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Research Article

Synthesis and Biological Evaluation of Novel Jatrorrhizine Derivatives with Amino Groups Linked at the 3-Position as Inhibitors of Acetylcholinesterase

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Jatrorrhizine was considered as one of the active constituents of *Coptis chinensis* Franch. Herein, jatrorrhizine derivatives with substituted amino groups linked at the 3-position were designed, synthesized, and biologically evaluated as inhibitors of acetylcholinesterase. Jatrorrhizine derivatives inhibited the activity of acetylcholinesterase (AChE) to a greater extent than the lead compound jatrorrhizine. All these jatrorrhizine derivatives were proved to be potent inhibitors of acetylcholinesterase (AChE) with submicromolar IC_{50} values, but less sensitive to butyrylcholinesterase (BuChE), which suggests that these jatrorrhizine derivatives are selective for AChE/BuChE. Compound **3g** gave the most potent inhibitor activity for AChE (IC_{50} = 0.301 μM), which is greater than the lead compound jatrorrhizine. All these results demonstrated that these jatrorrhizine derivatives are potential inhibitors for AChE.

1. Introduction

Alzheimer's disease (AD) is the most prevalent form of dementia affecting approximately six million people in China [1]. One possible approach to treat AD is to restore the level of acetylcholine (ACh) by inhibiting acetylcholinesterase (AChE) with reversible inhibitors. The aim of AChE inhibitors is to improve the endogenous levels of ACh in the brain of AD patients, thereby increasing cholinergic neurotransmission [2]. *Rhizoma Coptidis* can be used for treatment of cardiovascular and neurodegenerative diseases [3]; *Coptis chinensis* Franch extracts show good inhibitory activity for AChE *in vitro* [4]. Jatrorrhizine is a kind of quaternary protoberberine alkaloids (QPA) and was considered as one of the active constituents of *Coptis chinensis* Franch [5, 6]. Jatrorrhizine has multiple bioactivities, such as hypoglycemic [7], antimicrobial [8], and antioxidant activities [9]. In recent years, berberine derivatives with various heterocyclic rings, such as thiophene, pyrrole, piperidine, and carbazole, were demonstrated as both acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) inhibitors [10–12]. However, no literature reported that jatrorrhizine and its derivatives could be used as inhibitors of both AChE and BuChE. Taking into account the fact that jatrorrhizine and berberine belong to quaternary protoberberine alkaloid (QPA), we report the design, synthesis, and biological evaluation of a series of novel jatrorrhizine derivatives which have an amino group linked at the 3-position as both AChE and BuChE inhibitors in this paper, hoping that these derivatives could be used as agents for Alzheimer's disease (AD).

2. Results and Discussion

The spectra data and other characterization of the target compounds **3a–3f** are shown in the experimental section. The yield of the derivatives was ranged from 59% to 41%.

Table 1: *In vitro* inhibition IC_{50} (μM) and selectivity of jatrorrhizine derivatives for AChE and BuChE.

Compounds	IC_{50} (μM)		Selectivity for AChE[c]
	AChE[a]	BuChE[b]	
Jatrorrhizine	0.872 ± 0.87	>100	>115
Tacrine	0.223 ± 0.003	0.052 ± 0.009	0.23
3a	0.500 ± 0.016	>100	>216
3b	0.461 ± 0.004	>100	>260
3c	0.322 ± 0.016	>100	>310
3d	0.41 ± 0.011	>100	>243
3e	0.355 ± 0.012	>100	>338
3f	0.821 ± 0.023	>100	>121
3g	0.301 ± 0.038	>100	>300

[a]50% inhibitory concentration (means ± SEM of three experiments) of AChE from electric eel; [b]50% inhibitory concentration (means ± SEM of three experiments) of BuChE from equine serum; [c]selectivity for AChE = IC_{50} (BuChE)/IC_{50} (AChE).

