communicate with each other. As such, a person suffering from multiple sclerosis can exhibit a variety of neurological symptoms, including changes in sensation such as loss of sensitivity or tingling, muscle weakness, loss of coordination and paralysis. The disease generally occurs in two stages, a relapsing stage and a chronic progressive phase.

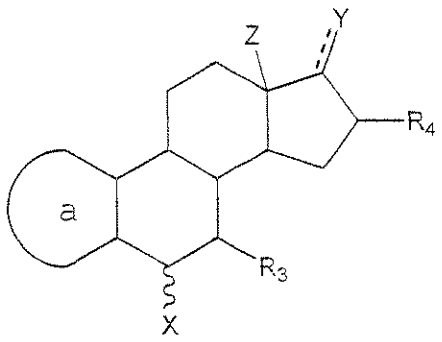
[0006] Current treatments for multiple sclerosis include anti-inflammatory and immuno-modulatory approaches. However, both are only partially effective in the relapsing stage of the disease, and little to no effect on the secondary progressive phase of the disease. Recently, estrogen receptor-β modulators have been shown to slow such neurodegeneration. Carswell, H.V.O. et al., *AJP-Heart Circ. Physiol.*, **2004**, vol. 287, 1501-04; Crawford, D.K. et al., **Brain**, **2010**, vol. 133, 2999-3016; Donzelli, A. et al., *J. Pharmacol. Sci.*, **2010**, vol. 114, 158-167.

[0007] Therefore, a need for an effective treatment for demyelinating diseases remains. Specifically, a compound which stimulates endogenous myelination and spares axon degeneration is preferred.

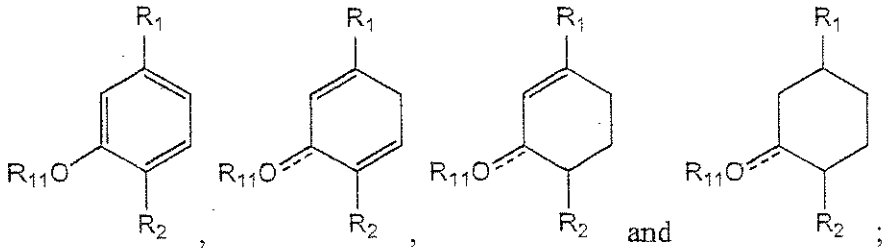
SUMMARY~~FIELD OF THE INVENTION~~

[0008] In light of the foregoing, it is an object of the present disclosure~~invention~~ to provide a method of preventing demyelination and/or enhancing remyelination of an axon of a nerve cell comprising contacting the nerve cell with an effective amount of a 6-substituted estradiol derivative. It will be understood by those skilled in the art that one or more aspects of this disclosure~~invention~~ can meet certain objectives, while one or more other aspects can meet certain other objectives. Each objective may not apply equally, in all its respects, to every aspect of this disclosure~~invention~~. As such, the following objects can be viewed in the alternative with respect to any one example~~aspect~~ of this disclosure~~invention~~.

[0008a] In one aspect, the present invention refers to the use of a 6-substituted estradiol derivative of the formula:



wherein the "a" ring is selected from the group consisting of



R_1, R_2, R_3 and R_4 are independently selected from the group consisting of H, C_1-C_6 alkyl, halo, a sulfate, a glucuronide, -OH, a bulky group, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, $-N(CH_2)_n$, a phosphate group, and a phosphinate group;

R_{11} is selected from the group consisting of H, C_1-C_6 alkyl, halogen, a sulfate, a glucoronide, $-SO_2NH_2$, -COOH, -CN, $-CH_2CN$-, -NHCN-, -CHO, $=CHOCH_3$, -COO salt, $-OSO_2$alkyl, $-NH_2$, and $-NHCO(CH_2)_n$;

