

Supporting Information

Structure-based exploration of selectivity for ATM inhibitors in Huntington's disease

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Purification methods

Preparative HPLC purification was performed by reverse phase HPLC using a Waters Fractionlynx™ preparative HPLC system (2525 pump, 2996/2998 UV/VIS detector, 2767 liquid handler) or an equivalent HPLC system such as a Gilson Trilution® UV directed system. The Waters® 2767 liquid handler acted as both auto-sampler and fraction collector.

The columns used for the preparative purification of the compounds were a Waters Sunfire® OBD Phenomenex Luna® Phenyl Hexyl or Waters Xbridge® Phenyl at 10 µm 19 × 150 mm or Waters CSH™ Phenyl Hexyl, 19 × 150, 5 µm column.

Appropriate focused gradients were selected based on acetonitrile and methanol solvent systems under either acidic or basic conditions. The modifiers used under acidic/basic conditions were formic acid or trifluoroacetic acid (0.1% v/v) and ammonium bicarbonate (10 mM) respectively.

The purification was controlled by Waters Fractionlynx™ software through monitoring at 210-400 nm and triggered a threshold collection value at 260 nm and, when using the Fractionlynx™, the presence of target molecular ion as observed under APi conditions. Collected fractions were analysed by LCMS (Waters Acquity® systems with Waters® SQD).

Analytical Method A:

Analytical UPLC-MS was performed on a Waters Acquity I-Class UPLC with Waters Diode Array Detector (210-400 nm) coupled to a Waters SQD2 single quadrupole UPLC mass spectrometer using an HSS C18 column (1.8 µm 100 x 2.1 mm plus guard). Method details are: 1) mobile phase: A: 0.1% formic acid (v/v) in water; B: 0.1% formic acid (v/v) in acetonitrile; 2) Gradient 0 – 1.2 min 95% A 5% B, 1.2 -3.5 min linear gradient to 0% A 100%

B, 3.5-4.9 min 0% A 100% B, 4.9 – 5.0 min gradient to 95% A 5% B, 5.0 min – 6.0 min 95% A to 5% B. 3) Flow rate 0.5 mL/min.

Analytical Method B:

Analytical UPLC-MS was performed on a Waters Acquity I-Class UPLC with Waters Diode Array Detector (210-400 nm) coupled to a Waters SQD2 single quadrupole UPLC mass spectrometer using a BEH Shield RP18 column (1.7 μ m 100 x 2.1 mm. plus guard cartridge). Method details are: 1) mobile phase: A: 10 mM ammonium bicarbonate in water; B: acetonitrile; 2) Gradient 0 – 1.2 min 95% A 5% B, 1.2 -3.5 min linear gradient to 0% A 100% B, 3.5-4.9 min 0% A 100% B, 4.9 – 5.0 min gradient to 95% A 5% B, 5.0 min – 6.0 min 95% A to 5% B. 3) Flow rate 0.5 mL/min.

Analytical Method C

Analytical UPLC-MS was performed on a Waters UPLC with Waters Diode Array Detector (210-400 nm) coupled to a Waters SQD2 single quadrupole UPLC mass spectrometer using a ACE-AR ACE excel column (2 μ m plus guard cartridge). Method details are: 1) mobile phase: A: Water with 0.1% formic acid; B: Acetonitrile with 0.1% (v/v) formic acid; 2) Gradient 0 – 1.2 min 95% A 5% B, 1.2 -3.5 min linear gradient to 0% A 100% B, 3.5-4.9 min 0% A 100% B, 4.9 – 5.0 min gradient to 95% A 5% B, 5.0 min – 6.0 min 95% A to 5% B. 3) Flow rate 0.5 mL/min.

Analytical Method D

Analytical UPLC-MS was performed on a Waters UPLC with Waters Diode Array Detector (210-400 nm) coupled to a Waters SQD2 single quadrupole UPLC mass spectrometer using a BEH Shield RP18 column (1.7 μ m 100 x 2.1 mm. plus guard cartridge). Method details are: 1) mobile phase: A: Water with 10 mM ammonium bicarbonate; B: Acetonitrile; 2) Gradient

0 – 1.2 min 95% A 5% B, 1.2 -3.5 min linear gradient to 0% A 100% B, 3.5-4.9 min 0% A 100% B, 4.9 – 5.0 min gradient to 95% A 5% B, 5.0 min – 6.0 min 95% A to 5% B. 3) Flow rate 0.5 mL/min.

Analytical Method E

Analytical UPLC-MS was performed on a Waters UPLC with Waters Diode Array Detector (210-400 nm) coupled to a Waters SQD2 single quadrupole UPLC mass spectrometer using an Acquity UPLC HSS C18 1.8 μ m column (100 x 2.1 mm plus guard cartridge). Method details are: 1) mobile phase: A: Water with 0.1% formic acid; B: Acetonitrile with 0.1% (v/v) formic acid; 2) Gradient 0 – 1.2 min 95% A 5% B, 1.2 -3.5 min linear gradient to 0% A 100% B, 3.5-4.9 min 0% A 100% B, 4.9 – 5.0 min gradient to 95% A 5% B, 5.0 min – 6.0 min 95% A to 5% B. 3) Flow rate 0.5 mL/min.

Analytical Method F

Analytical LCMS was performed on a Waters 2795/2695 separations module + Waters DAD + Micromass ZQ, single quadrupole LC-MS using a Waters Sunfire column 3.5 μ m 4.6*50 mm, maintained at 40 °C. Detectors used were UV diode array 210-400 nm, Resolution 1.2 nm, other wavelength traces are extracted from the DAD data. Method details are: 1) mobile phase A: Water + 0.1% Formic Acid; B: Acetonitrile (Far UV grade) + 0.1% Formic Acid; Gradient 0-0.5 min 95% A, 0.5-3.5 min gradient to 5% A, 3.5-4.5 min 5% A, 4.5-4.6 min gradient to 95% A, 4.6-5.0 min 95% A, Flow rate 2mL/min.

SFC methods:

All compounds purified using Supercritical Fluid Chromatography (SFC) used either Waters Thar Prep100 preparative SFC system (P200 CO₂ pump, 2545 modifier pump, 2998 UV/VIS detector, 2767 liquid handler with Stacked Injection Module) or Waters Thar Investigator semi

preparative system (Waters Fluid Delivery Module, 2998 UV/VIS detector, Waters Fraction Collection Module). Where the Waters 2767 liquid handler was used it acted as both auto-sampler and fraction collector.

The compounds were purified using an appropriate column from YMC Amylose-C, YMC Cellulose-C, Phenomenex LUX Cellulose-3 and Phenomenex LUX Cellulose-4. Appropriate isocratic methods were selected based on methanol, ethanol or isopropanol solvent systems under un-modified or basic conditions. The standard method used was modifier/CO₂, 100 mL/min (or as appropriate), 120 bar backpressure, 40 °C column temperature where the specific modifier composition was as stated by the method development.

The modifier used under basic conditions was diethylamine (0.1% v/v). The purification was controlled either by Waters Fractionlynx or Waters Chromscope software through monitoring at 210-400 nm and triggered a threshold collection value at an appropriate wavelength. Collected fractions were analysed by SFC (Waters/Thar SFC systems with Waters SQD or Waters UPCC with Waters QDa). The fractions that contained the desired product were concentrated by vacuum centrifugation.

Analytical Method SFC1

Column	See Specific Method	
Column Dimensions	250 x 4.6 mm id 5 um	
Mobile Phase	A - CO ₂ B - Primary Solvents B - Secondary Solvents	
Gradient	Time (min)	%B
	0	5
	0.5	5
	3	55
	4.5	55
	4.6	5
	5	5

Temperature	40 °C
Flow Rate	5.0 mL/min
System Back Pressure	120 bar
Detector	DAD 210-400 nm
Injection Volume	5 µL, variable
MS	Electrospray +/-ve ionization
Cone voltage	25 V
Source Temperature	150 °C
Mass Range	100-1000 amu
Solvents and reagents used are HPLC gradient grade or equivalent	
CO ₂ Grade	99.995%
B – Primary Solvents	Methanol / Ethanol / Isopropanol
B – Secondary Solvents	Methanol (+0.1% Diethylamine)/Ethanol (+0.1% Diethylamine)/Isopropanol (+0.1% Diethylamine) or as specified

Analytical Method SFC4

Column	See Specific Method	
Column Dimensions	150 x 2.1 mm id 5 µm 100 x 3.0 mm id 1.7 µm	
Mobile Phase	A - CO ₂ B - Primary Solvents B - Secondary Solvents	
Gradient	Time (min)	%B
	0	5
	0.5	5
	3	55
	4.5	55
	4.6	5
	5	5
Temperature	40 °C	
Flow Rate	0.95 mL/min	

System Back Pressure	120 bar
Detector	DAD 210-400 nm
Injection Volume	2 μ L, variable
MS	Electrospray +/-ve ionization
Cone voltage	25 V
Source Temperature	150 °C
Mass Range	100-1000 amu
Solvents and reagents used are HPLC gradient grade or equivalent	
CO ₂ Grade	99.995%
B – Primary Solvents	Methanol/Ethanol/Isopropanol
B – Secondary Solvents	Methanol (+0.1% Diethylamine)/Ethanol (+0.1% Diethylamine)/Isopropanol (+0.1% Diethylamine) or as specified

General synthetic methods

Method A: To a mixture of alcohol (1.1 eq) in THF (0.4 M) at 0 °C was added portionwise NaH (2 eq, 60% mineral oil). The reaction was stirred for 15 min. Aryl chloride (1 eq) was added dropwise as a solution in THF (0.7 M). After complete addition the reaction was warmed to r.t. and heated at reflux for 19 h. The reaction mixture was cooled to 0 °C and cautiously quenched with water. The THF was removed under reduced pressure. The residue was dissolved in EtOAc and washed sequentially with water and brine. The organic extract was dried (MgSO₄), filtered and concentrated under reduced pressure. The crude product was either triturated or purified by silica gel column chromatography.

Method B: A mixture of amine (1.0 eq), 2,6-dichloro-4-iodopyridine (1.0 eq.), NaOtBu (2 eq) and PdCl₂(tBu₂Pferrocene)₂ (0.025 eq) in toluene (0.3 M) was placed in a sealed reaction tube under nitrogen and heated at 50 °C for 20 h. The reaction mixture was cooled to rt and filtered

through Celite. The mixture was concentrated under reduced pressure and purified by silica gel chromatography.

Method C: A suspension of aryl halide (1.0 eq), amine (1.0 eq) and Cs₂CO₃ (1.5 eq) in dry 1,4-dioxane (0.2 M) was sparged with N₂ for 15 min. Pd₂(dba)₃ (0.053 eq) and 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.2 eq) were then added, the reaction tube was sealed under N₂ and stirred at 100 °C for 16-40 h. After cooling to r.t., the mixture was filtered through Celite, washing thoroughly with CH₂Cl₂ and the filtrate was concentrated.

Method D: For solid amines the following method was followed: A mixture of amine (1.0 – 1.4 eq), aryl halide (1.0 eq), Cs₂CO₃ or NaOtBu (1.1 eq), RuPhos (0.05-0.1 eq), and RuPhos palladacycle G1 methyl *tert*-butyl ether adduct (0.05-0.1eq) were placed in a stem block tube and sealed. The tube was evacuated and refilled with nitrogen (x3). 1,4-Dioxane (0.08-0.15 M) was added and the reaction heated at 85 °C for 16 h. The reaction mixture was cooled to r.t. and filtered through Celite. The mixture was concentrated under reduced pressure.

In the case of the amine being an oil, it was introduced as a solution in dry 1,4-dioxane.

Method E: To a solution of PMB protected compound (1.0 eq) in ethanol (0.15 M) was added 5% palladium on carbon (100% by weight of PMB compound) and the reaction mixture purged with N₂ for 20 min. 1-Methylcyclohexa-1,4-diene (10 eq) was added and the reaction heated at 75 °C for 1-18 h. The reaction was cooled to r.t. and filtered through Celite, washing with methanol. The solution was concentrated under reduced pressure.

Method F: TBAF hydrate (2.0 eq) was added to a solution of amine (1.08 eq) and sulfone (1.0 eq) in DMSO (0.5 M) at r.t. The reaction mixture was heated at 80 °C for 18-70 h. After this time the reaction was diluted with DCM and water and the layers were separated.

The organic extracts were dried (phase separator) and concentrated under reduced pressure. Used without further purification in the next step.

Method G: TBAF hydrate (2.0 eq) was added to a solution of amine (1.08 eq.), sulfone (1.0 eq.) and DIPEA (2.0 eq) in DMSO (0.5 M) at room temperature. The reaction mixture was heated at 80 °C for 18-70 h. After this time the reaction was diluted with DCM and water and the layers were separated. The organic extracts were dried (phase separator) and concentrated under reduced pressure. Used without further purification in the next step.

Method H: TFA (0.24 M) was added to a solution of PMB-protected compound in DCM (0.24 M). The reaction was stirred at r.t. for 1-4 hours before concentrating under reduced pressure. The residue was dissolved in DCM, washed with saturated sodium bicarbonate solution, dried (phase separator) and concentrated under reduced pressure. The crude material was purified by reverse phase preparative HPLC.

Method I: A stirred suspension of boronic acid/boronic ester (1 eq), aryl halide/triflate (1 eq) and K_2CO_3 (2.5 eq mmol) in dry dioxane (0.15 M) was degassed. $Pd(PPh_3)_4$ (0.05 eq) was added and the reaction stirred at 100 °C for 16 h. After cooling to r.t. the mixture was filtered through Celite, washing with CH_2Cl_2 . The filtrate was concentrated and purified by silica gel chromatography.

Method J: A suspension of aryl halide (0.19 mmol), tBu_3PHBF_4 (0.75 eq), and $NaOtBu$ (1 eq) in dry toluene (0.1 M) was sparged with N_2 for 20 min. $Pd(OAc)_2$ (0.2 eq), and amine (1.1 eq) were then added, the reaction tube was sealed under N_2 and stirred at 110 °C for 16 h. After cooling to r.t., the mixture was filtered through Celite, washing thoroughly with CH_2Cl_2 . The filtrate was concentrated and the residue purified by silica gel chromatography.

Method K: A stirred suspension of boronic acid (1.1 eq), aryl halide (1 eq) and Na₂CO₃ (2 M aqueous solution, 3 eq) in dimethoxyethane (0.15 M) was degassed. Pd(PPh₃)₄ (0.1 eq) was added and the reaction stirred at 85 °C for 16 h. The dimethoxyethane was then evaporated, and the residue was partitioned between CH₂Cl₂ and water. The organic was then passed through a phase separator, evaporated and purified by silica gel chromatography.

Method L: To a suspension of methoxyheteroaryl compound (1 eq) in acetonitrile (0.1 M) was added chlorotrimethylsilane (5 eq) followed by potassium iodide (5 eq). The mixture was degassed by sparging with N₂ for 20 min, before being heated to 80 °C for 21 h. The mixture was then cooled to r.t. and the solvent evaporated before being taken up with CH₂Cl₂ and washed with Na₂S₂O₃ aqueous solution. After passage through a phase separator and evaporation, the crude material was purified by normal phase HPLC or SFC.

Intermediate syntheses

(R)-2-Benzylazepane. Step 1: Tert-butyl (R)-(5-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-5-oxo-1-phenylpentan-2-yl)carbamate. (R)-4-((Tert-butoxycarbonyl)amino)-5-phenylpentanoic acid (3.0 g, 10.2 mmol) was dissolved in DCM (50 mL) and cooled to 0 °C. Meldrum's acid (1.47 g, 10.2 mmol), EDC hydrochloride (2.94 g, 15.3 mmol) and DMAP (1.87 g, 15.3 mmol) were added sequentially to the reaction. The reaction mixture was stirred for 19 h, removing the ice-bath after 1 h. The reaction was transferred to a separating funnel and washed with 1 M potassium bisulfate aqueous solution. The organic extracts were dried (phase separator) and concentrated under reduced pressure to afford the *title compound*. Used without further purification in the next step.

Step 2: Tert-butyl (R)-(5-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-1-phenylpentan-2-yl)carbamate. Tert-butyl (R)-(5-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-5-oxo-1-

phenylpentan-2-yl)carbamate (2.1 g, 5.01 mmol) was dissolved in DCM (50 mL) and cooled to 0 °C. Acetic acid (3.16 mL, 55.1 mmol) was added followed by portionwise addition of NaBH₄ (759 mg, 20.05 mmol). The reaction was stirred at 0 °C for 3.5 h. The reaction mixture was cautiously quenched by dropwise addition of water (5 mL) followed by brine (~100 mL). The layers were separated, and the aqueous layer extracted with DCM. The combined layers were washed with brine, dried (MgSO₄), filtered and concentrated under reduced pressure to afford the *title compound*. Used without further purification in the next step.

Step 3: Tert-butyl (R)-6-((tert-butoxycarbonyl)amino)-7-phenylheptanoate. Tert-butyl (R)-(5-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-1-phenylpentan-2-yl)carbamate (1.86 g, 4.59 mmol) was dissolved in toluene (5 mL) and *t*-BuOH (5 mL). The reaction mixture was refluxed for 6 h. After this time the solvents were removed under reduced pressure. The resultant oil was dissolved in toluene and heated at reflux for 25 h. The reaction mixture was concentrated under reduced pressure. The oil was dissolved in DCM and NaHCO₃ (saturated aqueous solution) added. The layers were inseparable. A small quantity of brine was added to separate the layers. The aqueous layer was extracted with EtOAc. The combined organic layers were dried (phase separator) and concentrated under reduced pressure. The crude oil was purified by silica gel column chromatography (gradient elution 0-30% EtOAc/*iso*-hexane) to afford the *title compound*. ¹H NMR (400 MHz, CDCl₃): δ 7.32-7.14 (5H, m), 4.32 (1H, d, J= 0.8 Hz), 3.78 (1H, br s), 3.32 (2H, s), 2.80-2.71 (2H, m), 2.60 (2H, t, J= 0.8 Hz), 1.83-1.81 (1H, m), 1.45 (9H, s), 1.39 (9H, s).

Step 4: (R)-6-Amino-7-phenylheptanoic acid. TFA (2 mL) was added to tert-butyl (R)-6-((tert-butoxycarbonyl)amino)-7-phenylheptanoate (457 mg, 1.21 mmol) in DCM (2 mL) at r.t. with stirring. After 1.5 h the reaction mixture was concentrated under reduced pressure to afford a yellow oil. The oil was dissolved in 4M HCl in dioxane (10 mL) and stirred at r.t. for 4 h. The reaction mixture was concentrated under reduced pressure and dissolved in 4M HCl in dioxane

(10 mL). After 6 h the reaction mixture was concentrated under reduced pressure and used without further purification in the next step.

Step 5: (R)-7-Benzylazepan-2-one. EDC (348 mg, 1.82 mmol) and HOPO (201 mg, 1.82 mmol) were added to a solution of (*R*)-6-amino-7-phenylheptanoic acid (1.21 mmol) and triethylamine (1.01 mL, 7.26 mmol) in DMF (13 mL) at r.t. with stirring. After 54.5 h the reaction mixture was transferred to a separating funnel and diluted with DCM. The reaction mixture was washed sequentially with 1 M HCl (aq), NaHCO₃ (saturated aqueous solution) and brine. The organics were dried (MgSO₄), filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (gradient elution 50-70% EtOAc/*iso*-hexane) to afford the *title compound*. ¹H NMR (400 MHz, CDCl₃): δ 7.34-7.17 (5H, m), 5.54 (1H, brs), 3.68-3.55 (1H, m), 2.87-2.72 (2H, m), 2.51-2.38 (2H, m), 1.98-1.81 (3H, m), 1.61-1.32 (3H, m).

Step 6: (R)-2-Benzylazepane. Lithium aluminium hydride (0.59 mL, 0.59 mmol, 1 M solution in THF) was added dropwise to an ice-cooled solution of (*R*)-7-benzylazepan-2-one (60 mg, 0.30 mmol) in THF (2 mL). The reaction mixture was warmed to r.t. and heated at reflux for 3 h. The reaction mixture was cooled to r.t., followed by 0 °C and cautiously quenched with water. The THF was removed under reduced pressure. The mixture was diluted with water and EtOAc. The layers were separated and the organic extract dried (MgSO₄), filtered and concentrated under reduced pressure. The resultant oil was purified by SCX cartridge. The sample was loaded in DCM and eluted with 3 column volumes of DCM, 3 column volumes of methanol and 3 column volumes 7N NH₃ in MeOH/DCM (1:9). The basic fractions were combined and concentrated under reduced pressure to afford the *title compound*. Used without further purification in the next step.

4-(2-Chloro-6-((4-methoxybenzyl)oxy)pyridin-4-yl)morpholine. *Step 1:* *4-(2,6-Dichloropyridin-4-yl)morpholine.* 2,6-Dichloropyridin-4-amine (10 g, 61.3 mmol) was

dissolved in DMF (200 mL) and cooled to 0°C. Sodium hydride (6.13 g, 153 mmol) was added portionwise over 20 min. After 15 min 1-chloro-2-(2-ethoxy)ethane (8.63 mL, 73.62 mmol) was added dropwise. The reaction mixture was warmed to r.t. and stirred for 21.5 h. After this time the reaction was cooled to 0 °C and cautiously quenched with water. The DMF was removed under reduced pressure. The resultant residue was dissolved in DCM and washed with water. The organic layers were dried (MgSO₄), filtered and concentrated under reduced pressure. The crude product was triturated with EtOAc and *iso*-hexane to afford the *title compound* as a white solid (9.27 g, 65%). ¹H NMR (400 MHz, CDCl₃): δ 6.59 (2H, s), 3.84 - 3.80 (4H, m), 3.33 - 3.29 (4H, m)

Step 2: 4-(2-Chloro-6-((4-methoxybenzyl)oxy)pyridin-4-yl)morpholine. Following **Method A** using 4-(2,6-dichloropyridin-4-yl)morpholine (9.27 g, 39.8 mmol) and *para*-methoxybenzyl alcohol (5.43 mL, 43.8 mmol). The crude product was triturated with EtOAc and *iso*-hexane to afford the *title compound*. ¹H NMR (400 MHz, CDCl₃): δ 7.39 - 7.35 (2H, m), 6.91 - 6.88 (2H, m), 6.40 (1H, d, J=2.0 Hz), 5.99 (1H, d, J=2.0 Hz), 5.25 (2H, s), 3.81 - 3.77 (7H, m), 3.25 - 3.21 (4H, m).

(R)-4-(2-Chloro-6-((4-methoxybenzyl)oxy)pyridin-4-yl)-2-methylmorpholine (Intermediate **42**). *Step 1: (R)-4-(2,6-Dichloropyridin-4-yl)-2-methylmorpholine* (Intermediate **38**). Following **Method B** using (2*R*)-methyl morpholine (0.5 g, 5 mmol). Purified by silica gel column chromatography (gradient elution, 10-50% EtOAc/*iso*-hexane) to afford the *title compound*. ¹H NMR (400 MHz, CDCl₃): δ 6.57 (2H, s), 4.02 (1H, ddt, J=1.3,5.1,5.8 Hz), 3.74-3.63 (2H, m), 3.58-3.49 (2H, m), 3.03 (1H, dt, J=4.4, 12.4 Hz), 2.67 (1H, dd, J=10.4, 12.4 Hz), 1.26 (3H, d, 6.4 Hz).

Step 2: (R)-4-(2-Chloro-6-((4-methoxybenzyl)oxy)pyridin-4-yl)-2-methylmorpholine (**42**). Following **Method A** using *(R)*-4-(2,6-dichloropyridin-4-yl)-2-methylmorpholine (1.6 g, 6.4

mmol) and *para*-methoxybenzyl alcohol (0.87 mL, 7.0 mmol). Purified by silica gel column chromatography (gradient elution, 5-40% EtOAc/*iso*-hexane) to afford the *title compound*. ¹H NMR (400 MHz, CDCl₃): δ 7.39 - 7.36 (2H, m), 6.91 - 6.88 (2H, m), 6.40 (1H, d, J=2.0 Hz), 5.98 (1H, d, J=2.0 Hz), 5.24 (2H, s), 4.00 - 3.95 (1H, m), 3.81 (3H, s), 3.71 - 3.61 (2H, m), 3.52 - 3.42 (2H, m), 2.96 - 2.88 (1H, m), 2.58 (1H, dd, J=10.4, 12.4 Hz), 1.24 - 1.21 (3H, m).

(1*R**,2*R**,5*S**)-2-Benzyl-3-azabicyclo[3.1.0]hexane and (1*R**,2*S**,5*S**)-2-benzyl-3-azabicyclo[3.1.0]hexane.

Step 1: Tert-butyl 3-azabicyclo[3.1.0]hexane-3-carboxylate. Boc anhydride (2.6 g, 11.9 mmol) and a solution of NaHCO₃ (3.32 g, 39.5 mmol) in water (78 mL) was added to a suspension of the 3-azabicyclo[3.1.0]hexane hydrochloride (950 mg, 7.9 mmol) in THF (26 mL). The resulting biphasic mixture was stirred vigorously overnight at r.t. The reaction mixture was diluted with water and DCM. The layers were separated and the organic phase dried (phase separator) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (gradient elution, 0-10% EtOAc/*iso*-hexane) to afford the *title compound* as a mixture of rotamers. ¹H NMR (400 MHz, CDCl₃): δ 3.51 (2H, dd, J=10.9, 36.1 Hz), 3.35-3.27 (2H, m), 1.42 (9H, s), 1.21-1.14 (1H, m), 0.93-0.84 (1H, m), 0.67-0.61 (1H, m), 0.16-0.13 (1H, m).

*Step 2: Tert-butyl (1*R**,2*R**,5*S**)-2-benzyl-3-azabicyclo[3.1.0]hexane-3-carboxylate and tert-butyl (1*R**,2*S**,5*S**)-2-benzyl-3-azabicyclo[3.1.0]hexane-3-carboxylate*. To a solution of *tert*-butyl 3-azabicyclo[3.1.0]hexane-3-carboxylate (1.50 g, 7.9 mmol) in diethyl ether (27 mL), under N₂ atmosphere, was added tetramethylethylenediamine (1.23 mL, 8.2 mmol) and the reaction mixture cooled to -78 °C. *sec*-BuLi (11.8 mL, 10.6 mmol, 0.9 M in cyclohexane) was added and the mixture was stirred at -78 °C for 30 min. Benzyl bromide (1.95 mL, 16.4 mmol) was added dropwise at -78 °C. After complete addition the reaction was allowed to slowly

warm to r.t. overnight. The reaction was quenched with saturated aqueous NH_4Cl solution, the layers separated and the aqueous further extracted with Et_2O (x2). The combined organic extracts were dried (MgSO_4) and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (gradient elution, 0-10% $\text{EtOAc}/\text{iso-hexane}$) to afford the *title compounds* as separate diastereomers *tert*-butyl ($1R^*,2S^*,5S^*$)-2-benzyl-3-azabicyclo[3.1.0]hexane-3-carboxylate and *tert*-butyl ($1R^*,2R^*,5S^*$)-2-benzyl-3-azabicyclo[3.1.0]hexane-3-carboxylate.

Isomer A (592 mg): LCMS (ES^+) 218 ($\text{M}^{\text{-tBu}}$)⁺, RT 1.77 min (Analytical Method F); ^1H NMR (400 MHz, CDCl_3): δ 7.31-7.18 (5H, m), 4.12-3.96 (1H, m), 3.61-3.39 (1H, m), 3.22-2.91 (2H, m), 2.77-2.64 (1H, m), 1.48-1.42 (9H, m), 1.38-1.28 (1H, m), 0.95-0.87 (1H, m), 0.59-0.53 (1H, m), 0.12-0.09 (1H, m), rotamers observed.

Isomer B (420 mg): LCMS (ES^+) 218 ($\text{M}^{\text{-tBu}}$)⁺, RT 1.83 min (Analytical Method F); ^1H NMR (400 MHz, CDCl_3): δ 7.33-7.27 (4H, m), 7.23-7.17 (1H, m), 4.04-3.95 (1H, m), 3.86-3.44 (3H, m), 2.40 (1H, dd, $J=10.8, 12.4$ Hz), 1.57-1.34 (11H, m), 0.69-0.63 (1H, m), 0.47-0.43 (1H, m), rotamers observed.

Step 3: ($1R^,2R^*,5S^*$)-2-Benzyl-3-azabicyclo[3.1.0]hexane.* To *tert*-butyl ($1R^*,2R^*,5S^*$)-2-benzyl-3-azabicyclo[3.1.0]hexane-3-carboxylate (570 mg, 2.09 mmol) was added DCM (5 mL) and TFA (5 mL) and the resulting mixture was stirred at r.t. for 1 h. The solvent was evaporated and purified by SCX cartridge eluting sequentially with DCM:MeOH, 1:1 then 3:1 DCM:7N ammonia in methanol. The ammonia in methanol fractions were combined and concentrated under reduced pressure to afford the *title compound*. nOe experiments allowed determination of the stereochemistry of the benzyl group relative to the cyclopropyl group. ^1H NMR (400 MHz, CDCl_3): δ 7.32 - 7.17 (5H, m), 3.41 (1H, ddd, $J=3.0, 5.5, 8.1$ Hz), 2.94 (2H,

d, J=1.8 Hz), 2.82 (1H, dd, J=5.9, 13.0 Hz), 2.61 (1H, dd, J=7.8, 13.1 Hz), 1.38 - 1.32 (1H, m), 1.30 - 1.23 (1H, m), 0.40 - 0.34 (1H, m), 0.34 - 0.30 (1H, m). NH not observed.

Step 4: (1R,2S*,5S*)-2-Benzyl-3-azabicyclo[3.1.0]hexane.* To *tert*-butyl (1R*,2S*,5S*)-2-benzyl-3-azabicyclo[3.1.0]hexane-3-carboxylate (400 mg, 1.46 mmol) was added DCM (3.5 mL) and TFA (3.5 mL) and the resulting mixture was stirred at r.t. for 1 h. The solvent was evaporated and purified by SCX cartridge eluting sequentially with DCM:MeOH, 1:1 then 3:1 DCM:7N ammonia in methanol. The ammonia in methanol fractions were combined and concentrated under reduced pressure to afford the *title compound*. nOe experiments allowed determination of the stereochemistry of the benzyl group relative to the cyclopropyl group. ¹H NMR (400 MHz, CDCl₃): δ 7.32 - 7.17 (5H, m), 3.29 (1H, t, J=7.2 Hz), 3.00 (1H, dd, J=3.2, 11.2 Hz), 2.87 (1H, d, J=11.0 Hz), 2.69 (1H, dd, J=7.2, 13.5 Hz), 2.60 (1H, dd, J=7.5, 13.4 Hz), 1.43 - 1.36 (1H, m), 1.29 (1H, ddd, J=4.0, 6.2, 7.9 Hz), 0.45 (1H, dt, J=5.0, 7.7 Hz), 0.15 (1H, dd, J=4.0, 8.7 Hz). NH not observed.

4-(6-((4-Methoxybenzyl)oxy)-2-(methylsulfonyl)pyrimidin-4-yl)morpholine

Step 1: 4-(6-((4-Methoxybenzyl)oxy)-2-(methylthio)pyrimidin-4-yl)morpholine. NaH (3.43 g, 85.8 mmol, 60% dispersion in mineral oil) was suspended in DMF (70 mL) and cooled to 0 °C. 4-methoxy benzyl alcohol (6.52 g, 47.2 mmol) in DMF (30 mL) was added dropwise to the suspension over 15 minutes. After stirring at 0 °C for 15 min 4-(6-chloro-2-(methylthio)pyrimidin-4-yl)morpholine (10.54 g, 42.9 mmol, prepared according to WO 2008/125839) in DMF (90 mL). The reaction was allowed to warm to r.t. and stirred for 4.5 h. The reaction was cooled to 0 °C and cautiously quenched with water. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in EtOAc and washed with brine and water. The organic extracts were dried (MgSO₄), filtered and concentrated under reduced pressure. Purified by silica gel column chromatography (gradient elution, 10-

50% EtOAc/*iso*-hexane) to afford the *title compound*. LCMS (ES⁺) 348 (M+H)⁺, RT 1.69 min (Analytical Method F); ¹H NMR (400 MHz, CDCl₃): δ 7.37-7.33 (2H, m), 6.91-6.87 (2H, m), 5.53 (1H, s), 5.30 (2H, s), 3.80 (3H, s), 3.76-3.72 (4H, m), 3.55-3.51 (4H, m), 2.51 (3H, s).

Step 2: 4-(6-((4-Methoxybenzyl)oxy)-2-(methylsulfonyl)pyrimidin-4-yl)morpholine. *m*-CPBA (759 mg, 4.4 mmol, 50-55 wt.% in H₂O) was added portionwise to a solution of 4-(6-((4-methoxybenzyl)oxy)-2-(methylthio)pyrimidin-4-yl)morpholine (695 mg, 2.0 mmol) in DCM (20 mL) at r.t. After 2 h the reaction was filtered, washing the precipitate with DCM. The filtrate was washed successively with saturated NaHCO₃ (aqueous solution), brine, dried (phase separator) and concentrated under reduced pressure to afford the product, which was used without further purification in the next step. ¹H NMR (400 MHz, CDCl₃): δ 7.38 - 7.35 (2H, m), 6.91 - 6.88 (2H, m), 5.88 (1H, s), 5.36 (2H, s), 3.81 (3H, s), 3.78 - 3.74 (4H, m), 3.63 - 3.57 (4H, m), 3.26 (3H, s).

(R)-4-(6-((4-Methoxybenzyl)oxy)-2-(methylsulfonyl)pyrimidin-4-yl)-2-methylmorpholine. *Step 1: 4-Chloro-6-((4-methoxybenzyl)oxy)-2-(methylthio)pyrimidine.* A solution of 4,6-dichloro-2-(methylthio)pyrimidine (15.0 g, 77.0 mmol) in dry DMF (205 mL) was treated at r.t. with *para*-methoxybenzyl alcohol (11.7 g, 84.6 mmol) and K₂CO₃ (42.6 g, 308 mmol). The reaction was stirred at 60 °C for 64 h. After cooling to r.t., the mixture was diluted with water (700 mL) and stirred vigorously at r.t. for 2 h. The solids that formed were collected by filtration, washing with water, to give the *title compound*. ¹H NMR (400 MHz, CDCl₃): δ 7.35 (2H, d, J=8.8 Hz), 6.92 - 6.89 (2H, m), 6.42 (1H, s), 5.35 (2H, s), 3.81 (3H, s), 2.56 (3H, s).

Step 2: (R)-4-(6-((4-Methoxybenzyl)oxy)-2-(methylthio)pyrimidin-4-yl)-2-methylmorpholine. A solution of 4-chloro-6-((4-methoxybenzyl)oxy)-2-(methylthio)pyrimidine (11.3 g, 38.0 mmol) in dry THF (95 mL) was treated with DIPEA (20 mL, 114 mmol) and (2*R*)-methylmorpholine hydrochloride (5.75 g, 41.8 mmol). The mixture was stirred at 65 °C for 16

h. After cooling to r.t., the reaction mixture was poured into water. DCM was added, and the layers were separated by passage through a hydrophobic frit. The DCM layer was concentrated and purified by silica gel column chromatography (gradient elution, 0-25% EtOAc/*iso*-hexane) to give the *title compound*. ¹H NMR (400 MHz, CDCl₃): δ 7.36 - 7.33 (2H, m), 6.90 - 6.87 (2H, m), 5.53 (1H, s), 5.30 (2H, s), 4.09 - 3.91 (3H, m), 3.81 (3H, s), 3.64 - 3.54 (2H, m), 2.96 (1H, ddd, J=3.6, 11.9, 13.0 Hz), 2.61 (1H, dd, J=10.5, 13.0 Hz), 2.51 (3H, s), 1.22 (3H, d, J=6.5 Hz).

Step 3: (R)-4-(6-((4-Methoxybenzyl)oxy)-2-(methylsulfonyl)pyrimidin-4-yl)-2-methylmorpholine. A solution of (*R*)-4-(6-((4-methoxybenzyl)oxy)-2-(methylthio)pyrimidin-4-yl)-2-methylmorpholine (9.37 g, 25.9 mmol) in DCM (172 mL) was treated with *m*-CPBA (19.7 g, 57.0 mmol, 50-55 wt.% in H₂O) at rt and the mixture was stirred at r.t. for 4 h. The solid impurity was then filtered off and the organic filtrate was shaken with NaHCO₃ saturated solution (2 x). The organic phase was dried (phase separator) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (gradient elution, 0-65% EtOAc/*iso*-hexane) to give the *title compound*. ¹H NMR (400 MHz, CDCl₃): δ 7.36 (2H, d, J=8.7 Hz), 6.90 (2H, d, J=8.7 Hz), 5.88 (1H, s), 5.35 (2H, s), 4.14 - 4.02 (2H, m), 3.98 (1H, ddd, J=1.4, 3.7, 11.8 Hz), 3.81 (3H, s), 3.69 - 3.55 (2H, m), 3.26 (3H, s), 3.07 (1H, ddd, J=3.7, 11.9, 13.0 Hz), 2.71 (1H, dd, J=10.5, 13.0 Hz), 1.24 (3H, d, J=6.4 Hz).

