2011/0251407.

[Citation List]

[Patent Literature]

[0005]

[PTL 1] International Publication No. WO 2009/061744

[PTL 2] US Patent No. 3,947,473

[PTL 3] US Patent No. 4,003,919

[PTL 4] US Patent No. 4,026,907

[PTL 5] US Patent Application Publication No. 2011/0251407

[Summary]

[Solution to Problem]

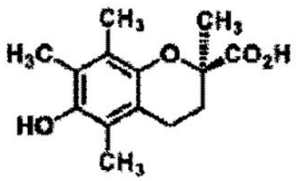
[0006]

The inventors have completed the present disclosure by finding a method of optically resolving Trolox stably as a result of diligent study. The present application has also found that an amide-based solvent is useful for optically resolving a compound.

[0006a]

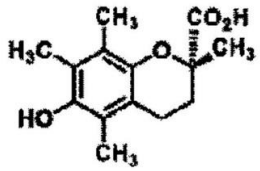
In aspect, there is provided a method of manufacturing a solid salt of a compound of formula I, comprising adding an amide-based solvent in the presence of an optical resolving agent to a sample comprising the compound of formula I and suspected of comprising a compound of formula II:

[Chemical Formula 1]



Formula I: (R)-6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (hereinafter R Trolox)

[Chemical Formula 2]

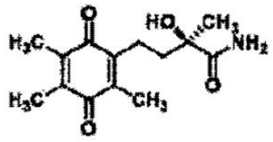


Formula II: (S)-6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (hereinafter S Trolox).

[0006b]

In another aspect, there is provided a method of manufacturing a compound of formula IIIa, comprising converting a solid salt of a compound of formula I manufactured by the method as defined above into a compound of formula IIIa:

[Chemical Formula 3]

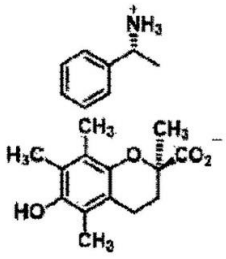


Formula IIIa: (R)-2-hydroxy-2-methyl-4-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dienyl)butanamide.

[0006c]

In another aspect, there is provided a compound of formula IVa:

[Chemical Formula 4]



Formula IVa

or a solvate thereof.

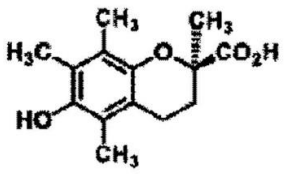
[0006d]

In another aspect, there is provided a pharmaceutical ingredient comprising the compound or solvate as defined above.

[0006e]

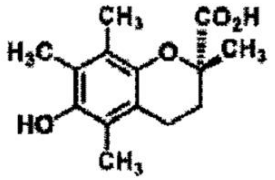
In another aspect, there is provided a method of manufacturing a solid salt of a compound of formula II, comprising adding an amide-based solvent in the presence of an optical resolving agent to a sample comprising a compound of formula II and suspected of comprising a compound of formula I:

[Chemical Formula 5]



Formula I: (R)-6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (hereinafter R Trolox)

[Chemical Formula 6]

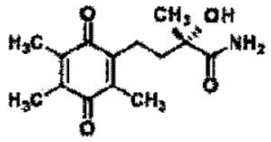


Formula II: (S)-6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (hereinafter S Trolox).

[0006f]

In another aspect, there is provided a method of manufacturing a compound of formula IIIb, comprising converting a solid salt of a compound of formula II manufactured by the method as defined above into a compound of formula IIIb:

[Chemical Formula 7]

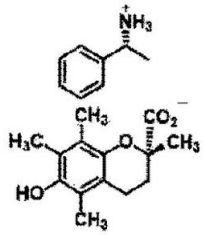


Formula IIIb: (S)-2-hydroxy-2-methyl-4-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dienyl)butanamide.

[0006g]

In another aspect, there is provided a compound of formula IVb:

[Chemical Formula 18]



Formula IVb

or a solvate thereof.

[0006h]

In another aspect, there is provided a pharmaceutical ingredient comprising the compound or solvate as defined above.

[0006i]

In another aspect, there is provided a composition for use in optically resolving a compound, comprising an amide-based solvent.

[0006j]

In another aspect, there is provided a method of optically resolving a compound, comprising adding an amide-based solvent to the compound.

[0006k]

In another aspect, there is provided the use of an amide-based solvent for optically resolving a compound.

[0007]

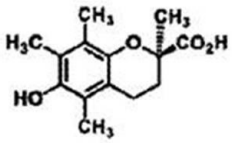
For example, the present disclosure provides the

following items.

(Item 1)

A method of manufacturing a solid salt of a compound of formula I, comprising adding an amide-based solvent in the presence of an optical resolving agent to a sample comprising the compound of formula I and suspected of comprising a compound of formula II:

[Chemical Formula 11]



Formula I: (R)-6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (hereinafter R Trolox)

[Chemical Formula 12]

from N-methylpyrrolidone (NMP), dimethylacetamide (DMA), and N,N-dimethylformamide (DMF).

(Item 72)

The composition of item 71, wherein the amide-based solvent is N-methylpyrrolidone.

(Item 73)

The composition of item 71, wherein the amide-based solvent is dimethylacetamide.

(Item 74)

The composition of item 71, wherein the amide-based solvent is N,N-dimethylformamide.

(Item 74A)

The method of item 67, further comprising a feature of any one or more of items 1 to 74.

(Item 75)

A method of optically resolving a compound, comprising adding an amide-based solvent to the compound.

(Item 75A)

The method of item 75, further comprising a feature of any one or more of items 1 to 74.

(Item 76)

Use of an amide-based solvent for optically resolving a compound.

(Item 76A)

The method of item 76, further comprising a feature of any one or more of items 1 to 75.

[0008]

The present disclosure is intended so that one or more of the aforementioned features can be provided not only as the explicitly disclosed combinations, but also as other combinations. Additional examples and advantages of the present disclosure are recognized by those skilled in the art by reading and understanding the following detailed descriptions as needed.

[Advantageous Effects]