Supplementary Material

Highlights of the Structure Activity Relationships of Benzimidazole Linked Pyrrolidines Leading to the Discovery of Pibrentasvir/ABT-530.

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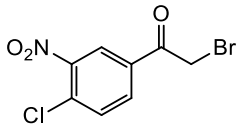
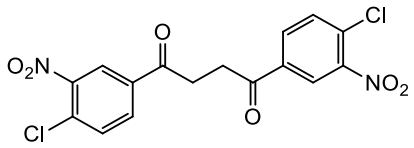
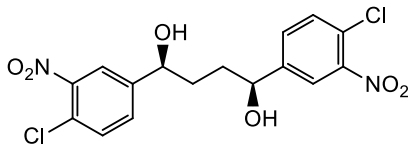


2-Bromo-1-(4-chloro-3-nitrophenyl)ethanone (2a). To a suspension of 1-(4-chloro-3-nitrophenyl)ethanone (**1a**, 12.0 g, 60 mmol) in benzene (75 mL) was added bromine (9.6 g, 60 mmol), drop-wise over 5 min. The resulting mixture was stirred at rt for 1 h to give a yellow solution, which was concentrated under vacuum to give a yellow solid. The solid was recrystallized from 9:1 hexanes:ethyl acetate to give **2a** as yellow needles (13.1 g, 78%).

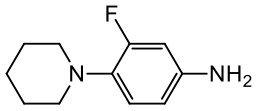


1,4-Bis(4-chloro-3-nitrophenyl)butane-1,4-dione (3a). A mixture of zinc chloride (9.79 g, 71.8 mmol), t-butanol (5.15 mL, 53.9 mmol) and diethylamine (5.60 mL, 53.9 mmol) in benzene (54 mmol) was stirred at rt for 1 h. Compound **2a** (10.0 g, 35.9 mmol) and **1a** (10.75 g, 53.9 mmol) were added, and the mixture was stirred at rt for 16 h. Dichloromethane (50 mL) and water (50 mL) were added, and the resulting solid was collected by filtration and washed successively with water, dichloromethane, ethyl acetate, and methanol. The solid was dried under vacuum to give **3a** (14.3 g, 100%): ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.62 (d, J = 2.0 Hz, 2H), 8.28 (dd, J = 8.4, 2.1 Hz, 2H), 7.97 (d, J = 8.4 Hz, 2H), 3.49 (s, 4H).

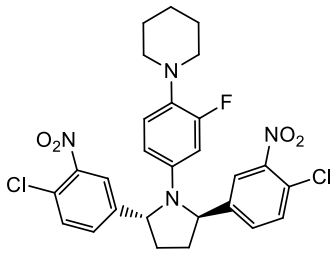


(1*S*,4*S*)-1,4-Bis(4-chloro-3-nitrophenyl)butane-1,4-diol (A). A solution of (*R*)-(+)-α,α-diphenyl-2-pyrrolidinemethanol (1.084 g, 4.28 mmol) and trimethyl borate (0.618 mL, 5.54 mmol) in anhydrous THF (50 mL) was stirred at rt for 1 h and then cooled in an ice bath. *N*,*N*-Diethylaniline borane (9.18 mL, 51.6 mmol) was added, and the mixture was stirred at <10 °C for 20 min. The cooled solution was added drop-wise to an ice bath cooled suspension of **3a** (10.0 g, 25.2 mmol) in anhydrous THF (220 mL). The cooling bath was removed, and the mixture was allowed to warm to rt and stirred for 4 h. The resulting solution was cooled in an ice-bath, and methanol (30 mL) was added dropwise. The mixture was filtered, and the filtrate was concentrated under vacuum. The crude product was dissolved in ethyl acetate and washed

with 1N aq HCl. The organic layer was dried over Na_2SO_4, filtered and concentrated under vacuum to give **A** as a yellowish solid (9.48 g, 94%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 (d, J = 2.0 Hz, 2H), 7.68 (d, J = 8.3 Hz, 2H), 7.59 (dd, J = 8.4, 2.0 Hz, 2H), 5.53 (d, J = 4.6 Hz, 2H), 4.69 – 4.58 (m, 2H), 1.70 – 1.50 (m, 4H).

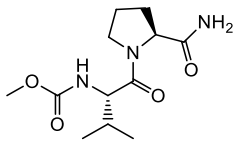


3-Fluoro-4-(piperidin-1-yl)aniline (B). To a solution of 1,2-difluoro-4-nitrobenzene (3.47 g, 21.8 mmol) in anhydrous acetonitrile (20 mL) was added piperidine (11 mL, 111 mmol), and the resulting solution was stirred at rt for 16 h. The mixture was partitioned between water and ethyl acetate, and the organic layer was washed with 1N aq HCl and brine, and dried over $MgSO_4$. The drying agent was filtered off, and the solution was concentrated and dried *in vacuo* to give a yellow oil (5.0 g). The oil was dissolved in methanol (50 mL) and THF (10 mL) in a 250 mL pressure bottle, and Raney-Ni (slurry in water, 5.06 g, 86 mmol) was added. The mixture was stirred at 30 psi H_2 for 2 h, and then filtered and concentrated under vacuum to give **B** as an oil (3.95 g, 90%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.72 (dd, J = 10.0, 8.2 Hz, 1H), 6.33 – 6.21 (m, 2H), 4.93 (s, 2H), 2.78 – 2.68 (m, 4H), 1.61 – 1.51 (m, 4H), 1.47 – 1.37 (m, 2H).



1-(4-((2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2-fluorophenyl)piperidine (C). A suspension of **A** (1.0 g, 2.49 mmol) in anhydrous dichloromethane (30 mL) was cooled in an ice bath, and triethylamine (1.042 mL, 7.48 mmol) was added dropwise, resulting in a solution. Methanesulfonyl chloride (4.24 mL, 54.4 mmol) was added dropwise, and the resulting

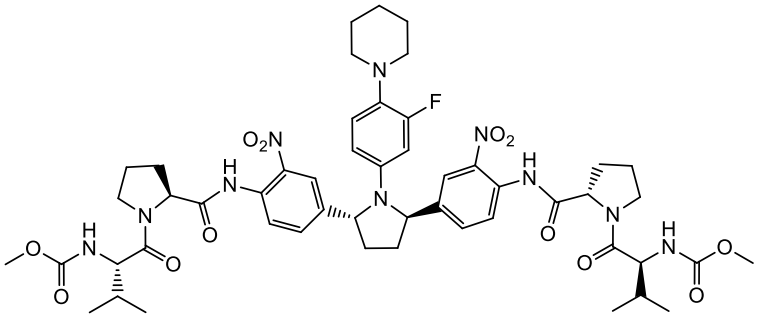
mixture was allowed to warm to rt and stirred for 2 h. The solution was concentrated under vacuum to give a solid. The solid was dissolved in anhydrous DMF (20 mL), and **B** (1.937 g, 9.97 mmol) was added. The resulting mixture was stirred at 65 ^{o}C for 16 h. The mixture was cooled to rt and partitioned between ethyl acetate and water. The organic layer was dried over Na_2SO_4, filtered and concentrated under vacuum. The crude product was purified by column chromatography on silica gel using a solvent gradient of 0-80% dichloromethane in hexanes to give **C** (0.34 g, 24%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (d, *J* = 2.1 Hz, 2H), 7.70 (d, *J* = 8.3 Hz, 2H), 7.47 (dd, *J* = 8.4, 2.1 Hz, 2H), 6.73 (dd, *J* = 10.1, 8.8 Hz, 1H), 6.09 (dd, *J* = 15.1, 2.7 Hz, 1H), 6.01 (dd, *J* = 8.8, 2.8 Hz, 1H), 5.39 (d, *J* = 7.0 Hz, 2H), 2.74 – 2.63 (m, 4H), 2.53 – 2.39 (m, 2H), 1.79 – 1.66 (m, 2H), 1.56 – 1.48 (m, 4H), 1.43 – 1.35 (m, 2H); MS (ESI) *m/z* 559.2 $[M+H]^+$.



Methyl ((*S*)-1-((*S*)-2-carbamoylpyrrolidin-1-yl)-3-methyl-1-oxobutan-2-yl)carbamate (D).

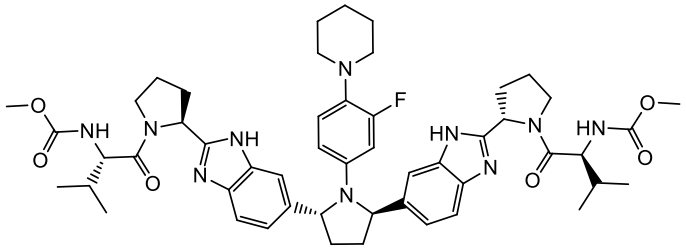
To a solution of (*S*)-2-amino-3-methylbutanoic acid (57 g, 487 mmol) in 1,4-dioxane (277 mL) was added a 2 N aq NaOH solution (803 mL, 1606 mmoll), followed by the dropwise addition of methyl chloroformate (75 mL, 973 mmol). The resulting mixture was heated at 60 °C while stirring for 22 h. The mixture was cooled to rt and extracted with dichloromethane (400 mL). The aq layer was cooled in an ice bath, and conc. aq HCl was added dropwise to adjust to pH = 2. The mixture was stirred at 0 °C for 2 hours, and the resulting solid was collected by filtration, and dried under vacuum to give a colorless solid (80g, 94%). A portion of this solid (29.1 g, 166 mmol), (*S*)-pyrrolidine-2-carboxamide hydrochloride (21.6 g, 144 mmol), HOBT (27.6 g, 180 mmol), EDCI (34.6 g, 180 mmol) and 4-methylmorpholine (63.5 mL, 578 mmol) in

dichloromethane (960 mL) was stirred at rt for 18 h. The mixture was concentrated under vacuum, and the residue was partitioned between water and 3:1 dichloromethane:isopropanol. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum to give a crude product that was purified by column chromatography on silica gel using a solvent gradient of 0-10% methanol in dichloromethane to provide **D** as a colorless solid (25 g, 64%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.30 – 7.18 (m, 2H), 6.80 (s, 1H), 4.21 (dd, J = 8.2, 4.4 Hz, 1H), 3.98 (t, J = 8.4 Hz, 1H), 3.74 – 3.64 (m, 1H), 3.59 – 3.50 (m, 1H), 3.49 (s, 3H), 2.05 – 1.70 (m, 4H), 0.92 – 0.78 (m, 7H).



