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# Synthesis and Biological Evaluation of 1,2,3,4-Tetrahydroisoquinolines Derivatives as Monoamine Oxidase Inhibitors for Treatment of Alzheimer's and Parkinson's Diseases

HONGMEI GUO, ZHENHAO LU, SHIQIANG CHEN and YU YU*

College of Pharmaceutical Sciences, Chongqing Medical University, Chongqing 400016, P.R. China

*Corresponding author: E-mail: taozhu006@163.com

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A series of 1,2,3,4-tetrahydroisoquinolines derivatives were synthesized and evaluated their inhibition effect on monoamine oxidase (MAO). The results of pharmacological test revealed that all the five compounds had certain monoamine oxidase inhibitory activity and compound **6h** displayed preferable selective inhibition on MAO-A. These data suggested that newly synthesized 1,2,3,4-tetrahydroisoquinoline derivatives can be evaluated as monoamine oxidase inhibitors which may have promising features in the treatment of Alzheimer's and Parkinson's diseases.

**Keywords: Tetrahydroisoquinoline, Monoamine oxidase, Inhibitor.**

## INTRODUCTION

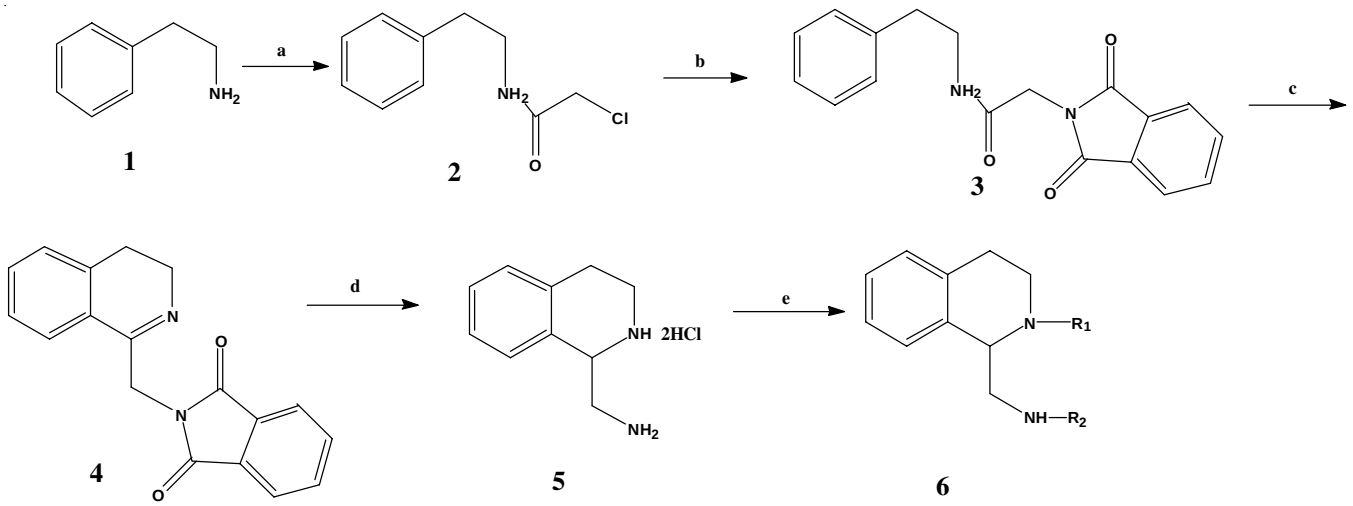
Monoamine oxidase (MAO, oxidoreductase, EC1.4.3.4) is a FAD-containing enzyme with two known isoforms (MAO-A and MAO-B) and is present in the mitochondrial outer membrane of glial, neuronal and other cells[1]. Monoamine oxidase enzymes intervene in the monoamines degradation and carry out an important physiologic function in the adrenaline, noradrenaline and serotonin deamination (preferentially MAO-A) and in the β-phenylethylamine and benzylamine deamination (preferentially MAO-B)[2]. This enzymatic function increases the synaptic concentration of these neurotransmitters and conditions to a great extent the neurone's excitement of those possessing receptors for these mediators[3]. The monoamine oxidase inhibitors are a class of compounds that act by blocking the monoamine oxidase enzymatic action, being used by several years in the treatment of the depression and anxiety diseases or in Parkinson's disease[4]. Nowadays is being studied also in the Alzheimer's disease.

