Supplementary materials

Molecular Docking, QSAR and ADME/T Studies of withanolide analogs against breast cancer

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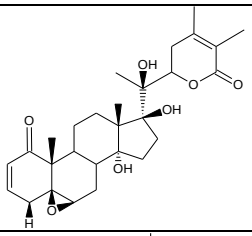
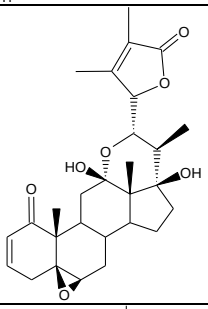
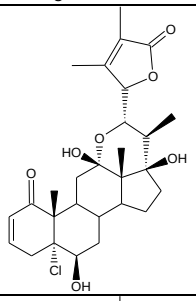
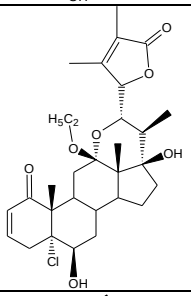
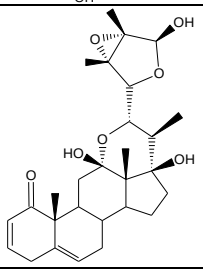
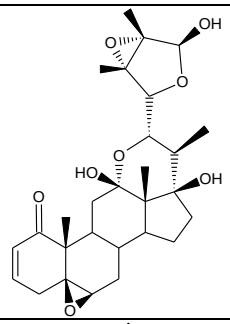
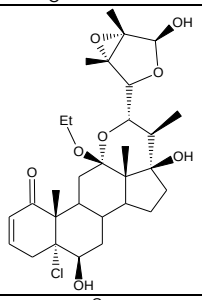
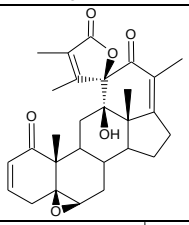
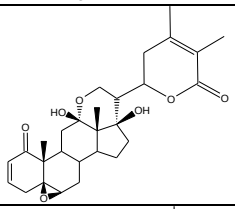
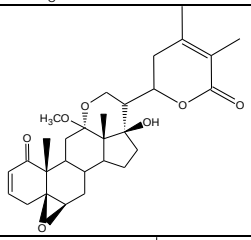
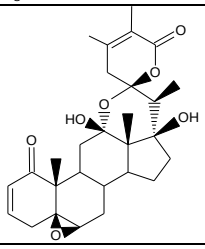
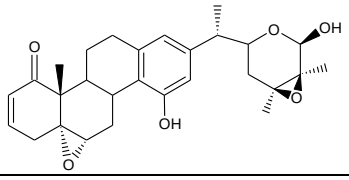
Table S1: Experimental and predicted activities of training data set compounds against the SK-BR-3breast cancer cell line.

Compound	Chemical Sample	Experimental log GI50 (nM)	Predicted log GI50 (nM)	Residual
1.		-0.149	-0.191	0.042
2.		0.279	0.449	-0.17
3.		0.398	0.23	0.168
4.		0.398	0.276	0.122
5.		1.255	1.063	0.192

6.		0.362	0.395	-0.033
7.		0.531	0.638	-0.107
8.		0.301	0.244	0.057
9.		0.415	0.537	-0.122
10.		0.301	0.568	-0.267
11.		0.398	0.296	0.102
12.		0.531	0.566	-0.035

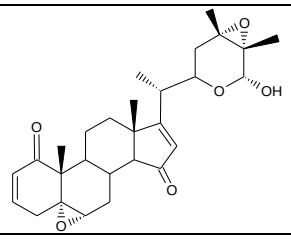
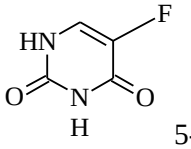
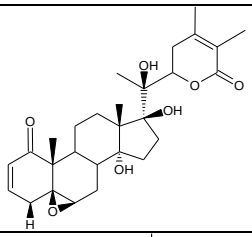
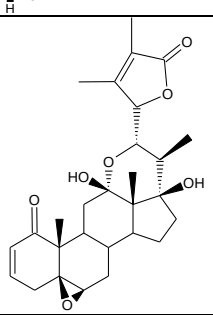
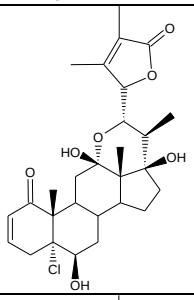
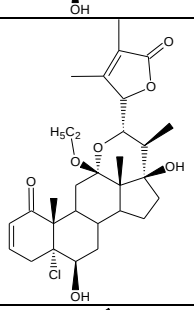
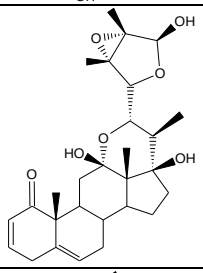
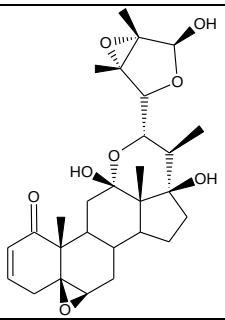
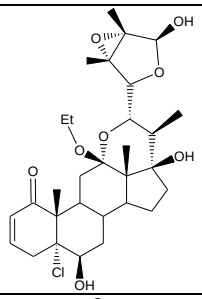
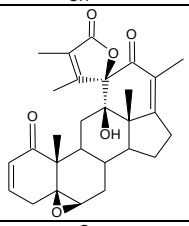
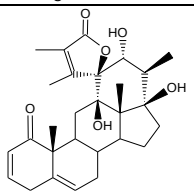
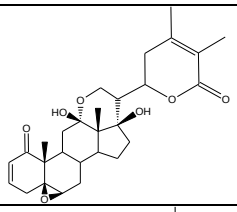
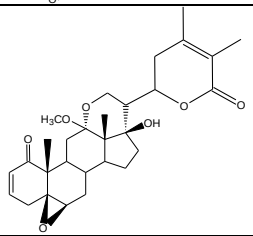
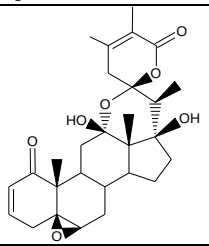
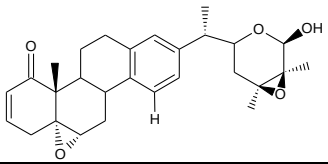
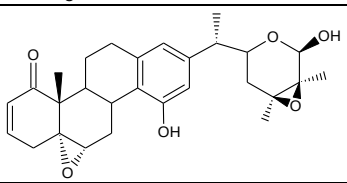
13.		1.322	1.263	0.059
14.	 5-Fluorouracil	-0.824	-0.815	-0.009

Table S2: Experimental and predicted activities of training data set compounds against the MCF7/BUS breast cancer cell line.

Compound S.No.	Chemical Sample	Experimental log GI50 (nM)	Predicted log GI50 (nM)	Residual
1.		0.041	0.261	-0.22
2.		0.491	0.577	-0.086
3.		0.415	0.292	0.123
4.		0.477	0.661	-0.184
5.		1.255	1.222	0.033
6.		0.415	0.472	-0.057

7.		0.708	0.537	0.171
8.		0.519	0.405	0.114
9.		1.519	1.526	-0.007
10.		0.447	0.472	-0.025
11.		0.431	0.663	-0.232
12.		0.462	0.294	0.168
13.		1.114	1.352	-0.238
14.		0.756	0.748	0.008

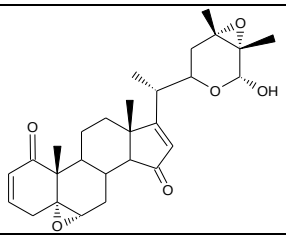
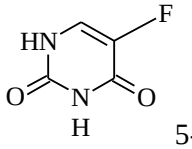
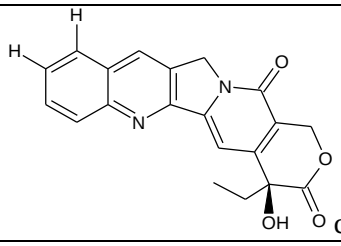
15.		1.114	0.852	0.262
16.	 5-Fluorouracil	-0.678	-0.656	-0.022
17.	 cpt	0.792	0.805	-0.013

Table S3: List of chemical descriptors with details used in QSAR modeling.

