Discovery of 3-Substituted Aminocyclopentanes as Potent and Orally Bioavailable NR2B Subtype-Selective NMDA Antagonists

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Supplementary Data.

General. All reagents and solvents were of commercial quality and used without further purification unless indicated otherwise. All reactions were carried out under an inert atmosphere of nitrogen. ^{1}H NMR spectra were obtained on a Varian Unity Inova 400 spectrometer. Chemical shifts are reported in parts per million relative to TMS as internal standard. Samples provided for accurate mass measurement were dissolved in acetonitrile:water:glacial acetic acid (50:50:0.1%v/v). The solutions were analyzed by use of electrospray ionization (ESI) or atmospheric pressure chemical ionization (APCI) on either a Bruker Daltonics 3T or 7T Fourier transform ion cyclotron resonance (FTICR) mass spectrometer. External calibration was accomplished with polypropylene glycol (425 or 750). Melting points were determined in open glass capillaries using a Thomas-Hoover UniMelt melting point apparatus and are uncorrected. Elemental analyses were performed by Quantitative Technologies Inc., Whitehouse, NJ. Silica gel chromatography was carried out with an Gilson purification system using Biotage silica gel cartridges. Preparative reverse-phase HPLC was performed using a Gilson 215 liquid handler and a Waters XTerra C8 column (20 x 100 mm I.D.) with a linear gradient over 15 minutes (95:5 to 5:95 H_2O:acetonitrile, containing 0.1% trifluoroacetic acid).

***tert*-butyl[(1*S*,3*R*)-3-{[(methylsulfonyl)oxy]methyl}cyclopentyl]carbamate ((*S*,*R*)-45).** To a solution of **(*S*,*R*)-44** (500 mg, 2.18 mmol) in THF (25 mL) at 0^{o}C was added 1M borane THF complex in THF (4.36 mL, 4.36 mmol). After 1 hour, the reaction was poured into brine and extracted with EA. The combined organic layers were dried over sodium sulfate, filtered and concentrated. Purification by silica gel chromatography (30% ethyl acetate / hexanes → 70% ethyl acetate / hexanes) gave the *tert*-butyl [(1*S*,3*R*)-3-(hydroxymethyl)cyclopentyl]carbamate

(289 mg) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.70 (br s, 1H), 3.95 (br s, 1H), 3.58 (d, *J* = 5.6 Hz, 2H), 2.23-2.14 (m, 2H), 1.97-1.90 (m, 1H), 1.79-1.73 (m, 1H), 1.54-1.46 (m, 3H), 1.45 (s, 9H), 1.16-1.09 (m, 1H) ppm.

To a solution of *tert*-butyl [(1*S*,3*R*)-3-(hydroxymethyl)cyclopentyl]carbamate (150 mg, 0.697 mmol) in DCM (7.0 mL) at 0°C was added triethylamine (0.486 mL, 3.48 mmol) and methanesulfonyl chloride (0.081 mL, 1.0 mmol). After 20 minutes, the reaction diluted with DCM, washed with water, saturated sodium bicarbonate and brine. The organic layer was dried over sodium sulfate, filtered and concentrated to give **(*S*,*R*)-45** (214 mg) as a peach solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.50 (br s, 1H), 4.18-4.11 (m, 2H), 4.01-3.90 (m, 1H), 3.01 (s, 3H), 2.41-2.21 (m, 1H), 2.06-1.94 (m, 1H), 1.89-1.76 (m, 1H), 1.54-1.38 (m, 11 H), 1.21-1.11 (m, 1H) ppm.

[(1*S*,3*R*)-3-({[(benzyloxy)carbonyl]amino}methyl)cyclopentyl]amine ((*S*,*R*)-46). To a solution of **(*S*,*R*)-45** (200 mg, 0.695 mmol) in DMF (2.0 mL) was added sodium azide (54 mg, 0.83 mmol) and the mixture was heated to 50°C. After 15 hours, the reaction was poured into ethyl acetate, and washed with water and brine. The organic layer was dried over sodium sulfate, filtered and concentrated. The crude residue was added to a suspension of 10% palladium on activated carbon (20 mg) in ethanol (3 mL) at room temperature and the flask was purged hydrogen. After 3.5 hours, the reaction was filtered and concentrated. To a solution of the crude amine in DCM (2.0 mL) was added *N*-methylmorpholine (0.119 mL, 1.08 mmol) and *N*-(benzyloxycarbonyloxy)succinimide (198 mg, 0.796 mmol) at room temperature. After 12 h, the reaction was diluted with methylene chloride and washed with water, 1M NaOH and brine. The organic layer was dried over sodium sulfate, filtered and concentrated. Purification by silica gel chromatography (1% IPA / DCM → 15% IPA / DCM) gave *tert*-butyl {(1*S*,3*R*)-3-

{[(benzyloxycarbonyl)amino]methyl} cyclopentylcarbamate (143 mg) as a white solid. HRMS (ESI) *m/z* 371.1937 [$(M+Na)^+$; calcd for $C_{19}H_{28}N_2O_4$: 371.1941].

To *tert*-butyl {(1*S*,3*R*)-3-[(benzyloxycarbonyl)amino]methyl}cyclopentylcarbamate (140 mg, 0.402 mmol) was added trifluoroacetic acid (0.5 mL) at room temperature. After 30 minutes, the reaction was concentrated and the residue was dissolved in ethyl acetate. The solution was treated with a saturated solution of anhydrous hydrochloric acid in ethyl acetate and concentrated. Recrystallization (EA / hexane) gave **(*S,R*)-46** (85 mg) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (br s, 3H), 7.37-7.31 (m, 5H), 5.01 (s, 2H), 3.43 (br s, 1H), 3.01 (t, *J* = 6.0 Hz, 2H), 2.13-1.99 (m, 2H), 1.91-1.84 (m, 1H), 1.68-1.54 (m, 2H), 1.45-1.38 (m, 1H), 1.19-1.11 (m, 1H) ppm; HRMS (ESI) *m/z* 249.1601 [$(M+H)^+$; calcd for $C_{14}H_{20}N_2O_2$: 249.1598].

***N*-[(1*S*,3*R*)-3-({[(benzyloxy)carbonyl]amino}methyl)cyclopentyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine ((*S,R*)-8).** To a solution of **(*S,R*)-46** (40 mg, 0.17 mmol) in isopropanol (3 mL) was added DIPEA (1 mL) and 4-chloro-1-(tetrahydro-pyran-2-yl)-1H-pyrazolo[3,4-d]pyrimidine (**47**) (44 mg, 0.18 mmol) and the solution was heated at 85ºC for 7 hours. The mixture was cooled and concentrated under reduced pressure. The resulting residue was dissolved in methanol (3 mL) and 6N HCl (0.5 mL) and was heated at 60ºC for 1 hour, at which time the reaction was cooled and quenched with saturated sodium bicarbonate. The solution was extracted with ethyl acetate, and the organic layer was dried over sodium sulfate, filtered and concentrated to dryness under reduced pressure. Purification by silica gel chromatography (1% isopropanol / methylene chloride → 25% isopropanol / methylene chloride) gave **(*S,R*)-8** (18 mg) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.32 (s, 1H), 8.19 (s, 1H), 8.11 (s, 1H), 8.09-8.03 (m, 1H), 7.39-7.27 (m, 6H), 5.01 (s, 2H), 4.54-4.40 (m, 1H), 3.04 (t, *J* = 6.0 Hz, 2H), 2.25-2.15 (m, 1H), 2.13-1.94 (m, 2H), 1.78-1.65 (m, 1H), 1.63-1.51 (m, 1H), 1.50-1.38 (m, 1H), 1.27-1.12 (m, 1H) ppm; HRMS (ESI) *m/z* 367.1888 [$(M+H)^+$; calcd for $C_{19}H_{22}N_6O_2$: 367.1877].

