European Journal of Medicinal Chemistry 79 (2014) 34–46

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Synthesis and evaluation of several oleanolic acid glycoconjugates as protein tyrosine phosphatase 1B inhibitors

Qingchao Liu [a], Tiantian Guo [b], Dong Li [a], Fahui Li [c], Wenhong Li [a,*]

[a] Department of Pharmaceutical Engineering, Northwest University, Xi'an 710069, Shaanxi, PR China
[b] Department of Chemical Medicine, Xi'an Institute for Food and Drug Control, Xi'an 710054, Shaanxi, PR China
[c] College of Chemistry and Chemical Engineering and Environmental Engineering, Weifang University, Weifang, Shandong 261061, PR China

ARTICLE INFO

Article history:
Received 4 February 2014
Received in revised form
17 March 2014
Accepted 28 March 2014
Available online 29 March 2014

Keywords:
Oleanolic acid triterpenoid saponins
PTP1B inhibitors
Glycosylation
Log *P*
Strucutre–activity relationships

ABSTRACT

Sixteen novel oleanolic acid triterpenoid saponins were synthesized in an efficient and practical strategy, and their inhibitory activities against protein tyrosine phosphatase 1B (PTP1B) and selectivity over T-cell protein tyrosine phosphatase (TCPTP) were evaluated *in vitro*. The preliminary structure–activity relationship studies demonstrated that sugar-substituted moiety attached to the C-3 and C-28 positions of OA scaffold greatly affected the inhibitory activity against PTP1B and the selectivity over TCPTP. All the compounds showed inhibitory potencies, and compounds **1h**, **1i** and **1j** exhibited remarkably potent inhibitory activities against PTP1B with IC_{50} values of 1.03, 0.78 and 3.12 μM, respectively. More significantly, compound **1h** showed greater than 4 folds selectivity over highly homologous TCPTP. In parallel, the lipophilicity evaluation of all synthesized compounds was tested as a prediction for pharmacological potency. According to the predicted log *P* values, the predicted Log *P* results showed that lipophilicity may correlate with the evaluated biological potency.

1. Introduction

Diabetes mellitus is reaching epidemic proportions, which is becoming the leading causes of public health care burdens all over the world. According to the World Health Organization (WHO), more than 346 million people around the world suffer from diabetes and its prevalence is projected to continue rising to over double by 2030 [1]. Type 2 diabetes mellitus (T2DM), constitutes 90% of diabetes mellitus, which is associated with chronic metabolic disorder that results from deficiency in both insulin secretion and action at target tissues [2]. Protein tyrosine phosphatase 1B (PTP1B), which is a major nontransmembrane phosphotyrosine phosphatase in human tissues and also a cytosolic non-receptor PTPase that has been implicated as a negative regular of insulin signal transduction, downregulates the insulin signaling pathway by dephosphorylating the activated insulin receptor (IR) or insulin receptor substrates (IRS). One research group disclosed that PTP1B knockout mice displayed enhanced insulin sensitivity, lower plasma glucose and insulin levels and resistance to high-fat-diet induced weight gain [3]. These experiment results were independently proved by L. D. klaman et al. [4] A recent study also revealed that PTP1B antisense oligonucleotides resulted in reduced PTP1B expression in insulin sensitive tissues [5]. Thus, PTP1B is currently considered to be a potent therapeutic target for type 2 diabetes and associated obesity. [6–8]

Considerable efforts have been made in the development of potent and selective small-molecule PTP1B inhibitors for the treatment of type 2 diabetes [9–15]. However, the endeavor to search for therapeutic PTP1B inhibitors proved largely abortive. Up to now, only Trodusquemine and Ertiprotafib PTP1B inhibitors have reached clinical trials [16,17]. The major reason could be the nature of the PTP1B catalytic site with highly conservative and cationic characteristic, which makes most PTP1B inhibitors with inadequate cell permeability and low selectivity for PTP1B over the most homogeneous T-cell protein tyrosine phosphatase (TCPTP) [18,19]. Therefore, there is an urgent need to develop novel potent and selective PTP1B inhibitors with improved physicochemical properties and in vivo efficacies.

In order to search for novel PTP1B small molecule inhibitor, our program was carried out with carbohydrate-based modification on the C_3–OH and C_{28}–COOH of oleanolic acid (OA) for enhancing the hydrosolubility and ameliorating the pharmacological and pharmacokinetic properties. Our previous studies on the structure–activity relationships (SAR) of sugar-substituted oleanolic acid

* Corresponding author.
E-mail address: liuqc21@nwu.edu.cn (W. Li).

http://dx.doi.org/10.1016/j.ejmech.2014.03.080
0223-5234/

derivatives showed that both the sugar moiety at the C-3 position and the long acidic chain at C-28 position of OA strongly influenced PTP1B activity, and also improved their inhibition gainst murine in vivo glucose absorption [20,21]. As part of an ongoing investigation, we herein report the synthesis and *in vitro* PTP1B inhibitory activities of novel sugar-substituted OA derivatives **1a**–**1j**, **2a**–**2c** and **3a**–**3c** (Fig. 1), and the selectivity between PTP1B and TCPTP of selected compounds were also evaluated. The present results obtained have provided valuable clues to the design and development of potent and selective PTP1B inhibitors.

2. Results and discussion

2.1. Chemistry

The synthetic route of bidesmosidic oleanolic acid saponins **1a**–**1j** was shown in Scheme 1. The glycosyl trichloroacetimidates donors **11a**–**11j** (Fig. 2) involved in the synthesis were readily prepared according to the previously reported procedures [20,22–25]. The C_6–OH group of compound **4**, which was readily synthesized from D-glucose via two steps reactions reported before [22], was first transformed into azide with *p*-toluenesulfonyl chloride (TsCl) and sodium azide (NaN_3), followed by addition of phthalic anhydride in THF to furnish carbamoylbenzoic acid-substituted compound **6** via PMe_3 mediated Staudinger protocol [26]. Treatment of **6** with BnBr and K_2CO_3 in THF afforded the benzyl protected compound **7** in 87% yield, which was brominated with hydrobromic acid in glacial acetic acid giving glycosyl bromide **8**. Treatment of oleanolic acid with glucosyl bromide **8** under the modified literature conditions (K_2CO_3, TBAB, CH_2Cl_2–H_2O, reflux) [27–28] afforded the desired 28-glucosyl ester **10** in 86% yield. Thereafter, glycosylation of the C_3–OH of **10** with trichloroacetimidate sugar donors **11a**–**11j** under the promotion of trimethylsilyl trifluoromethanesulfonate (TMSOTf) provided the expected glycosides **12a**–**12j** with the exclusive 1, 2-trans glycosidic linkages in isolated yields ranging from 81% to 89%. Subsequent deprotection of the benzyl ether with 10% Pd–C and the benzoyl ester with NaOMe in MeOH–CH_2Cl_2 was achieved to afford the target compounds **1a**–**1j** in good yields.

Oleanolic acid saponins **2a**–**2c** were afforded according to the procedure in Scheme 2. Treating **13** [29] (or **14**) [30] with MsCl and NaN_3 gave azide **15** (or **16**), which was then reacted with phthalic anhydride, Me_3P and BnBr to provide the key intermediate **17** (or **18**). Compound **19** (or **20**) was obtained via bromination at anomeric carbon position of **17** (or **18**), and then the fully protected saponin **19a** (or **20a**) was prepared by Phase transfer catalytic (PTC) reaction. The final step was conducted similar as that of **1a**–**1j** to yield the target compounds **2a**–**2c**.

Compounds **3a**–**3c** were synthesized as shown in Scheme 3. Treatment of **7** (or **17**, **18**) with NH_2NH_2–HOAc in DMF, followed by trichloroacetonitrile (Cl_3CCN) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dry CH_2Cl_2, afforded the corresponding imidate **7a** (or **17a**, **18a**) in satisfactory yield. Subsequent glycosylation of saponin acceptor **21** with trichloroacetimidate donor **7a** (or **17a**, **18a**) in the presence of TMSOTf (0.1 equiv) afforded the desired product **7b** (or **17b**, **18b**) in an excellent yield. Finally, removal of the benzyl group with 10% Pd–C and the benzoyl groups with NaOMe in MeOH–CH_2Cl_2 gave the target compounds **3a**–**3c**.

2.2. Biological evaluations

2.2.1. In vitro PTP1B inhibitory activities assays

The sugar-substituted OA derivatives **1a**–**1j**, **2a**–**2c** and **3a**–**3c** were evaluated *in vitro* for their ability to inhibit recombinant PTP1B activities by the method of *p*NPP using sodium orthovanadate as a positive control and results are presented in Fig. 3. We measured the inhibitory rates of all synthesized compounds at a concentration of 10 μg/mL, and the compounds with good

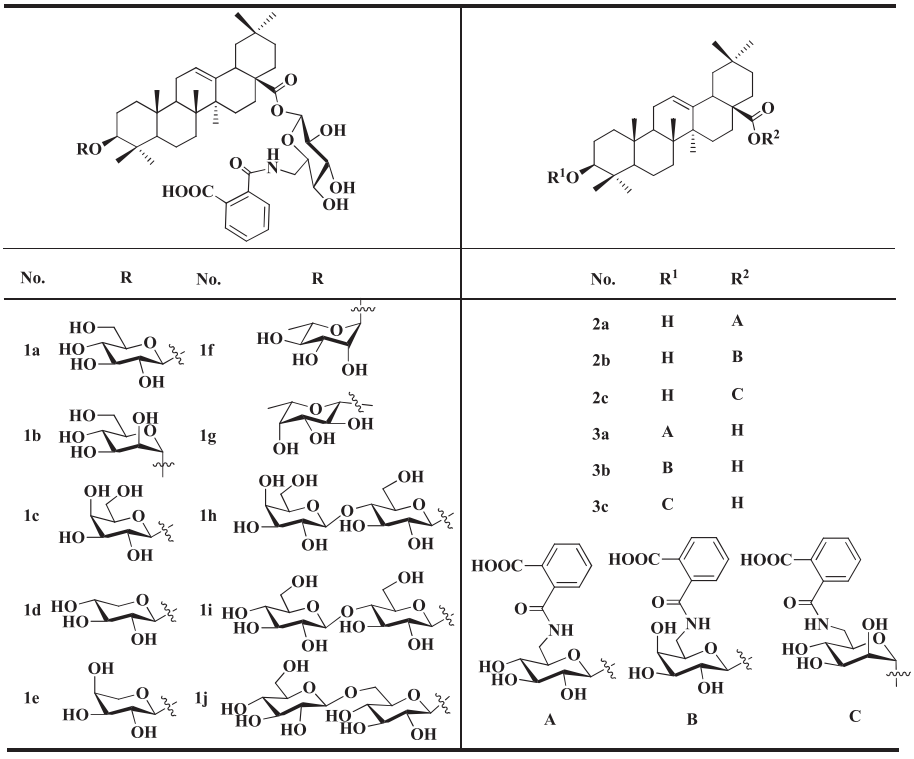
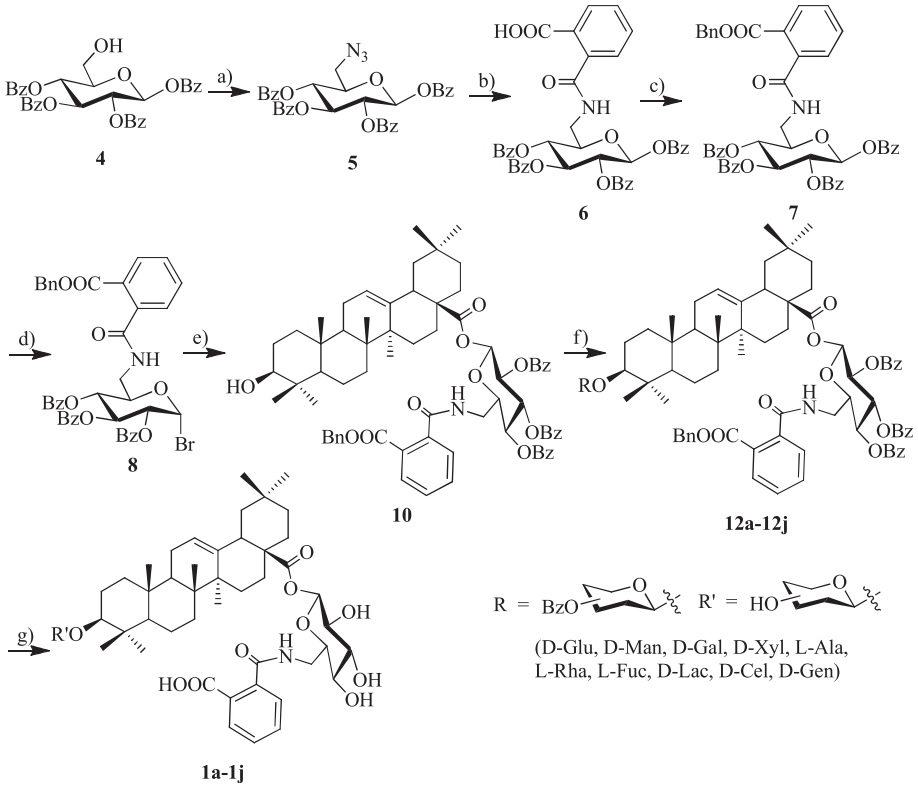


Fig. 1. Chemical structures of sugar-substituted OA derivatives **1a**–**1j**, **2a**–**2c** and **3a**–**3c**.



Scheme 1. Synthesis of compounds **1a**–**1j**, Reagents and conditions: (a) TsCl, DMAP, Pyridine; NaN_3, DMF, 65% for two steps; (b) phthalic anhydride, Me_3P, THF, 79%; (c) BnBr, K_2CO_3, THF, 87%; (d) 33% HBr in HOAc, CH_2Cl_2, 71%; (e) **oleanolic acid**, K_2CO_3, TBAB, CH_2Cl_2–H_2O, reflux, 86%; (f) **11a**–**11j**, 0.3 equiv TMSOTf, CH_2Cl_2, −30 °C, 81%–89% for **12a**–**12j**; (g) 10% Pd–C, H_2, MeOH–CH_2Cl_2; NaOMe, MeOH–CH_2Cl_2, 63%–79% for **1a**–**1j**.

inhibition rate (>50% at 10 μg/mL) were selected for further determination of IC_{50} values. Among all 16 compounds, three monodesmosidic saponins derivatives (**2a**–**2c**) on C-28 position of OA were favorable to PTP1B inhibitory activity, especially carbamoylbenzoic acid-substituted glucosyl saponin **2a** showed more higher inhibition with 54.67% inhibition rate at 10 μg/mL than compounds **2b**–**2c**. Interestingly, while OA was linked with the sugar moiety on C-3 and C-28, the resulting bidesmosidic saponins **1a**–**1j** (>54.67% inhibition rate at 10 μg/mL) exhibited more potent PTP1B inhibitory activities than **2a**. Furthermore, compounds **1h**–**1j** (inhibition%: **1h**, 93.14%; **1i**, 89.77%; **1j**, 79.89%) with disaccharide-substituted moiety displayed higher activity against PTP1B, as compared to those of **1a**–**1g** with monosaccharide-substituted moiety linked to the C-3 position of OA, indicating that introduction of more hydrophilic sugar moiety is more favorable to the inhibitory activity for PTP1B. And compounds **1h** with lactose moiety and **1i** with cellulose moiety exhibited more potent inhibitory activity than compound **1j** with gentiobiose moiety, which suggested that the spatial configuration of sugar residue had an important influence on the inhibitory activity against PTP1B. However, three monodesmosidic saponins derivatives (**3a**–**3c**) with structural modifications on C-3 position of OA led to a dramatic decrease in PTP1B inhibitory activity. These data demonstrated that substituent of sugar moiety on both C-3 and C-28

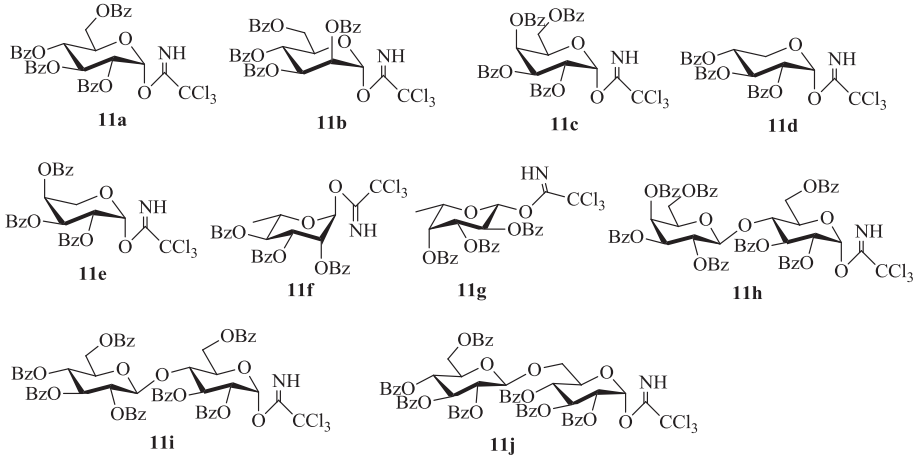
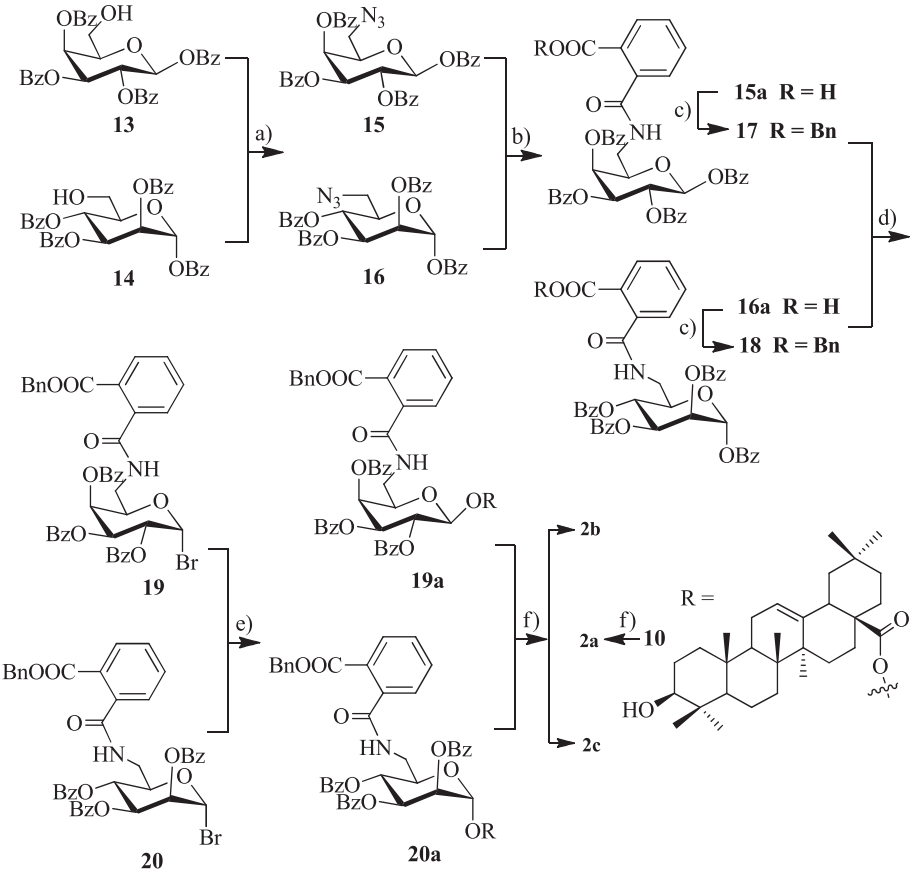


Fig. 2. Chemical structures of glycosyl trichloroacetimidates donors **11a**–**11j**.



