SUPPLEMENTARY FILE

2.1. Molecular docking

2.1.1 Protein preparation

The docking simulation study of 32 different bioactive molecules from the plant *Asparagus racemosus* was performed on the 1.9 A crystal structure of NSP15 Endoribonuclease from SARS CoV-2 in the complex with a citrate (PDB ID: 6W01) and prefusion 2019-nCoV spike glycoprotein with a single receptor-binding domain up (PDB ID: 6MOJ) which was retrieved from protein data bank (https://www.rcsb.org). The protein preparation wizard of Schrödinger maestro 2018-1 MM share version was used to prepare the structure by adding hydrogen, treating metal, deleting water molecules and assigning partial charges by using the OPLS-2005 force field, then assigning protonation states and determining restrained and further partial energy was minimized with 0.3Å RMSD limit. The binding sites were defined after removing the ligand then grid was generated using a grid box volume of 20_20_20 Å.

2.1.2 Ligand preparation

The 2D structure of ligands were downloaded from pubchem compound database (https://pubchem.ncbi.nlm.nih.gov) in SDF format and uploaded to the work space. Then ligprep module of maestro was used to generate the 3D structure and OPLS-2005 force field was used to generate the different conformation of each ligand. The stable conformer of each Saikosaponin with minimum potential energy was further processed.

2.1.3 Protein ligand docking

Glide module of Schrödinger suite was used to dock the each ligand into the identified binding site of grid, and the lowest binding pose of each docking run was retained. The results of simulations were analyzed using glide XP visualizer, and the important active site interactions were analyzed along with the scoring functions.

2.2 Molecular Dynamics (MD) Simulation and Molecular Mechanics-Generalized Born Solvent Accessibility (MM-GBSA) Analysis

2.2.1. System preparation

All the MD simulations were done on AMBER 18 software package. ANTECHAMBR was used for ligand preparation and to determine the charges on ligand and further GAF force field was used for parametrization. Complexes of protein and ligand were prepared with the help

of xleap. The SARS-CoV-2 spike protein receptor-binding domain and NSP 15 endoribonuclease were solvated separately in truncated octahedron of TIP3P box giving a total of 24515 and 20364 water molecules respectively. Sufficient number of counter ions Na^+ and Cl^- were added to neutralize the simulation system and 0.1M of ionic strength was achieved. To parameterize the amino acids and to model the proteins FF14SB force field was used.

2.2.2. Unbiased MD simulation

Simulations were performed for 100 ns of time step on Nvidia V100-SXM2-16GB Graphic Processing Unit using the PMEMD.CUDA module. Simulations were run at 1 atm constant pressure using Monte Carlo barostat and 300 K constant temperature by using Longevin thermostat with a collision frequency of $2ps^{-1}$ and the volume exchange was attempted for every 100 fs. An integration step of 2 fs was also used for simulation the hydrogen atoms involving bonds were constrained by using SHAKE algorithm. Long range electrostatic interactions were computed by using Particle Mesh Ewald method while for short range interaction a cutoff of 8 Å was used. Equilibration consisted of rounds of NVT and NPT equilibration for 10 ns in total. CPPTRAJ was used to analyze the interactions over full trajectory after taking configuration at every 4 ps. RMSD, RMSF and MMGBSA binding free energy was determined after analyzing the trajectories.

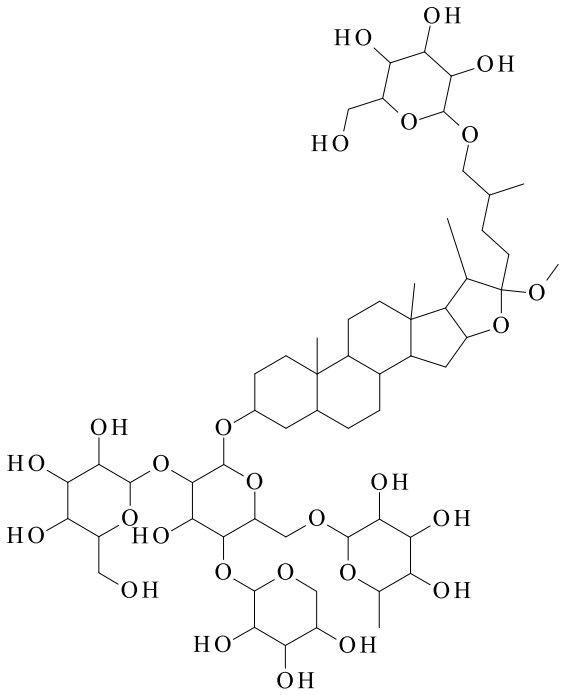
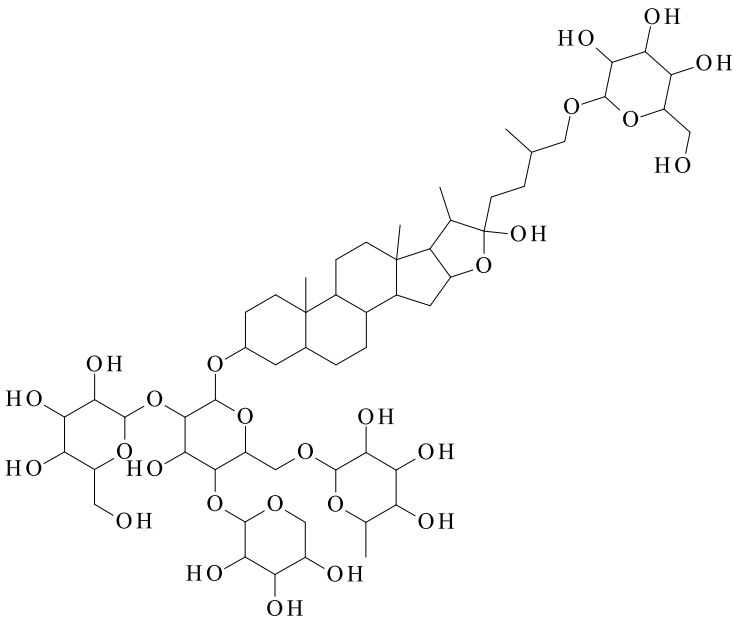
2.2.3. MM-GBSA analysis

