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LP99: Discovery and Synthesis of the First Selective BRD7/9 Bromodomain Inhibitor**

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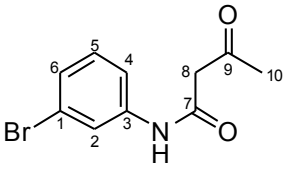
Synthetic Procedures

General Experimental Details

Reagents used were obtained from commercial suppliers or purified according to standard procedures. Petroleum ether (PE) refers to distilled light petroleum of fraction 30 - 40 °C. Anhydrous 1,4-dioxane was dried over 3Å molecular sieves. Degassing was achieved by bubbling argon through the reaction mixture for 15 minutes with sonication. Reactions were monitored by thin layer chromatography (TLC) using Merck silica gel 60 F254 plates and visualized by fluorescence quenching under UV light. In addition, TLC plates were stained with potassium permanganate solution. Chromatographic purification was performed on VWR 60 silica gel 40 - 63 µm using technical grade solvents that were used as supplied. 1-[(8*R*,9*R*)-1-benzyl-6'-methoxycinchonan-1-ium-9-yl]-3- [3,5-bis(trifluoromethyl)phenyl]urea bromide was prepared according to literature methods.[1] Melting points were obtained on a Leica Galen III Hot-stage melting point apparatus and microscope and on a Kofler hot block and are reported uncorrected. NMR spectra were recorded on a Bruker Spectrospin spectrometer operating at 200, 400 or 500 MHz (^{1}H acquisitions), and 100 or 125 MHz (^{13}C acquisitions). Chemical shifts (δ) are reported in ppm with the solvent resonance as the internal standard (e.g. Chloroform δ 7.27 ppm for ^{1}H and 77.0 ppm for ^{13}C). Coupling constants (*J*) are reported in hertz (Hz). Data are reported as follows: multiplicity [s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, ddd = doublet of doublets of doublets, td = triplet of doublets, m = multiplet, br = broad], coupling constants in Hz, integration, assignment. Two-dimensional spectroscopy (COSY, HSQC and HMBC) was used to assist in the assignment and the data is not reported. High-resolution mass spectra (ESI) were recorded on Bruker Daltonics MicroTOF mass spectrometer. Infrared spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer as a thin film. Only selected maximum absorbances are reported. Optical rotations were recorded using a Perkin Elmer 341 polarimeter; absolute optical rotation are quoted $[\alpha]_D^T$ where concentrations (c) are quoted in g/100 mL, D refers to the D-line of sodium (589 nm), and temperatures (T) are given in degrees Celsius (°C). The enantiomeric excesses were determined by HPLC analysis on an Agilent 1200 Series instrument employing a chiral stationary phase column specified in the individual experiment and by comparing the samples with the appropriate racemic mixtures, and the same instrument was used in the separation of enantiomers using the chiral stationary phase column specified in the experiments.

***N*-(3-bromophenyl)-3-oxobutanamide (S1)**

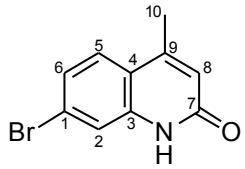
m-Bromoaniline (20.1 mL, 184 mmol) and ethyl acetoacetate (14.6 mL, 115 mmol) were dissolved in xylenes (87 mL, 1.3M) and the reaction was refluxed and stirred for 16 hours. The reaction mixture was cooled, $Na_2CO_{3(aq)}$ was added and the aqueous phase was extracted with DCM three times. The combined organic phases were dried and concentrated under reduced pressure. Hexanes was added, the sample was cooled with ice to aid precipitation and the resulting precipitate was filtered off to yield **S1** (7.16 g, 24%) as a white powder



Mpt: 109.8-110.8 °C (lit. 110 °C)[2]; ^{1}H-NMR (400MHz, $CDCl_3$): δ_H 9.29 (br s, 1H, N*H*), 7.83 (s, 1H, H-2), 7.44 (d, *J* = 8.1 Hz, 1H, H-6), 7.25 (d, *J* = 8.1 Hz, 1H, H-4), 7.18 (t, *J* = 7.8 Hz, 1H, H-5), 3.60 (s, 2H, H-8), 2.33 (s, 3H, H-10); ^{13}C-NMR (100MHz, $CDCl_3$): δ_C 205.3 (C-9), 163.5 (C-7), 138.7 (C-3), 130.2 (C-5), 127.5 (C-6), 123.0 (C-2), 122.6 (C-1), 118.6 (C-4), 49.3 (C-8), 31.3 (C-10); LR-ESI-MS: $C_{10}H_{10}BrNO_2$ $[M+H]^+$ *m/z* found 256.0, calcd 255.9.

7-bromo-4-methylquinolin-2(1*H*)-one (3)

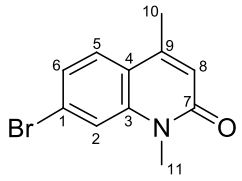
S1 (5.0 g, 19.5 mmol) was suspended in concentrated sulfuric acid (23.4 mL, 0.8M), heated to 95 °C and stirred for two hours. The reaction mixture was cooled, water (2.3L) was added and the resulting precipitate was filtered off to yield **3** (4.0 g, 88%) as an amorphous white solid.



^{1}H-NMR (400MHz, $CDCl_3$): δ_H 11.68 (br s, 1H, N*H*), 7.65 (d, *J* = 8.6 Hz, 1H, H-5), 7.47 (d, *J* = 1.9 Hz, 1H, H-2), 7.35 (dd, *J* = 8.6, 2.0 Hz, 1H, H-6), 6.43 (d, *J* = 1.1 Hz, 1H, H-8), 2.40 (d, *J* = 1.2 Hz, 3H, H-10); ^{13}C-NMR (100MHz, DMSO-d_6): δ_C 161.5 (C-7), 147.7 (C-9), 139.8 (C-3), 126.8 (C-5), 124.4 (C-6), 123.3 (C-1), 121.3 (C-2), 118.7 (C-4), 117.5 (C-8), 18.4 (C-10); LR-ESI-MS: $C_{10}H_9BrNO$ $[M+H]^+$ *m/z* found 237.9, calcd 238.0.

7-bromo-1,4-dimethylquinolin-2(1*H*)-one (4)

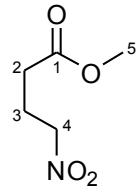
3 (1.136g, 4.8 mmol) and methyl iodide (0.75 mL, 5.3 mmol) were dissolved in DMF (60 mL, 0.1M) and the reaction mixture was cooled to 0 °C. Sodium hydride (0.23 g, 60% dispersion on mineral oil, 5.7 mmol) was added and the reaction was allowed to warm to ambient temperature and stirred for 12 hours. The reaction was quenched with NaOH (2mL, 1M) then water and EtOAc were added. The organic phase was separated and the aqueous phase was extracted with EtOAc three times. The combined organic phases were dried and concentrated under reduced pressure to yield **4** (915 mg, 76%) as white crystals.



Mpt: 105.7-107.3 °C; ν_{max} (cm^{-1}) 2364, 1640, 1581, 937, 842, 813; ^{1}H-NMR (400MHz, $CDCl_3$): δ_H 7.55 (d, *J* = 7.3 Hz, 1H, H-5), 7.53 (s, 1H, H-2), 7.37 (dd, *J* = 8.4, 1.9 Hz, 1H, H-6), 6.61 (d, *J* = 0.9 Hz, 1H, H-8), 3.68 (s, 3H, H-11), 2.45 (d, *J* = 1.1 Hz, 3H, H-10); ^{13}C-NMR (100MHz, $CDCl_3$): δ_C 161.9 (C-7), 146.0 (C-4), 139.2 (C-3), 126.5 (C-5), 125.1 (C-6), 124.8 (C-1), 121.4 (C-8), 120.3 (C-9), 117.4 (C-2), 29.4 (C-11), 18.9 (C-10); LR-ESI-MS: $C_{11}H_{11}BrNO$ $[M+H]^+$ *m/z* found 252.0, calcd 252.0; HR-ESI-MS: $C_{11}H_{11}BrNO$ $[M+H]^+$ *m/z* found 252.0033, calcd 252.0019.

Methyl 4-nitrobutanoate (11)

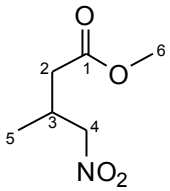
Methyl acrylate (4.2 mL, 46 mmol) was added dropwise to a suspension of potassium carbonate (0.63 g, 4.6 mmol) in nitromethane (12.5 mL, 230 mmol) and the reaction was stirred at ambient temperature for 16 hours. The reaction mixture was filtered and the fitrate was concentrated under reduced pressure. The crude material was then purified by FCC (20% EtOAc/PE) to yield **11** (1.6 g, 47%) as a yellow liquid.



ν_{max} (cm^{-1}) 2956, 1732, 1552, 1437, 1388, 1230; ^{1}H-NMR (400MHz, $CDCl_3$): δ_H 4.49 (t, *J* = 6.6 Hz, 2H, H-4), 3.72 (s, 3H, H-5), 2.49 (t, *J* = 7.1 Hz, 2H, H-2), 2.33 (quin, *J* = 6.8 Hz, 2H, H-3); ^{13}C-NMR (100MHz, $CDCl_3$): δ_C 169.8 (C-1), 74.3 (C-4), 51.9 (C-5), 30.2 (C-2), 22.3 (C-3); LR-ESI-MS: $C_5H_9NO_4Na$ $[M+Na]^+$ *m/z* found 170.1, calcd 170.1.

Methyl 3-methyl-4-nitrobutanoate (12)

Methyl crotonate (2.2 mL, 20.0 mmol) and nitromethane (2.7 mL, 50.0 mmol) were combined, DBU (3.3 mL, 22.0 mmol) was added and the reaction was stirred at ambient temperature for three days. The reaction mixture was concentrated under reduced pressure and purified by FCC (10% EtOAc/PE) to yield **12** (2.2 g, 69%) as a yellow liquid.



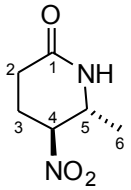
ν_{max} (cm^{-1}) 2976, 2956, 2884, 1733, 1548, 1461, 1195; ^{1}H-NMR (400MHz, $CDCl_3$): δ_H 4.48 (dd, *J* = 12.1, 6.2 Hz, 1H, H-4a), 4.35 (dd, *J* = 12.0, 7.1 Hz, 1H, H-4b), 3.70 (s, 3H, H-6), 2.79 (sptd, *J* = 7.1, 6.8, 6.6, 6.2 Hz, 1H, H-3), 2.46 (dd, *J* = 16.1, 6.6 Hz, 1H, H-2a), 2.37 (dd, *J* = 16.1, 6.8 Hz, 1H, H-2b), 1.11 (d, *J* = 6.8 Hz, 3H, H-5); ^{13}C-NMR (100MHz, $CDCl_3$): δ_C 171.7 (C-1), 80.1 (C-4), 51.8 (C-6), 37.6 (C-2), 29.4 (C-3), 17.3 (C-5); LR-ESI-MS: $C_6H_{11}NO_4Na$ $[M+Na]^+$ *m/z* found 184.1, calcd 184.1.

General procedure A

To a solution of the appropriate nitroalkane (1 eq.) in EtOH (3.1M) was added the appropriate aldehyde (1 eq.) and ammonium acetate (2 eq.). The reaction was heated to 90°C and refluxed for 24 hours. The reaction mixture was concentrated under reduced pressure and purified with FCC to yield the title compound.

(5*S,6*R**)-6-methyl-5-nitropiperidin-2-one (13)**

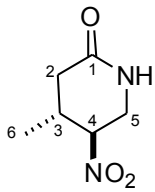
11 (200 mg, 1.36 mmol) and acetaldehyde (80 µL, 1.36 mmol) were reacted according to General Procedure **A**. The crude material was purified by FCC (MeOH/DCM) to yield **13** (86 mg, 40%) as a white powder.



Mpt: 160.5-162.1 °C (lit. 160 °C)[3]; ν_{max} (cm^{-1}) 3181, 2915, 1661, 1548, 1332; ^{1}H-NMR (400MHz, $CDCl_3$): δ_H 6.29 (s, 1H, N*H*), 4.47-4.42 (m, 1H, H-4), 4.13 (dqd, *J* = 6.8, 6.6, 1.5 Hz, 1H, H-5), 2.59-2.34 (m, 4H, H-2a/2b/3a/3b), 1.33 (d, *J* = 6.3 Hz, 3H, H-6); ^{13}C-NMR (100MHz, $CDCl_3$): δ_C 169.8 (C-1), 84.9 (C-4), 50.6 (C-5), 28.0 (C-2), 24.5 (C-3), 20.5 (C-6); LR-ESI-MS: $C_6H_{11}N_2O_3$ $[M+H]^+$ *m/z* found 159.2, calcd 159.1.

(4*R,5*S**)-4-methyl-5-nitropiperidin-2-one (14)**

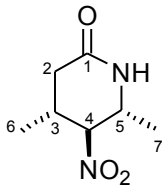
12 (0.5 g, 3.1 mmol) and paraformaldehyde (260 µL, 3.1 mmol) were reacted according to General Procedure **A**. The crude material was purified by FCC (PE:EtOAc:EtOH 6:3:1) to yield **14** (383 mg, 79%) as a yellow powder.



Mpt: 156.1-157.8 °C; ^{1}H-NMR (500MHz, $CDCl_3$): δ_H 6.55 (br s, 1H, N*H*), 4.53 (td, *J* = 7.4, 5.4 Hz, 1H, H-4), 3.93 (dd, *J* = 12.6, 6.9 Hz, 1H, H-5a), 3.75 (dd, *J* = 12.6, 2.8 Hz, 1H, H-5b), 2.82-2.73 (m, 1H, H-3), 2.61 (dd, *J* = 17.8, 5.8 Hz, 1H, H-2a), 2.19 (dd, *J* = 17.7, 8.5 Hz, 1H, H-2b), 1.17 (d, *J* = 6.6 Hz, 3H, H-6); ^{13}C-NMR (125MHz, $CDCl_3$): δ_C 169.9 (C-6), 84.6 (C-4), 42.8 (C-5), 36.0 (C-2), 31.4 (C-3), 18.3 (C-6); LR-ESI-MS: $C_6H_{11}N_2O_3$ $[M+H]^+$ *m/z* found 159.1, calcd 159.2; HR-ESI-MS: $C_6H_{10}N_2O_3Na$ $[M+Na]^+$ *m/z* found 181.0577, calcd 181.0584.

(4*R,5*S**,6*R**)-4,6-dimethyl-5-nitropiperidin-2-one (15)**

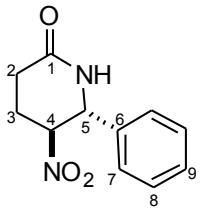
12 (100 mg, 0.62 mmol) and acetaldehyde (40 µL, 0.62 mmol) were reacted according to General Procedure **A**. The crude material was purified by FCC (PE:EtOAc:EtOH 6:3:1) to yield **15** (18mg, 30%) as a yellow powder.



Mpt: 150.7-152.1 °C; ν_{max} (cm^{-1}) 3193, 2976, 2916, 1655, 1564, 1317; ^{1}H-NMR (400MHz, $CDCl_3$): δ_H 6.68 (s, 1H, N*H*), 4.11 (t, *J* = 10.7 Hz, 1H, H-4), 3.99 (dq, *J* = 9.8, 6.3 Hz, 1H, H-5), 2.65 (dd, *J* = 17.4, 5.7 Hz, 1H, H-2a), 2.65-2.56 (m, 1H, H-3), 2.15 (dd, *J* = 17.3, 11.3 Hz, 1H, H-2b), 1.25 (d, *J* = 5.9 Hz, 3H, H-), 1.04 (d, *J* = 6.3 Hz, 3H, H-); ^{13}C-NMR (100MHz, $CDCl_3$): δ_C 169.8 (C-1), 93.2 (C-4), 51.2 (C-5), 37.0 (C-2), 32.2 (C-3), 19.4 (C-7), 17.6 (C-6); LR-ESI-MS: $C_7H_{13}N_2O_3$ $[M+H]^+$ *m/z* found 173.1, calcd 173.1; HR-ESI-MS: $C_7H_{12}N_2O_3Na$ $[M+Na]^+$ *m/z* found 195.0734, calcd 195.0740.

(5*S,6*R**)-5-Nitro-6-phenylpiperidin-2-one (16)**

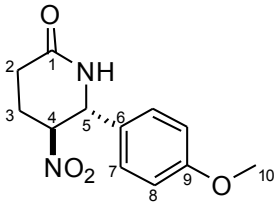
11 (1.0 g, 6.8 mmol) and benzaldehyde (700 µL, 6.8 mmol) were reacted according to General Procedure **A**. The crude material was purified by FCC (70% EtOAc/Hexanes) to yield **16** (1.80 g, 82%) as white crystals.



Mpt: 162.8-164.0 °C (lit. 164 °C)[3]; ν_{max} (cm^{-1}) 3169, 3053, 2923, 1651, 1550, 1333; ^{1}H-NMR (400MHz, $CDCl_3$): δ_H 7.45- 7.39 (m, 3H, H-7/9), 7.34-7.31 (m, 2H, H-8), 6.08 (br s, 1H, N*H*), 5.27 (dd, *J* = 6.0, 1.3 Hz, 1H, H-5), 4.72 (ddd, *J* = 7.8, 6.1, 3.4 Hz, 1H, H-4), 2.68-2.52 (m, 3H, H-2a/2b/3a), 2.38-2.30 (m, 1H, H-3b); ^{13}C-NMR (100MHz, $CDCl_3$): δ_C 169.6 (C-1), 137.3 (C-6), 129.4 (C-8), 126.6 (C-9), 126.5 (C-7), 85.2 (C-4), 58.9 (C-5), 27.8 (C-2), 23.3 (C-3); LR-ESI-MS: $C_{11}H_{13}N_2O_3$ $[M+H]^+$ *m/z* found 221.1, calcd 221.2.

(5*S,6*R**)-6-(4-methoxyphenyl)-5-nitropiperidin-2-one (25)**

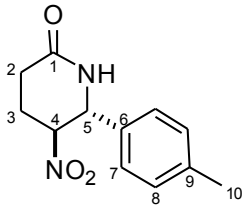
11 (106 mg, 0.72 mmol) and anisaldehyde (88 µL, 0.72 mmol) were reacted according to General Procedure **A**. The crude material was purified by FCC (0.5% MeOH/DCM) to yield **25** (43 mg, 26%) as a white powder.



Mpt: 187.8-188.9 °C; ν_{max} (cm^{-1}) 3167, 3010, 1651, 1256, 820, 623; ^{1}H-NMR (400MHz, $CDCl_3$): δ_H 7.24 (d, *J* = 8.6 Hz, 2H, H-7), 6.93 (d, *J* = 8.8 Hz, 2H, H-8), 5.97 (br s, 1H, N*H*), 5.16 (dd, *J* = 6.6, 1.2 Hz, 1H, H-5), 4.69 (ddd, *J* = 8.3, 6.6, 3.7 Hz, 1H, H-4), 3.81 (s, 3H, H-10), 2.73-2.50 (m, 3H, H-2a/2b/3a), 2.41-2.32 (m, 1H, H-3b); ^{13}C-NMR (100MHz, $CDCl_3$): δ_C 169.6 (C-1), 160.4 (C-9), 129.0 (C-6), 127.9 (C-7), 114.8 (C-8), 85.6 (C-4), 58.7 (C-5), 55.4 (C-10), 28.0 (C-2), 23.9 (C-3); LR-ESI-MS: $C_{12}H_{15}N_2O_4$ $[M+H]^+$ *m/z* found 251.0, calcd 251.1; $C_{12}H_{14}N_2O_4Na$ $[M+Na]^+$ *m/z* found 273.0, calcd 273.1; HR-ESI-MS: $C_{12}H_{15}N_2O_4$ $[M+H]^+$ *m/z* found 251.10233, calcd 251.10263, Δ = 1.23 ppm.

(5*S,6*R**)-5-nitro-6-p-tolylpiperidin-2-one (26)**

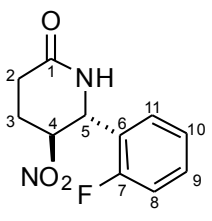
11 (106 mg, 0.72 mmol) and *p*-Tolualdehyde (85 µL, 0.72 mmol) were reacted according to General Procedure **A**. The crude material was purified by FCC (1% MeOH/DCM) to yield **26** (145 mg, 86%) as a white powder.



Mpt: 168.0-168.8 °C; ν_{max} (cm^{-1}) 3208, 3080, 2913, 1660, 1547, 1387, 741; ^{1}H-NMR (400MHz, $CDCl_3$): δ_H 7.22 (d, *J* = 8.6 Hz, 2H, H-8), 7.20 (d, *J* = 8.8 Hz, 2H, H-7), 6.26 (br s, 1H, N*H*), 5.20 (dd, *J* = 6.1, 1.5 Hz, 1H, H-5), 4.69 (ddd, *J* = 7.6, 6.1, 3.9 Hz, 1H, H-4), 2.70-2.47 (m, 3H, H-2a/2b/3a), 2.36 (s, 3H, H-10), 2.35-2.27 (m, 1H, H-3b); ^{13}C-NMR (100MHz, $CDCl_3$): δ_C 169.8 (C-1), 139.4 (C-6), 134.3 (C-9), 130.0 (C-8), 126.4 (C-7), 85.3 (C-4), 58.7 (C-5), 27.8 (C-2), 23.4 (C-3), 21.1 (C-10); LR-ESI-MS: $C_{12}H_{15}N_2O_3$ $[M+H]^+$ *m/z* found 235.1, calcd 235.1; $C_{12}H_{14}N_2O_3Na$ $[M+Na]^+$ *m/z* found 257.0, calcd 257.1; HR-ESI-MS: $C_{12}H_{14}N_2O_3Na$ $[M+Na]^+$ *m/z* found 257.08920, calcd 257.08966, Δ = 1.79 ppm.

(5*S,6*R**)-6-(2-fluorophenyl)-5-nitropiperidin-2-one (27)**

11 (106 mg, 0.72 mmol) and 2-fluorobenzaldehyde (76 µL, 0.72 mmol) were reacted according to General Procedure **A**. The crude material was purified by FCC (0.5% MeOH/DCM) to yield **27** (139 mg, 81%) as a white powder.

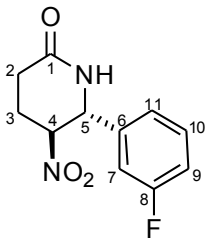


Mpt: 166.3-167.4 °C; ν_{max} (cm^{-1}) 3216, 3078, 2929, 1662, 1551, 771; ^{1}H-NMR (400MHz, $CDCl_3$): δ_H 7.40 (dddd, *J* = 8.1, 7.3, 5.4, 1.7 Hz, 1H, H-9), 7.35 (td, *J* = 7.6, 1.5 Hz, 1H, H-8), 7.24 (td, *J* = 7.6, 1.0 Hz, 1H, H-11), 7.14 (ddd, *J* = 10.6, 8.3, 1.0 Hz, 1H, H-10), 6.47 (br s, 1H, N*H*), 5.66 (t, *J* = 3.4 Hz, 1H, H-5), 4.85 (dt, *J* = 5.4, 4.2 Hz, 1H, H-4), 2.62-2.55 (m , 3H, H-2a/2b/3a), 2.28-2.18 (m, 1H, H-3b); ^{13}C-NMR (100MHz, $CDCl_3$): δ_C 170.1 (C-1), 159.7 (d, *J* = 252.7 Hz, C-7), 131.1 (d, *J* = 7.9 Hz, C-11), 128.1 (d, *J* = 3.2 Hz, C-9), 125.1 (d, J = 3.2 Hz, C-10), 124.9 (d, *J* = 12.7 Hz, C-

6), 116.3 (d, *J* = 21.5 Hz, C-8), 82.0 (C-4), 53.1 (C-5), 27.2 (C-2), 22.1 (C-3); LR-ESI-MS: $C_{11}H_{12}FN_2O_3$ $[M+H]^+$ *m/z* found 239.1, calcd 239.1; $C_{11}H_{11}FN_2O_3Na$ $[M+Na]^+$ *m/z* found 261.0, calcd 261.1; HR-ESI-MS: $C_{11}H_{11}FN_2O_3Na$ $[M+]^+$ *m/z* found 261.06452, calcd 261.06459, Δ = 0.30 ppm.

(5*S,6*R**)-6-(3-fluorophenyl)-5-nitropiperidin-2-one (28)**

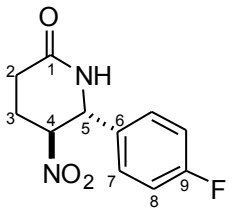
11 (106 mg, 0.72 mmol) and 3-fluorobenzaldehyde (76 µL, 0.72 mmol) were reacted according to General Procedure **A**. The crude material was purified by FCC (DCM) to yield **28** (45 mg, 26%) as a pale yellow oil.



ν_{max} (cm^{-1}) 3183, 3052, 1656, 1551, 790, 695; ^{1}H-NMR (400MHz, $CDCl_3$): δ_H 7.41 (td, *J* = 8.1, 5.9 Hz, 1H, H-10), 7.12 (dd, *J* = 6.8, 1.0 Hz, 1H, H-7), 7.13-7.03 (m, 2H, H-9/11), 6.77 (br s, 1H, N*H*), 5.30 (dd, *J* = 5.4, 1.2 Hz, 1H, H-5), 4.71 (ddd, *J* = 7.4, 5.9, 4.2 Hz, 1H, H-4), 2.72-2.53 (m, 3H, H-2a/2b/3a), 2.37-2.27 (m, 1H, H-3b); ^{13}C-NMR (100MHz, $CDCl_3$): δ_C 170.2 (C-), 163.2 (d, *J* = 248.8 Hz, C-8), 139.9 (d, *J* = 6.4 Hz, C-6), 131.2 (d, *J* = 7.9 Hz, C-10), 122.2 (d, *J* = 3.2 Hz, C-11), 116.5 (d, *J* = 21.5 Hz, C-7), 113.7 (d, *J* = 23.0 Hz, C-9), 84.7 (C-4), 58.3 (d, *J* = 2.4 Hz, C-5), 27.6 (C-2), 23.1 (C-3); LR-ESI-MS: $C_{11}H_{12}FN_2O_3$ $[M+H]^+$ *m/z* found 239.1, calcd 239.1; $C_{11}H_{11}FN_2O_3Na$ $[M+Na]^+$ *m/z* found 261.0, calcd 261.1; HR-ESI-MS: $C_{11}H_{11}FN_2O_3Na$ $[M+Na]^+$ *m/z* found 261.06458, calcd 261.06459, Δ = 0.06 ppm.