X is selected from the group consisting of C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, halogen, a glucoronide, $-NH_2$, $-SO_2NH_2$, -COOH, -CN, $-CH_2CN$, -NHCN, -CHO, -COOsalt, $-OSO_2$alkyl, -SH, $-SCH_3$, $-CH[(CH_2)_nCH_3]COOCH_3$, $-(CH_2)_mCOOCH_3$, $-(CH_2)_m$-O-CH_3, $-(CH_2)_m$-O-$(CH_2)_nCH_3$, $(CH_2)_m$-S-CH_3, $-(CH_2)_m$-S-$(CH_2)_nCH_3$, $-(CH_2)_m$-NH-$(CH_2)_nCH_3$, $-C_2$-C_8 alkenyl-O-$(CH_2)_nCH_3$, $-C_2$-C_8 alkenyl-S-$(CH_2)_nCH_3$, $-C_2$-C_8 alkenyl-N-$(CH_2)_nCH_3$, $-C_2$-C_8 alkynyl-O-$(CH_2)_nCH_3$, $-C_2$-C_8

alkynyl-S-$(CH_2)_nCH_3$, -C_2-C_8 alkynyl-N-$(CH_2)_nCH_3$, -$(CH_2)_m$-OH, -$(CH_2)_m$-NH_2, -$(CH_2)_m$-O-NH_2, -$(CH_2)_m$-S-NH_2, -$NH(CH_2)_mCH_3$, -$NH(CH_2)_mOCH_3$, -$NH(CH_2)_mCHOH$-COOH, -$N(CH_3)_2$, -$(CH_2)_m(NH)CH_2OH$, -NHCOOH, -$(CH_2)_m$NHCOOH, -NO_2, -SCN, -SO_2alkyl, -$B(OH)_2$, -$(CH_2)_m$ $N(CH_3)$-SO_2-NH_3, -$(CH_2)_m$-NH-SO_2-NH_2, -$NHC(=S)CH_3$, and -$NHNH_2$;

Y is selected from the group consisting of H, =O, -OCO(C_1-C_{20} alkyl) and -OH;

Z is selected from the group consisting of H and methyl;

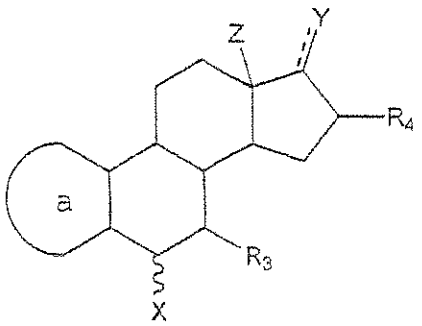
m is an integer between 0-20;

n is an integer between 0-8;

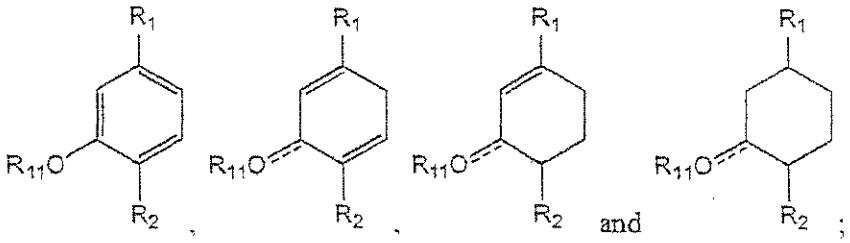
each ---- symbol independently represents either a single or a double bond capable of forming a keto group at position 3 or 17; and

the ~~~~ symbol represents any type of bond regardless of the stereochemistry; and the respective enantiomers, other stereochemical isomers, hydrates, solvates, tautomers and pharmaceutically acceptable salts of said compounds in the manufacture of a medicament for enhancing remyelination of an axon of a nerve cell, wherein the remyelination is associated with a disorder selected from the group consisting of multiple sclerosis, central pontine myelinolysis, experimental autoimmune encephalomyelitis, acute disseminated encephalomyelitis, transverse myelitis, progressive multifocal leukoencephalopathy; Alzheimer's Disease, subacute sclerosing panencephalitis, post-infectious encephalomyelitis, chronic inflammatory demyelinating polyneuropathy, progressive supernuclear palsy, multifocual motor neuropathy, Guillain-Barré Syndrome, progressive multifocal leucoencephalopathy, Devic's Disease, Balo's concentric sclerosis, Krabbe disease, Adrenoleukodystrophy (ALD), Pelizaeus-Merzbacher disease, Canavan disease, childhood ataxia with central hypomyelination, Alexander's disease, Cockayne syndrome, Van der Knapp syndrome, Zellweger syndrom and Refsum disease.

