The Synthesis and In Vitro Receptor Binding Profile of DDD-016, a Novel, Potential Atypical Antipsychotic

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SUPPORTING INFORMATION

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Experimental

General. Unless otherwise noted, all reagents were used as supplied. Solvents used in the reactions were anhydrous (sure seal) from Sigma-Aldrich and others were of reagent or HPLC grade from Fisher Scientific. Analytical TLC was performed on Analtech silica gel GF plates (250 μm). Automated flash chromatography was carried out on a Teldyne Isco Combi*Flash*®R_f system using pre-packed silica gel columns. NMR spectra were recorded on either a Varian Gemini-300 or a VNMRS-500 spectrometer. ^{1}H Chemical shifts are expressed in parts per million (δ) relative to TMS ($\delta = 0$) as an internal standard. ^{13}C Chemical shifts are referenced to either TMS ($\delta = 0$) or the residual solvent peaks in the spectra. Coupling constants (J) are reported in Hz. RP-LC/MS (ESI, positive ion mode) analyses were carried out on a ThermoElectron Hypersil Gold C18 3 μm (50 × 4.6 mm) column using H_2O–CH_3CN gradient with 0.05% TFA as modifier. HRMS (ESI) data was obtained on a Thermo Finnigan LTQ Orbitrap XL instrument in FTMS (Fourier Transform) mode with resolution ≥30K.

DDD-016. *Step 1*. To a well stirred solution of compound **1** (6.98 g, 32.7 mmol) in THF (30 mL) and AcOH (9 mL), a concentrated solution of $NaNO_2$ (7.03 g, 101.9 mmol) in water (12 mL) was added dropwise at ambient temperature. The reaction was stirred at ambient temperature for 20 min and treated with water (100 mL). The product was filtered, washed with water, and dried to give 7.67 g (97%) of the nitroso compound.

Step 2. To a stirred solution of nitroso compound from step 1 (14.6 g, 61.1 mmol) and N-methyl 4-pyridone (9.04g, 79.9 mmol) in ethanol (150 mL) and acetic acid (20 mL) at 55 ^{o}C, was added zinc dust (12.0 g, 183.5 mmol) in three equal portions allowing 10 mins between the additions. The reaction was stirred for another 5 minutes and filtered hot. The solid washed with ethanol, and the resultant solution was heated to reflux for 30 minutes, and thereafter the

solvent was removed in vacuo. The residue was treated with 8 mL of acetic acid, and heated to reflux for about 16 hours. The solvent was removed in vacuo, and the residue was dissolved in methylene chloride (500 mL). The solid impurity was removed by filtration, and the filtrate was washed with 10% NaOH solution. The combined organic layer was washed with water and brine, dried over anhydrous sodium sulfate, filtered an the filtrate taken to dryness in vacuo. The crude product was purified by flash chromatography on silica gel using 0-5% MeOH/chloroform as the eluent to give 3.0 g (16%) of the desired product **2**. LRMS: m/Z, 307.42 ($M+H^+$).

Single Crystal X-Ray Diffraction Data.

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for DDD-016 (**10d**). U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S(1)	2367(1)	2521(1)	9076(1)	20(1)
C(1)	3450(4)	2583(3)	10132(2)	19(1)
S(1')	3291(2)	2421(2)	10064(1)	20(1)
C(1')	2479(8)	2710(5)	8955(4)	19(1)
N(1)	5290(1)	4450(1)	9339(1)	13(1)
N(2)	9546(1)	6025(1)	8764(1)	18(1)
C(2)	3387(1)	3809(1)	10456(1)	15(1)
C(3)	2458(1)	4084(1)	11177(1)	19(1)
C(4)	2398(1)	5187(1)	11504(1)	20(1)
C(5)	3233(1)	6048(1)	11084(1)	19(1)
C(6)	4138(1)	5794(1)	10358(1)	16(1)
C(7)	4259(1)	4674(1)	10046(1)	14(1)
C(8)	6727(1)	5027(1)	9228(1)	13(1)
C(9)	7605(1)	5668(1)	9915(1)	18(1)
C(10)	9351(1)	5662(1)	9671(1)	19(1)
C(11)	8962(1)	5149(1)	8166(1)	16(1)
C(12)	7363(1)	4770(1)	8439(1)	13(1)

