

# Lathyrane Diterpenoids as Novel hPXR Agonists: Isolation, Structural Modification, and Structure–Activity Relationships

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Cite This: *ACS Med. Chem. Lett.* 2021, 12, 1159–1165

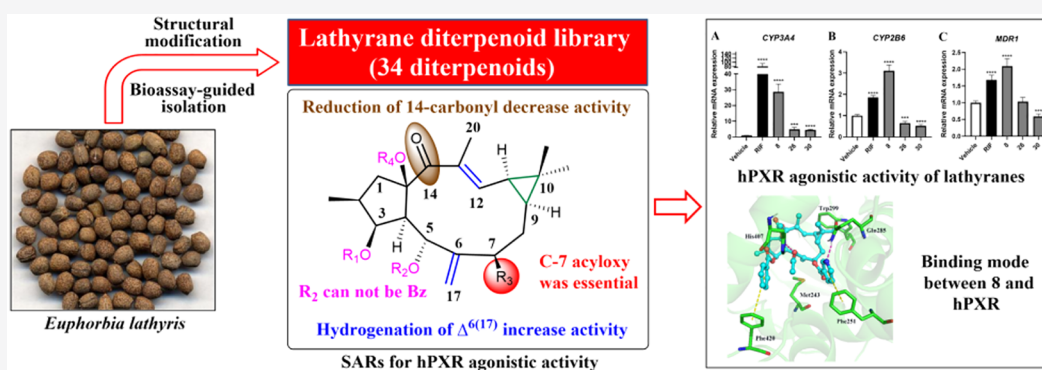
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**ABSTRACT:** Pregnane X receptor (PXR) that orchestrates the intricate network of xeno- and endobiotic metabolism is considered as a promising therapeutic target for cholestasis. In this study, the human PXR (hPXR) agonistic bioassay-guided isolation of *Euphorbia lathyris* followed by the structural modification led to the construction of a lathyrane diterpenoid library (1–34). Subsequent assay of this library led to the identification of a series of potent hPXR agonists, showing better efficacy than that of typical hPXR agonist, rifampicin. The most active compound, 8, could dose-dependently activate hPXR at micromolar concentrations and significantly up-regulate the expressions of PXR downstream genes *CYP3A4*, *CYP2B6*, and *MDR1*. The structure–activity relationships (SARs) studied in combination with molecular modeling suggested that acyloxy at C-7 and the presence of 14-carbonyl were essential to the activity. These findings suggested that lathyrane diterpenoids could serve as a new type of hPXR agonist for future anticholestasis drug development.

**KEYWORDS:** hPXR agonist, lathyrane diterpenoid, structural modification, structure–activity relationships

Cholestasis is a clinical condition where bile flow is defective, either due to impaired secretion by hepatocytes or by obstruction to the bile flow, resulting in intrahepatic accumulation of toxins such as bile acids (BAs).<sup>1</sup> The progression of cholestasis would induce hepatocellular damage, causing a series of cholestatic liver diseases such as primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC).<sup>1,2</sup> Thus, elimination of excess BAs or maintaining the homeostasis of bile flow is considered as the prevailing therapeutic strategy for the treatment of various cholestatic conditions. Until now, only two drugs, ursodeoxycholic acid (UDCA) and obeticholic acid (OCA), have been approved by the FDA for the treatment of cholestatic conditions. UDCA is the first choice of PBC drug that could stimulate secretion of hepatocytes and cholangiocytes via stabilization of the “biliary  $\text{HCO}_3^-$  umbrella”.<sup>3</sup> OCA is a farnesoid X receptor (FXR) agonist that inhibits bile acid synthesis and uptake by activation of BAs detoxification pathways.<sup>3</sup> However, only 50–60% PBC patients are able to respond to these drugs,<sup>1,4</sup>

leaving the nonresponders a high risk of progression to biliary fibrosis, cirrhosis, end-stage liver disease, and death.<sup>5</sup> Therefore, there remains an urgent need for development of novel therapeutic agents with different mechanism to delay or relieve cholestasis-associated symptoms.

Pregnane X receptor (PXR) is a member of the nuclear receptors (NRs) superfamily that orchestrates the intricate network of endobiotic and xenobiotic metabolism.<sup>6,7</sup> Compared with other NRs, PXR contains an N-terminal regulatory domain, a highly conserved DNA-binding domain (DBD), a hinge region, a less conserved ligand-binding domain (LBD), and a C-terminal domain.<sup>8</sup> PXR is predominantly distributed in

