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# A facile method to synthesize vildagliptin

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## Abstract

An efficient and high-yielding synthetic method for the preparation of vildagliptin via four steps is reported. The process starts from L-proline and involves a successful reaction with chloroacetyl chloride in tetrahydrofuran to afford (*S*)-1-(2-chloroacetyl)pyrrolidine-2-carboxylic acid, followed by a reaction with acetonitrile in the presence of sulfuric acid to give (*S*)-1-(2-chloroacetyl)pyrrolidine-2-carbonitrile. This is then reacted with 3-aminoadamantanol to give vildagliptin. 3-Aminoadamantanol is prepared from 1-aminoadamantane hydrochloride via oxidation with sulfuric acid/nitric acid and boric acid as the catalyst followed by ethanol extraction. The overall yield is 95%.

## Keywords

3-aminoadamantanol, central composite design-response surface methodology, (*S*)-1-(2-chloroacetyl)pyrrolidine-2-carbonitrile, synthesis, vildagliptin

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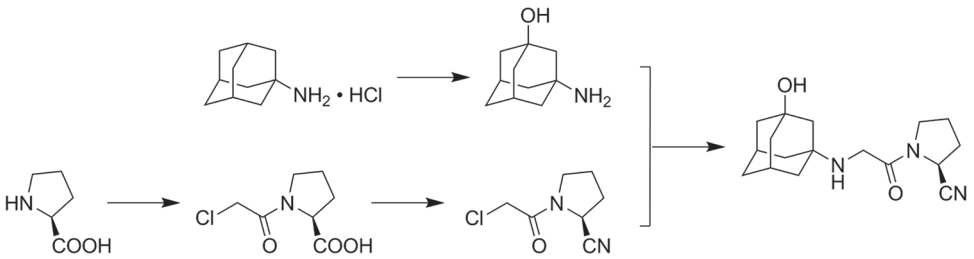


Vildagliptin was synthesized from L-proline and 1-aminoadamantane hydrochloride through hydroxylation, chloroacetylation, cyanation, and amino substitution.

## Introduction

Diabetes is a major threat to human health in the 21st century. It is a long-term and chronic metabolic disease that seriously affects the patient's quality of life. In recent years, the incidence of diabetes has increased rapidly. According to data until 2017, there were about 451 million people suffering from diabetes worldwide. In addition, this number is on the rise and is expected to be in the region of 693 million by 2045.[1] Vildagliptin (**1**), designed by Novartis,[2] is a highly selective, reversible, orally active dipeptidyl peptidase IV (DPP-IV) inhibitor for the treatment of type 2 diabetes.[3] The product enhances the sensitivity of $\alpha$ and $\beta$ cells to blood sugar by controlling the degradation of glucagon and insulin-releasing peptide cells that secrete insulin to achieve a hypoglycemic effect.[4] It was announced that vildagliptin had obtained European Commission approval to be marketed in 2008 under the trade name of Galvus.[5] Compared with traditional oral hypoglycemic agents, vildagliptin has less side effects,[6] high-drug safety,[7] and causes almost no obesity[8] or cardiovascular risk.[9]

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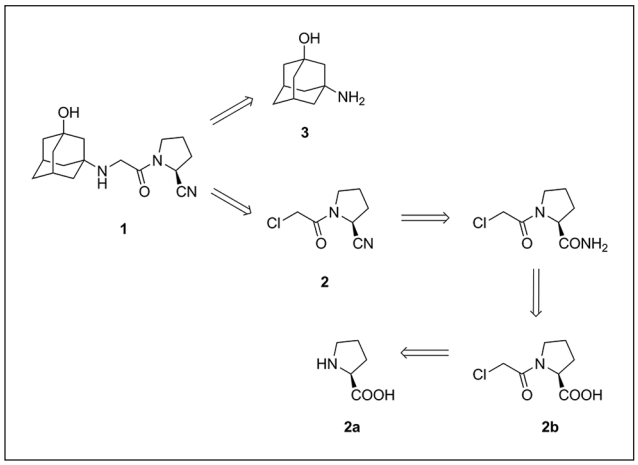
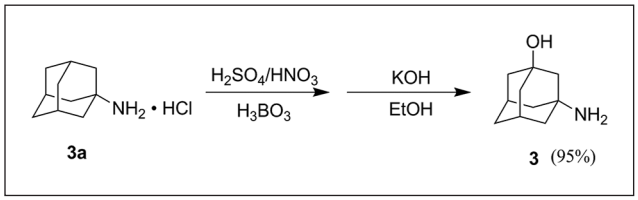



