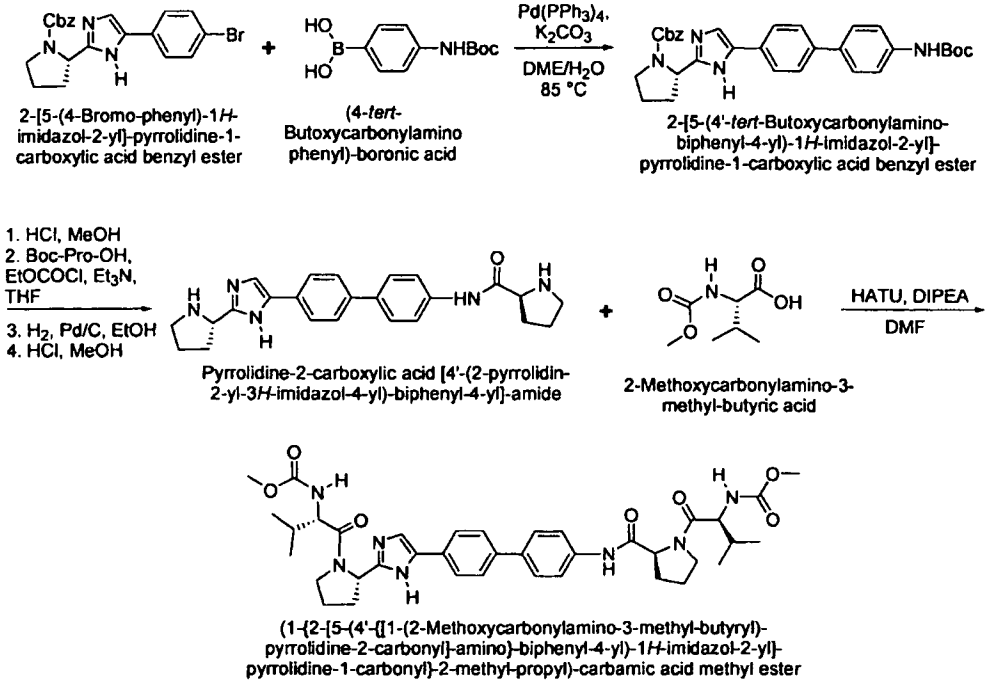
Example CN



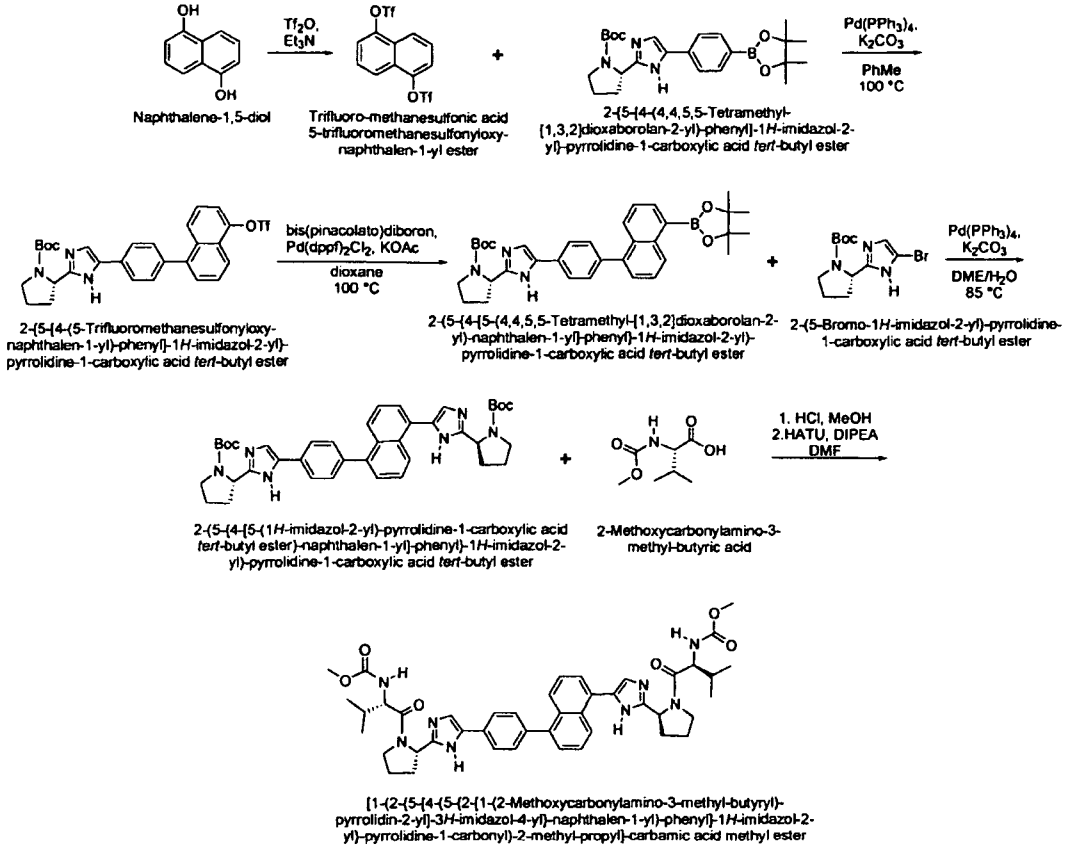
2-[5-(4'-*tert*-Butoxycarbonylamino-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid benzyl ester: 2-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid benzyl ester (2.31 g, 5.42 mmol), (4-*tert*-Butoxycarbonylaminophenyl)-boronic acid (1.28 g, 5.42 mmol), $Pd(PPh_3)_4$ (313 mg, 0.271 mmol) and K_2CO_3 (6 mL of 2 M aqueous solution, 11.92 mmol) were combined with 1,2-dimethoxyethane (20 mL). The suspension was stirred while N_2 was bubbled through the solution for 14 min. A reflux condenser was attached and the suspension was heated to 85°C for 15 hours. It was then cooled, diluted with ethyl acetate (150 mL), washed with water and brine, dried over sodium sulfate and concentrated. The crude product was purified by silica column chromatography (25% to 50% EtOAc/hexanes) to provide 2-[5-(4'-*tert*-Butoxycarbonylamino-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid benzyl ester (1.20 g, 41%).

Pyrrolidine-2-carboxylic acid [4'-(2-pyrrolidin-2-yl-3H-imidazol-4-yl)-biphenyl-4-yl]-amide: 2-[5-(4'-*tert*-Butoxycarbonylamino-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid benzyl ester (1.75 g, 3.25 mmol) was dissolved in methanol (40 mL) and concentrated HCl (2 mL) was added. The solution was stirred at 50°C for 19 hours before being concentrated to a volume of 10 mL, poured into saturated $NaHCO_3$ (60 mL). The organic phase was extracted 3 times with 30 mL dichloromethane. The combined organic phases were dried with sodium sulfate and concentrated. A portion of the resulting residue (963 mg, 2.20 mmol)

was dissolved in THF (4 mL). In a separate flask, ethylchloroformate (0.231 mL, 2.24 mmol) was added dropwise to a stirred 0°C solution of Boc-Pro-OH (568 mg, 2.64 mmol) and triethylamine (0.368 mL, 2.69 mmol) in THF (6 mL). After 10 minutes, the solution of biphenyl compound was added by cannula followed by a 2 mL rinse with THF. Following addition, the mixture was warmed to RT. After 70 min, the mixture was diluted with ethyl acetate (60 mL) and washed with water and brine. The organic phase was dried over sodium sulfate and concentrated. The residue was purified by silica column chromatography (25% to 50% EtOAc/hexanes) to provide the Boc-Pro compound (470 mg, 63%). This material was dissolved in ethanol (40 mL) and 10% Pd/C (300 mg) was added before the flask was sealed and a bladder containing hydrogen gas was attached. A venting needle was placed in the septum for 30 s to allow hydrogen to bubble through the solution. After 14 h, the mixture was filtered over CELITE and concentrated. A portion of this residue (169 mg, 0.337 mmol) was dissolved in methanol (20 mL) and concentrated HCl (2 mL) was added. The mixture was stirred at 60°C before being concentrated to provide Pyrrolidine-2-carboxylic acid [4'-(2-pyrrolidin-2-yl-3H-imidazol-4-yl)-biphenyl-4-yl]-amide (135 mg, 100%).

(1-{2-[5-(4'-{[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidine-2-carbonyl]-amino}-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: Pyrrolidine-2-carboxylic acid [4'-(2-pyrrolidin-2-yl-3H-imidazol-4-yl)-biphenyl-4-yl]-amide (135 mg, 0.337 mmol), 2-Methoxycarbonylamino-3-methyl-butyric acid (118 mg, 0.674 mmol) and HATU (282 mg, 0.741 mmol) were suspended in DMF (6 mL) and cooled to 0°C before DIPEA (0.470 mL, 2.70 mmol) was added. After 60 min, the mixture was warmed to RT then filtered and purified by reverse phase preparative HPLC, giving (1-{2-[5-(4'-{[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidine-2-carbonyl]-amino}-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (136 mg, 56%). ^{1}H NMR (DMSO-d6, 400 MHz) 10.16 (s, 1H), 8.07 (s, 1H), 7.80 (d, J = 4.5 Hz, 4H), 7.70 (d, J = 4.5 Hz, 4H), 7.30 (m, 1H), 5.09 (m, 1H), 4.44 (m, 1H), 4.08 (m, 1H), 4.02 (m, 1H), 3.85-3.77 (m, 3H), 3.61 (m, 1H), 3.54 (s, 3H), 3.53 (s, 3H), 2.37 (m, 1H), 2.16-1.84 (m, 10H), 0.92 (d, J = 6.7 Hz, 3H), 0.86 (d, 6.5 Hz, 3H), 0.80 (d, J = 6.9 Hz, 3H), 0.75 (d, J = 6.6 Hz, 3H); MS (ESI) *m/z* 716 $[M + H]^+$.

Example CO



Trifluoro-methanesulfonic acid 5-trifluoromethanesulfonyloxy-naphthalen-1-yl ester: Naphthalene-1,5-diol (1 g, 6.25 mmol) was dissolved in dichloromethane (25 mL) and triethylamine (2.6 mL, 18.73 mmol) and trifluoromethanesulfonic anhydride (1.58 mL, 9.86 mmol) were added. After stirring for 16 h, the mixture was diluted with ethyl acetate (250 mL) and washed with water, saturated aqueous sodium bicarbonate and brine. The organic phase was dried over sodium sulfate, concentrated and purified by silica column chromatography (0% to 10% EtOAc/hexanes) to provide Trifluoro-methanesulfonic acid 5-trifluoromethanesulfonyloxy-naphthalen-1-yl ester (957 mg, 48%).

2-{5-[4-(5-Trifluoromethanesulfonyloxy-naphthalen-1-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester: 2-{5-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (1.30 g, 2.96 mmol), Trifluoro-methanesulfonic acid 5-trifluoromethanesulfonyloxy-naphthalen-1-yl ester (982 mg, 2.31 mmol), $Pd(PPh_3)_4$ (134 mg, 0.116 mmol) and potassium carbonate (639 mg, 4.62 mmol) were suspended in toluene. After degassing with nitrogen for 28 min, the stirred suspension was heated to 100°C for 18 hours. The reaction mixture was then

cooled to RT, diluted with ethyl acetate (250 mL), washed with water, brine, dried over magnesium sulfate and concentrated. The resulting residue was purified by silica column chromatography (0% to 60% EtOAc/hexanes) to provide 2-{5-[4-(5-Trifluoromethanesulfonyloxy-naphthalen-1-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (1.09g, 80%).

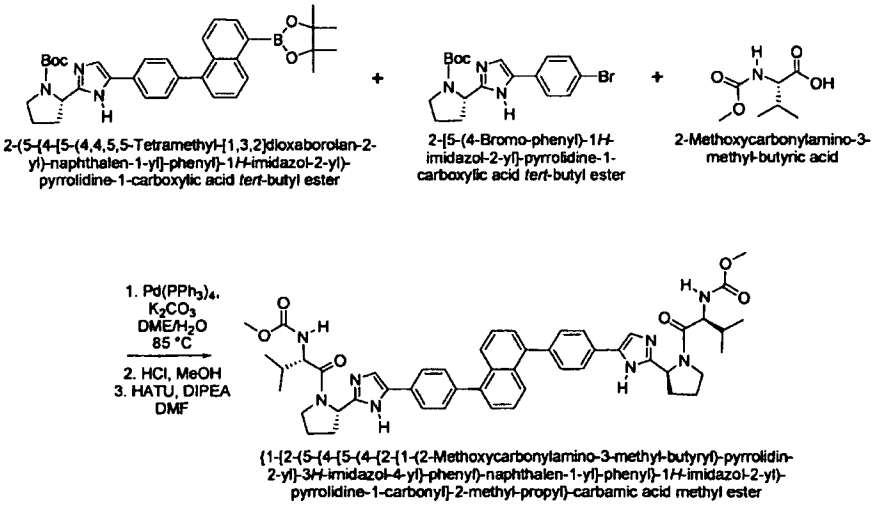
2-(5-{4-[5-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-1-yl]-phenyl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester: 2-{5-[4-(5-Trifluoromethanesulfonyloxy-naphthalen-1-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (468 mg, 0.796 mmol), bis(pinacolato)diboron (202 mg, 0.796 mmol), $Pd(dppf)_2Cl_2$ (29 mg, 0.0398 mmol) and potassium acetate (234 mg, 2.39 mmol) were suspended in dioxane (4 mL) and heated to 100°C for 90 min. After cooling to RT, the reaction mixture was diluted with ethyl acetate (100 mL) and washed with water and brine. The organic phase was dried over magnesium sulfate and concentrated. The resulting residue was purified by silica column chromatography (40% to 60% EtOAc/hexanes) to provide 2-(5-{4-[5-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-1-yl]-phenyl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (450 mg, 100%).

2-(5-{4-[5-(1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester)-naphthalen-1-yl]-phenyl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester: 2-(5-{4-[5-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-1-yl]-phenyl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (159 mg, 0.281 mmol), 2-(5-Bromo-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (178 mg (0.562 mmol), $Pd(PPh_3)_4$ (65 mg, 0.0562 mmol) and K_2CO_3 (0.281 mL of a 2 M aqueous solution, 0.562 mmol) were combined in 1,2-dimethoxyethane (3 mL) and degassed with bubbling N_2 for 12 min. The mixture was then heated to 85°C for 22 hours then cooled to RT, diluted with ethyl acetate (50 mL) and washed with water and brine. The organic phase was dried over magnesium sulfate and concentrated. The crude residue was purified by silica column chromatography (80% to 100% EtOAc/hexanes) to afford 2-(5-{4-[5-(1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester)-naphthalen-1-yl]-phenyl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (42 mg, 22%).

[1-(2-{5-[4-(5-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-naphthalen-1-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: 2-(5-{4-[5-(1H-imidazol-2-yl)-pyrrolidine-1-

carboxylic acid *tert*-butyl ester)-naphthalen-1-yl]-phenyl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (41 mg, 0.0607 mg) was dissolved in methanol (5 mL) and concentrated HCl (1 mL) was added. The mixture was stirred at 60°C for 2 hours then cooled and concentrated. To the residue was added 2-Methoxycarbonylamino-3-methyl-butyric acid (32 mg, 0.182 mmol), HATU (51 mg, 0.133 mmol) and DMF (2 mL). The mixture was cooled to 0°C and DIPEA (0.063 mL, 0.364 mmol) was added. After 30 min, water (1 mL) was added and the mixture was filtered and purified by reverse phase preparative HPLC, giving [1-(2-{5-[4-(5-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-naphthalen-1-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (17.6 mg, 38%). ^{1}H NMR (MeOH-d4, 400 MHz) 8.03 (d, J = 8.6 Hz, 1H), 7.98 (d, J = 8.6 Hz, 1H), 7.89 (m, 2H), 7.72-7.57 (m, 6H), 7.16 (m, 1H), 5.28 (m, 2H), 4.25 (m, 2H), 4.11 (m, 3H), 3.86 (m, 3H), 3.67 (s, 3H), 3.65 (s, 3H), 2.59 (m, 2H), 2.30-2.04 (m, 8H), 0.95-0.89 (m, 12H); MS (ESI) *m/z* 789 $[M + H]^+$.

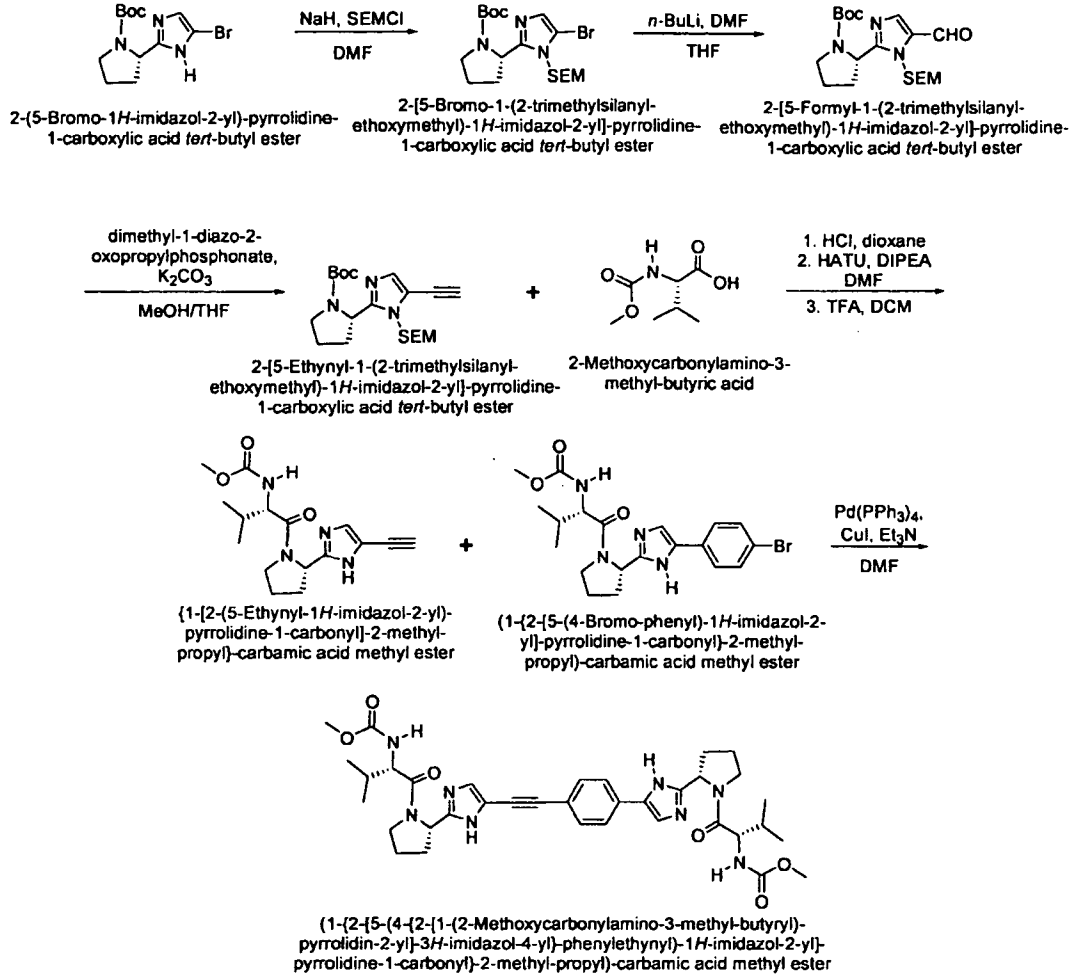
Example CP



{1-[2-(5-{4-[5-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-1-yl]-phenyl}-1H-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester: 2-(5-{4-[5-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-1-yl]-phenyl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (98 mg, 0.173 mmol), 2-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (102 mg, 0.260 mmol), $Pd(PPh_3)_4$ (40 mg, 0.035 mmol) and potassium carbonate (0.173 mL of a 2 M aqueous solution, 0.346 mmol) were suspended in 1,2-dimethoxyethane. The mixture was degassed for 10 min then heated to 85°C for 4 hours. The contents were then cooled to RT, diluted with ethyl acetate (50 mL), washed

with water and brine, dried over magnesium sulfate and concentrated. The crude residue was purified by silica column chromatography (80% to 100% EtOAc/hexanes) to provide {1-[2-(5-{4-[5-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-1-yl]-phenyl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid tert butyl ester (28 mg, 22%). The Suzuki product was dissolved in methanol (5 mL) and treated with concentrated HCl (1 mL). The mixture was heated to 60°C for 100 min then cooled and concentrated. To the residue was added 2-Methoxycarbonylamino-3-methyl-butyric acid (20 mg, 0.112 mmol), HATU (31 mg, 0.0821 mmol) and DMF (2 mL). The stirred mixture was cooled to 0°C then DIPEA (0.033 mL, 0.187 mmol) was added. After 50 min, the reaction mixture was diluted with 1 mL of water and purified by reverse phase preparative HPLC to provide {1-[2-(5-{4-[5-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-1-yl]-phenyl}-1H-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (12 mg, 38%). ^{1}H NMR (MeOH-d4, 400 MHz) 7.89-7.87 (m, 4H), 7.80-7.78 (m, 4H), 7.49-7.41 (m, 8H), 5.22 (m, 2H), 4.26 (m, 2H), 4.02 (m, 2H), 3.91 (m, 2H), 3.66 (s, 6H), 2.40-2.19 (m, 6H), 2.11-2.03 (m, 4H), 0.96 (d, J = 6.6 Hz, 6H), 0.92 (d, J = 6.6 Hz, 6H); MS (ESI) *m/z* 865 $[M + H]^+$.

Example CQ



2-[5-Bromo-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester: 2-(5-Bromo-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (4 g, 12.65 mmol) was dissolved in DMF and cooled to 0°C. NaH (658 mg of 60% mineral oil dispersion, 16.45 mmol) was added and the reaction mixture was aged for 13 min before addition of SEMCl (2.7 mL, 15.18 mmol) and warming to RT. After 16 h, the reaction was quenched by water, diluted with ethyl acetate (300 mL) and washed with water and brine. The organic phase was dried over magnesium sulfate and concentrated. The crude residue was purified by silica column chromatography (10% to 30% EtOAc/hexanes) to afford 2-[5-Bromo-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (4.67 g, 83%).

2-[5-Formyl-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester: 2-[5-Bromo-1-(2-trimethylsilanyl-ethoxymethyl)-1H-

imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (3.804 g, 8.52 mmol) was dissolved in THF (42 mL) and cooled to -78°C. *n*-BuLi (3.4 mL of a 2.5 M hexane solution, 8.52 mmol) was added dropwise over 3 min. After 65 min, DMF (4 mL) was added and the reaction mixture was warmed to RT. After stirring at RT for 75 min, a saturated aqueous solution of ammonium chloride (50 mL) was added and the entire content of the flask was poured into saturated aqueous sodium bicarbonate. The aqueous phase was extracted 3 times with diethyl ether. The combined organic layers were dried over magnesium sulfate, concentrated and purified by silica column chromatography (30% to 70% EtOAc/hexanes) to provide 2-[5-Formyl-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (1.50 g, 45%).

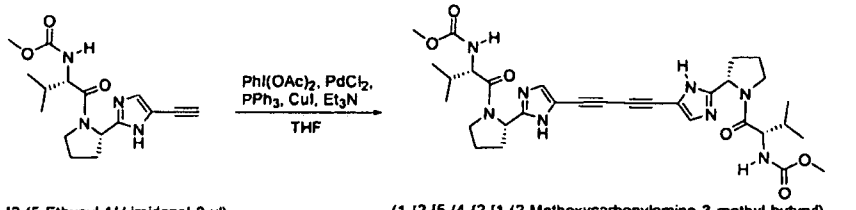
2-[5-Ethynyl-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester: 2-[5-Formyl-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (1.625 g, 4.11 mmol) and dimethyl-1-diazo-2-oxopropylphosphonate (1.056 g, 5.50 mmol) were dissolved in 1:1 MeOH/THF (10 mL) and potassium carbonate (1.14 g, 8.25 mmol) was added. After stirring for 200 min, more potassium carbonate (1.14 g, 8.25 mmol) was added. 45 min later, the reaction mixture was poured into 100 mL 1:1 water/saturated aqueous sodium bicarbonate. The aqueous phase was extracted 3 times with diethyl ether. The combined organic phases were dried with magnesium sulfate and concentrated. The crude residue was purified by silica column chromatography (20% to 45% EtOAc/hexanes) to afford 2-[5-Ethynyl-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (1.234 g, 77%).

{1-[2-(5-Ethynyl-1H-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester: 2-[5-Ethynyl-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (1.002 g, 2.56 mmol) was dissolved in dioxane (5 mL) and 4 M HCl in dioxane (5 mL) was added. The reaction mixture was stirred for 3 hours and concentrated. To the residue was added 2-Methoxycarbonylamino-3-methyl-butyric acid (561 mg, 3.20 mmol), HATU (1.22 g, 3.20 mmol) and DMF (15 mL). The stirred reaction mixture was cooled to 0°C and DIPEA (2.23 mL, 12.8 mmol) was added). After stirring for 3 h, the reaction mixture was diluted with ethyl acetate and washed with a saturated aqueous solution of sodium bicarbonate and brine. The combined organic layers were dried over magnesium sulfate and concentrated. The crude residue was purified by silica column chromatography (40% to 75% EtOAc/hexanes) to provide the coupled compound (741 mg, 65% over 2 steps). This material was dissolved in dichloromethane (10 mL) and trifluoroacetic acid (5 mL) was

added. The stirred reaction mixture was heated to reflux for 4 h, then cooled to RT, and poured into a saturated aqueous solution of sodium bicarbonate. The aqueous phase was extracted 3 times with dichloromethane. The combined organic layers were dried over magnesium sulfate and concentrated. The crude residue was purified by silica column chromatography (0% to 10% MeOH/DMC) to provide {1-[2-(5-Ethynyl-1H-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (525 mg, 100%).

(1-{2-[5-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenylethynyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: {1-[2-(5-Ethynyl-1H-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (46 mg, 0.144 mmol), (1-{2-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (78 mg, 0.173 mmol), $Pd(PPh_3)_4$ (17 mg, 0.0144 mmol), CuI (5 mg, 0.0288 mmol) and triethylamine (0.200 mL, 1.44 mmol) were suspended in DMF (1.5 mL). The reaction mixture was stirred at 80°C for 2 hours then 1 mL of water was added and the mixture was purified by reverse phase preparative HPLC, giving (1-{2-[5-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenylethynyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (24 mg, 24%). ^{1}H NMR (MeOH-d4, 400 MHz) 7.65 (d, J = 8.2 hz, 2H), 7.45 (d, J = 8.2 hz, 2H), 7.38 (s, 1H), 7.22 (s, 1H), 6.98 (m, 1H), 5.17 (m, 1H), 5.11 (m, 1H), 4.25-4.20 (m, 2H), 4.01-3.79 (m, 4H), 3.66 (s, 6H), 2.37-2.00 (m, 10H), 0.99-0.89 (m, 12H); MS (ESI) *m/z* 687 $[M + H]^+$.

Example CR



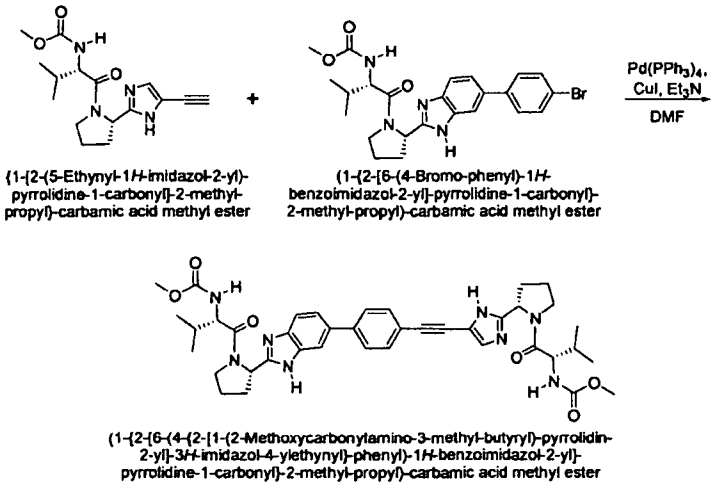
{1-[2-(5-Ethynyl-1*H*-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester

(1-{2-[5-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-buta-1,3-diynyl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

(1-{2-[5-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-buta-1,3-diynyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: Triethylamine (0.270 mL, 1.92 mmol) was added to a mixture of {1-[2-(5-Ethynyl-1H-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (61 mg, 0.192 mmol), $PhI(OAc)_2$ (247 mg, 0.766 mmol), $PdCl_2$

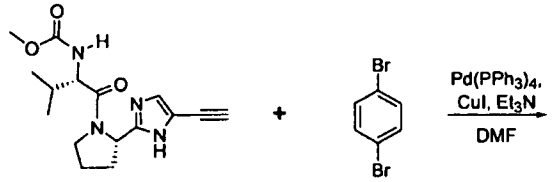
(7mg, 0.0389 mmol), PPh_3 (30 mg, 0.115 mmol) and CuI (7 mg, 0.0389 mmol) in THF (2 mL). After 50 min, the reaction mixture was filtered, concentrated and purified by reverse phase preparative HPLC, giving (1-{2-[5-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-buta-1,3-diynyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (3 mg, 5%). ^{1}H NMR (MeOH-d4, 400 MHz) 7.33 (s, 2H), 6.95 (d, J = 8.3 Hz, 2H), 5.07 (m, 2H), 4.18 (m, 2H), 3.95 (m, 2H), 3.82 (m, 2H), 3.64 (s, 6H), 2.31-1.98 (m, 10H), 1.02-0.87 (m, 12H); MS (ESI) m/z 635 $[M + H]^+$.

Example CS

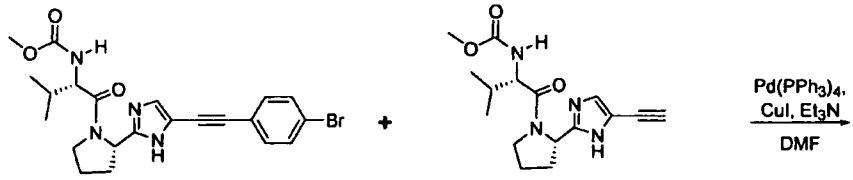


(1-{2-[6-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-ylethynyl}-phenyl)-1H-benzoimidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: {1-[2-(5-Ethynyl-1H-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (62 mg, 0.195 mmol), (1-{2-[6-(4-Bromo-phenyl)-1H-benzoimidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (73 mg, 0.146 mmol), $Pd(PPh_3)_4$ (11 mg, 0.00975 mmol), CuI (4 mg, 0.0195 mmol) and triethylamine (0.271 mL, 1.95 mmol) were suspended in DMF (2 mL). The reaction mixture was stirred at 80°C for 3 hours then 1 mL of water was added and the mixture was purified by reverse phase preparative HPLC, giving (1-{2-[6-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-ylethynyl}-phenyl)-1H-benzoimidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (12 mg, 11%). ^{1}H NMR (MeOH-d4, 400 MHz) 7.66-7.64 (m, 2H), 7.59-7.50 (m, 4H), 7.24 (s, 1H), 6.98 (m, 1H), 5.28 (m, 1H), 5.12 (m, 1H), 4.28-4.19 (m, 2H), 4.04-3.82 (m, 4H), 3.66 (s, 3H), 3.65 (s, 3H), 2.43-2.01 (m, 10H), 0.99-0.87 (m, 12H); MS (ESI) m/z 737 $[M + H]^+$.

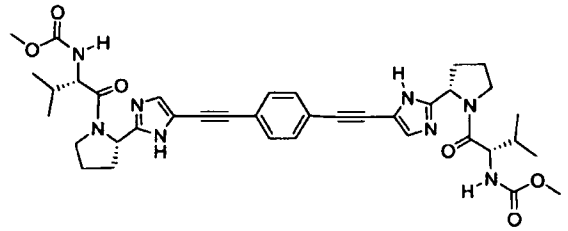
Example CT



{1-[2-(5-Ethynyl-1*H*-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester 1,4-Dibromo-benzene



(1-{2-[5-(4-Bromo-phenylethynyl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester {1-[2-(5-Ethynyl-1*H*-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester



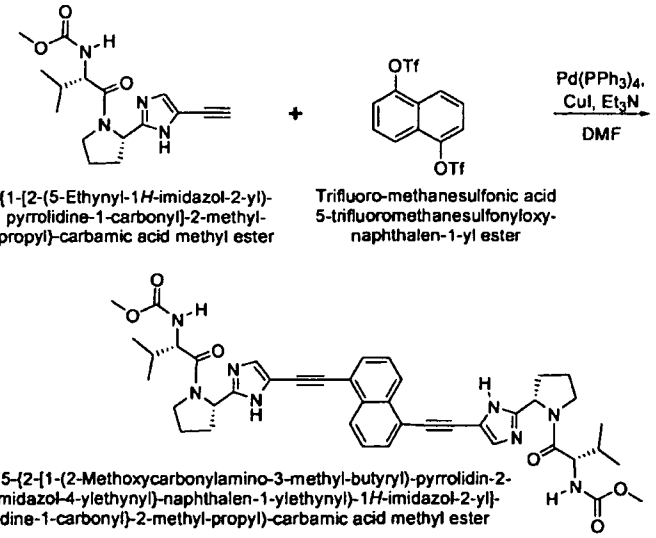
(1-{2-[5-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-ylethynyl}-phenylethynyl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

(1-{2-[5-(4-Bromo-phenylethynyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: {1-[2-(5-Ethynyl-1H-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (57 mg, 0.179 mmol), 1,4-dibromobenzene (211 mg, 0.895 mmol), $Pd(PPh_3)_4$ (10 mg, 0.00895 mmol), CuI (3 mg, 0.0179 mmol) and triethylamine (0.249 mL, 1.79 mmol) were suspended in DMF (2 mL) and the mixture was degassed for 10 min with nitrogen. The reaction mixture was stirred at 80°C for 70 min then diluted with 20 mL ethyl acetate and washed with saturated aqueous sodium bicarbonate and brine. The organic phase was dried with magnesium sulfate and concentrated. The crude residue was purified by silica column chromatography (0% to 5% MeOH/DCM) to afford (1-{2-[5-(4-Bromo-phenylethynyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (43 mg, 51%).

(1-{2-[5-(4-{2-[1-(2Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-ylethynyl}-phenylethynyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: {1-[2-(5-Ethynyl-1H-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (49 mg, 0.154 mmol), (1-{2-[5-(4-

bromo-phenylethynyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (43 mg, 0.0908 mmol), $Pd(PPh_3)_4$ (10 mg, 0.00908 mmol), CuI (2 mg, 0.00908 mmol) and triethylamine (0.127 mL, 0.908 mmol) were suspended in DMF (2 mL) and the mixture was degassed for 10 min with nitrogen. The reaction mixture was stirred at 80°C for 4 hours then cooled to RT. Formic acid (0.1 mL) and water (1 mL) were added and the mixture was purified by reverse phase preparative HPLC, giving (1-{2-[5-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-ylethynyl}-phenylethynyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (11 mg, 17%). ^{1}H NMR (MeOH-d4, 400 MHz) 7.46 (d, J = 3.9 Hz, 4H), 7.25 (s, 2H), 6.96 (d, J = 8.4 Hz, 2H), 5.10 (m, 2H), 4.20 (m, 2H), 3.97 (m, 2H), 3.83 (m, 2H), 3.64 (s, 6H), 2.32-2.00 (m, 10H), 0.98-0.88 (m, 12H); MS (ESI) *m/z* 711 $[M + H]^+$.

Example CU



{1-[2-(5-Ethynyl-1*H*-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester

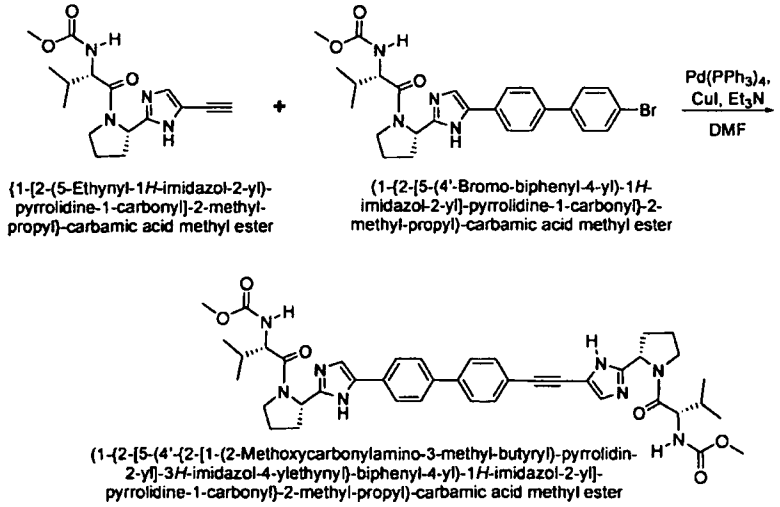
Trifluoro-methanesulfonic acid 5-trifluoromethanesulfonyloxy-naphthalen-1-yl ester

(1-{2-[5-(5-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-ylethynyl}-naphthalen-1-ylethynyl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

(1-{2-[5-(5-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-ylethynyl}-naphthalen-1-ylethynyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: {1-[2-(5-Ethynyl-1H-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (98 mg, 0.207 mmol), trifluoro-methanesulfonic acid 5-trifluoromethanesulfonyloxy-naphthalen-1-yl ester (29 mg, 0.0683 mmol), $Pd(PPh_3)_4$ (12 mg, 0.0104 mmol), CuI (2 mg, 0.0104 mmol) and triethylamine (0.144 mL, 1.04 mmol) were suspended in DMF (2 mL) and the mixture was degassed for 10 min with nitrogen. The reaction mixture was stirred at 80°C for 90 min then cooled to RT. Formic acid (0.1 mL) and water (1 mL) were added and the mixture was purified by reverse phase preparative HPLC, giving (1-{2-[5-(5-{2-[1-(2-Methoxycarbonylamino-3-methyl-

butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-ylethynyl}-naphthalen-1-ylethynyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (30 mg, 58%). ^{1}H NMR (MeOH-d4, 400 MHz) 8.38 (d, J = 8.2 Hz, 2H), 7.71 (d, J = 7.2 Hz, 2H), 7.57-7.51 (m, 2H), 7.35 (s, 2H), 6.96 (d, J = 8.4 Hz, 2H), 5.13 (m, 2H), 4.20 (m, 2H), 3.95 (m, 2H), 3.83 (m, 2H), 3.63 (s, 6H), 2.33-1.98 (m, 10H), 0.97-0.87 (m, 12H); MS (ESI) *m/z* 761 $[M + H]^+$.

Example CV



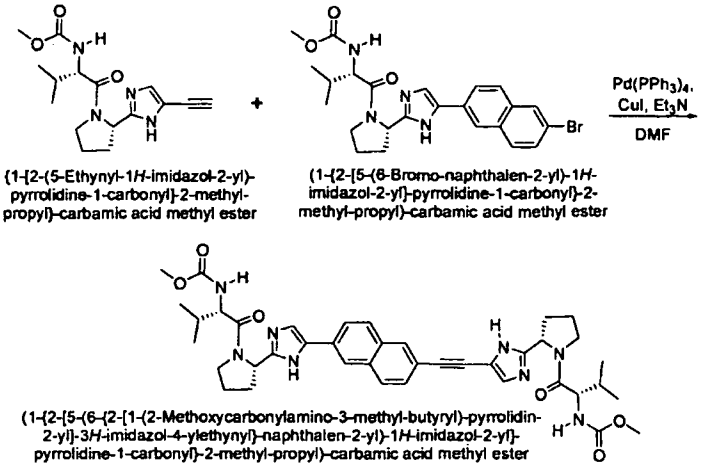
{1-[2-(5-Ethynyl-1*H*-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester

(1-{2-[5-(4'-Bromo-biphenyl-4-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

(1-{2-[5-(4'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-ylethynyl}-biphenyl-4-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

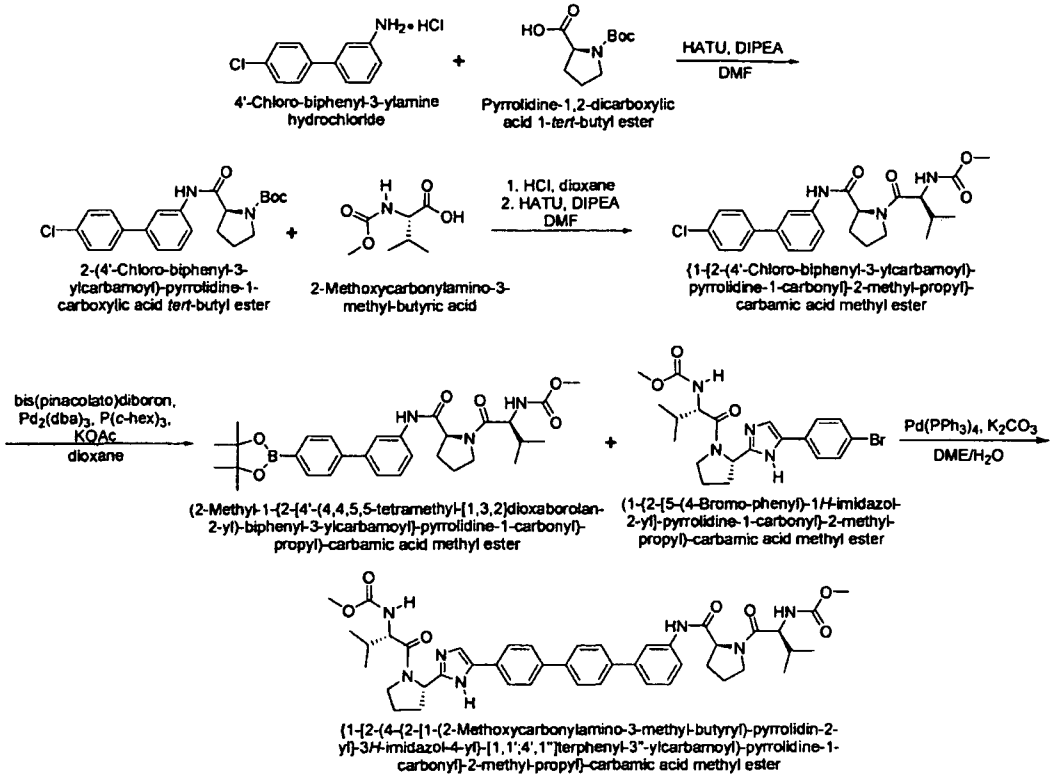
(1-{2-[5-(4'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-ylethynyl}-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: {1-[2-(5-Ethynyl-1H-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (44 mg, 0.138 mmol), (1-{2-[5-(4'-Bromo-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (67 mg, 0.128 mmol), $Pd(PPh_3)_4$ (15 mg, 0.0128 mmol), CuI (2 mg, 0.0128 mmol) and triethylamine (0.180 mL, 1.28 mmol) were suspended in DMF (2 mL) and the mixture was degassed for 10 min with nitrogen. The reaction mixture was stirred at 80°C for 15 hours then cooled to RT. Formic acid (0.1 mL) and water (1 mL) were added and the mixture was purified by reverse phase preparative HPLC, giving (1-{2-[5-(4'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-ylethynyl}-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (12 mg, 12%). ^{1}H NMR (MeOH-d4, 400 MHz) 7.73 (d, J = 8.4 Hz, 2H), 7.66-7.64 (m, 4 H), 7.52 (d, J = 8.2 Hz, 2H), 7.35 (s, 1H), 7.24 (s, 1H), 6.98 (m, 2H), 5.18 (m, 1H), 5.11 (m, 1H), 4.26-4.19 (m, 2H), 4.01-3.80 (m, 4H), 3.65 (s, 6H), 2.37-2.01 (m, 10H), 1.00-0.88 (m, 12H); MS (ESI) *m/z* 763 $[M + H]^+$.

Example CW



(1-{2-[5-(6-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-ylethynyl}-naphthalen-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: {1-[2-(5-Ethynyl-1H-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (53 mg, 0.166 mmol), (1-{2-[5-(6-Bromo-naphthalen-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (100 mg, 0.200 mmol), $Pd(PPh_3)_4$ (19 mg, 0.0166 mmol), CuI (3 mg, 0.0166 mmol) and triethylamine (0.230 mL, 1.66 mmol) were suspended in DMF (2 mL) and the mixture was degassed for 10 min with nitrogen. The reaction mixture was stirred at 80°C for 1 hours then cooled to RT. Formic acid (0.1 mL) and water (1 mL) were added and the mixture was purified by reverse phase preparative HPLC, giving (1-{2-[5-(6-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-ylethynyl}-naphthalen-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (24 mg, 20%). (DMSO-d6, 400 MHz) 12.00-11.85 (m, 2H), 7.99-7.83 (m, 4H), 7.64 (s, 1H), 7.48 (m, 1H), 7.42 (s, 1H), 7.29 (m, 2H), 5.10 (m, 1H), 5.03 (m, 1H), 4.06 (m, 2H), 3.82-3.76 (m, 4H), 3.54 (s, 6H), 2.15-1.97 (m, 10H), 0.94-0.81 (m, 12H); MS (ESI) *m/z* 737 $[M + H]^+$.

Example CX



2-(4'-Chloro-biphenyl-3-ylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester: 4'-Chloro-biphenyl-3-ylamine hydrochloride (1g, 4.16 mmol), Pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester (1.08 g, 5.00 mmol) and HATU (2.06 g, 5.41 mmol) were suspended in DMF (20 mL) and DIPEA (2.20 mL, 12.5 mmol) was added. The mixture was stirred for 16 hours before being diluted with ethyl acetate (250 mL) and washed with water and brine. The organic layer was dried over magnesium sulfate and concentrated. The crude residue was purified by silica column chromatography (25% to 45% EtOAc/hexanes) to provide 2-(4'-Chloro-biphenyl-3-ylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (1.66g, 99%).

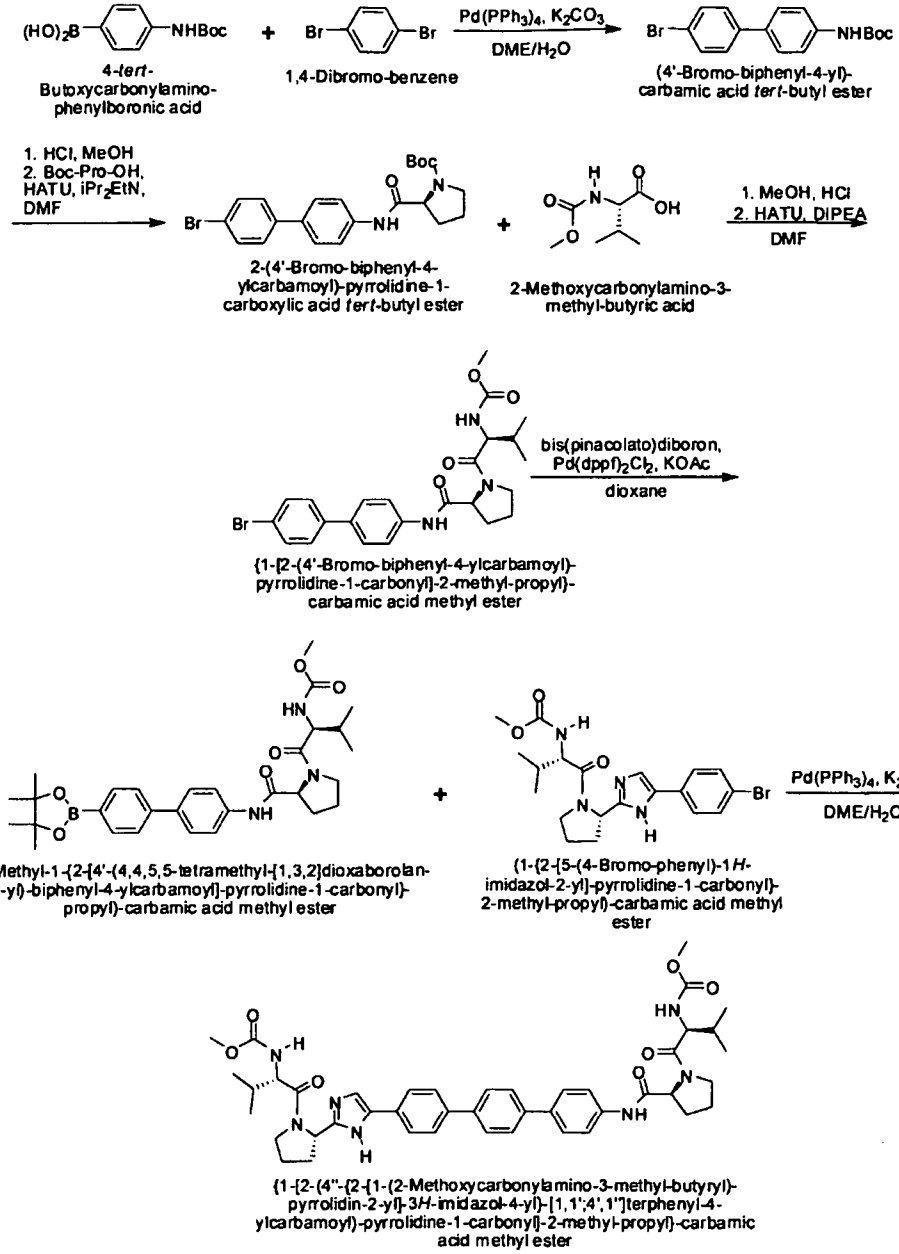
{1-[2-(4'-Chloro-biphenyl-3-ylcarbamoyl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester: 2-(4'-Chloro-biphenyl-3-ylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (1.66 g, 4.14 mmol) was dissolved in methanol (20 mL) and concentrated HCl (4 mL) was added. The mixture was stirred at 50°C for 80 min then cooled and concentrated. The residue was treated with 2-methoxycarbonylamino-3-methyl-butyric acid (870 mg, 4.97 mmol) and HATU (2.05 g, 5.38 mmol) and brought up in DMF (20 mL). The mixture was cooled to 0°C and DIPEA (3.60 mL, 20.7 mmol). After 100 min, the reaction mixture was diluted with ethyl acetate (250 mL) and washed with water and brine. The organic

phase was dried over magnesium sulfate and concentrated. The resulting residue was purified by silica column chromatography (50% to 80% EtOAc/hexanes) to afford {1-[2-(4'-Chloro-biphenyl-3-ylcarbamoyl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (1.83 g, 96% over 2 steps).

(2-Methyl-1-{2-[4'-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-biphenyl-3-ylcarbamoyl]-pyrrolidine-1-carbonyl}-propyl)-carbamic acid methyl ester: {1-[2-(4'-Chloro-biphenyl-3-ylcarbamoyl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (409 mg, 0.893 mmol), bis(pinacolato)diboron (249 mg, 0.982 mmol), $Pd_2(dba)_3$ (20 mg, 0.0223 mmol), tris(cyclohexyl)phosphine (30 mg, 0.107 mmol) and potassium acetate (131 mg, 1.34 mmol) were suspended in dioxane (5 mL) and degassed with nitrogen for 4 min. The stirred suspension was heated to 80°C for 14 hours before being cooled to RT, diluted with ethyl acetate (250 mL) and washed with water and brine. The organic phase was dried over magnesium sulfate and concentrated. The residue was purified by silica column chromatography (55% to 85% EtOAc/hexanes) to afford (2-Methyl-1-{2-[4'-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-biphenyl-3-ylcarbamoyl]-pyrrolidine-1-carbonyl}-propyl)-carbamic acid methyl ester (491 mg, 100%).

{1-[2-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-[1,1';4',1"]terphenyl-3"-ylcarbamoyl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester: (2-Methyl-1-{2-[4'-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-biphenyl-3-ylcarbamoyl]-pyrrolidine-1-carbonyl}-propyl)-carbamic acid methyl ester (135 mg, 0.246 mmol), (1-{2-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (110 mg, 0.246 mmol), $Pd(PPh_3)_4$ (14 mg, 0.0123 mmol) and a 2 M aqueous solution of potassium carbonate (0.246 mL, 0.492 mmol) were degassed in 1,2-dimethoxyethane (2.5 mL) for 13 min. The stirred suspension was heated to 85°C for 3 hours then concentrated, brought up in DMF/water and purified by reverse phase preparative HPLC to provide {1-[2-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-[1,1';4',1"]terphenyl-3"-ylcarbamoyl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (10 mg, 5%). (MeOH-d4, 400 MHz) 7.90 (s, 1H), 7.82-7.66 (m, 8H), 7.54-7.51 (m, 1H), 7.40-7.37 (m, 2H), 4.59 (m, 1H), 4.24 (m, 1H), 4.02-3.73 (m, 4H), 3.66 (s, 3H), 3.65 (s, 3H), 2.36-2.02 (m, 10H), 1.15-0.88 (m, 12H); MS (ESI) *m/z* 792 $[M + H]^+$.

Example CY



(4'-Bromo-biphenyl-4-yl)-carbamic acid *tert*-butyl ester: 4-*tert*-Butoxycarbonylamino-phenylboronic acid (500 mg, 2.11 mmol), 1,4-dibromo-benzene (2.00 g, 8.44 mmol) $Pd(PPh_3)_4$ (122 mg, 0.106 mmol) and a 2 M aqueous solution of potassium carbonate (4.2 mL, 8.44 mmol) were degassed in 1,2-dimethoxyethane (20 mL) for 10 min. The stirred suspension was heated to 80°C for 3 hours then diluted with ethyl acetate (60 mL) and washed with water and brine. The organic phase was dried over magnesium sulfate and concentrated. The residue was purified by silica column chromatography (0% to 20% EtOAc/hexanes) to provide (4'-Bromo-biphenyl-4-yl)-carbamic acid *tert*-butyl ester (430 mg, 59%).

2-(4'-Bromo-biphenyl-4-ylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester: (4'-Bromo-biphenyl-4-yl)-carbamic acid *tert*-butyl ester (407 mg, 1.17 mmol) was dissolved in methanol (10 mL) and concentrated HCl (2 mL) was added. The solution was stirred at 60°C for 1 hour then concentrated. The crude residue was treated with Boc-Pro-OH (302 mg, 1.40 mmol) and HATU (578 mg, 1.52 mmol) and suspended in DMF (6 mL). DIPEA (1.02 mL, 5.85 mmol) was added and the reaction mixture was stirred at RT for 4 hours after which it was diluted with ethyl acetate (200 mL) and washed with water and brine. The organic phase was dried over magnesium sulfate and concentrated. The residue was purified by silica column chromatography (30% to 55% EtOAc/hexanes) to afford 2-(4'-Bromo-biphenyl-4-ylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (496 mg, 95% over 2 steps).

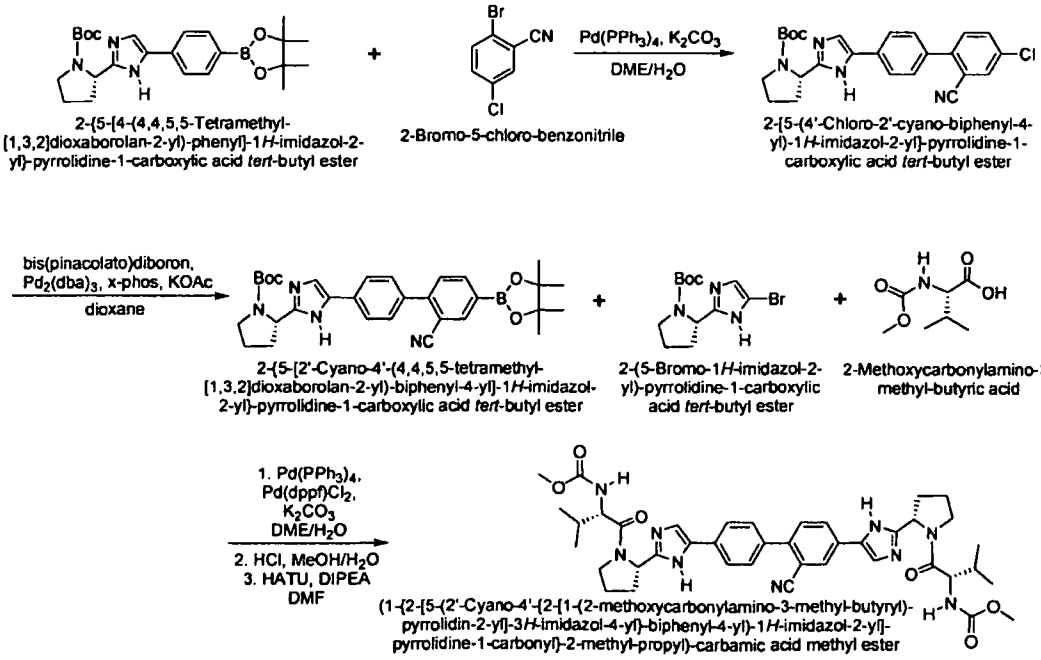
{1-[2-(4'-Bromo-biphenyl-4-ylcarbamoyl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester: 2-(4'-Bromo-biphenyl-4-ylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (496 mg, 1.11 mmol) was dissolved in methanol and concentrated HCl (2 mL) was added. The solution was stirred at 60°C for 30 min then concentrated. The resulting residue was treated with 2-methoxycarbonylamino-3-methyl-butyric acid (233 mg, 1.33 mmol), HATU (549 mg, 1.44 mmol) and DMF (10 mL). After cooling this mixture to 0°C, DIPEA (0.970 mL, 5.55 mmol) was added. The reaction mixture was Stirred for 5 hours then diluted with ethyl acetate (150 mL) and washed with water and brine. The organic phase was dried over magnesium sulfate and concentrated. The resulting residue was purified by silica column chromatography (70% to 90% EtOAc/hexanes) to afford {1-[2-(4'-Bromo-biphenyl-4-ylcarbamoyl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (520 mg, 93% over 2 steps).

2-Methyl-1-{2-[4'-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-biphenyl-4-ylcarbamoyl]-pyrrolidine-1-carbonyl}-propyl)-carbamic acid methyl ester: {1-[2-(4'-Bromo-biphenyl-4-ylcarbamoyl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (154 mg, 0.307 mmol), bis(pinacolato)diboron (156 mg, 0.613 mmol), $Pd(dppf)_2Cl_2$ (11 mg, 0.0154 mmol) and potassium acetate (90 mg, 1.21 mmol) were suspended in dioxane and degassed for 15 min. The stirred reaction mixture was heated to 100°C for 2 hours then cooled to RT, diluted with ethyl acetate (100 mL) and washed with water and brine. The organic phase was dried over magnesium sulfate and concentrated. The residue was purified by silica column chromatography (70% to 90% EtOAc/hexanes) to afford (2-Methyl-1-{2-[4'-(4,4,5,5-

tetramethyl-[1,3,2]dioxaborolan-2-yl)-biphenyl-4-ylcarbamoyl]-pyrrolidine-1-carbonyl}-propyl)-carbamic acid methyl ester (127 mg, 75%).

{1-[2-(4''-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-[1,1';4',1'']terphenyl-4-ylcarbamoyl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester: (2-Methyl-1-{2-[4'-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-biphenyl-4-ylcarbamoyl]-pyrrolidine-1-carbonyl}-propyl)-carbamic acid methyl ester (102 mg, 0.227 mmol), (1-{2-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (125 mg, 0.227 mmol), $Pd(PPh_3)_4$ (13 mg, 0.0114 mmol) and a 2 M aqueous solution of potassium carbonate (0.227 mL, 0.454 mmol) were degassed in 1,2-dimethoxyethane (2mL) for 15 min. The stirred suspension was heated to 85°C for 4 hours then concentrated, brought up in DMF/water and purified by reverse phase preparative HPLC to provide {1-[2-(4''-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-[1,1';4',1'']terphenyl-4-ylcarbamoyl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (49 mg, 27%). (DMSO-d6, 400 MHz) 11.78 (s, 1H), 10.14 (s, 1H), 7.82-7.67 (m, 11H), 7.52 (d, J = 1.8 Hz, 1H), 7.34-7.28 (m, 2H), 5.08 (m, 1H), 4.49 (m, 1H), 4.05 (m, 2H), 3.81 (m, 3H), 3.64 (m, 1H), 3.54 (s, 3H), 3.53 (s, 3H), 2.17-1.88 (m, 10H), 0.97-0.85 (m, 12H); MS (ESI) *m/z* 792 $[M + H]^+$.

Example CZ



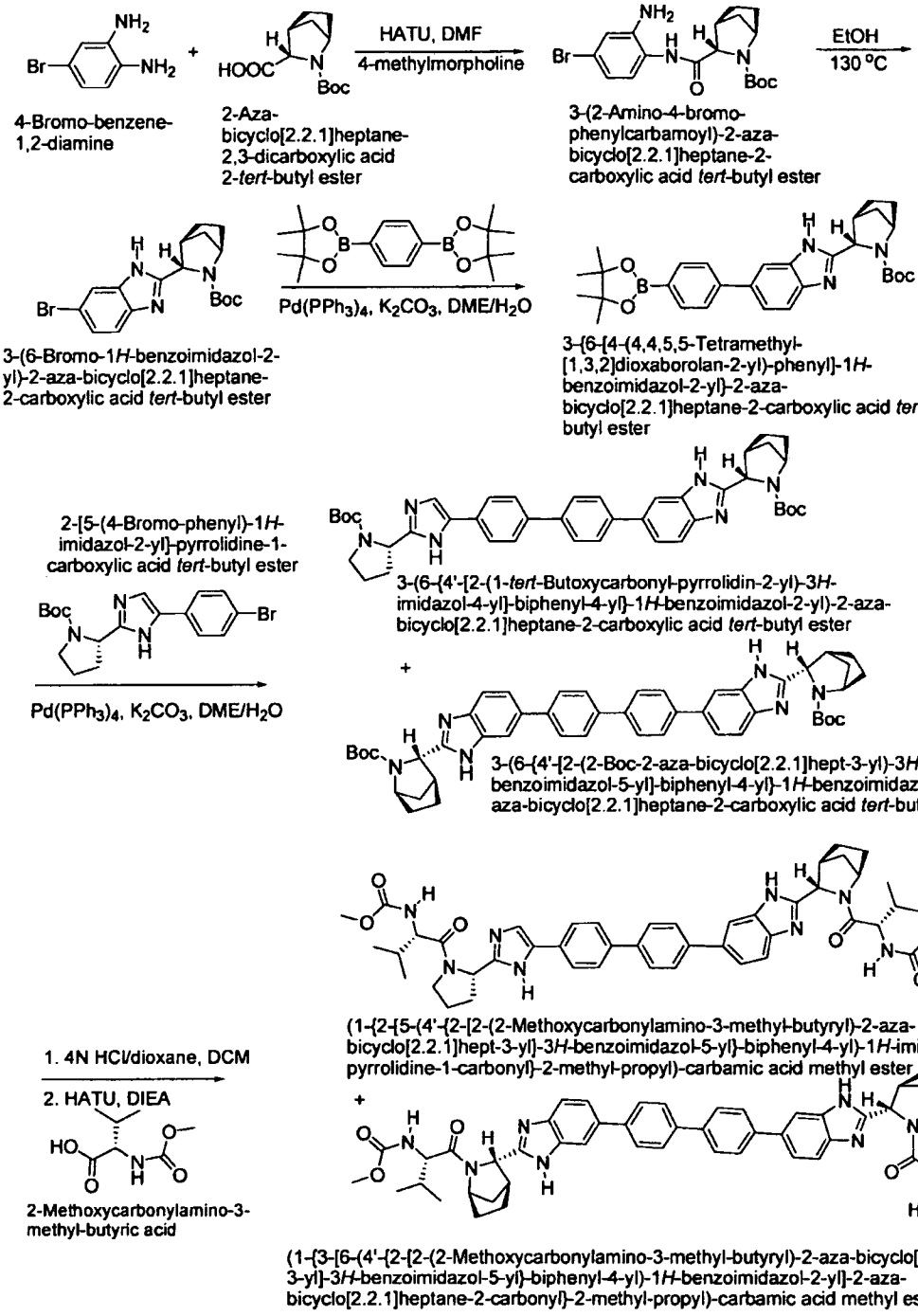
2-[5-(4'-Chloro-2'-cyano-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester: 2-{5-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (2 g, 4.55 mmol), 2-Bromo-5-chloro-benzonitrile (985 mg, 4.55 mmol), $Pd(PPh_3)_4$ (263 mg, 0.228 mmol) and a 2 M aqueous solution of potassium carbonate (4.6 mL, 9.2 mmol) were suspended in 1,2-methoxyethane (20 mL) and degassed for 10 min. The stirred reaction mixture was heated to 85°C for 21 hours then poured into a saturated aqueous solution of $NaHCO_3$ (250 mL). The aqueous phase was extracted 3 times with ethyl acetate and the combined organic layers were dried over magnesium sulfate and concentrated. The crude residue was purified by silica column chromatography (65% to 90% EtOAc/hexanes) to afford 2-[5-(4'-Chloro-2'-cyano-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (1.65 g, 81%).

2-{5-[2'-Cyano-4'-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-biphenyl-4-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester: 2-[5-(4'-Chloro-2'-cyano-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (1.68 g, 3.74 mmol), bis(pinacolato)diboron (1.43 g, 5.61 mmol), $Pd_2(dba)_3$ (86 mg, 0.0935 mmol), x-phos (214 mg, 0.449 mmol) and potassium acetate (1.10 g, 11.22 mmol) were suspended in dioxane (20 mL) and degassed for 10 min with nitrogen. The stirred reaction mixture was heated to 90°C for 15 h, then cooled and filtered over a bed of silica, eluting with ethyl acetate until all desired product was removed. The liquid was concentrated and the resulting residue was purified by silica column chromatography (55% to 80% EtOAc/hexanes) to afford 2-{5-[2'-Cyano-4'-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-biphenyl-4-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (1.57 g, 78%).

(1-{2-[5-(2'-Cyano-4'-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: 2-{5-[2'-Cyano-4'-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-biphenyl-4-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (1.60 g, 2.96 mmol), 2-(5-Bromo-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (935 mg, 2.96 mmol), $Pd(PPh_3)_4$ (171 mg, 0.148 mmol), $Pd(dppf)Cl_2$ (121 mg, 0.148 mmol) and a 2 M aqueous solution of potassium carbonate (3 mL, 6 mmol) were suspended in 1,2-dimethoxyethane and degassed for 11 min. The stirred reaction mixture was heated to 85°C for 100 min, then poured into a saturated aqueous solution of sodium bicarbonate (200 mL) and extracted 3 times with ethyl acetate. The combined organic layers were dried over magnesium sulfate and concentrated. The crude residue was purified by silica column

chromatography (5% to 10% MeOH/DCM) to afford the Suzuki coupled product (438 mg, 23%). This material (174 mg, 0.268 mmol) was treated with 4 M HCl in dioxane (4 mL). Solubility was poor so 2 mL dichloromethane and 4 mL DMF were added. After stirring for 40 min, the mixture was concentrated. The crude residue was treated with 2-Methoxycarbonylamino-3-methyl-butyric acid (103 mg, 0.590 mmol), HATU (255 mg, 0.670 mmol) and DMF (5 mL) and cooled to 0°C. DIPEA (0.470 mL, 2.68 mmol) was added and the reaction mixture was stirred for 4 hours then poured into a saturated aqueous solution of sodium bicarbonate (200 mL) and extracted 3 times with ethyl acetate. The combined organic layers were dried over magnesium sulfate and concentrated. The crude residue was brought up in DMF and water and purified by reverse phase preparative HPLC, giving (1-{2-[5-(2'-Cyano-4'-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (75 mg, 37%). (MeOH-d4, 400 MHz) 8.19-7.35 (m, 11H), 5.18 (m, 2H), 4.24 (m, 2H), 4.03-4.86 (m, 4H), 3.65 (s, 6H), 2.37-2.00 (m, 10H), 1.00-0.90 (m, 12H); MS (ESI) *m/z* 764 $[M + H]^+$.

Example DA and DB



3-(2-Amino-4-bromo-phenylcarbamoyl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester: To a solution of 2-Aza-bicyclo[2.2.1]heptane-2,3-dicarboxylic acid 2-*tert*-butyl ester (0.327 g, 1.36 mmol, 1 eq.), 4-Bromo-benzene-1,2-diamine (0.507 g, 2.71 mmol, 2 eq.) and 4-methylmorpholine (0.299 mL, 2 eq.) in 10 mL DMF was added HATU (0.543g, 1.05 eq.). The reaction mixture was stirred at room temperature for 1 hour then concentrated down. The

reaction mixture was diluted with ethyl acetate and washed with diluted NaHCO3 aqueous solution and brine. The organic layer was concentrated down and purified by flash column chromatography (silica gel, 20 to 80% ethyl acetate/hexane) to give a mixture of regioisomer 3-(2-Amino-4-bromo-phenylcarbamoyl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester.

3-(6-Bromo-1H-benzoimidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester: The above mixture of regioisomer 3-(2-Amino-4-bromo-phenylcarbamoyl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester was dissolved in ethanol and heated to 130°C in sealed tube overnight and continue heating at 170°C for 3 days. LC-MS showed desired product and Boc cleaved product (about 1:1 ratio). The mixture was concentrated down and dissolved DCM. Di-*tert*-butyl dicarbonate (0.6 eq.) was added and reaction was stirred overnight at room temperature. The reaction mixture was concentrated down and purified by flash column chromatography (silica gel, 20 to 80% ethyl acetate/hexane) to give 3-(6-Bromo-1H-benzoimidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (0.383 g, 72%) as an orange foam.

3-{6-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-benzoimidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester: A mixture of 3-(6-Bromo-1H-benzoimidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (264 mg, 0.673 mmol), Benzene-1,4-diboronic acid dipinocal ester (5 eq., 3.36 g, 6.95 mmol), tetrakis(triphenylphosphine)palladium (5%, 39 mg) and 2M potassium carbonate aqueous solution (3 eq., 1.01 mL) in 5 mL DME was heated to 90°C under Ar for 4 hours. The reaction mixture was cooled down and diluted in ethyl acetate and washed with saturated sodium bicarbonate solution. The organic layer dried (MgSO4), concentrated and purified by flash column chromatography (silica gel, 20 to 60% ethyl acetate/hexane) to give 3-{6-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-benzoimidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (295 mg, yield 85%). LCMS-ESI⁻: calc'd for $C_{30}H_{38}BN_3O_4$: 515.45; Found: 516.1 ($M+H^+$).

3-(6-{4'-[2-(1-*tert*-Butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-biphenyl-4-yl}-1H-benzoimidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester and 3-(6-{4'-[2-(2-Boc-2-aza-bicyclo[2.2.1]hept-3-yl)-3H-benzoimidazol-5-yl]-biphenyl-4-yl}-1H-benzoimidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester: A mixture of 2-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl

ester(295 mg, 0.573 mmol, 1 eq.), 3-{6-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-benzoimidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (269 mg, 0.687 mmol), tetrakis(triphenylphosphine)palladium (5%, 33 mg) and 2M potassium carbonate aqueous solution (5 eq., 1.43 mL) in 5 mL DME was heated to 90°C under Argon overnight. The reaction mixture was cooled and dissolved in ethyl acetate and washed with saturated sodium bicarbonate solution. The organic layer dried (MgSO4), concentrated and purified by flash column chromatography (silica gel, 50 to 100% ethyl acetate/hexane) to give 3-(6-{4'-[2-(1-*tert*-Butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-biphenyl-4-yl}-1H-benzoimidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (163 mg, yield 40%) and trace amount of byproduct 3-(6-{4'-[2-(2-Boc-2-aza-bicyclo[2.2.1]hept-3-yl)-3H-benzoimidazol-5-yl]-biphenyl-4-yl}-1H-benzoimidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester. LCMS-ESI$^-$ of 3-(6-{4'-[2-(1-*tert*-Butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-biphenyl-4-yl}-1H-benzoimidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester: calc'd for $C_{42}H_{48}N_6O_4$: 700.87; Found: 701.1 ($M+H^+$).

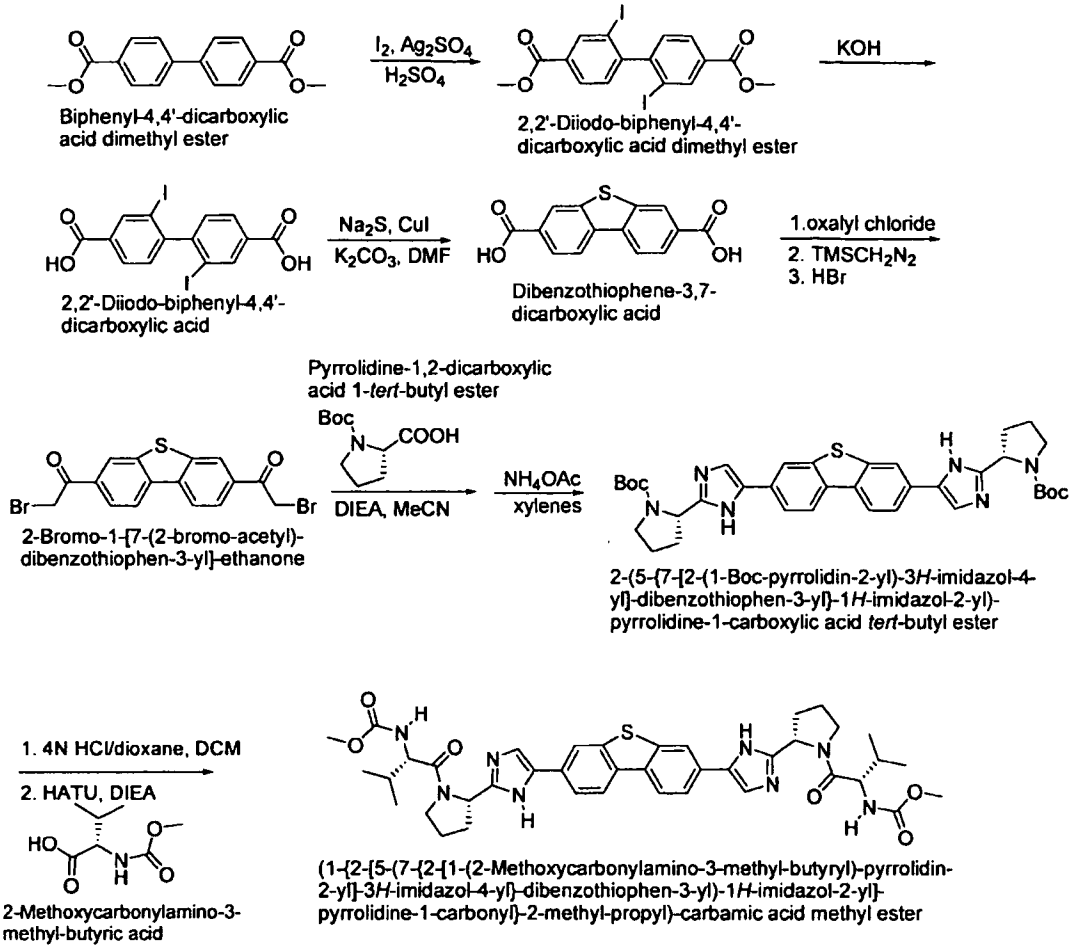
(1-{2-[5-(4'-{2-[2-(2-Methoxycarbonylamino-3-methyl-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-benzoimidazol-5-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (Example **DA**) and **(1-{3-[6-(4'-{2-[2-(2-Methoxycarbonylamino-3-methyl-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-benzoimidazol-5-yl}-biphenyl-4-yl)-1H-benzoimidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester** (Example **DB**): 4N HCl in dioxane (3 mL)was added to 3-(6-{4'-[2-(1-*tert*-Butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-biphenyl-4-yl}-1H-benzoimidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester and 3-(6-{4'-[2-(2-Boc-2-aza-bicyclo[2.2.1]hept-3-yl)-3H-benzoimidazol-5-yl]-biphenyl-4-yl}-1H-imidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester mixture (163 mg, 0.233 mmol) in 3 mL DCM and the reaction mixture was stirred at room temperature for 2hours. The reaction mixture was concentrated and dried overnight under vacuum. The residue was dissolved in DMF (3 mL) and to this solution was added 2-Methoxycarbonylamino-3-methyl-butyric acid (2.1 eq., 85 mg), 4-methylmorpholine (6 eq., 0.15 mL), followed by HATU (2 eq., 181 mg). Reaction mixture was stirred at 0°C for 50 minutes. The reaction mixture was dissolved in ethyl acetate and washed with dilute sodium bicarbonate solution. The organic layer was dried (MgSO4), concentrated and purified by preparative reverse phase HPLC (GEMINI, 5 to 100% MeCN/H_2O + 0.1% TFA). Product was lyophilized to give (1-{2-[5-(4'-{2-[2-(2-Methoxycarbonylamino-3-methyl-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-benzoimidazol-5-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-

1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (Example **DA**) (102 mg) and byproduct (1-{3-[6-(4'-{2-[2-(2-Methoxycarbonylamino-3-methyl-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-benzoimidazol-5-yl}-biphenyl-4-yl)-1H-benzoimidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (Example **DB**) (10.6 mg).

Example **DA**: ^{1}H-NMR: 300 MHz, (DMSO-d_6) δ: 8.13 (s, 1H), 7.95-7.80 (m, 12H), 7.40-7.20 (m, 2H), 5.18-5.10 (m, 1H), 4.76(m, 1H), 4.55(m,1H), 4.20-4.10 (m, 3H), 3.92-3.78 (m, 3H), 3.55(d, 6H), 2.76 (m, 1H), 2.40-1.55 (m, 10H), 0.95-0.78 (m, 12 H).
LCMS-ESI$^+$: calc'd for $C_{46}H_{54}N_8O_6$: 814.97; Found: 815.4 ($M+H^+$).

Example **DB** (byproduct): ^{1}H-NMR: 300 MHz, (DMSO-d_6) δ: 7.95-7.72 (m, 14H), 7.38-7.24 (m, 2H), 4.75 (m, 2H), 4.55(m, 2H), 4.24-4.16 (m, 3H), 3.55(d, 6H), 2.76 (m, 2H), 2.40-1.55 (m, 9H), 0.95-0.78 (m, 12 H).
LCMS-ESI$^+$: calc'd for $C_{52}H_{58}N_8O_6$: 891.07; Found: 891.4 ($M+H^+$).

Example DC



2,2'-Diiodo-biphenyl-4,4'-dicarboxylic acid dimethyl ester: Biphenyl-4,4'-dicarboxylic acid dimethyl ester(5g, 18.5 mmol) and silver sulfate (17 g, 54.5 mmol) were dissolved in 60 mL concentrated sulfuric acid with vigorous stirring. Iodine (11g, 43.3 mmol) was added portion wise to give a purple solution which was stirred at room temperature for 1 hour. The reaction mixture was heated to 80°C for overnight. The reaction mixture was cooled down, poured into ice water and sodium thiosulfate solution. Brown solid was formed, filtered and dried over vacuum at 80°C. The brown solid was extracted using a Soxhlet extraction with methanol in two batches. The product crystallized during extraction. Crystal was collected and dried to give a yellow solid 2,2'-Diiodo-biphenyl-4,4'-dicarboxylic acid dimethyl ester (5.7 g, 59%).

2,2'-Diiodo-biphenyl-4,4'-dicarboxylic acid: 2,2'-Diiodo-biphenyl-4,4'-dicarboxylic acid dimethyl ester (3.24 g, 6,21 mmol) was dissolved in 20 mL THF and KOH (1.02g, 2.5eq.) was added, followed by 5 mL water. The reaction was stirred at room tempature overnight. The

reaction was heated to 50°C for 7 hours. The reaction was cooled to room temprature. Organic solvent was removed by rotovap. The aqueous layer was acidified with concentrated HCl to give pale white solid. The solid was filtered and dried on vacumm overnight to give the product 2,2'-Diiodo-biphenyl-4,4'-dicarboxylic acid (2.74 g, yield 89%).

Dibenzothiophene-3,7-dicarboxylic acid: A mixture of 2,2'-Diiodo-biphenyl-4,4'-dicarboxylic acid (450 mg, 0.912 mmol, 1 eq.) and potassium carbonate (189 mg, 1.5 eq.) in 5 mL DMF was heated to 100°C to give a reddish brown mixture. Sodium sulfide (36 mg, 0.5 eq.) and copper(I) iodide (17 mg, 0.1 eq.) were added and reaction mixture was heated to 150°C under a slow stream of Ar. CuI (100 mg) was added and followed by sodium sulfide (100 mg). The reaction was kept at 150°C overnight. The reaction mixture was diluted with 25 mL water and active carbon (10 g) was added. The mixture was refluxed for 10 minutes then filtered through CELITE pad into 6N HCL (50 mL) and washed with water. The solid was formed and cooled to room tempature and filtered and washed with and dired to give product Dibenzothiophene-3,7-dicarboxylic acid (179 mg, 72%).

2-Bromo-1-[7-(2-bromo-acetyl)-dibenzothiophen-3-yl]-ethanone: A mixture of dibenzothiophene-3,7-dicarboxylic acid (179 mg, 0.644 mmol), oxalyl chloride (0.56 mL, 6.44 mmol) and 1 drop of DMF in 6 mL DCM was stirred at room tempature overnight. The resulting cloudy yellow solution was concentrated and co-evaporated with toluene. The residue was suspended in 6 mL DCM and cooled to 0°C. TMS diazomethane (1 ml, 3 eq.) was added to the reaction mixture dropwise. The reaction was stirred at 0°C for 1 hour and then warmed to room temperature overnight. The mixture was concentrated to give a brown solid. The solid was suspended in 5 mL ethyl acetate and treated with 5.7 M HBr in HOAc (0.28 mL, 2.5 eq.) at 0°C. The mixture was warmed to room temprature over 2 hours. And then stirred at room temprature for 1 hour. Solid sodium bicarbonate was added and stirred for 30 minutes. The mixture was diluted with sodium bicarbonate solution and extracted with ethylacetate 3 times. The organic layer was concentrated down and purified by flash column chromatography (silica gel, 20 to 80% ethyl acetate/hexane) to give impure product 2-Bromo-1-[7-(2-bromo-acetyl)-dibenzothiophen-3-yl]-ethanone.

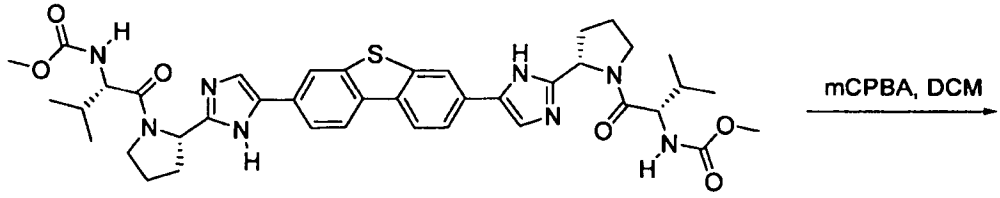
2-(5-{7-[2-(1-Boc-pyrrolidin-2-yl)-3H-imidazol-4-yl]-dibenzothiophen-3-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester:

The mixture of above impure 2-Bromo-1-[7-(2-bromo-acetyl)-dibenzothiophen-3-yl]-ethanone, Pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester (2.1 eq.), and DIEA (2.07 eq.) in 5 mL MeCN was stirred at room temperature overnight. The reaction mixture was concentrated down and diluted with ethyl acetate, washed with brine, dried over MgSO4, and concentrated down. The residue was dissolved in 1.5 mL xylenes and ammonium acetate (65 mg, 15 eq.) was added. The reaction was heated to 110°C for 2 days. The mixture was diluted with EtOAc and washed with sat.NaHCO3 aqueous solution. The organic layer was concentrated down and purified by preparative reverse phase HPLC (GEMINI, 5 to 100% MeCN/H_2O + 0.1% TFA). Product was lyophilized to give 2-(5-{7-[2-(1-Boc-pyrrolidin-2-yl)-3H-imidazol-4-yl]-dibenzothiophen-3-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (12.4 mg). LCMS-ESI$^-$: calc'd for $C_{36}H_{42}N_6O_4S$: 654.82; Found: 655.0 ($M+H^+$).

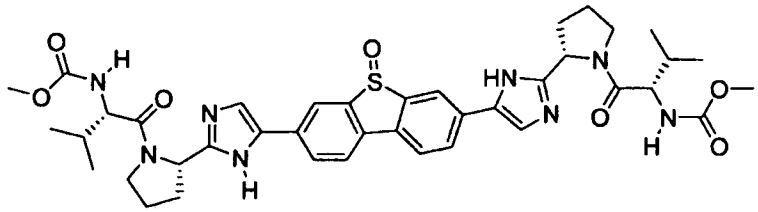
(1-{2-[5-(7-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-dibenzothiophen-3-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (Example **DC**): 4 N HCl in dioxane (1 mL)was added to 2-(5-{7-[2-(1-Boc-pyrrolidin-2-yl)-3H-imidazol-4-yl]-dibenzothiophen-3-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (12.4 mg, 0.014 mmol) and the reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated and dried overnight under vacuum. The residue was dissolved in DMF (1 mL) and to this solution was added 2-Methoxycarbonylamino-3-methyl-butyric acid (2.08 eq., 5.1 mg), 4-methylmorpholine (6 eq., 9.2 μL), followed by HATU (2.04 eq., 10.9 mg). Reaction mixture was stirred at 0°C for 90 minutes. The reaction mixture was diluted with ethyl acetate and washed with saturated sodium bicarbonate solution. The organic layer was dried (MgSO4), concentrated and purified by preparative reverse phase HPLC (GEMINI, 5 to 100% MeCN/H_2O + 0.1% TFA). Product was lyophilized to give (1-{2-[5-(7-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-dibenzothiophen-3-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (Example **DC**) (8.1 mg, 58%).

^{1}H-NMR: 300 MHz, (CD_3OD-d_4) δ: 8.41-8.25 (m, 4H), 7.92-7.78 (m, 4H), 5.22(m, 2H), 4.22(m, 2H), 4.08(m,2H), 3.86 (m, 2H), 3.62 (d, 6H), 2.60-2.50 (m, 2H), 2.30-1.92 (m, 8H), 0.97-0.82 (m, 12 H). LCMS-ESI$^+$: calc'd for $C_{40}H_{48}N_8O_6S$: 768.92; Found: 769.3 ($M+H^+$).

Example DD



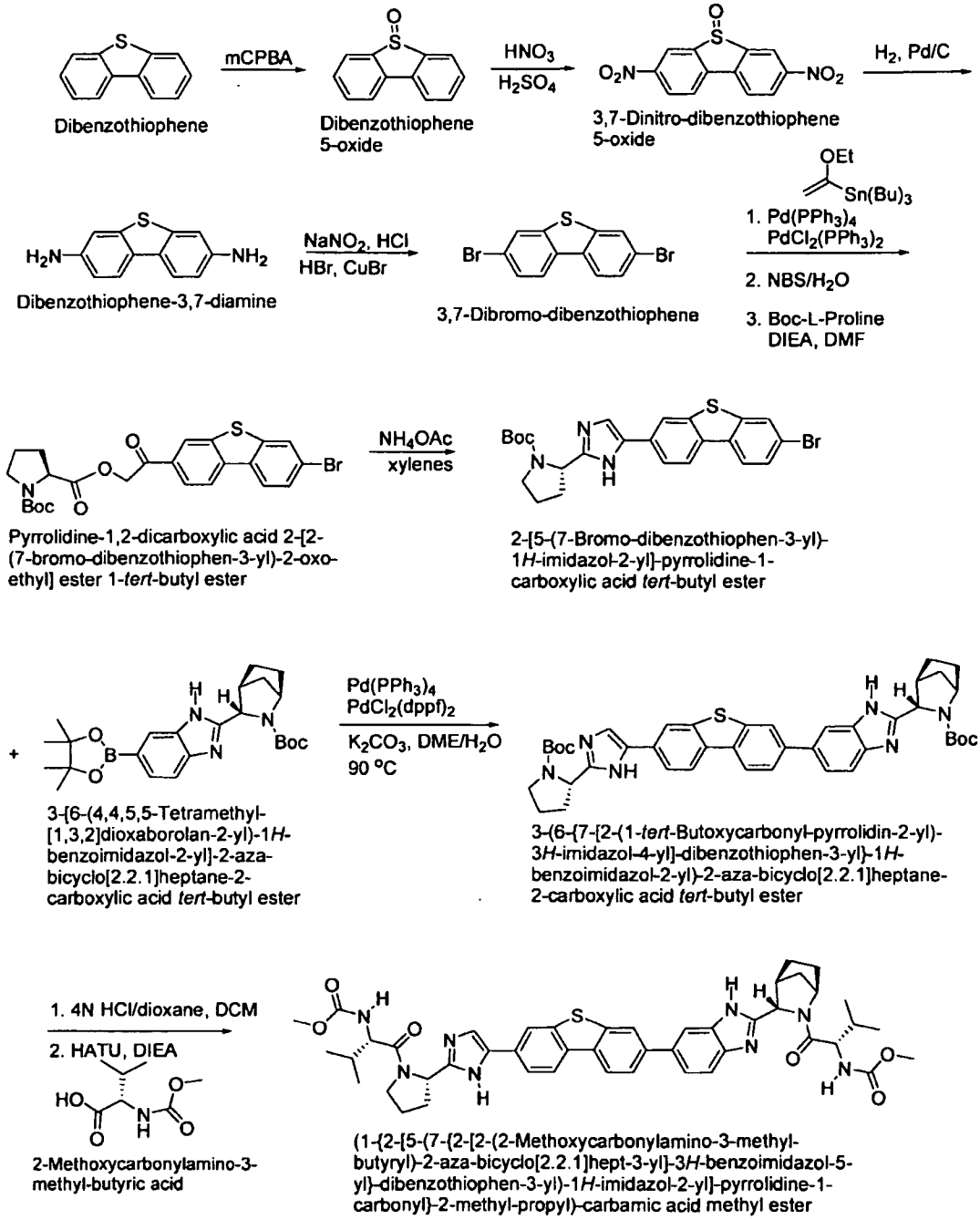
(1-{2-[5-(7-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-dibenzothiophen-3-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester



(1-{2-[5-(7-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-5-oxo-5*H*-5λ^4-dibenzothiophen-3-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

(1-{2-[5-(7-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-5-oxo-5H-5λ^4-dibenzothiophen-3-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (Example **DD**): (1-{2-[5-(7-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-dibenzothiophen-3-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (0.0041 mmol., 4 mg) was dissolved in 1 mL DCM and cooled to -40°C. mCPBA(0.4 mg, 0.9 eq.) was added. The reaction mixture was stirred at -40°C for 2 hours and warmed up to 0°C over 2 hours, then warmed up to room temperature overnight. The reaction mixture was diluted with ethyl acetate and washed with saturated sodium bicarbonate solution. The organic layer was dried (MgSO4), concentrated and purified by preparative reverse phase HPLC (GEMINI, 5 to 100% ACN/H_2O + 0.1% TFA). Product was lyophilized to give a yellow powder (1-{2-[5-(7-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-5-oxo-5H-5λ^4-dibenzothiophen-3-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (Example **DD**) (0.6 mg). ^{1}H-NMR: 300 MHz, (CD_3OD-d_4) δ: 8.36 (m, 2H), 8.18-7.90 (m, 6H), 5.22(m, 2H), 4.19(m, 2H), 4.05(m,2H), 3.84(m, 2H), 3.61 (d, 6H), 2.56-1.96 (m, 10H), 0.97-0.84 (m, 12 H). LCMS-ESI$^+$: calc'd for $C_{40}H_{48}N_8O_6S$: 768.92; Found: 769.3 ($M+H^+$).

Example DE



Dibenzothiophene 5-oxide: A solution of mCPBA (8.27 g, 36.9 mmol) in 71 mL chloroform was added dropwise over 30 minutes to a solution of dibenzothiophene in 89 mL chloroform at -35°C. The reaction mixture was stirred at -35°C for 1 hour and then warmed up to room. The reaction was quenched with saturated sodium bicarbonate aqueous solution. The organic layer was washed with saturated sodium bicarbonate solution twice and dried over MgSO4,

concentrated down to give an off-white solid. The solid was dissolved in refluxing ethanol and slowly cooled to room temperature to give a white crystalline solid Dibenzothiophene 5-oxide (5.65g, 76%). LCMS-ESI⁻: calc'd for $C_{12}H_8OS$: 200.26; Found: 200.9 ($M+H^+$).

3,7-Dinitro-dibenzothiophene 5-oxide: A solution of Dibenzothiophene 5-oxide (5.34g, 26.7 mmol) in concentrated sulfuric acid (120 mL) was cooled to 6°C. Nitric acid (108 mL) was added slowly so that the internal temperature stayed at 10°C. The reaction was stirred at 10°C for 30 minutes then warmed up to room temperature over 30 minutes. The reaction mixture was poured into ice and formed precipitate. The precipitate was washed with water and dried to give a yellow solid 3,7-Dinitro-dibenzothiophene 5-oxide (7.8 g, still containing some water and inorganic material).

Dibenzothiophene-3,7-diamine: Two batches of the above solid 3,7-dinitro-dibenzothiophene 5-oxide was hydrogenated at 45 psi in ethanol (250 mL for each batch) with 10% Pd on carbon (0.46 g each batch) for 2 hours. Two batches were combined and filtered through CELITE to give an orange solution. Hydrogen chloride gas was bubbled into the solution to form precipitate (at pH 1). The precipitate was filtered and washed with small amount of ethanol and dried on vacuum to give an orange solid Dibenzothiophene-3,7-diamine (2.46 g). LCMS-ESI⁻: calc'd for $C_{12}H_{10}N_2S$: 214.29; Found: 215.0 ($M+H^+$).

3,7-Dibromo-dibenzothiophene: A suspension of Dibenzothiophene-3,7-diamine (2.46 g, 8.57 mmol) in water (16 mL) and concentrated HCl (4.3 mL) was cooled to 5°C (internal temperature). A solution of sodium nitrite (1.54 g, 25.67 mmol) in water (5 mL) was added dropwise so that the internal temperature didn't exceed to 10°C. After 1 hour the reaction mixture was poured into a solution of CuBr (1.8 g, 12.55 mmol) in 48% HBr (18 mL). The mixture was transferred into a 1 L 3 neck flask using water (100 mL) and refluxed for 2 hours. The reaction mixture was cooled down and poured into ice water mixture. Precipitate formed and collected by filtration, dried and purified by flash column chromatography (silica gel, 0 to 10% MeOH/ethyl acetate) to give a white solid 3,7-Dibromo-dibenzothiophene (1.6 g, 55%).

Pyrrolidine-1,2-dicarboxylic acid 2-[2-(7-bromo-dibenzothiophen-3-yl)-2-oxo-ethyl] ester 1-*tert*-butyl ester:

[1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II)(3%, 69 mg, 0.098 mmol) and tetrakis(triphenylphosphine)palladium (3%, 113 mg, 0.098 mmol) were added to the mixture of 3,7-Dibromo-dibenzothiophene (1.12 g, 3.27 mmol) and tributyl(1-ethoxyvinyl)tin (1.2 eq., 1.33

mL) in 25 mL dioxane. The reaction was heated to 80°C under Ar overnight. The reaction was cooled to room temprature. 8 mL water was added and followed by NBS (1eq., 699 mg). The reaction was stirred at room for 1 hour. The reaction mixture was diluted with ethyl acetate and washed with saturated sodium bicarbonate solution. The organic layer dried (MgSO4), concentrated down and dried on vacuum to give a residue which was used in next step.

The residue was dissolved in 20 mL anhydrous DMF. Boc-L-Pro-OH (4 eq., 2.815 g) was added, followed by DIEA (3.5 eq., 1.60 mL) in 20 mL MeCN and 15 mL DMF dropwise. The reaction was stirred at room temperature overnight. The reaction crude was diluted with EtOAc and washed with saturated sodium bicarbonate solution. The organic layer was dried (MgSO4), concentrated and purified by flash column chromatography (silica gel, 0 to 50% ethyl acetate/hexane) to give Pyrrolidine-1,2-dicarboxylic acid 2-[2-(7-bromo-dibenzothiophen-3-yl)-2-oxo-ethyl] ester 1-*tert*-butyl ester (593 mg, yield 33%) and bis product. LCMS-ESI⁻: calc'd for $C_{24}H_{24}BrNO_5S$: 518.42; Found: 541.9(M+Na^+).

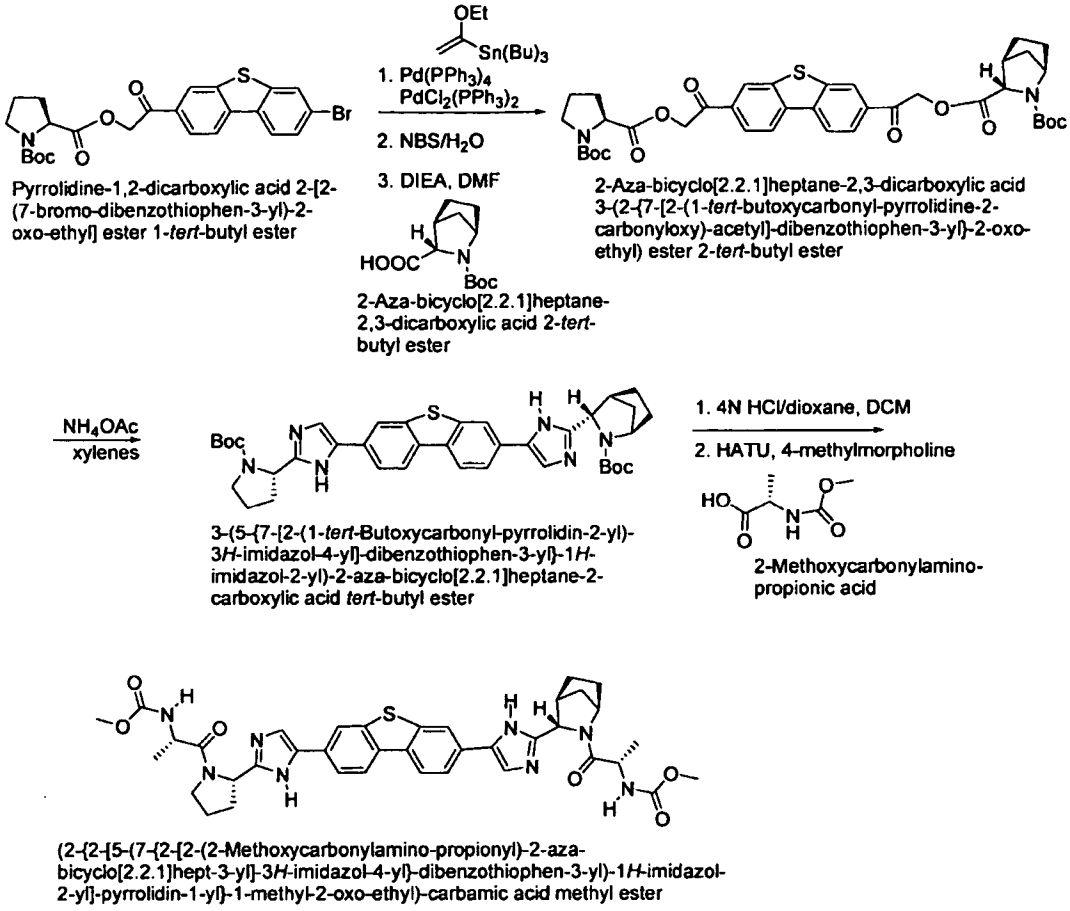
2-[5-(7-Bromo-dibenzothiophen-3-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester: 10 mL Xylenes was added to the mixture of Pyrrolidine-1,2-dicarboxylic acid 2-[2-(7-bromo-dibenzothiophen-3-yl)-2-oxo-ethyl] ester 1-*tert*-butyl ester (514 mg, 0.99 mmol) and ammonia acetate (20eq., 1.53 g). The mixture was heated in microwave at 140°C for 60 minutes. The mixture was diluted with EtOAc and washed with sat.NaHCO3 aqueous solution. The organic layer was concentrated down and purified by flash column chromatography (silica gel, 20 to 80% ethyl acetate/hexane) to give 2-[5-(7-Bromo-dibenzothiophen-3-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (391 mg, yield 79%). LCMS-ESI⁻: calc'd for $C_{24}H_{24}BrN_3O_2S$: 498.44; Found: 499.9(M+Na^+).

3-(6-{7-[2-(1-*tert*-Butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-dibenzothiophen-3-yl}-1H-benzoimidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester: A mixture of 2-[5-(7-Bromo-dibenzothiophen-3-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (300 mg, 0.48 mmol, 1 eq.), 3-[6-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-benzoimidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (1.1 eq., 530 mg), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)(3%, 12 mg), tetrakis(triphenylphosphine)palladium (3%, 17 mg) and 2N potassium carbonate aqueous solution (3.3 eq., 0.8 mL) in 2 mL DME was heated to 80°C under Argon for 5 hours. The reaction mixture was cooled and diluted in ethyl acetate and washed with saturated sodium bicarbonate solution. The organic layer dried (MgSO4), concentrated and purified by flash

column chromatography (silica gel, 20 to 100% ethyl acetate/hexane) to give a yellow foam 3-(6-{7-[2-(1-*tert*-Butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-dibenzothiophen-3-yl}-1H-benzoimidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (245 mg, yield 70%). LCMS-ESI$^-$: calc'd for $C_{42}H_{46}N_6O_4S$: 730.92; Found: 731.2($M+H^+$).

(1-{2-[5-(7-{2-[2-(2-Methoxycarbonylamino-3-methyl-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-benzoimidazol-5-yl}-dibenzothiophen-3-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (Example **DE**): 4N HCl in dioxane (3 mL) was added to 3-(6-{7-[2-(1-*tert*-Butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-dibenzothiophen-3-yl}-1H-benzoimidazol-2-yl)-2-aza-bicyclo [2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (141 mg, 0.194 mmol) in 3 mL DCM. The reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated and dried overnight under vacuum. The residue was dissolved in DMF (4 mL) and to this solution was added 2-Methoxycarbonylamino-3-methyl-butyric acid (2.08 eq., 71 mg), 4-methylmorpholine (6 eq., 0.12 mL), followed by HATU (2.04 eq., 150 mg). Reaction mixture was stirred at 0°C for 30 minutes. The reaction mixture was diluted in ethyl acetate and washed with saturated sodium bicarbonate solution. The organic layer was dried (MgSO4), concentrated and purified by flash column chromatography (silica gel, 0 to 20% MeOH/ethyl acetate), followed by preparative reverse phase HPLC (GEMINI, 5 to 100% ACN/H_2O + 0.1% TFA). Product was lyophilized to give (1-{2-[5-(7-{2-[2-(2-Methoxycarbonylamino-3-methyl-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-benzoimidazol-5-yl}-dibenzothiophen-3-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (Example **DE**) (121 mg, 59%). ^{1}H-NMR: 300 MHz, (DMSO-d_6) δ: 8.60-8.40 (m, 4H), 8.16(m, 1H), 8.01 (m, 1H), 7.90(m, 2H), 7.76(m, 1H), 7.33 (m, 2H), 5.15(m, 1H), 4.76(m,1H), 4.56(d, 1H), 4.22-4.08(m, 3H), 3.85(m, 2H), 3.55 (d, 6H), 2.76(m,1H), 2.30-1.50 (m, 9H), 0.96-0.75 (m, 12 H). ^{19}F-NMR: 300 MHz, (CD_3OD-d_4) δ: -112.88. LCMS-ESI$^+$: calc'd for $C_{46}H_{52}N_8O_6S$: 845.02; Found: 845.4 ($M+H^+$).

Example DF



Pyrrolidine-1,2-dicarboxylic acid 2-[2-(7-bromo-dibenzothiophen-3-yl)-2-oxo-ethyl] ester 1-*tert*-butyl ester

2-Aza-bicyclo[2.2.1]heptane-2,3-dicarboxylic acid 3-(2-{7-[2-(1-*tert*-butoxycarbonyl-pyrrolidine-2-carbonyloxy)-acetyl]-dibenzothiophen-3-yl}-2-oxo-ethyl) ester 2-*tert*-butyl ester

2-Aza-bicyclo[2.2.1]heptane-2,3-dicarboxylic acid 2-*tert*-butyl ester

3-(5-{7-[2-(1-*tert*-Butoxycarbonyl-pyrrolidin-2-yl)-3*H*-imidazol-4-yl]-dibenzothiophen-3-yl}-1*H*-imidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester

2-Methoxycarbonylamino-propionic acid

(2-{2-[5-(7-{2-[2-(2-Methoxycarbonylamino-propionyl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3*H*-imidazol-4-yl}-dibenzothiophen-3-yl)-1*H*-imidazol-2-yl]-pyrrolidin-1-yl}-1-methyl-2-oxo-ethyl)-carbamic acid methyl ester

2-Aza-bicyclo[2.2.1]heptane-2,3-dicarboxylic acid 3-(2-{7-[2-(1-*tert*-butoxycarbonyl-pyrrolidine-2-carbonyloxy)-acetyl]-dibenzothiophen-3-yl}-2-oxo-ethyl) ester 2-*tert*-butyl ester:

[1,1'-Bis(triphenylphosphine) dichloropalladium(II)(3%, 14 mg, 0.02 mmol) and tetrakis(triphenylphosphine)palladium (3%, 23 mg, 0.02 mmol) were added to the mixture of Pyrrolidine-1,2-dicarboxylic acid 2-[2-(7-bromo-dibenzothiophen-3-yl)-2-oxo-ethyl] ester 1-*tert*-butyl ester (345 mg, 0.665 mmol) and tributyl(1-ethoxyvinyl)tin (1.2 eq., 0.269 mL) in 5 mL dioxane. The reaction was heated to 80°C under Are for 4 hours. The reaction was cooled to room temperature. 1.5 mL water was added and followed by NBS (1eq., 142 mg). The reaction was stirred at room for 1 hour. The reaction mixture was diluted with ethyl acetate and washed with saturated sodium bicarbonate solution. The organic layer dried (MgSO4), concentrated down and dried on vacuum to give residue which was used in next step.

The residue was dissolved in 4 mL anhydrous DMF. 2-Aza-bicyclo[2.2.1]heptane-2,3-dicarboxylic acid 2-*tert*-butyl ester (2 eq., 321 mg, 1.33 mmol g) was added, followed by TEA (2.2 eq., 204 mg) in 4 mL MeCN and 3 mL DMF dropwise. The reaction was stirred at room temperature overnight. The reaction crude was diluted with EtOAc and washed with saturated sodium bicarbonate solution. The organic layer dried (MgSO4), concentrated and purified by flash column chromatography (silica gel, 0 to 50% ethyl acetate/hexane) to give 2-Aza-bicyclo[2.2.1]heptane-2,3-dicarboxylic acid 3-(2-{7-[2-(1-*tert*-butoxycarbonyl-pyrrolidine-2-carbonyloxy)-acetyl]-dibenzothiophen-3-yl]-2-oxo-ethyl) ester 2-*tert*-butyl ester as a yellow residue (92.5 mg, yield 19%). LCMS-ESI$^-$: calc'd for $C_{38}H_{44}N_2O_{10}S$: 720.83; Found: 743.2 ($M+Na^+$).

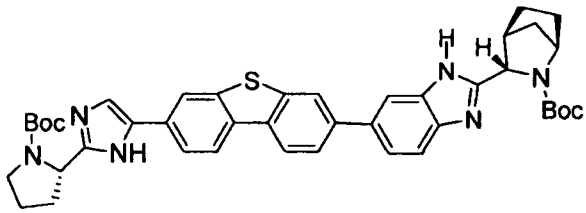
3-(5-{7-[2-(1-*tert*-Butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-dibenzothiophen-3-yl}-1H-imidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester: 3 mL Xylenes was added to 2-Aza-bicyclo[2.2.1]heptane-2,3-dicarboxylic acid 3-(2-{7-[2-(1-*tert*-butoxycarbonyl-pyrrolidine-2-carbonyloxy)-acetyl]-dibenzothiophen-3-yl]-2-oxo-ethyl) ester 2-*tert*-butyl ester (92.5 mg, 0.128 mmol) and ammonia acetate (20eq., 198 mg). The mixture was heated in microwave at 140°C for 60 minutes. The mixture was diluted with EtOAc and washed with sat.NaHCO3 aqueous solution. The organic layer was concentrated down and purified by flash column chromatography (silica gel, 20 to 80% ethyl acetate/hexane) to give 3-(5-{7-[2-(1-*tert*-Butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-dibenzothiophen-3-yl}-1H-imidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (62 mg, yield 71%). LCMS-ESI$^-$: calc'd for $C_{38}H_{44}N_6O_4S$: 680.86; Found: 681.2 ($M+H^+$).

(2-{2-[5-(7-{2-[2-(2-Methoxycarbonylamino-propionyl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-imidazol-4-yl}-dibenzothiophen-3-yl)-1H-imidazol-2-yl]-pyrrolidin-1-yl}-1-methyl-2-oxo-ethyl)-carbamic acid methyl ester (Example **DF**): 4N HCl in dioxane (1 mL) was added to 3-(5-{7-[2-(1-*tert*-Butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-dibenzothiophen-3-yl}-1H-imidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (62 mg, 0.091 mmol) in 2 mL DCM. The reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated and dried overnight under vacuum. The residue was dissolved in DMF (2 mL) and to this solution was added 2-Methoxycarbonylamino-propionic acid (2.08 eq., 28 mg), 4-methylmorpholine (6 eq., 0.06 mL), followed by HATU (2.04 eq., 71 mg). Reaction mixture was stirred at 0°C for 30 minutes. The reaction mixture was diluted with ethyl acetate and washed with saturated sodium bicarbonate solution. The organic layer was dried (MgSO4), concentrated and purified by flash column chromatography (silica gel, 0 to 20%

MeOH/ethyl acetate), followed by preparative reverse phase HPLC (GEMINI, 5 to 100% ACN/H_2O + 0.1% TFA). Product was lyophilized to give (2-{2-[5-(7-{2-[2-(2-Methoxycarbonylamino-propionyl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-imidazol-4-yl}-dibenzothiophen-3-yl)-1H-imidazol-2-yl]-pyrrolidin-1-yl}-1-methyl-2-oxo-ethyl)-carbamic acid methyl ester (Example **DF**) (52.7 mg, 60%).

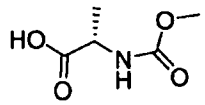
^{1}H-NMR: 300 MHz, (DMSO-d_6) δ: 8.60-8.40 (m, 4H), 8.12(m, 2H), 8.01 (m, 1H), 7.92(m, 2H), 7.57-7.40 (m, 2H), 5.15(m, 1H), 4.70 (m,1H), 4.50-4.30(m, 3H), 3.54 (d, 6H), 2.76(m,1H), 2.42-1.50 (m, 6H), 1.30 -1.10 (m, 12 H). LCMS-ESI$^+$: calc'd for $C_{42}H_{44}N_8O_6S$: 738.86; Found: 739.3 ($M+H^+$).

Example DG

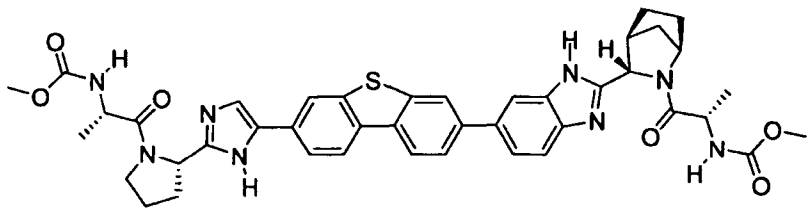


3-(6-{7-[2-(1-*tert*-Butoxycarbonyl-pyrrolidin-2-yl)-3*H*-imidazol-4-yl]-dibenzothiophen-3-yl}-1*H*-benzoimidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester

1. 4N HCl/dioxane, DCM
2. HATU, DIEA



2-Methoxycarbonylamino-propionic acid



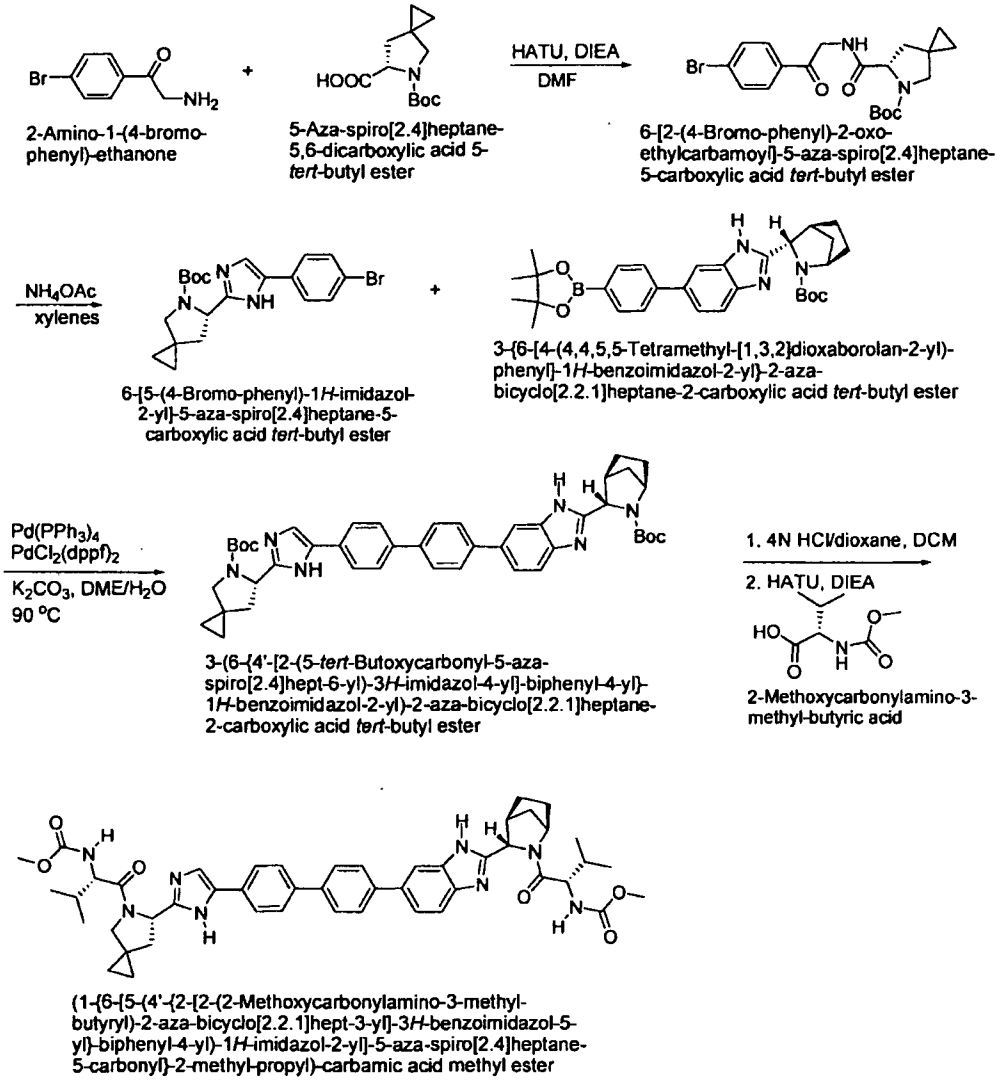
(2-{2-[5-(7-{2-[2-(2-Methoxycarbonylamino-propionyl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3*H*-benzoimidazol-5-yl}-dibenzothiophen-3-yl)-1*H*-imidazol-2-yl]-pyrrolidin-1-yl}-1-methyl-2-oxo-ethyl)-carbamic acid methyl ester

(2-{2-[5-(7-{2-[2-(2-Methoxycarbonylamino-propionyl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-benzoimidazol-5-yl}-dibenzothiophen-3-yl)-1H-imidazol-2-yl]-pyrrolidin-1-yl}-1-methyl-2-oxo-ethyl)-carbamic acid methyl ester (Example **DG**): 4N HCl in dioxane (2 mL) was added to 3-(6-{7-[2-(1-*tert*-Butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-dibenzothiophen-3-yl}-1H-benzoimidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (103 mg, 0.141 mmol) in 3 mL DCM. The reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated and dried overnight under vacuum. The residue

was dissolved in DMF (2 mL) and to this solution was added 2-Methoxycarbonylamino-propionic acid (2.08 eq., 43 mg), 4-methylmorpholine (6 eq., 0.093 mL), followed by HATU (2.04 eq., 109 mg). Reaction mixture was stirred at 0°C for 30 minutes. The reaction mixture was diluted with ethyl acetate and washed with saturated sodium bicarbonate solution. The organic layer was dried (MgSO4), concentrated and purified by flash column chromatography (silica gel, 0 to 20% MeOH/ethyl acetate), followed by preparative reverse phase HPLC (GEMINI, 5 to 100% ACN/H_2O + 0.1% TFA). Product was lyophilized to give (2-{2-[5-(7-{2-[2-(2-Methoxycarbonylamino-propionyl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-benzoimidazol-5-yl}-dibenzothiophen-3-yl)-1H-imidazol-2-yl]-pyrrolidin-1-yl}-1-methyl-2-oxo-ethyl)-carbamic acid methyl ester (Example **DG**) (91.3 mg, 80%).

^{1}H-NMR: 300 MHz, (DMSO-d_6) δ: 8.60-8.52 (m, 2H), 8.44(m, 2H), 8.15 (m, 1H), 8.05(m, 1H), 7.92 (m, 2H), 7.80 (m, 2H), 7.56-7.42(m, 2H), 5.15(m, 1H), 4.70 (m,1H), 4.50-4.30(m, 3H), 3.54 (d, 6H), 2.76(m,1H), 2.42-1.50 (m, 12H), 1.30 -1.10 (m, 6 H). LCMS-ESI$^+$: calc'd for $C_{42}H_{44}N_8O_6S$: 788.91; Found: 789.4 ($M+H^+$).

Example DH



6-[2-(4-Bromo-phenyl)-2-oxo-ethylcarbamoyl]-5-aza-spiro[2.4]heptane-5-carboxylic acid *tert*-butyl ester: 5-Aza-spiro[2.4]heptane-5,6-dicarboxylic acid 5-*tert*-butyl ester (350 mg, 1.45 mmol) was mixed with HATU (551 mg, 1.45 mmol) in DMF (5 mL) and the mixture was stirred at room temperature for 30 minutes. 2-Amino-1-(4-bromo-phenyl)-ethanone bis HCl salt (416 mg, 1.45 mmol) in 2 mL DMF was added, followed by DIEA (3.5 eq., 0.88 mL) dropwise at 0°C. The reaction was stirred at 0°C for 40 minutes. The reaction mixture was diluted in ethyl acetate and washed with saturated sodium bicarbonate solution. The organic layer was dried (MgSO4), concentrated and purified by flash column chromatography (silica gel, 20 to 100% ethyl acetate/hexane) to give 6-[2-(4-Bromo-phenyl)-2-oxo-ethylcarbamoyl]-5-aza-spiro[2.4]heptane-5-carboxylic acid *tert*-butyl ester (424 mg, 67%). LCMS-ESI$^-$: calc'd for $C_{20}H_{25}BrN_2O_4$: 437.33; Found: 460.1 ($M+Na^+$).

6-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carboxylic acid *tert*-butyl ester: 15 mL Xylenes was added to 6-[2-(4-Bromo-phenyl)-2-oxo-ethylcarbamoyl]-5-aza-spiro[2.4]heptane-5-carboxylic acid *tert*-butyl ester (424 mg, 0.97 mmol) and ammonium acetate (20eq., 1.5 g). The mixture was heated in microwave at 140°C for 60 minutes. The mixture was diluted with EtOAc and washed with sat.NaHCO3 aqueous solution. The organic layer was concentrated down and purified by flash column chromatography (silica gel, 20 to 80% ethyl acetate/hexane) to give 6-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carboxylic acid *tert*-butyl ester (249 mg, yield 61%). LCMS-ESI$^-$: calc'd for $C_{20}H_{24}BrN_3O_2$: 418.33; Found: 418. ($M+H^+$).

3-(6-{4'-[2-(5-*tert*-Butoxycarbonyl-5-aza-spiro[2.4]hept-6-yl)-3H-imidazol-4-yl]-biphenyl-4-yl}-1H-benzoimidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester: A mixture of 6-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carboxylic acid *tert*-butyl ester (101 mg, 0.243 mmol, 1 eq.), 3-{6-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-benzoimidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (150 mg, 0.291 mmol, 1.2 eq.), tetrakis(triphenylphosphine)palladium (5%, 17 mg) and 2M potassium carbonate aqueous solution (5 eq., 0.73 mL) in 1.5 mL DME was heated to 90°C under Are overnight. The reaction mixture was cooled and dissolved in ethyl acetate and washed with saturated sodium bicarbonate solution. The organic layer was dried (MgSO4), concentrated and purified by flash column chromatography (silica gel, 50 to 100% ethyl acetate/hexane) to give 3-(6-{4'-[2-(5-*tert*-Butoxycarbonyl-5-aza-spiro[2.4]hept-6-yl)-3H-imidazol-4-yl]-biphenyl-4-yl}-1H-benzoimidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (53 mg, yield 26%). LCMS-ESI$^-$: calc'd for $C_{44}H_{50}N_6O_4$: 726.91; Found: 727.2 ($M+H^+$).

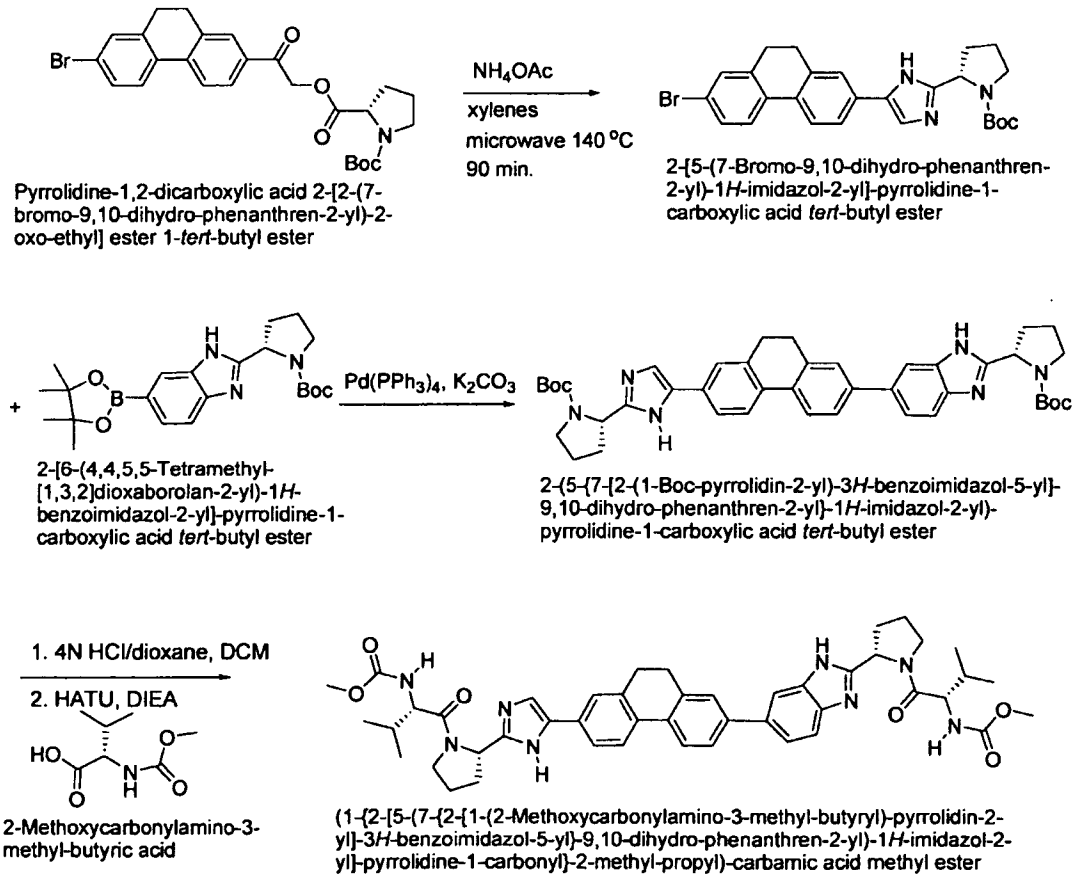
(1-{6-[5-(4'-{2-[2-(2-Methoxycarbonylamino-3-methyl-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-benzoimidazol-5-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (Example **DH**): 4N HCl in dioxane (2 mL)was added to 3-(6-{4'-[2-(5-*tert*-Butoxycarbonyl-5-aza-spiro[2.4]hept-6-yl)-3H-imidazol-4-yl]-biphenyl-4-yl}-1H-benzoimidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (53 mg, 0.073 mmol) in 2 mL DCM and the reaction mixture was stirred at room temperature for 2hours. The reaction mixture was concentrated and dried overnight under vacuum. The residue was dissolved in DMF (1 mL) and to this solution was added 2-Methoxycarbonylamino-3-methyl-butyric acid (2.1 eq., 26.6 mg), 4-methylmorpholine (6 eq.,

0.048 mL), followed by HATU (2 eq., 56 mg). Reaction mixture was stirred at 0°C for 50 minutes. The reaction mixture was dissolved in ethyl acetate and washed with dilute sodium bicarbonate solution. The organic layer was dried (MgSO4), concentrated and purified by preparative reverse phase HPLC (GEMINI, 5 to 100% ACN/H_2O + 0.1% TFA). Product was lyophilized to give (1-{6-[5-(4'-{2-[2-(2-Methoxycarbonylamino-3-methyl-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-benzoimidazol-5-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (Example **DH**) (41.6 mg, 53%).

^{1}H-NMR: 300 MHz, (DMSO-d_6) δ: 8.13 (s, 1H), 7.95-7.80 (m, 9H), 7.69 (m, 2H), 7.40-7.24 (m, 2H), 5.25 (m, 1H), 4.76(m, 1H), 4.55(m,1H), 4.20-3.80 (m, 3H), 3.55(d, 6H), 2.74 (m, 2H), 2.40-1.55 (m, 10H), 0.95-0.65 (m, 12 H).

LCMS-ESI$^+$: calc'd for $C_{46}H_{54}N_8O_6$: 841.01; Found: 841.5 ($M+H^+$).

Example DI



Pyrrolidine-1,2-dicarboxylic acid 2-[2-(7-bromo-9,10-dihydro-phenanthren-2-yl)-2-oxo-ethyl] ester 1-*tert*-butyl ester

2-[5-(7-Bromo-9,10-dihydro-phenanthren-2-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester

2-[6-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-benzoimidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester

2-{5-{7-[2-(1-Boc-pyrrolidin-2-yl)-3*H*-benzoimidazol-5-yl]-9,10-dihydro-phenanthren-2-yl}-1*H*-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester

2-Methoxycarbonylamino-3-methyl-butyric acid

(1-{2-[5-(7-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-benzoimidazol-5-yl}-9,10-dihydro-phenanthren-2-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

2-[5-(7-bromo-9,10-dihydro-phenanthren-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester: 10 mL Xylenes and 10 ml DME were added to the mixture of pyrrolidine-1,2-dicarboxylic acid 2-[2-(7-bromo-9,10-dihydro-phenanthren-2-yl)-2-oxo-ethyl] ester 1-*tert*-

butyl ester (480 mg, 0.935 mmol) and ammonia acetate (20eq., 1.44 g). The mixture was heated in microwave at 140°C for 90 minutes. The mixture was diluted with EtOAc and washed with sat.NaHCO3 aqueous solution. The organic layer was concentrated down and purified by flash column chromatography (silica gel, 20 to 80% ethyl acetate/hexane) to give 2-[5-(7-bromo-9,10-dihydro-phenanthren-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (246 mg, yield 53%). LCMS-ESI⁻: calc'd for $C_{26}H_{28}BrN_3O_2$: 494.42; Found: 495.5 ($M+H^+$).

2-(5-{7-[2-(1-Boc-pyrrolidin-2-yl)-3H-benzoimidazol-5-yl]-9,10-dihydro-phenanthren-2-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester: A mixture of 2-[5-(7-bromo-9,10-dihydro-phenanthren-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (246 mg, 0.497 mmol), 2-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-benzoimidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (1 eq., 206 mg), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)(5%, 20 mg), tetrakis(triphenylphosphine)palladium (5%, 29 mg) and potassium acetate (2 eq., 137 mg) in 5 mL DME and 1 mL water was heated to 80°C for 100 minutes. The reaction mixture was cooled and diluted with ethyl acetate and washed with saturated sodium bicarbonate solution. The organic layer dried (MgSO4), concentrated and purified by flash column chromatography (silica gel, 20 to 100% ethyl acetate/hexane) to give 2-(5-{7-[2-(1-Boc-pyrrolidin-2-yl)-3H-benzoimidazol-5-yl]-9,10-dihydro-phenanthren-2-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (220 mg, yield 63%). LCMS-ESI⁻: calc'd for $C_{42}H_{48}N_6O_4$: 700.87; Found: 701.1($M+H^+$).

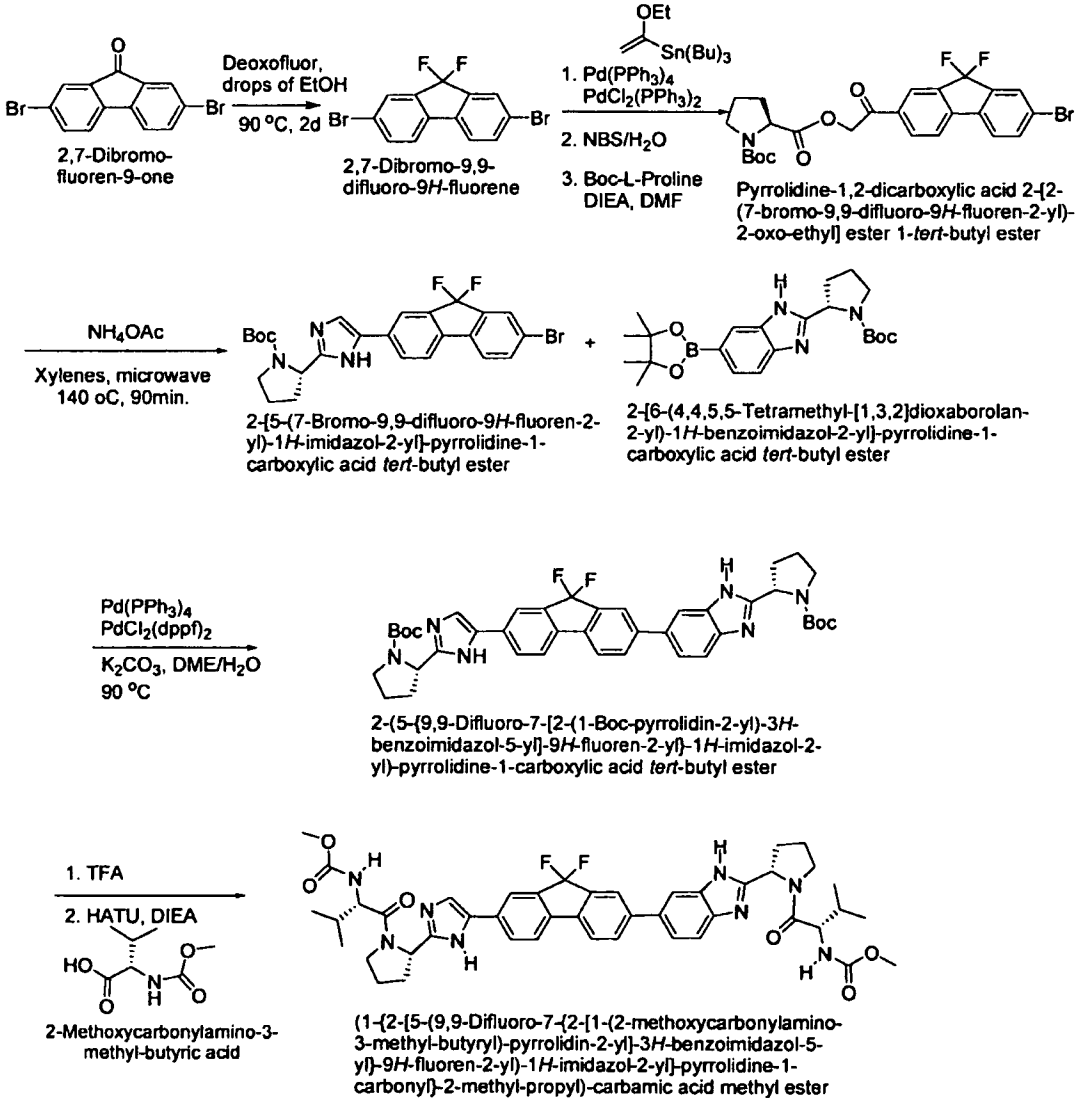
(1-{2-[5-(7-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-benzoimidazol-5-yl}-9,10-dihydro-phenanthren-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (Example A): 4N HCl in dioxane (2 mL)was added to 2-(5-{7-[2-(1-Boc-pyrrolidin-2-yl)-3H-benzoimidazol-5-yl]-9,10-dihydro-phenanthren-2-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (220 mg, 0.314 mmol) in 1 mL DCM and the reaction mixture was stirred at room temperature for 4 hours. The reaction mixture was concentrated and dried overnight under vacuum. The residue was dissolved in DMF (3 mL) and to this solution was added 2-Methoxycarbonylamino-3-methyl-butyric acid (2.1 eq., 116 mg), diisopropyl ethylamine (5 eq., 270 μL), followed by HATU (2 eq., 239 mg). Reaction mixture was stirred at 0°C for 30 minutes. The reaction mixture was dissolved in ethyl acetate and washed with dilute sodium bicarbonate solution. The organic layer was dried (MgSO4), concentrated and purified by preparative reverse phase HPLC (GEMINI, 5 to 100% ACN/H_2O + 0.1% TFA). Product was lyophilized to give (1-{2-[5-(7-{2-

[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-benzoimidazol-5-yl}-9,10-dihydro-phenanthren-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (Example **DI**) (115 mg, 45%).

^{1}H-NMR: 300 MHz, (CD_3OD-d_4) δ: 8.02-7.95 (m, 3H), 7.95-7.80 (m, 3H), 7.66-7.62 (m, 4H), 5.40-5.23(m, 2H), 4.22(m, 2H), 4.16(m,2H), 3.96-3.82 (m, 2H), 3.62 (s, 6H), 3.00(s, 4H), 2.60 (m, 2H), 2.40-2.18 (m, 6H), 2.08(m, 2H), 0.95-0.85 (m, 12 H).

LCMS-ESI$^+$: calc'd for $C_{46}H_{54}N_8O_6$: 814.97; Found: 815.4 ($M+H^+$).

Example DJ



2,7-Dibromo-9,9-difluoro-9H-fluorene: Deoxofluor (bis(2-methoxyethyl)aminosulfur trifluoride, 12 mL) was added to 2,7-dibromo-fluoren-9-one (3 grams, 8.87 mmol), followed by 2 drops of ethanol. The reaction mixture was heated to 90°C. The reaction progress was monitored by analytical HPLC and TLC (in pure hexane). The product is more non-polar than the starting material. The reaction was complete after 2 days. The reaction mixture was cooled down, poured into ice water and neutralized by saturated sodium bicarbonate solution, then was extracted using ethyl acetate and washed with saturated sodium bicarbonate solution twice. The organic layer was dried (MgSO4), concentrated and purified by flash column chromatography (silica gel, 0 to 20% ethyl acetate/hexane) give product 2,7-dibromo-9,9-difluoro-9H-fluorene (3.1 gram, yield 97%).
^{1}H-NMR: 300 MHz, ($CDCl_3$) δ: 7.76 (s, 2H), 7.62 (d, 2H), 7.42 (d, 2H). F-NMR: 300 MHz, ($CDCl_3$) δ: -111.57.

Pyrrolidine-1,2-dicarboxylic acid 2-[2-(7-bromo-9,9-difluoro-9H-fluoren-2-yl)-2-oxo-ethyl] ester 1-*tert*-butyl ester: [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II)(5%, 82 mg) and tetrakis(triphenylphosphine)palladium (5%, 115 mg) were added to the mixture of 2,7-dibromo-9,9-difluoro-9H-fluorene (720 mg, 3 mmol) and tributyl(1-ethoxyvinyl)tin (1 eq., 0.677 mL) in 12 mL dioxane. The reaction was heated to 70°C under Argon for 4 hours. The reaction was cooled to room temprature. 3 mL water was added and followed by NBS (1eq., 356 mg). The reaction was stirred at room temprature overnight. The reaction mixture was dissolved in ethyl acetate and washed with saturated sodium bicarbonate solution. The organic layer dried (MgSO4), concentrated down. The residue was dissolved in 15 mL anhydrous DMF. Boc-L-Pro-OH (4 eq., 1.72 g) was added, followed by DIEA (3.5 eq., 1.22 mL) in 5 mL MeCN and 5 mL DMF dropwise. The reaction was stirred at room temperature for 3 hours. The reaction crude was diluted with EtOAc and washed with saturated sodium bicarbonate solution. The organic layer dried (MgSO4), concentrated and purified by flash column chromatography (silica gel, 20 to 100% ethyl acetate/hexane) to give pyrrolidine-1,2-dicarboxylic acid 2-[2-(7-bromo-9,9-difluoro-9H-fluoren-2-yl)-2-oxo-ethyl] ester 1-*tert*-butyl ester (363 mg, yield 34%). LCMS-ESI$^-$: calc'd for $C_{25}H_{24}BrF_2NO_5$: 536.36; Found: 560.0(M+Na^+), 535.9 (M-H).

2-[5-(7-Bromo-9,9-difluoro-9H-fluoren-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester: 10 mL Xylenes was added to the mixture of pyrrolidine-1,2-dicarboxylic acid 2-[2-(7-bromo-9,9-difluoro-9H-fluoren-2-yl)-2-oxo-ethyl] ester 1-*tert*-butyl ester (363 mg, 0.677 mmol) and ammonia acetate (20eq., 1.04 g). The mixture was heated in microwave at 140°C for 90 minutes. The mixture was diluted with EtOAc and washed with sat.NaHCO3 aqueous solution. The organic layer was concentrated down and purified by flash column chromatography (silica gel, 20 to 80% ethyl acetate/hexane) to give 2-[5-(7-Bromo-9,9-difluoro-9H-fluoren-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (324 mg, yield 81%). LCMS-ESI$^-$: calc'd for $C_{25}H_{24}BrF_2N_3O_2$: 516.38; Found: 517.9 ($M+H^+$).

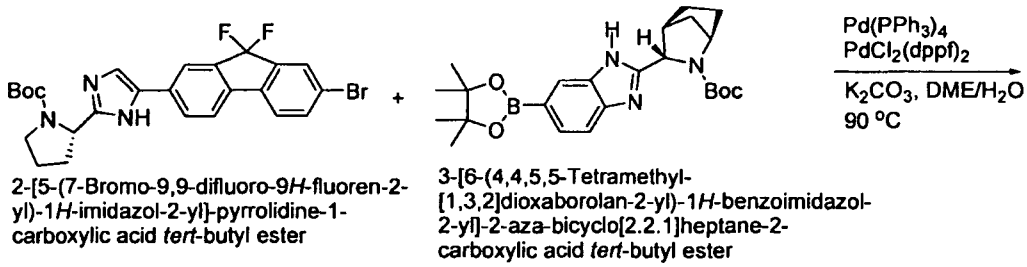
2-(5-{9,9-Difluoro-7-[2-(1-Boc-pyrrolidin-2-yl)-3H-benzoimidazol-5-yl]-9H-fluoren-2-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester: A mixture of 2-[5-(7-Bromo-9,9-difluoro-9H-fluoren-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (137 mg, 0.265 mmol), 2-[6-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-benzoimidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (1 eq., 110 mg), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)(5%, 11 mg), tetrakis(triphenylphosphine)palladium (5%, 16 mg) and potassium carbonate (2 eq., 73 mg) in 4 mL DME and 2 mL water was heated to 90°C for 2 hours. The reaction mixture was cooled and dissolved in ethyl acetate and washed with saturated sodium bicarbonate solution. The organic layer dried (MgSO4), concentrated and purified by flash column chromatography (silica gel, 20 to 100% ethyl acetate/hexane) to give 2-(5-{9,9-Difluoro-7-[2-(1-Boc-pyrrolidin-2-yl)-3H-benzoimidazol-5-yl]-9H-fluoren-2-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (83 mg, yield 43%). LCMS-ESI$^-$: calc'd for $C_{41}H_{44}F_2N_6O_4$: 722.82; Found: 723.1($M+H^+$).

(1-{2-[5-(9,9-Difluoro-7-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-benzoimidazol-5-yl}-9H-fluoren-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (Example **DJ**): TFA (2 mL)was added to 2-(5-{9,9-Difluoro-7-[2-(1-Boc-pyrrolidin-2-yl)-3H-benzoimidazol-5-yl]-9H-fluoren-2-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (83 mg, 0.115 mmol) and the reaction mixture was stirred at room temperature for 4 hours. The reaction mixture was concentrated and dried overnight under vacuum. The residue was dissolved in DMF (3 mL) and to this solution was added 2-Methoxycarbonylamino-3-methyl-butyric acid (2 eq., 40 mg), diisopropyl ethylamine (6 eq., 120 μL), followed by HATU (2 eq., 88 mg). Reaction mixture was stirred at 0°C for 30 minutes. The reaction mixture was dissolved in ethyl acetate and

washed with saturated sodium bicarbonate solution. The organic layer was dried (MgSO4), concentrated and purified by preparative reverse phase HPLC (GEMINI, 5 to 100% ACN/H_2O + 0.1% TFA). Product was lyophilized to give (1-{2-[5-(9,9-Difluoro-7-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-benzoimidazol-5-yl}-9H-fluoren-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (Example **DJ**) (37 mg, 39%).

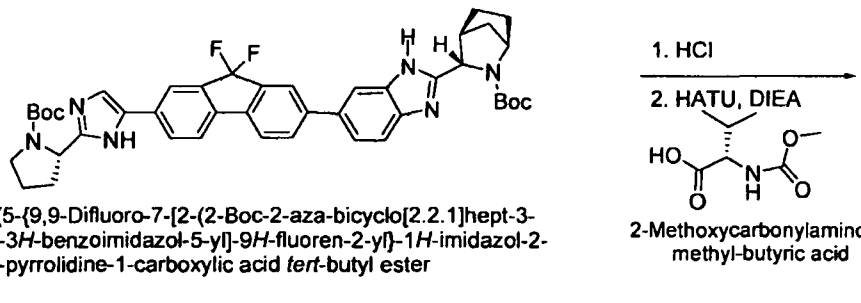
^{1}H-NMR: 300 MHz, (CD_3OD-d_4) δ: 8.05-7.82 (m, 9H), 5.40-5.22(m, 2H), 4.22(m, 2H), 4.16(m,2H), 4.00-3.82 (m, 2H), 3.62 (s, 6H), 2.60 (m, 2H), 2.42-2.18 (m, 6H), 2.08(m, 2H), 0.95-0.85 (m, 12 H). ^{19}F-NMR: 300 MHz, (CD_3OD-d_4) δ: -112.88. LCMS-ESI$^+$: calc'd for $C_{45}H_{50}F_2N_8O_6$: 836.93; Found: 837.3 ($M+H^+$).

Example DK



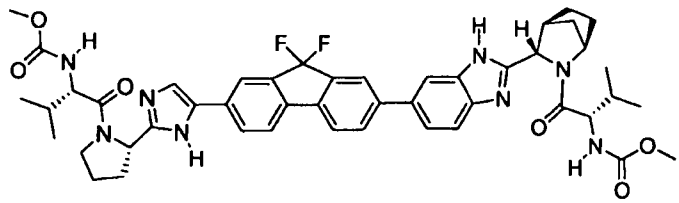
2-[5-(7-Bromo-9,9-difluoro-9*H*-fluoren-2-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester

3-[6-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-benzoimidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester



2-(5-{9,9-Difluoro-7-[2-(2-Boc-2-aza-bicyclo[2.2.1]hept-3-yl)-3*H*-benzoimidazol-5-yl]-9*H*-fluoren-2-yl}-1*H*-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester

2-Methoxycarbonylamino-3-methyl-butyric acid



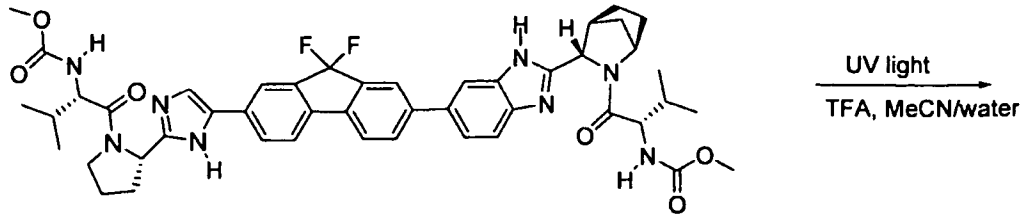
(1-{2-[5-(9,9-Difluoro-7-{2-[2-(2-methoxycarbonylamino-3-methyl-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3*H*-benzoimidazol-5-yl}-9*H*-fluoren-2-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

2-(5-{9,9-Difluoro-7-[2-(2-Boc-2-aza-bicyclo[2.2.1]hept-3-yl)-3H-benzoimidazol-5-yl]-9H-fluoren-2-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester: A mixture of 2-[5-(7-Bromo-9,9-difluoro-9H-fluoren-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (324 mg, 0.627 mmol), 3-[6-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-

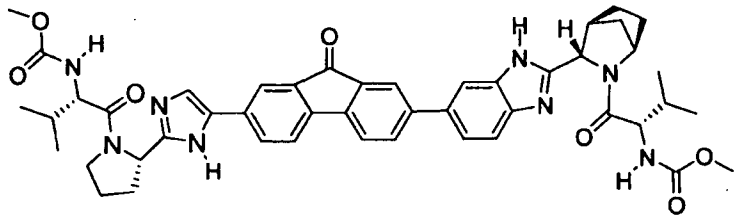
benzoimidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (1.1 eq., 304 mg), [1,1' bis(diphenylphosphino)ferrocene]dichloropalladium(II)(3%, 15 mg), tetrakis(triphenylphosphine)palladium (3%, 22 mg) and potassium carbonate (3.3 eq., 285 mg) in 10 mL DME and 3 mL water was heated to 90°C under Argon for 3 hours. The reaction mixture was cooled and diluted with ethyl acetate and washed with saturated sodium bicarbonate solution. The organic layer was dried (MgSO4), concentrated and purified by flash column chromatography (silica gel, 20 to 100% ethyl acetate/hexane) to give 2-(5-{9,9-Difluoro-7-[2-(2-Boc-2-aza-bicyclo[2.2.1]hept-3-yl)-3H-benzoimidazol-5-yl]-9H-fluoren-2-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (361 mg, yield 77%). LCMS-ESI$^-$: calc'd for $C_{43}H_{46}F_2N_6O_4$: 748.86; Found: 749.2($M+H^+$).

(1-{2-[5-(9,9-Difluoro-7-{2-[2-(2-methoxycarbonylamino-3-methyl-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-benzoimidazol-5-yl}-9H-fluoren-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (Example **DK**): 4N HCl in dioxane (2 mL) was added to 2-(5-{9,9-Difluoro-7-[2-(2-Boc-2-aza-bicyclo[2.2.1]hept-3-yl)-3H-benzoimidazol-5-yl]-9H-fluoren-2-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (361 mg, 0.482 mmol) and the reaction mixture was stirred at room temperature for 4 hours. The reaction mixture was concentrated and dried overnight under vacuum. The residue was dissolved in DMF (5 mL) and to this solution was added 2-Methoxycarbonylamino-3-methyl-butyric acid (2 eq., 169 mg), diisopropyl ethylamine (6 eq., 0.5 mL), followed by HATU (2 eq., 367 mg). Reaction mixture was stirred at 0°C for 30 minutes. The reaction mixture was dissolved in ethyl acetate and washed with saturated sodium bicarbonate solution. The organic layer was dried (MgSO4), concentrated and purified by flash column chromatography (silica gel, 0 to 20% MeOH/ethyl acetate), followed by preparative reverse phase HPLC (GEMINI, 5 to 100% ACN/H_2O + 0.1% TFA). Product was lyophilized to give (1-{2-[5-(9,9-Difluoro-7-{2-[2-(2-methoxycarbonylamino-3-methyl-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-benzoimidazol-5-yl}-9H-fluoren-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (285 mg, 59%). ^{1}H-NMR: 300 MHz, (CD_3OD-d_4) δ: 8.05-7.82 (m, 9H), 5.40-5.22(m, 2H), 4.72(m,1H), 4.39(d, 1H), 4.239d, 1H), 4.17(m, 1H), 3.91(m, 2H), 3.62 (d, 6H), 2.98(m,1H), 2.58 (m, 1H), 2.37-2.18 (m, 4H), 2.18-1.92(m, 4H), 1.80(m, 2H), 1.09-0.85 (m, 12 H). ^{19}F-NMR: 300 MHz, (CD_3OD-d_4) δ: -112.88. LCMS-ESI$^+$: calc'd for $C_{47}H_{52}F_2N_8O_6$ 862.96; Found: 863.5 ($M+H^+$).

Example DL



(1-{2-[5-(9,9-Difluoro-7-{2-[2-(2-methoxycarbonylamino-3-methyl-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3*H*-benzoimidazol-5-yl}-9*H*-fluoren-2-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester



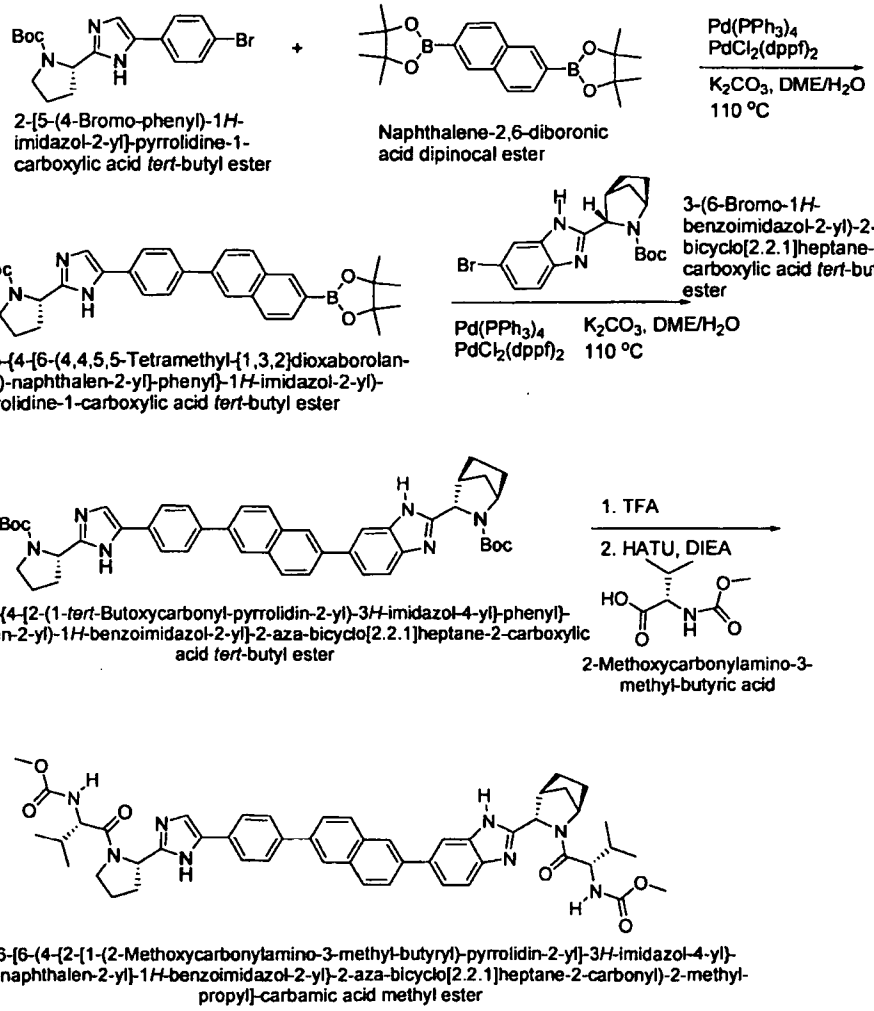
(1-{2-[5-(7-{2-[2-(2-Methoxycarbonylamino-3-methyl-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3*H*-benzoimidazol-5-yl}-9-oxo-9*H*-fluoren-2-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

(1-{2-[5-(7-{2-[2-(2-Methoxycarbonylamino-3-methyl-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-benzoimidazol-5-yl}-9-oxo-9H-fluoren-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (Example **DL**):

(1-{2-[5-(9,9-Difluoro-7-{2-[2-(2-methoxycarbonylamino-3-methyl-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-benzoimidazol-5-yl}-9H-fluoren-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (10 mg) is dissolve in MeCN (1mL) and water (1 mL). 1 drop of TFA was added. The mixture was treated with long wavelengh UV light at room temprature for 2 hours. The reaction crude was concentrated down and purified by preparative reverse phase HPLC (GEMINI, 5 to 100% ACN/H_2O + 0.1% TFA). Product was lyophilized to give (1-{2-[5-(7-{2-[2-(2-Methoxycarbonylamino-3-methyl-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-benzoimidazol-5-yl}-9-oxo-9H-fluoren-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (Example **DL**) (3.7 mg).

^{1}H-NMR: 300 MHz, (CD_3OD-d_4) δ: 8.05-7.82 (m, 9H), 5.27(m, 2H), 4.72 (m, 1H), 4.37(d,1H), 4.23(d, 1H), 4.19(m, 1H), 3.91(m, 2H), 3.62 (d, 6H), 2.98(m,1H), 2.58 (m, 2H), 2.37-2.18 (m, 4H), 2.18-1.92(m, 4H), 1.80(m, 2H), 1.09-0.85 (m, 12 H). LCMS-ESI$^+$: calc'd for $C_{47}H_{52}F_2N_8O_6$ 840.97; Found: 841.6 ($M+H^+$).

Example DM



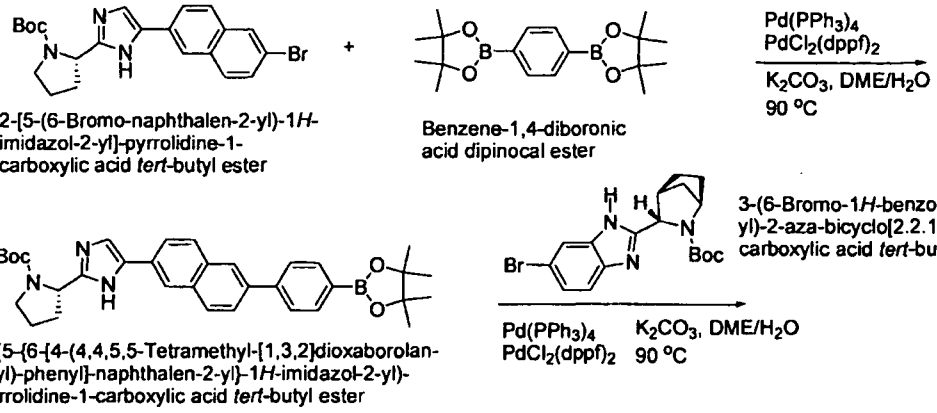
2-(5-{4-[6-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-yl]-phenyl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester: A mixture of 2-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (1.079g, 2.737 mmol), Naphthalene-2,6-diboronic acid dominical ester (5 eq., 5.2 g, 13.68 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)(5%, 96 mg), tetrakis(triphenylphosphine)palladium (5%, 158 mg) and potassium carbonate (5 eq., 757 mg) in 40 mL DME and 10 mL water was heated to 110°C under Argon for 2 hours. The reaction mixture was cooled and diluted with ethyl acetate and washed with saturated sodium bicarbonate solution. The organic layer dried (MgSO4), concentrated and purified by flash column chromatography (silica gel, 20 to 100% ethyl acetate/hexane) to give 2-(5-{4-[6-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-yl]-phenyl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (730 mg, yield 47%). LCMS-ESI$^+$: calc'd for $C_{34}H_{40}BN_3O_4$: 565.51; Found: 566.1 ($M+H^+$).

3-[6-(6-{4-[2-(1-tert-Butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-phenyl}-naphthalen-2-yl)-1H-benzoimidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid tert-butyl ester: A mixture of 2-(5-{4-[6-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-yl]-phenyl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (216 mg, 0.382 mmol), 3-(6-Bromo-1H-benzoimidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (1 eq., 150 mg, 0.382 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)(5%, 16 mg), tetrakis(triphenylphosphine)palladium (5%, 22 mg) and potassium carbonate (2 eq., 106 mg) in 4 mL DME and 1 mL water was heated to 90°C under Argon for 5 hours. The reaction mixture was cooled and diluted in ethyl acetate and washed with saturated sodium bicarbonate solution. The organic layer dried (MgSO4), concentrated and purified by flash column chromatography (silica gel, 20 to 100% ethyl acetate/hexane) to give 3-[6-(6-{4-[2-(1-tert-Butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-phenyl}-naphthalen-2-yl)-1H-benzoimidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid tert-butyl ester (100 mg, yield 35%). LCMS-ESI⁻: calc'd for $C_{46}H_{50}N_6O_4$: 750.93; Found: 751.2 ($M+H^+$).

[1-(3-{6-[6-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-benzoimidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (Example **DM**): TFA (2 mL) was added to 3-[6-(6-{4-[2-(1-*tert*-Butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-phenyl}-naphthalen-2-yl)-1H-benzoimidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (100 mg, 0133 mmol) and the reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated and dried overnight under vacuum. The residue was dissolved in DMF (2 mL) and to this solution was added 2-Methoxycarbonylamino-3-methyl-butyric acid (2 eq., 47 mg), diisopropyl ethylamine (6 eq., 0.14 mL), followed by HATU (2 eq., 101 mg). Reaction mixture was stirred at 0°C for 30 minutes. The reaction mixture was diluted in ethyl acetate and washed with saturated sodium bicarbonate solution. The organic layer was dried (MgSO4), concentrated and purified by preparative reverse phase HPLC (GEMINI, 5 to 100% ACN/H_2O + 0.1% TFA). Product was lyophilized to give [1-(3-{6-[6-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-benzoimidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (Example **DM**) (19.7 mg, 17%).

^{1}H-NMR: 300 MHz, (CD_3OD-d_4) δ: 8.13-7.82 (m, 14H), 5.40-5.22(m, 2H), 4.98(m,1H), 4.72(m, 1H), 4.38(d, 1H), 4.22(m, 1H), 4.10(m, 2H), 3.92 (m, 2H), 3.66(d, 6H), 2.98(m,1H), 2.58 (m, 1H), 2.37-2.18 (m, 4H), 2.18-1.92(m, 4H), 1.80(m, 2H), 1.09-0.85 (m, 12 H). LCMS-ESI$^+$: calc'd for $C_{50}H_{56}N_8O_6$: 865.03; Found: 866.3 ($M+H^+$).

Example DN



2-[5-(6-Bromo-naphthalen-2-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester

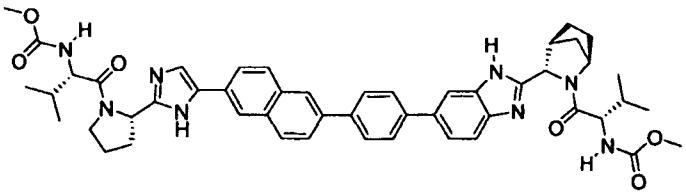
Benzene-1,4-diboronic acid dipinocal ester

3-(6-Bromo-1*H*-benzoimidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester

2-(5-{6-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-naphthalen-2-yl}-1*H*-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester

3-[6-(4-{6-[2-(1-*tert*-Butoxycarbonyl-pyrrolidin-2-yl)-3*H*-imidazol-4-yl]-naphthalen-2-yl}-phenyl)-1*H*-benzoimidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester

2-Methoxycarbonylamino-3-methyl-butyric acid



[1-(3-{6-[4-(6-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1*H*-benzoimidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester

2-(5-{6-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-naphthalen-2-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester: A mixture of 2-[5-(6-Bromo-naphthalen-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (615 mg, 1.39 mmol), Benzene-1,4-diboronic acid dipinocal ester (5 eq., 2.3 g, 6.95 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)(5%, 57 mg), tetrakis(triphenylphosphine)palladium (5%, 80 mg) and potassium carbonate (3 eq., 576 mg) in

20 mL DME and 10 mL water was heated to 90°C under Ar for 1 hour. The reaction mixture was cooled and diluted in ethyl acetate and washed with saturated sodium bicarbonate solution. The organic layer dried (MgSO4), concentrated and purified by flash column chromatography (silica gel, 20 to 100% ethyl acetate/hexane) to give 2-(5-{6-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-naphthalen-2-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (488 mg, yield 62%). LCMS-ESI⁻: calc'd for $C_{34}H_{40}BN_3O_4$: 565.51; Found: 566.2 ($M+H^+$).

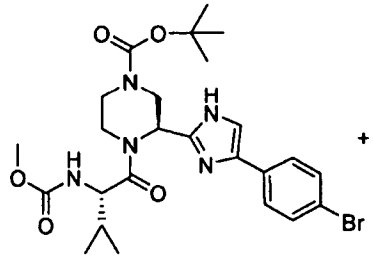
3-[6-(4-{6-[2-(1-*tert*-Butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-naphthalen-2-yl}-phenyl)-1H-benzoimidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester: A mixture of 2-(5-{6-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-naphthalen-2-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (248 mg, 0.438 mmol, 1.1 eq.), 3-(6-Bromo-1H-benzoimidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (1 eq., 156 mg, 0.399 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)(3%, 10 mg), tetrakis(triphenylphosphine)palladium (3%, 14 mg) and potassium carbonate (3.3 eq., 182 mg) in 4 mL DME and 2 mL water was heated to 90°C under Argon for 1 hour. The reaction mixture was cooled and diluted in ethyl acetate and washed with saturated sodium bicarbonate solution. The organic layer dried (MgSO4), concentrated and purified by flash column chromatography (silica gel, 20 to 100% ethyl acetate/hexane) to give 3-[6-(4-{6-[2-(1-*tert*-Butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-naphthalen-2-yl}-phenyl)-1H-benzoimidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (178 mg, yield 59%). LCMS-ESI⁻: calc'd for $C_{46}H_{50}N_6O_4$: 750.93; Found: 751.3 ($M+H^+$).

[1-(3-{6-[4-(6-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-benzoimidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (Example **DN**): 4N HCl in dioxane (1 mL) was added to 3-[6-(6-{4-[2-(1-*tert*-Butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-phenyl}-naphthalen-2-yl)-1H-benzoimidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (100 mg, 0133 mmol) in 2 mL DCM and the reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was concentrated and dried overnight under vacuum. The residue was dissolved in DMF (2 mL) and to this solution was added 2-Methoxycarbonylamino-3-methyl-butyric acid (2 eq., 83 mg), diisopropyl ethylamine (6 eq., 0.25 mL), followed by HATU (2 eq., 180 mg). Reaction mixture was stirred at 0°C for 30 minutes. The reaction mixture was dissolved in ethyl acetate and

washed with saturated sodium bicarbonate solution. The organic layer was dried (MgSO4), concentrated and purified by preparative reverse phase HPLC (GEMINI, 5 to 100% ACN/H_2O + 0.1% TFA). Product was lyophilized to give [1-(3-{6-[4-(6-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-benzoimidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (Example **DN**) (102 mg, 50%).

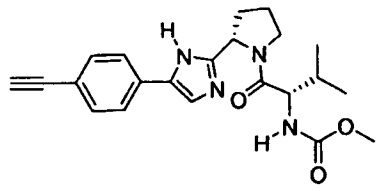
^{1}H-NMR: 300 MHz, (CD_3OD-d_4) δ: 8.13-7.82 (m, 14H), 5.40-5.22(m, 2H), 4.98(m,1H), 4.72(m, 1H), 4.38(d, 1H), 4.22(m, 1H), 4.10(m, 2H), 3.92 (m, 2H), 3.66(d, 6H), 2.98(m,1H), 2.58 (m, 1H), 2.37-2.18 (m, 4H), 2.18-1.92(m, 4H), 1.80(m, 2H), 1.09-0.85 (m, 12 H). LCMS-ESI$^+$: calc'd for $C_{50}H_{56}N_8O_6$: 865.03; Found: 866.4 ($M+H^+$).

Example DO



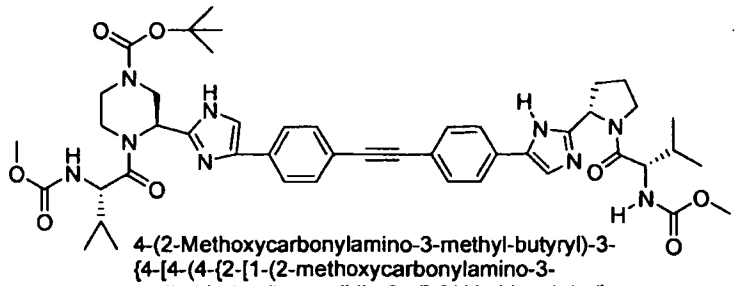
3-[4-(4-Bromo-phenyl)-1*H*-imidazol-2-yl]-4-(2-methoxycarbonylamino-3-methyl-butyryl)-piperazine-1-carboxylic acid *tert*-butyl ester

+



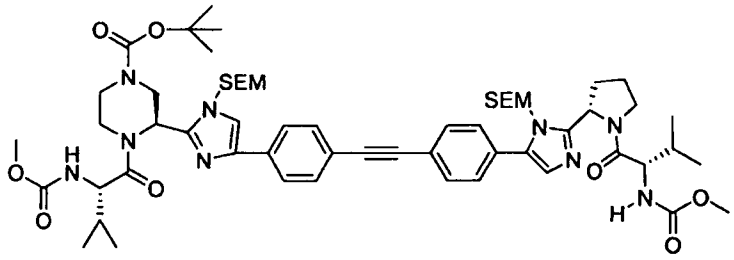
(1-{2-[5-(4-Ethynyl-phenyl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

$Pd(PPh_3)_4$
Cu(I)I

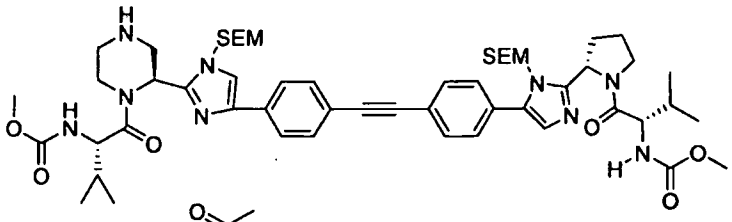


4-(2-Methoxycarbonylamino-3-methyl-butyryl)-3-{4-[4-(4-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-phenylethynyl)-phenyl]-1*H*-imidazol-2-yl}-piperazine-1-carboxylic acid *tert*-butyl ester

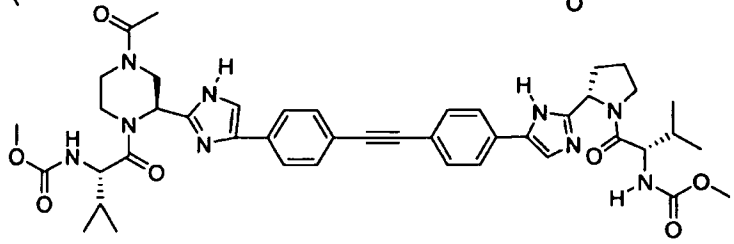
SEM-Cl, NaH
DMF



HCl in Dioxane / DCM



1. Ac_2O, NMM, DCM
2. TFA DCM



[1-(2-{5-[4-(4-{2-[4-Acetyl-1-(2-methoxycarbonylamino-3-methyl-butyryl)-piperazin-2-yl]-1*H*-imidazol-4-yl}-phenylethynyl)-phenyl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester

4-(2-Methoxycarbonylamino-3-methyl-butyryl)-3-{4-[4-(4-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenylethynyl)-phenyl]-1H-imidazol-2-yl}-piperazine-1-carboxylic acid *tert*-butyl ester: 3-[4-(4-Bromo-phenyl)-1H-imidazol-2-yl]-4-(2-methoxycarbonylamino-3-methyl-butyryl)-piperazine-1-carboxylic acid tert-butyl ester (600 mg, 1.06 mmol) was combined with (1-{2-[5-(4-Ethynyl-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (503 mg, 1.27 mmol) and $Pd(PPh_3)_4$ (122 mg, 0.106 mmol) under an argon atmosphere. DMF (degassed with Argon) was added followed by triethylamine (1.47 mL, 10.6 mmol) and copper(I) iodide (20.0 mg, 0.106 mmol). The mixture was heated at 80 °C. After 20 minutes, volatiles were removed *in vacuo* and the crude material was semi-purified via chromatography on silica gel (eluent: EtOAc w MeOH 10% / hexanes) to yield the product 4-(2-Methoxycarbonylamino-3-methyl-butyryl)-3-{4-[4-(4-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenylethynyl)-phenyl]-1H-imidazol-2-yl}-piperazine-1-carboxylic acid *tert*-butyl ester (542 mg). LCMS-ESI$^+$: calc'd for $C_{47}H_{59}N_9O_8$: 878.0 (M^+); Found: 878.5 ($M+H^+$).

SEM protected imidazole intermediate: 4-(2-Methoxycarbonylamino-3-methyl-butyryl)-3-{4-[4-(4-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenylethynyl)-phenyl]-1H-imidazol-2-yl}-piperazine-1-carboxylic acid *tert*-butyl ester (512 mg, 0.586 mmol) was dissolved in DMF (10 mL). Sodium hydride (60 % in mineral oil, 56 mg) was added at 0 °C, followed by SEM-Cl (0.217 mL). After two hours, the solvents were removed *in vacuo* and the crude material was partitioned between DCM and water. The organic layer was dried and the crude material was purified by flash chromatography in silica gel to yield 591 mg of the SEM protected imidazole product.
LCMS-ESI$^+$: calc'd for $C_{59}H_{87}N_9O_{10}Si_2$: 1138.6 ($M^+$); Found: 1138.7 ($M+H^+$).

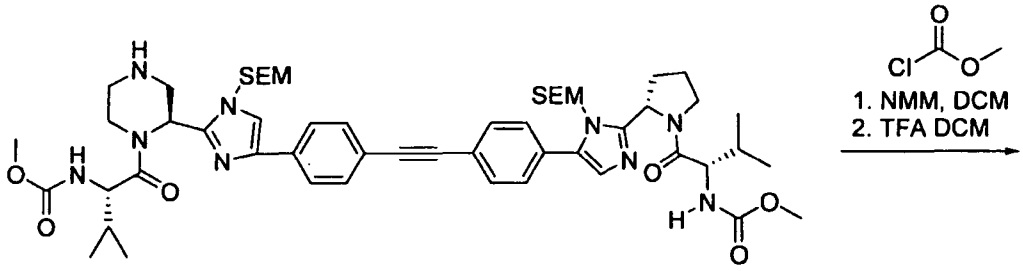
de-Boc piperazine material: The above SEM protected imidazole material was dissolved in DCM (2.5 mL) at room temperature. HCl (4M in dioxane, 5 mL) was added and stirring of the resultant suspension at room temperature was continued. After 60 minutes all volatiles were removed in vacuo and the crude material was used in the next reaction without further purification.

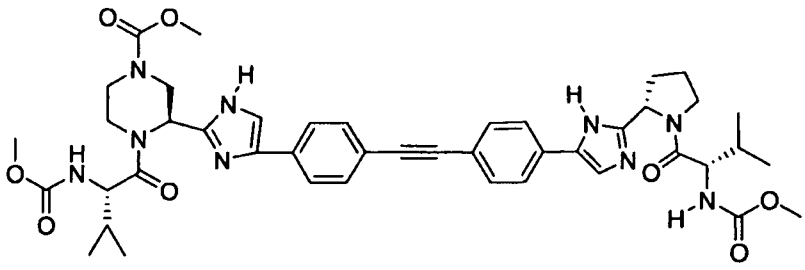
[1-(2-{5-[4-(4-{2-[4-Acetyl-1-(2-methoxycarbonylamino-3-methyl-butyryl)-piperazin-2-yl]-1H-imidazol-4-yl}-phenylethynyl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (Example A): The above de-Boc piperazine material (139 mg, 0.129 mmol) was dissolved in DCM (3 mL) containing NMM (0.057 mL) at room temperature. Acetic anhydride (0.0183 mL) was added and stirring at room temperature was continued. After 60 minutes all volatiles were removed *in vacuo* and the crude material was dissolved in a micture of DCM (5 mL) and TFA (5 mL). Stirring at room temperature was continued. After 16 hours, the volatiles were removed *in vacuo* and the material was purified by RP-HPLC (eluent: water / MeCN w/ 0.1% TFA). The product-containing fractions were combined and lyphilized to yield the product [1-(2-{5-[4-(4-{2-[4-Acetyl-1-(2-methoxycarbonylamino-3-methyl-butyryl)-piperazin-2-yl]-1H-imidazol-4-yl}-phenylethynyl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (example **DO**) as a TFA salt (15.7 mg).

LCMS-ESI$^+$: calc'd for $C_{44}H_{53}N_9O_7$: 819.9 (M^+); Found: 820.4 ($M+H^+$).

^{1}H-NMR: 300 MHz, (dmso-d_6) δ: 8.07 (m, 2 H), 7.91-7.68 (m, 10H), 7.28 (m, 2H), 5.64 (m, 1H), 5.38 (m, 1H), 5.17 (m, 2H), 4.23 (d, J=7.8Hz, 1H), 4.11 (m, 1H), 3.85 (m,1H), 3.68 (s, 3H), 3.66 (s, 3H), 3.49-3.45 (m, 2H), 3.15-3.02 (m, 3H), 2.77 (m, 1H), 2.58 (m, 1H), 2.29-2.01 (m, 5H), 1.07-0.83 (m, 12H) ppm.

Example DP

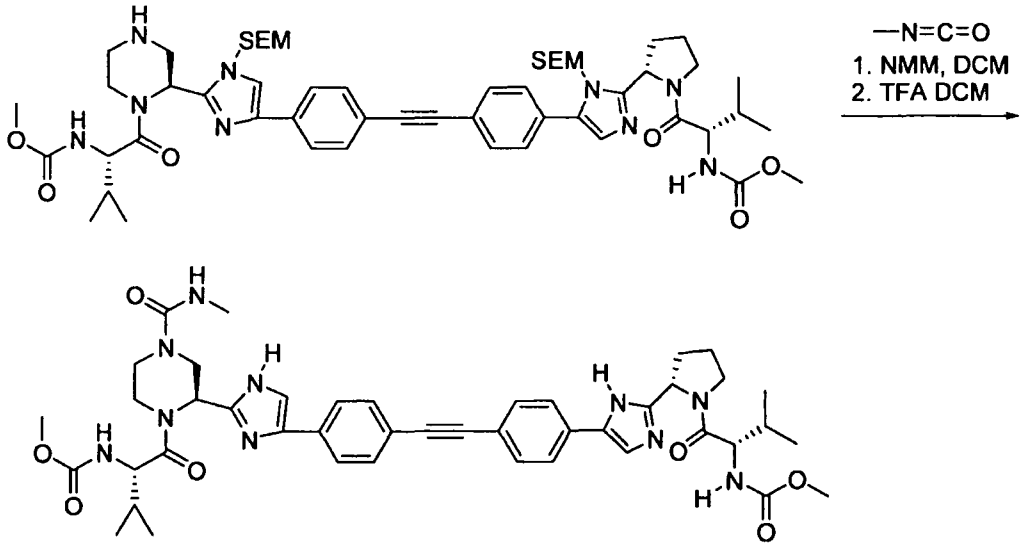




4-(2-Methoxycarbonylamino-3-methyl-butyryl)-3-{4-[4-(4-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-phenylethynyl)-phenyl]-1*H*-imidazol-2-yl}-piperazine-1-carboxylic acid methyl ester

4-(2-Methoxycarbonylamino-3-methyl-butyryl)-3-{4-[4-(4-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenylethynyl)-phenyl]-1H-imidazol-2-yl}-piperazine-1-carboxylic acid methyl ester (Example DP): It was prepared in a similar fashion to [1-(2-{5-[4-(4-{2-[4-Acetyl-1-(2-methoxycarbonylamino-3-methyl-butyryl)-piperazin-2-yl]-1H-imidazol-4-yl}-phenylethynyl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (example **DO**) replacing the acetic anhydride with methylchloro formate.
LCMS-ESI$^+$: calc'd for $C_{44}H_{53}N_9O_8$: 835.4 (M^+); Found: 835.9 ($M+H^+$).
^{1}H-NMR: 300 MHz, (dmso-d_6) δ: 8.08 (m, 1 H), 7.76-7.54 (m, 10H), 7.30 (m, 2H), 5.58 (m, 1H), 5.08 (m, 1H), 4.36 (m, 1H), 4.26 (m, 1H), 4.03 (m, 2H), 3.95 – 3.75 (m, 4H), 3.50 (m, 9H), 2.29 (m, 1H), 2.13-1.95 (m, 4H), 0.87-0.68 (m, 12H) ppm.

Example DQ



[1-(2-{5-[4-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-4-methylcarbamoyl-piperazin-2-yl]-1*H*-imidazol-4-yl}-phenylethynyl)-phenyl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester

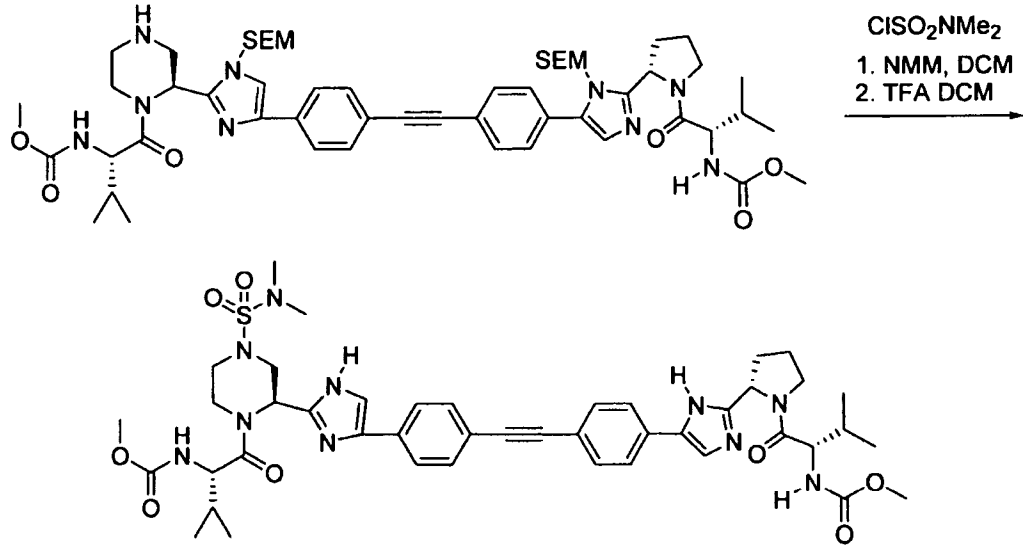
[1-(2-{5-[4-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-4-methylcarbamoyl-piperazin-2-yl]-1H-imidazol-4-yl}-phenylethynyl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (Example DQ): It was prepared in a similar fashion to [1-(2-{5-[4-(4-{2-[4-Acetyl-1-(2-methoxycarbonylamino-3-methyl-butyryl)-piperazin-2-yl]-1H-imidazol-4-yl}-phenylethynyl)-phenyl]-1H-imidazol-2-yl}-

pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (example **DO**), replacing the acetic anhydride with isocyanatomethane.

LCMS-ESI$^+$: calc'd for $C_{44}H_{54}N_{10}O_7$: 834.9 (M^+); Found: 835.4 (M^+).

^{1}H-NMR: 300 MHz, (dmso-d_6) δ: 8.08 (m, 1 H), 7.77-7.36 (m, 10H), 7.36 – 7.24 (m, 2H), 5.51 (m, 1H), 5.07 (m, 1H), 4.36 (m, 1H), 4.07 (m, 1H), 4.06 (m, 2H), 3.95 – 3.75 (m, 4H), 3.52 – 3.48 (m, 9H), 2.34 (m, 1H), 2.13-1.96 (m, 4H), 0.90-0.78 (m, 12H) ppm.

Example DR



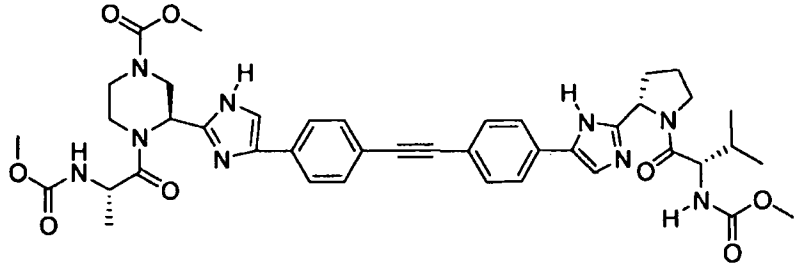
[1-(2-{5-[4-(4-{2-[4-Dimethylsulfamoyl-1-(2-methoxycarbonylamino-3-methyl-butyryl)-piperazin-2-yl]-1*H*-imidazol-4-yl}-phenylethynyl)-phenyl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester

[1-(2-{5-[4-(4-{2-[4-Dimethylsulfamoyl-1-(2-methoxycarbonylamino-3-methyl-butyryl)-piperazin-2-yl]-1H-imidazol-4-yl}-phenylethynyl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (Example **DR**): It was prepared in a similar fashion to [1-(2-{5-[4-(4-{2-[4-Acetyl-1-(2-methoxycarbonylamino-3-methyl-butyryl)-piperazin-2-yl]-1H-imidazol-4-yl}-phenylethynyl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (example **DO**), replacing the acetic anhydride with N,N-dimethyl sulfurylamido chloride.

LCMS-ESI$^+$: calc'd for $C_{44}H_{56}N_{10}O_8S$: 885.0 (M^+); Found: 885.4 (M^+).

^{1}H-NMR: 300 MHz, (dmso-d_6) δ: 8.05 (m, 1 H), 7.91-7.52 (m, 10H), 7.32 – 7.28 (m, 2H), 5.72 (s, 1H), 5.07 (m, 1H), 4.39 - 4.06 (m, 4H), 3.95 – 3.75 (m, 4H), 3.52 – 3.48 (m, 6H), 2.86 - 46 (m, 6H), 2.12-1.95 (m, 4H), 0.94-0.76 (m, 12H) ppm.

