Electronic Supplementary Material (ESI) for Molecular Systems Design & Engineering.

A computational-*cum*-experimental study provides some clues on the druggable binding site and design of anticancer therapeutics on ETV1 transcription factor oncoprotein

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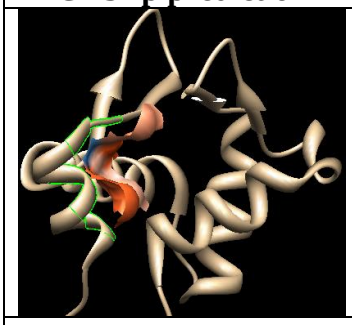
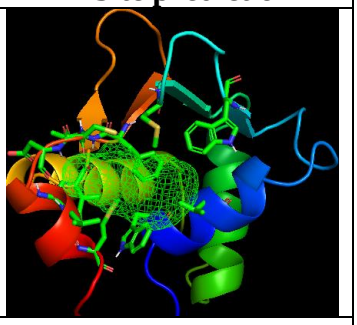
Supplementary Information

Supplementary Table S1: ETV1 ligand binding pockets and respective residues predicted by CASTp and FTSite.

CASTp prediction	FTSite prediction
	
Residues in PocID 1	**Residues in Site 2**
Val415	Trp338
Cys416	Val342
Asp417	Trp356
Ala420	Met361
Leu421	Phe414
Met424	Val415
	Cys416
	Ala420
	Leu421
	Phe422

Supplementary Table S2: PISA-annotated ETV1 dimer interface. [a]Residues making **H**ydrogen/**D**isulphide bond, **S**alt bridge or **C**ovalent link; [b]Accessible Surface Area (Å^2); [c]Buried Surface Area (Å^2); [d]Solvation energy effect (kcal/mol). *Dark blue*- inaccessible residues; *Light blue*- Solvent-accessible residues; *Pale yellow*- interfacing residues; ||||- buried area percentage, one bar per 10%.

Residues	HSDC[a]	ASA[b]	BSA[c]	Δ^iG[d]
A:SER 334		165.82	0.00	0.00
A:LEU 335		66.40	0.00	0.00
A:GLN 336		63.71	0.00	0.00
A:LEU 337		7.19	0.00	0.00
A:TRP 338		33.82	19.81 ||||||	0.32
A:GLN 339		66.86	0.00	0.00
A:PHE 340		17.71	0.00	0.00
A:LEU 341		0.00	0.00	0.00
A:VAL 342		37.94	16.57 |||||	0.27
A:ALA 343		60.90	0.00	0.00
A:LEU 344		20.72	0.00	0.00
A:LEU 345		7.62	0.00	0.00
A:ASP 346		114.92	0.00	0.00
A:ASP 347		62.96	0.00	0.00
A:PRO 348		113.84	0.00	0.00
A:SER 349		94.22	0.00	0.00
A:ASN 350		12.66	0.00	0.00
A:SER 351		56.11	0.00	0.00
A:HIS 352		168.97	0.00	0.00
A:PHE 353		16.09	0.00	0.00
A:ILE 354		1.73	0.00	0.00
A:ALA 355		37.47	0.00	0.00
A:TRP 356		99.37	9.22 |	0.15
A:THR 357		77.41	0.00	0.00
A:GLY 358		68.51	0.00	0.00
A:ARG 359		62.24	0.00	0.00
A:GLY 360		56.47	0.00	0.00
A:MET 361	**H**	81.52	23.59 |||	0.38
A:GLU 362		52.38	0.00	0.00
A:PHE 363		0.00	0.00	0.00
A:LYS 364		31.48	0.00	0.00
A:LEU 365		0.00	0.00	0.00
A:ILE 366		67.16	0.00	0.00
A:GLU 367		40.15	0.00	0.00

