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Identification and optimisation of 3,3-dimethyl-azetidin-2-ones as potent and selective inhibitors of 11β-hydroxysteroid dehydrogenase type 1 (11β -HSD1)†

William McCoull,*[a] Martin Augustin,[c] Caroline Blake,[a] Anne Ertan,[b] Elaine Kilgour,[a] Stephan Krapp,[c] Jane E. Moore,[a] Nicholas J. Newcombe,[a] Martin Packer,[a] Amanda Rees,[a] John Revill,[a] James S. Scott,[a] Nidhal Selmi,[a] Stefan Gerhardt,[a] Derek Ogg,[a] Stefan Steinbacher,[c] and Paul R.O. Whittamore[a]

Cardiovascular & Gastrointestinal Innovative Medicines Unit, AstraZeneca
Mereside, Alderley Park, Macclesfield, Cheshire, SK10 4TG, UK

Tel: +44 (0) 1625 519444; E-mail: william.mccoull@astrazeneca.com

Supplementary information contents:

Synthetic details for the preparation of compounds:

All solvents and chemicals used were reagent grade. Anhydrous solvents were purchased from Sigma Aldrich. Flash column chromatography was carried out using Redisep or Crawford prepacked silica cartridges (4−330 g) and elution was with an Isco Companion system. Following isolation, compounds were purified to >95% purity (UV and NMR) by silica gel chromatography and reverse phase preparative high performance liquid chromatography (HPLC) purification carried out using a Waters XBridge Prep C18 OBD column, 5 µm silica, 50 mm diameter, 150 mm length.

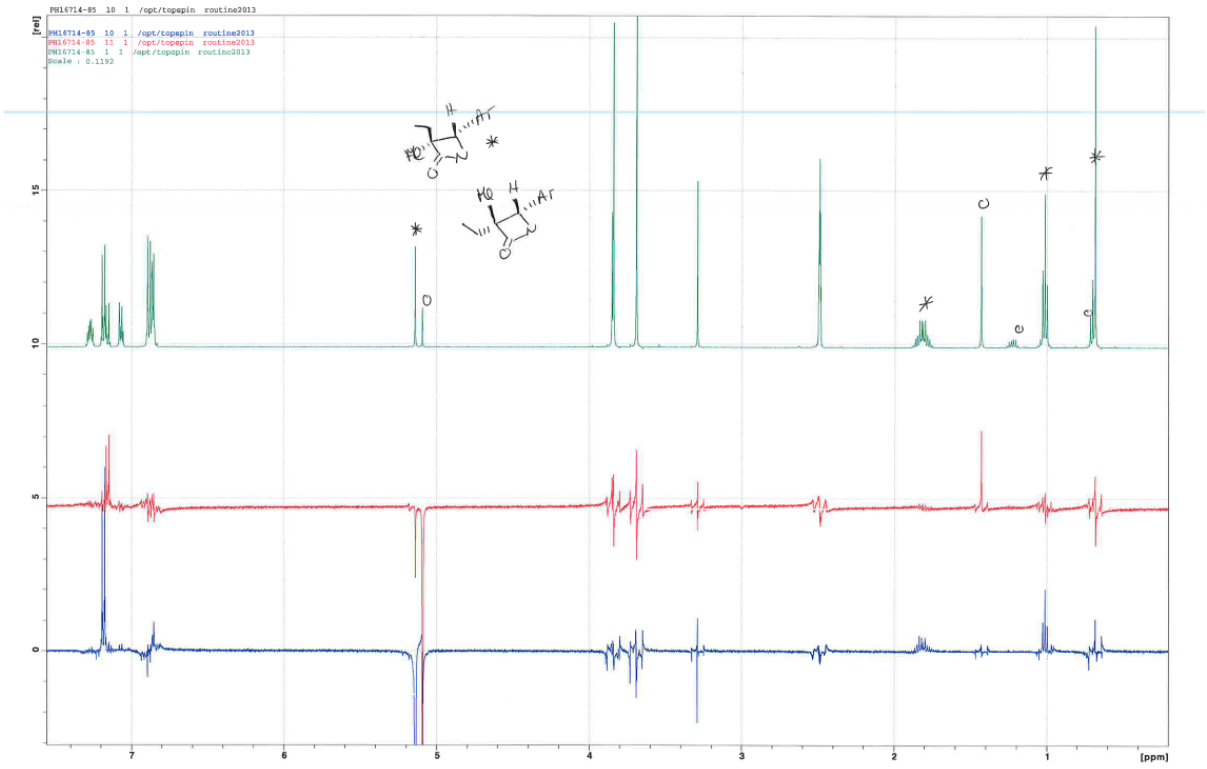
Mass spectrometry data were recorded by liquid chromatography-mass spectrometry (LCMS) on a Waters 2790 separations module with a Phenomenex 5 µm C18 50 mm × 2 mm column, a Waters 996 photodiode array detector, and Waters Micromass ZQ mass spectrometer, with detection by UV at 254 nm. Purity was >95% for all test compounds as determined by this HPLC/MS method. ^{1}H NMR spectra were recorded on Varian INOVA (600 MHz), Varian Gemini 2000 (300 MHz), Bruker Avance DPX400 (400 MHz), Bruker Ultrashield 400 Plus (400 MHz) or Bruker Advance 500 (500 MHz) in the indicated deuterated solvent. Chemical shifts are reported in ppm relative to tetramethylsilane (TMS) (0.00 ppm) or solvent peaks as the internal reference. Merck precoated thin layer chromatography (TLC) plates were used for TLC analysis. For workup, solutions were dried over anhydrous magnesium sulfate and the solvent was removed by rotary evaporation under reduced pressure.

Abbreviations used: MeCN, acetonitrile; DCM, dichloromethane; DMF, dimethylformamide; DMSO, dimethylsulfoxide; Et_2O, diethyl ether; EtOH , ethanol; EtOAc, ethyl acetate; LiHMDS, Lithium bistrimethylsyliyl amide; HPLC, high performance liquid chromatography; $MgSO_4$, magnesium sulfate; MeOH, methanol; $NaHCO_3$, sodium bicarbonate; RT, room temperature; THF, tetrahydrofuran; H_2O, water.

4-(2-methoxyphenyl)-1-(4-methoxyphenyl)-3,3-dimethylazetidin-2-one (4)

A mixture of ethyl isobutyrate (272 uL, 2.0 mmol) and toluene (20 mL) was cooled in an ice / salt bath under nitrogen. LiHMDS (1.0 M, 4 mL) and 4-methoxy-*N*-[(1*E*)-(2-methoxyphenyl)methylene]aniline (241 mg, 1 mmol) were added dropwise. The mixture was allowed to warm to RT and stirred overnight. The product was worked up in HCl (0.5 M, 25 mL) and EtOAc (25 mL). The product was separated and washed with water (25 mL) then brine (25 mL). The organic layer was dried over $MgSO_4$, concentrated *in vacuo* and purified by flash column chromatography, eluting with DCM to afford the title compound (270 mg, 87%).
^{1}H NMR (400 MHz, DMSO-d_6) δ 0.72 (s, 3H), 1.45 (s, 3H), 3.66 (s, 3H), 3.84 (s, 3H), 5.10 (s, 1H), 6.78 (m, 2H), 6.84 (d, 2H), 7.02 (d, 1H), 7.12 (d, 2H), 7.20 (m, 1H); m/z (ES^+) $(M+H)^+$ = 312; HRMS (ESI) calculated for $C_{19}H_{21}NO_3$ ($[M+H]^+$): 312.15942, found: 312.15942.

3-ethyl-4-(2-methoxyphenyl)-1-(4-methoxyphenyl)-3-methyl-azetidin-2-one (14)
A mixture of ethyl 2-methylbutyrate (603 uL, 4.0 mmol) and toluene (5 mL) was cooled in an ice / salt bath under nitrogen. LiHMDS 1.0M in THF (1.0 M, 8 mL) and 1-(2-methoxyphenyl)-*N*-(4-methoxyphenyl)methanimine (483 mg, 2.0 mmol) in THF (5 mL) were added dropwise. The mixture was allowed to warm to RT and stirred overnight. The product was worked up in HCl (1.0 M, 10 mL) and EtOAc (10 mL). The organic phase was removed, concentrated *in vacuo* and purified by flash silica chromatography eluting with EtOAc / isohexane, 0-50% gradient to afford the title compound (92 mg, 14%) as a *trans:cis* .2:1 mixture as discerned from nOe NMR experiment shown below.
^{1}H NMR (400 MHz, DMSO-d_6) δ 0.66 (s, 3H, major isomer), 0.68 (s, 3H, minor isomer), 0.97 (t, 3H), 1.19-1.25 (m, 2H, minor isomer) 1.71-1.89 (m, 2H, major isomer), 3.69 (s, 3H), 3.86 (s, 3H, major isomer), 3.88 (s, 3H, minor isomer), 5.08 (s, 1H, minor isomer), 5.17 (s, 1H, major isomer), 6.82-6.89 (m, 4H), 7.03-7.10 (m, 1H), 7.11-7.23 (m, 2H), 7.23-7.30 (m, 1H). m/z (ES^+) $(M+H)^+$ = 326; HRMS (ESI) calculated for $C_{20}H_{23}NO_3$ ($[M+H]^+$): 326.17507, found: 326.17505.



1-(2-methoxyphenyl)-*N*-(4-methoxyphenyl)methanimine

$MgSO_4$ (27.6 g, 200 mmol) and 2-methoxybenzaldehyde (12.0 ml, 100 mmol) were added to a solution of *p*-anisidine (12.3g, 100 mmol) in DCM (200 ml). The reaction was stirred at RT over night, filtered and washed with DCM (50 ml). The combined filtrate was concentrated *in vacuo* to afford the title compound (24.0 g, 99%) as a dark oil.

