

Tetramethylammonium Fluoride Tetrahydrate for S_NAr Fluorination of 4-Chlorothiazoles at Production Scale

AUTHOR NAMES

*Mai Khanh Hawk^{*iii} Sarah J. Ryan,^{*iii} Xin Zhang,ⁱ Ping Huang,ⁱ Jing Chen,ⁱ
Chuanren Liu,ⁱ Jianping Chen,ⁱ Peter J. Lindsay-Scott,ⁱⁱ John Burnett,ⁱⁱ Craig
White,ⁱⁱ Yu Lu,ⁱⁱⁱ John R. Rizzoⁱⁱⁱ*

AUTHOR ADDRESS

ⁱ) STA Pharmaceutical (WuXi STA), a subsidiary of WuXi AppTec., No. 7
Building, #90 Delin Rd, WaiGaoQiao Free Trade Zone, Shanghai, 200131,
People's Republic of China

ⁱⁱ) Eli Lilly and Company Limited, Erl Wood Manor, Windlesham, Surrey, GU20
6PH, UK

ⁱⁱⁱ) Eli Lilly and Company, Small Molecule Design and Development (SMDD),
Lilly Technology Center North, 1400 W Raymond Street, Indianapolis, IN,
46221

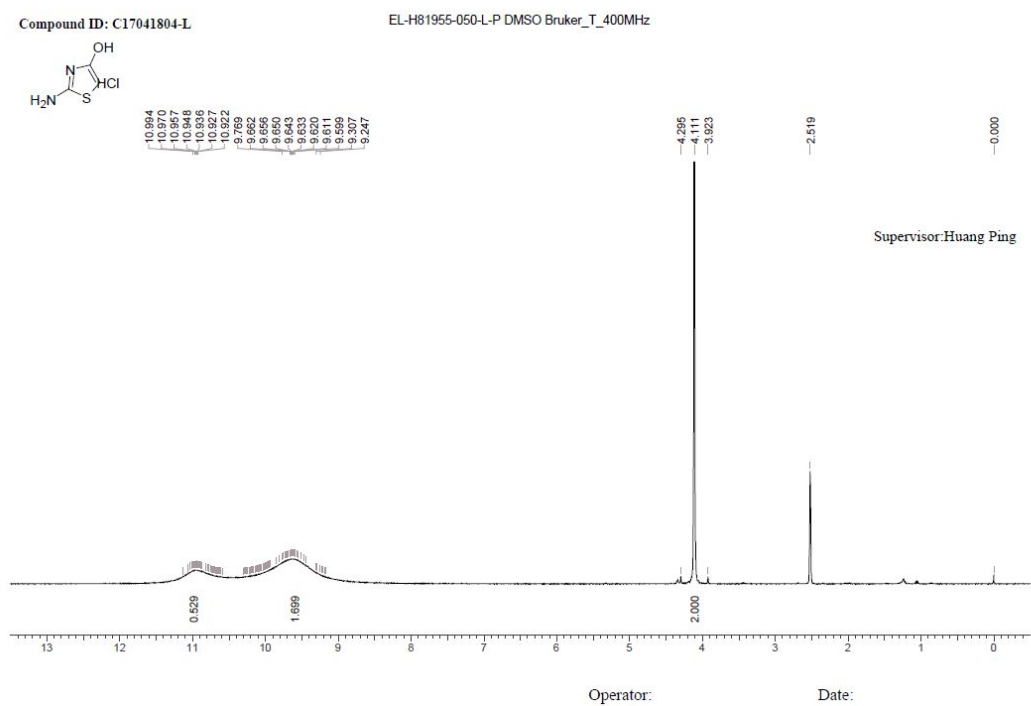
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^1H , ^{13}C and ^{19}F NMR spectra of compounds 4, 5, 2a, 2b, 1a and 1b

1) 2-aminothiazol-4-ol hydrochloride 4

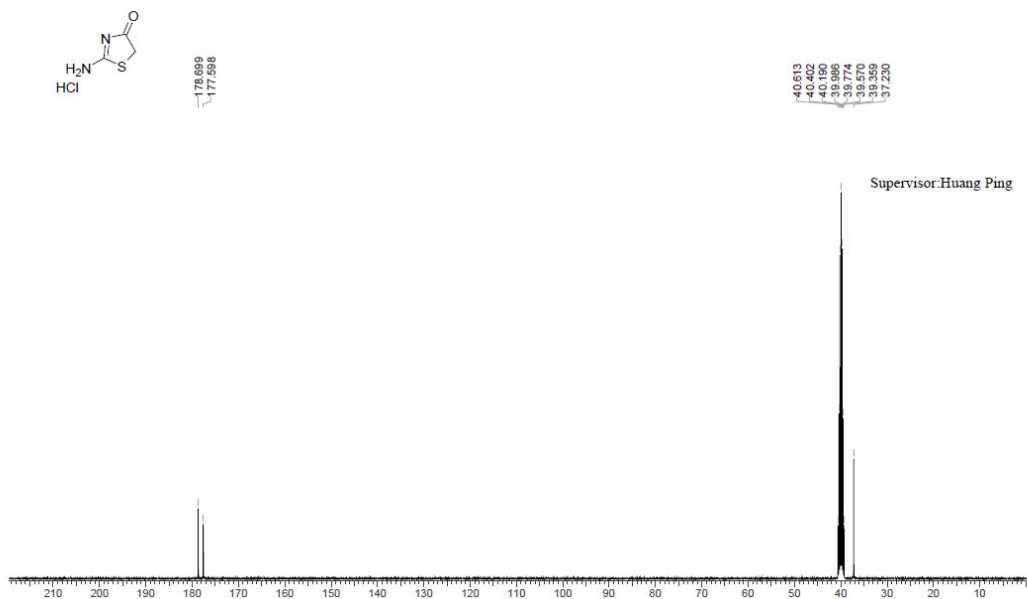
^1H NMR Spectrum of 2-aminothiazol-4-ol hydrochloride (4)



^{13}C NMR Spectrum of 2-aminothiazol-4-ol hydrochloride (4)