A:PRO 368		20.38	0.00	0.00
A:GLU 369		100.33	0.00	0.00
A:GLU 370		49.75	0.00	0.00
A:VAL 371		0.00	0.00	0.00
A:ALA 372		0.00	0.00	0.00
A:ARG 373		101.96	0.00	0.00
A:ARG 374		95.70	0.00	0.00
A:TRP 375		12.77	0.00	0.00
A:GLY 376		2.39	0.00	0.00
A:ILE 377		85.73	0.00	0.00
A:GLN 378		76.67	0.00	0.00
A:LYS 379		102.36	0.00	0.00
A:ASN 380		118.97	0.00	0.00
A:ARG 381		114.93	0.00	0.00
A:PRO 382		126.75	0.00	0.00
A:ALA 383		68.80	0.00	0.00
A:MET 384		42.93	0.00	0.00
A:ASN 385		54.75	0.00	0.00
A:TYR 386		38.02	0.00	0.00
A:ASP 387		107.17	0.00	0.00
A:LYS 388		89.48	0.00	0.00
A:LEU 389		0.34	0.00	0.00
A:SER 390		5.92	0.00	0.00
A:ARG 391		99.47	0.00	0.00
A:SER 392		42.14	0.00	0.00
A:LEU 393		0.00	0.00	0.00
A:ARG 394		96.40	0.00	0.00
A:TYR 395		130.27	0.00	0.00
A:TYR 396		22.25	0.00	0.00
A:TYR 397		77.56	0.00	0.00
A:GLU 398		118.76	0.00	0.00
A:LYS 399		69.54	0.00	0.00
A:GLY 400		26.33	0.00	0.00
A:ILE 401		7.54	0.00	0.00
A:MET 402		1.82	0.00	0.00
A:GLN 403		101.92	0.00	0.00
A:LYS 404		67.44	0.00	0.00
A:VAL 405		18.51	0.00	0.00
A:ALA 406		91.71	0.00	0.00
A:GLY 407		90.99	0.00	0.00
A:GLU 408		51.41	0.00	0.00
A:ARG 409		192.03	0.00	0.00
A:TYR 410		63.96	0.00	0.00
A:VAL 411		6.53	0.00	0.00
A:TYR 412		6.73	0.00	0.00

A:LYS 413		24.10	0.00	0.00
A:PHE 414		13.96	5.99 |||||	0.10
A:VAL 415		29.56	4.54 ||	-0.05
A:CYS 416		109.22	25.25 |||	0.80
A:ASP 417		67.28	3.87 |	0.01
A:PRO 418	H	116.68	0.00	0.00
A:GLU 419		63.47	0.00	0.00
A:ALA 420		1.18	1.18 ||||||||||	0.02
A:LEU 421		132.40	53.85 |||||	0.84
A:PHE 422		152.79	0.00	0.00
A:SER 423		41.04	0.00	0.00
A:MET 424		48.81	36.24 |||||||	1.01
A:ALA 425		76.88	17.00 |||	0.27
A:PHE 426		61.08	0.00	0.00
A:SER 427		94.13	0.00	0.00
A:ASP 428		161.67	0.00	0.00

Supplementary Table S3: Phytochemical hits shortlisted by similarity search of YK-4-279 and BRD32048 against IMPPAT.[21] [a]YK-4-279-similar compounds; [b]BRD32048-similar compounds; [c]Tanimoto coefficient.

Group Y[a]	**TC[c]**	**Chemical Class**
CID14157883	0.37	Linear 1,3-diarylpropanoids
CID7478	0.37	Benzene and substituted derivatives
CID7476	0.35	Organooxygen compounds
CID2196	0.34	Benzene and substituted derivatives
CID97141	0.33	Flavonoids
CHEMSPIDER4478714	0.34	“
CID5280378	0.34	Isoflavonoids
CID14079439	0.33	“
CID5711223	0.33	Linear 1,3-diarylpropanoids
CID5319771	0.32	Isoflavonoids
Group B[b]	**TC**	**Chemical Class**
CASID1204607-09-9	0.30	Pyridines and derivatives
CID7732	0.30	Phenol ethers
CID123775	0.29	Diazanaphthalenes
CID5282443	0.28	Benzene and substituted derivatives
CID13007	0.27	Piperidines
CID7738	0.27	Benzene and substituted derivatives
CID9015	0.26	Phenols

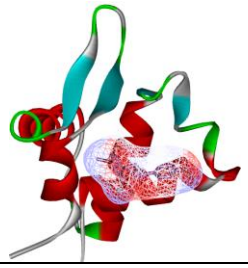
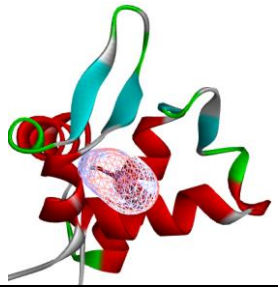
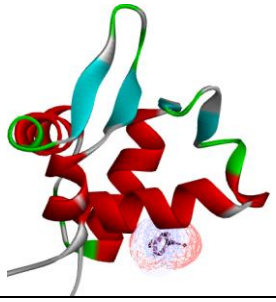
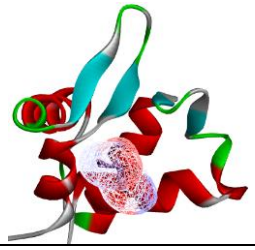
CHEMSPIDER30777501	0.26	“
CASID19879-50-6	0.26	Isoquinolines and derivatives

