrometer in $CDCl_3$ with tetramethylsilane as internal standard. Elemental analyses were performed on a Fisons 1108 microanalyser. Mass spectra were recorded on a TSQ-7000 FINNIGAN (Electospray ionisation).

3-Methyl-11-oxatricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5,9-tetraene (4)

A solution containing 50 mL of furan (46.8 g, 0.687 mol) in 50 mL of dimethoxyethane was refluxed. Then, we added dropwise, and simultaneously over 1 h, a solution of 6-methylanthranilic acid (**3**) (15.1 g, 0.1 mol) in 100 mL of dimethoxyethane and a solution containing 20 mL of isoamyl nitrite (17.44 g, 0.148 mol). After these additions, the resulting solution was refluxed for 1 h and treated with petroleum ether/1N NaOH. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to dryness. We obtained 14.8 g of a light yellow oil. The crude product was used in the next step without further purification.

8-Methyl-1-naphthol (5b) and 5-methyl-1-naphthol (5a)

A solution of 14.8 g of **4** (93 mmol) and 63 mL of conc. HCl in 500 mL of methanol was refluxed for 16 h. The solvent was evaporated, and the residue was diluted with CH_2Cl_2, and washed with water. The organic layer was dried over $MgSO_4$, and evaporated to dryness. The crude material was purified on flash column chromatography (petroleum ether/ethyl acetate 97/3). We isolated 5.04 g of **5a** (yield : 34 %) as an orange oil which solidified on standing (mp 95°C) , and 4.65 g of **5b** (yield : 32 %) which solidified on standing (mp 56°C).

8-Methyl-1-naphthol (5b)

^{1}H NMR (400 MHz, $CDCl_3$) : 7.61 (d, J=8.1 Hz, 1H, aromatic), 7.49 (d, J=8.1 Hz, 1H, aromatic), 7.29 (m, 1H, aromatic), 7.22 (m, 1H, aromatic), 7.18 (d, J=6.7 Hz, 1H, aromatic), 6.70 (d, J=7.3 Hz, 1H, aromatic), 5.20 (s, 1H, O*H*), 2.95 (s, 3H, CH_3).

5-Methyl-1-naphthol (5a)

^{1}H NMR (400 MHz, $CDCl_3$) : 8.05 (d, J=8.2 Hz, 1H, aromatic), 7.58 (d, J=8.5 Hz, 1H, aromatic), 7.30-7.41 (m, 3H, aromatic), 6.72 (d, J=7.4 Hz, 1H, aromatic), 5.24 (s, 1H, OH), 2.68 (s, 3H, CH_3).

Ethyl 2-(8-methyl-1-naphthyl)oxybutyrate (6)

A solution of 8-methyl-1-naphthol (**5b**) (5 g, 31.6 mmol), potassium carbonate (8.73 g, 63.2 mmol) and 4.91 mL of ethyl 2-bromobutyrate (6.78 g, 34.8 mmol) in 300 mL of acetonitrile was heated at 60°C for 48 h. The solution was allowed to cool at rt, and the solvent evaporated. We obtained 6.9 g of crude product. An analytical sample has been purified by flash column chromatography (petroleum ether/ ethyl acetate 99/1) to yield **6** as an yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) : 7.51 (d, J= 8.1 Hz, 1H, aromatic), 7.40 (d, J=8.1 Hz, 1H, aromatic), 7.32 (m, 1H, aromatic), 7.20-7.29 (m, 2H, aromatic), 6.64 (d, J=7.7 Hz, 1H, aromatic), 4.77 (t, J=5.6 Hz, 1H, C*H*CO_2Et), 4.20 (q, J=7.2 Hz, 2H, CH_3C*H*$_2$O), 2.91 (s, 3H, CH_3Ar), 2.12 (m, 2H, CH_3C*H*$_2$C), 1.19 (t, J=7.2 Hz, 3H, CH_3CH_2O), 1.15 (t, J=7.2 Hz, 3H, CH_3CH_2C). MS, m/z MH^+ : 273.

