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Design, synthesis and biological evaluation of lazabemide derivatives as inhibitors of monoamine oxidase

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ABSTRACT

In the studied a series novel of lazabemide derivatives were designed, synthesized and evaluated as inhibitors of monoamine oxidase (MAO-A or MAO-B). These compounds used lazabemide as the lead compound, and the chemistry structures were modified by used the bioisostere and modification of compound with alkyl principle. The two types of inhibitors (inhibition of MAO-A and inhibition of MAO-B) were screened by inhibition activity of MAO. *In vitro* experiments showed that compounds **3a**, **3d** and **3f** had intensity inhibition the biological activity of MAO-A, while compounds **3i** and **3m** had intensity inhibition the biological activity of MAO-B. It could be seen from the data of inhibition activity experiments *in vitro*, that the compound **3d** was IC_{50} = 3.12 ± 0.05 μmol/mL of MAO-A and compound **3m** was IC_{50} = 5.04 ± 0.06 μmol/mL. *In vivo* inhibition activity experiments were conducted to evaluate the inhibitory activity of compounds **3a**, **3d**, **3f, 3i** and **3m** by detecting the contents of 5-HT, NE, DA and activity of MAO-A and MAO-B in plasma and brain tissue. *In vivo* inhibition activity evaluation results showed that the compounds **3a**, **3d**, **3f**, **3i** and **3m** had increased the contents of 5-HT, NE and DA in plasma and brain tissues. Meanwhile, the determination results activity of MAO in plasma and brain tissue showed that the compounds **3a**, **3d**, and **3f** had a significant inhibitory effect on the activity of MAO-A, while the compounds **3i** and **3m** showed inhibitory effect on the activity of MAO-B. This study provided a new inhibitors for inhibiting of MAO activity.

1. Introduction

Monoamine oxidase (MAO) can be catalyst human and other biological *in vivo* monoamine neural metabolism (oxidative deamination reaction) inactivation of enzyme, the full name of monoamine-oxidoreductase, sometimes also called flavin amine oxidase.[1–3] According to the classification by the Enzyme Commission (EC) of the international society of biochemistry, MAO was EC1.4.3.4. MAO was first discovered in the liver in 1928 by Mary lias Christian Hare and was named tyramine oxidase.[4] MAO was a familial catalytic oxidase, *in vivo* distribution was widespread, mainly distributed in liver, kidney, brain, stomach and intestinal mucosa organisations such as the outer surface of mitochondria, and taken flavin adenine dinucleotide as coenzyme. Another group exists in the connective tissue of organisms, and taken pyridoxal phosphate as coenzyme.[5–8] MAO was a binding enzyme, and containing of Cu^{2+}, Fe^{2+} and phospholipid. And effects on primary amine and methylation of secondary and tertiary amine, the main catalytic deamination of monoamines (R-CH_2NH_2). The corresponding aldehydes, hydrogen peroxide and ammonia were produced. The aldehydes could be further metabolized into acids or alcohols *in vivo*. Based on the combination of substrate selectivity and inhibitors of different sensitivity, MAO was divided into two subtypes of type A and type B (MAO-A and MAO-B). They were composed of 527 and 520 amino acid residues, with 72.6% of the amino acid sequence was the same, and the homology was extremely high.[9,10] Studies on the MAO gene level have found that both MAO-A and MAO-B genes were located on the X chromosome, which it can be seen that these two subtypes of MAO were likely to come from the same ancestral gene.[11] But there have some different, MAO-A protein has a monopartite cavity of 550 Ã…, and MAO-B has a bipartite cavity of 290 Ã…. The protein structures of MAO-A[8] and MAO-B[9] were shown in Figs. 1 and 2. The MAO-A polarity was based on aromatic amines, such as 5-hydroxytryptamine (5-HT) and norepinephrine (NE), which were mainly distributed in the gastrointestinal tract, liver, kidney and lungs around the body. And it was mainly distributed in the brain in the adrenergic neurons. The MAO-B polarity was based on non-aromatic amines, such