***N*-[(1*R*,3*S*)-3-({[(benzyloxy)carbonyl]amino}methyl)cyclopentyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine ((*R*,*S*)-8).** The title compound was prepared from **(*R*,*S*)-44** according to the procedure reported for **(*S*,*R*)-8**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.32 (s, 1H), 8.19 (s, 1H), 8.14-8.02 (m, 2H), 7.39-7.26 (m, 5H), 5.01 (s, 2H), 4.54-4.42 (m, 1H), 3.09-2.97 (m, 2H), 2.26-2.15 (m, 1H), 2.13-1.94 (m, 2H), 1.76-1.65 (m, 1H), 1.62-1.50 (m, 1H), 1.49-1.38 (m, 1H), 1.30-1.12 (m, 2H) ppm; HRMS (ESI) *m/z* 367.1888 [$(M+H)^+$; calcd for $C_{19}H_{22}N_6O_2$: 367.1877].

***N*-[(1*R*,3*R*)-3-({[(benzyloxy)carbonyl]amino}methyl)cyclopentyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine ((*R*,*R*)-8).** The title compound was prepared from **(*R*,*R*)-44** according to the procedure reported for **(*S*,*R*)-8**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.32 (s, 1H), 8.20 (s, 1H), 8.12 (s, 1H), 8.05-7.99 (m, 1H), 7.40-7.25 (m, 5H), 5.01 (s, 2H), 4.58-4.47 (m, 1H), 3.04-2.95 (m, 2H), 2.35-2.19 (m, 1H), 2.12-2.00 (m, 1H), 1.90-1.80 (m, 1H), 1.76-1.63 (m, 2H), 1.62-1.49 (m, 1H), 1.38-1.18 (m, 1H) ppm; HRMS (ESI) *m/z* 367.1874 [$(M+H)^+$; calcd for $C_{19}H_{22}N_6O_2$: 367.1877].

***N*-[(1*S*,3*S*)-3-({[(benzyloxy)carbonyl]amino}methyl)cyclopentyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine ((*S*,*S*)-8).** The title compound was prepared from **(*S*,*S*)-44** according to the procedure reported for **(*S*,*R*)-8**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.33 (s, 1H), 8.20 (s, 1H), 8.12 (s, 1H), 8.05-7.99 (m, 1H), 7.40-7.26 (m, 5H), 5.02 (s, 2H), 4.59-4.48 (m, 1H), 3.04-2.94 (m, 2H), 2.36-2.21 (m, 1H), 2.13-2.01 (m, 1H), 1.91-1.80 (m, 1H), 1.76-1.64 (m, 2H), 1.62-1.50 (m, 1H), 1.33-1.20 (m, 1H) ppm; HRMS (ESI) *m/z* 367.1870 [$(M+H)^+$; calcd for $C_{19}H_{22}N_6O_2$: 367.1877].

***N*-[(1*S*,3*S*)-3-(3-phenyl-1,2,4-oxadiazol-5-yl)cyclopentyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (9).** The title compound was prepared from **(*S*,*S*)-44** according to the procedure reported for **22**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.39 (s, 1H), 8.23-8.15 (m, 3H), 8.02 (d, *J* = 6.8 Hz, 2H), 7.58 (d, *J* = 6.8 Hz, 3H), 4.74 (br s, 1H), 3.83-3.79 (m, 1H), 2.40-2.20

(m, 4H), 2.05-2.00 (m, 1H), 1.87-1.74 (m, 1H) ppm; HRMS (ESI) *m/z* 348.1569 [$(M+H)^+$; calcd for $C_{18}H_{17}N_7O$: 348.1568].

***N*-[(1*S*,3*R*)-3-(3-phenyl-1,2,4-oxadiazol-5-yl)cyclopentyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (10).** The title compound was prepared from **(*S*,*R*)-44** according to the procedure reported for **22**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.39 (s, 1H), 8.25-8.21 (m, 2H), 8.12 (s, 1H), 8.01-7.99 (m, 2H), 7.60-7.55 (m, 3H), 4.71 (m, 1H), 3.69-3.65 (m, 1H), 2.71-2.63 (m, 1H), 2.27-2.13 (m, 3H), 2.08-2.00 (m, 1H), 1.82 (m, 1H) ppm; HRMS (ESI) *m/z* 348.1556 [$(M+H)^+$; calcd for $C_{18}H_{17}N_7O$: 348.1567].

***N*-{(1*S*,3*S*)-3-[3-(2-methylphenyl)-1,2,4-oxadiazol-5-yl]cyclopentyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (11).** The title compound was prepared from **(*S*,*S*)-44** according to the procedure reported for **22**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.39 (s, 1H), 8.26-8.10 (m, 3H), 7.97-7.90 (m, 1H), 7.51-7.35 (m, 3H), 4.83-4.69 (m, 1H), 3.87-3.75 (m, 1H), 2.57 (s, 3H), 2.47-2.33 (m, 2H), 2.33-2.16 (m, 2H), 2.08-1.97 (m, 1H), 1.86-1.74 (m, 1H) ppm; HRMS (ESI) *m/z* 362.1728 [$(M+H)^+$; calcd for $C_{19}H_{19}N_7O$: 362.1724].

***N*-{(1*S*,3*S*)-3-[3-(3-methylphenyl)-1,2,4-oxadiazol-5-yl]cyclopentyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (12).** The title compound was prepared from **(*S*,*S*)-44** according to the procedure reported for **22**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.40 (s, 1H), 8.28-8.10 (m, 3H), 7.87-7.79 (m, 2H), 7.49-7.38 (m, 2H), 4.82-4.68 (m, 1H), 3.86-3.75 (m, 1H), 2.46-2.33 (m, 5H), 2.32-2.15 (m, 2H), 2.08-1.95 (m, 1H), 1.87-1.74 (m, 1H) ppm; HRMS (ESI) *m/z* 362.1729 [$(M+H)^+$; calcd for $C_{19}H_{19}N_7O$: 362.1724].