S.No.	Descriptor	Description
1.	Atom Count (all atoms)	The number of atoms of a given atomic number in the chemical sample at the time of evaluation.
2.	Bond Count (all bonds)	The number of bonds present in the chemical sample at the time of evaluation. Weak and ionic bonds are ignored.
3.	Formal Charge	The net positive or negative charge on the molecule.
4.	Conformation Minimum Energy (kcal/mole)	Energy calculated for an optimized conformation of the chemical sample. Depending on which procedure is used, the calculated energy may be steric energy (from Mechanics), heat of formation (from MO-G) or total energy (from ZINDO). The optimization procedures usually locate a minimum energy conformation near the starting geometry. Consequently, the resulting conformation may not be the global minimum energy. Use sequential searching, energy maps or dynamics followed by conformational analysis in the Visualizer to locate global minima.
5.	Connectivity Index (order 0, standard)	Zeroth-order (atomic) molecular connectivity index Chi0 for the chemical sample. [L.B. Kier and L.H. Hall, Molecular Connectivity in Structure-Activity Analysis, John Wiley and Sons, New York (1986)].
6.	Connectivity Index (order 1, standard)	First-order (bond) molecular connectivity index Chi1 for the chemical sample. [L.B. Kier and L.H. Hall, Molecular Connectivity in Structure-Activity Analysis, John Wiley and Sons, New York (1986)].
7.	Connectivity Index (order 2, standard)	Second-order (path) molecular connectivity index Chi2 for the chemical sample. [L.B. Kier and L.H. Hall, Molecular Connectivity in Structure-Activity Analysis, John Wiley and Sons, New York (1986)].
8.	Dipole Moment (debye)	The magnitude of the molecule's dipole.
9.	DipoleVector X (debye)	The X component of the molecule's dipole vector.
10.	DipoleVector Y (debye)	The Y component of the molecule's dipole vector.
11.	DipoleVector Z (debye)	The Z component of the molecule's dipole vector.
12.	Electron Affinity (eV)	The change in the total energy of a molecule when an electron is added.
13.	DielectricEnergy (kcal/mole)	The dielectric energy is a portion of the total energy of a molecule embedded in a dielectric. It is the stabilizing portion that results from screening the charges in the molecule by a dielectric. [A. Klamt and G. Schuurmann, J. Chem. Soc. Perkin Trans. 2, 799, 1993]
14.	StericEnergy (kcal/mole)	The steric energy of a molecule is the sum of the molecular mechanics potential energies calculated for the bonds, bond angles, dihedral angles, nonbonded atoms and so forth. It is specific to Mechanics and depends upon the force-field used. [T. Clark, A Handbook of Computational Chemistry, John Wiley and Sons, New York, 1985]
15.	Total Energy (Hartree)	The total energy is the work required to separate the electrons and nuclei infinitely far apart.
16.	Group Count (aldehyde)	The number of aldehyde groups (-R-C(=O)H).
17.	Group Count	The number of amide groups (-C(=O)-NH-).

	(amide)	
18.	Group Count (amine)	The number of primary amine groups (-NH2). Excludes NH2 in amide.
19.	Group Count (sec-amine)	The number of secondary amine groups (-NH-).
20.	Group Count (carbonyl)	The number of carbonyl groups (R-C(=O)-R). Excludes aldehyde.
21.	Group Count (carboxyl)	The number of carboxyl groups (-COOH).
22.	Group Count (carboxylate)	The number of carboxylate anion groups (-COO(-)).
23.	Group Count (cyano)	The number of cyano groups (-CN).
24.	Group Count (ether)	The number of ether groups (R-O-R).
25.	Group Count (hydroxyl)	The number of hydroxyl groups (-OH). This excludes -OH in carboxyl.
26.	Group Count (methyl)	The number of methyl groups (-CH3).
27.	Group Count (methylene)	The number of methylene groups (=CH2).
28.	Group Count (nitro)	The number of nitro groups (-NO2).
29.	Group Count (nitroso)	The number of nitroso groups (-N=O).
30.	Group Count (sulfide)	The number of divalent sulphur atoms (X-S-X). Includes thiol.
31.	Group Count (sulfone)	The number of sulfone groups (R-S(=O)(=O)-R).
32.	Group Count (sulfoxide)	The number of sulfoxide groups (R-S(=O)-R).
33.	Group Count (thiol)	The number of thiol groups (R-SH).
34.	Heat of Formation (kcal/mole)	The energy released or used when a molecule is formed from elements in their standard states.
35.	HOMO Energy (eV)	The energy required to remove an electron from the highest occupied molecular orbital (HOMO).
36.	Ionization Potential (eV)	The energy required to remove an electron from a molecule in its ground state.
37.	Lambda Max Visible (nm)	The maximum absorption line in the visible spectrum (400-1000 nm).
38.	Lambda Max UV-Visible (nm)	The maximum absorption line in the UV-visible spectrum (190-1000 nm).
39.	Lambda Max far-UV-Visible (nm)	The maximum absorption line in the far UV-visible spectrum (150-1000 nm).
40.	Log P	The octanol-water partition coefficient.
41.	LUMO Energy (eV)	The energy gained when an electron is added to the lowest unoccupied molecular orbital (LUMO).

42.	Molar Refractivity	Molar refractivity is calculated using the atom typing scheme of Ghose and Crippen [A.K. Ghose, et al, J. Comput. Chem. 9: 80 (1988)].
43.	Molecular Weight	The molecular formula is determined from the atoms in the chemical sample at the time of evaluation.
44.	Polarizability	Values for this property are ones that existed in the chemical sample when the extraction was evaluated.
45.	Ring Count (all rings)	The number of rings present in the chemical sample at the time of evaluation. Rings with more than 12 atoms are ignored, as are large rings which can be built entirely from the edges of smaller rings.
46.	Size of Smallest Ring	The number of atoms forming the smallest ring in the chemical sample, or 0 if the chemical sample contains no ring of size 12 or less.
47.	Size of largest Ring	The number of atoms forming the largest ring in the chemical sample, or 0 if the chemical sample contains no ring of size 12 or less.
48.	Shape Index (basic kappa, order 1)	A topological index quantifying the shape of a chemical sample [L.H. Hall and L.B. Kier, Reviews in Computational Chemistry, Ch. 9, ed. K.B. Lipkowitz and D.B. Boyd, 1992]. The shape index of order 1 (Kappa 1) quantifies the number of cycles in the chemical sample.
49.	Shape Index (basic kappa, order 2)	A topological index quantifying the shape of a chemical sample [L.H. Hall and L.B. Kier, Reviews in Computational Chemistry, Ch. 9, ed. K.B. Lipkowitz and D.B. Boyd, 1992]. The shape index of order 2 (Kappa 2) quantifies the degree of linearity or star-likeness of the chemical sample.
50.	Shape Index (basic kappa, order 3)	A topological index quantifying the shape of a chemical sample [L.H. Hall and L.B. Kier, Reviews in Computational Chemistry, Ch. 9, ed. K.B. Lipkowitz and D.B. Boyd, 1992]. The shape index of order 3 (Kappa 3) quantifies the degree of branching toward the center of the chemical sample.
51.	Solvent Accessibility Surface Area (angstromsquare)	The solvent accessible surface (SAS) area is calculated at an optimized geometry in water, The water geometry is from optimization using MO-G with PM3 parameters and the Conductor like Screening Model (COSMO). [A. Klamt and G. Schuurmann, J. Chem. Soc. Perkin Trans. 2, 799, 1993]
52.	Elemental analysis	Values for this property are calculated from the mass of each element and the atoms extracted from the chemical sample.