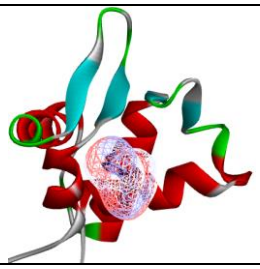
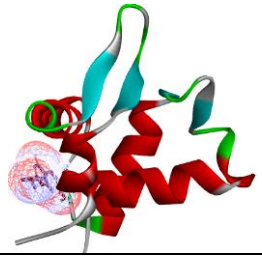
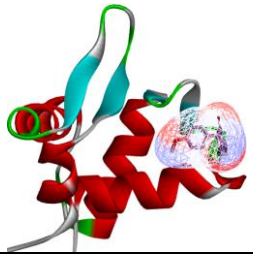
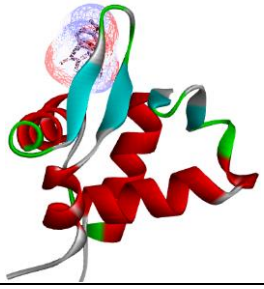
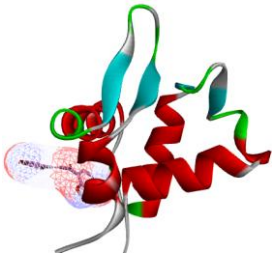
Supplementary Table S4: Druglikeness profile of phytocompounds.[21] [a]YK-4-279-similar compounds; [b]BRD32048-similar compounds; [c]Octanol/water partition coefficient; [d]Number of aromatic rings; [e]Number of hydrogen bond acceptors; [f]Number of hydrogen bond donors; [g]Number of rotatable bonds; [h]Polar surface area; [i]Absorption; [j]Solubility; [k]Blood Brain Barrier Penetration; [l]Cytochromoe P450 2D6; [m]Hepatotoxicity; [n]Plasma Protein Binding.

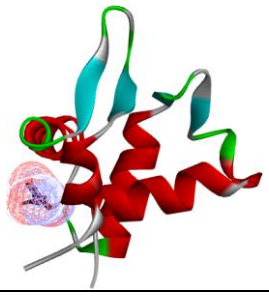
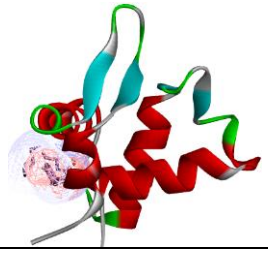
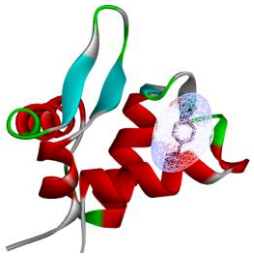
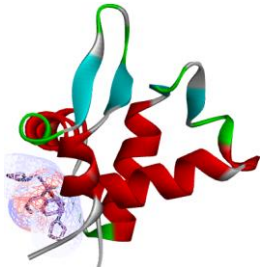
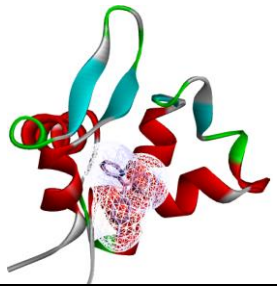
Physicochemical profile							
Group Y[a]	**MW**	**AlogP[c]**	**nAR[d]**	**nHA[e]**	**nHD[f]**	**nRB[g]**	**PSA[h]**
CID14157883	272.3	3.2	2	4	2	5	120.52
CID7478	152.15	1.4	1	3	1	2	85.02
CID7476	150.17	1.6	1	2	0	2	49.52
CID2196	219.24	1.23	1	3	0	2	71.49
CID97141	268.26	2.58	2	4	1	2	91.05
CHEMSPIDER4478714	268.26	2.88	2	4	1	2	91.05
CID5280378	268.26	2.61	2	4	1	2	91.05
CID14079439	282.29	3.14	2	4	1	2	91.05
CID5711223	270.28	3.2	2	4	2	4	120.52
CID5319771	298.29	2.59	2	5	1	3	97.08
Group B[b]	**MW**	**AlogP**	**nAR**	**nHA**	**nHD**	**nRB**	**PSA**
CASID1204607-09-9	370.46	4.33	2	5	2	8	85.78
CID7732	123.15	1.07	1	2	1	1	75.21
CID123775	403.52	4.30	3	6	2	6	85.94
CID5282443	278.39	4.08	2	2	0	4	26.00
CID13007	113.20	1.59	0	1	0	1	11.78
CID7738	138.16	1.21	1	2	1	2	58.18