Scheme 2. Synthesis of compounds **2a**–**2c**, Reagents and conditions: (a) MsCl, TEA; NaN_3, DMF, 71% for **15**, 63% for **16** (2 steps); (b) phthalic anhydride, Me_3P, THF, 81% for **15a**, 83% for **16a**; (c) BnBr, K_2CO_3, THF, 90% for **17**, 89% for **18**; (d) 33% HBr in HOAc, CH_2Cl_2, 75% for **19**, 69% for **20**; (e) **oleanolic acid**, K_2CO_3, TBAB, CH_2Cl_2–H_2O, reflux, 82% for **19a**, 79% for **20a**; (f) 10% Pd–C, H_2, MeOH–CH_2Cl_2; NaOMe, MeOH–CH_2Cl_2, 75% for **2a**, 66% for **2b**, 63% for **2c** (2 steps).

positions of OA is responsible for enhancing inhibitory activity against PTP1B.

2.2.2. Selectivity over TCPTP

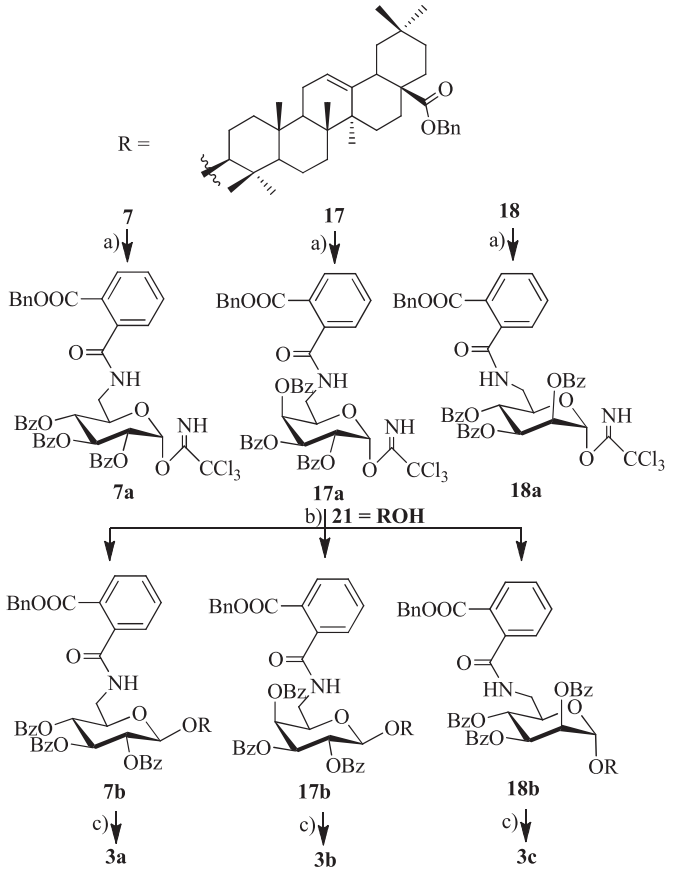
To investigate the specificity of sugar-substituted oleanolic acid derivatives against PTPs, some synthetic derivatives were also tested for homogeneous TCPTP inhibitory activities. The results with the IC_{50} values and the ratio of PTP1B and TCPTP were depicted in Table 1. The assay results indicated that most of the synthetic compounds showed potent inhibition of PTP1B and TCPTP, and these compounds exhibited 0.9–4.0-fold selectivity for PTP1B over TCPTP. The comparison of **1a**–**1j** (except compound 1f, IC_{50}: 26.49 μM) and **2a** (IC_{50}: 20.37 μM) indicated that modified OA analogs with sugar moiety on C-3 and C-28 positions exhibited more inhibitory activity than that with sugar moiety only on C-28 position. Moreover, comparison of **1a**–**1g** (IC_{50}: 5.67–26.49 μM) with **1h**–**1j** (IC_{50}: 0.78–3.12 μM) showed the disaccharide-substituted derivatives showed more PTP1B inhibitory activity than the monosaccharide-substituted derivatives on C-3 position. Obviously, compound **1i** (IC_{50}: 0.78 μM) with D-cellobiose moiety on C-3 position is around 4-fold more active than compound **1j** (IC_{50}: 3.12 μM) with D-gentiobiose moiety on C-3 position, and for **1i**, the selectivity of TCPTP reached to 2.8-fold with relatively more potent on PTP1B activity, demonstrating the specific stereochemistry of D-cellobiose moiety on C-3 position of OA was favorable to PTP1B inhibitory activity. For comparison, compounds **1h** (IC_{50}: 1.03 μM) and **1i** (IC_{50}: 0.78 μM) showed a similar activity against PTP1B. Interestingly, compound **1h** exhibited the best selectivity (TCPTP/PTP1B: 4.0) between the two homogenous enzymes. It was worth noting that compound **1j** showed more potent PTP1B inhibitory activity than **1a**–**1g**, however, **1j** did not show good PTP1B selectivity over TCPTP.

2.2.3. The prediction of the permeability

Lipophilicity (permeability) of drugs strongly influenced the absorption, the distribution, the biological availability, and pharmacological activity of drugs [31]. The prediction of the permeability, which demonstrates the transport of the drugs through cellular membranes, has been proved to be one of the most important physical properties of bioactive compounds [32]. In this study, lipophilicity of all synthesized oleanolic acid saponins **1a**–**1j**, **2a**–**2c**, and **3a**–**3c**, the logarithm of the partition coefficient between polar (water) and non-polar (octanol) phases (Log *P*), was calculated by employing the ACD lab program. The results are shown in Table 2. As expected, compounds **1h**–**1j** possessed the highest lipophilicity (Log *P*), while compounds **3a**–**3c** showed the lowest lipophilicity. Generally, oleanolic acid bidesmosides **1a**–**1j** (except compounds **1f** and **1g**) have higher predicted permeability than oleanolic acid monodesmosides **2a**–**2c** and **3a**–**3c**. These displayed data showed that the order of PTP1B inhibitory activity was slightly consistent with the order of lipophilicity, which indicated that lipophilicity of all the synthesized compounds was in association with the evaluated pharmacological potency.

3. Conclusions

In conclusion, we have prepared a series of novel oleanolic acid saponins in a highly concise and practical strategy, and their PTP1B



Scheme 3. Synthesis of compounds **3a**–**3c**, Reagents and conditions: (a) NH_2NH_2-HOAc, DMF; $CNCCl_3$, DBU, CH_2Cl_2, 83% for **7a**, 85% for **17a**, 78% for **18a** (2 steps); (b) TMSOTf, CH_2Cl_2, 0 °C, 91% for **7b**, 87% for **17b**, 89% for **18b**; (c) 10% Pd–C, H_2, MeOH–CH_2Cl_2; NaOMe, MeOH–CH_2Cl_2, 69% for **3a**, 67% for **3b**, 71% for **3c**.

inhibitory activity was evaluated *in vitro*. The preliminary structure–activity relationship acquired demonstrated that sugar-substituted moieties attached to the C-3 and C-28 positions of OA scaffold have greatly helped to enhance the inhibitory activity against PTP1B. These sugar-substituted moieties may facilitate the binding to the active site of PTP1B. Among these derivatives, compounds **1h**, **1i** and **1j** exhibited potent inhibitory activities against PTP1B with IC_{50} values of 1.03, 0.78 and 3.12 μM, respectively. More importantly, compound **1h** showed a remarkably 4 folds selectivity over TCPTP. In parallel, the lipophilicity evaluation of all synthesized compounds was tested as a prediction for pharmacological potency. The predicted Log *P* results showed that lipophilicity may correlate with the evaluated biological potency. Further investigations to improve pharmacological profile and clarify action mechanism for this series of sugar-substituted OA PTP1B inhibitors are currently under way in our research group and will be reported in due time.

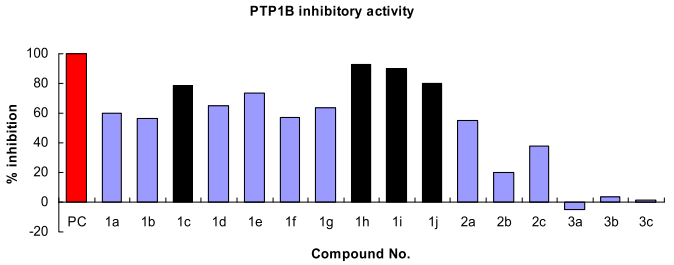


Fig. 3. PTP1B inhibitory activity of oleanolic acid saponins **1a**–**1j**, **2a**–**2c** and **3a**–**3c** (10 μg/mL in DMSO). Positive Control: Sodium orthovanadate (100 μg/mL in DMSO).

4. Experimental section

4.1. Chemistry

Commercial reagents were used without further purification unless specialized. Solvents were dried and redistilled prior to use in the usual way. Thin-layer chromatography (TLC) was performed on precoated E. Merck Silica Gel 60 F254 plates. Flash column chromatography was performed on silica gel (200–300 mesh). Optical rotations were determined with a Perkin–Elmer Model 241 MC polarimeter. ^{1}H NMR and ^{13}C NMR spectra were taken on a JEOL JNM-ECP 600 spectrometer with tetramethylsilane as the internal standard, and chemical shifts are recorded in δ values. Mass spectra were recorded on a Q-TOF Global mass spectrometer.

4.1.1. Typical procedure for the synthesis of compounds *5*, *15* and *16*

A solution of compound **4** (or **13**–**14**) (2 g, 3.35 mmol), 4-(dimethylamino)pyridine (0.82 g, 6.70 mmol) in pyridine (10 mL) and CH_2Cl_2 (3 mL) was treated with *p*-toluenesulfonyl chloride (0.96 g, 5.03 mmol), and the mixture was stirred at room temperature. After 20 h, the reaction mixture was concentrated and the residue was dissolved in CH_2Cl_2, which was then washed with 1 N HCl, aq. sat. $NaHCO_3$, brine, dried over Na_2SO_4, and concentrated. The residue was dissolved in DMF (15 mL), and then sodium azide (0.87 g, 13.4 mmol) was added to the above reaction mixture. After stirring for 24 h at 60 °C, the reaction mixture was concentrated under reduced pressure. The residue was diluted with CH_2Cl_2, washed with water, brine, dried over Na_2SO_4, and concentrated. The residue was purified by a silica gel column chromatography (5:1, petroleum ether-EtOAc) to afford the product **5** (or **15**–**16**) as a white solid.

*4.1.1.1. 6-Azide-1,2,3,4-tetra-O-benzoyl-6-deoxy-β-D-glucopyranose (**5**).* Yield: 65%; $[\alpha]_D^{27}$ + 68.5 (c 1.15, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.27–8.11 (m, 20H, Ph-H), 6.31 (d, *J* = 7.9 Hz, 1H, H-1), 6.07 (t, *J* = 9.6 Hz, 1H, H-3), 5.79 (dd, *J* = 9.6, 7.9 Hz, 1H, H-2), 5.57 (t, *J* = 9.6 Hz, 1H, H-4), 4.07 (m, 1H, H-5), 3.47 (dd, *J* = 12.8, 5.1 Hz, 1H, H-6–1), 3.32 (dd, *J* = 12.8, 3.0 Hz, 1H, H-6–2); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 166.5, 165.9, 165.3, 164.9, 134.1, 133.9, 133.5, 133.3, 130.3, 130.1, 129.9129.8, 128.7, 128.5, 128.3, 93.1 (C-1), 75.6, 72.6, 70.8, 69.3, 60.3; HRESIMS: *m/z* calcd for $C_{34}H_{27}N_3O_9Na$ [M+Na$^+$] 644.1640; found: 644.1623.

*4.1.1.2. 6-Azide-1,2,3,4-tetra-O-benzoyl-6-deoxy-β-D-galactopyranose (**15**).* Yield: 71%; $[\alpha]_D^{27}$ + 47.1 (c 1.03, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.27–8.09 (m, 20H, Ph-H), 6.23 (d, *J* = 8.0 Hz, 1H, H-1), 5.89 (dd, *J* = 9.7, 3.7 Hz, 1H, H-3), 5.83 (dd, *J* = 9.7, 8.0 Hz, 1H, H-2), 5.43 (t, *J* = 3.7 Hz, 1H, H-4), 4.23 (m, 1H, H-5), 3.51 (dd, *J* = 12.3, 5.1 Hz, 1H, H-6-1), 3.31 (dd, *J* = 12.3, 3.2 Hz, 1H, H-6-2); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 166.5, 165.7, 165.3, 164.9, 134.0, 133.7, 133.5, 133.1, 130.3, 130.1, 129.9, 129.7, 128.7, 128.5, 128.1, 94.3 (C-1), 73.9, 72.3, 70.3, 69.5, 59.9; HRESIMS: *m/z* calcd for $C_{34}H_{27}N_3O_9Na$ [M+Na$^+$] 644.1640; found: 644.1658.

*4.1.1.3. 6-Azide-1,2,3,4-tetra-O-benzoyl-6-deoxy-α-D-mannopyranose (**16**).* Yield: 63%; $[\alpha]_D^{27}$ + 78.1 (c 1.12, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.23–8.01 (m, 20H, Ph-H), 6.39 (s, 1H, H-1), 5.99 (dd, *J* = 3.9, 2.1 Hz, 1H, H-2), 5.65 (dd, *J* = 9.6, 3.9 Hz, 1H, H-3), 5.51 (t, *J* = 9.6 Hz, 1H, H-4), 4.10 (m, 1H, H-5), 3.41 (dd, *J* = 11.9, 5.3 Hz, 1H, H-6-1), 3.29 (dd, *J* = 11.9, 3.2 Hz, 1H, H-6-2); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 166.3, 165.7, 165.3, 165.1, 134.1, 133.9, 133.7, 133.5, 130.3,

Table 1
In vitro PTP1B and TCPTP inhibitory activities of oleanolic acid derivatives.

Compounds	IC_{50} (μM)[a]		TCPTP/PTP1B[c]
	PTP1B	TCPTP	
1a	17.23 ± 2.11	30.51 ± 2.97	1.8
1b	15.87 ± 1.73	nd[b]	
1c	6.53 ± 0.71	14.57 ± 1.59	2.2
1d	16.56 ± 1.24	15.49 ± 1.71	0.9
1e	5.67 ± 0.83	12.39 ± 1.31	2.2
1f	26.49 ± 2.32	nd	
1g	10.36 ± 0.97	8.73 ± 0.97	0.8
1h	1.03 ± 0.16	4.11 ± 0.34	4.0
1i	0.78 ± 0.09	2.16 ± 0.43	2.8
1j	3.12 ± 0.53	2.98 ± 0.62	1.0
2a	20.37 ± 1.96	24.42 ± 3.01	1.2
Sodium orthorandate[d]	7.83 ± 0.91	nd	

[a] Results are expressed as IC_{50} values (μM), determined by regression analyses and expressed as the mean ± SD of three replicates.
[b] nd, not determined.
[c] TCPTP/PTP1B, the ratio of IC_{50} of TCPTP and PTP1B.
[d] Sodium orthovanadate was used as the positive control, of which the max inhibition concentration is 100 μg/mL.

130.1, 129.6, 129.1, 128.9, 128.5, 128.1, 91.9 (C-1), 75.3, 71.8, 69.9, 69.1, 60.5; HRESIMS: *m/z* calcd for $C_{34}H_{27}N_3O_9Na$ [M+Na^+] 644.1640; found: 644.1629.

4.1.2. Typical procedure for the synthesis of compounds ***6***, ***15a*** and ***16a***

A solution of compound **5** (or **15**–**16**) (1 g, 1.61 mmol) in THF (20 mL) was treated with Me_3P (3.22 mL, 3.22 mmol), and the mixture was stirred at room temperature. When no N_2 appeared, the resulting mixture was treated with phthalic anhydride (360 mg, 2.42 mmol) and stirred at room temperature for 5 d. The reaction mixture was concentrated and the residue was dissolved in EtOAc, washed with water, brine, dried over Na_2SO_4, and concentrated. The residue was purified by a silica gel column chromatography (3:1, petroleum ether-EtOAc) to afford the product **6** (or **15a**–**16a**) as a white solid.

*4.1.2.1. 6-Phthalimido-1,2,3,4-tetra-O-benzoyl-6-deoxy-β-D-glucopyranose (**6**).* Yield: 79%; $[\alpha]_D^{27}$ + 57.9 (c 0.91, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.20–8.07 (m, 24H, Ph-H), 6.67 (m, 1H, NHCO), 6.27 (d, *J* = 8.0 Hz, 1H, H-1), 6.03 (t, *J* = 9.6 Hz, 1H, H-3), 5.81 (dd, *J* = 9.6, 8.0 Hz, 1H, H-2), 5.54 (t, *J* = 9.6 Hz, 1H, H-4), 4.15 (m, 1H, H-5), 3.53 (dd, *J* = 13.2, 5.3 Hz, 1H, H-6-1), 3.31 (dd, *J* = 13.2, 3.5 Hz, 1H, H-6-2); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 166.3, 166.0, 165.7, 165.3, 164.9, 137.1, 136.3, 134.3, 133.7, 133.5, 133.1, 132.2, 131.7, 130.3, 130.0, 129.9, 129.7, 128.9, 128.5, 128.3, 128.0, 125.9, 93.6 (C-1), 75.1, 73.5, 71.8, 70.6, 50.3; HRESIMS: *m/z* calcd for $C_{42}H_{33}NO_{12}Na$ [M+Na^+] 766.1895; found: 766.1879.

Table 2
Prediction of lipophilicity (Log *P*) of oleanolic acid derivatives **1a**–**1j**, **2a**–**2c**, and **3a**–**3c**.

