Supporting Information.

Towards a New Generation of Potential Antipsychotic Agents Combining D_2 and 5-HT_{1A} Receptor Activities

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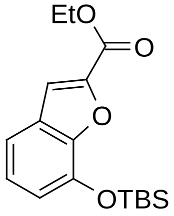
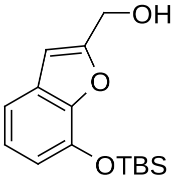
<u>*Preparation of the benzofuranol*</u> **(If)**

7-(*tert*-Butyl-dimethyl-silanyloxy)-benzofuran-2-methoxycarbonyle.



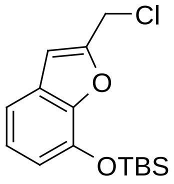
tert-Butyl-dimethyl-silyl chloride (1.61 g, 10.7 mmol) and imidazole (0.73 g, 10.7 mmol) were added to a solution of ethyl 7-hydroxy-2-benzofurancarboxylate [39543-86-7] (1.96 g, 10.2 mmol), in DMF (10 mL) at 0 °C. The reaction mixture was slowly warmed to room temperature and stirred for 16 hours. The mixture was then poured into water, extracted with ethyl acetate and the combined organic layer was washed with water, brine, dried over sodium sulfate and concentrated *in vacuo*. Purification by flash column chromatography (silica gel, cyclohexane-ethyl acetate, 95:5) gave 3.10 g (100%) of the product as a pale yellow oil; ^{1}H NMR ($CDCl_3$): δ 0.27 (s, 6H), 1.05 (s, 9H), 3.95 (s, 3H), 6.92 (d, J = 7.7 Hz, 1H), 7.14 (t, J = 7.8 Hz, 1H), 7.25 (d, J = 7.8 Hz, 1H), 7.49 (s, 1H).

[7-(*tert*-Butyl-dimethyl-silanyloxy)-benzofuran-2-yl]-methanol.



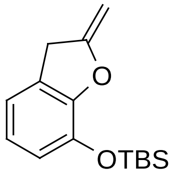
To a solution of $LiAlH_4$ (8.40 mL, 8.4 mmol) in diethyl ether (1.0 M) at 0 °C was added dropwise a solution of ethyl 7-(*tert*-butyl-dimethyl-silanyloxy)-2-benzofurancarboxylate (2.15 g, 7 mmol) in diethyl ether (14 mL). The reaction mixture was stirred for 18 hours at room temperature then quenched at 0 °C by the addition of 1.60 mL of a solution of sodium hydroxide (2.5 M). The reaction mixture was stirred for 15 min at 0 °C then another 15 min at room temperature and the solid filtered off. The filtrate was concentrated *under vacuo* to give 1.80 g (92%) of the product as a colorless oil which was used without further purification; ^{1}H NMR (CDCl$_3$): δ 0.24 (s, 6H), 1.04 (s, 9H), 1.85 (t, J = 6.4 Hz, 1H), 4.76 (d, J = 6 Hz, 2H), 6.64 (s, 1H), 6.76 (d, J = 7.7 Hz, 1H), 7.04 (t, J = 7.7 Hz, 1H), 7.14 (d, J = 7.7 Hz, 1H).

***tert*-Butyl-dimethyl-(2-chloromethyl- benzofuran-7-yloxy)-silane.**



To a solution of [7-(*tert*-butyl-dimethyl-silanyloxy)-benzofuran-2-yl]-methanol (1.78 g, 6.4 mmol) in methylene chloride (9 mL) at 0 °C was added triphenylphosphine (2.50 g, 9.5 mmol) and tetrachloromethane (0.92 mL, 9.5 mmol). The reaction mixture was stirred at 0 °C for 1 hour then the solvent removed *under vacuo*. The residue was diluted with 30 mL of cyclohexane and stirred for 1 hour. The precipitate formed was filtered off and the filtrate concentrated *under vacuo*. The residue was purified by flash column chromatography (silica gel, cyclohexane-ethyl acetate, 95:5) to give 1.50 g (79%) of the product as a pale yellow oil; ^{1}H NMR (CDCl$_3$): δ 0.25 (s, 6H), 1.04 (s, 9H), 4.70 (s, 2H), 6.70 (s, 1H), 6.80 (d, J = 7.5 Hz, 1H), 7.07 (t, J = 7.7 Hz, 1H), 7.14 (d, J = 7.2 Hz, 1H).

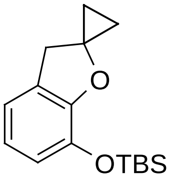
***tert*-Butyl-dimethyl-(2-methylene-2,3-dihydro-benzofuran-7-yloxy)-silane.**



LiAlH$_4$ (1.0 M in THF, 4.50 mL, 4.5 mmol) was added dropwise to a suspension of CrCl$_3$ (1.40 g, 8.85 mmol) in THF (10 mL) at 0 °C and the mixture was stirred at this temperature for 15 min. The green solution was then diluted with DMF (18 mL) and isopropanol (1.35 mL) and a solution of *tert*-

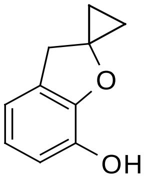
butyl-dimethyl-(2-chloromethyl-benzofuran-7-yloxy)-silane (1.05 g, 3.54 mmol) in DMF (15 mL) was added dropwise at 0 °C. The reaction mixture was stirred at room temperature for 18 hours then poured into water and extracted with pentane. The combined organic layer was dried over Na_2SO_4, filtered and the solvent removed *under vacuo* to give 0.78 g (84%) of the product as a colorless oil; ^1H NMR ($CDCl_3$): δ 0.21 (s, 6H), 1 (s, 9H), 3.89 (s, 2H), 4.26 (d, J = 2 Hz, 1H), 4.69 (d, J = 2 Hz, 1H), 7.72 (m, 1H), 7.79 (m, 1H).

tert-Butyl-dimethyl-(2-spirocyclopropane-2,3-dihydro-benzofuran-7-yloxy)-silane.