Example DS



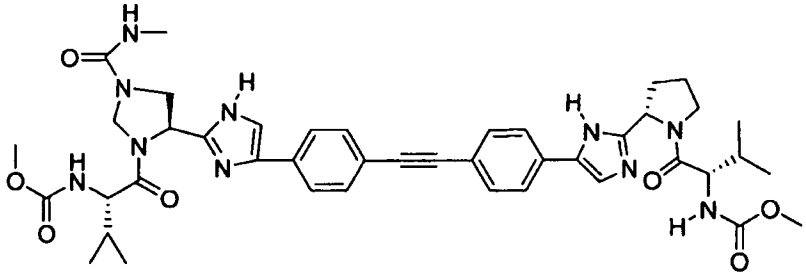
3-{4-[4-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-phenylethynyl)-phenyl]-1*H*-imidazol-2-yl}-4-(2-methoxycarbonylamino-propionyl)-piperazine-1-carboxylic acid methyl ester

3-{4-[4-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenylethynyl)-phenyl]-1H-imidazol-2-yl}-4-(2-methoxycarbonylamino-propionyl)-piperazine-1-carboxylic acid methyl ester (example **DS**) was prepared in a similar fashion to 4-(2-Methoxycarbonylamino-3-methyl-butyryl)-3-{4-[4-(4-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenylethynyl)-phenyl]-1H-imidazol-2-yl}-piperazine-1-carboxylic acid methyl ester (example **DP**), replacing the valine derived carbamate with the corresponding alanine derived carbamate.

LCMS-ESI$^+$: calc'd for $C_{40}H_{49}N_9O_8$: 783.8 (M^+); Found: 784.3 ($M+H^+$).

^{1}H-NMR: 300 MHz, (dmso-d_6) δ: 8.08 (m, 1 H), 7.95-7.80 (m, 10H), 7.47 (m, 1H), 7.30 (m, 1H), 5.72 (s, 1H), 5.55 (s, 1H), 5.09 (m, 1H), 4.58 (m, 1H), 4.09 (m, 1H), 3.89 – 3.80 (m, 5H), 3.50 – 3.30 (m, 9H), 2.29 (m, 1H), 2.09-1.98 (m, 4H), 1.21 (m, 3H) 0.81-0.75 (m, 6H) ppm.

Example DT



(1-{2-[5-(4-{4-[3'-(2-Methoxycarbonylamino-3-methyl-butyryl)-1'-methylcarbamoyl-2',3',4',5'-tetrahydro-1*H*,1'*H*-[2,4']biimidazolyl-4-yl]-phenylethynyl}-phenyl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

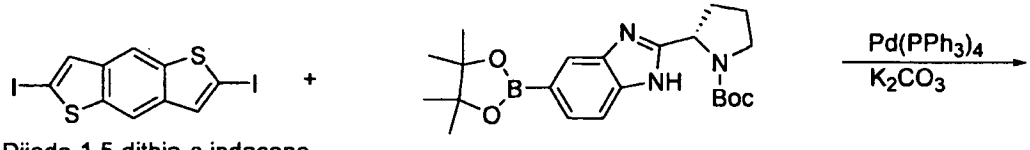
(1-{2-[5-(4-{4-[3'-(2-Methoxycarbonylamino-3-methyl-butyryl)-1'-methylcarbamoyl-2',3',4',5'-tetrahydro-1H,1'H-[2,4']biimidazolyl-4-yl]-phenylethynyl}-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (example DT) was prepared in a similar fashion to [1-(2-{5-[4-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-4-methylcarbamoyl-piperazin-2-yl]-1H-imidazol-4-yl}-phenylethynyl)-phenyl]-1H-

imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (example **DQ**), replacing the piperazine carboxylic acid with the corresponding 4-amino-pyrrolidine derivative, using methodology described under examples BU and DO.

LCMS-ESI$^+$: calc'd for $C_{43}H_{52}N_{10}O_7$: 820.9 (M^+); Found: 821.4 (M^+).

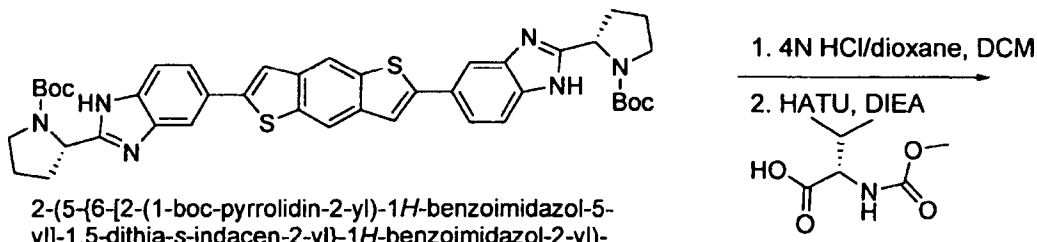
^{1}H-NMR: 300 MHz, (dmso-d_6) δ: 8.05 (m, 1 H), 7.91 (s, 1H), 7.77-7.50 (m, 10H) 7.32 (m, 1H), 6.54 (m, 1H), 5.51 (m, 1H), 5.36 (m, 1H), 5.21 (m, 2H), 4.51 (m, 1H), 4.07 (m, 1H), 3.95 – 3.75 (m, 2H), 3.51 (s, 6H), 2.57 (m, 3H), 2.13 (m, 1H), 2.05-1.95 (m, 4H), 0.94-0.77 (m, 12H) ppm.

Example DU



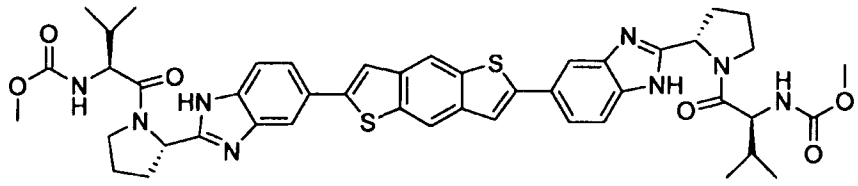
2,6-Diiodo-1,5-dithia-*s*-indacene

2-[5-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-benzoimidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester



2-(5-{6-[2-(1-boc-pyrrolidin-2-yl)-1*H*-benzoimidazol-5-yl]-1,5-dithia-*s*-indacen-2-yl}-1*H*-benzoimidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester

2-Methoxycarbonylamino-3-methyl-butyric acid



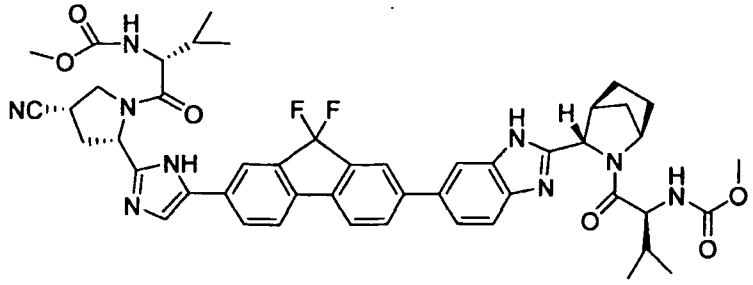
(1-{2-[5-(6-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-1*H*-benzoimidazol-5-yl}-1,5-dithia-*s*-indacen-2-yl)-1*H*-benzoimidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

2-(5-{6-[2-(1-boc-pyrrolidin-2-yl)-1H-benzoimidazol-5-yl]-1,5-dithia-s-indacen-2-yl}-1H-benzoimidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester: 2,6-Diiodo-1,5-dithia-s-indacene (117 mg, 0.263 mmol), 2-[5-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-benzoimidazol-2-yl]-pyrrolidine-1-carboxylic acid tert-butyl ester (109 mg, 0.263 mmol), $Pd(PPh_3)_4$ (9.1 mg), K_2CO_3 (69 mg, 0.52 mmol), were dissolved in toluene (5 mL) / water (1

mL) under an argon atmosphere. The mixture was heated for 30 minutes at 130 °C (microwave) and 30 minutes at 140 °C. Removed all volatiles *in vacuo* and purified via silica gel chromatography (eluent: EtOAc / hexanes) to yield the product 2-(5-{6-[2-(1-Boc-pyrrolidin-2-yl)-1H-benzoimidazol-5-yl]-1,5-dithia-s-indacen-2-yl}-1H-benzoimidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (36.3 mg).
LCMS-ESI$^+$: calc'd for $C_{42}H_{44}S_2N_6O_4$: 760.3 (M^+); Found: 761.3 ($M+H^+$).

(1-{2-[5-(6-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-1H-benzoimidazol-5-yl}-1,5-dithia-s-indacen-2-yl)-1H-benzoimidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (Example DU): 2-(5-{6-[2-(1-Boc-pyrrolidin-2-yl)-1H-benzoimidazol-5-yl]-1,5-dithia-s-indacen-2-yl}-1H-benzoimidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (36 mg) was dissolved in DCM (3 mL) and HCl in dioxane (4M, 4 mL) was added and stirring at room temperature was continued. After 20 minutes, all volatiles were removed *in vacuo*. The crude material was used in the next step without further purification.
The above crude material was dissolved in DMF (3 mL) and NMM (0.025 mL) was added. A solution of 2- (*L*) Methoxycarbonylamino-3-methyl-butyric acid (17 mg, 0.094 mmol), HATU (36 mg, 0.094 mmol) and NMM (0.025 mL) in DMF (1 mL) was added. The reaction was stirred at room temperature. After 20 minutes, the reaction was diluted with EtOAc and was washed with aqueous bicarbonate solution, aqueous LiCl solution (5%), brine, and was dried over sodium sulfate. Filtration and removal of solvents *in vacuo* gave the crude material, which was purified by RP-HPLC (eluent: water / MeCN w/ 0.1% TFA) to yield the product (1-{2-[5-(6-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-1H-benzoimidazol-5-yl}-1,5-dithia-s-indacen-2-yl)-1H-benzoimidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (3.8 mg).
LCMS-ESI$^+$: calc'd for $C_{46}H_{50}N_8O_6S_2$: 875.1 (M^+); Found: 875.4 ($M+H^+$).
^{1}H-NMR: 300 MHz, (dmso-d_6) δ: 8.41 (s, 2 H), 7.94 – 7.91 (m, 4H), 7.73-7.67 (m, 4H), 7.31 (m, 2H), 5.19 (m, 2H), 4.09 (m, 2H), 3.85 (m, 4H), 3.51 (s, 6H), 2.31-1.82 (m, 10H), 0.94-0.77 (m, 12H) ppm.

Example DV



(1-{3-[6-(7-{2-[4-Cyano-1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-9,9-difluoro-9*H*-fluoren-2-yl)-1*H*-benzoimidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

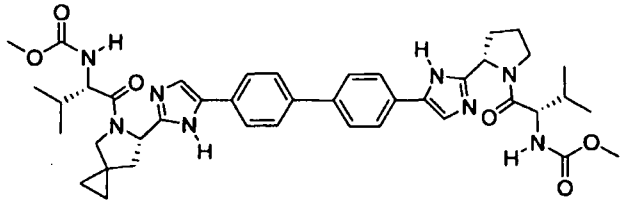
(1-{3-[6-(7-{2-[4-Cyano-1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-9,9-difluoro-9H-fluoren-2-yl)-1H-benzoimidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (Example **DV**) was prepared in a similar fashion to (1-{2-[5-(9,9-Difluoro-7-{2-[2-(2-methoxycarbonylamino-3-methyl-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-benzoimidazol-5-yl}-9H-fluoren-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (Example **DK**), replacing the proline derivative with the corresponding 4-cyano-proline derivative.

LCMS-ESI$^+$: calc'd for $C_{48}H_{51}F_2N_9O_6$: 887.9 (M^+); Found: 888.3 ($M+H^+$).

^{1}H-NMR: 300 MHz, (dmso-d_6) δ: 8.10-7.95 (m, 8H), 7.70 (s, 2H), 7.34 (m, 1H), 7.26 (m, 1H), 5.12 (dd, J = 8.4 Hz, 1H), 4.72 (s, 1H) 4.52 (s, 1H), 4.42 (m, 1H), 4.16 (m, 1H), 4.05 (m, 1H), 3.94 (m,1H), 3.74 (m, 1H), 3.53 (s, 3H), 3.52 (s, 3H), 2.85 (m, 1H), 2.73 (m, 1H), 2.39 (m, 1H), 2.25 (m, 1H), 2.03 – 1.72 (m, 6H), 1.54 (m, 2H), 0.94 - 0.77 (m, 15H) ppm.

^{19}F-NMR: 282 MHz, (dmso-d_6) δ: -108.6 ppm [-74.3 ppm TFA].

Example DW



(1-{6-[5-(4'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-biphenyl-4-yl)-1*H*-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

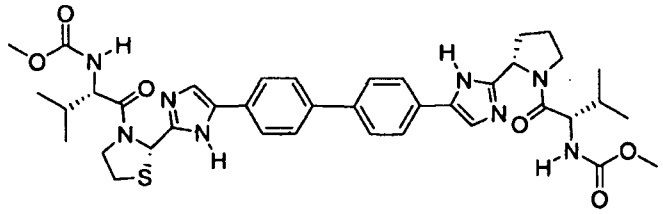
(1-{6-[5-(4'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (Example **DW**) was prepared in a similar fashion to (1-{2-[5-(4'-{2-[2-Hydroxy-1-(2-methoxycarbonylamino-3-methyl-butyrylamino)-ethyl]-3H-

imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester, replacing the oxazolidine derived carboxylic acid with the corresponding 4-cyclopropyl-proline derivative and using HCl in dioxane for the Boc deprotection.

LCMS-ESI$^+$: calc'd for $C_{42}H_{52}N_8O_6$: 764.9 (M^+); Found: 765.3 ($M+H^+$).

^{1}H-NMR: 300 MHz, (dmso-d_6) δ: 8.08 (m, 2 H), 7.91-7.84 (m, 10H) 7.33 (m, 2H), 5.23 (m, 1H), 5.11 (m, 1H), 4.10 (m, 1H), 4.01 (m, 1H), 3.95 – 3.75 (m, 4H), 3.53 (s, 6H), 2.40 (m, 1H), 2.23 (m, 1H), 2.05-1.95 (m, 4H), 0.94-0.80 (m, 12H), 0.63 (m, 4H) ppm.

Example DX



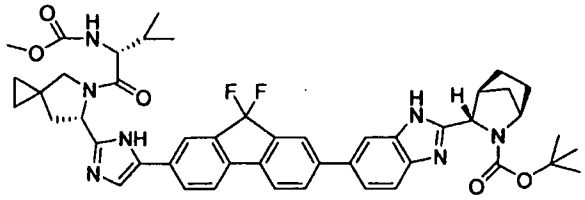
(1-{2-[5-(4'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-biphenyl-4-yl)-1*H*-imidazol-2-yl]-thiazolidine-3-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

(1-{2-[5-(4'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-thiazolidine-3-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (Example **DX**) was prepared in a similar fashion to (1-{6-[5-(4'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (Example **DW**), replacing the cyclopropyl proline carboxylic acid with the corresponding thiazolidine derivative.

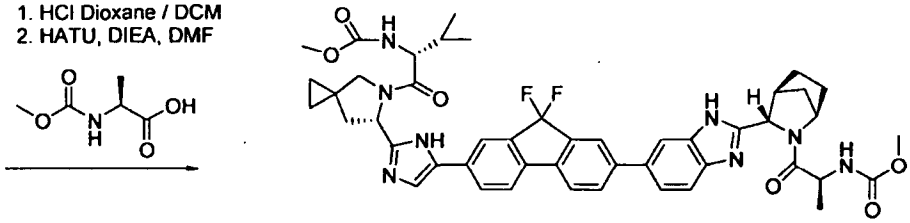
LCMS-ESI$^+$: calc'd for $C_{39}H_{48}N_8O_6S$: 756.9 (M^+); Found: 757.0 (M^+).

^{1}H-NMR: 300 MHz, (dmso-d_6) δ: 8.06 (m, 2 H), 7.86-7.70 (m, 10H), 7.45 (m, 1H), 7.22 (m, 1H), 6.33 (s, 1H), 5.09 (m, 1H), 4.18 – 4.08 (m, 4H), 3.80 (m, 2H), 3.56 (s, 6H), 3.30 (m, 2H), 2.40 (m, 1H), 2.05-1.95 (m, 5H), 0.94-0.75 (m, 12H) ppm.

Example DY



3-[6-(9,9-Difluoro-7-{2-[5-(2-methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3*H*-imidazol-4-yl}-9*H*-fluoren-2-yl)-1*H*-benzoimidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester



(1-{6-[5-(9,9-Difluoro-7-{2-[2-(2-methoxycarbonylamino-propionyl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3*H*-benzoimidazol-5-yl}-9*H*-fluoren-2-yl)-1*H*-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

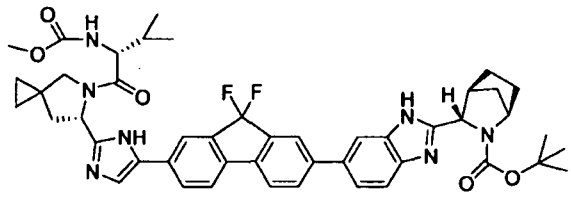
(1-{6-[5-(9,9-Difluoro-7-{2-[2-(2-methoxycarbonylamino-propionyl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-benzoimidazol-5-yl}-9H-fluoren-2-yl)-1H-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester:

3-[6-(9,9-Difluoro-7-{2-[5-(2-methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3H-imidazol-4-yl}-9H-fluoren-2-yl)-1H-benzoimidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (57.6 mg, 0.068 mmol) was dissolved in DCM (1 mL) and HCl in dioxane (4M, 1 mL) was added and stirring at room temperature was continued. After 45 minutes, all volatiles were removed *in vacuo*. The crude material was used in the next step without further purification. The crude material was dissolved in DMF (1.0 mL) and DIEA (26.4 mg, 0.204 mmol) was added. A solution of 2- (*L*) methoxycarbonylamino-propionic acid (9.95 mg, 0.068 mmol), HATU (25.9 mg, 0.068 mmol) and DIEA (8.8 mg, 0.068 mmol) in DMF (1 mL) was added. The reaction was stirred at room temperature. After 45 minutes, the reaction was diluted with EtOAc and was washed with aqueous bicarbonate solution, aqueous LiCl solution (5%), brine, and was dried over sodium sulfate. Filtration and removal of solvents *in vacuo* gave the crude material, which was purified by RP-HPLC (eluent: water / MeCN w/ 0.1% TFA) to yield the product (1-{6-[5-(9,9-Difluoro-7-{2-[2-(2-methoxycarbonylamino-propionyl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-benzoimidazol-5-yl}-9H-fluoren-2-yl)-1H-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (25.4 mg) as a TFA salt.

LCMS-ESI$^+$: calc'd for $C_{47}H_{50}F_2N_8O_6$: 860.9 (M^+); Found: 861.8 ($M+H^+$).

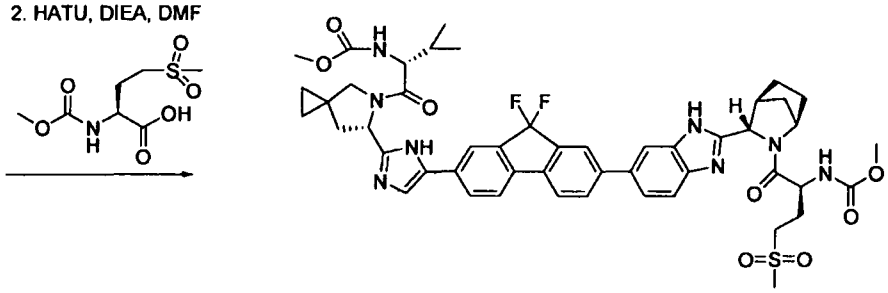
^{1}H-NMR: 300 MHz, (dmso-d_6) δ: 8.20-7.99 (m, 8H), 7.73 (s, 2H), 7.37 – 7.27 (m, 2H), 5.24 (dd, J = 7.2 Hz, 1H), 4.76 (s, 1H) 4.50 (s, 1H), 4.41 (m,1H), 4.02 (m, 1H), 3.85 (m,1H), 3.74 (m, 1H), 3.55 (s, 3H), 3.53 (s, 3H), 2.77 (m, 1H), 2.25 (m, 2H), 2.09 – 2.04 (m, 2H), 1.88 – 1.79 (m, 2H), 1.54 (m, 1H), 1.25 (d, J= 7.8 Hz, 3H), 0.94 - 0.77 (m, 9H) 0.63 (m, 4H) ppm.
^{19}F-NMR: 282 MHz, (dmso-d_6) δ: -109.1 ppm [-74.8 ppm TFA].

Example DZ



3-[6-(9,9-Difluoro-7-{2-[5-(2-methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3*H*-imidazol-4-yl}-9*H*-fluoren-2-yl)-1*H*-benzoimidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester

1. HCl Dioxane / DCM
2. HATU, DIEA, DMF



(1-{6-[5-(9,9-Difluoro-7-{2-[2-(2-methoxycarbonylamino-4-methylsulfonyl-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3*H*-benzoimidazol-5-yl}-9*H*-fluoren-2-yl)-1*H*-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

(1-{6-[5-(9,9-Difluoro-7-{2-[2-(2-methoxycarbonylamino-4-methylsulfonyl-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-benzoimidazol-5-yl}-9H-fluoren-2-yl)-1H-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester:
3-[6-(9,9-Difluoro-7-{2-[5-(2-methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3H-imidazol-4-yl}-9H-fluoren-2-yl)-1H-benzoimidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (55.6 mg, 0.067 mmol) was dissolved in DCM (1 mL) and HCl in dioxane (4M, 1 mL) was added and stirring at room temperature was continued. After 30 minutes, all volatiles were removed *in vacuo*. The crude material was used in the next step without further purification. The crude material was dissolved in DMF (1.0 mL) and DIEA (25.8 mg, 0.201 mmol) was added. A solution of 2- (*L*) methoxycarbonylamino-4-methyl-sulfonyl-butyric acid (15.9 mg, 0.067 mmol), HATU (25.4 mg, 0.067 mmol) and DIEA (8.6 mg, 0.067 mmol) in DMF (1 mL) was added. The reaction was stirred at room temperature. After

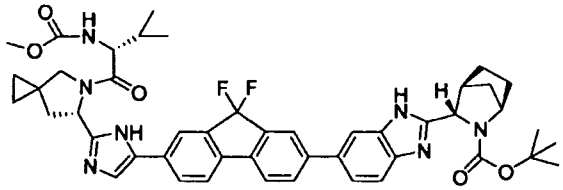
20 minutes, the reaction was diluted with EtOAc and was washed with aqueous bicarbonate solution, aqueous LiCl solution (5%), brine, and was dried over sodium sulfate. Filtration and removal of solvents *in vacuo* gave the crude material, which was purified by RP-HPLC (eluent: water / MeCN w/ 0.1% TFA) to yield the product (1-{6-[5-(9,9-Difluoro-7-{2-[2-(2-methoxycarbonylamino-4-methylsulfonyl-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-benzoimidazol-5-yl}-9H-fluoren-2-yl)-1H-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (23 mg) as a TFA salt.

LCMS-ESI$^+$: calc'd for $C_{49}H_{54}F_2N_8O_8S$: 953.1 (M^+); Found: 954.0 ($M+H^+$).

^{1}H-NMR: 300 MHz, (dmso-d_6) δ: 8.20-7.99 (m, 8H), 7.77 (s, 2H), 7.65 (m, 1H), 7.35 (m, 1H), 5.25 (dd, J = 7.2 Hz, 1H), 4.79 (s, 1H) 4.56 (s, 1H), 4.53 (m, 1H), 4.02 (m, 1H), 3.88 (m,1H), 3.72 (m, 1H), 3.56 (s, 3H), 3.53 (s, 3H), 3.27 (m, 2H), 3.01 (s, 3H), 2.78 (m, 1H), 2.25 (m, 2H), 2.09 – 2.04 (m, 2H), 1.88 – 1.79 (m, 4H), 1.56 (m, 1H), 0.94 - 0.77 (m, 9H) 0.63 (m, 4H) ppm.

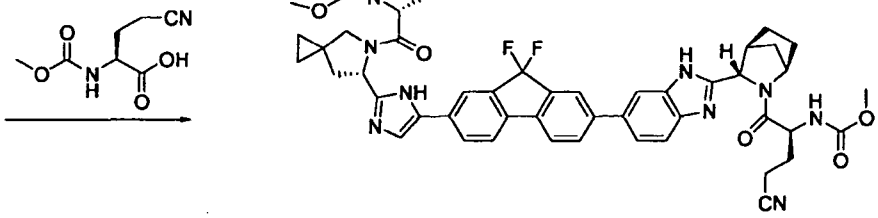
^{19}F-NMR: 282 MHz, (dmso-d_6) δ: -109.1 ppm [-74.8 ppm TFA].

Example EA



3-[6-(9,9-Difluoro-7-{2-[5-(2-methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3*H*-imidazol-4-yl}-9*H*-fluoren-2-yl)-1*H*-benzoimidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester

1. HCl Dioxane / DCM
2. HATU, DIEA, DMF



(3-Cyano-1-{3-[6-(9,9-difluoro-7-{2-[5-(2-methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3*H*-imidazol-4-yl}-9*H*-fluoren-2-yl)-1*H*-benzoimidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carbonyl}-propyl)-carbamic acid methyl ester

(3-Cyano-1-{3-[6-(9,9-difluoro-7-{2-[5-(2-methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3H-imidazol-4-yl}-9H-fluoren-2-yl)-1H-benzoimidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carbonyl}-propyl)-carbamic acid methyl ester:

3-[6-(9,9-Difluoro-7-{2-[5-(2-methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3H-imidazol-4-yl}-9H-fluoren-2-yl)-1H-benzoimidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (61.9 mg, 0.074 mmol) was dissolved in DCM (1 mL) and HCl in dioxane (4M, 1 mL) was added and stirring at room temperature was continued. After 30

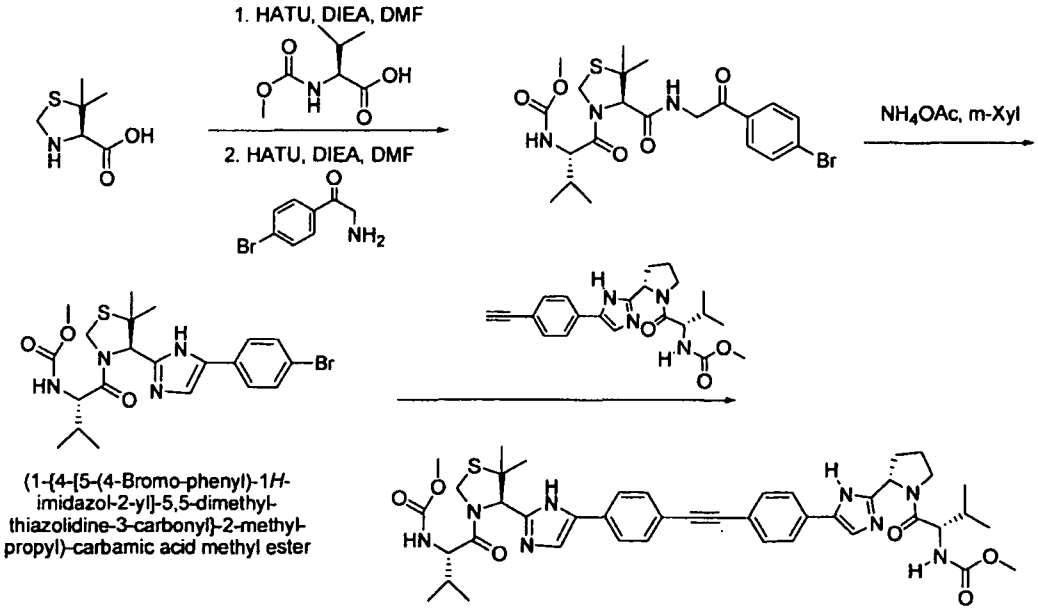
minutes, all volatiles were removed *in vacuo*. The crude material was used in the next step without further purification. The crude material was dissolved in DMF (1.0 mL) and DIEA (28.5 mg, 0.186 mmol) was added. A solution of 2- (*L*) Methoxycarbonylamino-3-cyano-butyric acid (13.8 mg, 0.074 mmol), HATU (28.3 mg, 0.074 mmol) and DIEA (9.5 mg, 0.074 mmol) in DMF (0.5 mL) was added. The reaction was stirred at room temperature. After 30 minutes, the reaction was diluted with EtOAc and was washed with aqueous bicarbonate solution, aqueous LiCl solution (5%), brine, and was dried over sodium sulfate. Filtration and removal of solvents *in vacuo* gave the crude material, which was purified by RP-HPLC (eluent: water / MeCN w/ 0.1% TFA) to yield the product (3-Cyano-1-{3-[6-(9,9-difluoro-7-{2-[5-(2-methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3H-imidazol-4-yl}-9H-fluoren-2-yl)-1H-benzoimidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carbonyl}-propyl)-carbamic acid methyl ester (33.1 mg) as a TFA salt.

LCMS-ESI$^+$: calc'd for $C_{49}H_{51}F_2N_9O_6$: 899.9 (M^+); Found: 900.4 ($M+H^+$).

^{1}H-NMR: 300 MHz, (dmso-d_6) δ: 8.20-7.99 (m, 8H), 7.76 (s, 2H), 7.59 (m, 1H), 7.36 (m, 1H), 5.25 (dd, J = 7.2 Hz, 1H), 4.79 (s, 1H) 4.55 (s, 1H), 4.41 (m, 1H), 3.99 (m, 1H), 3.86 (m,1H), 3.74 (m, 1H), 3.56 (s, 3H), 3.54 (s, 3H), 2.77 (m, 1H), 2.62 (m, 2H), 2.25 (m, 2H), 2.14 (m, 2H), 1.88 – 1.79 (m, 4H), 1.54 (m, 1H), 0.94 - 0.77 (m, 9H) 0.63 (m, 4H) ppm.

^{19}F-NMR: 282 MHz, (dmso-d_6) δ: -109.1 ppm [-74.7 ppm TFA].

Example EB



(1-{4-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-5,5-dimethyl-thiazolidine-3-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester:

5,5-Dimethyl-thiazolidine-4-carboxylic acid (1.1 g, 6.91 mmol) and DIEA (891 mg, 6.91 mmol) were added as a DMF (5 mL) suspension to a premixed solution of *N*-(methylcarbamoyl)(*L*)-valine (1.21 g, 6.91 mmol), HATU (2.26g, 6.91 mmol) and DIEA (891 mg, 6.91 mmol) at room temperature. After 20 minutes, additional HATU (2.26g, 6.91 mmol) and DIEA (891 mg, 6.91 mmol) were added and stirring at room temperature was continued. After 5 minutes, as suspension of amino-(4'bromo) acetophenone hydrochloride salt (1.72 g, 6.91 mmol) and DIEA (891 mg, 6.91 mmol) in DMF (3 mL) was added. Stirring at room temperature was continued. After 10 minutes, all volatiles were removed *in vacuo* and the crude material was taken into EtOAc. The organic layer was washed with aqueous hydrochloric acid (0.1M), aqueous lithium chloride solution (5%), saturated aqueous sodium bicarbonate solution, brine and was dried over sodium sulfate. Filtration and evaporation of solvents yielded crude material. Purification via silica gel chromatography (eluent EtOAc / hexanes) yielded the product (3.46 g, 6.73 mmol).

LCMS-ESI$^+$: calc'd for $C_{21}H_{28}BrN_3O_5S$: 514.3 (M^+); Found: 515.4 / 513.4 ($M+H^+$).

The product of the previous step (1.04mg, 1.94 mmol) was dissolved in m-xylenes (9.0 mL) and heated at 135 °C. Solid ammonium acetate (700 mg, 9.07 mmol) was added and the reaction was stirred at 135 °C. After 240 minutes, the reaction was cooled to room temperature and the volatiles were removed *in vacuo*. The crude material was purified via silica gel chromatography (eluent: EtOAc / hexanes) to yield the product (1-{4-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-5,5-dimethyl-thiazolidine-3-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (190 mg).

LCMS-ESI$^+$: calc'd for $C_{21}H_{28}BrN_4O_3S$: 495.4 (M^+); Found: 496.4 / 494.4 ($M+H^+$).

[1-(4-{5-[4-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenylethynyl)-phenyl]-1H-imidazol-2-yl}-5,5-dimethyl-thiazolidine-3-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester:

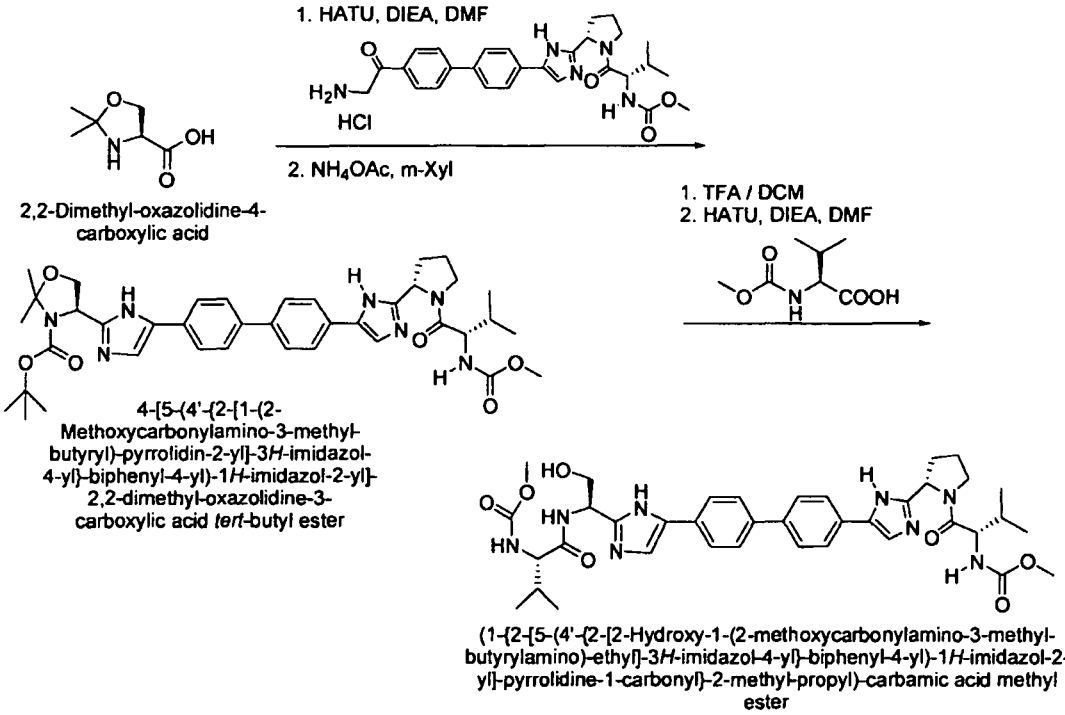
(1-{4-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-5,5-dimethyl-thiazolidine-3-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (83 mg, 0.167 mmol) was combined with (1-{2-[5-(4-Ethynyl-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (66.0 mg, 0.167 mmol) and $PdCl_2(PPh_3)_2$ (11.7 mg, 0.017 mmol) under an argon atmosphere. DMF (2.0 mL degassed with Argon) was added followed by triethylamine (168 mg, 1.67 mmol) and copper(I) iodide (3.2 mg, 0.017 mmol). The mixture was heated at 80 °C. After 20 hours, volatiles were removed *in vacuo* and the crude material was semi-purified via chromatography on silica gel (eluent EtOAc w MeOH 10% / hexanes) and further purified via

RP-HPLC (eluent: water/ MeCN w 0.1% TFA) to yield the product [1-(4-{5-[4-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenylethynyl)-phenyl]-1H-imidazol-2-yl}-5,5-dimethyl-thiazolidine-3-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (32.1 mg) as a TFA salt.

LCMS-ESI$^+$: calc'd for $C_{43}H_{52}N_8O_6S$: 808.9 (M^+); Found: 809.9 ($M+H^+$).

^{1}H-NMR: 300 MHz, (dmso-d_6) δ: 8.09 (m, 2H), 7.83 – 7.69 (m, 12H), 7.56 (m, 1H), 7.34 (m, 1H), 5.33 (s, 1H), 5.12 (m, 2H), 5.01 (m, 1H) 4.01 (m, 2H), 3.83 (m, 2H), 3.55 (s, 3H), 3.53 (s, 3H), 2.37 (m, 1H), 2.09 – 2.04 (m, 3H), 1.55 (s, 3H), 1.11 (s, 3H), 0.92 - 0.76 (m, 12H) ppm.

Example EC



4-[5-(4'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester:

2,2-Dimethyl-oxazolidine-4-carboxylic acid (350 mg, 1.02 mmol) was dissolved in DMF (2.5 mL) and HATU (387 mg, 0.102 mmol) and DIEA (129.0 mg, 1.02 mmol) were added. The reaction was stirred at room temperature for five minutes, after which [1-(2-{5-[4'-(2-Amino-acetyl)-biphenyl-4-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester hydrochloride salt (503 mg, 1.0 mmol) and DIEA (129.0 mg, 1.02 mmol) were added. Stirring at room temperature was continued. After 18 hours, all volatiles were

removed *in vacuo* and the crude material was purified via silica gel chromatography (eluent: EtOAc / hexanes) to yield the product (323 mg). The material was dissolved was dissolved in *m*-xylenes (5.0 mL) and heated at 135 °C. Solid ammonium acetate (280 mg, 3.63 mmol) was added and the reaction was stirred at 135 °C. After 180 minutes, the reaction was cooled to room temperature and the volatiles were removed *in vacuo*. The crude material was purified via silica gel chromatography (eluent: EtOAc / hexanes) to yield the product 4-[5-(4'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester (123 mg, 0.172 mmol).

LCMS-ESI$^+$: calc'd for $C_{39}H_{49}N_7O_6$: 711.8 (M^+); Found: 712.7 ($M+H^+$).

(1-{2-[5-(4'-{2-[2-Hydroxy-1-(2-methoxycarbonylamino-3-methyl-butyrylamino)-ethyl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester:

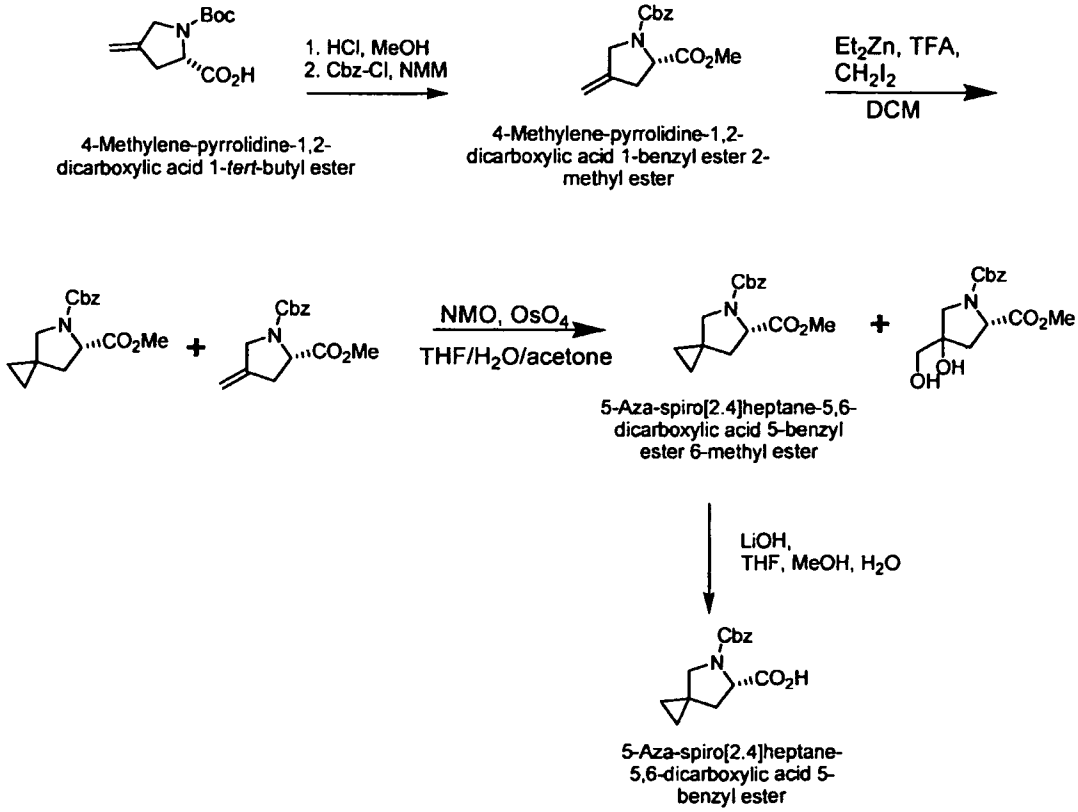
4-[5-(4'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester (61 mg, 0.086 mmol) was dissolved in DCM (1 mL) and TFA (4M, 0.2 mL) was added and stirring at 0 °C was continued. After 30 minutes, all volatiles were removed *in vacuo*. The crude material was used in the next step without further purification. The crude material was dissolved in DMF (1.5 mL) and DIEA (33.0 mg, 0.255 mmol) was added. A solution of 2- (*L*) Methoxycarbonylamino-3-methyl-butyric acid (15.2 mg, 0.086 mmol), HATU (32.5 mg, 0.086 mmol) and DIEA (11.0 mg, 0.086 mmol) in DMF (0.5 mL) was added. The reaction was stirred at room temperature. After 20 minutes, the reaction was diluted with EtOAc and was washed with aqueous bicarbonate solution, aqueous LiCl solution (5%), brine, and was dried over sodium sulfate. Filtration and removal of solvents *in vacuo* gave the crude material, which was purified by RP-HPLC (eluent: water / MeCN w/ 0.1% TFA) to yield the product (1-{2-[5-(4'-{2-[2-Hydroxy-1-(2-methoxycarbonylamino-3-methyl-butyrylamino)-ethyl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (11.2 mg) as a TFA salt.

LCMS-ESI$^+$: calc'd for $C_{38}H_{48}N_8O_7$: 728.8 (M^+); Found: 729.7 ($M+H^+$).

^{1}H-NMR: 300 MHz, (dmso-d_6) δ: 8.62 (m, 1H), 8.11 (m, 2H), 7.95 – 7.86 (m, 8H), 7.34 (m, 1H), 7.22 (m, 1H), 5.10 (m, 2H), 4.78 (s, 1H) 4.13 (m, 1H), 3.94 (m, 1H), 3.83 (m, 4H), 3.54 (s, 3H), 3.53 (s, 3H), 2.37 (m, 1H), 2.09 – 2.04 (m, 5H), 0.88 - 0.75 (m, 12H) ppm.

Example ED

Preparation of Intermediate 5-Aza-spiro[2.4]heptane-5,6-dicarboxylic acid 5-benzyl ester 6-methyl ester



4-Methylene-pyrrolidine-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester:

4-Methylene-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester (10.0 g, 44 mmol) was dissolved in MeOH (75 mL) at room temperature and HCl (4M in dioxane, 75 mL) was added. Stirring at room temperature was continued for 4 hours. All volatiles were removed *in vacuo* and a beige solid was obtained.

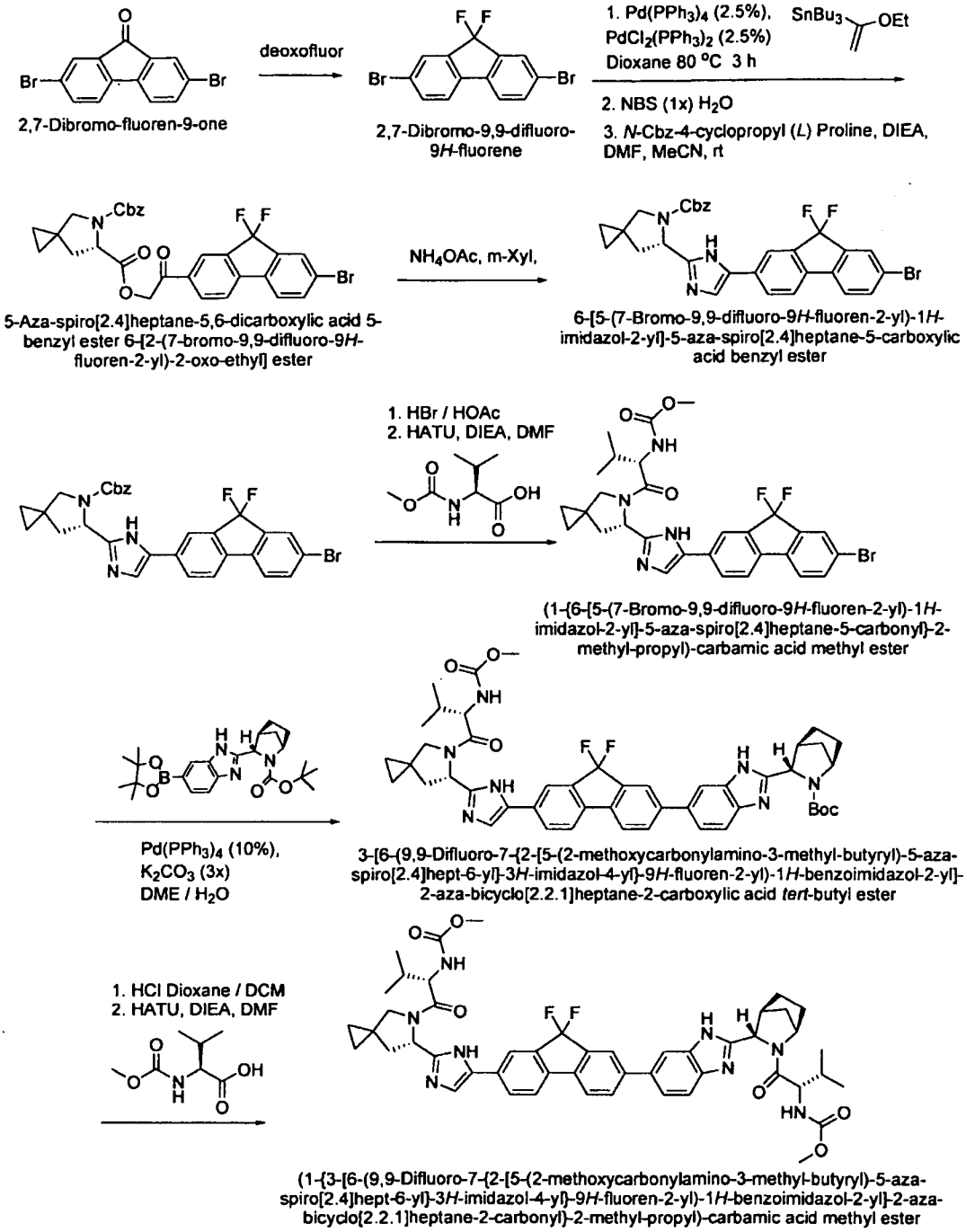
The crude material was suspended in DCM (100 mL) and N-Methyl morpholine (13.3 g, 132 mmol) was added. The mixture was cooled to 0 °C and benzyl chloroformate (8.26 g, 48.4 mmol) was added while stirring. After 30 minutes, the reaction was warmed to room temperature and the solution was washed with water and aqueous HCl (1M). The solution was dried over sodium sulfate. Filtration and evaporation of solvents gave crude product, which was purified by silica gel chromatography (eluent: EtOAc / hexanes) to yield the product (10.2 g). LCMS-ESI$^+$: calc'd for $C_{15}H_{17}NO_4$: 275.3 (M^+); Found: 276.4 ($M+H^+$).

5-aza-spiro[2.4]heptanes-5,6-dicarboxylic acid benzyl ester: An oven-dried 3-neck round bottom flask was equipped with a nitrogen inlet adaptor and a 250 mL addition funnel. The third neck was sealed with a septum. The flask was charged with a stir bar, diclorormethane (120 mL) and diethyl zinc (1.0 M in hexane, 118 mL, 118 mmol) then cooled to 0 °C in an ice bath. The addition funnel was charged with dichloromethane (40 mL) and trifluoroacetic acid (9.1 mL, 118 mmol). After the diethyl zinc solution had cooled to 0 °C (about 25 minutes), the trifluoroacetic acid solution was added dropwise over 20 minutes to the stirred reaction mixture. After stirring for another 20 minutes at 0 °C, diiodomethane (9.5 mL, 118 mmol) was added slowly over 4 minutes. After another 20 minutes, 4-methylene-pyrrolidine-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (8.10 g, 29.4 mmol) was added in 30 mL dichloromethane by cannula. The flask containing 4-methylene-pyrrolidine-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester was then rinsed with another 10 mL dichloromethane and this solution was also transferred to the reaction mixture by cannula. The reaction mixture was allowed to warm to RT and stirred for 110 hours (about 5 days) after which the reagents were quenched with saturated aqueous ammonium chloride (~150 mL). The contents of the flask were slowly poured into a 2 L sep funnel containing saturated aqueous sodium bicarbonate (~800 mL). The aqueous phase was extracted three times with 300 mL ethyl acetate. The combined organics were dried over magnesium sulfate and concentrated to provide the crude material. The crude material was dissolved in 3:1:1 THF/water/acetone (165 mL) then treated with *N*-methylmorpholine-*N*-oxide (3.45 g, 29.4 mmol) and osmium tetroxide (4 wt% in water, 5 mL, 0.818 mmol). After stirring at RT for 7 h, the reagents were quenched with 1 M aqueous sodium thiosulfate (~100 mL). The contents of the flask were then poured into a 1 L sep funnel containing water (~300 mL). The aqueous phase was extracted three times with 300 mL dichloromethane. The combined organics were dried over magnesium sulfate and concentrated. The crude residue was purified by silica column chromatography (5% to 45% EtOAc/hexane) to provide 5-aza-spiro[2.4]heptane-5,6-dicarboxylic acid 5-benzyl ester 6-methyl ester as a clear oil (5.54g, 19.15 mmol, 65%) as a clear oil. ^{1}H NMR ($CDCl_3$) δ 7.36-7.29 (m, 5H), 5.21-5.04 (m, 2H), 4.56-4.47 (m, 1H), 3.75 (s, 1.5H), 3.60 (m, 1.5H), 03.51-3.37 (m, 2H), 2.32-2.25 (m, 1H), 1.87-1.80 (m, 1H), 0.64-0.51 (m, 4H).

5-Aza-spiro[2.4]heptane-5,6-dicarboxylic acid 5-benzyl ester:
5-Aza-spiro[2.4]heptane-5,6-dicarboxylic acid 5-benzyl ester 6-methyl ester (244 mg, 0.840 mmol) was dissolved in THF (2.0 mL)/MeOH (1.5 mL). An aqueous solution of LiOH (35.5 mg, 0.84 mmol) was added and stirring at room temperature was continued. After 3 hours, the reaction was neutralized with aqueous HCl (1M) and the organic solvents were removed *in*

vacuo. The crude mixture was diluted with water and EtOAc and the organic layer was collected. All volatiles were removed *in vacuo* and the crude acid was used without further purification. LCMS-ESI$^+$: calc'd for $C_{15}H_{17}NO_4$: 275.3 (M^+); Found: 276.3 ($M+H^+$).

Example ED'



2,7-Dibromo-fluoren-9-one

2,7-Dibromo-9,9-difluoro-9*H*-fluorene

5-Aza-spiro[2.4]heptane-5,6-dicarboxylic acid 5-benzyl ester 6-[2-(7-bromo-9,9-difluoro-9*H*-fluoren-2-yl)-2-oxo-ethyl] ester

6-[5-(7-Bromo-9,9-difluoro-9*H*-fluoren-2-yl)-1*H*-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carboxylic acid benzyl ester

(1-{6-[5-(7-Bromo-9,9-difluoro-9*H*-fluoren-2-yl)-1*H*-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

3-[6-(9,9-Difluoro-7-{2-[5-(2-methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3*H*-imidazol-4-yl}-9*H*-fluoren-2-yl)-1*H*-benzoimidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester

(1-{3-[6-(9,9-Difluoro-7-{2-[5-(2-methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3*H*-imidazol-4-yl}-9*H*-fluoren-2-yl)-1*H*-benzoimidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

2,7-Dibromo-9,9-difluoro-9H-fluorene:

2,7-Dibromo-fluoren-9-one (4.0 g, 11.8 mmol) was suspended in deoxofluor (12 mL) at room temperature and EtOH (4 drops) was added. The stirred suspension was heated at T = 90° C for 24 hours (**CAUTION: Use of deoxofluor at elevated temperatures, as described above, is strongly discouraged as rapid and violent exotherms may occur**). The reaction was cooled to room temperature and poured onto ice containing sodium bicarbonate. A solid formed and was collected via filtration. The crude material was taken into EtOAc and was washed with

aqueous HCl (1M) and brine. The solution was dried over sodium sulfate. Filtration and evaporation of solvents gave crude product, which was purified by silica gel chromatography (eluent: EtOAc / hexanes) to yield the product 2,7-Dibromo-9,9-difluoro-9H-fluorene (3.2 g). ^{19}F-NMR: 282 MHz, (dmso-d_6) δ: -111.6 ppm.
Before using the material in the next step, it was exposed as a solution in EtOAc to charcoal.

5-Aza-spiro[2.4]heptane-5,6-dicarboxylic acid 5-benzyl ester 6-[2-(7-bromo-9,9-difluoro-9H-fluoren-2-yl)-2-oxo-ethyl] ester:
2,7-Dibromo-9,9-difluoro-9H-fluorene (372 mg, 1.04 mmol), $Pd(PPh_3)_4$ (30.0 mg, 0.026 mmol), $PdCl_2(PPh_3)_2$ (18.2 mg, 0.026 mmol), $As(PPh_3)_3$ (5.0 mg) were dissolved in dioxane (10 mL) under an argon atmosphere. Ethoxyvinyl-tributyl tin (376.4 mg, 1.04 mmol) was added. The mixture was heated for 140 minutes at 85°C (oil bath). The reaction was cooled to room temperature. *N*-bromo succinimide (177 mg, 1.0 mmol) was added followed by water (2 mL). The reaction was stirred at room temperature for 3 hours, after which the majority of the dioxane was removed *in vacuo*. The crude reaction mixture was diluted with EtOAc and was washed with water. All volatiles were removed *in vacuo*. Toluene was added and all volatiles were removed *in vacuo* for a second time. The crude material was dissolved in DMF / MeCN (2 mL, 1:1) at room temperature. A solution of *N*-Cbz-4-cyclopropyl (*L*) Proline (0.84 mmol) and DIEA (268 mg, 2.08 mmol) in MeCN (2 mL) was added and stirring at room temperature was continued. After 14 hours, most of the MeCN was removed *in vacuo* and the crude reaction mixture was diluted with EtOAc. The mixture was washed with aqueous HCl (1M), aqueous LiCl solution (5%), brine, and was dried over sodium sulfate. Filtration and evaporation of solvents gave the crude reaction product, which was purified via silica gel chromatography (eluent: EtOAc / hexanes) to yield the product 5-Aza-spiro[2.4]heptane-5,6-dicarboxylic acid 5-benzyl ester 6-[2-(7-bromo-9,9-difluoro-9H-fluoren-2-yl)-2-oxo-ethyl] ester (176 mg). LCMS-ESI$^+$: calc'd for $C_{30}H_{24}BrF_2NO_5$: 596.4 (M^+); Found: 595.2 / 597.2 ($M+H^+$).

6-[5-(7-Bromo-9,9-difluoro-9H-fluoren-2-yl)-1H-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carboxylic acid benzyl ester:
5-Aza-spiro[2.4]heptane-5,6-dicarboxylic acid 5-benzyl ester 6-[2-(7-bromo-9,9-difluoro-9H-fluoren-2-yl)-2-oxo-ethyl] ester (172 mg, 0.293 mmol) was dissolved in *m*-xylenes (6.0 mL). Ammonium acetate (226 mg, 2.93 mmol) was added and the reaction was stirred at 140°C for 60 minutes under microwave conditions. The reaction was cooled to room temperature and all volatiles were removed *in vacuo*. The crude material was purified via silica gel chromatography

(eluent: EtOAc / hexanes) to yield the product 6-[5-(7-Bromo-9,9-difluoro-9H-fluoren-2-yl)-1H-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carboxylic acid benzyl ester (80.3 mg). LCMS-ESI$^+$: calc'd for $C_{30}H_{24}BrF_2N_3O_2$: 576.4 (M^+); Found: 575.2 / 577.2 ($M+H^+$).

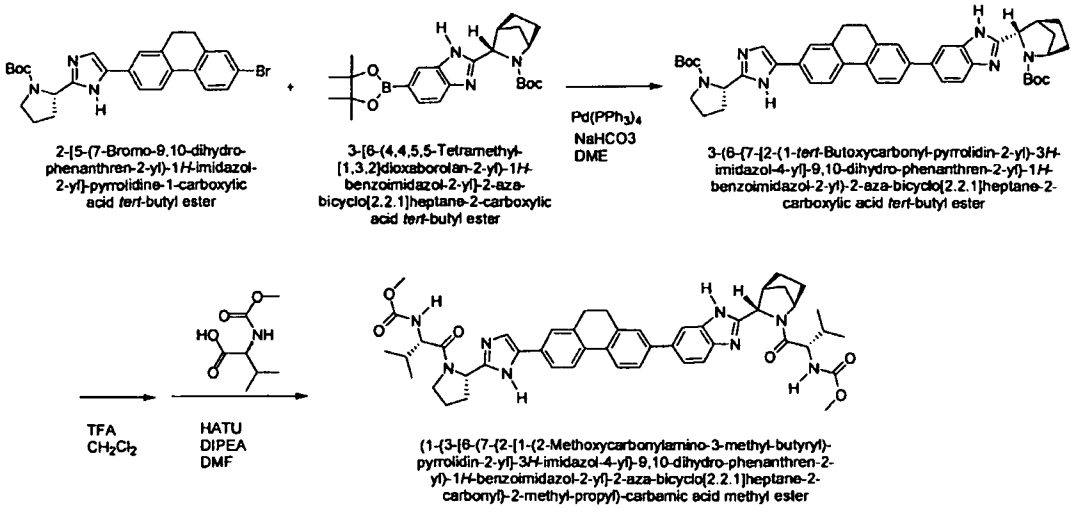
(1-{6-[5-(7-Bromo-9,9-difluoro-9H-fluoren-2-yl)-1H-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: 6-[5-(7-Bromo-9,9-difluoro-9H-fluoren-2-yl)-1H-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carboxylic acid benzyl ester (800 mg, 1.38 mmol) was dissolved in DCM (15 mL) and HBr in AcOH (37%, 2 mL) was added and stirring at room temperature was continued. After 180 minutes, the suspension was diluted with hexanes and the solid was collected via filtration and was washed with hexanes and subjected to vacuum. The crude material was used in the next step without further purification. The crude material was dissolved in DMF (4.0 mL) and DIEA (356 mg, 2.76 mmol) was added. A solution of 2-(*L*)-Methoxycarbonylamino-3-methyl-butyric acid (242 mg, 1.38 mmol), HATU (524 mg, 1.38 mmol) and DIEA (178 mg, 1.38 mmol) in DMF (1 mL) was added. The reaction was stirred at room temperature. After 50 minutes, the reaction was diluted with EtOAc and was washed with aqueous bicarbonate solution, aqueous LiCl solution (5%), brine, and was dried over sodium sulfate. Filtration and removal of solvents *in vacuo* gave the crude material, which was purified by silica gel chromatography (eluent: EtOAc / hexanes) to yield the slightly impure product (1-{6-[5-(7-Bromo-9,9-difluoro-9H-fluoren-2-yl)-1H-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (878 mg). LCMS-ESI$^+$: calc'd for $C_{29}H_{29}BrF_2N_4O_3$: 599.5 (M^+); Found: 598.5 / 600.5 ($M+H^+$).

3-[6-(9,9-Difluoro-7-{2-[5-(2-methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3H-imidazol-4-yl}-9H-fluoren-2-yl)-1H-benzoimidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester: (1-{6-[5-(7-Bromo-9,9-difluoro-9H-fluoren-2-yl)-1H-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (840 mg, 1.4 mmol), 3-[6-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-benzoimidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (615 mg, 1.4 mmol), $Pd(PPh_3)_4$ (161 mg, 0.14 mmol), K_2CO_3 (579 mg, 4.2 mmol), were dissolved in DME (15 mL) / water (3 mL) under an argon atmosphere. The mixture was heated for 120 minutes at 85 – 90°C (oil bath). After 120 minutes additional boronate ester (61 mg, 0.14 mmol) was added and heating was continued. After 3 hours, the reaction was cooled to room temperature. Most of the DME was removed *in vacuo*

and the crude reaction mixture was diluted with EtOAc. The mixture was washed with brine and was dried over sodium sulfate. Filtration and evaporation of solvents gave the crude reaction product, which was purified via silica gel chromatography (eluent: EtOAc / hexanes) to yield the product 3-[6-(9,9-Difluoro-7-{2-[5-(2-methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3H-imidazol-4-yl}-9H-fluoren-2-yl)-1H-benzoimidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (878 mg). LCMS-ESI$^+$: calc'd for $C_{47}H_{51}F_2N_7O_5$: 831.9 (M^+); Found: 832.7 ($M+H^+$).

(1-{3-[6-(9,9-Difluoro-7-{2-[5-(2-methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3H-imidazol-4-yl}-9H-fluoren-2-yl)-1H-benzoimidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester:
3-[6-(9,9-Difluoro-7-{2-[5-(2-methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3H-imidazol-4-yl}-9H-fluoren-2-yl)-1H-benzoimidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (115 mg, 0.138 mmol) was dissolved in DCM (2 mL) and HCl in dioxane (4M, 2 mL) was added and stirring at room temperature was continued. After 20 minutes, all volatiles were removed *in vacuo*. The crude material was used in the next step without further purification. The crude material was dissolved in DMF (1.5 mL) and DIEA (53.4 mg, 0.414 mmol) was added. A solution of 2- (*L*) Methoxycarbonylamino-3-methyl-butyric acid (24.2 mg, 0.138 mmol), HATU (52.4 mg, 0.138 mmol) and DIEA (17.8 mg, 0.138 mmol) in DMF (1 mL) was added. The reaction was stirred at room temperature. After 20 minutes, the reaction was diluted with EtOAc and was washed with aqueous bicarbonate solution, aqueous LiCl solution (5%), brine, and was dried over sodium sulfate. Filtration and removal of solvents *in vacuo* gave the crude material, which was purified by RP-HPLC (eluent: water / MeCN w/ 0.1% TFA) to yield the product (1-{3-[6-(9,9-Difluoro-7-{2-[5-(2-methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3H-imidazol-4-yl}-9H-fluoren-2-yl)-1H-benzoimidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (76 mg). LCMS-ESI$^+$: calc'd for $C_{49}H_{54}F_2N_8O_6$: 888.9 (M^+); Found: 890.0 ($M+H^+$).
^{1}H-NMR: 300 MHz, (dmso-d_6) δ: 8.20-7.99 (m, 8H), 7.73 (s, 2H), 7.37 – 7.27 (m, 2H), 5.25 (dd, J = 7.2 Hz, 1H), 4.78 (s, 1H) 4.54 (s, 1H), 4.16 (m, 1H), 4.02 (m, 1H), 3.87 (m,1H), 3.74 (m, 1H), 3.55 (s, 3H), 3.53 (s, 3H), 2.75 (m, 1H), 2.25 (m, 2H), 2.09 – 2.04 (m, 2H), 1.88 – 1.79 (m, 2H), 1.54 (m, 1H), 0.94 - 0.77 (m, 15H) 0.63 (m, 4H) ppm. ^{19}F-NMR: 282 MHz, (dmso-d_6) δ: -109.1 ppm [-74.8 ppm TFA]

Example EE

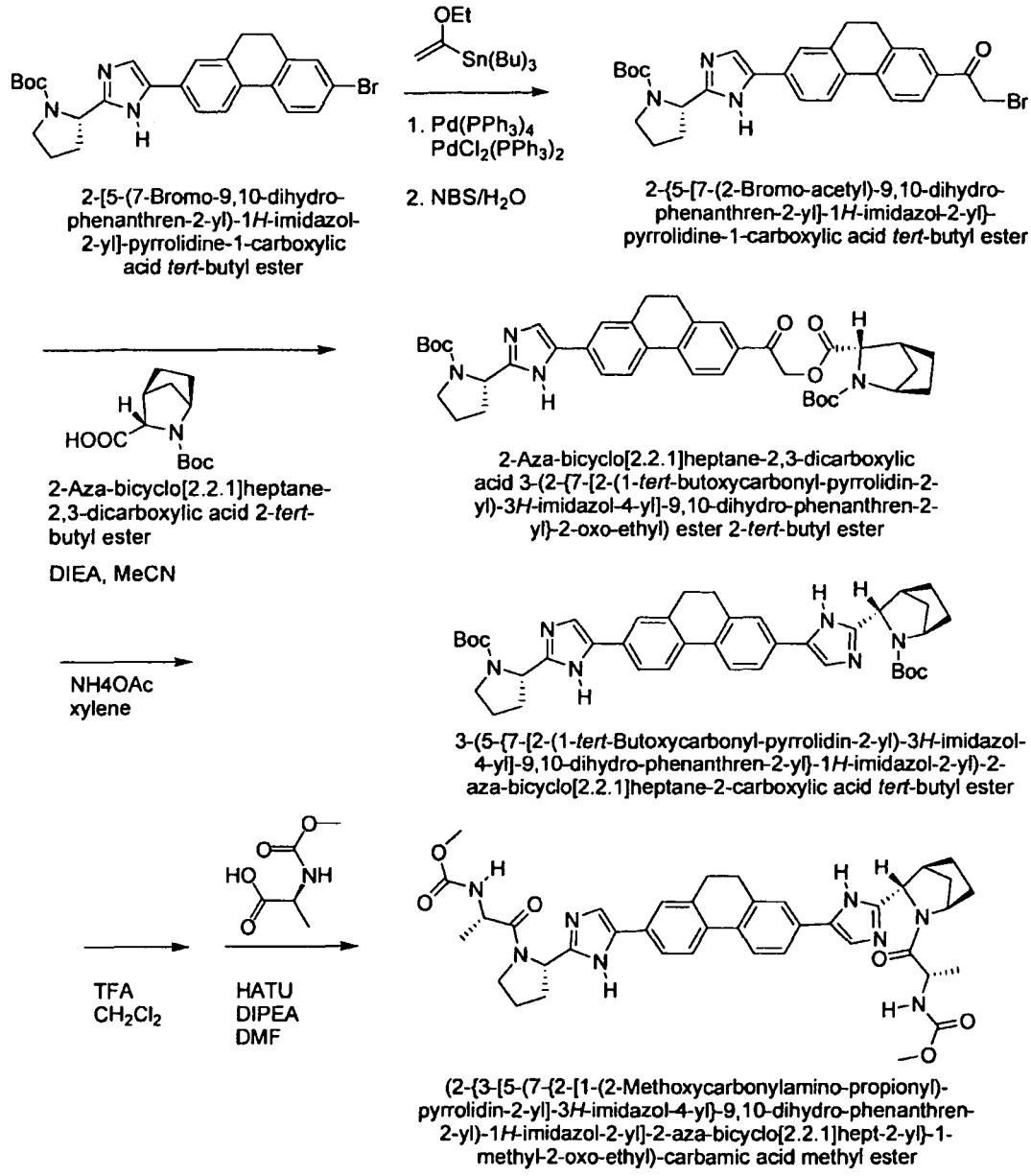


3-(6-{7-[2-(1-*tert*-Butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-9,10-dihydro-phenanthren-2-yl}-1H-benzoimidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester. $Pd(Ph_3)_4$ (20 mg, 0.017 mmol) was added to a mixture 2-[5-(7-bromo-9,10-dihydro-phenanthren-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (173 mg, 0.35 mmol), 3-[6-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-benzoimidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (154 mg, 0.35 mmol), $NaHCO_3$ (103 mg, 1.22 mmol) in 1,2-dimethoxyethane (5 mL) and water (1 mL). The reaction mixture was flushed with nitrogen, heated at 80°C for 16 hours, and then the volatile component was removed *in vacuo*. The residue was dissolved in ethyl acetate (100 mL), washed with $NaHCO_3$ solution, water and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The obtained residue was purified by flash chromatography to provide the desired product 3-(6-{7-[2-(1-*tert*-Butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-9,10-dihydro-phenanthren-2-yl}-1H-benzoimidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester as a white solid (150 mg, 59%). m/z 727.4 $(M+H)^+$.

(1-{3-[6-(7-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-9,10-dihydro-phenanthren-2-yl)-1H-benzoimidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: To a solution of 3-(6-{7-[2-(1-*tert*-Butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-9,10-dihydro-phenanthren-2-yl}-1H-benzoimidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (135 mg, 0.19 mmol) in dichloromethane (6 mL) was added trifluoroacetic acid (2 mL, excess). The mixture was stirred for 2 hours at ambient temperature and concentated under reduced pressure. The residue was treated with ether to remove excess trifluoroacetic acid. The

obtained white solid was dissoved in DMF (5 mL), to the solution was added 2-methoxycarbonylamino-3-methyl-butyric acid (65 mg, 0.37 mmol), HATU (156 mg, 0.41 mmol) and *N,N*-diisopropylethylamine (0.32 mL, 1.86 mmol). The mixture was stirred at ambient for 2 hours, and then the volatile component was removed *in vacuo*. The residue was dissolved in ethyl acetate (100 mL), washed with 1 N NaOH solution, water and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The obtained residue was purified by HPLC to provide the desired product (1-{3-[6-(7-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-9,10-dihydro-phenanthren-2-yl)-1H-benzoimidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester as a TFA salt (57 mg, 36%). ^{1}H-NMR (300 MHz, CD_3OD) δ 8.05-7.60 (m, 10H), 5.25 (t, 1H), 4.40-4.05 (m, 3H), 3.95-3.60 (m, 8H), 3.10-2.90 (m 6H), 2.65-2.50 (m, 1H), 2.40-1.70 (m, 11H), 1.05-0.90 (m, 12H); m/z 839.2 $(M+H)^+$.

Example EF



2-{5-[7-(2-Bromo-acetyl)-9,10-dihydro-phenanthren-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester. $Pd(Ph_3)_4$ (15 mg, 0.015 mmol) and $PdCl_2(Ph_3)_2$ (10 mg, 0.015 mmol) were added to a mixture 2-[5-(7-bromo-9,10-dihydro-phenanthren-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (180 mg, 0.37 mmol) and tributyl(1-ethoxyvinyl)tin (0.15 mL, 0.44 mL) in 5 mL dioxane. The reaction mixture was flushed with nitrogen, heated at 80°C for 16 hours, then cooled to ambient temperature. Water (1.5 mL) and NBS (78 mg, 0.44 mmol) was added and the mixture was stirred at room temperature for 40

minutes, then diluted with ethyl acetate (100 mL). Washed with water and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The obtained residue was carried on to next step reaction without purification.

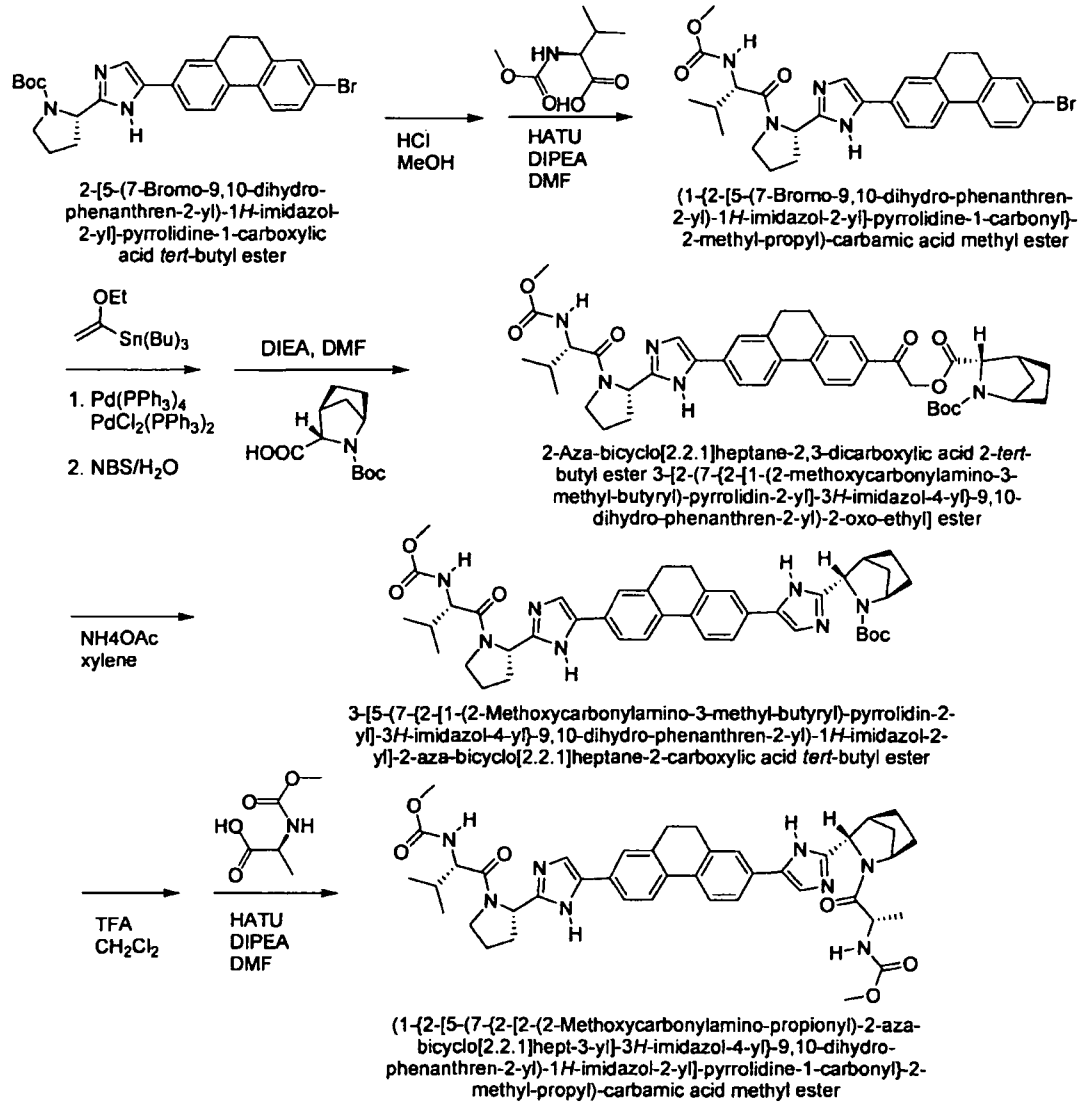
2-Aza-bicyclo[2.2.1]heptane-2,3-dicarboxylic acid 3-(2-{7-[2-(1-*tert*-butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-9,10-dihydro-phenanthren-2-yl}-2-oxo-ethyl) ester 2-*tert*-butyl ester. A mixture of 2-aza-bicyclo[2.2.1]heptane-2,3-dicarboxylic acid 2-*tert*-butyl ester (167 mg, 0.69 mmol) and DIPEA (0.11 mL, 0.67 mmol) was added to a solution of 2-{5-[7-(2-bromo-acetyl)-9,10-dihydro-phenanthren-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.37 mmol, crude) in acetonitrile (5 mL). The mixture was stirred at room temperature for 16 hours, then diluted with ethyl acetate (100 mL). The organic layer was washed with $NaHCO_3$ solution and water, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The obtained residue was purified by flash chromatography to provide the desired product 2-aza-bicyclo[2.2.1]heptane-2,3-dicarboxylic acid 3-(2-{7-[2-(1-*tert*-butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-9,10-dihydro-phenanthren-2-yl}-2-oxo-ethyl) ester 2-*tert*-butyl ester as a brown solid (132 mg, 51% over two steps). m/z 697.2 $(M+H)^+$.

3-(5-{7-[2-(1-*tert*-Butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-9,10-dihydro-phenanthren-2-yl}-1H-imidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester. A mixture of 2-aza-bicyclo[2.2.1]heptane-2,3-dicarboxylic acid 3-(2-{7-[2-(1-*tert*-butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-9,10-dihydro-phenanthren-2-yl}-2-oxo-ethyl) ester 2-*tert*-butyl ester (132 mg, 0.19 mmol) and ammonium acetate (292 mg, 3.8 mmol) in xylene (10 mL) was heated in a sealed tube at 140°C for 1.5 hours under microwave condition. The volatile component was removed *in vacuo*, and the residue was dissolved in ethyl acetate (100 mL), washed with $NaHCO_3$ solution, water and brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The obtained residue was purified by flash chromatography to provide the desired product 3-(5-{7-[2-(1-*tert*-Butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-9,10-dihydro-phenanthren-2-yl}-1H-imidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester as a white solid (36 mg, 28%). m/z 677.4 $(M+H)^+$.

(2-{3-[5-(7-{2-[1-(2-Methoxycarbonylamino-propionyl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-9,10-dihydro-phenanthren-2-yl)-1H-imidazol-2-yl]-2-aza-bicyclo[2.2.1]hept-2-yl}-1-methyl-2-oxo-ethyl)-carbamic acid methyl ester. To a solution of 3-(5-{7-[2-(1-*tert*-Butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-9,10-dihydro-phenanthren-2-yl}-1H-imidazol-2-yl)-2-aza-

bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (36 mg, 0.053 mmol) in dichloromethane (6 mL) was added trifluoroacetic acid (2 mL, excess). The mixture was stirred for 2 hours at ambient temperature and concentated under reduced pressure. The residue was treated with ether to remove excess trifluoroacetic acid. The obtained white solid was dissoved in DMF (5 mL), to the solution was added 2-methoxycarbonylamino-propionic acid (17 mg, 0.12 mmol), HATU (50 mg, 0.13 mmol) and *N,N*-diisopropylethylamine (0.09 mL, 0.53 mmol). The mixture was stirred at ambient for 2 hours, and then the volatile component was removed *in vacuo*. The residue was dissolved in ethyl acetate (100 mL), washed with 1 N NaOH solution, water and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The obtained residue was purified by HPLC to provide the desired product (2-{3-[5-(7-{2-[1-(2-Methoxycarbonylamino-propionyl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-9,10-dihydro-phenanthren-2-yl)-1H-imidazol-2-yl]-2-aza-bicyclo[2.2.1]hept-2-yl}-1-methyl-2-oxo-ethyl)-carbamic acid methyl ester as a TFA salt (5.5 mg, 14%). ^{1}H-NMR (300 MHz, CD_3OD) δ 8.05-7.60 (m, 8H), 5.35-5.25 (m, 1H), 4.65-4.40 (m, 3H), 4.05-3.80 (m, 2H), 3.75-3.50 (m, 7H), 3.00 (s, 4H), 2.87 (s, 1H), 2.65 (m, 1H), 2.30-1.70 (m, 9H), 1.45-1.20 (m, 6H); m/z 735.3 $(M+H)^+$.

Example EG



2-[5-(7-Bromo-9,10-dihydro-phenanthren-2-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester

(1-{2-[5-(7-Bromo-9,10-dihydro-phenanthren-2-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

2-Aza-bicyclo[2.2.1]heptane-2,3-dicarboxylic acid 2-*tert*-butyl ester 3-[2-(7-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-9,10-dihydro-phenanthren-2-yl)-2-oxo-ethyl] ester

3-[5-(7-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-9,10-dihydro-phenanthren-2-yl)-1*H*-imidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester

(1-{2-[5-(7-{2-[2-(2-Methoxycarbonylamino-propionyl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3*H*-imidazol-4-yl}-9,10-dihydro-phenanthren-2-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

(1-{2-[5-(7-Bromo-9,10-dihydro-phenanthren-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester. To a solution of 2-[5-(7-bromo-9,10-dihydro-phenanthren-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (187 mg, 0.38 mmol) in methanol (5 mL) was added 4.0 M solution of HCl in dioxane (2 mL, excess). The mixture was stirred for 3 hours at 50°C and concentated under reduced pressure. The residue was treated with ether to remove excess HCl. The obtained white solid was dissoved in DMF (5 mL), to the solution was added 2-methoxycarbonylamino-3-methyl-butyric acid (70 mg, 0.40 mmol), HATU (173 mg, 0.46 mmol) and *N,N*-diisopropylethylamine (0.66 mL, 3.8 mmol). The mixture was stirred at ambient for 2 hours, and then the volatile component was removed *in vacuo*. The residue was dissolved in ethyl acetate (100 mL), washed with 1 N

NaOH solution, water and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The obtained residue was purified by flash chromatography to provide the desired product (1-{2-[5-(7-bromo-9,10-dihydro-phenanthren-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester as an oil (200 mg, 95%). m/z 551.2, 553.2 $(M+H)^+$.

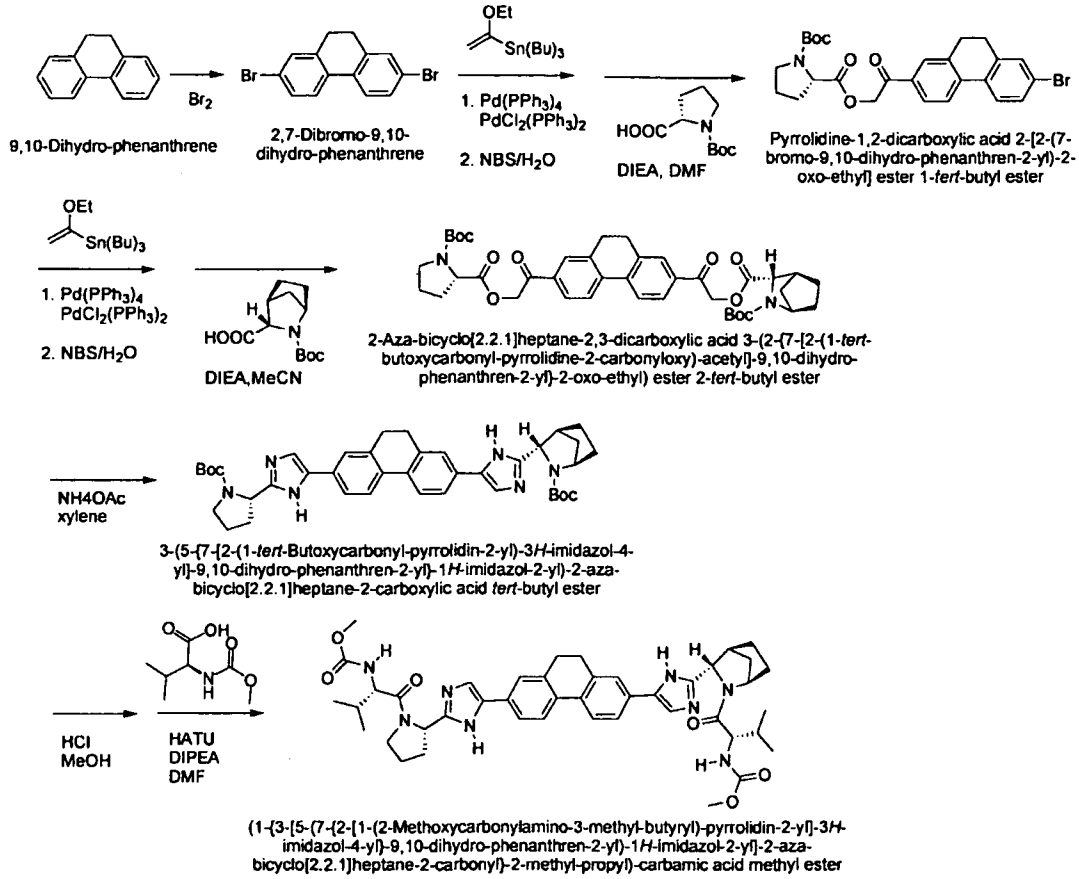
2-Aza-bicyclo[2.2.1]heptane-2,3-dicarboxylic acid 2-*tert*-butyl ester 3-[2-(7-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-9,10-dihydro-phenanthren-2-yl)-2-oxo-ethyl] ester: $Pd(Ph_3)_4$ (15 mg, 0.015 mmol) and $PdCl_2(Ph_3)_2$ (10 mg, 0.015 mmol) were added to a mixture of (1-{2-[5-(7-bromo-9,10-dihydro-phenanthren-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (200 mg, 0.37 mmol) and tributyl(1-ethoxyvinyl)tin (0.15 mL, 0.44 mL) in 5 mL dioxane. The reaction mixture was flushed with nitrogen, heated at 80°C for 16 hours, then cooled to ambient temperature. Water (1.5 mL) and NBS (78 mg, 0.44 mmol) was added and the mixture was stirred at room temperature for 40 minutes, then diluted with ethyl acetate (100 mL). Washed with water and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The obtained residue was disolved in acetonitrile (3 mL). To it was added a solution of 2-aza-bicyclo[2.2.1]heptane-2,3-dicarboxylic acid 2-*tert*-butyl ester (167 mg, 0.69 mmol) and DIPEA (0.11 mL, 0.67 mmol) in 2 mL acetonitrile. The mixture was stirred at room temperature for 16 hours, then diluted with ethyl acetate (100 mL). The organic layer was washed with $NaHCO_3$ solution and water, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The obtained residue was purified by flash chromatography to provide the desired product 2-Aza-bicyclo[2.2.1]heptane-2,3-dicarboxylic acid 2-*tert*-butyl ester 3-[2-(7-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-9,10-dihydro-phenanthren-2-yl)-2-oxo-ethyl] ester as a brown oil (130 mg, 47% over two steps). m/z 754.3 $(M+H)^+$.

3-[5-(7-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-9,10-dihydro-phenanthren-2-yl)-1H-imidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester. A mixture of 2-Aza-bicyclo[2.2.1]heptane-2,3-dicarboxylic acid 2-*tert*-butyl ester 3-[2-(7-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-9,10-dihydro-phenanthren-2-yl)-2-oxo-ethyl] ester (130 mg, 0.17 mmol) and ammonium acetate (292 mg, 3.8 mmol) in xylene (10 mL) was heated in a sealed tube at 140°C for 1.5 hours under microwave condition. The volatile component was removed *in vacuo*, and the residue was dissolved in ethyl acetate (100 mL), washed with $NaHCO_3$ solution, water and brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The obtained residue

was purified by flash chromatography to provide the desired product 3-[5-(7-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-9,10-dihydro-phenanthren-2-yl)-1H-imidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester as a white solid (38 mg, 28%). m/z 734.4 $(M+H)^+$.

(1-{2-[5-(7-{2-[2-(2-Methoxycarbonylamino-propionyl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-imidazol-4-yl}-9,10-dihydro-phenanthren-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester. To a solution of 3-[5-(7-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-9,10-dihydro-phenanthren-2-yl)-1H-imidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (38 mg, 0.052 mmol) in dichloromethane (6 mL) was added trifluoroacetic acid (2 mL, excess). The mixture was stirred for 2 hours at ambient temperature and concentated under reduced pressure. The residue was treated with ether to remove excess trifluoroacetic acid. The obtained white solid was dissoved in DMF (5 mL), to the solution was added 2-methoxycarbonylamino-propionic acid (9 mg, 0.06 mmol), HATU (30 mg, 0.08 mmol) and *N,N*-diisopropylethylamine (0.09 mL, 0.53 mmol). The mixture was stirred at ambient for 2 hours, and then the volatile component was removed *in vacuo*. The residue was dissolved in ethyl acetate (100 mL), washed with 1 N NaOH solution, water and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The obtained residue was purified by HPLC to provide the desired product (1-{2-[5-(7-{2-[2-(2-Methoxycarbonylamino-propionyl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-imidazol-4-yl}-9,10-dihydro-phenanthren-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester as a TFA salt (15 mg, 39%). ^{1}H-NMR (300 MHz, CD_3OD) δ 8.10-7.60 (m, 8H), 5.35-5.25 (m, 1H), 4.70-4.45 (m, 3H), 4.30-3.80 (m, 3H), 3.67 (s, 6H), 2.70-1.60 (m, 12H), 1.41 (d, 3H), 1.05-0.80 (m, 6H); m/z 763.3 $(M+H)^+$.

Example EH



2,7-Dibromo-9,10-dihydro-phenanthrene. Bromine (6.13 mL, 119.3 mmol) was added slowly to a solution of 9,10-dihydro-phenanthrene (10 g, 55.5 mmol) in trimethylphosphate (100 mL). The mixture was stirred at room temperature for 18 hours and concentrated *in vacuo*. The residue was recrystallized from chloroform to give product 2,7-Dibromo-9,10-dihydro-phenanthrene as a white crystal (9.45g, 51%).

Pyrrolidine-1,2-dicarboxylic acid 2-[2-(7-bromo-9,10-dihydro-phenanthren-2-yl)-2-oxo-ethyl] ester 1-*tert*-butyl ester. $Pd(Ph_3)_4$ (347 mg, 0.3 mmol) and $PdCl_2(Ph_3)_2$ (210 mg, 0.3 mmol) were added to a mixture 2,7-dibromo-9,10-dihydro-phenanthrene (2.5 g, 7.4 mmol) and tributyl(1-ethoxyvinyl)tin (2.5 mL, 7.4 mL) in 70 mL dioxane. The reaction mixture was flushed with nitrogen, heated at 80°C for 16 hours, then cooled to ambient temperature. Water (20 mL) and NBS (1.39 g, 7.8 mmol) were added and the mixture was stirred at room temperature for 40 minutes, then diluted with ethyl acetate (300 mL). Washed with water and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The obtained residue was

suspended in acetonitrile (70 mL). To it was added a solution of pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester (3.2 g, 14.9 mmol) and DIPEA (2.4 mL, 14.1 mmol) in 20 mL acetonitrile. The mixture was stirred at room temperature for 16 hours, then diluted with ethyl acetate (300 mL). The organic layer was washed with $NaHCO_3$ solution and water, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The obtained residue was purified by flash chromatography to provide the desired product pyrrolidine-1,2-dicarboxylic acid 2-[2-(7-bromo-9,10-dihydro-phenanthren-2-yl)-2-oxo-ethyl] ester 1-*tert*-butyl ester as a white solid (1.76 g, 46% over two steps). m/z 514.2, 516.2 $(M+H)^+$.

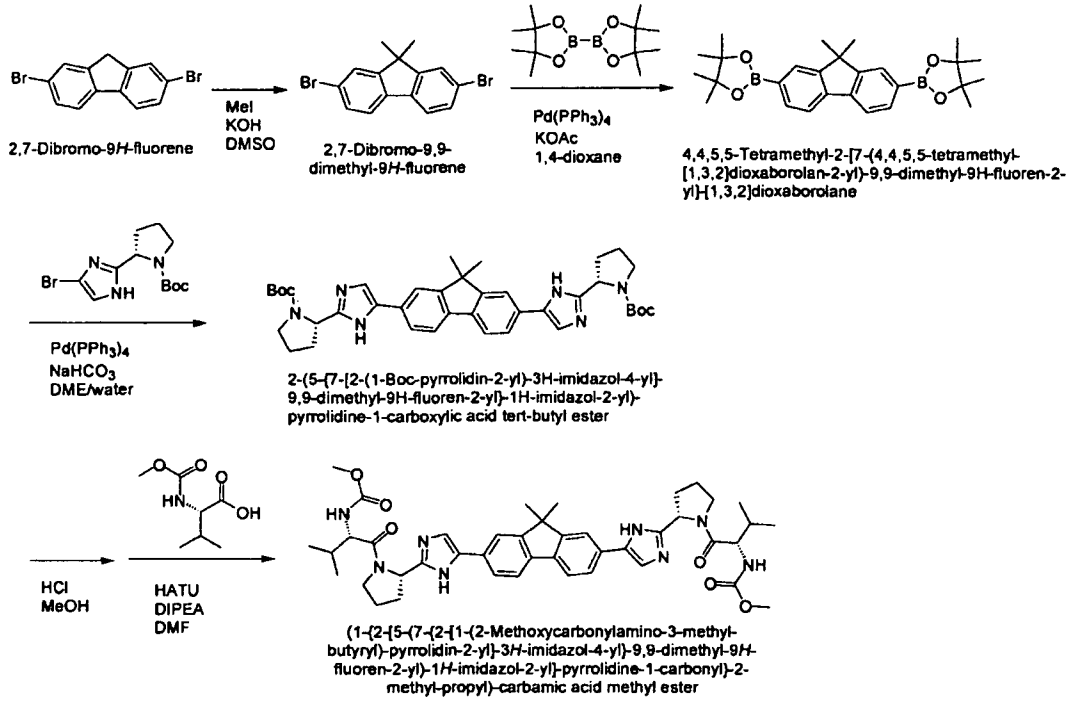
2-Aza-bicyclo[2.2.1]heptane-2,3-dicarboxylic acid 3-(2-{7-[2-(1-*tert*-butoxycarbonyl-pyrrolidine-2-carbonyloxy)-acetyl]-9,10-dihydro-phenanthren-2-yl}-2-oxo-ethyl) ester 2-*tert*-butyl ester. $Pd(Ph_3)_4$ (37 mg, 0.03 mmol) and $PdCl_2(Ph_3)_2$ (22 mg, 0.03 mmol) were added to a mixture of pyrrolidine-1,2-dicarboxylic acid 2-[2-(7-bromo-9,10-dihydro-phenanthren-2-yl)-2-oxo-ethyl] ester 1-*tert*-butyl ester (410 mg, 0.8 mmol) and tributyl(1-ethoxyvinyl)tin (0.32 mL, 0.96 mmol) in 8 mL dioxane. The reaction mixture was flushed with nitrogen, heated at 80°C for 16 hours, then cooled to ambient temperature. Water (2 mL) and NBS (171 mg, 0.96 mmol) were added and the mixture was stirred at room temperature for 40 minutes, then diluted with ethyl acetate (100 mL). Washed with water and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Half of the obtained residue was suspended in acetonitrile (5 mL). To it was added a solution of 2-aza-bicyclo[2.2.1]heptane-2,3-dicarboxylic acid 2-*tert*-butyl ester (100 mg, 0.41 mmol) and DIPEA (0.068 mL, 0.39 mmol) in 2 mL acetonitrile. The mixture was stirred at room temperature for 16 hours, then diluted with ethyl acetate (100 mL). The organic layer was washed with $NaHCO_3$ solution and water, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The obtained residue was purified by flash chromatography to provide the desired product 2-aza-bicyclo[2.2.1]heptane-2,3-dicarboxylic acid 3-(2-{7-[2-(1-*tert*-butoxycarbonyl-pyrrolidine-2-carbonyloxy)-acetyl]-9,10-dihydro-phenanthren-2-yl}-2-oxo-ethyl) ester 2-*tert*-butyl ester as a white solid (171 mg, 60% over two steps). m/z 717.2 $(M+H)^+$.

3-(5-{7-[2-(1-*tert*-Butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-9,10-dihydro-phenanthren-2-yl}-1H-imidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester. A mixture of 2-aza-bicyclo[2.2.1]heptane-2,3-dicarboxylic acid 3-(2-{7-[2-(1-*tert*-butoxycarbonyl-pyrrolidine-2-carbonyloxy)-acetyl]-9,10-dihydro-phenanthren-2-yl}-2-oxo-ethyl) ester 2-*tert*-butyl ester (171 mg, 0.24 mmol) and ammonium acetate (800 mg, 10.2 mmol) in xylene (5 mL) was heated in a sealed tube at 140°C for 1.5 hours under microwave condition. The volatile component was removed *in vacuo*, and the residue was dissolved in ethyl acetate

(100 mL), washed with $NaHCO_3$ solution, water and brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The obtained residue was purified by flash chromatography to provide the desired product of 3-(5-{7-[2-(1-*tert*-butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-9,10-dihydro-phenanthren-2-yl}-1H-imidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester as a white solid (100 mg, 62%). m/z 677.9 $(M+H)^+$.

(1-{3-[5-(7-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-9,10-dihydro-phenanthren-2-yl)-1H-imidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester. To a solution of 3-(5-{7-[2-(1-*tert*-butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-9,10-dihydro-phenanthren-2-yl}-1H-imidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (100 mg, 0.15 mmol) in methanol (5 mL) was added 4.0 M solution of HCl in dioxane (2 mL, excess). The mixture was stirred for 3 hours at 50°C and concentated under reduced pressure. The residue was treated with ether to remove excess HCl. The obtained white solid was dissoved in DMF (5 mL), to the solution was added 2-methoxycarbonylamino-3-methyl-butyric acid (54 mg, 0.31 mmol), HATU (141 mg, 0.37 mmol) and *N,N*-diisopropylethylamine (0.2 mL, 1.2 mmol). The mixture was stirred at ambient for 2 hours, and then the volatile component was removed *in vacuo*. The residue was dissolved in ethyl acetate (100 mL), washed with 1 N NaOH solution, water and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The obtained residue was purified by HPLC to provide the desired product (1-{3-[5-(7-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-9,10-dihydro-phenanthren-2-yl)-1H-imidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester as TFA salt (67 mg, 57%). ^{1}H-NMR (300 MHz, CD_3OD) δ 8.05-7.65 (m, 8H), 5.35-5.20 (m, 1H), 4.40-4.05 (m, 3H), 3.95-3.80 (m, 1H), 3.67 (d, 6H), 3.05-2.80 (m, 5H), 2.70-2.50 (m, 1H), 2.40-1.60 (m, 13H), 1.10-0.85 (m, 12H); m/z 791.3 $(M+H)^+$.

Example EI



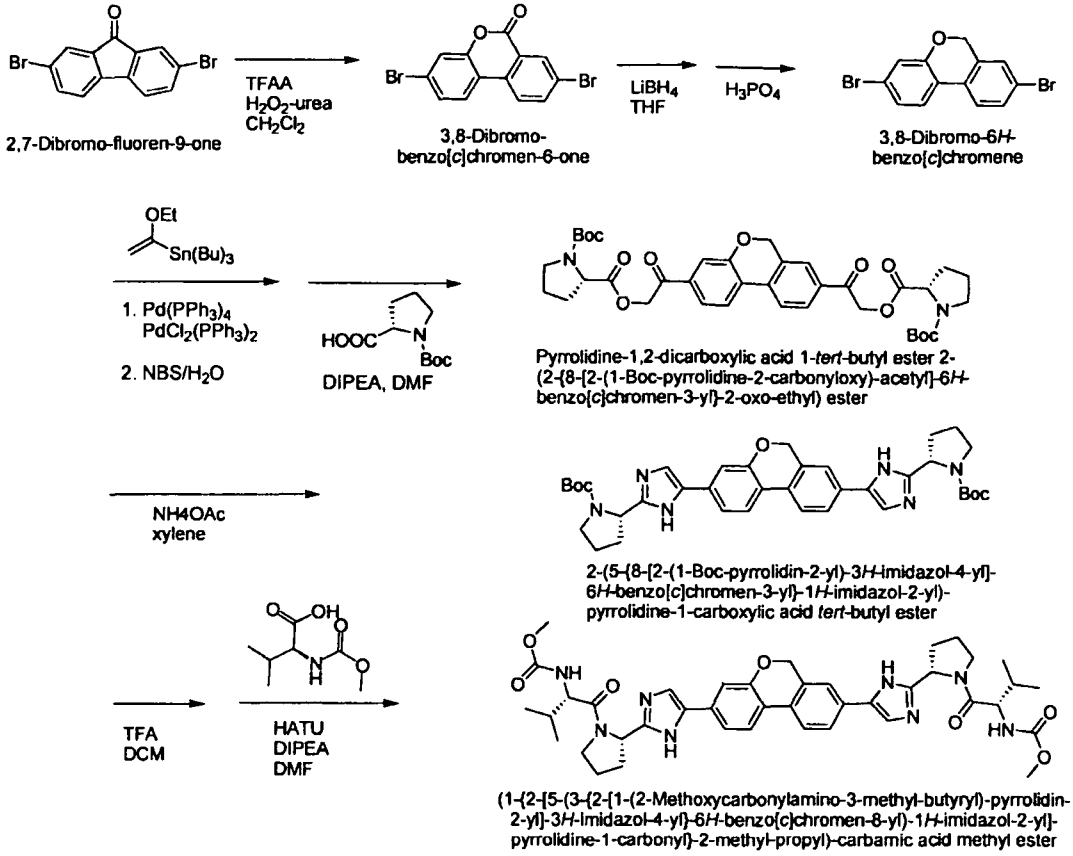
2,7-Dibromo-9,9-dimethyl-9H-fluorene. To a stirred solution of 2,7-dibromo-9H-fluorene (1.0 g, 3.1 mmol), KI (50 mg, 0.3 mmol) and KOH (750 mg, 13.3 mmol) in DMSO was added methyl iodide (0.42 mL, 6.8 mmol). The mixture was stirred at room temperature for 16 hours, then diluted with ethyl acetate (100 mL). The organic layer was washed with water and brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The obtained residue was purified by flash chromatography to provide the desired product 2,7-Dibromo-9,9-dimethyl-9H-fluorene as a white solid (1.1 g, 100%).

4,4,5,5-Tetramethyl-2-[7-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-9,9-dimethyl-9H-fluoren-2-yl]-[1,3,2]dioxaborolane. $Pd(PPh_3)_4$ (347 mg, 0.3 mmol) was added to a flask containing a mixture of 2,7-dibromo-9,9-dimethyl-9H-fluorene (1.0 g, 2.9 mmol), bis(pinacolato)diboron (2.9 g, 11.6 mmol), potassium acetate (1.4 g, 14.5 mmol) and 1,4-dioxane (30 mL). The reaction mixture was flushed with nitrogen, heated at 80°C for 16 hours, then the volatile component was removed *in vacuo*. The residue was dissolved in ethyl acetate (300 mL), washed with water and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The obtained residue was purified by flash chromatography to provide the desired product 4,4,5,5-Tetramethyl-2-[7-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-9,9-dimethyl-9H-fluoren-2-yl]-[1,3,2]dioxaborolane as a white solid (0.8 g, 62%).

2-(5-{7-[2-(1-Boc-pyrrolidin-2-yl)-3H-imidazol-4-yl]-9,9-dimethyl-9H-fluoren-2-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester. $Pd(Ph_3)_4$ (55 mg, 0.05 mmol) was added to a mixture 4,4,5,5-Tetramethyl-2-[7-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-9,9-dimethyl-9H-fluoren-2-yl]-[1,3,2]dioxaborolane (205 mg, 0.48 mmol), 2-(4-bromo-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (309 mg, 0.98 mmol), $NaHCO_3$ (282 mg, 3.4 mmol) in 1,2-dimethoxyethane (8 mL) and water (1 mL). The reaction mixture was flushed with nitrogen, heated at 80°C for 16 hours, and then the volatile component was removed *in vacuo*. The residue was dissolved in ethyl acetate (100 mL), washed with $NaHCO_3$ solution, water and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The obtained residue was purified by HPLC to provide the desired product 2-(5-{7-[2-(1-Boc-pyrrolidin-2-yl)-3H-imidazol-4-yl]-9,9-dimethyl-9H-fluoren-2-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester as a TFA salt (45 mg, 14%). m/z 665.4 $(M+H)^+$.

(1-{2-[5-(7-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-9,9-dimethyl-9H-fluoren-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester. To a solution of 2-(5-{7-[2-(1-Boc-pyrrolidin-2-yl)-3H-imidazol-4-yl]-9,9-dimethyl-9H-fluoren-2-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (45 mg, 0.07 mmol) in methanol (5 mL) was added 4.0 M solution of HCl in dioxane (1 mL, excess). The mixture was stirred for 3 hours at 50°C and concentated under reduced pressure. The residue was treated with ether to remove excess HCl. The obtained white solid was dissoved in DMF (5 mL), to the solution was added 2-methoxycarbonylamino-3-methyl-butyric acid (25 mg, 0.14 mmol), HATU (65 mg, 0.17 mmol) and *N,N*-diisopropylethylamine (0.09 mL, 0.54 mmol). The mixture was stirred at ambient for 2 hours, and then the volatile component was removed *in vacuo*. The residue was dissolved in ethyl acetate (100 mL), washed with 1 N NaOH solution, water and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The obtained residue was purified by HPLC to provide the desired product (1-{2-[5-(7-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-9,9-dimethyl-9H-fluoren-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester as TFA salt (15 mg, 28%). ^{1}H-NMR (300 MHz, CD_3OD) δ 8.05-7.70 (m, 8H), 5.35-5.20 (m, 2H), 4.30-3.80 (m, 6H), 3.67 (s, 6H), 2.65-2.00 (m, 10H), 1.61 (s, 6H), 1.05-0.85 (m, 12H); m/z 779.4 $(M+H)^+$.

Example EJ



3,8-Dibromo-benzo[c]chromen-6-one. A solution of TFAA (2.1 mL, 3.15 mmol) in dichloromethane (5 mL) was added dropwise to a suspension of 2,7-dibromo-fluoren-9-one (3.3 g, 10 mmol) and H_2O_2-urea (1.4 g, 15 mL) in dichloromethane (50 mL). The mixture was stirred at room temperature for 48 hours, a second portion of H_2O_2-urea was added, and stirring was continued at room temperature for a further 72 hours. The mixture was filtered, the organic phase was extracted with water (50 mL), and dried over Na_2SO_4. After removal of solvent, the residue was heated with 2N NaOH at 80°C for 10 minutes, filtered, the cooled filtrate extracted with ether. The aqueous phase was acidified with 2N HCl and extracted with ethyl acetate (200 mL). HCl (2 mL 4M solution) was added to the ethyl acetate and heated for 2 hours. The solvent was removed under vacuum, the residue was recrystallized from ethyl acetate/ethanol to give the final product 3,8-Dibromo-benzo[c]chromen-6-one as a white solid (1.5 g, 40%).

3,8-Dibromo-6H-benzo[c]chromene. To a solution of 3,8-dibromo-benzo[c]chromen-6-one (650 mg, 1.85 mmol) in THF (20 mL) was added 2 M solution of $LiBH_4$ in THF (3.7 mL, 7.4 mmol). The mixture was stirred for 3 hours at room temperature. Quenched slowly with ammonium chloride solution. The mixture was extracted with ethyl acetate, dried over Na_2SO_4,

filtered and concentrated *in vacuo*. The obtained residue was suspended in 85% phosphoric acid (20 mL) and heated at 160°C for 4h. The mixture was extracted with ethyl acetate, washed with water, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The obtained residue was purified by flash chromatography to provide the desired product 3,8-Dibromo-6H-benzo[c]chromene as a white solid (539 mg, 86%).

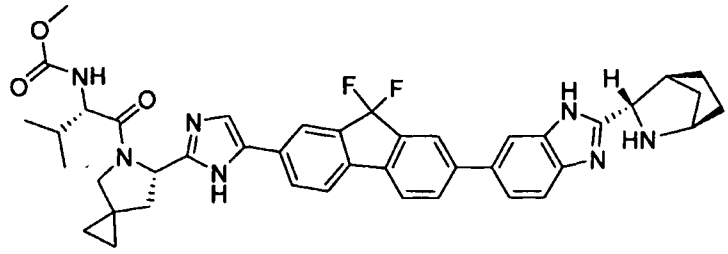
Pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-(2-{8-[2-(1-Boc-pyrrolidine-2-carbonyloxy)-acetyl]-6H-benzo[c]chromen-3-yl}-2-oxo-ethyl) ester. $Pd(PPh_3)_4$ (74 mg, 0.064 mmol) and $PdCl_2(Ph_3)_2$ (45 mg, 0.064 mmol) were added to a mixture 3,8-dibromo-6H-benzo[c]chromene (539 mg, 1.6 mmol) and tributyl(1-ethoxyvinyl)tin (1.2 mL, 3.5 mL) in 20 mL dioxane. The reaction mixture was flushed with nitrogen, heated at 80°C for 16 hours, then cooled to ambient temperature. Water (7 mL) and NBS (623 mg, 3.5 mmol) were added and the mixture was stirred at room temperature for 40 minutes, then diluted with ethyl acetate (300 mL). The solid was filtered and kept separately. The ethyl acetate layer was washed with water and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The obtained residue conbine with the solid collected before was suspended in acetonitrile (20 mL) and DMF (10 mL). To it was added a solution of pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester (1.6 g, 7.4 mmol) and DIPEA (1.2 mL, 7.1 mmol) in 5 mL acetonitrile. The mixture was stirred at room temperature for 16 hours, then diluted with ethyl acetate (300 mL). The organic layer was washed with $NaHCO_3$ solution and water, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The obtained residue was purified by flash chromatography to provide the desired product Pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-(2-{8-[2-(1-Boc-pyrrolidine-2-carbonyloxy)-acetyl]-6H-benzo[c]chromen-3-yl}-2-oxo-ethyl) ester as a white solid (602 mg, 54% over two steps). m/z 715.2 $(M+Na)^+$.

2-(5-{8-[2-(1-Boc-pyrrolidin-2-yl)-3H-imidazol-4-yl]-6H-benzo[c]chromen-3-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester. A mixture of pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-(2-{8-[2-(1-Boc-pyrrolidine-2-carbonyloxy)-acetyl]-6H-benzo[c]chromen-3-yl}-2-oxo-ethyl) ester (168 mg, 0.24 mmol) and ammonium acetate (374 mg, 4.8 mmol) in xylene (10 mL) was heated in a sealed tube at 140°C for 1.5 hours under microwave condition. The volatile component was removed *in vacuo*, and the residue was dissolved in ethyl acetate (100 mL), washed with $NaHCO_3$ solution, water and brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The obtained residue was purified by flash chromatography to provide the desired product 2-(5-{8-[2-(1-Boc-pyrrolidin-2-yl)-3H-imidazol-

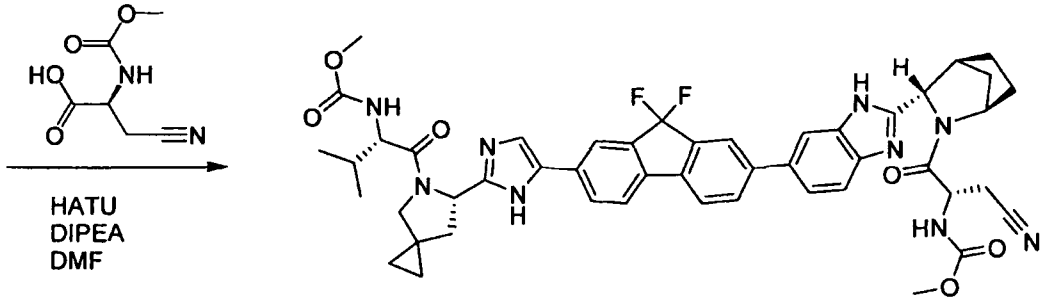
4-yl]-6H-benzo[c]chromen-3-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester as a white solid (100 mg, 64%). m/z 653.4 $(M+H)^+$.

(1-{2-[5-(3-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-6H-benzo[c]chromen-8-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester. To a solution of 2-(5-{8-[2-(1-Boc-pyrrolidin-2-yl)-3H-imidazol-4-yl]-6H-benzo[c]chromen-3-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (300 mg, 0.46 mmol) in dichloromethane (10 mL) was added trifluoroacetic acid (2.5 mL, excess). The mixture was stirred for 2 hours at ambient temperature and concentrated under reduced pressure. The residue was treated with ether to remove excess trifluoroacetic acid. The obtained white solid was dissolved in DMF (10 mL), to the solution was added 2-methoxycarbonylamino-3-methyl-butyric acid (161 mg, 0.92 mmol), HATU (437 mg, 1.2 mmol) and *N,N*-diisopropylethylamine (0.64 mL, 3.7 mmol). The mixture was stirred at ambient for 2 hours, and then the volatile component was removed *in vacuo*. The residue was dissolved in ethyl acetate (100 mL), washed with 1 N NaOH solution, water and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The obtained residue was purified by HPLC to provide the desired product (1-{2-[5-(3-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-6H-benzo[c]chromen-8-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester as a TFA salt (130 mg, 37%). ^{1}H-NMR (300 MHz, CD_3OD) δ 7.80-7.20 (m, 8H), 5.40-5.05 (m, 4H), 4.65-3.80 (m, 6H), 3.75-3.40 (m, 6H), 2.40-1.90 (m, 10H), 1.05-0.80 (m, 12H); m/z 767.3 $(M+H)^+$.

Example EK



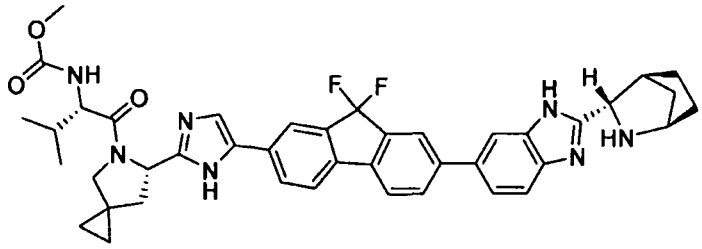
{1-[6-(5-{7-[2-(2-Aza-bicyclo[2.2.1]hept-3-yl)-3*H*-benzoimidazol-5-yl]-9,9-difluoro-9*H*-fluoren-2-yl}-1*H*-imidazol-2-yl)-5-aza-spiro[2.4]heptane-5-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester



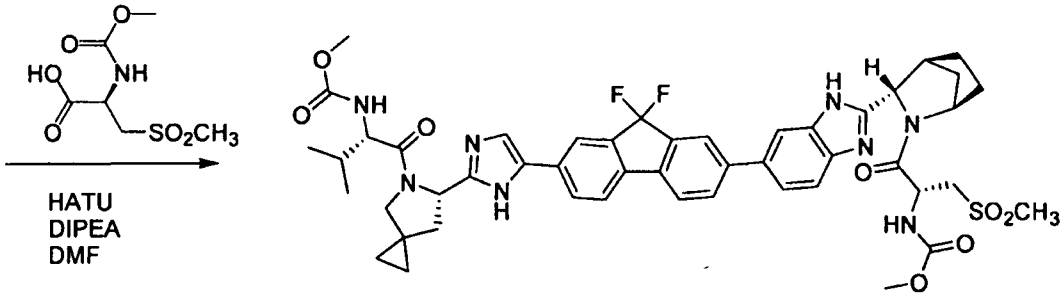
(1-{6-[5-(7-{2-[2-(3-Cyano-2-methoxycarbonylamino-propionyl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3*H*-benzoimidazol-5-yl}-9,9-difluoro-9*H*-fluoren-2-yl)-1*H*-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

(1-{6-[5-(7-{2-[2-(3-Cyano-2-methoxycarbonylamino-propionyl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-benzoimidazol-5-yl}-9,9-difluoro-9H-fluoren-2-yl)-1H-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester. To a solution of {1-[6-(5-{7-[2-(2-aza-bicyclo[2.2.1]hept-3-yl)-3H-benzoimidazol-5-yl]-9,9-difluoro-9H-fluoren-2-yl}-1H-imidazol-2-yl)-5-aza-spiro[2.4]heptane-5-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (30 mg, 0.037 mmol) in DMF (2 mL) was added 3-cyano-2-methoxycarbonylamino-propionic acid (8 mg, 0.045 mmol), HATU (20 mg, 0.052 mmol) and *N,N*-diisopropylethylamine (0.051 mL, 0.3 mmol). The mixture was stirred at ambient for 2 hours, and then the volatile component was removed *in vacuo*. The residue was dissolved in ethyl acetate (50 mL), washed with 1 N NaOH solution, water and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The obtained residue was purified by HPLC to provide the desired product (1-{6-[5-(7-{2-[2-(3-Cyano-2-methoxycarbonylamino-propionyl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-benzoimidazol-5-yl}-9,9-difluoro-9H-fluoren-2-yl)-1H-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester as a TFA salt (18 mg, 54%). ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.30-7.70 (m, 10H), 7.45-7.30 (m, 1H), 5.26 (t, 1H), 5.00-4.80 (m, 2H), 4.60-4.45 (m, 1H), 4.10-3.70 (m, 4H), 3.63 (s, 3H), 3.54 (s, 3H), 3.00-2.65 (m, 4H), 2.30-1.10 (m, 12H), 1.00-0.60 (m, 8H); m/z 886.4 $(M+H)^+$.

Example EL



{1-[6-(5-{7-[2-(2-Aza-bicyclo[2.2.1]hept-3-yl)-3*H*-benzoimidazol-5-yl]-9,9-difluoro-9*H*-fluoren-2-yl}-1*H*-imidazol-2-yl)-5-aza-spiro[2.4]heptane-5-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester

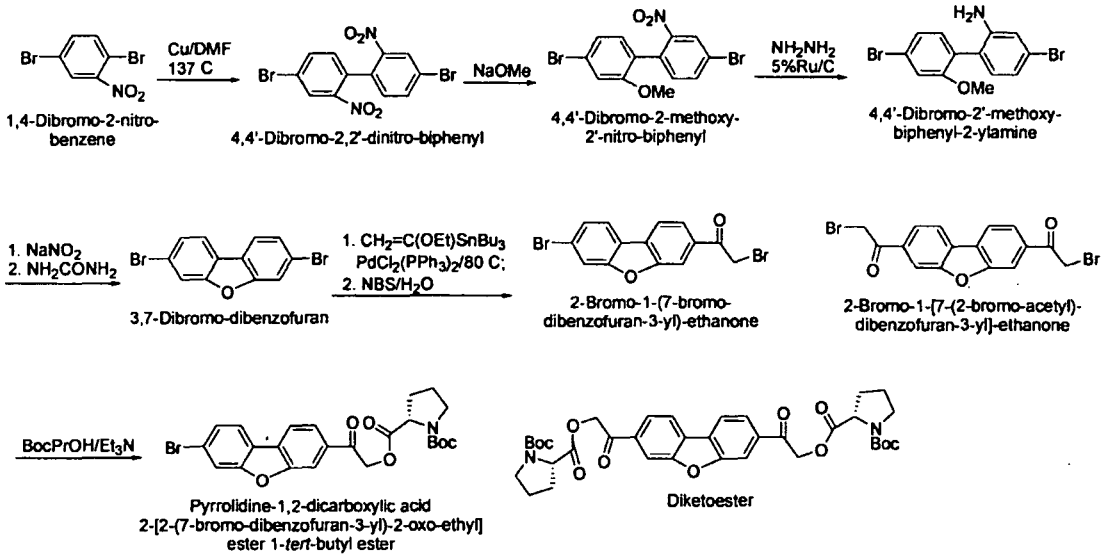


(1-{6-[5-(7-{2-[2-(3-Methanesulfonyl-2-methoxycarbonylamino-propionyl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3*H*-benzoimidazol-5-yl}-9,9-difluoro-9*H*-fluoren-2-yl)-1*H*-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

(1-{6-[5-(7-{2-[2-(3-Methanesulfonyl-2-methoxycarbonylamino-propionyl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-benzoimidazol-5-yl}-9,9-difluoro-9H-fluoren-2-yl)-1H-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester. To a solution of {1-[6-(5-{7-[2-(2-aza-bicyclo[2.2.1]hept-3-yl)-3H-benzoimidazol-5-yl]-9,9-difluoro-9H-fluoren-2-yl}-1H-imidazol-2-yl)-5-aza-spiro[2.4]heptane-5-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (30 mg, 0.037 mmol) in DMF (2 mL) was added 3-methanesulfonyl-2-methoxycarbonylamino-propionic acid (8 mg, 0.045 mmol), HATU (20 mg, 0.052 mmol) and *N,N*-diisopropylethylamine (0.051 mL, 0.3 mmol). The mixture was stirred at ambient for 2 hours, and then the volatile component was removed *in vacuo*. The residue was dissolved in ethyl acetate (50 mL), washed with 1 N NaOH solution, water and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The obtained residue was purified by HPLC to provide the desired product (1-{6-[5-(7-{2-[2-(3-Methanesulfonyl-2-methoxycarbonylamino-propionyl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-benzoimidazol-5-yl}-9,9-difluoro-9H-fluoren-2-yl)-1H-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester as a TFA salt (18 mg, 54%). ^{1}H-NMR (300 MHz, DMSO-

d_6) δ 8.30-7.70 (m, 10H), 7.40-7.30 (m, 1H), 5.26 (t, 1H), 5.00-4.80 (m, 2H), 4.60-4.45 (m, 1H), 4.10-3.70 (m, 5H), 3.63 (s, 3H), 3.54 (s, 3H), 3.00-2.65 (m, 4H), 2.30-1.10 (m, 12H), 1.00-0.60 (m, 10H); m/z 939.4 $(M+H)^+$.

A. Example EM



1,4-Dibromo-2-nitro-benzene: The compound was bought from Sigma-Aldrich Co.

4,4'-Dibromo-2,2'-dinitro-biphenyl: The mixture of 1,4-dibromo-2-nitro-benzene (25 g, 89 mmol) and copper powder (12.5 g, 197 mmol) in DMF (150 ml) was heated at 137 C for 2 hours. The mixture was cooled to 25°C and was quenched with water. The mixture was extracted with EtOAc (2x). The combined organic solution was washed with water and brine and was dried with Na_2SO_4. Concentration and purification by flash column chromatography (hexanes/EtOAc) gave 4,4'-dibromo-2,2'-dinitro-biphenyl (13.6 g).

4,4'-Dibromo-2-methoxy-2'-nitro-biphenyl: To the solution of 4,4'-dibromo-2,2'-dinitro-biphenyl (6.58 g, 16.5 mmol) in DMF (50 ml) at 0°C was added a solution of sodium methoxide in Methanol (4.4 M, 4.5 ml, 19.8 mmol). The mixture was stirred at 25°C for 12 hours and was poured into ice-water (140 ml). The mixture was extracted with EtOAc (2x). The combined organic phase was washed with water and brine and dried with Na2SO4. Concentration under

reduced pressure gave pale solid. The re-crystallization from CH3CN/MeOH gave 4,4'-dibromo-2-methoxy-2'-nitro-biphenyl as a white solid (3.76 g).

4,4'-Dibromo-2'-methoxy-biphenyl-2-ylamine: To a suspension of 4,4'-dibromo-2-methoxy-2'-nitro-biphenyl (3.76 g, 9.8 mmol) and 5%Ru/C (400 mg) in ethanol (37 ml) at 65-70°C was added dropwise a solution of hydrazine (4.6 ml, 59 mmol) in ethanol (5 ml). The mixture was refluxed for 7 hours and filtered through a pad of CELITE. The CELITE pad was washed with ethanol. The combined solution was concentrated under reduced pressure. Coevaporation with ethanol, EtOAc and DCM gave 4,4'-dibromo-2'-methoxy-biphenyl-2-ylamine as yellow solid (3.5 g).

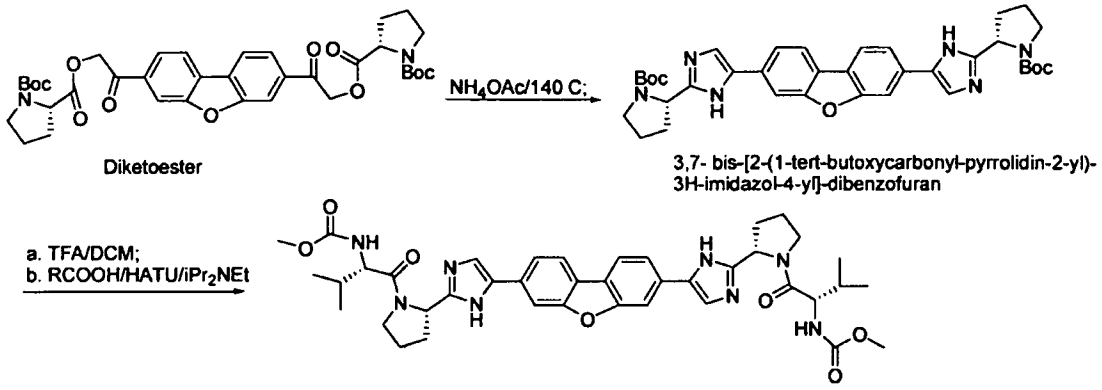
3,7-Dibromo-dibenzofuran: To a suspension of 4,4'-Dibromo-2'-methoxy-biphenyl-2-ylamine (3.5 g, 9.8 mmol) in H2SO4 (2.4 g) and water (8.5 ml) at 0°C was added slowly a solution of NaNO2 (682 mg, 9.8 mmol) in water (9 ml). The mixture was stirred at 0°C for 2 hours. Urea (1.2 g, 20 mmol) was added and the mixture was stirred for 12 hours. The mixture was diluted with water and was heated at 70°C for 24 hours. The mixture was cooled to 25°C and was filtered. The collected solid was re-crystallized from benzene/methanol to give 3,7-dibromo-dibenzofuran (2.27 g).

2-Bromo-1-(7-bromo-dibenzofuran-3-yl)-ethanone and **2-Bromo-1-[7-(2-bromo-acetyl)-dibenzofuran-3-yl]-ethanone**: To the solution of 3,7-dibromo-dibenzofuran (972 mg, 3 mmol) and tributyl(ethoxyvinyl)stannane (1.22 ml, 3.6 mmol) in dioxane (20 ml) was added $PdCl_2(PPh_3)_2$ (90 mg) and Pd(PPh3)4 (90 mg). The mixture was heated at 80°C for 16 hours and was cooled to 0°C. Water (7 ml) was added, followed by slow addition of NBS (641 mg, 3.6 mmol) over 5 minutes period. The mixture was stirred at 0°C for additional 40 minutes, and the solvent was removed under reduced pressure. The mixture was diluted with EtOAc, and was washed with water and brine and dried with sodium sulfate. Concentration under reduced pressure gave a mixture of 2-bromo-1-(7-bromo-dibenzofuran-3-yl)-ethanone and 2-Bromo-1-[7-(2-bromo-acetyl)-dibenzofuran-3-yl]-ethanone, which was used directly for the next step.

Pyrrolidine-1,2-dicarboxylic acid 2-[2-(7-bromo-dibenzofuran-3-yl)-2-oxo-ethyl]ester 1-*tert*-butyl ester and **Diketoester**: To the solution of (s)Boc-PrOH (2.58 g, 12 mmol) and triethylamine (1.46 ml, 10.5 mmol) in acetonitrile (20 ml)/DMF (15 ml) was added a solution of 2-bromo-1-(7-bromo-dibenzofuran-3-yl)-ethanone and 2-bromo-1-[7-(2-bromo-acetyl)-dibenzofuran-3-yl]-ethanone in DMF (20 ml). The mixture was stirred for 10 hours, and the

solvent was evaporated. The mixture was diluted with EtOAc, and washed with 0.5 N NaOH solution, water and brine, and was dried with sodium sulfate. Concentration and purification by flash column chromatography (hexanes/EtOAc) gave Pyrrolidine-1,2-dicarboxylic acid 2-[2-(7-bromo-dibenzofuran-3-yl)-2-oxo-ethyl] ester 1-*tert*-butyl ester (630 mg) and Diketoester (620 mg).

Example EN



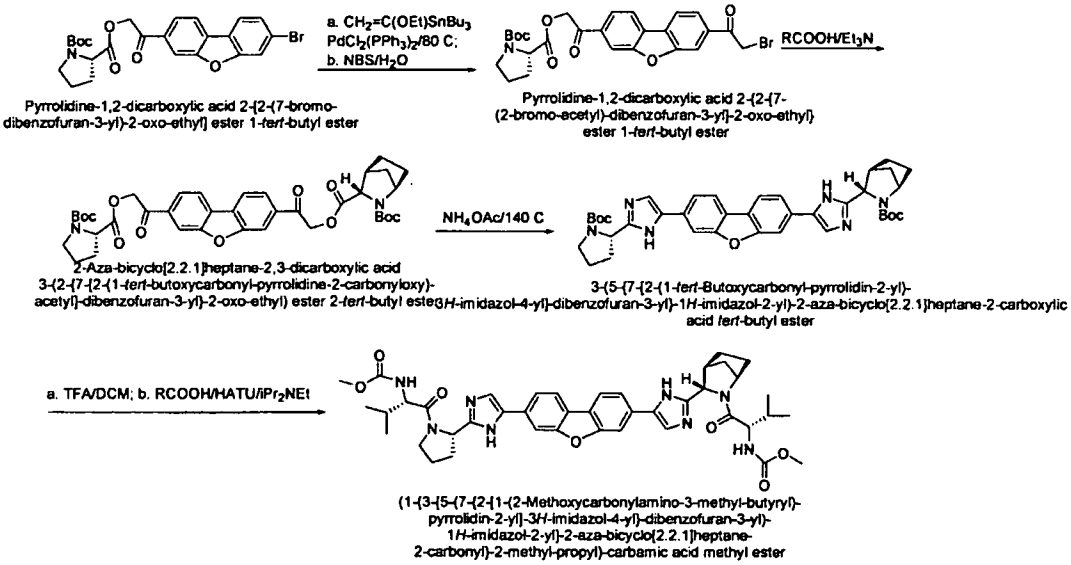
(1-{2-[5-(7-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-dibenzofuran-3-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

3,7- bis-[2-(1-*tert*-butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-dibenzofuran: The mixture of diketoester (600 mg, 0.89 mmol) and ammonium acetate (1.72g) in xylene (10 ml) was heated at 140°C for 80 minutes under microwave. The mixture was quenched with water, and extracted with EtOAc. The organic phase was washed with water and brine, and was dried with sodium sulfate. Concentration and purification by flash column chromatography (DCM/EtOAc) gave 3,7- bis-[2-(1-*tert*-butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-dibenzofuran (330 mg). m/z: 639.1 (M+1), 637.3 (M-1), 320.0 (M+2)/2.

(1-{2-[5-(7-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-dibenzofuran-3-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: To the solution of 3,7- bis-[2-(1-*tert*-butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-dibenzofuran (330 mg, 0.51 mmol) in DCM (4 ml) was added TFA (2 ml). The mixture was stirred for 60 minutes, and the solvent and reagent were removed under reduced pressure. The mixture was diluted with acetonitrile and water, and was freezer-dried to give brown powder. To the solution of above powder (0.51 mmol) and MeOCO-Val-OH (179 mg, 1.02 mmol) in DMF (15 ml) was added HATU (407 mg, 1.07 mmol), followed by diisopropylethylamine (0.9 ml, 5.1 mmol). The mixture was stirred for 60 minutes and was evaporated and then diluted with EtOAc. The organic phase was washed with 1 N NaOH solution, water, and brine, and was

dried with sodium sulfate. Concentration and purification by HPLC (0.1%TFA/CH_3CN/0.1%TFA/H_2O) gave (1-{2-[5-(7-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-dibenzofuran-3-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (130 mg). m/z: 753.4 (M+1), 751.3 (M-1), 377.3 (M+2)/2. ^1H NMR (CD_3OD, 300 MHz) δ 8.23 (2 H, d, J = 7.9 Hz), 8.0 (2 H, s), 7.98 (2 H, s), 7.78 (2 H, d, J = 7.9 Hz), 5.27 (2 H, m), 4.24 (2 H, d, J = 7.0 Hz), 4.15 (2 H, m), 3.90 (2 H, m), 3.67 (6 H, s), 2.60 (2 H, m), 2.35-2.0 (8 H, m), 1.0-0.8 (12 H, m).

B. Example EO



Pyrrolidine-1,2-dicarboxylic acid 2-{2-[7-(2-bromo-acetyl)-dibenzofuran-3-yl]-2-oxo-ethyl}ester 1-*tert*-butyl ester: To the solution of Pyrrolidine-1,2-dicarboxylic acid 2-[2-(7-bromo-dibenzofuran-3-yl)-2-oxo-ethyl] ester 1-*tert*-butyl ester (250 mg, 0.5 mmol) and tributyl(ethoxyvinyl)stannane (188 µl, 0.55 mmol) in dioxane (3.3 ml) was added $PdCl_2(PPh_3)_2$ (15 mg). The mixture was heated at 80°C for 16 hours and was cooled to 0°C. Water (1.1 ml) was added, followed by slow addition of NBS (98 mg, 0.55 mmol) over 5 minutes period. The mixture was stirred at 0°C for additional 40 minutes, and the solvent was removed under reduced pressure. The mixture was diluted with EtOAc, and was washed with water and brine and dried with sodium sulfate. Concentration and purification by flash column chromatography (hexane/EtOAc) gave Pyrrolidine-1,2-dicarboxylic acid 2-{2-[7-(2-bromo-acetyl)-dibenzofuran-3-yl]-2-oxo-ethyl}ester 1-*tert*-butyl ester (205 mg).

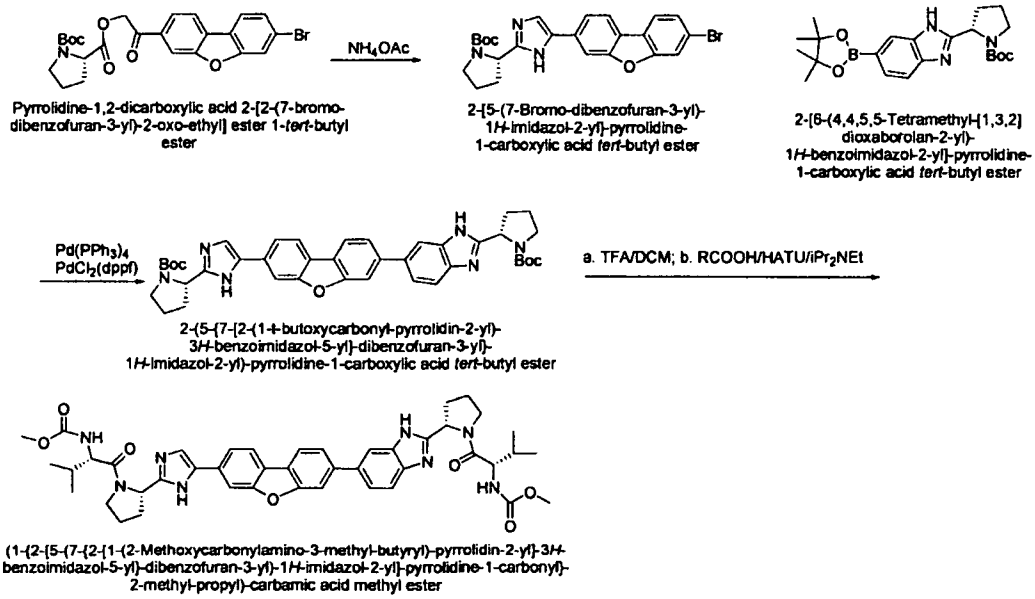
2-Aza-bicyclo[2.2.1]heptane-2,3-dicarboxylic acid 3-(2-{7-[2-(1-*tert*-butoxycarbonyl-pyrrolidine-2-carbonyloxy)-acetyl]-dibenzofuran-3-yl}-2-oxo-ethyl) ester 2-*tert*-butyl ester: To the solution of 2-Aza-bicyclo[2.2.1]heptane-2,3-dicarboxylic acid 2-*tert*-butyl ester (155 mg, 0.64 mmol) and triethylamine (77 μl, 0.55 mmol) in acetonitrile (3 ml) was added a solution of Pyrrolidine-1,2-dicarboxylic acid 2-{2-[7-(2-bromo-acetyl)-dibenzofuran-3-yl]-2-oxo-ethyl}ester 1-*tert*-butyl ester (200 mg, 0.37 mmol) in DMF (6 ml). The mixture was stirred for 10 hours, and the solvent was evaporated. The mixture was diluted with EtOAc, and washed with water and brine, and was dried with sodium sulfate. Concentration gave 2-Aza-bicyclo[2.2.1]heptane-2,3-dicarboxylic acid 3-(2-{7-[2-(1-*tert*-butoxycarbonyl-pyrrolidine-2-carbonyloxy)-acetyl]-dibenzofuran-3-yl}-2-oxo-ethyl) ester 2-*tert*-butyl ester (243 mg). m/z: 703.3 (M-1), 727.2 (M+Na)

3-(5-{7-[2-(1-*tert*-Butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]dibenzofuran-3-yl}-1H-imidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester: The mixture of 2-Aza-bicyclo[2.2.1]heptane-2,3-dicarboxylic acid 3-(2-{7-[2-(1-*tert*-butoxycarbonyl-pyrrolidine-2-carbonyloxy)-acetyl]-dibenzofuran-3-yl}-2-oxo-ethyl) ester 2-*tert*-butyl ester (243 mg) and ammonium acetate (860 mg, 11 mmol) in xylene (5 ml) was heated at 140°C for 80 minutes under microwave. The mixture was quenched with water, and extracted with EtOAc. The organic phase was washed with water and brine, and was dried with sodium sulfate. Concentration and purification by flash column chromatography (DCM/EtOAc) gave 3-(5-{7-[2-(1-*tert*-Butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]dibenzofuran-3-yl}-1H-imidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (170 mg). m/z: 665.0 (M+1), 663.4 (M-1), 333.0 (M+2)/2.

(1-{3-[5-(7-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-dibenzofuran-3-yl)-1H-imidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: To the solution of 3-(5-{7-[2-(1-*tert*-Butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]dibenzofuran-3-yl}-1H-imidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (170 mg) in DCM (6 ml) was added TFA (3 ml). The mixture was stirred for 60 minutes, and the solvent and reagent were removed under reduced pressure. The mixture was diluted with acetonitrile and water, and was freezer-dried to give brown powder. To the solution of above powder (0.256 mmol) and MeOCO-Val-OH (90 mg, 0.51 mmol) in DMF (7.5 ml) was added HATU (204 mg, 0.54 mmol), followed by diisopropylethylamine (0.45 ml, 2.56 mmol). The mixture was stirred for 90 minutes and was diluted with EtOAc. The organic phase was washed with 1 N NaOH solution,

water, and brine, and was dried with sodium sulfate. Concentration and purification by HPLC (0.1%TFA/CH_3CN/0.1%TFA/H_2O) gave (1-{3-[5-(7-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-dibenzofuran-3-yl)-1H-imidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (127 mg). m/z: 779.3 (M+1), 777.3 (M-1), 390.2 (M+2)/2. ^1H NMR (CD_3OD, 300 MHz) δ 8.23 (2 H, d, J = 8.2 Hz), 8.03 (2 H, s), 7.98 (2 H, m), 7.88 (2 H, d, J = 8.2 Hz), 5.25 (1 H, m), 4.85 (1 H, m), 4.33 (1 H, d, J = 6.1 Hz), 4.24 (1 H, d, J = 7.0 Hz), 4.15 (1 H, m), 3.88 (1 H, m), 3.69 (3 H, s), 3.67 (3 H, s), 3.45 (1 H, m), 2.89 (1 H, m), 2.60 (1 H, m), 2.35-1.6 (11 H, m), 1.05-0.8 (12 H, m).

C. Example EP

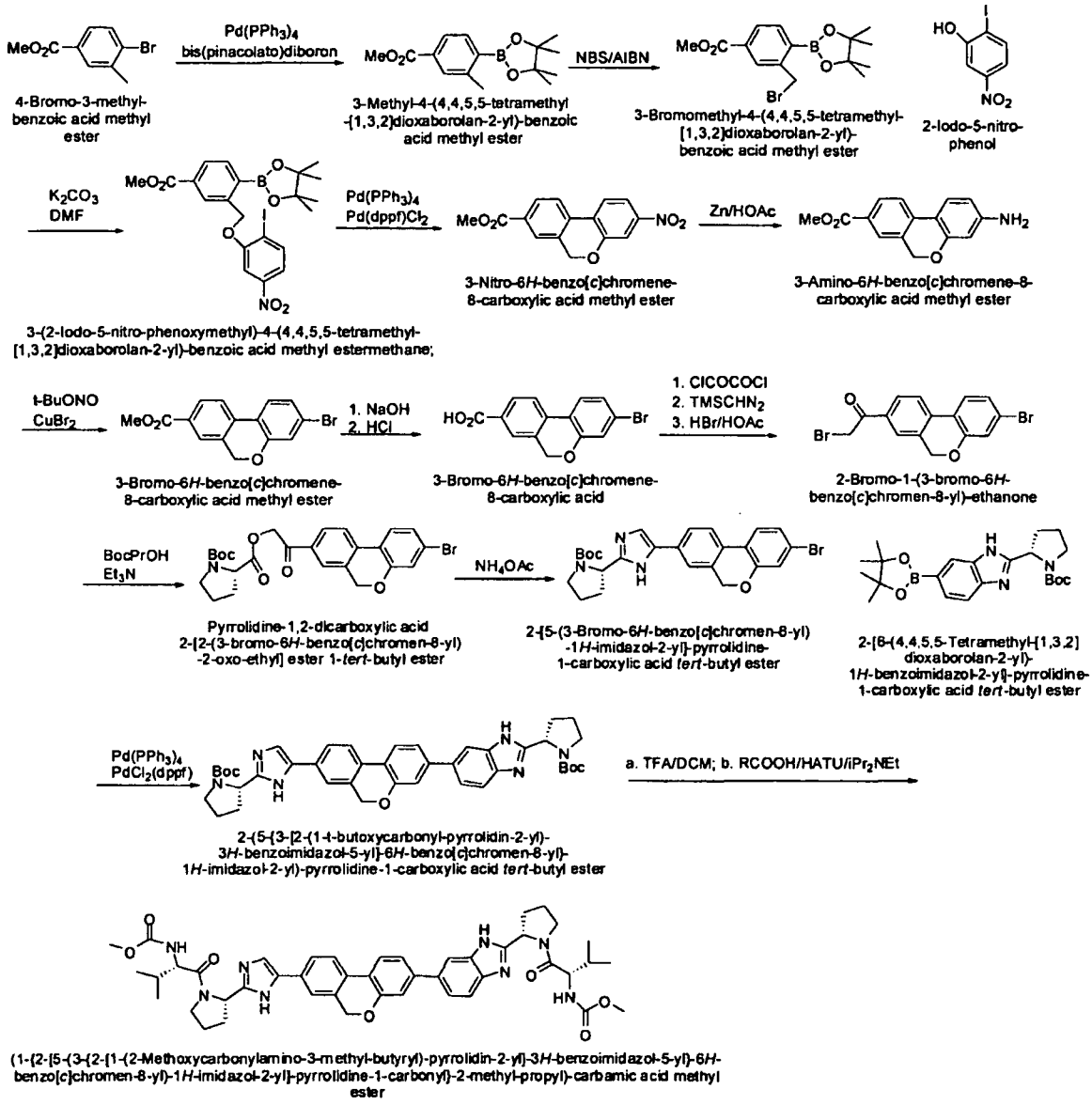


2-[5-(7-Bromo-dibenzofuran-3-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester: The mixture of Pyrrolidine-1,2-dicarboxylic acid 2-[2-(7-bromo-dibenzofuran-3-yl)-2-oxo-ethyl] ester 1-*tert*-butyl ester (200 mg) and ammonium acetate (860 mg, 11 mmol) in xylene (5 ml) was heated at 140°C for 80 minutes under microwave. The mixture was quenched with water, and extracted with EtOAc. The organic phase was washed with water and brine, and was dried with sodium sulfate. Concentration and purification by flash column chromatography (DCM/EtOAc) gave 2-[5-(7-Bromo-dibenzofuran-3-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (124 mg). m/z: 481.9 (M+1), 480.2 (M-1).

2-(5-{7-[2-(1-t-butoxycarbonyl-pyrrolidin-2-yl)-3H-benzoimidazol-5-yl]-dibenzofuran-3-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester: To the solution of 2-[5-(7-Bromo-dibenzofuran-3-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (124 mg, 0.26 mmol) and 2-[6-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-benzoimidazol-2-yl]-pyrrolidine-
1-carboxylic acid *tert*-butyl ester (107 mg, 0.26 mmol) in DME (2.25 ml) and water (0.75 ml) was added potassium carbonate (72 mg, 0.52 mmol), followed by $Pd(PPh_3)_4$ (15 mg) and $PdCl_2(dppf)CH_2Cl_2$ (15 mg). The mixture was heated at 90°C for 6 hours. The mixture was diluted with EtOAc, and was washed with water and brine, and was dried with sodium sulfate. Concentration and purification by flash column chromatography (EtOAc) gave 2-(5-{7-[2-(1-t-butoxycarbonyl-pyrrolidin-2-yl)-3H-benzoimidazol-5-yl]-dibenzofuran-3-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (83 mg). m/z: 689.1 (M+1), 687.3 (M-1), 345.0 (M+2)/2.

(1-{2-[5-(7-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-benzoimidazol-5-yl}-dibenzofuran-3-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: To the solution of 2-(5-{7-[2-(1-t-butoxycarbonyl-pyrrolidin-2-yl)-3H-benzoimidazol-5-yl]-dibenzofuran-3-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (82 mg, 0.12) in DCM (4 ml) was added TFA (2 ml). The mixture was stirred for 60 minutes, and the solvent and reagent were removed under reduced pressure. The mixture was diluted with acetonitrile and water, and was freezer-dried to give brown powder. To the solution of above powder (0.12 mmol) and MeOCO-Val-OH (42 mg, 0.24 mmol) in DMF (3.5 ml) was added HATU (95 mg, 0.25 mmol), followed by diisopropylethylamine (0.21 ml, 1.2 mmol). The mixture was stirred for 90 minutes and was diluted with EtOAc. The organic phase was washed with 1 N NaOH solution, water, and brine, and was dried with sodium sulfate. Concentration and purification by HPLC ($0.1\%TFA/CH_3CN/0.1\%TFA/H_2O$) gave (1-{2-[5-(7-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-benzoimidazol-5-yl}-dibenzofuran-3-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (79 mg). m/z: 803.4 (M+1), 801.1 (M-1), 402.2 (M+2)/2. ^1H NMR (CD_3OD, 300 MHz) δ 8.25 (2 H, m), 8.1-7.9 (5 H, m), 7.9-7.75 (3 H, m), 5.4-5.2 (2 H, m), 4.25 (2 H, m), 4.2-3.8 (4 H, m), 3.67 (6 H, s), 2.60 (2 H, m), 2.4-2.0 (8 H, m), 1.05 -0.8 (12 H, m).

D. Example EQ



4-Bromo-3-methyl-benzoic acid methyl ester: The chemical was bought from Sigma-Aldrich Co.

3-Methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzoic acid methyl ester: To the solution of 4-Bromo-3-methyl-benzoic acid methyl ester (4.56 g, 20 mmol) and bis(pinacolato)diboron (10.2 g, 40 mmol) in 1,4-dioxane (160 ml) was added potassium acetate (5.0 g, 51 mmol), followed by $Pd(PPh_3)_4$ (924 mg). The mixture was heated at 80°C for 16 hours. The mixture was diluted with EtOAc, and was washed with water and brine, and was dried with sodium sulfate. Concentration and purification by flash column chromatography

(hexanes/EtOAc) gave 3-Methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzoic acid methyl ester (4.8 g).

3-Bromomethyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzoic acid methyl ester: The solution of 3-Methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzoic acid methyl ester (3.71 g, 13.4 mmol), NBS (2.39 g, 13.4 mmol), and AIBN (235 mg) in CCl_4 (20 ml) was heated at 80°C for 14 hours. The mixture was cooled to 25°C, and was filtered and washed with CCl_4. The solution was concentrated under reduced pressure, and was diluted with EtOAc. The solution was washed with water and brine and was dried with Na2SO4. Concentration gave 3-Bromomethyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzoic acid methyl ester (4.9 g).

3-(2-Iodo-5-nitro-phenoxymethyl)-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzoic acid methyl estermethane: The mixture of 3-Bromomethyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzoic acid methyl ester (3.63 g, 10.3 mmol), 2-Iodo-5-nitro-phenol (2.72 g, 10.3 mmol), and potassium carbonate (2.26 g, 16.4 mmol) in DMF (21 ml) was heated at 75°C for 3 hours. The mixture was cooled to 25°C, and DMF was removed under reduced pressure. The mixture was diluted with EtOAc, and was acidified with 0.5 N HCl until pH=4. More water (total volume of water 100 ml) was added and the mixture was stirred for 5 minutes. The mixture was filtered and washed with water. The solid was collected and dried under reduced pressure. 3-(2-Iodo-5-nitro-phenoxymethyl)-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzoic acid methyl estermethane was obtained as solid (1.8 g).

3-Nitro-6H-benzo[c]chromene-8-carboxylic acid methyl ester: To the solution of 3-(2-Iodo-5-nitro-phenoxymethyl)-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzoic acid methyl estermethane (2.7 g, 5 mmol) in 1,2-dimethoxyether (75 ml) and water (25 ml) was added sodium bicarbonate (1.26 g, 15 mmol), followed by $Pd(PPh_3)_4$ (250 mg) and $Pd(dppf)Cl_2$ (250 mg). The mixture was heated at 80°C for 16 hours. The mixture was diluted with EtOAc, and was washed with water and brine, and was dried with sodium sulfate. Concentration and purification by flash column chromatography (DCM/hexanes) gave 3-Nitro-6H-benzo[c]chromene-8-carboxylic acid methyl ester (690 mg).

3-Amino-6H-benzo[c]chromene-8-carboxylic acid methyl ester: To the solution of 3-Nitro-6H-benzo[c]chromene-8-carboxylic acid methyl ester (690 mg) in THF/DMF (5 ml/5 ml) was added acetic acid (10 ml), followed by slow addition of Zinc (800 mg). The mixture was stirred

for 12 hours and solvents were removed under reduced pressure. The mixture was diluted with EtOAc, and 0.2 N sodium hydroxide solution was added until pH=10. The organic layer was separated and was washed with water and brine and dried with Na2SO4. Concentration and purification by flash column chromatography (DCM/EtOAc) gave 3-Amino-6H-benzo[c]chromene-8-carboxylic acid methyl ester (300 mg).

3-Bromo-6H-benzo[c]chromene-8-carboxylic acid methyl ester: To a solution of copper (II) bromide (315 mg, 1.42 mmol) and t-butyl nitrite (233 µl, 1.77 mmol) in CH_3CN (4 ml) at 65°C was added dropwise a suspension of 3-Amino-6H-benzo[c]chromene-8-carboxylic acid methyl ester (300 mg, 1.18 mmol) in CH_3CN (5 ml). The mixture was heated at 65°C for 3 hours. Concentration and purification by flash column chromatography (DCM/EtOAc) gave 3-Bromo-6H-benzo[c]chromene-8-carboxylic acid methyl ester (160 mg).

3-Bromo-6H-benzo[c]chromene-8-carboxylic acid: The solution of 3-Bromo-6H-benzo[c]chromene-8-carboxylic acid methyl ester (160 mg, 0.5 mmol) and sodium hydroxide (1.0 N, 1 ml, 1 mmol) in THF/MeOH (2 ml/2 ml) was heated at 50°C for 3 hours. The mixture was cooled to 25°C and was acidified with 2 N HCl (0.6 ml). The solvents were removed under reduced pressure. The mixture was diluted with acetonitrile and water, and was freezer-dried to give 3-Bromo-6H-benzo[c]chromene-8-carboxylic acid as brown powder.

2-Bromo-1-(3-bromo-6H-benzo[c]chromen-8-yl)-ethanone: To 3-Bromo-6H-benzo[c]chromene-8-carboxylic acid (0.5 mmol) was added a solution of oxalyl chloride in DCM (2.0 N, 5 ml, 10 mmol). The mixture was heated at 45°C for 2 hours and cooled to 25°C. Excess reagents and solvent were removed under reduced pressure and co-evaporated with toluene. To the solution of above residue in DCM (5 ml) at 0°C trimethylsilyldiazomethane (2.0 N, 0.75 ml, 1.5 mmol) was added dropwise. The mixture was stirred at 25°C for 12 hours and was concentrated. The residue was dissolved in EtOAc and was cooled to 0°C. To above solution HBr/HOAc (0.28 ml, 1.5 mmol) was added dropwise. The mixture was stirred at 25°C for 1 hour. Solid sodium bicarbonate was added and the mixture was stirred for 30 minutes. The mixture was diluted with EtOAc, and was washed with water and brine and was dried with Na_2SO_4. Concentration gave 2-Bromo-1-(3-bromo-6H-benzo[c]chromen-8-yl)-ethanone, which was used for next step without purification.

Pyrrolidine-1,2-dicarboxylic acid 2-[2-(3-bromo-6H-benzo[c]chromen-8-yl) -2-oxo-ethyl] ester 1-*tert*-butyl ester: To the solution of (s)Boc-PrOH (1.07 g, 5 mmol) and triethylamine

(0.63 ml, 4.5 mmol) in acetonitrile (20 ml) was added a solution of 2-Bromo-1-(3-bromo-6H-benzo[c]chromen-8-yl)-ethanone (0.5 mmol) in DMF (10 ml). The mixture was stirred for 10 hours, and the solvent was evaporated. The mixture was diluted with EtOAc, and washed with 0.5 N NaOH solution, water and brine, and was dried with sodium sulfate. Concentration gave Pyrrolidine-1,2-dicarboxylic acid 2-[2-(3-bromo-6H-benzo[c]chromen-8-yl)-2-oxo-ethyl] ester 1-*tert*-butyl ester, which was used for the next step without further purification.

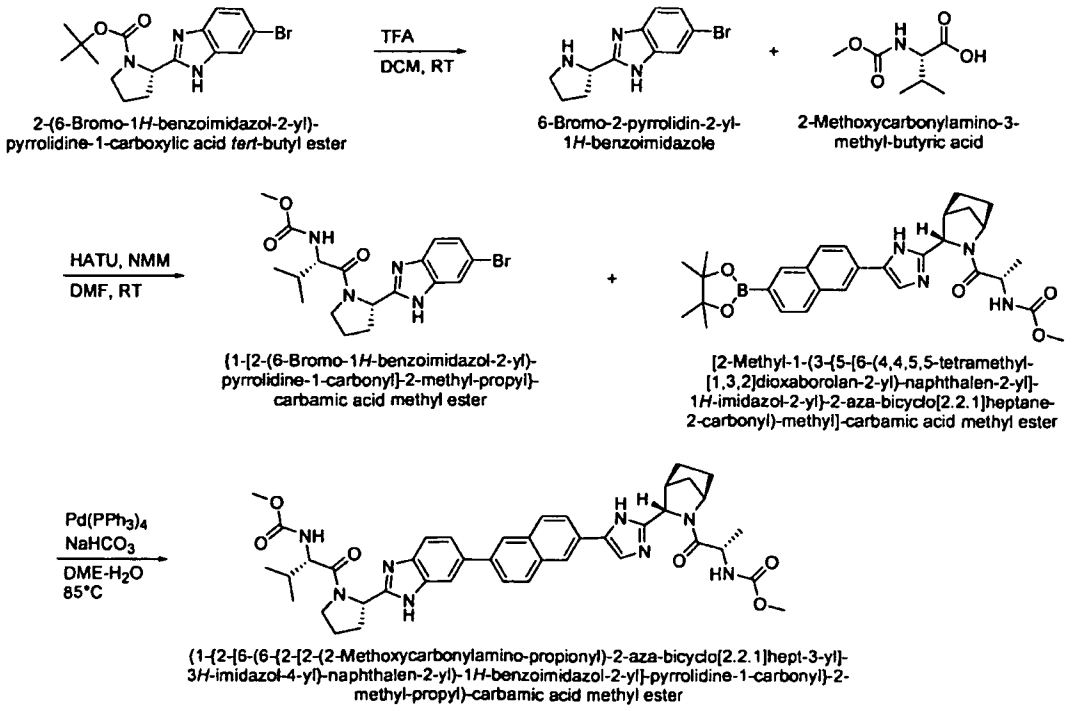
2-[5-(3-Bromo-6H-benzo[c]chromen-8-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester: The mixture of Pyrrolidine-1,2-dicarboxylic acid 2-[2-(3-bromo-6H-benzo[c]chromen-8-yl) -2-oxo-ethyl] ester 1-*tert*-butyl ester (0.5 mmol) and ammonium acetate (860 mg, 11 mmol) in xylene (5 ml) was heated at 140°C for 80 minutes under microwave. The mixture was quenched with water, and extracted with EtOAc. The organic phase was washed with water and brine, and was dried with sodium sulfate. Concentration and purification by HPLC (0.1%TFA/CH_3CN/0.1%TFA/H_2O) gave 2-[5-(3-Bromo-6H-benzo[c]chromen-8-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (8 mg). m/z: 496.0 (M+1), 494.1 (M-1).

2-(5-{3-[2-(1-t-butoxycarbonyl-pyrrolidin-2-yl)-3H-benzoimidazol-5-yl]-6H-benzo[c]chromen-8-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester: To the solution of 2-[5-(3-Bromo-6H-benzo[c]chromen-8-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (9 mg, 0.02 mmol) and 2-[6-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-benzoimidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (9.6 mg, 0.02 mmol) in DME (0.75 ml) and water (0.25 ml) was added potassium carbonate (10 mg, 0.07 mmol), followed by $Pd(PPh_3)_4$ (2 mg) and $PdCl_2(dppf)CH_2Cl_2$ (2 mg). The mixture was heated at 90°C for 6 hours. The mixture was diluted with EtOAc, and was washed with water and brine, and was dried with sodium sulfate. Concentration and purification by flash column chromatography (EtOAc) gave 2-(5-{3-[2-(1-t-butoxycarbonyl-pyrrolidin-2-yl)-3H-benzoimidazol-5-yl]-6H-benzo[c]chromen-8-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (4.2 mg). m/z: 729.2 (M+1), 727.3 (M-1), 365.2 (M+2)/2.

(1-{2-[5-(3-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-benzoimidazol-5-yl}-6H-benzo[c]chromen-8-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: To the solution of 2-(5-{3-[2-(1-t-butoxycarbonyl-pyrrolidin-2-yl)-3H-benzoimidazol-5-yl]-6H-benzo[c]chromen-8-yl}-1H-

imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (4.2 mg, 0.006) in DCM (2 ml) was added TFA (1 ml). The mixture was stirred for 60 minutes, and the solvent and reagent were removed under reduced pressure. The mixture was diluted with acetonitrile and water, and was freezer-dried to give brown powder. To the solution of above powder (0.006 mmol) and MeOCO-Val-OH (2 mg, 0.012 mmol) in DMF (1 ml) was added HATU (4.6 mg, 0.012 mmol), followed by diisopropylethylamine (10 µl, 0.058 mmol). The mixture was stirred for 90 minutes and was diluted with EtOAc. The organic phase was washed with 1 N NaOH solution, water, and brine, and was dried with sodium sulfate. Concentration and purification by HPLC (0.1%TFA/CH_3CN/0.1%TFA/H_2O) gave (1-{2-[5-(3-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-benzoimidazol-5-yl}-6H-benzo[c]chromen-8-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (2.5 mg). m/z: (M+1), (M-1), (M+2)/2. ^1H NMR (CD_3OD, 300 MHz) δ 8.07-7.7 (7 H, m), 7.62 (1 H, s), 7.45 (1 H, m), 7.38 (1 H, s), 5.25 (4 H, m), 4.35 (1 H, m), 4.22 (1 H, m), 4.15 (2 H, m), 3.85 (2 H, m), 3.65 (6 H, m), 2.98 (1 H, s), 2.6 (1 H, m), 2.3-1.7 (8 H, m), 1.05-0.85 (12 H, m).

Example ER



2-(6-Bromo-1*H*-benzoimidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester

6-Bromo-2-pyrrolidin-2-yl-1*H*-benzoimidazole

2-Methoxycarbonylamino-3-methyl-butyric acid

{1-[2-(6-Bromo-1*H*-benzoimidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester

[2-Methyl-1-(3-{5-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-yl]-1*H*-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carbonyl)-methyl]-carbamic acid methyl ester

{1-{2-[6-(6-{2-[2-(2-Methoxycarbonylamino-propionyl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3*H*-imidazol-4-yl}-naphthalen-2-yl)-1*H*-benzoimidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

6-Bromo-2-pyrrolidin-2-yl-1H-benzoimidazole: Prepared by the same method as (1-{2-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-

carbonyl}-2-methyl-propyl)-carbamic acid methyl ester, except that 2-(6-Bromo-1H-benzoimidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester was used as the substrate. 120 mg light yellow solid (66% yield).

{1-[2-(6-Bromo-1H-benzoimidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester: Prepared by the same method as (1-{2-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester but using 6-bromo-2-pyrrolidin-2-yl-1H-benzoimidazole as the substrate. 193 mg crude solid were used for the next step.

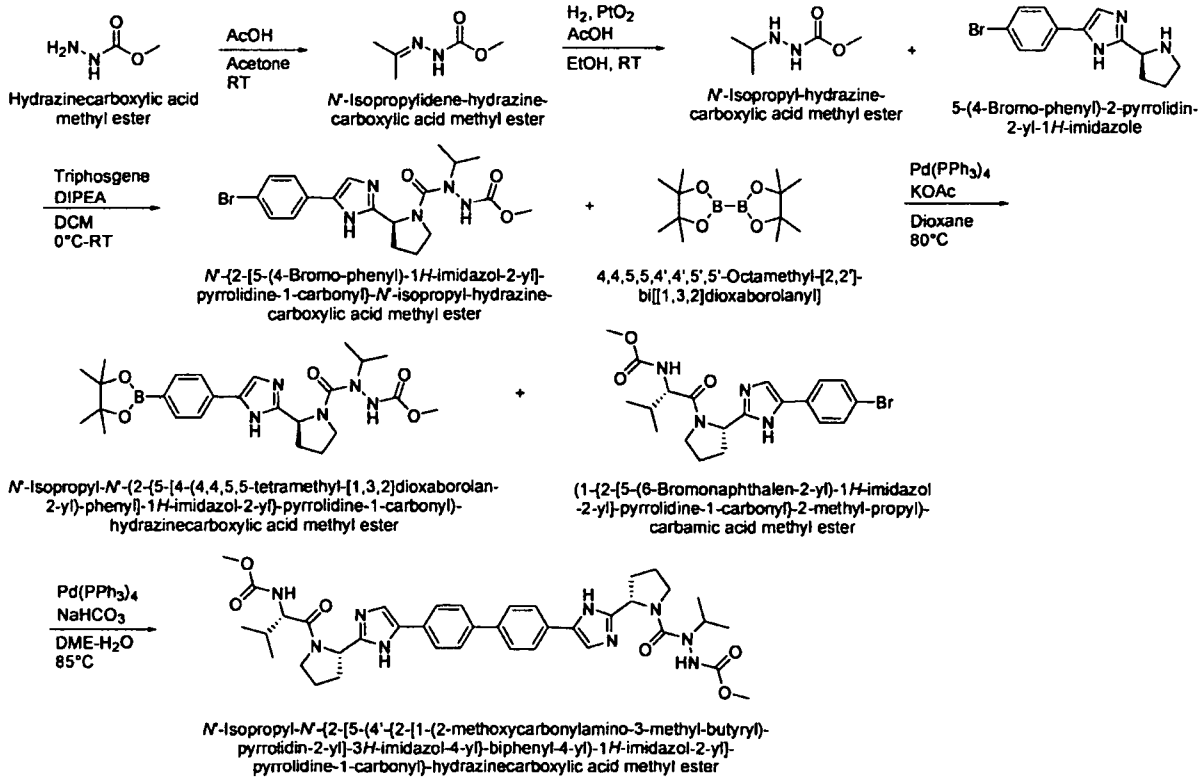
[2-Methyl-1-(3-{5-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-yl]-1H-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carbonyl)-methyl]-carbamic acid methyl ester: This compound was made using the same procedure as for [2-Methyl-1-(2-{5-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-propyl]-carbamic acid methyl ester, except that 2-Aza-bicyclo[2.2.1]heptane-2,3-dicarboxylic acid 2-*tert*-butyl ester was used in place of Pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester and 2-Methoxycarbonylamino-propionic acid was used in place of 2-Methoxycarbonylamino-3-methyl-butyric acid 2-Methoxycarbonylamino-propionic acid.

(1-{2-[6-(6-{2-[2-(2-Methoxycarbonylamino-propionyl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-imidazol-4-yl}-naphthalen-2-yl)-1H-benzoimidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: {1-[2-(6-Bromo-1H-benzoimidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (0.193 g), [2-Methyl-1-(3-{5-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-yl]-1H-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carbonyl)-methyl]-carbamic acid methyl ester (0.241 g), and $NaHCO_3$ (0.123 g) were dissolved in a mixture of 1,2-dimethoxyethane (6 mL) and water (2 mL). The solution was degassed with nitrogen, and $Pd(PPh_3)_4$ (0.0219 g) was added. The reaction mixture was stirred at 85°C for 2 days and evaporated under vacuum. Solid was dissolved in ethyl acetate (15 mL) and extracted twice with water (10 mL) and once with brine (10 mL). The resulting oil was subjected to silica gel chromatography using a 40 g ISCO column and effluent of 0-5% MeOH:DCM. The fractions containing product were combined and the solvent was removed under reduced pressure. Oil was dissolved in DMF, purified by reverse phase HPLC (5-70% acetonitrile:water), and lyophilized, giving (1-{2-[6-(6-{2-[2-(2-Methoxycarbonylamino-propionyl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-imidazol-4-yl}-

naphthalen-2-yl)-1H-benzoimidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (0.039 g, 12%) as a white solid.

^{1}H-NMR: 300 MHz, (DMSO-d_6) δ: 11.8 (s, 1H), 8.2 (d, J = 27 Hz, 2H), 7.9 (m, 4H), 7.6 (m, 3H), 7.3 (m, 2H), 5.3 (m, 2H), 4.1 (m, 2H), 3.8 (m, 2H), 3.5 (s, 6H), 2.5 (s, 6H), 2.8 (m, 1H), 2.1 (m, 4H), 2.0 (m, 4H), 0.9 (m, 12H); MS (ESI): *m/z* 763 $[M + H]^+$.

Example ES



N'-Isopropylidene-hydrazine-carboxylic acid methyl ester: Hydrazinecarboxylic acid methyl ester (5.01 g) were dissolved in acetone (28 mL), and acetic acid (0.0636 mL) was added. The reaction mixture was stirred at room temperature for 24 hours. Water (50 mL) was added, and mixture was extracted three times with DCM (50 mL) and evaporated under vacuum, giving N'-Isopropylidene-hydrazine-carboxylic acid methyl ester (6.45 g, 89%).

N'-Isopropyl-hydrazine-carboxylic acid methyl ester: N'-Isopropylidene-hydrazine-carboxylic acid methyl ester (6.45 g) were dissolved in ethanol (50 mL) and acetic acid (50 mL). PtO_2 (0.231 g) was added, and reaction was stirred at room temperature for 22 hours under an atmosphere of hydrogen. Mixture was evaporated under vacuum, giving N'-Isopropyl-hydrazine-carboxylic acid methyl ester (5.08 g, 77%) as a white solid.

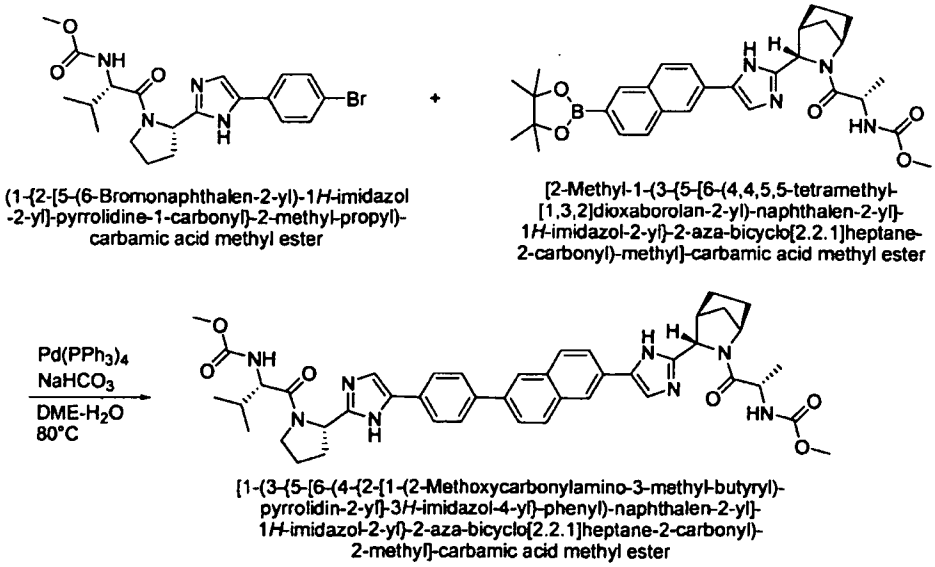
N'-{2-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-N'-isopropyl-hydrazine-carboxylic acid methyl ester: Triphosgene (1.05 g) was dissolved in DCM (17 mL) and stirred at 0°C. N'-Isopropyl-hydrazine-carboxylic acid methyl ester (1.00 g) and DIPEA (1.5 mL) were dissolved in DCM (25 mL), and mixture was added to triphosgene solution and stirred for 10 minutes. 5-(4-Bromo-phenyl)-2-pyrrolidin-2-yl-1H-imidazole (2.65 g) was added. Reaction was stirred at room temperature for 1 hour and extracted twice with water (10 mL), once with brine (10 mL), and evaporated under vacuum. The resulting oil was subjected to silica gel chromatography using a 40 g ISCO column and effluent of 0-100% ethyl acetate:hexanes. The fractions containing product were combined and the solvent was removed under vacuum, giving N'-{2-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-N'-isopropyl-hydrazine-carboxylic acid methyl ester (533 mg, 16%).

N'-Isopropyl-N'-(2-{5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-hydrazinecarboxylic acid methyl ester: N'-{2-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-N'-isopropyl-hydrazine-carboxylic acid methyl ester (0.533 g), 4,4,5,5,4',4',5',5'-Octamethyl-[2,2']-bi[[1,3,2]dioxaborolanyl] (0.644 g), and KOAc (0.309 g) were dissolved in dioxane (8 mL). The solution was degassed with nitrogen, and $Pd(PPh_3)_4$ (0.0562 g) was added, and reaction was stirred at 80°C for 2 days. Solid was removed by vacuum filtration, and solvent was removed under vacuum. The resulting oil was subjected to silica gel chromatography using a 40 g ISCO column and effluent of 0-5% MeOH:DCM. The fractions containing product were combined and the solvent was removed under vacuum, giving N'-Isopropyl-N'-(2-{5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-hydrazinecarboxylic acid methyl ester (0.564 g, 96%) as a yellow solid.

N'-Isopropyl-N'-{2-[5-(4'-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-hydrazinecarboxylic acid methyl ester: N'-Isopropyl-N'-(2-{5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-hydrazinecarboxylic acid methyl ester (0.295 g), (1-{2-[5-(6-Bromophenyl-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (0.280 g), and $NaHCO_3$ were dissolved in DME (9 mL) and water (3 mL). The solution was degassed with nitrogen, and $Pd(PPh_3)_4$ (0.0282 g) was added, and reaction was stirred at 85°C for 19 hours. Solvent was removed under vacuum. Solid was dissolved in DMF, purified by reverse phase HPLC (5-70% acetonitrile:water) two times, and lyophilized, giving N'-Isopropyl-N'-{2-[5-(4'-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-hydrazinecarboxylic acid methyl ester (0.017 g, 4%) as a white solid.

^{1}H-NMR: 300 MHz, (CH_3OH-d_4) δ: 7.9 (m, 12H), 5.3 (m, 2H), 4.4 (m, 1H), 4.2 (d, J = 7 Hz, 2H), 4.1 (m, 1H), 3.9 (m, 4H), 3.6 (m, 6H), 3.3 (s, 3H), 2.6 (m, 2H), 2.0 (m, 8H), 1.1 (m, 6H), 0.9 (m, 6H); MS (ESI): *m/z* 740 $[M + H]^+$.

Example ET



(1-{2-[5-(6-Bromonaphthalen-2-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

[2-Methyl-1-(3-{5-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-yl]-1*H*-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carbonyl)-methyl]-carbamic acid methyl ester

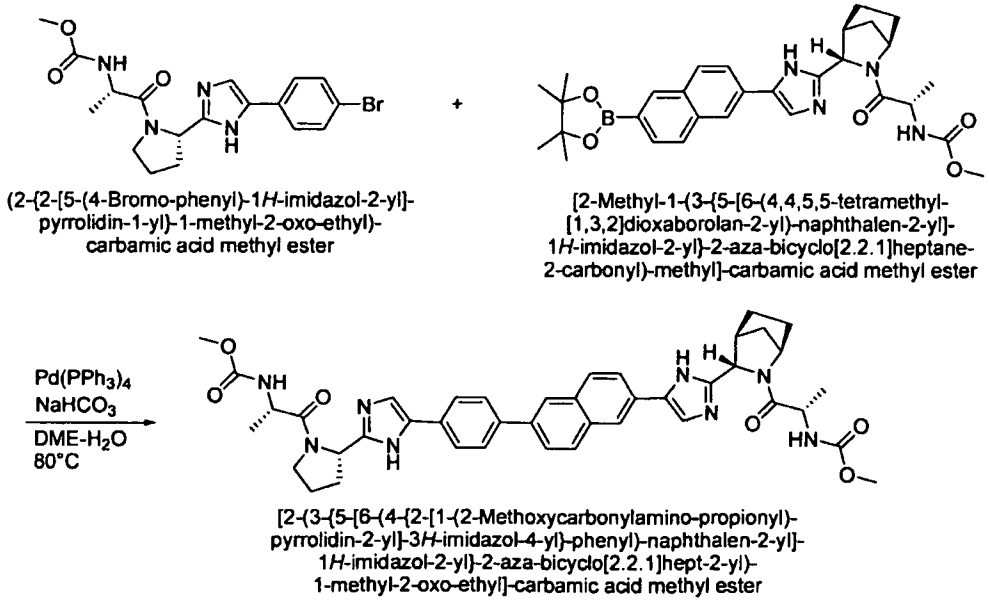
[1-(3-{5-[6-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1*H*-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carbonyl)-2-methyl]-carbamic acid methyl ester

[1-(3-{5-[6-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carbonyl)-2-methyl]-carbamic acid methyl ester: (1-{2-[5-(6-Bromonaphthalen-2-yl)-1H-

imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (0.226 g), [2-Methyl-1-(3-{5-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-yl]-1H-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carbonyl)-methyl]-carbamic acid methyl ester (0.297 g), and $NaHCO_3$ (0.154 g) were dissolved in a mixture of 1,2-dimethoxyethane (9 mL) and water (3 mL). The solution was degassed with nitrogen, and $Pd(PPh_3)_4$ (0.0263 g) was added. The reaction mixture was stirred at 80°C for 19 hours and evaporated under vacuum. Solid was dissolved in DCM (15 mL) and extracted twice with water (10 mL) and once with brine (10 mL). The resulting oil was subjected to silica gel chromatography using a 40 g ISCO column and effluent of 0 -5 % MeOH:DCM. The fractions containing product were combined and the solvent was removed under reduced pressure. Oil was dissolved in DMF, purified by reverse phase HPLC (5-70% acetonitrile:water), and lyophilized, giving [1-(3-{5-[6-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carbonyl)-2-methyl]-carbamic acid methyl ester (0.138 g, 32%) as a white solid.

^{1}H-NMR: 300 MHz, (CH_3OH-d_4) δ: 8.3 (d, J = 9 Hz, 2H), 8.1 (m, 2H), 8.0 (m, 4H), 7.9 (m, 4H), 5.3 (t, J = 7 Hz, 2H), 4.6 (s, 2H), 4.5 (m, 2H), 4.2 (d, J = 7 Hz, 2H), 4.1 (m, 2H), 3.9 (m, 2H), 3.6 (s, 6H), 3.3 (s, 2H), 2.9 (s, 1H), 2.8 (m, 1H), 2.0 (m, 8H), 1.8 (m, 1H), 1.4 (d, J = 7 Hz, 3H), 0.9 (m, 6H); MS (ESI): *m/z* 787 $[M + H]^+$.

Example EU



(2-{2-[5-(4-Bromo-phenyl)-1*H*-imidazol-2-yl]-pyrrolidin-1-yl}-1-methyl-2-oxo-ethyl)-carbamic acid methyl ester

[2-Methyl-1-(3-{5-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-yl]-1*H*-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carbonyl)-methyl]-carbamic acid methyl ester

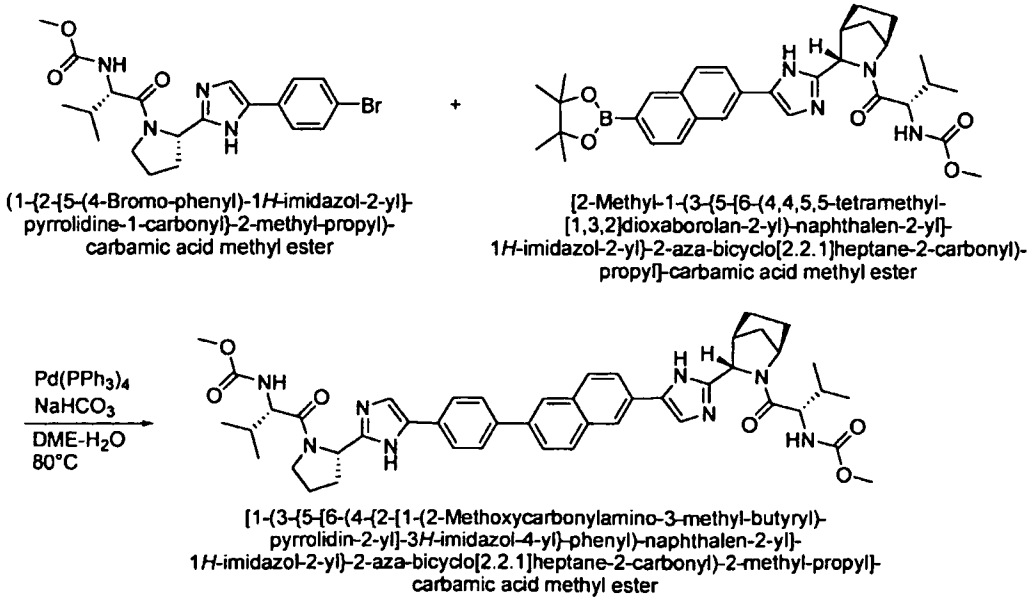
[2-(3-{5-[6-(4-{2-[1-(2-Methoxycarbonylamino-propionyl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1*H*-imidazol-2-yl}-2-aza-bicyclo[2.2.1]hept-2-yl)-1-methyl-2-oxo-ethyl]-carbamic acid methyl ester

[2-(3-{5-[6-(4-{2-[1-(2-Methoxycarbonylamino-propionyl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-2-aza-bicyclo[2.2.1]hept-2-yl)-1-methyl-2-oxo-ethyl]-carbamic acid methyl ester: (2-{2-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-

pyrrolidin-1-yl}-1-methyl-2-oxo-ethyl)-carbamic acid methyl ester (0.241 g), [2-Methyl-1-(3-{5-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-yl]-1H-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carbonyl)-methyl]-carbamic acid methyl ester (0.303 g), and $NaHCO_3$ (0.164 g) were dissolved in a mixture of 1,2-dimethoxyethane (9 mL) and water (3 mL). The solution was degassed with nitrogen, and $Pd(PPh_3)_4$ (0.0263 g) was added. The reaction mixture was stirred at 80°C for 19 hours and evaporated under vacuum. Solid was dissolved in DCM (15 mL) and extracted twice with water (10 mL) and once with brine (10 mL). The resulting oil was subjected to silica gel chromatography using a 40 g ISCO column and effluent of 0-5 % MeOH:DCM. The fractions containing product were combined and the solvent was removed under reduced pressure. Oil was dissolved in DMF, purified by reverse phase HPLC (5-70% acetonitrile:water), and lyophilized, giving [2-(3-{5-[6-(4-{2-[1-(2-Methoxycarbonylamino-propionyl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-2-aza-bicyclo[2.2.1]hept-2-yl)-1-methyl-2-oxo-ethyl]-carbamic acid methyl ester (0.159 g, 38%) as a white solid.

^{1}H-NMR: 300 MHz, (CH_3OH-d_4) δ: 8.3 (d, J = 9 Hz, 2H), 8.1 (m, 2H), 8.0 (m, 4H), 7.9 (m, 4H), 5.3 (m, 2H), 4.6 (s, 2H), 4.5 (m, 4H), 4.0 (m, 2H), 3.9 (m, 2H), 3.7 (d, J = 7 Hz, 6H), 3.3 (m, 2H), 2.9 (s, 1H), 2.8 (s, 1H), 2.6 (m, 1H), 2.0 (m, 8H), 1.8 (m, 2H), 1.4 (m, 6H); MS (ESI): m/z 759 $[M + H]^+$.

Example EV



(1-{2-[5-(4-Bromo-phenyl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

[2-Methyl-1-(3-{5-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-yl]-1*H*-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carbonyl)-propyl]-carbamic acid methyl ester

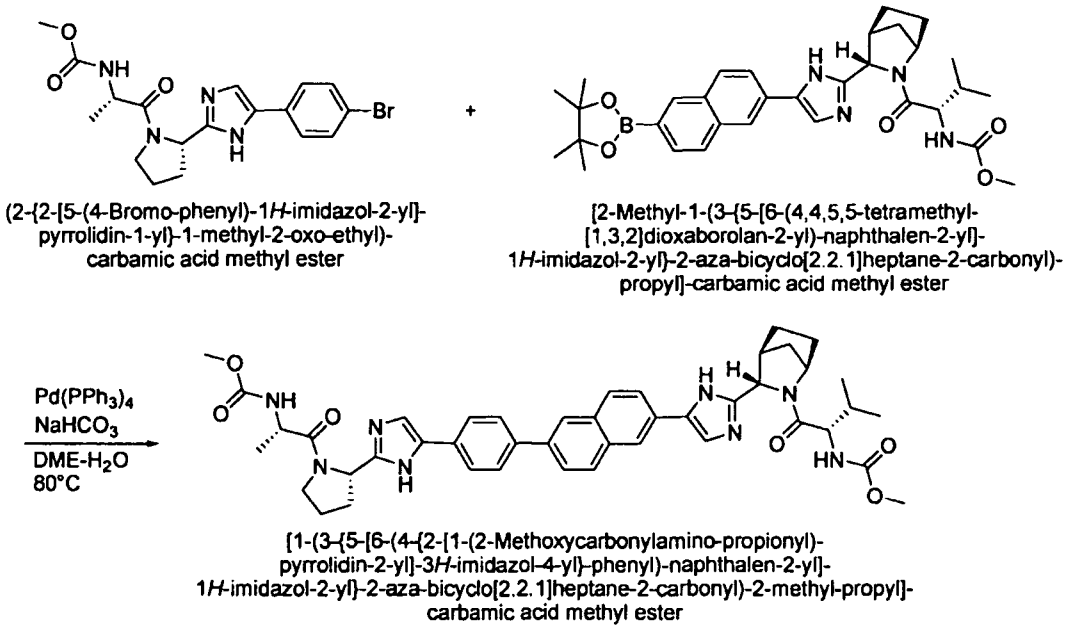
[1-(3-{5-[6-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1*H*-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester

[2-Methyl-1-(2-{5-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-propyl]-carbamic acid methyl ester: This compound was made using the same procedure as for [2-Methyl-1-(2-{5-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-propyl]-carbamic acid methyl ester, except that 2-Aza-bicyclo[2.2.1]heptane-2,3-dicarboxylic acid 2-*tert*-butyl ester was used in place of Pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester as described in example CL.