The spectra data of jatrorrhizine **(1)** was reported in [15]. The ^{1}H NMR spectrum of the target compounds showed that some new proton signals of CH_2 and CH_3 appeared at high field region. The compounds **3a–f** at δ 13–60 area increased the signal of compound C, the increased number of C is the same as C of substituent group switching on at the 3-position of jatrorrhizine. MS tested compounds formula. Both analytical and spectral data of all the newly synthesized compounds are in full agreement with the proposed structures.

The IC_{50} values for AChE and BuChE inhibition are shown in Table 1. All the jatrorrhizine derivatives demonstrated potent inhibitory activity against AChE with submicromolar IC_{50} values. The optimal AChE inhibition potency (IC_{50} = 0.301 μM) was provided by compound **3g**; the inhibition activity of jatrorrhizine derivatives to BuChE is lower than AChE. It is interesting that all of the jatrorrhizine derivatives exhibited potent inhibitory activity for AChE compared to jatrorrhizine. The volume of the substituted amino groups has important impact on inhibitory activity. Among all the jatrorrhizine derivatives, the amino group gave the best results (IC_{50} = 0.301 μM). Interestingly, the cyclic substituted amino groups appeared to have weak activity compared to chain substituted amino groups. For example, compound **3g** showed the highest inhibitory activity. This result indicated that the groups at the end of the molecule influenced inhibitory activity. *In vitro*, BuChE inhibition was also determined using the same method. The jatrorrhizine and jatrorrhizine derivatives demonstrated poor inhibitory potency against BuChE. These results proved that the jatrorrhizine derivatives have good selectivity for AChE and BuChE (Table 1).

3. Experimental Section

3.1. Chemistry. Jatrorrhizine was extracted and purified from *Coptis chinensis* Franch according to [16]. The purity of jatrorrhizine was up to 98% by HPLC. All of the other reagents were AR grade, purchased from Shanghai Aladdin Bio-Chem Technology Co., Ltd. Melting points were determined on an RD-2C electrothermal melting point apparatus and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded on Bruker 400 (400 MHz) using TMS as the internal standard and CD_3OD as solvent. Mass spectrometry (MS) spectra were collected on 1100 series LC/MSD instrument. The separation of the compounds was performed on silica gel-GF254 thin layers, with a moving phase of C_6H_6/EtOAc/MeOH/i-C_3H_7OH/$NH_3 \cdot H_2O$ (6 : 3 : 1.5 : 1.5 : 0.5).

3.2. Synthesis of Monomodified Jatrorrhizine Derivatives. Jatrorrhizine derivatives were synthesized according to [17]. The synthetic pathway of 3-substituted jatrorrhizine derivatives are shown in Figure 1. The alkylation of jatrorrhizine using 1,4-dibromoethane was conducted under the basic condition in CH_3CN and afforded product **2** in 69% yield. **3a–3f** were prepared by intermediates **2** (0.1 mol) with commercially available secondary amines (0.11 mol) (dimethylamine, pyrrolidine, etc.) in DMF, and additional alkaline catalyst (K_2CO_3, 0.2 mol) was added, giving a 41–59% yield, respectively. Ammonolysis of jatrorrhizine (0.05 mol) with ammonia solution (3 mL) -NH_4Cl (0.05 mol) in CH_3OH at r.t. gave compounds **3g**. Heating the 2-iodoethanol (0.01 mmol) and jatrorrhizine (0.01 mmol) in DMF at 60°C would afford the desired product **3f.** These compounds were added to reflux MeOH containing AgCl and converted into corresponding chlorides. All of the compounds were purified by chromatography on an Al_2O_3 column with CH_3OH/CH_3Cl (9 : 1) as eluent to give the target products (Figure 1).

