

Supporting Information for

Conformationally Restricted Benzothienoazepine Respiratory Syncytial Virus Inhibitors: Their Synthesis, Structural Analysis and 5 Biological Activities

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Table of contents

25

I. Compound Synthesis and Characterisation	S2
II. Biological Testing: Experimental Methods	S27
III. NMR Spectra of Compounds 7 , (4 <i>S</i>)- 13 and (5 <i>R</i>)- 19	S28

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I. Compound Synthesis and Characterisation

All starting materials and solvents were obtained either from commercial sources or prepared according to the literature citation. Unless otherwise stated all reactions were stirred. Organic solutions were routinely dried over anhydrous magnesium sulfate. Hydrogenations were
5 performed on a Thales H-cube flow reactor under the conditions stated or under pressure in a gas autoclave (bomb).

Column chromatography was performed on pre-packed silica cartridges (230-400 mesh, 40-63 μm) containing the amount indicated. The cation exchange resin, SCX, was purchased
10 from Supelco and treated with 1M hydrochloric acid prior to use. Unless stated otherwise the reaction mixture to be purified by solid supported exchange was first diluted with MeOH and made acidic with a few drops of glacial AcOH. The resulting solution was loaded onto the SCX bed, the resin washed with MeOH and the desired material then recovered by elution with 0.7 M NH_3 in MeOH.

15

Preparative Chiral High Performance Liquid Chromatography

Method 1: Chiralpak® IA (Daicel Ltd.) column (2 x 25 cm), flow rate 13.5 mL min^{-1} eluting with a mixture of ethanol:DCM:isohexane (10:18:72) containing 0.2% Et_2NH , using UV detection at 254 nm. Samples were loaded onto the column via an at-column dilution pump,
20 pumping chloroform (1.5 mL min^{-1}) for the duration of the run, giving a combined flow rate of 15 mL min^{-1} .

Analytical Methods

Reverse Phase HPLC Conditions for the LCMS Analytical Methods

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Methods 1a and 1b: Waters Xselect CSH C18 XP column, 2.5 μm (4.6 x 30 mm) at 40 °C; flow rate 2.5-4.5 mL min^{-1} eluting with a H_2O -MeCN gradient containing either 0.1% v/v formic acid (**Method 1a**) or 10 mM NH_4HCO_3 in water (**Method 1b**) over 4 min employing UV

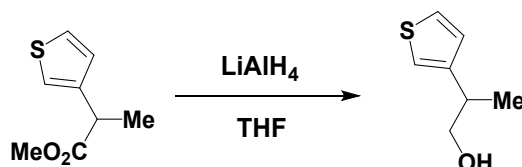
detection at 254 nm. Gradient information: 0-3.00 min, ramped from 95% H₂O-5% MeCN to 5% H₂O-95% MeCN; 3.00-3.01 min, held at 5% H₂O-95% MeCN, flow rate increased to 4.5 mL min⁻¹; 3.01-3.50 min, held at 5% H₂O-95% MeCN; 3.50-3.60 min, returned to 95% H₂O-5% MeCN, flow rate reduced to 3.50 mL min⁻¹; 3.60-3.90 min, held at 95% H₂O-5% MeCN; 5 3.90-4.00 min, held at 95% H₂O-5% MeCN, flow rate reduced to 2.5 mL min⁻¹.

Chiral High Performance Liquid Chromatography Analytical Methods

Method 2 : Chiralpak® IA (Daicel Ltd.) column (4.6 mm x 25 mm), flow rate 1.5 mL min⁻¹
10 eluting with a mixture of EtOH:DCM:isohexane (10:18:72) + 0.2% diethylamine, UV detection
at 254 nm.

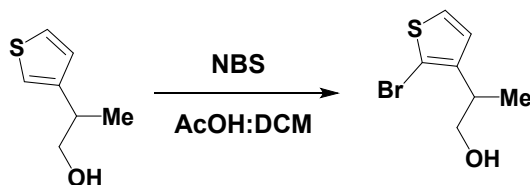
¹H NMR Spectroscopy

¹H NMR spectra were acquired on a Bruker Avance III spectrometer at 400 MHz using
15 residual undeuterated solvent as reference and unless specified otherwise were run in
DMSO-d₆.

Synthesis of (rac)-14**2-Methyl-2-(thien-3-yl)ethanol (25).**

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To an ice cold solution of 2-methyl-2-(thien-3-yl)acetic acid methyl ester (4.40 g, 25.8 mmol) in THF (20 mL) was added LiAlH₄ (2.0 M in THF, 25.8 mL) dropwise and the resulting mixture was warmed to RT and maintained at this temperature for 1 h. The mixture was cooled to 0 °C, carefully quenched with water (20 mL) and then diluted with HCl (1 M, 100 mL) and extracted with EtOAc (100 mL). The organic extracts were washed with water (2 x 30 mL), dried (Na₂SO₄) and evaporated *in vacuo* to afford the title compound as a yellow oil (3.40 g, 92% yield); ¹H NMR δ: 7.42 (dd, *J* = 4.9, 2.9 Hz, 1H), 7.17-7.14 (m, 1H), 7.04 (dd, *J* = 4.9, 1.3 Hz, 1H), 4.82-4.48 (br, 1H), 3.53 (dd, *J* = 10.3, 5.8 Hz, 1H), 3.37 (dd, *J* = 10.3, 7.5 Hz, 1H), 2.92-2.84 (m, 1H), 1.19 (d, *J* = 6.9 Hz, 3H). Residual EtOAc (6 wt%) and THF (1 wt%) were present.

2-Methyl-2-(2-bromothien-3-yl)ethanol (26).

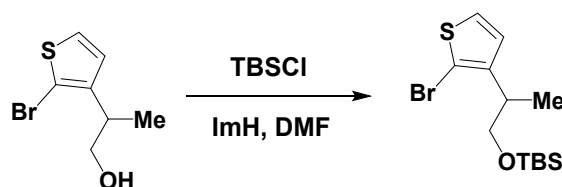
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To a solution of 2-methyl-2-(thien-3-yl)ethanol (3.40 g, 23.9 mmol) in DCM (40 mL) at RT was added a solution of NBS (4.26 g, 23.9 mmol) in AcOH (130 mL). After 15 min at RT the reaction mixture was evaporated *in vacuo* and the residue was partitioned between Et₂O

(200 mL) and sat aq NaHCO₃ (100 mL). The organic layer was separated, dried (Na₂SO₄) and evaporated *in vacuo*. The residue thus obtained was purified by flash column chromatography (SiO₂, 120 g, 0-10% EtOAc in isohexanes, gradient elution) to afford the title compound as a colourless oil (3.71 g, 86% pure by ¹H NMR, 60% yield); ¹H NMR δ: 7.53 (dd, *J* = 5.8, 0.6 Hz, 1H), 6.98 (d, *J* = 5.8 Hz, 1H), 4.73 (t, *J* = 5.4 Hz, 1H), 3.51-3.38 (m, 2H), 2.98-2.90 (m, 1H), 1.13 (d, *J* = 7.0 Hz, 3H). Major impurity present in ¹H NMR is unreacted starting material (14 wt%).

(2-(2-Bromothiophen-3-yl)propoxy)(*tert*-butyl)dimethylsilane (10).

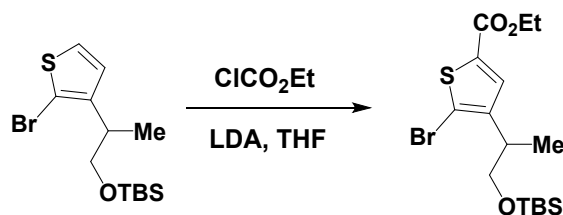
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A mixture of 2-methyl-2-(2-bromothiophen-3-yl)ethanol (3.70 g, 16.7 mmol), imidazole (1.71 g, 25.1 mmol) and TBSCl (3.03 g, 20.1 mmol) in DMF (10 mL) was stirred at RT for 1 h. Water (200 mL) and Et₂O (200 mL) were added and the resulting biphasic mixture separated. The organic extracts were then washed with water (2 x 100 mL), dried and evaporated *in vacuo*. The residue thus obtained was purified by flash column chromatography (SiO₂, 330 g, isohexanes, isocratic elution) to afford the title compound as a colourless oil (4.00 g, 70% yield); ¹H NMR δ: 7.54 (dd, *J* = 5.7, 0.6 Hz, 1H), 6.99 (d, *J* = 5.7 Hz, 1H), 3.61 (d, *J* = 6.6 Hz, 2H), 3.00 (sext, *J* = 6.8 Hz, 1H), 1.15 (d, *J* = 7.0 Hz, 3H), 0.81 (s, 9H), -0.04 (s, 3H), -0.05 (s, 3H).

Ethyl 5-bromo-4-(1-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)thiophene-2-carboxylate (27).

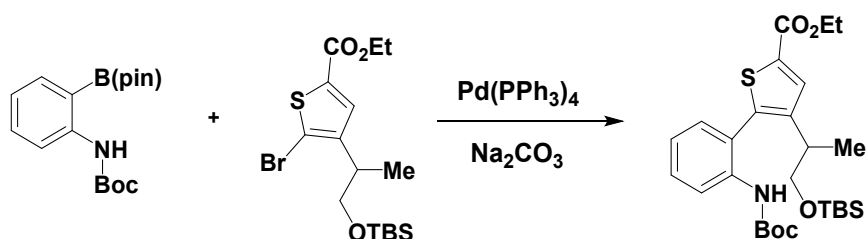
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To a solution of diisopropylamine (1.87 mL, 13.1 mmol) in THF (10 mL) at -78 °C was added *n*-butyllithium (2.5 M in hexanes, 4.77 mL, 11.9 mmol) and the mixture maintained at this temperature for 10 min. To this solution was added (2-(2-bromothien-3-yl)propoxy)(*tert*-butyl)dimethylsilane (4.00 g, 11.9 mmol) in THF (10 mL) and the mixture maintained at -78 °C for 1 h. Ethyl chloroformate (1.15 mL, 11.9 mmol) was added and the mixture was allowed to warm to -40 °C, then quenched by the addition of sat aq NH₄Cl (20 mL) and then diluted with EtOAc (100 mL). The organic phase was separated, washed with water (2 x 40 mL) and then dried (Na₂SO₄) and evaporated *in vacuo*. The residue thus obtained was purified by flash column chromatography (SiO₂, 330 g, 0-10% Et₂O in isohexanes, gradient elution) to afford the title compound as a yellow oil (2.10 g, 90% pure by ¹H NMR, 39% yield); ¹H NMR δ: 7.69 (s, 1H), 4.33-4.21 (m, 2H), 3.65 (d, *J* = 6.2 Hz, 2H), 3.01 (m, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.17 (d, *J* = 7.0 Hz, 3H), 0.80 (s, 9H), -0.05 (s, 3H), -0.06 (s, 3H).