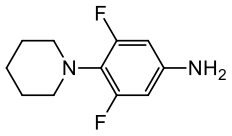
Dimethyl ((2*S*,2'*S*)-((2*S*,2'*S*)-2,2'-(((((2*R*,5*R*)-1-(3-fluoro-4-(piperidin-1-yl)phenyl)-pyrrolidine-2,5-diyl)bis(2-nitro-4,1-phenylene))bis(azanediyl))bis(carbonyl))-bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl))dicarbamate (E). A mixture of **C** (338 mg, 0.604 mmol), **D** (361 mg, 1.329 mmol), Cs_2CO_3 (551 mg, 1.692 mmol), Xantphos (62.9 mg, 0.109 mmol) and 1,4-dioxane (3.0 mL) was de-gassed by bubbling with N_2 for 30 min. Tris(dibenzylidineacetone)dipalladium(0) (33.2 mg, 0.036 mmol) was added, and the mixture was bubbled with N_2 for 10 min more. The reaction tube was sealed, and the mixture was stirred while heating at 100 ^{o}C for 16 h and then allowed to cool to rt. The mixture was diluted with ethyl acetate, washed with 1N aq HCl and brine, and dried over Na_2SO_4. The drying agent was filtered off, and the solvent was removed under vacuum to give a crude product that was purified by column chromatography on silica gel using a solvent gradient of 0-3% methanol in

dichloromethane to give **E** (396 mg, 64 %): ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.43 – 10.31 (m, 2H), 7.81 – 7.72 (m, 2H), 7.61 – 7.43 (m, 4H), 7.29 (d, *J* = 8.4 Hz, 2H), 6.77 – 6.67 (m, 1H), 6.13 – 5.97 (m, 2H), 5.41 – 5.29 (m, 2H), 4.51 – 4.42 (m, 2H), 4.05 – 3.93 (m, 2H), 3.81 – 3.69 (m, 2H), 3.64 – 3.53 (m, 2H), 3.50 (s, 6H), 2.75 – 2.38 (m, 6H), 2.18 – 2.03 (m, 2H), 2.00 – 1.79 (m, 8H), 1.78 – 1.62 (m, 2H), 1.57 – 1.43 (m, 4H), 1.43 – 1.31 (m, 2H), 0.90 – 0.74 (m, 12H); MS (ESI) *m/z* 1029.5 $[M+H]^+$.

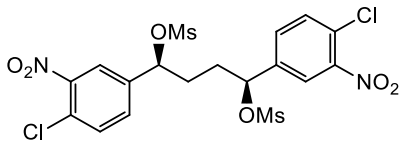


Dimethyl ((2*S*,2'*S*)-((2*S*,2'*S*)-2,2'-(6,6'-((2*R*,5*R*)-1-(3-fluoro-4-(piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(1H-benzo[d]imidazole-6,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl))dicarbamate (28). To a solution of **E** (394 mg, 0.383 mmol) in ethanol (2.0 mL) and THF (2.0 mL) was added PtO_2 (21.7 mg, 0.096 mmol) and the mixture was stirred at rt under 1 atm H_2 for 16 h. The mixture was filtered through Celite, and the solvent was removed under vacuum. To the residue was added toluene (3.0 mL) and acetic acid (0.22 mL, 3.83 mmol), and the mixture was stirred while heating at 50 ^{o}C for 16 h. The mixture was allowed to cool to rt and diluted with ethyl acetate, washed with 1N aq HCl and brine, and dried over Na_2SO_4. The drying agent was filtered off, and the solvent was removed under vacuum to give a crude product that was purified by column chromatography on silica gel using a solvent gradient of 0-5% methanol in dichloromethane to give **28** (0.21 g, 59%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.09 – 11.93 (m, 2H), 7.43 (d, *J* = 8.3 Hz, 1H), 7.36 (dd, *J* = 8.2, 2.7 Hz, 1H), 7.30 – 7.23 (m, 3H), 7.17 (s, 1H), 7.10 – 6.98 (m, 2H), 6.67 – 6.56 (m, 1H), 6.08 – 5.98 (m, 2H), 5.37 – 5.26 (m, 2H), 5.11 (t, *J* = 8.4 Hz, 2H), 4.08 – 3.95 (m, 2H), 3.87 – 3.72 (m,

4H), 3.51 (s, 6H), 2.66 – 2.57 (m, 4H), 2.24 – 2.08 (m, 4H), 2.03 – 1.81 (m, 6H), 1.70 – 1.61 (m, 2H), 1.52 – 1.43 (m, 4H), 1.40 – 1.29 (m, 2H), 0.89 – 0.73 (m, 12H); MS (ESI) *m/z* 933.5 $[M+H]^+$.

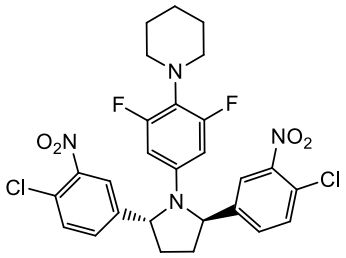


3,5-Difluoro-4-(piperidin-1-yl)aniline (F). To a solution of 3,4,5-trifluoronitrobenzene (3.50 mL, 30 mmol) in anhydrous DMSO (30 mL) was added piperidine (5.94 mL, 60 mmol) and K_2HPO_4 (10.45 g, 60.0 mmol). The resulting yellow suspension was stirred while heating at 60º for 16 h. The mixture was allowed to cool to rt, diluted with ethyl acetate, and washed with water and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under vacuum to give a yellow oil. The oil was mixed with NH_4Cl (2.407 g, 45.0 mmol) in ethanol (60 mL), THF (60 mL), and water (20 mL). Iron powder (8.38 g, 150 mmol) was added, and the mixture was stirred vigorously while heating at 90 ºC for 3 h. The mixture was filtered through Celite, and the filtrate was concentrated under vacuum. The crude product was dissolved in ethyl acetate, washed with water and brine, and dried over Na_2SO_4. The drying agent was filtered off, and the filtrate was concentrated under vacuum to give a crude product that was purified by column chromatography on silica gel using a solvent gradient of 0-40% ethyl acetate in hexanes to give **F** (3.94 g, 62%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.13 – 6.03 (m, 2H), 5.36 (s, 2H), 2.84 (t, *J* = 5.2 Hz, 4H), 1.52 (p, *J* = 5.4 Hz, 4H), 1.47 – 1.38 (m, 2H).



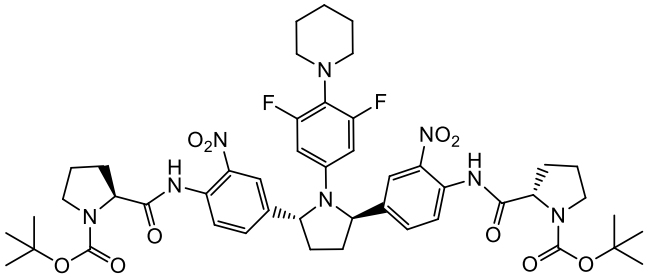
(1*S*,4*S*)-1,4-Bis(4-chloro-3-nitrophenyl)butane-1,4-diyl dimethanesulfonate (4a). A suspension of **A** (10.0 g, 24.93 mmol) in anhydrous dichloromethane (190 mL) was stirred while

cooling in an ice bath. Triethylamine (10.4 mL, 74.8 mmol) was slowly added, and stirring was continued for 15 min before a solution of methanesulfonyl chloride (4.25 mL, 54.8 mmol) in anhydrous dichloromethane (10 mL) was added dropwise. Once the addition was complete, the mixture was allowed to slowly warm to rt and stirred for 3 h, during which time a colorless precipitate formed. Water (300 mL) was added, and the mixture was stirred for 20 min. The solid product was collected by filtration and washed with dichloromethane, followed by ether. The solid was dried under vacuum to give **4a** (10.71 g, 77%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (d, J = 2.1 Hz, 2H), 7.80 (d, J = 8.4 Hz, 2H), 7.72 (dd, J = 8.4, 2.1 Hz, 2H), 5.77 (dd, J = 7.5, 4.4 Hz, 2H), 3.29 (s, 6H), 2.11 – 1.78 (m, 4H).

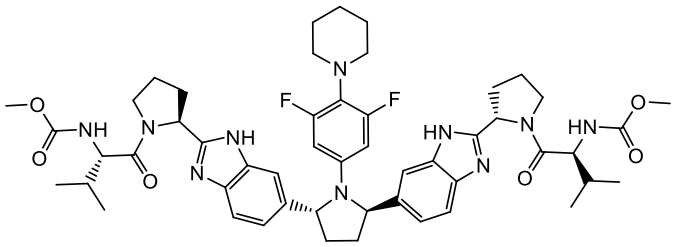


1-(4-((2*R*,5*R*)-2,5-Bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)piperidine (G). To a solution of **F** (3.94 g, 18.56 mmol), and **4a** (3.0 g, 5.38 mmol) in anhydrous DMF (10.8 mL) was added Hunig's Base (3.5 mL, 20.04 mmol), and the resulting solution was stirred under N_2 while heating at 65 ºC for 4 h. The mixture was allowed to cool to rt and was partitioned between ethyl acetate and 1N aq. HCl, and the organic layer was washed with water and brine and dried over Na_2SO_4. The drying agent was filtered off, and the filtrate was concentrated under vacuum to give a crude product that was purified by column chromatography on silica gel using a solvent gradient of 5-40% ethyl acetate in hexanes to give **G** as a yellowish, waxy solid (1.90 g, 61%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 (d, J = 2.1 Hz, 2H), 7.72 (d, J = 8.3 Hz, 2H), 7.47 (dd, J = 8.4, 2.2 Hz, 2H), 5.93 (d, J = 11.9 Hz, 2H), 5.41 (d, J = 7.0 Hz, 2H),

2.82 – 2.76 (m, 4H), 2.45 – 2.38 (m, 2H), 1.78 – 1.68 (m, 2H), 1.55 – 1.34 (m, 6H); MS (ESI) *m/z* 577.2 $[M+H]^+$.

