Research Article

The Design, Synthesis, and Characterization of Resveratrol Derivatives Modified by Different γ-Aminobutyric Acid Esters

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A novel series of resveratrol modified by γ-aminobutyric acid esters were designed and synthesized. Then, the products were characterized by 1H-NMR, 13C-NMR, and MS, and the melting point was determined. Molecular water solubility, polar surface area, and octanol-water partition were calculated, which correlated well with molecular transport through membranes and, therefore, enabled prediction of transport properties of drugs.

1. Introduction

Resveratrol (trans-3, 4′, 5-trihydroxy stilbene [Figure 1]) is a natural polyphenol [1, 2]. It is widely distributed in edible plants, such as Polygonum cuspidatum and grapes [3, 4]. Modern pharmacological studies have indicated that resveratrol has beneficial effects on human health. For example, resveratrol can reduce blood fat levels [5], inhibit platelet activity [6], and protect against atherosclerosis and coronary heart disease [7]. Moreover, numerous studies have described the possible antifatigue function of resveratrol, and several researchers have paid increased attention to the physicochemical properties of resveratrol. Wu et al. found that resveratrol supplementation significantly increases exercise power. Therefore, they suggested that resveratrol may be applied as a potential food additive [8]. Hsu et al. found that the combination of resveratrol with kefir could reduce fatigue and improve exercise performance in mice when administered as a food supplement [9]. Resveratrol has been successfully combined with other protective chemical groups [10, 11]. Mattarei et al. prepared amino acid carbamates as resveratrol prodrugs. They investigated the abilities and pharmacokinetic characteristics of these prodrugs and found that these products have appropriate stabilities [12].

Recently, prodrug was designed which had amino acids as promoieties [13]. Some properties of new prodrugs would be changed because of amino acid presence. Moreover, we hypothesized that incorporating suitable amino acids with promoieties that present antifatigue ability into prodrugs might have a positive effect. γ-Aminobutyric acid (GABA) (Figure 2), a four-carbon amino acid, is widely exist in numerous plants [14]. GABA plays an important role in the nervous system [15, 16]. Supplementation with GABA or GABA-rich food for several weeks could exert a positive effect on exercise [17]. Although resveratrol and GABA can be employed as antifatigue additives, they cannot be combined together through chemical bonds. We selected GABA given its good research foundation.

The water solubility of liquids and solids is a crucial molecular property that influences the release, transport, and absorption of drugs in the body and is a key determinant of the environmental fate of agrochemicals and pollutants [18–21]. The octanol-water partition coefficient (log $P_{ow}$) and polar surface area (PSA) are widely used as general measures of lipophilicity and as parameters for predicting transcellular membrane transport properties in drug discovery research [22]. Numerous methods for the prediction of these properties have been developed [18, 22–24].
In this study, we designed and synthesized novel resveratrol derivatives that had been modified with different GABA esters. Then, we applied $^1$H-NMR, $^{13}$C-NMR, MS, and melting point to characterize the compounds. In addition, we predicted and evaluated several qualities of the derivatives.

2. Experiment

2.1. Materials. Resveratrol was obtained from Chengdu Yuannuotiancheng Co., Ltd. (Sichuan, China). GABA, methanol, ethanol, n-propanol, thionyl chloride (SOCl$_2$), acetonitrile, bis(4-nitrophenyl) carbonate, and 4-dimethylaminopyridine (DMAP) were purchased from Sigma-Aldrich (Shanghai, China). All materials were used without further purification or modification.

2.2. Methods

2.2.1. General. Nuclear magnetic resonance (NMR, Bruker, 400 MHz, Germany) spectra were obtained using deuterated dimethyl sulfoxide (d$_6$-DMSO) as a solvent, deuterated chloroform (CDCl$_3$), deuterated H$_2$O (D$_2$O), or 400MHz, Germany) spectra were obtained using deuterated dimethyl sulfoxide (d$_6$-DMSO) as a solvent.

