

# Computer Analysis Inhibition ACE2 by Flavonoids and Identification of their Potential Antiviral Pharmacophore Site

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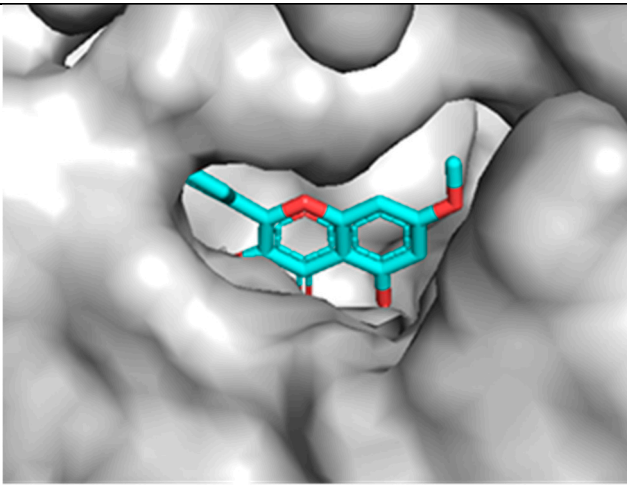
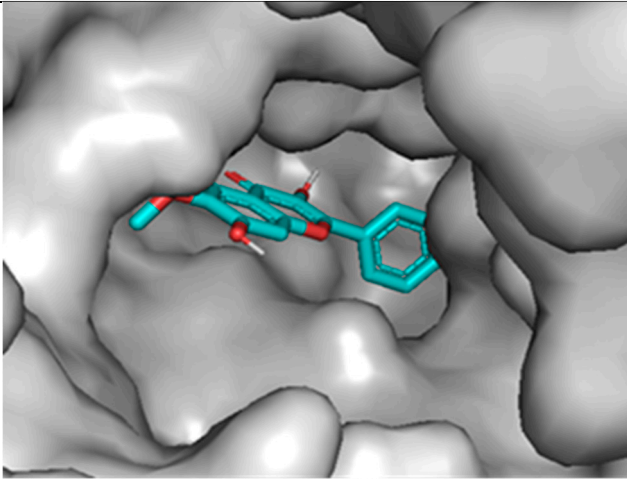
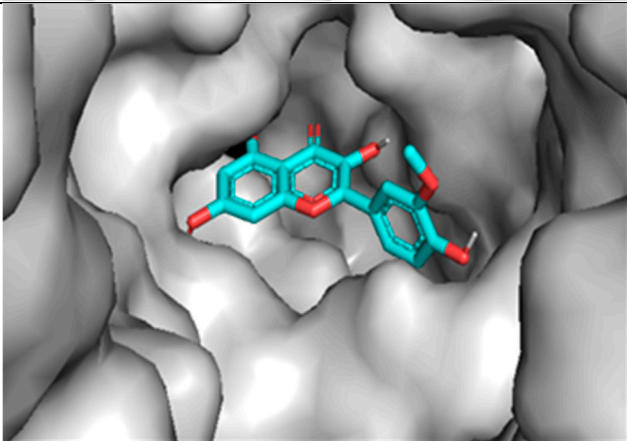
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<sup>5</sup> Department of Pharmaceutical and Pharmacological Sciences, University of Padova, Via Marzolo 5, 35121 Padova, Italy; stefano.dallacqua@unipd.it

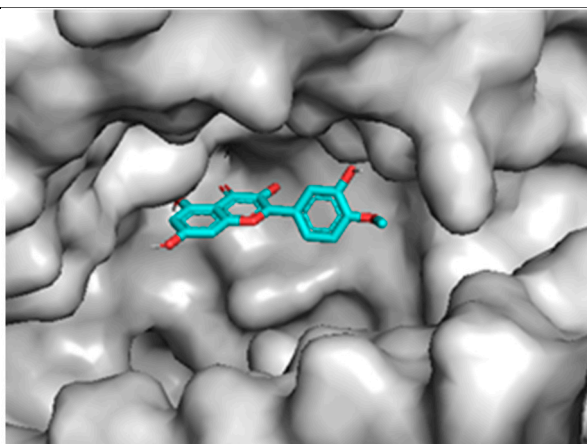
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\* Correspondence: anpav\_63@mail.ru (A.B.); taibi.ben.hadda@gmail.com (T.B.H.); joazaizulfazli@utm.my (J.J.)

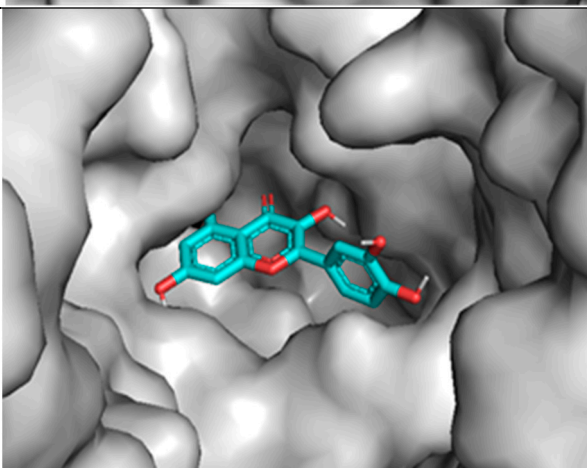
**Table S1a** 2D and 3D visualization of ligand binding to the protein under study.

