Experimental Section:

Solvents were purified and dried by standard procedures. If not otherwise stated reactions were performed under dry N_2. Melting points: Büchi melting point apparatus, uncorrected. MS were run on Finnegan MAT TSQ 70 by EI (70eV) with solid inlet. ^{1}H NMR spectra were obtained on a Bruker AM 360 (360 MHz) spectrometer, if not otherwise stated in $CDCl_3$ relative to TMS (*J* values in Hz). IR spectra were performed on a Jasco FT/IR 410 spectrometer. Chromatography purification was performed using silica gel 60 (Merck).

Dimethyl pyrazolo[1,5-*a*]pyridine-2,3-dicarboxylate (9).[15]

Dimethyl acetylenedicarboxylate (3.50 g, 24.6 mmol) was added tropwise to a stirred suspension of **8** (5.00 g, 23.5 mmol) and K_2CO_3 (4.70 g, 47.5 mmol) in 40 ml DMF at room temperature. The mixture was stirred for 2 h while a stream of air was introduced under the liquid level. After filtration and subsequent evaporation of the solvent the residue was treated with water (100 ml) and extracted with diethylether (3x 100 ml). The organic layer was dried (Na_2SO_4), filtered and evaporated under reduced pressure. Purification by flash chromatography (petroleum ether-EtOAc 1:1) gave **9** (2.18 g, 45%) as a white solid: mp 65 °C.

Ethyl pyrazolo[1,5-*a*]pyridine-2-carboxylate (10).[15]

A solution of **9** (500 mg, 2.4 mmol) in aq. sulfuric acid (20 ml, v/v 50%) was heated for 3 h at 80°C. The cooled mixture was neutralized with 5n NaOH solution followed by treatment with 2n aq. HCl until pH 2-3 was reached. After extraction with $CHCl_3$ (2x 100 ml) and evaporation of the organic layer the residue was treated with EtOH (20 ml) and conc. H_2SO_4 (5 ml) followed by heating for 16 h at reflux temperature. Addition of Na_2CO_3 (5.0 g) to the cooled solution, filtration and evaporation of the solvent gave the crude product which was purified by flash chromatography (petroleum ether-EtOAc 7:3) yielding **10** (290 mg, 72%) as a white solid: mp 42-43 °C.

2-[4-(4-Chlorophenyl)piperazin-1-ylmethyl]pyrazolo2[1,5-*a*]pyridine (2).

A solution of N-(4-chlorophenyl)piperazine (100 mg, 0.5 mmol) in THF (10 ml) was treated with $LiAlH_4$ (1 M in THF, 0.5 ml, 0.5 mmol) at room temperature and stirred for 30 min. After heating the mixture to 60°C a solution of **10** (150 mg, 0.8 mmol) in THF (4 ml) was added

dropwise during a period of 20 min followed by stirring for additional 15 min. The cooled solution was treated with saturated aq. $NaHCO_3$ (10 ml) and extracted with CH_2Cl_2 (3x 15 ml). The organic layer was dried (Na_2SO_4) and concentrated and the residue was purified by flash chromatography (CH_2Cl_2-MeOH 95:5) to give **2** (58 mg, 35%) as a white solid: mp 110 °C; IR 2941, 2822, 1634, 1595, 1520, 1496, 1330, 1230, 1144 cm^{-1}; ^{1}H-NMR δ 2.68-2.74 (m, 4H), 3.17-3.22 (m, 4H), 3.81 (s, 2H), 6.47 (s, 1H), 6.71 (ddd, ^{3}J=7.0/7.0 Hz ^{4}J=1.4 Hz, 1H), 6.80-6.85 (m, 2H), 7.08 (ddd, ^{3}J=8.5/7.0 Hz ^{4}J=0.8 Hz, 1H), 7.16-7.21 (m, 2H), 7.47 (br d, J=8.5 Hz, 1H), 8.47 (br d, J=7.0 Hz, 1H); EIMS 326 (M^+), 328 (M^+). Anal. ($C_{18}H_{19}ClN_4$) C,H,N.

Ethyl pyrazolo[1,5-*a*]pyridine-3-carboxylate (11).

Compound **11** was prepared according to a previous reported protocol[18] starting from **8** (33.38 g; 150 mmol) and ethyl propiolate (16.19 g; 165 mmol) to yield 20.50 g **11** (108 mmol; 72%). $bp_{(2mbar)}$ 130-132°C.