Compound	Log *P*[a]	Compound	Log *P*[a]
1a	6.63 ± 0.70	**1i**	5.95 ± 0.83
1b	6.63 ± 0.70	**1j**	6.08 ± 0.84
1c	6.63 ± 0.70	**2a**	8.60 ± 0.67
1d	8.45 ± 0.81	**2b**	8.60 ± 0.67
1e	8.45 ± 0.81	**2c**	8.60 ± 0.67
1f	8.95 ± 0.81	**3a**	9.64 ± 0.69
1g	8.95 ± 0.81	**3b**	9.64 ± 0.69
1h	5.95 ± 0.83	**3c**	9.64 ± 0.69

[a] Predicted octanol/water partition coefficient by ACD/Log *P* ver. 1.0.

*4.1.2.2. 6-Phthalimido-1,2,3,4-tetra-O-benzoyl-6-deoxy-β-D-galactopyranose (**15a**).* Yield: 81%; $[\alpha]_D^{27}$ + 59.3 (c 0.95, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.17–8.00 (m, 24H, Ph-H), 6.69 (m, 1H, NHCO), 6.35 (d, *J* = 8.3 Hz, 1H, H-1), 5.89 (dd, *J* = 9.7, 8.3 Hz, 1H, H-2), 5.79 (dd, *J* = 9.7, 3.6 Hz, 1H, H-3), 5.36 (t, *J* = 3.6 Hz, 1H, H-4), 4.23 (m, 1H, H-5), 3.49 (dd, *J* = 12.1, 5.6 Hz, 1H, H-6-1), 3.35 (dd, *J* = 12.1, 2.9 Hz, 1H, H-6-2); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 166.5, 166.1, 165.7, 165.1, 164.9, 137.5, 136.9, 134.5, 133.7, 133.3, 132.9, 132.2, 131.7, 130.5, 130.0, 129.9, 129.7, 128.9, 128.5, 128.3, 127.9, 125.7, 95.2 (C-1), 75.6, 73.9, 71.8, 69.9, 50.1; HRESIMS: *m/z* calcd for $C_{42}H_{33}NO_{12}Na$ [M + Na^+] 766.1895; found: 766.1911.

*4.1.2.3. 6-Phthalimido-1,2,3,4-tetra-O-benzoyl-6-deoxy-α-D-mannopyranose (**16a**).* Yield: 83%; $[\alpha]_D^{27}$ + 23.4 (c 0.87, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.27–8.07 (m, 24H, Ph-H), 6.67 (m, 1H, NHCO), 6.41 (d, *J* = 2.3 Hz, 1H, H-1), 6.00 (dd, *J* = 9.3, 3.3 Hz, 1H, H-3), 5.76 (dd, *J* = 3.3, 2.3 Hz, 1H, H-2), 5.57 (t, *J* = 9.3 Hz, 1H, H-4), 4.03 (m, 1H, H-5), 3.59 (dd, *J* = 11.9, 4.7 Hz, 1H, H-6-1), 3.34 (dd, *J* = 11.9, 3.1 Hz, 1H, H-6-2); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 166.9, 165.9, 165.7, 165.1, 164.9, 137.5, 136.3, 135.0, 133.7, 133.5, 133.1, 132.2, 131.5, 130.3, 130.0, 129.9, 129.5, 128.9, 128.5, 128.3, 128.1, 124.8, 92.0 (C-1), 77.3, 72.9, 71.8, 68.9, 50.3; HRESIMS: *m/z* calcd for $C_{42}H_{33}NO_{12}Na$ [M + Na^+] 766.1895; found: 766.1873.

4.1.3. Typical procedure for the synthesis of compounds ***7***, ***17*** and ***18***

A solution of compound **6** (or **15a**–**16a**) (800 mg, 1.08 mmol), K_2CO_3 (1.50 g, 10.8 mmol) in THF (25 mL) was treated with BnBr (0.21 mL, 1.62 mmol), and the mixture was stirred at 60 °C for 5 h, then concentrated. The residue was diluted with CH_2Cl_2, and the extract was washed successively with HCl (1M), H_2O, and brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by a silica gel column chromatography (6:1, petroleum ether-EtOAc) to afford the product **7** (or **17**–**18**) as a white solid.

*4.1.3.1. 6-(2′-O-Benzyl-phthalimido)-1,2,3,4-tetra-O-benzoyl-6-deoxy-β-D-glucopyranose (**7**).* Yield: 87%; $[\alpha]_D^{27}$ + 43.7 (c 0.72, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.21–8.05 (m, 29H, Ph-H), 6.71 (m, 1H, NHCO), 6.21 (d, *J* = 7.9 Hz, 1H, H-1), 6.06 (t, *J* = 9.7 Hz, 1H, H-3), 5.83 (dd, *J* = 9.7, 7.9 Hz, 1H, H-2), 5.63 (m, 2H, PhCH_2), 5.53 (t, *J* = 9.7 Hz, 1H, H-4), 4.10 (m, 1H, H-5), 3.57 (dd, *J* = 12.7, 5.1 Hz, 1H, H-6-1), 3.27 (dd, *J* = 12.7, 3.3 Hz, 1H, H-6-2); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 166.5, 166.0, 165.7, 165.5, 164.7, 136.9, 136.3, 134.3, 133.9, 133.8, 133.5, 133.3, 132.1, 131.7, 131.3, 130.3, 130.1130.0, 129.9, 129.6, 128.8, 128.5, 128.2, 128.0, 125.7, 93.3 (C-1), 74.9, 73.5, 71.7, 70.3, 50.3; HRESIMS: *m/z* calcd for $C_{49}H_{39}NO_{12}Na$ [M+Na^+] 856.2365; found: 856.2381.

*4.1.3.2. 6-(2′-O-Benzyl-phthalimido)-1,2,3,4-tetra-O-benzoyl-6-deoxy-β-D-galactopyranose (**17**).* Yield: 90%; $[\alpha]_D^{27}$ + 87.1 (c 0.79, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.27–8.11 (m, 29H, Ph-H), 6.68 (m, 1H, NHCO), 6.37 (d, *J* = 8.0 Hz, 1H, H-1), 6.00 (dd, *J* = 9.6, 3.8 Hz, 1H, H-3), 5.87 (dd, *J* = 9.6, 8.0 Hz, 1H, H-2), 5.59 (m, 2H, PhCH_2), 5.47 (t, *J* = 3.8 Hz, 1H, H-4), 4.24 (m, 1H, H-5), 3.63 (dd, *J* = 11.9, 5.3 Hz, 1H, H-6-1), 3.23 (dd, *J* = 11.9, 3.7 Hz, 1H, H-6-2); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 166.9, 166.3, 165.7, 165.1, 164.7, 136.9, 136.3, 134.5, 133.9, 133.7, 133.5, 133.1, 132.1, 131.7, 130.7, 130.3, 130.1, 129.8, 129.7, 129.3, 128.8, 128.5, 128.2, 127.9, 125.9, 95.1 (C-1), 75.2, 73.1, 70.5, 68.9, 49.7; HRESIMS: *m/z* calcd for $C_{49}H_{39}NO_{12}Na$ [M+Na^+] 856.2365; found: 856.2349.

*4.1.3.3. 6-(2′-O-Benzyl-phthalimido)-1,2,3,4-tetra-O-benzoyl-6-deoxy-α-D-mannopyranose (**18**).* Yield: 89%; $[\alpha]_D^{27}$ + 8.73 (c 0.56, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.25–8.01 (m, 29H, Ph-H), 6.73 (m, 1H, NHCO), 6.39 (s, 1H, H-1), 5.99 (dd, *J* = 9.1, 3.5 Hz, 1H, H-3), 5.81 (br s, 1H, H-2), 5.56 (t, *J* = 9.1 Hz, 1H, H-4), 5.50 (m, 2H, PhCH_2),

4.23 (m, 1H, H-5), 3.49 (dd, J = 12.1, 5.3 Hz, 1H, H-6-1), 3.31 (dd, J = 12.1, 3.7 Hz, 1H, H-6-2); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 167.0, 166.5, 165.7, 165.1, 164.7, 137.1, 136.3, 134.3, 133.9, 133.6, 133.5, 133.0, 132.1, 131.7, 131.3, 130.3, 130.1, 130.0, 129.9, 129.6, 128.7, 128.5, 128.2, 127.7, 125.9, 91.7 (C-1), 75.1, 73.5, 71.3, 69.7, 50.3; HRESIMS: *m/z* calcd for $C_{49}H_{39}NO_{12}Na$ [M+Na$^+$] 856.2365; found: 856.2390.

4.1.4. Typical procedure for the synthesis of compounds **7a**, **17a** and **18a**

To a solution of compound **7** (or **17**–**18**) (500 mg, 0.60 mmol) in 7 mL of DMF, NH_2NH_2–HOAc (83 g, 0.90 mmol) was added at 0 °C. The mixture was stirred for 12 h, then concentrated. The residue was diluted with CH_2Cl_2, and the extract was washed successively with satd aq $NaHCO_3$, brine, dried over Na_2SO_4, filtered, and concentrated. The residue was then dissolved in dry CH_2Cl_2 (10 mL), $CNCCl_3$ (0.45 mL, 4.80 mmol) and DBU (0.11 mL, 0.30 mmol) were added at 0 °C. The reaction mixture was stirred for 3 h at room temperature, then the solvent was evaporated *in vacuo* to give a residue, which was purified by a silica gel column chromatography (5:1, petroleum ether-EtOAc) to afford the product **7a** (or **17a**–**18a**) as a white solid.

*4.1.4.1. 6-(2′-O-Benzyl-phthalimido)-2,3,4-tri-O-benzoyl-6-deoxy-α-D-glucopyranoside trichloroacet-imidate (**7a**).* Yield: 83%; $[\alpha]_D^{27}$ + 23.5 (c 0.21, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.55 (s, 1H, N–H), 7.21–8.11 (m, 24H, Ph-H), 6.71 (m, 1H, NHCO), 6.60 (d, J = 3.7 Hz, 1H, H-1), 6.01 (t, J = 9.6 Hz, 1H, H-3), 5.67 (m, 2H, PhCH_2), 5.53 (t, J = 9.6 Hz, 1H, H-4), 5.41 (dd, J = 9.6, 3.7 Hz, 1H, H-2), 3.99 (m, 1H, H-5), 3.89 (dd, J = 11.5, 5.3 Hz, 1H, H-6-1), 3.67 (dd, J = 11.5, 3.4 Hz, 1H, H-6-2); HRESIMS: *m/z* calcd for $C_{44}H_{36}Cl_3N_2O_{11}$ [M+H$^+$] 873.1379; found: 873.1393.

*4.1.4.2. 6-(2′-O-benzyl-phthalimido)-2,3,4-tri-O-benzoyl-6-deoxy-α-D-galactopyranoside trichloroace-timidate (**17a**).* Yield: 85%; $[\alpha]_D^{27}$ + 7.81 (c 0.31, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.51 (s, 1H, N–H), 7.21–8.06 (m, 24H, Ph-H), 6.73 (m, 1H, NHCO), 6.57 (d, J = 3.6 Hz, 1H, H-1), 5.99 (dd, J = 9.7, 3.7 Hz, 1H, H-3), 5.67 (m, 2H, PhCH_2), 5.61 (t, J = 3.7 Hz, 1H, H-4), 5.37 (dd, J = 9.7, 3.6 Hz, 1H, H-2), 4.19 (m, 1H, H-5), 3.73 (dd, J = 11.9, 5.0 Hz, 1H, H-6-1), 3.57 (dd, J = 11.9, 3.4 Hz, 1H, H-6-2); HRESIMS: *m/z* calcd for $C_{44}H_{36}Cl_3N_2O_{11}$ [M+H$^+$] 873.1379; found: 873.1390.

*4.1.4.3. 6-(2′-O-Benzyl-phthalimido)-2,3,4-tri-O-benzoyl-6-deoxy-α-D-mannopyranose trichloroacet-imidate (**18a**).* Yield: 78%; $[\alpha]_D^{27}$ + 30.9 (c 0.19, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.60 (s, 1H, N–H), 7.23–8.11 (m, 24H, Ph-H), 6.65 (m, 2H, H-1, NHCO), 6.11 (dd, J = 9.3, 3.7 Hz, 1 H, H-3), 5.89 (s, 1H, H-2), 5.64 (m, 3H, H-4, PhCH_2), 4.29 (m, 1H, H-5), 3.75 (dd, J = 12.1, 5.1 Hz, 1 H, H-6-1), 3.52 (dd, J = 12.1, 3.3 Hz, 1H, H-6-2); HRESIMS: *m/z* calcd for $C_{44}H_{36}Cl_3N_2O_{11}$ [M+H$^+$] 873.1379; found: 873.1361.

4.1.5. Typical procedure for the synthesis of compounds **7b**, **17b** and **18b**

A mixture of compound **21** (100 mg, 0.18 mmol), trichloroacetimidates **7a**, **17b** or **18b** (0.22 mmol, 1.2 equiv.) and powdered 4 Å molecular sieves in dry CH_2Cl_2 (8 mL) were stirred for 30 min at room temperature and then cooled to 0 °C. TMSOTf (10 μL, 0.05 mmol, 0.3 equiv.) was added. After being stirred at 0 °C for 30 min, the reaction mixture was warmed up to room temperature for 1 h. The reaction was quenched by addition of Et_3N and then filtered. The filtrate was concentrated and purified by a silica gel column chromatography (petroleum ether-EtOAc) to afford the products **7b**, **17b** and **18b**.

*4.1.5.1. Benzyl oleanate 3-O-6-(2′-O-benzyl-phthalimido)-2,3,4-tri-O-benzoyl-6-deoxy-β-D-glucopy-ranoside (**7b**).* Yield: 91%; $[\alpha]_D^{27}$ + 37.2 (c 1.29, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.29–8.07 (m, 29H, Ph-H), 6.71 (m, 1H, NHCO), 5.96 (t, J = 9.6 Hz, 1H, H-3′), 5.60–5.65 (m 2H, H-2′, H-4′), 5.43 (m, 2H, PhCH_2), 5.30 (t, J = 3.6 Hz, 1H, H-12), 5.12 (dd, J = 29.8, 12.4 Hz, 2H, PhCH_2), 4.95 (d, J = 7.9 Hz, 1H, H-1′), 4.67 (dd, J = 12.0, 3.4 Hz, 1H, H-6′-1), 4.59 (dd, J = 12.0, 6.3 Hz, 1H, H-6′-2), 4.27 (m, 1H, H-5′), 3.12 (dd, J = 11.9, 4.6 Hz, 1H, H-3), 2.87 (dd, J = 13.7, 4.3 Hz, 1H, H-18), 1.07, 0.95, 0.91, 0.80, 0.69, 0.63, 0.51 (s each, 3H each, CH_3 × 7); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 177.3 (C-28), 166.3, 165.9, 165.7, 165.6, 143.9 (C-13), 137.1, 136.1, 133.3, 133.0, 132.9, 130.1, 130.0, 129.9, 129.8, 129.5, 129.3, 128.9, 128.3, 128.2, 127.6, 127.1, 122.9 (C-12), 105.1 (C-1′), 89.9 (C-3), 74.5, 72.3, 70.9, 69.3, 67.6, 65.7, 56.9, 52.1, 47.9, 46.8, 45.9, 41.6, 39.9, 38.7, 38.5, 37.1, 36.3, 34.1, 32.7, 31.8, 30.6, 29.7, 27.9, 25.7, 25.4, 23.8, 17.6, 16.4, 15.1; HRMALDIMS: *m/z* calcd for $C_{79}H_{87}NO_{13}Na$ [M + Na$^+$] 1280.6070; found: 1280.6089.

*4.1.5.2. Benzyl oleanate 3-O-6-(2′-O-benzyl-phthalimido)-2,3,4-tri-O-benzoyl-6-deoxy-β-D-galactopy-ranoside (**17b**).* Yield: 87%; $[\alpha]_D^{27}$ + 56.3 (c 1.03, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.21–8.11 (m, 29H, Ph-H), 6.73 (m, 1H, NHCO), 5.97 (t, J = 3.7 Hz, 1H, H-4′), 5.85 (dd, J = 9.7, 8.2 Hz, 1H, H-2′), 5.67 (dd, J = 9.7, 3.7 Hz, 1H, H-3′), 5.45 (m, 2H, PhCH_2), 5.27 (t, J = 3.5 Hz, 1H, H-12), 5.09 (dd, J = 29.5, 12.9 Hz, 2H, PhCH_2), 4.89 (d, J = 8.2 Hz, 1H, H-1′), 4.69 (dd, J = 11.9, 6.1 Hz, 1H, H-6′-1), 4.49 (dd, J = 11.9, 4.9 Hz, 1H, H-6′-2), 4.33 (m, 1H, H-5′), 3.13 (dd, J = 11.9, 4.6 Hz, 1H, H-3), 2.91 (dd, J = 14.3, 3.7 Hz, 1H, H-18), 1.09, 0.93, 0.90, 0.83, 0.69, 0.67, 0.53 (s each, 3H each, CH_3 × 7); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 176.9 (C-28), 166.1, 165.9, 165.7, 165.3, 143.5 (C-13), 136.9, 136.1, 133.6, 133.1, 132.9, 130.1, 130.0, 129.9, 129.8, 129.5, 129.1, 128.9, 128.3, 128.2, 127.6, 126.8, 122.7 (C-12), 104.3 (C-1′), 89.7 (C-3), 73.9, 72.1, 71.3, 69.5, 67.6, 65.3, 57.3, 56.1, 47.9, 46.9, 45.9, 41.7, 39.9, 38.7, 38.3, 37.1, 36.3, 34.1, 32.7, 31.7, 30.6, 29.7, 27.9, 25.7, 25.4, 23.8, 17.3, 16.4, 15.3; HRMALDIMS: *m/z* calcd for $C_{79}H_{87}NO_{13}Na$ [M+Na$^+$] 1280.6070; found: 1280.6053.