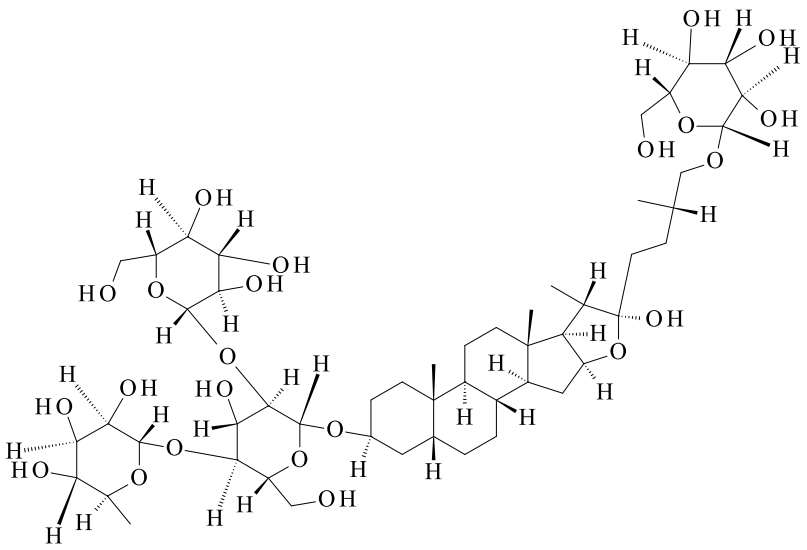
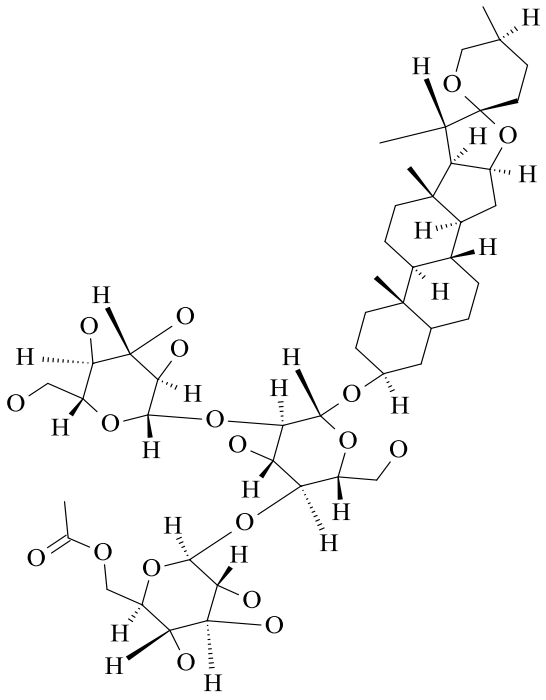
The MM-GBSA was performed on Amber18 and Amber18 tools. After simulation of the protein-ligand complexes, all the trajectories of 100 ns covering all the 10000 frames were used for MM-GBSA analysis. All the results in the form of energies were tabulated and reported in Kcal/mol.

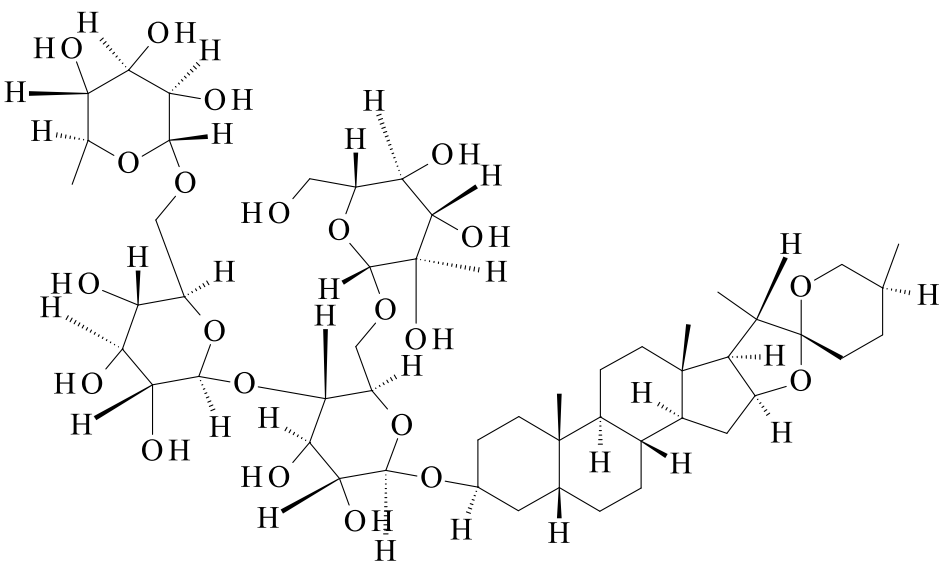
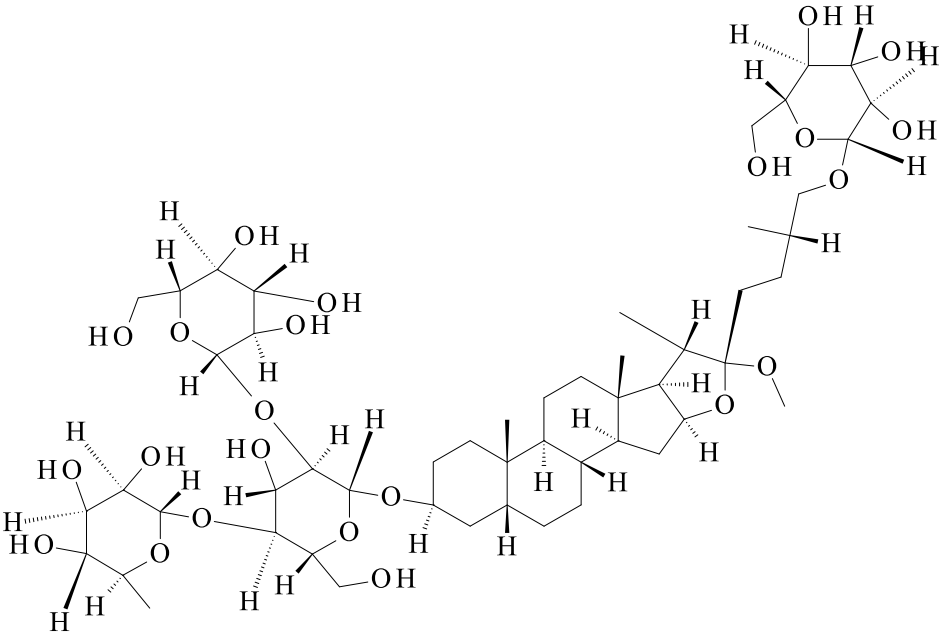
Table S1: List of bio-actives with binding interaction parameter i.e. binding energy with the PDB: **6W01** and PDB: **6M0J** of SARS-CoV-2

