Supplementary Materials

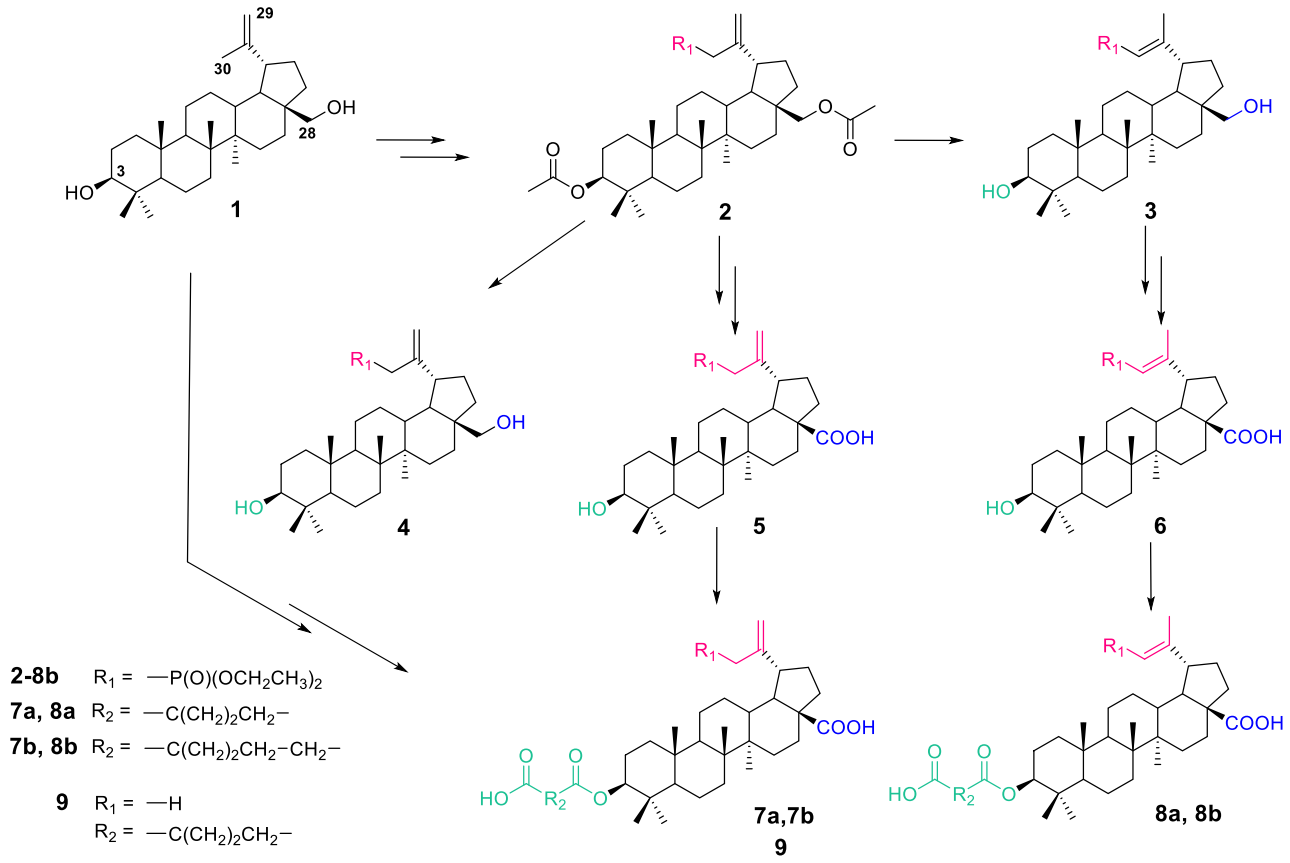

Figure S1. Scheme of the synthesis of the tested compounds 2-9.

S1 Procedure for the synthesis of compounds **2-9**.

The 3,28-diacetylbetulin obtained from betulin **1** was brominated in the allyl position with N-bromosuccinimide. From the formed 30-bromo-3,28-diacetylbetulin, in the reaction with triethyl phosphite, the 30-phosphonate derivative of 3,28-diacetylbetulin **2** was obtained. Then, the hydrolysis of the acetyl groups in the compound **2** under the influence of potassium hydroxide in boiling ethanol was carried out. The reaction conditions used led to allyl-vinyl isomerization in the isopropenyl group, resulting in the formation of 29-diethoxy-phosphonylbetulin **3**. To obtain a series of derivatives containing a phosphonate group at position C30, milder hydrolysis conditions were used, which led to the formation of compound **4**. The yield of this reaction was not satisfactory and therefore, derivative **5** was synthesized in a different reaction sequence running through the stage of the 30-phosphonate

derivative of 3-acetylbetulin [37]. In the last stage, acylation reactions of compounds **5** and **6** with acid anhydrides (dimethylsuccinyl and 2,2-dimethylglutaryl) were carried out in a microwave reactor, obtaining derivatives **7a**, **7b**, **8a**, **8b**. Oxidation of betulin **1** with Jones reagent followed by reduction with sodium borohydride yielded betulinic acid, which was converted to 3-O-(3′,3′-dimethylsuccinyl) betulinic acid **9** (bevirimat, BVM).

S2 Methodology of *in silico* studies

S2.1. Assessment of ADME Properties and Drug-likeness of the Screened Molecules

The structures of the tested compounds **1**, **3**-**9** were converted to SMILES codes using the ChemDraw application and sent for analysis in pkCSM (http://biosig.unimelb.edu.au/pkcsm/prediction accessed on 22 January 2023) and SwissADME (http://www.swissadme.ch/index.php accessed on 22 January 2023).
ADMET parameters were predicted using pkCSM software [45]. Calculations of physicochemical parameters and assessment of drug similarity were carried out using the SwissADME platform [46].

S2.2. Calculations of Quantum Descriptors

The optimized chemistry structure of compound **3** was calculated using the DFT (B3LYP/6-311G+(d.p)) method implemented in the Gaussian 16 program package [47]. The calculated geometry was used to determine the HOMO-LUMO energy, quantum chemical descriptor, the molecular electrostatic potential, and the molecular docking study [48]. All obtained results were visualized in the GaussView, Version 5 software package [49].

S.2.3. Method for Molecular Docking

Low-energy conformations of the studied compounds were obtained using the General Atomic and Molecular Electronic Structure System computer program (ver. 30SEP2019(R2), GAMESS, https://www.msg.chem.iastate.edu/gamess/). Density func-tional at the B3LYP/6e31þ(g,d,p) level of theory was used. The macromolecular structure of HadV-5 virus protease [50], which was used as the target protein, was obtained from the Protein Data Bank (https:// www.rcsb.org/, PDB ID: 4PIE). The AutoLigand extension in AutoDockTools was used to search for the ligand-binding site in the protein [51]. All input files were prepared using AutoDockTools (ver. 1.5.6). Docking poses were obtained and ranked by their score values in kcal/mol. The BIOVIA Discovery Studio package and LigPlot+ software were used to analyze and visualize the results [52, 53]. AutoDock Vina software (ver. 1.1.2) was used to perform molecular docking [54].