Supporting Information

Discovery of Quinoxaline-Based P1–P3 Macrocyclic NS3/4A Protease Inhibitors with Potent Activity Against Drug-Resistant HCV Variants

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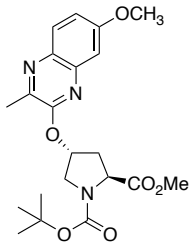
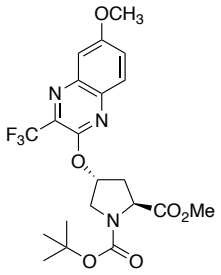
1-(*tert*-Butyl) 2-methyl (2*S*,4*R*)-4-((7-methoxy-3-methylquinoxalin-2-yl)oxy)pyrolidine-1,2-dicarboxylate (55).



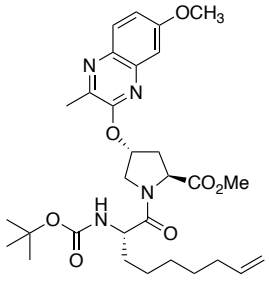
A solution of 7-methoxy-3-methylquinoxalin-2(1*H*)-one **53** (6.20 g, 32.6 mmol) in anhydrous NMP (100 mL) was treated with Cs_2CO_3 (16.0 g, 49.0 mmol). After stirring the reaction mixture at room temperature for 15 min, activated *cis*-hydroxyproline derivative **52** (14.0 g, 30.2 mmol) was added in one portion. The reaction mixture was heated to 55 °C, stirred for 4 h, and then another portion of activated *cis*-hydroxyproline (1.0 g, 2.15 mmol) was added. The resulting reaction mixture was stirred at 55 °C for additional 2 h, cooled to room temperature, quenched with aqueous 1 N HCl solution (250 mL), and extracted with EtOAc (400 mL). The organic fraction was washed successively with saturated aqueous $NaHCO_3$ and NaCl (250 mL each), dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue was purified by flash column chromatography (RediSep Gold column, 2 × 80 g, gradient elution with 0–60% EtOAc/hexanes) to provide **55** (10.0 g, 74%) as a white foamy solid. ^{1}H NMR (500 MHz, $CDCl_3$) (mixture of rotamers, major rotamer) δ 7.80 (d, J = 9.0 Hz, 1 H), 7.17 (dd, J = 9.0, 3.0 Hz, 1 H), 7.11 (d, J = 2.5 Hz, 1 H), 5.71 (br s, 1 H), 4.48 (t, J = 8.0 Hz, 1 H), 3.99–3.91 (m, 4 H), 3.87 (d, J = 12.5 Hz, 1 H), 3.78 (s, 3 H), 2.67–2.58 (m, 1 H), 2.56 (s, 3 H), 2.43–2.37 (m, 1 H), 1.43 (s, 9 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.36, 160.24, 155.51, 153.81, 144.60, 141.04, 134.22, 128.95, 118.63, 105.95, 80.54, 73.59, 58.20, 55.68, 52.48, 52.20, 36.70, 28.26, 19.93 ppm; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{28}N_3O_6$, 418.1973; found 418.1976.

1-(*tert*-Butyl) 2-methyl (2*S*,4*R*)-4-((6-methoxy-3-(trifluoromethyl)quinoxalin-2-yl)oxy)pyrrolidine-1,2-dicarboxylate (56).



The same procedure was used as described above for compound **55**. 6-Methoxy-3-(trifluoromethyl)quinoxalin-2(1*H*)-one **54** (4.76 g, 19.5 mmol) in NMP (65 mL) was treated with Cs_2CO_3 (9.80 g, 30.0 mmol) and proline derivative **52** (9.0 g, 19.3 mmol) to provide **56** (6.50 g, 71%) as a pale-yellow foamy solid. ^{1}H NMR (500 MHz, $CDCl_3$) (mixture of rotamers, major rotamer) δ 7.77 (d, J = 9.0 Hz, 1 H), 7.48−7.43 (m, 2 H), 5.76 (br s, 1 H), 4.50 (t, J = 8.0 Hz, 1 H), 3.97−3.91 (m, 5 H),3.78 (s, 3 H), 2.69−2.64 (m, 1 H), 2.41−2.34 (m, 1 H), 1.42 (s, 9 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.43, 159.58, 153.98, 152.11, 138.39, 137.22, 127.99, 125.73, 120.70 (q, J = 273.4 Hz), 107.64, 80.69, 74.62, 58.27, 56.02, 52.32, 52.11, 36.70, 28.34 ppm; ^{19}F NMR (470 MHz, $CDCl_3$) δ −67.73 ppm; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{21}H_{25}F_3N_3O_6$, 472.1690; found, 472.1689.

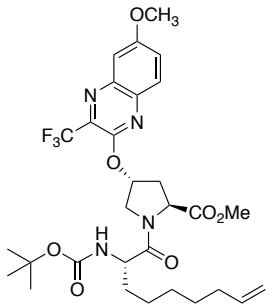
Methyl (2*S*,4*R*)-1-((*S*)-2-((*tert*-butoxycarbonyl)amino)non-8-enoyl)-4-((7-methoxy-3-methylquinoxalin-2-yl)oxy)pyrrolidine-2-carboxylate (60).



A solution of P2 intermediate **55** (10.0 g, 24.0 mmol) in anhydrous CH_2Cl_2 (50 mL) was treated with a solution of 4 N HCl in 1,4-dioxane (100 mL). After stirring the reaction mixture at room temperature for 3 h, solvents were evaporated under reduced pressure, and the residue was dried under high vacuum. The pale-yellow solid was triturated with diethyl ether (3 × 25 mL) and dried under high vacuum to yield the amine salt **57** (8.50 g, 100%) as an off-white solid.

A mixture of amine salt **57** (8.50 g, 24.0 mmol) and (*S*)-2-((*tert*-butoxycarbonyl)amino)non-8-enoic acid **59** (6.70 g, 24.7 mmol) in anhydrous DMF (110 mL) was treated with DIEA (19.2 mL, 110 mmol) and HATU (14.1 g, 37.1 mmol). The resulting reaction mixture was stirred at room temperature for 4 h, then diluted with EtOAc (500 mL), and washed successively with aqueous 0.5 N HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl (300 mL each). The organic portion was dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue was purified by flash column chromatography (RediSep Gold column, 2 × 80 g, gradient elution with 0–60% EtOAc/hexanes) to provide **60** (10.9 g, 80%) as a white foamy solid. ^{1}H NMR (500 MHz, $CDCl_3$) (mixture of rotamers, major rotamer) δ 7.81 (d, J = 9.0 Hz, 1 H), 7.18 (dd, J = 9.0, 2.5 Hz, 1 H), 7.12 (d, J = 2.5 Hz, 1 H), 5.84–5.75 (m, 2 H), 5.21 (d, J = 8.5 Hz, 1 H), 5.01–4.92 (m, 2 H), 4.75 (t, J = 8.0 Hz, 1 H), 4.38 (q, J = 7.5 Hz, 1 H), 4.18 (d, J = 11.5 Hz, 1 H), 4.06 (dd, J = 12.0, 4.5 Hz, 1 H), 3.94 (s, 3 H), 3.77 (s, 3 H), 2.69–2.64 (m, 1 H), 2.54 (s, 3 H), 2.41–2.35 (m, 1 H), 2.04 (app q, J = 7.0 Hz, 2 H), 1.80–1.75 (m, 1 H), 1.63–1.55 (m, 1 H), 1.46–1.24 (m, 15 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.13, 171.78, 160.27, 155.40, 155.27, 144.62, 140.89, 138.96, 134.39, 129.03, 118.73, 114.35, 105.99, 79.61, 74.30, 57.97, 55.66, 52.67, 52.43, 51.83, 34.94, 33.65, 32.66, 28.91, 28.74, 28.25, 24.68, 19.87 ppm; HRMS(ESI) *m/z*: $[M + H]^+$calcd for $C_{30}H_{43}N_4O_7$, 571.3126; found 571.3128.

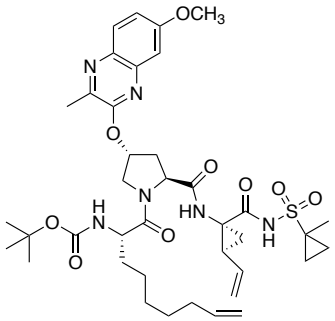
Methyl (2*S*,4*R*)-1-((*S*)-2-((*tert*-butoxycarbonyl)amino)non-8-enoyl)-4-((6-methoxy-3-(trifluoromethyl)quinoxalin-2-yl)oxy)pyrrolidine-2-carboxylate (61).



The same procedure was used as described above for compound **60**. Compound **56** (6.0 g, 12.7 mmol) was treated with 4 N HCl (40 mL) to afford amine salt **58** (5.10 g,12.5 mmol), which was coupled with acid **59** (3.80 g, 14.0 mmol) using DIEA (9.25 mL, 56.0 mmol) and HATU (7.60 g, 20.0 mmol) to provide **61** (6.40 g, 82%) as a pale-yellow foamy solid. ^{1}H NMR (500MHz, $CDCl_3$) (mixture of rotamers, major rotamer) δ 7.78 (d, J = 9.0Hz, 1 H), 7.48 (dd, J = 9.0, 2.5 Hz, 1 H),

7.44 (d, J = 2.5 Hz, 1 H), 5.86 (br s, 1 H), 5.84−5.78 (m, 1 H), 5.18 (d, J = 9.0 Hz, 1 H), 5.01−4.92 (m, 2 H), 4.75 (t, J = 8.0 Hz, 1 H), 4.35 (q, J = 7.5 Hz, 1 H), 4.19 (d, J = 12.0 Hz, 1 H), 4.08 (dd, J = 11.5, 4.5 Hz, 1 H), 3.95 (s, 3 H), 3.78 (s, 3 H), 2.70−2.65 (m, 1 H), 2.41−2.35 (m, 1 H), 2.04 (app q, J= 7.0 Hz, 2 H), 1.80−1.75 (m, 1 H), 1.60−1.54 (m, 1 H), 1.45−1.28 (m, 15 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.10, 171.60, 159.99, 155.37, 151.78, 138.98, 138.41, 136.93, 134.40 (q, J = 36.3 Hz), 127.85, 125.66, 120.53 (q, J = 273.4 Hz), 114.33, 107.54, 79.58, 75.05, 57.83, 55.91, 52.44, 52.33, 51.75, 34.77, 33.65, 32.70, 28.91, 28.73, 28.18, 24.70 ppm; ^{19}F NMR (470 MHz, CDCl3) δ −67.73 ppm; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{30}H_{40}F_3N_4O_7$, 625.2844; found, 625.2844.