Pyrazolo[1,5-*a*]pyridine (12).[17]

A solution of **11** (4.0 g; 21 mmol) in aq. sulfuric acid (40 ml; v/v 50%) was heated at reflux temperature for 3 h, cooled, treated with aq. 2n NaOH (150 ml) and $NaHCO_3$ (20 g) and extracted with diethyl ether. The organic layer was dried (Na_2SO_4) and evaporated under reduced pressure. The crude product was purified by flash chromatography (petroleum ether-EtOAc 7:3) yielding **12** (2.15 g, 86%) as a colourless oil: $bp_{(20mbar)}$ 95°C.

Pyrazolo[1,5-*a*]pyridine-7-carboxaldehyde (13).

n-Butyllithium (1,6 M hexan, 1.2 ml, 1.9 mmol) was added to a solution of **12** (200 mg, 1.7 mmol) in THF (6 ml) at -78 °C. After being stirred for 30 min the mixture was added to a precooled (- 78 °C) solution of ethyl formiate (150 mg, 2.0 mmol) in THF (4 ml). After 10 min the cooling bath was removed, the reaction mixture was allowed to warm to 0°C and then poured into 1 N HCl (20 ml). Addition of $CHCl_3$ (30 ml) was followed by rapid stirring for 5 h and separation of the organic layer. The aqueous layer was treated with 2 N NaOH (15 ml) and extracted with $CHCl_3$ (30 ml). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure. Purification of the crude product by flash chromatography (petroleum ether-EtOAc 7:3) gave **13** (203 mg, 82%) as a pale yellow solid: mp 74-75 °C; IR 3089, 3071,

3028, 1688, 1622, 1306, 796 cm $^{-1}$; ^{1}H-NMR δ 6.72 (d, 2.0 Hz 1 H), 7.22 (dd, 9.0 Hz, 7.0 Hz, 1 H), 7.48 (dd, ^{3}J=7.0 Hz ^{4}J=1.5 Hz, 1 H), 7.82 (dd, ^{3}J=9.0 Hz ^{4}J=1.5 Hz, 1 H), 8.08 (d, 2.0 Hz, 1H), 10.88 (s, 1 H); EIMS 146 (M^+); Anal. ($C_8H_6N_2O$) C,H,N.

7-[4-(4-Chlorophenyl)piperazin-1-ylmethyl]pyrazolo[1,5-*a*]pyridine (7).

$Na(OAc)_3BH$ (85 mg, 0.40 mmol) was added to a solution of **13** (45 mg, 0.31 mmol) and 1-(4-chlorophenyl)piperazine (75 mg, 0.36 mmol) in CH_2Cl_2 (4 ml). After being stirred for 16 h the reaction mixture was washed with sat. $NaHCO_3$ (5 ml), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by flash chromatography (petroleum ether-EtOAc 1:1) yielding **7** (85 mg, 87%) as a white solid: mp 122 °C; IR 2941, 2821, 1636, 1596, 1496, 1233, 785 cm^{-1}; ^{1}H-NMR δ 2.82-2.87 (m, 4H), 3.22-3.27 (m, 4H), 4.15 (s, 2H), 6.58 (d, 2.0 Hz, 1 H), 6.98 (dd, ^{3}J=7.0 Hz ^{4}J=1.0 Hz, 1H), 6.83-6.88 (m, 2H), 7.16 (dd, 9.0/7.0 Hz, 1 H), 7.19-7.24 (m, 2H), 7.52 (br d, 9.0 Hz , 1H), 7.99 (d, 2.0 Hz, 1H); EIMS 326 (M^+), 328 (M^+). Anal. ($C_{18}H_{19}ClN_4$) C,H,N.

Ethyl 4-(hydroxymethyl)pyrazolo[1,5-*a*]pyridine-3-caboxylate (15) and

Ethyl 6-(hydroxymethyl)pyrazolo[1,5-*a*]pyridine-3-caboxylate (16) .

The compounds **15** and **16** were prepared following a previous reported protocol[20] starting from 3-(hydroxymethyl)pyridine (16.2 g; 149 mmol), hydroxylamin-*O*-mesitylene sulfonic acid (90% purity; 35.5 g; 149 mmol) and ethyl propiolate (14.2 g; 145 mmol) yielding 8.2 g **15** (25 %) as pale yellow solid (mp: 113°C) and 5.6 g **16** (17 %) as a colourless solid (mp: 107°C).

