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(54) Title: NON-TOXIC IRON CHELATORS WITH NEUROPROTECTIVE POTENTIAL

(57) Abstract: The present invention relates to new desferrioxamine B-based compounds that may be useful to treat neurodegenerative diseases, to their preparation, and to compositions including the compounds. The present invention also relates to the use of the compounds, as well as compositions including the compounds, in the treatment of neurodegenerative disorders (such as Parkinson's disease).



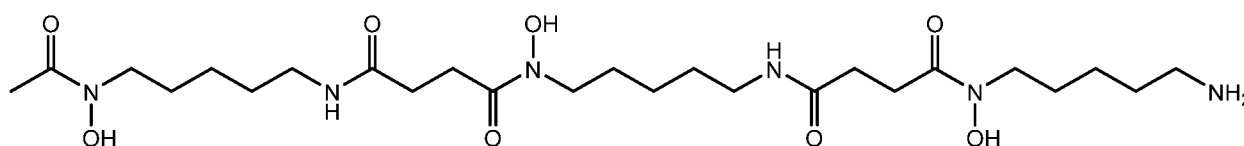
Non-toxic iron chelators with neuroprotective potential

Field of the invention

The present invention relates to new desferrioxamine B-based compounds that have potential utility for treating neurodegenerative conditions, to their preparation, and to compositions including the compounds. The present invention also relates to the use of the compounds, as well as compositions including the compounds, in the treatment of neurodegenerative disorders (such as Parkinson's disease).

Background of the invention

Desferrioxamine B (DFOB) is an iron(III) chelating molecule produced by the bacterium *Streptomyces pilosus* (*S. pilosus*) and other *Actinomycetes*. The bacteria produce DFOB to bind iron in the local environment as an essential requirement for supplying iron to the cell for growth. The structure of DFOB is:



desferrioxamine B (DFOB)

DFOB has been used in the clinic to treat patients with secondary iron overload, which can occur as a complication of the treatment of transfusion-dependent blood disorders, including beta-thalassaemia, sickle cell anaemia and myelodysplastic syndromes. Various neurodegenerative diseases are also associated with excess iron. For example, Parkinson's disease is associated with an increase in iron in the substantia nigra brain region (compared to age-matched controls), and this increased iron has been implicated in damage to dopaminergic neurons and aggregation of alpha-synuclein (via the iron-mediated production of damaging free radicals).

DFOB is effective at removing iron from plasma and it is non-toxic. However, it has poor Blood-Brain Barrier (BBB) permeability and is inefficient at removing iron

stored inside cells. It also has a short plasma half-life ($t_{1/2}$ 10-20 min) due to its high water solubility and low plasma protein binding (about 10%).

Current treatments for Parkinson's disease may assist with the symptoms of the disease, but there are currently no treatments available that slow disease progression.

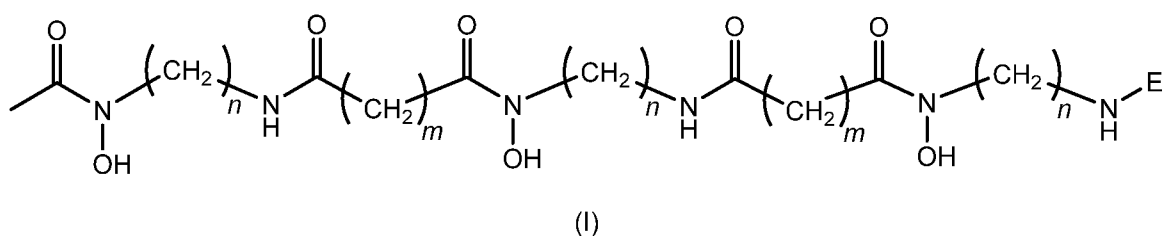
5 It would be useful if agents, which provide an improvement over the current neurodegenerative therapies, could be developed.

Reference to any prior art in the specification is not an acknowledgment or suggestion that this prior art forms part of the common general knowledge in any jurisdiction or that this prior art could reasonably be expected to be understood, regarded as relevant, and/or combined with other pieces of prior art by a skilled person in the art.

Summary of the invention

The present inventors have proposed that the issues with current agents used in therapy of neurodegenerative disorders could be overcome by developing an agent that has multiple modes of action. Specifically, the present inventors have sought to develop compounds that have high affinity for iron and antioxidant activity. In addition, the agents should have BBB permeability.

In a first aspect, the present invention relates to a compound of formula (I):



20

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

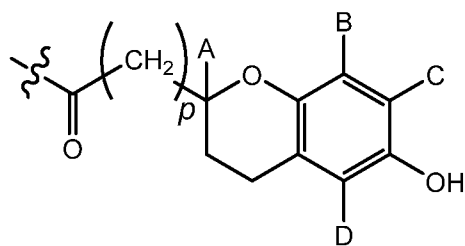
each n is independently selected from 4 and 5;

m is 2; and

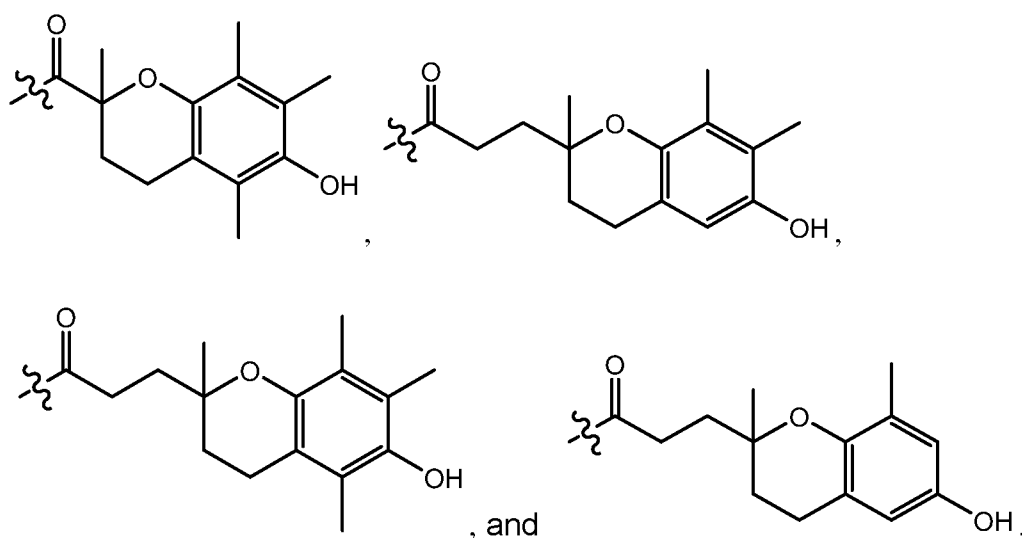
E is a vitamin E analogue or an edaravone analogue.

n may be 5.

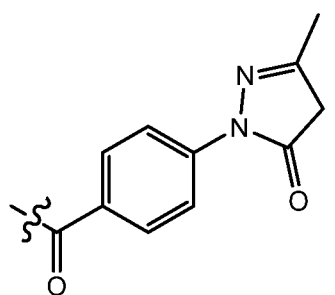
E may be a vitamin E analogue. For example, E may be



, wherein A, B, C and D are independently selected from H and alkyl (e.g. C₁ to C₃ alkyl), and p is 0, 1 or 2. A, B, C and D may be the same or different. A, B, C and D may be alkyl (e.g. methyl). A, B and C may be alkyl (e.g. methyl), and D may be H. A and B may be alkyl (e.g. methyl), and C and D may be H. p may be 0 or 2. The vitamin E analogue may be selected from:



E may be an antioxidant fragment such as an analogue or derivative of edaravone, e.g.:



In a second aspect, the present invention relates to a pharmaceutical composition including a compound of formula (I) (according to the first aspect of the invention) together with a pharmaceutically acceptable carrier, diluent or excipient.

Compounds and pharmaceutical compositions according to the present invention
5 may be suitable for the treatment of neurodegenerative disorders. Accordingly, in another aspect, the present invention relates to a method of treating a neurodegenerative disorder in a subject, the method including administering to the subject an effective amount of a compound of formula (I) according to the first aspect of the invention, or a pharmaceutical composition according to the second aspect of the
10 invention.

In a further aspect the present invention relates to the use of an effective amount of a compound of formula (I) according to the first aspect of the invention, or a pharmaceutical composition according to the second aspect of the invention, in the manufacture of a medicament for treating a neurodegenerative disorder.

15 In a further aspect the present invention relates to the use of an effective amount of a compound of formula (I) according to the first aspect of the invention, or a pharmaceutical composition according to the second aspect of the invention, for the treatment of a neurodegenerative disorder in a subject.

In a further aspect the present invention relates to an effective amount of a
20 compound of formula (I) according to the first aspect of the invention, or a pharmaceutical composition according to the second aspect of the invention, for use in the treatment of a neurodegenerative disorder in a subject.

The neurodegenerative disorder to be treated is associated with metal ion (in particular, iron) dyshomeostasis. The neurodegenerative disorder may be selected from
25 Parkinson's disease, Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis, Friedreich's ataxia, and Multiple Sclerosis.

The compounds of formula (I) may be used in therapy alone or in combination with one or more other therapeutic agents, for example, as part of a combination therapy.

Further aspects of the present invention and further embodiments of the aspects described in the preceding paragraphs will become apparent from the following description, given by way of example and with reference to the accompanying drawings.

Brief description of the drawings

5 **Figure 1.** Extracted ion chromatogram for the single charged species of DFOB-(rac)-TLX (m/z 793 $[M+H]^+$). The sample was run on a 5-95% ACN gradient over 40 min at a 0.4 mL min^{-1} flow rate using an Agilent Eclipse XDB-C18 column.

Figure 2. High resolution mass spectrometry of DFOB-(rac)-TLX (ESI+) found m/z 815.45264 ($[M+Na]^+$), $C_{39}H_{64}N_6O_{11}Na$ requires 815.45308.

10 **Figure 3.** 1H NMR spectrum (DMSO- d_6 , 400 MHz) of DFOB-(rac)-TLX.

Figure 4. ^{13}C -NMR spectrum (DMSO- d_6 , 100 MHz) of DFOB-(rac)-TLX.

Figure 5. SIM traces and corresponding integrals for DFOB-(rac)-TLX (m/z 397.3 for $[M+2H]^{2+}$) and FOB-(rac)-TLX (m/z 424.2 for $[M-3H+Fe(III)+2H]^{2+}$).

15 **Figure 6.** High resolution mass spectrometry of DFOB-(R)-TLX (ESI+) found m/z 815.45306 ($[M+Na]^+$), $C_{39}H_{64}N_6O_{11}Na$ requires 815.45308.

Figure 7. High resolution mass spectrometry of DFOB-(S)-TLX (ESI+) found m/z 815.45256 ($[M+Na]^+$), $C_{39}H_{64}N_6O_{11}Na$ requires 815.45308.

20 **Figure 8.** Extracted ion chromatogram for the single charged species of DFOB- α -CEHC (m/z 821.5 $[M+H]^+$). The sample was run on a 5-95% ACN gradient over 40 min at a 0.4 mL min^{-1} flow rate using an Agilent Eclipse XDB-C18 column.

Figure 9. High resolution mass spectrometry of DFOB- α -CEHC (ESI+) found m/z 843.48393 ($[M+Na]^+$), $C_{41}H_{68}N_6O_{11}Na$ requires 843.48438.

Figure 10. 1H NMR spectrum (DMSO- d_6 , 400 MHz) of DFOB- α -CEHC.

Figure 11. ^{13}C NMR spectrum (DMSO- d_6 , 100 MHz) of DFOB- α -CEHC.

25 **Figure 12.** Extracted ion chromatogram for the single charged species of DFOB- δ -CEHC (m/z 793.4 $[M+H]^+$). The sample was run on a 5-95% ACN gradient over 40 min at a 0.4 mL min^{-1} flow rate using an Agilent Eclipse XDB-C18 column.

Figure 13. High resolution mass spectrometry of DFOB- δ -CEHC (ESI+) found m/z 815.45294 ($[M+Na]^+$), $C_{39}H_{64}N_6O_{11}Na$ requires 815.45308.

Figure 14. ^1H NMR spectrum (DMSO- d_6 , 400 MHz) of DFOB- δ -CEHC.

Figure 15. ^{13}C NMR spectrum (DMSO- d_6 , 100 MHz) of DFOB- δ -CEHC.

Figure 16. Extracted ion chromatogram for the single charged species of DFOB- γ -CEHC (m/z 807.5 $[\text{M}+\text{H}]^+$). The sample was run on a 5-95% ACN gradient over 40 min at a 0.4 mL min $^{-1}$ flow rate using an Agilent Eclipse XDB-C18 column.

Figure 17. High resolution mass spectrometry of DFOB- γ -CEHC (ESI+) found m/z 829.46865 ($[\text{M}+\text{Na}]^+$), $\text{C}_{40}\text{H}_{66}\text{N}_6\text{O}_{11}\text{Na}$ requires 829.46873.

Figure 18. ^1H NMR spectrum (DMSO- d_6 , 400 MHz) of DFOB- γ -CEHC.

Figure 19. ^{13}C NMR spectrum (DMSO- d_6 , 100 MHz) of DFOB- γ -CEHC.

Figure 20. Extracted ion chromatogram for the single charged species of DFOB-EDA (m/z 761.3 $[\text{M}+\text{H}]^+$). The sample was run on a 5-95% ACN gradient over 40 min at a 0.4 mL min $^{-1}$ flow rate using an Agilent Eclipse XDB-C18 column.

Figure 21. High resolution mass spectrometry of DFOB-EDA (ESI+) found m/z 783.40121 ($[\text{M}+\text{Na}]^+$), $\text{C}_{36}\text{H}_{56}\text{N}_8\text{O}_{10}\text{Na}$ requires 783.40171.

Figure 22. ^1H NMR spectrum (DMSO- d_6 , 400 MHz) of DFOB-EDA.

Figure 23. ^{13}C NMR spectrum (DMSO- d_6 , 100 MHz) of DFOB-EDA.

Figure 24. Results for ascorbate (AH_2) autoxidation assay. **(A)** and **(B)** show that DFOB and its derivatives (DFOB-(rac)-TLX, DFOB-(*R*)-TLX, DFOB-(*S*)-TLX, DFOB- α -CEHC, DFOB- δ -CEHC, DFOB- γ -CEHC and DFOB-EDA) are effectively chelating iron and minimising ascorbate autoxidation.

Figure 25. Antiradical activity, as determined by the ABTS $^{+\bullet}$ assay, for selected compounds and standards. DFOB (circle), (rac)-TLX (square) and DFOB-(rac)-TLX (triangle).

Figure 26. Neurons in the substantia nigra **(A)**.

Figure 27. Pole test results as turn time ($n = 15$ /per group) **(B)**.

Detailed description of the embodiments

Herein, "TLX" represents the compound Trolox (6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid) and "EDA" represents the 4-(5-hydroxy-3-methyl-1H-pyrazol-1-yl) benzoic acid-derived moiety.

5 Compounds are generally described herein using standard nomenclature. For compounds having asymmetric centres, it will be understood that, unless otherwise specified, all of the optical isomers and mixtures thereof are encompassed. Compounds with two or more asymmetric elements can also be present as mixtures of diastereomers. Where a compound exists in various tautomeric forms, a recited
10 compound is not limited to any one specific tautomer, but rather is intended to encompass all tautomeric forms. Recited compounds are further intended to encompass compounds in which one or more atoms are replaced with an isotope, i.e., an atom having the same atomic number but a different mass number. By way of general example, and without limitation, isotopes of hydrogen include tritium and
15 deuterium and isotopes of carbon include ^{11}C , ^{13}C , and ^{14}C .

Compounds according to the formula provided herein, which have one or more stereogenic centres, may have an enantiomeric excess of at least 50%. For example, such compounds may have an enantiomeric excess of at least 60%, 70%, 80%, 85%, 90%, 95%, or 98%. Some embodiments of the compounds have an enantiomeric
20 excess of at least 99%. It will be apparent that single enantiomers (optically active forms) can be obtained by asymmetric synthesis, synthesis from optically pure precursors, biosynthesis or by resolution of the racemates, for example, enzymatic resolution or resolution by conventional methods such as crystallization in the presence of a resolving agent, or chromatography, using, for example, a chiral HPLC column. The
25 compounds of the present invention may be racemic mixtures.

Certain compounds are described herein using a general formula that includes variables such as m , n , p and E . Unless otherwise specified, each variable within such a formula is defined independently of any other variable, and any variable that occurs more than one time in a formula is defined independently at each occurrence. Also,
30 combinations of substituents and/or variables are permissible only if such combinations

result in stable compounds, i.e., compounds that can be isolated, characterized and tested for biological activity.

A "pharmaceutically acceptable salt" of a compound disclosed herein is an acid or base salt that is generally considered in the art to be suitable for use in contact with the tissues of human beings or animals without excessive toxicity or carcinogenicity, and preferably without irritation, allergic response, or other problem or complication. In particular, pharmaceutically acceptable salts in accordance with the present invention are those that do not adversely affect the ability of the compound to cross the BBB. Such salts include mineral and organic acid salts of basic residues such as amines, as well as alkali or organic salts of acidic residues such as carboxylic acids.

Suitable pharmaceutically acceptable salts include, but are not limited to, salts of acids such as hydrochloric, phosphoric, hydrobromic, malic, glycolic, fumaric, sulfuric, sulfamic, sulfanilic, formic, toluenesulfonic, methanesulfonic, benzenesulfonic, ethane disulfonic, 2-hydroxyethylsulfonic, nitric, benzoic, 2-acetoxybenzoic, citric, tartaric, lactic, stearic, salicylic, glutamic, ascorbic, pantoic, succinic, fumaric, maleic, propionic, hydroxymaleic, hydroiodic, phenylacetic, alkanolic (such as acetic, $\text{HOOC}-(\text{CH}_2)_n-\text{COOH}$ where n is any integer from 0 to 6, i.e. 0, 1, 2, 3, 4, 5 or 6), and the like. Similarly, pharmaceutically acceptable cations include, but are not limited to sodium, potassium, calcium, lithium and ammonium. A person skilled in the art will recognize further pharmaceutically acceptable salts for the compounds provided herein. In general, a pharmaceutically acceptable acid or base salt can be synthesized from a parent compound that contains a basic or acidic moiety by any conventional chemical method. Briefly, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent (such as ether, ethyl acetate, ethanol, isopropanol or acetonitrile), or in a mixture of the two.

It will be apparent that each compound of formula (I) may, but need not, be present as a hydrate, solvate or non-covalent complex. In addition, the various crystal forms and polymorphs are within the scope of the present invention, as are prodrugs of the compounds of formula (I) provided herein.

A "prodrug" is a compound that may not fully satisfy the structural requirements of the compounds provided herein, but is modified *in vivo*, following administration to a subject or patient, to produce a compound of formula (I) provided herein. For example, a prodrug may be an acylated derivative of a compound as provided herein. Prodrugs include compounds wherein hydroxy, carboxy, amine or sulfhydryl groups are bonded to any group that, when administered to a mammalian subject, cleaves to form a free hydroxy, carboxy, amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate, phosphate and benzoate derivatives of alcohol and amine functional groups within the compounds provided herein. Prodrugs of the compounds provided herein may be prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved *in vivo* to generate the parent compounds.

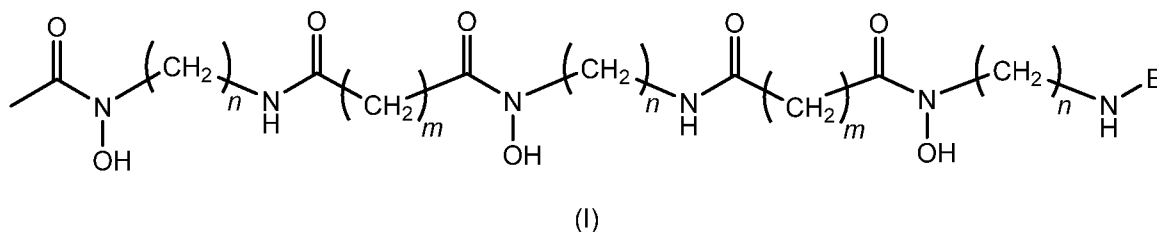
A "substituent" as used herein, refers to a molecular moiety that is covalently bonded to an atom within a molecule of interest. For example, a "CH₂ substituent" is a moiety such as a halogen or an alkyl group that is covalently bonded to the carbon atom of the CH₂ group. The term "substituted," as used herein, means that any one or more hydrogens on the designated atom is replaced with a selection from the indicated substituents, provided that the designated atom's normal valence is not exceeded, and that the substitution results in a stable compound, i.e., a compound that can be isolated, characterized and tested for biological activity. Suitable substituents are halogen (for example, fluorine, chlorine, bromine or iodine atoms).

The compound of formula (I) may not be substituted with one or more halogen atoms. The compound of formula (I) may not be substituted with any additional substituents.

As used herein a wording defining the limits of a range of length such as, for example, "from 1 to 5" means any integer from 1 to 5, i.e. 1, 2, 3, 4 and 5. In other words, any range defined by two integers explicitly mentioned is meant to comprise and disclose any integer defining said limits and any integer comprised in said range.

The term "alkyl" refers to a saturated, straight-chain or branched hydrocarbon group. Specific examples of alkyl groups are methyl, ethyl, propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, *n*-pentyl, *iso*-pentyl, *n*-hexyl and 2,2-dimethylbutyl.

As discussed above, the present invention relates to a compound of formula (I):



or a pharmaceutically acceptable salt or prodrug thereof, wherein:

5 each n is independently selected from 4 and 5;

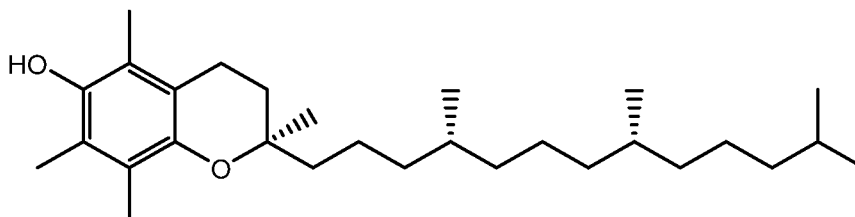
m is 2; and

E is a vitamin E analogue or an edaravone analogue.

In the compounds of formula (I), n may be 5.

The compounds of the present invention are conjugates of a DFOB-based moiety
10 and an antioxidant. The antioxidant will be any compound that is suitable for reducing oxidative stress that leads, or contributes, to the onset or development of a neurodegenerative disorder.

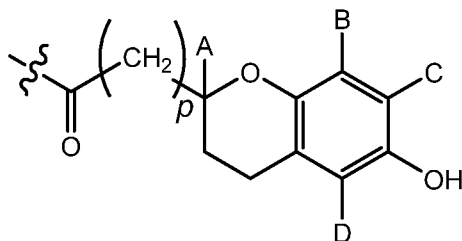
With regard to the vitamin E analogue, vitamin E (depicted below) is lipophilic and it does not contain a free carboxylic acid group as necessary for conjugation to the
15 free amine group of DFOB using amide chemistry. Therefore, it is difficult to conjugate native vitamin E to another compound, such as a drug.



Vitamin E

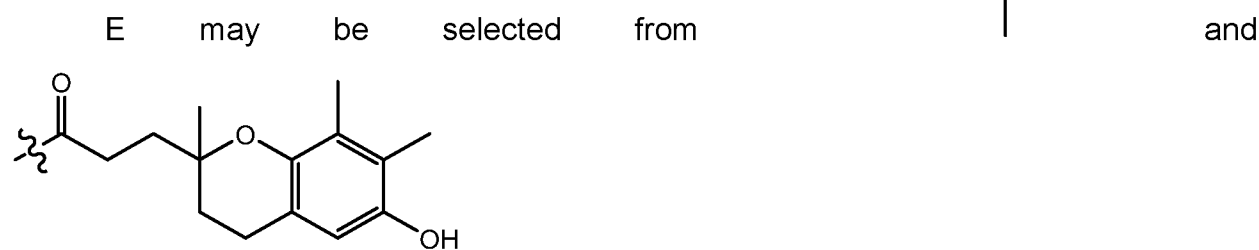
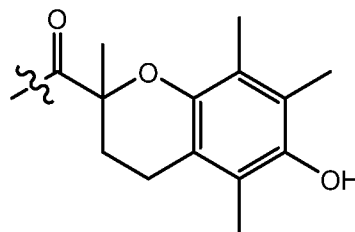
In light of these issues with vitamin E, vitamin E analogues have been employed
20 by the present inventors in place of the native vitamin E compound. These analogues

are intended to mimic the antioxidant activity of vitamin E and also may have the potential to promote brain uptake of the resulting conjugate *via* the tocopherol transport protein. However, in contrast to native vitamin E, they are more water soluble and contain a free carboxylic group, and therefore can be easily conjugated to the DFOB-based moiety.

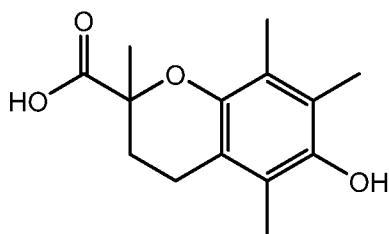


The vitamin E analogue may be , wherein A, B, C and D are independently selected from H and alkyl (e.g. C₁ to C₃ alkyl), and *p* is 0, 1 or 2.