***tert*-Butyl ((*S*)-1-((2*S*,4*R*)-4-((7-methoxy-3-methylquinoxalin-2-yl)oxy)-2-(((1*R*,2*S*)-1-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-2-vinylcyclopropyl)carbamoyl)pyrolidine-1-yl)-1-oxonon-8-en-2-yl)carbamate (65).**

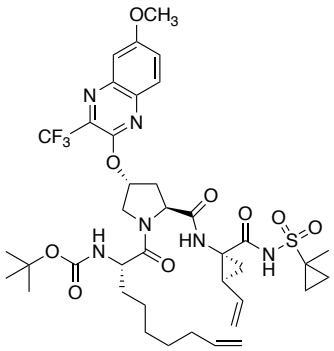


A solution of ester **60** (6.0 g, 10.5 mmol) in THF-H_2O mixture (1:1, 150 mL) was treated with LiOH.H_2O (1.55 g, 36.9 mmol). The resulting reaction mixture was stirred at room temperature for 24 h. The reaction mixture was cooled to ~5 °C, acidified to a pH of 2.0 by slow addition of aqueous 0.25 N HCl (~ 200 mL), and extracted with EtOAc (2 × 400 mL). The organic portions were washed separately with saturated aqueous NaCl (200 ml), dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The gummy residue was dissolved in $CHCl_3$ (50 mL), concentrated under reduced pressure, and the residue was dried under high vacuum overnight to yield the acid **62** (5.80 g, 99%) as a white solid.

A mixture of acid **62** (5.57 g, 10.0 mmol) and amine salt **64** (3.10 g, 11.0 mmol) in anhydrous DMF (100 mL) was treated with DIEA (6.70 mL, 40.5 mmol) and HATU (5.70 g, 15.0 mmol). The resulting reaction mixture was stirred at room temperature for 2.5 h, then diluted with EtOAc (400 mL) and washed successively with aqueous 0.5 N HCl, saturated aqueous $NaHCO_3$, and

saturated aqueous NaCl (250 mL each). The organic portion was dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue was purified by flash column chromatography (RediSep Gold column, 2 × 80 g, gradient elution with 20–90% EtOAc/hexanes) to provide the *bis*-olefin compound **65** (6.50 g, 83%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.02 (s, 1 H), 7.81 (d, J = 8.8 Hz, 1 H), 7.18 (dd, J = 8.8, 2.8 Hz, 1 H), 7.13 (d, J = 2.8 Hz, 1 H), 7.11 (s, 1 H), 5.88 (br s, 1 H), 5.82–5.72 (m, 2 H), 5.42 (d, J = 9.2 Hz, 1 H), 5.26 (d, J = 17.2 Hz, 1 H), 5.14 (d, J = 11.6 Hz, 1 H), 5.00–4.90 (m, 2 H), 4.50 (t, J = 8.4 Hz, 1 H), 4.39–4.33 (m, 1 H), 4.18 (d, J = 11.6 Hz, 1 H), 4.02 (dd, J = 11.6, 4.0 Hz, 1 H), 3.93 (s, 3 H), 2.58–2.50 (m, 5 H), 2.10 (q, J = 8.4 Hz, 1 H), 2.05–1.98 (m, 3 H), 1.73–1.58 (m, 4 H), 1.49 (s, 3 H), 1.44–1.24 (m, 16 H), 0.92–0.86 (m, 1 H), 0.84–0.78 (m, 1 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.65, 172.52, 167.55, 160.31, 155.70, 155.16, 144.41, 140.87, 138.83, 134.33, 132.61, 128.96, 118.87, 118.54, 114.41, 105.96, 79.73, 74.59, 60.30, 55.67, 53.15, 52.37, 41.73, 36.56, 35.16, 34.25, 33.62, 32.24, 28.71, 28.67, 28.26, 25.31, 23.42, 19.84, 18.37, 14.27, 13.26 ppm; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{39}H_{55}N_6O_9S$, 783.3746; found 783.3734.

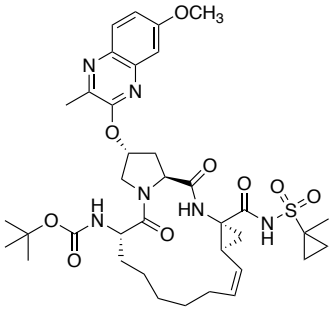
tert-Butyl ((*S*)-1-((2*S*,4*R*)-4-((6-methoxy-3-(trifluoromethyl)quinoxalin-2-yl)oxy)-2-(((1*R*,2*S*)-1-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-2-vinylcyclopropyl)carbamoyl)pyrrolidin-1-yl)-1-oxonon-8-en-2-yl)carbamate (66).



The same procedure was used as described above for compound **65**. Compound **61** (8.14 g, 13.0 mmol) was treated with $LiOH.H_2O$ (1.92 g, 45.6 mmol). to afford acid as a white solid **63** (7.5 g, 12.5 mmol), which was coupled with amine salt **64** (3.91 g, 13.9 mmol) using DIEA (8.62 mL, 49.2 mmol) and HATU (7.31 g, 19.2 mmol) to provide the bis-olefin compound **66** (8.10 g, 77%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.01 (s, 1 H), 7.80 (d, J = 9.2 Hz, 1 H), 7.49 (dd, J = 9.2, 2.8 Hz, 1 H), 7.45 (d, J = 2.8 Hz, 1 H), 7.01 (s, 1 H), 5.93 (br s, 1 H), 5.86–5.71 (m, 2 H), 5.33 (d, J = 8.8 Hz, 1 H), 5.28 (d, J = 15.8 Hz, 1 H), 5.15 (d, J = 11.4 Hz, 1 H), 5.00–4.91 (m, 2

H), 4.53–4.41 (m, 1 H), 4.32 (td, J = 8.8, 4.8 Hz, 1 H), 4.21 (d, J = 12.0 Hz, 1 H), 4.02 (dd, J = 11.9, 3.9 Hz, 1 H), 3.95 (s, 3 H), 2.78–2.43 (m, 2 H), 2.14 (q, J = 8.8 Hz, 1 H), 2.05–2.01 (m, 3 H), 1.78–1.55 (m, 4 H), 1.49 (s, 3 H), 1.47–1.23 (m, 16 H), 0.91–0.80 (m, 2 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.87, 172.37, 167.59, 159.77, 155.79, 151.77, 139.04, 138.61, 137.06, 134.42 (q, J = 36.0 Hz), 132.76, 128.02, 125.92, 120.75 (d, J = 275.3 Hz), 118.67, 114.52, 107.67, 79.84, 75.50, 60.48, 56.06, 53.01, 52.53, 41.90, 36.73, 35.37, 34.32, 33.78, 32.42, 28.84, 28.81, 28.34, 25.48, 23.61, 18.55, 14.35, 13.52 ppm; ^{19}F NMR (470 MHz, $CDCl_3$) δ −67.63 ppm; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{39}H_{52}F_3N_6O_9S$, 837.3463; found 837.3433.

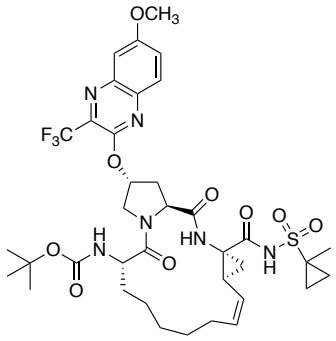
***tert*-Butyl ((2*R*,6*S*,13a*S*,14a*R*,16a*S*,*Z*)-2-((7-methoxy-3-methylquinoxalin-2-yl)oxy)-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[*e*]pyrrolo[1,2-*a*][1,4]diazacyclopentadecin-6-yl)carbamate (2).**



A degassed solution of *bis*-olefin **65** (6.20 g, 7.92 mmol) in 1,2-DCE (1.60 L) was heated to 50 °C under argon, then Zhan catalyst-1B (0.50 g, 0.68 mmol) was added in two portions over 10 min. The resulting reaction mixture was heated to 70 °C and stirred for 6 h. The reaction mixture was cooled to room temperature and solvents were evaporated under reduced pressure. The residue was purified by flash column chromatography (RediSep Gold column, 2 × 80 g, gradient elution with 20–90% EtOAc/hexanes) to yield the P1–P3 macrocyclic product **2** (4.20 g, 70%) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.16 (s, 1 H), 7.82 (d, J = 9.2 Hz, 1 H), 7.19–7.16 (m, 2 H), 6.92 (s, 1 H), 5.88 (br s, 1 H), 5.69 (q, J = 9.2 Hz, 1 H), 5.12 (d, J = 7.6 Hz, 1 H), 4.99 (t, J = 8.8 Hz, 1 H), 4.61 (t, J = 8.0 Hz, 1 H), 4.51 (d, J = 11.2 Hz, 1 H), 4.28–4.22 (m, 1 H), 4.03 (dd, J = 11.2, 4.0 Hz, 1 H), 3.95 (s, 3 H), 2.70–2.50 (m, 6 H), 2.31 (q, J = 8.8 Hz, 1 H), 1.92–1.66 (m, 4 H), 1.60–1.20 (m, 21 H), 0.85–0.78 (m, 2 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.16, 173.33, 166.94, 160.33, 155.32, 155.04, 144.46, 141.03, 134.20, 136.25, 128.66, 124.89, 118.93,

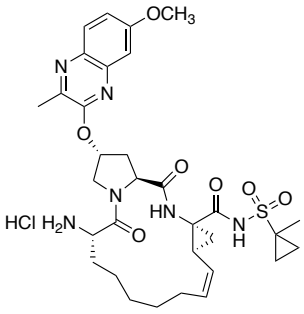
105.98, 79.85, 74.88, 59.46, 55.72, 53.08, 51.97, 44.73, 36.43, 34.61, 32.72, 29.65, 28.15, 27.06, 26.07, 22.21, 20.96, 19.71, 18.17, 14.51, 12.51 ppm; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{37}H_{51}N_6O_9S$, 755.3433; found 755.3404; Anal. HPLC: t_R 13.57 min, purity 99%.