Table S4: Details of Correlation Matrix for chemical descriptors revealing highly correlated descriptors (in red colour) and QSAR equation descriptors (in blue) for SK-BR-3.

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	X	Y	Z	AA	AB	AC	AD
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
1		1.00	0.76	0.46	0.97	0.96	0.12	0.01	0.23	0.07	0.57	0.18	0.19	0.10	0.10	0.96	0.96	0.77	0.48	0.47	0.43	0.67	0.44	0.94	0.28	0.11	0.87	0.31	0.03	0.80
2	1.00		0.74	0.45	0.96	0.98	0.14	0.01	0.25	0.06	0.60	0.18	0.23	0.10	0.10	0.95	0.95	0.75	0.49	0.49	0.41	0.70	0.42	0.92	0.34	0.14	0.82	0.26	0.01	0.79
3	0.76	0.74		0.41	0.75	0.74	0.05	0.06	0.24	0.17	0.27	0.13	0.01	0.08	0.09	0.86	0.86	1.00	0.47	0.46	0.44	0.32	0.60	0.83	0.10	0.01	0.79	0.35	0.09	0.45
4	0.46	0.45	0.41		0.97	0.91	0.06	0.00	0.25	0.08	0.43	0.23	0.08	0.11	0.12	0.98	0.98	0.81	0.45	0.45	0.47	0.53	0.47	0.99	0.18	0.04	0.95	0.42	0.06	0.71
5	0.97	0.96	0.75	0.47		0.92	0.07	0.01	0.27	0.05	0.47	0.21	0.13	0.09	0.09	0.97	0.97	0.75	0.45	0.44	0.50	0.58	0.47	0.97	0.27	0.07	0.89	0.38	0.05	0.74
6	0.96	0.98	0.74	0.41	0.92		0.14	0.03	0.29	0.08	0.62	0.19	0.28	0.09	0.08	0.93	0.93	0.74	0.54	0.53	0.36	0.70	0.86	0.88	0.43	0.18	0.75	0.16	0.00	0.70
7	0.12	0.14	0.05	0.06	0.07	0.14		0.06	0.01	0.09	0.30	0.05	0.38	0.03	0.04	0.08	0.08	0.05	0.04	0.04	0.01	0.21	0.05	0.05	0.16	0.17	0.03	0.01	0.03	0.25
8	0.01	0.01	0.06	0.00	0.01	0.03	0.06		0.12	0.11	0.17	0.02	0.32	0.01	0.01	0.00	0.00	0.05	0.00	0.00	0.03	0.14	0.00	0.00	0.19	0.28	0.01	0.14	0.30	0.01
9	0.23	0.25	0.24	0.25	0.27	0.29	0.01	0.12		0.00	0.11	0.11	0.04	0.06	0.09	0.26	0.26	0.24	0.20	0.19	0.08	0.14	0.20	0.22	0.26	0.28	0.16	0.00	0.11	0.03
10	0.07	0.06	0.17	0.08	0.05	0.08	0.09	0.11	0.00		0.03	0.01	0.01	0.02	0.02	0.09	0.09	0.17	0.05	0.06	0.29	0.04	0.06	0.09	0.00	0.05	0.08	0.04	0.06	0.04
11	0.57	0.60	0.27	0.43	0.47	0.62	0.30	0.17	0.11	0.03		0.03	0.48	0.06	0.05	0.43	0.43	0.28	0.13	0.13	0.25	0.96	0.45	0.37	0.46	0.32	0.29	0.01	0.02	0.70
12	0.18	0.18	0.13	0.23	0.21	0.19	0.05	0.02	0.11	0.01	0.03		0.01	0.22	0.22	0.23	0.23	0.13	0.01	0.01	0.05	0.03	0.21	0.24	0.05	0.00	0.20	0.07	0.00	0.06
13	0.19	0.23	0.01	0.08	0.13	0.28	0.38	0.32	0.04	0.01	0.48	0.01		0.00	0.00	0.10	0.10	0.01	0.16	0.16	0.01	0.47	0.09	0.06	0.73	0.70	0.01	0.14	0.34	0.23
14	0.10	0.10	0.08	0.11	0.09	0.09	0.03	0.01	0.06	0.02	0.06	0.22	0.00		0.99	0.08	0.08	0.08	0.33	0.34	0.01	0.08	0.10	0.07	0.01	0.02	0.11	0.03	0.00	0.07
15	0.10	0.10	0.09	0.12	0.09	0.08	0.04	0.01	0.09	0.02	0.05	0.22	0.00	0.99		0.08	0.08	0.09	0.31	0.31	0.01	0.08	0.10	0.08	0.00	0.02	0.11	0.03	0.00	0.06
16	0.96	0.95	0.86	0.98	0.97	0.93	0.08	0.00	0.26	0.09	0.43	0.23	0.10	0.08	0.08		1.00	0.86	0.50	0.50	0.46	0.52	0.33	0.98	0.23	0.05	0.91	0.36	0.05	0.68
17	0.96	0.95	0.86	0.98	0.97	0.93	0.08	0.00	0.26	0.09	0.43	0.23	0.10	0.08	0.08	1.00		0.86	0.50	0.50	0.46	0.52	0.43	0.98	0.23	0.05	0.91	0.36	0.05	0.68
18	0.77	0.75	1.00	0.81	0.75	0.74	0.05	0.05	0.24	0.17	0.28	0.13	0.01	0.08	0.09	0.86	0.86		0.47	0.46	0.45	0.32	0.70	0.83	0.10	0.01	0.79	0.35	0.08	0.46
19	0.48	0.49	0.47	0.45	0.45	0.54	0.04	0.00	0.20	0.05	0.13	0.01	0.16	0.33	0.31	0.50	0.50	0.47		1.00	0.02	0.17	0.35	0.44	0.32	0.13	0.33	0.02	0.05	0.19
20	0.47	0.49	0.46	0.45	0.44	0.53	0.04	0.00	0.19	0.06	0.13	0.01	0.16	0.34	0.31	0.50	0.50	0.46	1.00		0.02	0.17	0.34	0.43	0.32	0.13	0.33	0.02	0.05	0.19
21	0.43	0.41	0.44	0.47	0.50	0.36	0.01	0.03	0.08	0.29	0.25	0.05	0.01	0.01	0.01	0.46	0.46	0.45	0.02	0.02		0.32	0.53	0.51	0.02	0.02	0.53	0.50	0.31	0.45
22	0.67	0.70	0.32	0.53	0.58	0.70	0.21	0.14	0.14	0.04	0.96	0.03	0.47	0.08	0.08	0.52	0.52	0.32	0.17	0.17	0.32		0.57	0.47	0.44	0.34	0.40	0.05	0.01	0.78
23	0.44	0.42	0.70	0.47	0.47	0.46	0.05	0.00	0.20	0.06	0.45	0.21	0.09	0.10	0.10	0.93	0.93	0.70	0.35	0.34	0.53	0.57		0.96	0.16	0.03	0.95	0.48	0.10	0.78
24	0.94	0.92	0.83	0.99	0.97	0.88	0.05	0.00	0.22	0.09	0.37	0.24	0.06	0.07	0.08	0.98	0.98	0.83	0.44	0.43	0.51	0.47	0.96		0.17	0.02	0.95	0.45	0.09	0.67
25	0.28	0.34	0.10	0.18	0.27	0.43	0.16	0.19	0.26	0.00	0.46	0.05	0.73	0.01	0.00	0.23	0.23	0.10	0.32	0.32	0.02	0.44	0.16	0.17		0.61	0.05	0.10	0.40	0.19
26	0.11	0.14	0.01	0.04	0.07	0.18	0.17	0.28	0.28	0.05	0.32	0.00	0.70	0.02	0.02	0.05	0.05	0.01	0.13	0.13	0.02	0.34	0.03	0.02	0.61		0.00	0.19	0.43	0.09
27	0.87	0.82	0.79	0.45	0.89	0.75	0.03	0.01	0.16	0.08	0.29	0.20	0.01	0.11	0.11	0.91	0.91	0.79	0.33	0.33	0.53	0.40	0.45	0.95	0.05	0.00		0.63	0.21	0.67
28	0.31	0.26	0.35	0.42	0.38	0.16	0.01	0.14	0.00	0.04	0.01	0.07	0.14	0.03	0.03	0.36	0.36	0.35	0.02	0.02	0.50	0.05	0.48	0.45	0.10	0.19	0.63		0.77	0.34
29	0.03	0.01	0.09	0.06	0.05	0.00	0.03	0.30	0.11	0.06	0.02	0.00	0.34	0.00	0.00	0.05	0.05	0.08	0.05	0.05	0.31	0.01	0.10	0.09	0.40	0.43	0.21	0.47		0.09
30	0.80	0.79	0.45	0.71	0.74	0.70	0.25	0.01	0.03	0.04	0.70	0.06	0.23	0.07	0.06	0.68	0.68	0.46	0.19	0.19	0.45	0.78	0.48	0.67	0.19	0.09	0.67	0.34	0.09	

