

Supporting information available

Heterobiaryl Human Immunodeficiency Virus Entry Inhibitors

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Experimental procedures and characterization data for newly synthesized compounds. The purity of newly synthesized compounds was determined by LC-MS with ELSD detection, and combustion analysis confirming $\geq 95\%$ purity.

HPLC Purification: Compounds requiring HPLC purification were purified on a system using a Sedex 75 ELSD as the fraction-determining detector, the Gilson 215 as autosampler and fraction collector, and Gilson 321 pumps. Mobile phases used were one of the following:

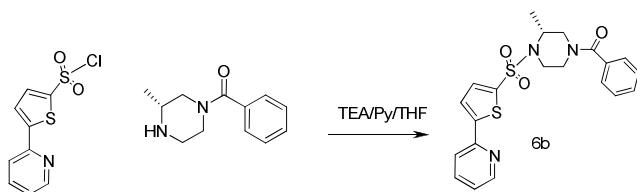
1. Water/Acetonitrile/0.05% Trifluoroacetic Acid
2. 20 mM ammonium formate at pH 4 – 6 and Acetonitrile
3. 0.1% ammonium hydroxide and acetonitrile at pH 9.0.

Columns used were either Phenomenex Gemini, 5 μm , 21.2 X 50 mm or Peeke Scientific Ultro 60 C18 5 μm , 20 mm X 50 mm.

Analytical LCMS Compounds were analyzed on an Applied Biosystems/Sciex 150EX single quad mass spectrometer in positive ion mode using either an ESI (Electrospray Ionization) source or an APCI (Atmospheric Pressure Chemical Ionization) source. Scan range is 100 – 1000 amu. Mobile phase used

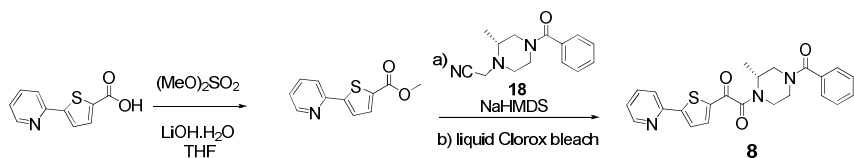
was one of the above as described in the purification section. Sedex 75 ELSD and Agilent PDA (photodiode array) UV detection was used. The column most commonly used was the Phenomenex Gemini, 5 μ m, 4.6 X 50 mm. When necessary to achieve greater separation of close-eluting impurities, other columns were used including the Phenomenex Gemini, 5 μ m, 4.6 X 100 or 250 mm, the Kromasil 100, C18, 5 μ m, 4.6 X 100 or 250, and the DuraGel HS, 5 μ m, phenyl 4.6 X 250 mm from Peeke Scientific. Mass calculations were made using the monoisotopic mass for the compound.

Method A. Parallel Synthesis of Sulfonamides. *(R)-3-Methyl-4-(5-pyridinyl-2-yl-thiophene-2-sulfonyl)-piperazin-1-yl]-phenyl-methanone 6b*



A 0.125 M solution of *R*-(3-methyl-piperazin-1-yl)-phenyl-methanone in pyridine (2 mL, 0.25mmol) was added to a vial containing 65 mg (0.25 mmol) 5-(pyridinyl-2-yl)-2-yl-thiophenesulfonyl chloride dissolved in 4 ml of THF. The resulting mixture was treated with 2.5mmol of triethylamine and then stirred overnight at room temperature. The volatiles were removed under vacuum and the remaining crude product was purified by reverse-phase HPLC. Yield: 21 mg (20%). The purified material was characterized by LCMS MS: Calculated for $C_{21}H_{21}N_3O_3S_2$: 427.10. Found: 427.06. Purity (ELSD) > 95%.

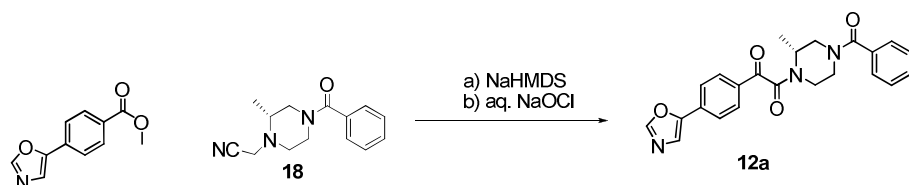
Methods B and C. *(R)-1-(4-benzoyl-2-methylpiperazin-1-yl)-2-(5-(pyridin-2-yl)thiophen-2-yl)ethane-1,2-dione 8*



To a mixture of 1.0 g (4.8 mmol) of 2-(2-pyridyl)thiophene-5-carboxylic acid and 1 gram (25 mmol) of lithium hydroxide monohydrate in 15 mL of THF was added 0.61 g (4.8 mmol) of dimethyl sulfate. The mixture was refluxed for 3 hours and then cooled to 25 °C. The mixture was partitioned between

ethyl acetate and water. The organic extracts were washed with brine and then dried over MgSO_4 . The solvent was evaporated. The residual material was dissolved in 25 mL of THF and treated with ((R)-4-benzoyl-2-methyl-piperazin-1-yl)-acetonitrile **18**¹⁵ (400 mg, 1.6 mmol). Sodium hexamethyldisilazide (NaHMDS, 500 mg, 2.7 mmol) was then added directly to the solution in portions while stirring at ambient temperature. The resulting mixture was allowed to stir for 3 hours. Liquid Clorox™ bleach (20 mL) was then added in one portion and the resulting biphasic emulsion stirred or shaken rapidly for 5 to 10 minutes. 30 mL of EtOAc was added and the resulting organic layer washed once with an equal volume of saturated aqueous sodium sulfite. The organic fraction was then washed with two portions of saturated ammonium chloride and then brine. After drying over MgSO_4 , the organic fraction was concentrated *in-vacuo* to give a brown residue that was purified by chromatography to give 506 mg of the product (66%). LCMS: Calc'd for $\text{C}_{23}\text{H}_{21}\text{N}_3\text{O}_3\text{S} \cdot \text{H}^+$: 419.1. Found: 420.5. Purity (ELSD): 100%. ¹H-NMR (CDCl_3): δ 8.77 (d, $J = 4$ Hz, 1H), 8.1 – 7.7 (m, 3H), 7.6 – 7.4 (m, 5H), 7.1 (s, 2H), 5.0 – 3.0 (m, 7H), 1.5 – 1.3 (m, 3H).

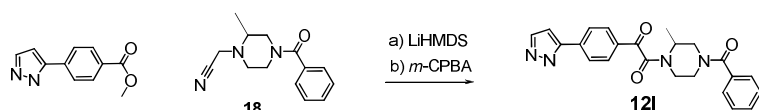
Method D-1. 1-((R)-4-Benzoyl-2-methyl-piperazin-1-yl)-2-(4-oxazol-5-yl-phenyl)-ethane-1,2-dione **12a**



((R)-4-Benzoyl-2-methyl-piperazin-1-yl)-acetonitrile¹⁵ (182 mg, 0.896 mmol) and 4-oxazol-5-yl-benzoic acid methyl ester¹ (245 mg, 1 mmol) were dissolved in 10 mL of anhydrous THF. Sodium hexamethyldisilazide (NaHMDS, 500 mg, 2.7 mmol) was then added directly to the solution in portions while stirring at ambient temperature. The resulting mixture was allowed to stir for 2 to 5 hours. Liquid Clorox™ bleach (10 mL) was then added in one portion and the resulting biphasic emulsion stirred or shaken rapidly for 5 to 10 minutes. 30 mL of EtOAc was added and the resulting organic layer washed once with an equal volume of saturated aqueous sodium sulfite. The organic fraction was then washed with two portions of saturated ammonium chloride and then brine. After drying over MgSO_4 , the

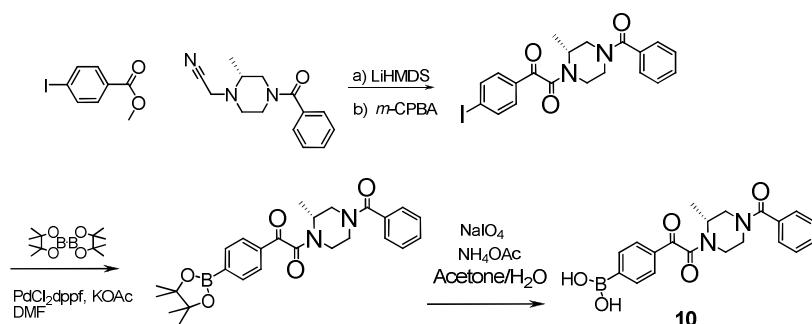
organic fraction was concentrated in-vacuo to give 265 mg of a brown residue that was subjected to purification by reverse-phase HPLC ultimately affording 49 mg of pure 1-((R)-4-benzoyl-2-methyl-piperazin-1-yl)-2-(4-oxazol-5-yl-phenyl)-ethane-1,2-dione as light yellow syrup (13 %, isolated yield). LCMS: Calculated for $C_{23}H_{21}N_3O_4 \cdot H^+$: 404.15. Found: 404.5. Purity (ELSD): 99%. 1H -NMR ($CDCl_3$): 8.07-8.00 (m, 3H), 7.82 (d, $J = 5.7$ Hz, 2H), 7.57 (s, 1H), 7.5-7.35 (br. m, 5H), 5.2-2.9 (br. m, 7H), 1.3 (br. s, 3H). Analysis: Calc'd for $C_{23}H_{21}N_3O_4 \cdot 0.6 CF_3CO_2H$: C, 61.60; H, 4.61; N, 8.91. Found: C, 61.57; H, 4.59; N, 8.90.

Method D-2. 1-(4-Benzoyl-2-methyl-piperazin-1-yl)-2-[4-(2H-pyrazol-3-yl)-phenyl]-ethane-1,2-dione **12l**



This compound was prepared by a variation of Method D-1 in which lithium hexamethyldisilazide was used in place of sodium hexamethyldisilazide, and 4 equivalents of MCPBA were used in place of bleach. Methyl 4-(2H-pyrazol-3-yl)-benzoate was used as the ester component of the reaction mixture. The crude product was purified by SiO_2 chromatography using 10% MeOH/ethyl acetate as eluent to obtain 1-(4-benzoyl-2-methyl-piperazin-1-yl)-2-[4-(2H-pyrazol-3-yl)-phenyl]-ethane-1,2-dione (0.09 g, 22%). LCMS: Calc'd for $C_{23}H_{22}N_4O_3 \cdot H^+$: $m/z = 403.5$. Found: $m/z = 403$. Purity (ELSD): 100%. Purity (UV, 254 nm): 94%. 1H -NMR ($DMSO-d_6$): 13.59 and 13.16 (br. 1H, NH-pyrazole); 8.06 (m, 2H); 7.95-7.86 (m, 3H); 7.45-7.40 (m, 5H); 6.89 (br s, 1H); 4.68-4.30 (br., 2H); 3.29-3.43 (br., 2H); 3.16 (m, 1H); 3.08-2.85 (br., 2H); 1.20 (br., 3H). Analysis: Calc'd for $C_{23}H_{22}N_4O_3 \cdot 0.25 EtOAc$: C, 67.91; H, 5.70; N, 13.20. Found: C, 68.15; H, 5.62; N, 12.86. The presence of 0.25 equivalents of ethyl acetate was confirmed by 1H -NMR.

Method E. 4-[2-(4-Benzoyl-2(R)-methyl-piperazin-1-yl)-2-oxo-acetyl]phenylboronic acid **10**

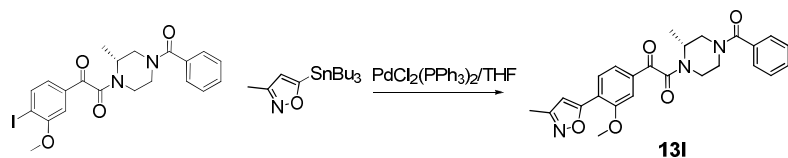


1-(4-benzoyl-2(R)-methyl-piperazin-1-yl)-2-(4-iodo-phenyl)-ethane-1,2-dione was prepared according to Method D-1, using (R)-4-benzoyl-2-methyl-piperazin-1-yl)-acetonitrile¹⁵ and methyl 4-iodobenzoate as starting materials. ¹H-NMR (DMSO-d₆): 8.03 (m, 2H); 7.46 (m, 2H); 7.46-7.42 (m, 5H); 4.84-4.03 (br., 2H); 3.99-3.34 (br., 3H); 3.23-2.79 (br., 2H); 1.21 (br., 3H).

