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## Separation of Methionine Sulfoxide Diastereomers.

Tech ID: 34709 / UC Case 2020-267-0

### BACKGROUND

Methionine (Met) is a common amino acid found in almost all proteins. When it undergoes oxidation (a common process in aging and disease), it transforms into methionine sulfoxide (Met-SO).

The challenge is that this chemical reaction creates a new chiral center at the sulfur atom. This means that for every oxidized methionine, two different mirror-image versions (diastereomers) can exist: The (S,S) form and the (S,R) form.

Before this invention, researchers struggled to separate these two forms. This resulted in two major technical hurdles:

Standard techniques like High Performance Liquid Chromatography (HPLC) or fractional crystallization (a method dating back to 1947) were unreliable, difficult to reproduce, and failed to produce high-purity samples

Because the two forms were so difficult to separate, almost all previous research on methionine oxidation used a mixture of both. This meant that if one form was toxic and the other was harmless, the results would be averaged out, hiding the true biological mechanism.

A core motivation for this invention is the "staggering degree of disagreement" in Alzheimer's Disease research regarding the protein Amyloid beta (A $\beta$ 42)

Some studies claimed that oxidized A $\beta$ 42 increased brain plaque toxicity, while others claimed it decreased it

It is plausible that these contradictions exist because previous researchers didn't know which specific diastereomer—(S,S) or (S,R)—they were testing

Once these two forms are created, they are remarkably stable. The energy barrier to flip from one form to the other is roughly 45.2 kcal/mol, which is significantly higher than other enantiomeric structures. This means that in the human body, the "wrong" version won't just flip back to the "right" one; it stays in that specific shape, potentially causing long-term damage if not properly regulated by specific enzymes (reductases).

### TECHNOLOGY DESCRIPTION

The invention solves a key tools gap.

**Met35 Oxidation:** Up to 50% of A $\beta$ 42 found in AD brains is oxidized at the 35th residue (Met35)

**Toxicity Research:** There has been long-standing disagreement over whether oxidized A $\beta$ 42 is more or less toxic than the un-oxidized version. The inventors hypothesize that the **sulfur chirality** (which version of the diastereomer is present) is the hidden variable causing these discrepancies

**New Tools:** By producing pure (*R*) and (*S*) versions of A $\beta$ 42-Met35SO, researchers can finally determine how each specific version affects protein aggregation and neurotoxicity.

The claimed invention describes a method of creating an A $\beta$ 42 peptide with a diastereomerically pure methionine sulfoxide at amino acid 38 (as described in the patent application).

The method relies on Supercritical Fluid Chromatography (SFC) to solve the separation problem. This technique is often described as a hybrid of gas and liquid chromatography, offering unique advantages for delicate chemical separations.

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### INVENTORS

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### OTHER INFORMATION

#### KEYWORDS

chiral, methionine, methionine sulfoxide, enantiomeric, Ab42, Alzheimer's, Ab42 oxidation, supercritical fluid chromatography, sulfur chirality

#### CATEGORIZED AS

- **Materials & Chemicals**
  - Biological
  - Polymers
- **Research Tools**
  - Protein Synthesis
  - Reagents

#### RELATED CASES

2020-267-0

The mobile phase is generally made up of supercritical carbon dioxide that is formed when CO<sub>2</sub> is put under specific temperature and pressure conditions where it expands to fill space like a gas, but can dissolve substances like a liquid. For this application, a mobile phase of 50-60% supercritical fluid is used. Polar co-solvents such as methanol, isopropanol, or trifluoroacetic acid can be included.

The mixture of (S,S) and (S,R) diastereomers is dissolved in an eluent (e.g. ethanol) and loaded onto a chromatography column appropriate for supercritical fluid chromatography.

As the scCO<sub>2</sub> mixture traverses the column, the different shapes of the two diastereomers cause them to interact differently with the column's internal lining. This causes one version to move faster than the other, creating a separation. Unlike older methods that only worked for tiny droplets, this SFC method allows researchers to collect gram quantities of each diastereomer at close to 100% purity as verified by X-Ray crystallography and NMR.

## APPLICATIONS

More accurate Ab42 tool compounds for studying the effects of Ab42 on Alzheimer's disease

Potentially a component of an Ab42 based Alzheimer's disease therapeutic

## ADVANTAGES

No other method produces enantiomerically pure methionine sulfoxide and methionine sulfoxide containing compounds at high quantities.

Allows the reliable study of the effect of methionine stereochemistry on the effect of Ab42 for the first time.

## INTELLECTUAL PROPERTY INFORMATION

Country	Type	Number	Dated	Case
United States Of America	Published Application	2021-023011	07/29/2021	2020-267

## RELATED MATERIALS

- ▶ [Facile Method for the Separation of Methionine Sulfoxide Diastereomers, Structural Assignment, and DFT Analysis - 02/06/2020](#)

## ADDITIONAL TECHNOLOGIES BY THESE INVENTORS

- ▶ [Rippled Beta-Sheets From Mixed Chirality Linear And Cyclic Peptides](#)
- ▶ [Design Of Functional Protein Materials Based on Beta-Rippled Sheet Architectures](#)
- ▶ [Rippled Beta-Sheets and Related Materials and Methods](#)

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