(5*S,6*R**)-6-(4-fluorophenyl)-5-nitropiperidin-2-one (29)**

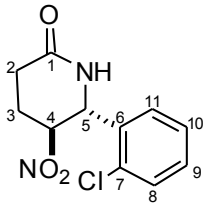
11 (106 mg, 0.72 mmol) and 4-fluorobenzaldehyde (76 µL, 0.72 mmol) were reacted according to General Procedure **A**. The crude material was purified by FCC (0.5% MeOH/DCM) to yield **29** (132 mg, 77%) as a white powder.



Mpt: 101.7-103.2 ^{o}C; ν_{max} (cm^{-1}) 3210, 2950, 1680, 1542, 1202, 780; ^{1}H-NMR (400MHz, $CDCl_3$): δ_H 7.31 (dd, *J* = 8.6, 5.1 Hz, 2H, H-7), 7.17 (br s, 1H, N*H*), 7.12 (t, *J* = 8.6 Hz, 2H, H-8), 5.25 (dd, *J* = 6.1, 1.2 Hz, 1H, H-5), 4.68 (ddd, *J* = 7.8, 6.1, 3.7 Hz, 1H, H-4), 2.72-2.51 (m, 3H, H-2a/2b/3a), 2.37-2.28 (m, 1H, H-3b); ^{13}C-NMR (100MHz, $CDCl_3$): δ_C 170.8 (C-1), 163.1 (d, *J* = 248.0 Hz, C-9), 132.8 (d, *J* = 3.2 Hz, C-6), 128.4 (d, *J* = 8.7 Hz, C-7), 116.5 (d, *J* = 22.3 Hz, C-8), 85.1 (C-4), 58.2 (C-5), 27.6 (C-2), 23.3 (C-3); LR-ESI-MS: $C_{11}H_{12}FN_2O_3$ $[M+H]^+$ *m/z* found 239.1, calcd 239.1; $C_{11}H_{11}FN_2O_3Na$ $[M+Na]^+$ *m/z* found 261.0, calcd 261.1; HR-ESI-MS: $C_{11}H_{11}FN_2O_3Na$ $[M+Na]^+$ *m/z* found 261.06470, calcd 261.06459, Δ = 0.40 ppm.

(5*S,6*R**)-6-(2-chlorophenyl)-5-nitropiperidin-2-one (30)**

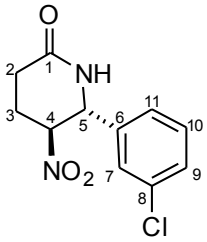
11 (106 mg, 0.72 mmol) and 2-chlorobenzaldehyde (81 µL, 0.72 mmol) were reacted according to General Procedure **A**. The crude material was purified by FCC (4% MeOH/DCM) to yield **30** (49 mg, 27%) as pale yellow crystals.



Mpt: 163.7-164.9 ^{o}C; ν_{max} (cm^{-1}) 3210, 2927, 1660, 1549, 1330, 767; ^{1}H-NMR (400MHz, $CDCl_3$): δ_H 7.45 (dd, *J* = 6.8, 1.5 Hz, 1H, H-8), 7.42-7.33 (m, 3H, H-9/10/11), 6.83 (br s, 1H, N*H*), 5.85 (t, *J* = 2.4 Hz, 1H, H-5), 4.87-4.83 (m, 1H, H-4), 2.58 (ddd, *J* = 6.6, 3.9, 1.5 Hz, 1H, H-2a), 2.56-2.46 (m, 2H, H-2b/3a), 2.15-2.07 (m, 1H, H-3b); ^{13}C-NMR (100MHz, $CDCl_3$): δ_C 170.4 (C-1), 135.3 (C-6), 132.3 (C-7), 130.5 (C-11), 130.3 (C-8), 128.1 (C-9), 127.8 (C-10), 80.7 (C-4), 55.3 (C-5), 26.6 (C-2), 20.7 (C-3); LR-ESI-MS: $C_{11}H_{12}ClN_2O_3$ $[M+H]^+$ *m/z* found 255.0, calcd 255.1; $C_{11}H_{11}ClN_2O_3Na$ $[M+Na]^+$ *m/z* found 277.0, calcd 277.0; HR-ESI-MS: $C_{11}H_{11}ClN_2O_3Na$ $[M+Na]^+$ *m/z* found 277.03489, calcd 277.03504, Δ = 0.58 ppm.

(5*S,6*R**)-6-(3-chlorophenyl)-5-nitropiperidin-2-one (31)**

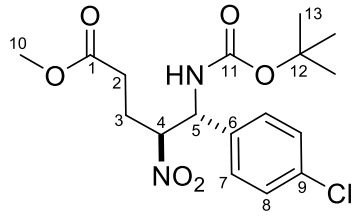
11 (106 mg, 0.72 mmol) and 3-chlorobenzaldehyde (81 µL, 0.72 mmol) were reacted according to General Procedure **A**. The crude material was purified by FCC (0.5% MeOH/DCM) to yield **31** (125 mg, 69%) as a yellow solid.



Mpt: 110.1-111.3 °C; ν_{max} (cm^{-1}) 3065, 2901, 1654, 1549, 786, 695; ^{1}H-NMR (400MHz, $CDCl_3$): δ_H 7.39-7.36 (m, 2H, H-9/10), 7.35 (s, 1H, H-7), 7.24-7.21 (m, 1H, H-11), 6.01 (br s, 1H, N*H*), 5.27 (d, *J* = 6.1 Hz, 1H, H-5), 4.71 (ddd, *J* = 7.6, 6.1, 4.0 Hz, 1H, H-4), 2.68-2.55 (m, 3H, H-2a/2b/3a), 2.35 (dddd, *J* = 11.6, 7.3, 3.4, 2.6 Hz, 1H, H-3b); ^{13}C-NMR (100MHz, $CDCl_3$): δ_C 172.6 (C-1), 147.9 (C-6), 135.0 (C-8), 130.8 (C-7), 129.8 (C-10), 126.8 (C-11), 124.8 (C-9), 84.8 (C-4), 58.4 (C-5), 26.8 (C-5), 23.3 (C-4); LR-ESI-MS: $C_{11}H_{12}ClN_2O_3$ $[M+H]^+$ *m/z* found 255.0, calcd 255.1; $C_{11}H_{11}ClN_2O_3Na$ $[M+Na]^+$ *m/z* found 277.0, calcd 277.0; HR-ESI-MS: $C_{11}H_{11}ClN_2O_3Na$ $[M+Na]^+$ *m/z* found 277.03492, calcd 277.03504, Δ = 0.47 ppm.

methyl (4*S*,5*R*)-5-((tert-butoxycarbonyl)amino)-5-(4-chlorophenyl)-4-nitropentanoate (67)

11 (6.68 g, 45.4 mmol), **66** (2.18 g, 9.08 mmol), K_2CO_3 (6.27 g, 45.4 mmol) and 1-[(8*R*, 9*R*)-1-benzyl-6'-methoxycinchonan-1-ium-9-yl]-3-[3,5-bis(trifluoromethyl)phenyl]-urea bromide **68** (0.68 g, 0.91 mmol) were combined in TBME (90.6 mL, 0.1M) at -20 °C and the reaction was stirred for 36 hours. Saturated $NaHCO_3$ was added and the aqueous phase was extracted with DCM seven times. The combined organic phases were dried, filtered and concentrated under reduced pressure. The resulting crude material was purified by FCC (1:1 Et_2O:PE) to give **67** (2.46 g, dr 7:1 70%) as a colourless oil. The ee was determined by HPLC analysis (Chiralpak AD, hexane/iso-propanol 80:20, λ 220 nm, 0.5 mL/min): $t_{(trans\text{-}\mathbf{67},\ \text{minor enantiomer})}$ = 21.87 min, 2.23%; $t_{(trans\text{-}\mathbf{67},\ \text{major enantiomer})}$ = 23.53 min, 42.74%; $t_{(cis\text{-}\mathbf{67},\ \text{minor enantiomer})}$ = 26.49 min, 2.65%; $t_{(cis\text{-}\mathbf{67},\ \text{major enantiomer})}$ 27.95 min, 52.38% [*trans*-**67** 90% ee, *cis*-**67** 90% ee].



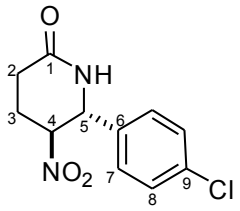
ν_{max} (cm^{-1}) 3379, 2977, 1736, 1707, 1682, 1551, 1163, 830; ^{1}H-NMR (400MHz, $CDCl_3$): δ_H 7.36 (dd, *J* = 8.3, 5.6 Hz, 2H, H-7 or 8), 7.23 (dd, *J* = 8.3, 3.9 Hz, 2H, H-7 or 8), 5.70 (br s, 1H, N*H*), 5.18 (br s, 1H, H-5), 4.94 (br s, 1H, H-4), 3.72 (s, 3H, H-10), 2.54-2.25 (m, 4H, H-2a/2b/3a/3b), 1.45 (s, 9H, H-13); ^{13}C-NMR (100MHz, $CDCl_3$): δ_C 186.1 (C-11), 172.4 (C-1), 134.7 (C-9), 134.5 (C-6), 129.3 (C-7 or 8), 128.3 (C-7 or 8), 89.9 (C-4), 77.2 (C-12), 56.4 (C-5), 52.0 (C-10), 29.7 (C-2), 28.2 (C-13), 25.4 (C-3); LR-ESI-MS: $C_{17}H_{24}ClN_2O_6$ $[M+H]^+$ *m/z* found 387.2, calcd 387.1; HR-ESI-MS: $C_{17}H_{24}ClN_2O_6$ $[M+H]^+$ *m/z* found 387.1321, calcd 387.1317, Δ = -0.49 ppm.

(5*S,6*R**)-6-(4-chlorophenyl)-5-nitropiperidin-2-one (32)**

Method A. 11 (4.08 g, 27.8 mmol) and 4-chlorobenzaldehyde (3.90 g, 27.8 mmol) were reacted according to General Procedure **A**. The crude material was purified by FCC (0.5% MeOH/DCM) to yield **32** (5.49 g, 78%) as a white powder.

Method B. To **67** (3.84 g, 10.9 mmol) in DCM (140 mL, 0.08M) was added TFA (4.2 mL, 54.5 mmol) and the reaction was stirred at ambient temperature for 6 hours. The reaction mixture was concentrated under reduced pressure. Saturated $NaHCO_{3(aq)}$ (56 mL, 0.2M) and DCM (84 mL, 0.13M) were added and the reaction was stirred for 6 hours at ambient temperature. The reaction was quenched with 1M HCl and the organic phase was separated. The aqueous phase was extracted with ethyl acetate three times and the combined organic phases were dried, filtered and concentrated under reduced pressure. The crude material was dissolved in DCM (56 mL, 0.2M), DBU (0.16 mL, 1.09 mmol) was added and the reaction was stirred at ambient temperature for 4 days. The reaction was quenched with 1M HCl and the aqueous phase was extracted with DCM three times. The

combined organic phases were dried, filtered and concentrated to give crude material that was purified by FCC (0.5% MeOH/DCM) to yield **32** (2.03 g, 73%) as a white powder.



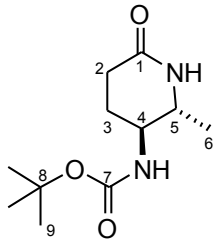
Mpt: 138.1-139.3 ^{o}C; ν_{max} (cm^{-1}) 3166, 3043, 2897,1653, 1555, 843, 818, 622; ^{1}H-NMR (400MHz, $CDCl_3$): δ_H 7.42 (d, *J* = 8.5 Hz, 2H, H-7), 7.29 (d, *J* = 8.5 Hz, 2H, H-8), 5.84 (br s, 1H, N*H*), 5.24 (d, *J* = 6.3 Hz, 1H, H-5), 4.68 (ddd, *J* = 7.6, 6.7, 4.0 Hz, 1H, H-4), 2.74-2.55 (m, 3H, H-2a/2b/3a), 2.40-2.31 (m, 1H, H-3b); ^{13}C-NMR (100MHz, $CDCl_3$): δ_C 169.6 (C-1), 135.8 (C-6), 135.5 (C-9), 129.7 (C-8), 127.9 (C-7), 85.1 (C-4), 58.4 (C-5), 27.8 (C-2), 23.5 (C-3); LR-ESI-MS: $C_{11}H_{12}ClN_2O_3$ $[M+H]^+$ *m/z* found 255.0, calcd 255.1; $C_{11}H_{11}ClN_2O_3Na$ $[M+Na]^+$ *m/z* found 277.0, calcd 277.0; HR-ESI-MS: $C_{11}H_{11}ClN_2O_3Na$ $[M+Na]^+$ *m/z* found 277.03494, calcd 277.03504, Δ = -0.36 ppm.

General procedure B

The appropriate nitrolactam (1 eq) was dissolved in MeOH (0.15M) and the solution was cooled to 0^{o}C. Nickel (II) chloride hexahydrate (0.05 eq) was added and the reaction was stirred for five minutes. Sodium borohydride (4 eq) was added portionwise over 30 minutes, then the reaction was stirred at 0^{o}C for a further 30 minutes. Di-*tert*-butyl dicarbonate (1.2 eq) was added and the reaction was allowed to warm to ambient temperature with stirring for 12 hours. The reaction mixture was poured into a mixture of 2:1:2 brine:$NaHCO_{3(sat\ aq)}$:EtOAc and the organic phase was removed. The aqueous phase was extracted with EtOAc three times, then the organic phases were combined, dried over sodium sulfate and concentrated under reduced pressure. The crude material was purified with FCC to yield the title compound.

***tert*-butyl (2*R**,3*S**)-2-methyl-6-oxopiperidin-3-ylcarbamate (17)**

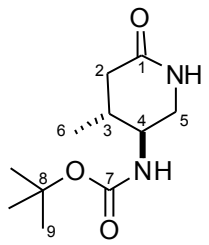
13 (86.1 mg, 0.54 mmol) was reacted according to General Procedure **B**. The crude material was purified by FCC (5% MeOH/DCM) to yield **17** (93 mg, 75%) as white crystals.



Mpt: 136.0-137.7 ^{o}C; ν_{max} (cm^{-1})3376, 2979, 2931, 1687, 1518, 1171; ^{1}H-NMR (400MHz, $CDCl_3$): δ_H 6.40 (s, 1H, N*H*), 4.63 (d, *J* = 7.0 Hz, 1H, N*H*), 3.63-3.53 (m, 1H, H-5), 3.31-3.25 (m, 1H, H-4), 2.41 (dd, *J* = 8.1, 6.4 Hz, 2H, H-2a/2b), 2.06-1.99 (m, 1H, H-3a), 1.80-1.67 (m, 1H, H-3b), 1.42 (s, 9H, H-9), 1.22 (d, *J* = 6.3 Hz, 3H, H-6); ^{13}C-NMR (100MHz, $CDCl_3$): δ_C 1a71.3 (C-1), 155.3 (C-7), 79.9 (C-8), 53.6 (C-4), 50.3 (C-5), 29.2 (C-2), 28.3 (C-9), 25.9 (C-3), 20.7 (C-6); LR-ESI-MS: $C_{11}H_{20}N_2O_3Na$ $[M+Na]^+$ *m/z* found 251.2, calcd 251.1; HR-ESI-MS: $C_{11}H_{20}N_2O_3Na$ $[M+Na]^+$ *m/z* found 251.1363, calcd 251.1366.

***tert*-butyl (3*S**,4*R**)-4-methyl-6-oxopiperidin-3-ylcarbamate (18)**

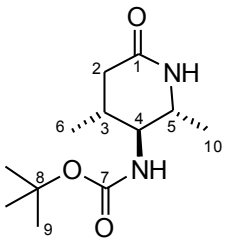
14 (100 mg, 0.63 mmol) was reacted according to General Procedure **B**. The crude material was purified by FCC (MeOH/DCM) to yield **18** (122 mg, 85%) as white crystals.



Mpt: 160.2-162.2 ^{o}C; ν_{max} (cm^{-1}) 3361, 3223, 2972, 1721, 1641, 1523, 1158; ^{1}H-NMR (400MHz, $CDCl_3$): δ_H 6.04 (s, 1H, N*H*), 4.55 (d, *J* = 7.8 Hz, 1H, N*H*), 3.64-6.62 (m, 1H, H-4), 3.56-3.54 (m, 1H, H-5a), 3.05 (dd, *J* = 11.4, 8.8 Hz, 1H, H-5b), 2.53 (dd, *J* = 17.8, 5.6 Hz, 1H, H-2a), 2.13 (dd, *J* = 17.8, 9.2 Hz, 1H, H-2b), 1.98-1.91 (m, 1H, H-3), 1.43 (s, 9H, H-9), 1.04 (d, *J* = 6.8 Hz, 3H, H-6); ^{13}C-NMR (100MHz, $CDCl_3$): δ_C 171.3 (C-1), 155.4 (C-7), 77.2 (C-8), 50.0 (C-4),45.7 (C-5), 37.3 (C-2), 32.3 (C-3), 28.3 (C-9), 18.2 (C-6); LR-ESI-MS: $C_{11}H_{20}N_2O_3Na$ $[M+Na]^+$ *m/z* found 251.1, calcd 251.1; HR-ESI-MS: $C_{11}H_{20}N_2O_3Na$ $[M+]^+$ *m/z* found 251.1375, calcd 251.1366.

***tert*-butyl (2*R**,3*S**,4*R**)-2,4-dimethyl-6-oxopiperidin-3-ylcarbamate (19)**

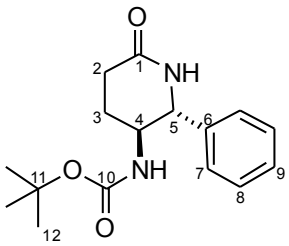
15 (70.1 mg, 0.41 mmol) was reacted according to General Procedure **B**. The crude material was purified by FCC (4% MeOH/DCM) to yield **19** (38 mg, 39%) as a white powder.



Mpt: 107.2-109.0 °C; ν_{max} (cm^{-1}) 3357, 3194, 2977, 2930, 1714, 1697, 1523, 1165; ^{1}H-NMR (400MHz, $CDCl_3$): δ_H 6.80 (s, 1H, N*H*), 4.47 (d, *J* = 8.8 Hz, 1H, N*H*), 3.24-3.14 (m, 2H, H-4/5), 2.46 (dd, *J* = 17.6, 4.9 Hz, 1H, H-2a), 2.08 (dd, *J* = 17.6, 11.9 Hz, 1H, H-2b), 1.87-1.77 (m, 1H, H-3), 1.40 (s, 9H, H-9), 1.20 (d, *J* = 5.6 Hz, 3H, H-10), 0.97 (d, *J* = 6.6 Hz, 3H, H-6); ^{13}C-NMR (100MHz, $CDCl_3$): δ_C 171.4 (C-1), 155.9 (C-7), 79.7 (C-8), 57.1 (C-5), 53.5 (C-4), 38.7 (C-2), 33.1 (C-3), 28.3 (C-9), 20.1 (C-10), 17.8 (C-6); LR-ESI-MS: $C_{12}H_{23}N_2O_3$ $[M+H]^+$ *m/z* found 243.2, calcd 243.1; HR-ESI-MS: $C_{12}H_{22}N_2O_3Na$ $[M+Na]^+$ *m/z* found 265.1527, calcd 265.1523.

***tert*-butyl (2*R**,3*S**)-6-oxo-2-phenylpiperidin-3-ylcarbamate (20)**

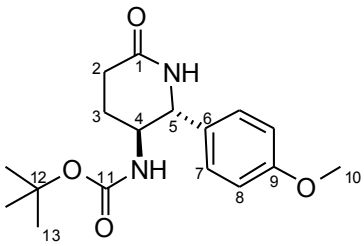
16 (100 mg, 0.45 mmol) was reacted according to General Procedure **B**. The crude material was purified by FCC (4% MeOH/DCM) to yield **20** (113 mg, 89%) as white crystals.



Mpt: 205.1-207.0°C; ν_{max} (cm^{-1}) 3383, 3065, 2981, 2932, 1676, 1515, 1170; ^{1}H-NMR (400MHz, DMSO-d_6): δ_H 7.66 (br s, 1H, N*H*), 7.35 (t, *J* = 7.3 Hz, 2H, H-8), 7.29-7.25 (m, 3H, H-7/9), 7.13 (d, *J* = 7.3 Hz, 1H, N*H*), 4.38 (d, *J* = 5.1 Hz, 1H, H-5), 3.58-3.52 (m, 1H, H-4), 2.41 (dt, *J* = 17.9, 6.4 Hz, 1H, H-2a), 2.30 (dt, *J* = 18.1, 6.8 Hz, 1H, H-2b), 1.78-1.62 (m, 2H, H-3a/3b), 1.30 (s, 9H, H-12); ^{13}C-NMR (100MHz, $CDCl_3$): δ_C 169.9 (C-1), 155.1 (C-10), 141.7 (C-6), 128.1 (C-8), 127.2 (C-9), 126.8 (C-7), 77.8 (C-10), 60.0 (C-5), 51.0 (C-4), 28.5 (C-2), 28.1 (C-12), 23.9 (C-3); LR-ESI-MS: $C_{16}H_{23}N_2O_3$ $[M+H]^+$ *m/z* found 291.1, calcd 291.1; HR-ESI-MS: $C_{16}H_{22}N_2O_3Na$ $[M+Na]^+$ *m/z* found 313.1512, calcd 313.1523.

***tert*-butyl (2*R**,3*S**)-2-(4-methoxyphenyl)-6-oxopiperidin-3-ylcarbamate (33)**

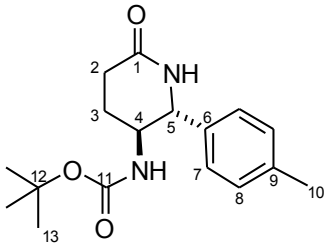
25 (45 mg, 0.18 mmol) was reacted according to General Procedure **B**. The crude material was purified by FCC (2.5% MeOH/DCM) to yield **33** (42 mg, 73%) as a white powder.



Mpt: 226.8-228.6 °C; ν_{max} (cm^{-1}) 3378, 2980, 1675, 1513, 1163, 838; H-NMR (400MHz, $CDCl_3$): δ_H 7.24 (d, *J* = 8.5 Hz, 2H, H-7), 6.89 (d, *J* = 8.7 Hz, 2H, H-8), 6.03 (br s, 1H, N*H*), 4.87 (d, *J* = 6.9 Hz, 1H, N*H*), 4.44 (br s, 1H, H-5), 3.85 (br s, 1H, H-4), 2.57-2.51 (m, 2H, H-2a/2b), 2.03 (dtd, *J* = 13.6, 6.9, 3.4 Hz, 1H, H-3a), 1.82 (dtd, *J* = 14.3, 7.1, 6.8 Hz, 1H, H-3b), 1.36 (s, 9H, H-13); ^{13}C-NMR (100MHz, $CDCl_3$): δ_C 171.2 (C-1), 159.5 (C-9), 155.0 (C-11), 131.7 (C-6), 127.9 (C-7), 114.1 (C-8), 79.9 (C-12), 60.4 (C-5), 55.3 (C-10), 53.4 (C-4), 28.5 (C-2), 28.2 (C-13), 21.0 (C-3); LR-ESI-MS: $C_{17}H_{25}N_2O_4$ $[M+H]^+$ *m/z* found 321.2, calcd 321.2; $C_{17}H_{24}N_2O_4Na$ $[M+Na]^+$ *m/z* found 343.0, calcd 343.1; HR-ESI-MS: $C_{17}H_{24}N_2O_4Na$ $[M+Na]^+$ *m/z* found 343.16247, calcd 343.16283, Δ = 1.03 ppm.

***tert*-butyl (2*R**,3*S**)-6-oxo-2-p-tolylpiperidin-3-ylcarbamate (34)**

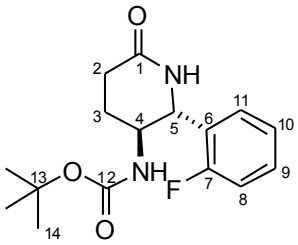
26 (135 mg, 0.58 mmol) was reacted according to General Procedure **B**. The crude material was purified by FCC (2.5% MeOH/DCM) to yield **34** (159 mg, 91%) as a white powder.