[0008b] In another aspect, the present invention refers to the use of a 6-substituted estradiol derivative of the formula:



wherein the "a" ring is selected from the group consisting of



R_1, R_2, R_3 and R_4 are independently selected from the group consisting of H, C_1-C_6 alkyl, halo, a sulfate, a glucuronide, -OH, a bulky group, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, $-N(CH_2)_n$, a phosphate group, and a phosphinate group;

R_{11} is selected from the group consisting of H, C_1-C_6 alkyl, halogen, a sulfate, a glucoronide, $-SO_2NH_2$, -COOH, -CN, $-CH_2CN$-, -NHCN-, -CHO, $=CHOCH_3$, -COO salt, $-OSO_2$alkyl, $-NH_2$, and $-NHCO(CH_2)_n$;

X is selected from the group consisting of C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, halogen, a glucoronide, $-NH_2$, $-SO_2NH_2$, -COOH, -CN, $-CH_2CN$, -NHCN, -CHO, -COOsalt, $-OSO_2$alkyl, -SH, $-SCH_3$, $-CH[(CH_2)_nCH_3]COOCH_3$, $-(CH_2)_mCOOCH_3$, $-(CH_2)_m$-O-CH_3, $-(CH_2)_m$-O-$(CH_2)_nCH_3$, $(CH_2)_m$-S-CH_3, $-(CH_2)_m$-S-$(CH_2)_nCH_3$, $-(CH_2)_m$-NH-$(CH_2)_nCH_3$, $-C_2$-C_8

alkenyl-O-$(CH_2)_nCH_3$, -C_2-C_8 alkenyl-S-$(CH_2)_nCH_3$, -C_2-C_8 alkenyl-N-$(CH_2)_nCH_3$, -C_2-C_8 alkynyl-O-$(CH_2)_nCH_3$, -C_2-C_8 alkynyl-S-$(CH_2)_nCH_3$, -C_2-C_8 alkynyl-N-$(CH_2)_nCH_3$, -$(CH_2)_m$-OH, -$(CH_2)_m$-NH_2, -$(CH_2)_m$-O-NH_2, -$(CH_2)_m$-S-NH_2, -$NH(CH_2)_mCH_3$, -$NH(CH_2)_mOCH_3$, -$NH(CH_2)_mCHOH$-COOH, -$N(CH_3)_2$, -$(CH_2)_m(NH)CH_2OH$, -NHCOOH, -$(CH_2)_m$NHCOOH, -NO_2, -SCN, -SO_2alkyl, -$B(OH)_2$, -$(CH_2)_m$ $N(CH_3)$-SO_2-NH_3, -$(CH_2)_m$-NH-SO_2-NH_2, -$NHC(=S)CH_3$, and -$NHNH_2$;

Y is selected from the group consisting of H, =O, -OCO(C_1-C_{20} alkyl) and -OH;

Z is selected from the group consisting of H and methyl;

m is an integer between 0-20;

n is an integer between 0-8;

each ---- symbol independently represents either a single or a double bond capable of forming a keto group at position 3 or 17; and

the ~~~~ symbol represents any type of bond regardless of the stereochemistry; and the respective enantiomers, other stereochemical isomers, hydrates, solvates, tautomers and pharmaceutically acceptable salts of said compounds in the manufacture of a medicament for treating a disorder associated with a lack of remyelination, wherein the disorder is selected from the group consisting of multiple sclerosis, central pontine myelinolysis, experimental autoimmune encephalomyelitis, acute disseminated encephalomyelitis, transverse myelitis, progressive multifocal leukoencephalopathy; Alzheimer's Disease, subacute sclerosing panencephalitis, post-infectious encephalomyelitis, chronic inflammatory demyelinating polyneuropathy, progressive supernuclear palsy, multifocual motor neuropathy, Guillain-Barré Syndrome, progressive multifocal leucoencephalopathy, Devic's Disease, Balo's concentric sclerosis, Krabbe disease, Adrenoleukodystrophy (ALD), Pelizaeus-Merzbacher disease, Canavan disease, childhood ataxia with central hypomyelination, Alexander's disease, Cockayne syndrome, Van der Knapp syndrome, Zellweger syndrom and Refsum disease, wherein the subject is to be administered an effective amount of a 6-substituted estradiol derivative and is to be monitored for remyelination.