*Intermediates **2**: 3-(4-Bromobutoxy)-2,9,10-trimethoxy-5,6-dihydroisoquinoli-no[3,2-a]isoquinolin-7-ium Chloride*. Yield: 69%, yellow solid; m.p.: 204-205°C. MS (m/z) 472.7 $[M]^+$, 475.5 $[M+2]^+$. ^{1}H NMR (400 MHz, CD_3OD), δ: 9.75 (s, 1H, 8-H), 8.81 (s, 1H, 13-H), 8.11 (d, J = 7.2 Hz, 1H, 11-H), 8.07 (d, J = 7.2 Hz, 1H, 12-H), 7.67 (s, 1H, 1-H), 7.01 (s, 1H, 4-H), 4.92 (t, J = 6.8 Hz, 2H, 6-H), 4.25 (t, J = 6.8 Hz, 2H, -CH_2-), 4.15 (s, 3H, -OCH_3-), 4.13 (t, J = 6.8 Hz, 2H, -CH_2O-), 4.09 (s, 3H, -OCH_3-), 4.06 (s, 3H, -OCH_3-), 2.04–2.08 (m, 2H, -CH_2-), 1.79–1.83 (m, 2H, -CH_2-). ^{13}C NMR (100 MHz, CD_3OD) δ: 153.0, 151.9, 151.0, 146.3, 145.7, 139.7, 135.2, 130.0, 128.0, 124.5, 123.3, 121.3, 120.5, 113.2, 110.0, 70.0, 62.5, 57.6, 57.4, 57.0, 47.7, 29.3, 27.8, 26.8.

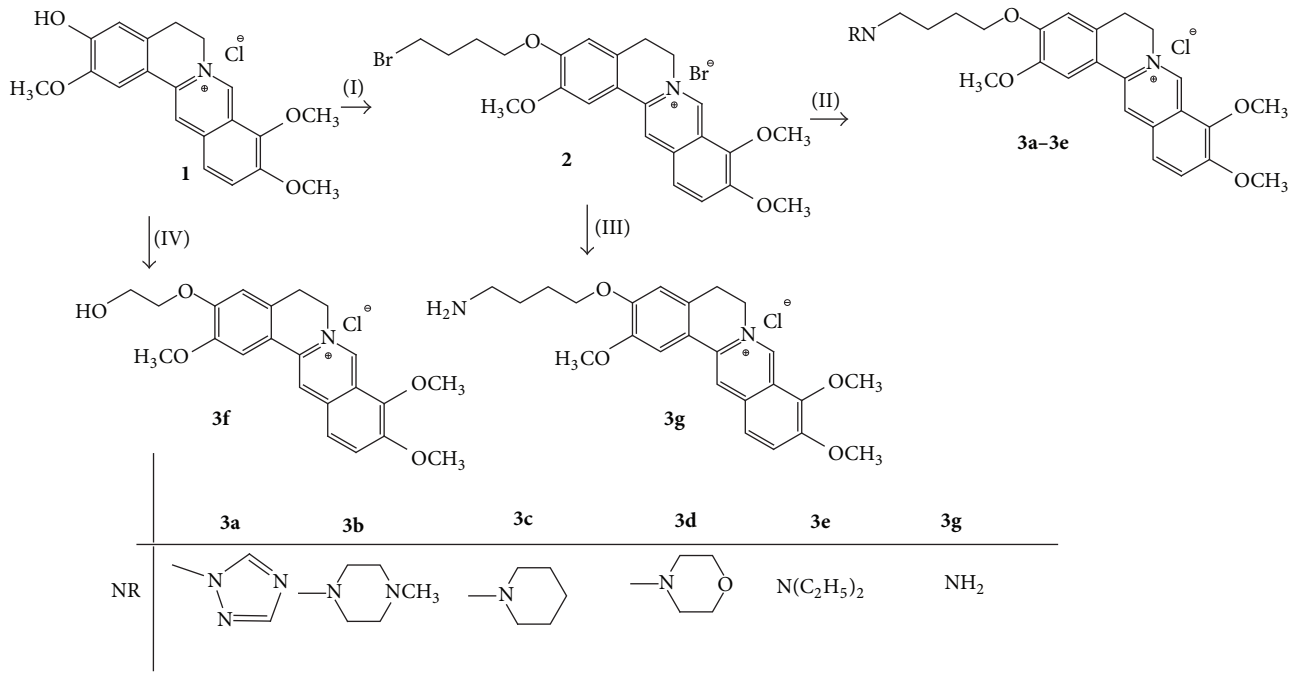

Figure 1: Synthetic route of 3-substituted jatrorrhizine derivatives **(3a–3g)**.

