2-Methoxycyclopentyl analogues of a *Pseudomonas aeruginosa* quorum sensing modulator

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Supporting Information

Experimental

Except as otherwise indicated, reactions were carried out under argon with dry, freshly distilled solvents. Dichloromethane was distilled from calcium hydride. All other reagents were purified in accordance with the instructions in *"Purification of Laboratory Chemicals"* (W. L. F. Amarego and D. D. Perrin, Butterworth-Heinemann, Oxford, 1997) or used as obtained from commercial sources.

Yields refer to chromatographically and spectroscopically pure compounds. All reactions were monitored by thin layer chromatography using glass plates precoated with Merck silica gel 60 F_{254} or aluminum oxide 60 F_{254}. Visualization was by the quenching of UV fluorescence (λ_{max} = 254 nm) or by staining with ceric ammonium molybdate or potassium permanganate. Retention factors (R_f) are quoted to 0.01. Melting points were obtained using a Mel-Temp II melting point apparatus and are uncorrected. Infrared spectra were recorded neat on a diamond/ZeSe plate using a Perkin-Elmer Spectrum One FT-IR Universal ATR sampling accessory spectrometer with internal referencing. Absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}). Proton magnetic resonance spectra were recorded on Bruker Ultrashield 400 or Bruker Ultrashield 500 instruments. Proton assignments are supported by ^1H–^1H spectra where necessary. Chemical shifts (δ_H) are quoted in ppm and are referenced to the residual non-deuterated solvent peak. Coupling constants (J) are reported in Hertz to the nearest 0.5 Hz. Data are reported as follows: chemical shift, integration, multiplicity [br, broad; s, singlet; d, doublet; t, triplet; q, quartet; qui, quintet; sept, septet; m, multiplet; or as a combination of these (*e.g.* dd, dt, *etc.*)], coupling constant(s) and assignment. Diastereotopic protons are assigned as X and X′, where the ′ indicates the lower field proton. Carbon magnetic resonance spectra were recorded on Bruker Ultrashield 500 spectrometers. Carbon spectra assignments are supported by DEPT editing and where necessary ^{13}C–^1H (HMQC) correlations. Chemical shifts (δ_C) are quoted in ppm to the nearest 0.01 ppm, and are referenced to the deuterated solvent. Low resolution mass spectra were obtained with Kratos MS890MS (CI/EI), and Micromass Q-TOF (APCI/ES) spectrometers. Only molecular ions, fractions from molecular ions and other major peaks are reported. High resolution mass measurements were performed by the University of Cambridge Mass Spectrometry Laboratory in the Department of Chemistry, and reported mass values are within the error limits of ±5 ppm mass units.

2-((1*S,2*S**)-2-Hydroxycyclopentyl)isoindoline-1,3-dione (6)**

A round-bottomed flask, equipped with a magnetic stirrer bar and reflux condenser, containing ground *trans*-2-aminocyclopentanol hydrochloride (0.5 g, 4.9 mmol), ground phthalic anhydride (0.725 g, 4.9 mmol) and diisopropylamine (0.824 ml, 5.88 mmol) was stirred under a nitrogen atmosphere at 130 °C for 2 hours. The reaction mixture was allowed to cool to room temperature and partioned between ethyl acetate (20 ml) and 2N hydrochloric acid (12 ml). The organic layer was washed with water (2 x 25 ml) followed by washing with sat sodium bicarbonate (10 ml) and brine (10 ml). The organic layer was dried with magnesium sulphate and filtered, the organic solvent was removed under vacuum. The crude product was chromatographed (SiO_2, CH_2Cl_2-EtOAc, 7:1) to give 2-((1*S**,2*S**)-2-hydroxycyclopentyl)-isoindoline-1,3-dione as a white solid (510 mg, 45%); m.p. 109-111 °C; ν_{max}(neat)/cm^{-1} 3403 (O-H), 2963 (C-H), 1769 (C=O), 1688 (C=C); δ_H (500 MHz, $CDCl_3$) 1.66-1.70 (1H, m, CH(OH)C***H***$_2$), 1.83-1.94 (2H, m, C***H***$_2$CH$_2$CH(OH)), 2.06-2.16 (2H, m, C***H***$_2$CH(N)), 2.20-2.24 (1H, m, CH(OH)C***H***$_2$), 4.37-4.42 (1H, m, C***H***(N)), 4.73-4.77 (1H, m, C***H***(OH)), 7.70-7.72 (2H, m, C***H***CHCHC***H***), 7.75-7.83 (2H, m, CHC***H***C***H***CH); δ_C (125 MHz, $CDCl_3$) 168.64, 131.99, 133.93, 123.13, 75.00, 59.22, 33.25, 27.16, 21.00.