***N*-{(1*S*,3*S*)-3-[3-(4-methylphenyl)-1,2,4-oxadiazol-5-yl]cyclopentyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (13).** The title compound was prepared from **(*S*,*S*)-44** according to the procedure reported for **22**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.39 (s, 1H), 8.27-8.08 (m, 3H), 7.94-7.86 (m, 2H), 7.42-7.33 (m, 2H), 4.80-4.67 (m, 1H), 3.85-3.73 (m, 1H), 2.46-2.31 (m, 5H),

2.31-2.14 (m, 2H), 2.07-1.96 (m, 1H), 1.86-1.73 (m, 1H) ppm; HRMS (ESI) *m/z* 362.1701 $[(M+H)^+$; calcd for $C_{19}H_{19}N_7O$: 362.1724].

***N*-{(1*S*,3*S*)-3-[3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl]cyclopentyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (14).** The title compound was prepared from **(*S*,*S*)-44** according to the procedure reported for **22**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.39 (s, 1h), 8.26-8.11 (m, 2H), 8.07-7.96 (m, 2H), 7.70-7.58 (m, 2H), 4.81-4.66 (m, 1H), 3.88-3.73 (m, 1H), 2.44-2.33 (m, 2H), 2.32-2.13 (m, 2H), 2.09-1.94 (m, 1H), 1.86-1.73 (m, 1H) ppm; HRMS (ESI) *m/z* 382.1178 $[(M+H)^+$; calcd for $C_{18}H_{16}ClN_7O$: 382.1161].

{(1*S*,3*S*)-3-[(*tert*-butoxycarbonyl)amino]cyclopentyl}acetic acid (50). To a solution of **(*S*,*S*)-45** (1.20 g, 4.09 mmol) in DMSO (20 mL) was added sodium cyanide (600 mg, 12.3 mmol) and the mixture was heated to 70^{o}C. After 24 hours, the reaction was poured into water and extracted with EA. The combined organics were washed with brine, dried over sodium sulfate, filtered and concentrated to give *tert*-butyl [(1*S*,3*S*)-3-(cyanomethyl)cyclopentyl]carbamate (968 mg) as a solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.90 (br d, J = 6.9 Hz, 1H), 3.90-3.78 (m, 1H), 2.53 (d, J = 6.9 Hz, 2H), 2.36-2.20 (m, 1H), 1.98-1.82 (m, 2H), 1.72-1.60 (m, 1H), 1.55-1.42 (m, 2H), 1.32 (s, 9H), 1.21-1.15 (m, 1H) ppm.

To a solution of *tert*-butyl [(1*S*,3*S*)-3-(cyanomethyl)cyclopentyl]carbamate (515 mg, 2.30 mmol) in methanol (50 mL) was added 6.25M sodium hydroxide (17 mL, 106 mmol) and the flask was heated to 70^{o}C. After 15 h, the reaction was cooled to 0^{o}C, acidified to pH 3 with 1M HCl, added brine and extracted with EA. The combined organics were dried over sodium sulfate, filtered and concentrated to give **17** (299 mg) as a yellow waxy solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.89 (br s, 1H), 6.94-6.74 (m, 1H), 3.85-3.72 (m, 1H), 3.54-3.31 (m, 2H), 3.34-2.21 (m, 1H), 1.93-1.77 (m, 2H), 1.65-1.56 (m, 1H), 1.37 (s, 9H), 1.22-1.15 (m, 1H), 1.14-1.01 (m, 1H) ppm.

{(1*S*,3*S*)-3-[(3-phenyl-1,2,4-oxadiazol-5-yl)methyl]cyclopentyl}amine (51). The title compound was prepared from **50** according to the procedure reported for **22**. MS (ESI) *m/z* 244.4 [$(M+H)^+$; calcd for $C_{14}H_{17}N_3O$: 244].

***N*-{(1*S*,3*S*)-3-[(3-phenyl-1,2,4-oxadiazol-5-yl)methyl]cyclopentyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (15).** The title compound was prepared from **51** according to the procedure reported for **22**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.44 (br s, 1H), 8.03-7.97 (m, 2H), 7.63-7.52 (m, 3H), 4.61 (br s, 1H), 3.19-3.06 (m, 2H), 2.75-2.62 (m, 1H), 2.31-2.17 (m, 1H), 2.12-1.93 (m, 2H), 1.92-1.82 (m, 1H), 1.81-1.69 (m, 1H), 1.49-1.36 (m, 1H) ppm; HRMS (ESI) *m/z* 362.1731 [$(M+H)^+$; calcd for $C_{19}H_{19}N_7O$: 362.1724].

***N*-[(1*S*,3*S*)-3-(3-benzyl-1,2,4-oxadiazol-5-yl)cyclopentyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (16).** The title compound was prepared from **(*S*,*S*)-44** according to the procedure reported for **22**. ^{1}H NMR (400 MHz, DMSO, d_6) δ 8.51 (br s, 1H), 8.50 (s, 1H), 7.35-7.19 (m, 5H), 4.86 (br s, 1H), 3.93-3.80 (m, 3H), 3.73-3.55 (m, 3H), 2.43-2.40 (m, 1H), 2.24-2.12 (m, 1H) ppm; HRMS (ESI) *m/z* 362.1732 [$(M+H)^+$; calcd for $C_{19}H_{19}N_7O$: 362.1724].

***N*-{(1*S*,3*S*)-3-[3-(2-phenylethyl)-1,2,4-oxadiazol-5-yl]cyclopentyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (17).** The title compound was prepared from **(*S*,*S*)-44** according to the procedure reported for **22**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.39 (s, 1H), 8.23-8.15 (m, 3H), 8.02 (d, J = 6.8 Hz, 2H), 7.58 (d, J = 6.8 Hz, 3H), 4.74 (br s, 1H), 3.83-3.79 (m, 1H), 2.40-2.20 (m, 4H), 2.05-2.00 (m, 1H), 1.81 (m, 1H) ppm; HRMS (ESI) *m/z* 376.1884 [$(M+H)^+$; calcd for $C_{21}H_{23}N_7O$: 376.1881].

***N*-{(1*S*,3*S*)-3-[3-(4-fluorobenzyl)-1,2,4-oxadiazol-5-yl]cyclopentyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (20).** The title compound was prepared from **(*S*,*S*)-44** according to the procedure reported for **22**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.80 (br s, 1H), 8.50 (s, 1H), 7.41-7.31 (m, 2H), 7.21-7.12 (m, 2H), 4.72 (br s, 1H), 4.09 (s, 2H), 3.85-3.67 (m, 1H), 2.41-2.20 (m,

4H), 1.99-1.84 (m, 2H) ppm; HRMS (ESI) *m/z* 380.1620 [$(M+H)^+$; calcd for $C_{19}H_{18}FN_7O$: 380.1630].

***N*-{(1*S*,3*S*)-3-[3-(4-chlorobenzyl)-1,2,4-oxadiazol-5-yl]cyclopentyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (23).** The title compound was prepared from **(*S*,*S*)-44** according to the procedure reported for **22**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.46 (s, 1H), 7.44-7.30 (m, 4H), 4.68 (br s, 1H), 4.09 (s, 2H), 3.81-3.68 (m, 1H), 2.42-2.19 (m, 4H), 1.97-1.79 (m, 2H) ppm; HRMS (ESI) *m/z* 396.1345 [$(M+H)^+$; calcd for $C_{19}H_{18}ClN_7O$: 396.1334].