Ethyl 2-[1-(4-bromo-8-methyl)naphthyl]oxybutyrate (7) and ethyl 2-[1-(4-bromo-8-bromomethyl)naphthyl]oxybutyrate (8)

Ethyl 2-[1-(4-bromo-8-methyl)naphthyl]oxybutyrate (7)

A solution of **6** (2.57 g, 9.4 mmol) and of *N*-bromosuccinimide (1.85 g, 10 mmol) and a catalytic amount of benzoyl peroxide in 100 mL of carbon tetrachloride was refluxed for 76 h. The solution was allowed to cool at rt. The precipitate was eliminated by filtration and the solvent evaporated to dryness. The crude mixture was separated by flash column chromatography (petroleum ether/ethyl acetate 99.5/0.5). We obtained 1.17 g of **7** as an orange oil (yield : 35 %), and 0.55 g of the dibrominated derivative (**8**) (yield : 14 %).

^{1}H NMR (400 MHz, $CDCl_3$) for compound (**7**) : 8.08 (d, J=8.5 Hz, 1H, H-7), 7.58 (d, J=8.4 Hz, 1H, H-3), 7.43 (dd, J=8.5 and 7.0 Hz, 1H, H-6), 7.30 (d, J=7.0 Hz, 1H, H-5), 6.52 (d, J=8.4 Hz, 1H, H-2), 4.74 (t, J=6.0 Hz, 1H, C*H*CO_2Et), 4.20 (q, J=7.2 Hz, 2H, $CH_3C\mathit{H}_2O$), 2.99 (s, 3H, CH_3), 2.10 (m, 2H, $CH_3C\mathit{H}_2C$), 1.21 (t, J=7.2 Hz, 3H, $C\mathit{H}_3CH_2O$), 1.15 (t, J=7.2 Hz, 3H, $C\mathit{H}_3CH_2C$). MS, m/z MH^+ : 351/353.

2-[1-(4-Bromo-8-bromomethyl)naphthyl]oxybutyrate (8)

A solution of **6** (0.53 g, 1.9 mmol) and 0.69 g of *N*-bromosuccinimide (3.9 mmol) and a catalytic amount of benzoyl peroxide in 10 mL of carbon tetrachloride was refluxed for 48 h. The solution was allowed to cool at rt. The precipitate was eliminated by filtration and the solvent evaporated to dryness. We obtained 795 mg of an orange oil which was used in the next step without further purification. An analytical sample has been purified by flash column chromatography (petroleum ether/ethyl acetate 99.5/0.5).

^{1}H NMR (400 MHz, $CDCl_3$) : 8.25 (d, J=8.3 Hz, 1H, H-7), 7.66 (d, J=8.4 Hz, 1H, H-3), 7.50-7.60 (m, 2H, H-5 and H-6), 6.55 (d, J=8.4 Hz, 1H, H-2), 5.70 (d, J=9.3 Hz, 1H, H_A from $C\mathit{H}_2$Br), 5.11 (d, J=9.3 Hz, 1H, H_B from $C\mathit{H}_2$Br), 4.74 (t, J=6.0 Hz, 1H, C*H*CO_2Et), 4.20 (q, J=7.2 Hz, 2H, $CH_3C\mathit{H}_2O$), 2.25 (m, 2H, $CH_3C\mathit{H}_2C$), 1.18-1.27 (m, 6H, $C\mathit{H}_3CH_2O$ and $C\mathit{H}_3CH_2C$).

Ethyl 2-ethyl-2,3-dihydro-7-bromobenzo[*de*]chromene-2-carboxylate (9)

Potassium *tert*-butoxide (0.41 g, 3.7 mmol) was added to a solution containing 795 mg of **8** (1.8 mmol) in 10 mL of anhydrous dioxane. The solution was stirred at rt for 24 h, then the solvent was evaporated and the residue diluted in CH_2Cl_2. The organic layer was successively washed with water and brine, dried over $MgSO_4$, and evaporated to dryness. We obtained 465 mg of **9** as an brown oil.