A, B, C and D may be the same or different. For example, all of A, B, C and D may be alkyl (e.g. methyl). Alternatively, A, B and C may be alkyl (e.g. methyl), and D may be H. Alternatively, A and B may be alkyl (e.g. methyl) and C and D may be H. *p* may be 0 or 2.

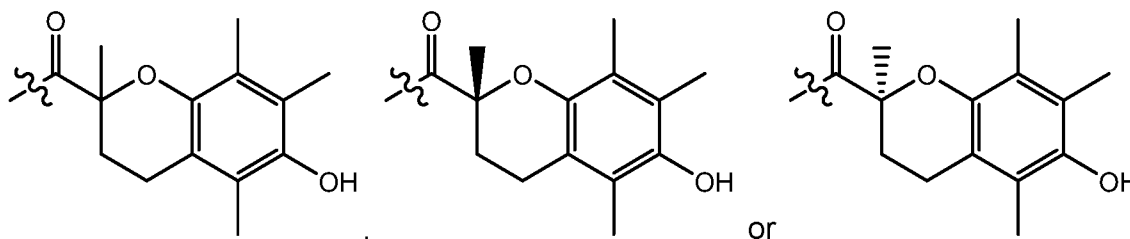


One example of a vitamin E analogue that may be used to prepare a compound of formula (I) is 6-hydroxy-2,5,7,8-tetramethylchromane-2-carboxylic acid ("Trolox"), which has the following structure:

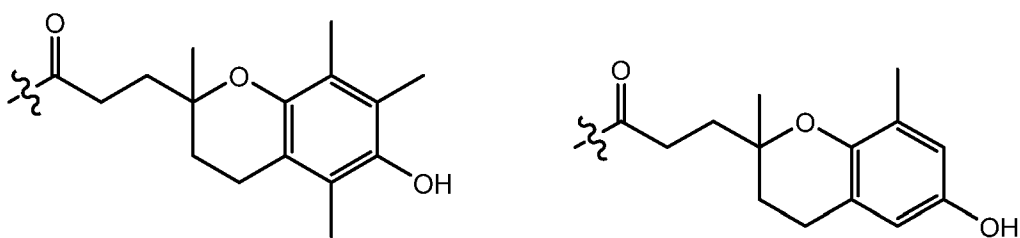
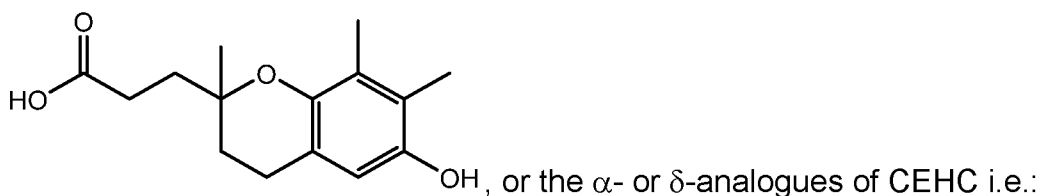


It will be apparent to a person skilled in the art that this compound (or any of the vitamin E analogues intended for use in the present invention) may be used as a racemic mixture, or may be conjugated to the DFOB-based moiety in an enantiomerically-pure form i.e. as the (*R*)- or (*S*)-isomer.

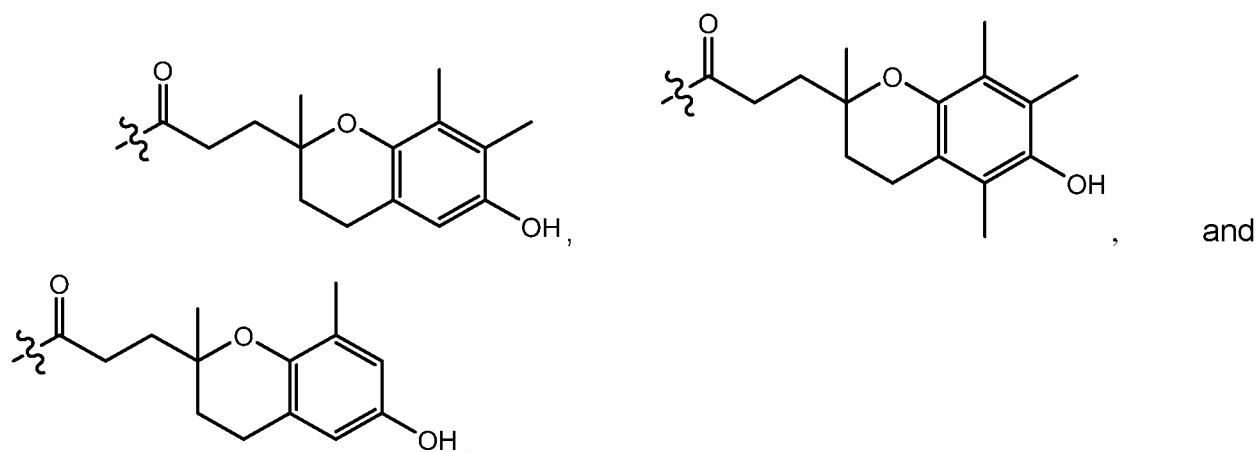
Accordingly, where Trolox is used as the vitamin E analogue in the compound of formula (I), the vitamin E analogue may be:



Another vitamin E analogue that may be used to prepare a compound of formula (I) is 2,7,8-trimethyl-2-(2-carboxyethyl)-6-hydroxychroman ("γ-CEHC"):



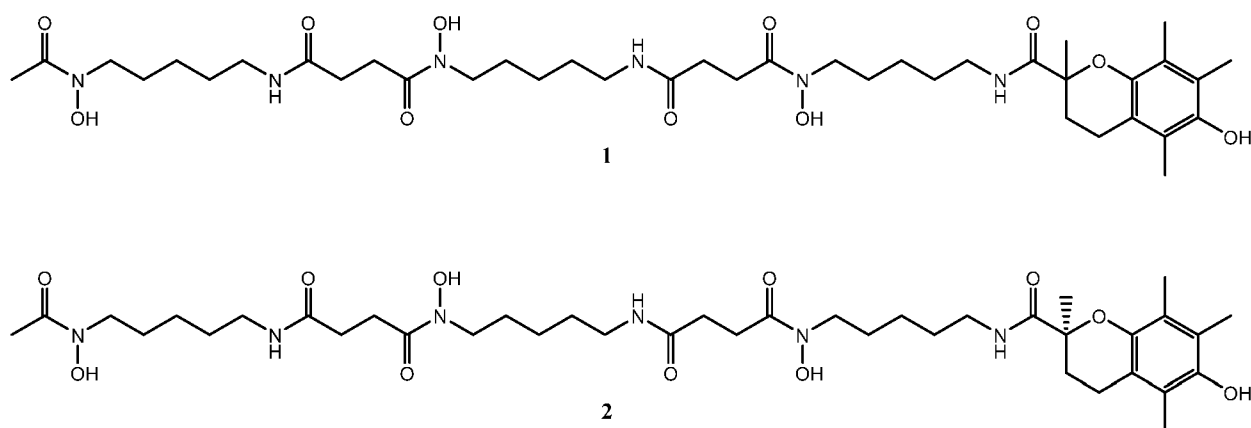
Accordingly, in the compound of formula (I) of the present invention, the vitamin E analogue may be selected from:

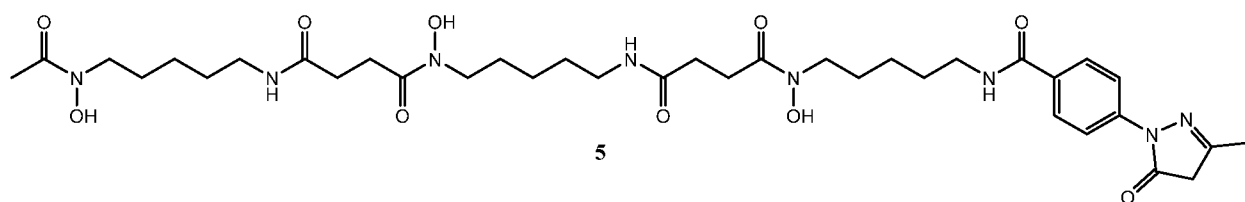
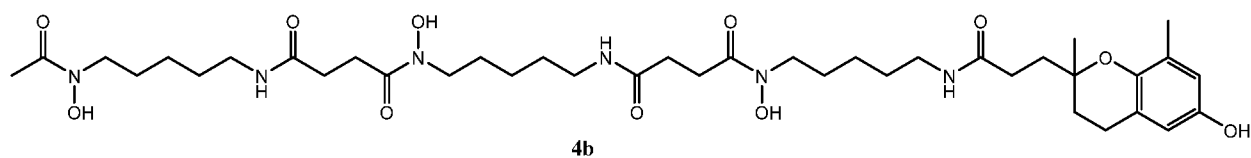
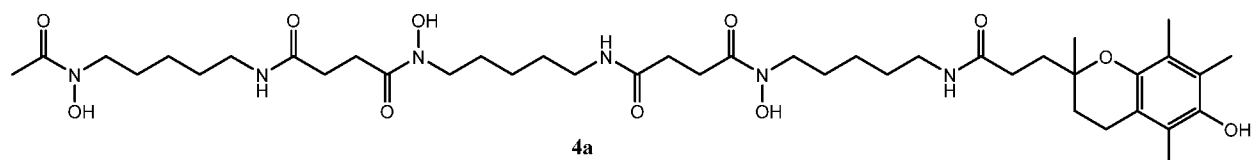
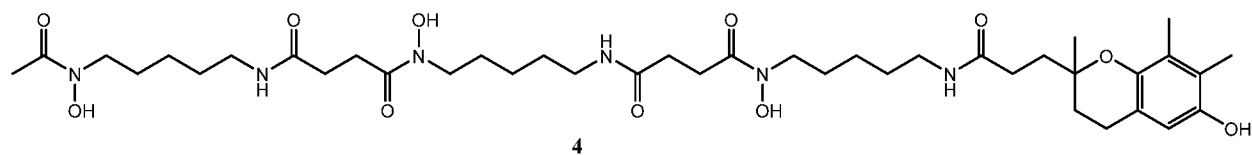
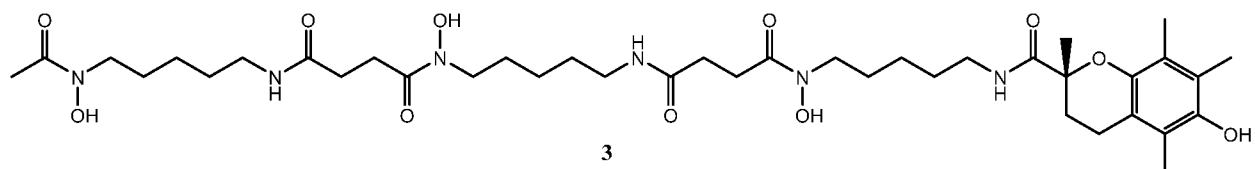


As mentioned above in relation to Trolox, each of the CEHC compounds may be used as a racemic mixture, or as the enantiomerically-pure form i.e. as the (*R*)- or (*S*)- isomer, and it is intended that all of these forms of the compounds of the present invention are covered by formula (I).

With regard to the edavarone analogue, edavarone, which has antioxidant properties, is used for the purpose of aiding neurological recovery following acute brain ischemia and subsequent cerebral infarction. Without wishing to be bound by theory, the present inventors believe that the edavarone moiety may carry the additional benefit in reducing oxidative stress in the brain.

Examples of compounds of formula (I), in accordance with the present invention, are:

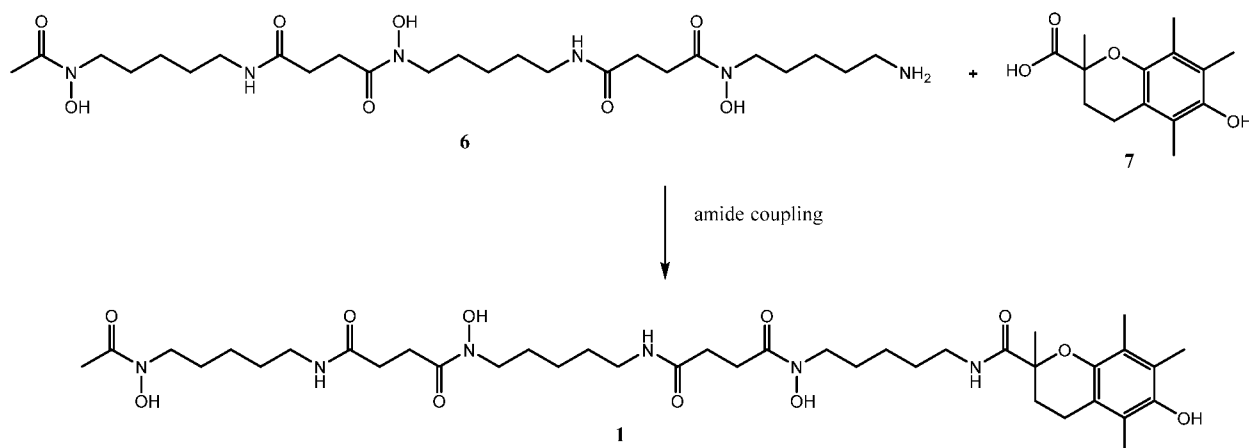




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The compounds of the present invention can be synthesised by any suitable method known to a person skilled in the art. For example, a DFOB-based moiety (e.g. compound **6** in Scheme 1 below) is reacted with a carboxyl-bearing vitamin E analogue (e.g. compound **7** in Scheme 1 below), to give conjugate **1** i.e. a compound of formula

10 (I).



Scheme 1.

The DFOB-based moiety (e.g. compound **6** in Scheme 1) is commercially
 5 available. Compound **7** is also available commercially.

The process may include the further step of reacting the primary amine group with a suitably-functionalised vitamin E analogue or edavarone analogue (such as those discussed above), to produce the compounds of formula (I) of the present invention.

Without wishing to be bound by theory or mode of action, the present inventors
 10 hypothesise that the compounds of the present invention have a dual mode of action in relation to mitigating the effects of excess iron in neurodegenerative disorders. Specifically, they may possess antioxidant activity, which may contribute to decreasing the effect that free radicals have on the development of neurodegenerative diseases (as discussed above, excess iron has been implicated in the production of free radicals,
 15 which are thought to contribute to these diseases). In addition, the DFOB-based portion of the compounds is an efficient iron chelator, further contributing to the sequestration of excess iron.

The lipophilic nature of the compounds is also believed to enhance the uptake of the compound of formula (I) into brain tissue, in addition to the fact that the antioxidant
 20 moiety may facilitate active transport of the compounds through the BBB by the tocopherol transport protein. The edaravone analogue has established BBB permeability and may act in a Trojan horse capacity to increase uptake of the DFOB-edaravone compound.

5 to a pharmaceutical composition including a compound of formula (I):



each n is independently selected from 4 and 5;

10 m is 2; and

E is a vitamin E analogue or an edaravone analogue;

together with a pharmaceutically acceptable carrier, diluent or excipient.

soluble carrier, conventional solvents, dispersion media, fillers, solid carriers, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents. Suitable water soluble carriers include, but are not limited to saline, dextrose, corn oil, dimethylsulfoxide, and gelatin capsules. Other conventional additives include lactose, mannitol, corn starch, potato starch, binders such as crystalline cellulose, cellulose derivatives, acacia, gelatins, disintegrators such as sodium carboxymethylcellulose, and lubricants such as talc or magnesium stearate.

25 herein includes subcutaneous, intradermal, intravascular (for example, intravenous),

intramuscular, spinal, intracranial, intrathecal, intraocular, periocular, intraorbital, intrasynovial and intraperitoneal injection, as well as any similar injection or infusion technique. In certain embodiments, compositions in a form suitable for oral use or parenteral use are preferred. Suitable oral forms include, for example, tablets, troches, 5 lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. For intravenous, intramuscular, subcutaneous, or intraperitoneal administration, one or more compounds may be combined with a sterile aqueous solution which is preferably isotonic with the blood of the recipient. Such formulations may be prepared by dissolving solid active ingredient in 10 water containing physiologically compatible substances such as sodium chloride or glycine, and having a buffered pH compatible with physiological conditions to produce an aqueous solution, and rendering said solution sterile. The formulations may be present in unit or multi-dose containers such as sealed ampoules or vials. Examples of suitable components are described in Martindale – The Extra Pharmacopoeia 15 (Pharmaceutical Press, London 1993) and Martin (ed.), Remington's Pharmaceutical Sciences.

For the treatment of a neurodegenerative disorder, the dose of the biologically-active compound according to the invention may vary within wide limits and may be adjusted to individual requirements. Active compounds according to the present 20 invention are generally administered in a therapeutically effective amount. Preferred doses range from about 0.1 mg to about 140 mg per kilogram of body weight per day (e.g. about 0.5 mg to about 7 g per patient per day). The daily dose may be administered as a single dose or in a plurality of doses. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will 25 vary depending upon the host treated and the particular mode of administration. Dosage unit forms will generally contain between about 1 mg to about 500 mg of an active ingredient.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific 30 compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination (i.e. other drugs being used to treat the patient), and the severity of the particular disorder

undergoing therapy. Such treatments may be administered as often as necessary and for the period of time judged necessary by the treating physician. A person skilled in the art will appreciate that the dosage regime or therapeutically effective amount of the compound of formula (I) to be administered may need to be optimized for each individual.

It will be appreciated that different dosages may be required for treating different disorders. An effective amount of an agent is that amount which causes a statistically significant decrease in the severity of the symptoms of the neurodegenerative disorder, or that slows the progression of the neurodegenerative disorder. As used herein, the term “neurodegenerative disorder” or “neurodegenerative disease” is intended to refer to a disorder that results in, or is characterized by, degeneration of the nervous system, especially the neurons in the brain. Examples of neurodegenerative disorders contemplated by the present invention include those that have a pathology dependent upon metal ion dyshomeostasis. In particular, the neurodegenerative disorders of interest are those associated with an accumulation of iron (i.e. an excess of iron) in the brain, such as Parkinson’s disease, Alzheimer’s disease, Huntington’s disease, amyotrophic lateral sclerosis, Friedreich’s ataxia, and Multiple Sclerosis.

The terms “therapeutically effective amount” or “effective amount” refer to an amount of the compound of formula (I) that results in an improvement or remediation of the symptoms of a neurodegenerative disorder, or slowing the progression of the disease. The dosage form and amount of the compounds or pharmaceutical compositions of the present invention can be readily established by reference to known treatment regimens.

Preferred compounds of the invention will have certain pharmacological properties. Such properties include, but are not limited to, oral bioavailability and BBB permeability, such that the preferred oral dosage forms discussed above can provide therapeutically effective levels of the compound *in vivo* and at the desired site of action.

The compounds of the present invention are preferably administered to a patient (for example, a human) orally or parenterally, and are present within at least one body fluid or tissue of the patient. Accordingly, the present invention further provides methods

for treating patients suffering from neurodegenerative disorders (including Parkinson's disease).

In the context of the present disclosure, the terms "treating", "treatment" and "therapy" encompass ameliorating the severity of a neurodegenerative disorder or its associated symptoms and/or slowing disease progression.

Patients may include but are not limited to primates, especially humans, domesticated companion animals such as dogs, cats, horses, and livestock such as cattle, pigs, sheep, with dosages as described herein.

Compounds and pharmaceutical compositions according to the present invention may be suitable for neurodegenerative therapy. Accordingly, the present invention also relates to a method of treating a neurodegenerative disorder in a patient including administration to the patient of a therapeutically effective amount of a compound of formula (I), or a pharmaceutically-acceptable salt, solvate, hydrate or prodrug thereof. The present invention also relates to the use of a therapeutically effective amount of a compound of formula (I), or a pharmaceutically-acceptable salt, solvate, hydrate or prodrug thereof, for treating a neurodegenerative disorder. The present invention also provides a pharmaceutical composition for use in treating a neurodegenerative disorder, in any of the embodiments described in the specification. The present invention also relates to the use of a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, hydrate or prodrug thereof, for the manufacture of a medicament for treating a neurodegenerative disorder.

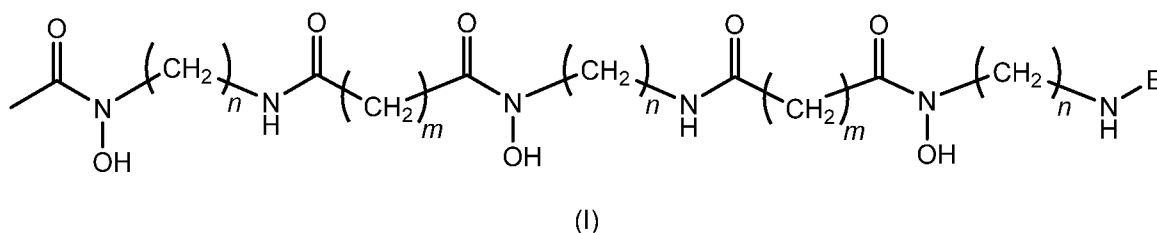
The present invention also relates to a compound of formula (I), or a pharmaceutically acceptable salt, solvate, hydrate or prodrug thereof, when used in a method of treating a neurodegenerative disorder. The present invention also relates to a composition having an active ingredient for use in treating a neurodegenerative disorder, wherein the active ingredient is a compound of formula (I), or a pharmaceutically acceptable salt, solvate, hydrate or prodrug thereof. The present invention also relates to the use of a pharmaceutical composition containing a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, hydrate or prodrug thereof, in treating a neurodegenerative disorder, such as described above. In

one embodiment, the compound of formula (I) is essentially the only active ingredient of the composition.

In one embodiment, the neurodegenerative disorder is associated with metal ion (in particular, iron) dyshomeostasis. Preferably, the disorder is selected from
 5 Parkinson's disease, Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis, Friedreich's ataxia, and Multiple Sclerosis.

Alternatively, or in addition to, the compounds may be administered in combination with other agents used in neurodegenerative therapy, such as, resveratrol, donepezil, apomorphine and other dopamine agonists, levodopa as monotherapy or in
 10 combination with peripherally acting inhibitors of dopamine decarboxylase (carbidopa, benserazide, and monoamine oxidase B inhibitors (selegiline and rasagiline).

In a first embodiment, the present invention relates to a compound of formula (I):



15 or a pharmaceutically acceptable salt or prodrug thereof, wherein:

each n is independently selected from 4 and 5;

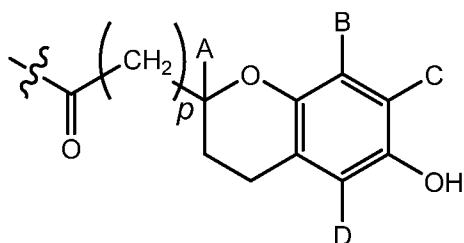
m is 2; and

E is a vitamin E analogue or an edaravone analogue.

In a second embodiment, the present invention relates to a compound of formula
 20 (I) according to the first embodiment, wherein n is 5.

In a third embodiment, the present invention relates to a compound of formula (I) according to the first or second embodiment, wherein p is 0 or 2.

In a fourth embodiment, the present invention relates to a compound of formula (I) according to the first, second or third embodiments, wherein E is:



wherein:

A, B, C and D are independently selected from H and alkyl, and

p is 0, 1 or 2.

5 In a fifth embodiment, the present invention relates to a compound of formula (I) according to the fourth embodiment, wherein alkyl is C_1 to C_3 alkyl.

In a sixth embodiment, the present invention relates to a compound of formula (I) according to the fourth or fifth embodiments, wherein A, B, C and D are the same.

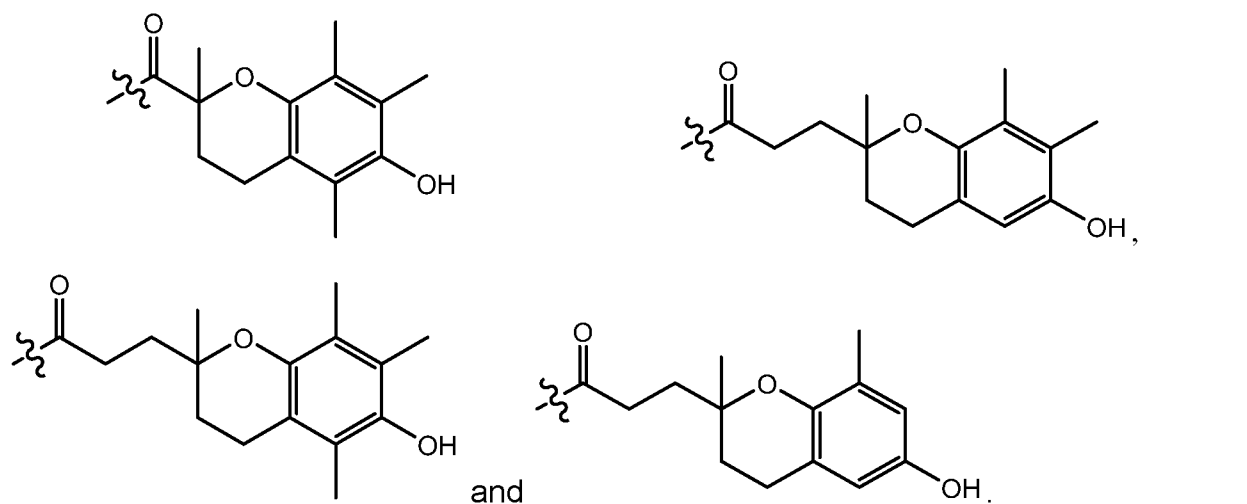
10 In a seventh embodiment, the present invention relates to a compound of formula (I) according to the sixth embodiment, wherein A, B, C and D are alkyl.