***N*-((1*S*,3*S*)-3-{3-[4-(trifluoromethyl)benzyl]-1,2,4-oxadiazol-5-yl}cyclopentyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (26).** The title compound was prepared from **(*S*,*S*)-44** according to the procedure reported for **22**. ^{1}H NMR (400 MHz, CD_3OD) δ 8.54 (br s, 1H), 8.49 (br s, 1H), 7.66-7.47 (m, 4H), 4.17 (s, 2H), 3.81-3.69 (m, 1H), 2.57-2.48 (m, 1H), 2.47-2.36 (m, 2H), 2.35-2.25 (m, 1H), 2.12-1.87 (m, 2H) ppm; HRMS (ESI) *m/z* 430.1600 [$(M+H)^+$; calcd for $C_{20}H_{18}F_3N_7O$: 430.1598].

***N*-{(1*S*,3*S*)-3-[3-(4-methoxybenzyl)-1,2,4-oxadiazol-5-yl]cyclopentyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (29).** The title compound was prepared from **(*S*,*S*)-44** according to the procedure reported for **22**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.82 (br s, 1H), 8.52 (s, 1H), 8.00-7.89 (m, 2H), 7.17-7.07 (m, 2H), 4.78 (br s, 1H), 3.97-3.76 (m, 4H), 2.49-2.26 (m, 4H), 2.12-1.88 (m, 2H) ppm; HRMS (ESI) *m/z* 392.1820 [$(M+H)^+$; calcd for $C_{20}H_{21}N_7O_2$: 392.1830].

***N*-{(1*S*,3*S*)-3-[3-(2-fluoro-4-methylbenzyl)-1,2,4-oxadiazol-5-yl]cyclopentyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (30).** The title compound was prepared from **(*S*,*S*)-44** according to the procedure reported for **22**. ^{1}H NMR (400 MHz, CD_3OD): δ 8.54 (s, 1H), 8.49 (s, 1H), 7.19 (t, *J* = 7.9 Hz, 1H), 6.98-6.90 (m, 2H), 4.05 (s, 2H), 3.77-3.68 (m, 1H), 3.30 (m, 1H),

2.56-2.48 (m, 1H), 2.46-2.35 (m, 2H), 2.33 (s, 3H), 2.31-2.24 (m, 1H), 2.11-1.99 (m, 1H), 1.97-1.89 (m, 1H). HRMS (ESI) *m/z* 394.1787 [$(M+H)^+$; calcd for $C_{20}H_{20}FN_7O$: 394.1786].

***tert*-butyl [(1*S*,3*S*)-3-(aminocarbonyl)cyclopentyl]carbamate (52)**

To a solution of **(1*S*,3*S*)-44** (480 mg, 2.09 mmol) and HOBt (849 mg, 6.28 mmol) in DMF (6 mL) at room temperature was added EDC (1.20 g, 6.28 mmol). After 30 minutes, ammonium hydroxide (1.3 mL) was added to the reaction. After 72 h, the reaction was poured into ethyl acetate. The organic layer was washed with water, brine, dried over sodium sulfate, filtered and concentrated to give **52** (306 mg) as a white solid. This material was sufficiently pure for the next step. ^{1}H NMR (400 MHz, DMSO-*d*6): δ 7.20 (s, 1H), 6.81 (d, *J* = 8.0 Hz, 1H), 6.67 (s, 1H), 3.82-3.80 (m, 1H), 2.69-2.64 (m, 1H), 1.89-1.76 (m, 3H), 1.61-1.52 (m, 2H), 1.37 (s, 9H).

N-[(1S,3S)-3-(4-benzyl-1,3-thiazol-2-yl)cyclopentyl]-1H-pyrazolo[3,4-d]pyrimidin-4-amine (31). To a suspension of **52** (1.64 g, 7.18 mmol) in THF (30 mL) at room temperature was added Lawesson's reagent (1.89 g, 4.67 mmol). After 17 h, the reaction was poured into ethyl acetate. The organic layer was washed with saturated sodium bicarbonate and brine, dried over sodium sulfate, filtered and concentrated. Purification by silica gel chromatography (15% ethyl acetate / hexanes → 90% ethyl acetate / hexanes) gave a mixture of diastereomers of *tert*-butyl [(1*S*,3*R*) and (1*S*,3*S*)-3-(aminocarbonothioyl)cyclopentyl]carbamate (1.22 g) as a white solid. MS 245 (M+1) and 189 (M-55).

To a solution of *tert*-butyl [(1*S*,3*R*) and (1*S*,3*R*)-3-(aminocarbonothioyl) cyclopentyl]carbamate (262 mg, 1.07 mmol; from Example 1, Step B) in ethanol (5 mL) was added 1-chloro-3-phenylacetone (181 mg, 1.07 mmol; McPhee, W. D.; Klingsberg, E. Organic Syntheses 26, 13-15 (1946) and McPhee, W. D.; Klingsberg, E. Journal of the American Chemical Society 66, 1132-1136 (1944)) and the resulting solution was heated to 85ºC. After 3

hours, the reaction was cooled to room temperature, concentrated and diluted with THF (1 mL). Triethylamine (2 mL) and BOC-ON (264 mg, 1.07 mmol) were added and the reaction was maintained at room temperature for 16 hours. The reaction mixture was concentrated and dissolved in ethyl acetate. The organic layer was washed with 1M sodium hydroxide, water, brine, dried over sodium sulfate, filtered and concentrated. Purification by silica gel chromatography (1% ethyl acetate / hexanes → 50% ethyl acetate / hexanes) gave *tert*-butyl [(1*S*,3*S*)-3-(4-benzyl-1,3-thiazol-2-yl)cyclopentyl]carbamate (115 mg). MS 359 (M+1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.23 (m, 5H), 6.57 (s, 1H), 4.57 (s, 1H), 4.18 (s, 1H), 4.09 (s, 2H), 3.62-3.57 (m, 1H), 2.29-2.18 (m, 3H), 2.07 (m, 1H), 1.89-1.84 (m, 1H), 1.53 (m, 1H), 1.45 (s, 9H).

To *tert*-butyl [(1*S*,3*S*)-3-(4-benzyl-1,3-thiazol-2-yl)cyclopentyl]carbamate (118 mg, 0.321 mmol) was added trifluoroacetic acid (0.5 mL) and the resulting solution was stirred at room temperature. After 20 minutes, the reaction was concentrated and the residue was dissolved in ethyl acetate. The solution was treated with anhydrous hydrochloric acid and filtered to give the hydrochloride salt of [(1*S*,3*S*)-3-(4-benzyl-1,3-thiazol-2-yl)cyclopentyl]amine (112 mg). HRMS ($M+H^+$): calculated = 259.1264, observed = 259.1271; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.82 (s, 2H), 7.30-7.24 (m, 5H), 7.13 (s, 1H), 4.02 (s, 2H), 3.69 (m, 2H), 2.24-2.02 (m, 4H), 1.80-1.60 (m, 2H).

