

METHOD OF ELECTROLYTIC OXIDATIVE CLEAVAGE OF TROLOX AMIDE

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the priority of Japanese Patent Application No. 2023-204269 (filed
5 December 1, 2023), which is incorporated by reference.

FIELD OF THE INVENTION

[0002] The present disclosure provides a method of the electrolytic oxidative cleavage of Trolox
amide.

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BACKGROUND OF THE INVENTION

[0003] International Publication No. WO 2009/061744 describes that racemic 2-hydroxy-2-methyl-4-
(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dienyl)butanamide, which is useful in treating and/or suppressing a
mitochondrial disorder and a specific pervasive developmental disorder, is synthesized from racemic Trolox
15 (6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid).

[0004] International Publication No. WO 2021/167095 describes an optically resolved Trolox
intermediate and a method for producing same. It has been reported that α -tocopherol (vitamin E) can be
converted to the quinone form by electrolytic oxidation (J. Am. Chem. Soc. 2004, 126, 12441-12450 (non-
patent literature 1)), but there are no reported cases of electrolytic oxidation of the Trolox derivative disclosed
20 in the present application.

SUMMARY OF THE INVENTION

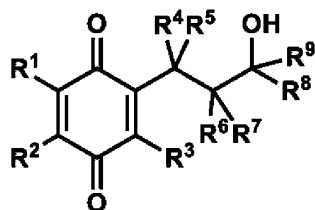
[0005] In certain aspects and embodiments, the inventors have completed the present disclosure by
discovering a novel electrolytic oxidative cleavage method for troloxamide-related compounds as a result of
25 their diligent study.

[0006] In certain embodiments, the present disclosure provides the following items:

[Item 1]

A method of manufacturing for a compound of formula I:

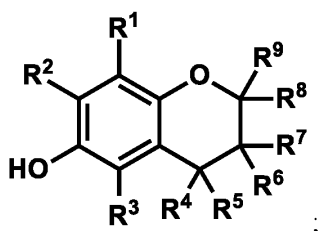
[0007] [Chemical Formula 1]



including the steps of:

- 5 performing electrolytic oxidation of a compound of formula II:

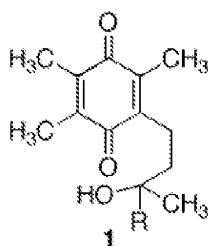
[0008] [Chemical Formula 2]



wherein

- 10 R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , and R^9 each independently represent a hydrogen atom, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} alkoxy, or $-C(=O)NR^A R^B$, and R^A and R^B each independently represent a hydrogen atom, optionally substituted C_{1-6} alkyl, or optionally substituted C_{1-6} alkoxy, provided that the compound of Formula I is not Formula III:

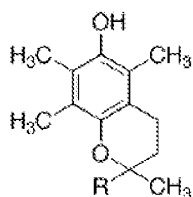
[0009] [Chemical Formula 3].



- 15 (wherein R is $(CH_2CH_2CH_2CH(CH_3)_3CH_3)$)

and the compound of formula II is not

[0010] [Chemical Formula 4].



(wherein R is $(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)_3\text{CH}_3)$).

[0011] [Item 2]

5 The method of item 1, wherein R^1 is a hydrogen atom or optionally substituted C_{1-6} alkyl.

[0012] [Item 3]

The method according to any one of the preceding items, wherein R^1 is methyl.

[0013] [Item 4]

The method according to any one of the preceding items, wherein R^2 is a hydrogen atom or
10 optionally substituted C_{1-6} alkyl.

[0014] [Item 5]

The method according to any one of the preceding items, wherein R^2 is methyl.

[0015] [Item 6]

The method according to any one of the preceding items, wherein R^3 is a hydrogen atom or
15 optionally substituted C_{1-6} alkyl.

[0016] [Item 7]

The method according to any one of the preceding items, wherein R^3 is methyl.

[0017] [Item 8]

The method according to any one of the preceding items, wherein R^4 is a hydrogen atom or
20 optionally substituted C_{1-6} alkyl.

[0018] [Item 9]

The method according to any one of the preceding items, wherein R^4 is a hydrogen atom.

[0019] [Item 10]

The method according to any one of the preceding items, wherein R^5 is a hydrogen atom or
25 optionally substituted C_{1-6} alkyl.

[0020] [Item 11]

The method of any one of the preceding items, wherein R^5 is a hydrogen atom.

[0021] [Item 12]

The method according to any one of the preceding items, wherein R^6 is a hydrogen atom or optionally substituted C_{1-6} alkyl.

[0022] [Item 13]

- 5 The method of any one of the preceding items, wherein R^6 is a hydrogen atom.

[0023] [Item 14]

The method according to any one of the preceding items, wherein R^7 is a hydrogen atom or optionally substituted C_{1-6} alkyl.

[0024] [Item 15]

- 10 The method of any one of the preceding items, wherein R^7 is a hydrogen atom.

[0025] [Item 16]

The method of any one of the preceding items, wherein R^8 is a hydrogen atom, optionally substituted C_{1-6} alkyl, or $-C(=O)NR^A R^B$.

[0026] [Item 17]

- 15 The method as described in any one of the preceding items, wherein R^8 is $-C(=O)NR^A R^B$.

[0027] [Item 18]

The method according to any one of the items above, wherein R^9 is a hydrogen atom or optionally substituted C_{1-6} alkyl.

[0028] [Item 19]

- 20 The method according to any one of the preceding items, wherein R^9 is methyl.

[0029] [Item 20]

The method of any one of the preceding items, R^A and R^B each represent a hydrogen atom.

[0030] [Item 21]

- 25 The method of any one of the preceding items, wherein the solvent is water or a nonprotic polar solvent.

[0031] [Item 22]

The method of any one of the preceding items, wherein the solvent is water and a nonprotic polar solvent.

[0032] [Item 23]

The method of any one of the preceding items, wherein in the electrolytic oxidation, the electrode used is a carbon-based electrode, a platinum-based electrode, or a stainless steel electrode, or a combination thereof.

5 [0033] [Item 23A]

The method of any one of the preceding items, wherein in electrolytic oxidation, the electrode used is (1) platinum foil electrode for the anode and glassy carbon electrode for the cathode; (2) platinum foil electrode for the anode and platinum foil for the cathode; (3) glassy carbon electrode for the anode and glassy carbon electrode for the cathode; (4) stainless steel electrode
10 for the anode and stainless steel electrode for the cathode; (5) platinum foil electrode, glassy carbon electrode for the cathode; or (6) glassy carbon electrode for the anode, stainless steel electrode for the cathode.

[0034] [Item 24]

The method of any one of the preceding items, wherein at least one selected from DMA,
15 MeCN, DMSO, DMF, and THF is used as the nonprotic polar solvent in said electrolytic oxidation.

[0035] [Item 24A]

The method of any one of the preceding items, wherein DMA is used as the nonprotic polar solvent in said electrolytic oxidation.

20 [0036] [Item 25]

The method described in any one of the items above, wherein an alkali metal salt or quaternary ammonium salt is used as the electrolyte in the electrolytic oxidation.

[0037] [Item 26]

The method of any one of the preceding items, in said electrolytic oxidation, wherein the
25 electrolyte comprises least one compound selected from the group consisting of lithium tetrafluoroborate (LiBF_4), lithium bromide (LiBr), tetrabutylammonium hexafluorophosphate (Bu_4NPF_6), tetrabutylammonium tetrafluoroborate (Bu_4NBF_4), sodium perchlorate, tetrabutylammonium bromide (Bu_4NBr), and lithium chloride (LiCl).

[0038] [Item 26]

30 The method of any one of the preceding items, in said electrolytic oxidation, wherein the electrolyte comprises least one compound selected from the group consisting of lithium tetrafluoroborate (LiBF_4), lithium bromide (LiBr), tetrabutylammonium hexafluorophosphate

(Bu₄NPF₆), tetrabutylammonium tetrafluoroborate (Bu₄NBF₄), sodium perchlorate, tetrabutylammonium bromide (Bu₄NBr), and lithium chloride (LiCl).

[0039] [Item 27]

The method of any one of the preceding items, wherein 10-100 mA is used as the current in
5 said electrolytic oxidation.

[0040] [Item 27A]

The method of any one of the preceding items, wherein 20-30 mA, 20 mA, or 30 mA is used as the current in said electrolytic oxidation.

[0041] [Item 28]

10 The method described in any one of the preceding items, wherein 5 mA/cm² -10 A/cm² is used as the current value per unit area of the electrode in the electrolytic oxidation.

[0042] [Item 28A]

The method described in any one of the preceding items, wherein 5 mA/cm² and 10 A/cm² are used as the current value per unit area of the electrode in the electrolytic oxidation.

15 [0043] [Item 29]

The method of any one of the preceding items, wherein 1-500 V is used as the voltage in said electrolytic oxidation.

[0044] [Item 29A]

The method described in any one of the preceding items, wherein 2V, 2.5V, 4V, 6V, or 8V is
20 used as the voltage in the electrolytic oxidation.

[0045] [Item 29A]

The method described in any one of the preceding items, wherein 2-10, 2-8, or 6-8 F/mol is used as an equivalent amount of electrons in the electrolytic oxidation.

[0046] [Item 30]

25 The method of any one of the preceding items, wherein (1) Bu₄ NPF₆ , DMA, and water;
(2) Bu₄ NPF₆ , THF, and water; (3) LiBr, MeCN, and water; or (4) Bu₄NBr, MeCN, and water

are used in the electrooxidation system as a combination of the electrolyte, the electrolyte nonprotic solvent, and the water.

[0047] [Item 31]

The method of any one of the preceding items, wherein in the electrolytic oxidation, the current
5 is stopped after the reaction is complete.

[0048] [Item 32]

The method of any one of the preceding items, wherein in the compound of Formula I, the carbon atom to which R⁸, R⁹ and OH bond is a chiral carbon.

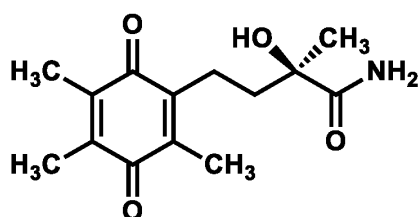
[0049] [Item 33]

10 The method of any one of the preceding items, wherein the compound of formula II is optically active and optical purity is maintained in the electrolytic oxidation reaction of the compound of formula II.

[0050] [Item 34]

The method of any one of preceding items, wherein the compound of formula I is

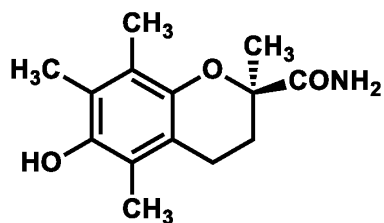
15 [0051] [Chemical Formula 5]



, and

the compound of formula II is

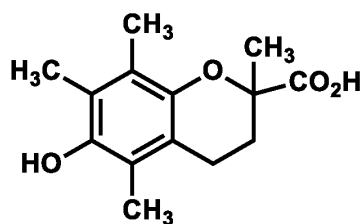
[0052] [Chemical Formula 6]



20 [0053] [Item 35]

The method of any one of the preceding items, wherein the compound of formula II is manufactured by the step of optically resolving and amidating a compound of formula III:

[0054] [Chemical Formula 7]



[0055] It is intended that in the present disclosure, one or more of the above features may be provided
5 in further combinations in addition to the explicitly stated combinations. Still further embodiments and
advantages of the present disclosure will be recognized by those skilled in the art upon reading and
understanding the following detailed description, if necessary.

Advantageous Effects of Invention

[0056] The present disclosure provides a method of preparing a compound represented by formula I at
10 a high reaction efficiency with a simple post-processing. The present disclosure allows the reaction to be
carried out with reduced or no use of oxidants, providing a cleaner method of production compared to
conventional methods. The present disclosure was also found to be able to convert compound 2 to
compound 1 at a yield at least comparable to conventional manufacturing methods. This means that a green
process with more reduced waste can be achieved by constructing a method for synthesizing the above
15 compound 1 by electrolytic oxidation with this disclosure.

BRIEF DESCRIPTION OF THE FIGURES

[0057] **FIG. 1** shows the HPLC chart of compound 1.

[0058] **FIG. 2** shows the HPLC chart of compound 2.

20 [0059] **FIG. 3** shows the HPLC chart of compound 3.