Abbreviations:- A: Atom Count (all atoms); B: Bond Count (all bonds); C: Conformation Minimum Energy (kcal/mole); D: Connectivity Index (order 0, standard); E: Connectivity Index (order 1, standard); F: Connectivity Index (order 2, standard); G: Dipole Moment (debye); H: Dipole Vector X (debye); I: Dipole Vector Y (debye); J: Dipole Vector Z (debye); K: Electron Affinity (eV); L: Dielectric Energy (kcal/mole); M: Steric Energy (kcal/mole); N: Lambda Max UV-Visible (nm); O: Lambda Max far-UV-Visible (nm); P: Total Energy (Hartree); Q: Total Energy (Hartree)1; R: Heat of Formation (kcal/mole); S: HOMO Energy (eV); T: Ionization Potential (eV); U: Log P; V: LUMO Energy (eV); W: Molar Refractivity; X: Molecular Weight; Y: Ring Count (all rings); Z: Size of Smallest Ring; AA: Shape Index (basic kappa, order 1); AB: Shape Index (basic kappa, order 2); AC: Shape Index (basic kappa, order 3); AD: Solvent Accessibility Surface Area (angstrom square)

Table S5: Details of Correlation Matrix for chemical descriptors revealing highly correlated descriptors (in red colour) and QSAR equation descriptors (in blue) for MCF7-BUS.

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	X	Y	Z	AA	AB	AC
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29
1		0.50	0.56	0.48	0.47	0.48	0.00	0.08	0.10	0.07	0.37	0.15	0.38	0.38	0.56	0.14	0.13	0.16	0.16	0.64	0.37	0.97	0.98	0.77	0.38	0.96	0.78	0.31	0.42
2	0.50		0.53	0.98	0.98	0.99	0.00	0.08	0.09	0.07	0.37	0.15	0.41	0.38	0.54	0.14	0.13	0.17	0.17	0.64	0.36	0.97	0.98	0.80	0.40	0.95	0.77	0.29	0.92
3	0.56	0.53		0.55	0.46	0.50	0.00	0.04	0.18	0.09	0.22	0.04	0.05	0.62	1.00	0.41	0.39	0.00	0.01	0.27	0.22	0.44	0.57	0.21	0.07	0.58	0.40	0.18	0.32
4	0.48	0.98	0.55		0.99	0.98	0.00	0.09	0.08	0.06	0.27	0.14	0.31	0.44	0.55	0.12	0.11	0.16	0.16	0.61	0.27	0.98	1.00	0.75	0.32	0.99	0.83	0.35	0.91
5	0.47	0.98	0.46	0.99		0.98	0.01	0.10	0.07	0.05	0.26	0.13	0.36	0.47	0.46	0.09	0.08	0.20	0.22	0.64	0.25	0.99	0.98	0.82	0.38	0.96	0.83	0.35	0.95
6	0.98	0.99	0.50	0.98	0.98		0.00	0.07	0.08	0.06	0.32	0.13	0.43	0.77	0.50	0.13	0.12	0.19	0.19	0.60	0.30	0.97	0.97	0.85	0.43	0.94	0.75	0.27	0.93
7	0.00	0.00	0.00	0.00	0.01	0.00		0.08	0.01	0.05	0.21	0.03	0.16	0.00	0.00	0.01	0.01	0.04	0.01	0.02	0.15	0.01	0.00	0.00	0.03	0.01	0.04	0.06	0.00
8	0.08	0.08	0.04	0.09	0.10	0.07	0.08		0.06	0.14	0.05	0.02	0.02	0.09	0.04	0.00	0.00	0.04	0.14	0.24	0.03	0.11	0.10	0.06	0.01	0.10	0.19	0.24	0.11
9	0.10	0.09	0.18	0.08	0.07	0.08	0.01	0.06		0.00	0.07	0.14	0.01	0.09	0.18	0.17	0.16	0.06	0.03	0.04	0.10	0.06	0.08	0.07	0.08	0.07	0.01	0.06	0.01
10	0.07	0.07	0.09	0.06	0.05	0.06	0.05	0.14	0.00		0.09	0.01	0.00	0.06	0.10	0.01	0.00	0.01	0.05	0.25	0.10	0.07	0.07	0.02	0.00	0.07	0.07	0.13	0.06
11	0.37	0.37	0.22	0.27	0.26	0.32	0.21	0.05	0.07	0.09		0.04	0.45	0.29	0.22	0.03	0.02	0.08	0.05	0.28	0.95	0.27	0.26	0.26	0.36	0.25	0.13	0.04	0.33
12	0.15	0.15	0.04	0.14	0.13	0.13	0.03	0.02	0.14	0.01	0.04		0.03	0.13	0.04	0.00	0.00	0.10	0.23	0.18	0.05	0.16	0.15	0.10	0.00	0.14	0.09	0.01	0.10
13	0.38	0.41	0.05	0.31	0.36	0.43	0.16	0.02	0.01	0.00	0.45	0.03		0.33	0.05	0.08	0.07	0.18	0.16	0.15	0.41	0.33	0.31	0.64	0.78	0.23	0.09	0.00	0.42
14	0.48	0.38	0.62	0.44	0.47	0.48	0.00	0.09	0.09	0.06	0.29	0.13	0.33		0.62	0.17	0.16	0.14	0.14	0.60	0.28	0.96	0.99	0.75	0.34	0.97	0.80	0.32	0.88
15	0.56	0.54	1.00	0.55	0.46	0.50	0.00	0.04	0.18	0.10	0.22	0.04	0.05	0.62		0.41	0.39	0.00	0.00	0.27	0.23	0.44	0.58	0.22	0.08	0.58	0.40	0.18	0.33
16	0.14	0.14	0.41	0.12	0.09	0.13	0.01	0.00	0.17	0.01	0.03	0.00	0.08	0.17	0.41		1.00	0.23	0.24	0.00	0.04	0.07	0.13	0.09	0.05	0.10	0.01	0.05	0.02
17	0.13	0.13	0.39	0.11	0.08	0.12	0.01	0.00	0.16	0.00	0.02	0.00	0.07	0.16	0.39	1.00		0.24	0.25	0.00	0.04	0.06	0.13	0.08	0.04	0.09	0.01	0.06	0.02
18	0.16	0.17	0.00	0.16	0.20	0.19	0.04	0.04	0.06	0.01	0.08	0.10	0.18	0.14	0.00	0.23	0.24		0.80	0.15	0.04	0.21	0.16	0.20	0.21	0.17	0.24	0.27	0.31
19	0.16	0.17	0.01	0.16	0.22	0.19	0.01	0.14	0.03	0.05	0.05	0.23	0.16	0.14	0.00	0.24	0.25	0.80		0.32	0.04	0.23	0.16	0.26	0.17	0.15	0.23	0.24	0.31
20	0.64	0.64	0.27	0.61	0.64	0.60	0.02	0.24	0.04	0.25	0.28	0.18	0.15	0.60	0.27	0.00	0.00	0.15	0.32		0.32	0.67	0.64	0.48	0.15	0.62	0.65	0.45	0.68
21	0.37	0.36	0.22	0.27	0.25	0.30	0.15	0.03	0.10	0.10	0.95	0.05	0.41	0.28	0.23	0.04	0.04	0.04	0.04	0.32		0.27	0.26	0.23	0.34	0.25	0.14	0.05	0.31
22	0.97	0.97	0.44	0.98	0.99	0.97	0.01	0.11	0.06	0.07	0.27	0.16	0.33	0.96	0.44	0.07	0.06	0.21	0.23	0.67	0.27		0.98	0.78	0.33	0.97	0.86	0.39	0.96
23	0.98	0.98	0.57	1.00	0.98	0.97	0.00	0.10	0.08	0.07	0.26	0.15	0.31	0.99	0.58	0.13	0.13	0.16	0.16	0.64	0.26	0.98		0.74	0.31	0.98	0.83	0.36	0.90
24	0.77	0.80	0.21	0.75	0.82	0.85	0.00	0.06	0.07	0.02	0.26	0.10	0.64	0.75	0.22	0.09	0.08	0.20	0.26	0.48	0.23	0.78	0.74		0.62	0.66	0.47	0.08	0.81
25	0.38	0.40	0.07	0.32	0.38	0.43	0.03	0.01	0.08	0.00	0.36	0.00	0.78	0.34	0.08	0.05	0.04	0.21	0.17	0.15	0.34	0.33	0.31	0.62		0.25	0.13	0.01	0.41
26	0.96	0.95	0.58	0.99	0.96	0.94	0.01	0.10	0.07	0.07	0.25	0.14	0.23	0.97	0.58	0.10	0.09	0.17	0.15	0.62	0.25	0.97	0.98	0.66	0.25		0.90	0.44	0.89
27	0.78	0.77	0.40	0.83	0.83	0.75	0.04	0.19	0.01	0.07	0.13	0.09	0.09	0.80	0.40	0.01	0.01	0.24	0.23	0.65	0.14	0.86	0.83	0.47	0.13	0.90		0.73	0.82
28	0.31	0.29	0.18	0.35	0.35	0.27	0.06	0.24	0.06	0.13	0.04	0.01	0.00	0.32	0.18	0.05	0.06	0.27	0.24	0.45	0.05	0.39	0.36	0.08	0.01	0.44	0.73		0.41
29	0.42	0.92	0.32	0.91	0.95	0.93	0.00	0.11	0.01	0.06	0.33	0.10	0.42	0.88	0.33	0.02	0.02	0.31	0.31	0.68	0.31	0.96	0.90	0.81	0.41	0.89	0.82	0.41	

