each L is independently selected from H, a metal ion, substituted or unsubstituted C_{1-30} alkyl, substituted or unsubstituted C_{2-30} alkenyl, substituted or unsubstituted C_{2-30} alkynyl, substituted or unsubstituted C_{3-30} cycloalkyl, a substituted or unsubstituted benzyl radical, $-CH_2CO_2H$, or $-(CH_2)_2SO_3H$; wherein when L is substituted, the substituent is independently selected from OH, SH, =O, =S, F, Cl, Br, SC_{1-6} alkyl, C_{1-6} alkyl or C_{1-6} alkoxy;

R^6 is $-(CH_2)_n-$ wherein n is 0 to 12, $-CH_2C(=O)NHCH_2-$, or $-CH_2C(=O)NHCH_2CH_2-$;

Y is -C- or -S(=O)-; and

R^a is -H or $-C(=O)CH_2CH_2COOH$;

or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof.

The compounds of Formula (I) have neuroprotective effects, anti-inflammatory activity, antioxidative properties, and epithelial cell protective effects. It is hypothesised that these useful and beneficial properties may be due to the phenolic structure of the compounds. The compounds of Formula (I) are therefore useful in the treatment or prevention of neurological disorders (including neurodegenerative conditions such as Alzheimer's disease, dementia caused by Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (motor neurone disease), multiple sclerosis, and brain injury), the cognitive decline associated with these neurological disorders (such as memory loss), and disorders caused by stress-induced cellular damage in the inner or middle ear of a subject (such as vestibular disorders, hearing impairment, and conditions related to hair cell degeneration or hair cell death).

In a further aspect, there is provided a pharmaceutical composition comprising a compound of Formula (I) or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, adjuvant or diluent.

In an example, there is provided a method of treating or preventing a neurological disorder or cognitive decline associated with a neurological disorder in a subject, the method comprising administering to the subject an effective amount of a compound of Formula (I) or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof. The neurological disorder may be Alzheimer's disease, dementia caused by Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (motor neurone disease), multiple sclerosis, or brain injury. Cognitive decline includes memory loss.

In a further aspect, there is provided a use of a compound as defined above in the manufacture of a medicament for treating or preventing a neurological disorder or cognitive decline associated with a neurological disorder in a subject.

In another example, there is provided a method for preventing, reducing or treating the incidence and/or severity of a disorder caused by stress-induced cellular damage in the middle or inner ear of a subject, the method comprising administering to the subject a therapeutically effective amount of a compound of Formula (I) or a stereoisomer thereof, or a

pharmaceutically acceptable salt thereof. The disorders caused by stress-induced cellular damage in the inner or middle ear may be vestibular disorders, hearing impairment, or conditions related to hair cell degeneration or hair cell death.

In a further aspect, there is provided a use of a compound as defined above in the manufacture of a medicament for preventing, reducing or treating the incidence and/or severity of a disorder caused by stress induced cellular damage in the middle or inner ear of a subject.

In a further aspect, there is provided a use of a compound as defined above in the manufacture of a medicament for preventing, reducing or inhibiting hair cell degeneration or hair cell death in a subject.

In a further aspect, there is provided a compound as defined above for use in therapy.

In another example, there is provided a method of producing a compound of Formula (I), comprising coupling probucol or succinobucol to the C17 of a bile acid or derivative thereof.

BRIEF DESCRIPTION OF THE FIGURES

Embodiments of the present invention will be further described, by way of example only, with reference to the accompanying figures. In the accompanying figures, *p<0.05, **p<0.001, ***p<0.0001, and ns = non-significant. The accompanying figures are described below:

Fig. 1: shows a cytotoxicity study by MTT cell viability assay. AM-MSCs were incubated with different concentrations of (A) probucol, (B) SPQ, (C) HA-1 and, (D) DMSO for 24 hours. D1 = DMSO control for 10 µM, D2 = DMSO control for 20 µM (n =3).

