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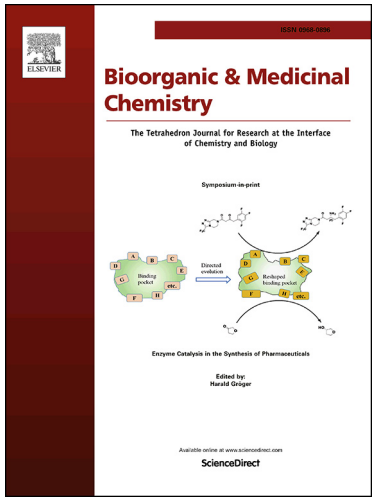

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Design, synthesis and biological evaluation of lazabemide derivatives as inhibitors of monoamine oxidase

Shiyang Zhou[a, b], Guangying Chen[a, b], Gangliang Huang[c*]

a. *College of Chemistry and Chemical Engineerin, Hainan Normal University, Hainan 571158, China*;

b. *Key Laboratory of Tropical Medicinal Plant Chemistry of Ministry of Education, Hainan Normal University, Hainan 571158, China;*

c. *College of Chemistry, Chongqing Normal University, Chongqing 401331, China*

E-mail: huangdoctor226@163.com

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.

Keyword: monoamine oxidase; inhibitors; design; synthesis, biological activities

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[5-7]. 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 ($R\text{-}CH_2NH_2$). 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 angstroms, and MAO-B has a bipartite cavity of 290 angstroms. The protein structures of MAO-A[12] and MAO-B[13] were shown in **Fig.1** and **Fig.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 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%[14,15]. According to current pathogenesis studies, DEP was associated with activity of MAO-A, while PD and AD were associated with activity of MAO-B.

Fig.1. The protein structure of MAO-A[12].

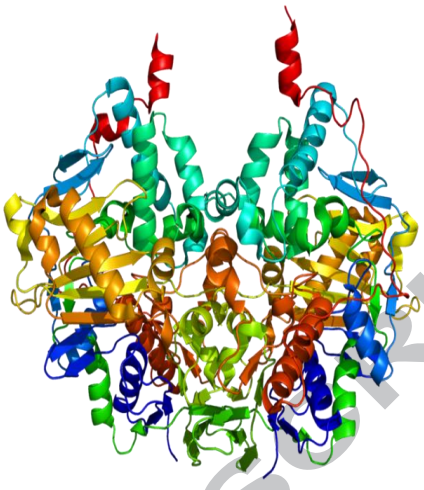


Fig.2. The protein structures of MAO-B[13].

Monoamine oxidase inhibitors (MAOIs) were mainly hydrazine and non-hydrazine compounds, which have the function of inhibiting MAO bioactivity and showed anti-depression effect[16]. 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[17-19]. There was the phenomenon that not consistent with physical signs, and the mood was obviously improved[20-23]. The studies found that isoniazid strongly inhibits MAO activity, and after the phenethylhydrazine inhibitors were synthesized[24-26]. 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[27-31]. 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[32]. 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 hydrazinecontaining 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[33]. 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.

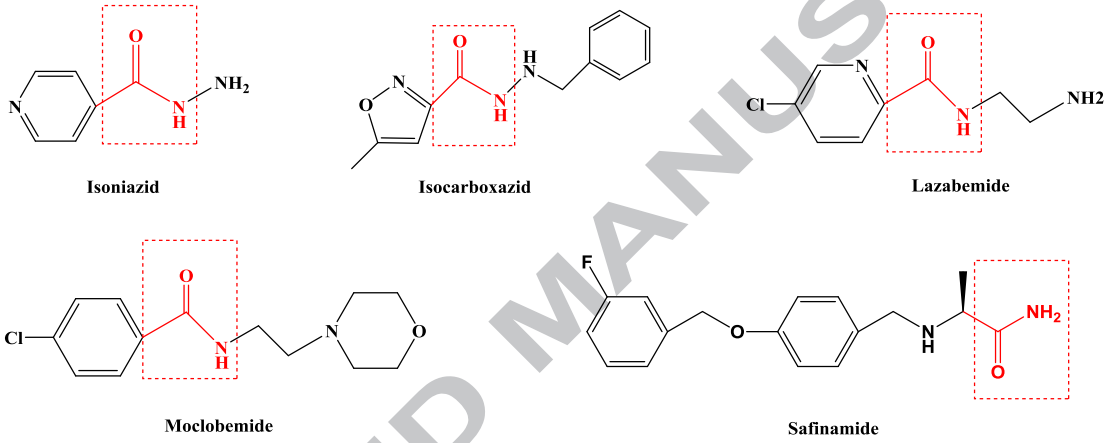


Fig.3. The amide groups of MAOIs.

