METHODS OF TREATING MULTIPLE SCLEROSIS

FIELD

The present invention relates generally to the field of multiple sclerosis treatment.

BACKGROUND

Multiple sclerosis (MS) is a chronic, immune-mediated demyelinating disease of the central nervous system (CNS). The immune system attacks the myelin coating around the nerves in the CNS and the nerve fibers themselves. MS is the most common autoimmune disorder affecting the CNS and is a leading cause of disability in young adults. The disease usually begins between the ages of 20 and 50. In 2015, about 2.3 million people were affected worldwide.

MS takes several forms, either with new symptoms occurring in isolated attacks (relapsing forms) or with the disease gradually progressing over time without typical relapses (progressive forms). Progressive forms include primary progressive MS and secondary progressive MS.

Despite intensive investigation, the mechanisms of disease pathogenesis remain unclear, and while there are a number of drugs approved by the FDA for MS, there is still no cure. Among these drugs, most are approved for the treatment of relapse-remitting MS, while there is only one drug approved by the FDA for the treatment of primary progressive MS. Current medications used to treat MS, either relapse-remitting or progressive forms, while modestly effective, can have serious side effects or be poorly tolerated. In addition, many of these drugs must be administered via parenteral route, which is a disadvantage for patients in the context of a chronic disease like MS.

Thus, there is a need for new drugs to treat MS, particularly for drugs that may be also effective against the progressive forms of the disease and/or that exhibit less side effects than current treatments, and which can be administered by the oral route. The present invention addresses these and other needs.

SUMMARY

The disclosure provides novel methods for treating multiple sclerosis by using (-) 5-((((trans)-2-(4-(benzyloxy)phenyl)cyclopropyl)amino)methyl)-1,3,4-oxadiazol-2-amine, or a pharmaceutically acceptable salt or solvate thereof.

In one aspect, the present invention refers to the use of (-) 5-((((trans)-2-(4-(benzyloxy)phenyl)cyclopropyl)amino)methyl)-1,3,4-oxadiazol-2-amine or a pharmaceutically acceptable salt or solvate thereof for the manufacture of a medicament for the treatment of multiple sclerosis.

Also described herein is: an example of, the present disclosure, which provides (-) 5-((((trans)-2-(4-(benzyloxy)phenyl)cyclopropyl)amino)methyl)-1,3,4-oxadiazol-2-amine or a pharmaceutically acceptable salt or solvate thereof for use in the treatment of multiple sclerosis.

In another example, the present disclosure further provides a method for treating multiple sclerosis in a patient (preferably a human), comprising administering to the patient a therapeutically effective amount of (-) 5-((((trans)-2-(4-(benzyloxy)phenyl)cyclopropyl)amino)methyl)-1,3,4-oxadiazol-2-amine or a pharmaceutically acceptable salt or solvate thereof.

In yet another example, the present disclosure further provides the use of (-) 5-((((trans)-2-(4-(benzyloxy)phenyl)cyclopropyl)amino)methyl)-1,3,4-oxadiazol-2-amine or a pharmaceutically acceptable salt or solvate thereof for the manufacture of a medicament for the treatment of multiple sclerosis.

In yet another example, the present disclosure further provides the use of (-) 5-((((trans)-2-(4-(benzyloxy)phenyl)cyclopropyl)amino)methyl)-1,3,4-oxadiazol-2-amine or a pharmaceutically acceptable salt or solvate thereof for the treatment of multiple sclerosis.

In some examples, the multiple sclerosis is chronic progressive multiple sclerosis, particularly primary progressive multiple sclerosis or secondary progressive multiple sclerosis.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the results obtained with Compound 1 at 1 and 3 mg/kg p.o. in the murine experimental autoimmune encephalomyelitis (EAE) model as described in Example 3.1 and 3.2. Data represent the progression of the disease for each group measured as the mean clinical score (± SEM).

Figure 2 shows the effects of Compound 1 at 1, 0.5 and 0.05 mg/kg p.o. in the EAE model as described in Example 3.3. Data represent the progression of the disease for each group measured as the mean clinical score (± SEM).

Figure 3 shows the effects of the LSD1 inhibitor designated "ORY-LSD1" (as defined further in Example 1) at 0.06 and 0.180 mg/kg p.o in the EAE model as described in Example 3.4. Data represent the progression of the disease for each group measured as the mean clinical score (± SEM).

Figure 4 shows the effects of Compound 1 at 0.5 mg/kg p.o. in the EAE assay as described in Example 4. Data represent the progression of the disease for each group measured as the mean clinical score (± SEM).

Figure 5 shows the results of histopathological analysis of spinal cords isolated at the end of treatment (26 days after immunization) from animals treated with Compound 1 at 0.5 mg/kg p.o. or vehicle in the EAE assay as described in Example 4. The images shown correspond to transverse cervical (A) and lumbar (B) spinal cord sections selected at the peak of clinical disease, stained with Kluver-Barrera. Arrows point to areas of demyelination and inflammatory cell infiltration. The horizontal bar indicates a scale of 200 μm.

Figure 6 shows the mean number of demyelination plaques in the lumbar and cervical regions corresponding to the spinal cords isolated in Example 4, demonstrating absent or greatly reduced demyelination in the cervical and lumbar spinal cord sections, respectively, of animals treated with Compound 1.

Figure 7 shows the number of immune cells isolated from the spleen and lymph nodes of animals treated with Compound 1 at 0.5 mg/kg p.o. or vehicle according to Example 4, demonstrating a significant increase in the number of T cells retained in the spleen and lymph nodes of Compound 1-treated animals, indicating a reduced egress of lymphocytes from immune tissues.

Figure 8 shows the levels of several cytokines and chemokines determined by ELISA in spinal cords collected at day 26 post immunization from animals treated with Compound 1 at 0.5 mg/kg p.o. or vehicle according to

CLAIMS

1. Use of (-) 5-((((trans)-2-(4-(benzyloxy)phenyl)cyclopropyl)amino)methyl)-1,3,4-oxadiazol-2-amine or a pharmaceutically acceptable salt or solvate thereof for the manufacture of a medicament for the treatment of multiple sclerosis.
2. The use according to claim 1, wherein the multiple sclerosis is chronic progressive multiple sclerosis.
3. The use according to claim 1 or 2, wherein (-) 5-((((trans)-2-(4-(benzyloxy)phenyl)cyclopropyl)amino)methyl)-1,3,4-oxadiazol-2-amine is used for the manufacture of said medicament.
4. The use according to any one of claims 1 to 3, wherein said medicament is for oral administration.
5. The use according to any one of claims 1 to 4, wherein said medicament is for the treatment of a human.