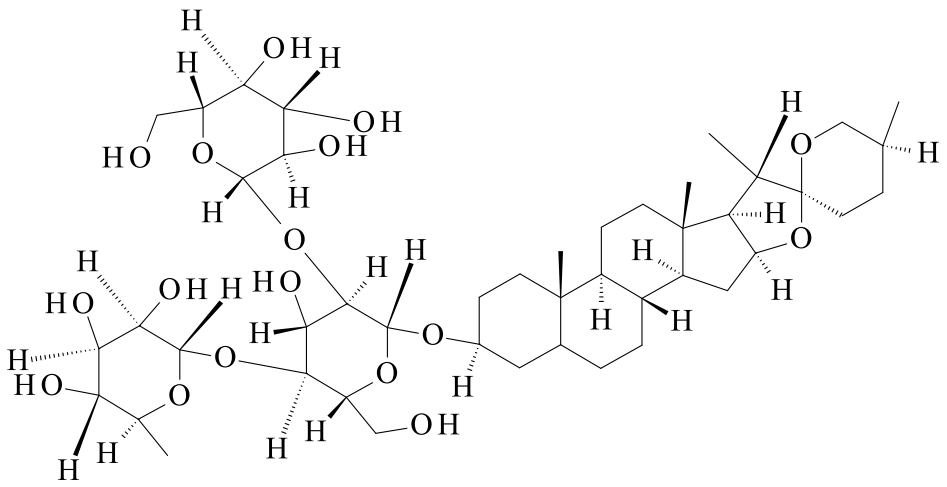
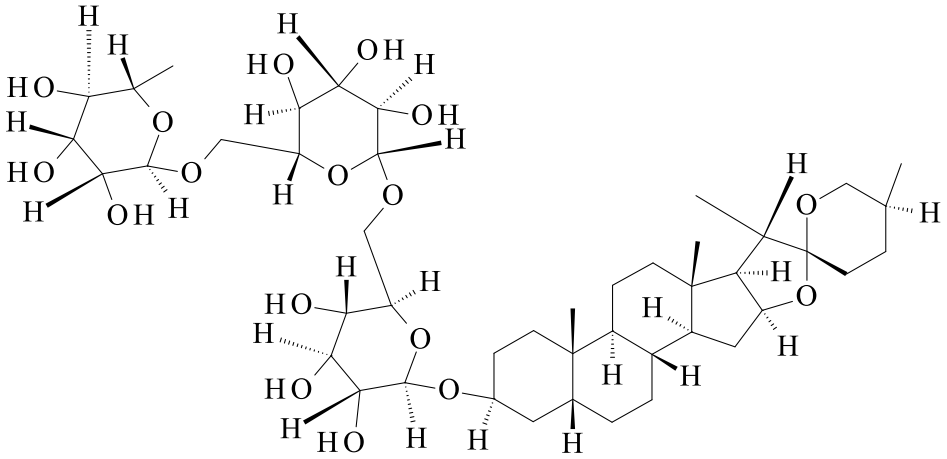
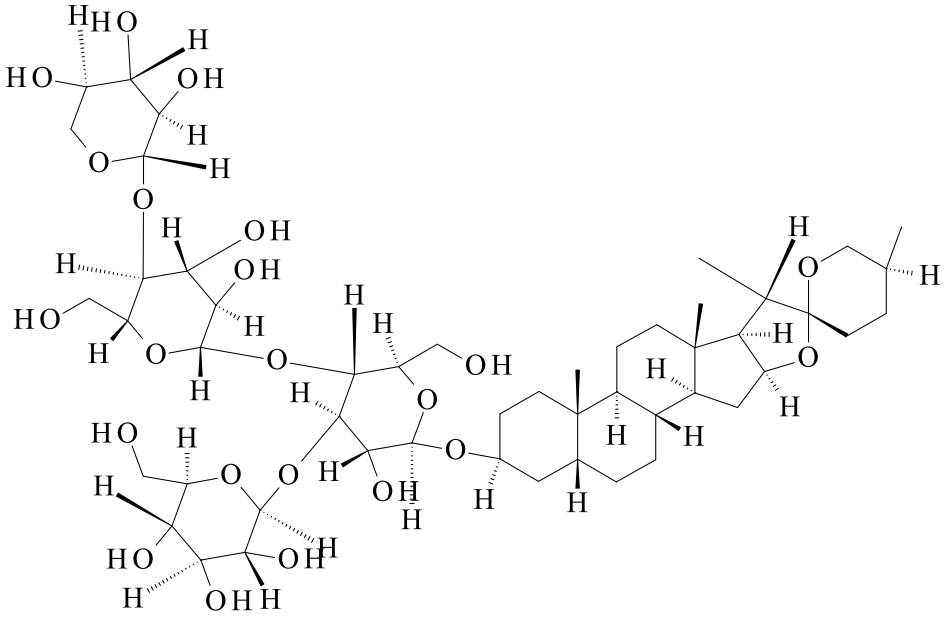
Sr. No.	Pubchem CID	Name	Binding energy Kcal/mol	
			6W01	**6M0J**
1	101847690	Shatavarin-IX	-4.961	-4.423
2	101847689	Shatavarin-VIII	-4.953	-5.062
3	101389835	Sarsasapogenin-N	-4.916	-4.652
4	5281643	Hyperoside (Hyperin)	-4.879	-4.641
5	101847688	Shatavarin-VII	-4.878	-5.245
6	21575007	Asparanin-A	-4.784	-3.425
7	102253064	Racemoside-C	-4.591	-4.581
8	624971	Racemosol	-4.061	-3.736
9	44203608	Shatavaroside-A	-3.953	-5.222
10	102473756	Curillin-G	-3.785	-4.1
11	92095	Sarsasapogenin	-3.432	0
12	158604	Asparanin-C	-3.421	-3.972
13	122364577	Racemosol-C	-2.233	-2.761
14	122364578	Racemosol-D	0	0
15	122209042	Racemosol-B	0	0
16	45269800	Racemosol-A	0	0