№	Compound	Visualization ACE2 + compound in PyMol
1	Rhamnetin	
2	Patuletin	
3	Isorhamnetin	

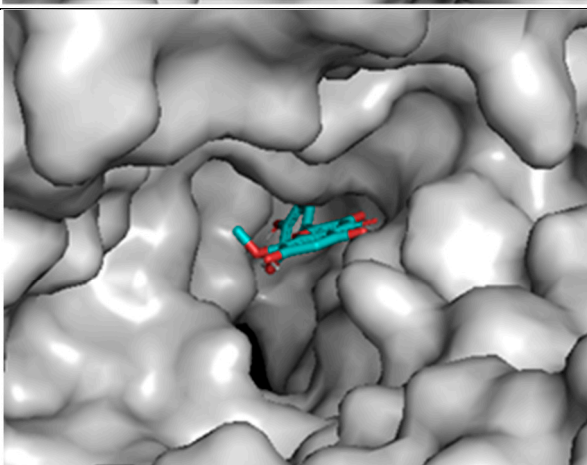
4 Tamarixetin



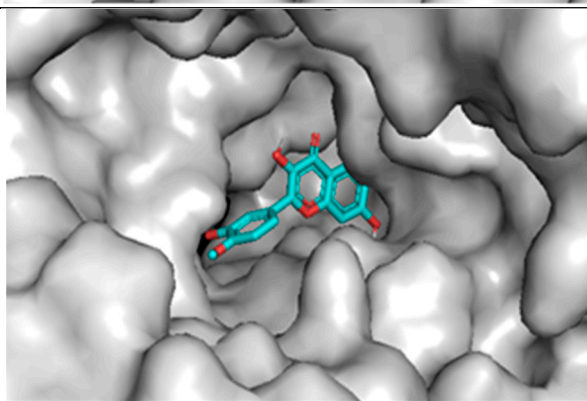
5 Quercetin



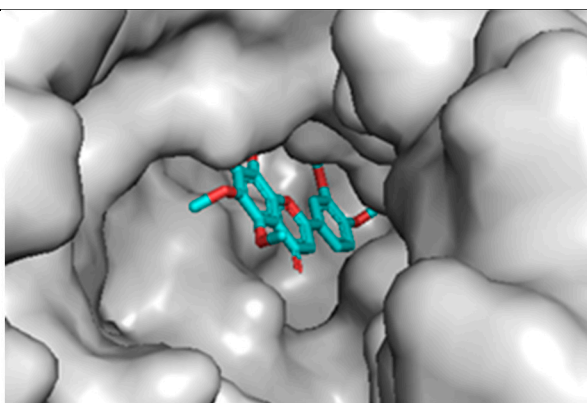
6 Corniculatus  
in



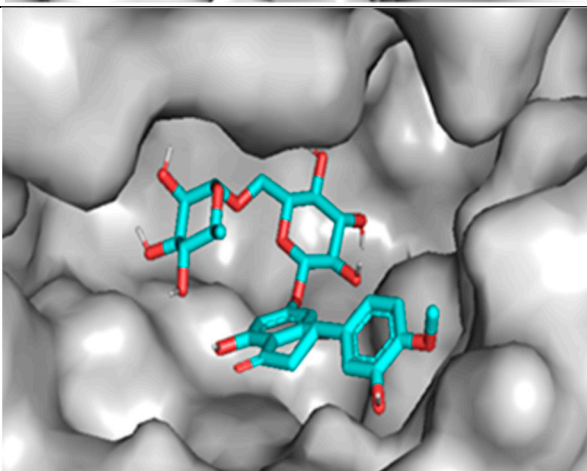
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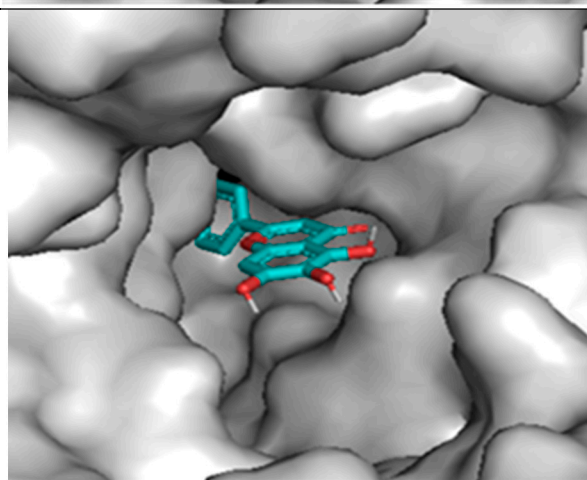
8 Nobiletin