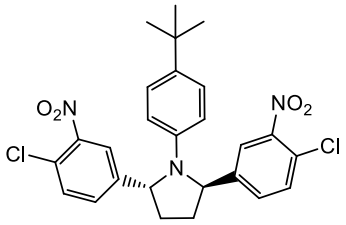


(*2S*,2'*S*)-Di-*tert*-butyl 2,2'-(((((2*R*,5*R*)-1-(3,5-difluoro-4-(piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-nitro-4,1-phenylene))bis(azanediyl))bis(carbonyl))bis(pyrrolidine-1-carboxylate) (H). A mixture of **G** (0.60 g, 1.04 mmol), (*S*)-*tert*-butyl 2-carbamoylpyrrolidine-1-carboxylate (0.579 g, 2.70 mmol), Cs_2CO_3 (1.016 g, 3.12 mmol), tris(dibenzylidineacetone)dipalladium(0) (0.057 g, 0.062 mmol), and Xantphos (0.090 g, 0.156 mmol) in 1,4-dioxane (11.5 mL) was degassed by bubbling with N_2 for 15 min. The reaction container was sealed and the mixture was stirred while being heated at 100 ºC for 1 h. The mixture was cooled to rt and diluted into ethyl acetate, and the solution was washed with water and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under vacuum, and the crude product was purified by column chromatography on silica gel using a solvent gradient of 15-70% ethyl acetate in hexanes to give **H** (0.75 g, 77%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.43 – 10.29 (m, 2H), 7.90 – 7.75 (m, 2H), 7.63 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 7.7 Hz, 2H), 5.94 (d, *J* = 12.1 Hz, 2H), 5.38 (d, *J* = 6.8 Hz, 2H), 4.29 – 4.19 (m, 2H), 3.44 – 3.29 (m, 4H), 2.79 (t, *J* = 5.0 Hz, 4H), 2.50 – 2.39 (m, 2H), 2.25 – 2.08 (m, 2H), 1.95 – 1.65 (m, 8H), 1.51 – 1.24 (m, 24H); MS (ESI) *m/z* 933.2 $[M+H]^+$.

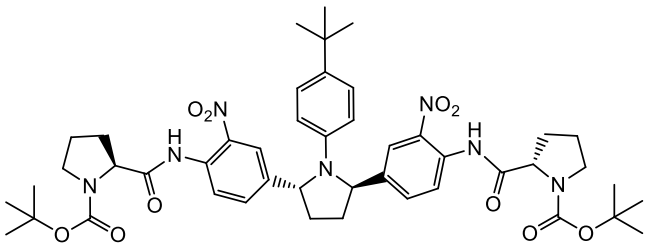


Dimethyl ((2*S*,2'*S*)-((2*S*,2'*S*)-2,2'-(6,6'-((2*R*,5*R*)-1-(3,5-difluoro-4-(piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(1H-benzo[d]imidazole-6,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl))dicarbamate (29). To a solution of intermediate **H** (0.75 g, 0.804 mmol) in THF (20 mL) was added PtO_2 (0.150 g, 0.661 mmol), and the mixture was stirred under H_2 at 30 psi for 1 h. The mixture was filtered, and the filtrate was concentrated under vacuum. To the resulting solid was added toluene (14 mL) and acetic acid (0.825 g, 13.75 mmol), and the mixture was stirred while heating at 70 ºC for 1 h. The solution was concentrated under vacuum and the residue was azeotroped with toluene (2x) and dried under vacuum to give an orange solid. The solid was dissolved in 1,4-dioxane (10 mL), and 4N HCl in 1,4-dioxane (8 mL) was added. The mixture was stirred at rt for 2 h and concentrated under vacuum. To the residue was added (*S*)-2-(methoxycarbonylamino)-3-methylbutanoic acid (0.228 g, 1.304 mmol) and HOBT (0.238 g, 1.553 mmol), and the mixture was dissolved in anhydrous DMF (12.42 mL). To the resulting solution was added *N*-methylmorpholine (0.683 mL, 6.21 mmol) and EDCI (0.298 g, 1.553 mmol), and the resulting mixture was stirred at rt for 2 h. The mixture was partitioned between ethyl acetate and saturated aq $NaHCO_3$, and the organic layer was washed with water and brine and dried over Na_2SO_4. The mixture was filtered, the filtrate was concentrated under vacuum, and the crude product was purified by column chromatography on silica gel using a solvent gradient of 2-6% methanol in dichloromethane to give **29** (0.50 g, 61%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.12 – 11.93 (m, 2H), 7.46 (d, J = 8.3 Hz, 1H), 7.38 (d, J = 8.2 Hz, 1H), 7.29 – 7.22 (m, 3H), 7.19 – 7.15 (m, 1H), 7.08 – 7.01 (m, 2H), 5.91 – 5.80

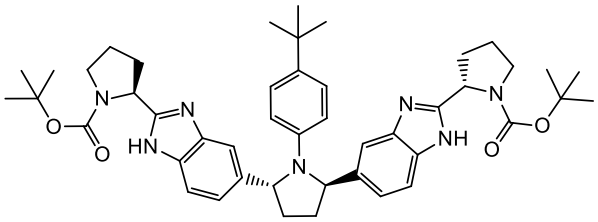
(m, 2H), 5.40 – 5.27 (m, 2H), 5.15 – 5.08 (m, 2H), 4.09 – 3.96 (m, 2H), 3.86 – 3.72 (m, 4H), 3.51 (s, 6H), 2.79 – 2.67 (m, 4H), 2.56 – 2.49 (m, 2H), 2.25 – 2.09 (m, 4H), 2.05 – 1.79 (m, 6H), 1.71 – 1.59 (m, 2H), 1.48 – 1.30 (m, 6H), 0.88 – 0.71 (m, 12H); MS (ESI) *m/z* 951.5 $[M+H]^+$.



(2*R*,5*R*)-1-(4-(*tert*-Butyl)phenyl)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidine (I). A solution of **A** (9.99 g, 24.9 mmol) and triethylamine (8.68 mL, 62.3 mmol) in anhydrous dichloromethane (200 mL) was cooled to -20 °C. A solution of methanesulfonyl chloride (4.27 mL, 54.8 mmol) in anhydrous dichloromethane (5 mL) was added dropwise. After the addition was complete, the mixture was allowed to slowly warm to rt, stirred for 1 h, and then concentrated under vacuum. Anhydrous DMF (20 mL) was added, followed by 4-*tert*-butylaniline (29.7 g, 199 mmol), and the resulting mixture was stirred for 90 min while heating at 65 °C. The mixture was cooled to rt, 1N aq HCl (500 mL) was added, and the solid product was collected by filtration. The crude product was purified by column chromatography on silica gel using with a solvent gradient of 0-30% ethyl acetate in hexanes to give **I** (7.39 g, 58%), which was contaminated with ~10% of the cis-pyrrolidine isomer by NMR analysis: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (d, *J* = 2.1 Hz, 2H), 7.69 (d, *J* = 8.3 Hz, 2H), 7.46 (dd, *J* = 8.4, 2.1 Hz, 2H), 7.03 – 6.97 (m, 2H), 6.23 – 6.17 (m, 2H), 5.39 (d, *J* = 7.1 Hz, 2H), 2.47 – 2.36 (m, 2H), 1.77 – 1.65 (m, 2H), 1.10 (s, 9H).

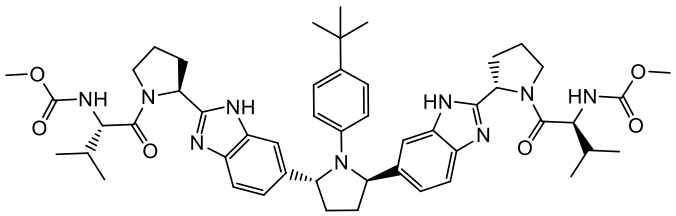


(2*S*,2'*S*)-Di-*tert*-butyl 2,2'-(((((2*R*,5*R*)-1-(4-(*tert*-butyl)phenyl)pyrrolidine-2,5-diyl)bis(2-nitro-4,1-phenylene))bis(azanediyl))bis(carbonyl))bis(pyrrolidine-1-carboxylate) (J). Using the method described for making **H**, compound **I** (2.00 g, 3.89 mmol) was converted to **J** (2.55 g, 75%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.42 – 10.24 (m, 2H), 7.86 – 7.72 (m, 3H), 7.61 – 7.48 (m, 3H), 7.01 – 6.96 (m, 2H), 6.23 (d, *J* = 8.5 Hz, 2H), 5.37 (d, *J* = 6.2 Hz, 2H), 4.22 (q, J = 7.0, 3.8 Hz, 2H), 3.44 – 3.28 (m, 4H), 2.25 – 2.07 (m, 2H), 1.94 – 1.63 (m, 10H), 1.40 – 1.25 (m, 18H), 1.09 (s, 9H); MS (ESI) *m/z* 870.4 $[M+H]^+$.