(2R, 3S*)-2-Benzyl-3-methylpyrrolidine. Step 1: Tert-butyl (2R*,3S*)-2-benzyl-3-methylpyrrolidine-1-carboxylate.* Palladium (II) acetate (18 mg, 0.08 mmol), Dpe-phos (86 mg, 0.16 mmol) and sodium *tert*-butoxide (884 mg, 9.2 mmol) were placed in a reaction tube sealed, evacuated and re-filled with nitrogen (x3). 3-Methylpent-4-en-1-ylcarbamate (798 mg, 4.0 mmol) was dissolved in dioxane (16 mL) and degassed. The solution was added to the reaction tube followed by bromobenzene (0.25 mL, 4.8 mmol) and the reaction heated at 100 °C for

17.5 h. The reaction mixture was cooled to r.t., diluted with NH₄Cl. The reaction mixture was extracted with EtOAc (x3). The organic extracts dried (phase separator) and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (gradient elution, 2-20% EtOAc/*iso*-hexane) to afford the *title compound*. ¹H NMR (400 MHz, CDCl₃): δ 7.31-7.13 (5H, m), 3.68-3.36 (2H, m), 3.27-2.98 (2H, m), 2.79-2.57 (1H, m), 2.11-1.76 (2H, m), 1.61-1.46 (9H, m), 0.95-0.81 (4H, m), rotamers observed.

Step 2: (2R,3S*)-2-Benzyl-3-methylpyrrolidine. Tert-butyl (2R*,3S*)-2-benzyl-3-methylpyrrolidine-1-carboxylate* (785 mg, 2.85 mmol) was dissolved in 4 M HCl in dioxane (7.1 mL) at r.t. with stirring. After 2 h the reaction mixture was concentrated under reduced pressure. The residue was dissolved in DCM and washed with saturated NaHCO₃ solution. The organic extract was dried (phase separator) and concentrated under reduced pressure to afford the *title compound*. ¹H NMR (400 MHz, CDCl₃): δ 7.32 - 7.16 (5H, m), 3.00 - 2.79 (3H, m), 2.77 - 2.68 (1H, m), 2.59 (1H, dd, J=8.5, 13.3 Hz), 2.08 - 1.96 (1H, m), 1.76 - 1.66 (1H, m), 1.42 - 1.31 (1H, m), 1.00 (3H, d, J=6.6 Hz), NH not observed.

Final compound syntheses

6-(7-Methoxy-9H-thioxanthen-4-yl)-4-morpholino-1H-pyridin-2-one (7).

Step 1: 4-Chloro-6-(7-methoxy-9H-thioxanthen-4-yl)-1H-pyridin-2-one (Intermediate **6**).

Following **Method I** from 4,6-dichloro-1H-pyridin-2-one (255 mg, 1.55 mmol) and 2-(7-methoxy-9H-thioxanthen-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane⁹ (549 mg, 1.55 mmol). Purification by silica gel chromatography (gradient elution; 0-75% ethyl acetate in *iso*-hexane) gave 78 mg (14%) of slightly impure *title compound*. LCMS (ES⁺) 356, 358 (M+H)⁺, RT 2.96 min (Analytical Method F); ¹H NMR (400 MHz, CDCl₃): δ 10.82 (1H, s),

7.42-7.39 (1H, m), 7.31-7.23 (3H, m), 6.92 (1H, d, J=2.4 Hz), 6.75 (1H, dd, J=2.4, 8.3 Hz), 6.55 (1H, J= 1.7 Hz), 6.35 (1H, d, J= 1.7 Hz), 3.87 (2H, s), 3.81 (3H, s).

Step 2: 6-(7-Methoxy-9H-thioxanthen-4-yl)-4-morpholino-1H-pyridin-2-one (7). A suspension of 4-chloro-6-(7-methoxy-9H-thioxanthen-4-yl)-1H-pyridin-2-one (69 mg, 0.19 mmol), *t*Bu₃PBHF₄ (44 mg, 0.15 mmol), and NaO*t*Bu (88 mg, 0.91 mmol) in dry toluene (2 mL) was sparged with N₂ for 20 min. Pd(OAc)₂ (8.5 mg, 0.038 mmol), and morpholine (19 μL, 0.21 mmol) were then added, the reaction tube was sealed under N₂ and stirred at 110 °C for 16 h. After cooling to r.t., the mixture was filtered through Celite, washing thoroughly with CH₂Cl₂. The filtrate was concentrated, and the residue purified by silica gel chromatography (gradient elution; 0-5% methanol in CH₂Cl₂) to give impure *title compound*. Further purification by normal phase HPLC yielded 28 mg of the *title compound* as a solid (36%). LCMS (ES⁺) 407 (M+H)⁺, RT 3.19 min (Analytical Method C); ¹H NMR (400 MHz, CDCl₃): δ 8.84 (1H, br s), 7.40 (1H, dd, J=1.9, 6.8 Hz), 7.26 (3H, m), 6.92 (1H, d, J=2.6 Hz), 6.76 (1H, dd, J=2.8, 8.5 Hz), 6.01 (1H, d, J=2.8 Hz), 5.72 (1H, d, J=2.4 Hz), 3.87 (2H, s), 3.84 - 3.80 (7H, m), 3.35 - 3.31 (4H, m). HRMS (ESI⁺) (M + H)⁺: calcd for C₂₃H₂₃N₂O₃S, 407.1429; found, 407.1436.

(R)-6-(7-Methoxy-9H-thioxanthen-4-yl)-4-(2-methylmorpholino)pyridin-2(1H)-one (8).

Following **Method J** from 4-chloro-6-(7-methoxy-9H-thioxanthen-4-yl)-1H-pyridin-2-one (0.19 mmol) and (*S*)-2-methylmorpholine (0.21 mmol). LCMS (ES⁺) 421 (M+H)⁺, RT 3.15 min (Analytical Method E); ¹H NMR (400 MHz, DMSO-*d*₆): δ 11.00 (1H, s), 7.54 (1H, dd, J=1.5, 7.3 Hz), 7.43 - 7.31 (3H, m), 7.13 (1H, d, J=2.5 Hz), 6.85 (1H, dd, J=2.5, 8.5 Hz), 6.08 (1H, s), 5.59 - 5.55 (1H, m), 3.96 - 3.90 (3H, m), 3.81 (4H, s), 3.71 - 3.55 (3H, m), 2.86 (1H, td, J=12.2, 3.5 Hz), 2.54 - 2.51 (1H, m), 1.17 (3H, d, J=6.3 Hz). HRMS (ESI⁺) (M + H)⁺: calcd for C₂₄H₂₅N₂O₃S, 421.1586; found, 421.1586.

6-(7-Methoxy-9H-thioxanthen-4-yl)-1-methyl-4-morpholino-pyridin-2-one (11). *Step 1: 4,6-Dichloro-1-methyl-pyridin-2-one (Intermediate 9)*. 4,6-Dichloro-1H-pyridin-2-one (100 mg, 0.61 mmol) was dissolved in acetone (3 mL). Methyl iodide (75 μ L, 1.2 mmol) and potassium carbonate (249 mg, 1.8 mmol) were added to the mixture and stirred at r.t. for 19 h. The insoluble material was filtered off, washed with acetone and the filtrate evaporated to afford 109 mg (quant.) of a 3.2:1 mixture of *title compound* as the major component together with 2,4-dichloro-6-methoxy-pyridine (structures confirmed by nOe experiments). LCMS (ES⁺) 177, 179 (M+H)⁺, RT 2.96 min (Analytical Method F); major isomer: ¹H NMR (400 MHz, CDCl₃): δ 6.55 (1H, d, J=2.2 Hz), 6.36 (1H, d, J=2.2 Hz), 3.64 (3H, s); minor isomer: ¹H NMR (400 MHz, CDCl₃): 6.93 (1H, d, J= 1.0 Hz), 6.68 (1H, d, J=1.0 Hz), 3.94 (3H, s).

Step 2: 4-Chloro-6-(7-methoxy-9H-thioxanthen-4-yl)-1-methyl-pyridin-2-one (Intermediate 10). Following **Method I** from the mixture of 4,6-dichloro-1-methyl-pyridin-2-one and 2,4-dichloro-6-methoxy-pyridine from the previous step (100 mg) and 2-(7-methoxy-9H-thioxanthen-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane⁹ (200 mg, 0.56 mmol). Purification by silica gel chromatography (gradient elution, 0-100% EtOAc/*iso*-hexane) gave 74 mg (47% yield, corrected for isomer contamination of SM) of the *title compound* (structures confirmed by nOe experiments). LCMS (ES⁺) 370 (M+H)⁺, RT 3.2 min (Analytical Method F); ¹H NMR (400 MHz, CDCl₃): δ 7.44 (1H, d, J= 8.4 Hz), 7.33-7.26 (2H, m), 7.12 (1H, dd, J= 1, 7.5 Hz), 6.93-6.90 (1H, m), 6.77 (1H, dd, J= 2.2, 8.4 Hz), 6.72 (1H, d, J=2.2 Hz), 6.18 (1H, d, J= 2.2 Hz), 3.83-3.81 (5H, m), 3.18 (1H, s).

Step 3: 6-(7-Methoxy-9H-thioxanthen-4-yl)-1-methyl-4-morpholino-pyridin-2-one (11). Following **Method J** from 4-chloro-6-(7-methoxy-9H-thioxanthen-4-yl)-1-methyl-pyridin-2-one (72 mg, 0.195 mmol) and morpholine (19 μ L, 0.21 mmol). Purification by normal phase HPLC yielded 14 mg of the *title compound* as a solid (17%). LCMS (ES⁺) 421 (M+H)⁺, RT 3.19 min (Analytical Method D); ¹H NMR (400 MHz, CDCl₃): δ 7.41 (1H, d, J=7.1 Hz), 7.32

- 7.28 (2H, m), 7.12 (1H, d, J=7.1 Hz), 6.93 (1H, d, J=2.3 Hz), 6.76 (1H, dd, J=2.3, 8.5 Hz), 5.88 - 5.86 (2H, m), 3.98 (1H, d, J=15.4 Hz), 3.82 - 3.77 (8H, m), 3.30 - 3.24 (4H, m), 3.13 (3H, s). HRMS (ESI⁺) (M + H)⁺: calcd for C₂₄H₂₅N₂O₃S, 421.1586; found, 421.1585.

2-(7-Methoxy-9H-thioxanthen-4-yl)-6-morpholino-pyridin-4-ol (16). *Step 1: 4-(4-Benzyloxy-6-chloro-2-pyridyl)morpholine (Intermediate 14)*. 4-Benzyloxy-2,6-dichloro-pyridine (1.00 g, 5.58 mmol), which was synthesised following the literature protocol (WO2011007856) was dissolved in 1,4-dioxane (10 mL) and morpholine (171 μ L, 6.0 mmol) was added. The mixture was heated to 110 °C for 18 h, after which additional morpholine (350 μ L, 12.0 mmol) was added and the mixture heated for 24 h, after which the solvent was evaporated to dryness. Purification by silica gel chromatography (gradient elution, 0-25% EtOAc/*iso*-hexane) gave 430 mg (70%) of the *title compound*. LCMS (ES⁺) 305 (M+H)⁺, RT 3.35 min (Analytical Method F).

Step 2: 4-[4-Benzyloxy-6-(7-methoxy-9H-thioxanthen-4-yl)-2-pyridyl]morpholine (Intermediate 15). Following **Method K** from 4-(4-benzyloxy-6-chloro-2-pyridyl)morpholine (0.1 g, 0.33 mmol) and 2-(7-methoxy-9H-thioxanthen-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane⁹ (117 mg, 0.33 mmol) to obtain the crude material. Purification by silica gel chromatography (gradient elution, 0-30% EtOAc/*iso*-hexane) gave 96 mg (57%) of the *title compound*. LCMS (ES⁺) 497 (M+H)⁺, RT 3.69 min (Analytical Method F); ¹H NMR (400 MHz, CDCl₃): δ 7.45-7.31 (7H, m), 7.24-7.22 (3H, m), 6.89 (1H, d, J= 3 Hz), 6.69 (1H, dd, J=3.0, 8.1 Hz), 6.63 (1H, d, J=1.5 Hz), 5.14 (2H, s), 3.88-3.84 (6H, m), 3.78 (3H, s), 3.66-3.63 (4H, m).

Step 3: 2-(7-Methoxy-9H-thioxanthen-4-yl)-6-morpholino-pyridin-4-ol (16). 4-[4-Benzyloxy-6-(7-methoxy-9H-thioxanthen-4-yl)-2-pyridyl]morpholine (90 mg, 0.18 mmol) in methanol (10 mL) was hydrogenated in an H-cube using Pd/C, in controlled mode, at r.t. Purification by silica gel chromatography (gradient elution, 0-4% NH₃ in MeOH (7N)/ CH₂Cl₂), then by SFC,

followed by freeze drying from acetonitrile/water gave 33 mg (45%) as a colorless solid. LCMS (ES⁺) 407 (M+H)⁺, RT 3.07 min (*Analytical Method A*); ¹H NMR (400 MHz, DMSO-d₆): δ 10.45 (1H, s), 7.48 - 7.43 (2H, m), 7.32 (2H, dd, J=8.0, 15.3 Hz), 7.10 (1H, d, J=2.8 Hz), 6.80 (1H, dd, J=2.8, 8.5 Hz), 6.47 (1H, d, J=1.5 Hz), 6.20 (1H, d, J=1.5 Hz), 3.93 (2H, s), 3.80 (3H, s), 3.79 - 3.75 (4H, m), 3.57 - 3.52 (4H, m). HRMS (ESI⁺) (M + H)⁺: calcd for C₂₃H₂₃N₂O₃S, 407.1429; found, 407.143.

4-(7-Methoxy-9H-thioxanthen-4-yl)-6-morpholino-1H-pyridin-2-one (19). *Step 1: 4-Iodo-6-morpholino-1H-pyridin-2-one (Intermediate 18)*. 4-(6-Chloro-4-iodo-2-pyridyl)morpholine (300 mg, 0.92 mmol, synthesized following the literature protocol in WO2012122383) was suspended in tBuOH (3.1 mL). Freshly powdered KOH (86 mg, 1.54 mmol) was added and the mixture was heated to 82 °C for 5 h. Additional freshly powdered KOH (300 mg, 5.3 mmol) was added and the mixture was heated to 82 °C for 92 h. Additional freshly powdered KOH (300 mg, 5.3 mmol) was added and the mixture was heated to 82 °C for 20 h. After cooling to r.t., the mixture was diluted with EtOAc and washed with water. The aqueous phase was acidified to pH 1-2 and extracted with EtOAc (x2). All organic phases were combined and purification by silica gel chromatography (gradient elution, 0-100% EtOAc/iso-hexane) gave 52 mg (18%) of the *title compound*. LCMS (ES⁺) 325 (M+H)⁺, RT 3.32 min (*Analytical Method F*).

Step 2: 4-(7-Methoxy-9H-thioxanthen-4-yl)-6-morpholino-1H-pyridin-2-one (19). Following **Method K** from 4-iodo-6-morpholino-1H-pyridin-2-one (51 mg, 0.17 mmol) and 2-(7-methoxy-9H-thioxanthen-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane⁹ (72 mg, 0.26 mmol) to obtain the crude material. Purification by silica gel chromatography (gradient elution, 0-4% 7N NH₃ in MeOH/CH₂Cl₂), followed by freeze drying from acetonitrile/water gave 42 mg (61% yield) as an off-white solid. LCMS (ES⁺) 407 (M+H)⁺, RT 3.07 min (*Analytical Method E*); ¹H NMR (400 MHz, CDCl₃): δ 10.90 (1H, s), 7.34 (1H, d, J=7.3 Hz), 7.28 (1H, d, J=8.5

Hz), 7.25 - 7.18 (2H, m), 6.91 (1H, d, J=2.6 Hz), 6.74 (1H, dd, J=2.6, 8.5 Hz), 6.05 (1H, s), 5.67 (1H, s), 3.89 - 3.83 (6H, m), 3.80 (3H, s), 3.43 - 3.39 (4H, m). HRMS (ESI⁺) (M + H)⁺: calcd for C₂₃H₂₃N₂O₃S, 407.1429; found, 407.1427.

2-(7-Methoxy-9H-thioxanthen-4-yl)-6-morpholino-pyrimidin-4-ol (25) and 6-(7-Methoxy-9H-thioxanthen-4-yl)-2-morpholino-pyrimidin-4-ol (26). Step 1: 4-(4-Chloro-6-methoxy-pyrimidin-2-yl)morpholine and 4-(2-chloro-6-methoxy-pyrimidin-4-yl)morpholine. 2,4-Dichloro-6-methoxy-pyrimidine (1.00 g, 5.58 mmol) was dissolved in DMF (11 mL) before morpholine (488 μ L, 5.4 mmol) and K₂CO₃ (1.54g, 11.20 mmol) were added. The mixture was stirred at r.t for 17 h, after which the inorganics were filtered off and washed with EtOAc. The filtrate was evaporated to dryness and partitioned between CH₂Cl₂ and 4% aqueous LiCl solution. The organic was passed through a phase separator and evaporated. Purification by normal phase HPLC gave 858 mg (67%) of 4-(4-chloro-6-methoxy-pyrimidin-2-yl)morpholine **21** together with 106 mg (8%) of 4-(2-chloro-6-methoxy-pyrimidin-4-yl)morpholine **22** (structures confirmed by nOe experiments).

Intermediate **21**: LCMS (ES⁺) 230 (M+H)⁺, RT 3.10 min (Analytical Method F); ¹H NMR (400 MHz, CDCl₃): δ 6.02 (1H, s), 3.89 (3H, s), 3.81-3.71 (8H, m).

Intermediate **22**: LCMS (ES⁺) 230 (M+H)⁺, RT 2.69 min (Analytical Method F); ¹H NMR (400 MHz, CDCl₃): δ 5.67 (1H, s), 3.92 (3H, s), 3.77-3.74 (4H, m), 3.58-3.53 (4H, m).

Step 2a: 4-[4-methoxy-6-(7-methoxy-9H-thioxanthen-4-yl)pyrimidin-2-yl]morpholine.

Following **Method K** from 4-(4-chloro-6-methoxy-pyrimidin-2-yl)morpholine (0.1 g, 0.44 mmol) and 2-(7-methoxy-9H-thioxanthen-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane⁹ (155 mg, 0.44 mmol) and purified by silica gel chromatography (gradient elution, 0-20% EtOAc/iso-hexane) to give 119 mg of target material. 30 mg was then further purified further by SFC to yield 23 mg (equivalent to 49% yield when extrapolated to whole crude) of 4-[4-methoxy-6-

(7-methoxy-9*H*-thioxanthen-4-yl)pyrimidin-2-yl]morpholine, after freeze drying from acetonitrile-water. LCMS (ES⁺) 422 (M+H)⁺, RT 4.01 min (Analytical Method E); ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.55 (2H, dd, J=2.7, 7.5 Hz), 7.40 - 7.32 (2H, m), 7.10 (1H, d, J=2.7 Hz), 6.81 (1H, dd, J=2.7, 8.5 Hz), 6.41 (1H, s), 3.98 (3H, s), 3.95 (2H, s), 3.92 - 3.86 (4H, m), 3.80 (3H, s), 3.79 - 3.74 (4H, m).

Step 2b: 4-[6-Methoxy-2-(7-methoxy-9H-thioxanthen-4-yl)pyrimidin-4-yl]morpholine

Following **Method K** from 4-(2-chloro-6-methoxy-pyrimidin-4-yl)morpholine (0.1 g, 0.44 mmol) and 2-(7-methoxy-9*H*-thioxanthen-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane⁹ (155 mg, 0.44 mmol) and purified by silica gel chromatography (gradient elution, 0-20% EtOAc/iso-hexane) to give 83 mg of target material. 20 mg was then further purified by SFC to yield 9 mg (equivalent to 20% yield when extrapolated to whole crude) of 4-[6-methoxy-2-(7-methoxy-9*H*-thioxanthen-4-yl)pyrimidin-4-yl]morpholine, after freeze drying from acetonitrile-water. LCMS (ES⁺) 422 (M+H)⁺, RT 3.91 min (Analytical Method E); ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.95 (1H, dd, J=1.4, 7.7 Hz), 7.57 - 7.54 (1H, m), 7.41 - 7.33 (2H, m), 7.11 (1H, d, J=2.5 Hz), 6.82 (1H, dd, J=2.5, 8.5 Hz), 6.17 (1H, s), 4.02 (3H, s), 3.95 (2H, s), 3.81 (3H, s), 3.79 - 3.70 (8H, m).

Step 3a: 2-(7-Methoxy-9H-thioxanthen-4-yl)-6-morpholino-pyrimidin-4-ol (25) Following **Method L** from 4-[6-methoxy-2-(7-methoxy-9*H*-thioxanthen-4-yl)pyrimidin-4-yl]morpholine (85 mg, 0.20 mmol) afforded material which was purified by SFC to yield 47 mg (58%) of compound **25**, after freeze drying from 1,4-dioxane-water. LCMS (ES⁺) 408 (M+H)⁺, RT 3.31 min (Analytical Method E); ¹H NMR (400 MHz, DMSO-*d*₆): δ 11.48 (1H, s), 7.51 (2H, dd, J=7.6, 10.4 Hz), 7.35 (2H, dd, J=8.1, 8.1 Hz), 7.10 (1H, d, J=2.5 Hz), 6.83 (1H, dd, J=2.5, 8.1 Hz), 6.01 (1H, s), 3.93 (2H, s), 3.81 - 3.77 (7H, m), 3.77 - 3.72 (4H, m). HRMS (ESI⁺) (M + H)⁺: calcd for C₂₂H₂₂N₃O₃S, 408.1382; found, 408.1381.

Step 3b: 6-(7-methoxy-9H-thioxanthen-4-yl)-2-morpholino-pyrimidin-4-ol (26) Following **Method L** from 4-[4-methoxy-6-(7-methoxy-9H-thioxanthen-4-yl)pyrimidin-2-yl]morpholine (60 mg, 0.14 mmol) afforded material which was purified by SFC to yield 57 mg (quantitative) of compound **26**, after freeze drying from 1,4-dioxane-water. LCMS (ES⁺) 408 (M+H)⁺, RT 3.19 min (Analytical Method E); ¹H NMR (400 MHz, DMSO-d₆): δ 12.13 (1H, s), 7.60 (2H, d, J=7.3 Hz), 7.42 - 7.37 (2H, m), 7.12 (1H, d, J=2.8 Hz), 6.84 (1H, dd, J=2.8, 8.6 Hz), 5.45 (1H, s), 3.95 (2H, s), 3.81 (3H, s), 3.75 (4H, t, J=4.7 Hz), 3.67 - 3.62 (4H, m). HRMS (ESI⁺) (M + H)⁺: calcd for C₂₂H₂₂N₃O₃S, 408.1382; found, 408.1379.

(R)-6-(2-Benzylpyrrolidin-1-yl)-2-morpholinopyrimidin-4-ol (30). Step 1: 4,6-Dichloro-2-((4-methoxybenzyl)oxy)pyrimidine and 2,4-dichloro-6-((4-methoxybenzyl)oxy)pyrimidine. A mixture of 2,4,6-trichloropyrimidine (9.17 g, 0.05 mol), 4-methoxybenzyl alcohol (6.91 g, 0.05 mol) and Cs₂CO₃ (32.6 g, 0.1 mol) in MeCN (150 mL) was stirred at r.t. for 48 h. The solvent was removed by evaporation and the residue partitioned between DCM (150 mL) and water (50 mL). The DCM fraction was concentrated to give the title compounds in a 2:1 molar ratio (identities not confirmed) as a yellow liquid (12.8 g), which was used without further purification.

Step 2: 4-(4-Chloro-6-((4-methoxybenzyl)oxy)pyrimidin-2-yl)morpholine. A mixture of 4,6-dichloro-2-((4-methoxybenzyl)oxy)pyrimidine and 2,4-dichloro-6-((4-methoxybenzyl)oxy)pyrimidine from step 1 (12.8 g), morpholine (4.31 mL, 0.05 mol) and Cs₂CO₃ (32.6 g, 0.1 mol) in MeCN (150 mL) was stirred at r.t. for 20 h. The solvent was removed by evaporation and the residue partitioned between DCM (250 mL) and water (50 mL). The DCM fraction was concentrated, and the residue was purified by silica gel column chromatography (gradient elution, 0-20% EtOAc/*iso*-hexane) to give the *title compound* (7.76 g, 23 mmol, 46% over two steps). All three morpholino isomers obtained from this reaction

were separated by column chromatography, and their structure confirmed by nOe NMR experiments.

Intermediate **27**: ^1H NMR (400 MHz, CDCl_3): δ 7.33-7.32 (2H, m), 6.91-6.88 (2H, m), 6.04 (1H, s), 5.26 (2H, s), 3.82-3.74 (11H, m).

Intermediate **28**: ^1H NMR (400 MHz, CDCl_3): δ 7.37-7.34 (2H, m), 6.93-6.87 (2H, m), 5.70 (1H, s), 5.30 (2H, s), 3.81 (3H, s), 3.76-3.72 (4H, m), 3.56-3.51 (4H, m).

Intermediate **29**: ^1H NMR (400 MHz, CDCl_3): δ 7.39-7.35 (2H, m), 6.89-6.86 (2H, m), 6.17 (1H, s), 5.28 (2H, s), 3.73 (3H, s), 3.75-3.72 (4H, m), 3.62-3.58 (4H, m).

Step 3: 4-(4-(2-Benzylpyrrolidin-1-yl)-6-((4-methoxybenzyl)oxy)pyrimidin-2-yl)morpholine.

2-Benzylpyrrolidine (180 mg, 1.12 mmol) was added to a solution of 4-(4-chloro-6-((4-methoxybenzyl)oxy)pyrimidin-2-yl)morpholine (250 mg, 0.75 mmol) and DIPEA (195 μL , 1.12 mmol) in DMF (2 mL). The reaction mixture was heated at 90 $^\circ\text{C}$. After 21 h the reaction mixture was cooled to r.t. and diluted with DCM and water. The layers were separated, and the organic extracts dried (phase separator). The solvents were removed under reduced pressure and the resultant oil purified by silica gel column chromatography (gradient elution, 7-60% ethyl acetate in *iso*-hexane) to afford the *title compound* as a colourless oil (240 mg, 69%). LCMS (ES^+) 461 ($\text{M}+\text{H}$) $^+$, RT 1.96 min (Analytical Method F).

Step 4: (R)-6-(2-Benzylpyrrolidin-1-yl)-2-morpholinopyrimidin-4-ol (30). TFA (2 mL) was added to a solution of 4-(4-(2-benzylpyrrolidin-1-yl)-6-((4-methoxybenzyl)oxy)pyrimidin-2-yl)morpholine (240 mg, 0.52 mmol) in DCM (2 mL) at r.t. with stirring. After 4 h the reaction mixture was concentrated under reduced pressure. The crude residue was dissolved in DCM, washed with saturated NaHCO_3 aqueous solution, dried (phase separator) and concentrated under reduced pressure. The resultant oil was purified by silica gel column chromatography (gradient elution, 2-20% methanol in DCM) to afford a yellow foaming oil. The enantiomers

were separated by SFC. (*R*)-6-(2-Benzylpyrrolidin-1-yl)-2-morpholinopyrimidin-4-ol was triturated with DCM/*iso*-hexane to afford the *title compound* as a beige powder (26 mg, 15%). LCMS (ES⁺) 341 (M+H)⁺, RT 3.25 min (Analytical Method E), RT 6.31 min (Analytical Method SFC1, LUX CELLULOSE-4 35% MeOH; 0.1% DEA/CO₂); ¹H NMR (400 MHz, CDCl₃): δ 11.26 (1H, s), 7.31 - 7.13 (5H, m), 4.85 - 4.78 (1H, m), 4.49 - 4.48 (1H, m), 3.81 - 3.69 (9H, m), 3.29 - 3.22 (1H, m), 3.15 - 3.09 (1H, m), 2.68 - 2.62 (1H, m), 1.83 - 1.77 (4H, m). HRMS (ESI⁺) (M + H)⁺: calcd for C₁₉H₂₅N₄O₂, 341.1977; found, 341.2.

(R)-2-(2-Benzylpyrrolidin-1-yl)-6-morpholinopyrimidin-4-ol (**31**). *Step 1*: 4-(2-(2-Benzylpyrrolidin-1-yl)-6-((4-methoxybenzyl)oxy)pyrimidin-4-yl)morpholine. 2-Benzylpyrrolidine (180 mg, 1.12 mmol) was added to a solution of 4-(2-chloro-6-((4-methoxybenzyl)oxy)pyrimidin-4-yl)morpholine (obtained from Step 2 for compound **30**) (250 mg, 0.75 mmol) and DIPEA (195 μL, 1.12 mmol) in DMF (2 mL). The reaction mixture was heated at 90 °C. After 21 h the reaction mixture was cooled to r.t. and diluted with DCM and water. The layers were separated, and the organic extracts dried (phase separator). The crude mixture was purified by silica gel column chromatography (gradient elution, 7-60% EtOAc/*iso*-hexane) to afford the *title compound*. LCMS (ES⁺) 461 (M+H)⁺, RT 1.9 min (Analytical Method F); ¹H NMR (400 MHz, CDCl₃): δ 7.40-7.16 (7H, m), 6.89-6.85 (2H, m), 5.35-5.28 (3H, m), 4.40-4.34 (1H, m), 3.80-3.69 (7H, m), 3.63-3.49 (6H, m), 3.38-3.32 (1H, m), 2.57 (1H, dd, J=8.7, 12.8 Hz), 1.88-1.76 (4H, m).

Step 2: (*S*)-2-(2-Benzylpyrrolidin-1-yl)-6-morpholinopyrimidin-4-ol and (*R*)-2-(2-benzylpyrrolidin-1-yl)-6-morpholinopyrimidin-4-ol (**31**). TFA (1.5 mL) was added to a solution of 4-(2-(2-benzylpyrrolidin-1-yl)-6-((4-methoxybenzyl)oxy)pyrimidin-4-yl)morpholine (187 mg, 0.41 mmol) in DCM (1.5 mL) at r.t. with stirring. After 4 h the reaction mixture was concentrated under reduced pressure. The crude residue was dissolved in DCM,

washed with saturated NaHCO₃ aqueous solution, dried (phase separator) and concentrated under reduced pressure. The resultant oil was purified by silica gel column chromatography (gradient elution, 2-20% methanol in DCM) to afford the product. The enantiomers were separated by SFC followed by preparative HPLC to afford the *title compounds* which were freeze dried from MeCN/water.

(R)-2-(2-Benzylpyrrolidin-1-yl)-6-morpholinopyrimidin-4-ol (**31**); LCMS (ES⁺) 341 (M+H)⁺, RT 3.12 min (*Analytical Method A*), RT 1.37 min (*Analytical Method SFC4*, LMC CELLULOSE-3 20% MeOH; 0.1% DEAIISO/CO₂); ¹H NMR (400 MHz, DMSO-d₆): δ 10.23 (1H, s), 7.38 - 7.33 (2H, m), 7.29 - 7.23 (3H, m), 4.85 (1H, s), 4.41 - 4.35 (1H, m), 3.70 (4H, m), 3.50 (5H, dd, J= 3.7, 3.7 Hz), 3.33 - 3.30 (1H, m), 3.17 - 3.11 (1H, m), 2.67 - 2.59 (1H, m), 1.90 - 1.71 (4H, m). HRMS (ESI⁺) (M + H)⁺: calcd for C₁₉H₂₅N₄O₂, 341.1977; found, 341.1996.

Data is given for the (*S*)-isomer as comparison:

(S)-2-(2-Benzylpyrrolidin-1-yl)-6-morpholinopyrimidin-4-ol; LCMS (ES⁺) 341 (M+H)⁺, RT 3.12 min (*Analytical Method A*), RT 0.94 min (*Analytical Method SFC4*, LMC CELLULOSE-3 20% MeOH; 0.1% DEAIISO/CO₂); ¹H NMR (400 MHz, DMSO-d₆): δ 10.25 (1H, s), 7.36 (2H, dd, J=7.5,7.5 Hz), 7.29 - 7.23 (3H, m), 4.86 (1H, s), 4.40 - 4.33 (1H, m), 3.72 - 3.67 (4H, m), 3.53 - 3.48 (5H, m), 3.34 - 3.30 (1H, m), 3.17 - 3.10 (1H, m), 2.68 - 2.60 (1H, m), 1.90 - 1.69 (4H, m).

(R)-2-(2-Benzylazepan-1-yl)-6-morpholinopyrimidin-4(3*H*)-one (**32**). *Step 1: (R)*-4-(2-(2-Benzylazepan-1-yl)-6-((4-methoxybenzyl)oxy)pyrimidin-4-yl)morpholine. 2-(*R*)-Benzylazepane (169 mg, 0.89 mmol) was added to a solution of 4-(2-chloro-6-((4-methoxybenzyl)oxy)pyrimidin-4-yl)morpholine (obtained from Step 2 for compound **30**) (200 mg, 0.60 mmol) and DIPEA (156 μL, 0.89 mmol) in DMF (1.6 mL). The reaction mixture was

heated at 100 °C. After 66 h the reaction mixture was cooled to r.t. and diluted with DCM and water. The layers were separated, and the organic extracts dried (phase separator). The crude mixture was purified by silica gel column chromatography (gradient elution, 10-80% EtOAc/*iso*-hexane) to afford the *title compound* as a yellow oil (144 mg). ¹H NMR (400 MHz, CDCl₃): δ 7.35 (2H, d, J= 9.3 Hz), 7.28-7.35 (5H, m), 6.88 (2H, d, J=9.3 Hz), 5.37-5.23 (3H, m), 4.83-4.66 (1H, m), 4.29-4.18 (1H, m), 3.83-3.71 (8H, m), 3.55-3.44 (4H, m), 3.02-2.76 (2H, m), 2.69-2.57 (1H, m), 1.96-1.86 (1H, m), 1.78-1.11 (6H, m).

Step 2: (R)-2-(2-Benzylazepan-1-yl)-6-morpholinopyrimidin-4(3H)-one (32). TFA (1 mL) was added to a solution of (*R*)-4-(2-(2-benzylazepan-1-yl)-6-((4-methoxybenzyl)oxy)pyrimidin-4-yl)morpholine (144 mg, 0.295 mmol) in DCM (1 mL) at r.t. with stirring. After 5 h the reaction mixture was concentrated under reduced pressure. The crude residue was dissolved in DCM, washed with saturated NaHCO₃ aqueous solution, dried (phase separator) and concentrated under reduced pressure. The resultant oil was dissolved in DMSO and purified by reverse phase preparative HPLC. The resultant solid was dissolved in DCM and washed with saturated aqueous solution of NaHCO₃. The organic extracts were dried (phase separator) and concentrated under reduced pressure followed by freeze drying from MeCN:water to afford the *title compound*. LCMS (ES⁺) 369 (M+H)⁺, RT 3.26 min (Analytical Method A), ¹H NMR (400 MHz, CDCl₃): δ 7.25 - 7.19 (3H, m), 7.16 - 7.11 (2H, m), 4.90 (1H, s), 4.71 (1H, br s), 3.75 - 3.60 (5H, m), 3.53 - 3.47 (4H, m), 2.92 - 2.82 (2H, m), 2.78 - 2.70 (1H, m), 2.08 - 1.98 (1H, m), 1.82 - 1.75 (3H, m), 1.49 - 1.39 (2H, m), 1.28 - 1.12 (2H, m), NH not observed. HRMS (ESI⁺) (M + H)⁺: calcd for C₂₁H₂₉N₄O₂, 369.229; found, 369.2317.

4-(7-Methoxy-9H-thioxanthen-4-yl)-6-morpholinopyrimidin-2-ol (34). *Step 1: 4-(6-Chloro-2-((4-methoxybenzyl)oxy)pyrimidin-4-yl)morpholine (Intermediate 29)*. Morpholine (4.35g, 0.05 mol) was added to a stirred suspension of 4,6-dichloro-2-((4-methoxybenzyl)oxy)pyrimidine

and, 2,4-dichloro-6-((4-methoxybenzyl)oxy)pyrimidine (from step 1 of compound **30**, 12.8g, 0.045 mol) and cesium carbonate (32.6 g, 0.05 mol) in acetonitrile (150 mL) at r.t. The resulting suspension was stirred at r.t. for 20 h. The reaction was evaporated, and the residue was treated with DCM (250 mL) and water (50 mL). The DCM was separated and evaporated to give a colorless oil which was purified by flash chromatography (0% to 20% ethyl acetate in isohexane) to give 5.74 g (34% over two steps) of the *title compound* as a colorless solid. ¹H NMR (400 MHz, CDCl₃): δ 7.39-7.35 (2H, m), 6.89-6.86 (2H, m), 6.17 (1H, s), 5.28 (2H, s), 3.73 (3H, s), 3.75-3.72 (4H, m), 3.62-3.58 (4H, m).

Step 2: 4-(6-(7-Methoxy-9H-thioxanthen-4-yl)-2-((4-methoxybenzyl)oxy)pyrimidin-4-yl)morpholine (Intermediate **33**). 4-(6-Chloro-2-((4-methoxybenzyl)oxy)pyrimidin-4-yl)morpholine (0.2 g, 0.6 mmol) was stirred with 2-(7-methoxy-9H-thioxanthen-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane⁹ (0.21 g, 0.6 mmol), potassium carbonate (0.21g, 1.5 mmol), and Pd(PPh₃)₄ in dioxane (20 mL, dry) under nitrogen for 15 min. The mixture was then stirred at 70 °C for 20 h. The reaction was evaporated, and the residue treated with DCM (50 mL) and water (25 mL), the DCM was separated and evaporated to give a yellow oil used in the next step without further purification.

