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]

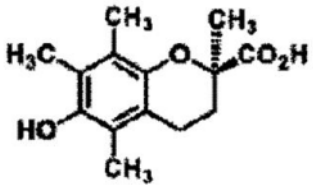
[0006]

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]

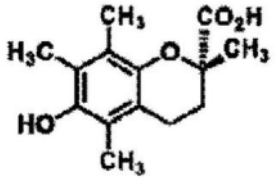
In aspect, there is provided a method of manufacturing a solid salt of a compound of formula I, comprising adding an amide-based solvent in the presence of an optical resolving agent which is (R)-phenylethylamine to a sample comprising the compound of formula I and suspected of comprising a compound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

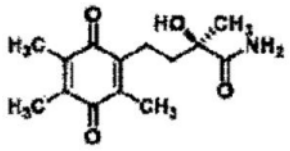
wherein the amide-based solvent is one or more solvents selected from N-methylpyrrolidone (NMP), dimethylacetamide (DMA), N,N-dimethylformamide (DMF), N,N-diethylformamide (DEF), tetramethylurea (TMU), and hexamethylphosphoric triamide (HMPA),

wherein the solid salt is an amide-based solvate.

[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]

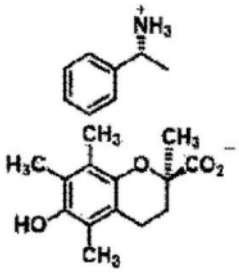


Formula IIIa: (R)-2-hydroxy-2-methyl-4-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dienyl)butanamide.

[0006c]

In another aspect, there is provided an amide-based solvate of a compound of formula IVa:

[Chemical Formula 4]



Formula IVa, wherein the amide-based solvent is one or more solvents selected from N-methylpyrrolidone (NMP), dimethylacetamide (DMA), N,N-dimethylformamide (DMF), N,N-diethylformamide (DEF), tetramethylurea (TMU), and hexamethylphosphoric triamide (HMPA).

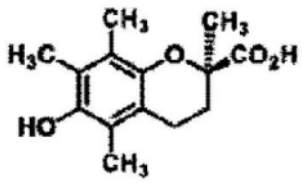
[0006d]

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

[0006e]

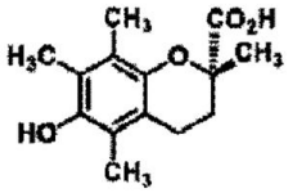
In another aspect, there is provided a method of manufacturing a solid salt of a compound of formula II, comprising adding an amide-based solvent in the presence of an optical resolving agent which is (S)-phenylethylamine to a sample comprising a compound of formula II and suspected of comprising a compound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

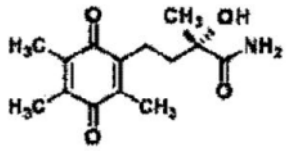
wherein the amide-based solvent is one or more solvents selected from N-methylpyrrolidone (NMP), dimethylacetamide (DMA), N,N-dimethylformamide (DMF), N,N-diethylformamide (DEF), tetramethylurea (TMU), and hexamethylphosphoric triamide (HMPA),

wherein the solid salt is an amide-based solvate.

[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]

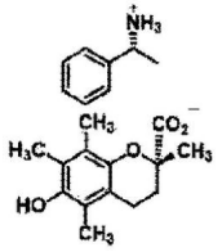


Formula IIIb: (S)-2-hydroxy-2-methyl-4-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dienyl)butanamide.

[0006g]

In another aspect, there is provided an amide-based solvate of a compound of formula IVb:

[Chemical Formula 18]



Formula IVb, wherein the amide-based solvent is one or more solvents selected from N-methylpyrrolidone (NMP), dimethylacetamide (DMA), N,N-dimethylformamide (DMF), N,N-diethylformamide (DEF), tetramethylurea (TMU), and hexamethylphosphoric triamide (HMPA).

