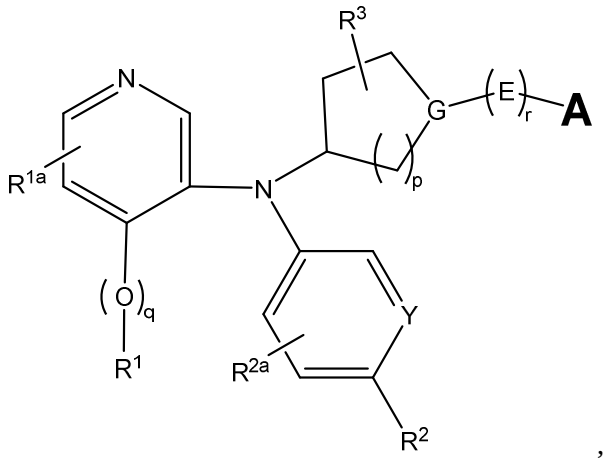
oligodendrocytes are unable to completely rebuild and restore the myelin sheath. Repeated attacks lead to successively less effective remyelination, until a scar-like plaque is built up around the damaged axons.

[5] At present, there is no cure for myelin-related disorders, and no current therapy prevents progression in MS. Accordingly, there is a need for new therapeutic approaches to the treatment of myelin-related disorders, including the promotion of remyelination. The subject matter described herein addresses this unmet need.

BRIEF SUMMARY

[6] In one aspect, the subject matter described herein is directed to a compound of Formula A:



A

,

wherein,

A is selected from the group consisting of C_1-C_6 alkyl, C_3-C_8 cycloalkyl, phenyl, 5- to 6-membered heteroaryl and 5- to 6-membered heterocyclyl, each of which is optionally substituted with one or more of R^{A1}, R^{A2} and R^{A3},

wherein, R^{A1}, R^{A2} and R^{A3} are each independently selected from the group consisting of C_1-C_6 alkyl, halo-C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, cyano, oxo, -C(O)-R^{A4}, -S(O)-R^{A4} and -$S(O)_2$-R^{A4},

wherein, R^{A4} is C_1-C_6 alkyl or C_3-C_8 cycloalkyl, and

wherein the oxo, if present, is formed by two of R^{A1}, R^{A2} and R^{A3} together with a carbon to which each is attached;

G is -CH, C-OH, or N;

E, if present, is -C(O)- or -O-;

Y is -CH or N;

p is 1, 2 or 3;

q is 1 or 0;

r is 1 or 0;

wherein, when r is 0, A is other than C_1-C_6 alkyl;

R^1 is selected from the group consisting of C_1-C_6 alkyl, C_3-C_8 cycloalkyl and halo-C_1-C_6 alkyl; or R^1 is halo and q is 0;

R^{1a} is selected from the group consisting of hydrogen, halo, C_1-C_6 alkyl;

R^2 is selected from the group consisting of halo, halo-C_1-C_6 alkyl, halo-C_1-C_6 alkoxy and -$S(O)_2$-(C_1-C_6 alkyl);

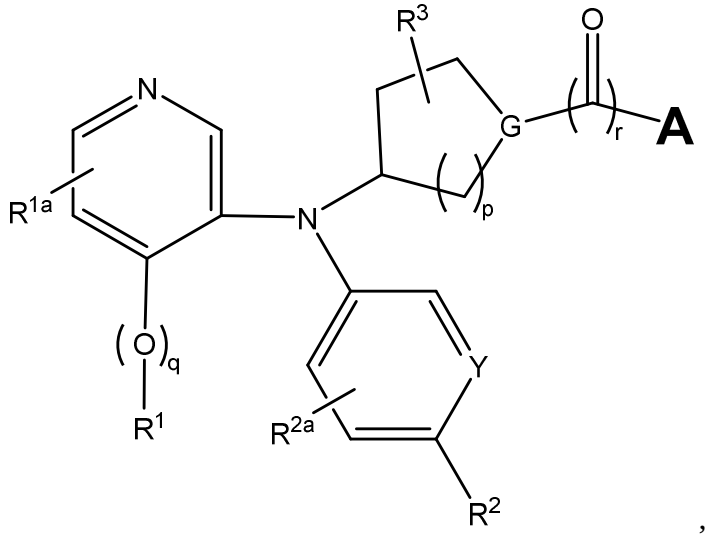
R^{2a} is selected from the group consisting of hydrogen and halo;

and,

R^3 is hydrogen, halo, or C_1-C_6 alkyl,

or a pharmaceutically acceptable salt or solvate thereof.

