European Journal of Medicinal Chemistry 135 (2017) 196–203

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Research paper

The evaluation of 1,4-benzoquinones as inhibitors of human monoamine oxidase

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ARTICLE INFO

Article history:
Received 27 January 2017
Received in revised form
3 April 2017
Accepted 20 April 2017
Available online 22 April 2017

Keywords:
Monoamine oxidase
MAO
Inhibition
Irreversible
Dialysis
1,4-Benzoquinone

ABSTRACT

The monoamine oxidase (MAO) enzymes are of considerable pharmacological interest and inhibitors are used in the clinic for the treatment of major depressive disorder and Parkinson's disease. A limited number of studies have shown that the quinone class of compounds possesses MAO inhibition properties. Most notable among these is a report that 2,3,6-trimethyl-1,4-naphthoquinone (TMN), present in extracts of cured tobacco leafs, is a non-selective inhibitor of both MAO isoforms. An older study reports that 1,4-benzoquinone inhibits MAO-A and MAO-B from human synaptosomes. Both 1,4-naphthoquinones and 1,4-benzoquinone are reported to inhibit the MAOs with a reversible mode of action. Since the MAO inhibition properties of additional members of the 1,4-benzoquinone class of compounds have not yet been explored, the present study investigates a small series of four 1,4-benzoquinones which incorporate phenyl, benzyl, benzyloxy and cyclopentyl monosubstitution on C2. The 1,4-benzoquinones were found to be moderately potent MAO inhibitors with IC_{50} values of 5.03 −13.2 μM (MAO-A) and 3.69−23.2 μM (MAO-B). These values are comparable to those recorded for 1,4-benzoquinone of 4.82 μM (MAO-A) and 10.2 μM (MAO-B). Of interest however, is the finding that the 1,4-benzoquinones are irreversible inhibitors of MAO-A since prolonged incubation results in near complete inhibition, and enzyme activity is not recovered by dialysis. MAO-B is much less sensitive to inactivation by the 1,4-benzoquinones. These findings are discussed with reference to a possible mechanism by which irreversible inhibition occurs. It may be concluded that irreversible 1,4-benzoquinone-derived inhibitors may act as probes for investigating quinone reactive sites in the MAOs.

1. Introduction

The monoamine oxidase (MAO) enzymes are involved in the metabolism of neurotransmitter amines and amine-containing compounds from the diet [1]. Mammals have two forms of the enzyme, namely MAO-A and MAO-B. Both isoforms are found in the brain [2]. In the periphery, MAO-A is predominantly present in the gastrointestinal mucosa and placenta, while MAO-B is the main isoform in platelets. Hepatic tissue expresses both MAO-A and MAO-B [3,4]. The MAO enzymes are encoded by distinct genes and exhibit a high degree of similarity (approximately 70%) at the amino acid level [5,6]. The active sites of MAO-A and MAO-B are also similar in amino acid residues and their respective orientations, and only six of the sixteen active site residues differ between the two isozymes [7,8]. It is therefore not surprising that significant overlap in substrate specificities occur between the two MAO isoforms. For example, epinephrine, norepinephrine, dopamine and tyramine are good substrates for both MAO-A and MAO-B. Serotonin, on the other hand, may be considered as a MAO-A specific substrate, while the dietary amines, benzylamine and 2-phenylethylamine are MAO-B specific [9]. Since the MAOs exhibit different tissue distributions, in certain instances they have tissue-specific functions. For example, MAO-B present in the microvasculature of the brain may act as a metabolic barrier for false neurotransmitters such as benzylamine and 2-phenylethylamine [10]. Similarly, in gastrointestinal mucosa, MAO-A is a barrier for the uptake of dietary tyramine into the systemic circulation. Tyramine is a sympathomimetic amine which may induce the release of norepinephrine from peripheral neurons if absorbed in excessive amounts from the gastrointestinal tract [1]. This leads to an acute increase in blood pressure, known as tyramine-induced hypertensive crisis or the “cheese effect” [11,12]. Tyramine-induced

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http://dx.doi.org/10.1016/j.ejmech.2017.04.055
0223-5234/

Abbreviations

Aβ	amyloid β peptide
APCI	atmospheric-pressure chemical ionization
Cys	cysteine
DMSO	dimethyl sulfoxide
equiv	equivalent
FAD	flavin adenine dinucleotide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectra
MAO	monoamine oxidase
mp	melting point
NMR	nuclear magnetic resonans
SD	standard deviation
TMN	2,3,6-trimethyl-1,4-naphthoquinone

hypertensive crisis often occurs when irreversible MAO-A inhibitors are taken with food such as cheese, which is rich in tyramine.