A diethyl zinc solution (1.1 M in toluene, 6.80 mL, 7.48 mmol) was added at 0 °C to a solution of *tert*-butyl-dimethyl-(2-methylene-2,3-dihydro-benzofuran-7-yloxy)-silane (0.78 g, 2.97 mmol) in 1,2-dichloroethane (15 mL), followed by chloroiodomethane (1.10 mL, 15 mmol). The reaction mixture was stirred at 0 °C for 1 hour, then at 50 °C for 1.5 hours. The mixture was cooled to 0 °C and an aqueous saturated solution of ammonium chloride (10 mL) was added. After 15 min the mixture was diluted with methylene chloride, washed with water and brine. The organic layer was dried over Na_2SO_4, filtered and the solvent removed *in vacuo*. The residue was purified by flash column chromatography (cyclohexane-ethyl acetate, 98:2) to give 0.75 g (90%) of the product as a colorless oil; ^1H NMR ($CDCl_3$): δ 0.15 (s, 6H), 0.67 (s, 2H), 0.96 (s, 9H), 1.16 (s, 2H), 3.28 (s, 2H), 6.67-6.71 (m, 2H), 6.75-6.78 (m, 1H); ^{13}C NMR ($CDCl_3$) δ -4.8, 12.3 (2C), 18.3, 25.7 (3 C), 36.9, 67.4, 117.6, 120.1, 120.7, 128.3, 139.6, 150.3.

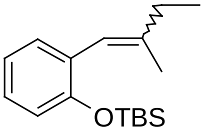
2-Spirocyclopropane-2,3-dihydro-benzofuran-7-ol (If).



A tetrabutyl ammonium fluoride solution (1.0 M in THF, 3.10 mL, 3.10 mmol) was added to a solution of *tert*-butyl-dimethyl-(2-spirocyclopropane-2,3-dihydro-benzofuran-7-yloxy)-silane (0.57 g, 2.06 mmol) in THF (10 mL) at 0 °C. The solution was stirred at 0 °C for 2 hours, then poured into water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, cyclohexane-ethyl acetate, 80:20) to give 0.30 g (89%) of **If** as a white solid, mp = 85-86 °C; ^{1}H NMR ($CDCl_3$): δ 0.71 (t, J = 6.4 Hz, 2H), 1.20 (t, J = 6.4 Hz, 2H), 3.34 (s, 2H), 4.77 (s, 1H), 6.76 (m, 3H).

<u>*Preparation of the benzofuranol*</u> **(Ig)**

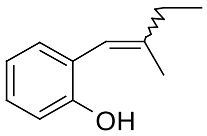
***tert*-Butyl-dimethyl-[2-((E/Z)-2-methyl-but-1-enyl)-phenoxy]-silane.**



n-Butyl lithium (1.6 M, 12 mL, 19 mmol) was added dropwise to a solution of 2-butyl triphenyl phosphonium bromide (6.67 g, 17 mmol) in THF (32 mL) at room temperature. The deep red reaction mixture was stirred for 1 hour at this temperature then cooled to 0 °C and a THF solution (34 mL) of 2-*tert*-butyl-dimethylsilyloxybenzaldehyde [116585-12-7] (3.80 g, 16 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 16 hours then diethyl ether was added. The mixture was stirred for 30 min, the precipitate formed was filtered off, the filtrate was washed with water, brine, dried over magnesium sulfate and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (silica gel, cyclohexane-ethyl acetate, 90:10) to give 2.64 g

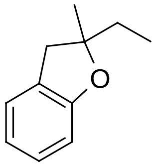
(60%) of the product as a pale yellow oil; ^{1}H NMR ($CDCl_3$): δ 0.01 (s, 6H), 0.85 (s, 9H), 0.98 (t, J = 7.6 Hz, 3H), 1.73 (s, 3H), 2.04-2.06 (m, 2H), 6.1 (s, 1H), 6.64-6.67 (m, 1H), 6.90-6.94 (m, 1H), 6.96-6.99 (m, 1H), 7.10-7.13 (m, 1H).

2-((E/Z)-2-Methyl-but-1-enyl)-phenol.



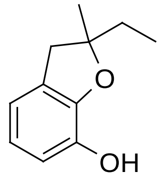
Tetrabutyl ammonium fluoride solution (1.0 M in THF, 10.40 mL, 10.4 mmol) was added to a solution of the phenoxysilane derivative (2.60 g, 9.44 mmol) in THF (19 mL) at 0 °C. After being stirred at room temperature for 15 hours, the solution was poured into water, extracted with ethyl acetate and the combined organic layer was washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, cyclohexane-ethyl acetate, 80:20) to give 1.26 g (82%) of the product as a yellow oil; ^{1}H NMR ($CDCl_3$): δ 0.99 (t, J = 7.6 Hz, 3H), 1.93 (s, 3H), 2.04 (q, J = 7.6 Hz, 2H), 5.03 (s, 1H), 6.08 (s, 1H), 6.85-6.88 (m, 2H), 7.01 (t, J = 7.6 Hz, 1H), 7.01 (t, J = 7.8 Hz, 1H).