[0009] Accordingly, in one example~~aspect~~ of the disclosure~~invention~~, the 6-substituted estradiol derivatives used in the methods disclosed herein are a compound of the formula I:

wherein m is an integer between 0-20, n is an integer between 0-8, the ---- symbol represents either a single or a double bond capable of forming a keto group at position 3 and/or 17; and the ~~~ symbol represents any type of bond regardless of the stereochemistry; and the respective enantiomers, other stereochemical isomers, hydrates, solvates, tautomers and pharmaceutically acceptable salts of said compounds.

[0010] In another example~~aspect~~ of the disclosure~~invention~~, the method specifically discloses~~provides for~~ compounds that bind to one or both of estrogen receptor-α (ER-α) and estrogen receptor-β (ER-β). Such a method can comprise initiating, enhancing or increasing gene transcription for RNA encoding genes involved in key signaling pathways for differentiation of precursor or progenitor cells to cells that form myelin.

[0011] Other objects, features, benefits and advantages of the present invention will be apparent from this summary and the following descriptions of certain embodiments, and will be readily apparent to those skilled in the art having knowledge of various steroid compounds and related therapeutic methods. Such objects, features, benefits and advantages will be apparent from the above as taken into conjunction with the accompanying examples, data, figures or with consideration of the references incorporated herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012] **FIG 1** shows the total number of differentiated oligodendrocyte precursor cells (OPCs) in mouse culture after 96 hours of treatment with various 6-substituted estradiol derivatives.

[0013] **FIG 2** depicts oligodendrocyte maturation in mouse culture after 96 hours of treatment with 10 μM of compound **21**; **a)** treatment with negative control (DMSO); **b)** treatment with positive control (MEKi); **c)** treatment with compound **21**.

[0014] **FIG 3** gives a comparison of the ability of various 6-substituted estradiol derivatives to differentiate OPCs into mature oligodendrocytes, to the ability of control drugs T3, CNTF and MEKi to differentiate OPCs into mature oligodendrocytes.

[0015] **FIG 4** depicts process extensions representative of oligodendrocytes after treatment with compound **8**.

alkynyl-S-$(CH_2)_nCH_3$, -C_2-C_8 alkynyl-N-$(CH_2)_nCH_3$, -$(CH_2)_m$-OH, -$(CH_2)_m$-NH_2, -$(CH_2)_m$-O-NH_2, -$(CH_2)_m$-S-NH_2, -$NH(CH_2)_mCH_3$, -$NH(CH_2)_mOCH_3$, -$NH(CH_2)_mCHOH$-COOH, -$N(CH_3)_2$, -$(CH_2)_m(NH)CH_2OH$, -NHCOOH, -$(CH_2)_m$NHCOOH, -NO_2, -SCN, -SO_2alkyl, -$B(OH)_2$, -$(CH_2)_m$ $N(CH_3)$-SO_2-NH_3, -$(CH_2)_m$-NH-SO_2-NH_2, -$NHC(=S)CH_3$, and -$NHNH_2$;

Y is selected from the group consisting of H, =O, -OCO(C_1-C_{20} alkyl) and -OH;

Z is selected from the group consisting of H and methyl;

m is an integer between 0-20;

n is an integer between 0-8;

each ---- symbol independently represents either a single or a double bond capable of forming a keto group at position 3 or 17; and

the ~~~~ symbol represents any type of bond regardless of the stereochemistry; and the respective enantiomers, other stereochemical isomers, hydrates, solvates, tautomers and pharmaceutically acceptable salts of said compounds in the manufacture of a medicament for enhancing remyelination of an axon of a nerve cell, wherein the remyelination is associated with a disorder selected from the group consisting of multiple sclerosis, central pontine myelinolysis, experimental autoimmune encephalomyelitis, acute disseminated encephalomyelitis, transverse myelitis, progressive multifocal leukoencephalopathy; Alzheimer's Disease, subacute sclerosing panencephalitis, post-infectious encephalomyelitis, chronic inflammatory demyelinating polyneuropathy, progressive supernuclear palsy, multifocual motor neuropathy, Guillain-Barré Syndrome, progressive multifocal leucoencephalopathy, Devic's Disease, Balo's concentric sclerosis, Krabbe disease, Adrenoleukodystrophy (ALD), Pelizaeus-Merzbacher disease, Canavan disease, childhood ataxia with central hypomyelination, Alexander's disease, Cockayne syndrome, Van der Knapp syndrome, Zellweger syndrom and Refsum disease.

2. The use according to claim 1 wherein

the "a" ring is