CNS-Agent Precursor: A Simple and Efficient Synthesis of an Antipsychotic Drug Fluanisone

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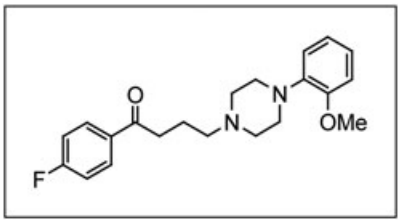

An efficient synthesis of antipsychotic drug fluanisone has been carried out in seven steps with an overall yield of 32.2%. The synthesis was started from 4-fluorobenzaldehyde. All the reactions were very clean and the isolation of products was very easy.

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INTRODUCTION

Antipsychotic is a tranquilizing psychiatric medication primarily used to manage psychosis particularly in schizophrenia and bipolar disorders. The antipsychotic drugs are mainly classified into first generation or typical antipsychotics [1] and second generation or atypical antipsychotics [2]. All the antipsychotic drugs tend to block D_2 receptors in the dopamine pathways of the brain. Dopamine receptors are implicated in many neurological processes, including motivation, pleasure, cognition, memory, learning, and fine motor control, as well as modulation of neuroendocrine signaling. Thus, dopamine receptors are common neurologic drug targets (Fig. 1).

Fluanisone (**1**) is a typical antipsychotic and sedative of the butyrophenone chemical class. It is used as an independent adjuvant drug for psychomotor excitement in severe and chronic schizophrenia and for manic depressive disorder. Schizophrenia is a devastating mental illness that affects about 1% of world's population. The first line of the antipsychotic therapy is represented by classical neuroleptics such as fluanisone [3]. There are few reports in the literature for the synthesis of fluanisone [4].

RESULTS AND DISCUSSIONS

The pharmaceutical importance of fluanisone is attracted us and as part of our research program in design and synthesis of biologically active compounds [5], herein we report, an efficient synthesis for fluanisone.

As shown in the retrosynthetic analysis (Scheme 1), our synthetic strategy was started from commercially available 4-fluorobenzaldehyde (**2**). This aldehyde was subjected to allylation [6] with allyl bromide in presence of zinc/NH_4Cl in tetrahydrofuran (THF)-H_2O mixture to afford the corresponding product, 1-(4-fluorophenyl)-but-3-en-1-ol (**3**) in very good yields. Thus, the obtained compound (**3**) was reacted with benzyl bromide in the presence of K_2CO_3 at acetonitrile reflux for 5 h to afford the corresponding product, 1-[1-(benzyloxy)-but-3-enyl]-4-fluorobenzene (**4**) in excellent yields. Oxidative hydroboration of the side chain was carried out with BH_3·DMS in THF at 0°C to afford the corresponding product, 4-(benzyloxy)-4-(4-fluorophenyl)-butan-1-ol (**5**) in very good yields [7]. Thus, the obtained alcohol **5** was subjected to oxidation with pyridinium chlorochromate in dichloromethane (DCM) at room temperature to afford the corresponding product, 4-benzyloxy)-4-(4-fluoro phenyl)-butanal (**6**) in very good yields.

The aldehyde compound (**6**) was reacted with 1-(2-methoxyphenyl)-piperazine for reductive amination [8] in presence of acetic acid to afford the corresponding

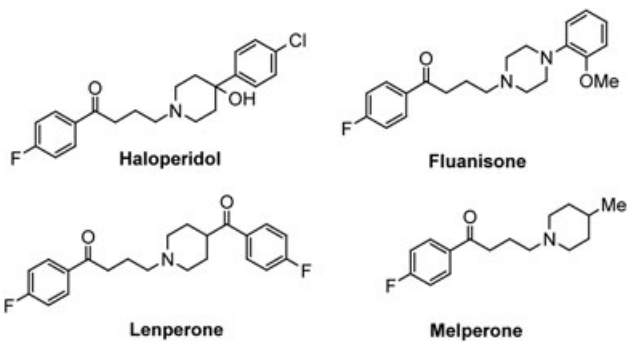
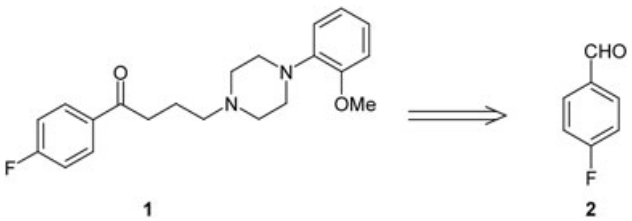


Figure 1. Antipsychotic drugs.