To a solution of [(1*S*,3*S*)-3-(4-benzyl-1,3-thiazol-2-yl)cyclopentyl]amine (95 mg, 0.287 mmol) in 1-butanol (0.5 mL) was added DIPEA (0.5 mL) and 4-chloro-1-(tetrahydro-pyran-2-yl)-1H-pyrazolo[3,4-d]pyrimidine (68 mg, 0.244 mmol) and the solution was heated at 150ºC for 10 minutes under microwave irradiation. The mixture was cooled and concentrated under reduced pressure. The resulting residue was dissolved in methanol (2 mL) and 6N HCl (1 mL) and was heated at 60ºC for 1 hour, at which time the reaction was cooled and quenched with

saturated sodium bicarbonate. The solution was extracted with ethyl acetate, and the organic layer was dried over sodium sulfate, filtered and concentrated to dryness under reduced pressure. Purification by silica gel chromatography (1% isopropanol / methylene chloride → 25% isopropanol / methylene chloride) gave N-[(1S,3S)-3-(4-benzyl-1,3-thiazol-2-yl)cyclopentyl]-1H-pyrazolo[3,4-d]pyrimidin-4-amine (**31**) (71 mg) as a white solid. HRMS ($M+H^+$): calculated = 377.1543, observed = 377.1556; ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.36 (s, 1H), 8.21 (s, 1H), 8.13 (s, 2H), 7.32-7.18 (m, 5H), 7.10 (s, 1H), 4.69 (m, 1H), 4.03 (s, 2H), 3.71 (m, 1H), 2.32-2.13 (m, 4H), 1.85-1.73 (m, 2H).

***N*-[(1*S*,3*S*)-3-(4-benzyl-1,3-oxazol-2-yl)cyclopentyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (32).** A mixture of **52** (200 mg, 0.876 mmol) and 1-chloro-3-phenylacetone (148 mg, 0.876 mmol) was heated to 130ºC. After 2 hours, the reaction was cooled to room temperature, dissolved in 1M sodium hydroxide and extracted with ethyl acetate. The organic layer dried over sodium sulfate, filtered and concentrated. To a solution of the crude residue in triethylamine (3 mL) was added BOC-ON (216 mg, 0.876 mmol) at room temperature. After 3 hours, the reaction was concentrated and dissolved in ethyl acetate. The organic layer was washed with 1M sodium hydroxide, water, brine, dried over sodium sulfate, filtered and concentrated. Purification by silica gel chromatography (1% ethyl acetate / hexanes → 45% ethyl acetate / hexanes) gave *tert*-butyl [(1*S*,3*S*)-3-(4-benzyl-1,3-oxazol-2-yl)cyclopentyl]carbamate (28 mg) as an oil. MS 343 (M+1); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.64 (s, 1H), 7.31-7.18 (m, 5H), 6.95 (s, 1H), 3.92 (s, 1H), 3.76 (s, 2H), 2.08-1.66 (m, 5H), 1.55-1.46 (m, 1H), 1.37 (s, 9H).

To *tert*-butyl [(1*S*,3*S*)-3-(4-benzyl-1,3-oxazol-2-yl)cyclopentyl]carbamate (28 mg, 0.082 mmol) was added trifluoroacetic acid (0.75 mL) and the resulting solution was stirred at room temperature. After 30 minutes, the reaction was concentrated and the residue was dissolved in ethyl acetate. The solution was treated with anhydrous hydrochloric acid and concentrated to

give the hydrochloride salt of [(1*S*,3*S*)-3-(4-benzyl-1,3-oxazol-2-yl)cyclopentyl]amine (40 mg) as a yellow oil. MS 243 (M+1).

To a solution of [(1*S*,3*S*)-3-(4-benzyl-1,3-oxazol-2-yl)cyclopentyl]amine (23 mg, 0.083 mmol) in isopropanol (3 mL) was added DIPEA (1 mL) and 4-chloro-1-(tetrahydro-pyran-2-yl)-1H-pyrazolo[3,4-d]pyrimidine (20 mg, 0.083 mmol) and the solution was heated at 70ºC. After 15 hours, the mixture was cooled and concentrated under reduced pressure. Purification by silica gel chromatography (1% isopropanol / methylene chloride → 15% isopropanol / methylene chloride) gave the THP-protected compound (22 mg) as an oil; MS 445 (M+1). The resulting residue was dissolved in methanol (3 mL) and 6N HCl (0.5 mL) and was heated at 60ºC for 1 hour, at which time the reaction was cooled and quenched with saturated sodium bicarbonate. The solution was partially concentrated under reduced pressure and the resulting solid was filtered to give **32** (9.4 mg) as a white solid. HRMS (M+ H^+): calculated = 361.1772, observed = 361.1769; ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.4 (s, 1H), 8.20-8.11 (m, 3H), 7.69 (s, 1H), 7.32-7.19 (m, 5H), 4.64 (br s, 1H), 3.79 (s, 2H), 3.49 (m, 1H), 2.25-2.17 (m, 3H), 2.05-1.83 (m, 2H), 1.70 (m, 1H).

***N*-[(1*S*,3*S*)-3-(5-benzyl-1,3-oxazol-2-yl)cyclopentyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (33).** HRMS (M+ H^+): calculated = 361.1772, observed = 361.1755.

***N*-[(1*S*,3*S*)-3-(5-benzyl-1,3,4-oxadiazol-2-yl)cyclopentyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (34).** To a solution of (1*S*,3*S*)-**44** (0.83 g, 3.6 mmol) in methylene chloride (15 mL) was added O-benzotriazol-1-yl-N, N, N^1, N^1, tetramethyluronium hexafluorophosphate (2.6 g, 5.9 mmol) at room temperature under N_2. After 30 minutes, 2-phenylacetohydrazide (0.55 g, 3.7 mmol) was added and the reaction was stirred for 14 hours. The gel-like mixture was poured into ethyl acetate and the organic layer was washed with 1 N sodium hydroxide, water, brine, dried over sodium sulfate, filtered and concentrated.

Purification by silica gel chromatography (1% isopropanol / methylene chloride → 15% isopropanol / methylene chloride) gave *tert*-butyl ((1*S*,3*S*)-3-{[2-(phenylacetyl)hydrazino]carbonyl}cyclopentyl)carbamate (**55**) (0.89 g) as a brown solid. This material was sufficiently pure for the next step. HRMS ($M+H^+$): calculated = 362.2075, observed = 362.2073.

A mixture of *tert*-butyl ((1*S*,3*S*)-3-{[2-(phenylacetyl)hydrazino]carbonyl}cyclopentyl) carbamate (**55**) (0.20 g, 0.56 mmol) and Burgess reagent (0.56 g, 2.4 mmol) in anhydrous tetrahydrofuran (4 mL) was heated in a sealed tube at 120ºC for 10 minutes under microwave irradiation. The reaction was cooled to room temperature and concentrated under reduced pressure. Purification by reverse phase chromatography (Xterra MS C8; 5-95% acetonitrile / 0.1 % trifluoroacetic acid / water) yielded *tert*-butyl [(1*S*,3*S*)-3-(5-benzyl-1,3,4-oxadiazol-2-yl)cyclopentyl]carbamate (0.06 g) as a white solid. HRMS ($M+H^+$): calculated = 344.1969, observed = 344.1959.

