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Design, synthesis and biological screening of monoamine oxidase inhibitors

Vishnu Nayak
Birla Institute of Technology, India

Monoamine oxidases (MAOs) are flavoenzymes bound to the outer mitochondrial membrane and are responsible for the oxidative deamination of neurotransmitters and dietary amines and trace of amines. Two isoforms, namely MAO-A and MAO-B, have been identified on the basis of their amino acid sequences, three dimensional structure, substrate preference, and inhibitor selectivity. MAO-A has a higher affinity for serotonin and noradrenaline, whereas MAO-B preferentially deaminates phenylethylamine and benzylamine, this leads to the rapid degradation of these molecules and ensure that the proper functioning of synaptic neurotransmission, regulation of emotional behaviors and other brain functions. The byproduct of MAO-mediated reactions includes several chemical species with neurotoxic potential, such as hydrogen peroxide, ammonia and aldehydes. As a consequence of prolonged excessive activity of these enzymes may lead to mitochondrial damages and neurodegenerative disturbances/disorder

MAOIs introduced into clinical practice during 1960's were abandoned due to adverse effects, Such as hepatotoxicity, orthostatic hypotension, and the so-called "cheese effect", which was characterized by hypertensive crisis. Then it was understood that most of the adverse effects are due to non-selective inhibition of MAO-isoforms. This has led to an intensive search for novel MAO inhibitors (MAOIs), selective towards isoforms, and this effort has increased considerably in recent years. Selective MAO-A inhibitors such as clorgyline (irreversible) and moclobemide (reversible) are used in the treatment of neurological disorders such as depression, whereas the selective and irreversible MAO-B inhibitors such as selegiline and rasagiline are useful in the treatment of Parkinson's and Alzheimer's diseases. Most of the inhibitors in the clinical practice are either selective & irreversible or non-selective reversible with few exceptions.

According to WHO, depression is a common phenomenon affecting about 350 million people worldwide and can lead to suicide. Suicide in an estimated 1 million deaths every year depression related suicides (on WHO site). On the other side it is estimated that Neurodegenerative diseases will become the world's second leading cause of death by the middle of this century. The cost of illness and economic burden due to depression and neurodegenerative disorders were estimated to be $91000 and $100 billion/annum respectively for a US and will be many-fold higher for our nation (on WHO site). India with total population of more than 120 million has a greater concern due to increasing number of cases of depression and neurodegenerative disorders (on WHO site). More than 60% of the population in India are in rural settings and are having restricted accesses to their medication needs. Moreover poor socio-economic condition, increase in life expectancy (63/66) etc compounding the situation. We are in greater need of cheaper drugs for the treatment of depression and neurodegenerative disorders and means to make it available for the people in remote rural settings.

Biography

Vishnu Nayak.B has completed his M.S. (Pharm.) Medicinal Chemistry at the age of 25 years from National Institute of Pharmaceutical Education and Research-Raebareli, Uttar Pradsesh, India and now he was Pursuing Ph.D from Birla Institute of Technology-Mesra, Ranchi. He has published few papers in reputed journals.

vishnu.niper@gmail.com