In an eighth embodiment, the present invention relates to a compound of formula (I) according to the fourth or fifth embodiment, wherein A, B, C and D are different.

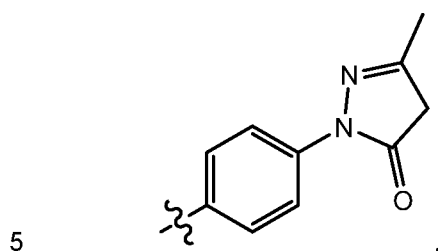
In a ninth embodiment, the present invention relates to a compound of formula (I) according to the eighth embodiment, wherein A, B and C are alkyl, and D is H.

15 In a tenth embodiment, the present invention relates to a compound of formula (I) according to the fourth or fifth embodiment, wherein A and B are alkyl and C and D are H.

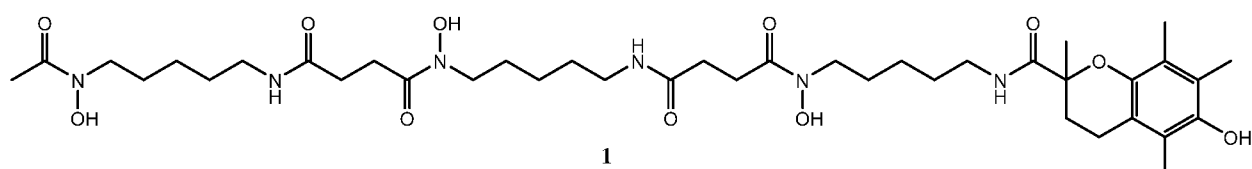
20 In an eleventh embodiment, the present invention relates to a compound of formula (I) according to any of the fourth to tenth embodiments, wherein E is selected from



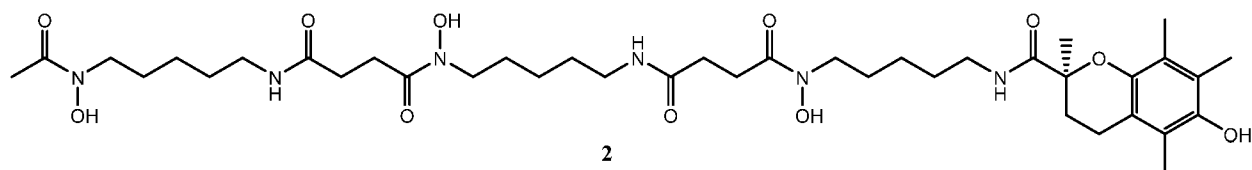
In a twelfth embodiment, the present invention relates to a compound of formula (I) according to any of the first to third embodiments, wherein E is:



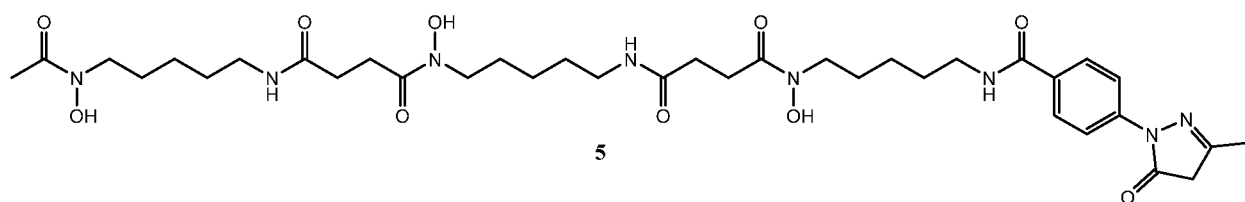
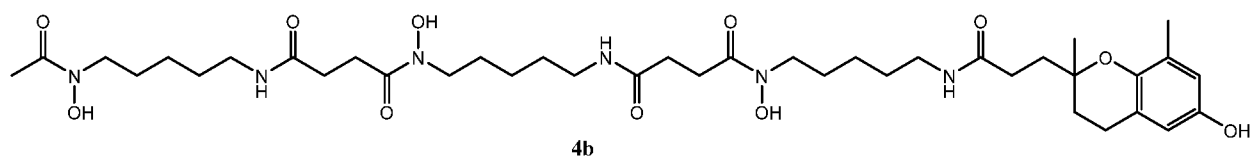
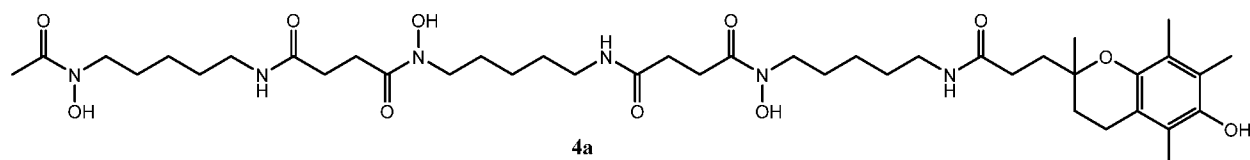
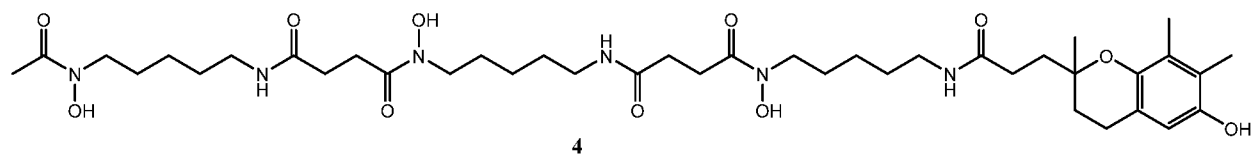
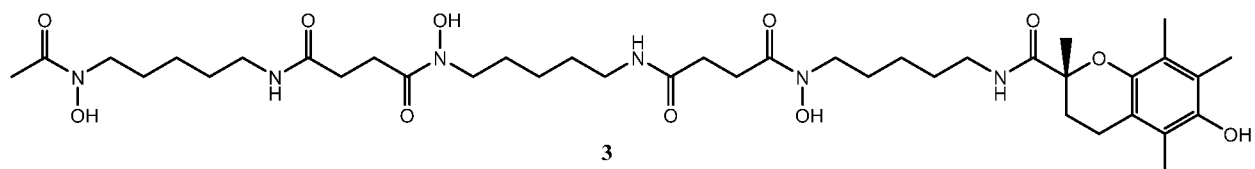
In a thirteenth embodiment, the present invention relates to a compound of formula (I) according to any of the first to twelfth embodiments, wherein the compound is selected from the group consisting of:



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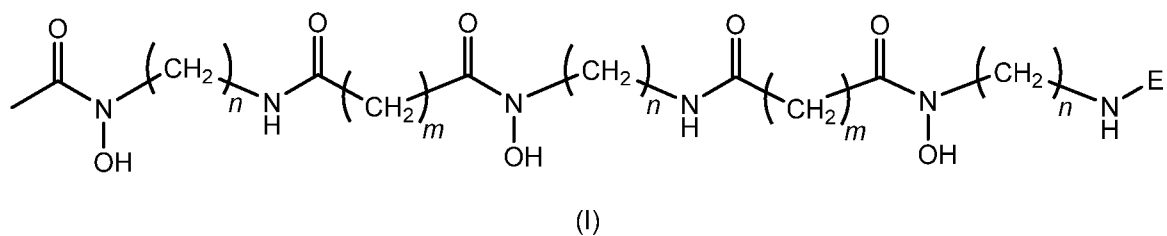


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In a fourteenth embodiment, the present invention relates to a pharmaceutical composition including an effective amount of a compound of formula (I):



10 or a pharmaceutically acceptable salt or prodrug thereof, wherein:

each n is independently selected from 4 and 5;

m is 2; and

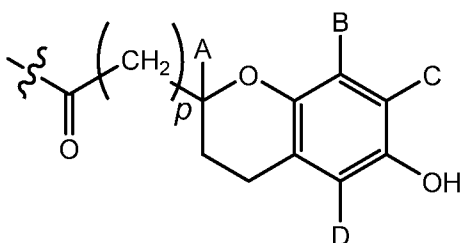
E is a vitamin E analogue or an edaravone analogue;

together with a pharmaceutically acceptable carrier, diluent or excipient.

In a fifteenth embodiment, the present invention relates to a pharmaceutical composition according to the fourteenth embodiment, wherein the composition is
5 suitable for parenteral or oral administration.

In a sixteenth embodiment, the present invention relates to a pharmaceutical composition according to the fourteenth or fifteenth embodiments, wherein n is 5.

In a seventeenth embodiment, the present invention relates to a pharmaceutical composition according to any one of the fourteenth to sixteenth embodiments, wherein
10 E is:



wherein:

A, B, C and D are independently selected from H and alkyl, and

p is 0, 1 or 2.

15 In an eighteenth embodiment, the present invention relates to a compound of formula (I) according to the seventeenth embodiment, wherein alkyl is C_1 to C_3 alkyl.

In a nineteenth embodiment, the present invention relates to a pharmaceutical composition according to the seventeenth or eighteenth embodiments, wherein A, B, C and D are the same.

20 In a twentieth embodiment, the present invention relates to a pharmaceutical composition according to the nineteenth embodiment, wherein A, B, C and D are alkyl.

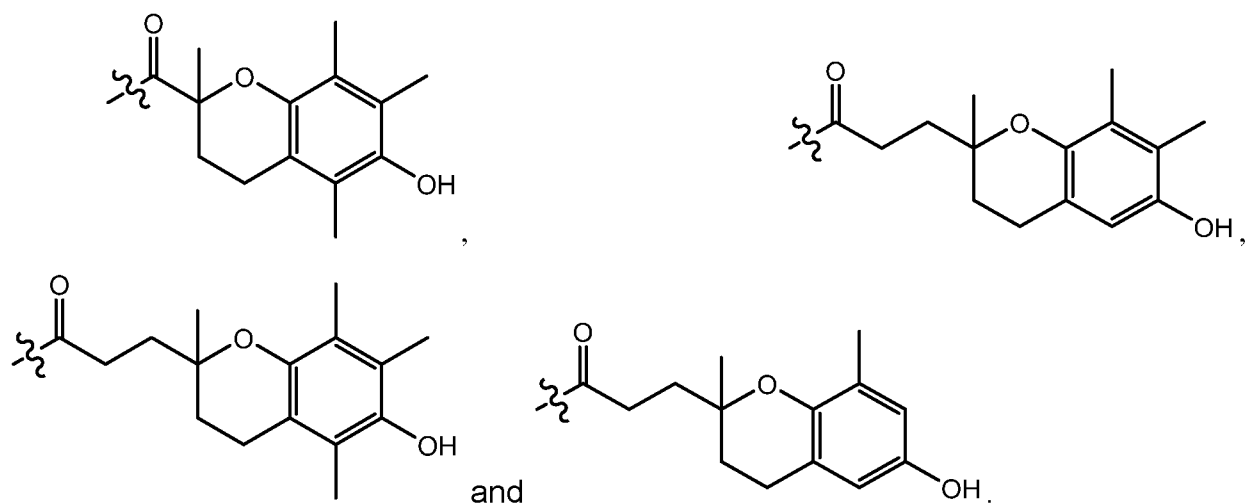
In a twenty-first embodiment, the present invention relates to a pharmaceutical composition according to the seventeenth or eighteenth embodiments, wherein A, B, C and D are different.

In a twenty-second embodiment, the present invention relates to a pharmaceutical composition according to the twenty-first embodiment, wherein A, B and C are alkyl, and D is H.

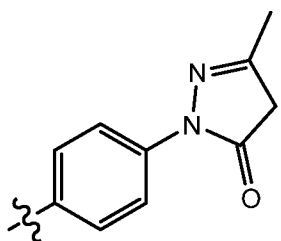
In a twenty-third embodiment, the present invention relates to a pharmaceutical composition according to the seventeenth or eighteenth embodiments, wherein A and B are alkyl and C and D are H.

In a twenty-fourth embodiment, the present invention relates to a pharmaceutical composition according to any one of the seventeenth to twenty-third embodiments, wherein p is 0 or 2.

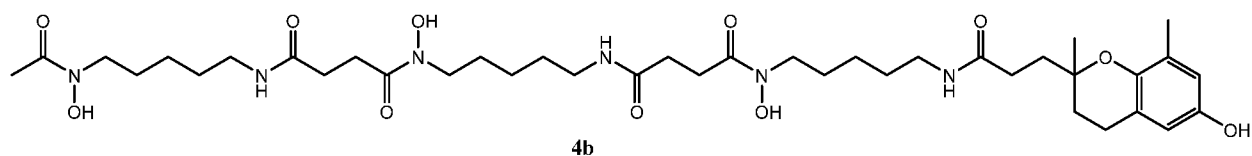
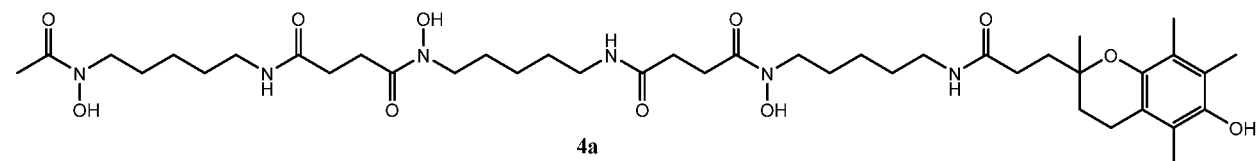
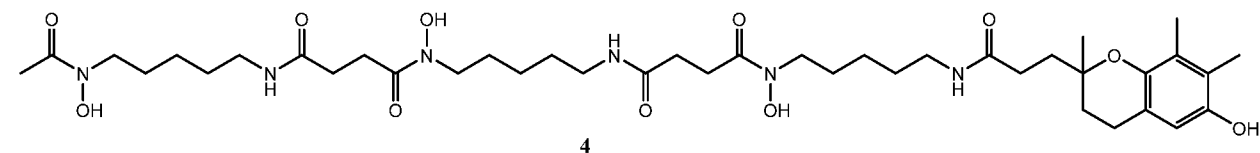
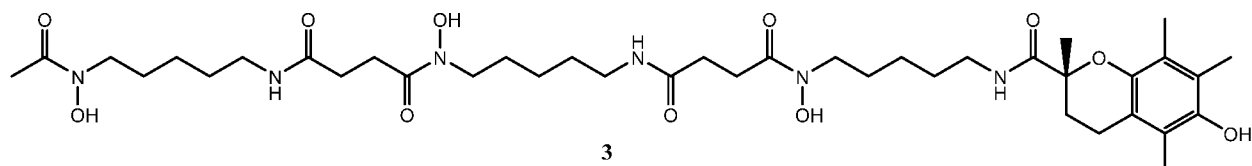
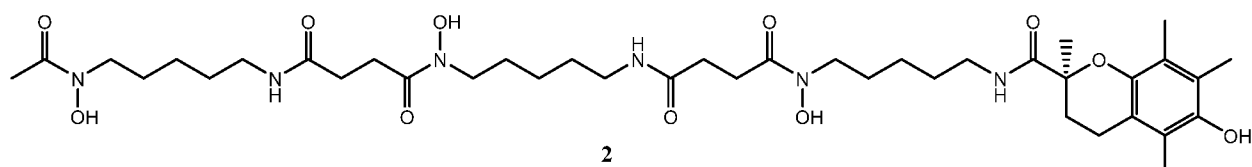
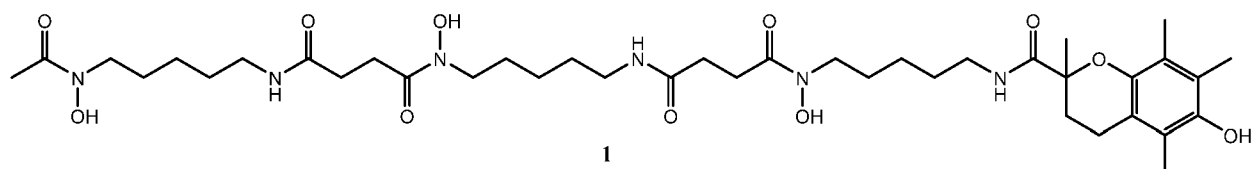
In a twenty-fifth embodiment, the present invention relates to a pharmaceutical composition according to any one of the seventeenth to twenty-fourth embodiments, wherein the E is selected from:

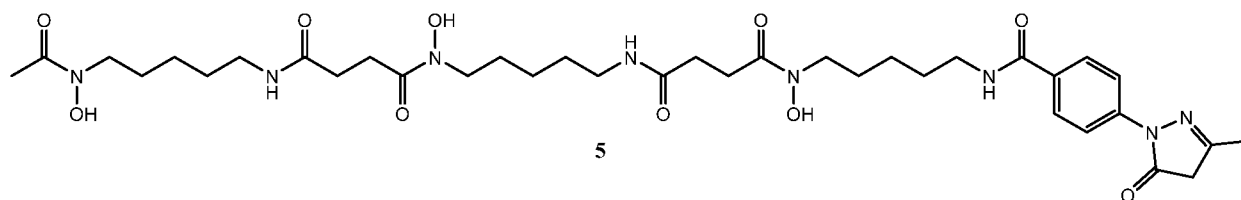


In a twenty-sixth embodiment, the present invention relates to a pharmaceutical composition according to any one of the fourteenth to sixteenth embodiments, wherein E is:

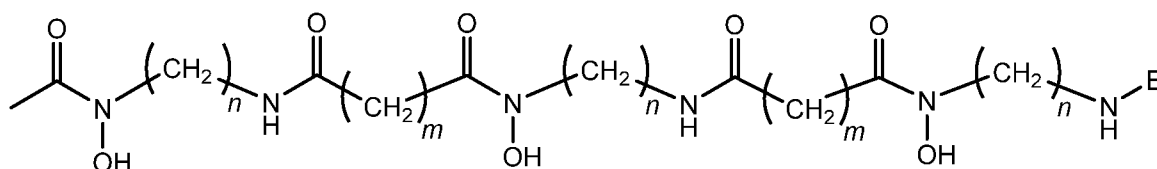


In a twenty-seventh embodiment, the present invention relates to a pharmaceutical composition according to any one of the fourteenth to twenty-sixth embodiments, wherein the compound is selected from the group consisting of:





In a twenty-eighth embodiment, the present invention relates to a method of treating a neurodegenerative disorder in a patient including administration to the patient of an effective amount of a compound of formula (I):



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or a pharmaceutically acceptable salt or prodrug thereof, wherein:

each n is independently selected from 4 and 5;

m is 2; and

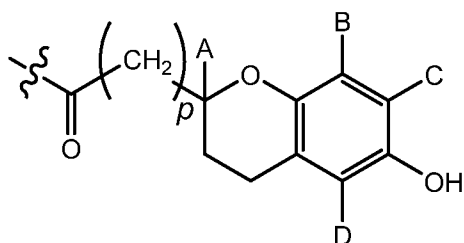
10 E is a vitamin E analogue or an edaravone analogue.

In a twenty-ninth embodiment, the present invention relates to a method according to the twenty-eighth embodiment, wherein the administration is selected from parenteral or oral administration.

15 In a thirtieth embodiment, the present invention relates to a method according to the twenty-eighth or twenty-ninth embodiment, wherein the neurodegenerative disorder is selected from Parkinson's disease, Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis, Friedreich's ataxia, and Multiple Sclerosis.

In a thirty-first embodiment, the present invention relates to a method according to any one of the twenty-eighth to thirtieth embodiments, wherein n is 5.

20 In a thirty-second embodiment, the present invention relates to a method according to any one of the twenty-eighth to thirty-first embodiments, wherein E is:



wherein:

A, B, C and D are independently selected from H and alkyl, and

p is 0, 1 or 2.

5 In a thirty-third embodiment, the present invention relates to a method according to the thirty-second embodiment, wherein alkyl is C_1 to C_3 alkyl.

In a thirty-fourth embodiment, the present invention relates to a method according to the thirty-second or thirty-third embodiment, wherein A, B, C and D are the same.

10 In a thirty-fifth embodiment, the present invention relates to a method according to the thirty-fourth embodiment, wherein A, B, C and D are alkyl.

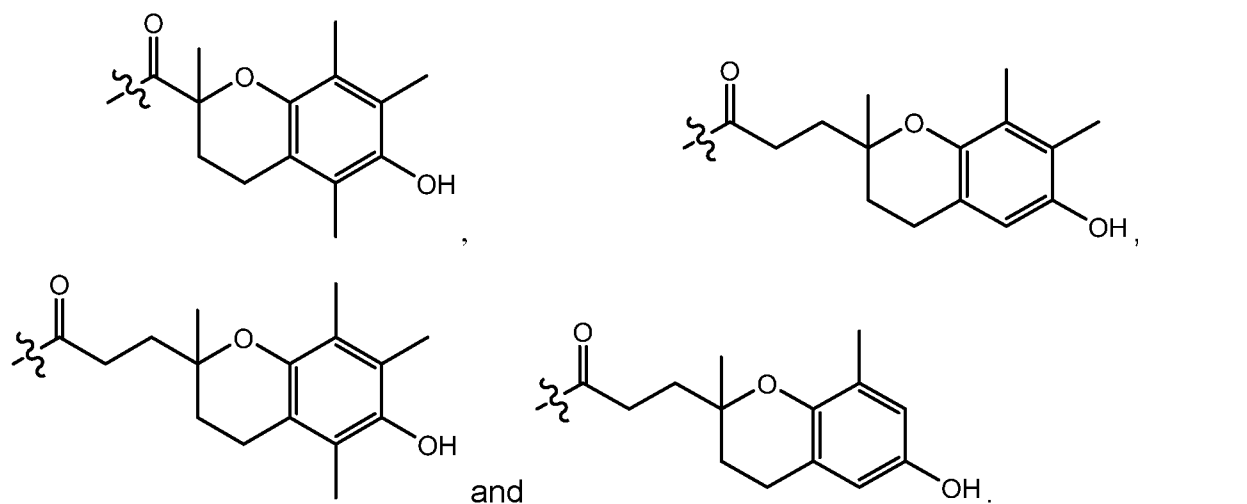
In a thirty-sixth embodiment, the present invention relates to a method according to the thirty second or thirty-third embodiment, wherein A, B, C and D are different.

15 In a thirty-seventh embodiment, the present invention relates to a method according to the thirty-sixth embodiment, wherein A, B and C are alkyl, and D is H.

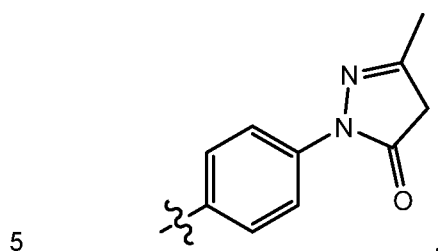
In a thirty-eighth embodiment, the present invention relates to a method according to the thirty-second or thirty-third embodiment, wherein A and B are alkyl and C and D are H.

20 In a thirty-ninth embodiment, the present invention relates to a method according to any one of the thirty-second to thirty-eighth embodiments, wherein p is 0 or 2.