Abbreviations:- A: Atom Count (all atoms); B: Bond Count (all bonds); C: Conformation Minimum Energy (kcal/mole); D: Connectivity Index (order 0, standard); E: Connectivity Index (order 1, standard); F: Connectivity Index (order 2, standard); G: Dipole Moment (debye); H: Dipole Vector X (debye); I: Dipole Vector Y (debye); J: Dipole Vector Z (debye); K: Electron Affinity (eV); L: Dielectric Energy (kcal/mole); M:

Steric Energy (kcal/mole); N: Total Energy (Hartree); O: Heat of Formation (kcal/mole); P: HOMO Energy (eV); Q: Ionization Potential (eV); R: Lambda Max UV-Visible (nm); S: Lambda Max far-UV-Visible (nm); T: Log P; U: LUMO Energy (eV); V: Molar Refractivity; W: Molecular Weight; X: Ring Count (all rings); Y: Size of Smallest Ring; Z: Shape Index (basic kappa, order 1); AA: Shape Index (basic kappa, order 2); AB: Shape Index (basic kappa, order 3); AC: Solvent Accessibility Surface Area (angstrom square)

Table S6: Y-randomization Study on Sk-Br-3 and MCF7/BUS QSAR model. (100 random trial was performed)

S.No.*	QSAR model on Sk-Br-3 Cell line		QSAR model on MCF7/BUS Cell line	
	r^2	rCV^2	r^2	rCV^2
1.	0.228412	0	0.254174	0
2.	0.444448	0	0.063249	0
3.	0.560646	0	0.026313	0
4.	0.271447	0	0.568193	0
5.	0.166437	0	0.326696	0
6.	0.082393	0	0.192285	0
7.	0.488564	0	0.032314	0
8.	0.231748	0	0.134195	0
9.	0.151062	0	0.300451	0
10.	0.403994	0	0.40003	0
11.	0.183564	0	0.221166	0
12.	0.401347	0	0.058783	0
13.	0.139927	0	0.417036	0
14.	0.529549	0	0.04406	0
15.	0.137105	0	0.465214	0.00829
16.	0.594439	0.159877	0.128062	0
17.	0.152974	0	0.336216	0.025037
18.	0.392295	0	0.153695	0
19.	0.121625	0	0.243869	0
20.	0.172229	0	0.060113	0
21.	0.184213	0	0.546777	0
22.	0.062702	0	0.225615	0
23.	0.378658	0	0.037342	0
24.	0.198573	0	0.212272	0
25.	0.454454	0	0.144914	0
26.	0.414192	0	0.439198	0
27.	0.385553	0	0.146932	0
28.	0.284724	0	0.018927	0
29.	0.253554	0	0.196546	0
30.	0.135598	0	0.417126	0
31.	0.791075	0.263961	0.321857	0
32.	0.057165	0	0.179217	0
33.	0.11928	0	0.229374	0
34.	0.113538	0	0.588544	0
35.	0.305981	0	0.385492	0
36.	0.32451	0	0.623317	0
37.	0.699109	0.045488	0.298354	0
38.	0.470896	0	0.028828	0
39.	0.322079	0	0.201069	0
40.	0.117956	0	0.176681	0
41.	0.356988	0	0.253063	0