Received: May 14, 2021

Accepted: June 23, 2021

Published: June 25, 2021



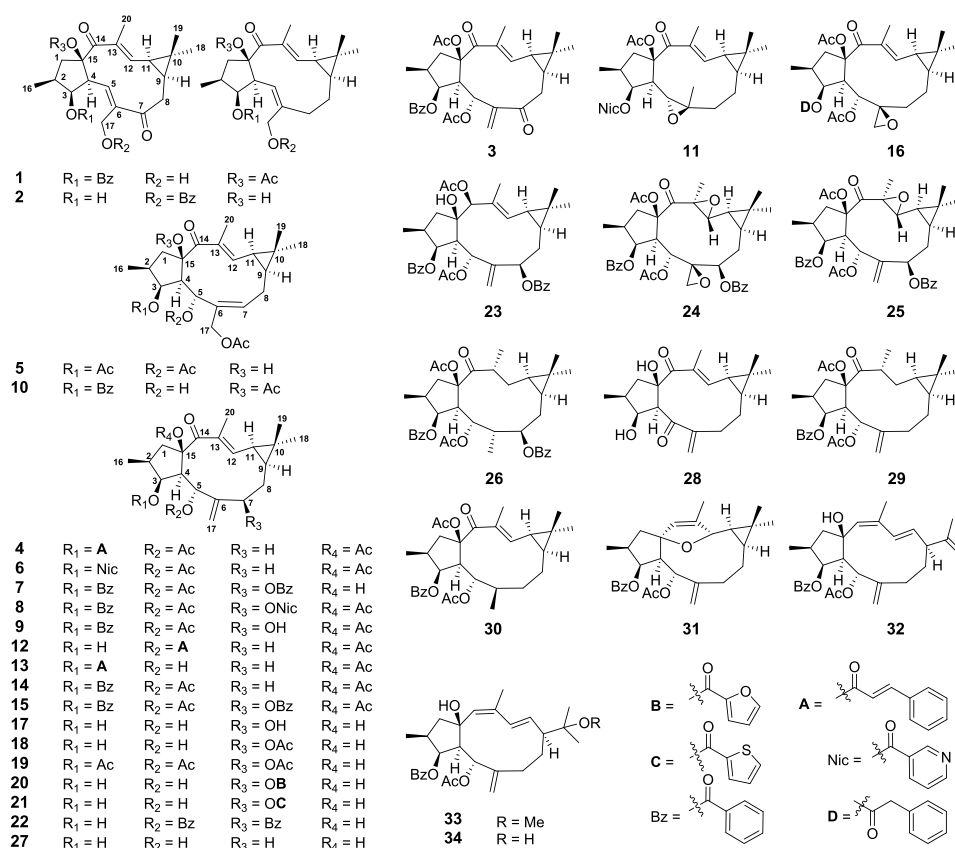


Figure 1. Structures of compounds 1–34.