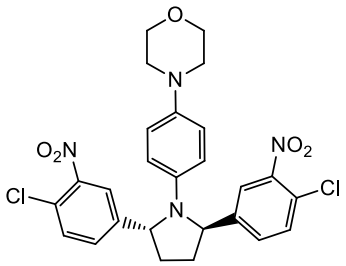


(2*S*,2'*S*)-Di-tert-butyl 2,2'-(5,5'-((2*R*,5*R*)-1-(4-(tert-butyl)phenyl)pyrrolidine-2,5-diyl)bis(1H-benzo[d]imidazole-5,2-diyl))bis(pyrrolidine-1-carboxylate) (K). To a solution of **J** (2.35 g, 2.70 mmol) in ethanol (12 mL) and THF (12 mL) was added PtO_2 (0.184 g, 0.81 mmol), and the mixture was stirred at rt under 1 atm H_2 for 5 h. The mixture was filtered and the filtrate was concentrated under vacuum. The crude product was purified by column chromatography on silica gel using a solvent gradient of 0-5% methanol in dichloromethane to give the diamine intermediate (1.86 g, 85%). This compound was stirred at 60 ºC in acetic acid (5 mL) for 1 h and concentrated under vacuum. Water was added to the residue, and $NaHCO_3$ was added to neutralize the mixture, which was extracted with dichloromethane (3X). The combined organic extract was dried over Na_2SO_4, filtered and concentrated under vacuum, and the crude product was purified by column chromatography on silica gel using a solvent gradient of 0-5% methanol to give **K** (0.84 g, 47%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.17 – 11.97 (m, 2H), 7.47 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.36 (d, *J* = 8.3 Hz, 1H), 7.27 (s, 1H), 7.14 (d, *J* = 10.5 Hz,

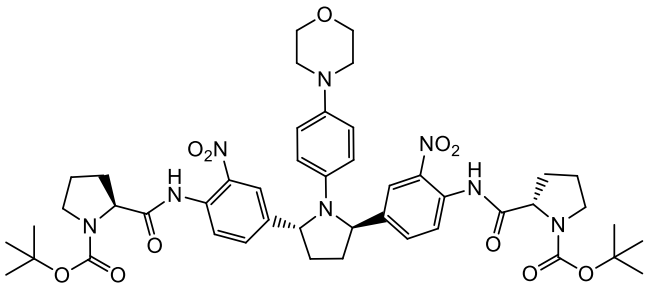
1H), 7.10 – 7.03 (m, 2H), 6.91 – 6.81 (m, 2H), 6.26 – 6.17 (m, 2H), 5.33 (q, *J* = 7.3 Hz, 2H), 4.94 – 4.80 (m, 2H), 3.59 – 3.48 (m, 2H), 3.40 – 3.31 (m, 2H), 2.53 – 2.41 (m, 2H), 2.34 – 2.13 (m, 2H), 2.05 – 1.77 (m, 6H), 1.76 – 1.62 (m, 2H), 1.41 – 0.99 (m, 27H); MS (ESI) *m/z* 774.3 $[M+H]^+$.



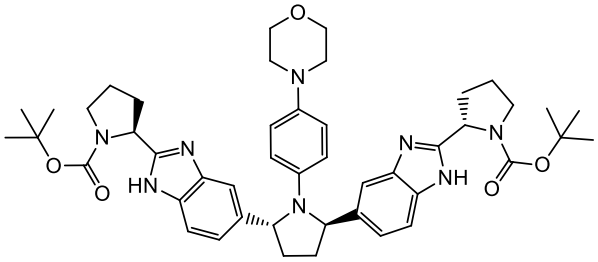
Dimethyl ((2*S*,2'*S*)-((2*S*,2'*S*)-2,2'-(6,6'-((2*R*,5*R*)-1-(4-(*tert*-butyl)phenyl)pyrrolidine-2,5-diyl)bis(1H-benzo[d]imidazole-6,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl))dicarbamate (18). To a solution of **K** (0.84 g, 1.09 mmol) in 1,4-dioxane (4 mL) was added 4N HCl in 1,4-dioxane (3 mL). The resulting solution was stirred at rt for 1 h and was concentrated and dried under vacuum. To the residue was added (*S*)-2-(methoxycarbonylamino)-3-methylbutanoic acid (0.40 g, 2.27 mmol) and HATU (0.842 g, 2.22 mmol). The mixture was dissolved in anhydrous DMSO (11 mL), Hunig's base (1.51 mL, 8.64 mmol) was added dropwise, and the resulting mixture was stirred at rt for 1 h. Water was added to precipitate the crude product, which was collected by filtration. The crude product was purified by column chromatography on silica gel using a solvent gradient of 0-5% methanol in dichloromethane to provide **18** (0.212 g, 22%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.06 – 11.89 (m, 2H), 7.43 (d, *J* = 8.3 Hz, 1H), 7.35 (d, *J* = 8.2 Hz, 1H), 7.29 – 7.22 (m, 3H), 7.19 – 7.15 (m, 1H), 7.08 – 7.00 (m, 2H), 6.91 – 6.82 (m, 2H), 6.26 – 6.19 (m, 2H), 5.37 – 5.28 (m, 2H), 5.14 – 5.06 (m, 2H), 4.07 – 4.00 (m, 2H), 3.84 – 3.73 (m, 4H), 3.51 (s, 6H), 2.56 – 2.49 (m, 2H), 2.23 – 2.08 (m, 4H), 2.01 – 1.81 (m, 6H), 1.72 – 1.61 (m, 2H), 1.05 (s, 9H), 0.88 – 0.72 (m, 12H); MS (ESI) *m/z* 888.5 $[M+H]^+$.



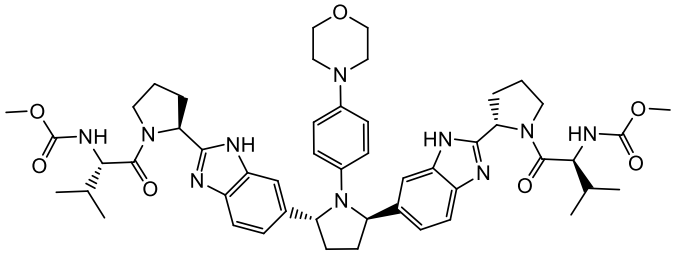
4-(4-((2*R*,5*R*)-2,5-Bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)phenyl)morpholine (L). Using the method described for making **I**, and substituting 4-morpholinoaniline for 4-*tert*-butylaniline, compound **A** (3.0 g, 7.5 mmol) was converted to **L** (2.71 g, 67%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.89 (d, *J* = 2.1 Hz, 2H), 7.69 (d, *J* = 8.3 Hz, 2H), 7.46 (dd, *J* = 8.4, 2.1 Hz, 2H), 6.67 – 6.62 (m, 2H), 6.25 – 6.19 (m, 2H), 5.38 (d, J = 6.8 Hz, 2H), 3.64 – 3.56 (m, 4H), 2.85 – 2.77 (m, 4H), 2.50 – 2.38 (m, 2H), 1.79 – 1.66 (m, 2H); MS (ESI) *m/z* 543.1 $[M+H]^+$.



(2*S*,2'*S*)-Di-*tert*-butyl 2,2'-(((((2*R*,5*R*)-1-(4-morpholinophenyl)pyrrolidine-2,5-diyl)bis(2-nitro-4,1-phenylene))bis(azanediyl))bis(carbonyl))bis(pyrrolidine-1-carboxylate) (M). Using the method described for making **H**, compound **L** (2.66 g, 4.90 mmol) was converted to **M** (2.36 g, 54%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.46 – 10.19 (m, 2H), 7.84 – 7.72 (m, 3H), 7.57 (d, *J* = 8.3 Hz, 1H), 7.51 (dd, *J* = 8.4, 2.0 Hz, 2H), 6.67 – 6.59 (m, 2H), 6.24 (d, *J* = 8.5 Hz, 2H), 5.39 – 5.31 (m, 2H), 4.28 – 4.17 (m, 2H), 3.64 – 3.54 (m, 4H), 3.44 – 3.26 (m, 4H), 2.84 – 2.76 (m, 4H), 2.50 – 2.38 (m, 2H), 2.25 – 2.08 (m, 2H), 1.94 – 1.66 (m, 8H), 1.41 – 1.24 (m, 18H); MS (ESI) *m/z* 899.2 $[M+H]^+$.

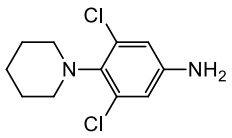


(2*S*,2'*S*)-Di-*tert*-butyl 2,2'-(5,5'-((2*R*,5*R*)-1-(4-morpholinophenyl)pyrrolidine-2,5-diyl)bis(1H-benzo[d]imidazole-5,2-diyl))bis(pyrrolidine-1-carboxylate) (N). To a solution of **M** (2.35 g, 2.61 mmol) in ethanol (12 mL) and THF (12 mL) was added PtO_2 (0.119 g, 0.523 mmol), and the mixture was stirred at rt under 1 atm H_2 for 16 h. The mixture was filtered, and the filtrate was concentrated under vacuum. The crude product was purified by column chromatography on silica gel using a solvent gradient of 1-4% methanol in dichloromethane to give the diamine intermediate (1.73 g, 79%). This compound was stirred at 50 ^{o}C in a mixture of toluene (20 mL) and acetic acid (0.35 mL, 6.2 mmol)) for 2 h. The mixture was concentrated under vacuum and azeotroped with toluene (2X) and dried under vacuum to give **N**, which was used without purification.

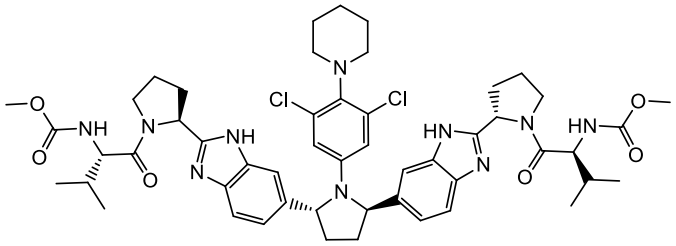


Dimethyl ((2*S*,2'*S*)-((2*S*,2'*S*)-2,2'-(6,6'-((2*R*,5*R*)-1-(4-morpholinophenyl)pyrrolidine-2,5-diyl)bis(1H-benzo[d]imidazole-6,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl))dicarbamate (26). Using the method described for making **18**, compound **N** (1.66 g, 2.06 mmol) was converted to **26** (0.10 g, 5%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.23 – 11.95 (m, 2H), 7.41 (d, J = 8.3 Hz, 1H), 7.33 (d, J = 8.2 Hz, 1H), 7.29 – 7.22 (m, 3H), 7.19 – 7.15 (m,

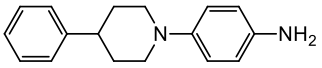
1H), 7.05 – 6.98 (m, 2H), 6.57 – 6.48 (m, 2H), 6.22 (d, *J* = 8.7 Hz, 2H), 5.36 – 5.26 (m, 2H), 5.14 – 5.06 (m, 2H), 4.10 – 3.96 (m, 2H), 3.87 – 3.71 (m, 4H), 3.61 – 3.54 (m, 4H), 3.51 (s, 6H), 2.77 – 2.68 (m, 4H), 2.57 – 2.50 (m, 2H), 2.22 – 2.10 (m, 4H), 2.02 – 1.81 (m, 6H), 1.72 – 1.61 (m, 2H), 0.88 – 0.72 (m, 12H); MS (ESI) *m/z* 917.5 $[M+H]^+$.