Mpt: 210.9-212.3 °C; ν_{max} (cm^{-1}) 3387, 2936, 1673, 1511, 1164, 727; ^{1}H-NMR (400MHz, $CDCl_3$): δ_H 7.21 (d, *J* = 8.1 Hz, 2H, H-8), 7.17 (d, *J* = 8.1 Hz, 2H, H-7), 6.16 (br s, 1H, N*H*), 4.97 (br s, 1H, N*H*), 4.49 (br s, 1H, H-5), 3.87 (br s, 1H, H-4), 2.58-2.52 (m, 2H, H-2a/2b), 2.34 (s, 3H, H-10), 2.00 (dtd, *J* = 13.8, 6.8, 3.4 Hz, 1H, H-3a), 1.81 (dtd, *J* = 14.4, 7.1, 6.4 Hz, 1-H, H-3b), 1.37 (s, 9H, H-13); ^{13}C-NMR (100MHz, $CDCl_3$): δ_C 171.3 (C-1), 155.0 (C-11), 138.0 (C-6), 136.8 (C-9), 129.4 (C-7), 126.6 (C-8), 79.9 (C-12), 61.6 (C-5), 50.8 (C-4), 28.4 (C-2), 28.2 (C-13), 23.4 (C-3), 21.0 (C-10); LR-ESI-MS: $C_{17}H_{25}N_2O_3$ $[M+H]^+$ *m/z* found 305.1, calcd 305.2; $C_{17}H_{24}N_2O_3Na$ $[M+Na]^+$ *m/z* found 327.1, calcd 327.2; HR-ESI-MS: $C_{17}H_{24}N_2O_3Na$ $[M+Na]^+$ *m/z* found 327.16733, calcd 327.16791, Δ = 1.79 ppm.

***tert*-butyl (2*R**,3*S**)-2-(2-fluorophenyl)-6-oxopiperidin-3-ylcarbamate (35)**

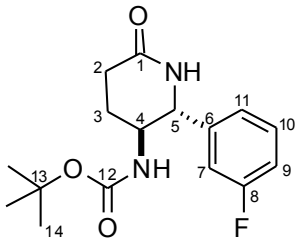
27 (117 mg, 0.5 mmol) was reacted according to General Procedure **B**. The crude material was purified by FCC (2.5% MeOH/DCM) to yield **35** (126 mg, 77%) as a white powder.



Mpt: 180.0-181.6 °C; ν_{max} (cm^{-1}) 3361, 2976, 1687, 1668, 1173, 760; ^{1}H-NMR (400MHz, $CDCl_3$): δ_H 7.41-7.28 (m, 2H, H-9/11), 7.19 (t, *J* = 7.6 Hz, 1H, H-10), 7.06 (dd, *J* = 9.8, 8.3 Hz, 1H, H-8), 6.05 (br s, 1H, N*H*), 4.85 (br s, 1H, *N*H), 4.76 (d, *J* = 5.1 Hz, 1H, H-5), 4.03-3.93 (m, 1H, H-4), 2.62-2.54 (m, 2H, H-2a/2b), 2.10-2.02 (m, 1H, H-3a), 1.95-1.85 (m, 1H, H-3b), 1.33 (s, 9H, H-14); ^{13}C-NMR (100MHz, $CDCl_3$): δ_C 171.5 (C-1), 160.3 (d, *J* = 250.3 Hz, C-7), 154.8 (C-12), 130.0 (d, *J* = 8.7 Hz, C-9), 128.1 (d, *J* = 9.4 Hz, C-11), 126.6 (d, *J* = 18.3 Hz, C-6), 124.7 (d, *J* = 3.2 Hz, C-10), 116.7 (d, *J* = 22.3 Hz, C-8), 79.8 (C-13), 55.6 (d, *J* = 7.2 Hz, C-5), 50.1 (C-4), 29.0 (C-2), 28.1 (C-14), 25.3 (C-3); LR-ESI-MS: $C_{16}H_{22}FN_2O_3$ $[M+H]^+$ *m/z* found 309.1, calcd 309.2; $C_{16}H_{21}FN_2O_3Na$ $[M+Na]^+$ *m/z* found 331.1, calcd 331.2; HR-ESI-MS: $C_{16}H_{21}FN_2O_3Na$ $[M+Na]^+$ *m/z* found 331.14268, calcd 331.14284, Δ = 0.52 ppm.

***tert*-butyl (2*R**,3*S**)-2-(4-fluorophenyl)-6-oxopiperidin-3-ylcarbamate (36)**

28 (47 mg, 0.5 mmol) was reacted according to General Procedure **B**. The crude material was purified by FCC (2.5% MeOH/DCM) to yield **36** (47 mg, 77%) as a white needles.

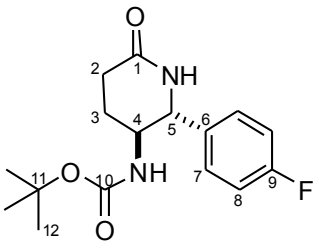


Mpt: 178.1-179.4 °C; ν_{max} (cm^{-1}) 3363, 2985, 1679, 1524, 1234, 1156, 855; ^{1}H-NMR (400MHz, $CDCl_3$): δ_H 7.35 (td, *J* = 7.9, 5.9 Hz, 1H, H-10), 7.15 (d, *J* = 7.6 Hz, 1H, H-11), 7.08-6.98 (m, 2H, H-7/9), 6.14 (br s, 1H, N*H*), 4.89 (br s, 1H, N*H*), 4.55 (br s, 1H, H-5), 3.9 (br s, 1H, H-4), 2.64-2.43 (m, 2H, H-2a/2b), (, *J* = , H, H-), 2.00 (dtd, *J* = 13.8, 7.0, 3.3 Hz, 1H, H-3a), 1.84 (dq, *J* = 14.1, 7.0 Hz, 1H, H-3b), 1.39 (s, 9H, H-14); ^{13}C-NMR (100MHz, $CDCl_3$): δ_C 171.1 (C-1), 163.0 (d, *J* = 247.2 Hz, C-8), 154.9 (C-12), 142.5 (d, *J* = 7.2 Hz, C-6), 130.4 (d, *J* = 7.9 Hz, C-10), 122.3 (d, *J* = 4.0 Hz, C-11), 115.2 (d, *J* = 20.7 Hz, C-9), 113.9 (d, *J* = 22.3 Hz, C-7), 80.1 (C-13), 61.4 (C-5), 50.7 (C-4), 28.2 (C-14), 28.1 (C-2), 23.4 (C-3); LR-ESI-MS: $C_{16}H_{21}FN_2O_3Na$ $[M+Na]^+$ *m/z* found 331.1, calcd 331.1; HR-ESI-MS: $C_{16}H_{21}FN_2O_3Na$ $[M+Na]^+$ *m/z* found 331.14248, calcd 311.14284, Δ = 1.13 ppm.

***tert*-butyl (2*R**,3*S**)-2-(4-fluorophenyl)-6-oxopiperidin-3-ylcarbamate (37)**

29 (118 mg, 0.5 mmol) was reacted according to General Procedure **B**. The crude material was purified by FCC (2.5% MeOH/DCM) to yield **37** (124 mg, 81%) as a white powder.

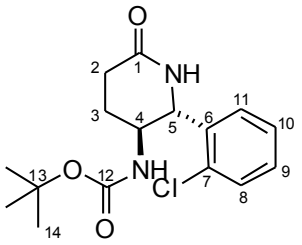
Mpt: 223.5-225.2 °C; ν_{max} (cm^{-1}) 3382, 1676, 1515, 1234, 836; ^{1}H-NMR (400MHz, $CDCl_3$): δ_H 7.32 (dd, *J* = 8.6, 5.1 Hz, 2H, H-7), 7.06 (t, *J* = 8.6 Hz, 2H, H-8), 6.20 (br s, 1H, N*H*), 4.89 (br s, 1H, N*H*), 4.49 (br s, 1H, H-5), 3.87 (br s, 1H, H-4), 2.63-2.51 (m, 2H, H-2a/2b), 2.01 (tdd, *J* = 70.3, 6.8, 3.4 Hz, 1H, H-3a),



1.88-1.77 (m, 1H, H-3b), 1.37 (s, 9H, H-12); ^{13}C-NMR (100MHz, $CDCl_3$): δ_C 171.2 (C-1), 162.6 (d, *J* = 247 Hz, C-9), 154.9 (C-10), 135.5 (d, *J* = 3.2 Hz, C-6), 128.5 (d, *J* = 7.9 Hz, C-7), 115.7 (d, *J* = 21.5 Hz, C-8), 80.1 (C-10), 61.4 (C-5), 50.8 (C-4), 28.4 (C-2), 28.2 (C-12), 23.7 (C-3); LR-ESI-MS: $C_{16}H_{22}FN_2O_3$ $[M+H]^+$ *m/z* found 309.1, calcd 309.2; $C_{16}H_{21}FN_2O_3Na$ $[M+Na]^+$ *m/z* found 331.1, calcd 331.1; HR-ESI-MS: $C_{16}H_{21}FN_2O_3Na$ $[M+Na]^+$ *m/z* found 331.14244, calcd 311.14284, Δ = 1.23 ppm.

***tert*-butyl (2*R**,3*S**)-2-(2-chlorophenyl)-6-oxopiperidin-3-ylcarbamate (38)**

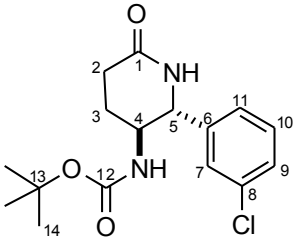
30 (47 mg, 0.19 mmol) was reacted according to General Procedure **B**. The crude material was purified by FCC (2.5% MeOH/DCM) to yield **38** (43 mg, 72%) as a white powder.



Mpt: 206.4-208.4 °C; ν_{max} (cm^{-1}) 3375, 1688, 1662, 1512, 1172, 758; ^{1}H-NMR (400MHz, $CDCl_3$): δ_H 7.41 (d, *J* = 7.6 Hz, 1H, H-8), 7.37 (td, *J* = 7.7, 1.2 Hz, 1H, H-11), 7.32 (dd, *J* = 7.6, 1.6 Hz, 1H, H-10), 7.27 (ddd, *J* = 7.8, 7.0, 1.7 Hz, H, H-), 6.12 (br s, 1H, N*H*), 4.91 (br s, 1H, N*H*), 4.89 (d, *J* = 5.1 Hz, 1H, H-5), 4.09-4.00 (m, 1H, H-4), 2.58-2.53 (m, 2H, H-2a/2b), 1.99 (dtd, *J* = 13.1, 6.6, 3.4 Hz, 1H, H-3a), 1.97-1.85 (m, 1H, H-3b), 1.33 (s, 9H, H-14); ^{13}C-NMR (100MHz, $CDCl_3$): δ_C 171.6 (C-1), 154.7 (C-12), 136.8 (C-6), 133.2 (C-7), 129.9 (C-11), 129.5 (C-9), 128.4 (C-10), 127.5 (C-10), 79.8 (C-13), 58.5 (C-5), 49.8 (C-4), 28.8 (C-2), 28.2 (C-14), 24.8 (C-3); LR-ESI-MS: $C_{16}H_{21}ClN_2O_3Na$ $[M+Na]^+$ *m/z* found 347.0, calcd 347.1; HR-ESI-MS: $C_{16}H_{21}ClN_2O_3Na$ $[M+Na]^+$ *m/z* found 347.11301, calcd 347.11329, Δ = 0.82 ppm.

***tert*-butyl (2*R**,3*S**)-2-(3-chlorophenyl)-6-oxopiperidin-3-ylcarbamate (39)**

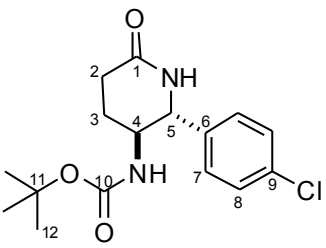
31 (157 mg, 0.62 mmol) was reacted according to General Procedure **B**. The crude material was purified by FCC (2.5% MeOH/DCM) to yield **39** (119 mg, 60%) as white crystals.



Mpt: 209.3-211.1 °C; ν_{max} (cm^{-1}) 3359, 2983, 1678, 1528, 1161, 795; ^{1}H-NMR (400MHz, $CDCl_3$): δ_H 7.42-7.30 (m, 4H, H-7/9/10/11), 5.98 (br s, 1H, N*H*), 4.80 (br s, 1H, N*H*), 4.53 (br s, 1H, H-5), 3.89 (br s, 1H, H-4), 2.68-2.50 (m, 2H, H-2a/2b), 2.08-1.97 (m, 1H, H-3a), 1.86 (dq, *J* = 13.6, 6.6 Hz, 1H, H-3b), 1.39 (s, 9H, H-14); ^{13}C-NMR (100MHz, $CDCl_3$): δ_C 175.1 (C-1), 152.6 (C-12), 141.9 (C-6), 132.5 (C-10), 130.2 (C-7, 9, 10 or 11), 128.8 (C-7, 9, 10 or 11), 128.5 (C-7, 9, 10 or 11), 127.0 (C-7, 9, 10 or 11), 81.4 (C-13), 61.5 (C-5), 50.6 (C-4), 30.8 (C-2), 28.2 (C-14), 23.5 (C-3); LR-ESI-MS: $C_{16}H_{22}ClN_2O_3$ $[M+H]^+$ *m/z* found 325.0, calcd 325.1; $C_{16}H_{21}ClN_2O_3Na$ $[M+Na]^+$ *m/z* found 347.0, calcd 347.1; HR-ESI-MS: $C_{16}H_{21}ClN_2O_3Na$ $[M+Na]^+$ *m/z* found 347.11249, calcd 347.11329, Δ = 2.32 ppm.

***tert*-butyl (2*R**,3*S**)-2-(4-chlorophenyl)-6-oxopiperidin-3-ylcarbamate (40)**

32 (101 mg, 0.72 mmol) was reacted according to General Procedure **B**. The crude material was purified by FCC (0.5% MeOH/DCM) to yield **40** (136 mg, 74%) as a white powder.



Mpt: 233.9-235.9 °C; ν_{max} (cm^{-1}) 3380, 2382, 1675, 1514, 1493, 1163, 841; ^{1}H-NMR (400MHz, CD_3OD): δ_H 7.70 (d, *J* = 1.2 Hz, 1H, N*H*), 7.38 (d, *J* = 8.3 Hz, 2H, H-7), 7.27 (d, *J* = 8.3 Hz, 2H, H-8), 7.11 (, *J* = 7.8 Hz, 1H, N*H*), 4.31 (d, *J* = 6.6 Hz, 1H, H-5), 3.56-3.47 (m, 1H, H-4), 2.41-2.26 (m, 2H, H-2a/2b), 1.76-1.61 (m, 2H, H-3a/3b), 1.27 (s, 9H, H-12); ^{13}C-NMR (100MHz, CD_3OD): δ_C 179.6 (C-1), 150.2 (C-10), 141.4 (C-6), 138.5 (C-8), 137.7 (C-7), 132.6 (C-9), 87.5 (C-11), 69.2 (C-5), 60.7 (C-4), 38.5 (C-2), 37.7 (C-12), 34.2 (C-3); LR-ESI-MS: $C_{16}H_{21}ClN_2O_3Na$? $[M+Na]^+$ *m/z* found

347.0, calcd 347.1; HR-ESI-MS: $C_{16}H_{21}ClN_2O_3Na$ $[M+Na]^+$ *m/z* found 347.11298, calcd 347.11329, Δ = 0.91 ppm.

General procedure C

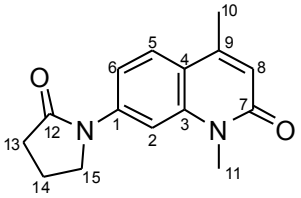
6 (1.0 eq) was dissolved in 1,4-dioxane (0.04M) and $Pd_2(dba)_3$ (0.1 eq), Xantphos (0.15 eq), the appropriate heterocycle (1.2 eq) and Cs_2CO_3 (1.4 eq) were added. The reaction was heated to 100 °C and stirred for 12 hours. The reaction was allowed to cool to ambient temperature, diluted with DCM, filtered and concentrated under reduced pressure. The crude material was purified by FCC (IPA/hexane) to yield the title compound.

General procedure D

1,4-Dioxane (0.1M) was added to the appropriate lactam (1 eq), **4** (1.5 eq) and K_3PO_4 (2 eq) under inert conditions and degassed. CuI (1 eq.) and (+/-)-*trans*-1,2-diaminocyclohexane (1 eq) were added, and the reaction was sealed and heated at 97 °C for 42 h. The reaction mixture was filtered through celite, which was then washed with DCM. The filtrate was concentrated under reduced pressure and purified with FCC (15% IPA/hexane then 30% IPA/hexane) to yield the title compound.

1,4-dimethyl-7-(2-oxopyrrolidin-1-yl)quinolin-2(1*H*)-one (5)

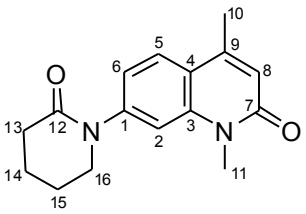
2-Pyrrolidinone (24.3 µL, 0.29 mmol) was reacted according to General Procedure **C** to yield **5** (59 mg, 96%) as a white powder.



Mpt: 226.0-226.9 °C; ν_{max} (cm^{-1}) 3152, 3128, 2978, 2945, 2927, 2897, 1689, 1640, 1617, 1588, 1415, 1257; ^{1}H-NMR (400MHz, $CDCl_3$): δ_H 7.94 (d, *J* = 1.9 Hz, 1H, H-5), 7.61 (d, *J* = 8.5 Hz, 1H, H-2), 7.30 (dd, *J* = 8.8, 1.9 Hz, 1H, H-6), 6.48 (s, 1H, H-8), 3.93 (t, *J* = 7.0 Hz, 2H, H-15a/15b), 3.65 (s, 3H, H-11), 2.65 (t, *J* = 8.0 Hz, 2H, H-13a/13b), 2.40 (s, 3H, H-10), 2.19 (q, *J* = 7.9 Hz, 2H, H-14a/14b); ^{13}C-NMR (100MHz, $CDCl_3$): δ_C 174.8 (C-12), 162.4 (C-7), 146.0 (C-4), 141.3 (C-1), 140.4 (C-3), 125.5 (C-5), 119.8 (C-8), 117.8 (C-9), 112.9 (C-6), 105.1 (C-2), 48.7 (C-15), 33.0 (C-11), 29.3 (C-13), 18.8 (C-14), 17.9 (C-10); LR-ESI-MS: $C_{15}H_{17}N_2O_2$ $[M+H]^+$ *m/z* found 257.1, calcd 257.3; HR-ESI-MS: $C_{15}H_{16}N_2O_2Na$ $[M+Na]^+$ *m/z* found 279.1097, calcd 279.1104.

1,4-dimethyl-7-(2-oxopiperidin-1-yl)quinolin-2(1*H*)-one (6)

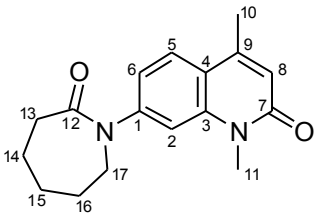
δ-Valerolactam (23.5 µL, 0.24 mmol) was reacted according to General Procedure **C** to yield **6** (40 mg, 76%) as a white solid.



Mpt: 274.8-276.1 °C; ν_{max} (cm^{-1}) 2984, 2947, 2862, 1663, 1630, 1597, 1383, 819; ^{1}H-NMR (400MHz, $CDCl_3$): δ_H 7.67 (d, *J* = 8.5 Hz, 1H, H-5), 7.26 (d, *J* = 1.7 Hz, 1H, H-2), 7.12 (dd, *J* = 8.5, 1.9 Hz, 1H, H-6), 6.52 (s, 1H, H-8), 3.69 (t, *J* = 1.7 Hz, 2H, H-16a/16b), 3.63 (s, 3H, H-11), 2.57 (t, *J* = 6.3 Hz, 2H, H-13a/13b), 2.40 (s, 3H, H-10), 2.00-1.93 (m, 4H, H-14a/14b/15a/15b); ^{13}C-NMR (100MHz, $CDCl_3$): δ_C 170.2 (C-12), 162.1 (C-7), 145.2 (C-4), 142.1 (C-1), 140.4 (C-3), 126.0 (C-5), 120.8 (C-8), 119.8 (C-9), 119.7 (C-6), 112.2 (C-2), 51.6 (C-16), 32.9 (C-13), 29.2 (C-11), 23.4 (C-14), 21.3 (C-15), 18.9 (C-10); LR-ESI-MS: $C_{18}H_{19}N_2O_2$ $[M+H]^+$ *m/z* found 271.1, calcd 271.2; HR-ESI-MS: $C_{18}H_{18}N_2O_2Na$ $[M+Na]^+$ *m/z* found 293.1250, calcd 293.1260.

1,4-dimethyl-7-(2-oxoazepan-1-yl)quinolin-2(1*H*)-one (7)

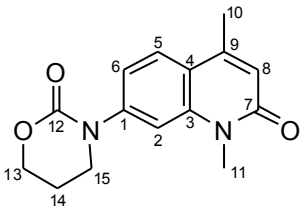
Caprolactam (27 mg, 0.24 mmol) was reacted according to General Procedure **C** to yield **7** (62 mg, 91%) as a white powder.



Mpt: 253.8-254.9 ^{o}C; ν_{max} (cm^{-1}) 2938, 2852, 1664, 1637, 1594, 1383, 976; ^{1}H-NMR (400MHz, $CDCl_3$): δ_H 7.65 (d, *J* = 8.3 Hz, 1H, H-5), 7.22 (d, *J* = 1.7 Hz, 1H, H-2), 7.07 (dd, *J* = 8.5, 1.7 Hz, 1H, H-6), 6.52 (s, 1H, H-8), 3.80 (br s, 2H, H-17a/17b), 3.63 (s, 3H, H-11), 2.71 (br s, 2H, H-13a/13b), 2.40 (s, 3H, H-10), 1.83 (br s, 6H, H-14a/14b/15a/15b/16a/16c); ^{13}C-NMR (100MHz, $CDCl_3$): δ_C 175.7 (C-12), 162.1 (C-7), 146.2 (C-4), 145.9 (C-1), 140.3 (C-3), 125.9 (C-5), 120.7 (C-8), 119.8 (C-6), 119.6 (C-9), 112.2 (C-2), 52.9 (C-17), 37.7 (C-13), 30.5 (C-15), 29.7 (C-11), 29.6 (C-16), 23.4 (C-14), 18.8 (C-10); LR-ESI-MS: $C_{17}H_{21}N_2O_2$ $[M+H]^+$ *m/z* found 285.1, calcd 285.1; HR-ESI-MS: $C_{17}H_{21}N_2O_2$ $[M+H]^+$ *m/z* found 285.1596, calcd 285.1598.

3-(1,4-dimethyl-2-oxo-1,2-dihydroquinolin-7-yl)-1,3-oxazinan-2-one (8)

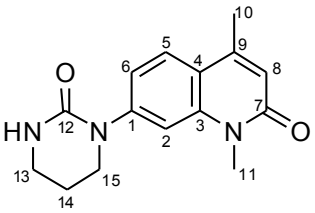
1,3-oxazinan-2-one (63.6 mg, 0.63 mmol) was reacted according to General Procedure **C** to yield **8** (7 mg, 5%) as a yellow oil.



ν_{max} (cm^{-1}) 2942, 1631, 1586, 1502, 1447, 1194, 851; ^{1}H-NMR (400MHz, DMSO-d_6): δ_H 7.76 (d, *J* = 8.6 Hz, 1H, H-5), 7.51 (d, *J* = 1.8 Hz, 1H, H-2), 7.28 (dd, *J* = 8.6, 1.9 Hz, 1H, H-6), 6.49 (s, 1H, H-8), 4.36 (t, *J* = 5.3 Hz, 2H, H-13a/13b), 3.76 (t, *J* = 6.0 Hz, 2H, H-15a/15b), 3.57 (s, 3H, H-11), 2.41 (s, 3H, H-10), 2.13 (q, *J* = 5.8 Hz, 2H, H-14a/14b); ^{13}C-NMR (100MHz, DMSO-d_6): δ_C 160.9 (C-7), 151.9 (C-12), 146.2 (C-4), 145.5 (C-1), 139.9 (C-3), 125.8 (C-5), 119.9 (C-8), 119.9 (C-6), 118.6 (C-9), 111.9 (C-2), 66.9 (C-13), 48.3 (C-15), 28.9 (C-11), 22.0 (C-14), 18.4 (C-10); LR-ESI-MS: $C_{15}H_{17}N_2O_3$ $[M+H]^+$ *m/z* found 273.1, calcd 273.1; HR-ESI-MS: $C_{15}H_{16}N_2O_3Na$ $[M+Na]^+$ *m/z* found 295.1046, calcd 295.1053.

1,4-dimethyl-7-(2-oxotetrahydropyrimidin-1(2H)-yl)quinolin-2(1H)-one (9)

Tetrahydropyrimidin-2(1*H*)-one (47.6 µL, 0.48 mmol) was reacted according to General Procedure **C** to yield **9** (33 mg, 52%) as a yellow powder.

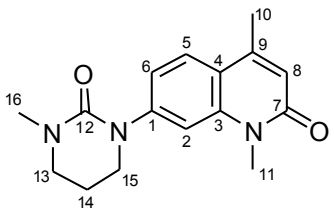


Mpt: 251.0-252.0 ^{o}C; ν_{max} (cm^{-1}) 3218, 2969, 2943, 2859, 1737, 1665, 1637, 1443, 1221, 1117; ^{1}H-NMR (400MHz, $CDCl_3$): δ_H 7.64 (d, *J* = 8.5 Hz, 1H, H-5), 7.35 (d, *J* = 1.9 Hz, 1H, H-2), 7.19 (dd, *J* = 8.8, 2.2 Hz, 1H, H-6), 6.51 (s, 1H, H-8), 5.56 (s , 1H, N*H*), 3.77 (t, *J* = 5.8 Hz, 2H, H-15a/15b), 3.66 (s, 3H, H-11), 3.44 (t, *J* = 5.6 Hz, 2H, H-13a/13b), 2.41 (s, 3H, H-10), 2.16-2.10 (m, 2H, H-14a/14b); ^{13}C-NMR (100MHz, $CDCl_3$): δ_C 162.3 (C-7), 155.3 (C-12), 146.0 (C-4), 145.5 (C-1), 140.2 (C-3), 125.5 (C-5), 120.3 (C-8), 118.9 (C-7), 118.7 (C-9), 111.2 (C-2), 48.5 (C-15), 40.7 (C-13), 29.3 (C-11), 22.3 (C-14), 18.9 (C-10); LR-ESI-MS: $C_{15}H_{18}N_3O_2$ $[M+H]^+$ *m/z* found 272.2, calcd 272.1; HR-ESI-MS: $C_{15}H_{17}N_3O_2Na$ $[M+Na]^+$ *m/z* found 294.1212, calcd 294.1213.