Scheme 1



product, 1-[4-(benzyloxy)-4-(4-fluorophenyl)-butyl]-4-(2-methoxyphenyl)-piperazine (**7**) in very good yields (Scheme 2). Thus, the obtained compound **7** was treated for debenzylation with Pd/C in methanol at hydrogen atmosphere to afford the corresponding derivative, 1-(4-fluoro phenyl)-4-[4-(2-methoxyphenyl)-piperazin-1-yl]-butan-1-ol (**8**) in very good yields. The free hydroxy compound **8** was subjected for oxidation with Dess–Martin periodinane [9]. The reaction was completed within 3 h at room temperature to afford the corresponding product, 1-(4-fluorophenyl)-4-[4-(2-methoxyphenyl)-piperazin-1-yl]-butan-1-one (**1**) in excellent yields as shown in the Scheme 1. All the products were confirmed by their spectral data.

In conclusion, we have demonstrated an efficient synthesis of antipsychotic agent fluanisone in seven steps with an overall yield, 32.2%. All the reactions were very clean, and the isolation of products was very easy.

EXPERIMENTAL

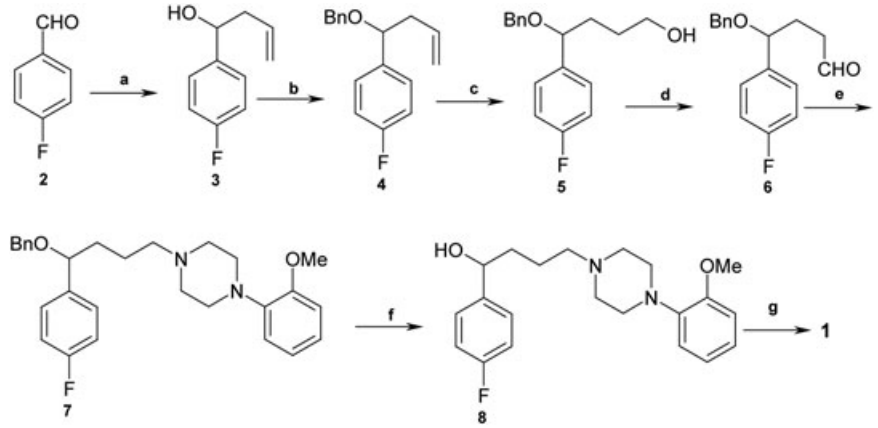
General methods. IR spectra were recorded on a Perkin-Elmer FTIR 240-c spectrophotometer. ^{1}H NMR spectra were recorded on Bruker-300 MHz, spectrometer in $CDCl_3$ using tetramethylsilane (TMS) as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV.

1-(4-Fluorophenyl)-but-3-en-1-ol (3). To a mixture of 4-fluro-benzaldehyde (1 g, 8.1 mmol) and zinc dust (0.47 g, 7.1 mmol) in tetrahydrofuran (10 mL), allyl bromide (1 g, 8.3 mmol) was added. The mixture was stirred at room temperature for 10–15 min, and the saturated ammonium chloride (1 mL) was slowly added at 0°C and continued stirring for 3 h at the same temperature. The progress of the reaction was monitored by the thin layer chromatography. After the completion of the reaction as indicated by thin layer chromatography (TLC), the reaction mixture was quenched by adding the saturated ammonium chloride (2 mL) slowly at 0°C with vigorous stirring. Then, the solvent was removed from reaction mixture under reduced pressure. To the residue, ethyl acetate (15 mL) was added and filtered on celite bed, and the cake was washed with ethyl acetate (10 × 2 mL). The combined filtrates were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography using 60–120 mesh silica gel while eluting with ethyl acetate–hexane mixture in 1:9 ratio. The pure product was obtained as a pale yellow liquid, yield, 1 g (80%).

IR (neat): υ 3384, 3077, 2980, 2908, 1641, 1605, 1510, 1423, 1296, 1225, 1157, 1049, 994, 919, 836, 782, 627 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.42–2.50 (m, 2H), 4.68 (t, 1H, J = 6.0 Hz), 5.15 (t, 2H, J = 6.5 Hz), 5.69–5.90 (m, 1H), 7.00 (t, 2H, J = 7.0 Hz), 7.22–7.48 (m, 2H).; EIMS m/z: 165 (m^{-1}), 147, 139, 119, 106, 97, 71, 57, 44, 41.

1-[1-(Benzyloxy)-but-3-enyl]-4-fluorobenzene (4). To a stirred mixture of compound 1-(4-fluorophenyl)but-3-en-1-ol (0.5 g, 3 mmol) in acetonitrile (10 mL), potassium carbonate (0.83 g, 6 mmol), benzyl bromide (0.42 mL, 3 mmol), and a catalytic amount of phase transfer catalyst (tetrabutylammonium iodide) were added. The resulting reaction mixture was refluxed for 5 h, and the completion of the reaction was confirmed by TLC. The solvent was removed under reduced pressure, and the residue was extracted with ethyl acetate (2 × 15 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography using 60–120 mesh silica gel while eluting with ethyl acetate–hexane mixture in 1:9 ratio. The pure product was obtained as yellow liquid, yield, 0.7 g (90%).