*3-(4-(4H-1,2,4-Triazol-4-yl)butoxy)-2,9,10-trimethoxy-5,6-dihydroisoquinolino[3,2-a]isoquinolin-7-ium Chloride **(3a)***. Yield: 46%. yellow solid; m.p: 210-211°C. MS (m/z) 461.3 $[M]^+$, ^{1}H NMR (400 MHz, CD_3OD), δ: 9.73 (s, 1H, 8-H), 8.78 (s, 1H, 13-H), 8.57 (s, 1H, Tri-H), 8.06 (d, J = 7.2 Hz, 1H, 11-H), 8.00 (s, 1H, Tri 5-H), 8.01 (d, J = 7.2 Hz, 1H, 12-H), 7.61 (s, 1H, 1-H), 6.99 (s, 1H, 4-H), 4.92 (t, J = 6.8 Hz, 2H, 6-H), 4.38 (t, J = 6.8 Hz, 2H, Tri-CH2), 4.19 (s, 3H, -OCH3), 4.12 (t, J = 6.8 Hz, 2H, $-OCH_2-$), 4.06 (s, 3H, -OCH3), 3.99 (s, 3H, -OCH3), 3.25 (t, J = 6.8 Hz, 2H, 5-H), 2.04–2.08 (m, 2H, $-CH_2-$), 1.79–1.83 (m, 2H, $-CH_2-$). ^{13}C NMR (100 MHz, CD_3OD) δ: 152.9, 152.2, 151.9, 151.0, 146.3, 145.6, 139.7, 135.2, 134.7, 129.9, 128.0, 124.5, 123.2, 121.3, 120.5, 113.3, 110.0, 69.9, 62.6, 57.6, 57.3, 57.0, 50.2, 28.0, 27.8, 26.7.

*2,9,10-Trimethoxy-3-(4-(4-methylpiperazin-1-yl)butoxy)-5,6-dihydroisoquinolino[3,2-a]isoquinolin-7-ium **(3b)***. Yellow solid; Yield: 43%, m.p.: 195-196°C. MS (m/z) 492.2 $[M]^+$, ^{1}H NMR (400 MHz, CD_3OD), δ: 9.76 (s, 1H, 8-H), 8.80 (s, 1H, 13-H), 8.11 (d, J = 7.2 Hz, 1H, 11-H), 8.02 (d, J = 7.2 Hz, 1H, 12-H), 7.66 (s, 1H, 1-H), 7.03 (s, 1H, 4-H), 4.92 (t, J = 6.8 Hz, 2H, 6-H), 4.20 (s, 3H, $-OCH_3$), 4.15 (t, J = 6.8 Hz, 2H, -CH2), 4.10 (s, 3H, $-OCH_3$), 3.99 (s, 3H, $-OCH_3$), 3.30 (t, J = 6.8 Hz, 2H, $-OCH_2-$), 3.26 (t, J = 6.8 Hz, 2H, 5-H), 2.60–2.50 (m, 8H), 2.34 (s, 3H N-CH_3), 1.84–1.91 (m, 2H, $-CH_2-$), 1.71–1.79 (m, 2H, $-CH_2-$). ^{13}C NMR (100 MHz, CD_3OD), δ: 153.3, 151.9, 151.1, 146.4, 145.8, 139.8, 135.5, 130.0, 128.1, 124.5, 123.3, 121.3, 120.5, 113.3, 110.1, 69.8, 62.6, 59.2, 57.7, 57.4, 57.1, 55.0 (overlap2), 27.82, 27.77, 25.5 (overlap2), 24.1, 23.3.