42.	0.076919	0	0.078142	0
43.	0.655927	0	0.061991	0
44.	0.081304	0	0.026313	0
45.	0.345904	0	0.217174	0
46.	0.158509	0	0.218493	0
47.	0.041687	0	0.04993	0
48.	0.129202	0	0.47039	0
49.	0.532907	0	0.440306	0
50.	0.482093	0	0.306274	0
51.	0.234274	0	0.11528	0
52.	0.207313	0	0.233826	0
53.	0.259706	0	0.234991	0
54.	0.215638	0	0.421396	0
55.	0.689518	0	0.023251	0
56.	0.510957	0	0.094649	0
57.	0.591041	0	0.281161	0
58.	0.267368	0	0.035185	0
59.	0.723245	0.321892	0.408309	0
60.	0.28838	0	0.280024	0
61.	0.48603	0	0.26823	0
62.	0.229358	0	0.266747	0
63.	0.086289	0	0.088927	0
64.	0.559663	0	0.343383	0
65.	0.624809	0	0.410198	0
66.	0.194237	0	0.25781	0
67.	0.069061	0	0.433152	0
68.	0.018036	0	0.199715	0
69.	0.510184	0	0.461438	0
70.	0.156183	0	0.280967	0
71.	0.530284	0	0.389276	0
72.	0.340364	0	0.164319	0
73.	0.163829	0	0.191446	0
74.	0.507181	0	0.096193	0
75.	0.137742	0	0.215697	0
76.	0.455805	0	0.276261	0
77.	0.067533	0	0.113709	0
78.	0.106054	0	0.228699	0
79.	0.291665	0	0.203117	0
80.	0.542769	0	0.211948	0
81.	0.105371	0	0.510257	0
82.	0.062408	0	0.076134	0
83.	0.436053	0	0.161932	0
84.	0.191631	0	0.078276	0
85.	0.319266	0	0.182872	0
86.	0.64851	0	0.625306	0.329851
87.	0.621119	0	0.384394	0

88.	0.616498	0	0.211031	0
89.	0.301207	0	0.270612	0
90.	0.098044	0	0.183745	0
91.	0.259581	0	0.17815	0
92.	0.568659	0	0.093351	0
93.	0.106404	0	0.173543	0
94.	0.188851	0	0.032314	0
95.	0.235524	0	0.157034	0
96.	0.293541	0	0.173729	0
97.	0.182563	0	0.565997	0
98.	0.45866	0	0.099137	0
99.	0.267666	0	0.0948	0
100.	0.542176	0	0.139138	0
Mean[$]	**0.314 (r^2)**	**0.008 (rCV^2)**	**0.236 (r^2)**	**0.004 (rCV^2)**

*100 random trial; [$]average value of squared correlation coefficient (r^2) and cross-validated correlation coefficient(rCV^2).

TableS7: Predicted chemical descriptors and *in vitro* activity against SK-BR-3 cell line.

Compound Name	Connectivity index (order 0, standard)	Dipole vector X (debye)	Molar refractivity	Shape index (basic kappa, order 2)	Predicted log GI50 µM
2,3-dihydrowithaferin A-3-beta-O-sulfate	24.206	-0.208	127.287	7.998	-0.199*
12-deoxy-withastramonolide	24.206	-3.299	127.364	7.998	0.147*
Withanolide 1	25.784	-0.498	132.213	8.75	-1.128
Withanolide 2	24.861	-1.938	127.712	8.764	-1.321
Withanolide 3	24.861	-1.938	127.712	8.764	-1.321
Withanolide 4	23.499	-1.193	125.589	7.508	0.633*
Withanolide 5	24.206	-0.924	127.364	7.998	-0.104*
Withanolide A	24.422	1.406	127.04	7.528	-0.088*
Withfarin A	24.206	-0.702	127.287	7.998	-0.147*
Withanolide D	24.422	0.867	135.358	7.528	2.025
CID_73621	26.267	4.077	129.71	7.592	-1.347*
CID_135887	25.767	0.065	130.302	8.248	-1.085*
CID_301754	24.422	3.834	126.963	5.699	1.679
CID_435144	26.267	3.766	129.994	7.592	-1.244*
CID_3034071	24.474	-2.885	127.205	7.308	0.608
CID_5315323	24.422	2.374	129.987	7.528	0.538
CID_10161347	24.422	6.204	129.987	7.528	0.133
CID_10413139	25.397	-1.041	128.502	7.345	-0.09*
CID_11294368	24.422	1.484	127.04	7.528	-0.096*
CID_53477765	24.422	4.242	126.963	7.528	-0.407*
CID_161671	24.422	0.128	126.963	7.528	0.028*
CID_135887	25.767	-8.022	130.302	8.248	-0.229*
CID_161671	25.345	0.358	134.625	7.556	1.084
CID_301751	25.397	-0.468	128.613	7.345	-0.123*
CID 3372729	25.397	1.201	128.502	7.345	-0.327*
CID_301751	25.397	-0.1	131.604	7.345	0.577
SID_50526634	24.422	1.379	129.987	7.528	0.644
CID_11294368	24.422	-0.412	127.04	7.528	0.105*
CID_161671	24.422	-2.479	126.963	7.528	0.304*
CPT	**Exp. log GI50 (µM)**				**-0.824**

Note: Prediction of withanolide analogs through QSAR model. Values in bold indicate predicted GI_{50} (µM) calculated through derived QSAR model with 93% accuracy for true positives

Table S8: Predicted chemical descriptors and *in-vitro* activity against MCF7/BUS cell line.

Compound Name	All atom count	Dielectric energy (kcal/mole)	Total energy (Hartree)	Heat of formation (kcal/mole)	Predicted log GI50 (µM)
2,3-dihydrowithaferin A-3-beta-O-sulfate	72	-0.855	-258.874	-220.933	1.435
12-deoxy-withastramonolide	72	-0.895	-258.874	-222.577	1.37
Withanolide 1	78	-0.969	-280.005	-273.711	1.224
Withanolide 2	75	-0.889	-272.858	-275.705	1.248
Withanolide 3	80	-0.906	-281.634	-326.061	1.953
Withanolide 4	71	-0.824	-246.681	-177.789	2.007
Withanolide 5	72	-0.937	-258.748	-179.09	1.077
Withanolide A	72	-0.885	-258.831	-215.772	1.356
Withfarin A	72	-0.931	-258.884	-219.454	1.287
Withanolide D	78	-0.401	-250.709	-136.351	3.894
CID_73621	74	-0.864	-283.133	-288.004	0.302*
CID_135887	75	-0.864	-272.643	-305.712	1.466
CID_301754	72	-0.59	-258.852	-207.588	1.857
CID_435144	74	-0.955	-283.06	-244.614	-0.084*
CID_3034071	72	-0.886	-258.827	-216.259	1.358
CID_5315323	74	-0.764	-253.817	-173.659	2.232
CID_10161347	74	-0.833	-253.845	-180.808	2.139
CID_10413139	73	-0.785	-271.009	-259.747	1.033
CID_11294368	72	-0.837	-258.846	-217.202	1.452
CID_53477765	72	-0.878	-258.853	-221.658	1.399
CID_161671	72	-0.872	-258.857	-218.163	1.391
CID_135887	75	-1.087	-272.629	-301.047	1.031
CID_161671	77	-0.735	-261.031	-193.53	2.519
CID_301751	73	-0.821	-271.006	-260.881	0.973*
CID 3372729	73	-0.803	-270.976	-250.641	0.955*
CID_301751	75	-0.771	-265.966	-211.337	1.68
SID_50526634	74	-0.777	-253.846	-182.358	2.251
CID_11294368	72	-0.972	-258.845	-216.248	1.199
CID_161671	72	-0.761	-258.852	-217.958	1.595
CPT	**Exp. log GI_{50} (µM)**				**-0.678**
5-FU					**0.792**

Note: Prediction of active withanolide analogs through QSAR model. Values in bold indicate predicted GI_{50} (µM) calculated through derived QSAR model with 91% accuracy for true positives.