Scheme 2 The reaction conditions and reagents are as follows: (a) Zn/NH_4Cl, allyl bromide, THF-H_2O, 3 h, rt, 80%. (b) Bn-Br, K_2CO_3, CH_3CN, reflux, 5 h, 90%. (c) BH_3·DMS, THF, CH_3OH, NaOH, H_2O_2, 0 to rt°C, 3 h, 75%. (d) PCC, DCM, rt, 2 h, 90%. (e) $NaBH_3CN$, 1-(2-methoxyphenyl)-piperazine, CH_3CO_2H, CH_3OH, 0 to rt°C, 3 h, 80%. (f) Pd/C, H_2, CH_3OH. rt, 8 h, 90%. (g) DMP, $NaHCO_3$, DCM, 0 to rt°C, 3 h, 92%.



IR (neat): υ 3070, 3032, 2929, 2861, 1641, 1604, 1507, 1453, 1389, 1343, 1295, 1223, 1156, 1075, 1027, 994, 916, 835, 772, 737, 697 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.20–2.32 (m, 1H), 2.42–2.55 (m, 1H), 4.20–4.32 (m, 2H), 4.45 (t, 1H, *J* = 6.5 Hz), 5.00 (t, 2H, *J* = 6.5 Hz), 5.67–5.80 (m, 1H), 7.00 (t, 2H, *J* = 7.0 Hz), 7.20–7.35 (m, 7H).; EIMS *m/z*: 279 (m^+ Na), 198, 150, 120, 91.

4-(Benzyloxy)-4-(4-fluorophenyl)-butan-1-ol (5). To a stirred mixture of compound **4** (0.5 g, 1.9 mmol) in dry THF (10 mL), BH_3·DMS (1.12 mL, 11.85 mmol) was added at 0°C and continued stirring at room temperature for 1.5 h. Then, the reaction mixture was cooled to 0°C, and methanol (1 mL) was added and followed by 3*N* NaOH (0.7 g in 6-mL water) and 30% H_2O_2 (7 mL) and continued stirring for 1 h. Then, the reaction mixture was extracted with ethyl acetate (2 × 10 mL), and organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography using 60–120 mesh silica gel while eluting with ethyl acetate–hexane mixture in 3:7 ratio. The pure product was obtained as yellow syrup and yield 0.4 g (75%).

IR (neat): υ 3395, 3064, 3032, 2937, 2866, 1650, 1604, 1507, 1453, 1390, 1344, 1296, 1222, 1156, 1060, 835, 737, 698 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.55–1.90 (m, 4H), 3.60 (t, 2H, *J* = 6.5 Hz), 4.19–4.35 (m, 2H), 4.45 (d, 1H, *J* = 6.5 Hz), 7.02 (t, 2H, *J* = 7.0 Hz), 7.20–7.40 (m, 7H).; EIMS *m/z*: 297 (m^+ Na), 167, 150, 149, 102, 91, 71.

4-(Benzyloxy)-4-(4-fluorophenyl)-butanal (6). To a stirred mixture of compound **5** (0.3 g, 1 mmol) in dry DCM (10 mL), pyridinium chlorochromate (PCC) (0.3 g, 1.6 mmol) was added at room temperature and continued stirring for 2 h. The progress of the reaction mixture was monitored by TLC. After the complete conversion of the starting material as indicated by TLC, the reaction mixture was filtered on celite bed, and the cake was washed with DCM (2 × 10 mL). The combined filtrates were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography using 60–120 mesh silica gel while eluting with ethyl acetate–hexane mixture in 2:8 ratio. The pure product was obtained as colorless liquid, yield, 0.27 g (90%).

IR (neat): υ 3064, 3032, 2926, 2857, 1724, 1604, 1508, 1454, 1391, 1345, 1296, 1222, 1157, 1092, 1030, 910, 837, 740, 698 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.90–2.10 (m, 2H), 2.50 (t, 2H, *J* = 6.5 Hz), 4.20 (d, 1H, *J* = 6.5 Hz), 4.25–4.32 (m, 1H), 4.40 (d, 1H, *J* = 6.0 Hz), 7.01 (t, 2H, *J* = 7.0 Hz), 7.20–7.30 (m, 7H), 9.65 (s, 1H).; EIMS *m/z*: 295 (m^+ Na), 165, 147, 109, 100, 79, 71.