Compound ID: C17041804-L

EL-H81955-050-L-PP1 DMSO 13C

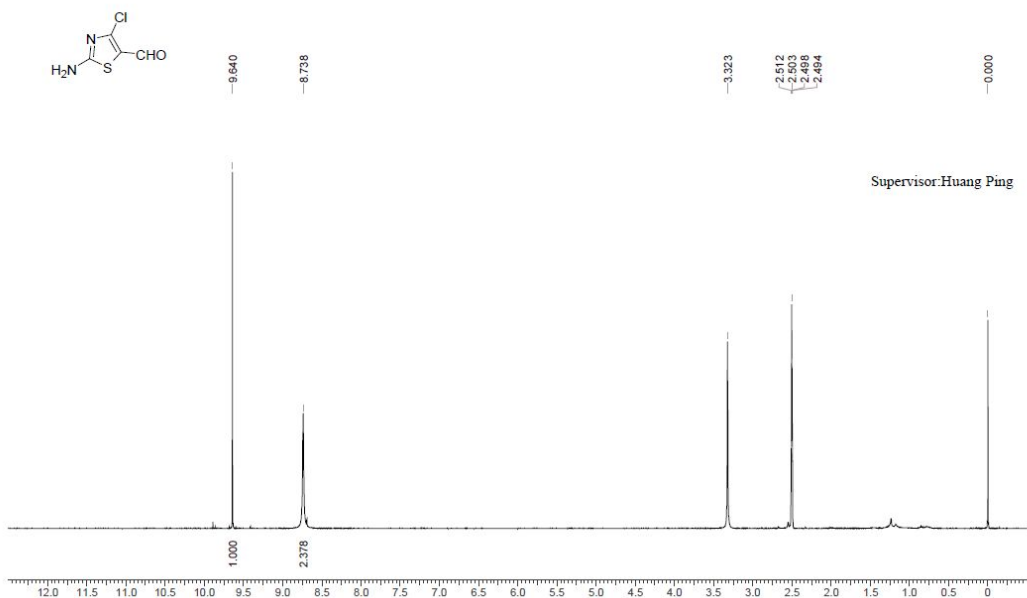


2) 2-amino-4-chlorothiazole-5-carbaldehyde 5

¹H NMR Spectrum of 2-amino-4-chlorothiazole-5-carbaldehyde (5)

Compound ID: C17041804-M

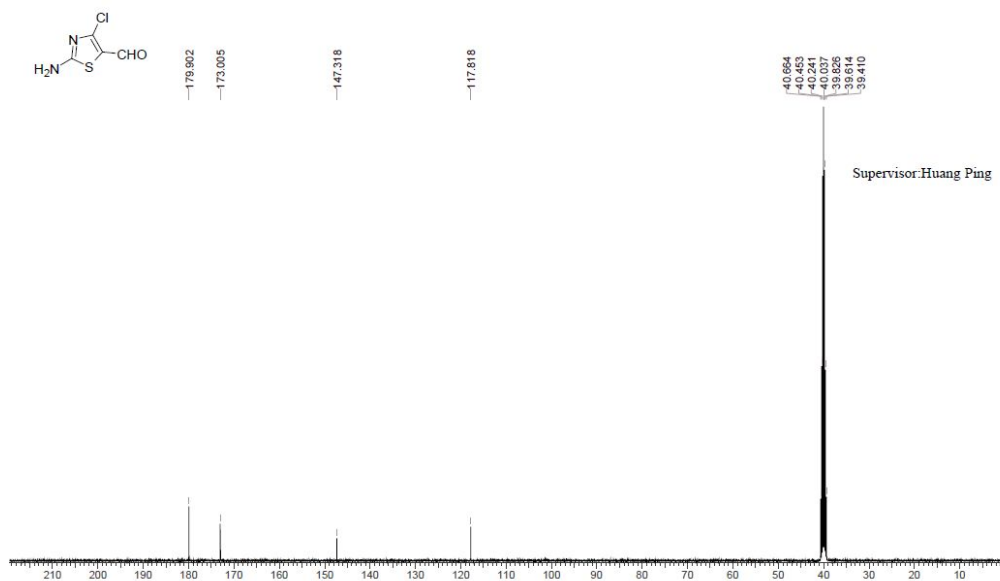
EL-H81955-050-M-P DMSO Bruker_T_400MHz



¹³C NMR Spectrum of 2-amino-4-chlorothiazole-5-carbaldehyde (5)

Compound ID: C17041804-M

EL-H81955-050-M-PP DMSO 13C

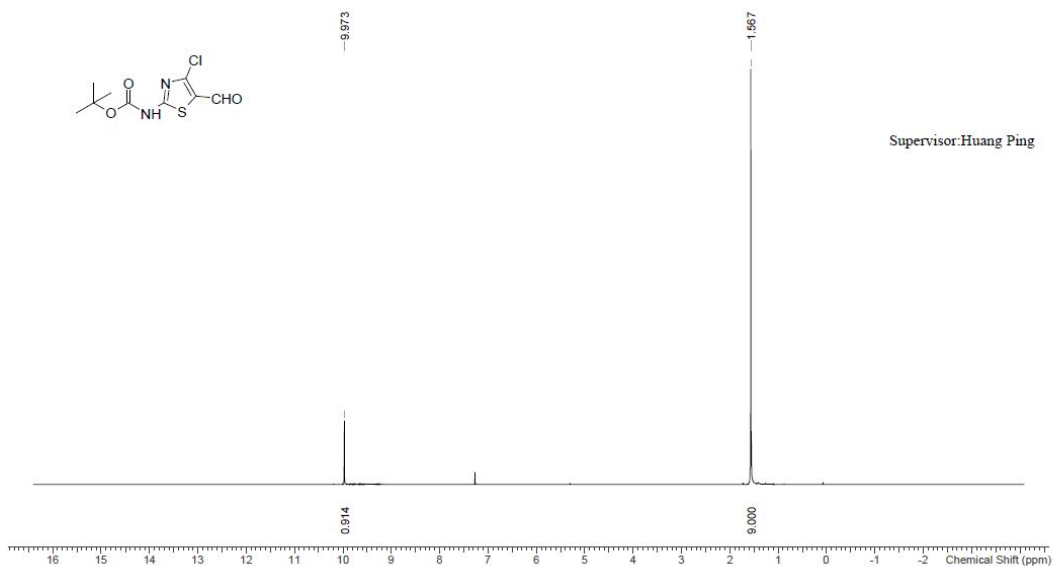


3) N-(4-chloro-5-formylthiazol-2-yl)pivalamide 2a

¹H NMR Spectrum of N-(4-chloro-5-formylthiazol-2-yl)pivalamide (2a)