3,3-diethyl-4-(2-methoxyphenyl)-1-(4-methoxyphenyl)azetidin-2-one (15)

A mixture of ethyl 2-ethylbutanoate (577 mg, 4.0 mmol) and toluene (5 mL) was cooled in an ice / salt bath under nitrogen. LiHMDS 1.0M in THF (1.0 M, 8 mL) and 1-(2-methoxyphenyl)-*N*-(4-methoxyphenyl)methanimine (483 mg, 2.0 mmol) in THF (5 mL) were added dropwise. The mixture was allowed to warm to RT and stirred overnight. The product was worked up in HCl (1.0 M, 10 mL) and EtOAc (10 mL). The organic phase was removed, concentrated *in vacuo* and purified by flash silica chromatography eluting with EtOAc / isohexane, 0-50% gradient and then HPLC using a C^{18} Silica Xtera column, 5 µm, 19 x 110mm, MeCN /water 0.5% NH_3, gradient 45-70% to afford the title compound (133 mg, 20%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 0.63 (t, 3H), 0.95 (t, 3H), 1.03 (q, 1H), 1.23 (q, 1H), 1.79 (q, 2H), 3.67 (s, 3H), 3.82 (s, 3H), 5.13 (s, 1H), 5.73 (s, 1H), 6.82 (m, 4H), 7.01 (d, 1H), 7.10 (d, 2H), 7.22 (t, 1H); m/z (ES^+) $(M+H)^+$ = 340; HRMS (ESI) calculated for $C_{21}H_{25}NO_3$ ($[M+H]^+$): 340.19072, found: 340.19077.

3-cyclopropyl-4-(2-methoxyphenyl)-1-(4-methoxyphenyl)azetidin-2-one (16)

A solution of oxalyl chloride (127 mg, 1.0 mmol) in toluene (3 mL) was stirred and cyclopropylacetic acid (100 mg, 1.0 mmol) was added. Following this DMF (2 drops) was added and immediate effervescence was observed. The clear, clourless solution was stirred at RT for 2 h then conc. *in vacuo* and re-dissolved in toluene (1 mL). A solution of 1-(2-methoxyphenyl)-*N*-(4-methoxyphenyl)methanimine (242 mg, 1.0 mmol) and tributylamine (0.26 mL, 2.0 mmol) in toluene (2 mL) was stirred and the solution of pre-formed acid chloride was added. The mixture was heated in the microwave at 120 °C for 15 min. The mixture was concentrated *in vacuo* and purified by flash column chromatography to afford the title compound (58.9 mg, 18%) as a colourless oil. A *trans:cis* = 24:1 was determined by ^{1}H NMR (*trans* azetidine protons *J= 2.3 Hz* while for the *cis* compound *J= 5.7 Hz*).

^{1}H NMR (400.13 MHz, $CDCl_3$) δ0.47 - 0.54 (2H, m), 0.56 - 0.67 (2H, m), 1.20 - 1.28 (1H, m), 2.88 - 2.90 (1H, dd, *J=2.3, 7.2 Hz*), 3.75 (3H, s), 3.90 (3H, s), 5.07 (1H, d, *J=2.3 Hz*), 6.78 - 6.81 (2H, m), 6.88 (2H, m), 7.11 - 7.14 (1H, m), 7.24 - 7.26 (3H, m); m/z (ES^+) $(M+H)^+$ = 324; HRMS (ESI) calculated for $C_{20}H_{21}NO_3$ ($[M+H]^+$): 324.15942, found: 324.15936.

4-(2-methoxyphenyl)-1-(4-methoxyphenyl)-3-propyl-azetidin-2-one (17)

1-(2-Methoxyphenyl)-*N*-(4-methoxyphenyl)methanimine (241 mg, 1.00 mmol) and tributylamine (0.26 mL, 2.00 mmol) were dissolved in toluene and valeroyl chloride (0.15 mL, 1.0 mmol) was added and the mixture heated to 120 °C for 15 min in the microwave. The reaction was stopped and concentrated *in vacuo*. The residue was dissolved in EtOAc (10 mL) and washed with HCl (1.0 M, 10 mL), saturated sodium bicarbonate (10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography gave a colourless oil which contained the desired product and aldehyde from decomposition of imine starting material. The mixture was purified by HPLC to to afford the title compound (52.2 mg, 16%) as a colourless oil. A

trans:cis = 25:1 was determined by ^{1}H NMR (*trans* azetidine protons *J= 2.2 Hz* while for the *cis* compound *J= 5.7 Hz*).
^{1}H NMR (400 MHz, $CDCl_3$) δ0.94 (3H, t), 1.31 (1H, q), 1.57 - 1.63 (2H, m), 1.82 - 1.91 (1H, m), 3.05 (1H, ddd, *J=2.2 ,6.7, 8.8 Hz*), 3.74 (3H, s), 3.89 (3H, s), 5.03 (1H, d, *J=2.2 Hz*), 6.77 - 6.81 (2H, m), 6.86 - 6.95 (2H, m), 6.87 - 6.97 (1H, m), 7.16 - 7.19 (1H, m), 7.22 -7.29 (2H, m); m/z (ES^+) $(M+H)^+$ = 326; HRMS (ESI) calculated for $C_{20}H_{23}NO_3$ ($[M+H]^+$): 326.17507, found: 326.17508.

1-(2-methoxyphenyl)-2-(4-methoxyphenyl)-2-azaspiro[3.4]octan-3-one (18)
To an ice cooled solution of methylcyclopentane carboxylate (284 mg, 2.0 mmol) in toluene (10 mL) was added dropwise LiHMDS 1.0 M solution (4 mL, 4 mmol,). After 15 min a solution of the imine in toluene was added dropwise and the reaction allowed to warm to RT and stirred for 18 h. The reaction was diluted with EtOAc (10 mL) and poured onto ice / water. The organic layer was removed and washed with 0.5M HCl (10 mL), water (10 mL), brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the title compound as a colourless gum.
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 - 1.09 (1H, m), 1.29 - 1.34 (1H, m), 1.54 - 1.71 (5H, m), 2.05 - 2.10 (1H, m), 2.11 - 2.18 (2H, m), 3.69 (3H, d), 3.79 (3H, s), 5.12 (1H, s), 6.71 - 6.75 (2H, m), 6.80 (1H, t), 6.84 - 6.86 (1H, m), 6.94 - 6.96 (1H, m), 7.17 - 7.21 (3H, m); m/z (ES^+) $(M+H)^+$ = 338; HRMS (ESI) calculated for $C_{21}H_{23}NO_3$ ($[M+H]^+$): 338.17507, found: 338.17499.

4-(2-methoxyphenyl)-3,3-dimethylazetidin-2-one
A solution of 4-(2-methoxyphenyl)-1-(4-methoxyphenyl)-3,3-dimethylazetidin-2-one (3.11 g, 10 mmol) in MeCN (100 mL) was cooled to 0 °C. A solution of ceric ammonium nitrate (16.4 g, 30 mmol) in water (150 mL) was added slowly to this and was stirred for 1 h 45min and diluted with water (500 mL). The mixture was extracted with EtOAc (500 mL). The organic extracts were washed with 5% $NaHCO_3$ (200 mL) and the aqueous extracts back-washed with EtOAc (200 mL). The combined organic layers were washed with 10% sodium sulfite (200 mL), 5% $NaHCO_3$ (200 mL) and brine (200 mL). This was dried over $MgSO_4$, concentrated *in vacuo* and purified by flash column chromatography, eluting with EtOAc / isohexane to afford the title compound (1.02 g, 50%).
^{1}H NMR (400 MHz, DMSO-d_6) δ 0.66 (s, 3H), 1.41 (s, 3H), 3.89 (s, 3H), 4.57 (s, 1H), 7.01 (m, 2H), 7.20 (d, 1H), 7.28 (m, 1H), 8.24 (s, 1H); m/z (ES^+) $(M+H)^+$ = 206.

1-ethyl-4-(2-methoxyphenyl)-3,3-dimethyl-azetidin-2-one (19)
To a solution of 4-(2-methoxyphenyl)-3,3-dimethylazetidin-2-one (93 mg, 0.45 mmol) in THF (5 mL) was added LiHMDS (0.5 mL, 0.50 mmol). The solution was kept under nitrogen and cooled to -73 °C and iodoethane (80 uL, 1.00 mmol) in THF (1 mL) was added dropwise. The solution was left for 1 h then allowed to warm to RT overnight. The reaction mixture was quenched with dilute HCl (10 mL) and separated using EtOAc (10 mL). The organic layer was washed with saturated sodium bicarbonate (10 mL), sodium thiosulfate (10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered, concentrated *in vacuo*, and purified by flash column chromatography, eluting with EtOAc / isohexane to afford the title compound (29 mg, 29%) as a brown oil.
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.71 (s, 3H), 1.09 (t, 3H), 1.41 (s, 3H), 2.95 (q, 1H), 3.63 (q, 1H), 3.82 (s, 3H), 4.70 (s, 1H), 6.83 (d, 1H), 6.91 (t, 1H), 7.06 (m, 1H), 7.21 (m, 1H); m/z (ES^+) $(M+H)^+$ = 234; HRMS (ESI) calculated for $C_{14}H_{19}NO_2$ ($[M+H]^+$): 234.14886, found: 234.14879.

1-benzyl-4-(2-methoxyphenyl)-3,3-dimethylazetidin-2-one (20)
To a solution of 4-(2-methoxyphenyl)-3,3-dimethylazetidin-2-one (93 mg, 0.45 mmol) in THF (5 mL) was added LiHMDS (0.5 mL, 0.50 mmol). The solution was kept under nitrogen and cooled to -73 °C and benzyl bromide (108 uL, 0.90 mmol) in THF (1 mL) was added dropwise. The solution was left for 1 h allowed to warm to RT overnight. The reaction mixture was quenched with dilute HCl (10 mL) and separated using EtOAc (10 mL). The organic layer was washed with saturated sodium bicarbonate (10 mL), sodium thiosulfate (10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, concentrated *in vacuo* and purified by flash column chromatography, eluting with EtOAc / isohexane to afford the title compound (60 mg, 45%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.76 (s, 3H), 1.35 (s, 3H), 3.76 (s, 3H), 3.92 (d, 1H), 4.45 (s, 1H), 4.92 (d, 1H), 6.79 (d, 1H), 6.91 (t, 1H), 7.09 (d, 1H), 7.20 (m, 6H); m/z (ES^+) $(M+H)^+$ = 296; HRMS (ESI) calculated for $C_{19}H_{21}NO_2$ ($[M+H]^+$): 296.16451, found: 296.16452.