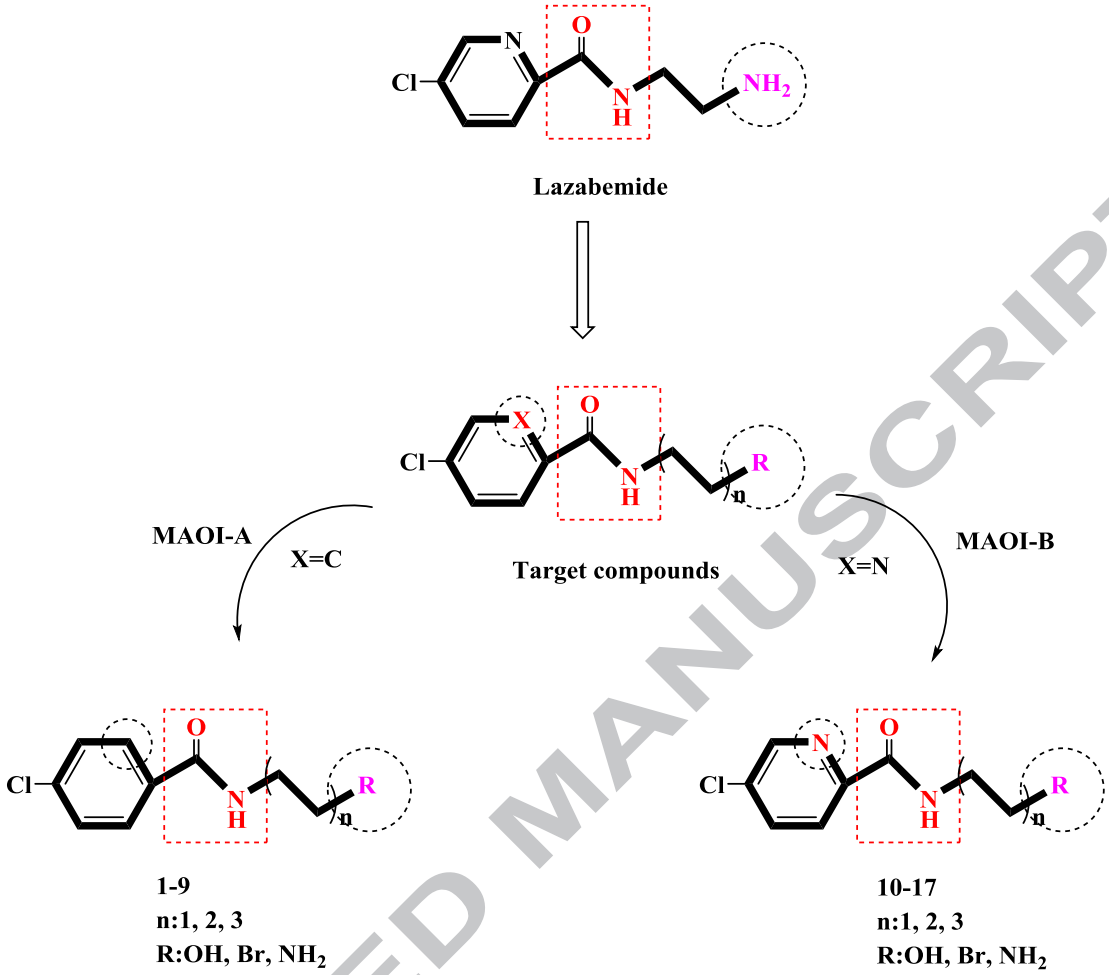


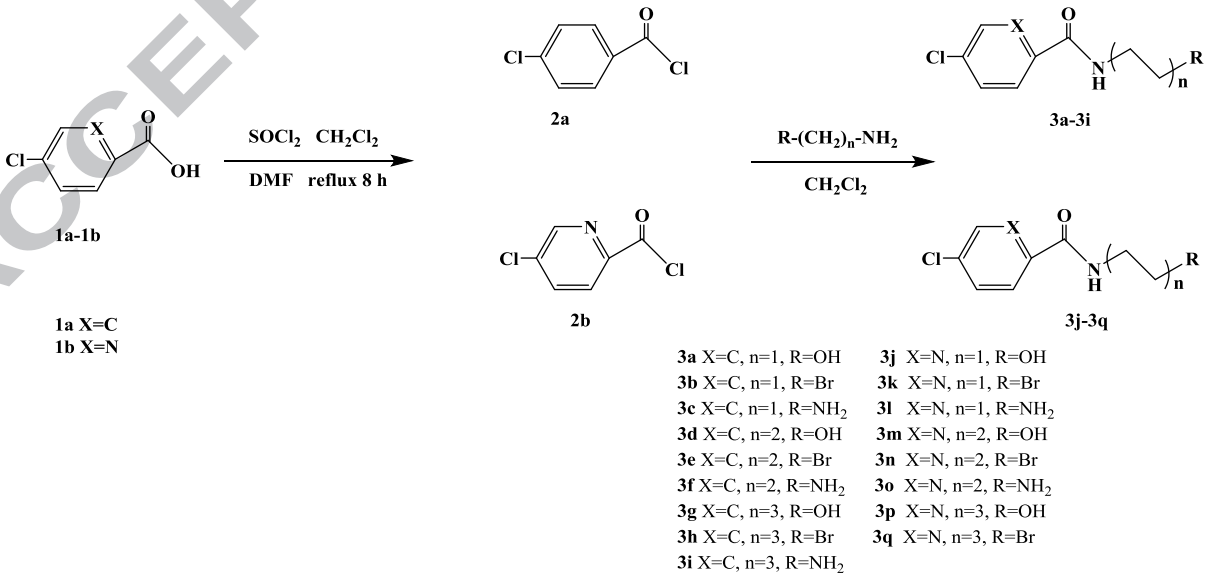
Fig.4. Design of of lazabemide derivatives.

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 activity of target compounds. In the synthesis of target compounds, we chose a simple and general synthetic route (**Scheme 1**). The synthesized target compounds were analyzed by ^{1}H NMR, ^{13}C NMR, MS and elemental analysis. In synthesis section, the compounds **2a-2b** were synthesised by general method of acyl chloride reaction, and the 4-chlorobenzoic acid (**1a**) or 5-chloropyridine-2-carboxylic (**1b**) as the starting material, with CH_2Cl_2 as solvent, DFM as catalyst, $SOCl_2$ as chloride reagent in the refluxing for 8 hours to complete reaction. The synthesis of compounds **3a-3i** and **3j-3q** by general method of amidation reaction, with CH_2Cl_2 as solvent, reaction temperature control in the 0-10 ℃. The crude target products were recrystallised with toluene, filtered, and dried in vacuum to give pure product. The synthesis of the target compounds superiority was a simple operation, safety, general, the target compounds high total yield, and the total yield of the target compounds **3a-3i** and **3j-3q** were 92.1%-98.6% and 92.8%-99.3% .



Scheme 1. The synthesis of lazabemide derivatives.