Fig. 2: shows an estimation of LDH release. Neurodegenerated cells were incubated with probucol (20 µM), SPQ (10 µM), HA-1 (10 µM), and rivastigmine (2 µM) for 24 hours (n =3).

Fig. 3: shows the effect of probucol, SPQ, HA-1 and rivastigmine on: (A) Acetylcholinesterase (AChE) activity and (B) Acetylcholine release in an Alzheimer's disease model using the Amplex Red reagent-based assay. Neurodegenerated cells were incubated with probucol (20 µM), SPQ (10 µM), HA-1 (10 µM) and rivastigmine (2 µM) for 24 hours (n =3).

Fig. 4: shows the measurement of mitochondrial membrane potential by TMRE assay. Neurodegenerated cells were incubated with probucol (20 µM), SPQ (10 µM), HA-1 (10 µM) and rivastigmine (2 µM) for 24 hours (n =3).

Fig. 5: shows gene expression analysis by qRT-PCR for neuronal, cholinergic and AD associated markers (A) BACE1, (B) ChAT, (C) Synapsin 1, and (D) Neuropilin (n =3).

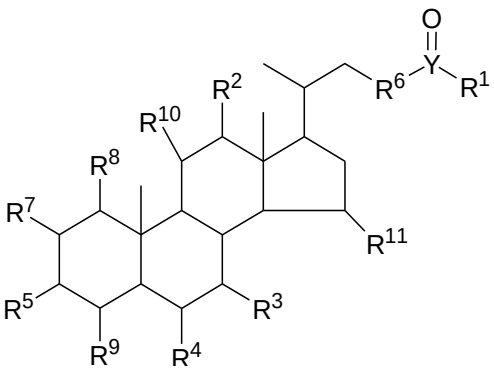
Fig. 6: shows the effect of probucol, SPQ, HA-1 and rivastigmine on (A) intracellular reactive oxidative stress and (B) nitric oxide.

Fig. 7: shows the effect of probucol, SPQ, HA-1 and rivastigmine on glutathione activity.

Fig. 8: shows the results of a cytotoxicity study by MTT cell viability assay. AM-MSCs were incubated with different concentrations of (A) probucol, (B) SPQ, (C) HA-1 and, (D) DMSO for 24 hours. D1 = DMSO control for 10 µM, D2 = DMSO control for 20 µM (n =3).

CLAIMS:

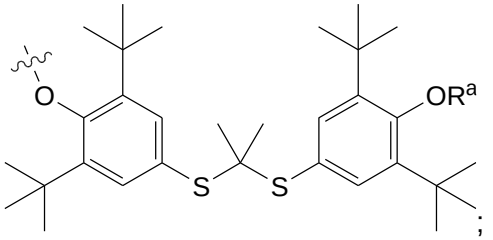
1. A compound of Formula (I):



(I)

wherein:

R^1 is:



;

each R^2, R^3, R^4, R^5, R^7, R^8, R^9, R^{10} and R^{11} is independently selected from H, substituted or unsubstituted $C_{1\text{-}30}$ acyloxy, substituted or unsubstituted benzoyloxy, substituted or unsubstituted $C_{1\text{-}30}$ alkyl, substituted or unsubstituted $C_{2\text{-}30}$ alkenyl, substituted or unsubstituted $C_{2\text{-}30}$ alkynyl, substituted or unsubstituted $C_{3\text{-}30}$ cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, an amino acid moiety, or GL, wherein GL is independently selected from OL, SL, PL_2, CL_3, or NL_2; wherein when R^2, R^3, R^4, R^5, R^7, R^8, R^9, R^{10} or R^{11} is substituted, the substituent is independently selected from OH, F, SH, =O, =S, Cl, Br, $SC_{1\text{-}6}$ alkyl, $C_{1\text{-}6}$ alkyl or $C_{1\text{-}6}$ alkoxy;