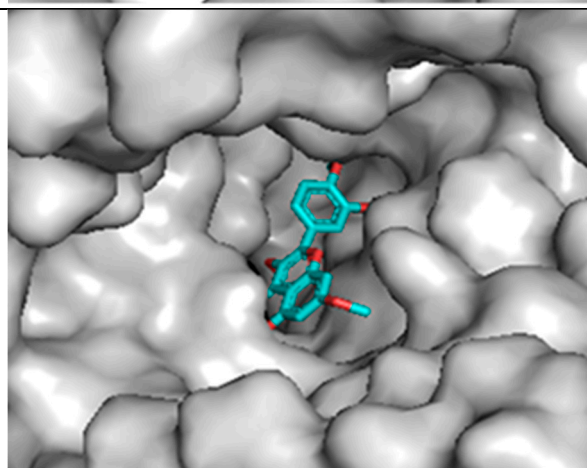
9 Hesperidin



10 Baicalein

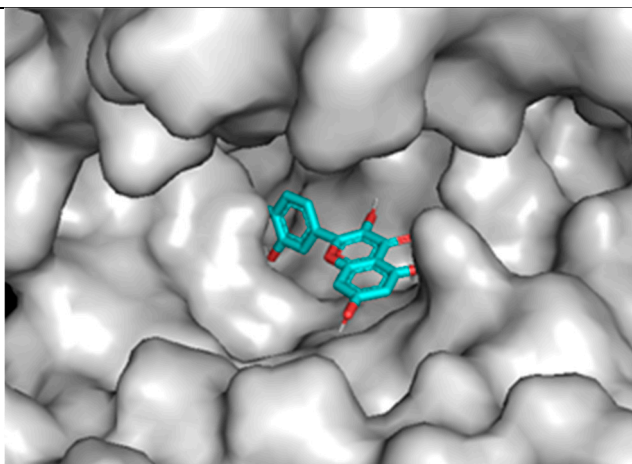


11 Ayanin

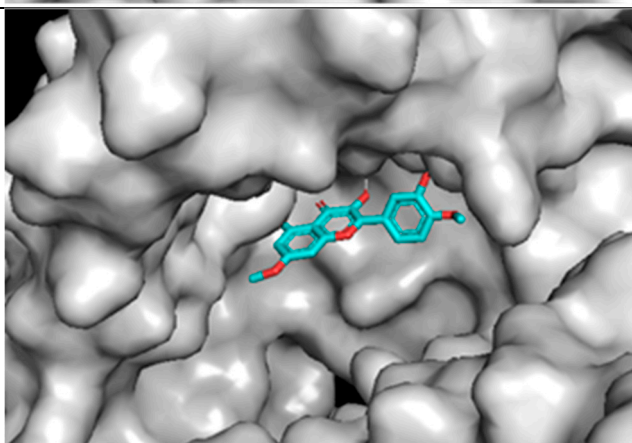




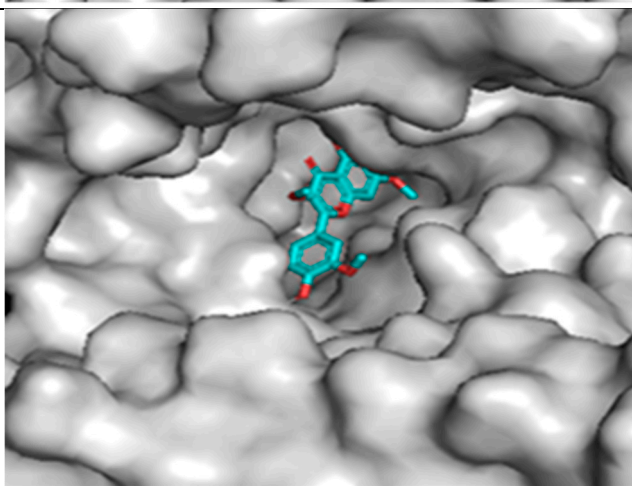
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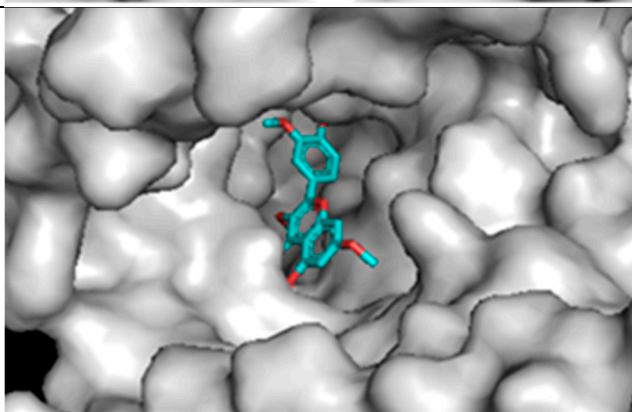
13 Ombuin

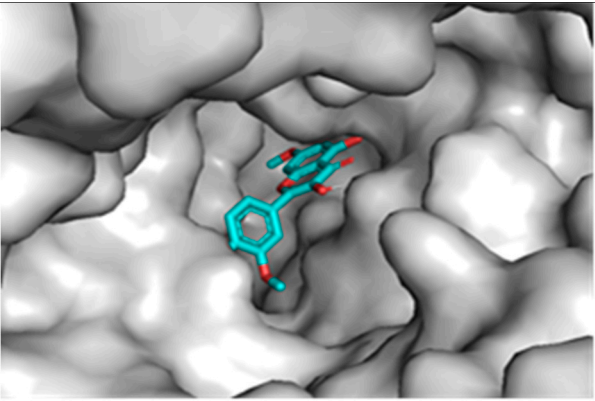
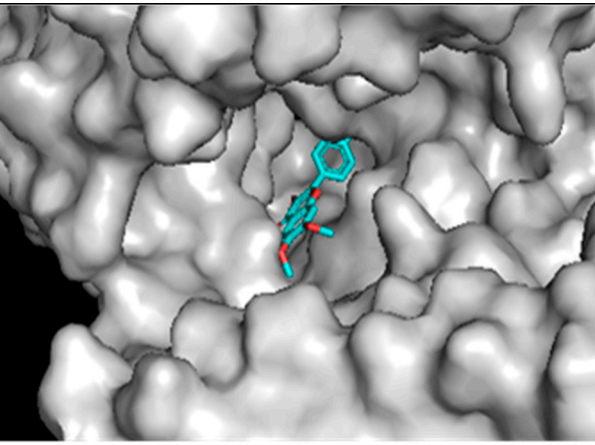


