Supporting Information to Accompany

Convergent Kilo-Scale Synthesis of a Potent Renin Inhibitor for the Treatment of Hypertension

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General Information. All reactions were performed in reaction vessels equipped with a mechanical stirrer and a thermocouple under an atmosphere of nitrogen. Commercially available reagents and solvents were used without further purification. ^{1}H and ^{13}C NMR spectra were recorded in the specified deuterated solvent. Chemical shifts of ^{1}H NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard of residual solvent ($CHCl_3$ 7.26 ppm; acetone-d_6 2.05 ppm; DMSO-d_6 2.50 ppm) or TMS. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and br = broad), coupling constant (Hz) and integration. Chemical shifts of proton-decoupled ^{13}C NMR spectra are reported in ppm from the central peak of $CDCl_3$ (77.0 ppm), acetone-d_6 (29.8 ppm) or DMSO-d_6 (39.5 ppm) on the δ scale. Melting points (mp) are uncorrected.

3-bromo-5-iodo-4-methylbenzoic acid
^{1}H NMR (400 MHz, DMSO-d$_6$): δ 8.27 (s, 1 H); 8.02 (s, 1 H); 2.60 (s, 3 H).
^{13}C NMR (101 MHz, DMSO-d$_6$): δ 164.5, 144.4, 138.9, 132.9, 131.5, 122.9, 101.8, 29.1
IR (neat): 3068, 2683, 2533, 1683, 1534, 1370, 1284, 1141, 902, 766, 718.
HRMS: (ESI) m/z calcd for $C_8H_6BrIO_2$ (M + H) 340.8669, found 340.8666.

3-bromo-5-(3-methoxyprop-1-yn-1-yl)-4-methylbenzoic acid

^{1}H NMR (400 MHz, Acetone-d$_6$): δ 8.13 (s, 1 H); 8.00 (s, 1 H); 4.40 (s, 2 H); 3.41 (s, 3 H); 2.59 (s, 3 H).

^{13}C NMR (101 MHz, Acetone-d$_6$): δ 165.6, 145.1, 134.1, 133.0, 130.8, 125.6, 125.5, 92.3, 84.0, 60.4, 57.7, 21.8.

IR (neat): 1692, 1548, 1421, 1304, 1099, 767.

HRMS: (ESI) m/z calcd for $C_{12}H_{11}BrO_3$ (M + H) 280.9818, found 280.9821.

Melting point = 134.2-135.2 °C.

3-bromo-*N*-cyclopropyl-5-(3-methoxyprop-1-yn-1-yl)-4-methylbenzamide

^{1}H NMR (500 MHz, Acetone-d$_6$): δ 8.01 (s, 1 H); 7.92 (s, 1 H); 7.86 (s, 1 H); 4.37 (s, 2 H); 3.39 (s, 3 H); 2.95-2.89 (m, 1 H); 2.53 (s, 3 H); 0.76-0.67 (m, 2 H); 0.68-0.60 (m, 2 H).

^{13}C NMR (126 MHz, Acetone-d$_6$): δ 166.1, 142.9, 134.8, 132.1, 130.7, 125.5, 125.1, 91.8, 84.3, 60.4, 57.7, 23.9, 21.5, 6.3.

IR (neat): 3268, 2821, 1635, 1525, 1313, 1098, 1028.

HRMS: (ESI) m/z calcd for $C_{15}H_{16}BrNO_2$ (M + H) 322.0437, found 322.0433

Melting point = 109.5-111.4 °C.

3-bromo-N-cyclopropyl-5-(3-methoxypropyl)-4-methyl benzamide

^{1}H NMR (500 MHz, Acetone-d$_6$): δ 7.87 (m, 2 H); 7.65 (s, 1 H); 3.35 (t, J = 6.12 Hz, 2 H); 3.27 (s, 3 H); 2.93-2.86 (m, 1 H); 2.75 (t, J = 7.91 Hz, 2 H); 2.39 (s, 3 H); 1.80-1.72 (m, 2 H); 0.75-0.67 (m, 2 H); 0.61-0.56 (m, 2 H).

^{13}C NMR (126 MHz, Acetone-d$_6$): δ 167.0, 143.6, 139.4, 134.7, 129.7, 128.0, 126.2, 72.2, 58.5, 31.7, 31.0, 23.8, 19.2, 6.4.

IR (neat): 3281, 2924, 2856, 1636, 1520, 1458, 1308, 1110, 1021.

HRMS: (ESI) m/z calcd for $C_{15}H_{20}BrNO_2$ (M + H) 326.0750, found 326.0745.

Melting point = 84.6-85.4 °C.

