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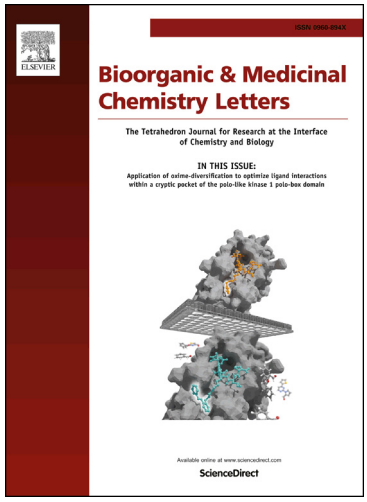


Synthesis and glucose-stimulate insulin secretion (GSIS) evaluation of vindoline derivatives

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## Graphical Abstract

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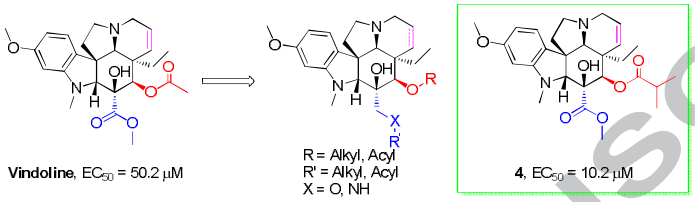

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# Synthesis and glucose-stimulate insulin secretion (GSIS) evaluation of vindoline derivatives

Chengqian Xiao[a,†], Yunan Tian[b,†], Min Lei[a,*], Fanglei Chen[a], Xianwen Gan[a], Xingang Yao[b], Jing Chen[b], Xu Shen[b,*] and Lihong Hu[a,*]

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ABSTRACT

It is demonstrated that natural product vindoline can enhance the glucose-stimulated insulin secretion (GSIS) in MIN6 cells with the $EC_{50}$ value of 50.2 μM. In order to improve the activities, a series of vindoline derivatives are synthesized and evaluated in MIN6 cells. Compounds **4**, **8**, **17** and **24** show about 4.5 times more effective stimulation insulin secretion ability ($EC_{50}$: 10.4, 14.2, 11.0 and 12.7 μM , respectively) than vindoline.



Diabetes mellitus containing type 1 and type 2 is a complex metabolic disordered disease worldwide with significant resulting morbidity and mortality. It is estimated by International Diabetes Federation that more than 415 million people have diabetes, 318 million have impaired glucose tolerance, and about 21 million women develop gestational diabetes in worldwide in 2015. Type 2 diabetes mellitus (T2DM) is reported to ranged between 90% and 95% of both types, which is primarily characterized by insulin resistance and relative insulin deficiency that eventually cause hyperglycemia.[1] At present, insulin secretagogues including sulfonylureas and glinides, which can promote endogenous insulin release and further increase glucose uptake and transformation in target tissues, are widely used clinically for the treatment of T2DM.[2] However, these agents readily lead to hypoglycemia. Therefore, the development of glucose-stimulated insulin secretion (GSIS) agents without hypoglycemia has been received a considerable attention.

In recent years, there has been a growing interest in anti-diabetes agents from folk medicinal plants.[3] Vindoline, as shown in Figure 1, is a main ingredient of an anti–T2DM herb *Catharanthus roseus*. It has been previously reported to possess diverse pharmacological properties.[4] Furthermore, vindoline is an important chemical precursor to synthesis of antitumor drugs, such as vinorelbine,[5] vinflunine,[6] and vindesine.[7] Recently, we reported vindoline could obviously enhanced the GSIS in MIN6 cells and primary mice pancreatic islets. Moreover, the assays on type 2 diabetic animal models (*db/db* mice and STZ/HFD-induced type 2 diabetic rats) demonstrated that vindoline effectually decreased fasting plasma glucose, improved oral glucose tolerance, lowered serum glycated hemoglobin ($HbA_{1c}$) and triglyceride (TG) levels.[8] Due to its obviously ant-T2DM activities *in vivo* and *vitro*, vindoline is chosen as a drug lead for further investigation.