In regard to the monoamine oxidase inhibition, the recent findings revealed that MAO-A and MAO-B affinity and selectivity can be efficiently modulated by appropriate substitutions in the 1,2,3,4-tetrahydroisoquinoline[5]. Retaining this 1,2,3,4-tetrahydroisoquinoline fragment, a series of novel 1-aminomethyl-1,2,3,4-tetrahydroisoquinoline derivatives were designed, synthesized and evaluated as the monoamine oxidase inhibitors. These modifications were studied to find out how these changes can contribute to the biological activity of these molecules, helping to understand a structure-activity relationship. According to the retrosynthetic analysis, the derivatives can be prepared from phenylethylamine (**1**) as shown in **Scheme-I**.

## EXPERIMENTAL

Male Sprague-Dawley rats were housed in cages at an environmental temperature of 20 °C and were fed rat chow *ad libitum* for the duration of the experiment. All reagents and chemicals were analytical grade and were purchased from either Sigma (Israel) or Merck (Germany).

**Determination of MAO-A and MAO-B inhibition *in vitro*:** Cerebral cortical tissue was homogenized in 0.3 M sucrose (one part tissue to 20 parts sucrose) using a glass-Teflon motor-driven homogenizer (brain and liver), or Ultraturrax (gut). The inhibitor under test was added to a suitable dilution of the enzyme preparation in 0.05 M phosphate buffer (pH 7.4) and incubated together with rasagiline 0.1 μM (for determination of MAO-A and MAO-B). Incubation was carried on for 60 min at 37 °C before addition of labelled substrates (5-hydroxy-tryptamine creatinine disulphate 100 μM for determination of MAO-A, phenylethylamine 10 μM for determination of MAO-B) and incubation continued for 30 or 20 min respectively. The reaction was then stopped by addition of citric acid (2 M). The metabolites were extracted into toluene/ethyl acetate (1:1 v/v) and metabolite content estimated by liquid scinti-llation counting. Activity in presence of drug was expressed as a percentage of that in control samples[6].




**Scheme-I:** Reagents and conditions: (a) $ClCH_2COCl$, Pyridine, $CH_2Cl_2$, 95.1 %; (b) Phthalimide potassium salt, DMF, 94.4 %; (c) $P_2O_5$, Acetonitrile, reflux, 85 %; (d) 80 % $NH_2NH_2{\cdot}H_2O$, $KBH_4$, HCl, 70 %; (e) Acylating agents, Pyridine, $CH_2Cl_2$

**Statistical analysis:** Values of $IC_{50}$ *in vitro* and *in vivo* analyses were calculated in each separate experimental run by non-linear regression analysis using the SPSS 18 statistical software.

All new compounds were characterized by $^1$H NMR and IR prior to biological evaluation. The $^1$H NMR spectra were recorded on a Bruker Avance 400 spectrometer (400 MHz). IR spectra were recorded on a Perkin Elmer UK spectrum one with KBr tablet.

**Preparation of N-(chloroacetyl)phenylethylamine (2):** A mixture of phenylethylamine (**1**) (25.2 mL, 0.2 mol) and pyridine (16.2 mL, 0.2 mol) was placed in the dichloromethane (60 mL), chloroacetyl chloride at 0 °C was added dropwise with stirring 2 h. Then the organic solution was washed successively with water (50 mL × 3) and dried by $Na_2SO_4$, filtered and the solvent was removed under reduced pressure to give the crude products. The residue was recrystallized from ethanol to give the compound **2** (38.1 g, 95.1 %) as a white solid. m.p.: 60.5-62.0 °C [lit[7]. 61-63 °C]

