Journal Pre-proof

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PII: S0223-5234(20)30480-3

DOI: https://doi.org/10.1016/j.ejmech.2020.112508

Reference: EJMECH 112508

To appear in: *European Journal of Medicinal Chemistry*

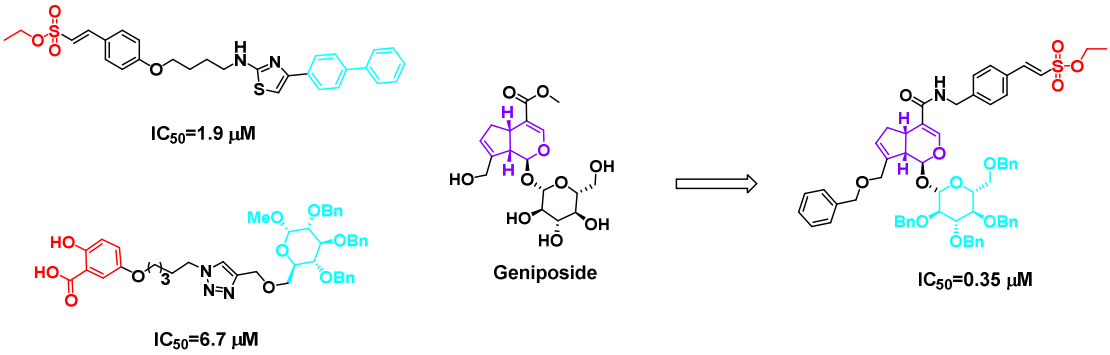
Received Date: 28 April 2020

Revised Date: 20 May 2020

Accepted Date: 23 May 2020

Please cite this article as: S. Lei, D. Zhang, Y. Qi, S.R. Chowdhury, R. Sun, J. Wang, Y. Du, L. Fu, F. Jiang, Synthesis and Biological Evaluation of Geniposide derivatives as potent and selective PTPIB inhibitors, *European Journal of Medicinal Chemistry*, https://doi.org/10.1016/j.ejmech.2020.112508.

Graphical abstract



Synthesis and Biological Evaluation of Geniposide derivatives as potent and selective PTPlB inhibitors

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Abstract

Herein a series of Geniposide derivatives were designed, synthesized and evaluated as protein tyrosine phosphatase 1B (PTP l B) inhibitors. Most of these compounds exhibited potent *in vitro* PTP1B inhibitory activities, the representative **7a** and **17f** were found to be the most potent inhibitors against the enzyme with IC_{50} value of 0.35 and 0.41 μM, respectively. More importantly, they showcased 4 to10-fold selectivity over SHP2 and 3-fold over TCPTP. Further biological activity studies revealed that compounds **17b** and **17f** could effectively enhance insulin-stimulated glucose uptake with no significant cytotoxicity. Subsequent molecular docking and structural activity relationship analyses demonstrated that the glucose scaffold, benzylated glycosyl groups, and arylethenesulfonic acid ester significantly impact on the activity and selectivity.

Key Words: Type 2 diabetes mellitus, PTP1B inhibitors, Selectivity, Geniposide, Genipin

1. Introduction

Protein tyrosine phosphatases (PTPs) play important roles in insulin signaling pathway by dephosphorylating tyrosine residues on insulin receptor (IR) and related downstream substrate proteins [1-2]. Protein tyrosine phosphatase 1B (PTP1B), the first discovered PTP family member, is a key negative regulator and effective therapeutic target for the treatment of type 2 diabetes mellitus (T2DM). PTP1B is a highly druggable target due to the presence of its conserved and polar active pocket. However, discovery of drugs that target PTPlB is still a challenging task due to the presence of the highly homologous proteins such as TCPTP and SHP2. Great effort has been made, but none of the PTP1B inhibitors have survived through all three phases of clinical trials, mostly due to their poor selectivity and low bioavailability [3-4].

Natural products are the abundant resources for drug discovery. *Gardenia jasminoides* Ellis, a traditional Chinese medicine, has been prescribed to treat T2DM for several decades. This natural product contains more than 40 ingredients, among which geniposide was found to be the most active component [5]. Geniposide (**Fig. 1**), a carbohydrate compound, has a good biocompatibility and spatial flexibility [6]. Genipin (Fig. 1), a natural product also derived from the *Gardenia jasminoides* Ellis, is an excellent water-soluble cross-linker.[5,7-8] Both geniposide and genipin have many pharmacological effects, such as anti-anxiety, neuroprotective activity, anti-Alzheimer's disease, antithrombosis effects, anti-tumor effects and hypoglycemic activity [9-13].

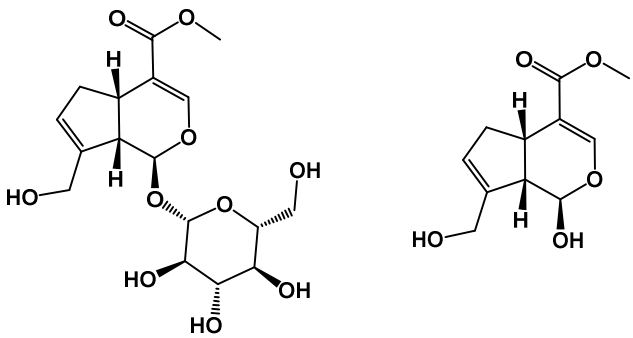


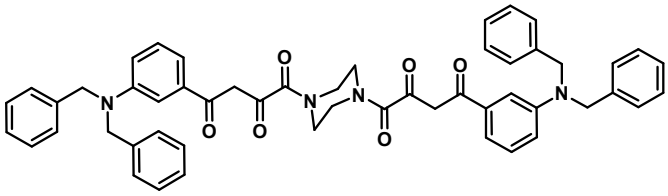
Fig. 1. The structure of geniposide and genipin.

Studies showed that introducing hydrophobic groups (**Fig. 2**, **I**) or phosphorylated tyrosine (pTyr) mimics to a molecule **(Fig. 2**, **II**) can enhance its binding affinity to PTP1B and the cell membrane permeability [14,15]. Our previous work also revealed that arylethenesulfonic acid ester derivatives could act as membrane-permeable PTP1B inhibitors (**Fig. 2**, **III**) [16-19]. In 2009, Zhang et al. demonstrated that kinsenoside, an active compound coupled with a glycosyl moiety (**Fig. 2**, **IV**) has a good inhibitory activity against PTP1B (IC_{50}=5.14 μM) and high selectivity over other PTPs [20].

The structure of geniposide is much similar to kinsenoside. Our molecular docking analysis of geniposide binding to the PTP1B (**Fig. 3**) indicates that the glycosyl moiety of geniposide locates in the catalytic active site of PTP1B and forms hydrogen bonds with Arg220, Ser215, Ala216 and Gln265. This binding conformation is much like that of the kinsenoside.

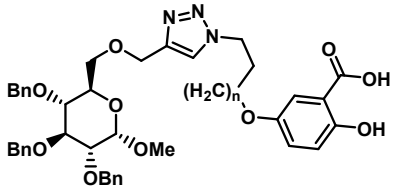
Based on the structural and binding conformation similarities between kinsenoside and geniposide, we hypothesize that geniposide derivatives would offer inhibitory activity towards PTP1B and the glycosyl group is likely to be the key moiety in our novel PTP1B inhibitors.

Herein, we report the design, synthesis, and evaluation of geniposide derivatives as a novel class of potent and selective PTP1B inhibitors. Specifically, to fine-tune the hydrophobicity of geniposide, we benzylate its glycosyl groups and introduce a variety of sulfonic esters mimicking pTyr analogs, individually and collectively.



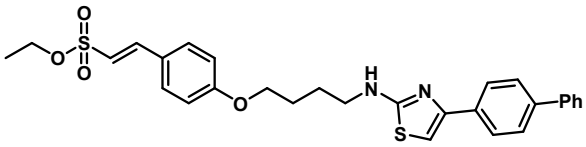
I

IC_{50}=2.8±1.0 μM (PTP1B)



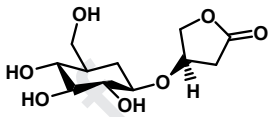
II

IC_{50}=6.7±0.5 μM (PTP1B)



III

IC_{50}=1.9 μM (PTP1B)



IV

IC_{50}=5.14 μM (PTP1B)

Fig. 2. Representative PTP1B inhibitors.

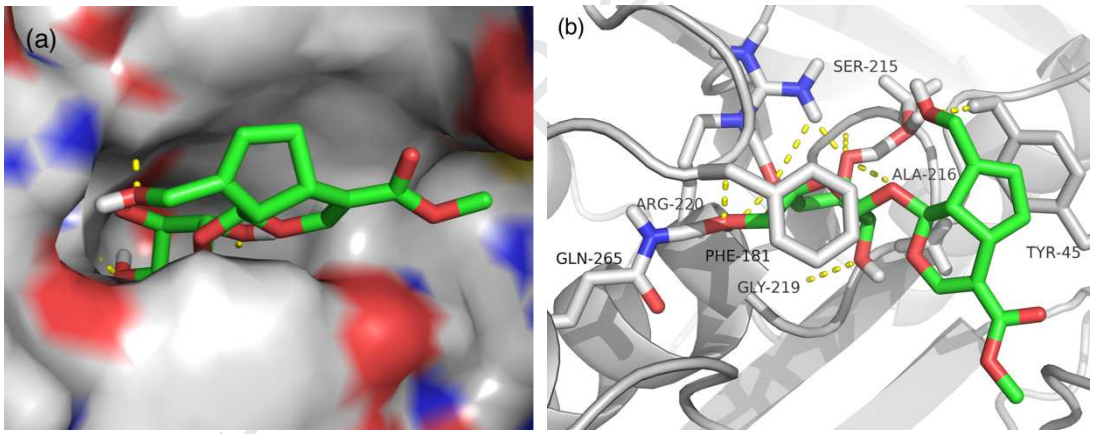


Fig. 3. Docking of geniposide to PTP1B (PDB code 1AAX). (a) Binding conformation of geniposide in PTP1B. (b) Geniposide in the PTP1B active site.