Compound ID: C17041804-N

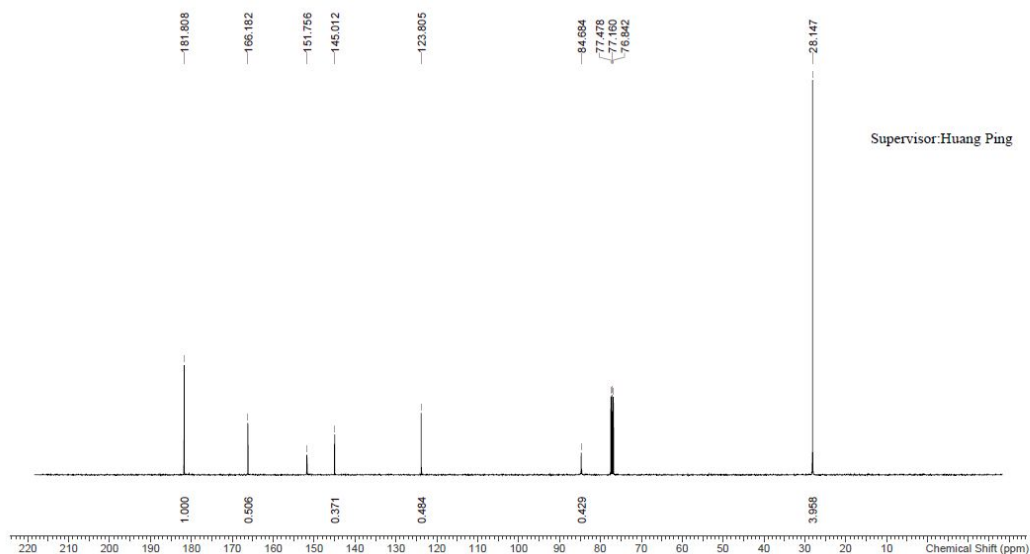
EL-H82064-021-N-P CDCl3 Bruker_T_400MHz



¹³C NMR Spectrum of N-(4-chloro-5-formylthiazol-2-yl)pivalamide (2a)

Compound ID: 00000000

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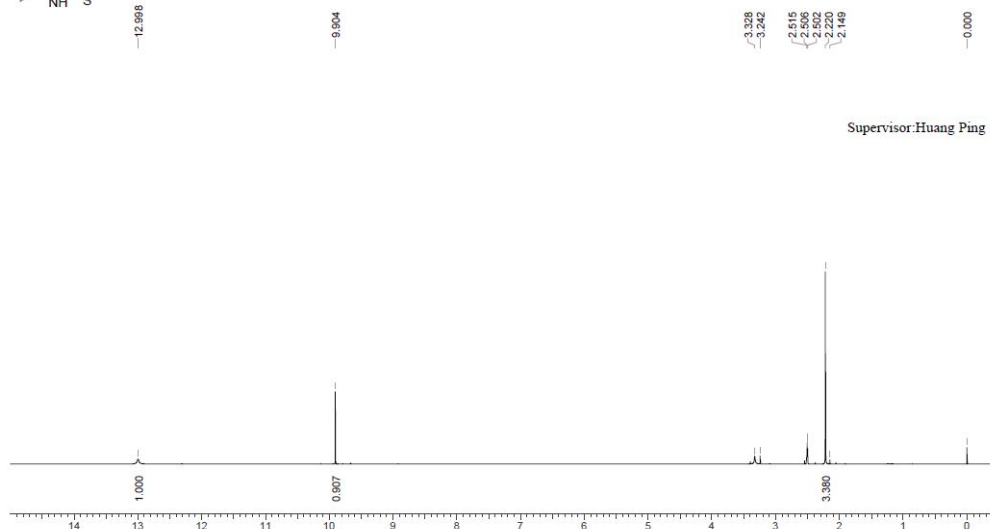
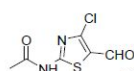


4) N-(4-chloro-5-formylthiazol-2-yl)acetamide **2b**

¹H NMR Spectrum of N-(4-chloro-5-formylthiazol-2-yl)acetamide (**2b**)

Compound ID: C17041804-X

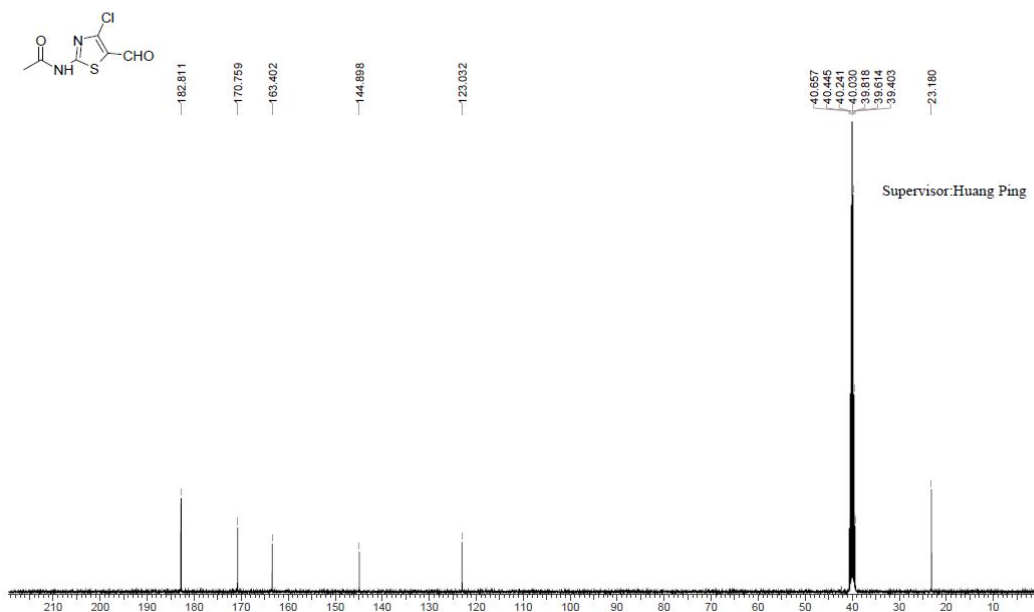
EL-H81955-050-X-P DMSO Bruker_T_400MHz



¹³C NMR Spectrum of N-(4-chloro-5-formylthiazol-2-yl)acetamide (**2b**)