Table S9: Drug-likeness properties of withania analogs.

Compound Name	Pharmacokinetic property (ADME) dependent on chemical descriptors							Rule of 5 violation
	AE	ADME	AD					
			H-bond donors			H-bond acceptors		
	MW	Log P	Amine group count	Sec-amine group count	Hydroxyl group count	Nitrogen atom count	Oxygen atom count	
2,3-dihydrowithaferin A-3beta-O-sulfate	470.605	2.739	0	0	2	0	6	0
12-deoxy-withastramonolide	470.605	2.667	0	0	2	0	6	0
Withanolide 1	502.647	3.107	0	0	2	0	7	1
Withanolide 2	488.62	2.441	0	0	2	0	7	0
Withanolide 3	504.662	3.195	0	0	3	0	7	1
Withanolide 4	454.605	3.669	0	0	1	0	5	0
Withanolide 5	470.605	2.667	0	0	2	0	6	0
Withanolide A	470.605	2.648	0	0	2	0	6	0
Withfarin A	470.605	2.739	0	0	2	0	6	0
Withanolide D	468.675	3.887	0	0	2	0	4	0
CID_73621	502.603	0.823	0	0	4	0	8	1
CID_135887	488.62	2.273	0	0	4	0	7	0
CID_301754	470.605	2.721	0	0	2	0	6	0
CID_435144	502.603	1.752	0	0	4	0	8	1
CID_3034071	470.605	2.324	0	0	2	0	6	0
CID_5315323	468.632	4.175	0	0	1	0	5	0
CID_10161347	468.632	4.175	0	0	1	0	5	0
CID_10413139	486.604	1.447	0	0	3	0	7	0
CID_11294368	470.605	2.648	0	0	2	0	6	0
CID_53477765	470.605	2.72	0	0	2	0	6	0
CID_161671	470.605	2.721	0	0	2	0	6	0
CID_135887	488.62	2.273	0	0	4	0	7	0
CID_161671	482.659	4.253	0	0	1	0	5	0
CID_301751	486.604	1.248	0	0	3	0	7	0
CID 3372729	486.604	1.447	0	0	3	0	7	0
CID_301751	484.631	2.829	0	0	2	0	6	0
SID_50526634	468.632	4.175	0	0	1	0	5	0
CID_11294368	470.605	2.648	0	0	2	0	6	0
CID_161671	470.605	2.721	0	0	2	0	6	0

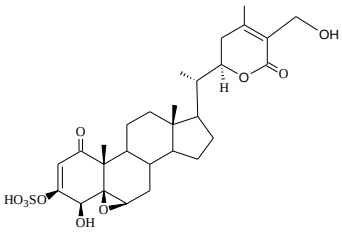
Abbreviations: A = absorption, D = distribution, M = metabolism, and E = excretion; TPSA = topological polar surface area; MW = molecular weight; Log P = log of octanol/water partition coefficient.

Table S10: *In silico* assessment of pharmacokinetic parameters.

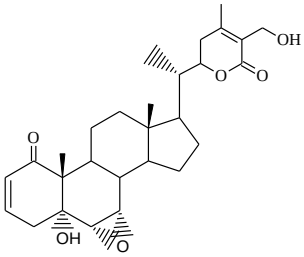
Compound Name	CYP2D6 binding	Aqueous solubility	BBB penetration	Intestinal absorption	Hepatotoxicity	PPB	PSA_2D	AlogP
2,3-dihydrowithaferin A-3-beta-O-sulfate	False	2	3	0	False	True	94.092	3.388
12-deoxy-withastramonolide	False	2	3	0	False	True	94.092	3.32
Withanolide 1	False	2	3	0	True	True	103.022	2.853
Withanolide 2	False	2	3	0	False	True	103.022	2.436
Withanolide 3	False	2	4	0	False	True	114.908	2.7
Withanolide 4	False	1	1	0	False	True	73.277	4.411
Withanolide 5	False	2	3	0	False	True	94.092	3.32
Withanolide A	False	2	3	0	False	True	94.092	3.397
Withfarin A	False	2	3	0	False	True	94.092	3.388
Withanolide D	False	2	1	0	False	True	59.491	4.613
CID_73621	False	3	4	1	True	True	135.723	1.573
CID_135887	False	3	4	1	True	True	126.793	2.357
CID_301754	False	2	3	0	False	True	94.092	3.465
CID_435144	False	3	4	1	True	True	135.723	1.635
CID_3034071	False	2	3	0	True	True	94.092	3.283
CID_5315323	False	1	1	0	False	True	73.277	4.685
CID_10161347	False	1	1	0	False	True	73.277	4.685
CID_10413139	False	2	4	0	True	True	114.908	2.404
CID_11294368	False	2	3	0	False	True	94.092	3.397
CID_53477765	False	2	3	0	False	True	94.092	3.465
CID_161671	False	2	3	0	False	True	94.092	3.465
CID_135887	False	3	4	1	True	True	126.793	2.357
CID_161671	False	1	1	0	True	True	73.277	4.89
CID_301751	False	2	4	0	False	True	114.908	2.146
CID 3372729	False	2	4	0	True	True	114.908	2.404
CID_301751	False	2	3	0	True	True	94.092	3.557
SID_50526634	False	1	1	0	False	True	73.277	4.685
CID_11294368	False	2	3	0	False	True	94.092	3.397
CID_161671	False	2	3	0	False	True	94.092	3.465
5-FU	False	4	3	1	True	False	60.222	-0.908
CPT	False	3	3	0	True	False	78.96	1.746

Abbreviations: CYP450: cytochrome P450, BBB: blood brain barrier, PPB: plasma protein binding, PSA: Polar surface area, AlogP: logarithm of the partition coefficient between n-octanol and water. CYP2D6 binding: False (non-inhibitor), True (inhibitor); Aqueous solubility: 1 (poor), 2 (low), 3 (good); BBB: 0 (very good), 1(good), 2 (medium), 3 (low) and 4 (undefined); Intestinal absorption: 0 (good), 1 (moderate); Hepatotoxicity: True (toxic), False (non-toxic); PPB: True (highly bounded), False (poorly bounded).

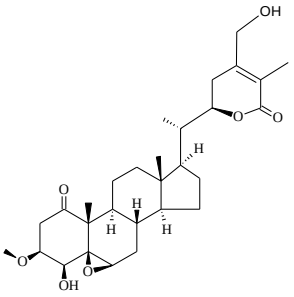
Figure S1: Chemical structures of screened withania analogs.



