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REVIEW

2nd Heterocyclic Update

Nitrogen heterocycles as potential monoamine oxidase inhibitors: Synthetic aspects

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Abstract The present review highlights the synthetic methods of monoamine oxidase inhibitors (MAO) belonging to a group of nitrogen heterocycles such as pyrazoline, indole, xanthine, oxadiazole, benzimidazole, pyrrole, quinoxaline, thiazole and other related compounds (1990–2012). Moreover, it emphasizes salient findings related to chemical structures and the bioactivities of these heterocycles as MAO inhibitors. The aim of this review is to find out different methods for the synthesis of nitrogen containing heterocycles and their bioactivity related aspects as MAO inhibitors.

Contents

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1. Introduction

Monoamine oxidase (MAO) is an important flavoenzyme present in the outer mitochondrial membrane of neuronal, glial and many other cells and responsible for the oxidative deamination of amines in the brain as well as peripheral tissues, regulating their level (Binda et al., 2007; Youdim and Bakhle, 2006; Novaroli et al., 2006). This reaction produces the corresponding aldehyde and free amine, with the generation of hydrogen peroxide. It exists in two isoforms namely MAO-A and MAO-B that have been identified based on their amino acid sequences, three-dimensional structure, substrate preference, and inhibitor selectivity (De Colibus et al., 2005; Binda et al., 2003; Shih et al., 1999). Dopamine, tyramine, and tryptamine are the substrates for both iso-forms of MAO (Kalgutkar et al., 2001; Ma et al., 2004; Weyler et al., 1990). MAO-A preferentially metabolizes serotonin and noradrenaline and is inhibited by low concentrations of clorgyline (Weyler et al., 1990). MAO-B acts preferentially on 2-phenylethylamine and benzylamine and is inhibited by selegiline (L-deprenyl) (Kalgutkar et al., 2001). Their regulation determines the interest of the monoamine oxidase inhibitors (MAOI) as drugs used in the treatment of neurodegenerative and neurological disorders. In particularly, MAO-A inhibitors are effective in the treatment of depression (Cesura and Pletscher, 1992; Youdim et al., 2004). The MAO-B inhibitors are useful in the management of Parkinson's disease (Guay, 2006; Riederer et al., 2004; Harfenist et al., 1996), their applications were also studied for Alzheimer's disease (Wouters, 1998).

The structural diversity and biological importance of nitrogen containing heterocycles made them striking targets for synthesis and maintained the interest of researchers through many years of historical development of classical organic synthesis (Valverde and Torroba, 2005). Almost many synthetic drugs such as diazepam, benzodiazepines, barbiturates, methotrexate, pesticides, herbicides and some dyes are nitrogen heterocycles. These compounds are of great significance to life because their structural subunits exist in many natural drugs such as papaverine, theobromine, quinine, emetine, etc. (Chin et al., 2006; Koehn and Carter, 2005; Cordell and Farnsworth, 2001; Hughes and Shanks, 2002). Vitamins in B group and the key components of the deoxyribonucleic acid (DNA) molecules are also nitrogen-containing heterocycles (Watson and Crick, 1953; Dahm, 2008).

The classical period of the MAO inhibitors started with hydrazine derivatives. They were originally proposed as tuberculostatic agents, their prototype, iproniazid, was the first modern antidepressant and was introduced into the market under the trade name Marsilid (Cesura and Pletscher, 1992). Subsequently, research has been directed towards the preparation of heterocyclic hydrazines and hydrazides and their potential use as therapeutic agents for the treatment of CNS depression (Tipton, 1972; Mc Kenna et al., 1991; Yamada et al., 1993). Literature survey revealed diversified nitrogen heterocycles, synthesized since decades and tested for their MAO inhibitory potentials. Therefore, the present review emphasizes synthetic aspects of nitrogen heterocycles as MAO inhibitors.

2. Discussion

2.1. Pyrazoline as MAO inhibitor

A series of pyrazoline derivatives **7** (Kelekci et al., 2009) have been prepared starting from a quinazolinone ring (Scheme 1). Methyl thioxo quinazolinone was prepared by the reaction of anthranilic acid with methyl isothiocyanate which on further treatment with hydrazine hydrate in 2-propanol (iPrOH) afforded 2-hydrazino-3-methyl-quinazolinone. Substituted chalcones have been synthesized by the Claisen–Schmidt reaction and consequently, they react with **4** and afforded **6,** which were refluxed in glacial acetic acid (AcOH) to result in pyrazoline derivatives. Most of the synthesized compounds showed high activity against MAO-A and MAO-B isoforms.

The synthesis of N-substituted pyrazolines **11** and **12** has been reported (Fioravanti et al., 2010). Synthesis of **10** was achieved by the treatment of 3,3-dimethylallyl bromide with 2,4-dihydroxy-acetophenone. The N-acetyl-3-(2′-hydroxy,4′-prenyloxy)-phenyl-5-phenyl-4,5-dihydro-*(1H)* pyrazole derivatives had been synthesized by the reaction of chalcone with hydrazine hydrate in ethanol (EtOH) while with thiosemicarbazide afforded N-thiocarbamoyl-3-(2′-hydroxy,4′-prenyloxy)-phenyl-5-phenyl-4,5-dihydro-(1*H*) pyrazoles (Scheme 2). Most of the derivatives synthesized, showed an interesting inhibitory activity on MAO-B isoform with no efficacy towards MAO-A.

Synthesis of 3,5-diaryl-1-carbothioamide-pyrazoline derivatives (Scheme 3) has been accomplished with hydroxychalcones (Jayaprakash et al., 2008). Most of the compounds