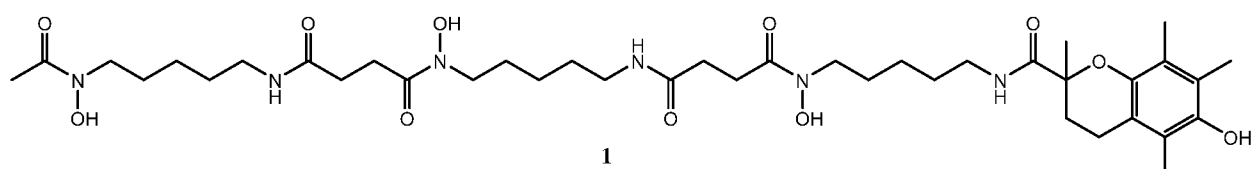
In a fortieth embodiment, the present invention relates to a method according to any one of the thirty-second to thirty-ninth embodiments, wherein E is selected from:



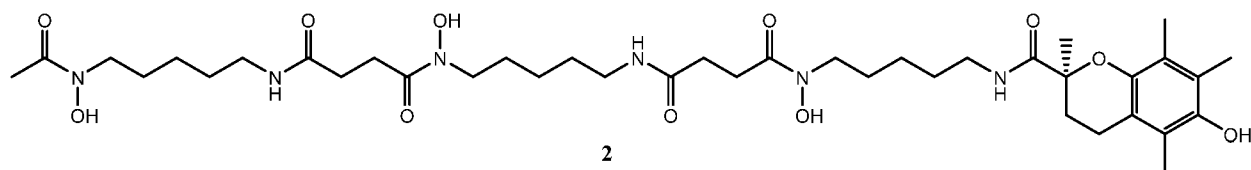
In a forty-first embodiment, the present invention relates to a method of any one of the twenty-eighth to thirty-first embodiments, wherein E is:



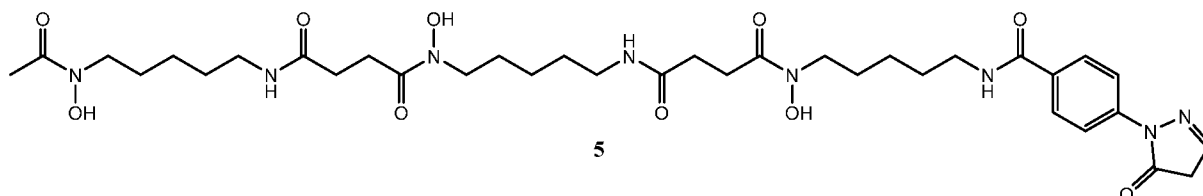
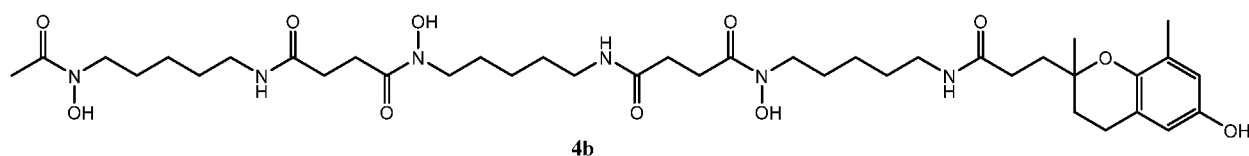
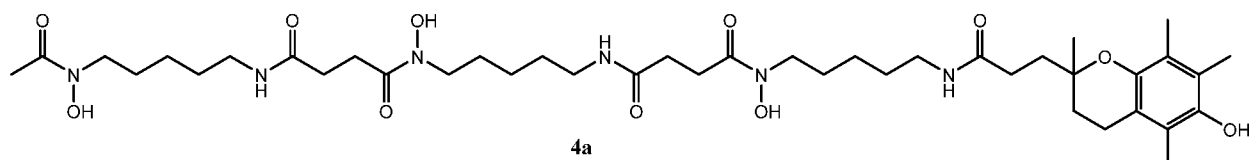
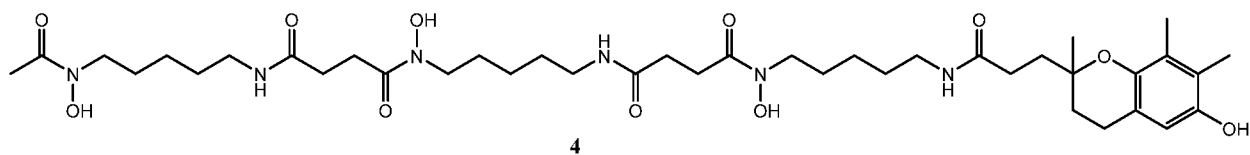
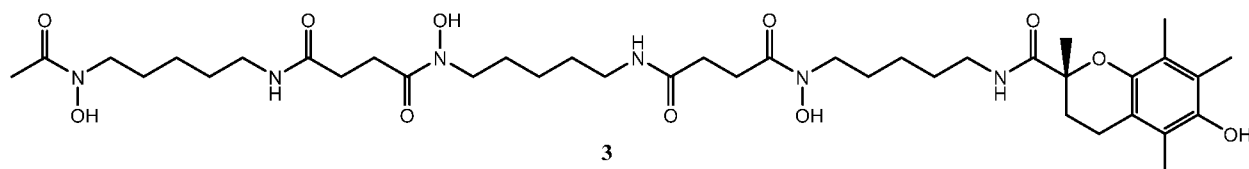
In a forty-second embodiment, the present invention relates to a method according to any one of the twenty-eighth to forty-first embodiments, wherein the compound is selected from the group consisting of:



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In a forty-third embodiment, the present invention relates to a method according to any one of the twenty-eighth to forty-second embodiments, wherein the neurodegenerative disorder is associated with metal ion dyshomeostasis.

10 In a forty-fourth embodiment, the present invention relates to a method according to the forty-third embodiment, wherein the neurodegenerative disorder is associated with accumulated brain iron.

It will be understood that the invention disclosed and defined in this specification
 extends to all alternative combinations of two or more of the individual features
 15 mentioned or evident from the text or drawings. All of these different combinations
 constitute various alternative aspects of the invention.

Embodiments of the invention will now be discussed in more detail with reference to the examples which is provided for exemplification only and which should not be considered limiting on the scope of the invention in any way.

5

Examples

Further details of experimental procedures (including instruments used) are given in Gotsbacher, MP, *et. al.* (2017) "*Analogues of desferrioxamine B designed to attenuate iron-mediated neurodegeneration: synthesis, characterization and activity in the MPTP-mouse model of Parkinson's disease*", Metallomics. DOI: 10/1039/C7MT0039A.

Preparation of compounds

*N*¹-hydroxy-*N*¹-(5-(4-(hydroxy(1-(6-hydroxy-2,5,7,8-tetramethylchromane-2-carboxamido)-1λ⁵,5λ³-pentyl)amino)-4-oxobutanamido)pentyl)-*N*⁴-(5-(*N*-hydroxyacetamido)pentyl)succinamide (DFOB-(rac)-TLX)

15 (±)-6-Hydroxy-2,5,7,8-tetramethylchromane-2-carboxylic acid (rac-TLX; 50.0 mg, 0.20 mmol), EDC (57.4 mg, 0.30 mmol) and HOBt (40.5 mg, 0.30 mmol) were dissolved in anhydrous dimethylformamide (2.2 mL), DIPEA (52.2 μL, 0.30 mmol) was added and the reaction mixture was stirred under nitrogen for 1 h. Desferrioxamine·mesylate (157.5 mg, 0.24 mmol) was added and the solution was kept stirring under nitrogen for
20 16 h. The reaction was stopped by adding ice cold water (0.5 mL) and the solvents were removed under reduced pressure. The residue was suspended in water and the suspension loaded onto a RP-C18 cartridge (2g bed weight). After washing the cartridge and residue with water (10 mL) and water:acetonitrile (9:1; 10 mL), the product was eluted with acetonitrile (10 mL) and methanol (10 mL). The organic eluates were
25 combined and the solvents removed under reduced pressure. The residue was redissolved in warm methanol, filtered (0.22 μm) and separated by RP-HPLC (Shimadzu system, semipreparative C18 ShimPack GIS column (10 x 150 mm, 5 μ), 5 mL/min, isocratic mode at 29% acetonitrile:aqueous TFA (0.05%)). The peak eluting at 21.1 min was collected. The combined fractions were reduced under pressure and the

aqueous solution frozen and freeze-dried to yield DFOB-(rac)-TLX as an off-white powder (109.0 mg, 68.8%).

^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 9.66, 7.78, 7.49, 7.22, 3.45, 3.37, 3.00, 2.57, 2.45-2.37, 2.26, 2.19-2.13, 2.09, 2.07, 1.99, 1.96, 1.74-1.67, 1.51-1.47, 1.41-1.30, 1.36, 1.25-1.19, 1.05-1.01 (Figure 3).

^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ 173.12, 171.94, 171.32, 171.29, 170.13, 145.82, 143.91, 122.70, 121.17, 120.29, 117.12, 77.24, 47.08, 46.79, 39.52, 38.44, 38.27, 29.92, 29.51, 28.85, 28.76, 27.60, 26.06, 26.01, 24.18, 23.52, 23.14, 20.39, 20.16, 12.81, 12.10, 11.83 (Figure 4).

The purity of the compound was verified by reinjecting an aliquot (10 μL ; 1.26 mM, in methanol) onto LC-MS system B, at 5-95% (phase B over 40 min). The trace contained one major peak (at 210 nm), which eluted after 22.01 min and showed absorbance maxima at 290 nm and 207 nm. Product purity was determined as 99.3% (Figure 1). No peak was observed at 450 nm, which is indicative of the absence of Fe(III)-loaded analogue (FOB-(rac)-TLX).

In selective ion mode (SIM) a search for FOB-(rac)-TLX (m/z 845.5 [$\text{M-3H+Fe(III)+H}]^+$) was performed and the integrals derived from SIM for Fe(III)-free and Fe(III)-loaded analogues compared (Figure 5). FOB-(rac)-TLX constituted 1.8% of the product.

HRMS (ESI+): m/z 815.45264 ($[\text{M+Na}]^+$); $\text{C}_{39}\text{H}_{64}\text{N}_6\text{O}_{11}\text{Na}$ requires 815.45308 (Figure 2).

The (*R*)- and (*S*)- versions of DFOB-TLX had the same ^1H and ^{13}C NMR spectra as the racemic version (Figures 3 and 4).

The synthetic method used to prepare DFOB-(rac)-TLX was also used to prepare DFOB-(*R*)-TLX and DFOB-(*S*)-TLX, in which the (rac)-TLX reagent was replaced with the cognate reagents (*R*)-TLX, (*S*)-TLX.

(R)-N¹-Hydroxy-N¹-(5-(4-(hydroxy(1-(6-hydroxy-2,5,7,8-tetra methyl-chromane-2-carboxamido)-1λ5,5λ3-pentyl)amino)-4-oxobutan-amido)pentyl)-N⁴-(5-(N-hydroxyacetamido)pentyl) succinamide.

(R)-TLX (50.0 mg, 0.20 mmol), HATU (113.9 mg, 0.30 mmol), DMF (2.2 mL),
 5 DIPEA (70 μL, 0.40 mmol), DFOB·MsO (157.5 mg, 0.24 mmol); HPLC system A: isocratic mode at 29% mobile phase B. The product eluted at 21.1 min. 98.2 mg (62.0%). HR-MS (ESI+) found *m/z* 815.45306 ([M + Na]⁺, C₃₉H₆₄N₆O₁₁Na requires 815.45308).

(S)-N¹-Hydroxy-N¹-(5-(4-(hydroxy(1-(6-hydroxy-2,5,7,8-tetra methyl-chromane-2-carboxamido)-1λ5,5λ3-pentyl)amino)-4-oxobutan-amido)pentyl)-N⁴-(5-(N-hydroxyacetamido)pentyl) succinamide.

(S)-TLX (50.0 mg, 0.20 mmol), HATU (113.9 mg, 0.30 mmol), DMF (2.2 mL),
 DIPEA (70 μL, 0.40 mmol), DFOB·MsO (157.5 mg, 0.24 mmol); HPLC system A: isocratic mode at 29% mobile phase B. The product eluted at 21.1 min. 92.2 mg
 15 (58.2%). HR-MS (ESI+) found *m/z* 815.45256 ([M + Na]⁺, C₃₉H₆₄N₆O₁₁Na requires 815.45308).

N¹-Hydroxy-N¹-(5-(4-(hydroxy(5-(3-(6-hydroxy-2,5,7,8-tetra methyl-chroman-2-yl)propanamido)pentyl)amino)-4-oxo butanamido)- pentyl)-N⁴-(5-(N-hydroxyacetamido)pentyl) succinamide.

α-CEHC (25.0 mg, 90 μmol), HATU (43.2 mg, 121 μmol), DMF (1.3 mL),
 DIPEA (32 μL, 200 μmol), DFOB·MsO (70.8 mg, 108 μmol); HPLC system A: isocratic mode at 30% mobile phase B. The product eluted at 17.9 min. 23.0 mg (31.2%). ¹H-NMR (400 MHz, DMSO-*d*₆) δ 9.70 (bs, 3H, 3 x N-OH), 7.80 (t, *J* = 5.3 Hz, 2H, 2 x C(O)NH), 7.77 (t, *J* = 5.8 Hz, 2 x C(O)NH), 3.45 (t, *J* = 7.0 Hz, 3 x 2H, H-4, H-15 & H-26), 2.99 (m, 3 x 2H, H-8, H-19 & H-30), 2.57 (t, *J* = 7.3 Hz, 2 x 2H, H-12 & H-23), 2.26 (t, *J* = 7.4 Hz, 2 x 2H, H-11 & H-22), 2.23–2.07 (m, 3H, H-33 & H-37α), 2.04 (s, 3H, CH₃), 2.01 (s, 3H, CH₃), 1.98 (s, 3H, CH₃), 1.96 (s, 3H, H-1), 1.77–1.69 (m, 5H, H-34, H-37β & H-38), 1.49 (m, 3 x 2H, H-5, H-16 & H-27), 1.38 (m, 3 x 2H, H-7, H-18 & H-29), 1.21 (m, 3 x 2H, H-6, H-17 & H-28), 1.13 (s, 3H, CH₃). ¹³C-NMR (100 MHz, DMSO-*d*₆) δ 171.93, 171.27, 170.09, 145.18,
 30

144.26, 122.56, 120.98, 120.26, 116.62, 73.44, 47.07, 46.78, 40.43, 40.15, 39.94, 39.73, 39.31, 39.10, 38.89, 38.40, 34.54, 31.15, 29.93, 29.90, 28.80, 27.58, 26.02, 23.52, 23.49, 23.38, 20.34, 20.16, 12.74, 11.79, 11.75. HR-MS (ESI+) found m/z 843.48393 ($[M + Na]^+$, $C_{41}H_{68}N_6O_{11}Na$ requires 843.48438).

5 N^1 -Hydroxy- N^1 -(5-(4-(hydroxy(5-(3-(6-hydroxy-2,7,8-trimethyl chroman-2-yl)propan-amido)pentyl)amino)-4-oxobutan amido)-pentyl)- N^4 -(5-(N -hydroxyacetamido)pentyl) succinamide.

γ -CEHC (25.0 mg, 0.20 mmol), EDC (57.4 mg, 0.30 mmol), HOBt (40.5 mg, 0.30 mmol), DMF (2.2 mL), DIPEA (52.2 μ L, 0.30 mmol), DFOB MsO (157.5 mg, 0.24 mmol);
 10 HPLC system A: isocratic mode at 29% mobile phase B. The product eluted at 16.1 min. 19.4 mg (25.4%). 1H -NMR (400 MHz, $DMSO-d_6$) δ 9.63 (s, 1H, N-OH), 9.59 (s, 2H, 2 x N-O H), 8.43 (s, 1H, acyl-OH), 7.80 (t, J = 5.5 Hz, 1H, C(O)NH), 7.76 (t, J = 5.2 Hz, 2H, 2 x C(O)NH), 6.32 (s, 1H, H-39), 3.45 (t, J = 6.9 Hz, 3 x 2H, H-4, H15 & H-26), 3.00 (m, 3 x 2H, H-8, H-19 & H-30), 2.58 (m, 3 x 2H, H-12, H-23 & H-37), 2.27 (t, J = 7.3 Hz, 2 x
 15 2H, H-11 & H-22), 2.21–2.09 (m, 3H, H-33 & H-36 α), 1.98 (s, 2 x 3H, 2 x CH₃), 1.96 (s, 3H, CH₃), 1.81–1.61 (m, 3H, H-34 & H-36 β), 1.49 (m, 3 x 2H, H-5, H-16 & H-27), 1.38 (m, 3 x 2H, H-7, H-18 & H-29), 1.21 (m, 3 x 2H, H-6, H-17 & H-28), 1.14 (s, 3H, CH₃). ^{13}C -NMR (100 MHz, $DMSO-d_6$) δ 172.96, 172.42, 172.18, 147.92, 144.13, 124.83, 121.78, 117.91, 112.22, 109.97, 74.73, 47.49, 47.23, 40.42, 35.22, 31.33, 30.33, 29.02,
 20 27.94, 26.30, 23.79, 22.02, 20.59, 12.24. HR-MS (ESI+) found m/z 829.46865 ($[M + Na]^+$, $C_{40}H_{66}N_6O_{11}Na$ requires 829.46873).

N^1 -Hydroxy- N^1 -(5-(4-(hydroxy(5-(3-(6-hydroxy-2,8-dimethyl chroman-2-yl)propan-amido)pentyl)amino)-4-oxobutan amido)-pentyl)- N^4 -(5-(N -hydroxyacetamido)pentyl) succinamide.

25 δ -CEHC (25.0 mg, 100 μ mol), HATU (51.3 mg, 135 μ mol), DMF (1.4 mL), DIPEA (26 μ L, 200 μ mol), DFOB·MsO (78.7 mg, 120 μ mol); HPLC system A: isocratic mode at 27% mobile phase B. The product eluted at 15.0 min. 21.1 mg (26.6%). 1H -NMR (400 MHz, $DMSO-d_6$) δ 9.65 (s, 1H, N-OH), 9.60 (s, 2H, 2 x N-OH), 8.53 (bs, 1H, acyl-OH), 7.80 (t, J = 5.5 Hz, 1H, C = ONH), 7.77 (t, J = 5.2 Hz, 2H, 2 x C(O)NH), 6.35 (d, J = 2.5 Hz, 1H, H-41), 6.27 (d, J = 2.7 Hz, 1H, H-39), 3.45 (t, J =
 30 7.0 Hz, 3 x 2H, H-4, H15 & H-26), 3.00 (m, 3 x 2H, H-8, H-19 & H-30), 2.63–2.53 (m, 3

x 2H, H12, H-23 & H-37), 2.26 (t, $J = 7.3$ Hz, 2 x 2H, H-11 & H-22), 2.21–2.09 (m, 3H, H-33 & H-36a), 2.00 (s, 3H, CH₃), 1.96 (s, 3H, CH₃), 1.80–1.60 (m, 3H, H-34 & H-36 β), 1.49 (m, 3 x 2H, H-5, H-16 & H-27), 1.38 (m, 3 x 2H, H-7, H-18 & H-29), 1.21 (m, 3 x 2H, H-6, H-17 & H-28), 1.15 (s, 3H, CH₃). ¹³C-NMR (100 MHz, DMSO-*d*₆) δ 171.89, 171.26, 149.44, 143.91, 125.68, 120.70, 115.45, 112.46, 74.43, 47.07, 46.77, 38.40, 34.73, 30.88, 29.90, 29.85, 28.80, 27.56, 26.02, 23.72, 23.51, 23.48, 21.82, 20.34, 15.88. HR-MS (ESI+) found m/z 815.45294 ([M + Na]⁺, C₃₉H₆₄N₆O₁₁Na requires 815.45308).

*N*¹-Hydroxy-*N*¹-(5-(4-(hydroxy(5-(4-(3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)benzamido)pentyl)amino)-4-oxobutanamido)pentyl)-*N*⁴-(5-(*N*-hydroxyacetamido)pentyl)succinamide.

EDA (50.0 mg, 0.23 mmol), HATU (104.5 mg, 0.28 mmol), DMF (3.1 mL), DIPEA (80 μ L, 0.46 mmol), DFOB·MsO (180.6 mg, 0.27 mmol); HPLC system A: a gradient of 15–26% mobile phase B over 22 min was applied. The product eluted at 21.7 min. 43.5 mg (25.0%). ¹H-NMR (400 MHz, DMSO-*d*₆) δ 9.63 (m, 3H, 3 x N-OH), 8.41 (t, $J = 5.6$ Hz, 1H), 7.89 (s, 0.7H, C⁴⁰-OH), 7.85 (dd, $J = 22.7, 9.0$ Hz, 4H, H-34 & H-35), 7.76 (t, $J = 4.7$ Hz, 2H, H), 5.37 (s, 0.8H, CH³⁹ = C⁴⁰), 3.73 (s, 0.4H, CH₂³⁹-C⁴⁰), 3.49 (t, $J = 7.1$ Hz, 2H, H-26), 3.45 (t, $J = 7.0$ Hz, 2 x 2H, H-4 & H-15), 3.24 (q, $J = 6.7$ Hz, 2H, H-30), 3.00 (q, $J = 6.5$ Hz, 4H, 2 x 2H, H-8 & H-19), 2.57 (t, $J = 7.0$ Hz, 2 x 2H, H-12 & H-23), 2.27 (t, $J = 7.2$ Hz, 2 x 2H, H-11 & H-22), 2.12 (s, 3H, CH₃), 1.96 (s, 3H, CH₃), 1.55–1.47 (m, 3 x 2H, H-5, H-16 & H-27), 1.42–1.28 (m, 3 x 2H, H-7, H-18 & H-29), 1.28–1.17 (m, 3 x 2H, H-6, H-17 & H-28). ¹³C-NMR (100 MHz, DMSO-*d*₆) δ 171.95, 171.25, 170.09, 165.44, 159.09, 130.54, 127.96, 118.84, 116.79, 47.10, 46.77, 38.40, 29.90, 28.86, 28.80, 27.56, 26.02, 23.63, 23.48, 20.32, 16.67, 13.94. HR-MS (ESI+) found m/z 783.40121 ([M + Na]⁺, C₃₆H₅₆N₈O₁₀Na requires 783.40171).

*N*¹-(5-((1*r*,3*R*,5*S*,7*r*)-3,5-Dimethyladamantane-1-carboxamido)-pentyl)-*N*¹-hydroxy-*N*⁴-(5-(*N*-hydroxy-4-((5-(*N*-hydroxyacetamido)-pentyl)amino)-4-oxobutanamido)pentyl)succinamide.

A solution of dimethyladamantane-1-carboxylic acid (260 mg, 1.25 mmol), EDC (340 mg, 1.78 mmol), and NHS (168 mg, 1.46 mmol) in DMF (10 mL) was stirred under nitrogen at 25 °C for 20 h. Half of the DMF (5 mL) was removed *in vacuo* and methanol

(2 mL) and water (6 mL) were added to promote precipitation. The precipitate was washed with water (5 x 10 mL) to yield the NHS-activated ancillary fragment as a white solid. A solution of this compound, DFOB (442 mg, 0.672 mmol), and NaOH (2 mg, 0.05 mmol) in methanol (20 mL) was stirred at reflux at 70 °C for 3 h. Reaction progress was monitored by TLC. The solution was evaporated to dryness *in vacuo* and the resulting solid was washed with diethyl ether (5 x 5 mL) and water (5 x 5 mL) before dissolution in methanol (4 mL). The compound was purified by semi-preparative RP-HPLC system C to give the product as a white solid (223.0 mg, 44%). ¹H-NMR (400 MHz, DMSO-*d*₆) δ 9.64 (s, 3H, OH), 7.76 (t, 2H, *J* = 4.8 Hz, NH), 7.30 (t, *J* = 5.6 Hz, 1H, NH), 3.42 (t, *J* = 6.8, 4H, CH₂), 3.42 (t, *J* = 7.2 Hz, 2H, CH₂), 2.97 (q, *J* = 6.0 Hz, 6H, CH₂), 2.55 (t, *J* = 7.2 Hz, 4H, CH₂), 2.47 (quint, *J* = 2.0 Hz, 2H, CH₂), 2.24 (t, *J* = 7.2 Hz, 4H, CH₂), 2.00 (quint, *J* = 2.8 Hz, 1H, CH), 1.93 (s, 3H, CH₃), 1.54 (d, *J* = 2.0 Hz, 4H, CH₂), 1.47 (quint, *J* = 6.8, 6H, CH₂), 1.40–1.00 (m, 18H, CH₂), 0.77 (s, 6H, CH₃). ¹³C-NMR (100 MHz, DMSO-*d*₆) δ 176.9, 172.4, 171.7, 171.7, 170.6, 50.8, 47.5, 47.2, 45.4, 42.8, 42.1, 38.8, 38.8, 37.9, 31.1, 30.9, 30.3, 29.3, 29.2, 28.0, 26.5, 23.9, 23.8, 20.8. HR-MS (ESI+) found *m/z* 773.4778 ([M + Na]⁺, C₃₈H₆₆N₆O₉Na requires 773.47890).

Assays

Details of methods for the following assays are in: Gotsbacher, MP, *et. al.* (2017) “Analogues of desferrioxamine B designed to attenuate iron-mediated neurodegeneration: synthesis, characterization and activity in the MPTP-mouse model of Parkinson’s disease”, Metallomics. DOI: 10/1039/C7MT0039A.

Iron chelation

Ascorbate autoxidises in aqueous solutions. In the presence of Fe³⁺, this oxidation progresses significantly faster. In the presence of Fe³⁺ and a metal chelator (e.g. DFOB or DFOB analogues), the oxidation process is reduced to a minimum. ROS-mediated auto-oxidation of ascorbic (AH₂) to dehydroascorbic acid was monitored at absorbance at λ = 265 nm (first-rate order 6 x 10⁻⁷ s⁻¹ at pH 7.0, 25°C).

The graphs in Figure 24 show that DFOB and its derivatives (DFOB-(rac)-TLX, DFOB-(R)-TLX, DFOB-(S)-TLX, DFOB- α -CEHC, DFOB- δ -CEHC, DFOB- γ -CEHC and DFOB-EDA) are effectively chelating iron and minimising ascorbate autoxidation.

Plasma Protein Binding

- 5 Rapid equilibrium dialysis was used to determine human plasma protein binding of DFOB, DFOB-(rac)-TLX, DFOB- α -CEHC, DFOB- γ -CEHC, DFOB- δ -CEHC and DFOB-EDA. Approximately 14% of DFOB bound to plasma proteins, which was in agreement with previous work (<10% DFOB).³ DFOB-(R)-TLX and DFOB-(S)-TLX were not expected to show different protein binding to the racemic mixture DFOB-(rac)-TLX
10 and were excluded from this part of the study. DFOB-EDA was unstable ($t_{1/2}$ = 28 min) in human plasma over the 4-h time period to reach equilibrium. DFOB-(rac)-TLX, DFOB- α -CEHC, DFOB- γ -CEHC, DFOB- δ -CEHC showed plasma protein binding ranging between 86-97% (Table 1). DFOB (unbound fraction 86%) is rapidly cleared in the urine within minutes to an hour, as an additional factor that could compromise BBB uptake.
15 The higher degree of protein binding shown by DFOB-(rac)-TLX, DFOB- α -CEHC, DFOB- γ -CEHC, DFOB- δ -CEHC (unbound fraction 3–24%) may increase circulation time to improve bioavailability and systemic distribution to support BBB uptake of the drug *via* passive mechanisms.