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Ethyl 5-(2-((*tert*-butoxycarbonyl)amino)phenyl)4--(1-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)thiophene-2-carboxylate (28).

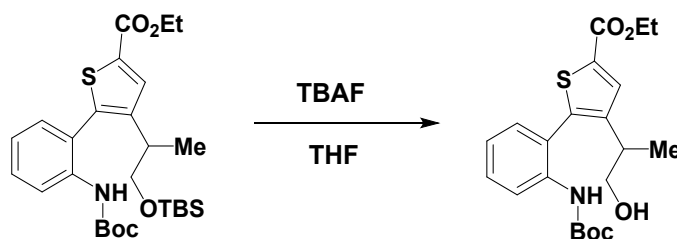


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To a solution of ethyl 5-bromo-4-(1-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)thiophene-2-carboxylate (2.10 g, 5.15 mmol), *tert*-butyl (2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-

yl)phenyl)carbamate (1.97 g, 6.18 mmol) and Pd(PPh₃)₄ (298 mg, 0.258 mmol) in 1,4-dioxane (25 mL) was added aq Na₂CO₃ (2.0 M, 7.7 mL). The resulting mixture was degassed with nitrogen and heated at 95 °C for 1 h. The mixture was cooled to RT, poured into water (100 mL) and extracted with EtOAc (50 mL). The organic layer was retained and the aq
 5 phase re-extracted with EtOAc (50 mL). The combined organic extracts were washed with water (2 x 20 mL) and then dried and evaporated *in vacuo*. The residue thus obtained was purified by flash column chromatography (SiO₂, 120 g, 0-10% Et₂O in isohexanes, gradient elution) to afford the title compound as a colourless gum (2.10 g, 76% yield); R_t 3.40 min (Method 1a); m/z 420 (M-Boc+H)⁺ (ES⁺); ¹H NMR δ: 8.41 (s, 1H), 7.80 (s, 1H), 7.51
 10 (apparent d, 1H), 7.41 (td, *J* = 7.4, 1.6 Hz, 1H), 7.31 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.21 (td, *J* = 7.5, 1.3 Hz, 1H), 4.35-4.23 (m, 2H), 3.58-3.51 (m, 2H), 2.67 (sext, *J* = 6.5 Hz, 1H), 1.35 (s, 9H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.16 (d, *J* = 6.9 Hz, 3H), 0.79 (s, 9H), -0.09 (s, 3H), -0.12 (s, 3H).

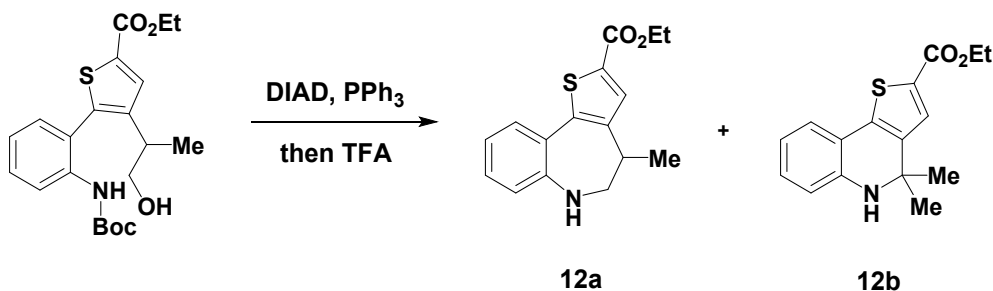
15 **Ethyl 5-(2-((*tert*-butoxycarbonyl)amino)phenyl)4--(1-hydroxypropan-2-yl)thiophene-2-carboxylate (11).**



20 To a solution of ethyl 5-(2-((*tert*-butoxycarbonyl)amino)phenyl)4-(1-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)thiophene-2-carboxylate (2.10 g, 4.04 mmol) in THF (10 mL) at 0 °C was added TBAF (1.0 M in THF, 4.04 mL). The mixture was warmed to RT, maintained at this temperature for 18 h and then partitioned between Et₂O (100 mL) and water (50 mL). The organic layer was separated, washed with further water (50 mL) and then dried and
 25 evaporated *in vacuo*. The residue thus obtained was purified by flash column

chromatography (SiO₂, 40 g, 0-50% EtOAc in isohexanes, gradient elution) to afford the title compound as a colourless gum (1.51 g, 90% yield). This material was used directly in the next step without any analysis.

5 Ethyl 4-methyl-5,6-dihydro-4*H*-benzo[*b*]thieno[2,3-*d*]azepine-2-carboxylate (12a).

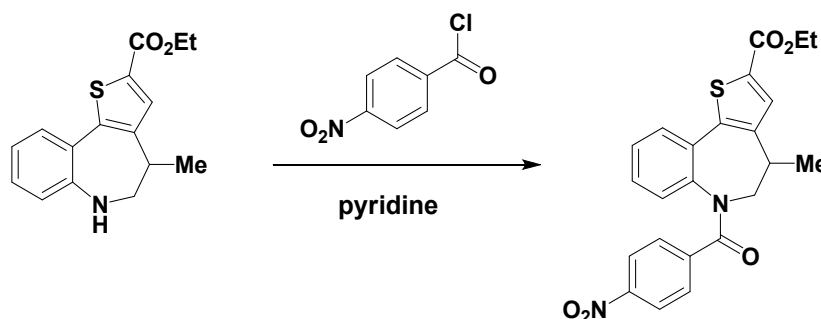


To a solution of ethyl 5-(2-((*tert*-butoxycarbonyl)amino)phenyl)-4-(1-hydroxypropan-2-yl)thiophene-2-carboxylate (1.50 g, 3.70 mmol) and triphenylphosphine (1.94 g, 7.40 mmol) in toluene (40 mL) at 0 °C was added DIAD (1.44 mL, 7.40 mmol) dropwise. The reaction mixture was warmed to RT, and then heated at reflux for 1 h. After cooling to RT, the mixture was treated with TFA (20.0 mL, 261 mmol) and left to stand for 30 min. The volatiles were evaporated *in vacuo* and the residue thus obtained taken up into MeOH (20 mL) and loaded onto SCX resin (ca. 30 g). The resin was washed with MeOH (100 mL) and the desired material then eluted with NH₃:MeOH (10%, 50 mL). The solution so obtained was evaporated *in vacuo* and the residue purified by flash column chromatography (SiO₂, 80 g, 0-30% Et₂O in isohexanes, gradient elution) to afford the title compound (580 mg, 54% yield); R_t 2.64 min (Method 1a); m/z 288 (M+H)⁺ (ES⁺); ¹H NMR δ: 7.64 (s, 1H), 7.58 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.06 (ddd, *J* = 8.1, 7.1, 1.4 Hz, 1H), 6.84 (dd, *J* = 8.1, 1.2 Hz, 1H), 6.68 (ddd, *J* = 8.0, 7.1, 1.2 Hz, 1H), 6.42 (apparent t, 1H), 4.27 (qd, *J* = 7.1, 0.7 Hz, 2H), 3.28-3.21 (m, 1H), 3.18-3.07 (m, 2H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.22 (d, *J* = 6.9 Hz, 3H).

Ethyl 4,4-dimethyl-4,5-dihydrothieno[3,2-*c*]quinoline-2-carboxylate (12b).

The title compound (210 mg, 19% yield) was the major impurity present in **Compound 12a** and was obtained from the crude product during its purification; R^t 2.65 min (Method 1a); m/z 288 (M+H)⁺ (ES⁺); ¹H NMR δ : 7.67 (s, 1H), 7.20 (dd, J = 7.6, 1.5 Hz, 1H), 7.02 (ddd, J = 8.1, 7.3, 1.5 Hz, 1H), 6.63 (dd, J = 8.1, 1.1 Hz, 1H), 6.54 (td, J = 7.5, 1.1 Hz, 1H), 6.28 (s, 1H), 4.28 (q, J = 7.1 Hz, 2H), 1.44 (s, 6H), 1.30 (t, J = 7.1 Hz, 3H).

Ethyl 4-methyl-6-(4-nitrobenzoyl)-5,6-dihydro-4H-benzo[*b*]thieno[2,3-*d*]azepine-2-carboxylate (29).



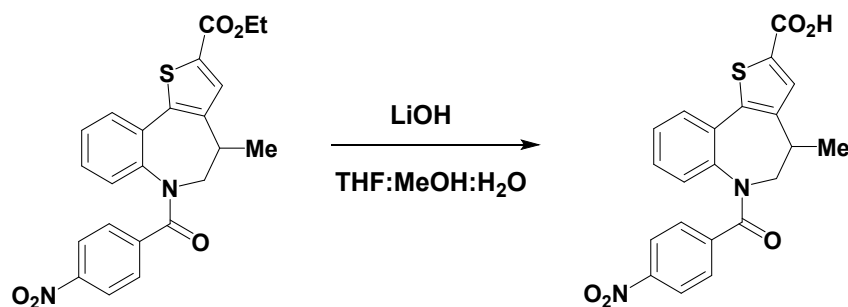
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To a solution of ethyl 4-methyl-5,6-dihydro-4H-benzo[*b*]thieno[2,3-*d*]azepine-2-carboxylate (580 mg, 2.02 mmol) in pyridine (10 mL) at RT was added 4-nitrobenzoyl chloride (412 mg, 2.22 mmol) and the mixture stirred at 50 °C for 1 h. The solvent was evaporated *in vacuo* and the residue triturated with water (20 mL). The solid so obtained was purified by flash column chromatography (SiO₂, 40 g, 0-50% EtOAc in isohexanes, gradient elution) to afford the title compound (present as an inseparable mixture of diastereomers; d.r 5:3) as a colourless solid, (810 mg, 90% yield); R^t 2.75 min (Method 1a); m/z 437 (M+H)⁺ (ES⁺); ¹H NMR δ : 8.07 (apparent d, 3.2H), 7.91 (s, 1H), 7.83 (dd, J = 7.8, 1.4 Hz, 1H), 7.84 (s, 0.6H), 7.70 (dd, J = 7.8, 1.4 Hz, 0.6H), 7.32-7.23 (over-lapping m, 4.8H), 7.10 (apparent t, 1.6H), 6.99 (dd, J = 8.0, 1.3 Hz, 0.6H), 6.91 (dd, J = 7.9, 1.3 Hz, 1H), 4.81 (dd, J = 13.6, 6.2 Hz, 1H), 4.75 (dd, J = 13.3, 6.9 Hz, 0.6H), 4.37-4.29 (m, 3.2H), 3.70-3.60 (m, 1H), 3.56 (dd, J = 13.2, 4.5 Hz, 0.6H), 3.29-3.21 (m, 0.6H), 3.00 (dd, J = 13.6, 12.2 Hz, 1H), 1.39 (d, J = 7.0 Hz,

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1.8H), 1.34-1.29 (over-lapping m, 7.8H). Residual 4-nitrobenzoic acid (4.5 wt%) and EtOAc (1 wt%) were present.