***tert*-Butyl ((2*R*,6*S*,13a*S*,14a*R*,16a*S*,*Z*)-2-((6-methoxy-3-(trifluoromethyl)quinoxalin-2-yl)oxy)-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[*e*]pyrrolo[1,2-*a*][1,4]diazacyclopentadecin-6-yl)carbamate (3).**



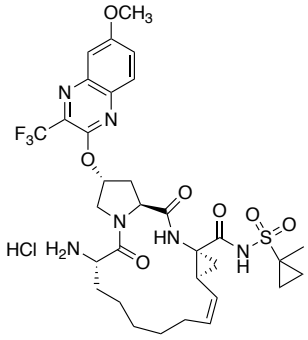
The same procedure was used as described above for compound **2**. Bis-olefin **66** (7.20 g, 8.60 mmol) was treated with Zhan 1B catalyst (0.70 g, 0.95 mmol) in 1,2-DCE (1.50 L) to afford the P1−P3 macrocyclic product **3** (5.10 g, 73%) as an off-white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.13 (s, 1 H), 7.83 (d, J = 9.0 Hz, 1 H), 7.48 (dd, J = 9.0, 2.5 Hz, 1 H), 7.42 (d, J = 2.5 Hz, 1 H), 6.85 (s, 1 H), 5.92 (br s, 1 H), 5.70 (q, J = 8.5 Hz, 1 H), 5.12 (d, J = 8.0 Hz, 1 H), 5.01 (t, J = 9.0 Hz, 1 H), 4.63−4.53 (m, 2 H), 4.24−4.18 (m, 1 H), 4.02 (dd, J = 11.5, 4.0 Hz, 1 H), 3.94 (s, 3 H), 2.71−2.51 (m, 3 H), 2.33 (q, J = 8.5 Hz, 1 H), 1.93−1.75 (m, 4 H), 1.63−1.15 (m, 21 H), 0.86−0.78 (m, 2 H) ppm; ^{13}C NMR (125 MHz,$CDCl_3$) δ 177.17, 173.35, 167.03, 159.60, 155.07, 151.92, 138.43, 137.14, 136.38, 134.49 (q, J = 36.0 Hz), 128.14, 125.68, 125.11, 120.66 (d, J = 274.0 Hz), 107.59, 79.91, 75.70, 59.63, 56.02, 52.88, 52.00, 44.94, 36.58, 34.76, 33.00, 29.74, 28.17, 27.22, 27.17, 26.24, 22.40, 21.16, 18.33, 14.64, 12.70 ppm; ^{19}F NMR (470 MHz, $CDCl_3$) δ −67.77 ppm; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{37}H_{48}F_3N_6O_9S$, 809.3150; found, 809.3129; Anal. HPLC: t_R 15.23 min, purity 99%.

(2*R*,6*S*,13a*S*,14a*R*,16a*S*,*Z*)-6-Amino-2-((7-methoxy-3-methylquinoxalin-2-yl)oxy)-*N*-((1-methylcyclopropyl)sulfonyl)-5,16-dioxo-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydrocyclopropa[*e*]pyrrolo[1,2-*a*][1,4]diazacyclopentadecine-14a(5*H*)-carboxamide hydrochloride (67).



A solution of compound **2** (3.25 g, 4.31 mmol) in anhydrous CH_2Cl_2 (15 mL) was treated with a solution of 4 N HCl in 1,4-dioxane (50 mL). The reaction mixture was stirred at room temperature for 3 h, concentrated under reduced pressure, and the residue was dried under high vacuum. The residue was triturated with diethyl ether (40 mL), and the solid was filtered, washed with Et_2O (2 × 15 mL), and dried under high vacuum to yield the amine salt **67** (2.90 g, 98%) as an off-white solid.

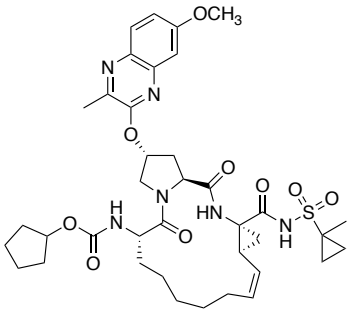
(2*R*,6*S*,13a*S*,14a*R*,16a*S*,*Z*)-6-Amino-2-((6-methoxy-3-(trifluoromethyl)quinoxalin-2-yl) oxy)-*N*-((1-methylcyclopropyl)sulfonyl)-5,16-dioxo-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydrocyclopropa[*e*]pyrrolo[1,2-*a*][1,4]diazacyclopentadecine-14a(5*H*)-carboxamide hydrochloride (68).



A solution of compound **3** (5.10 g, 6.85 mmol) in anhydrous CH_2Cl_2 (20 mL) was treated with a solution of 4 N HCl in 1,4-dioxane (70 mL). The reaction mixture was stirred at room temperature for 3 h, concentrated under reduced pressure, and the residue was dried under high vacuum. The

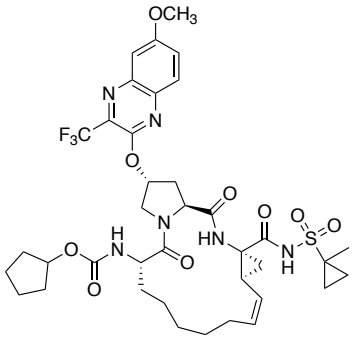
residue was triturated with diethyl ether (40 mL), and the solid was filtered, washed with Et_2O (2 × 20 mL), and dried under high vacuum to yield the amine salt **68** (4.50 g, 96%) as an off-white solid.

Cyclopentyl ((2*R*,6*S*,13a*S*,14a*R*,16a*S*,*Z*)-2-((7-methoxy-3-methylquinoxalin-2-yl)oxy)-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[*e*]pyrrolo[1,2-*a*][1,4]diazacyclopentadecin-6-yl)carbamate (4).



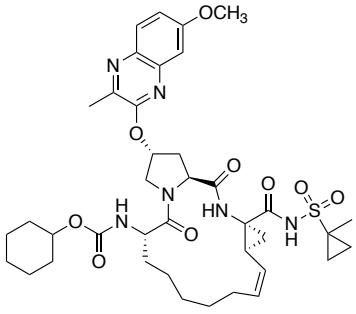
A solution of the above amine salt **67** (0.44 g, 0.58 mmol) in anhydrous CH_3CN (15 mL) was treated with DIEA (0.38 mL, 2.30 mmol) and *N*-(cyclopentyloxycarbonyloxy)-succinimide (0.15 g, 0.66 mmol). The reaction mixture was stirred at room temperature for 36 h, then concentrated under reduced pressure and dried under high vacuum. The residue was purified by flash column chromatography (RediSep Gold column, 24 g, gradient elution with 50–90% EtOAc/hexanes) to provide the target compound **4** (0.32 g, 72%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.17 (s, 1 H), 7.79 (d, J = 10.0 Hz, 1 H), 7.20–7.16 (m, 2 H), 6.96 (s, 1 H), 5.91 (br s, 1 H), 5.69 (q, J = 8.8 Hz, 1 H), 5.25 (d, J = 8.0 Hz, 1 H), 4.98 (t, J = 9.6 Hz, 1 H), 4.88–4.83 (m, 1 H), 4.61 (t, J = 8.0 Hz, 1 H), 4.43 (d, J = 11.2 Hz, 1 H), 4.34–4.27 (m, 1 H), 4.05 (dd, J = 10.8, 4.0 Hz, 1 H), 3.94 (s, 3 H), 2.70–2.48 (m, 5 H), 2.30 (q, J = 8.8 Hz, 1 H), 1.93–1.23 (m, 25 H), 0.85–0.78 (m, 2 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.20, 173.01, 167.0, 160.22, 155.68, 155.31, 144.67, 140.96, 136.21, 134.27, 128.85, 124.86, 118.79, 105.98, 77.89, 74.67, 59.48, 55.72, 53.05, 52.20, 44.67, 36.43, 34.58, 32.72, 32.65, 32.57, 29.64, 27.17, 27.04, 26.09, 23.59, 23.57, 22.18, 20.91, 19.85, 18.17, 14.49, 12.51 ppm; HRMS (ESI) *m/z*: calcd for $C_{38}H_{51}N_6O_9S$ $[M + H]^+$ 767.3433; found 767.3408. Anal. HPLC: t_R 13.88 min, purity 98%.

Cyclopentyl ((2*R*,6*S*,13a*S*,14a*R*,16a*S*,*Z*)-2-((7-methoxy-3-(trifluoromethyl)quinoxalin-2-yl)oxy)-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[*e*]pyrrolo[1,2-*a*][1,4]diazacyclopentadecin-6-yl)carbamate (5).