Based on their roles in the metabolism of neurotransmitters, the MAOs are of considerable pharmacological importance [9]. MAO-A inhibitors are used in the clinic for the treatment of major depressive disorder and act by inhibiting the metabolism of serotonin, norepinephrine and dopamine, thereby enhancing neurotransmission mediated by these neurotransmitters [9]. MAO-A inhibitors that have been used in the clinic for depression include phenelzine, isocarboxazid, tranylcypromine and iproniazid (Fig. 1) [9,13]. These are irreversible MAO-A inhibitors, which are used restrictively in the clinic due to the occurrence of tyramine-induced hypertensive crisis. Reversible inhibitors such as moclobemide and toloxatone, on the other hand, represent safer and better-tolerated MAO-A inhibitors [14,15]. A transdermal delivery system of the MAO-B selective inhibitor, (R)-deprenyl (selegiline), has also been shown to be effective in the treatment of major depressive disorder in clinical trials [16]. Since this formulation does not lead to the inhibition of MAO-A in the gastrointestinal and hepatic systems, the risk of tyramine-induced hypertension is low. MAO-B inhibitors are, however, most frequently used as adjuncts to L-Dopa in the treatment of Parkinson's disease [9,13]. In Parkinson's disease MAO-B inhibitors elevate central dopamine levels, especially when combined with L-Dopa, the metabolic precursor of dopamine. MAO inhibitors may also act as potential neuroprotective agents in Parkinson's disease. Hydrogen peroxide and aldehydes produced by the MAOs in the brain, are thought to contribute to neurodegeneration [1,17]. MAO inhibitors reduce the formation of these metabolic by-products and thus may slow the degenerative process. MAO-B inhibitors, in particular, may be of relevance in age-related degenerative disorders such as Parkinson's disease since MAO-B activity, and not MAO-A activity, increases in the brain with age [18]. Two irreversible MAO-B inhibitors, (R)-deprenyl and rasagiline, are registered for this purpose, while a reversible MAO-B inhibitor, safinamide, has completed phase III development for the management of Parkinson's disease [19,20].

MAO inhibitors may also be relevant to other conditions, and are thus under investigation as therapies for Alzheimer's disease, certain types of cancer and age-related impairment of cardiac function. In Alzheimer's disease, MAO inhibitors may reverse amyloid β peptide (Aβ) pathology and improve cognitive deficits [21], while MAO-A inhibitors acting synergistically with survivin suppressants, may inhibit prostate cancer cell growth, migration and invasion [22,23]. Based on the observation that hydrogen peroxide produced by MAO-A in the heart increases with age in rats, it has been suggested that MAO-A inhibitors may slow age-related impairment of cardiac function by reducing hydrogen peroxide-mediated cardiac cellular degeneration [24].

Motivated by a financial interest in MAO inhibitors, but also the academic challenge of designing high potency and isoform-specific inhibitors, the discovery of new MAO inhibitors is pursued by a number of research groups [25–29]. A limited number of studies have reported that the quinone class of compounds, specifically 1,4-naphthoquinones and 1,4-benzoquinone, possess MAO inhibition properties. For example, 2,3,6-trimethyl-1,4-naphthoquinone (TMN, **1**), a compound isolated form cured tobacco leafs, was shown to inhibit human MAO-A and MAO-B with K_i values of 3 μM and 6 μM, respectively (Fig. 2) [30]. Another study reported that other 1,4-naphthoquinones such as menadione (**2**) and the parent 1,4-naphthoquinone (**3**), also inhibits the MAO isoforms [31]. An older study reports that 1,4-benzoquinone (**4**) inhibits MAO-A and MAO-B from human brain synaptosomes with K_i values of 9.62 μM (MAO-A) and 20.3 μM (MAO-B) [32]. Both 1,4-naphthoquinones

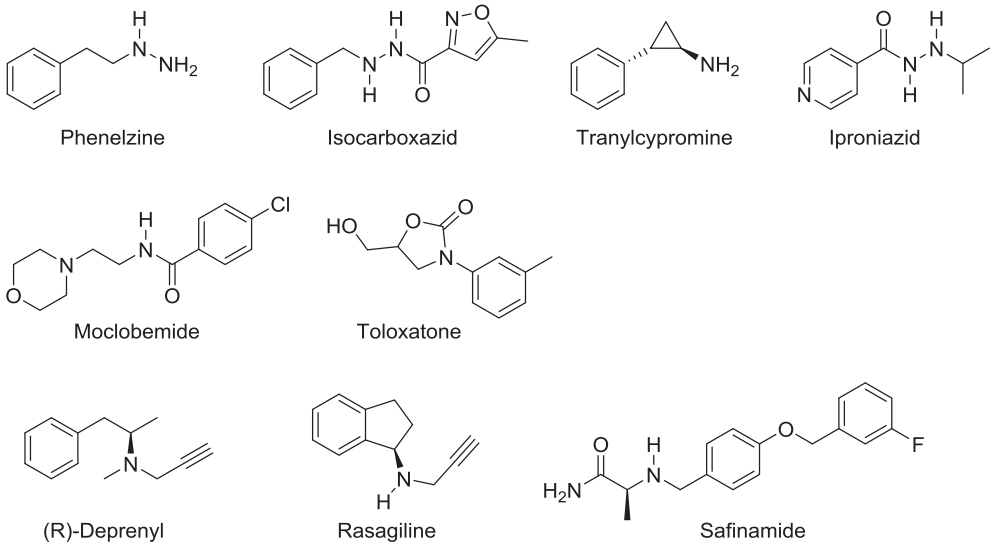

Fig. 1. The structures of selected MAO inhibitors discussed in the text.