4-Methyl-6-(4-nitrobenzoyl)-5,6-dihydro-4H-benzo[*b*]thieno[2,3-*d*]azepine-2-carboxylic acid (13).

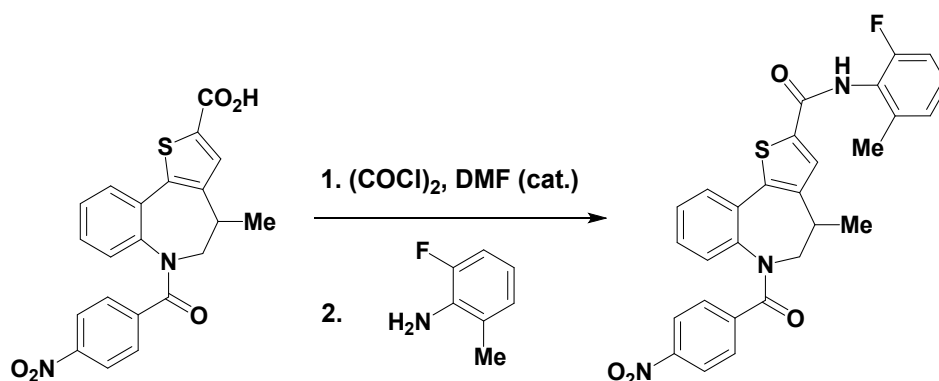


A mixture of ethyl 4-methyl-6-(4-nitrobenzoyl)-5,6-dihydro-4H-benzo[*b*]thieno[2,3-*d*]azepine-
10 2-carboxylate (798 mg, 1.83 mmol) and LiOH (48.2 mg, 2.01 mmol) in THF:MeOH:water
(1:1:1, 15 mL) was stirred at RT for 18 h. The resulting mixture was acidified to pH 1 by the
addition of aq HCl (1 M) and the solid that formed was isolated by filtration, washed with
water (20 mL) and dried to afford the title compound (present as an inseparable mixture of
diastereomers; d.r 5:3) as a white solid (680 mg, 88% yield); R_t 2.34 min (Method 1a); m/z
15 409 (M+H)⁺ (ES⁺); ¹H NMR δ: 13.31 (br, 1.6H), 8.07 (d, *J* = 8.6 Hz, 3.2H), 7.83 (s, 1H), 7.82
(dd, *J* = 7.9, 1.3 Hz, 1H), 7.77 (s, 0.6H), 7.69 (dd, *J* = 7.8, 1.5 Hz, 0.6H), 7.32-7.23 (over-
lapping m, 4.8H), 7.08 (t, *J* = 7.9 Hz, 1.6H), 6.98 (d, *J* = 7.9 Hz, 0.6H), 6.90 (d, *J* = 7.9 Hz,
1H), 4.81 (dd, *J* = 13.4, 6.1 Hz, 1H), 4.75 (dd, *J* = 13.3, 6.9 Hz, 0.6H), 3.68-3.59 (m, 1H),
3.54 (dd, *J* = 13.3, 4.5 Hz, 0.6H), 3.30-3.20 (m, 0.6H), 2.99 (t, *J* = 13.4 Hz, 1H), 1.39 (t, *J* =
20 6.9 Hz, 1.8H), 1.30 (d, *J* = 6.9 Hz, 3H); ¹³C NMR δ: 168.1 (C), 166.0 (C), 162.7 (C), 162.6
(C), 147.7 (C), 147.7 (C), 143.7 (C), 143.3 (C), 142.3 (C), 141.9 (C), 141.1 (C), 140.6 (C),
140.5 (C), 139.0 (C), 136.7 (CH), 134.6 (CH), 133.5 (C), 133.2 (C), 130.7 (CH), 129.8 (C),
129.7 (CH), 129.1 (CH), 128.9 (CH), 128.8 (CH), 128.7 (CH), 128.2 (CH), 128.2 (CH), 128.1

(CH), 123.7 (CH), 123.3 (CH), 54.6 (CH₂), 53.0 (CH₂), 35.7 (CH), 34.6 (CH), 19.8 (CH₃), 19.4 (CH₃). Residual 4-nitrobenzoic acid (4.0 wt%) was present.

***N*-(2-Fluoro-6-methylphenyl)-4-methyl-6-(4-nitrobenzoyl)-5,6-dihydro-4*H*-benzo[*b*]**

5 thieno[2,3-*d*]azepine-2-carboxamide (30).

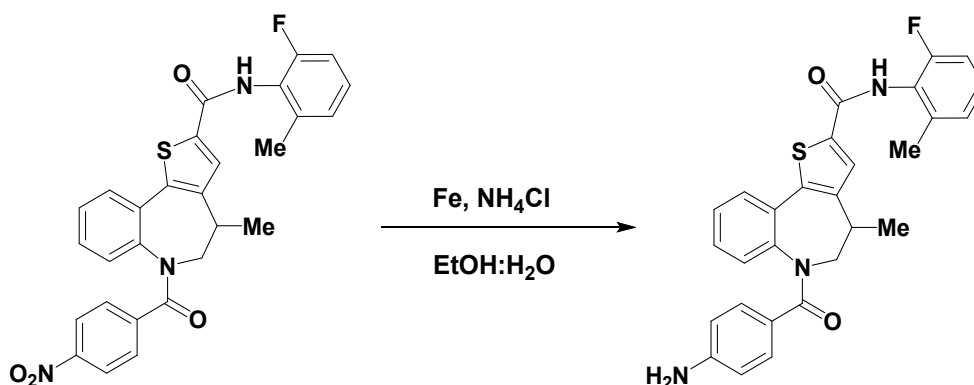


To a solution of 4-methyl-6-(4-nitrobenzoyl)-5,6-dihydro-4*H*-benzo[*b*]thieno[2,3-*d*]azepine-2-carboxylic acid (300 mg, 0.735 mmol) in DCM (10 mL) at RT was added oxalyl chloride (321
 10 μL, 3.67 mmol) followed by 1 drop of DMF. After 30 min the mixture was evaporated *in vacuo*, the resulting residue taken up into DCM (5 mL), and this solution added dropwise to a solution of 2-fluoro-6-methylaniline (184 mg, 1.47 mmol) in pyridine (5.0 mL). After 1 h the volatiles were evaporated *in vacuo* and the residue that was obtained was triturated with water (20 mL). The solid that formed was collected by filtration and purified by flash column
 15 chromatography (SiO₂, 40 g, 0-50% EtOAc in isohexanes, gradient elution) to afford the title compound (present as an inseparable mixture of diastereomers; d.r 5:3) as a yellow gum (310 mg, 80% pure by ¹H NMR, 65% yield); R_t 2.59 min (Method 1a); m/z 516 (M+H)⁺ (ES⁺); ¹H NMR δ: 10.06 (s, 0.6H), 10.05 (s, 1H), 8.14-8.05 (over-lapping m, 4.8H), 7.84 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.70 (dd, *J* = 7.9, 1.4 Hz, 0.6H), 7.33 (d, *J* = 8.8 Hz, 1.2H), 7.31-7.25 (over-
 20 lapping m, 5.2H), 7.18-7.12 (over-lapping m, 3.2H), 7.08 (br t, *J* = 7.7 Hz, 1.6H), 6.99 (dd, *J* = 7.9, 1.3 Hz, 0.6H), 6.90 (dd, *J* = 8.0, 1.3 Hz, 1H), 4.84 (dd, *J* = 13.6, 6.0 Hz, 1H), 4.78 (dd, *J* = 13.3, 7.0 Hz, 0.6H), 3.71-3.61 (m, 1H), 3.59 (dd, *J* = 13.3, 4.6 Hz, 0.6H), 3.32-3.23 (m,

0.6H), 3.03 (apparent t, $J = 12.9$ Hz, 1H), 2.27 (s, 4.8H), 1.44 (d, $J = 7.0$ Hz, 1.8H), 1.36 (d, $J = 7.0$ Hz, 3H). Residual EtOAc (20 wt%) was present.

6-(4-Aminobenzoyl)-*N*-(2-fluoro-6-methylphenyl)-4-methyl-5,6-dihydro-4*H*-benzo[*b*]

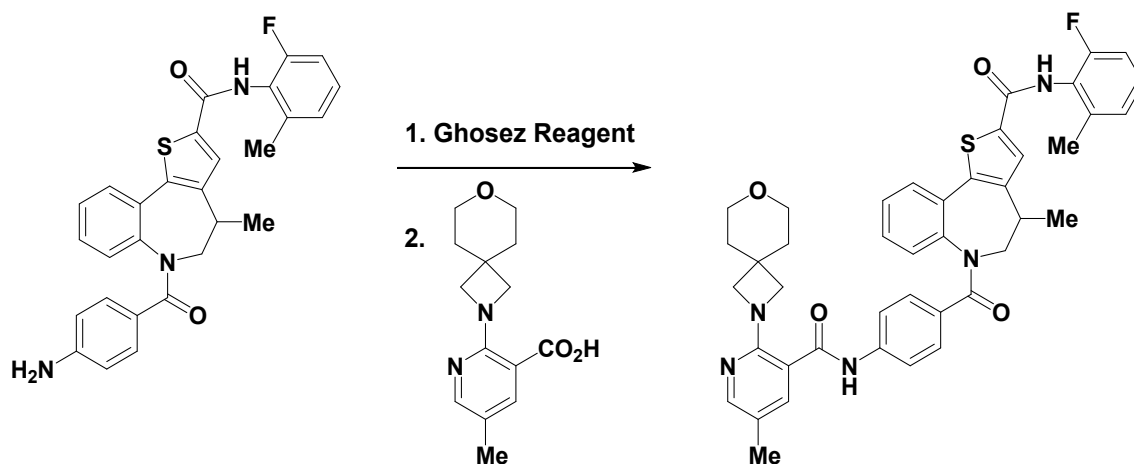
5 thieno[2,3-*d*]azepine-2-carboxamide (31).