*4.1.5.3. Benzyl oleanate 3-O-6-(2′-O-benzyl-phthalimido)-2,3,4-tri-O-benzoyl-6-deoxy-α-D-mannopyr-anoside (**18b**).* Yield: 89%; $[\alpha]_D^{27}$ + 10.3 (c 0.85, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.27–8.07 (m, 29H, Ph-H), 6.69 (m, 1H, NHCO), 5.87 (dd, J = 9.9, 3.6 Hz, 1H, H-3′), 5.81 (dd, J = 3.6, 1.9 Hz, 1H, H-2′), 5.69 (t, J = 9.9 Hz, 1H, H-4′), 5.39 (m, 2H, PhCH_2), 5.29 (t, J = 3.7 Hz, 1H, H-12), 5.13 (dd, J = 29.7, 12.5 Hz, 2H, PhCH_2), 4.93 (d, J = 1.9 Hz, 1H, H-1′), 4.63 (dd, J = 12.1, 5.6 Hz, 1H, H-6′-1), 4.41 (dd, J = 12.1, 3.9 Hz, 1H, H-6′-2), 4.30 (m, 1H, H-5′), 3.10 (dd, J = 12.1, 4.3 Hz, 1H, H-3), 2.89 (dd, J = 13.7, 3.7 Hz, 1H, H-18), 1.07, 0.93, 0.90, 0.81, 0.69, 0.65, 0.51 (s each, 3H each, CH_3 × 7); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 177.1 (C-28), 166.3, 165.9, 165.5, 165.1, 143.3 (C-13), 136.3, 136.1, 133.6, 133.3, 132.9, 130.1, 130.0, 129.9, 129.7, 129.5, 129.1, 128.9, 128.3, 128.2, 127.3, 126.1, 122.5 (C-12), 94.3 (C-1′), 88.9 (C-3), 74.5, 72.3, 70.7, 69.3, 67.7, 65.9, 57.8, 56.1, 47.8, 46.9, 45.9, 41.7, 39.3, 38.7, 37.9, 37.1, 36.3, 34.1, 32.7, 31.7, 30.5, 29.7, 27.8, 25.7, 25.3, 23.8, 17.1, 16.3, 15.1; HRMALDIMS: *m/z* calcd for $C_{79}H_{87}NO_{13}Na$ [M+Na$^+$] 1280.6073; found: 1280.6087.

4.1.6. Typical procedure for the synthesis of compounds **8**, **19** and **20**

A solution of compound **7** (or **17**–**18**) (700 mg, 0.84 mmol) in dry CH_2Cl_2 (20 mL) was treated with 33% HBr in HOAc (0.56 mL), and the mixture was stirred at room temperature for 6 h, then concentrated. The residue was purified by a silica gel column chromatography (5:1, petroleum ether-EtOAc) to afford the product **8** (or **19**–**20**) as a white solid;

*4.1.6.1. 6-(2′-O-Benzyl-phthalimido)-2,3,4-tri-O-benzoyl-6-deoxy-α-D-glucopyranosyl bromide (**8**).* Yield: 71%; $[\alpha]_D^{27}$ + 6.70 (c 0.45, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz): δ 7.23–8.01 (m, 24H, Ph-H), 6.85 (d, *J* = 3.7 Hz, 1H, H-1), 6.69 (m, 1H, NHCO), 6.41 (t, *J* = 9.6 Hz, 1H, H-3), 5.70 (t, *J* = 9.6 Hz, 1H, H-4), 5.65 (dd, *J* = 9.6, 3.7 Hz, 1H, H-2), 5.61 (m, 2H, PhCH$_2$), 4.24 (m, 1H, H-5), 3.87 (dd, *J* = 12.8, 4.7 Hz, 1H, H-6–1), 3.71 (dd, *J* = 12.8, 2.9 Hz, 1H, H-6–2); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 166.3, 165.9, 165.3, 164.5, 136.7, 135.3, 133.9, 133.5, 133.1, 132.3, 131.7, 131.3, 130.3, 130.0, 129.9, 129.6, 128.5, 128.3, 128.1, 125.7, 90.1 (C-1), 73.6, 72.1, 71.7, 69.3, 51.5; HRESIMS: *m/z* calcd for $C_{42}H_{34}NO_{10}BrNa$ [M+Na$^+$] 814.1258; found: 814.1273.

*4.1.6.2. 6-(2′-O-Benzyl-phthalimido)-2,3,4-tri-O-benzoyl-6-deoxy-α-D-galactopyranosyl bromide (**19**).* Yield: 75%; $[\alpha]_D^{27}$ + 21.7 (c 0.53, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz): δ 7.27–8.00 (m, 24H, Ph-H), 6.69 (m, 1H, NHCO), 6.37 (d, *J* = 3.5 Hz, 1H, H-1), 6.11 (dd, *J* = 9.3, 3.7 Hz, 1 H, H-3), 5.65 (t, *J* = 3.6 Hz, 1 H, H-4), 5.63 (m, 2H, PhCH$_2$), 5.59 (dd, *J* = 9.3, 3.5 Hz, 1H, H-2), 4.27 (m, 1H, H-5), 3.80 (dd, *J* = 12.3, 4.7 Hz, 1H, H-6-1), 3.69 (dd, *J* = 12.3, 3.1 Hz, 1H, H-6-2); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 166.6, 165.9, 164.8, 164.5, 136.7, 135.0, 133.9, 133.5, 132.9, 132.3, 131.7, 131.1, 130.3, 130.0, 129.9, 129.3, 128.5, 128.3, 127.9, 125.6, 89.8 (C-1), 74.1, 72.0, 69.9, 69.3, 50.3; HRESIMS: *m/z* calcd for $C_{42}H_{34}NO_{10}BrNa$ [M+Na$^+$] 814.1258; found: 814.1241.

*4.1.6.3. 6-(2′-O-Benzyl-phthalimido)-2,3,4-tri-O-benzoyl-6-deoxy-α-D-mannopyranosyl bromide (**20**).* Yield: 69%; $[\alpha]_D^{27}$ + 10.2 (c 0.31, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz): δ 7.21–7.99 (m, 24H, Ph-H), 6.71 (s, 1H, H-1), 6.63 (m, 1H, NHCO), 6.29 (dd, *J* = 9.6, 3.3 Hz, 1 H, H-3), 6.03 (s, 1 H, H-2), 5.68 (t, *J* = 9.6 Hz, 1H, H-4), 5.63 (m, 2H, PhCH$_2$), 4.27 (m, 1H, H-5), 3.67 (dd, *J* = 11.9, 5.1 Hz, 1H, H-6-1), 3.52 (dd, *J* = 11.9, 3.1 Hz, 1H, H-6-2); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 165.9, 165.7, 165.1, 164.5, 136.7, 135.3, 133.9, 133.7, 133.1, 132.7, 131.7, 131.3, 130.3, 129.9, 129.6, 129.1, 128.5, 128.3, 128.1, 126.0, 90.9 (C-1), 74.9, 72.3, 70.3, 68.9, 52.1; HRESIMS: *m/z* calcd for $C_{42}H_{34}NO_{10}BrNa$ [M+Na$^+$] 814.1258; found: 814.1281.

*4.1.7. Typical procedure for the synthesis of compounds **10**, **19a** and **20a***

To a solution of oleanolic acid (240 mg, 0.53 mmol) and bromide **8** (or **19**–**20**) (544 mg, 0.68 mmol) in CH_2Cl_2 (8 mL) were added K_2CO_3 (187 mg, 1.33 mmol), water (5.0 mL), and Bu_4NBr (69 mg, 0.21 mmol). The resulting mixture was refluxed for 6 h, and then diluted with CH_2Cl_2. The organic phase, after being washed with water and brine, was dried with Na_2SO_4, and then concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (6:1 to 4:1, petroleum ether-EtOAc) to afford the product **10** (or **19a**–**20a**) as a white solid.

*4.1.7.1. 6-(2′-O-Benzyl-phthalimido)-2,3,4-tri-O-benzoyl-6-deoxy-β-D-glucopyranosyl oleanate (**10**).* Yield: 86%; $[\alpha]_D^{27}$ + 43.7 (c 0.85, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz): δ 7.28–8.04 (m, 24H, Ph-H), 6.63 (m, 1H, NHCO), 6.07 (t, *J* = 9.6 Hz, 1H, H-3′), 5.97 (d, *J* = 8.0 Hz, 1H, H-1′), 5.76 (t, *J* = 9.6 Hz, 1H, H-4′), 5.69 (dd, *J* = 9.6, 8.0 Hz, 1H, H-2′), 5.59 (m, 2H, PhCH$_2$), 5.28 (t, *J* = 3.2 Hz, 1H, H-12), 4.51 (dd, *J* = 12.0, 4.5 Hz, 1H, H-6′-1), 4.37 (dd, *J* = 12.0, 2.3 Hz, 1H, H-6′-2), 4.28 (m, 1H, H-5′), 3.20 (dd, *J* = 11.5, 3.8 Hz, 1H, H-3), 2.80 (dd, *J* = 14.1, 3.7 Hz, 1H, H-18), 0.97, 0.95, 0.87, 0.83, 0.78, 0.74, 0.47 (s each, 3H each, CH_3 × 7); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 175.6 (C-28), 165.9, 165.6, 165.2, 164.6, 143.0 (C-13), 133.3, 133.1, 133.0, 132.9, 130.1, 130.0, 129.9, 129.8, 129.7, 129.5, 129.3, 128.9, 128.3, 128.2, 128.0, 122.7 (C-12), 91.9 (C-1′), 89.7 (C-3), 74.9, 73.5, 71.9, 69.3, 65.7, 52.9, 47.9, 46.8, 45.7, 41.6, 40.7, 38.9, 38.5, 38.1, 36.3, 33.9, 32.7, 31.8, 30.6, 29.7, 27.9, 25.7, 25.4, 23.4, 17.0, 16.4, 15.3; HRESIMS: *m/z* calcd for $C_{72}H_{81}NO_{13}Na$ [M+Na$^+$] 1190.5601; found: 1190.5619.

*4.1.7.2. 6-(2′-O-Benzyl-phthalimido)-2,3,4-tri-O-benzoyl-6-deoxy-β-D-galactopyranosyl oleanate (**19a**).* Yield: 82%; $[\alpha]_D^{27}$ + 56.1 (c 0.36, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz): δ 7.19–8.05 (m, 24H, Ph-H), 6.59 (m, 1H, NHCO), 6.01 (dd, *J* = 9.6, 3.6 Hz, 1H, H-3′), 5.93 (d, *J* = 7.9 Hz, 1H, H-1′), 5.75 (dd, *J* = 9.6, 7.9 Hz, 1H, H-2′), 5.63 (m, 2H, PhCH$_2$), 5.59 (t, *J* = 3.6 Hz, 1H, H-4′), 5.31 (t, *J* = 3.3 Hz, 1H, H-12), 4.53 (dd, *J* = 11.9, 4.3 Hz, 1H, H-6′-1), 4.29–4.33 (m, 2H, H-5′, H-6′-2), 3.17 (dd, *J* = 12.1, 3.7 Hz, 1H, H-3), 2.78 (dd, *J* = 13.7, 4.1 Hz, 1H, H-18), 0.99, 0.93, 0.87, 0.81, 0.76, 0.73, 0.51 (s each, 3H each, CH_3 × 7); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 175.9 (C-28), 166.0, 165.7, 165.3, 164.6, 143.5 (C-13), 133.5, 133.3, 133.0, 132.9, 130.1, 130.0, 129.9, 129.8, 129.7, 129.5, 129.3, 128.7, 128.3, 128.1, 127.9, 122.5 (C-12), 92.7 (C-1′), 89.9 (C-3), 75.1, 73.3, 70.6, 69.7, 65.3, 52.7, 47.9, 46.8, 45.3, 42.3, 40.7, 38.7, 38.5, 37.9, 36.3, 33.9, 32.7, 31.8, 30.6, 29.7, 27.9, 25.7, 25.6, 23.4, 17.1, 16.5, 14.9; HRESIMS: *m/z* calcd for $C_{72}H_{81}NO_{13}Na$ [M+Na$^+$] 1190.5601; found: 1190.5590.

*4.1.7.3. 6-(2′-O-Benzyl-phthalimido)-2,3,4-tri-O-benzoyl-6-deoxy-β-D-mannopyranosyl oleanate (**20a**).* Yield: 79%; $[\alpha]_D^{27}$ + 61.3 (c 0.41, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz): δ 7.27–8.00 (m, 24H, Ph-H), 6.66 (m, 1H, NHCO), 6.13 (dd, *J* = 9.3, 3.3 Hz, 1H, H-3′), 5.87 (s, 1H, H-1′), 5.79 (t, *J* = 9.3 Hz, 1H, H-4′), 5.63 (br s, 1H, H-2′), 5.59 (m, 2H, PhCH$_2$), 5.23 (t, *J* = 3.6 Hz, 1H, H-12), 4.57 (dd, *J* = 12.3, 4.1 Hz, 1H, H-6′-1), 4.37 (dd, *J* = 12.3, 2.9 Hz, 1H, H-6′-2), 4.31 (m, 1H, H-5′), 3.19 (dd, *J* = 12.3, 3.7 Hz, 1H, H-3), 2.78 (dd, *J* = 13.7, 3.7 Hz, 1H, H-18), 1.00, 0.95, 0.87, 0.81, 0.78, 0.73, 0.49 (s each, 3H each, CH_3 × 7); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 175.3 (C-28), 165.9, 165.3, 165.1, 164.3, 143.1 (C-13), 133.6, 133.3, 133.0, 132.9, 130.1, 130.0, 129.9, 129.7, 129.5, 129.1, 128.7, 128.3, 128.2, 127.8, 122.3 (C-12), 94.3 (C-1′), 90.1 (C-3), 76.1, 72.9, 71.5, 69.3, 66.1, 52.9, 47.9, 46.7, 45.7, 42.3, 40.7, 38.9, 38.4, 38.1, 36.5, 33.9, 32.7, 31.9, 30.6, 29.7, 27.9, 25.7, 25.3, 23.4, 17.1, 16.5, 15.9; HRESIMS: *m/z* calcd for $C_{72}H_{81}NO_{13}Na$ [M+Na$^+$] 1190.5601; found: 1190.5627.

*4.1.8. Typical procedure for the synthesis of compounds **12a**–**12j***

A mixture of compound **10** (100 mg, 0.086 mmol), trichloroacetimidates **11a**–**11j** (0.10 mmol, 1.2 equiv.) and powdered 4 Å molecular sieves in dry CH_2Cl_2 (5 mL) were stirred for 30 min at room temperature and then cooled to −30 °C. TMSOTf (5 μL, 0.03 mmol, 0.3 equiv.) was added. After being stirred at −30 °C for 30 min, the reaction mixture was warmed up to room temperature for 1 h. The reaction was quenched by addition of Et_3N and then filtered. The filtrate was concentrated and purified by a silica gel column chromatography (petroleum ether-EtOAc) to afford the products **12a**–**12j**.

*4.1.8.1. 28-O-6-(2′-O-Benzyl-phthalimido)-2,3,4-tri-O-benzoyl-6-deoxy-β-D-glucopyranosyl oleanate 3-O-2,3,4,6-tetra-O-benzoyl-β-D-glucopyranoside (**12a**).* Yield: 88%; $[\alpha]_D^{23}$ + 40.3 (c 0.87, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz): δ 7.09–8.03 (m, 44H, Ph-H), 6.59 (m, 1H, NHCO), 5.99 (t, *J* = 9.7 Hz, 1H, H-3″), 5.95 (d, *J* = 8.1 Hz, 1H, H-1″), 5.79 (t, *J* = 9.6 Hz, 1H, H-3′), 5.75 (t, *J* = 9.7 Hz, 1H, H-4″), 5.69 (t, *J* = 9.6 Hz, 1H, H-4′), 5.65 (dd, *J* = 9.7, 8.1 Hz, 1H, H-2″), 5.62 (t, *J* = 9.6 Hz, 1H, H-4′), 5.59 (m, 2H, PhCH$_2$), 5.55 (dd, *J* = 9.6, 7.9 Hz, 1H, H-2′), 5.41 (d, *J* = 7.9 Hz, 1H, H-1′), 5.30 (t, *J* = 3.7 Hz, 1H, H-12), 4.67 (dd, *J* = 12.3, 3.2 Hz, 1H, H-6′-1), 4.53 (dd, *J* = 12.3, 5.6 Hz, 1H, H-6′-2), 4.49 (dd, *J* = 11.9, 2.8 Hz, 1H, H-6″-1), 4.39 (dd, *J* = 11.9, 5.3 Hz, 1H, H-6″-2), 4.35 (d, *J* = 11.3 Hz, 1H, H-23–1), 4.27 (m, 1H, H-5″), 4.19 (m, 1H, H-5′), 3.23 (dd, *J* = 11.7, 3.7 Hz, 1H, H-3), 2.79 (dd, *J* = 13.7, 4.3 Hz, 1H, H-18), 0.93, 0.89, 0.81, 0.75, 0.71, 0.65, 0.51 (s each, 3H each, CH_3 × 7); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 175.4 (C-28), 165.9, 165.7, 165.5, 165.3, 165.2, 165.1, 164.7, 163.9, 143.3 (C-13), 138.3, 138.1, 137.9, 137.8, 137.6, 136.5, 136.3, 136.1, 135.9, 133.7, 133.4, 133.2, 133.1, 132.9, 129.7, 129.6, 128.7, 128.3, 128.1, 122.5 (C-12), 101.9 (C-1′), 91.7 (C-1″), 90.3 (C-3), 78.9, 76.5, 73.3, 72.9, 71.9, 70.1,

68.8, 66.9, 66.2, 65.8, 62.5, 55.7, 52.9, 47.8, 46.7, 41.9, 39.3, 36.7, 33.3, 31.8, 27.9, 26.7, 25.6, 24.7, 17.9, 16.4, 15.1; HRMALDIMS: *m/z* calcd for $C_{106}H_{107}O_{22}NNa$ [M + Na^+] 1768.7179; found: 1768.7191.

*4.1.8.2. 28-O-6-(2′-O-Benzyl-phthalimido)-2,3,4-tri-O-benzoyl-6-deoxy-β-D-glucopyranosyl oleanate 3-O-2,3,4,6-tetra-O-benzoyl-α-D-mannopyranoside (**12b**).* Yield: 86%; $[\alpha]_D^{23}$ − 8.76 (c 0.73, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz): δ 7.11–8.02 (m, 44H, Ph-H), 6.61 (m, 1H, NHCO), 5.97 (t, *J* = 9.6 Hz, 1H, H-3″), 5.89 (d, *J* = 7.9 Hz, 1H, H-1″), 5.80 (t, *J* = 9.6 Hz, 1H, H-4′), 5.75 (dd, *J* = 9.6, 3.2 Hz, 1H, H-3′), 5.71 (t, *J* = 9.6 Hz, 1H, H-4″), 5.65 (dd, *J* = 9.6, 8.0 Hz, 1H, H-2″), 5.55 (m, 2H, PhCH_2), 5.50 (dd, *J* = 3.2, 2.0 Hz, 1H, H-2′), 5.38 (d, *J* = 2.0 Hz, 1H, H-1′), 5.23 (br s, 1H, H-12), 4.53–4.60 (m, 3H, H-5′, H-6′-1, H-6″-1), 4.49 (dd, *J* = 12.1, 3.7 Hz, 1H, H-6′-2), 4.29–4.32 (m, 2H, H-5″, H-6″-2), 3.21 (dd, *J* = 13.7, 3.7 Hz, 1H, H-3), 2.78 (dd, *J* = 14.1, 3.7 Hz, 1H, H-18), 0.95, 0.91, 0.84, 0.75, 0.70, 0.67, 0.53 (s each, 3H each, CH_3 × 7); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 175.3 (C-28), 165.9, 165.8, 165.5, 165.4, 165.1, 165.0, 164.9, 163.5, 143.1 (C-13), 138.5, 138.3, 138.0, 137.7, 137.5, 136.7, 136.3, 136.1, 135.8, 133.5, 133.3, 133.1, 132.9, 132.7, 129.9, 129.7, 128.9, 128.3, 127.9, 122.3 (C-12), 95.7 (C-1′), 91.9 (C-1″), 89.5 (C-3), 78.1, 75.1, 73.3, 72.5, 71.6, 70.0, 68.5, 66.3, 66.1, 65.8, 60.9, 55.3, 52.7, 47.9, 45.7, 42.1, 39.3, 36.7, 33.5, 31.8, 27.8, 26.7, 25.6, 24.9, 17.9, 16.4, 15.1; HRMALDIMS: *m/z* calcd for $C_{106}H_{107}O_{22}NNa$ [M+Na^+] 1768.7179; found: 1768.7168.