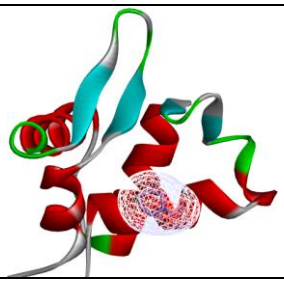
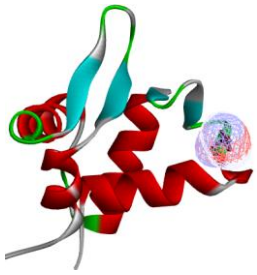
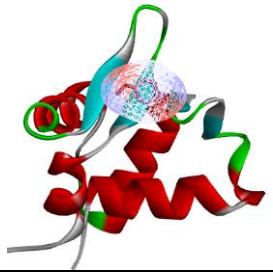
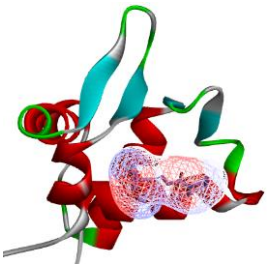
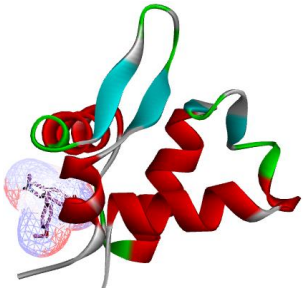
CID9015	124.14	1.57	1	2	1	1	58.18
CHEMSPIDER30777501	287.35	2.84	1	3	1	4	80.15
CASID19879-50-6	313.39	3.64	2	4	1	4	59.34
ADMET profile							
Group Y	**Ab[i]**	**Sol[j]**	**BBB[k]**	**CYP[l]**	**Hep[m]**	**PPB[n]**	
CID14157883	0	3	2	1.73	-0.41	3.10	
CID7478	0	4	2	-7.12	-2.83	-1.13	
CID7476	0	3	2	-3.43	-2.45	-1.08	
CID2196	0	3	2	-8.37	-3.26	-10.47	
CID97141	0	3	2	-3.82	0.69	3.44	
CHEMSPIDER4478714	0	3	2	-2.45	1.22	0.98	
CID5280378	0	3	2	-0.36	2.31	-2.01	
CID14079439	0	2	2	-4.15	-2.29	0.80	
CID5711223	0	3	2	-4.96	-3.40	1.03	
CID5319771	0	3	2	-2.28	1.30	-1.50	
Group B	**Ab**	**Sol**	**BBB**	**CYP**	**Hep**	**PPB**	
CASID1204607-09-9	0	2	1	2.68	-1.49	4.59	
CID7732	0	4	2	-8.04	-0.00	-2.31	
CID123775	0	2	1	4.09	-0.06	-0.33	
CID5282443	0	2	0	1.11	-13.7	10.07	
CID13007	1	4	1	1.99	-6.12	-3.00	
CID7738	0	4	2	-3.38	-5.10	-1.90	
CID9015	0	4	2	-3.80	-1.67	-5.21	
CHEMSPIDER30777501	0	3	2	-5.27	-7.23	1.47	
CASID19879-50-6	0	2	1	-2.02	0.02	-2.19	

Supplementary Table S5: Binding modes of ETV1-docked phytocompounds.[21] [a]YK-4-279-similar compounds; [b]BRD32048-similar compounds; [c]Hydrogen bonds; [d]Hydrophobic interactions; [e]Electrostatic interactions. The ligand (*violet*) shown in van der Waals (VDW) atom charge surface.

Group Y[a]	Affinity (kcal/mol)	Docked Site	HB[c]	HY[d]	E[e]
CID14157883 	-5.8	Dimer interface	Ser392, Ser423	Tyr396, Lys399	-
CID7478 	-4.1	"	Asp417	Met424, Cys416	-
CID7476 	-4.0	Between α1-α2	-	Phe340, Arg374	-
CID2196 	-5.0	Dimer interface	Cys416	Phe414, Ala420, Leu421, Met424	-
CID97141	-6.0		-	Val342, Ala420,	Cys416, Met424