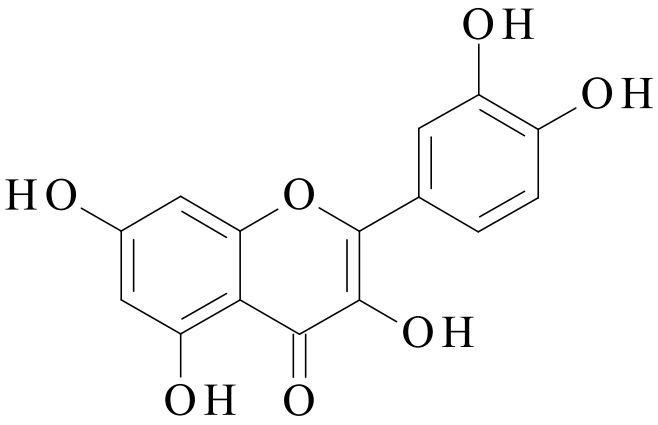
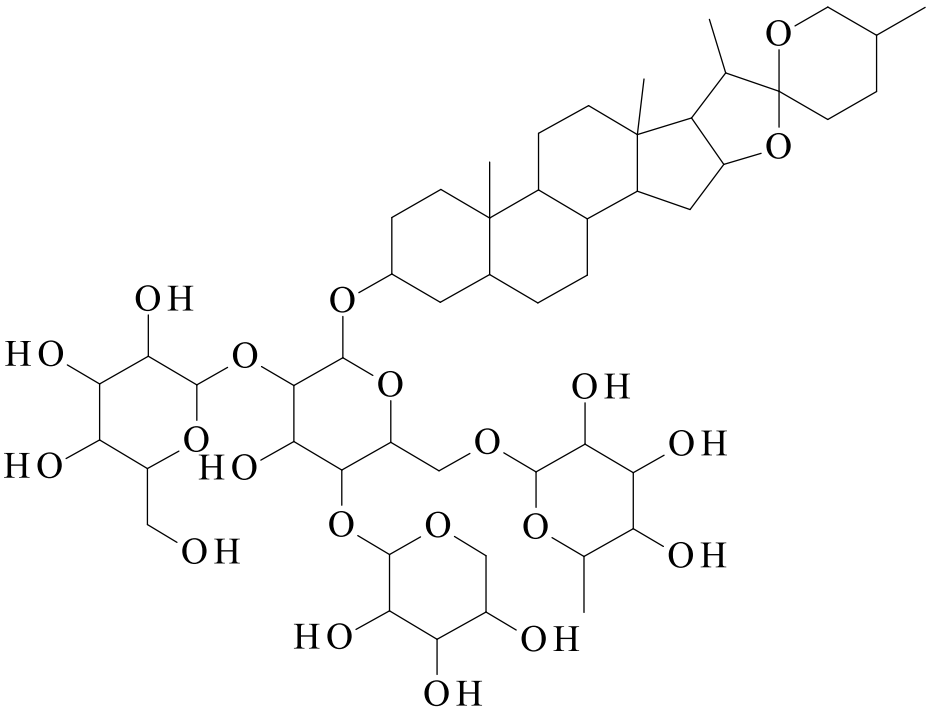
Figure S1. Structure of *Withania somnifera* phytochemicals

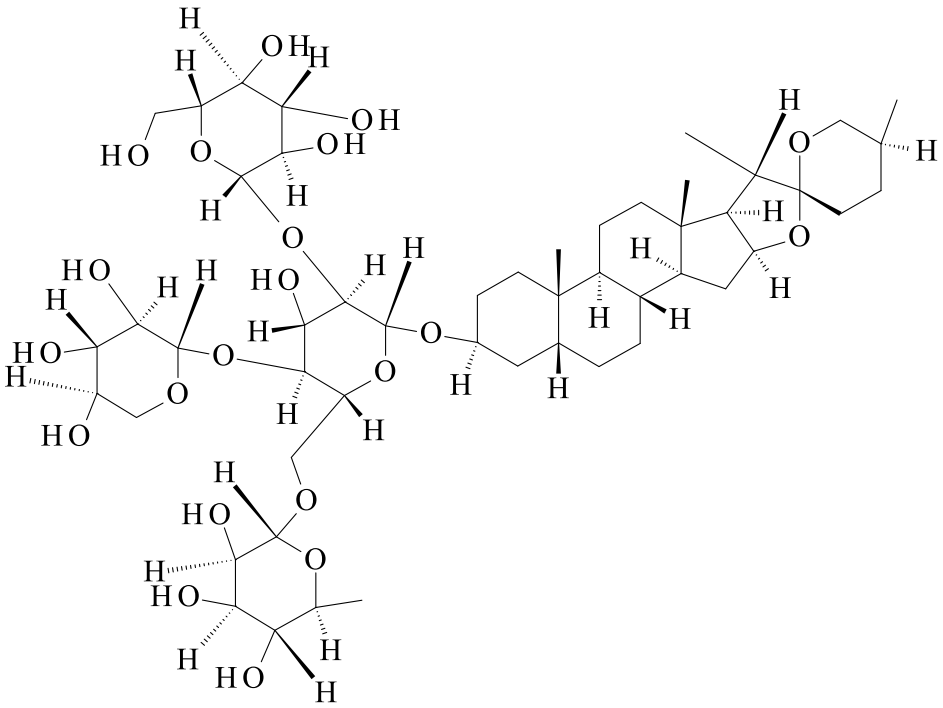
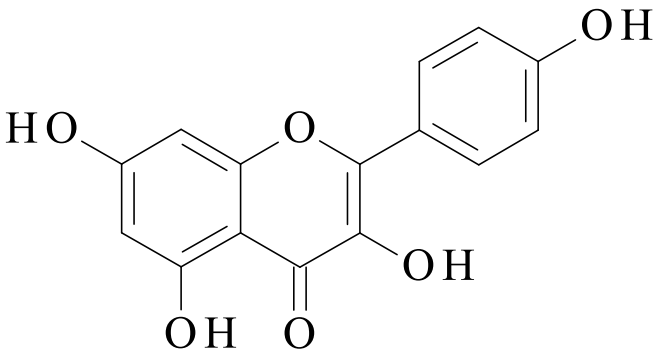
Name	Structure
Asparoside C	
Asparoside D	