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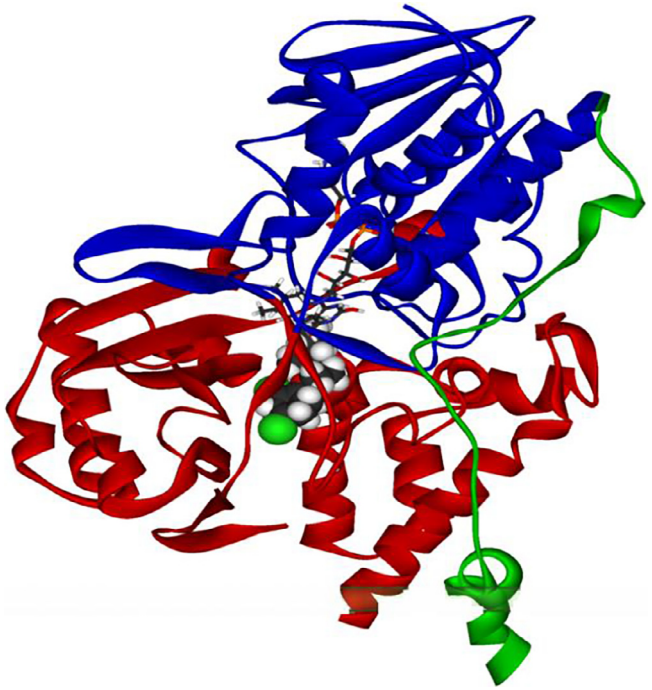

Fig. 1. The protein structure of MAO-A[8].

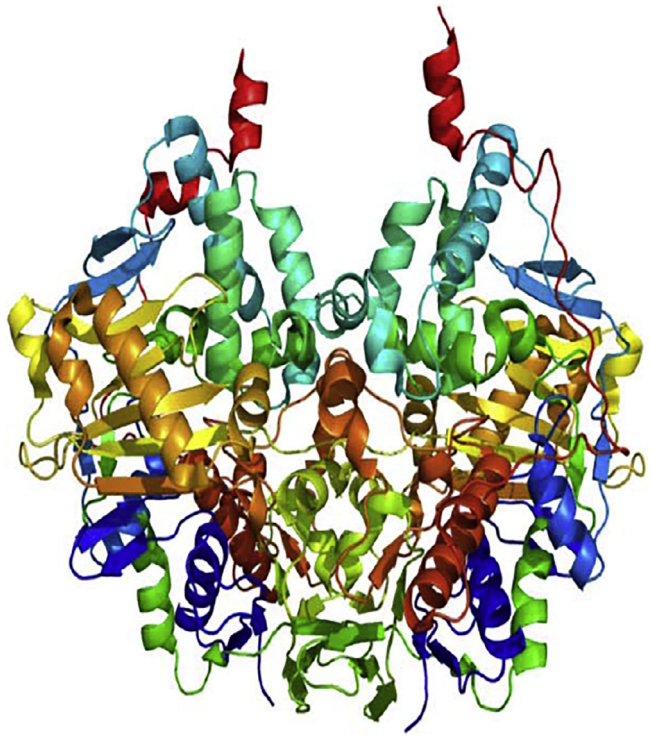

Fig. 2. The protein structures of MAO-B[9].

as phenethylhydrazine. The mainly exists in peripheral platelets, and was mainly distributed in 5-HT neurons and glial cells in the brain. Three major neurological diseases including Depression (DEP), Parkinson's disease (PD) and Alzheimer's disease (AD), and DEP of the highest risk, about 3–5% of all the world's adult population, particularly in the elderly rates can be 7–10%.[12,13] According to current pathogenesis studies, DEP was associated with activity of MAO-A, while PD and AD were associated with activity of MAO-B.