*2,9,10-Trimethoxy-3-(4-(piperidin-1-yl)butoxy)-5,6-dihydroisoquinolino[3,2-a]isoquinolin-7-ium Chloride **(3c)***. Yellow solid; Yield: 52%, m.p.: 197-198°C. MS (m/z) 477.2 $[M]^+$, ^{1}H NMR (400 MHz, CD_3OD) δ: 9.75 (s, 1H, 8-H), 8.81 (s, 1H, 13-H), 8.11 (d, J = 7.2 Hz, 1H, 11-H), 8.02 (d, J = 7.2 Hz, 1H, 12-H), 7.66 (s, 1H, 1-H), 7.04 (s, 1H, 4-H), 4.92 (t, J = 6.8 Hz, 2H, 6-H), 4.20 (s, 3H, -OCH3), 4.15 (t, J = 6.8 Hz, 2H, $-CH_2$), 4.10 (s, 3H, $-OCH_3$), 3.99 (s, 3H, $-OCH_3$), 3.27 (t, J = 6.8 Hz, 2H, 5-H), 2.78 (br, s, 6H), 1.86–1.89 (m, br, 4H), 1.71–1.74 (m, 4H), 1.58 (m, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ: 153.0, 151.9, 151.0, 146.3, 145.7, 139.8, 135.3, 130.0, 128.1, 124.5, 123.3, 121.3, 120.5, 113.3, 110.1, 70.0, 62.6, 59.2, 57.7, 57.4, 57.1, 55.0 (overlap2), 27.82, 27.77, 25.5 (overlap2), 24.2, 23.3.

*2,9,10-Trimethoxy-3-(4-morpholinobutoxy)-5,6-dihydroisoquinolino[3,2-a]isoquinolin-7-ium Chloride **(3d)***. Yellow solid; Yield: 59%, m.p. 200-201°C. MS (m/z) 478.8 $[M]^+$. ^{1}H NMR (400 MHz, CD_3OD), δ: 9.75 (s, 1H, 8-H), 8.80 (s, 1H, 13-H), 8.09 (d, J = 7.2 Hz, 1H, 11-H), 8.01 (d, J = 7.2 Hz, 1H, 12-H), 7.64 (s, 1H, 1-H), 7.02 (s, 1H, 4-H), 4.93 (t, J = 6.8 Hz, 2H, 6-H), 4.20 (s, 3H, $-OCH_3$), 4.14 (t, J = 6.8 Hz, 2H, $-CH_2$), 4.14 (s, 3H, -OCH3), 3.98 (s, 3H, $-OCH_3$), 3.7 (br, s, 4H), 3.29 (t, J = 6.0 Hz, 2H, 5-H), 2.51 (br, s, 6H), 1.84–1.88 (m, 2H), 1.72–1.76 (m, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ: 153.2, 151.9, 151.1, 146.3, 145.7, 139.8, 135.3, 130.0, 128.0, 124.5, 123.2, 121.2, 120.3, 113.2, 110.1, 70.0, 67.6 (overlap2), 62.5, 59.7, 57.6, 57.4, 57.0, 54.7 (overlap2), 28.1, 27.8, 23.8.

*3-(4-(Diethylamino)butoxy)-2,9,10-trimethoxy-5,6-dihydroisoquinolino[3,2-a]isoquinolin-7-ium Chloride **(3e)***. Yellow solid: Yield: 48%, m.p.: 197-198°C. MS (m/z) 465.1 $[M]^+$. ^{1}H NMR (400 MHz, CD_3OD), δ: 9.75 (s, 1H, 8-H), 8.80 (s, 1H, 13-H), 8.09 (d, J = 7.2 Hz, 1H, 11-H), 8.01 (d, J = 7.2 Hz, 1H, 12-H), 7.64 (s, 1H, 1-H), 7.02 (s, 1H, 4-H), 4.93 (t, J = 6.8 Hz, 2H, 6-H), 4.20 (s, 3H, $-OCH_3$), 4.12 (t, J = 6.8 Hz, 2H, $-CH_2$), 4.08 (s, 3H, $-OCH_3$), 3.98 (s, 3H, $-OCH_3$), 3.70 (br, s,