2.2. Monoamine oxidase inhibition studies

2.2.1. The inhibitory activity to MAO in vitro

The lazarabine was a compound containing amide group, and selective and reversible inhibition biological activity of MAO-B in the brain and peripheral organs. The drug was used to treat Parkinson's disease (PD) in clinical. This research used the lazarabine as a lead compounds, and the lazarabine derivatives were designed and synthesized. The a series of target compounds, we studying the inhibition activity of MAO-A or MAO-B *in vitro*. The drugs biological activity was related to the physical and chemical properties of their compounds, therefore, this research involved the log*P* and p*Ka* of all target compounds (**Table.1**). In **Table.1**, we could be found the target compounds belong fat-soluble and digested and absorbed in the gut. *In vitro* experiment, the two types of inhibitors (inhibition of MAO-A and inhibition of MAO-B) were screened by inhibition activity of MAO (**Table.1**). In the experiment *in vitro*, MAO-A and MAO-B were used as the inhibition biological activity targets, and the inhibition activity was measured by half maximal inhibitory concentration (IC_{50}). *In vitro* experiment moclobemide (inhibitory MAO-A) and rasagilin (inhibitory MOA-B) were used as the positive reference substance and DMSO was used as the blank control. Form the **Table.1**, we could be found compounds **3a**, **3d** and **3f** had intensity inhibition the biological activity of MAO-A, while compounds **3i** and **3m** had 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.

Table 1 *In vitro* IC_{50} values of test compounds 3a-3q for inhibition activity of MAO-A and MAO-B.

Compounds	X	n	R	log *P*	pK_a	IC_{50}±*SD*（μmol/mL）	
						MAO-A	MAO-B
3a	C	1	-OH	1.51	12.7	7.49±0.10	1435.43±15.93
3b	C	1	-Br	2.39	17.3	40.55±2.67	1370.43±13.65
3c	C	1	-NH_2	1.13	8.1	18.70±0.45	1569.65±17.21
3d	C	2	-OH	1.25	14.2	3.12±0.05	685.05±4.61
3e	C	2	-Br	2.59	20.2	26.78±1.06	894.65±6.76
3f	C	2	-NH_2	0.89	9.3	5.04±0.13	1396.50±15.03
3g	C	3	-OH	1.34	14.9	15.80±0.34	1509.56±17.23
3h	C	3	-Br	2.68	21.1	78.06±3.76	1873.23±20.13
3i	C	3	-NH_2	0.97	9.8	24.50±1.70	1609.44±18.90

3j	N	1	-OH	0.59	12.8	986.56±6.93	12.78±0.34
3k	N	1	-Br	1.48	16.8	569.65±6.46	60.69±1.90
3l	N	1	$-NH_2$	0.23	7.8	707.83±6.51	34.79±1.09
3m	N	2	-OH	0.35	14.0	586,86±4.67	5.04±0.06
3n	N	2	-Br	1.67	19.8	790.34±5.98	24.79±0.56
3o	N	3	-OH	0.45	14.5	1201.76±12.23	20.58±0.56
3p	N	3	-Br	1.78	20.5	1304.98±13.41	109.67±4.10
3q	N	3	$-NH_2$	0.06	9.5	1054.96±9.23	35.87±1.35
moclobemide						6.30±0.12	783.31±3.28
rasagilin						401.32±3.11	10.36±0.21
DMSO(control)						***	***

2.2.1. The inhibitory activity to MAO in vivo

In vivo biological activity experiments were conducted on the basis of *in vitro* biological activity screened, and it was further studied the pharmacology and toxicology of drugs *in vivo*. Through the *in vivo* biological activity experiment, the target compound will be prepared for the clinical experiment. The this research was used lazarabine as a lead compound, and the acute toxicity test (oral) of lazarabine, the results showed that LD_{50} was 1000-2000 $mg.kg^{-1}$, it belong low toxic compound. *In vivo* experiments, the research changes of monoamine contents (5-HT, NE and DA), and activity of monoamine oxidase (MAO-A and MAO-B) in plasma and brain tissue, when after administration of compounds **3a**, **3d**, **3f**, **3i** and **3m** (**Table 2**, **Fig.5** and **Fig.6**) . In **Table 2**, the compounds **3a**, **3d** and **3f** had increase the 5-HT and DA contents in brain tissue and plasma. And compounds **3i** and **3m** had increase the NE contents in brain tissue and plasma. In **Fig.5** and **Fig.6**, test activity of MAO-A or MAO-B in plasma and brain tissue. The result showed that the compounds **3a**, **3d** and **3f** had significantly inhibition of MAO-A, especially compound **3d**, and compounds **3i** and **3m** had significantly inhibition activity of MAO-B, especially compound **3m**. In toxicology, we studied the acute toxicity of these target compounds i*n vivo* (**Table 3**). In **Table 3**, we could be found these target compounds (**3a**, **3d**, **3f**, **3i** and **3m**) belong low acute toxicity, and oral dose LD_{50}≥ 2800 $mg.kg^{-1}$.

Table 2 *In vivo* content of test compounds 3a-3q for 5-HT, NE and DA.

Compounds	Content (ng/mg)					
	brain tissue			plasma		
	5-HT	NE	DA	5-HT	NE	DA

3a	0.545±0.006	2.641±0.211	0.832±0.231	123.2±10.6	436.9±21.8	231.1±11.5
3d	0.753±0.013	3.732±0.126	1.511±0.163	214.8±6.3	452.7±10.3	379.4±10.8
3f	0.613±0.032	3.135±0.218	1.214±0.326	150.4±8.6	440.4±9.6	307.5±9.6
3j	0.469±0.115	4.118±0.118	0.667±0.114	100.6±5.8	569.2±10.6	201.3±8.9
3m	0.515±0.154	4.988±0.125	0.768±0.164	116.4±9.5	628.3±10.9	211.6±11.2
DMSO	0.211±0.032	1.438±0.054	0.459±0.078	67.4±5.9	200.8±13.2	121.3±10.1

