psychotherapy and medications, such as anti-depressants. Unfortunately, current medications may take weeks to months to achieve their full effects and in the meantime, patients continue to suffer from their symptoms and continue to be at risk. Moreover, side effects from these medications can range from unpleasant to life-threatening; for instance, there can be an increased risk of suicide, hostility, and even homicidal behavior. Pharmacological treatments that have a rapid onset of antidepressant or anti-anxiety effects within hours or a few days and that are sustained are therefore desired.

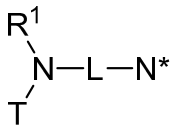
Multiple cross-sectional studies have consistently observed that migraine often co-occurs with depression ((Ashina et al., 2012; Fuller-Thomson et al., 2013; Yang et al., 2016). For example, a large proportion of patients suffering from mitochondrial disease are suffering from migraine and mood disorders such as depression (Kraya et al. 2017; Verhaak et al. 2016; Koene et al. 2009; Bansal & Kuhad 2016; Vollono et al. 2017).

WO2014/011047 and WO2017/060432 disclose amide-derivatives of 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid, including KH176, for treating or preventing mitochondrial disorders and/or conditions associated with mitochondrial dysfunction. In the recent clinical trial KHENERGY (clinicaltrials.gov identifier NCT02909400), the study drug KH176 of the present invention was shown to significantly reduce depression symptoms in mitochondrial disease patients carry a mutation in the mitochondrial DNA. Additionally, patients participating in the KHENERGY study who previously chronically suffered from migraine all reported a reduction of the intensity and number of migraine events during the KH176 treatment period.

On the basis thereof, it is an object of the present invention to provide for novel methods of treatment of subjects suffering from mood disorders, headaches and/or migraine.

Summary

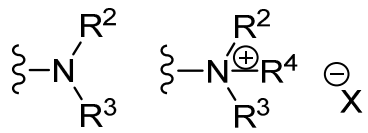
The present disclosure pertains to a compound represented by general structure (**I**):



(**I**)

wherein,

- T is a water-soluble vitamin E derivative having a core chromanyl or chromanyl quinone framework and a carboxylic acid moiety substituted at the 2-position, wherein T is connected to nitrogen via the carboxylic acid moiety, as such forming an amide moiety;
- L is a linker between the amide nitrogen atom and the distal nitrogen atom comprising 1 to 10 optionally substituted backbone atoms selected from carbon, nitrogen and oxygen;
- N* is represented by structure (**IIa**) or (**IIb**)

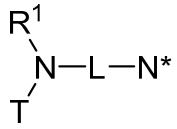


(**IIa**) (**IIb**)

- R^1 and R^2 are each independently selected from hydrogen (H), $C_1 - C_6$ alkyl or $C_1 - C_6$ alkenyl, or R^1 and R^2 are joined together and thus form a second linker between the amide nitrogen atom and the distal nitrogen atom, or R^1 is joined with a backbone atom of the linker L in a cyclic structure and/or R^2 is joined with a backbone atom of the linker L in a cyclic structure;
- R^3 is selected from hydrogen (H), $C_1 - C_6$ alkyl or $C_1 - C_6$ alkenyl, wherein the alkyl or alkenyl moiety may be substituted with one or more halogen atoms, hydroxyl moieties or (halo)alkoxy moieties, or R^3 is absent when the distal nitrogen atom is part of an imine moiety; or optionally R^3 is joined with a backbone atom of the linker L in a cyclic structure; and
- R^4 is selected from hydrogen (H) or $C_1 - C_6$ alkyl, wherein the alkyl moiety may be substituted with one or more halogen atoms or (halo)alkoxy moieties;
- X is an anion, preferably a pharmaceutically acceptable anion,

for use in treating, preventing or suppressing symptoms associated with at least one of: a) a mood disorder; and, b) headache and/or migraine.