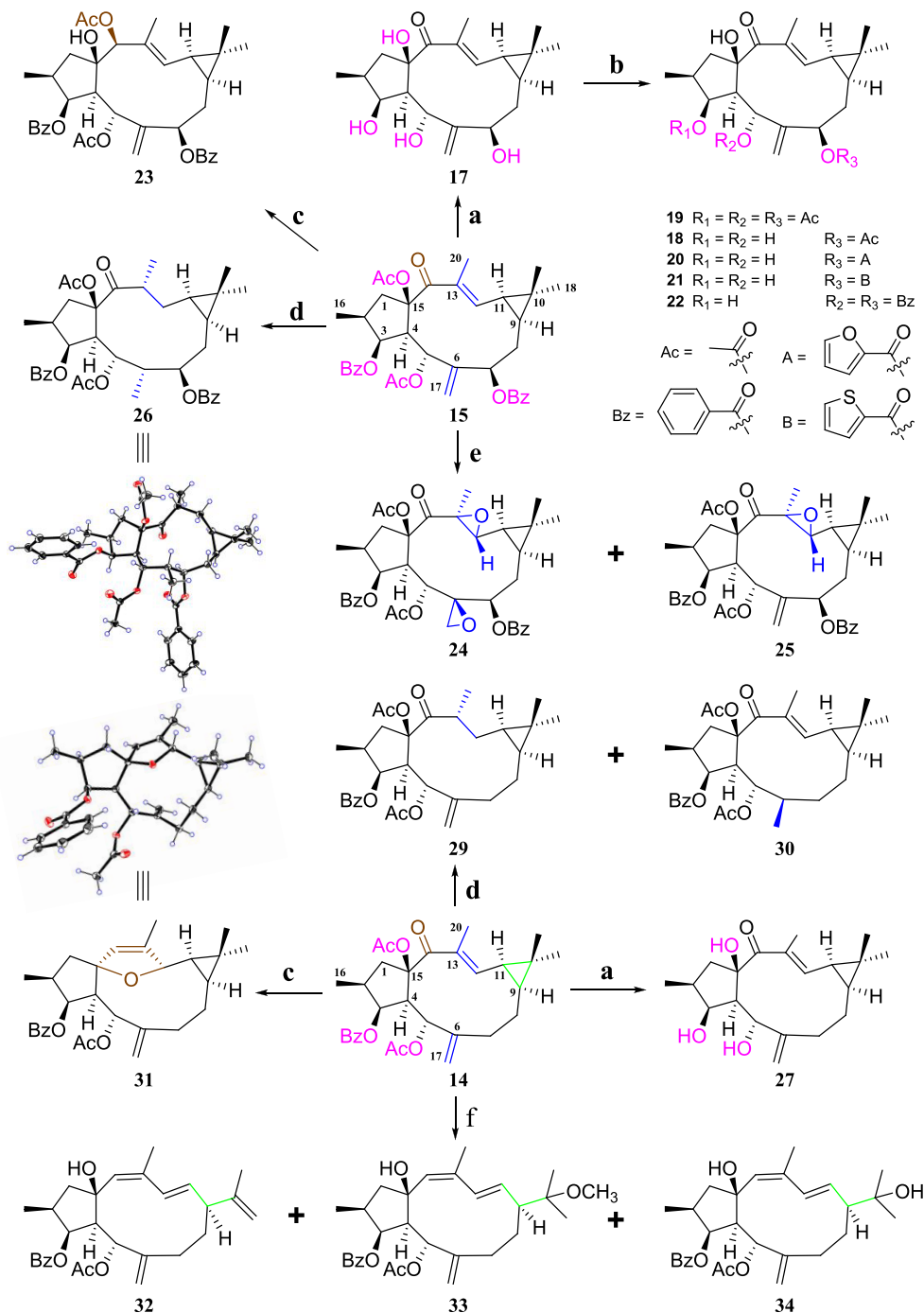
the liver and intestine, where it regulates the expression of phases I and II drug-metabolizing enzymes, such as cytochrome P450 (CYPs), alcohol and aldehyde dehydrogenases, sulfotransferases (SULTs) and glucuronyltransferases (UGTs),<sup>9</sup> and numerous phase III efflux transporters (e.g., MDR1 and MRP) to control the metabolism of endobiotics (e.g., BAs, glucose, and lipid) and xenobiotics (e.g., therapeutic agents).<sup>10–13</sup> Intensive evidences have proved the important role of PXR signaling in the maintenance of BA homeostasis.<sup>13</sup> Activated-PXR could promote BA detoxification by activation of the hydroxylation and conjugation pathways. The former converts BAs into its hydroxyl derivatives with the assistance of enzymes such as CYP3A and CYP2B, whereas the latter further transforms these hydroxyl derivatives to more hydrophilic conjugates under the catalysis of enzymes UGTs, GSTs, and SULTs. Meanwhile, the activation of PXR could upregulate transporters such as P-glycoprotein (P-gp, encoded by MDR1), which finally transports the detoxified BA metabolites into the bile or urine.<sup>14</sup> Strikingly, a recent study has shown that rifampicin, a typical human PXR (hPXR) agonist, could completely reverse severe persistent hepatocellular secretory failure induced by drugs or transient biliary obstruction in formerly healthy individuals, an enormous relief for otherwise desperate patients.<sup>15</sup> Thus, PXR has emerged as a promising therapeutic target in cholestasis, and the discovery of novel PXR agonist is of great value in anticholestasis drug development.

Natural products have historically played an important and irreplaceable role in drug discovery. This role has been underscored in anticholestasis drug development, as the only two approved PBC drugs, UDCA and OCA, are all derived

from natural products. In recent years, plenty of natural hPXR agonists, such as tanshinone IIA, schisandrol B, solomonsterols A and B, have been reported from various medicinal plants,<sup>16–18</sup> suggesting that the search for hPXR agonists from natural source might be a shortcut in anticholestasis drug campaign. In the frame of our interest in the discovery of biologically significant macrocyclic diterpenoids from *Euphorbiaceae* species,<sup>19,20</sup> we conducted the hPXR agonistic bioassay-guided isolation on a traditional Chinese medicine, *Euphorbia lathyris*, which led to the isolation of 16 lathyrane diterpenoids. The subsequent structural modification generated a lathyrane library containing 34 compounds for systematic investigation. Herein, we described the bioassay-guided isolation, structural elucidation, modification, hPXR agonistic activity, and SARs of these diterpenoids, as well as the molecular recognition mechanism between 8 and hPXR.

The dried seeds of *E. lathyris* (8 kg) were extracted with 95% ethanol at room temperature (rt) to give a crude extract, which was suspended in water and then successively partitioned with petroleum ether, EtOAc, and *n*-BuOH. Each fraction was tested for agonistic activity on the hPXR, and the EtOAc fraction which displayed a promising hPXR agonistic activity (2.1-fold increasing at 50  $\mu\text{g/mL}$ ) was selected for further chemical investigation. Subsequent systematic purification of this fraction using various chromatographic methods led to the identification of 16 structurally related lathyrane diterpenoids (1–16) (Figure 1), of which 1–5 were new compounds.