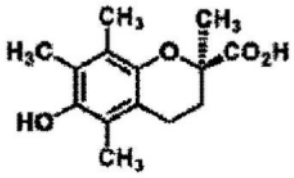
[0006h]

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

[0006i]

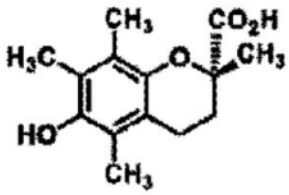
In another aspect, there is provided the use of a composition for optically resolving a mixture of a compound of formula I and a compound of formula II with an optical resolving agent which is (R)-phenylamine or (S)-phenylamine:

[Chemical Formula 9]



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

[Chemical Formula 10]



Formula II: (S)-6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (hereinafter S Trolox), comprising an amide-based solvent,

wherein the amide-based solvent is one or more solvents selected from N-methylpyrrolidone (NMP), dimethylacetamide (DMA), N,N-dimethylformamide (DMF), N,N-diethylformamide (DEF), tetramethylurea (TMU), and hexamethylphosphoric triamide (HMPA),

the compound of formula I or the compound of formula II forms an amide-based solvate.

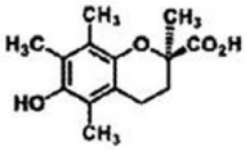
[0007]

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)

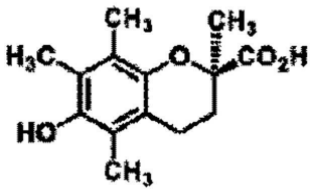
[Chemical Formula 12]

[Claims]

[Claim 1]

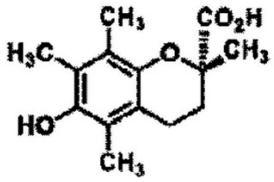
A method of manufacturing a solid salt of a compound of formula I, comprising adding an amide-based solvent in the presence of an optical resolving agent which is (R)-phenylethylamine to a sample comprising the compound of formula I and suspected of comprising a compound of formula II:

[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),

wherein the amide-based solvent is one or more solvents selected from N-methylpyrrolidone (NMP), dimethylacetamide (DMA), N,N-dimethylformamide (DMF), N,N-diethylformamide (DEF), tetramethylurea (TMU), and hexamethylphosphoric triamide (HMPA),

wherein the solid salt is an amide-based solvate.

[Claim 2]

The method of claim 1, wherein the optical resolving agent comprises at least an asymmetric carbon, and a moiety that can form a salt with the R Trolox and S Trolox.

[Claim 3]

The method of claim 1 or 2, comprising adding the optical resolving agent to the sample.

[Claim 4]

The method of any one of claims 1 to 3, wherein addition of the amide-based solvent comprises adding a mixture of the optical resolving agent and the amide-based solvent to the sample.

[Claim 5]

The method of any one of claims 1 to 4, wherein the sample comprises a complex with the optical resolving agent.

[Claim 6]

The method of any one of claims 1 to 5, wherein the sample comprises a mixture of a compound of formula I and a compound of formula II.

[Claim 7]

The method of claim 1, wherein the amide-based solvent is one or more solvents selected from N-methylpyrrolidone (NMP), dimethylacetamide (DMA), and N,N-dimethylformamide (DMF).

[Claim 8]

The method of claim 1, wherein the amide-based solvent is N-methylpyrrolidone.

[Claim 9]

The method of claim 1, wherein the amide-based solvent is dimethylacetamide.

[Claim 10]

The method of claim 1, wherein the amide-based solvent is N,N-dimethylformamide.

[Claim 11]

The method of any one of claims 1 to 10, wherein an enantiomeric excess of a manufactured solid salt of a compound of formula I is at least 98% or greater.

[Claim 12]

The method of any one of claims 1 to 11, wherein an enantiomeric excess of a manufactured solid salt of a compound of formula I is at least 99% or greater.

[Claim 13]

The method of any one of claims 1 to 12, further comprising dissolving the (R)-phenylethylamine into toluene.

[Claim 14]

The method of any one of claims 1 to 13, comprising adding a poor solvent to the sample.

[Claim 15]

The method of claim 14, wherein the poor solvent is toluene or ethyl acetate.