20

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Table 1. Measurements of plasma protein binding, and antioxidant activity of DFOB, DFOB-(*rac*)-TLX, DFOB-(*R*)-TLX, DFOB-(*S*)-TLX, DFOB- α -CEHC, DFOB- γ -CEHC, DFOB- δ -CEHC, DFOB-EDA and standard compounds, as determined by ascorbic acid autoxidation and ABTS^{••} assays.

CMD	plasma protein binding (%)	AH ₂ autoxid. (% inhibition) ^a	ABTS ^{••} IC ₅₀ (μ M) ^b
DFOB	14.0	95.8	5.92 (5.67 – 6.17) R ² = 0.991
DFOB-(<i>rac</i>)-TLX	93.2	94.1	4.12 (3.88 – 4.36) R ² = 0.985
DFOB-(<i>R</i>)-TLX	ND ^c	91.9	4.18 (3.96 – 4.40) R ² = 0.987
DFOB-(<i>S</i>)-TLX	ND	94.8	4.20 (3.97 – 4.44) R ² = 0.985
DFOB- α -CEHC	85.5	86.9	9.84 (9.17 – 10.55) R ² = 0.974
DFOB- γ -CEHC	97.3	91.4	6.95 (6.52 – 7.39) R ² = 0.981
DFOB- δ -CEHC	88.0	91.7	8.03 (7.58 – 8.50) R ² = 0.984
DFOB-EDA	NS ^d	88.8	9.06 (8.17 – 9.98) R ² = 0.948
(<i>rac</i>)-TLX	ND	71.5	10.19 (9.709 – 10.68) R ² = 0.987
EDA	ND	81.5	19.23 (15.99 – 23.38) R ² = 0.801

- 5 ^a Inhibition (%) at $t = 30$ min in ascorbic acid (AH₂) autoxidation assay. ^b IC₅₀ at $t = 3$ min in ABTS^{••} antioxidant assay. ^c ND = not determined. ^d NS = not stable under the assay conditions.

Antiradical ABTS^{••} assay

The blue/green ($\lambda_{\max}$ 734 nm) radical monocation of 2,2'-azino-bis-(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS^{••}) as generated by potassium persulfate oxidation of ABTS was reduced in the presence of DFOB, DFOB-(*rac*)-TLX, DFOB-(*R*)-TLX, DFOB-(*S*)-TLX, DFOB- α -CEHC, DFOB- γ -CEHC, DFOB- δ -CEHC, DFOB-EDA, (*rac*)-TLX or EDA, as a measure of antiradical activity (Table 1, Fig. 27 – data shown for DFOB, (*rac*)-DFOB, DFOB-(*rac*)-TLX). The IC₅₀ values for DFOB-(*rac*)-TLX, DFOB-(*R*)-TLX, DFOB-(*S*)-TLX, compared well, suggesting that the antioxidant potential of these compounds was independent of the chiral center. DFOB displayed an IC₅₀ of 5.9 μ M. In comparison, the antioxidant standard (*rac*)-TLX displayed an IC₅₀ of 10.2 μ M. The other standard, EDA, was significantly less active, as shown by its IC₅₀ value of 19.2 μ M. Each of DFOB-(*rac*)-TLX, DFOB-(*R*)-TLX, DFOB-(*S*)-TLX, DFOB- α -CEHC, DFOB- γ -CEHC, DFOB- δ -CEHC, DFOB-EDA showed IC₅₀ values similar to, or lower than, (*rac*)-TLX. These data support an additive antiradical potential for conjugates DFOB-(*rac*)-

TLX, DFOB-(*R*)-TLX, DFOB-(*S*)-TLX, DFOB- α -CEHC, DFOB- γ -CEHC, DFOB- δ -CEHC, DFOB-EDA, compared to the individual parent molecules (i.e. DFOB-(*rac*)-TLX compared to DFOB and (*rac*)-TLX), and support that the compounds had antioxidant activity ascribable to the ancillary fragment.

5

In vivo studies

Motor skills

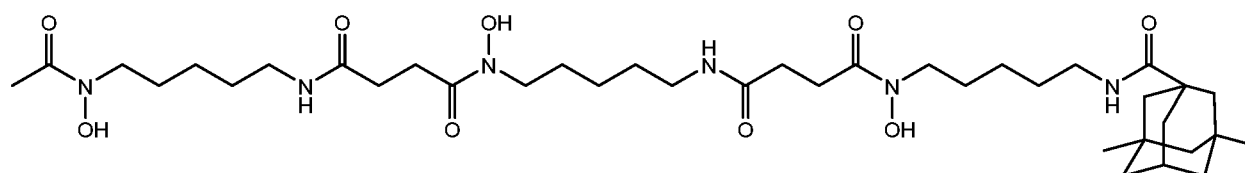
The neurotoxin MPTP, which recapitulates aspects of Parkinson's disease (PD) including brain iron deposition,² was administered to the mice on day 1 and each compound (vehicle, DFOB, DFOB-AdAdMe, DFOB-(*rac*)-TLX) in diluent (distilled water containing 10% DMSO and 0.5% carboxymethylcellulose (CMC)) was administered by IP injection at a concentration of 40 μ mol/kg once per day for 20 days post MPTP injection.

Compound	Molecular mass	Dose (40 μmol/kg) ^a	Dose (mg/kg)
DFOB.mesylate	656.79 g mol ⁻¹	40 μmol/kg	26 mg/kg
DFOB-AdA _{dMe}	750.98 g mol ⁻¹	40 μmol/kg	30 mg/kg
DFOB-(<i>rac</i>)-TLX	792.97 g mol ⁻¹	40 μmol/kg	32 mg/kg

^a Single dose selected based on dosing used in other reports for DFOB and other iron chelators

15 for PD.

The structure of DFOB-AdA_{dMe} (which can be prepared by following the procedure set out in US 8,309,583) is as follows:



Each treatment group contained 15 mice. The first phase of the study used the Pole test to measure the effect of the compounds on the speed of complex movements as the mouse equivalent to bradykinesia (slowness of movement) in people with PD.³ DFOB-(rac)-TLX significantly reduced the rotarod Turn Time (how long the mice take to turn around on the Pole), compared to vehicle and DFOB (see Figure 25). This correlates with an improvement in motor skills.²

Parkinson's disease (PD)

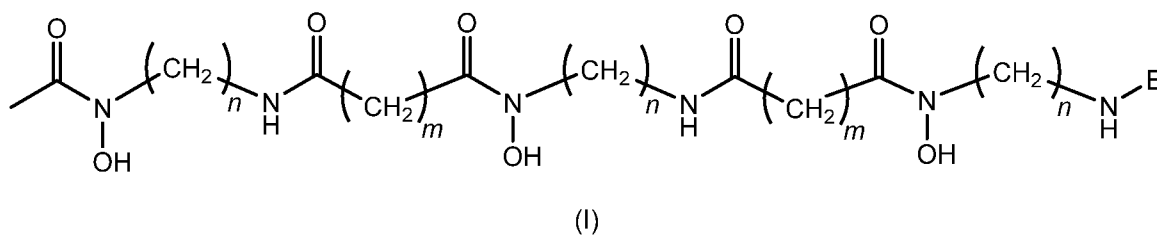
The compounds DFOB-(rac)-TLX and DFOB-AdA_{dMe} were tested in the MPTP-mouse model of PD, which is a widely accepted animal model of PD that recapitulates iron deposition in the substantia nigra. The MPTP neurotoxin was administered (65 mg/kg with 4 injections, 2 h apart) to 4 group of mice (C57BL/6 at about 14 weeks of age; each group = 15) and the compounds (40 micromol/kg) were administered at 1 day after the final MPTP injection. The compounds were administered (i.p.) daily (40 micromol/kg) for 20 days. DFOB was also tested. On day 18-20, the Pole test was performed. All mice were culled on day 21 and after appropriate processing, the substantia nigra was cut using a cryostat at 30 micrometers, and stained with 2% Neutral Red solution for 2.5 min and then re-hydrated and cover slipped. Neurons were counted using the Stereo Investigator program. Administration of DFOB to the MPTP-lesioned mouse (40 µmol/kg/day for 20 days; i.p. commencing 24 h after the last MPTP injection) did not protect neuronal cells. Administration of DFOB- AdA_{dMe} or DFOB-(rac)-TLX to the MPTP-lesioned mouse resulted in significant protection of neurons (up to 89% of the non-lesioned animals), demonstrating the neuroprotective potential of these compounds.

References

1. Hare, D. J.; Adlard, P. A.; Doble, P. A.; Finkelstein, D. I. (2013) *Metallomics*, 5, 91-109.
2. Park, G.; Park, Y.-J.; TYang, H. O.; Oh, M. S. (2013) *Pharmacol. Biochem. Behav.*, 104, 163-168.
3. Wishart, D. S., Knox, C., Guo, A. C., Shrivastava, S., Hassanali, M., Stothard, P., Chang, Z., and Woolsey, J. (2006) *Nucl. Acids Res.* 34, D668-D672.

CLAIMS

1. A compound of formula (I):



5

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

each n is independently selected from 4 and 5;

m is 2; and

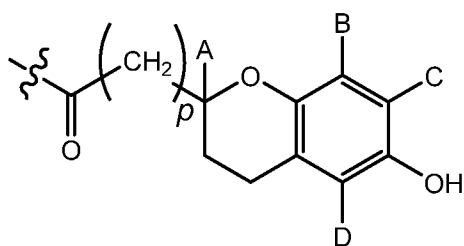
E is a vitamin E analogue or an edaravone analogue.

10

2. The compound of claim 1, wherein n is 5.

3. The compound of claim 1 or claim 2, wherein p is 0 or 2.

4. The compound of any one of the preceding claims, wherein E is:



wherein:

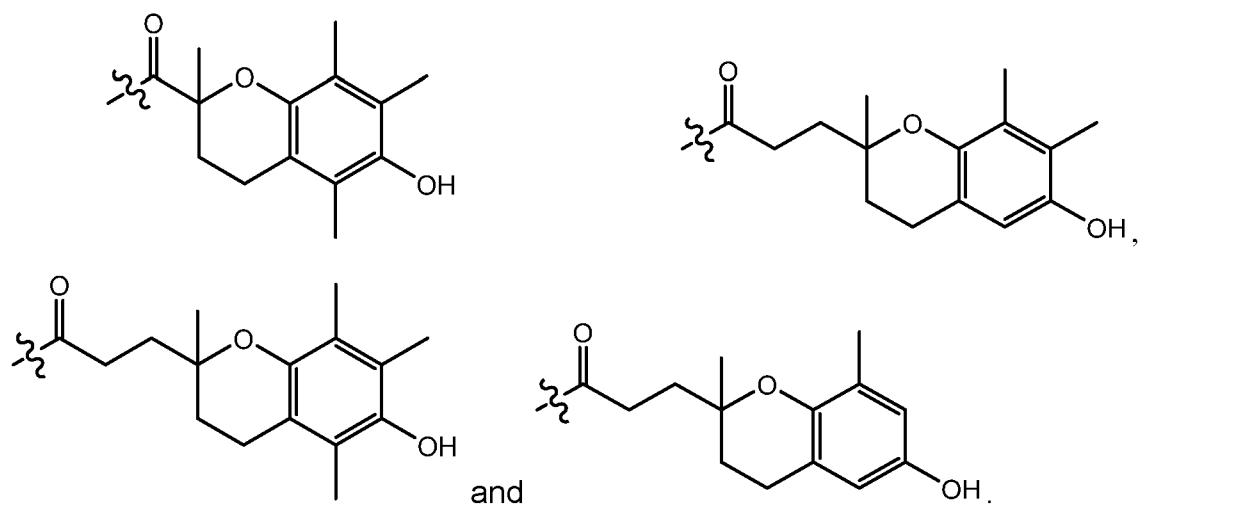
15

A, B, C and D are independently selected from H and alkyl, and

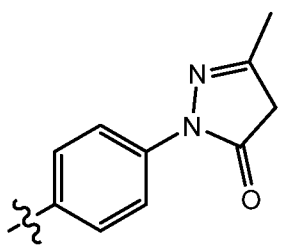
p is 0, 1 or 2.

5. The compound of claim 4, wherein alkyl is C_1 to C_3 alkyl.

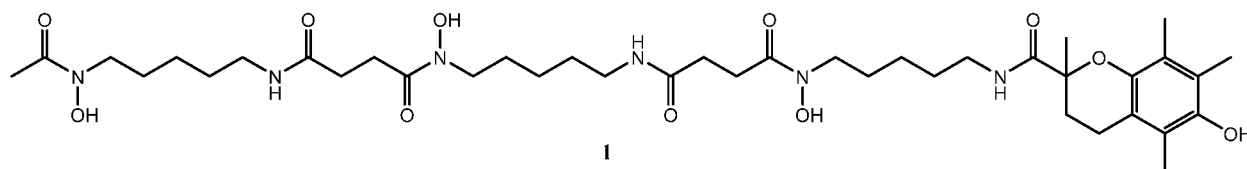
6. The compound of claim 4 or claim 5, wherein A, B, C and D are alkyl.
7. The compound of claim 4 or claim 5, wherein A, B and C are alkyl, and D is H.
8. The compound of claim 4 or claim 5, wherein A and B are alkyl and C and D are H.
9. The compound of any one of claims 4 to 8, wherein E is selected from

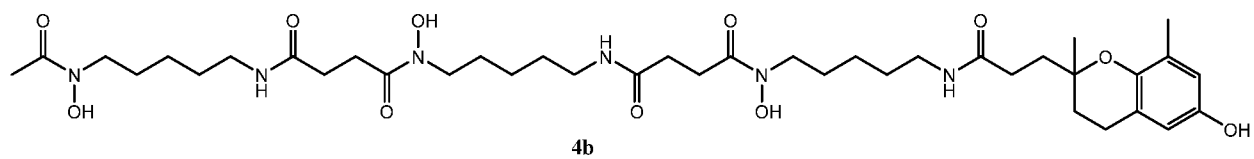
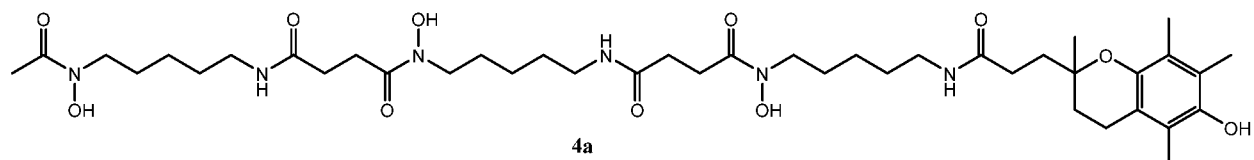
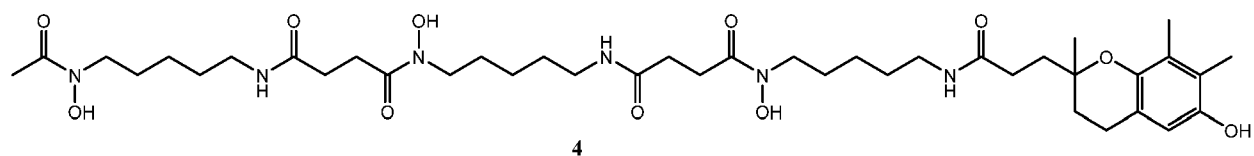
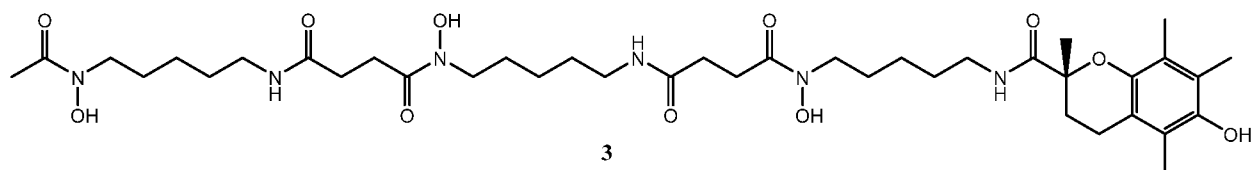
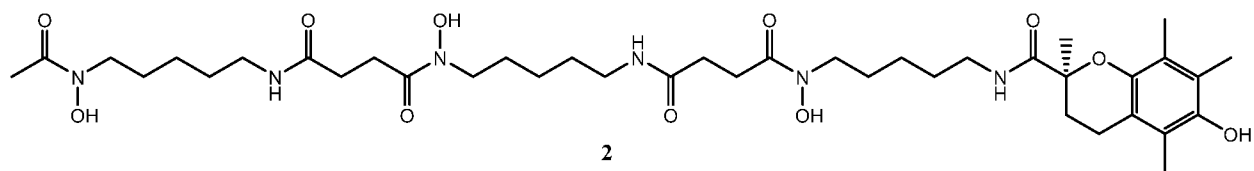


- 10 10. The compound of any one of claims 1 to 3, wherein E is:

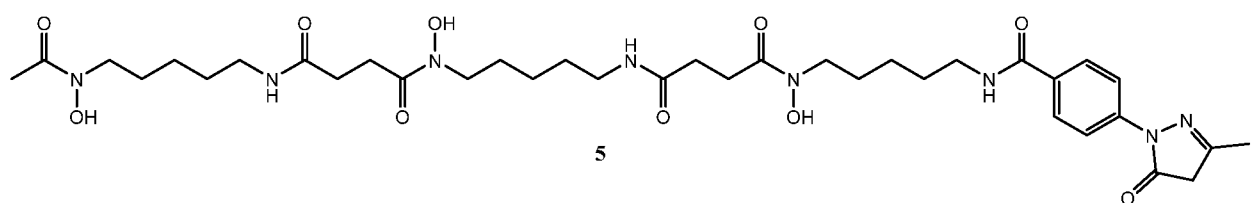


11. The compound of any one of claims 1 to 10, wherein the compound is selected from the group consisting of:

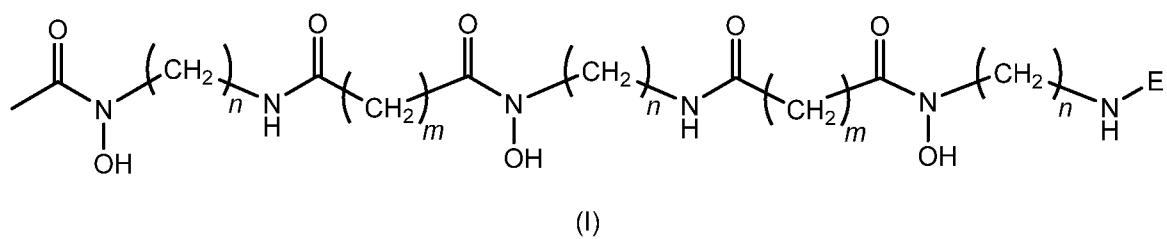




5



12. A pharmaceutical composition including a compound of formula (I):



10

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

each n is independently selected from 4 and 5;

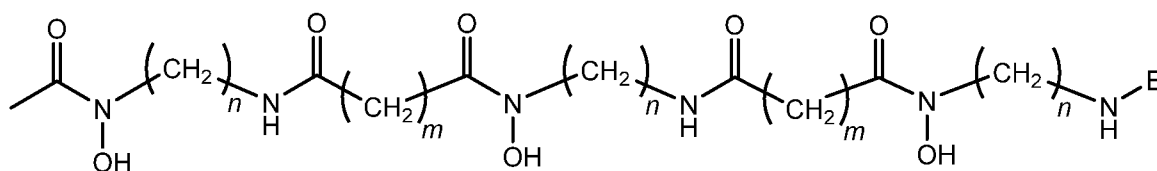
m is 2; and

E is a vitamin E analogue or an edaravone analogue;

together with a pharmaceutically acceptable carrier, diluent or excipient.

- 5 13. The pharmaceutical composition of claim 12, wherein the composition is suitable for parenteral or oral administration.

14. A method of treating a neurodegenerative disorder in a patient including administration to the patient of a therapeutically effective amount of a compound of formula (I):



(I)

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

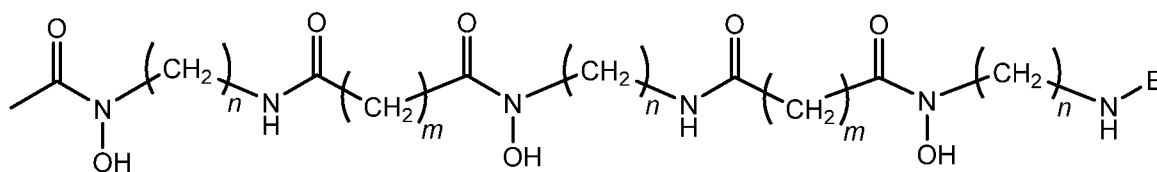
each n is independently selected from 4 and 5;

m is 2; and

- 15 E is a vitamin E analogue or an edaravone analogue.

15. The method of claim 14, wherein the administration is selected from parenteral or oral administration.

16. Use of an effective amount of a compound of formula (I):



(I)

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

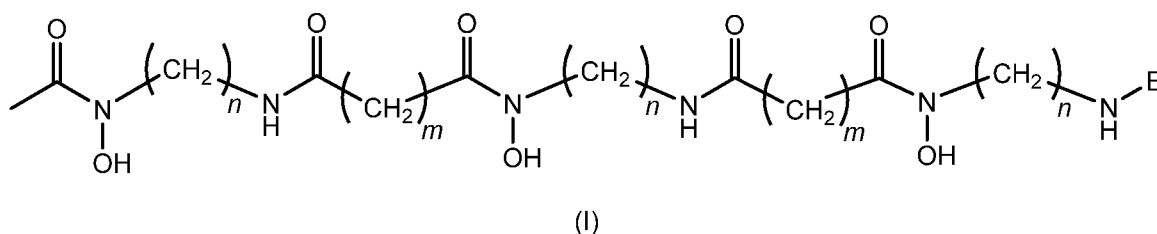
each n is independently selected from 4 and 5;

m is 2; and

E is a vitamin E analogue or an edaravone analogue,

- 5 in the preparation of a medicament for the treatment of a neurodegenerative disorder.

17. Use of an effective amount of a compound of formula (I):



- 10 or a pharmaceutically acceptable salt or prodrug thereof, wherein:

each n is independently selected from 4 and 5;

m is 2; and

E is a vitamin E analogue or an edaravone analogue

for the treatment of a neurodegenerative disorder.

- 15 18. The method of claim 14 or claim 15, or the use of claim 16 or claim 17, wherein the neurodegenerative disorder is selected from Parkinson's disease, Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis, Friedreich's ataxia, and Multiple Sclerosis.