1,4-Dimethyl-7-(3-methyl-2-oxotetrahydropyrimidin-1(2*H*)-yl)quinolin-2(1*H*)-one (10)

1-Methyltetrahydropyrimidin-2(1*H*)-one (41.1 µL, 0.36 mmol) was reacted according to General Procedure **C** to yield **10** (26 mg, 33%) as a yellow powder.

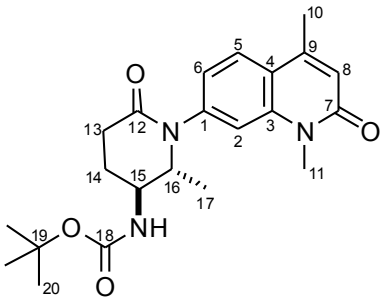
Mpt: 211.8-213.5 ^{o}C; ν_{max} (cm^{-1}) 2940, 1634, 1586, 1503, 1434, 1208, 845; ^{1}H-NMR (400MHz, DMSO-d_6): δ_H 7.65 (d, *J* = 8.8 Hz, 1H, H-5), 7.34 (d, *J* = 1.9 Hz, 1H, H-2), 7.20 (dd, *J* = 8.9, 1.9 Hz, 1H, H-6), 6.41 (s, 1H, H-8), 3.76 (t, *J* = 5.6 Hz, 2H, H-15a/15b), 3.53 (s, 3H, H-11), 3.35 (t, *J* = 6.1 Hz, 2H, H-13a/13b), 2.87 (s, 3H, H-16), 2.38 (s, 3H, H-10), 2.04 (q, *J* = 5.8 Hz, 2H, H-14a/14b); ^{13}C-NMR (100MHz, DMSO-



d_6): δ_C 161.0 (C-7), 154.2 (C-12), 146.6 (C-4), 146.2 (C-1), 139.6 (C-3), 124.9 (C-5), 118.9 (C-8), 118.8 (C-6), 116.8 (C-9), 110.0 (C-2), 48.0 (C-15), 47.5 (C-13), 35.3 (C-16), 28.8 (C-11), 22.1 (C-14), 18.4 (C-10); LR-ESI-MS: $C_{16}H_{20}N_3O_2$ $[M+H]^+$ *m/z* found 286.2, calcd 286.2; HR-ESI-MS: $C_{16}H_{19}N_3O_2Na$ $[M+Na]^+$ *m/z* found 308.1382, calcd 308.1369.

***tert*-Butyl (2*R**,3*S**)-1-(1,4-dimethyl-2-oxo-1,2-dihydroquinolin-7-yl)-2-methyl-6-oxopiperidin-3-ylcarbamate (21)**

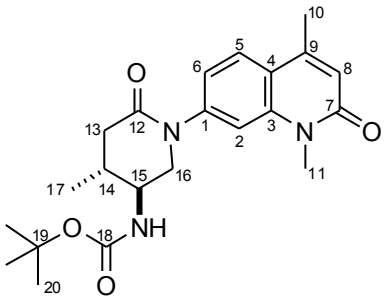
17 (50.5 mg, 0.22 mmol) was reacted according to General Procedure **C** to yield **21** (19.3 mg, 26%) as a pale yellow oil.



ν_{max} (cm^{-1}) 3278, 2975, 1650, 1592, 1169, 730; ^{1}H-NMR (400MHz, $CDCl_3$): δ_H 7.74 (d, *J* = 8.5 Hz, 1H, H-5), 7.18 (d, *J* = 1.9 Hz, 1H, H-2), 7.06 (dd, *J* = 8.4, 2.0 Hz, 1H, H-6), 6.61 (d, *J* = 1.1 Hz, 1H, H-8), 4.96 (br s, 1H, N*H*), 4.06 (br s, 1H, H-16), 3.92 (br s, 1H, H-15), 3.67 (s, 3H, H-11), 2.71 (ddd, *J* = 18.9, 7.6, 4.9 Hz, 1H, H-13a), 2.62 (ddd, *J* = 18.8, 9.5, 7.3 Hz, 1H, H-13b), 2.46 (d, *J* = 0.9 Hz, 3H, H-10), 2.36-2.28 (m, 1H, H-14a), 2.02-1.95 (m, 1H, H-14b), 1.50 (s, 9H, H-20), 1.25 (d, *J* = 6.6 Hz, 3H, H-17); ^{13}C-NMR (100MHz, $CDCl_3$): δ_C 168.9 (C-12), 162.1 (C-7), 155.3 (C-18), 146.0 (C-4), 143.3 (C-1), 140.6 (C-3), 126.2 (C-5), 121.4 (C-6), 121.3 (C-8), 120.5 (C-9), 113.9 (C-2), 80.3 (C-19), 61.0 (C-16), 49.6 (C-15), 29.3 (C-11), 28.4 (C-20), 28.2 (C-13), 22.5 (C-14), 19.4 (C-17), 19.0 (C-10); LR-ESI-MS: $C_{22}H_{30}N_3O_4$ $[M+H]^+$ *m/z* found 400.1, calcd 400.2; $C_{22}H_{39}N_3O_4Na$ $[M+Na]^+$ *m/z* found 422.1, calcd 422.2; HR-ESI-MS: $C_{22}H_{29}N_3O_4Na$ $[M+Na]^+$ *m/z* found 422.20431, calcd 422.20503, Δ = 1.69 ppm.

***tert*-Butyl (3*S**,4*R**)-1-(1,4-dimethyl-2-oxo-1,2-dihydroquinolin-7-yl)-4-methyl-6-oxopiperidin-3-ylcarbamate (22)**

18 (55.5 mg, 0.24 mmol) was reacted according to General Procedure **C** to yield **22** (60 mg, 75%) as a yellow powder.

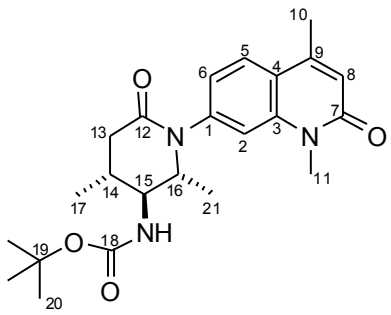


Mpt: 139.6-140.2 ^{o}C; ν_{max} (cm^{-1}) 3292, 3085, 3052, 2970, 2873, 1741, 1659, 1556, 1389, 1012; ^{1}H-NMR (400MHz, C_6D_6): δ_H 7.17-7.16 (m, 1H, H-5), 7.03 (s, 1H, H-2), 6.99 (dd, *J* = 8.3, 1.7 Hz, 1H, H-6), 6.54 (s, 1H, H-8), 4.44 (d, *J* = 6.3 Hz, 1H, N*H*), 3.71-3.63 (m, 1H, H-15), 3.57 (dd, *J* = 11.7, 4.6 Hz, 1H, H-16a), 3.26 (s , 3H, H-11), 3.14 (dd, *J* = 12.0, 8.6 Hz, 1H, H-16b), 2.46 (dd, *J* = 17.1, 5.6 Hz, 1H, H-13a), 1.96 (dd, *J* = 17.1, 10.5 Hz, 1H, H-13b), 1.86 (s , 3H, H-10), 1.44 (s, 9H, H-20), 1.41-1.35 (m, 1H, H-14), 0.67 (d, *J* = 6.30 Hz, 3H, H-17); ^{13}C-NMR (100MHz, C_6D_6): δ_C 168.2 (C-12), 161.6 (C-7), 155.4 (C-18), 145.2 (C-4), 144.9 (C-1), 140.9 (C-3), 125.4 (C-5), 121.3 (C-6), 119.3 (C-9), 118.7 (C-8), 111.3 (C-2), 79.4 (C-19), 54.0 (C-15), 51.8 (C-16), 39.8 (C-13), 33.1 (C-14), 28.6 (C-11), 28.4 (C-20), 18.4 (C-10), 18.2 (C-17); LR-ESI-MS: $C_{22}H_{30}N_3O_4$ $[M+H]^+$ *m/z* found 400.2, calcd 400.2; HR-ESI-MS: $C_{22}H_{29}N_3O_4Na$ $[M+Na]^+$ *m/z* found 422.2041, calcd 422.2050.

***tert*-Butyl (2*R**,3*S**,4*R**)-1-(1,4-dimethyl-2-oxo-1,2-dihydroquinolin-7-yl)-2,4-dimethyl-6-oxopiperidin-3-ylcarbamate (23)**

19 (30.0 mg, 0.12 mmol) was reacted according to General Procedure **C** to yield **23** (26 mg, 62%) as a pale yellow oil.

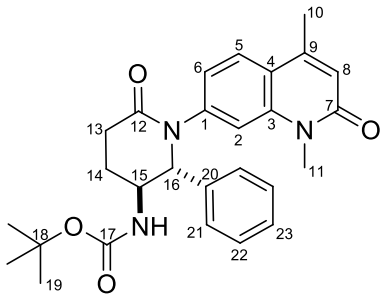
ν_{max} (cm^{-1}) 3390, 2987, 1650, 1580, 1176, 725; ^{1}H-NMR (400MHz, $CDCl_3$): δ_H 7.74 (d, *J* = 8.4 Hz, 1H, H-5), 7.17 (d, *J* = 1.4 Hz, 1H, H-2), 7.05 (dd, *J* = 8.4, 1.5 Hz, 1H, H-6), 6.60 (s, 1H, H-8), 4.56 (d, *J* = 8.5 Hz,



1H, N*H*), 3.75-3.67 (m, 1H, H-16), 3.67 (s, 3H, H-11), 3.50 (dt, *J* = 10.4, 9.7 Hz, 1H, H-15), 2.71 (dd, *J* = 17.2, 4.5 Hz, 1H, H-13a), 2.46 (s, 3H, H-10), 2.38 (dd, *J* = 17.1, 12.5 Hz, 1H, H-13b), 2.17-2.03 (m, 1H, H-14), 1.46 (s, 9H, H-20), 1.14 (d, *J* = 5.3 Hz, 3H, H-21), 1.13 (d, *J* = 5.5 Hz, 3H, H-17); ^{13}C-NMR (100MHz, $CDCl_3$): δ_C 169.7 (C-12), 162.1 (C-7), 155.7 (C-18), 146.0 (C-4), 142.5 (C-1), 140.6 (C-3), 126.2 (C-5), 121.7 (C-8), 121.3 (C-6), 120.6 (C-9), 114.1 (C-2), 80.1 (C-19), 60.8 (C-16), 58.2 (C-15), 40.0 (C-13), 32.7 (C-14), 29.4 (C-11), 28.4 (C-20), 19.9 (C-10), 19.0 (C-21), 18.0 (C-17); LR-ESI-MS: $C_{23}H_{32}N_3O_4$ $[M+H]^+$ *m/z* found 414.1, calcd 414.2; $C_{23}H_{31}N_3O_4Na$ $[M+Na]^+$ *m/z* found 436.1, calcd 436.2; HR-ESI-MS: $C_{23}H_{31}N_3O_4Na$ $[M+Na]^+$ *m/z* found 436.219581, calcd 436.22068, Δ = 2.53 ppm.

tert-Butyl (2*R,3*S**)-1-(1,4-dimethyl-2-oxo-1,2-dihydroquinolin-7-yl)-6-oxo-2-phenylpiperidin-3-ylcarbamate (24)**

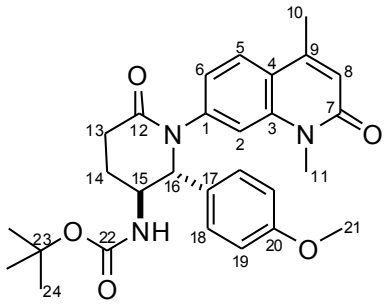
20 (205 mg, 0.63 mmol) was reacted with **4** (239 mg, 0.95 mmol) according to General Procedure **D**, to yield **24** (205 mg, 65%) as a colourless oil.



ν_{max} (cm^{-1}) 3274, 2976, 2362, 1703, 1650, 1594, 1169, 732; ^{1}H-NMR (400MHz, $CDCl_3$): δ_H 7.60 (d, *J* = 8.6 Hz, 1H, H-5), 7.43-7.29 (m, 5H, H-21/22/23), 7.15 (d, *J* = 1.2 Hz, 1H, H-2), 7.08 (dd, *J* = 8.6, 1.5 Hz, 1H, H-6), 6.52 (d, *J* = 1.0 Hz, 1H, H-8), 5.22 (d, *J* = 5.6 Hz, 1H, H-16), 4.08 (br s, 1H, H-15), 3.50 (s, 3H, H-11), 2.84 (ddd, *J* = 19.1, 8.1, 2.7 Hz, 1H, H-13a), 2.74 (ddd, *J* = 18.8, 10.5, 7.6 Hz, 1H, H-13b), 2.38 (d, *J* = 1.0 Hz, 3H, H-10), 2.23-2.11 (m, 1H, H-14a), 1.89-1.78 (m, 1H, H-14b), 1.50 (s, 9H, H-19); ^{13}C-NMR (100MHz, $CDCl_3$): δ_C 169.7 (C-12), 162.0 (C-7), 155.4 (C-17), 145.8 (C-4), 144.2 (C-1), 140.3 (C-3), 138.8 (C-20), 128.9 (C-22), 128.2 (C-23), 126.7 (C-21), 125.9 (C-5), 121.1 (C-8), 120.7 (C-6), 120.1 (C-9), 113.0 (C-2), 77.2 (C-18), 69.1 (C-16), 51.2 (C-15), 29.1 (C-11), 28.4 (C-19), 27.9 (C-13), 20.9 (C-14), 18.8 (C-10); LR-ESI-MS: $C_{27}H_{32}N_3O_4$ $[M+H]^+$ *m/z* found 462.1, calcd 462.2; HR-ESI-MS: $C_{27}H_{32}N_3O_4$ $[M+H]^+$ *m/z* found 462.2364, calcd 462.2387, Δ = 1.97 ppm.

tert-butyl (2*R,3*S**)-1-(1,4-dimethyl-2-oxo-1,2-dihydroquinolin-7-yl)-2-(4-methoxyphenyl)-6-oxopiperidin-3-ylcarbamate (41)**

33 (39 mg, 0.12 mmol) was reacted with **4** (46 mg, 0.18 mmol) according to General Procedure **D**, to yield **41** (17 mg, 28%) as a pale yellow, amorphous solid.

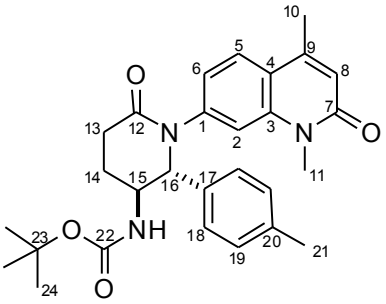


ν_{max} (cm^{-1}) 3278, 2975, 2360, 2341, 1704, 1650, 1594, 1512, 1249, 1172; ^{1}H-NMR (400MHz, $CDCl_3$): δ_H 7.60 (d, *J* = 8.6 Hz, 1H, H-5), 7.28 (d, *J* = 8.3 Hz, 2H, H-18), 7.15 (d, *J* = 1.5 Hz, 1H, H-2), 7.06 (dd, *J* = 8.3, 1.5 Hz, 1H, H-6), 6.90 (d, *J* = 8.6 Hz, 2H, H-19), 6.52 (d, *J* = 1.0 Hz, 1H, H-8), 5.25-5.18 (m, 1H, H-16), 4.05-3.99 (m, 1H, H-15), 3.79 (s, 3H, H-21), 3.52 (s, 3H, H-11), 2.82 (ddd, *J* = 19.1, 8.1, 2.9 Hz, 1H, H-13a), 2.72 (ddd, *J* = 19.1, 10.5, 8.1 Hz, 1H, H-13b), 2.38 (d, *J* = 0.7 Hz, 3H, H-10), 2.22-2.12 (m, 1H, H-14a), 1.88-1.76 (m, 1H, H-14b), 1.49 (s, 9H, H-24); ^{13}C-NMR (100MHz, $CDCl_3$): δ_C 169.6 (C-12), 162.0 (C-7), 159.3 (C-20), 155.4 (C-22), 145.9 (C-4), 144.2 (C-1), 140.2 (C-3), 130.6 (C-17), 127.9 (C-18), 125.8 (C-5), 121.2 (C-8), 120.7 (C-6), 120.0 (C-9), 114.2 (C-19), 113.0 (C-2), 80.3 (C-23), 68.6 (C-16), 55.3 (C-21), 51.3 (C-15), 29.1 (C-11), 28.4 (C-24), 28.0 (C-13), 21.0 (C-14), 181.8 (C-10); LR-ESI-MS: $C_{28}H_{34}N_3O_5$ $[M+H]^+$ *m/z* found 492.4, calcd 492.3; $C_{28}H_{33}N_3O_5Na$ $[M+Na]^+$ *m/z* found 514.2,

calcd 514.2; HR-ESI-MS: $C_{28}H_{33}N_3O_5Na$ $[M+Na]^+$ *m/z* found 514.23011, calcd 514.23124, Δ = 2.22 ppm.

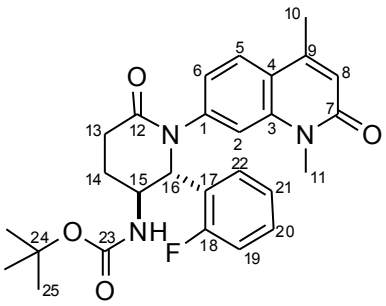
tert-Butyl (2*R,3*S**)-1-(1,4-dimethyl-2-oxo-1,2-dihydroquinolin-7-yl)-6-oxo-2-p-tolylpiperidin-3-ylcarbamate (42)**

34 (37 mg, 0.12 mmol) was reacted with **4** (46 mg, 0.18 mmol) according to General Procedure **D**, to yield **42** (26 mg, 45%) as a pale yellow, amorphous solid.



ν_{max} (cm^{-1}) 3277, 2976, 1704, 1649, 1594, 1168, 730.8; ^{1}H-NMR (400MHz, $CDCl_3$): δ_H 7.60 (d, *J* = 8.6 Hz, 1H, H-5), 7.26 (d, *J* = 7.1 Hz, 2H, H-19), 7.19 (s, 1H, H-2), 7.17 (dd, *J* = 4.9, 1.7 Hz, 2H, H-18), 7.07 (dd, *J* = 8.6, 1.2 Hz, 1H, H-6), 6.52 (d, *J* = 0.7 Hz, 1H, H-8), 5.26 (br s, 1H, H-16), 4.04 (br s, 1H, H-15), 3.51 (s, 3H, H-11), 2.82 (ddd, *J* = 18.8, 8.1, 2.4 Hz, 1H, H-13a), 2.72 (ddd, *J* = 19.1, 10.3, 7.6 Hz, 1H, H-13b), 2.37 (s, 3H, H-10), 2.33 (s, 3H, H-21), 2.21-2.11 (m, 1H, H-14a), 1.87-1.78 (m, 1H, H-14b), 1.50 (s, 9H, H-24); ^{13}C-NMR (100MHz, $CDCl_3$): δ_C 169.7 (C-12), 162.0 (C-7), 155.4 (C-22), 145.8 (C-4), 144.3 (C-1), 140.2 (C-3), 137.9 (C- 20), 135.7 (C-17), 129.5 (C-18), 126.6 (C-19), 125.8 (C-5), 121.0 (C-8), 120.6 (C-6), 120.0 (C-9), 113.1 (C-2), 80.3 (C-23), 68.9 (C-16), 53.4 (C-15), 29.1 (C-11), 28.4 (C-24), 27.8 (C-13), 21.0 (C-21), 20.9 (C-14), 18.8 (C-10); LR-ESI-MS: $C_{28}H_{34}N_3O_4$ $[M+H]^+$ *m/z* found 476.3, calcd 476.3; $C_{28}H_{33}N_3O_4Na$ $[M+Na]^+$ *m/z* found 498.4, calcd 498.2; HR-ESI-MS: $C_{28}H_{33}N_3O_4Na$ $[M+Na]^+$ *m/z* found 498.23474, calcd 498.23633, Δ = 3.18 ppm.

tert-butyl (2*R,3*S**)-1-(1,4-dimethyl-2-oxo-1,2-dihydroquinolin-7-yl)-2-(2-fluorophenyl)-6-oxopiperidin-3-ylcarbamate (43)**

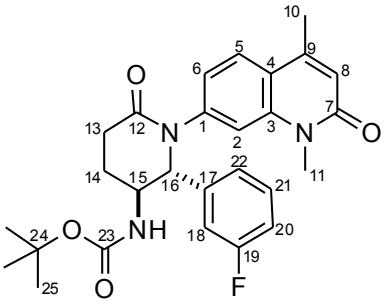


35 (38 mg, 0.12 mmol) was reacted with **4** (46 mg, 0.18 mmol) according to General Procedure **D**, to yield **43** (14 mg, 24%) as a pale yellow, amorphous solid.

ν_{max} (cm^{-1}) 3276, 2977, 1705, 1650, 1593, 1168, 730; ^{1}H-NMR (400MHz, $CDCl_3$): δ_H 7.59 (d, *J* = 8.6 Hz, 1H H-5), 7.36 (td, *J* = 7.6, 1.2 Hz, 1H, H-22), 7.29-7.26 (m, 1H, H-20), 7.15 (td, *J* = 7.6, 1.0 Hz, 1H, H-21), 7.13 (d, *J* = 1.7 Hz, 1H, H-2), 7.05 (dd, *J* = 8.3, 1.5 Hz, 1H, H-6), 7.03 (ddd, *J* = 10.8, 8.1, 0.7 Hz, 1H, H-19), 6.52 (d, J = 1.0 Hz, 1H, H-8), 5.40 (br s, 1H, N*H*), 5.09 (d, *J* = 5.1 Hz, 1H, H-16), 4.22-4.15 (m, 1H, H-15), 3.52 (s, 3H, H-11), 2.86 (ddd, *J* = 18.8, 7.6, 5.4 Hz, 1H, H-13a), 2.77 (ddd, *J* = 18.8, 8.6, 7.3 Hz, 1H, H-13b), 2.38 (d, *J* = 1.0 Hz, 3H, H-10), 2.23-2.14 (m, 1H, H-14a), 2.03-1.94 (m, 1H, H-14b), 1.43 (s, 9H, H-25); ^{13}C-NMR (100MHz, $CDCl_3$): δ_C 169.7 (C-12), 162.0 (C-7), 160.1 (d, *J* = 248.0 Hz, C-18), 155.0 (C-23), 154.8 (C-4), 143.5 (C-1), 140.2 (C-3), 130.2 (d, *J* = 7.9 Hz, C-20), 128.7 (d, *J* = 3.2 Hz, C-22), 125.9 (C-5), 124.4 (d, *J* = 3.2 Hz, C-21), 121.2 (C-8), 120.7 (C-6), 120.2 (C-9), 116.1 (d, *J* = 21.5 Hz, C-19), 113.1 (C-2), 107.4 (d, *J* = 20.7 Hz, C-17), 77.2 (C-24), 64.5 (C-16), 50.0 (C-15), 29.1 (C-11), 28.8 (C-13), 28.3 (C-25), 23.1 (C-14), 18.8 (C-10); ^{19}F-NMR (377MHz, $CDCl_3$): δ_F -117.2 (C-18*F*); LR-ESI-MS: $C_{27}H_{31}FN_3O_4$ $[M+H]^+$ *m/z* found 480.3, calcd 480.2; $C_{27}H_{30}FN_3O_4Na$ $[M+Na]^+$ *m/z* found 502.2, calcd 502.2; HR-ESI-MS: $C_{27}H_{31}FN_3O_4Na$ $[M+Na]^+$ *m/z* found 480.22833, calcd 480.22931, Δ = 2.04 ppm.

***tert*-butyl (2*R**,3*S**)-1-(1,4-dimethyl-2-oxo-1,2-dihydroquinolin-7-yl)-2-(3-fluorophenyl)-6-oxopiperidin-3-ylcarbamate (44)**

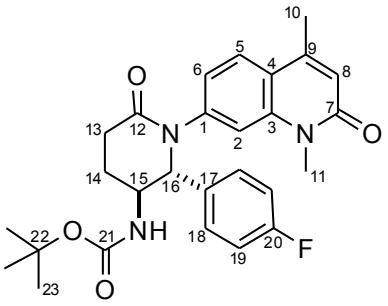
36 (38 mg, 0.12 mmol) was reacted with **4** (46 mg, 0.18 mmol) according to General Procedure **D**, to yield **44** (18 mg, 30%) as a pale yellow, amorphous solid.



