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Synthesis of 5-Fluoro-3-[3-[4-(2-[^{14}C]-5-methoxy-4-pyrimidinyl)-1 piperazinyl]propyl]-1H-indole dihydrochloride.

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SUMMARY

The synthesis of 5-Fluoro-3-[3-[4-(2-[^{14}C]-5-methoxy-4-pyrimidinyl)-1-piperazinyl]propyl]-1H-indole dihydrochloride (5) was achieved by coupling [^{14}C] formamidine acetate (1) and dimethylmethoxymalonate in methanol containing sodium methoxide at 60°C to provide 2-[^{14}C] 4,6-dihydroxy-5-methoxyprimidine (2). Reaction of (2) with phosphorous oxychloride produced the unstable chloro-compound (3) which was reacted with 5-Fluoro-3-(3-N-piperazinylpropyl) indole to give 5-Fluoro-3[3-[4-(2-[^{14}C]-6-chloro-5-methoxy-4-pyrimidinyl)-1-piperazinyl] propyl]-1H-indole (4). Catalytic reduction of (4) and addition of 2 equivalents of hydrochloric acid resulted in the title compound as the dihydrochloride (5).

KEY WORDS

5-Fluoro-3-[3-[4-(2-[^{14}C]-5-methoxy-4-pyrimidinyl)-1-piperazinyl)propyl]-1H-indole dihydrochloride

Antidepressant

INTRODUCTION

5-Fluoro-3-[3-[4-(5-methoxy-4-pyrimidinyl)-1-piperazinyl]propyl]-1H-indole dihydrochloride is currently under development for the treatment of depression. Its unique pharmacologic profile, in which excellent efficacy is demonstrated in animal models, is believed to be the result of multiple interactions with various central pre- and post-synaptic serotonin (5-hydroxytryptamine, 5-HT) receptors. The unique profile of this compound may provide rapid and robust antidepressant efficacy.

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Currently,5-Fluoro-3-[3-[4-(2-[^{14}C]-5-methoxy-4-pyrimidinyl)-1-piperazinyl)propyl]-1H-indole dihydrochloride is undergoing toxicity evaluation in rats and monkeys. The metabolite elucidation and identification are also ongoing. This study is designed to investigate the mass balance, the absolute bioavailability and the extent of absorption of 5-Fluoro-3-[3-[4-(5-methoxy-4-pyrimidinyl)-1-piperazinyl]propyl]-1H-indoledihydrochloride in rats. This report describes the synthesis of 5-Fluoro-3-[3-[4-(2-[^{14}C]-5-methoxy-4-pyrimidinyl)-1-piperazinyl]propyl]-1H-indoledihydrochloride.

EXPERIMENTAL

[^{14}C] Formamidine acetate was purchased from Moravek Biochemicals, Inc. All other reagents, chemicals and solvents used in the synthesis were purchased commercially in the highest purity available. NMR spectra were recorded on a Bruker AM360 spectrometer, using tetramethylsilane as an internal standard. Radioactivity was measured by a Beckman LS9000 liquid scintillator. HPLC were run on Waters Delta Prep. 3000 (analyt.) Model 481 detecter, Model 740 recorder.

2-[^{14}C]-4,6-Dihydroxy-5-methoxyprimidine (2)

To a 50 mL 4-necked round bottom flask equipped with a thermometer, reflux condenser, nitrogen inlet and septum was added sodium methoxide (5.4 ml, 0.023m, 25% in methanol). To this was added a solution of [^{14}C]-formamidine acetate (186 mg, 101 mCi, 56 mCi/mmole) and formamidine acetate (576 mg, 0.0073 m, Aldrich) in warm (40°C) methanol (5 ml). A white slurry resulted. Dimethylmethoxymalonate (1 ml, 0.0073 m, Aldrich) was added via syringe. The slurry was heated to 60°C. After 10 min. a clear yellow solution resulted. After approx. 30 min. a white solid precipitated which was heated for 1 hr. HPLC indicated approx. 1.5% of formamidine left and 87% product formation. The reaction mixture was cooled to 5°C and conc. hydrochloric acid (2 ml, 0.023 m) was added. The resulting precipitate was stirred for 30 min., filtered and dried to produce a white solid (873 mg). This was recrystallized from hot water (5 ml) yielding a white solid (563 mg) as product (2). (Yield = 55%). HPLC indicated desired material.