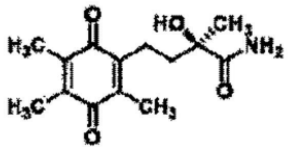
[Claim 16]

The method of any one of claims 1 to 15, further comprising removing the amide-based solvent.

[Claim 17]

A method of manufacturing a compound of formula IIIa, comprising converting a solid salt of a compound of formula I manufactured by the method of any one of claims 1 to 16 into a compound of formula IIIa:

[Chemical Formula 3]

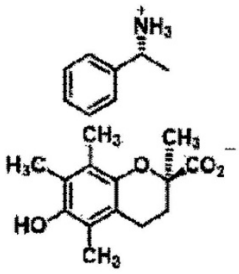


Formula IIIa: (R)-2-hydroxy-2-methyl-4-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dienyl)butanamide.

[Claim 18]

An amide-based solvate of a compound of formula IVa:

[Chemical Formula 4]



Formula IVa, wherein the amide-based solvent is one or more

solvents selected from N-methylpyrrolidone (NMP), dimethylacetamide (DMA), N,N-dimethylformamide (DMF), N,N-diethylformamide (DEF), tetramethylurea (TMU), and hexamethylphosphoric triamide (HMPA).

[Claim 19]

The solvate of claim 18, wherein an amide-based solvent is one or more solvents selected from NMP (N-methylpyrrolidone), DMA (dimethylacetamide), and DMF (N,N-dimethylformamide).

[Claim 20]

The solvate of claim 19, wherein the amide-based solvent is N-methylpyrrolidone.

[Claim 21]

The solvate of claim 19, wherein the amide-based solvent is dimethylacetamide.

[Claim 22]

The solvate of claim 20, wherein the amide-based solvent is N,N-dimethylformamide.

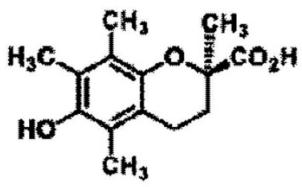
[Claim 23]

A pharmaceutical ingredient comprising the compound or solvate of any one of claims 18 to 22.

[Claim 24]

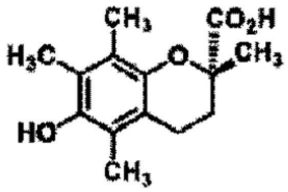
A method of manufacturing a solid salt of a compound of formula II, comprising adding an amide-based solvent in the presence of an optical resolving agent which is (S)-phenylethylamine to a sample comprising a compound of formula II and suspected of comprising a compound of formula I:

[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),

wherein the amide-based solvent is one or more solvents selected from N-methylpyrrolidone (NMP), dimethylacetamide (DMA), N,N-dimethylformamide (DMF), N,N-diethylformamide (DEF), tetramethylurea (TMU), and hexamethylphosphoric triamide (HMPA),

wherein the solid salt is an amide-based solvate.

[Claim 25]

The method of claim 24, wherein the optical resolving agent comprises at least an asymmetric carbon, and a moiety that can form a salt with the R Trolox and S Trolox.

[Claim 26]

The method of claim 24 or 25, comprising adding the optical resolving agent to the sample.

[Claim 27]

The method of any one of claims 24 to 26, wherein addition of the amide-based solvent comprises adding a mixture of the optical resolving agent and the amide-based solvent to the sample.

[Claim 28]

The method of any one of claims 24 to 27, wherein the sample comprises a complex with the optical resolving agent.

[Claim 29]

The method of any one of claims 24 to 28, wherein the sample comprises a mixture of a compound of formula I and a compound of formula II.

[Claim 30]

The method of any one of claims 24 to 29, wherein the amide-based solvent is one or more solvents selected from

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

[Claim 31]

The method of claim 30, wherein the amide-based solvent is N-methylpyrrolidone.

[Claim 32]

The method of claim 30, wherein the amide-based solvent is dimethylacetamide.

[Claim 33]

The method of claim 30, wherein the amide-based solvent is N,N-dimethylformamide.

[Claim 34]

The method of any one of claims 24 to 33, wherein an enantiomeric excess of a manufactured solid salt of a compound of formula II is at least 98% or greater.