4H), 3.29 (t, J = 6.0 Hz, 2H, 5-H), 2.51 (br, s, 6H), 1.84–1.88 (m, 2H), 1.72–1.76 (m, 2H).^{13}C NMR (100 MHz, CD_3OD) δ: 153.2, 151.9, 151.1, 146.3, 145.7, 139.8, 135.3, 130.0, 128.0, 124.5, 123.2, 121.2, 120.3, 113.2, 110.1, 70.0, 67.6 (overlap2), 62.5, 59.7, 57.6, 57.4, 57.0, 54.7 (overlap2), 28.1, 27.8, 23.8.

3-(4-Aminobutoxy)-2,9,10-trimethoxy-5,6-dihydroisoquinolino[3,2-a]isoquinolin-7-ium Chloride ***(3g)***. Yellow solid; Yield: 45%, m.p.: 198-199°C. MS (m/z) 409.8 $[M]^+$, ^{1}H NMR (400 MHz, CD_3OD) δ: 9.74 (s, 1H, 8-H), 8.80 (s, 1H, 13-H), 8.09 (d, J = 7.2 Hz, 1H, 11-H), 8.01 (d, J = 7.2 Hz, 1H, 12-H), 7.61 (s, 1H, 1-H), 7.01 (s, 1H, 4-H), 4.93 (t, J = 6.8 Hz, 2H, 6-H), 4.19 (s, 3H, -OCH_3), 4.13 (t, J = 6.8 Hz, 2H, -CH_2), 4.07 (s, 3H, -OCH_3), 3.98 (s, 3H, -OCH_3), 3.64 (t, J = 6.8 Hz, 2H), 3.29 (t, J = 6.8 Hz, 2H, 5-H), 1.88–1.91 (m, 2H), 1.71–1.75 (m, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ: 153.3, 151.9, 151.1, 146.3, 145.7, 139.8, 135.2, 130.0, 128.0, 124.5, 123.2, 121.2, 120.3, 113.2, 110.2, 70.1, 62.6, 57.6, 57.4, 57.1, 54.7, 30.2, 27.8, 26.8.

3-(2-Hydroxyethoxy)-2,9,10-trimethoxy-5,6-dihydroisoquinolino[3,2-a]isoquinolin-7-ium Chloride ***(3f)***. Yellow solid. Yield: 41%. m.p.: 219-220°C, MS (m/z) 382.3 $[M]^+$. ^{1}H NMR (400 MHz, CD_3OD) δ: 9.76 (s, 1H, 8-H), 8.80 (s, 1H, 13-H), 8.11 (d, J = 7.2 Hz, 1H, 11-H), 8.02 (d, J = 7.2 Hz, 1H, 12-H), 7.68 (s, 1H, 1-H), 7.07 (s, 1H, 4-H), 4.92 (t, J = 6.0 Hz, 2H, 6-H), 4.20 (s, 3H, -OCH_3), 4.18 (t, J = 6.0 Hz, 2H, -OCH_2), 4.10 (s, 3H, -OCH_3), 4.01 (s, 3H, -OCH_3), 3.93 (t, J = 6.0 Hz, 2H, -OCH_2-), 3.26 (t, J = 6.0 Hz, 2H, 5-H). ^{13}C NMR (100 MHz, CD_3OD) δ: 153.1, 151.9, 151.1, 146.4, 145.76, 139.8, 135.3, 130.1, 128.1, 124.5, 123.3, 121.3, 120.7, 113.5, 110.2, 71.9, 62.5, 61.5, 57.7, 57.4, 57.1, 27.8.