[1-(3-{5-[6-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: (1-{2-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (0.251 g), [2-Methyl-1-(3-{5-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-yl]-1H-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carbonyl)-propyl]-carbamic acid methyl ester (0.301 g), and $NaHCO_3$ (0.162 g) were dissolved in a mixture of 1,2-dimethoxyethane (9 mL) and water (3 mL). The solution was degassed with nitrogen, and $Pd(PPh_3)_4$ (0.0254 g) was added. The reaction mixture was stirred at 80°C for 21 hours and evaporated under vacuum. Solid was dissolved in DCM (20 mL) and extracted twice with water (10 mL) and once with brine (10 mL). The resulting oil was subjected to silica gel chromatography using a 40 g ISCO column and effluent of 0-5 % MeOH:DCM. The fractions containing product were combined and the solvent was removed under reduced pressure. Oil was dissolved in DMF, purified by reverse phase HPLC (5-70% acetonitrile:water), and lyophilized, giving [1-(3-{5-[6-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (0.187 g, 44%) as a white solid.

^{1}H-NMR: 300 MHz, (CH_3OH-d_4) δ: 8.3 (d, J = 9 Hz, 2H), 8.1 (m, 2H), 8.0 (m, 4H), 7.9 (m, 4H), 5.3 (m, 2H), 4.7 (s, 2H), 4.3 (m, 2H), 4.1 (m, 2H), 3.9 (m, 2H), 3.7 (d, J = 7 Hz, 6H), 3.3 (m, 2H), 2.9 (s, 1H), 2.6 (m, 2H), 2.1 (m, 8H), 1.8 (m, 2H), 1.4 (m, 12H); MS (ESI): *m/z* 815 $[M + H]^+$.

Example EW



(2-{2-[5-(4-Bromo-phenyl)-1*H*-imidazol-2-yl]-pyrrolidin-1-yl}-1-methyl-2-oxo-ethyl)-carbamic acid methyl ester

[2-Methyl-1-(3-{5-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-yl]-1*H*-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carbonyl)-propyl]-carbamic acid methyl ester

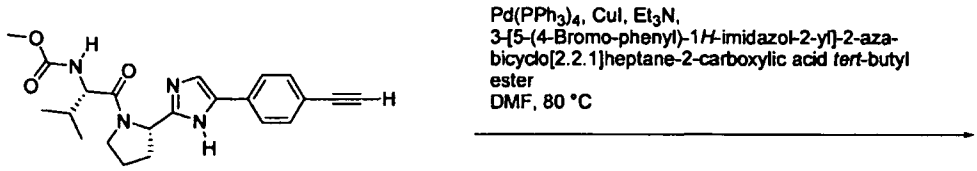
[1-(3-{5-[6-(4-{2-[1-(2-Methoxycarbonylamino-propionyl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1*H*-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester

[1-(3-{5-[6-(4-{2-[1-(2-Methoxycarbonylamino-propionyl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: (2-{2-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-pyrrolidin-1-yl}-1-methyl-2-oxo-ethyl)-carbamic acid methyl ester (0.235 g), [2-Methyl-1-(3-{5-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-yl]-1H-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carbonyl)-propyl]-carbamic acid methyl ester (0.310 g), and $NaHCO_3$ (0.145 g) were dissolved in a mixture of 1,2-dimethoxyethane (9 mL) and water (3 mL). The solution was degassed with nitrogen, and $Pd(PPh_3)_4$ (0.0260 g) was added. The reaction mixture was stirred at 80°C for 24 hours and evaporated under vacuum. Solid was dissolved in DCM (20 mL) and extracted twice with water (10 mL) and once with brine (10 mL). The resulting oil was subjected to silica gel chromatography using a 40 g ISCO column and effluent of 0-5 % MeOH:DCM. The fractions containing product were combined and the solvent was removed under reduced pressure. Oil was dissolved in DMF, purified by reverse phase HPLC (5-70% acetonitrile:water), and lyophilized, giving [1-(3-{5-[6-(4-{2-[1-(2-Methoxycarbonylamino-propionyl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (0.150 g, 36%) as a white solid.

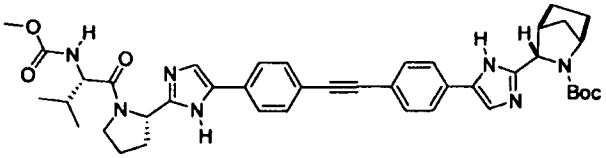
^{1}H-NMR: 300 MHz, (CH_3OH-d_1) δ: 8.3 (d, J = 9 Hz, 2H), 8.1 (m, 2H), 8.0 (m, 4H), 7.9 (m, 4H), 5.3 (m, 2H), 4.7 (s, 2H), 4.5 (m, 1H), 4.3 (d, J = 7 Hz, 1H), 4.0 (m, 2H), 3.7 (d, J = 7 Hz,

6H), 3.3 (s, 6H), 2.9 (s, 1H), 2.3 (m, 2H), 2.1 (m, 8H), 2.0 (m, 2H), 1.8 (m, 2H), 1.3 (d, J = 7 Hz, 3H)1.0 (m, 6H); MS (ESI): m/z 787 $[M + H]^+$.

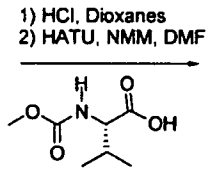
Example EX



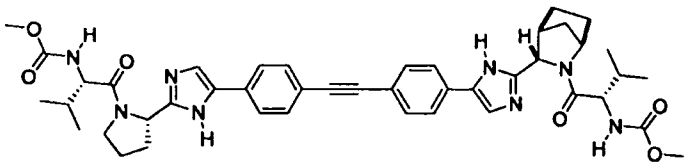
(1-{2-[5-(4-Ethynyl-phenyl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester



3-{5-[4-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-phenylethynyl)-phenyl]-1*H*-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester



2-Methoxycarbonylamino-3-methyl-butyric acid



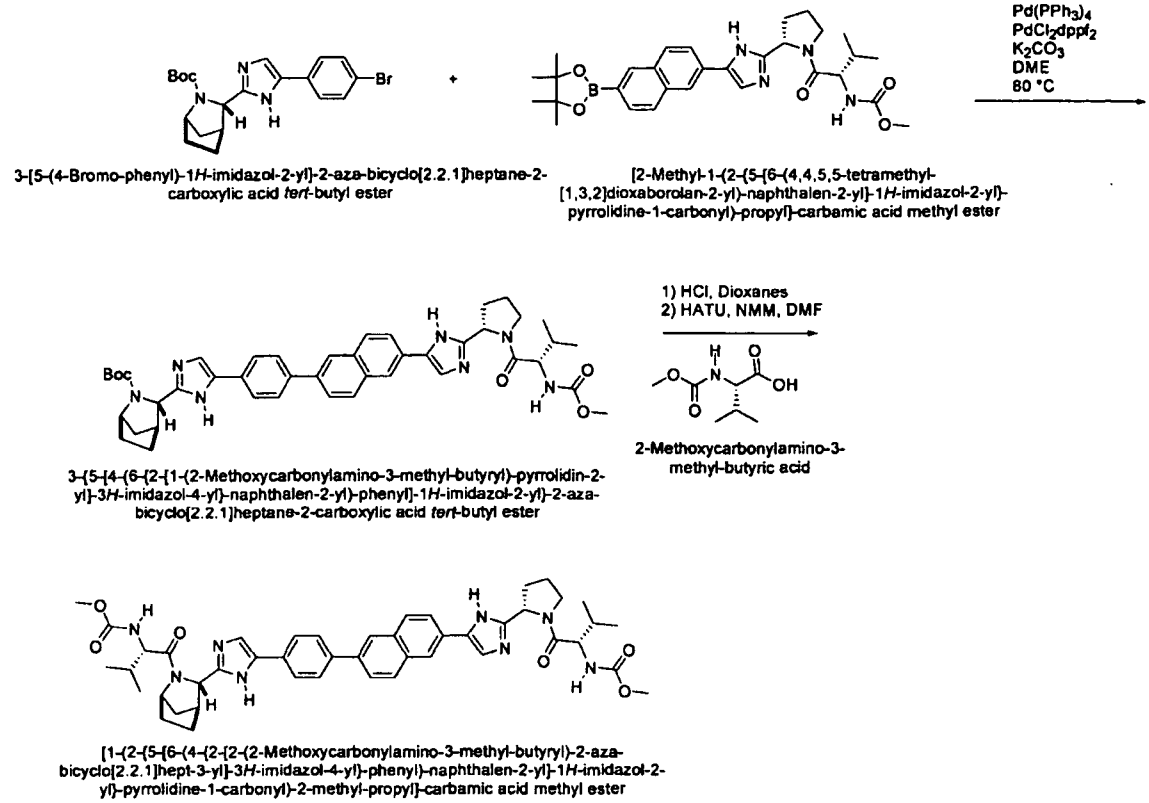
[1-(3-{5-[4-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-phenylethynyl)-phenyl]-1*H*-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester

3-{5-[4-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenylethynyl)-phenyl]-1H-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester: A solution of (1-{2-[5-(4-Ethynyl-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (500 mg, 1.27 mmol), 3-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (530 mg, 1.27 mmol), and triethylamine (531 □L, 3.81 mmol) in DMF (6.4 mL) was degassed with N_2 gas for 20 minutes. To the degassed solution was added $Pd(PPh_3)_4$ (150 mg, 0.13 mmol) and CuI (25 mg, 0.13 mmol). The pressure flask was sealed then heated at 80°C overnight. After cooling to room temperature, the reaction was quenched with AcOH then purified by reverse phase preparative HPLC (10-70% MeCN-H_2O; 0.1% formic acid modifier) then silica gel chromatography (0-10% MeOH-EtOAc gradient) to afford 3-{5-[4-(4-{2-[1-(2-

Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenylethynyl)-phenyl]-1H-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (500 mg, 0.68 mmol, 54% yield). LCMS-ESI$^+$: calc'd for $C_{42}H_{50}N_7O_5$: 732.4 (M+H$^+$); Found: 732.2 (M+H$^+$).

[1-(3-{5-[4-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenylethynyl)-phenyl]-1H-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: To 3-{5-[4-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenylethynyl)-phenyl]-1H-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (150 mg, 0.20 mmol) in dioxanes (2 mL) was added 4N HCl in dioxanes (250 □L). The suspension was stirred for 2 hours then concentrated to afford the HCl salt of the crude amine. To the crude amine in DMF (4 mL) was added *N*-methylmorpholine (330 □L, 0.30 mmol). After all material dissolved, 2-methoxycarbonylamino-3-methyl-butyric acid (53 mg, 0.30 mmol) and HATU (76 mg, 0.20 mmol) were added. After stirring for overnight the reaction was quenched with AcOH then purified by reverse phase preparative HPLC (5-45% MeCN-H_2O; 0.1% formic acid modifier) to afford the title product [1-(3-{5-[4-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenylethynyl)-phenyl]-1H-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (83 mg, 0.11 mmol, 53% yield). ^{1}H-NMR: 400 MHz, (DMSO-d_6) δ: 7.59-7.55 (m, 4H), 7.41-7.38 (m, 4H), 7.17 (s, 1H), 7.15 (s, 1H), 6.16 (m, 2H), 5.15 (m, 1H), 4.63 (s, 1H), 4.50 (s, 1H), 4.34-4.24 (m, 2H), 3.88-3.72 (m, 2H), 3.63 (s, 3H), 3.61 (s, 3H), 2.88 (m, 1H), 2.25-2.15 (m, 1H), 2.27-2.16 (m, 2H), 2.05-1.80 (m, 5H), 1.54 (d, 2H), 1.00-0.887 (m, 12H). LCMS-ESI$^+$: calc'd for $C_{44}H_{53}N_8O_6$: 789.4 (M+H$^+$); Found: 789.5 (M+H$^+$).

Example EY



3-[5-(4-Bromo-phenyl)-1*H*-imidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester

[2-Methyl-1-(2-{5-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-yl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-propyl]-carbamic acid methyl ester

2-Methoxycarbonylamino-3-methyl-butyric acid

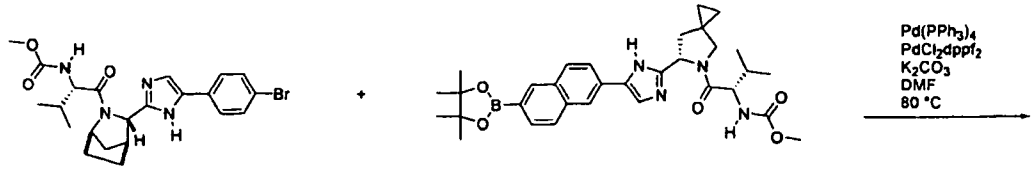
3-{5-[4-(6-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1*H*-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester

[1-(2-{5-[6-(4-{2-[2-(2-Methoxycarbonylamino-3-methyl-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3*H*-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester

3-{5-[4-(6-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester: A solution of [2-Methyl-1-(2-{5-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-propyl]-carbamic acid methyl ester (500 mg, 0.92 mmol), 3-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (383 mg, 0.92 mmol) and aq K_2CO_3 (920 µl of a 2M solution, 1.84 mmol) in DME (9 mL) was degassed with N_2 gas for 20 minutes. To the degassed solution was added $Pd(PPh_3)_4$ (106 mg, 0.092 mmol) and $PdCl_2dppf$ (75 mg, 0.092 mmol) and then the reaction was heated to 80°C overnight. After cooling to room temperature, the reaction was quenched with acetic acid, filtered, and then concentrated. The crude product was purified by reverse phase preparative HPLC (5-50% MeCN-H_2O; 0.1% formic acid modifier) to afford 3-{5-[4-(6-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (112 mg, 0.15 mmol, 16% yield). LCMS-ESI$^+$: calc'd for $C_{44}H_{52}N_7O_5$: 758.4 ($M+H^+$); Found: 758.0 ($M+H^+$).

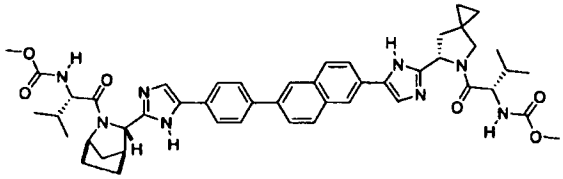
[1-(2-{5-[6-(4-{2-[2-(2-Methoxycarbonylamino-3-methyl-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: To 3-{5-[4-(6-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (60 mg, 0.092 mmol) in dioxanes (3 mL) was added 4N HCl in dioxanes (1 mL). The suspension was stirred overnight then concentrated to afford the HCl salt of the crude amine, which was purified by reverse phase preparative HPLC (5-45% MeCN-H_2O; 0.1% formic acid modifier) and concentrated. The formate salt was dissolved in MeOH then passed through an ion-exchange column (StratoSpheres SPE PL-HCO_3 MP SE) to afford the free amine (30 mg, 0.046 mmol, 58%). To the amine (30 mg, 0.046 mmol) in DMF (1 mL) was added *N*-methylmorpholine (10 □L, 0.092 mmol). After all material dissolved, 2-methoxycarbonylamino-3-methyl-butyric acid (12 mg, 0.068 mmol) and HATU (19 mg, 0.051 mmol) were added. After stirring for 3 hours the reaction was quenched with AcOH then purified by reverse phase preparative HPLC (5-45% MeCN-H_2O; 0.1% formic acid modifier) to afford [1-(2-{5-[6-(4-{2-[2-(2-Methoxycarbonylamino-3-methyl-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (29 mg, 0.036 mmol, 77% yield). ^{1}H-NMR: 400 MHz, (DMSO-d_6) δ: 8.04 (s, 1H), 7.86 (s, 1H), 7.71 (d, 2H), 7.63-7.58 (m, 4H), 7.52 (d, 2H), 7.26 (s, 1H), 7.14 (s, 1H), 6.17 (m, 2H), 5.21 (m, 1H), 4.67 (s, 1H), 4.52 (s, 1H), 4.35-4.26 (m, 2H), 3.86 (m, 1H), 3.79 (m, 1H), 3.64 (s, 6H), 2.90 (m, 1H), 2.43 (m, 1H), 2.30-2.1.82 (m, 9H), 1.55 (d, 2H), 1.02-0.87 (m, 12H). LCMS-ESI$^+$: calc'd for $C_{46}H_{55}N_8O_6$: 815.3 ($M+H^+$); Found: 815.4 ($M+H^+$).

Example EZ



(1-{3-[5-(4-Bromo-phenyl)-1*H*-imidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

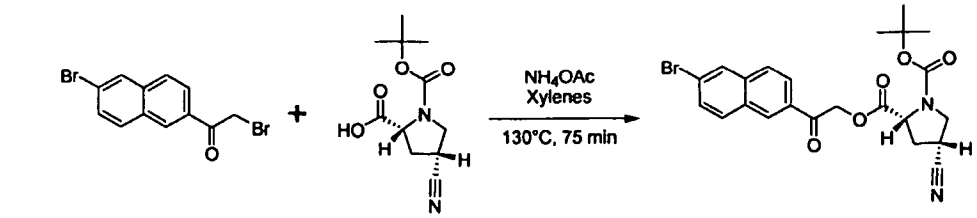
[2-Methyl-1-(6-{5-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-yl]-1*H*-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carbonyl)-propyl]-carbamic acid methyl ester



[1-(6-{5-[6-(4-{2-[2-(2-Methoxycarbonylamino-3-methyl-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3*H*-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1*H*-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester

[1-(6-{5-[6-(4-{2-[2-(2-Methoxycarbonylamino-3-methyl-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: A solution of (1-{3-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (151 mg, 0.32 mmol), [2-Methyl-1-(6-{5-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-yl]-1H-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carbonyl)-propyl]-carbamic acid methyl ester (200 mg, 0.35 mmol) and aq K_2CO_3 (438 µl of a 2M solution, 0.88 mmol) in DME (4 mL) was degassed with N_2 gas for 20 minutes. To the degassed solution was added $Pd(PPh_3)_4$ (40 mg, 0.035 mmol) and then the reaction was heated to 80°C overnight. After cooling to room temperature, the reaction was quenched with acetic acid, filtered, and then concentrated. The crude product was purified by reverse phase preparative HPLC (5-50% MeCN-H_2O; 0.1% formic acid modifier) to afford [1-(6-{5-[6-(4-{2-[2-(2-Methoxycarbonylamino-3-methyl-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (40 mg, 0.047 mmol, 14% yield). ^{1}H-NMR: 400 MHz, (DMSO-d_6) δ: 11.75 (s, 1H), 11.72 (s, 1H), 8.24 (s, 1H), 8.15 (d, 1H), 7.93-7.74 (m, 8H), 7.63 (s, 1H), 7.54 (s, 1H), 7.30 (d, 1H), 7.16 (d, 1H), 5.22 (t, 1H), 4.52-4.50 (m, 2H), 4.16 (t, 1H), 4.00 (t, 1H), 3.81 (d, 1H), 3.75 (d, 1H), 3.72 (s, 3H), 3.31 (s, 3H), 2.55 (m, 1H), 2.32-1.41 (m, 10H), 1.01-0.57 (m, 16H). LCMS-ESI$^+$: calc'd for $C_{48}H_{57}N_8O_6$: 841.4 ($M+H^+$); Found: 842.1 ($M+H^+$).

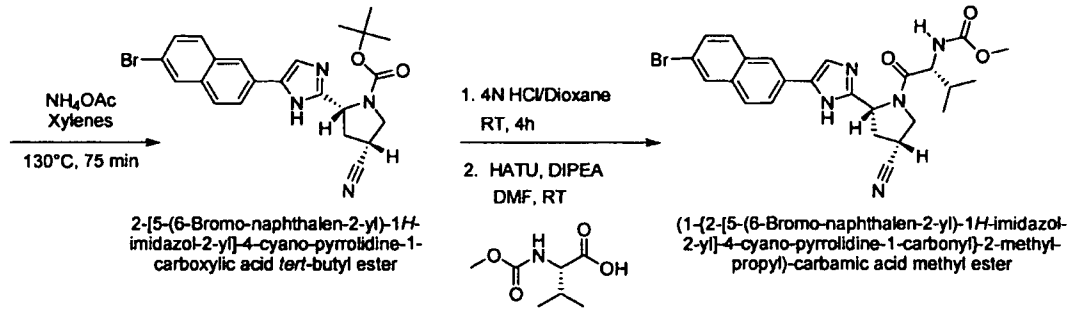
Example FA and FB



2-Bromo-1-(6-bromo-naphthalen-2-yl)-ethanone

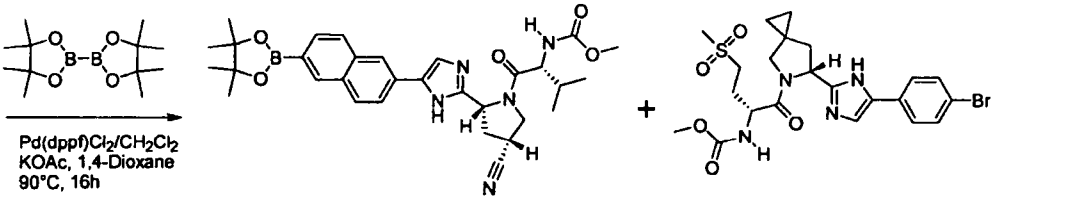
N-Boc-cis-4-cyano-L-proline methyl ester

4-Cyano-pyrrolidine-1,2-dicarboxylic acid 2-[2-(6-bromo-naphthalen-2-yl)-2-oxo-ethyl] ester 1-*tert*-butyl ester



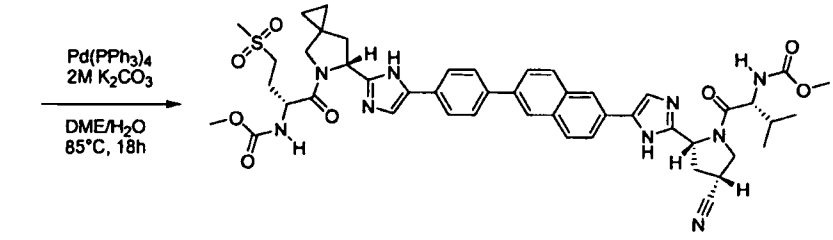
2-[5-(6-Bromo-naphthalen-2-yl)-1*H*-imidazol-2-yl]-4-cyano-pyrrolidine-1-carboxylic acid *tert*-butyl ester

(1-{2-[5-(6-Bromo-naphthalen-2-yl)-1*H*-imidazol-2-yl]-4-cyano-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester



[1-(4-Cyano-2-{5-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-yl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester

(1-{6-[5-(4-Bromo-phenyl)-1*H*-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carbonyl}-3-methanesulfonyl-propyl)-carbamic acid methyl ester



[1-(4-Cyano-2-{5-[6-(4-{2-[5-(4-methanesulfonyl-2-methoxycarbonylamino-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3*H*-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester

4-Cyano-pyrrolidine-1,2-dicarboxylic acid 2-[2-(6-bromo-naphthalen-2-yl)-2-oxo-ethyl] ester 1-*tert*-butyl ester:

Title compound was prepared according to the method employed to prepare pyrrolidine-1,2-dicarboxylic acid 2-[2-(6-bromo-naphthalen-2-yl)-2-oxo-ethyl] ester 1-*tert*-butyl ester in Example CL, substituting pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester with N-Boc-cis-4-cyano-L-proline methyl ester (643 mg, 67%)

2-[5-(6-Bromo-naphthalen-2-yl)-1H-imidazol-2-yl]-4-cyano-pyrrolidine-1-carboxylic acid *tert*-butyl ester:

Title compound was prepared according to the method employed to prepare 2-[5-(6-Bromo-naphthalen-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester: in Example CL, changing the reaction temperature to 130°C and the reaction time to 75 minutes. (396 mg, 64%) MS (ESI) *m/z* 468.99 $[M + H]^+$.

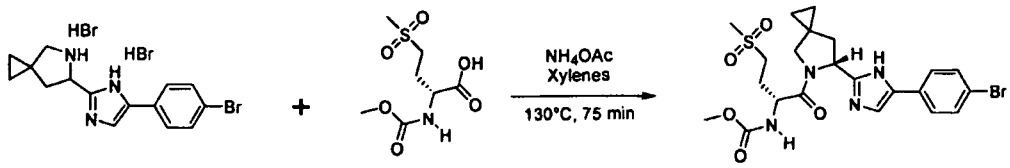
(1-{2-[5-(6-Bromo-naphthalen-2-yl)-1H-imidazol-2-yl]-4-cyano-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester:

Title compound was prepared according to the method employed to prepare (1-{2-[5-(7-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-thianthren-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester and (1-{2-[5-(8-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-thianthren-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester in Example BS, substituting N-methylmorpholine with five equivalents of diisopropylethylamine. (430 mg, 97%) MS (ESI) *m/z* 525.94 $[M + H]^+$.

[1-(4-Cyano-2-{5-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester:

Title compound was prepared according to the method employed to prepare 2-[6-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-benzoimidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester in Example CL, replacing N-Boc Proline with N-Boc-4-cyano-proline. (407 mg, 87%) MS (ESI) *m/z* 572.46 $[M + H]^+$.

(1-{6-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carbonyl}-3-methanesulfonyl-propyl)-carbamic acid methyl ester:



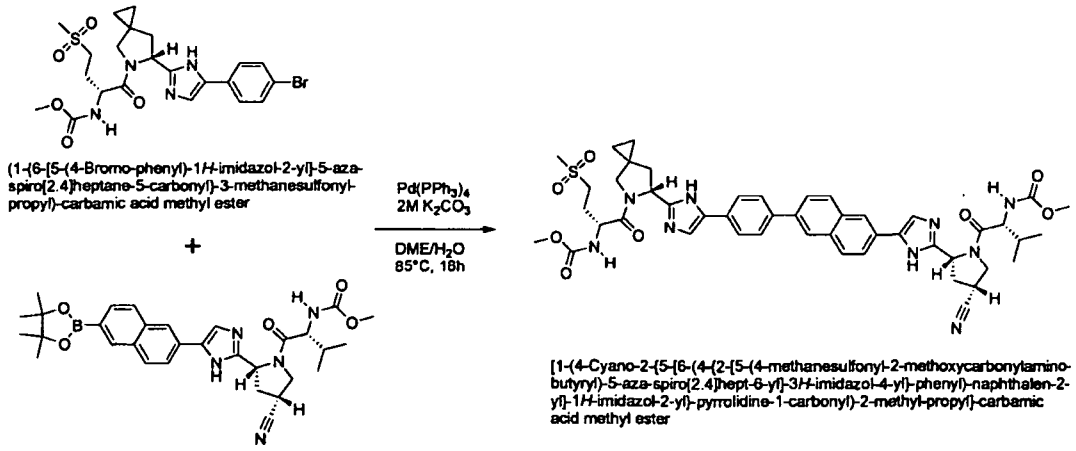
6-[5-(4-Bromo-phenyl)-1*H*-imidazol-2-yl]-5-aza-spiro[2.4]heptane X2 hydrogen bromide salt

4-Methanesulfonyl-2-methoxycarbonylamino-butyric acid

(1-{6-[5-(4-Bromo-phenyl)-1*H*-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carbonyl}-3-methanesulfonyl-propyl)-carbamic acid methyl ester

Title compound was prepared according to the method employed to prepare (1-{2-[5-(4-Bromonaphthalen-1-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester in Example CK, substituting N-methylmorpholine with five equivalents of diisopropylethylamine.(99%)

Example FA: [1-(4-Cyano-2-{5-[6-(4-{2-[5-(4-methanesulfonyl-2-methoxycarbonylamino-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester



(1-{6-[5-(4-Bromo-phenyl)-1*H*-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carbonyl}-3-methanesulfonyl-propyl)-carbamic acid methyl ester

+

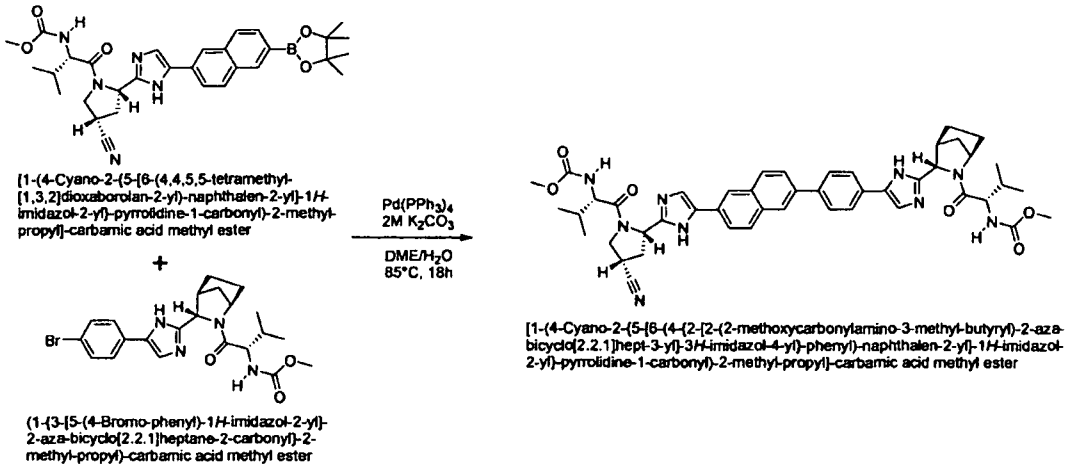
[1-(4-Cyano-2-[5-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-yl]-1*H*-imidazol-2-yl)-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester

[1-(4-Cyano-2-{5-[6-(4-{2-[5-(4-methanesulfonyl-2-methoxycarbonylamino-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3*H*-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester

Title compound was prepared according to the method employed to prepare (1-{2-[5-(6'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-[2,2']binaphthalenyl-6-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester in Example CL. (30%)

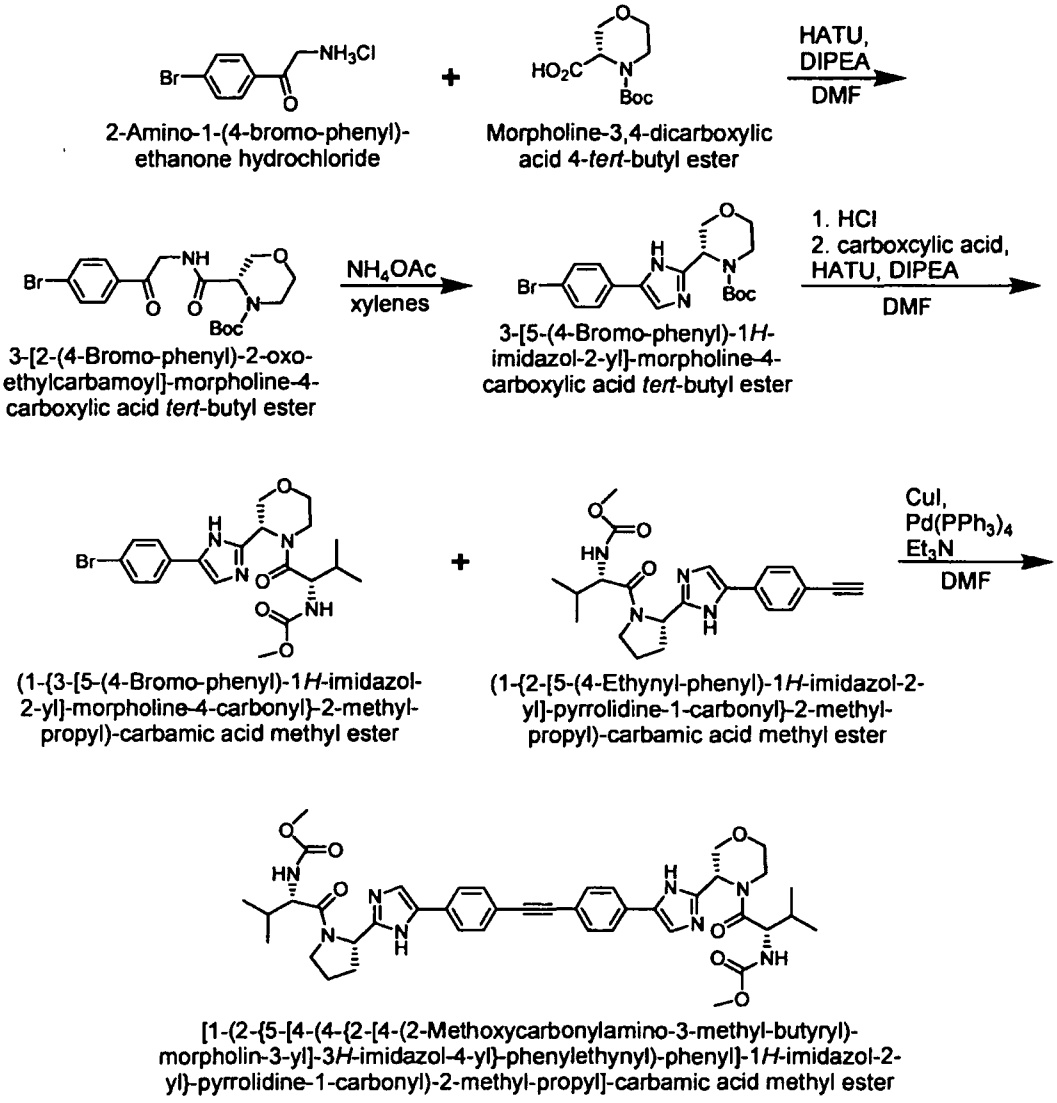
:^{1}H-NMR: 400 MHz, (CD_3OD) δ 8.14 (s, 2H), 8.09 (d, *J*= 5.6 Hz, 1H), 7.92 (d, *J*= 7.6 Hz, 2H), 7.85 – 7.78 (m, 5H), 7.46 (s, 1H), 7.41 (s, 1H), 5.33 (dd, *J*= 5.6 Hz, 7.6 Hz, 1H), 5.21 (t, *J*= 8.4 Hz, 1H), 4.63 – 4.58 (m, 2H), 4.17 – 4.13 (m, 1H), 4.05 (t, *J*= 10.4 Hz, 1H), 3.83 (s, 2H), 3.65 (d, *J*= 5.2 Hz, 6H), 3.48 – 3.42 (m, 3H), 3.21 (t, *J*= 7.6 Hz, 2H), 2.98 (s, 1H), 2.95 (s, 2H), 2.92 – 2.84 (m, 1H), 2.64 – 2.55 (m, 1H), 2.35 – 2.27 (m, 2H), 2.14 – 1.92 (m, 4H), 0.98 – 0.87 (m, 7H), 0.79 – 0.59 (m, 4H). MS (ESI) *m/z* 904.58 $[M + H]^+$.

Example FB: [1-(4-Cyano-2-{5-[6-(4-{2-[2-(2-methoxycarbonylamino-3-methyl-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester:



Title compound was prepared according to the method employed to prepare (1-{2-[5-(6'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-[2,2']binaphthalenyl-6-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester in Example CL. (35%)
:^{1}H-NMR: 400 MHz, (CD_3OD) δ 8.22 (s, 1H), 8.15 (s, 1H), 8.07 (s, 1H), 7.92 (dd, *J*= 2 Hz, 8.4 Hz, 2H), 7.85 – 7.76 (m, 6H), 7.44 (s, 1H), 7.33 (s, 1H), 5.21 (t, *J*= 8.8 Hz, 1H), 4.71 (s, 1H), 4.62 – 4.55 (m, 2H), 4.33 – 4.27 (m, 1H), 4.16 (d, *J*= 7.6 Hz, 1H), 4.05 (t, *J*= 10.4 Hz, 1H), 3.65 (d, *J*= 5.6 Hz, 4H), 3.51 (m, 2H), 2.90 (m, 1H), 2.76 (s, 1H), 2.64 (m, 1H), 2.29 (d, *J*= 9.6 Hz, 1H), 2.19 – 2.10 (m, 1H), 2.00 – 1.84 (m, 4H), 1.65 – 1.56 (m, 2H), 1.31 (m, 1H), 1.02 (d, *J*= 6.8 Hz, 2H), 0.971 – 0.86 (m, 8H). MS (ESI) *m/z* 840.64 $[M + H]^+$.

Example FC



2-Amino-1-(4-bromo-phenyl)-ethanone hydrochloride

Morpholine-3,4-dicarboxylic acid 4-*tert*-butyl ester

3-[2-(4-Bromo-phenyl)-2-oxo-ethylcarbamoyl]-morpholine-4-carboxylic acid *tert*-butyl ester

3-[5-(4-Bromo-phenyl)-1*H*-imidazol-2-yl]-morpholine-4-carboxylic acid *tert*-butyl ester

(1-{3-[5-(4-Bromo-phenyl)-1*H*-imidazol-2-yl]-morpholine-4-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

(1-{2-[5-(4-Ethynyl-phenyl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

[1-(2-{5-[4-(4-{2-[4-(2-Methoxycarbonylamino-3-methyl-butyryl)-morpholin-3-yl]-3*H*-imidazol-4-yl}-phenylethynyl)-phenyl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester

3-[2-(4-Bromo-phenyl)-2-oxo-ethylcarbamoyl]-morpholine-4-carboxylic acid *tert*-butyl ester: Title compound was prepared according to the method employed to prepare 3-[2-(4-Bromo-phenyl)-2-oxo-ethylcarbamoyl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (Example AE), substituting Morpholine-3,4-dicarboxylic acid 4-*tert*-butyl ester for 2-aza-bicyclo[2.2.1]heptane-2,3-dicarboxylic acid 2-*tert*-butyl ester.

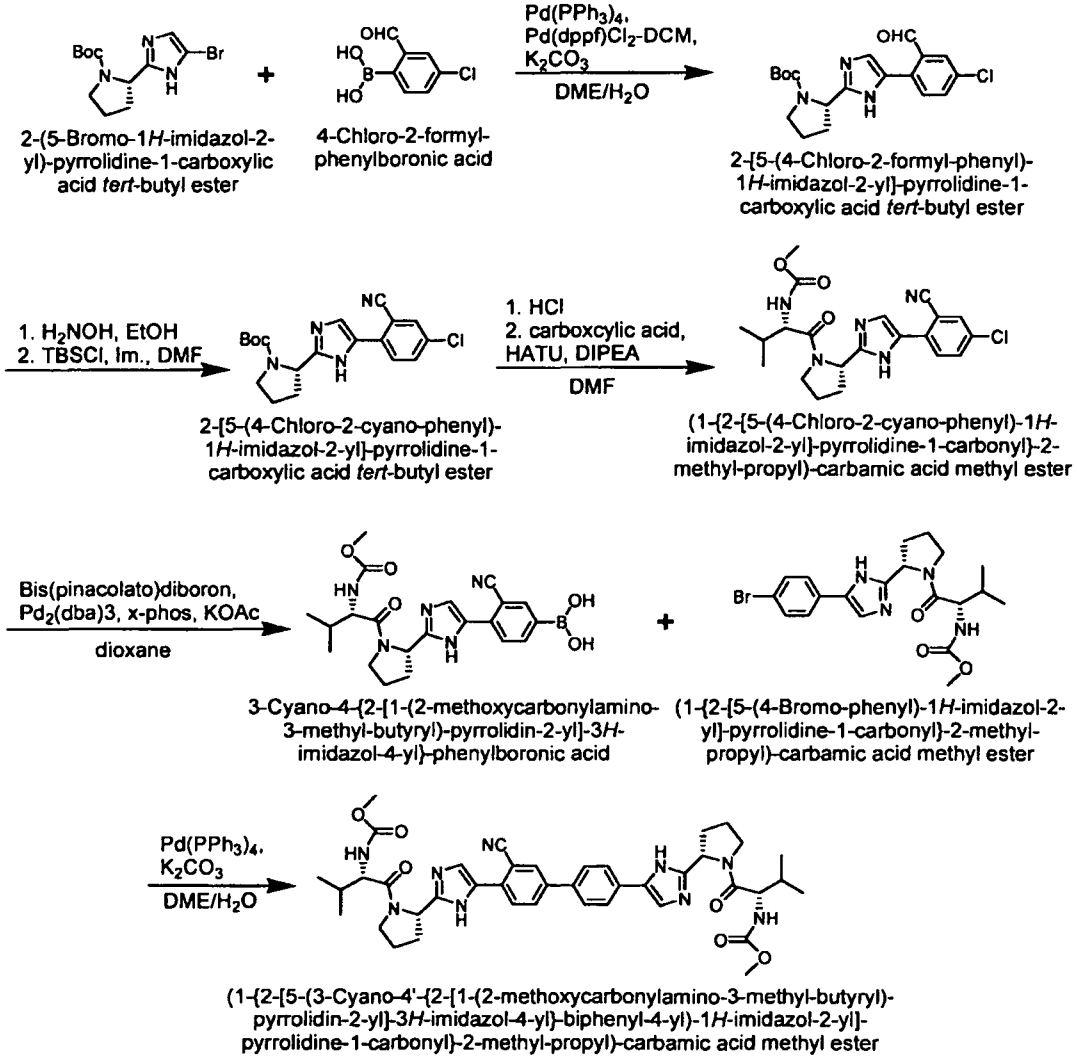
3-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-morpholine-4-carboxylic acid *tert*-butyl ester: Title compound was prepared according to the method employed to prepare 3-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (Example AS), substituting 3-[2-(4-Bromo-phenyl)-2-oxo-ethylcarbamoyl]-morpholine-4-

carboxylic acid *tert*-butyl ester for 3-[2-(4-bromo-phenyl)-2-oxo-ethylcarbamoyl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester.

(1-{3-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-morpholine-4-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: Title compound was prepared according to the method employed to prepare {1-[2-(4'-Bromo-biphenyl-4-ylcarbamoyl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (Example CY), substituting 3-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-morpholine-4-carboxylic acid *tert*-butyl ester for 2-(4'-Bromo-biphenyl-4-ylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester.

[1-(2-{5-[4-(4-{2-[4-(2-Methoxycarbonylamino-3-methyl-butyryl)-morpholin-3-yl]-3H-imidazol-4-yl}-phenylethynyl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: Title compound was prepared according to the method employed to prepare Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-ylethynyl}-phenylethynyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (Example CT), substituting (1-{3-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-morpholine-4-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester for (1-{2-[5-(4-bromo-phenylethynyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester. ^{1}H-NMR: 400 MHz, (DMSO-d_6) δ 12.05 (s, 1H), 11.84 (s, 1H), 7.81 – 7.74 (m, 4H), 7.69 (s, 1H), 7.56 (s, 1H), 7.50 – 7.47 (m, 4H), 7.32 – 7.27 (m, 2H), 4.42 – 4.34 (m, 2H), 4.08 – 3.95 (m, 2H), 3.85 – 3.79 (m, 3H), 3.72 – 3.68 (m, 2H), 3.56 (d, *J*= 7.6 Hz, 5H), 3.46 – 3.40 (m, 2H), 2.2 – 2.07 (m, 3H), 2.01 – 1.90 (m, 4H), 1.02 – 1.00 (d, *J*= 6.4 Hz, 2H), 0.953 – 0.837 (m, 12H); MS (ESI) *m/z* 779 $[M + H]^+$.

Example FD



2-(5-Bromo-1*H*-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester

4-Chloro-2-formyl-phenylboronic acid

2-[5-(4-Chloro-2-formyl-phenyl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester

2-[5-(4-Chloro-2-cyano-phenyl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester

(1-{2-[5-(4-Chloro-2-cyano-phenyl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

3-Cyano-4-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-phenylboronic acid

(1-{2-[5-(4-Bromo-phenyl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

(1-{2-[5-(3-Cyano-4'-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-biphenyl-4-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

2-[5-(4-Chloro-2-formyl-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester: 2-(5-Bromo-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (2.00 g, 6.32 mmol), 4-Chloro-2-formyl-phenylboronic acid (1.17 g, 6.32 mmol), $Pd(PPh_3)_4$ (365 mg, 0.316 mmol), $Pd(dppf)Cl_2$-DCM (258 mg, 0.316 mmol) K_2CO_3 (2 M, 6.3 mL, 12.6 mmol) and DME (30 mL) were combined in a round bottom flask. The stirred suspension was degassed for 10 minutes with bubbling N_2 then heated to 85 °C. After 4 h, the reaction mixture was poured into saturated aqueous $NaHCO_3$. The aqueous phase was extracted 3x with EtOAc and the combined organics were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by silica column chromatography (25% to 75% EtOAc/Hexane) to afford the title compound 2-[5-(4-Chloro-2-formyl-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (1.85 g, 78%).

2-[5-(4-Chloro-2-cyano-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester: 2-[5-(4-Chloro-2-formyl-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (985 mg, 2.62 mmol) was dissolved in ethanol (20 mL) and hydroxylamine (50% w/w in H_2O, 642 μL, 10.48 mmol) was added. After stirring at room temperature for 15 h, the solution was concentrated. To the crude oxime was added TBSCl (474 mg, 3.14 mmol), imidazole (357 mg, 5.24 mmol) and DMF (10 mL). The reaction mixture was stirred at 120 °C for 80 minutes at which point more TBSCl (237 mg, 1.58 mmol) and imidazole (177 mg, 2.60 mmol) were added. The reaction mixture was stirred an additional 17 hours at 120 °C then cooled to room temperature, diluted with EtOAc. The organic phase was washed with saturated aqueous $NaHCO_3$ and brine then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by silica column chromatography (25% to 50% EtOAc/Hexane) to afford the title compound 2-[5-(4-Chloro-2-cyano-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (500 mg, 51%).

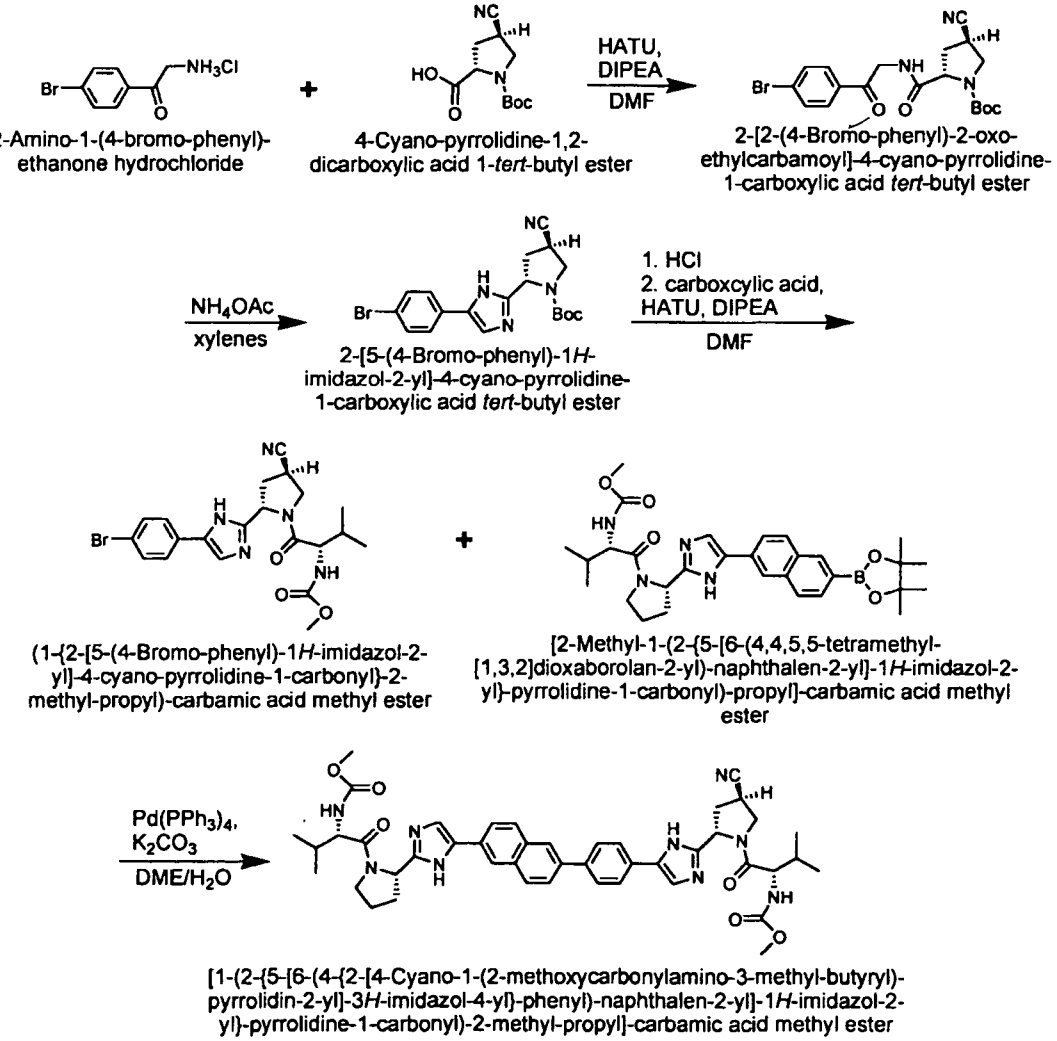
(1-{2-[5-(4-Chloro-2-cyano-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: Title compound was prepared according to the method employed to prepare {1-[2-(4'-Chloro-biphenyl-3-ylcarbamoyl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (Example CX), substituting 2-[5-(4-Chloro-2-cyano-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester for 2-(4'-Chloro-biphenyl-3-ylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester.

3-Cyano-4-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenylboronic acid: Title compound was prepared according to the method employed to prepare 2-{5-[2'-Cyano-4'-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-biphenyl-4-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (Example CZ), substituting (1-{2-[5-(4-Chloro-2-cyano-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester for 2-[5-(4'-Chloro-2'-cyano-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester.

(1-{2-[5-(3-Cyano-4'-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: Title compound was prepared according to the method employed to prepare [1-(2-{5-[6-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-

carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (Example AZ), substituting 3-Cyano-4-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenylboronic acid for [2-methyl-1-(2-{5-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-propyl]-carbamic acid methyl ester. ^{1}H-NMR: 400 MHz, (DMSO-d_6) δ 12.13 (s, 1H), 8.13 – 8.04 (m, 2H), 7.85 – 7.75 (m, 4H), 7.57 (s, 1H), 7.31 (dd, J= 3.6 Hz, 8.4 Hz, 1H), 5.13 – 5.10 (m, 2H); MS (ESI) *m/z* 764 [M + H]$^+$.

Example FE



2-[2-(4-Bromo-phenyl)-2-oxo-ethylcarbamoyl]-4-cyano-pyrrolidine-1-carboxylic acid *tert*-butyl ester: Title compound was prepared according to the method employed to prepare 3-[2-(4-Bromo-phenyl)-2-oxo-ethylcarbamoyl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-

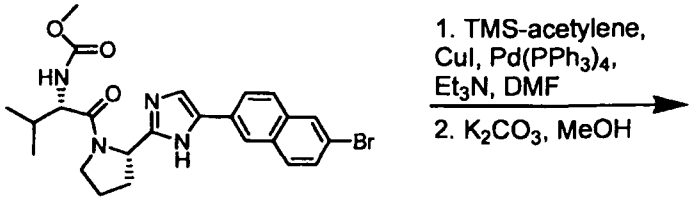
butyl ester (Example AE), substituting 4-Cyano-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester for 2-aza-bicyclo[2.2.1]heptane-2,3-dicarboxylic acid 2-*tert*-butyl ester.

2-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-4-cyano-pyrrolidine-1-carboxylic acid *tert*-butyl ester: Title compound was prepared according to the method employed to prepare 3-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (Example AS), 2-[2-(4-Bromo-phenyl)-2-oxo-ethylcarbamoyl]-4-cyano-pyrrolidine-1-carboxylic acid *tert*-butyl ester for 3-[2-(4-bromo-phenyl)-2-oxo-ethylcarbamoyl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester.

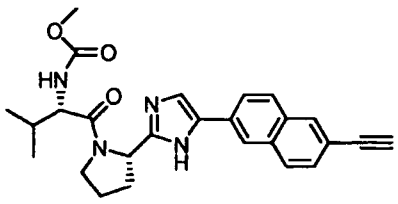
(1-{2-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-4-cyano-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: Title compound was prepared according to the method employed to prepare {1-[2-(4'-Chloro-biphenyl-3-ylcarbamoyl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (Example CX), substituting 2-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-4-cyano-pyrrolidine-1-carboxylic acid *tert*-butyl ester for 2-(4'-Chloro-biphenyl-3-ylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester.

[1-(2-{5-[6-(4-{2-[4-Cyano-1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: Title compound was prepared according to the method employed to prepare [1-(2-{5-[6-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (Example AZ), substituting (1-{2-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-4-cyano-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester for [2-methyl-1-(2-{5-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-propyl]-carbamic acid methyl ester. ^{1}H-NMR: 400 MHz, (DMSO-d_6) δ 11.98 (s, 1H), 11.82 (s, 1H), 8.22 (m, 2H), 7.92 – 7.77 (m, 6H), 7.62 (m, 2H), 7.44 (d, J= 7.6 Hz, 1H), 7.31 (d, J= 8.0, 1H), 5.24 (t, J= 5.2 Hz, 1H), 5.12 (d, J= 4.0, 1H), 4.22 – 4.19 (m, 1H), 4.09 – 4.0 (m, 4H), 3.89 – 3.83 (m, 4H), 3.56 (d, J= 5.6 Hz, 6H), 2.17 (brs, 2H), 2.06 – 1.90 (m, 4H), 0.95 – 0.84 (m, 14H); MS (ESI) *m/z* 814 $[M + H]^+$.

Example FF

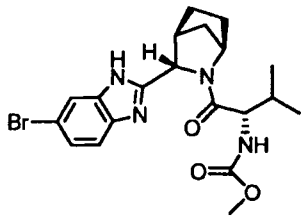


(1-{2-[5-(6-Bromo-naphthalen-2-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

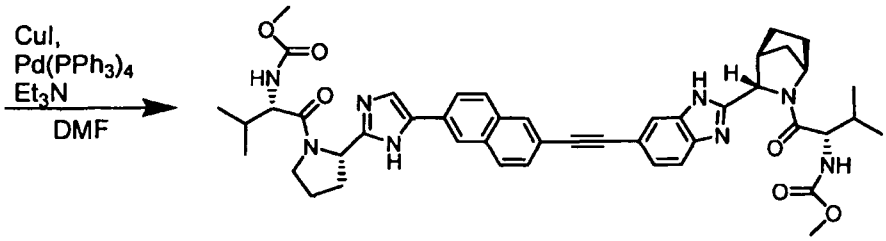


(1-{2-[5-(6-Ethynyl-naphthalen-2-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

+



{1-[3-(6-Bromo-1*H*-benzoimidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester



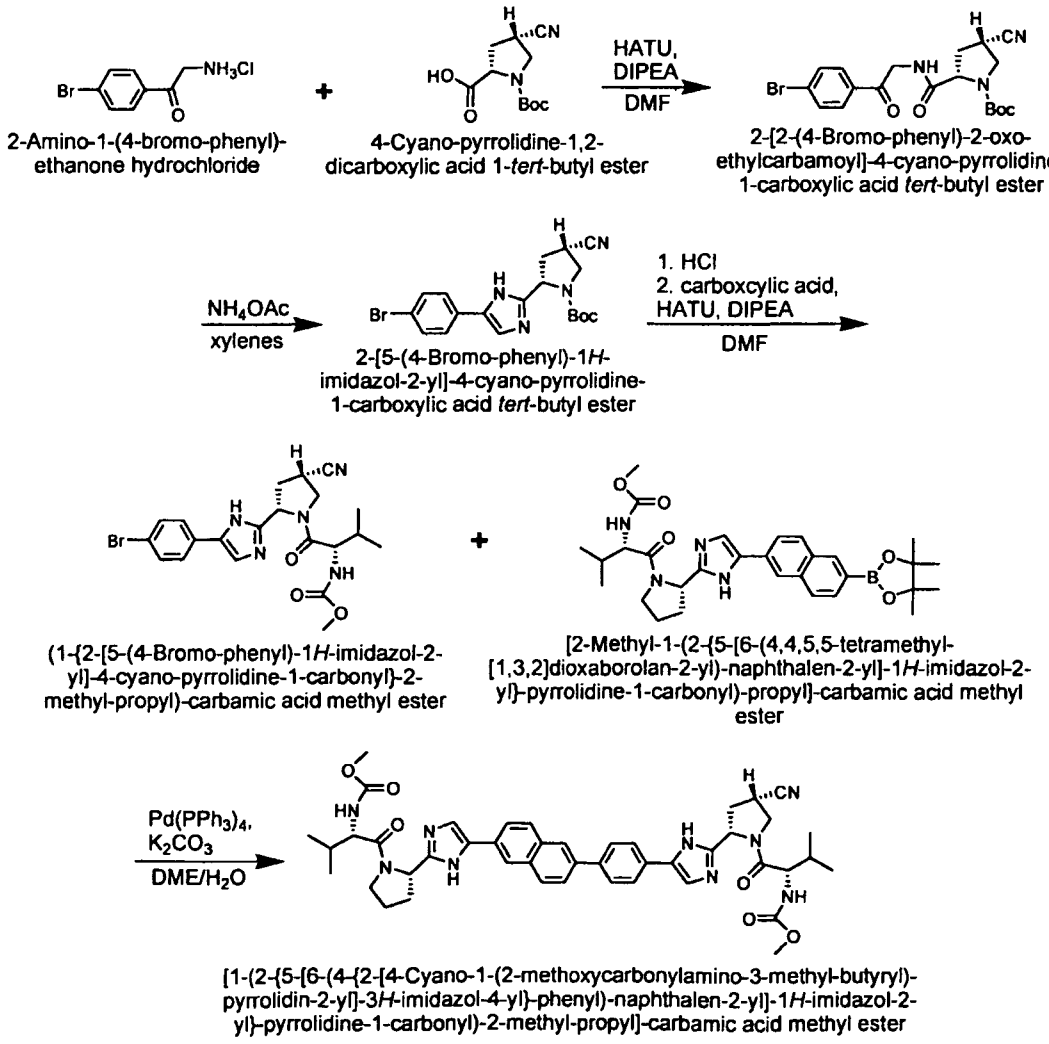
(1-{2-[5-(6-{2-[2-(2-Methoxycarbonylamino-3-methyl-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3*H*-benzoimidazol-5-ylethynyl}-naphthalen-2-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

(1-{2-[5-(6-Ethynyl-naphthalen-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: Title compound was prepared according to the method employed to prepare (1-{2-[5-(4-Ethynyl-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester from (1-{2-[5-(4-bromo-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (Example AY), substituting (1-{2-[5-(6-Bromo-naphthalen-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester for (1-{2-[5-(4-bromo-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester.

(1-{2-[5-(6-{2-[2-(2-Methoxycarbonylamino-3-methyl-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-benzoimidazol-5-ylethynyl}-naphthalen-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: Title compound was prepared

according to the method employed to prepare Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-ylethynyl}-phenylethynyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (Example CT), substituting {1-[3-(6-Bromo-1H-benzoimidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester for (1-{2-[5-(4-bromo-phenylethynyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester and (1-{2-[5-(6-Ethynyl-naphthalen-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester for {1-[2-(5-Ethynyl-1H-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester. NMR (MeOH-d4, 400 MHz) δ: 8.19-8.11 (m, 1H), 8.01-7.99 (m, 1H), 7.86-7.71 (m, 3H), 7.57-7.39 (m, 3H), 7.02-6.99 (m, 1H); MS (ESI) *m/z* 813 $[M + H]^+$.

Example FG



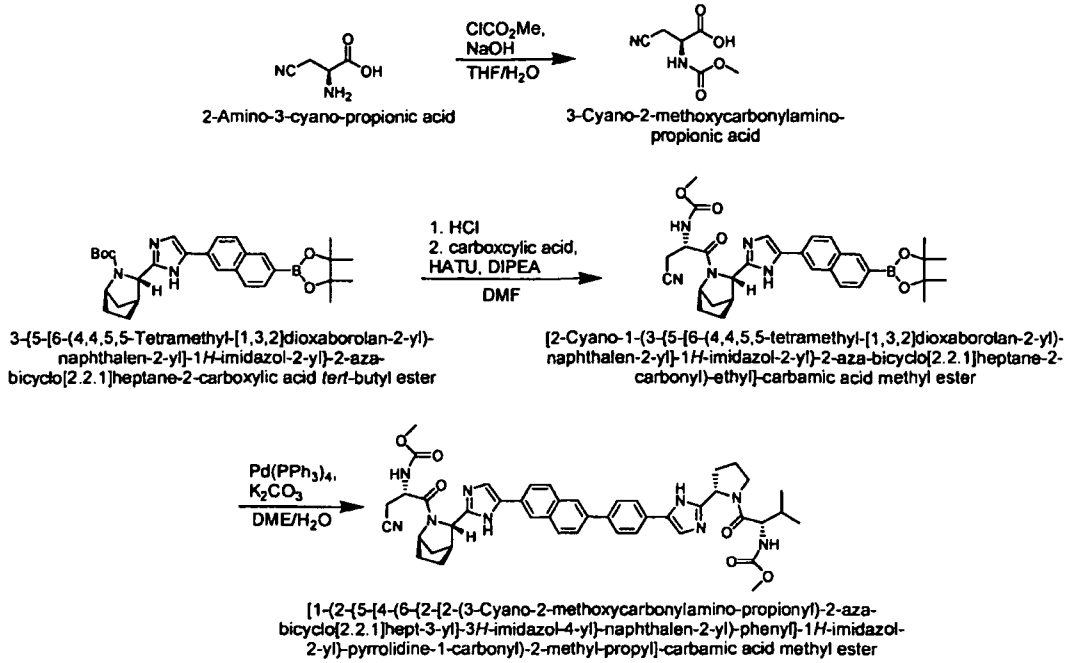
2-[2-(4-Bromo-phenyl)-2-oxo-ethylcarbamoyl]-4-cyano-pyrrolidine-1-carboxylic acid *tert*-butyl ester: Title compound was prepared according to the method employed to prepare 3-[2-(4-Bromo-phenyl)-2-oxo-ethylcarbamoyl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (Example AE), substituting 4-Cyano-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester for 2-aza-bicyclo[2.2.1]heptane-2,3-dicarboxylic acid 2-*tert*-butyl ester.

2-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-4-cyano-pyrrolidine-1-carboxylic acid *tert*-butyl ester: Title compound was prepared according to the method employed to prepare 3-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (Example AS), and substituting 2-[2-(4-Bromo-phenyl)-2-oxo-ethylcarbamoyl]-4-cyano-pyrrolidine-1-carboxylic acid *tert*-butyl ester for 3-[2-(4-bromo-phenyl)-2-oxo-ethylcarbamoyl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester.

(1-{2-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-4-cyano-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: Title compound was prepared according to the method employed to prepare {1-[2-(4'-Chloro-biphenyl-3-ylcarbamoyl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (Example CX), substituting 2-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-4-cyano-pyrrolidine-1-carboxylic acid *tert*-butyl ester for 2-(4'-Chloro-biphenyl-3-ylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester.

[1-(2-{5-[6-(4-{2-[4-Cyano-1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: Title compound was prepared according to the method employed to prepare [1-(2-{5-[6-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (Example AZ), substituting (1-{2-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-4-cyano-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester for [2-methyl-1-(2-{5-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-propyl]-carbamic acid methyl ester. NMR (MeOH-d4, 400 MHz) δ: 8.12-8.03 (m, 2H), 7.89-7.74 (m, 6H), 7.48-7.36 (m, 2H), 5.20 (m, 2H), 4.60 (m, 1H), 4.28-3.88 (m, 6H), 3.66 (s, 6H), 2.86 (m, 1H), 2.60 (m, 1H), 2.40-2.19 (m, 3H), 2.11-1.97 (m, 3H), 1.00-0.88 (m, 12H); MS (ESI) *m/z* 814 $[M + H]^+$.

Example FH



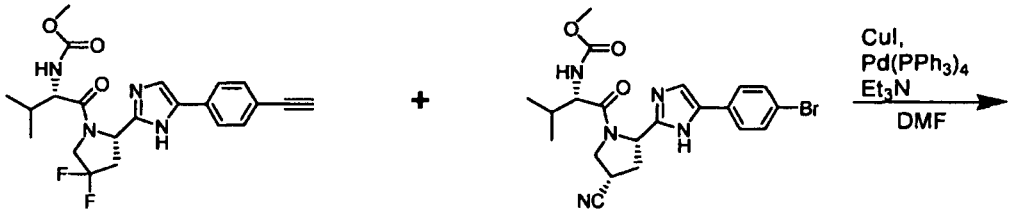
3-Cyano-2-methoxycarbonylamino-propionic acid: Methyl chloroformate (0.81 mL, 10.51 mmol) was added dropwise to a stirred suspension of 2-Amino-3-cyano-propionic acid (1.00g, 8.76 mmol) and NaOH (5 N in H_2O, 4.2 mL, 21.0 mmol) in THF (20 mL). After stirring at room temperature for 7h, the reaction mixture was poured into 10% HCl and the aqueous phase was extracted 3x with diethyl ether. The combined organics were dried over $MgSO_4$, filtered and concentrated to afford 3-Cyano-2-methoxycarbonylamino-propionic acid (295 mg, 20%).

[2-Cyano-1-(3-{5-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-yl]-1H-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carbonyl)-ethyl]-carbamic acid methyl ester: Title compound was prepared according to the method employed to prepare {1-[2-(4'-Chloro-biphenyl-3-ylcarbamoyl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (Example CX), substituting 3-{5-[6-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-yl]-1H-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester for 2-(4'-Chloro-biphenyl-3-ylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester and 3-Cyano-2-methoxycarbonylamino-propionic acid for 2-methoxycarbonylamino-3-methyl-butyric acid.

[1-(2-{5-[4-(6-{2-[2-(3-Cyano-2-methoxycarbonylamino-propionyl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: Title compound was prepared according to the method employed to prepare [1-(2-{5-[6-(4-{2-[1-(2-

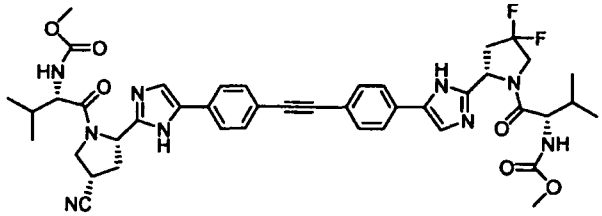
Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (Example AZ), substituting [2-Cyano-1-(3-{5-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-yl]-1H-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carbonyl)-ethyl]-carbamic acid methyl ester for [2-methyl-1-(2-{5-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-propyl]-carbamic acid methyl ester. ^{1}H NMR (DMSO-d6, 400 MHz) δ: 8.24-8.18 (m, 2H), 7.99-7.79 (m, 6H), 7.63-7.54 (m, 2H), 5.09 (m, 1H), 4.84 (m, 1H), 4.53 (s, 1H), 4.41 (s, 1H), 4.07 (m, 1H), 3.82 (m, 2H), 3.62 (s, 3H), 3.54 (s, 3H), 2.92-2.87 (m, 1H), 2.79-2.75 (m, 1H), 2.72-2.67 (m, 1H), 2.16-1.42 (m, 9H), 0.91-0.87 (m, 12H); MS (ESI) *m/z* 812 $[M + H]^+$.

Example FI



(1-{2-[5-(4-Ethynyl-phenyl)-1*H*-imidazol-2-yl]-4,4-difluoro-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

(1-{2-[5-(4-Bromo-phenyl)-1*H*-imidazol-2-yl]-4-cyano-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

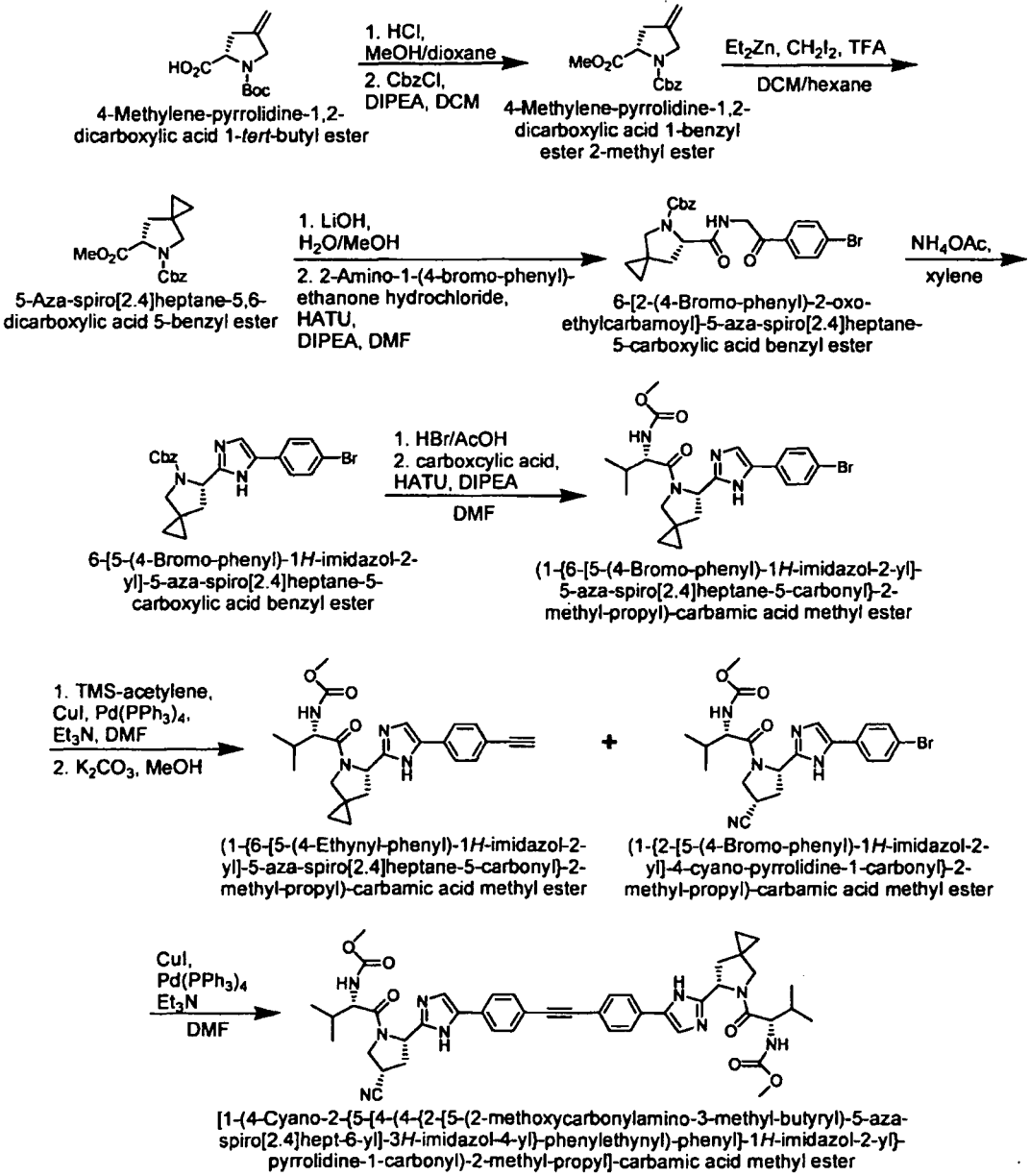


[1-(4-Cyano-2-{5-[4-(4-{2-[4,4-difluoro-1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-phenylethynyl)-phenyl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester

[1-(4-Cyano-2-{5-[4-(4-{2-[4,4-difluoro-1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenylethynyl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: Title compound was prepared according to the method employed to prepare [1-(2-{5-[4-(4-{2-[4,4-Difluoro-1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenylethynyl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (Example AB1) substituting (1-{2-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-4-cyano-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester for (1-{2-[5-(4-bromo-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl

ester (400 mg, 0.89 mmol), and (1-{2-[5-(4-ethynyl-phenyl)-1H-imidazol-2-yl]-4,4-difluoro-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester for (1-{2-[5-(4-ethynyl-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester. ^{1}H NMR (MeOH-d4, 400 MHz) δ: 7.71-7.61 (m, 4H) 7.46-7.34 (m, 4H), 5.30 (m, 1H), 5.14 (m, 1H), 4.55-4.45 (m, 2H), 4.20-3.94 (m, 5H), 3.61 (s, 6H), 3.47-3.40 (m, 2H), 2.84-2.76 (m, 3H), 2.52 (m, 1H), 1.96-1.91 (m, 2H), 0.96-0.83 (m, 12H); MS (ESI) *m/z* 824 $[M + H]^+$.

Example FJ



4-Methylene-pyrrolidine-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester: 4-Methylene-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester (12.00 g, 52.80 mmol) was dissolved in MeOH (200 mL) and treated with 4.0 M HCl/dioxane (50 mL). After stirring for 3.5 hours at room temperature, the reaction mixture was concentrated under reduced pressure. The crude residue was dissolved in DCM (200 mL) and treated with DIPEA (22 mL, 127 mmol) and BnOCOCl (9.64 mL, 63.4 mmol). After stirring for 1 hours at room temperature, the reaction mixture was poured into H_2O. The aqueous layer was extracted 3x with DCM. The combined organics were dried over $MgSO_4$, filtered and concentrated. The residue was purified by silica column chromatography (10% to 25% EtOAc/hexane) to provide 4-Methylene-pyrrolidine-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (8.20 g, 56%).

5-Aza-spiro[2.4]heptane-5,6-dicarboxylic acid 5-benzyl ester: Diethyl zinc (1.0 M in hexane (118 mL, 118 mmol) was added to a 3-neck round bottom flask containing a stir bar, DCM (120 mL) and equipped with an addition funnel and an Argon inlet adaptor. The solution was cooled to 0 °C before TFA (9.5 mL, 118 mmol) in DCM (40 mL) was added dropwise by addition funnel over 22 minutes. 20 minutes after completion of the addition, CH_2I_2 was added slowly over 4 minutes. 20 minutes after completion of addition, 4-Methylene-pyrrolidine-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (8.10 g, 29.4 mmol) in DCM (30 mL) was added by cannula followed by a rinse with DCM (10 mL). 10 minutes later, the reaction mixture was warmed to room temperature and stirred for 110 hours. The reaction was quenched by addition of 100 mL saturated aqueous NH_4Cl. The entire contents of the flask were poured into saturated aqueous $NaHCO_3$ and the aqueous phase was extracted 3x with EtOAc. The combined organics were dried over $MgSO_4$, filtered and concentrated. The residue was dissolved in THF (100 mL), acetone (33 mL) and H_2O (33 mL) and *N*-methylmorpholine-*N*-oxide (3.45 g, 29.41 mmol) and osmium tetroxide (4 wt% in H_2O, 5 mL, 0.818 mmol) were added sequentially. The reaction mixture was stirred 7 hours at room temperature then quenched with 100 mL saturated aqueous $Na_2S_2O_3$. The entire contents of the flask was poured into H_2O and the aqueous layer was extracted 3x with DCM. The combined organics were dried over $MgSO_4$, filtered and concentrated. The resulting residue was purified by silica column chromatography (10% to 25% EtOAc/hexane) to provide 5-Aza-spiro[2.4]heptane-5,6-dicarboxylic acid 5-benzyl ester (5.54 g, 65%).

6-[2-(4-Bromo-phenyl)-2-oxo-ethylcarbamoyl]-5-aza-spiro[2.4]heptane-5-carboxylic acid benzyl ester: 5-Aza-spiro[2.4]heptane-5,6-dicarboxylic acid 5-benzyl ester (361 mg, 1.25 mmol) was dissolved in MeOH (10 mL) and LiOH (1 M in H_2O, 5 mL, 5 mmol) was added.

After stirring for 15 hours at room temperature, the reaction mixture was poured into 10% HCl and the aqueous phase was extracted 3x with DCM. The combined organics were dried over $MgSO_4$, filtered and concentrated. The residue was treated with 2-Amino-1-(4-bromo-phenyl)-ethanone hydrochloride (344 mg, 1.38 mmol), HATU (525 mg, 1.38 mmol) and DMF (14 mL). The suspension was stirred at 0 °C for 21 minutes before DIPEA (0.72 mL, 4.1 mmol) was added dropwise. Immediately after addition, the reaction mixture was warmed to room temperature. 40 minutes later the mixture was diluted with EtOAc. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, then dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by silica column chromatography (30% to 50% EtOAc/hexane) to afford 6-[2-(4-Bromo-phenyl)-2-oxo-ethylcarbamoyl]-5-aza-spiro[2.4]heptane-5-carboxylic acid benzyl ester (589 mg, 100%).

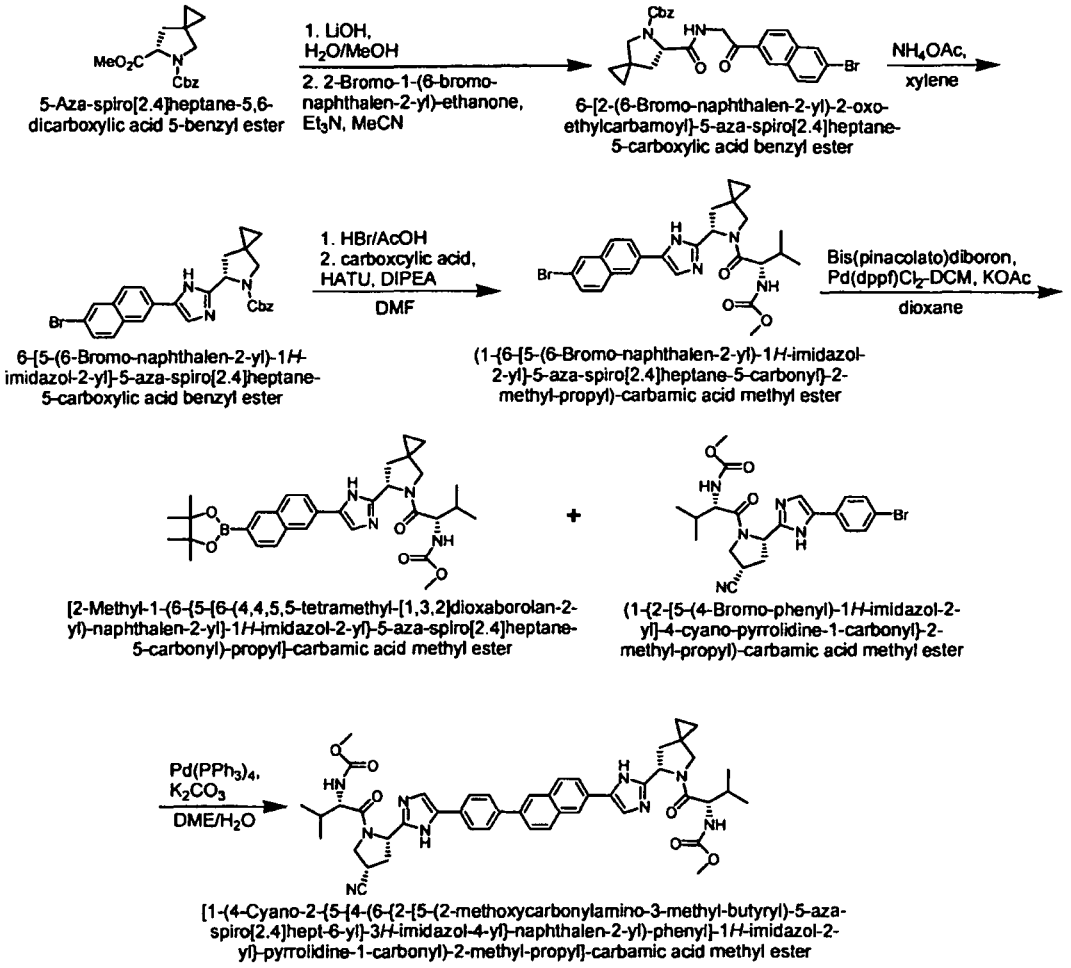
6-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carboxylic acid benzyl ester: Title compound was prepared according to the method employed to prepare 3-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (Example AS), substituting 6-[2-(4-Bromo-phenyl)-2-oxo-ethylcarbamoyl]-5-aza-spiro[2.4]heptane-5-carboxylic acid benzyl ester for 3-[2-(4-bromo-phenyl)-2-oxo-ethylcarbamoyl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester.

(1-{6-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: 6-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carboxylic acid benzyl ester (478 mg, 1.04 mmol) was treated with DCM (5 mL) then HBr (33 wt% in AcOH, 5 mL). The mixture was stirred for 160 minutes at room temperature, concentrated under reduced pressure then coevaporated 2x with toluene to remove excess AcOH. The crude residue was treated with 2-Methoxycarbonylamino-3-methyl-butyric acid (274 mg, 1.56 mmol), HATU (435 mg, 1.14 mmol) and DMF (10 mL). The stirred mixture was cooled to 0 °C and DIPEA (0.91 mL, 5.2 mmol) was added before the warming to room temperature. After 1h, the reaction mixture was diluted with EtOAc and washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated and the crude residue was purified by silica column chromatography (75% to 100% EtOAc/hexane) to yield (1-{6-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (297 mg, 60%).

(1-{6-[5-(4-Ethynyl-phenyl)-1H-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: Title compound was prepared according to the method employed to prepare (1-{2-[5-(4-Ethynyl-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester from (1-{2-[5-(4-bromo-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (Example AY), substituting (1-{6-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester for (1-{2-[5-(4-bromo-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester.

[1-(4-Cyano-2-{5-[4-(4-{2-[5-(2-methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3H-imidazol-4-yl}-phenylethynyl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: Title compound was prepared according to the method employed to prepare [1-(2-{5-[4-(4-{2-[4,4-Difluoro-1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenylethynyl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (Example AB1) , substituting (1-{2-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-4-cyano-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester for (1-{2-[5-(4-bromo-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (400 mg, 0.89 mmol), and (1-{6-[5-(4-Ethynyl-phenyl)-1H-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester for (1-{2-[5-(4-Ethynyl-phenyl)-1H-imidazol-2-yl]-4,4-difluoro-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester. ^{1}H NMR (MeOH-d4, 400 MHz) δ: 7.78-7.66 (m, 4H), 7.52-7.37 (m, 4H), 5.29 (m, 1H), 5.17 (m, 1H), 4.59 (m, 1H), 4.17-4.09 (m, 3H), 4.01 (m, 1H), 3.93-3.80 (m, 2H), 3.65 (s, 6H), 3.50-3.42 (m, 2H), 2.88-2.81 (m, 1H), 2.66-2.52 (m, 2H), 2.36-2.31 (m, 1H), 2.18-2.13 (m, 1H), 2.05-1.94 (m, 3H), 1.01-0.87 (m, 12H), 0.82-0.63 (m, 4H); MS (ESI) *m/z* 814 $[M + H]^+$.

Example FK



6-[2-(6-Bromo-naphthalen-2-yl)-2-oxo-ethylcarbamoyl]-5-aza-spiro[2.4]heptane-5-carboxylic acid benzyl ester: 5-Aza-spiro[2.4]heptane-5,6-dicarboxylic acid 5-benzyl ester (2.217 g, 7.66 mmol) was dissolved in MeOH (30 mL) and LiOH (1 M in H_2O, 15 mL, 15 mmol) was added. After stirring for 15 hours at room temperature, the reaction mixture was poured into 10% HCl and the aqueous phase was extracted 3x with DCM. The combined organics were dried over $MgSO_4$, filtered and concentrated. The residue was treated with MeCN (40 mL), Et_3N (1.2 mL, 8.4 mmol) and 2-Bromo-1-(6-bromo-naphthalen-2-yl)-ethanone and the mixture was stirred at room temperature for 20 hours before being filtered over CELITE and concentrated. The resulting oil was dissolved in the minimum amount of DCM and EtOAc (30 mL) was added causing the product to precipitate. The mixture was cooled to 0 °C then the solid was filtered off and rinsed with EtOAc giving clean product (4.00g, 100%).

6-[5-(6-Bromo-naphthalen-2-yl)-1H-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carboxylic acid benzyl ester: Title compound was prepared according to the method employed to prepare

3-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (Example AS), substituting 6-[2-(6-Bromo-naphthalen-2-yl)-2-oxo-ethylcarbamoyl]-5-aza-spiro[2.4]heptane-5-carboxylic acid benzyl ester for 3-[2-(4-bromo-phenyl)-2-oxo-ethylcarbamoyl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester.

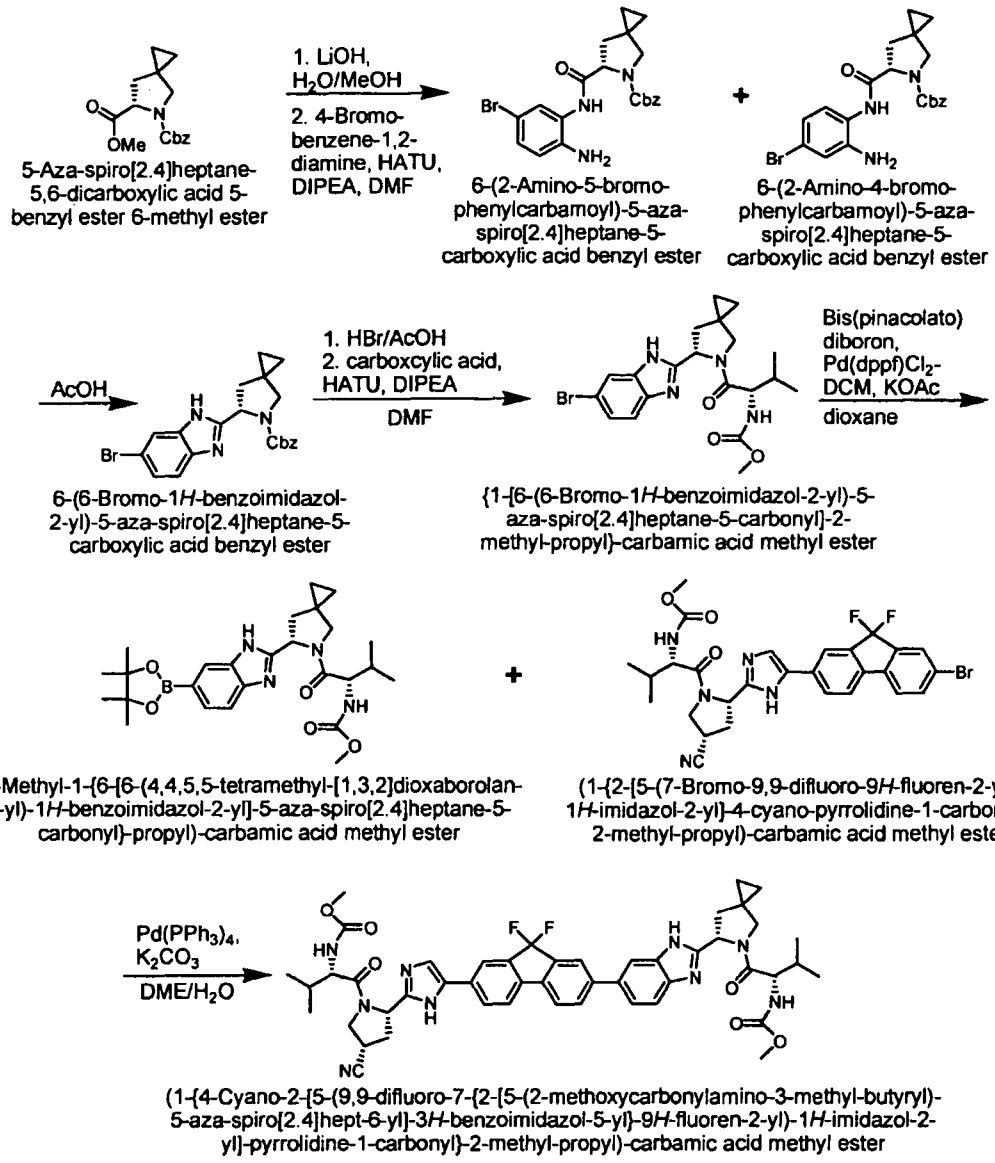
(1-{6-[5-(6-Bromo-naphthalen-2-yl)-1H-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: Title compound was prepared according to the method employed to prepare (1-{6-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester, substituting 6-[5-(6-Bromo-naphthalen-2-yl)-1H-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carboxylic acid benzyl ester for 6-[2-(4-Bromo-phenyl)-2-oxo-ethylcarbamoyl]-5-aza-spiro[2.4]heptane-5-carboxylic acid benzyl ester according to example FJ.

[2-Methyl-1-(6-{5-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-yl]-1H-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carbonyl)-propyl]-carbamic acid methyl ester: Title compound was prepared according to the method employed to prepare Methyl-1-{2-[4'-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-biphenyl-4-ylcarbamoyl]-pyrrolidine-1-carbonyl}-propyl)-carbamic acid methyl ester (Example CY), substituting (1-{6-[5-(6-Bromo-naphthalen-2-yl)-1H-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester for {1-[2-(4'-Bromo-biphenyl-4-ylcarbamoyl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester.

[1-(4-Cyano-2-{5-[4-(6-{2-[5-(2-methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: Title compound was prepared according to the method employed to prepare [1-(2-{5-[6-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (Example AZ), substituting (1-{2-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-4-cyano-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester for (1-{2-[5-(4-bromo-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester and [2-Methyl-1-(6-{5-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-yl]-1H-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carbonyl)-propyl]-carbamic acid methyl ester for [2-methyl-1-(2-{5-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-propyl]-carbamic acid methyl

ester. ^{1}H NMR (DMSO-d6, 400 MHz) δ: 8.20-8.10 (m, 2H), 7.90-7.68 (m, 6H), 7.60-7.55 (m, 2H), 7.33-7.30 (m, 2H), 5.18 (m, 1H), 5.07 (m, 1H), 4.44 (m, 1H), 4.04-3.69 (m, 6H), 3.40-3.38 (m, 1H), 3.30 (s, 6H), 2.71 (m, 1H), 2.40-1.90 (m, 5H), 0.90-0.79 (m, 12H), 0.70-0.54 (m, 4H); MS (ESI) *m/z* 841 $[M + H]^+$.

Example DL



6-(2-Amino-5-bromo-phenylcarbamoyl)-5-aza-spiro[2.4]heptane-5-carboxylic acid benzyl ester and 6-(2-Amino-4-bromo-phenylcarbamoyl)-5-aza-spiro[2.4]heptane-5-carboxylic acid benzyl ester: 5-Aza-spiro[2.4]heptane-5,6-dicarboxylic acid 5-benzyl ester 6 methyl ester (987 mg, 3.41 mmol) was dissolved in EtOH (10 mL) and LiOH (1 M in H_2O, 5 mL, 5 mmol) was added. After stirring for 2 hours at 50 °C, the reaction mixture was poured into 10% HCl and the aqueous phase was extracted 3x with DCM. The combined organics were dried over

$MgSO_4$, filtered and concentrated. The residue was treated with 4-Bromo-benzene-1,2-diamine (1.60 g, 8.53 mmol), HATU (1.43 g, 3.75 mmol) and DMF (17 mL) then cooled to 0 °C. DIPEA (0.712 mL, 4.09 mmol) was added and the reaction mixture was allowed to warm to room temperature slowly overnight. The reaction mixture was then diluted with EtOAc and the organic layer was washed with saturated aqueous $NaHCO_3$ and brine then dried over $MgSO_4$, filtered and concentrated. The crude material was purified by silica column chromatography to afford a mixture of 6-(2-Amino-5-bromo-phenylcarbamoyl)-5-aza-spiro[2.4]heptane-5-carboxylic acid benzyl ester and 6-(2-Amino-4-bromo-phenylcarbamoyl)-5-aza-spiro[2.4]heptane-5-carboxylic acid benzyl ester (1.47 g, 97%).

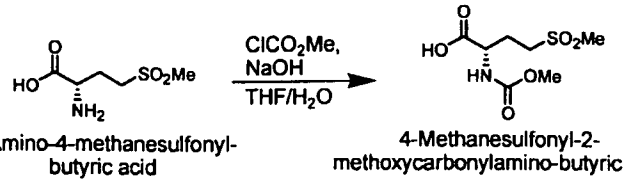
6-(6-Bromo-1H-benzoimidazol-2-yl)-5-aza-spiro[2.4]heptane-5-carboxylic acid benzyl ester: A mixture of 6-(2-Amino-5-bromo-phenylcarbamoyl)-5-aza-spiro[2.4]heptane-5-carboxylic acid benzyl ester and 6-(2-Amino-4-bromo-phenylcarbamoyl)-5-aza-spiro[2.4]heptane-5-carboxylic acid benzyl ester (1.446 g, 3.25 mmol) was dissolved in AcOH (20 mL) and the reaction mixture was stirred at 40 °C for 18 hours then concentrated under reduced pressure. The residue was dissolved in EtOAc and washed with saturated aqueous $NaHCO_3$. The aqueous layer was extracted 2x with EtOAc and the combined organics were dried over $MgSO_4$, filtered and concentrated to provide 6-(6-Bromo-1H-benzoimidazol-2-yl)-5-aza-spiro[2.4]heptane-5-carboxylic acid benzyl ester (1.385 g, 100%).

{1-[6-(6-Bromo-1H-benzoimidazol-2-yl)-5-aza-spiro[2.4]heptane-5-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester: 6-(6-Bromo-1H-benzoimidazol-2-yl)-5-aza-spiro[2.4]heptane-5-carboxylic acid benzyl ester (301 mg, 0.706 mmol) was dissolved in DCM (10 mL) and HBr (33 wt% in AcOH, 5 mL) was added. After 2h the reaction mixture was concentrated and placed under hi-vac. The residue was co-evaporated with PhMe, MeOH, then again with PhMe and MeOH and placed under hi-vac. The residue was treated with 2-Methoxycarbonylamino-3-methyl-butyric acid (130 mg, 0.741 mmol, HATU (282 mg, 0.741 mmol) and DMF (7 mL). The reaction mixture was cooled to 0 °C then DIPEA (0.615 mL, 3.53 mmol) was added before warming to room temperature. After 30 minutes, the reaction mixture was diluted with EtOAc and the organic phase was washed with saturated aqueous $NaHCO_3$ and brine, then dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by silica column chromatography (50% to 80% EtOAc/hexane) to afford {1-[6-(6-Bromo-1H-benzoimidazol-2-yl)-5-aza-spiro[2.4]heptane-5-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (238 mg, 75%).

(2-Methyl-1-{6-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-benzoimidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carbonyl}-propyl)-carbamic acid methyl ester: Title compound was prepared according to the method employed to prepare Methyl-1-{2-[4'-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-biphenyl-4-ylcarbamoyl]-pyrrolidine-1-carbonyl}-propyl)-carbamic acid methyl ester (Example CY), substituting {1-[6-(6-Bromo-1H-benzoimidazol-2-yl)-5-aza-spiro[2.4]heptane-5-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester for {1-[2-(4'-Bromo-biphenyl-4-ylcarbamoyl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester.

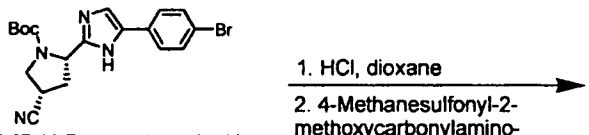
(1-{4-Cyano-2-[5-(9,9-difluoro-7-{2-[5-(2-methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3H-benzoimidazol-5-yl}-9H-fluoren-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: Title compound was prepared according to the method employed to prepare [1-(2-{5-[6-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (Example AZ), substituting (1-{2-[5-(7-Bromo-9,9-difluoro-9H-fluoren-2-yl)-1H-imidazol-2-yl]-4-cyano-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester for (1-{2-[5-(4-bromo-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester and (2-Methyl-1-{6-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-benzoimidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carbonyl}-propyl)-carbamic acid methyl ester for [2-methyl-1-(2-{5-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-propyl]-carbamic acid methyl ester. ^{1}H NMR (DMSO-d6, 400 MHz) δ: 8.07-7.55 (m, 9H), 7.34 (m, 2H), 5.31 (m, 1H), 5.11 (m, 1H), 4.45 (m, 1H), 4.08-3.87 (m, 6H), 3.63-3.54 (m, 9H), 3.41-3.28 (m, 4H), 2.73 (m, 1H), 2.40-2.25 (m, 2H), 2.15-2.13 (m, 1H), 1.95 (m, 3H), 0.93-0.83 (m, 12H), 0.74-0.57 (m, 4H); MS (ESI) *m/z* 889 [M + H]$^+$.

Example FM

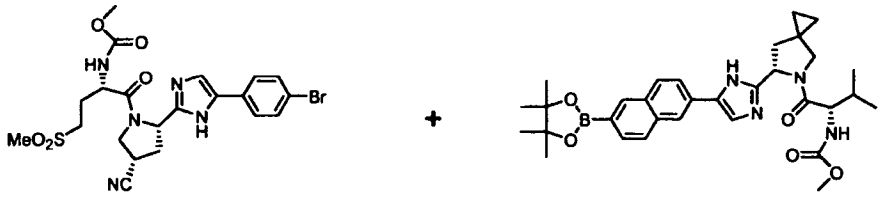


2-Amino-4-methanesulfonyl-butyric acid

4-Methanesulfonyl-2-methoxycarbonylamino-butyric acid

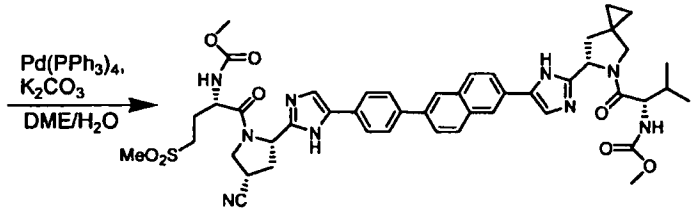


2-[5-(4-Bromo-phenyl)-1*H*-imidazol-2-yl]-4-cyano-pyrrolidine-1-carboxylic acid *tert*-butyl ester



(1-{2-[5-(4-Bromo-phenyl)-1*H*-imidazol-2-yl]-4-cyano-pyrrolidine-1-carbonyl}-3-methanesulfonyl-propyl)-carbamic acid methyl ester

[2-Methyl-1-(6-{5-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-yl]-1*H*-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carbonyl)-propyl]-carbamic acid methyl ester



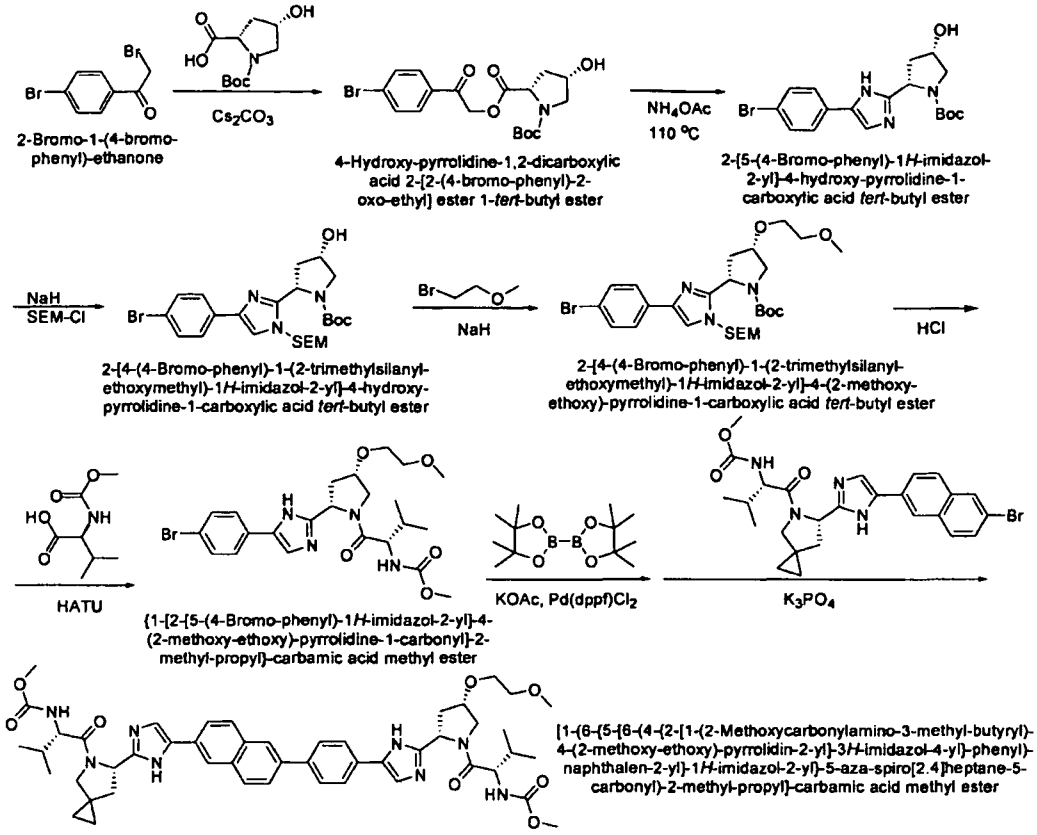
[1-(6-{5-[6-(4-{2-[4-Cyano-1-(4-methanesulfonyl-2-methoxycarbonylamino-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1*H*-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester

4-Methanesulfonyl-2-methoxycarbonylamino-butyric acid: Methyl chloroformate (2.6 mL, 33 mmol) was added dropwise to a stirred suspension of 2-Amino-4-methanesulfonyl-butyric acid (5.03 g, 27.8 mmol) and NaOH (5 N in H_2O, 13.3 mL, 66.6 mmol) in THF (50 mL). After stirring at room temperature for 9h, additional methyl chloroformate (5.2 mL, 66.6 mmol) and NaOH (5 N in H_2O, 30 mL, 150 mmol) were added. After another 14 h, the reaction mixture was poured into H_2O. The aqueous phase was washed with DCM 2x then acidified to pH 1 with 10% HCl. The acidified aqueous phase was extracted 3x with EtOAc. The combined organics were dried over $MgSO_4$, filtered and concentrated to provide 4-Methanesulfonyl-2-methoxycarbonylamino-butyric acid (970 mg, 15%).

(1-{2-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-4-cyano-pyrrolidine-1-carbonyl}-3-methanesulfonyl-propyl)-carbamic acid methyl ester: Title compound was prepared according to the method employed to prepare {1-[2-(4'-Chloro-biphenyl-3-ylcarbamoyl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (Example CX), substituting 2-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-4-cyano-pyrrolidine-1-carboxylic acid *tert*-butyl ester for 2-(4'-Chloro-biphenyl-3-ylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester and 4-Methanesulfonyl-2-methoxycarbonylamino-butyric acid for 2-methoxycarbonylamino-3-methyl-butyric acid.

[1-(6-{5-[6-(4-{2-[4-Cyano-1-(4-methanesulfonyl-2-methoxycarbonylamino-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: Title compound was prepared according to the method employed to prepare [1-(2-{5-[6-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (Example AZ), substituting (1-{2-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-4-cyano-pyrrolidine-1-carbonyl}-3-methanesulfonyl-propyl)-carbamic acid methyl ester for (1-{2-[5-(4-bromo-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester and [2-Methyl-1-(6-{5-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-yl]-1H-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carbonyl)-propyl]-carbamic acid methyl ester for [2-methyl-1-(2-{5-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-propyl]-carbamic acid methyl ester. ^{1}H NMR (MeOH-d4, 400 MHz) δ: 8.09-8.07 (m, 2H), 7.92-7.22 (m, 8H), 7.42-7.38 (m, 2H), 5.33 (t, J = 7.5 Hz, 1H), 5.21 (t, J = 8.0 Hz, 1H), 4.65 (m, 1H), 4.49 (m, 1H), 4.17-4.11 (m, 2H), 3.95 (d, J = 9.6 Hz, 1H), 3.83 (d, J = 10.2 Hz, 1H), 3.66 (s, 6H), 3.55-3.49 (m, 3H), 3.19-3.15 (m, 3H), 2.94 (s, 3H), 2.89-2.03 (m, 10 H), 1.03-0.64 (m, 14H); MS (ESI) *m/z* 904 [M + H]$^+$.

Example FN



4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 2-[2-(4-bromo-phenyl)-2-oxo-ethyl] ester 1-*tert*-butyl ester: 4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester (5.0 g) was dissolved in methanol (87 mL), and Cs_2CO_3 (3.5 g) in water (56 mL) was added. The mixture was stirred over 10 min. and evaporated under vacuum. The solid was dissolved in DMF (100 mL), and 2-bromo-1-(4-bromo-phenyl)-ethanone (6.0 g) was added. Reaction mixture was stirred over 3 hours and evaporated under vacuum. The crude solid was used for the next step.

2-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-4-hydroxy-pyrrolidine-1-carboxylic acid *tert*-butyl ester: The crude 4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 2-[2-(4-bromo-phenyl)-2-oxo-ethyl] ester 1-*tert*-butyl ester (10.8 g) and ammonium acetate (13.3 g) were suspended in toluene (80 mL). The reaction mixture was stirred at 110°C for 80 min. and evaporated under reduced pressure and resulting residue was taken up in ethyl acetate (200 mL). The organic phase was washed with saturated sodium bicarbonate (1 x 150 mL) and dried over sodium sulfate. After the solvent was removed, the resulting oil was subjected to silica gel chromatography using effluent of 50 -90 % ethyl acetate and hexanes. The fractions containing product were combined and the solvent was removed under reduced pressure to provide 2-[5-(4-

Bromo-phenyl)-1H-imidazol-2-yl]-4-hydroxy-pyrrolidine-1-carboxylic acid *tert*-butyl ester (2.3 g, 32 % over 2 steps) as an off-white solid.

2-[4-(4-Bromo-phenyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-4-hydroxy-pyrrolidine-1-carboxylic acid *tert*-butyl ester: 2-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-4-hydroxy-pyrrolidine-1-carboxylic acid *tert*-butyl ester (500 mg) was dissolved in DMF (8 mL), and NaH (54 mg) was added. The mixture was stirred over 10 min. and SEM-Cl was added slowly, and then stirred for 2 hours. The mixture was quenched with 3 mL of sat. NH_4Cl and was taken up in ethyl acetate (100 mL). The organic phase was washed with saturated sodium bicarbonate (1 x 100 mL) and dried over sodium sulfate. After the solvent was removed, the resulting oil was subjected to silica gel chromatography using effluent of 20 -50 % ethyl acetate and hexanes. The fractions containing product were combined and the solvent was removed under reduced pressure to provide 2-[4-(4-Bromo-phenyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-4-hydroxy-pyrrolidine-1-carboxylic acid *tert*-butyl ester (648 mg, 98 %) as an off-white solid.

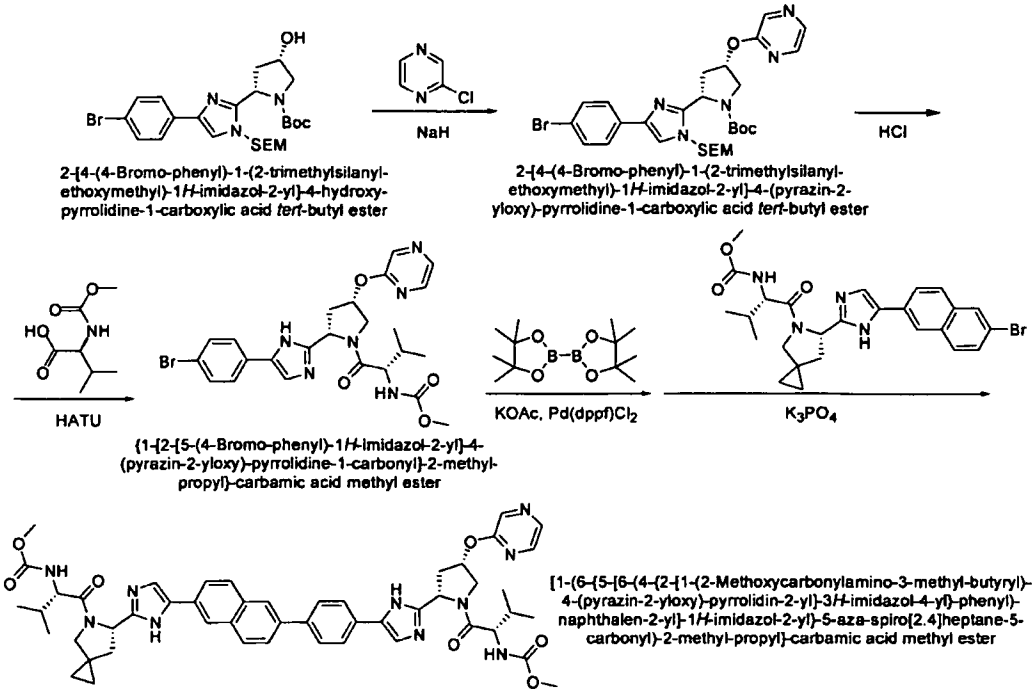
2-[4-(4-Bromo-phenyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-4-(2-methoxy-ethoxy)-pyrrolidine-1-carboxylic acid *tert*-butyl ester: 2-[4-(4-Bromo-phenyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-4-hydroxy-pyrrolidine-1-carboxylic acid *tert*-butyl ester (222 mg) was dissolved in DMF (4 mL), and NaH (25 mg) was added. The mixture was stirred over 20 min. and 1-bromo-2-methoxy-ethane was added slowly, and then stirred for 2.5 hours. The mixture was quenched with 3 mL of sat. NH_4Cl and was taken up in ethyl acetate (50 mL). The organic phase was washed with saturated sodium bicarbonate (1 x 50 mL) and dried over sodium sulfate. After the solvent was removed, the resulting oil was subjected to silica gel chromatography using effluent of 20 -60 % ethyl acetate and hexanes. The fractions containing product were combined and the solvent was removed under reduced pressure to provide 2-[4-(4-Bromo-phenyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-4-(2-methoxy-ethoxy)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (209 mg, 85 %) as a clear oil.

{1-[2[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-4-(2-methoxy-ethoxy)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester: To 2-[4-(4-Bromo-phenyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-4-(2-methoxy-ethoxy)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (209 mg) in DCM (3 mL) was added 4N HCl in dioxane (2.6 mL). The suspension was stirred for 16 hours then concentrated to afford the HCl salt of the

crude amine. To the crude amine in DMF (3 mL) was added *N*-methylmorpholine (193 μL). After all material dissolved, 2-methoxycarbonylamino-3-methyl-butyric acid (123 mg) and HATU (267 mg) were added. After stirring for 30 min. the reaction was purified by a preparative HPLC (10-60% MeCN-H_2O; 0.1% formic acid modifier) to afford the title product (169 mg, 92%).

[1-(6-{5-[6-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-4-(2-methoxy-ethoxy)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: A mixture of {1-[2[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-4-(2-methoxy-ethoxy)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (169 mg), bis(pinacolato)diboron(107 mg), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)(24 mg) and potassium acetate (95 mg) in 1.6 mL of dioxane was heated to 90 ^{0}C for 1.5 hour. (1-{6-[5-(6-Bromo-naphthalen-2-yl)-1H-imidazol-2-yl]-5-aza-spiro[2.4] heptane-5-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (170 mg) in 1mL of dioxane and 2M tripotassium phosphate (565 μl) were added and stirred at 90 ^{0}C for overnight. The mixture was purified by a preparative HPLC (10-60% MeCN-H_2O; 0.1% formic acid modifier) to afford the title product (119 mg, 41%). ^{1}H NMR (DMSO-d6, 400 MHz) δ: 8.20-8.10 (m, 2H), 7.90-7.68 (m, 6H), 7.60-7.55 (m. 2H), 7.33-7.30 (m, 2H), 5.18 (m, 1H), 5.07 (m, 1H), 4.44 (m, 1H), 4.04-3.69 (m, 6H), 3.80-3.38 (m, 5H), 3.30 (m, 9H), 2.71 (m, 1H), 2.40-1.90 (m, 5H), 0.90-0.79 (m, 12H), 0.70-0.54 (m, 4H); MS (ESI) *m/z* 889.5 $[M + H]^+$.

Example FO



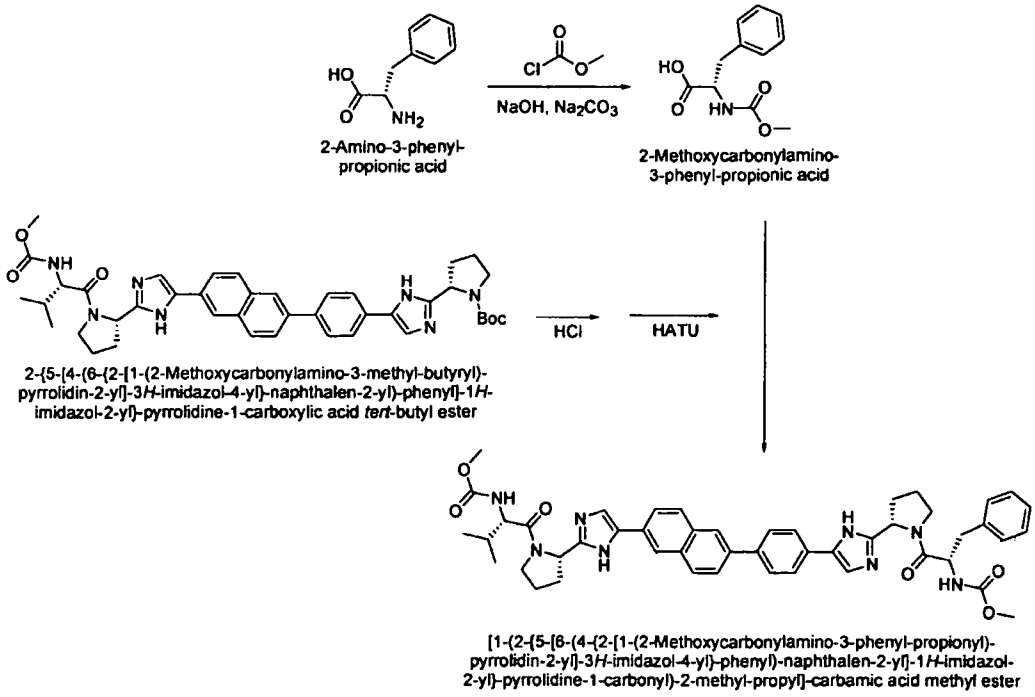
2-[4-(4-Bromo-phenyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-4-(pyrazin-2-yloxy)-pyrrolidine-1-carboxylic acid *tert*-butyl ester: Title compound was prepared according to the method employed to prepare 2-[4-(4-Bromo-phenyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-4-(2-methoxy-ethoxy)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (Example 1), substituting 2-chloro-pyrazine (50 μl) for 1-bromo-2-methoxy-ethane (94 mg, 40%).

{1-[2[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-4-(pyrazin-2-yloxy)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester: Title compound was prepared according to the method employed to prepare {1-[2-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-4-(2-methoxy-ethoxy)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (Example 1), substituting 2-[4-(4-Bromo-phenyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-4-(pyrazin-2-yloxy)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (94 mg) for 2-[4-(4-Bromo-phenyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-4-(2-methoxy-ethoxy)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (88 mg, 99%).

[1-(6-{5-[6-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-4-(pyrazin-2-yloxy)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: Title compound was prepared according to the method employed to prepare [1-(6-{5-[6-(4-{2-[1-(2-

Methoxycarbonylamino-3-methyl-butyryl)-4-(2-methoxy-ethoxy)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (Example 1), substituting {1-[2[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-4-(pyrazin-2-yloxy)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (88 mg) for {1-[2[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-4-(2-methoxy-ethoxy)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (38 mg, 26 %). ^{1}H NMR (MeOH-d4, 400 MHz) δ: 8.20-8.10 (m, 3H), 7.90-7.68 (m, 8H), 7.60-7.55 (m. 2H), 7.33-7.30 (m, 2H), 5.68 (m, 1H), 5.39 (m, 1H), 4.44 (m, 1H), 4.04-3.69 (m, 6H), 3.80-3.38 (m, 1H), 3.30 (m, 6H), 2.71 (m, 1H), 2.40-1.90 (m, 5H), 0.90-0.79 (m, 12H), 0.70-0.54 (m, 4H); MS (ESI) *m/z* 910.5 $[M + H]^+$.

Example FP



2-Amino-3-phenyl-propionic acid

2-Methoxycarbonylamino-3-phenyl-propionic acid

2-{5-[4-(6-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester

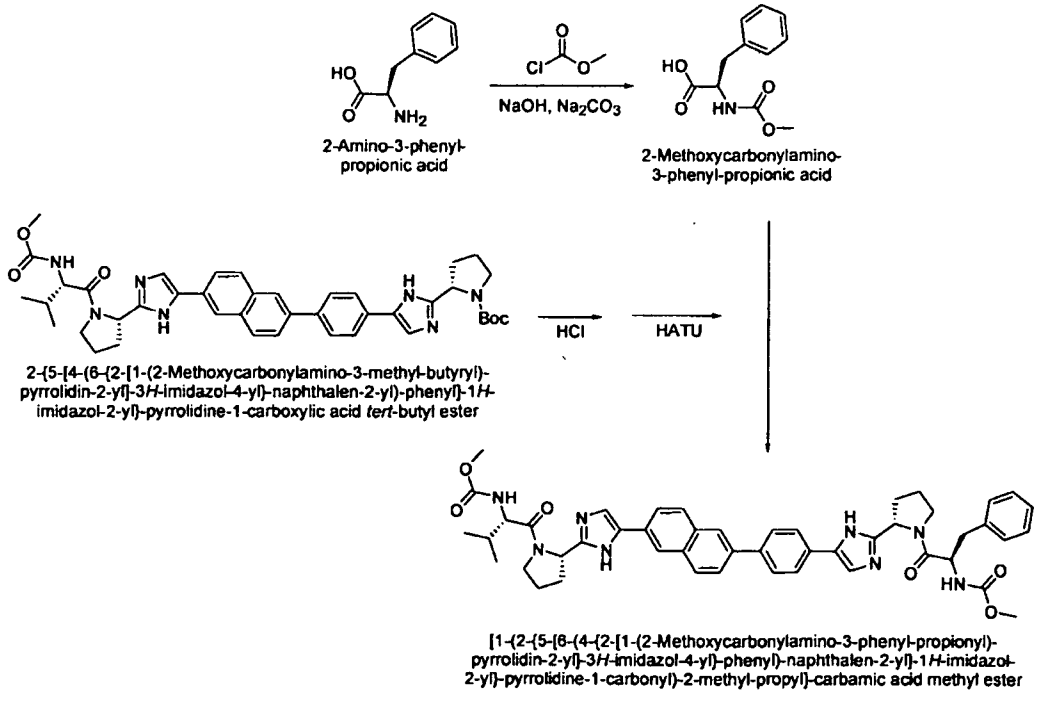
[1-(2-{5-[6-(4-{2-[1-(2-Methoxycarbonylamino-3-phenyl-propionyl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester

2-Methoxycarbonylamino-3-phenyl-propionic acid: 2-Amino-3-phenyl-propionic acid (1.65 g) was dissolved in 1 N NaOH (10 mL), and Na_2CO_3 (530 mg) was added. The mixture was cooled to 0°C and methyl chloroformate was added slowly, and then stirred for overnight at room temperature. The mixture was washed with DCM and acidified with 3 mL of 2N HCl, and then was taken up in ether (200 mL). The organic phase was dried over sodium sulfate. Removing the solvent to give 2-Methoxycarbonylamino-3-phenyl-propionic acid (1.95 g, 87 %) as an off-white solid.

[1-(2-{5-[6-(4-{2-[1-(2-Methoxycarbonylamino-3-phenyl-propionyl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester:

To 2-{5-[4-(6-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (40 mg) in methanol (0.5 mL) was added 4N HCl in dioxanes (0.5 mL). The mixture was stirred for 1.5 hours then concentrated to afford the HCl salt of the crude amine. To the crude amine in DMF (2 mL) was added *N*-methylmorpholine (30 μL). After all material dissolved, 2-methoxy carbonylamino-3-phenyl-propionic acid (24 mg) and HATU (42 mg) were added. After stirring for 30 min. the reaction was purified by a preparative HPLC (10-60% MeCN-H_2O; 0.1% formic acid modifier) to afford the title product (34 mg, 37%). ^{1}H NMR (MeOH-d4, 400 MHz) δ: 8.22-8.03 (m, 4H), 7.89-7.74 (m, 8H), 7.54-7.05 (m, 5H), 5.20 (m, 2H), 4.63 (m, 1H), 4.48(m, 1H), 4.25 (m, 1H), 4.15-3.88 (m, 4H), 3.69-3.51 (m, 8H), 3.45-3.15 (m, 4H) 3.10 (m, 1H), 2.95 (m, 1H), 2.86 (m, 1H), 2.45-2.04 (m, 7H), 1.00-0.88 (m, 6H); MS (ESI) *m/z* 837.4 [M + H]$^+$.

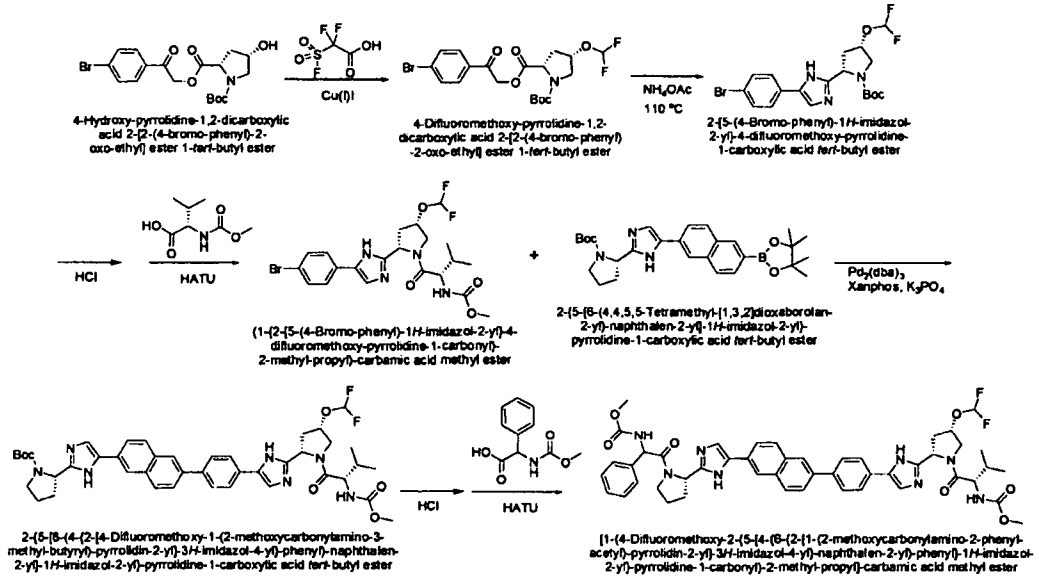
Example FQ



[1-(2-{5-[6-(4-{2-[1-(2-Methoxycarbonylamino-3-phenyl-propionyl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: Title compound was prepared according to the

method employed to prepare [1-(2-{5-[6-(4-{2-[1-(2-Methoxycarbonylamino-3-phenyl-propionyl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (Example 3), (33 mg, 36%). ^{1}H NMR (MeOH-d4, 400 MHz) δ: 8.22-8.03 (m, 4H), 7.89-7.74 (m, 9H), 7.54-7.05 (m, 4H), 5.20 (m, 2H), 4.63 (m, 1H), 4.48(m, 1H), 4.25 (m, 1H), 4.15-3.88 (m, 4H), 3.69-3.51 (m, 8H), 3.45-3.15 (m, 4H) 3.10 (m, 1H), 2.95 (m, 1H), 2.86 (m, 1H), 2.45-1.97 (m, 5H), 1.80 (m, 1H), 1.63 (m, 1H), 1.00-0.88 (m, 6H); MS (ESI) *m/z* 837.4 $[M + H]^+$.

Example FR



4-Difluoromethoxy-pyrrolidine-1,2-dicarboxylic acid 2-[2-(4-bromo-phenyl)-2-oxo-ethyl] ester 1-*tert*-butyl ester : To 4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 2-[2-(4-bromo-phenyl)-2-oxo-ethyl] ester 1-*tert*-butyl ester (500 mg) and Cu(I)I (45 mg) in MeCN (8 mL) at 45 ^{0}C was added 242 µl of difluoro-fluorosulfonyl-acetic acid in 2 mL of MeCN dropwise for 60 min. The reaction mixture was stirred at 45°C for 60 min. and evaporated under reduced pressure, and resulting residue was taken up in ethyl acetate (100 mL). The organic phase was washed with brine (1 x 100 mL) and dried over sodium sulfate. After the solvent was removed, the resulting oil was subjected to silica gel chromatography using effluent of 10 -50 % ethyl acetate and hexanes. The fractions containing product were combined and the solvent was removed under reduced pressure to provide 4-Difluoromethoxy-pyrrolidine-1,2-dicarboxylic acid 2-[2-(4-bromo-phenyl)-2-oxo-ethyl] ester 1-*tert*-butyl ester (339 mg, 61 %) as a clear oil.

2-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl-4-difluoromethoxy-pyrrolidine-1-carboxylic acid *tert*-butyl ester : Title compound was prepared according to the method employed to prepare 2-

[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-4-hydroxy-pyrrolidine-1-carboxylic acid *tert*-butyl ester (Example 1), substituting 4-Difluoromethoxy-pyrrolidine-1,2-dicarboxylic acid 2-[2-(4-bromo-phenyl)-2-oxo-ethyl] ester 1-*tert*-butyl ester (305 mg) for 4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 2-[2-(4-bromo-phenyl)-2-oxo-ethyl] ester 1-*tert*-butyl ester (244 mg, 83 %).

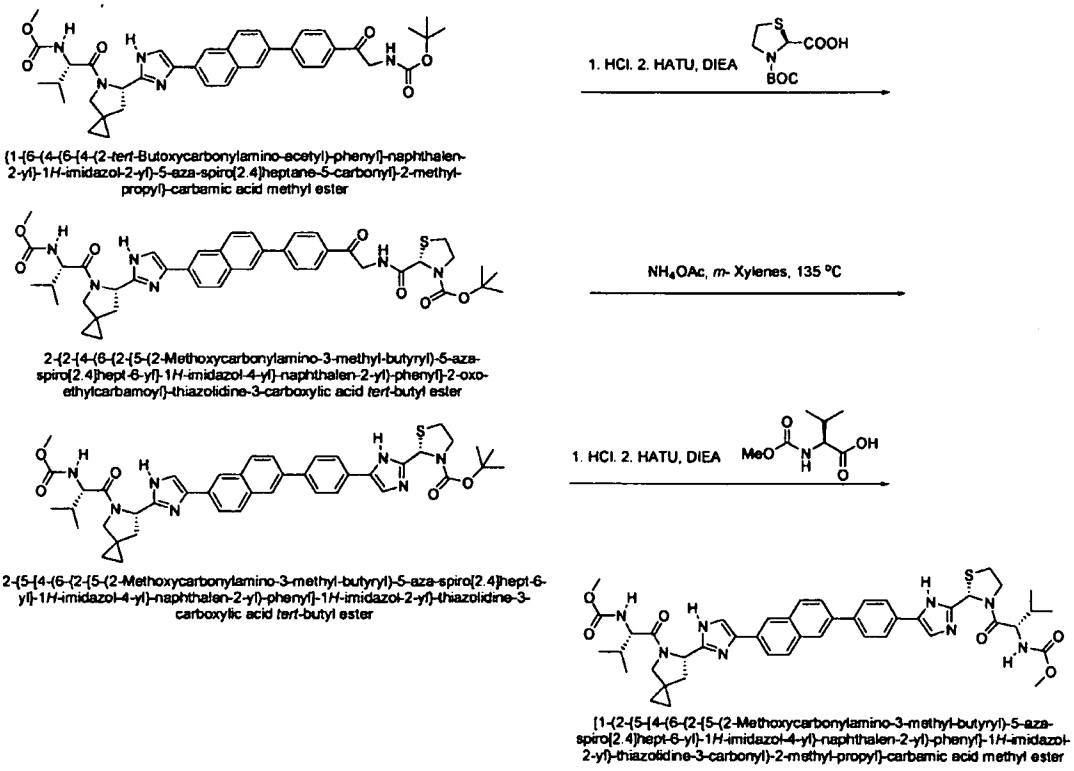
(1-{2-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl-4-difluoromethoxy-pyrrolidine-1-carbonyl}-2-methoxy-propyl)-carbamic acid methyl ester: To 2-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl-4-difluoromethoxy-pyrrolidine-1-carboxylic acid *tert*-butyl ester (244 mg) in DCM (4 mL) was added 4N HCl in dioxanes (1.3 mL). The mixture was stirred for 1 hours then concentrated to afford the HCl salt of the crude amine. To the crude amine in DMF (2.7 mL) was added *N*-methylmorpholine (234 μL). After all material dissolved, 2-methoxycarbonylamino-3-methyl-butyric acid (103 mg) and HATU (263 mg) were added. After stirring for 60 min. the reaction was evaporated under reduced pressure, and resulting residue was taken up in ethyl acetate (100 mL). The organic phase was washed with saturated sodium bicarbonate (1 x 100 mL) and dried over sodium sulfate. After the solvent was removed, the resulting oil was subjected to silica gel chromatography using effluent of 80 -100 % ethyl acetate and hexanes. The fractions containing product were combined and the solvent was removed under reduced pressure to provide (1-{2-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl-4-difluoromethoxy-pyrrolidine-1-carbonyl}-2-methoxy-propyl)-carbamic acid methyl ester (166 mg, 61 %) as a clear oil.

2-{5-[6-(4-{2-[4-Difluoromethoxy-1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-bytyl ester: To (1-{2-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl-4-difluoromethoxy-pyrrolidine-1-carbonyl}-2-methoxy-propyl)-carbamic acid methyl ester (166 mg) and 2-{5-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (237 mg) in DME (1.6 mL) were added $Pd_2(dba)_3$ (15 mg), Xanphos (19 mg), and 2M K_3PO_4 (483 μl). After stirring for overnight at 80°C, the mixture was filtered and evaporated under reduced pressure, and resulting residue was subjected to silica gel chromatography using effluent of 10 -15 % MeOH and DCM. The fractions containing product were combined and the solvent was removed under reduced pressure to provide the title product (30 mg, 12 %) as a clear film.

[1-(4-Difluoromethoxy-2-{5-[4-(6-{2-[1-(2-methoxycarbonylamino-2-phenyl-acetyl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: Title compound was

prepared according to the method employed to prepare (1-{2-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl-4-difluoromethoxy-pyrrolidine-1-carbonyl}-2-methoxy-propyl)-carbamic acid methyl ester (Example 5), substituting methoxycarbonylamino-phenyl-acetic acid (30 mg) for 2-methoxycarbonylamino-3-methyl-butyric acid (22 mg, 58 %). ^{1}H NMR (MeOH-d4, 400 MHz) δ: 8.20-8.05 (m, 3H), 7.95-7.72 (m, 5H), 7.56-7.35 (m. 8H), 7.15 (m, 1H), 6.71-6.35 (m, 1H), 5.55 (m, 1H), 5.30-5.20 (m, 3H), 5.05-4.90 (m, 3H), 4.36 (m, 1H), 4.20 (m, 1H), 4.12-3.82 (m, 2H), 3.65 (m, 6H), 3.50 (m, 1H), 2.75 (m, 1H), 2.45 (m, 1H), 2.35-1.90 (m, 2H), 0.98-0.85 (m, 6H); MS (ESI) *m/z* 889.3 $[M + H]^+$.

Example FS



2-{2-[4-(6-{2-[5-(2-Methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-1H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-2-oxo-ethylcarbamoyl}-thiazolidine-3-carboxylic acid *tert*-butyl ester:

{1-[6-(4-{6-[4-(2-*tert*-Butoxycarbonylamino-acetyl)-phenyl]-naphthalen-2-yl}-1H-imidazol-2-yl)-5-aza-spiro[2.4]heptane-5-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (395.0 mg, 0.581 mmol) was dissolved in DCM (4 mL) and HCl in dioxane (4M, 4 mL) was added and stirring at room temperature was continued. After 60 minutes, all volatiles were removed *in vacuo*. The crude material was used in the next step without further purification. The crude

material was dissolved in DMF (2.0 mL) and DIEA (110.8 mg, 0.860 mmol) was added. A solution of N-Boc (*S*) thiazolidine -2-carboxylic acid (100.0 mg, 0.430 mmol), HATU (163.0 mg, 0.430 mmol) and DIEA (55.4 mg, 0.430 mmol) in DMF (1 mL) was added. The reaction was stirred at room temperature. After 20 minutes, the reaction was diluted with EtOAc and was washed with brine, sodium hydroxyl solution (1M), brine, and was dried over sodium sulfate. Filtration and removal of solvents *in vacuo* gave the crude material (350 mg), which was used in the next step without further purification.
LCMS-ESI$^+$: calc'd for $C_{43}H_{50}N_6O_7S$: 794.9 (M^+); Found: 795.8 ($M+H^+$).

2-{5-[4-(6-{2-[5-(2-Methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-1H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-thiazolidine-3-carboxylic acid *tert*-butyl ester:
2-{2-[4-(6-{2-[5-(2-Methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-1H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-2-oxo-ethylcarbamoyl}-thiazolidine-3-carboxylic acid *tert*-butyl ester (350 mg, 0.44 mmol) was dissolved in m-xylenes (3.0 mL) and heated at 135 °C. Solid ammonium acetate (400 mg, 9.07 mmol) was added and the reaction was stirred at 135 °C. After 45 minutes, the reaction was cooled to room temperature and the volatiles were removed *in vacuo*. The crude reaction product was partitioned between chloroform and water. The organic layer was collected and dried over sodium sulfate. Filtration and evaporation of solvents gave the crude product. The crude material was purified via silica gel chromatography (eluent: EtOAc / hexanes) to yield the product (151.3 mg, 0.195 mmol).
LCMS-ESI$^+$: calc'd for $C_{43}H_{49}N_7O_5S$: 775.9 (M^+); Found: 776.8 ($M+H^+$).

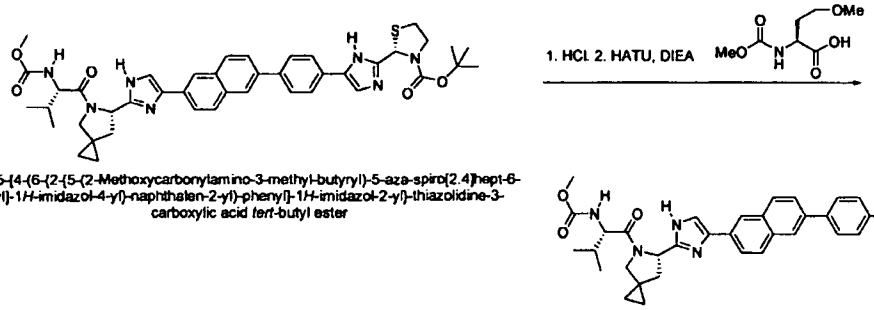
[1-(2-{5-[4-(6-{2-[5-(2-Methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-1H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-thiazolidine-3-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester:
2-{5-[4-(6-{2-[5-(2-Methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-1H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-thiazolidine-3-carboxylic acid *tert*-butyl ester (49.9 mg, 0.064 mmol) was dissolved in DCM (0.33 mL) and HCl in dioxane (4M, 0.33 mL) was added and stirring at room temperature was continued. After 45 minutes, all volatiles were removed *in vacuo*. The crude material was used in the next step without further purification. The crude material was dissolved in DMF (0.5 mL) and DIEA (24.6 mg, 0.191 mmol) was added. A solution of 2- (*L*) methoxycarbonylamino-3-methyl-butyric acid (11.2 mg, 0.064 mmol), HATU (24.1 mg, 0.064 mmol) and DIEA (8.2 mg, 0.064 mmol) in DMF (0.5 mL) was added. The reaction was stirred at room temperature. After 18 hrs all volatiles were

removed *in vacuo*. The crude material, which was purified by RP-HPLC (eluent: water / MeCN w/ 0.1% TFA) to yield the product (8.5 mg) as a TFA salt.

LCMS-ESI$^+$: calc'd for $C_{45}H_{52}N_8O_6S$: 833.0 (M^+); Found: 833.7 ($M+H^+$).

^{1}H-NMR: 300 MHz, (dmso-d_6) δ: 8.35-7.88 (m, 14H), 7.36 – 7.33 (m, 2H), 6.36 (m, 1H), 5.28 (dd, J = 7.2 Hz, 1H), 4.24 (m, 1H) 4.16 (m, 1H), 4.03 - 3.74 (m, 6H), 3.55 (s, 3H), 3.54 (s, 3H), 2.27 (m, 2H), 2.08 (m, 2H), 0.90 - 0.76 (m, 12H) 0.65 (m, 4H) ppm.

Example FT



2-{5-[4-(6-{2-[5-(2-Methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-1*H*-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1*H*-imidazol-2-yl}-thiazolidine-3-carboxylic acid *tert*-butyl ester

[1-(6-{4-[6-(4-{2-[3-(4-Methoxy-2-methoxycarbonylamino-butyryl)-thiazolidin-2-yl]-3*H*-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1*H*-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester

[1-(6-{4-[6-(4-{2-[3-(4-Methoxy-2-methoxycarbonylamino-butyryl)-thiazolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester:

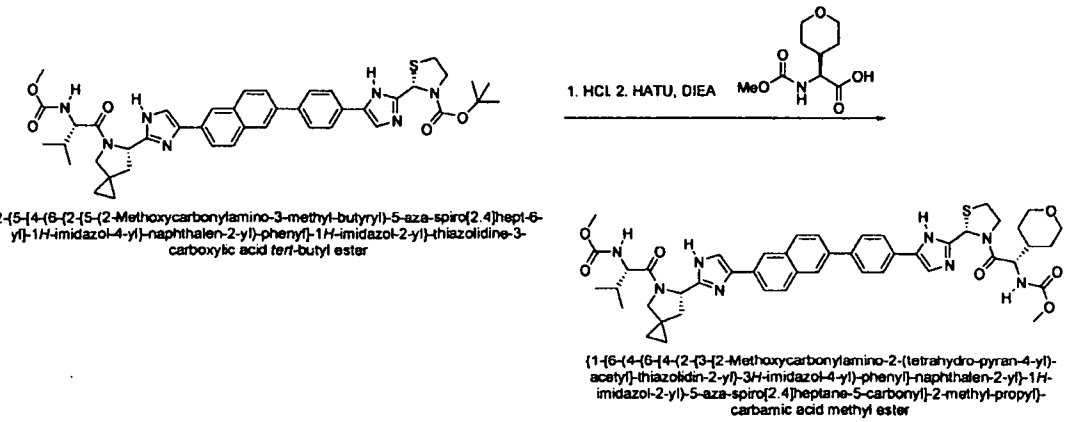
2-{5-[4-(6-{2-[5-(2-Methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-1H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-thiazolidine-3-carboxylic acid *tert*-butyl ester (49.9 mg, 0.064 mmol) was dissolved in DCM (0.33 mL) and HCl in dioxane (4M, 0.33 mL) was added and stirring at room temperature was continued. After 45 minutes, all volatiles were removed *in vacuo*. The crude material was used in the next step without further purification. The crude material was dissolved in DMF (0.5 mL) and DIEA (24.6 mg, 0.191 mmol) was added. A solution of (*L*) 4-methoxy-2-methoxycarbonylamino-butyric acid (12.1 mg, 0.064 mmol), HATU (24.1 mg, 0.064 mmol) and DIEA (8.2 mg, 0.064 mmol) in DMF (0.5 mL) was added. The reaction was stirred at room temperature. After 3 hrs all volatiles were removed *in vacuo*. The crude material, which was purified by RP-HPLC (eluent: water / MeCN w/ 0.1% TFA) to yield the product (21.3 mg) as a TFA salt.

LCMS-ESI$^+$: calc'd for $C_{45}H_{52}N_8O_7S$: 849.0 (M^+); Found: 849.7 ($M+H^+$).

^{1}H-NMR: 300 MHz, (dmso-d_6) δ: 8.37 (m, 2H), 8.20 – 8.14 (m, 2H), 8.06 - 7.88 (m, 10H), 7.36 – 7.33 (m, 2H), 6.36 (m, 1H), 5.30 (dd, J = 7.2 Hz, 1H), 4.45 (m, 1H) 4.06 (m, 1H), 4.06 - 3.69

(m, 6H), 3.55 (s, 3H), 3.54 (s, 3H), 3.36 (m,2H), 3.25 (m, 3H), 2.26 (m, 2H), 2.02 (m, 2H), 1.81 (m,1H), 0.90 - 0.76 (m, 6H) 0.65 (m, 4H) ppm.

Example FU



2-{5-[4-(6-{2-[5-(2-Methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-1*H*-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1*H*-imidazol-2-yl}-thiazolidine-3-carboxylic acid *tert*-butyl ester

{1-[6-(4-{6-[4-(2-{3-[2-Methoxycarbonylamino-2-(tetrahydro-pyran-4-yl)-acetyl]-thiazolidin-2-yl}-3*H*-imidazol-4-yl)-phenyl]-naphthalen-2-yl}-1*H*-imidazol-2-yl)-5-aza-spiro[2.4]heptane-5-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester

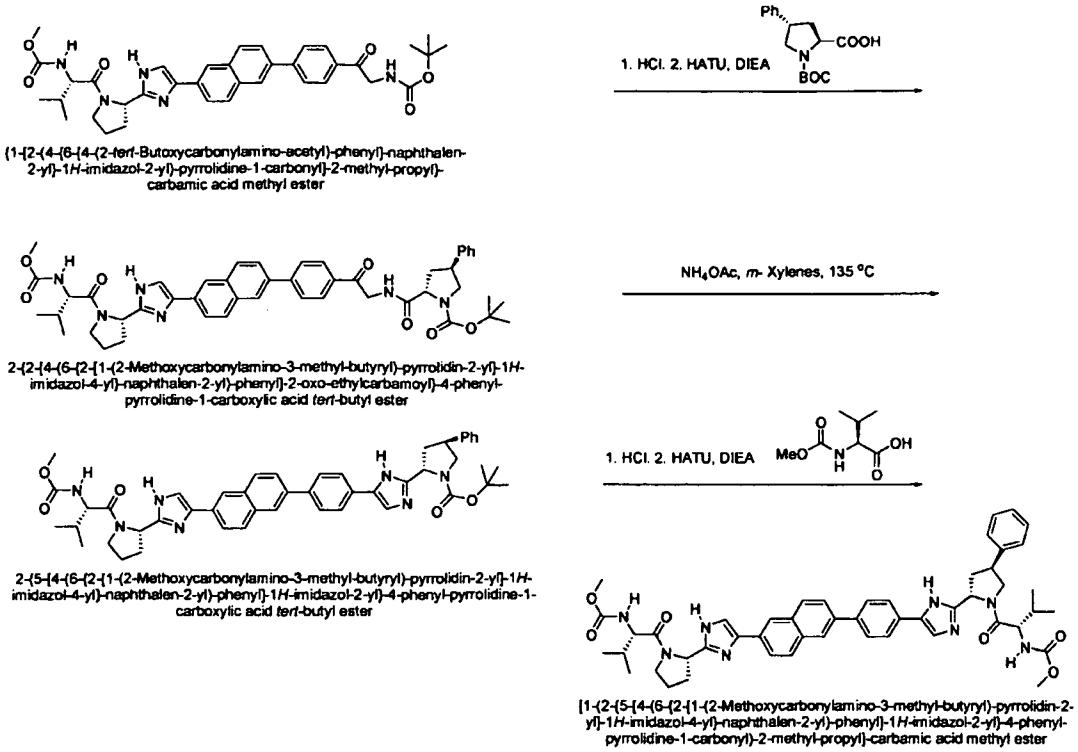
{1-[6-(4-{6-[4-(2-{3-[2-Methoxycarbonylamino-2-(tetrahydro-pyran-4-yl)-acetyl]-thiazolidin-2-yl}-3H-imidazol-4-yl)-phenyl]-naphthalen-2-yl}-1H-imidazol-2-yl)-5-aza-spiro[2.4]heptane-5-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester:

2-{5-[4-(6-{2-[5-(2-Methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-1H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-thiazolidine-3-carboxylic acid *tert*-butyl ester (49.9 mg, 0.064 mmol) was dissolved in DCM (0.33 mL) and HCl in dioxane (4M, 0.33 mL) was added and stirring at room temperature was continued. After 45 minutes, all volatiles were removed *in vacuo*. The crude material was used in the next step without further purification. The crude material was dissolved in DMF (0.5 mL) and DIEA (24.6 mg, 0.191 mmol) was added. A solution of 2- (*L*) methoxycarbonylamino-(tetrahydro-pyran-4-yl)-acetic acid (13.8 mg, 0.064 mmol), HATU (24.1 mg, 0.064 mmol) and DIEA (8.2 mg, 0.064 mmol) in DMF (0.5 mL) was added. The reaction was stirred at room temperature. After 18 hrs all volatiles were removed *in vacuo*. The crude material, which was purified by RP-HPLC (eluent: water / MeCN w/ 0.1% TFA) to yield the product (6.2 mg) as a TFA salt.

LCMS-ESI$^+$: calc'd for $C_{47}H_{52}N_8O_7S$: 875.0 (M^+); Found: 875.7 ($M+H^+$).

^{1}H-NMR: 300 MHz, (dmso-d_6) δ: ^{1}H-NMR: 300 MHz, (dmso-d_6) δ: 8.31 - 7.89 (m, 14H), 7.36 – 7.33 (m, 2H), 6.34 (m, 1H), 5.27 (m, 1H), 4.30 (m, 1H) 4.03 (m, 1H), 4.06 - 3.69 (m, 6H), 3.57 (s, 3H), 3.54 (s, 3H), 3.28 – 2.95 (m, 4H), 2.26 (m, 2H), 2.02 (m, 2H), 1.50-1.32 (m,4H), 0.85 - 0.73 (m, 6H) 0.65 (m, 4H) ppm.

Example FV



{1-[2-(4-{6-[4-(2-*tert*-Butoxycarbonylamino-acetyl)-phenyl]-naphthalen-2-yl}-1*H*-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester

2-{2-[4-(6-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-1*H*-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-2-oxo-ethylcarbamoyl}-4-phenyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester

2-{5-[4-(6-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-1*H*-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1*H*-imidazol-2-yl}-4-phenyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester

[1-(2-{5-[4-(6-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-1*H*-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1*H*-imidazol-2-yl}-4-phenyl-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester

2-{2-[4-(6-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-1H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-2-oxo-ethylcarbamoyl}-4-phenyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester:

{1-[2-(4-{6-[4-(2-*tert*-Butoxycarbonylamino-acetyl)-phenyl]-naphthalen-2-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (61.0 mg, 0.095 mmol) was dissolved in DCM (1 mL) and HCl in dioxane (4M, 1 mL) was added and stirring at room temperature was continued. After 90 minutes, all volatiles were removed *in vacuo*. The crude material was used in the next step without further purification. The crude material was dissolved in DMF (1.0 mL) and DIEA (23.7 mg, 0.183 mmol) was added. A solution of 4-Phenyl-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester (17.8 mg, 0.061 mmol), HATU (23.3 mg, 0.061 mmol) and DIEA (7.9 mg, 0.061 mmol) in DMF (0.5 mL) was added. The reaction was stirred at room temperature. After 20 minutes, the reaction was diluted with EtOAc and was washed with brine, saturated sodium bicarbonate solution, brine, and was dried over sodium sulfate. Filtration and removal of solvents *in vacuo* gave the crude material (88 mg), which was used in the next step without further purification.

LCMS-ESI$^+$: calc'd for $C_{48}H_{54}N_6O_7$: 826.9 (M^+); Found: 827.7 ($M+H^+$).

2-{5-[4-(6-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-1H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-4-phenyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester:

2-{2-[4-(6-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-1H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-2-oxo-ethylcarbamoyl}-4-phenyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester (88 mg) was dissolved in m-xylenes (1.0 mL) and heated at 135 °C. Solid ammonium acetate (100 mg, 1.2 mmol) was added and the reaction was stirred at 135 °C. After 180 minutes, the reaction was cooled to room temperature and the volatiles were removed *in vacuo*. The crude reaction product was partitioned between chloroform and water. The organic layer was collected and dried over sodium sulfate. Filtration and evaporation of solvents gave the crude product. The crude material was purified via silica gel chromatography (eluent: EtOAc / hexanes) to yield the product (51.0 mg, 0.195 mmol).

LCMS-ESI$^+$: calc'd for $C_{48}H_{53}N_7O_5$: 807.9 (M^+); Found: 808.4 ($M+H^+$).

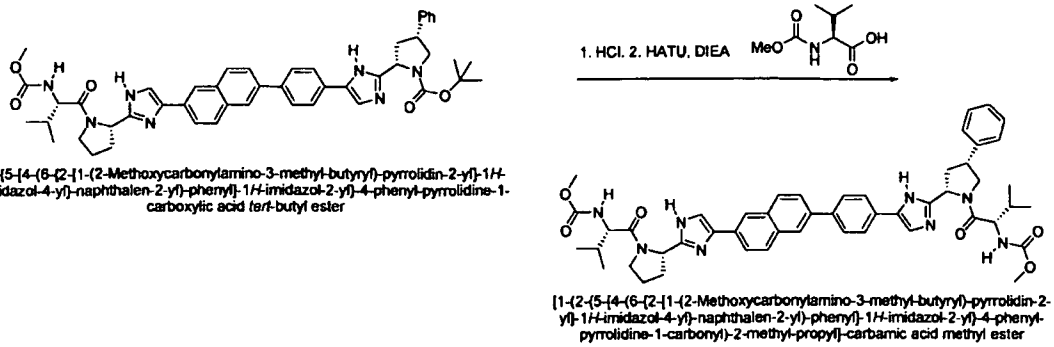
[1-(2-{5-[4-(6-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-1H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-4-phenyl-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester:

2-{5-[4-(6-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-1H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-4-phenyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester (51.0 mg, 0.063 mmol) was dissolved in DCM (1.0 mL) and HCl in dioxane (4M, 1.0 mL) was added and stirring at room temperature was continued. After 30 minutes, all volatiles were removed *in vacuo*. The crude material was used in the next step without further purification. The crude material was dissolved in DMF (0.5 mL) and DIEA (24.3 mg, 0.190 mmol) was added. A solution of 2- (*L*) methoxycarbonylamino-3-methyl-butyric acid (11.1 mg, 0.063 mmol), HATU (24.0 mg, 0.063 mmol) and DIEA (8.1 mg, 0.063 mmol) in DMF (0.5 mL) was added. The reaction was stirred at room temperature. After 60 minutes, the crude reaction was quenched with aqueous hydrochloric acid (0.1 mL, 2 M) and was purified by RP-HPLC (eluent: water / MeCN w/ 0.1% TFA) to yield the product (12.1 mg) as a TFA salt.

LCMS-ESI$^+$: calc'd for $C_{50}H_{56}N_8O_6$: 865.0 (M^+); Found: 865.4 ($M+H^+$).

^{1}H-NMR: 300 MHz, (dmso-d_6) δ: 8.31 – 8.30 (d, J = 3 Hz, 2H), 8.08 (d, J = 6.6 Hz, 2h), 7.98 – 7.86 (m, 10H), 7.34 – 7.21 (m, 7H), 5.28 (dd, J = 6.0 / 2.7 Hz, 1H), 5.10 (dd, J = 6.0 / 5.7 Hz, 1H), 4.26 (m, 1H) 4.11 (m, 1H), 4.06 (m, 1H) 3.85 - 3.73 (m, 3H), 3.48 (s, 3H), 3.47 (s, 3H), 2.27 (m, 2H), 2.14 – 2.09 (m, 7H), 0.89 - 0.72 (m, 12H) ppm.

Example FW



2-{5-[4-(6-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-1*H*-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1*H*-imidazol-2-yl}-4-phenyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester

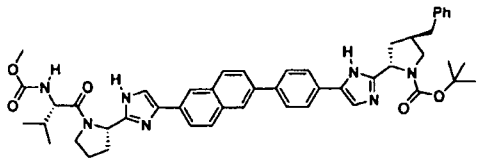
[1-(2-{5-[4-(6-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-1*H*-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1*H*-imidazol-2-yl}-4-phenyl-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester

[1-(2-{5-[4-(6-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-1H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-4-phenyl-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester:

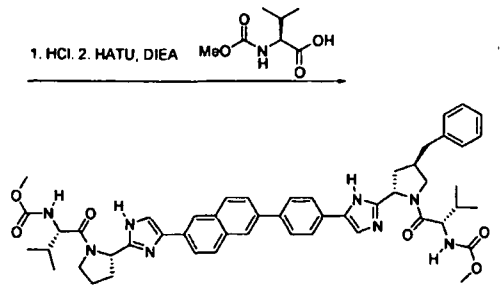
2-{5-[4-(6-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-1H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-4-phenyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester (88.mg, 0.107 mmol) was dissolved in DCM (1.0 mL) and HCl in dioxane (4M, 1.0 mL) was added and stirring at room temperature was continued. After 40 minutes, all volatiles were removed *in vacuo.* The crude material was used in the next step without further purification. The crude material was dissolved in DMF (0.4 mL) and DIEA (40.8 mg, 0.321 mmol) was added. A solution of 2- (*L*) methoxycarbonylamino-3-methyl-butyric acid (18.7 mg, 0.107 mmol), HATU (40.6 mg, 0.107 mmol) and DIEA (13.6 mg, 0.107 mmol) in DMF (0.4 mL) was added. The reaction was stirred at room temperature. After 20 minutes, the crude reaction was quenched with aqueous hydrochloric acid (0.1 mL, 2 M) and was purified by RP-HPLC (eluent: water / MeCN w/ 0.1% TFA) to yield the product (38.7 mg) as a TFA salt. LCMS-ESI$^+$: calc'd for $C_{50}H_{56}N_8O_6$: 865.0 (M^+); Found: 865.4 ($M+H^+$).

^{1}H-NMR: 300 MHz, (dmso-d_6) δ: 8.37 – 8.35 (m, 2H), 8.16 – 7.91 (m, 12H), 7.47 – 7.28 (m, 7H), 5.24 (dd, J = 7.8 / 5.4 Hz, 1H), 5.16 (dd, J = 4.8 / 4..8 Hz, 1H), 4.44 (dd, J = 6.3 / 6.3 Hz, 1H) 4.16 - 4.09 (m, 2H) 3.85 - 3.80 (m, 3H), 3.57 (s, 3H), 3.56 (s, 3H), 2.78 (m, 1H), 2.30 – 1.96 (m, 8H), 0.90 - 0.75 (m, 12H) ppm.

Example FX



4-Benzyl-2-{5-[4-(6-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-1*H*-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester



[1-(4-Benzyl-2-{5-[4-(6-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-1*H*-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester

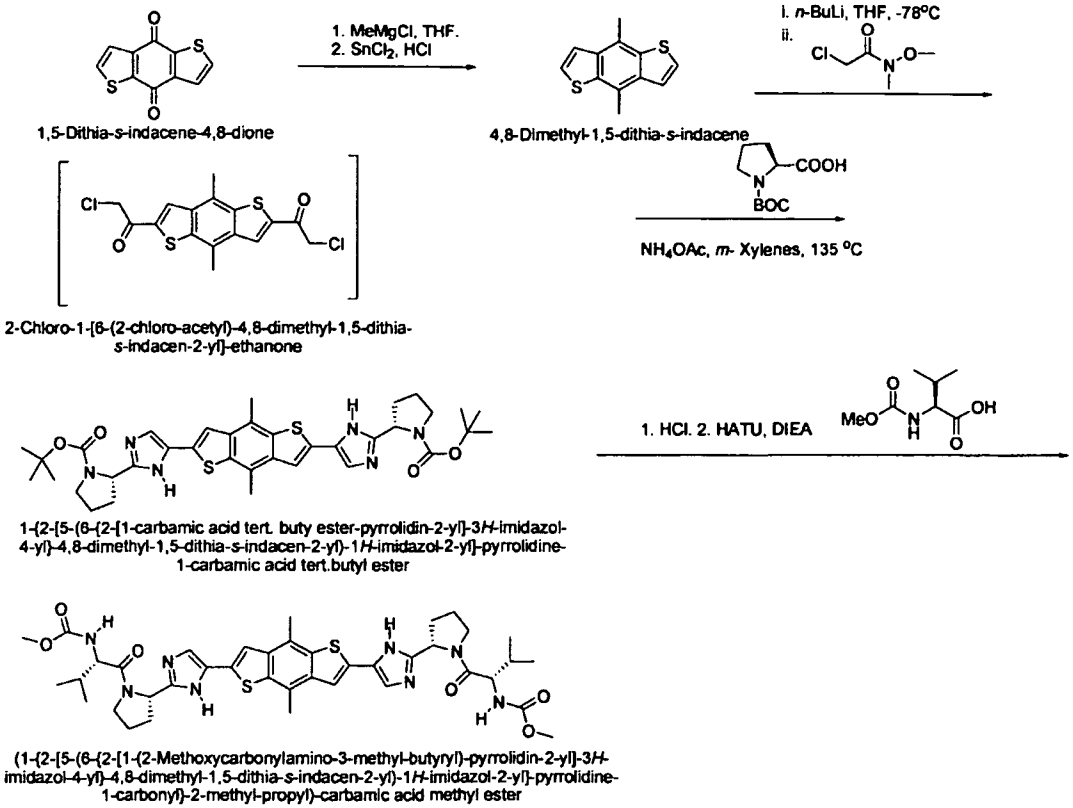
[1-(4-Benzyl-2-{5-[4-(6-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-1H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester:

4-Benzyl-2-{5-[4-(6-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-1H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (58.0 mg, 0.071 mmol) was dissolved in DCM (1.0 mL) and HCl in dioxane (4M, 1.0 mL) was added and stirring at room temperature was continued. After 30 minutes, all volatiles were removed *in vacuo*. The crude material was used in the next step without further purification. The crude material was dissolved in DMF (0.5 mL) and DIEA (27.3 mg, 0.211 mmol) was added. A solution of 2- (*L*) methoxycarbonylamino-3-methyl-butyric acid (12.3 mg, 0.071 mmol), HATU (26.8 mg, 0.071 mmol) and DIEA (9.1 mg, 0.071 mmol) in DMF (0.5 mL) was added. The reaction was stirred at room temperature. After 30 minutes, the crude reaction was quenched with aqueous hydrochloric acid (0.1 mL, 2 M) and was purified by RP-HPLC (eluent: water / MeCN w/ 0.1% TFA) to yield the product (25.1 mg) as a TFA salt.

LCMS-ESI$^+$: calc'd for $C_{51}H_{57}N_8O_6$: 878.0 (M^+); Found: 879.6 ($M+H^+$).

^{1}H-NMR: 300 MHz, (dmso-d_6) δ: 8.36 (s, 2H), 8.16 – 7.89 (m, 12H), 7.38 – 7.19 (m, 7H), 5.29 (dd, J = 5.7 / 3.9 Hz, 1H), 5.16 (dd, J = 5.1 / 5.1 Hz, 1H), 4.18 - 4.05 (m, 2H), 3.93 - 3.86 (m, 2H), 3.56 (s, 3H), 3.53 (s, 3H), 3.52 (m, 2H), 2.79 (m, 1H), 2.48 (m, 2H), 2.39 (m, 1H), 2.18 – 2.01 (m, 7H), 0.91 - 0.77 (m, 12H) ppm.

Example FY



4,8-Dimethyl-1,5-dithia-s-indacene:

1,5-Dithia-s-indacene-4,8-dione (2.0 g, 9.17 mmol) was added to a methyl magnesium chloride solution (60 mmol) in THF (80 mL) [Org. Lett., 2008, 10:4421-4424]. The reaction mixture was heated at 55° C (oil bath). After 14 hrs, a solution of tin(II)chloride (10 g) in aqueous HCl (2M, 50 mL) was added carefully and the heating was continued for 4 additional hours. The reaction was cooled to room temperature and the THF was removed *in vacuo*. The crude mixture was partitioned between chloroform and brine. The resultant thick suspension was filtered and the solid was discarded. The organic layer was dried over sodium sulfate. Filtration and removal of solvents *in vacuo* gave the crude material, which was via silica gel chromatography (eluent: EtOAc / hexanes) to yield the product (355.0 mg, 1.63 mmol).

^{1}H-NMR: 300 MHz, ($CDCl_3$) δ: 7.49 (d, J = 4.2 Hz, 2H), 7.46 (d, J = 4.2 Hz, 2H), 2.81 (s, 6H)ppm.

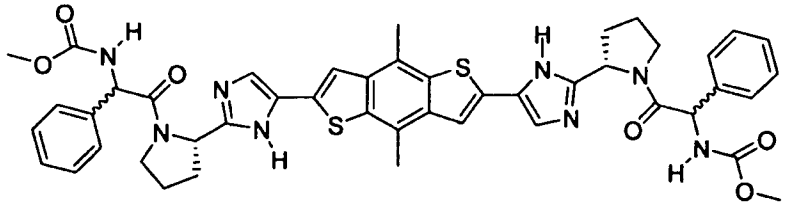
2-Chloro-1-[6-(2-chloro-acetyl)-4,8-dimethyl-1,5-dithia-s-indacen-2-yl]-ethanone:
4,8-Dimethyl-1,5-dithia-s-indacene (61.0 mg, 0.095 mmol) was dissolved in THF (9 mL) and was cooled to -78° C. A solution of *n*-BuLi (1.6 M hexanes, 0.946 mL) was added and stirring at -78° C was continued for 90 minutes. To the resultant suspension was added a solution of *N*-Methyl, *N*-Methoxy-2-chloroacetate (209 mg, 1.51 mmol) in THF (1 mL). Stirring at -78° C was continued for 45 minutes. The reaction was quenched with ammonium chloride solution and methanol and was warmed to room temperature. The bright yellow solid was collected and used in the next step without further purification.

1-{2-[5-(6-{2-[1-carbamic acid *tert.* butyl ester-pyrrolidin-2-yl]-3H-imidazol-4-yl}-4,8-dimethyl-1,5-dithia-s-indacen-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbamic acid *tert*-butyl ester
2-Chloro-1-[6-(2-chloro-acetyl)-4,8-dimethyl-1,5-dithia-s-indacen-2-yl]-ethanone (crude solid from previous step)) was combined and with (*L*)-*N*-Boc Proline carboxylic acid (324 mg, 1.51 mmol), potassium carbonate (304 mg, 2.2 mmol), sodium iodide (21.6 mg) and was heated in acetone (10 mL) at -78° C. After 120 minutes, all volatiles were removed *in vacuo.* The reaction was diluted with chloroform and was washed with brine, saturated sodium bicarbonate solution, brine, and was dried over sodium sulfate. Filtration and removal of solvents *in vacuo* gave the crude material (580 mg, 0.797 mmol), which was used in the next step without further purification.
The crude product from the previous step (580.1 mg, 0.797 mol) was dissolved in *m*-xylenes (7.0 mL) and heated at 140 °C. Solid ammonium acetate (500 mg, 6.41 mmol) was added and the reaction was stirred at 140 °C. After 240 minutes, the reaction was cooled to room temperature and the volatiles were removed *in vacuo*. The crude reaction product was partitioned between chloroform and aqueous sodium bicarbonate solution. The organic layer was collected, washed with brine and dried over sodium sulfate. Filtration and evaporation of solvents gave the crude product (303.0 mg, 0.440 mmol).
LCMS-ESI$^+$: calc'd for $C_{36}H_{44}N_6O_4S_2$: 688.9 (M^+); Found: 688.3 ($M+H^+$).

(1-{2-[5-(6-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-4,8-dimethyl-1,5-dithia-s-indacen-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester:
1-{2-[5-(6-{2-[1-carbamic acid *tert*-butyl ester-pyrrolidin-2-yl]-3H-imidazol-4-yl}-4,8-dimethyl-1,5-dithia-s-indacen-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbamic acid *tert*-butyl ester (51.0 mg, 0.073 mmol) was dissolved in DCM (0.67 mL) and HCl in dioxane (4M, 0.67

mL) was added and stirring at room temperature was continued. After 45 minutes, all volatiles were removed *in vacuo*. The crude material was used in the next step without further purification. The crude material was dissolved in DMF (0.8 mL) and DIEA (37.6 mg, 0.292 mmol) was added. A solution of 2- (*L*) methoxycarbonylamino-3-methyl-butyric acid (25.5 mg, 0.146 mmol), HATU (55.5 mg, 0.146 mmol) and DIEA (18.8 mg, 0.146 mmol) in DMF (0.5 mL) was added. The reaction was stirred at room temperature. After 30 minutes, the reaction was quenched with aqueous hydrochloric acid (0.2 mL, 2 M) and was purified by RP-HPLC (eluent: water / MeCN w/ 0.1% TFA) to yield the product (5.1 mg) as a TFA salt.
LCMS-ESI$^+$: calc'd for $C_{40}H_{50}N_8O_6S_2$: 803.0 (M^+); Found: 803.2 ($M+H^+$).
^{1}H-NMR: 300 MHz, (dmso-d_6) δ: 7.88 (s, 4H), 7.30 (m, 2H), 5.10 (m, 2H), 4.12 (dd, J = 8.1 / 8.1 Hz, 2H), 3.83 (m, 4H) 3.53 (s, 6H), 2.73 (s, 6H), 2.27 (m, 2H), 2.14 – 1.98 (m, 8H), 0.89 - 0.80 (m, 12H) ppm.

Example FZ



(2-{2-[5-(6-{2-[1-(2-Methoxycarbonylamino-2-phenyl-acetyl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-4,8-dimethyl-1,5-dithia-s-indacen-2-yl)-1*H*-imidazol-2-yl]-pyrrolidin-1-yl}-2-oxo-1-phenyl-ethyl)-carbamic acid methyl ester

(2-{2-[5-(6-{2-[1-(2-Methoxycarbonylamino-2-phenyl-acetyl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-4,8-dimethyl-1,5-dithia-s-indacen-2-yl)-1H-imidazol-2-yl]-pyrrolidin-1-yl}-2-oxo-1-phenyl-ethyl)-carbamic acid methyl ester

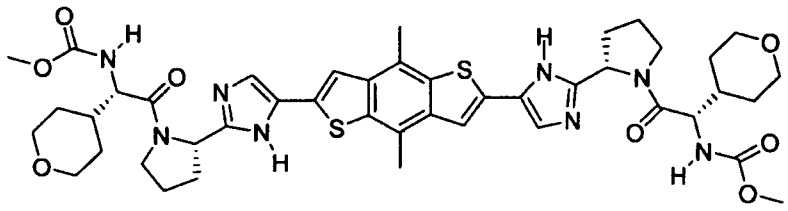
1-{2-[5-(6-{2-[1-carbamic acid *tert*-butyl ester-pyrrolidin-2-yl]-3H-imidazol-4-yl}-4,8-dimethyl-1,5-dithia-s-indacen-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbamic acid *tert*-butyl ester (51.0 mg, 0.073 mmol) was dissolved in DCM (0.67 mL) and HCl in dioxane (4M, 0.67 mL) was added and stirring at room temperature was continued. After 45 minutes, all volatiles were removed *in vacuo*. The crude material was used in the next step without further purification. The crude material was dissolved in DMF (0.8 mL) and DIEA (37.6 mg, 0.292 mmol) was added. A solution of 2- (*D*) methoxycarbonylamino-2-phenyl-acetic acid (30.5 mg, 0.146 mmol), HATU (55.5 mg, 0.146 mmol) and DIEA (18.8 mg, 0.146 mmol) in DMF (0.5 mL) was added. The reaction was stirred at room temperature. After 30 minutes, the reaction was quenched with aqueous hydrochloric acid (0.2 mL, 2 M) and was purified by RP-HPLC

(eluent: water / MeCN w/ 0.1% TFA) to yield the product (6.7 mg) as a mixture of isomers and in the form of the TFA salt.

LCMS-ESI$^+$: calc'd for $C_{40}H_{50}N_8O_6S_2$: 871.0 (M^+); Found: 871.7 ($M+H^+$).

^{1}H-NMR: 300 MHz, (dmso-d_6) δ: 7.95 – 7.66 (m, 6H), 7.40 – 7.34 (m, 8H), 7.06 (m, 2H), 5.51 (m, 2H), 5.13 (m, 2H), 3.91 (m, 2H), 3.54 and 3.52 (2x s, 6H), 3.16 (m, 2H), 2.76 (s, 6H), 2.19 – 1.98 (m, 8H) ppm.

Example GA



(2-{2-[5-(6-{2-[1-(2-Methoxycarbonylamino-2-tetrahydropyranyl-acetyl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-4,8-dimethyl-1,5-dithia-*s*-indacen-2-yl)-1*H*-imidazol-2-yl]-pyrrolidin-1-yl}-2-oxo-1-tetrahydropyranyl-ethyl)-carbamic acid methyl ester

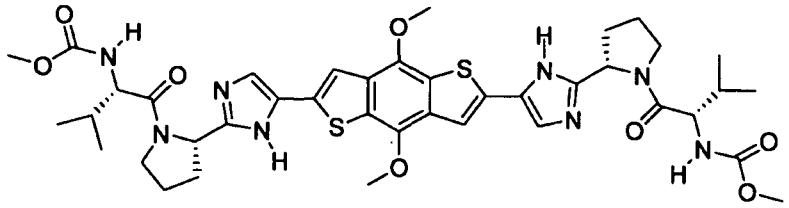
(2-{2-[5-(6-{2-[1-(2-Methoxycarbonylamino-2-tetrahydropyranyl-acetyl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-4,8-dimethyl-1,5-dithia-s-indacen-2-yl)-1H-imidazol-2-yl]-pyrrolidin-1-yl}-2-oxo-1-tetrahydropyranyl-ethyl)-carbamic acid methyl ester:

1-{2-[5-(6-{2-[1-carbamic acid *tert*-butyl ester-pyrrolidin-2-yl]-3H-imidazol-4-yl}-4,8-dimethyl-1,5-dithia-s-indacen-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbamic acid *tert*-butyl ester (51.0 mg, 0.073 mmol) was dissolved in DCM (0.67 mL) and HCl in dioxane (4M, 0.67 mL) was added and stirring at room temperature was continued. After 45 minutes, all volatiles were removed *in vacuo*. The crude material was used in the next step without further purification. The crude material was dissolved in DMF (0.8 mL) and DIEA (37.6 mg, 0.292 mmol) was added. A solution of 2- (*L*) methoxycarbonylamino-2-(4-tetrahydropyranyl)-acetic acid (31.6 mg, 0.146 mmol), HATU (55.5 mg, 0.146 mmol) and DIEA (18.8 mg, 0.146 mmol) in DMF (0.5 mL) was added. The reaction was stirred at room temperature. After 20 minutes, the reaction was quenched with aqueous hydrochloric acid (0.2 mL, 2 M) and was purified by RP-HPLC (eluent: water / MeCN w/ 0.1% TFA) to yield the product (8.1 mg) as a TFA salt.

LCMS-ESI$^+$: calc'd for $C_{44}H_{54}N_8O_8S_2$: 887.0 (M^+); Found: 887.9 ($M+H^+$).

^{1}H-NMR: 300 MHz, (dmso-d_6) δ: 7.81 (s, 4H), 7.39 (m, 2H), 5.08 (m, 2H), 4.18 (m, 2H), 3.85 (m, 8H) 3.53 (s, 6H), 3.22 (m, 4H), 2.72 (s, 6H), 2.27 (m, 2H), 2.14 – 1.98 (m, 8H), 1.58 - 1.25 (m, 8H) ppm.

Example GB



(1-{2-[5-(4,8-Dimethoxy-6-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-1,5-dithia-s-indacen-2-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

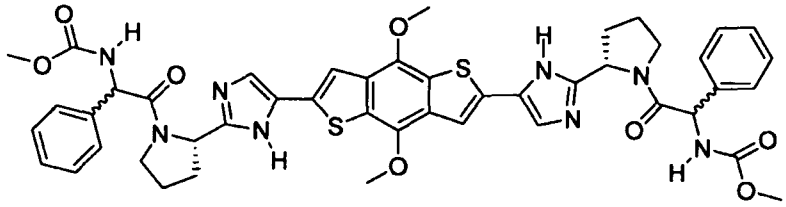
(1-{2-[5-(4,8-Dimethoxy-6-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-1,5-dithia-s-indacen-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester:

1-{2-[5-(6-{2-[1-carbamic acid *tert*-butyl ester-pyrrolidin-2-yl]-3H-imidazol-4-yl}-4,8-dimethoxy-1,5-dithia-s-indacen-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbamic acid *tert*-butyl ester (49.3 mg, 0.070 mmol) was dissolved in DCM (0.67 mL) and HCl in dioxane (4M, 0.67 mL) was added and stirring at room temperature was continued. After 45 minutes, all volatiles were removed *in vacuo*. The crude material was used in the next step without further purification. The crude material was dissolved in DMF (0.8 mL) and DIEA (36.0 mg, 0.280 mmol) was added. A solution of 2- (*L*) methoxycarbonylamino-3-methyl-butyric acid (24.5 mg, 0.140 mmol), HATU (53.2 mg, 0.140 mmol) and DIEA (18.0 mg, 0.140 mmol) in DMF (0.5 mL) was added. The reaction was stirred at room temperature. After 45 minutes, the crude reaction was quenched with aqueous hydrochloric acid (0.2 mL, 2 M) and was purified by RP-HPLC (eluent: water / MeCN w/ 0.1% TFA) to yield the product (5.1 mg) as a TFA salt. [The required starting material for the modified sequence was described in Org. Lett., 2008, 10:4421-4424.]

LCMS-ESI$^+$: calc'd for $C_{40}H_{50}N_8O_8S_2$: 835.0 (M^+); Found: 835.2 ($M+H^+$).

^{1}H-NMR: 300 MHz, (dmso-d_6) δ: 7.95 (s, 2H), 7.85 (s, 2H), 7.30 (d, J = 8.4 Hz, 2H), 5.09 (dd, J = 4.8 / 4.8 Hz, 2H), 4.10 – 4.07 (m, 8H), 3.82 (m, 4H) 3.57 (s, 6H), 2.30 (m, 2H), 2.15 – 1.96 (m, 8H), 0.87 - 0.80 (m, 12H) ppm.

Example GC



(2-{2-[5-(4,8-Dimethoxy-6-{2-[1-(2-methoxycarbonylamino-2-phenyl-acetyl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-1,5-dithia-s-indacen-2-yl)-1*H*-imidazol-2-yl]-pyrrolidin-1-yl}-2-oxo-1-phenyl-ethyl)-carbamic acid methyl ester

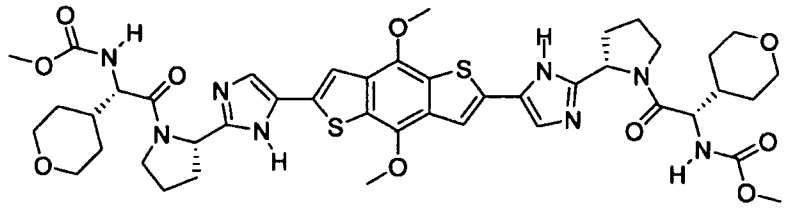
(2-{2-[5-(4,8-Dimethoxy-6-{2-[1-(2-methoxycarbonylamino-2-phenyl-acetyl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-1,5-dithia-s-indacen-2-yl)-1H-imidazol-2-yl]-pyrrolidin-1-yl}-2-oxo-1-phenyl-ethyl)-carbamic acid methyl ester:

1-{2-[5-(6-{2-[1-carbamic acid *tert*-butyl ester-pyrrolidin-2-yl]-3H-imidazol-4-yl}-4,8-dimethoxy-1,5-dithia-s-indacen-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbamic acid *tert*-butyl ester (49.3 mg, 0.070 mmol) was dissolved in DCM (0.67 mL) and HCl in dioxane (4M, 0.67 mL) was added and stirring at room temperature was continued. After 45 minutes, all volatiles were removed *in vacuo*. The crude material was used in the next step without further purification. The crude material was dissolved in DMF (0.8 mL) and DIEA (36.0 mg, 0.280 mmol) was added. A solution of 2- (*D*) methoxycarbonylamino-2-phenyl-acetic acid (29.3 mg, 0.140 mmol), HATU (53.2 mg, 0.140 mmol) and DIEA (18.0 mg, 0.140 mmol) in DMF (0.5 mL) was added. The reaction was stirred at room temperature. After 45 minutes, the crude reaction was quenched with aqueous hydrochloric acid (0.2 mL, 2 M) and was purified by RP-HPLC (eluent: water / MeCN w/ 0.1% TFA) to yield the product (6.7 mg) as a mixture of isomers and in the form of the TFA salt.

LCMS-ESI$^+$: calc'd for $C_{40}H_{50}N_8O_6S_2$: 871.0 (M^+); Found: 871.7 ($M+H^+$).

^{1}H-NMR: 300 MHz, (dmso-d_6) δ: 8.01 – 7.67 (m, 6H), 7.39 – 7.35 (m, 8H), 7.06 (m, 2H), 5.51 (m, 2H), 5.13 (m, 2H), 4.13 (s, 6H), 3.91 (m, 2H), 3.54 and 3.52 (2x s, 6H), 3.16 (m, 2H), 2.19 – 1.87 (m, 8H) ppm.

Example GD

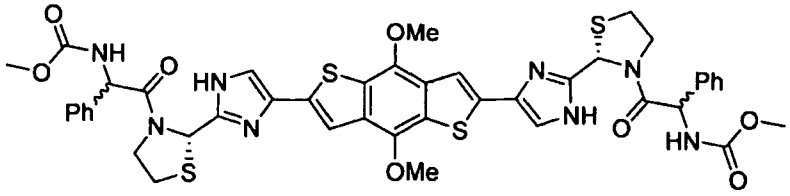


(2-{2-[5-(4,8-Dimethoxy-6-{2-[1-(2-methoxycarbonylamino-2-tetrahydropyranyl-acetyl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-1,5-dithia-*s*-indacen-2-yl)-1*H*-imidazol-2-yl]-pyrrolidin-1-yl}-2-oxo-1-tetrahydropyranyl-ethyl)-carbamic acid methyl ester

(2-{2-[5-(6-{2-[1-(2-Methoxycarbonylamino-2-tetrahydropyranyl-acetyl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-4,8-dimethyl-1,5-dithia-s-indacen-2-yl)-1H-imidazol-2-yl]-pyrrolidin-1-yl}-2-oxo-1-tetrahydropyranyl-ethyl)-carbamic acid methyl ester:

1-{2-[5-(6-{2-[1-carbamic acid *tert*-butyl ester-pyrrolidin-2-yl]-3H-imidazol-4-yl}-4,8-dimethoxy-1,5-dithia-s-indacen-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbamic acid *tert*-butyl ester (49.3 mg, 0.070 mmol) was dissolved in DCM (0.67 mL) and HCl in dioxane (4M, 0.67 mL) was added and stirring at room temperature was continued. After 45 minutes, all volatiles were removed *in vacuo.* The crude material was used in the next step without further purification. The crude material was dissolved in DMF (0.8 mL) and DIEA (36.0 mg, 0.280 mmol) was added. A solution of 2- (*L*) methoxycarbonylamino-2-(4-tetrahydropyranyl)-acetic acid (30.4 mg, 0.140 mmol), HATU (53.2 mg, 0.140 mmol) and DIEA (18.0 mg, 0.140 mmol) in DMF (0.5 mL) was added. The reaction was stirred at room temperature. After 20 minutes, the reaction was quenched with aqueous hydrochloric acid (0.2 mL, 2 M) and was purified by RP-HPLC (eluent: water / MeCN w/ 0.1% TFA) to yield the product (8.1 mg) as a TFA salt. LCMS-ESI$^+$: calc'd for $C_{44}H_{54}N_8O_8S_2$: 919.0 (M^+); Found: 919.6 ($M+H^+$).
^{1}H-NMR: 300 MHz, (dmso-d_6) δ: 7.86 (s, 2H), 7.74 (s, 2H), 7.39 (m, 2H), 5.07 (m, 2H), 4.18 (m, 2H), 4.08 (s, 6H), 3.84 (m, 8H), 3.53 (s, 6H), 3.21 (m, 4H), 2.26 (m, 2H), 2.15 – 1.92 (m, 8H), 1.64 - 1.27 (m, 8H) ppm.

Example GE



(2-{2-[4-(4,8-Dimethoxy-6-{2-[3-(2-methoxycarbonylamino-2-phenyl-acetyl)-thiazolidin-2-yl]-1*H*-imidazol-4-yl}-1,5-dithia-*s*-indacen-2-yl)-1*H*-imidazol-2-yl]-thiazolidin-3-yl}-2-oxo-1-phenyl-ethyl)-carbamic acid methyl ester

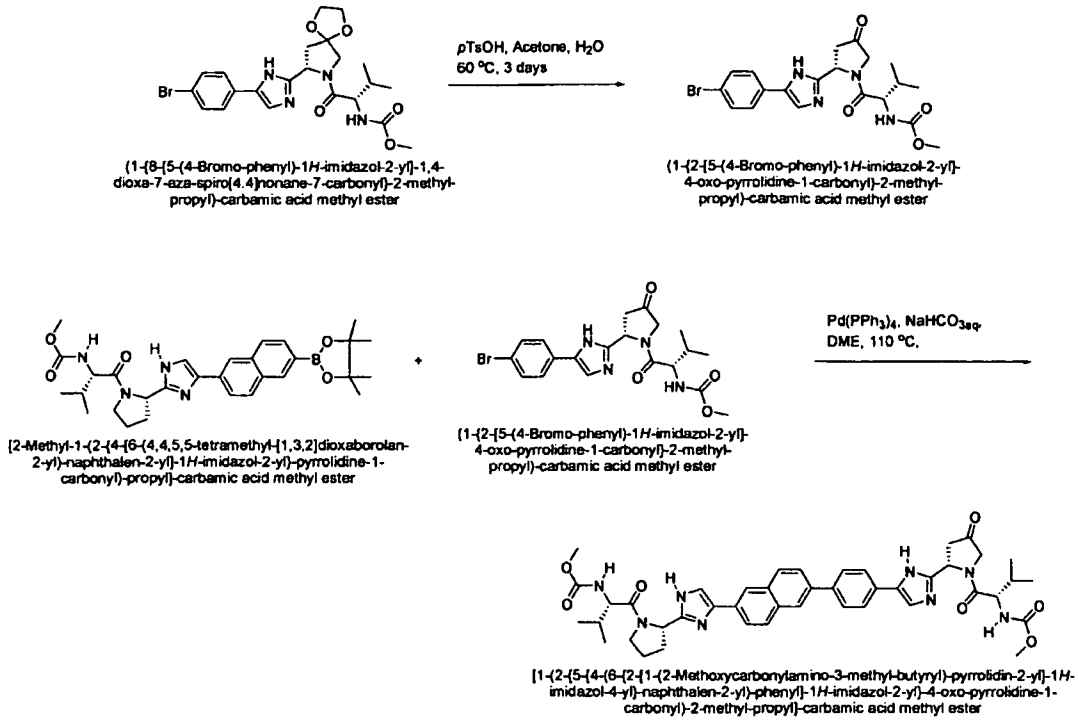
(2-{2-[5-(6-{2-[1-(2-Methoxycarbonylamino-2-phenyl-acetyl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-4,8-dimethyl-1,5-dithia-s-indacen-2-yl)-1*H*-imidazol-2-yl]-pyrrolidin-1-yl}-2-oxo-1-phenyl-ethyl)-carbamic acid methyl ester

(2-{2-[5-(6-{2-[1-(2-Methoxycarbonylamino-2-phenyl-acetyl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-4,8-dimethyl-1,5-dithia-s-indacen-2-yl)-1*H*-imidazol-2-yl]-pyrrolidin-1-yl}-2-oxo-1-phenyl-ethyl)-carbamic acid methyl ester was prepared following method used for (2-{2-[5-(4,8-Dimethoxy-6-{2-[1-(2-methoxycarbonylamino-2-phenyl-acetyl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-1,5-dithia-s-indacen-2-yl)-1*H*-imidazol-2-yl]-pyrrolidin-1-yl}-2-oxo-1-phenyl-ethyl)-carbamic acid methyl ester substituting *L*- thiazolidine-2,3-dicarboxylic acid 3-*tert*-butyl ester for *L*-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester.