2.2.2. Synthesis Procedures. For an outline of the general strategy, refer to the Results and Discussion section.

1) Methyl 4-Aminobutanoate (2a). Methanol (20 ml, 493.13 mmol, 12.27 equiv) was added to a reaction flask (50 ml). Next, SOCl$_2$ (2.81 ml, 38.80 mmol, 1 equiv) was slowly added dropwise. Then, the mixture was stirred at 0°C for 1.5 h. GABA (4 g, 38.80 mmol, 1 equiv) was added to the reaction system upon the completion of the first step of the reaction. The mixture was heated at 65°C under reflux for 1.5 h. The reaction was monitored through TLC. The solvent was evaporated under reduced pressure, and the residue was purified through flash chromatography (eluent: CH$_2$Cl$_2$/methanol, 1:1) to afford 1a (3.97 g, 87%). C$_9$H$_{11}$NO$_2$ (117.15) [M + H]$^+$ = 118.2. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 3.70 (s, 2H, -O-CH$_3$), 3.16 (s, 2H, NH$_2$-CH$_2$-CH$_2$), 2.55 (t, J = 6.6, 2H, -C(=O)-CH$_2$-), 2.15 (m, J = 5.5, 2H, -CH$_2$-CH$_2$-CH$_2$). $^{13}$C NMR (101 MHz, DMSO) $\delta$ = 173.12, 51.90, 38.44, 30.63, 22.82; melting point: 115-116°C.

2) Methyl 4-(((4-nitrophenoxy)carbonyl)amino)butanoate (2b). First, 2a (0.96 g, 8.2 mmol, 1 equiv), DMAP (2.00 g, 16.4 mmol, 2 equiv), and acetonitrile (15 ml) were added to a reaction flask (50 ml). Next, bis(4-nitrophenyl) carbonate (2.74 g, 9.00 mmol, 1.1 equiv) was added to a reaction flask with acetonitrile (15 ml). Next, the mixture was heated (50°C) for 3 h. The mixture was extracted three times with dichloromethane (150 ml) and hydrochloric acid (0.5 mol/L, 100 ml) after the completion of the reaction. The organic layer was collected and then dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified through flash chromatography (eluent: CH$_2$Cl$_2$/methanol, 1:1) to afford 2b (1.91 g, 82.7%). C$_{12}$H$_{14}$N$_2$O$_6$ (282.25), [M + H]$^+$ = 281.0. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 8.27 (d, J = 9.1, 2H, Ar-H), 7.34 (d, J = 9.1, 2H, Ar-H), 3.73 (s, 3H, -O-CH$_3$), 3.38 (d, J = 6.3, 2H, -NH-CH$_2$-), 2.47 (t, J = 7.1, 2H, -C(=O)-CH$_2$-), 1.97 (dd, J = 13.9, 7.0, 2H, -CH$_2$-CH$_2$-CH$_2$-). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ = 173.74, 155.89, 153.21, 144.72, 125.13, 121.97, 51.88, 40.80, 31.29, 24.69; melting point: 92-93°C.

3) Dimethyl 4,4’-(((5-(((4-methoxy-4-oxobutyl)carbamoyl)oxy)styryl))-I,3-phenylenebis(oxy))bis(carbonyl))bis(azanediyldiyi)(E)-dibutyrate (2c). Resveratrol (0.25 g, 1.1 mmol, 1 equiv) and DMAP (0.52 g, 4.2 mmol, 4 equiv) were added to a reaction flask (50 ml). The mixture was stirred and dissolved with acetonitrile (15 ml). Next, 2b (1.35 g, 4.8 mmol, 4.5 equiv) was dissolved and added to the above reaction system with acetonitrile (15 ml). The mixture was then reacted under heating (50°C) for 24 h. The reaction was monitored through TLC. The solvent was evaporated under reduced pressure, and the residue was purified through flash chromatography (eluent: PE/EA, 3:2) to afford 2c (1.32 g, 87%). C$_{32}$H$_{39}$N$_3$O$_{12}$ (657.67), [M + H]$^+$ = 658.8. $^1$H NMR (400 MHz, DMSO) $\delta$ = 6.77-7.90 (m, J = 12.6, 6.8, 9H, Ar-H), 3.61 (s, 9H, 3×-O-CH$_3$), 3.10 (dd, J = 7.1, 2H, -O-CH$_2$-), 2.55 (t, J = 6.6, 2H, -C(=O)-CH$_2$-), 2.15 (m, J = 5.5, 2H, -CH$_2$-CH$_2$-CH$_2$-). $^{13}$C NMR (101 MHz, DMSO) $\delta$ = 173.12, 51.90, 38.44, 30.63, 22.82; melting point: 115-116°C.