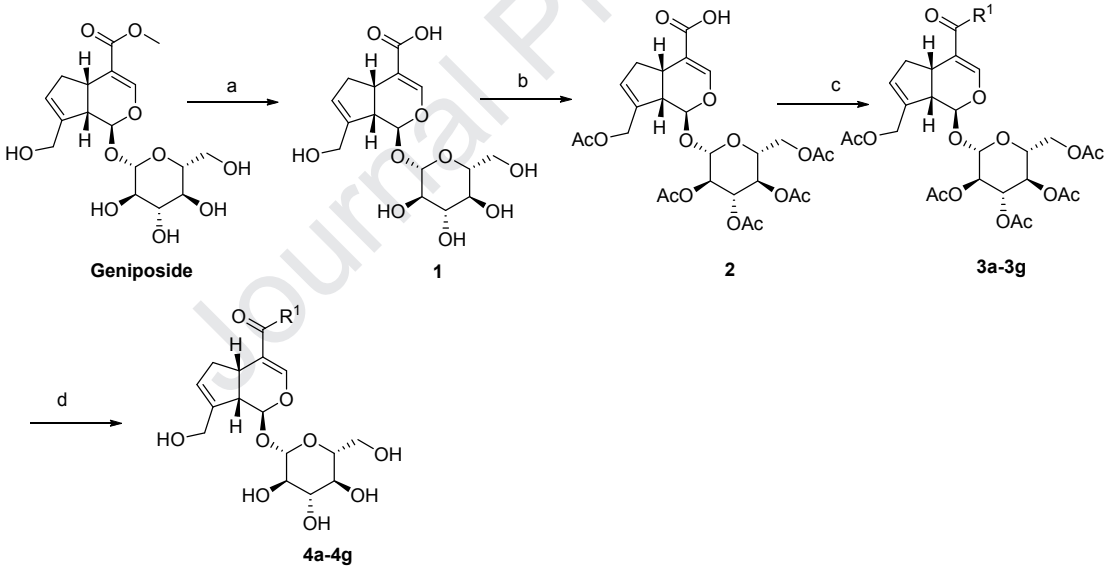
2. Results and discussion

2.1. Chemistry

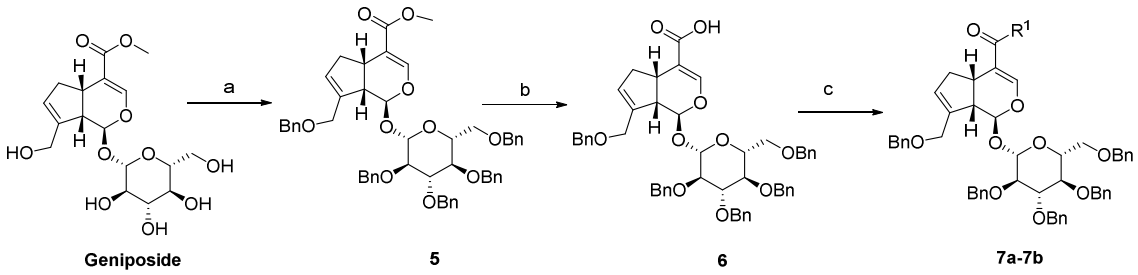
The synthetic routes of three series of geniposide derivatives are outlined in **Schemes 1-3**. Geniposide was hydrolyzed with 2 M LiOH solution overnight to afford compound **1**. The hydroxyl groups of **1** were protected by acetyl group in the presence of Ac_2O and AcONa under reflux for 2 h to give **2**. Compound **2** was condensed with various amines with EDCI overnight to give intermediate **3**, which was hydrolyzed with 2 M LiOH in 2 h to yield compounds **4a-4g**.

Compounds **5, 6, 7a-7b** were synthesized in three steps starting from geniposide. The hydroxyl groups of geniposide were protected through BnBr treatment to develop **5**. Subsequently, **5** was hydrolyzed with 1 M NaOH solution to give **6**. Compound **6** was interacted with various amines to generate compounds **7a-7b**.

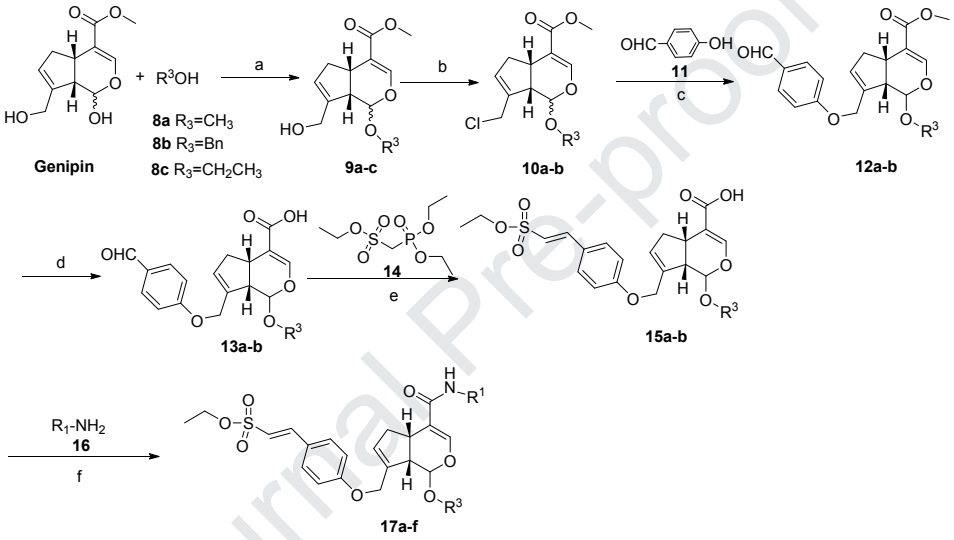
Compounds **17a-17f** were synthesized according to the procedure indicated in **Scheme 3**. Esterification of genipin with different alcohols was catalyzed by a drop of hydrochloric acid to obtain compounds **9a-9c**. Compounds **9a-9b** were chlorinated by $PhSO_2Cl$ to yield compounds **10a-10b**. The halogen of **9a-9b** was substituted with compound **11** to give **12a-12b**. Subsequently, compounds **12a-12b** was hydrolyzed with 2 M LiOH to afford the **13a-13b**. The coupling of **14** with compounds **13a-13b** was carried out by Wittig-Horner reactions to generate respective compounds **15a-15b**. The final compounds **17a-17f** were synthesized by a condensation between compounds **15a-15b** and various amines.



Scheme 1. Synthesis of compounds **4a-4g**. Reagents and conditions: (a) MeOH, 2 M $LiOH·H_2O$, 50 °C, overnight, 90%; (b) Ac_2O, AcONa, reflux, 2 h, 68%; (c) EDCI, HOBT, DIPEA, DMAP, DMF, r.t., overnight, 19%-27%; (d) THF/H_2O, 2 M $LiOH·H_2O$, r.t., 2 h, 86%-97%.



Scheme 2. Synthesis of compounds **5**, **6**, **7a-7b**. Reagents and conditions: (a) BnBr, NaH, TBAI, DMF, r.t., overnight, 42%; (b) MeOH, 1 M NaOH·H_2O, reflux, overnight, 90%; (c) Amine, EDCI, HOBT, DIPEA, DMAP, DMF, r.t., overnight, 32%-52%.



Scheme 3. Synthesis of compounds **17a-17f**. Reagents and conditions: (a) HCl, reflux, 7 h, 56%-98%; (b) $PhSO_2Cl$, TEA, DCM, DMAP, r.t., 40h, 48%-49%; (c) K_2CO_3, ACN, reflux, 12 h, 89%-91%; (d) MeOH, 2 M LiOH·H_2O, r.t., 30 h, 73%-90%; (e) NaH, THF, r.t., 12 h, 42%-46%; (f) HATU, TEA, DMF, r.t., 2.5 h, 23%-36%.

2.2. Inhibition of PTP1B

PTP1B inhibitory assay was performed on the synthesized ligands according to the known method with sodium vanadate as a positive control [21-23]. The results are shown in **Table 1**, where we firstly introduced glycosyl ring to the core structure and verified the impact brought by different amides on the inhibitory activity. Different anilines were introduced to improve their hydrophobic property (**4a**, **4b**, **4c** and **4d**). Compared with parent compound geniposide (IC_{50}>500 μM), all showed obvious enhancement in activity with IC_{50} value ranging from 17.69 to 100 μM accordingly with the increase of their cLogP values. An ethyl group or an F- on the ortho- position brings more positive effect to the ligand activity than 2-methoxyl group. We further

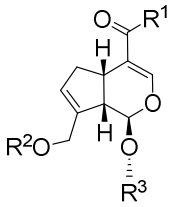
introduced more bulky aromatic rings on the para- position of the aniline (**4e**, **4f** and **4g**). They all generate moderate activity to PTP1B. The best ligand of this series is **4g**, which has an IC_{50} of 17 μM. However, the improvement is not significant.

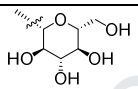
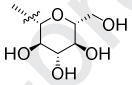
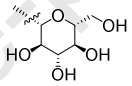
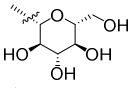
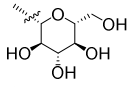
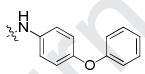
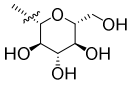
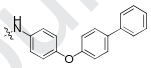
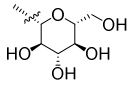
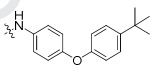
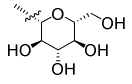
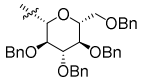
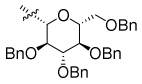
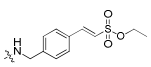
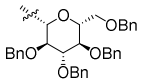
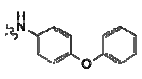
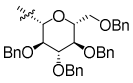
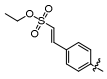
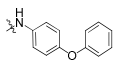
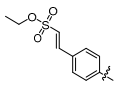
Inspired by the former findings about increasing hydrophobicity of PTP1B ligands, we tried to benzylate all free hydroxyl group of glycosyl moiety in the second round of modification. As shown in **Table 1**, the modification brings significant increase of hydrophobicity with cLog P value= 2.4-4.8, which lead to great improvement in ligand activity (**5**, **6**, **7a-7g**) accordingly with IC_{50} value=0.35-0.68 μM. We made such an improvement regardless the different substituted amides attached on the core structure. We then concluded that the benzylation of the glysosyl group weights more than the modification of the amide building block. The most potent ligands are **7a** and **7b**, whose IC_{50} values are 0.35 μM and 0.40 μM respectively.

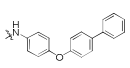
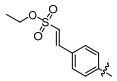
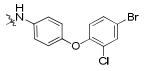
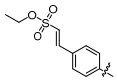
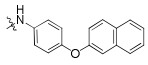
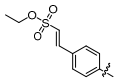
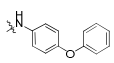
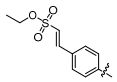
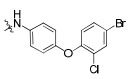
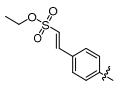
Though the benzylation of the glycosyl ring significantly boost the PTP1B inhibition activity, the molecular weight increased greatly and became less drug-like . We herein considered to use a smaller hydrophobic group as a substitution. Not only it could bring up similar chemical physical property to the ligands as benzylated glucose, but it has a much smaller size which makes the compounds more drug-like. Another modification is that a sulfonic esters as pTyr mimics was introduced to the core structure. We hope the combination of the two modifications would bring about more significant improvement to the ligand activity. We therefore constructed genipin derivatives as the third round modification. As shown in **Table 1**, genipin derivatives (IC_{50}=0.41-13.15 μM) with methyl or benzyl at R^3 position and a sulfonic esters at R^2 position exhibited better activity than genipin (IC_{50}>500 μM). On the contrary to the previous two rounds of modification, the benzamides greatly affect the activity of the ligands (**17a** vs **9a**, **17f** vs **9b**). The benzamide modification boost the activity over 100 times. The best ligands of this series are **17c** and **17f**, whose IC_{50} values are 1.05 μM and 0.41 μM, respectively. Based on the above findings, SARs of geniposide derivatives can be concluded as follows, benzylation of the glycosyl groups of

geniposide or introduction of sulfonic esters as pTyr mimics to genipin can increase the hydrophobicity of the ligand and achieve high active PTP1B inhibitors.