Monoamine oxidase inhibitors (MAOIs) were mainly hydrazine and non-hydrazine compounds, which have the function of inhibiting MAO bioactivity and showed anti-depression effect[14] MAOIs could be inhibition of 5-HT, NE and DA, thus reducing the brain oxidative deamination metabolism of 5-HT and NE, and neurotransmitter receptors in the brain areas content of 5-HT or NE concentration, and raise the level of prompting synaptic neurotransmitter metabolism to antidepressant effect. MAOIs found that it was an accident. During the treatment of tuberculosis, patients with tuberculosis were found to be taking isoniazid unexpectedly.[15–17] There was the phenomenon that not consistent with physical signs, and the mood was obviously improved.[18–21] The studies found that isoniazid strongly inhibits MAO activity, and after the phenethylhydrazine inhibitors were synthesized.[22–24] Depending on the selectivity, MAOIs could be divided into non-selective MAOIs, MAO-A inhibitors and MAO-B inhibitors. At present, MAOIs mainly have toloxatone, moclobemide, lazabemide, rasagiline and safinamide.[25–29]

They have the advantages of selectivity and effect, therefore, it was commonly used in clinical treatment or improvement of DEP, PD and AD patients. In recent years, although many new inhibitors have been reported to inhibition the biological activity of MAO, most of them remain at the stage of *in vitro* activity screening, and few of them are actually marketed[30]. These MAOIs have the same amide group, which have been listed in the sales, such as moclobemide, lazabemide, safinamide, isoniazid and isocarboxazid (Fig. 3). Isoniazid and isocarboxazid were the early for hydrazine containing drugs in clinic. It could be seen from the existing MAOIs structure that compounds with amide groups were likely to have the inhibition to MAO.[31] In this paper, a series of novel lazabemide derivatives with amide groups were designed by used the bioisostere and modification of compound with alkyl principle. From the structure–activity relationship (SAR), the newly designed compounds have similar chemical structure to lazabemide and may be inhibition the biological activity of MAO-A or MAO-B (Fig. 4). This series novel of lazabemide analogues or derivatives used 4-chlorobenzoic acid (**1a**) or 5-chloropyridine-2-carboxylic (**1b**) as the starting material, and the target compounds was synthesized by acyl chloride reaction and amidation reaction (Scheme 1). Biological activity experiments result showed that the series of compounds had good inhibition and selective effects on MAO-A or MAO-B.

2. Results and discussion

2.1. Chemistry

The lazabemide had on effect inhibition of MAO-B. In this research, we used lazabemide as the lead compound, and used bioisostere and modification of compound with alkyl principle (Fig. 4) to modified lazabemide (the lead compound). Thus a series of novel monoamine oxidase inhibitors (MAOIs) were designed. The moclobemide, lazabemide, safinamide, isoniazid and Isocarboxazid were MAO inhibitors (inhibition of MAO-A or MAO-B). From their chemical structure (Fig.3), we could be found they have the same amide group. This means that compounds with amide groups be likely to inhibition of MAO-A or MAO-B. Form Fig.4, the target compounds have the same spatial structure and amide group for lazabemide. According to the structure–activity relationship(SAR) of drugs, these compounds were likely to have inhibition biological activity of MAO-A or MAO-B. In the chemistry structural modification of lazabemide, the amide group, hexatomic ring and alkyl chain (basic framework) was retained. In modification of hexatomic ring, the benzene ring was added, the two atoms in the ring we chose carbon and nitrogen atom. In modification of alkyl chain, the length and substituents of alkyl chains were modified. The designed of alkyl chains chemistry structural 1, 2 and 3 carbons were chose, and the substituent R in the alkyl chains increased –OH, –Br and $–NH_2$. In modification of alkyl chain and substituent R, the mainly purpose was to change the physical and chemical properties (log*P* and *pKa*) of target compounds, so as to change the inhibition