ν_{max} (cm^{-1}) 3282, 2977, 1704, 1650, 1593, 1169, 731; ^{1}H-NMR (400MHz, $CDCl_3$): δ_H 7.62 (d, *J* = 8.6 Hz, 1H, H-5), 7.36 (td, *J* = 8.1, 5.6 Hz, 1H, H-21), 7.19 (d, *J* = 7.3 Hz, 1H, H-22), 7.16 (d, *J* = 1.7 Hz, 1H, H-2), 7.11 (d, *J* = 9.0 Hz, 1H, H-18), 7.06 (dd, *J* = 8.3, 1.2 Hz, 1H, H-6), 7.00 (td, *J* = 8.3, 2.4 Hz, 1H, H-20), 6.53 (d, *J* = 1.0 Hz, 1H, H-8), 5.35 (br s, 1H, N*H*), 5.23 (br s, 1H, H-16), 4.06 (br s, 1H, H-15), 3.54 (s, 3H, H-11), 2.84 (ddd, *J* = 19.1, 8.1, 2.9 Hz, 1H, H-13a), 2.74 (ddd, *J* = 18.8, 10.3, 7.8 Hz, 1H, H-13b), 2.39 (d, *J* = 0.7 Hz, 3H, H-10), 2.20-2.11 (m, 1H, H-14a), 1.90-1.82 (m, 1H, H-14b), 1.50 (s, 9H, H-25); ^{13}C-NMR (100MHz, $CDCl_3$): δ_C 169.5 (C-12), 163.1 (d, *J* = 248.8 Hz, C-19), 162.0 (C-7), 155.4 (C-23), 145.8 (C-4), 144.0 (C-1), 141.5 (d, *J* = 6.4 Hz, C-17), 140.3 (C-3), 130.6 (d, *J* = 7.9 Hz, C-21), 126.0 (C-5), 122.4 (d, *J* = 3.2 Hz, C-22), 121.2 (C-8), 120.6 (C-6), 120.2 (C-9), 115.2 (d, *J* = 20.7 Hz, C-20), 113.9 (d, *J* = 22.3 Hz, C-18), 113.1 (2); ^{19}F-NMR (377MHz, $CDCl_3$): δ_F -111.6 (C-19*F*); LR-ESI-MS: $C_{27}H_{31}FN_3O_4$ $[M+H]^+$ *m/z* found 480.3, calcd 480.2; $C_{27}H_{30}FN_3O_4Na$ $[M+Na]^+$ *m/z* found 502.2, calcd 502.2; HR-ESI-MS: $C_{27}H_{31}FN_3O_4$ $[M+H]^+$ *m/z* found 480.22834, calcd 480.22931, Δ = 1.87 ppm.

***tert*-butyl (2*R**,3*S**)-1-(1,4-dimethyl-2-oxo-1,2-dihydroquinolin-7-yl)-2-(4-fluorophenyl)-6-oxopiperidin-3-ylcarbamate (45)**

37 (38 mg, 0.12 mmol) was reacted with **4** (46 mg, 0.18 mmol) according to General Procedure **D**, to yield **45** (11 mg, 21%) as a pale yellow, amorphous solid.

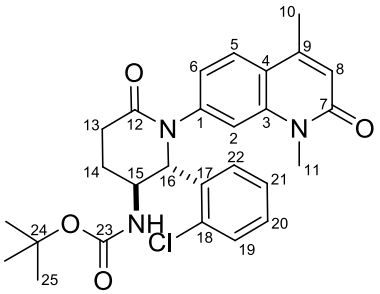


ν_{max} (cm^{-1}) 3284, 2977, 1704, 1652, 1595, 1168, 732; ^{1}H-NMR (500MHz, $CDCl_3$): δ_H 7.61 (d, *J* = 8.5 Hz, 1H, H-5), 7.36 (t, *J* = 6.8 Hz, 2H, H-18), 7.13 (d, *J* = 1.6 Hz, 1H, H-2), 7.08 (t, *J* = 8.6 Hz, 2H, H-19), 7.04 (dd, *J* = 8.5, 1.3 Hz, 1H, H-6), 6.54 (d, *J* = 0.9 Hz, 1H, H-8), 5.12 (d, *J* = 6.5 Hz, 1H, H-16), 4.03 (br s, 1H, H-15), 3.54 (s, 3H, H-11), 2.84 (ddd, *J* = 18.8, 7.7, 2.7 Hz, 1H, H-13a), 2.73 (ddd, *J* = 18.3, 10.2, 8.0 Hz, 1H, H-13b), 2.39 (d, *J* = 0.9 Hz, 3H, H-10), 2.19-2.11 (m, 1H, H-14a), 1.88-1.82 (m, 1H, H-14b), 1.50 (s, 9H, H-23); ^{13}C-NMR (125MHz, $CDCl_3$): δ_C 169.5 (C-12), 162.4 (d, *J* = 247.0 Hz, C-20), 162.0 (C-7), 155.4 (C-21), 145.9 (C-4), 144.0 (C-1), 140.3 (C-3), 134.5 (d, *J* = 2.9 Hz, C-17), 128.5 (d, *J* = 8.6 Hz, C-18), 126.0 (C-5), 121.2 (C-8), 120.7 (C-6), 120.2 (C-9), 115.9 (d, *J* = 21 Hz, C-19), 113.0 (C-2), 80.5 (C-22), 68.5 (C-16), 53.4 (C-15), 29.1 (C-11), 28.4 (C-23), 27.9 (C-13), 21.0 (C-14), 18.9 (C-10); ^{19}F-NMR (377MHz, $CDCl_3$): δ_F -113.5 (C-20*F*); LR-ESI-MS: $C_{27}H_{31}FN_3O_4$ $[M+H]^+$ *m/z* found 480.3, calcd 480.2; $C_{27}H_{30}FN_3O_4Na$ $[M+Na]^+$ *m/z* found 502.3, calcd 502.2; HR-ESI-MS: $C_{27}H_{30}FN_3O_4Na$ $[M+Na]^+$ *m/z* found 502.21002, calcd 502.21126, Δ = 2.46 ppm.

***tert*-butyl (2*R**,3*S**)-2-(2-chlorophenyl)-1-(1,4-dimethyl-2-oxo-1,2-dihydroquinolin-7-yl)-6-oxopiperidin-3-ylcarbamate (46)**

38 (40 mg, 0.12 mmol) was reacted with **4** (46 mg, 0.18 mmol) according to General Procedure **D**, to yield **46** (4 mg, 7%) as a pale yellow, amorphous solid.

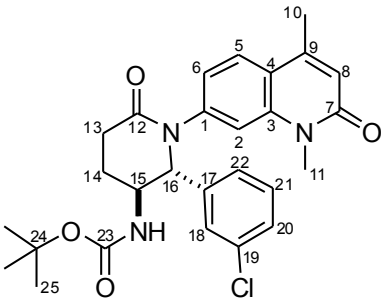
ν_{max} (cm^{-1}) 3281, 2976, 1706, 1652, 1594, 1168, 731; ^{1}H-NMR (500MHz, $CDCl_3$): δ_H 7.59 (d, *J* = 8.5 Hz, 1H, H-5), 7.44 (d, *J* = 7.6 Hz, 1H, H-19), 7.33-7.28 (m, 2H, H-20/22), 7.22 (td, *J* = 7.6, 1.1 Hz, 1H, H-21), 7.12 (d, *J* = 1.7 Hz, 1H, H-2), 7.07 (dd, *J* = 8.5, 1.7 Hz, 1H, H-6), 6.53 (d, *J* = 0.8 Hz, 1H, H-8), 5.52 (br s, 1H, N*H*), 4.94 (d, *J* = 7.9 Hz, 1H, H-16), 4.31-4.25 (m, 1H, H-15), 3.54 (s, 3H, H-11), 2.91-2.80 (m, 2H, H-13a/13b), 2.38 (d, *J* = 0.6 Hz, 3H, H-10), 2.17-2.12 (m, 1H, H-14a), 2.07-2.00 (m, 1H, H-14b), 1.41 (s,



9H, H-25); ^{13}C-NMR (125MHz, $CDCl_3$): δ_C 170.0 (C-12), 162.0 (C-7), 154.7 (C-23), 145.9 (C-4), 143.3 (C-1), 140.2 (C-3), 135.7 (C-17), 133.2 (C-18), 130.3 (C-22), 129.6 (C-21), 128.9 (C-19), 127.1 (C-20), 125.8 (C-5), 121.1 (C-8), 120.7 (C-6), 120.1 (C-13), 112.7 (C-2), 80.2 (C-24), 66.2 (C-16), 53.4 (C-15), 29.4 (C-13), 29.2 (C-11), 28.3 (C-25), 23.7 (C-14), 18.9 (C-10); LR-ESI-MS: $C_{27}H_{31}ClN_3O_4$ $[M+H]^+$ *m/z* found 496.1, calcd 496.2; $C_{27}H_{30}ClN_3O_4Na$ $[M+Na]^+$ *m/z* found 518.2, calcd 518.2; HR-ESI-MS: $C_{27}H_{31}ClN_3O_4Na$ $[M+Na]^+$ *m/z* found 496.19867, calcd 496.19976, Δ = 2.20 ppm.

tert-butyl (2*R,3*S**)-2-(3-chlorophenyl)-1-(1,4-dimethyl-2-oxo-1,2-dihydroquinolin-7-yl)-6-oxopiperidin-3-ylcarbamate (47)**

39 (40 mg, 0.12 mmol) was reacted with **4** (46 mg, 0.18 mmol) according to General Procedure **D**, to yield **47** (27 mg, 60%) as a pale yellow, amorphous solid.

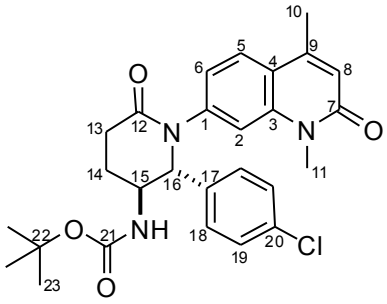


ν_{max} (cm^{-1}) 3280, 2976, 1704, 1650, 1594, 1168, 731; ^{1}H-NMR (400MHz, $CDCl_3$): δ_H 7.62 (d, *J* = 8.6 Hz, 1H, H-5), 7.38 (br s, 1H, H-18), 7.34-7.26 (m, 3H, H-20/21/22), 7.16 (d, *J* = 1.7 Hz, 1H, H-2), 7.04 (d, *J* = 8.6 Hz, 1H, H-6), 6.53 (s, 1H, H-8), 5.32 (br s, 1H, H-16), 4.05 (br s, 1H, H-15), 3.54 (s, 3H, H-11), 2.84 (ddd, *J* = 19.1, 8.1, 2.2 Hz, 1H, H-13a), 2.74 (ddd, *J* = 18.8, 10.3, 7.8 Hz, 1H, H-13b), 2.38 (s, 3H, H-10), 2.19-2.10 (m, 1H, H-14a), 1.90-1.77 (m, 1H, H-14b), 1.50 (s, 9H, H-25); ^{13}C-NMR (100MHz, $CDCl_3$): δ_C 169.5 (C-12), 162.0 (C-7), 155.4 (C-23), 145.8 (C-4), 143.9 (C-1), 140.9 (C-17), 140.3 (C-3), 135.0 (C-19), 130.2 (C-20, 21 or 22), 128.4 (C-20, 21 or 22), 127.0 (C-18), 126.0 (C-5), 124.9 (C-20, 21 or 22), 121.2 (C-8), 120.6 (C-6), 120.2 (C-9), 113.2 (C-2), 80.5 (C-24), 68.5 (C-16), 53.4 (C-15), 29.1 (C-11), 28.3 (C-25), 27.8 (C-13), 20.9 (C-14), 18.8 (C-11); LR-ESI-MS: $C_{27}H_{31}ClN_3O_4$ $[M+H]^+$ *m/z* found 496.2, calcd 496.2; $C_{27}H_{30}ClN_3O_4Na$ $[M+Na]^+$ *m/z* found 518.2, calcd 518.2; HR-ESI-MS: $C_{27}H_{31}ClN_3O_4Na$ $[M+Na]^+$ *m/z* found 496.19864, calcd 496.19976, Δ = 1.97 ppm.

tert-butyl ((2*R,3*S**)-2-(4-chlorophenyl)-1-(1,4-dimethyl-2-oxo-1,2-dihydroquinolin-7-yl)-6-oxopiperidin-3-yl)carbamate (48);**

tert-butyl ((2*R*,3*S*)-2-(4-chlorophenyl)-1-(1,4-dimethyl-2-oxo-1,2-dihydroquinolin-7-yl)-6-oxopiperidin-3-yl)carbamate ((2*R*,3*S*)-**48);**

40 (205 mg, 0.63 mmol) was reacted with **4** (239 mg, 0.95 mmol) according to General Procedure **D**, to yield **48** (205 mg, 65%) as a white powder. The enantiomers were separated by chiral HPLC (Semipreparative Chiralpak AD, 10 mm ID, hexane/iso-propanol 80:20, λ 220 nm, 2.5 mL/min): $t_{(2R,3S)\text{-}\mathbf{48}}$ = 23.36 min, $t_{(2S,3R)\text{-}\mathbf{48}}$ = 42.13 min. The purity of the enantio-enriched sample was determined by HPLC analysis (Chiralpak AD, hexane/iso-propanol 80:20, λ 220 nm, 1 mL/min): $t_{(2R,3S)\text{-}\mathbf{48}}$ = 12.89 min, 99.97%, $t_{(2S,3R)\text{-}\mathbf{48}}$ = 24.20 min, 0.03% (>99% ee).

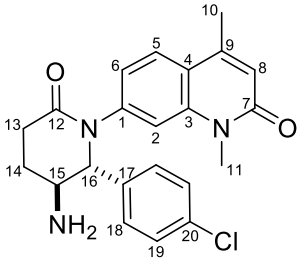


Mpt: 138.2-139.6 ^{o}C; ν_{max} (cm^{-1}) 3282, 2976, 1704, 1650, 1594, 1168, 731; ^{1}H-NMR (500MHz, $CDCl_3$): δ_H 7.60 (d, *J* = 8.5 Hz, 1H, H-5), 7.39-7.30 (m, 4H, H-18 & 19), 7.13 (d, *J* = 1.7 Hz, 1H, H-2), 7.02 (dd, *J* =8.5, 1.4 Hz, 1H, H-6), 6.53 (d, *J* = 0.9 Hz, 1H, H-8), 5.30 (br s, 1H, N*H*), 5.12 (d, *J* = 6.1 Hz, 1H, H-16), 4.05-3.99 (m, 1H, H-15), 3.54 (s, 3H, H-11), 2.82 (ddd, *J* = 19.1, 8.0 & 3.0 Hz, 1H, H-13a), 2.71 (ddd, *J* = 19.2, 10.2 & 7.7 Hz, 1H, H-13b), 2.38 (s, 3H, H-10), 2.17-2.08 (m, 1H, H-14a), 1.88-1.81 (m, 1H, H-14b), 1.49 (s, 9H, H-23); ^{13}C-NMR (100MHz, $CDCl_3$): δ_C 187.7 (C-21), 169.5 (C-12), 162.0 (C-7), 145.9 (C-4), 144.0 (C-1), 140.4 (C-3), 137.3 (C-17), 134.1 (C-20), 129.1 (C-19), 128.2 (C-18),

126.0 (C-5), 121.3 (C-8), 120.7 (C-6), 120.2 (C-9), 113.1 (C-2), 80.5 (C-22), 68.6 (C-16), 51.2 (C-15), 29.2 (C-11), 28.4 (C-23), 28.0 (C-13), 18.9 (C-10); LR-ESI-MS: $C_{27}H_{31}ClN_3O_4$ $[M+H]^+$ *m/z* found 496.2, calcd 496.2; $C_{27}H_{30}ClN_3O_4Na$ $[M+Na]^+$ *m/z* found 518.3, calcd 518.2; HR-ESI-MS: $C_{27}H_{31}ClN_3O_4Na$ $[M+Na]^+$ *m/z* found 496.19868, calcd 496.19976, Δ = 2.40 ppm; $[\alpha]_D^{20}$ (2*R*,3*S*)-**48**: -21.0 (*c* 0.17, $CHCl_3$).

7-((2*R,3*S**)-3-amino-2-(4-chlorophenyl)-6-oxopiperidin-1-yl)-1,4-dimethylquinolin-2(1H)-one (S2)**

HCl/Dioxane (10 mL, 0.15M) was added to **48** (654 mg, 1.32 mmol) and the reaction was stirred at ambient temperature for 11 hours. The solvent was removed under a stream of nitrogen, EtOAc was added and the solvent was again removed. The material was acidifed with 1M HCl and the aqueous phase was washed with DCM. The aqueous phase was basified with Na_2CO_3 and extracted with DCM. The combined organic extractions were dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield **S2** (502 mg, 96%) as a white amorphous solid.



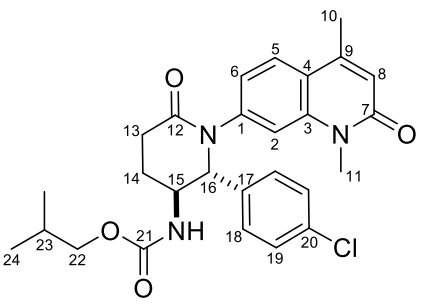
ν_{max} (cm^{-1}) 3367, 3293, 2943, 2882, 2238, 1644, 1590, 725; ^{1}H-NMR (400MHz, $CDCl_3$): δ_H 7.53 (d, *J* = 8.4 Hz, 1H, H-5), 7.26 (d, *J* = 8.7 Hz, 2H, H-18 or 19), 7.18 (d, *J* = 8.1 Hz), 7.03 (d, *J* = 1.1 Hz, 1H, H-2), 6.95 (d, *J* = 8.5 Hz, 1H, H-6), 6.48 (s, 1H H-8), 4.66 (d, *J* = 6.1 Hz, 1H, H-16), 3.49 (s 3H, H-11), 3.36 (br s, 1H H-15), 2.90-2.80 (m, 1H, H-13a), 4.77 (ddd, *J* = 17.8, 9.2, 6.1 Hz, 1H, H-13b), 2.34 (s, 3H, H-10), 1.89 (tdd, *J* = 14.6, 7.8, 0.6 Hz, 1H, H-14a), 1.80 (tdd, *J* = 21.1, 10.5, 1.8 Hz); ^{13}C-NMR (100MHz, $CDCl_3$): δ_C 170.4 (C-12), 162.0 (C-7), 146.0 (C-4), 143.6 (C-1), 140.2 (C-3), 137.9 (C-17), 134.1 (C-20), 129.1 (C-18 or 19), 128.9 (C-18 or 19), 125.8 (C-5), 121.3 (C-8), 121.1 (C-6), 120.1 (C-9), 113.7 (C-2), 72.4 (C-16), 52.9 (C-15), 29.9 (C-13), 29.2 (C-11), 26.6 (C-14), 18.9 (C-10); LR-ESI-MS: $C_{22}H_{23}ClN_3O_2$ $[M+H]^+$ *m/z* found 396.2, calcd 396.1; $C_{22}H_{22}ClN_3O_2Na$ $[M+Na]^+$ *m/z* found 418.1, calcd 418.1; HR-ESI-MS: $C_{22}H_{23}ClN_3O_2$ $[M+H]^+$ *m/z* found 396.14642, calcd 396.14733, Δ = -2.29 ppm.

General Procedure E

S2 (20 mg, 0.05 mmol) was dissolved in DCM (0.22 mL, 0.25M) and TEA (20 µL, 0.14 mmol) was added. The appropriate chloride was added dropwise and the reaction was stirred at ambient temperature for six hours. H_2O was added and the organic phase was separated. The aqueous phase was then extracted with DCM three times. The organic phases were combined, dried over sodium sulfate and concentrated under reduced pressure. The resulting crude material was purified through silica chromatography to yield the title compound.

isobutyl ((2*R,3*S**)-2-(4-chlorophenyl)-1-(1,4-dimethyl-2-oxo-1,2-dihydroquinolin-7-yl)-6-oxopiperidin-3-yl)carbamate (49)**

Isobutyl chloroformate (20 µL, 0.15 mmol) was reacted with **S2** (20 mg, 0.05 mmol) according to General Procedure **E**. The crude material was purified by FCC (15% IPA/hexane) followed by preparative TLC (40% IPA/hexane) to yield **49** (6.0 mg, 24%) as a white powder.

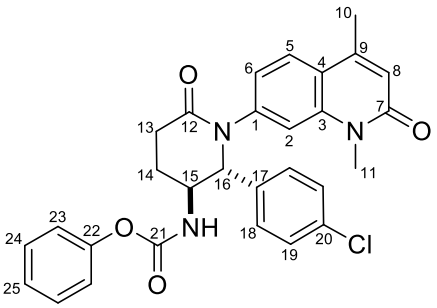


Mpt: 216.2-218.0 ^oC; ν_{max} (cm^{-1}) 3272, 2959, 1711, 1649, 1593, 722; ^{1}H-NMR (400MHz, $CDCl_3$): δ_H 7.60 (d, *J* = 8.6 Hz, 1H, H-5), 7.36 (d, *J* = 8.6 Hz, 2H, H-18 or 19), 7.31 (d, *J* = 8.3 Hz, 2H, H-18 or 19), 7.12 (d, *J* = 2.0 Hz, 1H, H-2), 7.01 (dd, *J* = 8.3, 1.7 Hz, 1H, H-6), 6.53 (d, *J* = 0.7 Hz, 1H, H-8), 5.36-5.31 (m, 1H, H-16), 5.26 (br s, 1H, N*H*), 4.12-4.07 (m, 1H, H-15), 3.91 (d, *J* = 6.6 Hz, 2H, H-22a/22b), 3.52 (s, 3H, H-11), 2.84 (ddd, *J* = 19.1, 7.9, 3.3 Hz, 1H, H-13a), 2.74 (ddd, *J* = 19.1, 10.1, 7.7 Hz, 1H, H-13b), 2.38 (s, 3H, H-10), 2.22-2.11 (m, 1H, H-14a), 1.99-1.86 (m, 2H, H-

14b/23), 0.95 (d, *J* = 6.6 Hz, 6H, H-24); ^{13}C-NMR (100MHz, $CDCl_3$): δ_C 169.6 (C-12), 162.1 (C-11), 161.0 (C-21), 146.0 (C-4), 144.0 (C-1), 143.3 (C-3), 137.4 (C-17), 134.4 (C-20), 129.4 (C-18 or 19), 128.2 (C-18 or 19), 126.2 (C-5), 121.4 (C-8), 120.6 (C-6), 120.4 (C-9), 113.1 (C-2), 71.8 (C-22), 70.2 (C-16), 51.7 (C-15), 29.3 (C-11), 28.2 (C-13), 28.1 (C-23), 22.1 (C-14), 19.2 (C-24), 19.0 (C-10); LR-ESI-MS: $C_{27}H_{31}ClN_3O_4$ $[M+H]^+$ *m/z* found 496.2, calcd 496.2; $C_{27}H_{30}ClN_3O_4Na$ $[M+Na]^+$ *m/z* found 518.2, calcd 518.2; HR-ESI-MS: $C_{27}H_{30}ClN_3O_4Na$ $[M+Na]^+$ *m/z* found 518.18108, calcd 518.18171, Δ = -1.18 ppm.

phenyl ((2*R,3*S**)-2-(4-chlorophenyl)-1-(1,4-dimethyl-2-oxo-1,2-dihydroquinolin-7-yl)-6-oxopiperidin-3-yl)carbamate (50)**

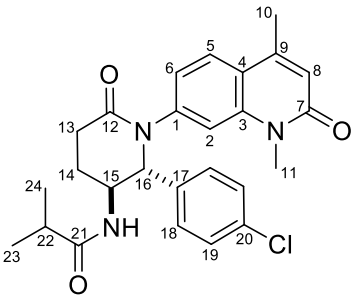
Phenyl chloroformate (20 µL, 0.16 mmol) was reacted with **S2** (20 mg, 0.05 mmol) according to General Procedure **E**. The crude material was purified by FCC (1% MeOH/DCM) followed by preparative TLC (2.5% MeOH/EtOAc) to yield **50** (9.8 mg, 38%) as an opaque oil.



ν_{max} (cm^{-1}) 3254, 2361, 1649, 1593, 1491, 1202, 727; ^{1}H-NMR (400MHz, $CDCl_3$): δ_H 7.61 (d, *J* = 8.5 Hz, 1H, H-5), 7.41-7.31 (m, 6H, H-18, 19 & 24), 7.25 (t, *J* = 7.4 Hz, 1H, H-25), 7.16 (s, 1H, H-2), 7.12 (d, *J* = 7.9 Hz, 2H, H-23), 7.05 (d, *J* = 8.2 Hz, 1H, H-6), 6.54 (s, 1H, H-8), 5.96 (d, *J* = 6.1 Hz, 1H, N*H*), 5.35 (br s, 1H, H-16), 4.17 (br s, 1H, H-15), 3.50 (s, 3H, H-11), 2.88 (ddd, *J* = 15.6, 8.2, 3.5 Hz, 1H, H-13a), 2.82 (ddd, *J* = 19.1, 9.9, 7.3 Hz, 1H, H-13b), 2.38 (s, 3H, H-10), 2.25-2.18 (m, 1H, H-14a), 2.01-1.95 (m, 1H, H-14b); ^{13}C-NMR (100MHz, $CDCl_3$): δ_C 169.7 (C-12), 162.2 (C-7), 154.7 (C-21), 150.7 (C-22), 146.0 (C-4), 143.9 (C-1), 140.5 (C-3), 137.5 (C-17), 134.5 (C-20), 129.7 (C-18, 19 or 24), 129.4 (C-18, 19 or 24), 128.3 (C-18, 19 or 24), 126.2 (C-5), 126.0 (C-25), 121.5 (C-23), 121.4 (C-8), 120.6 (C-6), 120.4 (C-9), 113.2 (C-2), 68.5 (C-16), 52.1 (C-15), 29.3 (C-11), 28.1 (C-13), 21.2 (C-14), 19.0 (C-10); LR-ESI-MS: $C_{29}H_{27}ClN_3O_4$ $[M+H]^+$ *m/z* found 516.2, calcd 516.2; $C_{29}H_{26}ClN_3O_4Na$ $[M+Na]^+$ *m/z* found 538.2, calcd 538.2; HR-ESI-MS: $C_{29}H_{26}ClN_3O_4Na$ $[M+Na]^+$ *m/z* found 538.1511, calcd 538.1504, Δ = -1.3 ppm.

***N*-((2*R**,3*S**)-2-(4-chlorophenyl)-1-(1,4-dimethyl-2-oxo-1,2-dihydroquinolin-7-yl)-6-oxopiperidin-3-yl)isobutyramide (51)**

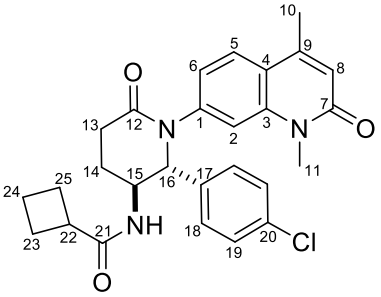
Isobutyryl chloride (20 µL, 0.19 mmol) was reacted with **S2** (20 mg, 0.05 mmol) according to General Procedure **E**. The crude material was purified by FCC (10% IPA/hexane) followed by preparative TLC (8% MeOH/DCM) to yield **51** (4.1 mg, 18%) as a white powder.