Table 1 PTP1B inhibitory activities of genipin and geniposide derivatives



Compound	R^1	R^2	R^3	cLogP[a]	$IC_{50}(\mu M)$[b]
Geniposide	$-OCH_3$	H		-2.980	>500
Genipin	$-OCH_3$	H	H	-1.016	>500
4a		H		-1. 976	>100
4b		H		-1.714	20.82
4c		H		-1.906	18.27
4d		H		-2.214	50.76
4e		H		-0.676	25.23
4f		H		0.499	21.74
4g		H		-0.362	17.69
5	$-OCH_3$	-Bn		2.497	0.68
6	-OH	-Bn		2.480	0.38
7a		-Bn		3.614	0.35
7b		-Bn		4.803	0.40
9a	$-OCH_3$	H	$-CH_3$	-0.731	236.14
9b	$-OCH_3$	H	-Bn	0.348	40.30
9c	$-OCH_3$	H	$-CH_2CH_3$	-0.586	64.74
15b	$-OCH_3$		-Bn	2.232	13.15
17a			$-CH_3$	3.459	2.67

17b			-CH_3	4.634	0.43
17c			-CH_3	5.121	1.05
17d			-CH_3	5.445	0.75
17e			-Bn	4.538	0.99
17f			-Bn	6.199	0.41
Sodium vanadate	-	-	-		0.046

[a] Values are calculated by Indraw software;

[b] Values are means of triplicates, repeated two times;

2.3. Selectivity over TCPTP and SHP2

Those with excellent PTP1B inhibitory activity were further assayed for their selectivities over the other PTPs, TCPTP and SHP2. The results are shown in **Table 2**. As shown in **Table 2**, most of the representatives of geniposide derivatives (**4c** & **g**) had no inhibitory activity towards TCPTP or SHP2. The geniposide derivative (**6**) showed moderate selective inhibitory activity over TCPTP and SHP2. Approximately 4-fold selectivity over TCPTP and 9-fold selectivity over SHP2 were obtained. Genipin derivatives (**17b & f**) exhibited 3-fold selectivity over TCPTP and 4-10-fold selectivity over SHP2.

Table 2 Inhibitory activities of geniposide derivatives on PTP1B, TCPTP and SHP2

Compound	$IC_{50}(\mu M)$[a]		
	PTP1B	TCPTP	SHP2
Geniposide	>500	>500	>500
Genipin	>500	>500	>500
4c	18.27	>100	>100
4g	17.69	>100	>100
6	0.38	1.32	3.32
17b	0.43	0.95	1.24
17f	0.41	1.29	3.97
Sodium vanadate[b]	0.046	0.014	NT

[a] Values are means of triplicates, repeated two times;

[b] Sodium vanadate as a positive control;

NT means not tested.

2.4. Effects of compounds on cell viability

In order to determine the cytotoxicity of geniposide derivatives, ten compounds (**5**, **6**, **7a**, **17a**, **7b, 17b**, **17c**, **17d**, **17e**, **17f**) were selected to evaluate their effects on Chinese Hamster Ovarian (CHO) cell viability. The data is given in **Table 3**.

Table 3 Cytotoxicity of compounds **5**, **6**, **7a**, **7b, 17a**, **17b**, **17c**, **17d**, **17e**, **17f** against CHO cells.

Compound	CHO IC_{50} (μM)[a]
5	42
6	>200
7a	>200
7b	>200
17a	>200
17b	>200
17c	>200
17d	>200
17e	62
17f	>200

[a] Values are means of triplicates, repeated two times;

Overall, compounds **6**, **7a**, **7b, 17a**, **17b**, **17c**, **17d**, **17f** exhibited low toxicity against CHO cell-line. These results indicated that the newly prepared PTP1B inhibitors have no significant cytotoxicity.

2.5. Effects of compounds **17b** and **17f** on insulin-stimulated glucose uptake

It has been reported that PTP1B inhibition leads to a remarkable improvement in insulin sensitivity and glucose metabolism [24]. We evaluated compounds **17b** and **17f** on 2-NBDG uptake in HepG2 cells to determine the effect. As shown in **Fig. 4**, insulin-stimulated glucose uptake in HepG2 cells was increased by Pioglitazone which was used as the positive control, and the increased percentages were 33.8%, 46.0%, and 63.5% at the concentrations of 5, 10 and 20 μM, respectively. The glucose uptake in HepG2 cells was also significantly increased by treatment with tested compounds (**17b** and **17f**). The increased percentages were 38.6%, 68% and 69.6% for **17b**, and 43.8%, 68.3% and 64.4% for **17f** at 5, 10 and 20 μM, respectively. The results were slightly better than the positive control.

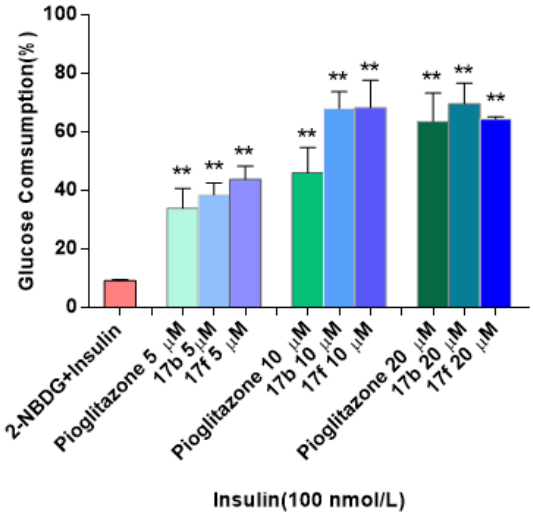
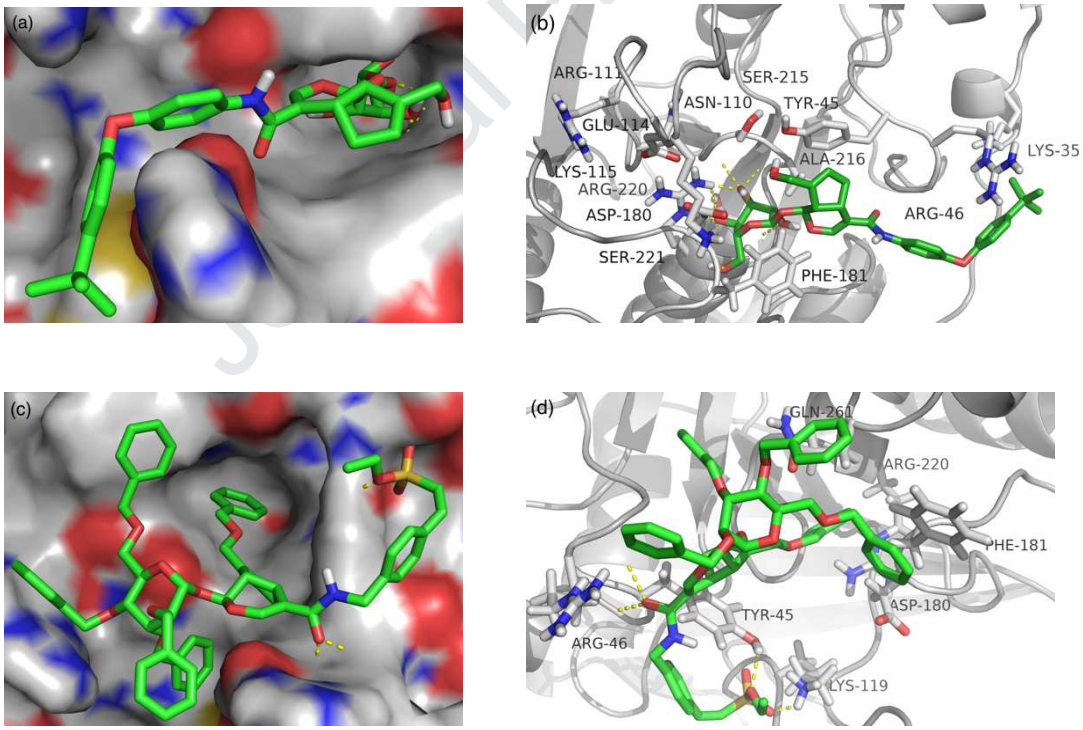


Fig. 4. Effect of compound **17b** and **17f** on insulin-stimulated glucose uptake. Each value was presented as mean ±SD, n=3; (**) P<0.01 vs the insulin-treated group.

2.6. Molecular docking study



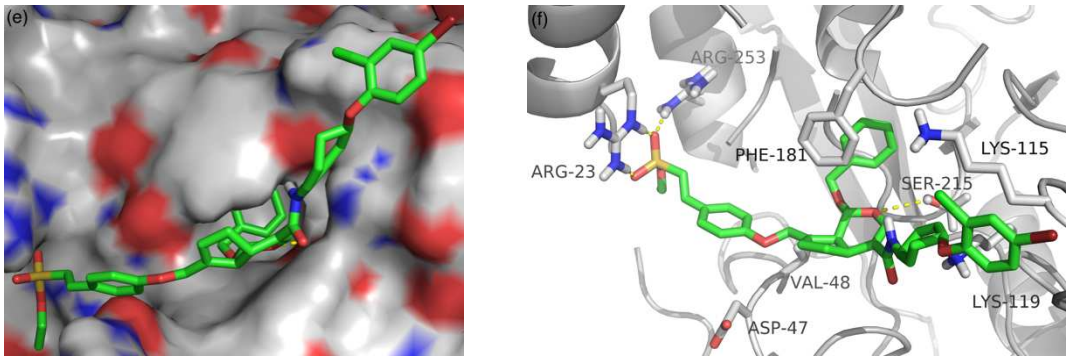


Fig. 5. Docking of compound **4g**, **7a** and **17f** to PTP1B (PDB code 1AAX). (a) Binding conformation of compound **4g** in PTP1B. (b) Compound **4g** in the PTP1B active site. (c) Binding conformation of compound **7a** in PTP1B. (d) Compound **7a** in the PTP1B active site. (e) Binding conformation of compound **17f** in PTP1B. (f) Compound **17f** in the PTP1B active site.

The representative compounds **4g**, **7a** and **17f** were selected for molecular docking studies (**Fig. 5**). The glycosyl moiety of compound **4g** was found to locate in the catalytic active site of PTP1B. The hydroxyl group on the glycosyl group formed multiple hydrogen bonds with Ser215, Asp180, Ser221, Ala216, Phe181 and Arg220. The diphenyl ether partially extended into the secondary aryl phosphorylation binding site and established hydrophobic interaction with several residues including Lys35, Arg46. The core structure of geniposide formed a π-π conjugation with Tyr45. These multiple interactions determined the activity of **4g**. The benzyl groups of **7a** bound to the peripheral hydrophobic surface of PTP1B, formed hydrophobic interactions with Arg220, Asp180, and Gln261, which enhanced the binding affinity with PTP1B. The amide carbonyl formed two hydrogen bonds with Arg46. The sulfonic acid ester formed hydrogen bonds with Try45 and Lys119. In addition, the benzyl rings on the glycosyl group formed a π-π conjugation with Phe181, which improved the binding to PTP1B. The sulfonic acid ester of **17f** extended to the catalytic active site of PTP1B and formed hydrogen bonds with Arg23 and Arg253, which enhanced the binding affinity. The diphenylether side chain formed hydrophobic interactions with Lys115 and Asp28. The benzyl groups of **17f** formed a π-π conjugation with Phe181. Then, the core structure of genipin formed a hydrogen bond with Ser215, which increased the binding to PTP1B.

3. Conclusions

In this study, a series of geniposide and genipin derivatives were designed and synthesized as potent and selective PTP1B inhibitors. Most compounds demonstrated potent PTP1B inhibitory activity and moderate selectivity over TCPTP and SHP2. SARs study showed that benzylated glycosyl group on geniposide derivatives and sulfonic ester as pTyr mimics on genipin derivatives are vital for the enhancement of hydrophobic property and activity. Molecular docking analysis suggested the binding mode and explained the reasons for better inhibitory activity and selectivity. We further verified the effects of compounds **17b** and **17f** on insulin-stimulated glucose uptake with no significant cytotoxicity. This study demonstrated a good strategy to discover effective and safe genipin-based PTP1B inhibitors.