Compound 1 exhibited a molecular formula of  $\text{C}_{29}\text{H}_{34}\text{O}_7$  as determined by HRESIMS ion at  $m/z$  517.2193 [ $\text{M} + \text{Na}$ ]<sup>+</sup> (calcd 517.2197). The 1D NMR spectra of 1 were similar to those of a known compound 15,17-di-O-acetyl-3-O-benzoyl-

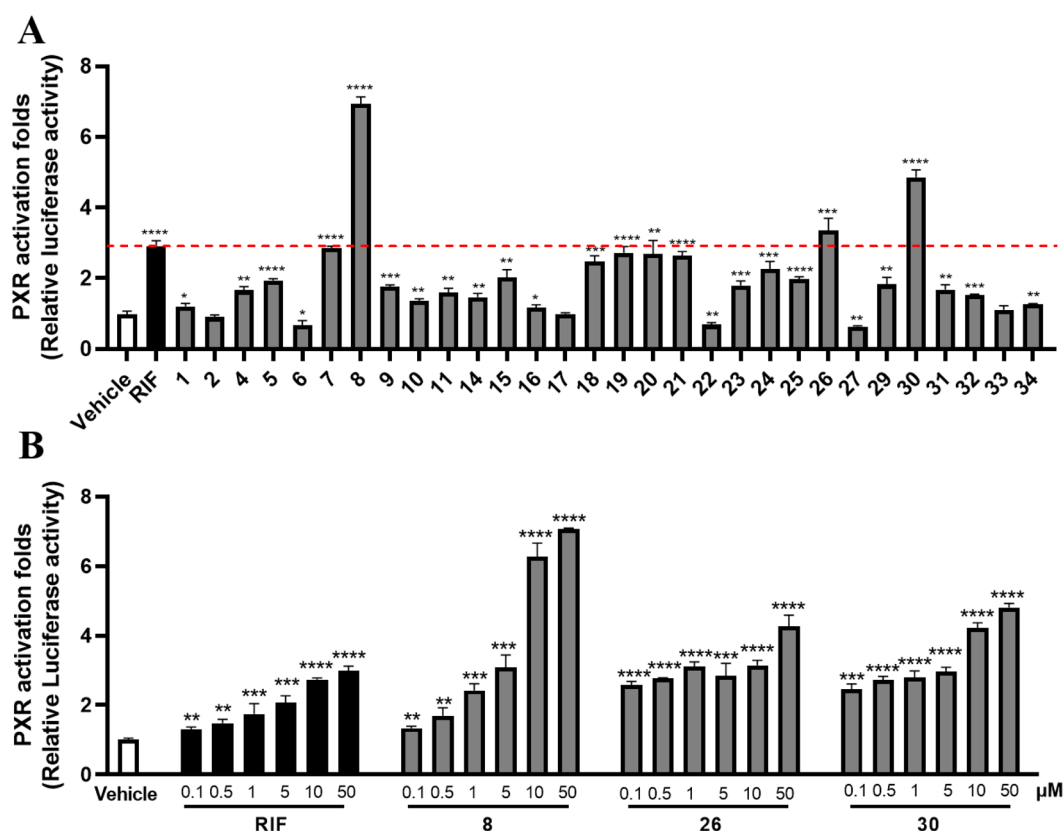
Scheme 1. Synthesis of Lathyrane Diterpenoid Derivatives.<sup>a</sup>

<sup>a</sup>Reagents and conditions: (a) 1% NaOH in MeOH (m/v), rt, 1 h; (b) acetic anhydrides/2-furoyl/2-thiophenecarbonyl/benzoyl chlorides, Pyr, rt or 0 °C, 2 h; (c) sodium borohydride, MeOH, rt, 15 min; (d) 10% Pd/C, H<sub>2</sub>, EtOAc, 50 °C, 24 h; (e) *m*-CPBA, CH<sub>2</sub>Cl<sub>2</sub>, 60 °C, 1 h; (f) (1) sodium borohydride, MeOH, rt, 15 min; (2) 10% HCl in MeOH (m/v), 30 min.

17-hydroxyjolkinol,<sup>21</sup> with the major differences being the absence of the 17-acetyl group and the presence of the C-7 ketone group ( $\delta_{\text{C}}$  203.7) in **1**. This was supported by the upfield-shifted carbon signal of C-17 and the downfield-shifted carbon signals of C-5 and C-8 in **1** with respect to those in known compound [ $\delta_{\text{C}}$  58.0 (C-17), 137.1 (C-5), 36.3 (C-8) in **1**;  $\delta_{\text{C}}$  64.0 (C-17), 124.9 (C-5), 28.5 (C-8) in known compound]. The planar structure of **1** was further secured by detailed analyses of its 2D NMR data (Figure S2.1). The stereochemistry of **1** was assigned to be the same as that of

15,17-di-*O*-acetyl-3-*O*-benzoyl-17-hydroxyjolkinol by a NOESY experiment and comparison of their 1D NMR data (Table S1). Therefore, the structure of **1** was elucidated as 15-acetoxy-3-benzoyloxy-17-hydroxy-14-oxolathyr-5*E*,12*E*-diene and was given the trivial name euphlathyrinoid A.