4. Biological Activity

4.1. In Vitro Inhibition Studies of AChE and BuChE. Acetylcholinesterase (AChE, from electric eel), butyrylcholinesterase (BuChE, from equine serum), 5,5′-dithiobis-(2-nitrobenzoic acid) (Ellman's reagent, DTNB), acetylthiocholine chloride (ATC), and butyrylthiocholine chloride (BTC) were got from Sigma Aldrich. Jatrorrhizine derivatives were dissolved in DMSO and then diluted in 0.1 M KH_2PO4/K_2HPO4 buffer (pH 8.0) to provide a final concentration range.

All the assays were carried out under 0.1 M KH_2PO_4/K_2HPO_4 buffer, pH 8.0, using a Shimadzu UV-2450 Spectrophotometer. AChE and BuChE solutions were prepared to give 2.0 units/mL in 2 mL aliquots. The assay medium (1 mL) consisted of phosphate buffer (pH 8.0), 50 μL of 0.01 M DTNB, 10 μL of enzyme, and 50 μL of 0.01 M substrate (ACh chloride solution). Test compounds were added to the assay solution and preincubated at 37°C with the enzyme for 15 min followed by the addition of substrate. The activity was determined by measuring the increase in absorbance at 412 nm at 1 min intervals at 37°C. Calculations were performed according to the method of the equation of Suzuki et al. [18, 19]. Each concentration was assayed in triplicate. *In vitro* BuChE assay was similar to the method described above. The IC_{50} values for AChE and BuChE inhibition are shown in Table 1.

5. Molecular Modeling Studies

To determine the possible mode of reaction between compounds and *T. californica* enzyme (TcAChE), one of the jatrorrhizine derivatives was docked to the AChE active site gorge using the Autodock Vina software [20], based on the structure of the complex of TcAChE (PDB entry 5FUM) [21]. The most probable conformations of the ligands were chosen based on the docked energy value. The position of compound **3g** in the binding site with respect to the key residues is shown in Figures 2(a) and 2(b). In TcAChE, the amino acid residues Tyr72, Tyr124, Tyr337, Tyr341, Asp74, Trp86, Trp286, Gly120, Ser293, and Phe338 are in hydrophobic contact with compound **3g**, and Tyr133 and Glu202 are shown to be involved in hydrogen-bonding interactions with molecule **3g**. These interactions are significant and might explain the high affinity of the compound **3g** to TcAChE (Figure 2).

6. Conclusion

In conclusion, a series of jatrorrhizine derivatives with substituted amino groups linked at the 3-position were designed, synthesized, and biologically evaluated as inhibitors of acetylcholinesterase. All these jatrorrhizine derivatives were proved to be potent inhibitors of acetylcholinesterase (AChE) with submicromolar IC_{50} values, but less sensitive to butyrylcholinesterase (BuChE), which suggests that these jatrorrhizine derivatives are selective for AChE/BuChE. Compound **3g** gave the most potent inhibitor activity for AChE (IC_{50} = 0.301 μM), which is greater than the lead compound jatrorrhizine. All these results demonstrated that these jatrorrhizine derivatives are potential inhibitors for Alzheimer's disease (AD).

Abbreviations

AchE: Acetylcholinesterase
BuChE: Butyrylcholinesterase
Ach: Acetylcholine
NMR: Nuclear magnetic resonance spectroscopy
MS: Mass spectrometer.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Acknowledgments