^{1}H NMR (400 MHz, $CDCl_3$) : 8.01 (d, J=8.6 Hz, 1H, H-7), 7.68 (d, J=8.2 Hz, 1H, H-3), 7.50 (dd, J=7.1 and 8.6 Hz, 1H, H-6), 7.22 (d, J=7.1 Hz, 1H, H-6), 6.96 (d, J=8.2 Hz, 1H, H-2), 4.00 (q, J=7.2 Hz, 2H, $CH_3C\mathit{H}_2O$), 3.60 (d, J=15.6 Hz, 1H, H_A from $C\mathit{H}_2$), 3.29 (d, J=15.6 Hz, 1H, H_B from $C\mathit{H}_2$), 2.08 (m, 2H, $CH_3C\mathit{H}_2C$),), 1.09 (t, J=7.2 Hz, 3H, CH_3CH_2O), 1.02 (t, J=7.2 Hz, 3H, $C\mathit{H}_3CH_2C$).

Ethyl 2-ethyl-2,3-dihydrobenzo[*de*]chromene-2-carboxylate (10)

0.50 g of 10% Pd/C was cautiously added to a solution containing 0.465 g of **9** in 10 mL of ethanol. The suspension was vigorously stirred at rt under an atmosphere of hydrogen for 24 h. After removal of the catalyst by filtration, the solution was evaporated to dryness. We obtained 0.356 g of a crude oil.

^{1}H NMR (400 MHz, $CDCl_3$) : 7.68 (d, J= 8.3 Hz, 1H, aromatic), 7.35-7.42 (m, 3H, aromatic), 7.15 (d, J 6.9 Hz, 1H, aromatic), 7.05 (dd, J=2.6 and 5.9 Hz, 1H aromatic), 4.00 (q, J=7.2 Hz, 2H, $CH_3C\mathit{H}_2O$), 3.57 (d, J=16.0 Hz, 1H, H_A from $C\mathit{H}_2$), 3.30 (d, J=16.0 Hz, 1H, H_B from $C\mathit{H}_2$), 2.05 (m, 2H, $CH_3C\mathit{H}_2C$), 1.09 (t, J=7.2 Hz, 3H, CH_3CH_2O), 1.00 (t, J=7.2 Hz, 3H, $C\mathit{H}_3CH_2C$).

2-(2-Ethyl-2,3-dihydrobenzo[*de*]chromene-2-yl)-4,5-dihydro-*1H*-imidazole (2)

We added dropwise 0.17 mL of ethylenediamine (0.15g, 2.6 mmol) to a solution containing 1.29 mL of a 2M solution of trimethylaluminum in toluene diluted with 10 mL of toluene and maintained at 0°C. The mixture was stirred at 0°C for 15 min before the addition of **10** (0.348 g, 1.3 mmol) in 10 mL of toluene. The solution was stirred at rt for 15 min and refluxed for 22 h. The reaction mixture was hydrolysed by the addition of water and extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$ and evaporated to dryness. The crude product was purified by flash column chromatography (CH_2Cl_2/MeOH/NH_4OH 95/4.5/0.5). 70 mg of pure **2** were obtained (yield : 20 %)

^1H NMR (400 MHz, $CDCl_3$) : 7.68 (d, J= 8.2 Hz, 1H, aromatic), 7.36-7.46 (m, 3H, aromatic), 7.21 (d, J=7.1 Hz, 1H, aromatic), 6.96 (d, J=7.3 Hz, 1H aromatic), 3.64 (d, J=15.2 Hz, 1H, H_A from C*H*$_2$), 3.60 (m, 4H, C*H*$_2$N), 3.31 (d, J=15.2 Hz, 1H, H_B from C*H*$_2$), 1.97 (m, 2H, CH_3C*H*$_2$C), 1.00 (t, J=7.2 Hz, 3H, C*H*$_3$$CH_2$C).

The salt from fumaric acid was obtained by dissolution of 70 mg of **2** with 31 mg of fumaric acid in ethyl acetate. The solvent was removed by evaporation, and the residue was taken up with ether. The white solid was recovered by filtration and dried under vacuum.

Anal. Calcd for $C_{17}H_{18}N_2O$, $C_4H_4O_4$: C 65.96, H 5.80, N 7.33 . Found C 65.76, H 5.83, N 7.42. mp 190°C. MS, m/z MH^+ : 267.

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