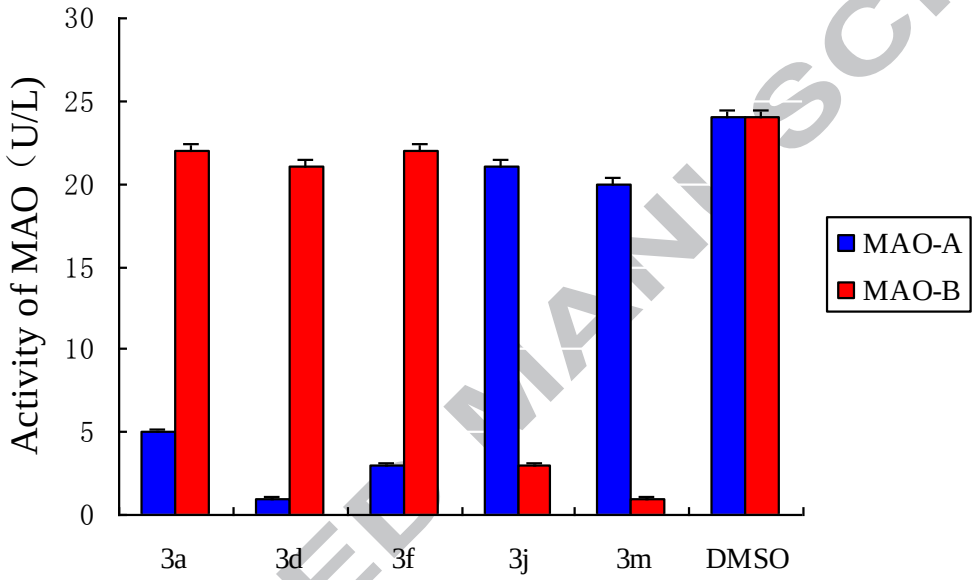


Fig.5 *In vivo* activity of MAO test for compounds in plasma.

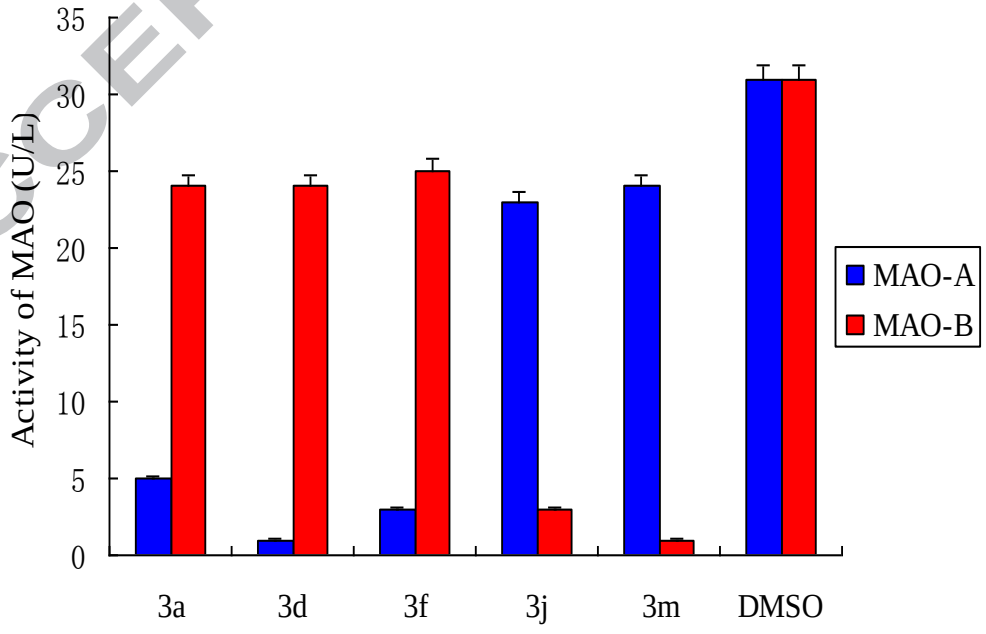
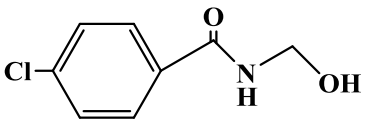
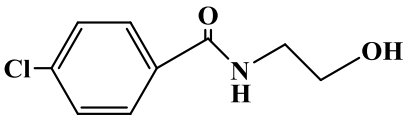
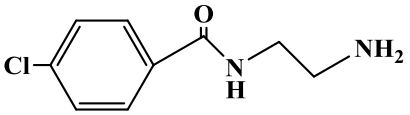
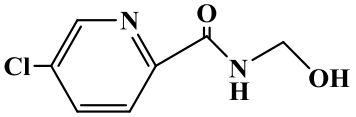
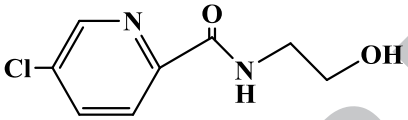


Fig.6 *In vivo* activity of MAO test for compounds in brain tissue.

Table 3 *In vivo* LD_{50} of test compounds.

Compounds	Structures	LD_{50}±*SD*（mg.kg^{-1}）
3a		3004.5±3.0
3d		3087.2±3.4
3f		2808.6±2.8
3j		2996.4±2.9
3m		3056.2 ±3.1

3. Conclusion

We report a series novel of compounds that inhibition biological activity of MAO (A/B). In this research lazabemide derivatives were designed, synthesized and evaluated as inhibitors of MAO. 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. *In vitro* experiments result showed that compounds **3a**, **3d** and **3f** had intensity inhibition the biological activity of MAO-A, while compounds **3i** and **3m** had 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 and DA, and activity of MAO-A and MAO-B in plasma and brain tissue. *In vivo* inhibition activity evaluation results showed that compounds **3a**, **3d**, **3f**, **3i** and **3m** had increased the content 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 compounds **3a**, **3d**, and **3f** had a significant inhibitory effect on the activity of MAO-A, while compound **3i** and **3m** showed inhibitory effect on the activity of MAO-B. The acute toxicity experiment showed that their compounds belong to low toxicity.

4. Experimental section

4.1. Chemistry section

*4.1.1. A general method for synthesis of compounds 2**a** to **2b***

The 4-chlorobenzoic acid (**1a**, 15.65 g, 0.10 mol) was put into 500mL round bottom flask, then 200 mL methylene chloride as solvent and 10 drops of *N, N'*-dimethyl formamide (DMF) used as catalyst for the reaction were added. The flask was placed in the ice water bath (≤10 ℃), and a magnetic mixer was used to stir until the reaction liquid became clarified. The thionyl chloride (11.25 mL, 0.15 mol) was constantly dropped into the flask under stirring, and the drop speed rate and reaction temperature were controlled (≤10 ℃ and ≥20 min). After the reactants were added, the reaction lasted 8 h under refluxing. The methylene chloride and excessive thionyl chloride were removed under vacuum. The mixture was dried to get the crude product of 4-chlorobenzoyl chloride (**2a**). The crude product was atmospheric distillation, collect the product of 221 ℃, and give pure product of 4-chlorobenzoyl chloride (**2a**) as a colorless transparent liquid. The general method was used to synthesis crude 5-chloropyridine-2-carbonyl chloride (**2b**) **,** the crude product was recrystallised with hexane, filtered, and dried in vacuum to give pure product of 5-chloropyridine-2-carbonyl chloride (**2b**) as a white crystal.