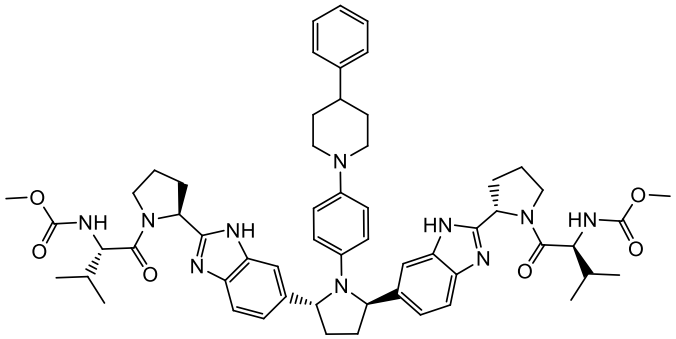
3,5-Dichloro-4-(piperidin-1-yl)aniline (O). Using the method described for making intermediate **F**, 1,3-dichloro-2-fluoro-5-nitrobenzene (4.8 g, 22.9 mmol) was converted to **O** (5.7 g, quant.): ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.50 (s, 2H), 5.38 (s, 2H), 2.97 – 2.88 (m, 4H), 1.58 – 1.39 (m, 6H).



Dimethyl ((2*S*,2'*S*)-((2*S*,2'*S*)-2,2'-(6,6'-((2*R*,5*R*)-1-(3,5-dichloro-4-(piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(1H-benzo[d]imidazole-6,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl))dicarbamate (30). This compound was prepared using the methods described for converting **4a** to **29**, substituting **O** for compound **F**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.28 – 11.97 (m, 2H), 7.46 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.37 (d, *J* = 8.2 Hz, 1H), 7.29 – 7.21 (m, 3H), 7.17 (s, 1H), 7.07 – 7.01 (m, 2H), 6.31 – 6.24 (m, 2H), 5.43 – 5.31 (m, 2H), 5.10 (d, J = 8.5 Hz, 2H), 4.06 – 4.00 (m, 2H), 3.85 – 3.72 (m, 4H), 3.50 (s, 6H), 2.87 – 2.74 (m, 4H), 2.55 – 2.48 (m, 2H), 2.26 – 2.09 (m, 4H), 2.06 – 1.79 (m, 4H), 1.72 – 1.56 (m, 2H), 1.51 – 1.32 (m, 6H), 0.88 – 0.70 (m, 12H); MS (ESI) *m/z* 983.5 $[M+H]^+$.

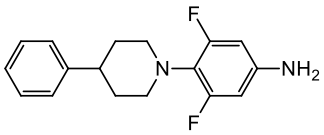


4-(4-Phenylpiperidin-1-yl)aniline (P). A mixture of 4-fluoronitrobenzene (0.752 mL, 7.02 mmol), 4-phenylpiperidine (1.166 g, 7.02 mmol), and K_2CO_3 (0.970 g, 7.02 mmol) in anhydrous DMSO (7 mL) was stirred while heating at 190 °C for 10 min. The mixture was cooled to rt and poured into water (50 mL), and the mixture was stirred for 5 min to give a yellow solid that was collected by filtration and dried under vacuum to give 1-(4-nitrophenyl)-4-phenylpiperidine (1.71 g, 86%). To the yellow solid (1.71 g) was added ethyl acetate (50 mL) and 10% Pd-C (0.297 g, 0.279 mmol). The mixture was stirred at rt under 1 atm H_2 for 1 h. The mixture was filtered, and the filtrate was concentrated under vacuum to give **P** as a colorless solid (1.47 g, 96%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.30 – 7.22 (m, 4H), 7.19 – 7.13 (m, 1H), 6.73 – 6.67 (m, 2H), 6.49 – 6.44 (m, 2H), 3.46 – 3.38 (m, 2H), 2.61 – 2.48 (m, 5H), 1.84 – 1.69 (m, 4H).

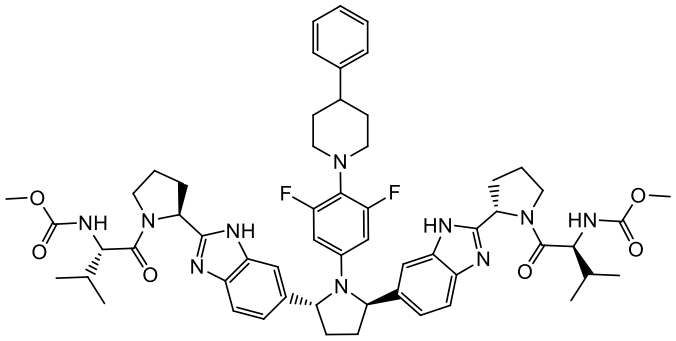


Dimethyl ((2*S*,2'*S*)-((2*S*,2'*S*)-2,2'-(6,6'-((2*R*,5*R*)-1-(4-(4-phenylpiperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(1H-benzo[d]imidazole-6,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl))dicarbamate (31). This compound was prepared using the methods described for converting compound **4a** to **29**, substituting **P** for compound **F**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.22 – 11.95 (m, 2H), 7.42 (d, J = 8.2 Hz, 1H), 7.34 (d, J = 8.2 Hz, 1H), 7.29 – 7.16 (m, 8H), 7.12 (t, J = 7.0 Hz, 1H), 7.03 (t, J = 7.5 Hz, 2H), 6.61 – 6.53 (m, 2H), 6.22 (d, J = 8.6 Hz, 2H), 5.36 – 5.26 (m, 2H), 5.15 – 5.05 (m, 2H), 4.02 (t, J = 8.3 Hz,

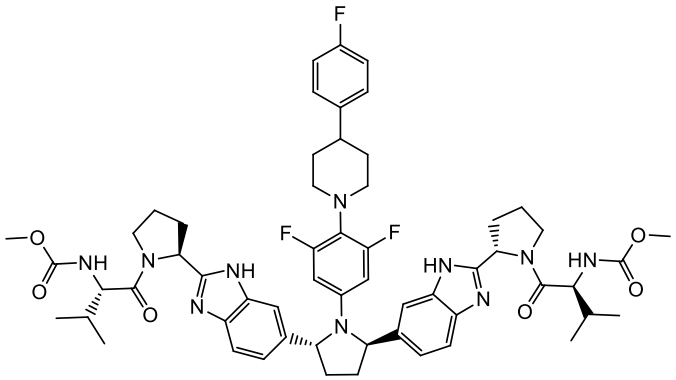
2H), 3.85 – 3.72 (m, 4H), 3.50 (s, 6H), 3.37 – 3.28 (m, 2H), 2.57 – 2.39 (m, 4H), 2.22 – 2.09 (m, 4H), 2.03 – 1.79 (m, 6H), 1.76 – 1.57 (m, 7H), 0.89 – 0.72 (m, 12H); MS (ESI) *m/z* 991.4 $[M+H]^+$.



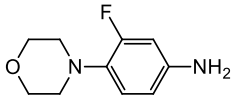
3,5-Difluoro-4-(4-phenylpiperidin-1-yl)aniline (R). This compound was prepared using the method described to make **F**, substituting 4-phenyl-piperidine for piperidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.30 – 7.22 (m, 4H), 7.19 – 7.12 (m, 1H), 6.16 – 6.08 (m, 2H), 5.39 (s, 2H), 3.12 – 2.92 (m, 4H), 2.60 – 2.49 (m, 1H), 1.77 – 1.64 (m, 4H).



Dimethyl ((2*S*,2'*S*)-((2*S*,2'*S*)-2,2'-(6,6'-((2*R*,5*R*)-1-(3,5-difluoro-4-(4-phenylpiperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(1H-benzo[d]imidazole-6,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl))dicarbamate (32). This compound was prepared using the methods described for converting compound **4a** to **29**, substituting **R** for compound **F**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.30 – 11.99 (m, 2H), 7.46 (d, *J* = 8.3 Hz, 1H), 7.38 (d, *J* = 8.2 Hz, 1H), 7.30 – 7.15 (m, 9H), 7.15 – 7.09 (m, 1H), 7.09 – 7.01 (m, 2H), 5.89 (d, *J* = 12.9 Hz, 2H), 5.42 – 5.27 (m, 2H), 5.16 – 5.07 (m, 2H), 4.08 – 3.99 (m, 2H), 3.87 – 3.69 (m, 4H), 3.50 (s, 6H), 3.02 – 2.81 (m, 5H), 2.58 – 2.50 (m, 1H), 2.25 – 2.09 (m, 4H), 2.06 – 1.80 (m, 6H), 1.73 – 1.54 (m, 6H), 0.89 – 0.69 (m, 12H); MS (ESI) *m/z* 1027.4 $[M+H]^+$.

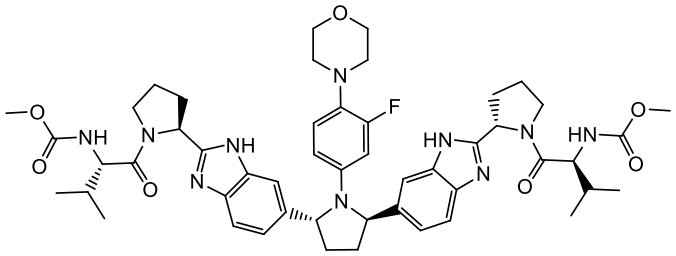


Dimethyl ((2*S*,2'*S*)-((2*S*,2'*S*)-2,2'-(6,6'-((2*R*,5*R*)-1-(3,5-difluoro-4-(4-(4-fluorophenyl)piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(1H-benzo[d]imidazole-6,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl))dicarbamate (33). This compound was prepared using the methods described for converting intermediate **15** to PIB, substituting (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid for (2*S*,3*R*)-3-methoxy-2-((methoxycarbonyl)amino)butanoic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.27 – 12.00 (m, 2H), 7.46 (d, *J* = 8.4 Hz, 1H), 7.38 (d, *J* = 8.2 Hz, 1H), 7.30 – 7.16 (m, 5H), 7.09 – 6.99 (m, 4H), 5.88 (d, *J* = 13.2 Hz, 2H), 5.39 – 5.29 (m, 2H), 5.15 – 5.07 (m, 2H), 4.03 (t, *J* = 8.5 Hz, 2H), 3.84 – 3.73 (m, 2H), 3.50 (s, 6H), 3.11 – 2.79 (m, 5H), 2.57 – 2.49 (m, 2H), 2.24 – 2.10 (m, 4H), 2.05 – 1.76 (m, 6H), 1.63 (d, J = 17.4 Hz, 8H), 0.88 – 0.71 (m, 12H); MS (ESI) *m/z* 1045.4 $[M+H]^+$.