To *tert*-butyl [(1*S*,3*S*)-3-(5-benzyl-1,3,4-oxadiazol-2-yl)cyclopentyl]carbamate (0.060 g 0.16 mmol) was added anhydrous hydrochloric acid in ethyl acetate (6 mL) and the resulting solution was stirred at room temperature. After 20 minutes, the reaction was concentrated. Purification by reverse phase chromatography (Xterra MS C8; 5-95% acetonitrile / 0.1 % trifluoroacetic acid / water) yielded the title compound which was dissolved in methanol, treated with anhydrous hydrochloric acid in ethyl acetate, and concentrated to yield the hydrochloride salt of [(1*S*,3*S*)-3-(5-benzyl-1,3,4-oxadiazol-2-yl)cyclopentyl]amine (0.04 g) as a white solid. HRMS ($M+H^+$): calculated = 244.1445, observed = 244.1436.

To a solution of [(1*S*,3*S*)-3-(5-benzyl-1,3,4-oxadiazol-2-yl)cyclopentyl]amine (0.040 g 0.16 mmol) in 1-butanol (1.5 mL) was added DIPEA (1.5 mL) and 4-chloro-1-(tetrahydro-pyran-2-yl)-1H-pyrazolo[3,4-d]pyrimidine (**47**) (0.050 g, 0.20 mmol) and the solution was heated at

150ºC for 10 minutes under microwave irradiation. The mixture was cooled and concentrated under reduced pressure. The resulting residue was dissolved in methanol (2 mL) and anhydrous hydrochloric acid in ethyl acetate (3 mL) was added. After 1 hour, the reaction was quenched with saturated sodium bicarbonate. The solution was extracted with ethyl acetate, and the organic layer was dried over sodium sulfate, filtered and concentrated to dryness under reduced pressure. Purification by reverse phase chromatography (Xterra MS C8; 5-95% acetonitrile / 0.1 % trifluoroacetic acid / water) yielded **34** which was dissolved in methanol, treated with anhydrous hydrochloric acid in ethyl acetate, and concentrated to yield the hydrochloride salt of **34** (0.01 g) as a white solid. HRMS ($M+H^+$): calculated = 380.1380, observed = 380.1825; ^1H NMR (400 MHz, CD_3OD): δ 8.53 (s, 1H), 8.46 (s, 1H), 7.38-7.19 (m, 5H), 4.80-4.59 (m, 1H), 3.58 (s, 2H), 3.11-3.00 (s, 1H), 2.50-2.39 (m, 1H), 2.39-2.27 (m, 1H), 2.26-2.14 (m, 1H), 2.06-1.91 (m, 2H), 2.23 (m, 2H),1.88-1.77 (m, 1H).

***N*-{(1*S*,3*S*)-3-[5-(4-methylbenzyl)-1,3,4-thiadiazol-2-yl]cyclopentyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (36).**

To a solution of (4-methylphenyl)acetic acid (2.05 g, 13.6 mmol) in anhydrous acetonitrile (50 mL) at room temperature was added EDC (4.52 g, 23.6 mmol). After 30 minutes, 98% anhydrous hydrazine (1.49 mL, 47.3 mmol) was added to the reaction. The reaction was permitted to stir overnight under N_2, at which point the reaction was poured into ethyl acetate. The organic layer was washed with water, brine, dried over sodium sulfate, filtered and concentrated. Purification by silica gel chromatography (10% isopropanol / methylene chloride → 60% isopropanol / methylene chloride) gave 2-(4-methylphenyl)acetohydrazide (0.90 g) as a white solid. HRMS ($M+H^+$): calculated = 165.1072, observed = 165.1067.

A mixture of (1*S*,3*S*)-**44** (1.10 g, 4.80 mmol), HOBt (0.78 g, 5.07 mmol), and EDC (0.97 g, 5.07 mmol) in methylene chloride (220 mL) and DMF (25 mL) was stirred at room

temperature under N_2. After 30 minutes, 2-(4-methylphenyl)acetohydrazide (0.80 g, 4.87mmol) was added to the reaction. After 14 hours, the gel-like mixture was poured into ethyl acetate. The organic layer was washed with 1 N sodium hydroxide, water, brine, dried over sodium sulfate, filtered and concentrated to yield *tert*-butyl [(1*S*,3*S*)-3-({2-[(4-methylphenyl)acetyl]hydrazino}carbonyl)cyclopentyl]carbamate (1.82 g) as a white solid. HRMS ($M+Na^+$): calculated = 398.2050, observed = 398.2059.

The reaction mixture was prepared by addition of *tert*-butyl [(1*S*,3*S*)-3-({2-[(4-methylphenyl)acetyl]hydrazino}carbonyl)cyclopentyl]carbamate (0.50 g, 1.3 mmol) and Lawesson's reagent (1.2 g, 2.9 mmol) in anhydrous toluene (5 mL). The reaction mixture was heated to 150ºC for 10 minutes under microwave irradiation. The reaction was cooled to room temperature, concentrated and dissolved in ethyl acetate. The organic layer was washed with 1M sodium hydroxide, water, brine, dried over sodium sulfate, filtered and concentrated. Then trifluoroacetic acid (5.0 mL) was added and the resulting solution was stirred at room temperature. After 20 minutes, the reaction was concentrated and the residue was dissolved in ethyl acetate. The solution was treated with anhydrous hydrochloric acid and concentrated. Purification by reverse phase chromatography (Xterra MS C8; 5-95% acetonitrile / 0.1 % trifluoroacetic acid / water) gave the title compound which was dissolved in methanol, treated with anhydrous hydrochloric acid in ethyl acetate, and concentrated to yield the hydrochloride salt of a mixture of {(1*S*,3*S*) and (1*S*,3*R*)-3-[5-(4-methylbenzyl)-1,3,4-thiadiazol-2-yl]cyclopentyl}amine (0.24 g) as a tan solid. HRMS ($M+H^+$): calculated = 274.1313, observed = 274.1365.

To a solution of {(1*S*,3*S*) and (1*S*,3*R*)-3-[5-(4-methylbenzyl)-1,3,4-thiadiazol-2-yl]cyclopentyl}amine (0.15 g, 0.50 mmol) in 1-butanol (1.5 mL) was added DIPEA (1.5 mL) and 4-chloro-1-(tetrahydro-pyran-2-yl)-1H-pyrazolo[3,4-d]pyrimidine (**47**) (0.14 g, 0.58 mmol) and

the solution was heated at 150ºC for 10 minutes under microwave irradiation. The mixture was cooled and concentrated under reduced pressure. The resulting residue was dissolved in methanol (3 mL) and anhydrous hydrochloric acid in ethyl acetate (5 mL) was added. The reaction was stirred for 1 hour, at which time the reaction was quenched with saturated sodium bicarbonate. The solution was extracted with ethyl acetate, and the organic layer was dried over sodium sulfate, filtered and concentrated to dryness under reduced pressure. Purification by reverse phase chromatography (ChiralPak AD; 60% isopropanol / 40% hexane) gave **36** which was dissolved in methanol, treated with anhydrous hydrochloric acid in ethyl acetate, and concentrated to yield the hydrochloride salt of **36**. HRMS ($M+H^+$): calculated = 392.1692, observed = 392.1693. ^{1}H NMR (400 MHz, CD_3OD): δ 8.52 (s, 1H), 8.48 (s, 1H), 7.23-7.13 (m, 4H), 4.82-4.78 (m, 1H), 4.36 (s, 2H), 3.92-3.82 (m, 1H), 2.52-2.38 (m, 3H), 2.37-2.32 (m, 1H), 2.31 (s, 3H), 2.03-1.86 (m, 2H).