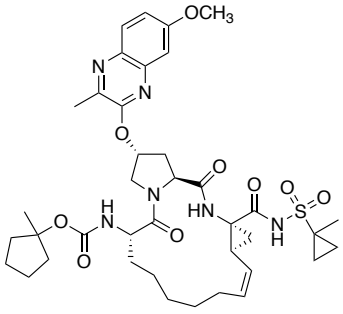
The same procedure was used as described above for compound **4**. A solution of amine salt **68** (0.40 g, 0.52 mmol) in CH_3CN (20 mL) was treated with DIEA (0.45 mL, 2.58 mmol) and *N*-(cyclopentyloxycarbonyloxy)-succinimide (0.15 g, 0.66 mmol) to provide the target compound **5** (0.30 g, 70%) as a white solid. ^{1}H NMR (400 MHz, CDCl3) δ 10.18 (s, 1 H), 7.83 (d, J = 9.6 Hz, 1 H), 7.48 (dd, J = 8.8, 2.8 Hz, 1 H), 7.41 (d, J = 2.8 Hz, 1 H), 6.94 (s, 1 H), 5.94 (s, 1 H), 5.70 (q, J = 8.8 Hz, 1 H), 5.28 (d, J = 7.6 Hz, 1 H), 5.00 (t, J = 8.8 Hz, 1 H), 4.74–4.69 (m, 1 H), 4.60 (t, J = 7.6, 1 H), 4.54 (d, J = 12.0, 1 H), 4.25–4.19 (m, 1 H), 4.00 (dd, J = 11.6, 3.6 Hz, 1 H), 3.94 (s, 3 H), 2.68–2.50 (m, 3 H), 2.31 (q, J = 8.4 Hz, 1 H), 1.92–1.20 (m, 24 H), 0.85–0.78 (m, 2 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.33, 173.25, 167.13, 159.68, 155.84, 152.08, 138.56, 137.24, 136.44, 134.75 (q, J = 35.2 Hz), 128.25, 125.74, 125.21, 120.86 (d, J = 274.0 Hz), 107.62, 78.02, 75.71, 59.73, 56.12, 52.89, 52.34, 45.03, 36.65, 34.73, 32.93, 32.82, 32.64, 29.83, 27.26, 27.21, 26.29, 23.81, 23.75, 22.52, 21.23, 18.42, 14.73, 12.76 ppm. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{38}H_{48}F_3N_6O_9S$, 821.3150; found 821.3133. Anal. HPLC: t_R 15.65 min, purity 97%.

Cyclohexyl ((2*R*,6*S*,13a*S*,14a*R*,16a*S*,*Z*)-2-((7-methoxy-3-methylquinoxalin-2-yl)oxy)-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[*e*]pyrrolo[1,2-*a*][1,4]diazacyclopentadecin-6-yl)carbamate (17).



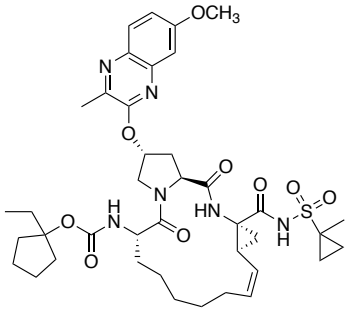
The same procedure was used as described above for compound **7**. A mixture of amine salt **67** (0.10 g, 0.15 mmol) in CH_3CN (5 mL) was treated with DIEA (0.18 mL, 1.0 mmol) and cyclohexyl (4-nitrophenyl) carbonate **69m** (0.043 g, 0.16 mmol) to provide the target compound **17** (0.11 g, 94%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.13 (s, 1 H), 7.80 (d, J = 9.5 Hz, 1 H), 7.22–7.16 (m, 2 H), 6.86 (s, 1 H), 5.91 (br s, 1 H), 5.71 (q, J = 8.5 Hz, 1 H), 5.25 (d, J = 7.5 Hz, 1 H), 5.01 (t, J = 9.5 Hz, 1 H), 4.61 (t, J = 7.5 Hz, 1 H), 4.46 (d, J = 11.0 Hz, 1 H), 4.43–4.34 (m, 1 H), 4.30 (t, J = 7.5 Hz, 1 H), 4.05 (dd, J = 11.0, 4.0 Hz, 1 H), 3.95 (s, 3 H), 2.73–2.66 (m, 1 H), 2.64–2.49 (m, 5 H), 2.31 (q, J = 8.5 Hz, 1 H), 2.15 (q, J = 9.0 Hz, 2 H), 1.95–1.55 (m, 9 H), 1.54–1.22 (m, 15 H), 0.86–0.79 (m, 2 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.26, 173.27, 166.98, 160.40, 155.59, 155.48, 144.81, 141.11, 136.32, 134.45, 129.04, 125.05, 118.91, 106.17, 74.84, 73.83, 59.64, 55.86, 53.18, 52.41, 44.89, 38.76, 36.60, 34.67, 32.74, 32.10, 32.04, 29.86, 27.28, 27.17, 26.20, 25.43, 23.94, 22.41, 21.12, 19.94, 18.35, 14.64, 12.72 ppm; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{39}H_{53}N_6O_9S$, 781.3589; found 781.3565; Anal. HPLC: t_R 12.54 min, purity 98.9%.

1-Methylcyclopentyl ((2*R*,6*S*,13a*S*,14a*R*,16a*S*,*Z*)-2-((7-methoxy-3-methylquinoxalin-2-yl)oxy)-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[*e*]pyrrolo[1,2-*a*][1,4]diazacyclopentadecin-6-yl) carbamate (18).



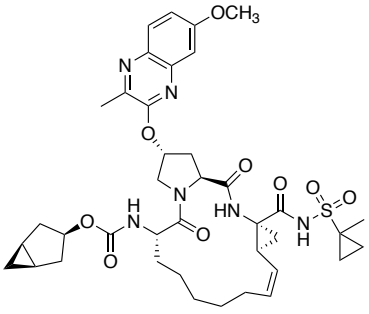
The same procedure was used as described above for compound **7**. A solution of amine salt **67** (0.25 g, 0.36 mmol) in CH_3CN (10 mL) was treated with DIEA (0.45 mL, 2.58 mmol) and 1-methylcyclopentyl (4-nitrophenyl) carbonate **69n** (0.10 g, 0.37 mmol) to provide the target compound **18** (0.24 g, 85%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.13 (s, 1 H), 7.79 (d, J = 10.0 Hz, 1 H), 7.18–7.16 (m, 2 H), 6.87 (s, 1 H), 5.89 (br s, 1 H), 5.70 (q, J = 9.0 Hz, 1 H), 5.12 (d, J = 7.5 Hz, 1 H), 5.00 (t, J = 9.0 Hz, 1 H), 4.61 (t, J = 7.5 Hz, 1 H), 4.50 (d, J = 11.5 Hz, 1 H), 4.28 (t, J = 8.0 Hz, 1 H), 4.04 (dd, J = 11.0, 4.0 Hz, 1 H), 3.95 (s, 3 H), 2.69–2.50 (m, 6 H), 2.31 (q, J = 8.5 Hz, 1 H), 1.93–1.76 (m, 6 H), 1.65–1.25 (m, 21 H), 0.85–0.79 (m, 2 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.11, 173.33, 166.90, 160.27, 155.31, 155.20, 144.50, 140.98, 136.24, 134.31, 128.89, 124.92, 118.78, 106.03, 89.54, 74.79, 59.47, 55.72, 53.11, 52.03, 44.75, 39.28, 39.08, 36.47, 34.61, 32.79, 29.71, 27.11, 27.06, 26.09, 24.59, 23.77, 22.26, 21.00, 19.86, 18.20, 14.52, 12.57 ppm; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{39}H_{53}N_6O_9S^+$, 781.3589; found 781.3570; Anal. HPLC: t_R 12.57 min, purity 100%.

1-Ethylcyclopentyl ((2*R*,6*S*,13a*S*,14a*R*,16a*S*,*Z*)-2-((7-methoxy-3-methylquinoxalin-2-yl)oxy)-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[*e*]pyrrolo[1,2-*a*][1,4]diazacyclopentadecin-6-yl)carbamate (19).



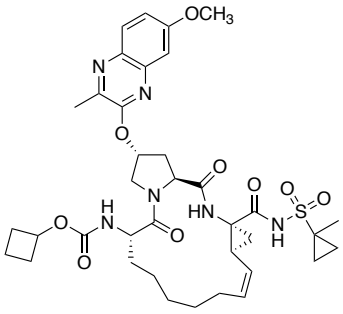
The same procedure was used as described above for compound **7**. A solution of amine salt **67** (0.12 g, 0.17 mmol) in CH_3CN (8 mL) was treated with DIEA (0.21 mL, 1.21 mmol) and 1-ethylcyclopentyl (4-nitrophenyl) carbonate **69o** (0.05 g, 0.18 mmol) to provide the target compound **19** (0.11 g, 81%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.12 (s, 1 H), 7.85–7.83 (d, J = 9.6 Hz, 1 H), 7.19 (dd, J = 4.7, 2.2 Hz, 2 H), 6.86 (s, 1 H), 5.89 (br s, 1 H), 5.70 (dd, J = 18.2, 8.7 Hz, 1 H), 5.15 (d, J = 7.3 Hz, 1 H), 5.05–4.94 (m, 1 H), 4.61 (t, J = 7.7 Hz, 1 H), 4.52 (d, J = 11.4 Hz, 1 H), 4.29–4.25 (m, 1 H), 4.04 (dd, J = 11.3, 3.8 Hz, 1 H), 3.95 (s, 3 H), 2.84–2.67 (m, 2 H), 2.66–2.50 (m, 3 H), 2.31 (q, J = 8.7 Hz, 1 H), 1.93–1.67 (m, 8 H), 1.68–1.22 (m, 19 H), 0.90–0.79 (m, 2 H), 0.76 (t, J = 7.4 Hz, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.21, 173.51, 166.99, 160.58, 155.49, 155.26, 144.50, 141.24, 136.38, 128.66, 125.06, 119.17, 106.18, 93.18, 75.09, 59.56, 55.89, 53.56, 53.22, 52.18, 44.90, 38.76, 37.34, 37.32, 36.61, 34.74, 32.94, 31.58, 30.25, 29.85, 27.21, 26.21, 24.14, 22.42, 21.13, 19.72, 18.34, 14.67, 12.71, 8.90 ppm; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{40}H_{55}N_6O_9S$, 795.3746; found 795.3714; Anal. HPLC: t_R 13.38 min, purity 98%.

