A Medical Approach to the Monoamine Oxidase Inhibition by Using 7H-benzo[e]perimidin-7-one Derivatives

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Abstract: Background: A series of perimidinone derivatives (7H-benzo[e]perimidin-7-one) were synthesized and assessed by means of in vitro assays as human MAO inhibitors. These compounds inhibited reversibly the enzymes with inhibitory constants in the range of 2 to 20 µM. In addition, the selectivity of inhibition of the MAO isoforms seems to be significantly dependent on the presence whether either of heteroatoms or electron donating and withdrawing groups on the perimidinone framework, which was verified by using molecular docking simulation with the crystalized MAO receptors. Most of these inhibitors were highly selective: 9 and 11 inhibited selectively the MAO-B isofrom while 12 had 10-fold selectivity for MAO-A isofrom. Moreover, the compound 12 was both the most selective and potent MAO-A inhibitor among perimidinones.

Result: These results have important implications for the drug design of molecules targeting depression and movement-related disorders.

Keywords: Monoamine oxidase (MAO), 7H-benzo[e]perimidin-7-one, Perimidinones, MAO-A, Anti-Parkinson.

1. INTRODUCTION

MAO (amine: oxygen oxidoreductase (deamination) (flavin containing) EC 1.4.3.4.) catalyzes the oxidative deamination of endogenous monoamines including neurotransmitters, such as dopamine and 5-hydroxytryptamine, and exogenous amines, such as the xenobiotics neurotoxin as MPTP [1]. Two MAO isoforms have been identified, MAO-A and MAO-B, which differ from each other in relation to substrate and inhibitor specificity [2]. Serotonin, adrenaline and noradrenaline are substrates for MAO-A, while dopamine, phenylethylamine and benzylamine are substrates for MAO-B [3]. An abnormal activity of the MAO-B isoform is related with neurological disorders such as Alzheimer's (AD) and Parkinson's disease (PD), whereas the MAO-A isoform appears to be related with psychiatric conditions, such as depression [4]. In this context, numerous studies have focus on the inhibition of MAO as a strategy for the treatment of depression (MAO-A inhibitors) and the symptomatic treatment of PD patients (MAO-B inhibitors) [5].

Considering that many potent inhibitors of both MAO-A and MAO-B isoforms are clinically available or in development, there are interesting differences on the biological activity for each MAO isoform. First, few inhibitors as pyrazoline and hydradine derivatives are reversible but non-selective MAO inhibitors [6]. The low selectivity is an important feature for increase the dopamine levels since when one MAO isoform is inhibited, the other isoform balances this loss of activity. For instance, in brain of patients treated with either selegiline or clorgyline, the increase of dopamine was not as significant as the increase in phenylethylamine, noradrenaline and serotonin [7]. Second, the administration of irreversible MAO-A inhibitors might result in hypertension crises [8] associated with the potentializing of sympathetic cardiovascular activity through the release of noradrenaline due to the ingestion of food or drinks containing a high level of tyramine ("cheese-reaction") [9]. Therefore, hypertensive crises may be avoided by the use of re-