LCMS-ESI$^+$: calc'd for $C_{44}H_{42}N_8O_8S_4$: 938.2 (M^+) found: 939.1 ($M + H^+$)

^{1}H-NMR: 300 MHz, (dmso-d_6) δ: 7.85 - 7.63 (m 2H), 7.46 -7.29 (m10H), 7.08 -7.01 (m, 2H), 6.31 (m, 2H), 5.60 (d, J = 7.6 Hz, 2H), 4.24 (m 2H), 4.13 (s, 6H), 4.06 - 3.76 (m 2H), 3.54 (m, 6H), 3.28 (m, 2H), 3.15 (m, 2H).

Example GF



(1-{2-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-4-oxo-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester:

(1-{8-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-1,4-dioxa-7-aza-spiro[4.4]nonane-7-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (230.0 mg, 0.453 mmol) was dissolved in acetone (10 mL) and water (0.2 mL) and p-TsOH ∘ H2O (53 mg, 0.278 mmol) were added. The reaction was heated at 60 °C for 20 hours, after which additional p-TsOH ∘ H_2O (53 mg, 0.278 mmol) was added heating at 60 °C was continued. After three days, all volatiles were removed *in vacuo*. The crude material was taken into EtOAc and was washed with aqueous sodium bicarbonate solution and dried over sodium sulfate. Filtration and evaporation of solvents *in vacuo* gives the crude product. The crude material was purified via silica gel chromatography (eluent: EtOAc containing 10%MeOH / hexanes) to yield the product (93.9 mg, 0.202 mmol). LCMS-ESI$^+$: calc'd for $C_{20}H_{23}BrN_4O_4$: 463.3 (M^+); Found: 463.6 ($M+H^+$).

^{1}H-NMR: 300 MHz, (dmso-d_6) δ: 7.92 (m, 1H), 7.64 (m, 5H), 7.49 (d, J = 6.5Hz, 1H), 5.56 (dd, J = 7.5 / 3.6 Hz, 1H), 4.34 (m, 2H), 3.91 (dd, J = 6.3 / 6.3 Hz, 1H), 3.52 (s, 3H), 3.20 (dd, J = 14.4 / 7.8 Hz, 1H), 2.82 (br-d, J = 14.4 Hz, 1H), 1.87 (m, 1H), 0.78 (d, J= 5.1 Hz, 3H), 0.71 (d, J = 4.8 Hz, 3H) ppm.

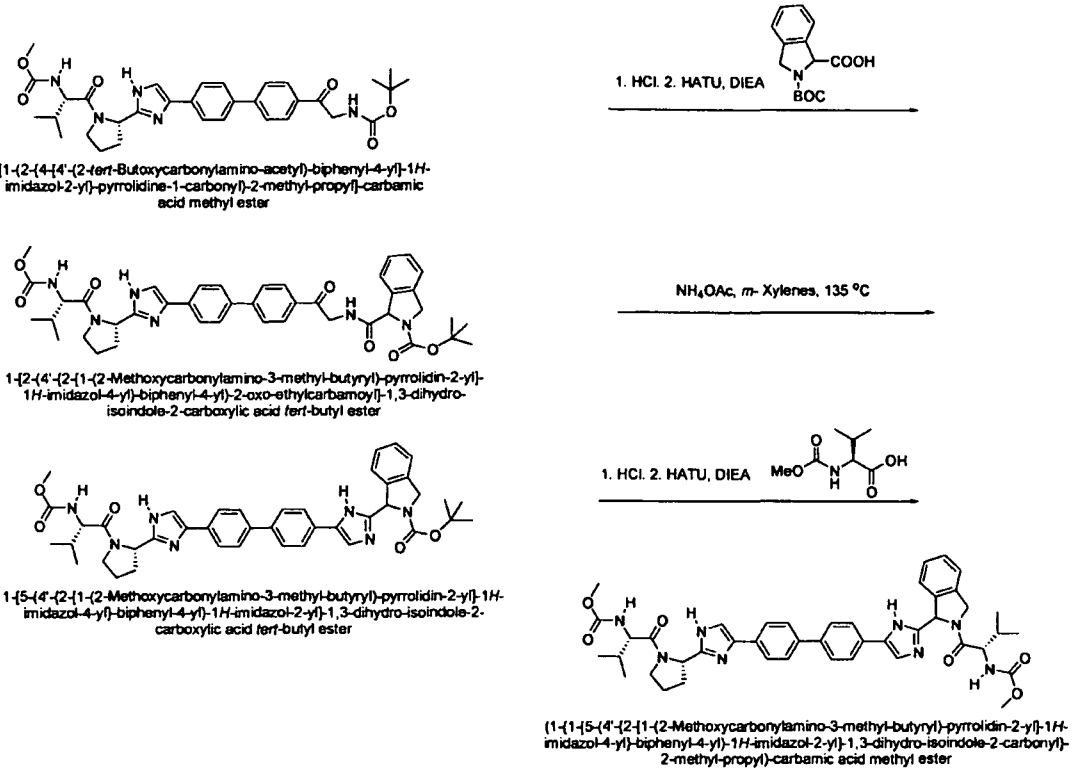
[1-(2-{5-[4-(6-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-1H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-4-oxo-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester:

(1-{2-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-4-oxo-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (46.0 mg, 0.1 mmol), [2-Methyl-1-(2-{4-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-propyl]-carbamic acid methyl ester (54 mg, 0.1 mmol), and $Pd[PPh_3]_4$ (11.5 mg, 0.01 mmol) were dissolved in DME (2 mL) under an atmosphere of argon. Saturated, aqueous sodium bicarbonate solution (0.3 mL) was added and the reaction was heated under microwave conditions at 120 °C for 20 minutes. The solids were discarded and the volatiles were removed *in vacuo*. The crude reaction mixture was purified by RP-HPLC (eluent: water / MeCN w/ 0.1% TFA) to yield the product (4.0 mg) as a TFA salt.

LCMS-ESI$^+$: calc'd for $C_{44}H_{50}N_8O_7$: 802.9 (M^+); Found: 803.4 ($M+H^+$).

^{1}H-NMR: 300 MHz, (dmso-d_6) δ: 8.32 (m, 2H), 8.12 – 7.84 (m, 10H), 7.52 (d, J = 7.8Hz, 1H), 7.32 (d, J = 8.4Hz, 1H), 5.61 (m, 1H), 5.14 (m, 1H), 4.39 (m, 2H), 4.12 (dd, J = 7.5 Hz, 1H), 3.94 (dd, J = 8.4 / 8.4 Hz, 1H), 3.85 (m, 2H), 3.54 (2x s, 6H), 3.26 (m, 1H), 2.90 (m, 1H), 2.13 – 1.90 (m, 6H), 0.86 - 0.74 (m, 12H) ppm.

Example GG



1-[2-(4'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-1H-imidazol-4-yl}-biphenyl-4-yl)-2-oxo-ethylcarbamoyl]-1,3-dihydro-isoindole-2-carboxylic acid *tert*-butyl ester:

[1-(2-{4-[4'-(2-*tert*-Butoxycarbonylamino-acetyl)-biphenyl-4-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (107.0 mg, 0.177 mmol) was dissolved in DCM (1 mL) and HCl in dioxane (4M, 1 mL) was added and stirring at room temperature was continued. After 45 minutes, all volatiles were removed *in vacuo*. The crude material was used in the next step without further purification. The crude material was dissolved in DMF (0.6 mL) and DIEA (68.4 mg, 0.531 mmol) was added. A solution of racemic 1,3-dihydro-isoindole-1,2-dicarboxylic acid 2-*tert*-butyl ester (46.6 mg, 0.177 mmol), HATU (67.3 mg, 0.177 mmol) and DIEA (22.8 mg, 0.177 mmol) in DMF (0.4 mL) was added. The reaction was stirred at room temperature. After 15 minutes, the reaction was diluted with EtOAc and was washed with brine, saturated sodium bicarbonate solution, brine, and was dried over sodium

sulfate. Filtration and removal of solvents *in vacuo* gave the crude material (147.8 mg), which was used in the next step without further purification.
LCMS-ESI$^+$: calc'd for $C_{42}H_{48}N_6O_7$: 748.8 (M^+); Found: 749.2 ($M+H^+$).

1-[5-(4'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-1H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-1,3-dihydro-isoindole-2-carboxylic acid *tert*-butyl ester:
1-[2-(4'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-1H-imidazol-4-yl}-biphenyl-4-yl)-2-oxo-ethylcarbamoyl]-1,3-dihydro-isoindole-2-carboxylic acid *tert*-butyl ester (147.8 mg) was taken into m-xylenes (2.0 mL) and heated at 135 °C. Solid ammonium acetate (120 mg, 1.5 mmol) was added and the reaction was stirred at 135 °C. After 180 minutes, the reaction was cooled to room temperature and the volatiles were removed *in vacuo*. The crude reaction product was partitioned between EtOAc and water. The organic layer was collected and dried over sodium sulfate. Filtration and evaporation of solvents gave the crude product (142 mg).
LCMS-ESI$^+$: calc'd for $C_{42}H_{47}N_7O_5$: 729.8 (M^+); Found: 730.4 ($M+H^+$).
^{1}H-NMR: 300 MHz, (dmso-d_6) δ: 8.07 (m, 2H), 7.90 – 7.85 (m, 8H), 7.49 – 7.27 (m, 5H), 6.31 (s, 1H), 5.12 (dd, J = 6.9 / 6.9 Hz, 1H), 4.95 – 4.70 (m, 2H), 4.11 (dd, J = 7.5 / 7.5 Hz, 1H), 3.83 (m, 2H), 3.53 (s, 3H), 2.41 (m, 1H), 2.13 – 1.95 (m, 4H), 1.45 and 1.22 (2 x s, 9H), 0.88 - 0.78 (m, 6H) ppm.

(1-{1-[5-(4'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-1H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-1,3-dihydro-isoindole-2-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester:
1-[5-(4'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-1H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-1,3-dihydro-isoindole-2-carboxylic acid *tert*-butyl ester (71.0 mg, 0.086 mmol) was dissolved in DCM (1.0 mL) and HCl in dioxane (4M, 0.5 mL) was added and stirring at room temperature was continued. After 5 minutes, all volatiles were removed *in vacuo*. The crude material was used in the next step without further purification. The crude material was dissolved in DMF (0.5 mL) and DIEA (30.9 mg, 0.24 mmol) was added. A solution of 2- (*L*) methoxycarbonylamino-3-methyl-butyric acid (14.0 mg, 0.080 mmol), HATU (30.4 mg, 0.08 mmol) and DIEA (10.3 mg, 0.08 mmol) in DMF (0.4 mL) was added. The reaction was stirred at room temperature. After 120 minutes, the crude reaction was quenched with aqueous hydrochloric acid (0.1 mL, 2 M) and was purified by RP-HPLC (eluent: water /

MeCN w/ 0.1% TFA) to yield the two diastereomeric products (1.5 mg and 2.4 mg) as TFA salts.

Compound A (faster eluding material on RP-HPLC)

LCMS-ESI$^+$: calc'd for $C_{44}H_{50}N_8O_6$: 786.9 (M^+); Found: 787.4 ($M+H^+$).

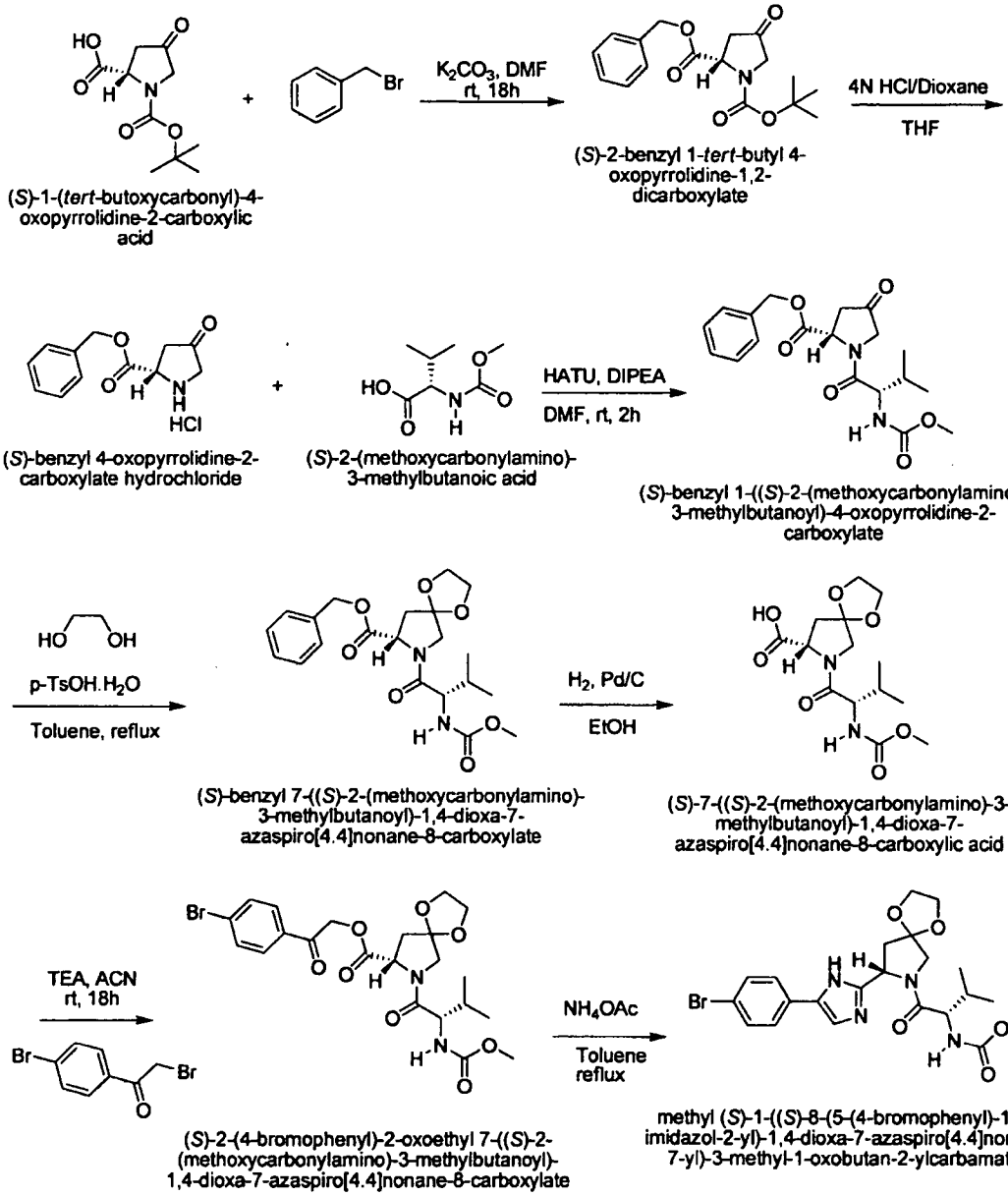
^{1}H-NMR: 300 MHz, (dmso-d_6) δ: 7.90 – 7.75 (m, 10H), 7.50 – 7.27 (m, 6H), 6.42 (m, 1H), 5.39 – 5.21 (m, 2H), 5.09 (m, 1H), 4.16 – 4.08 (m, 2H), 3.81 (m, 2H), 3.52 (s, 6H), 2.41 (m, 1H), 2.13 – 1.95 (m, 5H), 0.91 - 0.79 (m, 12H) ppm.

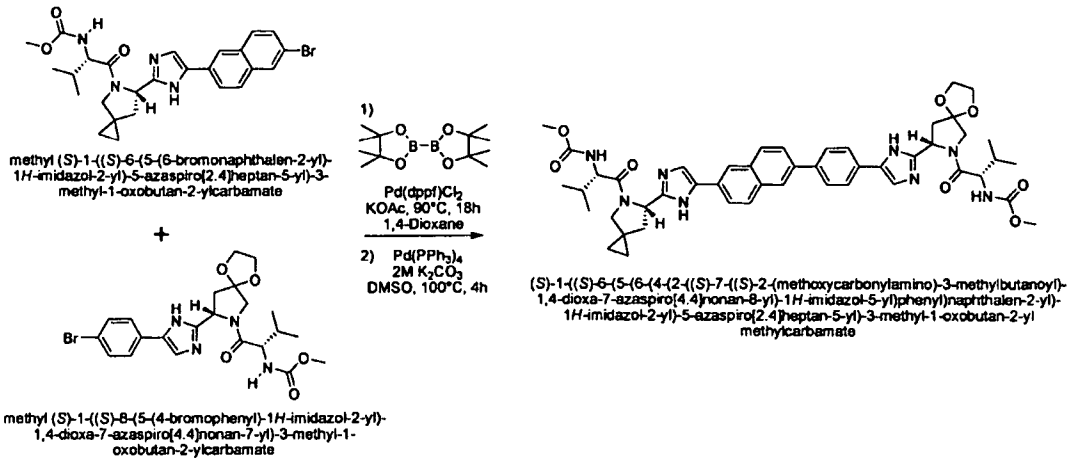
Compound B (later eluding material on RP-HPLC)

LCMS-ESI$^+$: calc'd for $C_{44}H_{50}N_8O_6$: 786.9 (M^+); Found: 787.4 ($M+H^+$).

^{1}H-NMR: 300 MHz, (dmso-d_6) δ: 7.80 – 7.58 (m, 10H), 7.40 – 7.13 (m, 6H), 6.29 (m, 1H), 5.09 – 4.70 (m, 3H), 4.06 (m, 1H), 3.91 (m, 1H), 3.65 (m, 2H), 3.34 (s, 3H), 3.33 (s, 3H), 2.18 (m, 1H), 1.98 – 1.82 (m, 5H), 0.75 - 0.59 (m, 12H) ppm.

Example GH


HO
O
H
N
O
O
Br
K_2CO_3, DMF
rt, 18h
4N HCl/Dioxane
THF
(S)-1-(tert-butoxycarbonyl)-4-oxopyrrolidine-2-carboxylic acid
(S)-2-benzyl 1-tert-butyl 4-oxopyrrolidine-1,2-dicarboxylate
HCl
(S)-benzyl 4-oxopyrrolidine-2-carboxylate hydrochloride
(S)-2-(methoxycarbonylamino)-3-methylbutanoic acid
HATU, DIPEA
DMF, rt, 2h
(S)-benzyl 1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-4-oxopyrrolidine-2-carboxylate
HO
OH
p-TsOH.H_2O
Toluene, reflux
H_2, Pd/C
EtOH
(S)-benzyl 7-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-1,4-dioxa-7-azaspiro[4.4]nonane-8-carboxylate
(S)-7-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-1,4-dioxa-7-azaspiro[4.4]nonane-8-carboxylic acid
TEA, ACN
rt, 18h
(S)-2-(4-bromophenyl)-2-oxoethyl 7-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-1,4-dioxa-7-azaspiro[4.4]nonane-8-carboxylate
NH_4OAc
Toluene
reflux
methyl (S)-1-((S)-8-(5-(4-bromophenyl)-1H-imidazol-2-yl)-1,4-dioxa-7-azaspiro[4.4]nonan-7-yl)-3-methyl-1-oxobutan-2-ylcarbamate



(S)-2-benzyl 1-*tert*-butyl 4-oxopyrrolidine-1,2-dicarboxylate

To a stirring solution of a mixture of (S)-1-(*tert*-butoxycarbonyl)-4-oxopyrrolidine-2-carboxylic acid (2.85 g, 12.43 mmol) and potassium carbonate (4.33 g, 24.87 mmol) in anhydrous N,N-dimethylformamide (60 mL) was added benzyl bromide (4.25 g, 24.87 mmol). The mixture was stirred at room temperature overnight.

The resulting crude mixture was diluted with ethylacetate and the organic layer was washed with 10% sodium carbonate and brine. The organic layer was dried over sodium sulfate and volatiles were removed *in-vacuo*. The residue was purified on normal phase column to yield 2.82 g (71%) of desired product.

(S)-benzyl 4-oxopyrrolidine-2-carboxylate hydrochloride

To a stirring solution of (S)-2-benzyl 1-*tert*-butyl 4-oxopyrrolidine-1,2-dicarboxylate (2.82 g, 8.8 mmol) in anhydrous tetrahydrofuran (44 mL) was added 4N HCl in 1,4-dioxane (9.3 mL) at room temperature. The mixture was stirred for 18 hours at room temperature. The product was then three times with toluene on rotovap to dryness to remove all the excess acid and further dried on a high vacuum overnight and used as is in the next step. Quantitative yield.

(S)-benzyl 1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-4-oxopyrrolidine-2-carboxylate

Following the procedure used to prepare compound (S)-benzyl 1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-4-oxopyrrolidine-2-carboxylate, except that (S)-benzyl 4-oxopyrrolidine-2-carboxylate and (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid were used instead of 2-{5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-

imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester and 3-[5-(4-bromo-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester.

(S)-benzyl 7-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-1,4-dioxa-7-azaspiro[4.4]nonane-8-carboxylate

(S)-benzyl 1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-4-oxopyrrolidine-2-carboxylate (2.45 g, 6.51 mmol) in a round bottom flask was dissolved in anhydrous toluene (200 mL) and p-toluene sulfonic acid monohydride (124 mg, 0.1 mmol) and ethylene glycol (808 mg, 13.02 mmol) were added and the mixture was refluxed for 18 hours, removing the generated byproduct water with a Dean-Stark apparatus. The crude mixture was then diluted with ethyl acetate and washed, respectively, with 10% citric acid, saturated ammonium chloride, 10% sodium carbonate and finally with brine. The organic layers were combined and dried over sodium sulfate and concentrated down on rotovap. The crude residue was then purified on normal phase column chromatography with 5% MeOH/DCM. (2.3 g, 84%)

(S)-7-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-1,4-dioxa-7-azaspiro[4.4]nonane-8-carboxylic acid

(S)-benzyl 7-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-1,4-dioxa-7-azaspiro[4.4]nonane-8-carboxylate (2.3 g, 5.47 mmol) was dissolved in ethyl alcohol (55 mL) and under Argon charged with 10% Pd/C in a round bottom flask. The flask was then sealed with a rubber septa and the air was removed by vacuum and replaced with H2 from a balloon. This process repeated three times and the mixture was stirred under H2 atmosphere for 18 hours. The resulting mixture was then passed through a elite plug and concentrated down on rotovap to yield 1.76 g, 98% desired product.

(S)-2-(4-bromophenyl)-2-oxoethyl 7-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-1,4-dioxa-7-azaspiro[4.4]nonane-8-carboxylate

Title compound was prepared according to the method employed to prepare (S)-2-(4-bromophenyl)-2-oxoethyl 5-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-5-azaspiro[2.4]heptane-6-carboxylate (2.07g, 74%)

Methyl (S)-1-((S)-8-(5-(4-bromophenyl)-1H-imidazol-2-yl)-1,4-dioxa-7-azaspiro[4.4]nonan-7-yl)-3-methyl-1-oxobutan-2-ylcarbamate

Title compound was prepared according to the method employed to prepare methyl (S)-1-((S)-6-(5-(4-bromophenyl)-1H-imidazol-2-yl)-5-azaspiro[2.4]heptan-5-yl)-3-methyl-1-oxobutan-2-ylcarbamate (1.64 g, 82.2%)

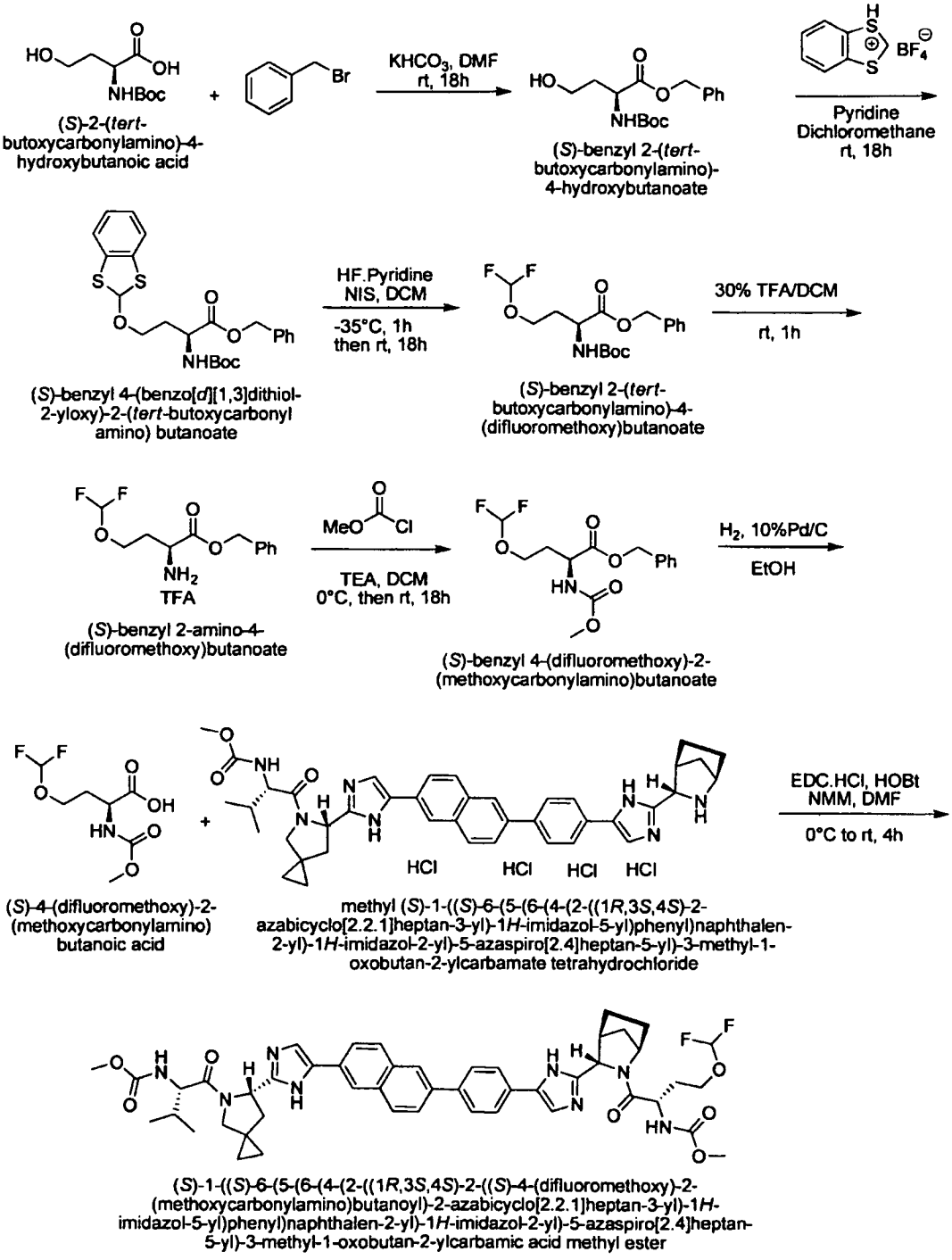
(S)-1-((S)-6-(5-(6-(4-(2-((S)-7-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-1,4-dioxa-7-azaspiro[4.4]nonan-8-yl)-1H-imidazol-5-yl)phenyl)naphthalen-2-yl)-1H-imidazol-2-yl)-5-azaspiro[2.4]heptan-5-yl)-3-methyl-1-oxobutan-2-yl-carbamic acid methyl ester:

Methyl (S)-1-((S)-8-(5-(4-bromophenyl)-1H-imidazol-2-yl)-1,4-dioxa-7-azaspiro[4.4]nonan-7-yl)-3-methyl-1-oxobutan-2-ylcarbamate (200 mg, 0.39 mmol), bis(pinacolato)diboron (130 mg, 0.51 mmol), potassium acetate (116 mg, 1.18 mmol), and $Pd(dppf)Cl_2$ (29 mg, 0.039 mmol) were all weighed out in a glass pressure vessel and anhydrous 1,4-Dioxane (2 mL) was added. The mixture was bubbled with nitrogen gas for about 5 min. The vessel was then capped and sealed and heated in an oil bath at 90°C overnight with continuous stirring.

The reaction vessel was cooled down to room temperature and methyl (S)-1-((S)-6-(5-(6-bromonaphthalen-2-yl)-1H-imidazol-2-yl)-5-azaspiro[2.4]heptan-5-yl)-3-methyl-1-oxobutan-2-ylcarbamate (215 mg, 0.41 mmol), 2M K_2CO_3, and Pd(PPh3)4 (46 mg, 0.04 mmol) were all added along with 2 mL of DMSO and the mixture was bubbled with nitrogen gas for 5 minutes. The vessel, again, was capped, sealed and placed in an oil bath at 100°C for 4 hours.

The resulting crude mixture was diluted with ethyl acetate and washed, respectively, with brine, 10% Na_2CO_3, 10% citric acid, saturated solution of NH_4Cl, and brine. The organic layer was then dried over Na_2SO_4 and the volatiles were removed on rotovap. The residue was first purified on normal phase chromatography and then on prep HPLC. Yield= 205 mg (60%). ^{1}H-NMR: 400 MHz, ($CDCl_3$) δ 8.18 – 7.97 (m, 1H), 7.83 – 7.6 (m, 8H), 7.82 – 7.22 (m, 3H), 5.47 – 5.34 (m, 4H),4.33 – 4.26 (m, 1H), 4.08 – 4.03 (m, 4H), 3.94 – 3.89 (m, 1H), 3.78 – 3.69 (m, 8H), 3.22 (brs, 1H), 2.96 – 2.94 (m, 1H), 2.49 – 2.46 (m, 1H), 2.22 – 2.17 (m, 1H), 1.99 (brs, 1H), 1.08 – 1.04 (m, 2H), 0.94 – 0.79 (m, 12H), 0.71 (m, 4H). MS (ESI) *m/z* 873.79 $[M + H]^+$.

Example GI



(*S*)-2-(*tert*-butoxycarbonylamino)-4-hydroxybutanoic acid

(*S*)-benzyl 2-(*tert*-butoxycarbonylamino)-4-hydroxybutanoate

(*S*)-benzyl 4-(benzo[*d*][1,3]dithiol-2-yloxy)-2-(*tert*-butoxycarbonyl amino) butanoate

(*S*)-benzyl 2-(*tert*-butoxycarbonylamino)-4-(difluoromethoxy)butanoate

(*S*)-benzyl 2-amino-4-(difluoromethoxy)butanoate

(*S*)-benzyl 4-(difluoromethoxy)-2-(methoxycarbonylamino)butanoate

(*S*)-4-(difluoromethoxy)-2-(methoxycarbonylamino) butanoic acid

methyl (*S*)-1-((*S*)-6-(5-(6-(4-(2-((1*R*,3*S*,4*S*)-2-azabicyclo[2.2.1]heptan-3-yl)-1*H*-imidazol-5-yl)phenyl)naphthalen-2-yl)-1*H*-imidazol-2-yl)-5-azaspiro[2.4]heptan-5-yl)-3-methyl-1-oxobutan-2-ylcarbamate tetrahydrochloride

(*S*)-1-((*S*)-6-(5-(6-(4-(2-((1*R*,3*S*,4*S*)-2-((*S*)-4-(difluoromethoxy)-2-(methoxycarbonylamino)butanoyl)-2-azabicyclo[2.2.1]heptan-3-yl)-1*H*-imidazol-5-yl)phenyl)naphthalen-2-yl)-1*H*-imidazol-2-yl)-5-azaspiro[2.4]heptan-5-yl)-3-methyl-1-oxobutan-2-ylcarbamic acid methyl ester

(S)-benzyl 2-(*tert*-butoxycarbonylamino)-4-hydroxybutanoate:

N-t-Boc-L-homoserine (5.14 g, 23.45 mmol) and potassium bicarbonate (2.46g, 24.6 mmol) was weighed out in a round bottom flask and to it was added anhydrous N,N-dimethylformamide (100 mL) and benzyl bromide (4.2 g, 24.6 mmol). The mixture was stirred at room temperature for 18 hours. The crude mixture was then diluted with ethyl acetate and washed, respectively, with brine, saturated $NaHCO_3$ and brine, and dried over Na_2SO_4. The organic layer was then concentrated down on rotovap and purified on normal phase column chromatography. Yield= 7.27 g (100%).

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(S)-benzyl 4-(benzo[d][1,3]dithiol-2-yloxy)-2-(*tert*-butoxycarbonyl amino) butanoate:

(S)-Benzyl 2-(*tert*-butoxycarbonylamino)-4-hydroxybutanoate (5.76 g, 18.62 mmol) and 1,3-benzodithiol-2-ylium tetrafluoroborate (4.69 g, 19.55 mmol) were dissolved in dichloromethane (186 mL) and pyridine (4.42 g, 55.86 mmol) was added at room temperature. The mixture was stirred overnight. Upon completion of the reaction, it was quenched with triethylamine (11.5 g, 113.5 mmol) and diluted with dichloromethane. The organic layer was then washed with saturated $NaHCO_3$ and brine. The organic layer was dried over MgSO4 and concentrated down *in vacuo*. The residue was then purified on normal phase column to obtain a clear oil. 7.6 g (88%).

(S)-Benzyl 2-(*tert*-butoxycarbonylamino)-4-(difluoromethoxy)butanoate:

N-Iodosuccinimide (783 mg, 3.48 mmol) was suspended in anhydrous dichloromethane (10 mL) and at -35°C was slowly added HF.pyridine (70% HF)(50 µl, 1.91 mmol) and the mixture was stirred for 5 – 10 min. At this temperature was then dropwise added a solution of (S)-benzyl 4-(benzo[d][1,3]dithiol-2-yloxy)-2-(*tert*-butoxycarbonyl amino) butanoate (400 mg, 0.87 mmol) in dichloromethane (3 mL). The reaction content was then stirred for 1 hour at - 35°C and 1 hour at room temperature.

To the reaction mixture was added ice-cold saturated $NaHCO_3$ and extracted with dichloromethane. The organic layer was washed with a saturated solution of sodium thiosulfate and washed with brine and dried over sodium sulfate. The volatiles were removed *in vacuo* and the residue was purified on normal phase column. 161 mg (52%).

(S)-benzyl 2-amino-4-(difluoromethoxy)butanoate:

(S)-benzyl 2-(*tert*-butoxycarbonylamino)-4-(difluoromethoxy)butanoate (161 mg, 0.448 mmol) was stirred in 30% TFA in dichloromethane (5 mL) for 1h. The resulting mixture was concentrated down on rotovap and redissolved and concentrated down with toluene three times,

and finally the residue was dried on high vacuum pump. The desired product was used as-is in the next step.

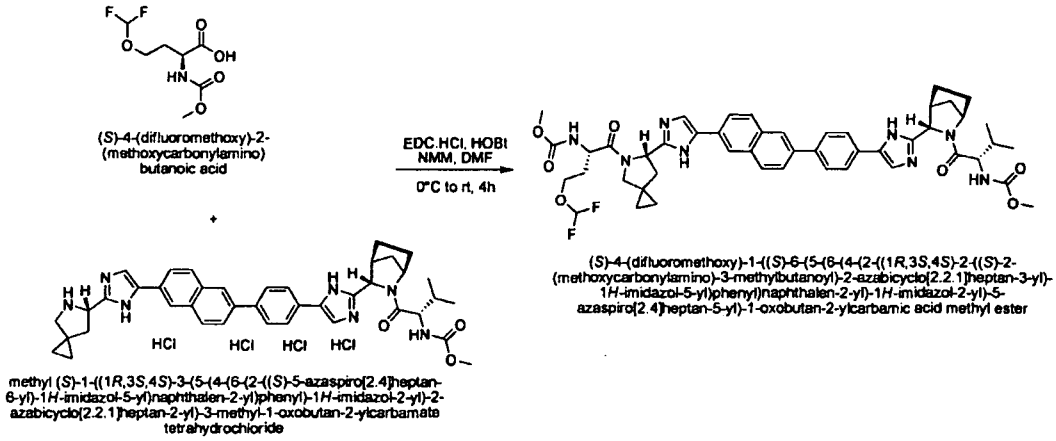
(S)-benzyl 4-(difluoromethoxy)-2-(methoxycarbonylamino)butanoate:
(S)-Benzyl 2-amino-4-(difluoromethoxy)butanoate (116 mg, 0.448 mmol) was dissolved in anhydrous dichloromethane (2.5 mL) and cooled down to 0°C and TEA (181 mg, 1.79 mmol) and methylchloroformate (51 mg, 0.538 mmol) were added respectively. The mixture was stirred for 30 minutes and then it was stirred at room temperature overnight. The resulting product mixture was quenched with saturated $NaHCO_3$ and extracted with dichloromethane. The organic layer was washed with saturated NH_4Cl solution and brine and dried over Na_2SO_4. The volatiles were removed *in vacuo* to afford 56 mg (40%) of desired product after column purification.

(S)-4-(Difluoromethoxy)-2-(methoxycarbonylamino) butanoic acid:
(S)-Benzyl 4-(difluoromethoxy)-2-(methoxycarbonylamino)butanoate (56 mg, 0.176 mmol) was dissolved in ethyl alcohol (3.5 mL) and under Argon charged with 10% Pd/C (19 mg). The flask was sealed with a rubber septa and the air atmosphere was replaced with H_2 from a balloon by applying vacuum and then releasing H_2 and repeating this three times. The mixture was stirred for 4 hours at room temperature. Upon completion, the crude mixture was passed through a Elite plug, concentrated down on rotovap and used as-is in the next step. 40 mg (100%).

(S)-1-((S)-6-(5-(6-(4-(2-((1R,3S,4S)-2-((S)-4-(difluoromethoxy)-2-(methoxycarbonylamino)butanoyl)-2-azabicyclo[2.2.1]heptan-3-yl)-1H-imidazol-5-yl)phenyl)naphthalen-2-yl)-1H-imidazol-2-yl)-5-azaspiro[2.4]heptan-5-yl)-3-methyl-1-oxobutan-2-ylcarbamic acid methyl ester:
Methyl (S)-1-((S)-6-(5-(6-(4-(2-((1R,3S,4S)-2-azabicyclo[2.2.1]heptan-3-yl)-1H-imidazol-5-yl)phenyl)naphthalen-2-yl)-1H-imidazol-2-yl)-5-azaspiro[2.4]heptan-5-yl)-3-methyl-1-oxobutan-2-ylcarbamate tetrahydrochloride (66 mg, 0.096 mmol), (S)-4-(difluoromethoxy)-2-(methoxycarbonylamino) butanoic acid (20 mg, 0.088 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (24 mg, and hydroxybenzotriazole hydrate (HOBt)(17 mg, 0.125 mmol) were all weighed out in a flask and anhydrous N,N-dimethylformamide (1 mL) was added. The mixture was cooled down in an ice bath to 0°C and N-methylmorpholine (NMM)(58 mg, 0.576 mmol) was added from a syringe to the mixture. The reaction content was stirred for 4 hours at room temperature. The resulting mixture was then directly purified on reverse phase prep. HPLC. 37 mg, (43%). ^{1}H-NMR: 400 MHz, (CD_3OD) δ 8.08 (s, 1H), 8.01 (d,

J= 16 Hz, 1H), 7.86 – 7.66 (m, 10H), 7.38 (s, 1H), 7.27 (s, 1H), 7.03 (d, J= 8.4 Hz, 1H), 6.58 (t, J= 75.6 Hz, 1H), 5.32 (t, J= 7.2 Hz, 1H), 4.70 (s, 1H), 6.66 – 6.25 (m, 1H), 4.51 (s, 1H), 4.14 (m, 1H), 3.98 – 3.78 (m, 4H), 3.63 (s, 6H), 3.50 – 3.46 (m, 1H), 2.70 (brs, 1H), 2.39 – 1.78 (m, 7H), 1.71 – 1.40 (m, 2H), 0.99 – 0.90 (m, 5H), 0.82 – 0.60 (m, 4H). MS (ESI) *m/z* 894.16 $[M + H]^+$.

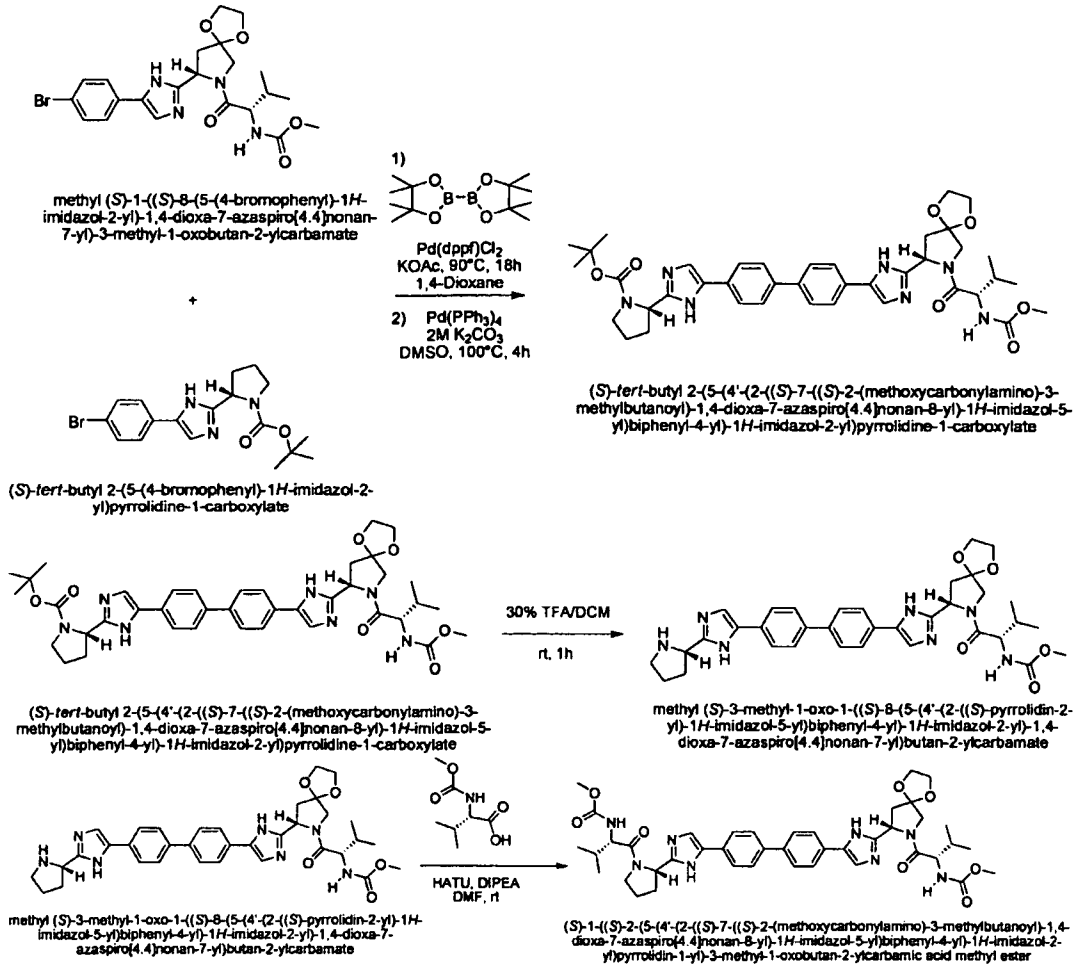
Example GJ



(S)-4-(difluoromethoxy)-1-((S)-6-(5-(6-(4-(2-((1R,3S,4S)-2-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-2-azabicyclo[2.2.1]heptan-3-yl)-1H-imidazol-5-yl)phenyl)naphthalen-2-yl)-1H-imidazol-2-yl)-5-azaspiro[2.4]heptan-5-yl)-1-oxobutan-2-ylcarbamic acid methyl ester

Title compound was prepared according to the method employed to prepare (S)-1-((S)-6-(5-(6-(4-(2-((1R,3S,4S)-2-((S)-4-(difluoromethoxy)-2-(methoxycarbonylamino)butanoyl)-2-azabicyclo[2.2.1]heptan-3-yl)-1H-imidazol-5-yl)phenyl)naphthalen-2-yl)-1H-imidazol-2-yl)-5-azaspiro[2.4]heptan-5-yl)-3-methyl-1-oxobutan-2-ylcarbamic acid methyl ester. ^{1}H-NMR: 400 MHz, (CD_3OD) δ 8.13 (s, 1H), 8.03 (m,1H), 7.91 – 7.85 (m, 2H), 7.80 – 7.71 (m, 6H), 7.42 (s, 1H), 7.31 (s, 1H), 6.97 (m, 1H), 6.56 (t, J= 76 Hz, 1H), 5.40 – 5.35 (m, 1H), 4.83 (m, 1H), 4.71 (s, 1H), 4.56 (m, 1H), 4.44 – 4.33 (m, 1H), 3.93 (brs, 2H), 3.82 (m, 2H), 3.76 – 3.66 (m, 5H), 3.51 – 3.42 (m, 1H), 2.80 – 2.64 (m, 1H), 2.32 – 2.25 (m, 1H), 2.17 – 2.12 (m, 2H), 2.07 – 1.86 (m, 5H), 1.73 – 1.57 (m, 2H), 1.03 – 0.9 (m, 4H), 0.77 – 0.57 (m, 4H). MS (ESI) *m/z* 894.00 $[M + H]^+$.

Example GK



(S)-*Tert*-butyl 2-(5-(4'-(2-((S)-7-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-1,4-dioxa-7-azaspiro[4.4]nonan-8-yl)-1H-imidazol-5-yl)biphenyl-4-yl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate:

Title compound was prepared according to the method employed to prepare (S)-1-((S)-6-(5-(6-(4-(2-((S)-7-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-1,4-dioxa-7-azaspiro[4.4]nonan-8-yl)-1H-imidazol-5-yl)phenyl)naphthalen-2-yl)-1H-imidazol-2-yl)-5-azaspiro[2.4]heptan-5-yl)-3-methyl-1-oxobutan-2-yl-carbamic acid methyl ester, except instead of methyl (S)-1-((S)-6-(5-(6-bromonaphthalen-2-yl)-1H-imidazol-2-yl)-5-azaspiro[2.4]heptan-5-yl)-3-methyl-1-oxobutan-2-ylcarbamate and methyl (S)-1-((S)-8-(5-(4-bromophenyl)-1H-imidazol-2-yl)-1,4-dioxa-7-azaspiro[4.4]nonan-7-yl)-3-methyl-1-oxobutan-2-ylcarbamate, methyl (S)-1-((S)-8-(5-(4-bromophenyl)-1H-imidazol-2-yl)-1,4-dioxa-7-azaspiro[4.4]nonan-7-yl)-3-methyl-1-oxobutan-2-ylcarbamate (600 mg, 1.182 mmol) and (S)-*tert*-butyl 2-(5-(4-

bromophenyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (510 mg, 1.3 mmol). The amount for all the other reagents were adjusted accordingly. 489 mg (56%).

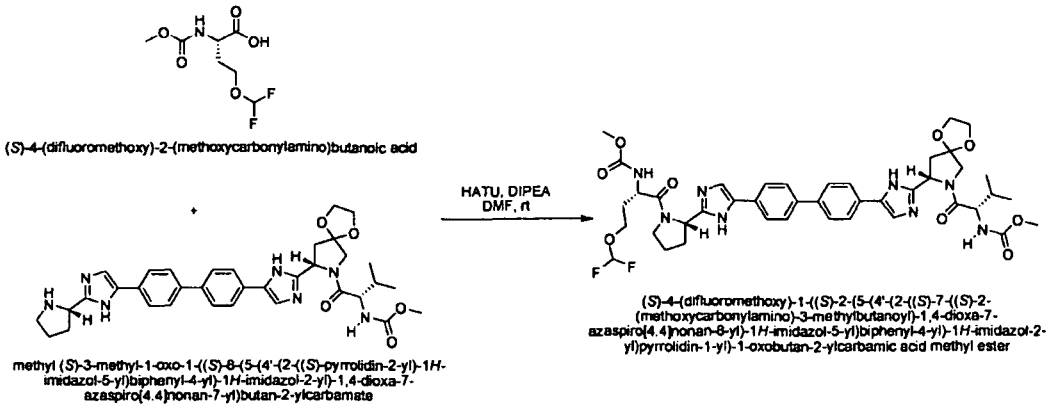
Methyl (S)-3-methyl-1-oxo-1-((S)-8-(5-(4'-(2-((S)-pyrrolidin-2-yl)-1H-imidazol-5-yl)biphenyl-4-yl)-1H-imidazol-2-yl)-1,4-dioxa-7-azaspiro[4.4]nonan-7-yl)butan-2-ylcarbamate:

Title compound was prepared according to the method employed to prepare (S)-benzyl 2-amino-4-(difluoromethoxy)butanoate, except it was freebased as follows: The volatiles were removed and the residue was taken up in EtOAc and washed with water to get the desired product in aqueous layer. The organic layer was again washed with some more water and the aqueous layers were combined and basified with 50% NaOH solution to adjust the pH to 9. The desired product was then back-extracted into EtOAc layer and the aqueous layer was extracted three times with EtOAc. The organic phase was dried over Na_2SO_4 and concentrated down on rotovap to afford 290 mg (69%) of desired compound as free base.

(S)-1-((S)-2-(5-(4'-(2-((S)-7-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-1,4-dioxa-7-azaspiro[4.4]nonan-8-yl)-1H-imidazol-5-yl)biphenyl-4-yl)-1H-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamic acid methyl ester:

Title compound was prepared according to the method employed to prepare1-{2-[5-(9-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-6-methyl-6,7-dihydro-5H-dibenzo[c,e]azepin-3-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester. ^{1}H-NMR: 400 MHz, (CD_3OD) δ 7.80 (d, J= 8.0 Hz, 1H), 7.74 – 7.70 (m, 4H), 7.66 – 7.62 (m, 5H), 7.36 – 7.31 (m, 2H), 7.02 (t, J=7.6 Hz, 1H), 5.24 (m, 2H), 4.25 (d, J= 7.2 Hz, 1H), 4.17 (d, J= 7.6 Hz, 1H), 4.11 – 3.85 (m, 8H), 3.66 (s, 5H), 3.50 – 3.45 (m, 1H), 2.56 – 2.44 (m, 2H), 2.36 – 2.17 (m, 3H), 2.09 – 1.99 (m, 3H), 1.01 – 0.86 (m, 12H). MS (ESI) *m/z* 797.84 $[M + H]^+$.

Example GL



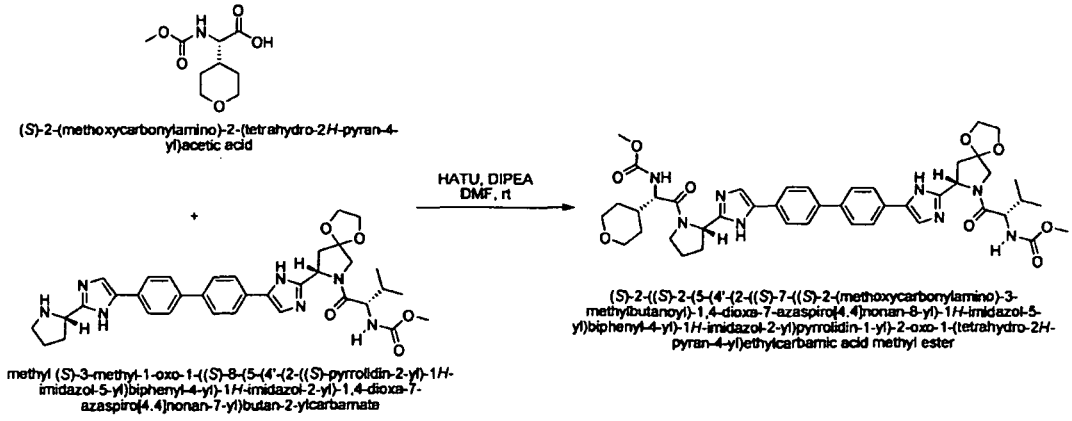
(S)-4-(difluoromethoxy)-1-((S)-2-(5-(4'-(2-((S)-7-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-1,4-dioxa-7-azaspiro[4.4]nonan-8-yl)-1H-imidazol-5-yl)biphenyl-4-yl)-1H-imidazol-2-yl)pyrrolidin-1-yl)-1-oxobutan-2-ylcarbamic acid methyl ester:

Title compound was prepared according to the method employed to prepare1-{2-[5-(9-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-6-methyl-6,7-dihydro-5H-dibenzo[c,e]azepin-3-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester.

^{1}H-NMR: 400 MHz, (CD_3OD) δ 7.69 (d, J= 8.0 Hz, 1H), 7.61 – 7.57 (m, 4H), 7.56 – 7.52 (m, 5H), 7.28 – 7.24 (m, 2H), 6.46 (t, J=7.6 Hz, 1H), 5.14 (m, 2H), 4.62 (m, 1H), 4.24(m, 11H), 3.64 (s, 5H), 2.54 – 2.43 (m, 2H), 2.36 – 1.81 (m, 8H), 099 – 0.84 (m, 6H). MS (ESI) *m/z* 849.76 [M + H]$^+$.

Example GM

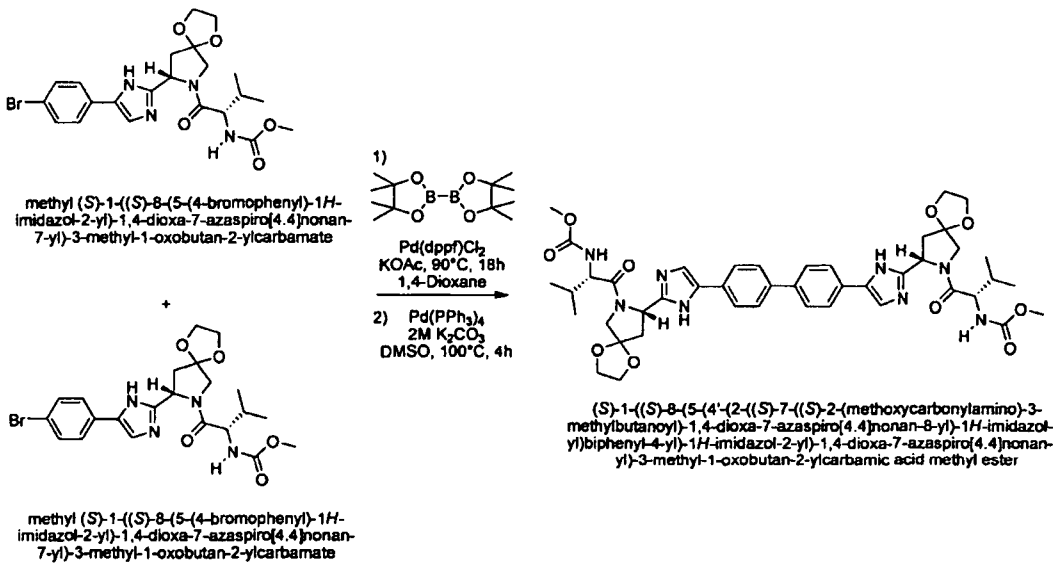
:



(S)-2-((S)-2-(5-(4'-(2-((S)-7-((S)-2-(Methoxycarbonylamino)-3-methylbutanoyl)-1,4-dioxa-7-azaspiro[4.4]nonan-8-yl)-1H-imidazol-5-yl)biphenyl-4-yl)-1H-imidazol-2-yl)pyrrolidin-1-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethylcarbamic acid methyl ester:

Title compound was prepared according to the method employed to prepare1-{2-[5-(9-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-6-methyl-6,7-dihydro-5H-dibenzo[c,e]azepin-3-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester. ^{1}H-NMR: 400 MHz, (CD_3OD) δ 7.68 (d, J= 8.0 Hz, 1H), 7.63 – 7.50 (m, 8H), 7.25 – 7.19 (m, 2H), 5.13 – 5.05 (m, 2H), 4.22 (d, J= 8.4 Hz, 1H), 4.07 (d, J= 7.2 Hz, 1H), 4.01 – 3.80 (m, 10H), 3.56 (s, 5H), 3.36 (s, 1H), 3.29 – 3.18 (m, 3H), 2.46 – 2.34 (m, 2H), 2.27 – 2.07 (m, 3H), 1.99 – 1.87 (m, 4H), 1.54 – 1.19 (m, 5H), 0.85 – 0.76 (m, 6H). MS (ESI) *m/z* 839.84 $[M + H]^+$.

Example GN

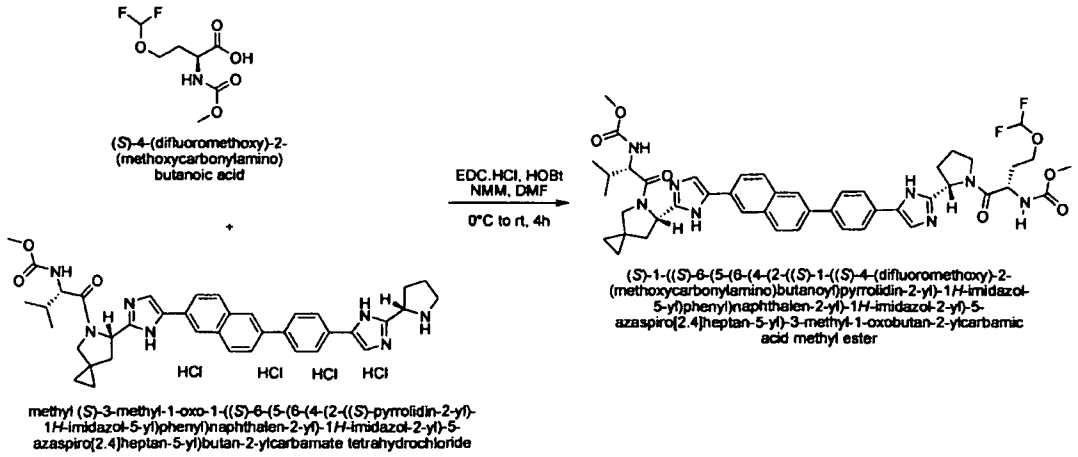


(S)-1-((S)-8-(5-(4'-(2-((S)-7-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-1,4-dioxa-7-azaspiro[4.4]nonan-8-yl)-1H-imidazol-5-yl)biphenyl-4-yl)-1H-imidazol-2-yl)-1,4-dioxa-7-azaspiro[4.4]nonan-7-yl)-3-methyl-1-oxobutan-2-ylcarbamic acid methyl ester:

Title compound was prepared according to the method employed to prepare (S)-*tert*-butyl 2-(5-(4'-(2-((S)-7-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-1,4-dioxa-7-azaspiro[4.4]nonan-8-yl)-1H-imidazol-5-yl)biphenyl-4-yl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate. ^{1}H-NMR: 400 MHz, (CD_3OD) δ 7.78 (d, J= 8.0 Hz, 1H), 7.71 – 7.69 (m, 4H), 7.65 – 7.61 (m, 5H), 5.23 (t, J= 8.4 Hz, 2H), 4.17 (d, J= 7.6 Hz, 1H), 4.10 (m, 14H), 3.65 (s, 5H),

3.46 (s, 1H), 2.65 (s, 1H), 2.55 – 2.44 (m, 4H), 2.04 – 1.96 (m, 2H), 1.00 (d, J= 6.8 Hz, 1H), 0.95 – 0.85 (m, 12H). MS (ESI) *m/z* 855.80 $[M + H]^+$.

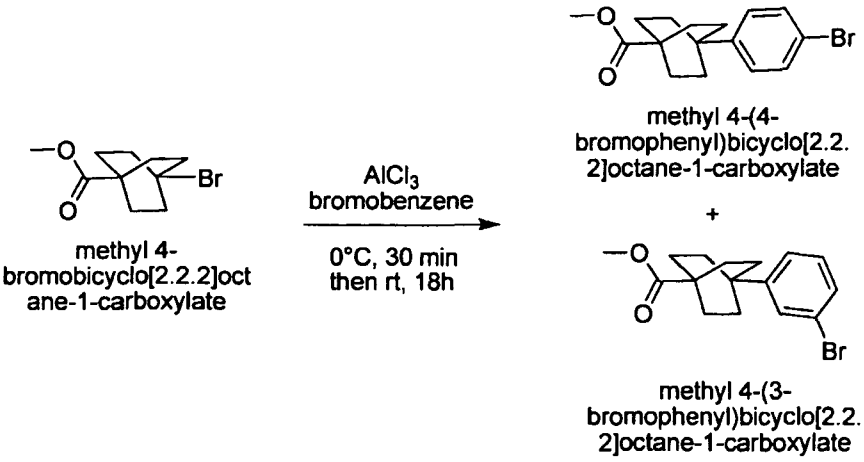
Example GO



(S)-1-((S)-6-(5-(6-(4-(2-((S)-1-((S)-4-(Difluoromethoxy)-2-(methoxycarbonylamino)butanoyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)phenyl)naphthalen-2-yl)-1H-imidazol-2-yl)-5-azaspiro[2.4]heptan-5-yl)-3-methyl-1-oxobutan-2-ylcarbamic acid methyl ester:

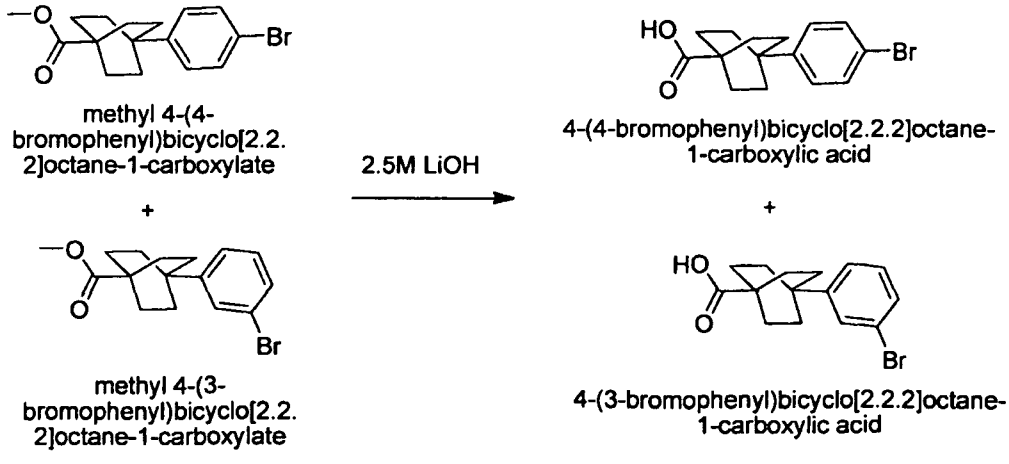
Title compound was prepared according to the method employed to prepare (S)-1-((S)-6-(5-(6-(4-(2-((1R,3S,4S)-2-((S)-4-(difluoromethoxy)-2-(methoxycarbonylamino)butanoyl)-2-azabicyclo[2.2.1]heptan-3-yl)-1H-imidazol-5-yl)phenyl)naphthalen-2-yl)-1H-imidazol-2-yl)-5-azaspiro[2.4]heptan-5-yl)-3-methyl-1-oxobutan-2-ylcarbamic acid methyl ester. ^{1}H-NMR: 400 MHz, (CD_3OD) δ 8.00 – 7.98 (m, 1H), 7.91 – 7.84 (m, 1H), 7.78 – 7.55 (m, 8H), 7.37 – 7.20 (m, 2H), 6.49 (t, J= 75.6 Hz, 1H), 5.25 – 5.20 (m, 1H), 5.14 (m, 1H), 4.57 (m, 1H), 4.12 – 4.01 (m, 1H), 3.89 – 3.81 (m, 4H), 3.75 – 3.66 (m, 1H), 3.58 (s, 5H), 3.42 – 3.39 (m, 1H), 2.33 – 1.77 (m, 9H), 0.94 – 0.83 (m, 6H), 0.72 – 0.52 (m, 4H). MS (ESI) *m/z* 867.86 $[M + H]^+$.

Example GP and GQ



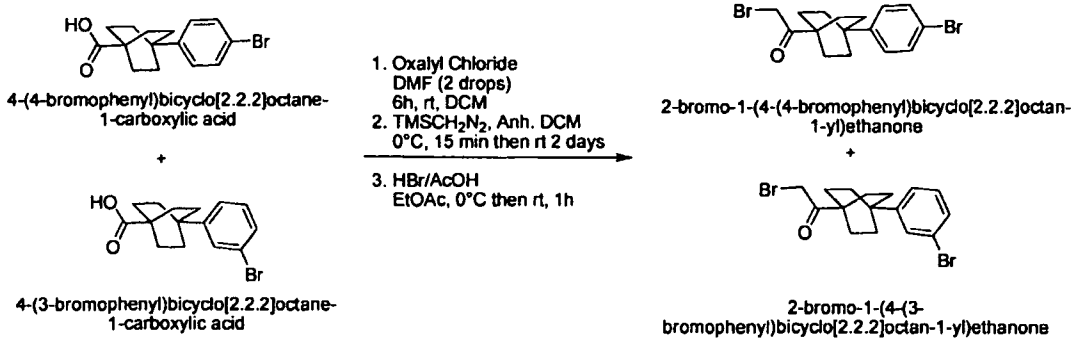
Mixture of methyl 4-(4-bromophenyl)bicyclo[2.2.2]octane-1-carboxylate and methyl 4-(3-bromophenyl)bicyclo[2.2.2]octane-1-carboxylate:

A solution of methyl 4-bromobicyclo[2.2.2]octane-1-carboxylate (1 g, 4.05 mmol) in anhydrous bromobenzene (6.75 mL) was added dropwise to an ice-water cooled suspension of aluminum chloride (2.16 g, 16.2 mmol) in bromobenzene (3.25 mL) under nitrogen. The resulting reaction mixture was allowed to stir in the ice bath for 30 min and then at ambient temperature overnight. The mixture was cautiously poured onto ice (100 g) and concentrated HCl (3.3 mL) and the mixture was extracted into ether (4 100 mL). The ether extracts were combined, washed with brine (100 mL), separated, and dried over MgSO4 to leave a-brown solid. Purification by silica chromatography (5% ethyl acetate / hexane) gave a mixture of para- and meta substituted derivatives. (970 mg, 74%). (For a more detailed procedure see *J. Med. Chem.*, **2009**, 52, 6, 1563).



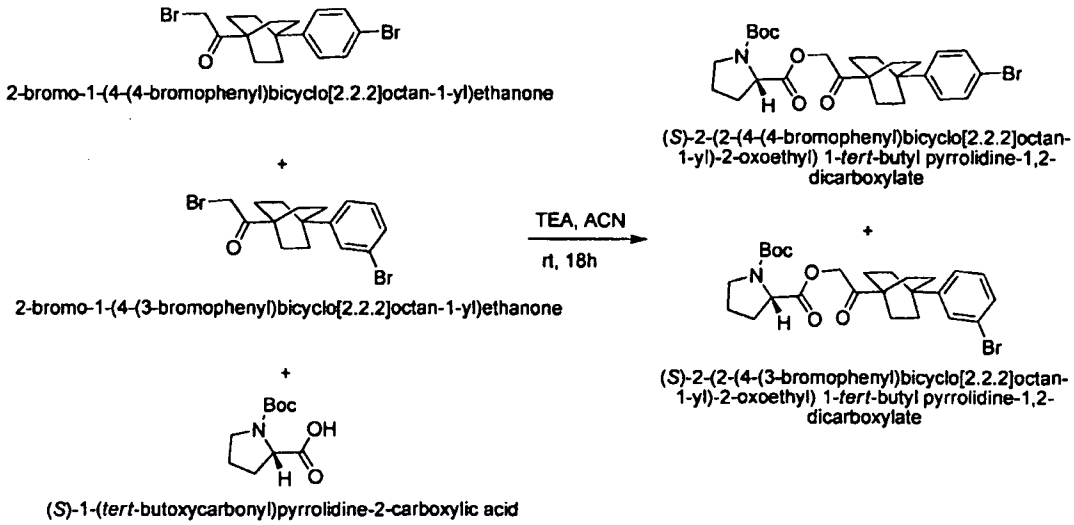
Mixture of 4-(4-bromophenyl)bicyclo[2.2.2]octane-1-carboxylic acid and 4-(3-bromophenyl)bicyclo[2.2.2]octane-1-carboxylic acid:

A mixture of the title compounds were prepared according to the method employed to prepare (1-{3-Acetyl-5-[2-(4-bromo-phenyl)-2-oxo-ethylcarbamoyl]-imidazolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester. (638 mg, 94%)



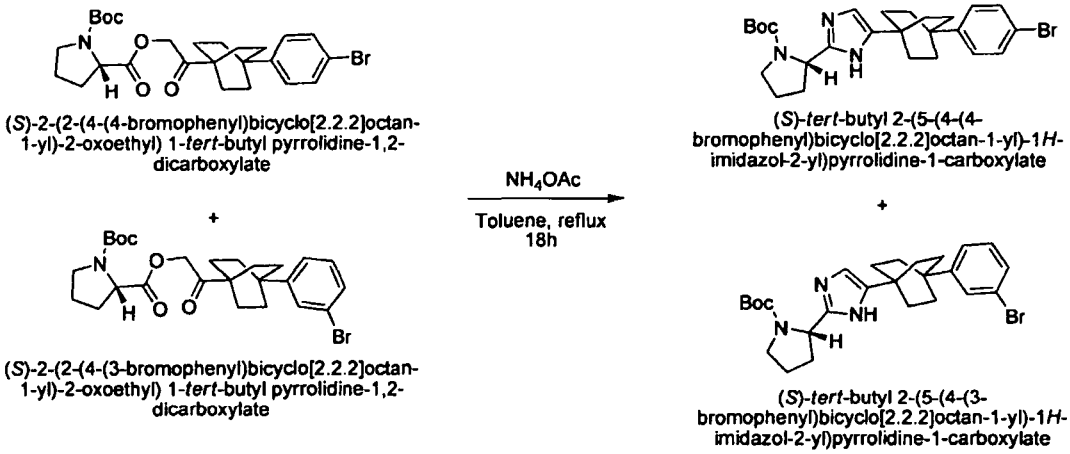
Mixture of 2-bromo-1-(4-(4-bromophenyl)bicyclo[2.2.2]octan-1-yl)ethanone and 2-bromo-1-(4-(3-bromophenyl)bicyclo[2.2.2]octan-1-yl)ethanone:

A mixture of the title compounds were prepared according to the method employed to prepare 2-Bromo-1-{4-[3-(2-bromo-acetyl)-phenoxy]-phenyl}-ethanone.(290 mg, 43%)



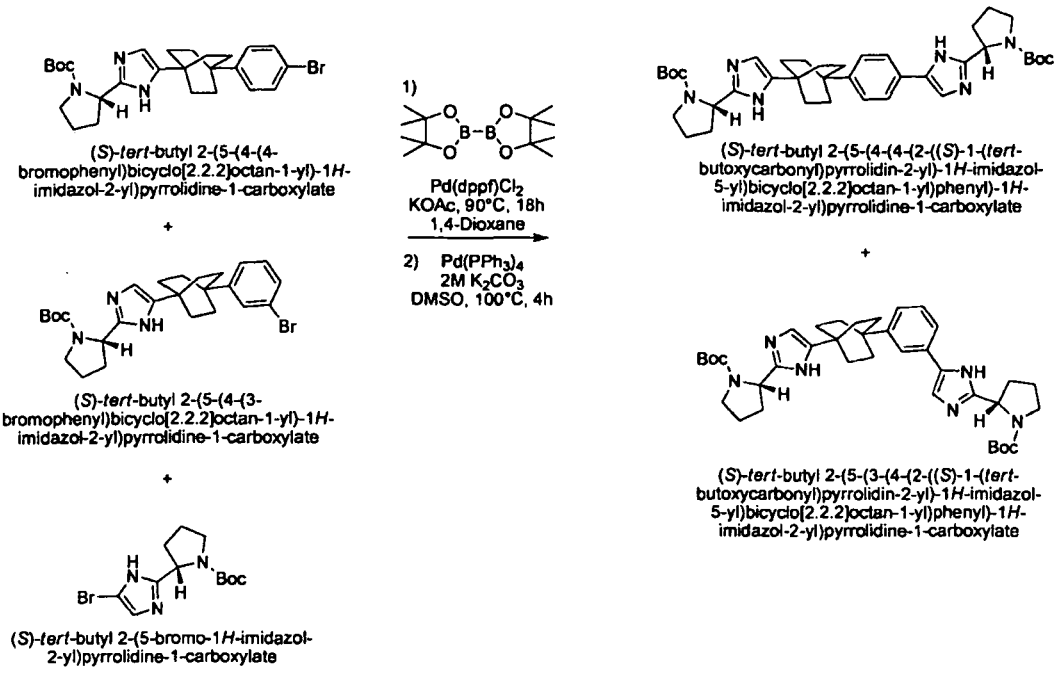
Mixture of (S)-2-(2-(4-(4-bromophenyl)bicyclo[2.2.2]octan-1-yl)-2-oxoethyl) 1-*tert*-butyl pyrrolidine-1,2-dicarboxylate and (S)-2-(2-(4-(3-bromophenyl)bicyclo[2.2.2]octan-1-yl)-2-oxoethyl) 1-*tert*-butyl pyrrolidine-1,2-dicarboxylate:

A mixture of the title compounds were prepared according to the method employed to prepare 2-Aza-bicyclo[2.2.1]heptane-2,3-dicarboxylic acid 3-(2-{9-[2-(1-*tert*-butoxycarbonyl-pyrrolidine-2-carbonyloxy)-acetyl]-5,7-dihydro-dibenzo[c,e]oxepin-3-yl}-2-oxo-ethyl) ester 2-*tert*-butyl ester. (365 mg, 94%).



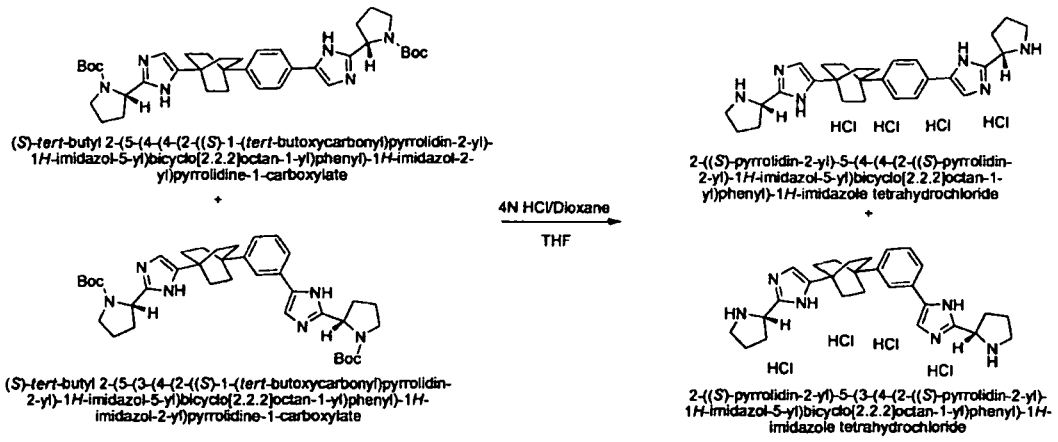
Mixture of (S)-*tert*-butyl 2-(5-(4-(4-bromophenyl)bicyclo[2.2.2]octan-1-yl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate and (S)-*tert*-butyl 2-(5-(4-(3-bromophenyl)bicyclo[2.2.2]octan-1-yl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate:

A mixture of the title compounds were prepared according to the method employed to prepare methyl (S)-1-((S)-6-(5-(4-bromophenyl)-1H-imidazol-2-yl)-5-azaspiro[2.4]heptan-5-yl)-3-methyl-1-oxobutan-2-ylcarbamate. (298 mg, 85%).



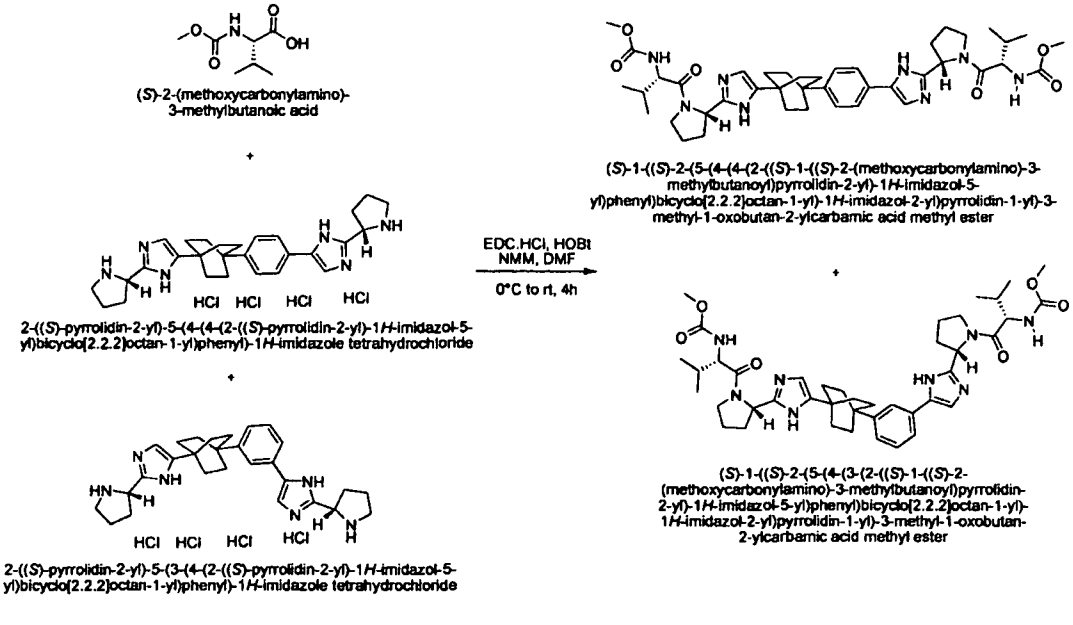
Mixture of (S)-*tert*-butyl 2-(5-(4-(4-(2-((S)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)bicyclo[2.2.2]octan-1-yl)phenyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate and (S)-*tert*-butyl 2-(5-(3-(4-(2-((S)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)bicyclo[2.2.2]octan-1-yl)phenyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate

A mixture of the title compounds were prepared according to the method employed to prepare (S)-*tert*-butyl 2-(5-(4'-(2-((S)-7-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-1,4-dioxa-7-azaspiro[4.4]nonan-8-yl)-1H-imidazol-5-yl)biphenyl-4-yl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate. (287 mg, 73%).



Mixture of 2-((S)-pyrrolidin-2-yl)-5-(4-(4-(2-((S)-pyrrolidin-2-yl)-1H-imidazol-5-yl)bicyclo[2.2.2]octan-1-yl)phenyl)-1H-imidazole tetrahydrochloride and 2-((S)-pyrrolidin-2-yl)-5-(3-(4-(2-((S)-pyrrolidin-2-yl)-1H-imidazol-5-yl)bicyclo[2.2.2]octan-1-yl)phenyl)-1H-imidazole tetrahydrochloride

A mixture of the title compounds were prepared according to the method employed to prepare (S)-benzyl 4-oxopyrrolidine-2-carboxylate hydrochloride.



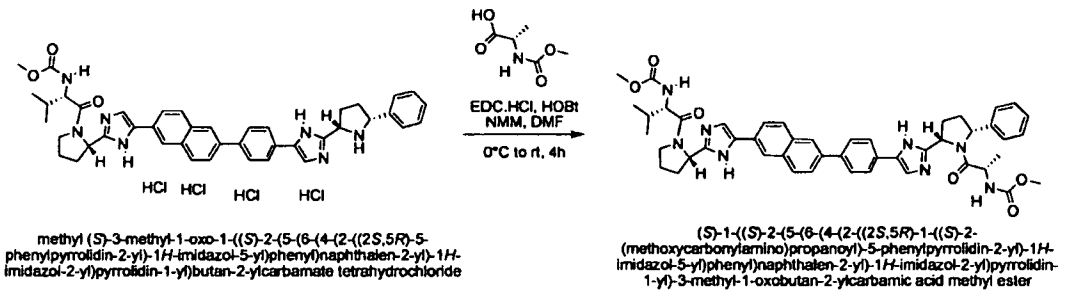
(S)-1-((S)-2-(5-(4-(4-(2-((S)-1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)phenyl)bicyclo[2.2.2]octan-1-yl)-1H-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamic acid methyl ester:

Title compound was prepared according to the method employed to prepare (S)-1-((S)-6-(5-(6-(4-(2-((1R,3S,4S)-2-((S)-4-(difluoromethoxy)-2-(methoxycarbonylamino)butanoyl)-2-azabicyclo[2.2.1]heptan-3-yl)-1H-imidazol-5-yl)phenyl)naphthalen-2-yl)-1H-imidazol-2-yl)-5-azaspiro[2.4]heptan-5-yl)-3-methyl-1-oxobutan-2-ylcarbamic acid methyl ester and separated from (S)-1-((S)-2-(5-(4-(3-(2-((S)-1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)phenyl)bicyclo[2.2.2]octan-1-yl)-1H-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamic acid methyl ester by prep HPLC. (41 mg, 23%) ^{1}H-NMR: 400 MHz, (CD_3OD) δ 7.63 (d, J= 8 Hz, 1H), 7.55 (d, J= 8.4 Hz, 2H), 7.42 (s, 1H), 7.34 (d, J= 8.4 Hz, 2H), 7.20 (s, 1H), 7.01 – 6.95 (m, 1H), 5.17 – 5.11 (m, 2H), 4.24 – 4.19 (m, 2H), 4.00 – 3.96 (m, 2H), 3.88 – 3.81 (m, 2H), 3.64 (s, 5H), 3.54 – 3.48 (m, 1H), 2.34 – 1.96 (m, 10H), 1.91 (brs, 12H), 1.01 – 0.88 (m, 12H). MS (ESI) *m/z* 772.56 [M + H]$^+$.

(S)-1-((S)-2-(5-(4-(3-(2-((S)-1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)phenyl)bicyclo[2.2.2]octan-1-yl)-1H-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamic acid methyl ester:

Title compound was prepared according to the method employed to prepare (S)-1-((S)-6-(5-(6-(4-(2-((1R,3S,4S)-2-((S)-4-(difluoromethoxy)-2-(methoxycarbonylamino)butanoyl)-2-azabicyclo[2.2.1]heptan-3-yl)-1H-imidazol-5-yl)phenyl)naphthalen-2-yl)-1H-imidazol-2-yl)-5-azaspiro[2.4]heptan-5-yl)-3-methyl-1-oxobutan-2-ylcarbamic acid methyl ester and separated from (S)-1-((S)-2-(5-(4-(4-(2-((S)-1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)phenyl)bicyclo[2.2.2]octan-1-yl)-1H-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamic acid methyl ester by prep HPLC. (54 mg, 30%). ^{1}H-NMR: 400 MHz, (CD_3OD) δ 7.66 (s, 1H), 7.43 (d, J= 8 Hz, 2H), 7.28 – 7.21 (m, 3H), 7.01 – 6.95 (m, 1H), 5.17 – 5.11 (m, 2H), 4.25 – 4.20 (m, 2H), 3.99 – 3.94 (m, 2H), 3.89 – 3.81 (m, 2H), 3.64 (s, 5H), 3.57 – 3.45 (m, 1H), 2.34 – 1.88 (m, 22H), 1.02 – 0.89 (m, 12H). MS (ESI) *m/z* 772.96 $[M + H]^+$.

Example GR



methyl (*S*)-3-methyl-1-oxo-1-((*S*)-2-(5-(6-(4-(2-((2*S*,5*R*)-5-phenylpyrrolidin-2-yl)-1*H*-imidazol-5-yl)phenyl)naphthalen-2-yl)-1*H*-imidazol-2-yl)pyrrolidin-1-yl)butan-2-ylcarbamate tetrahydrochloride

(*S*)-1-((*S*)-2-(5-(6-(4-(2-((2*S*,5*R*)-1-((*S*)-2-(methoxycarbonylamino)propanoyl)-5-phenylpyrrolidin-2-yl)-1*H*-imidazol-5-yl)phenyl)naphthalen-2-yl)-1*H*-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamic acid methyl ester

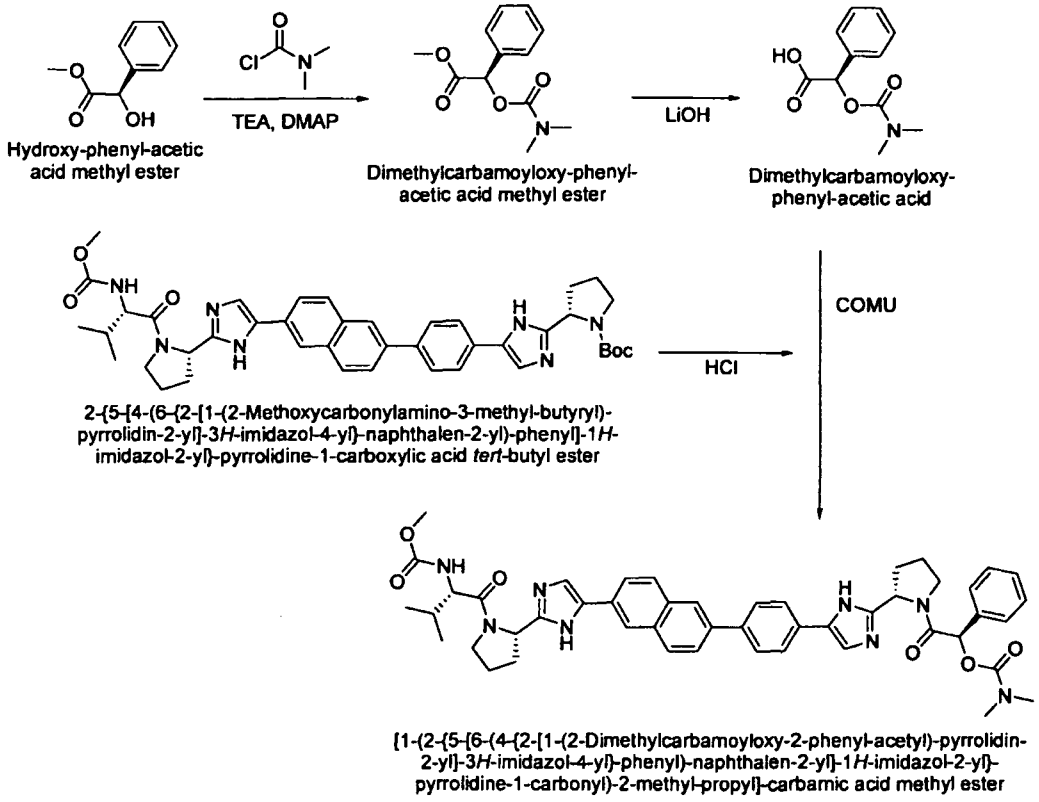
(S)-1-((S)-2-(5-(6-(4-(2-((2S,5R)-1-((S)-2-(methoxycarbonylamino)propanoyl)-5-phenylpyrrolidin-2-yl)-1H-imidazol-5-yl)phenyl)naphthalen-2-yl)-1H-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamic acid methyl ester

Title compound was prepared according to the method employed to prepare (S)-1-((S)-6-(5-(6-(4-(2-((1R,3S,4S)-2-((S)-4-(difluoromethoxy)-2-(methoxycarbonylamino)butanoyl)-2-azabicyclo[2.2.1]heptan-3-yl)-1H-imidazol-5-yl)phenyl)naphthalen-2-yl)-1H-imidazol-2-yl)-5-azaspiro[2.4]heptan-5-yl)-3-methyl-1-oxobutan-2-ylcarbamic acid methyl ester.

^{1}H-NMR: 400 MHz, (CD_3OD) δ 8.13 (s, 1H), 8.08 (s, 1H), 7.94 – 7.77 (m, 8H), 7.50 – 7.42 (m, 3H), 7.36 – 7.25 (m, 2H), 7.17 – 6.99 (m, 2H), 5.49 – 5.36 (m, 2H), 5.23 (d, J= 5.2 Hz, 1H), 4.27 – 4.21 (m, 2H), 4.04 – 3.99 (m, 1HN, 3.93 – 3.87 (m, 1H), 3.70 (s, 1H), 3.66 (s, 4H), 2.68 –

2.48 (m, 2H), 2.39 – 2.20 (m, 4H), 2.11 – 2.03 (m, 2H), 1.39 (d, J= 6.8 Hz, 1H), 1.04 – 0.96 (m, 4H), 0.93 (d, J= 6.8 Hz, 2H), 0.70 (d, J= 6.8 Hz, 2H). MS (ESI) *m/z* 837.92 $[M + H]^+$.

Example GS

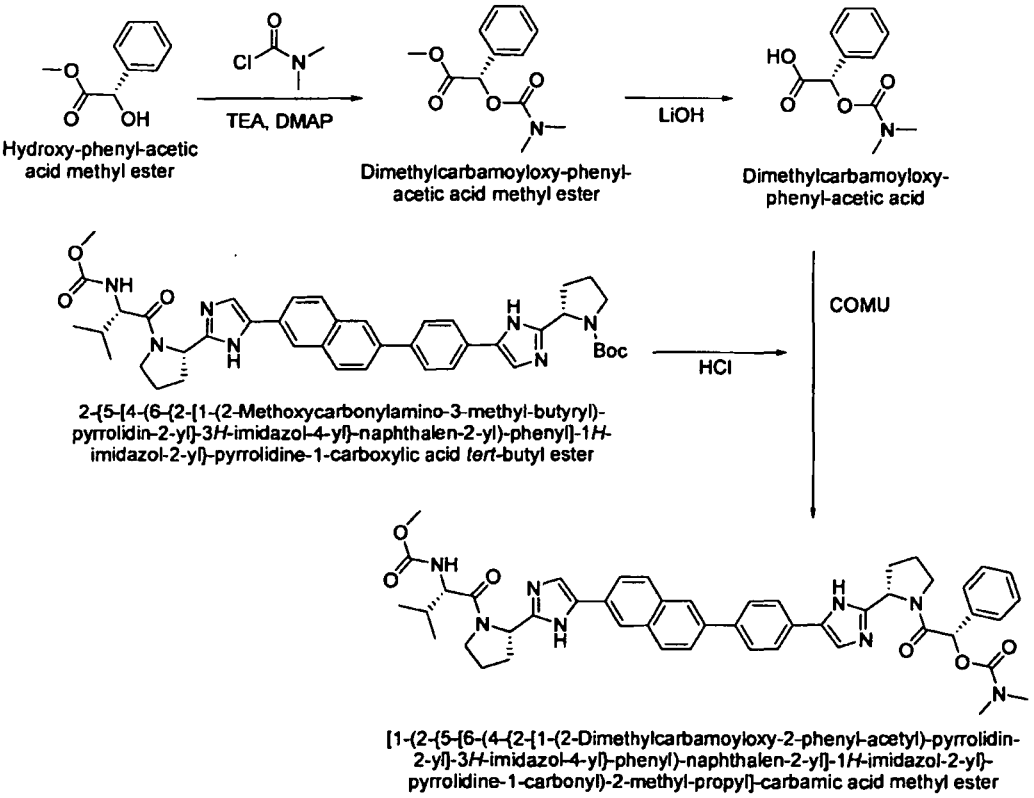


Dimethylcarbamoyloxy-phenyl-acetic acid: To hydroxyl-phenyl-acetic acid methyl ester (500 mg) in THF (10 mL) were added dimethylcarbamoyl chloride (304 µl), TEA (503 µl), and DMAP (37 mg). After stirring for overnight at room temperature, the mixture was taken up in ethyl acetate (150 mL). The organic phase was washed with 1 N HCl (1 x 100 mL) and saturated sodium bicarbonate (1 x 100 mL), and dried over sodium sulfate. After the solvent was removed, the resulting solid was dissolved in THF (6 mL). To the solution was added 2 M LiOH (3 mL). After stirring for 90 min. at room temperature, the reaction mixture was acidified with 2 N HCl (3.2 mL). The mixture was extracted with ethyl acetate (50 mL). The organic phase was dried over sodium sulfate. The solvent was removed under reduced pressure to provide dimethylcarbamoyloxy-phenyl-acetic acid (561 mg, 83 %) as an off-white solid.

[1-(2-{5-[6-(4-{2-[1-(2-Dimethylcarbamoyloxy-2-phenyl-acetyl)-pyrrolidin-2-yl]-3H-imidazol-4-yl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: To 2-{5-[4-(6-{2-[1-(2-Methoxycarbonylamino-3-

methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (40 mg) in methanol (0.5 mL) was added 4N HCl in dioxanes (0.5 mL). The mixture was stirred for 2 hours then concentrated to afford the HCl salt of the crude amine. To the crude amine in DMF (1 mL) was added DIEA (14 µl). After all material dissolved, dimethylcarbamoyloxy-phenyl-acetic acid (12 mg) and (1-cyano-2-ethoxy-2-oxoethylidenaminooxy)dimethylamino-morpholino-carbenium hexafluorophosphate (COMU, 23 mg) were added. After stirring for 30 min. the reaction was purified by a preparative HPLC (10-60% MeCN-H_2O; 0.1% formic acid modifier) to afford the title product (22 mg, 48%). ^1H NMR (MeOH-d4, 400 MHz) δ: 8.22-8.05 (m, 2H), 7.92-7.69 (m, 9H), 7.56-7.44 (m, 6H), 6.08-5.92 (d, 1H), 5.27-5.20 (m, 2H), 4.28-4.24 (m, 1H), 4.13-4.00 (m, 2H), 3.90-3.68 (m, 2H), 3.66 (s, 3H), 3.45-3.38 (m, 2H), 2.92-2.90 (m, 6H), 2.47-1.96 (m, 10H), 1.05-0.91 (m, 6H) ; MS (ESI) *m/z* 837.3 $[M + H]^+$.

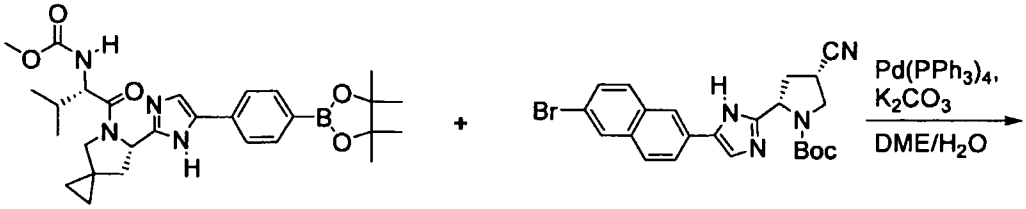
Example GT



[1-(2-{5-[6-(4-{2-[1-(2-Dimethylcarbamoyloxy-2-phenyl-acetyl)-pyrrolidin-2-yl]-3H-imidazol-4-yl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: Title compound was prepared according to the method

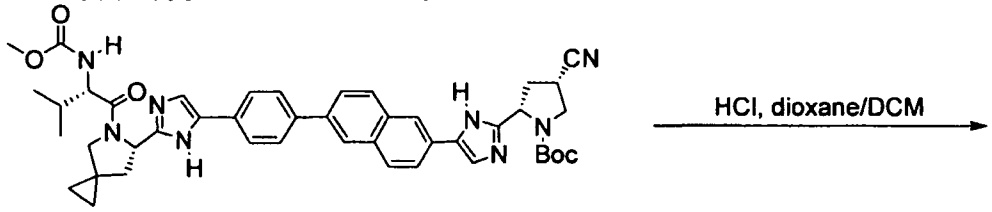
employed to [1-(2-{5-[6-(4-{2-[1-(2-Dimethylcarbamoyloxy-2-phenyl-acetyl)-pyrrolidin-2-yl]-3H-imidazol-4-yl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (Example 6), (20 mg, 43%). ^{1}H NMR (MeOH-d4, 400 MHz) δ: 8.21-8.04 (m, 2H), 7.93-7.89 (m, 3H), 7.81-7.68 (m, 5H), 7.53-7.41 (m, 7H), 6.10-5.78 (d, 1H), 5.28-5.21 (m, 2H), 4.28-4.26 (m, 1H), 4.03-3.81 (m, 4H), 3.66 (s, 3H), 3.62-3.45 (m, 2H), 2.92-2.85 (m, 6H), 2.42-1.90 (m, 10H), 1.01-0.89 (m, 6H); MS (ESI) *m/z* 837.5 $[M + H]^+$.

Example GU

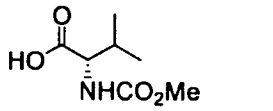


[2-Methyl-1-(6-{5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1*H*-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carbonyl)-propyl]-carbamic acid methyl ester

2-[5-(6-Bromo-naphthalen-2-yl)-1*H*-imidazol-2-yl]-4-cyano-pyrrolidine-1-carboxylic acid *tert*-butyl ester

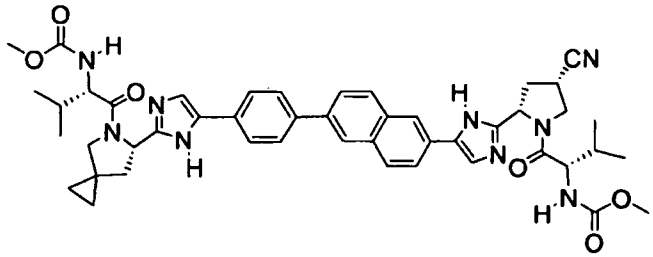


4-Cyano-2-{5-[6-(4-{2-[5-(2-methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3*H*-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester



2-Methoxycarbonylamino-3-methyl-butyric acid

(1-{6-[5-(4-{6-[2-(4-Cyano-pyrrolidin-2-yl)-3*H*-imidazol-4-yl]-naphthalen-2-yl}-phenyl)-1*H*-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester-*tris*-hydrochloride



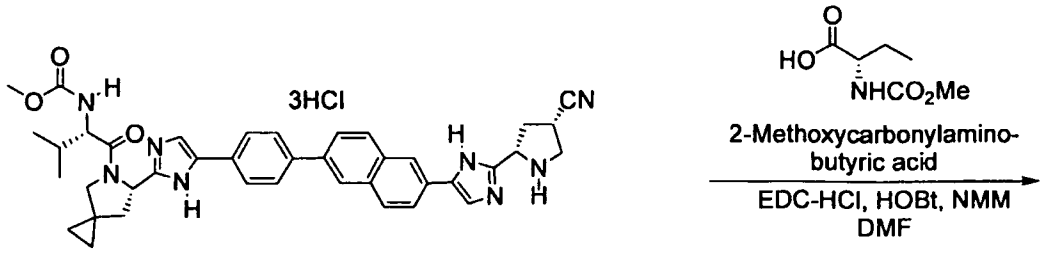
[1-(6-{5-[4-(6-{2-[4-Cyano-1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1*H*-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester

4-Cyano-2-{5-[6-(4-{2-[5-(2-methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester: [2-Methyl-1-(6-{5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carbonyl)-propyl]-carbamic acid methyl ester (997 mg, 1.91 mmol), 2-[5-(6-Bromo-naphthalen-2-yl)-1H-imidazol-2-yl]-4-cyano-pyrrolidine-1-carboxylic acid *tert*-butyl ester, $Pd(PPh_3)_4$ (184 mg, 0.159 mmol), and K_2CO_3 (2 M in H_2O, 1.9 mL, 3.8 mmol) were combined in 1,2-dimethoxyethane (16 mL). The reaction mixture was degassed with bubbling N_2 for 10 minutes then heated to reflux for 3.5 h. After heating, the reaction mixture was cooled to RT, diluted with EtOAc and washed with H_2O and brine. The organic phase was dried over $MgSO_4$, then filtered and concentrated. The resulting residue was purified with silica column chromatography 0% to 100% (10% MeOH/DCM)/EtOAc to afford the title compound (641 mg, 51%).

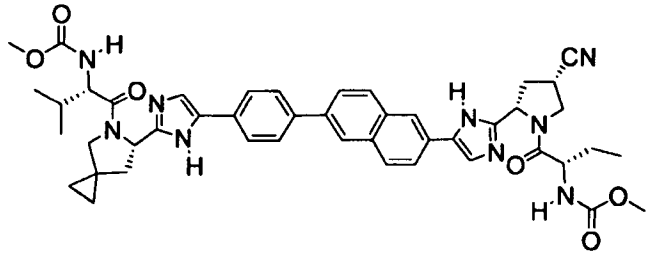
(1-{6-[5-(4-{6-[2-(4-Cyano-pyrrolidin-2-yl)-3H-imidazol-4-yl]-naphthalen-2-yl}-phenyl)-1H-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester-tris-hydrochloride: 4-Cyano-2-{5-[6-(4-{2-[5-(2-methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (639 mg, 0.816 mmol) was dissolved in DCM (8 mL) and 4.0 M HCl in dioxane (2 mL, 8 mmol) was added. After stirring for 37 min, the solid was filtered off and rinsed with EtOAc, affording the title compound (597 mg, 92%).

[1-(6-{5-[4-(6-{2-[4-Cyano-1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: 2-Methoxycarbonylamino-3-methyl-butyric acid (40 mg, 0.227 mmol) EDC-HCl (44 mg, 0.227 mmol) and HOBt (32 mg, 0.237 mmol) were combined in DMF (2 mL) and stirred for 20 min at RT. (1-{6-[5-(4-{6-[2-(4-Cyano-pyrrolidin-2-yl)-3H-imidazol-4-yl]-naphthalen-2-yl}-phenyl)-1H-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester-tris-hydrochloride (150 mg, 0.189 mg) was added, the reaction mixture was cooled to 0 °C and NMM (0.104 mL, 0.947 mmol) was added dropwise. After 1.5h, the reaction mixture was warmed to RT. 30 min later, the mixture was diluted with EtOAc and washed with $NaHCO_3$, then 1:1 brine/5M NaOH. The organic phase was dried over $MgSO_4$, then filtered and concentrated. The resulting residue was purified by HPLC to afford the title compound (18 mg, 11%). MS (ESI) *m/z* 840 $[M + H]^+$.

Example GV



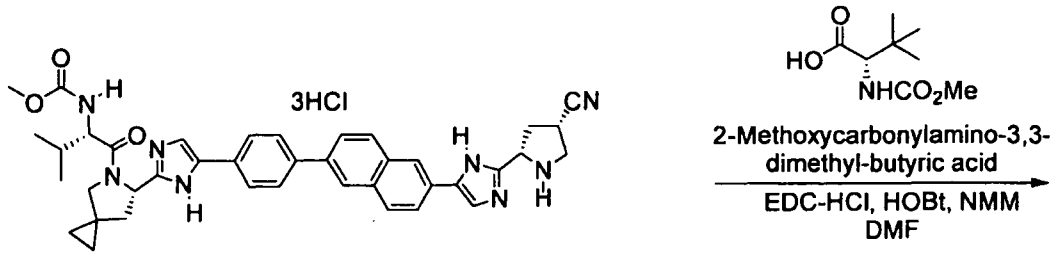
(1-{6-[5-(4-{6-[2-(4-Cyano-pyrrolidin-2-yl)-3*H*-imidazol-4-yl]-naphthalen-2-yl}-phenyl)-1*H*-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester-*tris*-hydrochloride



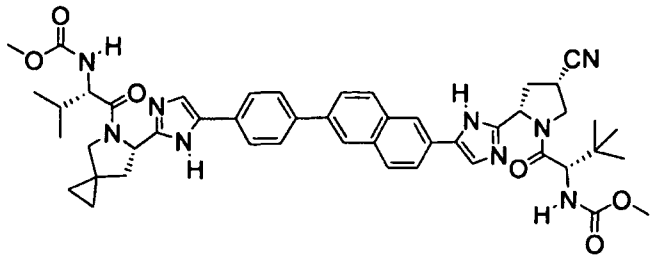
[1-(6-{5-[4-(6-{2-[4-Cyano-1-(2-methoxycarbonylamino-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1*H*-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester

[1-(6-{5-[4-(6-{2-[4-Cyano-1-(2-methoxycarbonylamino-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: 2-Methoxycarbonylamino-butyric acid (37 mg, 0.227 mmol) EDC-HCl (44 mg, 0.227 mmol) and HOBt (32 mg, 0.237 mmol) were combined in DMF (2 mL) and stirred for 20 min at RT. (1-{6-[5-(4-{6-[2-(4-Cyano-pyrrolidin-2-yl)-3H-imidazol-4-yl]-naphthalen-2-yl}-phenyl)-1H-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester-tris-hydrochloride (150 mg, 0.189 mg) was added, the reaction mixture was cooled to 0 °C and NMM (0.104 mL, 0.947 mmol) was added dropwise. After 1.5h, the reaction mixture was warmed to RT. 30 min later, the mixture was diluted with EtOAc and washed with $NaHCO_3$, then 1:1 brine/5M NaOH. The organic phase was dried over $MgSO_4$, then filtered and concentrated. The resulting residue was purified by HPLC to afford the title compound (85 mg, 54%). MS (ESI) *m/z* 826 $[M + H]^+$.

Example GW



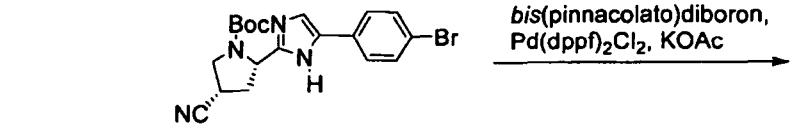
(1-{6-[5-(4-{6-[2-(4-Cyano-pyrrolidin-2-yl)-3*H*-imidazol-4-yl]-naphthalen-2-yl}-phenyl)-1*H*-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester-*tris*-hydrochloride



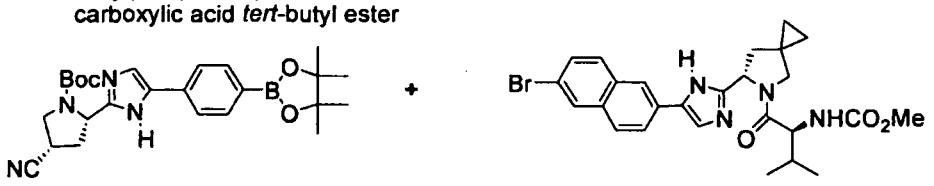
[1-(4-Cyano-2-{5-[6-(4-{2-[5-(2-methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3*H*-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2,2-dimethyl-propyl]-carbamic acid methyl ester

[1-(4-Cyano-2-{5-[6-(4-{2-[5-(2-methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2,2-dimethyl-propyl]-carbamic acid methyl ester: 2-Methoxycarbonylamino-3,3-dimethyl-butyric acid (37 mg, 0.227 mmol) EDC-HCl (44 mg, 0.227 mmol) and HOBt (32 mg, 0.237 mmol) were combined in DMF (2 mL) and stirred for 20 min at RT. (1-{6-[5-(4-{6-[2-(4-Cyano-pyrrolidin-2-yl)-3H-imidazol-4-yl]-naphthalen-2-yl}-phenyl)-1H-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester-tris-hydrochloride (150 mg, 0.189 mg) was added, the reaction mixture was cooled to 0 °C and NMM (0.104 mL, 0.947 mmol) was added dropwise. After 1.5h, the reaction mixture was warmed to RT. 30 min later, the mixture was diluted with EtOAc and washed with $NaHCO_3$, then 1:1 brine/5M NaOH. The organic phase was dried over $MgSO_4$, then filtered and concentrated. The resulting residue was purified by HPLC to afford the title compound (77 mg, 48%). MS (ESI) *m/z* 855 $[M + H]^+$.

Example GX

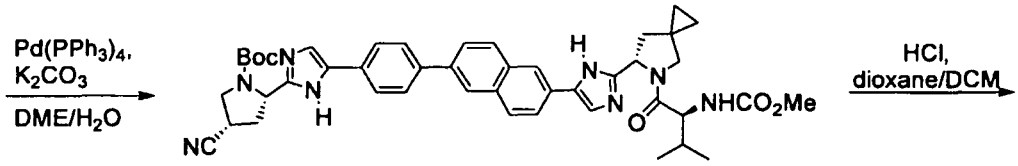


2-[5-(4-Bromo-phenyl)-1*H*-imidazol-2-yl]-4-cyano-pyrrolidine-1-carboxylic acid *tert*-butyl ester

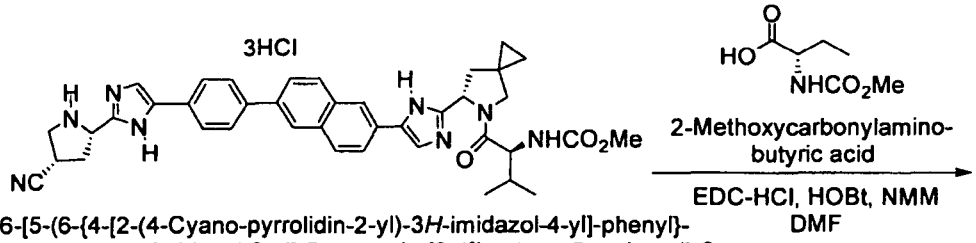


4-Cyano-2-{5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester

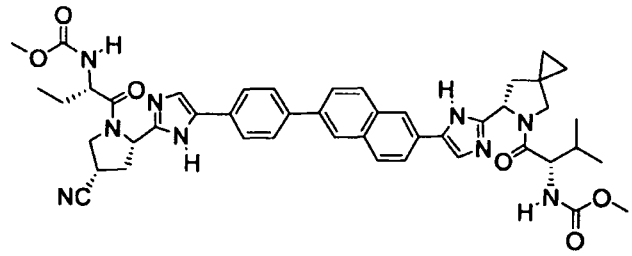
(1-{6-[5-(6-Bromo-naphthalen-2-yl)-1*H*-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester



4-Cyano-2-{5-[4-(6-{2-[5-(2-methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3*H*-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester



(1-{6-[5-(6-{4-[2-(4-Cyano-pyrrolidin-2-yl)-3*H*-imidazol-4-yl]-phenyl}-naphthalen-2-yl)-1*H*-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester *tris*-hydrochloride



[1-(6-{5-[6-(4-{2-[4-Cyano-1-(2-methoxycarbonylamino-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1*H*-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester

4-Cyano-2-{5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester: 2-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-4-cyano-pyrrolidine-1-carboxylic acid *tert*-butyl ester (2.895 g, 6.94 mmol), bis(pinacolato)diboron (2.64 g, 10.41 mmol), $Pd(dppf)_2Cl_2$ (254 mg, 0.347 mmol) and KOAc

(2.04 g, 20.82 mmol) were combined in dioxane and degassed for 12 min with bubbling N_2. The reaction mixture was then stirred at 90 °C for 18h, cooled to RT and diluted with EtOAc. The organic mixture was washed with saturated aqueous $NaHCO_3$ and brine before being dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by silica column chromatography (50% to 100% EtOAc/Hex) to provide the title compound (1.56 g, 48%).

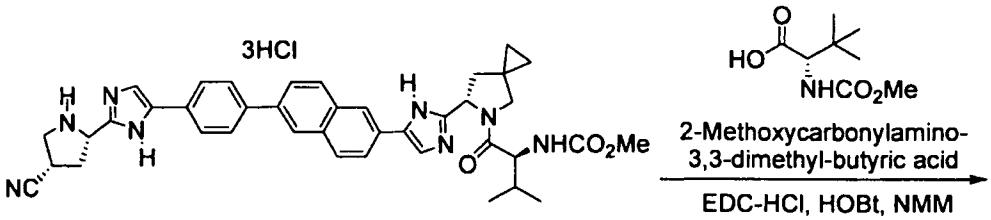
4-Cyano-2-{5-[4-(6-{2-[5-(2-methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester: 4-Cyano-2-{5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.990 g, 2.13 mmol), (1-{6-[5-(6-Bromo-naphthalen-2-yl)-1H-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (1.007 g, 1.92 mmol), $Pd(PPh_3)_4$ (222 mg, 0.192 mmol) and K_2CO_3 (2.0 M in H_2O, 2.1 mL, 4.2 mmol) were combined in 1,2-dimethoxymethane. The mixture was degassed for 10 min with bubbling N_2 then heated to reflux for 4h then cooled. The reaction mixture was diluted with EtOAc and washed with saturated aqueous $NaHCO_3$ and brine before being dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by silica column chromatography (EtOAc, then 2% MeOH/DCM, then 4% MeOH/DCM) to provide the title compound (1.028 g, 68%).

(1-{6-[5-(6-{4-[2-(4-Cyano-pyrrolidin-2-yl)-3H-imidazol-4-yl]-phenyl}-naphthalen-2-yl)-1H-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester tris-hydrochloride: A solution of 4-Cyano-2-{5-[4-(6-{2-[5-(2-methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (1.000g, 1.28 mmol) in DCM (16 mL) was treated with HCl (4.0 M in dioxane, 3.2 mL, 12.8 mmol). After 2.5 h, the solid was filtered off and rinsed with EtOAc to provide the title compound (1.004 g, 99%).

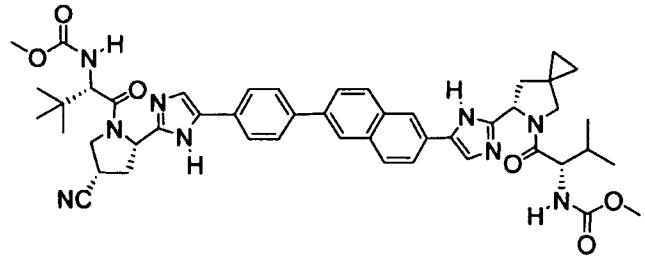
[1-(6-{5-[6-(4-{2-[4-Cyano-1-(2-methoxycarbonylamino-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: 2-2-Methoxycarbonylamino-butyric acid (37 mg, 0.227 mmol) EDC-HCl (44 mg, 0.227 mmol) and HOBt (32 mg, 0.237 mmol) were combined in DMF (2 mL) and stirred for 20 min at RT. (1-{6-[5-(6-{4-[2-(4-Cyano-pyrrolidin-2-yl)-3H-imidazol-4-yl]-phenyl}-naphthalen-2-yl)-1H-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester tris-hydrochloride (150 mg, 0.189 mg)

was added, the reaction mixture was cooled to 0 °C and NMM (0.104 mL, 0.947 mmol) was added dropwise. After 1.5h, the reaction mixture was warmed to RT. 30 min later, the mixture was diluted with EtOAc and washed with $NaHCO_3$, then brine. The organic phase was dried over $MgSO_4$, then filtered and concentrated. The resulting residue was purified by HPLC to afford the title compound (78 mg, 49%). MS (ESI) *m/z* 826 $[M + H]^+$.

Example GY



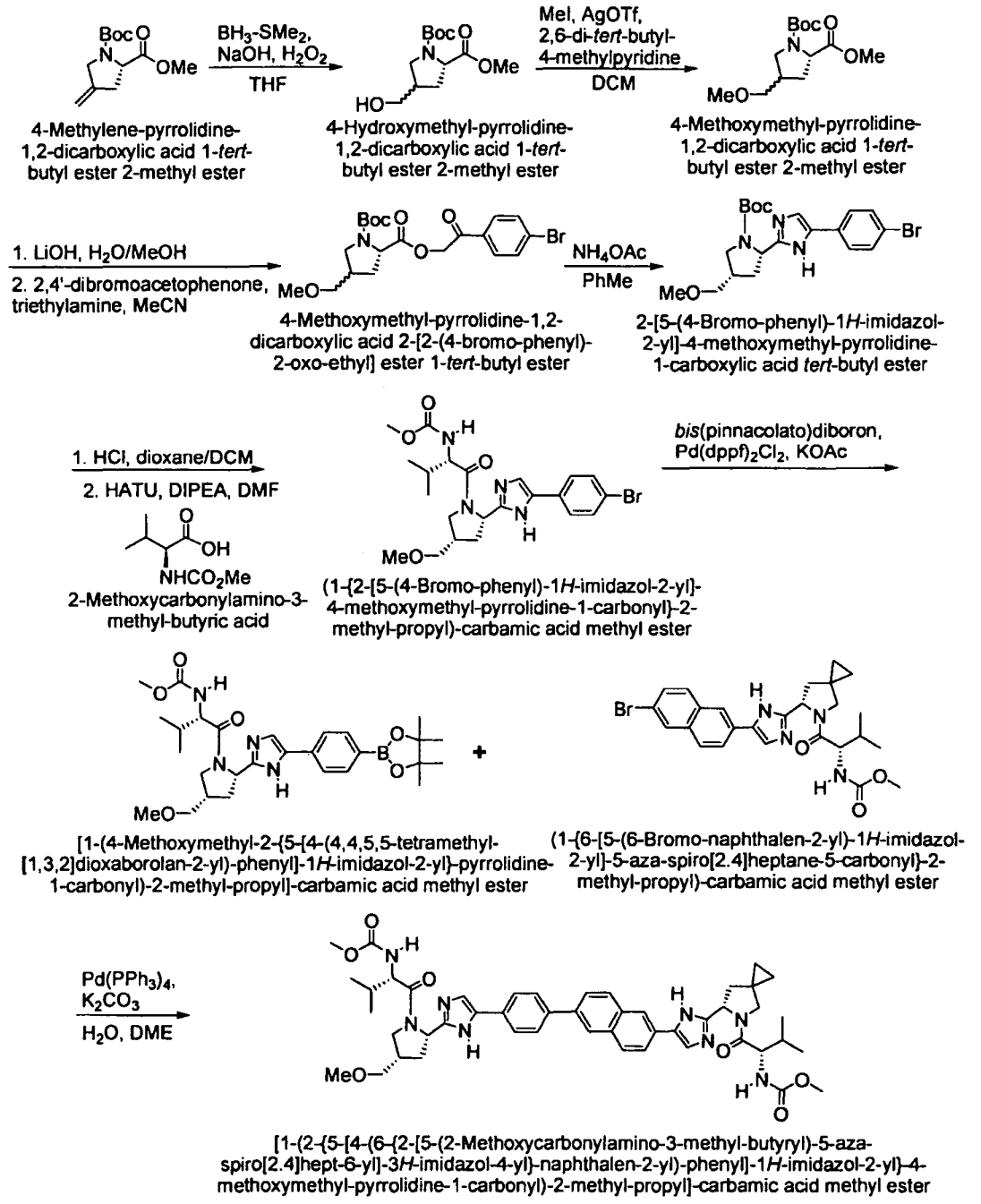
(1-{6-[5-(6-{4-[2-(4-Cyano-pyrrolidin-2-yl)-3*H*-imidazol-4-yl]-phenyl}-naphthalen-2-yl)-1*H*-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester *tris*-hydrochloride



[1-(4-Cyano-2-{5-[4-(6-{2-[5-(2-methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3*H*-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2,2-dimethyl-propyl]-carbamic acid methyl ester

[1-(4-Cyano-2-{5-[4-(6-{2-[5-(2-methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2,2-dimethyl-propyl]-carbamic acid methyl ester: 2-Methoxycarbonylamino-3,3-dimethyl-butyric acid (43 mg, 0.227 mmol) EDC-HCl (44 mg, 0.227 mmol) and HOBt (32 mg, 0.237 mmol) were combined in DMF (2 mL) and stirred for 20 min at RT. (1-{6-[5-(6-{4-[2-(4-Cyano-pyrrolidin-2-yl)-3H-imidazol-4-yl]-phenyl}-naphthalen-2-yl)-1H-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester tris-hydrochloride (150 mg, 0.189 mg) was added, the reaction mixture was cooled to 0 °C and NMM (0.104 mL, 0.947 mmol) was added dropwise. After 20, the reaction mixture was warmed to RT. 30 min later, the mixture was diluted with EtOAc and washed with $NaHCO_3$, then brine. The organic phase was dried over $MgSO_4$, then filtered and concentrated. The resulting residue was purified by HPLC to afford the title compound (73 mg, 45%). MS (ESI) *m/z* 854 $[M + H]^+$.

Example GZ



4-Hydroxymethyl-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester: 4-Methylene-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (4.48 g, 19.71 mmol) was dissolved in THF (100 mL) and the stirred solution was cooled to 0 °C. Borane-dimethylsulfide complex (1.9 mL, 19.7 mmol) was added and the reaction mixture was allowed to warm to RT o/n. After 16h, water was added dropwise until no bubbling was observed. The

stirred mixture was then cooled to 0 °C. Aqueous NaOH (5M in H_2O, 5.3 mL, 26.6 mmol), then H_2O_2 (30 wt% in H_2O, 6.0 mL, 58.5 mmol) were added dropwise. The reaction was then warmed to 50 °C. After 30 min, the mixture was diluted with ethyl ether and washed with water and brine. The organic phase was dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by silica column chromatography (25% to 75% EtOAc/Hex) to afford the title compound (2.08 g, 41%).

4-Methoxymethyl-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester: 4-Hydroxymethyl-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (861 mg, 3.32 mmol) was dissolved in DCM (6.6 mL) then 2,6-di-*tert*-butyl-4-methylpyridine (1.023 g, 4.98 mmol) and AgOTf (938 mg, 3.65 mmol) were added. The reaction mixture was cooled to 0 °C and iodomethane (0.25 mL, 3.98 mmol) was added. After 4 min, the reaction mixture was diluted with DCM and it was filtered over elite. The filtrate was concentrated to a residue which was dissolved in diethyl ether. The organic solution was washed with 10% HCl and brine, then dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by silica column chromatography (20% to 80% EtOAc/Hex) to afford the title compound (479 mg, 53%).

4-Methoxymethyl-pyrrolidine-1,2-dicarboxylic acid 2-[2-(4-bromo-phenyl)-2-oxo-ethyl] ester 1-*tert*-butyl ester: 4-Methoxymethyl-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (461 mg, 1.68 mmol) was dissolved in MeOH (17 mL) and LiOH (1 M in H_2O, 8.5 mL, 8.5 mmol) was added. After stirring at RT for 5h, the MeOH was removed under reduced pressure. The aqueous solution was poured into a separatory funnel, diluted with 1 M HCl (9 mL, 9 mmol) and extracted with DCM (3x). The combined organics were dried over $MgSO_4$, filtered and concentrated. The residue was dissolved in MeCN (17 mL) and treated with 2,4'-dibromoacetophenone (514 mg, 1.85 mmol), and triethylamine (0.258 mL, 1.85 mmol). After stirring for 2 h, the solvent was removed and the solid was suspended in EtOAc. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine then dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by silica column chromatography (15% to 35% EtOAc/Hex) to afford the title compound (746 mg, 97%).

2-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-4-methoxymethyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester: 4-Methoxymethyl-pyrrolidine-1,2-dicarboxylic acid 2-[2-(4-bromo-phenyl)-2-oxo-ethyl] ester 1-*tert*-butyl ester (746 mg, 1.63 mmol) was dissolved in PhMe (16 mL) and treated with NH_4OAc (2.52 g, 32.7 mmol). The stirred mixture was refluxed for 19 h then cooled to RT and diluted with EtOAc. The organic phase was washed with saturated aqueous

$NaHCO_3$ and brine then dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by silica column chromatography (35% to 65% EtOAc/Hex) to afford the title compound (334 mg, 47%).

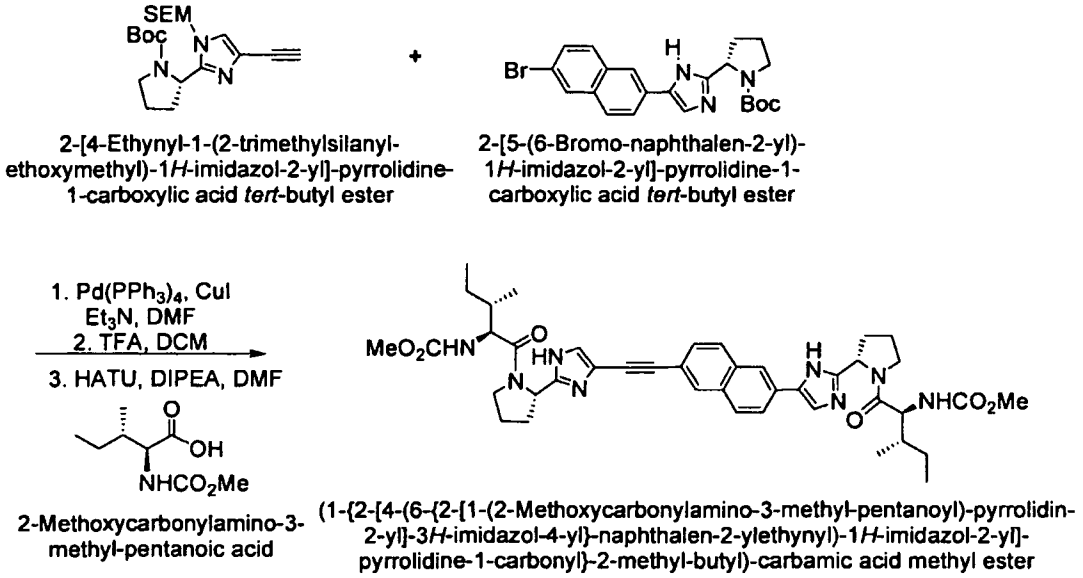
(1-{2-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-4-methoxymethyl-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: 2-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-4-methoxymethyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester (334 mg, 0.765 mmol) was dissolved in DCM (4 mL) and treated with HCl (4.0M in dioxane, 0.960 mL, 3.83 mmol). After 2.5 h, the solution was concentrated and the residue was treated with 2-Methoxycarbonylamino-3-methyl-butyric acid (146 mg, 0.832 mmol) and HATU (316 mg, 0.832 mmol). The solids were suspended in DMF (4 mL) and the reaction mixture was cooled to 0 °C before triethylamine (0.67 mL, 3.83 mmol) was added in a dropwise fashion. After 30 min, the mixture was warmed to RT. After another 1 h, it was diluted with EtOAc and washed with saturated aqueous $NaHCO_3$ and brine. Then it was dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by silica column chromatography (80% to 100% EtOAc/Hex) to afford the title compound (369 mg, 98%).

[1-(4-Methoxymethyl-2-{5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: (1-{2-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-4-methoxymethyl-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (348 mg, 0.705 mmol), bis(pinacolato)diboron (269 mg, 1.06 mmol), $Pd(dppf)_2Cl_2$ (52 mg, 0.0705 mmol) and KOAc (208 g, 2.12 mmol) were combined in dioxane and degassed for 12 min with bubbling N_2. The reaction mixture was then stirred at 90 °C for 18h, cooled to RT and diluted with EtOAc. The organic mixture was washed with saturated aqueous $NaHCO_3$ and brine before being dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by silica column chromatography (80% to 100% EtOAc/Hex) to provide the title compound (297 mg, 78%).

[1-(2-{5-[4-(6-{2-[5-(2-Methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-4-methoxymethyl-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: [1-(4-Methoxymethyl-2-{5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (132 mg, 0.244 mmol), (1-{6-[5-(6-Bromo-naphthalen-2-yl)-1H-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (154 mg, 0.293 mmol) $Pd(PPh_3)_4$ (28

mg, 0.0244 mmol) and K_2CO_3 (2M in H_2O, 0.488 mL, 0.976 mmol) were combined in 1,2-dimethoxyethane (5 mL). The mixture was degassed with bubbling N_2 for 12 min then heated to 85 °C for 4 h. After cooling to RT, the reaction mixture was diluted with EtOAc then washed with water and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by HPLC to provide the title compound (118 mg, 56%). MS (ESI) *m/z* 859 $[M + H]^+$.

Example HA



2-[4-Ethynyl-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester

2-[5-(6-Bromo-naphthalen-2-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester

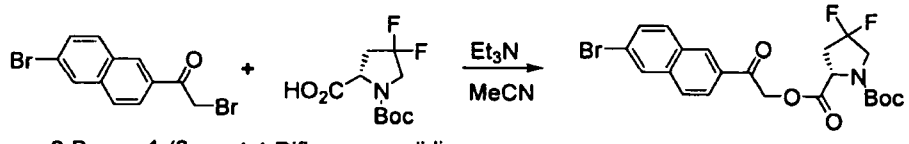
2-Methoxycarbonylamino-3-methyl-pentanoic acid

(1-{2-[4-(6-{2-[1-(2-Methoxycarbonylamino-3-methyl-pentanoyl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-naphthalen-2-ylethynyl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-butyl)-carbamic acid methyl ester

(1-{2-[4-(6-{2-[1-(2-Methoxycarbonylamino-3-methyl-pentanoyl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-naphthalen-2-ylethynyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-butyl)-carbamic acid methyl ester: 2-[4-Ethynyl-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (192 mg, 0.490 mmol), 2-[5-(6-Bromo-naphthalen-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (260 mg, 0.588 mmol), $Pd(PPh_3)_4$ (57 mg, 0.0490 mmol), CuI (19 mg, 0.0980 mmol) and Et_3N (0.683 mL, 4.90 mmol) were combined in DMF (5 mL). The stirred reaction mixture was degassed for 10 min, then heated to 80 °C for 3h, after which it was diluted with EtOAc, washed with H_2O and brine. The organic phase was dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by silica column chromatography (45% to 75% EtOAc/Hex) to provide the naphthyl alkyne compound (147 mg, 40%). This product was dissolved in DCM (10 mL) and treated with TFA (5 mL). After stirring for 20h, the mixture was concentrated. The residue was free-based then treated with 2-Methoxycarbonylamino-3-methyl-pentanoic acid (52 mg, 0.276 mmol), HATU (84 mg, 0.222 mmol) and DMF (2 mL). The stirred mixture was cooled to 0 °C

and DIPEA (0.160 mL, 0.923 mmol) was added dropwise. The reaction was allowed to come to RT slowly o/n. After 30h, 6 drops of 5 M NaOH were added and the mixture was stirred for 20 min, after which it was diluted with EtOAc and washed with 1M LiOH and brine. The organic phase was dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by HPLC to afford the title compound (33 mg, 22%). MS (ESI) *m/z* 765 $[M + H]^+$.

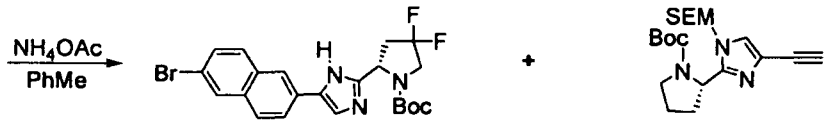
Example HB



2-Bromo-1-(6-bromo-naphthalen-2-yl)-ethanone

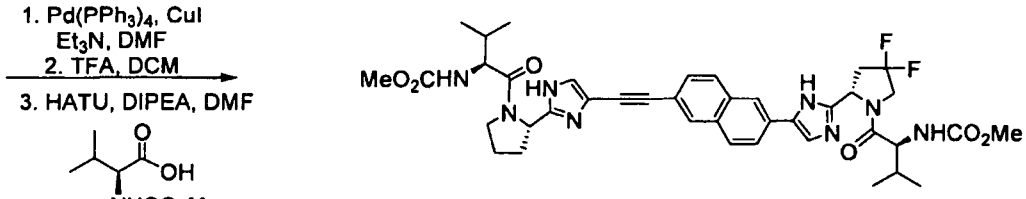
4,4-Difluoro-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester

4,4-Difluoro-pyrrolidine-1,2-dicarboxylic acid 2-[2-(6-bromo-naphthalen-2-yl)-2-oxo-ethyl] ester 1-*tert*-butyl ester



2-[5-(6-Bromo-naphthalen-2-yl)-1*H*-imidazol-2-yl]-4,4-difluoro-pyrrolidine-1-carboxylic acid *tert*-butyl ester

2-[4-Ethynyl-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester



2-Methoxycarbonylamino-3-methyl-butyric acid

(1-{2-[4-(6-{2-[4,4-Difluoro-1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-naphthalen-2-ylethynyl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

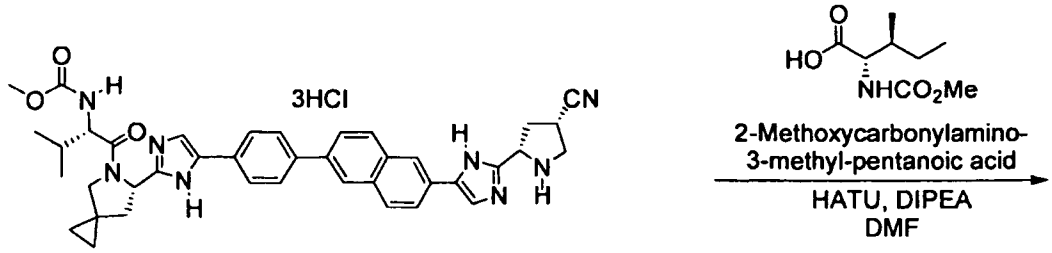
4,4-Difluoro-pyrrolidine-1,2-dicarboxylic acid 2-[2-(6-bromo-naphthalen-2-yl)-2-oxo-ethyl] ester 1-*tert*-butyl ester: 2-Bromo-1-(6-bromo-naphthalen-2-yl)-ethanone (1 g, 3.07 mmol) and 4,4-Difluoro-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester (849 mg, 3.38 mmol) were suspended in MeCN (15 mL) and treated with Et_3N (0.45 mL, 3.22 mmol). After stirring o/n, the reaction mixture was concentrated. The resulting residue was dissolved in EtOAc and washed with water, saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated. The crude material was purified by silica column chromatography (0% to 20% EtOAc/Hex) to provide the title compound (1.27 g, 83%).

2-[5-(6-Bromo-naphthalen-2-yl)-1H-imidazol-2-yl]-4,4-difluoro-pyrrolidine-1-carboxylic acid *tert*-butyl ester: 4,4-Difluoro-pyrrolidine-1,2-dicarboxylic acid 2-[2-(6-bromo-naphthalen-

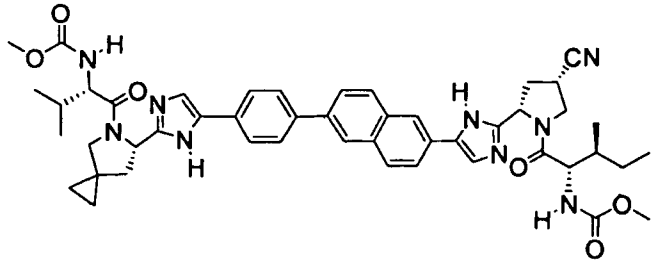
2-yl)-2-oxo-ethyl] ester 1-*tert*-butyl ester (1.2 g, 2.41 mmol) was treated with NH_4OAc (3.72 g, 96.4 mmol) and PhMe (48 mL). The reaction mixture was refluxed with stirring for 18 h. After this period, it was cooled to RT, diluted with EtOAc and washed with saturated aqueous $NaHCO_3$ and brine. Filtration and concentration provided a crude residue that was purified by silica column chromatography (20% to 60% EtOAc/Hex) to provide the title compound (803 mg, 70%).

(1-{2-[4-(6-{2-[4,4-Difluoro-1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-naphthalen-2-ylethynyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: 2-[4-Ethynyl-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (199 mg, 0.508 mmol), 2-[5-(6-Bromo-naphthalen-2-yl)-1H-imidazol-2-yl]-4,4-difluoro-pyrrolidine-1-carboxylic acid *tert*-butyl ester (364 mg, 0.762 mmol), $Pd(PPh_3)_4$ (118 mg, 0.102 mmol), CuI (19 mg, 0.102 mmol) and triethylamine (0.71 mL, 5.08 mmol) were suspended in DMF (5 mL). The reaction mixture was degassed with bubbling N_2 then heated to 80 °C for 4h. Following this period, the mixture was cooled to RT, diluted with EtOAc and washed with water, saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated. The crude material was purified by silica column chromatography (50% to 100% EtOAc/Hex) to provide the naphthyl alkyne (284 mg, 71%). A fraction of this material (123 mg, 0.156 mg) was dissolved in EtOH (4 mL) and treated with conc. HCl. The reaction mixture was stirred at reflux for 18h. The solution was then concentrated. The resulting residue treated with 2-Methoxycarbonylamino-3-methyl-butyric acid (60 mg, 0.343 mmol) and HATU (130 mg, 0.343 mmol), suspended in DMF (3 mL) and cooled to 0 °C. DIPEA (0.272 mL, 1.56 mmol) was added dropwise. After stirring for 4h, NaOH (5M in H_2O, 0.300 mL, 1.5 mmol) was added. This mixture was stirred for 3h then diluted with EtOAc and washed with 1 M LiOH (2x) then brine. The organic phase was dried over $MgSO_4$, filtered and concentrated. The crude residue was then purified by HPLC to afford the title compound (53 mg, 44%). MS (ESI) *m/z* 773 $[M + H]^+$.

Example HC



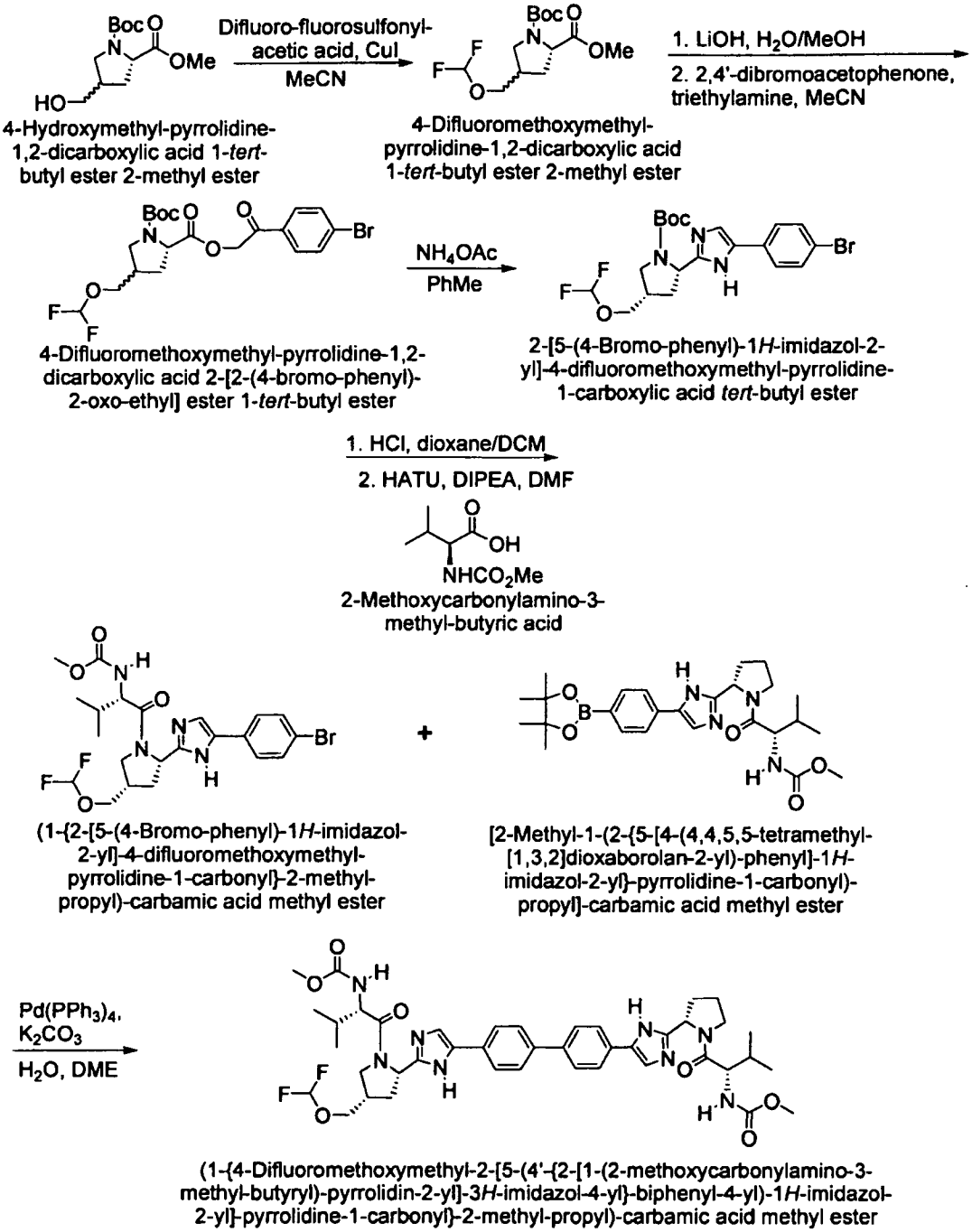
(1-{6-[5-(4-{6-[2-(4-Cyano-pyrrolidin-2-yl)-3*H*-imidazol-4-yl]-naphthalen-2-yl}-phenyl)-1*H*-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester-*tris*-hydrochloride



[1-(4-Cyano-2-{5-[6-(4-{2-[5-(2-methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3*H*-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-butyl]-carbamic acid methyl ester

[1-(4-Cyano-2-{5-[6-(4-{2-[5-(2-methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-butyl]-carbamic acid methyl ester: (1-{6-[5-(4-{6-[2-(4-Cyano-pyrrolidin-2-yl)-3H-imidazol-4-yl]-naphthalen-2-yl}-phenyl)-1H-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester-tris-hydrochloride (148 mg, 0.187 mmol), 2- 2-Methoxycarbonylamino-3-methyl-pentanoic acid (42 mg, 0.224 mmol) and HATU (78 mg, 0.206 mmol) were combined in DMF (2 mL) and cooled to 0 °C. DIPEA (0.163 mL, 0.935 mmol) was added dropwise. The reaction mixture was allowed to warm to RT slowly. After12 h, it was diluted with EtOAc and washed with saturated aqueous $NaHCO_3$, then brine. The organic phase was dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by HPLC to afford the title compound (80 mg, 50%). MS (ESI) *m/z* 854 $[M + H]^+$.

Example HD



4-Difluoromethoxymethyl-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester: 4-Hydroxymethyl-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (584 mg, 2.25 mmol) and CuI (86 mg, 0.45 mmol) were suspended in MeCN (10 mL). The reaction mixture was heated to 45 °C and difluoro-fluorosulfonyl-acetic acid (0.465 mL, 4.5 mmol) was added dropwise over the course of 30 min. Stirring was continued for another 3h, after which the

reaction mixture was cooled to RT and concentrated. The residue was taken up in EtOAc and washed with saturated aqueous $NaHCO_3$ and brine then dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by silica column chromatography (19% to 40% EtOAc/Hex) to afford the title compound (394 mg, 57%).

4-Difluoromethoxymethyl-pyrrolidine-1,2-dicarboxylic acid 2-[2-(4-bromo-phenyl)-2-oxo-ethyl] ester 1-*tert*-butyl ester: 4-Difluoromethoxymethyl-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (398 mg, 1.29 mmol) was dissolved in MeOH (8 mL) and LiOH (1 M in H_2O, 2mL, 2 mmol) was added. After stirring at RT for 5h, the MeOH was removed under reduced pressure. The aqueous solution was poured into a separatory funnel, diluted with 1 M HCl (2 mL, 2 mmol) and extracted with DCM (3x). The combined organics were dried over $MgSO_4$, filtered and concentrated. The residue was dissolved in MeCN (4 mL) and treated with 2,4'-dibromoacetophenone (200 mg, 0.719 mmol), and triethylamine (0.100 mL, 0.719 mmol). After stirring for 15 h, the solvent was removed. The crude residue was purified by silica column chromatography (10% to 35% EtOAc/Hex) to afford the title compound (303 mg, 94%).

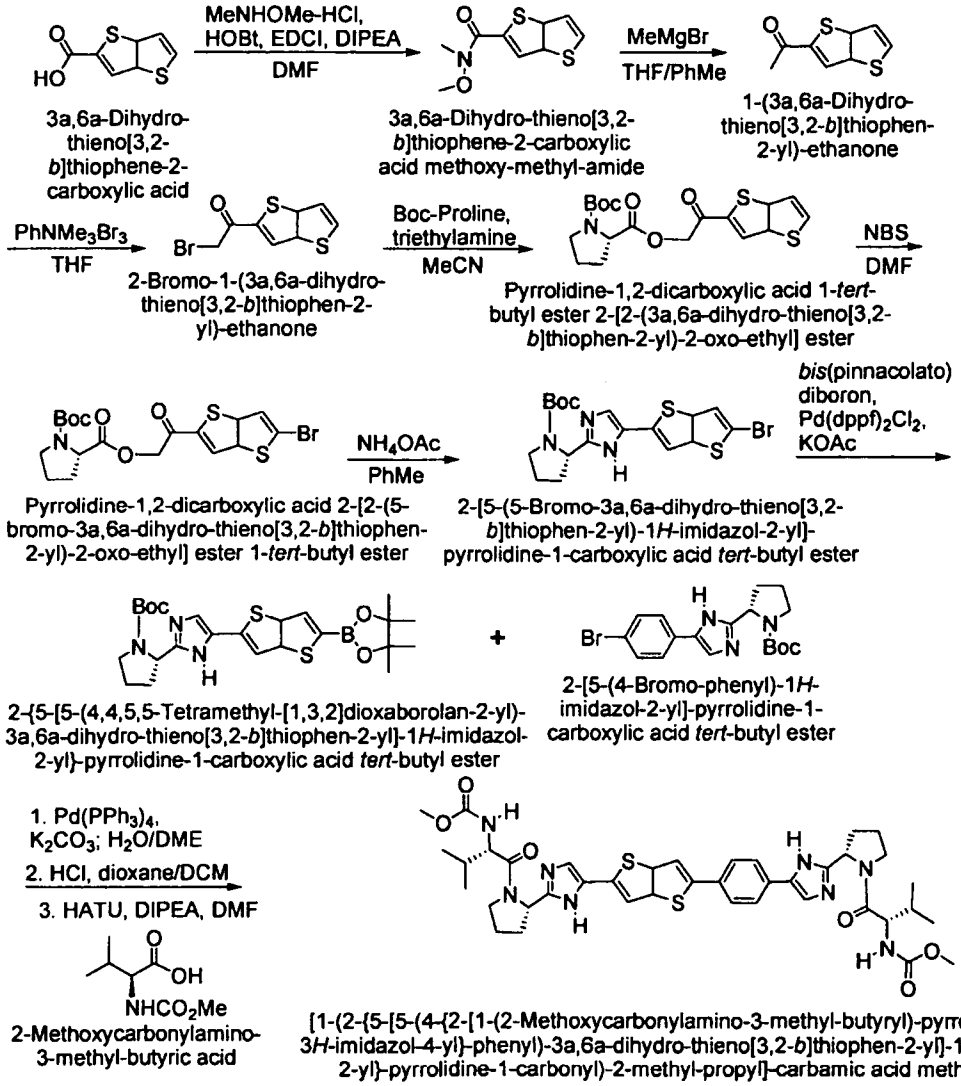
2-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-4-difluoromethoxymethyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester: 4-Difluoromethoxymethyl-pyrrolidine-1,2-dicarboxylic acid 2-[2-(4-bromo-phenyl)-2-oxo-ethyl] ester 1-*tert*-butyl ester (303 mg, 0.615 mmol) was dissolved in PhMe (12 mL) and treated with NH_4OAc (948 mg, 12.3 mmol). The stirred mixture was refluxed for 23 h then cooled to RT and diluted with EtOAc. The organic phase was washed with saturated aqueous $NaHCO_3$ and brine then dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by silica column chromatography (25% to 50% EtOAc/Hex) to afford the title compound (130 mg, 45%).

(1-{2-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-4-difluoromethoxymethyl-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: 2-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-4-difluoromethoxymethyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester was dissolved in DCM (4 mL) and treated with HCl (4.0M in dioxane, 1 mL, 4 mmol). After 2.5 h, the solution was concentrated and the residue was treated with 2-Methoxycarbonylamino-3-methyl-butyric acid (55 mg, 0.315 mmol) and HATU (120 mg, 0.315 mmol). The solids were suspended in DMF (3 mL) and the reaction mixture was cooled to 0 °C before triethylamine (0.25 mL, 1.43 mmol) was added in a dropwise fashion. After 30 min, the mixture was warmed to RT. After another 1 h, it was diluted with EtOAc and washed with saturated aqueous $NaHCO_3$ and brine. Then it was dried over $MgSO_4$, filtered and concentrated. The crude residue

was purified by silica column chromatography (60% to 100% EtOAc/Hex) to afford the title compound (92 mg, 61%).

(1-{4-Difluoromethoxymethyl-2-[5-(4'-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: (1-{2-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-4-difluoromethoxymethyl-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (42 mg, 0.174 mmol), [2-Methyl-1-(2-{5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-propyl]-carbamic acid methyl ester (95 mg, 0.191 mmol), $Pd(PPh_3)_4$ (20 mg, 0.0174 mmol) and K_2CO_3 (2M in H_2O, 0.191 mL, 0.383 mmol) were combined in 1,2-dimethoxyethane (2 mL). The mixture was degassed with bubbling N_2 for 12 min then heated to 85 °C for 4 h. After cooling to RT, the reaction mixture was diluted with EtOAc then washed with water and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by HPLC to provide the title compound (42 mg, 30%). MS (ESI) *m/z* 819 $[M + H]^+$.

Example HE



3a,6a-Dihydro-thieno[3,2-b]thiophene-2-carboxylic acid methoxy-methyl-amide: 3a,6a-Dihydro-thieno[3,2-b]thiophene-2-carboxylic acid (2g, 10.86 mmol) MeNHOMe-HCl (1.06 g, 10.86 mmol), HOBt (1.47 g, 10.86 mmol) and DIPEA (5.9 mL, 33.67 mmol) were combined in DMF (40 mL). To the stirred mixture was added EDCI (2.72 g, 14.12 mmol). After 5h, EtOAc (100 mL) was added and the organics were washed with saturated aqueous $NaHCO_3$ and brine then dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by silica column chromatography (20% to 45% EtOAc/Hex) to afford the title compound (1.98 g, 80%).

1-(3a,6a-Dihydro-thieno[3,2-b]thiophen-2-yl)-ethanone: 3a,6a-Dihydro-thieno[3,2-b]thiophene-2-carboxylic acid methoxy-methyl-amide (1.955 g, 8.60 mmol) was dissolved in

THF. The stirred solution was cooled to 0 °C before methylmagnesium bromide (1.4 M in PhMe, 8.6 mL, 12.04 mmol) was added. The reaction was allowed to gradually warm to RT o/n, then it was quenched by addition of 10% HCl. The aqueous phase was extracted with diethyl ether. The organic phase was washed with brine then dried over $MgSO_4$, filtered and concentrated to afford the title compound (1.98 g, 80%).

2-Bromo-1-(3a,6a-dihydro-thieno[3,2-b]thiophen-2-yl)-ethanone: 1-(3a,6a-Dihydro-thieno[3,2-b]thiophen-2-yl)-ethanone (453 mg, 2.48 mmol) was dissolved in THF (12 mL) and phenyltrimethylammonium tribromide (932 mg, 2.48 mmol) was added. After stirring for 1h, the suspension was filtered over CELITE. The filtrate was diluted with diethyl ether, then washed with saturated aqueous $NaHCO_3$ and brine then dried over $MgSO_4$, filtered and concentrated to afford the title compound which was carried on without purification.

Pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-[2-(3a,6a-dihydro-thieno[3,2-b]thiophen-2-yl)-2-oxo-ethyl] ester: Crude 2-Bromo-1-(3a,6a-dihydro-thieno[3,2-b]thiophen-2-yl)-ethanone (2.48 mmol assuming complete conversion from starting material) was treated with Boc-proline and MeCN (25 mL). Triethylamine was added and the solution was stirred at RT for 1h then concentrated. The crude residue was purified by silica column chromatography (14% to 35% EtOAc/Hex) to afford the title compound (595 mg, 61%).

Pyrrolidine-1,2-dicarboxylic acid 2-[2-(5-bromo-3a,6a-dihydro-thieno[3,2-b]thiophen-2-yl)-2-oxo-ethyl] ester 1-*tert*-butyl ester: Pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-[2-(3a,6a-dihydro-thieno[3,2-b]thiophen-2-yl)-2-oxo-ethyl] ester (595 mg, 1.5 mmol) was dissolved in DMF (7.5 mL) and treated with *N*—bromosuccinimide (295 mg, 1.65 mmol). The reaction mixture was stirred for 4d at RT then diluted with EtOAc and washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by silica column chromatography (20% to 50% EtOAc/Hex) to afford the title compound (469 mg, 66%).

2-[5-(5-Bromo-3a,6a-dihydro-thieno[3,2-b]thiophen-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester: Pyrrolidine-1,2-dicarboxylic acid 2-[2-(5-bromo-3a,6a-dihydro-thieno[3,2-b]thiophen-2-yl)-2-oxo-ethyl] ester 1-*tert*-butyl ester (480 mg, 1.01 mmol) was treated with PhMe (10 mL) and ammonium acetate (1.56 g, 20.24 mmol). The reaction mixture was refluxed while stirring for 16h, then cooled to RT. EtOAc was added and the organic phase was washed with saturated aqueous $NaHCO_3$ and brine. After it was dried over

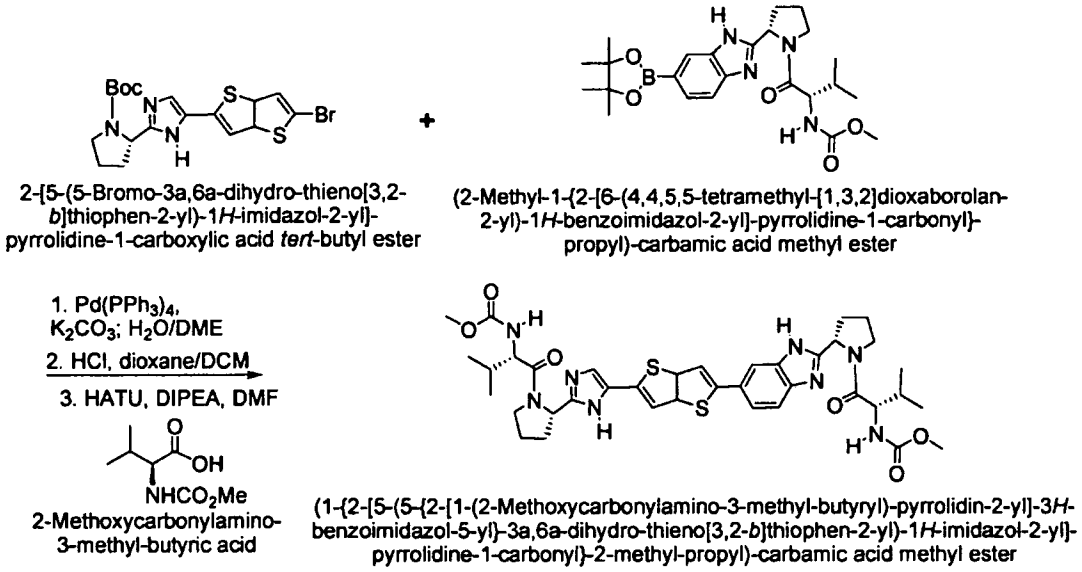
$MgSO_4$, it was filtered and concentrated. The crude residue was purified by silica column chromatography (25% to 60% EtOAc/Hex) to afford the title compound (378 mg, 82%).

2-{5-[5-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-3a,6a-dihydro-thieno[3,2-b]thiophen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester: 2-[5-(5-Bromo-3a,6a-dihydro-thieno[3,2-b]thiophen-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester
(273 mg, 0.598 mmol), bis(pinacolato)diboron (0.228 mg, 0.897 mmol), $Pd(dppf)_2Cl_2$ (44 mg, 0.0598 mmol) and KOAc (176 mg, 1.79 mmol) were combined in dioxane and degassed for 12 min with bubbling N_2. The reaction mixture was then stirred at 85 °C for 2.5h, cooled to RT and diluted with EtOAc. The organic mixture was washed with saturated aqueous $NaHCO_3$ and brine before being dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by silica column chromatography (25% to 60% EtOAc/Hex) to provide the title compound (0.159 g, 53%). The product was contaminated with an equimolar amount of a byproduct which was believed to be the proteodebrominated starting material.

[1-(2-{5-[5-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-3a,6a-dihydro-thieno[3,2-b]thiophen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: 2-{5-[5-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-3a,6a-dihydro-thieno[3,2-b]thiophen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (159 mg, 0.317 mmol), 2-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (124 mg, 0.317 mmol), $Pd(PPh_3)_4$ (37 mg, 0.0317 mmol) and K_2CO_3 (2 M in H_2O, 0.32 mL, 0.64 mmol) were combined in 1,2-dimethoxyethane (3 mL) and degassed with bubbling N_2 for 10 min. The stirred reaction mixture was warmed to 85 °C for 3.5h then cooled to RT and diluted with EtOAc. The organic phase was washed with saturated aqueous $NaHCO_3$ and brine before being dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by silica column chromatography (EtOAc then 5% MeOH/DCM) to afford the Suzuki-coupled product (89 mg, 41%). This material was dissolved in DCM (4 mL) and treated with HCl (4 M in dioxane, 1 mL, 4 mmol). After stirring for 73min, the reaction mixture was diluted with EtOAc and the solid was filtered off and rinsed with EtOAc. The solid was dried, then combined with 2-Methoxycarbonylamino-3-methyl-butyric acid (37 mg, 0.212 mmol), HATU (81 mg, 0.212 mmol) and DMF (2 mL). The stirred reaction mixture was cooled to 0 °C and DIPEA (0.17 mL, 0.96 mmol) was added dropwise. After 15min, it was warmed to RT. 17h later, the reaction mixture was diluted with EtOAc. . The organic phase was washed with saturated aqueous $NaHCO_3$ and brine before being

dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by HPLC to afford the title compound (23 mg, 22%). MS (ESI) *m/z* 801 $[M + H]^+$.

Example HF



2-[5-(5-Bromo-3a,6a-dihydro-thieno[3,2-*b*]thiophen-2-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester

(2-Methyl-1-{2-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-benzoimidazol-2-yl]-pyrrolidine-1-carbonyl}-propyl)-carbamic acid methyl ester

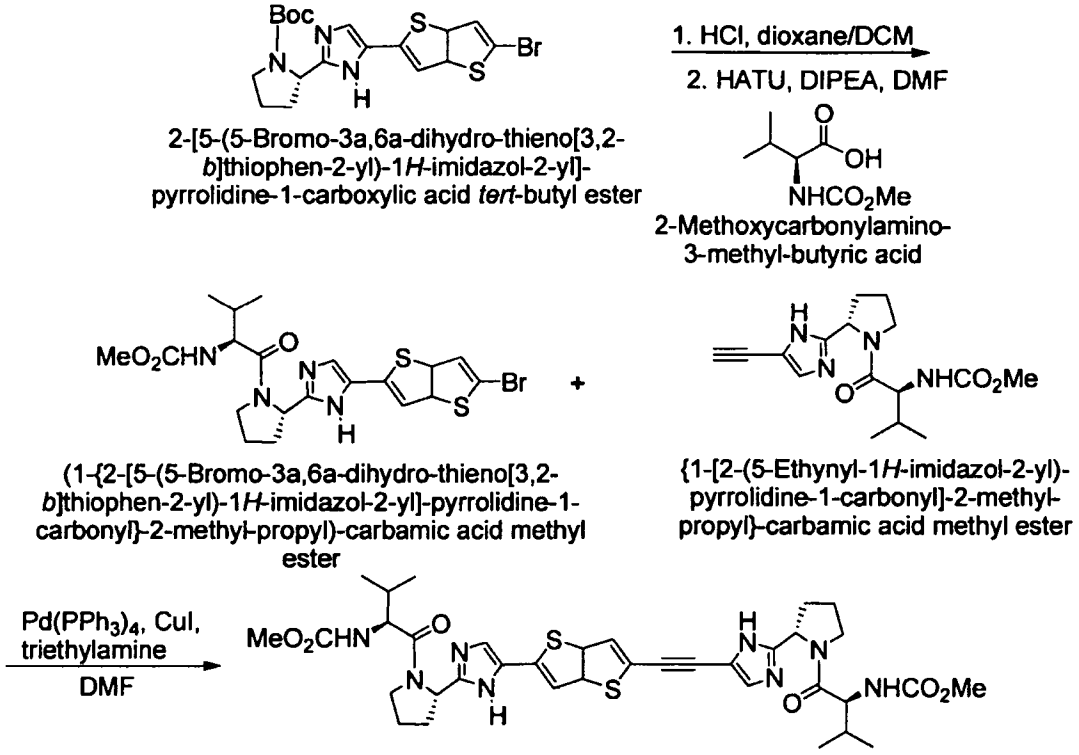
2-Methoxycarbonylamino-3-methyl-butyric acid

(1-{2-[5-(5-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-benzoimidazol-5-yl}-3a,6a-dihydro-thieno[3,2-*b*]thiophen-2-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

(1-{2-[5-(5-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-benzoimidazol-5-yl}-3a,6a-dihydro-thieno[3,2-b]thiophen-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: 2-[5-(5-Bromo-3a,6a-dihydro-thieno[3,2-b]thiophen-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (100 mg, 0.219 mmol), (2-Methyl-1-{2-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-benzoimidazol-2-yl]-pyrrolidine-1-carbonyl}-propyl)-carbamic acid methyl ester (117 mg, 0.283 mmol), $Pd(PPh_3)_4$ (51 mg, 0.0438 mmol) and K_2CO_3 (2 M in H_2O, 0.33 mL, 0.66 mmol) were combined in 1,2-dimethoxyethane (4 mL) and degassed with bubbling N_2 for 10 min. The stirred reaction mixture was warmed to 85 °C for 3.5h then cooled to RT and diluted with EtOAc. The organic phase was washed with saturated aqueous $NaHCO_3$ and brine before being dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by silica column chromatography (EtOAc) to afford the Suzuki-coupled product (71 mg, 49%). This material was dissolved in DCM (4 mL) and treated with HCl (4 M in dioxane, 1 mL, 4 mmol). After stirring for 97min, the reaction mixture was concentrated. The solid was dried, then combined with 2-Methoxycarbonylamino-3-methyl-butyric acid (39 mg, 0.225 mmol), HATU (86 mg, 0.225 mmol) and DMF (4 mL). The stirred reaction mixture was cooled to 0 °C and DIPEA (0.18 mL, 1.07 mmol) was added dropwise. After 30min, it was warmed to RT. 12min

later, the reaction mixture was diluted with EtOAc. . The organic phase was washed with saturated aqueous $NaHCO_3$ and brine before being dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by HPLC to afford the title compound (32 mg, 39%). MS (ESI) *m/z* 775 $[M + H]^+$.

Example HG



2-[5-(5-Bromo-3a,6a-dihydro-thieno[3,2-*b*]thiophen-2-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester

2-Methoxycarbonylamino-3-methyl-butyric acid

(1-{2-[5-(5-Bromo-3a,6a-dihydro-thieno[3,2-*b*]thiophen-2-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

{1-[2-(5-Ethynyl-1*H*-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester

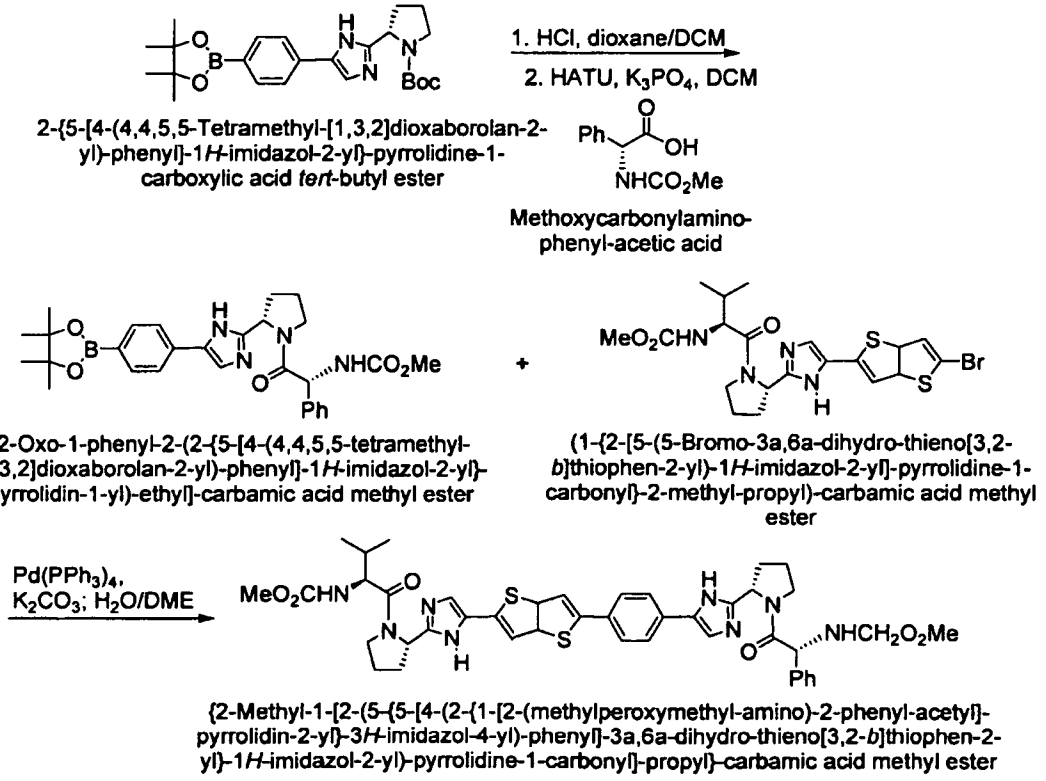
(1-{2-[5-(5-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-ylethynyl}-3a,6a-dihydro-thieno[3,2-*b*]thiophen-2-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

(1-{2-[5-(5-Bromo-3a,6a-dihydro-thieno[3,2-b]thiophen-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: 2-[5-(5-Bromo-3a,6a-dihydro-thieno[3,2-b]thiophen-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (250 mg, 0.548 mmol) was dissolved in DCM (4 mL) and treated with HCl (4 M in dioxane, 1 mL, 4 mmol). After stirring for 1.5h, the reaction mixture was concentrated. The solid was dried, then combined with 2-Methoxycarbonylamino-3-methyl-butyric acid (106 mg, 0.603 mmol), HATU (229 mg, 0.603 mmol) and DMF (6 mL). The stirred reaction mixture was cooled to 0 °C and DIPEA (0.48 mL, 2.74 mmol) was added dropwise. After 50min, it was warmed to RT. 12min later, the reaction mixture was diluted with EtOAc. . The organic phase was washed with saturated aqueous $NaHCO_3$ and brine before being dried over $MgSO_4$, filtered

and concentrated. The crude residue was purified by silica column chromatography to afford the title compound (252 mg, 90%).

(1-{2-[5-(5-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-ylethynyl}-3a,6a-dihydro-thieno[3,2-b]thiophen-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: (1-{2-[5-(5-Bromo-3a,6a-dihydro-thieno[3,2-b]thiophen-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (140 mg, 0.440 mmol), {1-[2-(5-Ethynyl-1H-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (130 mg, 0.254 mmol), $Pd(PPh_3)_4$ (29 mg, 0.0254 mmol), CuI (10 mg, 0.0508 mmol) and triethylamine (0.354 mmol, 2.54 mmol) were combined in DMF (2.5 mL) and degassed with N_2 for 17min. The reaction was heated to 85 °C for 4h then cooled to RT, diluted with EtOAc and washed with saturated aqueous $NaHCO_3$ (2x) and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by HPLC chromatography to afford the title compound (34 mg, 18%). MS (ESI) *m/z* 749 $[M + H]^+$.

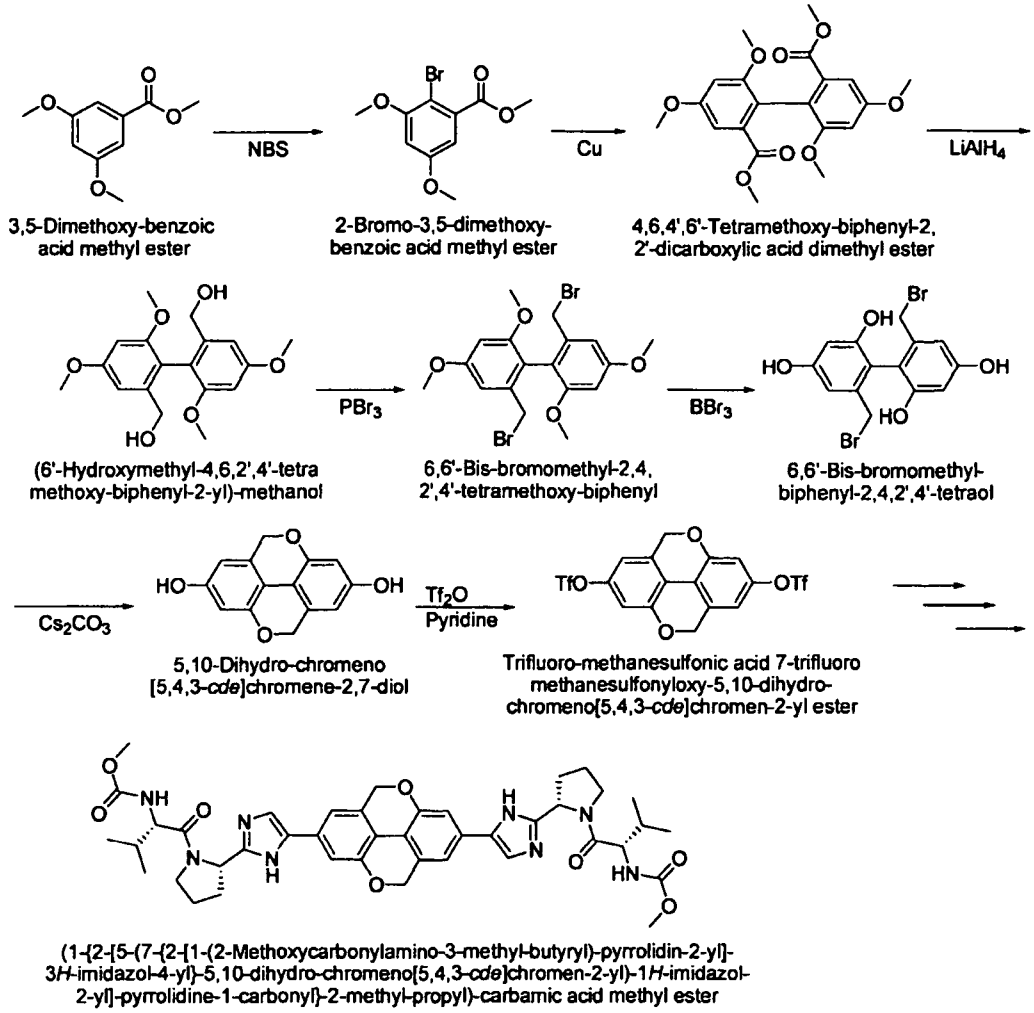
Example HH



[2-Oxo-1-phenyl-2-(2-{5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidin-1-yl)-ethyl]-carbamic acid methyl ester: 2-{5-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (530 mg, 1.21 mmol) was dissolved in DCM (4 mL) and treated with HCl (4M in dioxane, 1 mL, 4 mmol). The reaction mixture was stirred at RT for 19h then the solid was filtered off and rinsed with DCM. After being thoroughly dried (461 mg, 92%), a portion of this solid (200 mg, 0.485 mmol) was combined with Methoxycarbonylamino-phenyl-acetic acid (122 mg, 0.582 mmol) and HATU (221 mg, 0.582 mmol)were suspended in DCM (5 mL) and K_3PO_4 (309 mg, 1.455 mmol) was added. After stirring 24h, the reaction mixture was diluted with EtOAc and washed with 1M LiOH and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by silica column chromatography (75% to 100% EtOAc) to provide the title compound (204 mg , 79%).

{2-Methyl-1-[2-(5-{5-[4-(2-{1-[2-(methylperoxymethyl-amino)-2-phenyl-acetyl]-pyrrolidin-2-yl}-3H-imidazol-4-yl)-phenyl]-3a,6a-dihydro-thieno[3,2-b]thiophen-2-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carbonyl]-propyl}-carbamic acid methyl ester: [2-Oxo-1-phenyl-2-(2-{5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidin-1-yl)-ethyl]-carbamic acid methyl ester (204 mg, 0.385 mmol), (1-{2-[5-(5-Bromo-3a,6a-dihydro-thieno[3,2-b]thiophen-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (137 mg, 0.268 mmol), $Pd(PPh_3)_4$ (31 mg, 0.0268 mmol) and K_2CO_3 (2M in H_2O, 0.4 mL, 0.8 mmol) were combined in 1,2-dimethoxyethane (2.7 mL). After 10 min of degassing with bubbling N_2, the reaction mixture was heated to 85 °C for 19h. After this period, it was cooled and diluted MeOH. The suspension was filtered over a thiol SPE cartridge to remove the palladium, then concentrated. The crude residue was purified by HPLC to afford the title compound (103 mg, 46%). MS (ESI) *m/z* 835 $[M + H]^+$.

Example HI



2-Bromo-3,5-dimethoxy-benzoic acid methyl ester: 3,5-Dimethoxy-benzoic acid methyl ester (4.0 g) was dissolved in MeCN (28 mL), and NBS (4.4 g) was added at 0°C. After stirring at room temperature for 3 hours, saturated Na_2SO_3 (15 mL) was added. The mixture was evaporated under vacuum and extracted with ether (1x, 500 mL). After the solvent was removed, the crude material was subjected to silica gel chromatography using effluent of 10 -40 % ethyl acetate and hexanes. The fractions containing product were combined and the solvent was removed under reduced pressure to provide 2-bromo-3,5-dimethoxy-benzoic acid methyl ester (5.2 g, 93 %) as a clear oil.

4,6,4',6'-Tetramethoxy-biphenyl-2,2'-dicarboxylic acid dimethyl ester : 2-Bromo-3,5-dimethoxy-benzoic acid methyl ester (5.2 g) was dissolved in DMF (16 mL), and Cu powder (2.4 g) was added . After stirring at 150°C for 3 days, the mixture was filtered and evaporated under vacuum. The crude material was subjected to silica gel chromatography using effluent of

30 -60 % ethyl acetate and hexanes. The fractions containing product were combined and the solvent was removed under reduced pressure to provide 4,6,4',6'-tetramethoxy-biphenyl-2,2'-dicarboxylic acid dimethyl ester (2.5 g, 68 %) as a clear oil.

(6'-Hydroxymethyl-4,6,2',4'-tetramethoxy-biphenyl-2-yl)-methanol : 4,6,4',6'-tetramethoxy-biphenyl-2,2'-dicarboxylic acid dimethyl ester (2.5 g) was dissolved in THF (96 mL), and 1M $LiAlH_4$ in THF (9.6 mL) was added . After stirring at room temperature for overnight, the mixture was quenched with water and 2N HCl (24 mL) was added. The mixture was evaporated under vacuum and partitioned with DCM (300 mL) and water (200mL). The organic layer was dried over Na_2SO_4 and crystallized with DCM to provide (6'-hydroxymethyl-4,6,2',4'-tetramethoxy-biphenyl-2-yl)-methanol (1.7 g, 77 %) as a pale blue white triclinic crystals.

6,6'-Bis-bromomethyl-2,4,2',4'-tetramethoxy-biphenyl : (6'-hydroxymethyl-4,6,2',4'-tetramethoxy-biphenyl-2-yl)-methanol (779 mg) was dissolved in DCM (5.8 mL), and PBr_3 (527 µl) was slowly added at 0°C. After stirring at 0°C for 30 min. and at room temperature for 1 hour, H_2O (40 mL) was added. The mixture was extracted with ether (1x, 50 mL). After the solvent was removed, the crude material was subjected to silica gel chromatography using effluent of 10 -40 % ethyl acetate and hexanes. The fractions containing product were combined and the solvent was removed under reduced pressure to provide 6,6'-bis-bromomethyl-2,4,2',4'-tetramethoxy-biphenyl (700 mg, 65 %) as a thick oil.

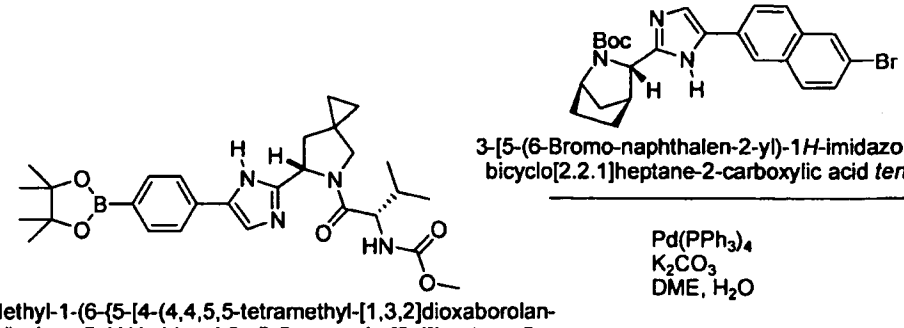
6,6'-Bis-bromomethyl-biphenyl-2,4,2',4'-tetraol : 6,6'-bis-bromomethyl-2,4,2',4'-tetramethoxy-biphenyl (685 mg) was dissolved in DCM (3.0 mL), and 1M BBr_3 in DCM (16.4 mL) was slowly added. After stirring for 2 days, the mixture was poured on to ice and concentrated. The crude material was used for the next step without a further purification.

5-10-Dihydro-chromeno[5,4,3-cde]chromene-2,7-diol : The crude 6,6'-bis-bromomethyl-biphenyl-2,4,2',4'-tetraol was dissolved in DMF (30 mL), and Cs_2CO_3 (1.9 g) was added. After stirring at room temperature for 1 hour, the mixture was partitioned with 1 N HCl (100 mL) and ethyl acetate (100 mL), and extracted with ethyl acetate (3X, 100 mL). After the solvent was removed, the crude material was subjected to silica gel chromatography using effluent of 10 -15 % methanol and DCM. The fractions containing product were combined and the solvent was removed under reduced pressure to provide 5-10-dihydro-chromeno[5,4,3-cde]chromene-2,7-diol (301 mg, 84 %) as a white solid.

Trifluoro-methanesulfonic acid 7-trifluoromethanesulfonyloxy-5,10-dihydro-chromeno[5,4,3-cde]chromen-2-yl ester : 5-10-Dihydro-chromeno[5,4,3-cde]chromene-2,7-diol (290 mg) was dissolved in DCM (12 mL), and Tf_2O (1.2 mL) and pyridine (969 µl) were added. After stirring at room temperature for overnight, the mixture was partitioned with 2 N HCl (50 mL) and DCM (50 mL), and washed with 2 N HCl (2 x 50 mL) and saturated sodium bicarbonate (1 x 50 mL). After the solvent was removed, the resulting oil was subjected to silica gel chromatography using effluent of 0 -30 % ethyl acetate and hexanes. The fractions containing product were combined and the solvent was removed under reduced pressure to provide trifluoro-methanesulfonic acid 7-trifluoromethanesulfonyloxy-5,10-dihydro-chromeno[5,4,3-cde]chromen-2-yl ester (472 mg, 78%) as an off-white solid.

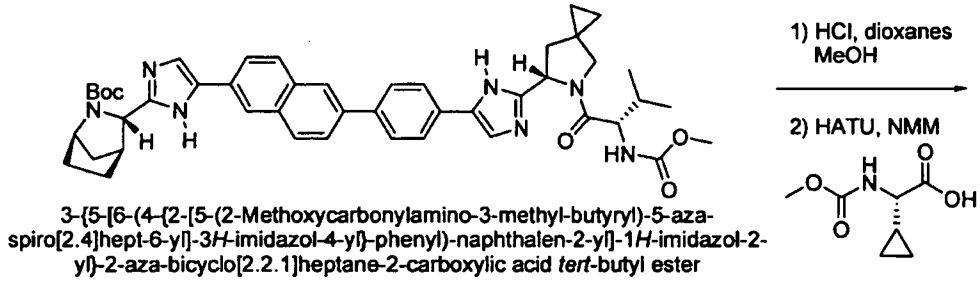
(1-{2-[5-(7-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-5,10-dihydro-chromeno[5,4,3-cde]chromen-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester : Title compound was prepared according to the method employed to prepare (1-{2-[5-(2-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-6-H-dibenzo[c,h]chromen-8-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester, substituting trifluoro-methanesulfonic acid 7-trifluoromethane sulfonyloxy-5,10-dihydro-chromeno[5,4,3-cde]chromen-2-yl ester for trifluoro-methanesulfonic acid 2-trifluoromethanesulfonyloxy-6-H-dibenzo[c,h]chromen-8-yl ester.