Compound ID: C17041804-X

EL-H81955-050-X-PP DMSO 13C

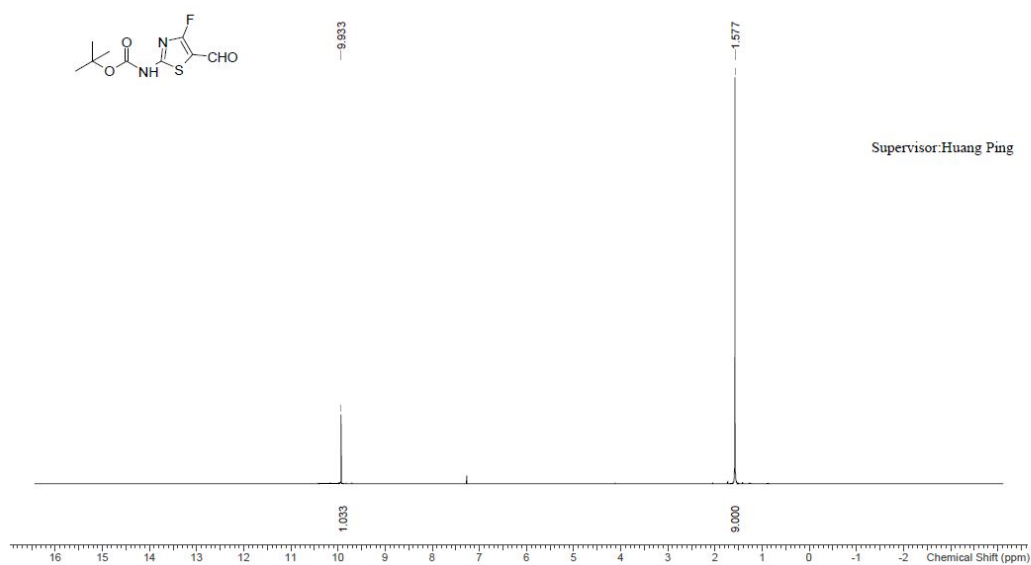


5) N-(4-fluoro-5-formylthiazol-2-yl)pivalamide **1a**

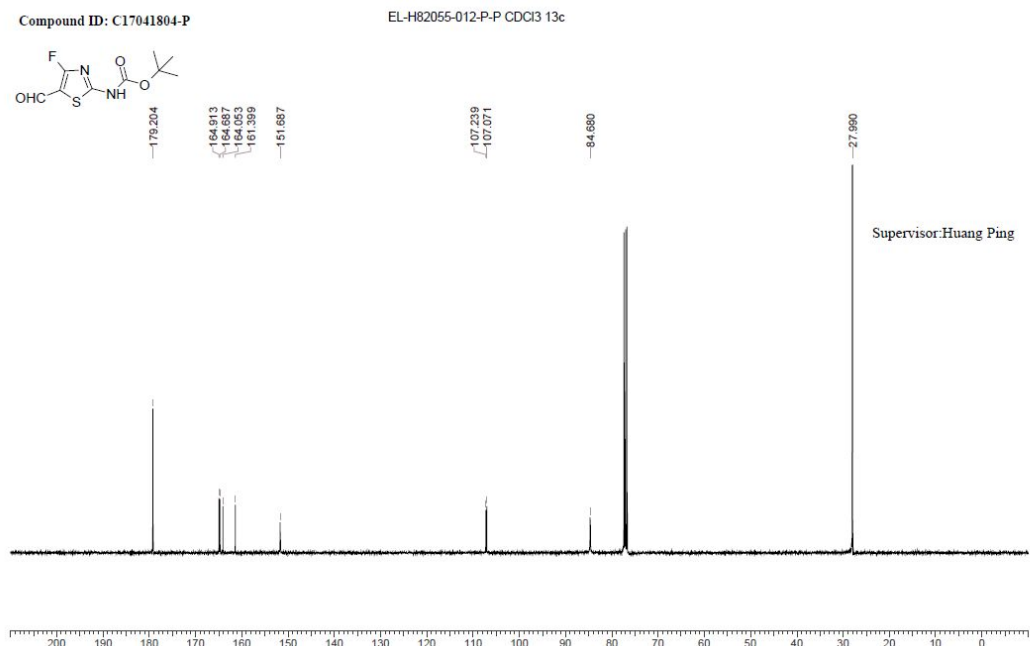
¹H NMR Spectrum of N-(4-fluoro-5-formylthiazol-2-yl)pivalamide (**1a**)

Compound ID: C17041804-P

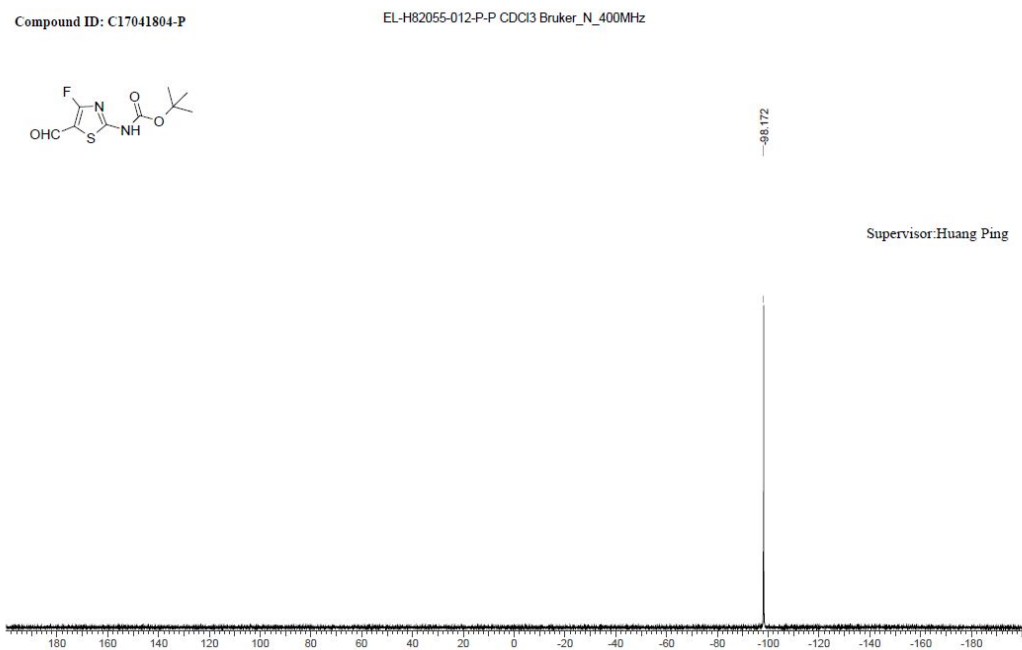
EL-H82055-012-P-P CDCl₃ Bruker_A_400MHz



¹³C NMR Spectrum of N-(4-fluoro-5-formylthiazol-2-yl)pivalamide (1a)