C(13)	6322(1)	3985(1)	8019(1)	13(1)
C(14)	6434(1)	3415(1)	7220(1)	16(1)
C(15)	5289(1)	2622(1)	7011(1)	18(1)
C(16)	4056(1)	2391(1)	7590(1)	18(1)
C(17)	3897(1)	2962(1)	8382(1)	15(1)
C(18)	5048(1)	3781(1)	8592(1)	13(1)
C(19)	11186(1)	6279(1)	8572(1)	28(1)

Table 3. Bond lengths [Å] and angles [°] for DDD-016.

S(1)-C(17)	1.7567(11)
S(1)-C(1)	1.863(3)
C(1)-C(2)	1.520(3)
C(1)-H(1A)	0.9900
C(1)-H(1B)	0.9900
S(1')-C(2)	1.7343(19)
S(1')-C(1')	1.865(6)
C(1')-C(17)	1.519(6)
C(1')-H(1'A)	0.9900
C(1')-H(1'B)	0.9900
N(1)-C(18)	1.4025(12)
N(1)-C(8)	1.4048(11)
N(1)-C(7)	1.4184(12)
N(2)-C(19)	1.4537(14)
N(2)-C(11)	1.4620(13)
N(2)-C(10)	1.4630(14)
C(2)-C(3)	1.3950(14)
C(2)-C(7)	1.4016(13)
C(3)-C(4)	1.3857(14)
C(3)-H(3)	0.9500
C(4)-C(5)	1.3900(15)
C(4)-H(4)	0.9500
C(5)-C(6)	1.3847(14)
C(5)-H(5)	0.9500

C(6)-C(7)	1.3999(13)
C(6)-H(6)	0.9500
C(8)-C(12)	1.3581(13)
C(8)-C(9)	1.4926(13)
C(9)-C(10)	1.5283(14)
C(9)-H(9A)	0.9900
C(9)-H(9B)	0.9900
C(10)-H(10A)	0.9900
C(10)-H(10B)	0.9900
C(11)-C(12)	1.4871(13)
C(11)-H(11A)	0.9900
C(11)-H(11B)	0.9900
C(12)-C(13)	1.4283(13)
C(13)-C(14)	1.3980(13)
C(13)-C(18)	1.4134(13)
C(14)-C(15)	1.3817(14)
C(14)-H(14)	0.9500
C(15)-C(16)	1.3985(15)
C(15)-H(15)	0.9500
C(16)-C(17)	1.3926(14)
C(16)-H(16)	0.9500
C(17)-C(18)	1.4057(13)
C(19)-H(19A)	0.9800
C(19)-H(19B)	0.9800
C(19)-H(19C)	0.9800

C(17)-S(1)-C(1)	98.66(14)
C(2)-C(1)-S(1)	107.67(19)
C(2)-C(1)-H(1A)	110.2
S(1)-C(1)-H(1A)	110.2
C(2)-C(1)-H(1B)	110.2
S(1)-C(1)-H(1B)	110.2
H(1A)-C(1)-H(1B)	108.5
C(2)-S(1')-C(1')	99.4(3)
C(17)-C(1')-S(1')	105.7(4)
C(17)-C(1')-H(1'A)	110.6