Example HJ

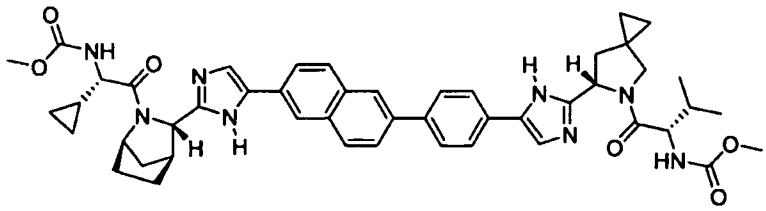


3-[5-(6-Bromo-naphthalen-2-yl)-1*H*-imidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester

[2-Methyl-1-(6-{5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1*H*-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carbonyl)-propyl]-carbamic acid methyl ester



3-{5-[6-(4-{2-[5-(2-Methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3*H*-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1*H*-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester



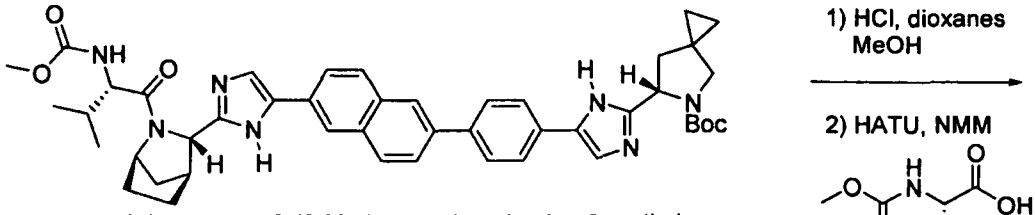
[1-(6-{5-[4-(6-{2-[2-(2-Cyclopropyl-2-methoxycarbonylamino-acetyl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester

3-{5-[6-(4-{2-[5-(2-Methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester. To a solution of [2-Methyl-1-(6-{5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carbonyl)-propyl]-carbamic acid methyl ester (0.95 g, 1.82 mmol) and 3-[5-(6-Bromo-naphthalen-2-yl)-1H-imidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (0.96 g, 1.82 mmol, 1 equiv.) in DME (20 mL) was added K_2CO_3 (aqueous, 2 M, 3.6 mL, 7.2 mmol, 4 equiv.) and $Pd(PPh_3)_4$ (0.11 g, 0.09 mmol, 0.05 equiv.). The slurry was degassed with argon for 5 minutes and heated to 80 °C for 12 hours. The resulting reaction mixture was diluted with EtOAc and washed with water. The aqueous layer was back-extracted with EtOAc and the combined organic layers were dried over Na_2SO_4 and concentrated. The crude oil was purified by column chromatography (SiO_2, 50→100% EtOAc in Hexanes) to

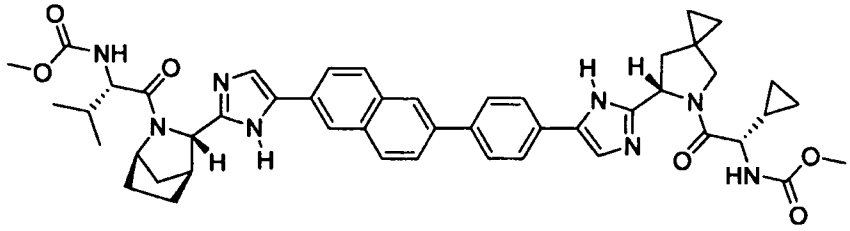
provide 3-{5-[6-(4-{2-[5-(2-Methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (0.53 g, 37%) as a yellow powder. LCMS-ESI$^+$: calc'd for $C_{46}H_{53}N_7O_5$: 783.4 (M^+); Found: 784.3 ($M+H^+$).

[1-(6-{5-[4-(6-{2-[2-(2-Cyclopropyl-2-methoxycarbonylamino-acetyl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester. To a slurry of 3-{5-[6-(4-{2-[5-(2-Methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (0.05 g, 0.06 mmol) in MeOH (0.1 mL) was added HCl in dioxanes (4 M, 0.6 mL). The resulting solution was stirred at room temperature for 1 hour and the concentrated to dryness. Cyclopropyl-methoxycarbonylamino-acetic acid (0.02 g, 0.09 mmol, 1.5 equiv.) and CH_2Cl_2 (0.6 mL) were then added, followed by HATU (0.03 g, 0.08 mmol, 1.25 equiv.) and NMM (0.05 mL, 0.45 mmol, 5 equiv.). The resulting solution was stirred at room temperature for 18 hours. The reaction mixture was concentrated and purified by preparative HPLC (Gemini, 15→40% MeCN in H_2O (0.1% formic acid)) and lyophilized to provide [1-(6-{5-[4-(6-{2-[2-(2-Cyclopropyl-2-methoxycarbonylamino-acetyl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (0.03 g, 49%) as a white powder. LCMS-ESI$^+$: calc'd for $C_{48}H_{54}N_8O_6$: 838.4 (M^+); Found: 839.9 ($M+H^+$). ^{1}H-NMR: 400 MHz, ($CDCl_3$) δ: (mixture of rotomers) 8.22 (s, 2H), 7.81-7.96 (m, 10H), 7.63 (d, 1H), 7.29 (d, 1H), 5.18 (t, 1H), 4.56 (d, 1H), 3.96 (t, 1H), 3.74 (m, 1H), 3.51 (s, 6H), 3.12 (t, 1H), 2.48 (s, 1H), 1.93-2.29 (m, 6H), 1.58-1.77 (m, 5H), 0.85 (d, 3H), 0.80 (d, 3H), 0.58 (m, 4H), 0.34 (m, 1H), 0.26 (m, 1H), 0.03 (m, 1H), -0.12 (m, 1H).

Example HK



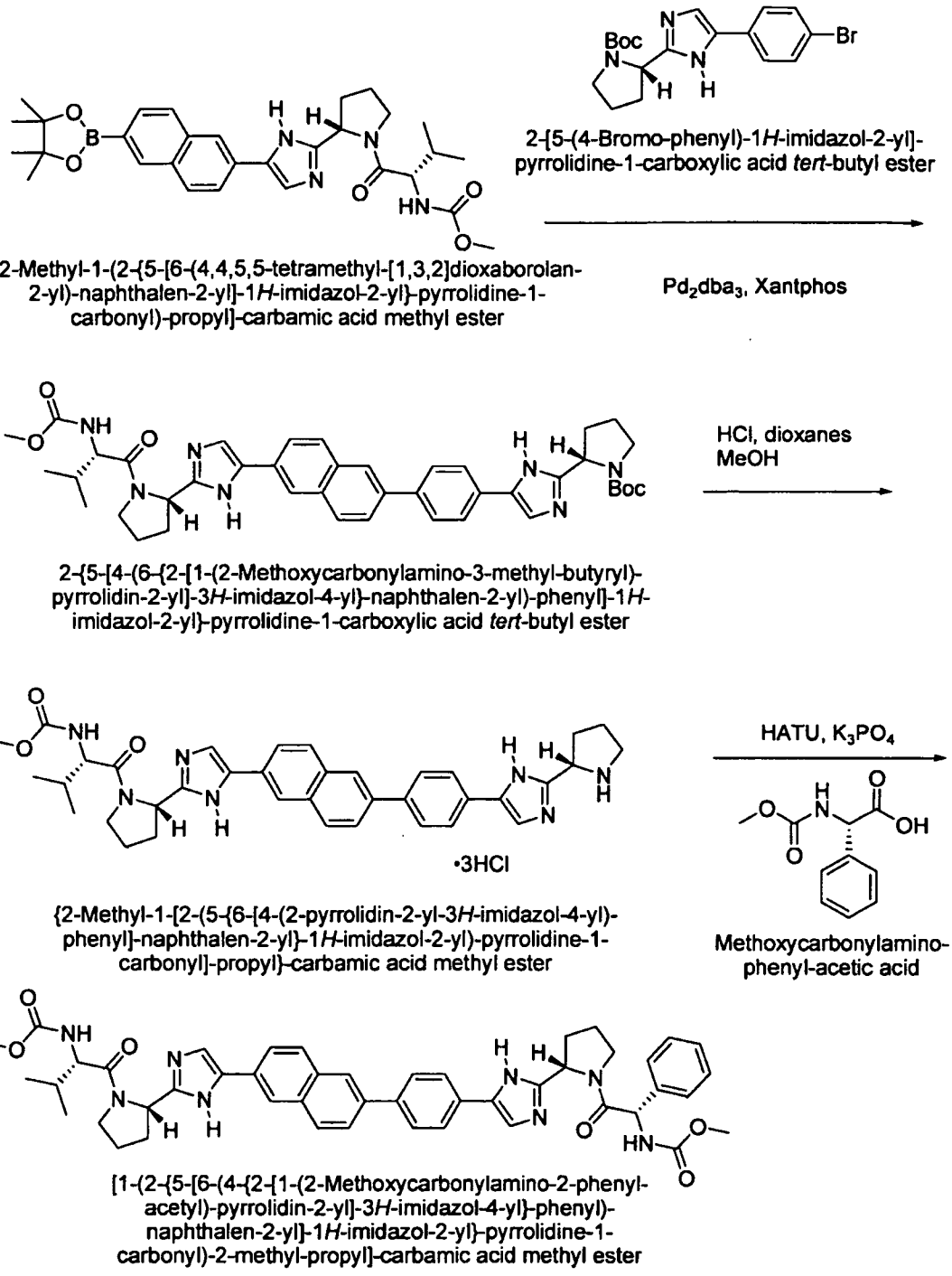
6-{5-[4-(6-{2-[2-(2-Methoxycarbonylamino-3-methyl-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3*H*-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1*H*-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carboxylic acid *tert*-butyl ester



[1-(3-{5-[6-(4-{2-[5-(2-Cyclopropyl-2-methoxycarbonylamino-acetyl)-5-aza-spiro[2.4]hept-6-yl]-3*H*-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1*H*-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester

[1-(3-{5-[6-(4-{2-[5-(2-Cyclopropyl-2-methoxycarbonylamino-acetyl)-5-aza-spiro[2.4]hept-6-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester. This compound was prepared following the procedure for [1-(6-{5-[4-(6-{2-[2-(2-Cyclopropyl-2-methoxycarbonylamino-acetyl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester using 6-{5-[4-(6-{2-[2-(2-Methoxycarbonylamino-3-methyl-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carboxylic acid *tert*-butyl ester (0.05 g, 0.06 mmol) to provide [1-(3-{5-[6-(4-{2-[5-(2-Cyclopropyl-2-methoxycarbonylamino-acetyl)-5-aza-spiro[2.4]hept-6-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (0.02 g, 46%) as a white powder. LCMS-ESI$^+$: calc'd for $C_{48}H_{54}N_8O_6$: 838.4 (M^+); Found: 839.9 ($M+H^+$). ^{1}H-NMR: 400 MHz, ($CDCl_3$) δ: (mixture of rotomers) 8.18 (s, 2H), 7.80-7.91 (m, 10H), 7.58 (s, 1H), 7.14 (d, 1H), 5.19 (d, 1H), 4.50 (d, 1H), 4.13 (t, 1H), 3.57 (m, 1H), 3.51 (s, 6H), 3.28 (m, 1H), 2.48 (s, 1H), 1.94-2.04 (m, 2H), 1.71-1.83 (m, 5H), 1.42-1.49 (m, 4H), 0.97 (d, 3H), 0.87 (d, 3H), 0.52-0.68 (m, 4H), 0.33 (m, 1H), 0.23 (m, 1H), 0.03 (m, 1H), -0.12 (m, 1H).

Example HL



2-{5-[4-(6-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester. To a solution of 2-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-

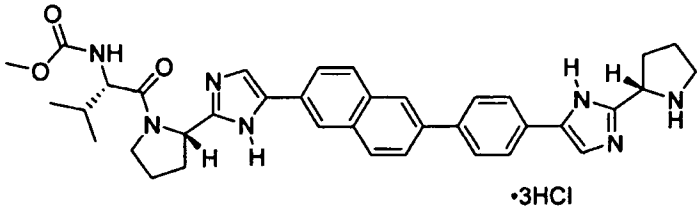
carboxylic acid *tert*-butyl ester (1.00 g, 2.5 mmol) and [2-Methyl-1-(2-{5-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-propyl]-carbamic acid methyl ester (1.97 g, 3.6 mmol, 1.5 equiv.) in DME (12.5 mL) was added K_3PO_4 (aqueous, 2 M, 3.9 mL, 7.8 mmol, 3 equiv.), Pd_2dba_3 (0.12 g, 0.13 mmol, 0.05 equiv.), and Xantphos (0.15 g, 0.26 mmol, 0.1 equiv.). The slurry was degassed with argon for 5 minutes and heated to 80 °C for 18 hours. The resulting reaction mixture was diluted with EtOAc/MeOH (10:1) and filtered through CELITE. The solution was washed with water and brine. The aqueous layer was back-extracted with EtOAc and the combined organic layers were dried over Na_2SO_4 and concentrated. The crude oil was purified by column chromatography (SiO_2, 50→100% EtOAc in Hexanes) to provide 2-{5-[4-(6-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.93 g, 49%) as a yellow powder. LCMS-ESI$^+$: calc'd for $C_{42}H_{49}N_7O_5$: 731.4 (M^+); Found: 732.9 ($M+H^+$).

{2-Methyl-1-[2-(5-{6-[4-(2-pyrrolidin-2-yl-3H-imidazol-4-yl)-phenyl]-naphthalen-2-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carbonyl]-propyl}-carbamic acid methyl ester. To a slurry of 2-{5-[4-(6-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.1 g, 0.14 mmol) in MeOH (0.15 mL) was added HCl in dioxanes (4 M, 0.7 mL). The resulting solution was stirred at room temperature for 1 hour and diluted with Et_2O. The resulting precipitate was filtered and dried to provide {2-Methyl-1-[2-(5-{6-[4-(2-pyrrolidin-2-yl-3H-imidazol-4-yl)-phenyl]-naphthalen-2-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carbonyl]-propyl}-carbamic acid methyl ester trihydrochloric acid salt (0.09 g, 87%) as a white powder. LCMS-ESI$^+$: calc'd for $C_{37}H_{41}N_7O_3$: 631.3 (M^+); Found: 632.7 ($M+H^+$).

[1-(2-{5-[6-(4-{2-[1-(2S)-(2-Methoxycarbonylamino-2-phenyl-acetyl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester. To a slurry of {2-Methyl-1-[2-(5-{6-[4-(2-pyrrolidin-2-yl-3H-imidazol-4-yl)-phenyl]-naphthalen-2-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carbonyl]-propyl}-carbamic acid methyl ester (0.045 g, 0.06 mmol) and (*S*)-methoxycarbonylamino-phenyl-acetic acid (0.02 g, 0.09 mmol, 1.5 equiv.) in CH_2Cl_2 (0.6 mL) was added HATU (0.03 g, 0.08, 1.25 equiv.) and K_3PO_4 (0.05 g, 0.22 mmol, 3 equiv.). The reaction mixture was stirred at room temperature for 18 hours and diluted with CH_2Cl_2. The salts were filtered and the filtrate was concentrated. The crude oil was purified by preparative HPLC (Gemini, 15→40% MeCN in H_2O (0.1% formic acid)) and lyophilized to provide [1-(2-

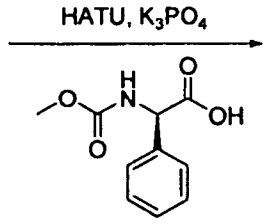
{5-[6-(4-{2-[1-(2S)-(2-Methoxycarbonylamino-2-phenyl-acetyl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (0.03 g, 65%) as a white powder. LCMS-ESI$^+$: calc'd for $C_{47}H_{50}N_8O_6$: 822.4 (M^+); Found: 823.5 ($M+H^+$). ^{1}H-NMR: 400 MHz, ($CDCl_3$) δ: (Mixture of rotomers) 7.64-8.03 (m, 9H), 7.20-7.40 (m, 6H), 7.17 (s, 2H), 6.14 (m, 1H), 5.53 (dd, 2H), 5.25-5.33 (m, 2H), 4.33 (t, 1H), 3.85 (m, 1H), 3.73 (m, 1H), 3.68 (s, 3H), 3.66 (s, 3H), 3.27 (m, 1H), 2.86-2.96 (m, 3H), 2.35 (m, 1H), 1.94-2.23 (m, 6H), 0.87-0.90 (m, 6H).

Example HM

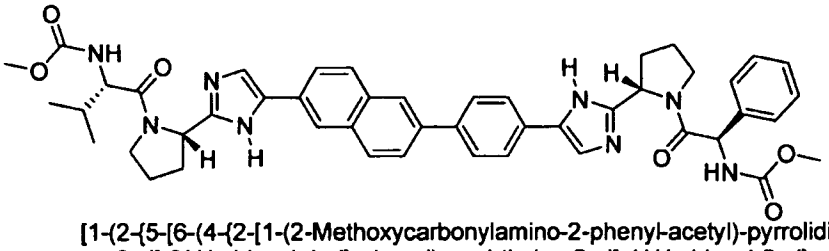


•3HCl

{2-Methyl-1-[2-(5-{6-[4-(2-pyrrolidin-2-yl-3*H*-imidazol-4-yl)-phenyl]-naphthalen-2-yl}-1*H*-imidazol-2-yl)-pyrrolidine-1-carbonyl]-propyl}-carbamic acid methyl ester



Methoxycarbonylamino-phenyl-acetic acid

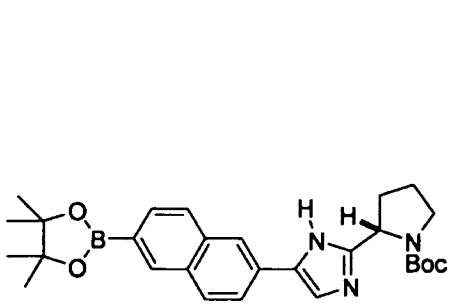


[1-(2-{5-[6-(4-{2-[1-(2-Methoxycarbonylamino-2-phenyl-acetyl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester

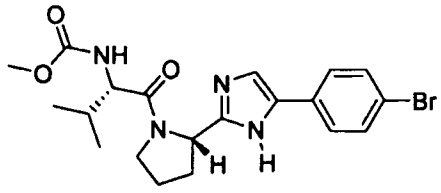
[1-(2-{5-[6-(4-{2-[1-(2R)-(2-Methoxycarbonylamino-2-phenyl-acetyl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester. This compound was prepared following the procedure for [1-(2-{5-[6-(4-{2-[1-(2S)-(2-Methoxycarbonylamino-2-phenyl-acetyl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester using (*R*)-methoxycarbonylamino-phenyl-acetic acid (0.02 g, 0.09 mmol, 1.5 equiv.) to provide [1-(2-{5-[6-(4-{2-[1-(2R)-(2-Methoxycarbonylamino-2-phenyl-acetyl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (0.03 g, 65%) as a white powder. LCMS-ESI$^+$: calc'd for $C_{47}H_{50}N_8O_6$: 822.4 (M^+); Found: 823.8 ($M+H^+$). ^{1}H-NMR: 400 MHz, ($CDCl_3$) δ: (Mixture of rotomers) 7.62-8.02 (m, 9H), 7.36-7.43 (m, 6H), 7.22 (s, 2H), 6.01 (s, 1H), 5.29-5.53 (m, 4H), 4.35 (t, 1H), 3.73-3.87 (m,

2H), 3.68 (s, 3H), 3.63 (s, 3H), 3.22 (q, 2H), 2.82-2.96 (m, 2H), 2.37 (m, 1H), 2.23 (m, 2H), 1.90-2.11 (m, 4H), 0.87-0.93 (m, 6H).

Example HN

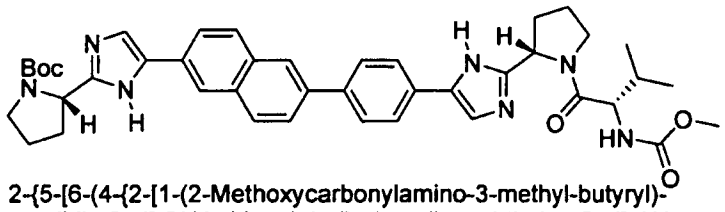


2-{5-[6-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-yl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester



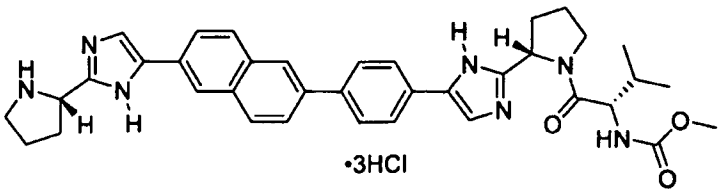
(1-{2-[5-(4-Bromo-phenyl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

Pd_2dba_3, Xantphos



2-{5-[6-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester

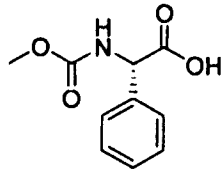
HCl, dioxanes
MeOH

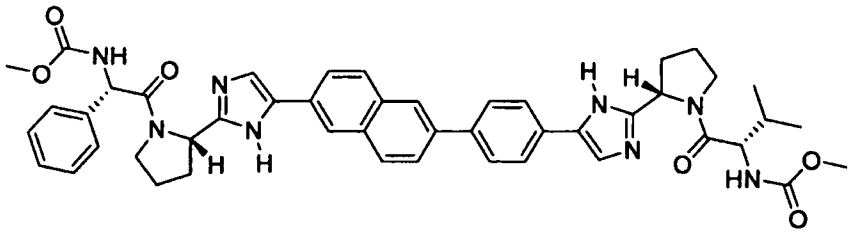


•3HCl

{2-Methyl-1-[2-(5-{4-[6-(2-pyrrolidin-2-yl-3*H*-imidazol-4-yl)-naphthalen-2-yl]-phenyl}-1*H*-imidazol-2-yl)-pyrrolidine-1-carbonyl]-propyl}-carbamic acid methyl ester

HATU, K_3PO_4

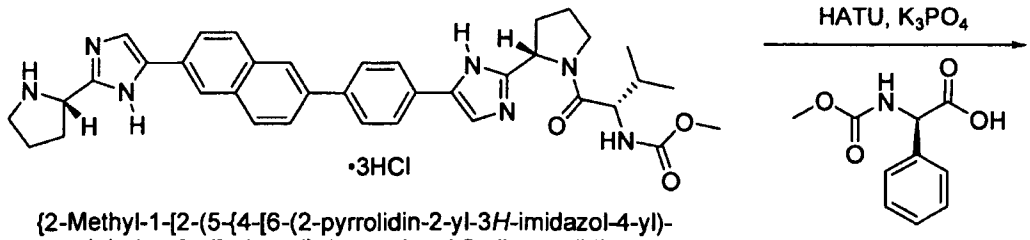




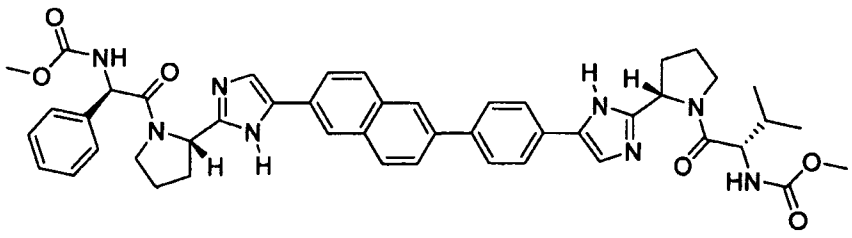
[1-(2-{5-[4-(6-{2-[1-(2-Methoxycarbonylamino-2-phenyl-acetyl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester

[1-(2-{5-[4-(6-{2-[1-(2S)-(2-Methoxycarbonylamino-2-phenyl-acetyl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester. This compound was prepared following the procedure for [1-(2-{5-[6-(4-{2-[1-(2S)-(2-Methoxycarbonylamino-2-phenyl-acetyl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester using (1-{2-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (1.0 g, 2.2 mmol) and 2-{5-[6-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (1.6 g, 3.4 mmol, 1.5 equiv.) to provide [1-(2-{5-[4-(6-{2-[1-(2-Methoxycarbonylamino-2-phenyl-acetyl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (0.03 g, 54%) as a white powder. LCMS-ESI$^+$: calc'd for $C_{47}H_{50}N_8O_6$: 822.4 (M^+); Found: 823.9 ($M+H^+$). ^{1}H-NMR: 400 MHz, ($CDCl_3$) δ: (Mixture of rotomers) 7.52-7.93 (m, 9H), 7.27-7.42 (m, 6H), 7.16 (s, 2H), 6.08 (m, 1H), 5.48-5.56 (m, 2H), 5.34 (s, 1H), 5.24 (s, 1H), 4.35 (t, 1H), 3.93 (m, 1H), 3.73 (m, 1H), 3.68 (s, 3H), 3.66 (s, 3H), 3.38 (m, 1H), 2.78-2.83 (m, 3H), 2.36 (m, 1H), 2.04-2.23 (m, 6H), 0.86-0.97 (m, 6H).

Example HO



{2-Methyl-1-[2-(5-{4-[6-(2-pyrrolidin-2-yl-3*H*-imidazol-4-yl)-naphthalen-2-yl]-phenyl}-1*H*-imidazol-2-yl)-pyrrolidine-1-carbonyl]-propyl}-carbamic acid methyl ester

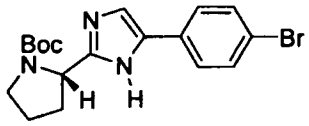


[1-(2-{5-[4-(6-{2-[1-(2-Methoxycarbonylamino-2-phenyl-acetyl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester

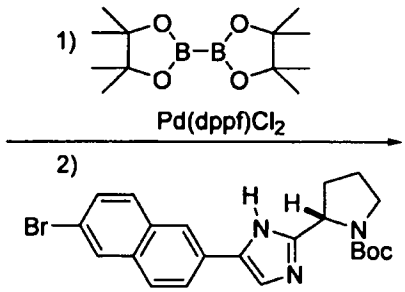
[1-(2-{5-[4-(6-{2-[1-(2R)-(2-Methoxycarbonylamino-2-phenyl-acetyl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester. This compound was prepared following the procedure for [1-(2-{5-[4-(6-{2-[1-(2S)-(2-Methoxycarbonylamino-2-phenyl-acetyl)-pyrrolidin-

2-yl]-3H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester using (*R*)-methoxycarbonylamino-phenyl-acetic acid (0.02 g, 0.09 mmol, 1.5 equiv.) to provide [1-(2-{5-[4-(6-{2-[1-(2-Methoxycarbonylamino-2-phenyl-acetyl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (0.03 g, 58%) as a white powder. LCMS-ESI$^+$: calc'd for $C_{47}H_{50}N_8O_6$: 822.4 (M^+); Found: 823.8 ($M+H^+$). ^{1}H-NMR: 400 MHz, ($CDCl_3$) δ: (Mixture of rotomers) 7.62-7.87 (m, 9H), 7.29-7.43 (m, 6H), 7.18 (s, 2H), 6.09 (m, 1H), 5.46 (m, 2H), 5.33 (s, 1H), 5.27 (s, 1H), 4.33 (t, 1H), 3.84 (m, 1H), 3.71 (m, 1H), 3.68 (s, 3H), 3.61 (s, 3H), 3.24 (m, 1H), 2.83-2.93 (m, 3H), 2.35 (m, 1H), 1.92-2.23 (m, 6H), 0.86-0.97 (m, 6H).

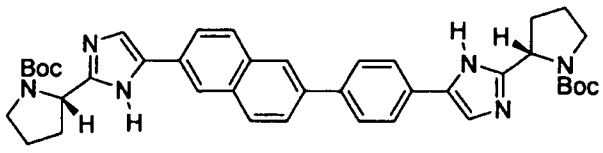
Example HP



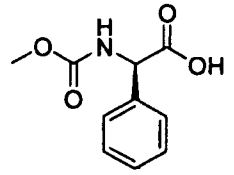
2-[5-(4-Bromo-phenyl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester

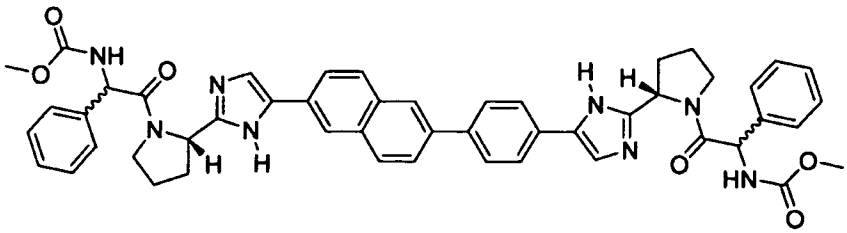


2-[5-(6-Bromo-naphthalen-2-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester



2-[5-(6-{4-[2-(1-*tert*-butyloxycarbonyl-pyrrolidin-2-yl)-3*H*-imidazol-4-yl]-phenyl}-naphthalen-2-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester



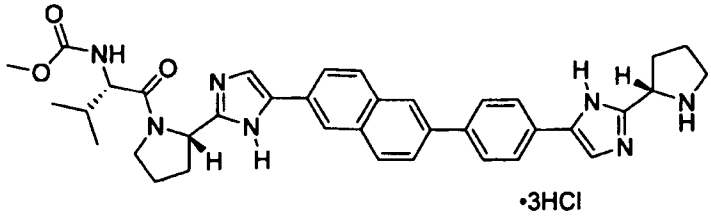


[2-(2-{5-[4-(6-{2-[1-(2-Methoxycarbonylamino-2-phenyl-acetyl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1*H*-imidazol-2-yl}-pyrrolidin-1-yl)-2-oxo-1-phenyl-ethyl]-carbamic acid methyl ester

2-[5-(6-{4-[2-(1-*tert*-butyloxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-phenyl}-naphthalen-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester. To a solution of 2-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.39 g, 1.0 mmol) and bis(pinacolato)diborane (0.31 g, 1.2 mmol, 1.2 equiv.) in dioxane (5 mL) was added KOAc (0.30 g, 3.0 mmol, 3 equiv.) and $Pd(dppf)Cl_2$ (0.04 g, 0.05 mmol, 0.05 equiv.). The slurry was degassed with argon for 5 minutes and heated to 85 °C for 2.5 hours. The resulting solution was cooled to room temperature and 2-[5-(6-Bromo-naphthalen-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.45 g, 1.0 mmol, 1 equiv.) and K_3PO_4 (aqueous, 2 M, 1.75 mL, 3.5 mmol, 3.5 equiv.) was added. The reaction mixture was heated to 85 °C for 6 hours. The slurry was filtered through CELITE and concentrated. The crude product was purified by column chromatography (SiO_2, 50→100% EtOAc in Hexanes (2% MeOH)) and preparative HPLC (Gemini, 15→40% MeCN in H_2O (0.1% formic acid)) to provide 2-[5-(6-{4-[2-(1-*tert*-butyloxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-phenyl}-naphthalen-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.07 g, 10%) as a white powder. LCMS-ESI$^+$: calc'd for $C_{40}H_{46}N_6O_4$: 674.4 (M^+); Found: 675.6 ($M+H^+$).

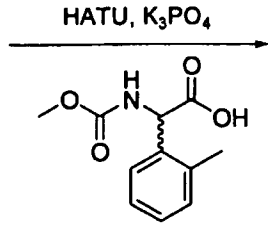
[2-(2-{5-[4-(6-{2-[1-(2-Methoxycarbonylamino-2-phenyl-acetyl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidin-1-yl)-2-oxo-1-phenyl-ethyl]-carbamic acid methyl ester. To a slurry of 2-[5-(6-{4-[2-(1-*tert*-butyloxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-phenyl}-naphthalen-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.07 g, 0.09 mmol) in MeOH (0.1 mL) was added HCl in dioxanes (4 M, 1.5 mL). The resulting solution was stirred at room temperature for 2 hour and basified with NaOH (2 N). The crude product was extracted with CH_2Cl_2. The organic extracts were combined, dried over Na_2SO_4 and concentrated. (*R*)-Methoxycarbonylamino-phenyl-acetic acid (0.08 g, 0.4 mmol, 4.4 equiv.) and DMF (1.0 mL) were then added, followed by DEPBT (0.12 g, 0.4, 4 equiv.) and $NaHCO_3$ (0.04 g, 0.43 mmol, 4 equiv.). The resulting slurry was stirred at room temperature for 7 days. The reaction mixture was purified by preparative HPLC (Gemini, 15→40% MeCN in H_2O (0.1% formic acid)) and lyophilized to provide [2-(2-{5-[4-(6-{2-[1-(2-Methoxycarbonylamino-2-phenyl-acetyl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidin-1-yl)-2-oxo-1-phenyl-ethyl]-carbamic acid methyl ester (0.04 g, 49%) as a white powder. LCMS-ESI$^+$: calc'd for $C_{50}H_{48}N_8O_6$: 856.4 (M^+); Found: 858.1 ($M+H^+$). ^{1}H-NMR: 400 MHz, ($CDCl_3$) δ: (Mixture of rotomers) 10.32-10.45 (m, 2H), 8.26 (s, 1H), 8.00 (s, 1H), 7.72-7.98 (m, 8H), 7.19-7.50 (m, 12H), 6.07 (m, 2H), 5.28-5.55 (m, 4H), 3.73 (m, 2H), 3.66 (s, 3H), 3.65 (s, 3H), 3.22 (m, 2H), 2.86-2.96 (m, 2H), 2.22 (m, 2H), 2.04 (m, 2H), 1.92 (m, 2H).

Example HQ

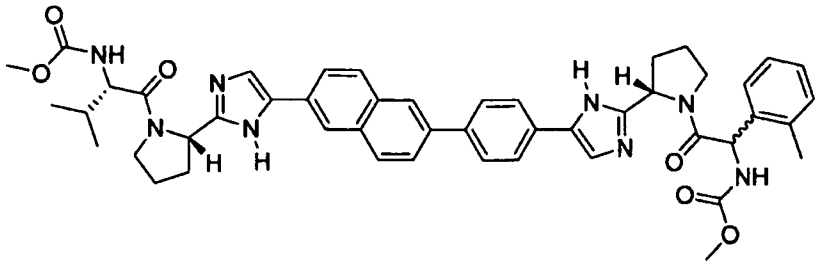


•3HCl

{2-Methyl-1-[2-(5-{6-[4-(2-pyrrolidin-2-yl-3*H*-imidazol-4-yl)-phenyl]-naphthalen-2-yl}-1*H*-imidazol-2-yl)-pyrrolidine-1-carbonyl]-propyl}-carbamic acid methyl ester



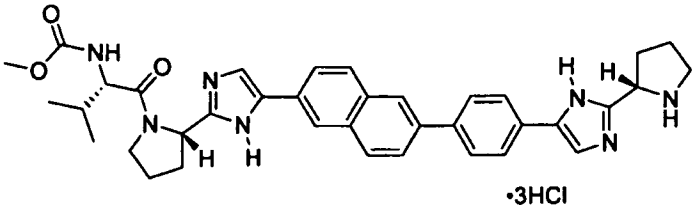
Methoxycarbonylamino-*o*-tolyl-acetic acid



[1-(2-{5-[6-(4-{2-[1-(2-Methoxycarbonylamino-2-*o*-tolyl-acetyl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester

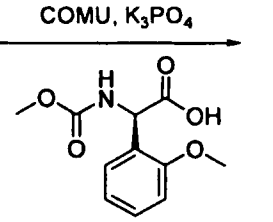
[1-(2-{5-[6-(4-{2-[1-(2-Methoxycarbonylamino-2-o-tolyl-acetyl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester. This compound was prepared following the procedure for [1-(2-{5-[6-(4-{2-[1-(2S)-(2-Methoxycarbonylamino-2-phenyl-acetyl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester using Methoxycarbonylamino-o-tolyl-acetic acid (0.03 g, 0.12 mmol, 1.75 equiv.) to provide [1-(2-{5-[6-(4-{2-[1-(2-Methoxycarbonylamino-2-o-tolyl-acetyl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (0.03 g, 50%) as a white powder. LCMS-ESI$^+$: calc'd for $C_{48}H_{52}N_8O_6$: 836.4 (M^+); Found: 837.4 ($M+H^+$). ^{1}H-NMR: 400 MHz, ($CDCl_3$) δ: (Mixture of diastereomers) 7.61-8.00 (m, 16H), 7.18-7.41 (m, 12H), 7.10 (s, 2H), 5.28-5.63 (m, 10H), 4.36 (t, 2H), 3.72-3.86 (m, 4H), 3.68 (s, 6H), 3.66 (s, 6H), 2.79-3.07 (m, 8H), 2.50 (s, 3H), 2.44 (s, 3H), 2.38 (m, 4H), 1.86-2.28 (m, 8H), 0.88-0.94 (m, 12H).

Example HR

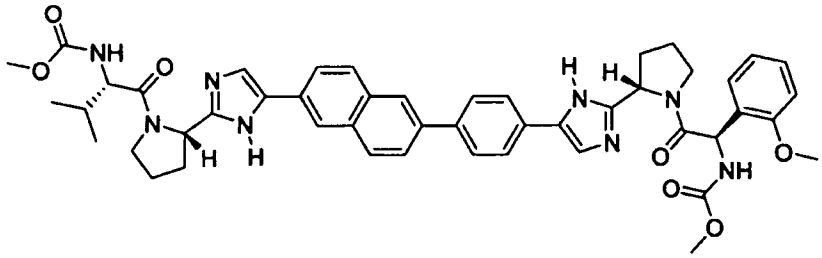


•3HCl

{2-Methyl-1-[2-(5-{6-[4-(2-pyrrolidin-2-yl-3*H*-imidazol-4-yl)-phenyl]-naphthalen-2-yl}-1*H*-imidazol-2-yl)-pyrrolidine-1-carbonyl]-propyl}-carbamic acid methyl ester



Methoxycarbonylamino-(2-methoxy-phenyl)-acetic acid



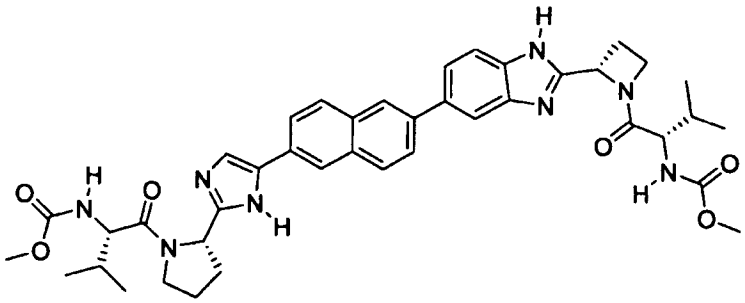
{1-[2-(5-{6-[4-(2-{1-[2-Methoxycarbonylamino-2-(2-methoxy-phenyl)-acetyl]-pyrrolidin-2-yl}-3*H*-imidazol-4-yl)-phenyl]-naphthalen-2-yl}-1*H*-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester

{1-[2-(5-{6-[4-(2-{1-[2-Methoxycarbonylamino-2-(2-methoxy-phenyl)-acetyl]-pyrrolidin-2-yl}-3H-imidazol-4-yl)-phenyl]-naphthalen-2-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester. To a solution of {2-Methyl-1-[2-(5-{6-[4-(2-pyrrolidin-2-yl-3H-imidazol-4-yl)-phenyl]-naphthalen-2-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carbonyl]-propyl}-carbamic acid methyl ester (0.04 g, 0.05 mmol) and (*S*)-Methoxycarbonylamino-(2-methoxy-phenyl)-acetic acid (0.02 g, 0.08 mmol, 1.5 equiv.) in CH_2Cl_2 (0.5 mL) was added K_3PO_4 (0.03 g, 0.15 mmol, 3 equiv.). The slurry was cooled to 0 °C and COMU (0.03 g, 0.06 mmol, 1.25 equiv.) and the reaction was stirred at 0 °C for 1 hour. The slurry was diluted with CH_2Cl_2 and filtered. The filtrate was concentrated and the crude product was purified by preparative HPLC (Gemini, 15→40% MeCN in H_2O (0.1% formic acid)) and lyophilized to provide {1-[2-(5-{6-[4-(2-{1-[2-Methoxycarbonylamino-2-(2-methoxy-phenyl)-acetyl]-pyrrolidin-2-yl}-3H-imidazol-4-yl)-phenyl]-naphthalen-2-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (0.02 g, 50%) as a white powder. LCMS-ESI$^+$: calc'd for $C_{48}H_{52}N_8O_7$: 852.4 (M^+); Found: 853.6 ($M+H^+$). ^{1}H-NMR: 400 MHz, (acetone-d_6) δ: (Mixture of rotomers) 10.96-11.01 (m, 2H), 8.29 (s, 1H), 8.07 (s, 1H), 7.73-7.89 (m, 7H), 7.35-7.48 (m, 4H), 7.33 (t, 1H), 7.05 (d, 1H), 6.96 (t, 1H), 6.36 (d, 1H), 5.91 (d, 1H), 5.21-5.26 (m, 3H), 4.29 (t, 1H), 3.90 (s, 3H), 3.78-3.93 (m, 2H),

3.60 (s, 3H), 3.58 (s, 3H), 3.30 (q, 2H), 2.59-2.65 (m, 2H), 2.36 (m, 1H), 1.90-2.21 (m, 6H), 0.85-0.93 (m, 6H).

Example HS

(1-{2-[5-(6-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-naphthalen-2-yl)-1*H*-benzoimidazol-2-yl]-azetidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

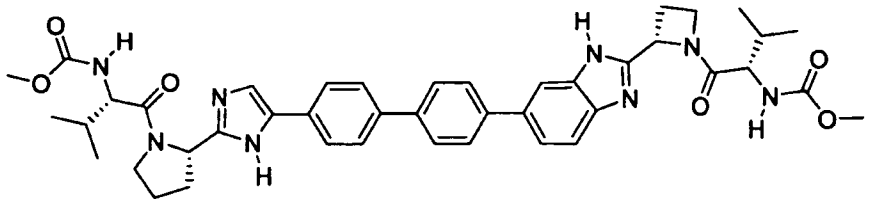


(1-{2-[5-(6-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-naphthalen-2-yl)-1*H*-benzoimidazol-2-yl]-azetidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

(1-{2-[5-(6-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-naphthalen-2-yl)-1H-benzoimidazol-2-yl]-azetidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester was prepared following method **YYY** substituting azetidine-1,2-dicarboxylic acid 1-*tert*-butyl ester for pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester. $C_{41}H_{48}N_8O_6$ calculated 748.4 observed $[M + 1]^+$ 749.4; rt = 1.59 min. ^1H (DMSO-d6): δ = 8.31 (d, J = 6.4 Hz, 2H), 8.16 (m, 2H), 8.04 (m, 2H), 7.98 (m, 1H), 7.90 (d, J = 8.8 Hz, 1H), 7.78 (s, 2H), 7.42 (d, J = 7.6 Hz, 1H), 7.32 (d, J = 8.8 Hz, 1H), 5.49 (t, J = 6.8 Hz, 1H), 5.15 (t, J = 6.8 Hz, 1H), 4.41 (m, 2H), 4.12 (t, J = 8.0 Hz, 2H), 3.85 (m, 1H), 3.78 (t, J = 8.0 Hz, 1H), 3.55 (s, 3H), 3.53 (s, 3H), 2.76 (m, 1H), 2.65 (m, 1H), 2.41 (m,1H), 2.17 – 2.08 (m, 2H), 2.03 (m, 2H), 1.86 (m, 1H), 0.83 (m, 6H).

Example HT

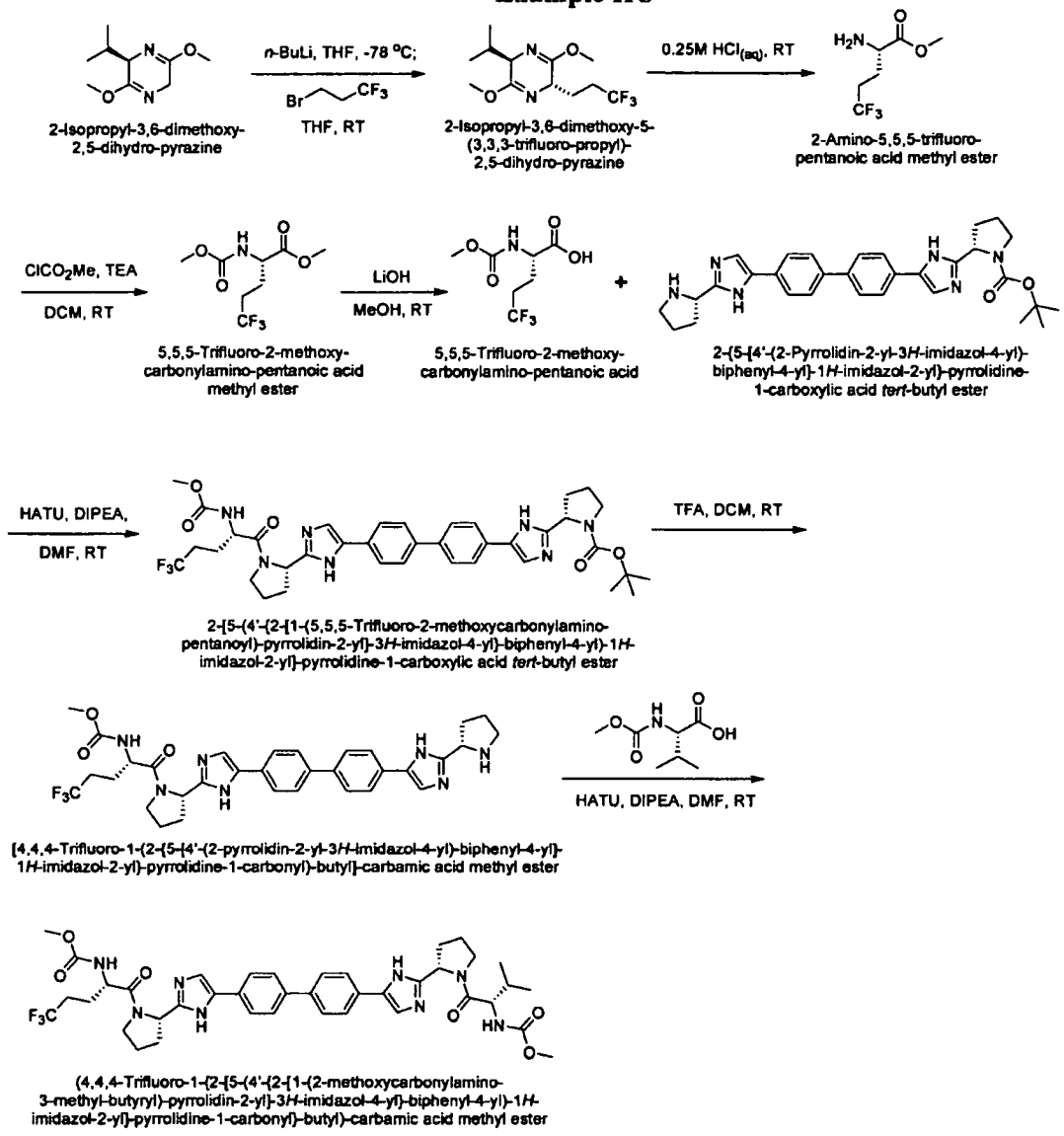
(1-{2-[5-(4'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-azetidin-2-yl]-3*H*-benzoimidazol-5-yl}-biphenyl-4-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester



(1-{2-[5-(4'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-azetidin-2-yl]-3*H*-benzoimidazol-5-yl}-biphenyl-4-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

(1-{2-[5-(4'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-azetidin-2-yl]-3H-benzoimidazol-5-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester was prepared following method **YYY** substituting azetidine-1,2-dicarboxylic acid 1-*tert*-butyl ester for pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester. $C_{43}H_{50}N_8O_6$: calculated 774.4 observed $[M + 1]^+$ 775.8; rt = 1.66 min. ^1H (DMSO-d6): δ = 8.11 (s, 1H), 7.91 (m, 3H), 7.86 (m, 5H), 7.72 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 8.4 Hz, 1H), 7.42 (d, J = 7.6 Hz, 1H), 7.32 (d, J = 8.4 Hz, 1H), 5.47 (t, J = 6.4 Hz, 1H), 5.12 (t, J = 7.2 Hz, 1H), 4.40 (m, 2H), 4.11 (t, J = 7.6 Hz, 1H), 3.84 (m, 2H), 3.69 (m, 2H), 3.55 (s, 3H), 3.53 (s, 3H), 2.75 (m, 1H), 2.63 (m, 1H), 2.39 (m, 1H), 2.18 – 2.03 (m, 2H), 2.01 (m, 2H), 1.86 (m, 1H), 0.83 (m, 6H).

Example HU



2-Isopropyl-3,6-dimethoxy-5-(3,3,3-trifluoro-propyl)-2,5-dihydro-pyrazine: To a stirred solution of 2-isopropyl-3,6-dimethoxy-2,5-dihydro-pyrazine (1 mL, 5.58 mmol) in THF (13.5 mL) under argon at -78° C was added a solution of *n*-butyllithium (2.5 M, 2.3 mL, 5.75 mmol). The solution was stirred at -78° C for 30 minutes. A solution of 1-Iodo-3,3,3-trifluoropropane (925 µL, 5.87 mmol) in THF (11.5 mL) was added slowly. The resulting solution was stirred at -78° C for 5 hours, warmed to room temperature and diluted with ethyl acetate. The organic layer was washed successively with saturated aqueous NH_4Cl solution, water and brine. The organic layer was then dried ($MgSO_4$), concentrated and purified by flash chromatography to yield 2-Isopropyl-3,6-dimethoxy-5-(3,3,3-trifluoro-propyl)-2,5-dihydro-pyrazine (915 mg, 59%). ^{1}H-NMR: 400 MHz, ($CDCl_3$) δ: 4.04-3.99 (m, 1H), 3.98-3.95 (m, 1H), 3.71 (s, 3H), 3.68

(s, 3H), 2.29-2.20 (m, 1H), 2.18-2.04 (m, 3H), 1.94-1.84 (m, 1H), 1.03 (d, J = 6.9 Hz, 3H), 0.71 (d, J = 6.8 Hz, 3H) ppm.

5,5,5-Trifluoro-2-methoxycarbonylamino-pentanoic acid methyl ester: A solution of 2-Isopropyl-3,6-dimethoxy-5-(3,3,3-trifluoro-propyl)-2,5-dihydro-pyrazine (725 mg, 2.59 mmol) in 0.25N HCl was stirred at room temperature for 3 hours. The aqueous solution was washed once with ethyl acetate. The ethyl acetate rinsing was discarded and the aqueous layer was basified to pH~10 with saturated aqueous $NaHCO_3$. The aqueous layer was extracted twice with ethyl acetate. The combined organics were washed with brine, dried ($MgSO_4$) and concentrated to give crude (2S)-amino-5,5,5-trifluoro-pentanoic acid methyl ester contaminated with D-valine methyl ester. The crude material was dissolved in dichloromethane (20 mL) and cooled to 0° C. Triethylamine (1.75 mL, 12.6 mmol) and methyl chloroformate (480 µL, 6.2 mmol) were successively added to the solution. After 1 hour the reaction was concentrated and purified by flash chromatography to yield 5,5,5-Trifluoro-2-methoxy-carbonylamino-pentanoic acid methyl ester (465 mg, 74%). ^{1}H-NMR: 400 MHz, ($CDCl_3$) δ: 5.27 (br, 1 H), 4.42 (br, 1H), 3.79 (s, 3H), 3.70 (s, 3H), 2.29-2.09 (m, 3H), 1.94-1.84 (m, 1H) ppm.

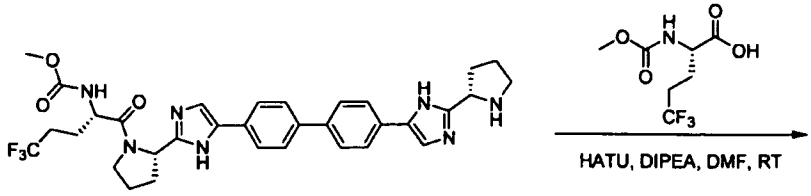
2-[5-(4'-{2-[1-(5,5,5-Trifluoro-2-methoxycarbonylamino-pentanoyl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester: To a solution of 5,5,5-Trifluoro-2-methoxycarbonylamino-pentanoic acid methyl ester (194 mg, 0.80 mmol) in methanol (3 mL) was added an aqueous LiOH solution (1M, 2 mL, 2 mmol). The resulting solution was stirred at room temperature for 45 minutes and then washed with ethyl acetate. The ethyl acetate washing was discarded and the aqueous layer was acidified with concentrated HCl. The acidified aqueous layer was extracted twice with ethyl acetate. The combined organics were washed with brine, dried ($MgSO_4$), and concentrated to give clean 5,5,5-Trifluoro-2-methoxy-carbonylamino-pentanoic acid. To a solution of the pentanoic acid in dimethylformamide (2 mL) was added HATU (300 mg, 0.79 mmol). After stirring for 5 minutes, a solution of 2-{5-[4'-(2-pyrrolidin-2-yl-3H-imidazol-4-yl)-biphenyl-4-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (412 mg, 0.79 mmol) in dimethylformamide (1.9 mL) was added to the reaction, followed immediately by diisopropylethylamine (275 µL, 1.58 mmol). The reaction was stirred for 1 hour at room temperature then diluted with ethyl acetate. The organic layer was washed with water and brine, dried ($MgSO_4$), concentrated and purified by flash chromatography to yield 2-[5-(4'-{2-[1-(5,5,5-trifluoro-2-methoxycarbonylamino-pentanoyl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-

biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (340 mg, 59%). LCMS-ESI$^+$: calculated for $C_{38}H_{44}F_3N_7O_5$: 735.34; observed $[M+1]^+$: 736.05.

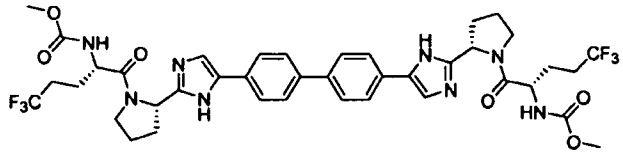
[4,4,4-Trifluoro-1-(2-{5-[4'-(2-pyrrolidin-2-yl-3H-imidazol-4-yl)-biphenyl-4-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-butyl]-carbamic acid methyl ester: To a solution of 2-[5-(4'-{2-[1-(5,5,5-trifluoro-2-methoxycarbonylamino-pentanoyl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (340 mg, 0.46 mmol) in dichloromethane (5 mL) was added trifluoroacetic acid (1 mL). The reaction was stirred at room temperature for 3 hours and then thoroughly concentrated. The resulting residue was dissolved in dichloromethane and washed three times with saturated aqueous $NaHCO_3$ solution. The organic layer was dried ($MgSO_4$), and concentrated to give the crude free pyrrolidine (270 mg, 92%), which was clean enough to use without further purification. LCMS-ESI$^+$: calculated for $C_{33}H_{36}F_3N_7O_3$: 635.28; observed $[M+1]^+$: 636.17.

(4,4,4-Trifluoro-1-{2-[5-(4'-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-butyl)-carbamic acid methyl ester: To a solution of crude [4,4,4-Trifluoro-1-(2-{5-[4'-(2-pyrrolidin-2-yl-3H-imidazol-4-yl)-biphenyl-4-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-butyl]-carbamic acid methyl ester (125 mg, 0.20 mmol) in dimethylformamide (0.6 mL) was added a solution of 2-methoxycarbonylamino-3-methyl-butyric acid (38 mg, 0.22 mmol) and HATU (82 mg, 0.22 mmol) in dimethylformamide (0.6 mL). Diisopropylethylamine (70 μL, 0.40 mmol) was then added and the reaction was stirred at room temperature for 16 hours. The solution was concentrated and purified by preparative reverse phase HPLC (Gemini, 15 to 50% ACN/H_2O + 0.1% HCO_2H) to yield (4,4,4-trifluoro-1-{2-[5-(4'-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-butyl)-carbamic acid methyl ester (73 mg, 47%). LCMS-ESI$^+$: calculated for $C_{40}H_{47}F_3N_8O_6$: 792.85; observed $[M+1]^+$: 794.33. ^{1}H-NMR: 400 MHz, (CD_3OD) δ: 7.82-7.70 (m, 4H), 7.68-7.63 (m, 4H), 7.32-7.31 (m, 2H), 5.20-5.16 (m, 2H), 4.56-4.51 (m, 1H), 4.26-4.22 (m, 1H), 4.04-3.96 (m, 1H), 3.91-3.84 (m, 2H), 3.67 (s, 3H), 3.66 (s, 3H), 3.51-3.46 (m, 1H), 2.38-1.96 (m, 12H), 1.90-1.78 (m, 1H), 1.01-0.89 (m, 6H) ppm.

Example HV

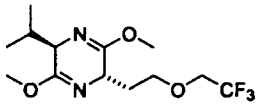


[4,4,4-Trifluoro-1-(2-{5-[4'-(2-pyrrolidin-2-yl-3H-imidazol-4-yl)-biphenyl-4-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-butyl]-carbamic acid methyl ester



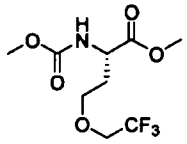
(4,4,4-Trifluoro-1-{2-[5-(4'-{2-[1-(5,5,5-trifluoro-2-methoxycarbonylamino-pentanoyl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-biphenyl-4-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-butyl)-carbamic acid methyl ester

(4,4,4-Trifluoro-1-{2-[5-(4'-{2-[1-(5,5,5-trifluoro-2-methoxycarbonylamino-pentanoyl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-butyl)-carbamic acid methyl ester: To a solution of crude [4,4,4-Trifluoro-1-(2-{5-[4'-(2-pyrrolidin-2-yl-3H-imidazol-4-yl)-biphenyl-4-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-butyl]-carbamic acid methyl ester (115 mg, 0.18 mmol) in dimethylformamide (0.5 mL) was added a solution of 5,5,5-Trifluoro-2-methoxycarbonylamino-pentanoic acid (44 mg, 0.19 mmol) and HATU (72 mg, 0.19 mmol) in dimethylformamide (0.5 mL). Diisopropylethylamine (65 μL, 0.37 mmol) was then added and the reaction was stirred at room temperature for 16 hours. The solution was concentrated and purified by preparative reverse phase HPLC (Gemini, 15 to 50% ACN/H_2O + 0.1% HCO_2H) to yield (4,4,4-Trifluoro-1-{2-[5-(4'-{2-[1-(5,5,5-trifluoro-2-methoxycarbonylamino-pentanoyl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-butyl)-carbamic acid methyl ester (35 mg, 23%). LCMS-ESI$^+$: calculated for $C_{40}H_{44}F_6N_8O_6$: 846.82; observed $[M+1]^+$: 847.34. ^{1}H-NMR: 400 MHz, (CD_3OD) δ: 7.81-7.72 (m, 4H), 7.67-7.64 (m, 4H), 7.38-7.32 (m, 2H), 5.20-5.16 (m, 2H), 4.55-4.51 (m, 2H), 3.91-3.86 (m, 4H), 3.67 (s, 6H), 2.38-2.20 (m, 8H), 2.18-1.79 (m, 8H) ppm.



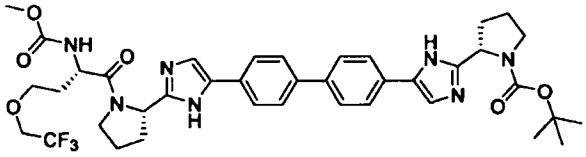
2-Isopropyl-3,6-dimethoxy-5-[2-(2,2,2-trifluoro-ethoxy)-ethyl]-2,5-dihydro-pyrazine

2-Isopropyl-3,6-dimethoxy-5-[2-(2,2,2-trifluoro-ethoxy)-ethyl]-2,5-dihydro-pyrazine: This compound was made in 65% yield by the same procedure as 2-Isopropyl-3,6-dimethoxy-5-(3,3,3-trifluoro-propyl)-2,5-dihydro-pyrazine, substituting 1-Iodo-3,3,3-trifluoropropane with 2-(2-Bromoethoxy)-1,1,1-trifluoroethane. ^{1}H-NMR: 400 MHz, ($CDCl_3$) δ: 4.11-4.05 (m, 1H), 3.95 (t, J = 3.5 Hz, 1H), 3.86-3.75 (m, 3H), 3.74-3.66 (m, 7H), 2.30-2.18 (m, 2H), 1.92-1.82 (m, 1H), 1.03 (d, J = 6.9 Hz, 3H), 0.70 (d, J = 6.8 Hz, 3H) ppm.



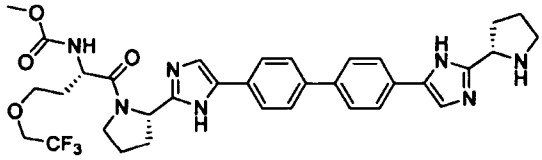
2-Methoxycarbonylamino-4-(2,2,2-trifluoro-ethoxy)-butyric acid methyl ester

2-Methoxycarbonylamino-4-(2,2,2-trifluoro-ethoxy)-butyric acid methyl ester: This compound was made by the same procedure as 5,5,5-Trifluoro-2-methoxycarbonylamino-pentanoic acid methyl ester, using 2-Isopropyl-3,6-dimethoxy-5-[2-(2,2,2-trifluoro-ethoxy)-ethyl]-2,5-dihydropyrazine as the starting material. ^{1}H-NMR: 400 MHz, ($CDCl_3$) δ: 5.51-5.43 (br, 1H), 4.51-4.43 (m, 1H), 3.83-3.63 (m, 10H), 2.22-2.13 (m, 1H), 2.13-2.03 (m, 1H) ppm.



2-{5-[4'-(2-{1-[2-Methoxycarbonylamino-4-(2,2,2-trifluoro-ethoxy)-butyryl]-pyrrolidin-2-yl}-3*H*-imidazol-4-yl)-biphenyl-4-yl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester

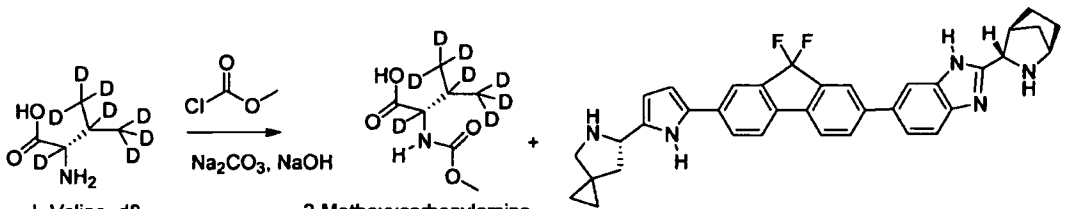
2-{5-[4'-(2-{1-[2-Methoxycarbonylamino-4-(2,2,2-trifluoro-ethoxy)-butyryl]-pyrrolidin-2-yl}-3H-imidazol-4-yl)-biphenyl-4-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester: This compound was made in 74% yield by the same procedure as 2-[5-(4'-{2-[1-(5,5,5-Trifluoro-2-methoxycarbonylamino-pentanoyl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester, using 2-Methoxycarbonylamino-4-(2,2,2-trifluoro-ethoxy)-butyric acid methyl ester as the starting material. LCMS-ESI$^+$: calculated for $C_{39}H_{46}F_3N_7O_6$: 765.35; observed $[M+1]^+$: 766.12.



[1-(2-{5-[4'-(2-Pyrrolidin-2-yl-3*H*-imidazol-4-yl)-biphenyl-4-yl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-3-(2,2,2-trifluoro-ethoxy)-propyl]-carbamic acid methyl ester

[1-(2-{5-[4'-(2-Pyrrolidin-2-yl-3H-imidazol-4-yl)-biphenyl-4-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-3-(2,2,2-trifluoroethoxy)-propyl]-carbamic acid methyl ester: This compound was made by the same procedure as [4,4,4-Trifluoro-1-(2-{5-[4'-(2-pyrrolidin-2-yl-3H-imidazol-4-yl)-biphenyl-4-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-butyl]-carbamic acid methyl ester, using 2-{5-[4'-(2-{1-[2-Methoxycarbonylamino-4-(2,2,2-trifluoro-ethoxy)-butyryl]-pyrrolidin-2-yl}-3H-imidazol-4-yl)-biphenyl-4-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester as the starting material. LCMS-ESI$^+$: calculated for $C_{34}H_{38}F_3N_7O_4$: 665.29; observed $[M+1]^+$: 666.20.

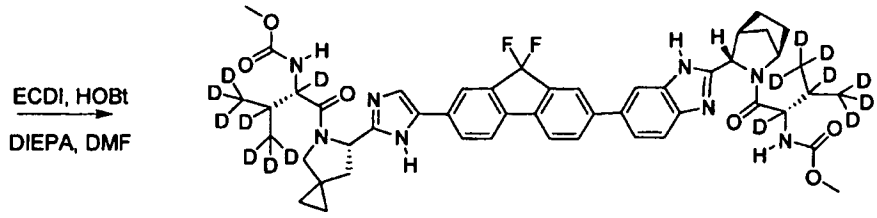
Example HW



L-Valine, d8

2-Methoxycarbonylamino-3-methyl-butyric acid, d8

2-(2-Aza-bicyclo[2.2.1]hept-3-yl)-6-{7-[5-(5-aza-spiro[2.4]hept-6-yl)-1*H*-pyrrol-2-yl]-9,9-difluoro-9*H*-fluoren-2-yl}-1*H*-benzoimidazole



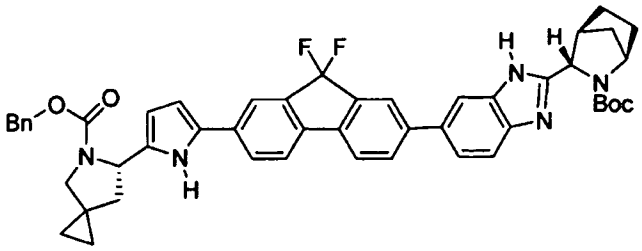
(1-{3-[6-(9,9-Difluoro-7-{2-[5-(2-methoxycarbonylamino-3-methyl-butyryl, d8)-5-aza-spiro[2.4]hept-6-yl]-3*H*-imidazol-4-yl}-9*H*-fluoren-2-yl)-1*H*-benzoimidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester,d8

To a solution of L-valine, d8 (Cambridge Isotope Laboratories, 0.4949 g) in 1N sodium hydroxide (3.95 mL) was added sodium carbonate (0.419 g). The solution was cooled to 0°C and methyl chloroformate (0.289 mL) was added dropwise over 30 minutes and reaction mixture

was stirred for 3 h at 0°C. Reaction mixture was washed with ethyl ether (3 x 15 mL) and aqueous layer was acidified to pH =1 with concentrated HCl. Aqueous layer was extracted dichloromethane (3 x 15 mL) and organic layers were dried ($MgSO_4$) and concentrated to give 2-Methoxycarbonylamino-3-methyl-butyric acid, d8 as a white solid (0.5681 g).
LCMS-ESI$^-$: calc'd for $C_7H_5D_8NO_4$: 184.2 ($M+H^+$); Found: 184.0 ($M+H^+$).

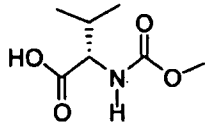
A solution of hydroxybenzotriazole (0.242 g), 1-(3-dimethylaminepropyl)-3-ethylcarbodiimide-HCl (0.328 g) and 2-Methoxycarbonylamino-3-methyl-butyric acid, d8 (0.315g) in DMF (5.0 mL) was stirred at rt for 1 hr. Reaction mixture was cooled to 0°C and a solution of 2-(2-Aza-bicyclo[2.2.1]hept-3-yl)-6-{7-[5-(5-aza-spiro[2.4]hept-6-yl)-1H-pyrrol-2-yl]-9,9-difluoro-9H-fluoren-2-yl}-1H-benzoimidazole in DMF (2.0 mL) was added, followed by dropwise addition of diisopropylethylamine over 15 min. Reaction mixture was warmed to rt overnight, diluted with ethyl acetate and washed with brine, brine/saturated sodium bicarbonate solution (1:1) and aqueous layers back-extracted with ethyl acetate. The combined organic layer was dried ($MgSO_4$), concentrated and purified by flash column chromatography (silica gel, 0 to 5% methanol/ethyl acetate), then and purified by preparative reverse phase HPLC (Gemini, 25 to 100% ACN/H_2O + 0.1% TFA). The product-containing fractions were pooled and treated with saturated sodium bicarbonate solution at 0 °C for 1h. Product was extracted with ethyl acetate (2x), combined organic layer was dried ($MgSO_4$), concentrated and lyophilized from ACN/H_2O to give (1-{3-[6-(9,9-Difluoro-7-{2-[5-(2-methoxycarbonylamino-3-methyl-butyryl, d8)-5-aza-spiro[2.4]hept-6-yl]-3H-imidazol-4-yl}-9H-fluoren-2-yl)-1H-benzoimidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester,d8 as a white powder (0.3947)
^{1}H-NMR: 300 MHz, (DMSO-d_6) δ: 12.13 (s, 1H), 11.77 (s, 1H), 8.1 – 7.1 (m, 12H), 7.23 (s, 1H), 7.14 (s, 1H), 5.2-5.1 (m, 1 H), 4.60 (d, J=4.5 Hz, 1H, 4.48 (s, 1H), 3.8-3.6 (m, 2H), 3.48 (s, 6H), 2.60 (s, 1H), 2.40-2.01 (m, 10H), 0.64-0.52 (m, 4 H).
LCMS-ESI$^+$: calc'd for $C_{49}H_{38}D_{16}F_2N_8O_6$: 906.1 ($M+H^+$); Found: 905.6 ($M+H^+$).

Example HX



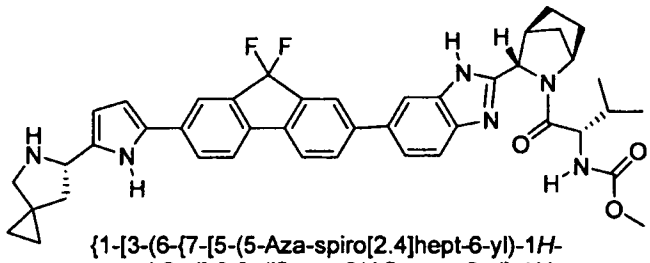
3-(6-{7-[5-(5-Benzyloxycarbonyl-5-aza-spiro[2.4]hept-6-yl)-1*H*-pyrrol-2-yl]-9,9-difluoro-9*H*-fluoren-2-yl}-1*H*-benzoimidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester

1. HCl, dioxane
2. ECDI, HOBt, DIEPA, DMF



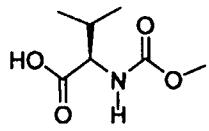
2-Methoxycarbonylamino-3-methyl-butyric acid

3. Pd/C, H_2, wet iPA



{1-[3-(6-{7-[5-(5-Aza-spiro[2.4]hept-6-yl)-1*H*-pyrrol-2-yl]-9,9-difluoro-9*H*-fluoren-2-yl}-1*H*-benzoimidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester

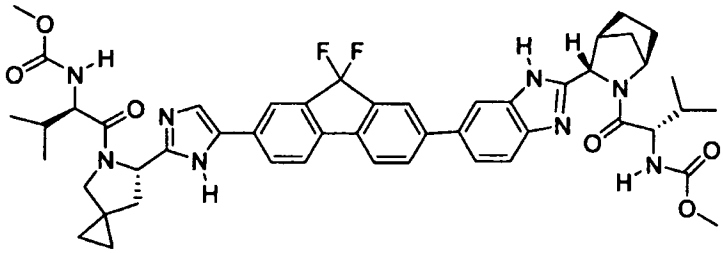
1. Pd/C, H_2, wet iPA
2. ECDI, HOBt, DIEPA, DMF



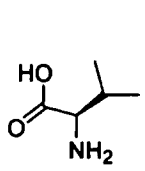
2-Methoxycarbonylamino-3-methyl-butyric acid

ECDI, HOBt

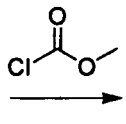
DIEPA, DMF



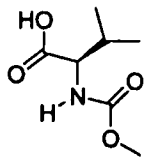
(1-{3-[6-(9,9-Difluoro-7-{2-[5-(2-methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3*H*-imidazol-4-yl}-9*H*-fluoren-2-yl)-1*H*-benzoimidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester



D-Valine



Na_2CO_3, NaOH



2-Methoxycarbonylamino-3-methyl-butyric acid

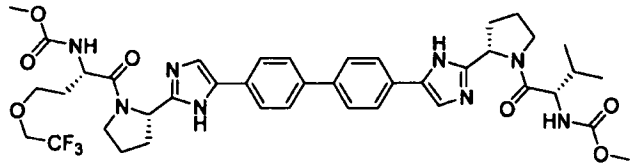
To a solution of 3-(6-{7-[5-(5-Benzyloxycarbonyl-5-aza-spiro[2.4]hept-6-yl)-1H-pyrrol-2-yl]-9,9-difluoro-9H-fluoren-2-yl}-1H-benzoimidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (1.0 g), in CH_2Cl_2 (10 mL) at 0 °C was added 4 N HCl in dioxane (2.0 mL). Reaction mixture was stirred at 0 °C for 5 minutes, then warmed to rt. After stirring for 1.5 h, reaction mixture was concentrated and dried overnight under vacuum to give an off-white powder (0.8826 g). Powder was suspended in ethyl acetate and saturated sodium bicarbonate solution and stirred for 1h. Aqueous layer was extracted with ethyl acetate (2x), dried ($MgSO_4$), and concentrated. A portion of this residue was used in the next step.
A solution of hydroxybenzotriazole (40 mg), 1-(3-dimethylaminepropyl)-3-ethylcarbodiimide-HCl (57 mg) and 2-Methoxycarbonylamino-3-methyl-butyric acid (54 mg) in DMF (0.5 mL) and CH_2Cl_2 (0.5 mL) was stirred at 0°C for 1 hr. This solution was added to a solution the above amine (150 mg) in DMF (0.5 mL) and CH_2Cl_2 (0.5 mL) at -20°C and stirred at this temperature overnight. Reaction mixture was diluted with ethyl acetate and washed with brine, brine/saturated sodium bicarbonate solution (1:1) and aqueous layers back-extracted with ethyl acetate. The combined organic layer was dried ($MgSO_4$), concentrated and purified by flash column chromatography (silica gel, 0 to 5% methanol/ethyl acetate) to 6-[5-(9,9-Difluoro-7-{2-[2-(2-methoxycarbonylamino-3-methyl-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-benzoimidazol-5-yl}-9H-fluoren-2-yl)-1H-pyrrol-2-yl]-5-aza-spiro[2.4]heptane-5-carboxylic acid benzyl ester as a yellow foam (127 mg).
LCMS-ESI$^+$: calc'd for $C_{50}H_{49}F_2N_7O_5$: 865.96 ($M+H^+$); Found: 866.3 ($M+H^+$).

A mixture of 6-[5-(9,9-Difluoro-7-{2-[2-(2-methoxycarbonylamino-3-methyl-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-benzoimidazol-5-yl}-9H-fluoren-2-yl)-1H-pyrrol-2-yl]-5-aza-spiro[2.4]heptane-5-carboxylic acid benzyl ester (127 mg) and 10% palladium on carbon, wet (29 mg) in ethanol (4 mL) was stirred under an hydrogen atmosphere for 18 h. Added more and 10% palladium on carbon, wet (50 mg) and continued reaction for 30 h. Reaction mixture was filtered through a pad of CELITE, concentrated and purified by flash column chromatography (silica gel, 5 to 20% methanol/dichloromethane) to give {1-[3-(6-{7-[5-(5-Aza-spiro[2.4]hept-6-yl)-1H-pyrrol-2-yl]-9,9-difluoro-9H-fluoren-2-yl}-1H-benzoimidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester as a pale yellow film (21 mg).
LCMS-ESI$^+$: calc'd for $C_{42}H_{43}F_2N_7O_3$: 732.8 ($M+H^+$); Found: 732.4 ($M+H^+$).

A solution of hydroxybenzotriazole (5.4 mg), 1-(3-dimethylaminepropyl)-3-ethylcarbodiimide-HCl (7.7 mg) and 2-Methoxycarbonylamino-3-methyl-butyric acid (7.0 mg) in DMF (0.2 mL) and CH_2Cl_2 (0.2 mL) was stirred at 0°C for 1 hr. This solution was added to a solution {1-[3-(6-{7-[5-(5-Aza-spiro[2.4]hept-6-yl)-1H-pyrrol-2-yl]-9,9-difluoro-9H-fluoren-2-yl}-1H-benzoimidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (21 mg) in DMF (0.4 mL) and CH_2Cl_2 (0.4 mL) at -25°C and stirred at this temperature overnight. Reaction mixture was diluted with ethyl acetate and washed with brine, brine/saturated sodium bicarbonate solution (1:1) and aqueous layers back-extracted with ethyl acetate. The combined organic layer was dried ($MgSO_4$), concentrated and purified by preparative reverse phase HPLC (Gemini, 25 to 100% ACN/H_2O + 0.1% TFA). The product-containing fractions were pooled, diluted with ethyl acetate and treated with saturated sodium bicarbonate solution at for 1h. Product was extracted with ethyl acetate (2x), combined organic layer was dried ($MgSO_4$), concentrated and lyophilized from ACN/H_2O to (1-{3-[6-(9,9-Difluoro-7-{2-[5-(2-methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3H-imidazol-4-yl}-9H-fluoren-2-yl)-1H-benzoimidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester as a white powder (11.8 mg)
^{1}H-NMR: 300 MHz, (DMSO-d_6) δ: 12.18 (s, 1H), 12.05 (s 0.5H), 11.48 (s, 0.5H), 8.1 – 7.1 (m, 10H), 5.75 (d, J=4.5 Hz, 0.5H), 5.190 (d, J=4.5 Hz, 0.5H), 4.63 (d, J=4.8 Hz, 1H), 4.54 (s, 1H), 4.12-4.0 (m, 2H), 3.8-3.2 (m , 9H), 2.65 (s, 1H), 2.40-2.01 (m, 27H).
LCMS-ESI$^+$: calc'd for $C_{49}H_{54}F_2N_8O_6$: 890.0 (M+H$^+$); Found: 889.4 (M+H$^+$).

To a solution of d-valine, (5.0 g) in 1N sodium hydroxide (42.7 mL) was added sodium carbonate (4.53 g). The solution was cooled to 0°C and methyl chloroformate (0.289 mL) was added dropwise over 2 h and reaction mixture was stirred for 2 h at 0°C. White reaction mixture was diluted with enough H_2O to form a colorless solution and washed with ethyl ether (3 x 30 mL). Aqueous layer was acidified to pH =2 with concentrated HCl to give a white precipitate that collected by filtration, washed with H_2O and dried under high vacuum to give 2-Methoxycarbonylamino-3-methyl-butyric acid as a crystalline white solid (4.668 g). LCMS-ESI$^-$: calc'd for $C_7H_{13}NO_4$: 176.2 (M+H$^+$); Found: 175.9 (M+H$^+$).

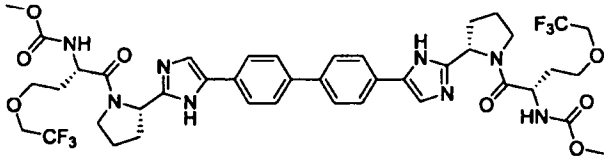
Example HY



[1-(2-{5-[4'-(2-{1-[2-Methoxycarbonylamino-4-(2,2,2-trifluoro-ethoxy)-butyryl]-pyrrolidin-2-yl}-3*H*-imidazol-4-yl)-biphenyl-4-yl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester

[1-(2-{5-[4'-(2-{1-[2-Methoxycarbonylamino-4-(2,2,2-trifluoro-ethoxy)-butyryl]-pyrrolidin-2-yl}-3H-imidazol-4-yl)-biphenyl-4-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: This compound was made in 45% yield by the same procedure as (4,4,4-Trifluoro-1-{2-[5-(4'-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-butyl)-carbamic acid methyl ester, using [1-(2-{5-[4'-(2-Pyrrolidin-2-yl-3H-imidazol-4-yl)-biphenyl-4-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-3-(2,2,2-trifluoroethoxy)-propyl]-carbamic acid methyl ester as the starting material. LCMS-ESI$^+$: calculated for $C_{41}H_{49}F_3N_8O_7$: 822.87; observed $[M+1]^+$: 823.45. ^{1}H-NMR: 400 MHz, (CD_3OD) δ: 7.82-7.72 (m, 4H), 7.69-7.65 (m, 4H), 7.38-7.32 (m, 2H), 5.22-5.16 (m, 2H), 4.65-4.61 (m, 1H), 4.26-4.21 (m, 1H), 4.04-3.84 (m, 6H), 3.72-3.48 (m, 8H), 2.39-1.98 (m, 10H), 1.88-1.78 (m, 1H), 1.01-0.89 (m, 6H) ppm.

Example HZ

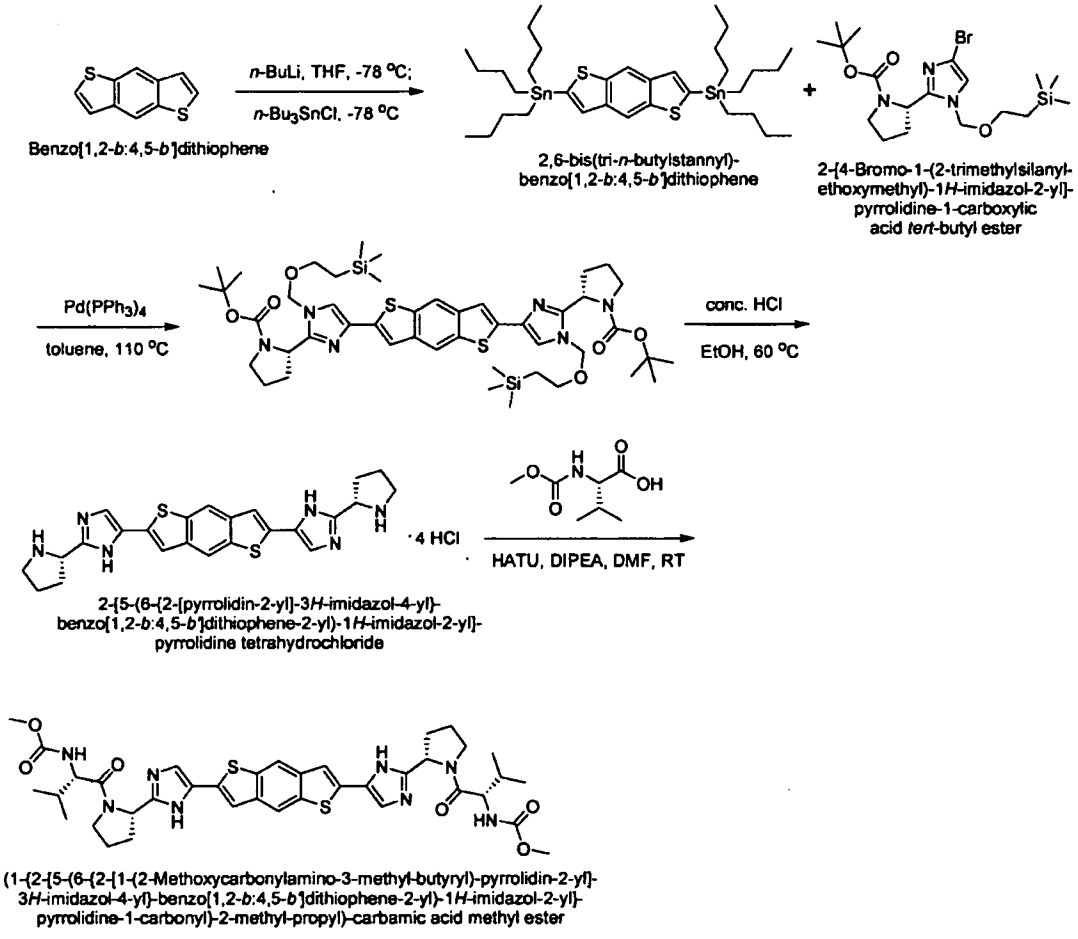


[1-(2-{5-[4'-(2-{1-[2-Methoxycarbonylamino-4-(2,2,2-trifluoro-ethoxy)-butyryl]-pyrrolidin-2-yl}-3*H*-imidazol-4-yl)-biphenyl-4-yl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-3-(2,2,2-trifluoro-ethoxy)-propyl]-carbamic acid methyl ester

[1-(2-{5-[4'-(2-{1-[2-Methoxycarbonylamino-4-(2,2,2-trifluoro-ethoxy)-butyryl]-pyrrolidin-2-yl}-3H-imidazol-4-yl)-biphenyl-4-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-3-(2,2,2-trifluoro-ethoxy)-propyl]-carbamic acid methyl ester: This compound was made in 27% yield by the same procedure as (4,4,4-Trifluoro-1-{2-[5-(4'-{2-[1-(5,5,5-trifluoro-2-methoxycarbonylamino-pentanoyl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-butyl)-carbamic acid methyl ester, using [1-(2-{5-[4'-(2-

Pyrrolidin-2-yl-3H-imidazol-4-yl)-biphenyl-4-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-3-(2,2,2-trifluoroethoxy)-propyl]-carbamic acid methyl ester as the starting material. LCMS-ESI$^+$: calculated for $C_{42}H_{48}F_6N_8O_8$: 906.87; observed $[M+1]^+$: 907.45. ^{1}H-NMR: 400 MHz, (CD_3OD) δ: 7.73-7.65 (m, 4H), 7.62-7.59 (m, 4H), 7.38-7.35 (m, 2H), 5.14-5.10 (m, 2H), 4.55-4.51 (m, 2H), 3.86-3.77 (m, 8H), 3.63-3.43 (m, 10H), 2.34-2.24 (m, 2H), 2.22-1.87 (m, 8H), 1.86-1.68 (m, 2H) ppm.

Example IA



2,6-Bis(tri-*n*-butylstannyl)-benzo[1,2-*b*:4,5-*b*']dithiophene: To a stirred solution of benzo[1,2-*b*:4,5-*b*']dithiophene (820 mg, 4.3 mmol) in THF (100 mL) under argon at -78° C was added a solution of *n*-butyllithium (2.5 M, 3.44 mL, 8.6 mmol). The solution was stirred at -78° C for 30 minutes and then warmed to -20° C for 30 minutes. Tri-*n*-butyltin chloride (2.34 mL, 8.6 mmol) was added and the reaction mixture was stirred at -20° C for 30 minutes and then allowed to warm to room temperature. After 16 hours, hexane was added and the reaction was

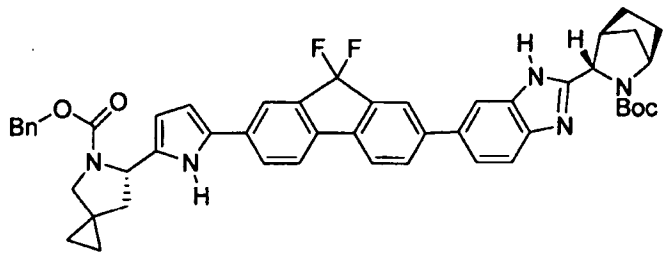
successively washed with water and brine, dried ($MgSO_4$), concentrated and purified by flash chromatography (100% hexanes). 2,6-bis(tri-*n*-butylstannyl)-benzo[1,2-*b*:4,5-*b*']dithiophene (1.4 g, 42%) was isolated along with product contaminated with the monostannylated benzodithiophene. ^{1}H-NMR: 400 MHz, ($CDCl_3$) δ: 8.27 (s, 2H), 7.38 (s, 2H), 1.65-1.57 (m, 12H), 1.41-1.32 (m, 12H), 1.26-1.11 (m, 12H), 0.91 (t, J = 7.3 Hz, 18H) ppm.

Fully protected 2-[5-(6-{2-[pyrrolidin-2-yl]-3H-imidazol-4-yl}-benzo[1,2-b:4,5-b']dithiophene-2-yl)-1H-imidazol-2-yl]-pyrrolidine: $Pd(PPh_3)_4$ (61 mg, 0.053 mmol) was added to a degassed solution of 2,6-bis(tri-*n*-butylstannyl)-benzo[1,2-*b*:4,5-*b*']dithiophene (202 mg, 0.26 mmol) and 2-[4-Bromo-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (260 mg, 0.58 mmol) in toluene (4 mL). The reaction was refluxed for 24 hours, then cooled to room temperature and filtered through CELITE and a palladium scavenging column (Stratospheres™ PL-Guanidine MP SPE+, Part #: PL3514-CM89). The solids were rinsed twice with toluene. The filtrate was concentrated and the crude product purified by flash chromatography to yield the desired, fully protected product (100 mg, 41%). LCMS-ESI$^+$: calculated for $C_{46}H_{68}N_6O_6S_2Si_2$: 920.42; observed $[M+1]^+$: 921.45.

(1-{2-[5-(6-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-benzo[1,2-b:4,5-b']dithiophene-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: A solution of fully protected 2-[5-(6-{2-[pyrrolidin-2-yl]-3H-imidazol-4-yl}-benzo[1,2-b:4,5-b']dithiophene-2-yl)-1H-imidazol-2-yl]-pyrrolidine (100 mg, 0.11 mmol), ethanol (4 mL) and concentrated HCl (1 mL) was heated to 60° C for 16 hours. The reaction was concentrated and the crude material dissolved in DCM (10 mL). This solution was concentrated to yield crude 2-[5-(6-{2-[pyrrolidin-2-yl]-3H-imidazol-4-yl}-benzo[1,2-b:4,5-b']dithiophene-2-yl)-1H-imidazol-2-yl]-pyrrolidine tetrahydrochloride. To this material was added a solution of 2-methoxycarbonylamino-3-methylbutyric acid (38 mg, 0.22 mmol) and HATU (83 mg, 0.22 mmol) in DMF (1.5 mL). To the resulting solution was added diisopropylethylamine (190 μL, 1.1 mmol). After stirring for 2 hours at room temperature, the reaction was concentrated and purified twice by preparative reverse phase HPLC (Gemini, 10 to 45% ACN/H_2O + 0.1% HCO_2H). The product fractions were passed through a freebasing column (STRATOSPHERES™ PL-HCO_3MP SPE, Part #: PL3540-C603) and lyophilized to give (1-{2-[5-(6-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-benzo[1,2-b:4,5-b']dithiophene-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-

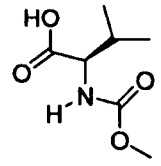
propyl)-carbamic acid methyl ester (29 mg, 34%). LCMS-ESI$^+$: calculated for $C_{38}H_{46}N_8O_6S_2$: 774.95; observed $[M+1]^+$: 775.96. ^{1}H-NMR: 400 MHz, (CD_3OD) δ: 8.16-8.11 (m, 2H), 7.49-7.47 (m, 2H), 7.38-7.29 (m, 2H), 5.18-5.15 (m, 2H), 4.24 (d, J = 7.4 Hz, 2H), 4.04-3.96 (m, 2H), 3.91-3.86 (m, 2H), 3.66 (br s, 6H), 2.38-2.17 (m, 6H), 2.11-1.98 (m, 4H), 1.00-0.89 (m, 12H) ppm.

Example IB

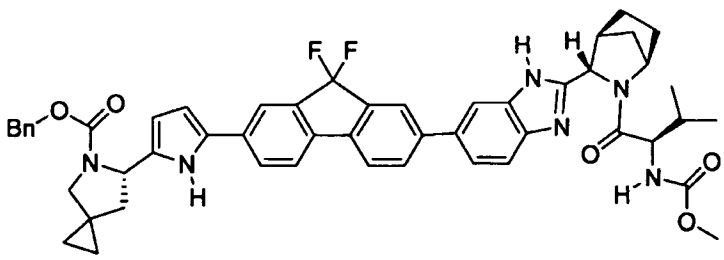


3-(6-{7-[5-(5-Benzyloxycarbonyl-5-aza-spiro[2.4]hept-6-yl)-1*H*-pyrrol-2-yl]-9,9-difluoro-9*H*-fluoren-2-yl}-1*H*-benzoimidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester

1. HCl, dioxane
2. ECDI, HOBt, DIEPA, DMF

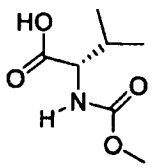


2-Methoxycarbonylamino-3-methyl-butyric acid



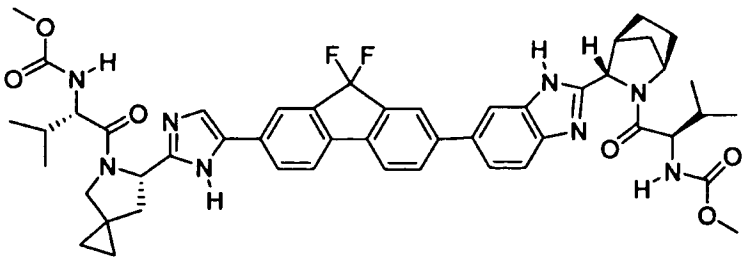
6-[5-(9,9-Difluoro-7-{2-[2-(2-methoxycarbonylamino-3-methyl-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3*H*-benzoimidazol-5-yl}-9*H*-fluoren-2-yl)-1*H*-pyrrol-2-yl]-5-aza-spiro[2.4]heptane-5-carboxylic acid benzyl ester

1. Pd/C, H_2, wet iPA
2. ECDI, HOBt, DIEPA, DMF



2-Methoxycarbonylamino-3-methyl-butyric acid

ECDI, HOBt
DIEPA, DMF



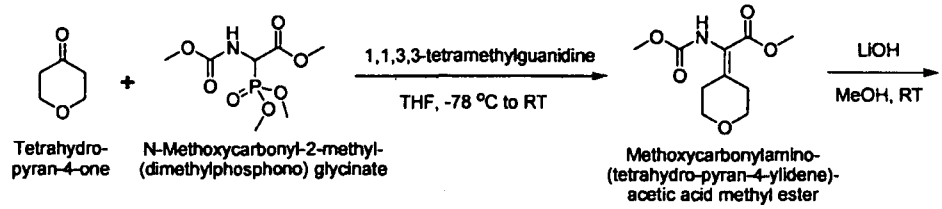
(1-{3-[6-(9,9-Difluoro-7-{2-[5-(2-methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3*H*-imidazol-4-yl}-9*H*-fluoren-2-yl)-1*H*-benzoimidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

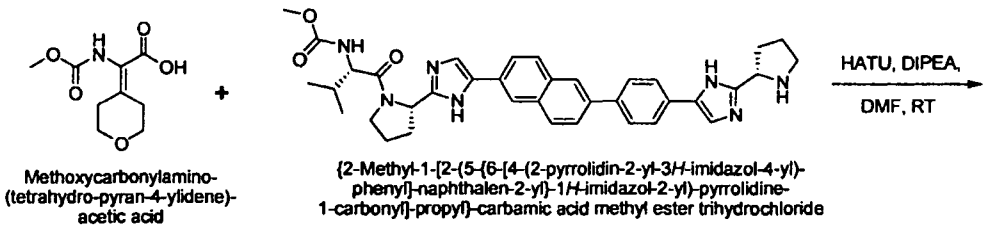
(1-{3-[6-(9,9-Difluoro-7-{2-[5-(2-methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3H-imidazol-4-yl}-9H-fluoren-2-yl)-1H-benzoimidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester was prepared in a similar manner as Example B to give title compound as a white powder (88.9 mg).

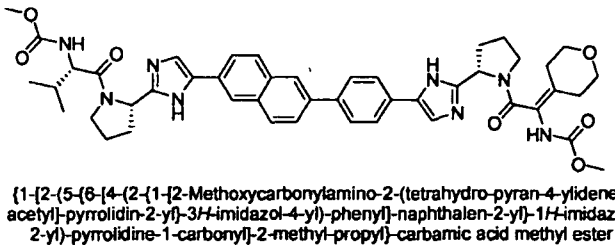
^{1}H-NMR: 300 MHz, (DMSO-d_6) δ: 12.56 (d, J=13.5Hz, 0.5H), 12.04 (d, J=17.1Hz, 0.5H), 11.84 (s, 1H), 8.1 – 7.1 (m, 12H), 5.3-5.1 (m, 1H), 4.8-4.5 (m, 1H), 4.1-3.7 (m, 4H), 3.6-3.2 (m, 20H), 2.8-1.1 (m, 12H), 0.9-0.4 (m , 16H).

LCMS-ESI$^+$: calc'd for $C_{49}H_{54}F_2N_8O_6$: 890.0 (M+H$^+$); Found: 889.4 (M+H$^+$).

Example IC





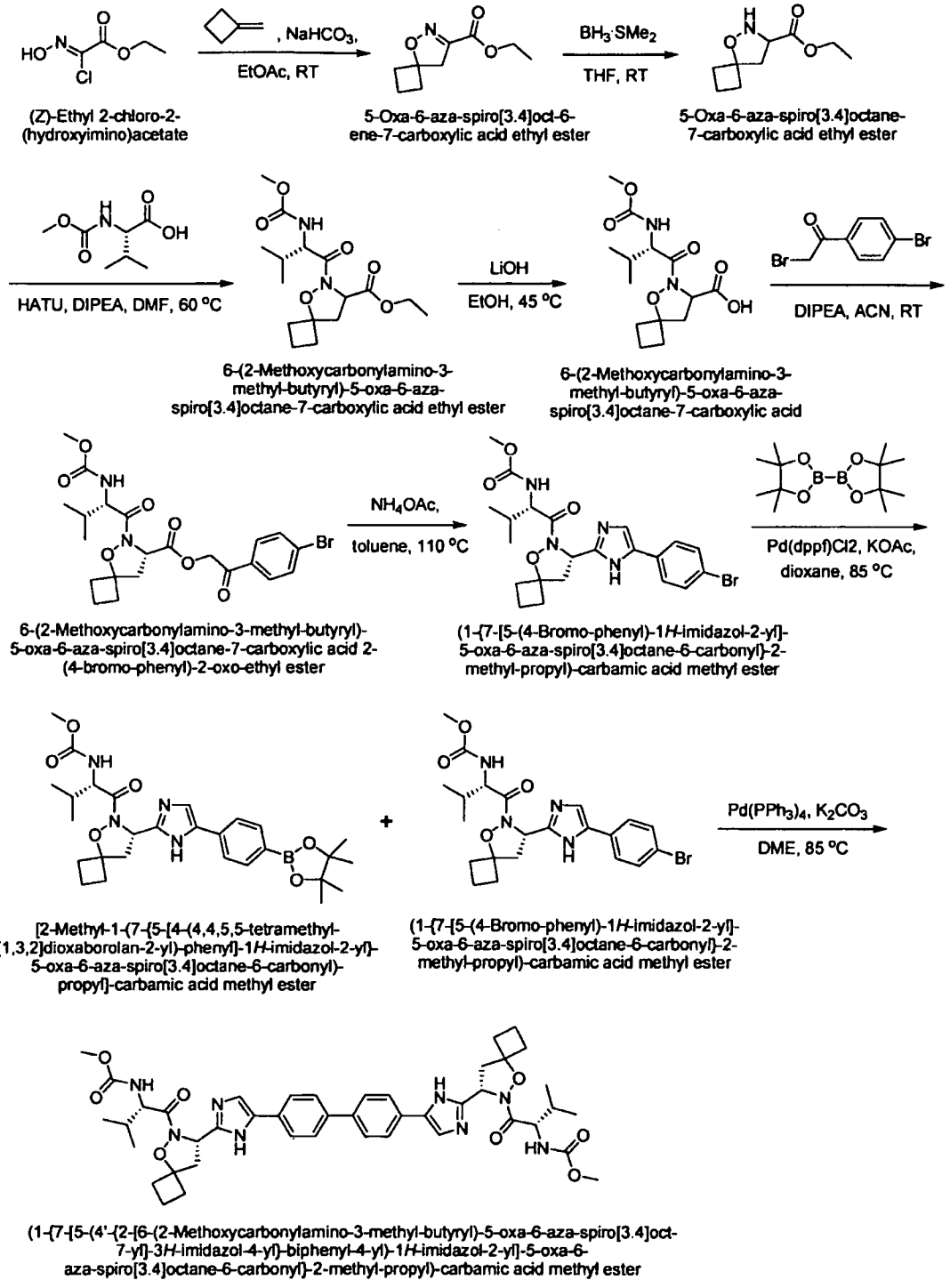


Methoxycarbonylamino-(tetrahydropyran-4-ylidene)-acetic acid methyl ester: A solution of N-methoxycarbonyl-2-methyl-(dimethylphosphono) glycinate (1.45 g, 5.68 mmol) in tetrahydrofuran (22 mL) was cooled to -78° C. 1,1,3,3-Tetramethylguanidine (0.680 mL, 5.42 mmol) was added and the resulting solution was stirred at -78° C for 30 minutes. Tetrahydropyran-4-one (0.500 mL, 5.42 mmol) was added and the reaction was stirred at -78° C for 1 hour. The ice bath was removed and the reaction was allowed to warm to room temperature overnight. In the morning, the reaction was diluted with ethyl acetate. The organics

were washed with 1N aqueous HCl and brine, dried ($MgSO_4$) and concentrated. The crude residue was purified by flash chromatography to yield methoxycarbonylamino-(tetrahydropyran-4-ylidene)-acetic acid methyl ester. ^{1}H-NMR: 400 MHz, ($CDCl_3$) δ: 5.94 (br s, 1H), 3.80-3.74 (m, 7H), 3.71 (s, 3H), 2.95-2.91 (m, 2H), 2.45-2.41 (m, 2H) ppm.

{1-[2-(5-{6-[4-(2-{1-[2-Methoxycarbonylamino-2-(tetrahydropyran-4-ylidene)-acetyl]-pyrrolidin-2-yl}-3H-imidazol-4-yl)-phenyl]-naphthalen-2-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester: To a solution of methoxycarbonylamino-(tetrahydropyran-4-ylidene)-acetic acid methyl ester (141 mg, 0.62 mmol) in methanol (1.8 mL) was added an aqueous LiOH solution (1M, 1.8 mL, 1.8 mmol). The resulting solution was stirred at room temperature for 16 hours and then washed with ethyl acetate. The ethyl acetate washing was discarded and the aqueous layer was acidified with concentrated HCl. The acidified aqueous layer was extracted twice with ethyl acetate. The combined organics were washed with brine, dried ($MgSO_4$), and concentrated to give methoxycarbonylamino-(tetrahydropyran-4-ylidene)-acetic acid. To a solution of methoxycarbonylamino-(tetrahydropyran-4-ylidene)-acetic acid (23 mg, 0.11 mmol) in dimethylformamide (0.6 mL) was added HATU (41 mg, 0.11 mmol). After stirring for 5 minutes, a solution of {2-methyl-1-[2-(5-{6-[4-(2-pyrrolidin-2-yl-3H-imidazol-4-yl)-phenyl]-naphthalen-2-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carbonyl]-propyl}-carbamic acid methyl ester trihydrochloride (50 mg, 0.068 mmol) in dimethylformamide (0.6 mL) was added to the reaction, followed immediately by diisopropylethylamine (85 μL, 0.49 mmol). The reaction was stirred for 1 hour at room temperature then diluted with ethyl acetate. The organic layer was washed successively with saturated aqueous $NaHCO_3$ solution, water and brine, dried ($MgSO_4$), concentrated and purified by preparative reverse phase HPLC (Gemini, 15 to 50% ACN/H_2O + 0.1% HCO_2H) to yield {1-[2-(5-{6-[4-(2-{1-[2-methoxycarbonylamino-2-(tetrahydropyran-4-ylidene)-acetyl]-pyrrolidin-2-yl}-3H-imidazol-4-yl)-phenyl]-naphthalen-2-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (28 mg, 50%). LCMS-ESI$^+$: calculated for $C_{46}H_{52}N_8O_7$: 828.95; observed $[M+1]^+$: 830.32. ^{1}H-NMR: 400 MHz, (CD_3OD) δ: 8.24-8.07 (m, 3H), 7.96-7.76 (m, 7H), 7.45-7.34 (m, 2H), 5.28-5.18 (m, 2H), 4.27-4.23 (m, 1H), 4.05-3.98 (m, 1H), 3.94-3.86 (m, 1H), 3.84-3.41 (m, 12H), 2.48-1.98 (m, 13H), 1.02-0.90 (m, 6H) ppm.

Example ID



(Z)-Ethyl 2-chloro-2-(hydroxyimino)acetate

5-Oxa-6-aza-spiro[3.4]oct-6-ene-7-carboxylic acid ethyl ester

5-Oxa-6-aza-spiro[3.4]octane-7-carboxylic acid ethyl ester

6-(2-Methoxycarbonylamino-3-methyl-butyryl)-5-oxa-6-aza-spiro[3.4]octane-7-carboxylic acid ethyl ester

6-(2-Methoxycarbonylamino-3-methyl-butyryl)-5-oxa-6-aza-spiro[3.4]octane-7-carboxylic acid

6-(2-Methoxycarbonylamino-3-methyl-butyryl)-5-oxa-6-aza-spiro[3.4]octane-7-carboxylic acid 2-(4-bromo-phenyl)-2-oxo-ethyl ester

(1-{7-[5-(4-Bromo-phenyl)-1*H*-imidazol-2-yl]-5-oxa-6-aza-spiro[3.4]octane-6-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

[2-Methyl-1-(7-{5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1*H*-imidazol-2-yl}-5-oxa-6-aza-spiro[3.4]octane-6-carbonyl)-propyl]-carbamic acid methyl ester

(1-{7-[5-(4-Bromo-phenyl)-1*H*-imidazol-2-yl]-5-oxa-6-aza-spiro[3.4]octane-6-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

(1-{7-[5-(4'-{2-[6-(2-Methoxycarbonylamino-3-methyl-butyryl)-5-oxa-6-aza-spiro[3.4]oct-7-yl]-3*H*-imidazol-4-yl}-biphenyl-4-yl)-1*H*-imidazol-2-yl]-5-oxa-6-aza-spiro[3.4]octane-6-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

5-Oxa-6-aza-spiro[3.4]oct-6-ene-7-carboxylic acid ethyl ester: To a solution of methylenecyclobutane (2 mL, 21.6 mmol) in ethyl acetate (125 mL) was added (Z)-ethyl 2-chloro-2-(hydroxyimino)acetate (6.55 g, 43.2 mmol) and solid sodium bicarbonate (16.3 g, 194 mmol). The reaction mixture was sealed and stirred at room temperature for 6 hours. More (Z)-ethyl 2-chloro-2-(hydroxyimino)acetate (4 g, 26.4 mmol) and sodium bicarbonate (8 g, 95.2 mmol) were added and the reaction was stirred at room temperature for an additional 12 hours. The reaction was diluted with ethyl acetate and washed successively with water and brine, dried ($MgSO_4$) and concentrated to yield crude 5-oxa-6-aza-spiro[3.4]oct-6-ene-7-carboxylic acid ethyl ester, contaminated with (Z)-Ethyl 2-chloro-2-(hydroxyimino)acetate and related compounds.

5-Oxa-6-aza-spiro[3.4]octane-7-carboxylic acid ethyl ester: To a solution of crude 5-oxa-6-aza-spiro[3.4]oct-6-ene-7-carboxylic acid ethyl ester (7.5 g, <40.9 mmol) in tetrahydrofuran (270 mL) at 0° C was slowly added a solution of borane-dimethyl sulfide complex (10 M in THF, 16.4 mL, 164 mmol). The reaction was allowed to warm to room temperature overnight then recooled to 0° C, and quenched by the careful addition of water. The mixture was diluted with ethyl acetate, washed with water and brine, dried ($MgSO_4$), and concentrated to yield a large amount of white solids. These solids were thoroughly triturated three times with dichloromethane (150 mL). The combined dichloromethane washings were concentrated and the resulting oil was purified by flash chromatography to yield 5-oxa-6-aza-spiro[3.4]octane-7-carboxylic acid ethyl ester (1.08 g, 29% over 2 steps). ^{1}H-NMR: 400 MHz, ($CDCl_3$) δ: 8.01-7.95 (br, 1H), 4.39-4.28 (m, 2H), 4.18-4.10 (m, 1H), 2.80-2.75 (m, 1H), 2.62-2.49 (m, 2H), 2.37-2.29 (m, 1H), 2.25-2.17 (m, 1H), 2.13-1.95 (m, 1H), 1.88-1.79 (m, 1H), 1.68-1.56 (m, 1H), 1.34 (t, J = 7.1 Hz, 3H) ppm.

6-(2-Methoxycarbonylamino-3-methyl-butyryl)-5-oxa-6-aza-spiro[3.4]octane-7-carboxylic acid ethyl ester: To a solution of 2-methoxycarbonylamino-3-methyl-butyric acid (1.11 g, 6.33 mmol) and HATU (2.41 g, 6.34 mmol) in dimethylformamide (13 mL) was added a solution of 5-oxa-6-aza-spiro[3.4]octane-7-carboxylic acid ethyl ester (980 mg, 5.3 mmol) in dimethylformamide (13mL). To the resulting reaction mixture was added diisopropylethylamine (1.85 mL, 10.6 mmol) and the reaction was heated to 60° C for 16 hours. The reaction was diluted with ethyl acetate, washed with water and brine, dried ($MgSO_4$) and concentrated. The resulting residue was purified by flash chromatography to give 6-(2-methoxycarbonylamino-3-methyl-butyryl)-5-oxa-6-aza-spiro[3.4]octane-7-carboxylic acid ethyl ester (1.31 g, 72%). LCMS-ESI$^+$: calculated for $C_{16}H_{26}N_2O_6$: 342.18; observed $[M+1]^+$: 342.90.

6-(2-Methoxycarbonylamino-3-methyl-butyryl)-5-oxa-6-aza-spiro[3.4]octane-7-carboxylic acid: To a solution of 6-(2-methoxycarbonylamino-3-methyl-butyryl)-5-oxa-6-aza-spiro[3.4]octane-7-carboxylic acid ethyl ester (1.31 g, 3.83 mmol) in ethanol (10 mL) was added a solution of lithium hydroxide (1M in water, 7.6 mL, 7.6 mmol). The reaction was stirred at room temperature for 30 minutes. The reaction was partially concentrated and the resulting aqueous solution was washed with ethyl acetate. The ethyl acetate layer was discarded and the aqueous layer was acidified using concentrated HCl. The acidic aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated to yield crude 6-(2-methoxycarbonylamino-3-methyl-butyryl)-5-oxa-6-aza-spiro[3.4]octane-7-carboxylic acid, which was used without further purification.

6-(2-Methoxycarbonylamino-3-methyl-butyryl)-5-oxa-6-aza-spiro[3.4]octane-7-carboxylic acid 2-(4-bromophenyl)-2-oxo-ethyl ester: To a solution of 6-(2-methoxycarbonylamino-3-methyl-butyryl)-5-oxa-6-aza-spiro[3.4]octane-7-carboxylic acid (~3.83 mmol) and 2,4'-dibromoacetophenone (1.1 g, 3.96 mmol) in acetonitrile (19 mL) was added diisopropylethylamine (1.32 mL, 7.59 mmol). The reaction was stirred at room temperature for 16 hours and was then diluted with ethyl acetate. The organics were washed with water and brine, dried ($MgSO_4$) and concentrated. The resulting crude residue was purified by flash chromatography, cleanly separating the two diastereomers of 6-(2-methoxycarbonylamino-3-methyl-butyryl)-5-oxa-6-aza-spiro[3.4]octane-7-carboxylic acid 2-(4-bromophenyl)-2-oxo-ethyl ester (330 mg of the (R) diastereomer, 360 mg of the (S) diastereomer, 35% total yield over 2 steps). ^{1}H-NMR for the desired (S) diastereomer: 400 MHz, ($CDCl_3$) δ: 7.74-7.71 (m, 2H), 7.62-7.60 (m, 2H), 5.47 (d, J = 16.4 Hz, 1H), 5.40-5.35 (m, 1H), 5.20 (d, J = 16.4 Hz, 1H), 4.92 (dd, J^1 = 7.1 Hz, J^2 = 9.0 Hz, 1H), 4.74-4.70 (m, 1H), 3.65 (s, 3H), 2.84 (dd, J^1 = 9.0 Hz, J^2 = 12.6 Hz, 1H), 2.60 (dd, J^1 = 7.0 Hz, J^2 = 12.6 Hz, 1H), 2.52-2.12 (m, 5H), 2.07-1.86 (m, 2H), 1.75-1.65 (m, 1H), 1.01 (d, J = 6.6 Hz, 3H), 0.89 (d, J = 7.1 Hz, 3H) ppm.

(1-{7-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-5-oxa-6-aza-spiro[3.4]octane-6-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: To a solution of 6-(2-methoxycarbonylamino-3-methyl-butyryl)-5-oxa-6-aza-spiro[3.4]octane-7-carboxylic acid 2-(4-bromophenyl)-2-oxo-ethyl ester (150 mg, 0.29 mmol) in toluene (3 mL) was added ammonium acetate (230 mg, 3.0 mmol). The reaction mixture was vigorously refluxed for 3 hours, cooled to room temperature and diluted with ethyl acetate. The organics were washed with water and brine, dried ($MgSO_4$), and concentrated. The crude residue was purified by flash chromatography to yield (1-{7-[5-(4-

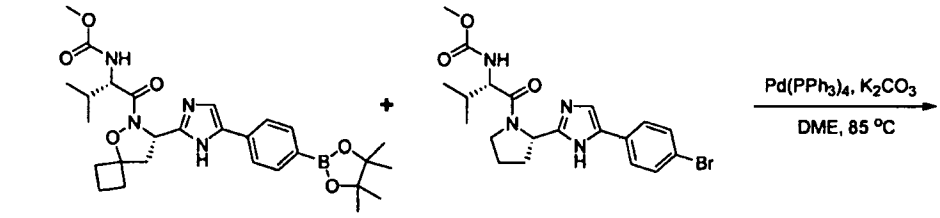
bromophenyl)-1H-imidazol-2-yl]-5-oxa-6-aza-spiro[3.4]octane-6-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (95 mg, 66%). LCMS-ESI$^+$: calculated for $C_{22}H_{27}BrN_4O_4$: 490.12/492.12; observed $[M+1]^+$: 490.99/492.99. ^{1}H-NMR: 400 MHz, ($CDCl_3$) δ: 7.60-7.55 (m, 2H), 7.50-7.46 (m, 2H), 7.26 (s, 1H), 5.38-5.29 (m ,2H), 4.76-4.70 (br, 1H), 3.70 (s, 3H), 3.36-3.29 (m, 1H), 2.84 (dd, J^1 = 8.2 Hz, J^2 = 12.5 Hz, 1H), 2.51-2.32 (m, 3H), 2.13-2.03 (m, 2H), 2.00-1.89 (m, 1H), 1.83-1.71 (m, 1H), 0.97 (d, J = 6.7 Hz, 3H), 0.84 (d, J = 6.8 Hz, 3H), ppm.

[2-Methyl-1-(7-{5-[4-(4,4,5,5-tetramethyl[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-5-oxa-6-azaspiro[3.4]octane-6-carbonyl)-propyl]-carbamic acid methyl ester: A degassed mixture of (1-{7-[5-(4-bromophenyl)-1H-imidazol-2-yl]-5-oxa-6-aza-spiro[3.4]octane-6-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (85 mg, 0.17 mmol), bis(pinacolato)diboron (66 mg, 0.26 mmol), potassium acetate (51 mg, 0.52 mmol) and dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) (13 mg, 0.018 mmol) in 1,4-dioxane (1.7 mL) was heated to 85° C for 75 minutes. After cooling to room temperature, the reaction was filtered through a palladium scavenging column (STRATOSPHERES^{TM} PL-Guanidine MP SPE+, Part #: PL3514-CM89) and the solids were rinsed with ethyl acetate. The filtrate was washed with water and brine, dried ($MgSO_4$), and concentrated. The crude residue was purified by flash chromatography to yield [2-methyl-1-(7-{5-[4-(4,4,5,5-tetramethyl[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-5-oxa-6-azaspiro[3.4]octane-6-carbonyl)-propyl]-carbamic acid methyl ester (81 mg, 87%). LCMS-ESI$^+$: calculated for $C_{28}H_{39}BN_4O_6$: 538.30; observed $[M+1]^+$: 539.12.

(1-{7-[5-(4'-{2-[6-(2-Methoxycarbonylamino-3-methyl-butyryl)-5-oxa-6-aza-spiro[3.4]oct-7-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-5-oxa-6-aza-spiro[3.4]octane-6-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: To a solution of [2-methyl-1-(7-{5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-5-oxa-6-azaspiro[3.4]octane-6-carbonyl)-propyl]-carbamic acid methyl ester (81 mg, 0.15 mmol), (1-{7-[5-(4-bromophenyl)-1H-imidazol-2-yl]-5-oxa-6-aza-spiro[3.4]octane-6-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (60 mg, 0.12 mmol) and tetrakis(triphenylphosphine)palladium(0) (14 mg, 0.012 mmol) in 1,2-dimethoxyethane (2.0 mL) was added a solution of potassium carbonate (2M in water, 0.250 mL, 0.50 mmol). The resulting mixture was degassed for15 minutes with a stream of argon and then heated to 85° C for 3 hours. After cooling to room temperature, the reaction was filtered through a palladium scavenging column (STRATOSPHERES^{TM} PL-Guanidine MP SPE+, Part #: PL3514-CM89) and the solids were rinsed with methanol. The filtrate was concentrated and purified by

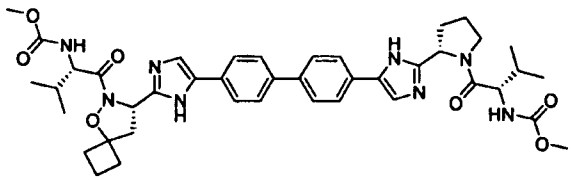
preparative reverse phase HPLC (Gemini, 15 to 51% ACN/H_2O + 0.1% HCO_2H) to yield (1-{7-[5-(4'-{2-[6-(2-Methoxycarbonylamino-3-methyl-butyryl)-5-oxa-6-aza-spiro[3.4]oct-7-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-5-oxa-6-aza-spiro[3.4]octane-6-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (26 mg, 26%). LCMS-ESI$^+$: calculated for $C_{44}H_{54}N_8O_8$: 822.41; observed $[M+1]^+$: 823.43. ^{1}H-NMR: 400 MHz, (CD_3OD) δ: 7.78-7.75 (m, 4H), 7.68-7.65 (m, 4H), 7.38 (s, 2H), 6.94-6.89 (br, 2H), 5.47-5.42 (m, 2H), 4.74-4.68 (br, 2H), 3.66 (s, 6H), 3.00-2.94 (m, 2H), 2.78-2.71 (m, 2H), 2.61-2.53 (m, 2H), 2.49-2.40 (m, 2H), 2.38-2.30 (m, 2H), 2.22-2.09 (m, 4H), 2.00-1.90 (m, 2H), 1.84-1.75 (m, 2H), 0.98 (d, J = 6.8 Hz, 6H), 0.88 (d, J = 6.7 Hz, 6H) ppm.

Example IE



[2-Methyl-1-(7-{5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1*H*-imidazol-2-yl}-5-oxa-6-aza-spiro[3.4]octane-6-carbonyl)-propyl]-carbamic acid methyl ester

(1-{2-[5-(4-Bromo-phenyl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester



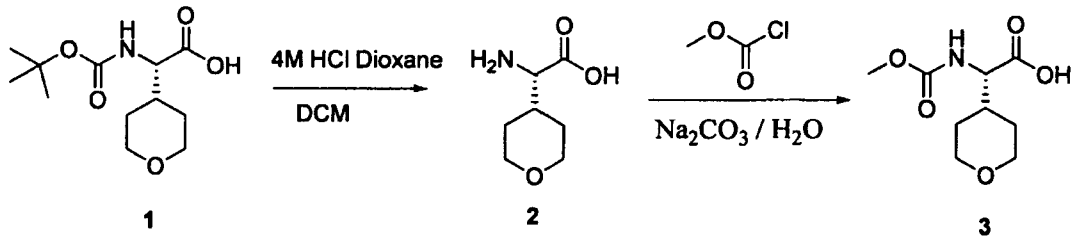
(1-{7-[5-(4'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-biphenyl-4-yl)-1*H*-imidazol-2-yl]-5-oxa-6-aza-spiro[3.4]octane-6-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

(1-{7-[5-(4'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-5-oxa-6-aza-spiro[3.4]octane-6-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: To a solution of [2-methyl-1-(7-{5-[4-(4,4,5,5-tetramethyl[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-5-oxa-6-azaspiro[3.4]octane-6-carbonyl)-propyl]-carbamic acid methyl ester (81 mg, 0.15 mmol), (1-{2-[5-(4-bromophenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (81 mg, 0.18 mmol) and tetrakis(triphenylphosphine)palladium(0) (18 mg, 0.015 mmol) in 1,2-dimethoxyethane (3.0 mL) was added a solution of potassium carbonate (2M in water, 0.300 mL, 0.60 mmol). The resulting mixture was degassed for15 minutes with a stream of argon and

then heated to 85° C for 3 hours. After cooling to room temperature, the reaction was filtered through a palladium scavenging column (STRATOSPHERES™ PL-Guanidine MP SPE+, Part #: PL3514-CM89) and the solids were rinsed with methanol. The filtrate was concentrated and purified by flash chromatography (0%-5% methanol/dichloromethane). The resulting residue was repurified by preparative reverse phase HPLC (Gemini, 15 to 50% ACN/H_2O + 0.1% HCO_2H) to yield (1-{7-[5-(4'-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-5-oxa-6-aza-spiro[3.4]octane-6-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (35 mg, 30%). LCMS-ESI$^+$: calculated for $C_{42}H_{52}N_8O_7$: 780.40; observed $[M+1]^+$: 781.29. ^{1}H-NMR: 400 MHz, (CD_3OD) δ: 7.82-7.72 (m, 4H), 7.69-7.65 (m, 4H), 7.38 (s, 1H), 7.32 (s, 1H), 6.99-6.90 (m, 2H), 5.47-5.42 (m, 1H), 5.20-5.16 (m, 1H), 4.75-4.68 (m, 1H), 4.226-4.21 (m, 1H), 4.03-3.96 (m, 1H), 3.91-3.85 (m, 1H), 3.71-3.48 (m, 7H), 3.00-2.94 (m, 1H), 2.78-2.71 (m, 1H), 2.61-1.90 (m, 10H), 1.83-1.73 (m, 1H), 1.00-0.86 (m, 12H) ppm.

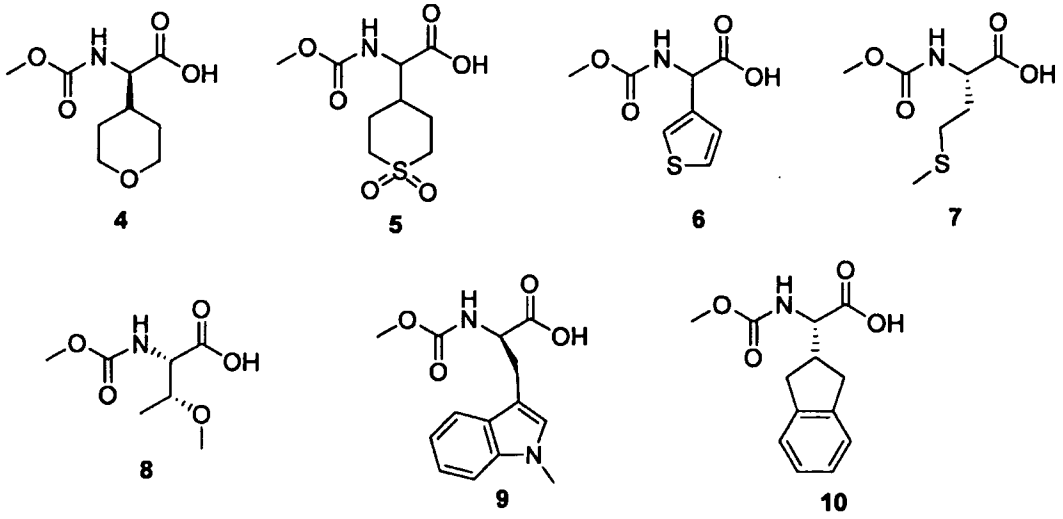
Example IF

(S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl) acetic acid (3)



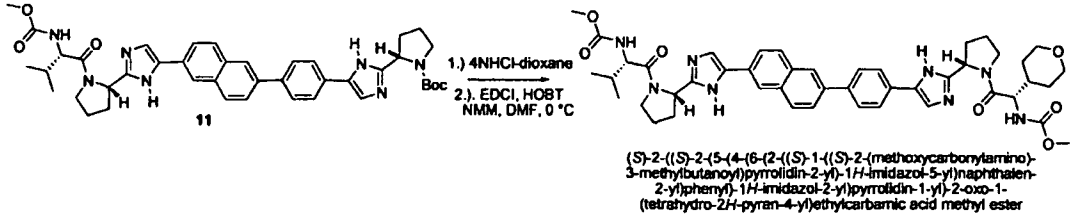
1 2 3

To (S)-2-(*tert*-butoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl) acetic acid **1** (1.5 g, 5.8 mmol) in dichloromethane (5 mL) was added 4M HCl in dioxane (5 mL) and the reaction mixture was cooled to 0°C and then stirred for 2 hours. After concentrated in vacuo to afford **2** To (S)-2-amino-2-(tetrahydro-2H-pyran-4-yl) acetic acid **2** (780 mg; 5 mmol) in water (25 ml) was added sodium carbonate (1.06g; 10 mmol), and the resultant mixture was cooled to 0.deg. C. and then methyl chloroformate (0.53 ml; 5.5 mmol) was added dropwise over 5 minutes. The reaction was allowed to stir for 18 hours while allowing the bath to thaw to ambient temperature. The reaction mixture was then partitioned between 1N HCl and ethyl acetate. The organic layer was removed and the aqueous layer was further extracted with 2 additional portions of ethyl acetate. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated in vacuo to afford **3** a colorless residue. MS (ESI) *m/z*: 218 $[M + H]^+$.



Compounds **4-10** were prepared according to the method employed to prepare ((S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl) acetic acid (**3**)

(S)-2-((S)-2-(5-(4-(6-(2-((S)-1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)pyrrolidin-1-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethylcarbamic acid methyl ester:



To compound **11** (50 mg, 0.068mmol) in dichloromethane (0.8 mL) was added 4M HCl in dioxane (0.8 mL) and the reaction mixture was cooled to 0°C and then stirred for 2 hours. After concentrated in vacuo to afford HCl salts.

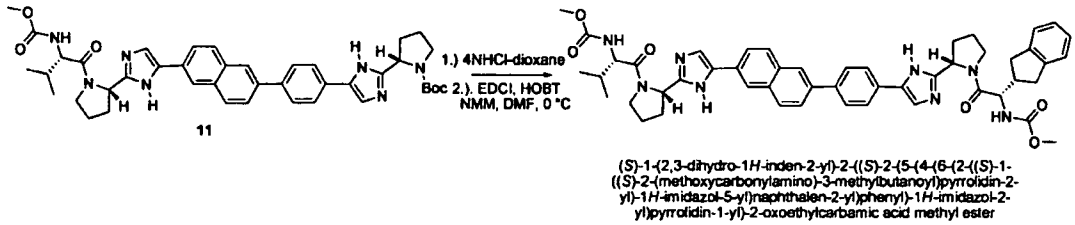
To these HCl salts in DMF (0.8 mL) was added compound **3**(20 mg, 0.09 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (18 mg, 0.09 mmol) and hydroxybenzotriazole hydrate (HOBt), (13 mg, 0.09 mmol). The mixture was cooled down in an ice bath to 0°C and N-methylmorpholine (NMM)(20μL, 0.18 mmol) was added from a syringe to the mixture. The reaction content was stirred for 4 hours at room temperature. The resulting

mixture was then directly purified on reverse phase prep. HPLC to afford title compound as white solid (36 mg, 65%).

^{1}H-NMR: 400 MHz, (CD_3OD) δ 8.03 (s, 1H), 7.99 (s, 1H), 7.79 – 7.66 (m, 10H), 7.33 (s, 1H), 7.24 (s, 1H), 7.05-6.91 (m, 1H), 5.22 -5.09(m, 1H), 4.23-4.15 (m, 1H), 3.98 – 3.78 (m, 4H), 3.57 (s, 6H), 3.38 – 3.31 (m, 8H), 2.65 (m, 1H), 2.30 – 2.09 (m, 5H), 2.02 – 1.95 (m, 2H), 1.56 – 1.29 (m, 5H), 0.92 – 0.82 (m, 6H). MS (ESI) *m/z* 832 $[M + H]^+$.

Example IG

(S)-1-(2,3-dihydro-1H-inden-2-yl)-2-((S)-2-(5-(4-(6-(2-((S)-1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)pyrrolidin-1-yl)-2-oxoethylcarbamic acid methyl ester



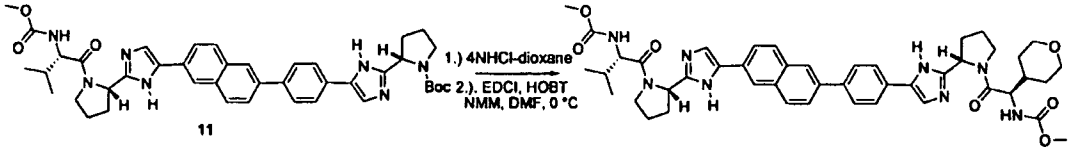
To compound **11** (50 mg, 0.068mmol) in dichloromethane (0.8 mL) was added 4M HCl in dioxane (0.8 mL) and the reaction mixture was cooled to 0°C and then stirred for 2 hours. After concentrated in vacuo to afford HCl salts.

To these HCl salts (32 mg) in DMF (0.7 mL) was added compound **10** (16 mg, 0.063 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (12 mg, 0.063 mmol) and hydroxybenzotriazole hydrate (HOBt), (9 mg, 0.063 mmol). The mixture was cooled down in an ice bath to 0°C and N-methylmorpholine (NMM)(20μL, 0.12 mmol) was added from a syringe to the mixture. The reaction content was stirred for 4 hours at room temperature. The resulting mixture was then directly purified on reverse phase prep. HPLC to afford title compound as white solid (23 mg, 62 %).

MS (ESI) *m/z* 864 $[M + H]^+$.

Example IH

(R)-2-((S)-2-(5-(4-(6-(2-((S)-1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)pyrrolidin-1-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethylcarbamic acid methyl ester



11

(*R*)-2-((*S*)-2-(5-(4-(6-(2-((*S*)-1-((*S*)-2-(methoxycarbonylamino)-3-methylbutanoyl)pyrrolidin-2-yl)-1*H*-imidazol-5-yl)naphthalen-2-yl)phenyl)-1*H*-imidazol-2-yl)pyrrolidin-1-yl)-2-oxo-1-(tetrahydro-2*H*-pyran-4-yl)ethylcarbamic acid methyl ester

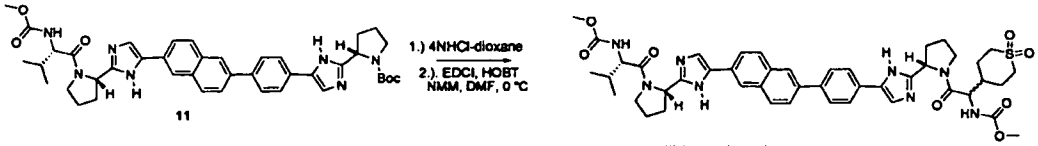
To compound **11** (50 mg, 0.068mmol) in dichloromethane (0.8 mL) was added 4M HCl in dioxane (0.8 mL) and the reaction mixture was cooled to 0°C and then stirred for 2 hours. After concentrated in vacuo to afford HCl salts.

To these HCl salts (33 mg) in DMF (0.8 mL) was added compound **4** (15 mg, 0.068 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (13 mg, 0.068 mmol) and hydroxybenzotriazole hydrate (HOBt), (11 mg, 0.068 mmol). The mixture was cooled down in an ice bath to 0°C and N-methylmorpholine (NMM)(14μL, 0.13mmol) was added from a syringe to the mixture. The reaction content was stirred for 4 hours at room temperature. The resulting mixture was then directly purified on reverse phase prep. HPLC to afford title compound as white solid (25 mg, 67%).

MS (ESI) *m/z* 832 $[M + H]^+$.

Example II

(2S)-1-((2S)-2-(5-(6-(4-(2-((2S)-1-(2-(1,1-dioxo-hexahydro-thiopyran-4-yl)-2-(methoxycarbonylamino)acetyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)phenyl)naphthalen-2-yl)-1H-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamic acid methyl ester



11

(2*S*)-1-((2*S*)-2-(5-(6-(4-(2-((2*S*)-1-(2-(1,1-dioxo-hexahydro-thiopyran-4-yl)-2-(methoxycarbonylamino)acetyl)pyrrolidin-2-yl)-1*H*-imidazol-5-yl)phenyl)naphthalen-2-yl)-1*H*-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamic acid methyl ester

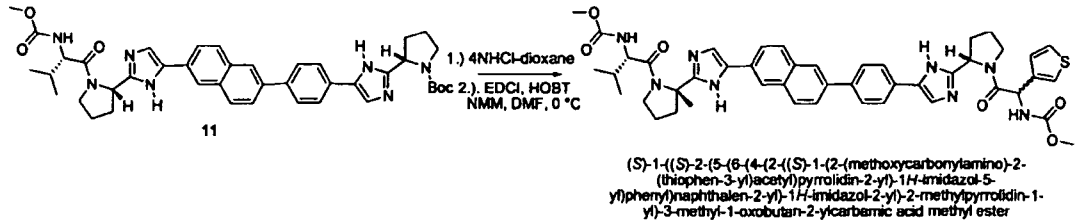
To compound **11** (50 mg, 0.068mmol) in dichloromethane (0.8 mL) was added 4M HCl in dioxane (0.8 mL) and the reaction mixture was cooled to 0°C and then stirred for 2 hours. After concentrated in vacuo to afford HCl salts.

To these HCl salts (33 mg) in DMF (0.8 mL) was added compound **5** (18 mg, 0.068 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (13 mg, 0.068 mmol) and hydroxybenzotriazole hydrate (HOBt), (11 mg, 0.068 mmol). The mixture was cooled down in an ice bath to 0°C and N-methylmorpholine (NMM)(14μL, 0.13mmol) was added from a syringe to the mixture. The reaction content was stirred for 4 hours at room temperature. The resulting mixture was then directly purified on reverse phase prep. HPLC to afford title compound as white solid (16 mg, 40%).

MS (ESI) *m/z* 880 $[M + H]^+$.

Example IJ

(S)-1-((S)-2-(5-(6-(4-(2-((S)-1-(2-(methoxycarbonylamino)-2-(thiophen-3-yl)acetyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)phenyl)naphthalen-2-yl)-1H-imidazol-2-yl)-2-methylpyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamic acid methyl ester



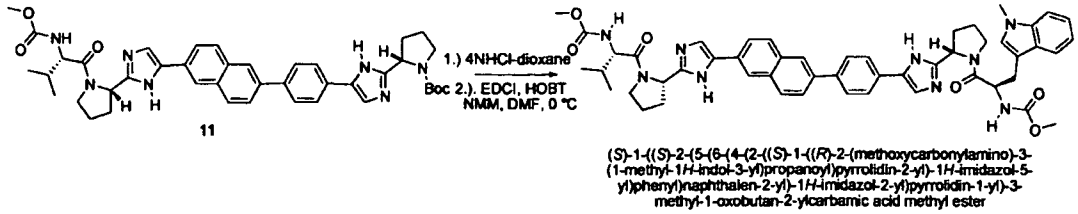
To compound **11** (50 mg, 0.068mmol) in dichloromethane (0.8 mL) was added 4M HCl in dioxane (0.8 mL) and the reaction mixture was cooled to 0°C and then stirred for 2 hours. After concentrated in vacuo to afford HCl salts.

To these HCl salts (33 mg) in DMF (0.8 mL) was added compound **6** (15 mg, 0.068 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (13 mg, 0.068 mmol) and hydroxybenzotriazole hydrate (HOBt), (11 mg, 0.068 mmol). The mixture was cooled down in an ice bath to 0°C and N-methylmorpholine (NMM)(14μL, 0.13mmol) was added from a syringe to the mixture. The reaction content was stirred for 4 hours at room temperature. The resulting mixture was then directly purified on reverse phase prep. HPLC to afford title compound as white solid (22 mg, 60%).

MS (ESI) *m/z* 830 $[M + H]^+$.

Example IK

(S)-1-((S)-2-(5-(6-(4-(2-((S)-1-((R)-2-(methoxycarbonylamino)-3-(1-methyl-1H-indol-3-yl)propanoyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)phenyl)naphthalen-2-yl)-1H-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamic acid methyl ester



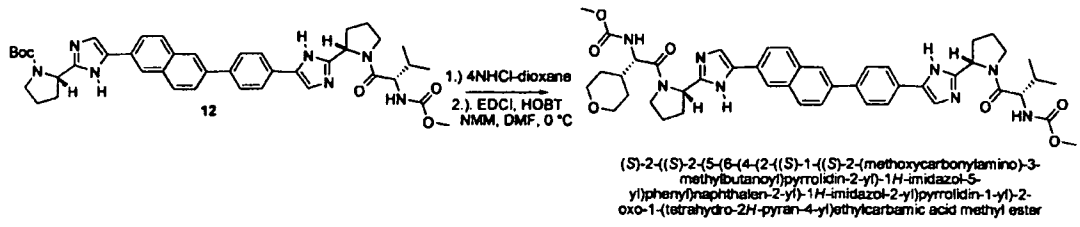
To compound **11** (50 mg, 0.068mmol) in dichloromethane (0.8 mL) was added 4M HCl in dioxane (0.8 mL) and the reaction mixture was cooled to 0°C and then stirred for 2 hours. After concentrated in vacuo to afford HCl salts.

To these HCl salts (20 mg) in DMF (0.5 mL) was added compound **9** (11 mg, 0.039 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (8 mg, 0.039 mmol) and hydroxybenzotriazole hydrate (HOBt), (6 mg, 0.039 mmol). The mixture was cooled down in an ice bath to 0°C and N-methylmorpholine (NMM)(8.3μL, 0.075mmol) was added from a syringe to the mixture. The reaction content was stirred for 4 hours at room temperature. The resulting mixture was then directly purified on reverse phase prep. HPLC to afford title compound as white solid (10 mg, 42%).

MS (ESI) *m/z* 891 $[M + H]^+$.

Example IL

(S)-2-((S)-2-(5-(6-(4-(2-((S)-1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)phenyl)naphthalen-2-yl)-1H-imidazol-2-yl)pyrrolidin-1-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethylcarbamic acid methyl ester

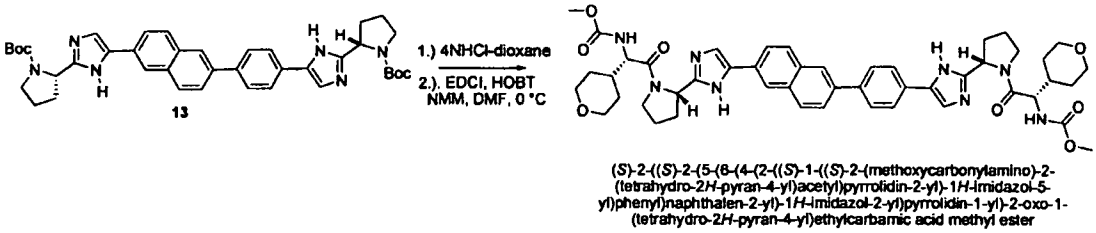


To compound **12** (50 mg, 0.068mmol) in dichloromethane (0.8 mL) was added 4M HCl in dioxane (0.8 mL) and the reaction mixture was cooled to 0°C and then stirred for 2 hours. After concentrated in vacuo to afford HCl salts.

To these HCl salts (43 mg) in DMF (0.8 mL) was added compound **3** (20 mg, 0.09 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (18 mg, 0.09 mmol) and hydroxybenzotriazole hydrate (HOBt), (13 mg, 0.09 mmol). The mixture was cooled down in an ice bath to 0°C and N-methylmorpholine (NMM)(20μL, 0.18mmol) was added from a syringe to the mixture. The reaction content was stirred for 4 hours at room temperature. The resulting mixture was then directly purified on reverse phase prep. HPLC to afford title compound as white solid (32 mg, 465%).
MS (ESI) *m/z* 832 $[M + H]^+$.

Example IM

(S)-2-((S)-2-(5-(6-(4-(2-((S)-1-((S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)phenyl)naphthalen-2-yl)-1H-imidazol-2-yl)pyrrolidin-1-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethylcarbamic acid methyl ester

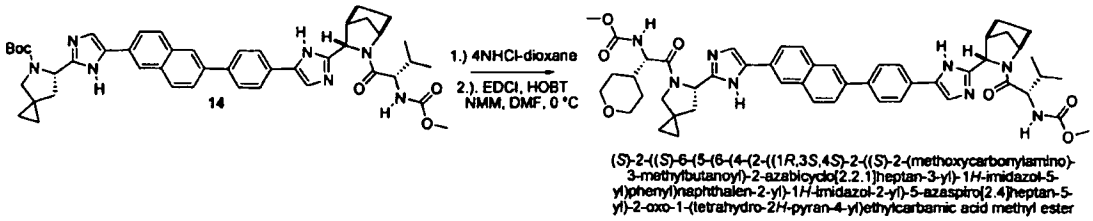


(*S*)-2-((*S*)-2-(5-(6-(4-(2-((*S*)-1-((*S*)-2-(methoxycarbonylamino)-2-(tetrahydro-2*H*-pyran-4-yl)acetyl)pyrrolidin-2-yl)-1*H*-imidazol-5-yl)phenyl)naphthalen-2-yl)-1*H*-imidazol-2-yl)pyrrolidin-1-yl)-2-oxo-1-(tetrahydro-2*H*-pyran-4-yl)ethylcarbamic acid methyl ester

To compound **13** (50 mg, 0.074mmol) in dichloromethane (0.9 mL) was added 4M HCl in dioxane (0.9 mL) and the reaction mixture was cooled to 0°C and then stirred for 2 hours. After concentrated in vacuo to afford HCl salts.
To these HCl salts in DMF (0.8 mL) was added compound **3**(41 mg, 0.19 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (36 mg, 0.19 mmol) and hydroxybenzotriazole hydrate (HOBt), (26 mg, 0.19 mmol). The mixture was cooled down in an ice bath to 0°C and N-methylmorpholine (NMM)(25μL, 0.22 mmol) was added from a syringe to the mixture. The reaction content was stirred for 4 hours at room temperature. The resulting mixture was then directly purified on reverse phase prep. HPLC to afford title compound as white solid (32 mg, 50%).
MS (ESI) *m/z* 874 $[M + H]^+$.

Example IN

(S)-2-((S)-6-(5-(6-(4-(2-((1R,3S,4S)-2-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-2-azabicyclo[2.2.1]heptan-3-yl)-1H-imidazol-5-yl)phenyl)naphthalen-2-yl)-1H-imidazol-2-yl)-5-azaspiro[2.4]heptan-5-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethylcarbamic acid methyl ester



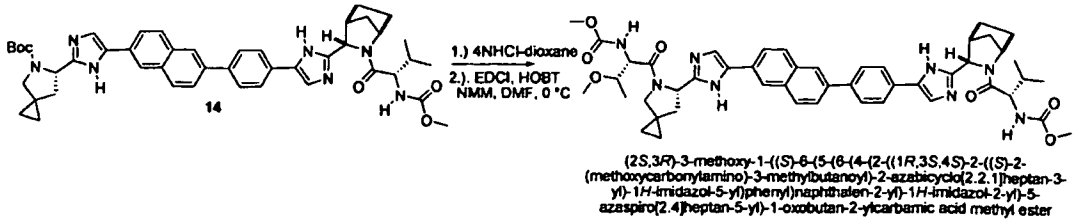
To compound **14** (50 mg, 0.064mmol) in dichloromethane (0.8 mL) was added 4M HCl in dioxane (0.8 mL) and the reaction mixture was cooled to 0°C and then stirred for 2 hours. After concentrated in vacuo to afford HCl salts.

To these HCl salts in DMF (0.8 mL) was added compound **3**(20 mg, 0.09 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (18 mg, 0.09 mmol) and hydroxybenzotriazole hydrate (HOBt), (13 mg, 0.09 mmol). The mixture was cooled down in an ice bath to 0°C and N-methylmorpholine (NMM)(18μL, 0.16 mmol) was added from a syringe to the mixture. The reaction content was stirred for 4 hours at room temperature. The resulting mixture was then directly purified on reverse phase prep. HPLC to afford title compound as white solid (30 mg, 54%).

MS (ESI) *m/z* 884 $[M + H]^+$.

Example IO

(2S,3R)-3-methoxy-1-((S)-6-(5-(6-(4-(2-((1R,3S,4S)-2-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-2-azabicyclo[2.2.1]heptan-3-yl)-1H-imidazol-5-yl)phenyl)naphthalen-2-yl)-1H-imidazol-2-yl)-5-azaspiro[2.4]heptan-5-yl)-1-oxobutan-2-ylcarbamic acid methyl ester



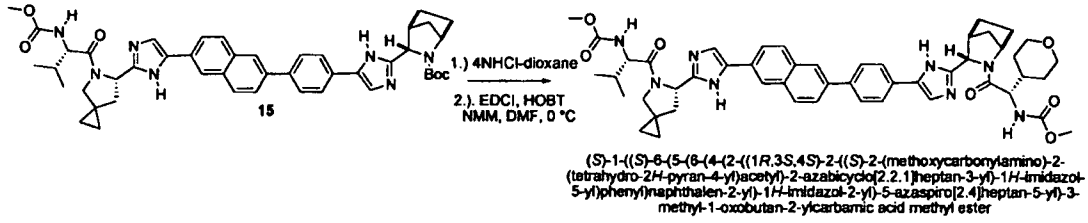
To compound **14** (50 mg, 0.064mmol) in dichloromethane (0.8 mL) was added 4M HCl in dioxane (0.8 mL) and the reaction mixture was cooled to 0°C and then stirred for 2 hours. After concentrated in vacuo to afford HCl salts.

To these HCl salts in DMF (0.8 mL) was added compound **8**(17 mg, 0.09 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (18 mg, 0.09 mmol) and hydroxybenzotriazole hydrate (HOBt), (13 mg, 0.09 mmol). The mixture was cooled down in an ice bath to 0°C and N-methylmorpholine (NMM)(18μL, 0.16 mmol) was added from a syringe to the mixture. The reaction content was stirred for 4 hours at room temperature. The resulting mixture was then directly purified on reverse phase prep. HPLC to afford title compound as white solid (30 mg, 54%).

MS (ESI) *m/z* 858 $[M + H]^+$.

Example IP

(S)-1-((S)-6-(5-(6-(4-(2-((1R,3S,4S)-2-((S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-azabicyclo[2.2.1]heptan-3-yl)-1H-imidazol-5-yl)phenyl)naphthalen-2-yl)-1H-imidazol-2-yl)-5-azaspiro[2.4]heptan-5-yl)-3-methyl-1-oxobutan-2-ylcarbamic acid methyl ester



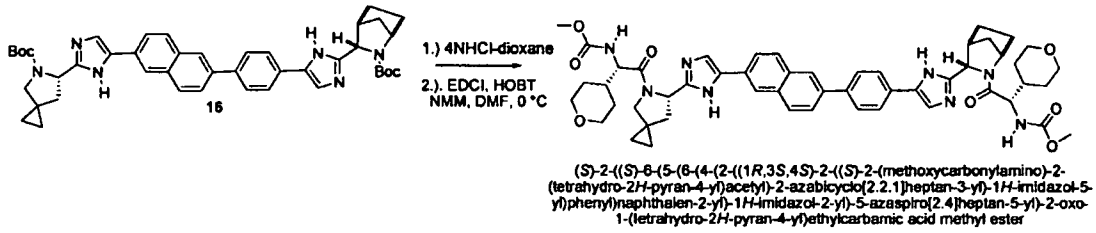
To compound **15** (50 mg, 0.064mmol) in dichloromethane (0.8 mL) was added 4M HCl in dioxane (0.8 mL) and the reaction mixture was cooled to 0°C and then stirred for 2 hours. After concentrated in vacuo to afford HCl salts.

To these HCl salts in DMF (0.8 mL) was added compound **3**(20 mg, 0.09 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (18 mg, 0.09 mmol) and hydroxybenzotriazole hydrate (HOBt), (13 mg, 0.09 mmol). The mixture was cooled down in an ice bath to 0°C and N-methylmorpholine (NMM)(20μL, 0.16 mmol) was added from a syringe to the mixture. The reaction content was stirred for 4 hours at room temperature. The resulting mixture was then directly purified on reverse phase prep. HPLC to afford title compound as white solid (25 mg, 45%).

MS (ESI) *m/z* 884 $[M + H]^+$.

Example IQ

(S)-2-((S)-6-(5-(6-(4-(2-((1R,3S,4S)-2-((S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-azabicyclo[2.2.1]heptan-3-yl)-1H-imidazol-5-yl)phenyl)naphthalen-2-yl)-1H-imidazol-2-yl)-5-azaspiro[2.4]heptan-5-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethylcarbamic acid methyl ester



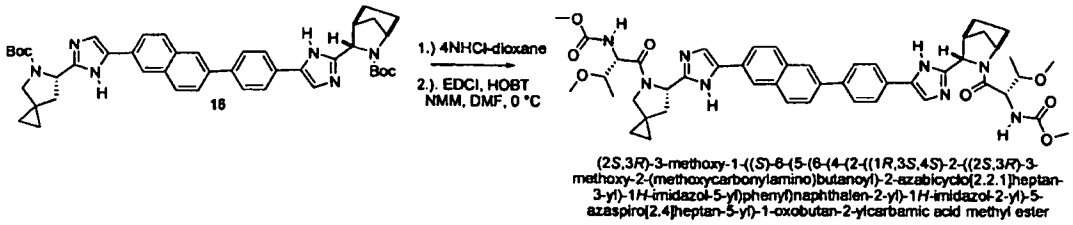
To compound **16** (50 mg, 0.069mmol) in dichloromethane (0.8 mL) was added 4M HCl in dioxane (0.8 mL) and the reaction mixture was cooled to 0°C and then stirred for 2 hours. After concentrated in vacuo to afford HCl salts.

To these HCl salts in DMF (0.8 mL) was added compound **3**(41 mg, 0.19 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (36 mg, 0.19 mmol) and hydroxybenzotriazole hydrate (HOBt), (26 mg, 0.19 mmol). The mixture was cooled down in an ice bath to 0°C and N-methylmorpholine (NMM)(25μL, 0.22 mmol) was added from a syringe to the mixture. The reaction content was stirred for 4 hours at room temperature. The resulting mixture was then directly purified on reverse phase prep. HPLC to afford title compound as white solid (28 mg, 44%).

MS (ESI) *m/z* 926 $[M + H]^+$.

Example IR

(2S,3R)-3-methoxy-1-((S)-6-(5-(6-(4-(2-((1R,3S,4S)-2-((2S,3R)-3-methoxy-2-(methoxycarbonylamino)butanoyl)-2-azabicyclo[2.2.1]heptan-3-yl)-1H-imidazol-5-yl)phenyl)naphthalen-2-yl)-1H-imidazol-2-yl)-5-azaspiro[2.4]heptan-5-yl)-1-oxobutan-2-ylcarbamic acid methyl ester



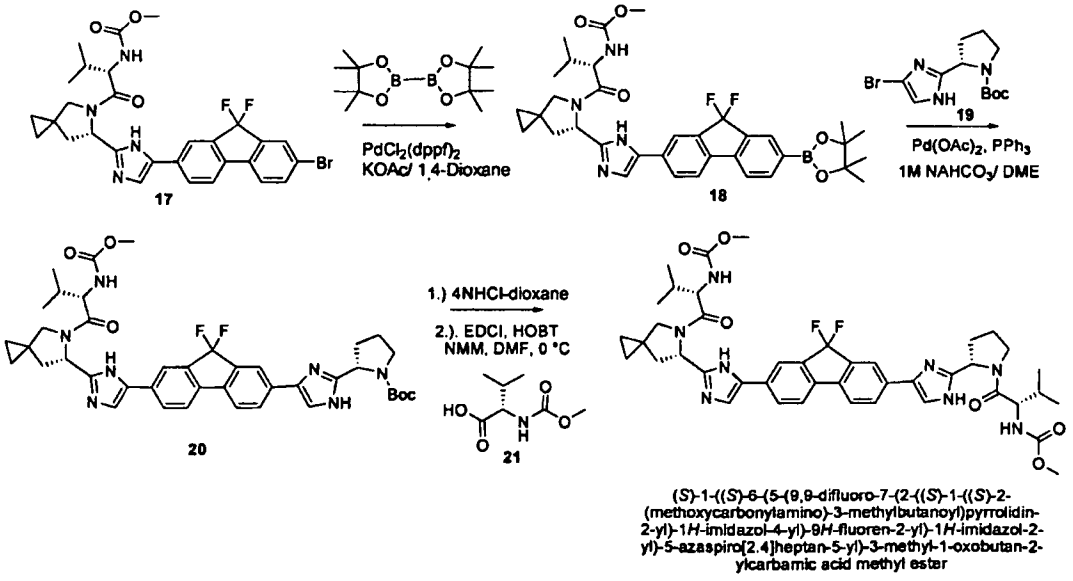
To compound **16** (50 mg, 0.069mmol) in dichloromethane (0.8 mL) was added 4M HCl in dioxane (0.8 mL) and the reaction mixture was cooled to 0°C and then stirred for 2 hours. After concentrated in vacuo to afford HCl salts.

To these HCl salts in DMF (0.8 mL) was added compound **8**(38 mg, 0.2 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (38 mg, 0.2 mmol) and hydroxybenzotriazole hydrate (HOBt), (27 mg, 0.2 mmol). The mixture was cooled down in an ice bath to 0°C and N-methylmorpholine (NMM) (55μL, 0.5 mmol) was added from a syringe to the mixture. The reaction content was stirred for 4 hours at room temperature. The resulting mixture was then directly purified on reverse phase prep. HPLC to afford title compound as white solid (29 mg, 40%).

MS (ESI) *m/z* 874 $[M + H]^+$.

Example IS

(S)-1-((S)-6-(5-(9,9-difluoro-7-(2-((S)-1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)pyrrolidin-2-yl)-1H-imidazol-4-yl)-9H-fluoren-2-yl)-1H-imidazol-2-yl)-5-azaspiro[2.4]heptan-5-yl)-3-methyl-1-oxobutan-2-ylcarbamic acid methyl ester



Compound **17** (1.2 g, 2 mmol), bis(pinacolato)diboron (1g, 4 mmol), potassium acetate (510 mg, 5.2 mmol), and $Pd(dppf)Cl_2$ (82 mg, 0.1 mmol) were all weighed out in a glass pressure vessel and anhydrous 1,4-Dioxane (10 mL) was added. The mixture was bubbled with nitrogen gas for about 5 min. The vessel was then capped and sealed and heated in an oil bath at 90°C overnight with continuous stirring. The reaction vessel was cooled down to room temperature and all volatiles were removed under reduced pressure and the resulting oil was subjected to silica gel chromatography with an eluent of ethyl acetate and hexane at a gradient of 0 – 50 % with an ISCO column (12 g silica gel). The fractions containing product were combined and the solvent was removed under reduced pressure to provide (**18**) (968 mg, 75 %).

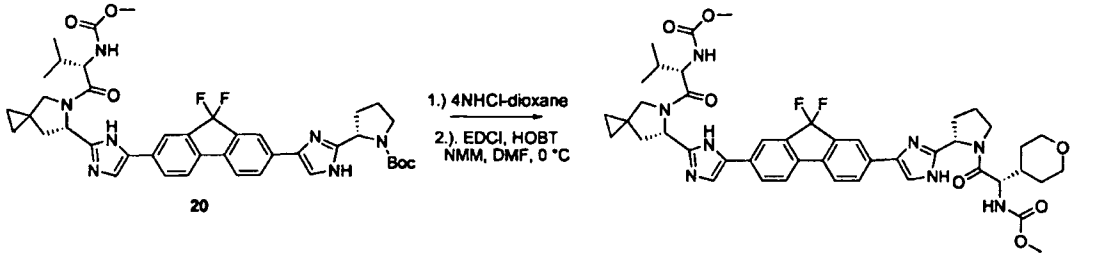
To compound **18** (950 mg, 1.47 mmol), compound **19** (488 mg, 1.54 mmol, .), Pd(OAc)2 (23mg, 0.1 mmol) and PPh3 (42mg, 0.16 mmol). DME (16 mL) was added and followed by 6 mL 1M NaHCO3 aqueous solution. The reaction was purged with Argon and heated to 90° C for 3 hours under Ar. The reaction was cooled to room temperature and concentrated down. EtOAc was added and washed with sat. NaHCO3 aqueous (2X) and sat. NaCl aqueous (1X). The organic layer was concentrated down after drying over sodium sulfate and subject to silica gel chromatography with an eluent of ethyl acetate and hexane at a gradient of 40 – 100 % with an ISCO column (12 g silica gel). The fractions containing product were combined and the solvent was removed under reduced pressure to provide product **20** (1g, 90 %). MS (ESI) *m/z* 757 $[M + H]^+$.

To compound **20** (50 mg, 0.066mmol) in dichloromethane (0.8 mL) was added 4M HCl in dioxane (0.8 mL) and the reaction mixture was cooled to 0°C and then stirred for 2 hours. After concentrated in vacuo to afford HCl salts.

To these HCl salts in DMF (0.8 mL) was added compound **21**(16 mg, 0.09 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (18 mg, 0.09 mmol) and hydroxybenzotriazole hydrate (HOBt), (13 mg, 0.09 mmol). The mixture was cooled down in an ice bath to 0°C and N-methylmorpholine (NMM)(20μL, 0.18 mmol) was added from a syringe to the mixture. The reaction content was stirred for 4 hours at room temperature. The resulting mixture was then directly purified on reverse phase prep. HPLC to afford title compound as white solid (33 mg, 62 %). MS (ESI) *m/z* 814 $[M + H]^+$.

Example IT

(S)-1-((S)-6-(5-(9,9-difluoro-7-(2-((S)-1-((S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)pyrrolidin-2-yl)-1H-imidazol-4-yl)-9H-fluoren-2-yl)-1H-imidazol-2-yl)-5-azaspiro[2.4]heptan-5-yl)-3-methyl-1-oxobutan-2-ylcarbamic acid methyl ester



20

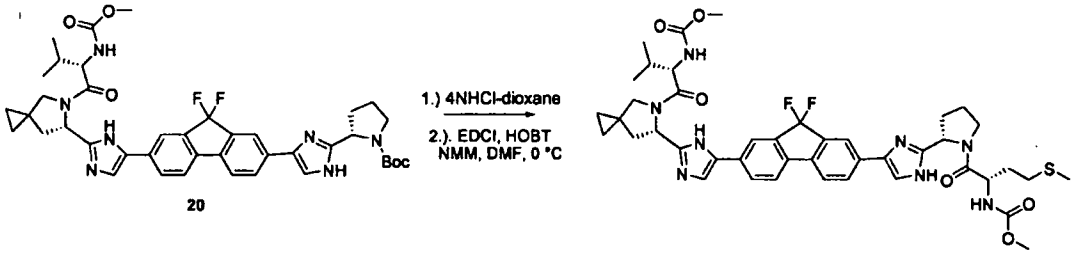
(*S*)-1-((*S*)-6-(5-(9,9-difluoro-7-(2-((*S*)-1-((*S*)-2-(methoxycarbonylamino)-2-(tetrahydro-2*H*-pyran-4-yl)acetyl)pyrrolidin-2-yl)-1*H*-imidazol-4-yl)-9*H*-fluoren-2-yl)-1*H*-imidazol-2-yl)-5-azaspiro[2.4]heptan-5-yl)-3-methyl-1-oxobutan-2-ylcarbamic acid methyl ester

To compound **20** (50 mg, 0.066mmol) in dichloromethane (0.8 mL) was added 4M HCl in dioxane (0.8 mL) and the reaction mixture was cooled to 0°C and then stirred for 2 hours. After concentrated in vacuo to afford HCl salts.

To these HCl salts in DMF (0.8 mL) was added compound **3**(20 mg, 0.09 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (18 mg, 0.09 mmol) and hydroxybenzotriazole hydrate (HOBt), (13 mg, 0.09 mmol). The mixture was cooled down in an ice bath to 0°C and N-methylmorpholine (NMM)(20μL, 0.18 mmol) was added from a syringe to the mixture. The reaction content was stirred for 4 hours at room temperature. The resulting mixture was then directly purified on reverse phase prep. HPLC to afford title compound as white solid (30 mg, 54 %). MS (ESI) *m/z* 856 $[M + H]^+$.

Example IU

(S)-1-((S)-6-(5-(9,9-difluoro-7-(2-((S)-1-((S)-2-(methoxycarbonylamino)-4-(methylthio)butanoyl)pyrrolidin-2-yl)-1H-imidazol-4-yl)-9H-fluoren-2-yl)-1H-imidazol-2-yl)-5-azaspiro[2.4]heptan-5-yl)-3-methyl-1-oxobutan-2-ylcarbamic acid methyl ester

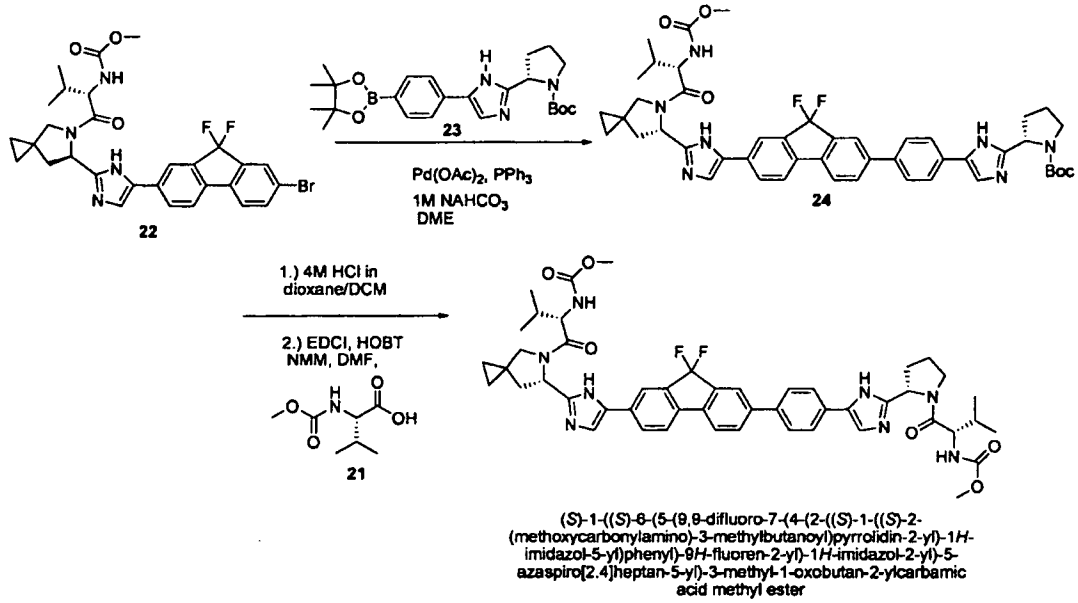


To compound **20** (50 mg, 0.066mmol) in dichloromethane (0.8 mL) was added 4M HCl in dioxane (0.8 mL) and the reaction mixture was cooled to 0°C and then stirred for 2 hours. After concentrated in vacuo to afford HCl salts.

To these HCl salts in DMF (0.8 mL) was added compound **7**(19 mg, 0.09 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (18 mg, 0.09 mmol) and hydroxybenzotriazole hydrate (HOBt), (13 mg, 0.09 mmol). The mixture was cooled down in an ice bath to 0°C and N-methylmorpholine (NMM)(20μL, 0.18 mmol) was added from a syringe to the mixture. The reaction content was stirred for 4 hours at room temperature. The resulting mixture was then directly purified on reverse phase prep. HPLC to afford title compound as white solid (30 mg, 55 %). MS (ESI) *m/z* 846 $[M + H]^+$.

Example IV

(S)-1-((S)-6-(5-(9,9-difluoro-7-(4-(2-((S)-1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)phenyl)-9H-fluoren-2-yl)-1H-imidazol-2-yl)-5-azaspiro[2.4]heptan-5-yl)-3-methyl-1-oxobutan-2-ylcarbamic acid methyl ester



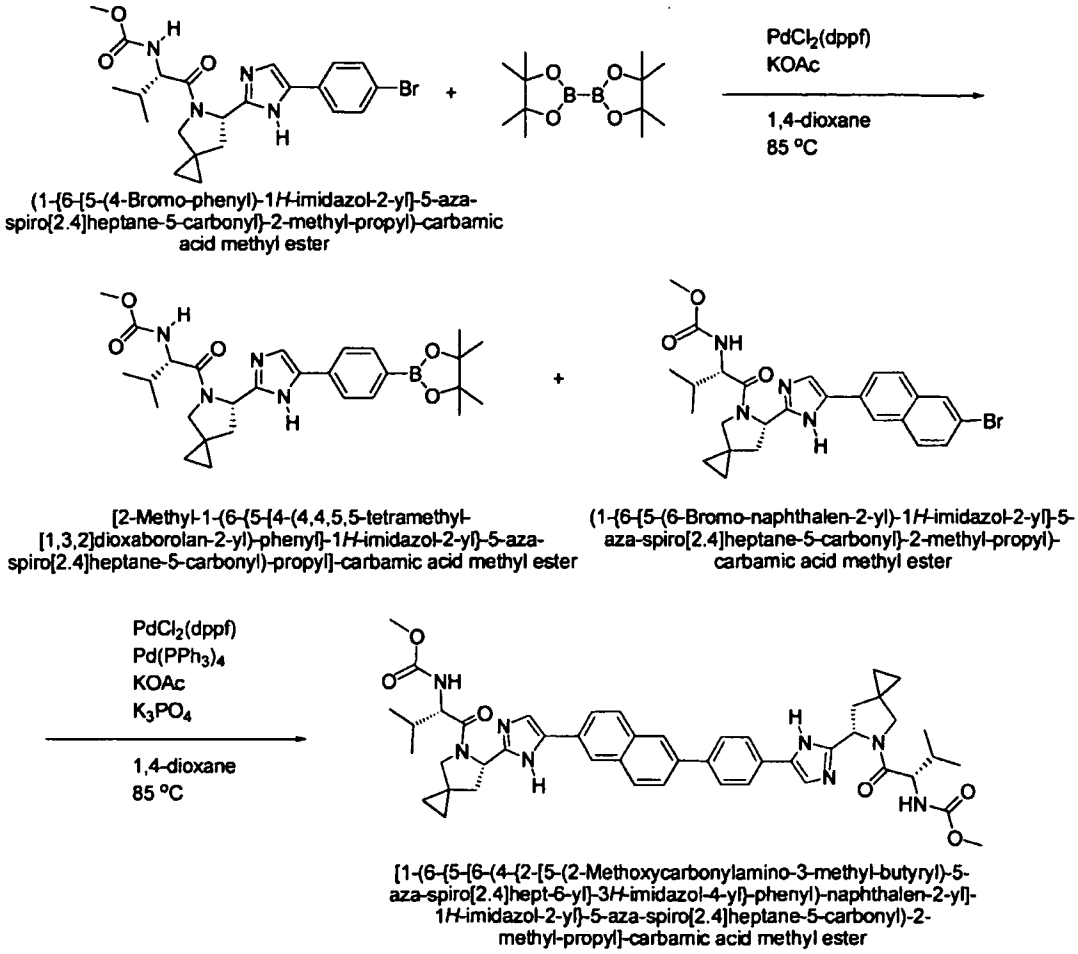
To compound **22** (320 mg, 0.53 mmol), compound **23** (282mg, 0.64 mmol, .), Pd(OAc)2 (8.4mg, 0.04 mmol) and PPh3 (16mg, 0.06 mmol). DME (5.5 mL) was added and followed by 2.2 mL 1M NaHCO3 aqueous solution. The reaction was purged with Argon and heated to 90° C for 3 hours under Ar. The reaction was cooled to room temperature and concentrated down. EtOAc was added and washed with sat. NaHCO3 aqueous (2X) and sat. NaCl aqueous (1X). The organic layer was concentrated down after drying over sodium sulfate and subject to silica gel chromatography with an eluent of ethyl acetate and hexane at a gradient of 40 – 100 % with an ISCO column (12 g silica gel). The fractions containing product were combined and the solvent was removed under reduced pressure to provide product **24** (266 mg, 60 %). MS (ESI) *m/z* 833 $[M + H]^+$.

To compound **24** (120 mg, 0.15mmol) in dichloromethane (1.5 mL) was added 4M HCl in dioxane (1.5 mL) and the reaction mixture was cooled to 0°C and then stirred for 2 hours. After concentrated in vacuo to afford HCl salts.

To these HCl salts in DMF (1.5 mL) was added compound **21**(35 mg, 0.2 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (38 mg, 0.2 mmol) and hydroxybenzotriazole hydrate (HOBt), (27 mg, 0.2 mmol). The mixture was cooled down in an ice bath to 0°C and N-methylmorpholine (NMM)(50μL, 0.45 mmol) was added from a syringe to the mixture. The reaction content was stirred for 4 hours at room temperature. The resulting

mixture was then directly purified on reverse phase prep. HPLC to afford title compound as white solid (65 mg, 56 %). MS (ESI) *m/z* 890 $[M + H]^+$.

Example IW



[1-(6-{5-[6-(4-{2-[5-(2-Methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester:

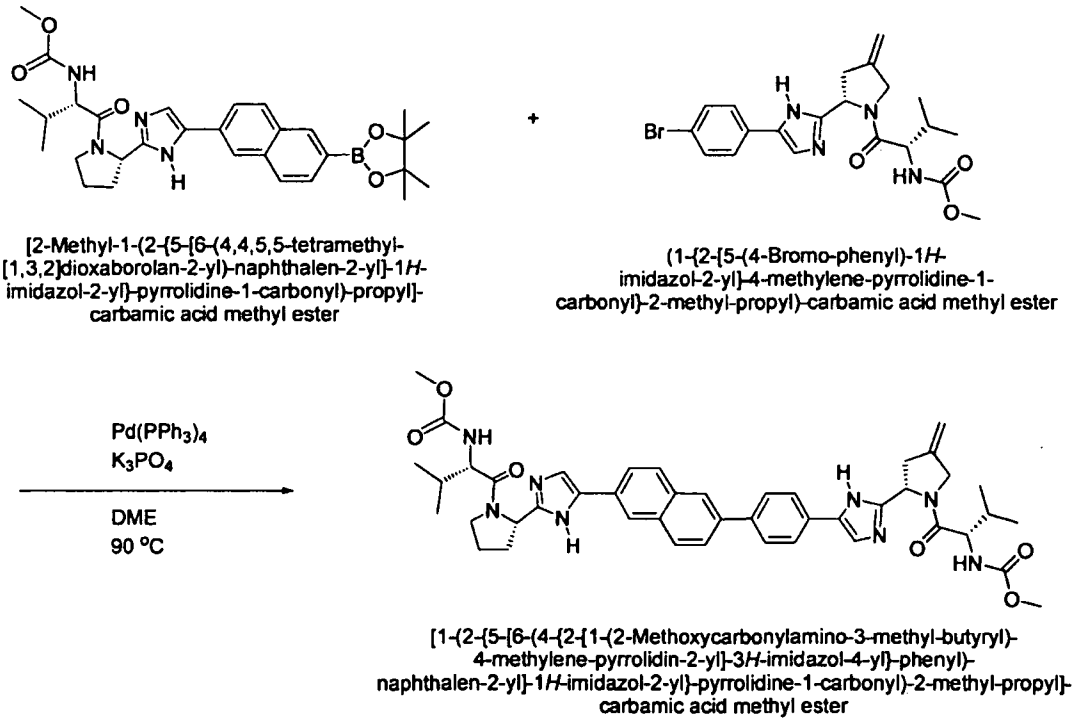
(1-{6-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (0.10g, 0.24mmol), bis(pinacolato)diboron (0.073g, 0.29mmol), Palladium dichloride(dppf) (0.018g, 0.024mmol), and potassium acetate (0.071g, 0.72mmol) were suspended in 1,4-dioxane (1.2mL) and degassed with argon for 30 minutes. The suspension was heated at 85° C for 2 hours. The mixture was cooled, (1-{6-[5-(6-Bromo-naphthalen-2-yl)-1H-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (0.182g, 0.346mmol) and aqueous potassium phosphate (2M, 0.84mL, 0.84mmol) was added. The mixture was returned to heat for 16 hours at which time,

Palladium(tetrakis)triphenylphosphine (0.014g, 0.012mmol) was added. The reaction was heated for an additional 4 hours. Upon completion, the crude reaction mixture was concentrated in vacuo and filtered through a Pd scavenging cartridge (Polymer Labs, PL-Guanidine MP SPE). The resulting slurry was diluted in DMF and purified by reverse phase HPLC (15-40% acetonitrile: water; 0.1% formic acid modifier), and lyophilized giving [1-(6-{5-[6-(4-{2-[5-(2-Methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (0.048g, 24%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 – 7.34 (m, 12H), 5.65 – 5.20 (m, 3H), 4.30 (s, 2H), 4.03 – 3.87 (m, 1H), 3.74 (d, 9H), 3.53 (s, 1H), 2.97 (s, 1H), 2.34 – 1.88 (m, 5H), 1.26 (s, 1H), 1.10 (m, 3H), 0.91 (m, 12H), 0.71 (s, 6H).

LCMS-ESI$^+$: calc'd for $C_{48}H_{56}N_8O_6$: 840.43 (M^+); Found: 841.9 ($M+H^+$).

Example IX



[2-Methyl-1-(2-{5-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-yl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-propyl]-carbamic acid methyl ester

(1-{2-[5-(4-Bromo-phenyl)-1*H*-imidazol-2-yl]-4-methylene-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

[1-(2-{5-[6-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-4-methylene-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester

(1-{2-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-4-methylene-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: This compound was prepared using the procedure used to prepare (1-{2-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester using 4-Methylene-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester.

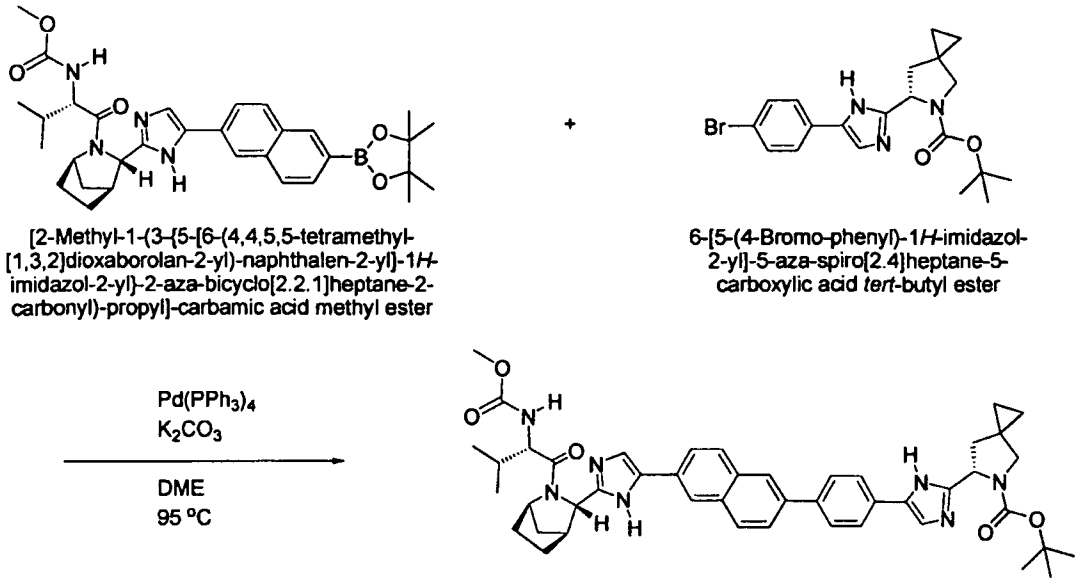
LCMS-ESI$^+$: calc'd for $C_{21}H_{25}BrN_4O_3$: 460.11 (M^+); Found: 463.61 ($M+H^+$).

[1-(2-{5-[6-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-4-methylene pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: This compound was prepared using the procedure used to prepare [1-(6-{5-[6-(4-{2-[2-(2-Methoxycarbonylamino-3-methyl-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester using [2-Methyl-1-(2-{5-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-propyl]-carbamic acid methyl ester (0.177g, 0.324mmol) and (1-{2-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-4-methylene-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (0.100g, 0.216mmol). Potassium phosphate (aqueous, 0.32mL, 0.648mmol) was substituted for potassium carbonate and the reaction was performed under an argon atmosphere. The crude reaction was purified by reverse phase HPLC (10-45% acetonitrile: water; 0.1% formic acid modifier), and lyophilized giving [1-(2-{5-[6-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-4-methylene pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (0.009g, 5%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 – 7.96 (m, 1H), 7.93 – 7.79 (m, 5H), 7.77 – 7.67 (m, 5H), 6.32 (s, 1H), 5.73 – 5.54 (m, 1H), 5.50 – 5.22 (m, 6H), 4.49 – 4.28 (m, 3H), 3.96 – 3.82 (m, 2H), 3.72 (s, 9H), 3.06 – 2.86 (m, 2H), 2.50 – 2.34 (m, 1H), 2.31 – 2.21 (m, 1H), 2.18 – 2.09 (m, 2H), 2.05 – 1.95 (m, 3H), 1.90 (s, 4H), 1.26 (s, 3H), 1.13 – 1.04 (m, 3H).

LCMS-ESI$^+$: calc'd for $C_{45}H_{52}N_8O_6$: 800.4 (M^+); Found: 801.90 ($M+H^+$).

Example IY



[2-Methyl-1-(3-{5-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-yl]-1*H*-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carbonyl)-propyl]-carbamic acid methyl ester

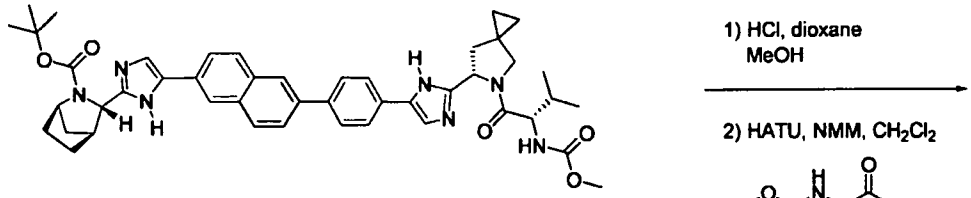
6-[5-(4-Bromo-phenyl)-1*H*-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carboxylic acid *tert*-butyl ester

6-{5-[4-(6-{2-[2-(2-Methoxycarbonylamino-3-methyl-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3*H*-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1*H*-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carboxylic acid *tert*-butyl ester

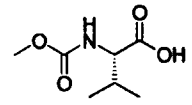
6-{5-[4-(6-{2-[2-(2-Methoxycarbonylamino-3-methyl-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carboxylic acid *tert*-butyl ester: This compound was prepared using the procedure used to prepare [1-(6-{5-[6-(4-{2-[2-(2-Methoxycarbonylamino-3-methyl-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (example EZ) using [2-Methyl-1-(3-{5-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-yl]-1H-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carbonyl)-propyl]-carbamic acid methyl ester (2.25mmol), 6-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carboxylic acid *tert*-butyl ester (2.39mmol), and potassium carbonate (2M, 4.3mL, 8.55mmol). The reaction was performed under an argon atmosphere. The crude reaction was diluted in ethyl acetate, washed with water and purified by normal phase silica chromatography (50-100% Hexanes:EthylAcetate+10%Methanol). 6-{5-[4-(6-{2-[2-(2-Methoxycarbonylamino-3-methyl-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carboxylic acid *tert*-butyl ester (1.05g, 60%) was obtained as a tan solid.

LCMS-ESI$^+$: calc'd for $C_{46}H_{53}N_7O_5$: 783.41 (M^+); Found: 784.35 ($M+H^+$).

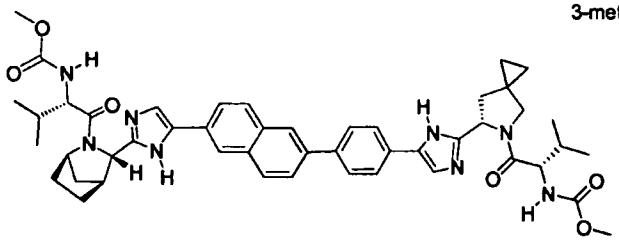
Example IZ



3-{5-[6-(4-{2-[5-(2-Methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3*H*-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1*H*-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester



2-Methoxycarbonylamino-3-methyl-butyric acid



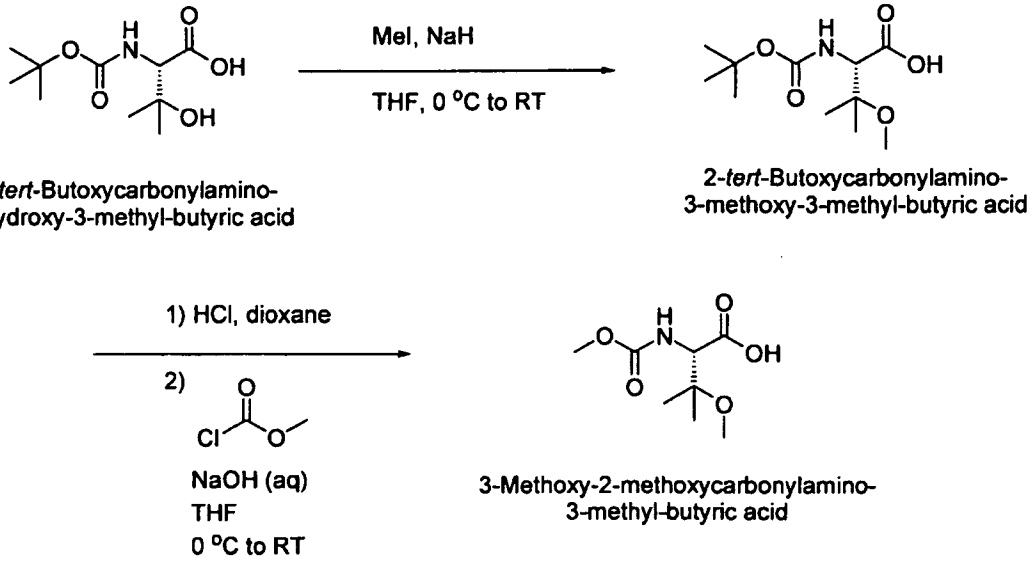
[1-(3-{5-[6-(4-{2-[5-(2-Methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3*H*-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1*H*-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester

[1-(3-{5-[6-(4-{2-[5-(2-Methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: This compound was prepared using the procedure used to prepare [1-(6-{5-[4-(6-{2-[2-(2-Cyclopropyl-2-methoxycarbonylamino-acetyl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester using 2-Methoxycarbonylamino-3-methyl-butyric acid to provide [1-(3-{5-[6-(4-{2-[5-(2-Methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (0.070g, 65%) as a white powder.

^{1}H-NMR: 400 MHz, (DMSO-d_6) δ: 11.75 (s, 1H), 11.72 (s, 1H), 8.24 (s, 1H), 8.15 (d, 1H), 7.93-7.74 (m, 8H), 7.63 (s, 1H), 7.54 (s, 1H), 7.30 (d, 1H), 7.16 (d, 1H), 5.22 (t, 1H), 4.52-4.50 (m, 2H), 4.16 (t, 1H), 4.00 (t, 1H), 3.81 (d, 1H), 3.75 (d, 1H), 3.72 (s, 3H), 3.31 (s, 3H), 2.55 (m, 1H), 2.32-1.41 (m, 10H), 1.01-0.57 (m, 16H).