Anhydrous DMF (100 mL) was added to a mixture of this iodide (3.75 g, 8.1 mmol), 4,4,5,5,4',4',5',5'-octamethyl-[2,2']bi[[1,3,2]dioxaborolanyl] (2.68 g, 10 mmol) and anhydrous KOAc (2.38 g, 24 mmol). Argon was bubbled through the reaction mixture for ~20 min. Then PdCl₂dppf (0.18 g, 0.24 mmol) was added. The reaction mixture was stirred at 75°C for 1.5 h (LCMS-monitoring), then cooled to RT, diluted with benzene (300 mL) and washed with water (3x200 mL). The organic layer was evaporated, the residue was extracted with Et₂O and filtered. The filtrate was evaporated to give crude 1-((R)-4-benzoyl-2-methyl-piperazin-1-yl)-2-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-ethane-1,2-dione which was used for the next step without additional purification. LCMS: Calc'd for C₂₆H₃₂BN₂O₅ · H⁺: *m/z* = 463.4. Found: *m/z* = 463.0.

NaIO₄ (6.5 g, 30 mmol) and NH₄OAc (2.42 g, 31 mmol) were added to an acetone –water (1:1, 200 mL) solution of crude 1-((R)-4-benzoyl-2-methyl-piperazin-1-yl)-2-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-ethane-1,2-dione. The reaction mixture was kept under stirring for 24 h at 25 °C, diluted with water (200 mL), and the precipitate was filtered off. The solution was extracted with EtOAc (2x200 mL). The organic phase was dried with Na₂SO₄, and evaporated to afford 4-[2-((R)-4-benzoyl-2-methyl-piperazin-1-yl)-2-oxo-acetyl]phenylboronic acid (2.3 g, 74% for two steps). LCMS: Calc'd for C₂₀H₂₁BN₂O₅ · H⁺: *m/z* = 381.2. Found: *m/z* = 381.0.

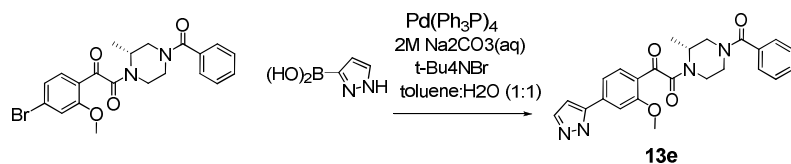
Method F. (R)-1-(4-benzoyl-2-methylpiperazin-1-yl)-2-(3-methoxy-4-(3-methylisoxazol-5-yl)phenyl)ethane-1,2-dione, **13l**.



A solution of 216 mg (R)-1-(4-benzoyl-2-methylpiperazin-1-yl)-2-(4-iodo-3-methoxyphenyl)ethane-1,2-dione and 150 mg of 3-methyl-5-(tributylstannyl)isoxazole in 4 mL of THF was treated with 14 mg of bis(triphenylphosphine)palladium(II) dichloride. The solution was refluxed for 18 hours. The mixture was filtered and the filtrate was partitioned between ethyl acetate and aqueous sodium chloride solution.

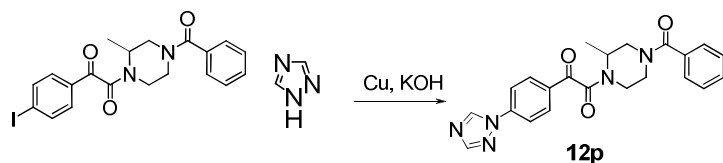
The organic phase was dried (MgSO₄) and the solvent was evaporated at reduced pressure. The residue was purified by reverse-phase HPLC to give 10 mg of a brown solid. LCMS (Calc'd for C₂₅H₂₅N₃O₅ · H⁺: 448.2. Found: 448.5. Purity (ELSD): 100%. ¹H-NMR (CDCl₃): δ 8.10 (d, *J* = 8 Hz, 1H), 7.63 (bs, 1H), 7.57 (t, *J* = 8 Hz, 1H), 7.42 (s, 5H), 6.80 (s, 1H), 5.0 – 3.0 (m, 7H), 4.04 (s, 3H), 2.39 (s, 3H), 1.5 – 1.2 (sm, 3H). The starting ester, (R)-1-(4-benzoyl-2-methylpiperazin-1-yl)-2-(4-iodo-3-methoxyphenyl)ethane-1,2-dione, was prepared according to Method D-1 using methyl 4-iodo-3-methoxybenzoate and (R)-4-Benzoyl-2-methyl-piperazin-1-yl)-acetonitrile¹⁵ as starting materials (yield 25%). MS Calc'd for C₂₁H₂₁IN₂O₄ · H⁺: 493.0. Found: 493.4.

Method G. (R)-1-(4-benzoyl-2-methylpiperazin-1-yl)-2-(2-methoxy-4-(1H-pyrazol-5-yl)phenyl)ethane-1,2-dione **13e**.



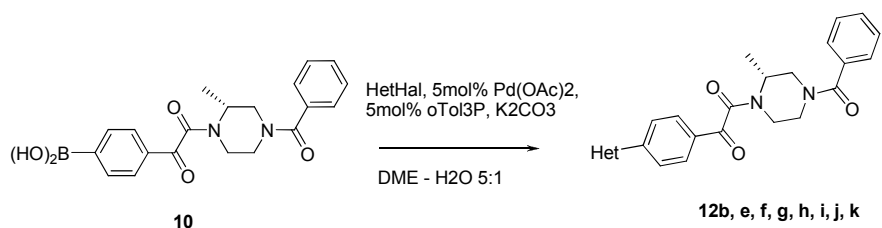
A mixture of 35 mg of 3-pyrazoleboronic acid, 89 mg of 1-(4-benzoyl-2(R)-methylpiperazin-1-yl)-2-(4-bromo-2-methoxyphenyl)ethane-1,2-dione (see S23), 4 mL of toluene, 4 mL of ethanol, 0.3 mL of a 2 M aqueous solution of sodium carbonate, 5.5 mg of tetrabutylammonium bromide, and 12 mg of tetrakis(triphenylphosphine)palladium(0) was flushed with nitrogen and then refluxed for 16 hours. The mixture was filtered and partitioned between ethyl acetate and water. The aqueous phase was washed with ethyl acetate, and the combined organic extracts were washed with brine and dried (MgSO₄). The solvent was evaporated at reduced pressure and the residue was purified by reverse-phase HPLC. The title compound was obtained as 36 mg of a tan powder. MS (ESI): Calc'd for C₂₄H₂₄N₄O₄ · H⁺: 433.2. Found: 433.3 ¹H-NMR (CDCl₃): δ 7.94 (d, *J* = 8 Hz, 1H), 7.61 (s, 1H), 7.5 – 7.4 (m, 7H), 6.69 (s, 1H), 3.95 – 3.85 (m, 3H), 5.0 – 3.0 (m, 7H), 1.5 – 1.2 (m, 3H).

Method H 1-(4-Benzoyl-2-methyl-piperazin-1-yl)-2-(4-[1,2,4]triazol-1-yl-phenyl)-ethane-1,2-dione **12p**.



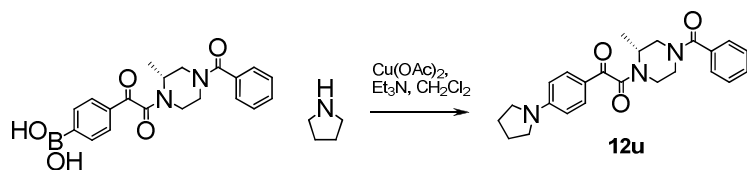
Mixture of 1-(4-benzoyl-2-methyl-piperazin-1-yl)-2-(4-iodo-phenyl)-ethane-1,2-dione (0.33 g, 0.71 mmol), Cu-powder (0.09 g, 1.42 mmole), 1,2,4-triazole (1.47 mL, 21.3 mmole), and powdered KOH (0.08 g, 1.42 mmole) was heated to 160°C and kept under stirring at this temperature for 24 h (TLC monitoring, 10% MeOH/CHCl₃). The reaction mixture was then cooled to 25 °C and diluted with EtOAc (~2 mL). The solution was placed onto a silica gel column and eluted with EtOAc. Fractions containing product were combined and evaporated to afford 1-(4-benzoyl-2-methyl-piperazin-1-yl)-2-(4-[1,2,4]triazol-1-yl-phenyl)-ethane-1,2-dione (0.17 g, 59 %). LCMS: Calc'd for C₂₂H₂₁N₅O₃ · H⁺: *m/z* = 404.5. Found: *m/z* = 404.1. Purity (ELSD): 100%. ¹H-NMR (DMSO-d₆): 9.50 (d, *J* = 3.1 Hz, 1H); 8.34 (s, 1H); 8.14-7.98 (m, 4H); 7.45-7.42 (m, 5H); 4.90-4.10 (br., 2H); 3.95-3.35 (br., 3H); 3.23-2.80 (br., 2H); 1.20 (br., 3H).

Method I. Parallel Suzuki Couplings



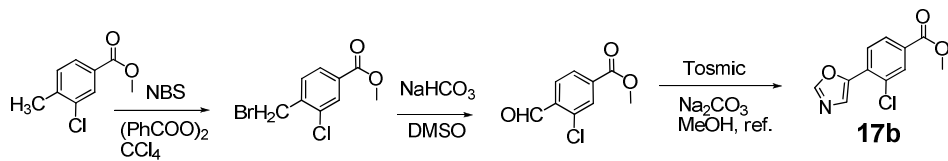
The starting aryl halides (100 uM, 1 eq) were placed in vials. Then 600 uL of a 0.167 M solution of **10** in DME (1 eq) was added. The tubes were flushed with argon and placed in a glove box (N₂). Then 400 uL of a 0.0125 M *o*-Tol₃P solution in DME (0.05 eq), 100 uL of 0.05 M aqueous Pd(OAc)₂ (0.05 eq), and 100 uL of 0.33 M aqueous K₂CO₃ (3 eq) prepared in a glove box were added. The reaction mixtures were stirred at 100 °C for 18. After cooling, DCM (3 mL) was added. The mixtures were shaken on a Vortex shaker and passed through a 5 mL column of Celite packed in DCM. The eluates were evaporated in a flow of argon (ZyMark). The residues were dissolved in DMSO, and the 48 well plates were submitted for mass-triggered preparative LCMS.

Method J 1-((R)-4-Benzoyl-2-methyl-piperazin-1-yl)-2-(4-pyrrolidin-1-yl-phenyl)-ethane-1,2-dione **12u**,



A mixture of 4-[2-((R)-4-benzoyl-2-methyl-piperazin-1-yl)-2-oxo-acetyl]-boronic acid (0.20 g, 0.53 mmol), pyrrolidine (0.04 g, 0.56 mmol), Et₃N (0.16 mL, 1.11 mmol) and anhydrous Cu(OAc)₂ (0.10 g, 0.055 mmol) in CH₂Cl₂ (5 mL) was stirred for 1 h at 25 °C. Then H₂O (10 mL) and CH₂Cl₂ (20 mL) were added. The organic layer was separated, washed with brine, dried over sodium sulfate, filtered and concentrated. The crude residue was purified by SiO₂ chromatography using ethyl acetate as eluent to obtain 1-((R)-4-benzoyl-2-methyl-piperazin-1-yl)-2-(4-pyrrolidin-1-yl-phenyl)-ethane-1,2-dione (0.12 g, 56%). LCMS: Calc'd for C₂₄H₂₇N₃O₃ · H⁺: *m/z* = 406.5. Found: *m/z* = 406.0. Purity (ELSD): 100%. Purity (UV): 95%. ¹H-NMR (DMSO-d₆): 7.65 (m, 2H); 7.45 (m, 5H); 6.63 (m, 2H); 4.81-4.03 (br., 2H); 3.99-3.49 (br., 2H); 3.36 (m, 4H); 3.21-2.77 (br., 3H); 1.98 (m, 4H); 1.18 (br., 3H).