DETAILED DESCRIPTION

[0060] Provided herein are additional details regarding the method of the electrolytic oxidative cleavage of Trolox amide.

Definitions

5 [0061] Throughout the entire specification, a singular expression should be understood as encompassing the concept thereof in the plural form, unless specifically noted otherwise. Thus, singular articles (e.g., "a," "an," "the," and the like) should also be understood as encompassing the concept thereof in the plural form, unless specifically noted otherwise.

[0062] Further, the terms used herein should be understood as being used in the meaning that is
10 commonly used in the art, unless specifically noted otherwise. Therefore, unless defined otherwise, all terminologies and scientific technical terms that are used herein have the same meaning as the general understanding of those skilled in the art to which the present disclosure pertains. In case of a contradiction, the present specification (including the definitions) takes precedence.

[0063] The abbreviations used herein have the conventional meaning within the scope of the art unless
15 specifically noted otherwise.

[0064] The term "about" for a value or parameter herein includes variations about the value or parameter itself. Unless specifically noted otherwise, "about X" for example includes "X" itself as well as values with an acceptable error of $\pm 10\%$ therefrom.

[0065] As used herein, "Trolox" indicates 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid.
20 The R form is referred to as R-Trolox, and the the S form is referred to as S Trolox. Trolox can be prepared by a synthesis method that is well known to those skilled in the art, such as the methods described in US Patent No. 3,947,473, US Patent No. 4,003,919, and US Patent No. 4,026,907.

[0066] As used herein, "electrolytic oxidation" refers to an oxidation reaction that occurs at the anode of electrolysis in water, aqueous solution or non-protic solvent, or a mixture thereof.

25 [0067] As used herein, "nonprotic polar solvent" refers to polar solvents that lack an easily exchangeable or acidic hydrogen. Nonprotic polar solvents include tetrahydrofuran (THF), 2-methyl-tetrahydrofuran, acetone, acetonitrile (MeCN), N-methylpyrrolidone, and dimethyl sulfoxide (DMSO), dimethylacetamide

(DMA), and dimethylformamide (DMF), but not limited to these. Preferably, but without limitation, DMA is used.

[0068] As used herein, the "time" of electrolytic oxidation refers to the time that voltage is applied to the reactant substance or the time that the reactant substance is energized in the reaction system.

5 [0069] As used herein, "electrode" refers to an electrical conductor used to contact a non-metallic part of an electrical circuit. The electrode can be a carbon-based electrode, a platinum-based electrode, a stainless steel electrode, or a combination of these. Preferably, but without limitation, the electrode can be carbon.

[0070] As used herein, "electrolyte" is used in the usual sense used in the field. In certain embodiments, alkali metal salts, such as lithium salts, or quaternary ammonium salts can be used, such as Bu_4NPF_6 ,
10 Bu_4NBF_4 , Bu_4NBr , Et_4NPF_6 , LiBr , LiCl , LiBF_4 , and the like. Preferably, but without limitation, Bu_4NBr can be used..

[0071] Any value of current used in electrolytic oxidation can be used herein, typically 10 to 100 mA, or 20 to 30 mA, 20mA, 30mA, and the like. In certain embodiments, the current used in electrolytic oxidation can be stopped after the reaction is complete.

15 [0072] The current values used in electrolytic oxidation herein can be specified in terms of current per electrode unit area, such as 5 mA/cm^2 - 10 A/cm^2 , 10 mA/cm^2 - 1 A/cm^2 , 100 mA/cm^2 - 1 A/cm^2 , 10 - 100 mA/cm^2 , and the like. In certain embodiments, any combination of ranges of values can be used.

[0073] Any value can be used as the voltage used in electrolytic oxidation herein. In certain embodiments, the voltage can be, for example, 1 to 500 V, 1 to 100 V, 1 to 10 V, 2 to 8 V, 4 to 8 V or 2.5 V,
20 and the like.

[0074] Any value can be used herein as the equivalent amount of electrons used in electrolytic oxidation. In certain embodiments, any range of values, such as 2-10 F/mol, 2-6 F/mol, 6-8 F/mol, and the like can be used.

[0075] In certain embodiments, the combinations of electrolytes and solvents are set by those skilled in
25 the art as appropriate based on Examples demonstrated herein. In certain embodiments, they include, but are not limited to, the combinations of electrolytes and solvents that include Bu_4NPF_6 with DMA and water,

Bu₄NPF₆ with THF and water, LiBr with MeCN and water combinations, Bu₄ combinations of NBr, MeCN and water, and the like.

[0076] There is no restriction on the number of substituents in the groups defined by "optionally substituted" or "substituted" as long as they are substitutable. Unless otherwise indicated, the description of
5 each group also applies when that group is a part of or a substituent of another group.

[0077] A substituent in an "optionally substituted" group is selected from a substituent group α that consists of the following. The group is optionally substituted with from 1 to 5 of the same or different substituents.

[0078] While not particularly limited by the type of substituent, if an atom to which the substituent
10 attaches is an oxygen atom, a nitrogen atom, or a sulfur atom, the substituent is limited to the following substituents that can attach to a carbon atom.

[0079] In certain aspects and embodiments, the substituent group α may be:

- 1) a halogen atom
- 2) a hydroxyl group
- 15 3) a carboxyl group
- 4) a cyano group
- 5) a C₁₋₆ alkyl group
- 6) a C₂₋₆ alkenyl group
- 7) a C₂₋₆ alkynyl group
- 20 8) a C₁₋₆ alkoxy group
- 9) a C₁₋₆ alkylthio group
- 10) a C₁₋₆ alkylcarbonyl group
- 11) a C₁₋₆ alkylsulfonyl group
- 12) a C₃₋₁₀ alicyclic group
- 25 13) a C₃₋₁₀ alicyclic oxy group
- 14) a C₆₋₁₀ aryloxy group
- 15) a 5- or 6-membered heteroaryloxy group
- 16) a 4- to 10-membered non-aryl heterocyclyl oxy group
- 17) a C₃₋₁₀ alicyclic thio group
- 30 18) a C₆₋₁₀ arylthio group
- 19) a 5- or 6-membered heteroarylthio group
- 20) a 4- to 10-membered non-aryl heterocyclyl thio group
- 21) C₆₋₁₀ aryl

- 22) 5- or 6-membered heteroaryl
 23) a 4- to 10-membered non-aryl heterocycle
 24) a C₃₋₁₀ alicyclic carbonyl group
 25) a C₆₋₁₀ arylcarbonyl group
 5 26) a 5- or 6-membered heteroarylcarbonyl group
 27) a 4- to 10-membered non-aryl heterocyclyl carbonyl group
 28) a C₃₋₁₀ alicyclic sulfonyl group
 29) a C₆₋₁₀ arylsulfonyl group
 30) a 5- or 6-membered heteroarylsulfonyl group
 10 31) a 4- to 10-membered non-aryl heterocyclyl sulfonyl group
 (wherein each substituent from 12) to 31) is optionally substituted with 1 to 5 of substituent group β or 1) a C₁₋₆ alkyl group)
 32) -NR^{10a}R^{11a}
 33) -SO₂-NR^{10b}R^{11b}
 15 34) -NR^{10c}-C(=O)R^{11c}
 35) -NR^{10d}-C(=O)OR^{11d}
 36) -NR^{12a}-C(=O)NR^{10e}R^{11e}
 37) -NR^{10f}-C(=S)R^{11f}
 38) -NR^{10g}-C(=S)OR^{11g},
 20 39) -NR^{12b}-C(=S)NR^{10h}R^{11h}
 40) -NR¹⁰ⁱ-SO₂-R¹¹ⁱ
 41) -NR^{12c}-SO₂-NR^{10j}R^{11j}
 42) -C(=O)OR^{10k}
 43) -C(=O)NR^{10l}R^{11k}
 25 44) -C(=O)NR^{10m}OR^{11l}
 45) -C(=O)NR^{12d}-NR¹⁰ⁿR^{11m}
 46) -C(=S)OR^{10o}
 47) -C(=S)NR^{10p}R¹¹ⁿ
 48) -C(=S)NR^{10q}OR^{11o}
 30 49) -C(=S)NR^{12e}-NR^{10r}R^{11p}
 50) -C(=NR^{13a})R^{10s}
 51) -C(=NR^{13b})CHO
 52) -C(=NR^{13c})NR^{10t}R^{11q}
 53) -C(=NR^{13d})NR^{12f}-NR^{10u}R^{11r}
 35 54) -NR^{17c}-C(=NR^{13k})R^{17d}

- 55) $-\text{NR}^{12g}-\text{C}(=\text{NR}^{13e})-\text{NR}^{10v}\text{R}^{11s}$
 56) $-\text{NR}^{14}-\text{C}(=\text{NR}^{13f})\text{NR}^{12h}-\text{NR}^{10w}\text{R}^{11t}$
 57) $-\text{OC}(=\text{O})\text{R}^{10x}$
 58) $-\text{OC}(=\text{O})\text{OR}^{10y}$
 59) $-\text{OC}(=\text{O})\text{NR}^{10z1}\text{R}^{11u}$
 60) $-\text{NR}^{12i}-\text{NR}^{10z2}\text{R}^{11v}$
 61) $-\text{NR}^{10z3}\text{OR}^{11w}$
 62) $-\text{C}(=\text{N}-\text{OR}^{13a})\text{R}^{10s}$
 63) $-\text{C}(=\text{N}-\text{OR}^{13b})\text{CHO}$
 64) $-\text{C}(=\text{N}-\text{OR}^{13c})\text{NR}^{10t}\text{R}^{11q}$
 65) $-\text{C}(=\text{N}-\text{OR}^{13d})\text{NR}^{12f}-\text{NR}^{10u}\text{R}^{11r}$ and
 66) $-\text{C}(=\text{O})\text{H}$,

[0080] In certain embodiments, a substituent group β is selected from the group including:

- 1) a halogen atom,
- 2) a hydroxyl group,
- 3) a carboxyl group,
- 4) a cyano group,
- 5) a C_{3-10} alicyclic group,
- 6) a C_{1-6} alkoxy group,
- 7) a C_{3-10} alicyclic oxy group,
- 8) a C_{1-6} alkylthio group,
- 9) a 5- or 6-membered heteroarylthio group,
- 10) C_{6-10} aryl,
- 11) 5- or 6-membered heteroaryl,
- 12) a 4- to 10-membered non-aryl heterocycle,
- 13) a C_{1-6} alkylcarbonyl group,
- 14) a C_{3-10} alicyclic carbonyl group,
- 15) a C_{6-10} arylcarbonyl group,
- 16) a 5- or 6-membered heteroarylcarbonyl group,
- 17) a 4- to 10-membered non-aryl heterocyclyl carbonyl group,
- 18) $-\text{NR}^{15a}\text{R}^{16a}$,
- 19) $-\text{SO}_2-\text{NR}^{15b}\text{R}^{16b}$,
- 20) $-\text{NR}^{15c}-\text{C}(=\text{O})\text{R}^{16c}$,
- 21) $-\text{NR}^{17a}-\text{C}(=\text{O})\text{NR}^{15d}\text{R}^{16d}$,

- 22) $-C(=O)NR^{15e}R^{16e}$,
 23) $-C(=NR^{13g})R^{15f}$,
 24) $-C(=NR^{13h})NR^{15g}R^{16f}$,
 25) $-NR^{16g}-C(=NR^{13i})R^{15h}$,
 5 26) $-NR^{17b}-C(=NR^{13j})-NR^{15i}R^{16h}$,
 27) $-C(=N-OR^{13g})R^{15f}$, and
 28) $-C(=N-OR^{13h})NR^{15g}R^{16f}$

(wherein each substituent from 5) to 17) in substituent group β is optionally substituted with 1 to 5 substituents selected from the group consisting of a halogen atom, a hydroxyl group, a cyano group, a
 10 carboxyl group, and $-NR^{18a}R^{18b}$).