*4.1.8.3. 28-O-6-(2′-O-benzyl-phthalimido)-2,3,4-tri-O-benzoyl-6-deoxy-β-D-glucopyranosyl oleanate 3-O-2,3,4,6-tetra-O-benzoyl-β-D-galactopyranoside (**12c**).* Yield: 87%; $[\alpha]_D^{23}$ + 27.9 (c 0.87, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz): δ 7.13–8.01 (m, 44H, Ph-H), 6.63 (m, 1H, NHCO), 5.97 (t, *J* = 9.6 Hz, 1H, H-3″), 5.86 (d, *J* = 8.1 Hz, 1H, H-1″), 5.69 (t, *J* = 9.6 Hz, 1H, H-4″), 5.65 (dd, *J* = 9.6, 8.1 Hz, 1H, H-2″), 5.63 (dd, *J* = 9.3, 3.6 Hz, 1H, H-3′), 5.56 (t, *J* = 3.6 Hz, 1H, H-4′), 5.53 (m, 2H, PhCH_2), 5.46 (dd, *J* = 9.3, 7.9 Hz, 1H, H-2′), 5.24 (br s, 1H, H-12), 5.21 (d, *J* = 7.9 Hz, 1H, H-1′), 4.56–4.65 (m, 3H, H-5′, H-6′-1, H-6″-1), 4.23–4.29 (m, 2H, H-6′-2, H-6″-2), 4.17 (m, 1H, H-5″), 3.19 (dd, *J* = 14.3, 3.6 Hz, 1H, H-3), 2.79 (dd, *J* = 13.7, 4.1 Hz, 1H, H-18), 0.99, 0.91, 0.86, 0.77, 0.70, 0.63, 0.51 (s each, 3H each, CH_3 × 7); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 175.3 (C-28), 165.9, 165.5, 165.4, 165.3, 165.1, 164.9, 164.7, 163.1, 143.5 (C-13), 138.5, 137.9, 137.7, 137.5, 137.1, 136.9, 136.0, 135.9, 135.8, 133.7, 133.3, 133.1, 132.9, 132.8, 129.9, 129.6, 128.9, 128.5, 128.1, 122.5 (C-12), 97.6 (C-1′), 91.9 (C-1″), 89.9 (C-3), 78.1, 77.3, 76.6, 74.9, 73.6, 72.5, 70.0, 69.1, 68.3, 66.3, 65.8, 60.9, 55.3, 52.9, 47.9, 45.7, 42.3, 39.3, 36.7, 33.5, 31.9, 27.8, 26.7, 25.7, 24.9, 17.9, 16.4, 15.3; HRMALDIMS: *m/z* calcd for $C_{106}H_{107}O_{22}NNa$ [M+Na^+] 1768.7179; found: 1768.7193.

*4.1.8.4. 28-O-6-(2′-O-benzyl-phthalimido)-2,3,4-tri-O-benzoyl-6-deoxy-β-D-glucopyranosyl oleanate 3-O-2,3,4,6-tetra-O-benzoyl-β-D-xylopyranoside (**12d**).* Yield: 81%; $[\alpha]_D^{23}$ + 37.1 (c 1.01, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz): δ 7.33–8.03 (m, 39H, Ph-H), 6.59 (m, 1H, NHCO), 5.97 (t, *J* = 9.6 Hz, 1H, H-3″), 5.91 (d, *J* = 8.3 Hz, 1H, H-1″), 5.77 (t, *J* = 8.6 Hz, 1H, H-3′), 5.72 (t, *J* = 9.6 Hz, 1H, H-4″), 5.69 (dd, *J* = 9.6, 8.3 Hz, 1H, H-2″), 5.50 (m, 2H, PhCH_2), 5.46 (dd, *J* = 8.6, 6.4 Hz, 1H, H-2′), 5.32 (m, 1H, H-4′), 5.27 (t, *J* = 3.6 Hz, 1H, H-12), 4.82 (d, *J* = 6.4 Hz, 1H, H-1′), 4.55 (dd, *J* = 11.9, 5.1 Hz, 1H, H-6″-1), 4.46 (dd, *J* = 11.9, 2.9 Hz, 1H, H-6″-2), 4.41 (dd, *J* = 11.9, 4.7 Hz, 1H, H-5′-1), 4.23–4.26 (m, 1H, H-5″), 3.65 (dd, *J* = 11.9, 6.9 Hz, 1H, H-5′-2), 3.13 (dd, *J* = 12.3, 4.1 Hz, 1H, H-3), 2.79 (dd, *J* = 13.3, 3.6 Hz, 1H, H-18), 0.95, 0.87, 0.83, 0.75, 0.72, 0.63, 0.47 (s each, 3H each, CH_3 × 7); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 175.1 (C-28), 165.9, 165.7, 165.5, 165.4, 164.7, 164.0, 163.3, 143.7 (C-13), 138.9, 137.9, 137.5, 137.3, 136.9, 136.3, 135.9, 133.7, 133.1, 132.9, 132.8, 129.8, 128.9, 128.5, 127.9, 122.3 (C-12), 102.3 (C-1′), 92.1 (C-1″), 89.9 (C-3), 78.3, 76.5, 74.3, 73.6, 70.0, 69.3, 68.1, 65.7, 60.9, 55.1, 52.7, 47.9, 45.5, 42.3, 39.1, 36.7, 33.3, 31.9, 27.9, 26.7, 25.7, 24.7, 17.9, 16.4, 15.1; HRMALDIMS: *m/z* calcd for $C_{98}H_{101}O_{20}NNa$ [M+Na^+] 1634.6809; found: 1634.6821.

*4.1.8.5. 28-O-6-(2′-O-Benzyl-phthalimido)-2,3,4-tri-O-benzoyl-6-deoxy-β-D-glucopyranosyl oleanate 3-O-2,3,4,6-tetra-Obenzoyl-α-L-arabinopyranoside (**12e**).* Yield: 86%; $[\alpha]_D^{23}$ + 29.3 (c 0.97, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz): δ 7.31–8.05 (m, 39H, Ph-H), 6.57 (m, 1H, NHCO), 5.95 (t, *J* = 9.5 Hz, 1H, H-3″), 5.89 (d, *J* = 8.5 Hz, 1H, H-1″), 5.78 (dd, *J* = 8.6, 3.7 Hz, 1H, H-3′), 5.75 (t, *J* = 9.5 Hz, 1H, H-4″), 5.68 (dd, *J* = 9.5, 8.5 Hz, 1H, H-2″), 5.63 (dd, *J* = 8.6, 6.5 Hz, 1H, H-2′), 5.53 (m, 2H, PhCH_2), 5.45 (m, 1H, H-4′), 5.26 (t, *J* = 3.4 Hz, 1H, H-12), 4.77 (d, *J* = 6.5 Hz, 1H, H-1′), 4.47–4.53 (m, 2H, H-6″-1, H-6″-2), 4.31–4.39 (m, 3H, H-5′-1, H-5′-2, H-5″), 3.19 (dd, *J* = 14.3, 3.7 Hz, 1H, H-3), 2.81 (dd, *J* = 13.9, 3.7 Hz, 1H, H-18), 0.93, 0.87, 0.81, 0.75, 0.71, 0.65, 0.50 (s each, 3H each, CH_3 × 7); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 175.6 (C-28), 165.8, 165.7, 165.4, 164.1, 163.7, 163.5, 143.3 (C-13), 138.9, 137.9, 137.7, 137.5, 137.3, 136.8, 136.3, 135.7, 133.6, 133.2, 132.9, 132.5, 129.8, 128.6, 128.5, 127.5, 122.5 (C-12), 103.6 (C-1′), 92.3 (C-1″), 89.3 (C-3), 78.1, 76.7, 74.3, 71.1, 70.2, 69.3, 66.3, 65.7, 61.9, 56.1, 52.7, 47.9, 45.5, 42.3, 39.1, 36.7, 33.5, 31.9, 27.9, 26.7, 25.6, 24.7, 17.9, 16.3, 15.1; HRMALDIMS: *m/z* calcd for $C_{98}H_{101}O_{20}NNa$ [M+Na^+] 1634.6809; found: 1634.6798.

*4.1.8.6. 28-O-6-(2′-O-Benzyl-phthalimido)-2,3,4-tri-O-benzoyl-6-deoxy-β-D-glucopyranosyl oleanate 3-O-2,3,4,6-tetra-O-benzoyl-α-L-rhamnopyranoside (**12f**).* Yield: 83%; $[\alpha]_D^{23}$ + 14.7 (c 0.65, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz): δ 7.23–8.07 (m, 39H, Ph-H), 6.60 (m, 1H, NHCO), 5.95 (t, *J* = 9.7 Hz, 1H, H-3″), 5.91 (d, *J* = 8.3 Hz, 1H, H-1″), 5.81 (dd, *J* = 9.7, 3.3 Hz, 1H, H-3′), 5.69–5.75 (m, 3H, H-2′, H-4′, H-4″), 5.63 (dd, *J* = 9.7, 8.3 Hz, 1H, H-2″), 5.51 (m, 2H, PhCH_2), 5.27 (t, *J* = 3.7 Hz, 1H, H-12), 5.01 (d, *J* = 1.3 Hz, 1H, H-1′), 4.47–4.51 (m, 2H, H-5′, H-6″-1), 4.39 (dd, *J* = 12.1, 5.1 Hz, 1H, H-6″-2), 4.21 (m, 1H, H-5″), 3.97 (m, 1H, H-5′), 3.21 (dd, *J* = 13.7, 3.7 Hz, 1H, H-3), 2.83 (dd, *J* = 13.7, 3.9 Hz, 1H, H-18), 1.36 (d, *J* = 5.9 Hz, 3H, H-6′), 0.97, 0.86, 0.80, 0.73, 0.71, 0.65, 0.51 (s each, 3H each, CH_3 × 7); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 175.9 (C-28), 166.0, 165.9, 165.4, 164.1, 163.9, 163.5, 143.3 (C-13), 138.9, 137.9, 137.6, 137.5, 137.1, 136.8, 136.3, 135.9, 133.6, 133.2, 132.9, 132.3, 129.8, 128.6, 128.3, 127.5, 122.6 (C-12), 98.3 (C-1′), 92.0 (C-1″), 88.9 (C-3), 78.1, 76.7, 72.7, 71.6, 70.2, 69.3, 66.5, 65.9, 63.1, 56.7, 52.3, 48.1, 45.5, 42.3, 39.1, 36.7, 33.7, 31.9, 27.9, 26.9, 25.6, 24.9, 23.8, 17.9, 16.3, 15.1; HRMALDIMS: *m/z* calcd for $C_{99}H_{103}O_{20}NNa$ [M+Na^+] 1648.6966; found: 1648.6979.

*4.1.8.7. 28-O-6-(2′-O-Benzyl-phthalimido)-2,3,4-tri-O-benzoyl-6-deoxy-β-D-glucopyranosyl oleanate 3-O-2,3,4,6-tetra-O-benzoyl-α-L-fucopyranoside (**12g**).* Yield: 85%; $[\alpha]_D^{23}$ − 31.7 (c 0.73, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz): δ 7.27–8.11 (m, 39H, Ph-H), 6.55 (m, 1H, NHCO), 5.91 (t, *J* = 9.7 Hz, 1H, H-3″), 5.87 (d, *J* = 8.1 Hz, 1H, H-1″), 5.63–5.67 (m, 3H, H-2′, H-4′, H-4″), 5.63 (dd, *J* = 9.7, 8.3 Hz, 1H, H-2″), 5.57 (dd, *J* = 9.9, 3.6 Hz, 1H, H-3′), 5.49 (m, 2H, PhCH_2), 5.30 (t, *J* = 3.3 Hz, 1H, H-12), 4.79 (d, *J* = 7.6 Hz, 1H, H-1′), 4.48 (dd, *J* = 11.9, 3.4 Hz, 1H, H-6″-1), 4.37 (dd, *J* = 11.9, 5.5 Hz, 1H, H-6″-2), 4.27 (m, 1H, H-5″), 4.03 (m, 1H, H-5′), 3.27 (dd, *J* = 13.7, 4.4 Hz, 1H, H-3), 2.70 (dd, *J* = 14.3, 3.9 Hz, 1H, H-18), 1.27 (d, *J* = 6.4 Hz, 3H, H-6′), 0.99, 0.90, 0.81, 0.73, 0.69, 0.65, 0.51 (s each, 3H each, CH_3 × 7); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 175.5 (C-28), 166.1, 165.7, 165.5, 164.1, 163.8, 163.5, 143.7 (C-13), 138.9, 137.9, 137.7, 137.5, 137.0, 136.8, 136.3, 135.9, 133.7, 133.2, 132.9, 132.7, 129.8, 128.7, 128.3, 128.0, 122.8 (C-12), 98.9 (C-1′), 92.3 (C-1″), 88.7 (C-3), 77.9, 76.3, 71.9, 71.0, 69.1, 66.5, 65.9, 65.3, 63.1, 55.7, 52.1, 48.1, 45.5, 42.5, 39.1, 36.7, 33.9, 31.9, 27.9, 26.7, 25.6, 24.9, 23.9, 17.9, 16.1, 15.3; HRMALDIMS: *m/z* calcd for $C_{99}H_{103}O_{20}NNa$ [M+Na^+] 1648.6966; found: 1648.6951.

*4.1.8.8. 28-O-6-(2′-O-Benzyl-phthalimido)-2,3,4-tri-O-benzoyl-6-deoxy-β-D-glucopyranosyl oleanate 3-O-2,3,6,2′,3′,4′,6′-hepta-O-benzoyl-β-D-lactopyranoside (**12h**).* Yield: 89%; $[\alpha]_D^{23}$ + 71.3 (c 1.12,

$CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz): δ 7.12–8.01 (m, 59H, Ph-H), 6.51 (m, 1H, NHCO), 5.87 (t, J = 9.6 Hz, 1H, H-3″), 5.81 (t, J = 9.4 Hz, 1H, H-3′), 5.76 (d, J = 7.8 Hz, 1H, H-1″), 5.73 (t, J = 9.9 Hz, 1H, H-3″), 5.70 (t, J = 9.9 Hz, 1H, H-4″), 5.63–5.67 (m, 2H, H-2″, H-4″), 5.51–5.54 (m, 3H, H-2″, PhCH_2), 5.38 (dd, J = 12.1, 3.6 Hz, 1H, H-6′-1), 5.32 (t, J = 3.7 Hz, 1H, H-12), 4.91 (d, J = 7.9 Hz, 1H, H-1‴), 4.75 (d, J = 8.0 Hz, 1H, H-1′), 4.51–4.55 (m, 2H, H-6′-2, H-6″-1), 4.49 (dd, J = 11.9, 5.3 Hz, 1H, H-6″-1), 4.23–4.31 (m, 4H, H-4′, H-5‴, H-6″-2, H-6‴-2), 3.99 (dd, J = 9.4, 8.0 Hz, 1H, H-2′), 3.87–3.97 (m, 2H, H-5′, H-5″), 3.15 (dd, J = 12.1, 4.3 Hz, 1H, H-3), 2.72 (dd, J = 14.3, 3.7 Hz, 1H, H-18), 1.01, 0.90, 0.81, 0.73, 0.69, 0.65, 0.55 (s each, 3H each, CH_3 × 7); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 175.7 (C-28), 166.0, 165.9, 165.8, 165.5, 165.3, 164.9, 164.5, 163.7, 143.9 (C-13), 138.9, 137.9, 137.5, 136.9, 136.7, 135.9, 133.8, 133.6, 133.2, 132.9, 132.3, 130.2, 130.0, 129.8, 128.9, 128.7, 128. 5, 122.7 (C-12), 103.6 (C-1′), 101.0 (C-1‴), 91.3 (C-1‴), 90.3 (C-3), 78.1, 75.3, 73.1, 72.9, 71.6, 71.3, 70.2, 69.1, 67.8, 66.0, 65.9, 64.5, 63.1, 61.4, 56.7, 51.7, 48.1, 45.5, 42.3, 39.5, 36.7, 34.3, 34.1, 33.2, 32.7, 27.9, 26.9, 25.6, 24.9, 23.8, 18.5, 17.9, 16.3, 15.4; HRMALDIMS: m/z calcd for $C_{133}H_{129}O_{30}NNa$ [M+Na^+] 2242.8492; found: 2242.8501.