Method K. Methyl 3-chloro-4-(oxazol-5-yl)benzoate (intermediate for 13n)

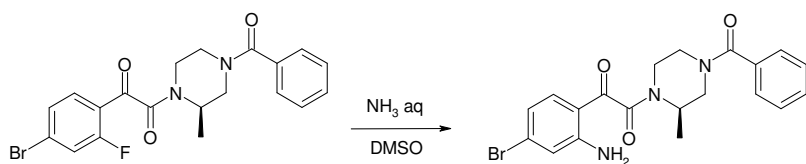


A mixture of 180 mg of methyl 3-chloro-4-formylbenzoate, 178 mg of Tosmic, 155 mg of anhydrous sodium carbonate, and 4 mL of methanol was refluxed for 4 h. The solvent was evaporated and the residue was partitioned between ethyl acetate and a saturated aqueous solution of ammonium chloride. The organic phase was washed with brine and then dried (MgSO₄). The product was obtained as 230 mg of a light brown solid. **MS** (Calc'd for C₁₁H₈ClNO₃ · H⁺: 238.0. Found: 238.1. ¹H-NMR (CDCl₃): δ 8.15 (s, 1H), 8.1 – 7.9 (m, 4H), 3.95 (s, 3H).

The methyl 3-chloro-4-formylbenzoate starting material was prepared as follows. A solution of 530 mg of methyl 4-(bromomethyl)-3-chlorobenzoate in 20 mL of DMSO was heated to 100 °C and treated with 2.2 g of sodium bicarbonate. The mixture was stirred at 100 °C for an additional 30 minutes and then it was poured into 100 mL of ice water. The precipitate was collected and dried to give 50 mg of a slightly yellowish solid. ¹H-NMR (CDCl₃): δ 10.58 (s, 1H), 8.14 (s, 1H), 8.1 – 7.9 (m, 2H), 3.98 (s, 3H).

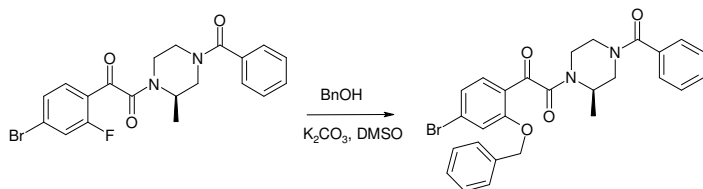
The methyl 4-(bromomethyl)-3-chlorobenzoate was prepared as follows. A mixture of 3 g of methyl 3-chloro-4-methylbenzoate, 2.9 grams of N-bromosuccinimide, and 156 mg of dibenzoyl peroxide in carbon tetrachloride was refluxed 4 h. The solution was cooled to 25 °C and filtered. The filtrate was washed with water and then brine. It was dried (MgSO₄) and the solvent was evaporated at reduced pressure to give the title compound as 4.1 g of a yellowish liquid. ¹H-NMR (CDCl₃): δ 8.05 (s, 1H), 7.90 (dd, *J* = 8, 2 Hz, 1H), 7.52 (d, *J* = 8 Hz, 1H), 4.59 (s, 2H), 3.90 (s, 3H).

Method L. *1-(2-Amino-4-bromo-phenyl)-2-((R)-4-benzoyl-2-methyl-piperazin-1-yl)-ethane-1,2-dione(intermediate 13f)*



To a solution of 1-((R)-4-benzoyl-2-methyl-piperazin-1-yl)-2-(4-bromo-2-fluoro-phenyl)-ethane-1,2-dione (0.5 g, 1.15 mmol) in DMSO (5mL), a 40% aqueous solution of ammonia (3 mL) was added. The reaction mixture was heated to 80°C and kept under stirring at this temperature for 1 h (TLC monitoring, EtOAc/n-hexane 3:1). It was cooled to 25 °C, poured into ice water (50 mL), and extracted with EtOAc (~2 mL). Organic phase was washed with water (3x30mL), dried over sodium sulfate, and then concentrated. The crude product was purified by silica-gel chromatography using EtOAc/n-hexane 3:1 as eluent to afford the title compound in 79% yield. ¹H-NMR (DMSO-d₆): δ 7.51-7.21 (m, 8H), 7.08 (s, 1H), 6.72 (m, 1H), 4.80 – 3.37 (br., 4H), 3.20-2.72 (br., 3H), 1.18 (s, 3H). LCMS: Calc'd for C₂₀H₂₀BrN₃O₃ · H⁺: *m/z* = 431. Found: *m/z* = 431.

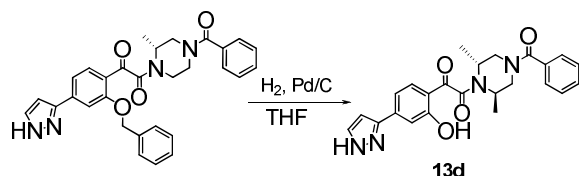
Method M. *1-((R)-4-Benzoyl-2-methyl-piperazin-1-yl)-2-(2-benzyloxy-4-bromo-phenyl)-ethane-1,2-dione*



To a solution of 1-((R)-4-benzoyl-2-methyl-piperazin-1-yl)-2-(4-bromo-2-fluoro-phenyl)-ethane-1,2-dione (0.15 g, 0.35 mmol) in DMSO (3 mL), benzyl alcohol (0.3 mL) and potassium carbonate (0.15 g,

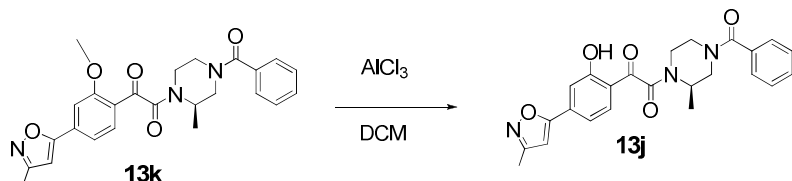
1.09 mmol) were added. The reaction mixture was heated to 80°C and kept under stirring at this temperature for ~2 h (LC/MS monitoring), cooled to RT, poured into ice water (50 mL), and extracted with Et₂O (~10 mL). The organic phase was washed with water (3x30mL), dried over sodium sulfate, and then concentrated. The crude product was purified by silica-gel chromatography using EtOAc/n-hexane 3:1 as eluent to afford 1-((R)-4-benzoyl-2-methyl-piperazin-1-yl)-2-(4-bromo-2-dimethylamino-phenyl)-ethane-1,2-dione (0.11 g, 62 %). LCMS: Calc'd for C₂₇H₂₅BrN₂O₄ · H⁺: m/z = 522. Found: m/z = 522.

Method N. 1-((R)-4-Benzoyl-2-methyl-piperazin-1-yl)-2-[2-hydroxy-4-(1H-pyrazol-3-yl)-phenyl]-ethane-1,2-dione **13d**



1-((R)-4-Benzoyl-2-methyl-piperazin-1-yl)-2-[2-benzyloxy-4-(1H-pyrazol-3-yl)-phenyl]-ethane-1,2-dione (see S23) (0.05 g, 0.1 mmol) was dissolved in anhydrous THF (10 mL). Argon was bubbled through the reaction mixture for ~20 min. Then 10% palladium on carbon (0.02 g) was added. Hydrogen was bubbled within reaction mixture under stirring and reflux for ~7 h (TLC-monitoring, CHCl₃/MeOH 9:1). The reaction mixture was cooled to RT, filtered through celite. Solvent was evaporated, the residue was purified by chromatography (silica gel, 10% MeOH/CHCl₃) to give product 1-((R)-4-benzoyl-2-methyl-piperazin-1-yl)-2-[2-hydroxy-4-(1H-pyrazol-3-yl)-phenyl]-ethane-1,2-dione (0.035 g, 83%). ¹H-NMR (DMSO-d₆): 13.01 (br., 1H, NH-pyrazole); 11.18 (br., OH in exchange with H₂O), 7.79-7.69, 7.45-7.40 (two m, 9H); 6.77 (m, 1H); 4.59-3.07 (br., 7H); 1.20 (br., 3H). LCMS: Calc'd for C₂₃H₂₂N₄O₄ · H⁺: m/z = 419.5. Found: m/z = 419.7. Purity (ELSD): 100%. Purity (UV): 100%.

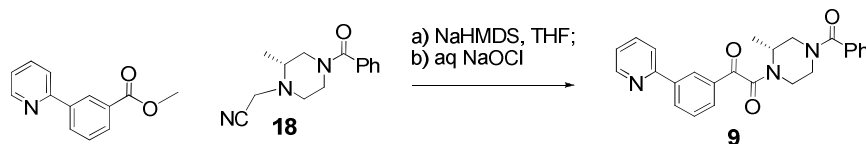
Method O. (R)-1-(4-benzoyl-2-methylpiperazin-1-yl)-2-(2-hydroxy-4-(3-methylisoxazol-5-yl)phenyl)ethane-1,2-dione **13j**



To a solution of 120 mg (0.27 mmol) of methoxy compound **13k** in 10 mL of dichloromethane was added 290 mg (2.1 mmol) of anhydrous aluminum chloride. The mixture was stirred for 16 hours and then an aqueous solution of sodium bicarbonate was added dropwise. The phases were separated and the

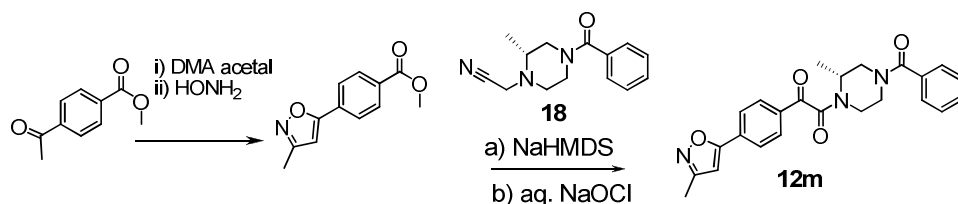
aqueous phase was washed with dichloromethane. The combined organic extracts were dried (MgSO₄) and the solvent was evaporated. The title compound was obtained as 30 mg of a pale orange solid. ¹H-NMR (CDCl₃): 11.31 (s, 1H), 8.70 – 8.55 (m, 1H), 8.60 – 7.25 (m, 7H), 6.53 (s, 1H), 5.0 – 3.0 (m, 7H), 2.39 (s, 3H), 1.5 – 1.3 (m, 3H). LCMS: Calc'd for C₂₄H₂₃N₃O₅ · H⁺: *m/z* 434.16. Found: 434.4. Purity (ELSD): 100%.

1-(4-Benzoyl-2(R)-methyl-piperazin-1-yl)-2-[3-pyrid-2-yl-phenyl]-ethane-1,2-dione **9**



This compound was prepared by applying Method D-1 to 3-(2-pyrid-2-yl)benzoic acid methyl ester and ((R)-4-Benzoyl-2-methyl-piperazin-1-yl)-acetonitrile¹⁵ **18** as starting materials. LCMS: Calculated for C₂₅H₂₃N₃O₃·H⁺: 414.17. Found: 414.3. Purity (ELSD): 100%. ¹H-NMR (CDCl₃): 8.77-8.65 (m, 3H), 8.35-8.25 (m, 2H), 8.08-7.97 (m, 2H), 7.55-7.35 (m, 6H), 5.0-3.0 (m, 7H), 1.5-1.0 (m, 3H).