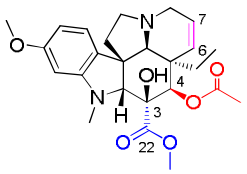


**Figure 1.** The structure of vindoline (**1**).

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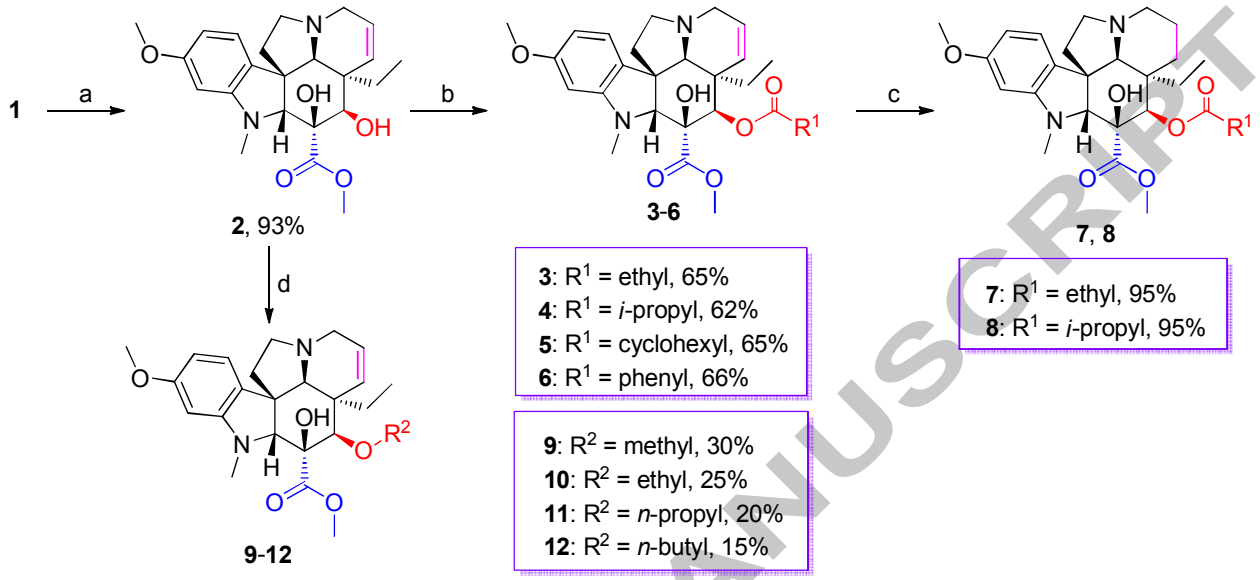
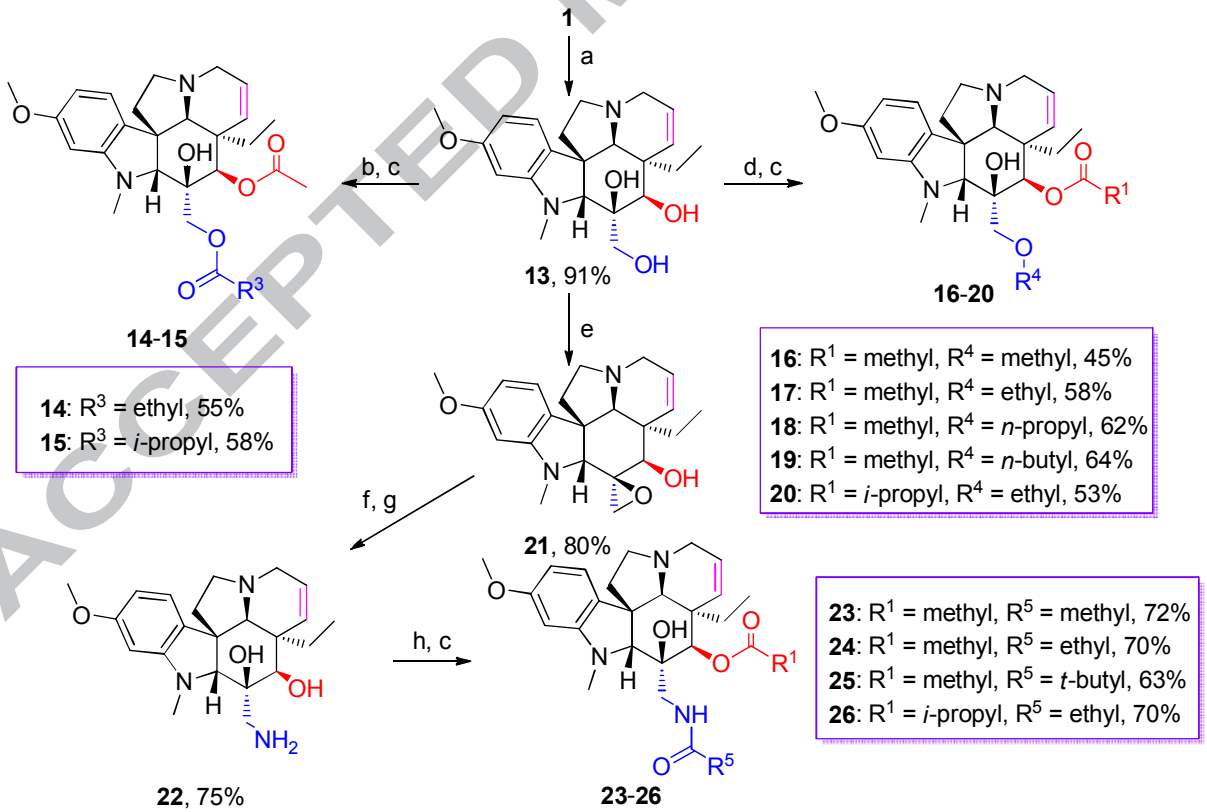
To study its structure–activity relationships (SARs) further, a series of vindoline derivatives were synthesized and their biological activities of GSIS ($EC_{50}$ values) were tested in MIN6 cells. According to the structural characteristic of vindoline, we carried out the modification of vindoline on C-4, C-6, C-7 and C-22. Initially, to investigate the effect of C-4 ester group on GSIS activities, compounds **2**–**6** were synthesized (Scheme 1). Hydrolysis of vindoline took place in the presence of MeONa as base in MeOH to obtain C-4 deacetyl vindoline (**2**) in 93% yield. Then, **2** reacted with acyl chloride to form **3**–**6** (62–66%). Compounds **3** and **4** were hydrogenated on Pd/C to give **7** and **8**, respectively. As shown in Scheme 2, compound **9**–**12** were synthesized from **2** by etherification in 15–30% yields.