4. Experiment section

4.1. Chemistry section

All the starting solvents and reagents were obtained from commercial suppliers, without further purification. PTP1B, TCPTP, SHP2 proteins were purchased from Viva Biotech (Shanghai) Ltd. 1H NMR spectra was recorded on an Agilent 400 MHz NMR. 13C NMR spectra was recorded on an Agilent 100 MHz NMR. Chemical shifts were expressed in parts per million (ppm). Coupling constants were in units of Hertz (Hz). Splitting patterns describe apparent multiplicities were designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). High-resolution mass spectra (HRMS) and compound purity data were acquired on an Agilent 6200 TOF LC/MS system, UV detector (220 and 254 nm). All the reactions were monitored by Thin-layer chromatography (silica gel, aluminum sheets 60 F254), which was conducted with Qingdao Huanghai (China). All the crude products were purified by column chromatography using silica gel (100-200 mesh or 300-400mesh), purchased from Qingdao Haiyang Chemical Co. Ltd. (China).

*4.1.1. Synthesis of geniposidic acid (**1**)*

Geniposide (3 g, 0.00773 mol) was dissolved in methanol (25 mL) and hydrolyzed with 2 M LiOH solution (8 mL, 0.01546 mol) at 50 °C overnight. Then 1 N hydrochloric acid solution (10 mL) was added by drops until the PH became a

weak acid. The reaction solution was concentrated under reduced pressure to afford a light brown solid (compound 1) in 90% yield. ^{1}H NMR (400 MHz, CD_3OD): δ 7.43 (s, 1H), 5.64 (br. s., 1H), 5.08 (d, *J*=6.65 Hz, 1H), 5.02 (d, *J*=5.09 Hz, 1H), 4.95 (d, *J*=5.09 Hz, 1H), 4.92 (d, *J*=5.48 Hz, 1H), 4.70 (t, *J*=5.48 Hz, 1H), 4.49 (d, *J*=7.83 Hz, 1H), 4.44 (t, *J*=5.87 Hz, 1H), 4.08 (br. s., 1H), 3.90-4.02 (m, 3H), 3.34-3.42 (m, 1H), 2.91-3.16 (m, 6H), 2.57-2.70 (m, 2H), 2.45-2.48 (m, 1H).

*4.1.2. Synthesis of 7-acetyl-1-(3,4,5,6-tetraacetate)geniposidic acid (**2**)*

To the solution of compound **1** (2.6 g, 0.00695 mol) in acetic anhydride (20 mL), sodium acetate (2 g, 0.024 mol) was slowly added and heated under reflux for 1 hour. After the initial reaction was completed, water (50 mL) was added, and the reaction solvent was extracted with ethyl acetate (40 mL×3). The combined organic was washed with saturated brine (30 mL×3), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to generate a crude product. The crude product was purified by silica gel column purification (petroleum ether: ethyl acetate=2:1) to give compound **2** as a light yellow solid (3.05 g, 0.00522 mol) with a yield of 68%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (s, 1H), 5.87 (br. s., 1H), 5.20-5.27 (m, 1H), 5.09-5.17 (m, 2H), 5.02 (t, *J*=8.80 Hz, 1H), 4.88 (d, *J*=8.22 Hz, 1H), 4.70 (d, *J*=8.22 Hz, 2H), 4.22-4.29 (m, 1H), 4.19 (d, *J*=2.35 Hz, 1H), 3.70-3.75 (m, 1H), 3.20-3.27 (m, 1H), 2.86-2.95 (m, 2H), 2.23-2.26 (m, 3H), 2.09 (d, *J*=3.13 Hz, 12H).

*4.1.3. General method for the synthesis of compound **3a-3g***

To the stirred solution of compound **2** (200 mg, 0.00034 mol) in DMF (3 mL), EDCI (78 mg, 0.00041 mol), HOBT (55 mg, 0.00041 mol) and DIPEA (0.2 mL, 0.00102 mol) was added, and stirred at room temperature for 2 hours. Then organic amine (0.00037 mol) and DMAP (63 mg, 0.00051 mol) was added, and continually stirred at room temperature overnight. After the reaction was completed, the solution was added to ice water (30 mL) and extracted with ethyl acetate (20 mL×3). The combined organic solvent was washed with 1 N aqueous citric acid (20 mL×3), 1 N aqueous dilute hydrochloric acid (20 mL×3) and saturated brine (20 mL×3). The

organic phase was dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by column chromatography on silica gel to afford compound **3a-3g** in a yield of 19-27%.

*4.1.3.1. 7-acetyl-1-(3,4,5,6-tetraacetate)-4-((phenylcarbamoyl)amide)geniposide **3a***

Yield 21%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (d, *J*=7.43 Hz, 2H), 7.32 (d, *J*=6.65 Hz, 2H), 7.18 (br. s., 1H), 7.10 (d, *J*=7.83 Hz, 1H), 5.82 (br. s., 1H), 5.18-5.29 (m, 2H), 5.10 (t, *J*=9.98 Hz, 1H), 5.00 (t, *J*=9.00 Hz, 1H), 4.87 (d, *J*=7.83 Hz, 1H), 4.62-4.76 (m, 2H), 4.26 (d, *J*=11.35 Hz, 1H), 4.15 (d, *J*=11.35 Hz, 1H), 3.72 (d, *J*=9.78 Hz, 1H), 3.31 (br. s., 1H), 3.02 (br. s., 1H), 2.82 (d, *J*=9.39 Hz, 1H), 2.26 (d, *J*=19.17 Hz, 1H), 2.15 (d, *J*=18.39 Hz, 2H), 1.94-2.03 (m, 14H).

4.1.3.2.

*7-acetyl-1-(3,4,5,6-tetraacetate)-4-(((2-fluorophenyl)carbamoyl)amide)geniposide **3b***

Yield 21%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (t, *J*=8.22 Hz, 1H), 7.40 (br. s., 1H), 7.34 (br. s., 1H), 7.00-7.15 (m, 3H), 5.82 (br. s., 1H), 5.18-5.29 (m, 2H), 5.10 (t, *J*=9.98 Hz, 1H), 5.00 (t, *J*=9.00 Hz, 1H), 4.87 (d, *J*=7.83 Hz, 1H), 4.62-4.76 (m, 2H), 4.26 (d, *J*=11.35 Hz, 1H), 4.15 (d, *J*=11.35 Hz, 1H), 3.72 (d, *J*=9.78 Hz, 1H), 3.31 (br. s., 1H), 3.02 (br. s., 1H), 2.82 (d, *J*=9.39 Hz, 1H), 2.26 (d, *J*=19.17 Hz, 1H), 2.15 (d, *J*=18.39 Hz, 2H), 1.94-2.03 (m, 14H).

4.1.3.3.

*7-acetyl-1-(3,4,5,6-tetraacetate)-4-(((2-ethylphenyl)carbamoyl)amide)geniposide **3c***

Yield 20%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, *J*=7.43 Hz, 1H), 7.32 (s, 1H), 7.20 (br. s., 2H), 7.06-7.14 (m, 2H), 5.82 (br. s., 1H), 5.18-5.29 (m, 2H), 5.10 (t, *J*=9.98 Hz, 1H), 5.00 (t, *J*=9.00 Hz, 1H), 4.87 (d, *J*=7.83 Hz, 1H), 4.62-4.76 (m, 2H), 4.26 (d, *J*=11.35 Hz, 1H), 4.15 (d, *J*=11.35 Hz, 1H), 3.72 (d, *J*=9.78 Hz, 1H), 3.31 (br. s., 1H), 3.02 (br. s., 1H), 2.82 (d, *J*=9.39 Hz, 1H), 2.60 (q, *J*=7.56 Hz, 2H), 2.26 (d, *J*=19.17 Hz, 1H), 2.15 (d, *J*=18.39 Hz, 2H), 1.94-2.03 (m, 14H), 1.29-1.38 (m, 3H).

4.1.3.4.

7-acetyl-1-(3,4,5,6-tetraacetate)-4-(((2-methoxyphenyl)carbamoyl)amide)geniposide ***3d***

Yield 27%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (d, *J*=7.43 Hz, 1H), 7.89 (br. s., 1H), 7.35 (br. s., 1H), 7.01 (d, *J*=7.04 Hz, 1H), 6.94 (t, *J*=7.24 Hz, 1H), 6.87 (d, *J*=7.43 Hz, 1H), 5.82 (br. s., 1H), 5.18-5.29 (m, 2H), 5.10 (t, *J*=9.98 Hz, 1H), 5.00 (t, *J*=9.00 Hz, 1H), 4.87 (d, *J*=7.83 Hz, 1H), 4.62-4.76 (m, 2H), 4.26 (d, *J*=11.35 Hz, 1H), 4.15 (d, *J*=11.35 Hz, 1H), 3.84-3.92 (s, 3H), 3.72 (d, *J*=9.78 Hz, 1H), 3.31 (br. s., 1H), 3.02 (br. s., 1H), 2.82 (d, *J*=9.39 Hz, 1H), 2.26 (d, *J*=19.17 Hz, 1H), 2.15 (d, *J*=18.39 Hz, 2H), 1.94-2.03 (m, 14H).

4.1.3.5.

7-acetyl-1-(3,4,5,6-tetraacetate)-4-(((4-phenoxyphenyl)carbamoyl)amide)geniposide ***3e***

Yield 19%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (d, *J*=8.22 Hz, 2H), 7.30 (t, *J*=8.02 Hz, 2H), 7.16 (br. s., 1H), 7.07 (t, *J*=7.43 Hz, 1H), 6.93-7.01 (m, 3H), 5.82 (br. s., 1H), 5.18-5.29 (m, 2H), 5.10 (t, *J*=9.98 Hz, 1H), 5.00 (t, *J*=9.00 Hz, 1H), 4.87 (d, *J*=7.83 Hz, 1H), 4.62-4.76 (m, 2H), 4.26 (d, *J*=11.35 Hz, 1H), 4.15 (d, *J*=11.35 Hz, 1H), 3.72 (d, *J*=9.78 Hz, 1H), 3.31 (br. s., 1H), 3.02 (br. s., 1H), 2.82 (d, *J*=9.39 Hz, 1H), 2.26 (d, *J*=19.17 Hz, 1H), 2.15 (d, *J*=18.39 Hz, 2H), 1.94-2.03 (m, 14H).

4.1.3.6.

7-acetyl-1-(3,4,5,6-tetraacetate)-4-(((4-([1,1'-biphenyl]-4-yloxy)phenyl)carbamoyl)amide)geniposide ***3f***

Yield 26%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50-7.57 (m, 4H), 7.48 (d, *J*=8.61 Hz, 2H), 7.37-7.44 (m, 2H), 7.32 (d, *J*=7.43 Hz, 1H), 7.19 (br. s., 1H), 7.02 (d, *J*=7.43 Hz, 4H), 5.82 (br. s., 1H), 5.18-5.29 (m, 2H), 5.10 (t, *J*=9.98 Hz, 1H), 5.00 (t, *J*=9.00 Hz, 1H), 4.87 (d, *J*=7.83 Hz, 1H), 4.62-4.76 (m, 2H), 4.26 (d, *J*=11.35 Hz, 1H), 4.15 (d, *J*=11.35 Hz, 1H), 3.72 (d, *J*=9.78 Hz, 1H), 3.31 (br. s., 1H), 3.02 (br. s., 1H), 2.82 (d,

J=9.39 Hz, 1H), 2.26 (d, *J*=19.17 Hz, 1H), 2.15 (d, *J*=18.39 Hz, 2H), 1.94-2.03 (m, 14H).