4-(2-methoxyphenyl)-3,3-dimethyl-1-phenyl-azetidin-2-one (21)
$Pd_2(dba)_3$ (3 mg, 0.003 mmol, 1 mol % Pd), Xantphos (5 mg, 0.01 mmol, 1.5 mol %), cesium carbonate (229 mg, 0.70 mmol) and 4-(2-methoxyphenyl)-3,3-dimethyl-azetidin-2-one (124 mg, 0.60 mmol) were put in a microwave tube which was sealed, evacuated and backfilled with nitrogen. To this was added bromobenzene (53 uL, 0.5 mmol) in 1,4-dioxane (2 mL) which was stirred in the microwave (Biotage Initiator) for 30 min at 150 °C. The reaction mixture was filtered and purified on HPLC using a C^{18} Silica Xtera column, 5 uM, 19x110mm, MeCN / H_2O 0.5% NH_3, gradient 50-70% to afford the title compound (50 mg, 30%).
^{1}H NMR (400 MHz, DMSO-d_6) δ 0.78 (s, 3H), 1.53 (s, 3H), 3.96 (s, 3H), 5.23 (s, 1H), 6.87 (m, 2H), 7.09 (q, 2H), 7.30 (m, 5H); m/z (ES^+) $(M+H)^+$ = 282; HRMS (ESI) calculated for $C_{18}H_{18}N_1O_2$ ($[M+H]^+$): 282.14886, found: 282.14874.

4-(2-methoxyphenyl)-3,3-dimethyl-1-pyridin-2-ylazetidin-2-one (22)
A mixture of ethyl isobutyrate (541 uL, 4.0 mmol) and toluene (5 mL) was cooled in an ice / salt bath under nitrogen. LiHMDS (1.0 M, 8 mL) and *N*-[(1E)-(2-methoxyphenyl)methylene]pyridin-2-amine (425 mg, 2.0 mmol) in THF (5 mL) were added dropwise. The mixture was allowed to warm to RT and stirred overnight. The product was worked up in HCl (0.5 M, 25 mL) and EtOAc (25 mL). The product was separated and washed with H_2O then brine. The organic layer was dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by flash column chromatography, eluting with EtOAc / isohexane, 0-100% gradient to afford the title compound (104 mg, 18%).
^{1}H NMR (400 MHz, DMSO-d_6) δ 0.79 (s, 3H), 1.54 (s, 3H), 3.92 (s, 3H), 5.24 (s, 1H), 6.84 (m, 2H), 7.07 (d, 1H), 7.13 (t, 1H), 7.26 (t, 1H), 7.76 (d, 1H), 7.86 (t, 1H), 8.21 (d, 1H); m/z (ES^+) $(M+H)^+$ =283; HRMS (ESI) calculated for $C_{17}H_{18}N_2O_2$ ($[M+H]^+$): 283.1441, found: 283.14392.

1-(2-fluorophenyl)-4-(2-methoxyphenyl)-3,3-dimethyl-azetidin-2-one (23)
A mixture of ethyl isobutyrate (541 uL, 4.0 mmol) and toluene (5 mL) was cooled in an ice / salt bath under nitrogen. LiHMDS (1.0 M, 8 mL) and *N*-(2-fluorophenyl)-1-(2-methoxyphenyl)methanimine (458 mg, 2.0 mmol) in THF (5 mL) were added dropwise. The mixture was allowed to warm to RT and stirred overnight. The product was worked up in HCl (1.0 M, 10 mL) and EtOAc (10 mL). The organic phase was separated. concentrated *in vacuo* and purified by flash column chromatography, eluting with EtOAc / isohexane, 0-50% gradient to afford the title compound (455 mg, 76%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 0.73 (3H, s), 1.49 (3H, s), 3.85 (3H, s), 5.37 (1H, d), 6.87 (2H, d), 7.06 - 7.08 (1H, m), 7.19 - 7.25 (4H, m), 7.85 (1H, s); m/z (ES^+) $(M+H)^+$ = 300; HRMS (ESI) calculated for $C_{18}H_{18}FNO_2$ ($[M+H]^+$): 300.13943, found: 300.13931.

1-(3-fluorophenyl)-4-(2-methoxyphenyl)-3,3-dimethyl-azetidin-2-one (24)
A mixture of ethyl isobutyrate (541 uL, 4.0 mmol) and toluene (5 mL) was cooled in an ice / salt bath under nitrogen. LiHMDS (1.0 M, 8 mL) and *N*-(3-fluorophenyl)-1-(2-methoxyphenyl)methanimine (458 mg, 2.0 mmol) in THF (5 mL) were added dropwise. The mixture was allowed to warm to RT and stirred overnight. The product was worked up in HCl (1.0 M, 10 mL) and EtOAc (10 mL). The organic phase was separated. concentrated *in vacuo* and purified by flash column chromatography, eluting with EtOAc / isohexane, 0-50% gradient to afford the title compound (399 mg, 67%).
^{1}H NMR (400 MHz, DMSO-d_6) δ 0.73 (3H, s), 1.49 (3H, s), 3.85 (3H, s), 5.37 (1H, d), 6.84 - 6.88 (2H, m), 7.07 (1H, d), 7.14 - 7.29 (4H, m), 7.83 - 7.88 (1H, m); m/z (ES^+) $(M+H)^+$ = 299; HRMS (ESI) calculated for $C_{18}H_{18}FNO_2$ ($[M+H]^+$): 300.13943, found: 300.13937.

1-(4-fluorophenyl)-4-(2-methoxyphenyl)-3,3-dimethyl-azetidin-2-one (25)
A mixture of ethyl isobutyrate (541 uL, 4.0 mmol) and toluene (5 mL) was cooled in an ice / salt bath under nitrogen. LiHMDS (1.0 M, 8 mL) and *N*-(4-fluorophenyl)-1-(2-methoxyphenyl)methanimine (458 mg, 2.0 mmol) in THF (5 mL) were added dropwise. The mixture was allowed to warm to RT and stirred overnight. The product was worked up in HCl (1.0 M, 10 mL) and EtOAc (10 mL). The organic phase was separated. concentrated *in vacuo* and purified by flash column chromatography, eluting with EtOAc / isohexane, 0-50% gradient to afford the title compound (325 mg, 54%).
^{1}H NMR (400 MHz, DMSO-d_6) δ 0.72 (s, 3H), 1.49 (s, 3H), 3.88 (s, 3H), 5.17 (s, 1H), 6.77 (d, 1H), 6.83 (t, 1H), 7.05 (d, 1H), 7.13 (t, 2H), 7.23 (m, 3H); m/z (ES^+) $(M+H)^+$ = 300; HRMS (ESI) calculated for $C_{18}H_{18}FNO_2$ ($[M+H]^+$): 300.13943, found: 300.13940.

4-(2-methoxyphenyl)-3,3-dimethyl-1-(2-methylphenyl)azetidin-2-one (26)
A mixture of ethyl isobutyrate (541 uL, 4.0 mmol) and toluene (5 mL) was cooled in an ice / salt bath under nitrogen. LiHMDS (1.0M, 8 mL) and 1-(2-methoxyphenyl)-*N*-(o-tolyl)methanimine (591 mg, 2.0 mmol) in THF (5 mL) were added dropwise. The mixture was allowed to warm to RT and stirred overnight. The product was worked up in HCl (1M, 10 mL) and EtOAc (10mL). The organic phase was separated. concentrated *in vacuo* and purified by flash column chromatography, eluting with EtOAc / isohexane, 0-50% gradient to afford the title compound (455 mg, 76%).
^{1}H NMR (400 MHz, DMSO-d_6) δ 0.77 (s, 3H), 1.53 (s, 3H), 3.92 (s, 3H), 5.24 (s, 1H), 6.88 (m, 2H), 7.14 (m, 3H), 7.34 (m, 3H); m/z (ES^+) $(M+H)^+$ = 296; HRMS (ESI) calculated for $C_{19}H_{21}NO_2$ ($[M+H]^+$): 296.16451, found: 296.16452.

4-(2-methoxyphenyl)-3,3-dimethyl-1-(3-methylphenyl)azetidin-2-one (27)
A mixture of ethyl isobutyrate (541 uL, 4.0 mmol) and toluene (5 mL) was cooled in an ice / salt bath under nitrogen. LiHMDS (1.0M, 8 mL) and 1-(2-methoxyphenyl)-*N*-(m-tolyl)methanimine (591 mg, 2.0 mmol) in THF (5 mL) were added dropwise. The mixture was allowed to warm to RT and stirred overnight. The product was worked up in HCl (1M, 10 mL) and EtOAc (10 mL). The organic phase was separated. concentrated *in vacuo* and purified by flash column chromatography, eluting with EtOAc / isohexane, 0-50% gradient to afford the title compound (398 mg, 67%).
^{1}H NMR (400 MHz, DMSO-d_6) δ 0.74 (s, 3H), 1.52 (s, 3H), 2.30 (s, 3H), 3.93 (s, 3H), 5.17 (s, 1H), 6.87 (m, 3H), 6.99 (d, 1H), 7.10 (d, 1H), 7.18 (s, 1H), 7.21 (t, 1H), 7.29 (t, 1H); m/z

(ES^+) $(M+H)^+$ = 296; HRMS (ESI) calculated for $C_{19}H_{21}NO_2$ ($[M+H]^+$): 296.16451, found: 296.16440.