4-(Hydroxymethyl)pyrazolo[1,5-*a*]pyridine (19).

A solution of **15** (0.72 g, 3.30 mmol) in aq. sulfuric acid (15 ml; v/v 40%) was heated at 100°C for 1.5 h, cooled and neutralized with aq. 2n NaOH and $NaHCO_3$. Extraction with CH_2Cl_2 followed by evaporation gave the crude product which was purified by flash chromatography (EtOAc) yielding **19** (402 mg, 83%) as a white solid: mp 38-40°C; IR 3347, 2918, 2870, 1632, 1510, 1459, 1428, 1156, 761 cm^{-1}; ^{1}H-NMR δ 2.62 (br s, 1H), 4.88 (s, 2H), 6.55 (d, 2.5 Hz, 1H), 6.72 (dd, 7.0/7.0 Hz, 1H), 7.13 (br d, 7.0 Hz, 1H), 7.93 (d, 2.5 Hz, 1H), 8.37 (br d, 7.0 Hz, 1H); EIMS 148 (M^+); Anal. ($C_8H_8N_2O$) C,H,N.

4-[4-(4-Chlorophenyl)piperazin-1-ylmethyl]pyrazolo[1,5-*a*]pyridine (1).

Et_3N (150 mg, 1.50 mmol) and MsCl (170 mg, 1.48 mmol) were added to a solution of **19** (170 mg, 1.15 mmol) in THF (10 ml). The reaction mixture was stirred at room temperature for 2 h, filtered and evaporated to dryness. After addition of DMF (10 ml), K_2CO_3 (300 mg, 3.0 mmol) and 1-(4-chlorophenyl)piperazine (225 mg, 1.15 mmol) the mixture was stirred for 16 h at ambient temperature, treated with H_2O (30 ml) and extracted with EtOAc (3x 20ml). The organic layer was washed with brine, dried (Na_2SO_4) and concentrated. Purification by flash chromatography (EtOAc-CH_2Cl_2 3:1) gave **1** (235 mg, 63%) as a white solid: mp 144-146°C; IR 2945, 2770, 1629, 1595, 1496, 1453, 1235, 763 cm^{-1}; ^{1}H-NMR δ 2.63-2.68 (m, 4H), 3.14-3.20 (m, 4H), 3.73 (s, 2H), 6.69 (br d, 2.5 Hz, 1H), 6.73 (dd, 7.0/7.0 Hz, 1H), 6.80-6.85 (m, 2H), 7.11 (d, 7.0 Hz, 1H), 7.17-7.22 (m, 2H), 7.94 (d, 2.5 Hz, 1H), 8.42 (br d, 7.0 Hz,1 H); EIMS 326 (M^+), 328 (M^+). Anal. ($C_{18}H_{19}ClN_4$) C,H,N.

6-(Hydroxymethyl)pyrazolo[1,5-*a*]pyridine (20).

A solution of **16** (0.80 g, 3.70 mmol) in aq. sulfuric acid (15 ml; v/v 40%) was heated at 100°C for 3 h, cooled and neutralized with aq. 2n NaOH and $NaHCO_3$. Extraction with CH_2Cl_2 followed by evaporation gave the crude product which was purified by flash chromatography (EtOAc) yielding **20** (420 mg, 78%) as a white solid: mp 40 °C; IR 3314, 2869, 1642, 1529, 1446, 1026, 807 cm^{-1}; ^{1}H-NMR δ 2.63 (br s, 1H), 4.67 (s, 2H), 6.48 (d, 2.5 Hz, 1H), 7.10 (br d, 9.0 Hz, 1H), 7.50 (br d, 9.0 Hz, 1H), 7.92 (d, 2.5 Hz, 1H), 8.44 (s, 1H); EIMS 148 (M^+); Anal. ($C_8H_8N_2O$) C,H,N.

6-[4-(4-Chlorophenyl)piperazin-1-ylmethyl]pyrazolo[1,5-*a*]pyridine (6).