14 Pachypodol

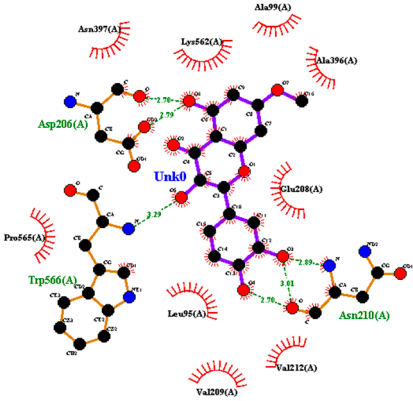


15 Retusin

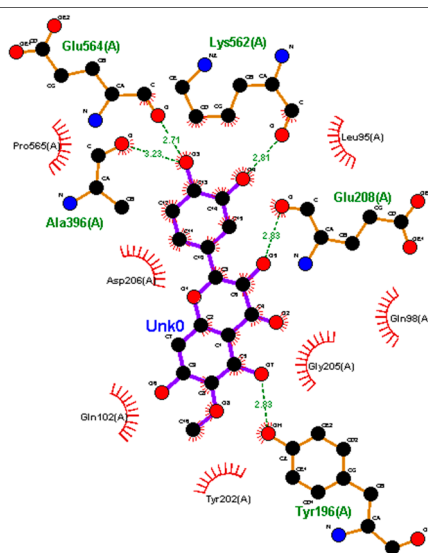


16	Rhamnazin	
17	Eupatolitin	

**Table S1b** 2D and 3D visualization of ligand binding to the protein under study.

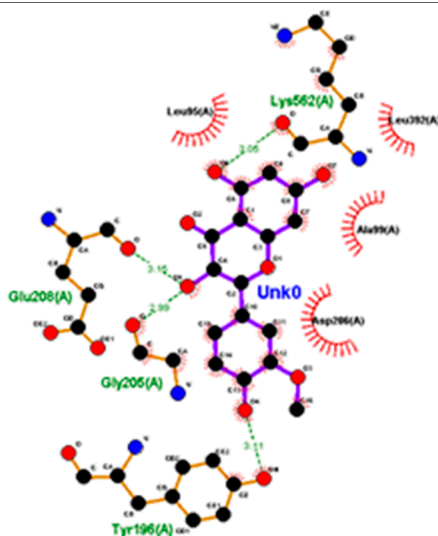
№	Compound	Visualization ACE2 + compound in LigPlot <sup>+</sup>
1	Rhamnetin	

2 Patuletin



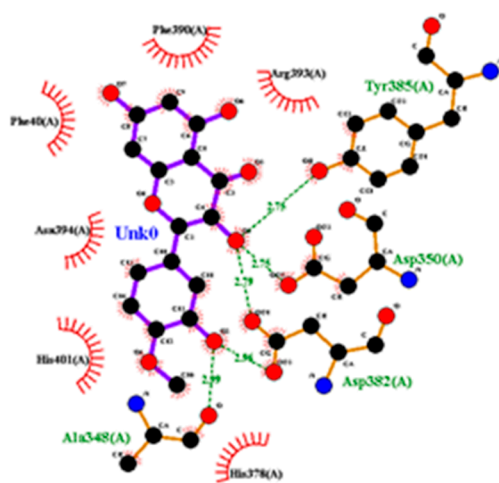
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3 Isorhamnetin



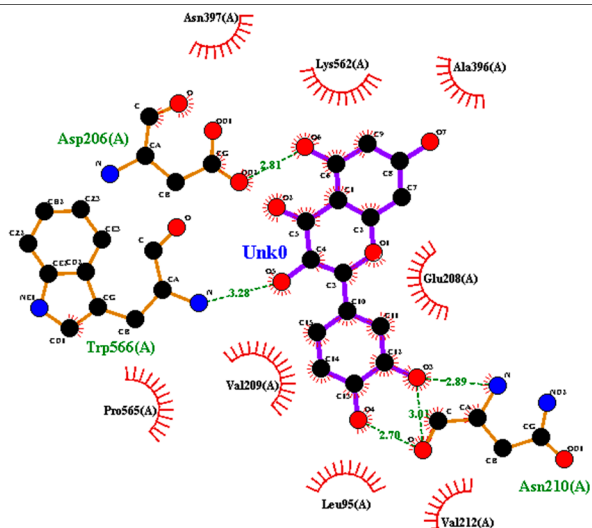
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4 Tamarixetin



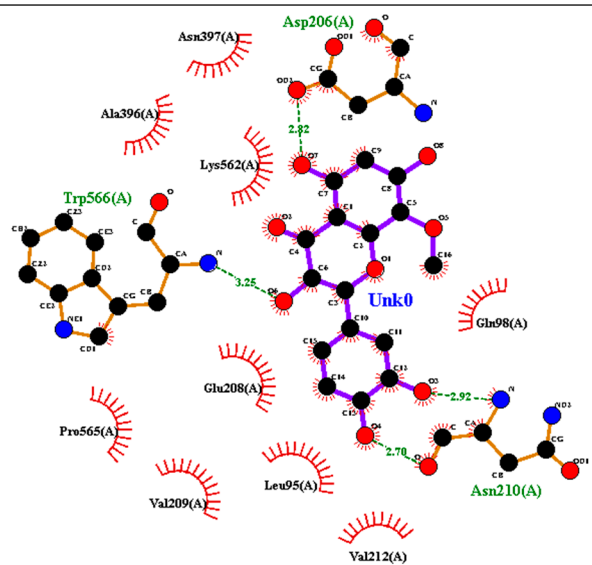
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5 Quercetin



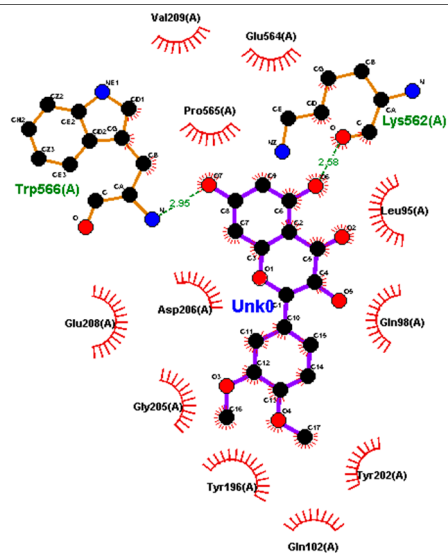
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6 Corniculatus in