HPLC: Waters Delta Prep. 3000 (analyt), Model 481 detector, Model 740 recorder.
Column: C_{18} Bondapak 3.9 x 300 mm (Waters)
Eluent: 100% 0.01M KH_2PO_4 buffer in water adjusted to pH 3.5
Retention Time: Formamidine=3.9 min., product 6.25 min.
Flow Rate: 1 ml/min.
Detection: UV 220 nm

5-Fluoro-3[3-[4-(2-[^{14}C]-6-chloro-5-methoxy-4-pyrimidinyl)-1-piperazinyl]propyl]-1H-indole(4)

2-[^{14}C]-4,6-dihydroxy-5-methoxypyrimidine(2) (553 mg), (0.0039 m) was suspended in toluene (7.7 ml) and triethylamine (0.55 ml, 0.0039 m) was added. The mixture was heated to 100°C followed by the slow addition of phosphoroxychloride (0.8 ml, 0.0085 m, Aldrich) in toluene (1 ml) while keeping the temperature of the mixture at 100°C by heating in an oil bath. The final mixture was heated to reflux for 1 hr. and monitored by HPLC. The resulting yellow solution with some brown oil was cooled to 0°C and quenched with cold water (5 ml). The organic phase was separated and washed with cold sodium bicarbonate solution (5 ml) followed by saturated cold sodium chloride (5 ml). The solution was dried over magnesium sulfate, filtered and concentrated to approx. 2 ml. This was diluted with acetonitrile followed by the addition of 5-fluoro-(3-N-piperazinylpropyl) indole (622 mg, 0.002 m) and N,N-diisopropylethylamine (0.5 ml, 0.0028 m). The mixture was refluxed for 1 hr. After 10 min. of heating a yellow solution resulted and after 30 min. some solid precipitated. HPLC indicated the absence of starting material. The reaction mixture was cooled to room temperature and then for 30 min. in an ice bath. The product was filtered, washed with cold acetonitrile (5 ml) and dried *in vacuo* for 15 hrs. A white solid resulted. HPLC indicated 98.5% product with a weight of 600 mg. Yield = 38.2%

HPLC: Waters Delta Prep. 3000 (analytical), Model 481 detector, Model 740 recorder.
Column: C_{18} Bondapak 39x300 mm (Waters)
Eluent: 40% Acetonitrile - 60% 0.05 M of KH_2PO_4 in water adjusted to pH 5.0
Flow Rate: 1 ml/min
Detection: UV 220 nm
Retention Time: Chloro-compound = 10.59 min. 5-Fluoro-(3-N piperazinylpropyl) indole = 4.08 min., product = 12.45 min.

5-Fluoro-3-[3-[4-(2-[^{14}C]-5-methoxy-4-pyrimidinyl)-1-piperazinyl]-propyl]-1H-indole dihydrochloride (5)

A slurry of (4) (600 mg, 0.00148 m) and magnesium hydroxide (178 mg, 0.003 m) was prepared in 90% ETOH-5% CH_3OH-5% H_2O (12 ml). To this was added 5% Palladium on activated carbon (50% water-wet, 250 mg). A septum sealed the 25 ml round-bottom flask and the air was drawn out via a syringe. A balloon of hydrogen was attached and the slurry was stirred vigorously and heated at 60°C in an oil bath. The reaction was monitored

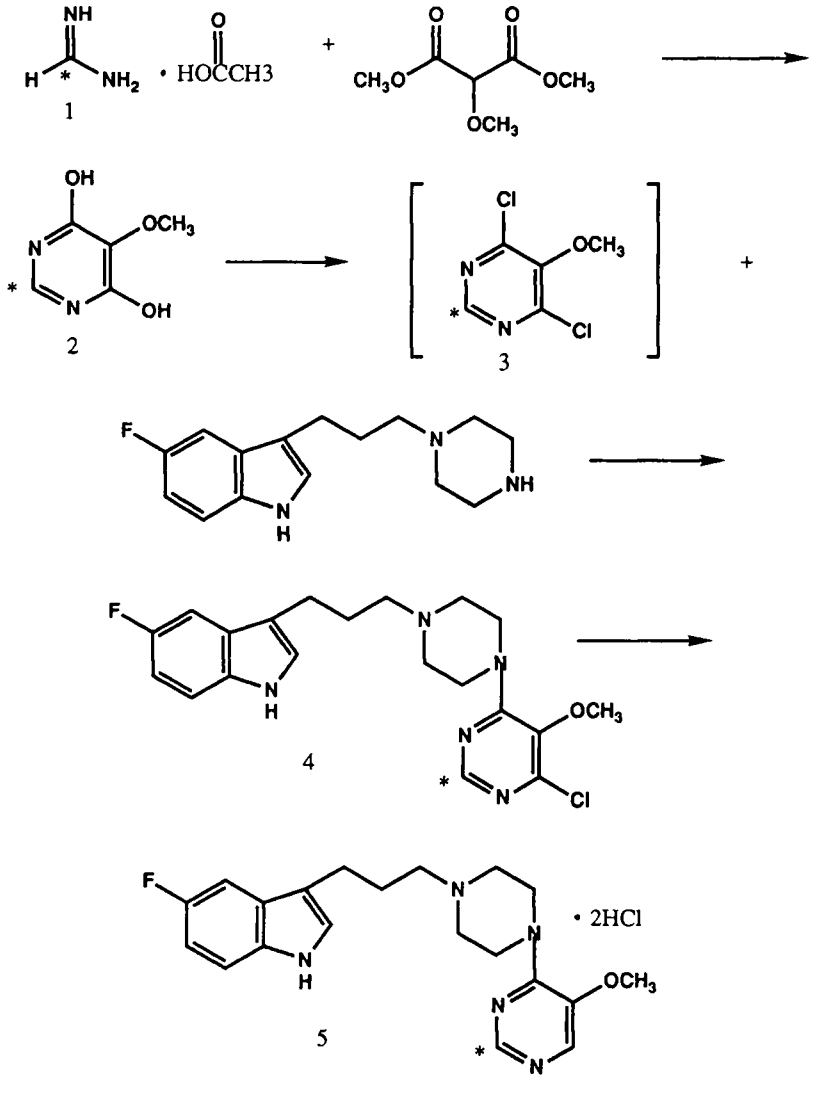
by HPLC. After 19 hours at 60°C, 99% of the product (5) resulted. The catalyst was removed by filtration through celite and washed with the mixture of 90% ETOH -5% CH_3OH -5% H_2O (5 ml). To this was added conc. HCl (0.3 ml, 0.0036m) and the resulting white precipitate was stirred at 5°C for 30 min. It was removed by filtration, washed with cold 90% ETOH-5% CH_3OH-5% H_2O (2 ml) and dried in vacuo for 15 hrs over P_2O_5. The resulting white solid (5) (498 mg, yield = 76%) had a specific activity of 31.2 μCi/mg and radiochemical purity of 98.5%.