1-[4-(Benzyloxy)-4-(4-fluorophenyl)-butyl]-4-(2-methoxyphenyl)-piperazine (7). To a stirred mixture of compound **6** (0.25 g, 0.9 mmol) in methanol (10 mL), 1-(2-methoxyphenyl)-piperazine (0.17 g, 0.9 mmol) and acetic acid (1 mL) were added at 0°C, and the resulting reaction mixture was stirred at room temperature for 1 h. Then, the reaction mixture was cooled to 0°C, and $NaBH_3CN$ (0.12 g, 1.8 mmol) was added and continued stirring at room temperature for 3 h. The progress of the reaction mixture was monitored by TLC. After the completion of the reaction as indicated by TLC, the reaction mixture was quenched by adding crushed ice. Then, the solvent was removed under reduced pressure, and the residue was neutralized with sodium bicarbonate solution and extracted with ethyl acetate (3 × 10 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography using 60–120 mesh silica gel while eluting with ethyl acetate–hexane mixture in 1:1 ratio. The pure product was obtained as yellow syrup and yield 0.33 g (80%).

IR (neat): υ 2927, 2861, 1598, 1499, 1442, 1348, 1228, 1154, 1099, 1051, 972, 836, 746, 698 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.30–1.40 (m, 2H), 1.55–1.65 (m, 2H), 3.00–3.15 (m, 2H), 3.20–3.40 (m, 6H), 3.80 (s, 3H), 4.00 (t, 2H, *J* = 6.5 Hz), 4.10–4.25 (m, 2H), 4.36 (d, 1H, *J* = 6.0 Hz), 6.70–7.00 (m, 6H), 7.15–7.35 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.3, 154.5, 138.8, 138.1, 128.9, 127.8, 127.2, 123.4, 122.5, 121.2, 115.8, 115.3, 111.8, 80.9, 70.9, 61.5, 55.4, 52.2, 49.8, 44.7, 41.6, 35.6, 23.4.; EIMS *m/z*: 448 (m^+), 385, 341, 302, 289, 259, 235, 230, 228, 200, 174, 172, 138, 116.

1-(4-Fluorophenyl)-4-[4-(2-methoxyphenyl)-piperazin-1-yl]-butan-1-ol(8). A mixture of compound **7** (0.33 g) in methanol (5 mL), 10% of Pd/C (35 mg) was added and stirred under hydrogen atmosphere for 10 h at room temperature. After the completion of the reaction as indicated by TLC, the reaction mixture was filtered on celite bed, and the cake was washed with methanol (2 × 5 mL). The combined filtrates were concentrated under reduced pressure to afford the crude product, which was purified by column chromatography using 60–120 mesh silica gel while eluting with ethyl acetate–hexane mixture in 1:1 ratio. The pure product was obtained as yellow syrup and yield 0.23 g (90%).

IR (neat): υ 3411, 2925, 1597, 1499, 1440, 1231, 1172, 1112, 1037, 753 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.50–1.60 (m, 2H), 1.65–1.75 (m, 2H), 3.02–3.20 (m, 2H), 3.24–3.40 (m, 6H), 3.80 (s, 3H), 4.00 (t, 2H, *J* = 6.5 Hz), 4.60 (t, 1H, *J* = 6.5 Hz), 6.80–7.08 (m, 6H), 7.20–7.30 (m, 2H).; EIMS *m/z*: 358, 333, 317, 301, 279, 277, 242, 239, 217, 195, 88.

1-(4-Fluorophenyl)-4-[4-(2-methoxyphenyl)-piperazin-1-yl]-butan-1-one (1). To a stirred mixture of compound **8** (0.23 g, 0.64 mmol) in methylenedichloride (5 mL), Dess–Martin periodinane (0.33 g, 0.77 mmol) and sodium bicarbonate (0.11 g, 1.28 mmol) were added under nitrogen atmosphere, and the stirring was continued for 3 h at room temperature. After the completion of the reaction as indicated by TLC, the reaction mixture was quenched by adding ice, and the reaction mixture was extracted with DCM (2 × 5 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to afford the crude product, which was purified by column chromatography using 60–120 mesh silica gel while eluting with ethyl acetate–hexane mixture in 2:8 ratio. The pure product was obtained as colorless syrup and yield 0.21 g (92%).

IR (neat): υ 2927, 2855, 1681, 1504, 1448, 1377, 1206, 1139, 1024, 840, 802, 723 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.80–1.92 (m, 2H), 2.99 (t, 2H, *J* = 6.0 Hz), 3.20 (t, 2H, *J* = 6.0 Hz), 3.30–3.50 (m, 6H), 3.80 (s, 3H), 4.05 (t, 2H, *J* = 6.0 Hz), 6.60–7.12 (m, 6H), 7.90–8.01 (m, 2H). EIMS *m/z*: 356 (m^+), 348, 317, 299, 279, 242, 237, 191, 165, 162, 157, 150.

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