2-Ethyl-2-methyl-2,3-dihydrobenzofuran.



Amberlyst 15 (12 g) was added in one portion to a methylene chloride solution (120 mL) of 2-((E/Z)-2-Methyl-but-1-enyl)-phenol (1.20 g, 7.4 mmol) and the reaction was vigorously stirred at room temperature for 24 hours. The resin was then filtered off and the solvent removed *in vacuo*. The residue was purified by flash column chromatography (silica gel, cyclohexane-ethyl acetate, 75:25) to afford 1 g (83%) of the product as a colorless oil; ^{1}H NMR ($CDCl_3$): δ 0.97 (t, J = 7.4 Hz, 3H), 1.40 (s, 3H), 1.75 (q, J = 7.2 Hz, 2H), 2.99 (ABq, $\Delta\nu_{AB}$ = 65.2 Hz, J = 15.4 Hz, 2H), 6.72 (d, J = 7.9 Hz, 1H), 6.80 (dd, J = 7.5, 7.4 Hz, 1H), 7.08 (d, J = 7.7 Hz, 1H), 7.11 (dd, J = 7.8, 7.7 Hz, 1H).

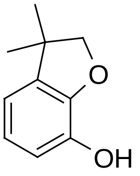
2-Ethyl-2-methyl-2,3-dihydrobenzofuran-7-ol (Ig).



n-Butyl lithium (1.6 M in THF, 5.80 mL, 9.25 mmol) was added to TMEDA (1.40 mL, 9.25 mmol) at 0 °C and the pale yellow solution was stirred for 30 min. A solution of 2-ethyl-2-methyl-2,3-dihydrobenzofuran derivative (1 g, 6.16 mmol) in hexane (6 mL) was added dropwise and the reaction mixture was then warmed to room temperature and stirred for 15 hours. The reaction mixture was then cooled to 0 °C and trimethyl borate (1.40 mL, 12.3 mmol) was added dropwise. After stirring for 6 hours at room temperature, THF was added (10 mL) followed by water (2.20 mL) and acetic acid (0.50 mL). The reaction mixture was cooled to 0 °C and H_2O_2 (1 mL) was added dropwise. The mixture was allowed to warm to room temperature and stirred for another 16 hours then diluted with ethyl acetate, washed with water, brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. Purification by flash column chromatography (silica gel, cyclohexane-ethyl acetate, 80:20) gave **Ig** (0.90 g, 82%) as a colorless oil; ^{1}H NMR ($CDCl_3$): δ 0.97 (t, J = 7.2 Hz, 3H), 1.39 (s, 3H), 1.79 (q, J = 7.4 Hz, 2H), 3.02 (ABq, $\Delta\nu_{AB}$ = 65.4 Hz, J = 15.6 Hz, 2H), 6.70-6.73 (m, 3H).

<u>*Preparation of the benzofuranol*</u> (**Ih**)

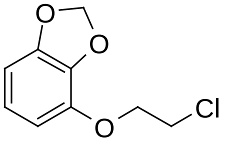
3,3-Dimethyl-2,3-dihydrobenzofuran-7-ol (Ih).



n-Butyl lithium (1.6 M in THF, 15.60 mL, 25 mmol) was added to TMEDA (3.80 mL, 24 mmol) at 0 °C and the pale yellow solution was stirred for 30 min. A solution of 3,3-dimethyl-2,3-dihydrobenzofuran [13524-78-2] (2.46 g, 16 mmol) in hexane (18 mL) was added dropwise at 0 °C then the reaction mixture stirred at room temperature for 15 hours. The reaction mixture was cooled to 0 °C and triisopropyl borate (7.70 mL, 33 mmol) was added dropwise. After stirring for 6 hours at room temperature, THF was added (30 mL) followed by water (5.40 mL) and acetic acid (1.20 mL). The reaction mixture was cooled to 0 °C, H_2O_2 (3 mL)was added dropwise and stirring was continued for 15 hours. The reaction mixture was diluted with ethyl acetate, washed with water, brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, cyclohexane-ethyl acetate, 90:10) to afford **Ih** (2.10 g, 77%) as a colorless oil; ^{1}H NMR ($CDCl_3$): δ 1.34 (s, 6H), 4.29 (s, 2H), 5.13 (s, 1H), 6.68 (dd, J = 7.1, 1.4 Hz, 1H), 6.75-6.85 (m, 2H).

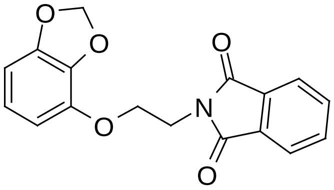
Preparation of new Gabriel's intermediates

4-(2-Chloro-ethoxy)-benzo[1,3]dioxole (IIc).