A mixture of *N*-(2-fluoro-6-methylphenyl)-4-methyl-6-(4-nitrobenzoyl)-5,6-dihydro-4*H*-benzo[*b*]thieno[2,3-*d*]azepine-2-carboxamide (300 mg, 0.582 mmol), iron powder (325 mg, 5.82 mmol) and NH₄Cl (311 mg, 5.82 mmol) in EtOH:water (3:1, 20 mL) was heated at reflux for 1 h. The reaction mixture was filtered, whilst still hot, through a pad of celite (ca. 3 g) and the filtrate evaporated *in vacuo*. The residue thus obtained was taken up into DCM (30 mL), washed with water (2 x 10 mL), dried (Na₂SO₄) and evaporated *in vacuo* to afford the title compound as a colourless solid (235 mg, 82% yield); R_t 2.27 min (Method 1a); *m/z* 486 (M+H)⁺ (ES⁺). This material was used in the subsequent step without additional purification or analysis.

***N*-(2-Fluoro-6-methylphenyl)-4-methyl-6-(4-(5-methyl-2-(7-oxa-2-azaspiro[3.5]nonan-2-yl)nicotinamido)benzoyl)-5,6-dihydro-4*H*-benzo[*b*]thieno[2,3-*d*]azepine-2-carboxamide**

20 (14).

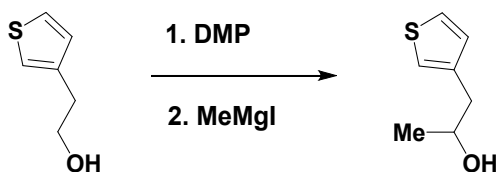


- To a solution of 5-methyl-2-(7-oxa-2-azaspiro[3.5]nonan-2-yl)nicotinic acid (186 mg, 0.711 mmol) in DCM (5.0 mL) was added Ghosez reagent (81.0 μ L, 0.616 mmol) and the mixture stirred at RT for 15 min. The resulting yellow solution was added to a solution of 6-(4-aminobenzoyl)-*N*-(2-fluoro-6-methylphenyl)-4-methyl-5,6-dihydro-4*H*-benzo[*b*]thieno[2,3-*d*]azepine-2-carboxamide (230 mg, 0.474 mmol) in pyridine (5.0 mL) and after 1h at RT the reaction mixture was evaporated *in vacuo*. The residue that formed was triturated with water (20 mL) and the resulting buff solid, was collected by filtration and dried. This solid was further purified by flash column chromatography (SiO₂, 40 g, 0-10% MeOH in DCM, gradient elution) to afford the title compound (present as an inseparable mixture of diastereomers; d.r 5:3) as a white solid (210 mg, 60% yield); *R*^t 1.96 min (Method 1a); *m/z* 730 (M+H)⁺ (ES⁺); ¹H NMR δ : 10.38 (s, 1.6H), 10.03 (s, 1.6H), 8.11 (br s, 1H), 8.08 (br s, 0.6H), 8.04 (dd, *J* = 2.3, 0.9 Hz, 1.6H), 7.83 (br d, *J* = 7.9 Hz, 1H), 7.73 (br d, *J* = 7.9 Hz, 0.6H), 7.52 (br d, 3.2H), 7.48 (d, *J* = 2.3 Hz, 1.6H), 7.30-7.25 (over-lapping m, 3.2H), 7.17-7.10 (over-lapping m, 6.4H), 7.02 (br d, 1.6H), 6.85 (br t, 1.6H), 4.93-4.76 (m, 1.6H), 3.60 (s, 6.4H), 3.46 (apparent t, 6.4H), 3.34-3.28 (obscured by solvent, assume 1.6H), 2.93 (broad t, 1.6H), 2.27 (s, 4.8H), 2.17 (s, 4.8H), 1.62 (apparent t, 6.4H), 1.41 (d, *J* = 6.9 Hz, 1.8H), 1.35 (d, *J* = 6.9 Hz, 3H);
- 20 **Chiral separation of *N*-(2-fluoro-6-methylphenyl)-4-methyl-6-(4-(5-methyl-2-(7-oxa-2-azaspiro[3.5]nonan-2-yl)nicotinamido)benzoyl)-5,6-dihydro-4*H*-benzo[*b*]thieno[2,3-*d*]azepine-2-carboxamide.**

A racemic sample of the title compound (130 mg, 0.178 mmol) was separated by chiral HPLC (**Method 1**) to afford Product A (15 mg, 12% yield) and Product B (12 mg, 9% yield), both present as an inseparable mixture of diastereomers (d.r 5:3). Product A was arbitrarily assigned as the (4*R*)-isomer; R^t 2.01 min (Method 1a); m/z 730 (M+H)⁺ (ES⁺); R^t 13.43 min (**Method 2**) >99%ee. Product B was arbitrarily assigned as the (4*S*)-isomer; R^t 2.02 min (Method 1a); m/z 730 (M+H)⁺ (ES⁺); R^t 21.03 min (**Method 2**) >99%ee; ¹H NMR spectra for both enantiomers were identical to that obtained on the racemate.

10 Synthesis of (*rac*)-20

1-Methyl-2-(thien-3-yl)ethanol (**32**).

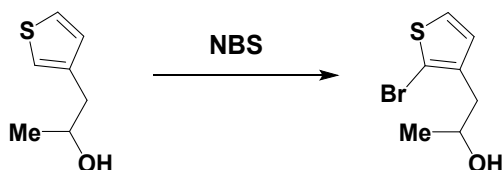


15

To a solution of 2-(thien-3-yl)ethanol (3.60 g, 28.1 mmol) in DCM (100 mL) was added DMP (11.9 g, 28.1 mmol) and the mixture stirred at RT for 18 h. The reaction mixture was washed sequentially with aq Na₂S₂O₃ (10% w/v, 100 mL) and with sat aq NaHCO₃ (100 mL) and then dried (Na₂SO₄) and evaporated *in vacuo*. The crude aldehyde (3.10 g) so obtained was taken up into Et₂O (30 mL) and was added slowly to an ice cold solution of MeMgI [prepared from Mg (2.05 g, 84.0 mmol) and MeI (5.27 mL, 84.0 mmol) in Et₂O (50 mL)]. The mixture was warmed to RT for 30 min, then cooled in an ice bath and carefully acidified to pH 1 by the addition of aq HCl (1 M). The resulting biphasic mixture was separated and the organic phase dried and evaporated *in vacuo*. The residue thus obtained was purified by flash column chromatography (SiO₂, 80 g, 0-50% EtOAc in isohexanes, gradient elution) to afford the title compound as a colourless oil (2.80 g, 69% yield); R^t 1.47 min (Method 1a); ¹H NMR

δ : 7.40 (dd, $J = 4.9, 2.9$ Hz, 1H), 7.15-7.13 (m, 1H), 6.99 (dd, $J = 4.9, 1.2$ Hz, 1H), 4.52 (d, $J = 4.8$ Hz, 1H), 3.87-3.78 (m, 1H), 2.70 (dd, $J = 13.9, 6.4$ Hz, 1H), 2.59 (dd, $J = 13.9, 6.3$ Hz, 1H), 1.03 (d, $J = 6.1$ Hz, 3H).

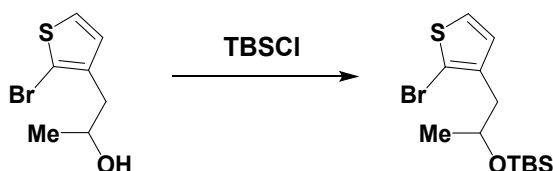
5 1-Methyl-2-(2-bromothien-3-yl)ethanol (33).



To a solution of 1-methyl-2-(thien-3-yl)ethanol (2.30 g, 16.2 mmol) in DCM (241 mL) was
10 added a solution of NBS (2.88 g, 16.2 mmol) in AcOH (130 mL) at RT. The resulting mixture
was maintained at RT for 15 min and then evaporated *in vacuo*. The residue thus obtained
was taken up into Et₂O (200 mL) and was washed with sat aq NaHCO₃ (100 mL). The
organic extracts were dried and evaporated *in vacuo* to afford the title compound as a pale
yellow oil (3.11 g, 92% pure by ¹H NMR, 78% yield); ¹H NMR δ : 7.51 (d, $J = 5.6$ Hz, 1H), 6.96
15 (d, $J = 5.6$ Hz, 1H), 4.69 (d, $J = 4.8$ Hz, 1H), 3.89-3.79 (m, 1H), 2.65 (dd, $J = 13.8, 6.5$ Hz,
1H), 2.55 (dd, $J = 13.8, 6.4$ Hz, 1H), 1.03 (d, $J = 6.2$ Hz, 3H). Residual 1-(thiophen-3-
yl)propan-2-ol (8 wt%) was present.

((1-(2-Bromothien-3-yl)propan-2-yl)oxy)(*tert*-butyl)dimethylsilane (34).

20

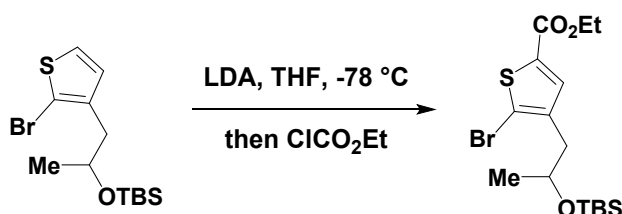


A mixture of 1-methyl-2-(2-bromothien-3-yl)ethanol (3.11 g, 14.1 mmol), TBSCl (2.12 g, 14.1 mmol) and imidazole (958 mg, 14.1 mmol) in DMF (50 mL) was stirred at RT for 5 h and then

evaporated *in vacuo*. The resulting residue was taken up into Et₂O (50 mL), washed sequentially with brine (20 mL) and with water (20 mL) and the organic extracts then dried and evaporated *in vacuo*. The residue thus obtained was purified by flash column chromatography (SiO₂, 220 g, isohexanes, isocratic elution) to afford the title compound as a
 5 colourless oil (4.35 g, 90% yield); ¹H NMR δ: 7.51 (d, *J* = 5.6 Hz, 1H), 6.92 (d, *J* = 5.6 Hz, 1H), 4.07-3.99 (m, 1H), 2.67-2.58 (m, 2H), 1.12 (d, *J* = 6.1 Hz, 1H), 0.79 (s, 9H), -0.06 (s, 3H), -0.19 (s, 3H).

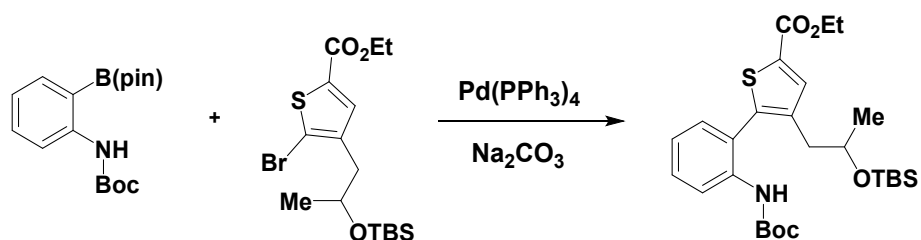
Ethyl 5-bromo-4-(2-((*tert*-butyldimethylsilyl)oxy)propyl)thiophene-2-carboxylate (16).