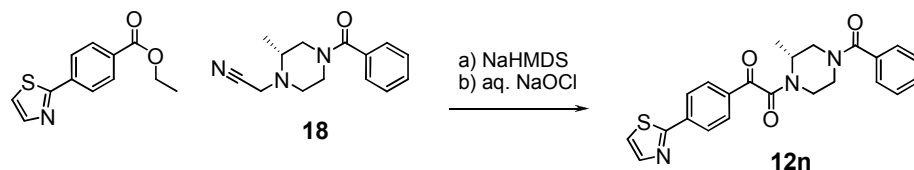
1-(4-Benzoyl-2(R)-methyl-piperazin-1-yl)-2-[4-(3-methyl-isoxazol-5-yl)-phenyl]-ethane-1,2-dione **12m**



This compound was prepared using Method D-1, using 4-(3-methyl-isoxazol-5-yl)-benzoic acid methyl ester and ((R)-4-Benzoyl-2-methyl-piperazin-1-yl)-acetonitrile¹⁵ **18** as starting materials. The crude product was subjected to purification by reverse-phase HPLC ultimately affording 407 mg of 1-((R)-4-benzoyl-2-methyl-piperazin-1-yl)-2-[4-(3-methyl-isoxazol-5-yl)-phenyl]-ethane-1,2-dione as light yellow foam (75 %). LCMS: Calculated for C₂₄H₂₃N₃O₄·H⁺: 418.5. Found: 418.4. Purity (ELSD): 99%. ¹H-NMR (CDCl₃): 8.03 (m, 2H) 7.91 (d, *J* = 8.1 Hz, 2H), 7.53-7.32 (m, 5H), 6.54 (s, 1H), 5.24-2.92 (m, 7H), 2.69 (s, 3H), 1.33 (br. s, 3H). The 4-(3-methyl-isoxazol-5-yl)-benzoic acid methyl ester

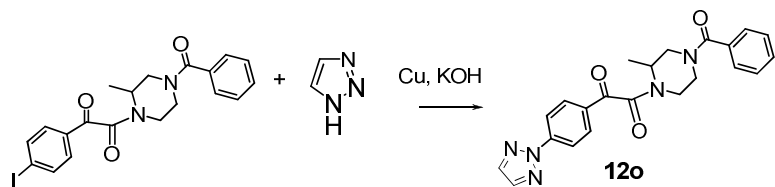
starting material was prepared as follows: 4-Acetyl-benzoic acid methyl ester (0.5 g, 2.8 mmol) was dissolved in 4 mL of DMA dimethyl acetal and heated to 100 degrees C for 2 hours. Upon cooling to room temperature, 30 mL of EtOAc was added. The sample was concentrated until the crude intermediate enamine precipitated. The precipitate was isolated by vacuum filtration yielding 412 mg of a brown solid that was immediately dissolved in 10 mL of anhydrous EtOH and combined with 150 mg (2.1 mmol) of hydroxylamine hydrochloride. The resulting mixture was refluxed for three hours and then slowly cooled to zero degrees. The sample was then thawed and the insoluble product collected while the mother liquor was still cool affording 280 mg of 4-(3-methyl-isoxazol-5-yl)-benzoic acid methyl ester as tan crystals (78%). ¹H-NMR (CDCl₃): 8.105 (d, *J* = 8.4 Hz, 2H), 8.00 (d, *J* = 8.1 Hz, 2H), 7.07 (s, 1H), 3.89 (s, 3H), 2.31 (s, 3H).

1-((R)-4-Benzoyl-2-methyl-piperazin-1-yl)-2-(4-thiazol-2-yl-phenyl)-ethane-1,2-dione **12n**



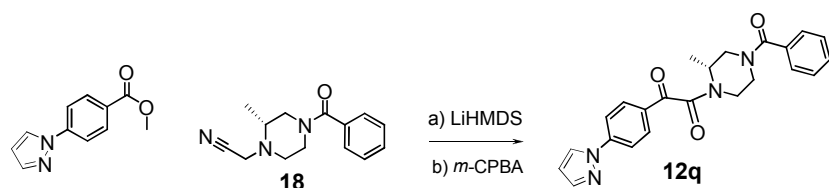
This compound was prepared by Method D-1, using ethyl 4-thiazol-2-ylbenzoate and ((R)-4-benzoyl-2-methyl-piperazin-1-yl)-acetonitrile¹⁵ **18** as starting materials. The crude product was subjected to initial purification by preparative TLC (eluting solvent: 95% DCM, 5 % MeOH, 1% TEA) giving 100 mg of off-white semisolid consisting of 60 % 1-((R)-4-benzoyl-2-methyl-piperazin-1-yl)-2-(4-thiazol-2-yl-phenyl)-ethane-1,2-dione and 40 % ((R)-4-benzoyl-2-methyl-piperazin-1-yl)-acetonitrile. This material was further purified by reverse-phase HPLC ultimately giving the product as 11 mg of colorless syrup (2.2%). LCMS: Calculated for C₂₃H₂₁N₃O₃S·H⁺: 420.1. Found: 420.4. Purity (ELSD): 100%. ¹H-NMR (CDCl₃): 8.14 (d, *J* = 8.1 Hz, 2H), 8.05-8.00 (m, 3H), 7.48 (d, *J* = 3.3 Hz, 1H), 7.5-7.3 (m, 5H), 5.24-2.84 (br. m, 7H), 1.3 (br. s, 3H).

1-(4-Benzoyl-2-methyl-piperazin-1-yl)-2-(4-[1,2,3]triazol-2-yl-phenyl)-ethane-1,2-dione **12o**



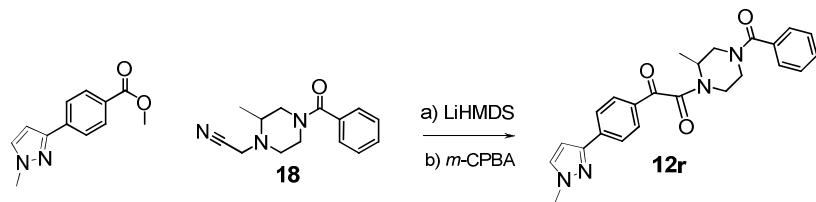
1-(4-Benzoyl-2-methyl-piperazin-1-yl)-2-(4-[1,2,3]triazol-2-yl-phenyl)-ethane-1,2-dione (see s4) (0.17 g, 59 %) was prepared according to Method H, using 1,2,3-triazole instead of 1,2,4-triazole and 2% MeOH/CH₂Cl₂ as eluent. LCMS: Calc'd for C₂₂H₂₁N₅O₃ · H⁺: m/z = 404.5. Found: m/z = 404.2. Purity (ELSD): 100%. ¹H-NMR (DMSO-*d*₆): 8.25-8.14 (m, 4H); 8.10 (m, 2H); 7.45 (m, 5H); 4.80-4.10 (br., 2H); 3.90-3.30 (br., 3H); 3.23-2.82 (br., 2H); 1.19 (br., 3H).

1-((R)-4-Benzoyl-2-methyl-piperazin-1-yl)-2-(4-pyrazol-1-yl-phenyl)-ethane-1,2-dione 12q



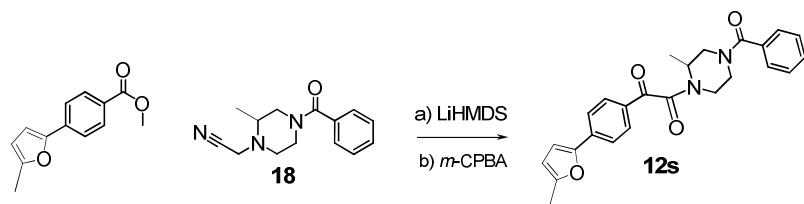
This compound was prepared by Method D-2 using methyl 4-(1-pyrazolyl)benzoate and ((R)-4-Benzoyl-2-methyl-piperazin-1-yl)-acetonitrile¹⁵ **18** as starting materials. LCMS: Calc'd for C₂₃H₂₂N₄O₃ · H⁺: m/z = 403.5. Found: m/z = 403.3. Purity (ELSD): 100%. Purity (UV, 254 nM): 95%. ¹H-NMR (DMSO-*d*₆): 8.69-8.61(m, 1H); 8.11-7.98 (m, 4H); 7.87-7.79(m, 1H); 7.45-7.40 (m, 5H); 6.65 (m, 1H); 4.86-4.10 (br., 2H); 3.96-3.41 (br., 3H); 3.18 (m, 1H); 3.08-2.85 (br., 1H); 1.20 (br., 3H).

1-(4-Benzoyl-2-methyl-piperazin-1-yl)-2-[4-(1-methyl-1H-pyrazol-3-yl)-phenyl]-ethane-1,2-dione 12r



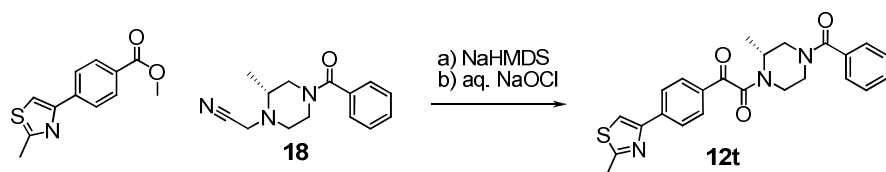
This compound was prepared by Method D-2 using 4-(1-methyl-1H-pyrazol-3-yl)-benzoic acid methyl ester as the reactive ester component. LCMS: Calc'd for C₂₄H₂₄N₄O₃ · H⁺: m/z = 417.5. Found: m/z = 417.1. Purity (ELSD): 100%. ¹H-NMR (DMSO-*d*₆): 8.02-7.96(m, 2H); 7.94-7.88 (m, 2H); 7.81-7.75 (m, 1H); 7.45-7.40 (m, 5H); 6.87-6.77(m, 1H); 4.84-4.18 (br., 2H); 3.92 (s, 3H); 3.90-2.85 (br., 5H); 1.20 (br., 3H).

1-(4-Benzoyl-2-methyl-piperazin-1-yl)-2-[4-(5-methyl-furan-2-yl)-phenyl]-ethane-1,2-dione **12s**



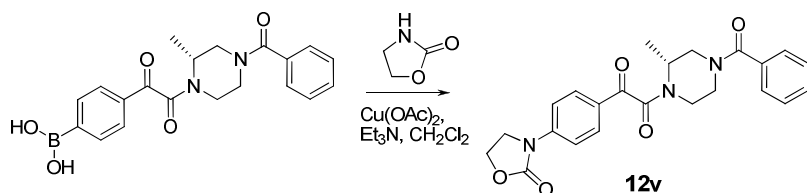
This compound was prepared using Method D-2 using methyl 4-(5-methylfuran-2-yl)benzoate and ((+/-)-4-Benzoyl-2-methyl-piperazin-1-yl)-acetonitrile¹⁵ **18** as starting materials. The product was purified by reverse phase preparative HPLC. LCMS: Calc'd for $C_{25}H_{24}N_2O_4 \cdot H^+$: $m/z = 417.5$. Found: $m/z = 417.2$. Purity (ELSD): 97%. ¹H-NMR (DMSO- d_6): 7.93-7.83 (m, 4H); 7.45-7.40 (m, 5H); 7.13-7.05 (m, 1H); 6.31-6.23 (m, 1H); 4.80-4.18 (br., 2H); 4.15-3.39 (br., 3H); 3.19-2.97 (br., 2H); 2.88 (s, 3H); 1.22 (br., 3H).

1-((R)-4-Benzoyl-2-methyl-piperazin-1-yl)-2-[4-(2-methyl-thiazol-4-yl)-phenyl]-ethane-1,2-dione **12t**



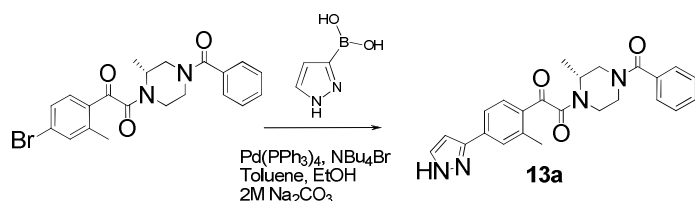
This compound was prepared by applying Method D-1 to 4-(2-methyl-thiazol-4-yl)-benzoic acid methyl ester and ((R)-4-Benzoyl-2-methyl-piperazin-1-yl)-acetonitrile¹⁵ **18** as starting materials. The crude product was purified by preparative TLC (eluting solvent: 94% DCM, 5%, MeOH, 1% TEA) affording 95 mg of 1-((R)-4-benzoyl-2-methylpiperazin-1-yl)-2-[4-(2-methyl-thiazol-4-yl)-phenyl]-ethane-1,2-dione (36%) LCMS: Calculated for $C_{24}H_{23}N_3O_3S \cdot H^+$: 434.15. Found: 433.9. Purity (ELSD): 97%. ¹H-NMR (CDCl₃): 8.07-7.94 (m, 4H), 7.52 (s, 1H), 7.48-7.36 (m, 7.5-7.3, 5H), 5.24-2.84 (br. m, 10H), 1.3 (br. s, 3H).