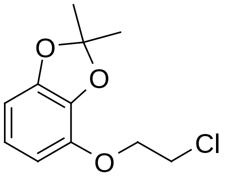
Prepared from the known 4-hydroxy-1,3-benzodioxole [69393-72-2] (3.60 g, 26 mmol), 1-bromo-2-chloroethane (8.70 mL, 104 mmol), potassium carbonate (7.20 g, 52 mmol) in ethylmethylketone (12 mL). Compound **IIc** was obtained as a yellow oil 5.60 g (100%) which was used as such in the next in step; ^{1}H NMR ($CDCl_3$): δ 3.80 (t, J = 6 Hz, 2H), 4.35 (t, J = 6 Hz, 2H), 5.96 (s, 2H), 6.53 (d, J = 8.1 Hz, 1H), 6.55 (d, J = 8.2 Hz, 1H), 6.79 (dd, J = 8.2, 8.1 Hz, 1H).

2-[2-(Benzo[1,3]dioxol-4-yloxy)-ethyl]-isoindole-1,3-dione: Gabriel's intermediate.



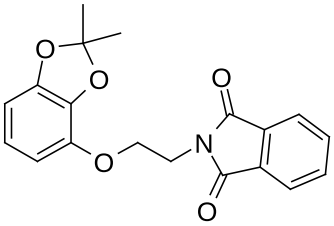
Synthesized from 5.20 g of 4-(2-chloro-ethoxy)-benzo[1,3]dioxole (26 mmol) and 5.24 g of potassium phtalimide (28.6 mmol) in DMF (75 mL). Recrystallization in diethyl ether-cyclohexane afforded 6.50 g (80%) of the product as a white solid; mp = 110 °C; ^{1}H NMR ($CDCl_3$): δ 4.1 (t, J = 6 Hz, 2H), 4.37 (t, J = 6 Hz, 2H), 5.88 (s, 2H), 6.50 (d, J = 8.1 Hz, 1H), 6.52 (d, J = 8.1 Hz, 1H), 6.71 (dd, J = 8.2, 8.1 Hz, 1H), 7.68-7.73 (m, 2H), 7.79-7.96 (m, 2H).

4-(2-Chloro-ethoxy)-2,2-dimethyl-benzo[1,3]dioxole (IId).



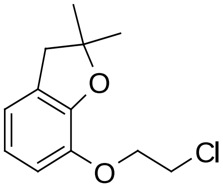
Synthesized from the known 2,2-dimethyl-4-hydroxy-1,3-benzodioxole [22961-82-6] (0.90 g, 5.4 mmol), 1-bromo-2-chloroethane (1.80 mL, 21.7 mmol), potassium carbonate (1.50 g, 10.8 mmol) in ethylmethylketone (11 mL). Compound **IId** was obtained as a brown oil 1.40 g (100%) of **IId** which was used as such in the next step; ^{1}H NMR ($CDCl_3$): δ 1.70 (s, 6H), 3.78 (t, J = 6 Hz, 2H), 4.34 (t, J = 6 Hz, 2H), 6.47 (d, J = 8.1 Hz, 1H), 6.50 (d, J = 10.4 Hz, 1H), 6.71 (dd, J = 10.4, 8.1 Hz, 1H).

2-[2-(2,2-Dimethyl-benzo[1,3]dioxol-4-yloxy)-ethyl]-isoindole-1,3-dione: Gabriel's intermediate.



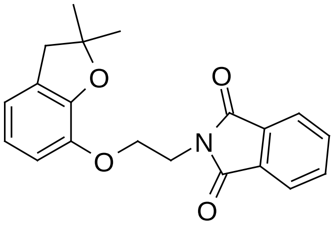
Prepared from 4-(2-chloro-ethoxy)-2,2-dimethyl-benzo[1,3]dioxole (1.20 g, 5.4 mmol) and potassium phtalimide (1.10 g, 6 mmol) in DMF (16mL). Recrystallization in diethyl ether-cyclohexane afforded 1.30 g (71%) of the product as white solid, mp = 125 °C; ^{1}H NMR ($CDCl_3$): δ 1.62 (s, 6H), 4.09 (t, J = 6 Hz, 2H), 4.35 (t, J = 6 Hz, 2H), 6.39 (d, J = 8.3 Hz, 1H), 6.48 (d, J = 8.6 Hz, 1H), 6.66 (dd, J = 8.5, 8.2 Hz, 1H), 7.68-7.75 (m, 2H), 7.83-8.07 (m, 2H).

7-(2-Chloro-ethoxy)-2,2-dimethyl-2,3-dihydro-benzofuran (IIe).



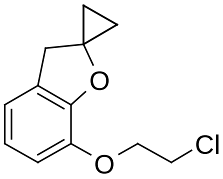
Synthesized from the known 2,3-dihydro-2,2-dimethyl-7-benzofuranol [1563-38-8] (15 g, 0.091 mol), 1-bromo-2-chloroethane (30.5 mL, 36.5 mol), potassium carbonate (20.2 g, 0.146 mol) in ethylmethylketone (150 mL). Compound **IIe** was obtained as a yellow oil (17 g, 82%) which was used as such in the next step; ^{1}H NMR ($CDCl_3$): δ 1.51 (s, 6H), 3.02 (s, 2H), 3.79 (t, J = 6.8 Hz, 2H), 4.31 (t, J = 6.8 Hz, 2H), 6.74-6.81 (m, 3H).

2-[2-(2,2-Dimethyl-2,3-dihydro-benzofuran-7-yloxy)-ethyl]-isoindole-1,3-dione: Gabriel's intermediate.