Mpt: 136.0-137.2 ^{o}C; ν_{max} (cm^{-1}) 3305, 2967, 1647, 1592, 730; ^{1}H-NMR (500MHz, $CDCl_3$): δ_H 7.60 (d, *J* = 8.7 Hz, 1H, H-5), 7.35 (ap d, *J* = 1.9 Hz, 4H, H-18/19), 7.09 (d, *J* = 1.9 Hz, 1H, H-2), 6.98 (dd, *J* = 8.5, 1.9 Hz, 1H, H-6), 6.53 (s, 1H, H-8), 6.03 (d, *J* = 6.5 Hz, 1H, N*H*), 5.29 (ap d, *J* = 2.8 Hz, 1H, H-16), 4.31 (ap sxt, *J* = 3.6 Hz, 1H, H-15), 3.52 (s, 3H, H-11), 2.86 (ddd, *J* = 18.9, 8.0, 3.2 Hz, 1H, H-13a), 2.74 (ddd, *J* = 19.1, 10.6, 7.7 Hz, 1H, H-13b), 2.46 (spt, *J* = 6.9 Hz, 1H, H-22), 2.38 (s, 3H, H-10), 2.17 (dddd, *J* = 14.8, 10.8, 8.0, 3.5 Hz, 1H, H-14a), 1.86 (dddd, *J* = 12.0, 7.4, 6.5, 3.5 Hz, 1H, H-14b), 1.21 (d, *J* = 6.8 Hz, 3H, H-23), 1.20 (d, *J* = 6.8 Hz, 3H, H-24); ^{13}C-NMR (125MHz, $CDCl_3$): δ_C 177.7 (C-21), 169.6 (12), 162.1 (C-7), 146.0 (C-4), 143.8 (C-1), 140.5 (C-3), 137.3 (C-17), 134.4 (C-20), 129.3 (C-18 or 19), 128.3 (C-18 or 19), 126.2 (C-5), 121.5 (C-8), 120.5 (C-6), 120.4 (C-9), 113.1 (C-2), 68.3 (C-16), 50.1 (C-15), 35.9 (C-22), 29.3 (C-11), 28.2 (C-13), 21.0 (C-14), 20.1 (C-23), 19.6 (C-24), 19.0 (C-10); LR-ESI-MS: $C_{26}H_{29}ClN_3O_3$ $[M+H]^+$ *m/z* found 466.1, calcd 466.2; $C_{26}H_{28}ClN_3O_3Na$ $[M+Na]^+$ *m/z* found 488.1, calcd 488.2; HR-ESI-MS: $C_{26}H_{29}ClN_3O_3$ $[M+H]^+$ *m/z* found 466.18893, calcd 466.18920, Δ = -0.56 ppm.

***N*-((2*R**,3*S**)-2-(4-chlorophenyl)-1-(1,4-dimethyl-2-oxo-1,2-dihydroquinolin-7-yl)-6-oxopiperidin-3-yl)cyclobutanecarboxamide (52)**

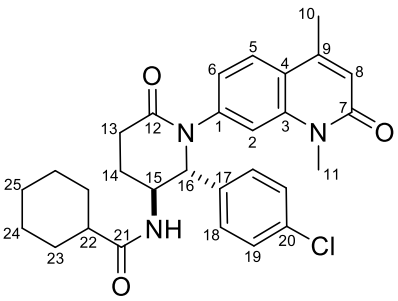
Cyclobutanecarbonyl chloride (20 µL, 0.18 mmol) was reacted with **S2** (20 mg, 0.05 mmol) according to General Procedure **E**. The crude material was purified by FCC (1% MeOH/DCM) followed by preparative TLC (40% IPA/hexane) to yield **52** (3.8 mg, 16%) as a white powder.



Mpt: 131.9-133.6 ^{o}C); ν_{max} (cm^{-1}) 3300, 2945, 2360, 1647, 1592, 725; ^{1}H-NMR (500MHz, $CDCl_3$): δ_H 7.60 (d, *J* = 8.7 Hz, 1H, H-5), 7.37-7.33 (m, 4H, H-18/19), 7.08 (d, *J* = 1.9 Hz, 1H, H-2), 6.97 (dd, *J* = 8.5, 1.9 Hz, 1H, H-6), 6.53 (d, *J* = 0.9 Hz, 1H, H-8), 5.92 (d, *J* = 6.8 Hz, 1H, N*H*), 5.29 (d, *J* = 2.5 Hz, 1H, H-16), 4.34-4.29 (m, 1H, H-15), 3.52 (s, 3H, H-11), 3.09 (dtd, *J* = 17.0, 8.7, 0.8 Hz, 1H, H-22), 2.84 (ddd, *J* = 19.1, 8.0, 3.2 Hz, 1H, H-13a), 2.72 (ddd, *J* = 18.9, 10.5, 7.8 Hz, 1H, H-13b), 2.38 (d, *J* = 0.9 Hz, 3H, H-10), 2.36-2.26 (m, 2H, H-23a/23b), 2.26-2.12 (m, 3H, H-14a/25a/25b), 2.08-1.99 (m, 1H, H-24a), 1.97-1.89 (m, 1H, H-24b), 1.88-1.82 (m, 1H, H-14b); ^{13}C-NMR (125MHz, $CDCl_3$): δ_C 175.6 (C-21), 169.6 (C-12), 162.1 (C-7), 146.0 (C-4), 143.9 (C-1), 140.5 (C-3), 137.3 (C-17), 134.3 (C-20), 129.3 (C-18 or 19), 128.2 (C-18 or 19), 126.2 (C-5), 121.5 (C-8), 120.5 (C-6), 113.1 (C-2), 68.4 (C-16), 50.2 (C-15), 40.0 (C-22), 29.3 (C-11), 28.2 (C-13), 25.6 (C-23), 25.3 (C-25), 21.0 (C-14), 19.0 (C-10), 18.4 (C-24); LR-ESI-MS: $C_{27}H_{29}ClN_3O_3$ [M+H]$^+$ *m/z* found 478.2, calcd 478.2; $C_{27}H_{28}ClN_3O_3Na$ [M+Na]$^+$ *m/z* found 500.2, calcd 500.2; HR-ESI-MS: $C_{27}H_{29}ClN_3O_3$ [M+H]$^+$ *m/z* found 478.18845, calcd 478.18920, Δ = -1.57 ppm.

***N*-((2*R**,3*S**)-2-(4-chlorophenyl)-1-(1,4-dimethyl-2-oxo-1,2-dihydroquinolin-7-yl)-6-oxopiperidin-3-yl)cyclohexanecarboxamide (53)**

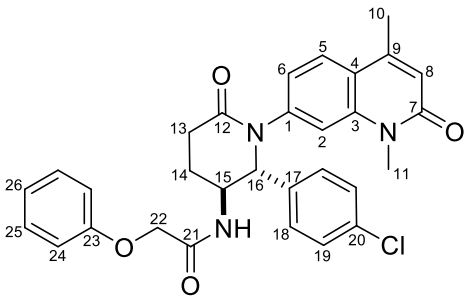
Cyclohexanecarbonyl chloride (20 µL, 0.15 mmol) was reacted with **S2** (20 mg, 0.05 mmol) according to General Procedure **E**. The crude material was purified by FCC (15% IPA/hexane) followed by preparative TLC (40% IPA/hexane) to yield **53** (3 mg, 12%) as a colourless oil.



ν_{max} (cm^{-1}) 3481, 3289, 2929, 1648, 1593, 721; ^{1}H-NMR (400MHz, $CDCl_3$): δ_H 7.57 (d, *J* = 8.6 Hz, 1H, H-5), 7.38 (d, *J* = 8.6 Hz, 2H, H-18 or 19), 7.14 (d, *J* = 8.6 Hz, 2H, H-18 or 19), 7.07 (d, *J* = 1.7 Hz, 1H, H-2), 6.96 (dd, *J* = 8.6, 2.0 Hz, 1H, H-6), 6.52 (d, *J* = 1.0 Hz, 1H, H-8), 5.23 (d, *J* = 5.4 Hz, 1H, H-16), 4.96 (d, *J* = 7.6, 1H, N*H*), 4.79-4.70 (m, 1H, H-15), 3.51 (s, 3H, H-11), 2.93-2.88 (m, 2H, H-13a/13b), 2.37 (d, *J* = 1.0 Hz, 3H, H-10), 2.04-1.85 (m, 2H, H-14a/14b), 1.82-1.73 (m, 3H, H-22/24a), 1.70-1.64 (m, 2H, H-24b), 1.44-1.32 (m, 2H, H-25a/25b), 1.28-1.17 (m, 4H, H-23a/23b); ^{13}C-NMR (100MHz, $CDCl_3$): δ_C 176.0 (C-21), 169.2 (C-12), 162.2 (C-7), 144.8 (C-4), 144.0 (C-1), 140.5 (C-3), 137.1 (C-17), 134.9 (C-20), 129.9 (C-18 or 19), 129.0 (C-18 or 19), 126.2 (C-5), 121.4 (C-8), 121.0 (C-6). 120.8 (C-9), 113.3 (C-2), 65.1 (C-16), 47.5 (C-15), 31.0 (C-13), 29.8 (C-22), 29.6 (C-25), 29.4 (C-11), 25.7 (C-23), 25.7 (C-24), 22.5 (C-14), 19.0 (C-10); LR-ESI-MS: $C_{29}H_{33}ClN_3O_3$ [M+H]$^+$ *m/z* found 506.2, calcd 506.2; $C_{29}H_{32}ClN_3O_3Na$ [M+Na]$^+$ *m/z* found 528.2, calcd 528.2; HR-ESI-MS: $C_{29}H_{32}ClN_3O_3Na$ [M+Na]$^+$ *m/z* found 528.20186, calcd 528.20244, Δ = -1.13 ppm.

***N*-((2*R**,3*S**)-2-(4-chlorophenyl)-1-(1,4-dimethyl-2-oxo-1,2-dihydroquinolin-7-yl)-6-oxopiperidin-3-yl)-2-phenoxyacetamide (54)**

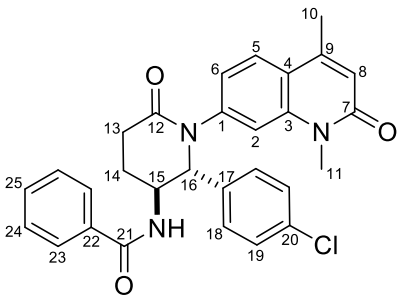
Phenoxyacetyl chloride (20 µL, 0.14 mmol) was reacted with **S2** (20 mg, 0.05 mmol) according to General Procedure **E**. The crude material was purified by FCC (15% IPA/hexane) followed by preparative TLC (IPA) to yield **54** (3.8 mg, 14%) as a colourless oil.



ν_{max} (cm^{-1}) 3284, 3059, 2948, 1652, 1594, 724; ^{1}H-NMR (500MHz, $CDCl_3$): δ_H 7.56 (d, *J* = 8.7 Hz, 1H, H-5), 7.35 (d, *J* = 8.7 Hz, 2H, H-18 or 19), 7.33 (dd, *J* = 8.7, 7.4 Hz, 2H, H-25), 7.30 (d, *J* = 8.5 Hz, 2H, H-18 or 19), 7.06 (tt, *J* = 7.4, 0.9 Hz, 1H, H-26), 7.05 (d, *J* = 1.9 Hz, 1H, H-2), 7.03 (d, *J* = 7.6 Hz, 1H, N*H*), 6.92 (dd, *J* = 8.7, 0.9 Hz, 2H, H-24), 6.89 (dd, *J* = 8.5, 2.0 Hz, 1H, H-6), 6.53 (d, *J* = 1.1 Hz, 1H, H-8), 5.13 (d, *J* = 3.8 Hz, 1H, H-16), 4.59 (d, *J* = 15.1 Hz, 1H, H-22a), 4.53 (d, *J* = 15.3 Hz, 1H, H-22b), 4.50-4.45 (m, 1H, H-15), 3.45 (s, 3H, H-11), 2.85 (ddd, *J* = 18.8, 7.6, 4.1 Hz, 1H, H-13a), 2.74 (ddd, *J* = 18.9, 9.6, 7.4 Hz, 1H, H-13b), 2.38 (d, *J* = 1.1 Hz, 3H, H-10), 2.25-2.16 (m, 1H, H-14a), 2.01-1.94 (m, 1H, H-14b); ^{13}C-NMR (125MHz, $CDCl_3$): δ_C 169.6 (C-21), 168.7 (C-12), 162.1 (C-7), 157.0 (C-23), 145.9 (C-4), 143.6 (C-1), 140.4 (C-3), 137.1 (C-17), 134.6 (C-20), 130.2 (C-25), 129.5 (C-18 or 19), 128.3 (C-18 or 19), 126.2 (C-5), 122.8 (C-26), 121.5 (C-8), 120.3 (C-6), 114.8 (C-24), 113.0 (C-2), 68.6 (C-16), 67.6 (C-22), 49.9 (C-15), 29.24 (C-11), 28.5 (C-13), 21.8 (C-14), 19.0 (C-10); LR-ESI-MS: $C_{30}H_{29}ClN_3O_4$ $[M+H]^+$ *m/z* found 530.2, calcd 530.2; $C_{30}H_{28}ClN_3O_4Na$ $[M+Na]^+$ *m/z* found 552.3, calcd 552.2; HR-ESI-MS: $C_{30}H_{29}ClN_3O_4$ $[M+H]^+$ *m/z* found 530.18329, calcd 530.18411, Δ = -1.55 ppm.

_N_-((2_R_*,3_S_*)-2-(4-chlorophenyl)-1-(1,4-dimethyl-2-oxo-1,2-dihydroquinolin-7-yl)-6-oxopiperidin-3-yl)benzamide (55);
_N_-((2_R_,3_S_)-2-(4-chlorophenyl)-1-(1,4-dimethyl-2-oxo-1,2-dihydroquinolin-7-yl)-6-oxopiperidin-3-yl)benzamide ((2*R*,3*S*)-**55)**

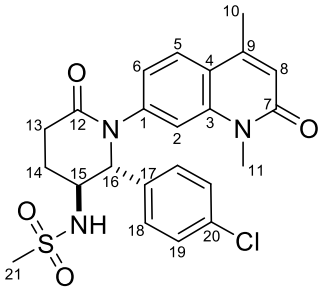
Benzoyl chloride (20 µL, 0.08 mmol) was reacted with **S2** (20 mg, 0.05 mmol) according to General Procedure **E**. The crude material was purified by FCC (1% MeOH/EtOAc) followed by preparative TLC (3% MeOH/EtOAc) to yield **55** (9.9 mg, 25%) as a colourless oil. The enantiomers were separated by HPLC (Semipreparative Chiralpak AD, 10 mm ID, hexane/iso-propanol 30:70, λ 220 nm, 1.8 mL/min): $t_{(2R,3S)\text{-}\mathbf{55}}$ = 19.00 min, $t_{(2S,3R)\text{-}\mathbf{55}}$ = 22.04 min. The purity of the enantioenriched sample was determined by HPLC analysis (Chiralpak AD, hexane/iso-propanol 60:40, λ 220 nm, 1.0 mL/min): $t_{(2R,3S)\text{-}\mathbf{55}}$ = 14.41 min, 99.48%, $t_{(2S,3R)\text{-}\mathbf{55}}$ = 32.19 min, 0.52% (99% ee).



ν_{max} (cm^{-1}) 3294, 2946, 2360, 2342, 1646, 1592, 727; ^{1}H-NMR (400MHz, $CDCl_3$): δ_H 7.84 (d, *J* = 7.1 Hz, 2H, H-23), 7.57 (tt, *J* = 7.5, 1.0 Hz, 1H, H-25), 7.56 (d, *J* = 8.8 Hz, 1H, H-5), 7.48 (dd, *J* = 8.0, 7.0 Hz, 2H, H-24), 7.40-7.38 (m, 4H, H-18 and 19), 7.06 (d, *J* = 1.5 Hz, 1H, H-2), 7.00 (dd, *J* = 8.6, 1.7 Hz, 1H, H-6), 6.93 (d, *J* = 6.4 Hz, 1H, N*H*), 6.49 (d, *J* = 0.7 Hz, 1H, H-8), 5.46-5.43 (m, 1H, H-16), 4.57-4.52 (m, 1H, H-15), 3.36 (s, 3H, H-11), 2.86 (dd, *J* = 6.6, 5.1 Hz, 1H, H-13a), 2.83 (dd, *J* = 6.4, 1.7 Hz, 1H, H-13b), 2.35 (d, *J* = 1.0 Hz, 3H, H-10), 2.23 (dddd, *J* = 14.2, 10.2, 9.7, 3.9 Hz, 1H, H-14a), 1.97 (ddt, *J* = 14.2, 5.5, 4.8 Hz, 1H, H-14b); ^{13}C-NMR (100MHz, $CDCl_3$): δ_C 169.8 (C-12), 168.1 (C-21), 162.1 (C-7), 146.0 (C-4), 144.0 (C-1), 140.5 (C-3), 137.3 (C-17), 134.4 (C-20), 133.8 (C-22), 132.4 (C-25), 129.4 (C-18 or 19), 129.0 (C-24), 128.2 (C-18 or 19), 127.1 (C-23), 126.2 (C-5), 121.3 (C-8), 120.6 (C-6), 120.4 (C-9), 113.0 (C-2), 68.2 (C-16), 50.8 (C-15), 29.2 (C-11), 28.2 (C-13), 21.2 (C-14), 19.0 (C-10); LR-ESI-MS: $C_{29}H_{27}ClN_3O_3$ $[M+H]^+$ *m/z* found 500.2, calcd 500.2; $C_{29}H_{26}ClN3O_3Na$ $[M+Na]^+$ *m/z* found 522.2, calcd 522.2; HR-ESI-MS: $C_{29}H_{26}ClN_3O_3Na$ $[M+Na]^+$ *m/z* found 522.1559, calcd 522.1555, Δ = -0.7 ppm; $[\alpha]_D^{20}$ (2*R*,3*S*)-**55**: +4.4 (*c* 0.14, $CHCl_3$).

***N*-((2*R**,3*S**)-2-(4-chlorophenyl)-1-(1,4-dimethyl-2-oxo-1,2-dihydroquinolin-7-yl)-6-oxopiperidin-3-yl)methanesulfonamide (56)**

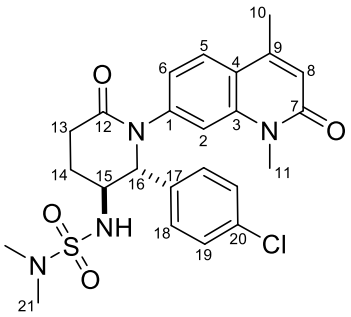
Methanesulfonyl chloride (20 µL, 0.25 mmol) was reacted with **S2** (20 mg, 0.05 mmol) according to General Procedure **E**. The crude material was purified by FCC (1% MeOH/DCM) followed by preparative TLC (IPA) to yield **56** (7.2 mg, 30%) as white crystals.



Mpt: 154.9-155.8 ^{o}C; ν_{max} (cm^{-1}) 3148, 2920, 2361, 2341, 1648, 1592, 1327, 1150, 730; ^{1}H-NMR (400MHz, $CDCl_3$): δ_H 7.59 (d, *J* = 8.6 Hz, 1H, H-5), 7.35 (d, *J* = 8.9 Hz, 2H, H-18 or 19), 7.32 (d, *J* = 2.0 Hz, 1H, H-2), 7.27 (d, *J* = 9.3 Hz, 2H, H-18 or 19), 7.11 (dd, *J* = 8.6, 2.0 Hz, 1H, H-6), 6.53 (d, *J* = 1.2 Hz, 1H, H-8), 6.50 (d, *J* = 8.3 Hz, 1H, N*H*), 5.27 (br s, 1H, H-16), 3.87-3.83 (m, 1H, H-15), 3.54 (s, 3H, H-11), 2.91 (s, 3H, H-21), 2.80 (ddd, *J* = 19.1, 8.6, 3.4 Hz, 1H, H-13a), 2.74 (ddd, *J* = 19.1, 10.3, 7.6 Hz, 1H, H-13b), 2.37 (d, *J* = 0.7 Hz, 3H, H-10), 2.17-2.07 (m, 1H, H-14a), 1.82-1.74 (m, 1H, H-14b); ^{13}C-NMR (100MHz, $CDCl_3$): δ_C 170.1 (C-12), 162.1 (C-7), 146.0 (C-4), 143.7 (C-1), 140.6 (C-3), 136.9 (C-17), 134.6 (C-20), 129.5 (C-18 or 19), 128.2 (C-18 or 19), 126.1 (C-5), 121.6 (C-8), 121.0 (C-6), 120.5 (C-9), 113.6 (C-2), 70.9 (C-16), 53.9 (C-15), 41.9 (C-21), 29.5 (C-11), 27.8 (C-13), 22.2 (C-14), 19.0 (C-10); LR-ESI-MS: $C_{23}H_{25}ClN_3O_4S$ $[M+H]^+$ *m/z* found 474.1, calcd 474.1; $C_{23}H_{24}ClN_3O_4S$ Na $[M+Na]^+$ *m/z* found 496.0, calcd 496.1; HR-ESI-MS: $C_{23}H_{25}ClN_3O_4S$ $[M+H]^+$ *m/z* found 474.12421, calcd 474.12488, Δ = -1.42 ppm.

***N*-((2*R**,3*S**)-2-(4-chlorophenyl)-1-(1,4-dimethyl-2-oxo-1,2-dihydroquinolin-7-yl)-6-oxopiperidin-3-yl)-1-dimethylaminesulfonamide (57)**

N,N-dimethylsulfamoyl chloride (20 µL, 0.08 mmol) was reacted with **S2** (20 mg, 0.05 mmol) according to General Procedure **E**. The crude material was purified by FCC (3% MeOH/DCM) followed by preparative TLC (3% MeOH/EtOAc) to yield **57** (5.7 mg, 22 %) as a colourless amorphous solid.

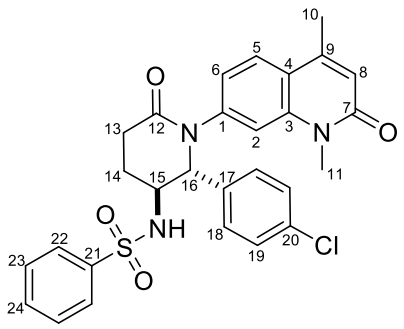


ν_{max} (cm^{-1}) 3148, 2889, 2361, 2341, 1649, 1593, 1329, 1149, 722; ^{1}H-NMR (400MHz, $CDCl_3$): δ_H 7.60 (d, *J* = 8.5 Hz, 1H, H-5), 7.36 (d, *J* = 8.4 Hz, 1H, H-18 or 19), 7.34 (d, *J* = 1.7 Hz, 1H, H-2), 7.26 (d, *J* = 8.4 Hz, 1H, H-18 or 19), 7.12 (dd, *J* = 8.5, 1.7 Hz, 1H, H-6), 6.56 (s, 1H, H-8), 5.55 (d, *J* = 6.5 Hz, 1H, N*H*), 5.35 (br s, 1H, H-16), 3.79 (br s, 1H, H-15), 3.56 (s, 3H, H-11), 2.84-2.73 (m, 8H, H-13/21), 2.38 (s, 3H, H-10), 2.19-2.12 (m, 1H, H-14a), 1.85-1.78 (m, 1H, H-14b); ^{13}C-NMR (100MHz, $CDCl_3$): δ_C 169.7 (C-12), 162.2 (C-7), 146.2 (C-4), 143.8 (C-1), 140.5 (C-3), 137.2 (C-17), 134.5 (C-20), 129.4 (C-18 or 19), 128.2 (C-18 or 19), 126.1 (C-5), 121.4 (C-8), 121.1 (C-6), 120.5 (C-9), 113.5 (C-2), 69.8 (C-16), 54.4 (C-3), 38.2 (C-21), 29.5 (C-11), 27.8 (C-6), 21.8 (C-14), 19.0 (C-10); LR-ESI-MS: $C_{24}H_{28}ClN_4O_4S$ $[M+H]^+$ *m/z* found 503.3, calcd 503.2; $C_{24}H_{27}ClN_4O_4SNa$ $[M+Na]^+$ *m/z* found 525.1, calcd 525.1; HR-ESI-MS: $C_{24}H_{28}ClN_4O_4S$ $[M+H]^+$ *m/z* found 525.1336, calcd 525.1334, Δ = -0.4 ppm.

***N*-((2*R**,3*S**)-2-(4-chlorophenyl)-1-(1,4-dimethyl-2-oxo-1,2-dihydroquinolin-7-yl)-6-oxopiperidin-3-yl)benzenesulfonamide (58)**

Benzenesulfonyl chloride (20 µL, 0.16 mmol) was reacted with **S2** (20 mg, 0.05 mmol) according to General Procedure **E**. The crude material was purified by FCC (1% MeOH/DCM) followed by preparative TLC (IPA) to yield **58** (7.3 mg, 27%) as a colourless oil.