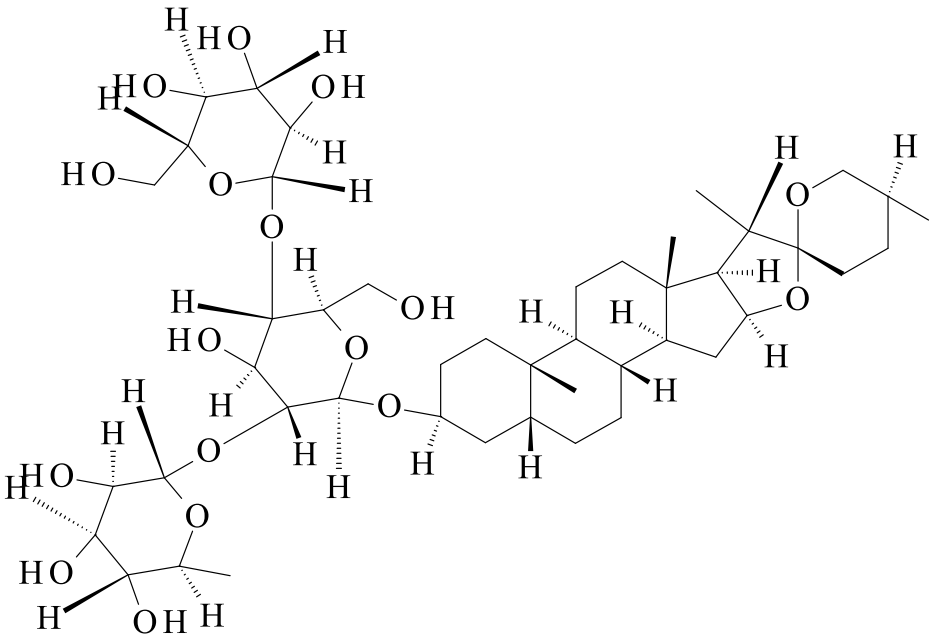
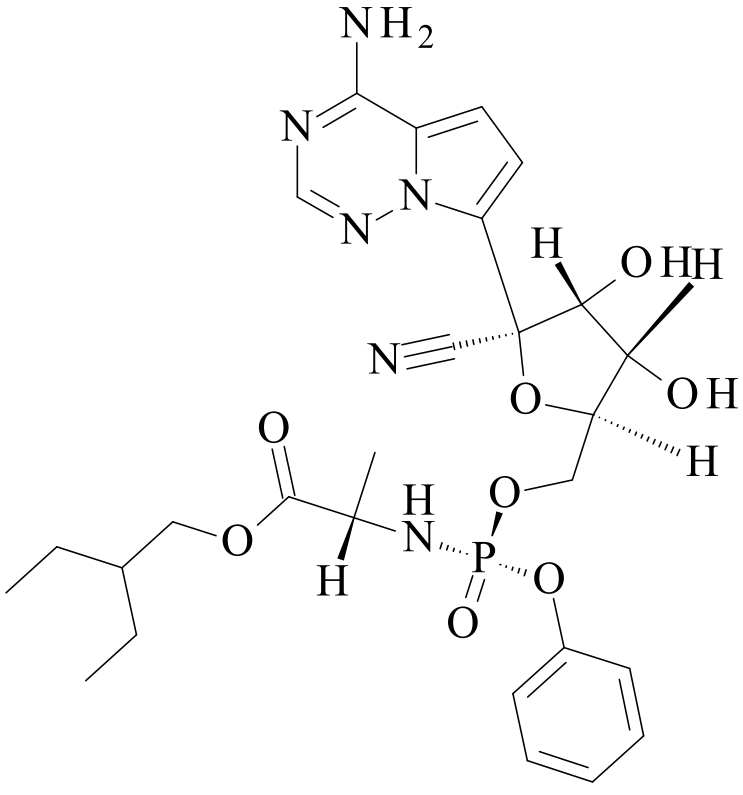
Shatavarin I (Asparaoside B)	
Shatavarin X	

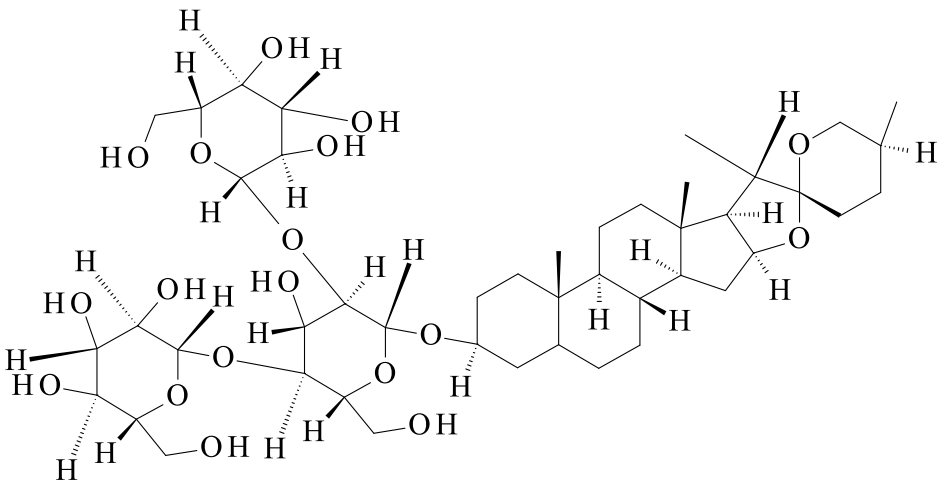
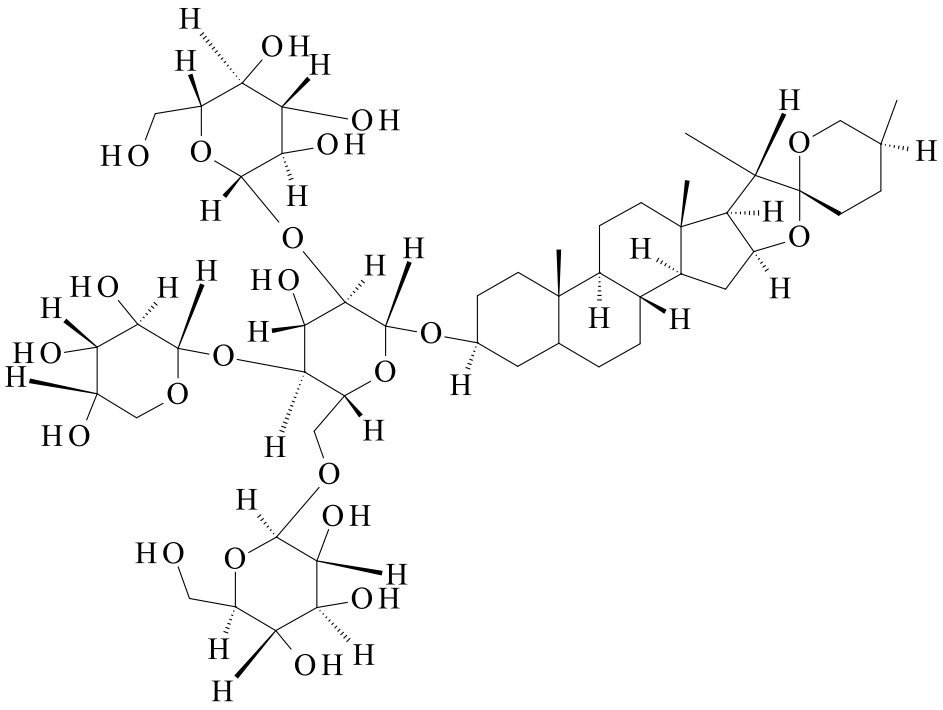
Racemoside A	
Asparoside A	