2-((1*S,2*S**)-2-Methoxycyclopentyl)isoindoline-1,3-dione (7)**

A round-bottomed flask, equipped with a magnetic stirrer bar, containing 2-((1*S**,2*S**)-2-hydroxycyclopentyl)isoindoline-1,3-dione (582 mg, 2.52 mmol) in dry CH_2Cl_2 (15 ml) was charged with proton sponge® (3.27 g, 15.3 mmol), (activated) molecular sieves (4 Å, 3.00 g) and trimethyloxonium tetrafluoroborate (889 mg, 6.01 mmol) and stirred under a nitrogen atmosphere at room temperature overnight. The reaction mixture was filtered and washed on the filter with ethyl acetate (6 x 20 ml). The combined organic phases were washed with water (x 1), 10% aqueous $CuSO_4$ solution (x 2), dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed (SiO_2, CH_2Cl_2-EtOAc, 5:1) to give 2-((1*S**,2*S**)-2-methoxycyclopentyl)isoindoline-1,3-dione as an orange solid (433 mg, 70%); m.p. 72-75 °C; R_f 0.79 (SiO_2, CH_2Cl_2:EtOAc, 5:1); ν_{max}(neat)/cm^{-1} 3055- 2775 (C-H), 1765 (C=O), 1708-1575 (C=C); δ_H (400 MHz, $CDCl_3$) 1.71-1.91 (2H, m, C***H***$_2$CH(N)), 2.01 (1H, m, C***H***$_2$CH$_2$CH(OMe)), 2.01-2.06 (2H, m, C***H***$_2$CH(OMe)), 2.17-2.22 (1H, m, C***H***$_2$CH$_2$CH(N)), 3.27 (3H, s, OC***H***$_3$), 4.23-4.27 (1H, m, C***H***(N)), 4.51 (1H, td, *J* 9.0, 5.5, C***H***(OMe)), 7.69-7.73 (2H, m, C***H***CHCHC***H***), 7.81-7.85 (2H, m, CHC***H***C***H***CH); δ_C (100 MHz, $CDCl_3$) 168.27, 132.05, 133.89, 123.14, 84.14, 56.93, 56.71, 30.99, 28.43, 22.37.

***N*-((1*S**,2*S**)-2-methoxycyclopentyl)butyramide (3)**

A round-bottomed flask, equipped with a stirrer bar and reflux condenser, containing 2-((1*S**,2*S**)-2-methoxy-cyclopentyl)isoindoline-1,3-dione (52 mg, 0.21 mmol), hydrazine monohydrate (20 µl, 0.41 mmol) and ethanol (5 ml) was stirred at 60 °C overnight. The ethanol was removed *in vacuo* and the flask charged with butyryl chloride (70 µl, 0.67 mmol), CH_2Cl_2 (5 ml), potassium carbonate (93 mg, 0.67 mmol) and water (5 ml) and stirred at room temperature overnight. The organic layer was separated from the reaction mixture and washed with aqueous K_2CO_3 (x 2), brine (x 2), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed (SiO_2, CH_2Cl_2:EtOAc 5:1) to give *N*-((1*S**,2*S**)-2-methoxycyclopentyl)butyramide as a colourless oil (36 mg, 93%); R_f 0.09 (SiO_2, CH_2Cl_2:EtOAc, 5:1); ν_{max}(neat)/cm^{-1} 3285 (O-H), 3071-2825 (C-H), 1638 (C=O), 1544 (N-C=O); δ_H (400 MHz, $CDCl_3$) 0.93 (3H, t, *J* 7.5, CH_2CH_3), 1.36-1.38 (1H, m, CH_2CH(N)), 1.61-1.69 (4H, m, CH_2CH_3, CH_2CH_2CH(OMe)), 1.83-1.85 (2H, m, CH_2CH(OMe)), 2.10-2.13 (3H, m, CH***H´***CH(N), CH_2CO(N)), 3.36 (3H, s, OCH_3), 3.56-3.60 (1H, m, C***H***(OMe)), 4.11-4.15 (1H, m, C*H*(N)), 5.44 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 172.51, 86.86, 56.89, 55.33, 38.74, 30.65, 30.10, 21.55, 19.10, 13.68.