10



To a solution of LDA (1.0 M in THF/hexanes, 8.95 mL) in THF (10 mL) at -78 °C was added a solution of ((1-(2-bromothiophen-3-yl)propan-2-yl)oxy)(*tert*-butyl)dimethylsilane (3.00 g, 8.95
 15 mmol) in THF (20 mL). The resulting mixture was maintained at -78 °C for 45 min and then was added to a solution of ethyl chloroformate (860 μL, 8.95 mmol) in THF (5.0 mL). After stirring at -78 °C for a further 2 h, sat aq NH₄Cl (20 mL) was added and the resulting biphasic mixture was diluted with EtOAc (50 mL). The organic layer was separated, washed with water (20 mL) and then dried and evaporated *in vacuo*. The residue thus obtained was
 20 purified by flash column chromatography (SiO₂, 40 g, 0-10% Et₂O in isohexanes, gradient elution) to afford the title compound as a colourless oil (1.49 g, 39% yield); ¹H NMR δ: 7.61 (s, 1H), 4.27 (qd, *J* = 7.1, 1.6 Hz, 2H), 4.07-4.00 (m, 1H), 2.69-2.60 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.12 (d, *J* = 6.1 Hz, 3H), 0.78 (s, 9H), -0.06 (s, 3H), -0.22 (s, 3H).

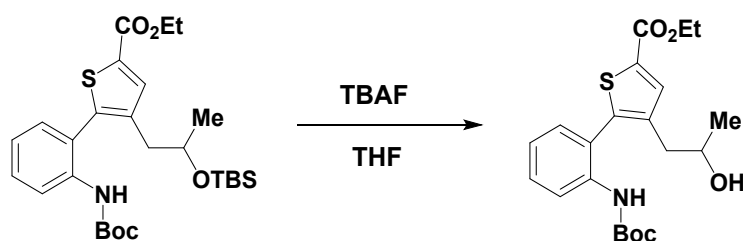
25 **Ethyl 5-(2-((*tert*-butoxycarbonyl)amino)phenyl)-4-(2-((*tert*-butyldimethylsilyl)oxy)propyl)thiophene-2-carboxylate (35).**



To a solution of ethyl 5-bromo-4-(2-((*tert*-butyldimethylsilyl)oxy)propyl)thiophene-2-carboxylate (1.30 g, 3.19 mmol), *tert*-butyl (2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)carbamate (1.22 g, 3.83 mmol) and Pd(PPh₃)₄ (184 mg, 0.160 mmol) in 1,4-dioxane (25 mL) was added aq Na₂CO₃ (2.0 M, 4.8 mL) and the mixture degassed with nitrogen and heated at 95 °C for 1 h. The mixture was cooled to RT, poured into water (100 mL) and diluted with Et₂O (100 mL). The organic layer was separated, washed with water (100 mL) and then dried and evaporated *in vacuo*. The residue thus obtained was purified by flash column chromatography (SiO₂, 80 g, 0-10% Et₂O in isohexanes, gradient elution) to afford the title compound as a colourless oil (1.41 g, 83% yield); R^t 3.34 min (Method 1a); m/z 420 (M-Boc+H)⁺ (ES⁺); ¹H NMR δ: 8.39 (s, 1H), 7.79 (s, 1H), 7.54 (apparent d, 1H), 7.41 (apparent td, 1H), 7.33 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.22 (td, *J* = 7.5, 1.3 Hz, 1H), 4.29 (q, 7.1 Hz, 2H), 3.97-3.90 (m, 1H), 2.52-2.43 (assume 2H, obscured by solvent), 1.36 (s, 9H), 1.28 (t, *J* = 7.1 Hz, 3H), 0.96 (d, *J* = 6.0 Hz, 3H), 0.77 (s, 9H), -0.08 (s, 3H), -0.18 (s, 3H).

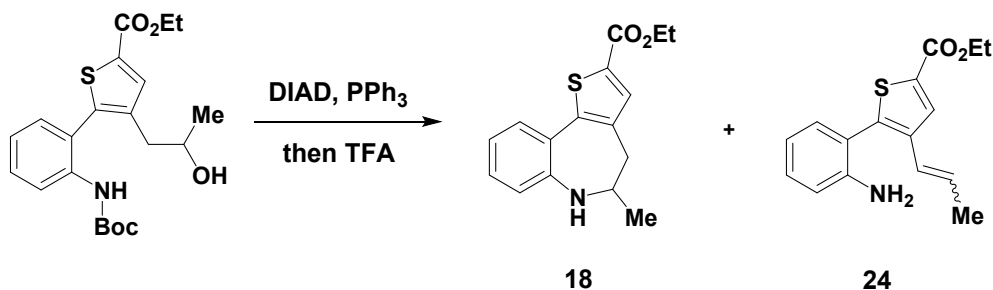
Ethyl 5-(2-((*tert*-butoxycarbonyl)amino)phenyl)-4-(2-hydroxypropyl)thiophene-2-carboxylate (17).

20



To an ice cold solution of ethyl 5-(2-((*tert*-butoxycarbonyl)amino)phenyl)-4-(2-((*tert*-butyldimethylsilyl)oxy)propyl)thiophene-2-carboxylate (1.40 g, 2.69 mmol) in THF (10 mL) was added TBAF (1.0 M in THF, 2.70 mL) and the reaction mixture warmed to RT for 18 h and then partitioned between Et₂O (100 mL) and water (50 mL). The organic layer was separated, washed with further water (50 mL), dried and evaporated *in vacuo*. The residue thus obtained was purified by flash column chromatography (SiO₂, 40 g, 0-50% EtOAc in isohexanes, gradient elution) to afford the title compound as a colourless gum (970 mg, 87% yield); R_t 2.61 min (Method 1a); ¹H NMR δ: 8.36 (s, 1H), 7.77 (s, 1H), 7.50 (apparent d, 1H), 7.41 (apparent td, 1H), 7.30 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.21 (td, *J* = 7.5, 1.3 Hz, 1H), 4.69 (d, *J* = 4.5 Hz, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 3.88-3.79 (m, 1H), 2.45 (dd, *J* = 14.3, 4.6 Hz, 1H), 2.38 (dd, *J* = 14.3, 8.0 Hz, 1H), 1.36 (s, 9H), 1.29 (t, *J* = 7.1 Hz, 3H), 0.96 (d, *J* = 6.1 Hz, 3H).

Ethyl 5-methyl-5,6-dihydro-4*H*-benzo[*b*]thieno[2,3-*d*]azepine-2-carboxylate (18).



15

To an ice cold solution of ethyl 5-(2-((*tert*-butoxycarbonyl)amino)phenyl)-4-(2-hydroxypropyl)thiophene-2-carboxylate (970 mg, 2.39 mmol) and triphenylphosphine (1.26 g, 4.78 mmol) in toluene (40 mL) was added DIAD (930 μL, 4.78 mmol) dropwise. The resulting mixture was warmed to RT, heated at reflux for 1 h, re-cooled to RT and was then treated with TFA (20.0 mL, 261 mmol). After 30 min the volatiles were evaporated *in vacuo* and the residue thus obtained taken up into MeOH (20 mL) and loaded onto SCX resin (ca. 30 g). The resin bed was washed with MeOH (100 mL) and the crude product then recovered by elution with NH₃:MeOH (10%, 50 mL). The solution so obtained was evaporated *in vacuo*

and the residue was purified by flash column chromatography (SiO₂, 80 g, 0-30% Et₂O in isohexanes, gradient elution) to afford the title compound as a yellow solid (.278 mg, 40% yield); R_t 2.56 min (Method 1a); m/z 288 (M+H)⁺ (ES⁺); ¹H NMR δ: 7.53 (s, 1H), 7.49 (dd, J = 8.0, 1.5 Hz, 1H), 7.04 (2 x dd, J = 8.0, 1.5 Hz, 1H), 6.87 (dd, J = 8.3, 1.3 Hz, 1H), 6.65 (2 x dd, J = 7.1, 1.3 Hz, 1H), 6.09 (apparent s, 1H), 4.27 (q, J = 7.1 Hz, 2H), 3.47-3.37 (m, 1H), 3.04 (dd, J = 15.8, 2.0 Hz, 1H), 2.77 (dd, J = 15.8, 8.1 Hz, 1H), 1.29 (t, J = 7.1 Hz, 3H), 1.22 (d, J = 6.5 Hz, 3H).

Ethyl 5-(2-aminophenyl)-4-(prop-1-en-1-yl)thiophene-2-carboxylate (24).

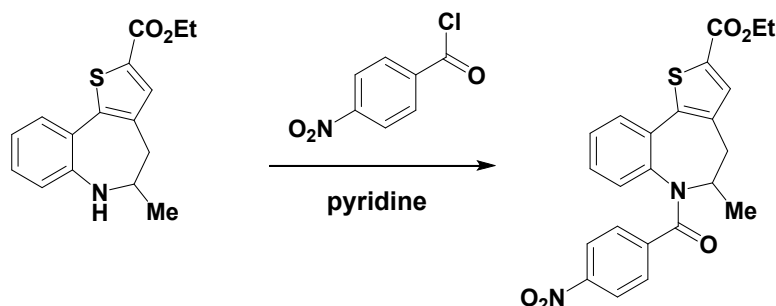
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The title compound (203 mg, 29% yield) was isolated, as a 4:1 mixture of *trans*:*cis* isomers, during the purification of **Compound 18**; R_t 2.69 min (Method 1a); m/z 288 (M+H)⁺ (ES⁺); ¹H NMR δ: 8.01 (s, 0.8H), 7.85 (s, 0.2H), 7.12 (over-lapping ddd, 1H), 6.98 (over-lapping dd, 1H), 6.76 (over-lapping dd, 1H), 6.60 (over-lapping td, 1H), 6.29 (dq, J = 15.8, 6.6 Hz, 0.8H), 6.03-5.95 (over-lapping m, 1H), 5.68 (dq, J = 11.6, 7.1 Hz, 0.2H), 4.95 (s, 0.4H), 4.92 (s, 1.6H), 4.31 (over-lapping q, 2H), 1.79 (dd, J = 7.1, 1.8 Hz, 0.6H), 1.74 (dd, J = 6.6, 1.7 Hz, 2.4H), 1.30 (over-lapping t, 3H).