Compound **2** had the molecular formula of C<sub>27</sub>H<sub>34</sub>O<sub>5</sub> as determined by HRESIMS and <sup>13</sup>C NMR data. The 1D NMR data of **2** bore a high resemblance to those of known compound 15,17-diacetoxy-3-hydroxy-14-oxolathyr-5*E*,12*E*-diene,<sup>22</sup> except for the presence of a benzoyl group in **2**



**Figure 2.** Effects of 8, 26, and 30 on human PXR activation. (A) Dual-luciferase reporter gene assay was performed in HEK293T cells transiently transfected with expression vectors encoding human PXR (pSG5-hPXR), reporter plasmid (pGL3-CYP3A4-XREM-Luc), and the control plasmid (pRL-TK). Cells were treated with the positive agonist RIF (10  $\mu$ M) or compounds 1–34 (10  $\mu$ M) for 24 h. (B) Dose–response assay for 8, 26, 30, and RIF (0.1, 0.5, 1, 5, 10, and 50  $\mu$ M). Data are presented as mean  $\pm$  SD ( $n = 3$ ). \* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.001$ , \*\*\*\* $P < 0.0001$ , versus the vehicle.

instead of two acetyl group in the known compound. The benzoyl group was located at C-17 by the HMBC correlation from H<sub>2</sub>-17 ( $\delta_{\text{H}}$  4.61 and 4.32) to the benzoyl carbonyl carbon ( $\delta_{\text{C}}$  166.5). The stereochemistry of 2 was assigned to be the same as that of known compound by comparison of their NOE correlations and 1D NMR data, except for the *Z* configuration of  $\Delta^5$  was assigned by the NOESY correlations of H-4/H-17a (Figure S2.2). Thus, the structure of 2 was elucidated as 17-benzoyloxy-3,15-dihydroxy-14-oxolathyr-6(17),12*E*-diene and was given a trivial name euphlathyrinoid B.

Compound 3 had a molecular formula of C<sub>31</sub>H<sub>36</sub>O<sub>8</sub> as established by HRESIMS data at  $m/z$  559.2306 [ $M + \text{Na}$ ]<sup>+</sup> (calcd 559.2302). The NMR data of 3 showed high similarity to those of coisolated known compound 5,15-diacetoxy-3-benzoyloxy-7-hydroxy-14-oxolathyr-6(17),12*E*-diene (9),<sup>22</sup> except for the presence of a ketone signal ( $\delta_{\text{C}}$  199.9) in 3 instead of an oxygenated-methine signal for C-7 ( $\delta_{\text{H}}$  4.23;  $\delta_{\text{C}}$  78.2) in 9, indicating that 3 was a C-7 oxidized derivative of 9. This was supported by the downfield-shifted carbon signal of C-17 in 3 as compared to those in 9 ( $\delta_{\text{C}}$  128.0 in 3;  $\delta_{\text{C}}$  118.7 in 9) and further confirmed by detailed 2D NMR analyses (HSQC, HMBC, and <sup>1</sup>H–<sup>1</sup>H COSY). The structure of 3 was further secured by chemical correlation of 14 to 3 via sequential oxidation. In brief, oxidation of the coisolated known compound 14 with selenium dioxide (SeO<sub>2</sub>) afforded 9, which was oxidized under Dess–Martin periodinane reagent to obtain 3 (Figure S2.4). Thus, the structure of 3 was identified as 5,15-diacetoxy-3-benzoyloxy-7,14-dioxolathyr-6(17),12*E*-diene and was named euphlathyrinoid C.

Compound 4 exhibited a molecular formula of C<sub>33</sub>H<sub>40</sub>O<sub>7</sub> as determined by HRESIMS ion at  $m/z$  571.2659 [ $M + \text{Na}$ ]<sup>+</sup> (calcd 571.2666). The NMR data of 4 were very similar to those of coisolated known compound 15-acetoxy-3-cinnamoyloxy-5-hydroxy-14-oxolathyr-6(17),12*E*-diene (13),<sup>22</sup> except for the presence of an additional acetyl group in 4 [ $\delta_{\text{H}}$  1.92 (s);  $\delta_{\text{C}}$  21.1 and 170.3], indicating 4 was an acetylated derivative of 13. The acetyl group was located at 5-OH by the HMBC correlation from H-5 ( $\delta_{\text{H}}$  6.17) to the acetyl carbonyl carbon as well as the downfield-shifted H-5 signal in 4 with respect to that in 13 [ $\delta_{\text{H}}$  6.17 (1H, d,  $J = 10.0$  Hz) in 4;  $\delta_{\text{H}}$  4.51 (1H, d,  $J = 9.8$  Hz) in 13]. The structure of 4 was further secured by the chemical correlation of 13 to 4 via acetylation (Figure S2.4). Thus, the structure of 4 was elucidated as 5,15-diacetoxy-3-cinnamoyloxy-14-oxolathyr-6(17),12*E*-diene and was given a trivial name euphlathyrinoid D.