**Scheme 1.** Retrosynthesis analysis of vildagliptin.




**Scheme 2.** Synthesis of 3-aminoadamantanol.

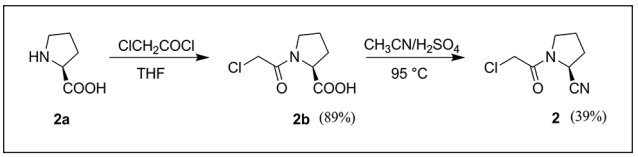
With the dramatic increase in the number of diabetics, the demand for **1** is expected to increase. However, the price of vildagliptin is very expensive due to the low yield of the important intermediates employed for its synthesis. Therefore, it is of great significance to improve the synthesis of vildagliptin using cheap raw materials and reagents.

3-Aminoadamantanol (**3**) and (*S*)-1-(2-chloroacetyl) pyrrolidine-2-carbonitrile (**2**) are important compounds because of their key roles in the synthesis of vildagliptin (Scheme 1).[10] In terms of the relevant literature, synthetic methods toward these intermediates have disadvantages of expensive starting materials,[11] complex synthetic routes, and low yields. Therefore, it is necessary to develop simple methods with good yields in order to obtain rapidly vildagliptin intermediates.

## Results and discussion

To prepare the final compound, vildagliptin (**1**), we first prepared 3-aminoadamantanol (**3**). Studies showed that almost all methods for the synthesis of **3** use dichloromethane to extract the target product during work-up. However, the results of several experiments demonstrated that the efficiency of dichloromethane extraction was quite low. This was because the compound **3** was soluble in aqueous solution and less soluble in dichloromethane. Therefore, it was of significance and practical application to optimize the extraction method and the conditions for synthesizing **3**.

Our group came up with a facile and high-yielding synthetic method to synthesize 3-aminoadamantanol (**3**). As described in Scheme 2, the first step was oxidation of 1-aminoadamantane hydrochloride (**3a**) by sulfuric acid/nitric acid ($H_2SO_4/HNO_3$)[12] with boric acid ($H_3BO_3$) as the




**Scheme 3.** Synthesis of (*S*)-1-(2-chloroacetyl)pyrrolidine-2-carbonitrile.

catalyst. The second step was hydrolysis using potassium hydroxide (KOH). The third step was extraction of compound **3** with ethanol extraction technology and the total yield was 95%.

The synthesis of the corresponding nitriles from carboxylic acids is not always a simple procedure. We found a facile one-pot transformation of (*S*)-1-(2-chloroacetyl) pyrrolidine-2-carboxylic acid (**2b**) into nitriles by reaction with acetonitrile in the presence of sulfuric acid (Scheme 3).[13] In order to confirm that compound **2** did not racemize because of heating during the reaction, we optimized the synthetic route and measured the optical rotation of **2** to identify whether racemization of **2b** had occurred. The accuracy of the chiral intermediate structure will also affect the efficiency and simplicity of the downstream synthetic route.[14]

In our strategy (Scheme 2), we decided to use L-proline (**2a**) as the starting material on account of its easy availability. Furthermore, we predicted that the chloroacetyl group could play a role in protecting the amino group and its removal could also be avoided. In our synthetic scheme, compound **2a** was *N*-acylated with chloroacetyl chloride in refluxing tetrahydrofuran (THF) to afford **2b**. We later observed that the *N*-acylation of L-proline proceeded faster in THF at 70 °C.[15] There are many methods that convert carboxylic acids into nitriles which consist of two or more steps.[16–18] Therefore, first, we attempted to convert the carboxylic acid moiety in compound **2b** to the amide and subsequently transform the amide into the corresponding nitrile. Unfortunately, several attempts failed in preparing the required amide via methods previously reported in the literature. Most of these methods were difficult with restrictions on the utility and applicability, involved cumbersome synthetic methods and costly reagents. However, after several attempts, a method was successfully applied to synthesize the carbonitrile moiety simply using acetonitrile in the presence of sulfuric acid.[13]

During the synthesis of **2**, it was found that three factors influenced its yield. These were the ratio of concentrated sulfuric acid to **2b**, the reaction temperature, and the reaction time. These three factors were optimized and the results are shown in Table 1. Optimized conditions were as follows: ratio of $H_2SO_4$/**2b** = 15:1 to 9:1, temperature = 85–105 °C, and reaction time = 4–6 h.