4-(2-methoxyphenyl)-3,3-dimethyl-1-(4-methylphenyl)azetidin-2-one (28)
A mixture of ethyl isobutyrate (541 uL, 4.0 mmol) and toluene (5 mL) was cooled in an ice / salt bath under nitrogen. LiHMDS (1.0M, 8 mL) and 1-(2-methoxyphenyl)-*N*-(p-tolyl)methanimine (591 mg, 2.0 mmol) in THF (5 mL) were added dropwise. The mixture was allowed to warm to RT and stirred overnight. The product was worked up in HCl (1M, 10 mL) and EtOAc (10 mL). The organic phase was separated. concentrated *in vacuo* and purified by flash column chromatography, eluting with EtOAc / isohexane, 0-50% gradient to afford the title compound (563 mg, 94%).
^{1}H NMR (400 MHz, DMSO-d_6) δ 0.71 (s, 3H), 1.46 (s, 3H), 2.25 (s, 3H), 3.85 (s, 3H), 5.09 (s, 1H), 6.78 (m, 2H), 7.02 (d, 1H), 7.07 (s, 4H), 7.21 (t, 1H); m/z (ES^+) $(M+H)^+$ = 296; HRMS (ESI) calculated for $C_{19}H_{21}NO_2$ ($[M+H]^+$): 296.16451, found: 296.16449.

4-(2-methoxyphenyl)-3,3-dimethyl-1-(2-methylsulfonylphenyl)-azetidin-2-one (29)
4-(2-methoxyphenyl)-3,3-dimethyl-1-(2-methylsulfanylphenyl)-azetidin-2-one (220 mg, 0.67 mmol) in DCM (10 mL) was cooled to 0 °C. To this was added 3-chloroperoxybenzoic acid (232 mg, 1.34 mmol) in DCM (10 mL) which was stirred at 0 °C for 1 h and then at RT for 6 h. Further 3-chloroperoxybenzoic acid (232 mg, 1.34 mmol) was added and the solution was stirred overnight. This was separated with saturated $NaHCO_3$ (50 mL) and the aqueous layer extracted with DCM (50 mL). The combined organic extracts were washed with H_2O (50 mL) then brine (50 mL), dried over $MgSO_4$, concentrated *in vacuo* and purified by flash column chromatography, eluting with EtOAc / isohexane, 0-60% gradient to afford the title compound (148 mg, 62%).
^{1}H NMR (400 MHz, DMSO-d_6) δ 0.82 (s, 3H), 1.50 (s, 3H), 3.51 (s, 3H), 3.89 (s, 3H), 5.64 (s, 1H), 6.82 (t, 1H), 7.04 (d, 1H), 7.21 (m, 2H), 7.51 (m, 2H), 7.70 (t, 1H), 8.03 (d, 1H); m/z (ES^+) $(M+H)^+$ = 360; HRMS (ESI) calculated for $C_{19}H_{21}NO_4S$ ($[M+H]^+$): 360.12641, found: 360.12671.

4-(2-methoxyphenyl)-3,3-dimethyl-1-(3-methylsulfonylphenyl)-azetidin-2-one (30)
4-(2-methoxyphenyl)-3,3-dimethyl-1-(3-methylsulfanylphenyl)-azetidin-2-one (223 mg, 0.68 mmol) in DCM (10 mL) was cooled to 0 °C. To this was added 3-chloroperoxybenzoic acid (235 mg, 1.36 mmol) in DCM (10 mL) which was stirred at 0 °C for 1 h and then at RT for 4 h. Further 3-chloroperoxybenzoic acid (235 mg, 1.36 mmol) was added and the reaction was stirred overnight. This was separated with saturated $NaHCO_3$ (50 mL) and the aqueous layer extracted with DCM (50 mL). The combined organic extracts were washed with H_2O (50 mL) then brine (50 mL), dried over $MgSO_4$, concentrated *in vacuo* and purified by flash column chromatography, eluting with EtOAc / isohexane, 0-60% gradient to afford the title compound (163 mg, 67%).
^{1}H NMR (400 MHz, DMSO-d_6) δ 0.76 (s, 3H), 1.52 (s, 3H), 3.24 (s, 3H), 3.92 (s, 3H), 5.31 (s, 1H), 6.88 (m, 2H), 7.13 (d, 1H), 7.32 (t, 1H), 7.42 (d, 1H), 7.63 (m, 2H), 7.94 (s, 1H); m/z (ES^+) $(M+H)^+$ = 360; HRMS (ESI) calculated for $C_{19}H_{21}NO_4S$ ($[M+H]^+$): 360.12641, found: 360.12640.

4-(2-methoxyphenyl)-3,3-dimethyl-1-(4-methylsulfonylphenyl)-azetidin-2-one (31)
4-(2-methoxyphenyl)-3,3-dimethyl-1-(4-methylsulfanylphenyl)-azetidin-2-one (197 mg, 0.60 mmol) in DCM (10 mL) was cooled to 0 °C. To this was added 3-chloroperoxybenzoic acid (415 mg, 2.40 mmol) in DCM (10 mL) which was stirred at 0 °C for 1 h and then at RT overnight. This was separated with saturated $NaHCO_3$ (50 mL) and the aqueous layer

extracted with DCM (50 mL). The combined organic extracts were washed with H_2O (50 mL) then brine (50 mL), dried over $MgSO_4$, concentrated *in vacuo* and purified by flash column chromatography, eluting with EtOAc / isohexane, 0-50% gradient to afford the title compound (126 mg, 59%).
^{1}H NMR (400 MHz, DMSO-d_6) δ 0.80 (s, 3H), 1.58 (s, 3H), 3.24 (s, 3H), 3.96 (s, 3H), 5.31 (s, 1H), 6.88 (m, 2H), 7.13 (d, 1H), 7.32 (t, 1H), 7.45 (d, 2H), 7.90 (d, 2H); m/z (ES$^+$) $(M+H)^+$ = 360; HRMS (ESI) calculated for $C_{19}H_{21}NO_4S$ ($[M+H]^+$): 360.12641, found: 360.12643.

4-(2-methoxyphenyl)-3,3-dimethyl-1-(3-methylsulfanylphenyl)azetidin-2-one (32)
A mixture of ethyl isobutyrate (541 uL, 4.0 mmol) and toluene (5 mL) was cooled in an ice / salt bath under nitrogen. LiHMDS (1.0M, 8 mL) and 1-(2-methoxyphenyl)-N-(3-methylsulfanylphenyl)methanimine (514 mg, 2.0 mmol) in THF (5 mL) were added dropwise. The mixture was allowed to warm to RT and stirred overnight. The product was worked up in HCl (1M, 10 mL) and EtOAc (10 mL). The organic phase was separated, concentrated *in vacuo* and purified by flash column chromatography, eluting with EtOAc / isohexane, 0-50% gradient to afford the title compound (50 mg, 8% yield).
^{1}H NMR (400 MHz, DMSO-d_6) δ 0.71 (3H, s), 1.47 (3H, s), 2.41 (3H, s), 3.87 (3H, s), 5.17 (1H, s), 6.84 - 6.93 (3H, m), 6.97 - 6.99 (1H, m), 7.11 (1H, d), 7.23 - 7.32 (3H, m); m/z (ES$^+$) $(M+H)^+$ = 327; HRMS (ESI) calculated for $C_{19}H_{21}NO_2S$ ($[M+H]^+$): 328.13658, found: 328.13672.

4-(2-methoxyphenyl)-3,3-dimethyl-1-(2-methylsulfanylphenyl)azetidin-2-one
A mixture of ethyl isobutyrate (541 uL, 4.0 mmol) and toluene (5 mL) was cooled in an ice / salt bath under nitrogen. LiHMDS (1.0 M, 8 mL) and 1-(2-methoxyphenyl)-*N*-(2-methylsulfanylphenyl)methanimine (514 mg, 2.0 mmol) in THF (5 mL) were added dropwise. The mixture was allowed to warm to RT and stirred overnight. The product was worked up in HCl (1M, 10 mL) and EtOAc (10 mL). The organic phase was separated. concentrated *in vacuo* and purified by flash column chromatography, eluting with EtOAc / isohexane, 0-50% gradient to afford the title compound (50 mg, 8% yield).
^{1}H NMR (400 MHz, DMSO-d_6) δ 0.71 (3H, s), 1.47 (3H, s), 2.41 (3H, s), 3.87 (3H, s), 5.17 (1H, s), 6.84 - 6.93 (3H, m), 6.97 - 6.99 (1H, m), 7.11 (1H, d), 7.23 - 7.32 (3H, m); m/z (ES$^+$) $(M+H)^+$ = 327.

4-(2-methoxyphenyl)-3,3-dimethyl-1-(4-methylsulfanylphenyl)azetidin-2-one
A mixture of ethyl isobutyrate (541 uL, 4.0 mmol) and toluene (5 mL) was cooled in an ice / salt bath under nitrogen. LiHMDS (1.0M, 8 mL) and 1-(2-methoxyphenyl)-*N*-(4-methylsulfanylphenyl)methanimine (514 mg, 2.0 mmol) in THF (5 mL) were added dropwise. The mixture was allowed to warm to RT and stirred overnight. The product was worked up in HCl (1M, 10 mL) and EtOAc (10 mL). The organic phase was separated. concentrated *in vacuo* and purified by flash column chromatography, eluting with EtOAc / isohexane, 0-50% gradient to afford the title compound (486 mg, 74% yield).
^{1}H NMR (400 MHz, DMSO-d_6) δ 0.71 (3H, s), 1.47 (3H, s), 2.41 (3H, s), 3.87 (3H, s), 5.17 (1H, s), 6.84 - 6.93 (3H, m), 6.97 - 6.99 (1H, m), 7.11 (1H, d), 7.23 - 7.32 (3H, m); m/z (ES$^+$) $(M+H)^+$ = 327.