**Scheme 1.** Synthesis of **2**–**12**: reagents and conditions: (a) MeONa, MeOH; (b) $R^1COCl$, $Et_3N$, DCM; (c) 10% Pd/C, MeOH; (d) $CH_3I$ or $R^2Br$, NaH, THF.




**Scheme 2.** Synthesis of **13**–**26**: reagents and conditions: (a) $LiAlH_4$, THF; (b) $BtCOR^3$, NaH, THF; (c) $Ac_2O$ or $R^1COCl$, Py or $Et_3N$; (d) NaOH, TBAI, MeI or $R^4Br$. (e) TsCl, TBAI, NaOH, THF; (f) $NaN_3$, $NH_4Cl$, $MeOH/H_2O$; (g) $LiAlH_4$, THF; (h) $R^5COCl$, NaOAc, DCM.

In addition, the modification of C-22 of vindoline was also carried out by a multi-step process (Scheme 2). Vindoline was reducted by $LiAlH_4$ in THF to afford **13** in 91% yield, then **13** was esterified to form **14** and **15**, or etherified to form **16**–**20**. Furthermore, anino substituted derivatives were also synthesized as shown in Scheme 4. Epoxy intermediate **21** was formed from **13** in the presence of TsCl in THF in 80% yield. Then ring opening reaction of **19** with NaN3 resulted in the formation of the azide, which was reduced by $LiAlH_4$ to give **20** in 75% yield. Further acylation reaction of **22** was carried out to give **23**–**26** (63–72%).

Then, we evaluated the GSIS activities of these compounds on MIN6 cell line, and the results are presented in Table 1. The $EC_{50}$ values of vindoline and C-4 deacetyl vindoline (**2**) were 50.2 μM and >100 μM, respectively. This result clearly indicated that C-4 ester group was important to keep the activities. Therefore, several C-4 ester group derivatives **3**–**6** were synthesized, and the $EC_{50}$ values of these compounds ranged from 10.4 to 80.5 μM. The GSIS activities of **3** ($R^1$ = ethyl) and **4** ($R^1$ = *i*-propyl) were increased greatly compared with vindoline. On the contrary, the activities of **5** ($R^1$ = cyclohexyl) and **6** ($R^1$ = phenyl) were decreased. These results revealed that increasing the group of $R^1$ properly was favorable for increased activities, however, the large steric hindrance group was unfavorable.

**Table 1**
GSIS activities of vindoline derivatives on MIN6 cell line.

| Compound | $EC_{50}$ (μM) | Compound | $EC_{50}$ (μM) |
|---|---|---|---|
| **vindoline** | 50.2 ± 3.4 | **14** | 51.0 ± 3.9 |
| **2** | >100 | **15** | >100 |
| **3** | 32.6 ± 2.6 | **16** | 41.0 ± 3.5 |
| **4** | 10.4 ± 0.6 | **17** | 11.0 ± 1.0 |
| **5** | 80.5 ± 9.2 | **18** | 41.5 ± 3.0 |
| **6** | 62.2 ± 4.4 | **19** | >100 |
| **7** | 38.5 ± 2.5 | **20** | 14.2 ± 1.1 |
| **8** | 14.2 ± 0.6 | **23** | 19.3 ± 1.4 |
| **9** | >100 | **24** | 12.7 ± 0.7 |
| **10** | 62.2 ± 4.6 | **25** | 21.0 ± 1.8 |
| **11** | 64.3 ± 4.3 | **26** | 18.5 ± 2.0 |
| **12** | >100 | | |

Then, compounds **3** and **4** were chosen to investigate the effect of C-6 and C-7 double bond on activity. The $EC_{50}$ values of **7** (38.5 μM) and **8** (14.2 μM) showed that the reduction of double bond led to the activity decreased. Furthermore, C-4 ether derivatives **9**–**12** were also synthesized, and activity test showed low activities ($EC_{50}$ > 62.2 μM).