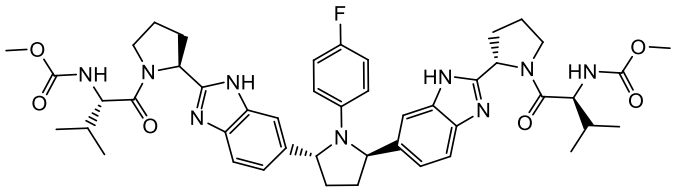


3-Fluoro-4-morpholinoaniline (S). To a mixture of morpholine (4.72 mL, 4.72 g, 54.2 mmol) and dibasic potassium phosphate (9.44 g, 54.2 mmol) in DMSO (27 mL) was added 3,4-difluoronitrobenzene (3.0 mL, 4.31 g, 27.1 mmol), and the resulting mixture was stirred at 60 ºC for 18 h. The resulting solution was allowed to cool to rt, diluted with ethyl acetate, and extracted with water (3x) and brine. The organic layer was separated and dried over Na_2SO_4, filtered and concentrated under vacuum to give a yellow solid (6.32 g, ca. 100%). A portion of

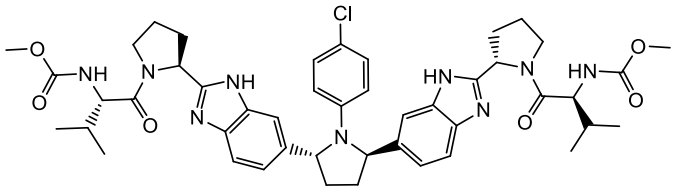
the solid (2.25 g, 9.95 mmol) was dissolved in ethyl acetate (40 mL), and 10% Pd-C (0.225 g) was added. The reaction vessel was flushed with N2, and the resulting mixture was stirred under 1 atm H_2 for 2 h. The mixture was filtered through Celite, and the filtrate was concentrated under vacuum to give **S** (1.95 g, quant.): ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.89 (dd, *J* = 9.5, 8.2 Hz, 1H), 6.55 – 6.47 (m, 2H), 3.99 – 3.92 (m, 4H), 3.10 – 3.03 (m, 4H).



Dimethyl ((2*S*,2'*S*)-((2*S*,2'*S*)-2,2'-(6,6'-((2*R*,5*R*)-1-(3-fluoro-4-morpholinophenyl)-pyrrolidine-2,5-diyl)bis(1H-benzo[d]imidazole-6,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl))dicarbamate (27). This compound was prepared using the methods described for converting compound **A** to **28**, substituting **S** for compound **B**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.26 – 11.96 (m, 2H), 7.43 (d, *J* = 8.3 Hz, 1H), 7.36 (dd, *J* = 8.2, 2.7 Hz, 1H), 7.31 – 7.22 (m, 3H), 7.17 (s, 1H), 7.09 – 6.98 (m, 2H), 6.67 – 6.56 (m, 1H), 6.07 – 5.97 (m, 2H), 5.38 – 5.25 (m, 2H), 5.15 – 5.06 (m, 2H), 4.08 – 3.95 (m, 2H), 3.85 – 3.71 (m, 4H), 3.51 (s, 6H), 3.21 – 3.06 (m, 1H), 2.66 – 2.57 (m, 4H), 2.26 – 2.07 (m, 4H), 2.05 – 1.81 (m, 6H), 1.72 – 1.60 (m, 2H), 1.53 – 1.42 (m, 4H), 1.41 – 1.31 (m, 2H), 0.90 – 0.70 (m, 12H); MS (ESI) *m/z* 933.5 $[M+H]^+$.

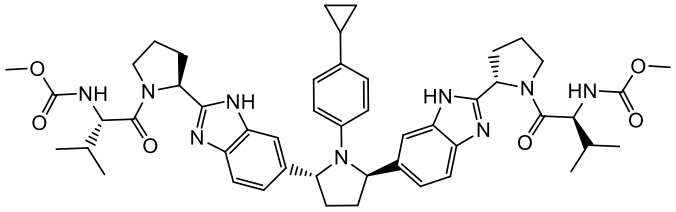


Dimethyl ((2*S*,2'*S*)-((2*S*,2'*S*)-2,2'-(6,6'-((2*R*,5*R*)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(1H-benzo[d]imidazole-6,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl))dicarbamate (19). This compound was prepared using the methods described for converting compound **4a** to **29**, substituting 4-fluoroaniline for compound **F**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.25 – 11.96 (m, 2H), 7.42 (d, *J* = 8.3 Hz, 1H), 7.34 (d, *J* = 8.2 Hz, 1H), 7.31 – 7.22 (m, 3H), 7.18 (s, 1H), 7.05 – 6.98 (m, 2H), 6.75 – 6.65 (m, 2H), 6.29 – 6.21 (m, 2H), 5.40 – 5.26 (m, 2H), 5.15 – 5.04 (m, 2H), 4.02 (t, *J* = 8.3 Hz, 2H), 3.86 – 3.71 (m, 4H), 3.50 (s, 6H), 2.60 – 2.50 (m, 2H), 2.21 – 2.07 (m, 4H), 2.03 – 1.80 (m, 6H), 1.74 – 1.58 (m, 2H), 0.89 – 0.69 (m, 12H); MS (ESI) *m/z* 850.5 $[M+H]^+$.

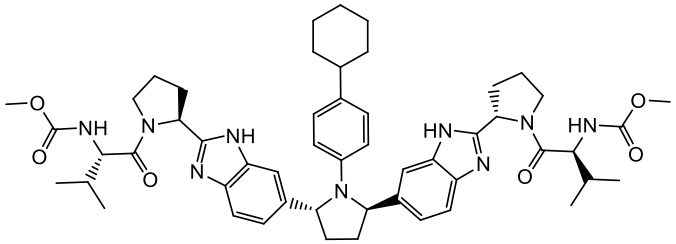


Dimethyl ((2*S*,2'*S*)-((2*S*,2'*S*)-2,2'-(6,6'-((2*R*,5*R*)-1-(4-chlorophenyl)pyrrolidine-2,5-diyl)bis(1H-benzo[d]imidazole-6,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl))dicarbamate (20). This compound was prepared using the methods described for converting compound **4a** to **29**, substituting 4-chloroaniline for compound **F**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.02 (s, 2H), 7.42 (d, *J* = 8.3 Hz, 1H), 7.34 (d, *J* = 8.2 Hz, 1H), 7.30 – 7.20 (m, 2H), 7.17 (s, 1H), 7.01 (t, J = 8.2 Hz, 2H), 6.91 – 6.82 (m, 3H), 6.27 (d, J = 8.9 Hz, 2H), 5.40 – 5.29 (m, 2H), 5.10 (d, *J* = 8.3 Hz, 2H), 4.02 (t, J = 8.4 Hz, 2H), 3.84 – 3.73 (m, 4H), 3.50 (s,

6H), 2.57 – 2.48 (m, 2H), 2.21 – 2.10 (m, 4H), 2.02 – 1.58 (m, 8H), 0.87 – 0.71 (m, 12H); MS (ESI) *m/z* 866.4 $[M+H]^+$.

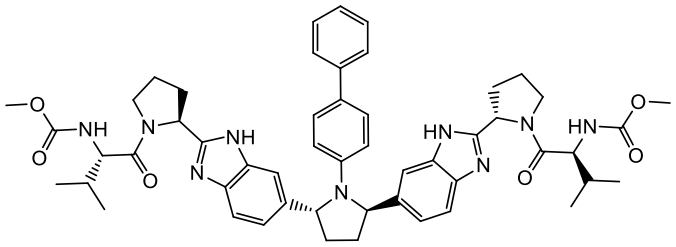


Dimethyl ((2*S*,2'*S*)-((2*S*,2'*S*)-2,2'-(6,6'-((2*R*,5*R*)-1-(4-cyclopropylphenyl)pyrrolidine-2,5-diyl)bis(1H-benzo[d]imidazole-6,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl))dicarbamate (21). This compound was prepared using the methods described for converting compound **4a** to **29**, substituting 4-cyclopropylaniline for compound **F**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.98 (s, 2H), 7.41 (d, *J* = 8.2 Hz, 1H), 7.33 (d, *J* = 8.2 Hz, 1H), 7.29 – 7.22 (m, 2H), 7.16 (s, 1H), 7.05 – 6.97 (m, 2H), 6.62 – 6.53 (m, 2H), 6.20 (d, *J* = 8.5 Hz, 2H), 5.37 – 5.27 (m, 2H), 5.14 – 5.06 (m, 2H), 4.09 – 3.97 (m, 2H), 3.85 – 3.74 (m, 4H), 3.51 (s, 6H), 2.55 – 2.49 (m, 2H), 2.23 – 2.08 (m, 4H), 2.03 – 1.78 (m, 6H), 1.71 – 1.61 (m, 2H), 1.59 – 1.50 (m, 1H), 0.90 – 0.71 (m, 12H), 0.69 – 0.60 (m, 2H), 0.37 – 0.28 (m, 2H); MS (ESI) *m/z* 872.5 $[M+H]^+$.