Figure 1

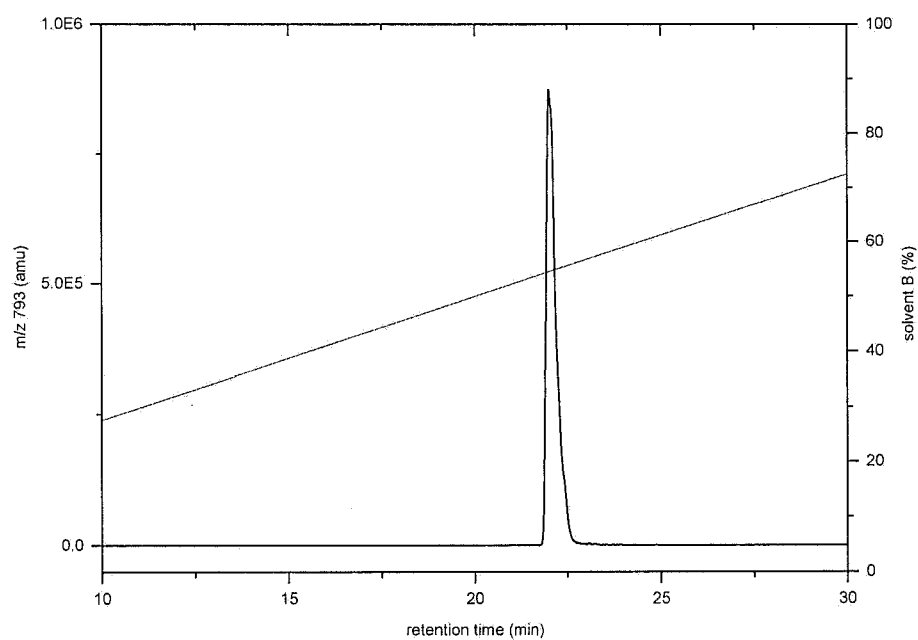


Figure 2

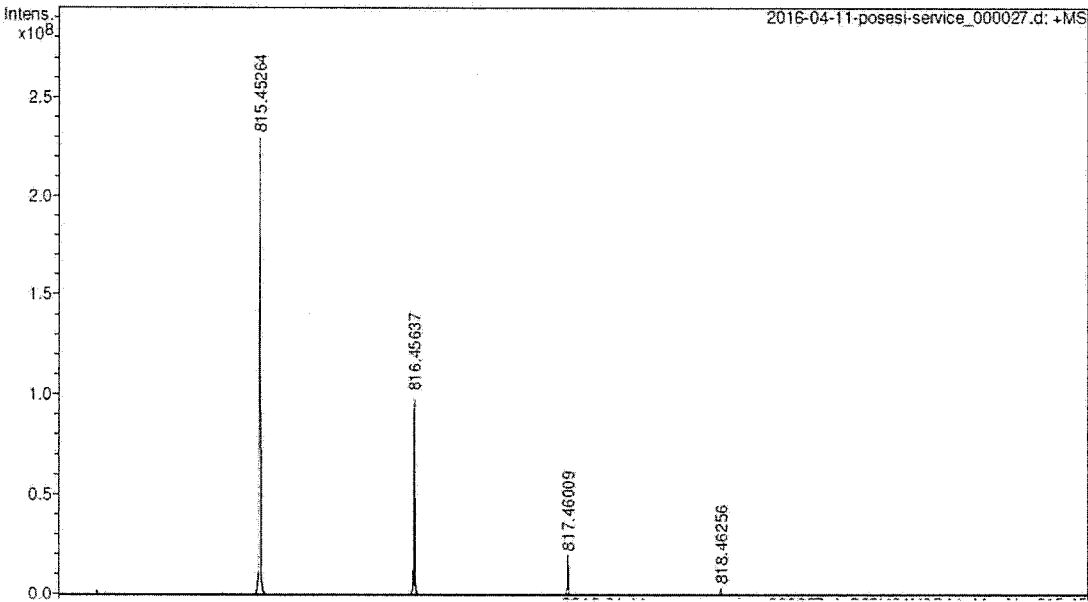


Figure 3

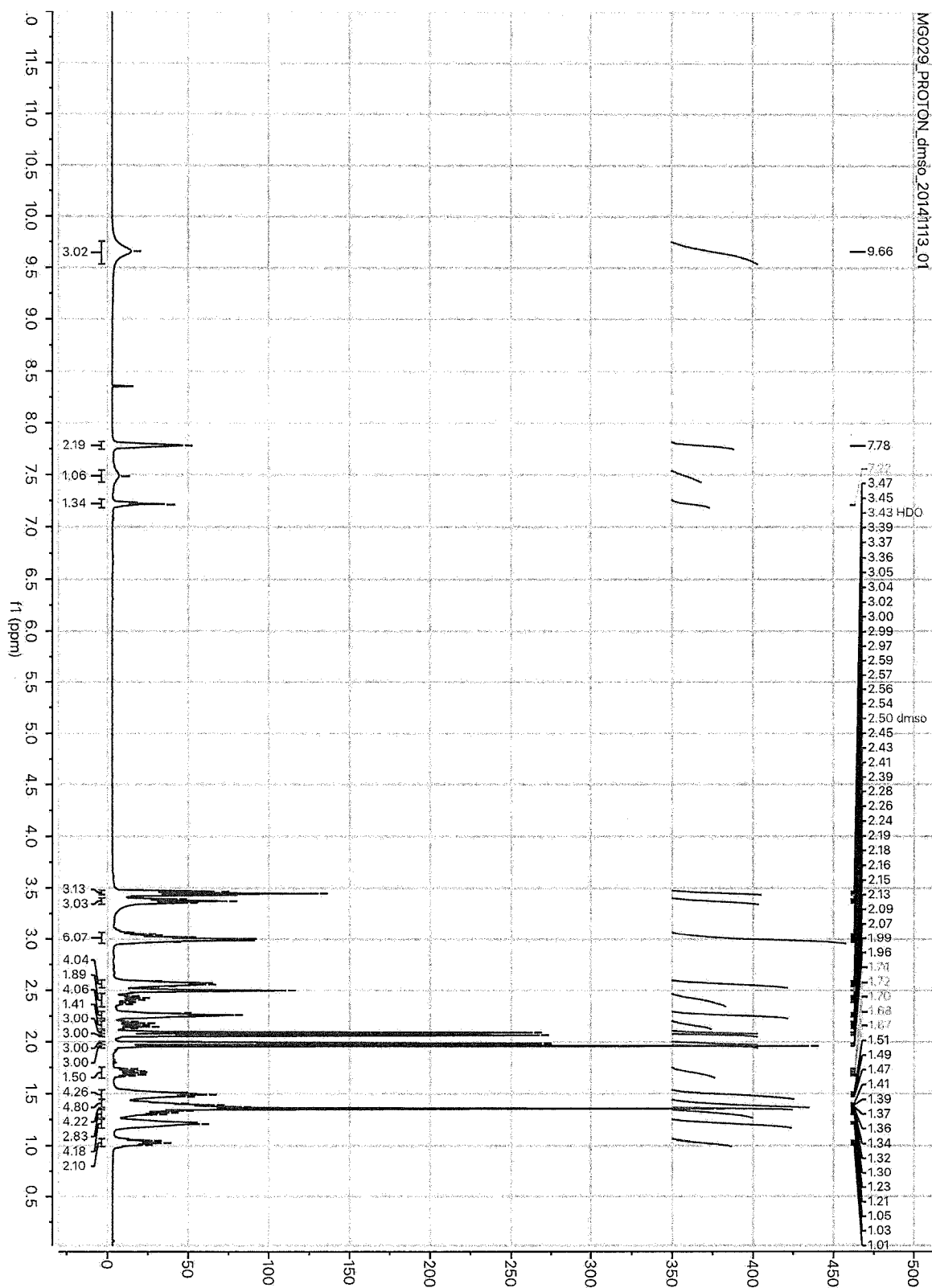


Figure 4

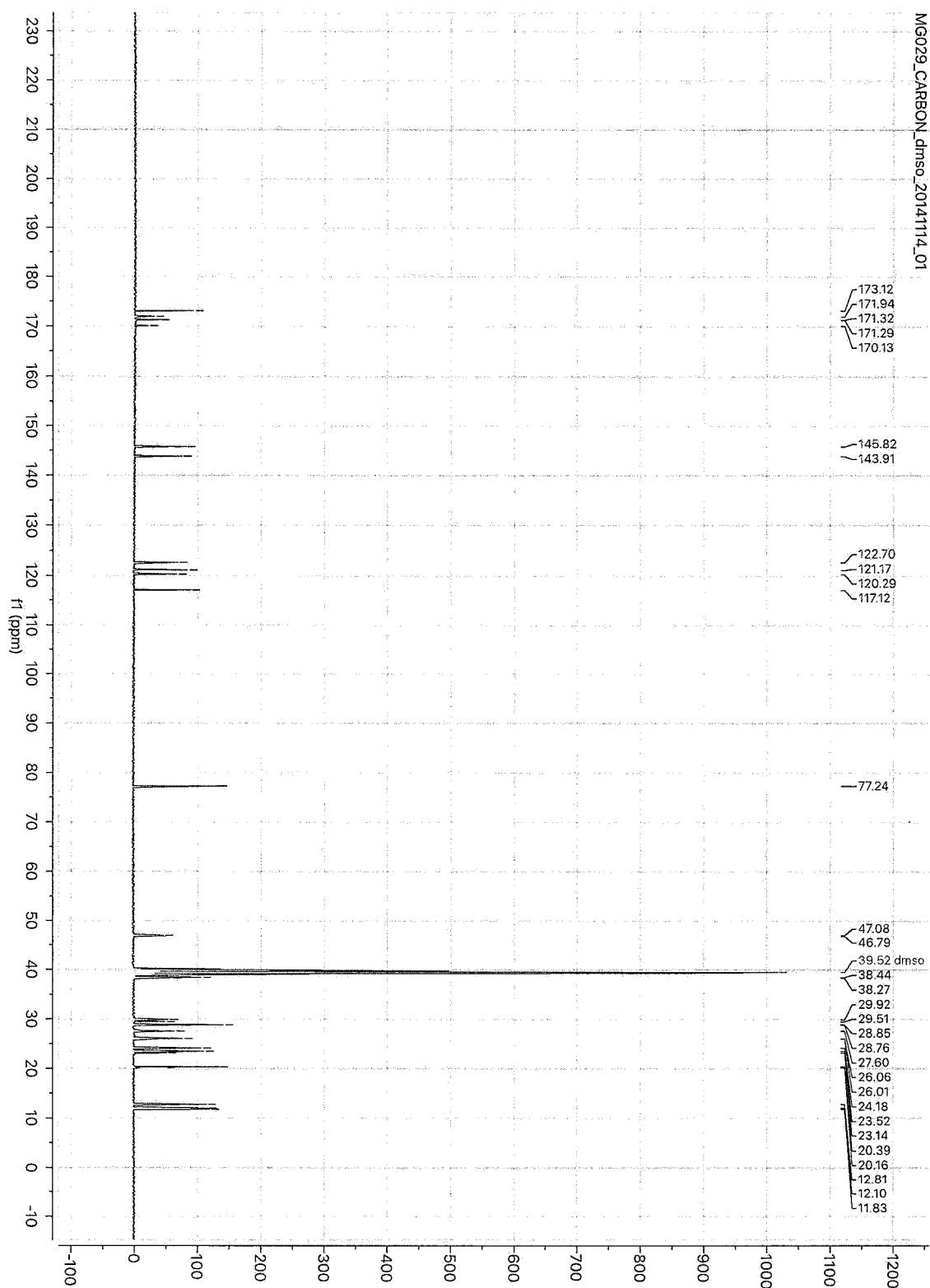


Figure 5

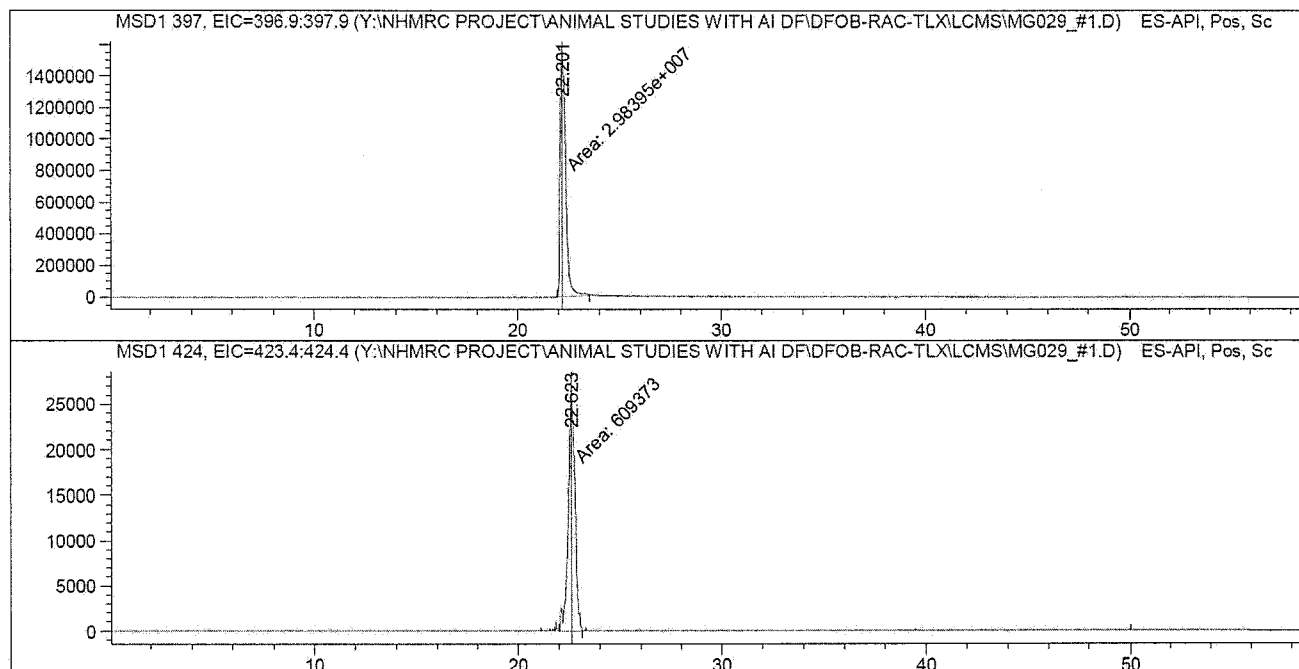


Figure 6

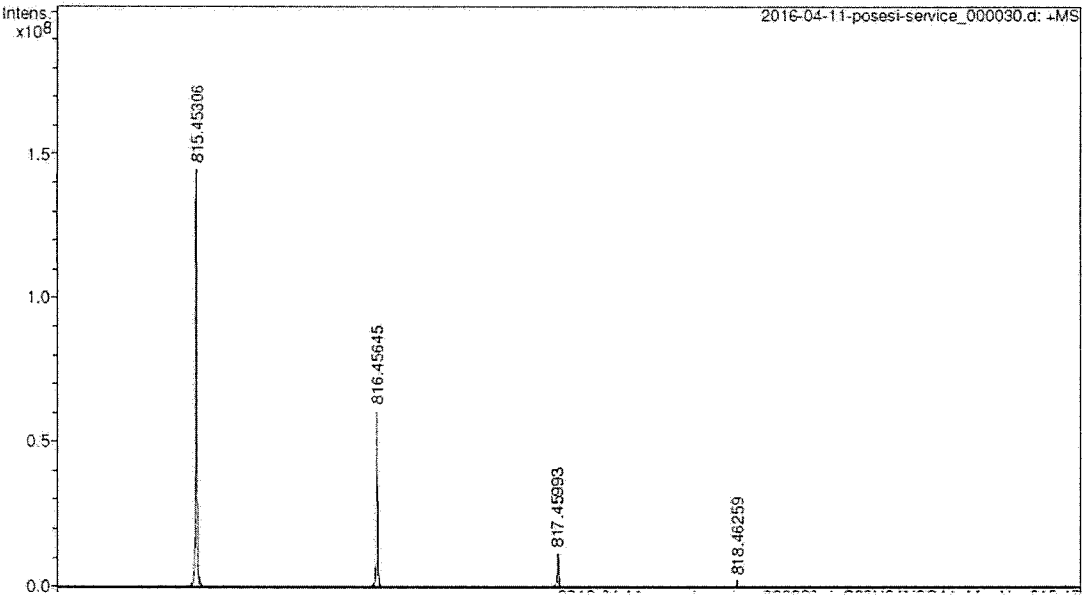


Figure 7

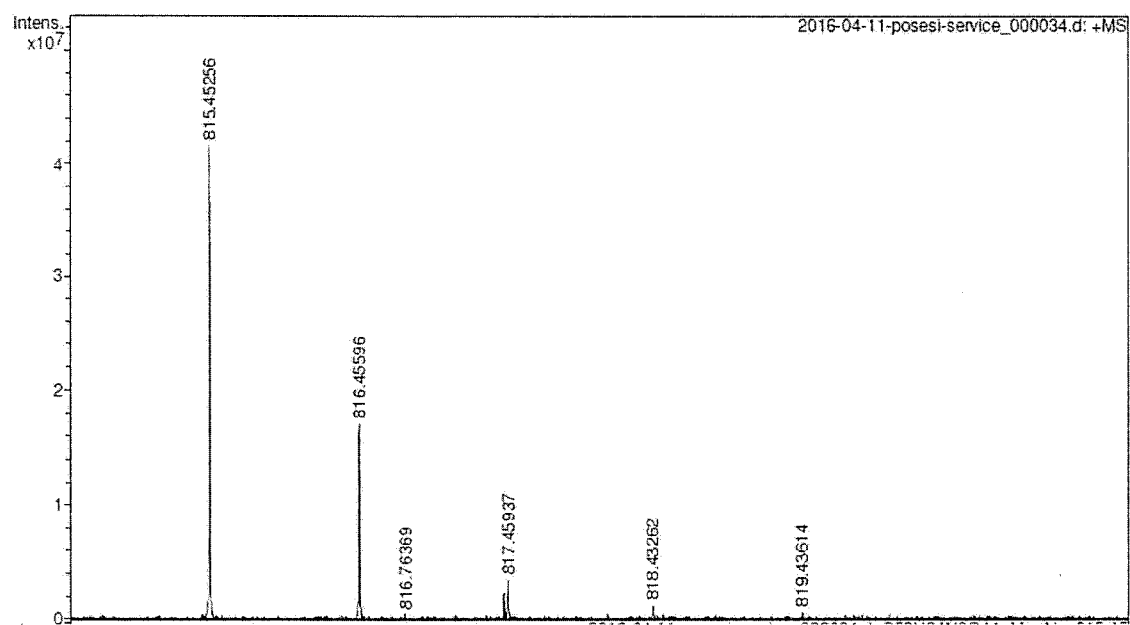


Figure 8

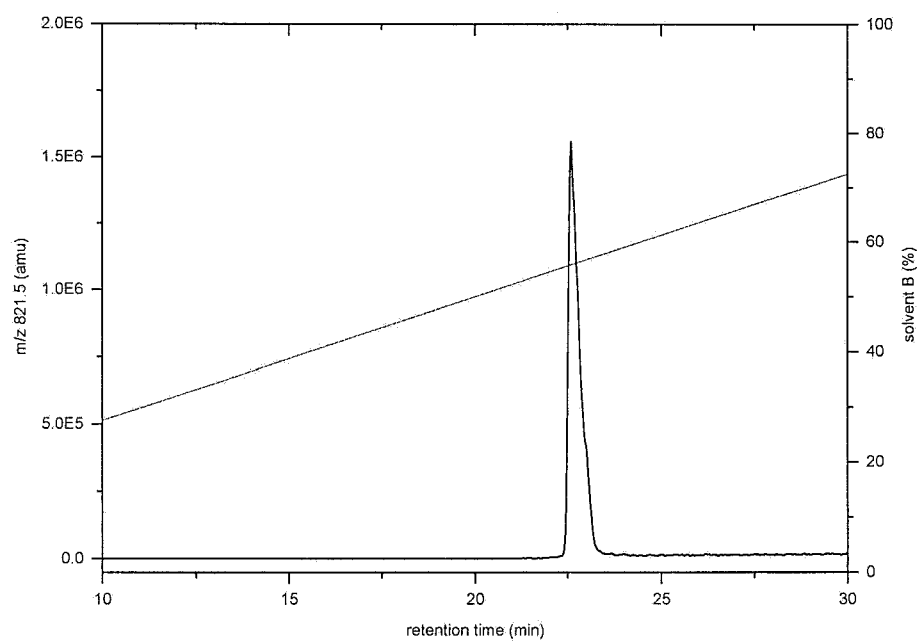


Figure 9

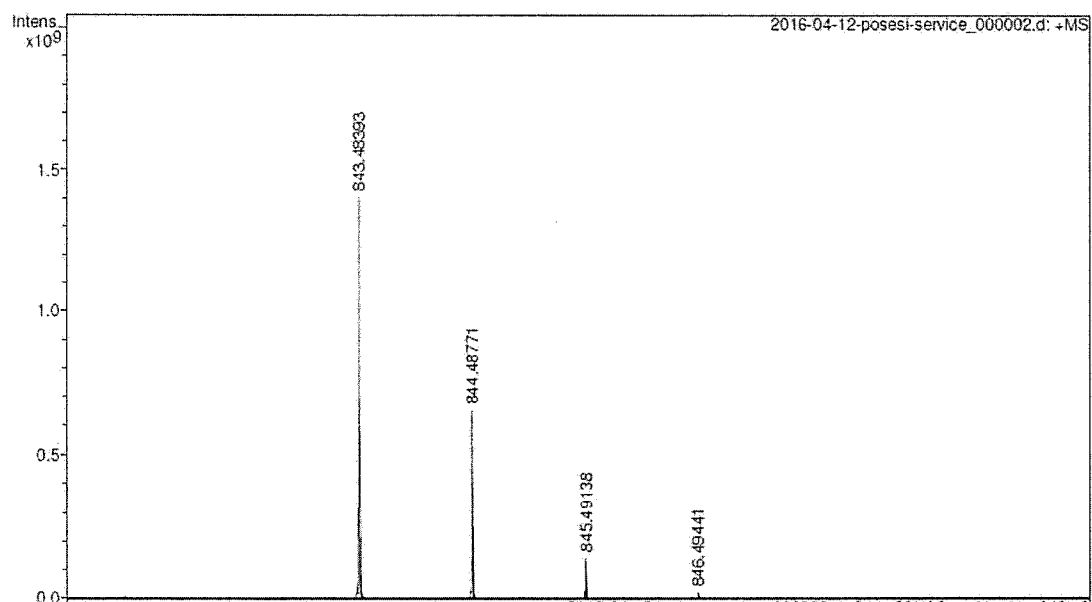


Figure 10

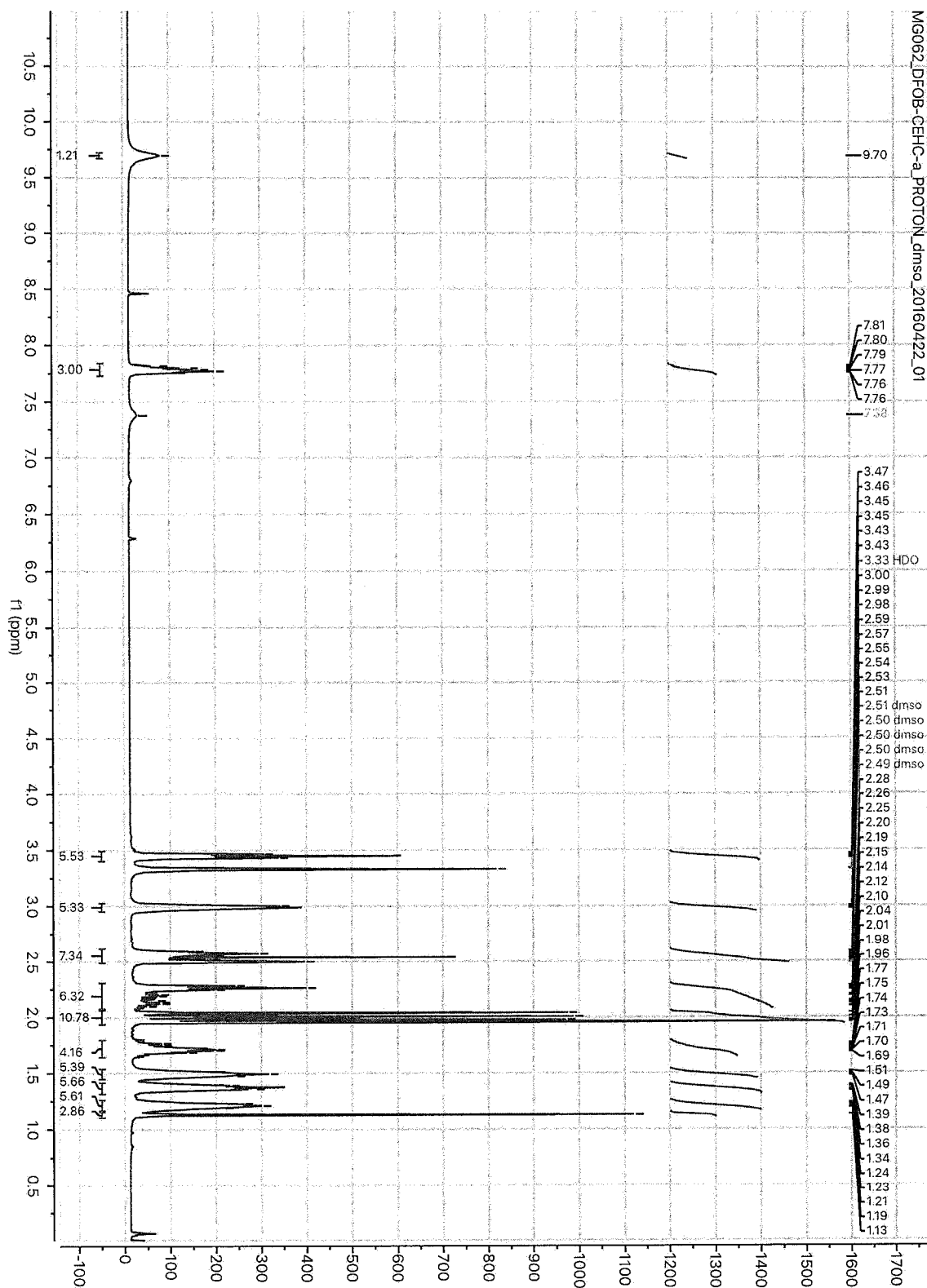


Figure 11

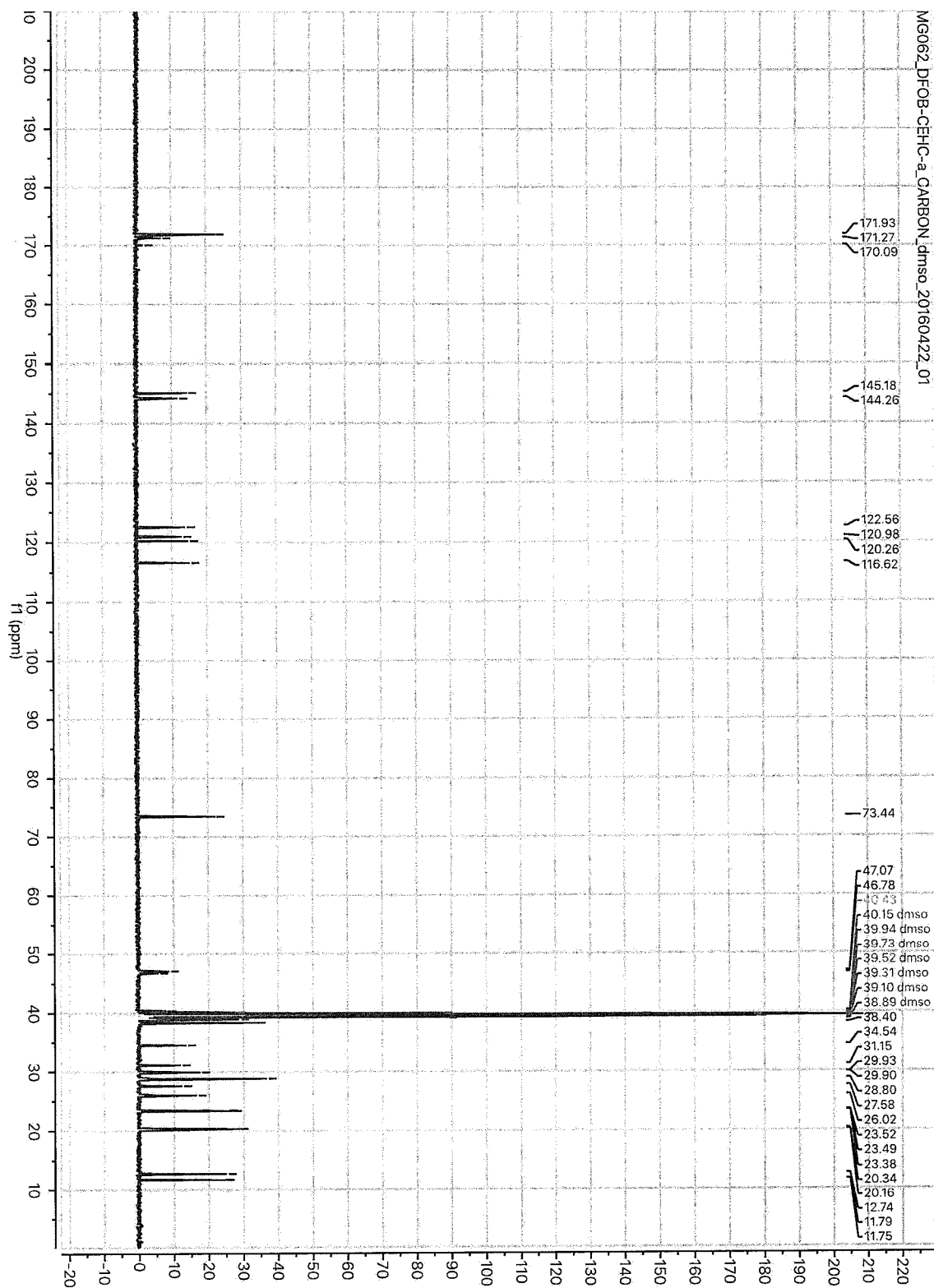


Figure 12

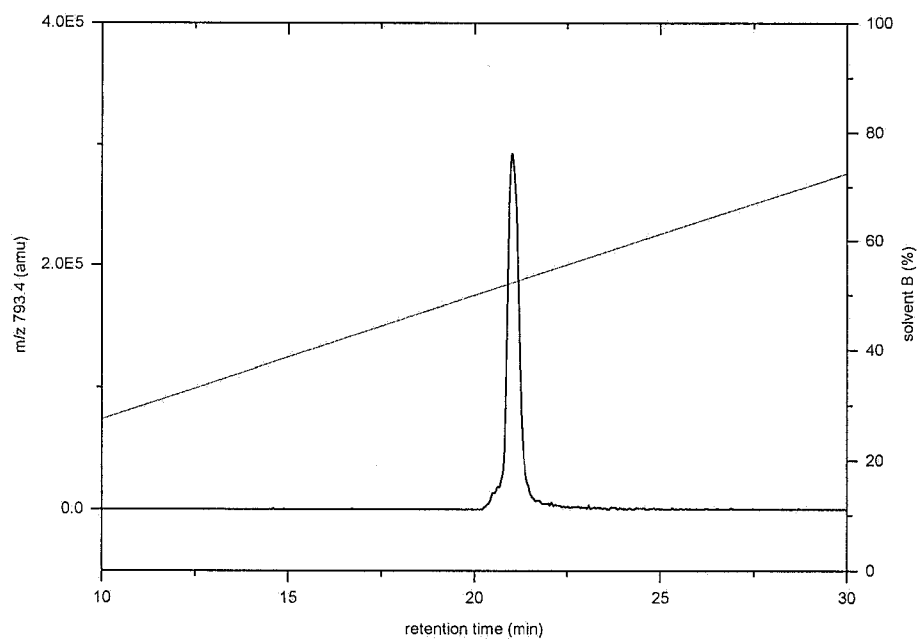


Figure 13

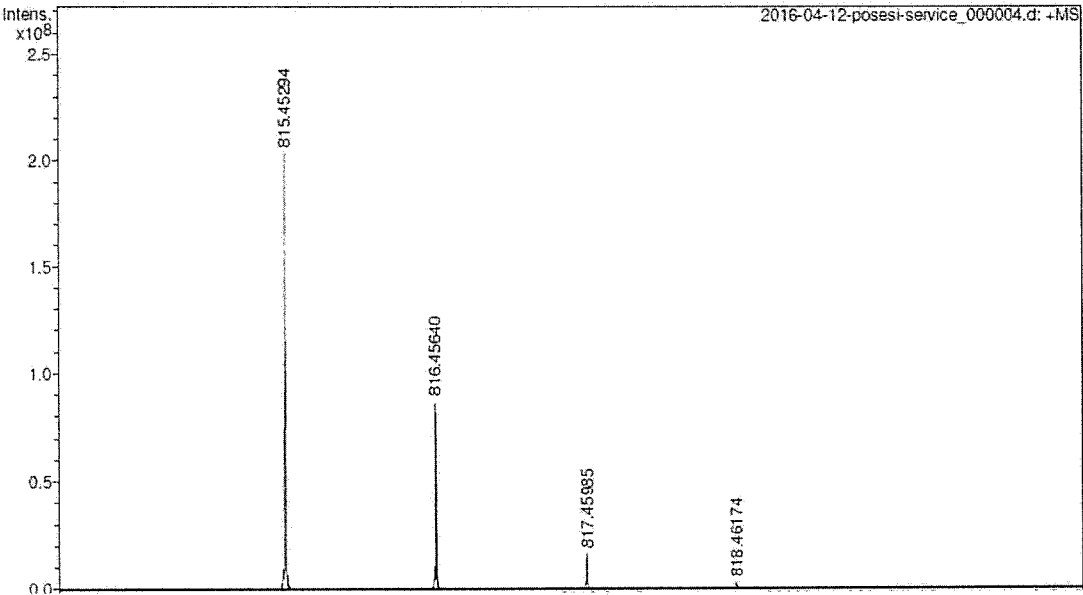


Figure 14

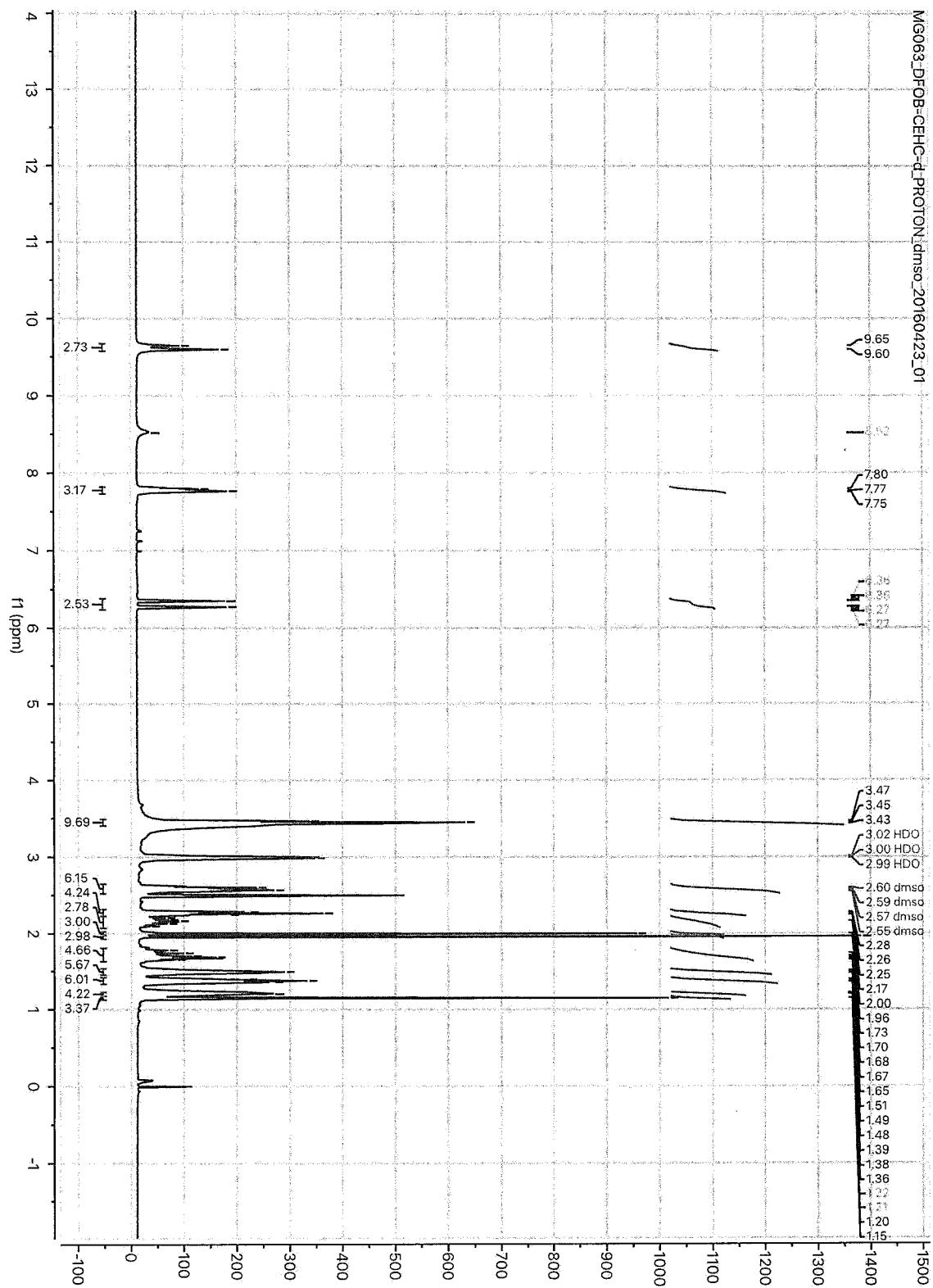


Figure 15

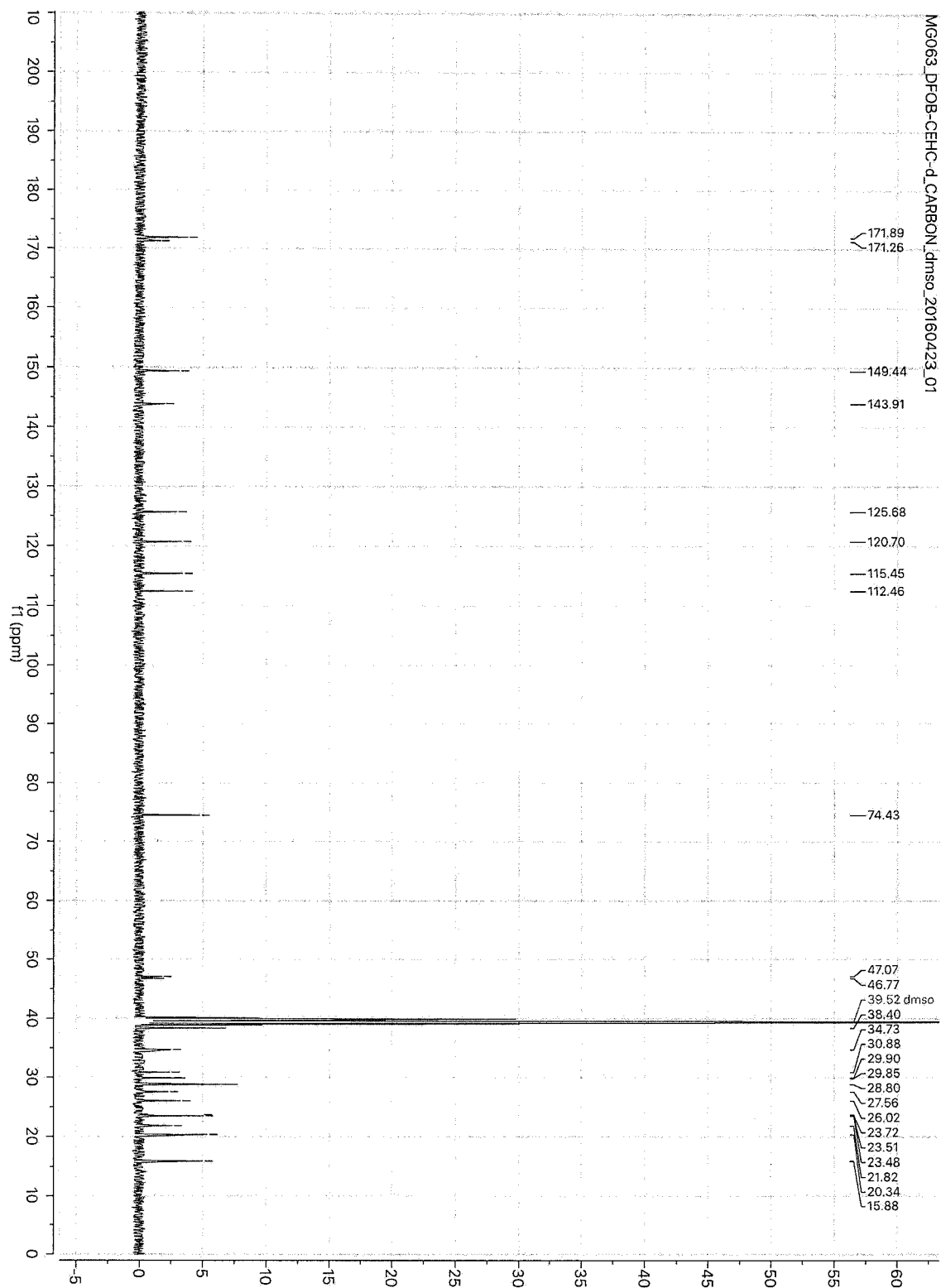


Figure 16

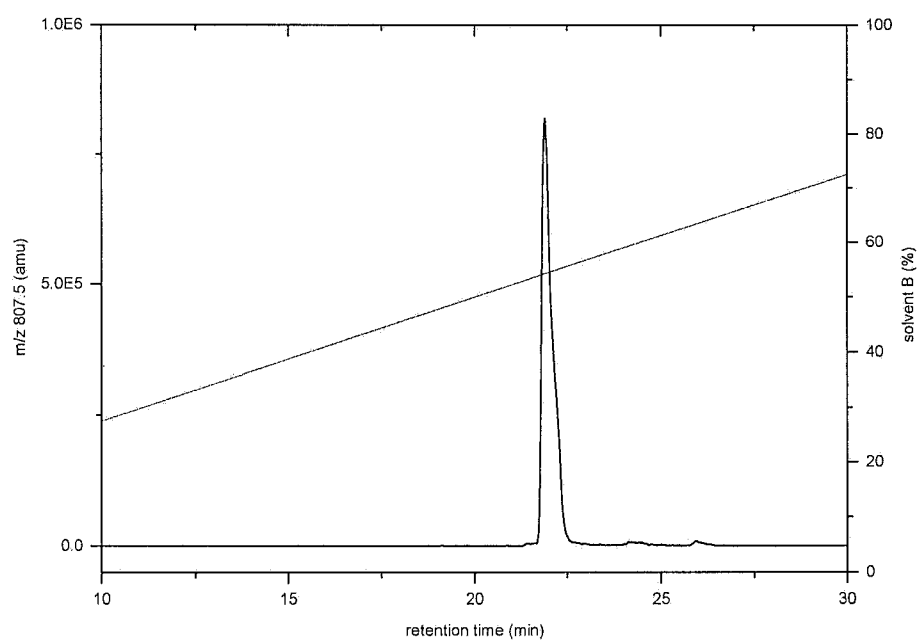


Figure 17

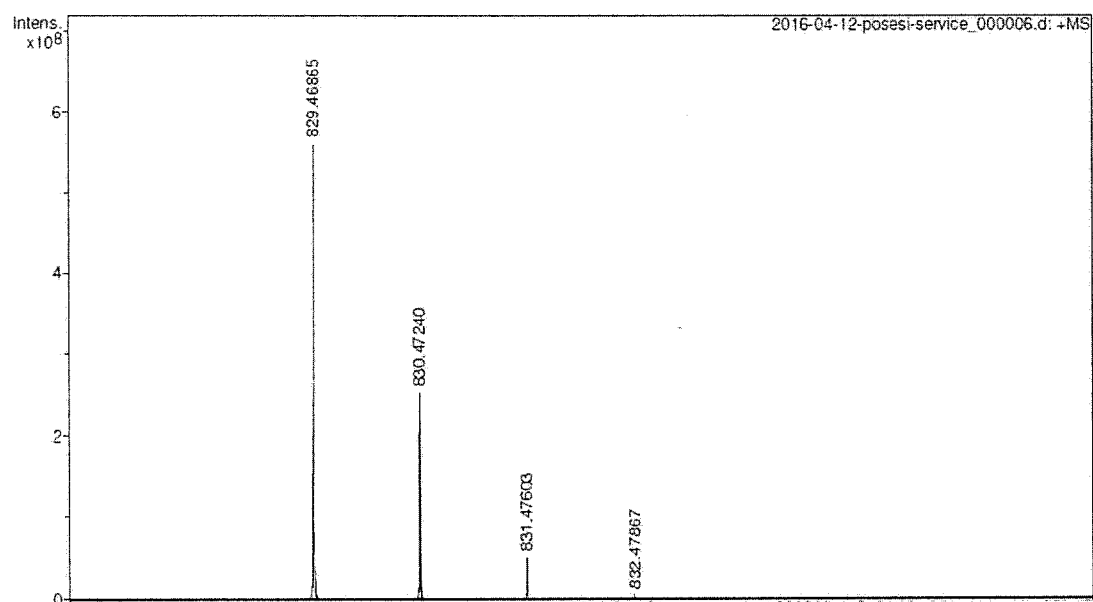


Figure 18

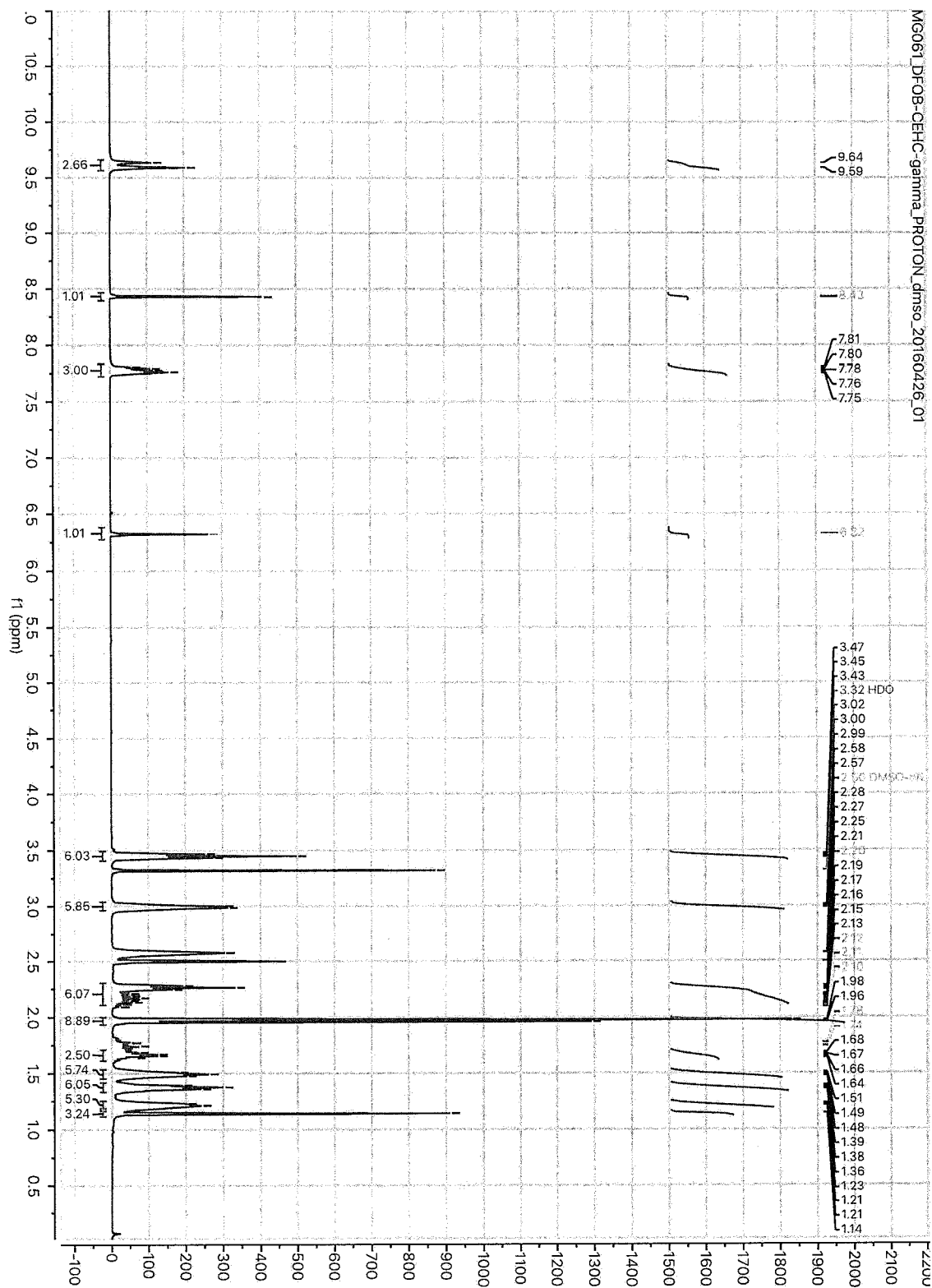


Figure 19

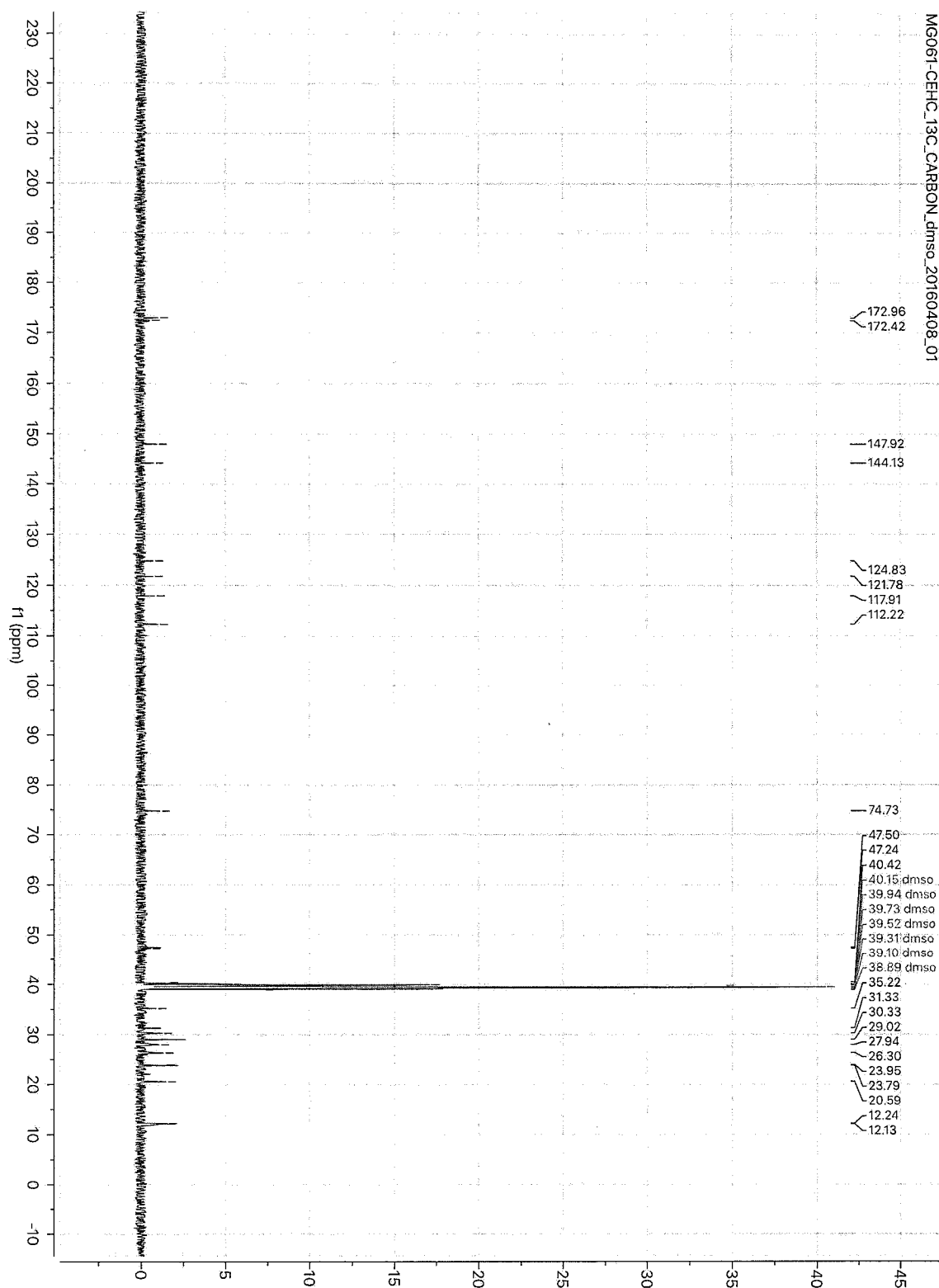


Figure 20

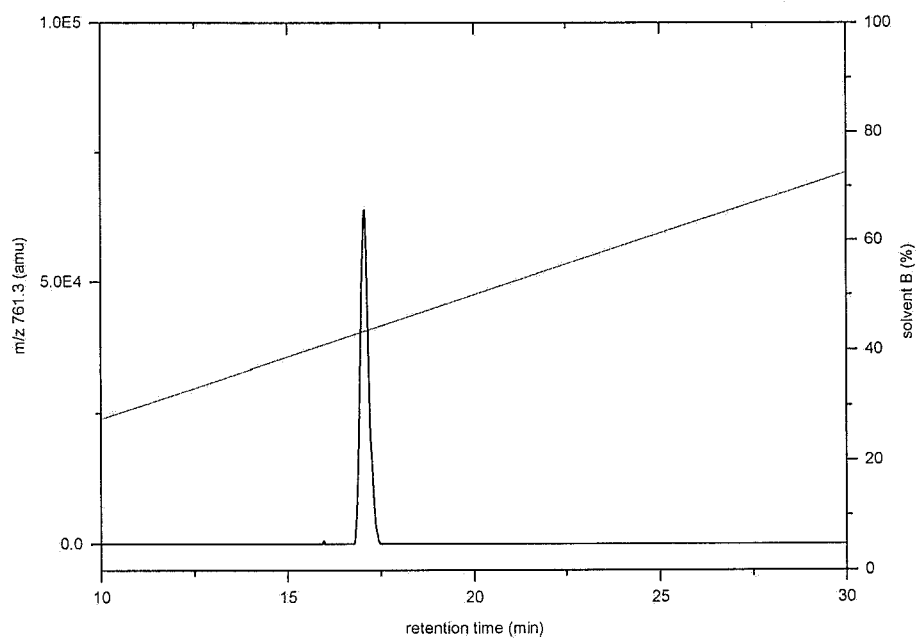


Figure 21

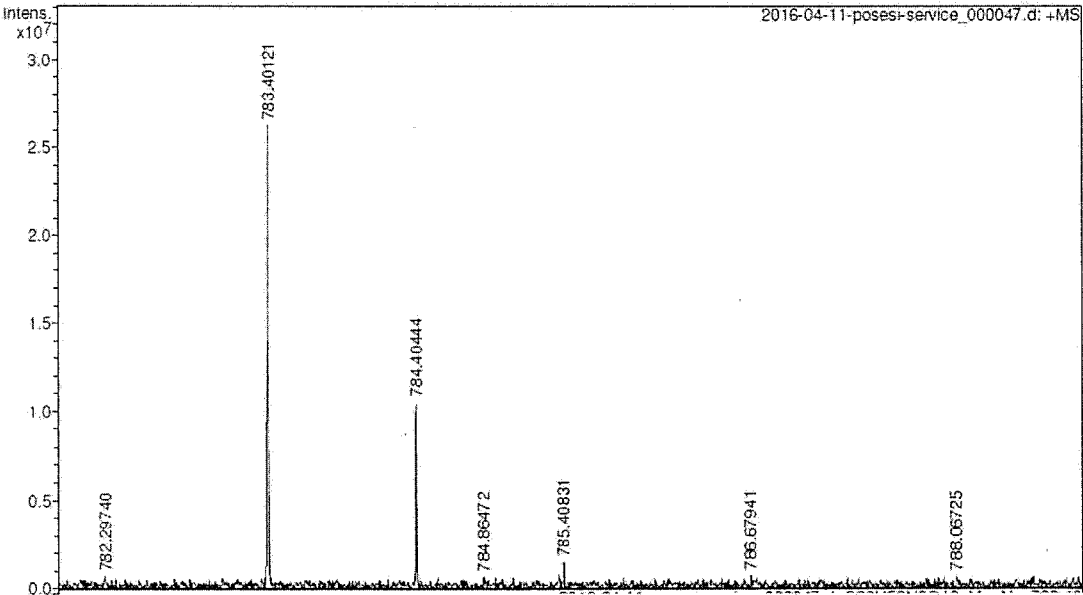


Figure 22

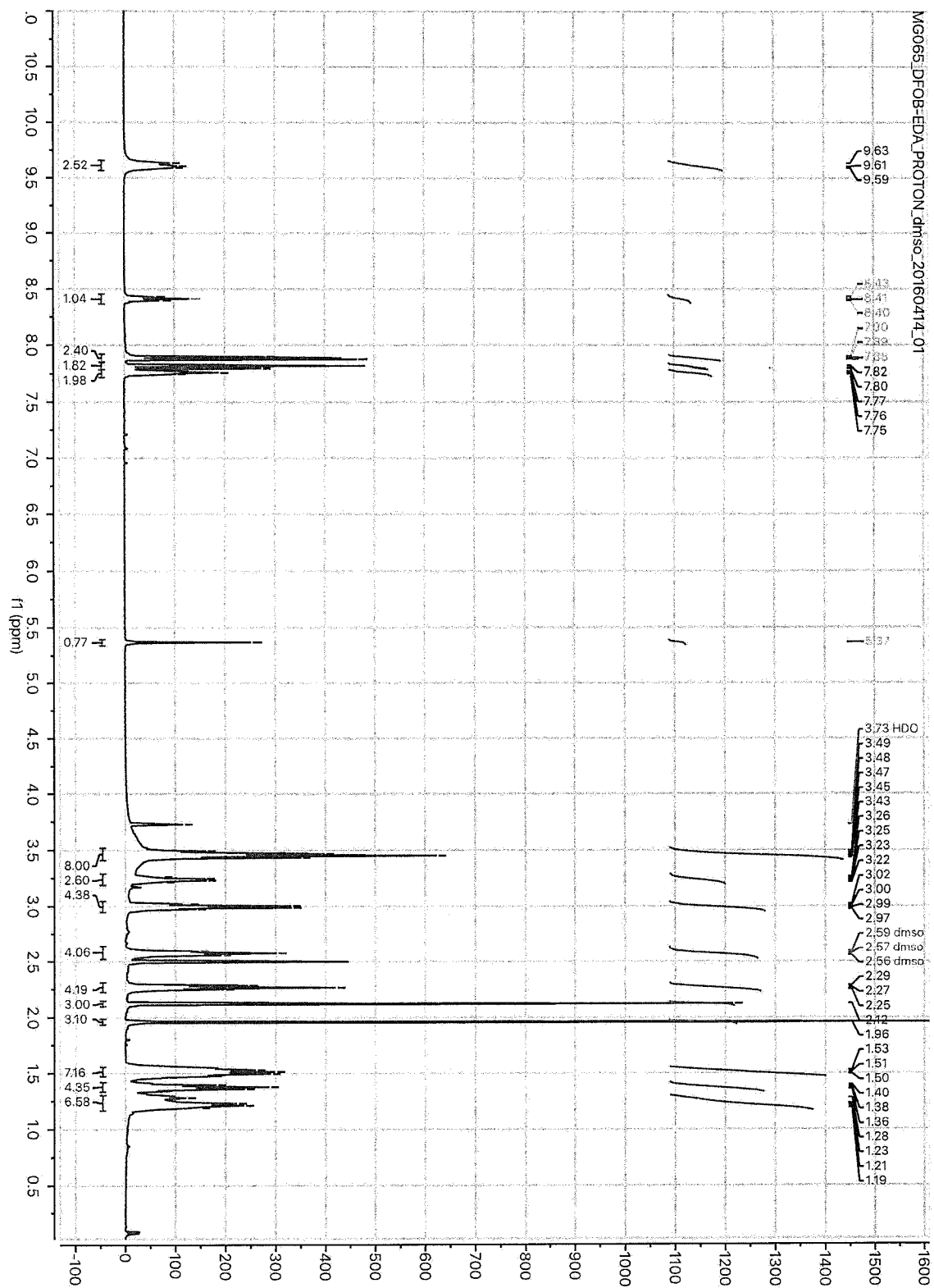


Figure 23

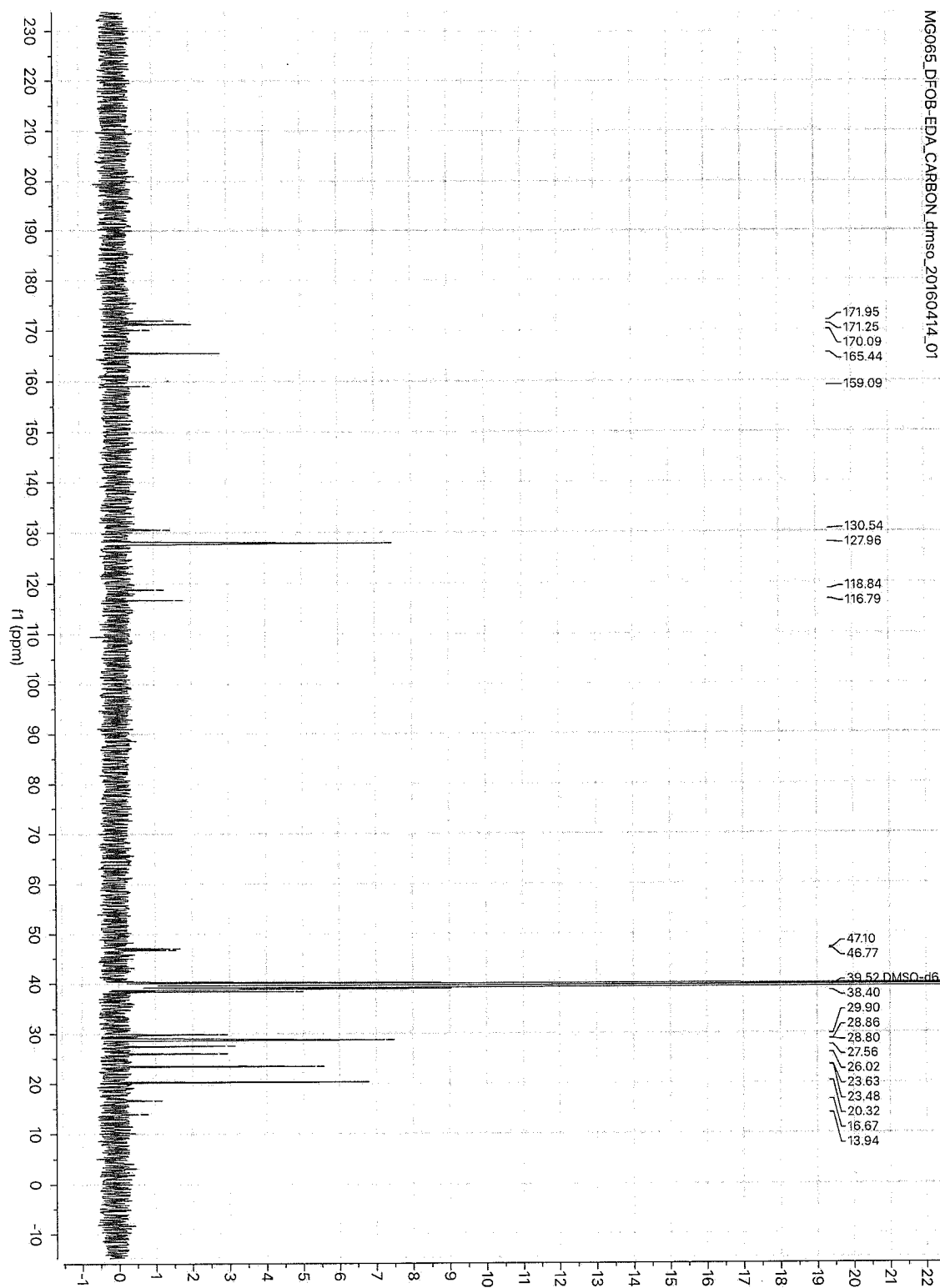


Figure 24

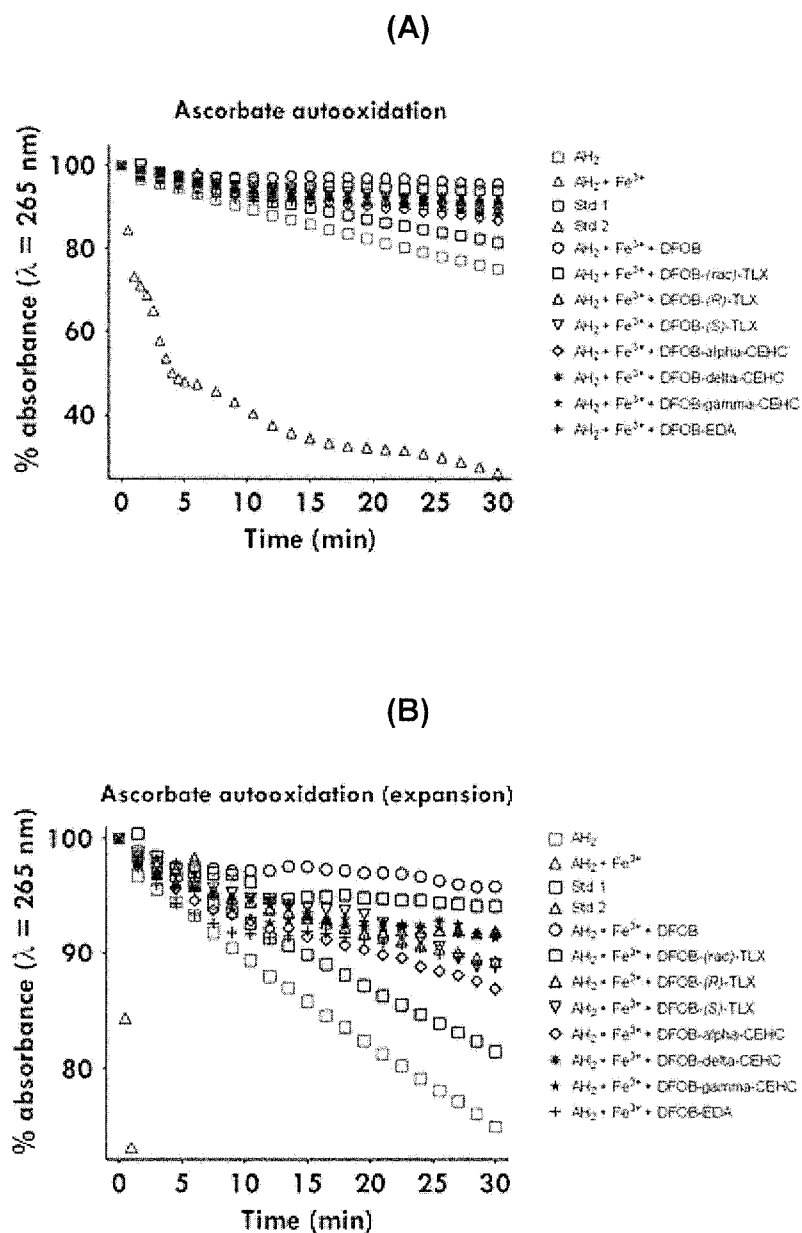


Figure 25

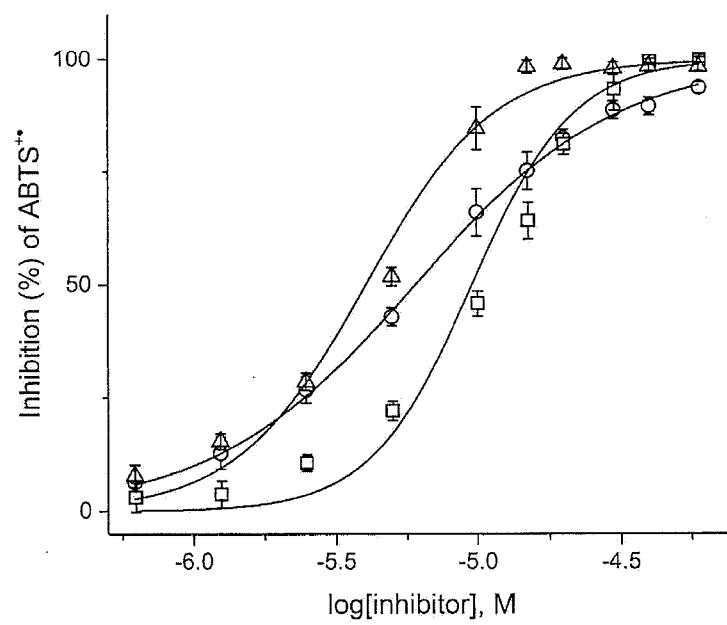
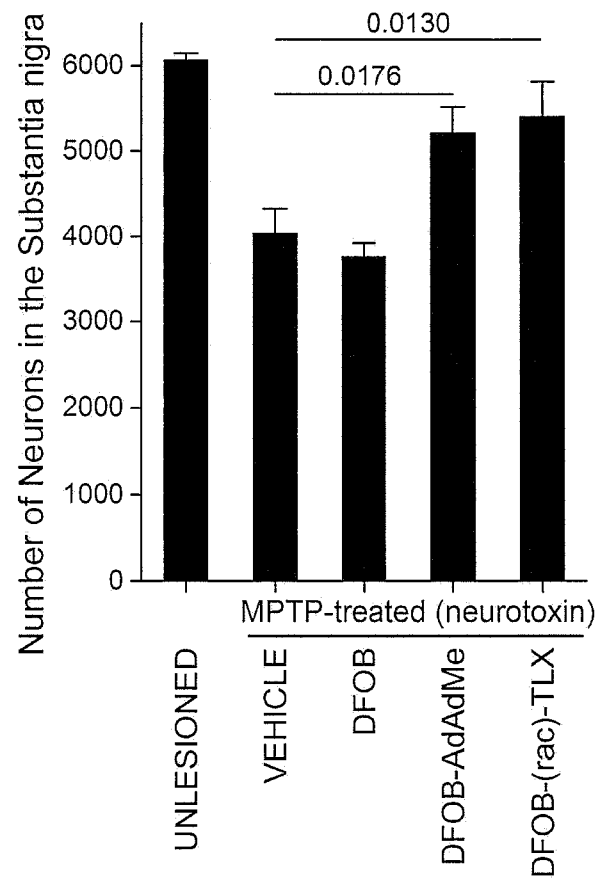
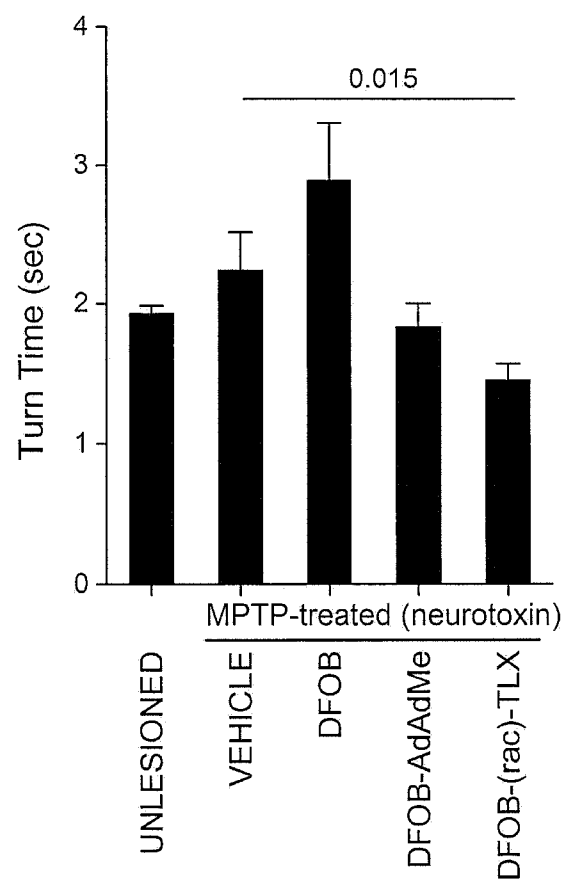


Figure 26



(A)

Figure 27



(B)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2017/050491

A. CLASSIFICATION OF SUBJECT MATTER

C07D 311/72 (2006.01)**C07D 231/22 (2006.01)****A61K 31/4152 (2006.01)****A61K 31/355 (2006.01)****A61K 31/353 (2006.01) A61P 25/00 (2006.01)**

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN (MEDLINE, CAPLUS, BIOSIS, REGISTRY). Structure search based on the compound of formula (I); control term and keyword search based upon control terms "vitamins", "antioxidants", or "tocopherols" or "nervous system agents" and keywords "edaravon?", "desferrioxamin?", "vitamin e" or "tocopherol" or "edavarone"