*4.1.2. A general method for synthesis of compounds 3**a** to **3s***

The 4-chlorobenzoyl chloride (**2a**, 17.50 g, 0.10 mol) was put into 500mL round bottom flask, then 200 mL methylene chloride as solvent for the reaction were added. The flask was placed in the ice water bath (0-10℃), and a magnetic mixer was used to stir until the reaction liquid became clarified. The aminomethanol (9.75 mL, 0.20 mol) was constantly dropped into the flask under stirring, and the drop speed rate and reaction temperature were controlled (0-10 ℃ and ≥30 min). After the reactants were added, the reaction lasted 24 h under standing. The methylene chloride was removed under vacuum. The mixture was dried to get the crude product of 4-chloro-*N*-(hydroxymethyl) benzamide (**3a**). The crude product was recrystallised with toluene, filtered, and dried in vacuum to give pure product of 4-chloro-*N*-(hydroxymethyl) benzamide (**3a**)

as a white crystal. The general method was used to synthesis compound **3b** to**3s**.

4-chloro-*N*-(hydroxymethyl) benzamide (**3a**): white crystal, yield 97.3%, m.p.105-107 ℃; ^{1}H NMR （300MHz, DMSO）δ: 4.29 (1H, t, *J* = 4.9 Hz, -OH), 5.44 (2H, d, *J* = 4.9 Hz, -CH_2-), 7.50 (2H, m, *J*=7.0 Hz, Ph-H), 7.74 (2H, m, *J*=7.0 Hz, Ph-H); ^{13}C NMR （75MHz, DMSO）δ: 59.3, 128.9, 130.6, 133.6, 136.8, 168.8; HR-ESI-MS *m/z*: calcd for $C_8H_8ClNO_2$ {［M+H］$^+$} 185.6071, found 185.0246; Anal.calcd for $C_8H_8ClNO_2$: C, 51.77; H, 4.34; Cl, 19.10; N, 7.55; O, 17.24; found: C, 51.78; H, 4.33; Cl, 19.11; N, 7.55; O, 17.23%.

4-chloro-*N*-(bromomethyl) benzamide (**3b**): white crystal, yield 96.5%, m.p.144-146 ℃; ^{1}H NMR （300MHz, DMSO）δ: 5.21 (2H, s, -CH_2-), 7.50 (2H, m, *J*=7.0 Hz, Ph-H), 7.92 (2H, m, *J*=7.0 Hz, Ph-H); ^{13}C NMR（75MHz, DMSO）δ: 46.6, 127.2, 128.9, 133.6, 136.8, 168.6; HR-ESI-MS *m/z*: calcd for $C_8H_7BrClNO$ {［M+H］$^+$} 248.5041, found 247.0405; Anal.calcd for $C_8H_7BrClNO$: C, 38.67; H, 2.84; Br, 32.15; Cl, 14.27; N, 5.64; O, 6.44; found: C, 38.66; H, 2.85; Br, 32.14; Cl, 14.28; N, 5.65; O, 6.43%.

4-chloro-*N*-(aminomethyl) benzamide (**3c**): white crystal, yield 98.6%, m.p.101-103 ℃; ^{1}H NMR （300MHz, DMSO δ: 3.38 (2H, t, *J* = 4.1 Hz, -CH_2-), 7.50 (2H, m, *J*=7.0 Hz, Ph-H), 7.83 (2H, m, *J*=7.0 Hz, Ph-H); ^{13}C NMR（75MHz, DMSO）δ: 53.0, 127.4, 128.9, 133.6, 136.8, 169.4; HR-ESI-MS *m/z*: calcd for $C_8H_9ClN_2O$ {［M+H］$^+$} 184.6232, found 184.0404; Anal.calcd for $C_8H_9ClN_2O$: C, 52.05; H, 4.91; Cl, 19.20; N, 15.17; O, 8.67; found: C, 52.06; H, 4.90; Cl, 19.21; N, 15.15; O, 8.68%.

4-chloro-*N*-(2-hydroxyethyl) benzamide (**3d**): white crystal, yield 96.8%, m.p.110-112 ℃; ^{1}H NMR（300MHz, DMSO δ: 4.56 (2H, s, -CH_2-), 7.50 (2H, m, *J*=7.0 Hz, Ph-H), 7.74 (2H, m, *J*=7.0 Hz, Ph-H); ^{13}C NMR（75MHz, DMSO）δ: 42.8, 61.4, 126.5, 128.9, 133.6, 136.8, 167.7; HR-ESI-MS *m/z*: calcd for $C_9H_{10}ClNO_2$ {［M+H］$^+$} 199.6343, found 199.0402; Anal.calcd for $C_9H_{10}ClNO_2$: C, 54.15; H, 5.05; Cl, 17.76; N, 7.02; O, 16.03; found: C, 54.16; H, 5.04; Cl, 17.76; N, 7.01; O, 16.04%.

4-chloro-*N*-(2-bromoethyl) benzamide (**3e**): white crystal, yield 94.8%, m.p.151-153 ℃; ^{1}H NMR （300MHz, DMSO）δ: 3.70 (2H, t, *J* = 4.4 Hz, -CH_2-), 3.87 (2H, t, *J* = 4.4 Hz, -CH_2-), 7.50 (2H, m, *J*=7.0 Hz, Ph-H), 7.83 (2H, m, *J*=7.0 Hz, Ph-H); ^{13}C NMR（75MHz，DMSO）δ: 35.5, 43.4, 126.9, 128.9, 133.6, 136.8, 168.4; HR-ESI-MS *m/z*: calcd for $C_9H_9BrClNO${［M+H］$^+$} 262.5311, found 260.9553; Anal.calcd for $C_9H_9BrClNO$: C, 41.18; H, 3.46; Br, 30.44; Cl, 13.50; N, 5.34; O,

6.09; found: C, 41.19; H, 3.45; Br, 30.45; Cl, 13.51; N, 5.33; O, 6.08%.