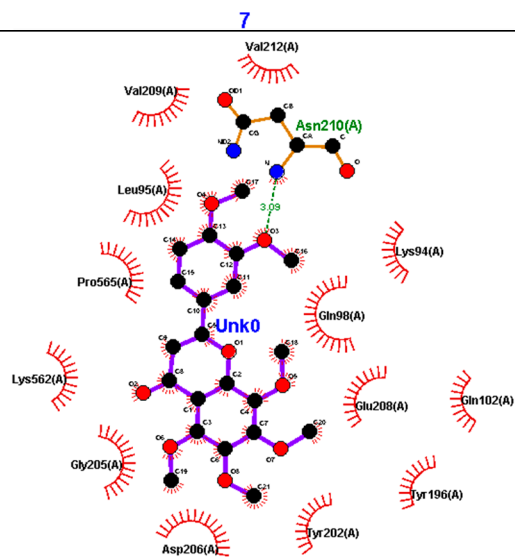


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7 Dillenetin

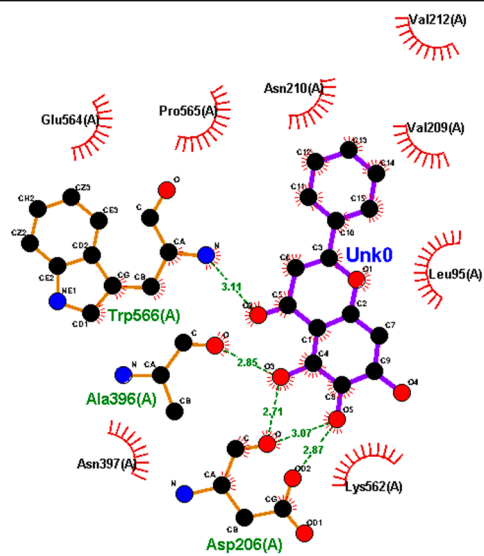


8 Nobiletin



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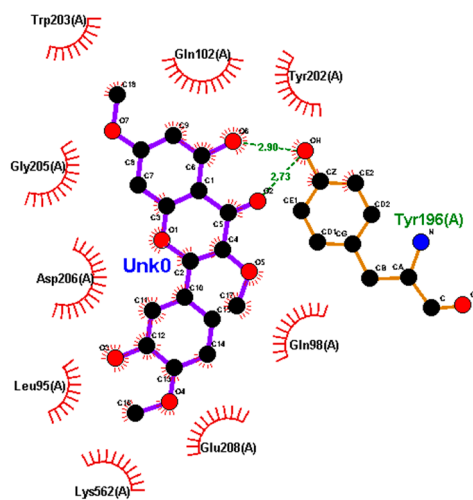
10 Baicalein



10

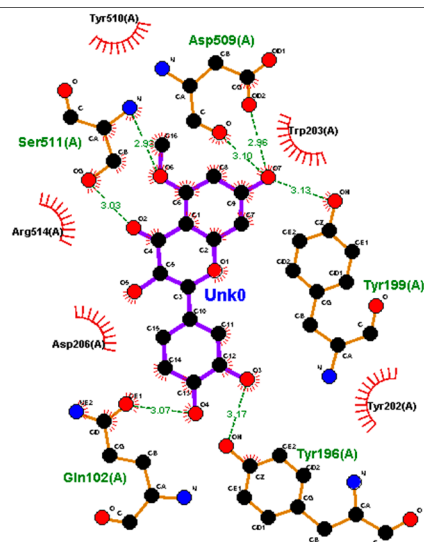


11 Ayanin



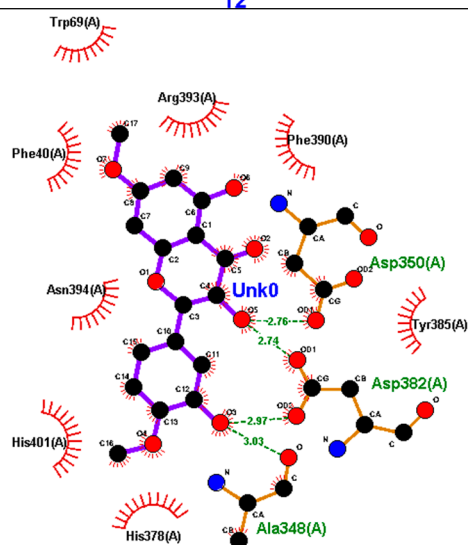
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12 Azaleatin



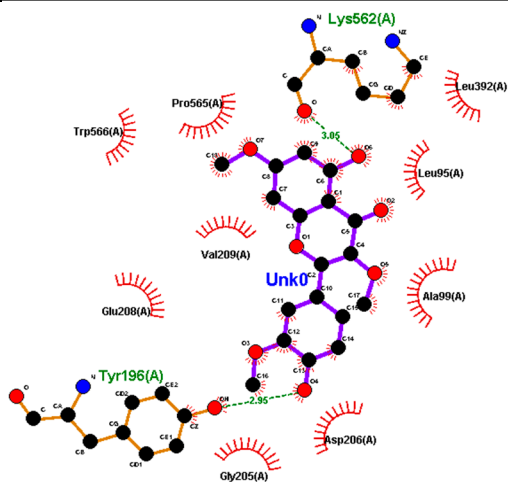
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13 Ombuin



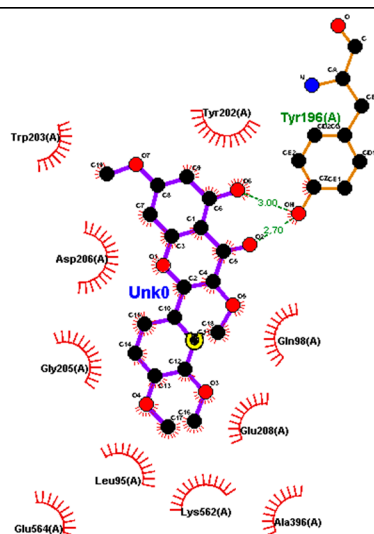
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14 Pachypodol



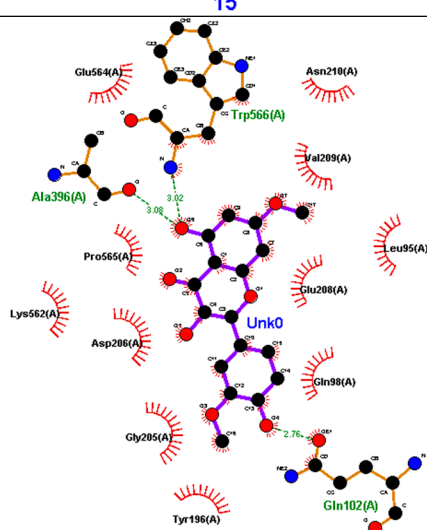
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15 Retusin



15

16 Rhamnazin



16

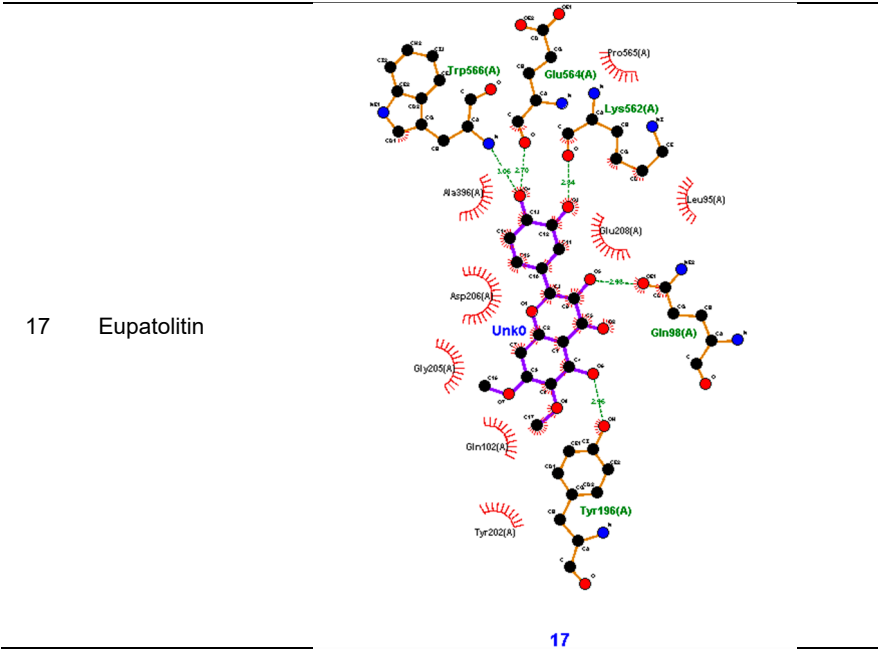
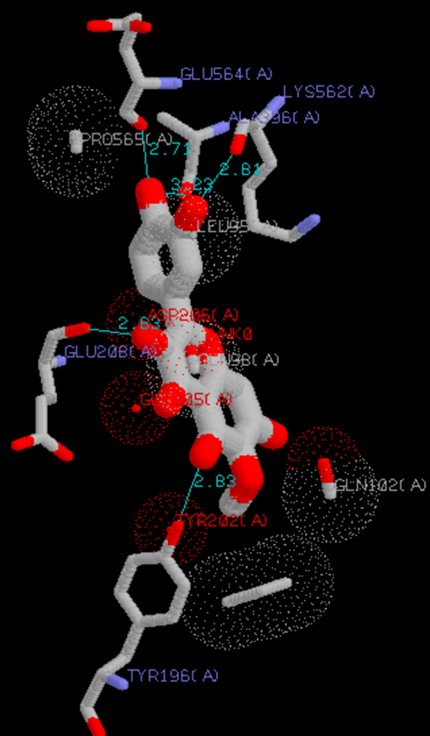


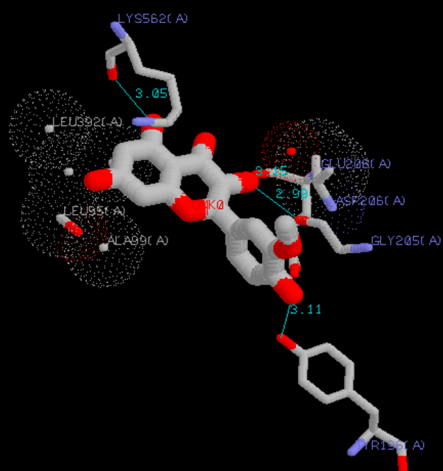
Table S1c 2D and 3D visualization of ligand binding to the protein under study.