**Preparation of N-(N-acetyl-phenylethylamino)phthalimide (3):** A mixture of compound **2** (20 g, 0.1 mol) and potassium phthalimide (22.5 g, 0.12 mol) was placed in the DMF (60 mL), which was heated to 110 °C. After reaction 10 h pour the reaction solution into the water (500 mL), precipitated the white solid, filter and wash by water. Finally it was obtained the white solid (29.4.1 g, 94.4 %) m.p.: 187.5-188.5 °C [lit[8]. 186-188 °C]

**Preparation of N-[(1-methylene)-3,4-dihydro-isoquinoline]phthalimide (4):** To a solution of compound **3** (10 g, 32.5 mmol) in acetonitrile (150 mL), $P_2O_5$ (18 g, 130 mmol) was added under continuous stirring. The reaction was heated at reflux for 5 h. The solvent was removed *in vacuo* and the residue was dissolved in water. The solution was adjusted to pH 6 by 20 % NaOH, precipitated the white solid, filter and wash by acetone. The residue was recrystallized from THF to give the compound **4** (8.6 g, 91.2 %) as a white solid. m.p.: 202.5-204.0 °C [lit[8]. 201-203 °C].

**Preparation of 1-aminomethyl-1,2,3,4-tetrahydroisoquinoline (5):** A solution of compound **4** (5.8 g, 20 mmol) and 80 % $NH_2NH_2{\cdot}H_2O$ (1.4 mL, 24 mmol) in methanol (50 mL) was heated to reflux. After stirring for 2 h $KBH_4$ (2.12 g, 24 mmol) was added at 10 °C and stirring was continued for another 4 h at room temperature. The solution was adjusted to pH 5 by 6 N HCl and the methanol was removed *in vacuo*. Then a solution of 20 % NaOH was added to alkaline. The resulting mixture was extracted with $CH_2Cl_2$ (10 mL × 3). The organic layer was washed with 2N HCl (10 mL × 3) and dried by $Na_2SO_4$, filtered and the solvent was removed under reduced pressure to give the white solid (3.3 g, 70 %). m.p.: 259.5-261.5 °C lit[9]. 264-268 °C].

**Compound 6a:** Compound **5** (2.0 g, 8.5 mmol) was dissolved in 10 % NaOH solution, the mixture was extracted with $CH_2Cl_2$ (15 mL) and dried by $Na_2SO_4$. The mixture was added to pyridine (1.4 mL) and chloroacetyl chloride (2.1 g, 18.7 mmol) was added dropwise to a stirred 2 h. The resulting mixture was washed with 2N HCl (30 mL) and collected the organic layer, dried on $Na_2SO_4$, filtered and the solvent was removed under reduced pressure to give the crude products. The residue was recrystallized from ethanol to give the compound **6a** as a white solid. m.p.: 178-180 °C. IR (KBr, $\nu_{max}$, $cm^{-1}$): 3301.54 (N-H), 3016 (ArH), 2929.06 ($CH_2$),1671.98 (C=O).1251.58 (C-N). $^1$H NMR ($CDCl_3$, 500 MHz); 1.963-2.188 (m, 6H, $COCH_3$), 2.916-3.679 (s, 6H, $CH_2$), 5.702-5.740 (m, 1H, CH), 7.140-7.237 (m, 4H, ArH), 7.277-7.279 (d, 1H, CONH).

The following compounds **6a-6h** were prepared using the experimental procedure described for the preparation of compound **6a**.

**Compound 6b:** m.p.: 127-129 °C. IR (KBr, $\nu_{max}$, $cm^{-1}$): 3332.39 (N-H), 3041.19 (ArH), 2927.21 ($CH_2$),1636.34 (C=O). 1255.43 (C-N). $^1$H NMR ($CDCl_3$, 400 MHz); 2.918-3.068 (m, 2H, $ArCH_2$), 3.492-4.159 (m, 2H, $CH_2N$), 5.756-5.780 (m, 1H, CHN), 7.172-7.235 (m, 4H, ArH), 7.277-7.326 (t, 4H, NH).

