electric impulse. Demyelination of axons in chronic MS can result in axon degeneration and neuronal cell death. Additionally, MS destroys oligodendrocytes, the highly specialized CNS cells that generate and maintain myelin. A repair process, called remyelination, takes place in early phases of the disease, but over time, the 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. These scars are the origin of the symptoms.

[5] At present, there is no cure for myelin-related disorders, and only a handful of disease-modifying therapies are available. 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 certain examples, the subject matter described herein is directed to a compound of Formulae I, Ia, Ia', Ib, Ib', Ia1, Ib1, Ia2, or Ib2, or a pharmaceutically acceptable salt thereof.

[7] In certain examples, the subject matter described herein is directed to a pharmaceutical composition comprising a compound of Formulae I, Ia, Ia', Ib, Ib', Ia1, Ib1, Ia2, or Ib2, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[8] In certain examples, the subject matter described herein is directed to methods of treating a disorder in a subject in need thereof, wherein the disorder is a myelin-related disorder, comprising administering to the subject an effective amount of a compound of Formula I, Ia, Ia', Ib, Ib', Ia1, Ib1, Ia2, or Ib2, or a pharmaceutically acceptable salt thereof; or a pharmaceutical composition comprising a compound of Formula I, Ia, Ia', Ib, Ib', Ia1, Ib1, Ia2, or Ib2, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

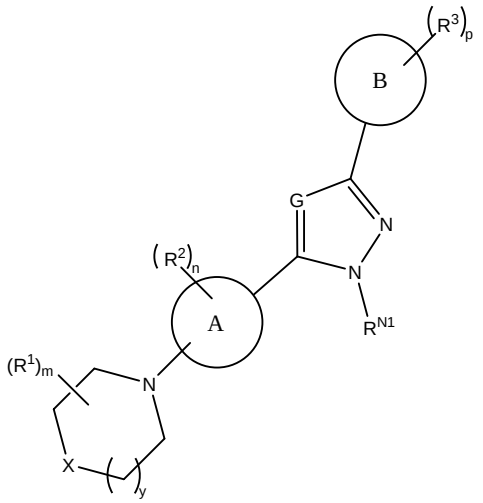
[9] In certain examples, the subject matter described herein is directed to a compound of Formula I, Ia, Ia', Ib, Ib', Ia1, Ib1, Ia2, or Ib2, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound of Formula I, Ia, Ia', Ib, Ib', Ia1, Ib1, Ia2, or Ib2, or a pharmaceutically acceptable salt thereof, for use in treating a myelin-related disorder.

[10] 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 a therapeutically effective amount of a compound of Formula I, Ia, Ia', Ib, Ib', Ia1, Ib1, Ia2, or Ib2, or a pharmaceutically acceptable salt thereof; or a pharmaceutical composition comprising a compound of Formula I, Ia, Ia', Ib, Ib', Ia1, Ib1, Ia2, or Ib2, or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable excipient.

[11] In certain examples, the subject matter described herein is directed to the use of a compound of Formula I, Ia, Ia', Ib, Ib', Ia1, Ib1, Ia2, or Ib2, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound of Formula I, Ia, Ia', Ib, Ib', Ia1, Ib1, Ia2, or Ib2, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a myelin-related disorder.

[12] In certain examples, the subject matter described herein is directed to methods of preparing compound of Formula I, Ia, Ia', Ib, Ib', Ia1, Ib1, Ia2, or Ib2, or a pharmaceutically acceptable salt thereof.

[12a] In one aspect, the disclosure provides a compound of Formula I:



I,

or a pharmaceutically acceptable salt thereof,

wherein:

n is 0 or 1;

p is 1 or 2;

Ring A is a saturated 5- or 6-membered monocyclic or bicyclic carbocyclyl;

Ring B is phenyl, 6-membered heteroaryl, or 6-membered saturated or partially saturated cycloalkyl, wherein the heteroaryl contains one or two heteroatoms;

R^3, in each instance, is independently selected from the group consisting of C_1-C_6 alkyl, halo-C_1-C_6 alkyl, hydroxy, C_1-C_6 alkoxy, halo-C_1-C_6 alkoxy, halo, and cyano;

G is N or CR^G, wherein R^G is selected from the group consisting of hydrogen, C_1-C_6 alkyl, and halo-C_1-C_6 alkyl;

R^{N1} is selected from the group consisting of hydrogen, C_1-C_6 alkyl, halo-C_1-C_6 alkyl, and C_3-C_5 cycloalkyl;

R^2 is selected from the group consisting of C_1-C_6 alkyl, halo, and halo-C_1-C_6 alkyl;

y is 1 or 2;

m is 0, 1, 2, or 3;

X is O or NR^H;

R^H is selected from the group consisting of hydrogen, C_1-C_6 alkyl, halo-C_1-C_6 alkyl, C_3-C_5 cycloalkyl, hydroxy-C_1-C_6 alkyl, and C_1-C_6 alkoxy-C_1-C_6 alkyl;

and,

R^1 in each instance, is selected from the group consisting of C_1-C_6 alkyl, halo-C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxy, NR^ER^F, halo-C_1-C_6 alkoxy, hydroxy-C_1-C_6 alkyl, and C_1-C_6 alkoxy-C_1-C_6 alkyl; or, two R^1 groups come together to form a -CH_2- or -CH_2CH_2- bridge;

R^E and R^F are each independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, halo-C_1-C_6 alkyl, C_3-C_5 cycloalkyl, hydroxy-C_1-C_6 alkyl, and C_1-C_6 alkoxy-C_1-C_6 alkyl.

[12b] In one aspect, the disclosure provides a pharmaceutical composition comprising a compound as disclosed herein or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[12c] In one aspect, the disclosure provides use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disorder in a subject in need thereof.

[12d] In one aspect, the disclosure provides use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for promoting myelination in a subject in need thereof.

[13] Other examples are also described.

DETAILED DESCRIPTION

[14] Described herein are compounds of Formulae I, Ia, Ia', Ib, Ib', Ia1, Ib1, Ia2, and Ib2, and pharmaceutically acceptable salts thereof, methods of making the compounds, their pharmaceutical compositions, and their use in the treatment of myelin-related disorders. In some embodiments, the compounds provided herein are myelin-promoting.

[15] Without wishing to be bound by theory, 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, for example, by modulating and/or inhibiting the enzymes within the OPC cholesterol biosynthesis pathway that inhibit 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 may promote OPC differentiation, survival, proliferation, and/or maturation, and it is thought this might treat disease and/or disorders in subjects where myelination is beneficial to the subject.

[16] As such, in some embodiments, an agent, such as a compound of Formula I, Ia, Ia', Ib, Ib', Ia1, Ib1, Ia2, or Ib2, or a pharmaceutically acceptable salt thereof, that can enhance and/or induce accumulation of Δ8,9-unsaturated sterol intermediates of the cholesterol biosynthesis pathway in OPCs can be administered to a subject, and/or to 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 I, Ia, Ia', Ib, Ib', Ia1, Ib1, Ia2, or Ib2, or a pharmaceutically acceptable salt 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.