(1*R*,3*R*,5*S*)-Bicyclo[3.1.0]hexan-3-yl ((2*R*,6*S*,13a*S*,14a*R*,16a*S*,*Z*)-2-((7-methoxy-3-methylquinoxalin-2-yl)oxy)-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[*e*]pyrrolo[1,2-*a*][1,4]diazacyclopentadecin-6-yl)carbamate (20).



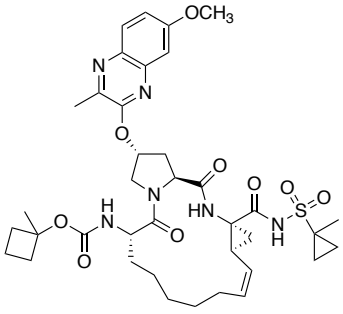
The same procedure was used as described above for compound **7**. A solution of amine salt **67** (0.12 g, 0.17 mmol) in CH_3CN (8 mL) was treated with DIEA (0.23 mL, 1.22 mmol) and (1*R*,3*R*,5*S*)-bicyclo[3.1.0]hexan-3-yl (4-nitrophenyl) carbonate **69p** (0.05 g, 0.19 mmol) to provide the target compound **20** (0.12 g, 91%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.11 (s, 1 H), 7.80 (d, J = 10.0 Hz, 1 H), 7.22–7.16 (m, 2 H), 6.83 (s, 1 H), 5.91 (br s, 1 H), 5.70 (q, J = 8.5 Hz, 1 H), 5.14 (d, J = 7.0 Hz, 1 H), 5.00 (t, J = 9.5 Hz, 1 H), 4.93 (t, J = 6.5 Hz, 1 H), 4.61 (t, J = 7.5 Hz, 1 H), 4.41 (d, J = 11.0 Hz, 1 H), 4.29 (t, J = 8.0 Hz, 1 H), 4.04 (dd, J = 11.0, 3.5 Hz, 1 H), 3.95 (s, 3 H), 2.77–2.53 (m, 1 H), 2.52–2.48 (m, 5 H), 2.30 (q, J = 9.0 Hz, 1 H), 2.10–1.72 (m, 6 H), 1.71–1.20 (m, 16 H), 0.87–0.79 (m, 2 H), 0.42 (dd, J = 12.5, 8.0 Hz, 1 H), 0.26 (d, J = 4.0 Hz, 1 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.21, 173.16, 167.01, 160.40, 155.46, 155.43, 144.82, 141.10, 136.31, 134.47, 129.02, 125.04, 118.93, 106.18, 74.81, 59.63, 55.85, 53.21, 52.36, 44.85, 36.60, 35.80, 34.69, 32.76, 29.84, 27.32, 27.14, 26.20, 22.36, 21.16, 19.99, 18.35, 16.83, 14.62, 12.71, 10.57 ppm; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{39}H_{51}N_6O_9S$, 779.3433; found 779.3411; Anal. HPLC: t_R 11.86 min, purity 97.7%.

Cyclobutyl ((2*R*,6*S*,13a*S*,14a*R*,16a*S*,*Z*)-2-((7-methoxy-3-methylquinoxalin-2-yl)oxy)-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[*e*]pyrrolo[1,2-*a*][1,4]diazacyclopentadecin-6-yl)carbamate (21).



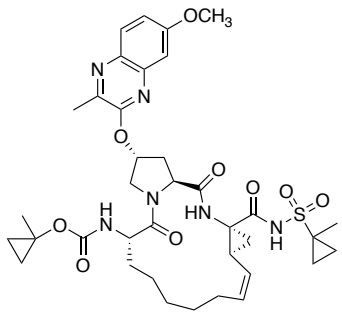
The same procedure was used as described above for compound **7**. A solution of amine salt **67** (0.20 g, 0.29 mmol) in CH_3CN (10 mL) was treated with DIEA (0.35 mL, 2.0 mmol) and cyclobutyl (4-nitrophenyl) carbonate **69q** (0.076 g, 0.32 mmol) to provide the target compound **21** (0.19 g, 87%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.17 (s, 1 H), 7.81 (d, J = 9.5 Hz, 1 H), 7.21–7.17 (m, 2 H), 7.07 (s, 1 H), 5.91 (br s, 1 H), 5.69 (q, J = 8.0 Hz, 1 H), 5.39 (d, J = 7.5 Hz, 1 H), 4.98 (t, J = 9.5 Hz, 1 H), 4.72 (p, J = 7.5 Hz, 1 H), 4.62 (t, J = 7.5 Hz, 1 H), 4.40 (d, J = 11.0 Hz, 1 H), 4.30 (t, J = 7.5 Hz, 1 H), 4.05 (dd, J = 11.5, 4.0 Hz, 1 H), 3.94 (s, 3 H), 2.73–2.64 (m, 1 H), 2.63–2.47 (m, 5 H), 2.30 (q, J = 8.5 Hz, 1 H), 2.24–2.13 (m, 2 H), 1.99–1.65 (m, 8 H), 1.62–1.26 (m, 12 H), 0.85–0.78 (m, 2 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.31, 173.00, 167.12, 160.49, 155.46, 155.23, 144.68, 141.16, 136.28, 134.18, 128.83, 125.01, 119.06, 106.18, 74.89, 69.26, 59.59, 55.87, 53.18, 52.30, 44.80, 36.60, 34.72, 32.69, 30.59, 30.40, 29.79, 27.36, 27.18, 26.24, 22.31, 20.93, 19.83, 18.32, 14.63, 13.25, 12.68 ppm; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{37}H_{49}N_6O_9S$, 753.3276; found 753.3248; Anal. HPLC: t_R 11.07 min, purity 99.4%.

1-Methylcyclobutyl ((2*R*,6*S*,13a*S*,14a*R*,16a*S*,*Z*)-2-((7-methoxy-3-methylquinoxalin-2-yl)oxy)-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[*e*]pyrrolo[1,2-*a*][1,4]diazacyclopentadecin-6-yl)carbamate (22).



The same procedure was used as described above for compound **7**. A solution of amine salt **67** (0.15 g, 0.22 mmol) in CH_3CN (10 mL) was treated with DIEA (0.27 mL, 1.55 mmol) and 1-methylcyclobutyl (4-nitrophenyl) carbonate **69r** (0.06 g, 0.24 mmol) to provide the target compound **22** (0.14 g, 83%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.13 (s, 1 H), 7.80 (d, J = 9.5 Hz, 1 H), 7.23–7.16 (m, 2 H), 6.90 (s, 1 H), 5.89 (br s, 1 H), 5.70 (q, J = 8.5 Hz, 1 H), 5.21 (d, J = 7.5 Hz, 1 H), 5.00 (t, J = 9.5 Hz, 1 H), 4.61 (t, J = 7.5 Hz, 1 H), 4.46 (d, J = 11.5 Hz, 1 H), 4.28 (t, J = 7.5 Hz, 1 H), 4.04 (dd, J = 11.0, 3.5 Hz, 1 H), 3.94 (s, 3 H), 2.73–2.64 (m, 1 H), 2.62–2.49 (m, 5 H), 2.31 (q, J = 9.0 Hz, 1 H), 2.15 (q, J = 10.0 Hz, 2 H), 1.98–1.75 (m, 6 H), 1.73–1.25 (m, 17 H), 0.86–0.78 (m, 2 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.22, 173.30, 167.03, 160.40, 155.42, 154.61, 144.69, 141.10, 136.33, 134.42, 129.01, 125.04, 118.94, 106.16, 79.63, 74.88, 59.58, 55.86, 53.23, 52.14, 44.86, 38.75, 36.60, 35.39, 34.74, 32.91, 29.85, 27.29, 27.18, 26.22, 23.58, 22.37, 21.07, 20.00, 18.34, 14.65, 13.69, 12.71 ppm; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{38}H_{51}N_6O_9S$, 767.3433; found 767.3406; Anal. HPLC: t_R 11.78 min, purity 98.8%.

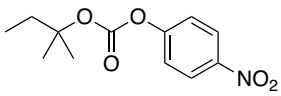
1-Methylcyclopropyl ((2*R*,6*S*,13a*S*,14a*R*,16a*S*,*Z*)-2-((7-methoxy-3-methylquinoxalin-2-yl)oxy)-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[*e*]pyrrolo[1,2-*a*][1,4]diazacyclopentadecin-6-yl)carbamate (23).



The same procedure was used as described above for compound **7**. A solution of amine salt **67** (0.20 g, 0.29 mmol) in CH_3CN (10 mL) was treated with DIEA (0.35 mL, 2.0 mmol) and 1-methylcyclopropyl (4-nitrophenyl) carbonate **69t** (0.076 g, 0.32 mmol) to provide the target compound **23** (0.19 g, 87%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.16 (s, 1 H), 7.79 (d, J = 9.5 Hz, 1 H), 7.23–7.16 (m, 2 H), 7.03 (s, 1 H), 5.91 (br s, 1 H), 5.68 (q, J = 9.0 Hz, 1 H), 5.29 (d, J = 5.0 Hz, 1 H), 4.98 (t, J = 9.5 Hz, 1 H), 4.61 (t, J = 7.5 Hz, 1 H), 4.46 (d, J = 11.5 Hz, 1 H), 4.31 (t, J = 7.5 Hz, 1 H), 4.06 (dd, J = 11.5, 4.0 Hz, 1 H), 3.94 (s, 3 H), 2.70–2.52 (m, 6 H), 2.30 (q, J = 8.5 Hz, 1 H), 1.94–1.71 (m, 5 H), 1.62–1.53 (m, 1 H), 1.50–1.25 (m, 13 H), 0.85–0.79 (m, 2 H), 0.76–0.69 (m, 2 H), 0.56–0.46 (m, 2 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.30, 173,01, 167.15, 160.43, 155.52, 155.45, 144.68, 141.14, 136.30, 134.26, 128.90, 125.00, 118.97, 106.18, 74.88, 59.57, 56.76, 55.86, 53.17, 52.27, 44.79, 38.74, 36.60, 34.76, 32.75, 29.78, 27.31, 27.18, 26.25, 22.29, 21.47, 20.95, 19.71, 18.31, 14.62, 13.04, 12.90, 12.67 ppm; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{37}H_{49}N_6O_9S$, 753.3276; found 753.3248; Anal. HPLC: t_R 10.60 min, purity 99.4%.