***tert*-Butyl (1*S**,2*S**)-2-hydroxycyclopentylcarbamate[1,2]**

A round-bottomed flask, equipped with a magnetic stirrer bar, containing *trans*-2-aminocyclopentanol hydrochloride (2.49 g, 18.1 mmol), distilled triethylamine (2.3 ml, 18.1 mmol) and MeOH (100 ml) was charged with di-*tert*-butyl-dicarbonate (3.95 g, 18.1 mmol) and stirred at room temperature overnight. The reaction mixture was concentrated *in vacuo* and the residue was chromatographed (SiO_2; diethyl ether: hexane, 4:1) to give *tert*-butyl (1*S**,2*S**)-2-hydroxy-cyclopentylcarbamate as a white solid (3.35 g, 16.6 mmol, 92%); m.p. 105-106 °C (diethyl ether: hexane, 4:1) (lit.[2] m.p. 77-78 °C, Hexane), R_f 0.28 (SiO_2; diethyl ether:hexane, 4:1); ν_{max}(neat)/cm^{-1} 3353 (O-H), 3274 (N-H), 2982-2961 (C-H), 1672 (C=O), 1553 (C-N); δ_H (400MHz; $CDCl_3$) 1.34 (1H, dq, *J* 13.0, 8.5, C***H***H´CHOH), 1.44 (9H, s, (C=O)OC(CH_3)$_3$), 1.60-1.82 (3H, m, CH_2CH_2CHOH, CH***H´***CHOH), 1.97-2.12 (2H, m, CH_2CHNH(C=O)), 3.58-3.65 (1H, m, C***H***NH(C=O)), 3.94-4.00 (1H, m, C***H***OH), 4.65 (1H, br s, N***H***); δ_C (125 MHz; $CDCl_3$) 157.29; 80.00, 79.82, 60.53, 32.44, 30.45, 28.33, 20.95. Data in agreement with literature values.

(3a*S,6a*R**)-Hexahydro-2H-cyclopenta[d]oxazol-2-one (8)[3]**

A round-bottomed flask, equipped with a magnetic stirrer bar, containing *tert*-butyl (1*S**,2*S**)-2-hydroxycyclopentyl carbamate (3.28 g, 16.3 mmol), *N,N*diisopropylethylamine (8.5 ml, 48.9 mmol) and CH_2Cl_2 (60 ml) was charged with methanesulfonyl chloride (1.90 ml, 24.4 mmol). The reaction mixture was stirred at 0 °C and slowly warmed to room temperature overnight. The reaction was quenched with saturated ammonium chloride solution (30 ml). The CH_2Cl_2 layer was separated from the reaction mixture, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 ml). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was chromatographed (SiO_2; 3:1 diethyl ether: petroleum ether (30:40), then ethyl acetate) to give (3a*S**,6a*R**)-Hexahydro-2H-cyclopenta-[d]-oxazol-2-one as an off-white solid (1.83 g, 14.4 mmol, 88%); m.p. 88-89 °C (ethyl acetate) (Lit.[3] m.p. 98-100 °C); R_f 0.30 (SiO_2; ethyl acetate); ν_{max} (neat)/cm^{-1} 3241 (N-H), 2969-2931 (C-H), 1698 (C=O), 1539 (C-N); δ_H (400MHz; $CDCl_3$) 1.54-1.88 (5H, m, CH_2), 2.07-2.13 (1H, m, C***H***H´CHNH(C=O)), 4.25 (1H, t, *J* 6.0, C***H***NH(C=O)), 5.05 (1H, t, *J* 6.0, C***H***O(C=O)), 5.19 (1H, br s, N***H***); δ_C (125 MHz; $CDCl_3$) 159.70, 82.37, 56.58, 34.62, 33.85, 21.99. Data in agreement with literature values.