*4.1.8.9. 28-O-6-(2′-O-Benzyl-phthalimido)-2,3,4-tri-O-benzoyl-6-deoxy-β-D-glucopyranosyl oleanate 3-O-2,3,6,2′,3′,4′,6′-hepta-O-benzoyl-β-D-cellopyranoside (**12i**).* Yield: 81%; $[\alpha]_D^{23}$ + 46.7 (c 0.91, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz): δ 7.15–8.02 (m, 59H, Ph-H), 6.47 (m, 1H, NHCO), 5.89 (t, J = 9.9 Hz, 1H, H-3‴), 5.79 (t, J = 9.6 Hz, 1H, H-3′), 5.73 (t, J = 9.9 Hz, 1H, H-3″), 5.70 (d, J = 8.1 Hz, 1H, H-1‴), 5.68 (t, J = 9.9 Hz, 1H, H-4‴), 5.65 (t, J = 9.9 Hz, 1H, H-4″), 5.70 (dd, J = 9.9, 8.1 Hz, 1H, H-2‴), 5.53 (m, 2H, PhCH_2), 5.49 (dd, J = 9.9, 7.8 Hz, 1H, H-2″), 5.31–5.35 (m, 2H, H-6′-1, H-12), 4.95 (d, J = 7.8 Hz, 1H, H-1″), 4.81 (d, J = 7.9 Hz, 1H, H-1′), 4.47–4.52 (m, 3H, H-6′-2, H-6‴-1, H-6‴-1), 4.17–4.23 (m, 4H, H-4′, H-5‴, H-6‴-2, H-6‴-2), 3.93–3.98 (m, 3H, H-2′, H-5′, H-5″), 3.09 (dd, J = 11.9, 3.7 Hz, 1H, H-3), 2.63 (dd, J = 14.3, 4.3 Hz, 1H, H-18), 0.99, 0.91, 0.83, 0.71, 0.69, 0.63, 0.49 (s each, 3H each, CH_3 × 7); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 175.5 (C-28), 166.3, 165.9, 165.7, 165.5, 165.3, 165.1, 164.3, 163.9, 143.5 (C-13), 138.9, 137.1, 137.0, 136.9, 136.5, 135.7, 133.8, 133.5, 133.1, 132.9, 132.5, 130.2, 130.0, 129.7, 128.9, 128.5, 128.1, 122.5 (C-12), 102.7 (C-1′), 100.1 (C-1″), 91.7 (C-1‴), 89.9 (C-3), 77.9, 74.9, 73.3, 72.7, 71.6, 71.3, 70.2, 68.9, 67.8, 66.3, 65.9, 63.5, 63.1, 61.8, 55.7, 51.7, 48.1, 45.5, 42.5, 39.5, 36.7, 34.9, 34.1, 33.2, 32.7, 27.9, 26.9, 25.6, 24.9, 23.9, 18.7, 17.9, 16.5, 15.3; HRMALDIMS: m/z calcd for $C_{133}H_{129}O_{30}NNa$ [M+Na^+] 2242.8492; found: 2242.8479.

*4.1.8.10. 28-O-6-(2′-O-Benzyl-phthalimido)-2,3,4-tri-O-benzoyl-6-deoxy-β-D-glucopyranosyl oleanate 3-O-2,3,4,2′,3′,4′,6′-hepta-O-benzoyl-β-D-gentiopyranoside (**12j**).* Yield: 83%; $[\alpha]_D^{23}$ + 59.3 (c 0.89, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz): δ 7.13–8.07 (m, 59H, Ph-H), 6.50 (m, 1H, NHCO), 5.93 (t, J = 10.1 Hz, 1H, H-3‴), 5.77 (t, J = 9.9 Hz, 1H, H-3′), 5.69 (t, J = 9.9 Hz, 1H, H-3″), 5.67 (t, J = 9.9 Hz, 1H, H-4″), 5.65 (t, J = 10.0 Hz, 1H, H-4‴), 5.62 (d, J = 8.3 Hz, 1H, H-1‴), 5.55–5.59 (m, 4H, H-2″, H-2‴, PhCH_2), 5.32 (t, J = 3.3 Hz, 1H, H-12), 5.07 (d, J = 7.9 Hz, 1H, H-1″), 4.79 (d, J = 7.9 Hz, 1H, H-1′), 4.53–4.57 (m, 4H, H-6′-1, H-6′-2, H-6″-1, H-6‴-1), 4.25–4.29 (m, 4H, H-2′, H-4′, H-6″-2, H-6‴-2), 4.03–4.07 (m, 3H, H-5‴, H-5′, H-5″), 3.06 (dd, J = 12.9, 4.3 Hz, 1H, H-3), 2.77 (dd, J = 13.7, 4.3 Hz, 1H, H-18), 0.97, 0.89, 0.83, 0.70, 0.69, 0.65, 0.53 (s each, 3H each, CH_3 × 7); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 175.3 (C-28), 165.9, 165.8, 165.7, 165.5, 165.3, 165.1, 164.7, 164.0, 143.9 (C-13), 139.0, 137.8, 137.3, 136.7, 136.5, 135.7, 133.9, 133.8, 133.6, 133.3, 132.9, 132.7, 132.5, 130.1, 130.0, 129.7, 128.9, 128.7, 127.9, 122.3 (C-12), 102.7 (C-1′), 99.7 (C-1″), 91.9 (C-1‴), 89.3 (C-3), 78.3, 75.1, 73.3, 72.7, 71.6, 71.1, 69.9, 68.9, 67.3, 66.5, 65.7, 63.5, 63.1, 61.5, 56.3, 51.7, 48.3, 45.5, 42.5, 39.7, 36.7, 35.2, 34.1, 33.2, 32.7, 27.9, 26.9, 25.6, 24.8, 23.9, 19.3, 17.9, 16.0, 15.1; HRMALDIMS: m/z calcd for $C_{133}H_{129}O_{30}NNa$ [M+Na^+] 2242.8490; found: 2242.8501.

*4.1.9. Typical procedure for the target compounds **1a–1j**, **2a–2c** and **3a–3c***

To a solution of **12a–12j**, **10**, **19a–20a**, **7b**, **17b–18b** (50 mg) in CH_2Cl_2–MeOH (V:V/1:1, 8 mL) was added 10% Pd–C (30 mg) under 1 atm of H_2 for 5 h. The reaction mixture was then filtered and the filtrate was concentrated to dryness to give a white solid. The solid was dissolved in CH_2Cl_2–MeOH (V:V/1:2, 9 mL), and then NaOMe (45 mg) was added. After stirring at room temperature for 9 h, the solution was neutralized with ion-exchange resin (H^+), then filtered and concentrated. The residue was purified by column chromatography on silica gel (8:1 to 6:1, $CHCl_3$–MeOH) to give the target compounds (**1a–1j**, **2a–2c and 3a–3c**) as white amorphous solids.

*4.1.9.1. 28-O-6-Phthalimido-6-deoxy-β-D-glucopyranosyl oleanate 3-O-β-D-glucopyranoside (**1a**).* Yield: 79%; $[\alpha]_D^{23}$ + 10.6 (c 0.31, CH_3OH); ^1H NMR (CD_3OD, 600 MHz): δ 7.95 (dd, J = 6.3, 0.9 Hz, 1H, H–Ar), 7.69 (d, J = 7.2 Hz, 1H, H–Ar), 7.61 (m, 2H, H–Ar), 6.93 (m, 1H, NHCO), 5.36 (d, J = 8.2 Hz, 1H, H-1″), 5.26 (t, J = 3.7 Hz, 1H, H-12), 4.39 (d, J = 7.9 Hz, 1H, H-1′), 3.87 (dd, J = 11.9, 2.3 Hz, 1H, H-6′-1), 3.81 (t, J = 9.6 Hz, 1H, H-4″), 3.69–3.73 (m, 2H, H-4′, H-6″-1), 3.47 (t, J = 9.6 Hz, 1H, H-3′), 3.35–3.39 (m, 4H, H-5′, H-5″, H-6′-2, H-6″-2), 3.31 (dd, J = 9.6, 8.2 Hz, 1H, H-2″), 3.25–3.29 (m, 2H, H-2′, H-3″), 3.10 (dd, J = 11.9, 4.6 Hz, 1H, H-3), 2.81 (dd, J = 14.3, 4.3 Hz, 1H, H-18), 1.13, 1.02, 0.95, 0.91, 0.89, 0.83, 0.79 (s each, 3H each, CH_3 × 7); ^{13}C NMR (CD_3OD, 150 MHz): δ 178.3 (C-28), 167.5, 167.0, 144.6 (C-13), 137.9, 134.1, 132.9, 129.7, 129.1, 128.3, 123.7 (C-12), 106.9 (C-1′), 95.9 (C-1″), 90.7 (C-3), 80.5, 78.9, 78.3, 76.5, 75.3, 74.3, 71.9, 71.3, 62.5, 62.3, 55.5, 48.1, 46.9, 42.7, 41.9, 39.9, 37.9, 35.7, 33.9, 33.3, 31.8, 28.9, 27.1, 26.3, 24.6, 24.1, 19.4, 17.8, 17.0, 16.3; HRESIMS: m/z calcd for $C_{50}H_{74}O_{15}N$ [M+H^+] 928.5053; found: 928.5071.

*4.1.9.2. 28-O-6-Phthalimido-6-deoxy-β-D-glucopyranosyl oleanate 3-O-α-D-mannopyranoside (**1b**).* Yield: 73%; $[\alpha]_D^{23}$ + 17.8 (c 0.21, CH_3OH); ^1H NMR (CD_3OD, 600 MHz): δ 7.93 (dd, J = 6.3, 1.0 Hz, 1H, H–Ar), 7.70 (d, J = 7.2 Hz, 1H, H–Ar), 7.59 (m, 2H, H–Ar), 6.89 (m, 1H, NHCO), 5.37 (d, J = 8.0 Hz, 1H, H-1″), 5.30 (t, J = 3.6 Hz, 1H, H-12), 4.89 (s, 1H, H-1′), 3.82 (t, J = 9.6 Hz, 1H, H-4″), 3.79 (dd, J = 11.0, 1.9 Hz, 1H, H-6′-1), 3.73 (dd, J = 12.3, 3.4 Hz, 1H, H-6″-1), 3.67–3.70 (m, 2H, H-5′, H-6′-2), 3.65 (t, J = 9.1 Hz, 1H, H-4′), 3.51 (dd, J = 9.1, 3.7 Hz, 1H, H-3′), 3.37–3.42 (m, 3H, H-2′, H-5″, H-6″-2), 3.34 (dd, J = 9.6, 8.0 Hz, 1H, H-2″), 3.27 (t, J = 9.6 Hz, 1H, H-3″), 3.18 (dd, J = 13.7, 4.1 Hz, 1H, H-3), 2.80 (dd, J = 14.3, 3.7 Hz, 1H, H-18), 1.15, 1.03, 0.95, 0.93, 0.90, 0.85, 0.79 (s each, 3H each, CH_3 × 7); ^{13}C NMR (CD_3OD, 150 MHz): δ 178.5 (C-28), 167.5, 167.1, 144.5 (C-13), 137.9, 133.9, 132.9, 129.8, 129.1, 128.5, 123.4 (C-12), 97.9 (C-1′), 95.7 (C-1″), 85.3 (C-3), 79.3, 78.3, 76.5, 75.3, 74.3, 73.1, 72.7, 71.3, 68.6, 62.5, 56.7, 48.1, 46.9, 42.5, 41.9, 39.7, 37.9, 35.7, 33.7, 33.3, 31.9, 28.9, 27.3, 26.3, 24.6, 23.9, 19.4, 17.8, 17.1, 16.3; HRESIMS: m/z calcd for $C_{50}H_{74}O_{15}N$ [M+H^+] 928.5053; found: 928.5029.

*4.1.9.3. 28-O-6-Phthalimido-6-deoxy-β-D-glucopyranosyl oleanate 3-O-β-D-galactopyranoside (**1c**).* Yield: 69%; $[\alpha]_D^{23}$ + 21.5 (c 0.31, CH_3OH); ^1H NMR (CD_3OD, 600 MHz): δ 7.97 (dd, J = 6.5, 1.2 Hz, 1H, H–Ar), 7.68 (d, J = 7.3 Hz, 1H, H–Ar), 7.61 (m, 2H, H–Ar), 6.85 (m, 1H, NHCO), 5.39 (d, J = 8.3 Hz, 1H, H-1″), 5.27 (t, J = 3.6 Hz, 1H, H-12), 4.41 (d, J = 8.2 Hz, 1H, H-1′), 3.86 (t, J = 9.7 Hz, 1H, H-4″), 3.76 (dd, J = 12.3, 3.7 Hz, 1H, H-6′-1), 3.70–3.74 (m, 3H, H-5′, H-6′-2, H-6″-1), 3.65 (dd, J = 9.6, 3.7 Hz, 1H, H-3′), 3.56 (t, J = 3.7 Hz, 1H, H-4′), 3.49 (dd, J = 9.6, 8.2 Hz, 1H, H-2′), 3.41–3.45 (m, 2H, H-5″, H-6″-2), 3.37 (dd, J = 9.7, 8.3 Hz, 1H, H-2″), 3.29 (t, J = 9.7 Hz, 1H, H-3″), 3.20

(dd, J = 12.3, 3.7 Hz, 1H, H-3), 2.79 (dd, J = 13.7, 4.3 Hz, 1H, H-18), 1.15, 1.01, 0.93, 0.90, 0.89, 0.83, 0.79 (s each, 3H each, $CH_3 \times 7$); ^{13}C NMR (CD_3OD, 150 MHz): δ 178.1 (C-28), 167.6, 167.1, 144.5 (C-13), 137.9, 133.7, 132.9, 129.7, 129.1, 128.3, 123.4 (C-12), 102.1 (C-1′), 95.9 (C-1″), 89.7 (C-3), 79.1, 78.5, 75.6, 74.5, 73.1, 72.3, 71.3, 68.9, 62.5, 56.9, 48.3, 46.9, 42.5, 41.0, 39.7, 37.9, 35.7, 33.9, 33.3, 31.9, 28.9, 27.3, 26.5, 24.6, 23.9, 19.5, 17.8, 17.3, 16.0; HRESIMS: *m/z* calcd for $C_{50}H_{74}O_{15}N$ [M+H$^+$] 928.5055; found: 928.5073.

*4.1.9.4. 28-O-6-Phthalimido-6-deoxy-β-D-glucopyranosyl oleanate 3-O-β-D-xylopyranoside (**1d**).* Yield: 71%; $[\alpha]_D^{23}$ + 15.7 (c 0.19, CH_3OH); ^1H NMR (CD_3OD, 600 MHz): δ 7.95 (dd, J = 6.3, 1.1 Hz, 1H, H–Ar), 7.69 (d, J = 7.4 Hz, 1H, H–Ar), 7.62 (m, 2H, H-Ar), 6.83 (m, 1H, N*H*CO), 5.36 (d, J = 8.2 Hz, 1H, H-1″), 5.25 (t, J = 3.6 Hz, 1H, H-12), 4.27 (d, J = 6.9 Hz, 1H, H-1′), 3.85 (dd, J = 11.9, 5.6 Hz, 1H, H-5′-1), 3.81 (t, J = 9.7 Hz, 1H, H-4″), 3.69 (dd, J = 12.5, 4.6 Hz, 1H, H-6″-1), 3.45–3.48 (m, 1H, H-4′), 3.43 (t, J = 9.3 Hz, 1H, H-3′), 3.34–3.38 (m, 2H, H-5″, H-5′-1), 3.31 (dd, J = 12.5, 2.9 Hz, 1H, H-6″-2), 3.27 (dd, J = 9.7, 8.2 Hz, 1H, H-2″), 3.19–3.24 (m, 2H, H-2′, H-3″), 3.15 (dd, J = 11.9, 4.3 Hz, 1H, H-3), 2.86 (dd, J = 13.7, 3.7 Hz, 1H, H-18), 1.15, 1.03, 0.95, 0.93, 0.89, 0.84, 0.79 (s each, 3H each, $CH_3 \times 7$); ^{13}C NMR (CD_3OD, 150 MHz): δ 177.5 (C-28), 167.5, 166.9, 144.3 (C-13), 137.9, 133.4, 132.9, 129.7, 129.3, 128.1, 123.3 (C-12), 106.0 (C-1′), 95.3 (C-1″), 82.7 (C-3), 79.3, 75.9, 74.5, 73.1, 71.7, 70.3, 66.7, 64.6, 59.8, 48.5, 47.6, 42.5, 41.7, 39.7, 37.9, 35.6, 33.9, 33.3, 31.9, 28.7, 27.3, 26.5, 24.7, 23.9, 19.5, 17.8, 17.3, 16.1; HRESIMS: *m/z* calcd for $C_{49}H_{72}O_{14}N$ [M+H$^+$] 898.4947; found: 898.4963.

*4.1.9.5. 28-O-6-Phthalimido-6-deoxy-β-D-glucopyranosyl oleanate 3-O-α-L-arabinopyranoside (**1e**).* Yield: 65%; $[\alpha]_D^{23}$ + 39.5 (c 0.31, CH_3OH); ^1H NMR (CD_3OD, 600 MHz): δ 7.95 (dd, J = 6.3, 1.2 Hz, 1H, H–Ar), 7.66 (d, J = 7.3 Hz, 1H, H–Ar), 7.59 (m, 2H, H-Ar), 6.87 (m, 1H, N*H*CO), 5.39 (d, J = 8.2 Hz, 1H, H-1″), 5.27 (t, J = 3.6 Hz, 1H, H-12), 4.38 (d, J = 7.1 Hz, 1H, H-1′), 3.86–3.89 (m, 2H, H-4″, H-5′-1), 3.65 (dd, J = 11.9, 5.3 Hz, 1H, H-6″-1), 3.47–3.50 (m, 2H, H-3′, H-4′), 3.37 (dd, J = 11.9, 2.7 Hz, 1H, H-6″-2), 3.29–3.35 (m, 4H, H-2″, H-3″, H-5″, H-5′-1), 3.27 (dd, J = 9.3, 7.1 Hz, 1H, H-2′), 3.17 (dd, J = 11.9, 3.7 Hz, 1H, H-3), 2.83 (dd, J = 14.3, 4.3 Hz, 1H, H-18), 1.13, 1.01, 0.97, 0.91, 0.89, 0.83, 0.79 (s each, 3H each, $CH_3 \times 7$); ^{13}C NMR (CD_3OD, 150 MHz): δ 177.8 (C-28), 167.5, 167.0, 144.3 (C-13), 137.9, 133.5, 132.9, 129.6, 129.3, 127.9, 123.7 (C-12), 102.9 (C-1′), 95.9 (C-1″), 89.0 (C-3), 79.1, 74.9, 73.5, 72.9, 71.7, 69.9, 66.7, 63.6, 60.1, 48.5, 47.6, 42.5, 41.9, 39.7, 37.9, 35.7, 33.9, 33.3, 31.9, 28.9, 27.3, 26.5, 24.7, 23.9, 19.3, 17.8, 17.3, 16.0; HRESIMS: *m/z* calcd for $C_{49}H_{72}O_{14}N$ [M+H$^+$] 898.4947; found: 898.4966.