15

Ethyl 5-methyl-6-(4-nitrobenzoyl)-5,6-dihydro-4H-benzo[*b*]thieno[2,3-*d*]azepine-2-

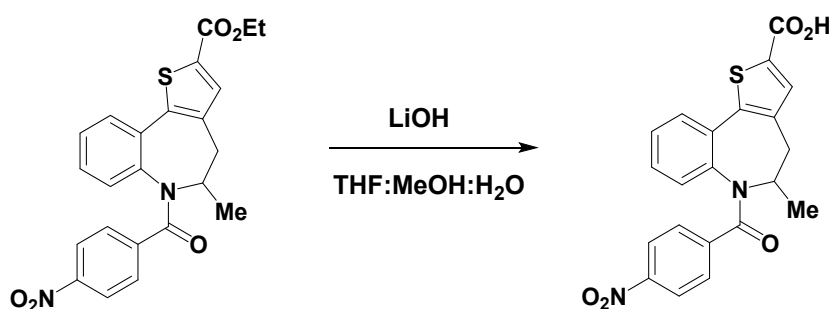
20 carboxylate (36).



To a solution of ethyl 5-methyl-5,6-dihydro-4H-benzo[*b*]thieno[2,3-*d*]azepine-2-carboxylate (275 mg, 0.957 mmol) in pyridine (10 mL) was added 4-nitrobenzoyl chloride (195 mg, 1.05

mmol) and the resulting mixture was stirred at RT for 18 h and then at 50 °C for 3 h. The solvent was evaporated *in vacuo* and the resulting residue taken up into EtOAc (30 mL) and washed with aq HCl (1 M, 20 mL). The organic extracts were dried and evaporated *in vacuo* and the crude product was purified by flash column chromatography (SiO₂, 12 g, 0-50%
5 EtOAc in isohexanes, gradient elution) to afford the title compound as a colourless solid (260 mg, 62% yield). Unreacted starting material (185 mg) was also isolated, which was re-subjected to the acylation conditions at RT overnight. The reaction was worked up and purified as above to afford a white solid (130 mg, 31%). The two batches were combined and analysed; R_t 2.64 min (Method 1a); m/z 437 (M+H)⁺ (ES⁺); ¹H NMR δ: 8.01 (d, *J* = 8.8 Hz,
10 2H), 7.87 (s, 1H), 7.56 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.35 (td, *J* = 7.6, 1.3 Hz, 1H), 7.19-7.07 (over-lapping m, 4H), 5.26-5.17 (m, 1H), 4.39-4.27 (m, 2H), 3.23 (dd, *J* = 14.7, 5.9 Hz, 1H), 2.34 (dd, *J* = 14.7, 11.3 Hz, 1H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.29 (d, *J* = 6.5 Hz, 3H).

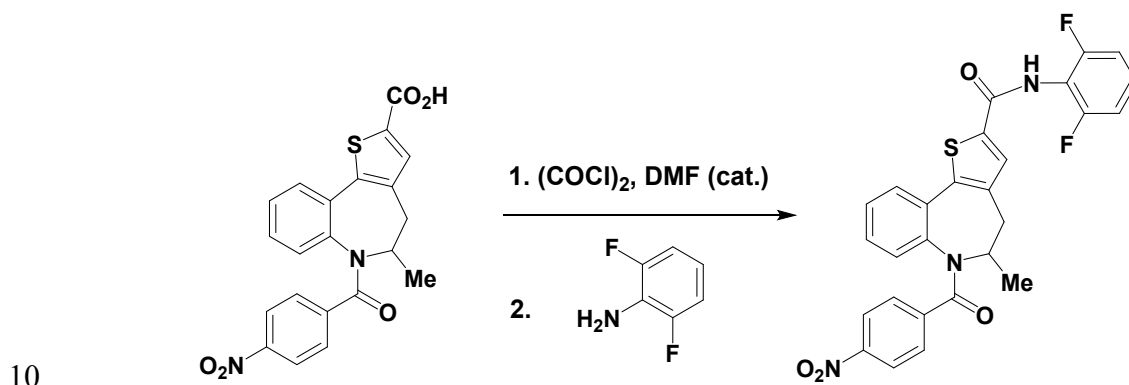
5-Methyl-6-(4-nitrobenzoyl)-5,6-dihydro-4*H*-benzo[*b*]thieno[2,3-*d*]azepine-2-carboxylic
15 **acid (19).**



A mixture of ethyl 5-methyl-6-(4-nitrobenzoyl)-5,6-dihydro-4*H*-benzo[*b*]thieno[2,3-*d*]azepine-
20 2-carboxylate (370 mg, 0.848 mmol) and LiOH (20.3 mg, 0.848 mmol) in THF:MeOH:water (1:1:1, 15 mL) was stirred at RT overnight. The resulting mixture was acidified to pH 1 by the addition of aq HCl (1 M) and then diluted with EtOAc (20 mL). The organic layer was separated and washed with water (2 x 10 mL) and was then dried and evaporated *in vacuo* to afford the title compound as a colourless solid (325 mg, 92% yield); R_t 2.30 min (Method

1a); m/z 409 (M+H)⁺ (ES⁺); ¹H NMR δ : 8.00 (d, J = 8.8 Hz, 2H), 7.75 (s, 1H), 7.52 (dd, J = 7.7, 1.5 Hz, 1H), 7.33 (td, J = 7.6, 1.3 Hz, 1H), 7.17-7.11 (over-lapping m, 3H), 7.06 (d, J = 7.9 Hz, 1H), 5.26-5.17 (m, 1H), 3.20 (dd, J = 14.8, 6.0 Hz, 1H), 2.34 (dd, J = 14.8, 11.2 Hz, 1H), 1.28 (d, J = 6.4 Hz, 3H); ¹³C NMR δ : 167.6 (C), 163.0 (C), 147.2 (C), 142.9 (C), 141.6 (C), 139.3 (C), 136.7 (C), 134.7 (CH), 134.3 (C), 133.0 (C), 132.2 (CH), 129.2 (CH), 129.2 (CH), 128.6 (CH), 128.1 (2 x CH), 123.1 (2 x CH), 58.6 (CH), 33.3 (CH₂), 18.4 (CH₃).

***N*-(2,6-Difluorophenyl)-5-methyl-6-(4-nitrobenzoyl)-5,6-dihydro-4*H*-benzo[*b*]thieno[2,3-*d*]azepine-2-carboxamide (37).**



To a solution of ethyl 5-methyl-6-(4-nitrobenzoyl)-5,6-dihydro-4*H*-benzo[*b*]thieno[2,3-*d*]azepine-2-carboxylate (190 mg, 0.465 mmol) in DCM (10 mL) was added oxalyl chloride (204 μ L, 2.33 mmol) followed by 1 drop of DMF. The resulting mixture was stirred for 30 min and then evaporated *in vacuo*. The residue thus obtained was taken up into DCM (5.0 mL), and was added dropwise to a solution of 2,6-difluoroaniline (120 mg, 0.930 mmol) in pyridine (5.0 mL) and stirred for 1 h. The solvent was evaporated *in vacuo* and the residue was triturated with water (10 mL). The solid that formed was collected by filtration and was purified by flash column chromatography (SiO₂, 12 g, 0-50% EtOAc in isohexanes, gradient elution) to afford the title compound as a white solid (230 mg, 93% yield); R_t 2.51 min (Method 1a); m/z 520 (M+H)⁺ (ES⁺); ¹H NMR δ : 10.33 (s, 1H), 8.04-7.99 (over-lapping s and d, 3H), 7.57 (dd, J = 7.7, 1.4 Hz, 1H), 7.47-7.40 (m, 1H), 7.35 (td, J = 7.6, 1.3 Hz, 1H), 7.28-7.20 (over-lapping m, 2H), 7.19-7.13 (over-lapping m, 3H), 7.09 (dd, J = 7.9, 1.3 Hz, 1H),

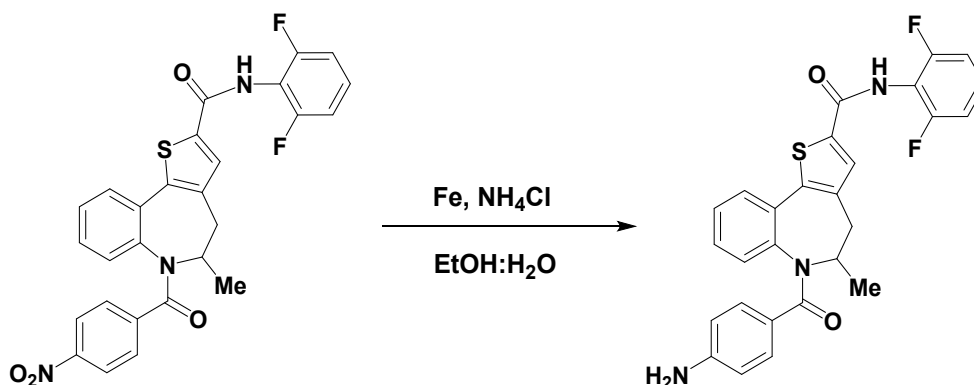
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5.33-5.23 (m, 1H), 3.21 (dd, $J = 14.9, 6.0$ Hz, 1H), 2.43 (dd, $J = 14.9, 11.0$ Hz, 1H), 1.30 (d, $J = 6.5$ Hz, 3H). Residual DCM (7.5 wt%) and EtOAc (1.5 wt%) present.

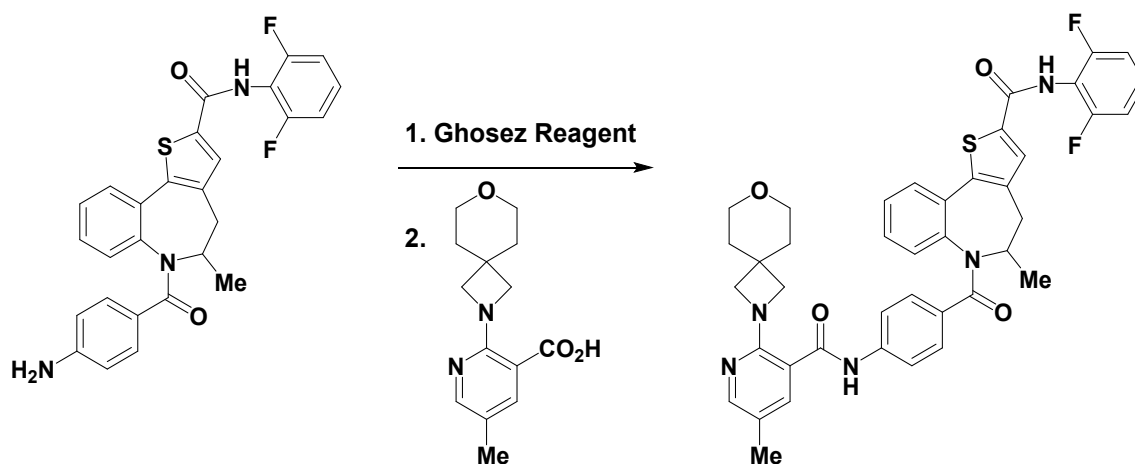
6-(4-Aminobenzoyl)-*N*-(2,6-difluorophenyl)-5-methyl-5,6-dihydro-4*H*-benzo[*b*]thieno

5 [2,3-*d*]azepine-2-carboxamide (38).