Step 3: 4-(7-Methoxy-9H-thioxanthen-4-yl)-6-morpholinopyrimidin-2-ol (**34**). The crude 4-(6-(7-methoxy-9H-thioxanthen-4-yl)-2-((4-methoxybenzyl)oxy)pyrimidin-4-yl)morpholine from Step 3 was dissolved in DCM (2.5 mL) and TFA (2.5 mL) was added, after standing for 1 h the solution was evaporated to give a yellow oil. The oil was dissolved in DCM (10 mL) and washed with saturated NaHCO₃ (10 mL), the DCM was separated and evaporated to give a colorless oil which was dissolved in a small volume of acetonitrile and loaded onto a 20 g C18 cartridge, eluting with acetonitrile in water (10% to 50%) to give 43 mg (14% over two steps) of the *title compound* as a colorless solid. LCMS(ES⁺) 408 (M+H)⁺, RT 2.93 min (*Analytical Method A*); ¹H NMR (400 MHz, DMSO-d₆) 10.95 (1H, s), 7.60 - 7.57 (1H, m), 7.45 - 7.34 (3H,

m), 7.14 (1H, d, J=2.8 Hz), 6.87 (1H, dd, J=2.8, 8.6 Hz), 6.10 (1H, s), 3.96 (2H, s), 3.81 (3H, s), 3.75-3.65 (8H, m). HRMS (ESI⁺) (M + H)⁺: calcd for C₂₂H₂₂N₃O₃S, 408.1382; found, 408.1388.

4-[2-Methoxy-6-(7-methoxy-9H-thioxanthen-4-yl)-4-pyridyl]morpholine (40). *Step 1: 4-(2,6-Dichloro-4-pyridyl)morpholine (Intermediate 37)*. A mixture of 2,6-dichloro-4-iodopyridine (1g, 3.7 mmol) and NaOtBu (711 mg, 7.4 mmol) in dry toluene (2 mL) was sparged with N₂ for 20 min. [1,1'-Bis(di-tert-butylphosphino)ferrocene]dichloropalladium(II) (60 mg, 0.093 mmol) and morpholine (320 μL, 3.7 mmol) were then added, the reaction tube was sealed under N₂ and stirred at 50 °C for 23 h. After cooling to r.t., the mixture was filtered through Celite, washing thoroughly with CH₂Cl₂ and the filtrate was evaporated. Purification by silica gel chromatography (gradient elution, 0-30% EtOAc/*iso*-hexane) gave 415 mg (48%) of the *title compound*. LCMS (ES⁺) 232 (M+H)⁺, RT 2.58 min (Analytical Method F); ¹H NMR (400 MHz, CDCl₃): δ 6.59 (2H, s), 3.84 - 3.80 (4H, m), 3.33 - 3.29 (4H, m).

Step 2: 4-(2-Chloro-6-methoxy-4-pyridyl)morpholine (Intermediate 39). 4-(2,6-Dichloro-4-pyridyl)morpholine (2.28 g, 9.78 mmol) was suspended in sodium methoxide in methanol (18 mL of 30 wt% solution) diluted with methanol (5 mL). The mixture was heated to 70 °C for 89 h after which the solvent was evaporated and partitioned between EtOAc and water. The aqueous phase was then re-extracted with EtOAc (x2), the combined organic phases were dried (MgSO₄) and evaporated. Purification by silica gel chromatography (gradient elution, 0-10% Et₂O/CH₂Cl₂) afforded 1.80 g (81%) of the *title compound*. LCMS (ES⁺) 354 (M+H)⁺, RT 3.53 min (Analytical Method F).

Step 3: 4-[2-Methoxy-6-(7-methoxy-9H-thioxanthen-4-yl)-4-pyridyl]morpholine (40). Following **Method K** from 4-(2-chloro-6-methoxy-4-pyridyl)morpholine (32 mg, 0.14 mmol) and 2-(7-methoxy-9H-thioxanthen-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane⁹ (50 mg, 0.14 mmol) to obtain the crude material. Purification by silica gel chromatography (gradient

elution, 0-25% EtOAc/*iso*-hexane) followed by SFC purification and freeze drying from acetonitrile–water gave 23 mg (39%) of the *title compound*. LCMS (ES⁺) 421 (M+H)⁺, RT 3.68 min (*Analytical Method B*); ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.56 - 7.48 (2H, m), 7.38 - 7.30 (2H, m), 7.11 (1H, d, J=2.5 Hz), 6.85 (1H, d, J=2.0 Hz), 6.80 (1H, dd, J=2.7, 8.5 Hz), 6.25 (1H, d, J=2.0 Hz), 3.95 (5H, d, J=6.8 Hz), 3.80 (3H, s), 3.79 - 3.75 (4H, m), 3.40 - 3.38 (4H, m). HRMS (ESI⁺) (M + H)⁺: calcd for C₂₄H₂₅N₂O₃S, 421.1586; found, 421.1591.

6-(2-Benzylpyrrolidin-1-yl)-4-morpholinopyridin-2(1H)-one (**43**). *Step 1*: *4-(2,6-Dichloropyridin-4-yl)morpholine* (Intermediate **37**). 2,6-Dichloropyridin-4-amine (10 g, 61.3 mmol) was dissolved in DMF (200 mL) and cooled to 0 °C. Sodium hydride (6.13 g, 153 mmol) was added portionwise over 20 min. After 15 min 1-chloro-2-(2-chloroethoxy)ethane (8.63 mL, 73.6 mmol) was added dropwise. The reaction mixture was warmed to r.t. and stirred for 21.5 h. After this time the reaction was cooled to 0 °C and cautiously quenched with water. The DMF was removed under reduced pressure. The resultant residue was dissolved in DCM and washed with water. The organic layers were dried (MgSO₄), filtered and concentrated under reduced pressure. The crude product was triturated with EtOAc and *iso*-hexane to afford the *title compound* as a white solid (9.27 g, 65%). LCMS (ES⁺) 233, 235 (M+H)⁺, RT 2.67 min (*Analytical Method F*); ¹H NMR (400 MHz, CDCl₃): δ 6.59 (2H, s), 3.84-3.80 (4H, m), 3.33-3.29 (4H, m).

Step 2: *4-(2-Chloro-6-((4-methoxybenzyl)oxy)pyridin-4-yl)morpholine* (Intermediate **41**). Following **Method A** using *4-(2,6-dichloropyridin-4-yl)morpholine* (9.27 g, 39.8 mmol). The crude product was triturated with EtOAc and *iso*-hexane to afford the *title compound* as an off-white solid (11.4 g, 86%). ¹H NMR (400 MHz, CDCl₃): δ 7.39 - 7.35 (2H, m), 6.91 - 6.88 (2H, m), 6.40 (1H, d, J=2.0 Hz), 5.99 (1H, d, J=2.0 Hz), 5.25 (2H, s), 3.81 - 3.77 (7H, m), 3.25 - 3.21 (4H, m).

Step 3: 4-(2-(2-Benzylpyrrolidin-1-yl)-6-((4-methoxybenzyl)oxy)pyridin-4-yl)morpholine.

Following **Method C**, starting from 2-benzylpyrrolidine (53 mg, 0.30 mmol) and 4-(2-chloro-6-((4-methoxybenzyl)oxy)pyridin-4-yl)morpholine (101 mg, 0.30 mmol). After heating at 105 °C for 18.5 h, a further 0.5 eq pyrrolidine, 1.6 eq cesium carbonate, 0.025 eq, Pd₂(dba)₃, and 0.1 eq BINAP were added and the reaction heated at 105 °C for a further 23 h. The reaction was cooled to r.t. and filtered through Celite, washing with DCM and the reaction concentrated under reduced pressure. The reaction was repeated on the same scale with 1,4-dioxane as the solvent. The crude mixtures of both reactions were combined and purified by silica gel column chromatography (gradient elution, 0-25% EtOAc/*iso*-hexane) to afford the *title compound* (170 mg, 61%). LCMS (ES⁺) 460 (M+H)⁺, RT 2.57 min (Analytical Method F); ¹H NMR (400 MHz, CDCl₃): δ 7.40-7.35 (2H, m), 7.29-7.17 (5H, m), 6.90-6.86 (2H, m), 5.62 (1H, d, J= 1.8 Hz), 5.43-5.27 (3H, m), 4.43-4.36 (1H, m), 3.84-3.76 (7H, m), 3.44-3.38 (1H, m), 3.31-3.17 (5H, m), 2.62 (1H, dd, J= 9.3, 13.2 Hz), 1.93-1.78 (3H, m), 1.58-1.24 (2H, m).

Step 4: 6-(2-Benzylpyrrolidin-1-yl)-4-morpholinopyridin-2(1H)-one (43). Following **Method E** from 4-(2-(2-benzylpyrrolidin-1-yl)-6-((4-methoxybenzyl)oxy)pyridin-4-yl)morpholine (150 mg, 0.32 mmol). Purification by reverse phase preparative HPLC yielded the *title compound*. LCMS (ES⁺) 340 (M+H)⁺, RT 2.96 min (Analytical Method B); ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.68 (1H, s), 7.32 - 7.29 (4H, m), 7.25 - 7.19 (1H, m), 5.15 (2H, s), 4.22 - 4.19 (1H, m), 3.71 - 3.67 (4H, m), 3.42 - 3.36 (1H, m), 3.21 - 3.14 (5H, m), 2.97 (1H, dd, J=3.5, 13.1 Hz), 2.56 (1H, dd, J=9.3, 13.2 Hz), 1.83 - 1.68 (4H, m). HRMS (ESI⁺) (M + H)⁺: calcd for C₂₀H₂₆N₃O₂, 340.2025; found, 340.2029.

(R)-6-(2-Benzylpyrrolidin-1-yl)-4-morpholinopyridin-2(1H)-one (**44**) and *(S)*-6-(2-benzylpyrrolidin-1-yl)-4-morpholinopyridin-2(1H)-one (**45**). A racemic sample of compound **43** was separated into its constituent enantiomers using chiral SFC.

6-[(2R)-2-Benzylpyrrolidin-1-yl]-4-morpholino-1H-pyridin-2-one (44); LCMS (ES⁺) 340 (M+H)⁺, RT 2.97 min (Analytical Method B); RT 4.62 min (Analytical Method SFC1, YMC CELLULOSE-SC, 45/55 IPA (0.1% DEA)/CO₂); ¹H NMR (400 MHz, DMSO-d₆): δ 9.68 (1H, s), 7.32 - 7.29 (4H, m), 7.25 - 7.19 (1H, m), 5.15 (2H, s), 4.22 - 4.19 (1H, m), 3.71 - 3.67 (4H, m), 3.42 - 3.36 (1H, m), 3.21 - 3.14 (5H, m), 2.97 (1H, dd, J=3.5, 13.1 Hz), 2.56 (1H, dd, J=9.3, 13.2 Hz), 1.83 - 1.68 (4H, m). HRMS (ESI⁺) (M + H)⁺: calcd for C₂₀H₂₆N₃O₂, 340.2025; found, 340.2032.

6-[(2S)-2-Benzylpyrrolidin-1-yl]-4-morpholino-1H-pyridin-2-one (45); LCMS (ES⁺) 340 (M+H)⁺, RT 2.96 min (Analytical Method B); RT 5.78 min (Analytical Method SFC1, YMC CELLULOSE-SC, 45/55 IPA (0.1% DEA)/CO₂); ¹H NMR (400 MHz, DMSO-d₆): δ 9.68 (1H, s), 7.32 - 7.29 (4H, m), 7.25 - 7.19 (1H, m), 5.15 (2H, s), 4.22 - 4.19 (1H, m), 3.71 - 3.67 (4H, m), 3.42 - 3.36 (1H, m), 3.21 - 3.14 (5H, m), 2.97 (1H, dd, J=3.5, 13.1 Hz), 2.56 (1H, dd, J=9.3, 13.1 Hz), 1.83 - 1.68 (4H, m).

Absolute synthesis of compound 45. Step 1: Tert-butyl (S)-2-(hydroxy(phenyl)methyl)pyrrolidine-1-carboxylate. Phenylmagnesium bromide (15 mL, 15 mmol, 1.0 M in THF) was added dropwise to a solution of *tert*-butyl (2S)-2-formylpyrrolidine-1-carboxylate (2.00 g, 10 mmol) in dry THF (20 mL) at -78 °C. The reaction mixture was stirred at -78 °C for 2.5 h, before quenching with saturated aqueous NH₄Cl solution and diluted with water (10 mL). The mixture was extracted with EtOAc (x 2), dried (MgSO₄), filtered and concentrated under reduced pressure. Purification by silica gel column chromatography (gradient elution, 0-25% EtOAc/*iso*-hexane) gave the *title compound* as a complex mixture of diastereomers and rotamers: ¹H NMR (400 MHz, CDCl₃): δ 7.39-7.28 (5H, m), 5.91-5.37 (1H, m), 5.20-4.82 (1H, m), 4.58-4.26 (1H, m), 3.59-3.24 (2H, m), 2.07-1.65 (4H, m), 1.55-1.44 (9H, m).

Step 2: Tert-butyl (S)-2-(((1H-imidazole-1-carbonothioyl)oxy)(phenyl)methyl)pyrrolidine-1-carboxylate. To a solution of *tert*-butyl (S)-2-(hydroxy(phenyl)methyl)pyrrolidine-1-carboxylate (242mg, 0.87 mmol) in anhydrous THF (10 mL) was added DMAP (11mg, 0.087 mmol) and diimidazole thiocarbonyl (233 mg, 1.31 mmol). The resultant solution was heated at reflux overnight. The solution was cooled to r.t. and the solvents removed *in vacuo*. The residue was dissolved in DCM, washed with water and the layers separated and dried (phase separator). The DCM was removed *in vacuo* and the resultant residue was purified by silica gel column chromatography (gradient 0-50% EtOAc/*iso*-hexane) to give the *title compound*. ¹H ¹NMR (400 MHz, CDCl₃): δ 8.52-8.39 (1H, m), 7.81-7.67 (1H, m), 7.48-7.28 (6H, m), 5.25 (1H, d, J=4.0 Hz), 4.19-4.10 (1H, m), 3.85-3.67 (2H, m), 2.23-2.09 (2H, m), 1.74-1.64 (2H, m), 1.43-1.35 (9H, m).

Step 3: Tert-butyl (S)-2-benzylpyrrolidine-1-carboxylate. To a solution of *tert*-butyl (S)-2-(((1H-imidazole-1-carbonothioyl)oxy)(phenyl)methyl)pyrrolidine-1-carboxylate (195 mg, 0.5 mmol) in anhydrous toluene (2 mL) was added tributyltin hydride (0.41 mL, 1.51 mmol) and AIBN (16 mg, 0.1 mmol). The solution was heated at reflux for 6 h and then cooled to r.t. The solvent was removed *in vacuo* and the residue purified by silica gel column chromatography (gradient 0-20% EtOAc/*iso*-hexane) to give the *title compound* as a mixture of rotamers. ¹H NMR (400 MHz, CDCl₃): δ 7.31-7.13 (5H, m), 4.14-3.89 (1H, m), 3.44-3.02 (3H, m), 2.61-2.47 (1H, m), 1.79-1.48 (13H, m).

Step 4: (S)-2-Benzylpyrrolidine. *Tert*-butyl (S)-2-benzylpyrrolidine-1-carboxylate (82 mg, 0.31 mmol) was dissolved in 4N HCl/dioxane (5 ml) and stirred at r.t. for 1 h. The solvent was removed *in vacuo* and the residue was purified by SCX chromatography (eluting with MeOH/DCM 1:1 and then collecting with 10% 7N NH₃ in MeOH/MeOH) to give the *title*

compound. ¹H NMR (400 MHz, CDCl₃): δ 7.32-7.18 (5H, m), 3.28-3.20 (1H, m), 3.07-3.01 (1H, m), 2.86-2.71 (3H, m), 2.10 (1H, s), 1.88-1.62 (3H, m), 1.44-1.35 (1H, m).

Step 5: (S)-4-(2-(2-Benzylpyrrolidin-1-yl)-6-((4-methoxybenzyl)oxy)pyridin-4-yl)morpholine.

Following **Method C** starting from (*S*)-2-benzylpyrrolidine (26 mg, 0.16 mmol) and 4-(2-chloro-6-((4-methoxybenzyl)oxy)pyridin-4-yl)morpholine (53 mg, 0.16 mmol, Scaffold 1). After heating at 105 °C for 115 h. The reaction mixture was cooled to r.t., filtered through Celite and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography (gradient elution, 0-20% EtOAc/*iso*-hexane) to give the *title compound*. LCMS (ES⁺) 460 (M+H)⁺, RT 1.41 min (Analytical Method F).

Step 6: (S)-6-(2-Benzylpyrrolidin-1-yl)-4-morpholinopyridin-2(1H)-one (45). Following **Method E** starting from (*S*)-4-(2-(2-benzylpyrrolidin-1-yl)-6-((4-methoxybenzyl)oxy)pyridin-4-yl)morpholine (35 mg, 0.08 mmol). The crude material was purified by reverse phase preparative HPLC and freeze dried from MeCN/H₂O to give the *title compound*. LCMS (ES⁺) 340 (M+H)⁺, RT 2.74 min (*Analytical Method A*); RT 7.62 min (Analytical Method SFC1, YMC CELLULOSE-SC, 45/55 IPA (0.1% DEA)/CO₂); ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.68 (1H, s), 7.32 - 7.29 (4H, m), 7.25 - 7.19 (1H, m), 5.15 (2H, s), 4.22 - 4.19 (1H, m), 3.71 - 3.67 (4H, m), 3.42 - 3.36 (1H, m), 3.21 - 3.14 (5H, m), 2.97 (1H, dd, J=3.5, 13.1 Hz), 2.56 (1H, dd, J=9.3, 13.1 Hz), 1.83 - 1.68 (4H, m). HRMS (ESI⁺) (M + H)⁺: calcd for C₂₀H₂₆N₃O₂, 340.2025; found, 340.205. The presence of 11% of the (*R*)-enantiomer in the sample allowed the absolute stereochemistry of the previously prepared samples of compounds **44** and **45** to be assigned based on their order of elution under the near identical analysis conditions.

For all subsequent chiral compounds where the enantiomers were separated by Chiral SFC purification, the stereochemical assignments were made based on the biological activity of each enantiomer in the biochemical assay: all *R*-enantiomers were assigned as the bioactive

conformation based on the biological activity results obtained by the chirally pure synthesized (*R*)-6-(2-benzylazepan-1-yl)-4-morpholinopyridin-2(1*H*)-one and the lack of biological activity shown by (*S*)-6-(2-benzylpyrrolidin-1-yl)-4-morpholinopyridin-2(1*H*)-one.

The compounds below were made by the same synthetic route as compound **43**, starting from the indicated amine and either 4-(2-chloro-6-((4-methoxybenzyl)oxy)pyridin-4-yl)morpholine or (*R*)-4-(2-chloro-6-((4-methoxybenzyl)oxy)pyridin-4-yl)-2-methylmorpholine as appropriate. Buchwald conditions **Method D** were used to couple the amine. The isomers were isolated after purification by Chiral SFC.

6-(3-Benzylpyrrolidin-1-yl)-4-morpholinopyridin-2(1H)-one (46). LCMS (ES⁺) 340 (M+H)⁺, RT 2.76 min (Analytical Method A); ¹H NMR (400 MHz, CDCl₃) 7.33-7.16 (5H, m), 5.17 (1H, d, J=2.0 Hz), 4.73 (1H, d, J=2.0 Hz), 3.77 (4H, t, J=5.0 Hz), 3.49-3.32 (3H, m), 3.23 (4H, t, J=5 Hz), 3.05 (1H, dd, J=8.0, 9.0 Hz), 2.75 (2H, m), 2.61 (1H, m), 2.12 (1H, m), 1.76 (1H, m). NH not observed. HRMS (ESI⁺) (M + H)⁺: calcd for C₂₀H₂₆N₃O₂, 340.2025; found, 340.2037.

*6-((1*S*,2*S*,5*R*)-2-Benzyl-3-azabicyclo[3.1.0]hexan-3-yl)-4-morpholinopyridin-2(1H)-one (50)*. LCMS (ES⁺) 352 (M+H)⁺, RT 2.95 min (Analytical Method A); RT 1.58 min (Analytical Method SFC4, YMC AMYLOSE-C, 30/70 MeOH + 0.1% DEAIISO/CO₂); ¹H NMR (400 MHz, CDCl₃): δ 7.35 - 7.24 (5H, m), 5.29 (1H, d, J=2.0 Hz), 5.02 (1H, d, J=2.0 Hz), 4.00 - 3.94 (1H, m), 3.91 (1H, d, J=8.4 Hz), 3.82 - 3.78 (4H, m), 3.45 (1H, dd, J=3.8, 9.1 Hz), 3.30 - 3.23 (5H, m), 2.54 (1H, dd, J=9.9, 13.6 Hz), 1.71 - 1.65 (2H, m), 0.77 (1H, dt, J=5.1, 8.0 Hz), 0.62 (1H, q, J=4.5 Hz), NH not observed. HRMS (ESI⁺) (M + H)⁺: calcd for C₂₁H₂₆N₃O₂, 352.2025; found, 352.2041.

*6-((1*R*,2*S*,5*S*)-2-Benzyl-3-azabicyclo[3.1.0]hexan-3-yl)-4-((*R*)-2-methylmorpholino) pyridin-2(1H)-one (53)*. LCMS (ES⁺) 366 (M+H)⁺, RT 2.91 min (Analytical Method A); RT 2.43 min (Analytical Method SFC4, YMC AMYLOSE-C, 30/70 IPA + 0.1% DEAIISO/CO₂); ¹H NMR (400 MHz, CDCl₃): δ 7.30 - 7.16 (5H, m), 5.22 (1H, d, J=2.0 Hz), 4.81 (1H, d, J=2.0 Hz), 4.26

(1H, dd, J=3.4, 8.0 Hz), 3.97 (1H, dd, J=2.3, 11.6 Hz), 3.73 - 3.62 (2H, m), 3.54 - 3.46 (2H, m), 3.35 (1H, d, J=9.1 Hz), 3.14 (1H, dd, J=4.0, 9.1 Hz), 3.02 - 2.90 (2H, m), 2.79 (1H, dd, J=8.0, 13.0 Hz), 2.60 (1H, dd, J=10.4, 13.0 Hz), 1.55 - 1.43 (2H, m), 1.23 (3H, d, J=6.3 Hz), 0.65 (1H, dt, J=5.1, 7.7 Hz), 0.20 (1H, q, J=4.4 Hz), NH not observed. HRMS (ESI⁺) (M + H)⁺: calcd for C₂₂H₂₈N₃O₂, 366.2181; found, 366.2184.

(R)-6-(2-Benzylpiperidin-1-yl)-4-morpholinopyridin-2(1H)-one (**54**). LCMS (ES⁺) 354 (M+H)⁺, RT 2.84 min (Analytical Method A); RT 2.68 min (Analytical Method SFC4, YMC CELLULOSE-C + 0.1% DEAIISO 25% IPA) ¹H NMR (400 MHz, CDCl₃): δ 7.28-7.21 (2H, m), 7.20-7.12 (3H, m), 5.23 (1H, d, J= 2.1 Hz), 5.04 (1H, d, J= 2.1 Hz), 4.14-4.07 (1H, m), 3.77 (4H, t, J= 4.9 Hz), 3.45-3.39 (1H, m), 3.25-3.09 (5H, m), 2.92-2.81 (2H, m), 1.81-1.60 (6H, m). NH not observed. HRMS (ESI⁺) (M + H)⁺: calcd for C₂₁H₂₈N₃O₂, 354.2181; found, 354.2216.

6-((*R*)-2-Benzylazepan-1-yl)-4-((*R*)-2-methylmorpholino)pyridin-2(1H)-one (**56**). LCMS (ES⁺) 383 (M+H)⁺, RT 3.52 min (Analytical Method A); ¹H NMR (400 MHz, CDCl₃): δ 7.29 - 7.12 (5H, m), 4.90 (1H, s), 4.70 (1H, br s), 4.08 (1H, br s), 3.98 - 3.91 (2H, m), 3.67 - 3.54 (3H, m), 3.00 - 2.86 (3H, m), 2.75 - 2.68 (1H, m), 2.61 (1H, dd, J=10.5, 13.0 Hz), 2.07 - 2.00 (1H, m), 1.83 - 1.73 (4H, m), 1.48 - 1.41 (2H, m), 1.31 - 1.12 (5H, m). HRMS (ESI⁺) (M + H)⁺: calcd for C₂₃H₃₂N₃O₂, 382.2494; found, 382.2516.

(S)-6-(2-Benzyl-3,3-difluoropyrrolidin-1-yl)-4-morpholinopyridin-2(1H)-one (**47**). *Step 1: Benzyl 2-benzyl-3-oxopyrrolidine-1-carboxylate*. KOtBu (1.58 g, 14.04 mmol) was added to a solution of ((benzyloxy)carbonyl)-L-phenylalanine (4.0 g, 12.7 mmol) in anhydrous THF (30 mL) at r.t. After 15 min a solution of methyl acrylate (1.16 mL, 12.76 mmol) in anhydrous THF (5 mL) was added dropwise and the resultant solution heated at reflux for 2.5 h. The reaction mixture was cooled to r.t. and diluted with 1M aqueous HCl. The solvent was removed under reduced pressure and the aqueous extracted with EtOAc. The organic extracts were

washed with brine and dried (MgSO₄). The solvent was removed *in vacuo* to give an oil which was stirred vigorously with 0.3M HCl at reflux for 4 days. The mixture was cooled to r.t. and the aqueous layer extracted with EtOAc. The organic layer was washed with NaHCO₃ (saturated aqueous solution), brine and dried (MgSO₄) and concentrated under reduced pressure. The resultant residue was purified by silica gel column chromatography (gradient elution 0-50% EtOAc/*iso*-hexane) to give the *title compound*. ¹H NMR (400 MHz, CDCl₃): δ 7.46-7.34 (8H, m), 7.03-6.91 (2H, m), 5.29-5.20 (2H, m), 4.36-4.18 (1H, m), 3.86-3.64 (1H, m), 3.51-3.01 (2H, m), 2.82-2.73 (1H, m), 2.45-2.34 (1H, m), 1.96-1.81 (1H, m).

Step 2: Benzyl 2-benzyl-3,3-difluoropyrrolidine-1-carboxylate. DAST (3.55 mmol) was added dropwise to a solution of benzyl 2-benzyl-3-oxopyrrolidine-1-carboxylate (500 mg, 1.62 mmol) in anhydrous DCM at -78 °C and the reaction allowed to warm to r.t. overnight. The reaction was cooled to 0 °C and quenched with NaHCO₃ (saturated aqueous solution). The phases were separated, and the organic extracts dried (phase separator). The DCM layer was concentrated *in vacuo*. The crude was purified by silica gel column chromatography (gradient 0-50% EtOAc/*iso*-hexane) to give the *title compound*. ¹H NMR (400 MHz, CDCl₃): δ 7.42-7.36 (7H, m), 7.24-7.13 (3H, m), 5.35-5.07 (3H, m), 5.58-2.83 (6H, m), 2.21-2.07 (1H, m), 1.82-1.63 (1H, m).

Step 3: 2-Benzyl-3,3-difluoropyrrolidine. Following **Method E** starting from benzyl 2-benzyl-3,3-difluoropyrrolidine-1-carboxylate (515 mg, 1.55 mmol). The reaction mixture was filtered through Celite and the solvent removed *in vacuo* to give the *title compound*, which was used without further purification. LCMS (ES⁺) 198 (M+H)⁺, RT 0.89 min (Analytical Method F); ¹H NMR (400 MHz, CDCl₃): δ 7.34-7.12 (5H, m), 3.42-3.13 (1H, m), 3.18-2.93 (3H, m), 2.68 (1H, dd, J=10.6, 14.0 Hz), 2.34-2.22 (2H, m).

Step 4: 4-(2-(2-Benzyl-3,3-difluoropyrrolidin-1-yl)-6-((4-methoxybenzyl)oxy)pyridin-4-yl)morpholine. Following **Method D** starting from 2-benzyl-3,3-difluoropyrrolidine (97 mg, 0.49 mmol) and 4-(2-chloro-6-((4-methoxybenzyl)oxy)pyridin-4-yl)morpholine (150 mg, 0.45 mmol). The residue was dissolved in DCM and washed with water. The organic extracts were dried (phase separator) and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (gradient 0-50% EtOAc/iso-hexane) to give the *title compound*. LCMS (ES⁺) 496 (M+H)⁺, RT 1.88 min (Analytical Method F).

Step 5: (*S*)-6-(2-Benzyl-3,3-difluoropyrrolidin-1-yl)-4-morpholinopyridin-2(1*H*)-one (**47**). Following **Method E** starting from 4-(2-(2-benzyl-3,3-difluoropyrrolidin-1-yl)-6-((4-methoxybenzyl)oxy)pyridin-4-yl)morpholine (208 mg, 0.42 mmol). The residue was purified by reverse phase preparative HPLC followed by separation of the enantiomers by SFC to afford the *title compound* (**47**). LCMS (ES⁺) 376 (M+H)⁺, RT 2.84 min (*Analytical Method A*); RT 2.09 min (Analytical Method SFC1, YMC AMYLOSE-C, 25/75 MeOH (0.1%DEA)/CO₂); ¹H NMR (400 MHz, CDCl₃): δ 7.29-7.20 (3H, m), 7.17-7.15 (2H, m), 5.27 (1H, d, J= 2.2 Hz), 4.80 (1H, d, J= 2.2 Hz), 4.35 (1H, dt, J= 4.6, 18.2 Hz), 3.76 (4H, t, J= 4.6 Hz), 3.51 (1H, dt, J= 2.2, 9.8 Hz), 3.42-3.35 (1H, m), 3.28-3.13 (5H, m), 2.88 (1H, td, J= 3, 14.3 Hz), 2.32-2.22 (1H, m), 1.92-1.74 (2H, m). HRMS (ESI⁺) (M + H)⁺: calcd for C₂₀H₂₄F₂N₃O₂, 376.1836; found, 376.1839.

Data is given for the (*R*)-enantiomer of **47** for comparison:

(*R*)-6-(2-Benzyl-3,3-difluoropyrrolidin-1-yl)-4-morpholinopyridin-2(1*H*)-one; LCMS (ES⁺) 376 (M+H)⁺, RT 2.84 min (*Analytical Method A*); RT 2.99 min (Analytical Method SFC1, YMC AMYLOSE-C, 25/75 MeOH (0.1%DEA)/CO₂); ¹H NMR (400 MHz, CDCl₃): δ 7.29-7.20 (3H, m), 7.17-7.15 (2H, m), 5.27 (1H, d, J= 2.2 Hz), 4.80 (1H, d, J= 2.2 Hz), 4.35 (1H, dt, J= 4.6, 18.2 Hz), 3.76 (4H, t, J= 5.1 Hz), 3.51 (1H, dt, J= 2.2, 9.8 Hz), 3.42-3.35 (1H, m), 3.28-3.13 (5H, m), 2.88 (1H, td, J= 3, 14.3 Hz), 2.32-2.22 (1H, m), 1.92-1.74 (2H, m).

6-((2*S*,3*R*)-2-Benzyl-3-fluoropyrrolidin-1-yl)-4-morpholinopyridin-2(1*H*)-one (**48**).

*Step 1: Benzyl (2*S**,3*S**)-2-benzyl-3-hydroxypyrrolidine-1-carboxylate.* Benzyl 2-benzyl-3-hydroxypyrrolidine-1-carboxylate (from step 1 of compound 47, 613 mg, 1.98 mmol) was dissolved in MeOH (0.2 M) and the resultant mixture cooled in an ice-bath. NaBH₄ (1.1 eq) was added in one portion and the reaction allowed to warm to r.t. over 1 h. The reaction was quenched by careful addition of water and the MeOH was removed under reduced pressure. The aqueous layer was extracted with DCM and the layers separated. The organic extracts were dried (phase separator) and concentrated under reduced pressure. The mixture was purified by silica gel column chromatography eluting with gradient 0-50% EtOAc/iso-hexane to afford the *title compound*. ¹H NMR (400 MHz, CDCl₃): δ 7.38-7.15 (10H, m), 5.20-4.96 (2H, m), 4.28 (1H, s), 4.14-4.08 (1H, m), 3.59-3.44 (2H, m), 3.01-2.87 (1H, m), 2.03-1.87 (2H, m), 1.81-1.73 (1H, m), 1.62-1.54 (2H, m),

*Step 2: Benzyl (2*S**,3*R**)-2-benzyl-3-fluoropyrrolidine-1-carboxylate.* DAST (2.28 mmol) was added dropwise to a solution of benzyl (2*S**,3*S**)-2-benzyl-3-hydroxypyrrolidine-1-carboxylate (step 1 of compound **48**, 203 mg, 0.65 mmol) in anhydrous DCM at -78 °C and the reaction allowed to warm to r.t. overnight. The reaction was cooled in an ice bath and quenched by the addition of NaHCO₃ (saturated aqueous solution). The phases were separated, and the organic extracts dried (phase separator). The DCM layer was concentrated *in vacuo*. The mixture was purified by silica gel column chromatography (gradient elution with gradient 0-50% EtOAc/iso-hexane) to afford the *title compound*. ¹H NMR (400 MHz, CDCl₃): δ 7.41-7.04 (10H, m), 5.23-5.14 (2H, m), 4.97-4.84 (1H, m), 4.38-4.19 (1H, m), 3.65-3.48 (2H, m), 3.22-3.00 (1H, m), 2.64-2.48 (1H, m), 2.17-1.67 (2H, m).

Step 3: (2S,3R*)-2-Benzyl-3-fluoropyrrolidine.* Following **Method E** starting from benzyl (2S*,3R*)-2-benzyl-3-fluoropyrrolidine-1-carboxylate (120 mg, 0.38 mmol) to afford the *title compound*. ¹H NMR (400 MHz, CDCl₃): δ 7.39-7.20 (5H, m), 4.95 (1H, dd, J= 0.8, 39.6 Hz), 3.61-3.49 (1H, m), 3.05-3.18 (2H, m), 2.80-2.48 (3H, m), 2.08-1.97 (2H, m).

Step 4: 4-(2-((2S,3R*)-2-Benzyl-3-fluoropyrrolidin-1-yl)-6-((4-methoxybenzyl)oxy)pyridin-4-yl)morpholine.* Following **Method D** starting from (2S*,3R*)-2-benzyl-3-fluoropyrrolidine (43 mg, 0.24 mmol) and 4-(2-chloro-6-((4-methoxybenzyl)oxy)pyridin-4-yl)morpholine (73 mg, 0.22 mmol). The residue was purified by silica gel column chromatography (gradient 0-50% EtOAc/*iso*-hexane) to give the *title compound*. LCMS (ES⁺) 478 (M+H)⁺, RT 1.56 min (Analytical Method F).

Step 5: 6-((2S,3R)-2-Benzyl-3-fluoropyrrolidin-1-yl)-4-morpholinopyridin-2(1H)-one (48). Following **Method E** starting from 6-((2S*,3R*)-2-benzyl-3-fluoropyrrolidin-1-yl)-4-morpholinopyridin-2(1H)-one (100 mg, 0.21 mmol). The residue was purified by reverse phase preparative HPLC followed by SFC to afford the *title compound*.

6-((2S,3R)-2-Benzyl-3-fluoropyrrolidin-1-yl)-4-morpholinopyridin-2(1H)-one (48); LCMS (ES⁺) 358 (M+H)⁺, RT 2.77 min (Analytical Method A); RT 1.75 min (Analytical Method SFC4, YMC AMYLOSE-C, 30/70 MeOH (0.1%DEAISO)/CO₂); ¹H NMR (400 MHz, CDCl₃): δ 7.34-7.24 (3H, m), 7.18-7.16 (2H, m), 5.25 (1H, d, J= 2.2 Hz), 5.02 (1H, dd, J= 51.6, 2.9 Hz), 4.91 (1H, d, J= 2.2 Hz), 4.32 (1H, dq, J= 4.1, 10.4 Hz), 3.79 (4H, t, J= 5.2 Hz), 3.63 (1H, t, J= 9.2 Hz), 3.51 (1H, dt, J= 7.0, 9.7 Hz), 3.24 (4H, dd, J= 4.1, 5.9 Hz), 3.05-2.99 (1H, m), 2.70 (1H, dd, J= 8.1, 14.0 Hz), 2.26-2.16 (1H, m), 1.95-1.75 (1H, m), NH not observed.

Data is shown for the (2R,3S)-isomer for comparison:

6-((2*R*,3*S*)-2-Benzyl-3-fluoropyrrolidin-1-yl)-4-morpholinopyridin-2(1*H*)-one; LCMS (ES⁺) 358 (M+H)⁺, RT 2.76 min (*Analytical Method A*); RT 2.23 min (*Analytical Method SFC4*, YMC AMYLOSE-C, 30/70 MeOH (0.1%DEAISO)/CO₂); ¹H NMR (400 MHz, CDCl₃): δ 7.34-7.24 (3H, m), 7.18-7.16 (2H, m), 5.25 (1H, d, J= 2.2 Hz), 5.02 (1H, dd, J= 51.6, 2.9 Hz), 4.91 (1H, d, J= 2.2 Hz), 4.32 (1H, dq, J= 4.1, 10.4 Hz), 3.79 (4H, t, J= 5.2 Hz), 3.63 (1H, t, J= 9.2 Hz), 3.51 (1H, dt, J= 7.0, 9.7 Hz), 3.24 (4H, dd, J= 4.1, 5.9 Hz), 3.05-2.99 (1H, m), 2.70 (1H, dd, J= 8.1, 14.0 Hz), 2.26-2.16 (1H, m), 1.95-1.75 (1H, m), NH not observed.

6-((2*S*,3*R*)-2-Benzyl-3-methoxypyrrrolidin-1-yl)-4-morpholinopyridin-2(1*H*)-one (**49**).