4-(2-methoxyphenyl)-3,3-dimethyl-1-(3-methylsulfinylphenyl)-azetidin-2-one (33)
4-(2-methoxyphenyl)-3,3-dimethyl-1-(3-methylsulfanylphenyl)-azetidin-2-one (223 mg, 0.68 mmol) in DCM (10 mL) was cooled to 0 °C. To this was added 3-chloroperoxybenzoic acid

(118 mg, 0.6 mmol) in DCM (10 mL) which was stirred at 0 °C for 15 min and at RT for 2 h. This was separated with saturated $NaHCO_3$ (50 mL). and the aqueous layer extracted with DCM (50 mL). The combined organic extracts were washed with H_2O (50 mL), then brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography, eluting with EtOAc / isohexane, 0-50% gradient afforded the title compound (167 mg, 72 %) as a white solid.
^{1}H NMR (400 MHz, DMSO-d_6) δ 0.79 (3H,s), 1.55 (3H,s), 2.78 (3H,s), 3.94 (3H,s), 5.28 (1H,s), 6.87 (2H,m), 7.12 (1H,d), 7.34 (3H,m), 7.52 (1H,m), 7.64 (1H,d); m/z (ES$^+$) $(M+H)^+$ = 344; HRMS (ESI) calculated for $C_{19}H_{21}NO_3S$ ($[M+H]^+$): 344.13149, found: 344.13141.

4-ethyl-1-(4-methoxyphenyl)-3,3-dimethylazetidin-2-one (12)
Methyltriphenyphosphonium iodide (404 mg, 1 mmol) was stirred under nitrogen in THF (10 mL). Potassium *tert*-butoxide solution 1.0M (1 mL, 1 mmol) was added dropwise giving a deep orange colour. After stirring for a further 15 min a solution of 1-(4-methoxyphenyl)-3,3-dimethyl-4-oxoazetidine-2-carbaldehyde (233 mg, 1 mmol) in THF (5 mL) was added dropwise. After 30 min the reaction was diluted with Et_2O (25 mL) and washed with H_2O (2 x 25 mL) brine (25 mL) dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography, eluting with EtOAc / isohexane 0-50% gave 1-(4-methoxyphenyl)-3,3-dimethyl-4-vinylazetidin-2-one (200 mg, 86 %) as a straw gum. 10% Pd/C (150 mg) was added to a stirred solution of 1-(4-methoxyphenyl)-3,3-dimethyl-4-vinylazetidin-2-one (100 mg, 0.43 mmol) in EtOAc (25 mL) and hydrogenated *via* a balloon for 3 h. The catalyst was filtered and the solvent concentrated *in vacuo* to afford the title compound (98 mg, 98%) as a clear oil.
^{1}H NMR (300 MHz, DMSO-d_6) δ 0.93 (3H, t), 1.19 (3H, s), 1.28 (3H, s), 1.45 - 1.55 (1H, m), 1.94 (1H, m), 3.70 - 3.75 (4H, m), 6.90 - 6.93 (2H, m), 7.27 - 7.30 (2H, m); m/z (ES$^+$) $(M+H)^+$ = 234; HRMS (ESI) calculated for $C_{14}H_{19}NO_2$ ($[M+H]^+$): 234.14886, found: 234.14885.

***N,N'*-(*1E,2E*)-ethane-1,2-diylidenebis(4-methoxyaniline) (10)**
A solution of glyoxal 40% in H_2O (2.9 mL, 20 mmol) was added to a rapidly stirred solution of *p*-anisidine (4.92 g, 40 mmol) in MeOH (25 mL) over 5 min, forming a brown precipitate. Isopropanol (20 mL) was added and MeOH distilled from the solution (~23 mL). More isopropanol (25 mL) was added and distillation continued until a clear brown solution was obtained. The solution was allowed to cool and the orange crystals precipitated were filtered and washed with cold isopropanol to afford the title compound (3.5 g, 65%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (6H, d), 6.87 - 6.91 (4H, m), 7.29 - 7.31 (4H, m), 8.39 (2H, s).

1-(4-methoxyphenyl)-4-{(*E*)-[(4-methoxyphenyl)imino]methyl}-3,3-dimethylazetidin-2-one
A solution of LDA was prepared by the addition of 1.6M butyl lithium (14 mL, 22 mmol) to diisopropylamine (3.3 mL, 23 mmol) in THF (25 mL) at -78 °C. To this was added ethyl isobutyrate (3.0 mL, 22 mmol) keeping the temperature below -70 °C and stirring for a further 15 min, followed by the addition of *N*,*N*'-(1*E*,2*E*)-ethane-1,2-diylidenebis(4-methoxyaniline) (3 g, 11.2 mmol) as a slurry in THF (50 mL). The reaction was allowed to to warm to RT and stir for a further 1 h. The reaction was diluted with Et_2O (150 mL) and washed successively with H_2O (2 x 75 mL) and brine (75 mL) dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography, eluting with EtOAc / isohexane afforded the title compound (2.1 g, 55%) as a white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.23 (3H, s), 1.42 (3H, s), 3.71 (3H, s), 3.75 (3H, s), 4.56 (1H, d), 6.91 - 6.96 (4H, m), 7.14 - 7.18 (2H, m), 7.27 - 7.31 (2H, m), 8.16 (1H, d); m/z (ES$^+$) $(M+H)^+$ = 339.

1-(4-methoxyphenyl)-3,3-dimethyl-4-oxoazetidine-2-carbaldehyde (11)

To 1-(4-methoxyphenyl)-4-{(*E*)-[(4-methoxyphenyl)imino]methyl}-3,3-dimethylazetidin-2-one (1.01 g,3 mmol) stirred in DCM (75 mL) was added 2M HCl (15 mL, 30 mmol) and stirred for 2 h. The DCM layer was removed and washed with H_2O (30 mL), brine (30 mL) dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography, eluting with EtOAc / isohexane afforded the title compound (550 mg, 78%) as a cream solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.17 (3H, s), 1.47 (3H, s), 3.73 (3H, s), 4.68 (1H, d), 6.91 - 6.94 (2H, m), 7.23 - 7.27 (2H, m), 9.84 (1H, d).

4-(hydroxymethyl)-1-(4-methoxyphenyl)-3,3-dimethylazetidin-2-one

1-(4-methoxyphenyl)-3,3-dimethyl-4-oxoazetidine-2-carbaldehyde (200 mg,0.86 mmol) was dissolved in dry MeOH (10 mL) and $NaBH_4$ (130 mg, 3.43 mmol) was added in portions. The reaction mixture was stirred for 15 min at RT. The solvent was concentrated *in vacuo* and the crude product diluted with H_2O (10 mL) and extracted with Et_2O (3 x 25 mL). The combined extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography, eluting with EtOAc / isohexane 0-60% afforded the title compound (155 mg,75 %) as a white solid after trituration with isohexane.

^{1}H NMR (500 MHz, DMSO-d_6) δ 1.21 (3H, s), 1.29 (3H, s), 3.73 (3H, s), 3.75 - 3.78 (2H, m), 3.80 - 3.82 (1H, m), 4.98 (1H, t), 6.91 - 6.93 (2H, m), 7.43 - 7.44 (2H, m); m/z (ES$^+$) $(M+H)^+$ = 236.

4-(methoxymethyl)-1-(4-methoxyphenyl)-3,3-dimethylazetidin-2-one (13)

4-(hydroxymethyl)-1-(4-methoxyphenyl)-3,3-dimethylazetidin-2-one (100 mg,0.43 mmol) in THF (5 mL) was added dropwise to a stirred suspension of sodium hydride 60% in oil (19 mg, 0.47 mmol) in THF (10 mL).After 15 min iodomethane (44 µl,0.47 mmol) was added and the reaction stirred at RT for 16 h. The reaction was quenched with NH_4Cl solution (20 mL) and extracted with Et_2O (2 x 20 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography, eluting with EtOAc / isohexane 0-60% afforded the title compound (58 mg, 55 %) as a clear oil.

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.19 (3H, s), 1.29 (3H, s), 3.29 (3H, s), 3.69 (2H, d), 3.73 (3H, s), 3.94 (1H, t), 6.91 - 6.93 (2H, m), 7.40 - 7.42 (2H, m); m/z (ES$^+$) $(M+H)^+$ = 250; HRMS (ESI) calculated for $C_{14}H_{19}NO_3$ ($[M+H]^+$): 250.14377, found: 250.14384.

1-(4-methoxyphenyl)-3,3-dimethyl-4-phenylazetidin-2-one (34)

To a solution of 4-methoxy-*N*-[(1*Z*)phenylmethylene]aniline (211 mg, 1 mmol) in DMF (2 mL) was added lithium acetate (7 mg,0.1 mmol) and methyl trimethylsilyldimethylketene acetal (203 µl,1 mmol). The solution was stirred under argon for 4 h. TLC showed the reaction to be incomplete, so a further 20 mol% of the ketene acetal was added and the reaction stirred for a further 2 h. The reaction did not go any further so was quenched with ice / H_2O (50 mL) and extracted with Et_2O (2 x 25 mL).The combined extracts were dried over $MgSO_4$ filtered and concentrated *in vacuo* to give a fawn solid. Purification by flash column chromatography, eluting with EtOAc / isohexane 0-50% afforded the title compound (76 mg, 27%) as a cream solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.42 - 7.35 (m, 2H),7.34 - 7.28 (m, 1H),7.24 - 7.15 (m, 4H),6.90 (d, 2H),5.02 (s, 1H),3.71 (s, 3H),1.46 (s, 3H),0.74 (s, 3H); m/z (ES^+) $(M+H)^+$ = 282; HRMS (ESI) calculated for $C_{18}H_{19}NO_2$ ($[M+H]^+$): 282.14886, found: 282.14874.