**Compound 6c:** m.p.: 148-150 °C. IR (KBr, $\nu_{max}$, $cm^{-1}$): 3293.82 (N-H), 3014.19 (ArH), 2969.84 ($CH_2$),1041.27 (S=O). $^1$H NMR ($CDCl_3$, 400 MHz): 1.594 (s,1H, $SO_2NH$), 2.807-3.087 (m, 6H, $SO_2CH_3$), 3.462-4.930 (m, 6H, $CH_2$), 3.945-4.004 (m, 1H, CH), 7.173-7.275 (m, 4H, ArH).

**Compound 6d:** m.p.: 162-164 °C. IR (KBr, $\nu_{max}$, $cm^{-1}$): 3192.82, (N-H), 3014.19 (ArH ), 2925.48 ($CH_2$), 1670.05

(C=O),1273.42 (C-N).$^1$H NMR ($CDCl_3$, 400 MHz): 1.44-1.68 ( m, 20H, $CH_2$), 2.38 (d, 2H, COCH), 2.81 (t,2H, $CH_2N$), 3.53-3.74 (t, 2H, $CH_2N$), 3.75 ( t, 2H, $CH_2N$), 5.5 (t, 1H, CHN), 7.03-7.07 ( m, 4H, ArH), 8.0 (t, 1H, NH).

**Compound 6e:** m.p.: 112-113 °C. IR (KBr, $\nu_{max}$, $cm^{-1}$): 3372.89, 3216.96 (N-H); 3054.19 (ArH ),2917.64 ($CH_2$) 1672.57 (C=O). $^1$H NMR ($CDCl_3$, 400 MHz): 1.16-1.84 (m, 10H, $CH_2$), 2.73-2.83 (d, 2H, COCH), 3.23-3.63 (t, 2H, $CH_2N$), 3.75 (t, 2H, $CH_2N$), 5.5 (t, 1H, CHN), 7.03-7.07 (m, 4H, ArH), 8.0 (t, 1H, NH).

**Compound 6f:** m.p.: 152-156 °C. IR (KBr, $\nu_{max}$, $cm^{-1}$): 3291.28 (N-H); 3014.19 (ArH), 2918.64 ($CH_2$).$^1$H NMR ($CDCl_3$, 400 MHz): 1.82-1.84 ( s, 1H, CH), 2.54-3.23 (d, 8H, $CH_2$), 5.2 (t, 1H, CHN),7.03-7.07 (m, 4H, ArH).

**Compound 6g:** m.p.: 173-176 °C. IR (KBr, $\nu_{max}$, $cm^{-1}$): 3285.46, (N-H); 3028.23 (ArH), 2922.53 ($CH_2$). $^1$H NMR ($CDCl_3$, 400 MHz): 1.85-1.88 ( s,1H, CH), 2.53-3.43 (d,10H, $CH_2$), 5.2 (t, 1H, CHN), 5.5-5.8 (m, 3H, CH),7.05-7.13 ( m,4H, ArH).

**Compound 6h:** m.p.: 144-146 °C. IR (KBr, $\nu_{max}$, $cm^{-1}$): 3291.28, (N-H); 3031.15 (ArH), 2917.76 ($CH_2$).$^1$H NMR ($CDCl_3$, 400 MHz): 1.82-1.92 ( m, 2H, CH), 2.51-3.29 (d,10H, $CH_2$), 5.3 (t, 1H, CHN),7.05-7.08 (m,4H, ArH).

## RESULTS AND DISCUSSION

With the aim of finding out new structural features for the monoamine oxidase inhibitory activity and selectivity, we decided in this work to explore the importance of the number and position of different groups under the 1,2,3,4-tetrahydroisoquinoline in 1-aminomethyl-position, to establish a relation between them and with the substituted analogue.