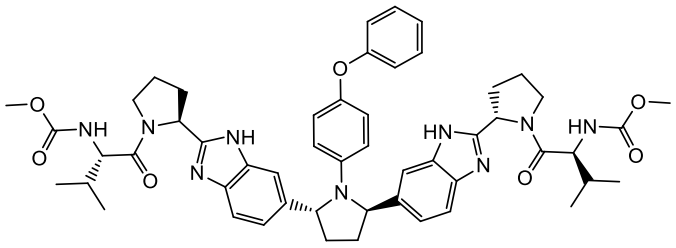


Dimethyl ((2*S*,2'*S*)-((2*S*,2'*S*)-2,2'-(6,6'-((2*R*,5*R*)-1-(4-cyclohexylphenyl)pyrrolidine-2,5-diyl)bis(1H-benzo[d]imidazole-6,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl))dicarbamate (22). This compound was prepared using the methods described for converting compound **A** to **18**, substituting 4-cyclohexylaniline for 4-*tert*-butylaniline. 1H NMR

(400 MHz, DMSO-d6) δ 12.20 – 11.89 (m, 2H), 7.42 (d, *J* = 8.3 Hz, 1H), 7.34 (d, *J* = 8.2 Hz, 1H), 7.29 – 7.22 (m, 3H), 7.16 (s, 1H), 7.03 (t, *J* = 7.5 Hz, 2H), 6.75 – 6.64 (m, 2H), 6.21 (d, *J* = 8.4 Hz, 2H), 5.38 – 5.27 (m, 2H), 5.14 – 5.06 (m, 2H), 4.08 – 4.00 (m, 2H), 3.85 – 3.72 (m, 4H), 3.51 (s, 6H), 2.56 – 2.50 (m, 2H), 2.23 – 2.09 (m, 6H), 2.03 – 1.81 (m, 6H), 1.70 – 1.52 (m, 8H), 1.26 – 1.11 (m, 3H), 0.88 – 0.72 (m, 12H); MS (ESI) *m/z* 914.5 $[M+H]^+$.

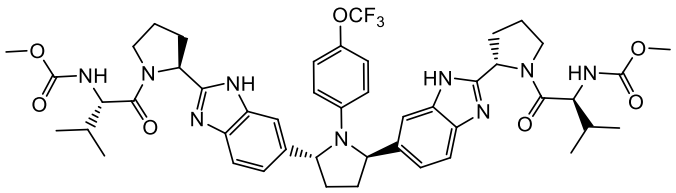


Dimethyl ((2*S*,2'*S*)-((2*S*,2'*S*)-2,2'-(6,6'-((2*R*,5*R*)-1-([1,1'-biphenyl]-4-yl)pyrrolidine-2,5-diyl)bis(1H-benzo[d]imidazole-6,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl))dicarbamate (23). This compound was prepared using the methods described for converting compound **4a** to **29**, substituting 4-aminobiphenyl for compound **F**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.24 – 11.98 (m, 2H), 7.44 (d, *J* = 8.3 Hz, 1H), 7.40 – 7.30 (m, 4H), 7.29 – 7.16 (m, 7H), 7.14 – 7.01 (m, 3H), 6.39 (d, *J* = 8.5 Hz, 2H), 5.48 – 5.38 (m, 2H), 5.15 – 5.05 (m, 2H), 4.02 (t, *J* = 8.4 Hz, 2H), 3.86 – 3.71 (m, 4H), 3.50 (s, 6H), 2.61 – 2.51 (m, 2H), 2.23 – 2.07 (m, 4H), 2.03 – 1.60 (m, 8H), 0.88 – 0.70 (m, 12H); MS (ESI) *m/z* 908.5 $[M+H]^+$.

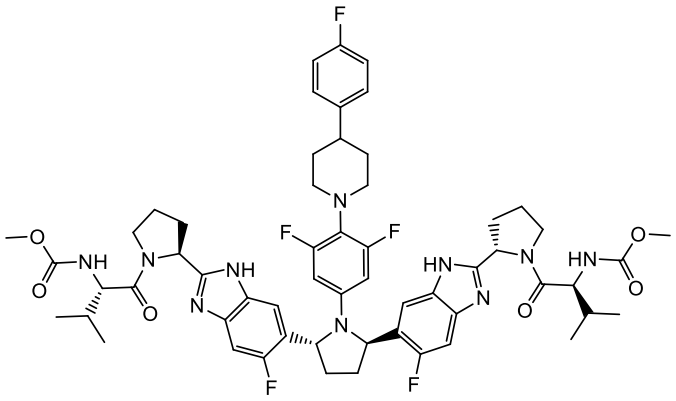


Dimethyl ((2*S*,2'*S*)-((2*S*,2'*S*)-2,2'-(6,6'-((2*R*,5*R*)-1-(4-phenoxyphenyl)pyrrolidine-2,5-diyl)bis(1H-benzo[d]imidazole-6,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-

2,1-diyl))dicarbamate (24). This compound was prepared using the methods described for converting compound **A** to **28**, substituting 4-phenoxyaniline for compound **B**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.25 – 11.97 (m, 2H), 7.44 (d, J = 8.6 Hz, 1H), 7.37 (d, J = 8.2 Hz, 1H), 7.32 – 7.24 (m, 3H), 7.23 – 7.14 (m, 3H), 7.05 (t, J = 9.6 Hz, 2H), 6.91 (t, J = 7.4 Hz, 1H), 6.73 – 6.66 (m, 2H), 6.66 – 6.58 (m, 2H), 6.32 (d, J = 8.9 Hz, 2H), 5.42 – 5.31 (m, 2H), 5.16 – 5.07 (m, 2H), 4.03 (t, J = 8.4 Hz, 2H), 3.85 – 3.74 (m, 4H), 3.51 (s, 6H), 2.61 – 2.51 (m, 2H), 2.25 – 2.09 (m, 4H), 2.05 – 1.81 (m, 6H), 1.73 – 1.61 (m, 2H), 0.89 – 0.72 (m, 12H); MS (ESI) *m/z* 924.4 $[M+H]^+$.

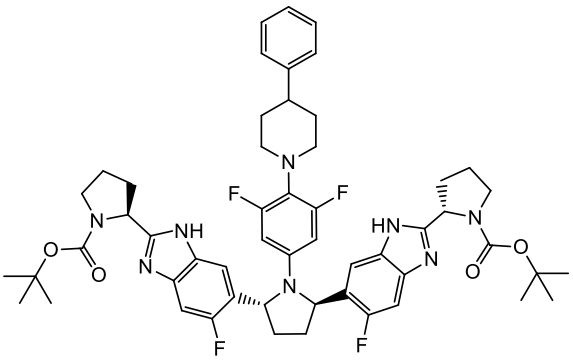


Dimethyl ((2*S*,2'*S*)-((2*S*,2'*S*)-2,2'-(6,6'-((2*R*,5*R*)-1-(4-(trifluoromethoxy)phenyl)pyrrolidine-2,5-diyl)bis(1H-benzo[d]imidazole-6,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl))dicarbamate (25). This compound was prepared using the methods described for converting compound **A** to **28**, substituting 4-trifluoromethoxyaniline for compound **B**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.25 – 11.93 (m, 2H), 7.44 (d, J = 8.3 Hz, 1H), 7.36 (d, J = 8.2 Hz, 1H), 7.29 – 7.22 (m, 2H), 7.18 (s, 1H), 7.04 (t, J = 9.6 Hz, 2H), 6.91 – 6.82 (m, 2H), 6.34 – 6.28 (m, 3H), 5.42 – 5.33 (m, 2H), 5.13 – 5.06 (m, 2H), 4.02 (t, J = 8.3 Hz, 2H), 3.85 – 3.74 (m, 4H), 3.51 (s, 6H), 2.60 – 2.50 (m, 2H), 2.22 – 2.09 (m, 4H), 2.02 – 1.81 (m, 6H), 1.74 – 1.63 (m, 2H), 0.88 – 0.71 (m, 12H); MS (ESI) *m/z* 916.4 $[M+H]^+$.

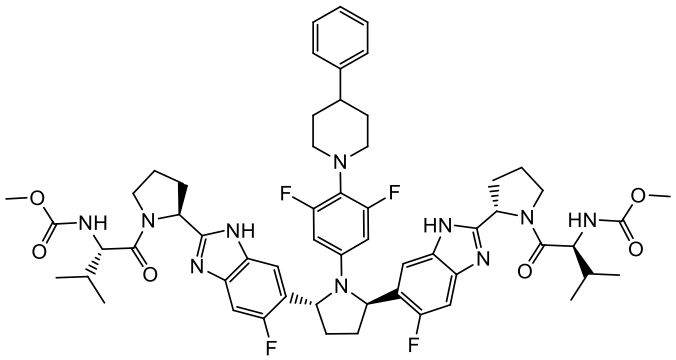


Dimethyl ((2*S*,2'*S*)-((2*S*,2'*S*)-2,2'-(6,6'-((2*R*,5*R*)-1-(3,5-difluoro-4-(4-(4-fluorophenyl)piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(5-fluoro-1H-benzo[d]imidazole-6,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl))dicarbamate (35). To a solution of **15** (0.22 g, 0.227 mmol) in 1,4-dioxane (2 mL) was added 4N HCl in 1,4-dioxane (2 mL) and methanol (1 mL). The resulting mixture was stirred at rt for 90 min and concentrated under vacuum. In a separate flask, (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (99 mg, 0.568 mmol) and EDCI (131 mg, 0.681 mmol) were dissolved in dichloromethane (2 mL), and the resulting solution was stirred at rt for 20 min. This solution was combined with a solution of the crude product obtained from **15** in dichloromethane (2 mL). The resulting solution was cooled in an ice bath, and Hunig's base (0.396 mL, 2.270 mmol) was added, followed by HOBT (104 mg, 0.681 mmol). The resulting mixture was allowed to warm to rt and was stirred for 2 h. The mixture was partitioned between water and dichloromethane (2X), and the combined organic extract was dried over Na_2SO_4. The drying agent was filtered off, and the filtrate was concentrated under vacuum to give a crude product that was purified by column chromatography on silica gel using a solvent gradient of 0-10% methanol in dichloromethane to give **35** (80 mg, 33%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.34 – 11.99 (m, 2H), 7.42 – 7.34 (m, 1H), 7.34 – 7.19 (m, 5H), 7.11 (d, J = 7.0 Hz, 1H), 7.08 –

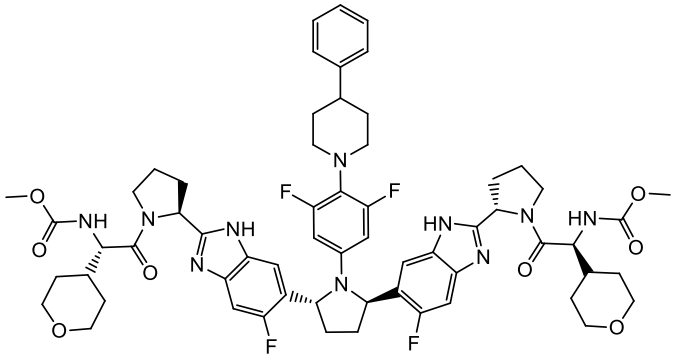
6.97 (m, 3H), 5.94 – 5.80 (m, 2H), 5.63 – 5.44 (m, 2H), 5.13 – 5.04 (m, 2H), 4.05 – 3.95 (m, 2H), 3.84 – 3.68 (m, 4H), 3.49 (s, 6H), 3.11 – 2.81 (m, 6H), 2.56 – 2.48 (m, 2H), 2.22 – 2.08 (m, 4H), 2.06 – 1.51 (m, 11H), 0.89 – 0.64 (m, 12H); MS (ESI) *m/z* 1081.4 $[M+H]^+$.