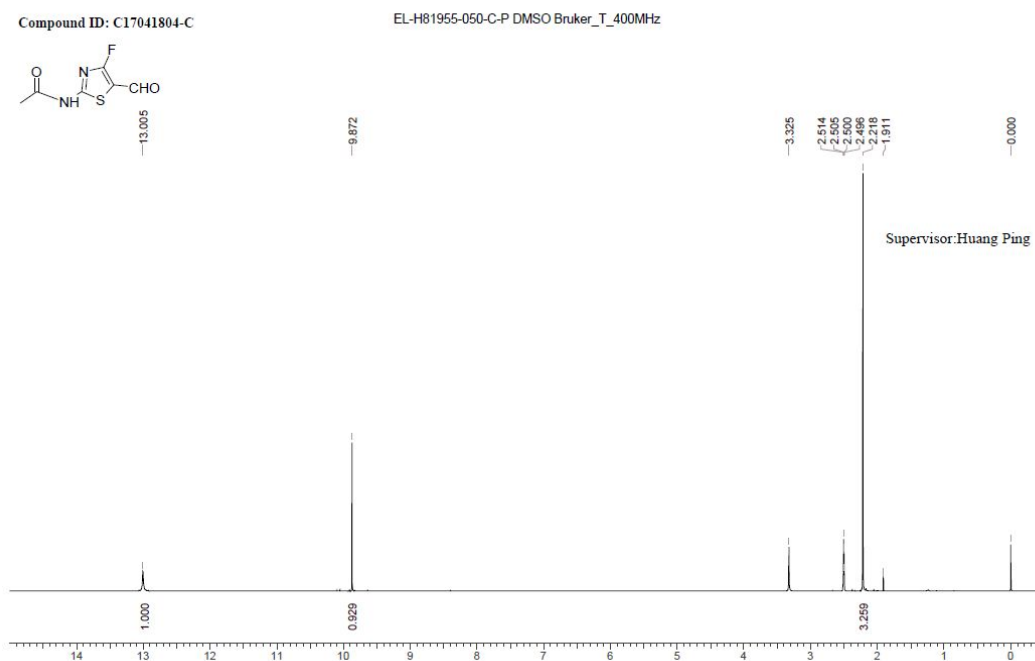


¹⁹F NMR Spectrum of N-(4-fluoro-5-formylthiazol-2-yl)pivalamide (1a)

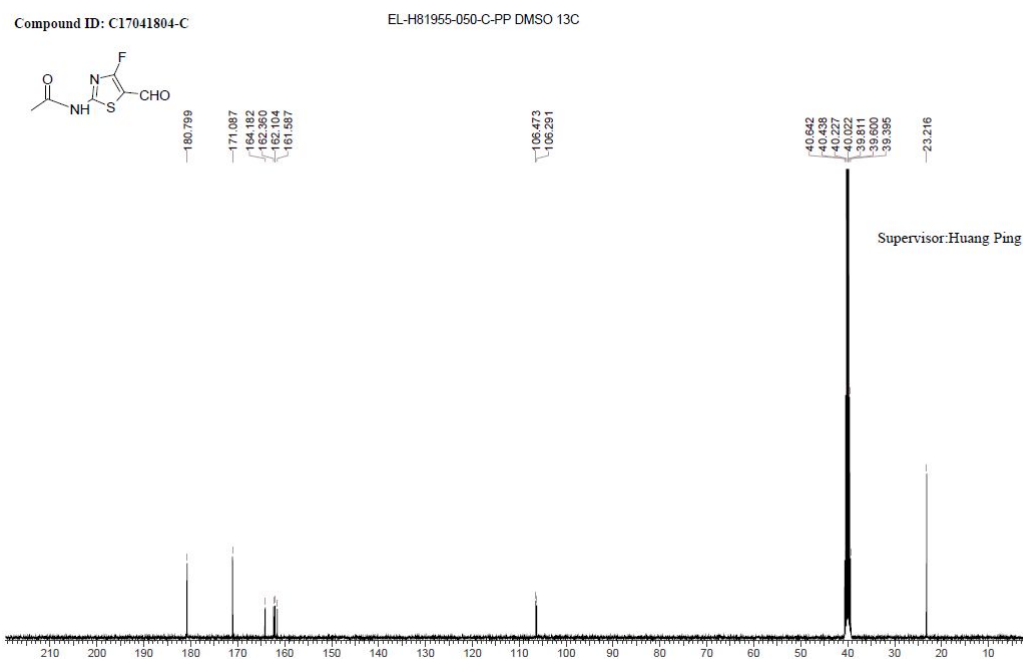


6) N-(4-fluoro-5-formylthiazol-2-yl)acetamide **1b**

¹H NMR Spectrum of N-(4-fluoro-5-formylthiazol-2-yl)acetamide (1b)



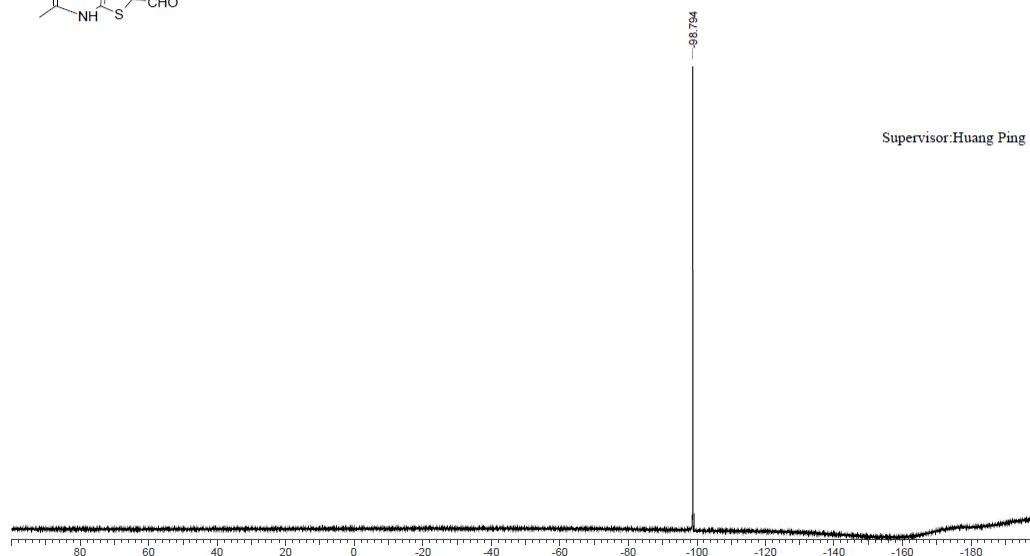
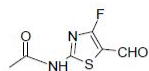
¹³C NMR Spectrum of N-(4-fluoro-5-formylthiazol-2-yl)acetamide (1b)