each L is independently selected from H, a metal ion, substituted or unsubstituted $C_{1\text{-}30}$ alkyl, substituted or unsubstituted $C_{2\text{-}30}$ alkenyl, substituted or unsubstituted $C_{2\text{-}30}$ alkynyl, substituted or unsubstituted $C_{3\text{-}30}$ cycloalkyl, a substituted or unsubstituted benzyl radical, $-CH_2CO_2H$, or $-(CH_2)_2SO_3H$; wherein when L is substituted, the substituent is independently selected from OH, SH, =O, =S, F, Cl, Br, $SC_{1\text{-}6}$ alkyl, $C_{1\text{-}6}$ alkyl or $C_{1\text{-}6}$ alkoxy;

R^6 is $-(CH_2)_n-$ wherein n is 0 to 12, $-CH_2C(=O)NHCH_2-$, or $-CH_2C(=O)NHCH_2CH_2-$;

Y is -C- or -S(=O)-; and

R^a is -H or $-C(=O)CH_2CH_2COOH$;

or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein R^a is -H.

3. A compound according to claim 1, wherein R^a is $-C(=O)CH_2CH_2COOH$.

4. A compound according to any one of claims 1 to 3, wherein each of R^2, R^3, R^4, R^5, R^7, R^8, R^9, R^{10} and R^{11} is independently selected from H; substituted or unsubstituted C_{1-30} acyloxy; substituted or unsubstituted benzoyloxy; substituted or unsubstituted C_{1-12} alkyl; substituted or unsubstituted C_{2-12} alkenyl; substituted or unsubstituted C_{2-12} alkynyl; substituted or unsubstituted C_{3-8} cycloalkyl; substituted or unsubstituted C_6 aryl; substituted or unsubstituted heteroaryl; an amino acid moiety; or GL, wherein GL is independently selected from OL, SL, PL_2, CL_3, or NL_2.

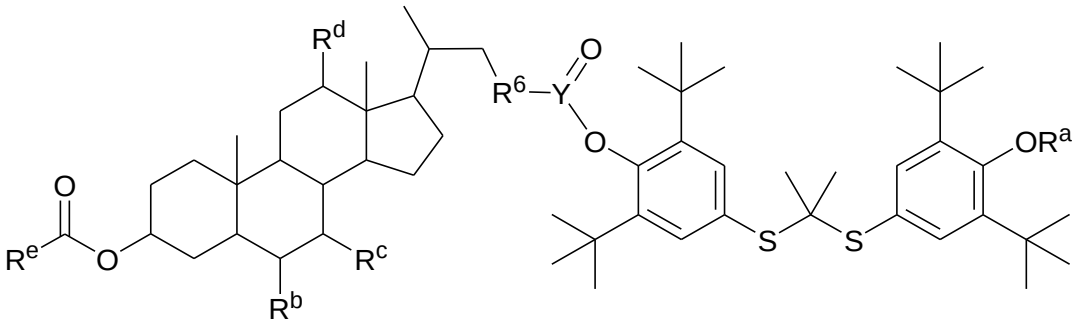
5. A compound according to any one of claims 1 to 4, wherein R^2, R^3, R^4, R^5, R^7, R^8, R^9, R^{10} and R^{11} is independently selected from H; substituted or unsubstituted C_{1-6} acyloxy; substituted or unsubstituted benzoyloxy; substituted or unsubstituted C_{1-6} alkyl; substituted or unsubstituted C_{2-6} alkenyl; substituted or unsubstituted C_{2-6} alkynyl; substituted or unsubstituted C_{3-8} cycloalkyl; substituted or unsubstituted phenyl; substituted or unsubstituted pyridyl; or OH.

6. A compound according to any one of claims 1 to 5, wherein R^2, R^3, R^4, R^5, R^7, R^8, R^9, R^{10} or R^{11} is independently selected from H, -OH and $-OC(=O)R^f$, wherein R^f is C_{1-6} alkyl.