***tert*-Butyl (1*S**,2*R**)-2-hydroxycyclopentylcarbamate (9)**

A mixture of (3a*S**,6a*R**)-hexahydro-2H-cyclopenta[d]oxazol-2-one (100 mg, 0.79 mmol) and lithium hydroxide (188 mg, 7.86 mmol) in an 8:1 water:methanol solvent mixture (5 ml) was refluxed at 100 °C for 2 h with stirring. The reaction mixture was then neutralised with 3N aqueous hydrochloric acid and concentrated *in vacuo* to yield the crude product *cis*-2-aminocyclopentanol hydrochloride. δ_H (400MHz; CD_3OD) 1.55-1.75 (3H, m, CH_2CH_2CHOH, C***H***H´$CHNH_2$), 1.82-2.01 (3H, m, CH_2CHOH, CH***H´***$CHNH_2$), 3.24-3.32 (1H, m, C***H***NH_2), 4.11 (1H, q, *J* 3.5, C***H***OH), 4.71 (2H, br s, N***H***$_2$). A round-bottomed flask, equipped with a magnetic stirrer bar, containing *cis*-2-aminocyclopentanol hydrochloride as the crude product, distilled triethylamine (0.10 ml, 0.79 mmol) and MeOH (10 ml) was charged with di-*tert*-butyl-dicarbonate (343 mg, 1.57 mmol) and stirred at room temperature overnight. The reaction mixture was concentrated *in vacuo*. Water (5 ml) was added to the residue, and the aqueous solution was extracted with CH_2Cl_2 (3 × 5 ml). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was chromatographed (SiO_2; 4:1 diethyl ether: hexane) to give *tert*-butyl (1*S**,2*R**)-2-hydroxycyclopentylcarbamate as a white solid (143 mg, 0.71 mmol, 91%); m.p. 62-64 °C (4:1 diethyl ether:hexane); R_f 0.41 (SiO_2; diethyl ether:hexane, 4:1); ν_{max}(neat)/cm^{-1} 3365 (O-H), 3266 (N-H), 2979-2931 (C-H), 1678 (C=O), 1530 (C-N); δ_H (500 MHz; $CDCl_3$) 1.45 (9H, s, (C=O)OC(CH_3)$_3$), 1.48-1.68 (4H, m, CH_2CH_2), 1.75-2.00 (2H, m, CH_2), 3.81 (1H, br s, C***H***NH(C=O)), 4.16 (1H, br s, C***H***OH), 4.82 (1H, br s, N***H***); δ_C (100 MHz; $CDCl_3$) 155.29, 79.43, 72.70, 55.43, 32.39, 29.06, 28.39, 20.09.

***tert*-Butyl (1*S**,2*R**)-2-methoxycyclopentylcarbamate (10)**

A round-bottomed flask, equipped with a magnetic stirrer bar, containing *tert*-butyl (1*S**,2*R**)-2-hydroxycyclopentyl carbamate (53 mg, 0.26 mmol), Proton Sponge® (0.40 g, 1.84 mmol), activated powdered 4Å molecular sieves (0.8 g) and CH_2Cl_2 (5 ml) was charged with trimethyloxonium tetrafluoroborate (156 mg, 1.05 mmol) and stirred overnight under nitrogen at room temperature. The reaction mixture was filtered and washed with ethyl acetate (6 × 10 ml). The combined organic layers were washed with water (10 ml), 10% aqueous copper sulphate solution (2 × 10 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was chromatographed (SiO_2; hexane: diethyl ether, 3:1) to give *tert*-butyl (1*S**,2*R**)-2-methoxy-cyclopentylcarbamate as a brown solid (11 mg, 0.051 mmol, 19%); R_f 0.20 (SiO_2; hexane: diethyl ether, 3:1); ν_{max}(neat)/cm^{-1} 2969-2931 (C-H), 1713 (C=O), 1496 (C-N), 1081 (C-O); δ_H (500MHz; $CDCl_3$) 1.23-1.27 (1H, m, C**H**H´CHNH(C=O)), 1.45 (9H, s,

(C=O)OC(C***H***$_3$)$_3$), 1.47-1.54 (2H, m, C***H***$_2$CH$_2$CH(OCH$_3$)), 1.66-1.76 (2H, m, C***H***$_2$CH(OCH$_3$)), 1.93-1.95 (1H, m, CH***H´***CHNH(C=O)), 3.28 (3H, s, CH(OC***H***$_3$)), 3.60 (1H, br s, C***H***NH(C=O)), 3.84 (1H, br s, C***H***(OCH$_3$)), 5.02 (1H, br s, N***H***); δ_C (100 MHz; CDCl$_3$). 155.75, 81.75, 78.97, 56.57, 54.05, 29.82, 28.49, 28.41, 20.19.