1-((R)-4-Benzoyl-2-methyl-piperazin-1-yl)-2-[4-(2-oxo-oxazolidin-3-yl)-phenyl]-ethane-1,2-dione **12v**



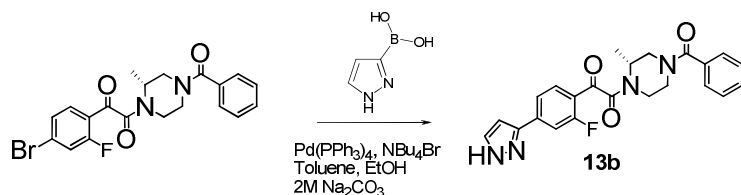
This compound was prepared in 36% yield according to the Method J, using 4-[2-((R)-4-benzoyl-2-methyl-piperazin-1-yl)-2-oxo-acetyl]-boronic acid and 2-oxo-1,3-oxazolidine as starting materials. The product was purified by HPLC. LCMS: Calc'd for $C_{23}H_{23}N_3O_5 \cdot H^+$: $m/z = 422.5$. Found: $m/z = 422.1$. Purity (ELSD): 100%. Purity (UV): 100%. 1H -NMR (DMSO- d_6): 7.96-7.90 (m, 2H); 7.80-7.74 (m, 2H); 7.45-7.40 (m, 5H); 4.87-4.53 (br., 1H); 4.50 (m, 2H); 4.43-4.19 (br., 1H); 4.14 (m, 2H); 3.90-3.34 (br., 3H); 3.19-2.77 (br., 2H); 1.20 (br., 3H).

1-((R)-4-Benzoyl-2-methyl-piperazin-1-yl)-2-[2-methyl-4-(1H-pyrazol-3-yl)-phenyl]-ethane-1,2-dione
13a



1-((R)-4-Benzoyl-2-methyl-piperazin-1-yl)-2-[2-methyl-4-(1H-pyrazol-3-yl)-phenyl]-ethane-1,2-dione (see s22) (46 %) was prepared according to Method G using 1-((R)-4-benzoyl-2-methyl-piperazin-1-yl)-2-(4-bromo-2-methylphenyl)ethane-1,2-dione (S21) and pyrazole-3-boronic acid as starting materials. LCMS: Calc'd for $C_{24}H_{24}N_4O_3 \cdot H^+$: $m/z = 417.5$. Found: $m/z = 417.1$. Purity (ELSD): 100%. Purity (UV): 100%. 1H -NMR (DMSO- d_6): 13.13 (s, 1H), 7.9-7.65 (m, 4H), 7.50-7.40 (m, 5H), 6.87 (s, 1H), 5.0 – 2.8 (m, 7H), 2.65 (s, 3H), 1.4-1.0 (m, 3H).

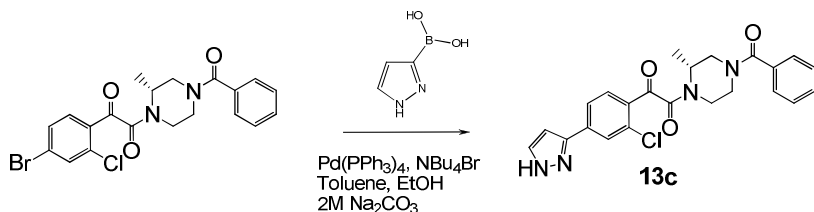
1-((R)-4-Benzoyl-2-methyl-piperazin-1-yl)-2-[2-fluoro-4-(1H-pyrazol-3-yl)-phenyl]-ethane-1,2-dione
13b



1-((R)-4-Benzoyl-2-methyl-piperazin-1-yl)-2-[2-fluoro-4-(1H-pyrazol-3-yl)-phenyl]-ethane-1,2-dione (see S22) (46 %) was prepared according to Method G using 1-((R)-4-benzoyl-2-methyl-piperazin-1-yl)-2-(4-bromo-2-fluoro-phenyl)-ethane-1,2-dione and pyrazole-2-boronic acid as starting materials. (1 h; TLC-monitoring, $CHCl_3/MeOH$ 9:1), using LCMS: Calc'd for $C_{23}H_{21}FN_4O_3 \cdot H^+$: $m/z = 421.5$. Found: $m/z = 421.2$. Purity (ELSD): 100%. Purity (UV): 95%. 1H -NMR (DMSO- d_6): 13.66, 13.25 (br., 1H, NH-pyrazole); 7.95-7.80 (m, 4H); 7.45-7.32(m, 5H); 6.97 (m, 1H); 4.74-4.10 (br., 2H); 4.04-3.39 (br., 3H); 3.18-2.85 (br., 2H); 1.20 (br., 3H). Analysis: Calc'd for $C_{23}H_{21}FN_4O_3 \cdot 0.3 EtOAc$:

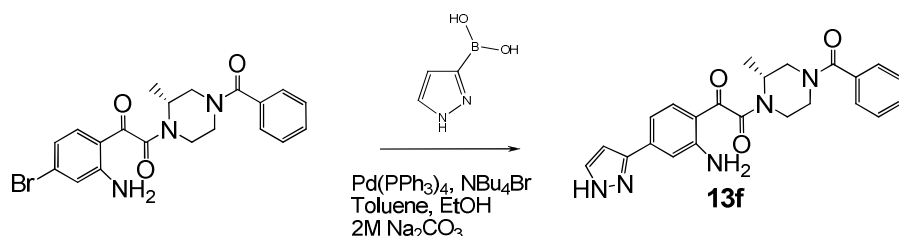
C, 65.04; H, 5.28; N, 12.54. Found: C, 64.67; H, 5.37; N, 12.28. The presence of 0.3 equivalents of ethyl acetate was confirmed by ^1H -NMR.

(R)-1-(4-benzoyl-2-methylpiperazin-1-yl)-2-(2-chloro-4-(1H-pyrazol-5-yl)phenyl)ethane-1,2-dione **13c**



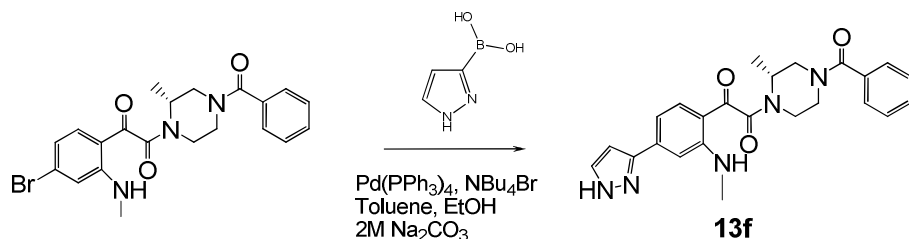
This compound was prepared from (*R*)-1-(4-benzoyl-2-methylpiperazin-1-yl)-2-(4-bromo-2-chloro)ethane-1,2-dione (see S22) and pyrazole-2-boronic acid as starting materials according to Method G. MS (ESI): Calc'd for $\text{C}_{23}\text{H}_{21}\text{ClN}_4\text{O}_3 \cdot \text{H}^+$: 437.1. Found: 437.5. Purity (ELSD): 96%. ^1H -NMR (CDCl_3): δ 7.95-7.85 (m, 2H), 7.85-7.80 (m, 1H), 7.62 (s, 2H), 7.44 (s, 5H), 6.69 (s, 1H), 5.10 -2.70(m, 7H), 1.5-1.2 (m, 3H).

1-((R)-4-Benzoyl-2-methyl-piperazin-1-yl)-2-[2-amino-4-(1H-pyrazol-3-yl)-phenyl]-ethane-1,2-dione **13f**



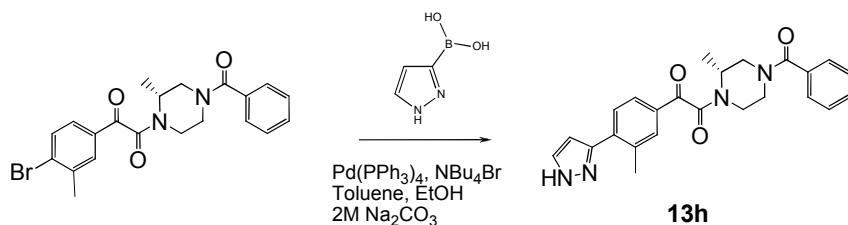
1-((*R*)-4-Benzoyl-2-methyl-piperazin-1-yl)-2-[2-amino-4-(1H-pyrazol-3-yl)-phenyl]-ethane-1,2-dione (52 %) was prepared according to Method G. (40 min; TLC-monitoring, $\text{CHCl}_3/\text{MeOH}$ 20:1), using 1-((*R*)-4-benzoyl-2-methyl-piperazin-1-yl)-2-(4-bromo-2-amino-phenyl)-ethane-1,2-dione (see s9) and pyrazole-2-boronic acid as starting materials LCMS: Calc'd for $\text{C}_{23}\text{H}_{23}\text{N}_5\text{O}_3 \cdot \text{H}^+$: m/z = 418.5. Found: m/z = 418.1. Purity (ELSD): 100%. Purity (UV): 96%. ^1H -NMR ($\text{DMSO}-d_6$): 13.14 (br., 1H, NH-pyrazole); 7.78 (m, 1H); 7.45-7.30 (m, 9H); 7.05 (m, 1H); 6.68 (m, 1H); 4.85-3.36 (br., 5H); 3.15-2.84 (br., 2H); 1.19 (br., 3H). Analysis: Calc'd for $\text{C}_{23}\text{H}_{23}\text{N}_5\text{O}_3 \cdot 0.15 \text{ CF}_3\text{CO}_2\text{H}$: C, 64.40; H, 5.37; F N, 16.12. Found: C, 64.28; H, 5.44; N, 16.13.

1-((R)-4-Benzoyl-2-methyl-piperazin-1-yl)-2-[2-methylamino-4-(1H-pyrazol-3-yl)-phenyl]-ethane-1,2-dione **13g**



1-((R)-4-Benzoyl-2-methyl-piperazin-1-yl)-2-[2-methylamino-4-(1H-pyrazol-3-yl)-phenyl]-ethane-1,2-dione (7%) was prepared according to Method G using pyrazole-2-boronic acid and 1-((R)-4-benzoyl-2-methyl-piperazin-1-yl)-2-[2-methylamino-4-bromophenyl]-ethane-1,2-dione (see S24) as starting materials (40 min; TLC-monitoring, CHCl₃/MeOH 20:1). The product was purified by silica gel chromatography using CHCl₃/MeOH 9:1 as eluent. LCMS: Calc'd for C₂₄H₂₅N₅O₃ · H⁺: *m/z* = 432.5. Found: *m/z* = 432.5. Purity (ELSD): 100%. Purity (UV): 96%. ¹H-NMR (DMSO-d₆): 13.54, 13.09 (two br., 1H, NH-pyrazole); 8.53-8.49 (m, 1 H); 7.83-7.79 (m, 1H); 7.60-7.13 (m, 8H); 6.86 (s, 1H); 4.67-3.38 (br., 5H); 3.12-2.99 (br., 5H); 1.18 (br., 3H).