Compound 5 possessed a molecular formula of C<sub>26</sub>H<sub>36</sub>O<sub>8</sub> as determined by HRESIMS data at  $m/z$  499.2295 [ $M + \text{Na}$ ]<sup>+</sup> (calcd 499.2302). The NMR data of 5 were very similar to those of known compound 5,17-diacetoxy-3-benzoyloxy-15-hydroxy-14-oxolathyr-6*Z*,12*E*-diene,<sup>22</sup> with the only differences being the replacement of C-3 benzoyl group in known compound by an acetyl group in 5. This was confirmed by HMBC correlation from H-3 ( $\delta_{\text{H}}$  5.66) to acetyl carbonyl carbon ( $\delta_{\text{C}}$  169.4). The structure of 5 was further secured by chemical correlation with the coisolated known analogue 15,17-di-*O*-acetyl-3-*O*-benzoyl-5,17-dihydroxyisolathyr-6(17),12*E*-diene (10).<sup>21</sup> The alkaline hydrolysis of 5 and 10 generated the same product, 35, which was verified by comparison of their <sup>1</sup>H



NMR spectra and optical rotation data. Thus, the structure of **5** was elucidated as 3,5,17-triacetoxy-15-hydroxy-14-oxolathyr-6Z,12E-diene and was given the trivial name euphlathyrinoid E.

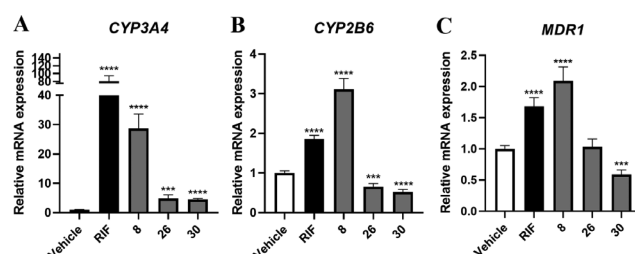
The known compounds, *Euphorbia* Factor L<sub>8</sub> (**6**),<sup>23</sup> *Euphorbia* Factor L<sub>11</sub> (**7**),<sup>24</sup> *Euphorbia* Factor L<sub>9</sub> (**8**),<sup>25</sup> 5,15-diacetoxy-3-benzoyloxy-7-hydroxy-14-oxolathyr-6(17),12E-diene (**9**),<sup>22</sup> 15,17-di-O-acetyl-3-O-benzoyl-5,17-dihydroxy-isolathyr-6(17),12E-diene (**10**),<sup>21</sup> 15-O-acetyl-3-O-nicotinoyl-jolkinol-5 $\beta$ ,6 $\beta$ -oxide (**11**),<sup>26</sup> *Euphorbia* Factor L<sub>31</sub> (**12**),<sup>27</sup> *Euphorbia* Factor L<sub>30</sub> (**13**),<sup>27</sup> *Euphorbia* Factor L<sub>3</sub> (**14**),<sup>25</sup> *Euphorbia* Factor L<sub>2</sub> (**15**),<sup>23</sup> and *Euphorbia* Factor L<sub>1</sub> (**16**),<sup>23</sup> were identified by comparison of their spectroscopic data with those in the literatures.

To clarify the SARs of lathyrane diterpenoids related to the hPXR, we used the major components, **14** and **15**, as the starting materials for the design of various derivatives (Scheme 1). Briefly, the structural modifications were mainly deployed on the  $\Delta^{6(17)}$  terminal double bond,  $\alpha,\beta$ -unsaturated ketone, cyclopropane ring as well as substituents on C-3, C-5, C-7, and C-15. First, alkaline hydrolysis of **15** and **14** afforded **17** and **27**, respectively, to increase their hydrophilicity. Then, the acylation of the free hydroxyls in **17** with acetic anhydride or 2-furoyl/2-thiophenecarbonyl/benzoyl chloride yielded corresponding esters **18–22**. The partial palladium catalyzed hydrogenation of **14** at  $\Delta^{6(17)}$  or  $\Delta^{12}$  afforded **30** or **29**, respectively. The complete hydrogenation of **15** via an excess of palladium generated **26**. The oxidation of **15** with *meta*-chlorobenzoic acid (*m*-CPBA) gave the epoxide derivatives **24** and **25**. Reduction of **14** and **15** with the sodium borohydride generated **31** [possessing a rare CH(12)–O–C(15) linkage] and **23**, respectively. Finally, the treatment of **14** with sodium borohydride followed with dilute hydrochloric acid afforded the cyclopropane-opening products **32**, **33**, and **34**.