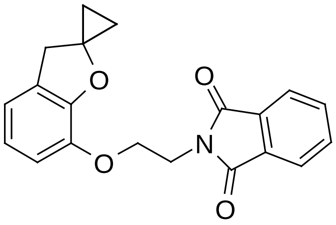
Prepared from 7-(2-chloro-ethoxy)-2,2-dimethyl-2,3-dihydro-benzofuran (17 g, 75 mmol) and potassium phtalimide (14.6 g, 79 mmol) in DMF (125 mL); recrystallization in diethyl ether-cyclohexane afforded 18 g (71%) of the product as white solid, mp = 113 °C; ^{1}H NMR ($CDCl_3$): δ 1.41 (s, 6H), 3.02 (s, 2H), 4.08 (t, J = 6.4 Hz, 2H), 4.32 (t, J = 6.4 Hz, 2H), 6.68-6.80 (m, 3H), 7.69-7.72 (m, 2H), 7.81-7.86 (m, 2H).

7-(2-Chloro-ethoxy)-2-spirocyclopropane-2,3-dihydro-benzofuran (IIf).



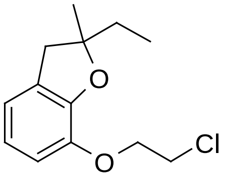
Prepared from 2-spirocyclopropane-2,3-dihydro-benzofuran-7-ol (2.55 g, 15.7 mmol), 1-bromo-2-chloroethane (5.30 mL, 63 mmol), potassium carbonate (3.48 g, 25 mmol) in ethylmethylketone (40 mL). Purification by flash column chromatography (silica gel, cyclohexane-ethyl acetate, 95:5) gave **IIf** (3.40 g, 95%) as a white solid, mp = 53 °C; ^{1}H NMR ($CDCl_3$): δ 0.70 (t, J = 6.4 Hz, 2H), 1.26 (t, J = 6.4 Hz, 2H), 3.32 (s, 2H), 3.78 (t, J = 6.4 Hz, 2H), 4.29 (t, J = 6.4 Hz, 2H), 6.74-6.86 (m, 3H).

2-[2-Spirocyclopropane -2,3-dihydro-benzofuran-7-yloxy)-ethyl]-isoindole-1,3-dione: Gabriel's intermediate.



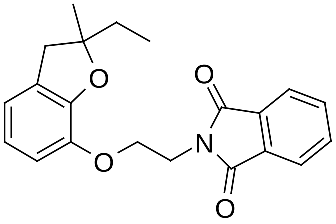
From 7-(2-chloro-ethoxy)-2-spirocyclopropane-2,3-dihydro-benzofuran (3.40 g, 15 mmol) and potassium phtalimide (3.08 g, 16.6 mmol) in DMF (25 mL); recrystallization in diethyl ether-cyclohexane afforded 3.50 g (70%) of the product as a white solid, mp = 122 °C; ^{1}H NMR (CDCl$_3$): δ 0.64 (t, J = 6.4 Hz, 2H), 1.11 (t, J = 6.4 Hz, 2H), 3.25 (s, 2H), 4.07 (t, J = 6.4 Hz, 2H), 4.30 (t, J = 6.4 Hz, 2H), 6.59-6.79 (m, 3H), 7.71-7.74 (m, 2H), 7.82-7.92 (m, 2H).

7-(2-Chloro-ethoxy)-2-ethyl-2-methyl-2,3-dihydrobenzofuran (IIg).



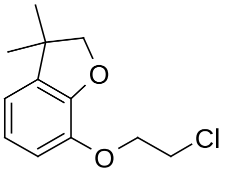
Prepared from 2-ethyl-2-methyl-2,3-dihydrobenzofuran-7-ol (1.12 g, 6.3 mmol), 1-bromo-2-chloroethane (2.10 mL, 25.2 mmol), potassium carbonate (1.74 g, 12.6 mmol) in ethylmethylketone (16 mL). Purification by flash column chromatography (silica gel, cyclohexane-ethyl acetate, 90:10) gave **IIg** (0.58 g, 40%) as a yellow oil; ^{1}H NMR (CDCl$_3$): δ 0.97 (t, J = 7.6 Hz, 3H), 1.44 (s, 3H), 1.76 (q, J = 7.6 Hz, 2H), 2.99 (ABq, $\Delta\nu_{AB}$ = 68.3 Hz, J = 15.2 Hz, 2H), 3.78 (t, J = 6.4 Hz, 2H), 4.31 (t, J = 6.4 Hz, 2H), 6.75-6.81 (m, 3H).

2-[2-(2-Ethyl-2-methyl-2,3-dihydrobenzofuran-7-yloxy)-ethyl]-isoindole-1,3-dione: Gabriel's intermediate.



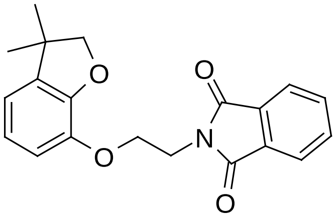
Prepared from 7-(2-chloro-ethoxy)-2-ethyl-2-methyl-2,3-dihydrobenzofuran (0.58 g, 2.4 mmol) and potassium phtalimide (0.66 g, 3.6 mmol) in DMF (5 mL). Recrystallization in diethyl ether-cyclohexane afforded 0.72 g (85%) of the product as a white solid, mp = 192 °C; ^{1}H NMR ($CDCl_3$): δ 0.88 (t, J = 7.2 Hz, 3H), 1.35 (s, 3H), 1.67 (q, J = 7.2 Hz, 2H), 2.95 (ABq, $\Delta\nu_{AB}$ = 70 Hz, J = 15.2 Hz, 2H), 4.1 (t, J = 6.4 Hz, 2H), 4.33 (t, J = 6.4 Hz, 2H), 6.67-6.79 (m, 3H), 7.70-7.73 (m, 2H), 7.83-7.88 (m, 2H).