[7] In certain examples, the subject matter described herein is directed to a compound of Formula I:



I

,

wherein,

A is selected from the group consisting of C_1-C_6 alkyl, C_3-C_8 cycloalkyl, phenyl, 5- to 6-membered heteroaryl and 5- to 6-membered heterocyclyl, each of which is optionally substituted with one or more of R^{A1}, R^{A2} and R^{A3},

wherein, R^{A1}, R^{A2} and R^{A3} are each independently selected from the group consisting of C_1-C_6 alkyl, halo-C_1-C_6 alkyl, halo, cyano, oxo, -C(O)-R^{A4}, -S(O)-R^{A4} and -$S(O)_2$-R^{A4},

wherein, R^{A4} is C_1-C_6 alkyl or C_3-C_8 cycloalkyl, and

wherein the oxo, if present, is formed by two of R^{A1}, R^{A2} and R^{A3} together with a carbon to which each is attached;

G is -CH or N;

Y is -CH or N;

p is 1, 2 or 3;

q is 1 or 0;

r is 1 or 0;

wherein, when r is 0, A is other than C_1-C_6 alkyl;

R^1 is selected from the group consisting of C_1-C_6 alkyl, C_3-C_8 cycloalkyl and halo-C_1-C_6 alkyl;

R^{1a} is selected from the group consisting of hydrogen, halo, and C_1-C_6 alkyl;

R^2 is selected from the group consisting of halo, halo-C_1-C_6 alkyl, halo-C_1-C_6 alkoxy and -$S(O)_2$-(C_1-C_6 alkyl);

R^{2a} is selected from the group consisting of hydrogen and halo;

and,

R^3 is hydrogen, halo, or C_1-C_6 alkyl,

or a pharmaceutically acceptable salt or solvate thereof.

[8] In certain examples, the subject matter described herein is directed to a pharmaceutical composition comprising a compound of Formula A or Formula I, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient. In one aspect, the disclosure provides a pharmaceutical composition comprising a compound as described herein, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient.

[9] In certain examples, the subject matter described herein is directed to methods of promoting myelination in a subject in need thereof, comprising administering to the subject an effective amount of a compound of Formula A or Formula I, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition comprising a compound of Formula A or Formula I, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient. In certain examples, the subject has a myelin-related disorder.

[10] In certain examples, the subject matter described herein is directed to a compound of Formula A or Formula I, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition comprising a compound of Formula A or Formula I, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient, for use in treating a myelin-related disorder.

[11] In certain examples, the subject matter described herein is directed to the use of a compound of Formula A or Formula I, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition comprising a compound of Formula A or Formula I, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient, in the manufacture of a medicament for treating a myelin-related disorder. In one aspect, the disclosure provides use of a compound as described herein or a pharmaceutically acceptable salt or solvate thereof, or the pharmaceutical composition as described herein, in the manufacture of a medicament for treating a disorder in a subject in need thereof or for promoting myelination in a subject in need thereof.

[12] In certain examples, the subject matter described herein is directed to methods of preparing compounds of Formula A or Formula I, or a pharmaceutically acceptable salt or solvate thereof.

[13] In certain examples, the subject matter described herein is directed to methods of inhibiting CYP51 (lanosterol demethylase) comprising, contacting CYP51 with a compound of Formula A or Formula I, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition comprising a compound of Formula A or Formula I, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient.

[14] Other examples are also described.

DETAILED DESCRIPTION

[15] Described herein are myelin-promoting compounds of Formula A and Formula I, methods of making the compounds, their pharmaceutical compositions, and their use in the treatment of myelin-related disorders.

[16] The enhancement and/or inducement of the accumulation of Δ8,9-unsaturated sterol intermediates of the cholesterol biosynthesis pathway in oligodendrocyte progenitor cells (OPCs) can induce oligodendrocyte generation. Enhancement and/or inducement of the accumulation of Δ8,9-unsaturated sterol intermediates can be provided by modulating and/or inhibiting enzymes within the cholesterol biosynthesis pathway in OPCs that enhance and/or induce Δ8,9-unsaturated sterol intermediate accumulation and/or for which the Δ8,9-unsaturated sterol intermediates are substrates as well as directly and/or indirectly administering Δ8,9-unsaturated sterol intermediates to the OPCs. Enhancement and/or inducement of the accumulation of Δ8,9-unsaturated sterol intermediates can promote OPC differentiation, survival, proliferation and/or maturation and treat disease and/or disorders in subjects where myelination is beneficial to the subject.

[17] As such, in some embodiments an agent, such as a compound of Formula A or Formula I, or a pharmaceutically acceptable salt or solvate thereof, that can enhance and/or induce accumulation of Δ8,9-unsaturated sterol intermediates of the cholesterol biosynthesis pathway in the OPCs can be administered to a subject and/or the OPCs at an amount effective to promote and/or induce OPC differentiation, proliferation and/or maturation as well as oligodendrocyte generation. In certain embodiments, the agent, for example a compound of Formula A or Formula I, or a pharmaceutically acceptable salt or solvate thereof, is a compound that inhibits enzyme mediated synthesis of one or more sterol intermediates in the cholesterol biosynthesis pathway of the OPCs and/or promotes accumulation of Δ8,9-unsaturated sterol intermediates.

[18] In certain embodiments, the compound of Formula A or Formula I, or a pharmaceutically acceptable salt or solvate thereof, can modulate and/or inhibit one or more enzyme-mediated conversion steps of the cholesterol biosynthesis pathway, such as in the pathway from lanosterol to cholesterol, for example, between lanosterol and/or lathosterol; modulating and/or inhibiting one or more of these steps in