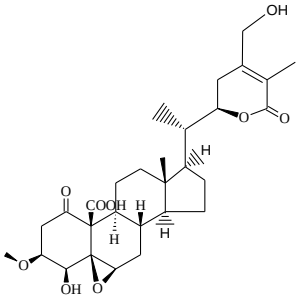
2,3-dihydrowithaferin A-3-beta-O-sulfate



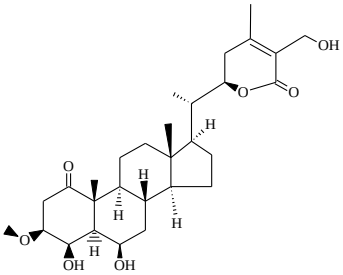
12-deoxy-withastramonolide



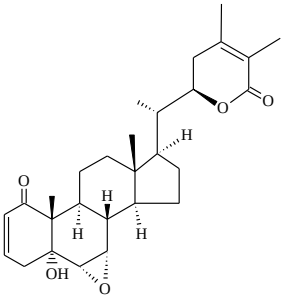
withanolide 1



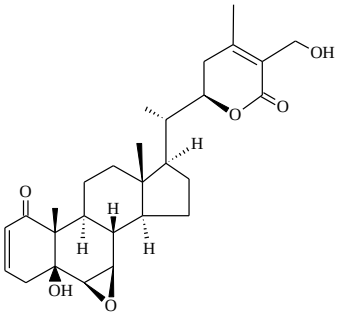
withanolide 2



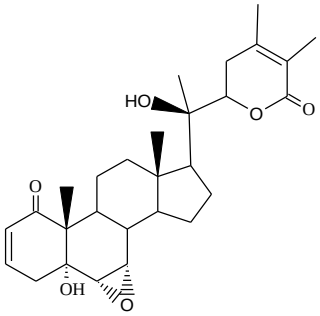
withanolide 3



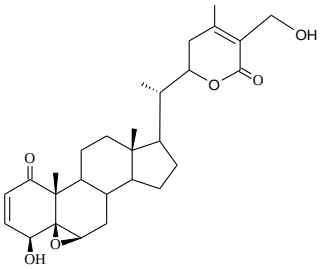
withanolide 4



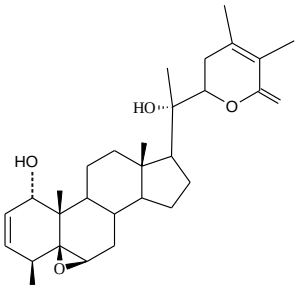
withanolide 5



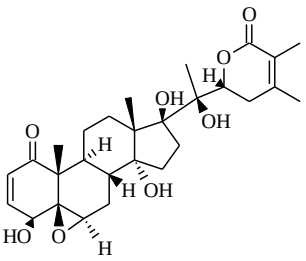
withanolide A



withfarin A



withanolide D



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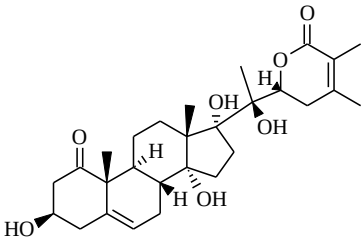

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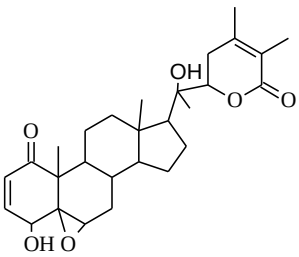

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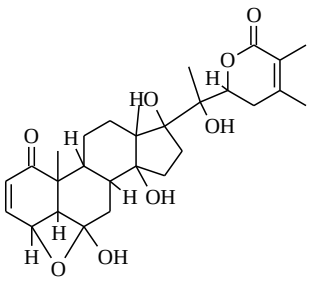

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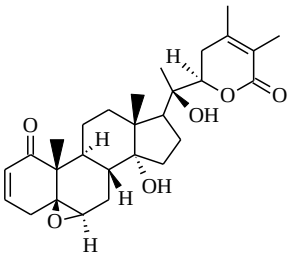

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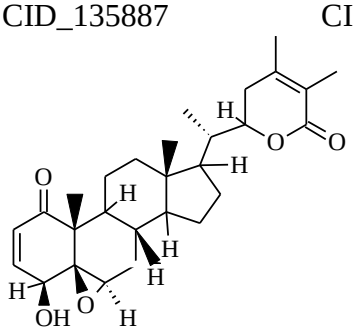

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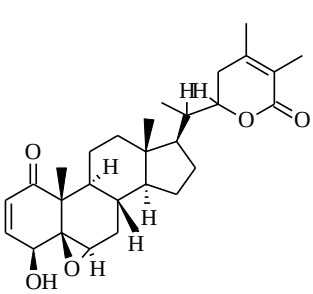

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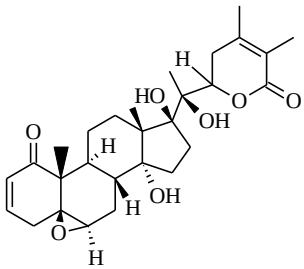

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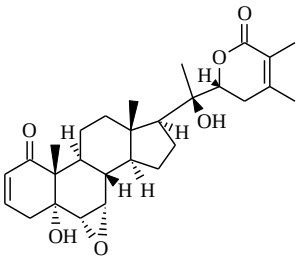

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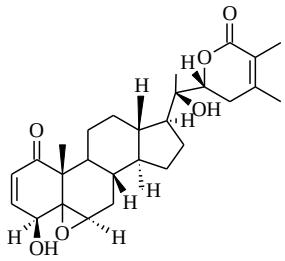

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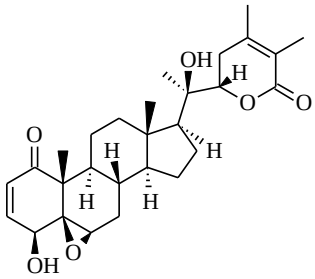

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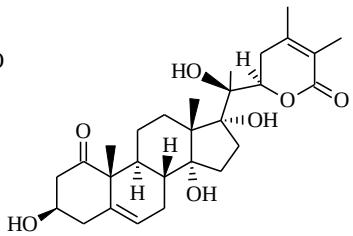

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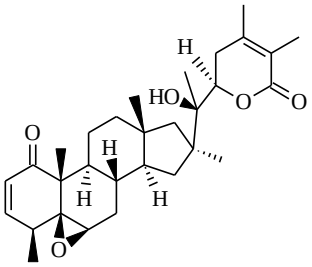

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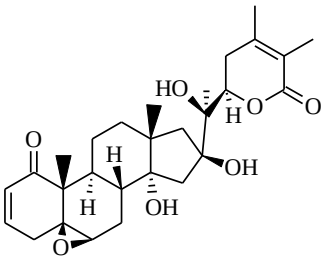

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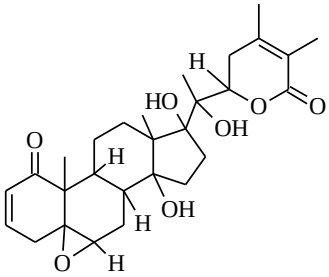

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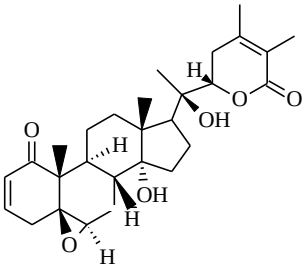

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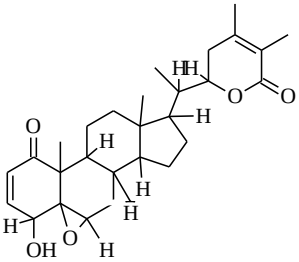

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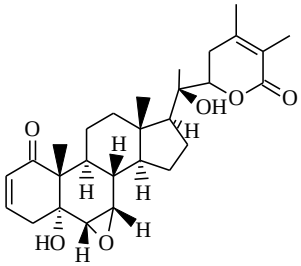

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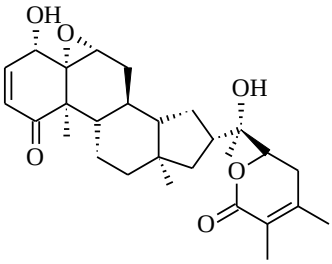

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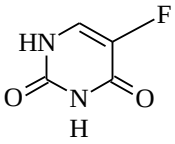
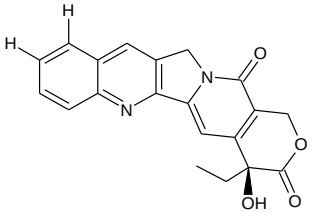


5-Fluorouracil (5-FU)



Camptothecin (CPT)