7-(2-Chloro-ethoxy)-3,3-dimethyl-2,3-dihydrobenzofuran (IIh).



From 3,3-dimethyl-2,3-dihydrobenzofuran-7-ol (2.10 g, 12.8 mmol), 1-bromo-2-chloroethane (4.30 mL, 51 mmol), potassium carbonate (2.84 g, 21 mmol) in ethylmethylketone (30 mL) compound **IIh** (2.60 g, 89%) was obtained as a yellow oil which was used as such in the next step; ^{1}H NMR ($CDCl_3$): δ 1.35 (s, 6H), 3.82 (t, J = 6 Hz, 2H), 4.29 (s, 2H), 4.31 (t, J = 6 Hz, 2H), 6.57-6.85 (m, 3H).

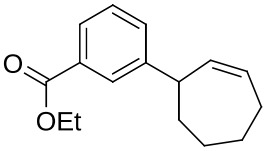
2-[2-(3,3-Dimethyl-2,3-dihydro-benzofuran-7-yloxy)-ethyl]-isoindole-1,3-dione: Gabriel's intermediate.



From 7-(2-chloro-ethoxy)-3,3-dimethyl-2,3-dihydrobenzofuran (2.59 g, 11 mmol) and potassium phtalimide (2.12 g, 11 mmol) in DMF (20 mL); recrystallization from diethyl ether-cyclohexane afforded 2.90 g (78%) of the product as a white solid, mp = 99 °C; ^{1}H NMR ($CDCl_3$): δ 1.34 (s, 6H), 4.11 (t, J = 6 Hz, 2H), 4.19 (s, 2H), 4.33 (t, J = 6 Hz, 2H), 6.71-6.75 (m, 1H), 6.77-6.80 (m, 2H), 7.70-7.75 (m, 2H), 7.83-7.87 (m, 2H).

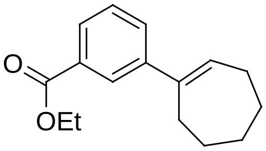
Preparation of the intermediates (IVe-g) according to Method (A)

2-(3-Ethylbenzoate)cycloheptene: precursor of (IVe).



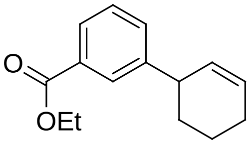
Prepared according to the general procedure reported in the experimental part for the Heck reaction. This intermediate was purified by flash column chromatography (silica gel, cyclohexane-ethyl acetate, 90:10) and obtained as a yellow oil (75%); ^{1}H NMR ($CDCl_3$): δ 1.41 (t, J = 7.2 Hz, 3H), 1.52-1.55 (m, 1H), 1.79-1.88 (m, 2H), 2.17-2.39 (m, 3H), 2.51-2.54 (m, 1H), 2.68-2.93 (m, 1H), 4.36 (q, J = 7.2 Hz, 2H), 5.79-5.94 (m, 2H), 7.32-7.47 (m, 2H), 7.84-8.03 (m, 2H).

1-(3-Ethylbenzoate)cycloheptene (IVe).



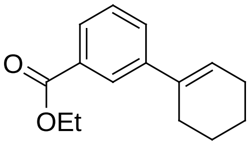
Prepared according to the general procedure reported in the experimental part for the isomerization of the product resulting from the Heck reaction. The compound **IVe** was purified by flash column chromatography (silica gel, cyclohexane-ethyl acetate, 95:5) and obtained as a pale yellow oil (70%); ^{1}H NMR ($CDCl_3$): δ 1.41 (t, J = 7.2 Hz, 3H), 1.54-1.58 (m, 2H), 1.63-1.691 (m, 2H), 1.82-1.86 (m, 2H), 2.28-2.33 (m, 2H), 2.61-2.79 (m, 2H), 4.39 (q, J = 7.2 Hz, 2H), 6.13 (t, J = 6.7 Hz, 1H), 7.34 (dd, J = 7.8, 7.7 Hz, 1H), 7.49 (d, J = 7.6, 1.0 Hz, 1H), 7.88 (dd, J = 7.6, 1.0 Hz, 1H), 7.98 (dd, J = 1.3 Hz, 1H).

2-(3-Ethylbenzoate)cyclohexene: precursor of (IVf).



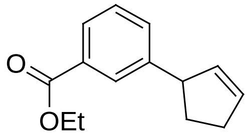
This intermediate was purified by flash column chromatography (silica gel, cyclohexane-ethyl acetate, 90:10) and obtained as a pale yellow oil (40%); ^{1}H NMR ($CDCl_3$): δ 1.38 (t, J = 7.2 Hz, 3H), 1.52-1.75 (m, 1H), 1.76-1.82 (m, 1H), 1.92-1.95 (m, 1H), 2.10-2.18 (m, 3H), 2.83-2.89 (m, 1H), 4.37 (q, J = 7.2 Hz, 2H), 5.71-5.80 (m, 2H), 7.36-7.41 (m, 2H), 7.87 (d, J = 7.68 Hz, 1H), 7.92 (s, 1H).

1-(3-Ethylbenzoate)cyclohexene (IVf).



