Bioorganic & Medicinal Chemistry Letters 26 (2016) 4092–4094

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Novel potent pyridoxine-based inhibitors of AChE and BChE, structural analogs of pyridostigmine, with improved in vivo safety profile

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ARTICLE INFO

Article history:
Received 2 June 2016
Revised 23 June 2016
Accepted 24 June 2016
Available online 25 June 2016

Keywords:
Substituted pyridoxines
Pyridostigmine analogs
Neuromuscular disorders treatment
Acetylcholinesterase (AChE) inhibitors
Carbamate cholinesterase inhibitors

ABSTRACT

We report a novel class of carbamate-type ChE inhibitors, structural analogs of pyridostigmine. A small library of congeneric pyridoxine-based compounds was designed, synthesized and evaluated for AChE and BChE enzymes inhibition in vitro. The most active compounds have potent enzyme inhibiting activity with IC_{50} values in the range of 0.46–2.1 μM (for AChE) and 0.59–8.1 μM (for BChE), with moderate selectivity for AChE comparable with that of pyridostigmine and neostigmine. Acute toxicity studies using mice models demonstrated excellent safety profile of the obtained compounds with LD_{50} in the range of 22–326 mg/kg, while pyridostigmine and neostigmine are much more toxic (LD_{50} 3.3 and 0.51 mg/kg, respectively). The obtained results pave the way to design of novel potent and safe cholinesterase inhibitors for symptomatic treatment of neuromuscular disorders.

Disorders of neuromuscular synaptic transmission (Myasthenia Gravis, Lambert Eaton Syndrome and Congenital Myasthenic Syndromes) are a group of diseases in which an abnormality of neurotransmitter-receptor interaction or an abnormality of neurotransmitter release at the neuromuscular junction (NMJ) provokes the muscles weakness. In many instances the diseases are mediated by an autoantibody directed to a specific epitope at the NMJ.[1] In others, there is a genetically acquired abnormality of the structure of the NMJ.[2] While primary therapy for the majority of the immune mediated disorders involves immunosuppressive drugs with or without thymectomy, patients are also treated with inhibitors of acetyl- and butyrylcholinesterase (BChE) for symptomatic improvement of muscles weakness.[3] For Congenital Myasthenic Syndromes, medications by inhibitors of cholinesterases (ChEs) are the standard of care.[4] Effectiveness of ChEs inhibition in symptomatic treatment of muscles weakness is based on their ability to potentiate the effects of neurotransmitter acetylcholine (ACh) due to a decrease in the rate of its enzymatic hydrolysis. When a selective acetylcholinesterase (AChE) inhibitors are used to increase the ACh concentration in the synaptic cleft, the functional improvement is better than with a non-selective inhibitor of ChEs, during which inhibition of BChE counteracts the positive action of AChE inhibition.[5]

Currently, the most frequently used ChEs inhibitor in treatment of muscle weakness symptoms is pyridostigmine[3] (Fig. 1). This pseudo-reversible carbamylating agent does not cross the blood–brain barrier, and its selectivity for human AChE is poor [K_i ratio (BChE/AChE) ≈ 6].[6] Neostigmine (Fig. 1) is another nonspecific ChEs inhibitor. Due to strong muscarinic side effects, it is less frequently used than pyridostigmine for the treatment of muscle weaknesses.[7] However, anaesthetists traditionally use neostigmine in daily routine practice to reverse the action of nondepolarizing muscle relaxants.[8]

There are serious safety concerns regarding the therapeutic use of ChEs inhibitors.[3] In particular, carbamates stimulate delayed neuropathy or make it more severe, when they are dosed after applying organophosphate (OP) neuropathic doses, inducing promotion of delayed neuropathy.[9] Thus, pyridostigmine bromide has been FDA approved for military use during combat situations as an agent to be given prior to exposure to the nerve agent soman in order to increase survival. However, used in particular during the first Gulf War, pyridostigmine itself has been implicated as a causal factor in Gulf War syndrome.[10]

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http://dx.doi.org/10.1016/j.bmcl.2016.06.070
0960-894X/