¹⁹F NMR Spectrum of N-(4-fluoro-5-formylthiazol-2-yl)acetamide (1b)

Compound ID: C17041804-C

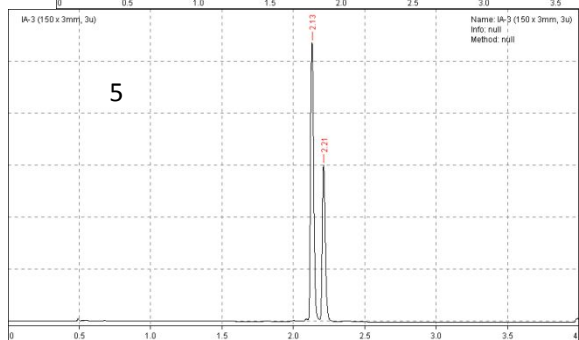
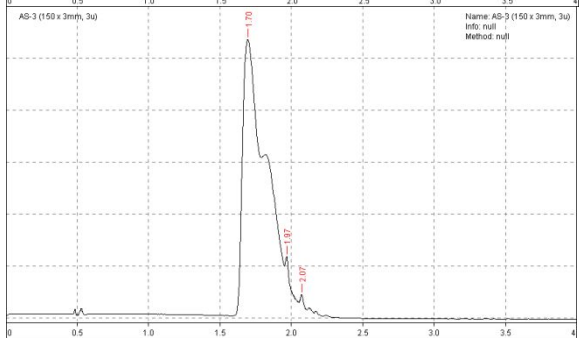
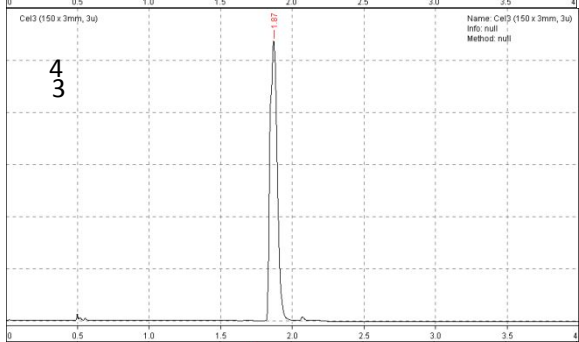
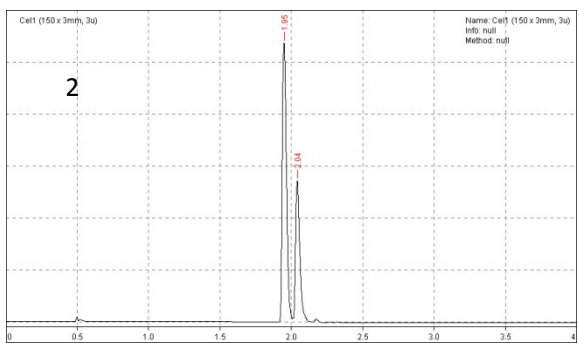
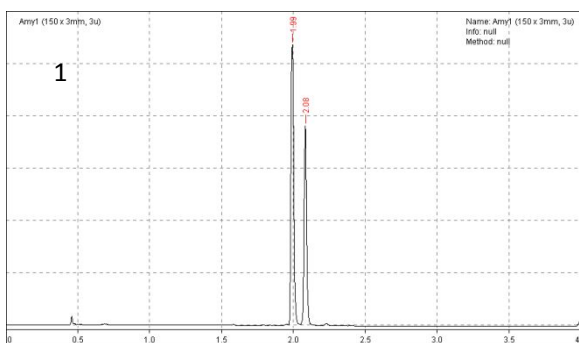
EL-H81955-050-C-P DMSO Bruker_T_400MHz



Development to enable preparative SFC conditions for the separation of compounds **1a** and **2a**

Development to enable preparative SFC conditions for the separation of compounds **1a** and **2a**

Analytical screening was conducted on the mixture of F-thiazole **1a** and Cl-thiazole **2a** on several achiral columns (Princeton 2-ethylpyridine (2-EP), Princeton Benzene-sulfonamide (BeSAM), Princeton Diethyl-aminophenyl (DEAP), Princeton Diol, Princeton Dinitrophenyl (DNP), Phenomenex Luna HILIC; each 150 × 4.6 mm, 5μ) by Supercritical Fluid Chromatography (SFC), but no resolution was observed. Subsequent screening of the same mixture was conducted across a matrix of six chiral columns (Phenomenex Amylose-1; Phenomenex Cellulose-1; Phenomenex Cellulose-3; Chiral Technologies Chiralpak AS-3; Chiral Technologies Chiralpak IA-3; Chiral Technologies Chiralpak IC-3) and three solvent systems (methanol; ethanol; isopropanol, each with 0.2% isopropylamine) using an SFC gradient screening process. Although methanol and ethanol provided some screening hits, isopropanol was selected as solvent for preparative work to avoid potential degradation issues on scale, whilst still providing sufficient resolution for purification (see **Figure S1**). The best separation was achieved on an IC-3 column (Figure S1, panel 6), with the target F-thiazole **1a** identified as the first eluting component.



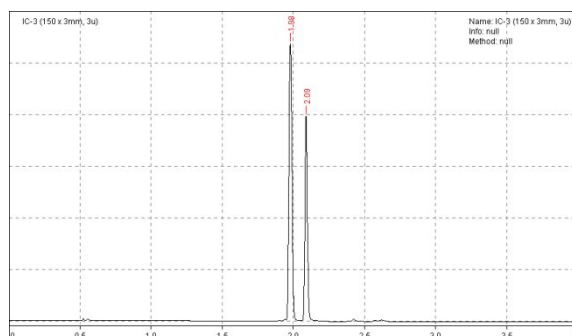


Figure S1: Chiral screening results for the mixture of F-thiazole 1a and Cl-thiazole 2a on a Waters UPCC instrument. Panel 1: Amylose-1 – Res = 2.87; Panel 2: Cellulose-1 – Res = 1.63; Panel 3: Cellulose-3 – Res = 0; Panel 4: Chiralpak AS-3 – Res = 0.48; Panel 5: Chiralpak IA-3 – Res = 1.89; Panel 6: Chiralpak IC-3 – Res = 2.94. Each column was 150 x 3 mm, 3 μ . *SFC method details:* all data was generated using a 5-50% IPA + 0.2% isopropylamine gradient over 1.6 minutes with a 2 min hold, 1.5 mL/min, 105 bar, 40 °C.

