# Supporting Information for

# Development of a Suitable Process for the Preparation of a TNF- α Converting Enzyme (TACE) Inhibitor–WAY-281418

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LC Conditions compounds **14** and **2**:

| | |
|---|---|
| Column: | Prodigy 5µ ODS2 4.6 x 250 mm |
| Mobile phase: | A: 1900 mL $H_2O$, 100 mL $CH_3CN$, 2.0 g $NH_4OAc$ |
| | B: 1900 mL $CH_3CN$, 100 mL $H_2O$, 0.1 g $NH_4OAc$ |
| Flow rate: | 1.0 mL/min |
| Detection: | 238 nm |
| Column oven temperature: | 20 - 25 °C |
| Sample volume injection: | 5 µ L |

Gradient program:

| Time (min) | Mobile Phase A (%) | Mobile Phase B (%) |
|---|---|---|
| 0 | 100 | 0 |
| 2 | 100 | 0: |
| 15 | 73 | 27 |
| 16 | 0 | 100 |
| 21 | 0 | 100 |
| 22 | 100 | 0 |
| 28 | 100 | 0 |

Retention Times:

| Compound | HPLC retention time (min) |
|---|---|
| 2-Methylquinoline-4-carboxylic acid (**14**) | 7.4 |
| (2-Methylquinolin-4-yl)methanol (**2**) | 8.0 |

LC Conditions for compounds **3**, **4**, **15**, **6** and **8**:

| | |
|---|---|
| Column: | Prodigy ODS 3, 4.6 x 250 mm, 5µm |
| Mobile phase: | A: water 950 mL, acetonitrile 50 mL, 0.2% TFA |
| | B: acetonitrile 950 mL, water 50 mL, 0.2% TFA |
| Flow rate: | 1.0 mL/min |
| Detection: | 238 nm |
| Column oven temperature: | 20~25°C |
| Sample volume injection: | 2.0 µ L |

Gradient program:

| Time (min) | Mobile Phase A (%) | Mobile Phase B (%) |
|---|---|---|
| 0 | 95 | 5 |
| 20 | 5 | 95 |
| 21 | 95 | 5 |
| 25 | 95 | 5 |

Retention Times:

| Compound | HPLC retention time (min) |
|---|---|
| 4-Chloromethyl-2-methylquinoline HCl salt (**3**) | 8.1 |
| Sodium 4-hydroxybenzenesulfonate dihydrate (**4**) | 4.3 |

| | |
|---|---|
| 4-(2-Methylquinolin-4-ylmethoxy)benzenesulfonic acid (**15**) | 7.4 |
| 4-(2-Methylquinolin-4-ylmethoxy)benzenesulfonyl chloride hydrochloride salt (**6**) | 10.2 (Morpholine derivative) |
| (1*S*, 2*R*)-2-[4-(2-Methylquinolin-4-ylmethoxyl)-benzenesulfonylamino]cyclopentanecarboxylic acid (**8**) | 9.9 |

LC Conditions for compounds **16**, **17** and **18**:

Column: YMC, AS12S03, diameter 3.0 μm, dimension 150 × 10 mm
Mobile phase: A: water 900 mL, acetonitrile 100 mL
B: acetonitrile 900 mL, water 100 mL
Flow rate: 1 mL/min
Detection: 220 nm
Column oven temperature: 25 °C
Sample volume injection: 10 μ L
Gradient program:

| Time (min) | Mobile Phase A (%) | Mobile Phase B (%) |
|---|---|---|
| 0 | 75 | 25 |
| 20 | 0 | 100 |
| 25 | 0 | 100 |
| 26 | 75 | 25 |
| 30 | 75 | 25 |

Retention Times:

| Compound | HPLC retention time (min) |
|---|---|
| Ethyl 2-oxocyclopentanecarboxylate (**16**) | 5.8 – 6.2 |
| Ethyl 2-amino-1-cyclopentene-1-carboxylate (**17**) | 7.8 – 8.2 |
| Ethyl 2-acetamido-1-cyclopentene-1-carboxylate (**18**) | 10.7 – 11.1 |

LC Conditions for compounds **18**, **19** and **7**:

Column: YMC-Pack Pro $C_4$, S-5um, 12nm, 150 x 4.6mm I.D., dimension
Mobile phase: A: water 1900 mL, acetonitrile 100 mL, $H_3PO_4$ 1mL
B: acetonitrile 1900 mL, water 100 mL, $H_3PO_4$ 1mL
Flow rate: 1 mL/min
Detection: 195 nm
Column oven temperature: 25 °C
Sample volume injection: 10 μ L
Gradient program:

| Time (min) | Mobile Phase A (%) | Mobile Phase B (%) |
|---|---|---|
| | 100 | 0 |

| | | |
|---|---|---|
| 2.00 | 100 | 0 |
| 50.00 | 0 | 100 |
| 60.00 | 0 | 100 |
| 61.00 | 100 | 0 |
| 75.00 | 100 | 0 |

Retention Times:

| Compound | HPLC retention time (min) |
|---|---|
| Ethyl-2-acetamido-1-cyclopentene-1-carboxylate (**18**) | 25.8 |
| Chiral acetamido ethyl ester (**19**) | 13.3 |
| (*1S, 2R*)- aminocyclopentane-1- carboxylic acid HCl salt (**7**) | Not visible |

LC Conditions for API (**9**):

Column: ACE C18 3µ 50 x 4.6 mm #A20738
Mobile phase: A: water 1000 mL, $H_3PO_4$ 1mL
B: acetonitrile 950 mL, water 50 mL, $H_3PO_4$ 1mL
Flow rate: 1 mL/min
Detection: 235 nm
Column oven temperature: 35 °C
Sample volume injection: 10 µ L
Gradient program:

| Time (min) | Mobile Phase A (%) | Mobile Phase B (%) |
|---|---|---|
| | 100 | 0 |
| 5.00 | 100 | 0 |
| 20.00 | 80 | 20 |
| 35.00 | 50 | 50 |
| 40.00 | 0 | 100 |
| 45.00 | 0 | 100 |
| 46.00 | 100 | 0 |
| 60.00 | 100 | 0 |

Retention Times:

| Compound | HPLC retention time (min) |
|---|---|
| (1*S*, 2*R*)-2-[4-(2-Methylquinolin-4-ylmethoxy)-benzenesulfonyl-amino]cyclopentanecarboxylic acid hydroxyamide-WAY-281418 (API, **9**) | 24.0 |