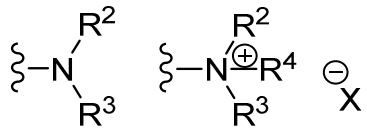
In one aspect, the present disclosure refers to use of a compound represented by general structure (**I**):



(**I**)

wherein,

- T is a water-soluble vitamin E derivative having a core chromanyl or chromanyl quinone framework and a carboxylic acid moiety substituted at the 2-position, wherein T is connected to nitrogen via the carboxylic acid moiety, as such forming an amide moiety;
- L is a linker between the amide nitrogen atom and the distal nitrogen atom comprising 1 to 10 optionally substituted backbone atoms selected from carbon, nitrogen and oxygen;
- N* is represented by structure (**IIa**) or (**IIb**)



(**IIa**) (**IIb**)

- R^1 and R^2 are each independently selected from hydrogen (H), $C_1 - C_6$ alkyl or $C_1 - C_6$ alkenyl, or R^1 and R^2 are joined together and thus form a second linker between the amide nitrogen atom and the distal nitrogen atom, or R^1 is joined with a backbone atom of the linker L in a cyclic structure and/or R^2 is joined with a backbone atom of the linker L in a cyclic structure;

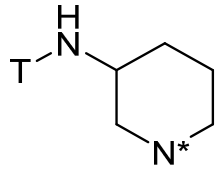
- R^3 is selected from hydrogen (H), $C_1 – C_6$ alkyl or $C_1 – C_6$ alkenyl, wherein the alkyl or alkenyl moiety may be substituted with one or more halogen atoms, hydroxyl moieties or (halo)alkoxy moieties, or R^3 is absent when the distal nitrogen atom is part of an imine moiety; or optionally R^3 is joined with a backbone atom of the linker L in a cyclic structure; and
- R^4 is selected from hydrogen (H) or $C_1 – C_6$ alkyl, wherein the alkyl moiety may be substituted with one or more halogen atoms or (halo)alkoxy moieties;
- X is an anion, preferably a pharmaceutically acceptable anion,

in the manufacture of a medicament for treating, preventing or suppressing symptoms associated with at least one of:

a) a mood disorder; and,

b) headache and/or migraine.

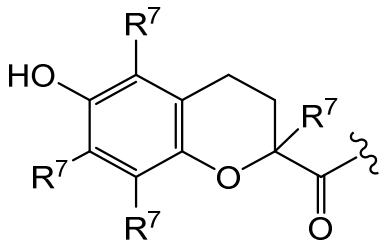
Preferably, the compound is represented by structure (**VI**):



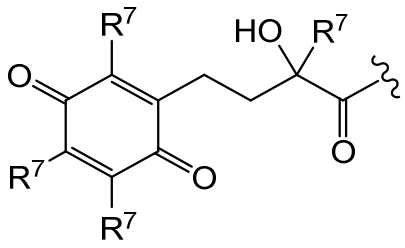
(**VI**)

wherein, N* is $–NR^3$ or $–N^+R^3R^4\ X^–$, wherein T, X, R^3, and R^4 are as defined above.

In a compound of the disclosure, preferably T is represented by structure (**IIIa**) or (**IIIb**):



(**IIIa**)



(**IIIb**)

wherein R^7 is individually a $C_1 – C_6$ alkyl moiety, preferably each R^7 is methyl.

In a first example, the compounds of the disclosure are for use in treating, preventing or suppressing symptoms associated with a mood disorder, wherein preferably, the mood disorder comprises depression. Preferably, in the treatment, the use of the compound according to this example of the disclosure eliminates, reduces the severity of, and/or reduces the frequency of occurrence of at least one symptom of the mood disorder, preferably as determined using the Beck Depression Index. Preferably, the symptom of the mood disorder includes at least one of apathy, persistent feelings of sadness, feelings of hopelessness or helplessness, having low self-esteem, feeling inadequate, excessive guilt, feelings of wanting to die, loss of interest in usual activities or activities once enjoyed, difficulty with relationships, sleep disturbances, changes in appetite or weight, decreased energy, difficulty concentrating, a decrease in the ability to make decisions,

suicidal thoughts or attempts, frequent physical complaints, running away or threats of running away from home, hypersensitivity to failure or rejection, irritability, hostility, or aggression. In one example according to this example of the disclosure, the treatment further comprises the administration of an additional active agent selected from the group consisting of a norepinephrine reuptake inhibitor, a selective serotonin reuptake inhibitor, a tricyclic antidepressant, a monoamine oxidase inhibitor, and combinations thereof.