4-chloro-*N*-(2-aminoethyl) benzamide (**3f**): white crystal, yield 96.8%, m.p.114-116 ℃; ^{1}H NMR （300MHz, DMSO）δ: 3.26 (2H, t, *J* = 4.9 Hz, -CH_2-),3.94 (2H, t, *J* = 4.9 Hz, -CH_2-) 7.50 (2H, m, *J*=7.0 Hz, Ph-H), 7.83(2H, m, *J*=7.0 Hz, Ph-H); ^{13}C NMR（75MHz, DMSO）δ: 37.9, 48.1, 127.2, 128.9, 133.6, 136.8, 168.4; HR-ESI-MS *m/z*: calcd for $C_9H_{11}ClN_2O$ {［M+H］$^+$} 198.6503, found 198.0561; Anal.calcd for $C_9H_{11}ClN_2O$: C, 54.42; H, 5.58; Cl, 17.85; N, 14.10; O, 8.05; found: C, 54.41; H, 5.58; Cl, 17.84; N, 14.11; O, 8.06%.

4-chloro-*N*-(3-hydroxypropyl) benzamide (**3g**): white crystal, yield 94.9%, m.p.126-128℃; ^{1}H NMR（300MHz, DMSO）δ: 1.72 (2H, m, *J* = 5.2 Hz, -CH_2-),3.41 (2H, q, *J* = 5.0 Hz, -CH_2-), 4.47 (2H, t, *J* = 5.3 Hz, -CH_2-), 4.72 (1H, t, *J* = 5.0 Hz, -OH),7.50 (2H, m, *J*=7.0 Hz, Ph-H), 7.83 (2H, m, *J*=7.0 Hz, Ph-H); ^{13}C NMR（75MHz, DMSO）δ: 31.8, 37.4, 59.9, 126.5, 128.8, 133.6, 136.8, 168.6; HR-ESI-MS *m/z*: calcd for $C_{10}H_{12}ClNO_2$ {［M+H］$^+$} 213.6613, found 213.0554; Anal.calcd for $C_{10}H_{12}ClNO_2$: C, 56.22; H, 5.66; Cl, 16.59; N, 6.56; O, 14.98; found: C, 56.21; H, 5.67; Cl, 16.58; N, 6.56; O, 14.99%.

4-chloro-*N*-(3-bromopropyl) benzamide (**3h**): white crystal, yield 92.1%, m.p.176-178 ℃; ^{1}H NMR（300MHz, DMSO）δ:2.09 (2H, t, *J* = 7.8 Hz, -CH_2-), 3.28 (2H, t, *J* = 7.8 Hz, -CH_2-), 3.48 (2H, t, *J* = 7.8 Hz, -CH_2-), 7.50 (2H, m, *J*=7.0 Hz, Ph-H), 7.83 (2H, m, *J*=7.0 Hz, Ph-H); ^{13}C NMR （75MHz, DMSO）δ: 30.8, 32.5, 40.8, 126.2, 128.7, 133.6, 136.8, 168.6; HR-ESI-MS *m/z*: calcd for $C_{10}H_{11}BrClNO$ {［M+H］$^+$} 276.5582, found 275.1713; Anal.calcd for $C_{10}H_{11}BrClNO$: C, 43.43; H, 4.01; Br, 28.89; Cl, 12.82; N, 5.06; O, 5.79; found: C, 43.44; H, 4.02; Br, 28.88; Cl, 12.83; N, 5.07; O, 5.78%.

4-chloro-*N*-(3-aminopropyl) benzamide (**3i**): white crystal, yield 94.5%, m.p.130-132 ℃; ^{1}H NMR （300MHz, DMSO）δ: 2.20 (2H, t, *J* = 7.7 Hz, -CH_2-), 2.63 (2H, t, *J* = 7.7 Hz, -CH_2-), 3.48 (2H, t, *J* = 7.7 Hz, -CH_2-), 7.50 (2H, m, *J*=7.0 Hz, Ph-H), 7.83 (2H, m, *J*=7.0 Hz, Ph-H); ^{13}C NMR （75MHz, DMSO）δ: 28.9, 37.1, 38.6, 127.6, 128.9, 133.6, 136.8, 168.6; HR-ESI-MS *m/z*: calcd for $C_{10}H_{13}ClN_2O$ {［M+H］$^+$} 212.6772, found 212.0713; Anal.calcd for $C_{10}H_{13}ClN_2O$: C, 56.48; H, 6.16; Cl, 16.67; N, 13.17; O, 7.52; found: C, 56.49; H, 6.17; Cl, 16.65; N, 13.16; O, 7.53%.

5-chloropyridine-*N*-(hydroxymethyl)-2-carbonylamide (**3j**): white crystal, yield 98.3%, m.p.100-102 ℃; ^{1}H NMR（300MHz, DMSO）δ: 4.67 (1H, t, *J* = 4.9 Hz, -OH), 5.18 (2H, d, *J* = 5.1 Hz, -CH_2-), 8.04 (1H, dd, *J* = 8.1, 1.3 Hz, Py-H), 8.12 (1H, d, *J* = 8.0 Hz, Py-H), 8.86 (1H, d, *J* = 1.3

Hz, Py-H); ^{13}C NMR（75MHz, DMSO）δ: 69.3, 126.4, 127.7, 132.9, 148.8, 150.8, 164.4; HR-ESI-MS *m/z*: calcd for $C_7H_7ClN_2O_2$ {［M+H］$^+$} 186.5952, found 186.0197; Anal.calcd for $C_7H_7ClN_2O_2$: C, 45.06; H, 3.78; Cl, 19.00; N, 15.01; O, 17.15; found: C, 45.07; H, 3.77; Cl, 19.02; N, 15.00; O, 17.14%.