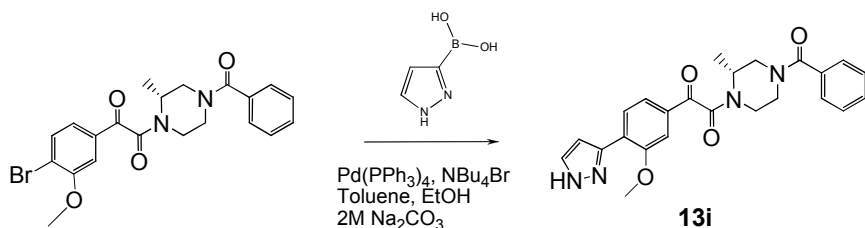
1-((R)-4-Benzoyl-2-methyl-piperazin-1-yl)-2-[3-methyl-4-(1H-pyrazol-3-yl)-phenyl]-ethane-1,2-dione
13h



1-((R)-4-Benzoyl-2-methyl-piperazin-1-yl)-2-[3-methyl-4-(1H-pyrazol-3-yl)-phenyl]-ethane-1,2-dione (55 %) was prepared according to Method G (2h 30 min; TLC-monitoring, CHCl₃/MeOH 9:1), using 1-((R)-4-benzoyl-2-methyl-piperazin-1-yl)-2-(4-bromo-3-methylphenyl)-ethane-1,2-dione (see S24) and pyrazole-2-boronic acid as starting materials. The product was purified by reverse-phase HPLC. LCMS: Calc'd for C₂₄H₂₄N₄O₃ · H⁺: *m/z* = 417.5. Found: *m/z* = 417.1. Purity (ELSD): 100%. Purity (UV): 95% ¹H-NMR (DMSO-d₆): 13.26, 13.16 (br., 1H, NH-pyrazole); 7.87-7.72 (m, 4H); 7.45 (m, 5H); 6.70, 6.61 (m, 1H); 4.88-4.07 (br., 2H); 4.03-3.34 (br., 3H); 3.21-2.82 (br., 2H); 2.59 (s, 3H); 1.21 (br., 3H). Analysis: Calc'd for C₂₄H₂₄N₄O₃ · 0.1 CF₃CO₂H: C, 67.93; H, 5.68; N, 13.09. Found: C, 68.06; H, 5.98; N, 13.01.

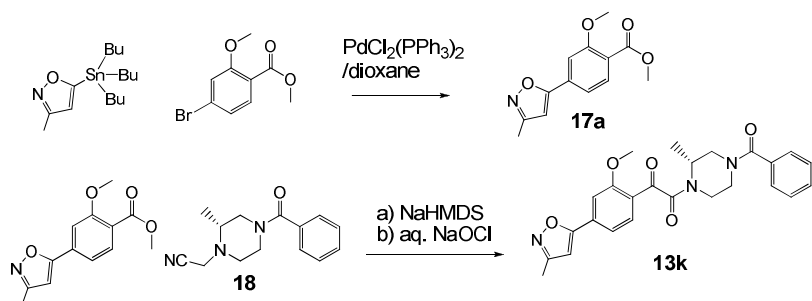
1-((R)-4-Benzoyl-2-methyl-piperazin-1-yl)-2-[3-methoxy-4-(1H-pyrazol-3-yl)-phenyl]-ethane-1,2-dione

13i



This compound was prepared according to Method G using pyrazole-2-boronic acid and ((R)-4-benzoyl-2-methyl-piperazin-1-yl)-2-[3-methoxy-4-bromophenyl]-ethane-1,2-dione as starting materials. LCMS (ESI): Calc'd for $C_{24}H_{24}N_4O_4 \cdot H^+$: 433.2. Found: 433.6 Purity (ELSD): 98%. 1H -NMR ($CDCl_3$): δ 7.85 (d, $J = 8$ Hz, 1H), 7.68 (br., 2H), 7.59 (t, $J = 8$ Hz, 1H), 7.55 – 7.40 (m, 5H), 7.3 – 7.0 (m, 1H), 6.83 (s, 1H), 5.0 – 3.0 (m, 7H), 4.09 (s, 3H), 1.5 – 1.5 (m, 3H). Analysis: Calc'd for $C_{24}H_{24}N_4O_4 \cdot 0.65$ CF_3CO_2H : , 59.84; H, 4.89; N, 11.02. Found: C, 60.12; H, 5.08; N, 10.70. ((R)-4-benzoyl-2-methyl-piperazin-1-yl)-2-[3-methoxy-4-bromophenyl]-ethane-1,2-dione was prepared according D-1 using ((R)-4-Benzoyl-2-methyl-piperazin-1-yl)-acetonitrile¹⁵ **18** and methyl 3-methoxy-4-bromobenzoate as starting materials (yield 35%). LCMS (ESI): Calc'd for $C_{21}H_{21}BrN_2O_4 \cdot H^+$: 445.1. Found: 445.4 Purity (ELSD): 98%.

(R)-1-(4-benzoyl-2-methylpiperazin-1-yl)-2-(2-methoxy-4-(3-methylisoxazol-5-yl)phenyl)ethane-1,2-dione, 13k

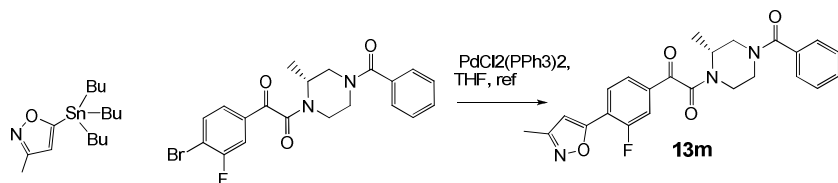


This compound was prepared by Method D-1, using methyl 2-methoxy-4-(3-methylisoxazol-5-yl)benzoate and ((R)-4-benzoyl-2-methyl-piperazin-1-yl)-acetonitrile¹⁵ **18** as starting materials. The product was purified by reverse-phase HPLC. LCMS (ESI): Calc'd for $C_{25}H_{25}N_3O_5 \cdot H^+$: 448.5. Found: 448.1. Purity (ELSD): 99%. 1H -NMR ($CDCl_3$): 7.99 (d, $J = 8$ Hz, 1H), 7.43 (s, 7H), 6.51 (s, 1H), 5.0 – 4.3 (m, 2H), 3.97 (s, 3H), 3.5 – 3.0 (m, 5H), 2.39 (s, 3H), 1.4 – 1.1 (m, 3H). Analysis: Calc'd for $C_{25}H_{25}N_3O_5 \cdot 0.75$ CF_3CO_2H : C, 59.72; H, 4.87; N, 7.88. Found: C, 59.72; H, 4.74; N, 7.86.

The methyl 2-methoxy-4-(3-methylisoxazol-5-yl)benzoate starting material was prepared as follows. A solution of 360 mg methyl 4-bromo-2-methoxybenzoate and 500 mg of 3-methyl-5-(tributylstannyl)isoxazole in 10 mL of dioxane was treated with 50 mg of bis(triphenylphosphine)palladium(II) dichloride. The solution was refluxed for 18 hours. The mixture was filtered and the filtrate was partitioned between ethyl acetate and aqueous sodium chloride solution. The organic phase was dried (MgSO_4) and the solvent was evaporated at reduced pressure. The residue was crystallized from dichloromethane/hexanes to give 0.3 g of a yellow solid (82%). $^1\text{H-NMR}$ (CDCl_3): δ 7.87 (d, J = 8 Hz, 1H), 7.39 (d, J = 1 Hz, 1H), 7.32 (dd, J = 8, 1 Hz, 1H), 6.46 (s, 1H), 3.99 (s, 3H), 3.91 (s, 3H), 2.37 (s, 3H). LCMS: The compound did not ionize. Purity (ELSD): (100%).

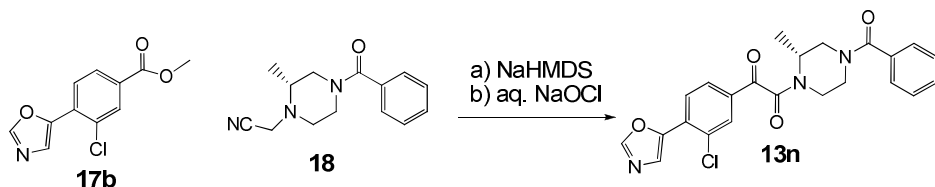
(R)-1-(4-benzoyl-2-methylpiperazin-1-yl)-2-(3-fluoro-4-(3-methylisoxazol-5-yl)phenyl)ethane-1,2-dione

13m



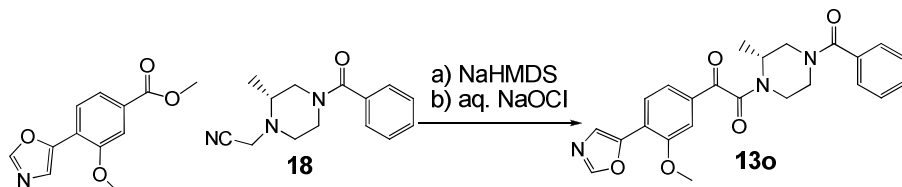
This compound was prepared from *(R)-1-(4-benzoyl-2-methylpiperazin-1-yl)-2-(4-bromo-3-fluorophenyl)ethane-1,2-dione* and 3-methyl-5-(tributylstannyl)isoxazole using Method F. **MS** (ESI): Calc'd for $\text{C}_{24}\text{H}_{22}\text{FN}_3\text{O}_4 \cdot \text{H}^+$: 436.2. Found: 436.4. Purity (ELSD): 100%. $^1\text{H-NMR}$ (CDCl_3): δ 8.11 (t, J = 8 Hz, 1H), 7.9 – 7.7 (m, 2H), 7.6 – 7.4 (m, 5H), 6.73 (d, J = 4 Hz, 1H), 5.0 – 3.0 (m, 7H), 2.40 (s, 3H), 1.4 – 1.2 (m, 3H). *(R)-1-(4-benzoyl-2-methylpiperazin-1-yl)-2-(4-bromo-3-fluorophenyl)ethane-1,2-dione* was in turn prepared using Method D-1 yield 31%, LCMS: Calc'd for $\text{C}_{20}\text{H}_{18}\text{BrFN}_2\text{O}_3 \cdot \text{H}^+$: 433.0. Found: 433.2.

(R)-1-(4-benzoyl-2-methylpiperazin-1-yl)-2-(3-chloro-4-(oxazol-5-yl)phenyl)ethane-1,2-dione, 13n



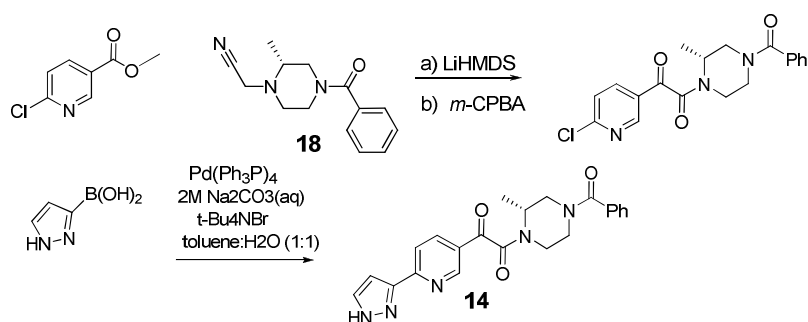
This compound was prepared by Method D-1 using methyl methyl 3-chloro-4-(oxazol-5-yl)benzoate (**17b**) and ((R)-4-Benzoyl-2-methyl-piperazin-1-yl)-acetonitrile¹⁵ **18** as starting materials. LCMS: (Calc'd for C₂₃H₂₀ClN₃O₄ · H⁺: 438.1. Found: 438.5. Purity (ELSD): 100%. ¹H-NMR (CDCl₃): δ 8.2 – 7.8 (m, 5H), 7.5 – 7.3 (s, 5H), 5.0 – 3.0 (m, 7H), 1.5 – 1.3 (m, 3H).

(R)-1-(4-benzoyl-2-methylpiperazin-1-yl)-2-(3-methoxy-4-(oxazol-5-yl)phenyl)ethane-1,2-dione, **13o**



This compound was prepared from methyl 3-methoxy-4-(oxazol-5-yl)benzoate and (R)-2-(4-benzoyl-2-methylpiperazin-1-yl)acetonitrile using Method D-1. **MS** (ESI): Calc'd for C₂₄H₂₃N₃O₅ · H⁺: 434.2 Found: 434.5. Purity (ELSD): 100%. ¹H-NMR (CDCl₃): δ 8.06 (s, 1H), 7.92 (d, *J* = 8 Hz, 1H), 7.78 (s, 1H), 7.7 – 7.5 (m, 2H), 7.42 (s, 5H), 5.0 – 3.0 (m, 7H), 4.06 (s, 3H), 1.5 – 1.2 (m, 3H). Methyl 3-methoxy-4-(oxazol-5-yl)benzoate was in turn prepared from methyl 3-methoxy-4-(bromomethyl)benzoate in close analogy to the procedure used to prepare methyl 4-(oxazol-5-yl)benzoate **MS** (ESI): Calc'd for C₁₂H₁₁NO₄ · H⁺: 234.0 Found: 234.0, Purity (ELSD): 100%. ¹H-NMR (CDCl₃): δ 8.01 (d, 1H), 7.11 (d, 1H), 7.79-7.52 (m, 3H), 4.02 (s, 3H), 3.94(s, 3H).