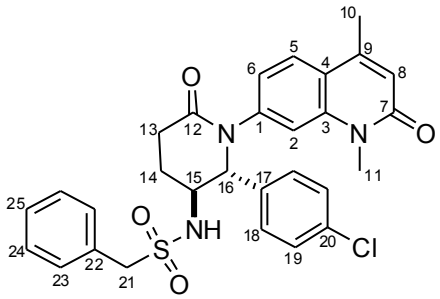
ν_{max} (cm^{-1}) 3096, 2919, 2362, 1647, 1591, 1160, 724; ^{1}H-NMR (400MHz, $CDCl_3$): δ_H 7.86 (dd, *J* = 8.1, 1.0 Hz, 2H, H-22), 7.56 (tt, *J* = 7.3, 1.2 Hz, 1H, H-24), 7.55 (d, *J* = 8.6 Hz, 1H, H-5), 7.44 (t, *J* = 7.8 Hz, 2H, H-23), 7.29 (d, *J* = 8.3 Hz, 2H, H-18 or 19), 7.25 (d, *J* = 2.0 Hz, 1H, H-2), 7.14 (d, *J* = 8.3 Hz, 2H, H-



18 or 19), 7.03 (dd, *J* = 8.6 Hz, 2.0 Hz, 1H, H-6), 6.77 (d, *J* = 7.1 Hz, 1H, N*H*), 6.53 (d, *J* = 1.2 Hz, 1H, H-8), 5.16 (br s, 1H, H-16), 3.66-3.60 (m, 1H, H-15), 3.44 (s, 3H, H-11), 2.82-2.77 (m, 2H, H-13a and 13b), 2.37 (d, *J* = 1.0 Hz, 3H, H-10), 2.04 (dtd, *J* = 13.9, 9.5, 3.7 Hz, 1H, H-14a), 1.66-1.62 (m, 1H, H-14b); ^{13}C-NMR (100MHz, $CDCl_3$): δ_C 170.4 (C-12), 162.1 (C-7), 146.0 (C-4), 143.8 (C-1), 140.5 (C-21), 140.4 (C-3), 136.8 (C-17), 134.5 (C-20), 133.2 (C-24), 129.4 (C-23), 129.4 (C-18 or 19), 128.1 (C-18 or 19), 127.0 (C-22), 126.0 (C-5), 121.5 (C-8), 120.9 (C-6), 120.4 (C-9), 113.5 (C-2), 70.1 (C-16), 53.6 (C-15), 29.4 (C-11), 27.7 (C-13), 21.8 (C-14), 19.0 (C-10); LR-ESI-MS: $C_{28}H_{27}ClN_3O_4S$ $[M+H]^+$ *m/z* found 536.2, calcd 536.1; $C_{28}H_{26}ClN_3O_4S$ Na $[M+Na]^+$ *m/z* found 558.2, calcd 558.1; HR-ESI-MS: $C_{28}H_{27}ClN_3O_4S$ $[M+H]^+$ *m/z* found 536.13983, calcd 536.14053, Δ = -1.31 ppm.

_N_-((2_R_*,3_S_*)-2-(4-chlorophenyl)-1-(1,4-dimethyl-2-oxo-1,2-dihydroquinolin-7-yl)-6-oxopiperidin-3-yl)-1-phenylmethanesulfonamide (59)

Phenylmethanesulfonyl chloride (20 mg, 0.1 mmol) was reacted with **S2** (20 mg, 0.05 mmol) according to General Procedure **E**. The crude material was purified by FCC (1% MeOH/EtOAc) followed by preparative TLC (30% IPA/hexane) to yield **59** (13.8 mg, 50%) as a colourless oil.



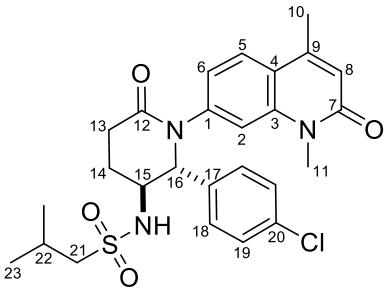
ν_{max} (cm^{-1}) 2918, 1648, 1593, 1456, 1328, 1152, 729; ^{1}H-NMR (500MHz, $CDCl_3$): δ_H 7.60 (d, *J* =8.5 Hz, 1H, H-5), 7.37-7.29 (m, 9H, H-18/19/23/24/25), 7.13 (s, 1H, H-2), 7.09 (dd, *J* = 8.8, 1.6 Hz, 1H, H-6), 6.56 (s, 1H, H-8), 6.06 (d, *J* = 7.6 Hz, 1H, N*H*), 5.18 (ap br s, 1H, H-16), 4.35 (d, *J* = 13.7 Hz, 1H, H-21a), 4.27 (d, *J* = 13.9 Hz, 1H, H-21b), 3.54 (s, 3H, H-11), 3.39-3.35 (m, 1H, H-15), 2.68 (ddd, *J* = 19.4, 8.5, 1.7 Hz, 1H, H-13a), 2.61 (ddd, *J* = 19.2, 10.4, 7.7 Hz, 1H, H-13b), 2.37 (s, 3H, H-10), 1.89-1.80 (m, 1H, H-14a), 1.57-1.51 (m, 1H, H-14b); ^{13}C-NMR (125MHz, $CDCl_3$): δ_C 169.9 (C-12), 162.1 (C-7), 146.2 (C-4), 144.0 (C-1), 140.5 (C-3), 136.8 (17), 134.4 (C-20), 130.8 (C-23), 129.4 (C-18 or 19), 129.2 (C-25), 129.2 (C-22), 129.0 (C-24), 127.9 (C-18 or 19), 126.1 (C-5), 121.3 (C-8), 121.0 (C-6), 120.6 (C-9), 113.5 (C-2), 71.0 (C-16), 60.6 (C-21), 54.3 (C-15), 29.6 (C-11), 27.3 (C-13), 21.3 (C-14), 19.0 (C-10); LR-ESI-MS: $C_{29}H_{28}ClN_3O_4SNa$ $[M+Na]^+$ *m/z* found 572.2, calcd 572.1; HR-ESI-MS: $C_{29}H_{28}ClN_3O_4SNa$ $[M+Na]^+$ *m/z* found 572.1387, calcd 572.1381, Δ = -1.0ppm.

_N_-((2_R_*,3_S_*)-2-(4-chlorophenyl)-1-(1,4-dimethyl-2-oxo-1,2-dihydroquinolin-7-yl)-6-oxopiperidin-3-yl)-2-methylpropane-1-sulfonamide (60);

_N_-((2_R_,3_S_)-2-(4-chlorophenyl)-1-(1,4-dimethyl-2-oxo-1,2-dihydroquinolin-7-yl)-6-oxopiperidin-3-yl)-2-methylpropane-1-sulfonamide ((2*R*,3*S*)-**60/LP99)**

Isobutanesulfonyl chloride (20 µL, 0.15 mmol) was reacted with **S2** (20 mg, 0.05 mmol) according to General Procedure **E**. The crude material was purified by FCC (1% MeOH/DCM) followed by preparative TLC (IPA) to yield **60** (7.6 mg, 29%) as a white powder. The enantiomers were separated by HPLC (Semipreparative Chiralpak AD, 10 mm ID, hexane/iso-propanol 60:40, λ 220 nm, 1.0 mL/min): $t_{(2R,3S)\text{-}\mathbf{60/LP99}}$= 10.81 min, $t_{(2S,3R)\text{-}\mathbf{60}}$ = 20.71 min. The purity of the enantio-enriched sample was determined by HPLC analysis (Chiralpak AD, hexane/iso-propanol 60:40, λ 220 nm, 1 mL/min): $t_{(2R,3S)\text{-}\mathbf{60/LP99}}$ = 7.21 min, 99.84%, $t_{(2S,3R)\text{-}\mathbf{60}}$ = 14.18 min, 0.16% (>99% ee).

Mpt: 137.6-139.6 ^{o}C; ν_{max} (cm^{-1}) 3157, 2960, 2361, 2340, 1649, 1593, 1325, 1144, 725; ^{1}H-NMR (400MHz, $CDCl_3$): δ_H 7.59 (d, *J* = 8.6 Hz, 1H, H-5), 7.35 (d, *J* = 8.6 Hz, 2H, H-18 or 19), 7.33 (d, *J* = 2.2



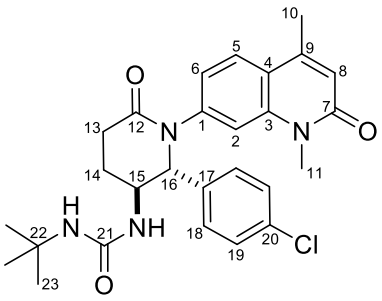
Hz, 1H, H-2), 7.27 (d, *J* = 8.5 Hz, 2H, H-18 or 19), 7.11 (d, *J* = 8.6 Hz, 1H, H-6), 6.53 (d, *J* = 0.7 Hz, 1H, N*H*), 5.27 (br s, 1H, H-16), 3.84 (br s, 1H, H-15), 3.55 (s, 3H, H-11), 2.90-2.68 (m, 4H, H-13a/13b/21a/21b), 2.37 (s, 3H, H-10), 2.27-2.09 (m, 2H, H-14a/22), 1.82-1.73 (m, 1H, H-14b), 1.06 (dd, *J* = 6.8, 2.9 Hz, 6H, H-23); ^{13}C-NMR (100MHz, $CDCl_3$): δ_C 169.7 (C-12), 162.1 (C-7), 146.0 (C-4), 143.8 (C-1), 140.6 (C-3), 137.0 (C-17), 134.6 (C-20), 129.4 (C-18 or 19), 128.2 (C-18 or 19), 126.1 (C-5), 121.6 (C-8), 121.0 (C-6), 120.5 (C-9), 113.6 (C-2), 71.1 (C-16), 62.0 (C-21), 53.9 (C-15), 29.5 (C-11), 27.7 (C-13), 25.1 (C-22), 22.7 (C-23), 22.6 (C-14), 19.0 (C-10); LR-ESI-MS: $C_{26}H_{31}ClN_3O_4S$ $[M+H]^+$ *m/z* found 516.2, calcd 516.2; $C_{26}H_{30}ClN_3O_4SNa$ $[M+Na]^+$ *m/z* found 538.2, calcd 538.2; HR-ESI-MS: $C_{26}H_{30}ClN_3O_4SNa$ $[M+Na]^+$ *m/z* found 538.1533, calcd 538.1538, Δ = -0.85 ppm; $[\alpha]_D^{20}$ (2*R*,3*S*)-**60**/**LP99**: -61.1 (*c* 0.09, $CHCl_3$).

General procedure F

The appropriate isocyanate or isothiocyanate (1 eq) was added dropwise to a solution of **S2** (1 eq) in DCM (0.25M). The reaction was stirred at ambient temperature for fifteen hours before the solvent was removed under reduced pressure. The resulting crude material was purified through silica chromatography to yield the title compound.

1-(*tert*-butyl)-3-((2*R,3*S**)-2-(4-chlorophenyl)-1-(1,4-dimethyl-2-oxo-1,2-dihydroquinolin-7-yl)-6-oxopiperidin-3-yl)urea (61)**

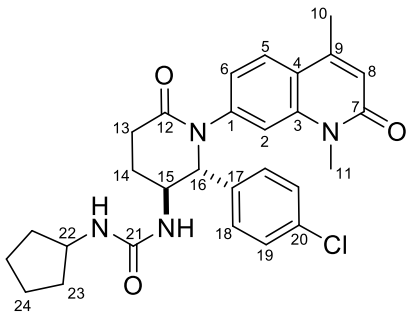
tert-Butylisocyanate (5.8 µL, 0.05 mmol) was reacted with **S2** (20 mg, 0.05 mmol) according to General Procedure **F**. The crude material was purified by FCC (5:95 IPA:petroleum ether then 30:70 IPA:petroleum ether) then by preparative TLC (35:65 IPA:hexane) to yield **61** (7.8 mg, 31%) as a white solid.



Mpt: 159.8-160.0 ^{o}C; ν_{max} (cm^{-1}) 3370, 2963, 1645, 1589, 1556, 731; ^{1}H-NMR (400MHz, $CDCl_3$): δ_H 7.53 (d, *J* = 8.6 Hz, 1H, H-5), 7.32-7.23 (m, 4H, H-18,19), 7.10 (d, *J* = 1.5 Hz, 1H, H-2), 6.98 (dd, *J* = 8.6, 1.7 Hz, 1H, H-6), 6.46 (s, 1H, H-8), 5.64 (br s, 1H, N*H*), 5.27 (br s, 1H, H-16), 4.06 (d, *J* = 2.0 Hz, 1H, H-15), 3.43 (s, 3H, H-11), 2.67 (dd, *J* = 18.8, 7.6 Hz, 1H, H-13a), 2.59-2.47 (m, 1H, H-13b), 2.31 (s, 3H, H-10), 2.00-1.88 (m, 1H, H-14a), 1.60-1.52 (m, 1H, H-14b), 1.29 (s, 9H, H-23); ^{13}C-NMR (100MHz, $CDCl_3$): δ_C 164.3 (C-21), 160.3 (C-12), 157.4 (C-7), 146.3 (C-4), 144.2 (C-1), 140.5 (C-3), 137.2 (C-16), 134.1 (C-20), 129.2 (C-18 or 19), 128.0 (C-18 or 19), 126.1 (C-5), 121.4 (C-8), 121.0 (C-6), 120.5 (C-9), 113.1 (C-2), 77.4 (C-22), 69.7 (C-16), 50.6 (C-15), 29.7 (C-23), 29.4 (C-11), 27.8 (C-13), 20.5 (C-14), 19.0 (C-10); LR-ESI-MS: $C_{27}H_{32}ClN_4O_3$ $[M+H]^+$ *m/z* found 495.3, calcd 495.2; $C_{27}H_{31}ClN_4O_3Na$ $[M+Na]^+$ *m/z* found 517.3, calcd 517.2; HR-ESI-MS: $C_{27}H_{32}ClN_4O_3$ $[M+H]^+$ *m/z* found 495.21475, calcd 495.21575, Δ = -2.0 ppm.

1-((2*R,3*S**)-2-(4-chlorophenyl)-1-(1,4-dimethyl-2-oxo-1,2-dihydroquinolin-7-yl)-6-oxopiperidin-3-yl)-3-cyclopentylurea (62)**

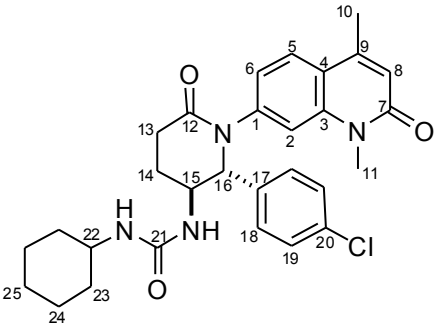
Cyclopentylisocyanate (5.7 µL, 0.05 mmol) was reacted with **S2** (20 mg, 0.05 mmol) according to General Procedure **F**. The crude material was purified by FCC (3:97 MeOH:DCM, then separately 15:85 IPA:hexane) followed by preparative TLC (40:60 IPA:hexane) to yield **62** (6.6 mg, 26%) as a colourless oil.



ν_{max} (cm^{-1}) 3364, 2956, 2361, 1645, 1591, 1556, 729; ^{1}H-NMR (400MHz, $CDCl_3$): δ_H 7.58 (d, *J* = 8.6 Hz, 1H, H-5), 7.39-7.30 (m, 4H, 1H, H-18,19), 7.14 (d, *J* = 2.0 Hz, 1H, H-2), 7.03 (dd, *J* = 8.6, 2.0 Hz, 1H, H-6), 6.51 (d, *J* = 1.0 Hz, 1H, H-8), 5.78 (d, *J* = 6.6 Hz, 1H, N*H*), 5.33-5.27 (m, 2H, H-16 & N*H*), 4.19-4.14 (m, 1H, H-15), 4.07 (ap tdt, *J* = 7.0, 6.8, 6.6 Hz, 1H, H-22), 3.47 (s, 3H, H-11), 2.73 (ap ddd, *J* =19.3, 8.6, 1.7 Hz, 1H, H-13a), 2.59 (ap ddd, *J* = 19.3, 10.8, 8.3 Hz, 1H, H-13b), 2.37 (d, *J* = 1.0 Hz, 3H, H-10), 2.09-1.91 (m, 3H, H-14a & H-23a), 1.72-1.58 (m, 5H, H-14b & H-24), 1.35 (ap dddd, *J* = 12.7, 6.6, 6.6, 6.6 Hz, 2H, H-23b); ^{13}C-NMR (100MHz, $CDCl_3$): δ_C 170.9 (C-21), 162.0 (C-7), 157.9 (C-12), 146.1 (C-4), 144.2 (C-1), 140.5 (C-3), 137.2 (C-17), 134.1 (C-20), 129.3 (C-18 or 19), 128.0 (C-18 or 19), 126.1 (C-5), 121.5 (C-8), 120.8 (C-6), 120.5 (C-9), 113.1 (C-2), 69.8 (C-16), 52.1 (C-22), 50.2 (C-15), 33.7 (C-23), 29.3 (C-11), 27.9 (C-13), 23.8 (C-24), 20.6 (C-14), 19.0 (C-10); LR-ESI-MS: $C_{28}H_{32}ClN_4O_3$ $[M+H]^+$ *m/z* found 507.2, calcd 507.2; $C_{28}H_{31}ClN_4O_3Na$ $[M+Na]^+$ *m/z* found 529.2, calcd 529.2; HR-ESI-MS: $C_{28}H_{32}ClN_4O_3$ $[M+H]^+$ *m/z* found 507.21487, calcd 507.21575, Δ = -1.72 ppm.

1-((2*R,3*S**)-2-(4-chlorophenyl)-1-(1,4-dimethyl-2-oxo-1,2-dihydroquinolin-7-yl)-6-oxopiperidin-3-yl)-3-cyclohexylurea (63)**

Cyclohexylisocyanate (6.5 µL, 0.05 mmol) was reacted with **S2** (20 mg, 0.05 mmol) according to General Procedure **F**. The crude material was purified by FCC (2.5:97.5 MeOH:DCM, then separately 15:85 IPA:DCM) followed by preparative TLC (40:60 IPA:hexane) to yield **63** (5.2 mg, 20%) as white crystals.



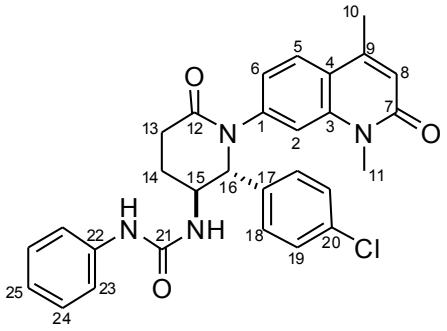
Mpt: 145.2-146.9 ^{o}C; ν_{max} (cm^{-1}) 3364, 2930, 2853, 1645, 1591, 1555, 730; ^{1}H-NMR (400MHz, $CDCl_3$): δ_H 7.59 (d, *J* = 8.6 Hz, 1H, H-5), 7.38-7.31 (m, 4H, H-18,19), 7.15 (d, *J* = 2.0 Hz, 1H, H-2), 7.03 (dd, *J* = 8.6, 2.0 Hz, 1H, H-6), 6.52 (d, *J* = 1.0 Hz, 1H, H-8), 5.70 (d, *J* =6.6 Hz, 1H, N*H*), 5.33 (ap br s, 1H, H-16), 5.13 (d, *J* = 7.8 Hz, 1H, N*H*), 4.18-4.13 (m, 1H, H-15), 3.67-3.57 (m, 1H, H-22), 3.50 (s, 3H, H-11), 2.74 (ddd, *J* = 18.8, 8.6, 1.7 Hz, 1H, H-13a), 2.60 (ddd, *J* = 19.1, 11.0, 8.3 Hz, 1H, H-13b), 2.38 (d, *J* = 1.0 Hz, 3H, H-10), 2.11-1.98 (m, 1H, H-14a), 1.96-1.87 (m, 2H, H-23a), 1.76-1.67 (m, 6H, H-14b, H-24 & H-25a), 1.44-1.32 (m, 1H, H-25b), 1.21-1.03 (m, 2H, H-23b);^{13}C-NMR (100MHz, $CDCl_3$): δ_C 170.9 (C-21), 169.5 (C-12), 157.4 (C-7), 146.1 (C-4), 144.2 (C-1), 140.6 (C-3), 137.3 (C-17), 134.1 (C-20), 129.3 (C-18 or 19), 128.0 (C-18 or 19), 126.2 (C-5), 121.5 (C-8), 120.8 (C-6), 120.6 (C-9), 113.2 (C-2), 69.9 (C-16), 50.2 (C-15), 49.1 (C-22), 34.1 (C-23), 29.3 (C-11), 27.9 (C-13), 25.7 (C-24), 25.1 (C-25), 20.6 (C-14), 19.0 (C-10); LR-ESI-MS: $C_{29}H_{34}ClN_4O_3$ $[M+H]^+$ *m/z* found 521.3, calcd 521.2; $C_{29}H_{33}ClN_4O_3Na$ $[M+Na]^+$ *m/z* found 543.2, calcd 543.2; HR-ESI-MS: $C_{29}H_{34}ClN_4O_3$ $[M+H]^+$ *m/z* found 521.23096, calcd 521.23140, Δ = -0.84 ppm.

1-((2*R,3*S**)-2-(4-chlorophenyl)-1-(1,4-dimethyl-2-oxo-1,2-dihydroquinolin-7-yl)-6-oxopiperidin-3-yl)-3-phenylurea (64);**

1-((2*R*,3*S*)-2-(4-chlorophenyl)-1-(1,4-dimethyl-2-oxo-1,2-dihydroquinolin-7-yl)-6-oxopiperidin-3-yl)-3-phenylurea ((2*R*,3*S*)-**64)**

Phenyl isocyanate (5.5 µL, 0.05 mmol) was reacted with **S2** (20 mg, 0.05 mmol) according to General Procedure **F**. The crude material was purified by FCC (1:99 MeOH:DCM) followed by preparative TLC (5:95 MeOH:DCM) to yield **64** (10.4 mg, 40%) as a colourless oil. The enantiomers were separated by

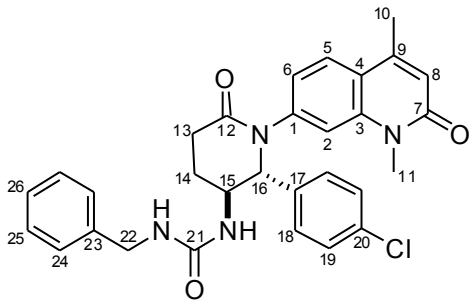
HPLC (Semipreparative Chiralpak AD, 10 mm ID, hexane/iso-propanol 70:30, λ 220 nm, 3.0 mL/min): $t_{(2R,3S)\text{-}\mathbf{64}}$ = 18.81 min, $t_{(2S,3R)\text{-}\mathbf{64}}$ = 23.28 min. The purity of the enantio-enriched sample was determined by HPLC analysis (Chiralpak AD, hexane/iso-propanol 80:20, λ 220 nm, 1 mL/min): $t_{(2R,3S)\text{-}\mathbf{64}}$ = 24.77 min, 99.94%, $t_{(2S,3R)\text{-}\mathbf{64}}$ = 29.11 min, 0.06% (>99% ee).



ν_{max} (cm^{-1}) 3344, 2950, 2361, 2341, 1645, 1596, 1550, 732; ^{1}H-NMR (400MHz, $CDCl_3$): δ_H 7.86 (s, 1H, N*H*), 7.52 (d, *J* = 8.6 Hz, 1H, H-5), 7.40-7.23 (m, 8H, H-18/19/23/24), 7.12 (d, *J* = 1.7 Hz, 1H, H-2), 7.07 (dd, *J* =8.4, 1.8 Hz, 1H, H-6), 7.03 (tt, *J* = 7.1, 1.2 Hz, 1H, H-25), 6.46 (d, *J* = 0.7 Hz, 1H, H-8), 6.41 (d, *J* = 6.6 Hz, 1H, N*H*), 5.36 (ap br s, 1H, H-16), 4.28-4.24 (m, 1H, H-15), 3.29 (s, 3H, H-11), 2.81 (ddd, *J* = 19.3, 8.8, 1.0 Hz, 1H, H-13a), 2.65 (ddd, *J* = 19.1, 10.3, 8.3 Hz, 1H, H-13b), 2.29 (d, *J* = 0.7 Hz, 3H, H-10), 2.13-2.02 (m, 1H, H-14a), 1.69-1.65 (m, 1H, H-14b); ^{13}C-NMR (100MHz, $CDCl_3$): δ_C 171.5 (C-12), 161.8 (C-7), 155.4 (C-21), 145.9 (C-4), 143.7 (C-1), 140.5 (C-3), 138.9 (C-22), 136.5 (C-17), 134.3 (C-20), 129.3 (C-18 or 19), 129.1 (C-24), 127.7 (C-18 or 19), 126.2 (C05), 123.1 (C-25), 121.6 (C-8), 120.5 (C-6), 118.9 (C-23), 112.8 (C-2), 69.8 (C-16), 49.7 (C-15), 29.1 (C-11), 27.8 (C-13), 20.2 (C-14), 18.8 (C-10); LR-ESI-MS: $C_{29}H_{28}ClN_4O_3$ $[M+H]^+$ *m/z* found 515.2, calcd 515.2; $C_{29}H_{27}ClN_4O_3Na$ $[M+Na]^+$ *m/z* found 537.2, calcd 537.2; HR-ESI-MS: $C_{29}H_{27}ClN_4O_3Na$ $[M+Na]^+$ *m/z* found 537.1669, calcd 537.1664, Δ = -1.0 ppm; $[\alpha]_D^{20}$ (2*R*,3*S*)-**64**: +9.3 (*c* 0.08, $CHCl_3$).

1-benzyl-3-((2*R,3*S**)-2-(4-chlorophenyl)-1-(1,4-dimethyl-2-oxo-1,2-dihydroquinolin-7-yl)-6-oxopiperidin-3-yl)urea (65)**

Benzyl isocyanate (6.2 µL, 0.05 mmol) was reacted with **S2** (20 mg, 0.05 mmol) according to General Procedure **F**. The crude material was purified by FCC (1:99 MeOH:EtOAc, then separately 15:85 IPA:hexane) followed by preparative TLC (30:70 IPA:hexane) to yield **65** (4.2 mg, 16%) as a colourless oil.