The cytotoxicity of **1–34** was initially performed on HEK293T cells to exclude the cytotoxic compounds **3**, **12**, **13**, and **28** (Figure S2.5). Then, the remaining compounds were subjected to the hPXR agonistic screening by using a dual-luciferase reporter gene system constructed in HEK293T cells via transient transfection with reporter plasmids.<sup>17</sup> Rifampicin (RIF), a classical hPXR agonist, was used as the positive drug. The results showed most of these lathyrane diterpenoids exhibited potent hPXR agonistic activity at the concentration of 10  $\mu$ M (Figure 2A). Among them, **8**, **26**, and **30** could significantly enhance the hPXR reporter gene activity by 6.9, 3.4, and 4.9 fold, respectively, being more active than that of RIF (activation fold = 2.9). Then, the dose–response assays of **8**, **26**, **30**, and RIF were performed. As shown in Figure 2B, all of these compounds could dose-dependently enhance the hPXR reporter gene activity.

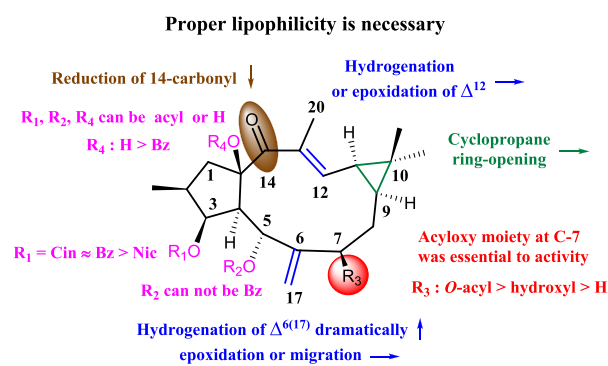
To confirm the hPXR activation effects of **8**, **26**, and **30**, we further evaluated their regulation on hPXR downstream key genes that are responsible for BAs metabolism and transport. HepaRG cells were incubated with **8**, **26**, and **30**, and the mRNA expressions of *CYP3A4*, *CYP2B6*, and *MDR1* were measured by RT-qPCR. The results indicated that **8** remarkably increased the expressions of *CYP3A4*, *CYP2B6*, and *MDR1*, suggesting that **8** may activate hPXR to promote BA detoxification (Figure 3).

In general, the hydrolysis products showed a dramatic decrease in the activity, as shown by **14** vs **27** and **15** vs **17**, indicating that proper lipophilicity is necessary for activity. On this basis, the different substituents on C-3, C-5, C-7, and C-15



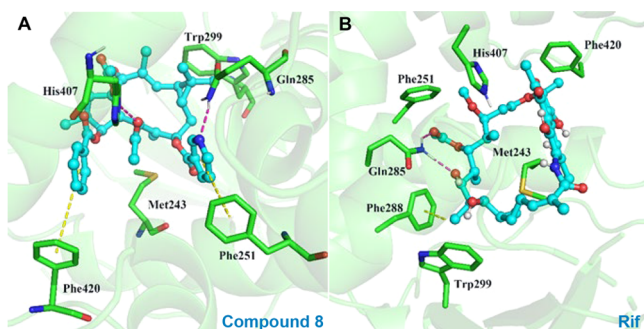
**Figure 3.** RT-qPCR analysis was used to detect the expressions of the PXR downstream genes (A) *CYP3A4*, (B) *CYP2B6*, and (C) *MDR1* in HepaRG cells after treatment of RIF (10  $\mu$ M) and compounds **8**, **26**, and **30** (10  $\mu$ M). Values were relative to house-keeping gene  $\beta$ -ACTIN. Data were presented as mean  $\pm$  SD ( $n = 3$ ). \* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.001$ , \*\*\*\* $P < 0.0001$ , versus the vehicle.

endowed with different agonistic activity on hPXR. In the 3-*O*-acyls series, the activities were ranked as 3-*O*-cinnamoyl (**4**)  $\approx$  3-*O*-benzoyl (**14**) > 3-*O*-nicotinoyl (**6**). In the C-7 substitutes series, different moiety contributed to the activity was ranked as 7-acyloxy > 7-hydroxyl > 7-alkyl (**8** and **15** > **9** > **14**; **18**, **20**, and **21** > **17** > **27**), indicating the presence of acyloxy moieties at C-7 were beneficial to activity. Remarkably, 7-*O*-nicotinoyl significantly increased the activity as compared to 7-*O*-benzoyl (6.93-fold in **8** vs 2.03-fold in **15**). The acylation of OH-15 was detrimental to activity, as shown by **7** vs **15**. In addition, the presence of 5-*O*-benzoyl led to a dramatic decrease of the activity, as shown by **18**, **20**, and **21** vs **22**, suggesting the unfavorableness of large substituent at C-5. In  $\alpha,\beta$ -unsaturated ketone group, the hydrogenation or epoxidation of  $\Delta^{12}$  generally had little influence on the activity as shown by **29** vs **14** and **25** vs **15**, whereas the reduction of 14-carbonyl decreased the activity (**23** vs **7**). The hydrogenation of  $\Delta^{6(17)}$  dramatically increased the activity as shown by **30** vs **14** and **26** vs **15**, whereas epoxidation or migration had little influence (**24** vs **25**; **16** vs **14**; **10** vs **14**). In addition, the cyclopropane ring-opening seemed indifferent to the activity, as shown by **32**, **33**, and **34** vs **14**. The above-mentioned SARs information is summarized in Figure 4.