[0081] $R^{13a}, R^{13b}, R^{13c}, R^{13d}, R^{13e}, R^{13f}, R^{13g}, R^{13h}, R^{13i}, R^{13j}$, and R^{13k} are the same or different, each independently a hydrogen atom, a hydroxyl group, a C_{1-6} alkyl group, or a C_{1-6} alkoxy group),

[0082] $R^{10a}, R^{10b}, R^{10c}, R^{10d}, R^{10e}, R^{10f}, R^{10g}, R^{10h}, R^{10i}, R^{10j}, R^{10k}, R^{10l}, R^{10m}, R^{10n}, R^{10o}, R^{10p}, R^{10q}, R^{10r}, R^{10s}, R^{10t}, R^{10u}, R^{10v}, R^{10w}, R^{10x}, R^{10y}, R^{10z1}, R^{10z2}, R^{10z3}, R^{11a}, R^{11b}, R^{11c}, R^{11d}, R^{11e}, R^{11f}, R^{11g}, R^{11h}, R^{11i}, R^{11j}, R^{11k}, R^{11l}, R^{11m}, R^{11n}, R^{11o}, R^{11p}, R^{11q}, R^{11r}, R^{11s}, R^{11t}, R^{11u}, R^{11v}, R^{11w}, R^{12a}, R^{12b}, R^{12c}, R^{12d}, R^{12e}, R^{12f}, R^{12g}, R^{12h}, R^{12i}, R^{12j}, R^{12k}, R^{12l}, R^{12m}, R^{12n}, R^{12o}, R^{12p}, R^{12q}, R^{12r}, R^{12s}, R^{12t}, R^{12u}, R^{12v}, R^{12w}, R^{12x}, R^{12y}, R^{12z1}, R^{12z2}, R^{12z3}, R^{13a}, R^{13b}, R^{13c}, R^{13d}, R^{13e}, R^{13f}, R^{13g}, R^{13h}, R^{13i}, R^{13j}, R^{13k}, R^{13l}, R^{13m}, R^{13n}, R^{13o}, R^{13p}, R^{13q}, R^{13r}, R^{13s}, R^{13t}, R^{13u}, R^{13v}, R^{13w}, R^{13x}, R^{13y}, R^{13z1}, R^{13z2}, R^{13z3}, R^{14a}, R^{14b}, R^{14c}, R^{14d}, R^{14e}, R^{14f}, R^{14g}, R^{14h}, R^{14i}, R^{14j}, R^{14k}, R^{14l}, R^{14m}, R^{14n}, R^{14o}, R^{14p}, R^{14q}, R^{14r}, R^{14s}, R^{14t}, R^{14u}, R^{14v}, R^{14w}, R^{14x}, R^{14y}, R^{14z1}, R^{14z2}, R^{14z3}, R^{15a}, R^{15b}, R^{15c}, R^{15d}, R^{15e}, R^{15f}, R^{15g}, R^{15h}, R^{15i}, R^{15j}, R^{15k}, R^{15l}, R^{15m}, R^{15n}, R^{15o}, R^{15p}, R^{15q}, R^{15r}, R^{15s}, R^{15t}, R^{15u}, R^{15v}, R^{15w}, R^{15x}, R^{15y}, R^{15z1}, R^{15z2}, R^{15z3}, R^{16a}, R^{16b}, R^{16c}, R^{16d}, R^{16e}, R^{16f}, R^{16g}, R^{16h}, R^{16i}, R^{16j}, R^{16k}, R^{16l}, R^{16m}, R^{16n}, R^{16o}, R^{16p}, R^{16q}, R^{16r}, R^{16s}, R^{16t}, R^{16u}, R^{16v}, R^{16w}, R^{16x}, R^{16y}, R^{16z1}, R^{16z2}, R^{16z3}, R^{17a}, R^{17b}, R^{17c}, R^{17d}, R^{17e}, R^{17f}, R^{17g}, R^{17h}, R^{17i}, R^{17j}, R^{17k}, R^{17l}, R^{17m}, R^{17n}, R^{17o}, R^{17p}, R^{17q}, R^{17r}, R^{17s}, R^{17t}, R^{17u}, R^{17v}, R^{17w}, R^{17x}, R^{17y}, R^{17z1}, R^{17z2}, R^{17z3}, R^{18a}, R^{18b}, R^{18c}, R^{18d}, R^{18e}, R^{18f}, R^{18g}, R^{18h}, R^{18i}, R^{18j}, R^{18k}, R^{18l}, R^{18m}, R^{18n}, R^{18o}, R^{18p}, R^{18q}, R^{18r}, R^{18s}, R^{18t}, R^{18u}, R^{18v}, R^{18w}, R^{18x}, R^{18y}, R^{18z1}, R^{18z2}, R^{18z3}$ are the same or different, each independently a hydrogen atom or a C_{1-6} alkyl group (wherein the alkyl group is optionally substituted with 1 to 3 of the same or different substituents selected from a hydroxyl group, a cyano group, a C_{1-6} alkoxy group, and $-NR^{18a}R^{18b}$), and

20 [0083] R^{18a} and R^{18b} are the same or different, each independently a hydrogen atom or a C_{1-6} alkyl group.

[0084] In certain preferred embodiments, the substituent group α is selected from the group including

- 1) a halogen atom
- 2) a hydroxyl group
- 3) a carboxyl group
- 25 4) a cyano group
- 5) a C_{1-6} alkyl group
- 6) a C_{1-6} alkoxy group
- 7) a C_{1-6} alkylthio group
- 8) a C_{1-6} alkylcarbonyl group

30

(wherein each substituent from 5) to 8) is optionally substituted with 1 to 5 of the same or different substituents selected from substituent group β)

- 9) a C₃₋₁₀ alicyclic group
- 10) a C₃₋₁₀ alicyclic oxy group
- 5 11) a C₆₋₁₀ aryloxy group
- 12) a 5- or 6-membered heteroaryloxy group
- 13) a 4- to 10-membered non-aryl heterocyclyl oxy group
- 14) a C₃₋₁₀ alicyclic thio group
- 15) a C₆₋₁₀ arylthio group
- 10 16) a 5- or 6-membered heteroarylthio group
- 17) a 4- to 10-membered non-aryl heterocyclyl thio group
- 18) C₆₋₁₀ aryl
- 19) 5- or 6-membered heteroaryl
- 20) a 4- to 10-membered non-aryl heterocycle
- 15 21) a C₃₋₁₀ alicyclic carbonyl group
- 22) a C₆₋₁₀ arylcarbonyl group
- 23) a 5- or 6-membered heteroarylcarbonyl group
- 24) a 4- to 10-membered non-aryl heterocyclyl carbonyl group
- (wherein each substituent from 9) to 24) is optionally substituted with 1 to 5 of substituent group β
- 20 or 1) a C₁₋₆ alkyl group)
- 25) -NR^{10a}R^{11a}
- 26) -SO₂-NR^{10b}R^{11b}
- 27) -NR^{10c}-C(=O)R^{11c}
- 28) -NR^{12a}-C(=O)NR^{10d}R^{11d}
- 25 29) -NR^{10e}-SO₂-R^{11e}
- 30) -NR^{12b}-SO₂-NR^{10f}R^{11f}
- 31) -C(=O)NR^{10g}R^{11g}
- 32) -C(=NR^{13a})R^{10h}
- 33) -C(=NR^{13b})NR¹⁰ⁱR^{11h}
- 30 34) -NR^{11f}-C(=NR^{13c})R^{10g}
- 35) -NR^{12c}-C(=NR^{13d})-NR^{10j}R¹¹ⁱ
- 36) -C(=N-OR^{13a})R^{10h} and
- 37) -C(=N-OR^{13b})NR¹⁰ⁱR^{11h}.

[0085] In certain preferred embodiments, the substituent group β is selected from the group including

- 1) a halogen atom
- 2) a hydroxyl group
- 3) a cyano group
- 5 4) a C₃₋₁₀ alicyclic group
- 5) a C₁₋₆ alkoxy group
- 6) a C₁₋₆ alkylthio group
- 7) a 5- or 6-membered heteroarylthio group
- 8) 5- or 6-membered heteroaryl
- 10 9) a 4- to 10-membered non-aryl heterocycle
- 10) a C₁₋₆ alkylcarbonyl group
- 11) a C₃₋₁₀ alicyclic carbonyl group
- 12) a C₆₋₁₀ arylcarbonyl group
- 13) a 5- or 6-membered heteroarylcarbonyl group
- 15 14) a 4- to 10-membered non-aryl heterocyclyl carbonyl group
- 15) -NR^{15a}R^{16a}
- 16) -NR^{15b}-C(=O)R^{16b}
- 17) -NR^{17a}-C(=O)NR^{15c}R^{16c}
- 18) -C(=O)NR^{15d}R^{16d}
- 20 19) -C(=NR^{13e})R^{15e}
- 20) -C(=NR^{13f})NR^{15f}R^{16e}
- 21) -NR^{16f}-C(=NR^{13g})R^{15g}
- 22) -NR^{17b}-C(=NR^{13h})-NR^{15h}R^{16g}
- 23) -C(=N-OR^{13e})R^{15e} and
- 25 24) -C(=N-OR^{13f})NR^{15f}R^{16e}

(wherein each substituent from 4) to 14) in substituent group β is optionally substituted with 1 to 5 substituents selected from the group including a halogen atom, a hydroxyl group, a cyano group, a carboxyl group, and -NR^{18a}R^{18b}),

- [0086] R^{13a}, R^{13b}, R^{13c}, R^{13d}, R^{13e}, R^{13f}, R^{13g}, and R^{13h} are the same or different, each independently a
- 30 hydrogen atom, a hydroxyl group, a C₁₋₆ alkyl group, or a C₁₋₆ alkoxy group,

[0087] R^{10a}, R^{10b}, R^{10c}, R^{10d}, R^{10e}, R^{10f}, R^{10g}, R^{10h}, R¹⁰ⁱ, R^{10j}, R^{11a}, R^{11b}, R^{11c}, R^{11d}, R^{11e}, R^{11f}, R^{11g}, R^{11h}, R¹¹ⁱ, R^{12a}, R^{12b}, R^{12c}, R^{15a}, R^{15b}, R^{15c}, R^{15d}, R^{15e}, R^{15f}, R^{15g}, R^{15h}, R^{16a}, R^{16b}, R^{16c}, R^{16d}, R^{16e}, R^{16f}, R^{16g}, R^{17a}, and R^{17b} are the same or different, each independently a hydrogen atom or a C₁₋₆ alkyl group (wherein the alkyl group

is optionally substituted with 1 to 3 of the same or different substituents selected from a hydroxyl group, a cyano group, a C₁₋₆ alkoxy group, and -NR^{18a}R^{18b}), and

[0088] R^{18a} and R^{18b} are the same or different, each independently a hydrogen atom or a C₁₋₆ alkyl group.

5 [0089] In certain more preferred examples, the substituents in "optionally substituted" include the following substituents.

[0090] In certain embodiments, the more preferred substituent group α is selected from the group including

- 1) a halogen atom
 - 10 2) a hydroxyl group
 - 3) a cyano group
 - 4) a C₁₋₆ alkyl group
 - 5) a C₁₋₆ alkoxy group
 - 6) a C₁₋₆ alkylthio group
 - 15 7) a C₁₋₆ alkylcarbonyl group
- (wherein each substituent from 4) to 7) is optionally substituted with 1 to 5 of the same or different substituents selected from substituent group β)
- 8) a 5- or 6-membered heteroaryloxy group
 - 9) a 4- to 10-membered non-aryl heterocyclyl oxy group
 - 20 10) a 5- or 6-membered heteroarylthio group
 - 11) a 4- to 10-membered non-aryl heterocyclyl thio group
 - 12) C₆₋₁₀ aryl
 - 13) 5- or 6-membered heteroaryl
 - 14) a 4- to 10-membered non-aryl heterocycle
- 25 (wherein each substituent from 4) to 14) is optionally substituted with 1 to 5 of a substituent selected from group β or 1) a C₁₋₆ alkyl group)
- 15) -NR^{10a}R^{11a}
 - 16) -NR^{11b}-C(=O)R^{10b}
 - 17) -NR^{12a}-C(=O)NR^{10c}R^{11c}
 - 30 18) -C(=O)NR^{10d}R^{11d}
 - 19) -C(=NR^{13a})R^{10e}
 - 20) -C(=NR^{13b})NR^{10f}R^{11e}
 - 21) -NR^{11f}-C(=NR^{13c})R^{10g}
 - 22) -NR^{12b}-C(=NR^{13d})-NR^{10h}R^{11g}

23) $-C(=N-OR^{13a})R^{10e}$ and

24) $-C(=N-OR^{13b})NR^{10f}R^{11e}$.