In order to further optimize the experimental conditions, we employed the central composite design-response surface methodology.[19,20] A central composite design-response surface methodology with three independent factors (α, ratio of $H_2SO_4$ to **2b**; β, reaction temperature; and γ, reaction time) at five levels was performed. For statistical calculation, the levels were coded as −1.682, −1, 0, +1, and

**Table 1.** Optimization of the reaction conditions.

| Entry | Ratio of $H_2SO_4$/**2b** (mol/mol) | Temperature (°C) | Time (h) | Yield (%) |
|---|---|---|---|---|
| 1 | 3:1 | 95 | 5.5 | 27 |
| 2 | 6:1 | 95 | 5.5 | 31 |
| 3 | 9:1 | 95 | 5.5 | 36 |
| 4 | 12:1 | 95 | 5.5 | 38 |
| 5 | 15:1 | 95 | 5.5 | 37 |
| 6 | 12:1 | 65 | 5.5 | 23 |
| 7 | 12:1 | 75 | 5.5 | 28 |
| 8 | 12:1 | 85 | 5.5 | 32 |
| 9 | 12:1 | 95 | 5.5 | 38 |
| 10 | 12:1 | 105 | 5.5 | 37 |
| 11 | 12:1 | 95 | 2.0 | 28 |
| 12 | 12:1 | 95 | 3.0 | 31 |
| 13 | 12:1 | 95 | 4.0 | 36 |
| 14 | 12:1 | 95 | 5.0 | 38 |
| 15 | 12:1 | 95 | 6.0 | 38 |

**Table 2.** Results of the central composite design-response surface methodology.

| Entry | *A* | β | γ | Yield (%) |
|---|---|---|---|---|
| 1 | 0 | 0 | 0 | 35 |
| 2 | 1 | −1 | −1 | 26 |
| 3 | 0 | 1.682 | 0 | 33 |
| 4 | 0 | 0 | 0 | 34 |
| 5 | −1 | −1 | −1 | 24 |
| 6 | −1 | 1 | −1 | 26 |
| 7 | 0 | 0 | 1.682 | 32 |
| 8 | 1 | −1 | 1 | 29 |
| 9 | 0 | 0 | 0 | 32 |
| 10 | 0 | −1.682 | 0 | 26 |
| 11 | 0 | 0 | 0 | 33 |
| 12 | −1 | −1 | 1 | 23 |
| 13 | −1.682 | 0 | 0 | 22 |
| 14 | 1.682 | 0 | 0 | 30 |
| 15 | −1 | 1 | 1 | 29 |
| 16 | 0 | 0 | 0 | 34 |
| 17 | 1 | 1 | −1 | 30 |
| 18 | 1 | 1 | 1 | 34 |
| 19 | 0 | 0 | −1.682 | 24 |
| 20 | 0 | 0 | 0 | 36 |

+1.682, respectively, in which −1.682 corresponds to the low level of each factor, +1.682 to the high level, and 0 to the mid-level. The results are shown in Table 2.

By processing the above data, the three-dimensional response surface plot of any two factors was obtained (Figure 1). Through analysis of the graph, we can see that the yield of **2** will increase as the values of the factors increase, which then gradually decrease. The optimal process conditions were obtained by analyzing the optimal intervals of the three surface effects: the material ratio ($\alpha$) of concentrated sulfuric acid to **2b** is 12:1, the reaction temperature ($\beta$) is 95 °C, and the reaction time ($\gamma$) is 5.5 h. Through five parallel experiments, the best reaction conditions gave **2** in a yield of 39% with a deviation of 1.08%.

Compound **2** is also a chiral compound which is an important intermediate for the preparation of vildagliptin. It is thought that the reaction under heating at 95 °C may cause racemization. Therefore, the optical purity (OP) of **2** was measured. The results are shown in Table 3.