(1) Polar Surface Area (PSA) Calculations. The PSA values of the investigated molecules were calculated by using ALOGPS 2.1 software (available at Virtual Computational Chemistry Laboratory, http://www.vcclab.org).

(2) Solubility Calculations. The solubility values of the investigated molecules were calculated by using ALOGPS 2.1 software (available at Virtual Computational Chemistry Laboratory, http://www.vcclab.org).

(3) Octanol-Water Partition (Log $P_{ow}$) Calculations. The log $P_{ow}$ values of the investigated molecules were calculated by using the Molinspiration Property Calculator (http://www.molinspiration.com).

Figure 1: Structure of resveratrol.

Figure 2: Structure of γ-aminobutyric acid.
40.31, 31.21, 24.92, 14.56; melting point: 77-78°C. Next, SOCl2 (2.81 ml, 38.80 mmol, 1 equiv) was added to the reaction system upon the completion of the first step of the reaction. The reaction was monitored through TLC. The solvent was evaporated under reduced pressure, and the residue was purified through flash chromatography (eluent: PE/EA, 3:1) to afford 4a (0.96 g, 82 mmol, 1 equiv). DMAP (2.00 g, 16.4 mmol, 2 equiv) was added dropwise to the reaction flask (50 ml). Next, bis(4-nitrophenyl) carbonate (2.74 g, 9.00 mmol, 1.1 equiv) was dissolved, added to the above reaction system with acetonitrile (15 ml), and reacted under heating (50°C) for 3 h after the reaction was completed. The mixture was extracted three times with dichloromethane (150 ml) and hydrochloric acid (0.5 mol/L, 100 ml). The organic layer was collected and then dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified through flash chromatography (eluent: PE/EA, 3:2) to afford 4b (1.91 g, 82.7%). C14H14N2O8 (301.31), [M + H]+ = 302.1. 1H NMR (400 MHz, DMSO) δ = 8.27 (d, J = 9.2, 2H, Ar-H), 7.41 (d, J = 9.2, 2H, Ar-H), 4.07 (q, J = 7.1, 2H, -O-CH2-CH3), 3.10 (d, J = 6.1, 6H, 3 × -NH-CH2-), 2.37 (td, J = 7.4, 2.8, 6H, 3 × -C (=O)-CH3), 1.82–1.65 (m, 6H, 3 × -CH2-CH2-CH2-). 13C NMR (101 MHz, DMSO) δ = 173.04, 154.52, 152.16, 152.14, 139.34, 133.98, 129.61, 127.92, 122.49, 116.77, 115.10, 60.27, 40.19, 31.27, 25.06, 14.58; melting point: 58-59°C.

(7) Propyl 4-amino-butanoyl (4a). n-Propanol (20 ml, 266.2 mmol, 6.9 equiv) was added to a reaction flask (50 ml). Next, SOCl2 (2.81 ml, 38.80 mmol, 1 equiv) was added to the reaction system when the first step of the reaction was completed. The mixture was heated (65°C) under reflux for 1.5 h. The reaction was monitored through TLC. The solvent was evaporated under reduced pressure, and the residue was purified through flash chromatography (eluent: CH2Cl2/methanol, 1:1) to afford 4a (5.29 g, 94%). C14H18N2O6 (310.31), [M + H]+ = 311.4. 1H NMR (400 MHz, DMSO) δ = 7.77 (d, J = 7.4, 2H, -NH-CH2-), 2.42 (t, J = 7.3, 2H, -CH2-CH2-), 1.94–1.81 (m, 2H, -CH2-CH2-CH2-), 1.55 (dd, J = 14.2, 7.1, 2H, -CH2-CH2-CH3), 0.81 (t, J = 7.5, 3H, -CH2-CH3). 13C NMR (101 MHz, DMSO) δ = 177.52, 63.73, 38.67, 30.72, 24.54, 21.25, 9.54; melting point: 104-105°C.