*4.1.3.7. 7-acetyl-1-(3,4,5,6-tetraacetate)-4-(((4-(4-(tert-butyl)phenoxy)phenyl)carbamoyl)amide)geniposide **3g***

Yield 24%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (d, *J*=8.61 Hz, 2H), 7.31 (d, *J*=8.22 Hz, 2H), 7.15 (br. s., 1H), 6.96 (d, *J*=8.22 Hz, 2H), 6.89 (d, *J*=7.43 Hz, 2H), 5.82 (br. s., 1H), 5.18-5.29 (m, 2H), 5.10 (t, *J*=9.98 Hz, 1H), 5.00 (t, *J*=9.00 Hz, 1H), 4.87 (d, *J*=7.83 Hz, 1H), 4.62-4.76 (m, 2H), 4.26 (d, *J*=11.35 Hz, 1H), 4.15 (d, *J*=11.35 Hz, 1H), 3.72 (d, *J*=9.78 Hz, 1H), 3.31 (br. s., 1H), 3.02 (br. s., 1H), 2.82 (d, *J*=9.39 Hz, 1H), 2.26 (d, *J*=19.17 Hz, 1H), 2.15 (d, *J*=18.39 Hz, 2H), 1.94-2.03 (m, 14H), 1.29 (s, 9H).

*4.1.4. General method for the synthesis of **4a-4g***

Compound **3**(**a**-**g**) (50 mg, 0.00007 mol) were dissolved in THF/H_2O (3 mL/1 mL). Then, 2 N aqueous lithium hydroxide solution (0.2 mL, 0.00042 mol) was added and the mixture was stirred at room temperature for 2 hours. Then 1 N hydrochloric acid solution (0.5 mL) was added dropwise until the PH to weak acid. The organic solvent was concentrated under reduced pressure and purified by column chromatography on silica gel to get compound **4a-4g** in a yield of 86-97%.

*4.1.4.1. 4-((phenylcarbamoyl)amide)geniposide **4a***

Brown solid, yield 86%.^{1}H NMR (400 MHz, CD_3OD): δ 7.54 (d, *J*=7.43 Hz, 2H), 7.32 (d, *J*=6.65 Hz, 2H), 7.18 (br. s., 1H), 7.10 (d, *J*=7.83 Hz, 1H), 5.82 (br. s., 1H), 5.18-5.29 (m, 2H), 5.10 (t, *J*=9.98 Hz, 1H), 5.00 (t, *J*=9.00 Hz, 1H), 4.87 (d, *J*=7.83 Hz, 1H), 4.62-4.76 (m, 2H), 4.26 (d, *J*=11.35 Hz, 1H), 4.15 (d, *J*=11.35 Hz, 1H), 3.72 (d, *J*=9.78 Hz, 1H), 3.31 (br. s., 1H), 3.02 (br. s., 1H), 2.82 (d, *J*=9.39 Hz, 1H), 2.26 (d, *J*=19.17 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD): δ 167.4, 147.3, 143.3, 138.3, 128.3, 126.7, 123.8, 120.9, 120.8, 115.6, 98.7, 96.3, 96.2, 76.9, 76.4, 74.9, 73.5, 70.1,

67.8, 61.2, 60.0, 46.0, 37.7, 34.8. HRMS (ESI): Calcd. for $C_{22}H_{27}NO_9$ $[M+H]^+$ 450.1759, found 450.1771.

4.1.4.2. 4-(((2-fluorophenyl)carbamoyl)amide)geniposide ***4b***

Light green solid, yield 91%.^{1}H NMR (400 MHz, CD_3OD): δ 8.28 (t, *J*=8.22 Hz, 1H), 7.40 (br. s., 1H), 7.34 (br. s., 1H), 7.00-7.15 (m, 3H), 5.82 (br. s., 1H), 5.18-5.29 (m, 2H), 5.10 (t, *J*=9.98 Hz, 1H), 5.00 (t, *J*=9.00 Hz, 1H), 4.87 (d, *J*=7.83 Hz, 1H), 4.62-4.76 (m, 2H), 4.26 (d, *J*=11.35 Hz, 1H), 4.15 (d, *J*=11.35 Hz, 1H), 3.72 (d, *J*=9.78 Hz, 1H), 3.31 (br. s., 1H), 3.02 (br. s., 1H), 2.82 (d, *J*=9.39 Hz, 1H), 2.26 (d, *J*=19.17 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD): δ 167.4, 147.3, 143.3, 138.3, 128.3, 126.7, 123.8, 120.9, 115.6, 98.7, 96.3, 76.9, 76.4, 74.9, 73.5, 70.1, 67.8, 61.2, 60.0, 46.0, 37.7, 34.8. HRMS (ESI): Calcd. for $C_{22}H_{26}FNO_9$ $[M+H]^+$ 468.1664, found 468.9272.

4.1.4.3. 4-(((2-ethylphenyl)carbamoyl)amide)geniposide ***4c***

White solid, yield 91%.^{1}H NMR (400 MHz, CD_3OD): δ 7,84 (d, *J*=7.43 Hz, 1H), 7.32 (s, 1H), 7.20 (br. s., 2H), 7.06-7.14 (m, 2H), 5.82 (br. s., 1H), 5.18-5.29 (m, 2H), 5.10 (t, *J*=9.98 Hz, 1H), 5.00 (t, *J*=9.00 Hz, 1H), 4.87 (d, *J*=7.83 Hz, 1H), 4.62-4.76 (m, 2H), 4.26 (d, *J*=11.35 Hz, 1H), 4.15 (d, *J*=11.35 Hz, 1H), 3.72 (d, *J*=9.78 Hz, 1H), 3.31 (br. s., 1H), 3.02 (br. s., 1H), 2.82 (d, *J*=9.39 Hz, 1H), 2.60 (q, *J*=7.56 Hz, 2H), 2.26 (d, *J*=19.17 Hz, 1H), 1.29-1.38 (m, 3H). ^{13}C NMR (100 MHz, CD_3OD): δ 168.1, 147.6, 143.4, 140.3, 134.9, 128.5, 127.3, 126.7, 126.6, 125.9, 114.9, 98.7, 96.4, 76.9, 76.4, 73.5, 70.1, 61.2, 60.0, 45.9, 37.9, 34.9, 24.2, 13.5. HRMS (ESI): Calcd. for $C_{24}H_{31}NO_9$ $[M+H]^+$ 478.2072, found 478.2074.

4.1.4.4. 4-(((2-methoxyphenyl)carbamoyl)amide)geniposide ***4d***

Black solid, yield 87%.^{1}H NMR (400 MHz, CD_3OD): δ 8.34 (d, *J*=7.43 Hz, 1H), 7.89 (br. s., 1H), 7.35 (br. s., 1H), 7.01 (d, *J*=7.04 Hz, 1H), 6.94 (t, *J*=7.24 Hz, 1H), 6.87 (d, *J*=7.43 Hz, 1H), 5.82 (br. s., 1H), 5.18-5.29 (m, 2H), 5.10 (t, *J*=9.98 Hz, 1H), 5.00 (t, *J*=9.00 Hz, 1H), 4.87 (d, *J*=7.83 Hz, 1H), 4.62-4.76 (m, 2H), 4.26 (d, *J*=11.35

Hz, 1H), 4.15 (d, *J*=11.35 Hz, 1H), 3.84-3.92 (s, 3H), 3.72 (d, *J*=9.78 Hz, 1H), 3.31 (br. s., 1H), 3.02 (br. s., 1H), 2.82 (d, *J*=9.39 Hz, 1H), 2.26 (d, *J*=19.17 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD): δ 168.1, 147.6, 143.4, 140.3, 134.9, 128.5, 127.3, 126.7, 126.6, 125.9, 114.9, 98.7, 96.4, 76.9, 76.4, 73.5, 70.1, 61.2, 60.0, 55.8, 45.9, 37.9, 34.9. HRMS (ESI): Calcd. for $C_{23}H_{29}NO_9$ $[M+H]^+$ 480.1864, found 480.1859.

4.1.4.5. 4-(((4-phenoxyphenyl)carbamoyl)amide)geniposide ***4e***

Green solid, yield 97%.^{1}H NMR (400 MHz, CD_3OD): δ 7.45 (d, *J*=8.22 Hz, 2H), 7.30 (t, *J*=8.02 Hz, 2H), 7.16 (br. s., 1H), 7.07 (t, *J*=7.43 Hz, 1H), 6.93-7.01 (m, 3H), 5.82 (br. s., 1H), 5.18-5.29 (m, 2H), 5.10 (t, *J*=9.98 Hz, 1H), 5.00 (t, *J*=9.00 Hz, 1H), 4.87 (d, *J*=7.83 Hz, 1H), 4.62-4.76 (m, 2H), 4.26 (d, *J*=11.35 Hz, 1H), 4.15 (d, *J*=11.35 Hz, 1H), 3.72 (d, *J*=9.78 Hz, 1H), 3.31 (br. s., 1H), 3.02 (br. s., 1H), 2.82 (d, *J*=9.39 Hz, 1H), 2.26 (d, *J*=19.17 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD): δ 167.3, 157.6, 153.4, 147.4, 143.3, 133.9, 129.5, 126.7, 122.8, 122.7, 122.6, 118.8, 118.7, 118.0, 115.4, 98.7, 96.3, 76.9, 76.4, 73.5, 70.1, 61.2, 60.0, 45.9, 37.8, 34.8, 29.4. HRMS (ESI): Calcd. for $C_{28}H_{31}NO_{10}$ $[M+H]^+$ 542.2021, found 542.2002.

4.1.4.6. 4-(((4-([1,1'-biphenyl]-4-yloxy)phenyl)carbamoyl)amide)geniposide ***4f***

Brown solid, yield 91%.^{1}H NMR (400 MHz, CD_3OD): δ 7.50-7.57 (m, 4H), 7.48 (d, *J*=8.61 Hz, 2H), 7.37-7.44 (m, 2H), 7.32 (d, *J*=7.43 Hz, 1H), 7.19 (br. s., 1H), 7.02 (d, *J*=7.43 Hz, 4H), 5.82 (br. s., 1H), 5.18-5.29 (m, 2H), 5.10 (t, *J*=9.98 Hz, 1H), 5.00 (t, *J*=9.00 Hz, 1H), 4.87 (d, *J*=7.83 Hz, 1H), 4.62-4.76 (m, 2H), 4.26 (d, *J*=11.35 Hz, 1H), 4.15 (d, *J*=11.35 Hz, 1H), 3.72 (d, *J*=9.78 Hz, 1H), 3.31 (br. s., 1H), 3.02 (br. s., 1H), 2.82 (d, *J*=9.39 Hz, 1H), 2.26 (d, *J*=19.17 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD): δ 167.3, 157.1, 153.3, 147.5, 143.2, 140.2, 136.0, 134.0, 128.5, 128.0, 126.8, 126.7, 126.3, 122.8, 122.7, 118.9, 118.3, 115.4, 98.7, 96.4, 76.8, 76.3, 73.4, 70.1, 61.1, 60.0, 45.9, 37.8, 34.8, 22.5. HRMS (ESI): Calcd. for $C_{34}H_{35}NO_{10}$ $[M+H]^+$ 618.2334, found 618.2299.