The OP value is close to 100%. These results suggest that our method for the conversion of **2b** into **2** does not lead to racemization during the reaction.

Finally, the intermediate compound **2** was reacted with compound **3**, $K_2CO_3$, and KI in the refluxing THF to afford the target product vildagliptin (**1**) in 82% yield (Scheme 4).

## Conclusion

In conclusion, we have demonstrated a simple and cost-effective route for the synthesis of vildagliptin (**1**). Moreover, we have provided a new method to prepare 3-aminoadamantanol in an improved yield, which used boric acid ($H_3BO_3$) as the catalyst and ethanol extraction technology. Finally, we think that the method is more suitable for the industrial production due to a reduction in cost.

## Experimental

All reagents and solvents were obtained from commercial supplies and were of laboratory reagent grade and used as received. All melting points were obtained using a RY-1 capillary melting point instrument and are uncorrected. The infrared (IR) spectra were recorded on a Nicolet Fourier transform IR (FTIR) 5700 spectrophotometer using the

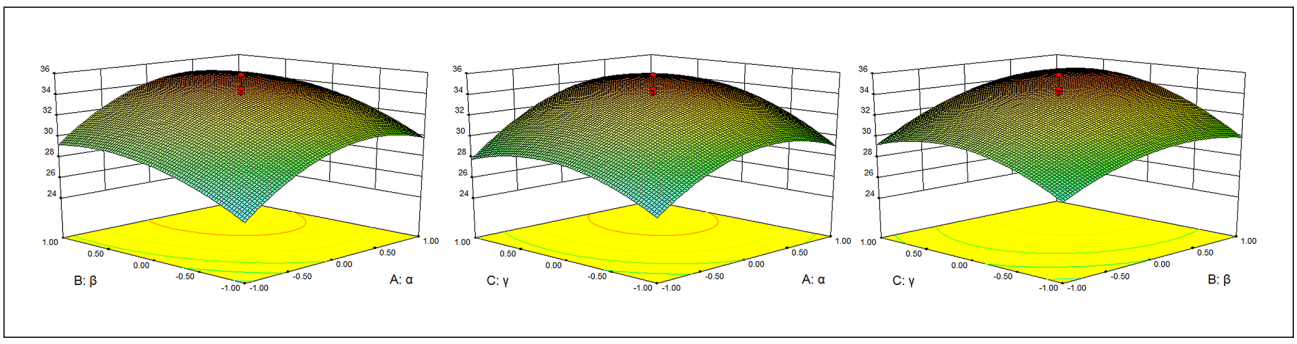
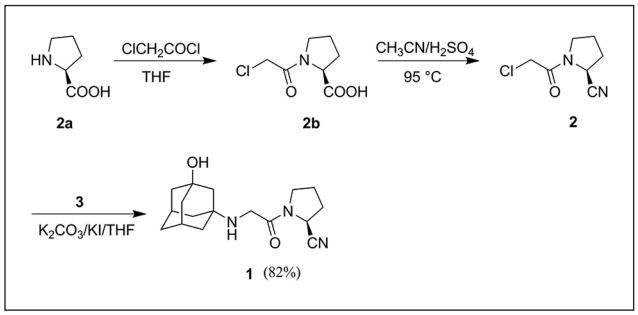



**Figure 1.** The response surface of compound **2**.

**Table 3.** Optical purity measurements on compound **2**.

| | Measured $[\alpha]_D^{20}$ (*c* 1 g/100 mL, $CHCl_3$) | Average $[\alpha]_D^{20}$ (*c* 1 g/100 mL, $CHCl_3$) | Literature $[\alpha]_D^{20}$ (*c* 1 g/100 mL, $CHCl_3$)[21] | OP (%) |
|---|---|---|---|---|
| Instrument | −1.526<br>−1.520<br>−1.535 | −1.527 | −1.531 | 99.74 |

OP: optical purity.




**Scheme 4.** Synthesis of vildagliptin.

KBr pellet technique. $^1$H nuclear magnetic resonance (NMR) spectra were obtained in $CDCl_3$ and DMSO-$d_6$ on a Bruker Avance 600 MHz NMR spectrometer. Optical rotations were measured on a Shanghai Precision Instruments WZZ-2B automatic polarimeter.