A mixture of *N*-(2,6-difluorophenyl)-5-methyl-6-(4-nitrobenzoyl)-5,6-dihydro-4*H*-benzo[*b*]thieno[2,3-*d*]azepine-2-carboxamide (175 mg, 0.337 mmol), iron powder (188 mg, 3.37 mmol) and NH₄Cl (180 mg, 3.37 mmol) in EtOH:water (3:1, 40 mL) was heated at reflux for 1 h. The mixture was filtered, whilst still hot, through a pad of celite and the filtrate was evaporated *in vacuo*. The residue thus obtained was taken up into DCM (30 mL), washed with water (30 mL) and then dried and evaporated *in vacuo* to afford the title compound as an off-white solid (162 mg, 97% yield); R_t 2.13 min (Method 1a); m/z 490 (M+H)⁺ (ES⁺); ¹H NMR δ : 10.27 (br s, 1H), 7.98 (s, 1H), 7.58 (dd, $J = 7.7, 1.5$ Hz, 1H), 7.46-7.39 (m, 1H), 7.35 (td, $J = 7.6, 1.2$ Hz, 1H), 7.26-7.18 (over-lapping m, 3H), 6.86 (apparent d, 1H), 6.63 (d, $J = 8.6$ Hz, 2H), 6.20 (d, $J = 8.6$ Hz, 2H), 5.39 (s, 2H), 5.21-5.09 (m, 1H), 3.13 (dd, $J = 15.0, 6.2$ Hz, 1H), 2.41 (dd, $J = 15.0, 10.8$ Hz, 1H), 1.22 (d, $J = 6.5$ Hz, 3H).

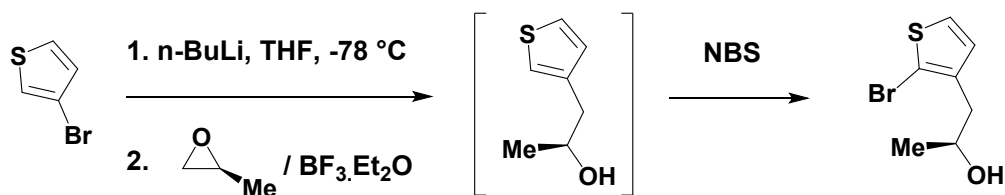
20 *N*-(2,6-Difluorophenyl)-5-methyl-6-(4-(5-methyl-2-(7-oxa-2-azaspiro[3.5]nonan-2-yl)nicotinamido)benzoyl)-5,6-dihydro-4*H*-benzo[*b*]thieno[2,3-*d*]azepine-2-carboxamide (20).



To a solution of 5-methyl-2-(7-oxa-2-azaspiro[3.5]nonan-2-yl)nicotinic acid (121 mg, 0.460 mmol) in DCM (5.0 mL) was added Ghosez reagent (52.7 μ L, 0.398 mmol) and the mixture stirred at RT for 15 min. The resulting yellow solution was evaporated *in vacuo* and the residue taken up in DCM (5.0 mL) and added to a solution of 6-(4-aminobenzoyl)-*N*-(2,6-difluorophenyl)-5-methyl-5,6-dihydro-4*H*-benzo[*b*]thieno[2,3-*d*]azepine-2-carboxamide (150 mg, 0.306 mmol) in pyridine (5.0 mL). After 1 h at RT the reaction mixture was evaporated *in vacuo*. The residue was triturated with water (20 mL) to provide a buff solid, which was collected by filtration, dried and then purified by flash column chromatography (SiO₂, 40 g, 0-10% MeOH in DCM, gradient elution) to afford the title compound as a white solid (174 mg, 77% yield); *R*_t 1.89 min (Method 1a); *m/z* 734 (M+H)⁺ (ES⁺); ¹H NMR δ : 10.32 (s, 1H), 10.30 (s, 1H), 8.03 (dd, *J* = 2.3, 0.8 Hz, 1H), 8.01 (s, 1H), 7.59 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.48-7.34 (over-lapping m, 5H), 7.29-7.17 (over-lapping m, 3H), 6.97 (br d, *J* = 7.9 Hz, 1H), 6.91 (br d, *J* = 8.2 Hz, 2H), 5.29-5.16 (m, 1H), 3.59 (s, 4H), 3.46 (apparent t, 4H), 3.17 (dd, *J* = 14.9, 6.1 Hz, 1H), 2.42 (dd, *J* = 14.9, 11.0 Hz, 1H), 2.16 (s, 3H), 1.62 (apparent t, 4H), 1.27 (d, *J* = 6.4 Hz, 3H).

Synthesis of (5*R*)-20

20 (S)-1-Methyl-2-(2-bromothien-3-yl)ethanol, (S)-33.



To a solution of *n*-BuLi (2.5 M in hexanes, 32 mL) in THF (50 mL) at -78 °C was added a solution of 3-bromothiophene (7.56 mL, 80.0 mmol) in THF (30 mL) and the resulting mixture
 5 maintained at -78 °C for 1 h and then treated with a solution of (*S*)-2-methyloxirane (8.37 mL, 120 mmol) in THF (30 mL), followed by BF₃·OEt₂ (11.1 mL, 88.0 mmol). The reaction mixture was maintained at -78 °C for 1 h, then warmed to RT, quenched with sat aq NH₄Cl solution (80 mL) and diluted with EtOAc (80 mL). The organic layer was separated and retained and the aqueous phase was extracted with EtOAc (80 mL). The combined organic extracts were
 10 dried, evaporated *in vacuo* and the residue purified by flash column chromatography (SiO₂, 330 g, 0-50% EtOAc in isohexanes, gradient elution) to afford (*S*)-1-(thiophen-3-yl)propan-2-ol as a yellow oil (8.41 g, 74% yield) which was used directly in the next step.

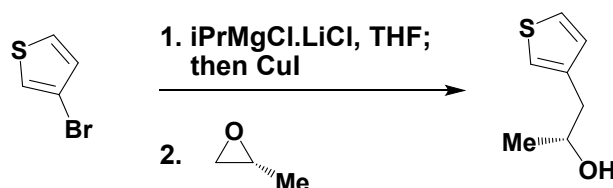
To a solution of (*S*)-1-methyl-2-(thien-3-yl)ethanol (2.00 g, 14.1 mmol) in DCM (210 mL) was
 15 added a solution of NBS (2.50 g, 14.1 mmol) in AcOH (18 mL) at RT. The mixture was maintained at RT for 15 min and was then evaporated *in vacuo*. The residue thus obtained was taken up into Et₂O (200 mL) and was washed with sat aq NaHCO₃ (100 mL). The organic phase was separated, dried and then evaporated *in vacuo*. This procedure was repeated on two additional batches of (*S*)-1-(thiophen-3-yl)propan-2-ol (2 x 3.00 g, 21.1
 20 mmol) to afford, after combining all three batches, the title compound as a pale yellow oil (10.9 g, 89% pure by ¹H NMR, 62% yield over 2 steps); ¹H NMR δ: 7.51 (d, *J* = 5.6 Hz, 1H), 6.96 (d, *J* = 5.6 Hz, 1H), 4.61 (br, 1H), 3.85 (sext, *J* = 6.3 Hz, 1H), 2.64 (dd, *J* = 13.8, 6.5 Hz, 1H), 2.54 (dd, *J* = 13.8, 6.5 Hz, 1H), 1.03 (d, *J* = 6.2 Hz, 3H). Residual EtOAc (11wt%) present.

(R)-N-(2,6-Difluorophenyl)-5-methyl-6-(4-(5-methyl-2-(7-oxa-2-azaspiro[3.5]nonan-2-yl)nicotinamido)benzoyl)-5,6-dihydro-4H-benzo[b]thieno[2,3-d]azepine-2-carboxamide.

The single enantiomers (*S*)-**16** through to (*5R*)-**20** were prepared using the procedures already described for the corresponding racemic intermediates and final compound and gave analytical data consistent with that reported hereinabove. The title compound was thereby obtained as a white solid (2.06 g); R^t 1.94 min (Method 1a); m/z 734 ($M+H$)⁺ (ES^+); R^t 7.16 min (**Method 2**) >99%ee.

10 Synthesis of (*5S*)-**20**

(R)-1-Methyl-2-(thien-3-yl)ethanol, (R)-32.



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To a solution of $iPrMgCl \cdot LiCl$ (1.3 M in THF, 51.5 mL) at RT was added 3-bromothiophene (6.05 mL, 63.8 mmol) and the mixture maintained at RT for 30 min, then cooled to -25 °C and treated with CuI (0.243 g, 1.28 mmol) followed by a solution of (*R*)-2-methyloxirane (3.80 mL, 54.2 mmol) in THF (20 mL). The resulting mixture was allowed to warm to RT and after 18 h it was cooled 0 °C, carefully quenched with sat aq NH_4Cl solution (100 mL) and then diluted with EtOAc (100 mL). The organic layer was separated and retained and the aqueous phase was extracted with EtOAc (100 mL). The combined organic extracts were washed with brine (2 x 100 mL), dried and evaporated *in vacuo*. The residue thus obtained purified by flash column chromatography (SiO_2 , 120 g, 0-50% EtOAc in isohexanes, gradient elution) to afford the title compound as a yellow oil (4.65 g, 50% yield); 1H NMR δ : 7.41 (dd, $J = 4.9, 2.9$ Hz, 1H), 7.15-7.13 (m, 1H), 6.99 (dd, $J = 4.9, 1.2$ Hz, 1H), 4.56 (d, $J = 4.8$ Hz, 1H), 3.86-3.77 (m, 1H), 2.69 (dd, $J = 13.9, 6.4$ Hz, 1H), 2.59 (dd, $J = 13.9, 6.4$ Hz, 1H), 1.02 (d, $J = 6.1$ Hz, 3H).

(S)-N-(2,6-Difluorophenyl)-5-methyl-6-(4-(5-methyl-2-(7-oxa-2-azaspiro[3.5]nonan-2-yl)nicotinamido)benzoyl)-5,6-dihydro-4H-benzo[*b*]thieno[2,3-*d*]azepine-2-carboxamide.