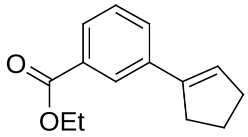
The compound **IVf** was purified by flash column chromatography (silica gel, cyclohexane-ethyl acetate, 95:5) and obtained as a pale yellow oil (77%); ^{1}H NMR ($CDCl_3$): δ 1.39 (t, J = 7.2 Hz, 3H), 1.65-1.69 (m, 2H), 1.78-1.81 (m, 2H), 2.21-2.24 (m, 2H), 2.41-2.86 (m, 2H), 4.37 (q, J = 7.2 Hz, 2H), 6.17-6.19 (m, 1H), 7.36 (dd, J = 7.9, 7.7 Hz, 1H), 7.55 (d, J = 7.9 Hz, 1H), 7.88 (d, J = 7.7 Hz, 1H), 8.1 (s, 1H).

2-(3-Ethylbenzoate)cyclopentene: precursor of (IVg).



This intermediate was purified by distillation (bp = 125 °C under 0.01 mmHg) and obtained as a colorless oil (75%); ^{1}H NMR ($CDCl_3$): δ 1.39 (t, J = 7.2 Hz, 3H), 1.59-1.62 (m, 1H), 2.36-2.57 (m, 3H), 3.93-3.96 (m, 1H), 4.35 (q, J = 7.2 Hz, 2H), 5.77-5.79 (m, 1H), 5.97-5.99 (m, 1H), 7.33-7.38 (m, 2H), 7.88-7.93 (m, 2H).

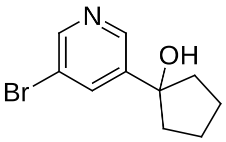
1-(3-Ethylbenzoate)cyclopentene (IVg).



The compound **IVg** was purified by flash column chromatography (silica gel, cyclohexane-ethyl acetate, 95:5) and obtained as a pale yellow oil (96%); ^{1}H NMR ($CDCl_3$): δ 1.39 (t, J = 7.1 Hz, 3H), 2.01-2.08 (m, 2H), 2.53-2.62 (m, 2H), 2.72-2.94 (m, 2H), 4.38 (q, J = 7.1 Hz, 2H), 6.27 (brs, 1H), 7.35 (dd, J = 7.8, 7.7 Hz, 1H), 7.61 (d, J = 7.8 Hz, 1H), 7.88 (d, J = 7.7 Hz, 1H), 8.09 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.3, 19.3, 33.1, 33.3, 60.9, 126.6, 127.3, 127.7, 128.2, 129.7, 130.4, 136.9, 141.6, 166.7; IR (KBr) ν : 2956, 2836, 1719, 1239 cm^{-1}.

Preparation of the intermediates (V)

1-(5-Bromo-pyridin-3-yl)-cyclopentanol: precursor of (V).



To a suspension of 2.25 g of magnesium (92.6 mmol) in THF (25 mL) was added a crystal of iodine and a few drops of 1,4-dibromobutane. The mixture was heated at 65 °C until it turned colorless, then a solution of 1,4-dibromobutane (10 g, 46.3 mmol) in THF (50 mL) was added dropwise while maintaining the reaction at 65 °C. The reaction mixture was then stirred at this temperature for 4 hours and cooled to 0 °C. A solution of ethyl 5-bromo-3-pyridinecarboxylate [20986-40-7] (10 g, 46.3 mmol) in 60 mL of THF was added dropwise. The mixture was slowly brought to room and stirred for 16 hours. The reaction was poured in a cold, saturated aqueous solution of ammonium chloride and extracted with ethyl acetate. The combined organic layer was washed with water, brine dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, cyclohexane-ethyl acetate, 70:30) to give 3.60 g (32%) of the product as a white solid, mp = 74 °C; ^{1}H NMR ($CDCl_3$): δ 1.74-1.77 (m, 2H), 1.85-1.88 (m, 6H), 2.70-2.73 (m, 2H), 3.93 (s, 1H), 7.15 (d, J = 5.0 Hz, 1H), 8.38 (d, J = 5.0 Hz, 1H), 8.64 (s, 1H).

3-Bromo-5-cyclopenten-1-yl-pyridine (V).

A solution of 1-(5-bromo-pyridin-3-yl)-cyclopentanol (1.70 g, 11.3 mmol) in 50 mL of toluene and containing 5 mL of concentrated HCl was heated at 120 °C for 12 hours with continuous removal of the water formed. The reaction mixture was cooled to room temperature and poured into a saturated aqueous solution of sodium bicarbonate, extracted with ethyl acetate and the combined organic layer washed with water and brine. The organic solution was dried over sodium sulfate, filtered and the solvent removed *in vacuo*. The residue was purified by flash column chromatography (silica gel, cyclohexane-ethyl acetate, 60:40) to give **V** (1.65 g, 65%) as an off-white solid, mp = 43 °C; ^{1}H NMR ($CDCl_3$): δ 2.03-2.06 (m, 2H), 2.55-2.58 (m, 2H), 2.70-2.73 (m, 2H), 6.31 (s, 1H), 7.80-7.82 (m, 1H), 8.49 (d, J = 2.0 Hz, 1H), 8.59 (d, J = 2.0 Hz, 1H).

