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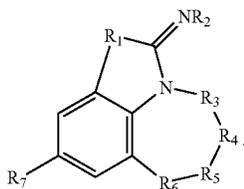
USE OF THIAZOLOBENZOHETEROCYCLES FOR TREATING MULTIPLE SCLEROSIS

CROSS REFERENCE TO RELATED APPLICATIONS

This application the benefit of U.S. Provisional Application No. 60/434,003, filed on 17 Dec. 2002.

FIELD OF THE INVENTION

The present invention relates to methods of treating multiple sclerosis. In particular, the present invention relates to the treatment of multiple sclerosis with the thiazolobenzoheterocyclic compounds of formula:



their isomers, racemates, enantiomers, their salts, and medicaments containing them.

BACKGROUND OF THE INVENTION

Thiazolobenzoheterocyclic compounds of formula I are disclosed generically in U.S. Pat. No. 6,369,221, issued on Apr. 9, 2002, wherein it is disclosed that the compounds are anticonvulsants and interfere with glutamatergic transmission and are therefore useful for the treatment or prevention of all ischaemias (such as local or global ischaemia) following cerebrovascular accidents such as thromboembolic and haemorrhagic stroke, cardiac arrest, arterial hypotension, cardiac, vascular or pulmonary surgery or severe hypoglycaemia. They are also useful in the treatment of the effects caused by anoxia, whether it is perinatal or subsequent to drowning, high pressure or cerebrospinal lesions. These compounds may also be used to treat or prevent the development of neurodegenerative diseases, of HUNTINGDON's chorea, of ALZHEIMER's disease and other dementias, of amyotrophic lateral sclerosis or of other motor neuron diseases, of olivopontocerebellar atrophy and of PARKINSON's disease. These compounds may also be used against epileptogenic (epilepsy) and/or convulsive manifestations, for the treatment of cerebral or spinal traumas, of traumas linked to degeneration of the inner ear (R. PUJOL et al., *Neuroreport*, 3, 299-302 (1992)) or of the retina (J. L. MONSINGER et al., *Exp. Neurol.*, 113, 10-17 (1991)), of tinnitus, of anxiety (KEHNE et al., *Eur. J. Pharmacol.*, 193, 283 (1991)), of depression (TRULLAS et al., *Eur. J. Pharmacol.*, 185, 1, (1990)), of schizophrenia (REYNOLDS, *TIPS*, 13, 116 (1992)), of TOURETTE's syndrome, of hepatic encephalopathies, of sleep disorders, of attention deficit disorders, of disorders of hormonal conditions (excess secretion of GH or LH, secretion of corticosterone), as analgesics (DICKENSON et al., *Neurosc. Letters*, 121, 263 (1991)), anti-inflammatory agents (SLUTA et al., *Neurosc. Letters*, 149, 99-102 (1993)), antianoretics (SORRELS et al., *Brain Res.*, 572, 265 (1992)), antimigraine drugs, antiemetics and to treat poisoning by neurotoxins and other substances which are NMDA or AMPA receptor agonists, as well as neurological disorders associated with viral diseases such as viral meningitis and

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encephalitis, AIDS (LIPTON et al., *Neuron* 7, 111 (1991)), rabies, measles and tetanus (BAGETTA et al., *Br. J. Pharmacol.*, 101, 776 (1990)). These compounds are also useful for the prevention of, tolerance to and dependency on the symptoms of withdrawal from drugs and alcohol, and of inhibition of addiction to and of dependency on opiates, barbiturates, amphetamine and benzodiazepines. They may also be used in the treatment of deficiencies linked to mitochondrial abnormalities such as mitochondrial myopathy, LEBER's syndrome, WERNICKE's encephalopathy, RETT's syndrome, homocysteinaemia, hyperprolinaemia, hydroxybutyric-aminoaciduria, saturnine encephalopathy (chronic lead poisoning) and sulphite oxidase deficiency.

(I) The contents of the aforementioned patent are hereby incorporated herein by reference.

Multiple sclerosis (MS) is a debilitating, inflammatory, neurological illness characterized by demyelination of the central nervous system. The disease primarily affects young adults with a higher incidence in females. Symptoms of the disease include fatigue, numbness, tremor, tingling, dysesthesias, visual disturbances, dizziness, cognitive impairment, urological dysfunction, decreased mobility, and depression. Four types classify the clinical patterns of the disease: relapsing-remitting, secondary progressive, primary-progressive and progressive-relapsing (S. L. Hauser and D. E. Goodkin, *Multiple Sclerosis and Other Demyelinating Diseases in Harrison's Principles of Internal Medicine 14th Edition*, vol. 2, Mc Graw-Hill, 1998, pp. 2409-2419).

The exact etiology of MS is unknown; however, it is strongly suspected that the demyelination characteristic of the disease is the result of an autoimmune response, perhaps triggered by an environmental insult, e.g. a viral infection. Specifically, it is hypothesized that MS is caused by a T-cell-mediated, autoimmune inflammatory reaction. The autoimmune basis is strongly supported by the fact that antibodies specific to myelin basic protein (MBP) have been found in the serum and cerebrospinal fluid of MS patients, and these antibodies, along with T-cells that are reactive to MBP and other myelin proteolipids, increase with disease activity. Furthermore, at the cellular, level it is speculated that T-cell proliferation and other cellular events, such as activation of B cells and macrophages and secretion of cytokines accompanied by a breakdown of the blood-brain barrier, can cause destruction of myelin and oligodendrocytes. (R. A. Adams, M. V. Victor and A. H. Ropper eds, *Principles of Neurology*, Mc Graw-Hill, New York, 1997, pp.903-921). Progressive MS (primary and secondary) may be based on a neurodegenerative process occurring with demyelination.

At the present time, there is no cure for MS. Current therapies are aimed at alleviating the symptoms of the disease and arresting its progress, as much as possible. Depending upon the type, drug treatment usually entails the use of disease-modifying agents such as the interferons (interferon beta 1-a, beta 1-b and alpha 2), glatiramer acetate or corticosteroids such as methylprednisolone and prednisone. Also, chemotherapeutic agents, such as methotrexate, azathioprine, cladribine, cyclophosphamide and cyclosporine, have been used. All of the above treatments have side-effect liabilities, little or no effect on fatigue and depression, as well as limited effects on relapse rates and on ability to prevent exacerbation of the disease.

Treatment with interferons may also induce the production of neutralizing antibodies, which may ultimately