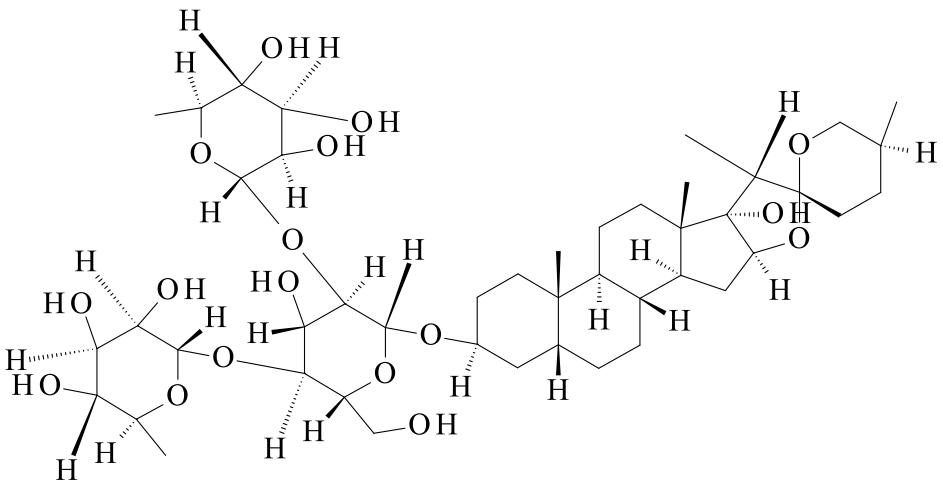
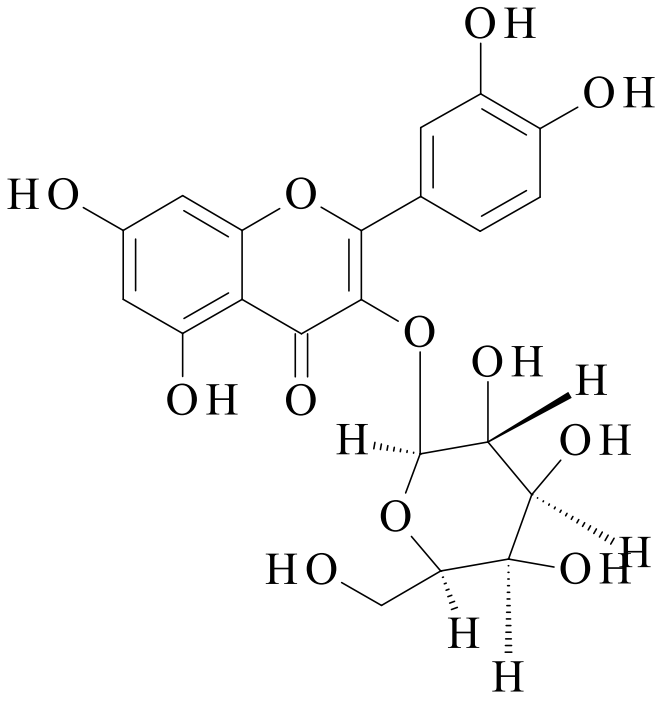
Shatavarin VI	
Racemoside B	
Asparagoside F	

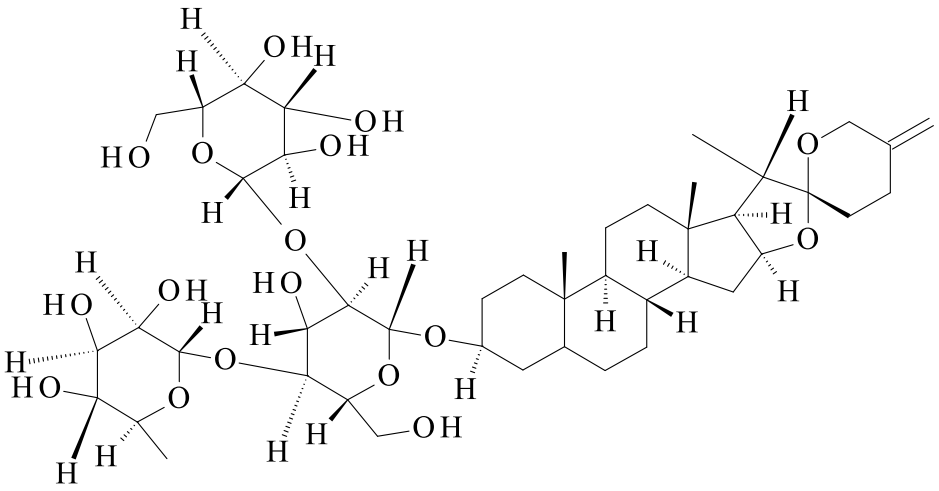
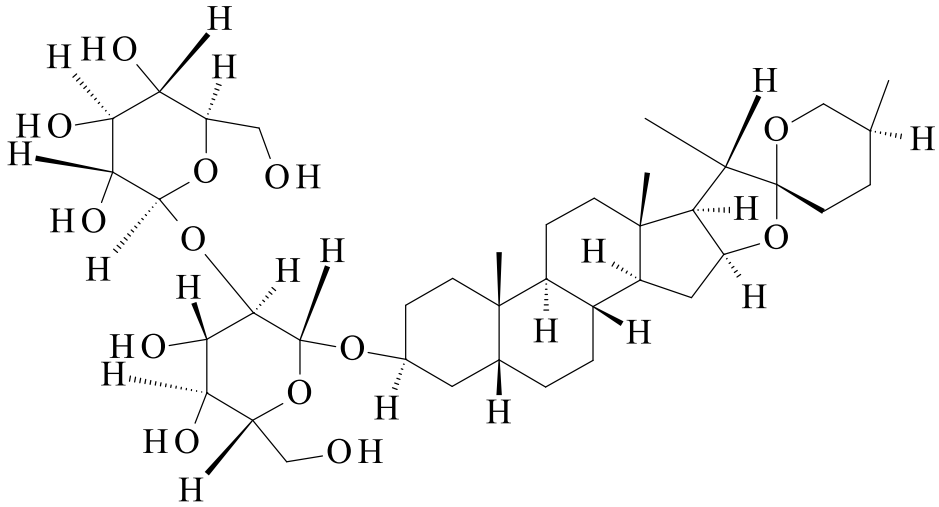
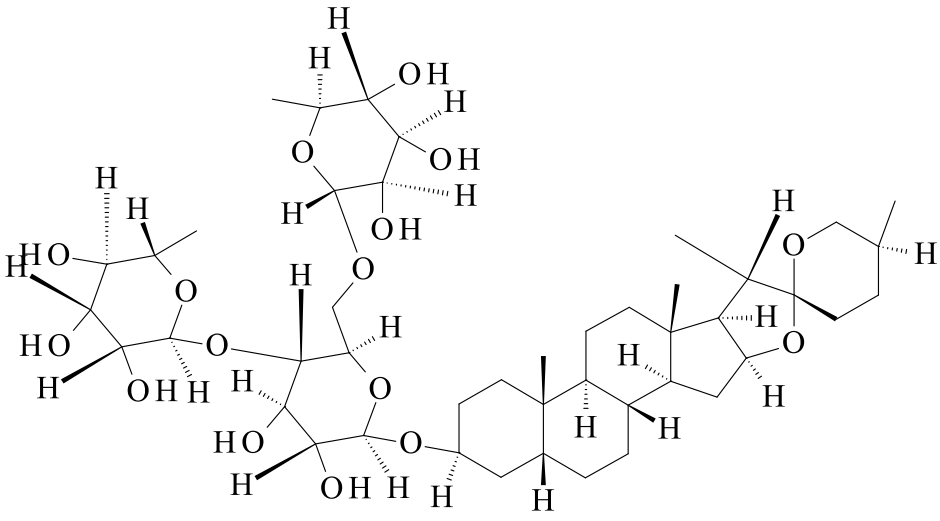
Quercetin	
Asparanin D	