Compd	Salt	Calculated (C,H,N)	Found
4	oxalate	C, 69.16; H, 6.47; N, 3.10	C, 68.91; H, 6.49; N, 2.94
5	oxalate	C, 63.00; H, 5.95; N, 3.06	C, 63.06; H, 5.97; N, 3.08
6	oxalate	C, 63.00; H, 5.95; N, 3.06	C, 62.70; H, 6.06; N, 3.14
7	oxalate	C, 65.29; H, 6.16; N, 3.17	C, 65.13; H, 6.02; N, 3.15
8	oxalate	C, 69.06; H, 7.51; N, 2.98	C, 68.76; H, 7.50; N, 3.05
9	oxalate 0.7 hydrate [a]	C, 68.55; H, 7.30; N, 3.07	C, 68.29; H, 7.30; N, 3.20; H_2O, 0.7
10	oxalate	C, 68.01; H, 7.08; N, 3.17	C, 67.87; H, 6.87; N, 3.39
11	oxalate	C, 67.70; H, 7.50; N, 3.16	C, 67.79; H, 7.60; N, 3.20
12	1.2 fumarate 0.3 hydrate [a]	C, 66.68; H, 6.90; N, 3.01	C, 66.39; H; 7.04; N, 3.15; H_2O, 0.33
13	fumarate	C, 66.80; H, 6.25; N, 3.00	C, 66.78; H, 6.39; N, 3.07
14	fumarate	C, 66.21; H, 6.00; N, 3.09	C, 65.92; H, 6.00; N, 3.02
15	fumarate	C, 67.35; H, 6.49; N, 2.91	C, 67.18; H, 6.64; N, 2.88
16	fumarate	C, 70.13; H, 6.94; N, 2.92	C, 69.92; H, 6.93; N, 2.89
17	maleate	C, 70.42; H, 6.54; N, 2.93	C, 70.27; H, 6.59; N, 3.14
18	fumarate 0.4 hydrate [a]	C, 70.57; H, 7.15; N, 2.84	C, 69.63; H, 7.09; N, 2.76; H_2O, 0.4
19	fumarate 0.4 hydrate [a]	C, 70.13; H, 6.94; N, 2.92	C, 69.92; H, 6.99; N, 3.04; H_2O, 0.41
20	maleate	C, 67.48; H, 6.71; N, 5.83	C, 67.68; H, 6.93; N, 5.70
21	fumarate	C, 67.77; H, 6.32; N, 5.85	C, 67.64; H, 6.32; N, 5.82

Elemental analyses. [a] Water percentage was determined by the Karl Fisher method with a coulometer.

In vitro characterization of antagonist properties of the compounds at rat D_2 receptors.

The procedure used here has been described previously (Newman-Tancredi, A.; Cussac, D.; Brocco, M.; Rivet, J-M.; Chaput, C.; Touzard, M.; Pasteau, V.; Millan, M. J. Dopamine D_2 receptor-mediated G-protein activation in rat striatum: functional autoradiography and influence of unilateral 6-hydroxydopamine lesions of the substantia nigra. *Brain Res.* **2001**, *920*, 41-54). Frozen brains were thawed in ice cold Hepes (50 mM, pH 7.4 at 25 °C) containing NaCl (150 mM), EDTA (0.2 mM), GTP (1 mM), dithiothreitol (0.2 mM). The striata were dissected and homogenized in 20 volumes of the same buffer then incubated at 37 °C for 10 min in order to dissociate the endogenous neurotransmitters from the receptors. The homogenate was centrifuged at 20000*g* for 15 min, at 4 °C. The pellet was suspended in the same volume of Hepes (50 mM) containing NaCl (150 mM), EDTA (0.2 mM), GDP (1 mM), dithiothreitol (0.2 mM) then centrifuged as before. The membranes (40-30 µM protein/tube) were incubated in presence of the test compounds for 1 hour at 37 °C. After 15 min $[^{35}S]GTP\gamma S$ (specific activity 1000 Ci/mmol) was added to a final concentration of 0.1 nM. Non specific binding was determined with unlabelled GTPγS (10µM). The reaction was terminated by filtration through Whatman filters using a Brandel harvester and radioactivity was counted by liquid scintillation spectrometry. Each concentration-response experiment was performed in duplicate and replicated three times. pEC_{50} and E_{max} values were estimated from the concentration response curves by means of non-linear regression using the program Graphpad Prism (version 3). Compounds were tested at six or ten concentrations from 10^{-10} M to 10^{-4} M, and $[^{35}S]GTP\gamma S$ binding values were expressed as % of the maximal response obtained with quinelorane (100 µM). The pKb (-log[Kb]) for the compound was calculated using the Cheng-Prusoff equation: $Kb = IC_{50} /(1 + [A]/EC_{50})$; IC_{50} is the compound concentration reducing the quinelorane concentration [A] by half, and EC_{50} is the quinelorane concentration reducing 50% of its E_{max}. The EC_{50} for quinelorane was $6.8 \pm 3.2 \times 10^{-5}$ M.

Table. Antagonist properties at rD_2 receptors determined by transduction assay *in vitro*.

compd	**D_2 antagonist properties**	
	PKb [a]	E_{max} [b]
1	7.81 ± 0.11	7 ± 2
haloperidol	8.13 ± 0.07	-3 ± 6
16	8.29 ± 0.10	-9 ± 9
20	9.29 ± 0.22	9 ± 5

[a] Quinerolane-stimulated [^{35}S]GTPγS binding to membranes of rat striatum.

[b] Stimulation obtained with 100µM quinerolane.