4.1.4.7. 4-(((4-(4-(tert-butyl)phenoxy)phenyl)carbamoyl)amide)geniposide ***4g***

Green solid, yield 97%.^{1}H NMR (400 MHz, CD_3OD): δ 7.43 (d, *J*=8.61 Hz, 2H), 7.31 (d, *J*=8.22 Hz, 2H), 7.15 (br. s., 1H), 6.96 (d, *J*=8.22 Hz, 2H), 6.89 (d, *J*=7.43 Hz, 2H), 5.82 (br. s., 1H), 5.18-5.29 (m, 2H), 5.10 (t, *J*=9.98 Hz, 1H), 5.00 (t, *J*=9.00 Hz, 1H), 4.87 (d, *J*=7.83 Hz, 1H), 4.62-4.76 (m, 2H), 4.26 (d, *J*=11.35 Hz, 1H), 4.15 (d, *J*=11.35 Hz, 1H), 3.72 (d, *J*=9.78 Hz, 1H), 3.31 (br. s., 1H), 3.02 (br. s., 1H), 2.82 (d, *J*=9.39 Hz, 1H), 2.26 (d, *J*=19.17 Hz, 1H), 1.29 (s, 9H). ^{13}C NMR (100 MHz, CD_3OD): δ 167.3, 155.0, 153.8, 147.6, 145.8, 143.1, 133.5, 126.9, 126.3, 122.8, 122.7, 118.4, 117.8, 115.4, 115.3, 98.7, 96.4, 76.7, 76.2, 73.4, 70.1, 67.8, 66.9, 61.1, 60.0, 45.9, 37.8, 34.8, 33.7, 30.7, 22.4. HRMS (ESI): Calcd. for $C_{32}H_{39}NO_{10}$ $[M+H]^+$ 598.2647, found 598.2619.

*4.1.5. Synthesis of 7-benzyl-1-(3,4,5,6-tetrabenzyl)geniposide (**compound 5**)*

To a stirred solution of geniposide (3 g, 0.00773 mol) in DMF (150 mL), in an ice-water bath, 60% sodium hydride (1.854 g, 0.04638 mol) was slowly added. After the mixture was stirred for 1 hour, benzyl bromide (5.5 mL, 0.04638 mol) was slowly added dropwise and stirred at room temperature overnight. After the reaction was over, the reaction solution was added to ice water (900 mL) and extracted with ethyl acetate (200 mL×3), then the combined organic solvent was washed with 1 N hydrochloric acid solution (50 mL×2) and saturated brine (100 mL×3), dried over anhydrous sodium sulfate and concentrated under reduced pressure to get crude product. The crude product was purified by silica gel column (petroleum ether: ethyl acetate=7:1) to give compound 5 as a colorless liquid (2.667 g, 0.00318 mol) with a yield of 42%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (s, 1H), 7.21-7.32 (m, 23H), 7.15-7.20 (m, 2H), 5.83 (br. s., 1H), 5.30 (d, *J*=5.8 Hz, 1H), 4.86-4.93 (m, 2H), 4.75-4.84 (m, 3H), 4.44-4.64 (m, 7H), 4.19 (br. s., 2H), 4.11 (q, *J*=7.0 Hz, 1H), 3.65 (s, 3H), 3.40-3.48 (m, 2H), 3.28 (q, *J*=7.4 Hz, 1H), 2.95 (t, *J*=6.8 Hz, 1H), 2.87 (dd, *J*=7.8, 16.4 Hz, 1H), 2.14-2.27 (m, 2H).

*4.1.6. Synthesis of 7-benzyl-1-(3,4,5,6-tetrabenzyl)geniposidic acid (**compound 6**)*

To a stirred solution of compound 5 (2.667 g, 0.00318 mol) in methanol (20 mL), 1 N aqueous sodium hydroxide (6.36 mL, 0.00636 mol) was added and refluxed overnight. After the reaction was over, the reaction solution was concentrated under reduced pressure, and 1 N hydrochloric acid solution was added dropwise until the PH to 1-2. A white solid precipitated, filtered and dried at vacuum to give compound **6** (2.36 g, 0.017 mol) as a pale yellow solid, yield of 90%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (s, 1H), 7.21-7.32 (m, 23H), 7.15-7.20 (m, 2H), 5.83 (br. s., 1H), 5.30 (d, *J*=5.8 Hz, 1H), 4.86-4.93 (m, 2H), 4.75-4.84 (m, 3H), 4.44-4.64 (m, 7H), 4.19 (br. s., 2H), 4.11 (q, *J*=7.0 Hz, 1H), 3.40-3.48 (m, 2H), 3.28 (q, *J*=7.4 Hz, 1H), 2.95 (t, *J*=6.8 Hz, 1H), 2.87 (dd, *J*=7.8, 16.4 Hz, 1H), 2.14-2.27 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ174.9, 148.8, 140.3, 138.6, 138.4, 138.2, 138.1, 129.9, 128.5,128.3, 127.9, 127.8, 127.7, 127.5, 127.4, 116.3, 99.3, 96.8, 84.3, 81.4, 77.4, 77.2, 75.5, 74.9, 74.5, 73.2, 72.4, 68.5, 46.3, 39.1, 36.1. HRMS (ESI): Calcd. for $C_{51}H_{52}O_{10}$ $[M+Na]^+$ 847.3453, found 847.3455.

*4.1.7. General method for the synthesis of **7a-7b***

Compound **6** (200 mg, 0.00024 mol) was dissolved in DMF (4 mL), then EDCI (56 mg, 0.00029 mol), HOBT (39 mg, 0.00029 mol) and DIPEA (0.13 mL, 0.00072 mol) were added and stirred at room temperature for 2 hours. Then organic amine (0.00026 mol) and DMAP (45 mg, 0.00036 mol) were added and stirred at room temperature overnight. After the reaction was completed, the solution was added to ice water (30 mL) and extracted with ethyl acetate (20 mL×3). The combined organic solvent were washed with 1 N aqueous citric acid (20 mL×3), 1 N aqueous dilute hydrochloric acid (20 mL×3) and saturated brine (20 mL×3), dried over anhydrous sodium sulfate, concentrated under reduced pressure and purified by column chromatography on silica gel to afford compound **7a-7b** in a yield of 32-52%.

*4.1.7.1. 7-benzyl-1-(3,4,5,6-tetrabenzyl)-4-(4-ethylvinylsulfonate benzyl)carbamoyl)amide)geniposide **7a***

Light yellow solid, yield 32%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, *J*=8.6 Hz, 1H), 8.01 (s, 1H), 7.19-7.43 (m, 29H), 5.93 (br. s., 1H), 5.46 (d, *J*=6.2 Hz, 1H), 4.80-5.00 (m, 5H), 4.72 (d, *J*=10.9 Hz, 1H), 4.48-4.62 (m, 5H), 4.25 (br. s., 2H), 3.63-3.78 (m, 4H), 3.41-3.56 (m, 4H), 3.09 (t, *J*=6.8 Hz, 1H), 2.99 (dd, *J*=8.2, 16.4 Hz, 1H), 2.39 (dd, *J*=5.4, 17.2 Hz, 1H), 0.83-0.93 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.1, 156.6, 143.5, 139.6, 138.5, 138.2, 138.1, 138.0, 137.9, 129.9, 128.9, 128.6, 128.5, 128.5, 128.4, 128.3, 128.0, 127.9, 127.9, 127.9, 127.8, 127.7, 127.7, 127.6, 124.7, 120.4, 108.4, 107.0, 99.7, 97.0, 84.5, 81.7, 77.5, 75.8, 75.3, 75.1, 75.0, 73.5, 72.4, 68.6, 67.9, 46.4, 38.4, 34.1. HRMS (ESI): Calcd. for $C_{62}H_{65}NO_{12}S$ $[M+K]^+$ 1086.38, found 1086.44.

4.1.7.2.

7-benzyl-1-(3,4,5,6-tetrabenzyl)-4-(((4-phenoxyphenyl)carbamoyl)amide)geniposide ***7b***

White solid, yield 52%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (d, *J*=8.6 Hz, 2H), 7.25-7.33 (m, 19H), 7.24 (s, 6H), 7.20 (d, *J*=4.7 Hz, 3H), 7.16 (d, *J*=7.4 Hz, 2H), 7.04-7.10 (m, 2H), 6.96 (d, *J*=8.6 Hz, 4H), 5.84 (br. s., 1H), 5.30 (d, *J*=6.2 Hz, 1H), 4.91 (d, *J*=10.9 Hz, 2H), 4.75-4.85 (m, 3H), 4.63 (d, *J*=10.5 Hz, 1H), 4.44-4.56 (m, 5H), 4.20 (s, 2H), 3.56-3.73 (m, 5H), 3.37-3.49 (m, 3H), 2.99-3.05 (m, 1H), 2.83 (d, *J*=8.6 Hz, 1H), 2.17-2.30 (m, 2H), 1.98 (br. s., 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.2, 157.6, 153.3, 147.2, 140.0, 138.5, 138.2, 138.1, 138.0, 138.0, 133.4, 129.7, 129.2, 128.4, 128.4, 128.3, 128.2, 128.0, 127.8, 127.7, 127.7, 127.6, 127.6, 123.0, 121.8, 119.7, 118.3, 115.6, 99.3, 95.8, 84.5, 81.8, 77.6, 75.8, 75.2, 75.1, 74.9, 73.4, 72.4, 68.7, 67.9, 46.9, 38.3, 34.2. HRMS (ESI): Calcd. for $C_{63}H_{61}NO_{10}$ $[M+Na]^+$ 1014.4188, found 1014.4153.

4.1.8. General method for the synthesis of ***9a-9c***

Genipin (10 g, 0.044 mol) was dissolved in corresponding alcohols (**8a**-**8c**) (70 mL). The solution was catalyzed by two drops of concentrated hydrochloric acid, and then heated at reflux for 7 hours. After this reaction was completed, the solution was

concentrated under reduced pressure. A few drops of 1 N sodium hydroxide solution were added to adjust the pH to neutral, and then it was extracted three times with ethyl acetate. The combined organic phase was washed three times with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to get compound **9a-9c** in a yield of 56-98%.

*4.1.8.1. 1-methoxygenipin **9a***

Brown oily liquid, yield 98%.^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.54 (m, 1H), 5.75-5.88 (m, 1H), 4.46 (d, *J*=8.2 Hz, 1H), 4.12-4.28 (m, 2H), 3.64-3.75 (m, 3H), 3.40-3.54 (m, 3H), 3.13-3.23 (m, 1H), 2.86 (dd, *J*=8.5, 16.5 Hz, 1H), 2.59 (t, *J*=7.6 Hz, 1H), 2.06 (dd, *J*=9.0, 16.4 Hz, 1H).

*4.1.8.2. 1-benzyloxygenipin **9b***

Yellow oil, yield 56%.^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (s, 1H), 7.28-7.42 (m, 5H), 5.82 (br. s., 1H), 5.00 (d, *J*=11.3 Hz, 1H), 4.60-4.72 (m, 2H), 4.23 (br. s., 2H), 3.68-3.77 (m, 3H), 3.13-3.27 (m, 1H), 2.74-2.94 (m, 1H), 2.69 (t, *J*=8.0 Hz, 1H), 2.08 (dd, *J*=9.0, 16.4 Hz, 1H).

*4.1.8.3. 1-ethoxygenipin **9c***

Brown oil, yield 97%.^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (s, 1H), 5.82 (br. s., 1H), 4.53 (d, *J*=8.4 Hz, 1H), 4.25 (br. s., 2H), 4.03 (qd, *J*=7.1, 9.5 Hz, 2H), 3.69-3.74 (m, 3H), 3.14-3.24 (m, 1H), 2.87 (tdd, *J*=1.3, 8.5, 16.5 Hz, 1H), 2.58 (t, *J*=8.0 Hz, 1H), 2.01-2.12 (m, 1H), 1.17-1.29 (t, 3H).