[0091] In certain embodiments, the more preferred substituent group β is selected from the group including

- 5 1) a halogen atom,
- 2) a hydroxyl group,
- 3) a cyano group,
- 4) $-NR^{15a}R^{16a}$,
- 5) $-NR^{15b}-C(=O)R^{16b}$,
- 10 6) $-NR^{17a}-C(=O)NR^{15c}R^{16c}$,
- 7) $-C(=O)NR^{15d}R^{16d}$,
- 8) $-C(=NR^{13e})R^{15e}$,
- 9) $-C(=NR^{13f})NR^{15f}R^{16e}$,
- 10) $-NR^{16f}-C(=NR^{13g})R^{15g}$,
- 15 11) $-NR^{17b}-C(=NR^{13h})-NR^{15h}R^{16g}$,
- 12) $-C(=N-OR^{13e})R^{15e}$, and
- 13) $-C(=N-OR^{13f})NR^{15f}R^{16e}$,

[0092] R^{13a} , R^{13b} , R^{13c} , R^{13d} , R^{13e} , R^{13f} , R^{13g} , and R^{13h} are the same or different, each independently a hydrogen atom, a hydroxyl group, a C_{1-6} alkyl group, or a C_{1-6} alkoxy group,

- 20 [0093] R^{10a} , R^{10b} , R^{10c} , R^{10d} , R^{10e} , R^{10f} , R^{10g} , R^{10h} , R^{11a} , R^{11b} , R^{11c} , R^{11d} , R^{11e} , R^{11f} , R^{11g} , R^{12a} , R^{12b} , R^{15a} , R^{15b} , R^{15c} , R^{15d} , R^{15e} , R^{15f} , R^{15g} , R^{15h} , R^{16a} , R^{16b} , R^{16c} , R^{16d} , R^{16e} , R^{16f} , R^{16g} , R^{17a} , and R^{17b} are the same or different, each independently a hydrogen atom or a C_{1-6} alkyl group (wherein the alkyl group is optionally substituted

with 1 to 3 of the same or different substituents selected from a hydroxyl group, a cyano group, a C₁₋₆ alkoxy group, and -NR^{18a}R^{18b}), and

[0094] R^{18a} and R^{18b} are the same or different, each independently a hydrogen atom or a C₁₋₆ alkyl group.

[0095] As used herein, "C₁₋₆" means that the number of carbon atoms is 1 to 6. The same applies to other
5 numbers. For example, "C₁₋₄" means that the number of carbon atoms is 1 to 4.

[0096] As used herein, a "heteroatom" refers to an oxygen atom, a nitrogen atom, a sulfur atom, and the like.

[0097] As used herein, a "halogen atom" refers to a fluorine atom, chlorine atom, bromine atom, or iodine atom. In particular, a fluorine atom and chlorine atom are preferable. A "halogen atom" is also referred to as
10 "halogen."

[0098] As used herein, "C₁₋₆ alkyl" or "C₁₋₆ alkyl group" refers to a linear or branched saturated hydrocarbon group with 1 to 6 carbon atoms. A C₁₋₆ alkyl group is preferably a "C₁₋₄ alkyl group," and more preferably a "C₁₋₃ alkyl group." Specific examples of "C₁₋₃ alkyl group" include methyl, ethyl, propyl, 1-methylethyl, and the like. Specific examples of "C₁₋₄ alkyl group" include, in addition to the specific
15 examples specified for the "C₁₋₃ alkyl group" described above, butyl, 1,1-dimethylethyl, 1-methylpropyl, 2-methylpropyl, and the like. Specific examples of "C₁₋₆ alkyl group" include, in addition to the specific examples specified for the "C₁₋₄ alkyl group" described above, pentyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 1-methylbutyl, 2-methylbutyl, 4-methylpentyl, 3-methylpentyl, 2-methylpentyl, 1-methylpentyl, hexyl, and the like.

20 [0099] As used herein, "C₂₋₆ alkenyl" or "C₂₋₆ alkenyl group" refers to a linear or branched unsaturated hydrocarbon group with 2 to 6 carbon atoms, comprising one or more carbon-carbon double bonds. "C₂₋₆ alkenyl group" is preferably a "C₂₋₄ alkenyl group." Specific examples of "C₂₋₆ alkenyl group" include, but are not limited to, a vinyl group, 1-propylenyl group, 2-propylenyl group, 1-butenyl group, 2-butenyl group, 3-butenyl group, 2-methyl-1-propylenyl group, 2-methyl-2-propylenyl group, and the like.

25 [00100] As used herein, "C₂₋₆ alkynyl" or "C₂₋₆ alkynyl group" refers to a linear or branched unsaturated aliphatic hydrocarbon group having one or more triple bonds. "C₂₋₆ alkynyl group" is preferably a "C₂₋₄ alkynyl group." Specific examples thereof include, but are not limited to, an ethynyl group, 1-propynyl group, 2-propynyl group, 1-butyne group, 1-methyl-2-propynyl group, 3-butyne group, 1-pentyne group, 1-hexynyl group, and the like.

30 [00101] As used herein, "C₃₋₂₀ alicyclic group" refers to a monocyclic or bicyclic non-aromatic hydrocarbon ring group with 3 to 20 carbon atoms, including those with a partially unsaturated bond, those with a partially crosslinked structure, those that have a partially spiro form, and those having one or more carbonyl

structures. "Alicyclic group" encompasses cycloalkyl groups, cycloalkenyl groups, and cycloalkynyl groups.

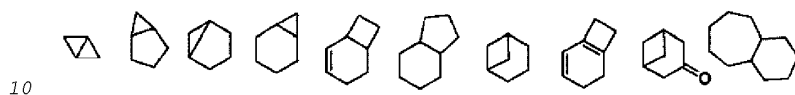
"C₃₋₂₀ alicyclic group" is preferably a "C₃₋₁₀ alicyclic group," and more preferably a "C₃₋₇ alicyclic group."

Specific examples of "C₃₋₇ alicyclic group" include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and the like. Specific examples of "C₃₋₁₀ alicyclic group" include, in addition to the specific

- 5 examples specified for the "C₃₋₇ alicyclic group" described above, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, adamantyl, and the like.

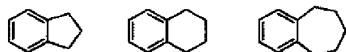
[00102] Specific examples of "C₃₋₂₀ alicyclic group" with a partially crosslinked structure include, but are not limited to, those with a structure shown below, and the like.

[00103] [Chemical Formula 8]



[00104] As used herein, "C₃₋₂₀ alicyclic group" also encompasses compounds fused to an aromatic ring. Specific examples thereof include the groups represented by the following, and the like.

[00105] [Chemical Formula 9]

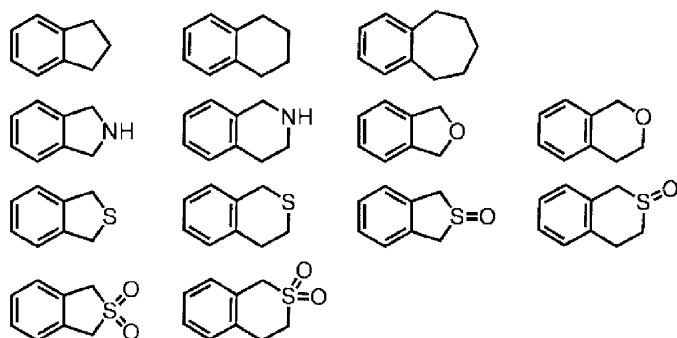


- 15 [00106] As used herein, "C₃₋₁₀ alicyclic group" refers to the "C₃₋₂₀ alicyclic group" described above wherein the "C₃₋₁₀ alicyclic group" is a monovalent group.

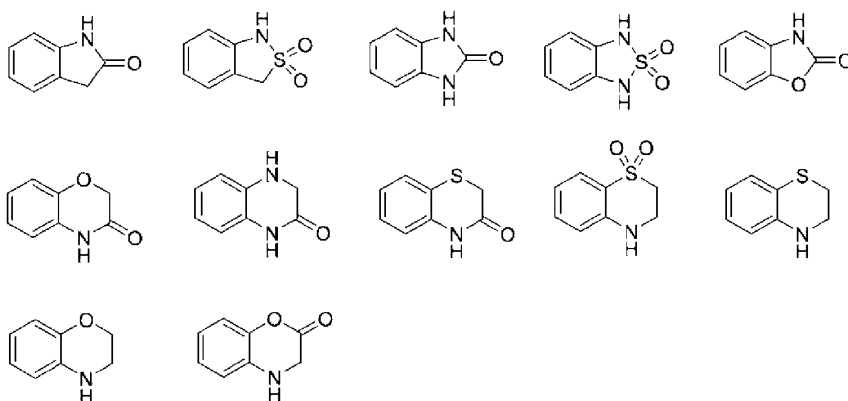
[00107] As used herein, "C₆₋₁₀ aryl" refers to a monocyclic or bicyclic aromatic hydrocarbon group with 6 to 10 carbon atoms. "C₆₋₁₀ aryl" may be fused to the "alicyclic group" or "non-aryl heterocycle" described above at any possible position. Specific examples of "C₆₋₁₀ aryl" include phenyl, 1-naphthyl, 2-naphthyl, and

20 the like. Preferred examples of "C₆₋₁₀ aryl" include phenyl. Specific examples of the fused ring structure include the groups represented by the following, and the like.

[00108] [Chemical Formula 10]



[00109] [Chemical Formula 11]

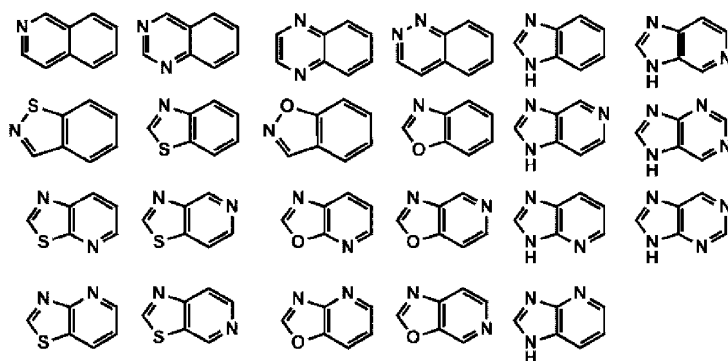


- 5 [00110] . As used herein, "6- to 10-membered heteroaryl" refers to a monocyclic or bicyclic aromatic heterocyclic group comprised of 6 to 10 atoms, comprising 1 to 4 atoms independently selected from the group consisting of a nitrogen atom, an oxygen atom, and a sulfur atom. "6- to 10-membered heteroaryl" may be fused to the "alicyclic group" or "non-aryl heterocycle" described above at any possible position. "6- to 10-membered heteroaryl" is preferably "6-membered heteroaryl," more preferably pyridyl, pyrazyl, pyrimidyl, or pyridazinyl, and still more preferably pyridyl or pyrimidyl. Specific examples of "6-membered heteroaryl" include pyridyl, pyrazinyl, pyrimidinyl, and pyridazinyl. Specific examples of "6- to 10-
- 10

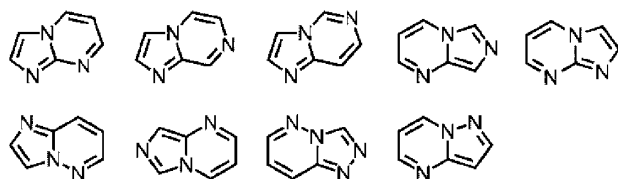
membered heteroaryl" include, in addition to the specific examples specified for the "6-membered heteroaryl" described above, quinoxalyl, triazolopyridyl, and the like.

[00111] Specific examples of "9- or 10-membered heteroaryl" include, but are not limited to, compounds with the structures described below, and the like.