***N*-[3-bromo-5-(3-methoxypropyl)-4-methylbenzyl] cyclopropanamine**

^{1}H NMR (500 MHz, $CHCl_3$-d): δ 7.34 (s, 1 H); 7.01 (s, 1 H); 3.71 (s, 2 H); 3.36 (t, J = 6.2 Hz, 2 H); 3.32 (s, 3 H); 2.69 (t, J = 7.8 Hz, 2 H); 2.34 (s, 3 H); 2.13-2.07 (m, 1 H); 1.97 (s, 1 H); 1.83-1.75 (m, 2 H); 0.43-0.37 (m, 2 H); 0.37-0.33 (m, 2 H).

^{13}C NMR (126 MHz, Acetone-d_6): δ 142.0, 139.3, 134.0, 130.0, 128.2, 126.0, 71.8, 58.5, 52.7, 31.1, 30.2, 29.9, 18.6, 6.4.

IR (neat): 3085, 2921, 2868, 2824, 1554, 1431, 1333, 1200, 1113, 1010.

HRMS: (ESI) m/z calcd for $C_{15}H_{22}BrNO$ (M + H) 312.0957, found 312.0955.

1-*tert*-butyl 3-ethyl 2'-methoxy-5,6-dihydro-4,4'-bipyridine-1,3(2*H*)-dicarboxylate

^{1}H NMR (400 MHz, Acetone-d$_6$): δ 8.09 (d, J = 5.24 Hz, 1 H); 6.74 (d, J = 5.23 Hz, 1 H); 6.55 (s, 1 H); 4.20 (s, 2 H); 3.93 (q, J = 7.11 Hz, 2 H); 3.87 (s, 3 H); 3.60 (s, 2 H); 2.49-2.45 (m, 2 H); 1.46 (s, 9 H); 0.97-0.89 (m, 3 H).

^{13}C NMR (101 MHz, Acetone-d$_6$): δ 166.4, 165.0, 154.8, 153.9, 147.4, 144.5, 126.8, 116.5, 109.3, 80.1, 72.7, 60.9, 53.5, 49.3, 28.5, 27.2, 13.8.

IR (ν_{max} /cm^{-1}): 2981, 1696, 1387, 1235, 760;

HRMS calculated for $C_{19}H_{26}N_2O_5$ (M+): 362.1842; Found: 362.1823

m.p. (EtOAc/Hex): 85.5-86.6 ºC

Ethyl 2'-methoxy-1-(trifluoroacetyl)-1,2,5,6-tetrahydro-4,4'-bipyridine-3-carboxylate

^{1}H NMR (600 MHz, DMSO-d$_6$, 363K): δ 8.10 (d, J = 5.20 Hz, 1 H); 6.77 (d, J = 5.17 Hz, 1 H); 6.60 (s, 1 H); 4.40 (s, 2 H); 3.97-3.91 (m, 2 H); 3.86 (s, 3 H); 3.78 (s, 2 H); 2.57 (s, 2 H); 0.92 (s, 3 H).

^{13}C NMR: spectra shown below. Peaks were not assigned because of rotamers at room temperature.

^{13}C NMR (obtained from HMBC, HMQC experiments at 363K): δ 12.6, 31.2, 40.9, 42.2, 52.4, 59.6, 107.9, 115.5, 123.8, 143.4, 146.3, 147.1, 154.1, 163.4, 164.3 (CF_3 carbon not observed)

IR (ν_{max} /cm^{-1}): 2984, 1692, 1389, 1131, 1042;

HRMS calculated for $C_{16}H_{17}F_3N_2O_4$ (M+): 358.1140; Found: 358.1130;

Ethyl (3*S*, 4*S*)-4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-1-(trifluoroacetyl) piperidine-3-carboxylate

^{1}H NMR (600 MHz, DMSO-d$_6$, 323K) Major rotamer: δ 7.57 (dd, J = 7.00, 4.61 Hz, 1 H); 6.15-6.11 (m, 2 H); 4.54 (d, J = 13.57 Hz, 1 H); 3.98 (d, J = 14.07 Hz, 1 H); 3.92-3.80 (m, 2 H); 3.39 (d, J = 13.33 Hz, 1 H); 3.34 (s, 3 H); 3.25 (dd, J = 13.59, 3.55 Hz, 1 H); 3.14 (s, 1 H); 3.07-3.02 (m, 1 H); 2.30-2.15 (m, 1 H); 1.78 (t, J = 13.70 Hz, 1 H); 0.98 (td, J = 7.09, 3.95 Hz, 3 H).

^{13}C NMR: spectra shown below. Peaks were not assigned because of rotamers at room temperature.

IR (ν_{max} /cm^{-1}): 1681, 1657, 1594, 1139, 867;

[α]-D: -18.8º (C=3.0, CH_2Cl_2).