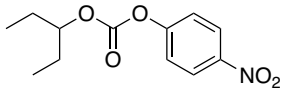
Synthesis of carbonate intermediates 69a–x.

4-Nitrophenyl *tert*-pentyl carbonate (69a).



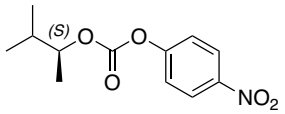
A solution of 2-methylbutan-2-ol (0.50 g, 5.67 mmol) in dichloromethane (30 mL) was cooled to 0 °C and treated with pyridine (1.85 mL, 22.6 mmol). After 10 min, solid 4-nitrobenzene chloroformate (2.30 g, 11.3 mmol) was added in one portion. The resulting reaction mixture was warmed to room temperature and stirred for 48 hours. Solvents were evaporated under reduced pressure; pyridine was removed by azeotrope with heptanes (50 mL). The residue was dried under high vacuumed for 4 h. The solid residue was triturated with EtOAc-hexanes mixture (1:1, 50 mL) and the mixture was stirred at room temperature for 10 min; solvents were carefully decanted; this process was repeated three times. Combined EtOAc-hexanes solution was evaporated to dryness. The residue was purified by flash column chromatography (RediSep Gold column, 40 g, gradient elution with 0–35% EtOAc/hexanes) to provide the compound **69a** (1.30 g, 90%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28–8.24 (m, 2 H), 7.37–7.33 (m, 2 H), 1.87 (q, J = 7.5 Hz, 2 H), 1.53 (s, 6 H), 0.97 (t, J = 7.5 Hz, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.88, 150.59, 145.26, 125.32, 122.05, 87.55, 33.26, 25.16, 8.37 ppm; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{12}H_{16}NO_5$, 254.1023; found 254.1021.

4-Nitrophenyl pentan-3-yl carbonate (69b).



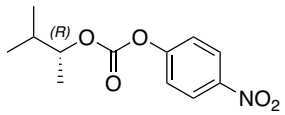
The same procedure was used as described above for compound **69a**. A mixture of pentan-3-ol (0.50 g, 5.67 mmol) and 4-nitrobenzene chloroformate (2.30 g, 11.3 mmol) was treated with pyridine (1.85 mL, 22.6 mmol) to provide the compound **69b** (1.20 g, 84%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29–8.25 (m, 2 H), 7.40–7.36 (m, 2 H), 4.72 (p, J = 6.5 Hz, 1 H), 1.75–1.69 (m, 4 H), 0.98 (t, J = 7.5 Hz, 6 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.89, 152.59, 145.37, 125.38, 121.91, 83.56, 26.38, 9.57 ppm; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{12}H_{16}NO_5$, 254.1023; found 254.1022.

(*S*)-3-Methylbutan-2-yl (4-nitrophenyl) carbonate (69c).



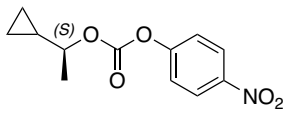
The same procedure was used as described above for compound **69a**. A mixture of (*S*)-3-methylbutan-2-ol (0.45 g, 5.10 mmol) and 4-nitrobenzene chloroformate (2.06 g, 11.3 mmol) was treated with pyridine (1.75 mL, 22.6 mmol) to provide the compound **69c** (1.10 g, 85%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29–8.26 (m, 2 H), 7.40–7.36 (m, 2 H), 4.72 (p, J = 6.5 Hz, 1 H), 1.99–1.90 (m, 1 H), 1.33 (d, J = 6.5 Hz, 3 H), 0.99 (dd, J = 7.0, 3.0 Hz, 6 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.87, 152.37, 145.40, 125.40, 121.95, 81.92, 32.80, 18.05, 17.96, 16.57 ppm; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{12}H_{16}NO_5$, 254.1023; found 254.1018.

(*R*)-3-Methylbutan-2-yl (4-nitrophenyl) carbonate (69d).



The same procedure was used as described above for compound **69a**. A mixture of (*R*)-3-methylbutan-2-ol (0.45 g, 5.10 mmol) and 4-nitrobenzene chloroformate (2.06 g, 11.3 mmol) was treated with pyridine (1.75 mL, 22.6 mmol) to provide the compound **69d** (1.10 g, 85%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29–8.26 (m, 2 H), 7.40–7.37 (m, 2 H), 4.72 (p, J = 6.0 Hz, 1 H), 1.98–1.90 (m, 1 H), 1.33 (d, J = 6.0 Hz, 3 H), 0.99 (dd, J = 6.5, 2.5 Hz, 6 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.87, 152.37, 145.40, 125.40, 121.95, 81.93, 32.80, 18.05, 17.96, 16.57 ppm; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{12}H_{16}NO_5$, 254.1023; found 254.1020.

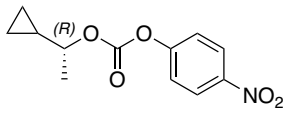
(*S*)-1-Cyclopropylethyl (4-nitrophenyl) carbonate (69e).



The same procedure was used as described above for compound **69a**. A mixture of (1*S*)-1-cyclopropylethan-1-ol (0.25 g, 2.9 mmol) and 4-nitrobenzene chloroformate (1.17 g, 5.8 mmol) was treated with pyridine (0.98 mL, 12.0 mmol) to provide the compound **69e** (0.55 g, 75%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29–8.25 (m, 2 H), 7.41–7.38 (m, 2 H), 4.29 (dq, J = 8.5, 6.0 Hz, 1 H), 1.46 (d, J = 6.5 Hz, 3 H), 1.17–1.09 (m, 1 H), 0.67–0.59 (m, 2 H), 0.55–0.50 (m,

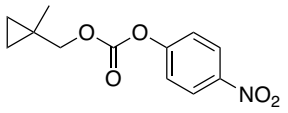
1 H), 0.35–0.30 (m, 1 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.86, 152.32, 145.39, 125.39, 121.92, 82.31, 19.76, 16.27, 4.14, 2.76 ppm; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{12}H_{14}NO_5$, 252.0866; found 252.0865.

(*R*)-1-Cyclopropylethyl (4-nitrophenyl) carbonate (69f).



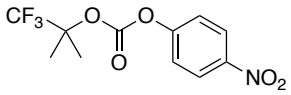
The same procedure was used as described above for compound **69a**. A mixture of (1*R*)-1-cyclopropylethan-1-ol (0.25 g, 2.90 mmol) and 4-nitrobenzene chloroformate (1.17 g, 5.80 mmol) was treated with pyridine (0.98 mL, 12.0 mmol) to provide the compound **69f** (0.56 g, 77%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29–8.25 (m, 2 H), 7.41–7.37 (m, 2 H), 4.29 (dq, J = 8.5, 6.0 Hz, 1 H), 1.46 (d, J = 6.5 Hz, 3 H), 1.17–1.09 (m, 1 H), 0.67–0.59 (m, 2 H), 0.56–0.50 (m, 1 H), 0.35–0.28 (m, 1 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.86, 152.32, 145.39, 125.39, 121.93, 82.32, 19.76, 16.27, 4.14, 2.77 ppm; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{12}H_{14}NO_5$, 252.0866; found 252.0864.

(1-Methylcyclopropyl)methyl (4-nitrophenyl) carbonate (69g).



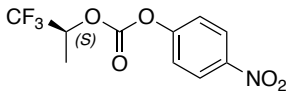
The same procedure was used as described above for compound **69a**. A mixture of (1-methylcyclopropyl)methanol (0.50 g, 5.80 mmol) and 4-nitrobenzene chloroformate (2.34 g, 11.6 mmol) was treated with pyridine (1.84 mL, 23.2 mmol) to provide the compound **69g** (1.20 g, 82%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30–8.26 (m, 2 H), 7.41–7.37 (m, 2 H), 4.09 (s, 2 H), 1.22 (s, 3 H), 0.58 (t, J = 6.0 Hz, 2 H), 0.47 (t, J = 6.0 Hz, 2 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.80, 152.86, 145.48, 125.443 121.93, 77.84, 20.88, 15.37, 11.68 ppm; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{12}H_{14}NO_5$ 252.0866; found 252.0865.

4-Nitrophenyl (1,1,1-trifluoro-2-methylpropan-2-yl) carbonate (69h).



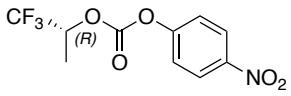
The same procedure was used as described above for compound **69a**. A mixture of 1,1,1-trifluoro-2-methylpropan-2-ol (0.50 g, 3.90 mmol) and 4-nitrobenzene chloroformate (1.57 g, 7.80 mmol) was treated with pyridine (1.06 mL, 13.0 mmol) to provide the compound **69h** (0.35 g, 31%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31–8.27 (m, 2 H), 7.41–7.37 (m, 2 H), 1.79 (s, 3 H), 1.78 (s, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.20, 149.67, 145.69, 125.48, 124.44 (q, J = 281.2 Hz), 121.93, 83.09 (q, J = 30.0 Hz), 19.15, 19.14 ppm; ^{19}F NMR (470 MHz, $CDCl_3$) δ −83.36 ppm; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{11}H_{11}F_3NO_5$, 294.0584; found 294.0580.