5 [00112] [Chemical Formula 12]



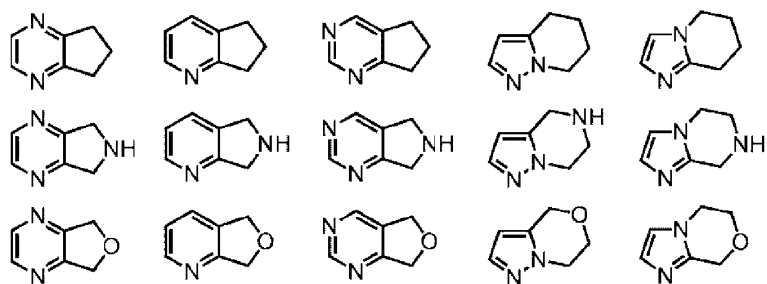
[00113] [Chemical Formula 13]



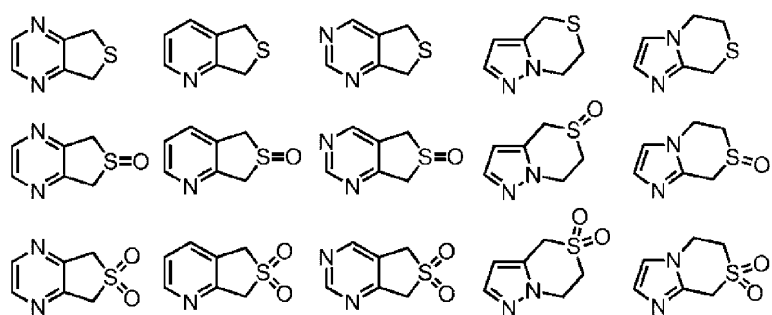
[00114] Specific examples of "5-membered heteroaryl" include, but are not limited to, thiophene, pyrrole, thiazole, isothiazole, pyrazole, imidazole, furan, oxazole, isoxazole, oxadiazole, thiadiazole, triazole, tetrazole, and the like. 5-membered heteroaryl is preferably pyrazole, imidazole, oxazole, triazole, tetrazole, or thiadiazole, and more preferably imidazole or thiadiazole.

[00115] Specific examples of "5- or 6-membered heteroaryl" include the specific examples for the "5-membered heteroaryl" and "6-membered heteroaryl" described above. The "5- or 6-membered heteroaryl" or "5- to 10-membered heteroaryl" described above may form a fused ring structure with a C₅₋₁₀ alicyclic group, or a fused ring structure with a 5- to 10-membered non-aryl heterocycle. Specific examples thereof include the groups represented by the following, and the like. .

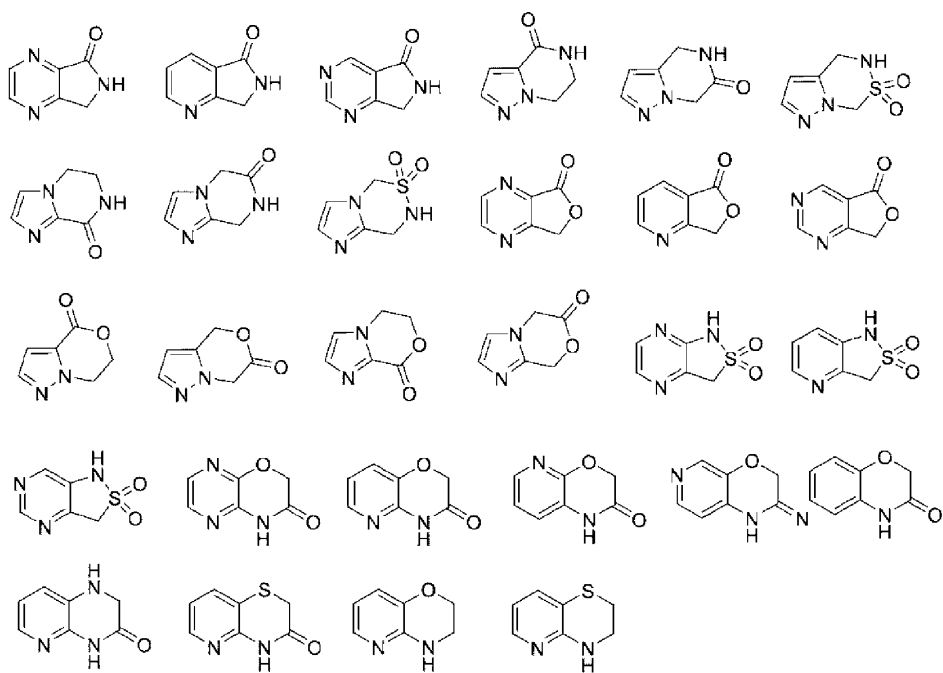
[00116] [Chemical Formula 14]



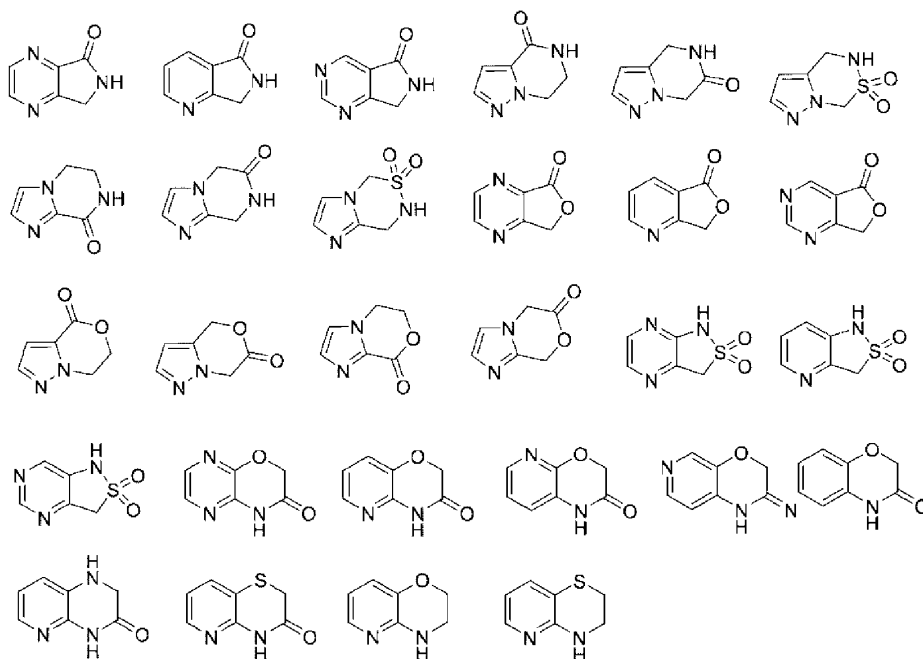
[00117] [Chemical Formula 15]



5 [00118] [Chemical Formula 15]



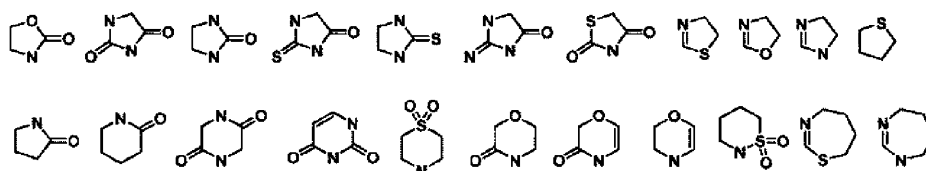
[00119] [Chemical Formula 16]



[00120] As used herein, "4- to 20-membered non-aryl heterocyclic group" refers to a monocyclic or
 5 bicyclic non-aromatic heterocycle comprised of 4 to 20 atoms, comprising 1 to 2 of the same or different
 heteroatoms independently selected from the group consisting of a nitrogen atom, an oxygen atom, and a
 sulfur atom in addition to carbon atoms, including those with a partially unsaturated bond, those with a
 partially crosslinked structure, and those that have a partially spiro form. "4- to 20-membered non-aryl
 heterocyclic group" is preferably "4- to 6-membered non-aryl heterocyclic group." Specific examples of "4-
 10 to 6-membered non-aryl heterocyclic group" include azetidiny, pyrrolidinyl, piperidyl, piperazinyl,
 morpholinyl, tetrahydrofuranyl, tetrahydropyranyl, and the like. In particular, azetidiny, pyrrolidinyl,
 piperidyl, morpholinyl, and oxetanyl are preferable. A non-aryl heterocycle may form a fused ring with aryl
 or heteroaryl. Non-aryl heterocycles also encompass those that are fused with, for example, C₆₋₁₀ aryl or 5- or
 6-membered heteroaryl. Further, the non-aryl heterocycle may be comprised by including one or more
 15 carbonyl, thiocarbonyl, sulfinyl, or sulfonyl. The non-aryl heterocycles also encompass, for example, lactam,
 thiolactam, lactone, thiolactone, cyclic imide, cyclic carbamate, cyclic thiocarbamate, and other cyclic
 groups. In this regard, oxygen atoms of carbonyl, sulfinyl, and sulfonyl and sulfur atoms of thiocarbonyl are
 not included in the number of 4 to 20 members (size of ring) or in the number of heteroatoms constituting a
 ring. Specific examples of "4- to 20-membered non-aryl heterocycle" include, but are not limited to,

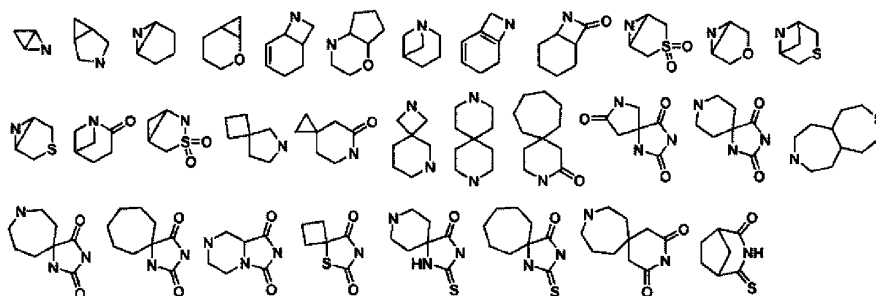
azetidine, pyrrolidine, piperidine, piperazine, morpholine, homopiperidine, oxetane, tetrahydrofuran, tetrahydropyran, heterocycles with the following structure, and the like.

[00121] [Chemical Formula 17]



- 5 [00122] Specific examples of "4- to 20-membered non-aryl heterocycle" with partial crosslinking or spiro structure include, but are not limited to, those with a structure shown below, and the like.

[00123] [Chemical Formula 18]



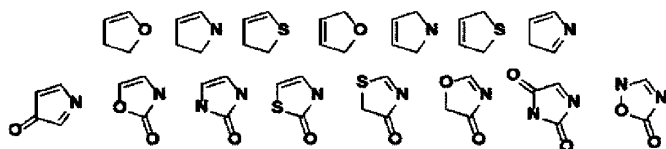
- [00124] Specific examples of "4-membered non-aryl heterocycle" having a partially unsaturated bond
10 include, but are not limited to, those with a structure shown below, and the like.

[00125] [Chemical Formula 19]



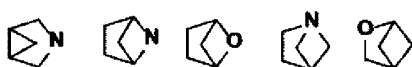
- [00126] . Specific examples of "5-membered non-aryl heterocycle" with a partially unsaturated bond
include, but are not limited to, those with a structure shown below, and the like.

[00127] [Chemical Formula 20]



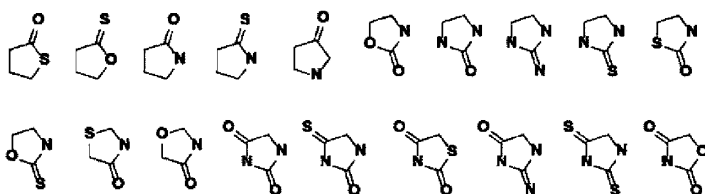
[00128] Specific examples of "5-membered non-aryl heterocycle" with a partially crosslinked structure include, but are not limited to, those with a structure shown below, and the like.

5 [00129] [Chemical Formula 21]



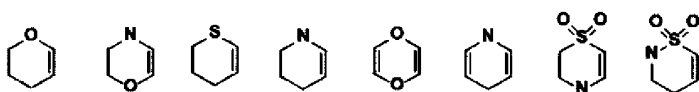
[00130] . Specific examples of "5-membered non-aryl heterocycle" comprising carbonyl, thiocarbonyl, and the like include, but are not limited to, those with a structure shown below, and the like.

[00131] [Chemical Formula 22]



[00132] . Specific examples of "6-membered non-aryl heterocycle" with a partially unsaturated bond include, but are not limited to, those with a structure shown below, and the like.

[00133] [Chemical Formula 23]



15 [00134] Specific examples of "6-membered non-aryl heterocycle" with a partially crosslinked structure include, but are not limited to, those with a structure shown below, and the like.