No	Compound	Visualization ACE2 + compound in RasMol
1	Rhamnetin	

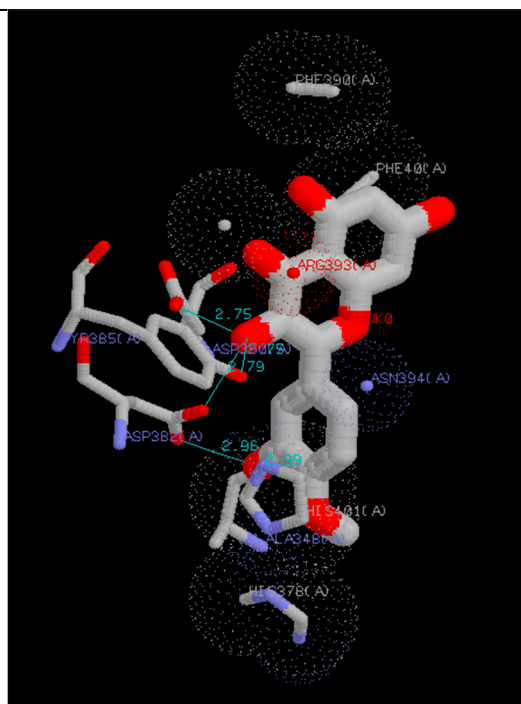
2 Patuletin



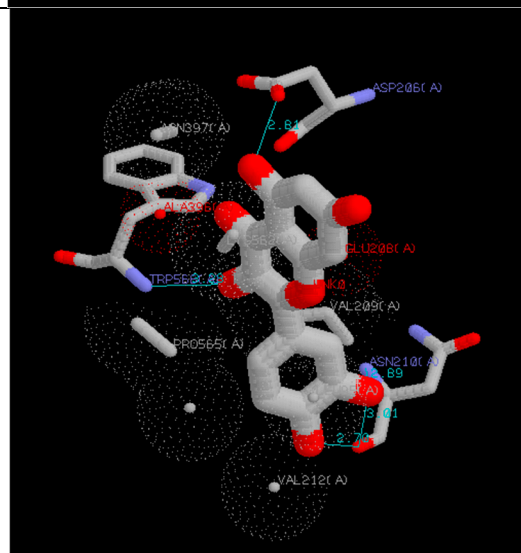
3 Isorhamnetin



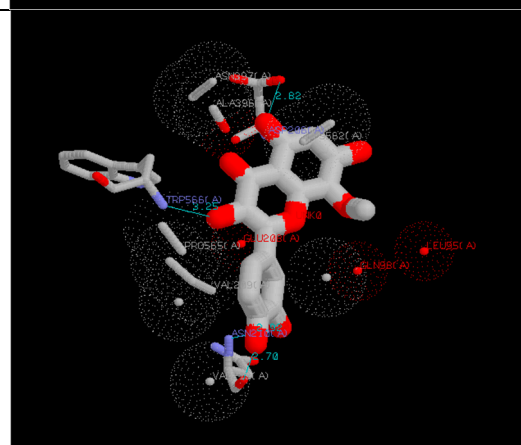
4 Tamarixetin

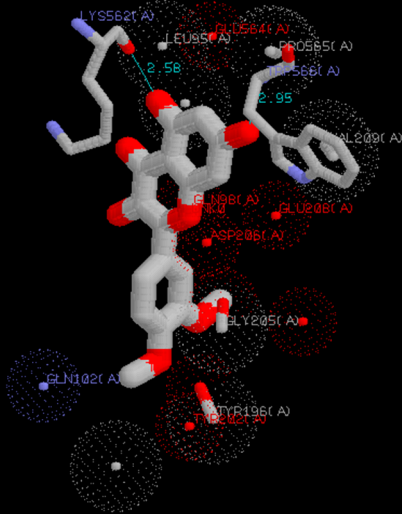


5 Quercetin

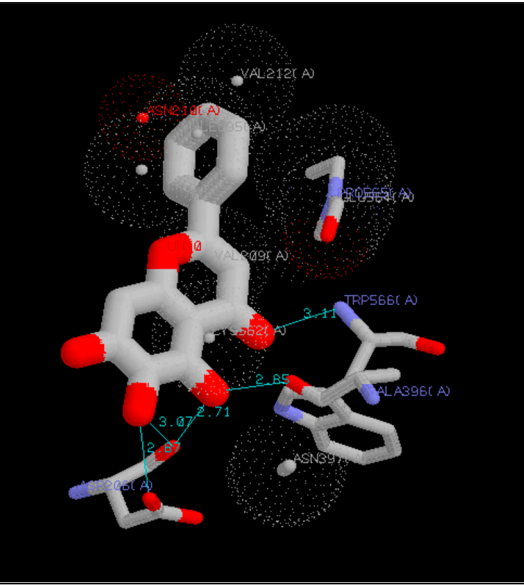
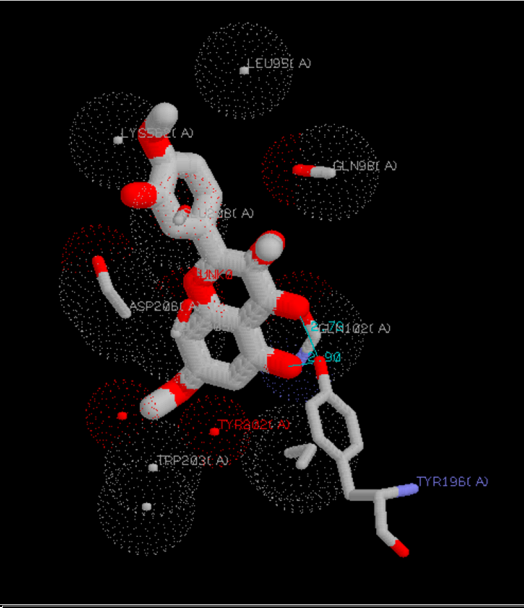
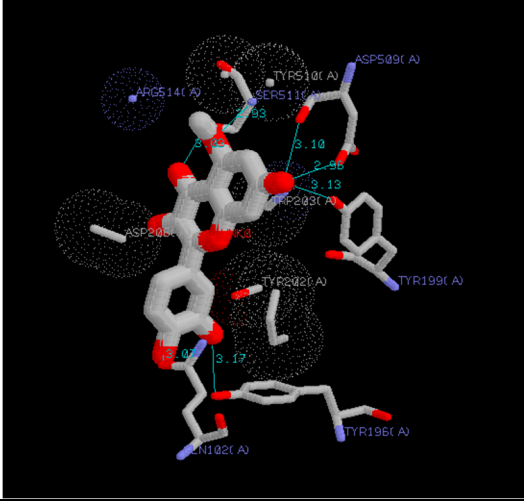