S(1')-C(1')-H(1'A)	110.6
C(17)-C(1')-H(1'B)	110.6
S(1')-C(1')-H(1'B)	110.6
H(1'A)-C(1')-H(1'B)	108.7
C(18)-N(1)-C(8)	107.29(7)
C(18)-N(1)-C(7)	129.61(8)
C(8)-N(1)-C(7)	122.63(7)
C(19)-N(2)-C(11)	109.96(9)
C(19)-N(2)-C(10)	111.11(9)
C(11)-N(2)-C(10)	110.73(8)
C(3)-C(2)-C(7)	119.15(9)
C(3)-C(2)-C(1)	119.75(16)
C(7)-C(2)-C(1)	121.10(16)
C(3)-C(2)-S(1')	117.62(10)
C(7)-C(2)-S(1')	123.07(10)
C(1)-C(2)-S(1')	4.86(15)
C(4)-C(3)-C(2)	121.44(9)
C(4)-C(3)-H(3)	119.3
C(2)-C(3)-H(3)	119.3
C(3)-C(4)-C(5)	119.32(9)
C(3)-C(4)-H(4)	120.3
C(5)-C(4)-H(4)	120.3
C(6)-C(5)-C(4)	119.96(9)
C(6)-C(5)-H(5)	120.0
C(4)-C(5)-H(5)	120.0
C(5)-C(6)-C(7)	121.05(9)
C(5)-C(6)-H(6)	119.5
C(7)-C(6)-H(6)	119.5
C(6)-C(7)-C(2)	119.00(8)
C(6)-C(7)-N(1)	118.65(8)
C(2)-C(7)-N(1)	122.34(8)
C(12)-C(8)-N(1)	110.24(8)
C(12)-C(8)-C(9)	122.80(8)
N(1)-C(8)-C(9)	126.15(8)
C(8)-C(9)-C(10)	107.96(8)
C(8)-C(9)-H(9A)	110.1

C(10)-C(9)-H(9A)	110.1
C(8)-C(9)-H(9B)	110.1
C(10)-C(9)-H(9B)	110.1
H(9A)-C(9)-H(9B)	108.4
N(2)-C(10)-C(9)	109.94(8)
N(2)-C(10)-H(10A)	109.7
C(9)-C(10)-H(10A)	109.7
N(2)-C(10)-H(10B)	109.7
C(9)-C(10)-H(10B)	109.7
H(10A)-C(10)-H(10B)	108.2
N(2)-C(11)-C(12)	110.01(8)
N(2)-C(11)-H(11A)	109.7
C(12)-C(11)-H(11A)	109.7
N(2)-C(11)-H(11B)	109.7
C(12)-C(11)-H(11B)	109.7
H(11A)-C(11)-H(11B)	108.2
C(8)-C(12)-C(13)	107.38(8)
C(8)-C(12)-C(11)	123.15(8)
C(13)-C(12)-C(11)	128.98(8)
C(14)-C(13)-C(18)	121.06(9)
C(14)-C(13)-C(12)	131.31(9)
C(18)-C(13)-C(12)	107.56(8)
C(15)-C(14)-C(13)	118.43(9)
C(15)-C(14)-H(14)	120.8
C(13)-C(14)-H(14)	120.8
C(14)-C(15)-C(16)	120.59(9)
C(14)-C(15)-H(15)	119.7
C(16)-C(15)-H(15)	119.7
C(17)-C(16)-C(15)	122.19(9)
C(17)-C(16)-H(16)	118.9
C(15)-C(16)-H(16)	118.9
C(16)-C(17)-C(18)	117.39(9)
C(16)-C(17)-C(1')	119.2(3)
C(18)-C(17)-C(1')	123.3(3)
C(16)-C(17)-S(1)	117.31(8)
C(18)-C(17)-S(1)	125.09(8)

C(1')-C(17)-S(1)	6.7(2)
N(1)-C(18)-C(17)	132.04(8)
N(1)-C(18)-C(13)	107.51(8)
C(17)-C(18)-C(13)	120.28(8)
N(2)-C(19)-H(19A)	109.5
N(2)-C(19)-H(19B)	109.5
H(19A)-C(19)-H(19B)	109.5
N(2)-C(19)-H(19C)	109.5
H(19A)-C(19)-H(19C)	109.5
H(19B)-C(19)-H(19C)	109.5