[00135] [Chemical Formula 24]



[00136] As used herein, "C₁₋₆alkoxy" or "C₁₋₆alkoxy group" refers to "C₁₋₆alkyloxy," and the "C₁₋₆alkyl" moiety is defined the same as the "C₁₋₆alkyl" described above. "C₁₋₆alkoxy" is preferably "C₁₋₄alkoxy," and
 5 more preferably "C₁₋₃alkoxy." Specific examples of "C₁₋₃alkoxy" include methoxy, ethoxy, propoxy, 1-methylethoxy, and the like. Specific examples of "C₁₋₄alkoxy" include, in addition to the specific examples specified for the "C₁₋₃alkoxy" described above, butoxy, 1,1-dimethylethoxy, 1-methylpropoxy, 2-methylpropoxy, and the like. Specific examples of "C₁₋₆alkoxy" include, in addition to the specific examples specified for the "C₁₋₄alkoxy" described above, pentyloxy, 1,1-dimethylpropoxy, 1,2-dimethylpropoxy, 1-
 10 methylbutoxy, 2-methylbutoxy, 4-methylpentyloxy, 3-methylpentyloxy, 2-methylpentyloxy, 1-methylpentyloxy, hexyloxy, and the like.

[00137] As used herein, "C₃₋₆alicyclic oxy" or "C₃₋₆alicyclic oxy group" refers to a (C₃₋₆alicyclic group)-O-group, and the C₃₋₆alicyclic moiety is defined the same as a C₃₋₆alicyclic group. "C₃₋₆alicyclic oxy group" includes "C₃₋₆cycloalkoxy group." "Cycloalkoxy group" refers to "cycloalkyloxy," and the "cycloalkyl" moiety is defined the same as the "cycloalkyl" described above. Specific examples of "C₃₋₆alicyclic oxy group" include a cyclopropoxy group, cyclobutoxy group, cyclopentoxy group, cyclohexoxy group, and the like.
 15

[00138] As used herein, the C₆₋₁₀aryl moiety of "C₆₋₁₀aryloxy group" is defined the same as the C₆₋₁₀aryl described above. "C₆₋₁₀aryloxy group" is preferably a "C₆ or C₁₀aryloxy group." Specific examples of "C₆₋₁₀aryloxy group" include, but are not limited to, a phenoxy group, 1-naphthyloxy group, 2-naphthyloxy group, and the like.
 20

[00139] As used herein, the 5- or 6-membered heteroaryl moiety of "5- or 6-membered heteroaryloxy group" is defined the same as the "5-membered heteroaryl" or "6-membered heteroaryl" described above. Specific examples of "5- or 6-membered heteroaryloxy group" include, but are not limited to, a pyrazoyloxy group, triazoyloxy group, thiazoyloxy group, thiadiazoyloxy group, pyridyloxy group, pyridazoyloxy group, and the like.
 25

[00140] As used herein, the 4- to 10-membered non-aryl heterocycle moiety of "4- to 10-membered non-aryl heterocyclyl oxy group" is defined the same as the "4- to 10-membered non-aryl heterocycle" described above. "4- to 10-membered non-aryl heterocyclyl oxy group" is preferably a "4- to 6-membered non-aryl heterocyclyl oxy group." Specific examples of "4- to 10-membered non-aryl heterocyclyl oxy group"
 30

include, but are not limited to, a tetrahydrofuranyloxy group, tetrahydropyranyloxy group, azetidinyloxy group, pyrrolidinyloxy group, piperidinyloxy group, and the like.

[00141] As used herein, the C₁₋₆ alkyl moiety of "C₁₋₆ alkylthio group" is defined the same as the C₁₋₆ alkyl described above. "C₁₋₆ alkylthio group" is preferably a "C₁₋₄ alkylthio group," and more preferably a "C₁₋₃ alkylthio group." Specific examples of "C₁₋₆ alkylthio group" include, but are not limited to, a methylthio group, ethylthio group, propylthio group, butylthio group, isopropylthio group, isobutylthio group, tert-butylthio group, sec-butylthio group, isopentylthio group, neopentylthio group, tert-pentylthio group, 1,2-dimethylpropylthio group, and the like.

[00142] As used herein, "C₃₋₁₀ alicyclic thio" or "C₃₋₁₀ alicyclic thio group" refers to a (C₃₋₁₀ alicyclic group)-S-group, and the C₃₋₁₀ alicyclic moiety is defined the same as the C₃₋₁₀ alicyclic group described above. "C₃₋₁₀ alicyclic thio group" is preferably a "C₃₋₆ alicyclic thio group." Specific examples of "C₃₋₆ alicyclic thio group" include, but are not limited to, a cyclopropylthio group, cyclobutylthio group, cyclopentylthio group, cyclohexylthio group, and the like.

[00143] As used herein, the C₆₋₁₀ aryl moiety of "C₆₋₁₀ arylthio" or "C₆₋₁₀ arylthio group" is defined the same as the C₆₋₁₀ aryl described above. "C₆₋₁₀ arylthio group" is preferably a "C₆ or C₁₀ arylthio group." Specific examples of "C₆₋₁₀ arylthio group" include, but are not limited to, a phenylthio group, 1-naphthylthio group, 2-naphthylthio group, and the like.

[00144] As used herein, the 5- or 6-membered heteroaryl moiety of "5- or 6-membered heteroarylthio" or "5- or 6-membered heteroarylthio group" is defined the same as the "5-membered heteroaryl" or "6-membered heteroaryl" described above. Specific examples of "5- or 6-membered heteroarylthio group" include, but are not limited to, a pyrazoylthio group, triazoylthio group, thiazoylthio group, thiadiazoylthio group, pyridylthio group, pyridazoylthio group, and the like.

[00145] As used herein, the 4- to 10-membered non-aryl heterocycle moiety of "4- to 10-membered non-aryl heterocyclyl thio" or "4- to 10-membered non-aryl heterocyclyl thio group" is defined the same as the "4- to 10-membered non-aryl heterocycle" described above. "4- to 10-membered non-aryl heterocyclyl thio group" is preferably a "4- to 6-membered non-aryl heterocyclyl thio group." Specific examples of "4- to 10-membered non-aryl heterocyclyl thio group" include, but are not limited to, a tetrahydropyranylthio group, piperidinylthio group, and the like.

[00146] As used herein, "C₁₋₆ alkylcarbonyl" or "C₁₋₆ alkylcarbonyl group" refers to a carbonyl group substituted with the "C₁₋₆ alkyl group" described above. "C₁₋₆ alkylcarbonyl group" is preferably a "C₁₋₄ alkylcarbonyl group." Specific examples of "C₁₋₆ alkylcarbonyl group" include, but are not limited to, an acetyl group, propionyl group, butyryl group, and the like.

[00147] As used herein, "C₃₋₁₀ alicyclic carbonyl" or "C₃₋₁₀ alicyclic carbonyl group" refers to a carbonyl group substituted with the "C₃₋₁₀ alicyclic group" described above. "C₃₋₁₀ alicyclic carbonyl group" is preferably a "C₃₋₆ alicyclic carbonyl group." Specific examples of "C₃₋₁₀ alicyclic carbonyl group" include, but are not limited to, a cyclopropylcarbonyl group, cyclopentylcarbonyl group, and the like.

5 [00148] As used herein, "C₆₋₁₀ arylcarbonyl" or "C₆₋₁₀ arylcarbonyl group" refers to a carbonyl group substituted with the "C₆₋₁₀ aryl" described above. "C₆₋₁₀ arylcarbonyl group" is preferably a "C₆ or C₁₀ arylcarbonyl group." Specific examples of "C₆₋₁₀ arylcarbonyl group" include, but are not limited to, a benzoyl group, 1-naphthylcarbonyl group, 2-naphthylcarbonyl group, and the like.

[00149] As used herein, "5- or 6-membered heteroarylcarbonyl" or "5- or 6-membered heteroarylcarbonyl
10 group" refers to a carbonyl group substituted with the "5- or 6-membered heteroaryl" described above. Specific examples of "5- or 6-membered heteroarylcarbonyl group" include, but are not limited to, a pyrazolcarbonyl group, triazolcarbonyl group, thiazolcarbonyl group, thiadiazolcarbonyl group, pyridylcarbonyl group, pyridazolcarbonyl group, and the like.

[00150] As used herein, "4- to 10-membered non-aryl heterocyclyl carbonyl" or "4- to 10-membered non-
15 aryl heterocyclyl carbonyl group" refers to a carbonyl group substituted with the "4- to 10-membered non-aryl heterocycle" described above. "4- to 10-membered non-aryl heterocyclyl carbonyl group" is preferably a "4- to 6-membered non-aryl heterocyclyl carbonyl group." Specific examples of "4- to 10-membered non-aryl heterocyclyl carbonyl group" include, but are not limited to, an azetidinylcarbonyl group, pyrrolidinylcarbonyl group, piperidinylcarbonyl group, morpholinylcarbonyl group, and the like.

20 [00151] As used herein, "C₁₋₆ alkylsulfonyl" or "C₁₋₆ alkylsulfonyl group" refers to a sulfonyl group substituted with the "C₁₋₆ alkyl group" described above. "C₁₋₆ alkylsulfonyl group" is preferably a "C₁₋₄ alkylsulfonyl group." Specific examples of "C₁₋₆ alkylsulfonyl group" include, but are not limited to, a methylsulfonyl group, propionylsulfonyl group, butyrylsulfonyl group, and the like.

[00152] As used herein, "C₃₋₁₀ alicyclic sulfonyl" or "C₃₋₁₀ alicyclic sulfonyl group" refers to a sulfonyl group
25 substituted with the "C₃₋₁₀ alicyclic group" described above. "C₃₋₁₀ alicyclic sulfonyl group" is preferably a "C₃₋₆ alicyclic sulfonyl group." Specific examples of "C₃₋₁₀ alicyclic sulfonyl group" include, but are not limited to, a cyclopropylsulfonyl group, cyclobutylsulfonyl group, cyclopentylsulfonyl group, cyclohexylsulfonyl group, and the like.

[00153] As used herein, "C₆₋₁₀ arylsulfonyl" or "C₆₋₁₀ arylsulfonyl group" refers to a sulfonyl group
30 substituted with the "C₆₋₁₀ aryl" described above. "C₆₋₁₀ arylsulfonyl group" is preferably a "C₆ or C₁₀ arylsulfonyl group." Specific examples of "C₆₋₁₀ arylsulfonyl group" include, but are not limited to, a phenylsulfonyl group, 1-naphthylsulfonyl group, 2-naphthylsulfonyl group, and the like.

[00154] As used herein, "5- or 6-membered heteroarylsulfonyl" or "5- or 6-membered heteroarylsulfonyl group" refers to a sulfonyl group substituted with the "5- or 6-membered heteroaryl" described above. Specific examples of "5- or 6-membered heteroarylsulfonyl group" include a pyrazoylsulfonyl group, triazoylsulfonyl group, thiazoylsulfonyl group, thiadiazoylsulfonyl group, pyridylsulfonyl group, pyridazoylsulfonyl group, and the like.

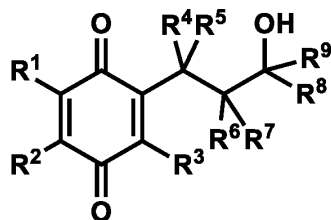
[00155] As used herein, "optical purity is maintained" indicates that optical purity does not change significantly when optical purity is measured before and after the mentioned reaction, and preferably indicates that the change is 20% ee or less. The change in optical purity when "optical purity is maintained" is, for example, 10% ee or less, 5% ee or less, 3% ee or less, 1% ee or less, or 0.5% ee or less.

10 Preferred Embodiments

[00156] Certain preferred embodiments of the present disclosure are described below. Embodiments described below are provided to facilitate the understanding of the present disclosure. The scope of the present disclosure should not be limited to the following descriptions. Thus, it is apparent that those skilled in the art can make appropriate modifications within the scope of the present disclosure by referring to the descriptions herein. The following embodiments of the present disclosure can be used independently or as a combination thereof.

[00157] One embodiment of the present disclosure provides a method of manufacturing a compound of formula I.