HPLC: Waters Delta Prep. 3000 (Analytical), Model 481 detector, Model 740 recorder
Column: C_{18} Bondapak 39x300 mm (Waters)
Eluent: 40% acetonitrile - 60% 0.05 M of KH_2PO_4 in water adjusted to pH 5.0
Flow rate: 1 ml/min
Detection: UV 220 nm
Retention time: 6.61 min.

RESULTS AND DISCUSSION

The synthesis of 5-Fluoro-3-[3-[4-(2-[^{14}C]-5-methoxy-4-pyrimidinyl)-1-piperazinyl]propyl]-1H-indole dihydrochloride (5) was achieved by condensing [^{14}C] formamidine acetate with dimethylmethoxymalonate in a methanolic sodium methoxide solution. This resulted in 2-[^{14}C]4,6-dihydroxy-5-methoxyprimidine[1] (2). It was reacted with triethylamine in toluene and heated to 100°C followed by the slow addition of phosphorous oxychloride in toluene while keeping the mixture at 100°C for 1 hour. After workup by quenching in water and replacing toluene with acetonitrile the addition of 5-Fluoro-3-(3-N-piperazinylpropyl) indole[2] and N,N-di-isopropylethylamine was followed and held at reflux for 1 hour. After cooling 5-Fluoro-3[3-[4-(2-[^{14}C]6-chloro-5-methoxy-4-pyrimidinyl)-1-piperazinyl] propyl]-1 H-indole (4)[3] was isolated as white crystalline solid. Catalytic reduction and addition of 2 equivalents of hydrochloric acid resulted in a crystalline white product as the dihydrochloride[4] (5) with a radiochemical purity of 98.5% and specific activity of 31.2 μCi/mg. The experimental conditions were optimized using nonradiolabeled materials.

SYNTHETIC PATHWAY



* = POSITION OF RADIOLABEL

REFERENCES

1. Bristol-Myers Squibb Pharmaceutical Research Institute, Pharmaceutical Development-Process Research and Development, New Brunswick Laboratory, Process Description No. PRD 143/91-1; issued 2-25-91 by Kim, Modi, Simpson.

2. Bristol-Myers Squibb Pharmaceutical Research Institute, Pharmaceutical Development-New Brunswick Process Research and Development-Chemical Process Technology Laboratory, Process Description No. PRD 163/91-1; issued 5-3-91 by Kodersha, Mode.

3. Bristol-Myers Squibb Pharmaceutical Research Institute Pharmaceutical Development, New Brunswick Process Research and Development-Chemical Process Technology/Engineering, Laboratory Process Description No. PRD 174/91-1. Issued: 7-10-91 by Chan, Chen, Haas.

4. Bristol-Myers Squibb Pharmaceutical Research Institute, Pharmaceutical Development-New Brunswick, Process Research and Development-Chemical Process Technology/Engineering, Laboratory Process Description No. PRD 173/91-2; issued 8-27-91 by Bernot, Haas, Kodersha, Modi, Simpson.