*Step 1: Benzyl (2*S*^{*},3*R*^{*})-3-(benzoyloxy)-2-benzylpyrrolidine-1-carboxylate.* Benzoic acid (1.92 mmol) and triphenylphosphine (1.92 mmol) were added to a solution of benzyl (2*S*^{*},3*S*^{*})-2-benzyl-3-hydroxypyrrrolidine-1-carboxylate (step 1 of compound **48**, 498 mg, 1.60 mmol) in THF (10 mL) and cooled to 0 °C. DIAD (1.92 mmol) was added dropwise and the reaction allowed to warm to r.t. over 5 h. The reaction mixture was concentrated *in vacuo* and purified by silica gel column chromatography (gradient elution, 0-50% EtOAc/*iso*-hexane) to afford the *title compound* as a rotameric mixture: ¹H NMR (400 MHz, CDCl₃): δ 8.12-7.11 (15H, m), 5.31-5.14 (3H, m), 4.35-4.23 (1H, m), 3.66-3.49 (2H, m), 3.21-3.03 (1H, m), 2.91-2.79 (1H, m), 2.04-1.98 (1H, m), 1.89-1.83 (1H, m).

*Step 2: Benzyl (2*S*^{*},3*R*^{*})-2-benzyl-3-hydroxypyrrrolidine-1-carboxylate.* Benzyl (2*S*^{*},3*R*^{*})-3-(benzoyloxy)-2-benzylpyrrolidine-1-carboxylate (465 mg, 1.12 mmol) was dissolved in MeOH (10 mL) and water (5 mL). Lithium hydroxide monohydrate (70.5 mg, 1.68 mmol) was added in one portion and the reaction heated at 50 °C for 3 h. The methanol was removed *in vacuo* and the aqueous layer was extracted with DCM. The layers were separated, dried (phase separator) and concentrated *in vacuo*. Purification by silica gel chromatography (gradient elution, 0-30% EtOAc/*iso*-hexane) yielded the *title compound*. ¹H NMR (400 MHz, CDCl₃): δ

7.48-7.05 (10H, m), 5.23-5.10 (2H, m), 4.18 (1H, s), 4.05-3.94 (1H, m), 3.70-3.45 (2H, m), 3.15 (1H, ddd, J= 0.4, 1.4, 7.4 Hz), 2.53-2.47 (1H, m), 1.93-1.84 (2H, m), 1.51-1.47 (1H, m).

Step 3: Benzyl (2S,3R*)-2-benzyl-3-methoxypyrrolidine-1-carboxylate.* NaH (77 mg, 1.93 mmol, 60% dispersion in mineral oil) was added in one portion to benzyl (2S*,3R*)-2-benzyl-3-hydroxypyrrolidine-1-carboxylate (300 mg, 0.96 mmol) in anhydrous DMF (5 mL) at 0 °C. After 20 min, methyl iodide (0.09 mL, 1.45 mmol) was added and the reaction allowed to warm to r.t. over 2 h. The reaction was cooled in an ice-bath and quenched by addition of water. The DMF was removed *in vacuo* and the residue dissolved in DCM. The DCM was washed with water and the layers separated. The organic extract was dried (phase separator) and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (gradient 0-30% EtOAc/iso-hexane) to give the *title compound*. LCMS (ES⁺) 326 (M+H)⁺, RT 1.73 min (Analytical Method F); ¹H NMR (400 MHz, CDCl₃): δ 7.41-7.06 (10H, m), 5.23-5.12 (2H, m), 4.15-4.02 (2H, m), 3.63-3.46 (2H, m), 3.23-3.01 (4H, m), 2.55-2.45 (1H, m), 1.98-1.71 (2H, m), rotamers observed.

Step 4: (2S,3R*)-2-Benzyl-3-methoxypyrrolidine.* Following **Method E** starting from *rac*-benzyl (2R,3S)-2-benzyl-3-methoxypyrrolidine-1-carboxylate (250 mg, 0.77 mmol). After filtering the reaction mixture through celite the solvent was removed *in vacuo* to give the *title compound*. Used without further purification.

Step 5: 4-(2-((2S,3R*)-2-Benzyl-3-methoxypyrrolidin-1-yl)-6-((4-methoxybenzyl)oxy)pyridin-4-yl)morpholine.* Following **Method D** starting from (2S*,3R*)-2-benzyl-3-methoxypyrrolidine (94 mg, 0.49 mmol) and 4-(2-chloro-6-((4-methoxybenzyl)oxy)pyridin-4-yl)morpholine (150 mg, 0.45 mmol). The residue was purified by silica gel column chromatography (gradient 0-50% EtOAc/iso-hexane) to give the *title compound*. LCMS (ES⁺) 490 (M+H)⁺, RT 3.10 min (Analytical Method F).

Step 6: 6-((2*S*,3*R*)-2-Benzyl-3-methoxypyrrolidin-1-yl)-4-morpholinopyridin-2(1*H*)-one (**49**) and 6-((2*R*,3*S*)-2-benzyl-3-methoxypyrrolidin-1-yl)-4-morpholinopyridin-2(1*H*)-one.

Following **Method E** starting from 4-(2-((2*S**,3*R**)-2-benzyl-3-methoxypyrrolidin-1-yl)-6-((4-methoxybenzyl)oxy)pyridin-4-yl)morpholine (190 mg, 0.39 mmol). The residue was purified by reverse phase preparative HPLC. The sample was further purified by SFC chiral chromatography to give the *title compound*.

6-((2*S*,3*R*)-2-Benzyl-3-methoxypyrrolidin-1-yl)-4-morpholinopyridin-2(1*H*)-one (**49**); LCMS (ES⁺) 370 (M+H)⁺, RT 2.85 min (Analytical Method A); RT 3.37 min (Analytical Method SFC4, YMC AMYLOSE-C, 30/70 IPA (0.1%DEAISO)/CO₂); ¹H NMR (400 MHz, CDCl₃): δ 7.36-7.17 (5H, m), 5.21 (1H, d, J= 2.1 Hz), 4.88 (1H, d, J= 2.1 Hz), 4.07 (1H, dd, J= 4.1, 8.5 Hz), 3.78 (4H, t, J= 4.9 Hz), 3.74 (1H, d, J= 4.1 Hz), 3.51-3.39 (2H, m), 3.23 (4H, dd, J= 3.7, 6.0 Hz), 3.16 (3H, s), 2.99 (1H, dd, J= 4.2, 14.2 Hz), 2.66 (1H, dd, J= 8.5, 14.2 Hz), 2.10-2.05 (1H, m), 1.89-1.80 (1H, m), NH not observed.

Data is given for the (2*R*,3*S*)-isomer for comparison:

6-((2*R*,3*S*)-2-Benzyl-3-methoxypyrrolidin-1-yl)-4-morpholinopyridin-2(1*H*)-one; LCMS (ES⁺) 370 (M+H)⁺, RT 2.85 min (Analytical Method A); RT 2.52 min (Analytical Method SFC4, YMC AMYLOSE-C, 30/70 IPA (0.1%DEAISO)/CO₂); ¹H NMR (400 MHz, CDCl₃): δ 7.36-7.17 (5H, m), 5.21 (1H, d, J= 2.1 Hz), 4.88 (1H, d, J= 2.1 Hz), 4.07 (1H, dd, J= 4.1, 8.5 Hz), 3.78 (4H, t, J= 4.9 Hz), 3.74 (1H, d, J= 4.0 Hz), 3.51-3.39 (2H, m), 3.23 (4H, dd, J= 3.7, 6.0 Hz), 3.16 (3H, s), 2.99 (1H, dd, J= 4.2, 14.2 Hz), 2.66 (1H, dd, J= 8.5, 14.2 Hz), 2.10-2.05 (1H, m), 1.89-1.80 (1H, m), NH not observed.

6-((1*S*,2*S*,5*R*)-2-Benzyl-3-azabicyclo[3.1.0]hexan-3-yl)-4-((*R*)-2-methylmorpholino)pyridin-2(1*H*)-one (**51**).

Step 1: Tert-butyl 3-azabicyclo[3.1.0]hexane-3-carboxylate. Boc anhydride (2.6 g, 11.9 mmol) and a solution of NaHCO₃ (3.32 g, 39.5 mmol) in water (78 mL) was added to a suspension of 3-azabicyclo[3.1.0]hexane hydrochloride (950 mg, 7.9 mmol) in THF (26 mL). The resulting biphasic mixture was stirred vigorously overnight at r.t. The reaction mixture was diluted with water and DCM. The layers were separated and the organic phase dried (phase separator) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (gradient elution, 0-10% EtOAc/*iso*-hexane) to afford the title compound. ¹H NMR (400 MHz, CDCl₃): δ 3.55 (1H, d, J= 11.0 Hz), 3.47 (1H, J=11.0 Hz), 3.35-3.27 (2H, m), 1.42 (9H, s), 1.21-1.14 (1H, m), 0.93-0.84 (1H, m), 0.67-0.61 (1H, m), 0.16-0.13 (1H, m).

Step 2: Tert-butyl (1R,2R*,5S*)-2-benzyl-3-azabicyclo[3.1.0]hexane-3-carboxylate and tert-butyl (1R*,2S*,5S*)-2-benzyl-3-azabicyclo[3.1.0]hexane-3-carboxylate.* To a solution of *tert*-butyl 3-azabicyclo[3.1.0]hexane-3-carboxylate (1.50 g, 7.9 mmol) in diethyl ether (27 mL), under N₂ atmosphere, was added tetramethylethylenediamine (1.23 mL, 8.2 mmol) and the reaction mixture cooled to -78 °C. *sec*-BuLi (11.8 mL, 10.6 mmol, 0.9 M in cyclohexane) was added and the mixture was stirred at -78 °C for 30 min. Benzyl bromide (1.95 mL, 16.4 mmol) was added dropwise at -78 °C. After complete addition the reaction was allowed to slowly warm to r.t. overnight. The reaction was quenched with saturated aqueous NH₄Cl solution, the layers separated and the aqueous further extracted with Et₂O (x2). The combined organic extracts were dried (MgSO₄) and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (gradient elution, 0-10% EtOAc/*iso*-hexane) to afford the title compounds as separate diastereomers *tert*-butyl (*1R**,*2S**,*5S**)-2-benzyl-3-azabicyclo[3.1.0]hexane-3-carboxylate and *tert*-butyl (*1R**,*2R**,*5S**)-2-benzyl-3-azabicyclo[3.1.0]hexane-3-carboxylate.

Isomer A (592 mg, later determined to be the (*1R**, *2R**, *5S**) isomer, see next step): LCMS (ES⁺) 218 (M-^tBu)⁺, RT 1.77 min (Analytical Method F); ¹H NMR (400 MHz, CDCl₃): δ 7.31-7.18 (5H, m), 4.12-3.96 (1H, m), 3.61-3.39 (1H, m), 3.22-2.91 (2H, m), 2.77-2.64 (1H, m), 1.48-1.42 (9H, m), 1.38-1.28 (1H, m), 0.95-0.87 (1H, m), 0.59-0.53 (1H, m), 0.12-0.09 (1H, m), rotamers observed.

Isomer B (420 mg, later determined to be the (*1R**, *2S**, *5S**) isomer, see next step): LCMS (ES⁺) 218 (M-^tBu)⁺, RT 1.83 min (Analytical Method F); ¹H NMR (400 MHz, CDCl₃): δ 7.33-7.27 (4H, m), 7.23-7.17 (1H, m), 4.04-3.95 (1H, m), 3.86-3.44 (3H, m), 2.40 (1H, dd, J= 10.8, 12.4 Hz), 1.57-1.34 (11H, m), 0.69-0.63 (1H, m), 0.47-0.43 (1H, m), rotamers observed.

*Step 3: (1R**,*2R**,*5S**)-2-Benzyl-3-azabicyclo[3.1.0]hexane. To tert-butyl (*1R**,*2R**,*5S**)-2-benzyl-3-azabicyclo[3.1.0]hexane-3-carboxylate (Isomer A from previous step, 570 mg, 2.09 mmol) was added DCM (5 mL) and TFA (5 mL) and the resulting mixture was stirred at r.t. for 1 h. The solvent was evaporated and purified by SCX cartridge eluting sequentially with DCM:MeOH, 1:1 then 3:1 DCM:7N ammonia in methanol. The ammonia in methanol fractions were combined and concentrated under reduced pressure to afford the *title compound*. nOe experiments allowed determination of the stereochemistry of the benzyl group relative to the cyclopropyl group. ¹H NMR (400 MHz, CDCl₃): δ 7.32 - 7.17 (5H, m), 3.41 (1H, ddd, J=3.0, 5.5, 8.1 Hz), 2.94 (2H, d, J=1.8 Hz), 2.82 (1H, dd, J=5.9, 13.0 Hz), 2.61 (1H, dd, J=8.0, 13.1 Hz), 1.38 - 1.32 (1H, m), 1.30 - 1.23 (1H, m), 0.40 - 0.34 (1H, m), 0.34 - 0.30 (1H, m). NH not observed.

Step 4: (R)-4-(2,6-Dichloropyridin-4-yl)-2-methylmorpholine (Intermediate **38**). Following **Method B** using (2*R*)-methyl morpholine (0.5 g, 5 mmol). Purified by silica gel column chromatography (gradient elution, 10-50% EtOAc/*iso*-hexane) to afford the *title compound*. ¹H NMR (400 MHz, CDCl₃): δ 6.57 (2H, s), 4.02 (1H, ddt, J=1.3,5.1,5.8 Hz), 3.74-3.63 (2H, m),

3.58-3.49 (2H, m), 3.03 (1H, dt, J=4.4, 12.4 Hz), 2.67 (1H, dd, J=10.4, 12.4 Hz), 1.26 (3H, d, 6.4 Hz).

Step 5: (R)-4-(2-Chloro-6-((4-methoxybenzyl)oxy)pyridin-4-yl)-2-methylmorpholine (Intermediate **42**). Following **Method A** using (R)-4-(2,6-dichloropyridin-4-yl)-2-methylmorpholine (1.6 g, 6.4 mmol) and *para*-methoxybenzyl alcohol (0.87 mL, 7.0 mmol). Purified by silica gel column chromatography (gradient elution, 5-40% EtOAc/*iso*-hexane) to afford the *title compound*. ¹H NMR (400 MHz, CDCl₃): δ 7.39 - 7.36 (2H, m), 6.91 - 6.88 (2H, m), 6.40 (1H, d, J=2.0 Hz), 5.98 (1H, d, J=2.0 Hz), 5.24 (2H, s), 4.00 - 3.95 (1H, m), 3.81 (3H, s), 3.71 - 3.61 (2H, m), 3.52 - 3.42 (2H, m), 2.96 - 2.88 (1H, m), 2.58 (1H, dd, J=10.4, 12.4 Hz), 1.24 - 1.21 (3H, m).

Step 6: (R)-4-(2-((1R*,2R*,5S*)-2-benzyl-3-azabicyclo[3.1.0]hexan-3-yl)-6-((4-methoxybenzyl)oxy)pyridin-4-yl)-2-methylmorpholine. A mixture of (R)-6-chloro-4-(2-methylmorpholino)pyridin-2(1H)-one (178 mg, 0.50 mmol), (1R*,2R*,5S*)-2-benzyl-3-azabicyclo[3.1.0]hexane (88 mg, 0.50 mmol), NaOtBu (55 mg, 0.55 mmol), RuPhos (12 mg, 0.025 mmol), and RuPhos palladacycle G1 methyl *tert*-butyl ether adduct (20 mg, 0.025 mmol) were placed in a stem block tube and sealed. The tube was evacuated and refilled with nitrogen (x3). 1,4-Dioxane (3.3 mL) was added and the reaction heated at 85 °C for 16 h. The reaction mixture was cooled to r.t. and filtered through Celite. The mixture was concentrated under reduced pressure and purified by silica gel column chromatography (gradient elution, 5-40% EtOAc/*iso*-hexane) to afford the *title compound* as a yellow oil (230 mg, 95%). LCMS (ES⁺) 486 (M+H)⁺, RT 1.77 min (Analytical Method F).

Step 7: 6-((1S,2S,5R)-2-Benzyl-3-azabicyclo[3.1.0]hexan-3-yl)-4-((R)-2-methylmorpholino)pyridin-2(1H)-one (**51**).

(*R*)-4-(2-((*1R**,*2R**,*5S**)-2-benzyl-3-azabicyclo[3.1.0]hexan-3-yl)-6-((4-methoxybenzyl)oxy)pyridin-4-yl)-2-methylmorpholine (220 mg, 0.45 mmol) was suspended in EtOH (4.5 mL) and the reaction warmed to obtained a homogeneous solution. 5% Pd/C (220 mg, 100% by wt.) was added followed by 1-methylcyclohexyl-1,4-diene (425 mg, 4.50 mmol). The reaction was heated at 75 °C for 3 h. The reaction was cooled to r.t. and filtered through a plug of cotton to give a residue, which was purified by chiral SFC to yield 29 mg (17%) of the *title compound*. Absolute configuration was assigned following determination of biological activity, the (*1S*) isomer being the more active. LCMS (ES+) 366 (M+H)⁺, RT 3.05 min (Analytical Method A); RT 2.43 min (Analytical Method SFC4, YMC AMYLOSE-C, 20/80 MeOH + 0.1% DEAIISO/CO₂); ¹H NMR (400 MHz, CDCl₃): δ 7.35 - 7.23 (5H, m), 5.28 (1H, d, J=2.3 Hz), 5.02 (1H, d, J=2.3 Hz), 4.00 - 3.92 (2H, m), 3.88 (1H, d, J=9.1 Hz), 3.73 - 3.63 (2H, m), 3.54 - 3.42 (3H, m), 3.25 (1H, dd, J=2.8, 13.6 Hz), 2.97 (1H, dt, J=3.6, 12.3 Hz), 2.65 - 2.51 (2H, m), 1.73 - 1.67 (2H, m), 1.23 (3H, d, J=6.1 Hz), 0.78 (1H, dt, J=5.1, 8.0 Hz), 0.62 (1H, q, J=4.4 Hz), NH not observed. HRMS (ESI+) (M + H)⁺: calcd for C₂₂H₂₈N₃O₂, 366.2181; found, 366.218.

6-((*1R*,*2S*,*5S*)-2-Benzyl-3-azabicyclo[3.1.0]hexan-3-yl)-4-morpholinopyridin-2(*1H*)-one (**52**).

*Step 1: (1R**,*2S**,*5S**)-2-Benzyl-3-azabicyclo[3.1.0]hexane. To *tert*-butyl (*1R**,*2S**,*5S**)-2-benzyl-3-azabicyclo[3.1.0]hexane-3-carboxylate (Isomer B from step 2 of compound **51**, 400 mg, 1.46 mmol) was added DCM (3.5 mL) and TFA (3.5 mL) and the resulting mixture was stirred at r.t. for 1 h. The solvent was evaporated and purified by SCX cartridge eluting sequentially with DCM:MeOH, 1:1 then 3:1 DCM:7N ammonia in methanol. The ammonia in methanol fractions were combined and concentrated under reduced pressure to afford the *title compound*. nOe experiments allowed determination of the stereochemistry of the benzyl group relative to the cyclopropyl group. ¹H NMR (400 MHz, CDCl₃): δ 7.32 - 7.17 (5H, m),

3.29 (1H, t, J=7.2 Hz), 3.00 (1H, dd, J=3.2, 11.0 Hz), 2.87 (1H, d, J=11.0 Hz), 2.69 (1H, dd, J=7.2, 13.5 Hz), 2.60 (1H, dd, J=7.5, 13.5 Hz), 1.43 - 1.36 (1H, m), 1.29 (1H, ddd, J=4.0, 6.2, 7.9 Hz), 0.45 (1H, dt, J=5.0, 7.7 Hz), 0.15 (1H, dd, J=4.0, 8.7 Hz). NH not observed.

Step 2: 4-(2,6-Dichloropyridin-4-yl)morpholine. 2,6-Dichloropyridin-4-amine (10 g, 61.3 mmol) was dissolved in DMF (200 mL) and cooled to 0 °C. Sodium hydride (6.13 g, 153 mmol) was added portionwise over 20 min. After 15 min 1-chloro-2-(2-chloroethoxy)ethane (8.63 mL, 73.6 mmol) was added dropwise. The reaction mixture was warmed to r.t. and stirred for 21.5 h. After this time the reaction was cooled to 0 °C and cautiously quenched with water. The DMF was removed under reduced pressure. The resultant residue was dissolved in DCM and washed with water. The organic layers were dried (MgSO₄), filtered and concentrated under reduced pressure. The crude product was triturated with EtOAc and *iso*-hexane to afford the *title compound* as a white solid (9.27 g, 65%). ¹H NMR (400 MHz, CDCl₃): δ 6.59 (2H, s), 3.84 - 3.80 (4H, m), 3.33 - 3.29 (4H, m)

Step 3: 4-(2-Chloro-6-((4-methoxybenzyl)oxy)pyridin-4-yl)morpholine. Following **Method A** using 4-(2,6-dichloropyridin-4-yl)morpholine (9.27 g, 39.8 mmol) and PMBOH (6.05 g, 43.8 mmol). The crude product was triturated with EtOAc and *iso*-hexane to afford the *title compound* as an off-white solid (11.4 g, 86%). ¹H NMR (400 MHz, CDCl₃): δ 7.39 - 7.35 (2H, m), 6.91 - 6.88 (2H, m), 6.40 (1H, d, J=2.0 Hz), 5.99 (1H, d, J=2.0 Hz), 5.25 (2H, s), 3.81 - 3.77 (7H, m), 3.25 - 3.21 (4H, m).

Step 4: 4-(2-((1R,2S*,5S*)-2-benzyl-3-azabicyclo[3.1.0]hexan-3-yl)-6-((4-methoxybenzyl)oxy)pyridin-4-yl)morpholine.* A mixture of 4-(2-chloro-6-((4-methoxybenzyl)oxy)pyridin-4-yl)morpholine (150 mg, 0.45 mmol), NaOtBu (48 mg, 0.50 mmol), RuPhos (11 mg, 0.023 mmol) and RuPhos Pd G1 catalyst (methyl t-butyl ether adduct, 18 mg, 0.023 mmol) was placed in a tube and sparged with N₂. A solution of (1R*,2S*,5S*)-

2-benzyl-3-azabicyclo[3.1.0]hexane (78 mg, 0.45 mmol) in anhydrous dioxane (3 mL) was added, the tube sealed, and stirring commenced at 85 °C for 16 h. The reaction was cooled to r.t. and filtered through Celite, washing with DCM, and the reaction concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography (gradient elution, 0-15% EtOAc/*iso*-hexane) to afford the title compound as a green solid (197 mg, 93%). LCMS (ES⁺) 472 (M+H)⁺, RT 1.48 min (Analytical Method F).

Step 5: 6-((1R,2S,5S)-2-Benzyl-3-azabicyclo[3.1.0]hexan-3-yl)-4-morpholinopyridin-2(1H)-one (52). Following **Method E** from 4-(2-((1R*,2S*,5S*)-2-benzyl-3-azabicyclo[3.1.0]hexan-3-yl)-6-((4-methoxybenzyl)oxy)pyridin-4-yl)morpholine (190 mg, 0.40 mmol). Purification by silica gel column chromatography (gradient elution, 0-20% MeOH/EtOAc) and chiral SFC yielded the *title compound* and its enantiomer. Absolute configuration was assigned following determination of biological activity, the (1R) isomer being the more active. LCMS (ES⁺) 352 (M+H)⁺, RT 2.83 min (Analytical Method A); RT 1.65 min (Analytical Method SFC4, YMC AMYLOSE-C, 40/60 IPA + 0.1% DEAIISO/CO₂); ¹H NMR (400 MHz, CDCl₃): δ 7.27 - 7.26 (3H, m), 7.19 - 7.15 (2H, m), 5.22 (1H, d, J=2.0 Hz), 4.82 (1H, d, J=2.0 Hz), 4.22 (1H, dd, J=3.4, 7.7 Hz), 3.81 - 3.77 (4H, m), 3.33 (1H, d, J=9.3 Hz), 3.27 - 3.23 (4H, m), 3.12 (1H, dd, J=4.0, 9.3 Hz), 2.99 (1H, dd, J=3.3, 13.6 Hz), 2.81 (1H, dd, J=8.0, 13.6 Hz), 1.56 - 1.39 (2H, m), 0.66 (1H, dt, J=5.2, 7.8 Hz), 0.19 (1H, q, J=4.3 Hz), NH not observed. HRMS (ESI⁺) (M + H)⁺: calcd for C₂₁H₂₆N₃O₂, 352.2025; found, 352.203.

(R)-6-(2-Benzylazepan-1-yl)-4-morpholinopyridin-2(1H)-one (55).

Step 1: Tert-butyl (R)-(5-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-5-oxo-1-phenylpentan-2-yl)carbamate. (R)-4-((Tert-butoxycarbonyl)amino)-5-phenylpentanoic acid (3.0 g, 10.2 mmol) was dissolved in DCM (50 mL) and cooled to 0 °C. Meldrum's acid (1.47 g, 10.2 mmol), EDC hydrochloride (2.94 g, 15.3 mmol) and DMAP (1.87 g, 15.3 mmol) were added sequentially to the reaction. The reaction mixture was stirred for 19 h, removing the ice-bath after 1 h. The

reaction was transferred to a separating funnel and washed with 1 M potassium bisulfate aqueous solution. The organic extracts were dried (phase separator) and concentrated under reduced pressure to afford the *title compound*. Used without further purification in the next step.

Step 2: Tert-butyl (R)-(5-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-1-phenylpentan-2-yl)carbamate. Tert-butyl (R)-(5-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-5-oxo-1-phenylpentan-2-yl)carbamate (2.1 g, 5.01 mmol) was dissolved in DCM (50 mL) and cooled to 0 °C. Acetic acid (3.16 mL, 55.1 mmol) was added followed by portionwise addition of NaBH₄ (759 mg, 20.05 mmol). The reaction was stirred at 0 °C for 3.5 h. The reaction mixture was cautiously quenched by dropwise addition of water (5 mL) followed by brine (~100 mL). The layers were separated, and the aqueous layer extracted with DCM. The combined layers were washed with brine, dried (MgSO₄), filtered and concentrated under reduced pressure to afford the *title compound*. Used without further purification in the next step.

Step 3: Tert-butyl (R)-6-((tert-butoxycarbonyl)amino)-7-phenylheptanoate. Tert-butyl (R)-(5-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-1-phenylpentan-2-yl)carbamate (1.86 g, 4.59 mmol) was dissolved in toluene (5 mL) and *t*-BuOH (5 mL). The reaction mixture was refluxed for 6 h. After this time the solvents were removed under reduced pressure. The resultant oil was dissolved in toluene and heated at reflux for 25 h. The reaction mixture was concentrated under reduced pressure. The oil was dissolved in DCM and NaHCO₃ (saturated aqueous solution) added. The layers were inseparable. A small quantity of brine was added to separate the layers. The aqueous layer was extracted with EtOAc. The combined organic layers were dried (phase separator) and concentrated under reduced pressure. The crude oil was purified by silica gel column chromatography (gradient elution 0-30% EtOAc/*iso*-hexane) to afford the *title compound*. ¹H NMR (400 MHz, CDCl₃): δ 7.32-7.14 (5H, m), 4.32 (1H, d, J= 0.8 Hz), 3.78

(1H, br s), 3.32 (2H, s), 2.80-2.71 (2H, m), 2.60 (2H, t, J= 0.8 Hz), 1.83-1.81 (1H, m), 1.45 (9H, s), 1.39 (9H, s).

Step 4: (R)-6-Amino-7-phenylheptanoic acid. TFA (2 mL) was added to *tert*-butyl (*R*)-6-((*tert*-butoxycarbonyl)amino)-7-phenylheptanoate (457 mg, 1.21 mmol) in DCM (2 mL) at r.t. with stirring. After 1.5 h the reaction mixture was concentrated under reduced pressure to afford a yellow oil. The oil was dissolved in 4M HCl in dioxane (10 mL) and stirred at r.t. for 4 h. The reaction mixture was concentrated under reduced pressure and dissolved in 4M HCl in dioxane (10 mL). After 6 h the reaction mixture was concentrated under reduced pressure and used without further purification in the next step.

Step 5: (R)-7-Benzylazepan-2-one. EDC (348 mg, 1.82 mmol) and HOPO (201 mg, 1.82 mmol) were added to a solution of (*R*)-6-amino-7-phenylheptanoic acid (1.21 mmol) and triethylamine (1.01 mL, 7.26 mmol) in DMF (13 mL) at r.t. with stirring. After 54.5 h the reaction mixture was transferred to a separating funnel and diluted with DCM. The reaction mixture was washed sequentially with 1 M HCl (aq), NaHCO₃ (saturated aqueous solution) and brine. The organics were dried (MgSO₄), filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (gradient elution 50-70% EtOAc/*iso*-hexane) to afford the *title compound*. ¹H NMR (400 MHz, CDCl₃): δ 7.34-7.17 (5H, m), 5.54 (1H, brs), 3.68-3.55 (1H, m), 2.87-2.72 (2H, m), 2.51-2.38 (2H, m), 1.98-1.81 (3H, m), 1.61-1.32 (3H, m).

Step 6: (R)-2-Benzylazepane. Lithium aluminium hydride (0.59 mL, 0.59 mmol, 1 M solution in THF) was added dropwise to an ice-cooled solution of (*R*)-7-benzylazepan-2-one (60 mg, 0.30 mmol) in THF (2 mL). The reaction mixture was warmed to r.t. and heated at reflux for 3 h. The reaction mixture was cooled to r.t., followed by 0 °C and cautiously quenched with water. The THF was removed under reduced pressure. The mixture was diluted with water and EtOAc. The layers were separated and the organic extract dried (MgSO₄), filtered and

concentrated under reduced pressure. The resultant oil was purified by SCX cartridge. The sample was loaded in DCM and eluted with 3 column volumes of DCM, 3 column volumes of methanol and 3 column volumes 7N NH₃ in MeOH/DCM (1:9). The basic fractions were combined and concentrated under reduced pressure to afford the *title compound*. Used without further purification in the next step.

Step 7: (R)-4-(2-(2-benzylazepan-1-yl)-6-((4-methoxybenzyl)oxy)pyridin-4-yl)morpholine A mixture of 4-(2-chloro-6-((4-methoxybenzyl)oxy)pyridin-4-yl)morpholine (64 mg, 0.19 mmol), (R)-2-benzylazepane (40 mg, 0.21 mmol), NaOtBu (20 mg, 0.021 mmol), RuPhos (4 mg, 0.01 mmol) and RuPhos Pd G1 catalyst (methyl t-butyl ether adduct, 8 mg, 0.01 mmol) was placed in a tube and sparged with N₂. Anhydrous dioxane (2.5 mL) was added, the tube sealed, and stirring commenced at 85 °C for 16 h. The reaction was cooled to r.t. and filtered through Celite, washing with DCM, and the reaction concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography (gradient elution, 10-100% Et₂O/*iso*-hexane) to afford the *title compound* as a colourless oil (31 mg, 33%).

¹H NMR (400 MHz, CDCl₃): δ 7.39 (2H, m), 7.54-7.15 (5H, m), 6.91-6.87 (2H, m), 5.57 (1H, d, J=1.8Hz), 5.48 (1H, d, J=1.8Hz), 5.31 (1H, dd, J=12.2, 18.0 Hz), 3.82-3.76 (7H, m), 3.22-3.17 (4H, m), 3.00-2.89 (2H, m), 2.68 (1H, dd, J=8.6, 12.9 Hz), 1.99-1.90 (1H, m), 1.81-1.55 (5H, m), 1.46-1.36 (1H, m), 1.30-1.09 (3H, m).

Step 8: (R)-6-(2-Benzylazepan-1-yl)-4-morpholinopyridin-2(1H)-one (55). Following **Method E** from (R)-4-(2-(2-benzylazepan-1-yl)-6-((4-methoxybenzyl)oxy)pyridin-4-yl)morpholine (31 mg, 0.06 mmol). Purification by silica gel column chromatography (gradient elution, 0-20% MeOH/EtOAc) yielded the *title compound* as an off-white solid (11 mg, 0.03 mmol, 50%).

LCMS (ES⁺) 368 (M+H)⁺, RT 2.91 min (Analytical Method A); RT 2.02 min (Analytical Method SFC1, YMC AMYLOSE-C, 35/65 IPA + 0.1% DEAIISO/CO₂); ¹H NMR (400 MHz,

CDCl₃): δ 7.31 - 7.21 (3H, m), 7.16 - 7.12 (2H, m), 5.17 (1H, d, J=2.0 Hz), 4.89 (1H, d, J=2.0 Hz), 3.80 - 3.75 (6H, m), 3.40 - 3.35 (1H, m), 3.22 - 3.18 (4H, m), 2.99 (1H, dd, J=11.7, 16.0 Hz), 2.87 - 2.76 (2H, m), 2.15 - 2.05 (1H, m), 1.84 - 1.70 (2H, m), 1.57 - 1.45 (2H, m), 1.31 - 1.13 (2H, m). HRMS (ESI⁺) (M + H)⁺: calcd for C₂₂H₃₀N₃O₂, 368.2338; found, 368.2346.

(R)-2-(2-Benzylazepan-1-yl)-6-morpholinopyrimidin-4(3H)-one (**62**). Step 1: *(R)*-4-(2-(2-Benzylazepan-1-yl)-6-((4-methoxybenzyl)oxy)pyrimidin-4-yl)morpholine. 2-(*R*)-

Benzylazepane (169 mg, 0.89 mmol) was added to a solution of 4-(2-chloro-6-((4-methoxybenzyl)oxy)pyrimidin-4-yl)morpholine (200 mg, 0.60 mmol) and DIPEA (156 μL, 0.89 mmol) in DMF (1.6 mL). The reaction mixture was heated at 100 °C. After 66.5 h the reaction mixture was cooled to r.t. and diluted with DCM and water. The layers were separated, and the organic extracts dried (phase separator). The crude mixture was purified by silica gel column chromatography (gradient elution, 10-80% EtOAc/*iso*-hexane) to afford the *title compound*. ¹H NMR (400 MHz, CDCl₃): δ 7.35 (2H, d, J= 9.3 Hz), 7.28-7.35 (5H, m), 6.88 (2H, d, J=9.3 Hz), 5.37-5.23 (3H, m), 4.83-4.66 (1H, m), 4.29-4.18 (1H, m), 3.83-3.71 (8H, m), 3.55-3.44 (4H, m), 3.02-2.76 (2H, m), 2.69-2.57 (1H, m), 1.96-1.86 (1H, m), 1.78-1.11 (6H, m).

Step 2: *(R)*-2-(2-Benzylazepan-1-yl)-6-morpholinopyrimidin-4(3H)-one (**62**). TFA (1 mL) was added to a solution of *(R)*-4-(2-(2-benzylazepan-1-yl)-6-((4-methoxybenzyl)oxy)pyrimidin-4-yl)morpholine (144 mg, 0.295 mmol) in DCM (1 mL) at r.t. with stirring. After 5 h the reaction mixture was concentrated under reduced pressure. The crude residue was dissolved in DCM, washed with saturated NaHCO₃ aqueous solution, dried (phase separator) and concentrated under reduced pressure. The resultant oil was dissolved in DMSO and purified by reverse phase preparative HPLC. The resultant solid was dissolved in DCM and washed with saturated aqueous solution of NaHCO₃. The organic extracts were dried (phase separator) and concentrated under reduced pressure followed by freeze drying from MeCN:water to afford the

title compound. LCMS (ES⁺) 369 (M+H)⁺, RT 3.26 min (Analytical Method A), ¹H NMR (400 MHz, CDCl₃): δ 7.25 - 7.19 (3H, m), 7.16 - 7.11 (2H, m), 4.90 (1H, s), 4.71 (1H, br s), 3.75 - 3.60 (5H, m), 3.53 - 3.47 (4H, m), 2.92 - 2.82 (2H, m), 2.78 - 2.70 (1H, m), 2.08 - 1.98 (1H, m), 1.82 - 1.75 (3H, m), 1.49 - 1.39 (2H, m), 1.28 - 1.12 (2H, m), NH not observed.

2-((R)-2-Benzylazepan-1-yl)-6-((R)-2-methylmorpholino)pyrimidin-4(3H)-one (63). *Step 1: (R)-4-(2-((R)-2-Benzylazepan-1-yl)-6-((4-methoxybenzyl)oxy)pyrimidin-4-yl)-2-methylmorpholine*. (R)-4-(6-((4-Methoxybenzyl)oxy)-2-(methylsulfonyl)pyrimidin-4-yl)-2-methylmorpholine (128 mg, 0.33 mmol), (R)-2-benzylazepane (40 mg, 0.21 mmol) and TBAF hydrate (131 mg, 0.50 mmol) were suspended in DMSO (0.7 mL). The reaction was heated at 80 °C for 6 days. After 42 h at 80 °C, further TBAF hydrate (50 mg, 0.19 mmol) was added, and after 68 h at 80 °C DIPEA (120 μL, 0.69 mmol) was added to the reaction. On completion of the reaction, and after cooling to r.t., water (2 mL) was added, whereupon a gum formed. The liquid supernatant was decanted off and the gum dissolved in a 1:1 mixture of DCM and water. The biphasic mixture was separated by passage through a hydrophobic frit; the DCM layer was concentrated to give the *title compound*, which was used without further purification.

Step 2: 2-((R)-2-Benzylazepan-1-yl)-6-((R)-2-methylmorpholino)pyrimidin-4(3H)-one (63). Following **Method H** from (R)-4-(2-((R)-2-benzylazepan-1-yl)-6-((4-methoxybenzyl)oxy)pyrimidin-4-yl)-2-methylmorpholine. The reaction was stirred at r.t. for 4.5 h. The reaction was quenched with MeOH and concentrated. Purification by reverse phase preparative HPLC was followed by freeze-drying gave the *title compound*. LCMS (ES⁺) 383 (M+H)⁺, RT 3.52 min (Analytical Method A); ¹H NMR (400 MHz, CDCl₃): δ 7.29 - 7.12 (5H, m), 4.90 (1H, s), 4.70 (1H, br s), 4.08 (1H, br s), 3.98 - 3.91 (2H, m), 3.67 - 3.54 (3H, m), 3.00 - 2.86 (3H, m), 2.75 - 2.68 (1H, m), 2.61 (1H, dd, J=10.5, 13.0 Hz), 2.07 - 2.00 (1H, m), 1.83

- 1.73 (4H, m), 1.48 - 1.41 (2H, m), 1.31 - 1.12 (5H, m). HRMS (ESI⁺) (M + H)⁺: calcd for C₂₂H₃₁N₄O₂, 383.2447; found, 383.2447.