1-(4-methoxyphenyl)-3,3-dimethyl-4-[pyridine-2-yl]azetidin-2-one (35)
To an ice cooled solution of ethyl isobutyrate (540 µl,4 mmol) in toluene (10 mL) was added dropwise LiHMDS 1.0M solution (8 mL,8 mmol). After 15 min a solution of *N*-{(1*E*)-[pyrimidin-2-ylmethylene]aniline (424 mg, 2 mmol) in toluene (5 mL) was added dropwise and the reaction allowed to warm to RT and stir for 2 h. The reaction was diluted with EtOAc (25 mL) and poured onto ice / H_2O. The organic layer was removed and washed with 0.5M HCl, H_2O (25 mL), brine (25 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a straw oil. Purification by flash column chromatography, eluting with EtOAc / isohexane 0-60% afforded the title compound**)** (340 mg, 60%) as a cream solid.
^{1}H NMR (400 MHz, DMSO-d_6) δ 0.75 (3H, s), 1.47 (3H, s), 3.70 (3H, s), 5.05 (1H, s), 6.87 - 6.91 (2H, m), 7.14 - 7.18 (2H, m), 7.26 (1H, d), 7.32 - 7.35 (1H, m), 7.78 - 7.82 (1H, m), 8.58 - 8.60 (1H, m); m/z (ES^+) $(M+H)^+$ = 283; HRMS (ESI) calculated for $C_{17}H_{18}N_2O_2$ ($[M+H]^+$): 283.14410, found: 283.14404.

4-(3-methoxyphenyl)-1-(4-methoxyphenyl)-3,3-dimethyl-azetidin-2-one (36)
To a stirred solution of 1-(3-methoxyphenyl)-*N*-(4-methoxyphenyl)methanimine (100 mg,0.41 mmol), ethyl isobutyrate (68 µl,0.5 mmol) in THF (2 mL) under nitrogen was added LiHMDS 1.0M in THF (500 µl, 0.5 mmol) and the reaction stirred at RT for 16 h. To the reaction was added 0.2M HCl (500 µl) and EtOAc (2 mL). The reaction was allowed to settle and the organic phase dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash column chromatography, eluting with EtOAc / isohexane 0-100% afforded the title compound (49 mg, 38%) as a white solid.
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.29 (1H, t), 7.18 (2H, d), 6.93 - 6.87 (3H, m), 6.75 (2H, d), 4.97 (1H, s), 3.72 - 3.70 (6H, m), 1.44 (3H, s), 0.75 (3H, s); m/z (ES^+) $(M+H)^+$ = 312; HRMS (ESI) calculated for $C_{19}H_{21}NO_3$ ($[M+H]^+$): 312.15942, found: 312.15939.

1,4-bis(4-methoxyphenyl)-3,3-dimethylazetidin-2-one (37)
To a ice cooled solution of ethyl isobutyrate (540 µl,4 mmol) in toluene (10 mL) was added dropwise LiHMDS 1.0M solution (8 mL, 8 mmol). After 15 min a solution of *N*-[(1*E/Z*)-[4-(methloxy)phenyl]methylene]4-methoxyaniline (482 mg, 2 mmol) in toluene (10 mL) was added dropwise and the reaction allowed to warm to RT and stir for 4 h. The reaction was diluted with EtOAc (50 mL) and poured onto ice / H_2O. The organic layer was removed and washed with 0.5M HCl (50 mL),, H_2O (50 mL), brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a straw coloured solid. This was triturated with Et_2O / isohexane 1:1 to afford the title compound (470 mg, 76%) as an off white solid.
^{1}H NMR (400 MHz, DMSO-d_6) δ 0.73 (3H, s), 1.42 (3H, s), 3.70 (3H, s), 3.75 (3H, s), 4.93 (1H, s), 6.87 - 6.91 (2H, m), 6.93 - 6.95 (2H, m)7.12 - 7.19 (4H, m); m/z (ES^+) $(M+H)^+$ = 312; HRMS (ESI) calculated for $C_{19}H_{21}NO_3$ ($[M+H]^+$): 312.15942, found: 312.15942.

4-[2-(benzyloxy)phenyl]-1-(4-methoxyphenyl)-3,3-dimethylazetidin-2-one
To a ice cooled solution of ethyl isobutyrate (1.35 mL, 10 mmol) in toluene (20 mL) was added dropwise LiHMDS 1.0M solution (20 mL, 20 mmol). After 15 min a solution of *N*-[(1*E/Z*)-[2(benzyloxy)phenyl]methylene]4-methoxyaniline(1.59 g, 5.0 mmol) in toluene (20 mL) was added dropwise and the reaction allowed to warm to RT and stir for 18 h. The reaction was diluted with EtOAc (50 mL) and poured onto ice / H_2O. The organic layer was removed and washed with 0.5M HCl (50 mL), H_2O (50 mL), brine (50 mL), dried over

$MgSO_4$, filtered and concentrated *in vacuo* to give a straw coloured solid. This was triturated with Et_2O / isohexane 1:1 to afford the title compound (1.6 g, 82%) as a white solid.
^1H NMR (400 MHz, DMSO-d_6) δ 0.72 (3H, s), 1.30 (3H, s), 3.72 (3H, s), 5.14 (1H, s), 5.20 (2H, s), 6.86 - 6.92 (4H, m), 7.17 - 7.22 (3H, m), 7.27 - 7.31 (1H, m), 7.36 - 7.38 (1H, m), 7.42 - 7.45 (2H, m), 7.54 (2H, d); m/z (ES^+) $(M+H)^+$ = 388; HRMS (ESI) calculated for $C_{18}H_{18}BrNO_2$ ($[M+H]^+$): 360.05927, found: 360.05937.

4-(2-hydroxyphenyl)-1-(4-methoxyphenyl)-3,3-dimethylazetidin-2-one (38)
4-[2-(Benzyloxy)phenyl]-1-(4-methoxyphenyl)-3,3-dimethylazetidin-2-one (1.5 g, 3.88 mmol) was dissolved in EtOH (50 mL) and $Pd(OH)_2/C$ (0.3 g, 50% wet) added. This was hydrogenated in Parr-hydrogenator @ 60 psi, for 4 h. The solution was filtered through celite® and concentrated *in vacuo* to afford the title compound as a white foam (1.1 g, 96%).
^1H NMR (400 MHz, DMSO-d_6) δ 0.76 (3H, s), 1.46 (3H, s), 3.71 (3H, s), 5.10 (1H, s), 6.72 (1H, t), 6.79 (1H, d), 6.89 - 6.92 (1H, m), 6.90 - 6.93 (2H, m), 7.09 - 7.13 (1H, m), 7.18 - 7.21 (2H, m), 9.72 (1H, s); m/z (ES^+) $(M+H)^+$ = 298; HRMS (ESI) calculated for $C_{18}H_{19}NO_3$ ($[M+H]^+$): 298.14377, found: 298.14380.

4-(4-fluorophenyl)-1-(4-methoxyphenyl)-3,3-dimethyl-azetidin-2-one (39)
A mixture of ethyl isobutyrate (6.73 mL, 49.8 mmol) and toluene (50 mL) was cooled in an ice / salt bath under nitrogen. LiHMDS (1.0M, 50 mL) and (*E*)-*N*-(4-fluorobenzylidene)-4-methoxyaniline (5.71 g, 24.9 mmol) in THF (50 mL) were added dropwise. The mixture was allowed to warm to RT and stirred overnight. The product was worked up in HCl (0.5M, 100 mL) and EtOAc (100 mL). The product was separated and washed with H_2O then brine. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. This was triturated with hexane to afford the title compound (6.72 g, 90%).
^1H NMR (300 MHz, DMSO-d_6) δ 0.84 (s, 3H), 1.54 (s, 3H), 3.78 (s, 3H), 5.19 (s, 1H), 6.89 (d, 2H), 7.16 (t, 3H), 7.25 (d, 3H); m/z (ES^+) $(M+H)^+$ = 300; HRMS (ESI) calculated for $C_{18}H_{18}FNO_2$ ($[M+H]^+$): 300.13943, found: 300.13934.

4-(4-bromophenyl)-1-(4-methoxyphenyl)-3,3-dimethylazetidin-2-one
To a stirred solution of (*E*)-*N*-(4-bromobenzylidene)-4-methoxyaniline (100 mg,0.42 mmol) ,ethyl isobutyrate (68 µl,0.5 mmol) in THF (2 mL) under nitrogen was added LiHMDS 1.0M in THF (500 µl,0.5 mmol) and the reaction stirred at RT for 16 h. To the reaction was added 0.2M HCl (500 µl) and EtOAc (2 mL). The reaction was allowed to settle and the organic phase dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash column chromatography, eluting with EtOAc / isohexane 0-100% afforded the title compound (49 mg, 38%) as a white solid.
^1H NMR (400 MHz, DMSO-d_6) δ 7.58 (2H, d), 7.19 - 7.15 (4H, m), 6.92 - 6.88 (2H, m), 5.03 (1H, s), 3.70 (3H, s), 1.44 (3H, s), 0.72 (3H, s); m/z (ES^+) $(M+H)^+$ = 360; HRMS (ESI) calculated for $C_{18}H_{18}BrNO_2$ ($[M+H]^+$): 360.05927, found: 360.05937.
Material was separated into enantiomers *R*-(**40**) & *S*-(**41**) by chiral chromatographic separation. *R*-(**40**): HRMS (ESI) calculated for $C_{18}H_{18}BrNO_2$ ($[M+H]^+$): 360.05927, found: 360.05957. *S*-(**41**): HRMS (ESI) calculated for $C_{18}H_{18}BrNO_2$ ($[M+H]^+$): 360.05927, found: 360.05939.

1-(4-methoxyphenyl)-3,3-dimethyl-4-(naphthalen-1-yl)azetidin-2-one (42)
To a stirred solution of 4-methoxy-*N*-(naphthalene-2-ylmethylene)aniline (100 mg, 0.42 mmol), ethyl isobutyrate (68 µl, 0.5 mmol) in THF (2 mL) under nitrogen was added LiHMDS 1.0M in THF (500 µl, 0.5 mmol) and the reaction stirred at RT for 16 h. To the reaction was added 0.2M HCl (500 µl) and EtOAc (2 mL). The reaction was allowed to settle

and the organic phase dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography, eluting with EtOAc / isohexane 0-100% afforded the title compound (49 mg, 38%) as a white solid.
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.02 (2H, t), 7.89 (1H, d), 7.68 (1H, t), 7.61 (1H, t), 7.45 (1H, t), 7.26 (2H, d), 7.14 (1H, d), 6.92 (2H, d), 5.87 (1H, s), 3.71 (3H, s), 1.66 (3H, s), 0.60 (3H, s). (M+H)+ =332; HRMS (ESI) calculated for $C_{22}H_{21}NO_2$ ($[M+H]^+$): 332.16451, found: 332.16442.

1-(4-methoxyphenyl)-3,3-dimethyl-4-quinoxalin-5-ylazetidin-2-one (43)
To a toluene (10 mL) solution of ethyl isobutyrate (541 µl, 4 mmol) cooled to 0 °C was added LiHMDS 1.0M in THF (8 mL, 8 mmol) dropwise. After stirring for a further 15 min a solution of 4-methoxy-*N*-[(1*E/Z*)-quinoxalin-5-ylmethylene]aniline (526 mg, 2 mmol) in THF (10 mL) on addition of the first drop an intense red colour was generated which got deeper as the addition continued. The reaction was allowed to warm to RT and stir for a further 16 h. The reaction was poured onto ice / 2N HCl and extracted with EtOAc (2 x 25 mL). The combined extracts were washed with H_2O (50 mL), brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting dark oil was purified by flash column chromatography, eluting with EtOAc / isohexane 0-100% to afford the title compound (150 mg, 22%) as a orange glass.
^{1}H NMR (400 MHz, DMSO-d_6) δ 0.60 (3H, s), 1.62 (3H, s), 3.72 (3H, s), 6.00 (1H, s), 6.90 - 6.93 (2H, m), 7.25 - 7.29 (2H, m), 7.43 (1H, d), 7.82 (1H, d), 8.04 - 8.07 (1H, m), 9.04 - 9.06 (2H, m); m/z (ES^+) $(M+H)^+$ = 334; HRMS (ESI) calculated for $C_{20}H_{19}N_3O_2$ ($[M+H]^+$): 334.15500, found: 334.15509.

General procedure for imine preparation:
***N*-(4-methoxyphenyl)-1-quinoxalin-5-yl-methanimine**
Magnesium sulfate (619 mg, 4.48 mmol) and quinoxaline aldehyde (355 mg, 2.24 mmol) was added to a solution of *p*-anisidine (276 mg, 2.24 mmol) in DCM (4.6 mL). The reaction was stirred at RT over night, filtered and washed with DCM. The combined filtrate was concentrated *in vacuo* to give a brown oil which was triturated from Et_2O to afford the title compound (400 mg, 39%) as a yellow solid.

4-(4-fluorophenyl)-3,3-dimethyl-1-[3-(methylsulfonyl)phenyl]azetidin-2-one (44)
3-chloroperbenzoic acid (230 mg.1.33 mmol) was added to 4-(4-fluorophenyl)-3,3-dimethyl-1-[3-(methylthio)phenyl]azetidin-2-one (21 mg,0.66 mmol) in DCM (25 mL) and stirred at RT for 16 h. The solution was washed with sat. $NaHCO_3$ (25 mL), H_2O (25 mL), brine (25 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography, eluting with EtOAc / isohexane 0-50% afforded the title compound (125 mg, 54%) as a white foam.
^{1}H NMR (400 MHz, DMSO-d_6) δ 0.77 (3H, s), 1.48 (3H, s), 3.18 (3H, s), 5.20 (1H, s), 7.23 (2H, t), 7.30 - 7.34 (3H, m), 7.59 - 7.63 (2H, m), 7.93 (1H, t); m/z (ES^+) $(M+H)^+$ = 348; HRMS (ESI) calculated for $C_{18}H_{18}FNO_3S$ ($[M+H]^+$): 348.10642, found: 348.10635.

3,3-dimethyl-1-[3-(methylthio)phenyl]-4-quinoxalin-5-ylazetidin-2-one
LiHMDS 1.0M in THF (4 mL, 4 mmol) was added to ethyl isobutyrate (271 µl, 2 mmol) in THF (10 mL) at 0 °C. After stirring for 10 min 4-fluoro-*N*-[(1*E*)-quinoxalin-5-ylmethylene]aniline (267 mg, 1 mmol) in THF (5 mL) was added. Stirring was continued for a further 1 h after warming to RT. The reaction was quenched with sat. NH_4Cl (10 mL) and extracted with EtOAc (15 mL). The organic layer removed, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography, eluting with EtOAc /

isohexane 0-50%, and then HPLC using a C^{18} Silica Xtera column, 5 µm, 19 x 110mm, MeCN / H_2O 0.5% NH_3, gradient 45-70% to afford the title compound (50 mg, 14%).
^{1}H NMR (400 MHz, DMSO-d_6) δ 0.75 (3H, s), 1.45 (3H, s), 2.38 (3H, s), 5.10 (1H, s), 6.90 - 6.98 (2H, m), 7.18 - 7.31 (6H, m); m/z (ES^+) $(M+H)^+$ = 316.

***N*-(3-methylsulfanylphenyl)-1-quinoxalin-5-yl-methanimine.**
3-(methylthio)-aniline (441 mg, 3.16 mmol) and quinoxaline aldehyde (0.500 g, 3.16 mmol) were dissolved in DCM (6.49 mL) and $MgSO_4$ (873 mg, 6.32 mmol) was added. The resulting suspension was stirred for 72 h at RT under a nitrogen atmosphere. Following this the $MgSO_4$ was removed by filtration and the organics concentrated *in vacuo* to afford the title compound as a yellow solid. The product was used without further purification.

3,3-dimethyl-1-(3-methylsulfanylphenyl)-4-quinoxalin-5-yl-azetidin-2-one
LiHMDS 1.0M in THF (7.16 mL, 7.16 mmol) was added to ethyl isobutyrate (484 µL, 3.58 mmol) in THF (10 mL) at 0 °C. After stirring for 10 min *N*-(3-methylsulfanylphenyl)-1-quinoxalin-5-yl-methanimine (500 mg, 1.79 mmol) in THF (8 mL) was added . Stirring was continued for a further 1 h after warming to RT. The reaction was quenched with sat. NH_4Cl (20 mL) and extracted with EtOAc (3 x 10 mL). The organic layer removed, dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford 699 mg of an orange gum which was used in the next stage without further purification.

(3,3-dimethyl-1-[3-(methylsulfonyl)phenyl]-4-quinoxalin-5-ylazetidin-2-one (45)
3-chloroperbenzoic acid (62 mg, 0.14 mmol) was added to 3,3-dimethyl-1-[3-(methylthio)phenyl]-4-quinoxalin-5-ylazetidin-2-one (50 mg,0.14 mmol) in DCM (25 mL) and stirred at RT for 2 h. The solution was washed with sat. $NaHCO_3$ (25 mL), H_2O (25 mL), brine (25 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography, eluting with EtOAc / isohexane 0-95% afforded the title compound (21 mg, 39%) as a yellow foam.
^{1}H NMR (400 MHz, DMSO-d_6) δ 0.64 (3H, s), 1.67 (3H, s), 3.19 (3H, s), 6.16 (1H, s), 7.46 - 7.49 (2H, m), 7.60 (1H, t), 7.65 - 7.68 (1H, m), 7.80 - 7.84 (1H, m), 8.01 (1H, t), 8.07 - 8.10 (1H, m), 9.06 - 9.07 (2H, m); m/z (ES^+) $(M+H)^+$ = 382; HRMS (ESI) calculated for $C_{20}H_{19}N_3O_3S$ ($[M+H]^+$): 382.12199, found: 382.12210.

1,4-bis(4-fluorophenyl)-3,3-dimethyl-azetidin-2-one
To a toluene (20 mL) solution of ethyl isobutyrate (1.35 mL,10 mmol) stirred at 0 °C under nitrogen was added LiHMDS 1.0M in THF (20 mL, 20 mmol) over 5 min. After stirring for a further 15 min a toluene (5 mL) solution of 4-fluoro-*N*-[(1*E*/*Z*)-(4-fluorophenyl)methylene]aniline (1.09 g,5 mmol) was added dropwise. The solution was allowed to warm to RT and stirred for a further 3 h. The reaction was diluted with EtOAc (50 mL) and extracted with 1M HCl. the organic was washed with H_2O, brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting solid was recrystallised from isohexane to afford the title compound (1.01 g, 70%) as cream needles.
^{1}H NMR (400 MHz, DMSO-d_6) δ 0.73 (3H, s), 1.45 (3H, s), 5.09 (1H, s), 7.16 - 7.30 (8H, m); m/z (ES^+) $(M+H)^+$ = 287.
Material was separated into enantiomers *R*-(**46**) & *S*-(**47**) by chiral chromatographic separation. *R*-(**46**): HRMS (ESI) calculated for $C_{17}H_{15}F_2NO$ ($[M+H]^+$): 288.11945, found: 288.11948. *S*-(**47**): HRMS (ESI) calculated for $C_{17}H_{15}F_2NO$ ($[M+H]^+$): 288.11945, found: 288.11945.

1-(4-fluorophenyl)-3,3-dimethyl-4-quinoxalin-5-yl-azetidin-2-one (48)

LiHMDS 1.0M in THF (4 mL, 4 mmol) was added to ethyl isobutyrate (271 µl, 2 mmol) in THF (10 mL) at 0 °C. After stirring for 10 min *N*-(4-fluorophenyl)-1-quinoxalin-5-yl-methanimine (252 mg, 1 mmol) in THF (5 mL) was added . Stirring was continued for a further 1 h after warming to RT. The reaction was quenched with sat. NH_4Cl (10 mL) and extracted with EtOAc (15 mL). The organic layer was removed dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography, eluting with EtOAc / isohexane 0-95% afforded the title compound (200 mg, 67%) as a yellow foam.
^{1}H NMR (400 MHz, DMSO-d_6) δ 0.77 (3H, s), 1.48 (3H, s), 5.16 (1H, s), 7.16 - 7.20 (2H, m), 7.26 - 7.29 (2H, m), 7.38 - 7.42 (1H, m), 7.61 - 7.64 (1H, m), 8.51 (1H, d), 8.53 - 8.55 (1H, m); m/z (ES^+) $(M+H)^+$ = 322; HRMS (ESI) calculated for $C_{19}H_{16}FN_3O$ ($[M+H]^+$): 322.13502, found: 322.13496.

Biological Protocols:

Measurement of 11β-HSD1 activity

The conversion of cortisone to the active steroid cortisol by 11β-HSD1 oxo-reductase can be measured using a cortisol competitive homogeneous time resolved fluorescence assay (HTRF) assay (CisBio International, R&D, Administration and Europe Office, In Vitro Technologies - HTRF® / Bioassays BP 84175, 30204 Bagnols/Cèze Cedex, France). The evaluation of compounds was carried out using a baculovirus expressed N terminal 6-His tagged full length human 11β-HSD1 enzyme. The enzyme was purified from a detergent solublised cell lysate, using a copper chelate column. Inhibitors of 11β-HSD1 reduce the conversion of cortisone to cortisol, which is identified by an increase in signal, in the above assay. The assay incubation was carried out in black 384 well plates (Matrix, Hudson NH, USA). consisting of cortisone (Sigma, Poole, Dorset, UK, 160 nM), glucose-6-phosphate (Roche Diagnostics, 1 mM), NADPH (Roche Diagnostics, 100 µM), glucose-6-phosphate dehydrogenase (Roche Diagnostics, 12.5 µg/mL), EDTA (Sigma, Poole, Dorset, UK, 1 mM), assay buffer (K_2HPO_4/KH_2PO_4, 100 mM) pH 7.5, recombinant 11β-HSD1 (1.5 µg/mL) plus test compound in a total volume of 20 µl. The assay plates were incubated for 25 min at 37 °C and the reaction stopped by the addition of 10 µl of 0.5 mM glycerrhetinic acid (Sigma) plus cortisol-XL665. 10 µl of anti-cortisol Cryptate was added and the plates and incubated for 2h at RT. Fluorescence at 665 nm and 620 nm was measured and the 665 nm:620 nm ratio calculated using an Envision plate reader. This data was used to calculate IC_{50} values for each compound (Origin 7.5, Microcal software, Northampton MA, USA).

Measurement of 11β-HSD2 activity: 11β-HSD2 catalyses the conversion of cortisol to cortisone. The compounds were incubated with a mixture consisting of 11β-HSD2 recombinant enzyme in 1 mM DTT, NAD (Roche Diagnostics, 2.5 mM) and cortisol (Sigma, Poole, Dorset, UK, 1 mM, 0.625 µM) in a total volume of 50 µl in 384 well plates. Assay plates were read 40 min post cortisol addition on a fluorescent plate reader (Envision) with signal excitation 340 nm (25 nm band width) and emission 460 nm.

Procedures for determination of physicochemical properties:

$logD_{7.4}$, plasma-protein binding and solubility measurements were made as described in; Buttar, D.; Colclough, N.; Gerhardt, S.; MacFaul, P. A.; Phillips, S. D.; Plowright, A.; Whittamore, P.; Tam, K.; Maskos, K.; Steinbacher, S.; Steuber, H. A. Combined spectroscopic and crystallographic approach to probing drug–human serum albumin interactions. *Bioorg. Med. Chem.* **2010**, *18,* 7486-7496.

$logD_{7.4}$:

$LogD_{7.4}$ measurements were made using a shake-flask method where the extent of partitioning between pH 7.4 buffer and octanol was measured. Compounds were dissolved in a known volume buffer, and following the addition of a known amount of octanol, the

solutions were shaken for 30 min. Following centrifugation, analysis of the aqueous layer was performed by LC–UV to quantify the amount of compound in solution and then compared to analysis of the compound in solution before the addition of octanol to calculate the partitioning coefficient, $D_{7.4}$.

Solubility:

Assessments of aqueous solubility were made after an incubation of 24 h in pH 7.4 phosphate buffer. After centrifugation, analysis of the supernatant liquid was performed by LC–UV to quantify the amount of compound in solution.

Protein binding strength *via* equilibrium dialysis:

Dialysis membranes (Spectra/Por 2, 12–14 kDa molecular weight cut-off, 47 mm diameter, Spectrum Laboratories) were prepared for use by washing with distiled water and subsequent soaking in phosphate buffer (pH 7.4). Membranes were then blotted dry and placed between two 1 mL Teflon dialysis half-cells (Braun ScienceTec, Les Ulis, France). Each half-cell was filled individually with 1 mL of protein solution containing the compound of interest, while the corresponding half-cell was filled with 1 mL of isotonic phosphate buffer. Dialysis units were immersed in a 37 °C temperature-controlled water bath and rotated at 30 rpm for 18–19 h using a Dianorm apparatus (Braun ScienceTec). After this period, samples from both the half-cell containing buffer (protein free) and the half-cell containing protein were submitted for HPLC analysis using an Agilent 1100 series HPLC with a 110 binary pump and a UV diode ray detector. Acquisition and integration were carried out using Chemstation software (Agilent Technologies) version A.06.03 with relevant customised macro software. Integration of the subsequent chromatograms, are used to calculate the concentration of drug in the protein containing solution (Dp) and in the protein-free solutions (Df), which are then used to derive the binding constant for the test compound (K_1) assuming a 1:1 binding model as shown in Eq. 1 where the compound can only bind to a single site on the protein molecule. This is expressed mathematically in Eq. 2 where D and Df are the total and free drug concentrations, respectively, and Pr is the total protein concentration.

$$\mathrm{D} + \mathrm{P} \overset{K_1}{\rightleftharpoons} \mathrm{DP} \qquad \text{Eq. 1}$$

$$D = (D_\mathrm{f} + D_\mathrm{p}) = \frac{K_1 \cdot D_\mathrm{f} \cdot \mathrm{Pr}}{1 + K_1 \cdot D_\mathrm{f}} + D_\mathrm{f} \qquad \text{Eq. 2}$$

Crystallography:

Recombinant murine 11β-HSD1 comprising residues 24 to 292 (triple mutant M175V, Q177Y and I180V), fused at the N-terminus with six-residue HIS-tag, was co-expressed with GroEL in E. coli at 20 °C over night. The protein was purified by Ni-NTA affinity, and after cleavage of the His-tag with TEV protease, further by ion exchange and size exclusion chromatography. For crystallisation, the protein was concentrated to about 9 mg/mL. The protein was crystallised in the presence of 2mM NADP(+) and the compound **30** which was added to a final concentration of 2 mM from a 100 mM stock solution in DMSO. Crystals were obtained from 1.9 M ammonium sulfate, 0.1 M citrate at pH 5.5 by hanging-drop vapour diffusion, appearing after 2 d and growing to the final size within one week. Crystals were flash-frozen in liquid nitrogen with 25% (v/v) glycerol as cryoprotectant. Diffraction data were collected at 100 K on beamline ID29 at the ESRF (Grenoble, France) on a ADSC detector. The data was integrated using the program XDS[1] and scaled with XSCALE[2] to a final resolution of 2.9Å. Molecular replacement was successfully used to solve the structure in spacegroup P21 using MOLREP[3] and with mouse 11β-HSD1 (1Y5M)[4] as the search model. Subsequent model building and refinement were conducted using COOT[5], Refmac[5,6] and BUSTER.[7] Table 1 gives a summary of the data collection and refinement statistics.

The crystal structure contains four monomers of 11β-HSD1 in the asymmetric unit which is organised as two dimers. The resulting electron density shows unambiguous binding mode for the ligand in all four monomers. All independent molecules of the asymmetric unit contain well ordered NADP+ which was included in the co-crystallisation experiment. All residues from Glu25 to Phe289 are well ordered. The stereo center of compound **30** could not be determined unambiguously. However the ligand fits better in the *S* conformation to the experimental electron density at 2.9 Å resolution.

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Table 1. Crystallographic Data Collection and Refinement Statistics for 11β-HSD1

Space Group:	$P2_1$	Cell Parameters:	96.1Å 70.8Å 95.6Å 90.0º 91.7º 90.0º
Number Observations:	73211	Number Unique Reflections:	25245
Low Resolution:	96.0Å	Outer Shell Low Resolution:	3.24Å
High Resolution:	2.9Å	Outer Shell High Resolution:	3.06Å
Overall Redundancy:	2.8	Outer Shell Redundancy:	2.6
Overall I/Sigma:	3.9	Outer Shell I/Sigma:	2.2
Overall Completeness:	87.8	Outer Shell Completeness:	88.9
Overall R-merge[a]:	0.154	Outer Shell R-merge[a]:	0.306
Resolution range	57.0-2.90	Rwork/Rfree	0.176/0.212
No of refined atoms	8534	Rms deviations Bonds (A) Angles(degrees) Torsions (degrees)	0.008 1.17 18.88
Ramachandran Preferred Regions	1009 (96.1%) 41 (3.9%)	Average B factors (A^2)	31.75

Allowed Outliers	0 (0%)		

[a] R-merge = $\Sigma|(I_{hkl}) - \langle I\rangle|/(\Sigma(I_{hkl})$ where I_{hkl} is the integrated intensity of a given reflection.
[b] Rwork = $\Sigma_h|F_o(h) - F_c(h)|/\Sigma_h|F_o(h)|$ where $F_o(h)$ and $F_c(h)$ are observed and calculated structure factors.