4-chloropyridine-*N*-(bromomethyl)-2-carbonylamide (**3k**): white crystal, yield 95.6%, m.p.130-132 ℃; ^{1}H NMR（300MHz, DMSO）δ: 4.97 (2H, s, -CH_2-), 8.04 (1H, dd, *J* = 8.1, 1.3 Hz, Py-H), 8.14 (1H, d, *J* = 8.0 Hz, Py-H), 8.87 (1H, d, *J* = 1.3 Hz, Py-H); ^{13}C NMR（75MHz, DMSO）δ: 44.2, 126.4, 127.7, 132.9, 148.8, 150.8, 164.0; HR-ESI-MS *m/z*: calcd for $C_7H_6BrClN_2O$ {［M+H］$^+$} 249.4922, found 247.9350; Anal.calcd for $C_7H_6BrClN_2O$: C, 33.70; H, 2.42; Br, 32.03; Cl, 14.21; N, 11.23; O, 6.41; found: C, 33.69; H, 2.44; Br, 32.03; Cl, 14.22; N, 11.24; O, 6.40%.

5-chloropyridine-*N*-(aminomethyl)-2-carbonylamide (**3l**): white crystal, yield 99.3%, m.p.98-100 ℃; ^{1}H NMR（300MHz, DMSO）δ: 4.32 (2H, s, -CH_2-), 8.01 (1H, dd, *J* = 8.1, 1.3 Hz, Py-H), 8.11 (1H, d, *J* = 8.0 Hz, Py-H), 8.84 (1H, d, *J* = 1.3 Hz, Py-H); ^{13}C NMR（75MHz, DMSO）δ: 53.0, 126.4, 127.7, 132.9, 148.8, 150.8, 164.9; HR-ESI-MS *m/z*: calcd for $C_7H_8ClN_3O$ {［M+H］$^+$} 185.6112, found 185.0357; Anal.calcd for $C_7H_8ClN_3O$: C, 45.30; H, 4.34; Cl, 19.10; N, 22.64; O, 8.62; found: C, 45.29; H, 4.32; Cl, 19.11; N, 22.65; O, 8.63%.

5-chloropyridine-*N*-(2-hydroxyethyl)-2-carbonylamide (**3m**): white crystal, yield 96.5%, m.p.118-120 ℃; ^{1}H NMR（300MHz, DMSO）δ: 3.39(2H, t, *J* = 4.0 Hz, -CH_2-), 3.54(2H, dt, J = 5.1, 4.1 Hz, -CH_2-), 4.86(1H, t, *J* = 6.1 Hz,-OH), 8.04 (1H, dd, *J* = 8.0, 1.2 Hz, Py-H), 8.10 (1H, d, *J* = 8.1 Hz, Py-H), 8.70 (1H, d, *J* = 1.3 Hz, Py-H); ^{13}C NMR（75MHz, DMSO）δ: 42.1, 60.1, 123.7, 134.3, 138.0, 147.4, 148.9, 163.4; HR-ESI-MS *m/z*: calcd for $C_8H_9ClN_2O_2$ {［M+H］$^+$} 200.6221, found 200.0355; Anal.calcd for $C_8H_9ClN_2O_2$: C, 47.90; H, 4.52; Cl, 17.67; N, 13.96; O, 15.95; found: C, 47.91; H, 4.53; Cl, 17.65; N, 13.97; O, 15.94%.

5-chloropyridine-*N*-(2-bromoethyl))-2-carbonylamide (**3n**): white crystal, yield 94.1%, m.p.170-171 ℃; ^{1}H NMR（300MHz, DMSO）δ: 3.15 (2H, t, *J* = 4.4 Hz, -CH_2-), 3.80 (2H, t, *J* = 4.4 Hz, -CH_2-), 7.74 (1H, dd, *J* = 8.1, 1.3 Hz, Py-H), 7.79 (1H, d, *J* = 7.9 Hz, Py-H), 8.40 (1H, d, *J* = 1.2 Hz, Py-H); ^{13}C NMR（75MHz, DMSO）δ: 33.6, 43.4, 126.4, 127.7, 132.9, 148.8, 150.8, 165.1; HR-ESI-MS *m/z*: calcd for $C_8H_8BrClN_2O$ {［M+H］$^+$} 263.5192, found 261.9507; Anal.calcd for $C_8H_8BrClN_2O$: C, 36.46; H, 3.06; Br, 30.32; Cl, 13.45; N, 10.63; O, 6.07; found: C, 36.47; H, 3.05; Br, 30.33; Cl, 13.44; N, 10.64; O, 6.06%.

6-chloropyridine-*N*-(3-hydroxypropyl)-2-carbonylamide (**3o**): white crystal, yield 93.1%, m.p.132 -134 ℃; ^{1}H NMR（300MHz, DMSO）δ: 1.68 (2H, p, *J* = 4.9 Hz, -CH_2-), 3.41 (2H, q, *J* = 4.7 Hz, -CH_2-), 3.61 (2H, t, *J* = 5.0 Hz, -CH_2-), 4.33(1H, t, *J* = 5.0 Hz,-OH), 8.03 (1H, dd, *J* = 8.0, 1.2 Hz, Py-H), 8.12 (1H, d, *J* = 8.0 Hz, Py-H), 8.86 (1H, d, *J* = 1.3 Hz, Py-H); ^{13}C NMR（75MHz, DMSO）δ: 32.0, 37.8, 59.9, 126.4, 127.7, 132.9, 148.8, 150.8, 164.0; HR-ESI-MS *m/z*: calcd for $C_9H_{11}ClN_2O_2$ {［M+H］$^+$} 214.6491, found 214.0507; Anal.calcd for $C_9H_{11}ClN_2O_2$: C, 50.36; H, 5.17; Cl, 16.52; N, 13.05; O, 14.91; found: C, 50.37; H, 5.17; Cl, 16.53; N, 13.04; O, 14.90%.