ν_{max} (cm^{-1}) 3363, 2920, 2361, 1645, 1588, 1558, 723; ^{1}H-NMR (400MHz, $CDCl_3$): δ_H 7.53 (d, *J* = 8.3 Hz, 1H, H-5), 7.37-7.25 (m, 9H, H-18, 19, 24, 25 & 26), 7.09 (d, *J* = 1.5 Hz, 1H, H-2), 6.95 (dd, *J* = 8.4, 1.6 Hz, 1H, H-6), 6.50 (s, (1H, H-8), 6.03 (d, *J* = 5.4 Hz, 1H, N*H*), 5.74 (s, 1H, N*H*), 5.28 (br s, 1H, H-16), 4.38 (s, 2H, H-22), 4.20-4.16 (m, 1H, H-15), 3.36 (s, 3H, H-11), 2.62 (ddd, *J* = 19.1, 8.3, 1.7 Hz, 1H, H-13a), 2.53 (ddd, *J* = 19.1, 10.0, 7.8 Hz, 1H, H-13b), 2.36 (s, 3H, H-10), 2.01-1.91 (m, 1H, H-14a), 1.61-1.58 (m, 1H, H-14b); ^{13}C-NMR (100MHz, $CDCl_3$): δ_C 170.9 (C-12), 161.8 (C-7), 157.8 (C-21), 145.8 (C-4), 143.8 (C-1), 140.3 (C-3), 139.4 (C-17), 136.8 (C-23), 134.0 (C-20), 129.1 (C-18 or 19), 128.7 (C-25), 127.8 (C-18 or 19), 127.4 (C-26), 127.2 (C-24), 126.0 (C-5), 121.5 (C-8), 120.4 (C-9), 120.4 (C-6), 113.0 (C-2), 69.6 (C-16), 50.0 (C-15), 44.0 (C-22), 29.0 (C-11), 27.6 (C-13), 20.3 (C-14), 18.9 (C-10); LR-ESI-MS: $C_{30}H_{30}ClN_4O_3$? $[M+H]^+$ *m/z* found 529.2, calcd 592.2; $C_{30}H_{29}ClN_4O_3Na$ $[M+Na]^+$ *m/z* found 551.2, calcd 551.2; HR-ESI-MS: $C_{30}H_{29}ClN_4O_3Na$ $[M+Na]^+$ *m/z* found 529.19965, calcd 529.20010, Δ = -0.85 ppm.

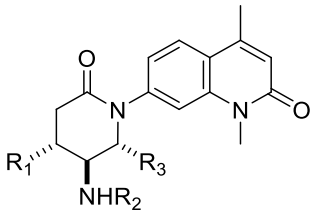
Protein Expression and Purification

cDNA encoding reported human bromodomains were cloned, expressed and purified as previously described.[4] Construct information for all expressed bromodomains is summarised in Supplemental Table 4.xls.

Differential Scanning Fluorimetry (DSF)

Thermal melting experiments were carried out using an Mx3005p Real Time PCR machine (Stratagene). Proteins were buffered in 10 mM HEPES pH 7.5, 500 mM NaCl and assayed in a 96-well plate at a final concentration of 2 µM in 20 µL volume. Compounds were added at a final concentration of 10 µM. SYPRO Orange (Molecular Probes) was used as a fluorescence probe at a dilution of 1:1000. Excitation and emission filters for the SYPRO-Orange dye were set to 465 nm and 590 nm, respectively. The temperature was raised with a step of 3 °C per minute from 25 °C to 96 °C and fluorescence readings were taken at each interval. Data was analysed as previously described.[5]

Supplemental Table 1. Potency of compounds against BRD9 and BRD4(1) by DSF



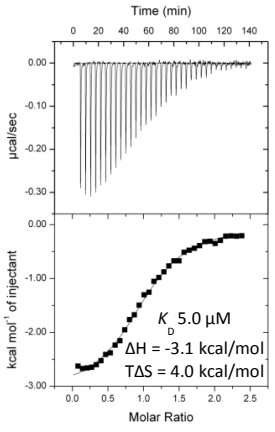
Cmpd	R_1	R_2	R_3	BRD9 ΔT_m (^oC)[a]	BRD4(1) ΔT_m (°C)[a]
21	H	Boc	Me	6.2 ± 0.73 (4)	0.33 ± 0.27 (3)
22	Me	Boc	H	3.0 ± 0.31 (4)	0.19 ± 0.21 (7)
23	Me	Boc	Me	4.8 ± 1.17 (4)	
24	H	Boc	Ph	5.8 ± 0.63 (4)	-0.56 ± 0.21 (3)
41	H	Boc	*p*-OMePh	1.1 ± 0.18 (5)	
42	H	Boc	*p*-MePh	2.7 ± 0.13 (5)	
43	H	Boc	*o*-FPh	3.2 ± 0.21 (5)	
44	H	Boc	*m*-FPh	3.0 ± 0.24 (5)	
45	H	Boc	*p*-FPh	2.9 ± 0.078 (5)	
46	H	Boc	*o*-ClPh	2.6 ± 0.097 (5)	
47	H	Boc	*m*-ClPh	3.5 ± 0.45 (5)	
48	H	Boc	*p*-ClPh	4.4 ± 0.72 (5)	
49	H	COO^iBu	*p*-ClPh	5.2 ± 0.53 (4)	
50	H	COOPh	*p*-ClPh	6.1 ± 1.75 (4)	
51	H	CO^iPr	*p*-ClPh	2.1 ± 0.70 (4)	
52	H	$CO(C_4H_7)$	*p*-ClPh	3.1 ± 0.49 (4)	
53	H	CO (C_6H_{11})	*p*-ClPh	0.9 ± 0.48 (4)	
54	H	$COCH_2OPh$	*p*-ClPh	2.8 ± 0.72 (4)	

55	H	Bz	*p*-ClPh	4.6 ± 0.67 (2)
56	H	SO_2Me	*p*-ClPh	4.7 ± 0.48 (4)
57	H	SO_2NMe_2	*p*-ClPh	3.7 ± 0.01 (2)
58	H	SO_2Ph	*p*-ClPh	5.0 ± 0.35 (4)
59	H	SO_2Bn	*p*-ClPh	3.4 ± 0.17 (2)
60	H	$SO_2{}^{i}Bu$	*p*-ClPh	6.2 ± 0.55 (4)
61	H	$CONH{}^{t}Bu$	*p*-ClPh	3.2 ± 0.47 (4)
62	H	$CONH(C_5H_9)$	*p*-ClPh	3.8 ± 0.74 (4)
63	H	$CONH(C_6H_{11})$	*p*-ClPh	4.2 ± 0.70 (4)
64	H	CONHPh	*p*-ClPh	5.4 ± 0.69 (4)
65	H	CONHBn	*p*-ClPh	4.1 ± 0.95 (4)

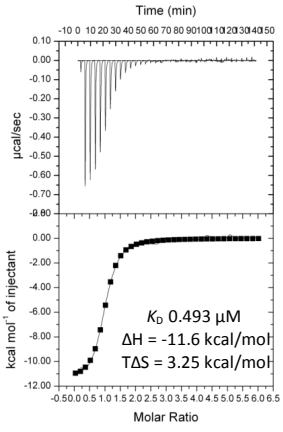
[a] Mean ΔTm ± SEM (number of measurements). All compounds were tested at 10 µM.

Isothermal Titration Calorimetry (ITC)

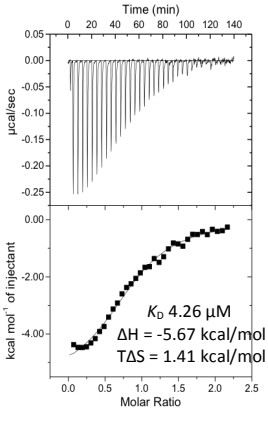
Experiments were carried out on a VP-ITC microcalorimeter (MicroCal™). All experiments were performed at 15 °C in 20 mM HEPES pH 7.5, 150 mM NaCl, 0.5 mM TCEP. BRD9 protein solution was buffer exchanged by gel filtration or dialysis into the ITC buffer. The titrations were conducted using an initial injection of 2 µl followed by 34 identical injections of 8 µl. The dilution heats were measured on separate experiments and were subtracted from the titration data. Thermodynamic parameters were calculated using $\Delta G = \Delta H - T\Delta S = -RT\ln K_B$, where ΔG, ΔH and ΔS are the changes in free energy, enthalpy and entropy of binding respectively. In all cases a single binding site model was employed.



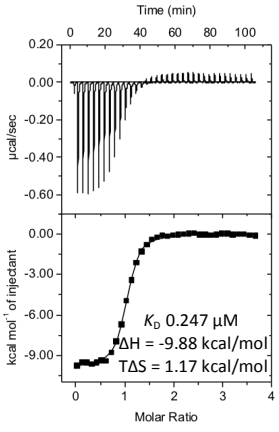
Supplemental Figure 1. ITC trace of compound **1** and BRD9



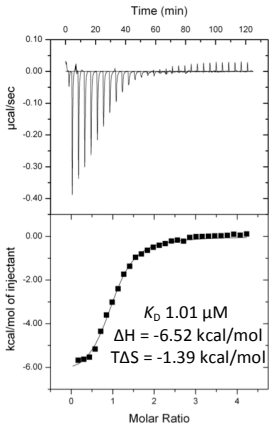
Supplemental Figure 2. ITC trace of compound **(-)-24** and BRD9



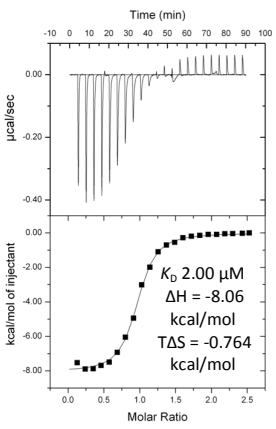
Supplemental Figure 3. ITC trace of compound **(+)-24** and BRD9



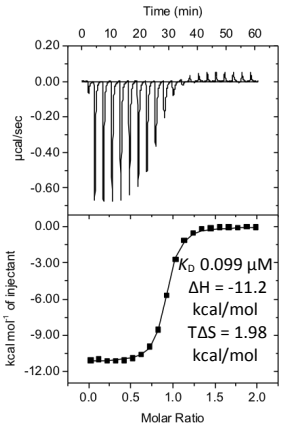
Supplemental Figure 4. ITC trace of compound **48** and BRD9



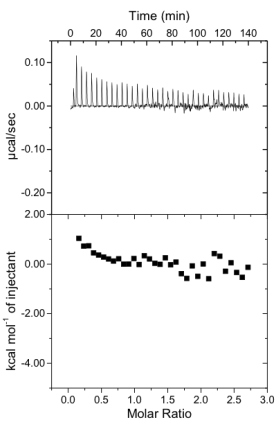
Supplemental Figure 5. ITC trace of compound **64** and BRD9



Supplemental Figure 6. ITC trace of compound **55** and BRD9



Supplemental Figure 7. ITC trace of compound (2*R*,3*S*)-**60**/**LP99** and BRD9



Supplemental Figure 8. ITC trace of compound (2*S*,3*R*)-**60** and BRD9

Crystallization

BRD9 construct (Uniprot identifier as BRD9 HUMAN Q9H8M2-1 fragment 14-134) was used for all crystallographic studies. Aliquots of the purified proteins were set up for crystallization using a mosquito® crystallization robot (TTP Labtech). Coarse screens were typically setup onto Greiner 3-well plates using three different drop ratios of precipitant to protein per condition (100 + 50 nL, 75 + 75 nL and 50 + 100 nL). All crystallizations were carried out using the sitting drop vapour diffusion method at 4°C. BRD9 crystals with compound **6** (5 mM final concentration) were obtained by mixing 100 nL of the protein (28 mg/ml) and 200 nL crystallization buffer (0.1 M PCB (sodium propionate, sodium cacodylate, and BIS-TRIS propane in the molar ratios 2:1:2) pH 8, 30% PEG 1K). Thin bar crystals of BRD9 with compound **(-)-24** (5 mM final concentration) were obtained by mixing 100 nL of the protein (28 mg/ml) and 200 nL crystallization buffer (0.1 M MMT (DL-malic acid, MES and Tris base in the molar ratios 1:2:2) pH 6, 30% PEG 1K).

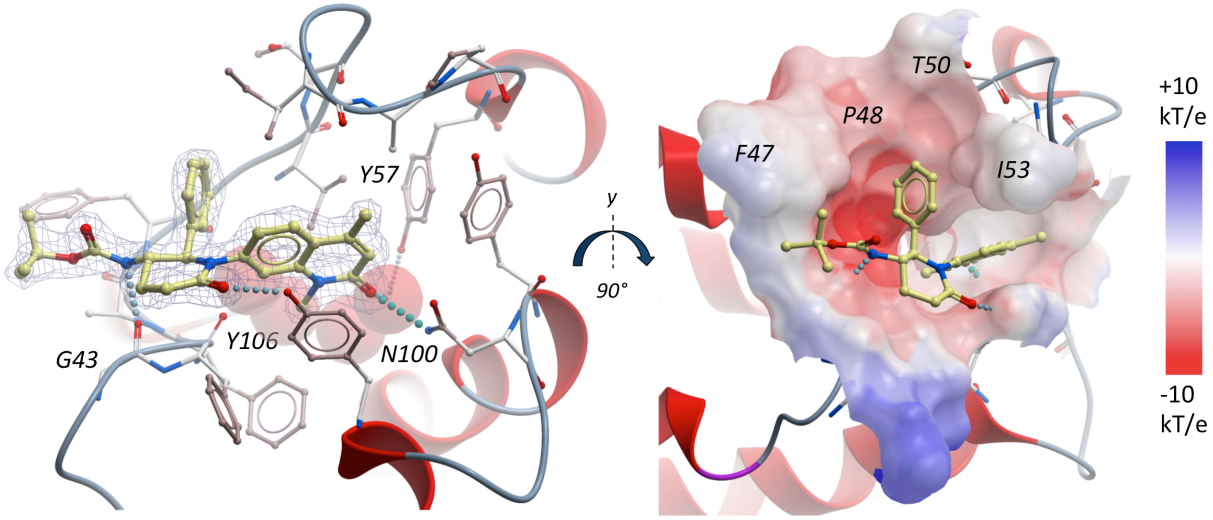
Data Collection and Structure Solution

Crystals were cryo-protected using the well solution supplemented with additional 20% ethylene glycol and were flash frozen in liquid nitrogen. Data were collected at Diamond Light Source beamlines I04, I24 and I02 at a wavelength of 0.9795 Å. Indexing and integration was carried out using XDS[6] and scaling was performed with AIMLESS.[7] Initial phases were calculated by molecular replacement with PHASER[8] using an ensemble of known bromodomain models (PDB IDs 2OSS, 2OUO, 2GRC, 2OO1, 3DAI, 3D7C, 3DWY, 3G0L). Unique and initial solutions were improved in a total of 50 cycles of automated protein chain tracing starting from existing model and computed using ARP/wARP. Further manual building with COOT and refinement against maximum likelihood target using REFMAC5. Thermal motions were analyzed using TLSMD[9] and hydrogen atoms were included in late refinement cycles. PRODRG[10] was used to generate compound coordinates and cif files. All model validations were carried out using MolProbity[11] Data collection and refinement statistics are compiled in Supplemental Table 2. The models and structure factors have been deposited into the pdb.

Supplemental Table 2. BRD9 crystallographic data collection and refinement statistics**.**

	Ligand	Compound **6**	Compound (2*R*,3*S*)-**24**
	PDB ID	4Z6H	4Z6I
Data Collection	Space Group	$P2_12_12$	I1 2 1
Cell Dimensions	a,b,c (Å)	71.23 125.22 29.77	60.01 29.46 141.2
	α, β, γ (°)	90.00 90.00 90.00	90.00 92.24 90.00
	Resolution (Å)	28.97 (1.80)*	28.84 (1.95)*
	Unique Observations	25,694 (3,641)	18,127 (1,308)
	Completeness (%)	99.8 (99.1)	98.3 (97.9)
	Redundancy	6.4 (6.6)	3.2 (3.0)
	R_{sym} or R_{merge}	0.033 (0.735)	0.033 (0.123)
	$I/\sigma I$	25.4 (2.4)	20.3 (6.1)
	Wavelength	0.9686	0.9795
	Phasing	MR	MR
Refinement	R_{work}/R_{free} (%)	22.07 / 27.08	18.12 / 22.99
Number of atoms	protein / other / solvent	1842 / 40 / 68	1840 / 68 / 111
B-Factors (Å^2)	protein / other / solvent	53.69 / 60.38 / 45.24	29.73 / 27.14 / 32.97
	R.M.S.D. Bond (Å)	0.017	0.021
	R.M.S.D. Angle (°)	1.717	2.069
Ramachandran	Allowed (%)	100.00	100.00
statistics	Favored (%)	100.00	99.55
	Outliers (%)	0.00	0.00

*Highest resolution shell (in Å) shown in parentheses



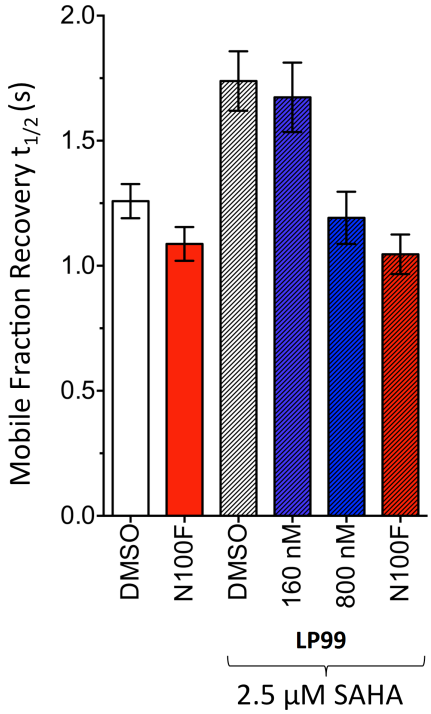
Supplemental Figure 9. Co-crystal structure of compound **(-)-24** and BRD9.
Compound **(-)-24** (pale sticks with electron density in blue mesh) binds to BRD9 and orients the R_3-phenyl group in the hydrophobic pocket of BRD9. H-bonds (dotted lines) are formed between the ligand and G43, Y99 (mediated by water molecule depicted as red sphere), N100, and Y106.

Cell Culture and Reagents

Human cell lines (HeLa U2OS, THP-1 and HEK293) were purchased from ATCC and cultivated according to the guidelines provided. THP-1 cells were stimulated with LPS from *E.coli* (Sigma Aldrich) at 100 ng/ml and inhibitor for 24h. IL-6 secretion was measured using Sandwich ELISA kit (R&D, D6050). Experiments were performed in duplicates with mean and SEM displayed.

Fluorescence Recovery After Photobleaching (FRAP) Assay

FRAP studies were performed using U2OS cells expressing a full-length BRD9 protein fused with an N-terminal eGFP as previously described.[12] In short, six hours after transfection 2.5 µM SAHA was and inhibitor were added 1 hour before imaging, which was carried out 24 hours after transfection. Percent inhibition was calculated between the DMSO treated (0%) and N100F expressing mutant (100%).



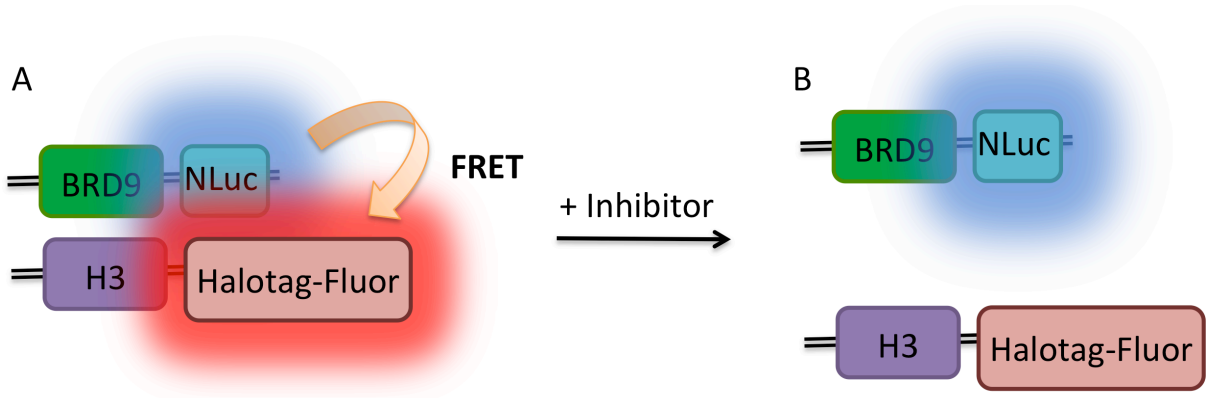
Supplemental Figure 10.

U2OS cells were transfected with an eGFP-BRD9 construct and SAHA to increase global histone acetylation. Treatment of cells with **LP99** was found to have a dose-dependent effect on FRAP recovery time, with higher doses showing t1/2 akin to that of cells expressing a N100F mutant unable to bind histone proteins.

NanoLuciferase Bioluminescent Resonance Energy Transfer (NanoBRET) Assay

HEK293 cell (8 x 10^5) were plated in each well of a 6-well plate and co-transfected with one acceptor, Histone H3.3-HaloTag (NM_002107) or Histone H4-HaloTag (P62805); and one donor, NanoLuc-BRD9 (Q9H8M2) BRD domain amino acids 120-240 or NanoLuc-BRD7 (NM001173984) BRD domain amino acids 120-237. Twenty hours after transfection cells were collected, washed with PBS, and exchanged into media containing phenol red-free DMEM and 4% FBS in the absence (control sample) or the presence (experimental sample) of 100 nM NanoBRET 618 fluorescent ligand (Promega). Cell density was adjusted to 2 x 10^5 cells/ml and then re-plated in a 96-well assay white

plate (Corning Costar #3917). **LP99** was added directly to media at final concentrations between 0-33 μM and the plates were incubated for 18 h at 37 ^{o}C in the presence of 5% CO_2. NanoBRET furimazine substrate (Promega) was added to both control and experimental samples at a final concentration of 10 µM. Readings were performed within 5 min using the CLARIOstar (BMG) equipped with 450/80 nm bandpass and 610 nm longpass filters with a 0.5 s reading setting. A corrected BRET ratio was calculated and is defined as the ratio of the emission at 610 nm/450 nm for experimental samples (i.e. those treated with NanoBRET fluorescent ligand) and the emission at 610 nm/450 nm for control samples (not treated with NanoBRET fluorescent ligand). BRET ratios are expressed as milli-BRET units (mBU), where 1 mBU corresponds to the corrected BRET ratio multiplied by 1000.



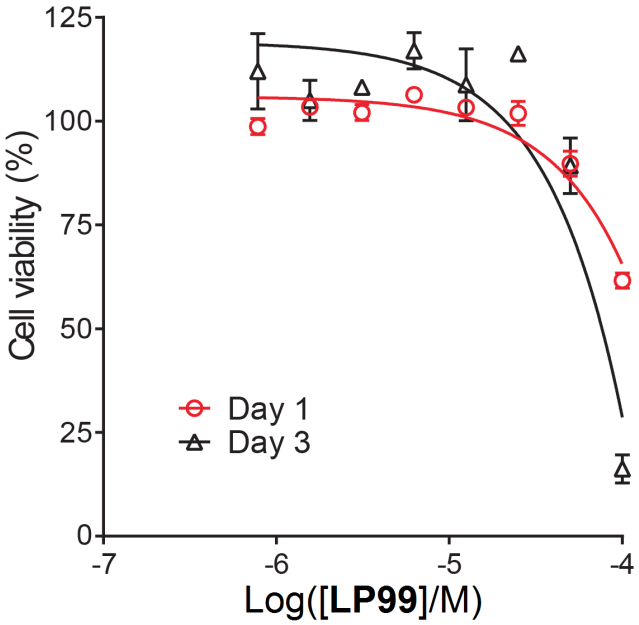
Supplemental Figure 11.
The NanoBRET assay measures BRD9 association with histone H3 in cells. (A) BRD9 (green) is expressed with a nano-lucoferase tag (NLuc, teal) and it binds via the bromodomain to histone H3 (purple) acetylated on lysine. Upon NLuc substrate addition, bioluminescent energy (blue cloud) is transferred via Förster resonence energy transfer (FRET – orange arrow) to the H3 acceptor construct which has been fluorescently tagged via the halotag domain. Emmision from the halotag-fluorophore (red cloud) is measured. (B) Upon bromodomain inhibitor treatment, the BRD9/H3 interaction is broken, FRET is not possible and emission ceases.

Supplemental Table 3.
Potency of **LP99** in cellular systems as assayed by NanoBRET.

Interaction	IC_{50} (µM)[a]	Interaction	IC_{50} (µM)[a]
BRD7-H3.3	3.7 ± 0.27 (4)	BRD9-H3.3	5.1 ± 0.50 (4)
BRD7-H4	3.3 ± 0.20 (4)	BRD9-H4	6.2 ± 0.59 (4)

Cytotoxicity Assay
U2OS cells were harvested from exponential phase cultures and plated in 96 well opaque flat-bottom plates at a cell density of 3 x 10^3 cells / well (100 µl). Compounds were dissolved in dimethyl sulfoxide (DMSO) at a concentration of 10 mM and serial dilutions performed. 5 µl of compound

solution was added to each well, thoroughly mixed and incubated for 24 and 72 h at 37 °C in a humidified atmosphere containing 5% CO_2. 10 µl of WST-1 (Roche) was added to each well and after mixing, the plates were returned to the incubator. Plates were read on a plate reader at 450 nm after 2 h for cells treated with compound for 24 h or after 1 h for cells treated with **LP99** for 72 h. Results were plotted as % of DMSO control.



Supplemental Figure 12.
Cytotoxicity of compound **LP99.** Cell viability of U2OS cells after 1 or 3 day treatment with increasing concentrations of **LP99**.

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