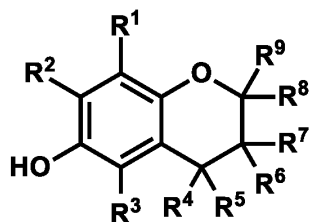
[00158] [Chemical Formula 25]



20 comprising the steps of:

[00159] performing, in a solvent, an electrolytic oxidation of a compound of formula II:

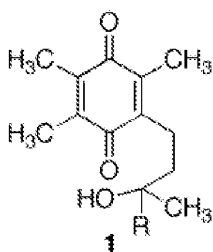
[00160] [Chemical Formula 26]



wherein

- R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , and R^9 each independently represent a hydrogen atom,
 5 halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} alkoxy, or $-C(=O)NR^A R^B$, and
 R^A and R^B each independently represent a hydrogen atom, optionally substituted C_{1-6} alkyl, or optionally substituted C_{1-6} alkoxy, provided that the compound of Formula I is not
 Formula III:

[00161] [Chemical Formula 27]

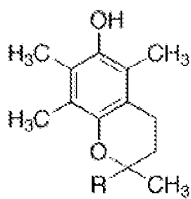


10

(wherein R is $(CH_2CH_2CH_2CH(CH_3)_3CH_3)$)

and the compound of formula II is not

[00162] [Chemical Formula 28]

15 (wherein R is $(CH_2CH_2CH_2CH(CH_3)_3CH_3)$).[00163] In the present disclosure, R^1 can be a hydrogen atom or optionally substituted C_{1-6} alkyl.[00164] In the present disclosure, R^1 can be methyl.[00165] In the present disclosure, R^2 can be a hydrogen atom or optionally substituted C_{1-6} alkyl.[00166] In the present disclosure, R^2 can be methyl.

- [00167] In the present disclosure, R^3 can be a hydrogen atom or optionally substituted C_{1-6} alkyl.
- [00168] In the present disclosure, R^3 can be methyl.
- [00169] In the present disclosure, R^4 can be a hydrogen atom or optionally substituted C_{1-6} alkyl.
- [00170] In the present disclosure, R^4 can be methyl.
- 5 [00171] In the present disclosure, R^5 can be a hydrogen atom or optionally substituted C_{1-6} alkyl.
- [00172] In the present disclosure, R^5 can be methyl.
- [00173] In the present disclosure, R^6 can be a hydrogen atom or optionally substituted C_{1-6} alkyl.
- [00174] In the present disclosure, R^6 can be methyl.
- [00175] In the present disclosure, R^7 can be a hydrogen atom or optionally substituted C_{1-6} alkyl.
- 10 [00176] In the present disclosure, R^7 can be methyl.
- [00177] In the present disclosure, R^8 can be a hydrogen atom, optionally substituted C_{1-6} alkyl, or $-C(=O)NR^A R^B$.
- [00178] In the present disclosure, R^8 can be $-C(=O)NR^A R^B$.
- [00179] In the present disclosure, R^9 can be a hydrogen atom or optionally substituted C_{1-6} alkyl.
- 15 [00180] In the present disclosure, R^9 can be methyl.
- [00181] In the present disclosure, R^A and R^B each can represent a hydrogen atom.
- [00182] In the present disclosure, the solvent can include water, preferably a mixture of water and non-protic polar solvents.
- [00183] In the present disclosure, the solvent can be water and, if necessary, a protic polar solvent, preferably
- 20 a mixture of both.
- [00184] In the present disclosure, in electrolytic oxidation, the electrode can be a carbon-based electrode, a platinum-based electrode, or a stainless steel electrode, or a combination thereof.
- [00185] In the present disclosure, the electrode can advantageously be a carbon-based electrode in electrolytic oxidation.
- 25 [00186] In the present disclosure, at least one selected from DMA, MeCN, DMSO, DMF, and THF, or a combination thereof, can be used as said nonprotic polar solvent in electrolytic oxidation.
- [00187] In the present disclosure, DMA can be advantageously used as said nonprotic polar solvent in electrolytic oxidation.

[00188] In the present disclosure, alkali metal salts or quaternary ammonium salts can be used as electrolytes in electrolytic oxidation.

[00189] In the present disclosure, the electrolytes include tetrabutylammonium hexafluorophosphate (Bu_4NPF_6), tetrabutylammonium tetrafluoroborate (Bu_4NBF_4), sodium perchlorate, tetrabutylammonium bromide (Bu_4NBr), chloride can be selected from the group consisting of lithium chloride (LiCl), lithium tetrafluoroborate (LiBF_4), lithium bromide (LiBr), and the like.

[00190] In the present disclosure, the electrolytes include tetrabutylammonium hexafluorophosphate (Bu_4NPF_6), tetrabutylammonium tetrafluoroborate (Bu_4NBF_4), sodium perchlorate, tetrabutylammonium bromide (Bu_4NBr), or lithium chloride (LiCl), and at least one selected from the group including lithium tetrafluoroborate (LiBF_4), and lithium bromide (LiBr) and the like.

[00191] In the present disclosure, Bu_4NBr may be advantageously used as the electrolyte.

[00192] In the present disclosure, for example, 10-100 mA (e.g., 20-30 mA) may be used as a current in electrolytic oxidation.

[00193] In the present disclosure, for example, 20 mA or 30 mA may be used as the current in electrolytic oxidation.

[00194] In the present disclosure, in electrolytic oxidation, values of 5 mA/cm^2 - 10 A/cm^2 , such as 10 mA/cm^2 - 1 A/cm^2 , 100 mA/cm^2 - 1 A/cm^2 , $10 - 100 \text{ mA/cm}^2$, and the like can be used as the current value per unit area of electrode.

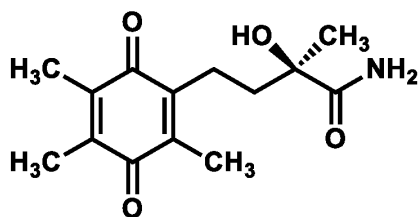
[00195] In the present disclosure, any value of 1-500V, 1-100V, 1-10V, 2-8V, 4-8V or 2.5V and the like. can be used as the voltage in electrolytic oxidation.

[00196] In the present disclosure, values such as 2- 10F/mol, 2-8F/mol, 6-8F/mol, and the like can be used as the equivalent amount of electrons in electrolytic oxidation.

[00197] In the present disclosure, a carbon atom, attached with R^8 , R^9 , and OH, are attached can be asymmetric carbon in the compound of formula I.

[00198] In the present disclosure, the compound of formula II can be optically active, and optical purity can be maintained during electrolytic oxidation of the compound of formula II.

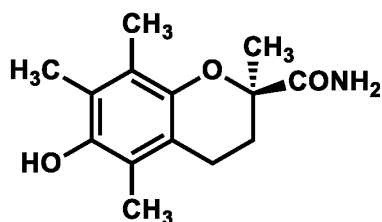
[00200] [Chemical Formula 29]



, and

the compound of formula II can be

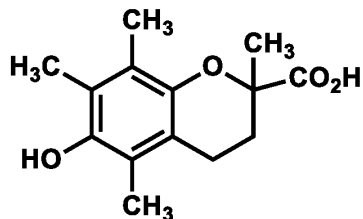
[00201] [Chemical Formula 30]



5

[00202] In the present disclosure, the compound of formula II can be manufactured by the step of optically resolving and amidating a compound of formula III:

[00203] [Chemical Formula 31]



10 [00204] Optical resolution of a compound of formula III can be performed by the method described in WO 2021/167095.

Manufacturing Method

[00205] In certain embodiments, a compound of formula I is manufactured by electrolytic oxidation with a compound of formula II in the present disclosure. In certain embodiments, the method of the present
15 disclosure includes the step of applying a voltage to a solution containing a compound of formula II.

EXAMPLES

[00206] The following examples, reference examples, test examples, and the like, are provided to explain the present disclosure in more detail, but the present disclosure is not limited thereto.

[00207] DMA: Dimethylacetamide

5 DMF: N,N-dimethylformamide

DMSO: Dimethyl sulfoxide

MeCN: acetonitrile

THF: Tetrahydrofuran

Bu₄NPF₆: Tetrabutylammonium hexafluorophosphate

10 Bu₄NBF₄: Tetrabutylammonium tetrafluoroborate

Bu₄NBr: tetrabutylammonium bromide

NaClO₄: sodium perchlorate

LiBF₄: Lithium tetrafluoroborate

LiBr: Lithium bromide

15 LiCl: Lithium chloride

[00208] The following analysis conditions were used in HPLC (high performance liquid chromatography) analysis.

[00209] Reagent/sample solution:

Acetonitrile: for liquid chromatography (FUJIFILM Wako Pure Chemical) or equivalent

20 Trifluoroacetic acid: special grade (FUJIFILM Wako Pure Chemical) or equivalent

Water: water manufactured for testing with an ultrapure water manufacturing system, and the like.

[00210] Solvent: Acetonitrile.

[00211] Mobile phase:

Mobile phase A: Water/trifluoroacetic acid mixture (2000:1). The mixture was prepared by

25 mixing 2000 mL of water and 1 mL of trifluoroacetic acid. The mixture was degassed using an ultrasonic cleaner.

Mobile phase B: Acetonitrile/trifluoroacetic acid mixture (2500:1). The mixture was prepared by mixing 2500 mL of acetonitrile and 1 mL of trifluoroacetic acid. The mixture was degassed using an ultrasonic washing machine.

30 [00212] Syringe detergent: Acetonitrile..

[00213] Apparatus and setting/conditions

[00214] Apparatus

High performance chromatograph: UFLCXR (Shimadzu) or equivalent

Electronic balance: XP205DRV (Mettler Toledo) or equivalent

⁵ Ultrapure water manufacturing system: Milli-Q Advantage A10 (Merck) or equivalent

Ultrasound washer: US-4R (AS ONE) or equivalent

[00215] Setting/condition for liquid chromatography

Detector: ultraviolet absorption spectrophotometer (measurement wavelength: 235 nm)

¹⁰ Column: stainless tube with an inner diameter of 4.6 mm and a length of 150 mm is loaded with octadecylsilyl silica gel for liquid chromatography with a particle size of 3.5 μm

[Zorbax SB C18 (Agilent) or equivalent]

Column temperature: constant temperature near 35°C

Mobile phase A: water/trifluoroacetic acid mixture (2000:1)

Mobile phase B: acetonitrile/trifluoroacetic acid mixture (2500:1)

¹⁵ Delivery of mobile phase: the mixing ratio of mobile phase A to mobile phase B is changed in the following manner to control the concentration gradient.

[00216] Table 1

Time after infusion (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 to 25.0	98 $\rightarrow$ 0	2 $\rightarrow$ 100
25.0 to 33.0	0	100
33.0 to 33.1	0 $\rightarrow$ 98	100 $\rightarrow$ 2
33.1 to 40.0	98	2

Flow rate: 1.0 mL per minute

²⁰ [00217] Area measurement range: 33 minutes after infusion of sample solution (data collection time is 40 minutes)

Amount infused: 5 μL

Sample cooler temperature: constant temperature near 25°C

Mixer volume: 0.5 mL

Syringe detergent: acetonitrile

²⁵ Sample concentration: 2.5 $\mu\text{g/mL}$ to 0.5 mg/mL

[00218] Example of waveform processing parameter setting

Minimum area: 5000 $\mu\text{V}\cdot\text{second}$

Minimum height: 100 μV

Detection sensitivity: 50 μ V/second

Peak width: 1 second

Output intensity range: -500 to 1000 mAU

Output time range: 0 to 33 minutes

5

Example 1

[00219] *Synthesis of (R)-2-Hydroxy-2-methyl-4-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dienyl)butanamide Using Electrochemical Oxidation Reaction*

[00220] (R)-6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxamide (125 mg, 0.501 mmol) and
10 tetrabutylammonium hexafluorophosphate (194 mg, 0.501 mg) were dissolved in a solvent (5 mL)
containing a 6:1 volume ratio of acetonitrile and water. A cell for electrolysis using the non-diaphragm
method with a platinum foil electrode as the anode and a glassy carbon electrode attached to the cathode was
used and energized at 30 mA. After a total of 8 F/mol energization, HPLC showed the disappearance of (R)-
6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxamide, and (R)-2-hydroxy-2-methyl-4-(2,4,5-trimethyl
15 The formation of (R)-2-hydroxy-2-methyl-4-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dienyl)butanamide
was confirmed (conversion ratio: 84.5%). The HPLC chart for compound 1 is shown in FIG. 1, the HPLC
chart for compound 2 is shown in FIG. 2, and the HPLC chart for this example is shown in FIG. 3.