The preparation of these 1-aminomethyl-1,2,3,4-tetrahydroisoquinoline was performed *via* the classical Gabriel reaction and Bischler-Napieralski reaction. First of all, phenylethylamine (**1**) reacted with chloroacetyl chloride and potassium phthalimide to give compound **3**, then dehydration cyclization and followed by reduction of the compound **4** afforded the key intermediates **5**. The key intermediate **5** was acylated to the derivatives **6a-h**. This cyclization reaction was carried out by $P_2O_5$ as dehydrating agent, under acetonitrile reflux, during 5 h. The reaction to obtain compound **4** is very simple and the yields are 85 %. The synthesis of the key intermediates **5** was accomplished in one-pot and the yields are 70 %.

The inhibitory monoamine oxidase activity of compounds **6a-h** was evaluated *in vitro* by the measurement of their inhibitions of MAO-A and MAO-B.

Then, the $IC_{50}$ values and MAO-B selectivity ratios [$IC_{50}$ (MAO-B)]/ [$IC_{50}$ (MAO-A)] for inhibitory effects of both, new compounds and reference inhibitor, were calculated (Table-1).

The prepared series of compounds proved to be selective as inhibitor of the MAO-A and MAO-B. Acetyl analog **6a-b** neither improved MAO-B inhibitory potency nor enhanced selectivity against MAO-A. Substitution with methylsulfonyl or cyclohexaneformyl (**6c-e**) gave less active compounds. Compound **6f**, none substituted in the $R_2$-positions, is by itself very active and selective against MAO-B. Compound **6g**, with propynyl and allyl groups, is more active than **6f** (none substituted in the $R_2$-positions) but it also selective against MAO-B. The most potent molecule of this family is compound **6h**, This one with two propynyl groups is the most active and selective inhibitor of MAO-B than others.

This inhibitor of MAO-B selectivity is an important factor to discriminate the potential therapeutic application of this kind of molecules. Comparing the inhibit MAO-B activities of **6f** and **6g**, the introduction of propynyl group increases the inhibitory activity. Substitution with two propynyl groups in the $R_1$- and $R_2$-positions, compound **6h**, improves the inhibit MAO-B activity. The presence of propynyl substituent in the $R_1$- and $R_2$-positions seems to be important to modulate and improve the inhibitory enzymatic activity of the 1-aminomethyl-1,2,3,4-tetrahydroisoquinoline.

### Conclusion

In conclusion, a series of 1-aminomethyl-1,2,3,4-tetrahydroisoquinoline derivatives was synthesized and found to have inhibitory activities against MAO-A and MAO-B. Compound **6h** showed good *in vitro* activities and moderate selectivity. Further studies are underway to optimize this class of compounds for the treatment of the Parkinson's disease.

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TABLE-1
MAO-A AND MAO-B INHIBITORY ACTIVITY RESULTS FOR COMPOUNDS **6a-h** AND REFERENCE COMPOUNDS

| Compound | $R_1$ | $R_2$ | $IC_{50}$[a] (μM) | | Ratio[b] |
|---|---|---|---|---|---|
| | | | MAO-A | MAO-B | |
| **6a** | $CH_3CO$ | $CH_3CO$ | 76.670 | 257.447 | 3.36 |
| **6b** | $ClCH_2CO$ | $ClCH_2CO$ | 59.541 | * | – |
| **6c** | $CH_3O_2S$ | $CH_3O_2S$ | 103.739 | 291.037 | 2.81 |
| **6d** | $C_6H_{11}CO$ | $C_6H_{11}CO$ | 50.866 | 424.237 | 8.34 |
| **6e** | H | $C_6H_{11}CO$ | * | 1167.665 | – |
| **6f** | $HC\equiv CCH_2$ | H | * | 394.088 | – |
| **6g** | $HC\equiv CCH_2$ | $H_2C=CHCH_2$ | * | 167.545 | – |
| **6h** | $HC\equiv CCH_2$ | $HC\equiv CCH_2$ | 39.773 | 92.399 | 2.32 |
| Rasagiline | | | 1.296 | 0.566 | 0.44 |

*Inactive at highest concentration tested; [a]Average values (at least two experiments); [b]Ratio = MAO-B $IC_{50}$/MAO-A $IC_{50}$

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