- 5 The single enantiomers (*R*)-**16** through to (*5S*)-**20** were prepared using the procedures already described for the corresponding racemic intermediates and final compound and gave analytical data consistent with that reported hereinabove. The title compound was thereby obtained as a white solid (1.48 g,); R^t 1.91 min (Method 1a); m/z 734 ($M+H$)⁺ (ES^+); R^t 9.19 min (**Method 2**) >99%ee.

II. Biological Testing: Experimental Methods

Assessment of RSV induced CPE in HEp2 cells

5 HEp2 cells were seeded (10^3 / well / 50 μ L) in 384-well plates (Catalogue number 353962, BD Falcon, Oxford, UK) in 5% FBS-DMEM (containing 2 mM L-glutamine and 1 mM sodium pyruvate) one day before infection. RSV A2 strain (#0709161v, NCPV, Public Health England, Wiltshire) or RSV B Washington strain (VR-1580, ATCC, Manassas, VA 20108) virus solutions were prepared in serum free-DMEM (containing 2 mM L-glutamine and 1 mM

10 sodium pyruvate), and then added (50 μ L/well) to achieve a final virus concentration of 1 MOI for RSV A2 and 0.2 MOI for RSV B. Simultaneously, test compounds (0.5 μ L DMSO solution) were added to 100 μ L of HEp2 cell culture with virus solution to provide a final DMSO solution of 0.5%. Plates were incubated ($37^\circ\text{C}/5\% \text{CO}_2$) for 5 days for studies using RSV A2 strain or 6 days for those using RSV B strain, and then resazurin sodium salt (5 μ L of 0.03%

15 solution; Sigma-Aldrich, Dorset, UK) was added to each well and the plate incubated for a further 6 h ($37^\circ\text{C}/5\% \text{CO}_2$). The fluorescence of each well [545 nm (excitation) / 590 nm (emission)] was determined using a multi-scanner (Clariostar: BMG, Buckinghamshire, UK). The percentage inhibition for each well was calculated and the IC_{50} , IC_{75} and IC_{90} values were calculated from the concentration-response curve generated for each test compound.

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III. NMR Spectra of Compounds 7, (4S)-13 and (5R)-19

Figure 1. ^1H NMR spectra of the C-4 and C-5 protons in the unsubstituted azepine **7** recorded in d_6 -DMSO + TFA

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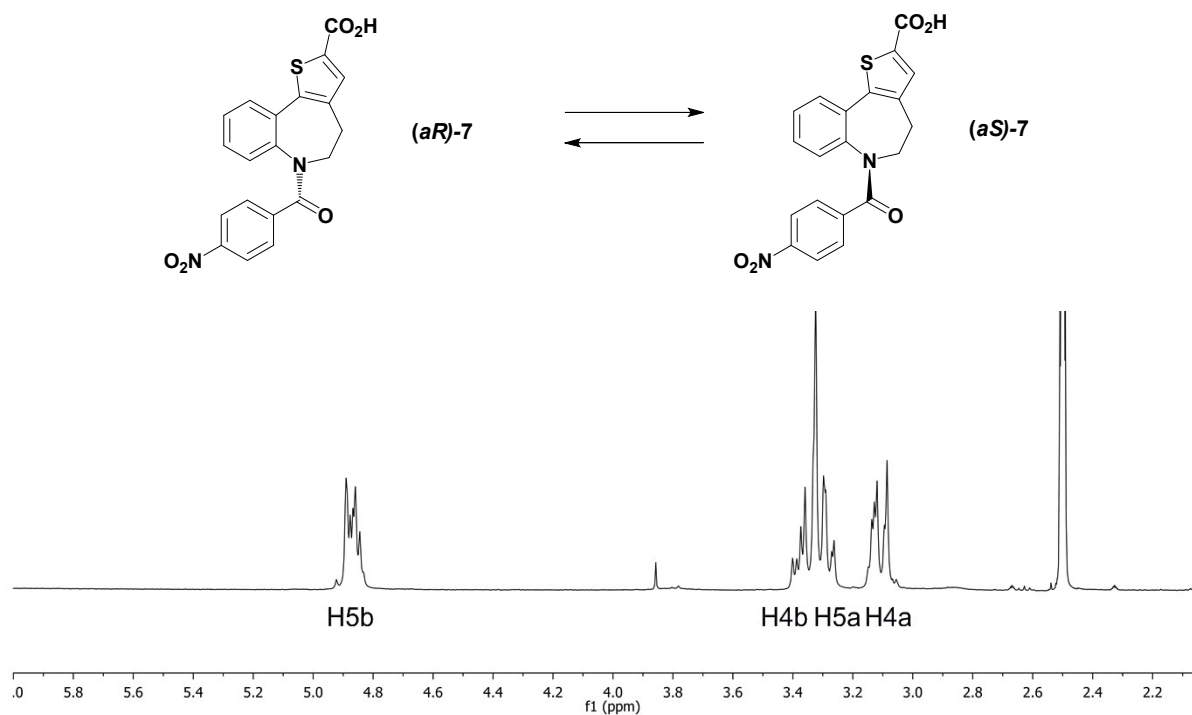
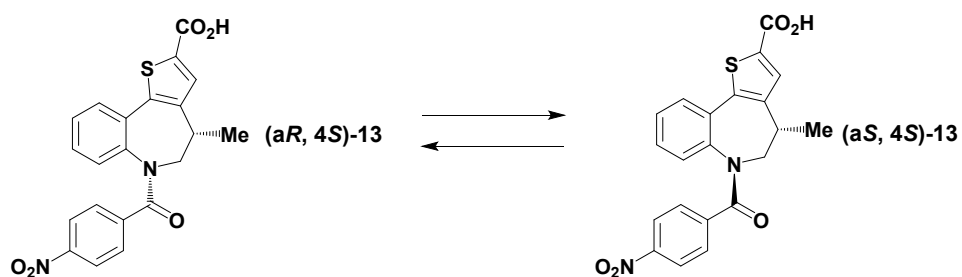


Figure 2. ^1H NMR spectra of the C-4 and C-5 protons in the C-4 methylated derivative (4S)-

10 **13** recorded in d_6 -DMSO + TFA



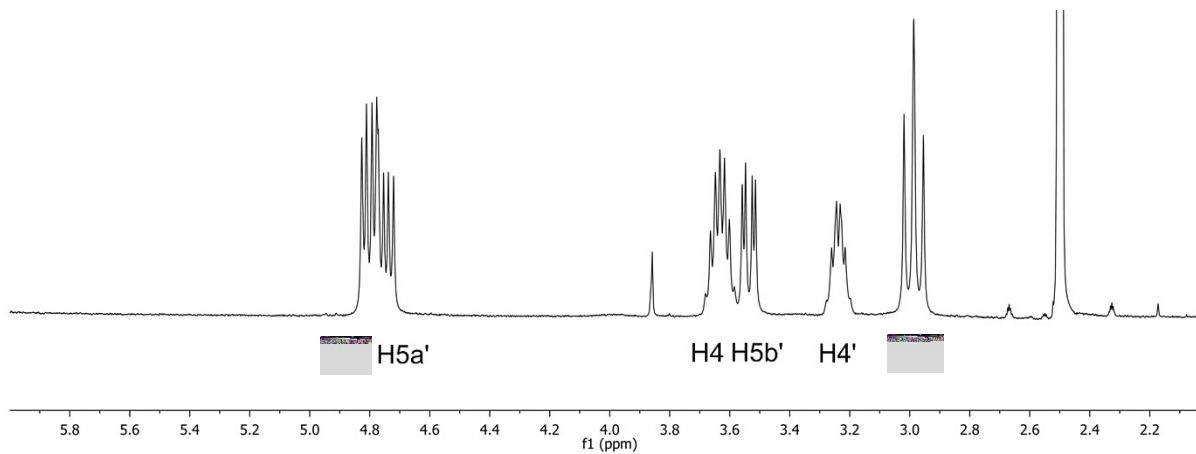
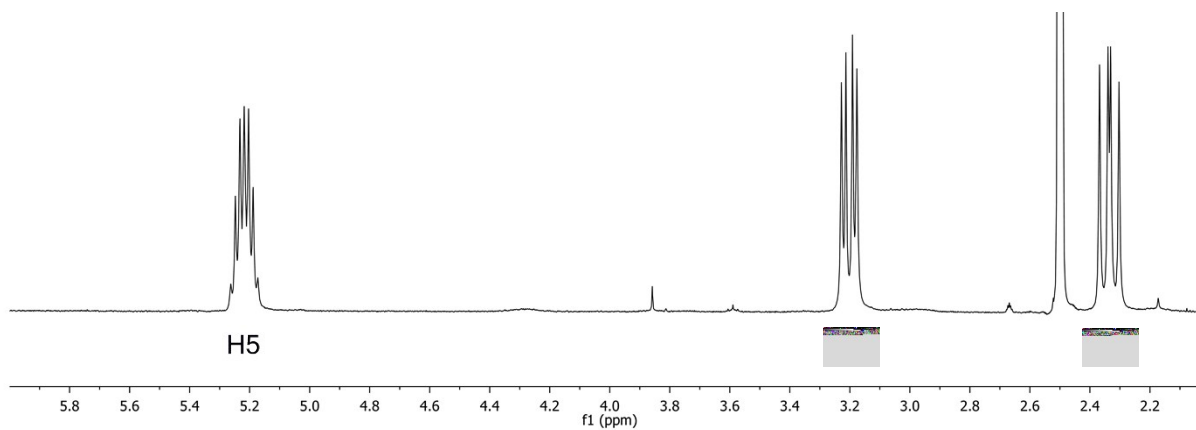
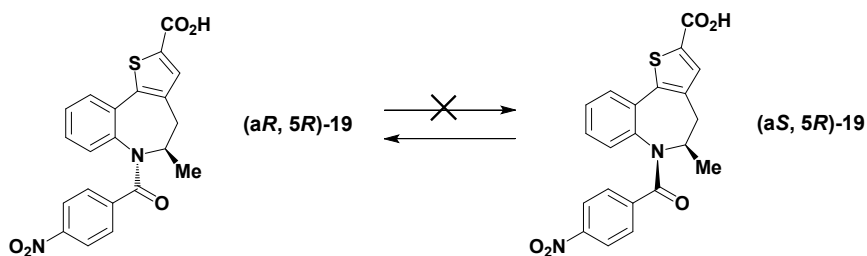


Figure 3. ^1H NMR spectra of the C-4 and C-5 protons in C-5 methylated, derivative (5*R*)-**19** recorded in d_6 -DMSO + TFA



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