Et_3N (150 mg, 1.50 mmol) and MsCl (170 mg, 1.48 mmol) were added to a solution of **20** (170 mg, 1.15 mmol) in THF (10 ml). The reaction mixture was stirred at room temperature for 2 h, filtered and evaporated to dryness. After addition of DMF (10 ml), K_2CO_3 (300 mg, 3.0 mmol) and 1-(4-chlorophenyl)piperazine (225 mg, 1.15 mmol) the mixture was stirred for 16 h at ambient temperature, treated with H_2O (30 ml) and extracted with EtOAc (3x 20ml). The organic layer was washed with brine, dried (Na_2SO_4) and concentrated. Purification by flash chromatography (EtOAc-CH_2Cl_2 3:1) gave **3** (228 mg, 61%) as a white solid: mp 102 °C; IR 2940, 2818, 1641, 1595, 1496, 1441, 1229, 817 cm^{-1}; ^{1}HMR δ 2.61-2.66 (m, 4H), 3.14-3.19 (m,

4H), 3.55 (s, 2H), 6.49 (br d, 2.5 Hz, 1H), 6.80-6.85 (m, 2H), 7.15-7.22 (m, 3H), 7.50 (br d, 9.0 Hz, 1H), 7.93 (d, 2.5 Hz, 1H), 8.42 (s, 1H); EIMS 326 (M^+), 328 (M^+). Anal. ($C_{18}H_{19}ClN_4$) C,H,N.

Ethyl 4-[4-(4-chlorophenyl)piperazin-1-ylmethyl]pyrazolo[1,5-*a*]pyridine-3-carboxylate (17).

Et_3N (150 mg, 1.50 mmol) and MsCl (170 mg, 1.48 mmol) were added to a solution of **15** (270 mg, 1.23 mmol) in THF (10 ml). The reaction mixture was stirred at room temperature for 2 h, filtered and evaporated to dryness. After addition of DMF (10 ml), K_2CO_3 (300 mg, 3.0 mmol) and 1-(4-chlorophenyl)piperazine (225 mg, 1.15 mmol) the mixture was stirred for 16 h at ambient temperature, treated with H_2O (30 ml) and extracted with EtOAc (3x 20ml). The organic layer was washed with brine, dried (Na_2SO_4) and concentrated. Purification by flash chromatography (CH_2Cl_2-MeOH 97:3) gave **17** (280 mg, 61%) as a white solid: mp 104-109°C; IR 2978, 2951, 2820, 1711, 1628, 1596, 1517, 1496, 1236, 1200, 1051 cm^{-1}; ^{1}H-NMR δ 1.39 (t, 7.0 Hz, 3H), 2.61-2.68 (m, 4H), 3.08-3.15 (m, 4H), 4.18 (s, 2H), 4.33 (q, 7.0 Hz, 2H), 6.78-6.84 (m, 2H), 6.92 (dd, 7.0/7.0 Hz, 1H), 7.15-7.22 (m, 2H), 7.47 (d, 7.0 Hz, 1H), 8.38 (s, 1H), 8.45 (d, 7.0 Hz, 1H); EIMS 398 (M^+), 400 (M^+). Anal. ($C_{21}H_{23}ClN_4O_2$) C,H,N.

{4-[4-(4-Chlorophenyl)piperazin-1-ylmethyl]pyrazolo[1,5-*a*]pyridin-3-yl}methanol (18).

A solution of $LiAlH_4$ (1M in THF, 0.06 ml, 0.06 mmol) was added to a solution of **17** (50 mg, 0.13 mmol) in THF (4 ml). The reaction mixture was stirred for 5 h at room temperature, treated with sat. $NaHCO_3$ (10 ml) and extracted with CH_2Cl_2. The organic layer was separated, dried (Na_2SO_4) and concentrated under reduced pressure. Purification by flash chromatography (EtOAc-MeOH 98:2) gave **18** (38 mg, 86%) as a colourless oil: IR 3192, 2918, 2828, 1540, 1496, 1240, 1000 cm^{-1}; ^{1}H-NMR δ 2.65-2.71 (m, 4H), 3.13-3.20 (m, 4H), 3.94 (s, 2H), 4.82 (s, 2H), 6.69 (dd, 7.0/7.0 Hz, 1H), 6.77-6.82 (m, 2H), 6.96 (d, 7.0 Hz, 1H), 7.16-7.21 (m, 2H), 7.92 (s, 1H), 8.44 (br d, 7.0 Hz, 1H); EIMS : 356 (M^+), 358 (M^+). Anal. ($C_{19}H_{21}ClN_4O$) C,H,N.