HRMS calculated for $C_{16}H_{19}F_3N_2O_4$ (M+): 360.1297; Found: 360.1306;

m.p. (iPAc/MTBE): 140.1-141.3 ºC

(3*R*,4*S*)-1-(*tert*-butoxycarbonyl)-4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)piperidine-3-carboxylic acid

^{1}H NMR (400 MHz, DMSO-d$_6$): δ 12.42 (s, 1 H); 7.57 (d, J = 6.83 Hz, 1 H); 6.20-6.14 (m, 2 H); 4.20 (s, 1 H); 4.00 (s, 1 H); 3.34 (s, 3 H); 2.81-2.43 (m, 4 H); 1.66 (d, J = 12.98 Hz, 1 H); 1.40 (m, 10 H).

^{13}C NMR (101 MHz, DMSO-d$_6$): δ 173.0, 161.9, 156.0, 153.6, 139.2, 116.3, 105.1, 79.1, 46.2, 43.7, 36.3, 30.9, 28.0. (overlaping peaks, no other peaks detected even after prolonged scans.)

IR (ν_{max} /cm^{-1}): 2919, 1682, 1533, 1426, 1167, 785;

[α]-D: +19.9º (C=3.0, CH_2Cl_2).

HRMS calculated for $C_{17}H_{24}N_2O_5$ (M+): 336.1685; Found: 336.1680;

m.p. (water): 208.0-209.1 ºC

***Tert*-butyl (3*R*, 4*S*)-3-{[[3-bromo-5-(3-methoxypropyl)-4-methylbenzyl](cyclopropyl) amino]carbonyl}-4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl) piperidine-1-carboxylate**

^{1}H NMR (400 MHz, $CHCl_3$-d): δ 7.07 (d, J = 6.82 Hz, 1 H); 7.01 (s, 1 H); 6.81 (s, 1 H); 6.32 (s, 1 H); 5.99 (d, J = 6.64 Hz, 1 H); 4.45-4.81 (m, 1 H); 4.43-3.70 (m, 3 H); 3.40 (s, 3 H); 3.36-3.28 (m, 6 H); 2.98 (t, J = 11.68 Hz, 1 H); 2.80 (s, 2 H); 2.62 (t, J = 7.74 Hz, 2 H); 2.39 (s, 1 H); 2.29 (s, 3 H); 1.77-1.68 (m, 3 H); 1.44 (s, 10 H); 0.84 (s, 3 H); 0.64 (s, 1 H).

^{13}C NMR (101 MHz, $CHCl_3$-d): δ 174.0, 162.9, 156.5, 154.2, 142.0, 137.8, 136.6, 134.3, 129.6, 128.3, 125.9, 116.8, 107.5, 80.0, 77.2, 71.7, 58.5, 48.9, 46.7, 45.5, 44.4, 43.4, 37.3, 31.1, 30.2, 29.7, 28.4, 18.7, 9.4.

IR (ν_{max} /cm^{-1}): 2921, 1695, 1646, 1421, 1116, 877, ;

[α]-D: +29.0º (C=3.0, CH_2Cl_2).

HRMS calculated for $C_{32}H_{44}BrN_3O_5$ (M+): 629.2464; Found: 629.2483;

m.p. (2-MeTHF): 172.4-173.8ºC

(3*R*,4*S*)-*N*-[3-bromo-5-(3-methoxypropyl)-4-methylbenzyl]-*N*-cyclopropyl-4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)piperidine-3-carboxamide hydrochloride

^{1}H NMR (400 MHz, H_2O-d_2): δ 7.16 (d, J = 6.85 Hz, 1 H); 6.74-6.56 (m, 1 H); 6.57 (s, 1 H); 6.20 (s, 1 H); 6.10 (d, J = 6.94 Hz, 1 H); 4.51 (d, J = 14.48 Hz, 1 H); 3.81 (t, J = 11.54 Hz, 1 H); 3.50-3.30 (m, 3 H); 3.22-3.06 (m, 8 H); 3.06-2.78 (m, 3 H); 2.31 (d, J = 9.94 Hz, 3 H); 1.95 (s, 3 H); 1.88 (d, J = 14.15 Hz, 1 H); 1.77 (q, J = 13.60 Hz, 1 H); 1.45 (t, J = 7.48 Hz, 2 H); 0.94 (d, J = 7.68 Hz, 1 H); 0.75-0.62 (m, 2 H); 0.50 (s, 1 H).

^{13}C NMR (101 MHz, H_2O-d_2): δ 173.7, 164.0, 156.2, 142.3, 139.9, 136.0, 134.7, 129.6, 128.8, 125.6, 116.3, 108.6, 71.8, 58.1, 45.2, 43.4, 41.7, 38.2, 30.8, 30.6, 29.6, 28.3, 18.5, 10.6, 8.2.

IR (ν_{max} /cm^{-1}): 1657, 1597, 1398. 1118, 962;

HRMS calculated for free base $C_{27}H_{36}BrN_3O_3$ (M+): 529.1940; Found: 529.1923

m.p. (IPA:MTBE): 222.1-222.9 ºC