An isocratic analytical method was then developed using the optimised conditions to provide a suitable starting point for purification and accurate post-purification analysis (see **Figure S2**).

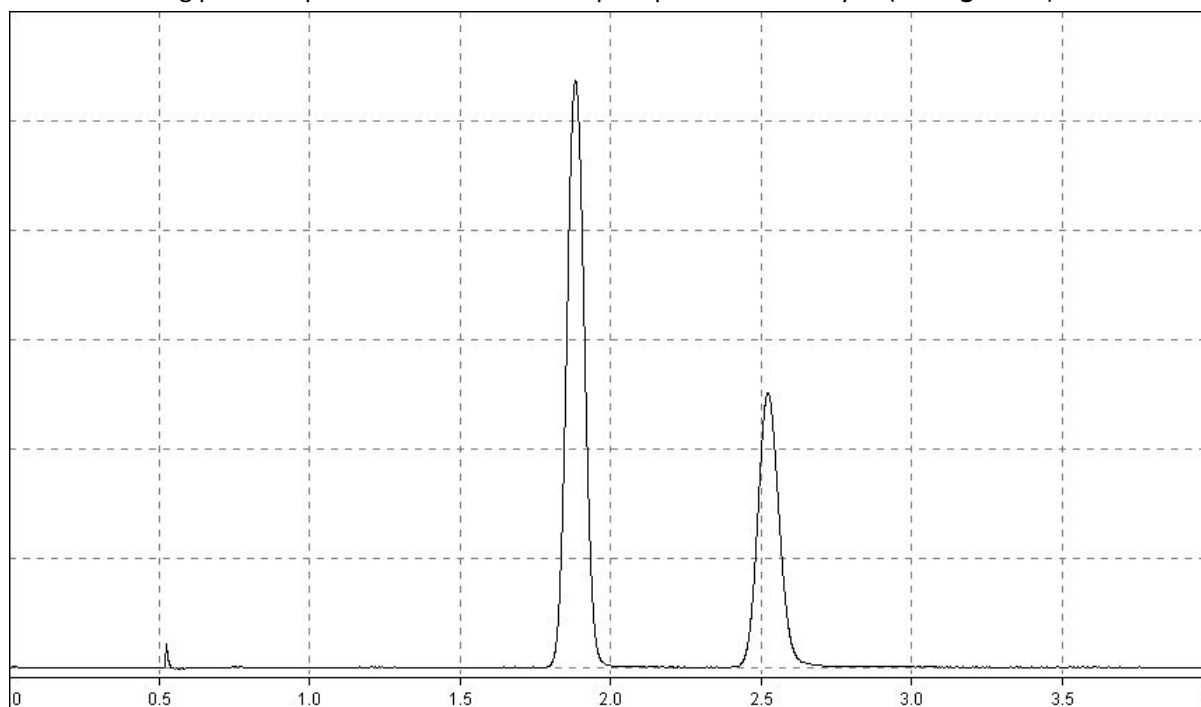


Figure S2: Isocratic analytical method developed for the mixture of F-thiazole 1a and Cl-thiazole 2a on a Waters UPCC instrument. *SFC method details:* 10% IPA (+ 0.2%isopropylamine), 1.5 mL/min, 105 bar, 35 °C, 150 x 3 mm, 3 μ , Chiralpak IC-3 column. Res = 5.06

Whilst IPA + 0.2%isopropylamine mixtures were utilized for analytical work, neutral IPA was selected for preparative work to avoid potential degradation issues (NOTE: MeCN and 1:1 IPA:MeCN were also assessed analytically, but provided no improvement in separation over that of pure IPA).

A preparative scale purification was performed as follows: The mixture of F-thiazole **1a** and Cl-thiazole **2a** (32.7 g, 133 mmol) was dissolved in IPA (303 mL) and was filtered. The filtrate was purified by SFC on a Berger Multigram 3 instrument using a Chiral Technologies Chiralpak IC column (30 x 250 mm, 5 μ) with 10% IPA (no additive) at 180 mL/minute with 3 mL injections. The

product-containing fractions were concentrated to give F-thiazole **1a** (16.1 g).

For subsequent larger batches, the purification conditions were optimised using stacked injections (see **Figure S3**) to reach a throughput of 12 g/hr on a 50 x 250mm 5 μ Chiralpak IC column with a solvent consumption of 2.4 L/hr and 0.2 L/g (NOTE: the majority of the IPA solvent could be recycled after evaporation).