Receptor binding studies. Receptor binding studies were carried out as described in literature.[24] In brief, the dopamine D1 receptor assay was done with bovine striatal membranes at a final protein concentration of 45 µg/assay tube and the radioligand [^{3}H]SCH 23390 at 0.3

nM (K_d = 0.27 nM).

Competition experiments with the human $D2_{long}$, $D2_{short}$, D3 and D4.4 receptors were run with preparations of membranes from CHO cells expressing the corresponding receptor and [^{3}H]spiperone at a final concentration of 0.1 nM. The assays were carried out with a final protein concentration of 5-25 µg/assay tube and K_d values of 0.10 nM for $D2_{long}$ and $D2_{short}$, 0.20-0.60 nM for D3 and 0.10-0.40 nM for the D4.4 receptor.

Protein concentration was established by the method of Lowry using bovine serum albumin as standard (for literature see: Lowry, O. H.; Rosebrough, N. J.; Farr, A. L.; Randall, R. J. Protein measurement with the folin phenol reagent. *J. Biol. Chem.* **1951**, *193*, 265-275.).

Mitogenesis Assay. The mitogenesis experiments were done with a CHO10001A cell line stably transfected with the human dopamine D4.2 receptor according to literature.[13] In brief, cells were grown in MEM α-medium supplemented with fetal calf serum, L-glutamine, penicillin G, streptomycin and hygromycin B at 37 °C under a humidified atmosphere of 5% CO_2-95% air at a density of 10 000 cells/well. After 72 h the growth medium was removed and the cells were rinsed twice with serum free medium. Incubation was started by adding seven different concentrations of the test compounds (with a final concentration of 0.001-1000 nM) diluted in 10 µL of sterile water to each well containing 90 µL serum free medium. Eight wells of every plate contained 100 µL serum free medium or medium supplemented with 10% fetal calf serum to control stimulation of growth. After incubation for 16-18 h, 0.25 µCi [^{3}H]thymidine (specific activity 2.0 Ci/mmol) in 10 µL serum free medium was added to each well for 2 h at 37 °C. Finally, cells were trypsinized and harvested onto GF/C filters using an automated cell harvester. Filters were washed four times with ice-cold PBS buffer and counted in a microplate scintillation counter.

Data analysis. The resulting competition curves of the receptor binding experiments were analyzed by nonlinear regression using the algorithms in PRISM (GraphPad Software, San Diego, USA). The data were fit using a sigmoid model to provide an EC_{50} value, representing the concentration corresponding to 50% of maximal inhibition and then transformed to K_i values according to the equation of Cheng and Prusoff (for literature see: Cheng, Y. C.; Prusoff, W. H.

Relationship between the inhibition constant (K_i) and the concentration of inhibitor which causes 50% inhibition (IC_{50}) of an enzymatic reaction. *Biochem. Pharmacol.* **1973**, *22*, 3099-3108.). Experimental data resulting from the mitogenesis assay were each normalized and then combined to get a mean curve. Nonlinear regression analysis of this curve provided an EC_{50} value indicating the concentration of the test compound which induced half of the maximal uptake of [^{3}H]thymidine. The top value of the curve represented the maximal intrinsic activity which could be correlated to the effect of the full agonist quinpirole (100%).

Appendix

Results of combustion analyses:

compound	mass percent	C	H	N
1	calculated	66.15	5.86	17.14
	found	66.09	5.90	17.28
2	calculated	66.15	5.86	17.14
	found	65.97	5.94	16.92
6	calculated	66.15	5.86	17.14
	found	65.98	5.98	16.85
7	calculated	66.15	5.86	17.14
	found	66.02	5.92	16.98
13	calculated	65.75	4.14	19.17
	found	65.65	4.18	19.00
17	calculated	63.23	5.81	14.04
	found	62.99	5.88	13.97
18	calculated	63.95	5.93	15.70
	found	63.68	5.85	15.33
19 (×0.1 H_2O)	calculated	64.07	5.51	18.68
	found	64.12	5.38	18.94
20 (×0.1 H_2O)	calculated	64.07	5.51	18.68
	found	64.18	5.40	18.52