*4.1.9.6. 28-O-6-Phthalimido-6-deoxy-β-D-glucopyranosyl oleanate 3-O-α-L-rhamnopyranoside (**1f**).* Yield: 69%; $[\alpha]_D^{23}$ − 8.76 (c 0.24, CH_3OH); ^1H NMR (CD_3OD, 600 MHz): δ 7.99 (dd, J = 6.0, 1.3 Hz, 1H, H–Ar), 7.65 (d, J = 7.5 Hz, 1H, H–Ar), 7.55 (m, 2H, H-Ar), 6.83 (m, 1H, N*H*CO), 5.33 (d, J = 8.2 Hz, 1H, H-1″), 5.30 (t, J = 3.7 Hz, 1H, H-12), 4.72 (d, J = 2.1 Hz, 1H, H-1′), 3.86 (t, J = 9.6 Hz, 1H, H-4″), 3.82 (dd, J = 3.8, 2.1 Hz, 1H, H-2′), 3.73 (dd, J = 9.6, 3.8 Hz, 1H, H-3′), 3.65 (dd, J = 11.9, 4.7 Hz, 1H, H-6″-1), 3.37 (dd, J = 11.9, 2.3 Hz, 1H, H-6″-2), 3.35 (t, J = 9.6 Hz, 1H, H-4′), 3.31–3.34 (m, 2H, H-2″, H-3″), 3.27–3.30 (m, 2H, H-5′, H-5″), 3.11 (dd, J = 12.3, 3.7 Hz, 1H, H-3), 2.86 (dd, J = 13.7, 3.7 Hz, 1H, H-18), 1.24 (d, J = 6.4 Hz, 3H, H-6′), 1.15, 1.03, 0.95, 0.93, 0.89, 0.85, 0.80 (s each, 3H each, $CH_3 \times 7$); ^{13}C NMR (CD_3OD, 150 MHz): δ 177.7 (C-28), 167.3, 166.7, 144.5 (C-13), 137.8, 133.5, 132.5, 129.6, 129.1, 127.9, 123.3 (C-12), 103.3 (C-1′), 95.4 (C-1″), 87.9 (C-3), 79.1, 72.4, 71.7, 71.3, 70.9, 69.9, 68.8, 66.7, 63.6, 59.3, 48.5, 47.6, 42.7, 41.9, 39.7, 37.8, 35.7, 33.9, 33.5, 31.9, 28.9, 27.3, 26.5, 24.7, 23.9, 19.3, 18.1, 17.8, 17.3, 15.9, 14.7; HRESIMS: *m/z* calcd for $C_{50}H_{74}O_{14}N$ [M+H$^+$] 912.5104; found: 912.5121.

*4.1.9.7. 28-O-6-Phthalimido-6-deoxy-β-D-glucopyranosyl oleanate 3-O-3-O-α-L-fucopyranoside (**1g**).* Yield: 65%; $[\alpha]_D^{23}$ + 11.3 (c 0.12, CH_3OH); ^1H NMR (CD_3OD, 600 MHz): δ 7.93 (dd, J = 6.5, 1.1 Hz, 1H, H–Ar), 7.66 (d, J = 7.5 Hz, 1H, H–Ar), 7.53 (m, 2H, H–Ar), 6.81 (m, 1H, N*H*CO), 5.35 (d, J = 8.1 Hz, 1H, H-1″), 5.32 (t, J = 3.6 Hz, 1H, H-12), 4.26 (d, J = 6.7 Hz, 1H, H-1′), 3.81 (t, J = 9.6 Hz, 1H, H-4″), 3.59–3.64 (m, 3H, H-2′, H-3′, H-6″-1), 3.49 (dd, J = 12.1, 3.1 Hz, 1H, H-6″-2), 3.43–3.46 (m, 3H, H-2″, H-4′, H-5′), 3.34 (m, 2H, H-3″, H-5″), 3.18 (dd, J = 13.7, 4.3 Hz, 1H, H-3), 2.81 (dd, J = 12.9, 3.7 Hz, 1H, H-18), 1.26 (d, J = 6.4 Hz, 3H, H-6′), 1.17, 1.03, 0.97, 0.91, 0.89, 0.85, 0.79 (s each, 3H each, $CH_3 \times 7$); ^{13}C NMR (CD_3OD, 150 MHz): δ 178.0 (C-28), 167.3, 166.7, 144.3 (C-13), 137.9, 133.5, 132.3, 129.6, 129.1, 127.5, 123.1 (C-12), 102.8 (C-1′), 95.1 (C-1″), 87.1 (C-3), 79.1, 75.3, 72.4, 71.7, 70.9, 68.8, 66.7, 63.7, 59.7, 48.7, 47.6, 42.3, 41.9, 39.7, 37.8, 35.5, 33.9, 33.5, 31.7, 28.9, 27.3, 26.3, 24.7, 23.7, 19.3, 18.1, 17.3, 15.9, 14.7; HRESIMS: *m/z* calcd for $C_{50}H_{74}O_{14}N$ [M + H$^+$] 912.5104; found: 912.5097.

*4.1.9.8. 28-O-6-Phthalimido-6-deoxy-β-D-glucopyranosyl oleanate 3-O-β-D-lactopyranoside (**1h**).* Yield: 71%; $[\alpha]_D^{23}$ + 50.3 (c 0.33, CH_3OH); ^1H NMR (CD_3OD, 600 MHz): δ 7.97 (dd, J = 6.3, 1.1 Hz, 1H, H–Ar), 7.64 (d, J = 7.3 Hz, 1H, H–Ar), 7.55 (m, 2H, H–Ar), 6.79 (m, 1H, N*H*CO), 5.38 (d, J = 8.1 Hz, 1H, H-1‴), 5.23 (t, J = 3.7 Hz, 1H, H-12), 4.36 (d, J = 7.6 Hz, 1H, H-1′), 4.31 (d, J = 7.8 Hz, 1H, H-1″), 3.78 (dd, J = 9.3, 3.8 Hz, 1H, H-3″), 3.74 (t, J = 3.8 Hz, 1H, H-4″), 3.72 (dd, J = 11.9, 6.3 Hz, 1H, H-6′-1), 3.67 (dd, J = 12.1, 4.5 Hz, 1H, H-6″-1), 3.53–3.57 (m, 4H, H-6′-2, H-6″-2, H-6‴-1, H-6‴-2), 3.47 (t, J = 9.6 Hz, 1H, H-4‴), 3.44 (t, J = 9.3 Hz, 1H, H-3′), 3.39–3.43 (m, 3H, H-2‴, H-3‴, H-4′), 3.34–3.37 (m, 2H, H-2′, H-2″), 3.21–3.26 (m, 3H, H-5′, H-5″, H-5‴), 3.12 (dd, J = 11.9, 4.0 Hz, 1H, H-3), 2.79 (dd, J = 13.7, 4.3 Hz, 1H, H-18), 1.07, 1.03, 0.97, 0.89, 0.87, 0.85, 0.79, 0.75 (s each, 3H each, $CH_3 \times 7$); ^{13}C NMR (CD_3OD, 150 MHz): δ 178.3 (C-28), 167.5, 166.5, 144.7 (C-13), 137.9, 133.6, 132.3, 129.7, 129.1, 127.3, 123.6 (C-12), 106.5 (C-1′), 104.5 (C-1″), 95.6 (C-1‴), 90.5 (C-3), 79.8, 78.6, 77.1, 76.5, 76.2, 75.3, 74.9, 73.7, 72.7, 71.6, 71.3, 70.2, 63.8, 62.5, 61.9, 51.7, 48.1, 47.5, 42.3, 39.7, 36.7, 34.9, 34.0, 33.4, 31.7, 27.9, 26.5, 25.6, 24.9, 23.8, 19.5, 17.8, 17.0, 16.1; HRESIMS: *m/z* calcd for $C_{56}H_{84}NO_{20}$ [M+H$^+$] 1090.5581; found: 1090.5597.

*4.1.9.9. 28-O-6-Phthalimido-6-deoxy-β-D-glucopyranosyl oleanate 3-O-β-D-cellopyranoside (**1i**).* Yield: 65%; $[\alpha]_D^{23}$ + 27.9 (c 0.21, CH_3OH); ^1H NMR (CD_3OD, 600 MHz): δ 7.99 (dd, J = 6.3, 1.2 Hz, 1H, H–Ar), 7.64 (d, J = 7.2 Hz, 1H, H–Ar), 7.56 (m, 2H, H–Ar), 6.86 (m, 1H, N*H*CO), 5.33 (d, J = 8.0 Hz, 1H, H-1‴), 5.21 (t, J = 3.6 Hz, 1H, H-12), 4.37 (d, J = 8.0 Hz, 1H, H-1′), 4.29 (d, J = 8.0 Hz, 1H, H-1″), 3.81 (t, J = 9.6 Hz, 1H, H-4″), 3.76–3.79 (m, 2H, H-6′-1, H-6″-1), 3.73 (dd, J = 11.9, 4.7 Hz, 1H, H-6″-2), 3.60 (dd, J = 12.3, 3.4 Hz, 1H, H-6′-2), 3.53–3.55 (m, 2H, H-6‴-1, H-6‴-2), 3.49 (t, J = 9.5 Hz, 1H, H-4‴), 3.46 (t, J = 9.5 Hz, 1H, H-3‴), 3.43 (t, J = 9.3 Hz, 1H, H-3″), 3.35–3.39 (m, 2H, H-2‴, H-4′), 3.29–3.35 (m, 3H, H-2′, H-5′, H-2″), 3.16–3.19 (m, 2H, H-5″, H-5‴), 3.10 (dd, J = 11.9, 3.9 Hz, 1H, H-3), 2.81 (dd, J = 13.2, 3.7 Hz, 1H, H-18), 1.09, 1.01, 0.97, 0.89, 0.87, 0.85, 0.79, 0.75 (s each, 3H each, $CH_3 \times 7$); ^{13}C NMR (CD_3OD, 150 MHz): δ 178.2 (C-28), 167.3, 166.5, 144.5 (C-13), 137.8, 133.5, 132.3, 129.7, 129.0, 127.3, 123.1 (C-12), 106.3 (C-1′), 103.9 (C-1″), 95.9 (C-1‴), 90.7 (C-3), 80.1, 78.6, 78.3, 79.7, 77.9, 76.5, 76.3, 75.3, 74.9, 73.5, 71.6, 71.3, 68.9, 63.8, 62.5, 61.9, 57.2, 48.1, 47.5, 42.3, 39.7, 36.9, 34.9, 34.0, 33.4, 31.9, 27.9, 26.5, 25.6, 24.7, 23.8, 19.6, 17.8, 17.0, 16.1; HRESIMS: *m/z* calcd for $C_{56}H_{84}NO_{20}$ [M+H$^+$] 1090.5581; found: 1090.5568.

*4.1.9.10. 28-O-6-Phthalimido-6-deoxy-β-D-glucopyranosyl oleanate 3-O-β-D-gentiopyranoside (**1j**).* Yield: 63%; $[\alpha]_D^{23}$ + 9.43 (c 0.19, CH_3OH); ^1H NMR (CD_3OD, 600 MHz): δ 7.98 (dd, J = 6.1, 0.9 Hz, 1H, H–Ar), 7.64 (d, J = 7.3 Hz, 1H, H–Ar), 7.57 (m, 2H, H–Ar), 6.81 (m, 1H, N*H*CO), 5.36 (d, J = 8.1 Hz, 1H, H-1‴), 5.23 (t, J = 3.6 Hz, 1H, H-

12), 4.39 (d, J = 8.0 Hz, 1H, H-1′), 4.23 (d, J = 8.1 Hz, 1H, H-1″), 3.73–3.77 (m, 3H, H-4″, H-6′-1, H-6″-1), 3.65–3.68 (m, 2H, H-6′-2, H-6″-2), 3.51 (t, J = 9.6 Hz, 1H, H-3‴), 3.44 (t, J = 9.3 Hz, 1H, H-3″), 3.39 (t, J = 9.6 Hz, 1H, H-4‴), 3.33–3.39 (m, 4H, H-2‴, H-4′, H-6‴-1, H-6‴-2), 3.29–3.32 (m, 2H, H-2′, H-2″), 3.17–3.22 (m, 3H, H-5′, H-5″, H-5‴), 3.06 (dd, J = 12.3, 3.7 Hz, 1H, H-3), 2.79 (dd, J = 13.7, 4.3 Hz, 1H, H-18), 1.07, 1.01, 0.99, 0.89, 0.87, 0.83, 0.79, 0.73 (s each, 3H each, CH_3 × 7); ^{13}C NMR (CD_3OD, 150 MHz): δ 178.5 (C-28), 167.1, 166.5, 144.5 (C-13), 137.9, 133.5, 132.1, 129.7, 129.3, 127.1, 123.5 (C-12), 106.6 (C-1′), 104.3 (C-1″), 95.3 (C-1‴), 90.5 (C-3), 79.9, 78.5, 78.3, 79.5, 77.9, 76.5, 75.9, 75.3, 74.9, 73.5, 71.5, 71.3, 68.3, 63.8, 62.5, 61.3, 57.9, 48.1, 47.9, 42.3, 39.7, 36.9, 34.9, 34.1, 33.4, 31.9, 27.9, 26.5, 25.7, 24.7, 23.9, 19.6, 17.8, 17.3, 16.1; HRESIMS: *m/z* calcd for $C_{56}H_{84}NO_{20}$ [M+H$^+$] 1090.5581; found: 1090.5599.

*4.1.9.11. Oleanate 28-O-6-phthalimido-6-deoxy-β-D-glucopyranoside (**2a**).* Yield: 75%; $[\alpha]_D^{23}$ + 23.7 (c 0.33, CH_3OH); ^{1}H NMR (CD_3OD, 600 MHz): δ 7.90 (dd, J = 6.3, 1.2 Hz, 1H, H–Ar), 7.63 (d, J = 7.3 Hz, 1H, H–Ar), 7.49 (m, 2H, H–Ar), 6.84 (m, 1H, N*H*CO), 5.28 (d, J = 8.0 Hz, 1H, H-1′), 5.27 (t, J = 3.7 Hz, 1H, H-12), 3.89 (t, J = 9.7 Hz, 1H, H-4′), 3.53 (dd, J = 12.1, 5.3 Hz, 1H, H-6′-1), 3.39 (dd, J = 9.7, 8.0 Hz, 1H, H-2′), 3.35 (dd, J = 12.1, 3.4 Hz, 1H, H-6′-2), 3.33 (dd, J = 9.7 Hz, 1H, H-3′), 3.30 (m, 1H, H-5′), 3.09 (dd, J = 11.9, 3.7 Hz, 1H, H-3), 2.80 (dd, J = 14.3, 3.7 Hz, 1H, H-18), 1.13, 1.01, 0.97, 0.93, 0.89, 0.85, 0.78 (s each, 3H each, CH_3 × 7); ^{13}C NMR (CD_3OD, 150 MHz): δ 177.3 (C-28), 167.1, 166.9, 144.3 (C-13), 137.3, 133.5, 132.7, 129.5, 129.1, 127.9, 123.5 (C-12), 95.3 (C-1″), 87.9 (C-3), 73.1, 71.5, 69.9, 66.7, 63.1, 59.3, 48.5, 47.6, 42.9, 41.7, 39.7, 37.8, 35.6, 33.9, 33.5, 31.9, 28.9, 27.3, 26.5, 24.7, 23.9, 19.5, 18.3, 17.8, 17.1, 15.9, 14.7; HRESIMS: *m/z* calcd for $C_{44}H_{64}O_{10}N$ [M+H$^+$] 766.4525; found: 766.4541.

*4.1.9.12. Oleanate 28-O-6-phthalimido -6-deoxy-β-D-galactopyranoside (**2b**).* Yield: 66%; $[\alpha]_D^{23}$ + 15.8 (c 0.21, CH_3OH); ^{1}H NMR (CD_3OD, 600 MHz): δ 7.95 (dd, J = 6.3, 1.1 Hz, 1H, H–Ar), 7.59 (d, J = 7.5 Hz, 1H, H–Ar), 7.50 (m, 2H, H–Ar), 6.81 (m, 1H, N*H*CO), 5.37 (d, J = 8.2 Hz, 1H, H-1′), 5.23 (t, J = 3.6 Hz, 1H, H-12), 3.79 (t, J = 3.7 Hz, 1H, H-4′), 3.51 (dd, J = 11.9, 5.7 Hz, 1H, H-6′-1), 3.41 (dd, J = 11.9, 3.3 Hz, 1H, H-6′-2), 3.25–3.32 (m, 3H, H-2′, H-3′, H-5′), 3.10 (dd, J = 11.5, 4.1 Hz, 1H, H-3), 2.81 (dd, J = 13.7, 4.1 Hz, 1H, H-18), 1.07, 0.97, 0.93, 0.89, 0.85, 0.78, 0.67 (s each, 3H each, CH_3 × 7); ^{13}C NMR (CD_3OD, 150 MHz): δ 177.5 (C-28), 167.3, 166.7, 144.7 (C-13), 137.1, 133.6, 131.9, 129.3, 129.1, 127.5, 123.3 (C-12), 94.0 (C-1″), 88.7 (C-3), 73.5, 70.9, 68.7, 66.5, 64.3, 59.9, 48.7, 47.6, 42.7, 41.6, 39.7, 37.8, 35.3, 33.9, 33.5, 31.9, 28.7, 27.3, 26.5, 24.7, 23.9, 19.1, 18.3, 17.8, 16.7, 15.3, 14.7; HRESIMS: *m/z* calcd for $C_{44}H_{64}O_{10}N$ [M+H$^+$] 766.4525; found: 766.4512.

*4.1.9.13. Oleanate 28-O-6-phthalimido-6-deoxy-α-D-mannopyranoside (**2c**).* Yield: 63%; $[\alpha]_D^{23}$ + 31.1 (c 0.18, CH_3OH); ^{1}H NMR (CD_3OD, 600 MHz): δ 7.93 (dd, J = 6.1, 1.2 Hz, 1H, H–Ar), 7.61 (d, J = 7.3 Hz, 1H, H–Ar), 7.55 (m, 2H, H–Ar), 6.83 (m, 1H, N*H*CO), 5.23 (t, J = 3.6 Hz, 1H, H-12), 4.97 (s, 1H, H-1′), 3.65 (dd, J = 12.1, 5.3 Hz, 1H, H-6′-1), 3.53 (s, 1H, H-2′), 3.45 (dd, J = 12.1, 4.2 Hz, 1H, H-6′-2), 3.37 (t, J = 9.7 Hz, 1H, H-4′), 3.35 (m, 1H, H-5′), 3.29–3.33 (m, 2H, H-2′, H-3′), 3.17 (dd, J = 11.5, 4.1 Hz, 1H, H-3), 2.79 (dd, J = 13.3, 4.1 Hz, 1H, H-18), 1.07, 0.95, 0.89, 0.87, 0.85, 0.73, 0.67 (s each, 3H each, CH_3 × 7); ^{13}C NMR (CD_3OD, 150 MHz): δ 176.3 (C-28), 166.9, 166.5, 144.5 (C-13), 136.9, 133.3, 131.7, 129.3, 128.9, 127.3, 123.7 (C-12), 92.1 (C-1″), 87.9 (C-3), 72.9, 70.1, 69.2, 67.5, 65.7, 59.3, 48.7, 47.3, 42.7, 41.5, 39.7, 37.8, 35.3, 33.9, 33.5, 31.9, 28.9, 27.5, 26.3, 24.7, 23.9, 19.1, 18.3, 17.8, 16.9, 16.7, 15.1; HRESIMS: *m/z* calcd for $C_{44}H_{64}O_{10}N$ [M+H$^+$] 766.4523; found: 766.4542.