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for rr9509. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + \quad + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	20(1)	19(1)	22(1)	-2(1)	3(1)	-6(1)
C(1)	24(1)	16(1)	15(1)	4(1)	-3(1)	-2(1)
S(1')	20(1)	19(1)	22(1)	-2(1)	3(1)	-6(1)
C(1')	24(1)	16(1)	15(1)	4(1)	-3(1)	-2(1)
N(1)	14(1)	12(1)	13(1)	-2(1)	2(1)	-1(1)
N(2)	17(1)	16(1)	22(1)	-1(1)	4(1)	-4(1)
C(2)	18(1)	13(1)	15(1)	2(1)	3(1)	-1(1)
C(3)	21(1)	18(1)	17(1)	4(1)	6(1)	-2(1)
C(4)	23(1)	21(1)	18(1)	0(1)	8(1)	2(1)
C(5)	23(1)	16(1)	17(1)	-2(1)	5(1)	2(1)
C(6)	19(1)	13(1)	15(1)	0(1)	4(1)	1(1)
C(7)	16(1)	13(1)	12(1)	0(1)	2(1)	0(1)
C(8)	14(1)	11(1)	14(1)	-1(1)	2(1)	-2(1)
C(9)	19(1)	18(1)	16(1)	-4(1)	2(1)	-5(1)
C(10)	18(1)	19(1)	20(1)	-3(1)	-1(1)	-4(1)
C(11)	15(1)	15(1)	17(1)	0(1)	4(1)	0(1)
C(12)	14(1)	12(1)	13(1)	1(1)	2(1)	0(1)
C(13)	15(1)	13(1)	11(1)	0(1)	0(1)	2(1)
C(14)	19(1)	17(1)	12(1)	-1(1)	0(1)	3(1)

C(15)	22(1)	19(1)	14(1)	-3(1)	-3(1)	3(1)
C(16)	19(1)	17(1)	18(1)	-4(1)	-5(1)	0(1)
C(17)	15(1)	14(1)	16(1)	-1(1)	-1(1)	-1(1)
C(18)	14(1)	12(1)	12(1)	-1(1)	0(1)	0(1)
C(19)	20(1)	30(1)	34(1)	-6(1)	8(1)	-10(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for DDD-016.

	x	y	z	U(eq)
H(1A)	2953	2066	10562	22
H(1B)	4558	2342	10049	22
H(1'A)	1897	2036	8734	22
H(1'B)	1755	3373	8969	22
H(3)	1853	3502	11450	22
H(4)	1793	5352	12009	24
H(5)	3183	6810	11296	22
H(6)	4686	6390	10067	19
H(9A)	7451	5300	10490	21
H(9B)	7213	6464	9951	21
H(10A)	9937	6186	10060	23
H(10B)	9786	4884	9747	23
H(11A)	9690	4488	8166	19
H(11B)	8917	5461	7566	19
H(14)	7277	3570	6830	19
H(15)	5340	2230	6469	22
H(16)	3301	1825	7437	22
H(19A)	11821	5586	8645	42
H(19B)	11566	6872	8971	42
H(19C)	11277	6551	7969	42

Table 6. Torsion angles [°] for DDD-016.