(*S*)-4-Nitrophenyl (1,1,1-trifluoropropan-2-yl) carbonate (69i).



The same procedure was used as described above for compound **69a**. A mixture of (*S*)-1,1,1-trifluoropropan-2-ol (0.25 g, 2.19 mmol) and 4-nitrobenzene chloroformate (0.89 g, 4.76 mmol) was treated with pyridine (0.72 mL, 9.80 mmol) to provide the compound **69i** (0.40 g, 65%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32–8.28 (m, 2 H), 7.44–7.40 (m, 2 H), 5.29–5.20 (m, 1 H), 1.57 (d, J = 6.5 Hz, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.18, 151.50, 145.87, 125.58, 123.45 (q, J = 277.5 Hz), 121.79, 72.02 (q, J = 33.7 Hz), 13.55 (d, J = 1.2 Hz) ppm; ^{19}F NMR (470 MHz, $CDCl_3$) δ −78.83 ppm; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{10}H_9F_3NO_5$, 280.0427; found 280.0425.

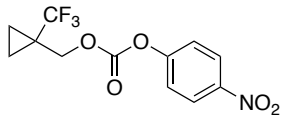
(*R*)-4-Nitrophenyl (1,1,1-trifluoropropan-2-yl) carbonate (69j).



The same procedure was used as described above for compound **69a**. A mixture of (*R*)-1,1,1-trifluoropropan-2-ol (0.30 g, 2.63 mmol) and 4-nitrobenzene chloroformate (1.06 g, 5.26 mmol) was treated with pyridine (0.90 mL, 10.5 mmol) to provide the compound **69j** (0.66 g, 89%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32–8.28 (m, 2 H), 7.43–7.39 (m, 2 H), 5.28–5.20 (m, 1 H), 1.57 (d, J = 7.0 Hz, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.18, 151.50, 145.86,

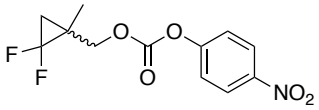
125.57, 123.46 (q, J = 278.7 Hz), 121.79, 72.02 (q, J = 33.7 Hz), 13.54 (d, J = 2.5 Hz) ppm; ^{19}F NMR (470 MHz, $CDCl_3$) δ −78.83 ppm; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{10}H_9F_3NO_5$, 280.0427; found 280.0425.

4-Nitrophenyl ((1-(trifluoromethyl)cyclopropyl)methyl) carbonate (69k).



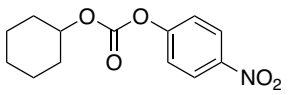
The same procedure was used as described above for compound **69a**. A mixture of (1-(trifluoromethyl)cyclopropyl)methanol (0.25 g, 1.80 mmol) and 4-nitrobenzene chloroformate (0.72 g, 3.56 mmol) was treated with pyridine (0.58 mL, 7.13 mmol) to provide the compound **69k** (0.50 g, 91%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31–8.27 (m, 2 H), 7.41–7.37 (m, 2 H), 4.40 (s, 2 H), 1.23–1.20 (m, 2 H), 0.97–0.93 (m, 2 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.51, 152.49, 145.66, 126.21 (q, J = 272.5 Hz), 125.48, 121.90, 69.91, 22.83 (q, J = 33.7 Hz), 8.58 (d, J = 1.2 Hz) ppm; ^{19}F NMR (470 MHz, $CDCl_3$) δ −69.80 ppm; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{12}H_{11}F_3NO_5$, 306.0584; found 306.0584.

(2,2-Difluoro-1-methylcyclopropyl)methyl (4-nitrophenyl) carbonate (69l).



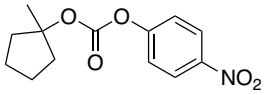
The same procedure was used as described above for compound **69a**. A mixture of (2,2-difluoro-1-methylcyclopropyl)methanol (0.25 g, 2.05 mmol) and 4-nitrobenzene chloroformate (0.83 g, 4.76 mmol) was treated with pyridine (0.67 mL, 9.80 mmol) to provide the compound **69l** (0.53 g, 90%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31–8.27 (m, 2 H), 7.42–7.38 (m, 2 H), 4.40 (ddd, J = 11.5, 2.5, 1.5 Hz, 1 H), 4.24 (dd, J = 11.5, 2.0 Hz, 1 H), 1.42 (ddd, J = 13.0, 8.0, 5.0 Hz, 1 H), 1.38 (dd, J = 2.5, 1.5 Hz, 3 H), 1.23 (ddd, J = 11.5, 8.0, 5.0 Hz, 1 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.55, 152.58, 145.63, 125.49, 121.87, 114.69 (t, J = 285.0 Hz), 70.49 (d, J = 7.5 Hz), 25.28 (dd, J = 11.2, 10.0 Hz), 21.29 (t, J = 11.2 Hz), 14.85 (d, J = 5.0 Hz) ppm; ^{19}F NMR (470 MHz, $CDCl_3$) δ −138.40 (d, J = 155.1 Hz), −139.10 (d, J = 155.1 Hz) ppm; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{12}H_{12}F_2NO_5$, 288.0678; found 288.0677.

Cyclohexyl (4-nitrophenyl) carbonate (69m).



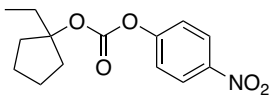
The same procedure was used as described above for compound **69a**. A mixture of cyclohexanol (1.0 g, 10.0 mmol) and 4-nitrobenzene chloroformate (4.10 g, 20.0 mmol) was treated with pyridine (3.32 mL, 41.1 mmol) to provide the compound **69m** (1.60 g, 60%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29–8.25 (m, 2 H), 7.40–7.36 (m, 2 H), 4.79–4.72 (m, 1 H), 2.04–1.96 (m, 2 H), 1.84–1.76 (m, 2 H), 1.63–1.54 (m, 3 H), 1.46–1.36 (m, 2 H), 1.35–1.26 (m, 1 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.84, 152.00, 145.39, 125.39, 121.94, 78.88, 31.50, 25.23, 23.66 ppm; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{13}H_{15}NO_5Na$, 288.0842; found 288.0843.

1-Methylcyclopentyl (4-nitrophenyl) carbonate (69n).



The same procedure was used as described above for compound **69a**. A mixture of 1-methylcyclopentan-1-ol (0.75 g, 7.50 mmol) and 4-nitrobenzene chloroformate (3.10 g, 15.4 mmol) was treated with pyridine (2.50 mL, 30.9 mmol) to provide the compound **69n** (1.40 g, 70%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28–8.24 (m, 2 H), 7.38–7.35 (m, 2 H), 2.26–2.20 (m, 2 H), 1.85–1.64 (m, 6 H), 1.67 (s, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.87, 150.97, 145.27, 125.33, 122.01, 94.71, 38.96, 23.98, 23.92 ppm; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{13}H_{16}NO_5$, 266.1023; found 266.1233.

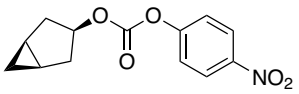
1-Ethylcyclopentyl (4-nitrophenyl) carbonate (69o).



The same procedure was used as described above for compound **69a**. A mixture of 1-ethylcyclopentan-1-ol (0.50 g, 4.34 mmol) and 4-nitrobenzene chloroformate (1.75 g, 8.68 mmol) was treated with pyridine (1.42 mL, 17.4 mmol) to provide the compound **69o** (1.0 g, 83%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28–8.24 (m, 2 H), 7.38–7.33 (m, 2 H), 2.25–2.18 (m, 2 H), 2.05 (q, J = 7.5 Hz, 2 H), 1.85–1.63 (m, 6 H), 0.98 (t, J = 7.5 Hz, 3 H) ppm; ^{13}C NMR (125

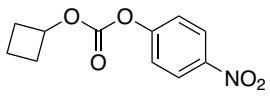
MHz, $CDCl_3$) δ 155.91, 150.74, 145.28, 125.35, 122.02, 98.37, 37.00, 29.59, 24.11, 8.91 ppm; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{14}H_{18}NO_5$, 280.1179; found 280.1183.

(1*R*,3*r*,5*S*)-Bicyclo[3.1.0]hexan-3-yl (4-nitrophenyl) carbonate (69p).



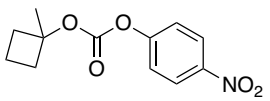
The same procedure was used as described above for compound **69a**. A mixture of (1*R*,3*r*,5*S*)-bicyclo[3.1.0]hexan-3-ol (0.25 g, 2.55 mmol) and 4-nitrobenzene chloroformate (1.03 g, 5.10 mmol) was treated with pyridine (0.86 mL, 10.5 mmol) to provide the compound **69p** (0.18 g, 27%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29–8.24 (m, 2 H), 7.38–7.33 (m, 2 H), 5.24 (t, J = 6.5 Hz, 1 H), 2.32–2.23 (m, 2 H), 2.03 (d, J = 15.0 Hz, 2 H), 1.40–1.34 (m, 2 H), 0.59–0.53 (m, 1 H), 0.42 (q, J = 4.0 Hz, 1 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.75, 152.02, 145.41, 125.39, 121.93, 82.51, 35.73, 16.76, 10.59 ppm; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{13}H_{13}NO_5Na$, 286.0686; found 286.0686.

Cyclobutyl (4-nitrophenyl) carbonate (69q).