*4.1.9. General method for the synthesis of **10a-10b***

Compound **9a-9b** (0.044 mol), triethylamine (8.905 g, 0.088 mol) was dissolved in dichloromethane (70 mL), and slowly added to benzenesulfonyl chloride (11.656 g, 0.066 mol) in ice water. After catalyzed by the addition of DMAP (200 mg), the reaction was carried out at room temperature for 40 hours. When the reaction was completed, the reaction solution was washed with 1 N sodium hydroxide solution (10

mL×3) and extracted with dichloromethane (30 mL×3). The combined organic solvent was washed with 1 N hydrochloric acid solution and saturated brine (30 mL×3), dried over anhydrous sodium sulfate, concentrated under reduced pressure and purified by silica gel column chromatography to generate compound **10a-10b** in a yield of 48-49%.

*4.1.9.1. 1-methoxy-2-(chloromethyl)genipin **10a***

Colorless liquid, yield 49%.^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (s, 1H), 5.95-6.01 (m, 1H), 4.51 (d, *J*=7.8 Hz, 1H), 4.20-4.25 (m, 2H), 3.73 (s, 3H), 3.57 (s, 3H), 3.24 (q, *J*=8.4 Hz, 1H), 2.91 (dd, *J*=8.4, 15.8 Hz, 1H), 2.73-2.81 (m, 1H), 2.01-2.18 (m, 1H).

*4.1.9.2. 1-benzyloxy-2-(chloromethyl)genipin **10b***

Light yellow liquid, yield 48%.^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (s, 1H), 7.28-7.42 (m, 5H), 5.82 (br. s., 1H), 5.00 (d, *J*=11.3Hz, 1H), 4.60-4.72 (m, 2H), 4.23 (br. s., 2H), 3.68-3.77 (m, 3H), 3.13-3.27 (m, 1H), 2.74-2.94 (m, 1H), 2.69 (t, *J*=8.0 Hz, 1H), 2.08 (dd, *J*=9.0, 16.4 Hz, 1H).

*4.1.10. General method for the synthesis of **12a-12b***

Compound **10a-10b** (0.022 mol), p-hydroxybenzaldehyde (3.175 g, 0.026 mol) and anhydrous potassium carbonate (4.561 g, 0.033 mol) was dissolved in acetonitrile (50 mL) and the mixture was heated under reflux for 12 hours. After the reaction was completed, it was concentrated under reduced pressure. The residue was washed with 1 N sodium hydroxide solution (10 mL), and extracted with dichloromethane (30 mL×3). The combined organic solvent was washed with 1 N hydrochloric acid solution, saturated brine and dried over anhydrous sodium sulfate, concentrated under reduced pressure to afford compound **12a-12b** in a yield of 89-91%.

*4.1.10.1. 1-methoxy-2-((4-formylphenoxy)methyl)genipin **12a***

Brown liquid, yield 89%.^{1}H NMR (400 MHz, $CDCl_3$): δ 9.90 (s, 1H), 7.83-7.86 (m, 2H), 7.50-7.55 (m, 1H), 7.01-7.05 (m, *J*=8.6 Hz, 2H), 5.96-6.03 (m, 1H), 4.69-4.84 (m, 2H), 4.53 (d, *J*=7.8 Hz, 1H), 3.74 (s, 3H), 3.56-3.60 (m, 3H), 3.20-3.29 (m, 1H), 2.87-2.99 (m, 1H), 2.70 (t, *J*=7.6 Hz, 1H), 2.13 (dd, *J*=8.7, 16.9 Hz, 1H).

4.1.10.2. 1-benzyloxy-2-((4-formylphenoxy)methyl)genipin ***12b***

White solid, yield 91%.^{1}H NMR (400 MHz, $CDCl_3$): δ 9.79-9.87 (m, 1H), 7.69-7.79 (m, 3H), 7.53 (s, 1H), 7.15-7.25 (m, 4H), 6.89 (d, *J*=8.6 Hz, 2H), 5.92 (br. s. 1H), 4.97 (d, *J*=11.3 Hz, 1H), 4.57-4.75 (m, 4H), 3.69-3.73 (m, 3H), 3.10-3.28 (m, 1H), 2.90 (dd, *J*=8.4, 16.0 Hz, 1H), 2.74 (t, *J*=8.0 Hz, 1H), 2.08 (dd, *J*=8.6, 16.8 Hz, 1H).

4.1.11. General method for the synthesis of ***13a-13b***

To a stirred solution of compound **12a-12b** (0.019 mol) in methanol (50 mL), 2 N aqueous lithium hydroxide solution (47.5 mL, 0.095 mol) was added at room temperature and maintained for 30 hours. After the reaction was completed, the reaction solution was concentrated under reduced pressure, and adjusted PH value to 1-2 with 1 N hydrochloric acid solution, and dried to get compound 13a-13b in a yield of 73-90%.

4.1.11.1. 1-methoxy-2-((4-formylphenoxy)methyl)genipher-5-carboxylic acid ***13a***

Yellow solid, yield 90%.^{1}H NMR (400 MHz, $CDCl_3$): δ 9.90 (s, 1H), 7.83-7.86 (m, 2H), 7.50-7.55 (m, 1H), 7.01-7.05 (m, *J*=8.6 Hz, 2H), 5.96-6.03 (m, 1H), 4.69-4.84 (m, 2H), 4.53 (d, *J*=7.8 Hz, 1H), 3.74 (s, 3H), 3.20-3.29 (m, 1H), 2.87-2.99 (m, 1H), 2.70 (t, *J*=7.6 Hz, 1H), 2.13 (dd, *J*=8.7, 16.9 Hz, 1H).

4.1.11.2. 1-benzyloxy-2-((4-formylphenoxy)methyl)genipher-5-carboxylic acid ***13b***

White solid, yield 73%.^{1}H NMR (400 MHz, $CDCl_3$): δ 9.79-9.87 (m, 1H), 7.69-7.79 (m, 3H), 7.53 (s, 1H), 7.15-7.25 (m, 4H), 6.89 (d, *J*=8.6 Hz, 2H), 5.92 (br. s.

1H), 4.97 (d, *J*=11.3 Hz, 1H), 4.57-4.75 (m, 4H), 3.10-3.28 (m, 1H), 2.90 (dd, *J*=8.4, 16.0 Hz, 1H), 2.74 (t, *J*=8.0 Hz, 1H), 2.08 (dd, *J*=8.6, 16.8 Hz, 1H).

*4.1.12. General method for the synthesis of **15a-15b***

Compound **13a-13b** (0.017 mol) and ethyl (diethoxyphosphoryl)methanesulfonate (6.194 g, 0.024 mol) was dissolved in tetrahydrofuran (30 mL). 60% sodium hydrogen (2.040 g, 0.051 mol) was added slowly in portions and stirred at room temperature for 12 hours. After the completion of this reaction, the mixture was concentrated under reduced pressure, adjusted pH to neutral with a 1 N hydrochloric acid solution and extracted with ethyl acetate (30 mL×3). The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified with silica gel column to afford compound **15a-15b** in a yield of 42-46%.

*4.1.12.1. 1-methoxy-2-((4-ethylvinylsulfonate phenoxy)methyl)genipin-5-carboxylic acid **15a***

White solid, yield 42%.^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (s, 1H), 7.55 (d, *J*=15.6 Hz, 1H), 7.43-7.49 (m, *J*=8.6 Hz, 2H), 6.94-6.99 (m, *J*=8.6 Hz, 2H), 6.60 (d, *J*=15.6 Hz, 1H), 5.98 (br. s., 1H), 4.65-4.79 (m, 2H), 4.57 (d, *J*=7.8 Hz, 1H), 4.08-4.26 (m, 2H), 3.59 (s, 3H), 3.19-3.28 (m, 1H), 2.94 (dd, *J*=8.8, 16.6 Hz, 1H), 2.71 (t, *J*=8.0 Hz, 1H), 2.16 (dd, *J*=8.4, 16.6 Hz, 1H), 1.32-1.44 (t, 3H).

*4.1.12.2. 1-benzyloxy-2-((4-ethylvinylsulfonate phenoxy)methyl)genipin-5-carboxylic acid **15b***

White solid, yield 46%.^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69-7.79 (m, 3H), 7.55 (d, *J*=15.6 Hz, 1H), 7.25 (s, 1H), 7.15-7.25 (m, 4H), 6.89 (d, *J*=8.6 Hz, 2H), 6.60 (d, *J*=15.6 Hz, 1H), 5.92 (br. s., 1H), 4.97 (d, *J*=11.3 Hz, 1H), 4.57-4.75 (m, 4H), 4.08-4.26 (m, 2H), 3.10-3.28 (m, 1H), 2.90 (dd, *J*=8.4, 16.0 Hz, 1H), 2.74 (t, *J*=8.0 Hz, 1H), 2.08 (dd, *J*=8.6, 16.8 Hz, 1H), 1.32-1.44 (t, 3H).

*4.1.12. General method for the synthesis of **17a-d***

Compound **15a** (0.00014 mol) and organic amine (0.00015 mol) was dissolved in DMF (3 mL), stirred in ice water bath. Then HATU (64 mg, 0.00017 mol) and triethylamine (28 mg, 0.00028 mol) were added and stirred at room temperature for 2.5 hours. After this reaction was completed, the solution was added to ice water (30 mL) and 1 N hydrochloric acid dropwise solution to PH =1-2. Yellow solids were precipitated, filtered, and then purified by silica gel column chromatography to develop compound **17a-17d** in a yield of 27-36%.

*4.1.12.1. 1-methoxy-2-((4- ethylvinylsulfonate phenoxy)methyl)-5-((4-(p-phenyleneoxy)phenyl)amide))genipin **17a***

Brown solid, yield 30%.^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, *J*=15.4 Hz, 1H), 7.41-7.52 (m, 5H), 7.28-7.36 (m, 3H), 7.06-7.12 (m, 1H), 6.94-7.03 (m, 5H), 6.60 (d, *J*=15.4 Hz, 1H), 5.96-6.04 (m, 1H), 4.61-4.81 (m, 2H), 4.57 (d, *J*=7.8 Hz, 1H), 4.08-4.27 (m, 2H), 3.52-3.64 (m, 3H), 3.34-3.45 (m, 1H), 2.86-2.97 (m, 1H), 2.78 (t, *J*=7.9 Hz, 1H), 2.18-2.29 (m, 1H), 1.35-1.44 (t, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.2, 161.2, 157.5, 153.4, 147.9, 144.3, 138.6, 133.3, 130.2, 130.0, 129.6, 124.7, 123.0, 121.9, 119.6, 118.3, 115.2, 115.2, 114.6, 102.2, 66.5, 66.4, 57.0, 46.4, 38.7, 35.6, 14.1. HRMS (ESI): Calcd. for $C_{33}H_{33}NO_8S$ $[M+Na]^+$ 626.1819, found 626.1815.