In addition, several ester and ether derivatives on C-22 (**14**–**20**) were synthesized. As shown in Table 1, **17** showed more potent GSIS activities on MIN6 cell line with the $EC_{50}$ value of 11.0 μM, which was 4.5-fold more potent than vindoline. The $EC_{50}$ values of **14**–**20** demonstrated that the activities were decreased significantly with the increase of group ($R^3$ or $R^4$). Furthermore, amide substituted derivatives on C-22 (**23**–**26**) showed good activities with the $EC_{50}$ value of 19.3, 12.7, 21.0 and 18.5 μM, respectively.

In conclusion, we have synthesized a series of vindoline derivatives on C-4, C-6, C-7 and C-22. All of these compounds were evaluated their GSIS activities on MIN6 cell line. The results indicate that both ester group and size of $R^1$ on C4 played a key role to keep the activities. The reduction of double bond of C-6 and C-7 led to the activity decreased. As for the ester and ether derivatives on C-22, the size of $R^3$ or $R^4$ also have a significant impact on GSIS activities. In addition, the activities are improved for those compound with amide substituted derivatives on C-22. Among all compounds, **4**, **8**, **17** and **24** show good GSIS activities, which were about 4.5-fold more potent than vindoline.

## Acknowledgments

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## References and notes

1. (a) Schwarz, P. E. H.; Gallein, G.; Ebermann, D.; Muller, A.; Lindner, A.; Rothe, U.; Nebel, I. T.; Muller, G. *Diabetes Res. Clin. Pract.* **2013**, *100*, 11; (b) Seo, W.-D.; Lee, J. H.; Jia, Y.; Wu, C.; Lee, S.-J. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 5237; (c) Bloomgarden, Z. T. *Diabetes Care* **1996**, *19*, 295. (d) Wild, S.; Roglic, G.; Green, A.; Sicree, R.; King, H. *Diabetes Care* **2004**, *27*, 1047.
2. Porte, D. Jr. *Diabetes Metab. Res. Rev.* **2001**, *17*, 181.
3. Zareba G.; Serradell N.; Castaner R.; Davies S. L.; Prous J.; Mealy N. *Drug Future* **2005**, *30*, 1253.
4. (a) Passarella, D.; Giardini, A.; Peretto, B.; Fontana, G.; Sacchetti, A.; Silvani, A.; Ronchi, C.; Cappelletti, G.; Cartelli, D. Borlake, J.; Danielia, B. *Bioorg. Med. Chem.* **2008**, *16*, 6269; (b) Nammi, S.; Boini, M. K.; Lodagala, S. D.; Behara, R. B. S. *BMC Comp. Altern. Med.* **2003**, *3*, 4; (c) Rasineni, K.; Bellamkonda, R.; Singareddy,S. R.; Desireddy, S. *Pharmacogn. Res.* **2010**, *2*, 195.
5. Mangeney, P.; Andriamialisoa, R. Z.; Langlois, N.; Langlois, Y.; Potier, P. *J. Org. Chem.* **1979**, *44*, 3765.
6. (a) Etievant, C.; Barret, J.-M.; Kruczynski, A.; Perrin, D.; Hill, B. T. *Invest. New Drug.* **1998**, *16*, 3; (b) Langlois, N.; Gueritte, F.; Langlois, Y.; Potier, P. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 505.
7. (a) Fahy, J.; Duflos, A.; Ribet, J. P.; Jacquesy, J. C.; Berrier, C.; Jouannetaud, M. P.; Zunino, F. *J. Am. Chem. Soc.* **1997**, *118*, 8576; (b) Bellmunt, J.; Delgado, F.-M.; George, C. *Semin. Oncol.* **2008**, 35, S34.
8. Yao, X.; Chen, F.; Li, P.; Quan, L.; Chen, J.; Yu, L.; Ding, H.; Li, C.; Chen, L.; Gao, Z.; Wan, P.; Hu, L.; Jiang, H.; Shen, X. *J. Ethnopharmacol.* **2013**, *150*, 285.

## Supplementary Material

Supplementary data (experimental procedures, spectral data and biological assay methods) associated with this article can be found, in the online version, at