The same procedure was used as described above for compound **69a**. A mixture of cyclobutanol (0.72 g, 10.0 mmol) and 4-nitrobenzene chloroformate (4.0 g, 20.0 mmol) was treated with pyridine (3.25 mL, 40.2 mmol) to provide the compound **69q** (1.50 g, 63%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29–8.25 (m, 2 H), 7.40–7.35 (m, 2 H), 5.10–5.02 (m, 1 H), 2.48–2.40 (m, 2 H), 2.38–2.22 (m, 2 H), 1.93–1.84 (m, 1 H), 1.71–1.61 (m, 1 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.66, 151.61, 145.47, 125.41, 121.91, 73.26, 30.13, 13.14 ppm; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{11}H_{12}NO_5$, 238.0710; found 238.0708.

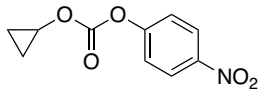
1-Methylcyclobutyl (4-nitrophenyl) carbonate (69r).



The same procedure was used as described above for compound **69a**. A mixture of 1-methylcyclobutan-1-ol (0.25 g, 2.90 mmol) and 4-nitrobenzene chloroformate (1.17 g, 5.80 mmol)

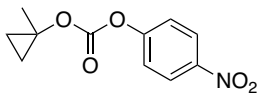
was treated with pyridine (0.95 mL, 11.6 mmol) to provide the target compound **69r** (0.53 g, 73%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29–8.24 (m, 2 H), 7.40–7.35 (m, 2 H), 2.50–2.41 (m, 2 H), 2.23–2.17 (m, 2 H), 1.93–1.85 (m, 1 H), 1.75–1.64 (m, 1 H), 1.65 (s, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.73, 150.44, 145.33, 125.35, 121.94, 83.55, 35.03, 22.88, 13.30 ppm; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{12}H_{14}NO_5$, 252.0866; found 252.0859.

Cyclopropyl (4-nitrophenyl) carbonate (69s).



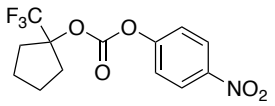
The same procedure was used as described above for compound **69a**. A mixture of cyclopropanol (0.50 g, 8.60 mmol) and 4-nitrobenzene chloroformate (3.46 g, 17.2 mmol) was treated with pyridine (2.79 mL, 34.4 mmol) to provide the compound **69s** (1.60 g, 83%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30–8.25 (m, 2 H), 7.40–7.36 (m, 2 H), 4.28 (tt, J = 6.5, 3.5 Hz, 1 H), 0.92–0.88 (m, 2 H), 0.87–0.81 (m, 2 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.53, 153.05, 145.53, 125.44, 121.85, 53.41, 5.34 ppm; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{10}H_{10}NO_5$, 224.0553; found 224.0552.

1-Methylcyclopropyl (4-nitrophenyl) carbonate (NR02-20) (69t).



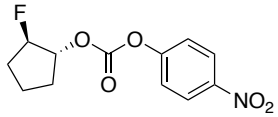
The same procedure was used as described above for compound **69a**. A mixture of 1-methylcyclopropan-1-ol (0.50 g, 6.93 mmol) and 4-nitrobenzene chloroformate (2.80 g, 13.9 mmol) was treated with pyridine (2.26 mL, 27.7 mmol) to provide the compound **69t** (1.30 g, 79%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29–8.24 (m, 2 H), 7.39–7.36 (m, 2 H), 1.65 (s, 3 H), 1.09–1.05 (m, 2 H), 0.77–0.73 (m, 2 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.60, 152.08, 145.43, 125.39, 121.86, 60.83, 20.66, 13.04 ppm; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{11}H_{12}NO_5$, 238.0710; found 238.0707.

4-Nitrophenyl (1-(trifluoromethyl)cyclopentyl) carbonate (69u).



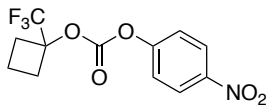
The same procedure was used as described above for compound **69a**. A mixture of 1-(trifluoromethyl)cyclopentan-1-ol (0.25 g, 1.62 mmol) and 4-nitrobenzene chloroformate (0.66 g, 3.26 mmol) was treated with pyridine (0.53 mL, 6.48 mmol) to provide the compound **69u** (0.45 g, 87%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31–8.27 (m, 2 H), 7.41–7.37 (m, 2 H), 2.41–2.34 (m, 2 H), 2.28–2.21 (m, 2 H), 2.08–1.99 (m, 2 H), 1.81–1.72 (m, 2 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.26, 149.89, 145.68, 125.48, 125.20 (q, J = 280.0 Hz), 121.94, 92.43 (q, J = 30.0 Hz), 32.98 , 25.55 ppm; ^{19}F NMR (470 MHz, $CDCl_3$) δ −79.93 ppm; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{13}H_{13}F_3NO_5$, 320.0740; found 320.0737.

(1*R*,2*R*)-2-Fluorocyclopentyl (4-nitrophenyl) carbonate (69v).



The same procedure was used as described above for compound **69a**. A mixture of (1*R*,2*R*)-2-fluorocyclopentan-1-ol (0.25 g, 2.38 mmol) and 4-nitrobenzene chloroformate (0.96 g, 4.76 mmol) was treated with pyridine (0.80 mL, 9.80 mmol) to provide the compound **69v** (0.55 g, 86%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31–8.26 (m, 2 H), 7.41–7.37 (m, 2 H), 5.26–5.08 (m, 2 H), 2.32–2.22 (m, 1 H), 2.13–1.82 (m, 5 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.51, 151.85, 145.60, 125.49, 121.84, 97.06 (d, J = 176.2 Hz), 83.93 (d, J = 31.2 Hz), 30.69 (d, J = 22.5 Hz), 29.86, 21.30 ppm; ^{19}F NMR (470 MHz, $CDCl_3$) δ −181.53 ppm; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{12}H_{13}FNO_5$, 270.0772; found 270.0770.

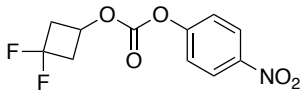
4-Nitrophenyl (1-(trifluoromethyl)cyclobutyl) carbonate (69w).



The same procedure was used as described above for compound **69a**. A mixture of 1-(trifluoromethyl)cyclobutan-1-ol (0.25 g, 1.79 mmol) and 4-nitrobenzene chloroformate (0.72 g, 3.58 mmol) was treated with pyridine (0.59 mL, 7.14 mmol) to provide the compound **69w** (0.44

g, 80%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31–8.27 (m, 2 H), 7.42–7.39 (m, 2 H), 2.88–2.79 (m, 2 H), 2.70–2.63 (m, 2 H), 2.10–2.00 (m, 1 H), 1.98–1.90 (m, 1 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.18, 149.84, 145.73, 125.50, 124.57 (q, J = 280.0 Hz), 121.87, 81.37 (q, J = 33.7 Hz), 28.62, 28.61, 13.21 ppm; ^{19}F NMR (470 MHz, $CDCl_3$) δ −82.44 ppm; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{12}H_{11}F_3NO_5$, 306.0584; found 306.0579.

3,3-Difluorocyclobutyl (4-nitrophenyl) carbonate (69x).



The same procedure was used as described above for compound **69a**. A mixture of 3,3-difluorocyclobutan-1-ol (0.50 g, 4.63 mmol) and 4-nitrobenzene chloroformate (1.87 g, 9.26 mmol) was treated with pyridine (1.50 mL, 18.5 mmol) to provide the compound **69x** (1.0 g, 79%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31–8.27 (m, 2 H), 7.41–7.37 (m, 2 H), 5.08–5.00 (m, 1 H), 3.18–3.08 (m, 2 H), 2.91–2.80 (m, 2 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.27, 151.81, 145.74, 125.54, 121.81, 117.47 (dd, J = 280.0, 267.5 Hz), 63.57 (dd, J = 17.5, 8.8 Hz), 43.16 (t, J = 22.5 Hz) ppm; ^{19}F NMR (470 MHz, $CDCl_3$) δ −85.22 (d, J = 202.1 Hz), −97.03 (d, J = 202.1 Hz) ppm; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{11}H_{10}F_2NO_5$, 274.0522; found 274.0519.

Table S1. X-ray data collection and crystallographic refinement statistics.

Inhibitor	**3**	**37**	**43**	**50**
PDB Code	7L7P	7L7L	7L7O	7L7N
Resolution (Å)	1.58	1.88	1.72	1.59
Space group	P 2_1 2_1 2_1	P 2_1 2_1 2_1	P 2_1 2_1 2_1	P 2_1 2_1 2_1
Cell dimensions:				
a (Å)	55.06	54.86	55.13	54.62
b (Å)	60.04	58.77	58.75	58.73
c (Å)	58.81	59.98	59.73	60.21
β (°)	90	90	90	90
Completeness (%)	97.22	99.51	99.14	98.55
Total reflections	126145	82558	121031	121688
Unique reflections	26628	15940	21030	26388
Average I/σ	23.46 (6.43)	10.02 (3.73)	18.43 (3.58)	12.48 (2.13)
Redundancy	4.7 (2.5)	5.2 (3.9)	5.8 (2.9)	4.6 (2.1)
R_{sym} (%)[a]	4.0 (14.7)	9.5 (35.4)	6.2 (28.3)	6.3 (36.3)
RMSD[b] in				
Bond lengths (Å)	0.012	0.01	0.01	0.006
Bond angles (°)	1.17	1.22	1.33	0.98
R_{factor} (%)[c]	16.3	16.5	15.1	18.2
R_{free} (%)[d]	18.4	21.0	17.1	20.9

[a] $R_{sym} = \Sigma \mid I - \langle I \rangle \mid / \Sigma I$, where I = observed intensity, $\langle I \rangle$ = average intensity over symmetry equivalent; values in parentheses are for the highest resolution shell.
[b] RMSD, root mean square deviation.
[c] $R_{factor} = \Sigma \mid\mid F_o \mid - \mid F_c \mid\mid / \Sigma \mid F_o \mid$.
[d] R_{free} was calculated from 5% of reflections, chosen randomly, which were omitted from the refinement process.