LCMS-ESI$^+$: calc'd for $C_{48}H_{56}N_8O_6$: 840.43 (M^+); Found: 841.99 ($M+H^+$).

Example JA



2-*tert*-Butoxycarbonylamino-3-hydroxy-3-methyl-butyric acid

2-*tert*-Butoxycarbonylamino-3-methoxy-3-methyl-butyric acid

3-Methoxy-2-methoxycarbonylamino-3-methyl-butyric acid

2-*tert*-Butoxycarbonylamino-3-methoxy-3-methyl-butyric acid:

2-*tert*-Butoxycarbonylamino-3-hydroxy-3-methyl-butyric acid (1.0g, 4.29mmol) was dissolved in THF (14mL) and cooled to 0° C in an external ice/brine bath. MeI (2.13mL, 34.3mmol) was added at 0° C. Solid NaH (60% dispersion in mineral oil, 0.514g, 12.87mmol) was added slowly at 0° C. Upon completion of the addition, the solution was removed from the ice bath and allowed to warm to room temperature, and stirred. After 18 hours, the crude reaction mixture was diluted in ethyl acetate and water was added slowly with stirring. The quenched mixture was concentrated in vacuo and partitioned between diethyl ether and water. The ether layer was extracted with sodium bicarbonate twice. The combined bicarbonate layers were acidified with aqueous citric acid to pH 3 and extracted three times with ethyl acetate. The combined ethyl acetate layers were washed with water, sodium thiosulfate, water, dried with sodium sulfate and concentrated to yield 2-*tert*-Butoxycarbonylamino-3-methoxy-3-methyl-butyric acid (0.99g, 94%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76 – 3.66 (m, 3H), 3.29 (s, 1H), 1.50 (s, 3H), 1.45 (s, 9H), 1.33 (s, 3H).

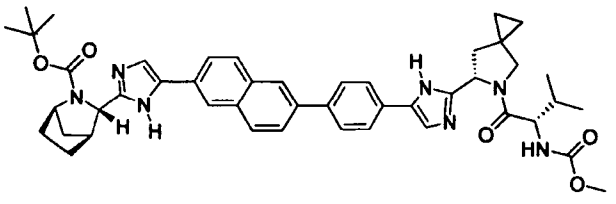
3-Methoxy-2-methoxycarbonylamino-3-methyl-butyric acid:

2-*tert*-Butoxycarbonylamino-3-methoxy-3-methyl-butyric acid was dissolved in dioxane (40mL) and HCl (4N in dioxane, 5.4mL, 21.6mmol) was added at room temperature. The resulting solution was stirred at room temperature for 18 hours and the concentrated to dryness. The solid was dissolved in THF (14mL) and cooled to 0° C in an external ice/brine bath. Aqueous sodium hydroxide (6.25M, 1.9mL, 11.76mmol) and methyl chloroformate (0.5mL, 5.88mmol) were

added at 0° C. Upon completion of the addition, the solution was removed from the ice bath and allowed to warm to room temperature, and stirred. After 18 hours, the crude reaction mixture was adjusted to pH 1 with 1N HCl and extracted twice with diethyl ether. The combined organic layers were washed with brine, dried with magnesium sulfate and concentrated to give 3-Methoxy-2-methoxycarbonylamino-3-methyl-butyric acid (0.653g, 65%) as an off-white solid.

^{1}H NMR (400 MHz, acetone) δ 3.76 (s, 3H), 3.60 (s, 3H), 3.22 (s, 3H), 3.18 (s, 3H), 1.37 – 1.31 (m, 1H).

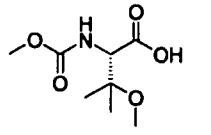
Example JB



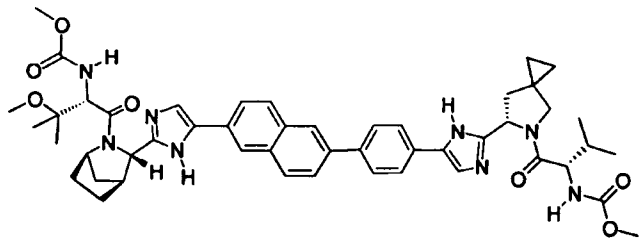
3-{5-[6-(4-{2-[5-(2-Methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3*H*-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1*H*-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester

1) HCl, dioxane
MeOH

2) HATU, NMM, CH_2Cl_2



3-Methoxy-2-methoxycarbonylamino-3-methyl-butyric acid



[2-Methoxy-1-(3-{5-[6-(4-{2-[5-(2-methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3*H*-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1*H*-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester

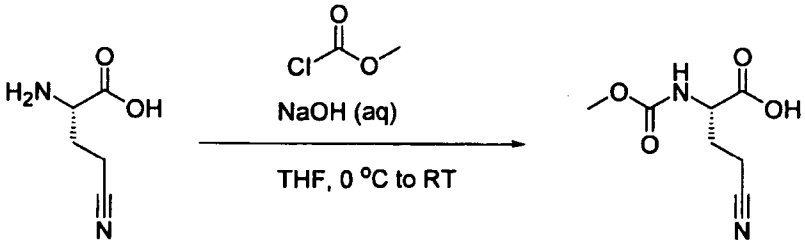
[2-Methoxy-1-(3-{5-[6-(4-{2-[5-(2-methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: This compound was prepared using the procedure used to prepare [1-(6-{5-[4-(6-{2-[2-(2-Cyclopropyl-2-methoxycarbonylamino-acetyl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (example from JJC) using 3-Methoxy-2-methoxycarbonylamino-3-methyl-butyric acid (0.020g, 0.096mmol) to provide [2-Methoxy-1-(3-{5-[6-(4-{2-[5-(2-methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3H-

imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (0.019g, 35%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 – 7.88 (m, 4H), 7.84 – 7.35 (m, 8H), 5.81 – 5.33 (m, 2H), 4.88 – 4.57 (m, 2H), 4.34 (s, 1H), 3.91 – 3.54 (m, 9H), 3.46 – 3.16 (m, 4H), 3.09 – 2.82 (m, 1H), 2.24 (dd, 2H), 1.93 (m, 6H), 1.61 (s, 1H), 1.47 – 1.17 (m, 7H), 1.11 (d, 1H), 1.02 – 0.83 (m, 7H), 0.72 (s, 3H).

LCMS-ESI$^+$: calc'd for $C_{49}H_{58}N_8O_7$: 870.44 (M^+); Found: 871.90 ($M+H^+$).

Example JC



2-Amino-4-cyano-butyric acid

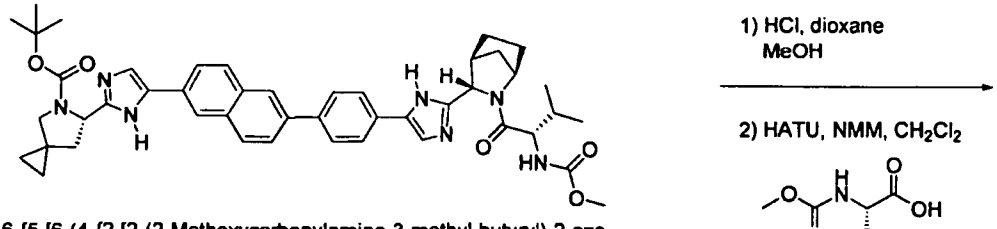
4-Cyano-2-methoxycarbonylamino-butyric acid

4-Cyano-2-methoxycarbonylamino-butyric acid:

This compound was prepared using the procedure used to prepare 3-Methoxy-2-methoxycarbonylamino-3-methyl-butyric acid using 2-Amino-4-cyano-butyric acid.

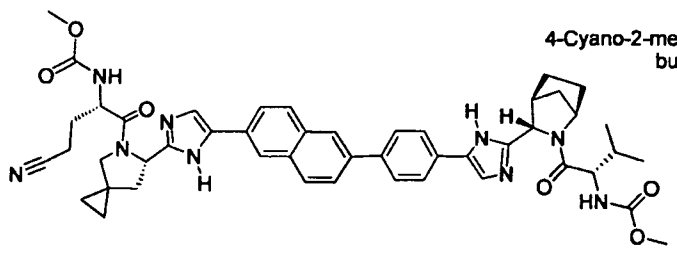
LCMS-ESI$^+$: calc'd for $C_7H_{10}N_2O_4$: 186.06 (M^+); Found: 187.09 ($M+H^+$).

Example JD



6-{5-[6-(4-{2-[2-(2-Methoxycarbonylamino-3-methyl-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3*H*-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1*H*-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carboxylic acid *tert*-butyl ester

4-Cyano-2-methoxycarbonylamino-butyric acid



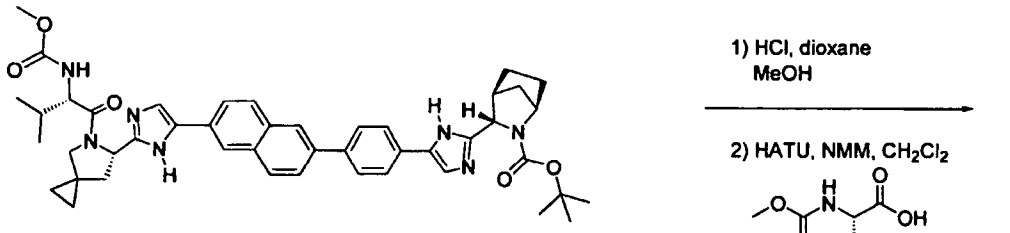
[3-Cyano-1-(6-{5-[6-(4-{2-[2-(2-methoxycarbonylamino-3-methyl-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3*H*-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1*H*-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carbonyl)-propyl]-carbamic acid methyl ester

[3-Cyano-1-(6-{5-[6-(4-{2-[2-(2-methoxycarbonylamino-3-methyl-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carbonyl)-propyl]-carbamic acid methyl ester: This compound was prepared using the procedure used to prepare [1-(6-{5-[4-(6-{2-[2-(2-Cyclopropyl-2-methoxycarbonylamino-acetyl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (example from JJC) using 4-Cyano-2-methoxycarbonylamino-butyric acid to provide [3-Cyano-1-(6-{5-[6-(4-{2-[2-(2-methoxycarbonylamino-3-methyl-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carbonyl)-propyl]-carbamic acid methyl ester (0.015g, 28%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 – 8.10 (m, 1H), 8.05 – 7.84 (m, 1H), 7.80 – 7.62 (m, 8H), 7.53 (d, 2H), 5.47 – 5.22 (m, 1H), 4.92 – 4.61 (m, 1H), 4.49 (d, 2H), 4.25 (s, 2H), 4.10 (d, 2H), 3.79 (s, 2H), 3.70 – 3.42 (m, 6H), 3.32 – 3.23 (m, 2H), 3.00 – 2.85 (m, 1H), 2.59 – 2.06 (m, 4H), 2.02 – 1.79 (m, 3H), 1.75 – 1.60 (m, 2H), 1.50 – 1.38 (m, 1H), 1.18 (s, 3H), 1.06 – 0.77 (m, 6H), 0.72 – 0.50 (m, 3H).

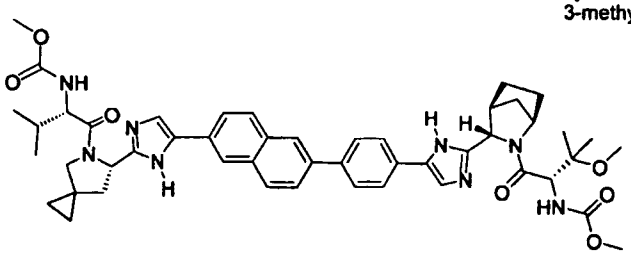
LCMS-ESI$^+$: calc'd for $C_{48}H_{53}N_9O_6$: 851.41 (M^+); Found: 852.90 ($M+H^+$).

Example JE



3-{5-[4-(6-{2-[5-(2-Methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3*H*-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1*H*-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester

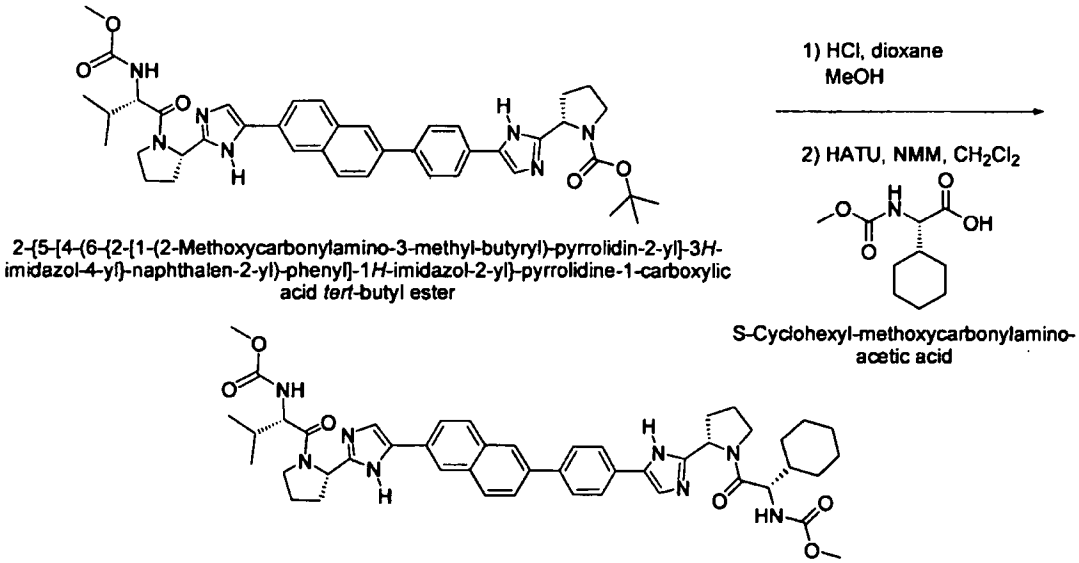
3-Methoxy-2-methoxycarbonylamino-3-methyl-butyric acid



[2-Methoxy-1-(3-{5-[4-(6-{2-[5-(2-methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3*H*-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1*H*-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester

[2-Methoxy-1-(3-{5-[4-(6-{2-[5-(2-methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: This compound was prepared using the procedure used to prepare [1-(6-{5-[4-(6-{2-[2-(2-Cyclopropyl-2-methoxycarbonylamino-acetyl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (example from JJC) using 3-Methoxy-2-methoxycarbonylamino-3-methyl-butyric acid (0.020g, 0.096mmol) to provide [2-Methoxy-1-(3-{5-[4-(6-{2-[5-(2-methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (0.016g, 29%) as a white solid.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 – 7.88 (m, 4H), 7.84 – 7.35 (m, 8H), 5.81 – 5.33 (m, 2H), 4.88 – 4.57 (m, 2H), 4.34 (s, 1H), 3.91 – 3.54 (m, 9H), 3.46 – 3.16 (m, 4H), 3.09 – 2.82 (m, 1H), 2.24 (dd, 2H), 1.93 (m, 6H), 1.61 (s, 1H), 1.47 – 1.17 (m, 7H), 1.11 (d, 1H), 1.02 – 0.83 (m, 7H), 0.72 (s, 3H).
LCMS-ESI$^+$: calc'd for $C_{49}H_{58}N_8O_7$: 870.44 (M^+); Found: 871.47 ($M+H^+$).

Example JF



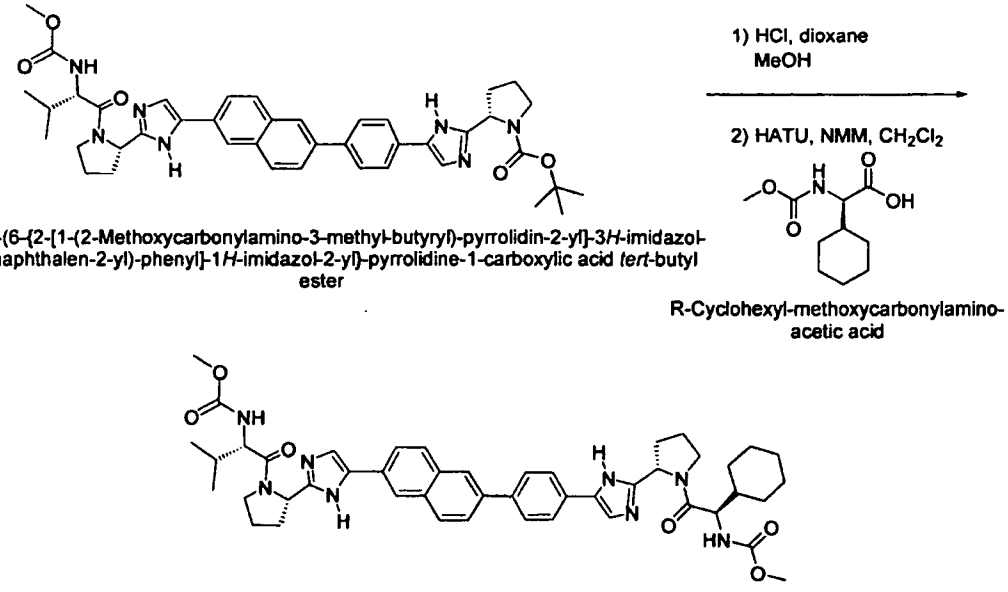
2-{5-[4-(6-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester

S-Cyclohexyl-methoxycarbonylamino-acetic acid

[1-(2-{5-[6-(4-{2-[1-(2-Cyclohexyl-2-methoxycarbonylamino-acetyl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester

[1-(2-{5-[6-(4-{2-[1-(2-Cyclohexyl-2-methoxycarbonylamino-acetyl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: This compound was prepared using the procedure used to prepare [1-(6-{5-[4-(6-{2-[2-(2-Cyclopropyl-2-methoxycarbonylamino-acetyl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (example from JJC) using S-Cyclohexyl-methoxycarbonylamino-acetic acid (0.022g, 0.102mmol) to provide [1-(2-{5-[6-(4-{2-[1-(2-Cyclohexyl-2-methoxycarbonylamino-acetyl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (0.036g, 28%) as a white solid.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.62 (m, 10H), 7.30 (s, 1H), 7.25 (s, 1H), 5.60 (d, 1H), 5.53 (d, 1H), 5.41 (d, 1H), 5.31 (dd, 1H), 4.38 (t, 1H), 4.25 (t, 1H), 4.03 – 3.74 (m, 5H), 3.72 – 3.65 (m, 6H), 2.97 – 2.65 (m, 2H), 2.39 (m, 1H), 2.13 (m, 6H), 1.96 – 1.63 (m, 6H), 1.36 – 0.99 (m, 6H), 0.93 (dd, 6H).
LCMS-ESI$^+$: calc'd for $C_{47}H_{56}N_8O_6$: 828.43 (M^+); Found: 829.70 ($M+H^+$).

Example JG



2-{5-[4-(6-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester

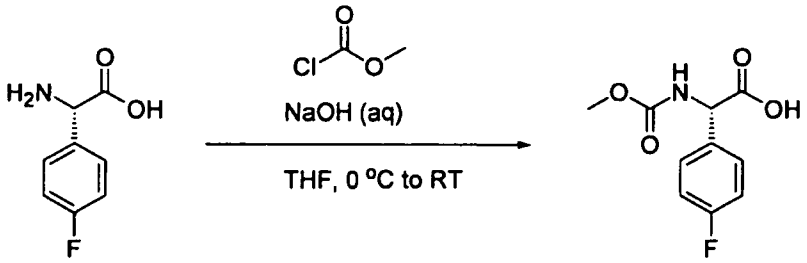
R-Cyclohexyl-methoxycarbonylamino-acetic acid

[1-(2-{5-[6-(4-{2-[1-(2-Cyclohexyl-2-methoxycarbonylamino-acetyl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester

[1-(2-{5-[6-(4-{2-[1-(2-Cyclohexyl-2-methoxycarbonylamino-acetyl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: This compound was prepared using the procedure used to prepare [1-(6-{5-[4-(6-{2-[2-(2-Cyclopropyl-2-methoxycarbonylamino-

acetyl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (example from JJC) using R-Cyclohexyl-methoxycarbonylamino-acetic acid (0.041g, 0.191mmol) to provide [1-(2-{5-[6-(4-{2-[1-(2-Cyclohexyl-2-methoxycarbonylamino-acetyl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (0.047g, 59%) as a white solid.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.62 (m, 10H), 7.30 (s, 1H), 7.25 (s, 1H), 5.60 (d, 1H), 5.53 (d, 1H), 5.41 (d, 1H), 5.31 (dd, 1H), 4.38 (t, 1H), 4.25 (t, 1H), 4.03 – 3.74 (m, 5H), 3.72 – 3.65 (m, 6H), 2.97 – 2.65 (m, 2H), 2.39 (m, 1H), 2.13 (m, 6H), 1.96 – 1.63 (m, 6H), 1.36 – 0.99 (m, 6H), 0.93 (dd, 6H).
LCMS-ESI$^+$: calc'd for $C_{47}H_{56}N_8O_6$: 828.43 (M^+); Found: 829.70 ($M+H^+$).

Example JH

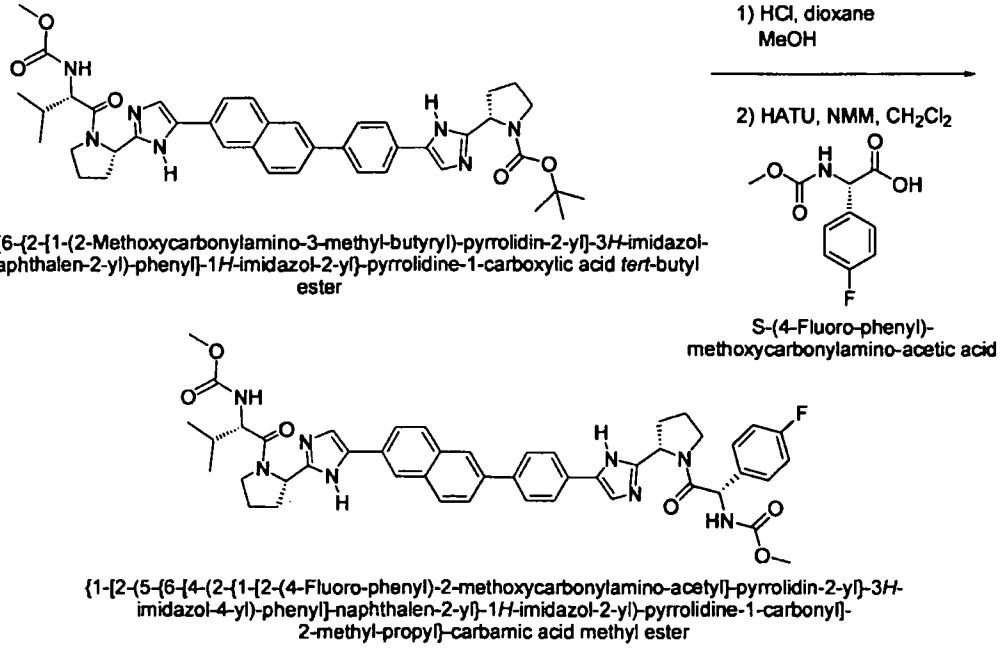


S-Amino-(4-fluoro-phenyl)-acetic acid

S-(4-Fluoro-phenyl)-methoxycarbonylamino-acetic acid

S-(4-Fluoro-phenyl)-methoxycarbonylamino-acetic acid: This compound was prepared using the procedure used to prepare 3-Methoxy-2-methoxycarbonylamino-3-methyl-butyric acid using S-Amino-(4-fluoro-phenyl)-acetic acid to give S-(4-Fluoro-phenyl)-methoxycarbonylamino-acetic acid (0.560g, 82%).
LCMS-ESI$^+$: calc'd for $C_{10}H_{10}FNO_4$: 227.06 (M^+); Found: 227.84 ($M+H^+$).

Example JI



2-{5-[4-(6-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester

S-(4-Fluoro-phenyl)-methoxycarbonylamino-acetic acid

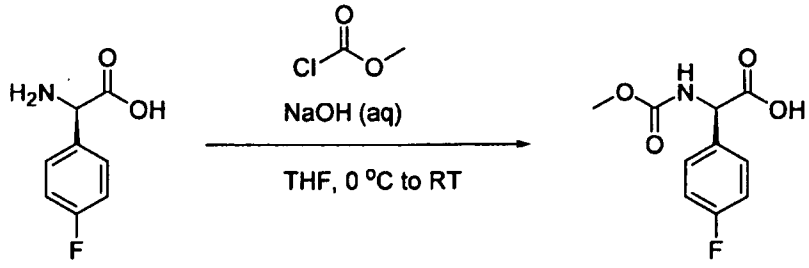
{1-[2-(5-{6-[4-(2-{1-[2-(4-Fluoro-phenyl)-2-methoxycarbonylamino-acetyl]-pyrrolidin-2-yl}-3*H*-imidazol-4-yl)-phenyl]-naphthalen-2-yl}-1*H*-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester

{1-[2-(5-{6-[4-(2-{1-[2-(4-Fluoro-phenyl)-2-methoxycarbonylamino-acetyl]-pyrrolidin-2-yl}-3H-imidazol-4-yl)-phenyl]-naphthalen-2-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester: This compound was prepared using the procedure used to prepare [1-(6-{5-[4-(6-{2-[2-(2-Cyclopropyl-2-methoxycarbonylamino-acetyl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (example from JJC) using S-(4-Fluoro-phenyl)-methoxycarbonylamino-acetic acid (0.023g, 0.100mmol) to provide {1-[2-(5-{6-[4-(2-{1-[2-(4-Fluoro-phenyl)-2-methoxycarbonylamino-acetyl]-pyrrolidin-2-yl}-3H-imidazol-4-yl)-phenyl]-naphthalen-2-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (0.015g, 27%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 – 7.71 (m, 8H), 7.55 – 6.93 (m, 8H), 6.06 (d, 1H), 5.43 (dd, 1H), 5.30 (m, 3H), 4.34 (t, 1H), 3.85 – 3.77 (m, 2H), 3.74 – 3.47 (d, 6H), 3.25 – 2.92 (m, 4H), 2.36 (s, 1H), 2.23 – 1.98 (m, 7H), 1.05 (t, 1H), 0.88 (t, 6H).

LCMS-ESI$^+$: calc'd for $C_{47}H_{49}FN_8O_6$: 840.38 (M^+); Found: 841.42 ($M+H^+$).

Example JJ



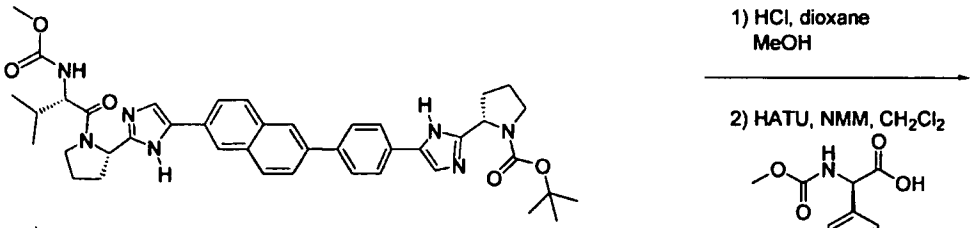
R-Amino-(4-fluoro-phenyl)-acetic acid

R-(4-Fluoro-phenyl)-methoxycarbonylamino-acetic acid

R-(4-Fluoro-phenyl)-methoxycarbonylamino-acetic acid: This compound was prepared using the procedure used to prepare 3-Methoxy-2-methoxycarbonylamino-3-methyl-butyric acid using R-Amino-(4-fluoro-phenyl)-acetic acid to give R-(4-Fluoro-phenyl)-methoxycarbonylamino-acetic acid (0.575g, 84%)

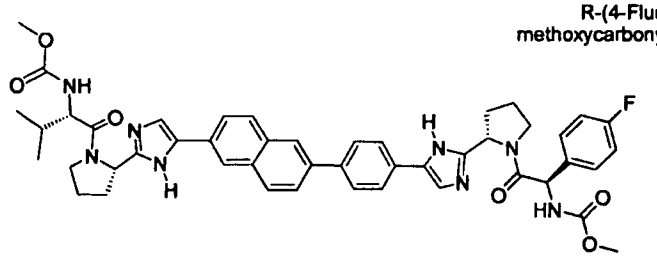
LCMS-ESI$^+$: calc'd for $C_{10}H_{10}FNO_4$: 227.06 (M^+); Found: 227.84 ($M+H^+$).

Example JK



2-{5-[4-(6-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester

R-(4-Fluoro-phenyl)-methoxycarbonylamino-acetic acid



{1-[2-(5-{6-[4-(2-{1-[2-(4-Fluoro-phenyl)-2-methoxycarbonylamino-acetyl]-pyrrolidin-2-yl}-3*H*-imidazol-4-yl)-phenyl]-naphthalen-2-yl}-1*H*-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester

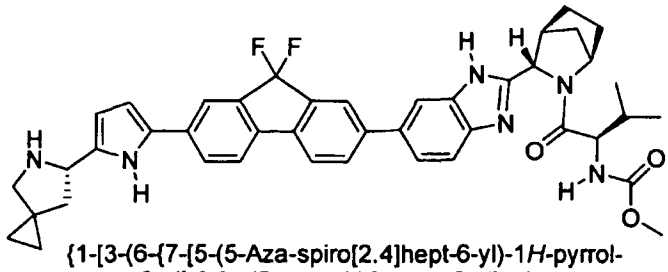
{1-[2-(5-{6-[4-(2-{1-[2-(4-Fluoro-phenyl)-2-methoxycarbonylamino-acetyl]-pyrrolidin-2-yl}-3H-imidazol-4-yl)-phenyl]-naphthalen-2-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester: This compound was prepared using the procedure used to prepare [1-(6-{5-[4-(6-{2-[2-(2-Cyclopropyl-2-methoxycarbonylamino-acetyl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-

imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (example from JJC) using R-(4-Fluoro-phenyl)-methoxycarbonylamino-acetic acid (0.023g, 0.100mmol) to provide {1-[2-(5-{6-[4-(2-{1-[2-(4-Fluoro-phenyl)-2-methoxycarbonylamino-acetyl]-pyrrolidin-2-yl}-3H-imidazol-4-yl)-phenyl]-naphthalen-2-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (0.008g, 14%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 – 7.71 (m, 8H), 7.55 – 6.93 (m, 8H), 6.06 (d, 1H), 5.43 (dd, 1H), 5.30 (m, 3H), 4.34 (t, 1H), 3.85 – 3.77 (m, 2H), 3.74 – 3.47 (d, 6H), 3.25 – 2.92 (m, 4H), 2.36 (s, 1H), 2.23 – 1.98 (m, 7H), 1.05 (t, 1H), 0.88 (t, 6H).

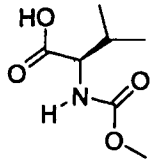
LCMS-ESI$^+$: calc'd for $C_{47}H_{49}FN_8O_6$: 840.38 (M^+); Found: 841.27 ($M+H^+$).

Example JL



{1-[3-(6-{7-[5-(5-Aza-spiro[2.4]hept-6-yl)-1*H*-pyrrol-2-yl]-9,9-difluoro-9*H*-fluoren-2-yl}-1*H*-benzoimidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester

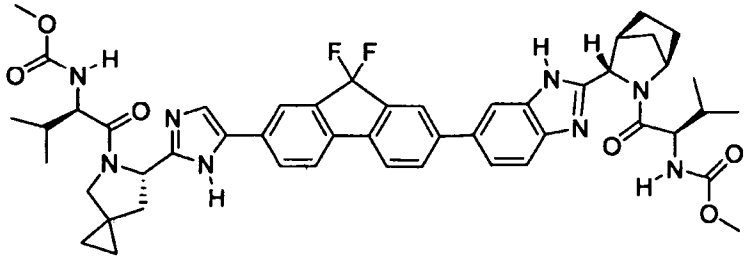
1. Pd/C, H_2, wet iPA
2. ECDI, HOBt, DIEPA, DMF



2-Methoxycarbonylamino-3-methyl-butyric acid

ECDI, HOBt

DIEPA, DMF

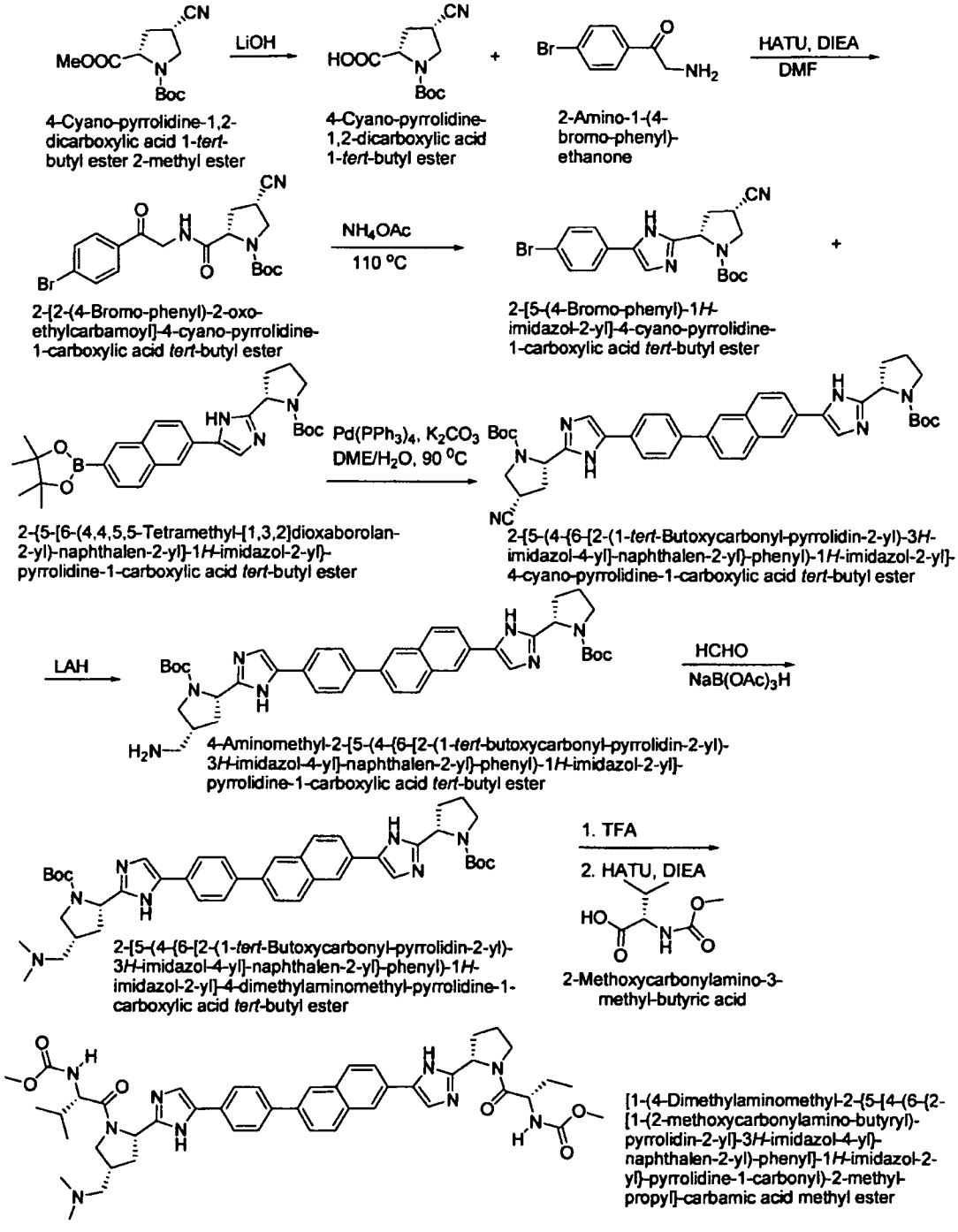


(1-{3-[6-(9,9-Difluoro-7-{2-[5-(2-methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3*H*-imidazol-4-yl}-9*H*-fluoren-2-yl)-1*H*-benzoimidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

(1-{3-[6-(9,9-Difluoro-7-{2-[5-(2-methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3H-imidazol-4-yl}-9H-fluoren-2-yl)-1H-benzoimidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester was prepared in a similar manner as Example C to give title compound as a white powder (68 mg).

^{1}H-NMR: 300 MHz, (DMSO-d_6) δ: 12.56 (d, J=13.5Hz, 0.5H), 12.05 (dd, 1H), 11.84 (s, 0.5H), 8.1 – 7.1 (m, 12H), 5.71 (d, 0.5H), 5.27 (s, 0.5H), 5.19 (d, 0.5H), 4.70 (s, 0.5H), 4.64 (s, 0.5H), 4.49 (s, 0.5H), 4.2-3.9(m, 2H), 3.6-3.2 (m, 20H), 2.8-1.1 (m, 12H), 0.9-0.4 (m , 16H).
LCMS-ESI$^+$: calc'd for $C_{49}H_{54}F_2N_8O_6$: 890.0 (M+H$^+$); Found: 889.4 (M+H$^+$).

Example JM



$LiOH.H_2O$ (167 mg, 3.98 mmol) was added to 4-cyano-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (674 mg, 2.65 mmol) in methanol (5 mL) solution. The reaction was stirred at room temperature overnight. The reaction mixture was concentrated down. The crude is used in next step reaction.

2-Amino-1-(4-bromo-phenyl)-ethanone HCl salt (664 mg, 2.65 mmol) was dissolved in DMF (10 mL) and to this solution was added 4-Cyano-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester crude from the previous step, diisopropyl ethylamine (0.93 mL, 5.3 mmol), followed by HATU (1 g, 2.65 mmol). Reaction mixture was stirred at 0 ^{0}C for 30 minutes. The reaction mixture was dissolved in ethyl acetate and washed with dilute sodium bicarbonate solution. The organic layer was dried (MgSO4), concentrated and purified by flash column chromatography (silica gel, 20 to 80% ethyl acetate/hexane) to give 2-[2-(4-Bromo-phenyl)-2-oxo-ethylcarbamoyl]-4-cyano-pyrrolidine-1-carboxylic acid *tert*-butyl ester (1.05 g, yield 91%). LCMS-ESI$^-$: calc'd for $C_{19}H_{22}BrN_3O_4$: 435.08; Found: 458.0 ($M+Na^+$).

A mixture of 2-[2-(4-Bromo-phenyl)-2-oxo-ethylcarbamoyl]-4-cyano-pyrrolidine-1-carboxylic acid *tert*-butyl ester (1.05 g, 2.4 mmol) and ammonia acetate (3.7 g, 20 eq.) in Xylene (2 mL) was heated in microwave at 110 ^{0}C for 2 hours. The mixture was concentrated and purified by flash column chromatography (silica gel, 20 to 80% ethyl acetate/hexane) to give 2-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-4-cyano-pyrrolidine-1-carboxylic acid *tert*-butyl ester (356 mg, containing 15% starting material, yield 35%). LCMS-ESI$^-$: calc'd for $C_{19}H_{21}BrN_4O_2$: 417.30; Found: 418.9 ($M+H^+$).

The mixture of 2-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-4-cyano-pyrrolidine-1-carboxylic acid *tert*-butyl ester (356 mg, 0.85 mmol), 2-{5-[6-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (501 mg, 1.02 mmol), tetrakis(triphenylphosphine)palladium(99 mg, 0.08 mmol) and potassium acetate (425 mg, 3.07 mmol) in 7 mL 1,2-dimethoxyethane and 2 mL water was heated to 90 ^{0}C for 2 hour. The reaction mixture was cooled and dissolved in ethyl acetate and washed with saturated sodium bicarbonate solution. The organic layer dried (MgSO4), concentrated and purified by flash column chromatography (silica gel, 20 to 80% ethyl acetate/hexane) to give 2-[5-(4-{6-[2-(1-*tert*-Butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-naphthalen-2-yl}-phenyl)-1H-

imidazol-2-yl]-4-cyano-pyrrolidine-1-carboxylic acid *tert*-butyl ester (200 mg, yield 33%) and the amide product. LCMS-ESI$^-$: calc'd for $C_{41}H_{45}N_7O_4$: 699.84; Found: 700.2 ($M+H^+$).

LAH (45 mg, 6 eq.) was added to the solution of mixture of 2-[5-(4-{6-[2-(1-*tert*-Butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-naphthalen-2-yl}-phenyl)-1H-imidazol-2-yl]-4-cyano-pyrrolidine-1-carboxylic acid *tert*-butyl ester (146 mg, 0.066 mmol) in 3 ml THF at 0 ^{0}C. The reaction was quenched after 30 minutes using water, 10%NaOH aqueous solution and water in 3 steps. The reaction mixture was filtered. The filtrate was concentrated down and purified by preparative reverse phase HPLC (Gemini, 5 to 100% ACN/H_2O + 0.1% TFA). Product lyophilized to give 4-Aminomethyl-2-[5-(4-{6-[2-(1-*tert*-butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-naphthalen-2-yl}-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester TFA salt (150 mg, yield 95%). LCMS-ESI$^-$: calc'd for $C_{41}H_{49}N_7O_4$: 703.87; Found: 704.2 ($M+H^+$).

Sodium triacetyl boron hydride (54mg, 3 eq.) was added to the mixture of 4-Aminomethyl-2-[5-(4-{6-[2-(1-*tert*-butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-naphthalen-2-yl}-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (60 mg, 0.085 mmol) and 0.1 mL formaldehyde (37% in water) in 3 ml THF, followed by 1 drop of acetic acid. The reaction was stirred at room temperature for 30 minutes. The reaction was complete by monitoring using LC-MS. The reaction mixture was filtered. The filtrate was concentrated down and purified by preparative reverse phase HPLC (Gemini, 5 to 100% ACN/H_2O + 0.1% TFA). Product lyophilized to give 2-[5-(4-{6-[2-(1-*tert*-Butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-naphthalen-2-yl}-phenyl)-1H-imidazol-2-yl]-4-dimethylaminomethyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester TFA salt (41.7 mg, yield 67%). LCMS-ESI$^-$: calc'd for $C_{43}H_{53}N_7O_4$: 731.93; Found: 732.3 ($M+H^+$).

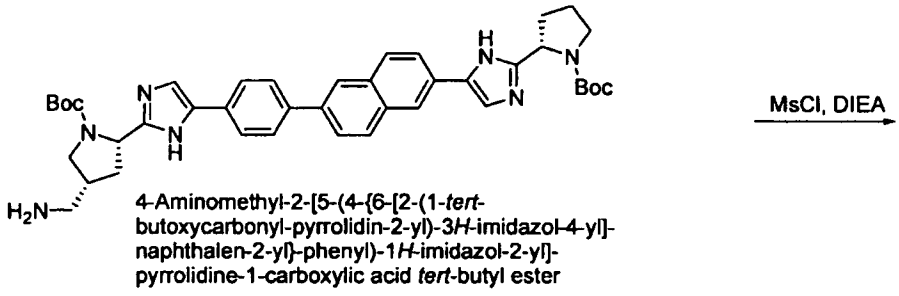
Trifluoroacetic acid (0.5 mL)was added to 2-[5-(4-{6-[2-(1-*tert*-Butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-naphthalen-2-yl}-phenyl)-1H-imidazol-2-yl]-4-dimethylaminomethyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester (41.7 mg, 0.057 mmol) in 1 ml DCM and the reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated and dried overnight under vacuum. The residue was dissolved in DMF (1.5 mL) and to this solution was added 2-Methoxycarbonylamino-3-methyl-butyric acid (20 mg, 0.124 mmol), diisopropyl ethylamine (60 µl), followed by HATU (43 mg). Reaction mixture was stirred at 0 ^{0}C for 60 minutes. The reaction mixture was dissolved in ethyl acetate and washed with dilute sodium bicarbonate solution. The organic layer was dried (MgSO4), concentrated

and purified by preparative reverse phase HPLC (Gemini, 5 to 100% ACN/H_2O + 0.1% TFA). Product lyophilized to give [1-(4-Dimethylaminomethyl-2-{5-[4-(6-{2-[1-(2-methoxycarbonylamino-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester the bis-TFA salt (Example **A**) (13.1 mg).

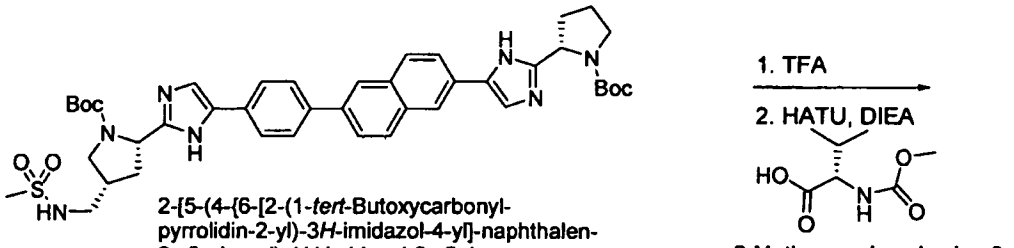
^{1}H-NMR: 300 MHz, (CD_3OD-d_4) δ: 8.28 (d, 2H), 8.02 (m, 2H), 7.83-7.92 (m, 8H), 5.38 (m, 2H), 4.58(m, 1H), 4.22(m, 2H), 4.18(m, 2H), 3.92 (m, 2H), 3.62 (s, 6H),3.42(m,2H), 3.02(s, 6H), 3.00(m,1H), 2.81(m,1H), 2.62 (m, 1H), 2.40-2.00 (m, 5H), 0.95-1.05 (m, 12 H).

LCMS-ESI$^+$: calc'd for $C_{47}H_{59}N_9O_6$: 846.03; Found: 848.4 ($M+H^+$).

Example JN

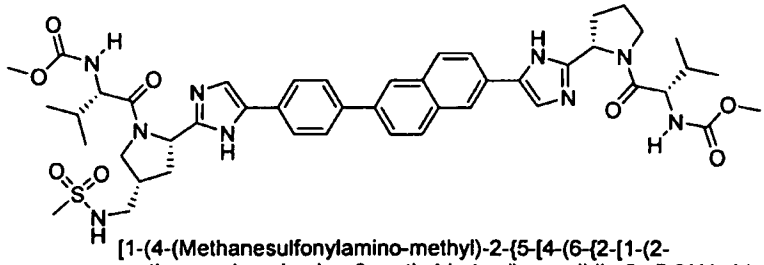


4-Aminomethyl-2-[5-(4-{6-[2-(1-*tert*-butoxycarbonyl-pyrrolidin-2-yl)-3*H*-imidazol-4-yl]-naphthalen-2-yl}-phenyl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester



2-{5-(4-{6-[2-(1-*tert*-Butoxycarbonyl-pyrrolidin-2-yl)-3*H*-imidazol-4-yl]-naphthalen-2-yl}-phenyl)-1*H*-imidazol-2-yl]-4-(methanesulfonylamino-methyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester

2-Methoxycarbonylamino-3-methyl-butyric acid



[1-(4-(Methanesulfonylamino-methyl)-2-{5-[4-(6-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester

MsCl (7.6 mg, 1 eq.) was added to the mixture of 4-Aminomethyl-2-[5-(4-{6-[2-(1-*tert*-butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-naphthalen-2-yl}-phenyl)-1H-imidazol-2-

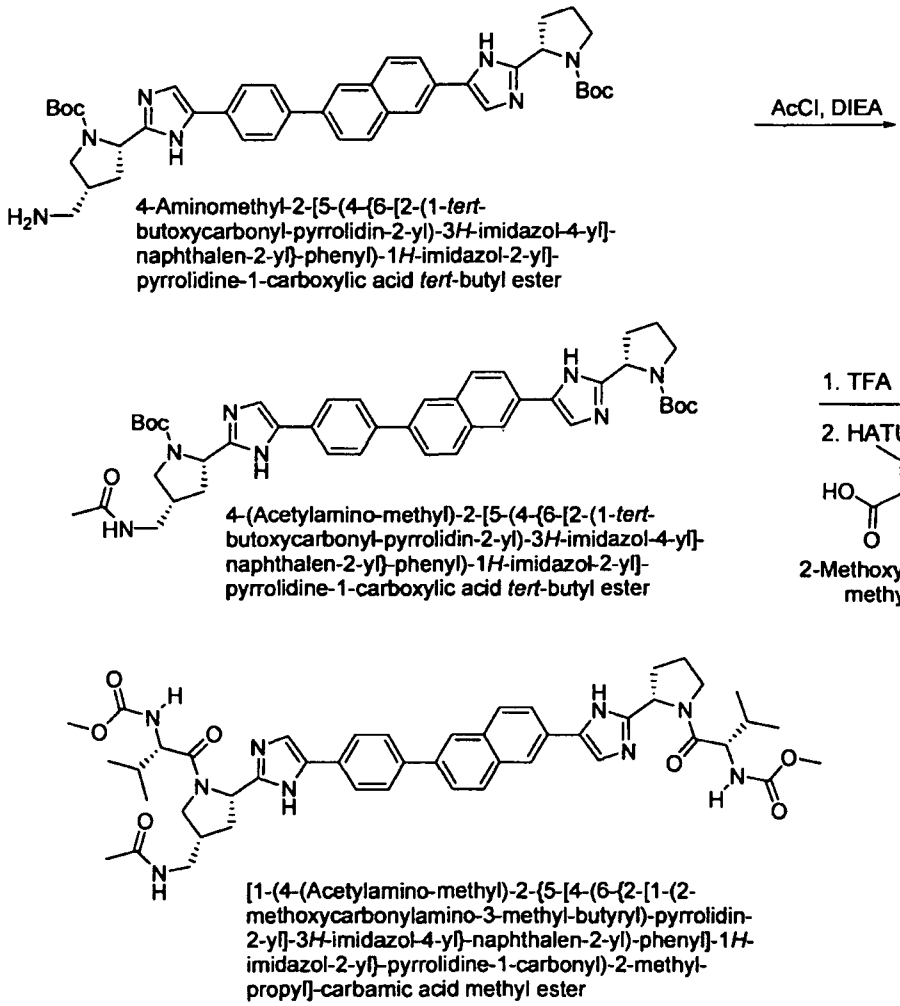
yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (69 mg, 0.098 mmol) and DIEA(51 µl, 3eq) in 1 ml MeCN. The reaction was stirred at room temperature for 30 minutes. The reaction mixture was concentrated down and purified by preparative reverse phase HPLC (Gemini, 5 to 100% ACN/H_2O + 0.1% TFA). Product lyophilized to give 2-[5-(4-{6-[2-(1-*tert*-Butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-naphthalen-2-yl}-phenyl)-1H-imidazol-2-yl]-4-(methanesulfonylamino-methyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester TFA salt (29 mg, yield 38%). LCMS-ESI$^-$: calc'd for $C_{42}H_{51}N_7O_6S$: 781.96; Found: 782.2 ($M+H^+$).

Trifluoroacetic acid (0.5 mL)was added to 2-[5-(4-{6-[2-(1-*tert*-Butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-naphthalen-2-yl}-phenyl)-1H-imidazol-2-yl]-4-(methanesulfonylamino-methyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (29 mg, 0.037 mmol) in 1 ml DCM and the reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated and dried overnight under vacuum. The residue was dissolved in DMF (0.5 mL) and to this solution was added 2-Methoxycarbonylamino-3-methyl-butyric acid (13 mg, 2 eq.), diisopropyl ethylamine (39 µl, 6 eq.), followed by HATU (28 mg, 2 eq.). Reaction mixture was stirred at 0 ^{0}C for 60 minutes. The reaction mixture was dissolved in ethyl acetate and washed with dilute sodium bicarbonate solution. The organic layer was dried (MgSO4), concentrated and purified by preparative reverse phase HPLC (Gemini, 5 to 100% ACN/H_2O + 0.1% TFA). Product lyophilized to give [1-(4-(Methanesulfonylamino-methyl)-2-{5-[4-(6-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester the bis-TFA salt (Example **B**) (12.9 mg).

^{1}H-NMR: 300 MHz, (CD_3OD-d_4) δ: 8.28 (d, 2H), 8.08 (m, 2H), 7.95 (m, 4H), 7.82(m, 4H), 5.28 (m, 2H), 4.38(m, 1H), 4.22(m, 2H), 4.12(m, 2H), 3.92 (m, 2H), 3.62 (s, 6H),3.61(m,2H), 3.02(s, 3H), 2.72(m,2H), 2.60 (m, 1H), 2.40-1.98 (m, 5H), 0.95-1.05 (m, 12 H).

LCMS-ESI$^+$: calc'd for $C_{46}H_{57}N_9O_8S$: 896.07; Found: 896.3 ($M+H^+$).

Example JO



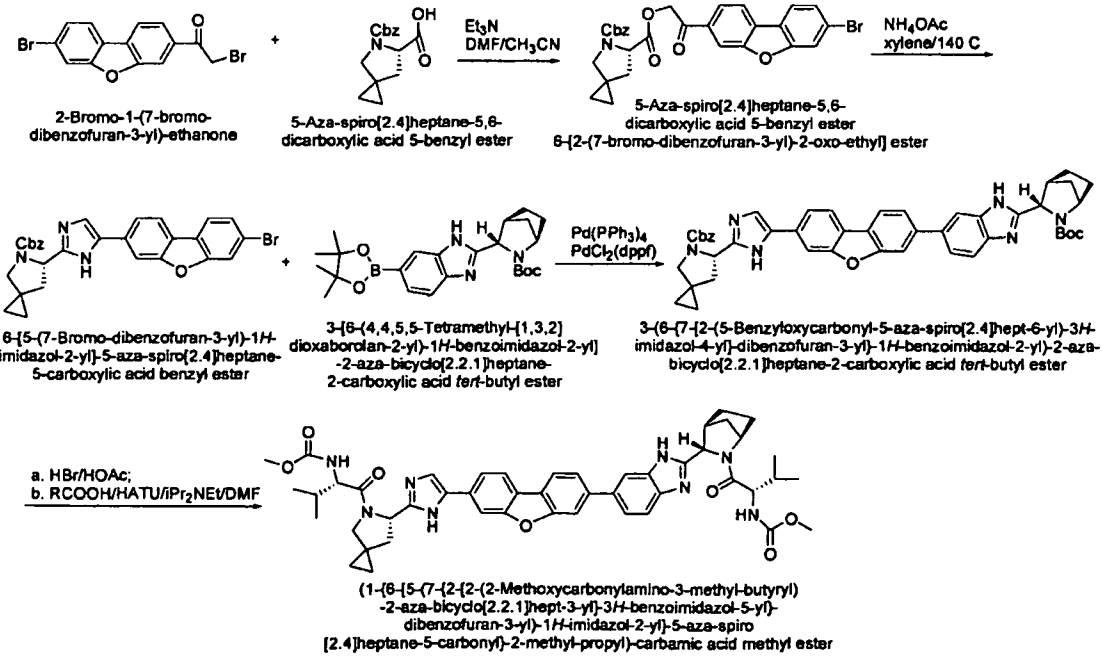
AcCl (5 µl, 1 eq.) was added to the mixture of 4-Aminomethyl-2-[5-(4-{6-[2-(1-*tert*-butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-naphthalen-2-yl}-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (50 mg, 0.071 mmol) and DIEA(37 µl, 3eq) in 1 ml DCM and 1 mL MeCN mixture. The reaction was stirred at room temperature for 1 hour. LC-MS shows desired and Bis-acetyl product. The reaction mixture was concentrated down and purified by preparative reverse phase HPLC (Gemini, 5 to 100% ACN/H_2O + 0.1% TFA). Product lyophilized to give 4-(Acetylamino-methyl)-2-[5-(4-{6-[2-(1-*tert*-butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-naphthalen-2-yl}-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester TFA salt (13 mg, yield 25%). LCMS-ESI$^-$: calc'd for $C_{43}H_{51}N_7O_5$: 745.91; Found: 746.2 ($M+H^+$).

Trifluoroacetic acid (0.5 mL)was added to 4-(Acetylamino-methyl)-2-[5-(4-{6-[2-(1-*tert*-butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-naphthalen-2-yl}-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (13 mg, 0.017 mmol) in 1 ml DCM and the reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated and dried overnight under vacuum. The residue was dissolved in DMF (0.5 mL) and to this solution was added 2-Methoxycarbonylamino-3-methyl-butyric acid (6 mg, 2 eq.), diisopropyl ethylamine (18 µl, 6 eq.), followed by HATU (13 mg, 2 eq.). Reaction mixture was stirred at 0 ^{0}C for 60 minutes. The reaction mixture was dissolved in ethyl acetate and washed with dilute sodium bicarbonate solution. The organic layer was dried (MgSO4), concentrated and purified by preparative reverse phase HPLC (Gemini, 5 to 100% ACN/H_2O + 0.1% TFA). Product lyophilized to give [1-(4-(Acetylamino-methyl)-2-{5-[4-(6-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester the bis-TFA salt (Example **C**) (6.6 mg).

^{1}H-NMR: 300 MHz, (CD_3OD-d_4) δ: 8.28 (d, 2H), 8.08 (m, 2H), 7.95 (m, 4H), 7.82(m, 4H), 5.28 (m, 2H), 4.38(m, 1H), 4.22(m, 2H), 4.17(m, 2H), 3.92 (m, 2H), 3.62 (s, 6H), 3.59(m,1H), 3.42(m, 2H), 2.64(m,2H), 2.24 (m, 3H), 2.10 (m, 2H), 1.99 (s, 3H), 0.95-1.05 (m, 12 H).

LCMS-ESI$^+$: calc'd for $C_{47}H_{57}N_9O_7$: 859.44; Found: 860.4 ($M+H^+$).

Example JP



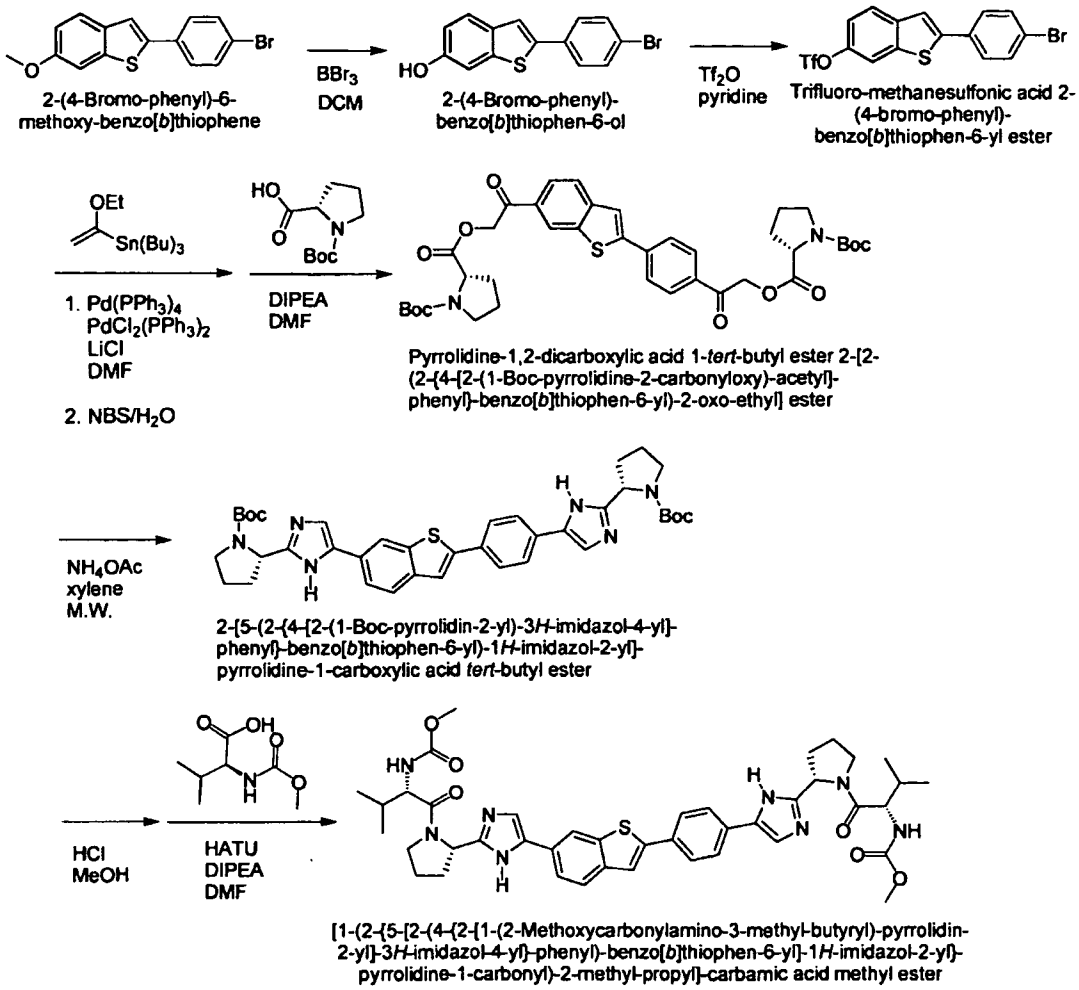
5-Aza-spiro[2.4]heptane-5,6-dicarboxylic acid 5-benzyl ester 6-[2-(7-bromo-dibenzofuran-3-yl)-2-oxo-ethyl] ester: To the solution of (s) 5-aza-spiro[2.4]heptane-5,6-dicarboxylic acid 5-benzyl ester (138 mg, 0.5 mmol) and triethylamine (65 µl, 0.47 mmol) in acetonitrile (3 ml) was added slowly a solution of 2-bromo-1-(7-bromo-dibenzofuran-3-yl)-ethanone (143 mg, 0.39 mmol) in DMF (4 ml). The mixture was stirred for 12 hours, and the solvent was evaporated. The mixture was diluted with EtOAc, and washed with 1.0 N NaOH solution, water and brine, and was dried with sodium sulfate. Concentration gave 5-Aza-spiro[2.4]heptane-5,6-dicarboxylic acid 5-benzyl ester 6-[2-(7-bromo-dibenzofuran-3-yl)-2-oxo-ethyl] ester (210 mg)

6-[5-(7-Bromo-dibenzofuran-3-yl)-1H-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carboxylic acid benzyl ester: The mixture of 5-aza-spiro[2.4]heptane-5,6-dicarboxylic acid 5-benzyl ester 6-[2-(7-bromo-dibenzofuran-3-yl)-2-oxo-ethyl] ester (210 mg, 0.39 mmol) and ammonium acetate (330 mg, 4.3 mmol) in xylene (3 ml) was heated at 140 C for 80 minutes under microwave. The mixture was quenched with water, and extracted with EtOAc. The organic phase was washed with water and brine, and was dried with sodium sulfate. Concentration and purification by flash column chromatography (EtOAc) gave 6-[5-(7-bromo-dibenzofuran-3-yl)-1H-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carboxylic acid benzyl ester (150 mg). m/z: 542.1 (M+1), 540.1 (M-1).

3-(6-{7-[2-(5-Benzyloxycarbonyl-5-aza-spiro[2.4]hept-6-yl)-3H-imidazol-4-yl]-dibenzofuran-3-yl}-1H-benzoimidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester: To the solution of 6-[5-(7-bromo-dibenzofuran-3-yl)-1H-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carboxylic acid benzyl ester (150 mg, 0.28 mmol) and 3-[6-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-benzoimidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (160 mg, 0.36 mmol) in DME (2.25 ml) and water (0.75 ml) was added potassium carbonate (78 mg, 0.56 mmol), followed by $Pd(PPh_3)_4$ (15 mg) and $PdCl_2(dppf)CH_2Cl_2$ (15 mg). The mixture was heated at 90 C for 16 hours. The mixture was diluted with EtOAc, and was washed with water and brine, and was dried with sodium sulfate. Concentration and purification by flash column chromatography (hexanes/EtOAc) gave 3-(6-{7-[2-(5-benzyloxycarbonyl-5-aza-spiro[2.4]hept-6-yl)-3H-imidazol-4-yl]-dibenzofuran-3-yl}-1H-benzoimidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (190 mg). m/z: 775.2 (M+1), 773.3 (M-1), 338.2 (M+2)/2.

(1-{6-[5-(7-{2-[2-(2-Methoxycarbonylamino-3-methyl-butyryl) -2-aza-bicyclo[2.2.1]hept-3-yl]-3H-benzoimidazol-5-yl}-dibenzofuran-3-yl)-1H-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: To the solution of 3-(6-{7-[2-(5-benzyloxycarbonyl-5-aza-spiro[2.4]hept-6-yl)-3H-imidazol-4-yl]-dibenzofuran-3-yl}-1H-benzoimidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (185 mg, 0.24 mmol) in DCM (3.6 ml) was added slowly 33% HBr/HOAc (1 ml). The mixture was stirred for two hours, and the solvent and reagent were removed under reduced pressure to give a brown solid. The solid was suspended in DCM/Et_2O (2.5 ml/25 ml) and was stirred. The solid was collected through filtration. To the solution of above solid (0.24 mmol) and MeOCO-Val-OH (84 mg, 0.48 mmol) in DMF (7.0 ml) was added HATU (192 mg, 0.50 mmol), followed by diisopropylethylamine (0.42 ml, 2.4 mmol). The mixture was stirred for ten hours and was evaporated and then diluted with EtOAc. The organic phase was washed with 1 N NaOH solution, water, and brine, and was dried with sodium sulfate. Concentration and purification by HPLC (0.1%TFA/CH_3CN/0.1%TFA/H_2O) gave (1-{6-[5-(7-{2-[2-(2-methoxycarbonylamino-3-methyl-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-benzoimidazol-5-yl}-dibenzofuran-3-yl)-1H-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (151 mg). m/z: 855.3 (M+1), 853.2 (M-1), 428.4 (M+2)/2. ^1H NMR (CD_3OD, 300 MHz) δ 8.25-7.70 (10 H, m), 5.4 (1 H, m), 4.95-4.7 (1 H, m), 4.38 (1 H, m), 4.16 (1 H, m), 3.95 (1 H, m), 3.83 (1 H, m), 3.69 (3 H, s), 3.67 (3 H, s), 3.5-3.2 (1 H, m), 2.98 (1 H, m), 2.5 -1.7 (10 H, m), 1.2-0.8 (16 H, m).

Example JQ



2-(4-Bromo-phenyl)-6-methoxy-benzo[b]thiophene was reported in the literature (Journal of Medicinal Chemistry, 2007, 50, 2682-2692).

2-(4-Bromo-phenyl)-benzo[b]thiophen-6-ol. To a stirred solution of 2-(4-bromo-phenyl)-6-methoxy-benzo[b]thiophene (80 mg, 0.25 mmol) was added BBr_3 (0.5 mL of 1 M in DCM, 0.5 mmol) at 0° C. The mixture was stirred for 3 hours at ambient temperature. DCM was removed under vacuum, and the residue was dissolved in ethyl acetate (30 mL). The organic layer was washed with $NaHCO_3$ solution, water and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The obtained residue was treated with hexane to give the product (67 mg, 88%). m/z 303.0, 305.0 $(M-H)^-$.

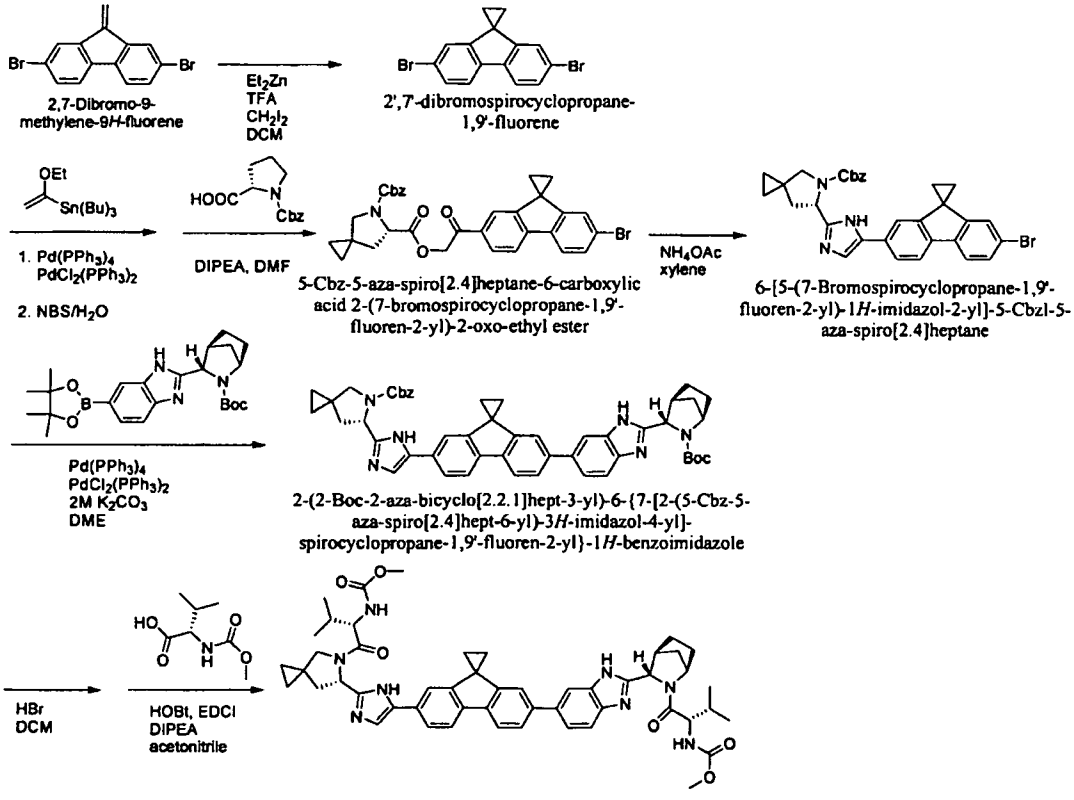
Trifluoro-methanesulfonic acid 2-(4-bromo-phenyl)-benzo[b]thiophen-6-yl ester. Tf_2O was added slowly to a mixture of 2-(4-bromo-phenyl)-benzo[b]thiophen-6-ol (200 mg, 0.66 mol) in pyridine (3 mL) at 0° C with stirring. The mixture was stirred at ambient temperature for 16 hours before quenched with $NaHCO_3$ solution. The mixture was extracted with ethyl acetate (50 mL). The organic layer was washed with water and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The obtained residue was used for next step reaction without further purification.

Pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-[2-(2-{4-[2-(1-Boc-pyrrolidine-2-carbonyloxy)-acetyl]-phenyl}-benzo[b]thiophen-6-yl)-2-oxo-ethyl] ester. $Pd(Ph_3)_4$ (43 mg, 0.037 mmol), $PdCl_2(Ph_3)_2$ (26 mg, 0.037 mmol) and LiCl (78 mg, 1.8 mmol) were added to a mixture trifluoro-methanesulfonic acid 2-(4-bromo-phenyl)-benzo[b]thiophen-6-yl ester (200 mg, 0.46 mmol) and tributyl(1-ethoxyvinyl)tin (0.37 mL, 1.1 mmol) in 8 mL DMF. The reaction mixture was flushed with nitrogen, heated at 80° C for 16 hours, then cooled to ambient temperature. Water (3 mL) and NBS (180 mg, 1.0 mmol) were added and the mixture was stirred at room temperature for 40 min, then diluted with ethyl acetate (300 mL). The ethyl acetate layer was washed with water and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The obtained residue was suspended in acetonitrile (30 mL). To it was added a solution of pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester (792 mg, 3.7 mmol) and DIPEA (0.56 mL, 3.2 mmol) in 5 mL acetonitrile. The mixture was stirred at room temperature for 16 hours, diluted with ethyl acetate (100 mL). The organic layer was washed with $NaHCO_3$ solution and water, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The obtained residue was purified by flash chromatography to provide the desired product (90 mg, 27% over two steps). m/z 743.2 $(M+Na)^+$.

2-[5-(2-{4-[2-(1-Boc-pyrrolidin-2-yl)-3H-imidazol-4-yl]-phenyl}-benzo[b]thiophen-6-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester. A mixture of pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-[2-(2-{4-[2-(1-Boc-pyrrolidine-2-carbonyloxy)-acetyl]-phenyl}-benzo[b]thiophen-6-yl)-2-oxo-ethyl] ester (90 mg, 0.12 mmol) and ammonium acetate (192 mg, 2.5 mmol) in xylene (10 mL) was heated in a sealed tube at 140° C for 1.5 hours under microwave condition. The volatile component was removed *in vacuo*, and the residue was dissolved in ethyl acetate (100 mL), washed with $NaHCO_3$ solution, water and brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The obtained residue was purified by flash chromatography to provide the desired product (60 mg, 70%). m/z 681.2 $(M+H)^+$.

[1-(2-{5-[2-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-benzo[b]thiophen-6-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester. To a solution of 2-[5-(2-{4-[2-(1-Boc-pyrrolidin-2-yl)-3H-imidazol-4-yl]-phenyl}-benzo[b]thiophen-6-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (60 mg, 0.09 mmol) in methanol (3 mL) was added 4N HCl in 1,4-dioxane (0.4 mL, excess). The mixture was stirred for 2 hours at 50° C and concentated under reduced pressure. The residue was dissolved in wather and freezing-dired overnight. The obtained white solid was dissoved in DMF (3 mL), to the solution was added 2-methoxycarbonylamino-3-methyl-butyric acid (34 mg, 0.19 mmol), HATU (84 mg, 0.22 mmol) and *N,N*-diisopropylethylamine (0.12 mL, 0.70 mmol). The mixture was stirred at ambient for 2 hours, and then the volatile component was removed *in vacuo*. The residue was dissolved in ethyl acetate (100 mL), washed with 1 N NaOH solution, water and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The obtained residue was purified by HPLC to provide the desired product as a TFA salt (45 mg, 64%). ^{1}H-NMR (300 MHz, CD_3OD) δ 8.26 (s, 1H), 8.00-7.70 (m, 9H), 5.30-5.20 (m, 2H), 4.23 (d, 2H), 4.18-4.10 (m, 2H), 3.95-3.80 (m, 2H), 3.75-3.60 (m, 6H), 2.65-2.50 (m, 2H), 2.35-2.00 (m, 8H), 1.00-0.80 (m, 12H); m/z 795.3 $(M+H)^+$.

Example JR



2,7-Dibromo-9-methylene-9*H*-fluorene was reported in the literature (Tetrahedron, 2006, 62, 3355-3361).

2',7'-Dibromospirocyclopropane-1,9'-fluorene. To a stirred solution of diethylzinc (9.0 mL of 1.0 M in hexane, 9.0 mmol) in DCM (10 mL) was added trifluoroacetic acid (0.69 mL, 9.0 mmol) in DCM (10 mL) slowly at 0° C. The mixture was stirred for 20 min at 0° C before the addition of diiodomethane (0.72 mL, 9.0 mmol). The mixture was stirred for another 20 min at 0° C, then a solution of 2,7-dibromo-9-methylene-9*H*-fluorene (750 mg, 2.2 mmol) in DCM (5 mL) was added. The mixture was stirred at ambient temperature for 5 days, then quenched slowly with NH_4Cl solution. The mixture was extracted with ethyl acetate, washed with water and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The obtained residue was dissolved in a mixed solvent of THF/water/acetone (18 mL with ration 12/4/4), NMO (264 mg, 2.2 mmol) and OsO_4 was added. The mixture was stirred for 16 hs at ambient temperature, quenched with 1 M $Na_2S_2O_3$, then extracted with ethyl acetate. The organic layer was washed with water and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The obtained residue was purified by flash chromatography to provide the desired product (480 mg, 61%).

5-Cbz-5-aza-spiro[2.4]heptane-6-carboxylic acid 2-(7-bromospirocyclopropane-1,9'-fluoren-2-yl)-2-oxo-ethyl ester. $Pd(Ph_3)_4$ (67 mg, 0.058 mmol) and $PdCl_2(Ph_3)_2$ (41 mg, 0.058 mmol) were added to a mixture 2',7'-dibromospirocyclopropane-1,9'-fluorene (670 mg, 1.93 mmol) and tributyl(1-ethoxyvinyl)tin (0.66 mL, 1.93 mmol) in 20 mL dioxane. The reaction mixture was flushed with nitrogen, heated at 80° C for 16 hours, then cooled to ambient temperature. Water (7 mL) and NBS (344 mg, 1.93 mmol) were added and the mixture was stirred at room temperature for 40 min, then diluted with ethyl acetate (300 mL). The ethyl acetate layer was washed with water and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The obtained residue was suspended in acetonitrile (30 mL). To it was added a solution of pyrrolidine-1,2-dicarboxylic acid 1-benzyl ester (780 mg, 2.8 mmol) and DIPEA (0.44 mL, 2.5 mmol) in 5 mL acetonitrile. The mixture was stirred at room temperature for 16 hours, diluted with ethyl acetate (100 mL). The organic layer was washed with $NaHCO_3$ solution and water, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The obtained residue was purified by flash chromatography to provide the desired product (825 mg, 73% over two steps). m/z 585.9, 587.9 $(M+H)^+$.

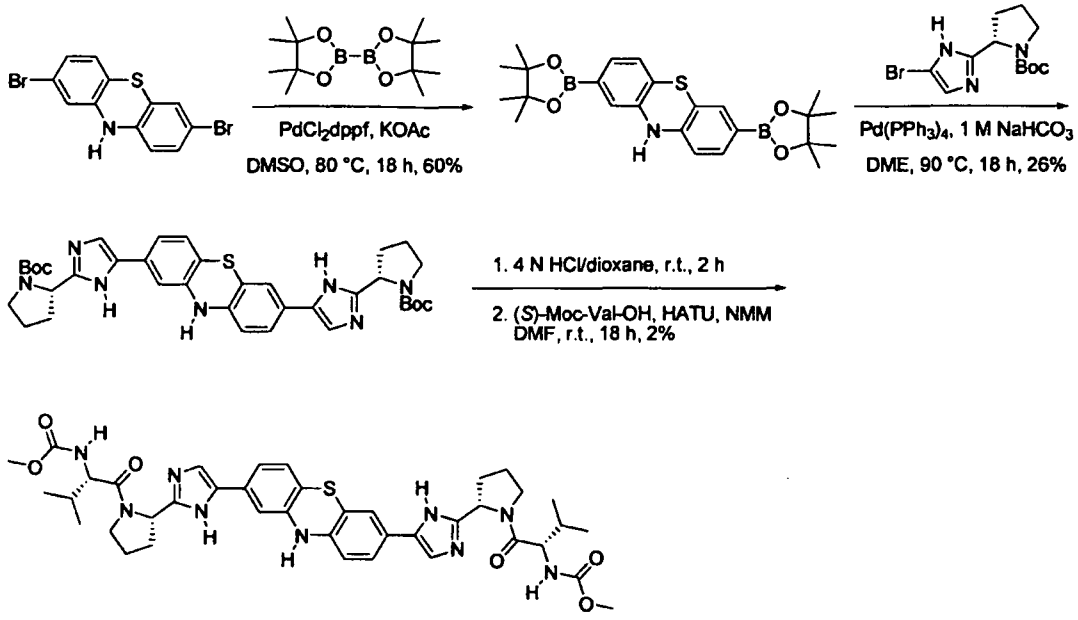
6-[5-(7-Bromospirocyclopropane-1,9'-fluoren-2-yl)-1H-imidazol-2-yl]-5-Cbzl-5-aza-spiro[2.4]heptane. A mixture of 5-Cbz-5-aza-spiro[2.4]heptane-6-carboxylic acid 2-(7-bromospirocyclopropane-1,9'-fluoren-2-yl)-2-oxo-ethyl ester (825 mg, 1.4 mmol) and ammonium acetate (1.5 g, 19.5 mmol) in xylene (15 mL) was heated in a sealed tube at 140° C for 1.5 hours under microwave condition. The volatile component was removed *in vacuo*, and the residue was dissolved in ethyl acetate (100 mL), washed with $NaHCO_3$ solution, water and brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The obtained residue was purified by flash chromatography to provide the desired product (140 mg, 18%). m/z 566.1, 568.1 $(M+H)^+$.

2-(2-Boc-2-aza-bicyclo[2.2.1]hept-3-yl)-6-{7-[2-(5-Cbz-5-aza-spiro[2.4]hept-6-yl)-3H-imidazol-4-yl]-spirocyclopropane-1,9'-fluoren-2-yl}-1H-benzoimidazole. $Pd(Ph_3)_4$ (14 mg, 0.012 mmol) and $PdCl_2(Ph_3)_2$ (9 mg, 0.012 mmol) were added to a mixture 6-[5-(7-bromospirocyclopropane-1,9'-fluoren-2-yl)-1H-imidazol-2-yl]-5-Cbzl-5-aza-spiro[2.4]heptane (140 mg, 0.25 mmol), 3-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-benzoimidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (120 mg, 0.27 mmol), 2M K_2CO_3 (0.5 mL, 1.0 mmol) in 1,2-dimethoxyethane (5 mL). The reaction mixture was flushed with nitrogen, heated at 80° C for 16 hours, and then the volatile component was removed *in vacuo*. The residue was dissolved in ethyl acetate (100 mL), washed with $NaHCO_3$ solution, water and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The obtained residue was purified by flash chromatography to provide the desired product (80 mg, 40%). m/z 799.3 $(M+H)^+$.

(1-{3-[6-(7-{2-[5-(2-Methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3H-imidazol-4-yl}-spirocyclopropane-1,9'-fluoren-2-yl)-1H-benzoimidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester. To a solution of 2-(2-Boc-2-aza-bicyclo[2.2.1]hept-3-yl)-6-{7-[2-(5-Cbz-5-aza-spiro[2.4]hept-6-yl)-3H-imidazol-4-yl]-spirocyclopropane-1,9'-fluoren-2-yl}-1H-benzoimidazole (80 mg, 0.1 mmol) in DCM (3 mL) was added HBr (0.8 mL 5.7M in AcOH, excess). The mixture was stirred for 2 hours at ambient temperature and concentated under reduced pressure. The residue was treated with with ether/DCM to give an off-white solid. The obtained product was dissoved in DMF (3 mL), to the solution was added 2-methoxycarbonylamino-3-methyl-butyric acid (39 mg, 0.22 mmol), HATU (95 mg, 0.25 mmol) and *N,N*-diisopropylethylamine (0.14 mL, 0.80 mmol). The mixture was stirred at ambient for 2 hours, and then the volatile component was removed *in vacuo*. The residue was dissolved in ethyl acetate (100 mL), washed with 1 N NaOH solution,

water and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The obtained residue was purified by HPLC to provide the desired product as a TFA salt (55 mg, 62%). m/z 879.4 $(M+H)^+$.

Example JS



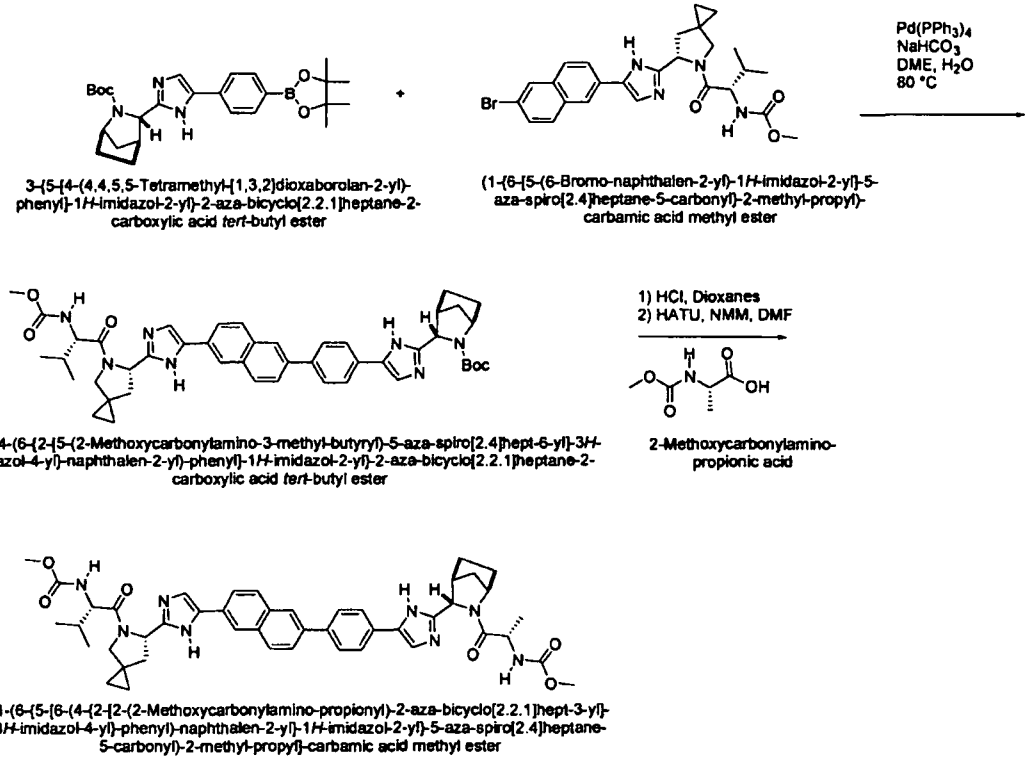
2,7-Bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-10H-phenothiazine: 2,7-Dibromo-10H-phenothiazine (590 mg, 1.65 mmol, WuXi AppTec) in DMSO (16 mL) was treated with bis(pinacolato)diboron (1.68 g, 6.60 mmol), KOAc (1.30 g, 13.2 mmol), and $PdCl_2dppf$ (135 mg, 0.165 mmol). The reaction mixture was stirred at 80 °C for 18 h and the mixture was cooled and filtered through a CELITE pad. The mixture was diluted with EtOAc (100 mL) and washed with H_2O (2 50 mL) and saturated NaCl solution (1 50 mL). The solution was dried over $MgSO_4$ and treated to a 80 g SiO_2 COMBIFLASH column (0–25% EtOAc–hexanes gradient) to afford 2,7-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-10H-phenothiazine (450 mg, 60%): HPLC (RP: 6–98% MeCN–H_2O gradient [non-polar], 0.05% TFA modifier) t_R = 6.821 min (~80% purity @ 254 nM).

(2*S*,2'*S*)-*tert*-Butyl 2,2'-(5,5'-(10H-phenothiazine-2,7-diyl)bis(1H-imidazole-5,2-diyl))dipyrrolidine-1-carboxylate: 2,7-Bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-10H-phenothiazine (450 mg, 1.00 mmol) in DME (10 mL) was treated with (*S*)-*tert*-butyl 2-(5-bromo-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (662 mg, 2.09 mmol), 1 M $NaHCO_3$ (5 mL, 5.00 mmol), and $Pd(PPh_3)_4$ (69 mg, 0.06 mmol). The reaction mixture was stirred at 90 °C for

18 h and the mixture was cooled and filtered through a CELITE pad. The mixture was diluted with EtOAc (100 mL) and washed with H_2O (2 50 mL) and satur ated NaCl solution (1 50 mL). The solution was dried over $MgSO_4$ and treated to a 40 g SiO_2 COMBIFLASH column (0–100% EtOAc–hexanes gradient, followed by a 0–100% 20%–MeOH/EtOAc–hexanes gradient) to afford (2*S*,2'*S*)-*tert*-butyl 2,2'-(5,5'-(10H-phenothiazine-2,7-diyl)bis(1H-imidazole-5,2-diyl))dipyrrolidine-1-carboxylate (175 mg, 26%): MS (ESI) *m/z* 670 $[M + H]^+$.

Dimethyl (2*S*,2'*S*)-1,1'-((2S,2'S)-2,2'-(5,5'-(10H-phenothiazine-2,7-diyl)bis(1H-imidazole-5,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate: (2*S*,2'*S*)-*tert*-butyl 2,2'-(5,5'-(10H-phenothiazine-2,7-diyl)bis(1H-imidazole-5,2-diyl))dipyrrolidine-1-carboxylate (175 mg, 0.26 mmol) was treated with 4 N HCl (5 mL) and stirred for 2 h. The reaction mixture was concentrated and the mixture was suspended in DMF (5.5 mL) and treated with (*S*)-Moc-Val-OH (96 mg, 0.55 mmol), HATU (219 mg, 0.57 mmol), and 4-methylmorpholine (143 μL, 1.31 mmol; or until basic). The stirred for 18 h then diluted with EtOAc (100 mL) and washed with saturated $NaHCO_3$ solution (2 50 mL), H_2O (2 50 mL), and saturated NaCl solution (1 50 mL). The solution was dried over $MgSO_4$ and treated to a 40 g SiO_2 COMBIFLASH column (0–100% EtOAc–hexanes gradient, followed by a 0–100% 20%–MeOH/EtOAc–hexanes gradient) and RP HPLC (6–98% MeCN–H_2O gradient, 0.1% TFA modifier). Finally, the material was subjected to a 20 20 preparative TLC (10% MeOH – EtOAc) to afford dimethyl (2*S*,2'*S*)-1,1'-((2S,2'S)-2,2'-(5,5'-(10H-phenothiazine-2,7-diyl)bis(1H-imidazole-5,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate (3.6 mg, 2%): MS (ESI) *m/z* 784 $[M + H]^+$.

Example JT



3-{5-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1*H*-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester

(1-{6-[5-(6-Bromo-naphthalen-2-yl)-1*H*-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

3-{5-[4-(6-{2-[5-(2-Methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3*H*-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1*H*-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester

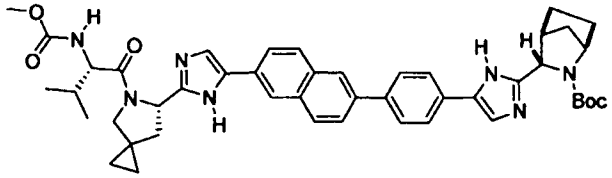
2-Methoxycarbonylamino-propionic acid

[1-(6-{5-[6-(4-{2-[2-(2-Methoxycarbonylamino-propionyl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3*H*-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1*H*-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester

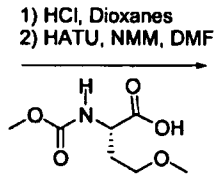
[1-(6-{5-[6-(4-{2-[2-(2-Methoxycarbonylamino-propionyl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: A solution of (1-{6-[5-(6-bromo-naphthalen-2-yl)-1H-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (1.00 g, 1.9 mmol), 3-{5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (1.31 g, 2.8 mmol) and aq $NaHCO_3$ (7.6 mL of a 1M solution, 7.6 mmol) in DME (20 mL) was degassed with N_2 gas for 20 minutes. To the degassed solution was added $Pd(PPh_3)_4$ (110 mg, 0.095 mmol) and then the reaction was heated to 80° C overnight. After cooling to room temperature, the solvent was removed under reduced pressure and the resulting residue was dissolved in ethyl acetate. The organic phase was washed with H_2O and then brine then dried over sodium sulfate. After filtration the solvent was removed from the filtrate under reduced pressure. The crude material was purified by silica gel chromatography (70-100% EtOAc/Hexanes) to afford 3-{5-[4-(6-{2-[5-(2-methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (835 mg, 1.07 mmol, 56% yield). LCMS-ESI$^+$: calc'd for $C_{46}H_{54}N_7O_5$: 784.4 ($M+H^+$); Found: 784.8 ($M+H^+$).

[1-(6-{5-[6-(4-{2-[2-(2-Methoxycarbonylamino-propionyl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: To 3-{5-[4-(6-{2-[5-(2-methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (46 mg, 0.059 mmol) in dioxanes (2 mL) and MeOH (0.5 mL) was added 4N HCl in dioxanes (160 μL). The suspension was stirred for 2 h then concentrated to afford the HCl salt of the crude amine. To the crude amine in DMF (1 mL) was added *N*-methylmorpholine (19.5 μL, 0.18 mmol), 2-methoxycarbonylamino-propionic acid (13 mg, 0.089 mmol) and HATU (25 mg, 0.065 mmol). After stirring for overnight the reaction was quenched with formic acid then purified by reverse phase preparative HPLC (5-45% MeCN-H_2O; 0.1% formic acid modifier) to afford the title product (26 mg, 0.032 mmol, 54% yield). LCMS-ESI$^+$: calc'd for $C_{46}H_{53}N_8O_6$: 813.4 ($M+H^+$); Found: 813.4 ($M+H^+$).

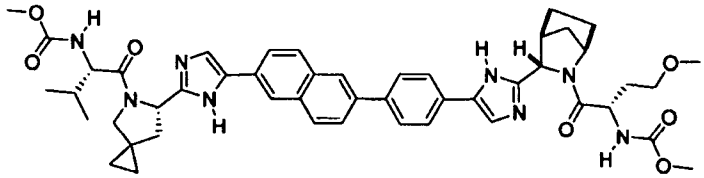
Example JU



3-{5-[4-(6-{2-[5-(2-Methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3*H*-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1*H*-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester



4-Methoxy-2-methoxycarbonylamino-butyric acid

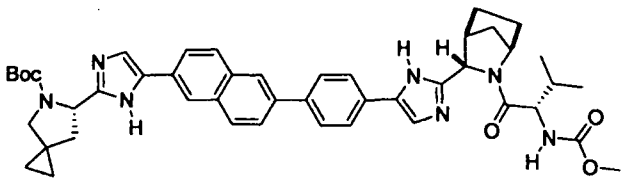


[1-(6-{5-[6-(4-{2-[2-(4-Methoxy-2-methoxycarbonylamino-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3*H*-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1*H*-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester

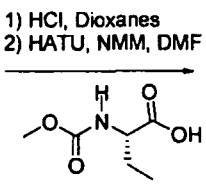
[1-(6-{5-[6-(4-{2-[2-(4-Methoxy-2-methoxycarbonylamino-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: To 3-{5-[4-(6-{2-[5-(2-methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (46 mg, 0.059 mmol) in dioxanes (2 mL) and MeOH (0.5 mL) was added 4N HCl in dioxanes (160 μL). The suspension was stirred for 2 h then concentrated to afford the HCl salt of the crude amine. To the crude amine in DMF (1 mL) was added *N*-

methylmorpholine (19.5 μL, 0.18 mmol), 4-methoxy-2-methoxycarbonylamino-butyric acid (17 mg, 0.089 mmol) and HATU (25 mg, 0.065 mmol). After stirring for overnight the reaction was quenched with formic acid then purified by reverse phase preparative HPLC (5-45% MeCN-H_2O; 0.1% formic acid modifier) to afford the title product (40 mg, 0.047 mmol, 79% yield). LCMS-ESI$^+$: calc'd for $C_{48}H_{57}N_8O_7$: 857.4 ($M+H^+$); Found: 857.4 ($M+H^+$).

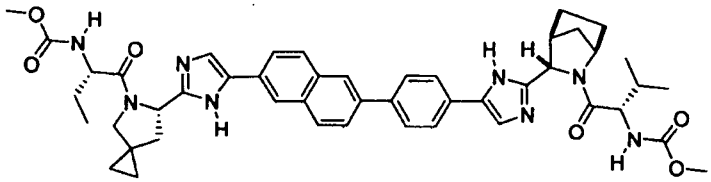
Example JV



6-{5-[6-(4-{2-[2-(2-Methoxycarbonylamino-3-methyl-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3*H*-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1*H*-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carboxylic acid *tert*-butyl ester



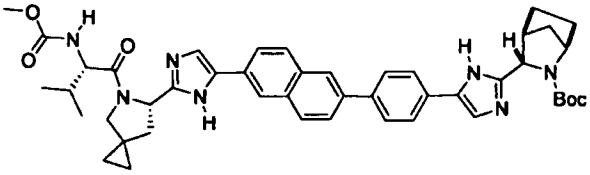
2-Methoxycarbonylamino-butyric acid



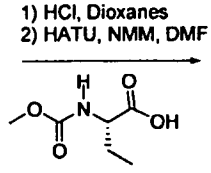
[1-(3-{5-[4-(6-{2-[5-(2-Methoxycarbonylamino-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3*H*-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1*H*-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester

[1-(3-{5-[4-(6-{2-[5-(2-Methoxycarbonylamino-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: To 6-{5-[6-(4-{2-[2-(2-methoxycarbonylamino-3-methyl-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carboxylic acid *tert*-butyl ester (50 mg, 0.064 mmol) in dioxanes (2 mL) and MeOH (0.5 mL) was added 4N HCl in dioxanes (160 μL). The suspension was stirred for 2 h then concentrated to afford the HCl salt of the crude amine. To the crude amine in DMF (1 mL) was added *N*-methylmorpholine (21 μL, 0.19 mmol), 2-methoxycarbonylamino-butyric acid (16 mg, 0.096 mmol) and HATU (27 mg, 0.070 mmol). After stirring for overnight the reaction was quenched with formic acid then purified by reverse phase preparative HPLC (5-45% MeCN-H_2O; 0.1% formic acid modifier) to afford the title product (30 mg, 0.036 mmol, 57% yield). LCMS-ESI$^+$: calc'd for $C_{47}H_{55}N_8O_6$: 827.4 ($M+H^+$); Found: 827.4 ($M+H^+$).

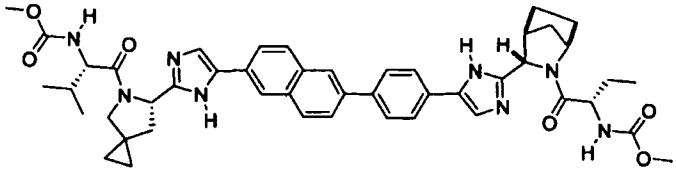
Example JW



3-{5-[4-(6-{2-[5-(2-Methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3*H*-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1*H*-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester



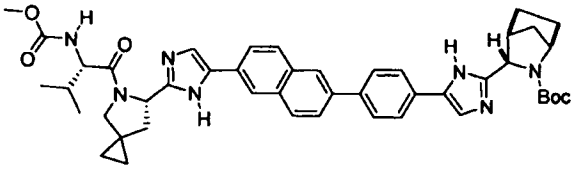
2-Methoxycarbonylamino-butyric acid



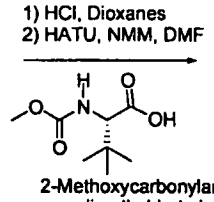
[1-(6-{5-[6-(4-{2-[2-(2-Methoxycarbonylamino-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3*H*-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1*H*-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester

[1-(6-{5-[6-(4-{2-[2-(2-Methoxycarbonylamino-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: To 3-{5-[4-(6-{2-[5-(2-methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (60 mg, 0.077 mmol) in dioxanes (2 mL) and MeOH (0.5 mL) was added 4N HCl in dioxanes (160 μL). The suspension was stirred for 2 h then concentrated to afford the HCl salt of the crude amine. To the crude amine in DMF (1 mL) was added *N*-methylmorpholine (34 μL, 0.31 mmol), 2-methoxycarbonylamino-butyric acid (19 mg, 0.11 mmol) and HATU (35 mg, 0.09 mmol). After stirring for overnight the reaction was quenched with formic acid then purified by reverse phase preparative HPLC (5-45% MeCN-H_2O; 0.1% formic acid modifier) to afford the title product (51 mg, 0.062 mmol, 80% yield). LCMS-ESI$^+$: calc'd for $C_{47}H_{55}N_8O_6$: 827.4 ($M+H^+$); Found: 827.4 ($M+H^+$).

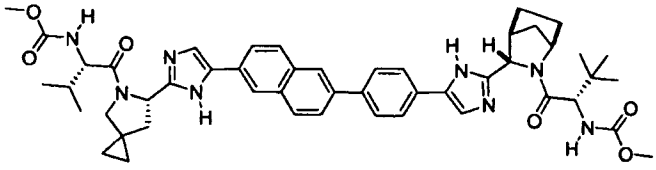
Example JX



3-{5-[4-(6-{2-[5-(2-Methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3*H*-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1*H*-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester



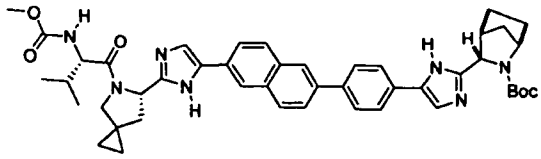
2-Methoxycarbonylamino-3,3-dimethyl-butyric acid



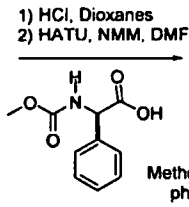
[1-(3-{5-[4-(6-{2-[5-(2-Methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3*H*-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1*H*-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carbonyl)-2,2-dimethyl-propyl]-carbamic acid methyl ester

[1-(3-{5-[4-(6-{2-[5-(2-Methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carbonyl)-2,2-dimethyl-propyl]-carbamic acid methyl ester: To 3-{5-[4-(6-{2-[5-(2-methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (60 mg, 0.077 mmol) in dioxanes (2 mL) and MeOH (0.5 mL) was added 4N HCl in dioxanes (160 μL). The suspension was stirred overnight then concentrated to afford the HCl salt of the crude amine. To the crude amine in DMF (1 mL) was added *N*-methylmorpholine (25 μL, 0.23 mmol), 2-methoxycarbonylamino-3,3-dimethyl-butyric acid (22 mg, 0.12 mmol) and HATU (35 mg, 0.092 mmol). After stirring for overnight the reaction was quenched with formic acid then purified by reverse phase preparative HPLC (5-45% MeCN-H_2O; 0.1% formic acid modifier) to afford the title product (42 mg, 0.049 mmol, 57% yield). LCMS-ESI$^+$: calc'd for $C_{49}H_{59}N_8O_6$: 855.5 ($M+H^+$); Found: 855.5 ($M+H^+$).

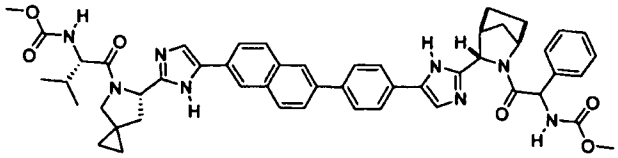
Example JY



3-{5-[4-(6-{2-[5-(2-Methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3*H*-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1*H*-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester



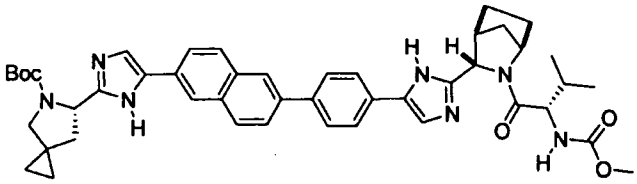
Methoxycarbonylamino-phenyl-acetic acid



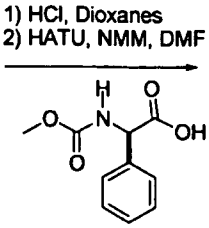
[1-(6-{5-[6-(4-{2-[2-(2-Methoxycarbonylamino-2-phenyl-acetyl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3*H*-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1*H*-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester

[1-(6-{5-[6-(4-{2-[2-(2-Methoxycarbonylamino-2-phenyl-acetyl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: To 3-{5-[4-(6-{2-[5-(2-methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (60 mg, 0.077 mmol) in dioxanes (2 mL) and MeOH (0.5 mL) was added 4N HCl in dioxanes (160 μL). The suspension was stirred for 6 h then concentrated to afford the HCl salt of the crude amine. To the crude amine in DMF (1 mL) was added *N*-methylmorpholine (25 μL, 0.23 mmol), methoxycarbonylamino-phenyl-acetic acid (22 mg, 0.12 mmol) and HATU (35 mg, 0.092 mmol). After stirring for overnight the reaction was quenched with formic acid then purified by reverse phase preparative HPLC (5-45% MeCN-H_2O; 0.1% formic acid modifier) to afford the different diastereomers of the title product (Diastereomer 1: 24 mg, 0.027 mmol, 36% yield; Diastereomer 2: 17 mg, 0.019 mmol, 22% yield). LCMS-ESI$^+$: calc'd for $C_{51}H_{55}N_8O_6$: 875.4 ($M+H^+$); Found: 875.5 ($M+H^+$).

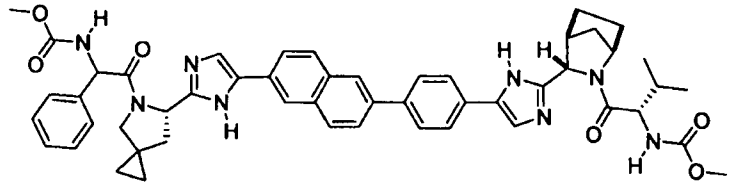
Example JZ



6-{5-[6-(4-{2-[2-(2-Methoxycarbonylamino-3-methyl-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3*H*-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1*H*-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carboxylic acid *tert*-butyl ester



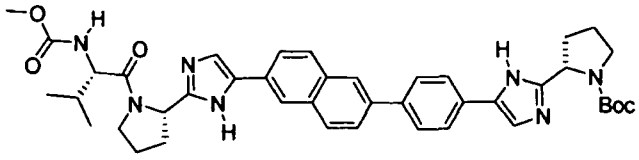
Methoxycarbonylamino-phenyl-acetic acid



[1-(3-{5-[4-(6-{2-[5-(2-Methoxycarbonylamino-2-phenyl-acetyl)-5-aza-spiro[2.4]hept-6-yl]-3*H*-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1*H*-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester

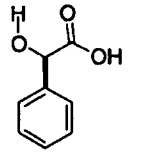
[1-(3-{5-[4-(6-{2-[5-(2-Methoxycarbonylamino-2-phenyl-acetyl)-5-aza-spiro[2.4]hept-6-yl]-3H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: To 6-{5-[6-(4-{2-[2-(2-Methoxycarbonylamino-3-methyl-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carboxylic acid *tert*-butyl ester (60 mg, 0.077 mmol) in dioxanes (2 mL) and MeOH (0.5 mL) was added 4N HCl in dioxanes (160 μL). The suspension was stirred for 6 h then concentrated to afford the HCl salt of the crude amine. To the crude amine in DMF (1 mL) was added *N*-methylmorpholine (25 μL, 0.23 mmol), methoxycarbonylamino-phenyl-acetic acid (22 mg, 0.12 mmol) and HATU (35 mg, 0.092 mmol). After stirring for overnight the reaction was quenched with formic acid then purified by reverse phase preparative HPLC (5-45% MeCN-H_2O; 0.1% formic acid modifier) to afford the title product as a diastereometric mixture (30 mg, 0.035 mmol, 39% yield). LCMS-ESI$^+$: calc'd for $C_{51}H_{55}N_8O_6$: 875.4 ($M+H^+$); Found: 875.6 ($M+H^+$).

Example KA

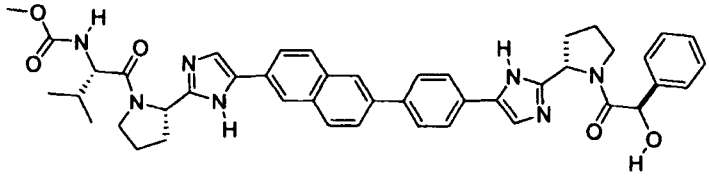


2-{5-[4-(6-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester

1) HCl, Dioxanes
2) HATU, NMM, DMF



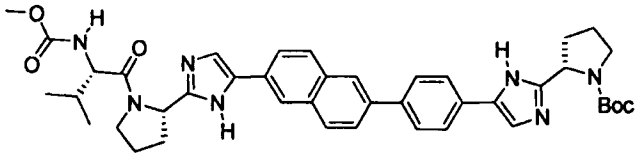
Hydroxy-phenyl-acetic acid



[1-(2-{5-[6-(4-{2-[1-(2-Hydroxy-2-phenyl-acetyl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester

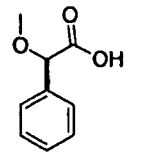
[1-(2-{5-[6-(4-{2-[1-(2-Hydroxy-2-phenyl-acetyl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: To 2-{5-[4-(6-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (40 mg, 0.055 mmol) in MeOH (1 mL) was added 4N HCl in dioxanes (160 μL). The reaction was stirred overnight then concentrated to afford the HCl salt of the crude amine. To the crude amine in DMF (1 mL) was added *N*-methylmorpholine (100 μL), hydroxy-phenyl-acetic acid (21 mg, 0.083 mmol) and HATU (35 mg, 0.092 mmol). After stirring overnight the reaction was quenched with formic acid then purified by reverse phase preparative HPLC (10-40% MeCN-H_2O; 0.1% formic acid modifier) to afford the title compound (32 mg, 0.042 mmol, 76% yield). LCMS-ESI$^+$: calc'd for $C_{45}H_{48}N_7O_5$: 766.4 ($M+H^+$); Found: 766.4 ($M+H^+$).

Example KB

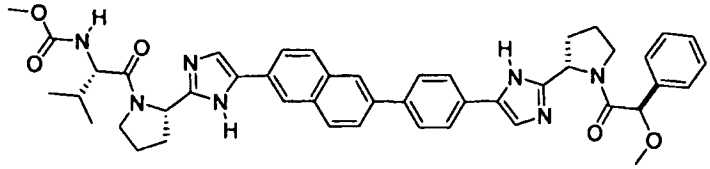


2-{5-[4-(6-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester

1) HCl, Dioxanes
2) EEDQ, DMF



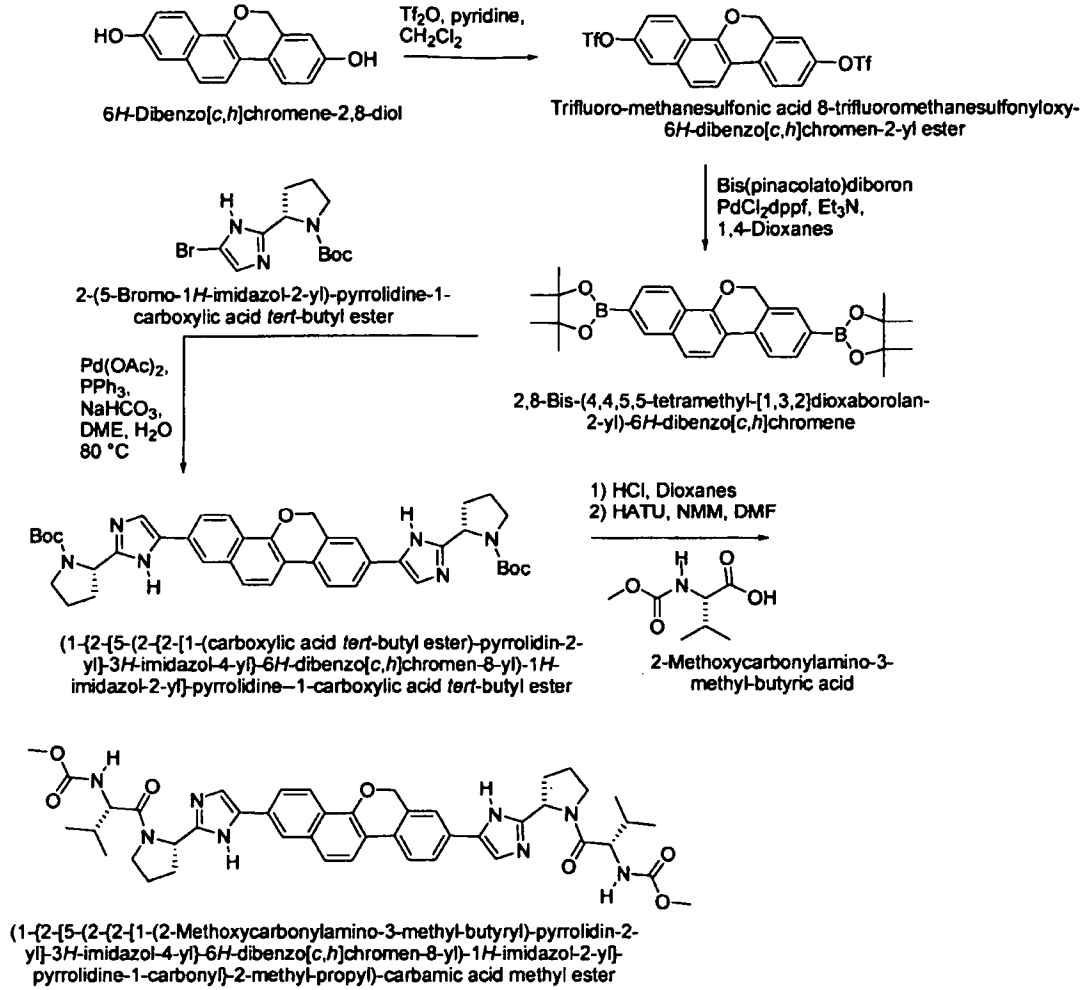
Methoxy-phenyl-acetic acid



[1-(2-{5-[6-(4-{2-[1-(2-Methoxy-2-phenyl-acetyl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester

[1-(2-{5-[6-(4-{2-[1-(2-Methoxy-2-phenyl-acetyl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: To 2-{5-[4-(6-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (40 mg, 0.055 mmol) in MeOH (1 mL) was added 4N HCl in dioxanes (160 μL). The reaction was stirred overnight then concentrated to afford the HCl salt of the crude amine. To the crude amine in CH_2Cl_2 and DMF (1 ml of 4:1 solution) was added (R)-methoxy-phenyl-acetic acid (13.7 mg, 0.083 mmol) and 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (17 mg, 0.069 mmol). After stirring overnight the reaction was concentrated then purified by reverse phase preparative HPLC (10-40% MeCN-H_2O; 0.1% formic acid modifier) to afford the title compound (13.1 mg, 0.017 mmol, 31% yield). LCMS-ESI$^+$: calc'd for $C_{46}H_{50}N_7O_5$: 780.4 ($M+H^+$); Found: 780.4 ($M+H^+$).

Example KC



Trifluoro-methanesulfonic acid 8-trifluoromethanesulfonyloxy-6H-dibenzo[c,h]chromen-2-yl ester: To a suspension of 6H-Dibenzo[c,h]chromene-2,8-diol (3.46 g, 13.1 mmol) in CH_2Cl_2 at 0 °C was added pyridine (2.65 mL, 32.8 mmol) followed by triflic anhydride (4.85 mL, 28.8 mmol). The reaction was allowed to warm to room temperature then poured into H_2O, The organic phase was collected then washed with 1N HCl and Brine. After concentration, the crude material was recrystallized from CH_2Cl_2/Hexanes to afford the title compound (4.07 g, 7.70 mmol, 59% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.35 (d, 1H), 7.88 (d, 1H), 7.79 (d, 1H), 7.71 (d, 1H), 7.57 (d, 1H), 7.40 (dd, 1H), 7.34 (dd, 1H), 7.18 (s, 1H), 5.34 (s, 2H).

2,8-Bis-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-6H-dibenzo[c,h]chromene: A solution of Trifluoro-methanesulfonic acid 8-trifluoromethanesulfonyloxy-6H-dibenzo[c,h]chromen-2-yl ester (1.00 g, 1.9 mmol), bis(pinacolato)diboron (1.44 g, 5.7 mmol)

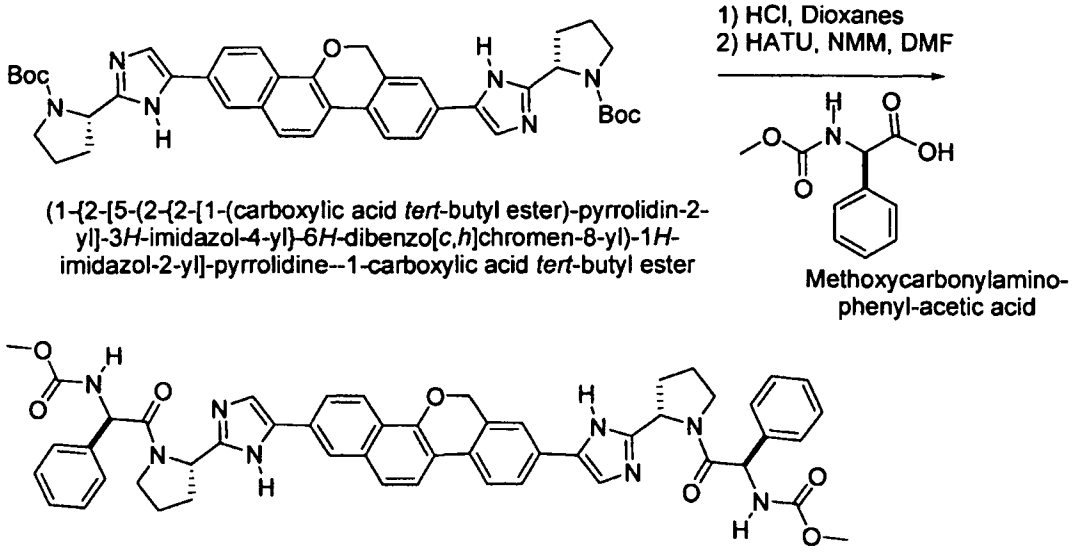
and triethylamine (1.32 mL, 9.5 mmol) in 1,4-Dioxanes (20 mL) was degassed with Argron gas for 20 minutes. To the degassed solution was added $PdCl_2$dppf (139 mg, 0.19 mmol) and then the reaction was heated to 90° C overnight. Reaction stalled at approximately 60% conversion so additional $PdCl_2$dppf (139 mg, 0.19 mmol) and bis(pinacolato)diboron (0.500 g, 1.97 mmol) was added and reaction stirred for 3 h. After cooling to room temperature, the crude material was preabsorbed onto silica then purified by silica gel chromatography (25-50% CH_2Cl_2/Hexanes) to afford the title compound [1.106 g, >100 % yield due to some bis(pinacolato)diboron impurity]. LCMS-ESI$^+$: calc'd for $C_{29}H_{35}B_2O_5$: 485.3 ($M+H^+$); Found: 485.3 ($M+H^+$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.28 (s, 1H), 8.21 (d, 1H), 7.84-7.81 (m, 3H), 7.72 (d, 1H), 7.64 (s, 1H), 7.55 (d, 1H), 5.31 (s, 2H), 1.38 (s, 12H), 1.35 (s, 12H).

(1-{2-[5-(2-{2-[1-(carboxylic acid *tert*-butyl ester)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-6H-dibenzo[c,h]chromen-8-yl)-1H-imidazol-2-yl]-pyrrolidine--1-carboxylic acid *tert*-butyl ester: A solution of 2,8-bis-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-6H-dibenzo[c,h]chromene (500 mg, 1.03 mmol), 2-(5-bromo-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (979 mg, 3.09 mmol) and $NaHCO_3$ (3.8 ml of 1N solution, 3.8 mmol) in DME (10 mL) and DMF (3 mL) was degassed with Argron gas for 20 minutes. To the degassed solution was added $Pd(OAc)_2$ (22 mg, 0.098 mmol) and PPh_3 (52 mg, 0.19 mmol) and then the reaction was heated to 90° C overnight. After cooling to room temperature, the reaction was poured into H_2O then extracted with EtOAc. The organic phase was then washed with Brine. Purification of the crude material by silica gel chromatography (50-100% EtOAc/Hexanes) afforded the title compound [250 mg, 0.35 mmol, 35% yield). LCMS-ESI$^+$: calc'd for $C_{41}H_{47}N_6O_5$: 703.4 ($M+H^+$); Found: 703.2 ($M+H^+$).

(1-{2-[5-(2-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-6H-dibenzo[c,h]chromen-8-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: To (1-{2-[5-(2-{2-[1-(carboxylic acid *tert*-butyl ester)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-6H-dibenzo[c,h]chromen-8-yl)-1H-imidazol-2-yl]-pyrrolidine--1-carboxylic acid *tert*-butyl ester (70 mg, 0.10 mmol) in MeOH (0.5 mL) was added 4N HCl in dioxanes (1 mL). The reaction was stirred overnight then concentrated to afford the HCl salt of the crude amine. To the crude amine in DMF (1 mL) was added *N*-methylmorpholine (44 μL, 0.40 mmol), HATU (46 mg, 0.12 mmol) and 2-methoxycarbonylamino-3-methyl-butyric acid (26 mg, 0.15 mmol). After stirring for 3h the reaction was quenched with formic acid then purified by reverse phase preparative HPLC (10-

40% MeCN-H_2O; 0.1% formic acid modifier) to afford the title compound (27 mg, 0.033 mmol, 33% yield). LCMS-ESI$^+$: calc'd for $C_{45}H_{53}N_8O_7$: 817.4 ($M+H^+$); Found: 817.4 ($M+H^+$).

Example KD



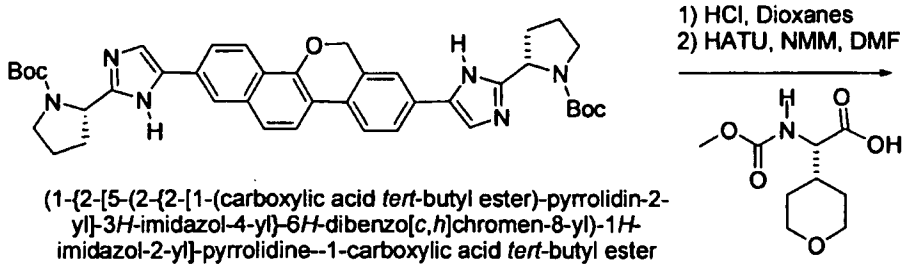
(1-{2-[5-(2-{2-[1-(carboxylic acid *tert*-butyl ester)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-6*H*-dibenzo[*c*,*h*]chromen-8-yl)-1*H*-imidazol-2-yl]-pyrrolidine--1-carboxylic acid *tert*-butyl ester

Methoxycarbonylamino-phenyl-acetic acid

(2-{2-[5-(2-{2-[1-(2-Methoxycarbonylamino-2-phenyl-acetyl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-6*H*-dibenzo[*c*,*h*]chromen-8-yl)-1*H*-imidazol-2-yl]-pyrrolidin-1-yl}-2-oxo-1-phenyl-ethyl)-carbamic acid methyl ester

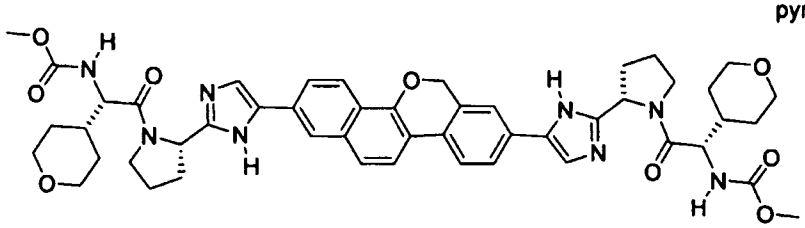
(2-{2-[5-(2-{2-[1-(2-Methoxycarbonylamino-2-phenyl-acetyl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-6H-dibenzo[c,h]chromen-8-yl)-1H-imidazol-2-yl]-pyrrolidin-1-yl}-2-oxo-1-phenyl-ethyl)-carbamic acid methyl ester: To (1-{2-[5-(2-{2-[1-(carboxylic acid *tert*-butyl ester)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-6H-dibenzo[c,h]chromen-8-yl)-1H-imidazol-2-yl]-pyrrolidine--1-carboxylic acid *tert*-butyl ester (60 mg, 0.85 mmol) in MeOH (0.5 mL) was added 4N HCl in dioxanes (0.5 mL). The reaction was stirred for 4h then concentrated to afford the HCl salt of the crude amine. To the crude amine in CH_2Cl_2 (1 mL) was added K_3PO_4 (90 mg, 0.42 mmol), HATU (80 mg, 0.21 mmol) and methoxycarbonylamino-phenyl-acetic acid (45 mg, 0.21 mmol). After stirring for 3h the reaction was filtered then concentrated. Purification by reverse phase preparative HPLC (10-40% MeCN-H_2O; 0.1% formic acid modifier) afforded the title compound (34 mg, 0.038 mmol, 45% yield). LCMS-ESI$^+$: calc'd for $C_{51}H_{49}N_8O_7$: 885.4 ($M+H^+$); Found: 885.9 ($M+H^+$).

Example KE



(1-{2-[5-(2-{2-[1-(carboxylic acid *tert*-butyl ester)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-6*H*-dibenzo[*c*,*h*]chromen-8-yl)-1*H*-imidazol-2-yl]-pyrrolidine--1-carboxylic acid *tert*-butyl ester

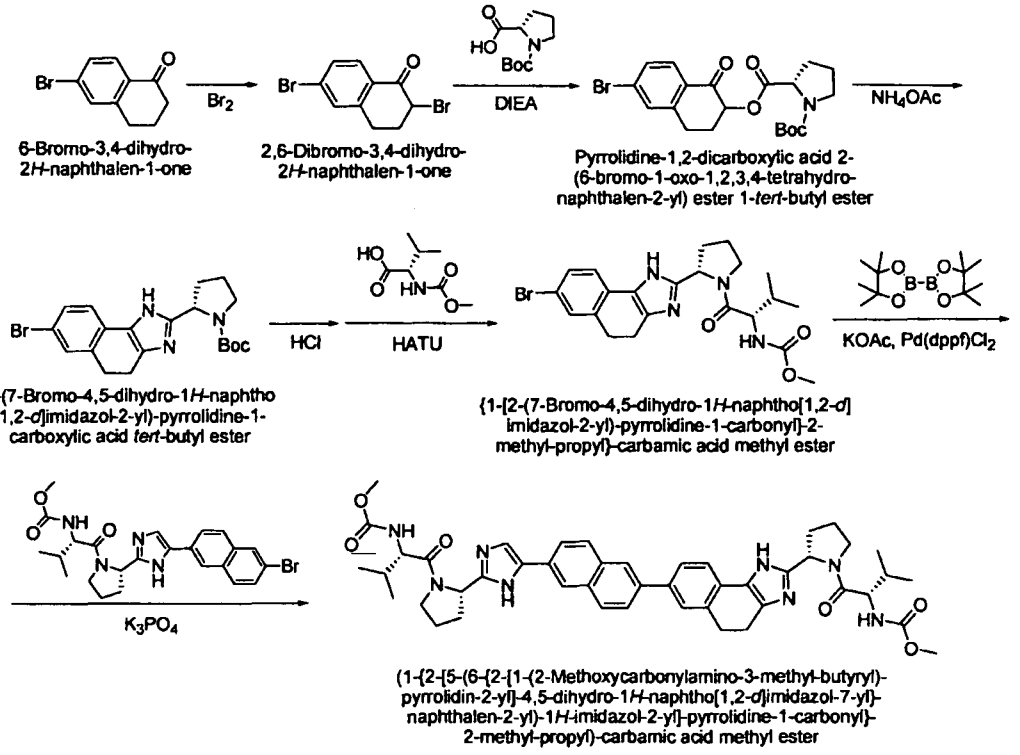
Methoxycarbonylamino-(tetrahydro-pyran-4-yl)-acetic acid



[2-(2-{5-[2-(2-{1-[2-Methoxycarbonylamino-2-(tetrahydro-pyran-4-yl)-acetyl]-pyrrolidin-2-yl}-3*H*-imidazol-4-yl)-6*H*-dibenzo[*c*,*h*]chromen-8-yl]-1*H*-imidazol-2-yl}-pyrrolidin-1-yl)-2-oxo-1-(tetrahydro-pyran-4-yl)-ethyl]-carbamic acid methyl ester

[2-(2-{5-[2-(2-{1-[2-Methoxycarbonylamino-2-(tetrahydro-pyran-4-yl)-acetyl]-pyrrolidin-2-yl}-3H-imidazol-4-yl)-6H-dibenzo[c,h]chromen-8-yl]-1H-imidazol-2-yl}-pyrrolidin-1-yl)-2-oxo-1-(tetrahydro-pyran-4-yl)-ethyl]-carbamic acid methyl ester: To (1-{2-[5-(2-{2-[1-(carboxylic acid *tert*-butyl ester)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-6H-dibenzo[c,h]chromen-8-yl)-1H-imidazol-2-yl]-pyrrolidine--1-carboxylic acid *tert*-butyl ester (20 mg, 0.028 mmol) in MeOH (0.5 mL) was added 4N HCl in dioxanes (0.5 mL). The reaction was stirred for 4h then concentrated to afford the HCl salt of the crude amine. To the crude amine in DMF (1 mL) was added *N*-methylmorpholine (15 μL, 0.14 mmol), HATU (33 mg, 0.085 mmol) and methoxycarbonylamino-(tetrahydro-pyran-4-yl)-acetic acid (19 mg, 0.085 mmol). After stirring overnight the reaction was quenched with formic acid then purified by reverse phase preparative HPLC (10-40% MeCN-H_2O; 0.1% formic acid modifier) to afford the title compound (15 mg, 0.017 mmol, 59% yield). LCMS-ESI$^+$: calc'd for $C_{49}H_{57}N_8O_9$: 901.4 ($M+H^+$); Found: 901.4 ($M+H^+$).

Example KF



2-6-Dibromo-3,4-dihydro-2H-naphthalen-1-one : 6-Bromo-3,4-dihydro-2H-naphthalen-1-one (2.0 g) was dissolved in ether (80 mL), and Br_2 (455 µl) was added at 0°C over 30 min. After diluting with ether (80 mL), the reaction mixture was washed with 10% Na_2SO_3, sat. $NaHCO_3$ and brine. After the solvent was removed, the crude material was used for the next step without further purification.

Pyrrolidine-1,2-dicarboxylic acid 2-(6-bromo-1-oxo-1,2,3,4-tetrahydro-naphthalen-2-yl) ester 1-*tert*-butyl ester : The crude 2-6-dibromo-3,4-dihydro-2H-naphthalen-1-one and pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester (3.15 g)were dissolved in MeCN (80 mL), and DIEA (2.55 mL) was added. The mixture was stirred at 65°C for overnight and diluted with ethyl acetate. The mixture was washed with 1 N HCl. $NaHCO_3$ and brine. After the solvent was removed, the resulting material was subjected to silica gel chromatography using effluent of 10 - 40 % ethyl acetate and hexanes. The fractions containing product were combined and the solvent was removed under reduced pressure to provide pyrrolidine-1,2-dicarboxylic acid 2-(6-bromo-1-oxo-1,2,3,4-tetrahydro-naphthalen-2-yl) ester 1-*tert*-butyl ester (1.54 g, 40 % over 2 steps).

2-(7-Bromo-4,5-dihydro-1H-naphtho[1,2-d]imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester : Pyrrolidine-1,2-dicarboxylic acid 2-(6-bromo-1-oxo-1,2,3,4-tetrahydro-naphthalen-2-yl) ester 1-*tert*-butyl ester (1.54 g) and ammonium acetate (2.71 g) were suspended in toluene (35 mL). The reaction mixture was stirred at 110°C for overnight and evaporated under reduced pressure and resulting residue was taken up in ethyl acetate (100 mL). The organic phase was washed with saturated sodium bicarbonate (1 x 150 mL) and dried over sodium sulfate. After the solvent was removed, the resulting oil was subjected to silica gel chromatography using effluent of 60 -90 % ethyl acetate and hexanes. The fractions containing product were combined and the solvent was removed under reduced pressure to provide 2-(7-bromo-4,5-dihydro-1H-naphtho[1,2-d]imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (1.05 g, 71 %) as a pale brown solid. MS (ESI) *m/z* 418.1 $[M + H]^+$.

(1-{2-[5-(6-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-4,5-dihydro-1H-naphtho[1,2-d]imidazol-7-yl}-naphthalen-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: Title compound was prepared according to the method employed to [1-(6-{5-[6-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-4-(2-methoxy-ethoxy)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: MS (ESI) *m/z* 815.5 $[M + H]^+$.

BIOLOGICAL ASSAYS

Effect of serum proteins on replicon potency

Replicon assays are conducted in normal cell culture medium (DMEM + 10%FBS) supplemented with physiologic concentrations of human serum albumin (40 mg/mL) or α-acid glycoprotein (1 mg/mL). EC_{50}s in the presence of human serum proteins are compared to the EC_{50} in normal medium to determine the fold shift in potency.

Enyzmatic Selectivity: The inhibition of mammalian proteases including Porcine Pancreatic Elastase, Human Leukocyte Elastase, Protease 3, and Cathepsin D are measured at K_m for the respective substrates for each enzyme. IC_{50} for each enzyme is compared to the IC_{50} obtained with NS3 1b protease to calculate selectivity. Representative compounds of the invention have shown activity.

MT-4 Cell Cytotoxicity: MT4 cells are treated with serial dilutions of compounds for a five day period. Cell viability is measured at the end of the treatment period using the Promega CellTiter-Glo assay and non-linear regression is performed to calculate CC_{50}.

Compound Concentration Associated with Cells at EC_{50}: Huh-luc cultures are incubated with compound at concentrations equal to EC_{50}. At multiple time points (0 – 72 hours), cells are washed 2X with cold medium and extracted with 85% acetonitrile; a sample of the media at each time-point will also be extracted. Cell and media extracts are analyzed by LC/MS/MS to determine the Molar concentration of compounds in each fraction. Representative compounds of the invention have shown activity.

Solubility and Stability: Solubility is determined by taking an aliquot of 10 mM DMSO stock solution and preparing the compound at a final concentration of 100 μM in the test media solutions (PBS, pH 7.4 and 0.1 N HCl, pH 1.5) with a total DMSO concentration of 1%. The test media solutions are incubated at room temperature with shaking for 1 hr. The solutions will then be centrifuged and the recovered supernatants are assayed on the HPLC/UV. Solubility will be calculated by comparing the amount of compound detected in the defined test solution compared to the amount detected in DMSO at the same concentration. Stability of compounds after an 1 hour incubation with PBS at 37°C will also be determined.

Stability in Cryopreserved Human, Dog, and Rat Hepatocytes: Each compound is incubated for up to 1 hour in hepatocyte suspensions (100 μl, 80,000°Cells per well) at 37°C. Cryopreserved hepatocytes are reconstituted in the serum-free incubation medium. The suspension is transferred into 96-well plates (50 μL/well). The compounds are diluted to 2 μM in incubation medium and then are added to hepatocyte suspensions to start the incubation. Samples are taken at 0, 10, 30 and 60 minutes after the start of incubation and reaction will be quenched with a mixture consisting of 0.3% formic acid in 90% acetonitrile/10% water. The concentration of the compound in each sample is analyzed using LC/MS/MS. The disappearance half-life of the compound in hepatocyte suspension is determined by fitting the concentration-time data with a monophasic exponential equation. The data will also be scaled up to represent intrinsic hepatic clearance and/or total hepatic clearance.

Stability in Hepatic S9 Fraction from Human, Dog, and Rat: Each compound is incubated for up to 1 hour in S9 suspension (500 μl, 3 mg protein/mL) at 37°C (n = 3). The compounds are added to the S9 suspension to start the incubation. Samples are taken at 0, 10, 30, and 60 minutes after the start of incubation. The concentration of the compound in each sample is analyzed using LC/MS/MS. The disappearance half-life of the compound in S9 suspension is determined by fitting the concentration-time data with a monophasic exponential equation.

Caco-2 Permeability: Compounds are assayed via a contract service (Absorption Systems, Exton, PA). Compounds are provided to the contractor in a blinded manner. Both forward (A-to-B) and reverse (B-to-A) permeability will be measured. Caco-2 monolayers are grown to

confluence on collagen-coated, microporous, polycarbonate membranes in 12-well Costar TRANSWELL® plates. The compounds are dosed on the apical side for forward permeability (A-to-B), and are dosed on the basolateral side for reverse permeability (B-to-A). The cells are incubated at 37°C with 5% CO_2 in a humidified incubator. At the beginning of incubation and at 1 hr and 2 hr after incubation, a 200-μL aliquot is taken from the receiver chamber and replaced with fresh assay buffer. The concentration of the compound in each sample is determined with LC/MS/MS. The apparent permeability, Papp, is calculated.

Plasma Protein Binding:

Plasma protein binding is measured by equilibrium dialysis. Each compound is spiked into blank plasma at a final concentration of 2 μM. The spiked plasma and phosphate buffer is placed into opposite sides of the assembled dialysis cells, which will then be rotated slowly in a 37°C water bath. At the end of the incubation, the concentration of the compound in plasma and phosphate buffer is determined. The percent unbound is calculated using the following equation:

$$\% \text{ Unbound} = 100 \bullet \left(\frac{C_f}{C_b + C_f} \right)$$

Where C_f and C_b are free and bound concentrations determined as the post-dialysis buffer and plasma concentrations, respectively.

CYP450 Profiling:

Each compound is incubated with each of 5 recombinant human CYP450 enzymes, including CYP1A2, CYP2C9, CYP3A4, CYP2D6 and CYP2C19 in the presence and absence of NADPH. Serial samples will be taken from the incubation mixture at the beginning of the incubation and at 5, 15, 30, 45 and 60 minutes after the start of the incubation. The concentration of the compound in the incubation mixture is determined by LC/MS/MS. The percentage of the compound remaining after incubation at each time point is calculated by comparing with the sampling at the start of incubation.

Stability in Rat, Dog, Monkey and Human Plasma:

Compounds will be incubated for up to 2 hours in plasma (rat, dog, monkey, or human) at 37°C. Compounds are added to the plasma at final concentrations of 1 and 10 μg/mL. Aliquots are taken at 0, 5, 15, 30, 60, and 120 minutes after adding the compound. Concentration of compounds and major metabolites at each timepoint are measured by LC/MS/MS.

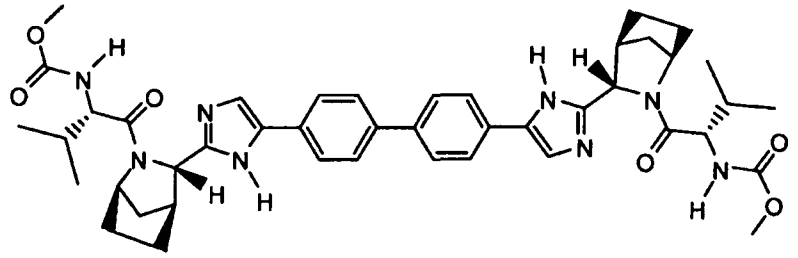
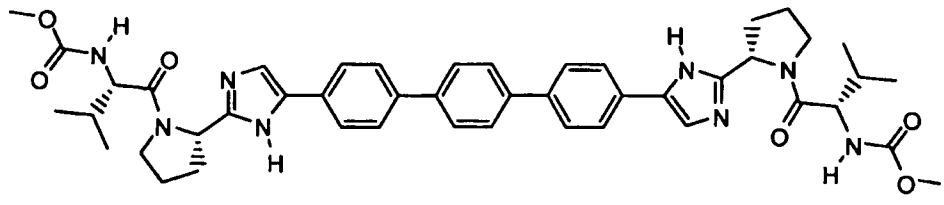
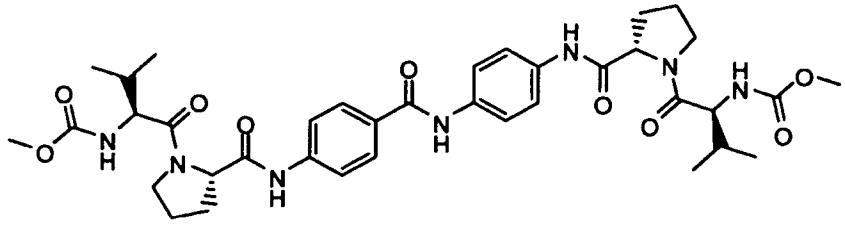
Evaluation of cell-based anti-HCV activity:

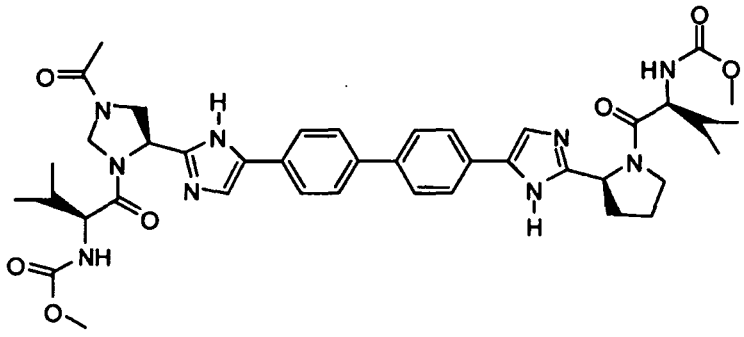
Antiviral potency (EC_{50}) was determined using a *Renilla* luciferase (RLuc)-based HCV replicon reporter assay. To perform the assay, HCV 1b RLuc cells (harboring a dicistronic

genotype 1b Con1 replicon that encodes a RLuc reporter), or HCV 1a RLuc cells (harboring a dicistronic genotype 1a H77 replicon that encodes a RLuc reporter), were dispensed into 384-well plates. Compounds were re-suspended in DMSO at a concentration of 10 mM and serially diluted in DMSO using an automated pipeting instrument. Serially diluted compounds were mixed with cell culture media and added to the seeded cells. DMSO was used as a negative (solvent) control, and the protease inhibitor ITMN-191 was included at a concentration > 100 x EC_{50} as a positive control. 72 hours later, cells were lysed and *Renilla* luciferase activity quantified as recommended by the manufacturer (Promega-Madison, WI). Non-linear regression was performed to calculate EC_{50} values.

Typically the compounds of the invention can inhibit multiple genotypes of HCV. For example, compounds of the present invention are active against multiple HCV genotypes selected from 1a, 1b, 2a, 2b, 3a, 4a, and 5a.

Biological data (antiviral potency [EC_{50}] was determined using a *Renilla* luciferase (RLuc)-based HCV replicon reporter assay - HCV 1b RLuc) for representative compounds of the invention is provided in the following table. These compounds can be prepared using procedures similar to those described above.

Representative Compound of the Invention	**Activity (nM)**
	0.0100
	0.0240
	37.7670



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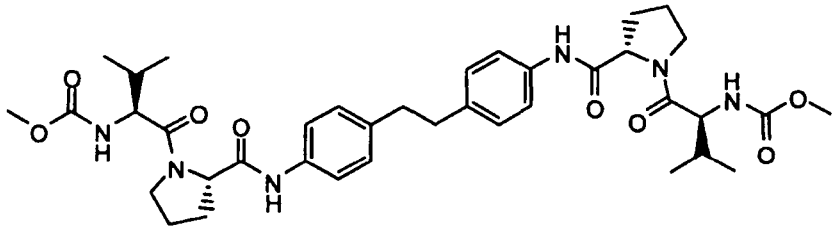

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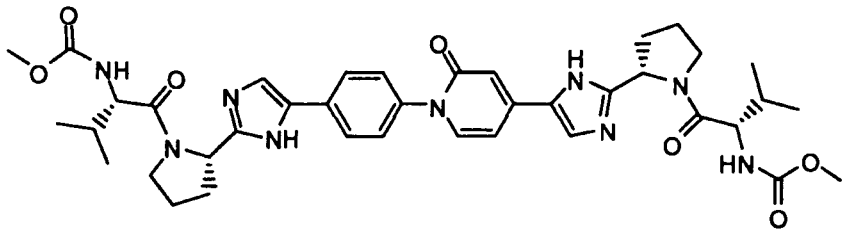
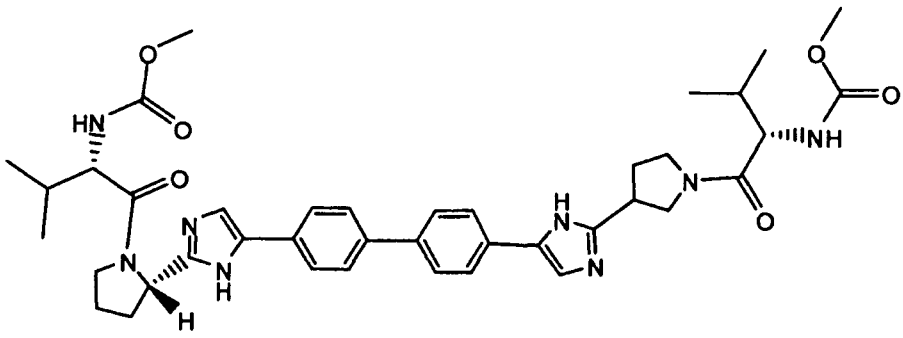


38.1323



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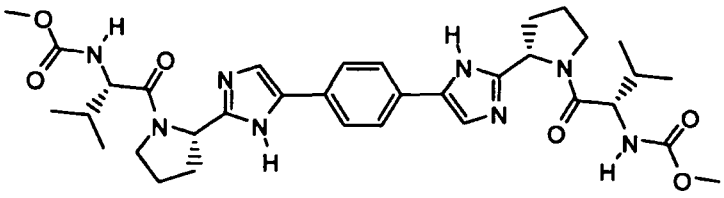

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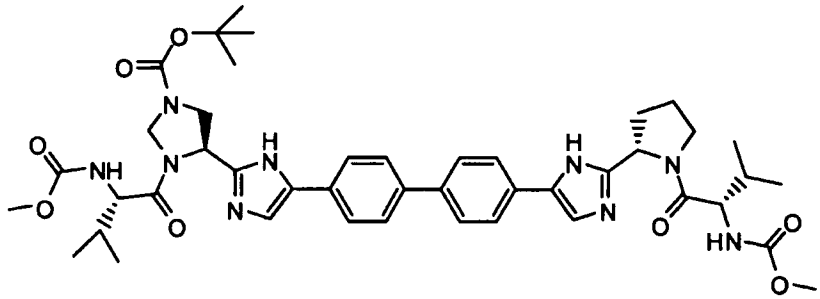

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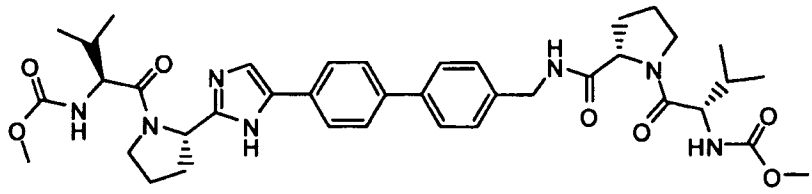

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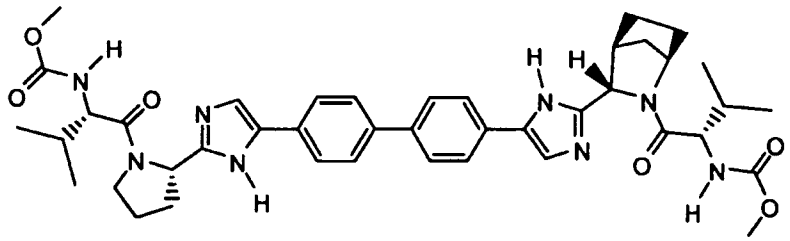

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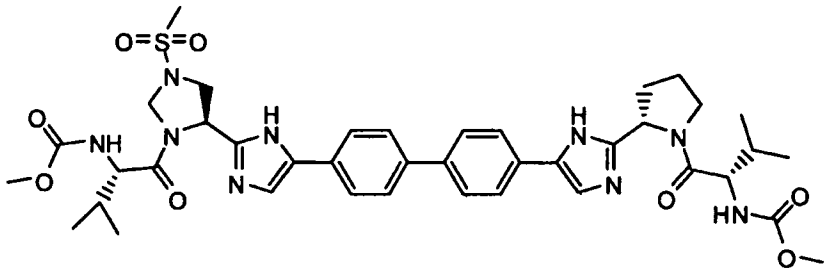

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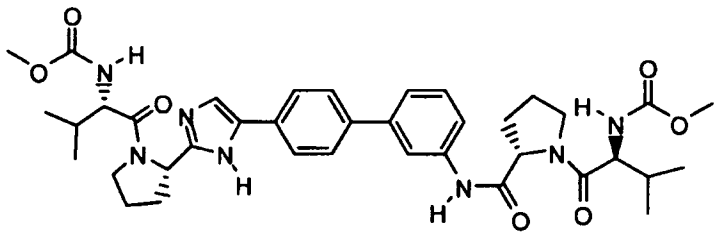

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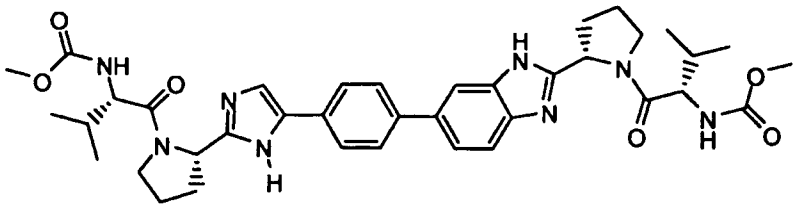

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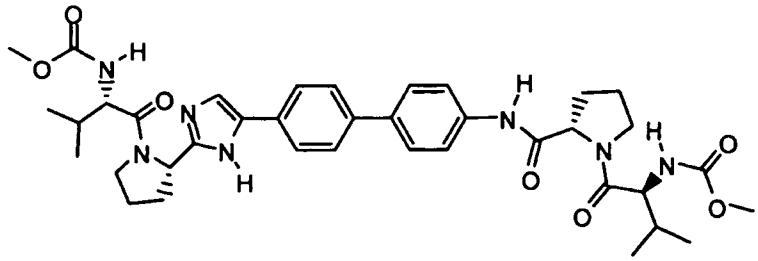

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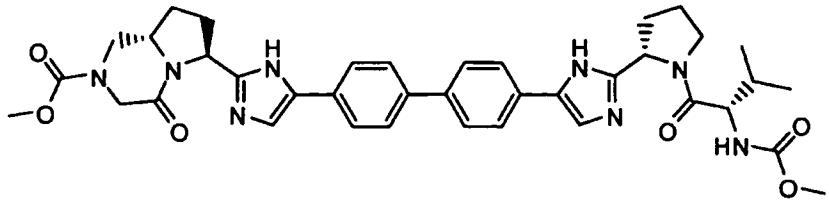

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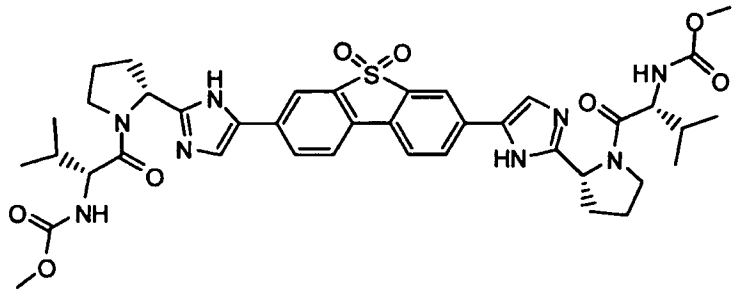

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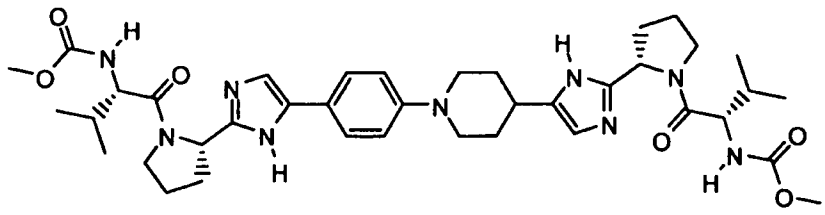

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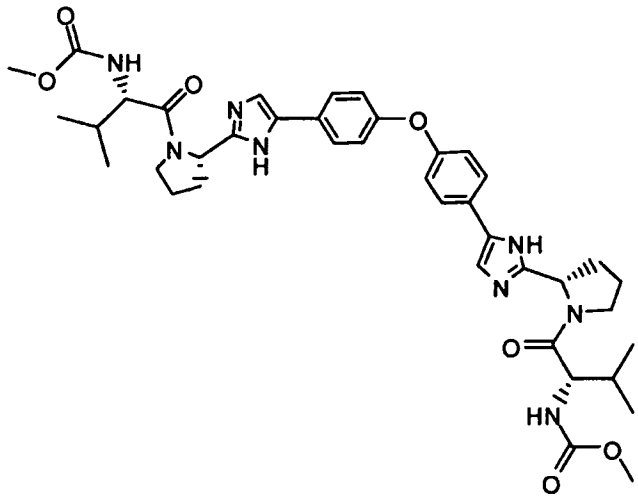

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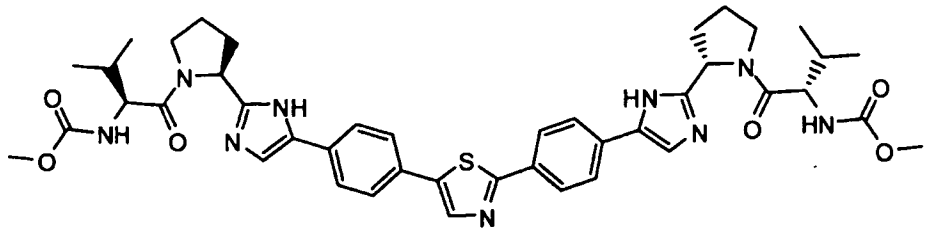

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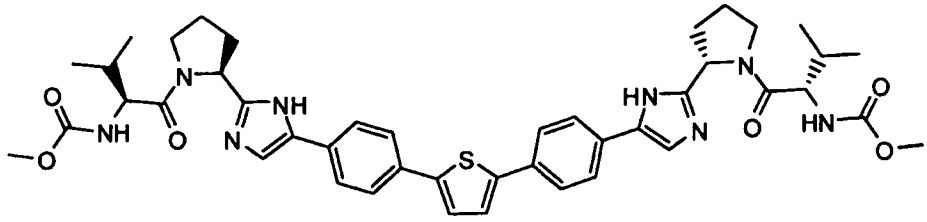

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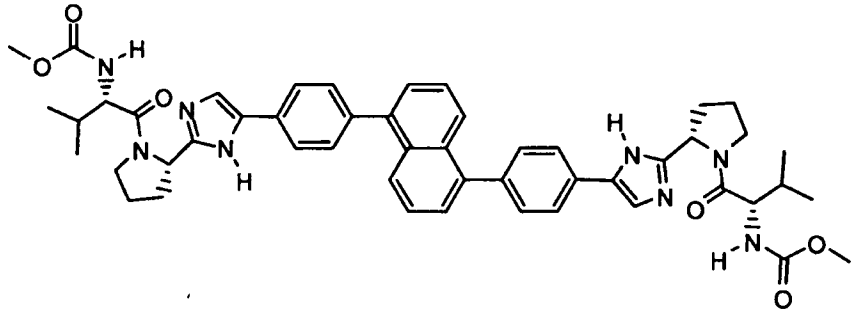

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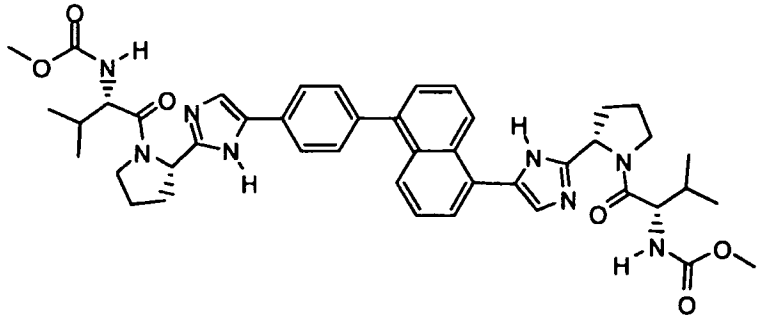

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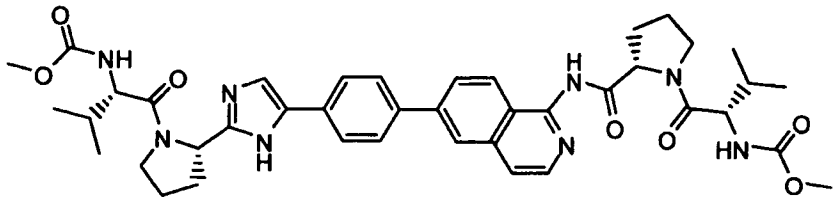

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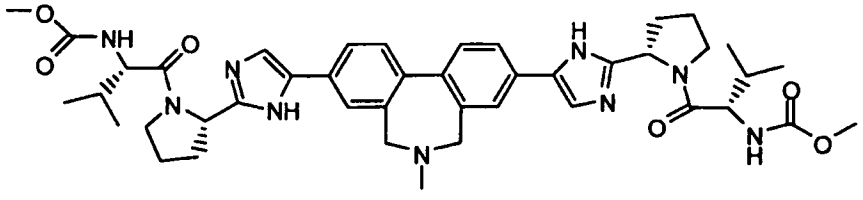

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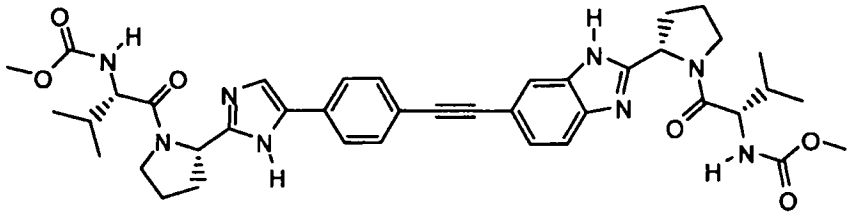

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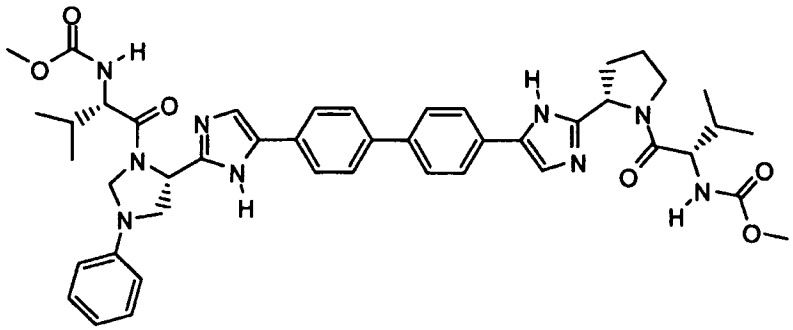

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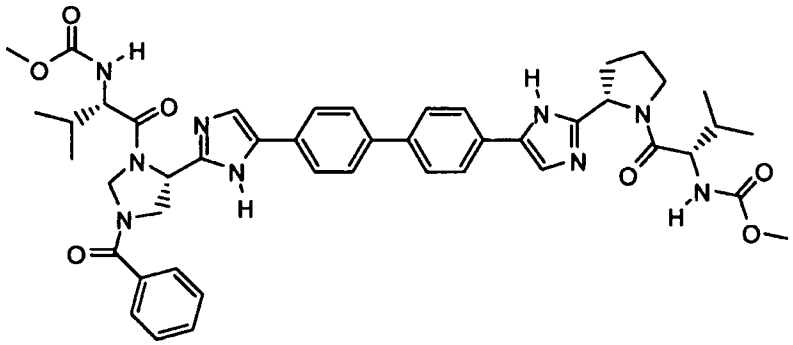

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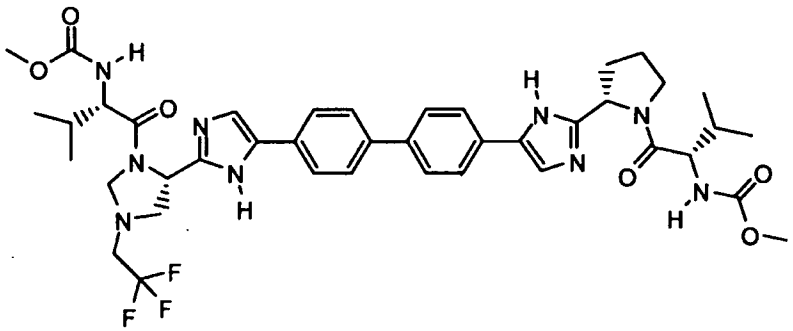

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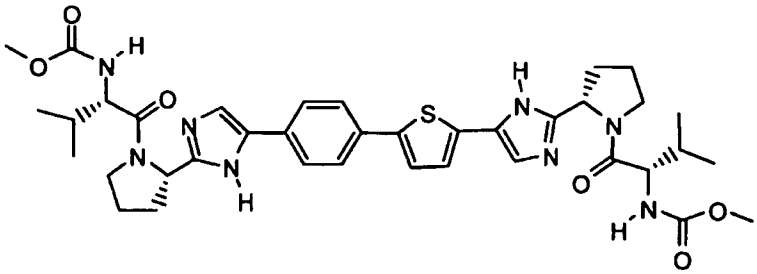

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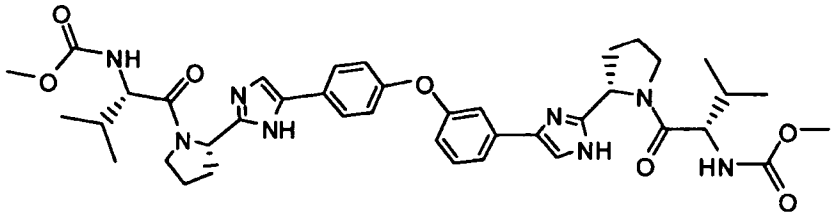

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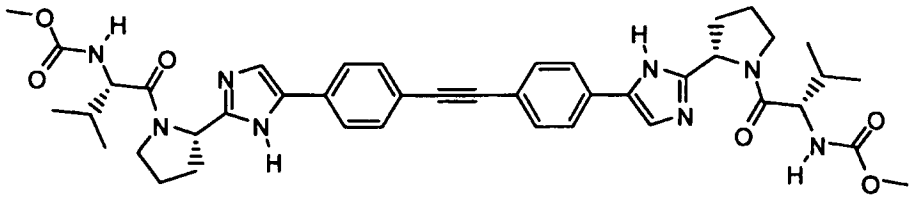

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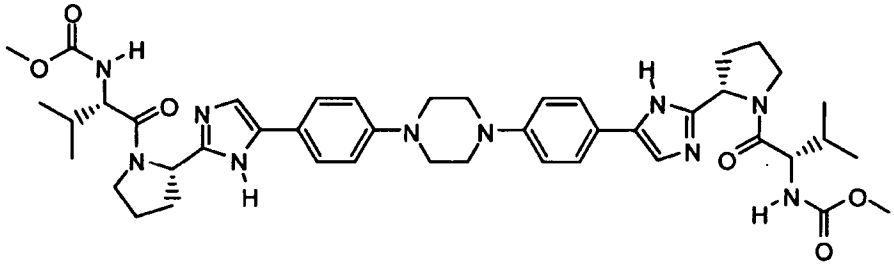

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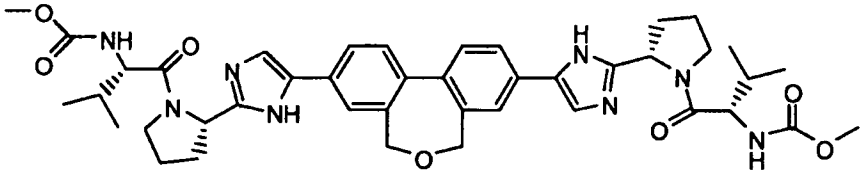

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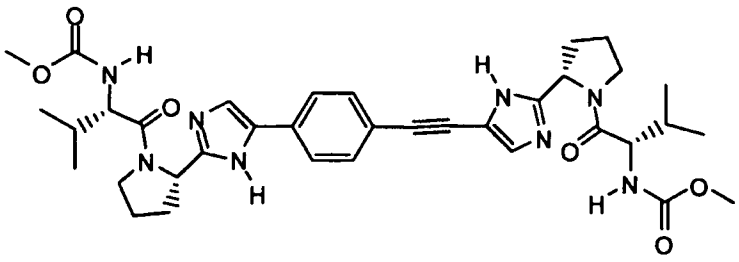

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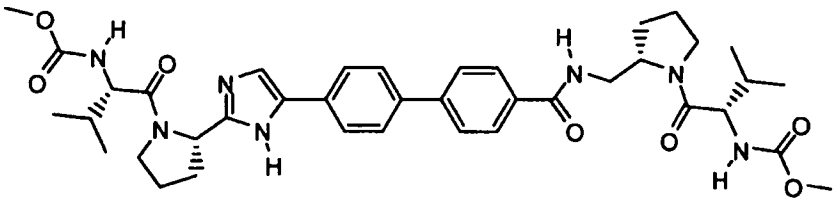

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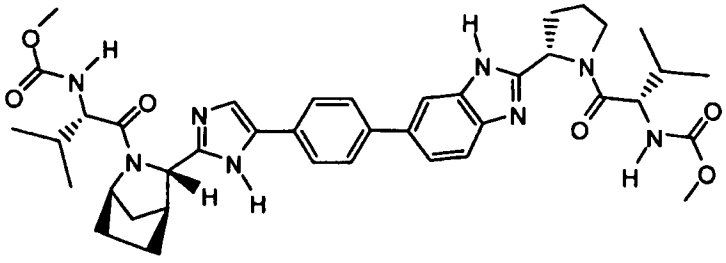

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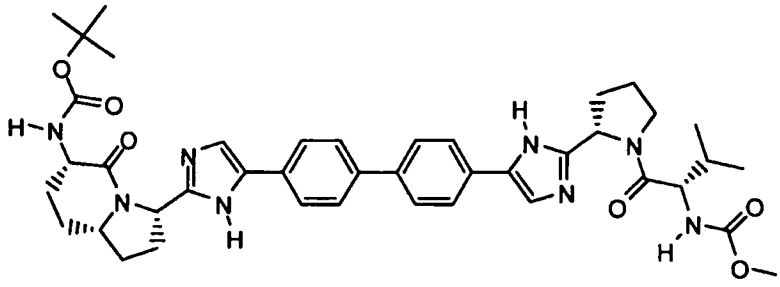

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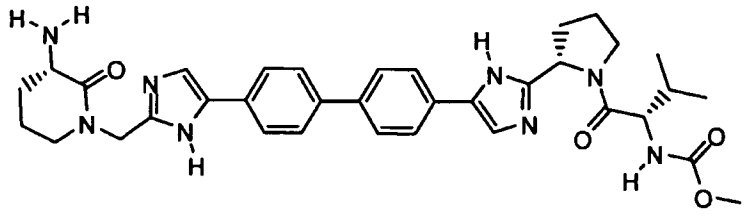

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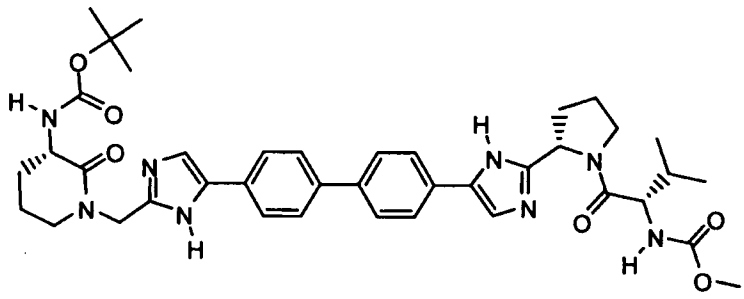

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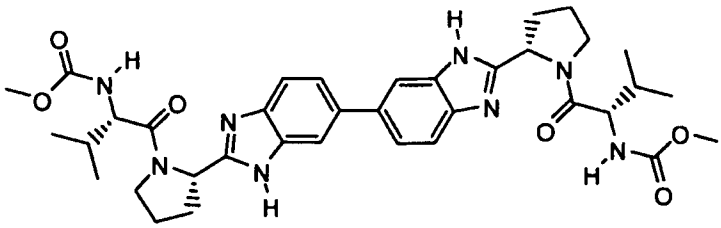

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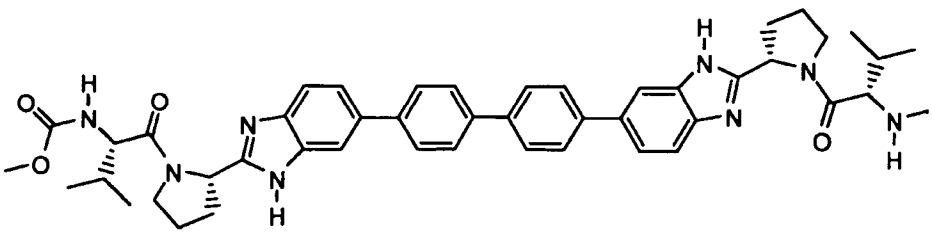

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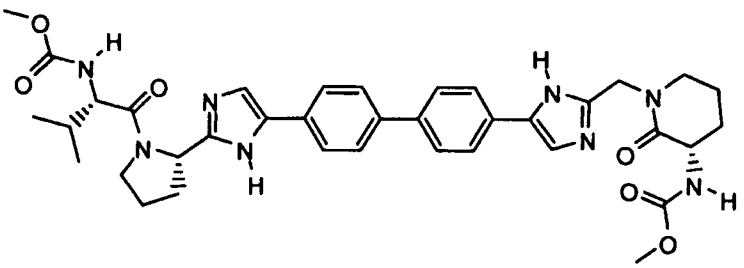

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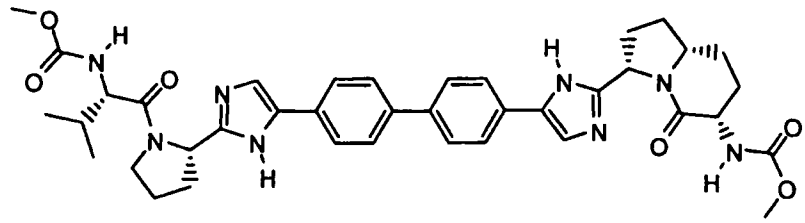

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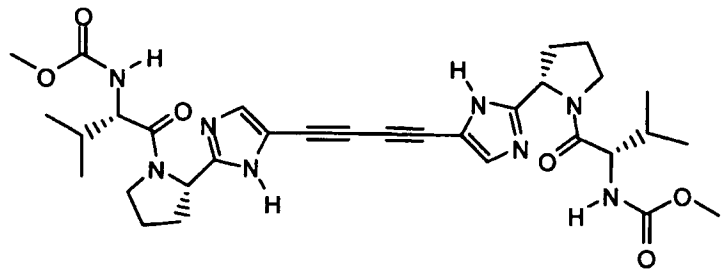

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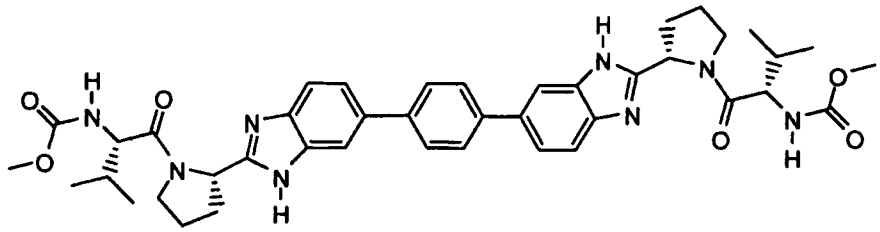

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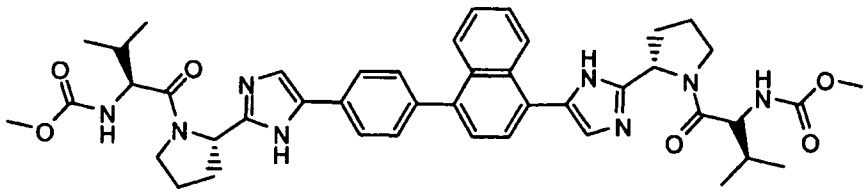

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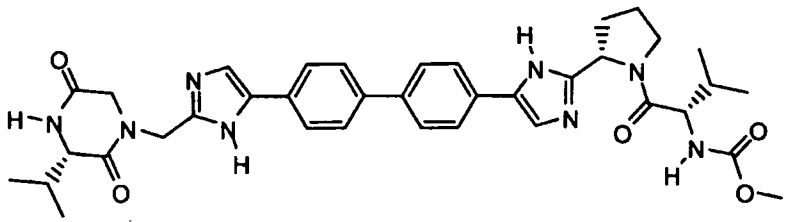

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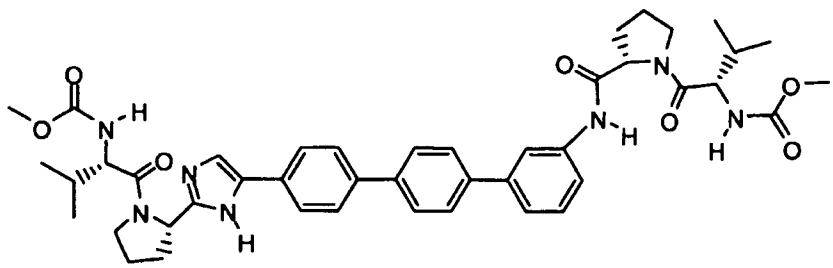

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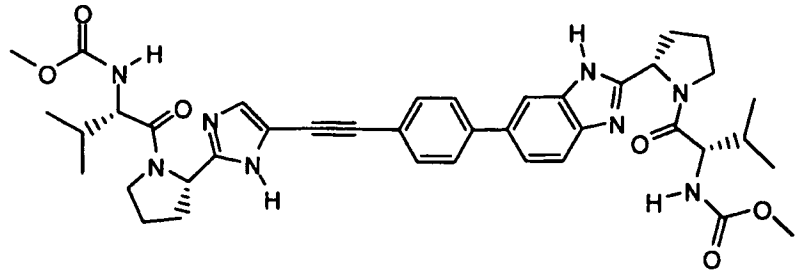

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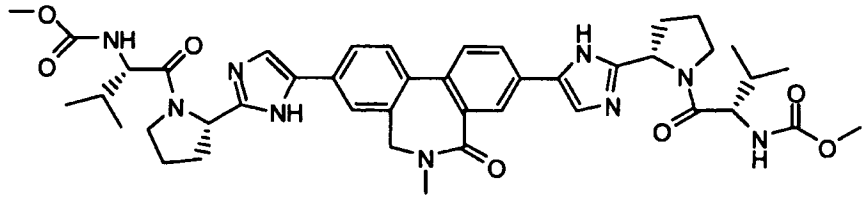

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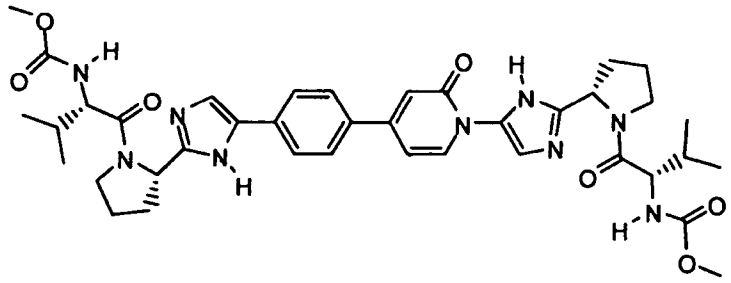

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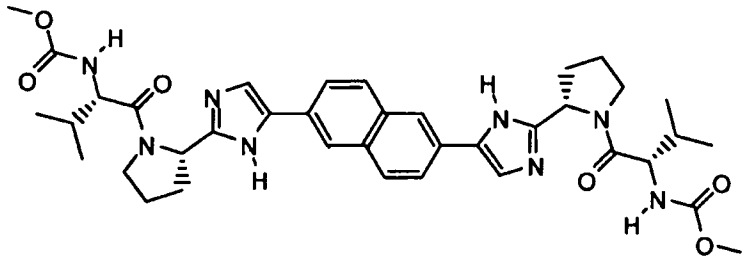

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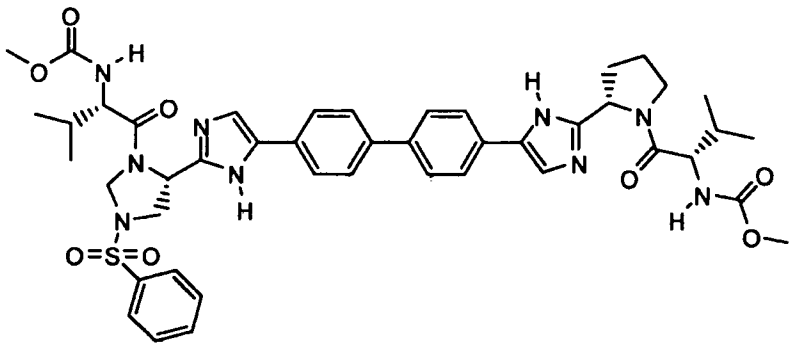

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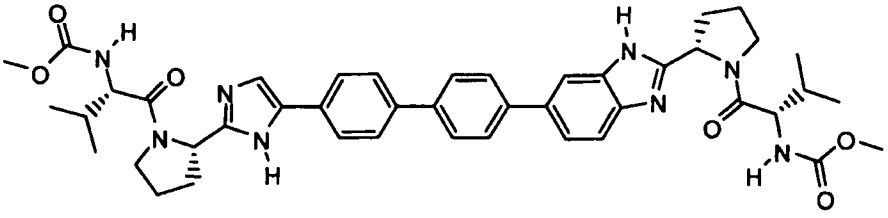

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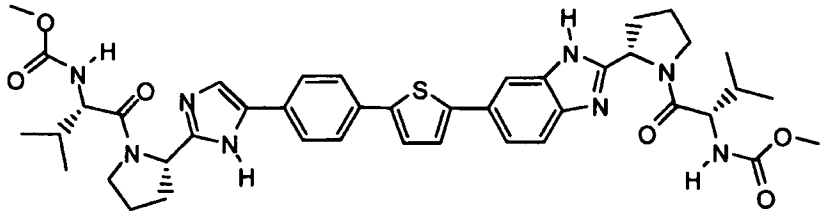

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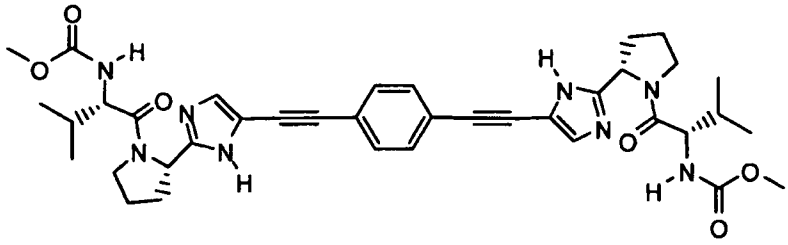

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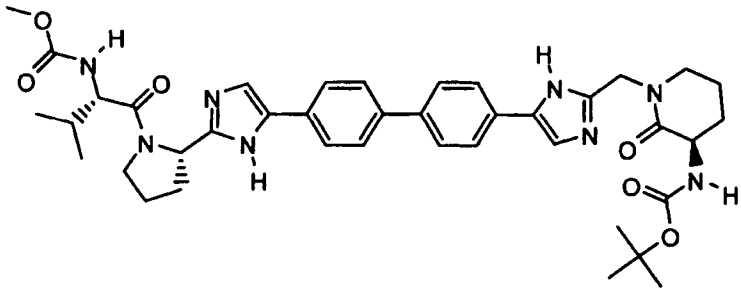

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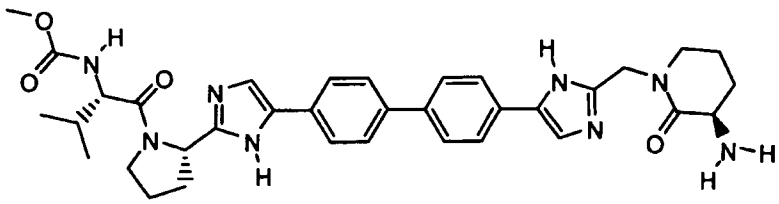

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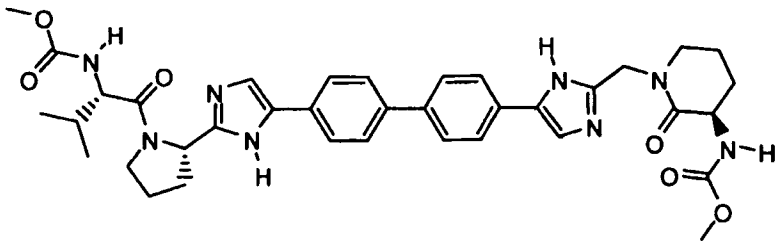

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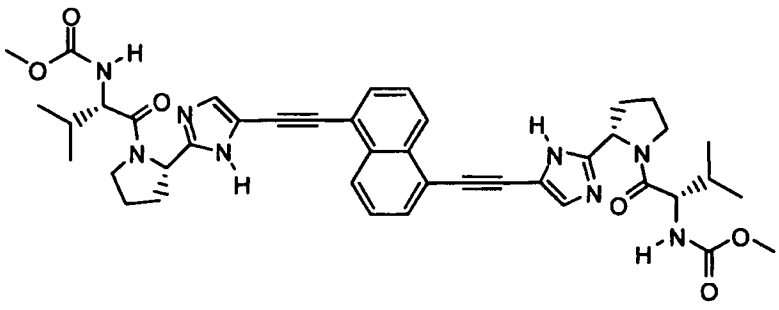

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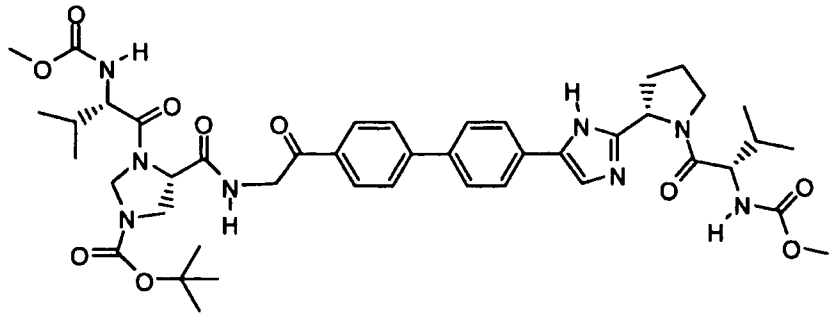

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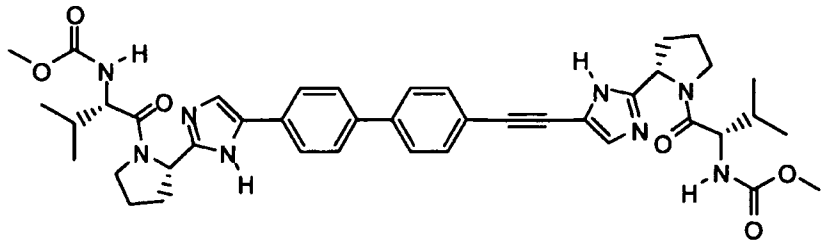

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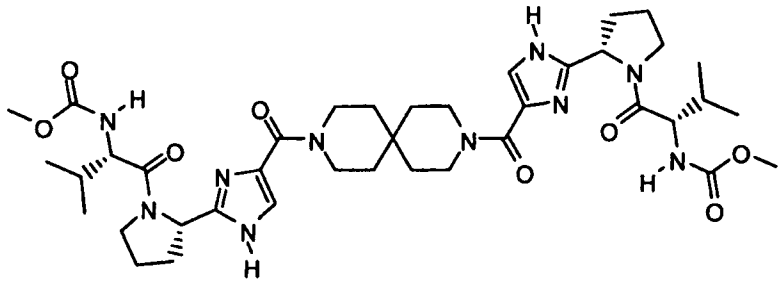