(1*S,2*R**)-2-Methoxycyclopentanamine hydrochloride**

A round-bottomed flask, equipped with a magnetic stirrer bar, containing *tert*-butyl (1*S**,2*R**)-2-methoxycyclopentyl carbamate (11 mg, 0.051 mmol) was charged with a solution of hydrochloric acid in ethyl acetate (0.5 ml) and stirred at room temperature for 1 h. The reaction mixture was concentrated *in vacuo* to yield the crude mixture that contained the product (1*S**,2*R**)-2-methoxy-cyclopentanamine hydrochloride. The residue used without further purification. ν_{max}(neat)/cm^{-1} 2918 (N-H), 1079 (C-O); δ_H (500 MHz; CD$_3$OD) 1.62-1.73 (2H, m, C***H***$_2$CH$_2$CH(OCH$_3$)), 1.79-1.90 (3H, m, C***H***$_2$CH(OCH$_3$), C***H***H´CHNH$_2$), 2.01-2.08 (1H, m, CH***H´***CHNH$_2$), 3.36 (3H, s, CH(OC***H***$_3$)), 3.50 (1H, q, *J* 7.5, C***H***NH$_2$), 3.82-3.85 (1H, m, C***H***(OCH$_3$)); δ_C (100 MHz; CD$_3$OD) 81.42, 56.93, 54.71, 29.15, 28.82, 21.39.

***N*-((1*S**,2*R**)-2-methoxycyclopentyl)butyramide (4)**

A round-bottomed flask, equipped with a magnetic stirrer bar, containing (1*S**,2*R**)-2-methoxycyclopentanamine hydrochloride (5 mg, 0.033 mmol), anhydrous potassium carbonate (14 mg, 0.1 mmol) and 1:1 CH$_2$Cl$_2$:H$_2$O solvent mixture (2 ml) was charged with butyryl chloride (8.0 µl, 66 µmol) and stirred overnight at room temperature. The CH$_2$Cl$_2$ layer was separated from the reaction mixture, and the aqueous layer was extracted with CH$_2$Cl$_2$ (3 × 2 ml). The combined organic layers were dried (MgSO$_4$), filtered, and concentrated *in vacuo*. The residue was chromatographed (SiO$_2$; CH$_2$Cl$_2$: diethyl ether, 5:2) to give *N*-((1*S**,2*R**)-2-methoxy-cyclopentyl)butyramide as a yellow solid (4 mg, 0.022 mmol, 66%); m.p. 44-46 °C (CH$_2$Cl$_2$: diethyl ether, 5:2); R_f 0.22 (SiO$_2$; CH$_2$Cl$_2$: diethyl ether, 5:2); ν_{max}(neat)/cm^{-1} 3298 (N-H), 2963-2875 (C-H), 1645 (C=O), 1544 (C-N), 1085 (C-O); δ_H (500 MHz; CDCl$_3$) 0.94 (3H, t, *J* 7.0, CH$_2$C***H***$_3$), 1.42-1.82 (6H, m, C***H***$_2$C***H***$_2$CH(OCH$_3$), (C=O)CH$_2$C***H***$_2$), 1.97-2.04 (1H, m, C***H***H´CHNH(C=O)), 2.15 (2H, t, *J* 8.0, NH(C=O)C***H***$_2$), 2.33 (1H, t, *J* 7.5, CH***H´***CHNH(C=O)), 3.29 (3H, s, CH(OC***H***$_3$)), 3.61-3.64 (1H, m, C***H***NH(C=O)), 4.10-4.18 (1H, m, C***H***(OCH$_3$)), 5.99 (1H, br s, N***H***); δ_C (100 MHz; CDCl$_3$) 172.77, 81.78, 56.46, 52.61, 38.84, 29.84, 28.40, 20.42, 19.23, 13.71.

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