[Claim 35]

The method of any one of claims 24 to 34, wherein an enantiomeric excess of a manufactured solid salt of a compound of formula II is at least 99% or greater.

[Claim 36]

The method of any one of claims 24 to 35, further comprising dissolving the (S)-phenylethylamine into toluene.

[Claim 37]

The method of any one of claims 24 to 36, comprising adding a poor solvent.

[Claim 38]

The method of claim 37, wherein the poor solvent is toluene or ethyl acetate.

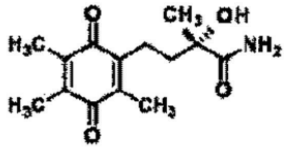
[Claim 39]

The method of any one of claims 24 to 38, further comprising removing the amide-based solvent.

[Claim 40]

A method of manufacturing a compound of formula IIIb, comprising converting a solid salt of a compound of formula II manufactured by the method of any one of claims 24 to 39 into a compound of formula IIIb:

[Chemical Formula 7]

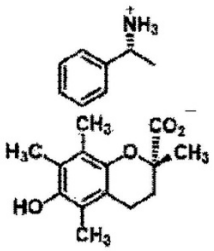


Formula IIIb: (S)-2-hydroxy-2-methyl-4-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dienyl)butanamide.

[Claim 41]

An amide-based solvate of a compound of formula IVb:

[Chemical Formula 18]



Formula IVb,

wherein the amide-based solvent is one or more solvents selected from N-methylpyrrolidone (NMP), dimethylacetamide (DMA), N,N-dimethylformamide (DMF), N,N-diethylformamide (DEF), tetramethylurea (TMU), and hexamethylphosphoric triamide (HMPA).

[Claim 42]

The solvate of claim 41, wherein the amide-based solvent is one or more solvents selected from NMP (N-methylpyrrolidone), DMA (dimethylacetamide), and DMF (N,N-dimethylformamide).

[Claim 43]

The solvate of claim 42, wherein the amide-based solvent is N-methylpyrrolidone.

[Claim 44]

The solvate of claim 42, wherein the amide-based solvent is dimethylacetamide.

[Claim 45]

The solvate of claim 42, wherein the amide-based

solvent is N,N-dimethylformamide.

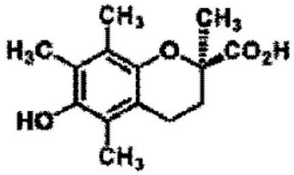
[Claim 46]

A pharmaceutical ingredient comprising the solvate of any one of claims 41 to 45.

[Claim 47]

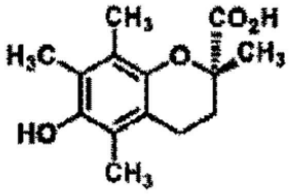
Use of a composition for optically resolving a mixture of a compound of formula I and a compound of formula II with an optical resolving agent which is (R)-phenylamine or (S)-phenylamine:

[Chemical Formula 9]



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

[Chemical Formula 10]



Formula II: (S)-6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (hereinafter S Trolox), comprising an amide-based solvent,

wherein the amide-based solvent is one or more solvents selected from N-methylpyrrolidone (NMP), dimethylacetamide (DMA), N,N-dimethylformamide (DMF), N,N-diethylformamide (DEF), tetramethylurea (TMU), and hexamethylphosphoric triamide (HMPA),

the compound of formula I or the compound of formula II forms an amide-based solvate.

[Claim 48]

The use of claim 47, wherein the composition is used

with another optical resolving agent.

[Claim 49]

The use of claim 48, wherein the another optical resolving agent itself has optical activity.

[Claim 50]

The use of any one of claims 47 to 49, wherein the amide-based solvent is one or more solvents selected from N-methylpyrrolidone (NMP), dimethylacetamide (DMA), and N,N-dimethylformamide (DMF).

[Claim 51]

The use of claim 50, wherein the amide-based solvent is N-methylpyrrolidone.

[Claim 52]

The use of claim 50, wherein the amide-based solvent is dimethylacetamide.

[Claim 53]

The use of claim 50, wherein the amide-based solvent is N,N-dimethylformamide.