In a second example, the compounds of the disclosure are for use in treating, preventing or suppressing symptoms associated with headache and/or migraine, whereby, preferably, the headache comprises tension-type headaches and whereby the migraine comprises common migraine, classic migraine, familial hemiplegic migraine, sporadic hemiplegic migraine, migraine with brainstem aura, retinal migraine, recurrent migraine and chronic migraine. Preferably, in the treatment, the use of the compound according to this example of the disclosure eliminates, reduces the severity of, and/or reduces the frequency of occurrence of at least one symptom of tension-type headaches and/or migraine, which symptom preferably includes at least one of (moderate to severe) headaches, and associated symptoms including aura, blurred vision, nausea, vomiting, delirium, nasal stuffiness, diarrhea, tinnitus, polyuria, pallor, sweating, localized edema of the scalp or face, scalp tenderness, prominence of a vein or artery in the temple, stiffness and tenderness of the neck, impairment of concentration and mood, cold and moist feeling in appendages, and sensitivity to light, sound, or smell. In one example according to this example of the disclosure, the treatment further comprises the administration of an additional active agent selected from the group consisting of a preventive migraine medication, an analgesic, a triptan and an ergotamine.

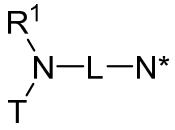
A compound for use according to both examples of the disclosure preferably is administered in a total daily dose that is in the range of about 5 to 2000 mg, preferably about 20 to 800 mg, more preferably the total daily dose is in the range of between about 30 to 400 mg and most preferably the total daily dose is in the range of about 150 to 250 mg.

A compound for use according to both examples of the disclosure preferably is administered orally. More preferably, the compound is administered in a solid form or in a liquid form, wherein preferably the compound is admixed with an aqueous solution prior to administration, wherein more preferably the aqueous solution is an isotonic aqueous solution and wherein even more preferably the isotonic aqueous solution is saline. A compound for use according to both examples of the disclosure preferably is administered at least twice daily, preferably wherein the compound is administered twice daily, wherein more preferably the compound is administered twice daily in two similar or equal doses. Preferably, the interval between two administrations is at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 hours.

A compound for use according to both examples of the disclosure is preferably used to treat a subject that is a primate, more preferably the subject is a human. The subject to be treated can be a patient suffering from a mitochondrial disease or the subject can be a patient who is not suffering from a mitochondrial disease, particularly not a patient suffering from a m.3243A>G related mitochondrial disease.

Claims

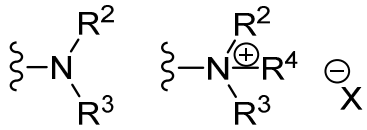
1. Use of a compound represented by general structure (**I**):



(**I**)

wherein,

- T is a water-soluble vitamin E derivative having a core chromanyl or chromanyl quinone framework and a carboxylic acid moiety substituted at the 2-position, wherein T is connected to nitrogen via the carboxylic acid moiety, as such forming an amide moiety;
- L is a linker between the amide nitrogen atom and the distal nitrogen atom comprising 1 to 10 optionally substituted backbone atoms selected from carbon, nitrogen and oxygen;
- N* is represented by structure (**IIa**) or (**IIb**)



(**IIa**) (**IIb**)

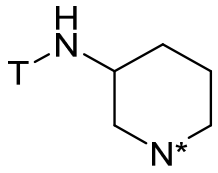
- R^1 and R^2 are each independently selected from hydrogen (H), C_1 – C_6 alkyl or C_1 – C_6 alkenyl, or R^1 and R^2 are joined together and thus form a second linker between the amide nitrogen atom and the distal nitrogen atom, or R^1 is joined with a backbone atom of the linker L in a cyclic structure and/or R^2 is joined with a backbone atom of the linker L in a cyclic structure;
- R^3 is selected from hydrogen (H), C_1 – C_6 alkyl or C_1 – C_6 alkenyl, wherein the alkyl or alkenyl moiety may be substituted with one or more halogen atoms, hydroxyl moieties or (halo)alkoxy moieties, or R^3 is absent when the distal nitrogen atom is part of an imine moiety; or optionally R^3 is joined with a backbone atom of the linker L in a cyclic structure; and
- R^4 is selected from hydrogen (H) or C_1 – C_6 alkyl, wherein the alkyl moiety may be substituted with one or more halogen atoms or (halo)alkoxy moieties;
- X is an anion, preferably a pharmaceutically acceptable anion,

in the manufacture of a medicament for treating, preventing or suppressing symptoms associated with at least one of:

a) a mood disorder; and,

b) headache and/or migraine.