## *Synthesis of (S)-1-(2-chloroacetyl)pyrrolidine-2-carboxylic acid (**2b**)*

To a solution of L-proline (10 g, 0.087 mol) in THF (200 mL), chloroacetyl chloride (9.8 mL, 0.129 mol) was slowly added dropwise at 0 °C and the mixture stirred reaction for 20 min. Next, the reaction was stirred for 2 h at 70 °C. After completion of the reaction, the mixture was diluted with water (25 mL) and stirred for 20 min. Brine (25 mL) and ethyl acetate (150 mL) were added and the organic layer was collected. The aqueous layer was subsequently extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were dried over anhydrous $Na_2SO_4$, filtered, and concentrated. The residue was crystallized from isopropyl ether to afford compound **2b** (14.87 g, 89%) as a white solid; m.p. 108–110.9 °C (literature[15]—m.p. 108–110 °C); IR (KBr, $cm^{-1}$): 3418, 3051, 2989, 2938, 2810, 1718, 1608, 1475, 1461;$^1$H NMR (600 MHz, DMSO-$d_6$): δ 1.97–2.34 (m, 4H, $CH_2$), 3.57–3.74 (m, 2H, $CH_2$), 4.04–4.15 (m, 2H, $CH_2Cl$), 4.55–4.64 (m, 1H, CHCOOH), 12.33–12.47 (s, 1H, COOH). The $^1$H NMR data of this compound are in good agreement with the reported data.[11]

## *Synthesis of (S)-1-(2-chloroacetyl)pyrrolidine-2-carbonitrile (**2**)*

To a solution of compound **2b** (3.0 g, 0.016 mol) in MeCN (30 mL), concentrated sulfuric acid (10.4 mL, 0.192 mol) was added slowly at 95 °C and the reaction was heated at this temperature for 5.5 h. The excess acetonitrile was evaporated to give a residue. Next, $CH_2Cl_2$ (20 mL) and saturated sodium bicarbonate (15 mL) were added to the mixture, and the organic layer was separated and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 30 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$, filtered, and concentrated. The residue was crystallized from ethyl acetate/*n*-hexane (1:3, v/v) to give compound **2** (1.05 g, 39%) as a white solid; m.p. 62–64 °C (literature[21]—m.p. 65–66 °C); IR (KBr, $cm^{-1}$): 2971, 2893, 2240, 1667; $^1$H NMR (600 MHz, $CDCl_3$): δ 2.17–2.39 (m, 4H, $CH_2$), 3.57–3.62 (m, 1H, $CH_2$), 3.74–3.78 (m, 1H, $CH_2$), 4.06–4.25 (s, 2H, $CH_2Cl$), 4.75–4.86 (m, 1H, CHCN); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 165.3, 117.9, 47.1, 47.0, 46.8, 46.5, 41.6, 32.5, 29.9, 25.2, 22.8. $[\alpha]_D^{20} = -1.53$ (*c* 1 g/100 mL, $CHCl_3$). The $^1$H and $^{13}$C NMR data of this compound are in good agreement with the reported data.[11]

## *Synthesis of 3-aminoadamantanol (**3**)*

Concentrated sulfuric acid (37.5 mL, 98% w/w aqueous solution) was stirred and cooled to 0–5 °C followed by the addition of nitric acid (3.75 mL, 65% w/w aqueous solution). The mixture was stirred for 10 min and then maintained at a temperature of 10–20 °C. Next, boric acid was added to the mixture and this solution was stirred for 30 min. 1-Aminoadamantane hydrochloride (**3a**) (3.75 g, 0.020 mol) was added to solution in batches until the solid was completely dissolved. The mixture was stirred at 10–20 °C for 4 h. The mixture was transferred to a three-neck flask (250 mL) and crushed ice (60 g) was added slowly and the mixture stirred for about 30 min until the liquid turned dark green. The pH was adjusted to 12 with KOH and then stirred at 10–20 °C for 4 h to produce a large amount of a white precipitate. The precipitate was filtered and then hydrochloric acid was added to adjust the pH of filtrate to 7–9. The above reaction solution was concentrated under reduced pressure to afford a white powder, and then anhydrous ethanol (80 mL) was added to the powder and the mixture was refluxed for 1 h. The mixture was allowed to slowly naturally cool to room temperature and filtered. The clear filtrate was concentrated under reduced pressure to give a white solid, which was treated with acetone/ethyl acetate 10 mL (7:3, v/v). Subsequently, the mixture was warmed to reflux and stirred at 52 °C for 1 h, then filtered, and dried to give the compound **3** (3.20 g, 95%) as a white solid; m.p. 262–264 °C (literature[22]—m.p. 261–263 °C); IR (KBr, $cm^{-1}$): 3364, 3250, 2926, 2851, 1626, 706; $^1$H NMR (600 MHz, DMSO-$d_6$): δ 1.41–1.42 (s, 2H, $CH_2$), 1.46–1.48 (s, 2H, CH × 2), 1.49–1.54 (m, 10H, $CH_2$), 2.08–2.2 (s, 3H,