5-chloropyridine-*N*-(3-bromopropyl))-2-carbonylamide (**3p**): white crystal, yield 92.8%, m.p.170-171 ℃; ^{1}H NMR（300MHz, DMSO）δ: 2.05 (2H, tt, *J* = 7.8, 5.1 Hz, -CH_2-), 3.24 (2H, t, *J* = 5.1 Hz, -CH_2-), 3.47 (2H, t, *J* = 7.9 Hz, -CH_2-), 8.00 (1H, dd, *J* = 7.9, 1.2 Hz, Py-H), 8.10 (1H, d, *J* = 8.0 Hz, Py-H), 8.86 (1H, d, *J* = 1.2 Hz, Py-H); ^{13}C NMR（75MHz, DMSO）δ: 30.8, 32.5, 40.8, 126.4, 127.7,132.9, 148.8, 150.8, 164.0; HR-ESI-MS *m/z*: calcd for $C_9H_{10}BrClN_2O$ {［M+H］$^+$} 277.5461, found 275.9663; Anal.calcd for $C_9H_{10}BrClN_2O$: C, 38.95; H, 3.63; Br, 28.79; Cl, 12.77; N, 10.09; O, 5.76; found: C, 38.94; H, 3.65; Br, 28.78; Cl, 12.77; N, 10.08; O, 5.77%.

5-chloropyridine-*N*-(3-aminopropyl)-2-carbonylamide (**3q**): white crystal, yield 95.1%, m.p.133-135 ℃; ^{1}H NMR（300MHz, DMSO）δ: 2.16 (2H, p, *J* = 5.1 Hz, -CH_2-), 2.63 (2H, t, *J* = 5.1 Hz, -CH_2-), 3.24 (2H, t, *J* = 5.1 Hz, -CH_2-), 7.95 (1H, dd, *J* = 8.0, 1.2 Hz, Py-H), 8.07 (1H, d, *J* = 8.0 Hz, Py-H), 8.79 (1H, d, *J* = 1.1 Hz, Py-H); ^{13}C NMR（75MHz, DMSO）δ: 28.9, 37.2, 38.1, 126.4, 127.7, 132.9, 148.8, 150.8, 164.6; HR-ESI-MS *m/z*: calcd for $C_9H_{12}ClN_3O$ {［M+H］$^+$} 213.6653, found 213.0668; Anal.calcd for $C_9H_{12}ClN_3O$: C, 50.59; H, 5.66; Cl, 16.59; N, 19.67; O, 7.49; found: C, 50.58; H, 5.67; Cl, 16.58; N, 19.68; O, 7.48%.

4.2. Biological section

4.2.1. Screening of biological activity of compounds in vitro

4.2.1.1. Preparation of MAO in vitro

According to the literature[6], with mature male rat, broken its marrow to death on the super net work quickly remove the liver, with 0.9% saline wash liver 3 times, with dry absorbent paper, in the in -80 ℃refrigerator frozen preservation, and later using.

Used electronic analytical balance said in 5 g frozen after liver tissue, add 1200 mL of 0.3 mol/L sucrose solution, slurry, and low temperature (0-5 ℃) at high speed refrigerated centrifuge in liver tissue in 25 r/s centrifugal about 600 s. Take that to 150 r/s centrifugal supernatant fluid of

1800 s, and precipitation suspension in the 5 mL of 0.3 mol/L sucrose solution, and then placed in 60 mL of 1.2 mol/L sucrose solution, and with 160 r/s centrifugal about 2400 s. Take the precipitation with a tendency for 100 mmol/L potassium phosphate buffer solution (pH7.9) washing, and the precipitation was suspended by 50 mL of 100 mmol/L potassium phosphate buffer to obtain MAO. Partial shipments into 1 mL each EP tube, and into the frozen storage in a freezer -80℃, and later using.

4.2.1.2. In vitro screening of MAO inhibitors

(a) Inhibition of MAO-A

The 5-HT was used as a reaction substrate to inhibit MAO-A biological activity. The tendency for 75 μL of 100 mmol/L potassium phosphate buffer solution (pH7.9), 25 μL different concentrations for compounds, and 50 μL MAO, and under the condition of 37℃and 5% CO_2 incubation of 1200 s. In addition, the 5-HT of 100 μL was added, so that the final concentration of MAO was 0.40 mg/mL and 5-HT was 5 mmol/L, and allowed to continue to react after 3600 s.The add 200 μL of 10% perchloric acid solution, and the reaction product 2-(5-hydroxyindole) acetaldehyde was extracted with 5 mL ethyl acetate, and its absorbance A value was determined at wavelength of 280 nm.

(b) Inhibition of MAO-B

The benzylamine was used as a reaction substrate to inhibit MAO-A biological activity. The tendency for 75 μL of 100 mmol/L potassium phosphate buffer solution (pH7.9), 25 μL different concentrations for compounds, and 50 μL MAO, and under the condition of 37 ℃and 5% CO_2 incubation of 1200 s. In addition, the benzylamine of 100 μL was added, so that the final concentration of MAO was 0.15 mg/mL and benzylamine was 2 mmol/L, and allowed to continue to react after 3600 s. The add 200 μL of 10% perchloric acid solution, and the reaction product benzaldehyde was extracted with 5 mL cyclohexane, and its absorbance A value was determined at wavelength of 240 nm. Moclobemide and Rasagilin were used as the positive reference substance and DMSO was used as the blank control.

4.2.2. Biological activity of compounds inhibition MAO in vivo

The 20 adult rats (half male and half female) were taken, and were given oral doses of 20 $mg.kg^{-1}.d^{-1}$ for one week. All the rats were put to death with their heads cut off, the rats were dissected on the ultra-clean working table and 100 mg of brain tissue was taken out. Added 1 mL

for 10% perchloric acid solution, homogenate at low temperature, and centrifuge at high speed 300 r/s at low temperature for 1200 s. Take the supernatant, and into the frozen storage in a freezer -80℃, and later using. At the same time, the 1 mL plasma was taken out, and 10% perchloric acid solution of the same volume was added, and violent vibration for 60 s. And then centrifuged at high speed 300 r/s at low temperature for 1200 s. Take the supernatant, and into the frozen storage in a freezer -80 ℃, and later using. The 20 μL spare liquid was taken out, and the contents of 5-HT, NE and DA were measured by High Performance Liquid Chromatography (HPLC, internal standard method). Moclobemide and Rasagilin were used as the positive reference substance and DMSO was used as the blank control.

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