Example 2

20 [00221] *Electrolyte Considerations*

[00222] (R)-6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxamide (125 mg, 0.501 mmol) and
electrolyte (0.501 mmol) were dissolved in a solvent (5 mL) containing a mixture of acetonitrile and water at
a volume ratio of 6 to 1. A non-diaphragm electrolysis cell with a platinum foil electrode as the anode and a
glassy carbon electrode as the cathode was used and energized at 30 mA. After energizing a total of 8 F/mol,
25 HPLC was performed to determine (R)-2-hydroxy-2-methyl-4-(2,4,5-) (R)-2-hydroxy-2-methyl-4-(2,4,5-
trimethyl-3,6-dioxocyclohexa-1,4-dienyl)butanamide by HPLC. The conversion to the target product was as
shown in Table 2.

[00223] Table 2

Electrolytes used	Conversion rate to the compound of interest
Bu ₄ NPF ₆	84.5%.
Bu ₄ NBF ₄	82.8%
NaClO ₄	61.7%
Bu ₄ NBr	92.8%
LiBF ₄	18.0%.
LiCl	31.1%
LiBr	13.6%

Example 3[00224] *Examination of Non-protic Polar Solvents*

5 [00225] (R)-6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxamide (125 mg, 0.501 mmol) and tetrabutylammonium hexafluorophosphate (194 mg, 0.501 mg) were dissolved in a solvent (5 mL) containing a 6:1 volume ratio of each of the nonprotic polar solvents in Table 3 below and water. A non-diaphragm electrolysis cell with a platinum foil electrode as the anode and a glassy carbon electrode as the cathode was used for electrolysis and energized at 30 mA. After energizing a total of 6 F/mol, HPLC was

10 performed to determine (R)-2-hydroxy-2-methyl-4-(2,4,5-) (R)-2-hydroxy-2-methyl-4-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dienyl)butanamide by HPLC. The conversion to the target product was as shown in Table 3.

[00226] Table 3

Nonprotic polar solvents used	Conversion rate to the compound of interest
MeCN	84.5% (%)
direct memory access	94.4% (%)
direct memory function	83.6% (%)
DMSO	54.4% (%)
THF	90.9%.

Example 4

[00227] *Consideration of Electrodes*

5 [00228] (R)-6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxamide (125 mg, 0.501 mmol) and tetrabutylammonium hexafluorophosphate (194 mg, 0.501 mg) were dissolved in a solvent (5 mL) containing a 6:1 volume ratio of acetonitrile and water. A cell for electrolysis using the diaphragmless method, in which the anode and cathode were attached in the combinations listed in Table 4, was energized at 30 mA. After energizing a total of 6 F/mol, HPLC was performed to determine (R)-2-hydroxy-2-methyl-
10 4-(2,4,5- (R)-2-hydroxy-2-methyl-4-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dienyl)butanamide by HPLC. The conversion to the target product results are shown in Table 4.

[00229] Table 4

Anode used	Cathode used	Conversion rate to the compound of interest
Platinum Foil	glassy carbon	84.5%
Platinum Foil	Platinum Foil	75.7%.
glassy carbon	glassy carbon	88.4%
stainless steel	stainless steel	90.3%.
Platinum Foil	stainless steel	32.1%
glassy carbon	stainless steel	45.0%.

[00230] The results in Table 4 indicate that this method gives good results even when the anode and cathode are glassy carbon or stainless steel electrodes, respectively, suggesting that a less expensive electrode can be used compared to a platinum foil electrode.

5

Example 5

[00231] *Electrolytic Oxidation Reaction Using Glassy Carbon Electrodes as Anode and Cathode*

[00232] (R)-6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxamide (125 mg, 0.501 mmol) and the electrolytes listed in Table 5 (0.501 mmol) were dissolved in a solvent (5 mL) containing a 6:1 volume ratio of nonprotic polar solvent and water as listed in Table 5. A cell for electrolysis using the non-diaphragm method with glassy carbon electrodes attached to the anode and cathode was used and energized at 20 or 30 mA. After energizing a total of 6 F/mol, HPLC was performed to determine (R)-2-hydroxy-2-methyl-4-(2,4,5- (R)-2-hydroxy-2-methyl-4-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dienyl)butanamide by HPLC. The conversion to the target product was shown in Table 5.

15

[00233] Table 5

Nonprotic polar solvents used	Electrolytes used	current value	Conversion rate to compound of interest
MeCN	Bu ₄ NPF ₆	30mA	88.4%
MeCN	Bu ₄ NBr	30mA	89.8%.
MeCN	LiBr	30mA	91.6%
DMA	Bu ₄ NPF ₆	20mA	85.6%.
DMA	Bu ₄ NBr	20mA	57.0%.
DMA	LiBr	20mA	83.4%

[00234] As described above, the present disclosure is exemplified in various preferred embodiments. It is understood that the scope of the present disclosure should be limited solely based on its claims. It is understood that any patent, any patent application, and any references cited herein should be incorporated herein by reference in the same manner as the contents are specifically described herein.

Industrial Applicability

[00235] The present disclosure is useful in the manufacture of medicaments.

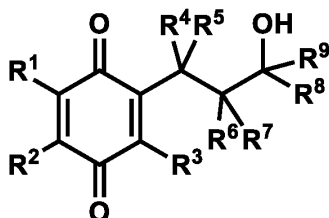
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WHAT IS CLAIMED

Claims

1. A method of manufacturing a compound of formula I:

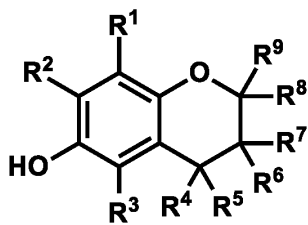
5 [Chemical Formula 1]



comprising the steps of:

performing electrolytic oxidation of a compound of formula II:

[Chemical Formula 2]



10

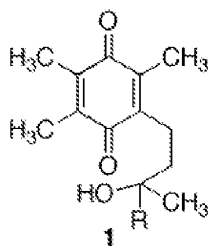
wherein

$R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8,$ and R^9 each independently represent a hydrogen atom, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} alkoxy, or $-C(=O)NR^A R^B$, and

R^A and R^B each independently represent a hydrogen atom, optionally substituted C_{1-6} alkyl, or optionally substituted C_{1-6} alkoxy, provided that the compound of Formula I is not

Formula III:

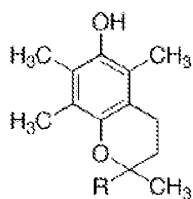
[Chemical Formula 3]



(wherein R is $(CH_2CH_2CH_2CH(CH_3)_3CH_3)$)

20 and the compound of formula II is not

[Chemical Formula 4]



(wherein R is $(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)_3\text{CH}_3)$).

2. The method of claim 1, wherein R^1 is a hydrogen atom or optionally substituted C_{1-6} alkyl.
5
3. The method of claim 1 or 2, wherein R^1 is methyl.
4. The method of any one of claims 1 to 3, wherein R^2 is a hydrogen atom or optionally substituted C_{1-6} alkyl.
10
5. The method of any one of claims 1 to 4, wherein R^2 is methyl.
6. The method of any one of claims 1 to 5, wherein R^3 is a hydrogen atom or optionally substituted C_{1-6} alkyl.
15
7. The method of any one of claims 1 to 6, wherein R^3 is methyl.
8. The method of any one of claims 1 to 7, wherein R^4 is a hydrogen atom or optionally substituted C_{1-6} alkyl.
20
9. The method of any one of claims 1 to 8, wherein R^4 is a hydrogen atom.
10. The method of any one of claims 1 to 9, wherein R^5 is a hydrogen atom or optionally substituted C_{1-6} alkyl.
25
11. The method of any one of claims 1 to 10, wherein R^5 is a hydrogen atom.
12. The method of any one of claims 1 to 11, wherein R^6 is a hydrogen atom or optionally substituted C_{1-6} alkyl.
30

13. The method of any one of claims 1 to 12, wherein R^6 is a hydrogen atom.
14. The method of any one of claims 1 to 13, wherein R^7 is a hydrogen atom or optionally substituted C_{1-6} alkyl.
- 5 15. The method of any one of claims 1 to 14, wherein R^7 is a hydrogen atom.
16. The method of any one of claims 1 to 15, wherein R^8 is a hydrogen atom, optionally substituted C_{1-6} alkyl, or $-C(=O)NR^A R^B$.
- 10 17. The method of any one of claims 1 to 16, wherein R^8 is $-C(=O)NR^A R^B$.
18. The method of any one of claims 1 to 17, wherein R^9 is a hydrogen atom or optionally substituted C_{1-6} alkyl.
- 15 19. The method of any one of claims 1 to 18, wherein R^9 is methyl.
20. The method of any one of claims 1 to 19, wherein R^A and R^B each represent a hydrogen atom.
- 20 21. The method of any one of claims 1 to 20, wherein the solvent is water or a non-protic polar solvent.
22. The method of any one of claims 1 to 21, wherein the solvent is water and a non-protic
25 polar solvent.
23. The method of any one of claims 1-22, wherein in said electrolytic oxidation, the electrode is a carbon-based electrode, a platinum-based electrode, or a stainless steel electrode, or a combination thereof.
- 30 24. The method of claim 21 or 22, wherein at least one selected from DMA, MeCN, DMSO, DMF, and THF is used as the nonprotic polar solvent in the electrooxidation.
25. The method of any one of claims 1-24, wherein an alkali metal salt or quaternary
35 ammonium salt is used as the electrolyte in said electrolytic oxidation.

26. The method of any one of claims 1-25, wherein in said electrolytic oxidation, the electrolyte comprises at least one compound selected from the group consisting of lithium tetrafluoroborate (LiBF_4), lithium bromide (LiBr), tetrabutylammonium hexafluorophosphate (Bu_4NPF_6), tetrabutylammonium tetrafluoroborate (Bu_4NBF_4), sodium perchlorate,
- 5 tetrabutylammonium bromide (Bu_4NBr), and lithium chloride (LiCl).
27. The method of any one of claims 1-26, wherein 10-100 mA is used as the current in said electrolytic oxidation.
- 10 28. The method of any one of claims 1-27, wherein 5 mA/cm^2 - 10 A/cm^2 is used as the current value per unit area of the electrode in electrolytic oxidation.
29. The method of any one of claims 1-28, wherein 1-500 V is used as the voltage in the electrolytic oxidation.
- 15 30. The method of any one of claims 1-29, wherein (1) Bu_4NPF_6 , DMA, and water (2) Bu_4NPF_6 , THF, and water (3) LiBr , MeCN, and water, or (4) Bu_4NBr , MeCN, and water are used

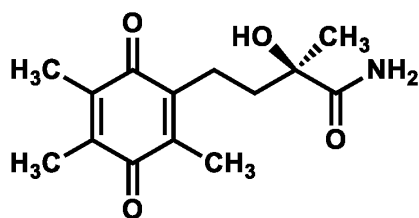
in the electrooxidation system as a combination of electrolyte, electrolyte nonprotic solvent, and water.

31. The method of any one of claims 1-30, wherein in the electrolytic oxidation, the current is
5 stopped after the reaction is complete.

32. The method of any one of claims 1-31, wherein in the compound of Formula I, the carbon atom to which R₈, R₉ and the -OH bond is a chiral carbon.

10 33. The method of any one of claims 1-32, wherein the compound of formula II is optically active and optical purity is maintained in the electrolytic oxidation reaction of the compound of formula II.

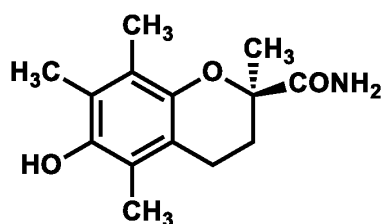
34. The method of any one of claims 1-33 wherein the compound of formula I is
15 [Chemical Formula 5]



, and

the compound of formula II is

[Chemical Formula 6]



20

35. The method of any one of claims 1-34, wherein the compound of formula II is manufactured by the step of optically resolving and amidating a compound of formula III:

[Chemical Formula 7]