C(17)-S(1)-C(1)-C(2)	83.96(18)
C(2)-S(1')-C(1')-C(17)	86.2(3)
S(1)-C(1)-C(2)-C(3)	108.92(19)
S(1)-C(1)-C(2)-C(7)	-71.6(2)
S(1)-C(1)-C(2)-S(1')	44(2)
C(1')-S(1')-C(2)-C(3)	116.9(2)
C(1')-S(1')-C(2)-C(7)	-58.4(3)
C(1')-S(1')-C(2)-C(1)	-126(3)
C(7)-C(2)-C(3)-C(4)	-0.99(16)
C(1)-C(2)-C(3)-C(4)	178.49(15)
S(1')-C(2)-C(3)-C(4)	-176.52(11)
C(2)-C(3)-C(4)-C(5)	2.54(17)
C(3)-C(4)-C(5)-C(6)	-1.32(17)
C(4)-C(5)-C(6)-C(7)	-1.44(16)
C(5)-C(6)-C(7)-C(2)	2.97(15)
C(5)-C(6)-C(7)-N(1)	-175.57(9)
C(3)-C(2)-C(7)-C(6)	-1.74(14)
C(1)-C(2)-C(7)-C(6)	178.78(14)
S(1')-C(2)-C(7)-C(6)	173.53(10)
C(3)-C(2)-C(7)-N(1)	176.74(9)
C(1)-C(2)-C(7)-N(1)	-2.74(18)
S(1')-C(2)-C(7)-N(1)	-7.99(15)
C(18)-N(1)-C(7)-C(6)	-135.89(10)
C(8)-N(1)-C(7)-C(6)	35.10(13)
C(18)-N(1)-C(7)-C(2)	45.62(14)
C(8)-N(1)-C(7)-C(2)	-143.39(9)
C(18)-N(1)-C(8)-C(12)	1.58(10)
C(7)-N(1)-C(8)-C(12)	-171.17(8)
C(18)-N(1)-C(8)-C(9)	-168.30(9)
C(7)-N(1)-C(8)-C(9)	18.95(14)
C(12)-C(8)-C(9)-C(10)	-15.21(13)
N(1)-C(8)-C(9)-C(10)	153.48(9)
C(19)-N(2)-C(10)-C(9)	166.93(9)
C(11)-N(2)-C(10)-C(9)	-70.55(10)

C(8)-C(9)-C(10)-N(2)	50.09(11)
C(19)-N(2)-C(11)-C(12)	172.04(9)
C(10)-N(2)-C(11)-C(12)	48.86(11)
N(1)-C(8)-C(12)-C(13)	-0.76(10)
C(9)-C(8)-C(12)-C(13)	169.53(9)
N(1)-C(8)-C(12)-C(11)	-173.36(8)
C(9)-C(8)-C(12)-C(11)	-3.08(14)
N(2)-C(11)-C(12)-C(8)	-13.14(12)
N(2)-C(11)-C(12)-C(13)	175.95(9)
C(8)-C(12)-C(13)-C(14)	-177.12(9)
C(11)-C(12)-C(13)-C(14)	-5.08(17)
C(8)-C(12)-C(13)-C(18)	-0.35(10)
C(11)-C(12)-C(13)-C(18)	171.68(9)
C(18)-C(13)-C(14)-C(15)	-1.72(14)
C(12)-C(13)-C(14)-C(15)	174.68(10)
C(13)-C(14)-C(15)-C(16)	-0.46(15)
C(14)-C(15)-C(16)-C(17)	1.82(16)
C(15)-C(16)-C(17)-C(18)	-0.92(14)
C(15)-C(16)-C(17)-C(1')	176.8(2)
C(15)-C(16)-C(17)-S(1)	-175.96(8)
S(1')-C(1')-C(17)-C(16)	130.0(3)
S(1')-C(1')-C(17)-C(18)	-52.4(4)
S(1')-C(1')-C(17)-S(1)	55(2)
C(1)-S(1)-C(17)-C(16)	138.69(13)
C(1)-S(1)-C(17)-C(18)	-35.93(14)
C(1)-S(1)-C(17)-C(1')	-113(3)
C(8)-N(1)-C(18)-C(17)	173.43(10)
C(7)-N(1)-C(18)-C(17)	-14.51(16)
C(8)-N(1)-C(18)-C(13)	-1.75(10)
C(7)-N(1)-C(18)-C(13)	170.31(9)
C(16)-C(17)-C(18)-N(1)	-175.93(9)
C(1')-C(17)-C(18)-N(1)	6.5(3)
S(1)-C(17)-C(18)-N(1)	-1.32(15)
C(16)-C(17)-C(18)-C(13)	-1.26(13)
C(1')-C(17)-C(18)-C(13)	-178.9(2)
S(1)-C(17)-C(18)-C(13)	173.36(7)

C(14)-C(13)-C(18)-N(1)	178.47(8)
C(12)-C(13)-C(18)-N(1)	1.31(10)
C(14)-C(13)-C(18)-C(17)	2.62(14)
C(12)-C(13)-C(18)-C(17)	-174.55(8)