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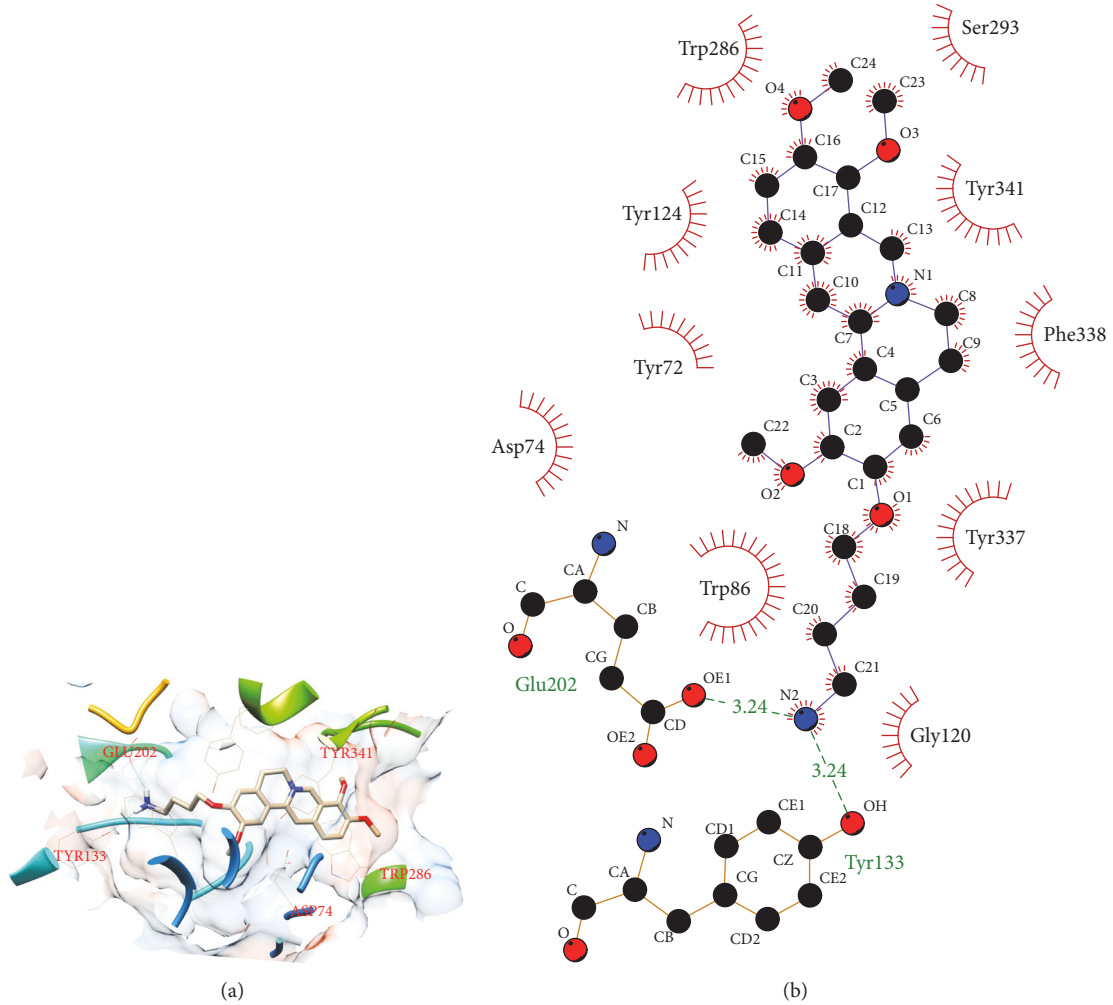

(a) (b)

FIGURE 2: Docking models of the compound-enzyme complex. (a) Stereoviews looking down the gorge of TcAChE binding with **3g**; (b) representation of compound **3g** docked into the binding site of AChE highlighting the protein residues that form the main interactions with the inhibitor. Hydrogen-bonding interaction between ligand and residues Tyr133 and Glu202 is shown with the green line. The residues of TcAChE involved in hydrogen-bonding and hydrophobic interactions with molecule **3g** were analyzed using Chimera 1.9 [13] and Ligplot+ [14].

Supplementary Materials

Supplementary data (ESI-MS, ^{1}H NMR, and ^{13}C NMR) associated with this article can be found in the online version. *(Supplementary Materials)*

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