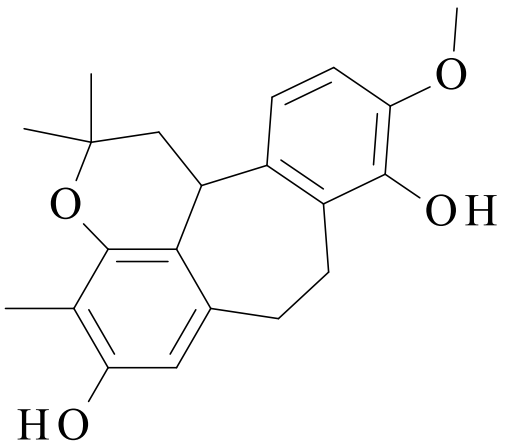
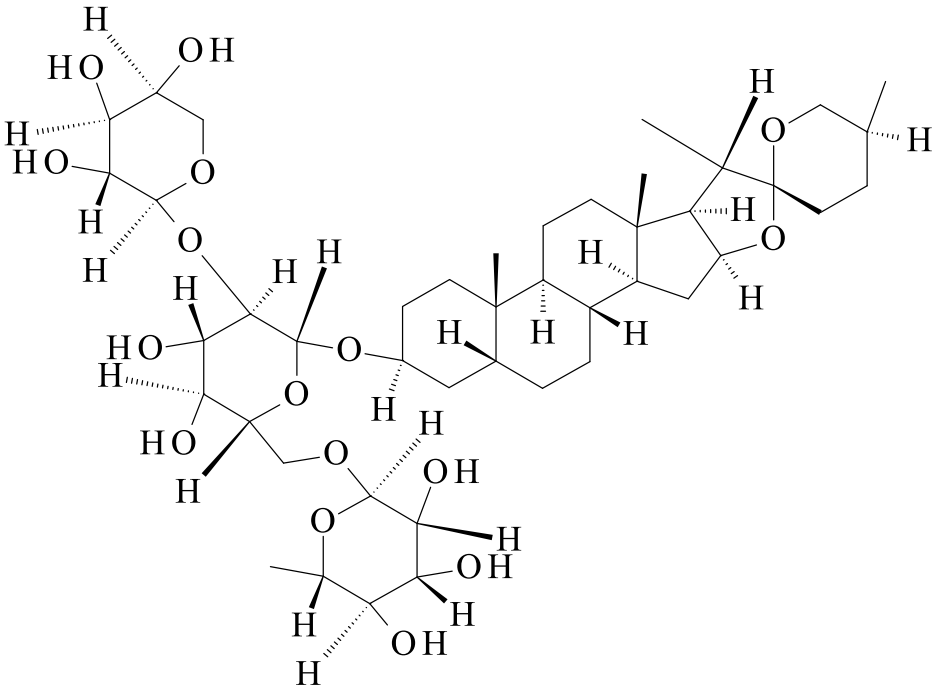
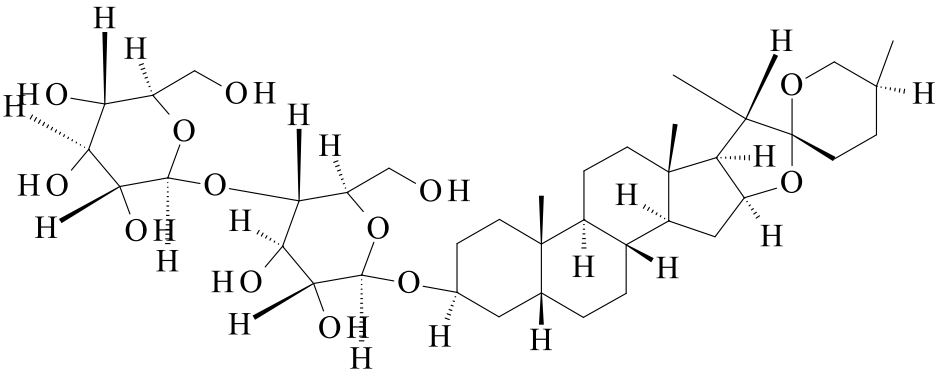
Shatavaroside B	
Kaempferol	

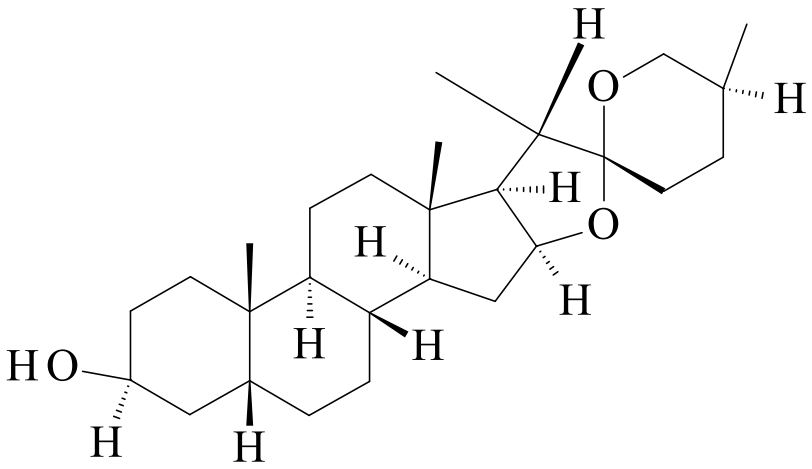
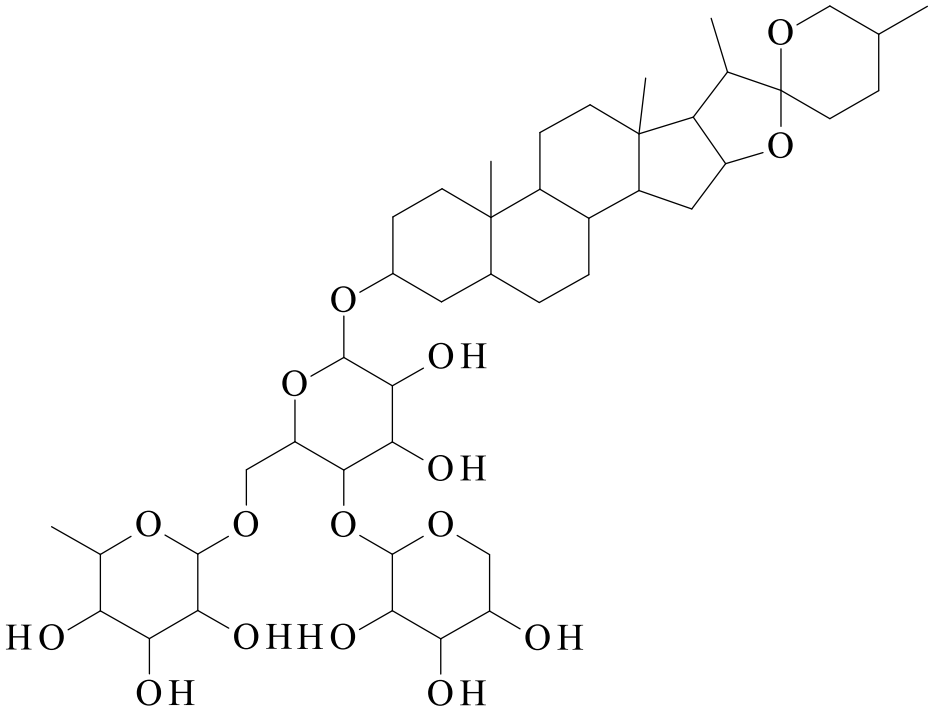
Curillin H	
Remdesivir	