*4.1.9.14. Oleanate 3-O-6-phthalimido-6-deoxy-β-D-glucopyranoside (**3a**).* Yield: 69%; $[\alpha]_D^{23}$ + 7.83 (c 0.64, CH_3OH); ^{1}H NMR (CD_3OD, 600 MHz): δ 7.96 (dd, J = 6.5, 1.0 Hz, 1H, H–Ar), 7.65 (d, J = 7.5 Hz, 1H, H–Ar), 7.53 (m, 2H, H-Ar), 6.89 (m, 1H, N*H*CO), 5.25 (t, J = 3.5 Hz, 1H, H-12), 5.01 (d, J = 7.9 Hz, 1H, H-1′), 3.67 (dd, J = 11.9, 5.1 Hz, 1H, H-6′-1), 3.54 (m, 1H, H-5′), 3.47 (dd, J = 11.9, 3.3 Hz, 1H, H-6′-2), 3.29 (t, J = 9.7 Hz, 1H, H-4′), 3.21 (dd, J = 9.7, 7.9 Hz, 1H, H-2′), 3.12 (dd, J = 9.7 Hz, 1H, H-3′), 3.05 (dd, J = 13.7, 3.7 Hz, 1H, H-3), 2.81 (dd, J = 13.3, 3.7 Hz, 1H, H-18), 1.10, 0.99, 0.89, 0.87, 0.83, 0.75, 0.57 (s each, 3H each, CH_3 × 7); ^{13}C NMR (CD_3OD, 150 MHz): δ 177.5 (C-28), 167.1, 166.7, 144.5 (C-13), 137.1, 133.7, 132.9, 129.3, 129.0, 127.9, 123.7 (C-12), 105.7 (C-1″), 90.3 (C-3), 75.6, 73.9, 71.6, 69.8, 63.1, 55.3, 48.7, 47.6, 43.1, 41.5, 39.7, 37.8, 35.3, 33.7, 33.5, 31.7, 28.9, 27.3, 26.5, 24.8, 23.6, 19.5, 18.1, 17.9, 16.3, 15.0; HRESIMS: *m/z* calcd for $C_{44}H_{64}O_{10}N$ [M+H$^+$] 766.4525; found: 766.4507.

*4.1.9.15. Oleanate 3-O-6-phthalimido -6-deoxy-β-D-galactopyranoside (**3b**).* Yield: 67%; $[\alpha]_D^{23}$ + 23.1 (c 0.34, CH_3OH); ^{1}H NMR (CD_3OD, 600 MHz): δ 7.90 (dd, J = 6.3, 1.0 Hz, 1H, H–Ar), 7.67 (d, J = 7.2 Hz, 1H, H–Ar), 7.49 (m, 2H, H–Ar), 6.77 (m, 1H, N*H*CO), 5.30 (t, J = 3.7 Hz, 1H, H-12), 4.83 (d, J = 7.7 Hz, 1H, H-1′), 3.70 (t, J = 3.5 Hz, 1H, H-4′), 3.63 (dd, J = 11.9, 4.7 Hz, 1H, H-6′-1), 3.51–3.55 (m, 2H, H-5′, H-6′-2), 3.15–3.20 (m, 2H, H-2′, H-3′), 3.07 (dd, J = 11.9, 3.7 Hz, 1H, H-3), 2.81 (dd, J = 13.7, 4.1 Hz, 1H, H-18), 1.09, 0.97, 0.89, 0.85, 0.79, 0.75, 0.63 (s each, 3H each, CH_3 × 7); ^{13}C NMR (CD_3OD, 150 MHz): δ 177.1 (C-28), 167.3, 166.6, 144.3 (C-13), 137.3, 133.5, 132.7, 129.3, 129.1, 127.5, 123.5 (C-12), 103.1 (C-1″), 89.7 (C-3), 75.1, 72.6, 71.0, 69.7, 61.9, 55.6, 48.7, 47.6, 43.1, 41.5, 39.7, 37.9, 35.3, 33.7, 33.1, 31.7, 28.7, 27.3, 26.5, 24.9, 23.6, 19.3, 18.1, 17.5, 16.3, 15.1; HRESIMS: *m/z* calcd for $C_{44}H_{64}O_{10}N$ [M+H$^+$] 766.4525; found: 766.4551.

*4.1.9.16. Oleanate 3-O-6-phthalimido-6-deoxy-α-D-mannopyranoside (**3c**).* Yield: 71%; $[\alpha]_D^{23}$ + 30.1 (c 0.21, CH_3OH); ^{1}H NMR (CD_3OD, 600 MHz): δ 7.88 (dd, J = 6.0, 0.9 Hz, 1H, H–Ar), 7.67 (d, J = 7.3 Hz, 1H, H–Ar), 7.49 (m, 2H, H–Ar), 6.73 (m, 1H, N*H*CO), 5.21 (t, J = 3.7 Hz, 1H, H-12), 4.67 (s, 1H, H-1′), 3.59 (dd, J = 12.1, 5.7 Hz, 1H, H-6′-1), 3.49 (t, J = 9.3 Hz, 1H, H-4′), 3.47 (dd, J = 12.1, 2.9 Hz, 1H, H-6′-2), 3.44 (m, 1H, H-5′), 3.23–3.27 (m, 2H, H-2′, H-3′), 3.10 (dd, J = 14.3, 3.7 Hz, 1H, H-3), 2.79 (dd, J = 13.3, 4.1 Hz, 1H, H-18), 1.07, 0.97, 0.89, 0.89, 0.81, 0.75, 0.60 (s each, 3H each, CH_3 × 7); ^{13}C NMR (CD_3OD, 150 MHz): δ 176.9 (C-28), 166.9, 166.3, 144.3 (C-13), 137.1, 133.9, 132.7, 129.3, 129.1, 127.9, 123.7 (C-12), 94.1 (C-1″), 88.9 (C-3), 74.1, 72.6, 70.5, 69.6, 65.2, 55.3, 48.7, 47.3, 43.1, 41.5, 39.7, 37.9, 35.3, 33.7, 33.5, 31.9, 28.9, 27.3, 26.5, 24.9, 22.7, 19.5, 18.1, 17.9, 17.1, 14.7; HRESIMS: *m/z* calcd for $C_{44}H_{64}O_{10}N$ [M+H$^+$] 766.4523; found: 766.4561.

4.2. Biological testing

The inhibitory activities of all synthesized OA derivatives against PTP1B and TCPTP were evaluated according to the published assay [17]. Inhibitory activity was determined by the release of *p*-nitrophenol from the hydrolysis of substrate, *p*-nitrophenyl phosphate (*p*NPP), for the PTP1B assay was purchased from Sigma in the di(Tris) salt form. The positive reference compound Sodium Orthovanadate was purchased from GSK.

4.2.1. PTP1B and TCPTP inhibitory activity

PTP1B enzyme (or TCPTP) was diluted to appropriate concentrations in enzyme dilution buffer (25 mM HEPES, 50 mM NaCl, 2.5 mM EDTA, 0.1% bovine serum albumin, pH 7.2), and inhibitors were dissolved in DMSO. The PTP1B (or TCPTP) enzyme activity was measured at 37 °C by monitoring the hydrolysis of *p*NPP in buffer A (50 mM HEPES, 2.5 mM EDTA, pH 7.0). The absorbance at 405 nm was measured to determine the amount of released *p*-nitrophenol. For a typical 50 μL reaction, inhibitor (5.0 μL) was added to a reaction mixture containing PTP1B (or TCPTP) enzyme (5.0 μL),

5 × buffer A (10 μL), and H_2O (25 μL). Meanwhile, Blank control (without PTP1B or TCPTP enzyme and samples) and negative control (without samples) were established. After the mixture had been incubated at 37 °C for 10 min, the PTP1B (or TCPTP) enzyme reaction was initiated by the addition of *p*NPP. After 30 min at 37 °C, the reaction was quenched by the addition of 2 M Na_2CO_3, with the absorbance at 405 nm measured to quantify the produced *p*-nitrophenol, providing the optical density (OD) values. According to the OD values, the inhibition rate against PTP1B (or TCPTP) enzyme was calculated. When inhibition rate is larger than 50% at 10 μg/mL, the IC_{50} values of the inhibitors were determined by measuring the *p*NPP hydrolase activity in a range of different concentrations of inhibitor, and calculated by 4 Parameter Logistic Model (Xlfit software). The results were obtained from duplicate or triplicate experiments and summarized in Fig. 3 and Table 1.

4.2.2. Lipophilicity calculations

Converting the logarithm of the partition coefficient for n-octanol/water (log *K*) to the lipophilicity coefficient (Log *P*) was calculated using the program ACD/Log*P* ver 1.0 (Advanced Chemistry Development Inc. Toronto, Canada) software. The results are displayed in Table 2.

Acknowledgments

This work was financial supported by the Doctoral Program Foundation of Institutions of Higher Education of China (No.20116101120025), HYPERLINKChina Postdoctoral Science Foundation funded project (No. 2012M512023, 2013T60887), the Postdoctoral Science Foundation of Northwest University (BSH11012) and the Foundation of Shaanxi Educational Committee (11JK0676).

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2014.03.080.

References

[1] S. Wild, G. Roglic, A. Green, R. Sicree, H. King, Global prevalence of diabetes: estimates for the year 2000 and projections for 2030, Diabetes Care 27 (2004) 1047–1053.
[2] M.I. McCarthy, Genomics, type 2 diabetes, and obesity, New England Journal of Medicine 363 (2010) 2339–2350.
[3] M. Elchebly, P. Payette, E. Michaliszyn, W. Cromlish, S. Collins, A.L. Loy, D. Normandin, A. Cheng, J. Himms-Hagen, C.C. Chan, C. Ramachandran, M.J. Gresser, M.L. Tremblay, B.P. Kennedy, Increased insulin sensitivity and obesity resistance in mice lacking the protein tyrosine phosphatase-1B gene, Science 283 (1999) 1544–1548.
[4] L.D. Klaman, O. Boss, O.D. Peroni, J.K. Kim, J.L. Martino, J.M. Zabolotny, N. Moghal, M. Lubkin, Y.B. Kim, A.H. Sharpe, A. Stricker-Krongrad, G.I. Shulman, B.G. Neel, B.B. Kahn, Increased energy expenditure, decreased adiposity, and tissue-specific insulin sensitivity in protein-tyrosine phosphatase 1B-deficient mice, Molecular and Cellular Biology 20 (2000) 5479–5489.
[5] B.A. Zinker, C.M. Rondinone, J.M. Trevillyan, R.J. Gum, J.E. Clampit, J.F. Waring, N. Xie, D. Wilcox, P. Jacobson, L. Frost, P.E. Kroeger, R.M. Reilly, S. Koterski, T.J. Opgenorth, R.G. Ulrich, S. Crosby, M. Butler, S.F. Murray, R.A. McKay, S. Bhanot, B.P. Monia, M.R. Jirousek, Proceedings of the National Academy of Sciences of the United States of America 99 (2002) 11357–11362.
[6] M. Traurig, R.L. Hanson, S. Kobes, C. Bogardus, L.J. Baier, Protein tyrosine phosphatase 1B is not a major susceptibility gene for type 2 diabetes mellitus or obesity among Pima Indians, Diabetologia 50 (2007) 985–989.
[7] H. Park, B.R. Bhattarai, S.W. Ham, H. Cho, Structure-based virtual screening approach to identify novel classes of PTP1B inhibitors, European Journal of Medicinal Chemistry 44 (2009) 3280–3284.
[8] S. Thareja, S. Aggarwal, T.R. Bhardwaj, M. Kumar, Protein tyrosine phosphatase 1B inhibitors: a molecular level legitimate approach for the management of diabetes mellitus, Medicinal Research Reviews 32 (2012) 459–517.
[9] G. Liu, Recent advances in protein-tyrosine-phosphatase 1B (PTP1B) inhibitors for the treatment of type 2 diabetes and obesity, Drugs of the Future 29 (2004) 1245–1259.
[10] Y.F. Li, J. Li, Q. Shen, L.H. Hu, Benzoquinones from Ardisia japonica with inhibitory activity towards human protein tyrosine phosphatase 1B (PTP1B), Chem. Biodiversity 4 (2007) 961–965.
[11] S. Zhang, Z.Y. Zhang, PTP1B as a drug target: recent developments in PTP1B inhibitor discovery, Drug Discovery Today 12 (2007) 373–381.
[12] A.P. Combs, Recent advances in the discovery of competitive protein tyrosine phosphatase 1B inhibitors for the treatment of diabetes, obesity, and cancer, Journal of Medicinal Chemistry 53 (2010) 2333–2344.
[13] L. Luo, X.P. He, Q. Shen, J.Y. Li, X.X. Shi, J. Xie, J. Li, G.R. Chen, Synthesis of (Glycopyranosyl-triazolyl)-purines and their inhibitory activities against protein tyrosine phosphatase 1B (PTP1B), Chemistry and Biodiversity 8 (2011) 2035–2044.
[14] B. Jiang, S.J. Guo, D.Y. Shi, C. Guo, T. Wang, Discovery of novel bromophenol 3,4-dibromo-5-(2-bromo-3,4-dihydroxy-6-(isobutoxymethyl) benzyl)benzene-1,2-diol as protein tyrosine phosphatase 1B inhibitor and its anti-diabetic properties in C57BL/KsJ-db/db mice, European Journal of Medicinal Chemistry 64 (2013) 129–136.
[15] J.Z. Liu, S.E. Zhang, F.L. Nie, Y. Yang, Y.B. Tang, W.W. Yin, J.Y. Tian, F. Ye, Z.Y. Xiao, Discovery of novel PTP1B inhibitors via pharmacophore-oriented scaffold hopping from Ertiprotafib, Bioorganic & Medicinal Chemistry Letters 23 (2013) 6217–6222.
[16] K.A. Lantz, S.G. Emeigh Hart, S.L. Planey, M.F. Roitman, I.A. Ruiz-White, H.R. Wolfe, M.P. McLane, Inhibition of PTP1B by trodusquemine (MSI-1436) causes fat-specific weight loss in diet-induced obese mice, Obesity 18 (2010) 1516–1523.
[17] Z.Y. Zhang, S.Y. Lee, PTP1B inhibitors as potential therapeutics in the treatment of Type 2 diabetes and obesity, Expert Opinion on Investigational Drugs 12 (2003) 223–233.
[18] L.F. Iversen, K.B. Moller, A.K. Pedersen, G.H. Peters, A.S. Petersen, H.S. Andersen, S. Branner, S.B. Mortensen, N.P. Moller, Structure determination of T cell protein-tyrosine phosphatase, Journal of Biological Chemistry 277 (2002) 19982–19990.
[19] S.D. Taylor, B. Hill, Recent advances in protein tyrosine phosphatase 1B inhibitors, Expert Opinion on Investigational Drugs 13 (2004) 199–214.
[20] Q.C. Liu, T.T. Guo, L. Zhang, Y. Yu, P. Wang, J.F. Yang, Y.X. Li, Synthesis and biological evaluation of oleanolic acid derivatives as PTP1B inhibitors, European Journal of Medicinal Chemistry 63 (2013) 511–522.
[21] F. Qu, Y.X. Li, Y.C. Zhang, J. Zang, Synthesis of oleanolic acid glycoconjugates, Chinese Journal of Organic Chemistry 23 (2003) 249–257 (in Chinese).
[22] T.T. Guo, Q.C. Liu, P. Wang, L. Zhang, W. Zhang, Y.X. Li, Facile synthesis of three bidesmosidic oleanolic acid saponins with strong inhibitory activity on pancreatic lipase, Carbohydrate Research 344 (2009) 1167–1174.
[23] Q.C. Liu, Z. Fan, D. Li, W.H. Li, T.T. Guo, Facile synthesis of several oleanane-type triterpenoid saponins, Journal of Carbohydrate Chemistry 29 (2010) 386–402.
[24] Q.C. Liu, T.T. Guo, S.D. Guo, W.H. Li, D. Li, Synthesis and evaluation of four hederagenin glycosides as α-glucosidase inhibitor, Helvetica Chimica Acta 96 (2013) 142–148.
[25] Q.C. Liu, H.C. Liu, L. Zhang, T.T. Guo, P. Wang, M.Y. Geng, Y.X. Li, Synthesis and antitumor activities of naturally occurring oleanolic acid triterpenoid saponins and their derivatives, European Journal of Medicinal Chemistry 64 (2013) 1–15.
[26] Z. Györgydeák, Z. Hadady, N. Felföldi, A. Krakomperger, V. Nagy, M. Tóth, A. Brunyánszki, T. Docsa, P. Gergely, L. Somsák, Synthesis of N-(β-glucopyranosyl) and N-(2-acetamido-2-deoxy-β-glucopyranosyl) amides as inhibitors of glycogen phosphorylase, Bioorganic and Medicinal Chemistry 12 (2004) 4861–4870.
[27] C. Bliard, G. Massiot, S. Nazabadioko, Glycosylation of acids under phase transfer conditions. Partial synthesis of saponins, Tetrahedron Letters 35 (1994) 6107–6108.
[28] W.J. Peng, J.S. Sun, F. Lin, X.W. Han, B. Yu, Facile synthesis of ginsenoside Ro, Synlett 2 (2004) 259–262.
[29] W. Birberg, H. Loenn, α-Selectivity and glycal formation are temperature dependent in glycosylation with sialic acid, synthesis of a Neu5Acα(2-6)Gal thioglycoside building block, Tetrahedron Letters 32 (1991) 7453–7456.
[30] D. Liu, W.J. Xie, L. Liu, H.Q. Yao, J.Y. Xu, G. Tanabe, O. Muraoka, X.M. Wu, Synthetic study on neoponkoranol and its side chain epimer as potent α-glucosidase inhibitors, optimization of protecting group, Tetrahedron Letters 54 (2013) 6333–6336.
[31] T. Hartmann, J. Schmitt, Lipophilicity-beyond octanol/water: a short comparison of modern technologies, Drug Discov. Today Technol 1 (2004) 431–439.
[32] P. Wils, A. Warnery, V. Phung-Ba, S. Legrain, D. Scherman, High lipophilicity decreases drug transport across intestinal epithelial cells, Journal of Pharmacology and Experimental Therapeutics 269 (1994) 654–658.