The compounds listed below were synthesised using the same synthetic route as described for compound **63**, starting from commercially available amines and either 4-(6-((4-methoxybenzyl)oxy)-2-(methylthio)pyrimidin-4-yl)morpholine or (R)-4-(6-((4-methoxybenzyl)oxy)-2-(methylsulfonyl)pyrimidin-4-yl)-2-methylmorpholine. Methylsulfonyl displacement conditions **Method F** or **Method G** were used, followed by **Method H** to remove the PMB protecting group. The isomers were isolated after purification by Chiral SFC unless indicated (*), in which cases the amine was used chirally pure in the synthesis.

2-((1R,2S,5S)-2-Benzyl-3-azabicyclo[3.1.0]hexan-3-yl)-6-morpholinopyrimidin-4(3H)-one (64). Method G. LCMS (ES⁺) 353 (M+H)⁺, RT 3.31 min (*Analytical Method A*), RT 2.71 min (*Analytical Method SFC1*, YMC AMYLOSE-C 40/60 IPA [0.1% DEAIISO]/CO₂); ¹H NMR (400 MHz, CDCl₃): δ 7.32 - 7.26 (2H, m), 7.25 - 7.16 (3H, m), 4.94 (1H, s), 4.49 (1H, dd, J=3.0, 7.8 Hz), 3.75 (4H, dd, J=4.9, 4.9 Hz), 3.59 - 3.48 (5H, m), 3.26 (1H, dd, J=3.0, 10.1 Hz), 3.12 - 3.06 (1H, m), 2.80 (1H, dd, J=8.5, 13.0 Hz), 1.50 - 1.43 (2H, m), 0.68 - 0.61 (1H, m), 0.18 - 0.13 (1H, m), NH not observed. HRMS (ESI⁺) (M + H)⁺: calcd for C₂₀H₂₅N₄O₂, 353.1977; found, 353.1976.

2-((1R,2S,5S)-2-Benzyl-3-azabicyclo[3.1.0]hexan-3-yl)-6-((R)-2-methylmorpholino)pyrimidin-4(3H)-one (65). Method G. LCMS (ES⁺) 367 (M+H)⁺, RT 3.45 min (*Analytical Method A*), RT 2.48 min (*Analytical Method SFC1*, YMC AMYLOSE-C 35/65 IPA [0.1% DEAIISO]/CO₂); ¹H NMR (400 MHz, CDCl₃): δ 10.42 - 10.42 (1H, br s), 7.31 - 7.26 (2H, m), 7.25 - 7.18 (3H, m), 4.94 (1H, s), 4.52 (1H, dd, J=3.6, 8.7 Hz), 4.08 - 3.94 (3H, m), 3.68 - 3.56 (3H, m), 3.35 - 3.34 (1H, m), 3.14 (1H, d, J=12.4 Hz), 2.97 (1H, dt, J=3.1, 12.4 Hz), 2.74 (1H, dd, J=8.8, 13.2 Hz), 2.63 (1H, dd, J=10.5, 12.4 Hz), 1.61 - 1.44 (2H, m),

1.23 (3H, d, J=6.1 Hz), 0.67 - 0.60 (1H, m), 0.19 - 0.14 (1H, m). HRMS (ESI⁺) (M + H)⁺: calcd for C₂₁H₂₇N₄O₂, 367.2134; found, 367.2141.

2-((1S,2S,5R)-2-Benzyl-3-azabicyclo[3.1.0]hexan-3-yl)-6-morpholinopyrimidin-4(3H)-one (66). **Method G**. LCMS (ES⁺) 353 (M+H)⁺, RT 3.16 min (Analytical Method B), RT 8.50 min (Analytical Method SFC1, LUX CELLULOSE-4 30/70 MeOH [0.1% DEAIISO]/CO₂); ¹H NMR (400 MHz, CDCl₃): δ 7.34 - 7.21 (5H, m), 5.00 (1H, s), 4.42 - 4.36 (1H, m), 3.85 - 3.74 (6H, m), 3.64 - 3.52 (5H, m), 2.40 (1H, dd, J=10.4, 12.6 Hz), 1.74 - 1.66 (1H, m), 1.58 - 1.50 (1H, m), 0.82 - 0.75 (1H, m), 0.58 (1H, q, J=4.5 Hz), NH not observed. HRMS (ESI⁺) (M + H)⁺: calcd for C₂₀H₂₅N₄O₂, 353.1977; found, 353.1986.

2-((1S,2S,5R)-2-Benzyl-3-azabicyclo[3.1.0]hexan-3-yl)-6-((R)-2-methylmorpholino)pyrimidin-4(3H)-one (67). **Method G**. LCMS (ES⁺) 367 (M+H)⁺, RT 3.32 min (Analytical Method A), RT 7.68 min (Analytical Method SFC1, LUX CELLULOSE-4 30/70 MeOH [0.1% DEAIISO]/CO₂); ¹H NMR (400 MHz, CDCl₃): δ 10.32 - 10.32 (1H, br s), 7.32 - 7.29 (4H, m), 7.25 - 7.21 (1H, m), 5.00 (1H, s), 4.43 - 4.36 (1H, m), 4.21 (1H, d, J=11.9 Hz), 4.04 - 3.94 (2H, m), 3.89 (2H, d, J=9.5 Hz), 3.83 (1H, dd, J=3.4, 12.9 Hz), 3.70 - 3.56 (2H, m), 3.01 (1H, dt, J=3.5, 12.4 Hz), 2.67 (1H, dd, J=10.5, 13.0 Hz), 2.38 (1H, dd, J=10.6, 12.6 Hz), 1.74 - 1.66 (1H, m), 1.57 - 1.50 (1H, m), 1.22 (3H, d, J=6.3 Hz), 0.82 - 0.75 (1H, m), 0.59 (1H, q, J=4.4 Hz). HRMS (ESI⁺) (M + H)⁺: calcd for C₂₁H₂₇N₄O₂, 367.2134; found, 367.2139.

2-((2S,3R)-2-Benzyl-3-methylpyrrolidin-1-yl)-6-morpholinopyrimidin-4(3H)-one (68)

Step 1: Tert-butyl (2R,3S*)-2-benzyl-3-methylpyrrolidine-1-carboxylate*. Palladium (II) acetate (18 mg, 0.08 mmol, Dpe-phos (86 mg, 0.16 mmol) and sodium *tert*-butoxide (884 mg, 9.2 mmol) were placed in a reaction tube sealed, evacuated and re-filled with nitrogen (x3). 3-Methylpent-4-en-1-yl)carbamate (798 mg, 4.0 mmol) was dissolved in dioxane (16 mL) and degassed. The solution was added to the reaction tube followed by bromobenzene (0.25 mL,

4.8 mmol) and the reaction heated at 100 °C for 17.5 h. The reaction mixture was cooled to r.t., diluted with NH₄Cl. The reaction mixture was extracted with EtOAc (x3). The organic extracts dried (phase separator) and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (gradient elution, 2-20% EtOAc/*iso*-hexane) to afford the *title compound*. ¹H NMR (400 MHz, CDCl₃): δ 7.31-7.13 (5H, m), 3.68-3.36 (2H, m), 3.27-2.98 (2H, m), 2.79-2.57 (1H, m), 2.11-1.76 (2H, m), 1.61-1.46 (9H, m), 0.95-0.81 (4H, m), rotamers observed.

Step 2: (2R,3S*)-2-Benzyl-3-methylpyrrolidine. Tert-butyl (2R*,3S*)-2-benzyl-3-methylpyrrolidine-1-carboxylate* (785 mg, 2.85 mmol) was dissolved in 4 M HCl in dioxane (7.1 mL) at r.t. with stirring. After 2 h the reaction mixture was concentrated under reduced pressure. The residue was dissolved in DCM and washed with saturated NaHCO₃ solution. The organic extract was dried (phase separator) and concentrated under reduced pressure to afford the *title compound*. ¹H NMR (400 MHz, CDCl₃): δ 7.32 - 7.16 (5H, m), 3.00 - 2.79 (3H, m), 2.77 - 2.68 (1H, m), 2.59 (1H, dd, J=8.5, 13.3 Hz), 2.08 - 1.96 (1H, m), 1.76 - 1.66 (1H, m), 1.42 - 1.31 (1H, m), 1.00 (3H, d, J=6.6 Hz), NH not observed.

Step 3: 4-(6-((4-Methoxybenzyl)oxy)-2-(methylthio)pyrimidin-4-yl)morpholine. NaH (3.43 g, 85.8 mmol, 60% dispersion in mineral oil) was suspended in DMF (70 mL) and cooled to 0 °C. 4-methoxy benzyl alcohol (6.52 g, 47.2 mmol) in DMF (30 mL) was added dropwise to the suspension over 15 minutes. After stirring at 0 °C for 15 min a solution of 4-(6-chloro-2-(methylthio)pyrimidin-4-yl)morpholine (10.54 g, 42.9 mmol, prepared according to WO 2008/125839) in DMF (90 mL) was added. The reaction was allowed to warm to r.t. and stirred for 4.5 h. The reaction was cooled to 0 °C and cautiously quenched with water. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in EtOAc and washed with brine and water. The organic extracts were dried (MgSO₄), filtered and

concentrated under reduced pressure. Purified by silica gel column chromatography (gradient elution, 10-50% EtOAc/*iso*-hexane) to afford the *title compound*. LCMS (ES⁺) 348 (M+H)⁺, RT 1.69 min (Analytical Method F); ¹H NMR (400 MHz, CDCl₃): δ 7.37-7.33 (2H, m), 6.91-6.87 (2H, m), 5.53 (1H, s), 5.30 (2H, s), 3.80 (3H, s), 3.76-3.72 (4H, m), 3.55-3.51 (4H, m), 2.51 (3H, s).

Step 4: 4-(6-((4-Methoxybenzyl)oxy)-2-(methylsulfonyl)pyrimidin-4-yl)morpholine. *m*-CPBA (759 mg, 4.4 mmol, 50-55 wt.% in H₂O) was added portionwise to a solution of 4-(6-((4-methoxybenzyl)oxy)-2-(methylthio)pyrimidin-4-yl)morpholine (695 mg, 2.0 mmol) in DCM (20 mL) at r.t. After 2 h the reaction was filtered, washing the precipitate with DCM. The filtrate was washed successively with saturated NaHCO₃ (aqueous solution), brine, dried (phase separator) and concentrated under reduced pressure to afford the product, which was used without further purification in the next step. ¹H NMR (400 MHz, CDCl₃): δ 7.38 - 7.35 (2H, m), 6.91 - 6.88 (2H, m), 5.88 (1H, s), 5.36 (2H, s), 3.81 (3H, s), 3.78 - 3.74 (4H, m), 3.63 - 3.57 (4H, m), 3.26 (3H, s).

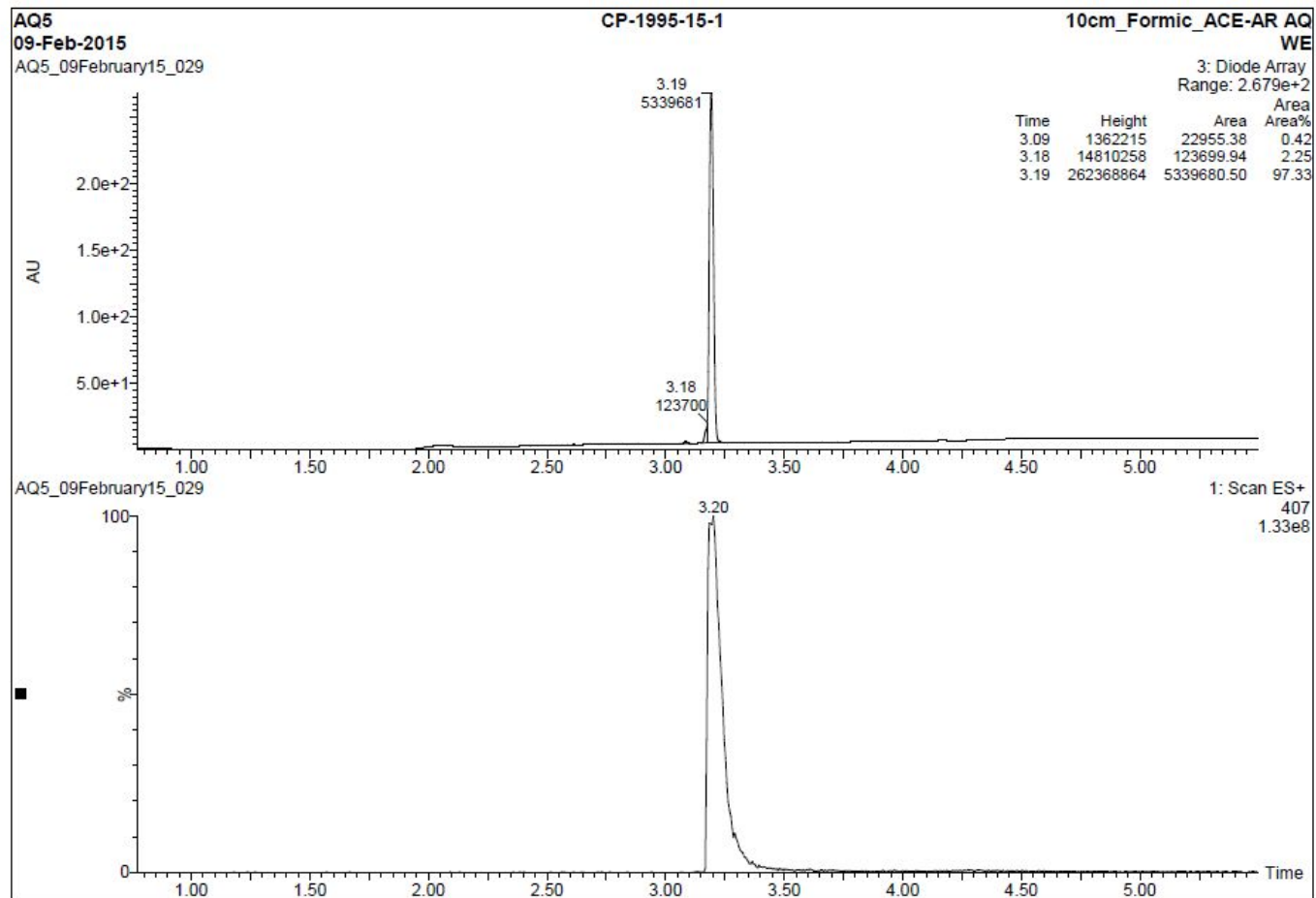
Step 5: 4-(2-((2R,3S*)-2-benzyl-3-methylpyrrolidin-1-yl)-6-((4-methoxybenzyl)oxy)pyrimidin-4-yl)morpholine.* A suspension of 4-(6-((4-methoxybenzyl)oxy)-2-(methylsulfonyl)pyrimidin-4-yl)morpholine (180 mg, 0.48 mmol), (2*R**,3*S**)-2-benzyl-3-methylpyrrolidine (90 mg, 0.51 mmol), DIPEA (166 μL, 0.95 mmol) and TBAF hydrate (249 mg, 0.95 mmol) in DMSO (0.95 mL) was stirred at 80 °C for 17 h. After cooling to RT, the mixture was dissolved in 20 mL 1:1 DCM:H₂O. The layers were separated, the organic layer dried by passage through a hydrophobic frit and concentrated. The residue was used without further purification in the next step.

*Step 6: 2-((2*S*,3*R*)-2-Benzyl-3-methylpyrrolidin-1-yl)-6-morpholinopyrimidin-4(3*H*)-one (68).* Following **method H** from 4-(2-((2*R**,3*S**)-2-benzyl-3-methylpyrrolidin-1-yl)-6-((4-

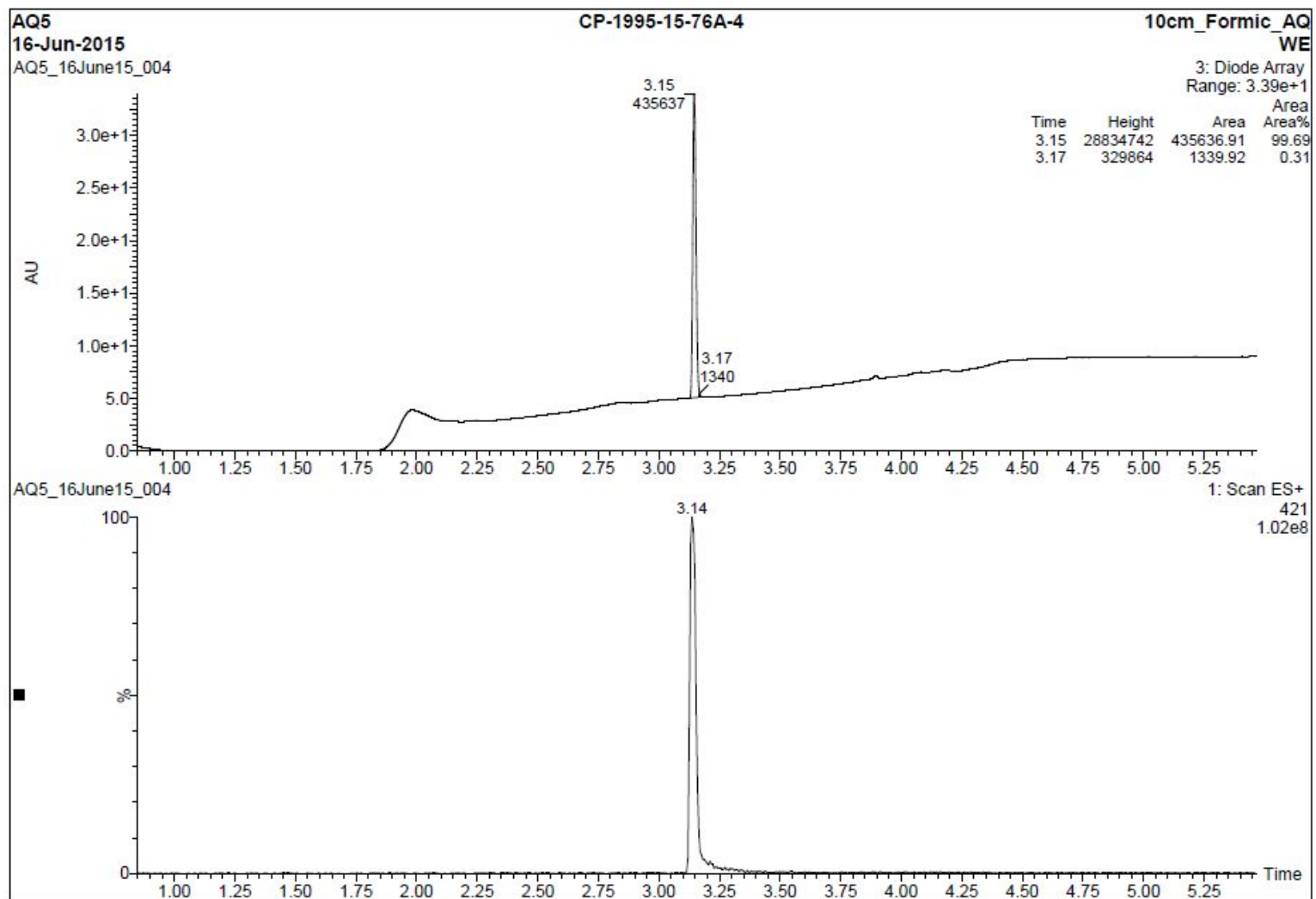
methoxybenzyl)oxy)pyrimidin-4-yl)morpholine (crude material from previous step), TFA (1.9 mL) and DCM (1.9 mL). Purification by silica gel chromatography (gradient elution, 2-20% MeOH/EtOAc), followed by chiral SFC, gave the *title compound* (23 mg, 13% over two steps) as a white solid, plus its enantiomer. Absolute configuration was assigned following determination of biological activity, the (2*S*) isomer being the more active. LCMS (ES⁺) 355 (M+H)⁺, RT 3.18 min (Analytical Method B), RT 2.71 min (Analytical Method SFC4, YMC AMYLOSE-C + 0.1% DEAIISO 25% IPA; ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.22 (1H, br s), 7.31 (2H, dd, J=7.4, 7.4 Hz), 7.20 (3H, dd, J=7.0, 13.2 Hz), 4.81 (1H, s), 3.93 (1H, br d, J=7.9 Hz), 3.67 - 3.62 (4H, m), 3.48 - 3.42 (6H, m), 3.08 (1H, dd, J=2.6, 13.1 Hz), 2.68 (1H, dd, J=9.2, 12.9 Hz), 2.08 - 1.94 (2H, m), 1.51 - 1.44 (1H, m), 0.80 (3H, d, J=6.8 Hz). HRMS (ESI⁺) (M + H)⁺: calcd for C₂₀H₂₇N₄O₂, 355.2134; found, 355.2133.

HPLC traces for final compounds

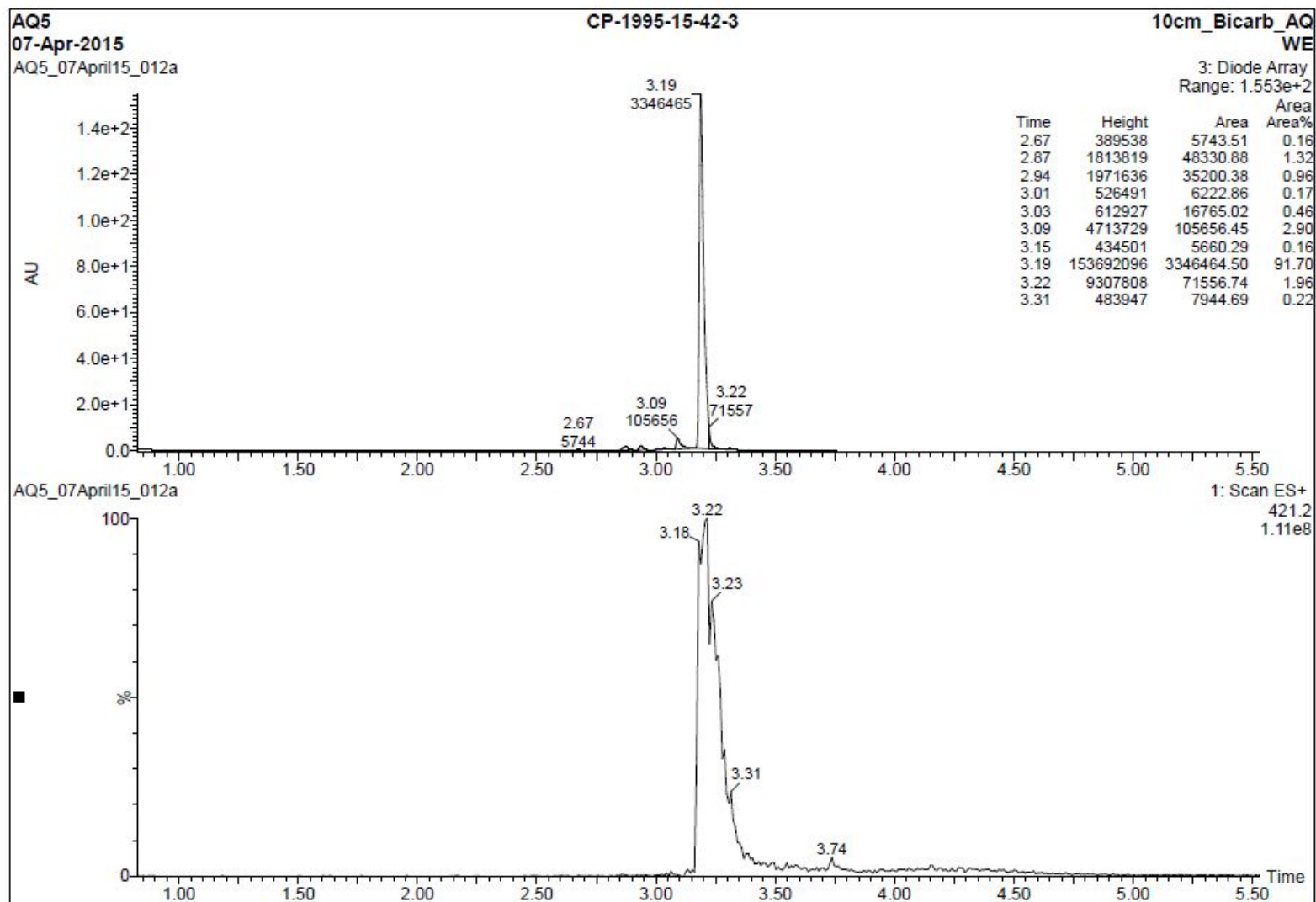
6-(7-Methoxy-9H-thioxanthen-4-yl)-4-morpholino-1H-pyridin-2-one (7)



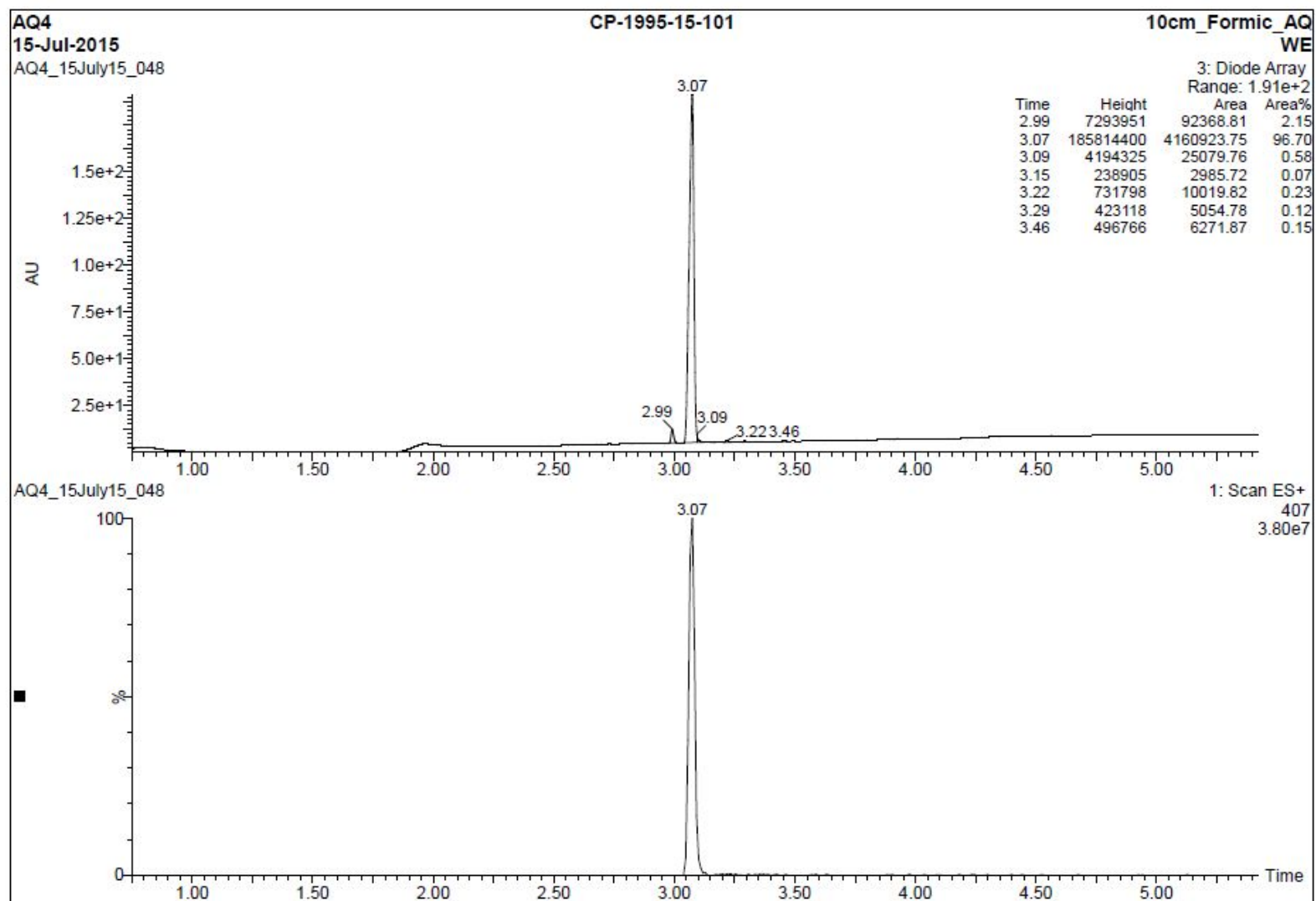
(R)-6-(7-Methoxy-9H-thioxanthen-4-yl)-4-(2-methylmorpholino)pyridin-2(1H)-one (8)



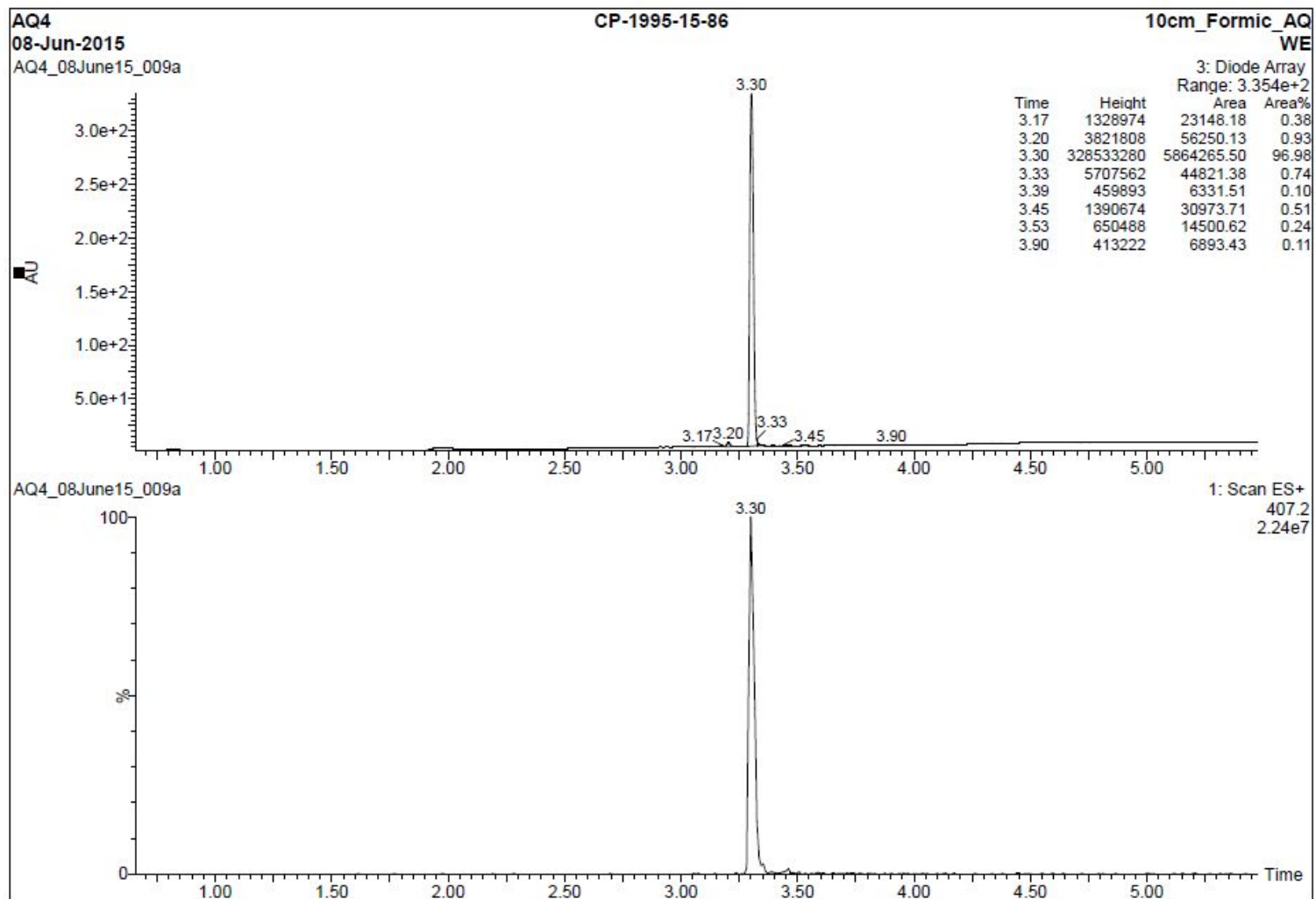
6-(7-Methoxy-9H-thioxanthen-4-yl)-1-methyl-4-morpholino-pyridin-2-one (11)



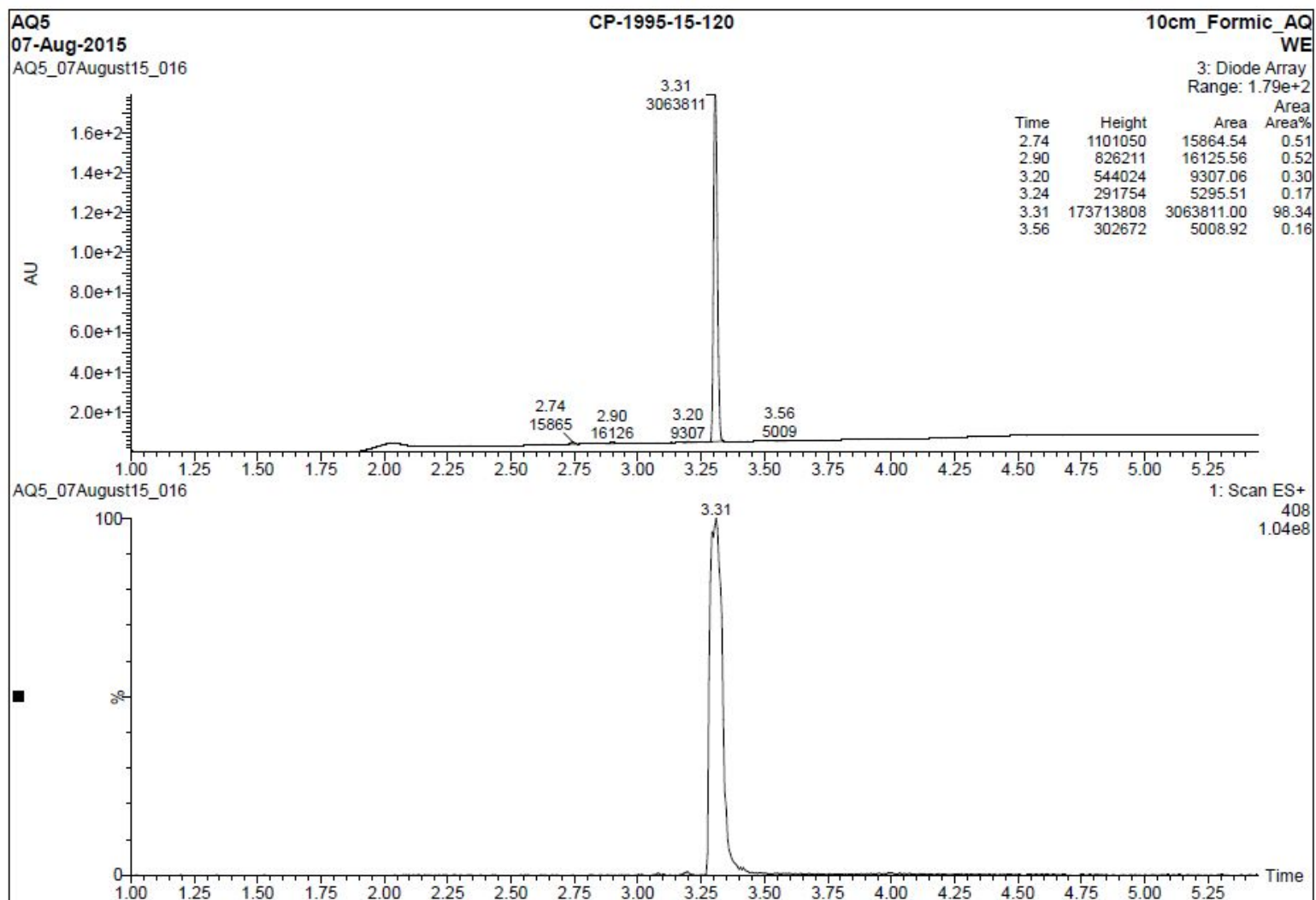
2-(7-Methoxy-9H-thioxanthen-4-yl)-6-morpholino-pyridin-4-ol (16)