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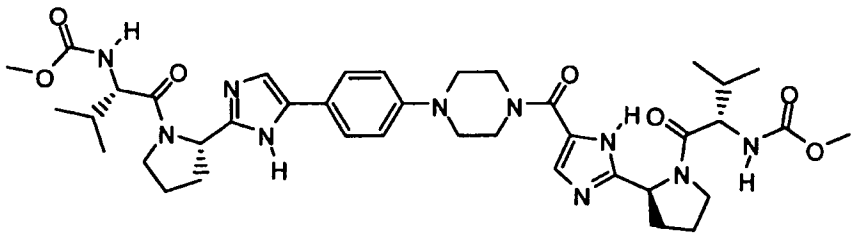

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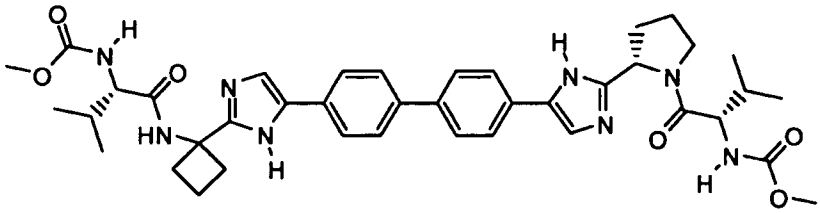

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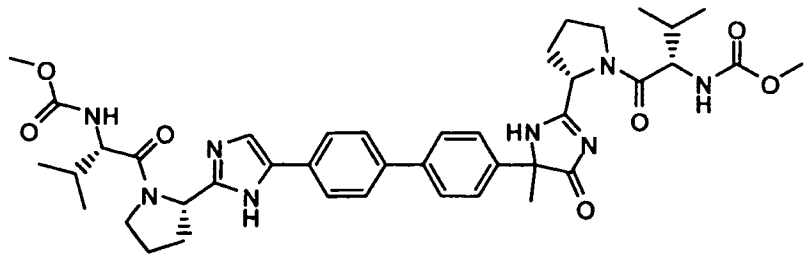

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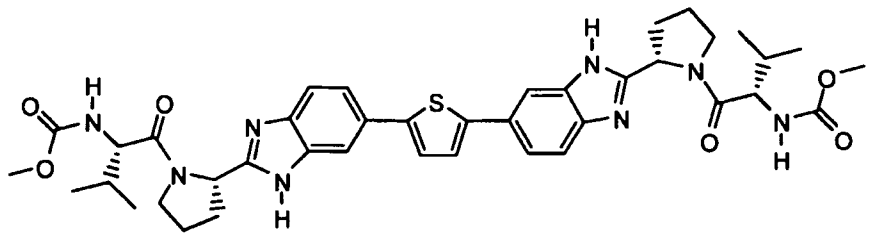

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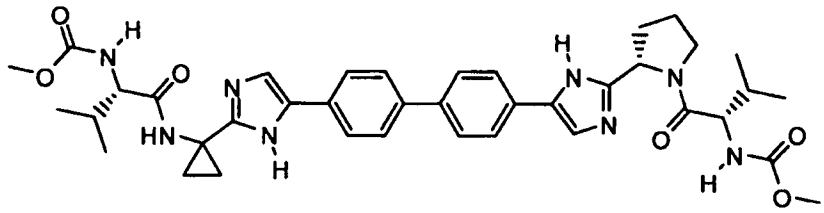

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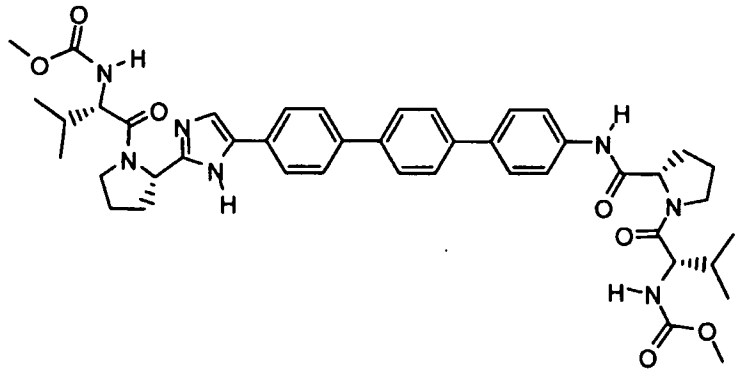

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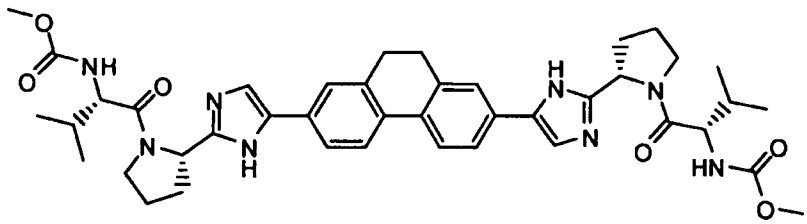

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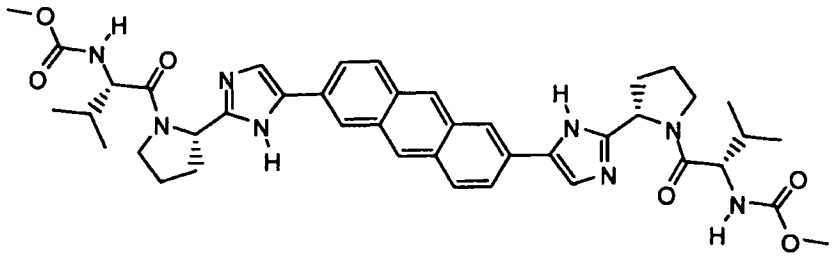

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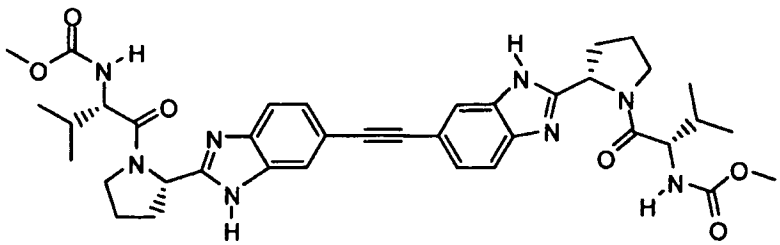

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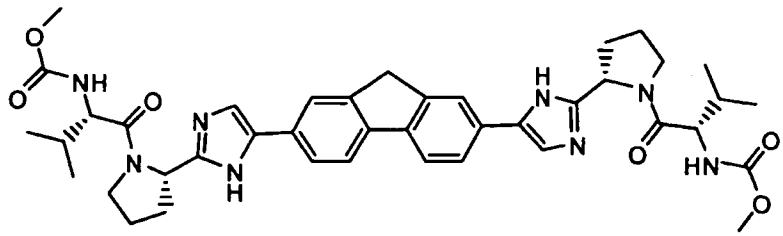

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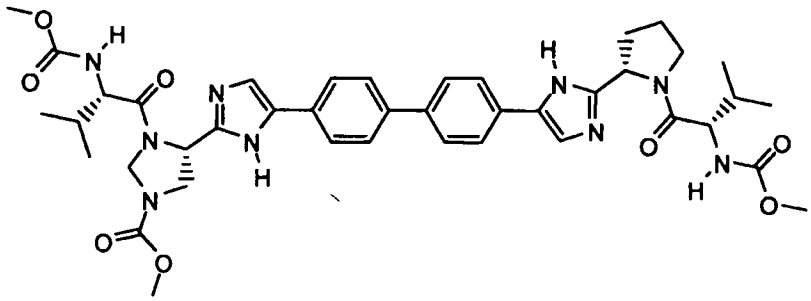

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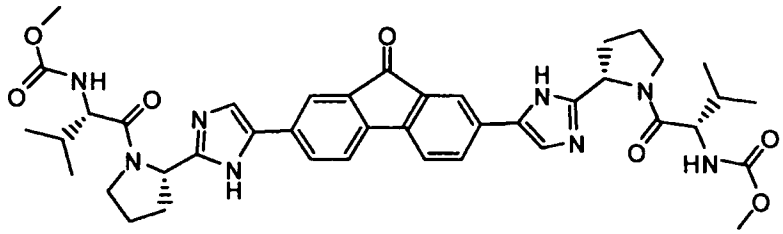

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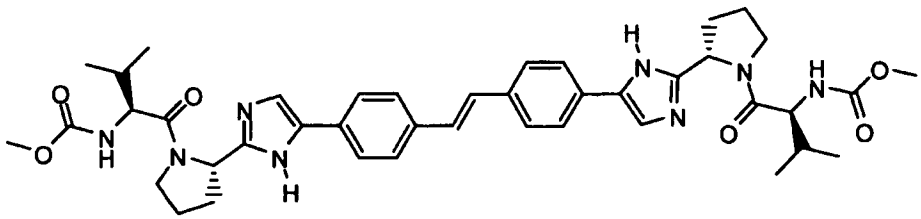

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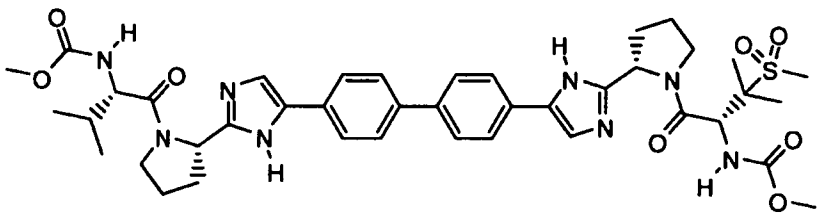

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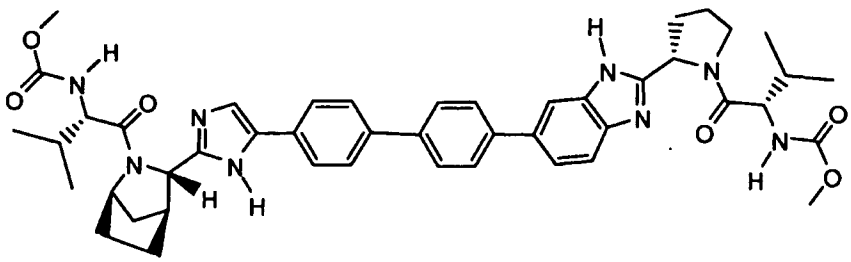

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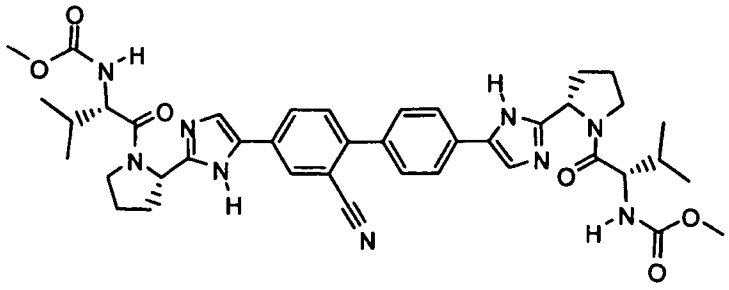

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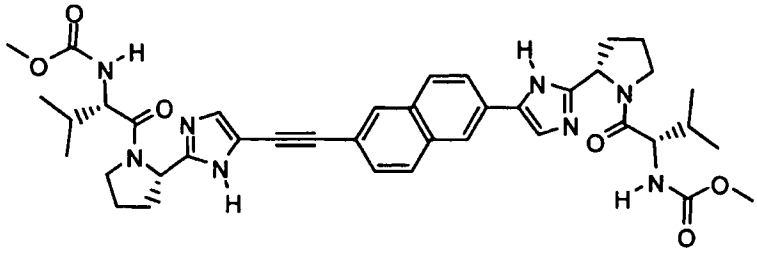

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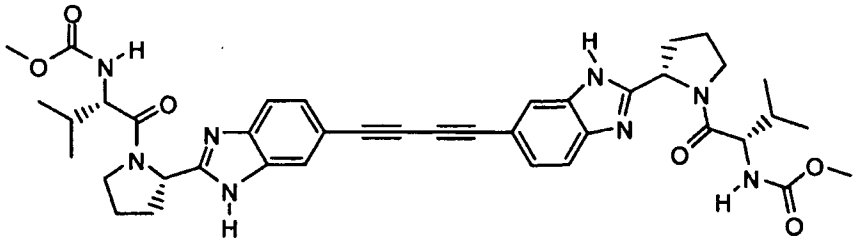

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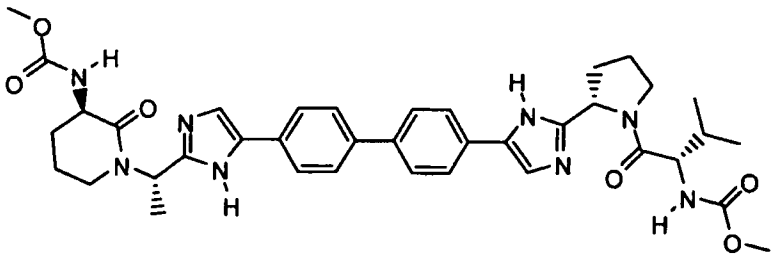

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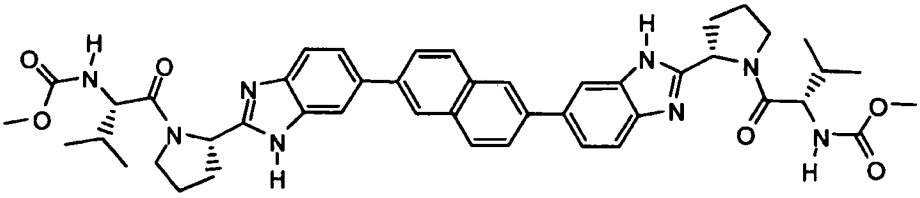

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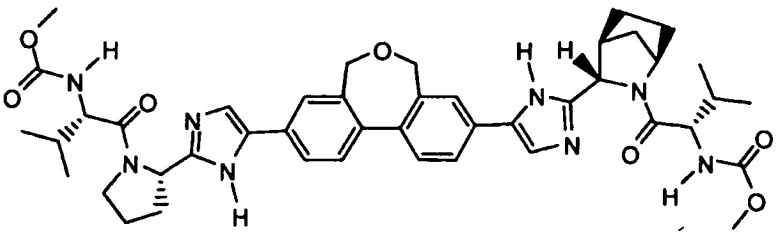

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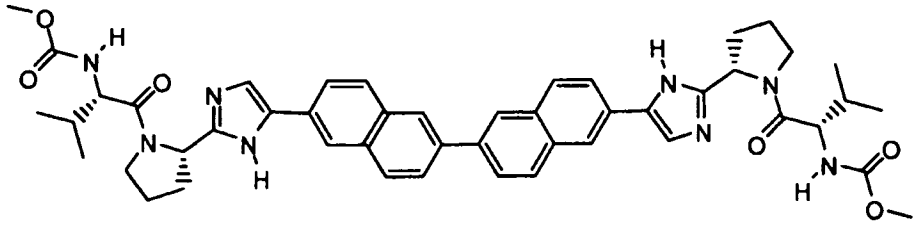

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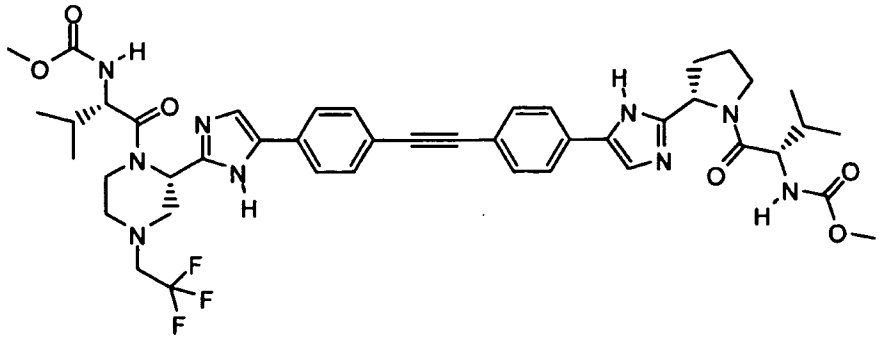

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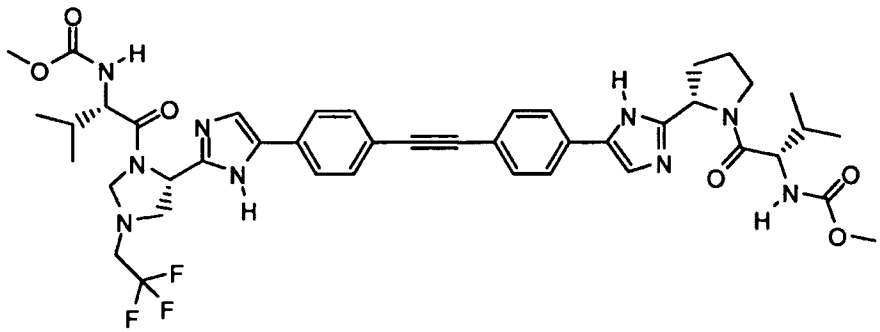

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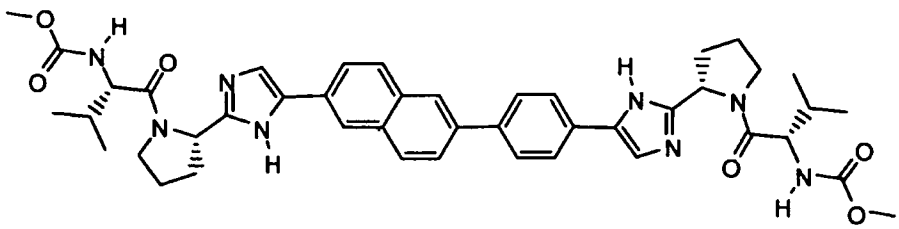

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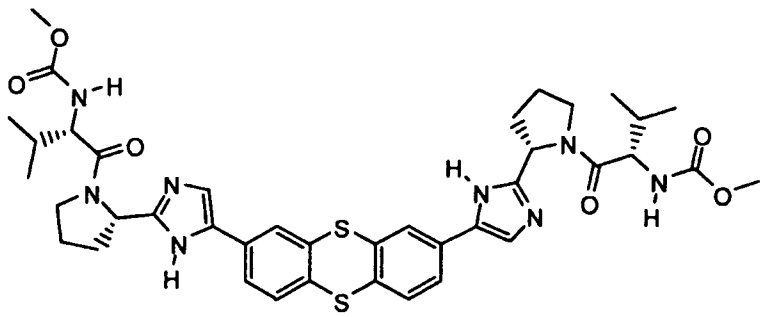

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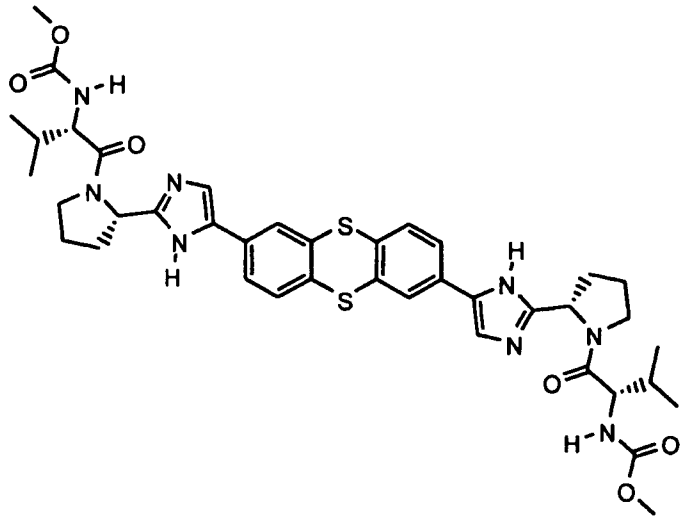

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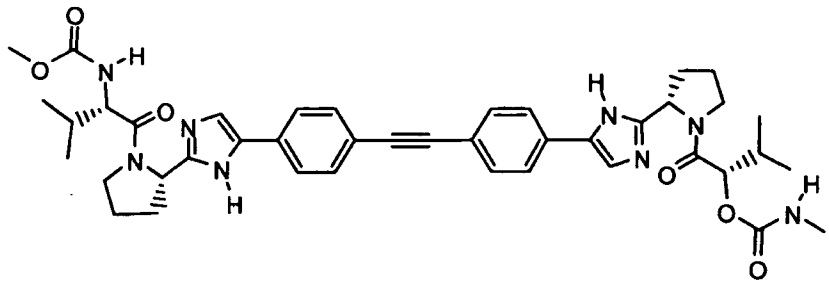

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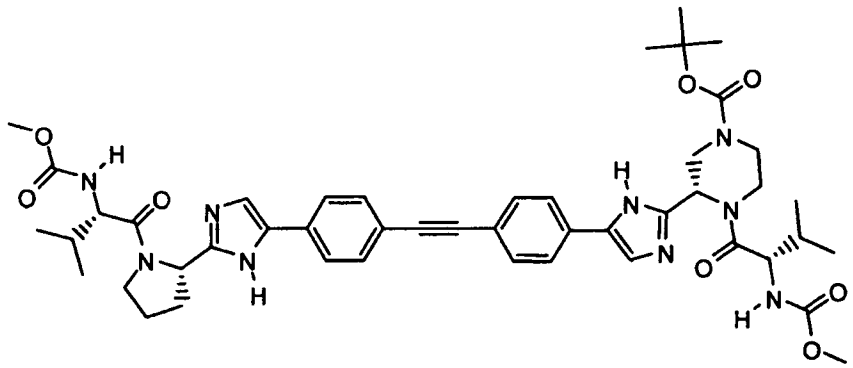

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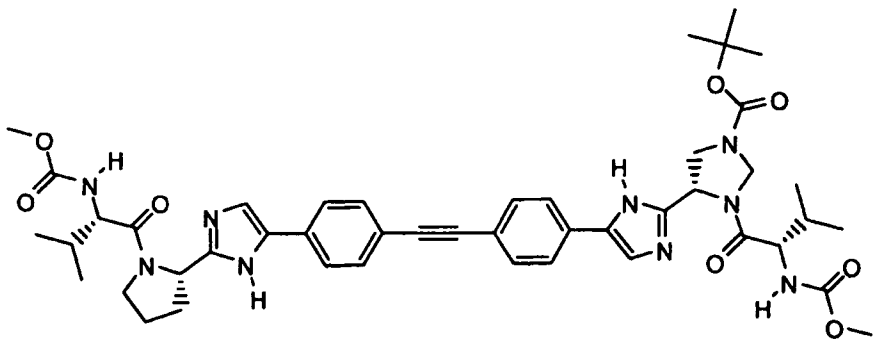

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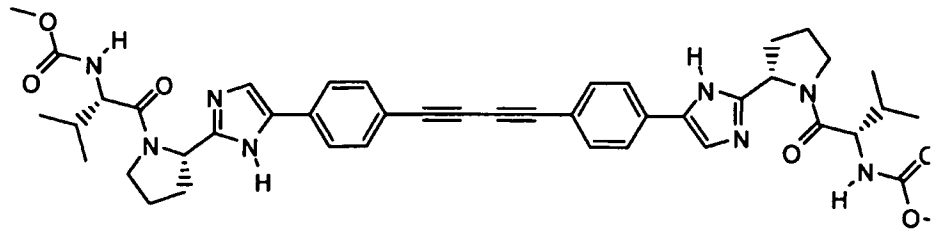

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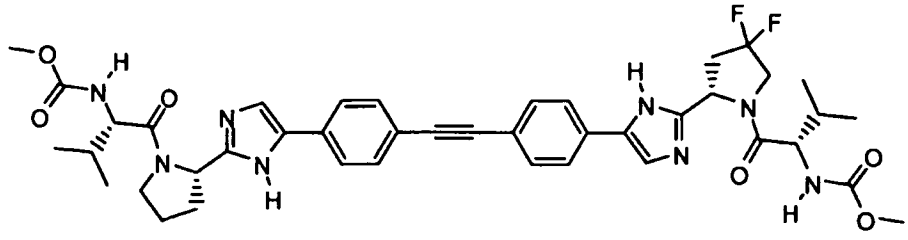

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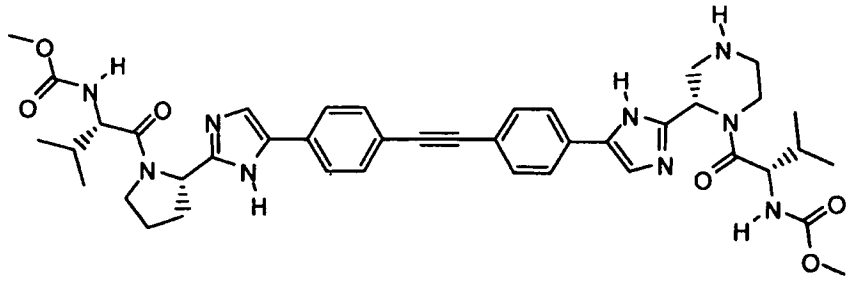

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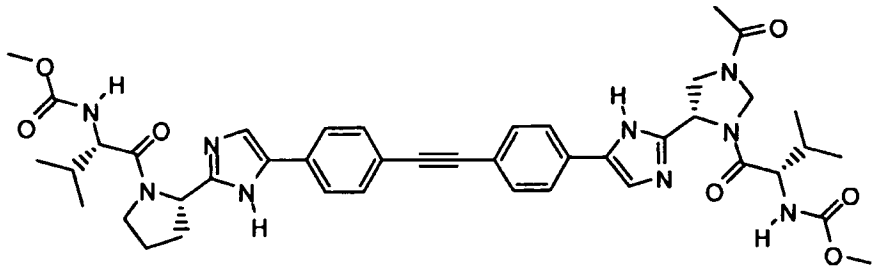

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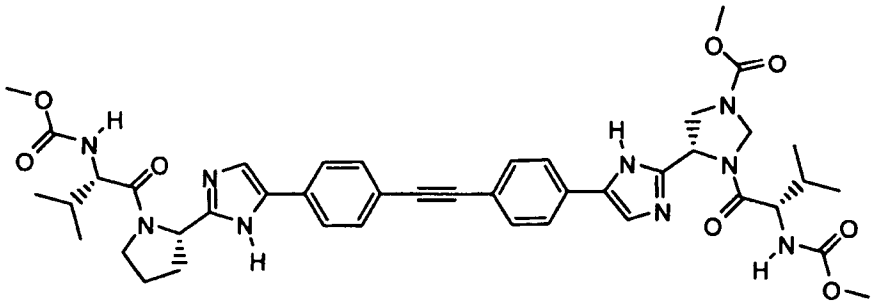

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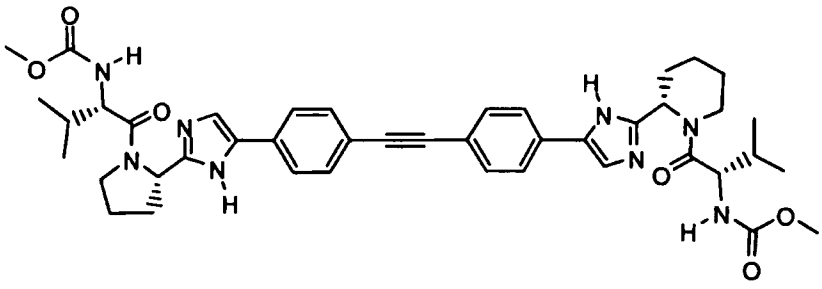

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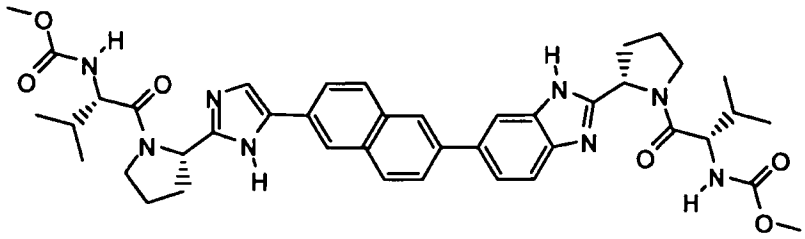

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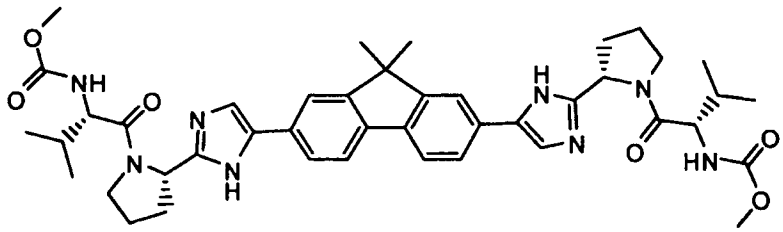

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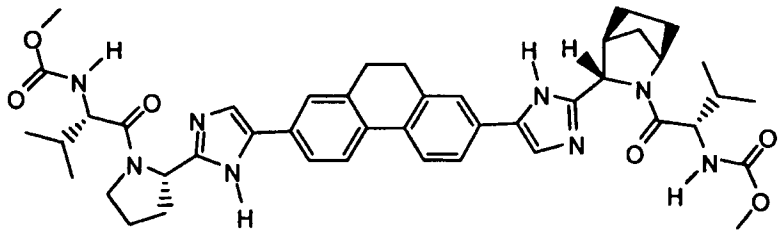

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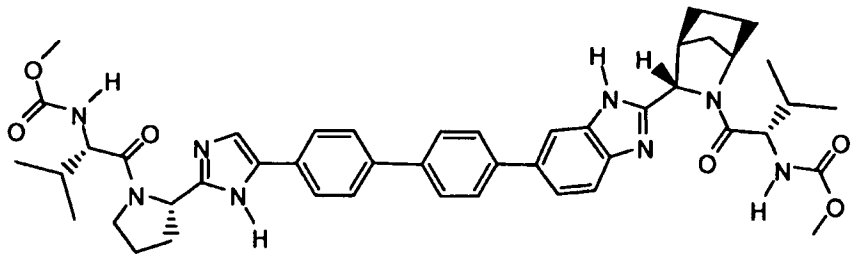

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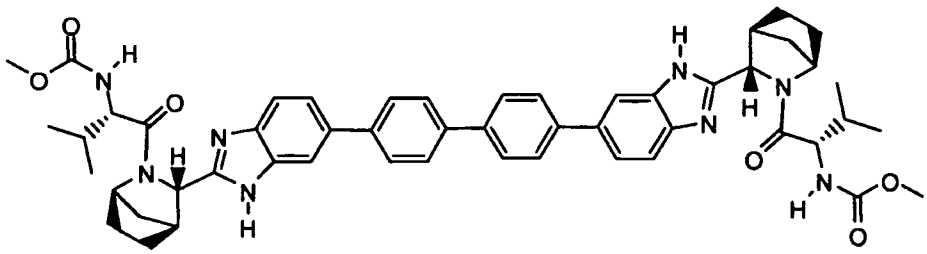

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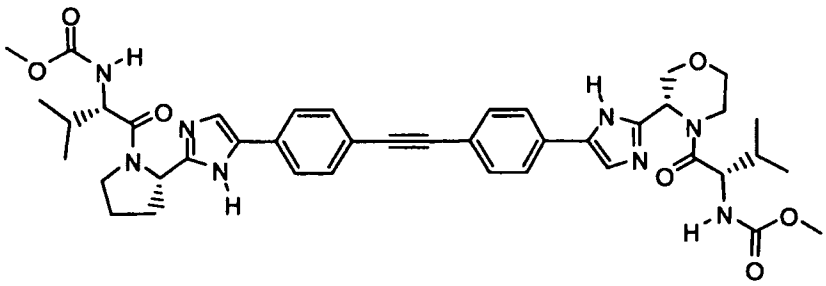

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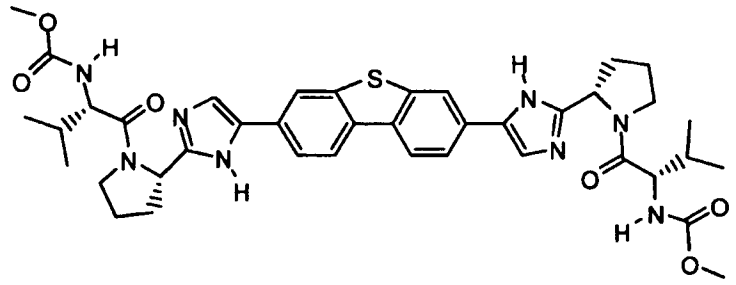

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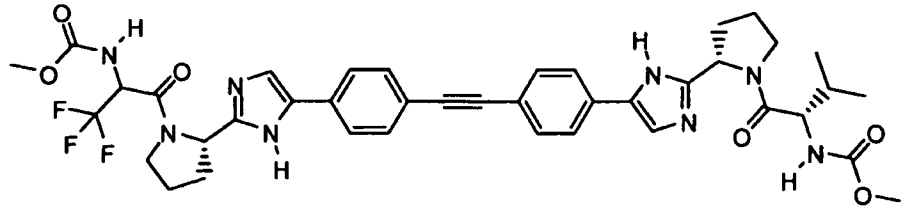

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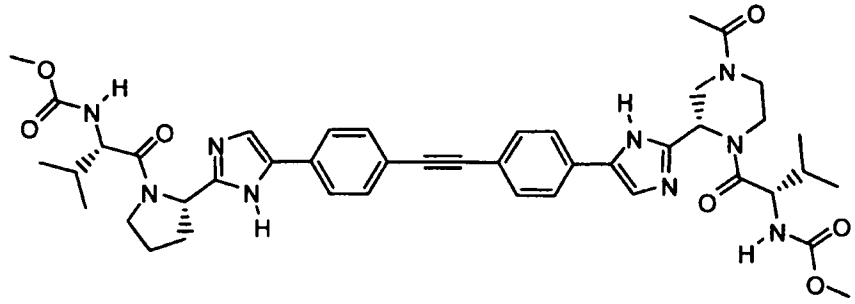

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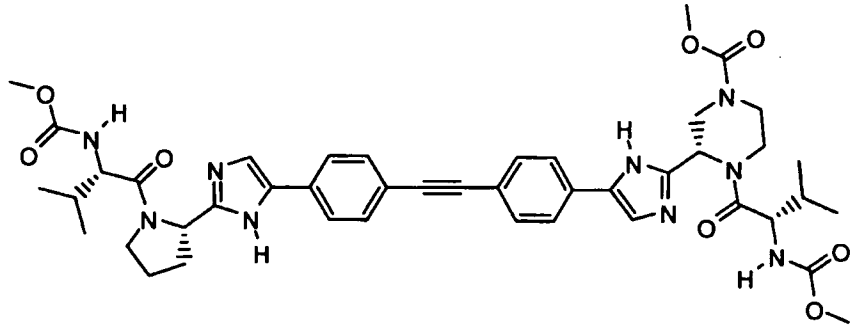

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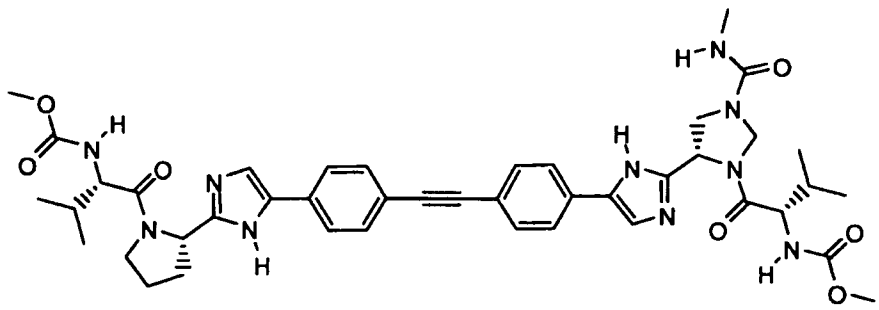

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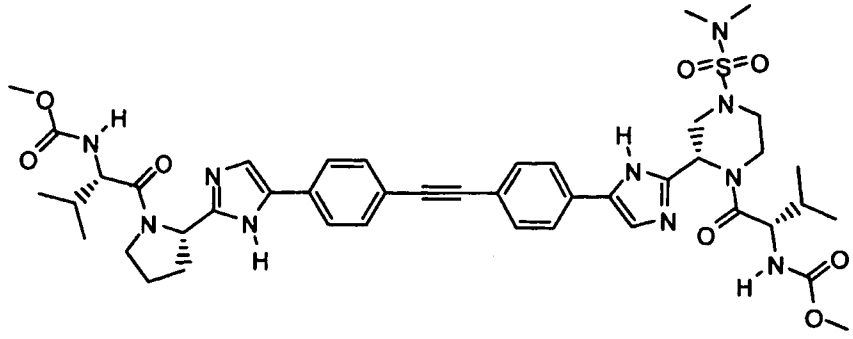

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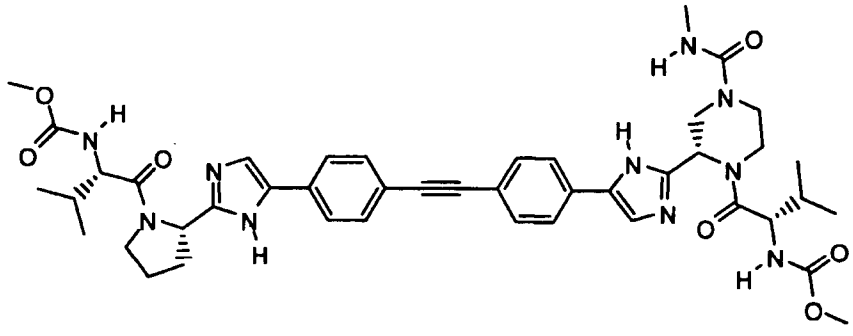

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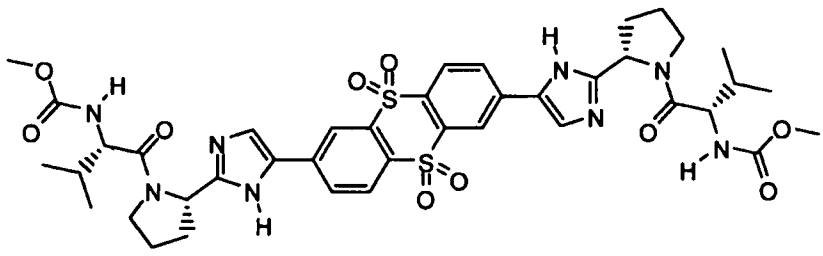

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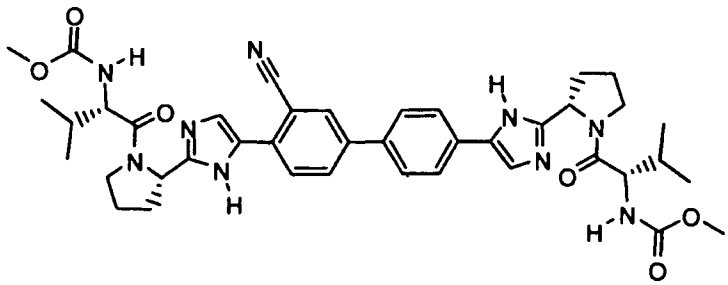

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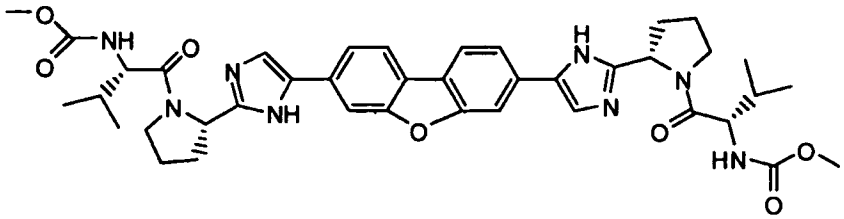

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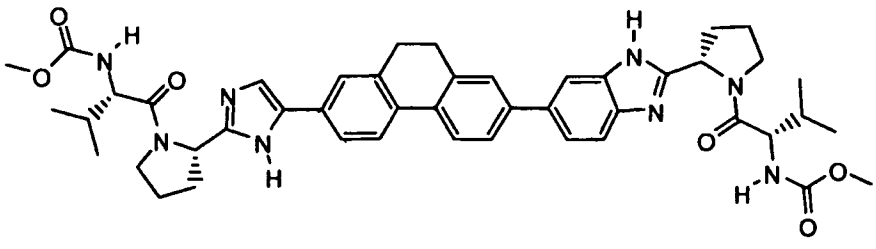

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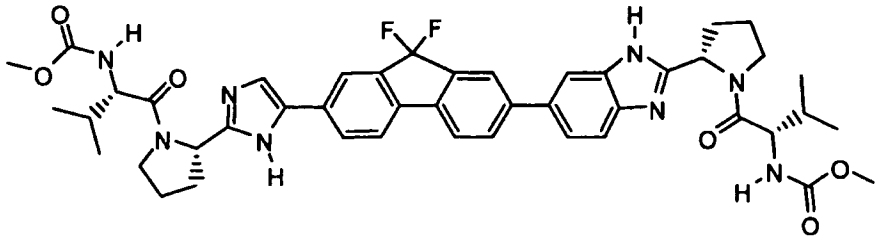

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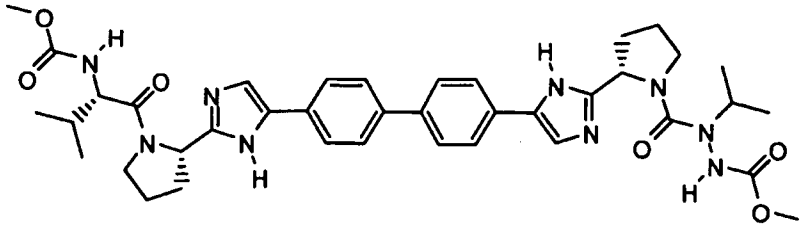

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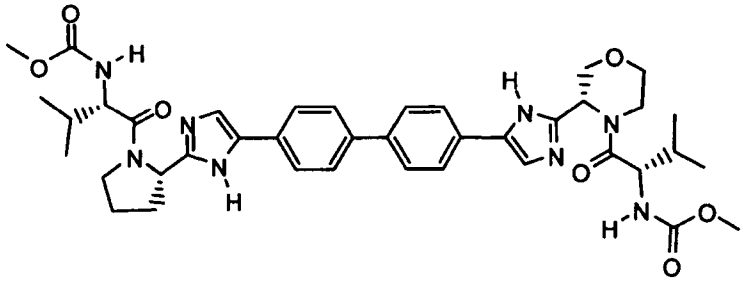

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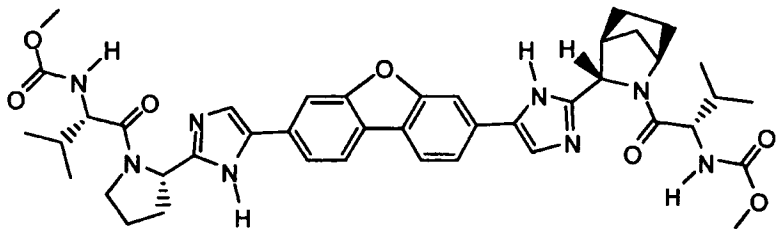

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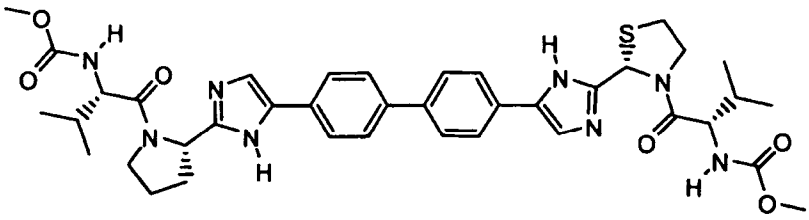

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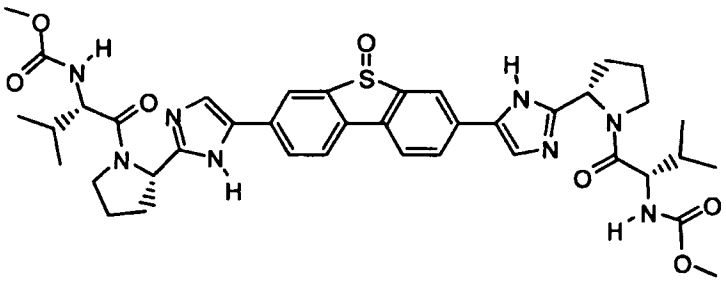

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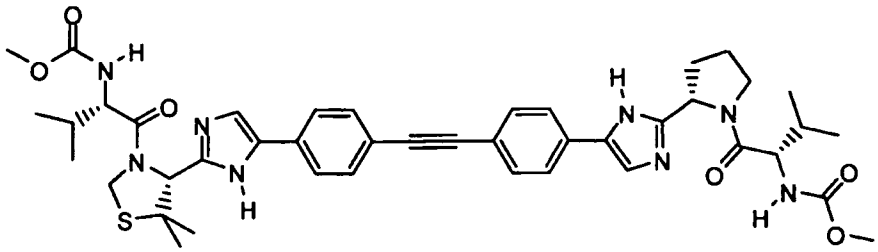

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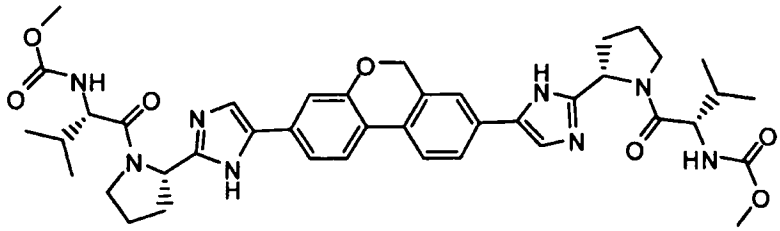

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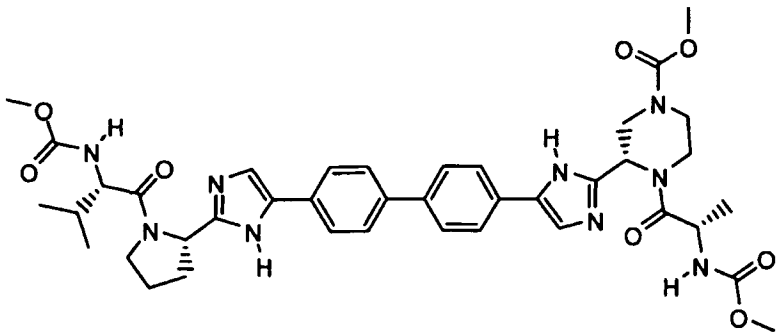

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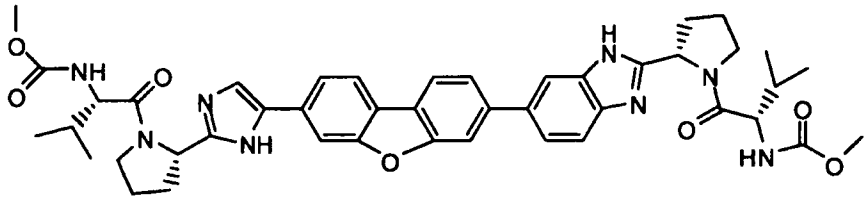

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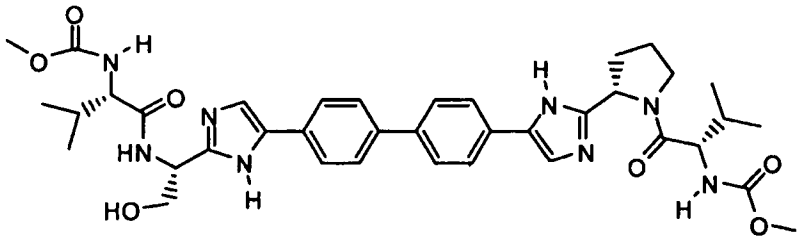

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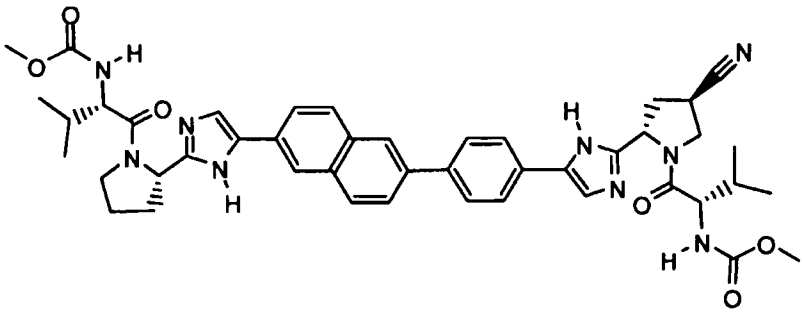

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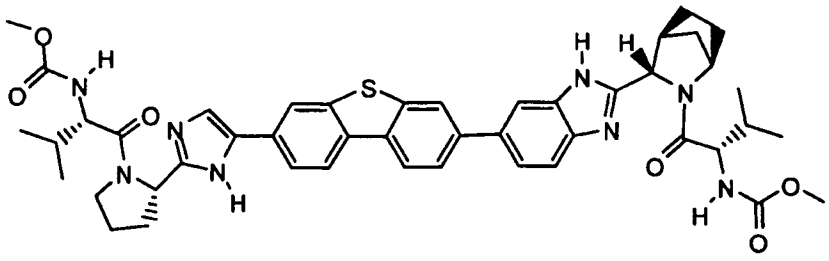

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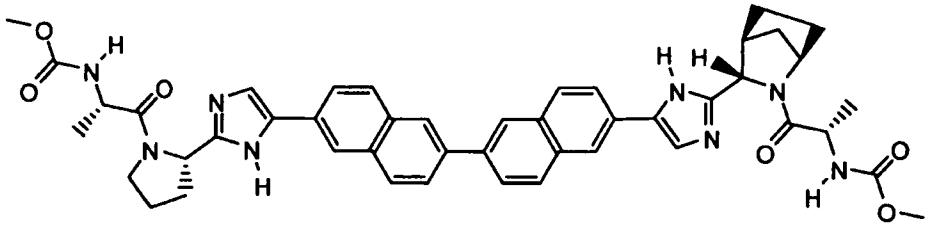

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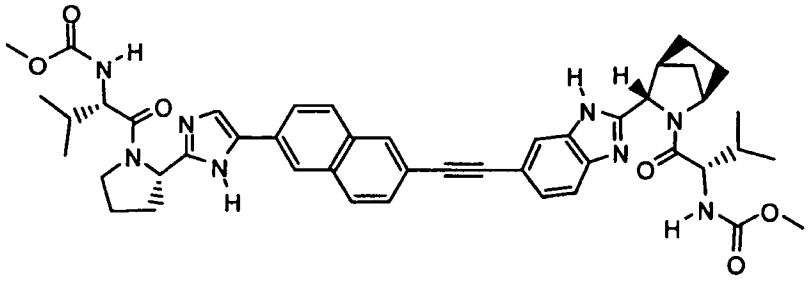

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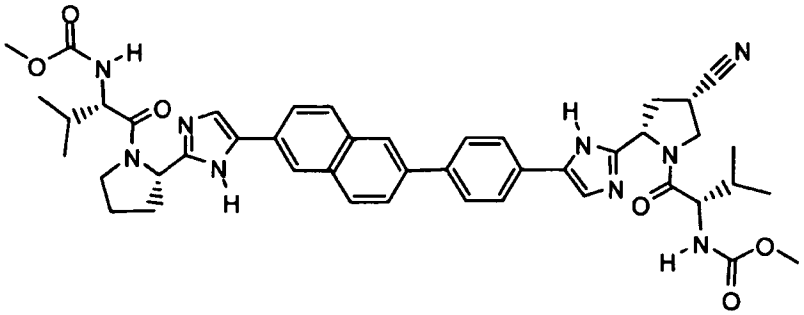

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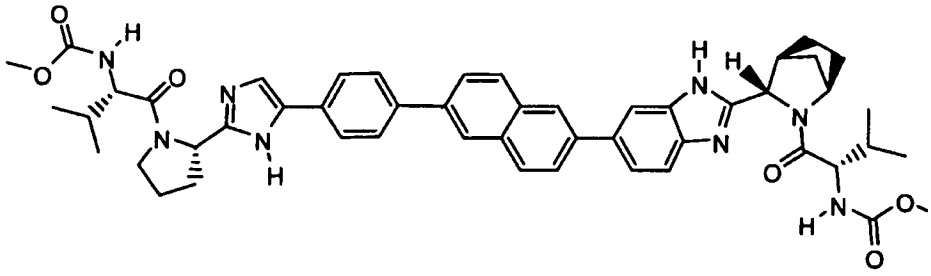

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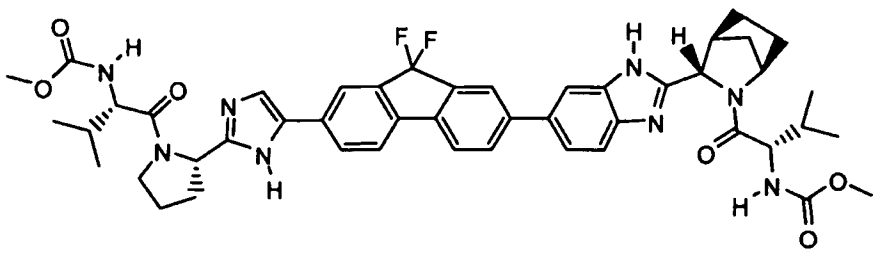

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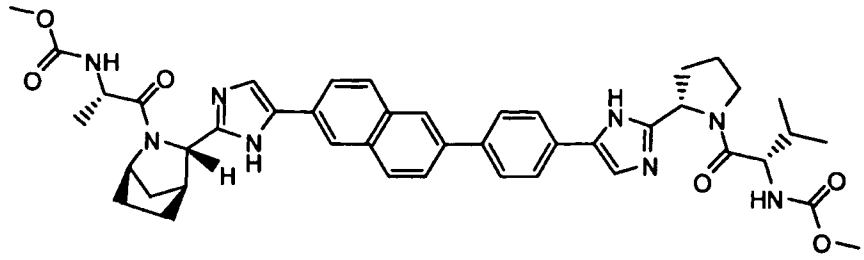

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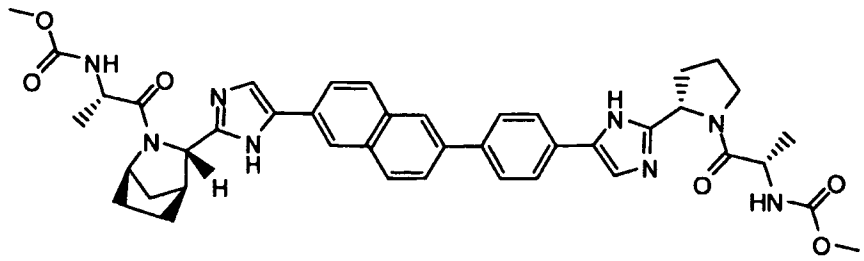

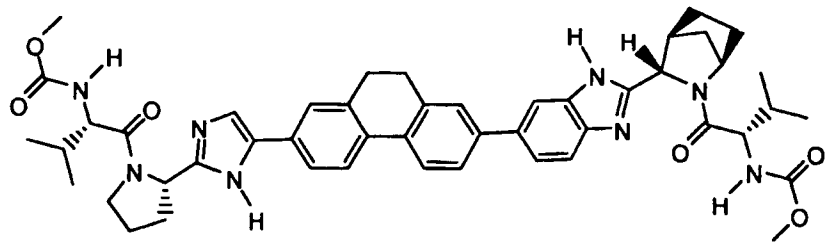

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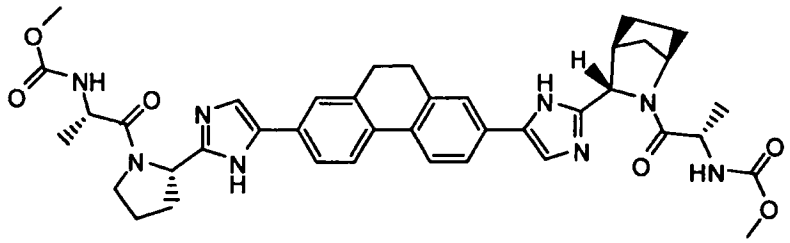

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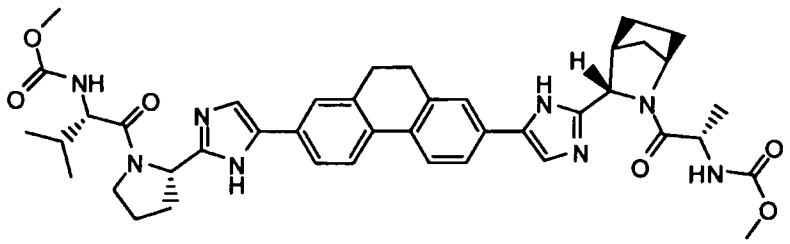

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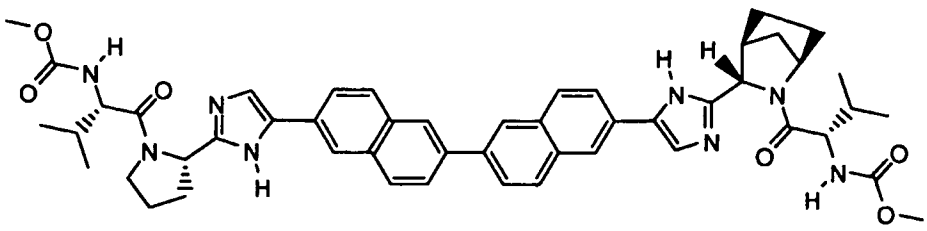

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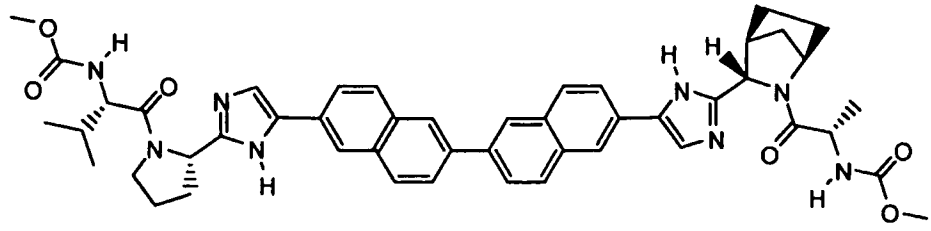

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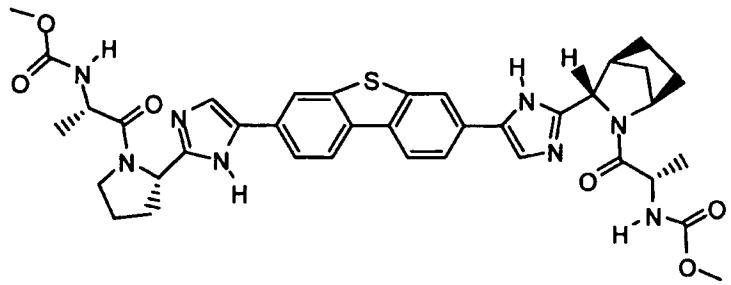

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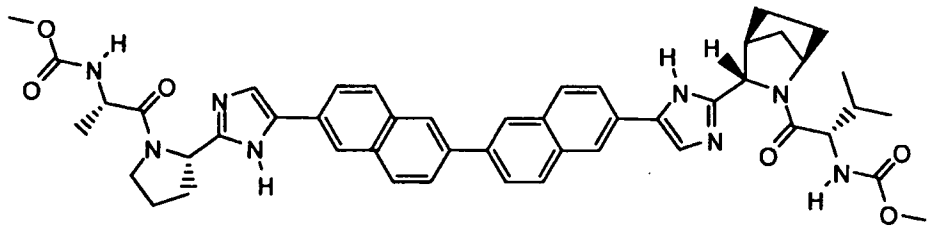

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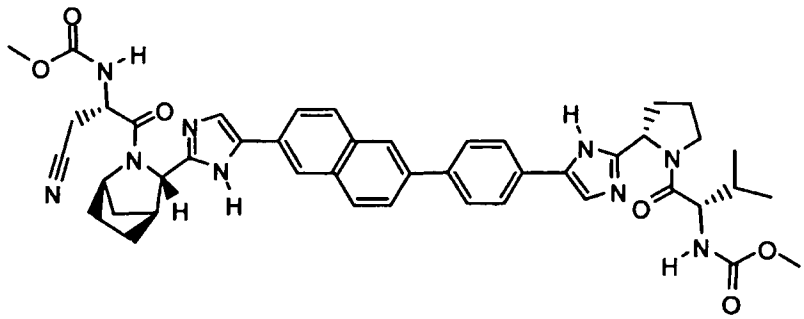

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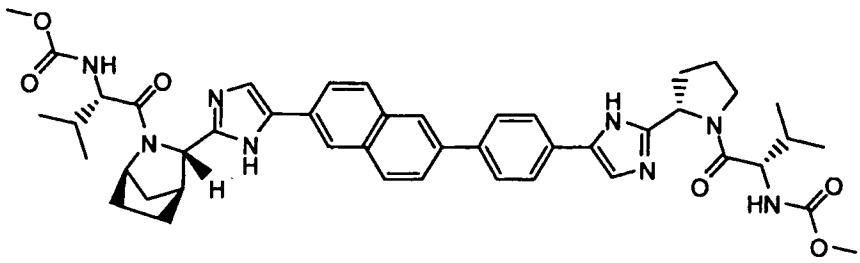

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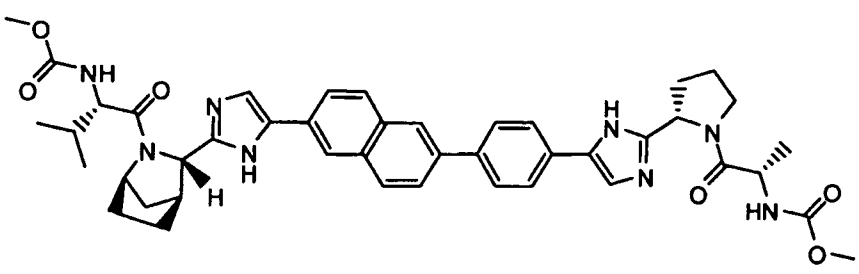

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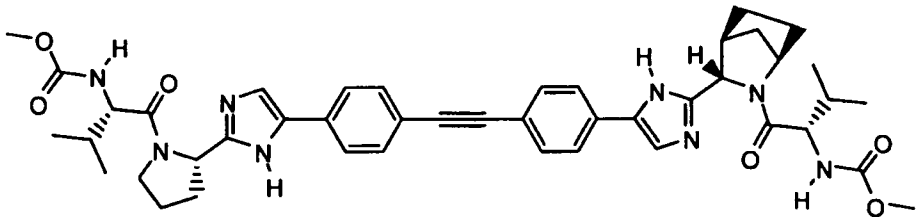

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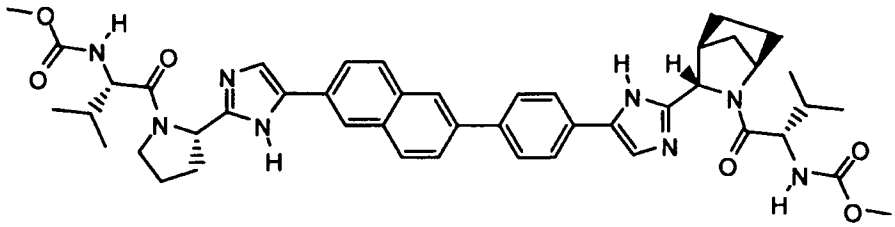

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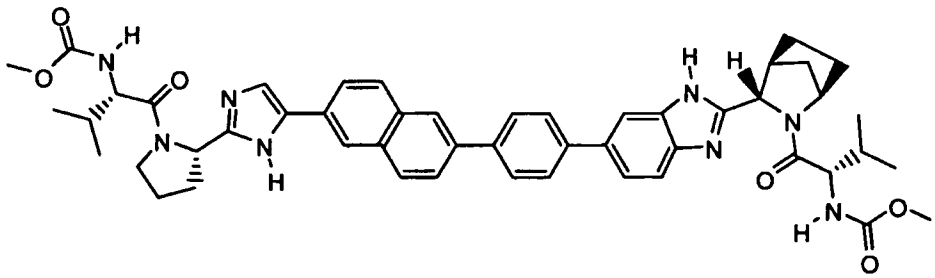

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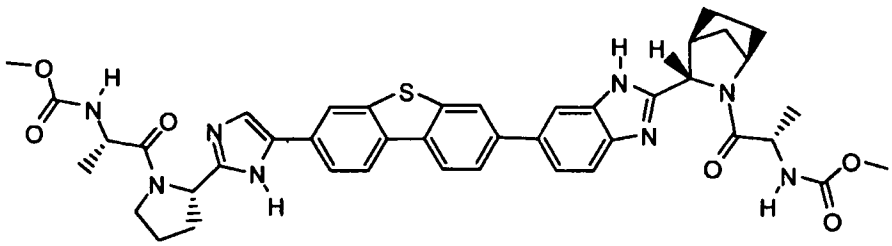

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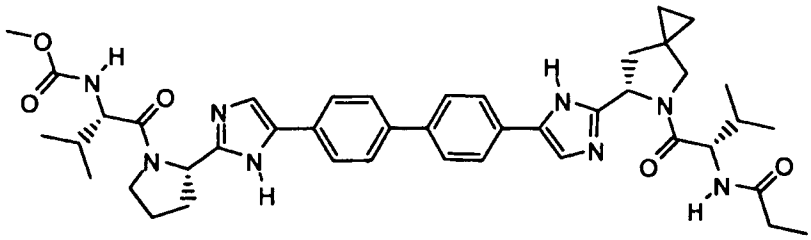

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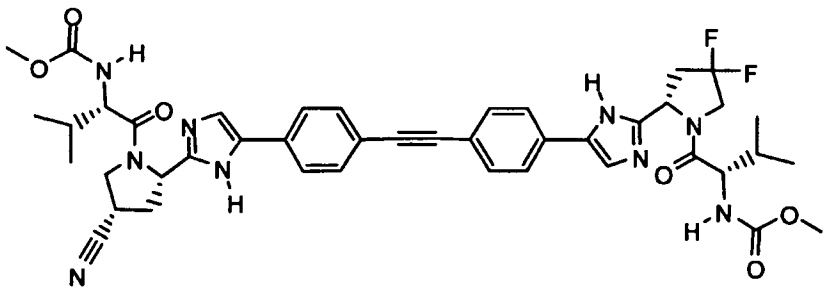

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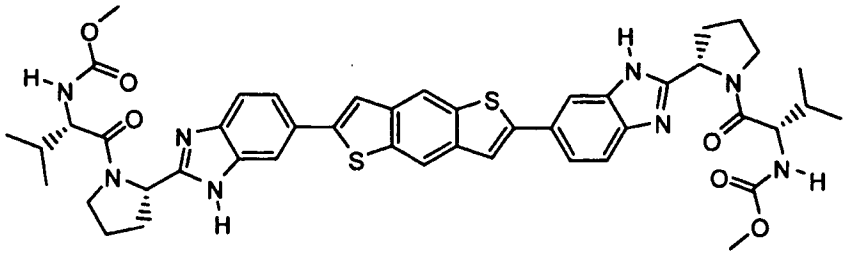

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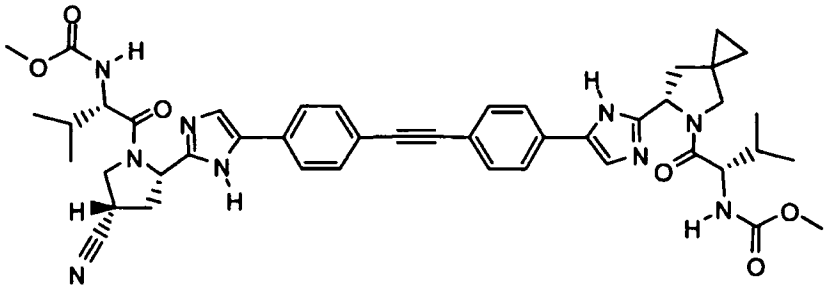

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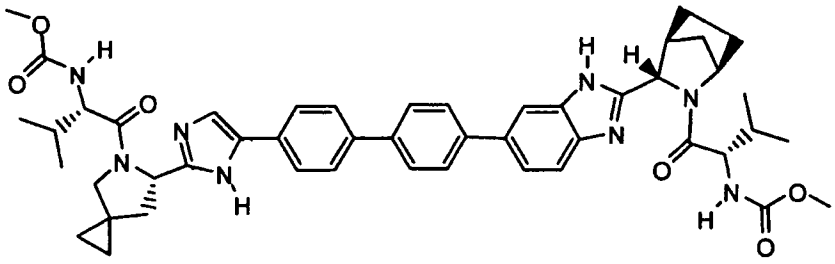

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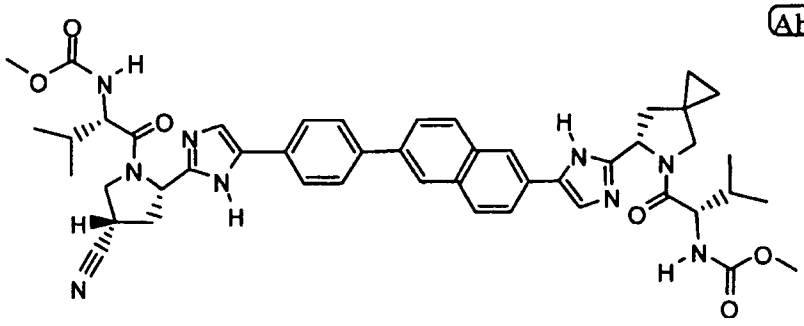

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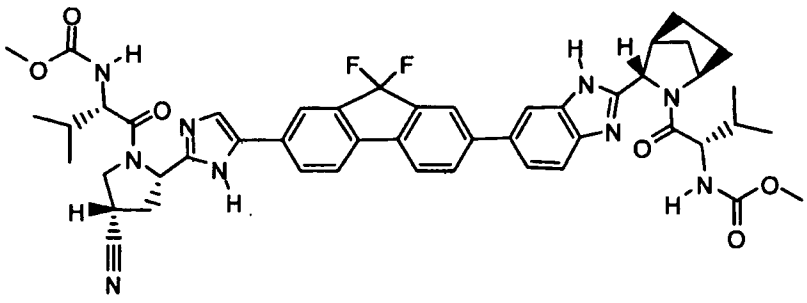

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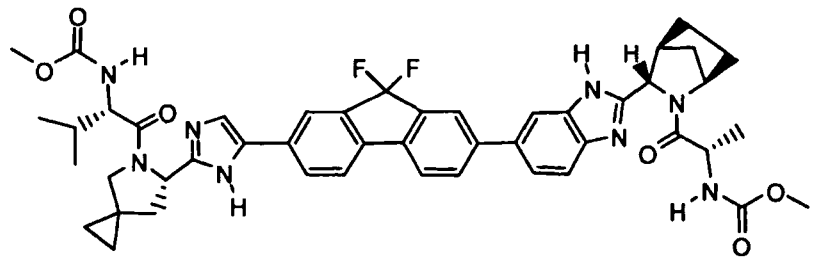

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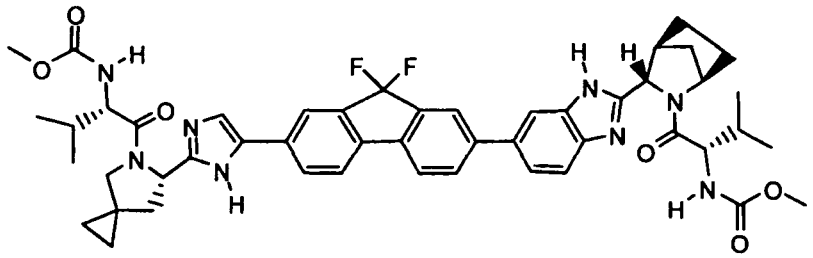

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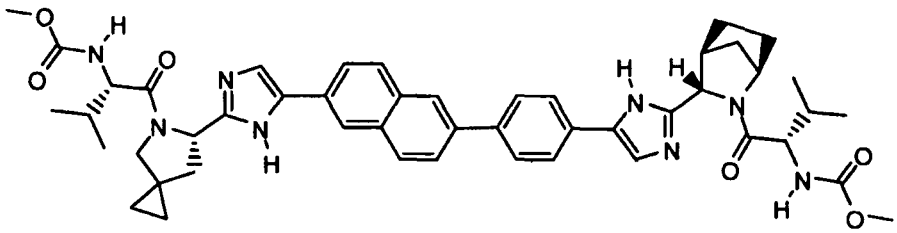

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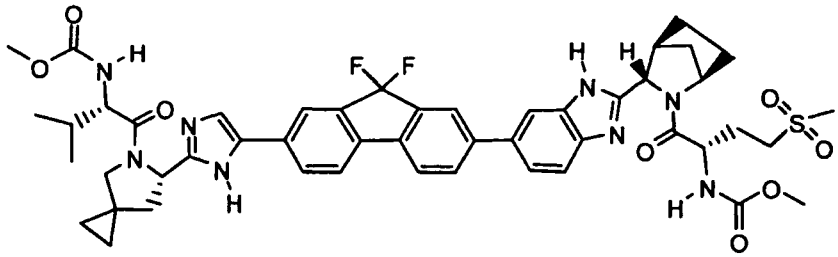

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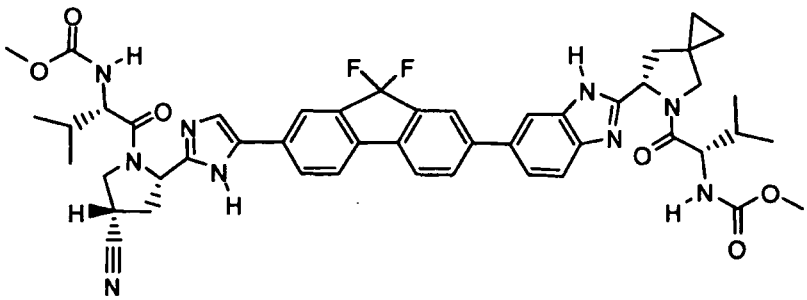

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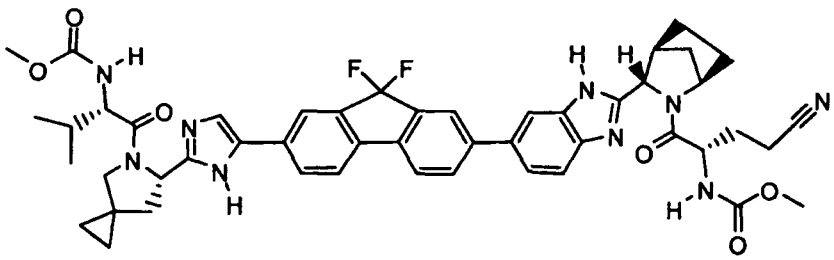

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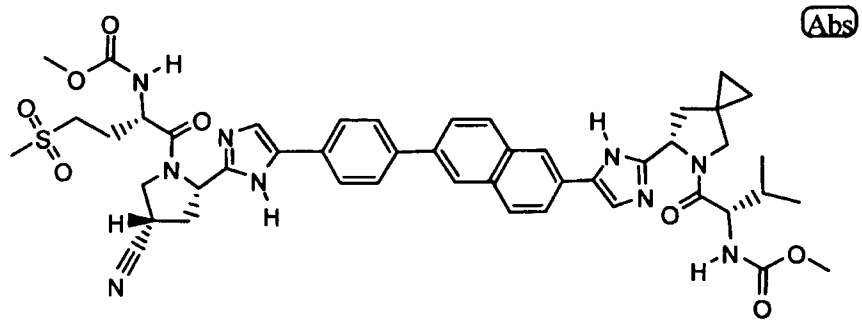

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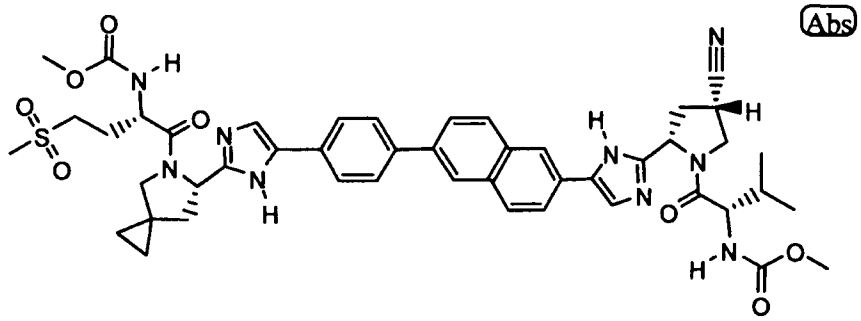

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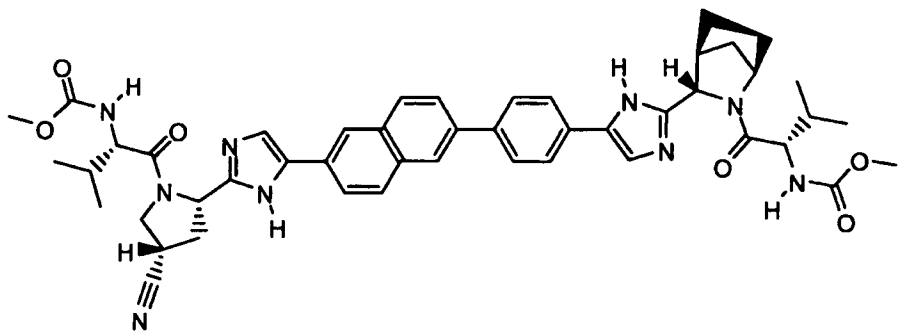

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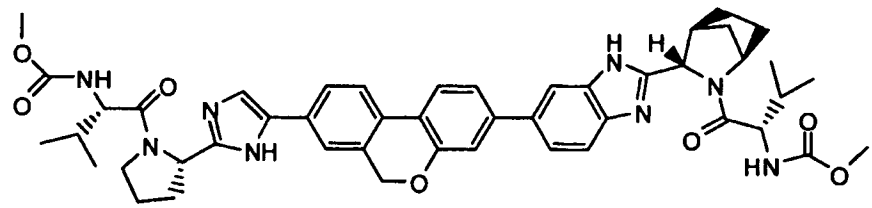

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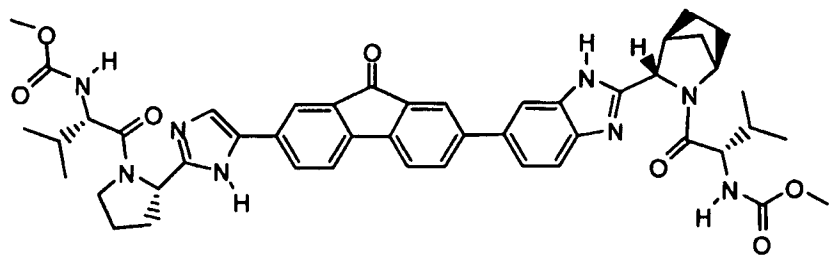

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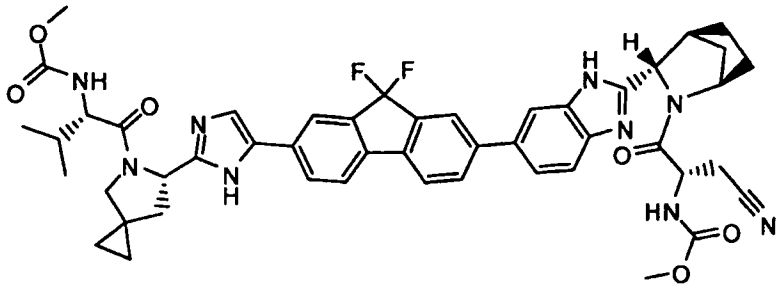

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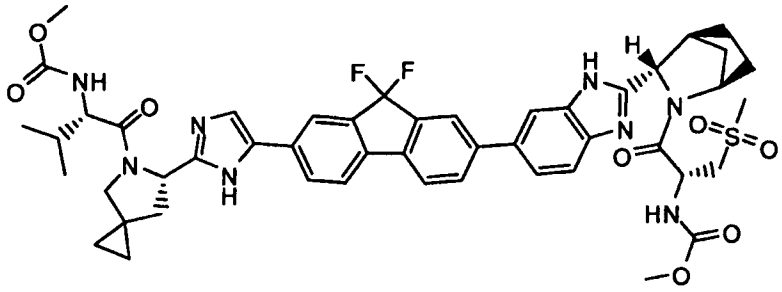

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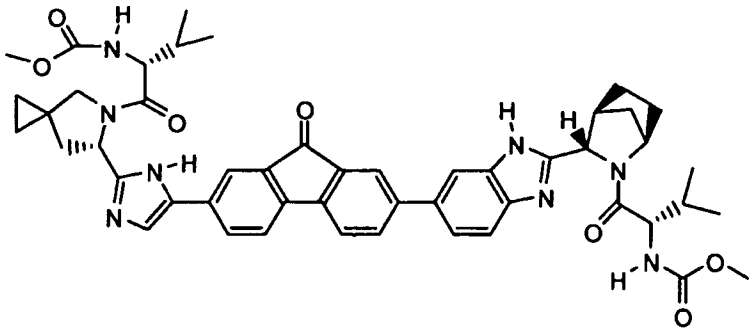

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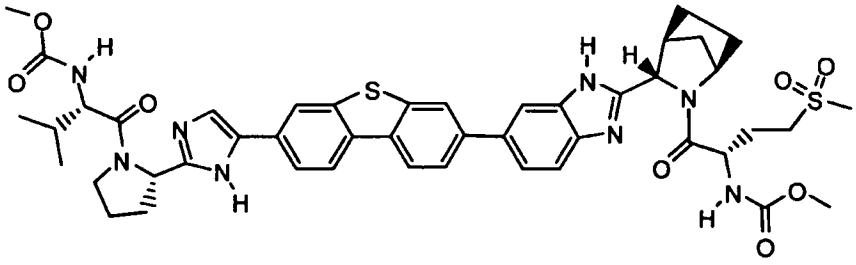
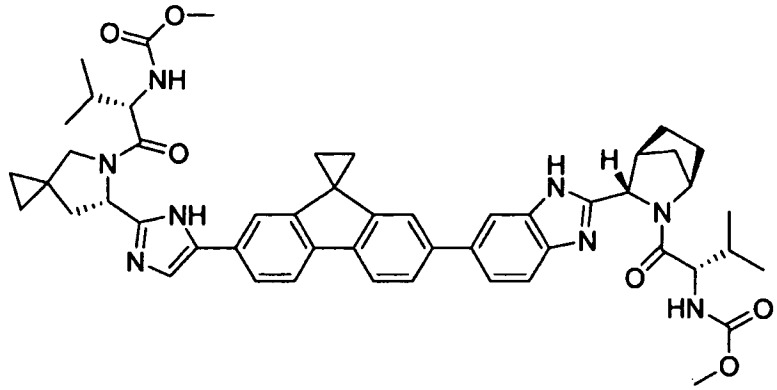
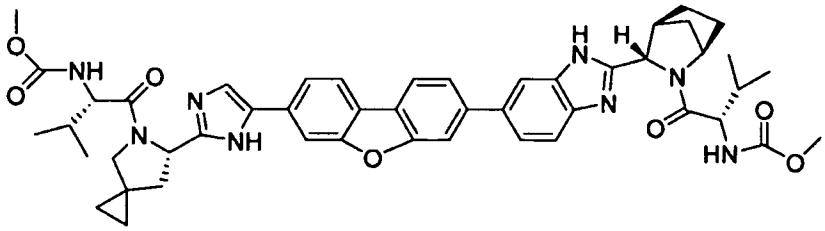
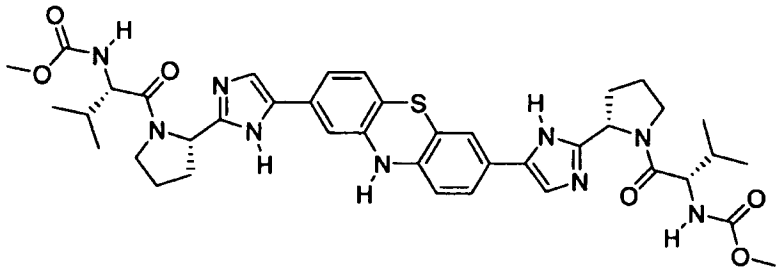
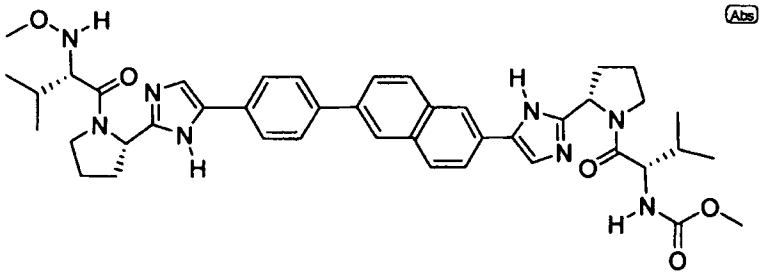
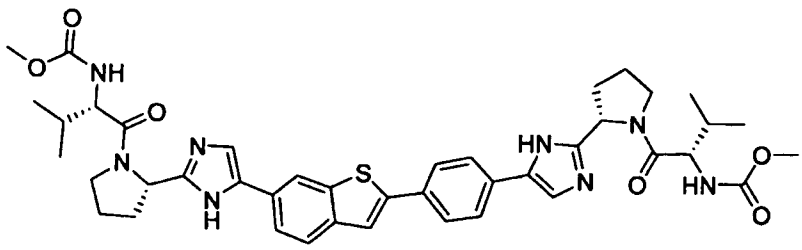
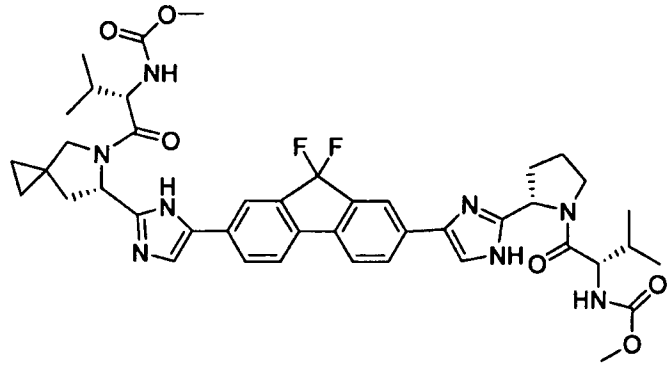


Additional Representative Compounds of the Invention	Activity (nM)
	0.0073
	0.0041
	1.7224
	0.525
	0.0093



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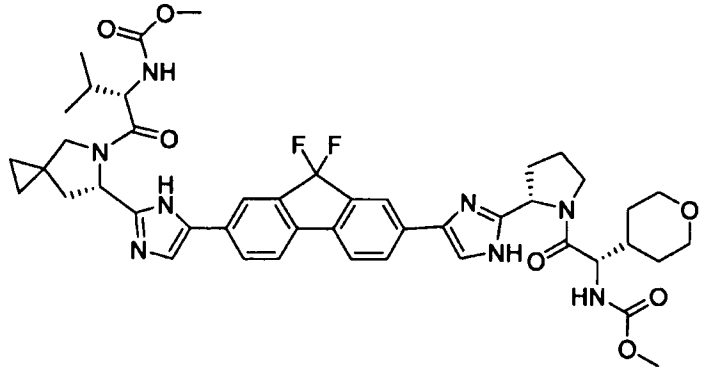

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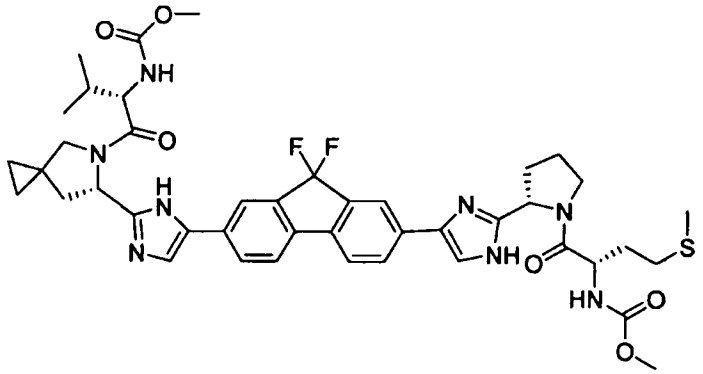

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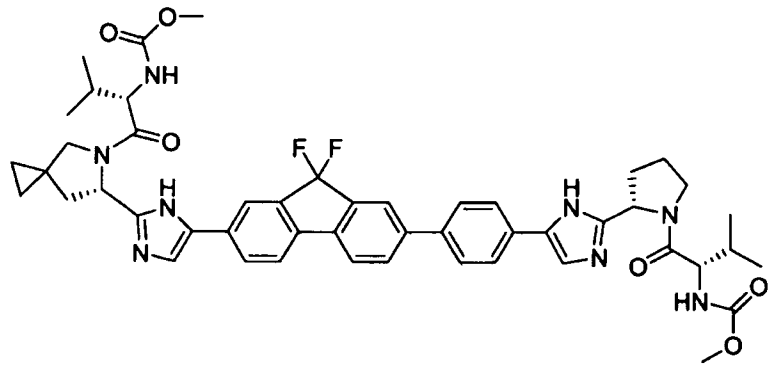

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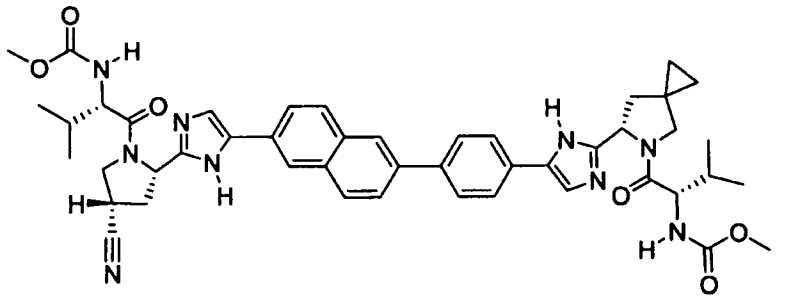

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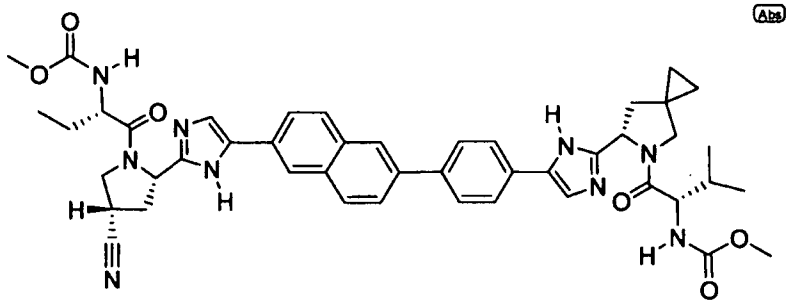

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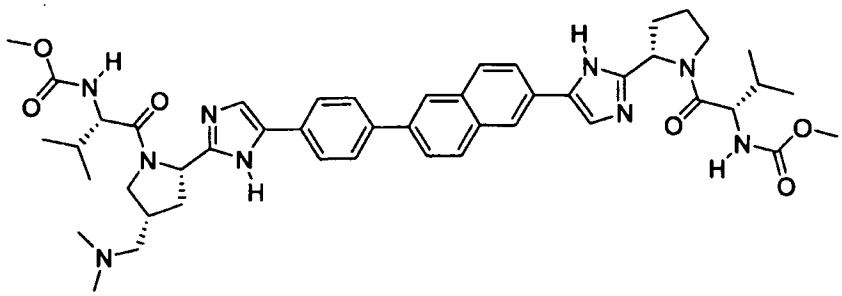

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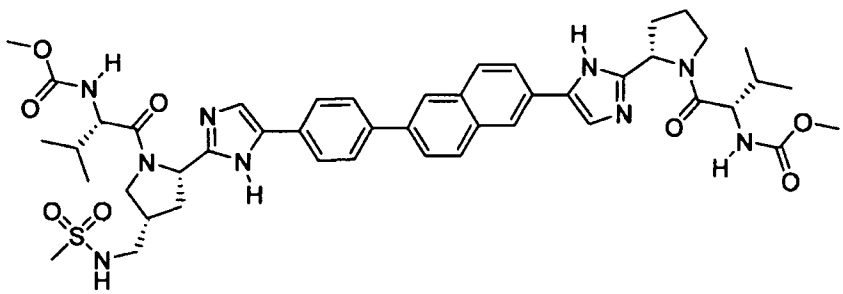

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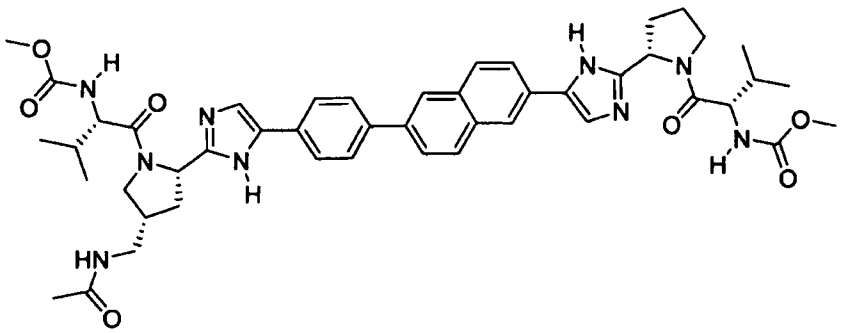

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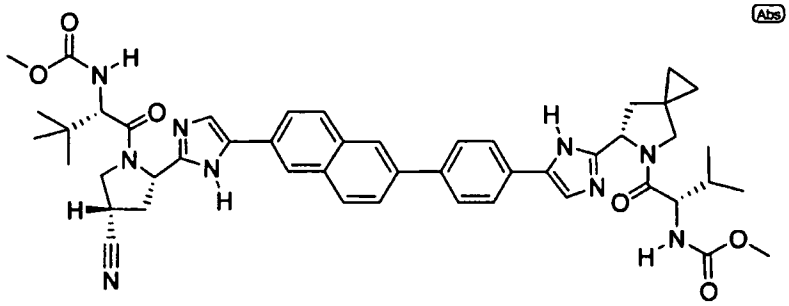

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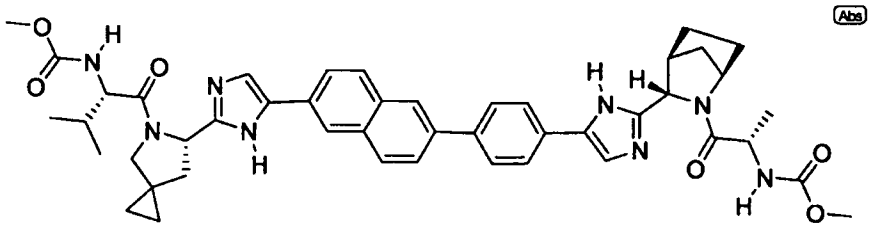

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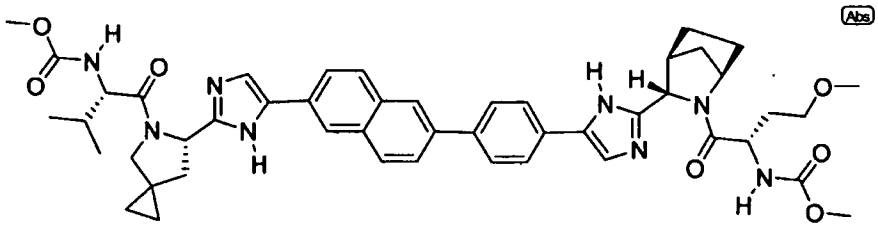

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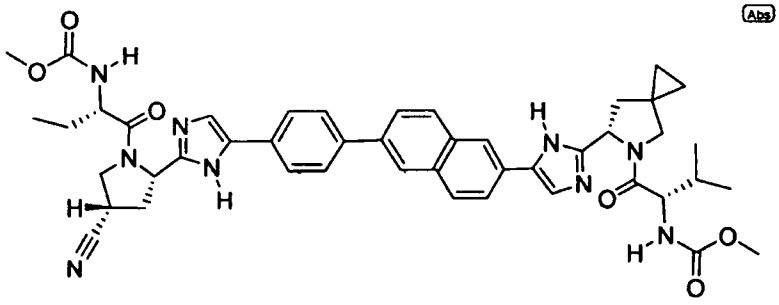

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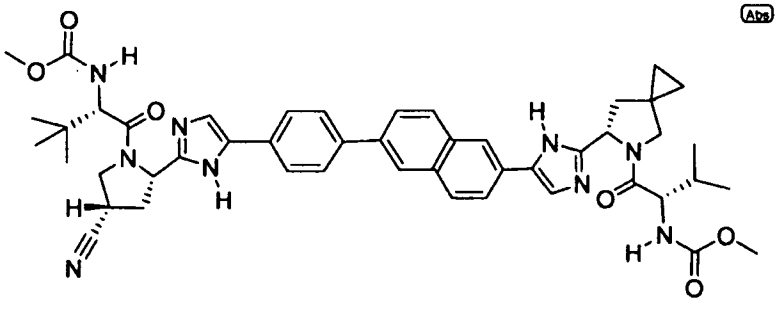

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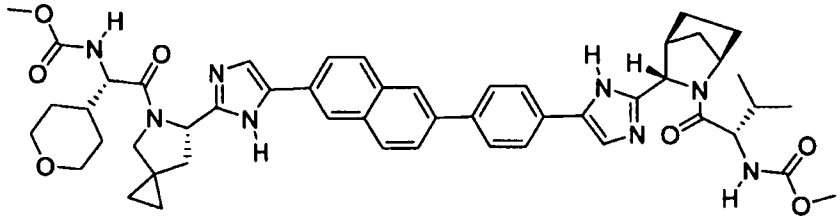

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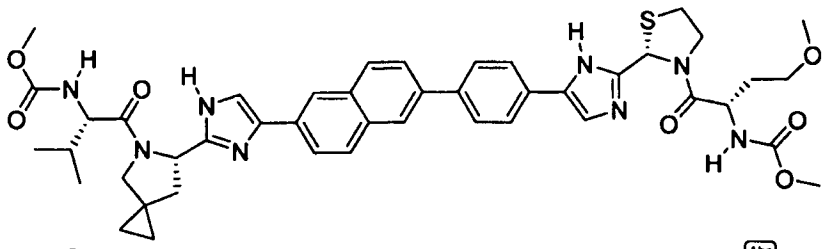

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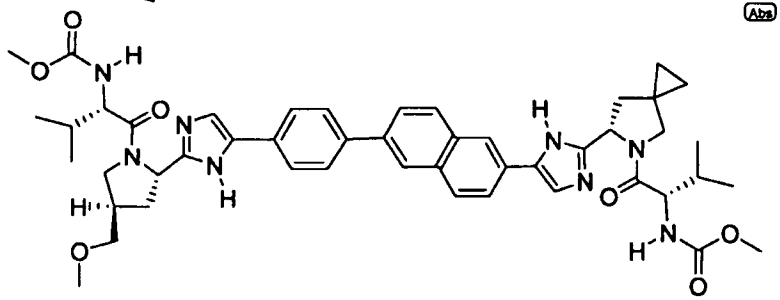

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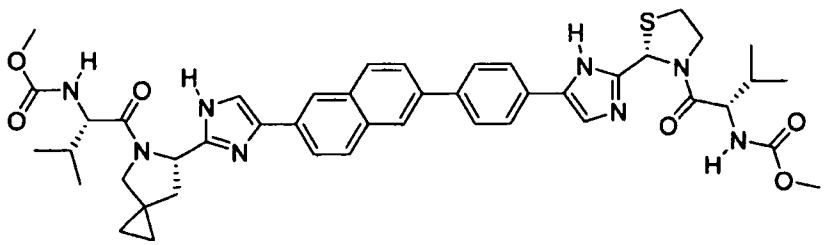

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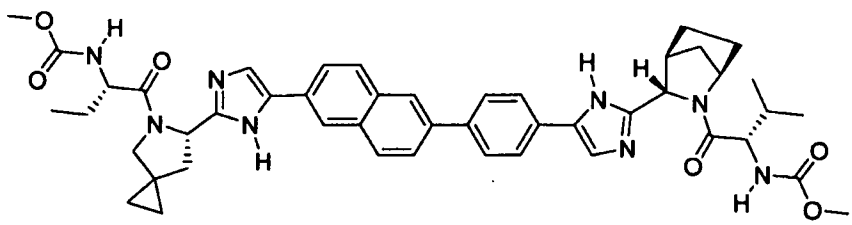

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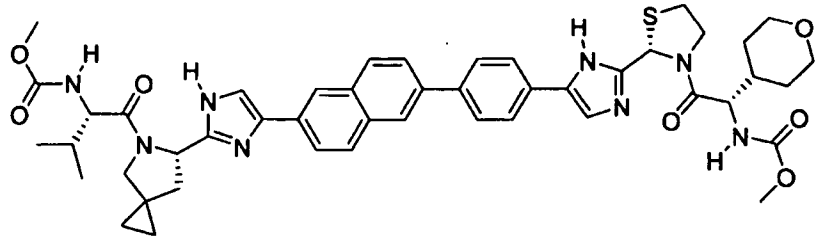

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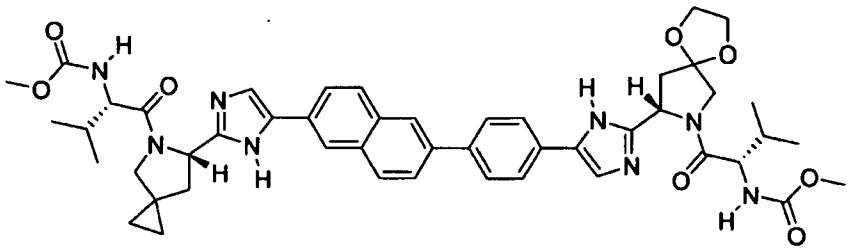

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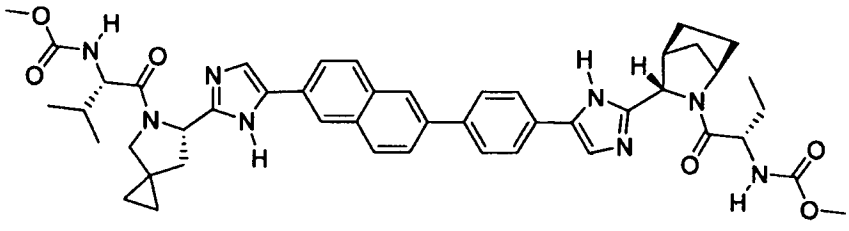

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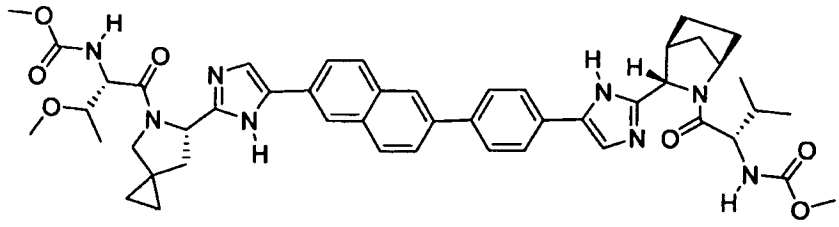

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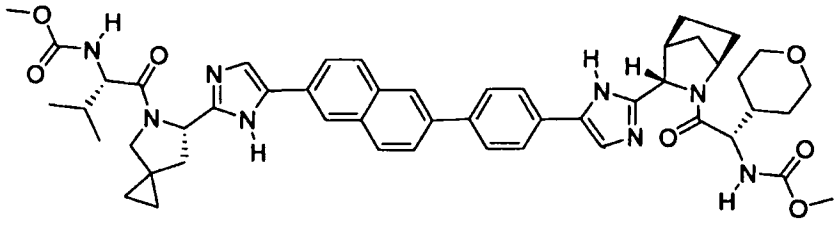

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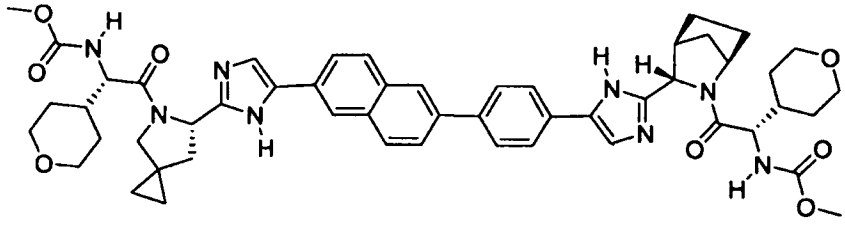

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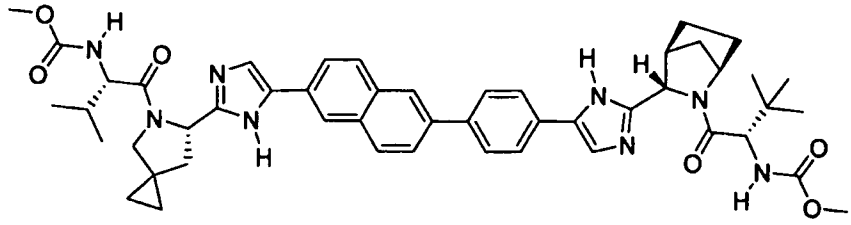

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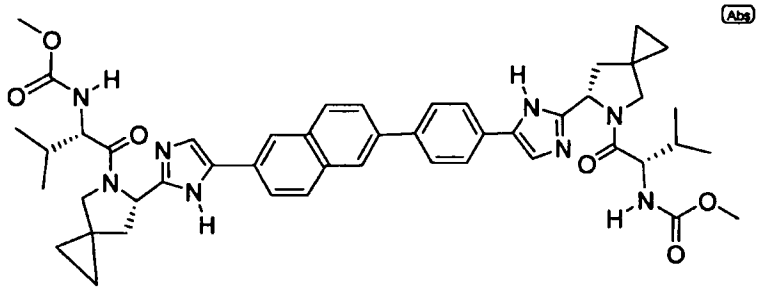

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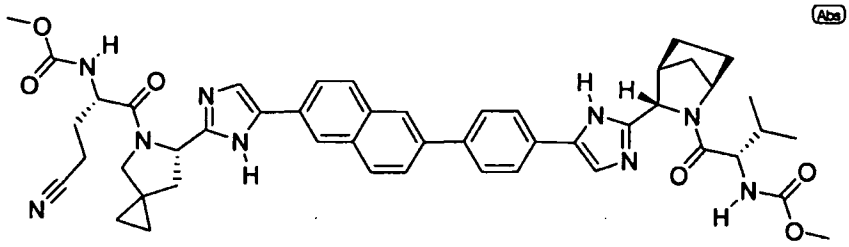

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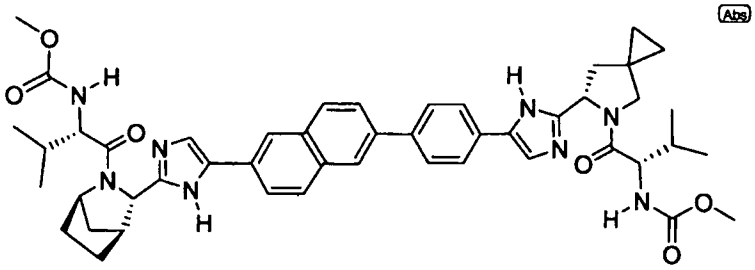

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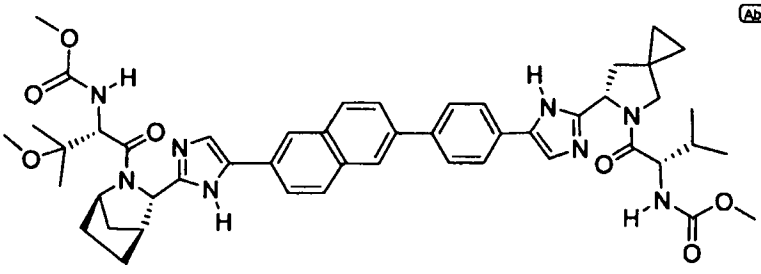

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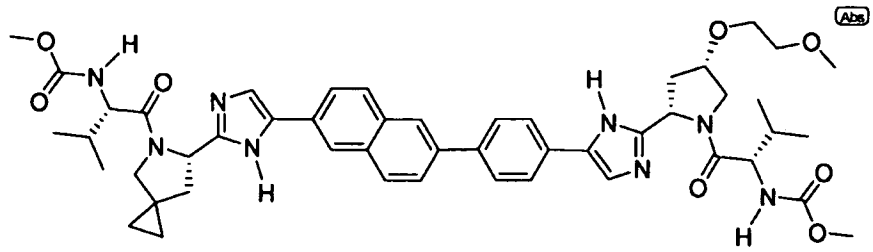

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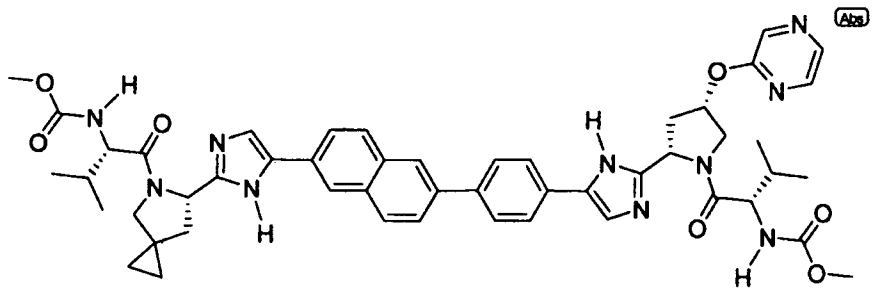

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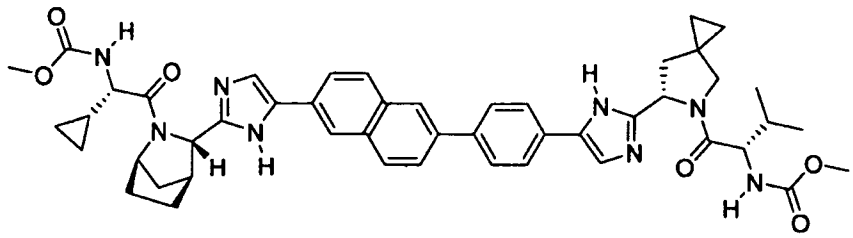

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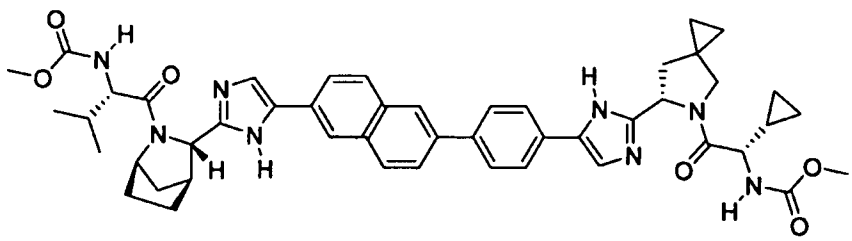

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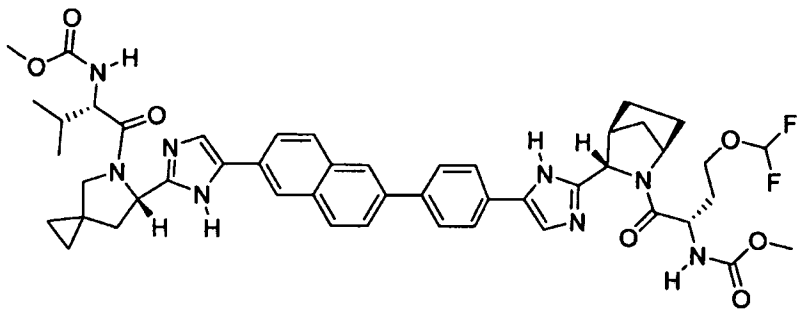

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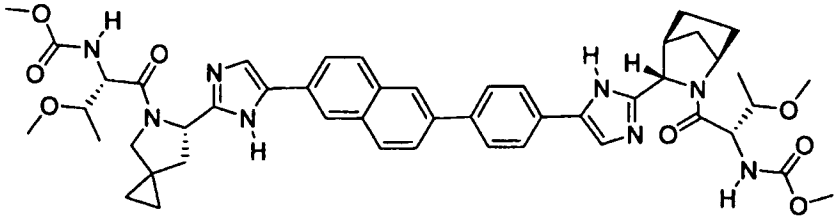

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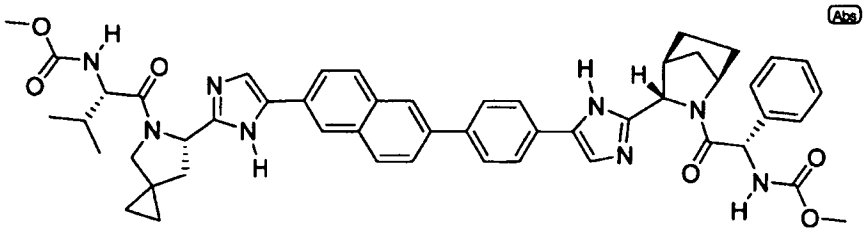

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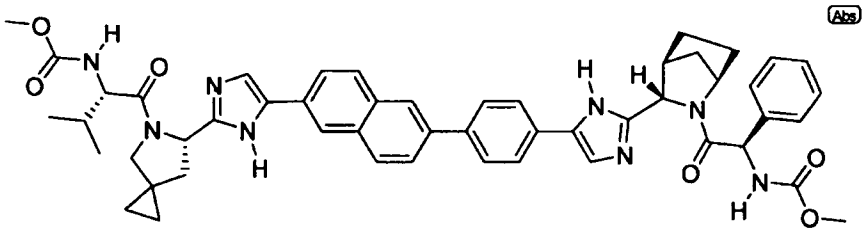

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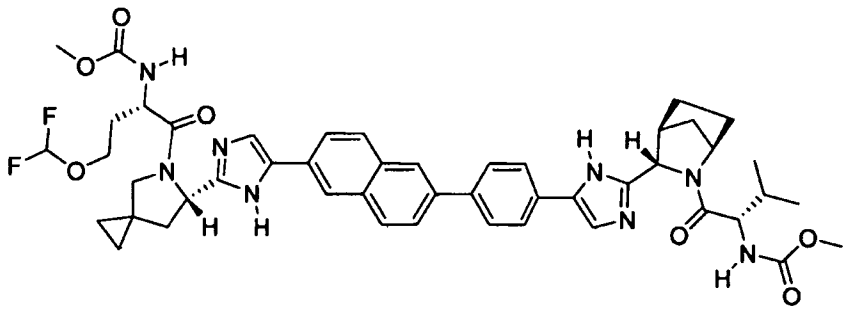

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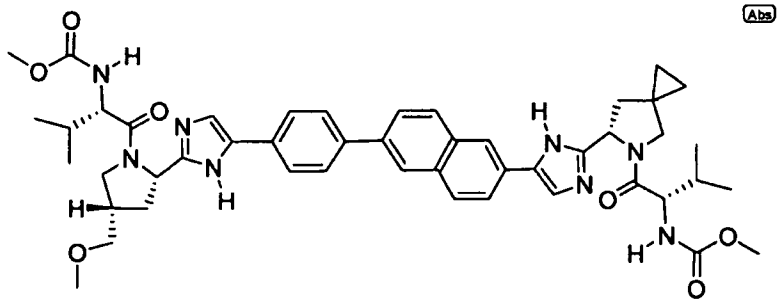

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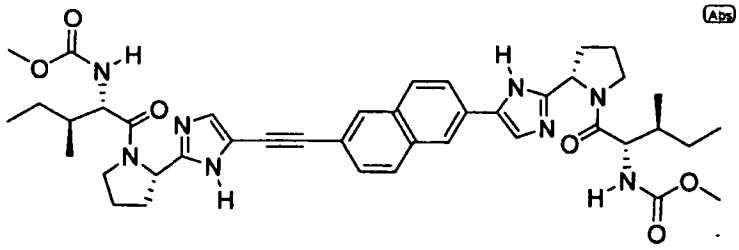

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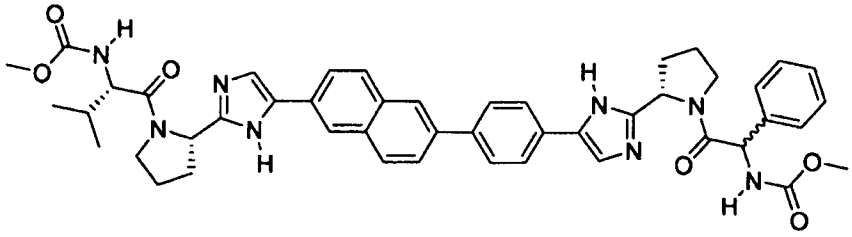

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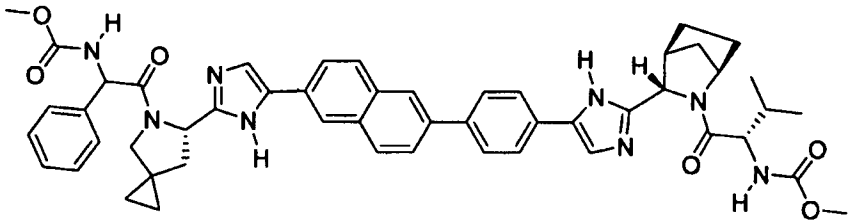

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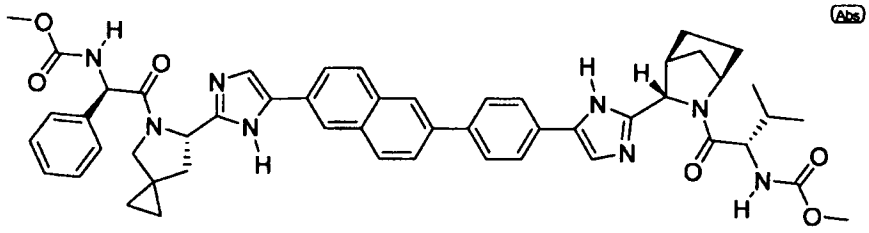

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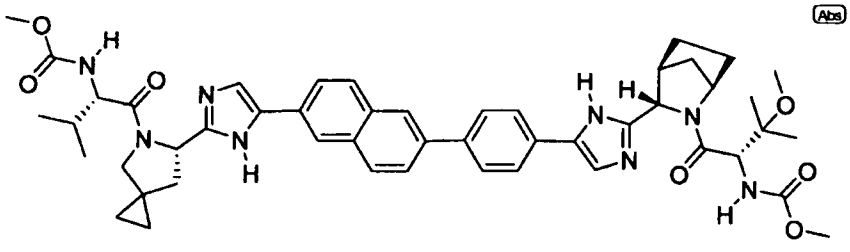

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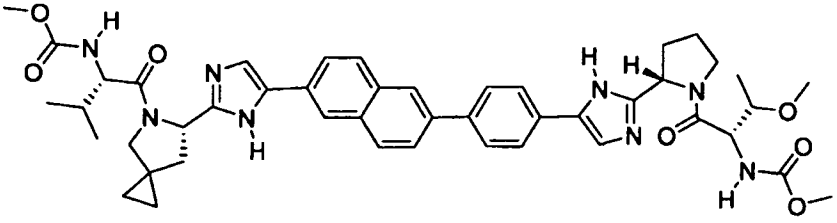

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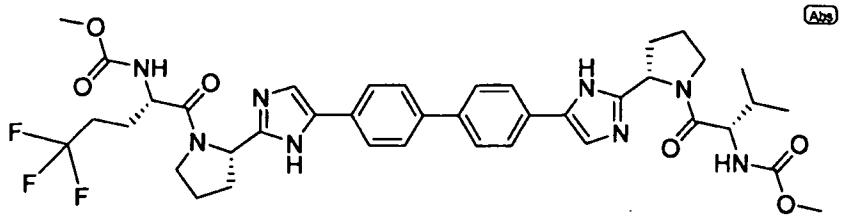

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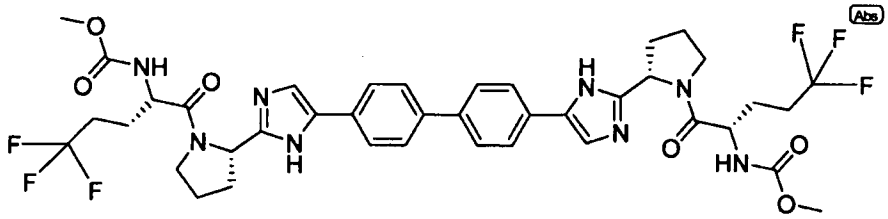

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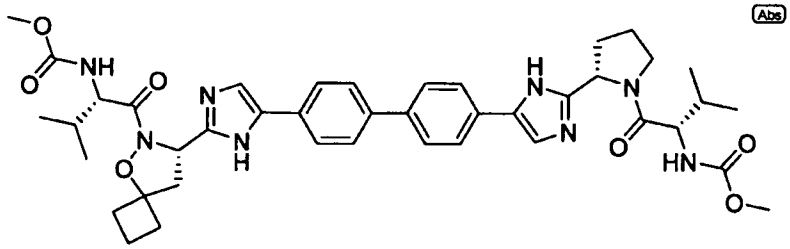

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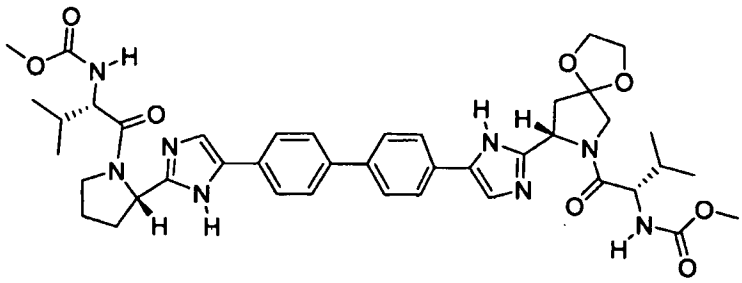

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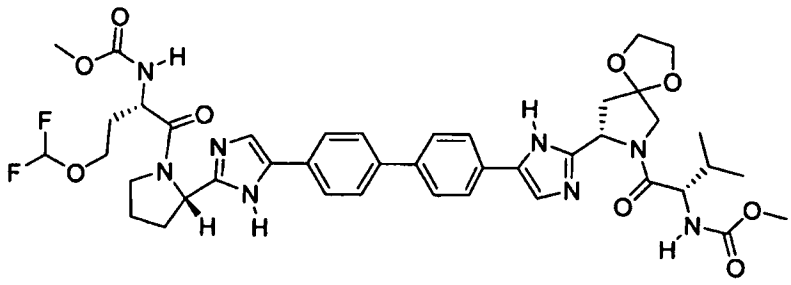

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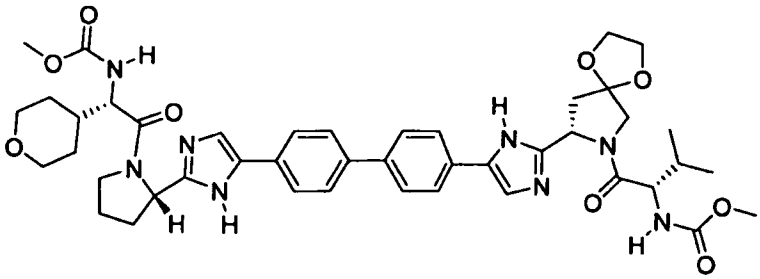

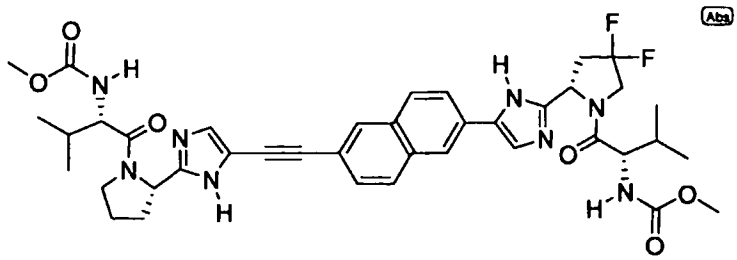

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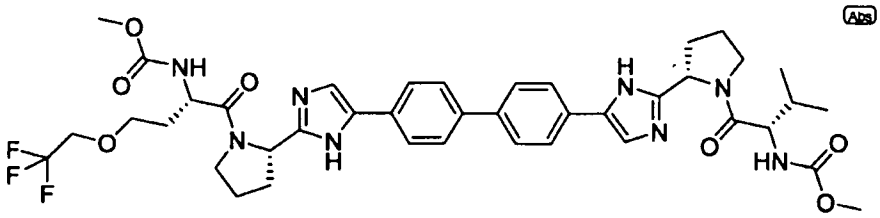

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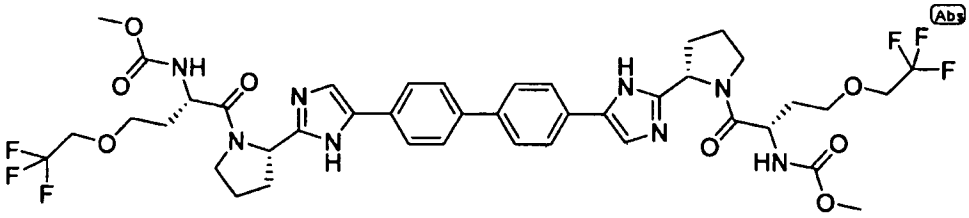

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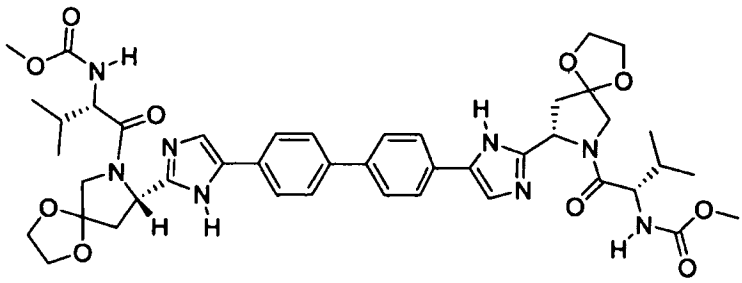

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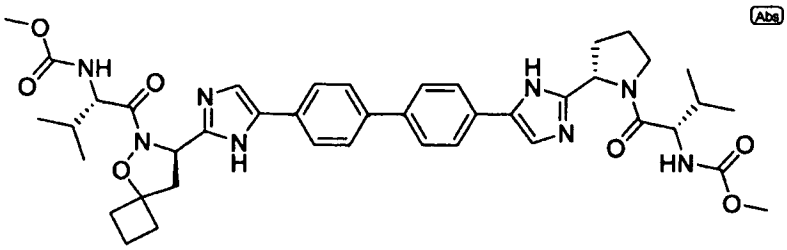

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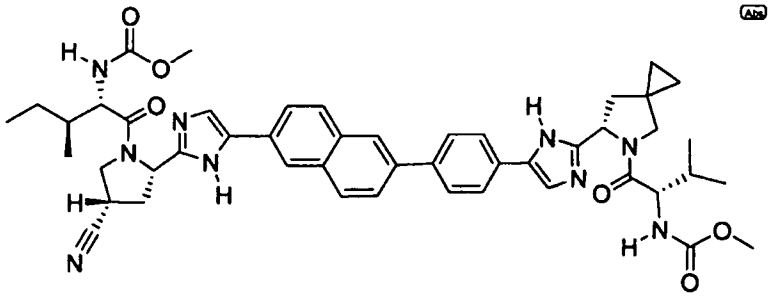

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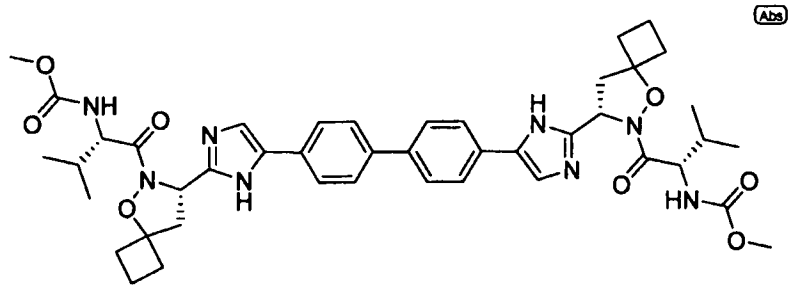

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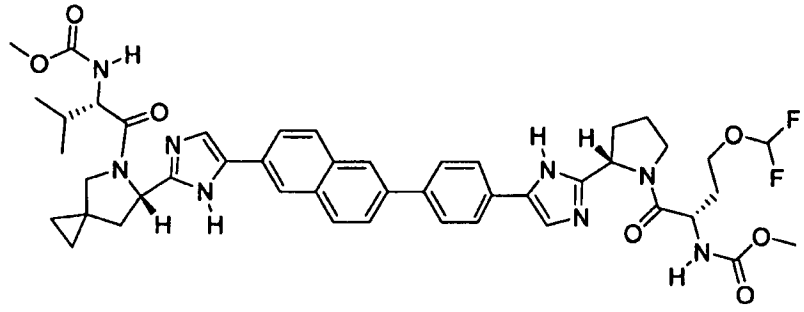

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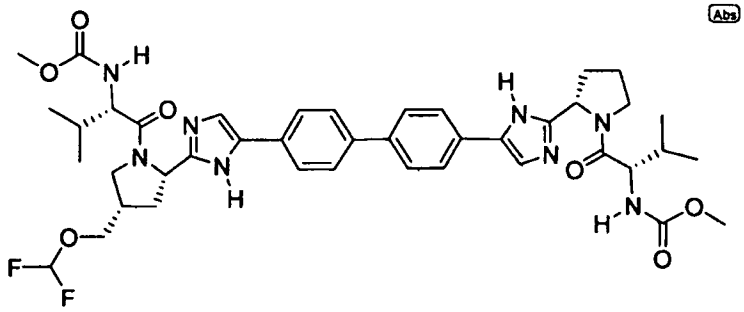

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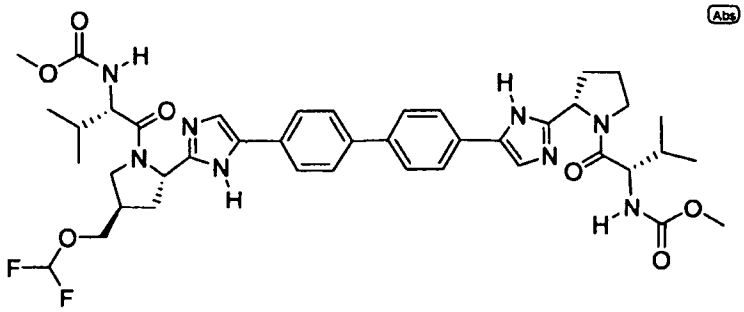

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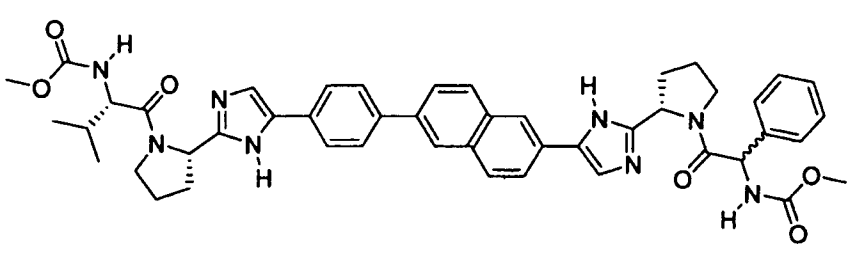

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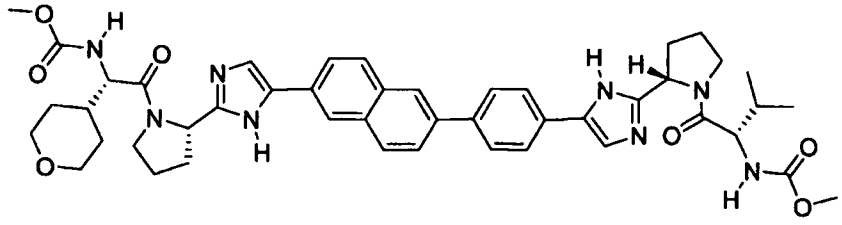

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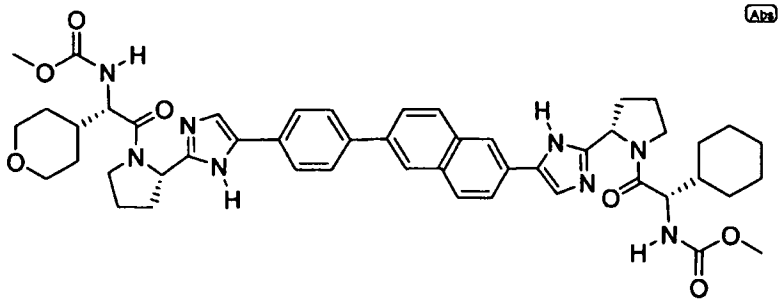

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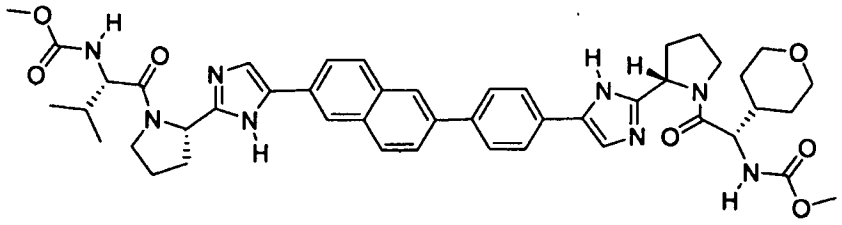

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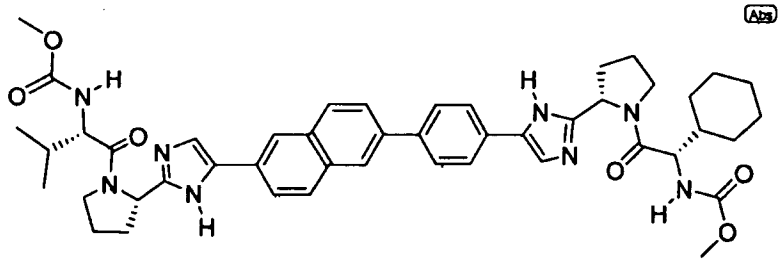

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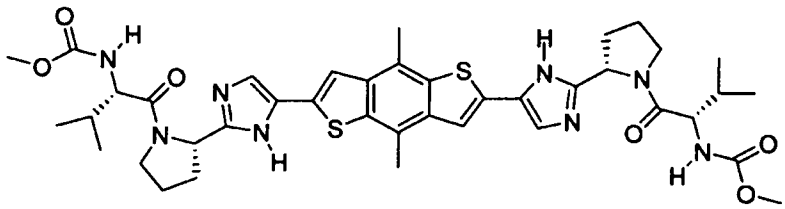

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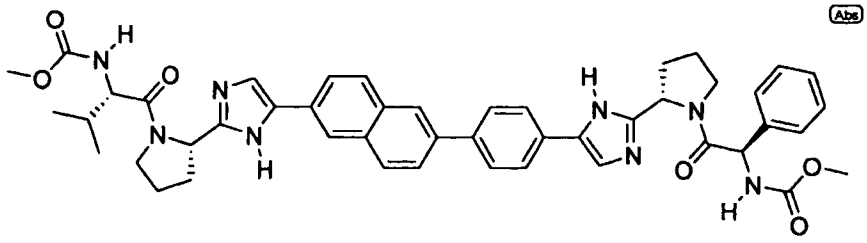

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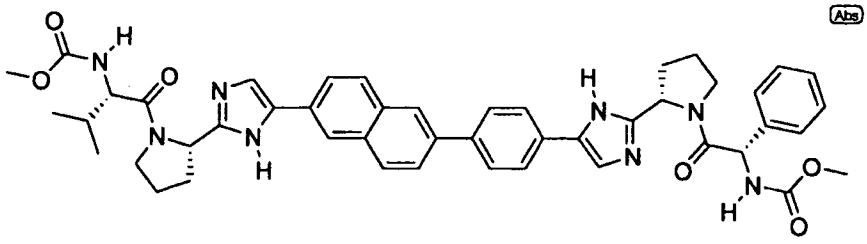

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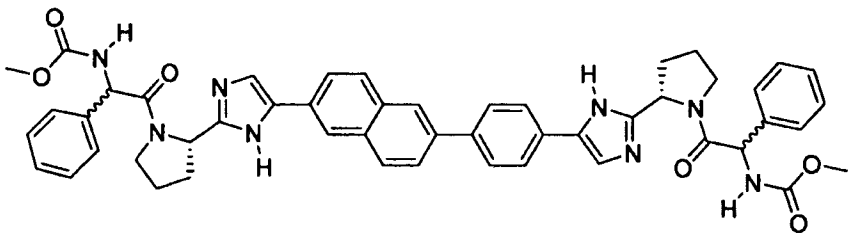

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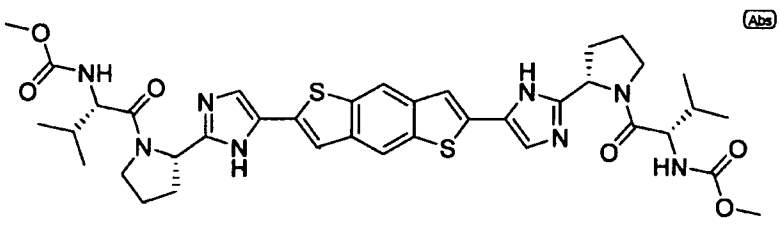

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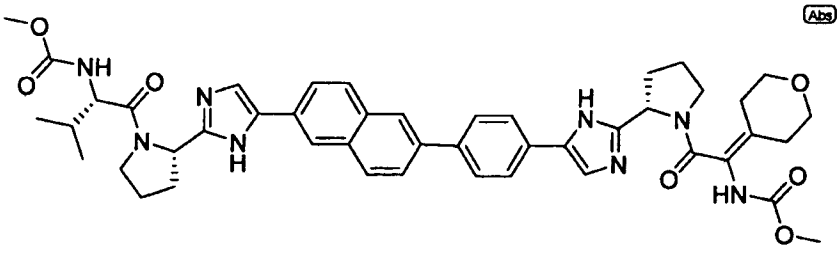

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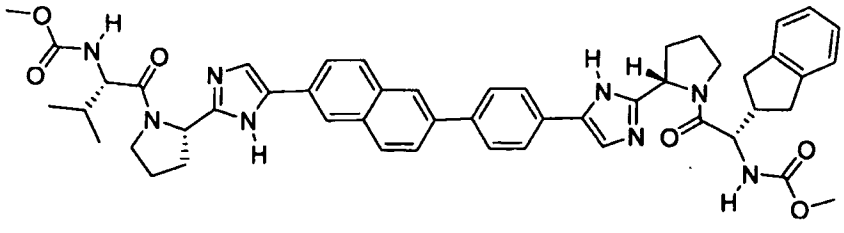

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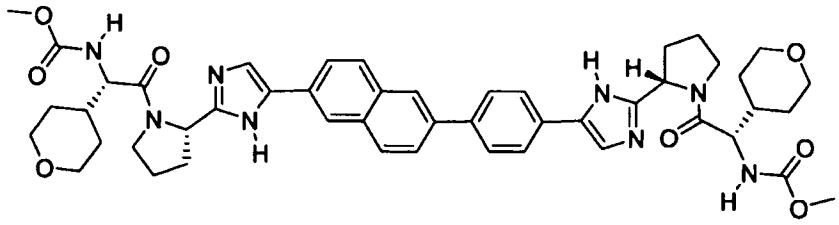

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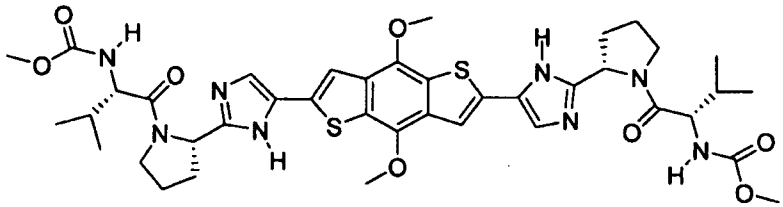

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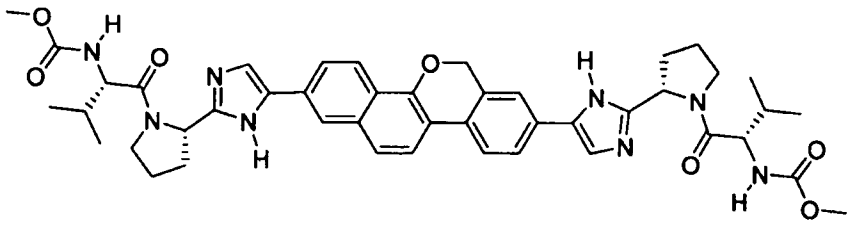

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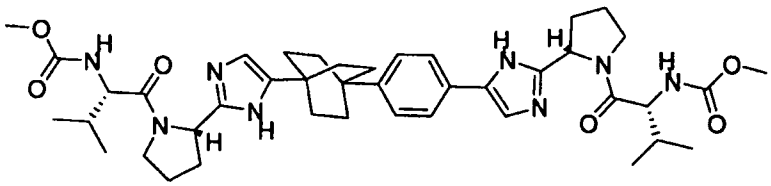

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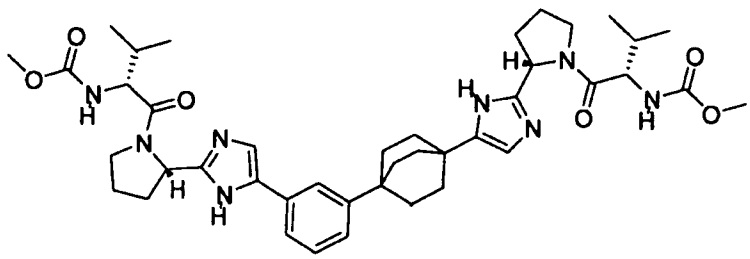

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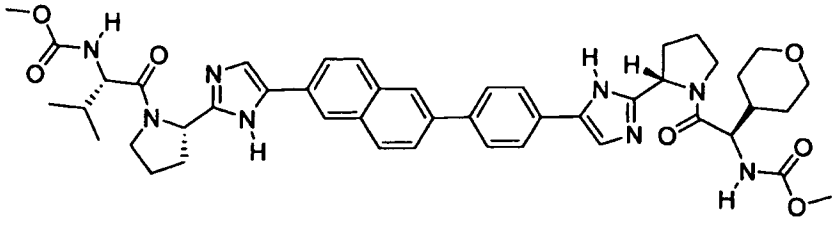

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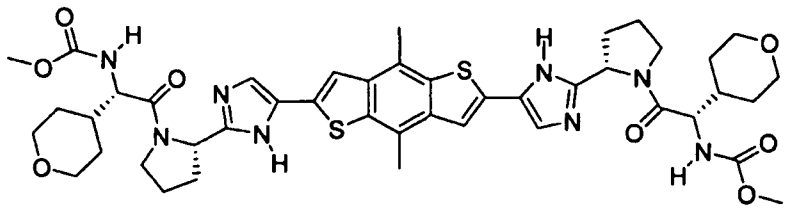

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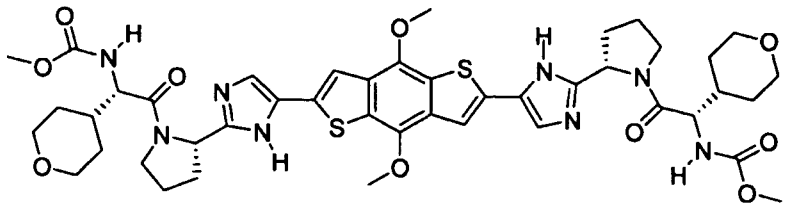

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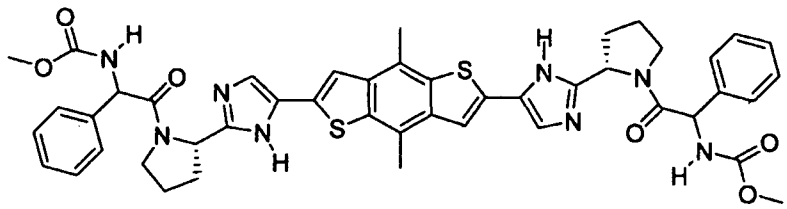

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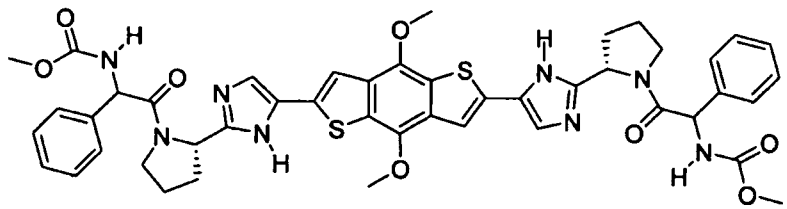

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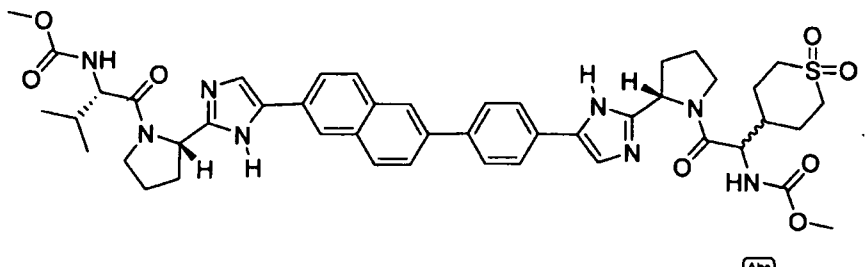

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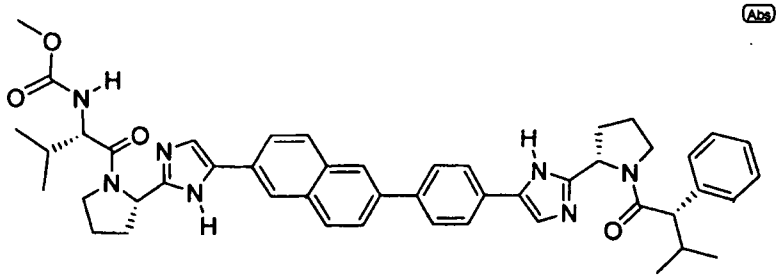

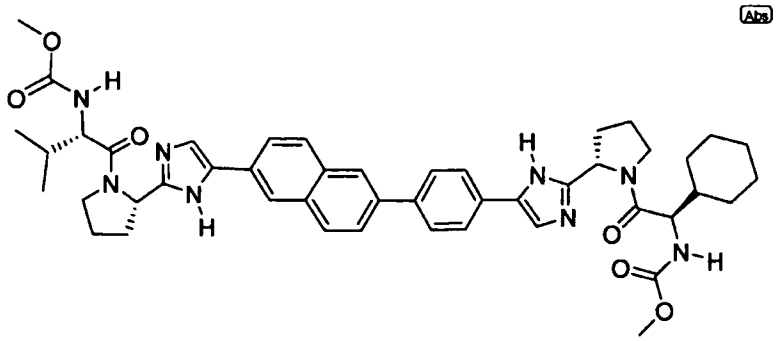

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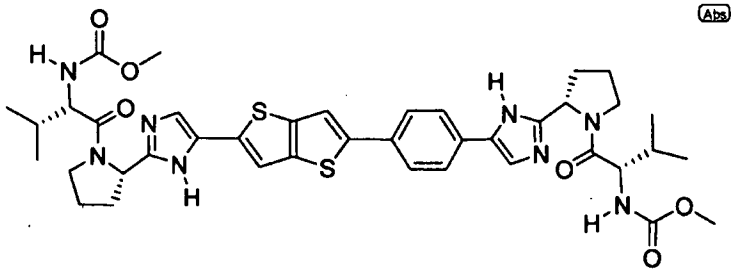

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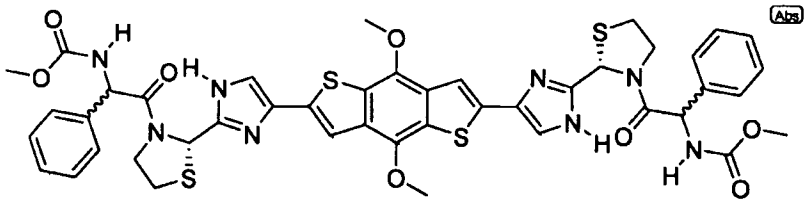

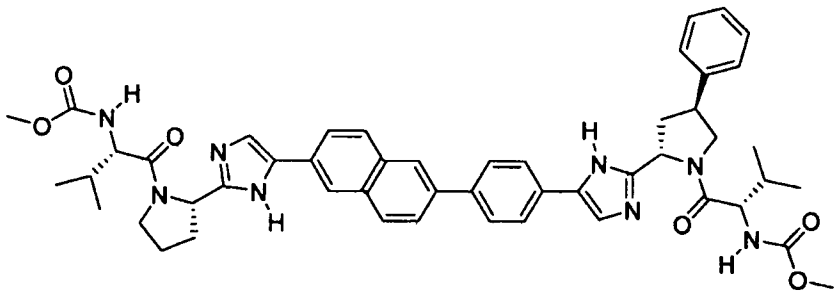

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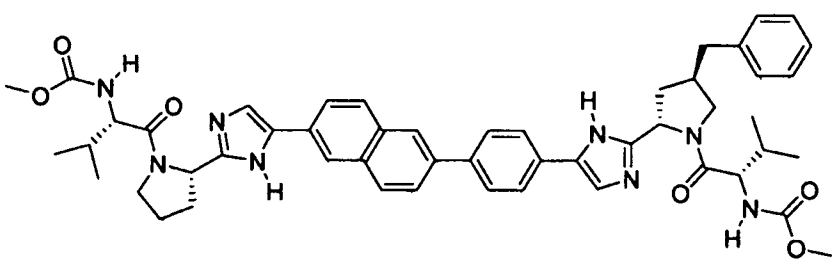

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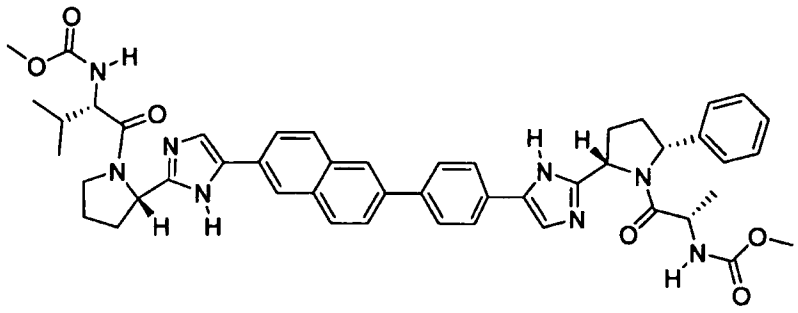

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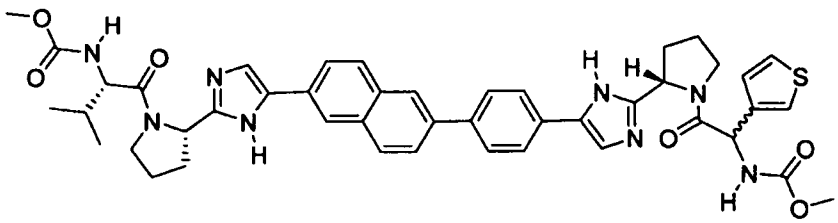

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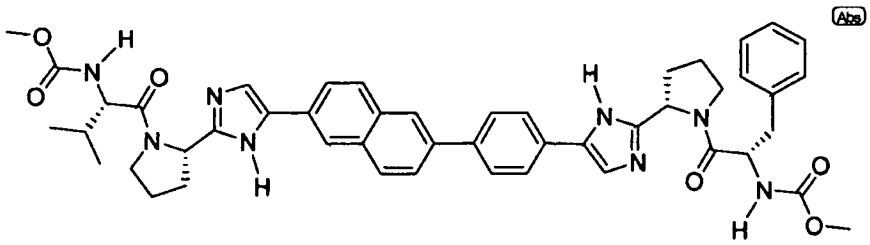

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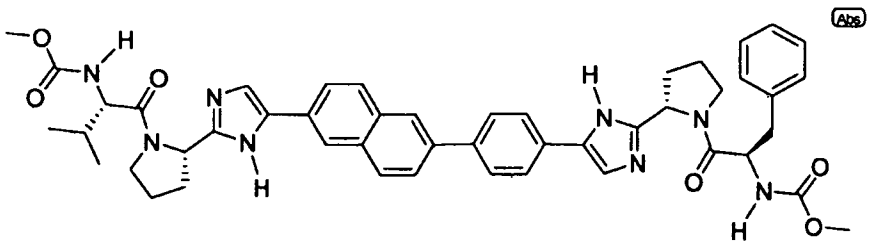

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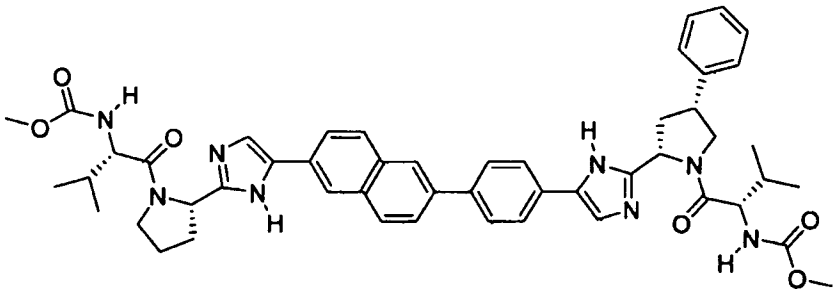

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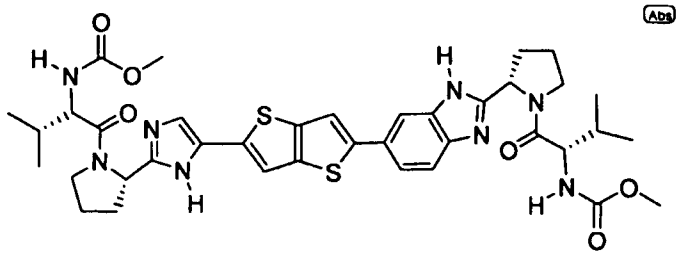

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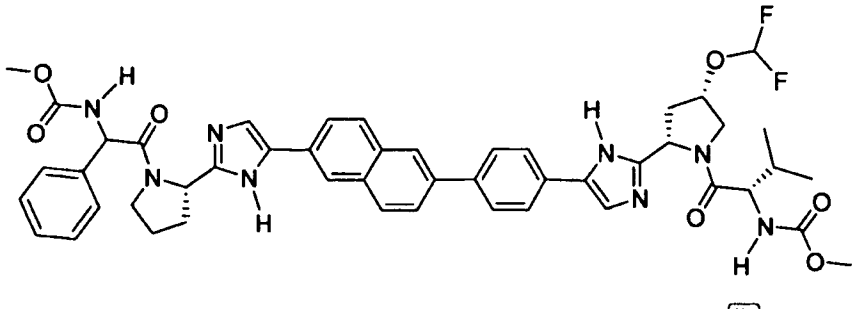

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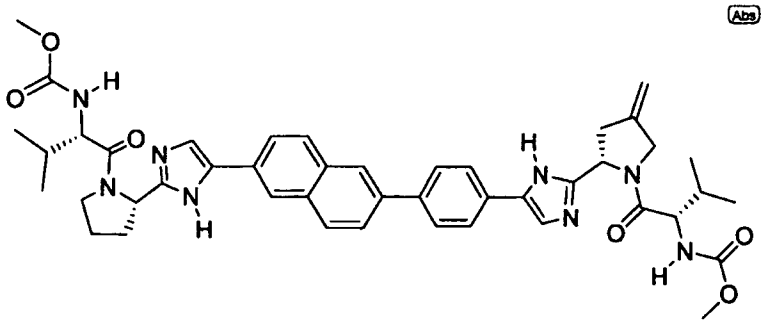

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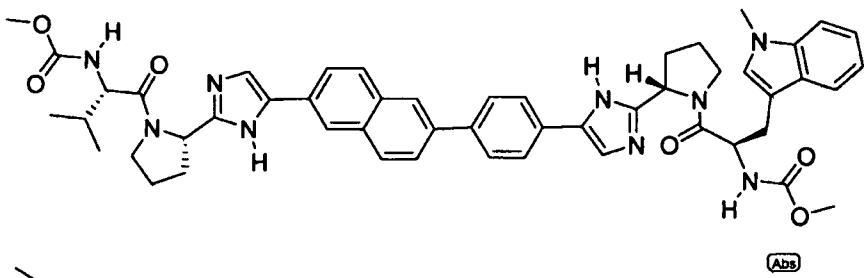

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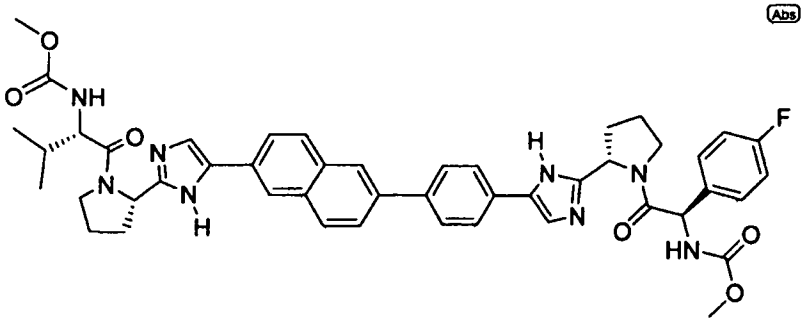

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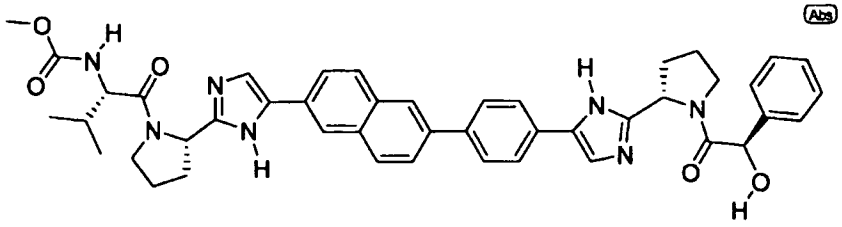

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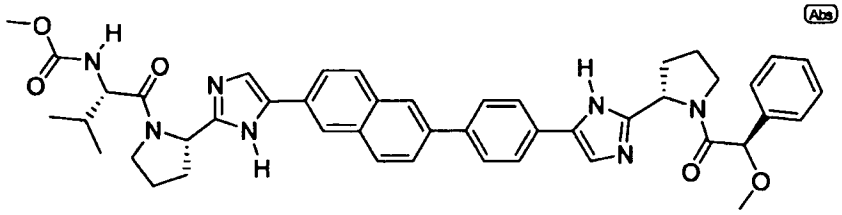

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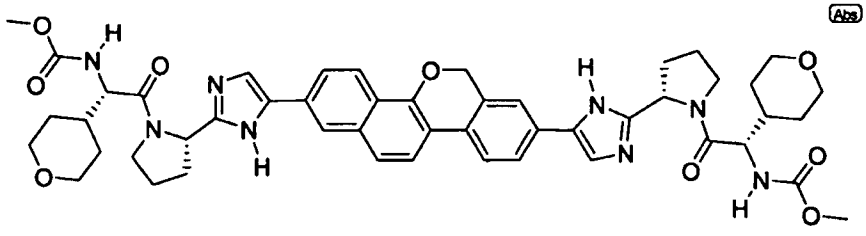

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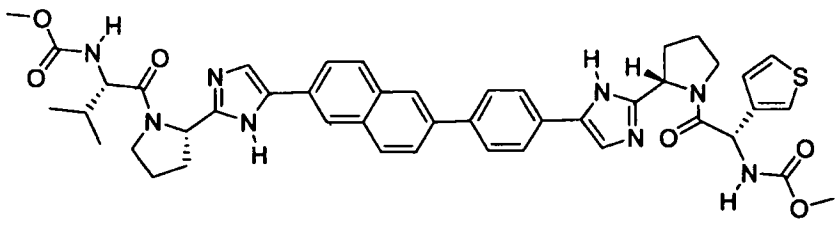

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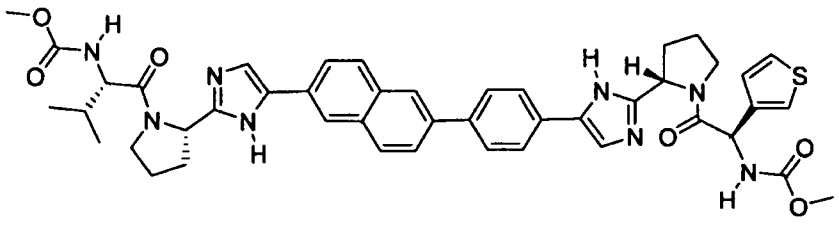

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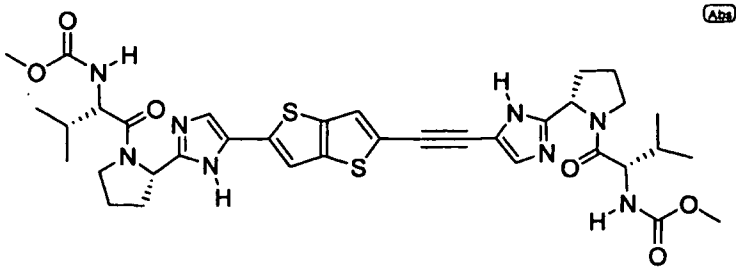

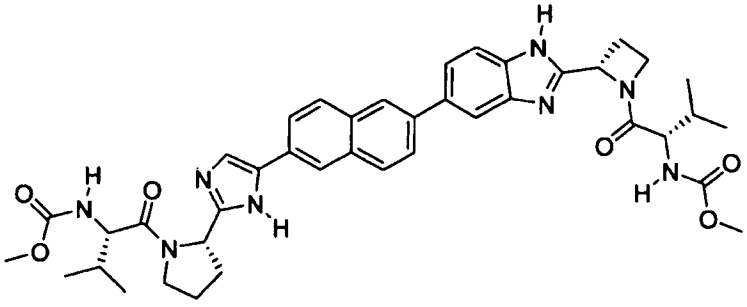

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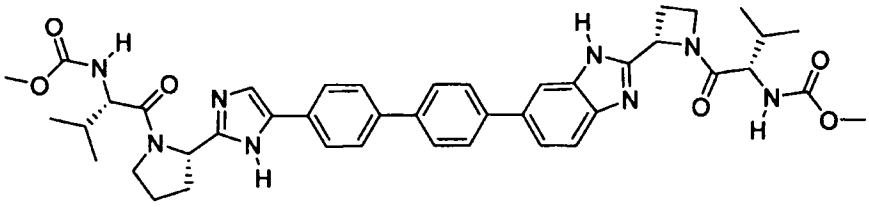

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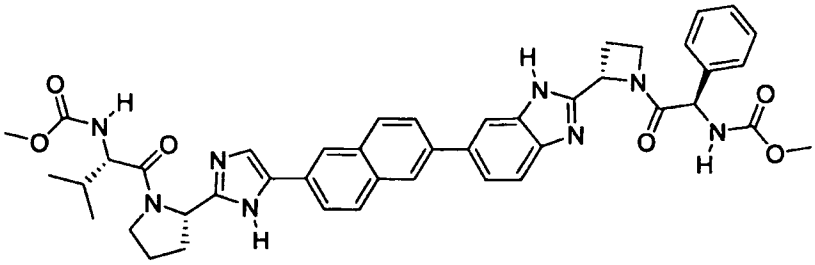

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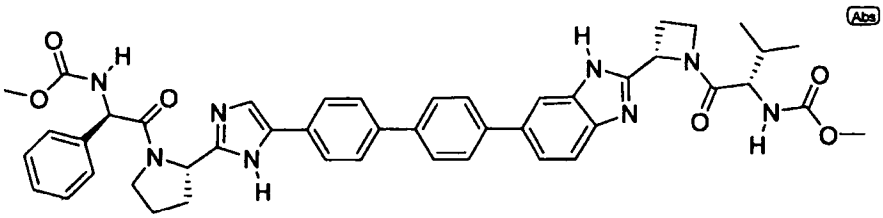

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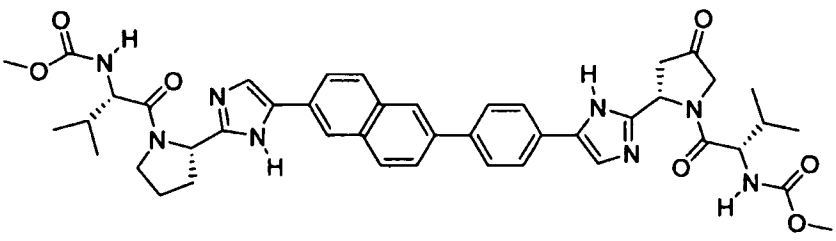

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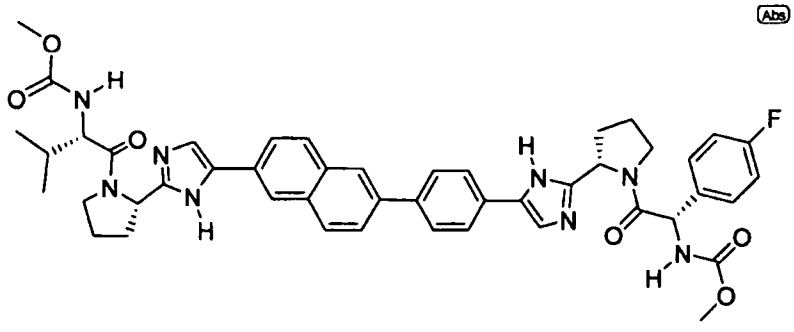

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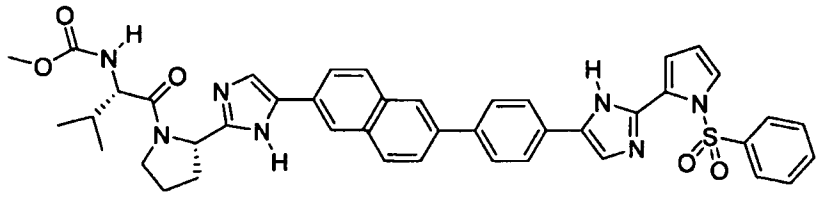

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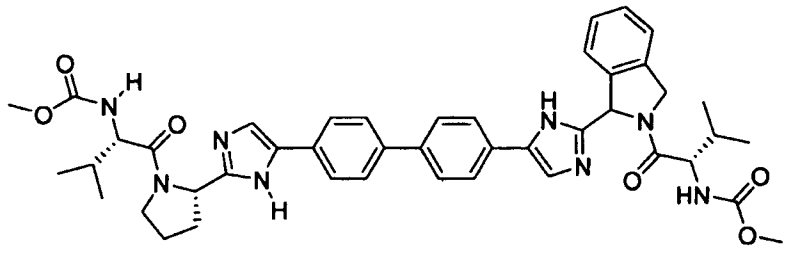

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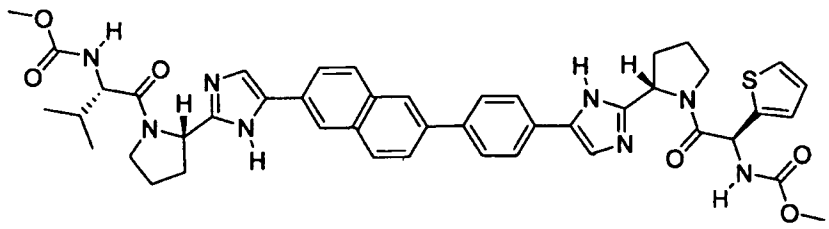

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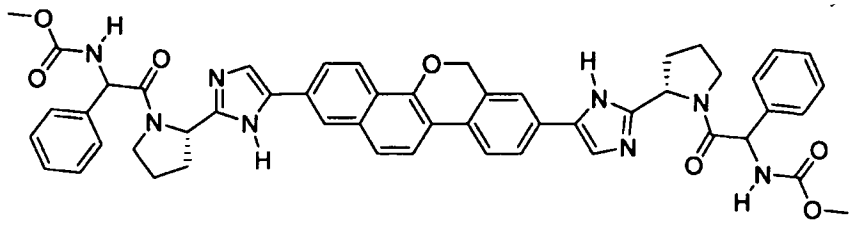

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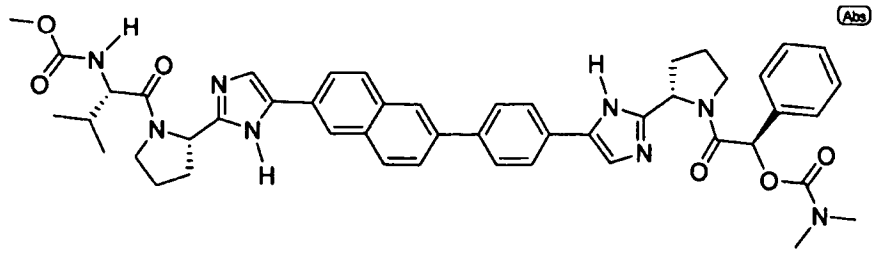

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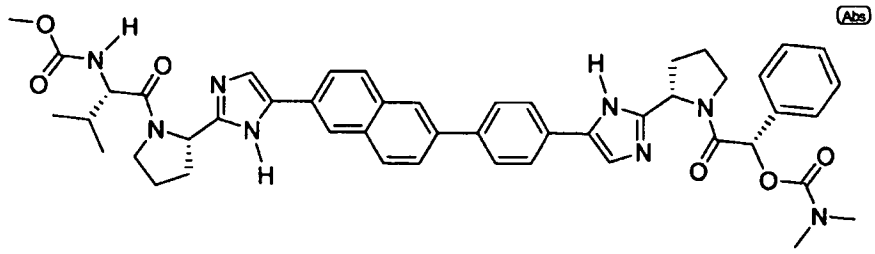

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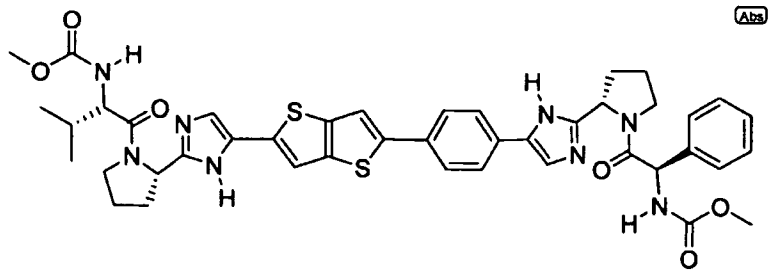

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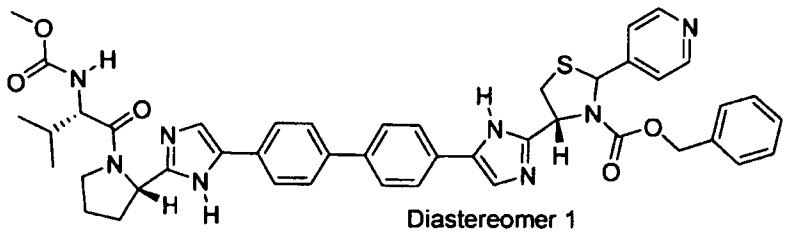

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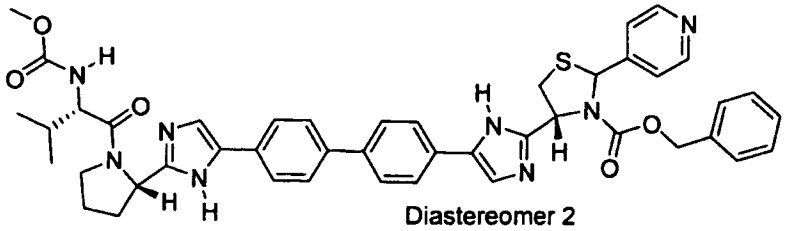

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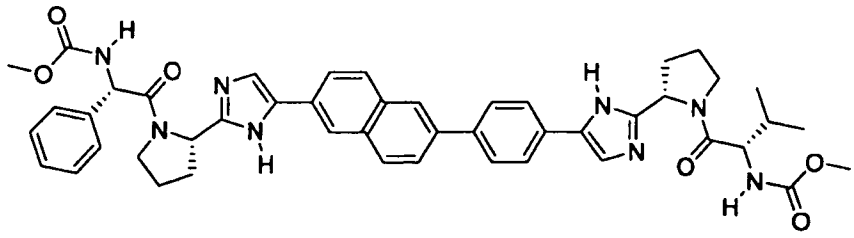

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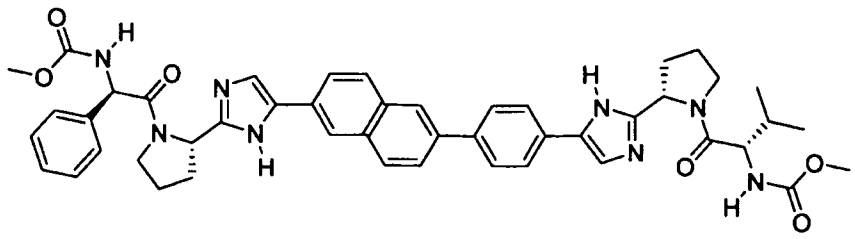
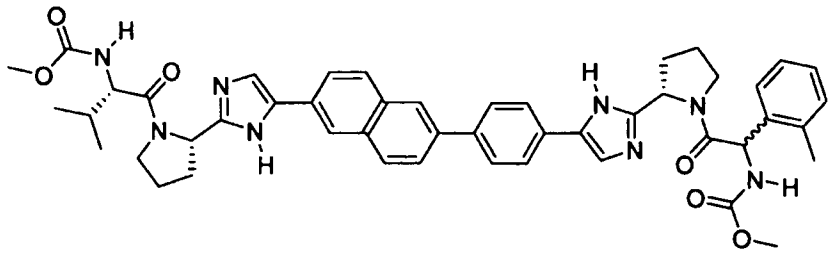
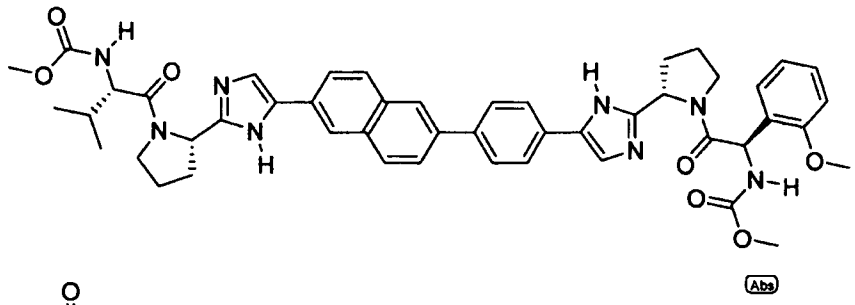


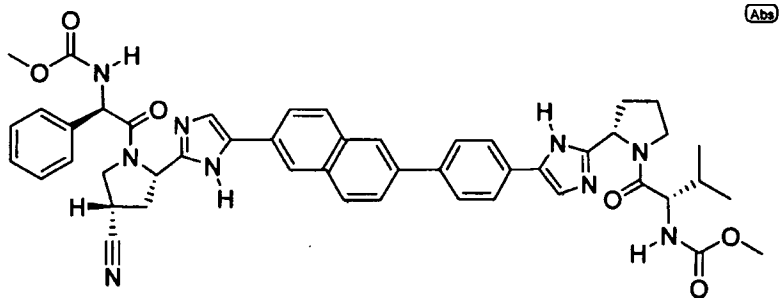
0.0117



0.0073



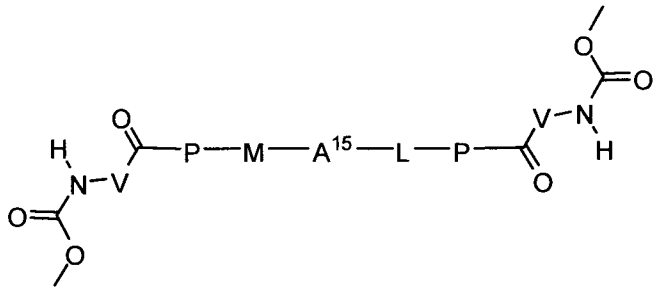
0.0097



All publications, patents, and patent documents are incorporated by reference herein, as though individually incorporated by reference. The invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications may be made while remaining within the spirit and scope of the invention.

Claims

1. A compound of formula:



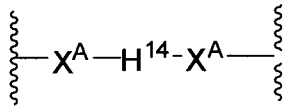
wherein:

V is alkyl;

L is benzimidazolyl;

M is a 5-membered heteroaryl ring;

A^{15} is:



each H^{14} is independently a fused unsaturated, partially unsaturated or saturated tricyclic carbocycle which is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3}; and

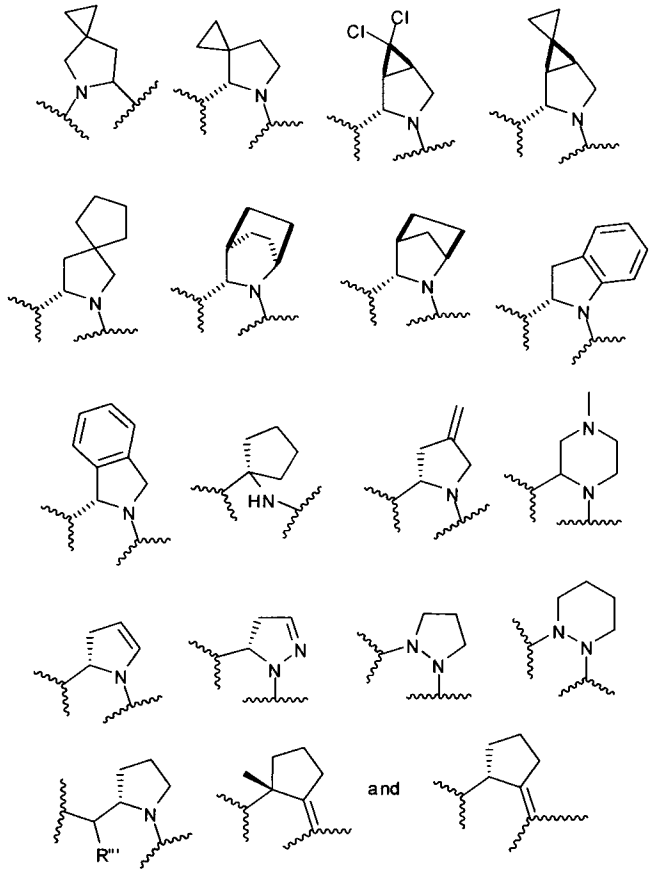
each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent; each R is independently selected from H or alkyl;

each R^{A1} is independently selected from cyano, nitro, SOR^4, SO_2R^4, -alkylSO_2R^4, haloalkoxy, cyanoalkyl, $NR^4SO_2R^4$, cycloalkyl, (halo)cycloalkyl, heterocycle, (cycloalkyl)alkyl, (heterocycle)alkyl, wherein each alkyl, heterocycle and cycloalkyl is optionally substituted with one or more halo;

each R^{A3} is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxy, hydroxyalkyl, $-NR^aR^b$, (NR^aR^b)alkyl, and (NR^aR^b)carbonyl; R^a and R^b are each independently selected from the group consisting of hydrogen, alkenyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylalkylcarbonyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl;

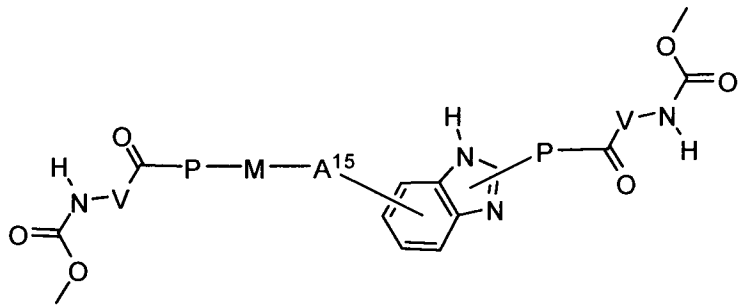
each R^4 is independently selected from H, alkyl, haloalkyl, aryl, and arylalkyl; and

each P is independently selected from:



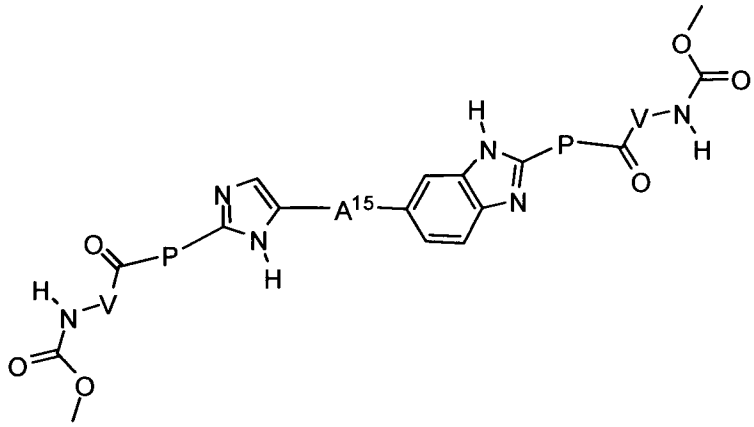
or a pharmaceutically acceptable salt, or prodrug thereof.

2. The compound of claim 1 that is:



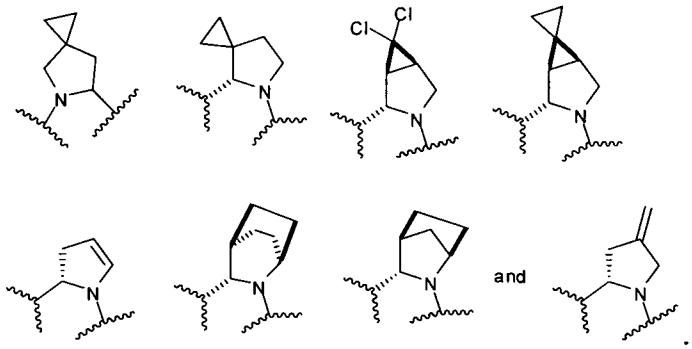
or a pharmaceutically acceptable salt, or prodrug thereof.

3. The compound of claim 1 that is:

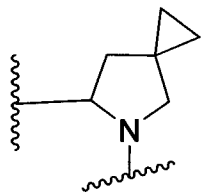


or a pharmaceutically acceptable salt, or prodrug thereof.