(8) Propyl 4-(((4-nitrophenoxy)carbonyl)amino)butanoyl (4b). n-Propanol (20 ml, 266.2 mmol, 6.9 equiv) was added to a reaction flask (50 ml). Next, SOCl2 (2.81 ml, 38.80 mmol, 1 equiv) was added to the reaction system when the first step of the reaction was completed. The mixture was heated (65°C) under reflux for 1.5 h. The reaction was monitored through TLC. The solvent was evaporated under reduced pressure, and the residue was purified through flash chromatography (eluent: PE/EA, 3:2) to afford 4b (1.91 g, 82.7%). C14H15NO2 (145.20), [M + H]+ = 146.2. 1H NMR (400 MHz, DMSO) δ = 7.67 (dd, J = 7.4, 2H, -Ar-H), 7.18 (d, J = 7.3, 2H, -O-CH2-CH3), 3.08–2.96 (m, 4H, -CH2-CH2-CH2-), 1.14 (t, J = 7.3, 3H, -CH3). 13C NMR (101 MHz, DMSO) δ = 172.87, 156.72, 153.59, 144.54, 125.59, 122.92, 60.28, 40.31, 31.21, 24.92, 14.56; melting point: 77-78°C.
[M + H]$^+$ = 742.5. $^1$H NMR (400 MHz, DMSO) $\delta$ = 8.29–6.70 (m, 9H), 3.99 (t, $J$ = 6.6, 6H, $3 \times$ CH$_3$-CH$_2$-O-), 3.10 (d, $J$ = 3.2, 6H, $3 \times$ -NH-CH$_2$-), 2.38 (td, $J$ = 7.4, 2.8, 6H, $3 \times$ -C(=O)-CH$_2$-), 1.74 (t, $J$ = 8.6, 6H, $3 \times$ -NH-CH$_2$-CH$_2$-), 1.59 (dd, $J$ = 14.2, 6.9, 6H, $3 \times$ CH$_1$-CH$_2$-), 0.89 (t, $J$ = 7.4, 9H, $3 \times$ CH$_3$-CH$_2$-). $^{13}$C NMR (101 MHz, DMSO) $\delta$ = 173.10, 154.52, 152.15, 139.34, 133.98, 129.60, 127.91, 122.49, 116.78, 116.25, 65.76, 40.26, 31.25, 25.09, 22.00, 10.74; melting point: 65–66°C.

3. Results and Discussion

3.1. Synthesis. Resveratrol was modified by various GABA esters to form the corresponding analogues 2c–4c, as depicted in Scheme 1. Resveratrol and GABA are beneficial compounds that individually present several shortcomings [25]. Therefore, linking resveratrol and GABA with a chemical bond may obtain the novel derivatives with properties that are different from the properties of the individual parent molecule.

GABA can be connected through two methods because its structure contains carboxyl and amino groups. Connecting resveratrol to GABA through the amino bonds of amino acids would have a positive effect on the afforded prodrugs [26]. Hence, we selected this method to connect GABA with resveratrol (Scheme 2).

N-Monosubstituted carbamate esters are usually synthesized through two steps: first, the desired primary amine is reacted with a phosgene or its equivalent to give a reactive isocyanate derivative; then, the intermediate is coupled with the phenolic functional group [12, 27]. These procedures, however, provide low yields of the desired trisubstituted resveratrol derivatives likely because the high reactivity of the isocyanate group promotes the polymerization side reaction that entrains the stilbene C–C double bond [28].