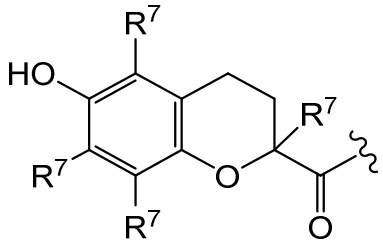
2. The use according to claim 1, wherein the compound is represented by structure (**VI**):



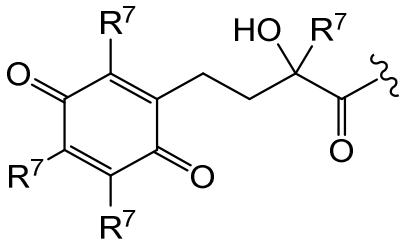
(**VI**)

wherein, N* is $–NR^3$ or $–N^+R^3R^4\ X^–$, wherein T, X, R^3, and R^4 are as defined in claim 1.

3. The use according to claim 1 or claim 2, wherein T is represented by structure (**IIIa**) or (**IIIb**):



(**IIIa**)



(**IIIb**)

wherein R^7 is individually a $C_1 – C_6$ alkyl moiety, preferably each R^7 is methyl.

4. The use according to any one of claims 1 – 3, wherein the mood disorder comprises depression.

5. The use according to any one of claims 1 – 4, wherein the medicament eliminates, reduces the severity of, and/or reduces the frequency of occurrence of at least one symptom of the mood disorder, preferably as determined using the Beck Depression Index.

6. The use according to any one of claims 1 – 5, wherein the symptom of the mood disorder includes at least one of apathy, persistent feelings of sadness, feelings of hopelessness or helplessness, having low self-esteem, feeling inadequate, excessive guilt, feelings of wanting to die, loss of interest in usual activities or activities once enjoyed, difficulty with relationships, sleep disturbances, changes in appetite or weight, decreased energy, difficulty concentrating, a decrease in the ability to make decisions, suicidal thoughts or attempts, frequent physical complaints, running away or threats of running away from home, hypersensitivity to failure or rejection, irritability, hostility, or aggression.

7. The use according to any one of claims 1 – 6, wherein an additional active agent selected from the group consisting of a norepinephrine reuptake inhibitor, a selective serotonin reuptake inhibitor, a tricyclic antidepressant, a monoamine oxidase inhibitor, and combinations thereof, is to be further administered.

8. The use according to any one of claims 1 – 3, wherein the headache comprises tension-type headaches or wherein the migraine comprises common migraine, classic migraine, familial hemiplegic migraine, sporadic hemiplegic migraine, migraine with brainstem aura, retinal migraine, recurrent migraine and chronic migraine.

9. The use according to any one of claims 1 – 3 and 8, wherein the medicament eliminates, reduces the severity of, and/or reduces the frequency of occurrence of at least one symptom of tension-type headaches or migraine, which symptom preferably includes at least one of (moderate to severe) headaches, and associated symptoms including aura, blurred vision, nausea, vomiting, delirium, nasal stuffiness, diarrhea, tinnitus, polyuria, pallor, sweating, localized edema of the scalp or face, scalp tenderness, prominence of a vein or artery in the temple, stiffness and tenderness of the neck, impairment of concentration and mood, cold and moist feeling in appendages, and sensitivity to light, sound, or smell.

10. The use according to any one of claims 1 – 3 and 8 – 9, wherein an additional active agent selected from the group consisting of a preventive migraine medication, an analgesic, a triptan and an ergotamine is to be further administered.

11. The use according to any one of claims 1 – 10, wherein the total daily dose that is to be administered is in the range of about 5 to 2000 mg, preferably about 20 to 800 mg, more preferably the total daily dose is in the range of between about 30 to 400 mg and most preferably the total daily dose is in the range of about 150 to 250 mg.

12. The use according to any one of claims 1 – 11, wherein the medicament is to be administered orally, wherein, preferably, the medicament is to be administered in a solid form or in a liquid form, wherein more preferably the compound is admixed with an aqueous solution prior to administration, wherein even more preferably the aqueous solution is an isotonic aqueous solution and wherein most preferably the isotonic aqueous solution is saline.

13. The use according to any one of claims 1 – 12, wherein the medicament is to be administered at least twice daily, preferably wherein the medicament is to be administered twice daily, wherein more preferably the medicament is to be administered twice daily in two similar or equal doses.

14. The use according to claim 13, wherein the interval between two administrations is at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 hours.

15. The use according to any one of claims 1 – 14, wherein the subject to be treated is a primate, wherein preferably the subject is a human, wherein preferably the subject to be treated is a patient suffering from a mitochondrial disease.