		“		Leu421, Met424	
CHEMSPIDER4478714 	-6.1	α3	Leu337, Tyr396, Ser423	-	-
CID5280378 	-6.0	Dimer interface	-	Ala355, Trp356	-
CID14079439 	-5.7	Opposite to α3	Glu369, Lys404, Arg409	-	-
CID5711223 	-5.4	α3	Leu337, Tyr396	Tyr395	-

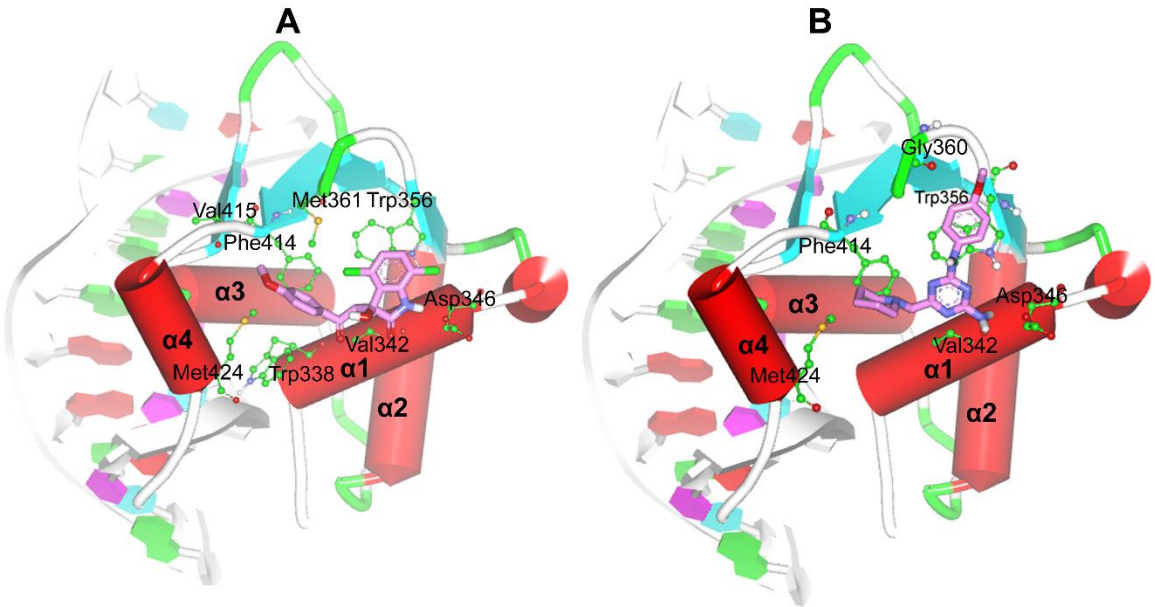
CID5319771 	-5.9	“	Ser392, Ser423	Tyr396, Lys399	-
Group B[b]	**Affinity (kcal/mol)**		**H-bonds**	**HY**	**E**
CASID1204607-09-9 	-5.6	α3	Trp375, Lys388, Ser392	-	Lys379
CID7732 	-3.6	Dimer interface	-	Trp356	-
CID123775 	-6.4	α3	Leu335	Lys379, Arg381, Tyr395	Lys379
CID5282443 	-5.6	Dimer interface	-	Val342, Phe414, Cys416, Ala420, Leu421, Met424, Ala425	-
CID13007	-3.2		-	Val342, Trp356, Phe414	-

		“			
CID7738 	-4.0	“	Leu345, Asp347	Peo348, Ala355, Trp356	-
CID9015 	-3.7	“	Arg359, Met361	Lys413	-
CHEMSPIDER30777501 	-5.3	“	-	Trp356, Met424	-
CASID19879-50-6 	-5.8	α3	Ser392	Tyr395, Tyr396, Lys399	-

Supplementary Table S6: Low concentration tests of CID5282443.

Trial 1			Trial 2		
Conc. (µg/ml)	**MCF-7**	**3T3-L1**	**Conc. (µg/ml)**	**MCF-7**	**3T3-L1**
31.25	108.05	131.46	0.3125	124.14	146.79
15.625	224.18	92.91	0.15625	113.32	104.79
7.8125	101.03	117.17	0.078125	98.10	134.34
3.90625	97.09	203.51	0.0390625	79.61	101.75
1.953125	109.35	170.51	0.01953125	49.53	82.33

Supplementary Figure S1: Vina-predicted binding modes of YK-4-279 and BRD32048 in ETV1.[21] A) YK-4-279 and B) BRD32048 in ETV1 with -5.6 kcal/mol binding affinity each. The structures shown in schematic representation with compounds in *violet* color.



Supplementary Figure S2: Clustering of phytochemicals.