Espacenet. Applicant and IPC search and inventor search. Applicant and IPC search: "University of Sydney" and "C07C237/00" or "C07D311/00" or "C07D231/00" or "A61P25/00". Inventor search: "Codd" or "Gotsbacher".

Google Scholar. Applicant and keyword search and inventor search. Applicant and keyword search: "University of Sydney" and "Parkinson" or "Desferrioxamine B". Inventor search: "Codd" or "Gotsbacher".

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	



Further documents are listed in the continuation of Box C



See patent family annex

* "A"	Special categories of cited documents: document defining the general state of the art which is not considered to be of particular relevance	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E"	earlier application or patent but published on or after the international filing date	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O"	document referring to an oral disclosure, use, exhibition or other means	"&"	document member of the same patent family
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search
3 August 2017

Date of mailing of the international search report
03 August 2017

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Telephone No. (02) 6222 3634

INTERNATIONAL SEARCH REPORT		International application No.
C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		PCT/AU2017/050491
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2015/061630 A2 (MILLER, M.J., et al.) 30 April 2015 Figure 9, compound 26; and Figure 2	1-2
A	WO 2009/055863 A1 (THE UNIVERSITY OF SYDNEY) 07 May 2009 Pages 6-7; and page 15, lines 10-25	1-18
A	Liu, J., et al. "Conjugates of Desferrioxamine B (DFOB) with Derivatives of Adamantane or with Orally Available Chelators as Potential Agents for Treating Iron Overload.", Journal of Medicinal Chemistry, 2010, Vol. 53, pages 1370-1382. Page 1372, Figure 2; page 1370, Abstract, and page 1378, Conclusions	1-18