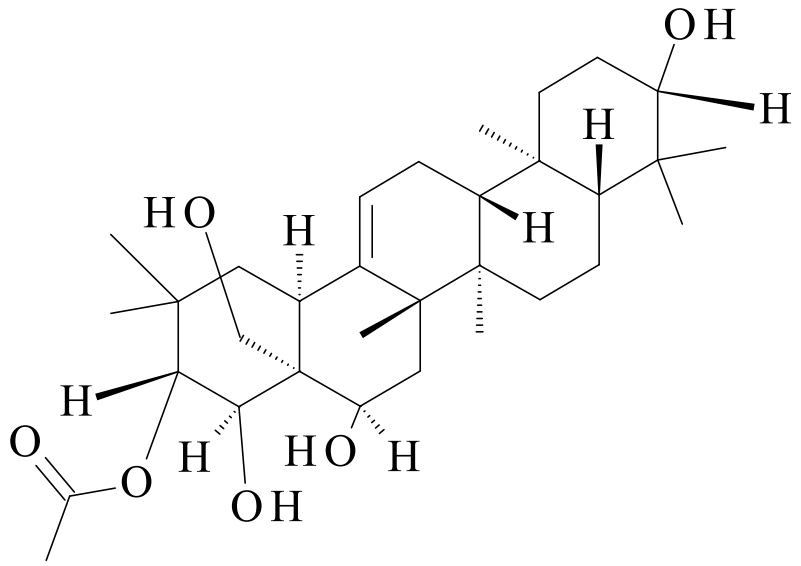
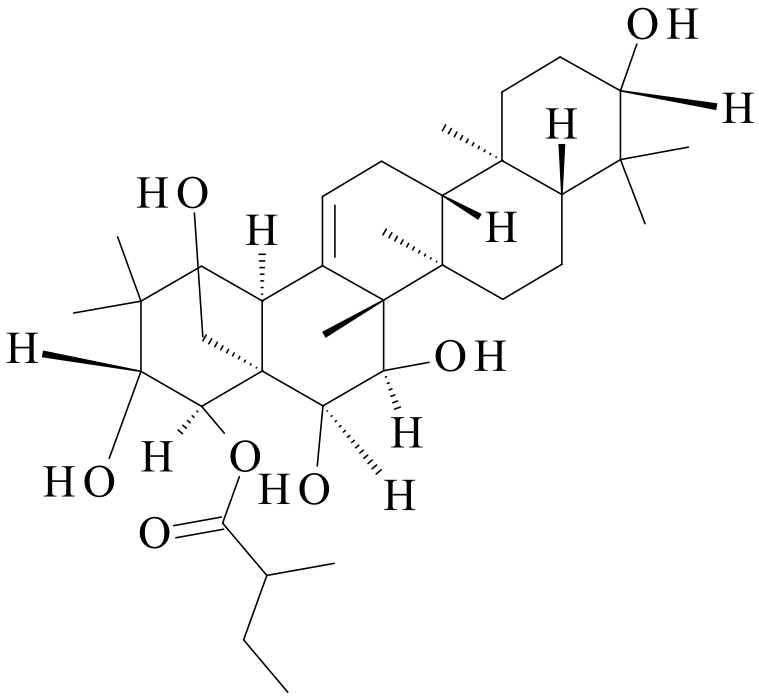
Shatavarin IX	
Shatavarin VIII	

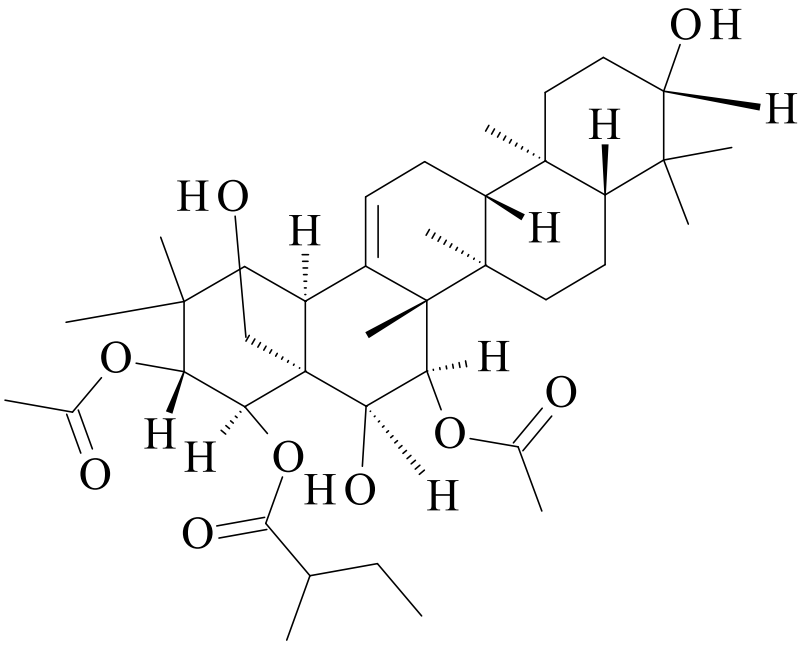
Sarsasapogenin N	
Hyperoside (Hyperin)	

Shatavarin VII	
Asparanin A	
Racemoside C	

Racemosol	
Shatavaroside A	
Curillin G	

Sarsasapogenin	
Asparanin C	

Racemosol C	
Racemosol D	

Racemosol B	
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