**Figure 4.** SARs of lathyrane diterpenoids on hPXR agonistic activity.  $\uparrow$ , increased activity;  $\downarrow$ , decreased activity;  $\rightarrow$ , little influence on activity.

To further explore the potential molecular recognition mechanism between these lathyrane diterpenoids and hPXR, we simulated the binding modes of **8** and RIF with hPXR, respectively, by docking these agonists into the hPXR ligand-binding domain (LBD, PDB ID: 1SKX) using MOE2014.0901. As shown in Figure 5, **8** was docked well into the LBD of



**Figure 5.** Binding modes of ligands with hPXR derived from docking simulations (red dashed lines for hydrogen bond and yellow dashed lines for  $\pi$ - $\pi$  stacking interaction or CH- $\pi$  interaction). (A) Binding mode of compound 8. (B) Binding mode of RIF.

hPXR. It engaged one hydrogen bond with His407 via 5-OAc, one hydrogen bond with Gln285 via 7-ONic, and two favorable  $\pi$ - $\pi$  stacking interactions with Phe420 and Phe251 via 3-OBz and 7-ONic, respectively. These interactions were different to those of RIF, which formed two hydrogen bonds with Gln 285 and one CH- $\pi$  interaction with Phe288. Generally, the calculated binding energy of 8 with the hPXR [S-score, S(Max) = -13.1065] was better than that of RIF [S(Max) = -12.8002], explaining the higher potency of 8. Among the interactions between 8 and hPXR, the 7-ONic of 8 contributed a hydrogen bond and a  $\pi$ - $\pi$  stacking interaction to the hPXR binding, suggesting its important role for activity. This was consistent with the above-mentioned SARs and also explained that the replacement of 7-ONic by a 7-OBz led to a dramatic decrease in the activity.

In summary, a lathyrane diterpenoid library (1–34), containing 19 new compounds, was constructed by bioassay-guided phytochemical investigation of *E. lathyris* and subsequent structural modification. The hPXR agonistic assay of this library led to the identification of a promising hPXR agonist, 8. Compound 8 could significantly activate hPXR as evidenced by the hPXR reporter gene activity (6.9-fold), and up-regulate the expressions of hPXR downstream key genes *CYP3A4*, *CYP2B6*, and *MDR1*. The SARs indicated that acyloxy substituents on C-7, and the presence of 14-carbonyl were essential to activity. The molecular recognition mechanism between 8 and hPXR further underscored the importance of C-7-acyloxy and commendably explained that the replacement of 7-ONic by a 7-OBz led to a dramatic decrease of the activity. Lathyrane diterpenoids featuring a 5/11/3-tricyclic carbon framework are the major components of *E. lathyris*. Our current study revealed for the first time that the lathyrane diterpenoids could serve as a new type of hPXR agonist. The easily accessible natural source and the clear SARs may provide opportunity for us to rationally design more potent lathyrane-type hPXR agonists and verify its in vivo anticholestatic effect in the near future.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsmedchemlett.1c00277>.

Full experimental procedures; 1D and 2D NMR, IR, MS, and HPLC spectra of 1–34; X-ray crystallographic data of 26, 30, and 31 (PDF)

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

This work was supported by Natural Science Foundation of China (81973195 and 81973203), the Fundamental Research Funds for the Central Universities (20ykjc04), the Guangdong Provincial Key Laboratory of Construction Foundation (2017B030314030), the China Postdoctoral Science Foundation (2020M683138), the Local Innovative and Research Teams Project of Guangdong Pearl River Talents Program (2017BT01Y093), the Shenzhen Science and Technology Program (KQTD20190929174023858), and the 111 project (B16047).

## ■ ABBREVIATIONS

hPXR, human pregnane X receptor  
BAs, bile acids  
PBC, primary biliary cholangitis  
PSC, primary sclerosing cholangitis  
UDCA, ursodeoxycholic acid  
OCA, obeticholic acid  
FXR, farnesoid X receptor  
DBD, DNA-binding domain  
LBD, ligand-binding domain  
CYPs, cytochrome P450  
SULTs, sulfotransferases  
UGTs, glucuronyltransferases  
m-CPBA, meta-chorobenzoic acid

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