A	Liddell, J., et al. "Lipophilic adamantyl- or deferasirox-based conjugates of desferrioxamine B have enhanced neuroprotective capacity: implications for Parkinson disease." Free Radical Biology and Medicine, 2013, Vol. 60, pages 147-156. Page 149, Figure 1 and page 147, Abstract	1-18
A	Ihnat, P., et al. "Synthesis and solution properties of deferoxamine amides." Journal of Pharmaceutical Sciences, 2000, Vol. 89, No. 12, pages 1525-1536. Page 1525, Abstract and page 1531, Table 3	1-18
A	Lan, J., et al. "Desferrioxamine and vitamin E protect against iron and MPTP-induced neurodegeneration in mice. " Journal of Neural Transmission, 1997, Vol. 104, No. 4-5, pages 469-81. Page 469, Abstract, and pages 472-475, Results	1-18
A	Uney, J., et al. "Changes in heat shock protein 70 and ubiquitin mRNA levels in C1300 N2A mouse neuroblastoma cells following treatment with iron. " Journal of Neurochemistry, 1993, Vol. 60, No. 2, pp. 659-665. Page 663, Figure 5	1-18
P,X	Gotsbacher, M., et al. "Analogues of desferrioxamine B designed to attenuate iron-mediated neurodegeneration: synthesis, characterisation and activity in the MPTP-mouse model of Parkinson's disease." Metallomics, 2017, Vol. 9, pages 852-864. Whole document, in particular, Fig. 1 and Results and Discussion section.	1-18
Form PCT/ISA/210 (fifth sheet) (July 2009)		

INTERNATIONAL SEARCH REPORT Information on patent family members		International application No. PCT/AU2017/050491	
This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.			
Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
WO 2015/061630 A2	30 April 2015	WO 2015061630 A2	30 Apr 2015
		US 2016368878 A1	22 Dec 2016
WO 2009/055863 A1	07 May 2009	WO 2009055863 A1	07 May 2009
		AU 2008318287 A1	07 May 2009
		AU 2008318287 B2	17 Jan 2013
		EP 2215052 A1	11 Aug 2010
		EP 2215052 B1	24 Jul 2013
		US 2010273847 A1	28 Oct 2010
		US 8309583 B2	13 Nov 2012
End of Annex			
Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001. Form PCT/ISA/210 (Family Annex)(July 2009)			