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Review article

Privileged scaffolds as MAO inhibitors: Retrospect and prospects

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ABSTRACT

This review aims to be a comprehensive, authoritative, critical, and readable review of general interest to the medicinal chemistry community because it focuses on the pharmacological, chemical, structural and computational aspects of diverse chemical categories as monoamine oxidase inhibitors (MAOIs). Monoamine oxidases (MAOs), namely MAO-A and MAO-B represent an enormously valuable class of neuronal enzymes embodying neurobiological origin and functions, serving as potential therapeutic target in neuronal pharmacotherapy, and hence we have coined the term "***Neurozymes***" which is being introduced for the first time ever. Nowadays, therapeutic attention on MAOIs engrosses two imperative categories; MAO-A inhibitors, in certain mental disorders such as depression and anxiety, and MAO-B inhibitors, in neurodegenerative disorders like Alzheimer's disease (AD) and Parkinson's disease (PD). The use of MAOIs declined due to some potential side effects, food and drug interactions, and introduction of other classes of drugs. However, curiosity in MAOIs is reviving and the recent developments of new generation of highly selective and reversible MAOIs, have renewed the therapeutic prospective of these compounds. The initial section of the review emphasizes on the detailed classification, structural and binding characteristics, therapeutic potential, current status and future challenges of the privileged pharmacophores. However, the chemical prospective of privileged scaffolds such as; aliphatic and aromatic amines, amides, hydrazines, azoles, diazoles, tetrazoles, indoles, azines, diazines, xanthenes, tricyclics, benzopyrones, and more interestingly natural products, along with their conclusive SARs have been discussed in the later segment of review. The last segment of the article encompasses some patents granted in the field of MAOIs, in a simplistic way.

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1. Introduction

The homeostasis of bigenic amines, such as 5-hydroxytryptamine (5-HT) or serotonin, dopamine (DA) and noradrenalin (NE), in the brain is maintained by its elimination from the synaptic cleft through a reuptake mechanism [1] and the oxidation by monoamine oxidases (MAOs) [2,3]. MAO [E.C. 1.4.3.4] is a flavin-containing key enzyme located on the outer membrane of mitochondria bound via a C-terminal transmembrane polypeptide segment [4] and inserted in the membrane by means of ubiquitin, with energy provided by ATP [5], in neuronal, glial, and other cells, which regulates monoaminergic homeostasis and neurotransmission. The action is achieved via deamination of neuroactive and vasoactive biogenic molecules in the central nervous system (CNS). These include: Indoleamines such as serotonin [6] and tryptamine; catecholamines, such as DA, NE and epinephrine; trace amines, such as β-phenylethylamine (β-PEA), tyramine and octopamine. The quick degradation of brain monoamines, such as 5-HT, NE and DA is essential for the correct functioning of synaptic neurotransmission. Modulation of mood/emotion, the control of motor, perceptual and cognitive functions is maintained by monoaminergic signaling mechanisms [7]. In addition, it is also responsible for metabolism of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) into 1-methyl-4-phenylpyridinium (MPP^+), a Parkinsonian producing neurotoxin [8,9].

MAO-A and MAO-B enzymes are firmly united to mitochondrial outer membrane, with a minute microsomal fraction. During development, MAO-A appears before MAO-B. However, after birth the intensity of MAO-B dramatically increases in the brain [10–12]. MAOs are present in a majority of the mammalian tissues, but their proportions fluctuate in different tissues. Histochemical studies have revealed that MAOs are confined to a small area in the endothelial cells of the endoneurial vessels, in Schwann cells and in the unmyelinated axons of rat peripheral nervous system (PNS) [13]. Microvessels in the blood-brain barrier (BBB) are affluent in MAO-B [14]. MAO activity in human brain differs regionally; highest activity is noticed in striatum (basal ganglia) and hypothalamus, whereas cerebellum and neocortex show minimum activity. *In vivo* distribution of MAO-A and MAO-B in human brain is monitored by Positron Emission Tomography (PET). Both the isoenzymes are inconsistently disseminated in the human brain. Immunohistochemical investigations have shown that basal ganglia, serotonergic neurons and astrocytes predominantly contain MAO-B, whereas catecholaminergic neurons including substantia nigra, periventricular parts of hypothalamus contain mainly MAO-A [15]. Specific uptake inhibition mechanisms demonstrated that dopaminergic nerve endings (caudatal) contained only MAO-A, whereas serotonergic nerve terminals contained only small amounts of this isoenzyme. After selective MAO-A inhibition, 5-HT levels increase in glial cells [16,17]. Percent of total MAO-A and B activity reported in different human tissues has been presented in Table 1.

Genes for MAO enzymes (A and B) are sited on the X chromosome, at Xp11.23–11.4 [18–21]. *h*MAO-A and B genes were isolated from X chromosome genomic libraries [22,23]. They consist of fifteen exons and have an indistinguishable exon-intron organization. Exon-12, coding covalent FAD binding site with 93.9% amino acid identity between MAO-A and B, is the most conserved exon. Results emphasized that MAO-A and B were duplicated from a familiar ancestral gene [23]. The coding sequence in the normal male human MAO-A gene were found to be highly conserved [24]. The fragments 0.14 and 0.15 kb of the 5′-flanking sequence possess the highest promoter activity for MAO-A and B, respectively [25]. Different MAO-A and B promoter organizations determine their tissue- and cell-type-specific expression, especially in catecholaminergic and serotoninergic neurons of brain [26].

1.1. Structure and binding site analysis of MAOs

The two MAO isoforms (MAO-A and MAO-B) are composed of

Table 1
Percentage of total MAO-A and B activity in selected human tissues.

Tissue	MAO-A (%)	MAO-B (%)
Brain	<20	>80
Gastrointestinal tract	>80	<20
Kidney	25	75
Lung	55	45
Platelets	<5	>95