***N*-{(1*S*,3*S*)-3-[5-(4-methylbenzyl)-1,2,4-oxadiazol-3-yl]cyclopentyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (37).** To a solution of **52** (200 mg, 0.876 mmol) in tetrahydrofuran (15 mL) at 0ºC was added pyridine (139 mg, 1.75 mmol) and trifluoroacetic anhydride (221 mg, 1.05 mmol). The reaction was slowly warmed to room temperature over a 2 hour period. The reaction was quenched with water, poured into saturated potassium carbonate, and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, filtered and concentrated to give *tert*-butyl [(1*S*,3*S*)-3-cyanocyclopentyl]carbamate (230 mg) as a white solid. This material was sufficiently pure for the next step. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.43 (br s, 1H), 4.15-4.10 (m, 1H), 2.96-2.88 (m, 1H), 2.34 (m, 1H), 2.27-2.13 (m, 3H), 2.02-1.88 (m, 2H), 1.44 (s, 9H).

To a solution of *tert*-butyl [(1*S*,3*S*)-3-cyanocyclopentyl]carbamate (220 mg, 1.07 mmol) in 95% ethanol (10 mL) was added hydroxylamine hydrochloride (95 mg, 1.36 mmol) and

sodium carbonate (144 mg, 1.36 mmol), and the resulting solution was heated to 85ºC. After 3 hours, another batch of hydroxylamine hydrochloride (95 mg, 1.36 mmol) and sodium carbonate (144 mg, 1.36 mmol) was added, and the resulting solution was maintained at 85ºC. After 72 hours, the reaction was cooled to room temperature, filtered, and concentrated. The residue was suspended in ether and extracted with 1M hydrochloric acid. The combined aqueous layers were basified with ammonium hydroxide, saturated with sodium chloride, and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, filtered and concentrated to give *tert*-butyl {(1*S*,3*S*)-3-[(*Z*)-amino(hydroxyimino)methyl]cyclopentyl}carbamate (**53**) (191 mg) as a white solid. This material was sufficiently pure for the next step. MS 244 (M+1); ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.80 (s, 1H), 5.22 (s, 2H), 3.83 (m, 1H), 2.62-2.57 (m, 1H), 1.90-1.75 (m, 4H), 1.61-1.56 (m, 2H), 1.37 (s, 9H).

To a solution of [4-(methyl)phenyl]acetic acid (62 mg, 0.41 mmol) in DMF (1.5 mL) at room temperature was added O-benzotriazol-1-yl-N, N, N^1, N^1, tetramethyluronium hexafluorophosphate (132 mg, 0.411 mmol), DIPEA (266 mg, 2.06 mmol) and HOBt (11 mg, 0.082 mmol). After 5 minutes, *tert*-butyl {(1*S*,3*S*)-3-[(*Z*)-amino(hydroxyimino)methyl] cyclopentyl}carbamate (**53**) (100 mg, 0.411 mmol) was added to the reaction. After 1.5 hours, the reaction was poured into ethyl acetate. The organic layer was washed with water, brine, dried over sodium sulfate, filtered and concentrated to give *tert*-butyl {(1*S*,3*S*)-3-[(*Z*)-amino({[(4-methylphenyl)acetyl]oxy}imino)methyl]cyclopentyl}carbamate (132 mg) as a yellow solid. This material was sufficiently pure for the next step. MS 376 (M+1).

To a solution of *tert*-butyl{(1*S*,3*S*)-3-[(*Z*)-amino({[(4-methylphenyl)acetyl]oxy} imino)methyl]cyclopentyl}carbamate (132 mg, 0.352 mmol) in ethanol (5 mL) and water (1.0 mL) was added sodium acetate (87 mg, 1.1 mmol) and the resulting solution was heated to 85ºC. After 20 hours, the reaction was cooled to room temperature, concentrated and dissolved in ethyl

acetate. The organic layer was washed with water, saturated potassium carbonate, dried over sodium sulfate, filtered and concentrated. Purification by silica gel chromatography (1% isopropanol / hexanes → 9% isopropanol / hexanes) gave *tert*-butyl {(1*S*,3*S*)-3-[5-(4-methylbenzyl)-1,2,4-oxadiazol-3-yl]cyclopentyl}carbamate (68 mg) as a colorless oil. MS 358 (M+1) and 302 (M-55).

To *tert*-butyl{(1*S*,3*S*)-3-[5-(4-methylbenzyl)-1,2,4-oxadiazol-3-yl]cyclopentyl} carbamate (68 mg, 0.19 mmol) was added trifluoroacetic acid (1.0 mL) and the resulting solution was stirred at room temperature. After 20 minutes, the reaction was concentrated and the residue was dissolved in ethyl acetate. The solution was treated with anhydrous hydrochloric acid and filtered to give {(1*S*,3*S*)-3-[5-(4-methylbenzyl)-1,2,4-oxadiazol-3-yl]cyclopentyl}amine (54 mg). HRMS ($M+H^+$): calculated = 258.1601, observed = 258.1592; ^{1}H NMR (400 MHz, CD_3OD): δ 7.19 (d, *J* = 8.0 Hz, 2H), 7.15 (d, *J* = 8.0 Hz, 2H), 4.20 (s, 2H), 3.81-3.78 (m, 1H), 3.53-3.49 (m, 1H), 2.40-2.24 (m, 6H), 2.09-2.02 (m, 1H), 1.95-1.90 (m, 1H), 1.77-1.70 (m, 1H).

To a solution of {(1*S*,3*S*)-3-[5-(4-methylbenzyl)-1,2,4-oxadiazol-3-yl]cyclopentyl}amine (54 mg, 0.19 mmol) in 1-butanol (1.0 mL) was added DIPEA (1.0 mL) and 4-chloro-1-(tetrahydro-pyran-2-yl)-1H-pyrazolo[3,4-d]pyrimidine (**47**) (48 mg, 0.20 mmol) and the solution was heated at 120°C for 3 hours. The mixture was cooled and concentrated under reduced pressure. The resulting residue was dissolved in methanol (3 mL) and 6N HCl (0.5 mL) was added at room temperature. After 2 hours, the reaction was quenched with saturated sodium bicarbonate. The solution was extracted with ethyl acetate, and the organic layer was dried over sodium sulfate, filtered and concentrated to dryness under reduced pressure. Purification by silica gel chromatography (1% isopropanol / methylene chloride → 35% isopropanol / methylene chloride) gave **37**, which was dissolved in ethyl acetate and treated with anhydrous hydrochloric acid and filtered to give the hydrochloride salt of **37** (53 mg) as a white solid.