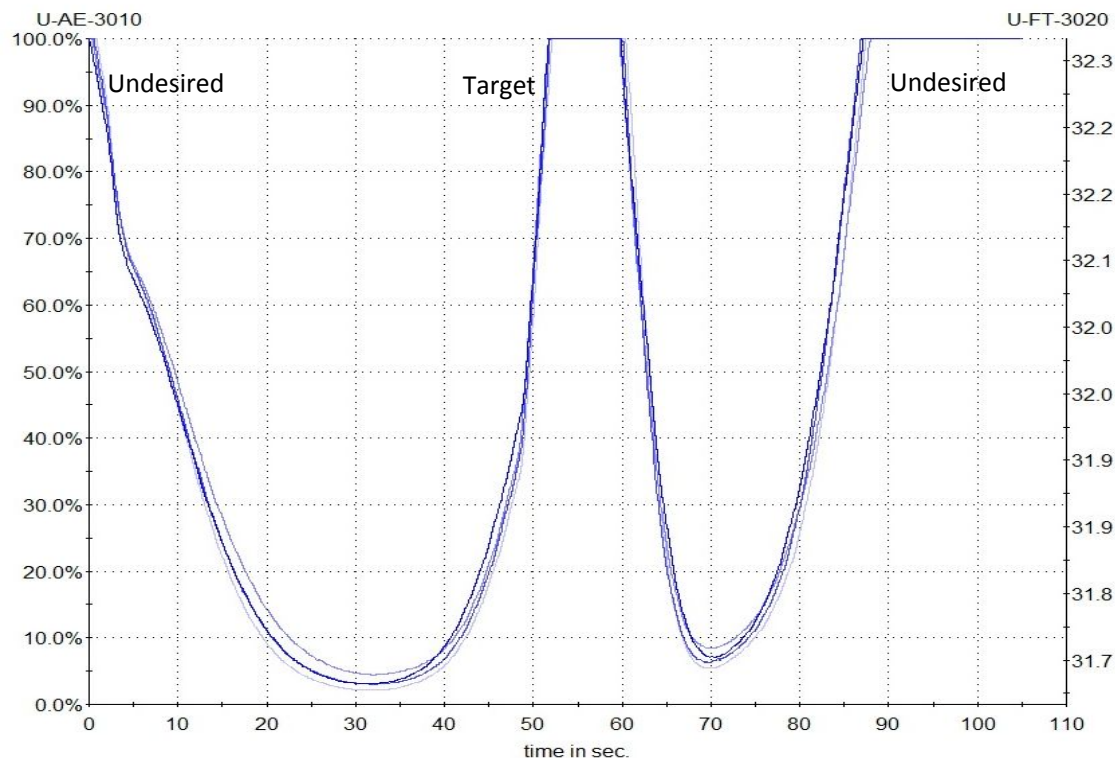


Figure S3: Overlay of 4 cycles of a 2.05 Kg-scale purification of the mixture of F-thiazole **1a and Cl-thiazole **2a** spanning over a 14 day period on a Novasep 400 instrument. SFC method details:** 8% IPA (no additive), 110 bar, 35°C, 400 g/min, 220 nm detection, 3.5 mL solution injected every 105s. Sample was dissolved to a concentration of 100 mg/mL in IPA. Collections performed by fixed time windows (consistent over a 14 day period) to give F-thiazole **1a** (1.07 Kg).

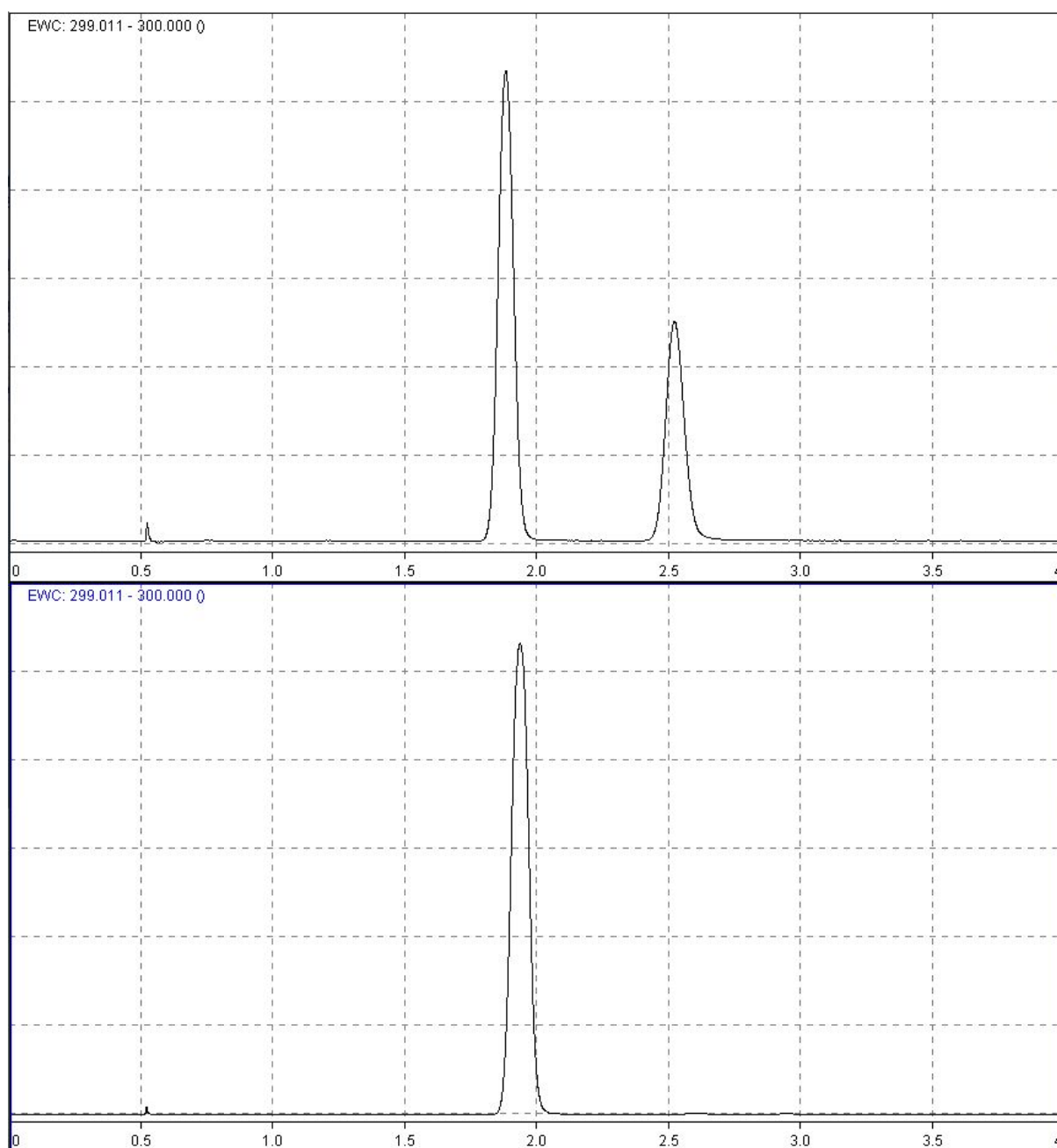


Figure S4: Final purity analysis after purification using the isocratic analytical method developed for the mixture of F-thiazole 1a and Cl-thiazole 2a on the Waters UPCC. SFC method details: 10% IPA (+ 0.2%isopropylamine), 1.5 mL/min, 105 bar, 35 °C, 150 x 3 mm, 3 μ , Chiralpak IC-3 column

Instrumentation details:

Waters UPCC, comprising a Sample Manager, Binary Solvent Manager, Column Manager, PDA Detector, QDA Detector, Isocratic Solvent Manager and Convergence Manager.

Berger Multigram 3, comprising a CO₂ pump and modifier pump, each capable of running up to 200ml/min

Novasep 400, comprising a dual head LEWA pump capable of 400 g/min, a modifier feed pump capable of 200 mL/min, each twinned with a flowrate meter for accurate solvent delivery, and CO₂ recycling to minimise CO₂ consumption.