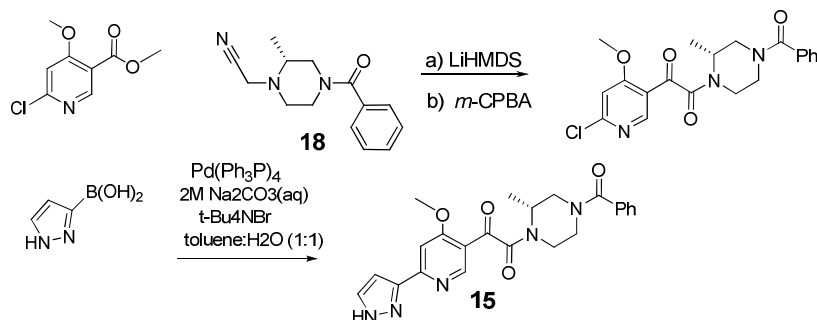
1-((R)-4-Benzoyl-2-methyl-piperazin-1-yl)-2-[6-(1*H*-pyrazol-3-yl)-pyridin-3-yl]-ethane-1,2-dione **14**



This compound was prepared according to Method G using 1-((R)-4-benzoyl-2-methyl-piperazin-1-yl)-2-[6-chloropyridin-3-yl]-ethane-1,2-dione and pyrazole-2-boronic acid as starting materials. LCMS: Calc'd for C₂₂H₂₁N₅O₃ · H⁺: *m/z* = 404.5. Found: *m/z* = 404.0. Purity (ELSD): 100%. Purity (UV): 96% ¹H-NMR (DMSO-*d*₆): 13.83, 13.34 (two broad signals, 1H, NH-pyrazole); 9.03 (m, 1H); 8.30-8.27 (m,

1H); 8.20-8.16 (m, 1H); 7.90 (s, 1H); 7.43.5-7.40(m, 5H); 7.07, 7.97 (two m, 1H); 4.86-4.09 (br., 2H); 4.03-3.37 (br., 3H); 3.22-2.86 (br., 2H); 1.22 (br., 3H). The 1-((R)-4-benzoyl-2-methyl-piperazin-1-yl)-2-[6-chloropyridin-3-yl]-ethane-1,2-dione starting material was prepared in 28% yield according to Method D-2. LCMS: Calc'd for $C_{19}H_{18}ClN_3O_3 \cdot H^+$: $m/z = 372.8$ Found: $m/z = 373.0$.

1-((R)-4-Benzoyl-2-methyl-piperazin-1-yl)-2-[6-(1*H*-pyrazol-3-yl)-4-methoxy-pyridin-3-yl]-ethane-1,2-dione **15**

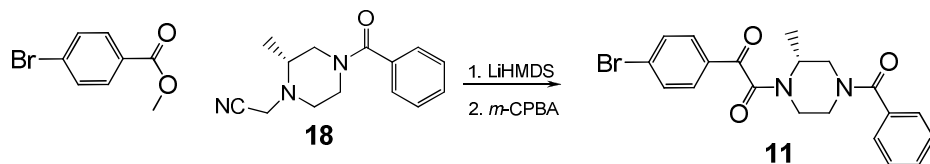


This compound was prepared according to Method G using 1-((R)-4-benzoyl-2-methyl-piperazin-1-yl)-2-[6-chloro-4-methoxypyridin-3-yl]-ethane-1,2-dione and pyrazole-2-boronic acid as starting materials. LCMS: Calc'd for $C_{23}H_{23}N_5O_4 \cdot H^+$: $m/z = 434.2$. Found: $m/z = 434.1$. Purity (ELSD): 100%. Purity (UV): 98% 1H -NMR (DMSO- d_6): 13.70, 13.40 (two broad signals, 1H, NH-pyrazole); 9.10(d, 1H); 8.35 (d, 1H); 8.10-8.06 (m, 1H); 7.86-7.81 (m, 1H); 7.41.5-7.38(m, 5H); 4.80-3.40(m, 5H); 3.89(s, 3H); 3.22-2.86 (br., 2H); 1.21 (br., 3H). The 1-((R)-4-benzoyl-2-methyl-piperazin-1-yl)-2-[6-chloro-4-methoxypyridin-3-yl]-ethane-1,2-dione starting material was prepared in 28% yield according to Method D-2. LCMS: Calc'd for $C_{20}H_{20}ClN_3O_4 \cdot H^+$: $m/z = 402.1$ Found: $m/z = 402.2$.

Preparation of non-commercially available intermediates

4-[2-(4-Benzoyl-2(R)-methyl-piperazin-1-yl)-2-oxo-acetyl]phenylboronic acid **10** (see S4)

1-((R)-4-Benzoyl-2-methyl-piperazin-1-yl)-2-(4-bromo-phenyl)-ethane-1,2-dione **11** (intermediate 12c, d)



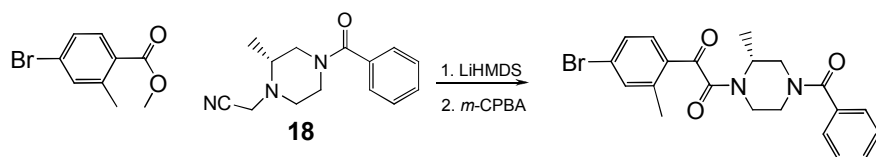
This compound was prepared according to Method D-1, using methyl 4-bromobenzoate and . and ((R)-4-benzoyl-2-methyl-piperazin-1-yl)-acetonitrile¹⁵ **18** as starting materials. 1H -NMR (DMSO- d_6):

7.85 (m, 4H); 7.46-7.42 (m, 5H); 4.88-4.09 (br., 2H); 3.97-3.35 (br., 3H); 3.20-2.77 (br., 2H); 1.18 (br., 3H).

1-(4-Benzoyl-2(R)-methyl-piperazin-1-yl)-2-(4-iodo-phenyl)-ethane-1,2-dione (intermediate for 10, 12o, 12p)(see S4)

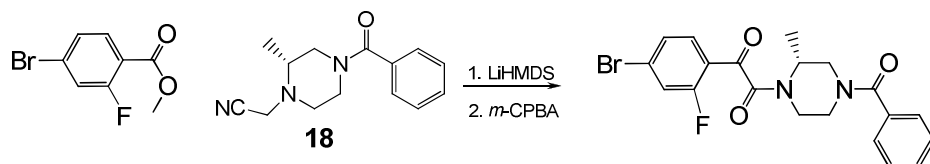
4-(3-Methyl-isoxazol-5-yl)-benzoic acid methyl ester (intermediate for 12m) (see S12).

1-((R)-4-Benzoyl-2-methyl-piperazin-1-yl)-2-(4-bromo-2-methyl-phenyl)-ethane-1,2-dione (intermediate for 13a)



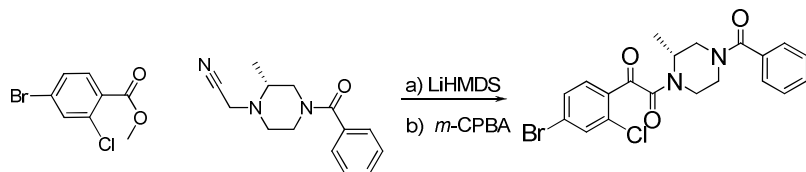
This compound was prepared in 57% yield according to Method D-1, using methyl 2-methyl-4-bromobenzoate and ((R)-4-benzoyl-2-methyl-piperazin-1-yl)-acetonitrile¹⁵ **18** as starting materials. ¹H-NMR (DMSO-d₆): 7.71-7.59 (m, 3H); 7.45 (m, 5H); 4.83-4.09 (br., 2H); 3.93-3.35 (br., 3H); 3.19-2.78 (br., 2H); 2.56 (m, 3H); 1.20 (br., 3H).

1-((R)-4-Benzoyl-2-methyl-piperazin-1-yl)-2-(4-bromo-2-fluoro-phenyl)-ethane-1,2-dione (intermediate 13b)



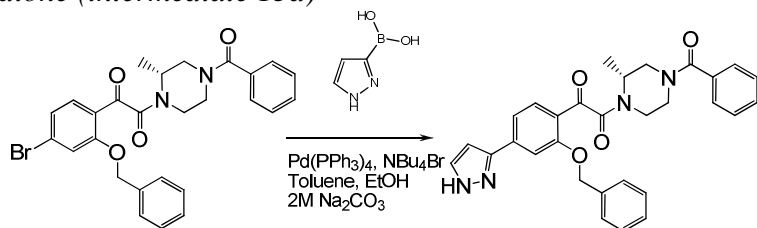
This compound was prepared in 25% yield according to Method D-1, using methyl 2-fluoro-4-bromobenzoate and ((R)-4-benzoyl-2-methyl-piperazin-1-yl)-acetonitrile¹⁵ **18** as starting materials. LCMS: Calc'd for C₂₀H₁₈BrFN₂O₃ · H⁺: 433.1. Found: 433.1. ¹H-NMR (DMSO-d₆): 7.86-7.81 (m, 2H); 7.68 (m, 1H); 7.46-7.42 (m, 5H); 4.74-3.41 (br., 5H); 3.19-2.80 (br., 2H); 1.18 (br., 3H).

1-(4-benzoyl-2(R)-methylpiperazin-1-yl)-2-(4-bromo-2-chloro)ethane-1,2-dione (intermediate for 13c)



1-(4-benzoyl-2(R)-methylpiperazin-1-yl)-2-(4-bromo-2-chloro)ethane-1,2-dione was prepared from methyl 2-chloro-4-bromobenzoate and (R)-2-(4-benzoyl-2-methylpiperazin-1-yl)acetonitrile using Method D-2. The crude product was purified by SiO₂ chromatography using 1% MeOH/ethyl acetate as eluent to obtain 1-(4-benzoyl-2(R)-methylpiperazin-1-yl)-2-(4-bromo-2-chloro)ethane-1,2-dione (47%). LCMS: Calc'd for C₂₀H₁₈BrClN₂O₃ · H⁺: *m/z* = 449.0 Found: *m/z* = 449.1 Purity (ELSD): 100%. Purity (UV, 254 nM): 97%. ¹H-NMR (DMSO-d₆): 7.90-7.81(m, 2H); 7.67 (m, 1H); 7.48-7.40 (m, 5H); 4.77-3.42 (br., 5H); 3.20-2.77 (br., 2H); 1.18 (br., 3H).

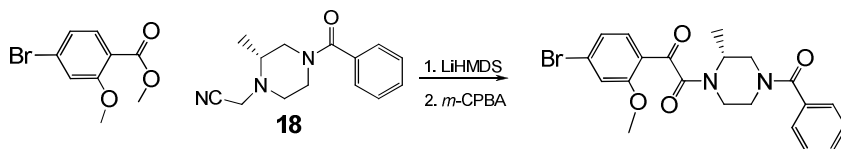
1-((R)-4-Benzoyl-2-methyl-piperazin-1-yl)-2-[2-benzyloxy-4-(1H-pyrazol-3-yl)-phenyl]-ethane-1,2-dione (intermediate 13d)



1-((R)-4-Benzoyl-2-methyl-piperazin-1-yl)-2-[2-benzyloxy-4-(1H-pyrazol-3-yl)-phenyl]-ethane-1,2-dione (49%) was prepared according to Method G, using 1-((R)-4-benzoyl-2-methylpiperazin-1-yl)-2-[2-benzyloxy-4-bromophenyl]-ethane-1,2-dione (see s9, method M) and pyrazole-2-boronic acid as starting materials. The product was purified by silica gel chromatography using EtOAc/n-hexane 4:1 as eluent. LCMS: Calc'd for C₃₀H₂₈N₄O₄ · H⁺: *m/z* = 509.6. Found: *m/z* = 509.7. Purity (ELSD): 100%. Purity (UV): 89%. ¹H-NMR (DMSO-d₆): 13.15 (br., 1H, NH-pyrazole); 7.91-7.33 (m, 13H); 7.05-6.99(m, 1H); 6.89-6.84(m, 1H); 5.35-5.29(m, 2H); 4.48-3.32 (br, 5H); 3.21-2.58 (br, 2H); 0.97 (br, 3H).