(2*S*,2'*S*)-Di-*tert*-butyl 2,2'-(6,6'-((2*R*,5*R*)-1-(3,5-difluoro-4-(4-phenylpiperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(5-fluoro-1H-benzo[d]imidazole-6,2-diyl))bis(pyrrolidine-1-carboxylate) (T). This compound was prepared using the methods described for making **15**, substituting compound **R** for **12**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.48 – 12.06 (m, 2H), 7.42 (d, *J* = 11.2 Hz, 1H), 7.31 (d, *J* = 10.2 Hz, 1H), 7.27 – 7.09 (m, 6H), 7.06 – 6.89 (m, 1H), 5.95 – 5.76 (m, 2H), 5.63 – 5.45 (m, 2H), 4.93 – 4.74 (m, 2H), 3.59 – 3.44 (m, 2H), 3.40 – 3.31 (m, 2H), 3.04 – 2.78 (m, 4H), 2.29 – 2.12 (m, 2H), 2.03 – 1.54 (m, 15H), 1.41 – 0.90 (m, 18H); MS (ESI) *m/z* 949.2 $[M+H]^+$.

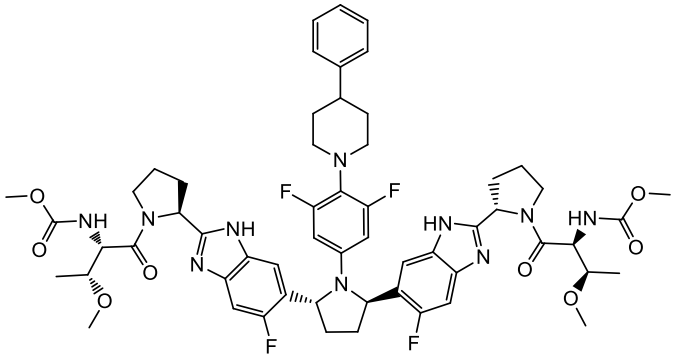


Dimethyl ((2*S*,2'*S*)-((2*S*,2'*S*)-2,2'-(6,6'-((2*R*,5*R*)-1-(3,5-difluoro-4-(4-phenylpiperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(5-fluoro-1H-benzo[d]imidazole-6,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl))dicarbamate (34). This compound was prepared using the method described for converting **15** to **35**, substituting compound **T** for **15**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.75 – 10.27 (m, 2H), 7.49 (d, *J* = 10.5 Hz, 1H), 7.42 – 7.12 (m, 7H), 7.01 – 6.93 (m, 1H), 5.86 (d, *J* = 12.9 Hz, 2H), 5.53 – 5.30 (m, 6H), 4.40 – 4.29 (m, 2H), 3.93 – 3.79 (m, 2H), 3.72 (s, 6H), 3.69 – 3.57 (m, 2H), 2.64 – 1.72 (m, 23H), 0.96 – 0.81 (m, 12H); MS (ESI) *m/z* 1063.4 $[M+H]^+$.



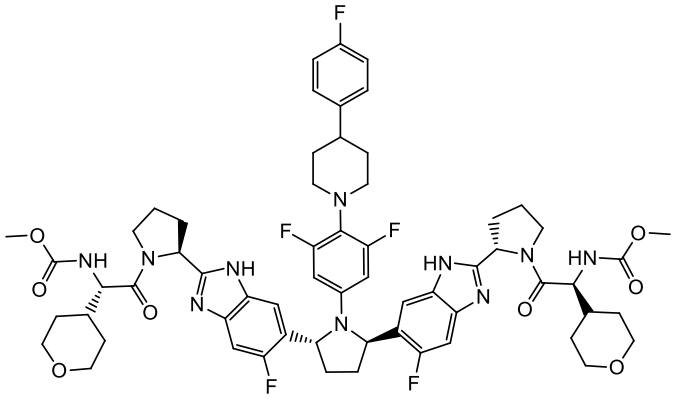
Dimethyl ((1*S*,1'*S*)-((2*S*,2'*S*)-2,2'-(6,6'-((2*R*,5*R*)-1-(3,5-difluoro-4-(4-phenylpiperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(5-fluoro-1*H*-benzo[d]imidazole-6,2-diyl))bis(pyrrolidine-2,1-diyl))bis(2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethane-2,1-diyl))dicarbamate (36). A solution of compound **T** (0.887 g, 0.935 mmol) in 4N HCl in 1,4-dioxane (2.5 mL) was stirred at

rt for 90 min and concentrated *in vacuo*. The residue was combined with (S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid (0.542 g, 2.50 mmol), and the mixture was dissolved in anhydrous DMSO (2 mL). Hunig's base (1.59 mL, 9.08 mmol) and HATU (0.885 g, 2.33 mmol) were added, and the resulting mixture was stirred at rt for 1 h. The mixture was partitioned between water and EtOAc (3X), and the combined organic extract was dried over Na_2SO_4, filtered, and concentrated under vacuum. The crude product was purified by column chromatography on silica gel using a solvent gradient of 0-6% methanol in dichloromethane to give **36** (0.445 g, 34%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.43 – 12.01 (m, 2H), 7.42 – 7.30 (m, 4H), 7.27 – 7.16 (m, 4H), 7.16 – 7.09 (m, 1H), 7.09 – 6.95 (m, 2H), 5.96 – 5.76 (m, 2H), 5.62 – 5.43 (m, 2H), 5.14 – 5.03 (m, 2H), 4.15 – 4.02 (m, 2H), 3.87 – 3.58 (m, 8H), 3.49 (s, 6H), 3.22 – 2.77 (m, 9H), 2.22 – 2.05 (m, 4H), 2.03 – 1.88 (m, 4H), 1.87 – 1.54 (m, 10H), 1.53 – 1.35 (m, 4H), 1.33 – 1.04 (m, 4H); MS (ESI) *m/z* 1147.5 $[M+H]^+$.



Dimethyl ((2*S*,2'*S*,3*R*,3'*R*)-((2*S*,2'*S*)-2,2'-(6,6'-((2*R*,5*R*)-1-(3,5-difluoro-4-(4-phenylpiperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(5-fluoro-1*H*-benzo[d]imidazole-6,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methoxy-1-oxobutane-2,1-diyl))dicarbamate (37). This compound was prepared using the method for converting compound **T** to **36**, substituting (2*S*,3*R*)-3-methoxy-2-(methoxycarbonylamino)butanoic acid for (*S*)-2-(methoxycarbonylamino)-2-(tetrahydro-2*H*-pyran-4-yl)acetic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.35 – 11.98 (m,

2H), 7.38 (dd, *J* = 11.2, 6.2 Hz, 1H), 7.31 (dd, *J* = 10.4, 4.7 Hz, 1H), 7.28 – 7.16 (m, 6H), 7.16 – 7.06 (m, 2H), 7.01 (dd, *J* = 6.9, 2.9 Hz, 1H), 5.95 – 5.79 (m, 2H), 5.63 – 5.43 (m, 2H), 5.13 – 5.03 (m, 2H), 4.21 (q, *J* = 8.0 Hz, 2H), 3.85 – 3.72 (m, 4H), 3.50 (s, 6H), 3.47 – 3.34 (m, 2H), 3.19 – 2.82 (m, 10H), 2.24 – 1.53 (m, 17H), 1.08 – 0.85 (m, 6H); MS (ESI) *m/z* 1095.4 $[M+H]^+$.



Dimethyl ((1*S*,1'*S*)-((2*S*,2'*S*)-2,2'-(6,6'-((2*R*,5*R*)-1-(3,5-difluoro-4-(4-(4-fluorophenyl)piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(5-fluoro-1H-benzo[d]imidazole-6,2-diyl))bis(pyrrolidine-2,1-diyl))bis(2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethane-2,1-diyl))dicarbamate (38). This compound was prepared using the method described for converting **15** to PIB, substituting (*S*)-2-(methoxycarbonylamino)-2-(tetrahydro-2*H*-pyran-4-yl)acetic acid for (2*S*,3*R*)-3-methoxy-2-(methoxycarbonylamino)-butanoic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.37 – 11.98 (m, 2H), 7.40 – 7.27 (m, 3H), 7.27 – 7.20 (m, 2H), 7.08 – 6.95 (m, 5H), 5.92 – 5.79 (m, 2H), 5.61 – 5.44 (m, 2H), 5.11 – 5.03 (m, 2H), 4.14 – 4.02 (m, 2H), 3.86 – 3.58 (m, 8H), 3.49 (s, 3H), 3.48 (s, 3H), 3.24 – 2.78 (m, 9H), 2.22 – 1.01 (m, 26H); MS (ESI) *m/z* 1165.5 $[M+H]^+$.