OH, $NH_2$). The $^1H$ NMR data of this compound are in good agreement with the reported data.[23]

### *Synthesis of 1-[[(3-hydroxytricyclo[3.3.1.1(3,7)]dec-1-yl)amino]acetyl]-2-pyrrolidine carbonitrile (Vildagliptin) (**1**)*

3-Aminoadamantanol (**3**) (3 g, 18 mmol), THF (21 mL), potassium carbonate (10 g, 72.5 mmol), and potassium iodide (0.25 g, 1.5 mmol) were added to a 150-mL three-neck round bottom flask which was equipped with a condenser, a thermometer, and a constant pressure funnel. The mixture was heated to 40 °C under stirring and then the compound **2** (3 g, 16.5 mmol) dissolved in THF (22 mL) was added dropwise over 1.5 h. The reaction mixture was then stirred at 40 °C for 1 h and then at reflux for 0.5 h. The reaction was monitored by thin layer chromatography (TLC; 5% $CH_3OH$–$CH_2Cl_2$). After completing the reaction, the hot mixture was filtered and the filter cake was washed with hot 2-butanone (3 × 20 mL). The collected filtrate was concentrated under vacuum and stirred while slowly cooling. After the mixture became viscous, it was stirred in an ice bath. The resulting white crystalline solid was filtered, washed with ethyl acetate (3 × 20 mL), and then dried at 45 °C under vacuum to afford vildagliptin (**1**) (4.1 g, 82%) as a white solid; m.p. 148–150 °C (literature[24]—m.p. 150 °C); IR (KBr, $cm^{-1}$): 3293, 2915, 2848, 2241, 1656, 1405; $^1H$ NMR (600 MHz, DMSO-$d_6$): δ 1.41–1.49 (m, 14H, $CH_2$), 1.97–2.02 (m, 2H, OH, NH), 3.44–3.63 (m, 2H, $COCH_2$), 4.72–4.74 (dd, $J$ = 7.7, 3.4 Hz, 1H, CHCN), 2.10–2.14 (m, 4H, $CH_2$), 3.26–3.32 (m, 2H, $NCH_2$); $^{13}C$ NMR (125 MHz, DMSO-$d_6$): δ 25.2, 30.6, 35.5, 39.7, 39.9, 40.0, 40.1, 40.3, 41.5, 43.5, 44.9, 45.6, 46.6, 53.2, 68.2, 119.8, 171.1. $[\alpha]_D^{20} = -0.09$ ($c$ 1 g/100 mL, MeOH) (literatur[25]—$[\alpha]_D^{20} = -0.087$ ($c$ 1 g/100 mL, MeOH)); The $^1H$ and $^{13}C$ NMR data of this compound are in good agreement with the reported data.[11]

### *OP test*

Compound **2** (0.25 g, 1.448 mmol) was dissolved in chloroform to ensure that the solution was clear and transparent without any solid particles. Volumetric flasks (25 mL) were used for volumetric determination and then tested. The WZZ-2B automatic polarimeter (λ = 589.3 nm) was allowed to preheat for at least 30 min after being switched on. Three sample tubes were each loaded with chloroform and then put into the polarimeter to set zero. The sample tube was then rinsed with the test solution 2–3 times before recording specific solution. The solution to be tested was injected into the sample tube at 20 °C to measure the OP. This process was repeated three times. The values were recorded and the averages were calculated.

## Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this paper.

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## Supplemental material

Supplemental material for this paper is available online.

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