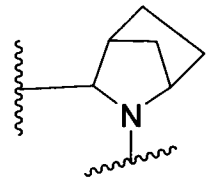
4. The compound of any one of claims 1-3 wherein P is selected from:



5. The compound of any one of claims 1-3 wherein P is



6. The compound of any one of claims 1-3 wherein P is

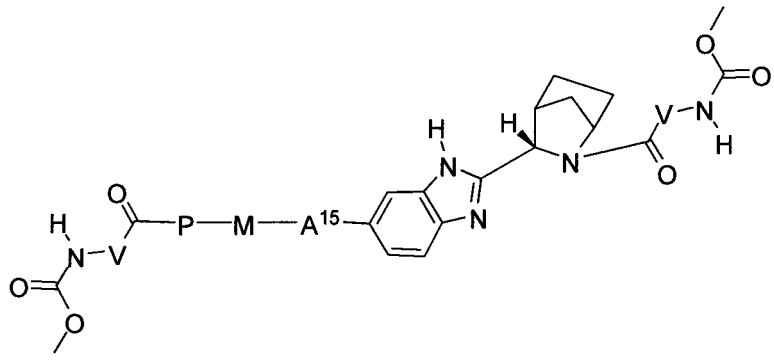


optionally substituted with one or more groups independently selected from R^{P6} and R^{P11};

each R^{P6} is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups; R^{Pa} and R^{Pb} are each independently H, alkyl, aryl, or arylalkyl; or R^{Pa} and R^{Pb} taken together with the atom to which they are attached form a heterocycle;

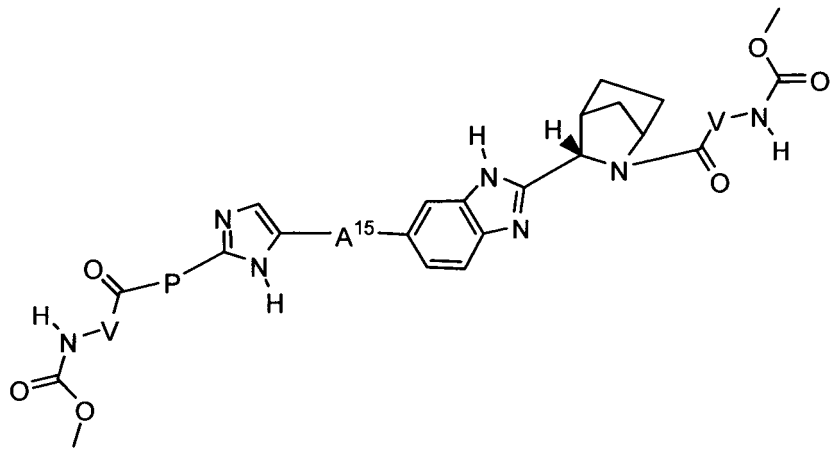
each R^{P11} is independently selected from cyano, alkylsulfonyl, arylsulfonyl, NR^hR^hsulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, NR^hR^halkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl, $-NR^{hh}R^h$, $(NR^{hh}R^h)$alkyl, $(NR^{hh}R^h)$carbonyl, wherein each R^h is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two R^h groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring; wherein each R^{hh} is independently aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, NR^hR^hsulfonyl, heteroarylsulfonyl, and $-S(=O)_2R^h$, $-C(=O)R^h$, $-C(=O)NR^hR^h$.

7. The compound of claim 1 that is:



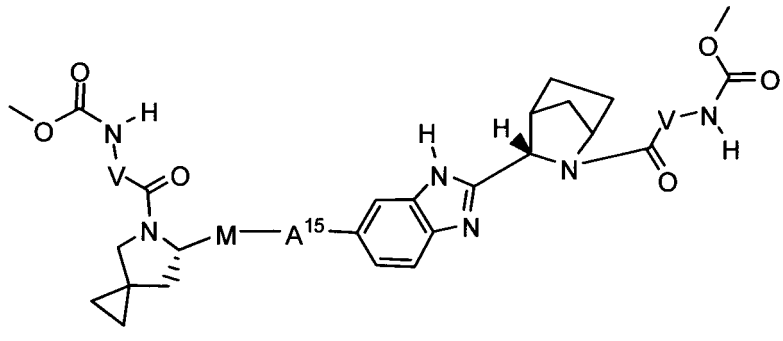
or a pharmaceutically acceptable salt, or prodrug thereof.

8. The compound of claim 1 that is:



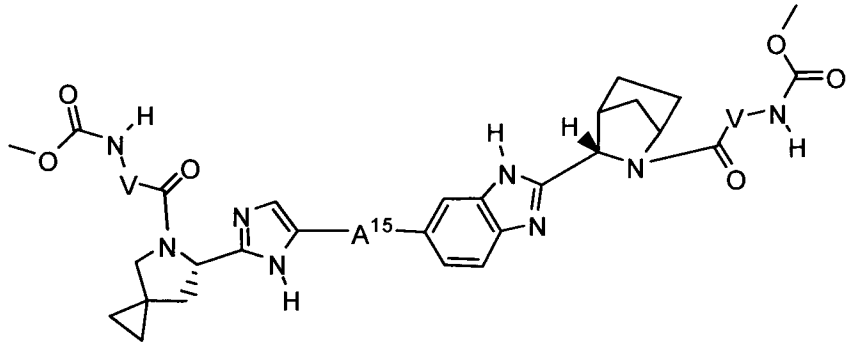
or a pharmaceutically acceptable salt, or prodrug thereof.

9. The compound of claim 1 that is:



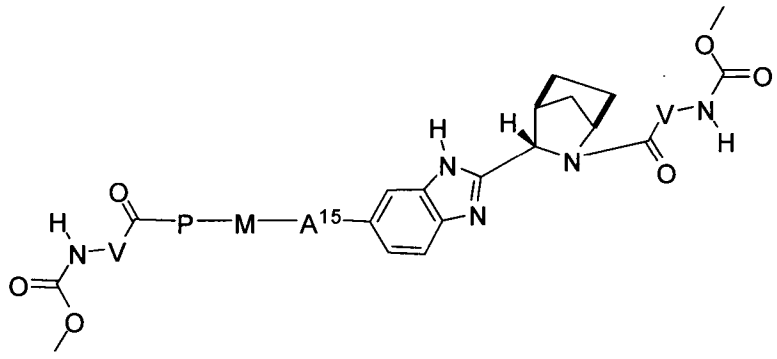
or a pharmaceutically acceptable salt, or prodrug thereof.

10. The compound of claim 1 that is:



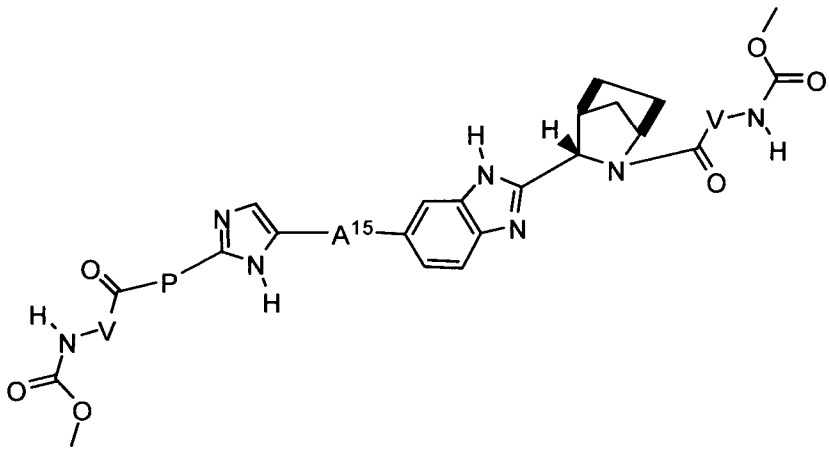
or a pharmaceutically acceptable salt, or prodrug thereof.

11. The compound of claim 1 that is:



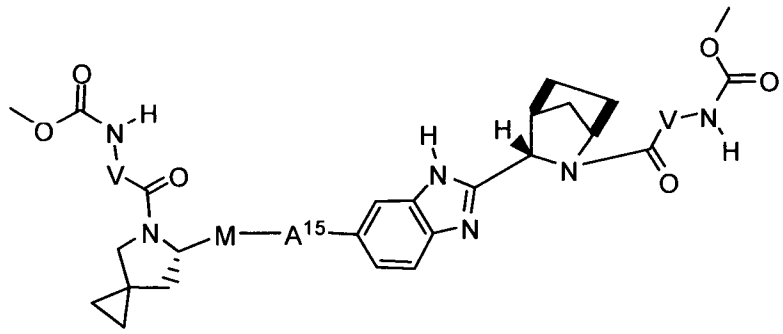
or a pharmaceutically acceptable salt, or prodrug thereof.

12. The compound of claim 1 that is:



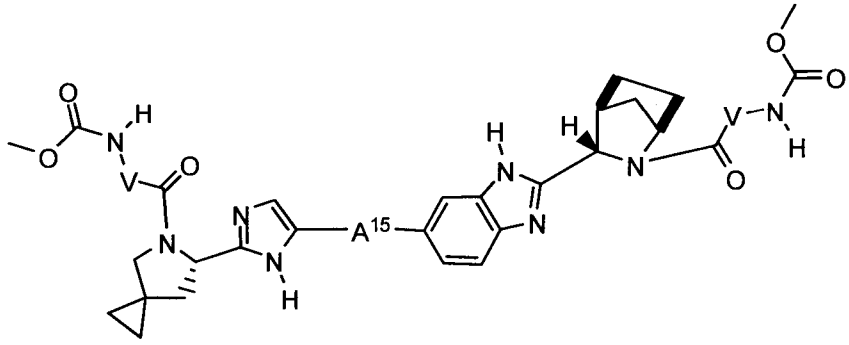
or a pharmaceutically acceptable salt, or prodrug thereof.

13. The compound of claim 1 that is:



or a pharmaceutically acceptable salt, or prodrug thereof.

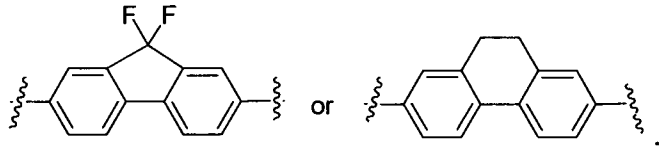
14. The compound of claim 1 that is:



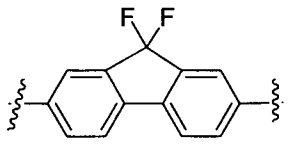
or a pharmaceutically acceptable salt, or prodrug thereof.

15. The compound of any one of claims 1-14 wherein each X^A is absent.

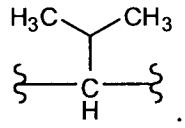
16. The compound of any one of claims 1-14 wherein A^{15} is selected from:



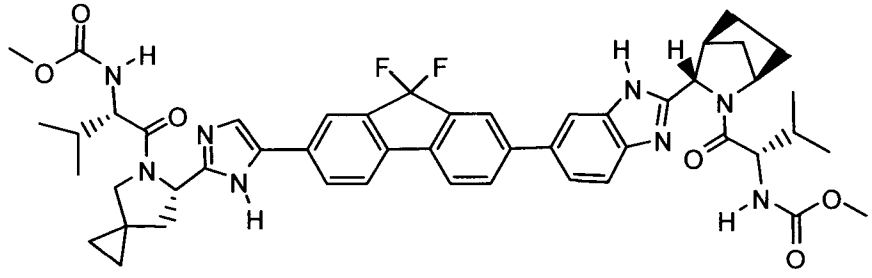
17. The compound of any one of claims 1-14 wherein A^{15} is selected from:



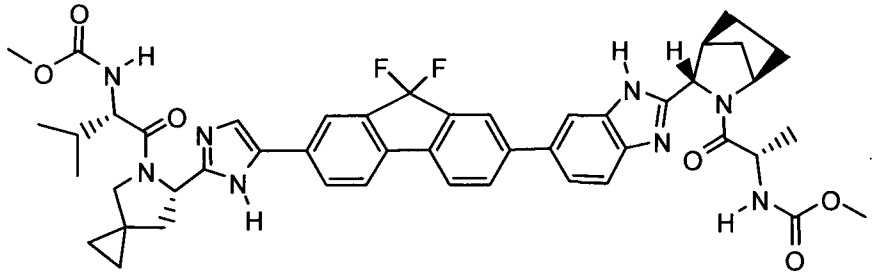
18. The compound of any one of claims 1-16 wherein each V is:



19. The compound of claim 1 which is:



or



or a pharmaceutically acceptable salt, or prodrug thereof.

20. A compound of formula (I):

J-Y-J (I)

wherein:

Y is –L-L-, –M-W-M- or Y^y;

J is T-P-, -P-T or -J^m;

W is a bond or –W^r-;

L is –M-A-, -A-M-, or –L^n;

T is R9-Z-, -Z-R9, or –T^p;

R9 is E-V-, or –V-E, or –$R9^q$;

each A is selected from –A^s;

each M is selected from –M^t;

each P is selected from –P^u;

each Z is selected from $-Z^v$;

each V is selected from $-V^w$;

each E is selected from $-E^x$;

each m is 1

each n is 0, 1, 2, 3, 4, 5, 6, 7, 9, or 10;

each p is 1, 2, 3, 4, 5, 6, 7, or 8;

each q is 0, 1, 2, or 3;

each r is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20;

each s is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, or 21;

each t is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or 11;

each u is 0, 1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19;

each v is 0, 1, 2, 3, 4, 5, or 6;

each w is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24;

each x is 0, 1, 2, 3, 4, 5, 6, or 7;

each y is 0, 1, or 2;

wherein the sum of m, n, p, q, r, s, t, u, v, w, x, and y is not 0; P is connected to M, L, or Y^y; A is connected to A or L; M is connected to P or J; Z is connected to P; V is connected to Z; and when W is a bond M is connected to M;

each Y^1 is independently:
a fused nine-ring system with up to thirty-five atoms that may be fully aromatic or partially saturated and contains atoms selected from C, N, O, and S and which ring system is optionally substituted with one or more groups independently selected from H, oxo, R^{A1} and R^{A3};

each Y^2 is independently:
a fused five to eight ring system with up to thirty-two atoms that may be fully aromatic or partially saturated and contains atoms selected from C, N, O, and S and which ring system is optionally substituted with one or more groups independently selected from H, oxo, R^{A1} and R^{A3};

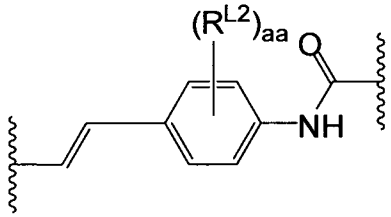
each J^1 is independently a fused bicyclic saturated, partially unsaturated, or aromatic heterocyclic ring system that is substituted with one or more $-N(R^{L7})C(=O)OR^{L7}$, and that is optionally substituted with one or more groups independently selected from oxo, halo, $-R^{L7}$, $-OR^{L7}$, $-SR^{L7}$, $-CF_3$, $-CCl_3$, $-OCF_3$,-CN, $-NO_2$, $-N(R^{L7})C(=O)R^{L7}$, $-C(=O)R^{L7}$, $-OC(=O)R$

^{L7}, -C(O)OR^{L7}, -C(=O)NR^{L7}, -S(=O)R^{L7}, -S(=O)$_2$OR^{L7}, -S(=O)$_2$R^{L7}, -OS(=O)$_2$OR^{L7}, -S(=O)$_2$NR^{L7}, alkoxyalkyl, arylalkoxycarbonyl, halo, haloalkyl, hydroxyalkyl, -NR^{a}R^b, (NR^{a}R^b)alkyl, and (NR^{a}R^b)carbonyl;

each R^{L7} is independently -H, alkyl, aryl, arylalkyl, or heterocycle;

R^a and R^b are independently selected from the group consisting of hydrogen, alkenyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylalkylcarbonyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl;

each L^0 is independently:

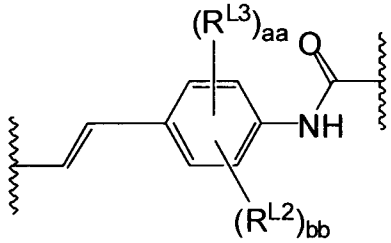


wherein:

each R^{L2} is independently selected from hydrogen, alkenyl, alkoxy, alkyl, halo, and haloalkyl; and

each aa is independently 1, 2, 3, or 4;

each L^1 is independently:



wherein:

each R^{L2} is independently selected from hydrogen, alkenyl, alkoxy, alkyl, halo, and haloalkyl;

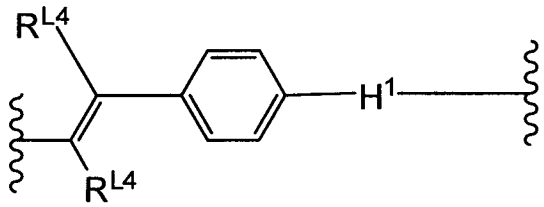
each R^{L3} is independently selected from cyano, nitro, SOR^4, SO$_2$R^4, -alkylSO$_2$R^4, haloalkoxy, cyanoalkyl, NR^{4}SO$_2$R^4, cycloalkyl, (halo)cycloalkyl, heterocycle,

(cycloalkyl)alkyl, (heterocycle)alkyl, wherein each alkyl, heterocycle and cycloalkyl is optionally substituted with one or more halo; and

each R^4 is independently selected from H, alkyl, haloalkyl, aryl, and arylalkyl;

each bb is 0, 1, 2, 3, or 4; each aa is 1, 2, 3, or 4; and the sum of bb and aa is 1, 2, 3, or 4;

each L^2 is independently:



wherein:

the phenyl ring shown in L^2 is optionally substituted with one or more groups independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxy, hydroxyalkyl, -NR^aR^b, (NR^aR^b)alkyl, (NR^aR^b)carbonyl, cyano, nitro, SOR^4, SO_2R^4, -alkylSO_2R^4, haloalkoxy, cyanoalkyl, $NR^4SO_2R^4$, cycloalkyl, (halo)cycloalkyl, heterocycle, (cycloalkyl)alkyl, (heterocycle)alkyl, wherein each alkyl, heterocycle and cycloalkyl is optionally substituted with one or more halo;

each R^{L4} is independently -H, alkyl, aryl, arylalkyl, or heterocycle;

each R^4 is independently selected from H, alkyl, haloalkyl, aryl, and arylalkyl;

R^a and R^b are independently selected from the group consisting of hydrogen, alkenyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylalkylcarbonyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl; and

each H^1 is a 5 membered saturated, partially unsaturated, or aromatic ring comprising one or more heteroatoms.

each L^3 is independently a fused-bicyclic saturated, partially unsaturated, or aromatic heterocyclic ring system that is optionally substituted with one or more groups independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxy, hydroxyalkyl, -NR^aR^b, (NR^aR^b)alkyl, (NR^aR^b)carbonyl, cyano, nitro, SOR^4, SO_2R^4, -alkylSO_2R^4, haloalkoxy, cyanoalkyl, $NR^4SO_2R^4$, cycloalkyl,

(halo)cycloalkyl, heterocycle, (cycloalkyl)alkyl, (heterocycle)alkyl, wherein each alkyl, heterocycle and cycloalkyl is optionally substituted with one or more halo;

each R^4 is independently selected from H, alkyl, haloalkyl, aryl, and arylalkyl; and

R^a and R^b are independently selected from the group consisting of hydrogen, alkenyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylalkylcarbonyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl;

each L^4 is independently a fused-tricyclic saturated, partially unsaturated, or aromatic heterocyclic ring system that is optionally substituted with one or more groups independently selected from oxo, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxy, hydroxyalkyl, $-NR^aR^b$, (NR^aR^b)alkyl, (NR^aR^b)carbonyl, cyano, nitro, SOR^4, SO_2R^4, -alkylSO_2R^4, haloalkoxy, cyanoalkyl, $NR^4SO_2R^4$, cycloalkyl, (halo)cycloalkyl, heterocycle, (cycloalkyl)alkyl, (heterocycle)alkyl, wherein each alkyl, heterocycle and cycloalkyl is optionally substituted with one or more halo;

each R^4 is independently selected from H, alkyl, haloalkyl, aryl, and arylalkyl; and

R^a and R^b are independently selected from the group consisting of hydrogen, alkenyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylalkylcarbonyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl;

each L^5 is independently a –CR=CR-fusedbicyclic saturated, partially unsaturated, or aromatic heterocyclic ring system that is optionally substituted with one or more groups independently selected from oxo, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxy, hydroxyalkyl, $-NR^aR^b$, (NR^aR^b)alkyl, (NR^aR^b)carbonyl, cyano, nitro, SOR^4, SO_2R^4, -alkylSO_2R^4, haloalkoxy, cyanoalkyl, $NR^4SO_2R^4$, cycloalkyl, (halo)cycloalkyl, heterocycle, (cycloalkyl)alkyl, (heterocycle)alkyl, wherein each alkyl, heterocycle and cycloalkyl is optionally substituted with one or more halo;

each R is independently selected from H or alkyl;

each R^4 is independently selected from H, alkyl, haloalkyl, aryl, and arylalkyl; and

R^a and R^b are independently selected from the group consisting of hydrogen, alkenyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylalkylcarbonyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl;

each L^6 is independently a –CR=CR-fused-tricyclic saturated, partially unsaturated, or aromatic heterocyclic ring system that is optionally substituted with one or more groups independently selected from oxo, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy,

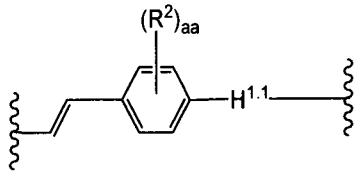
formyl, halo, haloalkyl, hydroxy, hydroxyalkyl, -NR^aR^b, (NR^aR^b)alkyl, (NR^aR^b)carbonyl, cyano, nitro, SOR^4, SO_2R^4, -alkylSO_2R^4, haloalkoxy, cyanoalkyl, $NR^4SO_2R^4$, cycloalkyl, (halo)cycloalkyl, heterocycle, (cycloalkyl)alkyl, (heterocycle)alkyl, wherein each alkyl, heterocycle and cycloalkyl is optionally substituted with one or more halo;

each R is independently selected from H or alkyl;

each R^4 is independently selected from H, alkyl, haloalkyl, aryl, and arylalkyl; and

R^a and R^b are independently selected from the group consisting of hydrogen, alkenyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylalkylcarbonyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl;

each L^7 is independently:



wherein:

each $H^{1.1}$ is independently a fused-bicyclic saturated, partially unsaturated, or aromatic heterocyclic ring system that is optionally substituted with one or more R^2;

each R^2 is independently selected from halo, -R^{L7}, -OR^{L7}, -SR^{L7}, -$N(R^{L7})_2$, -CF_3, -CCl_3, -OCF_3,-CN, -NO_2, -$N(R^{L7})C(=O)R^{L7}$, -$C(=O)R^{L7}$, -$OC(=O)R^{L7}$, -$C(O)OR^{L7}$, -$C(=O)NR^{L7}$, -$S(=O)R^{L7}$, -$S(=O)_2OR^{L7}$, -$S(=O)_2R^{L7}$, -$OS(=O)_2OR^{L7}$, and -$S(=O)_2NR^{L7}$;

each R^{L7} is independently -H, alkyl, aryl, arylalkyl, or heterocycle; and

each aa is independently 1, 2, 3, or 4;

each L^9 is independently a fused-tetracyclic saturated, partially unsaturated, or aromatic heterocyclic ring system that is optionally substituted with one or more groups independently selected from oxo, halo, -R^{L7}, -OR^{L7}, -SR^{L7}, -CF_3, -CCl_3, -OCF_3,-CN, -NO_2, -$N(R^{L7})C(=O)R^{L7}$, -$C(=O)R^{L7}$, -$OC(=O)R^{L7}$, -$C(O)OR^{L7}$, -$C(=O)NR^{L7}$, -$S(=O)R^{L7}$, -$S(=O)_2OR^{L7}$, -$S(=O)_2R^{L7}$, -$OS(=O)_2OR^{L7}$, -$S(=O)_2NR^{L7}$, alkoxyalkyl, arylalkoxycarbonyl, halo, haloalkyl, hydroxyalkyl, -NR^aR^b, (NR^aR^b)alkyl, and (NR^aR^b)carbonyl;

each R^{L7} is independently -H, alkyl, aryl, arylalkyl, or heterocycle;

R^a and R^b are each independently selected from the group consisting of hydrogen, alkenyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylalkylcarbonyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl;

each L^{10} is independently a fused-pentacyclic saturated, partially unsaturated, or aromatic heterocyclic ring system that is optionally substituted with one or more groups independently selected from oxo, halo, $-R^{L7}$, $-OR^{L7}$, $-SR^{L7}$, $-CF_3$, $-CCl_3$, $-OCF_3$,-CN, $-NO_2$, $-N(R^{L7})C(=O)R^{L7}$, $-C(=O)R^{L7}$, $-OC(=O)R^{L7}$, $-C(O)OR^{L7}$, $-C(=O)NR^{L7}$, $-S(=O)R^{L7}$, $-S(=O)_2OR^{L7}$, $-S(=O)_2R^{L7}$, $-OS(=O)_2OR^{L7}$, $-S(=O)_2NR^{L7}$, alkoxyalkyl, arylalkoxycarbonyl, halo, haloalkyl, hydroxyalkyl, $-NR^aR^b$, (NR^aR^b)alkyl, and (NR^aR^b)carbonyl;

each R^{L7} is independently -H, alkyl, aryl, arylalkyl, or heterocycle;

R^a and R^b are each independently selected from the group consisting of hydrogen, alkenyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylalkylcarbonyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl;

each L^{11} is independently a six-ring fused saturated, partially unsaturated, or aromatic heterocyclic ring system that is optionally substituted with one or more groups independently selected from oxo, halo, $-R^{L7}$, $-OR^{L7}$, $-SR^{L7}$, $-CF_3$, $-CCl_3$, $-OCF_3$,-CN, $-NO_2$, $-N(R^{L7})C(=O)R^{L7}$, $-C(=O)R^{L7}$, $-OC(=O)R^{L7}$, $-C(O)OR^{L7}$, $-C(=O)NR^{L7}$, $-S(=O)R^{L7}$, $-S(=O)_2OR^{L7}$, $-S(=O)_2R^{L7}$, $-OS(=O)_2OR^{L7}$, $-S(=O)_2NR^{L7}$, alkoxyalkyl, arylalkoxycarbonyl, halo, haloalkyl, hydroxyalkyl, $-NR^aR^b$, (NR^aR^b)alkyl, and (NR^aR^b)carbonyl;

each R^{L7} is independently -H, alkyl, aryl, arylalkyl, or heterocycle;

R^a and R^b are each independently selected from the group consisting of hydrogen, alkenyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylalkylcarbonyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl;

each $R9^0$ is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonylalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, aryloxyalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, cycloalkyloxyalkyl, haloalkyl, heterocyclyl, heterocyclylalkenyl, heterocyclylalkoxy, heterocyclylalkyl, heterocyclyloxyalkyl, hydroxyalkyl, $-NR^cR^d$, (NR^cR^d)alkenyl, (NR^cR^d)alkyl, and (NR^cR^d)carbonyl;

R^c and R^d are independently selected from hydrogen, alkenyloxycarbonyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfonyl, aryl,

arylalkoxycarbonyl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, aryloxycarbonyl, arylsulfonyl, cycloalkyl, cycloalkylsulfonyl, formyl, haloalkoxycarbonyl, heterocyclyl, heterocyclylalkoxycarbonyl, heterocyclylalkyl, heterocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, hydroxyalkylcarbonyl, (NR^eR^f)alkyl, (NR^eR^f)alkylcarbonyl, (NR^eR^f)carbonyl, (NR^eR^f)sulfonyl, -C(NCN)OR', and - C(NCN)NR^XR^Y, wherein R' is selected from alkyl and unsubstituted phenyl, and wherein the alkyl part of the arylalkyl, the arylalkylcarbonyl, the heterocyclylalkyl, and the heterocyclylalkylcarbonyl are further optionally substituted with one -NR^eR^f group; and wherein the aryl, the aryl part of the arylalkoxycarbonyl, the arylalkyl, the arylalkylcarbonyl, the arylcarbonyl, the aryloxycarbonyl, and the arylsulfonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkoxycarbonyl, the heterocyclylalkyl, the heterocyclylalkylcarbonyl, the heterocyclylcarbonyl, and the heterocyclyloxycarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro;

R^X and R^Y are independently selected from hydrogen, alkoxycarbonyl, alkyl, alkylcarbonyl, unsubstituted aryl, unsubstituted arylalkoxycarbonyl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted heterocyclyl, and ($NR^{X'}R^{Y'}$)carbonyl, wherein $R^{X'}$ and $R^{Y'}$ are independently selected from hydrogen and alkyl;

each $R9^1$ is independently –N(R^{9a})-NHC(=O)O-R^{9b}, wherein each R^{9a} is independently arylalkyl, alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkoxy, halocycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkoxy, alkylSO_2alkyl, cycloalkylalkylSO_2alkyl, cyanoalkyl, haloalkyl, cycloalkylalkyl, cycloalkyl, alkoxyalkyl, alkoxyalkylcarbonylalkyl, alkoxycarbonylalkyl, alkylsulfanylalkyl, aryalkoxyalkylcarbonylalkyl, carboxyalkyl, heterocyclylalkyl, heterocyclyl, heterocyclylcarbonylalkyl, hydroxyalkyl, NRRCOalkyl, wherein each R is independently selected from hydrogen and alkyl;
and wherein arylalkyl the alkyl can be substituted with up to three aryl groups, and the alkyl part of the arylalkyl is further optionally substituted with one or two additional groups independently selected from alkoxy, alkylcarbonyloxy, halo, haloalkoxy, haloalkyl, heterocyclyl, hydroxy;

and the aryl part can be substituted with 1, 2, 3, 4, or 5 substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, a second aryl group, arylalkoxy, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, heterocyclyl, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, -NR^XR^Y, -(NR^XR^Y)alkyl, oxo, and -P(O)OR_2, wherein each R is independently selected from hydrogen and alkyl; and wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted

and wherein the second aryl group, the aryl part of the arylalkyl, the aryl part of the arylcarbonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro;

and the heterocyclyl can be substituted with 1, 2, 3, 4, or 5 substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, a second heterocyclyl group, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, $-NR^XR^Y$, (NR^XR^Y)alkyl, and oxo, wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted and wherein the aryl, the aryl part of the arylalkyl; the aryl part of the arylcarbonyl, the second heterocyclyl group, and the heterocyclyl
part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro; R^{9b} is independently H, alkyl, aryl, haloalkyl, or arylalkyl;

each $R9^2$ is independently $-N(R^{9a})$-$NHC(=O)NR^{9b}{}_2$; wherein each R^{9a} is independently arylalkyl, alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkoxy, halocycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkoxy, alkylSO_2alkyl, cycloalkylalkylSO_2alkyl, cyanoalkyl, haloalkyl cycloalkylalkyl, cycloalkyl, alkoxyalkyl, alkoxyalkylcarbonylalkyl, alkoxycarbonylalkyl, alkylsulfanylalkyl, aryalkoxyalkylcarbonylalkyl, carboxyalkyl, heterocyclylalkyl, heterocyclylcarbonylalkyl, hydroxyalkyl, NRRCOalkyl, wherein each R is independently selected from hydrogen and alkyl;
and where in arylalkyl the alkyl can be substituted with up to three aryl groups, and the alkyl part of the arylalkyl is further optionally substituted with one or two additional groups independently selected from alkoxy, alkylcarbonyloxy, halo, haloalkoxy, haloalkyl, heterocyclyl, hydroxy;

and the aryl part can be substituted with 1, 2, 3, 4, or 5 substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, a second aryl group, arylalkoxy, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, heterocyclyl, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, $-NR^XR^Y$, $-(NR^XR^Y)$alkyl, oxo, and $-P(O)OR_2$, wherein each R is independently selected from hydrogen and alkyl; and wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted and wherein the second aryl group, the aryl part of the arylalkyl, the aryl part of the arylcarbonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkyl and the

heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro;

and the heterocyclyl can be substituted with 1, 2, 3, 4, or 5 substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, a second heterocyclyl group, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, $-NR^XR^Y$, (NR^XR^Y)alkyl, and oxo, wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted and wherein the aryl, the aryl part of the arylalkyl; the aryl part of the arylcarbonyl, the second heterocyclyl group, and the heterocyclyl

part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro; R^{9b} is independently H, alkyl, aryl, haloalkyl, or arylalkyl;

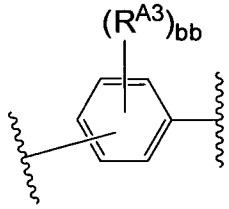
each $R9^3$ is independently $-N(R^{9a})$-$NHC(=O)R^{9b}$, wherein each R^{9a} is independently arylalkyl, alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkoxy, halocycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkoxy, alkylSO_2alkyl, cycloalkylalkylSO_2alkyl, cyanoalkyl, haloalkyl, cycloalkylalkyl, cycloalkyl, alkoxyalkyl, alkoxyalkylcarbonylalkyl, alkoxycarbonylalkyl, alkylsulfanylalkyl, aryalkoxyalkylcarbonylalkyl, carboxyalkyl, heterocyclylalkyl, heterocyclyl, heterocyclylcarbonylalkyl, hydroxyalkyl, NRRCOalkyl, wherein each R is independently selected from hydrogen and alkyl; and where in arylalkyl the alkyl can be substituted with up to three aryl groups, and the alkyl part of the arylalkyl is further optionally substituted with one or two additional groups independently selected from alkoxy, alkylcarbonyloxy, halo, haloalkoxy, haloalkyl, heterocyclyl, hydroxy;

and the aryl part can be substituted with 1, 2, 3, 4, or 5 substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, a second aryl group, arylalkoxy, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, heterocyclyl, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, $-NR^XR^Y$, -(NR^XR^Y)alkyl, oxo, and $-P(O)OR_2$, wherein each R is independently selected from hydrogen and alkyl; and wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted and wherein the second aryl group, the aryl part of the arylalkyl, the aryl part of the arylcarbonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro;

and the heterocyclyl can be substituted with 1, 2, 3, 4, or 5 substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, aryl, arylalkyl,

arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, a second heterocyclyl group, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, $-NR^XR^Y$, $-(NR^XR^Y)$alkyl, and oxo, wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted and wherein the aryl, the aryl part of the arylalkyl; the aryl part of the arylcarbonyl, the second heterocyclyl group, and the heterocyclyl part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro; R^{9b} is independently H, alkyl, aryl, haloalkyl, or arylalkyl;

each A^0 is independently:



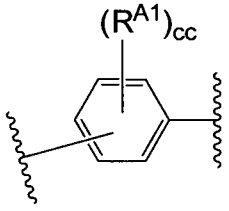
wherein:

each R^{A3} is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxy, hydroxyalkyl, $-NR^aR^b$, (NR^aR^b)alkyl, and (NR^aR^b)carbonyl; R^a and R^b are each independently selected from the group consisting of hydrogen, alkenyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylalkylcarbonyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl; and each

bb is independently 0, 1, 2, 3, or 4; or

each A^0 is independently a six-membered heteroaromatic ring containing one, two, or three nitrogen atoms, which ring is optionally substituted with 1, 2, 3, or 4 R^{A3} groups;

each A^1 is independently:



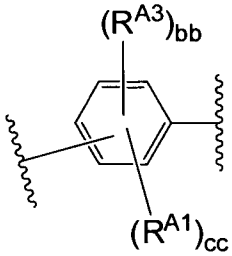
wherein:

each R^{A1} is independently selected from cyano, nitro, SOR^4, SO_2R^4, -alkylSO_2R^4, haloalkoxy, cyanoalkyl, $NR^4SO_2R^4$, cycloalkyl, (halo)cycloalkyl, heterocycle, (cycloalkyl)alkyl, (heterocycle)alkyl, wherein each alkyl, heterocycle and cycloalkyl is optionally substituted with one or more halo; and

each R^4 is independently selected from H, alkyl, haloalkyl, aryl, and arylalkyl;

each cc is independently 1, 2, 3, or 4

each A^2 is independently:



wherein:

each R^{A1} is independently selected from cyano, nitro, SOR^4, SO_2R^4, -alkylSO_2R^4, haloalkoxy, cyanoalkyl, $NR^4SO_2R^4$, cycloalkyl, (halo)cycloalkyl, heterocycle, (cycloalkyl)alkyl, (heterocycle)alkyl, wherein each alkyl, heterocycle and cycloalkyl is optionally substituted with one or more halo;

each R^{A3} is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxy, hydroxyalkyl, -NR^aR^b, (NR^aR^b)alkyl, and (NR^aR^b)carbonyl; R^a and R^b are each independently selected from the group consisting of hydrogen, alkenyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylalkylcarbonyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl;

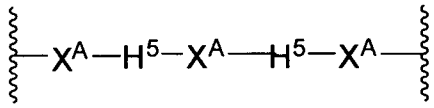
each R^4 is independently selected from H, alkyl, haloalkyl, aryl, and arylalkyl;

R^a and R^b are independently selected from the group consisting of hydrogen, alkenyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylalkylcarbonyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl;

each bb is 0, 1, 2, 3, or 4; each cc is 1, 2, 3, or 4; and the sum of bb and cc is 1, 2, 3, or 4;

each A^3 is independently a six-membered heteroaromatic ring containing one, two, or three nitrogen atoms, which ring is substituted with one or more R^{A1} groups, and which ring is optionally substituted with one or more R^{A3} groups;

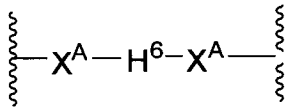
each A^4 is independently:



wherein:

each H^5 is independently a phenyl ring or a six-membered heteroaromatic ring, which H^5 is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3}; and each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent and each R is independently selected from H or alkyl;

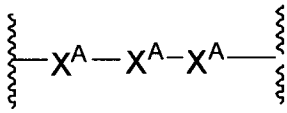
each A^5 is independently:



wherein:

each H^6 is independently a phenyl ring or a six-membered heteroaromatic ring, which H^6 is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3}; and each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent; provided that at least one X^A is present and each R is independently selected from H or alkyl;

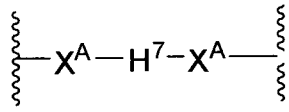
each A^6 is independently:



wherein:

each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, allenyl, alkynyl, or absent; provided that at least one X^A is present and each R is independently selected from H or alkyl;

each A^7 is independently:

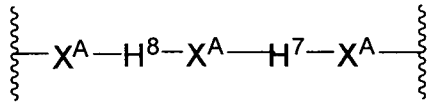


wherein:

each H^7 is independently a five-membered heteroaromatic ring, which H^7 is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3}; and

each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent; and each R is independently selected from H or alkyl;

each A^8 is independently:



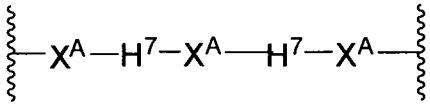
wherein:

each H^7 is independently a five-membered heteroaromatic ring, which H^7 is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3};

each H^8 is independently a phenyl ring, which is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3}; and

each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent and each R is independently selected from H or alkyl;

each A^9 is independently:

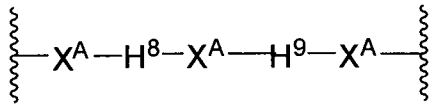


wherein:

each H^7 is independently a five-membered heteroaromatic ring, which H^7 is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3}; and

each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent and each R is independently selected from H or alkyl;

each A^{10} is independently:



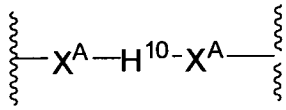
wherein:

each H^8 is independently a phenyl ring, which is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3};

each H^9 is independently a six-membered heteroaromatic ring, which is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3}; and

each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent and each R is independently selected from H or alkyl;

each A^{11} is independently:



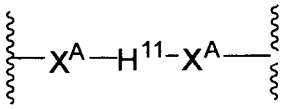
wherein:

each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent and each R is independently selected from H or alkyl;

each H^{10} is independently a 5-15 carbon unsaturated, partially unsaturated or saturated bicyclic ring system that is optionally fused to an aryl, which H^{10} is optionally substituted with one or more groups independently selected from oxo, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxy, hydroxyalkyl, $-NR^aR^b$, (NR^aR^b)alkyl, and (NR^aR^b)carbonyl, cyano, nitro, SOR^4, SO_2R^4, -alkylSO_2R^4, haloalkoxy, cyanoalkyl, $NR^4SO_2R^4$, cycloalkyl, (halo)cycloalkyl, heterocycle, (cycloalkyl)alkyl, and (heterocycle)alkyl, wherein each alkyl, heterocycle and cycloalkyl is optionally substituted with one or more halo; and

each R^4 is independently selected from H, alkyl, haloalkyl, aryl, and arylalkyl

each A^{12} is independently:



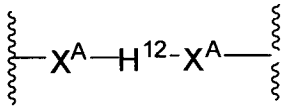
wherein:

each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent and each R is independently selected from H or alkyl;

each H^{11} is independently a 5-15 carbon unsaturated, partially unsaturated or saturated bicyclic ring system that contains one or more heteroatoms that is optionally fused to an aryl, which H^{11} is optionally substituted with one or more groups independently selected from oxo, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxy, hydroxyalkyl, $-NR^aR^b$, (NR^aR^b)alkyl, and (NR^aR^b)carbonyl, cyano, nitro, SOR^4, SO_2R^4, -alkylSO_2R^4, haloalkoxy, cyanoalkyl, $NR^4SO_2R^4$, cycloalkyl, (halo)cycloalkyl, heterocycle, (cycloalkyl)alkyl, and (heterocycle)alkyl, wherein each alkyl, heterocycle and cycloalkyl is optionally substituted with one or more halo; and

each R^4 is independently selected from H, alkyl, haloalkyl, aryl, and arylalkyl; and

each A^{13} is independently:

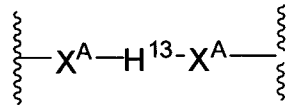


wherein:

each H^{12} is independently a fused aromatic bicyclic carbocycle, which is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3}; and

each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent and each R is independently selected from H or alkyl;

each A^{14} is independently:

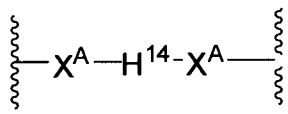


wherein:

each H^{13} is independently a fused aromatic bicyclic heterocycle that comprises at least one heteroatom in the ring system, which ring system is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3}; and

each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent and each R is independently selected from H or alkyl;

each A^{15} is independently:

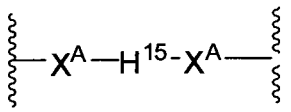


wherein:

each H^{14} is independently a fused unsaturated, partially unsaturated or saturated tricyclic carbocycle which is optionally substituted with one or more groups independently selected from oxo, R^{A1} and R^{A3}; and

each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent and each R is independently selected from H or alkyl;

each A^{16} is independently:

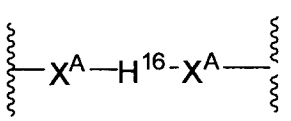


wherein:

each H^{15} is independently a fused unsaturated, partially unsaturated or saturated tricyclic heterocycle that comprises at least one heteroatom in the ring system, which ring system is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3}; and

each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent and each R is independently selected from H or alkyl;

each A^{17} is independently:

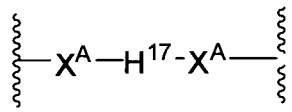


wherein:

each H^{16} is independently a fused bicyclic carbocyclic ring system wherein one ring is aromatic and another ring is partially or fully saturated, which ring system is optionally substituted with one or more groups independently selected from oxo, R^{A1} and R^{A3}; and

each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent and each R is independently selected from H or alkyl;

each A^{18} is independently:

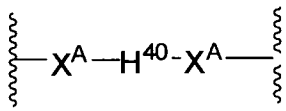


wherein:

each H^{17} is independently a fused bicyclic ring system comprising at least one heteroatom, wherein one ring is aromatic and another ring is partially or fully saturated, which ring system is optionally substituted with one or more groups independently selected from oxo, R^{A1} and R^{A3}; and

each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent and each R is independently selected from H or alkyl;

each A^{21} is independently:



wherein:

each H^{40} is independently an anti-aromatic monocyclic or fused carbocyclic ring system, which carbocyclic ring system is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3}; and

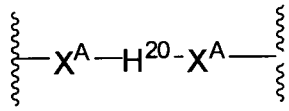
each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent and each R is independently selected from H or alkyl;

each W^1 is independently $-X^A-$:

wherein:

each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent and each R is independently selected from H or alkyl;

each W^2 is independently:

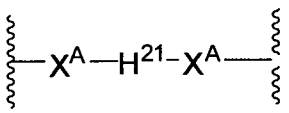


wherein:

each H^{20} is independently a fused aromatic bicyclic carbocycle, which is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3}; and

each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent and each R is independently selected from H or alkyl;

each W^3 is independently:

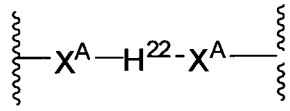


wherein:

each H^{21} is independently a fused bicyclic carbocyclic ring system wherein one ring is aromatic and another ring is partially or fully saturated, which ring system is optionally substituted with one or more groups independently selected from oxo, R^{A1} and R^{A3}; and

each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent and each R is independently selected from H or alkyl;

each W^4 is independently:

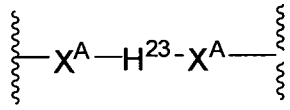


wherein:

each H^{22} is independently a fused aromatic bicyclic heterocycle that comprises at least one heteroatom in the ring system, which ring system is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3}; and

each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent and each R is independently selected from H or alkyl;

each W^5 is independently:

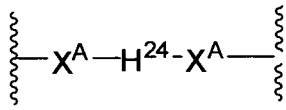


wherein:

each H^{23} is independently a fused bicyclic ring system comprising at least one heteroatom, wherein one ring is aromatic and another ring is partially or fully saturated, which ring system is optionally substituted with one or more groups independently selected from oxo, R^{A1} and R^{A3}; and

each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent and each R is independently selected from H or alkyl;

each W^6 is independently:

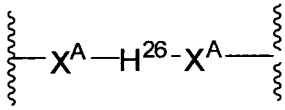


wherein:

each H^{24} is independently a fused unsaturated, partially unsaturated or saturated tricyclic carbocycle, which is optionally substituted with one or more groups independently selected from oxo, R^{A1} and R^{A3}; and

each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent and each R is independently selected from H or alkyl;

each W^7 is independently:

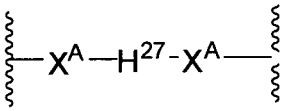


wherein:

each H^{26} is independently a 5-15 carbon unsaturated, partially unsaturated or saturated bicyclic ring system which ring system is optionally substituted with one or more groups independently selected from oxo, R^{A1} and R^{A3}; and

each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent and each R is independently selected from H or alkyl;

each W^8 is independently:

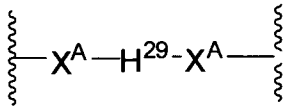


wherein:

each H^{27} is independently a fused unsaturated, partially unsaturated or saturated tricyclic heterocycle that comprises at least one heteroatom in the ring system, which ring system is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3}; and

each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent and each R is independently selected from H or alkyl;

each W^9 is independently:



wherein:

each H^{29} is independently a 5-15 carbon unsaturated, partially unsaturated or saturated bicyclic ring system that contains one or more heteroatoms; and

each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent and each R is independently selected from H or alkyl;

each W^{10} is independently $-H^{30}=C=H^{31}-$

wherein each of $-H^{30}$ and H^{31} is independently a saturated 6-membered heterocyclic ring comprising one or more heteroatoms, which ring is optionally substituted with oxo;

each W^{11} is independently $-H^{32}=C=H^{33}-$

wherein each of $-H^{32}$ and H^{33} is independently a saturated 5-membered heterocyclic ring comprising one or more heteroatoms, which ring is optionally substituted with oxo;

each W^{12} is independently an anti-aromatic monocyclic or fused carbocyclic ring system, which carbocyclic ring system is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3};

each W^{13} is independently a phenyl ring that is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3};

each W^{14} is independently a 5 or 6 membered heteroaryl ring that is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3};

each W^{15} is independently a fused unsaturated, partially unsaturated or saturated tetracyclic carbocyclic ring, which ring system is optionally substituted with one or more groups independently selected from oxo, R^{A1} and R^{A3};

each W^{16} is independently a fused unsaturated, partially unsaturated or saturated tetracyclic heterocycle that comprises at least one heteroatom in the ring system, which ring system is optionally substituted with one or more groups independently selected from oxo, R^{A1} and R^{A3};

each W^{17} is independently a fused unsaturated, partially unsaturated or saturated pentacyclic carbocyclic ring system, which ring system is optionally substituted with one or more groups independently selected from oxo, R^{A1} and R^{A3};

each W^{18} is independently a fused unsaturated, partially unsaturated or saturated pentacyclic heterocycle that comprises at least one heteroatom in the ring system, which ring system is optionally substituted with one or more groups independently selected from oxo, R^{A1} and R^{A3};

each W^{19} is independently a fused unsaturated, partially unsaturated or saturated hexacyclic carbocyclic ring system, which ring system is optionally substituted with one or more groups independently selected from oxo, R^{A1} and R^{A3};

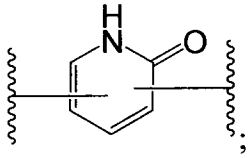
each W^{20} is independently a fused unsaturated, partially unsaturated or saturated hexacyclic heterocycle that comprises at least one heteroatom in the ring system, which ring system is optionally substituted with one or more groups independently selected from oxo, R^{A1} and R^{A3};

each M^0 is independently a five membered heteroaryl group optionally substituted with one or more alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, haloalkyl, (NR^aR^b)carbonyl and trialkylsilylalkoxyalkyl;

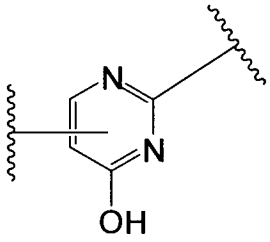
each M^1 is independently selected from –C(=O)NH-, –C(=O)NH-$C(R^M)_2$-, -NHC(=O) -, -$C(R^M)_2$NHC(=O)-, –NHC(=O)N R^M -, –NHC(=O)O -; wherein each R^M is independently selected from H and alkyl;

each M^2 is independently a six-membered heteroaromatic ring, which is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3};

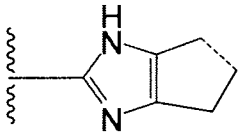
each M^3 is independently:



each M^4 is independently:



each M^5 is independently:



wherein the bond designated with --- is fused to a ring defined for P;

each M^6 is independently a bicyclic bridged ring system comprising 5-15 atoms wherein at least one of the atoms is a heteroatom;

each M^7 is independently a pyrid-di-yl;

each M^8 is independently partially saturated or a saturated five-membered ring that comprises one or more heteroatoms and that is optionally substituted with one or two oxo;

each M^9 is independently a fused-bicyclic saturated, partially unsaturated, or aromatic heterocyclic ring system that is optionally substituted with one or more R^{P11};

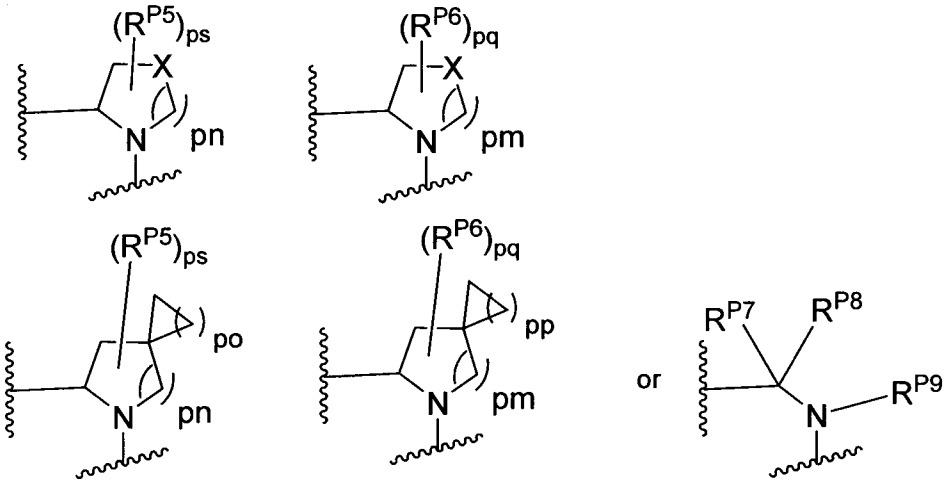
each M^{10} is independently a five membered heteroaryl group substituted with at least one alkoxy, cycloalkyl, cyano, alkylsulfonyl, arylsulfonyl, NR^hR^h, (NR^hR^h)sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkoxy, haloalkoxyalkyloxy,

cycloalkoxyalkoxy, aryloxyalkoxy, heteroaryloxyalkoxy, heterocyclyloxyalkyloxy, (NR^hR^h)alkoxy, cyanoalkoxy, cycloalkoxy, heterocyclyl, alkoxyalkyl, cycloalkoxyalkyl, (NR^hR^h)alkyl, wherein each R^h is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyloxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, and sulfonylalkyl; and wherein the five membered ring is also optionally substituted with one or more alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, haloalkyl, and (NR^aR^b)carbonyl;

each M^{11} is independently a fused-tricyclic saturated, partially unsaturated, or aromatic heterocyclic ring system that is optionally substituted with one or more oxo, halo, $-R^{M7}$, $-OR^{M7}$, $-SR^{M7}$, $-N(R^{M7})_2$, $-CF_3$, $-CCl_3$, $-OCF_3$,-CN, $-NO_2$, $-N(R^{M7})C(=O)R^{M7}$, $-C(=O)R^{M7}$, $-OC(=O)R^{M7}$, $-C(O)OR^{M7}$, $-C(=O)NR^{M7}$, $-S(=O)R^{M7}$, $-S(=O)_2OR^{M7}$, $-S(=O)_2R^{M7}$, $-OS(=O)_2OR^{M7}$, or $-S(=O)_2NR^{M7}$; each R^{M7} is independently -H, alkyl, aryl, arylalkyl, or heterocycle;

each M^{12} is independently a fused-pentacyclic, hexacyclic, or heptacyclic partially unsaturated, or aromatic heterocyclic ring system that is optionally substituted with one or more oxo halo, $-R^{M7}$, $-OR^{M7}$, $-SR^{M7}$, $-N(R^{M7})_2$, $-CF_3$, $-CCl_3$, $-OCF_3$,-CN, $-NO_2$, $-N(R^{M7})C(=O)R^{M7}$, $-C(=O)R^{M7}$, $-OC(=O)R^{M7}$, $-C(O)OR^{M7}$, $-C(=O)NR^{M7}$, $-S(=O)R^{M7}$, $-S(=O)_2OR^{M7}$, $-S(=O)_2R^{M7}$, $-OS(=O)_2OR^{M7}$, or $-S(=O)_2NR^{M7}$;
each R^{M7} is independently -H, alkyl, aryl, arylalkyl, or heterocycle;

each P^0 is independently:



wherein:

X is selected from O, S, S(O), SO_2, CH_2, CHR^{P10}, and $C(R^{P10})_2$; provided that when pn or pm is 0, X is selected from CH_2, CHR^{P10}, and $C(R^{P10})_2$;

each R^{P10} is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

each R^{P5} and R^{P6} is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups; R^{Pa} and R^{Pb} are each independently H, alkyl, aryl, or arylalkyl; or R^{Pa} and R^{Pb} taken together with the atom to which they are attached form a heterocycle;

pq and ps are independently 0, 1, 2, 3, or 4;

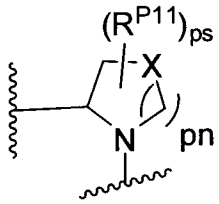
pm and pn are independently 0, 1, or 2;

po and pp are independently 1, 2, or 3;

R^{P7} and R^{P8} are each independently selected from hydrogen, alkenyl, alkoxyalkyl, alkyl, haloalkyl, and $(NR^{Pa}R^{Pb})$alkyl; or R^{P7} and R^{P8}, together with the carbon atom to which they are attached, form a five or six membered saturated ring optionally containing one or two heteroatoms selected from NR^{Pz}, 0, and S; wherein R^{Pz} is selected from hydrogen and alkyl;

R^{P9} is selected from hydrogen and alkyl;

each P^1 is independently:



wherein:

X is selected from O, S, S(O), SO_2, CH_2, CHR^{P10}, and $C(R^{P10})_2$; provided that when pn is 0, X is selected from CH_2, CHR^{P10}, and $C(R^{P10})_2$;

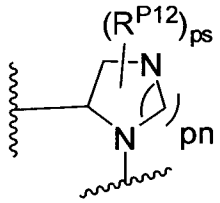
each R^{P10} is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

at least one R^{P11} is independently selected from cyano, alkylsulfonyl, arylsulfonyl, (NR^hR^h)sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, (NR^hR^ha)lkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl, -$NR^{hh}R^h$, ($NR^{hh}R^h$)alkyl, ($NR^{hh}R^h$)carbonyl, wherein each R^h is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two R^h groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring; wherein each R^{hh} is independently aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, (NR^hR^h)sulfonyl, heteroarylsulfonyl, -$S(=O)_2R^h$, -$C(=O)R^h$, -$C(=O)NR^hR^h$; and the remaining R^{P11} are independently selected from R^{P5}, cyano, alkylsulfonyl, arylsulfonyl, (NR^hR^h)sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, (NR^hR^h)alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl; wherein each R^h is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two R^h groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

ps is 1, 2, 3, or 4;

pn is 0, 1, or 2;

each P^2 is independently:



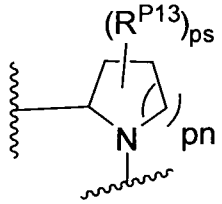
wherein:

each R^{P12} is independently selected from R^{P5}, R^{P11},-C(=O)OR^h, cyano, alkylsulfonyl, arylsulfonyl, (NR^hR^h)sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, (NR^hR^h)alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl; wherein each R^h is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two R^h groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

ps is 1, 2, 3, or 4;

pn is 0, 1, or 2;

each P^3 is independently a ring of the formula:



wherein:

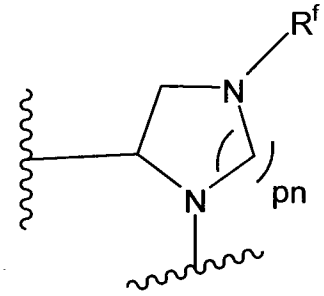
the ring is substituted with one or more oxo group;

each R^{P13} is independently selected from R^{P5}, cyano, alkylsulfonyl, arylsulfonyl, (NR^hR^h)sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, (NR^hR^h)alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl; wherein each R^h is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two R^h groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

ps is 0, 1, 2, 3, or 4;

pn is 0, 1, or 2;

each P^4 is independently a ring of the formula:



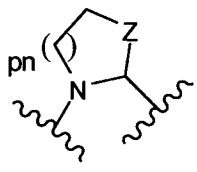
wherein:

the ring is optionally substituted with one or more groups R^{P14} that are independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and –$NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups; and where two groups R^{P14} that are attached to the same carbon when taken together with the carbon to which they are attached can form a 3-6 membered carbocyclic or heterocyclic ring;

pn is 0, 1, or 2;

each R^f is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, $-S(=O)_2NR^hR^h$, $-S(=O)_2R^h$, $C(=O)R^h$, $C(=O)OR^h$, $-C(=O)NR^hR^h$; each R^h is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; or when two R^h groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

each P^5 is independently a ring of the formula:



wherein:

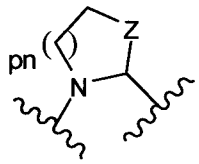
the ring is optionally substituted with one or more groups R^{P15} that are independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups; and where two groups R^{P15} that are attached to the same carbon when taken together with the carbon to which they are attached can form a 3-6 membered carbocyclic or heterocyclic ring;

pn is 0, 1, or 2;

Z is O, S, S(=O), $S(=O)_2$, or NR^f;

each R^f is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, $-S(=O)_2NR^hR^h$, $-S(=O)_2R^h$, $C(=O)R^h$, $C(=O)OR^h$, $-C(=O)NR^hR^h$; each R^h is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; or when two R^h groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

each P^6 is independently a ring of the formula:



wherein:

the ring is substituted with one or more oxo and is optionally substituted with one or more groups R^{P16} that are independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

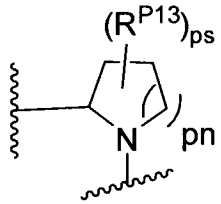
Z is O, S, S(=O), $S(=O)_2$, or NR^f;

pn is 0, 1, or 2;

each R^f is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, $-S(=O)_2NR^hR^h$, $-S(=O)_2R^h$, $C(=O)R^h$, $C(=O)OR^h$, $-C(=O)NR^hR^h$; each R^h is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; or when two R^h groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

each P^7 is a bridged 5-15 membered bicyclic heterocyclic ring that is attached to the remainder of the compound of formula I through one N-link and through one C-link; wherein the ring is optionally substituted with one or more groups independently selected from $R^{P6}$and R^{P11};

each P^8 is independently a ring of the formula:



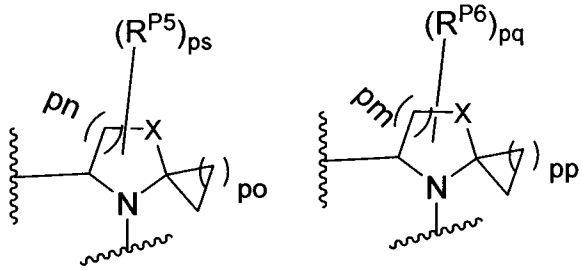
wherein:

ps is 2, 3, 4, 5, or 6;

pn is 0, 1 or 2;

each R^{P13} is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups; where in at least one case two groups R^{P13} that are attached to the same carbon are taken together with the carbon to which they are attached and form a 4-6 membered heterocyclic ring;

each P^{10} is independently:



wherein:

X is selected from O, S, S(O), SO_2, CH_2, CHR^{P10}, and $C(R^{P10})_2$; provided that when pn or pm is 0, X is selected from CH_2, CHR^{P10}, and $C(R^{P10})_2$;

each R^{P10} is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

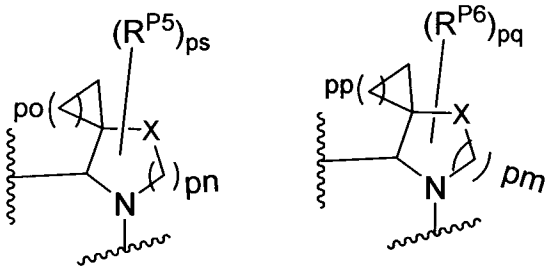
each R^{P5} and R^{P6} is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

pq and ps are independently 0, 1, 2, 3, or 4;

pm and pn are independently 0, 1, or 2;

po and pp are independently 1, 2, or 3;

each P^{11} is independently:



wherein:

X is selected from O, S, S(O), SO_2, CH_2, CHR^{P10}, and $C(R^{P10})_2$; provided that when pn or pm is 0, X is selected from CH_2, CHR^{P10}, and $C(R^{P10})_2$;

each R^{P10} is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

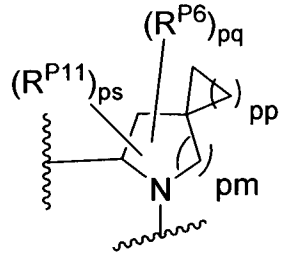
each R^{P5} and R^{P6} is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

pq and ps are independently 0, 1, 2, 3, or 4;

pm and pn are independently 0, 1, or 2;

po and pp are independently 1, 2, or 3;

each P^{12} is independently:



wherein:

each R^{P6} is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

pq is independently 0, 1, 2, 3, or 4;

pm is independently 0, 1, or 2;

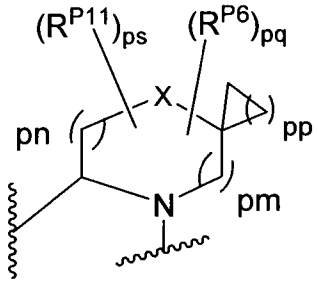
pp is independently 1, 2, or 3;

ps is 1, 2, 3, or 4;

R^{P11} is independently selected from cyano, alkylsulfonyl, arylsulfonyl, (NR^hR^h)sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, (NR^hR^h)alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl, $-NR^{hh}R^h$, $(NR^{hh}R^h)$alkyl, $(NR^{hh}R^h)$carbonyl, wherein each R^h is independently

-H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two R^h groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring; wherein each R^{hh} is independently aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, (NR^hR^h)sulfonyl, heteroarylsulfonyl, $-S(=O)_2R^h$, $-C(=O)R^h$, $-C(=O)NR^hR^h$; and the remaining R^{P11} are independently selected from R^{P5}, cyano, alkylsulfonyl, arylsulfonyl, (NR^hR^h)sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, (NR^hR^h)alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl; wherein each R^h is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two R^h groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

each P^{13} is independently:



wherein:

X is selected from O, S, S(O), SO_2, or NR^h;

each R^{P6} is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

pq is independently 0, 1, 2, 3, or 4;

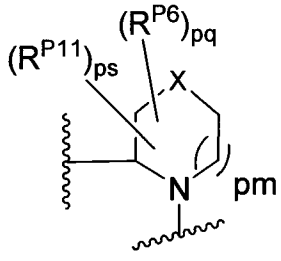
pm and pn are independently 0, 1, or 2 but the sum of pn and pm is greater than zero;

pp are independently 1, 2, or 3;

ps is 1, 2, 3, or 4;

each R^{P11} is independently selected from cyano, alkylsulfonyl, arylsulfonyl, (NR^hR^h)sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, (NR^hR^h)alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl, $-NR^{hh}R^h$, $(NR^{hh}R^h)$alkyl, $(NR^{hh}R^h)$carbonyl, wherein each R^h is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two R^h groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring; wherein each R^{hh} is independently aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, (NR^hR^h)sulfonyl, heteroarylsulfonyl, $-S(=O)_2R^h$, $-C(=O)R^h$, $-C(=O)NR^hR^h$, R^{P5}, cyano, alkylsulfonyl, arylsulfonyl, (NR^hR^h)sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, (NR^hR^h)alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl; wherein each R^h is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two R^h groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

each P^{14} is independently:



wherein:

the ring is substituted with one or more oxo group;

X is NR^f;

each R^f is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, $-S(=O)_2NR^hR^h$, $-S(=O)_2R^h$, $C(=O)R^h$, $C(=O)OR^h$, $-C(=O)NR^hR^h$; each R^h is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; or when two R^h groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

each R^{P6} is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

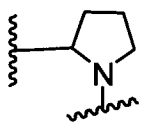
pq is independently 0, 1, 2, 3, or 4;

pm is independently 0, 1, or 2;

ps is 1, 2, 3, or 4;

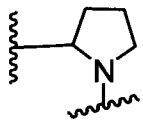
R^{P11} is independently selected from cyano, alkylsulfonyl, arylsulfonyl, (NR^hR^h)sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, (NR^hR^h)alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl; wherein each R^h is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, or sulfonylalkyl; and when two R^h groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

each P^{15} is:



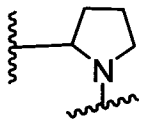
which is substituted with one or two groups independently selected from alkoxyalkyl, haloalkoxyalkyl, alkylsulfanyl, alkylsulfanylalkyl, cyanoalkyl, and cycloalkylalkyl.

each P^{16} is:



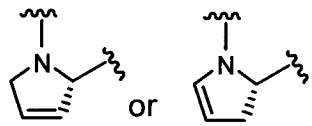
which is substituted with methylene;

each P^{17} is:



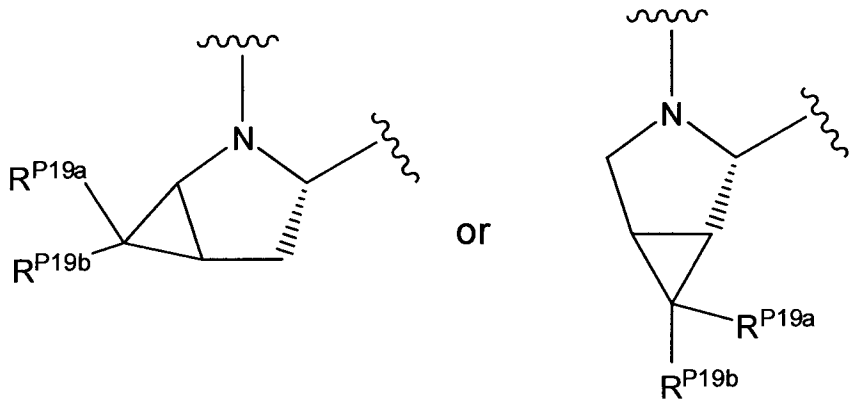
which is substituted with one or two groups independently selected from alkenyl, alkynyl, cycloalkyl, cycloalkylalkenyl, and cycloalkylalkynyl.

each P^{18} is:



which is optionally substituted with one or two groups independently selected from halo, alkyl, alkoxyalkyl, haloalkyl, cycloalkyl, and cycloalkylalkyl;

each P^{19} is:



wherein each R^{P19a} is independently selected from H and halo; and each R^{P19b} is independently selected from halo;

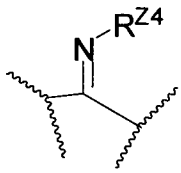
each $-Z^0-$ is –C(=O)- or –C(=S)-;

each $–Z^1-$ is independently a bond, or $-C(R^{Z1})_2-$; wherein each R^{Z1} is independently H, alkyl, haloalkyl, or halo;

each $–Z^2-$ is independently saturated or partially unsaturated (C_3-C_8)cycloalkyl that is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3};

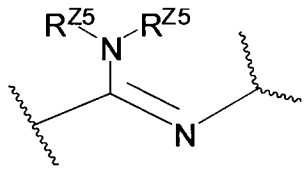
each $–Z^3-$ is independently saturated, partially unsaturated, or aromatic 4-8 membered heterocyclic or heteroaryl ring that is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3};

each $-Z^4-$ is independently:



wherein each R^{Z4} is independently H, alkyl, cyano, aryl, or heteroaryl;

each $-Z^5-$ is independently:



wherein each R^{Z5} is independently H, alkyl, cyano, aryl, or heteroaryl; or two R^{Z5}s together with the nitrogen to which they are attached form a 4-8 membered heterocyclic ring that is optionally substituted with one or more oxo and with one or more groups independently selected from R^{A1} and R^{A3};

each $-Z^6-$ is independently $-C(R^{Z1})-$ and is doublebonded to a carbocyclic P; wherein R^{Z1} is independently H, alkyl, haloalkyl, or halo;

each E^0 is independently $-NR^{Ec}R^{Ed}$ wherein

R^{Ec} and R^{Ed} are each independently selected from hydrogen, alkenyloxycarbonyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, arylalkoxycarbonyl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, aryloxycarbonyl, arylsulfonyl, cycloalkyl, cycloalkylsulfonyl, formyl, haloalkoxycarbonyl, heterocyclyl, heterocyclylalkoxycarbonyl, heterocyclylalkyl, heterocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, hydroxyalkylcarbonyl, (NR^eR^f)alkyl, (NR^eR^f)alkylcarbonyl, (NR^eR^f)carbonyl, (NR^eR^f)sulfonyl, -C(NCN)OR', and - $C(NCN)NR^XR^Y$, wherein R' is selected from alkyl and unsubstituted phenyl, and wherein the alkyl part of the arylalkyl, the arylalkylcarbonyl, the heterocyclylalkyl, and the heterocyclylalkylcarbonyl are further optionally substituted with one $-NR^eR^f$ group; and wherein the aryl, the aryl part of the arylalkoxycarbonyl, the arylalkyl, the arylalkylcarbonyl, the arylcarbonyl, the aryloxycarbonyl, and the arylsulfonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkoxycarbonyl, the heterocyclylalkyl, the heterocyclylalkylcarbonyl, the heterocyclylcarbonyl, and the heterocyclyloxycarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro;

each E^1 is independently $-OC(=O)NR^{Ee}R^{Ef}$ wherein each R^{Ee} and R^{Ef} are each independently selected from hydrogen, alkenyloxycarbonyl, alkoxyalkylcarbonyl,

alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, arylalkoxycarbonyl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, aryloxycarbonyl, arylsulfonyl, cycloalkyl, cycloalkylsulfonyl, formyl, haloalkoxycarbonyl, heterocyclyl, heterocyclylalkoxycarbonyl, heterocyclylalkyl, heterocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, hydroxyalkylcarbonyl, (NR^eR^f)alkyl, (NR^eR^f)alkylcarbonyl, (NR^eR^f)carbonyl, (NR^eR^f)sulfonyl, -C(NCN)OR', and - C(NCN)NR^XR^Y, wherein R' is selected from alkyl and unsubstituted phenyl, and wherein the alkyl part of the arylalkyl, the arylalkylcarbonyl, the heterocyclylalkyl, and the heterocyclylalkylcarbonyl are further optionally substituted with one $-NR^eR^f$ group; and wherein the aryl, the aryl part of the arylalkoxycarbonyl, the arylalkyl, the arylalkylcarbonyl, the arylcarbonyl, the aryloxycarbonyl, and the arylsulfonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkoxycarbonyl, the heterocyclylalkyl, the heterocyclylalkylcarbonyl, the heterocyclylcarbonyl, and the heterocyclyloxycarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro; or wherein R^{Ec} and R^{Ef}, together with the nitrogen atom to which they are attached, form a heterocycle;

each E^2 is independently $-NR^aR^b$, wherein R^a is haloalkyl and R^b is H, alkyl, alkoxycarbonyl. or haloalkyl;

each E^3 is independently $-NR^{Ec}R^{E3a}$, wherein R^{E3a} is $(C_3\text{-}C_6)$cycloalkyloxycarbonyl;

each E^4 is independently $-OC(=O)OR^{E4a}$, wherein R^{E4a} is cycloalkyl, aryl, or alkyl;

each E^5 is independently $-NR^{Ec}S(=O)_2OR^{E5a}$, wherein R^{E5a} is is cycloalkyl, aryl or alkyl;

each E^6 is independently $-NR^{Ec}S(=O)_2R^{E6a}$, wherein R^{E6a} is cycloalkyl, aryl, or alkyl;

each E^7 is independently $-NR^{Ec}OR^{E7a}$, wherein R^{E7a} is cycloalkyl, aryl, alkyl, haloalkyl, cycloalkylalkyl or heteroaryl;

each V^0 is independently H, alkyl, arylalkyl, alkenyl, CO, cycloalkylalkyl, cycloalkyl, alkoxyalkyl, alkoxyalkylcarbonylalkyl, alkoxycarbonylalkyl, alkylsulfanylalkyl, aryalkoxyalkylcarbonylalkyl, carboxyalkyl, heterocyclylalkyl, heterocyclylcarbonylalkyl, hydroxyalkyl, NRRCOalkyl, wherein each R is independently selected from hydrogen and alkyl;

and where in arylalkyl the alkyl can be substituted with up to three aryl groups, and the alkyl part of the arylalkyl is further optionally substituted with one or two additional groups independently selected from alkoxy, alkyocarbonyloxy, halo, haloalkoxy, haloalkyl, heterocyclyl, hydroxy;

and the aryl part can be substituted with 1, 2, 3, 4, or 5 substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, a second aryl group, arylalkoxy, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, heterocyclyl, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, $-NR^XR^Y$, $-(NR^XR^Y)$alkyl, oxo, and $-P(O)OR_2$, wherein each R is independently selected from hydrogen and alkyl; and wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted and wherein the second aryl group, the aryl part of the arylalkyl, the aryl part of the arylcarbonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro;

and the heterocyclyl can be substituted with 1, 2, 3, 4, or 5 substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, a second heterocyclyl group, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, $-NR^XR^Y$, (NR^XR^Y)alkyl, and oxo, wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted and wherein the aryl, the aryl part of the arylalkyl; the aryl part of the arylcarbonyl, the second heterocyclyl group, and the heterocyclyl part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro;

each V^1 is independently cyanoalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O-$; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^2 is independently haloalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O-$; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^3 is independently alkyl, which is substituted with one or more oxo, and which is optionally substituted with one or more groups independently selected from cycloalkyl, halo, aryl, alkenyl, and cyano;

each V^4 is independently haloalkoxyalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; wherein R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^5 is independently alkylsulfonylalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^6 is independently arylsulfonylalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^7 is independently heterocyclosulfonylalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^8 is independently spirocycloalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^9 is independently spirocycloalkylalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^{10} is independently fusedbicycliccycloalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^{11} is independently fusedbicycliccycloalkylalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^{12} is independently bridged-bicycliccycloalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^{13} is independently bridged-bicyclic-cycloalkylalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^{14} is independently aryloxyalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^{15} is independently arylalkoxyalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^{16} is independently cycloalkyloxyalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^{17} is independently cycloalkylalkyloxyalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^{18} is independently heterocyclooxyalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^{19} is independently heterocycloalkyloxyalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^{20} is independently heteroaryloxyalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^{21} is independently heteroarylalkyloxyalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^{22} is independently cycloalkenylalkyl;

each V^{23} is independently arylalkyl, wherein the aryl is substituted with one or more groups independently selected from cycloalkyl, alkenyl, cycloalkylalkyl, cyanoalkyl, cycloalkoxy, hydroxyalkoxy, $-C(=O)NR^XR^Y$, $S(=O)_2NR^XR^Y$, alkylsulfanyl, alkylsulfonyl, haloalkylsulfanyl, haloalkylsulfonyl, alkylsulfonylalkyl, alkylsulfonylalkyl, arylsulfanyl, arylsulfonyl, alkoxyalkoxy, alkynyl, aryloxy, heteroaryloxy, alkylsulfonylamino;

R^X and R^Y are independently selected from hydrogen, alkoxycarbonyl, alkyl, alkylcarbonyl, unsubstituted aryl, unsubstituted arylalkoxycarbonyl, unsubstituted arylalkyl,

unsubstituted cycloalkyl, unsubstituted heterocyclyl, and ($NR^{X'}R^{Y'}$)carbonyl, wherein $R^{X'}$ and $R^{Y'}$ are independently selected from hydrogen and alkyl;

each V^{24} is independently heterocycloalkyl, wherein the heterocycle is substituted with one or more groups independently selected from cycloalkyl, alkenyl, cycloalkylalkyl, cyanoalkyl, cycloalkoxy, hydroxyalkoxy, $-C(=O)NR^XR^Y$, $S(=O)_2NR^XR^Y$, alkylsulfanyl, alkylsulfonyl, haloalkylsulfanyl, haloalkylsulfonyl, alkylsulfonylalkyl, alkylsulfonylalkyl, arylsulfanyl, arylsulfonyl, alkoxyalkyoxy, alkynyl, aryloxy, heteroaryloxy, alkylfulfonylamino;

R^X and R^Y are independently selected from hydrogen, alkoxycarbonyl, alkyl, alkylcarbonyl, unsubstituted aryl, unsubstituted arylalkoxycarbonyl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted heterocyclyl, and ($NR^{X'}R^{Y'}$)carbonyl, wherein $R^{X'}$ and $R^{Y'}$ are independently selected from hydrogen and alkyl;

each T^1 is independently a spiro, branched or fused bicycloalkyl;
each T^2 is independently aryl;
each T^3 is independently heteroaryl;
each T^4 is independently arylalkyl;
each T^5 is independently haloalkyl;
each T^6 is independently heteroarylalkyl;
each T^7 is independently heterocycle; and
each T^8 is independently heterocycloalkyl;

or a pharmaceutically acceptable salt, or prodrug thereof.

21. A compound of formula (I):

J-Y-J (I)

wherein:

Y is –L-L-, –M-W-M- or Y^y;

J is T-P-, -P-T or $-J^m$;

W is a bond or $-W^r-$;

L is –M-A-, -A-M-, or $-L^n$;

T is R9-Z-, -Z-R9, or $-T^p$;

R9 is E-V-, or –V-E, or $-R9^q$;

each A is selected from $-A^s$;

each M is selected from $-M^t$;

each P is selected from $-P^u$;

each Z is selected from $-Z^v$;

each V is selected from $-V^w$;

each E is selected from $-E^x$;

each m is 1

each n is 0, 1, 2, 3, 4, 5, 6, 7, 9, or 10;

each p is 1, 2, 3, 4, 5, 6, 7, or 8;

each q is 0, 1, 2, or 3;

each r is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20;

each s is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, or 21;

each t is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or 11;

each u is 0, 1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 12, 13, or 14;

each v is 0, 1, 2, 3, 4, 5, or 6;

each w is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or 21;

each x is 0 or 1;

each y is 0, 1, or 2;

wherein the sum of m, n, p, q, r, s, t, u, v, w, x, and y is not 0; P is connected to M, L, or Y^y; A is connected to A or L; M is connected to P or J; Z is connected to P; V is connected to Z; and when W is a bond M is connected to M;

each Y^1 is independently:

a fused nine-ring system with up to thirty-five atoms that may be fully aromatic or partially saturated and contains atoms selected from C, N, O, and S, and which ring system is optionally substituted with one or more groups independently selected from H, oxo, R^{A1} and R^{A3}; each R^{A1} is independently selected from cyano, nitro, SOR^4, SO_2R^4, -alkylSO_2R^4, haloalkoxy, cyanoalkyl, $NR^4SO_2R^4$, cycloalkyl, (halo)cycloalkyl, heterocycle, (cycloalkyl)alkyl, (heterocycle)alkyl, wherein each alkyl, heterocycle and cycloalkyl is optionally substituted with one or more halo; each R^{A3} is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxy, hydroxyalkyl, $-NR^aR^b$, (NR^aR^b)alkyl, and (NR^aR^b)carbonyl; R^a and R^b are each independently selected from the group consisting of hydrogen, alkenyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylalkylcarbonyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl;

each Y^2 is independently:

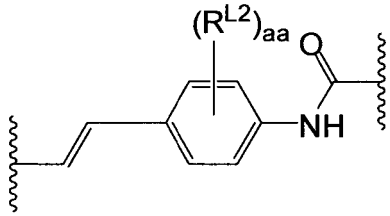
a fused five to eight ring system with up to thirty-two atoms that may be fully aromatic or partially saturated and contains atoms selected from C, N, O, and S, and which ring system is optionally substituted with one or more groups independently selected from H, oxo, R^{A1} and R^{A3};

each J^1 is independently a fused bicyclic saturated, partially unsaturated, or aromatic heterocyclic ring system that is substituted with one or more $-N(R^{L7})C(=O)OR^{L7}$, and that is optionally substituted with one or more groups independently selected from oxo, halo, $-R^{L7}$, $-OR^{L7}$, $-SR^{L7}$, $-CF_3$, $-CCl_3$, $-OCF_3$,-CN, $-NO_2$, $-N(R^{L7})C(=O)R^{L7}$, $-C(=O)R^{L7}$, $-OC(=O)R^{L7}$, $-C(O)OR^{L7}$, $-C(=O)NR^{L7}$, $-S(=O)R^{L7}$, $-S(=O)_2OR^{L7}$, $-S(=O)_2R^{L7}$, $-OS(=O)_2OR^{L7}$, $-S(=O)_2NR^{L7}$, alkoxyalkyl, arylalkoxycarbonyl, halo, haloalkyl, hydroxyalkyl, $-NR^aR^b$, (NR^aR^b)alkyl, and (NR^aR^b)carbonyl;

each R^{L7} is independently -H, alkyl, aryl, arylalkyl, or heterocycle;

R^a and R^b are independently selected from the group consisting of hydrogen, alkenyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylalkylcarbonyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl;

each L^0 is independently:

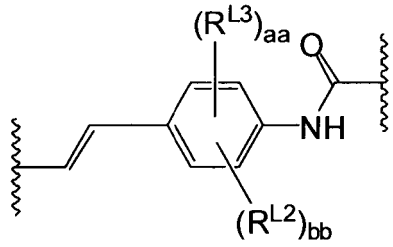


wherein:

each R^{L2} is independently selected from hydrogen, alkenyl, alkoxy, alkyl, halo, and haloalkyl; and

each aa is independently 1, 2, 3, or 4;

each L^1 is independently:



wherein:

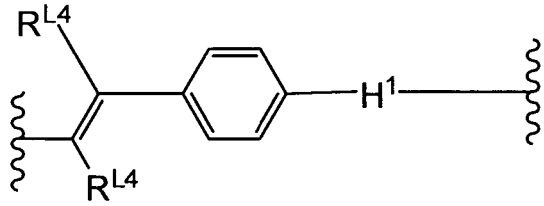
each R^{L2} is independently selected from hydrogen, alkenyl, alkoxy, alkyl, halo, and haloalkyl;

each R^{L3} is independently selected from cyano, nitro, SOR^4, SO_2R^4, -alkylSO_2R^4, haloalkoxy, cyanoalkyl, $NR^4SO_2R^4$, cycloalkyl, (halo)cycloalkyl, heterocycle, (cycloalkyl)alkyl, (heterocycle)alkyl, wherein each alkyl, heterocycle and cycloalkyl is optionally substituted with one or more halo; and

each R^4 is independently selected from H, alkyl, haloalkyl, aryl, and arylalkyl;

each bb is 0, 1, 2, 3, or 4; each aa is 1, 2, 3, or 4; and the sum of bb and aa is 1, 2, 3, or 4;

each L^2 is independently:



wherein:

the phenyl ring shown in L^2 is optionally substituted with one or more groups independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxy, hydroxyalkyl, -NR^aR^b, (NR^aR^b)alkyl, (NR^aR^b)carbonyl, cyano, nitro, SOR^4, SO_2R^4, -alkylSO_2R^4, haloalkoxy, cyanoalkyl, $NR^4SO_2R^4$, cycloalkyl, (halo)cycloalkyl, heterocycle, (cycloalkyl)alkyl, (heterocycle)alkyl, wherein each alkyl, heterocycle and cycloalkyl is optionally substituted with one or more halo;

each R^{L4} is independently -H, alkyl, aryl, arylalkyl, or heterocycle;

each R^4 is independently selected from H, alkyl, haloalkyl, aryl, and arylalkyl;

R^a and R^b are independently selected from the group consisting of hydrogen, alkenyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylalkylcarbonyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl; and

each H^1 is a 5 membered saturated, partially unsaturated, or aromatic ring comprising one or more heteroatoms.

each L^3 is independently a fused-bicyclic saturated, partially unsaturated, or aromatic heterocyclic ring system that is optionally substituted with one or more groups independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxy, hydroxyalkyl, $-NR^aR^b$, (NR^aR^b)alkyl, (NR^aR^b)carbonyl, cyano, nitro, SOR^4, SO_2R^4, -alkylSO_2R^4, haloalkoxy, cyanoalkyl, $NR^4SO_2R^4$, cycloalkyl, (halo)cycloalkyl, heterocycle, (cycloalkyl)alkyl, (heterocycle)alkyl, wherein each alkyl, heterocycle and cycloalkyl is optionally substituted with one or more halo;

each R^4 is independently selected from H, alkyl, haloalkyl, aryl, and arylalkyl; and

R^a and R^b are independently selected from the group consisting of hydrogen, alkenyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylalkylcarbonyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl;

each L^4 is independently a fused-tricyclic saturated, partially unsaturated, or aromatic heterocyclic ring system that is optionally substituted with one or more groups independently selected from oxo, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxy, hydroxyalkyl, $-NR^aR^b$, (NR^aR^b)alkyl, (NR^aR^b)carbonyl, cyano, nitro, SOR^4, SO_2R^4, -alkylSO_2R^4, haloalkoxy, cyanoalkyl, $NR^4SO_2R^4$, cycloalkyl, (halo)cycloalkyl, heterocycle, (cycloalkyl)alkyl, (heterocycle)alkyl, wherein each alkyl, heterocycle and cycloalkyl is optionally substituted with one or more halo;

each R^4 is independently selected from H, alkyl, haloalkyl, aryl, and arylalkyl; and

R^a and R^b are independently selected from the group consisting of hydrogen, alkenyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylalkylcarbonyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl;

each L^5 is independently a –CR=CR-fusedbicyclic saturated, partially unsaturated, or aromatic heterocyclic ring system that is optionally substituted with one or more groups independently selected from oxo, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxy, hydroxyalkyl, $-NR^aR^b$, (NR^aR^b)alkyl, (NR^aR^b)carbonyl,

cyano, nitro, SOR^4, SO_2R^4, -alkylSO_2R^4, haloalkoxy, cyanoalkyl, $NR^4SO_2R^4$, cycloalkyl, (halo)cycloalkyl, heterocycle, (cycloalkyl)alkyl, (heterocycle)alkyl, wherein each alkyl, heterocycle and cycloalkyl is optionally substituted with one or more halo;

each R is independently selected from H or alkyl;

each R^4 is independently selected from H, alkyl, haloalkyl, aryl, and arylalkyl; and

R^a and R^b are independently selected from the group consisting of hydrogen, alkenyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylalkylcarbonyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl;

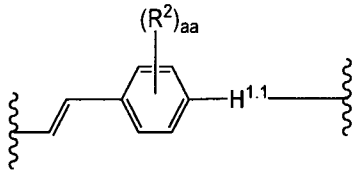
each L^6 is independently a –CR=CR-fused-tricyclic saturated, partially unsaturated, or aromatic heterocyclic ring system that is optionally substituted with one or more groups independently selected from oxo, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxy, hydroxyalkyl, -NR^aR^b, (NR^aR^b)alkyl, (NR^aR^b)carbonyl, cyano, nitro, SOR^4, SO_2R^4, -alkylSO_2R^4, haloalkoxy, cyanoalkyl, $NR^4SO_2R^4$, cycloalkyl, (halo)cycloalkyl, heterocycle, (cycloalkyl)alkyl, (heterocycle)alkyl, wherein each alkyl, heterocycle and cycloalkyl is optionally substituted with one or more halo;

each R is independently selected from H or alkyl;

each R^4 is independently selected from H, alkyl, haloalkyl, aryl, and arylalkyl; and

R^a and R^b are independently selected from the group consisting of hydrogen, alkenyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylalkylcarbonyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl;

each L^7 is independently:



wherein:

each $H^{1.1}$ is independently a fused-bicyclic saturated, partially unsaturated, or aromatic heterocyclic ring system that is optionally substituted with one or more R^2;

each R^2 is independently selected from halo, $-R^{L7}$, $-OR^{L7}$, $-SR^{L7}$, $-N(R^{L7})_2$, $-CF_3$, $-CCl_3$, $-OCF_3$,-CN, $-NO_2$, $-N(R^{L7})C(=O)R^{L7}$, $-C(=O)R^{L7}$, $-OC(=O)R^{L7}$, $-C(O)OR^{L7}$, $-C(=O)NR^{L7}$, $-S(=O)R^{L7}$, $-S(=O)_2OR^{L7}$, $-S(=O)_2R^{L7}$, $-OS(=O)_2OR^{L7}$, and $-S(=O)_2NR^{L7}$;

each R^{L7} is independently -H, alkyl, aryl, arylalkyl, or heterocycle; and

each aa is independently 1, 2, 3, or 4;

each L^9 is independently a fused-tetracyclic saturated, partially unsaturated, or aromatic heterocyclic ring system that is optionally substituted with one or more groups independently selected from oxo, halo, $-R^{L7}$, $-OR^{L7}$, $-SR^{L7}$, $-CF_3$, $-CCl_3$, $-OCF_3$,-CN, $-NO_2$, $-N(R^{L7})C(=O)R^{L7}$, $-C(=O)R^{L7}$, $-OC(=O)R^{L7}$, $-C(O)OR^{L7}$, $-C(=O)NR^{L7}$, $-S(=O)R^{L7}$, $-S(=O)_2OR^{L7}$, $-S(=O)_2R^{L7}$, $-OS(=O)_2OR^{L7}$, $-S(=O)_2NR^{L7}$, alkoxyalkyl, arylalkoxycarbonyl, halo, haloalkyl, hydroxyalkyl, $-NR^aR^b$, (NR^aR^b)alkyl, and (NR^aR^b)carbonyl;

each R^{L7} is independently -H, alkyl, aryl, arylalkyl, or heterocycle;

R^a and R^b are each independently selected from the group consisting of hydrogen, alkenyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylalkylcarbonyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl;

each L^{10} is independently a fused-pentacyclic saturated, partially unsaturated, or aromatic heterocyclic ring system that is optionally substituted with one or more groups independently selected from oxo, halo, $-R^{L7}$, $-OR^{L7}$, $-SR^{L7}$, $-CF_3$, $-CCl_3$, $-OCF_3$,-CN, $-NO_2$, $-N(R^{L7})C(=O)R^{L7}$, $-C(=O)R^{L7}$, $-OC(=O)R^{L7}$, $-C(O)OR^{L7}$, $-C(=O)NR^{L7}$, $-S(=O)R^{L7}$, $-S(=O)_2OR^{L7}$, $-S(=O)_2R^{L7}$, $-OS(=O)_2OR^{L7}$, $-S(=O)_2NR^{L7}$, alkoxyalkyl, arylalkoxycarbonyl, halo, haloalkyl, hydroxyalkyl, $-NR^aR^b$, (NR^aR^b)alkyl, and (NR^aR^b)carbonyl;

each R^{L7} is independently -H, alkyl, aryl, arylalkyl, or heterocycle;

R^a and R^b are each independently selected from the group consisting of hydrogen, alkenyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylalkylcarbonyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl;

each L^{11} is independently a six-ring fused saturated, partially unsaturated, or aromatic heterocyclic ring system that is optionally substituted with one or more groups independently selected from oxo, halo, $-R^{L7}$, $-OR^{L7}$, $-SR^{L7}$, $-CF_3$, $-CCl_3$, $-OCF_3$,-CN, $-NO_2$, $-N(R^{L7})C(=O)R^{L7}$, $-C(=O)R^{L7}$, $-OC(=O)R^{L7}$, $-C(O)OR^{L7}$, $-C(=O)NR^{L7}$, $-S(=O)R^{L7}$, $-S(=O)_2OR^{L7}$, $-S(=O)_2R^{L7}$, -

$OS(=O)_2OR^{L7}$, $-S(=O)_2NR^{L7}$, alkoxyalkyl, arylalkoxycarbonyl, halo, haloalkyl, hydroxyalkyl, $-NR^aR^b$, (NR^aR^b)alkyl, and (NR^aR^b)carbonyl;

each R^{L7} is independently -H, alkyl, aryl, arylalkyl, or heterocycle;

R^a and R^b are each independently selected from the group consisting of hydrogen, alkenyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylalkylcarbonyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl;

each $R9^0$ is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonylalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, aryloxyalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, cycloalkyloxyalkyl, haloalkyl, heterocyclyl, heterocyclylalkenyl, heterocyclylalkoxy, heterocyclylalkyl, heterocyclyloxyalkyl, hydroxyalkyl, $-NR^cR^d$, (NR^cR^d)alkenyl, (NR^cR^d)alkyl, and (NR^cR^d)carbonyl;

R^c and R^d are independently selected from hydrogen, alkenyloxycarbonyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, arylalkoxycarbonyl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, aryloxycarbonyl, arylsulfonyl, cycloalkyl, cycloalkylsulfonyl, formyl, haloalkoxycarbonyl, heterocyclyl, heterocyclylalkoxycarbonyl, heterocyclylalkyl, heterocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, hydroxyalkylcarbonyl, (NR^eR^f)alkyl, (NR^eR^f)alkylcarbonyl, (NR^eR^f)carbonyl, (NR^eR^f)sulfonyl, -C(NCN)OR', and - $C(NCN)NR^XR^Y$, wherein R' is selected from alkyl and unsubstituted phenyl, and wherein the alkyl part of the arylalkyl, the arylalkylcarbonyl, the heterocyclylalkyl, and the heterocyclylalkylcarbonyl are further optionally substituted with one $-NR^eR^f$ group; and wherein the aryl, the aryl part of the arylalkoxycarbonyl, the arylalkyl, the arylalkylcarbonyl, the arylcarbonyl, the aryloxycarbonyl, and the arylsulfonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkoxycarbonyl, the heterocyclylalkyl, the heterocyclylalkylcarbonyl, the heterocyclylcarbonyl, and the heterocyclyloxycarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro;

R^X and R^Y are independently selected from hydrogen, alkoxycarbonyl, alkyl, alkylcarbonyl, unsubstituted aryl, unsubstituted arylalkoxycarbonyl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted heterocyclyl, and $(NR^{X'}R^{Y'})$carbonyl, wherein $R^{X'}$ and $R^{Y'}$ are independently selected from hydrogen and alkyl;

each $R9^1$ is independently $-N(R^{9a})$-NHC(=O)O-R^{9b}, wherein each R^{9a} is independently arylalkyl, alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkoxy, halocycloalkyl,

(cycloalkyl)alkenyl, (cycloalkyl)alkoxy, alkylSO$_2$alkyl, cycloalkylalkylSO$_2$alkyl, cyanoalkyl, haloalkyl, cycloalkylalkyl, cycloalkyl, alkoxyalkyl, alkoxyalkylcarbonylalkyl, alkoxycarbonylalkyl, alkylsulfanylalkyl, aryalkoxyalkylcarbonylalkyl, carboxyalkyl, heterocyclylalkyl, heterocyclylcarbonylalkyl, hydroxyalkyl, NRRCOalkyl, wherein each R is independently selected from hydrogen and alkyl;

and where in arylalkyl the alkyl can be substituted with up to three aryl groups, and the alkyl part of the arylalkyl is further optionally substituted with one or two additional groups independently selected from alkoxy, alkyocarbonyloxy, halo, haloalkoxy, haloalkyl, heterocyclyl, hydroxy;

and the aryl part can be substituted with 1, 2, 3, 4, or 5 substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, a second aryl group, arylalkoxy, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, heterocyclyl, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, -NR^{X}R^Y, -(NR^{X}R^Y)alkyl, oxo, and -P(O)OR$_2$, wherein each R is independently selected from hydrogen and alkyl; and wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted and wherein the second aryl group, the aryl part of the arylalkyl, the aryl part of the arylcarbonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro;

and the heterocyclyl can be substituted with 1, 2, 3, 4, or 5 substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, a second heterocyclyl group, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, -NR^{X}R^Y, -(NR^{X}R^Y)alkyl, and oxo, wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted and wherein the aryl, the aryl part of the arylalkyl; the aryl part of the arylcarbonyl, the second heterocyclyl group, and the heterocyclyl

part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro; R^{9b} is independently H, alkyl, aryl, haloalkyl, or arylalkyl;

each R9^2 is independently –N(R^{9a})-NHC(=O)NR$^{9b}{}_2$; wherein each R^{9a} is independently arylalkyl, alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkoxy, halocycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkoxy, alkylSO2alkyl, cycloalkylalkylSO2alkyl, cyanoalkyl, haloalkyl, cycloalkylalkyl, cycloalkyl, alkoxyalkyl, alkoxyalkylcarbonylalkyl, alkoxycarbonylalkyl, alkylsulfanylalkyl, aryalkoxyalkylcarbonylalkyl, carboxyalkyl,

heterocyclylalkyl, heterocyclylcarbonylalkyl, hydroxyalkyl, NRRCOalkyl, wherein each R is independently selected from hydrogen and alkyl;

and where in arylalkyl the alkyl can be substituted with up to three aryl groups, and the alkyl part of the arylalkyl is further optionally substituted with one or two additional groups independently selected from alkoxy, alkyocarbonyloxy, halo, haloalkoxy, haloalkyl, heterocyclyl, hydroxy;

and the aryl part can be substituted with 1, 2, 3, 4, or 5 substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, a second aryl group, arylalkoxy, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, heterocyclyl, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, $-NR^XR^Y$, $-(NR^XR^Y)$alkyl, oxo, and $-P(O)OR_2$, wherein each R is independently selected from hydrogen and alkyl; and wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted and wherein the second aryl group, the aryl part of the arylalkyl, the aryl part of the arylcarbonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro;

and the heterocyclyl can be substituted with 1, 2, 3, 4, or 5 substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, a second heterocyclyl group, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, $-NR^XR^Y$, $-(NR^XR^Y)$alkyl, and oxo, wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted and wherein the aryl, the aryl part of the arylalkyl; the aryl part of the arylcarbonyl, the second heterocyclyl group, and the heterocyclyl

part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro; R^{9b} is independently H, alkyl, aryl, haloalkyl, or arylalkyl;

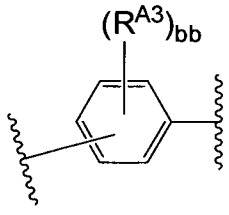
each $R9^3$ is independently $-N(R^{9a})$-$NHC(=O)R^{9b}$, wherein each R^{9a} is independently arylalkyl, alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkoxy, halocycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkoxy, alkylSO_2alkyl, cycloalkylalkylSO_2alkyl, cyanoalkyl, haloalkyl cycloalkylalkyl, cycloalkyl, alkoxyalkyl, alkoxyalkylcarbonylalkyl, alkoxycarbonylalkyl, alkylsulfanylalkyl, aryalkoxyalkylcarbonylalkyl, carboxyalkyl, heterocyclylalkyl, heterocyclylcarbonylalkyl, hydroxyalkyl, NRRCOalkyl, wherein each R is independently selected from H or alkyl;

and where in arylalkyl the alkyl can be substituted with up to three aryl groups, and the alkyl part of the arylalkyl is further optionally substituted with one or two additional groups independently selected from alkoxy, alkyocarbonyloxy, halo, haloalkoxy, haloalkyl, heterocyclyl, hydroxy;

and the aryl part can be substituted with 1, 2, 3, 4, or 5 substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, a second aryl group, arylalkoxy, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, heterocyclyl, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, $-NR^XR^Y$, $-(NR^XR^Y)$alkyl, oxo, and $-P(O)OR_2$, wherein each R is independently selected from hydrogen and alkyl; and wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted and wherein the second aryl group, the aryl part of the arylalkyl, the aryl part of the arylcarbonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro;

and the heterocyclyl can be substituted with 1, 2, 3, 4, or 5 substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, a second heterocyclyl group, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, $-NR^XR^Y$, $-(NR^XR^Y)$alkyl, and oxo, wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted and wherein the aryl, the aryl part of the arylalkyl; the aryl part of the arylcarbonyl, the second heterocyclyl group, and the heterocyclyl part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro; R^{9b} is independently H, alkyl, aryl, haloalkyl, or arylalkyl;

each A^0 is independently:



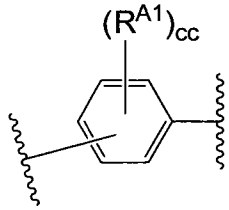
wherein:

each R^{A3} is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxy, hydroxyalkyl, -NR^aR^b, (NR^aR^b)alkyl, and (NR^aR^b)carbonyl; R^a and R^b are each independently selected from the group consisting of hydrogen, alkenyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylalkylcarbonyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl; and each

bb is independently 0, 1, 2, 3, or 4; or

each A^0 is independently a six-membered heteroaromatic ring containing one, two, or three nitrogen atoms, which ring is optionally substituted with 1, 2, 3, or 4 R^{A3} groups;

each A^1 is independently:



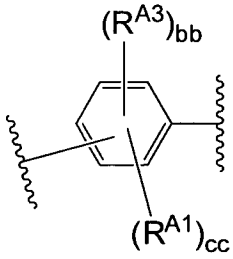
wherein:

each R^{A1} is independently selected from cyano, nitro, SOR^4, SO_2R^4, -alkylSO_2R^4, haloalkoxy, cyanoalkyl, $NR^4SO_2R^4$, cycloalkyl, (halo)cycloalkyl, heterocycle, (cycloalkyl)alkyl, (heterocycle)alkyl, wherein each alkyl, heterocycle and cycloalkyl is optionally substituted with one or more halo; and

each R^4 is independently selected from H, alkyl, haloalkyl, aryl, and arylalkyl;

each cc is independently 1, 2, 3, or 4

each A^2 is independently:



wherein:

each R^{A1} is independently selected from cyano, nitro, SOR^4, SO_2R^4, -alkylSO_2R^4, haloalkoxy, cyanoalkyl, $NR^4SO_2R^4$, cycloalkyl, (halo)cycloalkyl, heterocycle, (cycloalkyl)alkyl, (heterocycle)alkyl, wherein each alkyl, heterocycle and cycloalkyl is optionally substituted with one or more halo;

each R^{A3} is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxy, hydroxyalkyl, -NR^aR^b, (NR^aR^b)alkyl, and (NR^aR^b)carbonyl; R^a and R^b are each independently selected from the group consisting of hydrogen, alkenyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylalkylcarbonyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl;

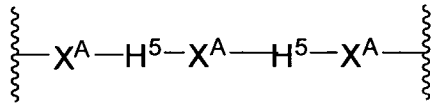
each R^4 is independently selected from H, alkyl, haloalkyl, aryl, and arylalkyl;

R^a and R^b are independently selected from the group consisting of hydrogen, alkenyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylalkylcarbonyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl;

each bb is 0, 1, 2, 3, or 4; each cc is 1, 2, 3, or 4; and the sum of bb and cc is 1, 2, 3, or 4;

each A^3 is independently a six-membered heteroaromatic ring containing one, two, or three nitrogen atoms, which ring is substituted with one or more R^{A1} groups, and which ring is optionally substituted with one or more R^{A3} groups;

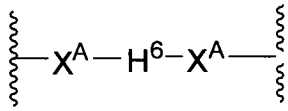
each A^4 is independently:



wherein:

each H^5 is independently a phenyl ring or a six-membered heteroaromatic ring, which H^5 is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3}; and each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent and each R is independently selected from H or alkyl;

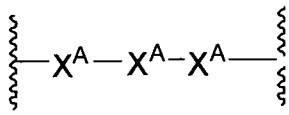
each A^5 is independently:



wherein:

each H^6 is independently a phenyl ring or a six-membered heteroaromatic ring, which H^6 is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3}; and each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent; provided that at least one X^A is present and each R is independently selected from H or alkyl;

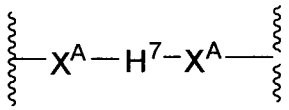
each A^6 is independently:



wherein:

each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, allenyl, alkynyl, or absent; provided that at least one X^A is present and each R is independently selected from H or alkyl;

each A^7 is independently:

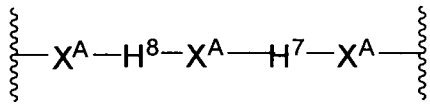


wherein:

each H^7 is independently a five-membered heteroaromatic ring, which H^7 is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3}; and

each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent and each R is independently selected from H or alkyl;

each A^8 is independently:



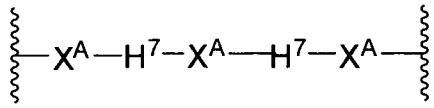
wherein:

each H^7 is independently a five-membered heteroaromatic ring, which H^7 is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3};

each H^8 is independently a phenyl ring, which is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3}; and

each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent and each R is independently selected from H or alkyl;

each A^9 is independently:

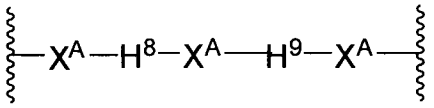


wherein:

each H^7 is independently a five-membered heteroaromatic ring, which H^7 is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3}; and

each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent and each R is independently selected from H or alkyl;

each A^{10} is independently:



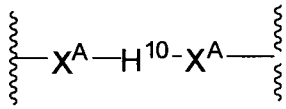
wherein:

each H^8 is independently a phenyl ring, which is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3};

each H^9 is independently a six-membered heteroaromatic ring, which is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3}; and

each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent and each R is independently selected from H or alkyl;

each A^{11} is independently:



wherein:

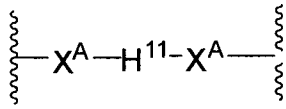
each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent and each R is independently selected from H or alkyl;

each H^{10} is independently a 5-15 carbon unsaturated, partially unsaturated or saturated bicyclic ring system that is optionally fused to an aryl, which H^{10} is optionally substituted with one or more groups independently selected from oxo, alkoxy, alkoxyalkyl,

alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxy, hydroxyalkyl, -NR^aR^b, (NR^aR^b)alkyl, and (NR^aR^b)carbonyl, cyano, nitro, SOR^4, SO_2R^4, -alkylSO_2R^4, haloalkoxy, cyanoalkyl, $NR^4SO_2R^4$, cycloalkyl, (halo)cycloalkyl, heterocycle, (cycloalkyl)alkyl, and (heterocycle)alkyl, wherein each alkyl, heterocycle and cycloalkyl is optionally substituted with one or more halo; and

each R^4 is independently selected from H, alkyl, haloalkyl, aryl, and arylalkyl

each A^{12} is independently:



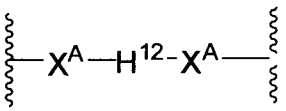
wherein:

each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent and each R is independently selected from H or alkyl;

each H^{11} is independently a 5-15 carbon unsaturated, partially unsaturated or saturated bicyclic ring system that contains one or more heteroatoms that is optionally fused to an aryl, which H^{11} is optionally substituted with one or more groups independently selected from oxo, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxy, hydroxyalkyl, -NR^aR^b, (NR^aR^b)alkyl, and (NR^aR^b)carbonyl, cyano, nitro, SOR^4, SO_2R^4, -alkylSO_2R^4, haloalkoxy, cyanoalkyl, $NR^4SO_2R^4$, cycloalkyl, (halo)cycloalkyl, heterocycle, (cycloalkyl)alkyl, and (heterocycle)alkyl, wherein each alkyl, heterocycle and cycloalkyl is optionally substituted with one or more halo; and

each R^4 is independently selected from H, alkyl, haloalkyl, aryl, and arylalkyl; and

each A^{13} is independently:

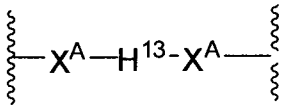


wherein:

each H^{12} is independently a fused aromatic bicyclic carbocycle, which is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3}; and

each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent and each R is independently selected from H or alkyl;

each A^{14} is independently:

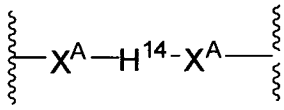


wherein:

each H^{13} is independently a fused aromatic bicyclic heterocycle that comprises at least one heteroatom in the ring system, which ring system is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3}; and

each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent and each R is independently selected from H or alkyl;

each A^{15} is independently:

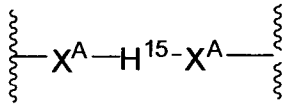


wherein:

each H^{14} is independently a fused unsaturated, partially unsaturated or saturated tricyclic carbocycle which is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3}; and

each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent and each R is independently selected from H or alkyl;

each A^{16} is independently:

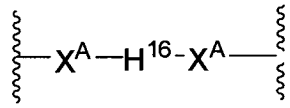


wherein:

each H^{15} is independently a fused unsaturated, partially unsaturated or saturated tricyclic heterocycle that comprises at least one heteroatom in the ring system, which ring system is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3}; and

each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent and each R is independently selected from H or alkyl;

each A^{17} is independently:

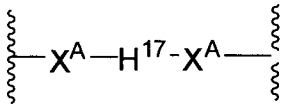


wherein:

each H^{16} is independently a fused bicyclic carbocyclic ring system wherein one ring is aromatic and another ring is partially or fully saturated, which ring system is optionally substituted with one or more groups independently selected from oxo, R^{A1} and R^{A3}; and

each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent and each R is independently selected from H or alkyl;

each A^{18} is independently:

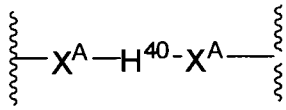


wherein:

each H^{17} is independently a fused bicyclic ring system comprising at least one heteroatom, wherein one ring is aromatic and another ring is partially or fully saturated, which ring system is optionally substituted with one or more groups independently selected from oxo, R^{A1} and R^{A3}; and

each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent and each R is independently selected from H or alkyl;

each A^{21} is independently:



wherein:

each H^{40} is independently an anti-aromatic monocyclic or fused carbocyclic ring system, which carbocyclic ring system is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3}; and

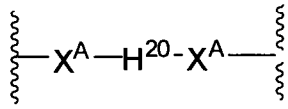
each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent and each R is independently selected from H or alkyl;

each W^1 is independently $-X^A-$:

wherein:

each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent and each R is independently selected from H or alkyl;

each W^2 is independently:

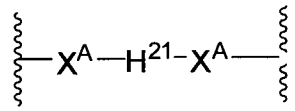


wherein:

each H^{20} is independently is independently a fused aromatic bicyclic carbocycle, which is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3}; and

each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent and each R is independently selected from H or alkyl;

each W^3 is independently:

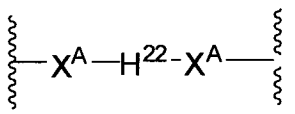


wherein:

each H^{21} is independently a fused bicyclic carbocyclic ring system wherein one ring is aromatic and another ring is partially or fully saturated, which ring system is optionally substituted with one or more groups independently selected from oxo, R^{A1} and R^{A3}; and

each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent and each R is independently selected from H or alkyl;

each W^4 is independently:

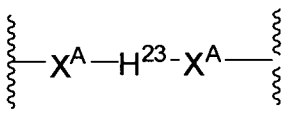


wherein:

each H^{22} is independently a fused aromatic bicyclic heterocycle that comprises at least one heteroatom in the ring system, which ring system is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3}; and

each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent and each R is independently selected from H or alkyl;

each W^5 is independently:



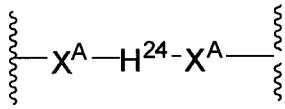
wherein:

each H^{23} is independently a fused bicyclic ring system comprising at least one heteroatom, wherein one ring is aromatic and another ring is partially or fully saturated,

which ring system is optionally substituted with one or more groups independently selected from oxo, R^{A1} and R^{A3}; and

each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent and each R is independently selected from H or alkyl;

each W^6 is independently:

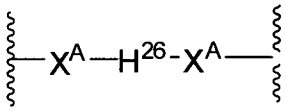


wherein:

each H^{24} is independently a fused unsaturated, partially unsaturated or saturated tricyclic carbocycle, which is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3}; and

each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent and each R is independently selected from H or alkyl;

each W^7 is independently:

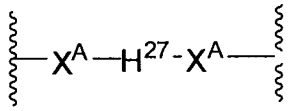


wherein:

each H^{26} is independently a 5-15 carbon unsaturated, partially unsaturated or saturated bicyclic ring system which ring system is optionally substituted with one or more groups independently selected from oxo, R^{A1} and R^{A3}; and

each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent and each R is independently selected from H or alkyl;

each W^8 is independently:

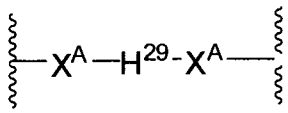


wherein:

each H^{27} is independently a fused unsaturated, partially unsaturated or saturated tricyclic heterocycle that comprises at least one heteroatom in the ring system, which ring system is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3}; and

each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent and each R is independently selected from H or alkyl;

each W^9 is independently:



wherein:

each H^{29} is independently a 5-15 carbon unsaturated, partially unsaturated or saturated bicyclic ring system that contains one or more heteroatoms; and

each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent and each R is independently selected from H or alkyl;

each W^{10} is independently $-H^{30}=C=H^{31}-$

wherein each of $-H^{30}$ and H^{31} is independently a saturated 6-membered heterocyclic ring comprising one or more heteroatoms, which ring is optionally substituted with oxo;

each W^{11} is independently $-H^{32}=C=H^{33}-$

wherein each of $-H^{32}$ and H^{33} is independently a saturated 5-membered heterocyclic ring comprising one or more heteroatoms, which ring is optionally substituted with oxo;

each W^{12} is independently an anti-aromatic monocyclic or fused carbocyclic ring system, which carbocyclic ring system is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3};

each W^{13} is independently a phenyl ring that is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3};

each W^{14} is independently a 5 or 6 membered heteroaryl ring that is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3};

each W^{15} is independently a fused unsaturated, partially unsaturated or saturated tetracyclic carbocyclic ring, which ring system is optionally substituted with one or more groups independently selected from oxo, R^{A1} and R^{A3};

each W^{16} is independently a fused unsaturated, partially unsaturated or saturated tetracyclic heterocycle that comprises at least one heteroatom in the ring system, which ring system is optionally substituted with one or more groups independently selected from oxo, R^{A1} and R^{A3};

each W^{17} is independently a fused unsaturated, partially unsaturated or saturated pentacyclic carbocyclic ring system, which ring system is optionally substituted with one or more groups independently selected from oxo, R^{A1} and R^{A3};

each W^{18} is independently a fused unsaturated, partially unsaturated or saturated pentacyclic heterocycle that comprises at least one heteroatom in the ring system, which ring system is optionally substituted with one or more groups independently selected from oxo, R^{A1} and R^{A3};

each W^{19} is independently a fused unsaturated, partially unsaturated or saturated hexacyclic carbocyclic ring system, which ring system is optionally substituted with one or more groups independently selected from oxo, R^{A1} and R^{A3};

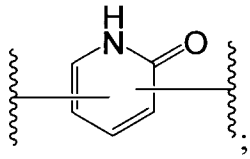
each W^{20} is independently a fused unsaturated, partially unsaturated or saturated hexacyclic heterocycle that comprises at least one heteroatom in the ring system, which ring system is optionally substituted with one or more groups independently selected from oxo, R^{A1} and R^{A3};

each M^0 is independently a five membered heteroaryl group optionally substituted with one or more alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, haloalkyl, (NR^aR^b)carbonyl and trialkylsilylalkoxyalkyl;

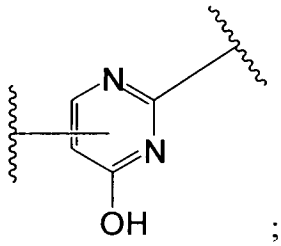
each M^1 is independently selected from –C(=O)NH-, –C(=O)NH-C(R^M)$_2$-, -NHC(=O) -, -C(R^M)$_2$NHC(=O)-, –NHC(=O)N R^M -, –NHC(=O)O -; wherein each R^M is independently selected from H and alkyl;

each M^2 is independently a six-membered heteroaromatic ring, which is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3};

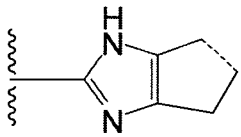
each M^3 is independently:



each M^4 is independently:



each M^5 is independently:



wherein the bond designated with --- is fused to a ring defined for P;

each M^6 is independently a bicyclic bridged ring system comprising 5-15 atoms wherein at least one of the atoms is a heteroatom;

each M^7 is independently a pyrid-di-yl;

each M^8 is independently partially saturated or a saturated five-membered ring that comprises one or more heteroatoms and that is optionally substituted with one or two oxo;

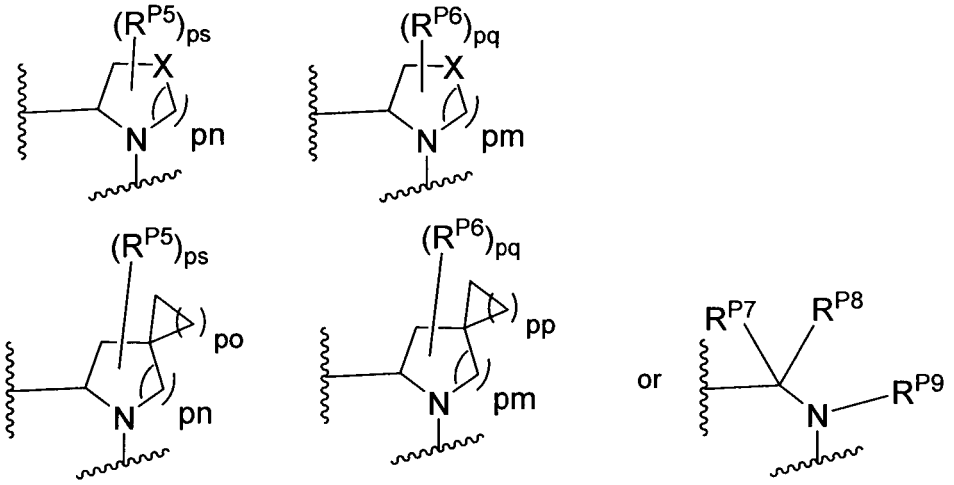
each M^9 is independently a fused-bicyclic saturated, partially unsaturated, or aromatic heterocyclic ring system that is optionally substituted with one or more R^{P11};

each M^{10} is independently a five membered heteroaryl group;

each M^{11} is independently a fused-tricyclic saturated, partially unsaturated, or aromatic heterocyclic ring system that is optionally substituted with one or more oxo, halo, $-R^{M7}$, $-OR^{M7}$, $-SR^{M7}$, $-N(R^{M7})_2$, $-CF_3$, $-CCl_3$, $-OCF_3$,-CN, $-NO_2$, $-N(R^{M7})C(=O)R^{M7}$, $-C(=O)R^{M7}$, $-OC(=O)R^{M7}$, $-C(O)OR^{M7}$, $-C(=O)NR^{M7}$, $-S(=O)R^{M7}$, $-S(=O)_2OR^{M7}$, $-S(=O)_2R^{M7}$, $-OS(=O)_2OR^{M7}$, or $-S(=O)_2NR^{M7}$;

each R^{M7} is independently -H, alkyl, aryl, arylalkyl, or heterocycle;

each P^0 is independently:



wherein:

X is selected from O, S, S(O), SO_2, CH_2, CHR^{P10}, and $C(R^{P10})_2$; provided that when pn or pm is 0, X is selected from CH_2, CHR^{P10}, and $C(R^{P10})_2$;

each R^{P10} is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

each R^{P5} and R^{P6} is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups; R^{Pa} and R^{Pb} are each independently

H, alkyl, aryl, or arylalkyl; or R^{Pa} and R^{Pb} taken together with the atom to which they are attached form a heterocycle;

pq and ps are independently 0, 1, 2, 3, or 4;

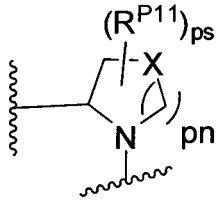
pm and pn are independently 0, 1, or 2;

po and pp are independently 1, 2, or 3;

R^{P7} and R^{P8} are each independently selected from hydrogen, alkenyl, alkoxyalkyl, alkyl, haloalkyl, and $(NR^{Pa}R^{Pb})$alkyl; or R^{P7} and R^{P8}, together with the carbon atom to which they are attached, form a five or six membered saturated ring optionally containing one or two heteroatoms selected from NR^{Pz}, 0, and S; wherein R^{Pz} is selected from hydrogen and alkyl;

R^{P9} is selected from hydrogen and alkyl;

each P^1 is independently:



wherein:

X is selected from O, S, S(O), SO_2, CH_2, CHR^{P10}, and $C(R^{P10})_2$; provided that when pn is 0, X is selected from CH_2, CHR^{P10}, and $C(R^{P10})_2$;

each R^{P10} is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

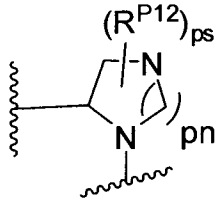
at least one R^{P11} is independently selected from cyano, alkylsulfonyl, arylsulfonyl, (NR^hR^h)sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, (NR^hR^h)alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl, $-NR^{hh}R^h$, $(NR^{hh}R^h)$alkyl, $(NR^{hh}R^h)$carbonyl, wherein each R^h is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two R^h groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring; wherein each R^{hh} is independently aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl,

haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, (NR^hR^h)sulfonyl, heteroarylsulfonyl, $-S(=O)_2R^h$, $-C(=O)R^h$, $-C(=O)NR^hR^h$; and the remaining R^{P11} are independently selected from R^{P5}, cyano, alkylsulfonyl, arylsulfonyl, (NR^hR^h)sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, (NR^hR^h)alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl; wherein each R^h is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two R^h groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

ps is 1, 2, 3, or 4;

pn is 0, 1, or 2;

each P^2 is independently:



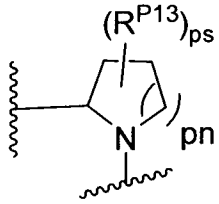
wherein:

each R^{P12} is independently selected from R^{P5}, R^{P11},$-C(=O)OR^h$, cyano, alkylsulfonyl, arylsulfonyl, (NR^hR^h)sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, (NR^hR^h)alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl; wherein each R^h is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two R^h groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

ps is 1, 2, 3, or 4;

pn is 0, 1, or 2;

each P^3 is independently a ring of the formula:



wherein:

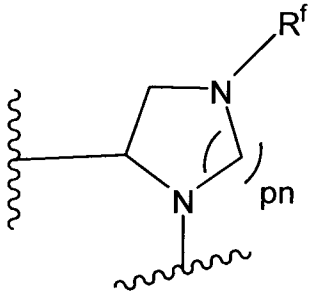
the ring is substituted with one or more oxo group;

each R^{P13} is independently selected from R^{P5}, cyano, alkylsulfonyl, arylsulfonyl, (NR^hR^h)sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, (NR^hR^h)alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl; wherein each R^h is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two R^h groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

ps is 0, 1, 2, 3, or 4;

pn is 0, 1, or 2;

each P^4 is independently a ring of the formula:



wherein:

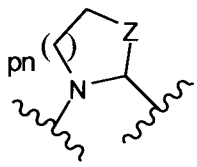
the ring is optionally substituted with one or more groups R^{P14} that are independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an

adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups; and where two groups R^{P14} that are attached to the same carbon when taken together with the carbon to which they are attached can form a 3-6 membered carbocyclic or heterocyclic ring;

pn is 0, 1, or 2;

each R^f is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, $-S(=O)_2NR^hR^h$, $-S(=O)_2R^h$, $C(=O)R^h$, $C(=O)OR^h$, $-C(=O)NR^hR^h$; each R^h is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; or when two R^h groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

each P^5 is independently a ring of the formula:



wherein:

the ring is optionally substituted with one or more groups R^{P15} that are independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups; and where two groups R^{P15} that are attached to the same carbon when taken together with the carbon to which they are attached can form a 3-6 membered carbocyclic or heterocyclic ring;

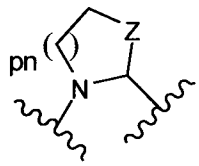
pn is 0, 1, or 2;

Z is O, S, $S(=O)$, $S(=O)_2$, or NR^f;

each R^f is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, $-S(=O)_2NR^hR^h$, $-S(=O)_2R^h$, $C(=O)R^h$, $C(=O)OR^h$, $-C(=O)NR^hR^h$; each R^h is

independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; or when two R^h groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

each P^6 is independently a ring of the formula:



wherein:

the ring is substituted with one or more oxo and is optionally substituted with one or more groups R^{P16} that are independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

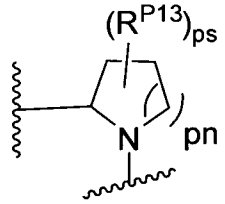
Z is O, S, S(=O), $S(=O)_2$, or NR^f;

pn is 0, 1, or 2;

each R^f is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, $-S(=O)_2NR^hR^h$, $-S(=O)_2R^h$, $C(=O)R^h$, $C(=O)OR^h$, $-C(=O)NR^hR^h$; each R^h is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; or when two R^h groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

each P^7 is a bridged 5-15 membered bicyclic heterocyclic ring that is attached to the remainder of the compound of formula I through one N-link and through one C-link; wherein the ring is optionally substituted with one or more groups independently selected from $R^{P6}$and R^{P11};

each P^8 is independently a ring of the formula:



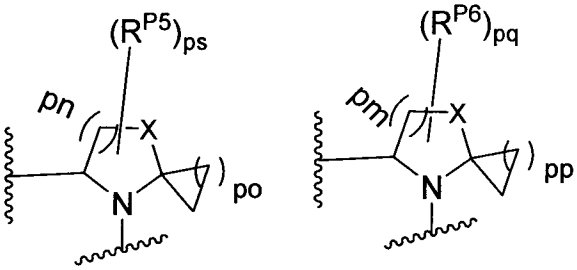
wherein:

ps is 2, 3, 4, 5, or 6;

pn is 0, 1, or 2;

each R^{P13} is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups; where in at least one case two groups R^{P13} that are attached to the same carbon are taken together with the carbon to which they are attached and form a 4-6 membered heterocyclic ring;

each P^{10} is independently:



wherein:

X is selected from O, S, S(O), SO_2, CH_2, CHR^{P10}, and $C(R^{P10})_2$; provided that when pn or pm is 0, X is selected from CH_2, CHR^{P10}, and $C(R^{P10})_2$;

each R^{P10} is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

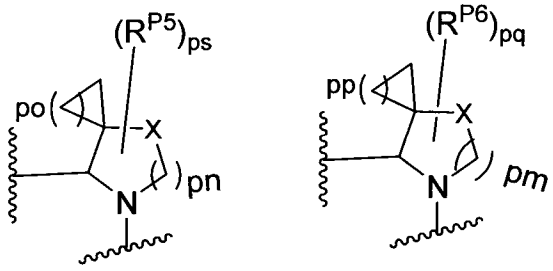
each R^{P5} and R^{P6} is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

pq and ps are independently 0, 1, 2, 3, or 4;

pm and pn are independently 0, 1, or 2;

po and pp are independently 1, 2, or 3;

each P^{11} is independently:



wherein:

X is selected from O, S, S(O), SO_2, CH_2, CHR^{P10}, and $C(R^{P10})_2$; provided that when pn or pm is 0, X is selected from CH_2, CHR^{P10}, and $C(R^{P10})_2$;

each R^{P10} is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

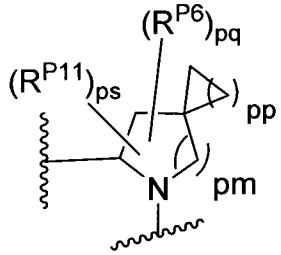
each R^{P5} and R^{P6} is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

pq and ps are independently 0, 1, 2, 3, or 4;

pm and pn are independently 0, 1, or 2;

po and pp are independently 1, 2, or 3;

each P^{12} is independently:



wherein:

each R^{P6} is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

pq is independently 0, 1, 2, 3, or 4;

pm is independently 0, 1, or 2;

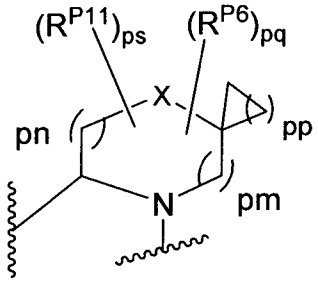
pp is independently 1, 2, or 3;

ps is 1, 2, 3, or 4;

R^{P11} is independently selected from cyano, alkylsulfonyl, arylsulfonyl, (NR^hR^h)sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, (NR^hR^h)alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl, $-NR^{hh}R^h$, $(NR^{hh}R^h)$alkyl, $(NR^{hh}R^h)$carbonyl, wherein each R^h is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two R^h groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring; wherein each R^{hh} is independently aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, NR^hR^hsulfonyl, heteroarylsulfonyl, $-S(=O)_2R^h$, $-C(=O)R^h$, $-C(=O)NR^hR^h$; and the remaining R^{P11} are independently selected from R^{P5}, cyano, alkylsulfonyl, arylsulfonyl, (NR^hR^h)sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, (NR^hR^h)alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl; wherein each R^h is independently -H,

alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two R^h groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

each P^{13} is independently:



wherein:

X is selected from O, S, S(O), SO_2, or NR^h;

each R^{P6} is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

pq is independently 0, 1, 2, 3, or 4;

pm and pn are independently 0, 1, or 2 but the sum of pn and pm is greater than zero;

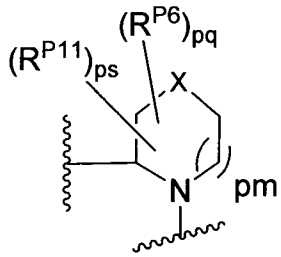
pp are independently 1, 2, or 3;

ps is 1, 2, 3, or 4;

each R^{P11} is independently selected from cyano, alkylsulfonyl, arylsulfonyl, (NR^hR^h)sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, (NR^hR^h)alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl, $-NR^{hh}R^h$, $(NR^{hh}R^h)$alkyl, $(NR^{hh}R^h)$carbonyl, wherein each R^h is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two R^h groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

wherein each R^{hh} is independently aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, (NR^hR^h)sulfonyl, heteroarylsulfonyl, $-S(=O)_2R^h$, $-C(=O)R^h$, $-C(=O)NR^hR^h$, R^{P5}, cyano, alkylsulfonyl, arylsulfonyl, (NR^hR^h)sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, (NR^hR^h)alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl; wherein each R^h is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two R^h groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

each P^{14} is independently:



wherein:

the ring is substituted with one or more oxo group;

X is NR^f;

each R^f is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, $-S(=O)_2NR^hR^h$, $-S(=O)_2R^h$, $C(=O)R^h$, $C(=O)OR^h$, $-C(=O)NR^hR^h$; each R^h is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; or when two R^h groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

each R^{P6} is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to

six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

pq is independently 0, 1, 2, 3, or 4;

pm is independently 0, 1, or 2;

ps is 1, 2, 3, or 4;

R^{P11} is independently selected from cyano, alkylsulfonyl, arylsulfonyl, (NR^hR^h)sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy
aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, (NR^hR^h)alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl; wherein each R^h is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, or sulfonylalkyl; and when two R^h groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

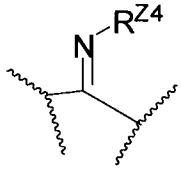
each $-Z^0-$ is –C(=O)- or –C(=S)-;

each $-Z^1-$ is independently a bond, or $-C(R^{Z1})_2-$; wherein each R^{Z1} is independently H, alkyl, haloalkyl, or halo;

each $-Z^2-$ is independently saturated or partially unsaturated (C_3-C_8)cycloalkyl that is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3};

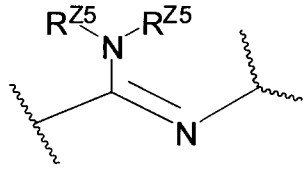
each $-Z^3-$ is independently saturated, partially unsaturated, or aromatic 4-8 membered heterocyclic or heteroaryl ring that is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3};

each $-Z^4-$ is independently:



wherein each R^{Z4} is independently H, alkyl, cyano, aryl, or heteroaryl;

each $-Z^5-$ is independently:



wherein each R^{Z5} is independently H, alkyl, cyano, aryl, or heteroaryl; or two R^{Z5}s together with the nitrogen to which they are attached form a 4-8 membered heterocyclic ring that is optionally substituted with one or more oxo and with one or more groups independently selected from R^{A1} and R^{A3};

each $-Z^6-$ is independently $-C(R^{Z1})-$ and is doublebonded to a carbocyclic P; wherein R^{Z1} is independently H, alkyl, haloalkyl, or halo;

each E^0 is independently $-NR^{Ec}R^{Ed}$ wherein

R^{Ec} and R^{Ed} are each independently selected from hydrogen, alkenyloxycarbonyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, arylalkoxycarbonyl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, aryloxycarbonyl, arylsulfonyl, cycloalkyl, cycloalkylsulfonyl, formyl, haloalkoxycarbonyl, heterocyclyl, heterocyclylalkoxycarbonyl, heterocyclylalkyl, heterocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, hydroxyalkylcarbonyl, (NR^eR^f)alkyl, (NR^eR^f)alkylcarbonyl, (NR^eR^f)carbonyl, (NR^eR^f)sulfonyl, -C(NCN)OR', and - $C(NCN)NR^XR^Y$, wherein R' is selected from alkyl and unsubstituted phenyl, and wherein the alkyl part of the arylalkyl, the arylalkylcarbonyl, the heterocyclylalkyl, and the heterocyclylalkylcarbonyl are further optionally substituted with one $-NR^eR^f$ group; and wherein the aryl, the aryl part of the arylalkoxycarbonyl, the arylalkyl, the arylalkylcarbonyl, the arylcarbonyl, the aryloxycarbonyl, and the arylsulfonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkoxycarbonyl, the heterocyclylalkyl, the heterocyclylalkylcarbonyl, the heterocyclylcarbonyl, and the heterocyclyloxycarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro;

each E^1 is independently -OC(=O)$NR^{Ee}R^{Ef}$ wherein each R^{Ee} and R^{Ef} are each independently selected from hydrogen, alkenyloxycarbonyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, arylalkoxycarbonyl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, aryloxycarbonyl, arylsulfonyl, cycloalkyl, cycloalkylsulfonyl, formyl, haloalkoxycarbonyl, heterocyclyl, heterocyclylalkoxycarbonyl, heterocyclylalkyl, heterocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, hydroxyalkylcarbonyl, (NR^eR^f)alkyl, (NR^eR^f)alkylcarbonyl, (NR^eR^f)carbonyl, (NR^eR^f)sulfonyl, -C(NCN)OR', and - C(NCN)NR^XR^Y, wherein R' is selected from alkyl and unsubstituted phenyl, and wherein the alkyl part of the arylalkyl, the arylalkylcarbonyl, the heterocyclylalkyl, and the heterocyclylalkylcarbonyl are further optionally substituted with one -NR^eR^f group; and wherein the aryl, the aryl part of the arylalkoxycarbonyl, the arylalkyl, the arylalkylcarbonyl, the arylcarbonyl, the aryloxycarbonyl, and the arylsulfonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkoxycarbonyl, the heterocyclylalkyl, the heterocyclylalkylcarbonyl, the heterocyclylcarbonyl, and the heterocyclyloxycarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro; or wherein R^{Ee} and R^{Ef}, together with the nitrogen atom to which they are attached, form a heterocycle;

each V^0 is independently H, alkyl, arylalkyl, alkenyl, CO, cycloalkylalkyl, cycloalkyl, alkoxyalkyl, alkoxyalkylcarbonylalkyl, alkoxycarbonylalkyl, alkylsulfanylalkyl, aryalkoxyalkylcarbonylalkyl, carboxyalkyl, heterocyclylalkyl, heterocyclylcarbonylalkyl, hydroxyalkyl, NRRCOalkyl, wherein each R is independently selected from hydrogen and alkyl;
and where in arylalkyl the alkyl can be substituted with up to three aryl groups, and the alkyl part of the arylalkyl is further optionally substituted with one or two additional groups independently selected from alkoxy, alkyocarbonyloxy, halo, haloalkoxy, haloalkyl, heterocyclyl, hydroxy;
and the aryl part can be substituted with 1, 2, 3, 4, or 5 substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, a second aryl group, arylalkoxy, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, heterocyclyl, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, -NR^XR^Y, -(NR^XR^Y)alkyl, oxo, and -P(O)OR_2, wherein each R is independently selected from hydrogen and alkyl; and wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted and wherein the second aryl group, the aryl part of the arylalkyl, the aryl part of the arylcarbonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkyl and the

heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro;

and the heterocyclyl can be substituted with 1, 2, 3, 4, or 5 substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, a second heterocyclyl group, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, $-NR^XR^Y$, (NR^XR^Y)alkyl, and oxo, wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted and wherein the aryl, the aryl part of the arylalkyl; the aryl part of the arylcarbonyl, the second heterocyclyl group, and the heterocyclyl part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro;

each V^1 is independently cyanoalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O-$; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^2 is independently haloalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O-$; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^3 is independently alkyl, which is substituted with one or more oxo, and which is optionally substituted with one or more groups independently selected from cycloalkyl, halo, aryl, alkenyl, and cyano;

each V^4 is independently haloalkoxyalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O-$; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^5 is independently alkylsulfonylalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle,

heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^6 is independently arylsulfonylalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^7 is independently heterocyclosulfonylalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^8 is independently spirocycloalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^9 is independently spirocycloalkylalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^{10} is independently fusedbicycliccycloalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^{11} is independently fusedbicycliccycloalkylalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^{12} is independently bridged-bicycliccycloalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl,

heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^{13} is independently bridged-bicyclic-cycloalkylalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^{14} is independently aryloxyalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^{15} is independently arylalkoxyalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^{16} is independently cycloalkyloxyalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^{17} is independently cycloalkylalkyloxyalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^{18} is independently heterocyclooxyalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^{19} is independently heterocycloalkyloxyalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^{20} is independently heteroaryloxyalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^{21} is independently heteroarylalkylalkoxyalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;
each T^1 is independently a spiro, branched or fused bicycloalkyl;
each T^2 is independently aryl;
each T^3 is independently heteroaryl;
each T^4 is independently arylalkyl;
each T^5 is independently haloalkyl;
each T^6 is independently heteroarylalkyl;
each T^7 is independently heterocycle; and
each T^8 is independently heterocyclealkyl.

22. The compound of claim 21 which comprises M^0-W-M^0, M^0-W-M^9, M^9-W-M^0, or M^9-W-M^9, M^{10}-W-M^0, M^0-W-M^{10}, M^{10}-W-M^9, M^9-W-M^{10}, or M^{10}-W-M^{10}.

23. The compound of claim 22 wherein W is W^2.

24. The compound of claim 22 wherein W is W^8.

25. The compound of claim 22 wherein W is W^{15}.

26. The compound of claim 22 wherein W is W^{16}.

27. The compound of claim 22 wherein W is W^{18}.

28. The compound of claim 21 which comprises M^0-A-A-M^0, M^0-A-A-M^9, M^9- A-A-M^0, or M^9-A-A-M^9. M^{10}- A-A-M^0, M^0-A-A-M^{10}, M^{10}- A-A-M^9, M^9- A-A-M^{10}, or M^{10}- A-A-M^{10}

29. The compound of claim 28 wherein –A-A- is –A^0-A^5-.

30. The compound of claim 28 wherein –A-A- is –A^0-A^{13}-.

31. The compound of claim 28 wherein –A-A- is –A^{13}-A^{13}-.

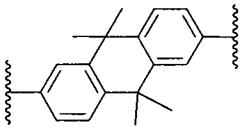
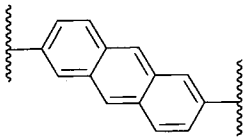
32. The compound of claim 28 wherein –A-A- is –A^0-A^{11}-.

33. The compound of claim 28 wherein –A-A- is –A^{13}-A^6-.

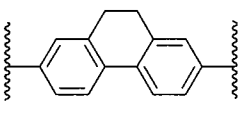
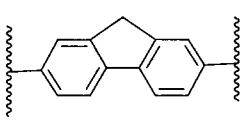
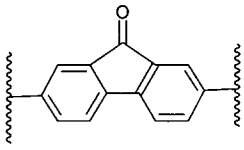
34. The compound of claim 21 wherein W is W^6.

35. The compound of claim 34 wherein each X^A is absent.

36. The compound of claim 34 or 35 wherein W^6 is selected from:

 and  .

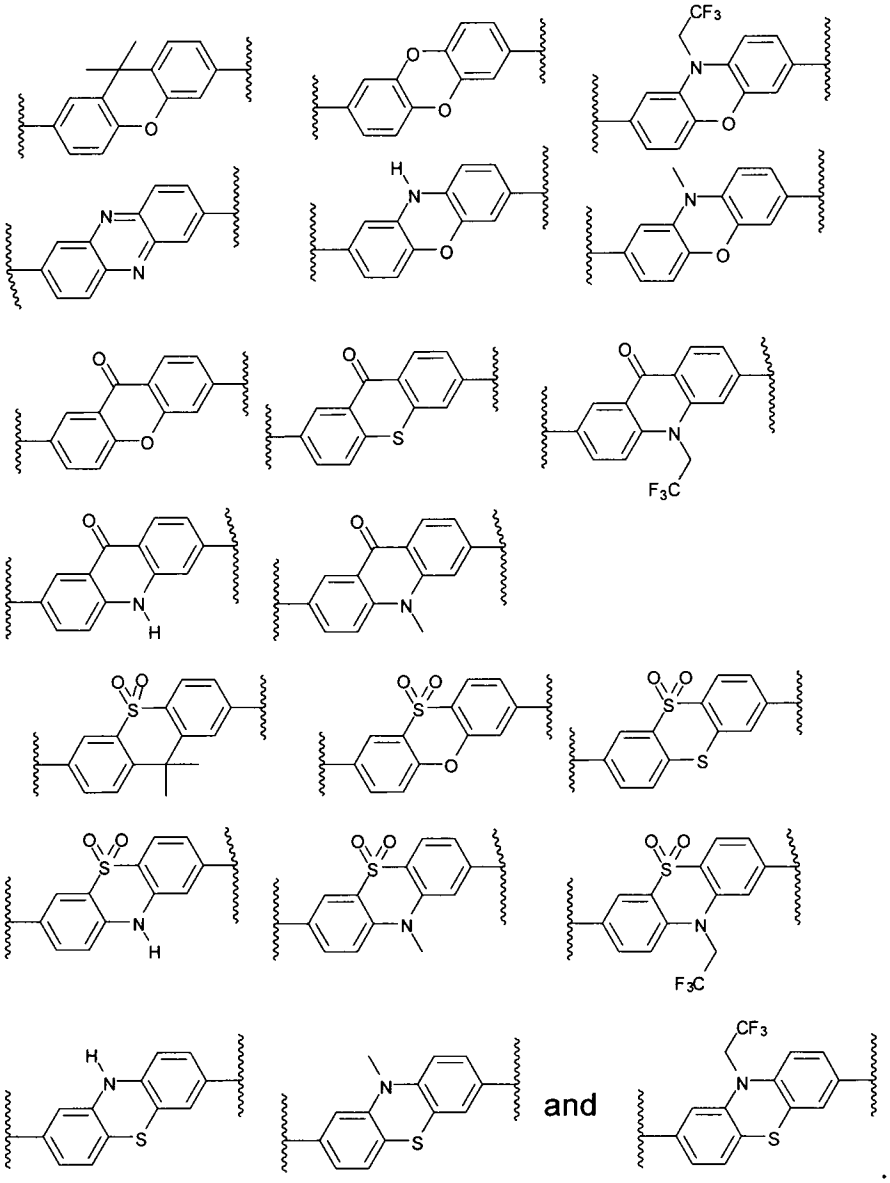
37. The compound of claim 34 or 35 wherein W^6 is selected from:

  and  .

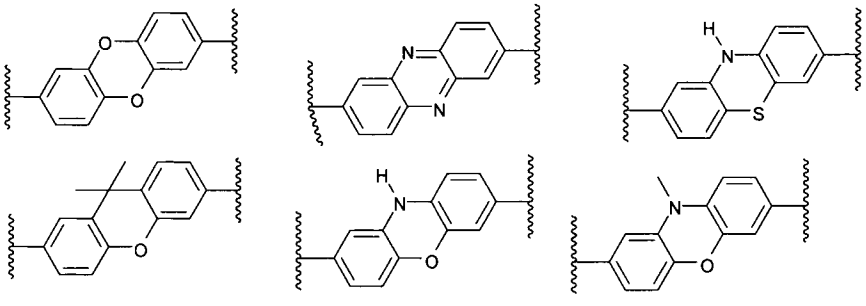
38. The compound of claim 21 wherein W is W^8.

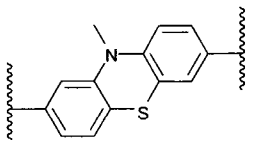
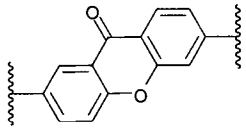
39. The compound of claim 38 wherein each X^A is absent.

40. The compound of claim 38 or 39 wherein W^8 is selected from:

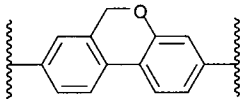
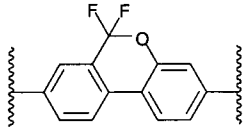
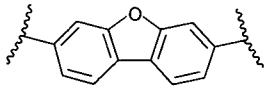
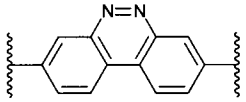


41. The compound of claim 38 or 39 wherein W^8 is selected from:

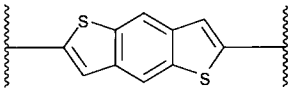
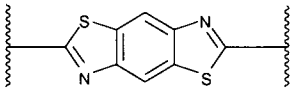
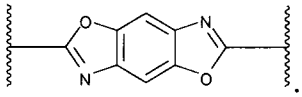



and


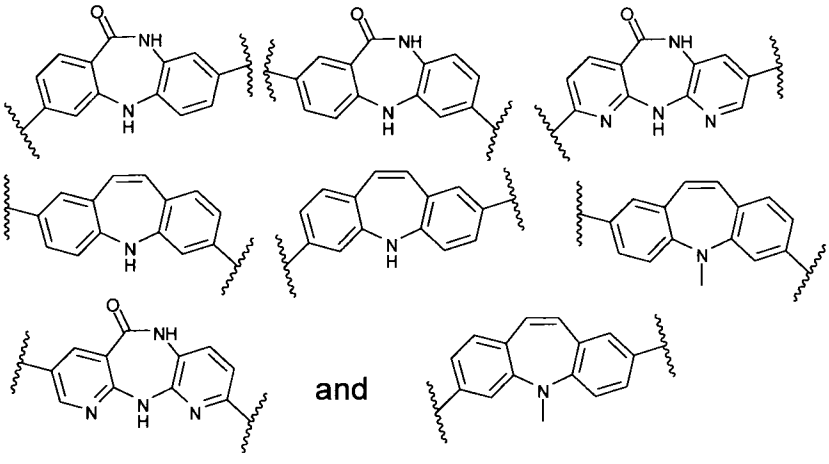
42. The compound of claim 38 or 39 wherein W^8 is selected from:




and


43. The compound of claim 38 or 39 wherein W^8 is selected from:

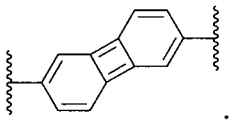


and


44. The compound of claim 38 or 39 wherein W^8 is selected from:



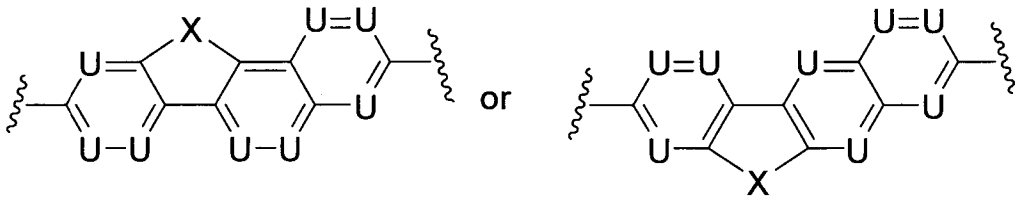
45. The compound of claim 21 wherein W is W^8 that is unsubstituted.

46. The compound of claim 21 wherein W^{12} is:



47. The compound of claim 21 wherein W is W^{15} or W^{16}.

48. The compound of claim 21 wherein W is a ring system of formula:



wherein :

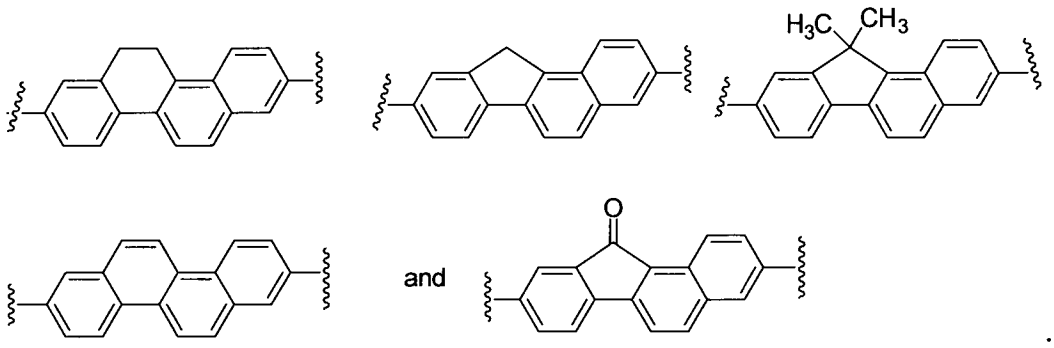
U is CH or N; and

X is $-CH_2-$, $-C(=O)-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, or $-CH=CH-$;

wherein the ring system is optionally substituted with one or more R^1 or R^3.

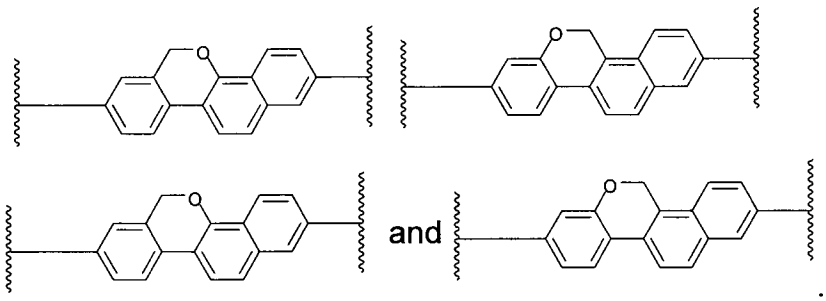
49. The compound of claim 21 wherein W is W^{15}.

50. The compound of claim 21 wherein W is selected from:



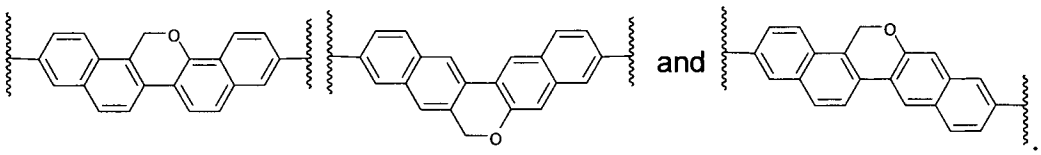
51. The compound of claim 21 wherein W is W^{16}.

52. The compound of claim 21 wherein W is selected from:



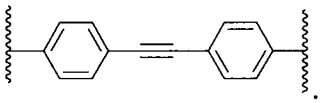
53. The compound of claim 21 wherein W is W^{18}.

54. The compound of claim 21 wherein W is selected from:



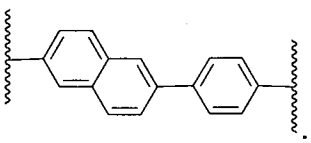
55. The compound of claim 21 wherein one A is A^0 and one A is A^5, wherein one X^A in the A^5 is absent and the other X^A in the A^5 is alkynyl.

56. The compound of claim 21 or 29 wherein $-A^0-A^5-$ has the following structure:



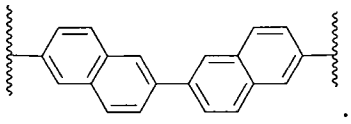
57. The compound of claim 21 wherein one A is A^0 and one A is A^{13}, wherein both X^A in the A^{13} are absent.

58. The compound of claim 21 or 30 wherein $-A^0-A^{13}-$ has the following structure:



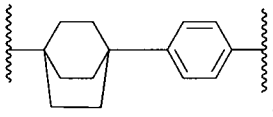
59. The compound of claim 21 that comprises A^{13}- A^{13}, wherein all X^A in both A^{13} are absent.

60. The compound of claim 21 or 31 wherein $-A^{13}-A^{13}-$ has the following structure:



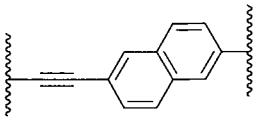
61. The compound of claim 21 that comprises A^0- A^{11} wherein all X^A in both the A^0 and the A^{11}, are absent or alkynyl.

62. The compound of claim 21 or 32 wherein $-A^0-A^{11}-$ has the following structure:



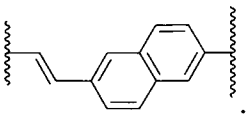
63. The compound of claim 21 that comprises one A^{13} and one A^6 wherein all X^A in the A^{13} are bonds.

64. The compound of claim 21 or 33 wherein $-A^{13}-A^6-$ has the following structure:



65. The compound of claim 21 wherein W is W^2 and within the W^2 one X^A is absent and one X^A is RC=CR.

66. The compound of claim 21 wherein W^2 has the following structure:

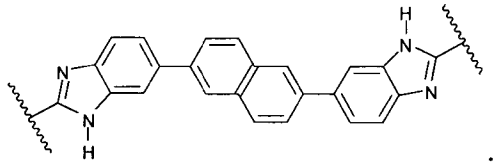


67. The compound of claim 21 wherein W is W^2 and within the W^2 one X^A is absent and one X^A is selected from absent, alkynyl, or RC=CR; and M is selected from M^0 or M^9.

68. The compound of claim 67 wherein M^0 is imidazolyl and M^9 is benzimidazolyl.

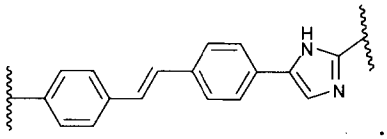
69. The compound of claim 21 that comprises a group M^9-W^2-M^9.

70. The compound of claim 69 wherein the group M^9- W^2-M^9 has the following structure:



71. The compound of claim 21 wherein A is A^0 and L is L^2.

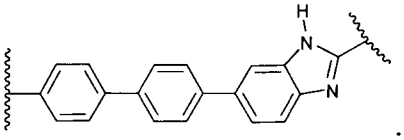
72. The compound of claim 71 wherein A^0-L^2 has the following structure:



73. The compound of claim 21 that comprises two A^0 and one M is M^9.

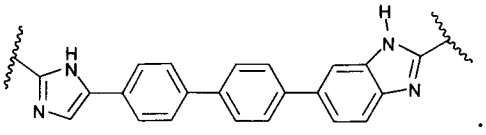
74. The compound of claim 21 that comprises two A^0 and one M is M^0 and another M is M^9.

75. The compound of claim 74 wherein A^0-A^0-M^9 has the following structure:



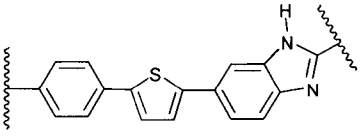
76. The compound of claim 21 that comprises M^0-A^0-A^0-M^9.

77. The compound of claim 76 wherein M^0-A^0-A^0-M^9 has the following structure:



78. The compound of claim 21 that comprises A^0-A^7-M^9.

79. The compound of claim 78 wherein A^0-A^7-M^9 has the following structure:



80. The compound of claim 21 that comprises one or two M and each M is M^0.

81. The compound of claim 21 that comprises one or two M and each M is imidazolyl.

82. The compound of claim 21 that comprises one or two M and each M is M^9.

83. The compound of claim 21 that comprises one or two M and each M is benzimidazolyl.

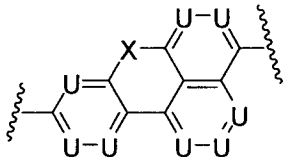
84. The compound of claim 21 that comprises two M wherein one M is M^0 and one M is M^9.

85. The compound of claim 21 that comprises two M wherein one M is imidazolyl and one M is benzimidazolyl.

86. The compound of claim 21 that comprises one or two L wherein each L is L^3.

87. The compound of claim 21 that comprises one or two L wherein each L is benzimidazolyl.

88. The compound of claim 21 wherein W is a ring system of formula:



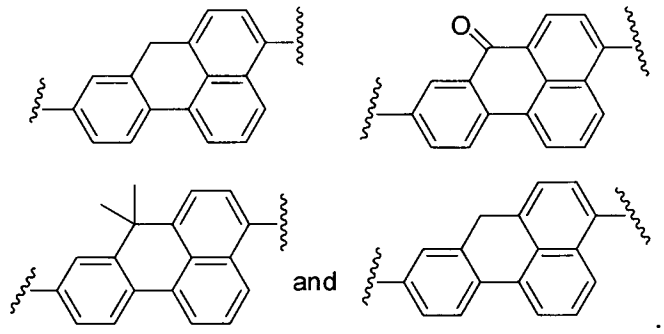
wherein :

U is CH or N; and

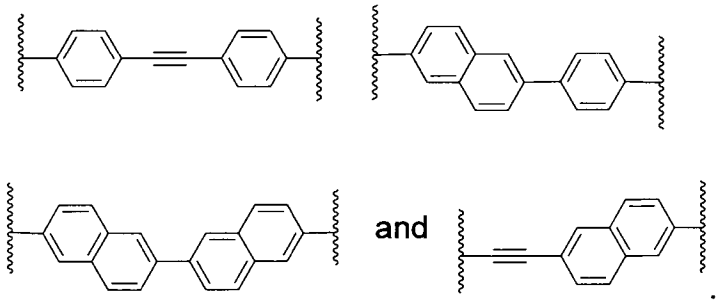
X is $-CH_2-$, $-C(=O)-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, or $-CH=CH-$;

wherein the ring system is optionally substituted with one or more R^1 or R^3.

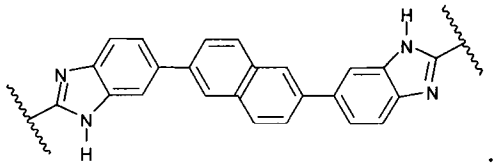
89. The compound of claim 21 wherein W is selected from:



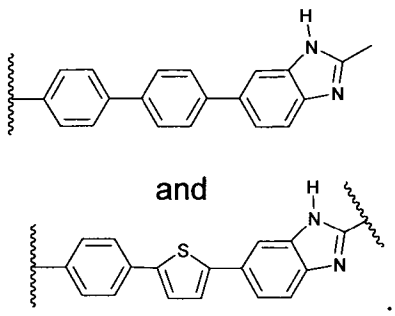
90. The compound of claim 21 wherein A-A is selected from:



91. The compound of claim 21 wherein M-W-M is:

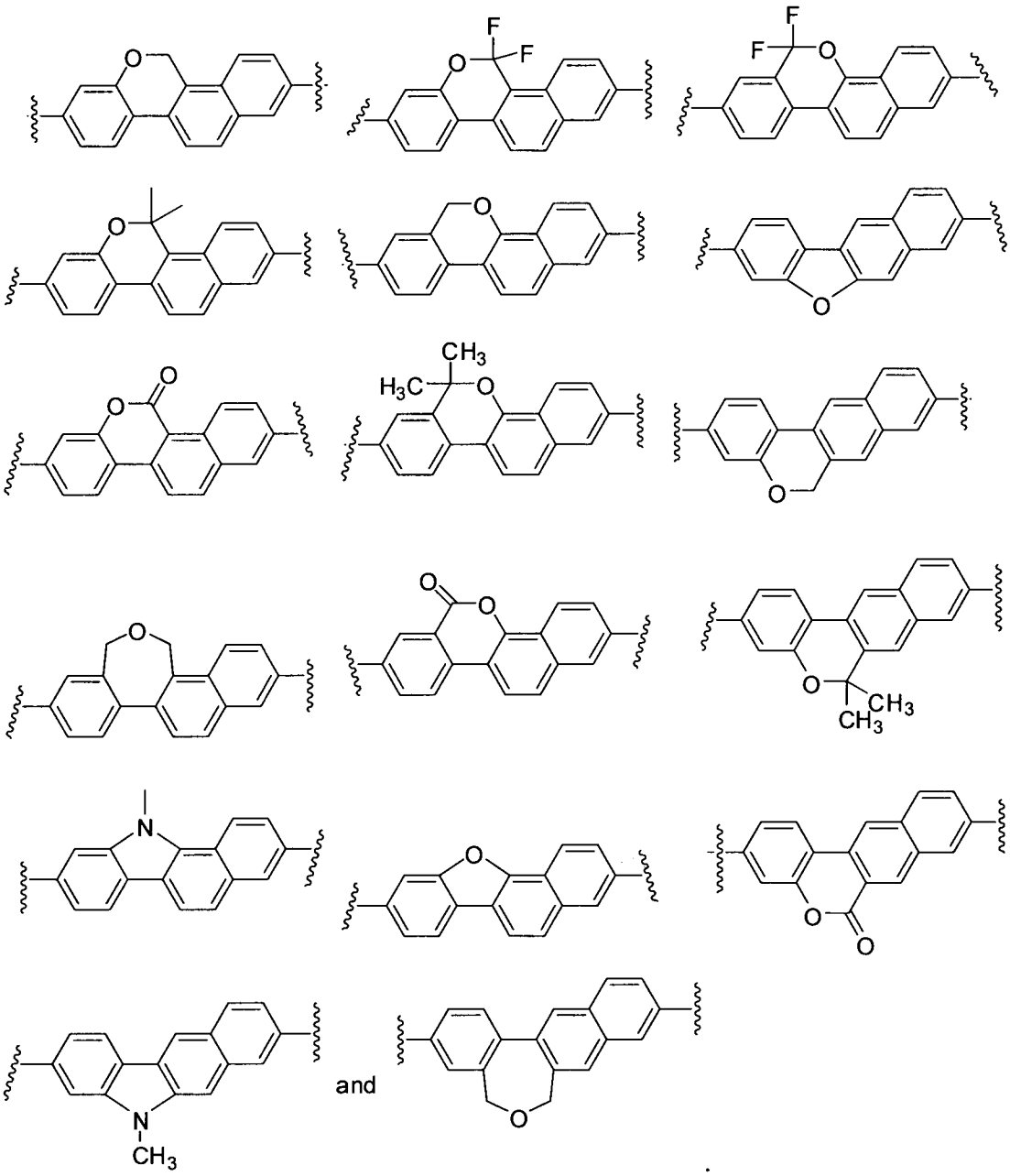


92. The compound of claim 21 wherein -A-L- is selected from:



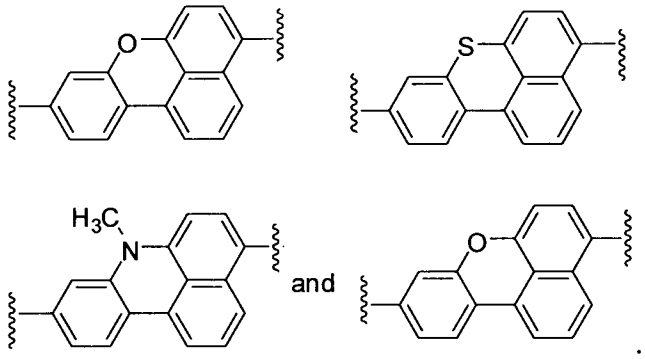
93. The compound of claim 21 wherein the compound of formula I has the formula E-V-Z-P-M-A-L-P-Z-V-E .

94. The compound of claim 21 wherein W is selected from:



95. The compound of claim 21 wherein W is W^{17}.

96. The compound of claim 21 wherein W is selected from:



97. The compound of claim 21 wherein the compound of formula I has the formula J-M-W-M-J.

98. The compound of claim 21 wherein the compound of formula I has the formula E-V-Z-P-M-W-M- P-Z-V-E.

99. The compound of claim 21 wherein the compound of formula I has the formula E-V-Z-P-M-W-M-P-Z-V-E.

100. The compound of claim 21 wherein the compound of formula I has the formula E-V-Z-P-M-A-A-M-P-Z-V-E.

101. The compound of claim 21 having the structure E-V-Z-P-M-A-L-P-Z-V-E

102. The compound of claim 21 having the structure E-V-Z-P-M-W-M-P-Z-V-E

103. The compound of claim 102 wherein –M-W-M- is selected from M^0-W-M^0, M^0-W-M^9, M^9-W-M^0, and M^9-W-M^9.

104. The compound of claim 102 wherein –M-W-M- is selected from M^{10}-W-M^0, M^0-W-M^{10}, M^{10}-W-M^9, M^9-W-M^{10}, and M^{10}-W-M^{10}.

105. The compound of claim 100 wherein –M-A-A-M- is selected from M^0-A-A-M^0, M^0-A-A-M^9, M^9-A-A-M^0, and M^9-A-A-M^9.

106. The compound of claim 100 wherein –M-A-A-M- is selected from M^{10}-A-A-M^0, M^0-A-A-M^{10}, M^{10}-A-A-M^9, M^9-A-A-M^{10}, and M^{10}-A-A-M^{10}.

107. The compound of any one of claims 21-106 wherein each E is E^0.

108. The compound of any one of claims 21-106 wherein each E is -NHC(=O)Oalkyl.

109. The compound of any one of claims 21-106 wherein each E is methoxycarbonylamino.

110. The compound of any one of claims 21-109 wherein each V is V^0.

111. The compound of any one of claims 21-109 wherein each V is alkyl.

112. The compound of any one of claims 21-109 wherein each V is isopropyl.

113. The compound of any one of claims 21-109 wherein each V is V^2.

114. The compound of any one of claims 21-109 wherein each V is haloalkyl.

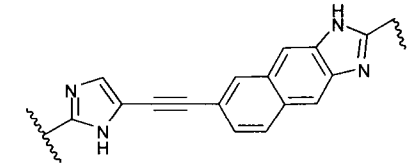
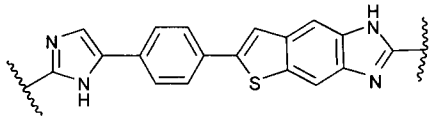
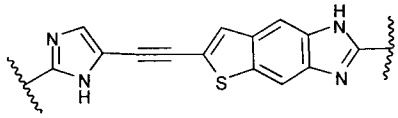
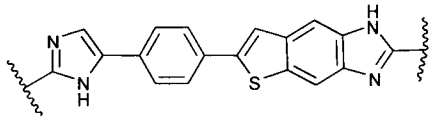
115. The compound of any one of claims 21-114 wherein each Z is Z^0.

116. The compound of any one of claims 21-114 wherein each Z is –C(=O)-.

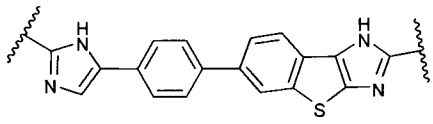
117. The compound of any one of claims 21-116 wherein each M is independently a 5-membered heteroaryl ring.

118. The compound of any one of claims 21-116 wherein each M is 2,5-imidazoldiyl.

119. The compound of any one of claims 21 and 107-116 wherein -M-A-L- is selected from:

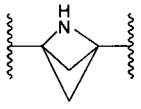
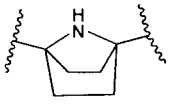





and



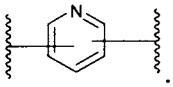
120. The compound of any one of claims 21 and 107-116 wherein M is M^6.

121. The compound of any one of claims 21 and 107-116 wherein M is selected from:


and


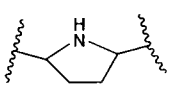
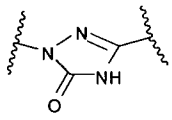
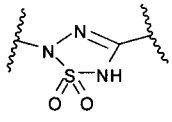
122. The compound of any one of claims 21 and 107-116 wherein M is M^7.

123. The compound of any one of claims 21 and 107-116 wherein M is:



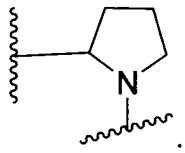
124. The compound of any one of claims 21 and 107-116 wherein M is M^8.

125. The compound of any one of claims 21 and 107-116 wherein M is:

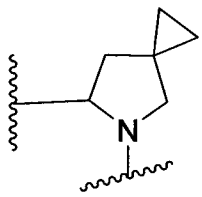


and


126. The compound of any one of claims 21-125 wherein P is P^0.

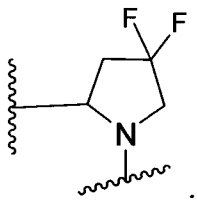
127. The compound of any one of claims 21-125 wherein P is



128. The compound of any one of claims 21-125 wherein P is



129. The compound of any one of claims 21-125 wherein P is



130. The compound of any one of claims 21-125 wherein P is P^1.

131. The compound of any one of claims 21-125 wherein P is P^2.

132. The compound of any one of claims 21-125 wherein P is P^2; and pn is 1.

133. The compound of any one of claims 21-125 wherein P is P^2; pn is 1; and R^{P12} is independently selected from alkylsulfonyl, arylsulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, $-C(=O)R^h$, $-C(=O)NR^hR^h$; $-C(=O)OR^h$, and haloalkyl.

134. The compound of any one of claims 21-125 wherein P is P^3; pn is 1 and ps is zero.

135. The compound of any one of claims 21-125 wherein P is P^5.

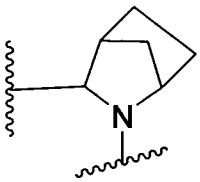
136. The compound of any one of claims 21-125 wherein P is P^5; pn is 1; and Z is O, S, S(=O), $S(=O)_2$, or NR^f.

137. The compound of any one of claims 21-125 wherein P is P^6.

138. The compound of any one of claims 21-125 wherein P is P^6; pn is 1; and Z is O, S, S(=O), $S(=O)_2$, or NR^f.

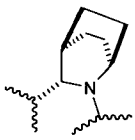
139. The compound of any one of claims 21-125 wherein P is P^7 wherein P^7 is a [2.2.1] or a [2.2.2] ring system.

140. The compound of any one of claims 21-125 wherein P is



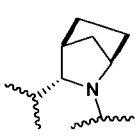
optionally substituted with one or more groups independently selected from R^{P6} and R^{P11}.

141. The compound of any one of claims 21-125 wherein P is



optionally substituted with one or more groups independently selected from R^{P6} and R^{P11}.

142. The compound of any one of claims 21-125 wherein P is

 or  .

optionally substituted with one or more groups independently selected from R^{P6} and R^{P11}.

143. The compound of any one of claims 21-125 wherein P is P^8.

144. The compound of any one of claims 21-125 wherein P is P^8; and pn is 1.

145. The compound of any one of claims 21-125 wherein P is P^8; pn is 1; and ps is 2.

146. The compound of any one of claims 21-125 wherein P is P^{10}.

147. The compound of any one of claims 21-125 wherein P is P^{10}; pn is 1; and X is O, S, S(=O), $S(=O)_2$, CHR^{P10}, or $C(R^{P10})_2$.

148. The compound of any one of claims 21-125 wherein P is P^{10}; pn is 1; po is 1; and X is O, S, S(=O), $S(=O)_2$, CHR^{P10}, or $C(R^{P10})_2$.

149. The compound of any one of claims 21-125 wherein P is P^{10}; pn is 1; po is 1; ps is 0; and X is O, S, S(=O), $S(=O)_2$, CHR^{P10}, or $C(R^{P10})_2$.

150. The compound of any one of claims 21-125 wherein P is P^{11}.

151. The compound of any one of claims 21-125 wherein P is P^{11}; pn is 1; po is 1; ps is 0; and X is O, S, S(=O), $S(=O)_2$, CHR^{P10}, or $C(R^{P10})_2$.

152. The compound of any one of claims 21-125 wherein P is P^{12}.

153. The compound of any one of claims 21-125 wherein P is P^{12}; pm is 1; and pp is 1.

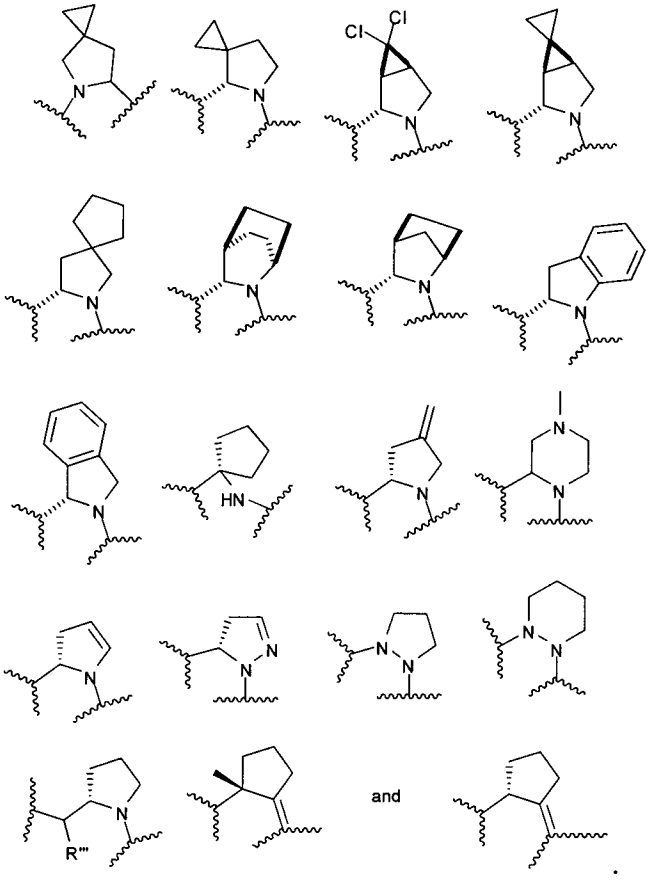
154. The compound of any one of claims 21-125 wherein P is P^{13}.

155. The compound of any one of claims 21-125 wherein P is P^{13}; pm is 1; po is 0; ps is 0; pp is 1; pq is 0; and X is O, S, or $S(=O)_2$.

156. The compound of any one of claims 21-125 wherein P is P^{14}.

157. The compound of any one of claims 21-125 wherein P is P^{14}; pm is 0; and pq is 0.

158. The compound of any one of claims 21-125 wherein P is selected from:



159. The compound of formula I as described in claim 21 which is a compound having a formula selected from: T-P-Y-P-T; T-P-Y-J; J-Y-J; T-P-Y-P-Z-R9; R9-Z-P-Y-P-Z-R9; J-Y-P-Z-R9; T-P-Y-P-Z-V-E; E-V-Z-P-Y-P-Z-V-E; J-Y-P-Z-V-E; R9-Z-P-Y-P-Z-V-E; T-P-L-L-P-T; T-P-L-L-J; J-L-L-J; T-P-L-L- P-Z-R9; R9-Z-P-L-L-P-Z-R9; J-L-L-P-Z-R9; T-P-L-L-P-Z-V-E; E-V-Z-P-L-L-P-Z-V-E; J-L-L-P-Z-V-E; R9-Z-P-L-L-P-Z-V-E; T-P-M-A-L-P-T; T-P-M-A-L-J; J-M-A-L-J; T-P-M-A-L-P-Z-R9; R9-Z-P-M-A-L-P-Z-R9; J-M-A-L-P-Z-R9; T-P-M-A-L-P-Z-V-E; E-V-Z-P-M-A-L-P-Z-V-E; J-M-A-L-P-Z-V-E; J-M-A-L-P-T; R9-Z-P-M-A-L-J; R9-Z-P-M-A-L-P-T; R9-Z-P-M-A-L-P-Z-V-E; E-V-Z-P-M-A-L-J; E-V-Z-P-M-A-L-P-T; E-V-Z-P-M-A-L-P-Z-R9; T-P-M-A-A-M-P-T; T-P-M-A-A-M-J; J-M-A-A-M-J; T-P-M-A-A-M-P-Z-R9; R9-Z-P-M-A-A-M-P-Z-R9; J-M-A-A-M-P-Z-R9; T-P-M-A-A-M-P-Z-V-E; E-V-Z-P-M-A-A-M-P-Z-V-E; J-M-A-A-M-P-Z-V-E; R9-Z-P-M-A-A-M-P-Z-V-E; T-P-M-W-M-P-T; T-P-M-W-M-J; J-M-W-M-J; T-P-M-W-M-P-Z-R9; R9-Z-P-M-W-M-P-Z-R9; J-M-W-M-P-Z-R9; T-P-M-W-M-P-Z-V-E; E-V-Z-P-M-W-M-P-Z-V-E; J-M-W-M-P-Z-V-E; R9-Z-P-M-W-M-P-Z-V-E; T-

P-M-M-P-T; T-P-M-M-J; J-M-M-J; T-P-M-M-P-Z-R9; R9-Z-P-M-M-P-Z-R9; J-M-M-P-Z-R9; T-P-M-M-P-Z-V-E; E-V-Z-P-M-M-P-Z-V-E; J-M-M-P-Z-V-E; R9-Z-P-M-M-P-Z-V-E; or a pharmaceutically acceptable salt thereof.

160. The compound of any one of claims 1-159 wherein the compound of formula (I) is a compound of formula (Ia), (Ib), (Ic), (Id), or (Ie).

161. The compound of any one of claims 1-160 which is a prodrug or a pharmaceutically acceptable salt thereof.

162. A pharmaceutical composition comprising the compound as described in any of claims 1-160 or a pharmaceutically acceptable salt, or prodrug thereof; and at least one pharmaceutically acceptable carrier.

163. The pharmaceutical composition according to claim 162 for use in treating disorders associated with HCV.

164. The pharmaceutical composition of claim 162, further comprising at least one additional therapeutic agent.

165. The pharmaceutical composition of claim 164, wherein said additional therapeutic agent is selected from the group consisting of interferons, ribavirin analogs, NS3 protease inhibitors, NS5b polymerase inhibitors, alpha-glucosidase 1 inhibitors, hepatoprotectants, non-nucleoside inhibitors of HCV, and other drugs for treating HCV.

166. The pharmaceutical composition according to claim 162, further comprising a nucleoside analogue.

167. The pharmaceutical composition according to claim 166, further comprising an interferon or pegylated interferon.

168. The pharmaceutical composition according to claim 167, wherein said nucleoside analogue is selected from ribavirin, viramidine, levovirin, a L-nucleoside, and isatoribine and said interferon is α-interferon or pegylated interferon.

169. A method of treating disorders associated with hepatitis C, said method comprising administering to an individual a pharmaceutical composition which comprises a therapeutically effective amount of the compound as described in any of claims 1-160 or a pharmaceutically acceptable salt, or prodrug thereof.

170. A compound as described in any of claims 1-160 or a pharmaceutically acceptable salt, or prodrug thereof for use in medical therapy.

171. Use of a compound as described in any one of claims 1-160 or a pharmaceutically acceptable salt, or prodrug thereof for preparing a medicament for treating hepatitis C or a hepatitis C associated disorder in an animal.

172. A compound as described in any of claims 1-160 or a pharmaceutically acceptable salt, or prodrug thereof for use in the prophylactic or therapeutic treatment of hepatitis C or a hepatitis C associated disorder.

173. A novel compound or synthetic method as described herein.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/034600

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/14 C07D403/04 C07D403/14 C07D405/14 C07D409/14
C07D413/04 C07D417/04 C07D417/14 C07D495/04
ADD. A61K31/4188 A61K31/4178 A61P31/12
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/021927 A2 (SQUIBB BRISTOL MYERS CO [US]; BACHAND CAROL [CA]; BELEMA MAKONEN [US];) 21 February 2008 (2008-02-21)	20-173
A	claims 1, 41 and examples	1-19
E	WO 2010/065668 A1 (PRESIDIO PHARMACEUTICALS INC [US]; LI LEPING [US]; ZHONG MIN [US]) 10 June 2010 (2010-06-10) claims 1, 105 and examples	20-173
E	WO 2010/065681 A1 (PRESIDIO PHARMACEUTICALS INC [US]; LI LEPING [US]; ZHONG MIN [US]) 10 June 2010 (2010-06-10) claims 1, 64 and examples	20-173

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 September 2010	09/09/2010

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Sahagún Krause, H

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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X,P	WO 2010/017401 A1 (SQUIBB BRISTOL MYERS CO [US]; BELEMA MAKONEN [US]; GOOD ANDREW C [US];) 11 February 2010 (2010-02-11)	20-173
Y,P	claims 1, 23 and examples	1-19
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X	WO 2008/021928 A2 (SQUIBB BRISTOL MYERS CO [US]; BACHAND CAROL [CA]; BELEMA MAKONEN [US];) 21 February 2008 (2008-02-21) claims 1 and 25	20-173
X,P	WO 2009/102568 A1 (SQUIBB BRISTOL MYERS CO [US]; BACHAND CAROL [CA]; BELEMA MAKONEN [US];) 20 August 2009 (2009-08-20)	20-173
Y,P	claims 1, 20 and examples	1-19

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2010/034600

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