4.1.12.2. 1-methoxy-2-((4- ethylvinylsulfonate *phenoxy)methyl)-5-((4-p-diphenylether)phenyl)amide))genipin **17b***

Brown liquid, yield 27%.^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55-7.59 (m, 4H), 7.51-7.55 (m, 2H), 7.49 (d, *J*=7.4 Hz, 2H), 7.41-7.47 (m, 4H), 7.31-7.36 (m, 1H), 7.02-7.09 (m, 4H), 6.97 (d, *J*=8.8 Hz, 2H), 6.60 (d, *J*=15.6 Hz, 1H), 5.96-6.04 (m, 1H), 4.66-4.81 (m, 2H), 4.57 (d, *J*=7.8 Hz, 1H), 4.09-4.27 (m, 2H), 3.60 (s, 3H), 3.35-3.44 (m, 1H), 2.88-2.98 (m, 2H), 2.79 (t, *J*=7.8 Hz, 1H), 2.20-2.31 (m, 1H), 1.38-1.45 (t, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.2, 161.2, 157.1, 153.3, 150.5, 147.9, 144.3, 140.4, 138.6, 136.1, 133.4, 133.1, 130.3, 130.0, 128.8, 128.4, 127.0, 126.9, 124.7, 121.9, 119.8, 118.5, 118.3, 115.3, 114.6, 102.2, 66.6, 66.4, 57.0, 46.4,

38.8, 35.6, 14.9. HRMS (ESI): Calcd. for $C_{39}H_{37}NO_8S$ $[M+Na]^+$ 702.2132, found 702.2127.

4.1.12.3. 1-methoxy-2-((4- ethylvinylsulfonate *phenoxy)methyl)-5-((4-(2-chloro-4-fluoro-phenylene ether)benzeneamide)genipin* ***17c***

Brown liquid, yield 36%.^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.58 (m, 7H), 7.17-7.23 (m, 1H), 7.07 (dt, *J*=1.3, 7.7 Hz, 1H), 6.91-6.98 (m, 4H), 6.59 (d, *J*=15.4 Hz, 1H), 5.94-6.03 (m, 1H), 4.65-4.80 (m, 2H), 4.55 (d, *J*=7.8 Hz, 1H), 4.09-4.25 (m, 2H), 3.58 (s, 3H), 3.36-3.42 (m, 1H), 2.90 (dd, *J*=8.6, 16.2 Hz, 1H), 2.76 (t, *J*=7.9 Hz, 1H), 2.22 (dd, *J*=8.3, 16.3 Hz, 1H), 1.36-1.43 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.2, 161.2, 153.1, 152.7, 147.9, 144.4, 138.6, 133.5, 130.7, 130.3, 130.1, 127.9, 125.4, 124.7, 124.5, 121.9, 120.2, 118.7, 118.3, 115.3, 114.6, 102.2, 66.6, 66.4, 57.0, 46.4, 38.7, 35.6, 14.8. HRMS (ESI): Calcd. for $C_{33}H_{31}BrClNO_8S$ $[M+Na]^+$ 738, found 739.

4.1.12.4. 1-methoxy-2-((4- ethylvinylsulfonate *phenoxy)methyl)-5-((4-(biphenylether)phenyl)amide)genipin* ***17d***

Brown solid, yield 32%.^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76-7.82 (m, 2H), 7.65 (d, *J*=7.8 Hz, 1H), 7.47-7.53 (m, 3H), 7.40-7.46 (m, 3H), 7.30-7.40 (m, 2H), 7.19-7.25(m, 2H), 7.00-7.05 (m, 2H), 6.93 (d, *J*=8.6 Hz, 2H), 6.57 (d, *J*=15.2 Hz, 1H), 5.94-6.02 (m, 1H), 4.62-4.77 (m, 2H), 4.54 (d, *J*=7.8 Hz, 1H), 4.06-4.22 (m, 2H), 3.56 (s, 3H), 3.37 (q, *J*=8.2 Hz, 1H), 2.90 (dd, *J*=8.4, 16.2 Hz, 1H), 2.72-2.80 (m, 1H), 2.17-2.27 (m, 1H), 1.37 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.2, 161.2, 155.4, 153.3, 148.0, 144.3, 138.6, 134.2, 133.6, 130.3, 130.0, 129.9, 127.7, 127.0, 126.5, 124.7, 124.6, 122.0, 120.0, 119.6, 118.3, 115.3, 114.6, 113.3, 102.3, 66.6, 66.4, 57.0, 46.4, 38.8, 35.6, 14.9. HRMS (ESI): Calcd. for $C_{37}H_{35}NO_8S$ $[M+Na]^+$ 676.1976, found 676.1972.

4.1.13. General method for the synthesis of ***17e-17f***

Compound **15b** (0.00014 mol) and organic amine (0.00015 mol) in DMF (3 mL), was stirred in an ice water bath, and then HATU (64 mg, 0.00017 mol) as well as triethylamine (28 mg, 0.00028 mol) was added. The mixture was stirred at room temperature for 2.5 hours. After the reaction was completed, the solution was added to ice water (30 mL). Then, 1 N hydrochloric acid solution was added by drop until the PH reached 1-2, a large number of yellow solids precipitated. The yellow solid was purified by silica gel column chromatography to generate compound **17e-f** in a yield of 23-26%.

4.1.13.1. 1-benzyloxy-2-((4- ethylvinylsulfonate *phenoxy)methyl)-5-((4-(p-phenyleneoxy)phenyl))benzeneamide)genipin **17e***

Brown liquid, yield 23%.^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69-7.79 (m, 5H), 7.55 (d, *J*=15.4 Hz, 4H), 7.25 (s, 1H), 7.15-7.25 (m, 6H), 6.89 (d, *J*=8.6 Hz, 4H), 6.60 (d, *J*=15.6 Hz, 1H), 5.92 (br. s., 1H), 4.97 (d, *J*=11.3 Hz, 1H), 4.57-4.75 (m, 4H), 4.08-4.26 (m, 2H), 3.10-3.28 (m, 1H), 2.90 (dd, *J*=8.4, 16.0 Hz, 1H), 2.74 (t, *J*=8.0 Hz, 1H), 2.08 (dd, *J*=8.6, 16.8 Hz, 1H), 1.32-1.44 (t, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.2, 161.2, 157.1, 153.3, 150.5, 147.9, 144.3, 140.4, 138.6, 136.1, 133.4, 133.1, 130.3, 130.0, 128.8, 128.4, 127.0, 126.9, 124.7, 121.9, 119.8, 118.5, 118.3, 115.3, 114.6, 102.2, 66.5, 66.4, 57.0, 46.4, 38.8, 35.6, 14.9. HRMS (ESI): Calcd. for $C_{39}H_{37}NO_8S$ $[M+Na]^+$ 680, found 681.

4.1.13.2. 1- benzyloxy-2-((4- ethylvinylsulfonate *phenoxy)methyl)-5-((4-(2-chloro-4-fluoro-phenylene ether)phenyl)amide)genipin **17f***

Brown liquid, yield 26%.^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69-7.79 (m, 5H), 7.55 (d, *J*=15.6 Hz, 4H), 7.25 (s, 1H), 7.15-7.25 (m, 4H), 6.89 (d, *J*=8.6 Hz, 4H), 6.60 (d, *J*=15.6 Hz, 1H), 5.92 (br. s., 1H), 4.97 (d, *J*=11.3 Hz, 1H), 4.57-4.75 (m, 4H), 4.08-4.26 (m, 2H), 3.10-3.28 (m, 1H), 2.90 (dd, *J*=8.4, 16.0 Hz, 1H), 2.74 (t, *J*=8.0 Hz, 1H), 2.08 (dd, *J*=8.6, 16.8 Hz, 1H), 1.32-1.44 (t, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 165.4, 165.1, 161.2, 161.1, 153.2, 153.2, 152.7, 148.0, 146.0, 144.3, 138.6, 137.5, 136.9, 136.5, 133.5, 133.4, 133.3, 130.8, 130.2, 130.0, 129.9, 129.8, 128.6,

128.5, 128.3, 128.2, 128.1, 128.0, 127.9, 127.7, 127.6, 127.4, 125.4, 124.7, 124.5, 121.9, 121.8, 121.4, 120.2, 120.1, 118.7, 118.3, 115.3, 115.2, 114.7, 100.4, 66.6, 66.4, 66.4, 57.0, 46.4, 38.8, 35.6, 14.9. HRMS (ESI): Calcd. for $C_{39}H_{35}BrClNO_8S$ $[M+Na]^+$ 814.08, found 814.24.

4.2. In vitro protein inhibition assays

The inhibitory activities of geniposide and genipin derivatives against PTP1B, TCPTP and SHP2 were determined with our published procedure [16]. P-nitrophenylphosphonic acid (pNPP) was hydrolyzed by PTP1B, TCPTP or SHP2 to pNP can be detected at 405 nm. Test compounds were predisposed in 96-well micro plates as 1.0 μL aliquots per well in DMSO. The protein enzymatic assay was carried out in a total volume of 100 μL per well in assay plates with 75 nM recombinant protein (PTP1B, TCPTP or SHP2), 2.5 mM pNPP, 10 mMTris, 25 mM NaCl and 1 mM EDTA (pH 7.1). After being incubated at room temperature for 30 min, the reaction was terminated by the addition of 2.0 N NaOH (50 μL). Then the amount of hydrolysis product, pNP, was monitored by detection of absorbance at 405 nm. Sodium vanadate was used as the positive control. Inhibition constants (IC_{50}) were calculated from the enzyme progress curves using standard mathematical models.

4.3. Cell viability assay

CHO cells were cultured in DMEM (10% fetal bovine serum and 1% penicillin-streptomycin solution) with 5% CO_2 at 37 ^oC. Each well of 96-well plates was seeded with 5×10^3 cells. After 24 hours, each well treated with varying concentrations of compounds. Then, the cells were incubated in DMEM (10% fetal bovine serum and 1% penicillin-streptomycin solution) for 24 hours with 5% CO_2 at 37 ^oC. Each well treated with 10 μL MTT solution, and cells were incubated for another 4 hours in the incubator at 37 ^oC within a dark place. Then the medium was removed and added 150 μL DMSO into each well. Finally, the optical density was measured at 490 nm by a micro plate reader.

4.4. Effect of compounds on 2-NBDG uptake by HepG2 cells

The glucose uptake was assayed according to our published method in HepG2 cells using 2-NBDG [18]. Cells were cultured in DMEM (10% fetal bovine serum and 1% penicillin-streptomycin solution) with 5% CO2 at 37 ^{o}C. 5 × 104 cells were seeded in each well of the 24-well plates. And each well was treated with different concentrations of compounds for 24 hours. The medium was removed, and washed with PBS twice. Then, the cells were treated with 100 nM insulin for 20 min, and then 50 μM 2-NBDG was added and maintained for 60 min. The glucose uptake was measured by FACS Calibur (BD) F1 channel.

4.5. Molecular modeling

Interactions between ligands and PTP1B (PDB code: 1AAX) are explained by molecular modeling using GOLD Suite v5.0.1(CCDC, Cambridge, U.K., 2010). Before docking was run, parameters were specifically addressed. After the protein was introduced, crystal waters and the ligand were removed and hydrogens were added.The binding site was defined to include all residues within a 22.5 Å radius of the point 45.484, 14.573 and 5.329 as the center. GoldScore was applied as a scoring function and other parameters were set as standard default. 10 conformations were produced after the docking runs were complete. We referred to the 20 conformations and selected the most reasonable docking conformations as our solutions.

Acknowledgments

We appreciate the financial support of the Medicine and Engineering Interdisciplinary Research Fund of Shanghai Jiao Tong University (YG2015QN03, YG2014MS10 and YG2017MS77), National Natural Science Foundation of China (81202397) and Shanghai Natural Science Fund (12ZR1415400).

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Highlight

- Potent PTP1B inhibitors were designed and synthesized.
- Most compounds exhibited excellent inhibitory activity (IC_{50}=0.35-64.74 μM).
- The structure-activity relationship and molecular docking were studied.
- Compounds **7a**, **17b** and **17f** effectively enhanced insulin-stimulated glucose uptake with no significant cytotoxicity.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: