Supporting Information

Supplementary Tables

Table S-I. PubChem ID and canonical SMILES of Baicalein and reference compounds

Ligands	Name of Ligands	Synonyms	PubChem ID	Canonical SMILES
A	Baicalein	Noroxylin	5281605	C1=CC=C(C=C1)C2=CC(=O)C3=C(O2)C=C(C(=C3O)O)O
B	1,5-Naphthyridine	1,5-Pyridopyridine	136070	C1=CC2=C(C=CC=N2)N=C1
C	4-(4-(benzo[d][1,3]dioxol-5-yl)-5-(1yridine-2-yl)-1H-imidazol-2-yl)benzamide	SB431542	4521392	C1OC2=C(O1)C=C(C=C2)C3=C(NC(=N3)C4=CC=C(C=C4)C(=O)N)C5=CC=CC=N5
D	5-[(3S)-5,5-dimethyloxolan-3-yl]-6-methoxy-3-(2-methoxypyridin-4-yl)pyrazolo[1,5-a]pyrimidine	CHEMBL4792464	156022737	CC1(C[C@H](CO1)C2=NC3=C(C=NN3C=C2OC)C4=CC(=NC=C4)OC)C

Table S-II. Ramachandran plot statistical analysis

S.N.	Target model	Region			
		Most favoured	Additional allowed	Generously allowed	Disallowed
1.	1VJY	90.7%	9.3%	0.0%	0.0%
2.	3TZM	92.5%	7.5%	0.0%	0.0%
3.	7DV6	95.3%	4.7%	0.0%	0.0%

Table S-III. Swiss ADME and drug-likeness prediction summary

S. N.	ADME Parameters	Baicalein
Physicochemical Properties		
1.	Formula	$C_{15}H_{10}O_5$

2.	Molecular weight (g/mol)	270.24
3.	Num. heavy atoms	20
4.	Num. arom. heavy atoms	16
5.	Fraction Csp3	0.00
6.	Num. rotatable bonds	1
7.	Num. H-bond acceptors	5
8.	Num. H-bond donors	3
9.	Molar Refractivity (MR)	73.99
10.	TPSA (Å²)	90.90
Lipophilicity		
11.	Log Po/w (iLOGP)	2.43
12.	Log Po/w (XLOGP3)	3.16
13.	Log Po/w (WLOGP)	2.58
Water solubility		
14.	Log S (ESOL)	-4.0
15.	Qualitative solubility	Moderately soluble
Pharmacokinetics		
16.	GI absorption	High
17.	Intestinal absorption (human)*	90.14%
18.	BBB permeant	No
19.	P-gp substrate	No
20.	CYP1A2 inhibitor	Yes
21.	CYP2C19 inhibitor	No
22.	CYP2C9 inhibitor	No
23.	CYP2D6 inhibitor	Yes
24.	CYP3A4 inhibitor	Yes
25.	Log Kp (skin permeation) (cm/s)	-5.70
26.	Skin Permeability (Log Kp)*	-3.433
27.	Total Clearance (log ml/min/kg)*	0.273
28.	Renal OCT2# substrate*	No
Drug-likeness		
29.	Lipinski (RO5)	Yes; 0 violation
30.	Ghose	Yes
31.	Veber	Yes
32.	Bioavailability score	0.55
33.	Lead-likeness	Yes
34.	SA	3.02

Fraction Csp3 : Fraction of carbon atoms that are sp3 hybridised; TPSA : Topological polar surface area; Log Po/w : partition coefficient between n-octanol and water; Log S : decimal logarithm of the molar solubility in water; Lipinski (RO5) : Range are MW ≤ 500, MLOGP ≤ 4.15, N or O ≤ 10, NH or OH ≤ 5; Ghose : Range 160 ≤ MW ≤ 480, -0.4 ≤ WLOGP ≤ 5.6, 40 ≤ MR ≤ 130, 20 ≤ atoms ≤ 70; Veber's rule : Range are Rotatable bonds ≤ 10, TPSA ≤ 140; SA : Synthetic accessibility score ranges from 1 (very easy) to 10 (very difficult). *According to pkCSM - Biosig Lab prediction tool. #OCT2: Organic cation transporter 2

Table S-IV. List of the various targets, Baicalein may bind with probable score ranges from 1.0000 to 0.3299

Target	Common name	Uniprot ID	ChEMBL ID	Target Class	Probability*	Known actives (3D/2D)
Lysine-specific demethylase 4D-like	KDM4E	B2RXH2	CHEMBL1293226	Eraser	1	2 / 2
Xanthine dehydrogenase	XDH	P47989	CHEMBL1929	Oxidoreductase	1	10 / 21
Arachidonate 15-lipoxygenase	ALOX15	P16050	CHEMBL2903	Enzyme	1	7 / 9
Cyclin-dependent kinase 1	CDK1	P06493	CHEMBL308	Kinase	1	3 / 10
Arachidonate 12-lipoxygenase	ALOX12	P18054	CHEMBL3687	Enzyme	1	10 / 12
G protein-coupled receptor kinase 6	GRK6	P43250	CHEMBL6144	Kinase	1	3 / 4
Cytochrome P450 19A1	CYP19A1	P11511	CHEMBL1978	Cytochrome P450	0.436430316	6 / 19
Carbonic anhydrase VII	CA7	P43166	CHEMBL2326	Lyase	0.346270483	8 / 11
Carbonic anhydrase XII	CA12	O43570	CHEMBL3242	Lyase	0.346270483	13 / 16
Carbonic anhydrase IV	CA4	P22748	CHEMBL3729	Lyase	0.346270483	9 / 11
P-glycoprotein 1	ABCB1	P08183	CHEMBL4302	Primary active transporter	0.346270483	12 / 45
Cytochrome P450 1B1	CYP1B1	Q16678	CHEMBL4878	Cytochrome P450	0.346270483	12 / 47
Estradiol 17-beta-dehydrogenase 1	HSD17B1	P14061	CHEMBL3181	Enzyme	0.33811031	8 / 4
Aldose reductase	AKR1B1	P15121	CHEMBL1900	Enzyme	0.329868485	22 / 69
Cyclin-dependent kinase 5/CDK5 activator 1	CDK5R1 CDK5	Q15078 Q00535	CHEMBL1907600	Kinase	0.329868485	6 / 18

*Probability for the query molecule - assumed as bioactive - to have the protein as target.

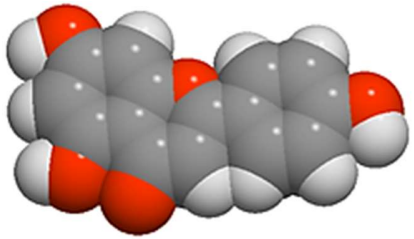
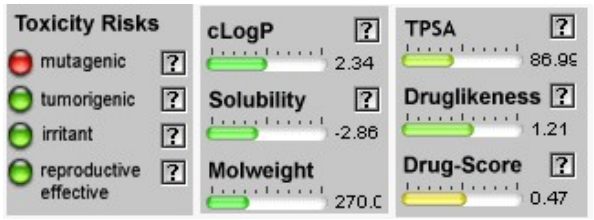
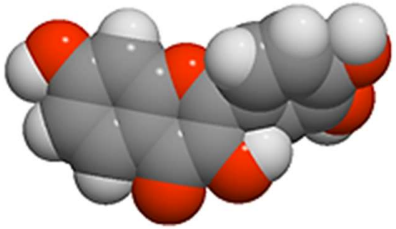
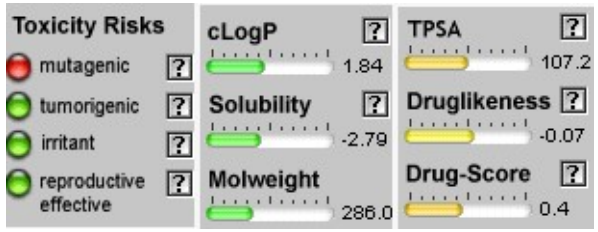
Table S-V. Oral toxicity model report of Baicalein

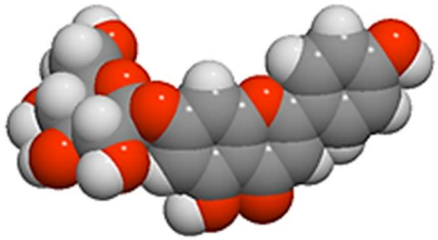
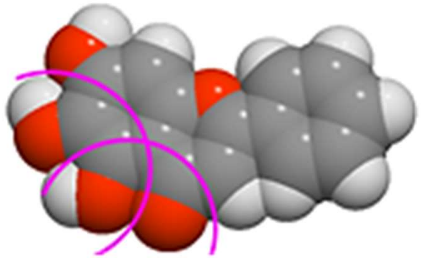
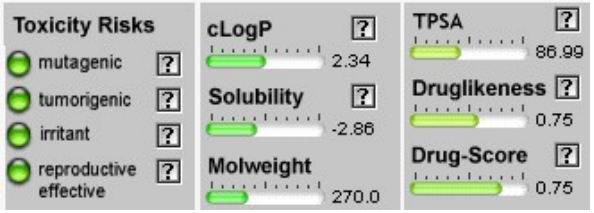
Classification	Target	Shorthand	Prediction	Probability
Organ toxicity	Hepatotoxicity	dili	Inactive	0.69
Organ toxicity	Neurotoxicity	neuro	Inactive	0.89
Organ toxicity	Nephrotoxicity	nephro	Active	0.62
Organ toxicity	Respiratory toxicity	respi	Active	0.83
Organ toxicity	Cardiotoxicity	cardio	Inactive	0.99
Toxicity end points	Carcinogenicity	carcino	Active	0.68
Toxicity end points	Immunotoxicity	immuno	Inactive	0.99
Toxicity end points	Mutagenicity	mutagen	Active	0.51
Toxicity end points	Cytotoxicity	cyto	Inactive	0.99
Toxicity end points	BBB-barrier	bbb	Active	0.53
Toxicity end points	Ecotoxicity	eco	Inactive	0.53
Toxicity end points	Clinical toxicity	clinical	Inactive	0.53
Toxicity end points	Nutritional toxicity	nutri	Active	0.63
Tox21-Nuclear receptor signalling pathways	Aryl hydrocarbon Receptor (AhR)	nr_ahr	Active	0.91
Tox21-Nuclear receptor signalling pathways	Androgen Receptor (AR)	nr_ar	Inactive	0.99
Tox21-Nuclear receptor signalling pathways	Androgen Receptor Ligand Binding Domain (AR-LBD)	nr_ar_lbd	Inactive	0.97
Tox21-Nuclear receptor signalling pathways	Aromatase	nr_aromatase	Inactive	0.91
Tox21-Nuclear receptor signalling pathways	Estrogen Receptor Alpha (ER)	nr_er	Active	0.87
Tox21-Nuclear receptor signalling pathways	Estrogen Receptor Ligand Binding Domain (ER-LBD)	nr_er_lbd	Active	0.95
Tox21-Nuclear receptor signalling pathways	Peroxisome Proliferator Activated Receptor Gamma (PPAR-Gamma)	nr_ppar_gamma	Inactive	0.98
Tox21-Stress response pathways	Nuclear factor (erythroid-derived 2)-like 2/antioxidant responsive element (nrf2/ARE)	sr_are	Inactive	0.99
Tox21-Stress response pathways	Heat shock factor response element (HSE)	sr_hse	Inactive	0.99

Tox21-Stress pathways	response	Mitochondrial Membrane Potential (MMP)	sr_mmp	Active	1
Tox21-Stress pathways	response	Phosphoprotein (Tumor Supressor) p53	sr_p53	Inactive	0.97
Tox21-Stress pathways	response	ATPase family AAA domain-containing protein 5 (ATAD5)	sr_atad5	Inactive	0.99
Molecular Events	Initiating	Thyroid hormone receptor alpha (THRα)	mie_thr_alpha	Inactive	0.90
Molecular Events	Initiating	Thyroid hormone receptor beta (THRβ)	mie_thr_beta	Inactive	0.78
Molecular Events	Initiating	Transtyretrin (TTR)	mie_ttr	Inactive	0.97
Molecular Events	Initiating	Ryanodine receptor (RYR)	mie_ryr	Inactive	0.98
Molecular Events	Initiating	GABA receptor (GABAR)	mie_gabar	Inactive	0.96
Molecular Events	Initiating	Glutamate N-methyl-D-aspartate receptor (NMDAR)	mie_nmdar	Inactive	0.92
Molecular Events	Initiating	alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate receptor (AMPAR)	mie_ampar	Inactive	0.97
Molecular Events	Initiating	Kainate receptor (KAR)	mie_kar	Inactive	0.99
Molecular Events	Initiating	Achetylcholinesterase (AChE)	mie_ache	Inactive	0.69
Molecular Events	Initiating	Constitutive androstane receptor (CAR)	mie_car	Inactive	0.98
Molecular Events	Initiating	Pregnane X receptor (PXR)	mie_pxr	Inactive	0.92
Molecular Events	Initiating	NADH-quinone oxidoreductase (NADHOX)	mie_nadhox	Inactive	0.97
Molecular Events	Initiating	Voltage gated sodium channel (VGSC)	mie_vgsc	Inactive	0.95
Molecular Events	Initiating	Na+/I- symporter (NIS)	mie_nis	Inactive	0.98
Metabolism		Cytochrome CYP1A2	CYP1A2	Active	1
Metabolism		Cytochrome CYP2C19	CYP2C19	Active	0.77

Metabolism	Cytochrome CYP2C9	CYP2C9	Active	0.99
Metabolism	Cytochrome CYP2D6	CYP2D6	Inactive	0.85
Metabolism	Cytochrome CYP3A4	CYP3A4	Inactive	0.79
Metabolism	Cytochrome CYP2E1	CYP2E1	Inactive	1

Table S-VI. Osiris and molinspiration calculation of apigenin, fisetin acid, cosmosiin and baicalein.

Compound name	2D/3D Molecular structure		Drug Score (DS)
Apigenin		miLogP 2.46 TPSA 90.89 natoms 20 MW 270.24 nON 5 nOHNH 3 nviolations 0 nrotb 1 volume 224.05	
Fisetin acid		miLogP 1.97 TPSA 111.12 natoms 21 MW 286.24 nON 6 nOHNH 4 nviolations 0 nrotb 1 volume 232.07	

Cosmosiin		miLogP 0.39 TPSA 190.28 natoms 32 MW 448.38 nON 11 nOHNH 7 nviolations 2 nrotb 4 volume 364.19	
Baicalein		miLogP 2.68 TPSA 90.89 natoms 20 MW 270.24 nON 5 nOHNH 3 nviolations 0 nrotb 1 volume 224.05	

Supplementary Figures

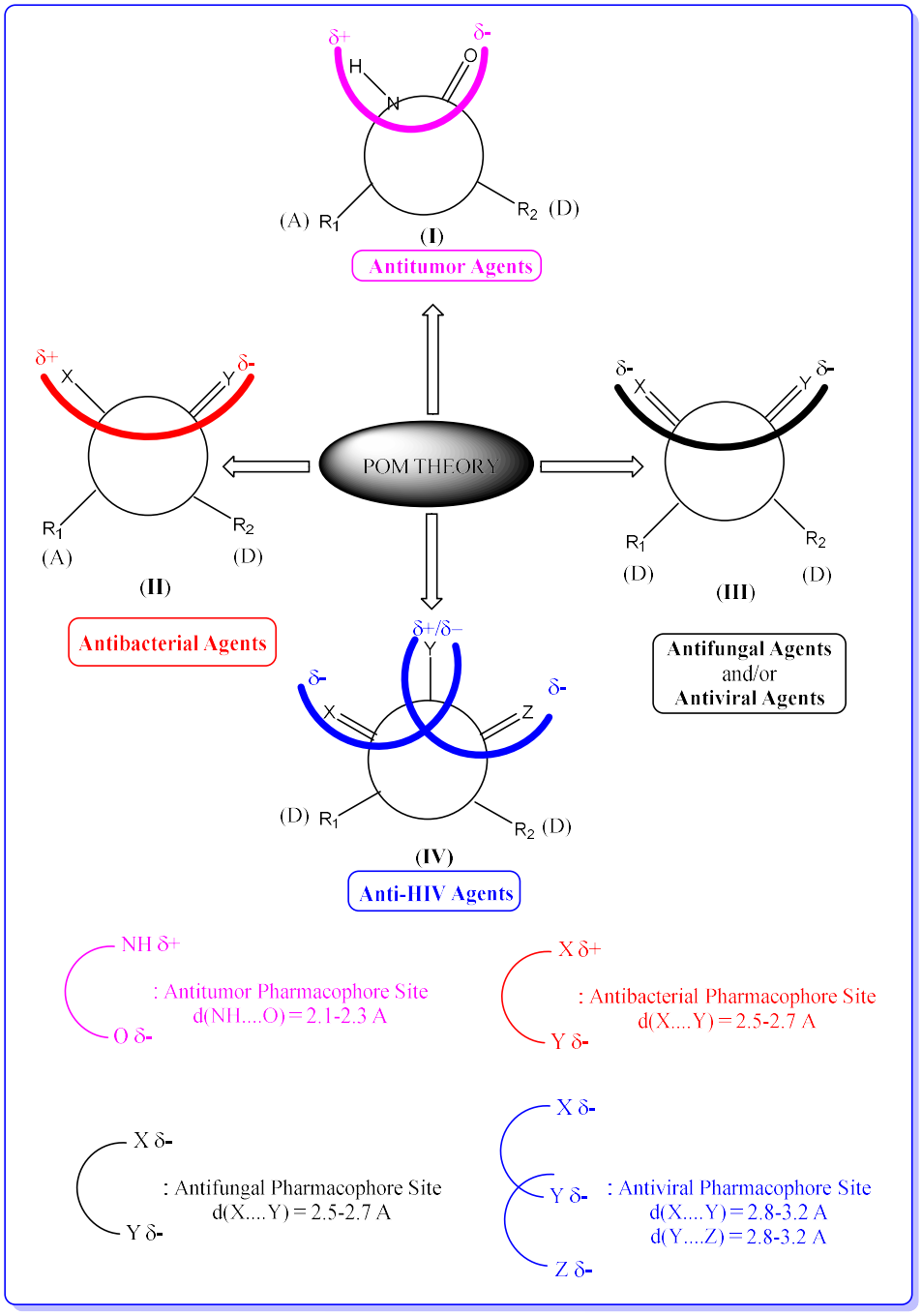


Fig. S1. Organigram of POM Theory, serving as a guide to identify various pharmacophore sites of bioactive molecules (46,47).

A **B** **C** **D**

Fig. S2. Chemical structures of Baicalein (**A**), 1,5-Naphthyridine (**B**), 4-(5-benzo(1,3)dioxol-5-yl-4-pyridin-2-yl-1H-imidazol-2-yl)benzamide (**C**) and 5-[(3S)-5,5-dimethyloxolan-3-yl]-6-methoxy-3-(2-methoxypyridin-4-yl)pyrazolo[1,5-a]pyrimidine (**D**).

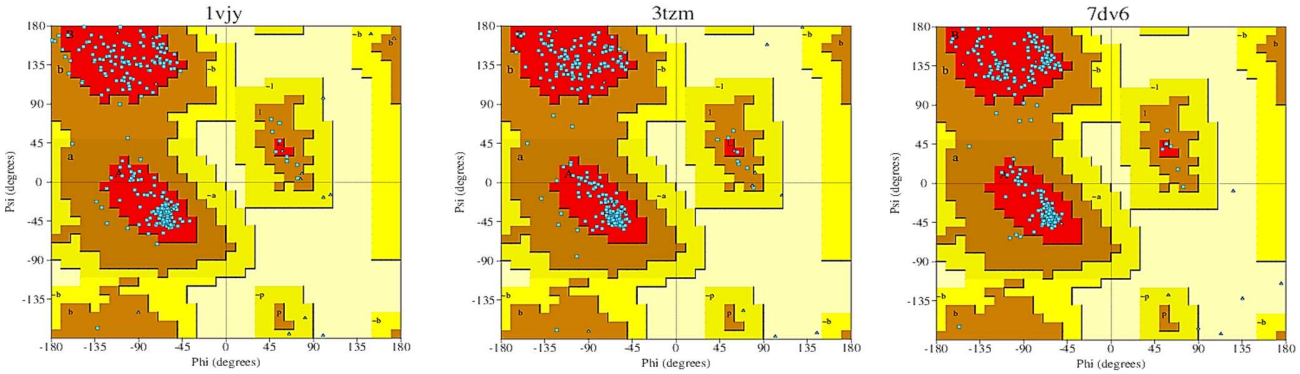


Fig. S3. Ramachandran plots generated via PROCHECK for 1VJY, 3TZM (B), and 7DV6 demonstrate that the target protein's geometry matches the most likely shape based on the torsional angles (ϕ and Ψ) of its amino acid residues. PROCHECK displays the residues in most favoured (red), additionally allowed (light brown), generously allowed (yellow) and disallowed regions (pale yellow).

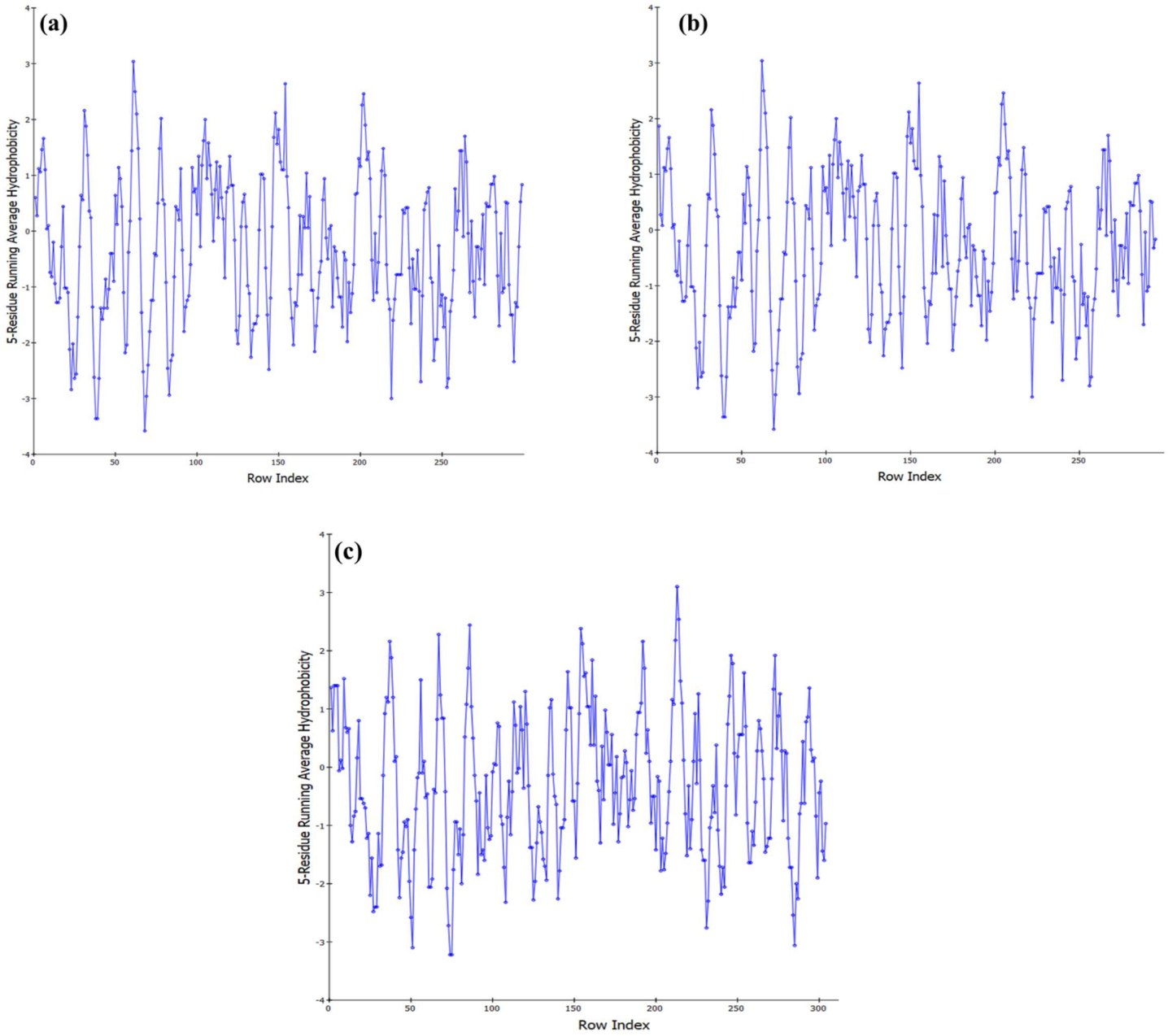


Fig. S4. Analysis of hydropathy demonstrating the presence of hydrophilic and hydrophobic regions in the chain of amino acids, (a): 1VJY, (b): 3TZM, and (c): 7DV6.

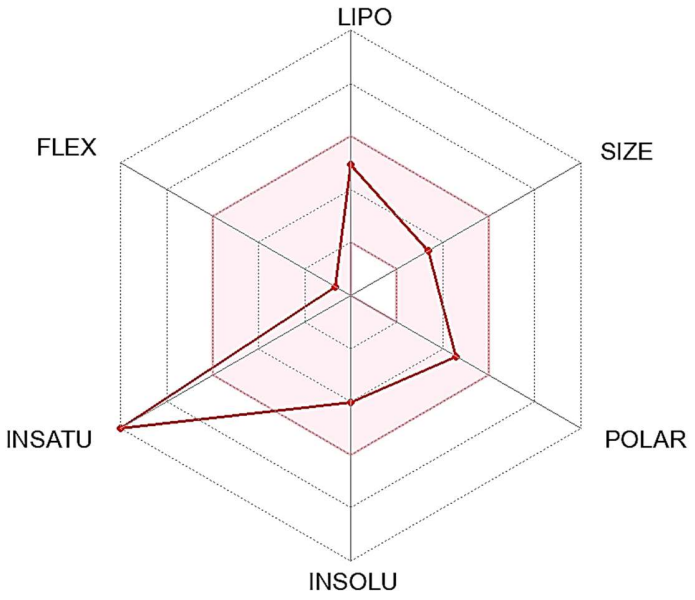


Fig. S5. Bioavailability radar plots of Baicalein.

The colour zone is the suitable physicochemical space for oral bioavailability. LIPO = lipophilicity (−0.7 < XLOGP3 < +5.0 and +3.0), SIZE: 150 < MV < 500 g/mol, POLAR = polarity (20 Å2 < TPSA < 130 Å2), INSOLU = Insolubility (not higher than -6 < Log S (ESOL) < 0), INSATU = Instauration (0.25 < Fraction Csp3 < 1), FLEX = Flexibility (0 < no of rotatable bonds < 9).

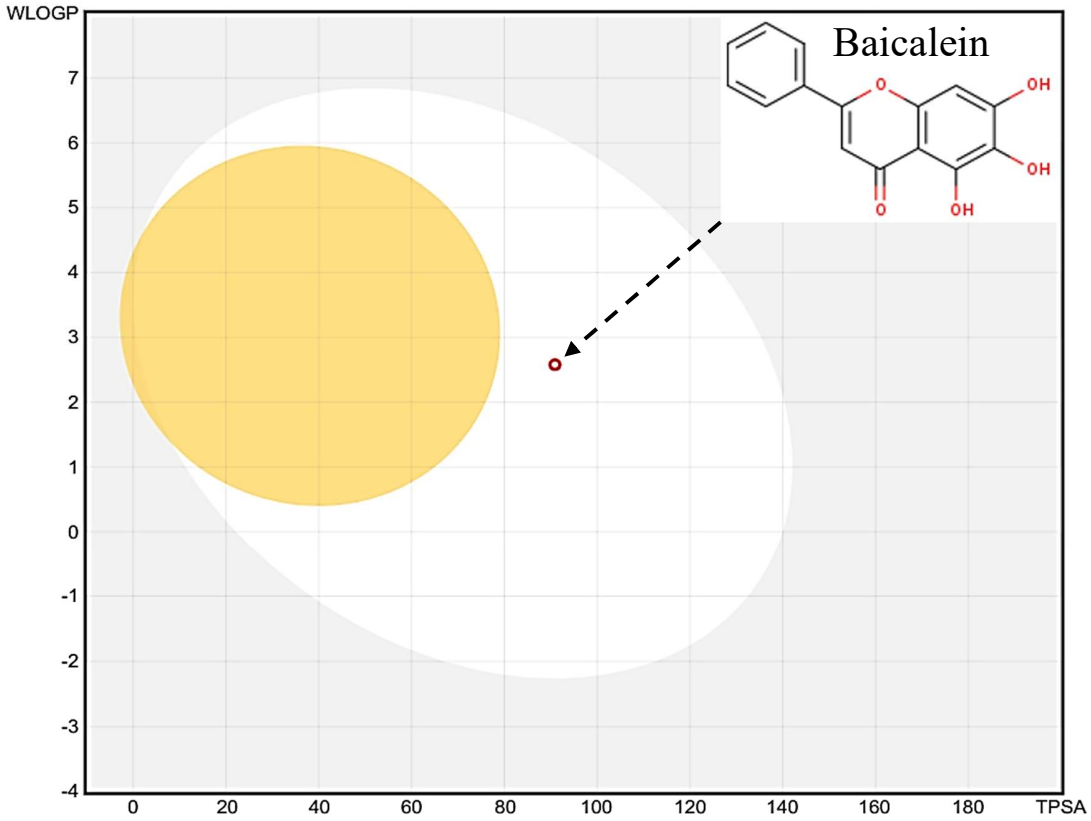


Fig. S6. Boiled-egg plot between lipophilicity (WLOGP) and polarity (TPSA) showing Baicalein is not able to permeate blood–brain barrier (BBB) but passive absorption by the gastrointestinal tract is possible.

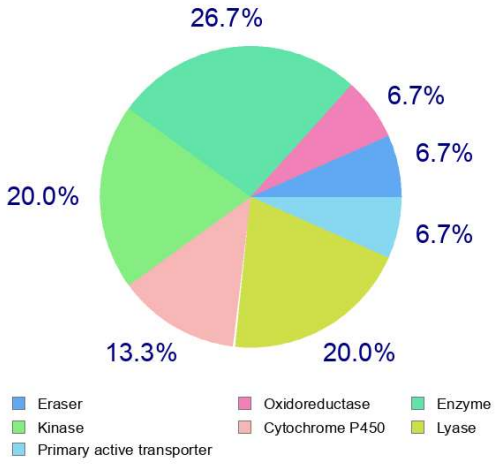


Fig. S7. Top 15 targets predicted for Baicalein.

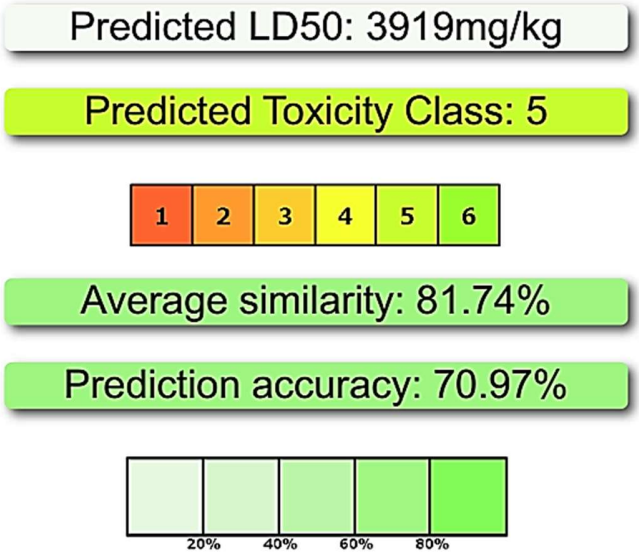


Fig. S8. Oral toxicity model report of Baicalein.

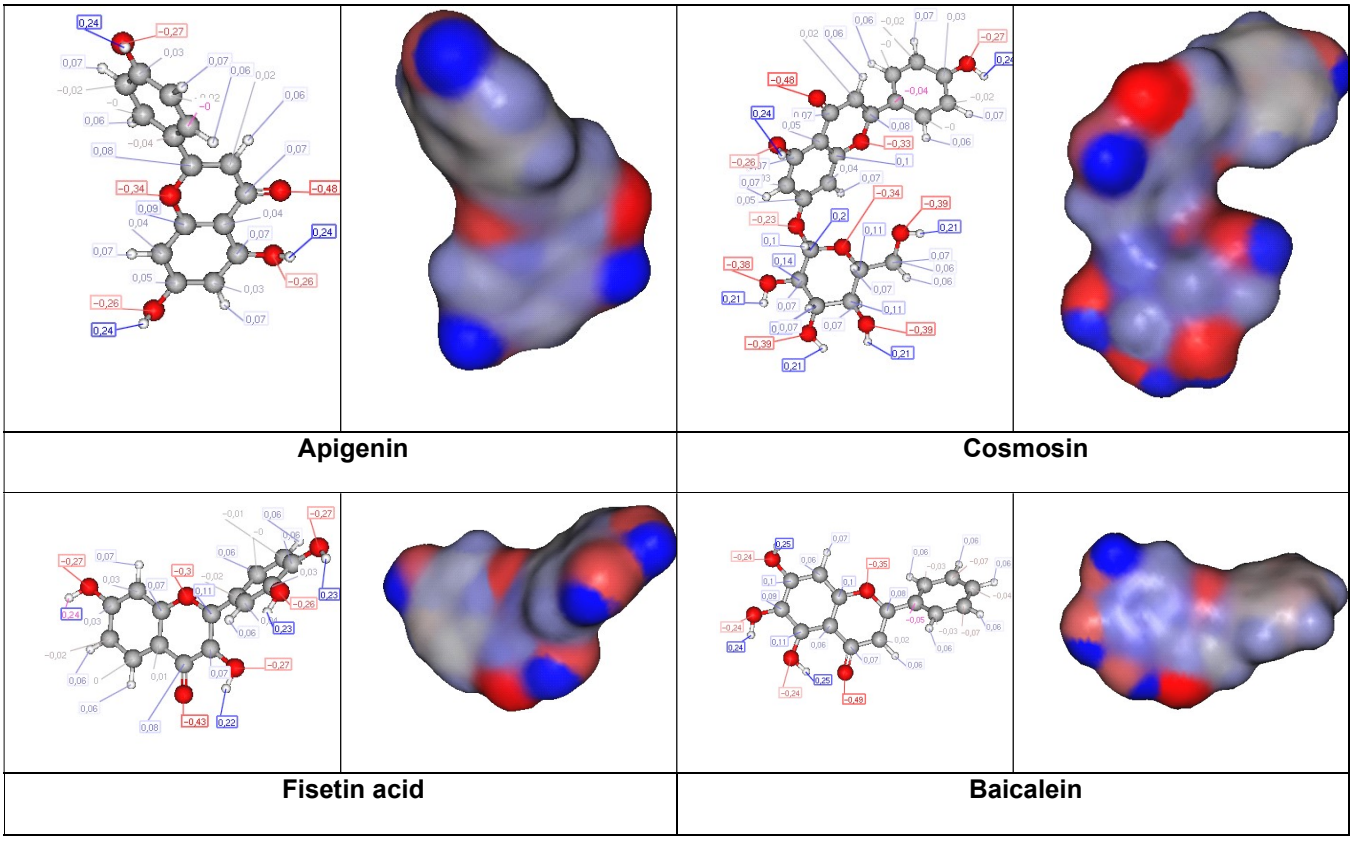


Fig. S9. Atomic charge of the compounds.