The final products were obtained with good yields through this route. In this study, we first protected carboxyl to obtain 2a–4a. Then, we optimized and synthesized the 4-nitrophenyl carbamate intermediates 2b–4b. We next reacted resveratrol with the isolated intermediates to acquire the transesterification products. Good to excellent yields of the final conjugates 2c–4c were obtained under mild conditions.

3.2. Prediction of Log $P_{ow}$, Solubility, and PSA. The log $P_{ow}$ values, water solubility, and the polar surface area (PSA) values of all novel synthesized compounds were estimated (Table 1).

Molecular PSA is a highly useful indicator for predicting drug transport properties. PSA is the sum of the surfaces of polar atoms in a molecule. This parameter is highly correlated with human intestinal absorption, blood-brain barrier permeability, and Caco-2 permeability through a single-layer film [22].

However, the classical PSA calculation method is time consuming because it requires the generation and surface determination of a reasonable three-dimensional molecular geometry. In addition, specialized software is needed to generate three-dimensional molecular structures and to determine surfaces.

A virtual library that consists of hundreds of thousands or even millions of molecules is needed to enable rapid bioavailability screening in the current era of high-throughput screening and combinatorial chemistry-driven drug development. Nowadays, this process is based on the summation of the surface contributions of polar fragments (atoms are also affected by their environment). We determined fragment contributions by fitting drugs from 34,810 World Drug Index through single-conformation 3D PSA least-square methods. Three-dimensional classical PSA...
Table 1: Log $P_{ow}$, water solubility, and topological PSA values of resveratrol and corresponding derivatives.

| Compound   | Log $P_{ow}$ | PSA (Å$^2$) | Solubility (g/L) |
|------------|--------------|-------------|-----------------|
| Resveratrol| 2.57         | 60.68       | 0.03            |
| GABA       | -2.99        | 63.32       | 1.73            |
| 2a         | -1.07        | 52.33       | 0.49            |
| 2b         | 1.44         | 110.46      | 0.03            |
| 2c         | 3.22         | 193.91      | 0.0033          |
| 3a         | -0.46        | 52.33       | 0.66            |
| 3b         | 1.86         | 110.46      | 0.02            |
| 3c         | 4.36         | 193.91      | 0.0025          |
| 4a         | 0.02         | 52.33       | 1.03            |
| 4b         | 2.23         | 110.46      | 0.01            |
| 4c         | 5.03         | 193.19      | 0.0018          |

Results for the topological PSA were virtually of the same quality, and the calculation speed was accelerated by 2 to 3 orders of magnitude [22]. The prediction results indicate that the final products (2c–4c) would have poor absorption ($PSA \geq 140$ Å$^2$) [29].

The ability to penetrate cell membranes is related not only to PSA, but also to water solubility and octanol-water partitioning. Log $P_{ow}$ is used as an indicator of molecular hydrophobicity in QSAR studies and rational drug design. Hydrophobicity affects drug absorption, bioavailability, metabolism, and toxicity and hydrophobic drug-receptor interactions. Log $P_{ow}$ has become also a key parameter in studies on the environmental fate of chemicals. In addition, we used a database to calculate the water solubility of these products. Our results indicate that some properties of the derivatives have changed. Specifically, solubility decreased and log $P_{ow}$ increased when the number of hydrophobic groups increased.

4. Conclusion

A series of resveratrol derivatives that had been modified with different GABA esters was successfully synthesized. The log $P_{ow}$, water solubility, and topological PSA values of the derivatives were predicted by using software. Prediction results indicate that the properties of the derivatives were different from those of resveratrol. Finally, the melting point of the derivatives products was analyzed. The conjugates will be subjected to further formulation studies and biological evaluation on the basis of the results obtained in the present work.

Data Availability

The NMR and predicted data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors declare no conflicts of interest.

Authors’ Contributions

Bing Ren Tian and Jia Yue Liu have contributed equally to this work and are joint first authors.

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