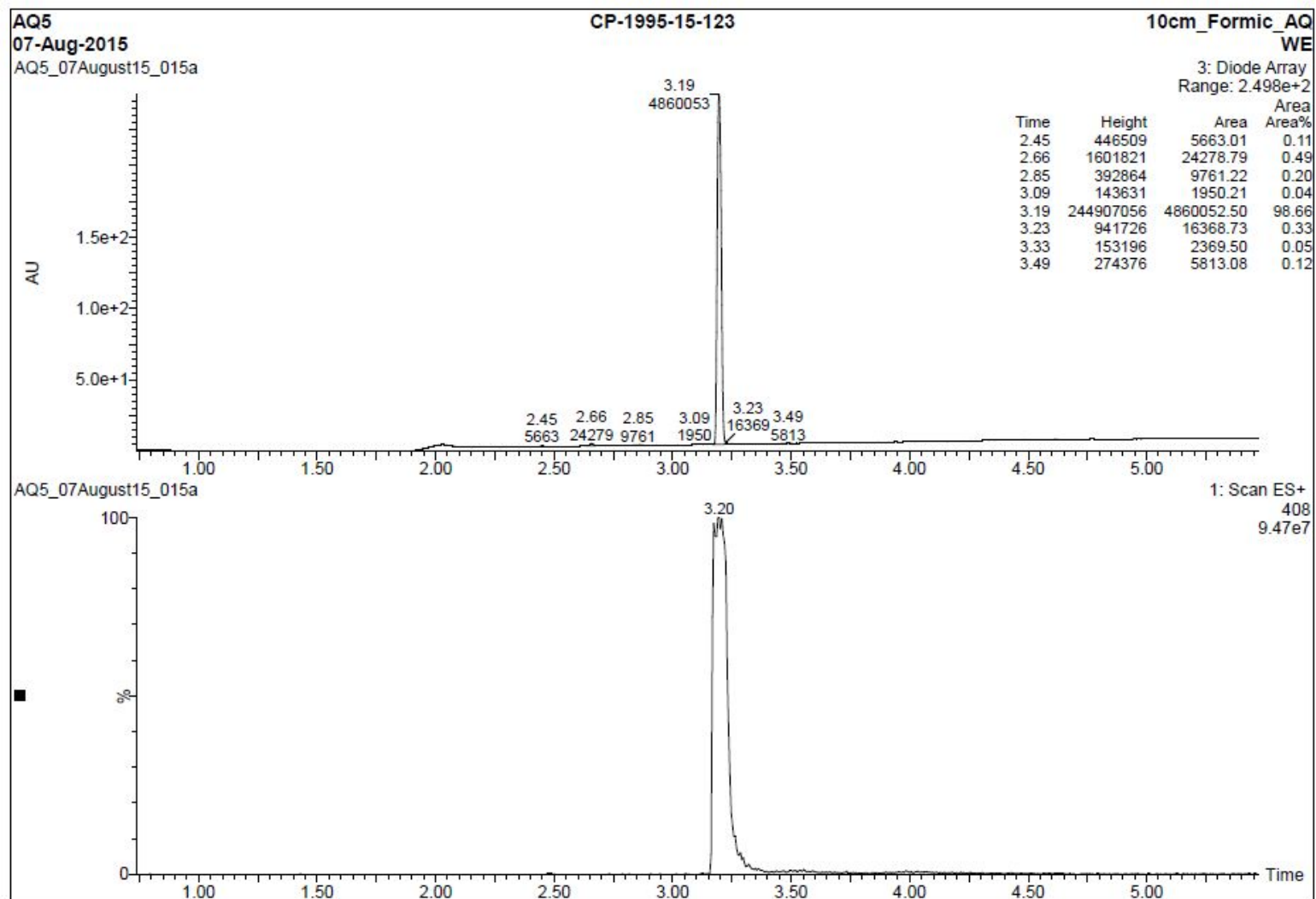
4-(7-Methoxy-9H-thioxanthen-4-yl)-6-morpholino-1H-pyridin-2-one (19)



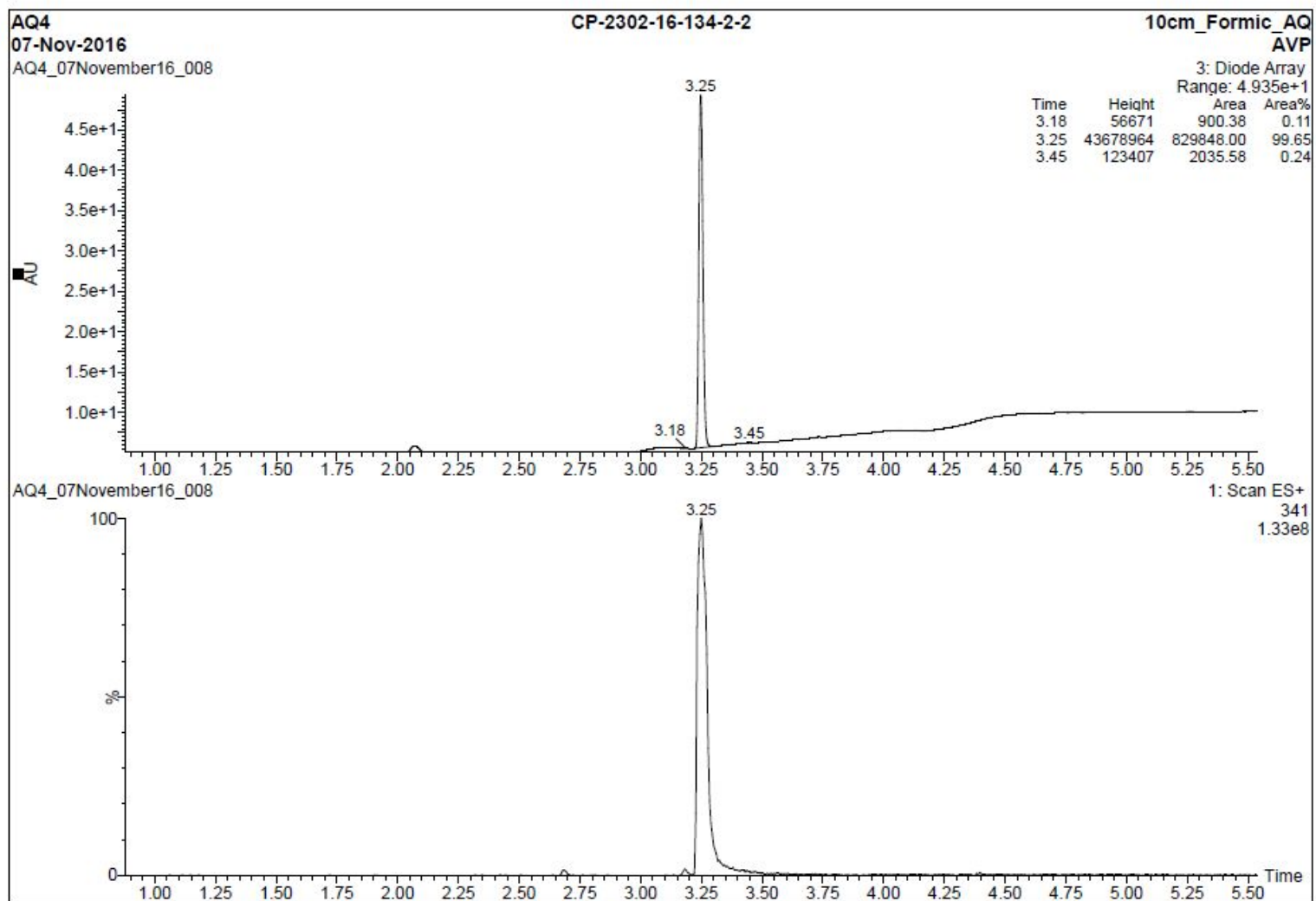
2-(7-Methoxy-9H-thioxanthen-4-yl)-6-morpholino-pyrimidin-4-ol (25)



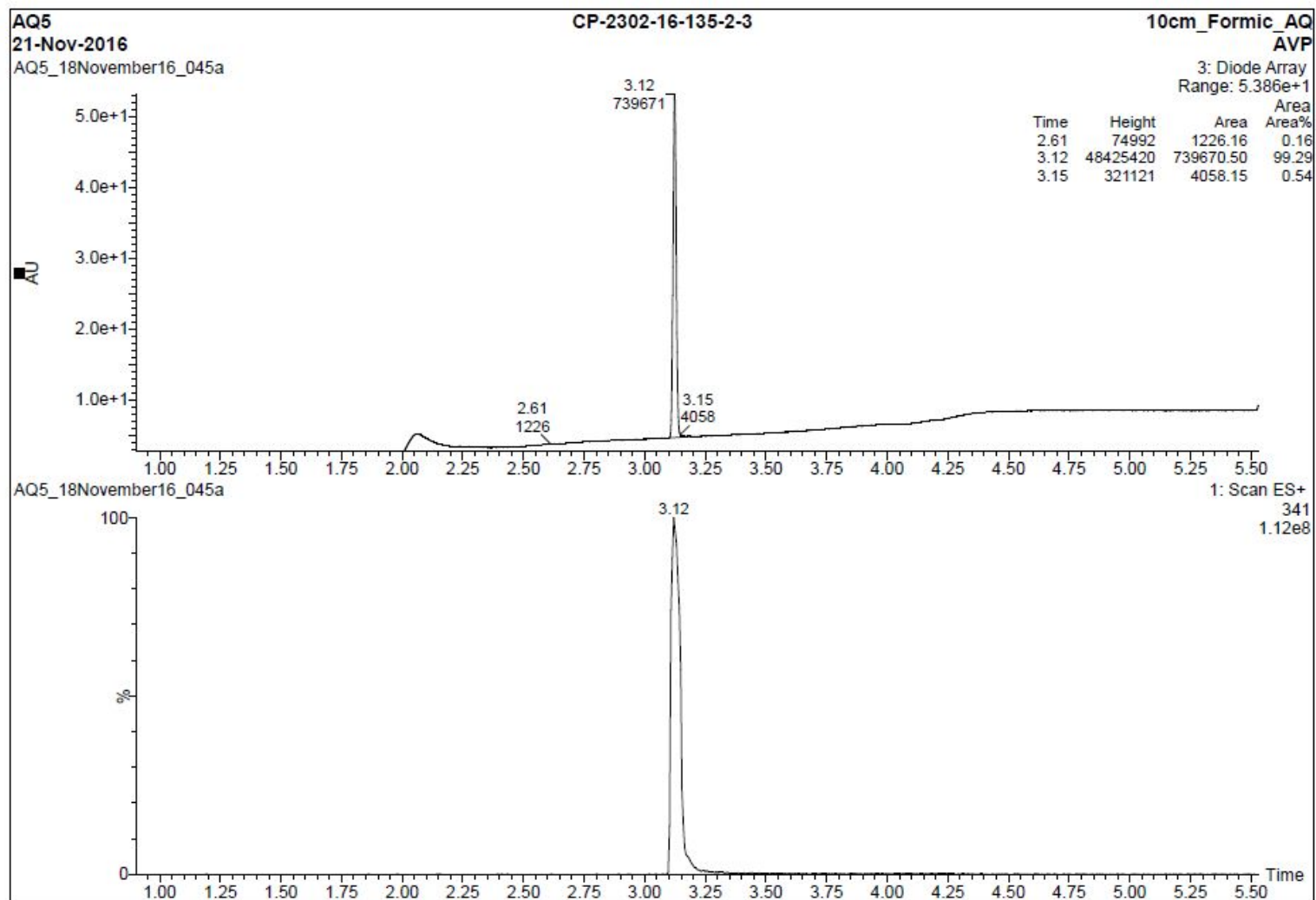
6-(7-Methoxy-9H-thioxanthen-4-yl)-2-morpholino-pyrimidin-4-ol (26)



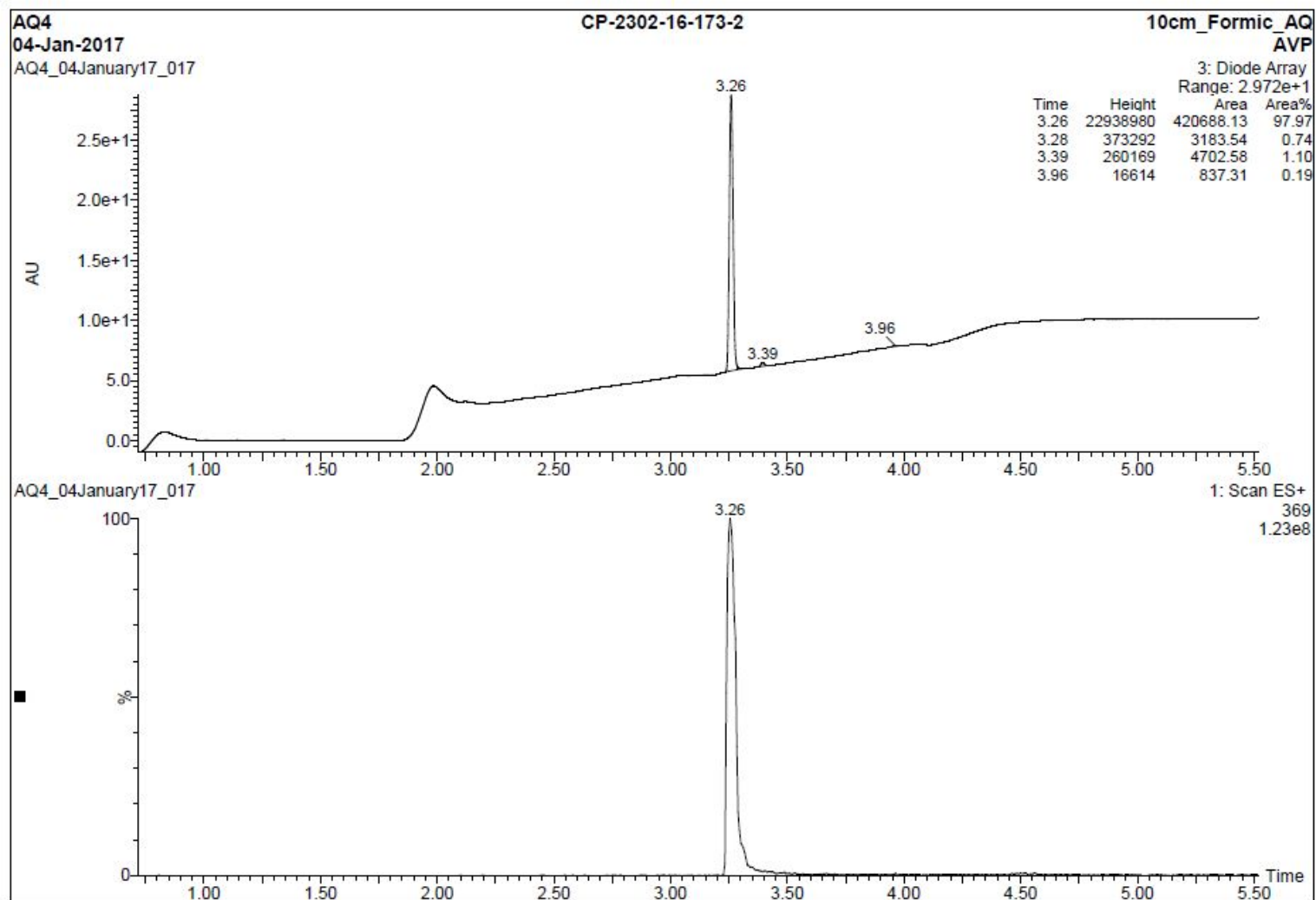
(R)-6-(2-Benzylpyrrolidin-1-yl)-2-morpholinopyrimidin-4-ol (**30**)



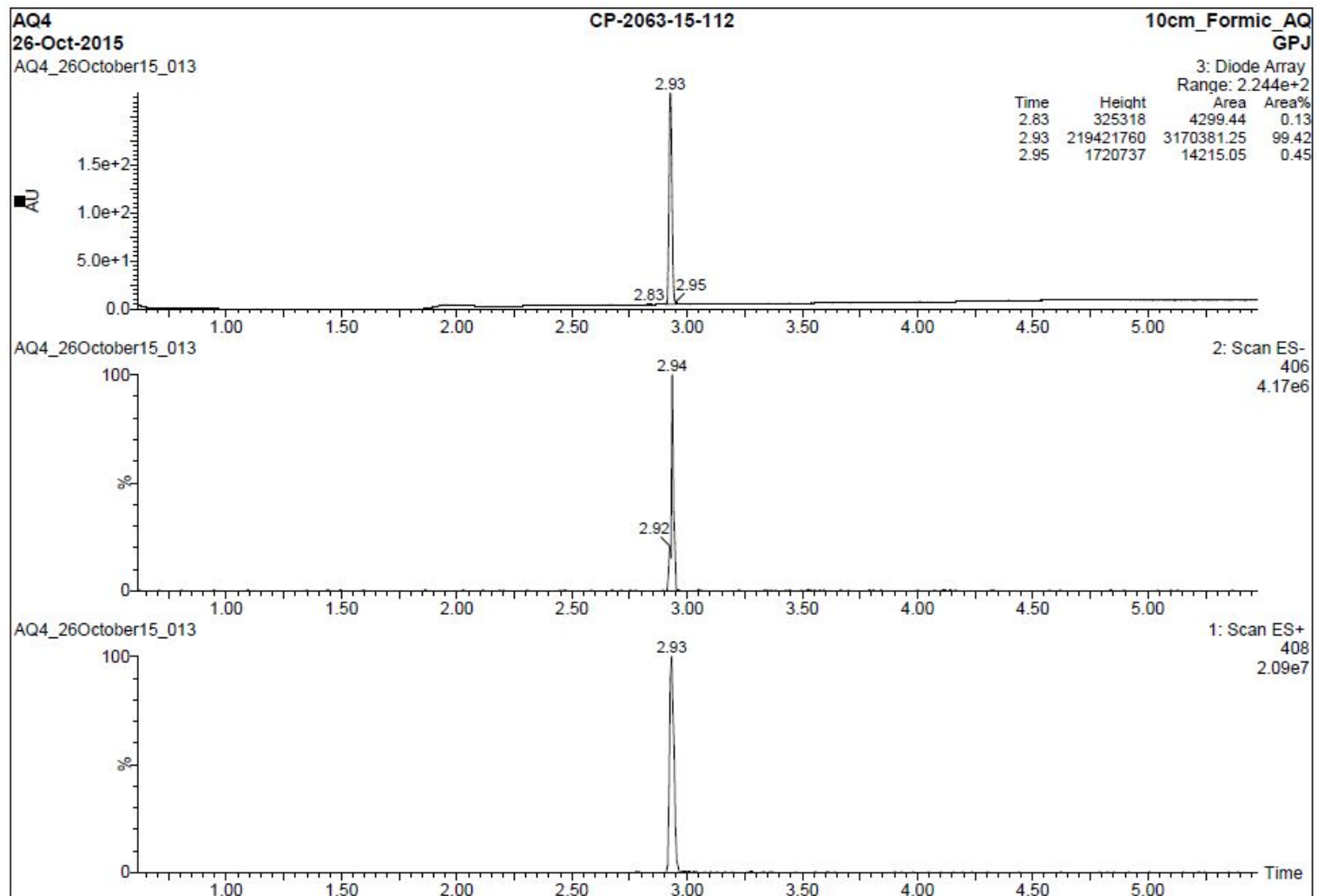
(R)-2-(2-Benzylpyrrolidin-1-yl)-6-morpholinopyrimidin-4-ol (**31**)



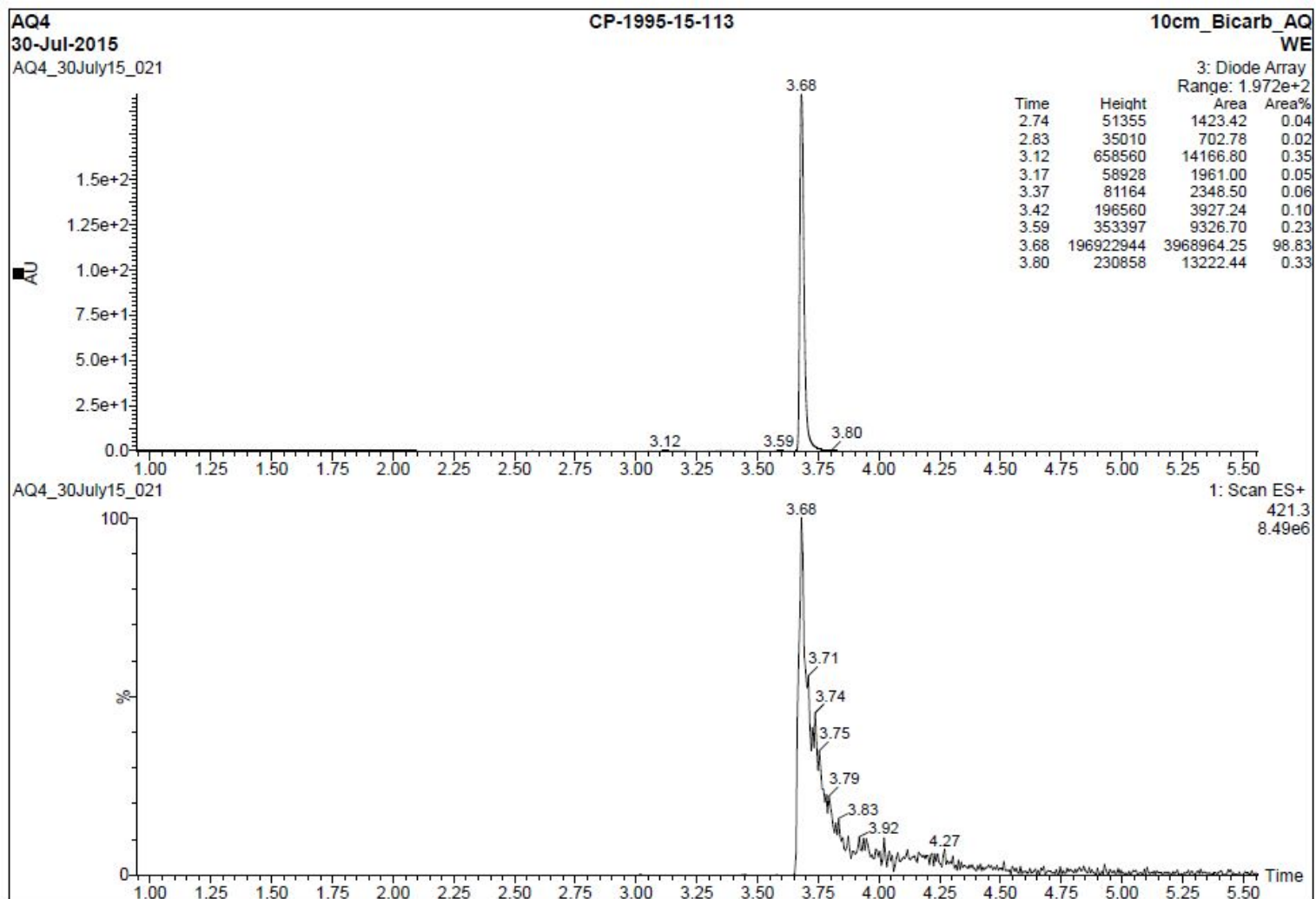
(R)-2-(2-Benzylazepan-1-yl)-6-morpholinopyrimidin-4(3H)-one (32)



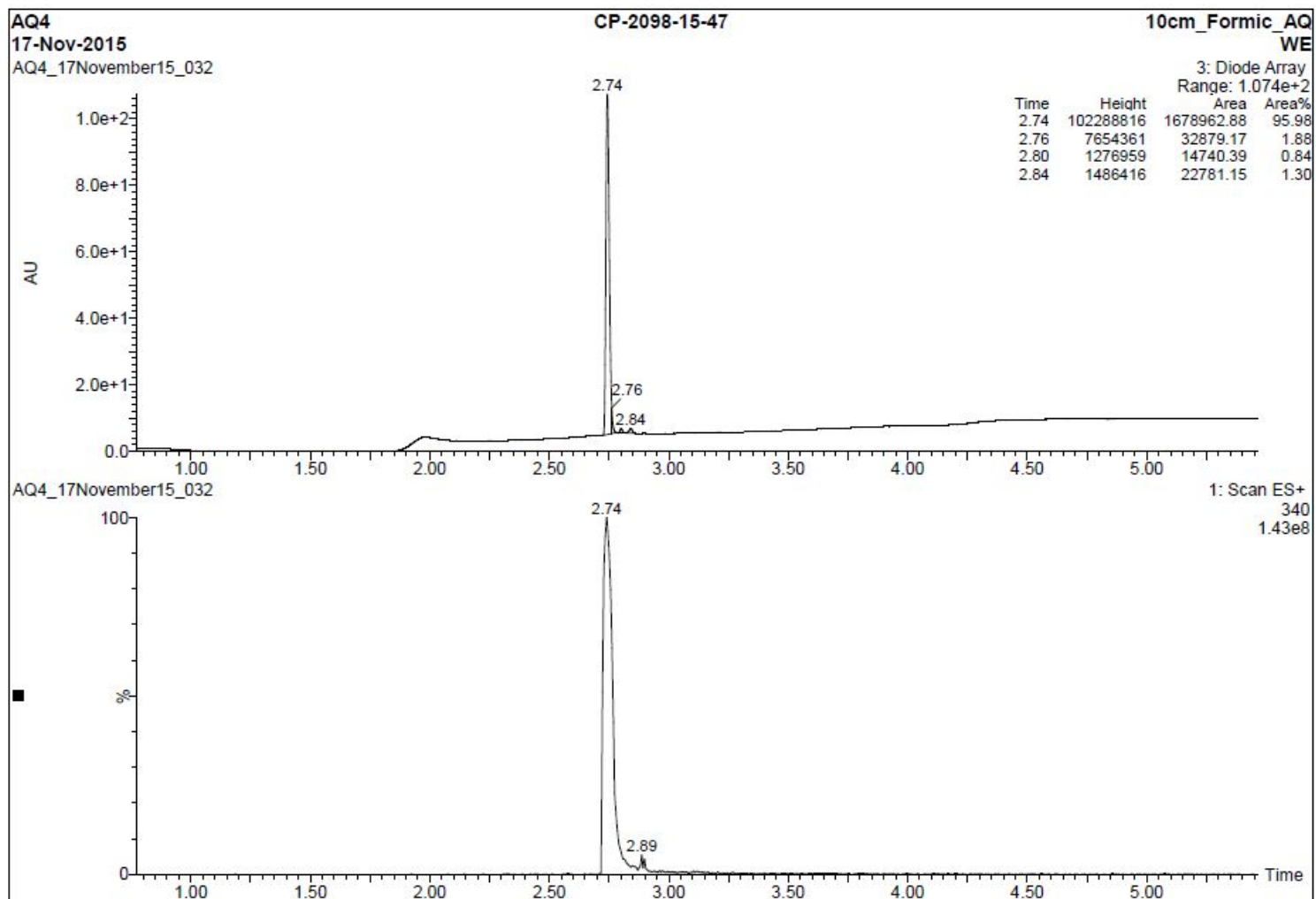
4-(7-Methoxy-9H-thioxanthen-4-yl)-6-morpholinopyrimidin-2-ol (34)



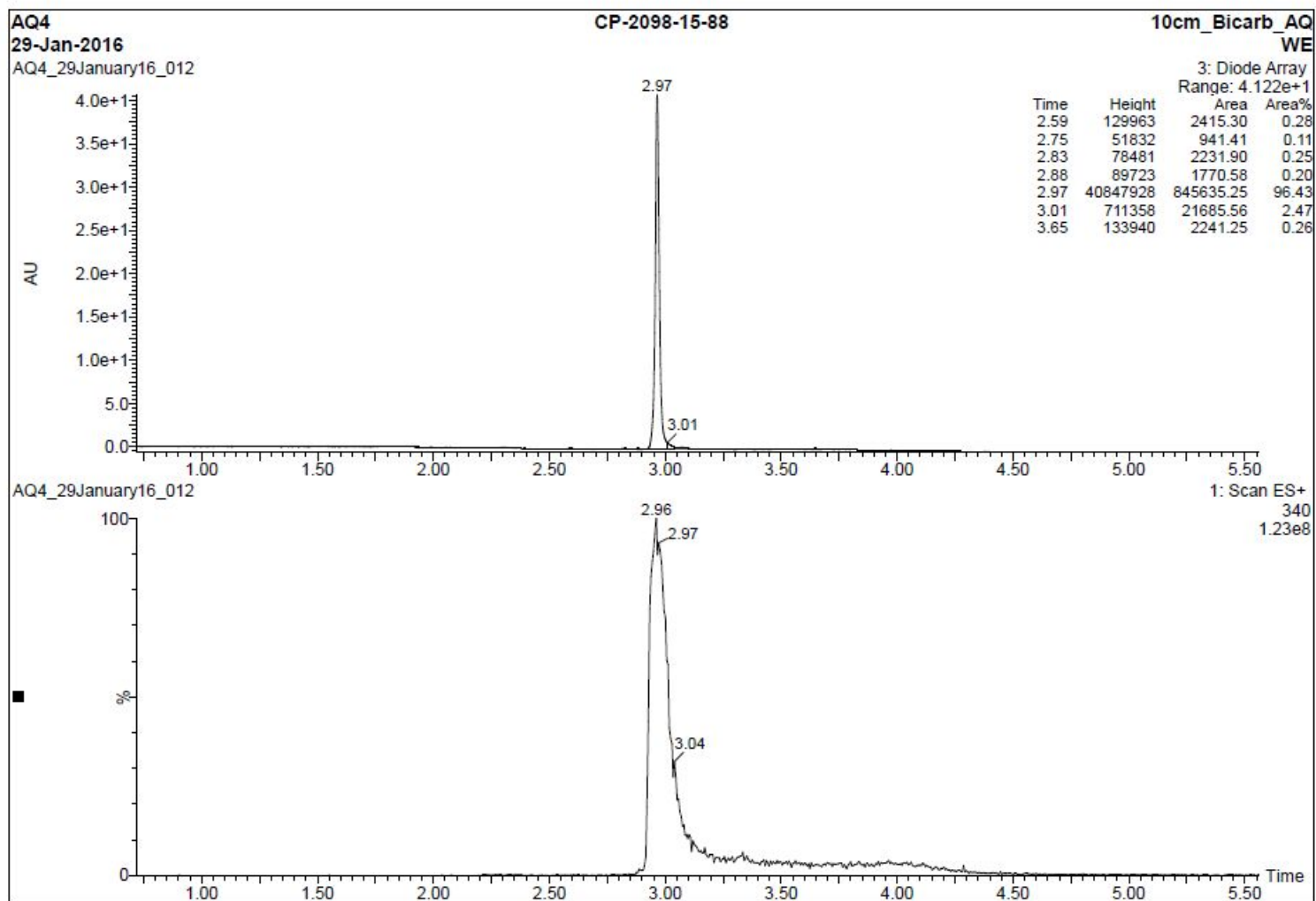
4-[2-Methoxy-6-(7-methoxy-9H-thioxanthen-4-yl)-4-pyridyl]morpholine (40)



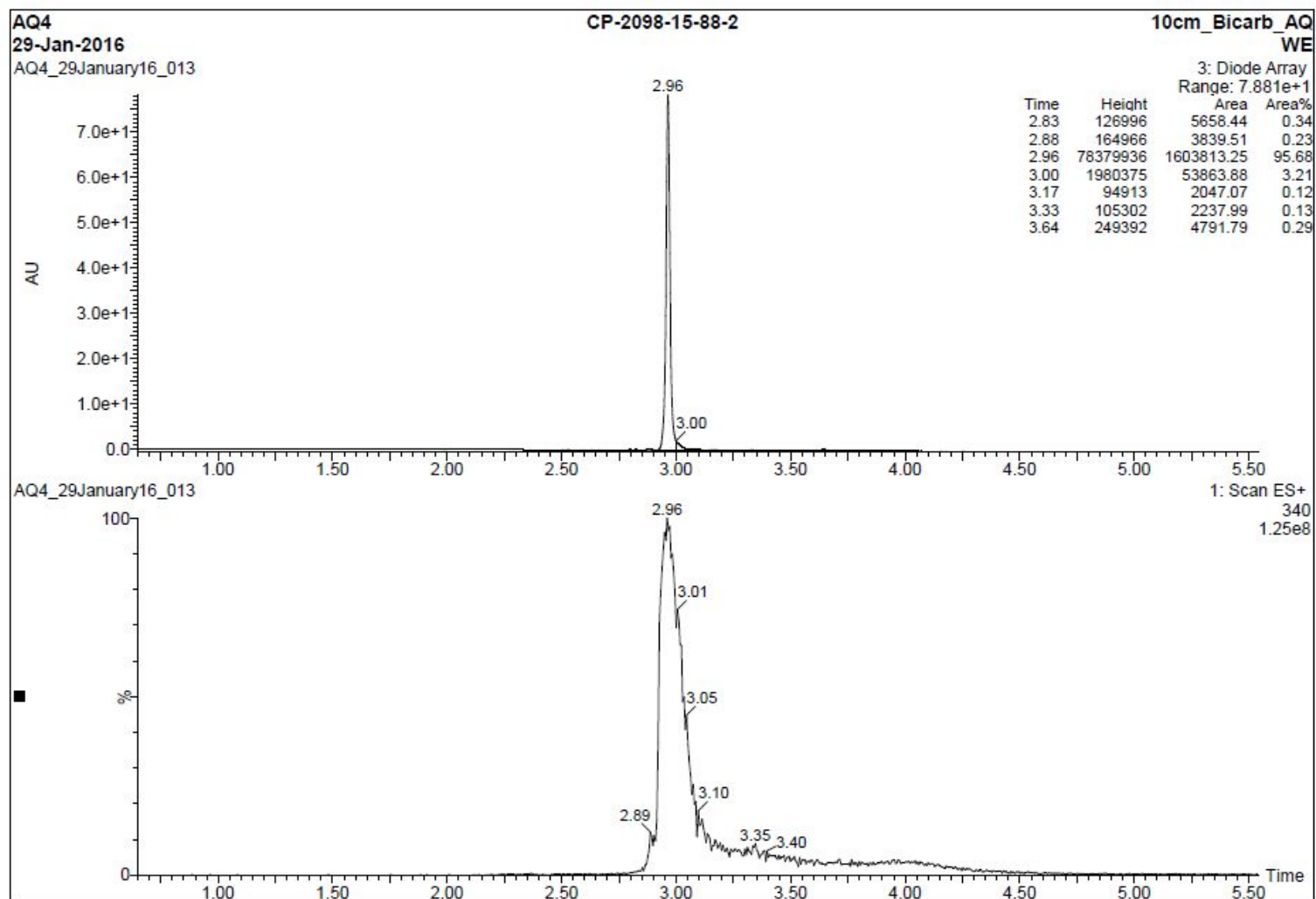
6-(2-Benzylpyrrolidin-1-yl)-4-morpholinopyridin-2(1H)-one (43)



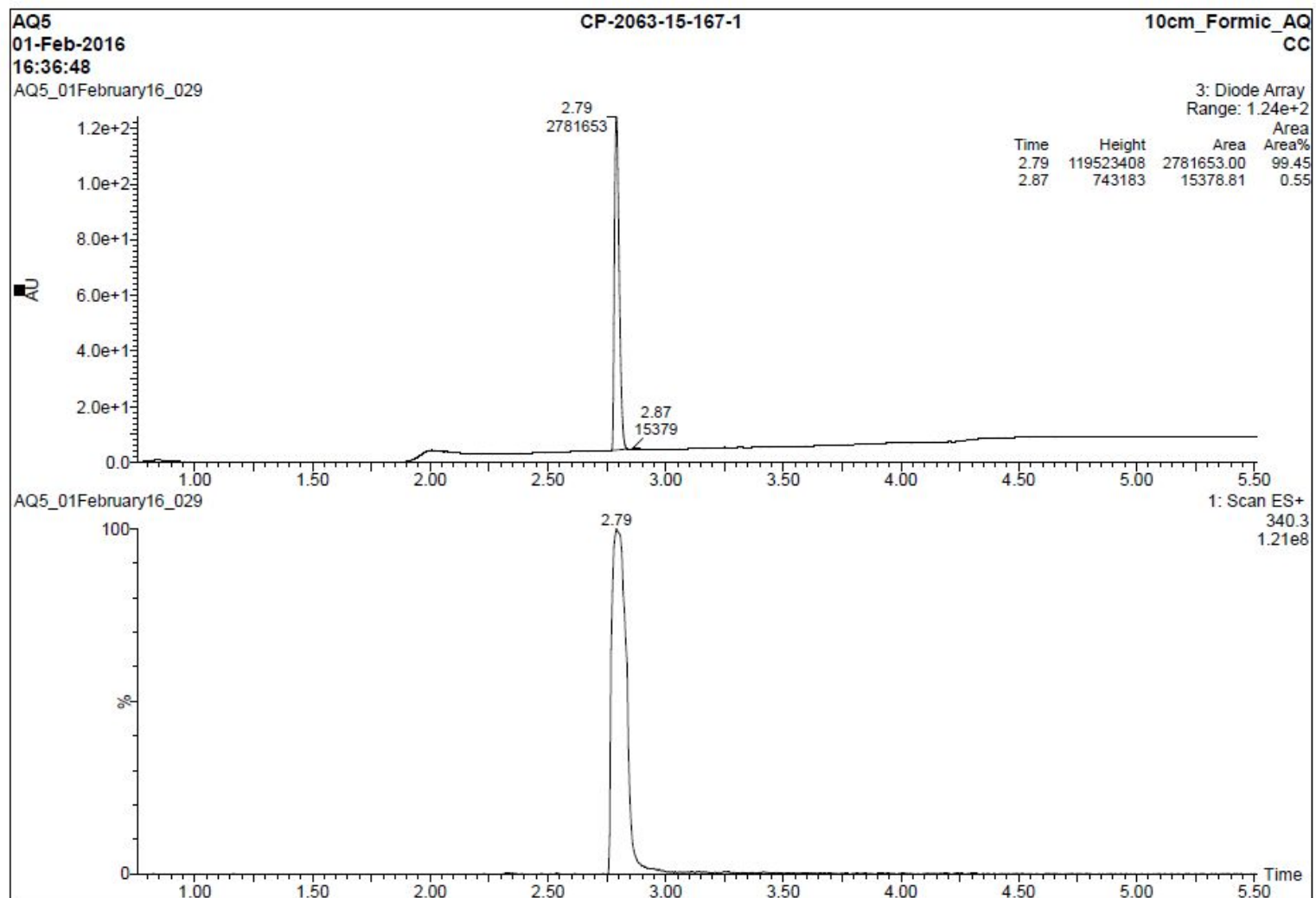
(R)-6-(2-Benzylpyrrolidin-1-yl)-4-morpholinopyridin-2(1H)-one (44)