HRMS ($M+H^+$): calculated = 376.1881, observed = 376.1862; ^{1}H NMR (400 MHz, CD_3OD): δ 8.50-8.46 (m, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 4.85 (m, 1H), 4.22 (s, 2H), 3.59-3.55 (m, 1H), 2.46-2.36 (m, 3H), 2.32 (s, 3H), 2.21 (m, 1H), 2.02-1.89 (m, 2H).

N-(1-(3-benzyl-1,2,4-oxadiazol-5-yl)pyrrolidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (38). The title compound was prepared according to the procedure reported for **39**. HRMS ($M+H^+$): calculated = 363.1677, observed = 363.1675.

***N*-[(3*S*)-1-(3-phenyl-1,2,4-oxadiazol-5-yl)pyrrolidin-3-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (39).** To a solution of *N*'-hydroxybenzenecarboximidamide (5.00 g, 36.7 mmol) in toluene (100 mL) was added trichloroacetic anhydride (11.3 g, 36.7 mmol) and the solution was heated to 120ºC. After 2.5 hours, the reaction was cooled to room temperature and poured into water. The aqueous layer was extracted with ethyl acetate and the combined organics were washed with saturated bicarbonate, dried over sodium sulfate, filtered and concentrated. Purification by silica gel chromatography (0.5% ethyl acetate / hexanes → 25% ethyl acetate / hexanes) gave 3-phenyl-5-(trichloromethyl)-1,2,4-oxadiazole (7.80 g) as a colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.06 (d, *J* = 7.2 Hz, 2H), 7.70-7.61 (m, 3H).

To a solution of *tert*-butyl (3*S*)-pyrrolidin-3-ylcarbamate (1.00 g, 5.37 mmol) in methanol (10 mL) was added 3-phenyl-5-(trichloromethyl)-1,2,4-oxadiazole (1.41 g, 5.37 mmol) at room temperature. After 10 days, the reaction was concentrated and dissolved in ethyl acetate. The organic layer was washed with water, 1M citric acid, saturated sodium bicarbonate, brine, dried over sodium sulfate, filtered and concentrated. Purification by silica gel chromatography (15% ethyl acetate / 5% methylene chloride / hexanes → 95% ethyl acetate / 5% methylene chloride / hexanes) gave *tert*-butyl [(3*S*)-1-(3-phenyl-1,2,4-oxadiazol-5-yl)pyrrolidin-3-yl]carbamate (233 mg) as a white solid. HRMS ($M+H^+$): calculated = 331.1765, observed = 331.1755; ^{1}H NMR

(400 MHz, DMSO-d_6): δ 7.91 (d, J = 8.0 Hz, 2H), 7.54-7.49 (m, 3H), 7.31 (m, 1H), 4.14 (m, 1H), 3.75-3.58 (m, 3H), 3.41-3.38 (m, 1H), 2.18-2.14 (m, 1H), 1.94-1.89 (m, 1H), 1.40 (s, 9H).

To *tert*-butyl [(3*S*)-1-(3-phenyl-1,2,4-oxadiazol-5-yl)pyrrolidin-3-yl]carbamate (215 mg, 0.651 mmol) was added trifluoroacetic acid (1.5 mL) and the resulting solution was stirred at room temperature. After 1 hour, the reaction was concentrated and the residue was dissolved in ethyl acetate, treated with anhydrous hydrochloric acid and concentrated. The solid was suspended in ether / hexane and filtered to give (3*S*)-1-(3-phenyl-1,2,4-oxadiazol-5-yl)pyrrolidin-3-amine (173 mg) as a white solid. HRMS ($M+H^+$): calculated = 231.1241, observed = 231.1242; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 (br s, 3H), 7.92 (dd, J = 1.6, 8.0 Hz, 2H), 7.55-7.49 (m, 3H), 3.97 (m, 1H), 3.87-3.65 (m, 4H), 2.36-2.33 (m, 1H), 2.19-2.17 (m, 1H).

To a solution of (3*S*)-1-(3-phenyl-1,2,4-oxadiazol-5-yl)pyrrolidin-3-amine (60 mg, 0.22 mmol) in 1-butanol (1.1 mL) was added DIPEA (1.1 mL) and 4-chloro-1-(tetrahydro-pyran-2-yl)-1H-pyrazolo[3,4-d]pyrimidine (**47**) (54 mg, 0.22 mmol) and the solution was heated at 150ºC for 15 minutes under microwave irradiation. The mixture was cooled and concentrated under reduced pressure. The resulting residue was dissolved in methanol (3 mL) and 6N HCl (0.5 mL) and was heated at 60ºC for 1 hour, at which time the reaction was cooled and quenched with saturated sodium bicarbonate. The solution was extracted with ethyl acetate, and the organic layer was dried over sodium sulfate, filtered and concentrated to dryness under reduced pressure. Purification by silica gel chromatography (3% isopropanol / methylene chloride → 35% isopropanol / methylene chloride) gave **39** (21 mg) as a white solid. HRMS ($M+H^+$): calculated = 349.1520, observed = 349.1560; ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.46 (s, 1H), 8.38 (d, J = 5.2 Hz, 1H), 8.29 (s, 1H), 8.13 (s, 1H), 7.92 (d, J = 8.0 Hz, 2H), 7.54-7.51 (m, 3H), 4.86 (m, 1H), 4.00-3.96 (m, 1H), 3.79-3.73 (m, 2H), 3.64-3.61 (m, 1H), 2.39-2.36 (m, 1H), 2.18-2.16 (m, 1H).

***N*-{(3*S*)-1-[3-(4-methylphenyl)-1,2,4-oxadiazol-5-yl]pyrrolidin-3-yl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (40).** The title compound was prepared according to the procedure reported for **39**. HRMS ($M+H^+$): calculated = 363.1677, observed = 363.1680.

CYP Inhibition Assays. Incubations (100 μL) containing 100 mM potassium phosphate buffer (pH 7.4), NADP (1 mM), glucose-6-phosphate (2 mM), glucose-6-phosphate dehydrogenase (0.3 U/mL), $MgCl_2$ (5 mM), test compound at various concentrations, 0.25 mg/mL (3A4 and 2C9) or 0.5 mg/mL (2D6) pooled human liver microsomes and substrate (3A4, 50 μM testosterone; 2D6, 10 μM dextromethorphan; 2C9, 10 μM diclofenac) were incubated for 15 min (3A4, 2C9) or 45 min (2D6) at 37 ^oC. The incubations were stopped by the addition of 20 μL of a solution that containing an internal standard (3A4, 5 μM cortisone; 2D6, 7 μM propanolol; 2C9, 5 μM labetalol), 3.4% formic acid and 5% CH_3CN. The degree of product formation, 3A4, 6β-hydroxytestosterone; 2D6, dextrorphan; 2C9, 4-hydroxydiclofenac), was quantified using reverse phase liquid chromatography and a Sciex API3000 triple quadrupole mass spectrometer for detection. The mass spectrometer was equipped with an APCI source using positive ionization in selected reaction monitoring (SRM) mode.