7. A compound according to any one of claims 1 to 6, wherein R^6 is selected from $-(CH_2)_n-$ wherein n is 1, 2 or 3; $-CH_2C(=O)NHCH_2-$; or $-CH_2C(=O)NHCH_2CH_2-$.

8. A compound according to any one of claims 1 to 7, wherein Y is -C-.

9. A compound according to claim 1, wherein the compound of Formula (I) is a compound of Formula (Ia):



(Ia)

wherein:

R^a is -H or $-C(=O)CH_2CH_2COOH$;

R^b is selected from -H, -OH and $-OC(=O)R^f$, wherein R^f is C_{1-6} alkyl;

R^c is selected from -H, -OH and $-OC(=O)R^f$, wherein R^f is C_{1-6} alkyl;

R^d is selected from -H, -OH and $-OC(=O)R^f$, wherein R^f is C_{1-6} alkyl;

R^e is selected from $-C_{1-6}$ alkyl;

R^6 is $-CH_2-$, $-CH_2C(=O)NHCH_2-$, or $-CH_2C(=O)NHCH_2CH_2-$; and

Y is C or S(=O);

or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof.

10. A compound according to claim 9, wherein R^e is selected from methyl (Me), ethyl (Et), or propyl (Pr).

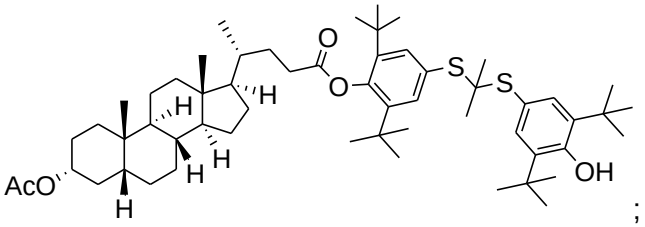
11. A compound according to claim 9 or 10, wherein R^6 is $-CH_2-$.

12. A compound according to any one of claims 9 to 11, wherein Y is C.

13. A compound according to any one of claims 9 to 12, wherein R^a is -H.

14. A compound according to any one of claims 9 to 13, wherein R^b is H; R^c is H or OAc; and R^d is H.

15. A compound according to any one of claims 9 to 14, wherein the compound is 2,6-di-*tert*-butyl-4-((2-((3,5-di-*tert*-butyl-4-hydroxyphenyl)thio)propan-2-yl)thio)phenyl (4*R*)-4-[(3*R*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-3-acetoxy-10,13-dimethyl-2,3,4,5,6,7,8,9,11,12,14,15,16,17-tetradecahydro-1*H*-cyclopenta[a]phenanthren-17-yl]pentanoate:



;

or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof.

16. A pharmaceutical composition comprising a compound according to any one of claims 1 to 15, and a pharmaceutically acceptable carrier, adjuvant or diluent.

17. Use of a compound according to any one of claims 1 to 15 in the manufacture of a medicament for treating or preventing a neurological disorder or cognitive decline associated with a neurological disorder in a subject.

18. The use according to claim 17, wherein the neurological disorder is Alzheimer's disease, dementia caused by Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (motor neurone disease), or multiple sclerosis; and/or the cognitive decline is memory loss.

19. Use of a compound according to any one of claims 1 to 15 in the manufacture of a medicament for preventing, reducing or treating the incidence and/or severity of a disorder caused by stress-induced cellular damage in the middle or inner ear of a subject.

20. The use according to claim 19, wherein the disorder caused by stress-induced cellular damage in the middle or inner ear is a vestibular disorder or hearing impairment.

21. Use of a compound according to any one of claims 1 to 15 in the manufacture of a medicament for preventing, reducing or inhibiting hair cell degeneration or hair cell death in a subject.

22. A compound according to any one of claims 1 to 15 for use in therapy.