(R)-1-(4-benzoyl-2-methylpiperazin-1-yl)-2-(4-bromo-2-methoxyphenyl)ethane-1,2-dione

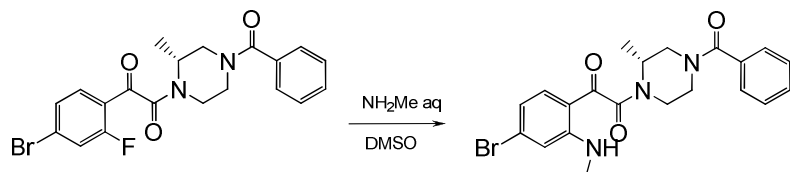
(intermediate for 13e)



This compound was prepared according to Method D-1 using ((R)-4-benzoyl-2-methyl-piperazin-1-yl)-acetonitrile¹⁵ **18** and methyl 2-methoxy-4-bromobenzoate as starting materials. ¹H-NMR (CDCl₃): δ 7.63 (d, *J* = 8 Hz, 1H), 7.28 (s, 5H), 7.10 (d, *J* = 8 Hz, 1H), 7.01 (s, 1H), 4.7 – 2.7 (br. m, 7H), 3.75-3.73 (ds, 3H), 1.3 – 1.0 (m, 3H).

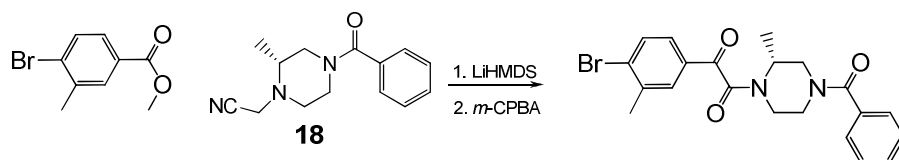
1-(2-Amino-4-bromo-phenyl)-2-((R)-4-benzoyl-2-methyl-piperazin-1-yl)-ethane-1,2-dione(intermediate 13f) (see S9)

1-((R)-4-Benzoyl-2-methyl-piperazin-1-yl)-2-(4-bromo-2-methylamino-phenyl)-ethane-1,2-dione (intermediate for 13g)



1-(2-Methylamino-4-bromo-phenyl)-2-((R)-4-benzoyl-2-methyl-piperazin-1-yl)-ethane-1,2-dione was prepared in 50% yield (0.22 g) by applying procedure L to (2-fluoro-4-bromophenyl)-2-((R)-4-benzoyl-2-methyl-piperazin-1-yl)-ethane-1,2-dione, using 40%-aqueous solution of MeNH₂. LCMS: Calc'd for C₂₁H₂₂BrN₃O₃ · H⁺: *m/z* = 445.0 Found: *m/z* = 445.0

1-((R)-4-Benzoyl-2-methyl-piperazin-1-yl)-2-(4-bromo-3-methyl-phenyl)-ethane-1,2-dione (intermediate for 13h)



This compound was prepared in 49% yield according to Method D-1, using ((R)-4-benzoyl-2-methyl-piperazin-1-yl)-acetonitrile¹⁵ **18** and 3-methyl-4-bromobenzoate as starting materials. ¹H-NMR (DMSO-d₆): 7.86-7.82 (m, 2H); 7.66-7.58 (m, 1H); 7.45 (m, 5H); 4.86-4.01 (br., 2H); 3.98-3.36 (br., 3H); 3.21-2.78 (br., 2H); 2.45 (m, 3H); 1.20 (br., 3H).

((R)-4-Benzoyl-2-methyl-piperazin-1-yl)-2-[3-methoxyl-4-bromophenyl]-ethane-1,2-dione (intermediate 13i)(see S18)

Methyl 2-methoxy-4-(3-methylisoxazol-5-yl)benzoate **17a** (intermediate 13 k) (see S18).

1-(4-Benzoyl-2(R)-methylpiperazin-1-yl)-2-(4-iodo-3-methoxyphenyl)ethane-1,2-dione(intermediate 13l) (see S6)

(R)-1-(4-Benzoyl-2-methylpiperazin-1-yl)-2-(4-bromo-3-fluorophenyl)ethane-1,2-dione (intermediate 13m) (See S19)

Methyl 3-chloro-4-(oxazol-5-yl)benzoate **17b** (intermediate for 13n)(see S8)

Table 1s. Characterization data for parallel synthesis-derived analogs					
No	Calc'd M+H	Found M+H	ELSD Purity	H-NMR (DMSO-d₆)	Method
6a	418.0	418.2	99%		A
12b	417.2	417.1	98%	1.05-1.32(bs, 3H); 2.84-3.24(m, 2H); 3.33-3.83(m,3H); 3.89(s, 3H); 4.17-4.87(m, 2H); 7.35-7.55(m, 5H); 7.76-7.91(m, 4H); 8.02(d, J=2.2, 1H); 8.34(d, J=3.4, 1H)	I
12c	420.1	420.5	100%		F
12d	420.1	420.5	100%		F
12e	419.1	419.1	99%		I
12f	419.1	419.1	94%	1.05-1.36(bs, 3H); 2.84-3.23(m, 2H) & 3.33-3.94(m, 3H); 4.15-4.86(m, 2H); 7.35-7.56(m, 5H); 7.65-7.70(m, 1H); 7.70-7.74(m, 1H); 7.86-8.05(m, 4H); 8.13-8.17(m, 1H)	I
12g	461.2	461.1	98%	1.05-1.36(bs, 3H); 2.63(s, 3H); 2.84-3.23(m, 2H); 3.33-3.94(m, 3H); 4.15-4.86(m, 2H); 7.35-7.56(m, 5H); 7.91-8.03(m, 2H); 8.06(bd, J = 8.3, 2H); 8.52(br, 1H); 8.55(br, 1H)	I
12h	458.2	458.1	98%		I
12i	461.2	461.1	100%	1.04-1.37(br, 3H); 2.84-3.24(m, 2H); 3.33-3.93(m, 3H); 4.17-4.87(m, 2H); 7.33-7.57(m, 5H); 7.84-7.88(m, 1H); 7.91-8.10(m, 5H)	I
12j	432.2	432.1	100%		I
12k	414.1	414.1	100%	1.03-1.40(br, 3H); 2.84-3.95(m,5H); 4.11-4.50(br, 2H); 7.32-7.55(m, 5H); 7.94-8.00(m, 2H); 8.01-8.12(m, 4H); 8.80(d, J = 6.1, 2H)	I

Antiviral Assay.

Pseudotyped viruses are generated by cotransfection of the pNL4-3.luc.R-E- luciferase reporter vector and either an expression vector containing the M33 HIV-1 envelope clone or an expression vector containing the AMLV envelope. Transfections are performed with Polyfect reagent (Qiagen, Inc.) on

293T cells using the standard Polyfect protocol and a 1:3 (w/w) ratio of backbone to envelope plasmids. Following a 48 hour incubation at 37°C and 5% CO₂, virus stocks are harvested, brought to 30% FBS, aliquoted, and stored at -80°C until use. Virus aliquots are discarded after a single use.

Antiviral assays are performed using U87.CD4.CCR5 cells. Cells are seeded at 7.5x10³ cells/well in a flat-bottom 96-well plate with opaque white walls 24 hours prior to the assay. Compound stocks of 10, 20, or 40mM in DMSO are aliquoted to minimize freeze-thaw cycles and stored at -80°C until use. At the time of the assay, Compounds are diluted to 2x the starting concentration of 20 μM in complete media and serially diluted 2 fold. Virus and drug are added to cells at a 1:1 ratio and incubated for 72 hours at 37°C and 5% CO₂. After incubation, cells are washed 2x with warm PBS and lysed with 1x CCLR reagent (Promega, Madison, WI). Luciferase is measured on a luminometer (PerkinElmer, Wellesley, MA) using a luciferase substrate kit (Promega, Madison, WI). IC₅₀s are determined by comparing luciferase output in the presence of drug to an infected drug-free control using Assay Explorer software (Elsevier MDL, San Ramon, CA)

Cytotoxicity.

U87.CD4.CXCR4 cells (obtained through the NIH AIDS Research and Reference Reagent Program, Division of AIDS, NIAID, NIH; U87.CD4.CxCR4 from Dr. HongKui Deng and Dr. Dan R. Littman) are seeded in a 96well flat-bottom plate at 7.5x10³ cells per well. Compounds are diluted to 40uM in complete medium and diluted 2 fold. Compound dilutions are added to cells, and then incubated for 72hrs. Following incubation, the cells are inspected and scored visually for toxicity. CellTiter-Blue (Promega, Madison, WI) is added to cells. After a 2 hour incubation at 37°C and 5% CO₂, cell viability is quantified by measuring the reduction of the Resazurin substrate to a fluorescent Resorufin product on a fluorometer (PerkinElmer, Wellesley, MA). CC₅₀s are determined by comparison of drug-treated wells with a drug-free control using Assay Explorer software (Elsevier MDL, San Ramon, CA).

ELISA Assay

Ninety-six well microtiter plates were coated with 100 µl/well of 5.0 µg/ml D7324 antibody (Cliniqa, Fallbrook, CA) in 0.05 M Carbonate – Bicarbonate buffer, pH 9.6 and incubated overnight at 4 °C. After equilibration to room temperature, coating solutions were removed by plate inversion and the plates were blocked with 200 µl/well Blocking Buffer (Tris Buffered Saline + 1.0% BSA) for 1 hour at room temperature. Blocking Buffer was removed by plate inversion and 100 µl/well of 0.1 µg/ml IIIB gp120 (Advanced Bioscience Laboratories, Kensington, MD) in Assay Diluent (Tris Buffered Saline + Tween 20, pH 8.0 + 0.1% BSA) was added to the plates. The contents of the plates were mixed on a shaker for approximately 5 minutes at room temperature and subsequently incubated for 1 hour at 37 °C. The plates were then washed three times with Wash Buffer (Tris Buffered Saline + Tween 20, pH 8.0). Test compounds were prepared at a maximum concentration of 80 µM in Assay Diluent and added to the plates at a volume of 50 µl/well in either a titration series or a single dilution. Immediately following the addition of the test compounds, 50 µl/well of 0.1 µg/ml soluble CD4 (ImmunoDiagnostics, Woburn, MA) in Assay Diluent was added to the plates. Plates were again placed on a shaker for approximately 5 minutes at room temperature and then incubated for 1 hour at 37 °C. After incubation, the plates were washed three times with Wash Buffer and 100 µl/well of 0.25 µg/ml OKT4 antibody (eBioscience, San Diego, CA) in Assay Diluent was added. The plates were placed on a shaker for approximately 5 minutes at room temperature and then incubated for 1 hour at 37 °C. After incubation, the plates were washed three times with Wash Buffer followed by the addition of 100 µl/well of 0.25 µg/ml peroxidase-labeled goat anti-Mouse IgG (H+L) antibody. After shaking at room temperature for approximately 5 minutes, plates were again incubated for 1 hour at 37 °C. Finally, the plates were washed three times with Wash Buffer and developed by adding 100 µl of TMB (3,3',5,5'-tetramethylbenzidine peroxidase substrate). After 10-20 minutes, the substrate reactions were stopped by adding 100 µl of 1N sulfuric acid (H₂SO₄). Absorbance values were measured by reading the optical density at 450 nm on a microtiter plate reader. IC₅₀ and % Inhibition values for test compounds were calculated using Assay Explorer software (Elsevier MDL, San Ramon, CA).