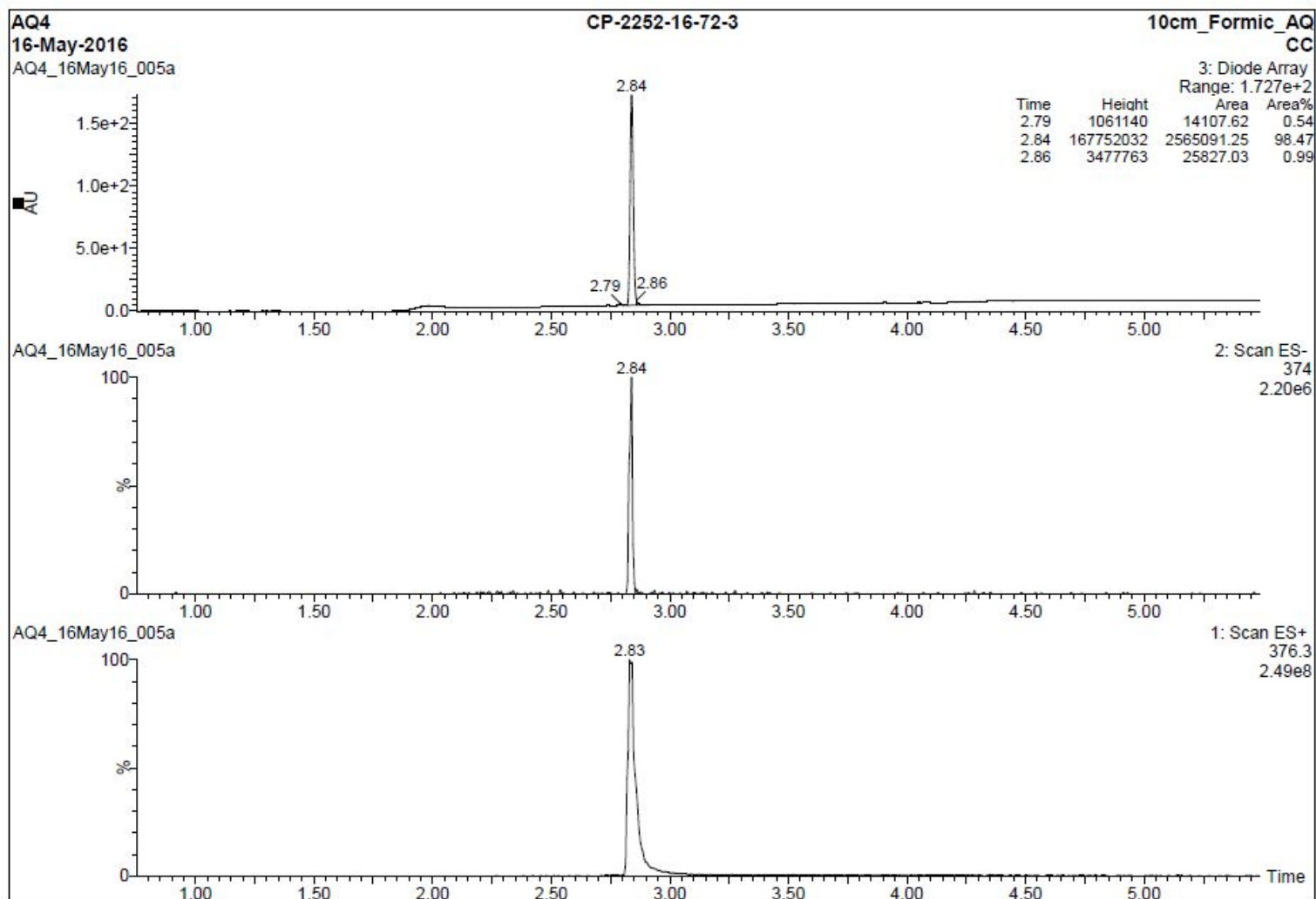
(S)-6-(2-benzylpyrrolidin-1-yl)-4-morpholinopyridin-2(1H)-one (45)



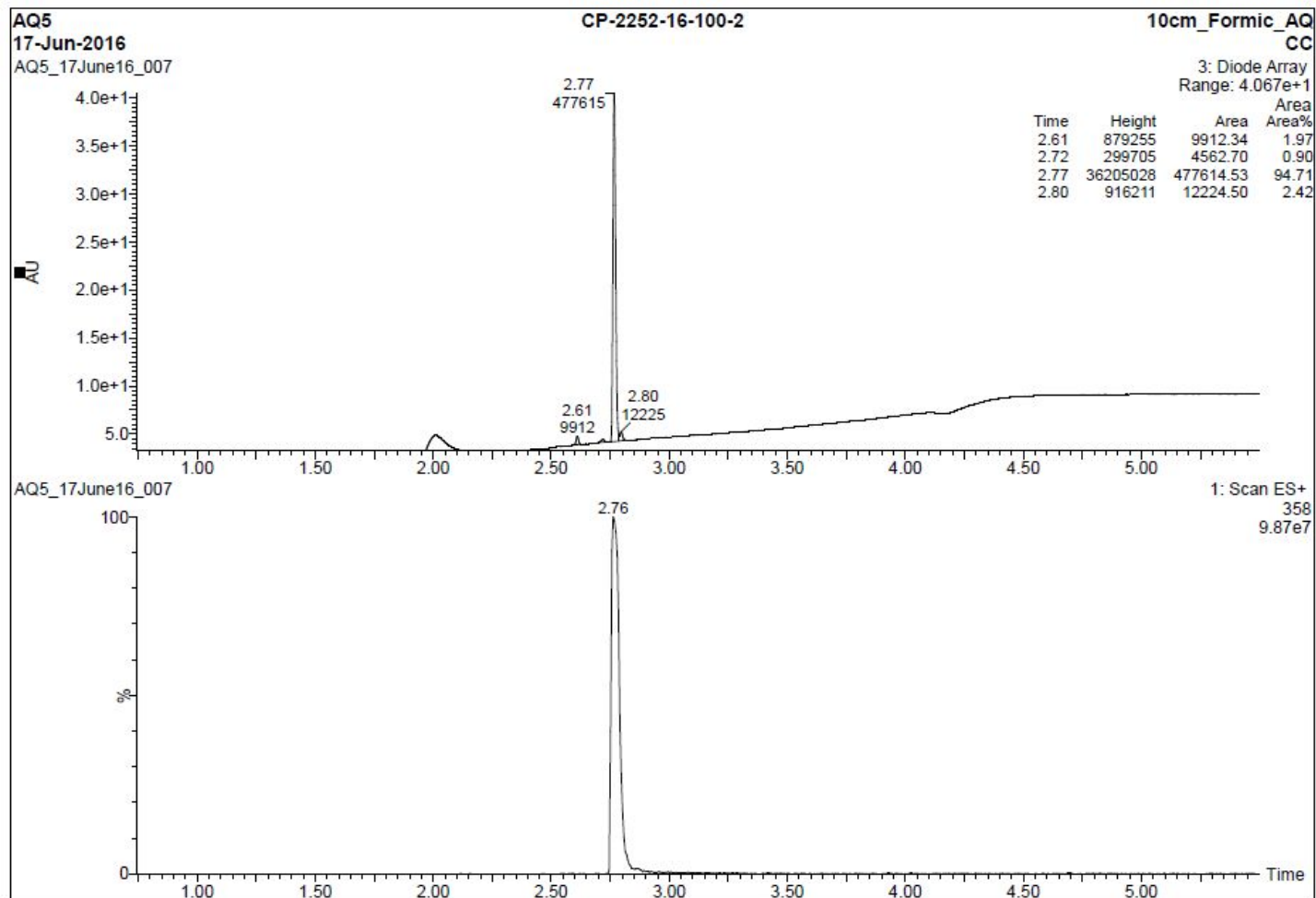
6-(3-Benzylpyrrolidin-1-yl)-4-morpholinopyridin-2(1H)-one (46)



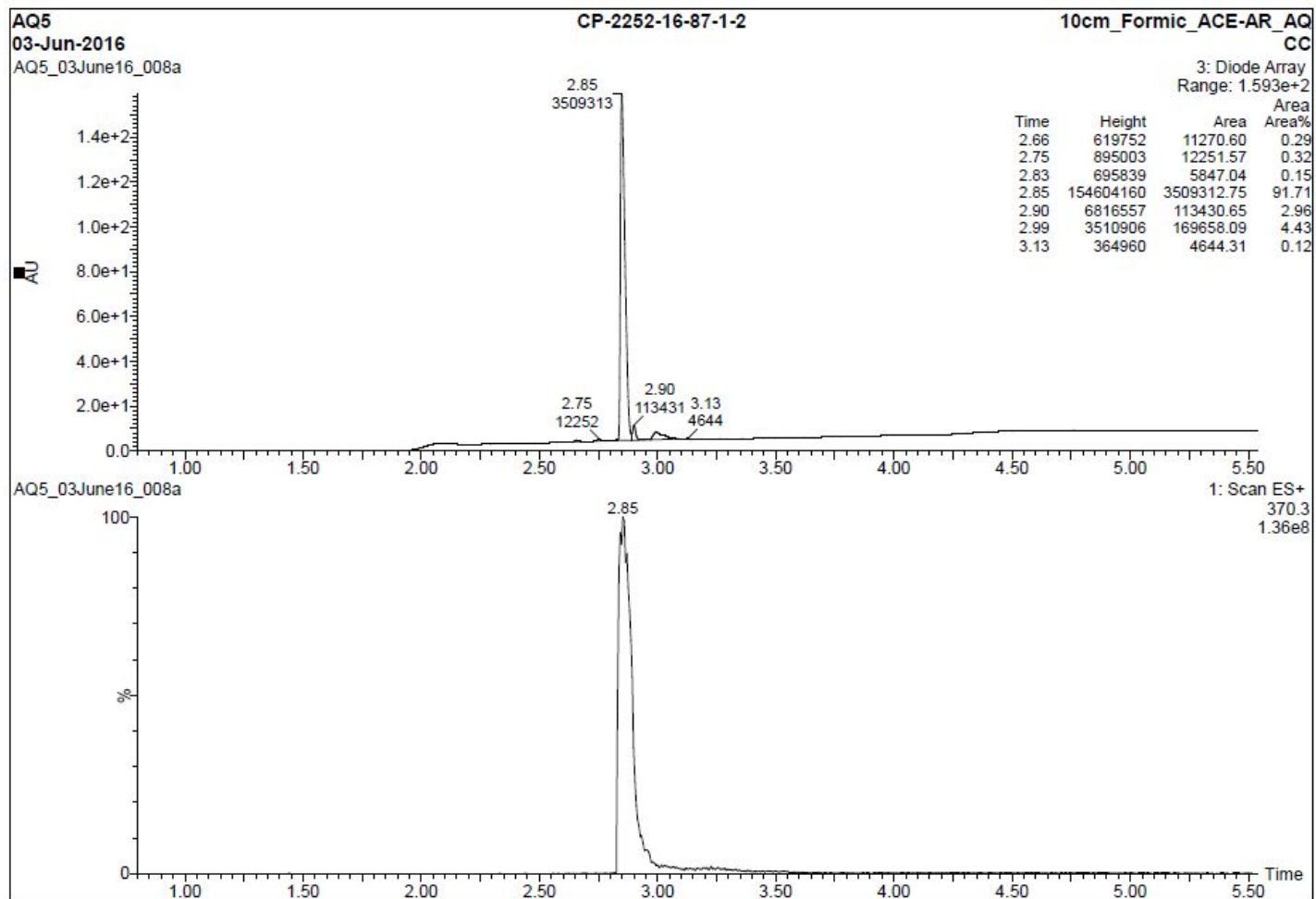
(S)-6-(2-Benzyl-3,3-difluoropyrrolidin-1-yl)-4-morpholinopyridin-2(1H)-one (47)



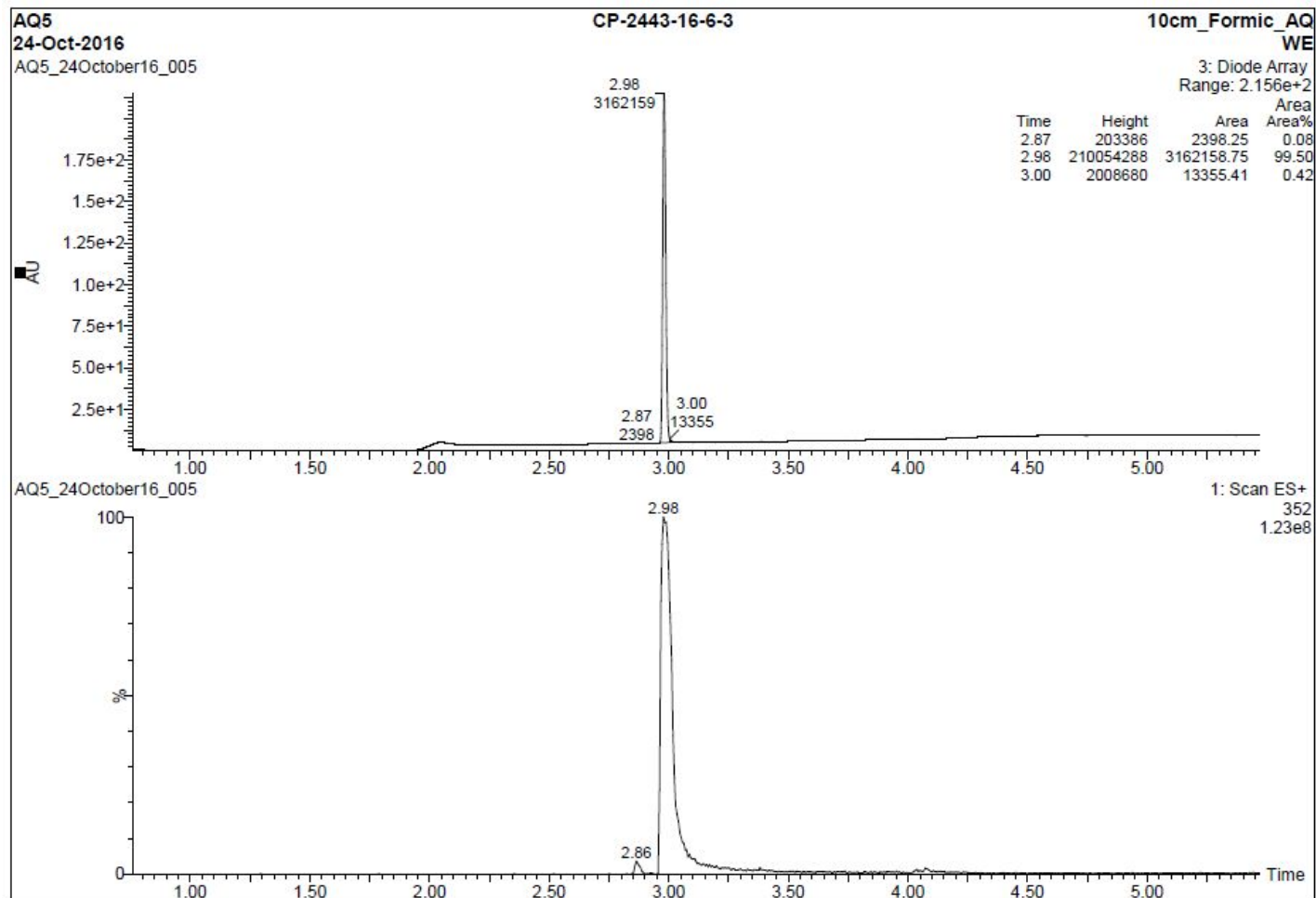
6-((2S,3R)-2-Benzyl-3-fluoropyrrolidin-1-yl)-4-morpholinopyridin-2(1H)-one (48).



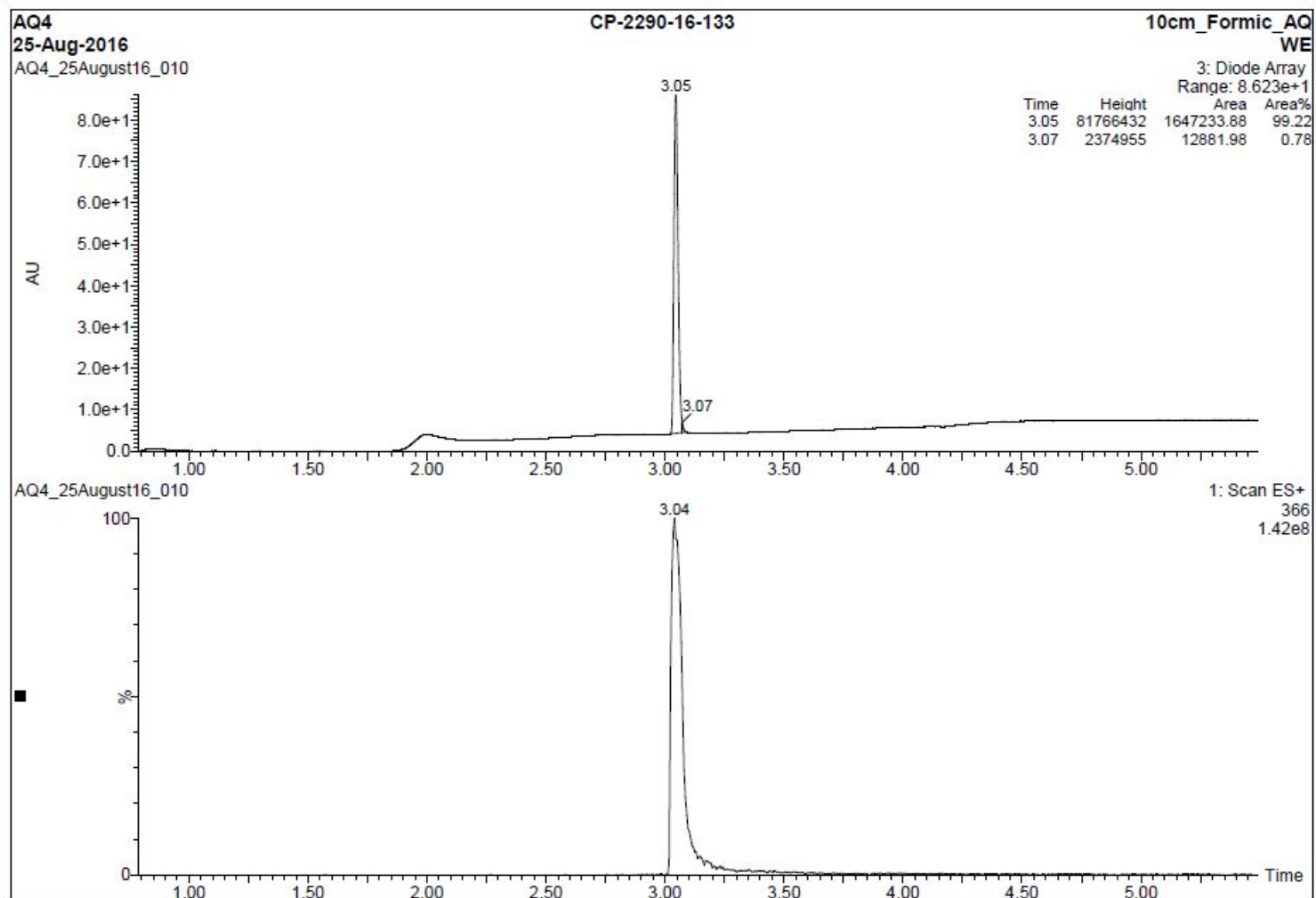
6-((2S,3R)-2-Benzyl-3-methoxypyrrolidin-1-yl)-4-morpholinopyridin-2(1H)-one (49)



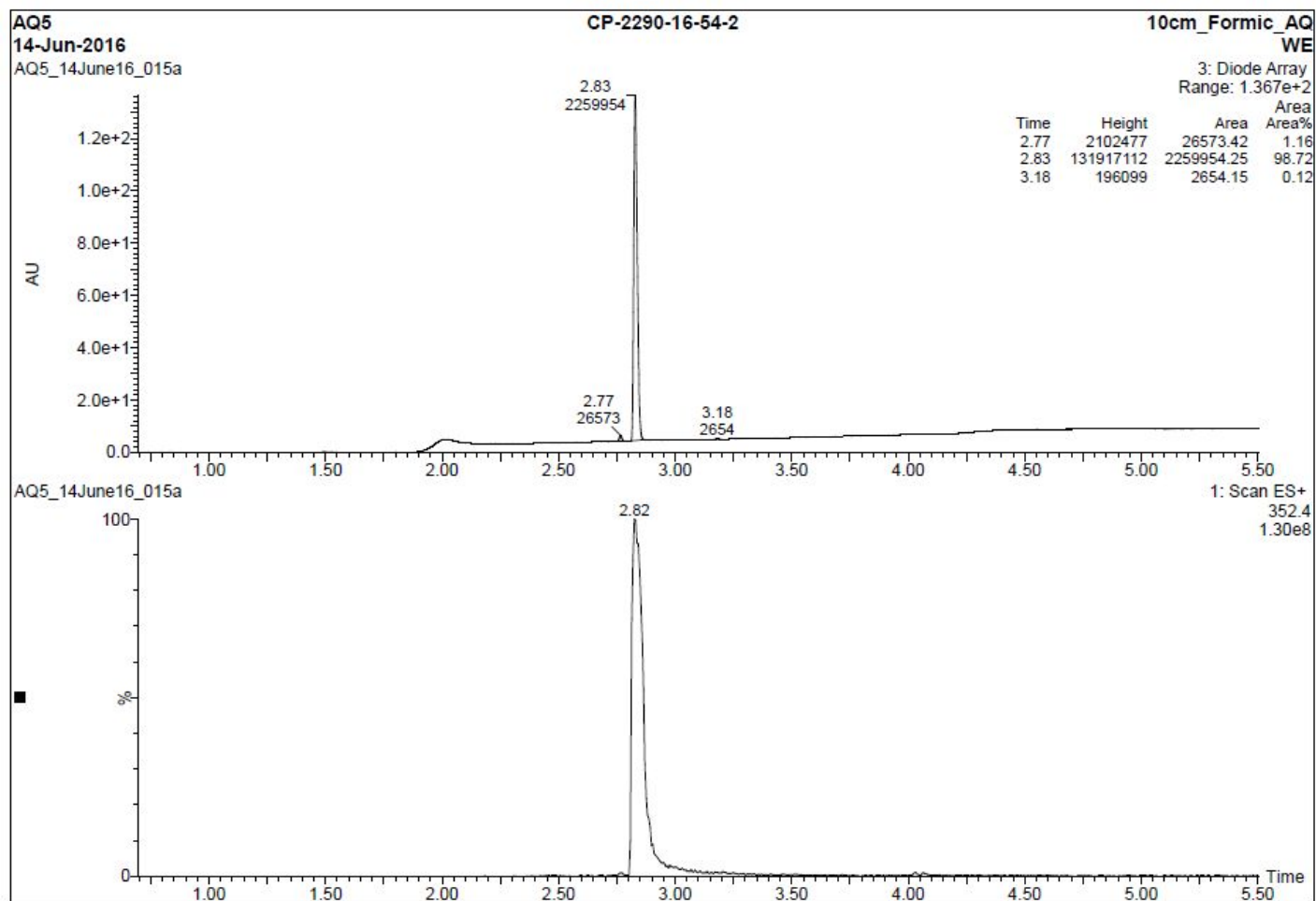
6-((1S,2S,5R)-2-Benzyl-3-azabicyclo[3.1.0]hexan-3-yl)-4-morpholinopyridin-2(1H)-one (50)



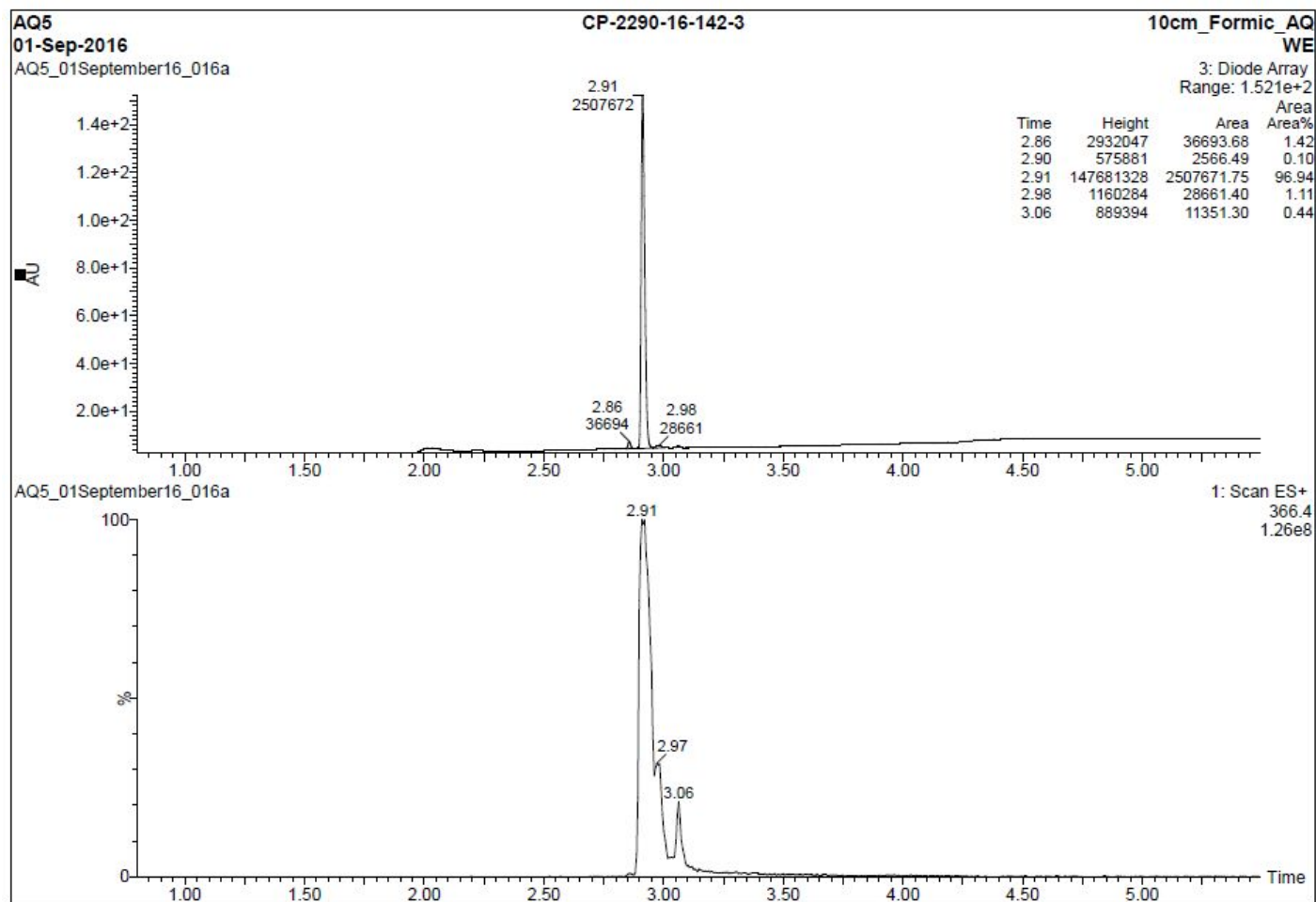
6-((1S,2S,5R)-2-Benzyl-3-azabicyclo[3.1.0]hexan-3-yl)-4-((R)-2-methylmorpholino)pyridin-2(1H)-one (51)



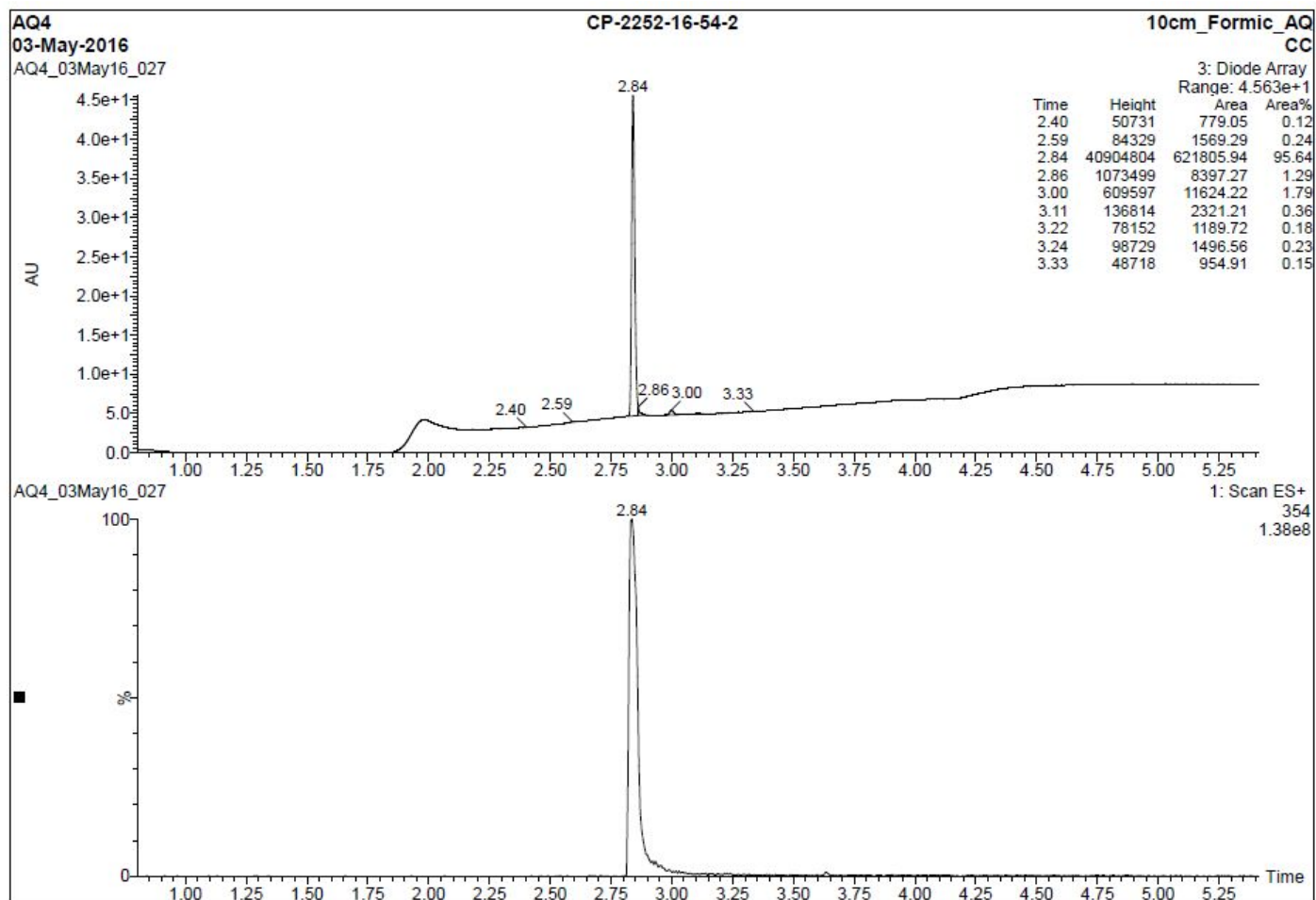
6-((1R,2S,5S)-2-Benzyl-3-azabicyclo[3.1.0]hexan-3-yl)-4-morpholinopyridin-2(1H)-one (52)



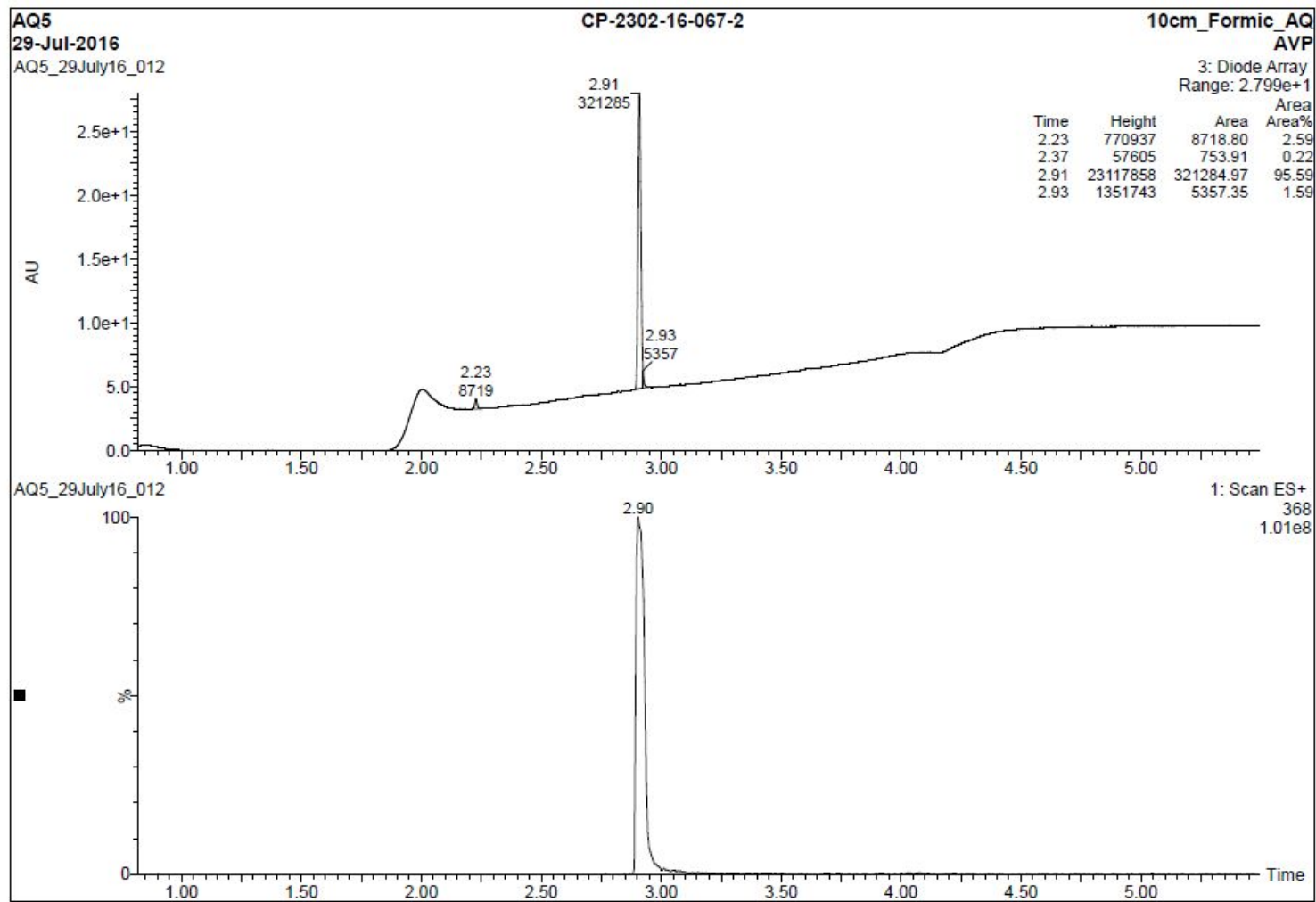
6-((1R,2S,5S)-2-Benzyl-3-azabicyclo[3.1.0]hexan-3-yl)-4-((R)-2-methylmorpholino) pyridin-2(1H)-one (53)



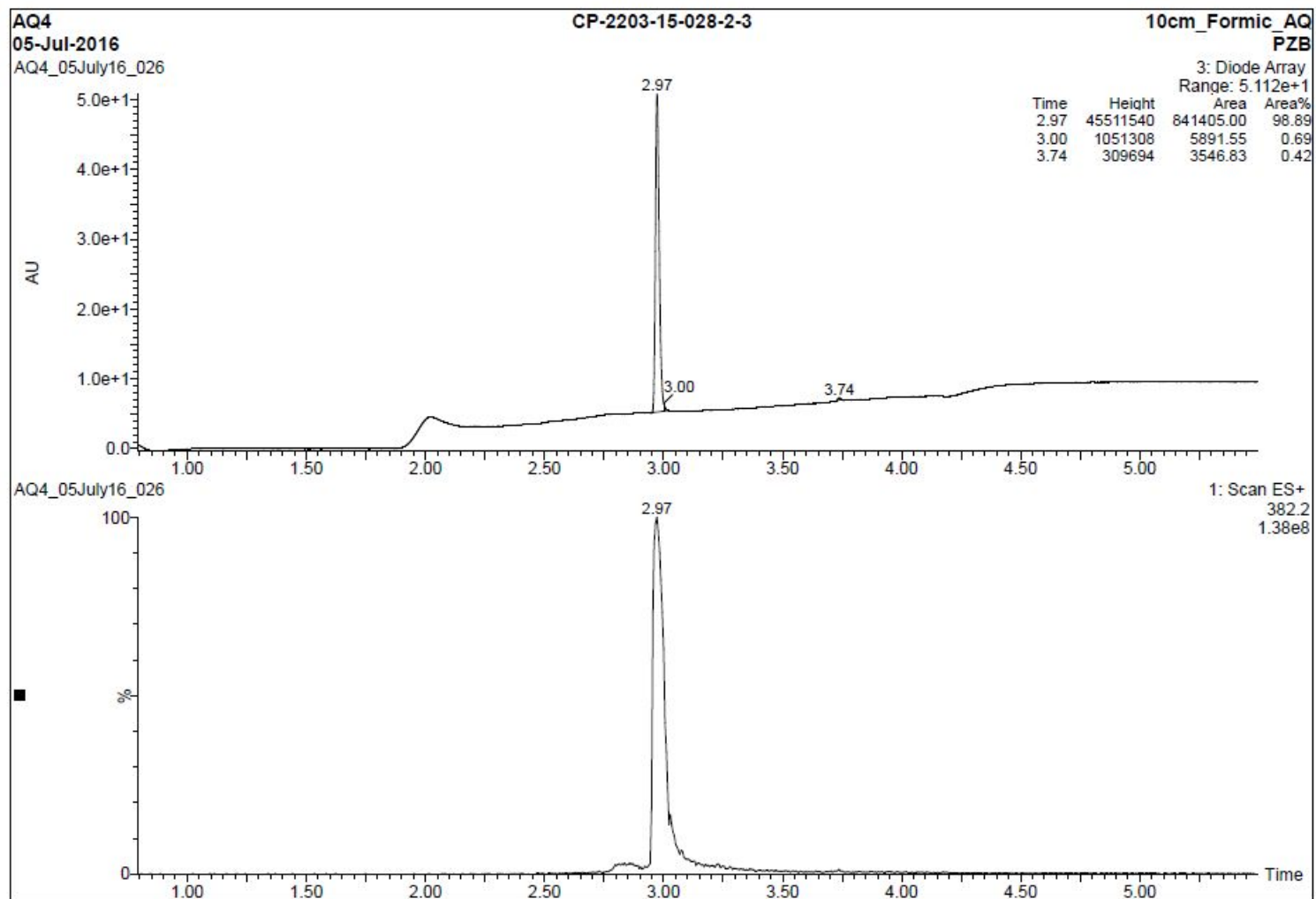
(R)-6-(2-Benzylpiperidin-1-yl)-4-morpholinopyridin-2(1H)-one (54)



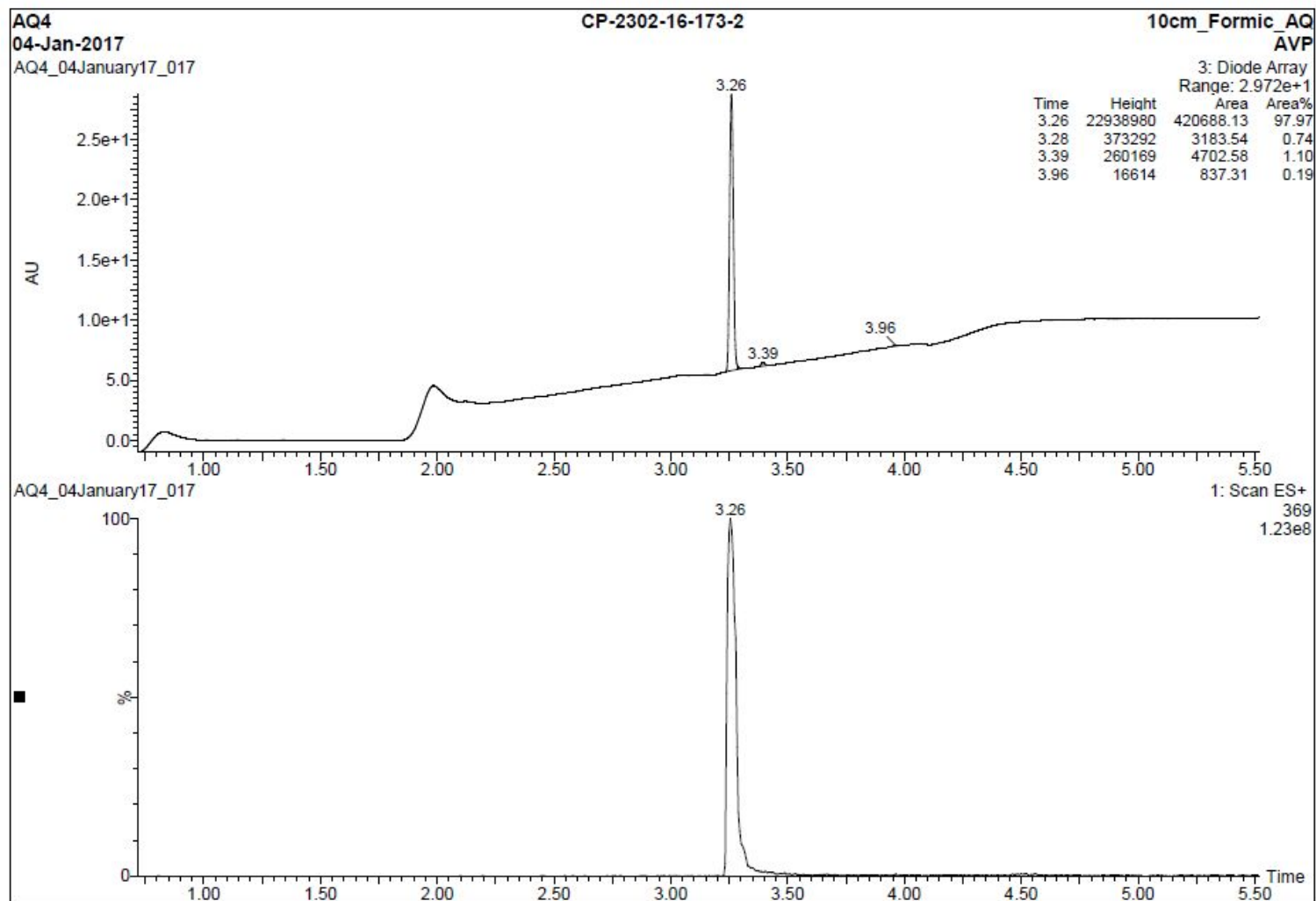
(R)-6-(2-Benzylazepan-1-yl)-4-morpholinopyridin-2(1H)-one (55)



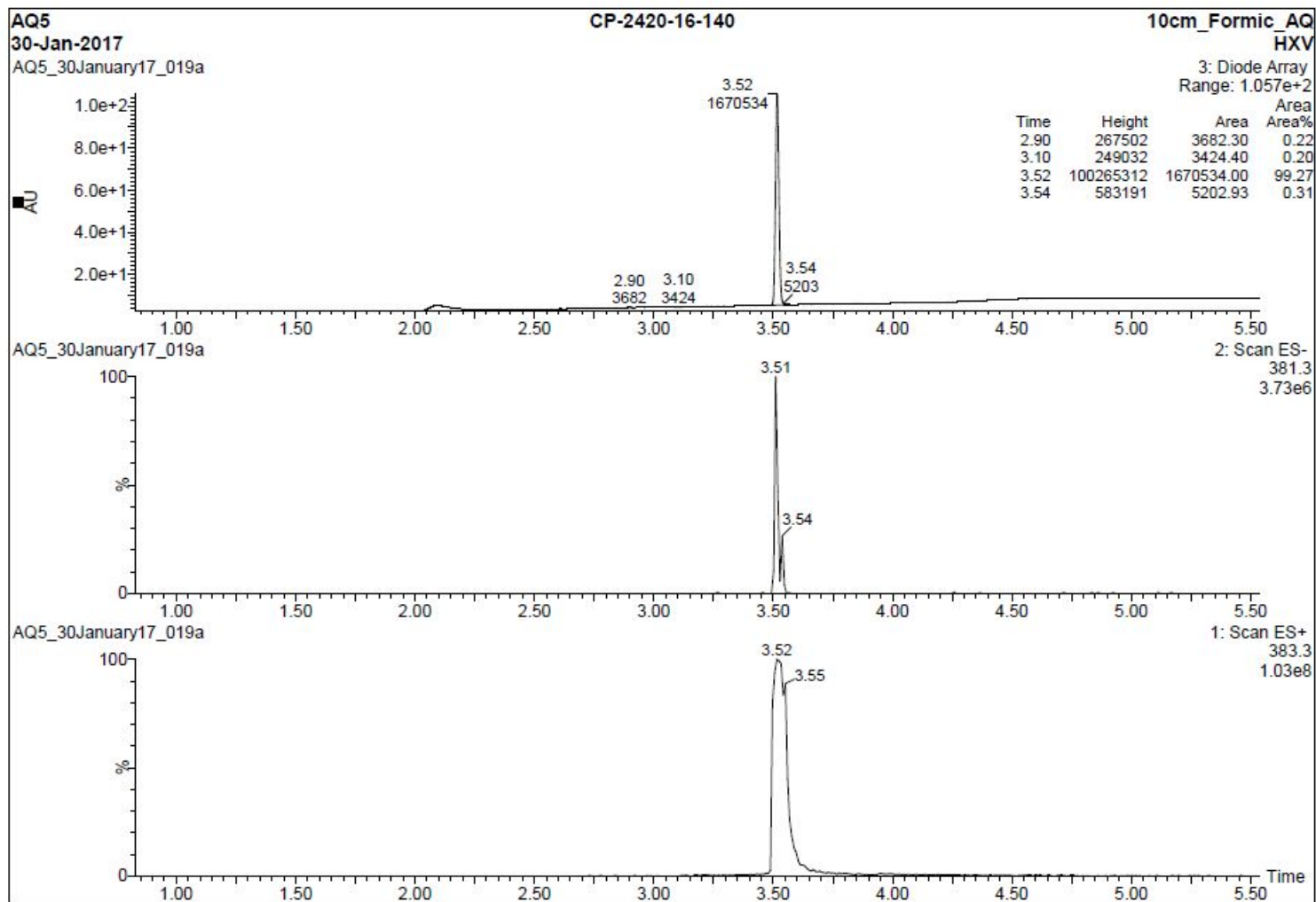
6-((R)-2-Benzylazepan-1-yl)-4-((R)-2-methylmorpholino)pyridin-2(1H)-one (56)



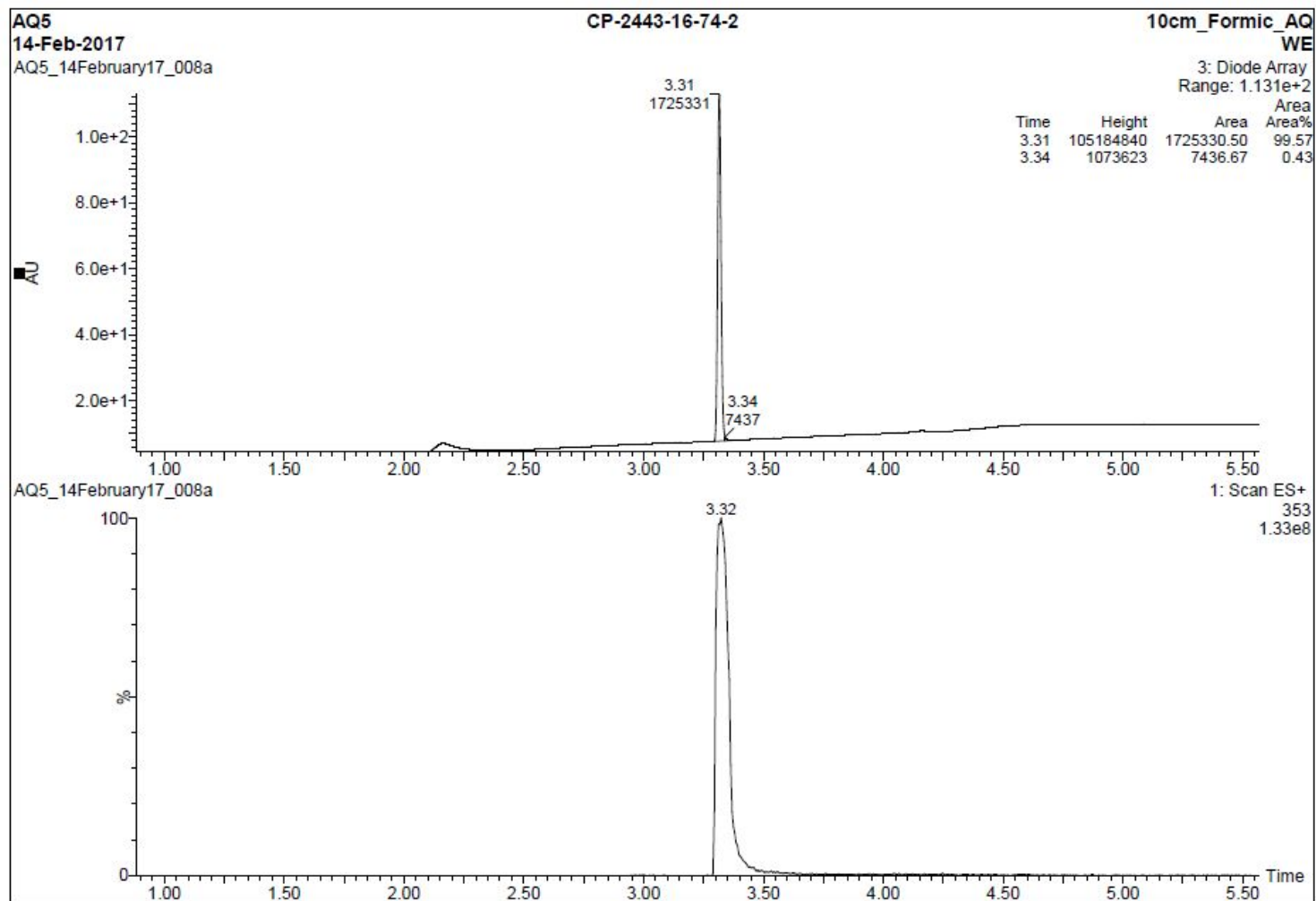
(R)-2-(2-Benzylazepan-1-yl)-6-morpholinopyrimidin-4(3H)-one (62)



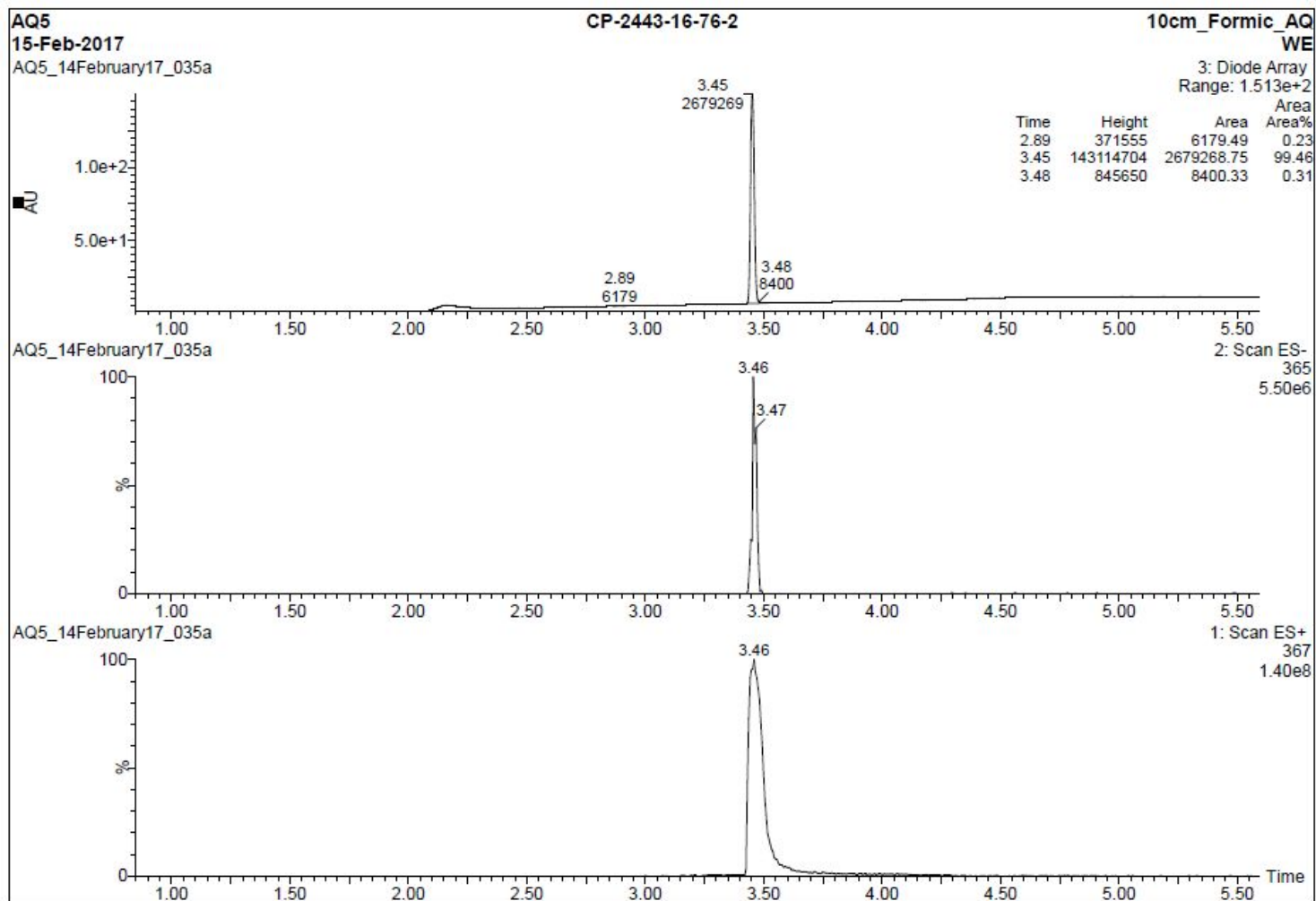
2-((R)-2-Benzylazepan-1-yl)-6-((R)-2-methylmorpholino)pyrimidin-4(3H)-one (63)



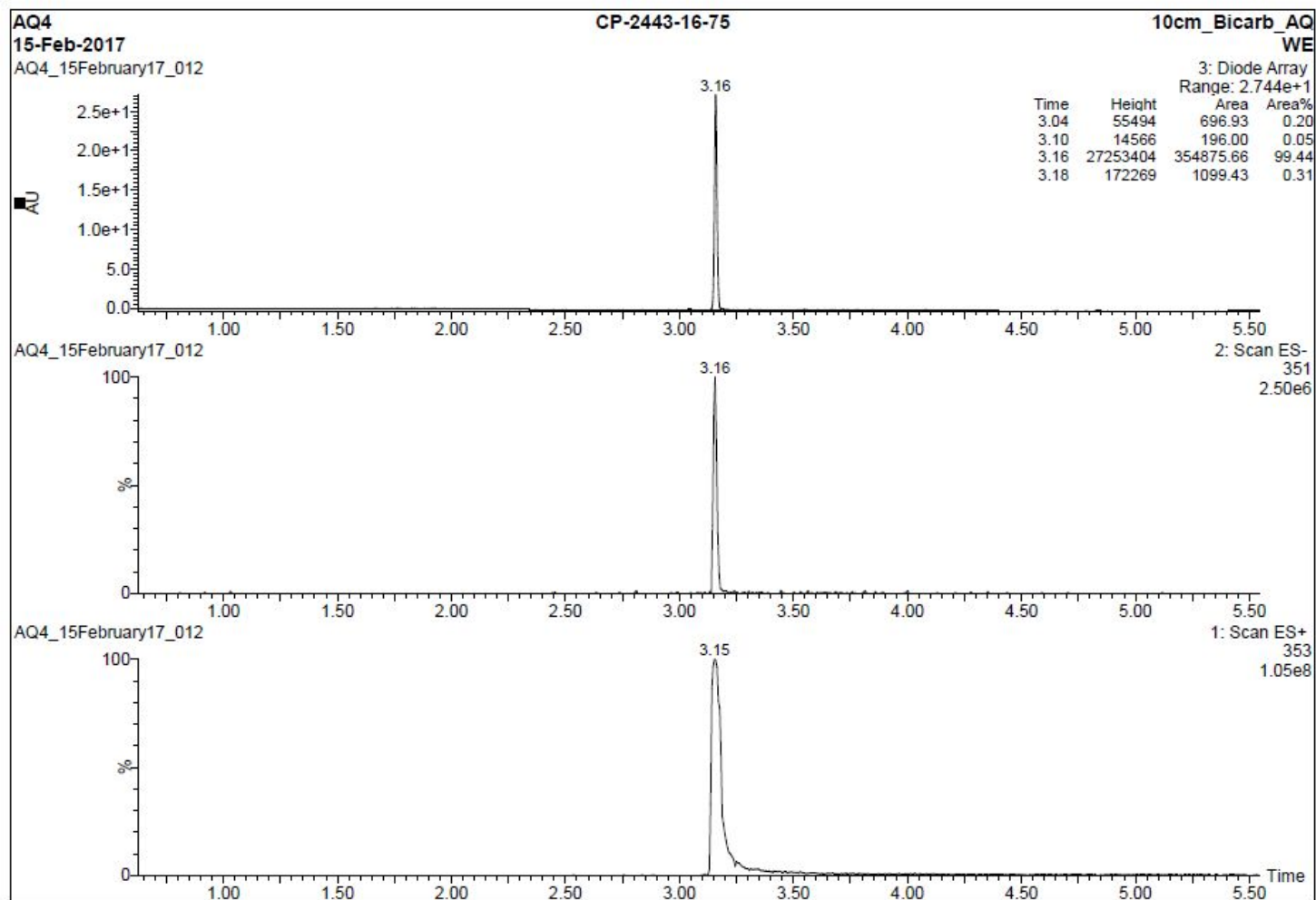
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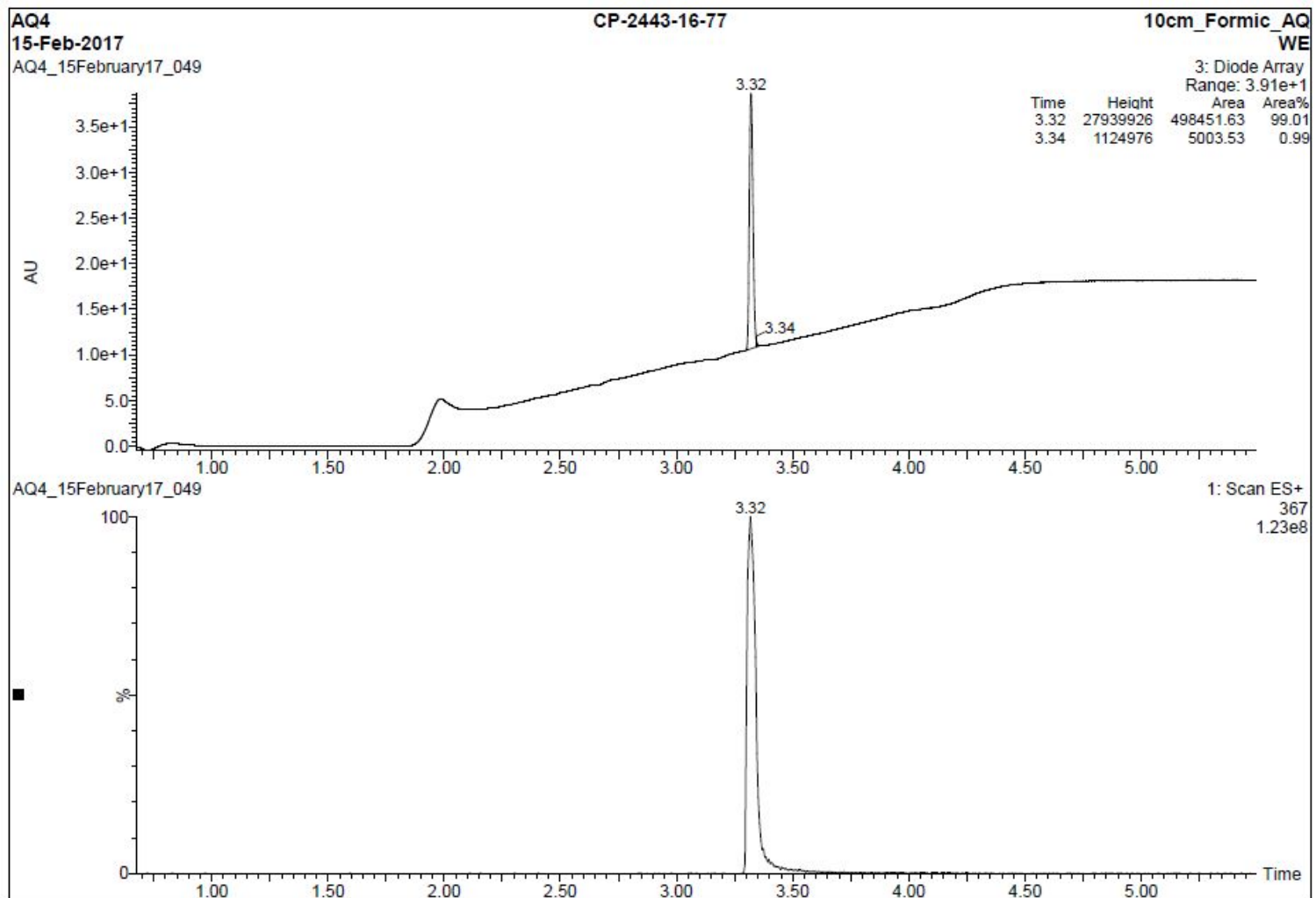
2-((1R,2S,5S)-2-Benzyl-3-azabicyclo[3.1.0]hexan-3-yl)-6-((R)-2-methylmorpholino)pyrimidin-4(3H)-one (65)



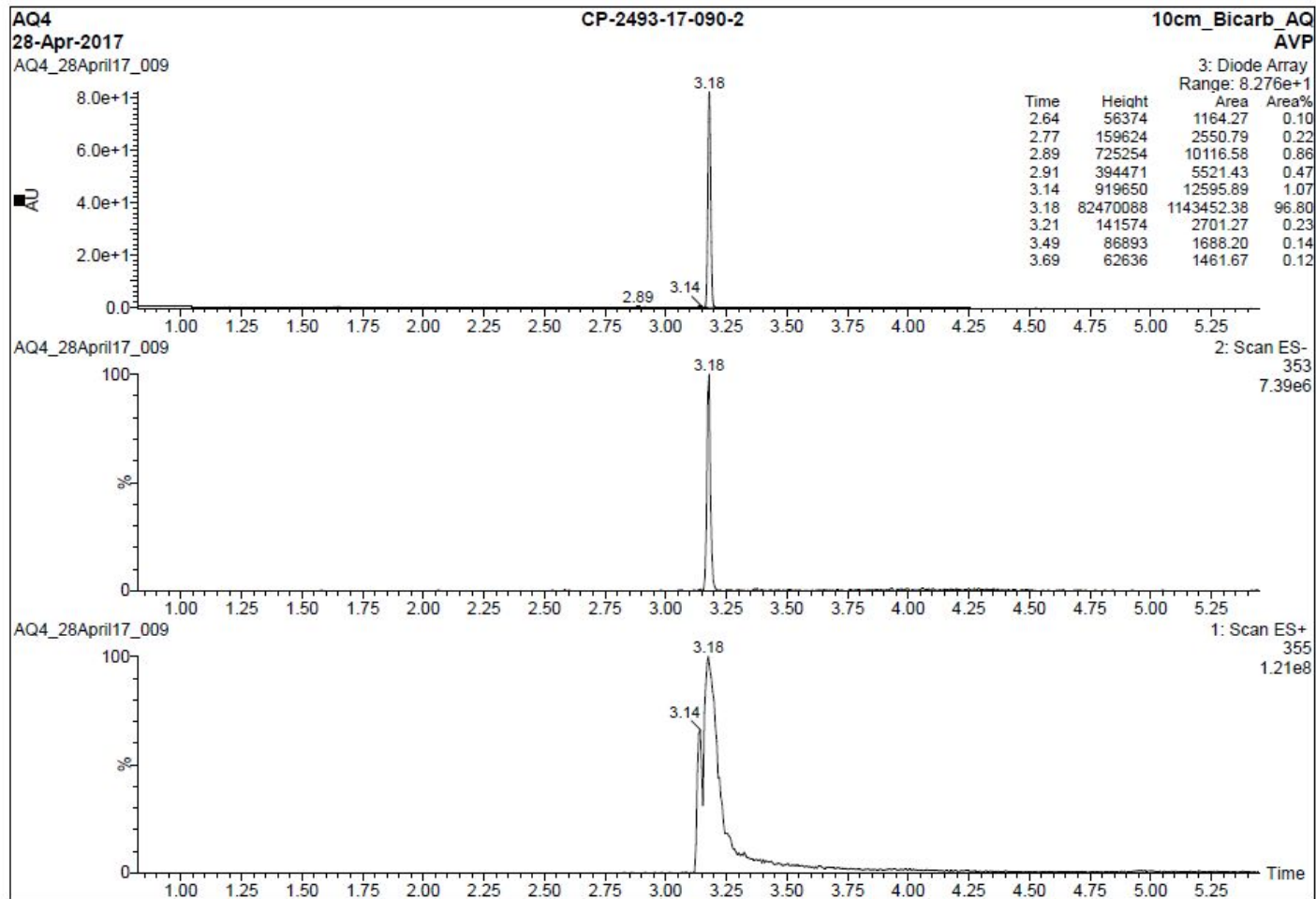
2-((1S,2S,5R)-2-Benzyl-3-azabicyclo[3.1.0]hexan-3-yl)-6-morpholinopyrimidin-4(3H)-one (66)



2-((1S,2S,5R)-2-Benzyl-3-azabicyclo[3.1.0]hexan-3-yl)-6-((R)-2-methylmorpholino)pyrimidin-4(3H)-one (67)



2-((2S,3R)-2-Benzyl-3-methylpyrrolidin-1-yl)-6-morpholinopyrimidin-4(3H)-one (68)



Biological data: Statistical analysis

Activities are reported in micromolar. The data for each of the compounds in Table S1 below represents the geometric mean of 2-7 independent tests, and the limits of the 95% confidence interval are given. Values marked greater than (>) showed less than 50% inhibition at the highest concentration tested in at least one run.

Table S1: Biological activity and statistical analysis for the synthesised ATM inhibitors

Compound	ATM K _i	ATM cell IC ₅₀	ATR cell IC ₅₀	Vps34 K _i	DNA-PK K _i
4	0.0005 ± 0.0002	1.3 ± 0.3	>30	0.0145 ± 0.01	0.14 ± 0.19
7	0.004 ± 0.0016	0.88 ± 0.47	>30	0.126 ± 0.100	0.11 ± 0.097
8	0.026 ± 0.015	>26	>30	>5	0.016 ± 0.011
11	>1.2	>30		0.910 ± 0.079	
16	0.10 ± 0.10	>30	>30		
19	>1	>30			
25	>1.6	>30		>5	
26	0.025 ± 0.016	6.7 ± 4.5	>30	0.035 ± 0.006	
30	0.087 ± 0.099	>30		0.27 ± 0.31	
31	0.0012 ± 0.001	0.45 ± 0.48	>20	0.016 ± 0.018	0.056 ± 0.058
32	0.0001 ± 0.0001	0.2 ± 0.12	3 ± 2	0.0079 ± 0.0058	0.46 ± 0.43
34	0.16 ± 0.073	>30	>30	3.3 ± 2.7	
40	>1.6	>30		>5	
43	0.030 ± 0.0085	4.0 ± 2.5	>25	0.049 ± 0.0093	
44	0.0056 ± 0.0048	3.4 ± 4.4	>30	0.0092 ± 0.0052	0.089 ± 0.023
45	>0.9	>30	>29	0.63 ± 0.49	

46	>1.2	>30	>30		
47	0.006 ± 0.0027	0.92 ± 0.008	>30	0.039 ± 0.0053	0.047 ± 0.016
48	0.0027 ± 0.0029	1.3 ± 1.1	>30	0.11 ± 0.14	0.025 ± 0.05
49	0.023 ± 0.012	3.5 ± 1.5			
50	0.0003 ± 0.0001	0.15 ± 0.13	6.5 ± 4.9	0.0035 ± 0.0025	0.039 ± 0.042
51	0.0041 ± 0.0041	0.52 ± 0.25	12.6 ± 6.4	0.75 ± 0.79	0.0072 ± 0.0038
52	0.0016 ± 0.0012	0.29 ± 0.26	>30	0.098 ± 0.078	0.16 ± 0.14
53	0.011 ± 0.0025	1.04 ± 0.032	>24	>5	0.069 ± 0.041
54	0.0083 ± 0.0056	2.48 ± 2.03	>30	0.17 ± 0.13	0.44 ± 0.35
55	0.0015 ± 0.0013	0.23 ± 0.055	>30	0.05 ± 0.034	0.18 ± 0.13
56	0.0086 ± 0.0007	1.6 ± 1.0	>25	1.8 ± 2.6	0.37 ± 0.21
62	0.0001 ± 0.0001	0.2 ± 0.115	3 ± 2	0.0079 ± 0.0058	0.46 ± 0.43
63	0.0011 ± 0.0001	0.82 ± 0.19	5.8 ± 1.4	0.84 ± 0.40	0.063 ± 0.091
64	0.0002 ± 0.0001	0.13 ± 0.061	10.5 ± 2	0.021 ± 0.019	0.040 ± 0.0066
65	0.0017 ± 0.0002	0.56 ± 0.29	8.9 ± 8.9	0.88 ± 0.72	0.0058 ± 0.0008
66	0.0006 ± 0.0005	0.45 ± 0.39	3.9 ± 2.1	0.0054 ± 0.0048	0.061 ± 0.064
67	0.0009 ± 0.0009	1.31 ± 1.09	7.9 ± 6.4	1.5 ± 1.7	0.002 ± 0.0018
68	0.0004 ± 0.0011	0.09 ± 0.042	5.5 ± 6.9	0.0064 ± 0.0066	0.11 ± 0.086

Table S2: Mouse PK parameters for compound 55 after dosing at 2 mg/kg IV, 10 mg/kg PO and 30 mg/kg PO

PK PARAMETER	UNITS	Plasma			Brain	
		IV 2 mg /kg	PO 10 mg /kg	PO 30 mg /kg	PO 10 mg /kg	PO 30 mg /kg
AUC(0-last)	nM h	2600	8600	44000	3900	20000
AUC(0-inf)	nM h	2600	8800	46000	4000	20000
AUCnorm	nM h kg/mg	1300	880	1500	400	680
Oral Bioavailability (F)	%	NA	68	115	NA	NA
Observed C _{max}	nM	NA	2900	17000	2000	9100
Observed C _{max} Norm	nM kg/mg	NA	290	560	200	300
Observed T _{max}	h	NA	0.5	0.25	0.5	0.5
Clearance (CL)	L/h/kg	2.1	NA	NA	NA	NA
Volume of Distribution at Steady State (V _{dss})	L/kg	3.4	NA	NA	NA	NA
Mean Residency Time (MRT)	h	1.6	NA	NA	NA	NA
Half-life (t _{1/2})	h	1.9	2.4	3.1	2.2	2.6
Half-life Regression Time Points	h	1, 2, 4, 8, 12	1, 2, 4, 8, 12	1, 2, 4, 8, 12	1, 2, 4, 8, 12	1, 2, 4, 8, 12

Vps34 ATM surrogate crystal structures

Purification of Vps34 ATM surrogate protein

In brief, Vps34, comprising residues 268-879 was cloned into an *E. coli* expression vector, adding a TEV cleavable 6His tag at its N-terminus. The following mutations were introduced by site-directed mutagenesis: F612A, L616N, I634L, M682L, F684W, along with a glycine residue insertion between Gln686 and Ser687. The mutant construct was expressed in *E. coli* BL21 (DE3) cells. The protein was purified by immobilized metal affinity chromatography (IMAC) followed by His tag removal and size exclusion chromatography. The protein was eluted in 25 mM Tris pH 8.0, 250 mM NaCl and 0.5 mM THP. The protein was concentrated to 8.5 mg/mL prior to co-crystallization.

Crystallization, structure determination and analysis

A 20 mM stock solution of compound **44** in 100% v/v DMSO was added to the purified Vps34 ATM surrogate protein to a final ligand concentration of 1 mM, and the complex was incubated

at r.t for 1 h before crystallization trials were set up. Co-crystals were grown using the hanging drop method of vapour diffusion, with streak seeding, over reservoirs containing 1.4 M sodium malonate pH 7.0, 0.1 M BIS-TRIS propane pH 7.0. Co-crystals were cryo-cooled for data collection by briefly transferring them to a drop containing precipitant solution plus 20% v/v glycerol, before plunging them into liquid nitrogen.

Data sets were collected at beamline id30a-1 at the ESRF synchrotron in Grenoble, France. The diffraction data were indexed, integrated and scaled using MOSFLM and AIMLESS. Details of data collection and processing are given in Table S3 below.

The Vps34 coordinates (PDB ID: 3LS8) were used as a search model for molecular replacement (MR) with the compound **44** data. In this search model, side-chains were truncated at C β for non-identical amino acids. MR was carried out in PHASER, locating one protein chain per asymmetric unit.

The difference electron density maps calculated after MR and initial refinement in REFMAC5 were used to check, and if necessary, re-model the protein conformation manually in COOT. Any missing side-chain atoms that were supported by the electron density maps were added to the model. The hinge was also re-modelled to accommodate the inserted glycine residue. After another round of refinement in REFMAC5, the maps were further examined for the presence of compound. Once the ligand electron density was located, a molecular structure file and refinement library file were produced using ACEDRG. The compound was fitted into the electron density maps using COOT and refined using REFMAC5. Water molecules were then added using the water placement option in COOT and refined using REFMAC5. Details of structure refinement and final model analysis are given in Table S3 below.

Table S3: Details of data collection, processing and structure refinement statistics for the VPS34 ATM surrogate protein structure in complex with compound 44.

Compound No.	44
Data collection and processing statistics	
Unit cell dimensions (Å)	a = 79.86 b = 168.12 c = 61.69
Space group	P21212
Resolution range (Å)	49.73-3.12 (3.34-3.12)
No. of unique reflections	15383 (2732)
Completeness (%)	99.8 (99.9)
CC(1/2)	0.999 (0.500)
Structure refinement statistics	
Resolution range (Å)	84.06-3.12
No. of reflections (working/test)	14568/815
R_{work}/R_{free} (%)	21.3/26.2
Rmsd bond lengths (Å)/angles (°)	0.011/1.329
No. of protein atoms	4442
No. of solvent atoms	1
No. of ligand atoms	25
Mean overall B value (Å²)	62.4
Mean water B value (Å²)	30.2
Mean ligand B value (Å²)	44.7
Ramachandran plot favoured region	532 (96.2%)
Ramachandran plot allowed region	20 (3.6%)
Ramachandran plot outlier region	1 (0.2%)