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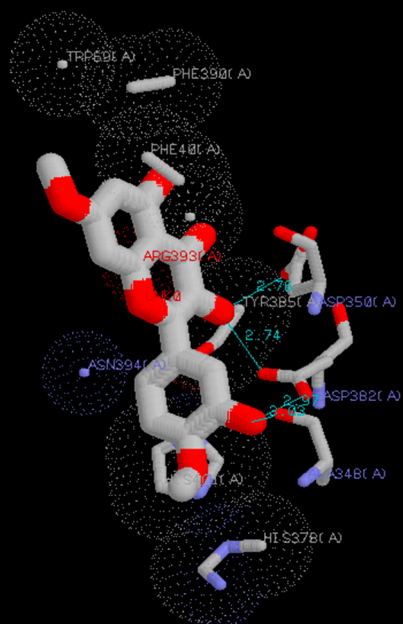


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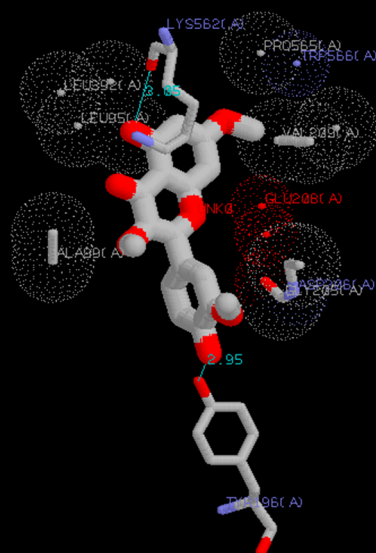


10	Baicalein	
11	Ayanin	
12	Azaleatin	

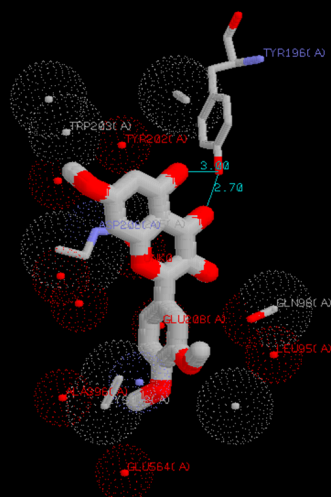
13 Ombuin



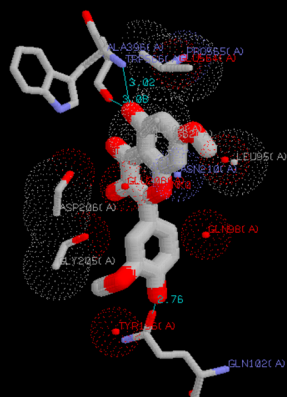
14 Pachypodol



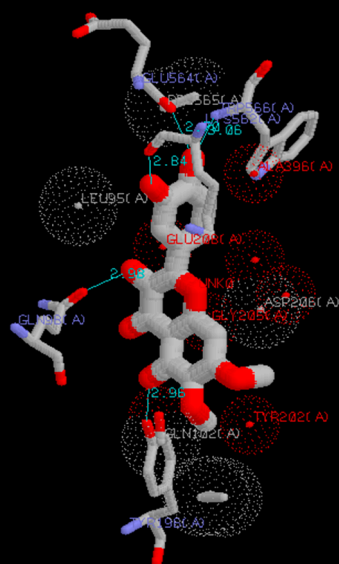
15 Retusin







































































16 Rhamnazin






17 Eupatolitin

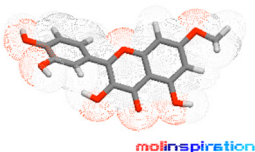


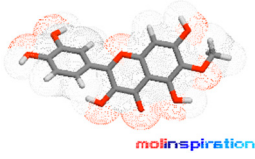
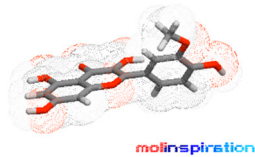
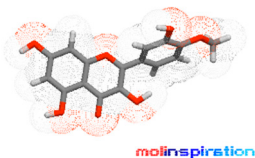

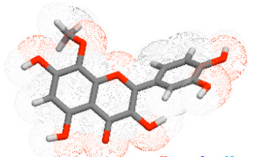
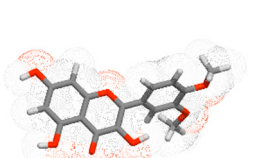
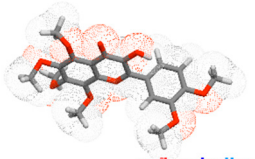
**Table S2** Comparison of Toxicity Risks and Drug Score of compounds **1-17**.

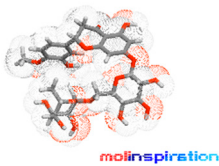
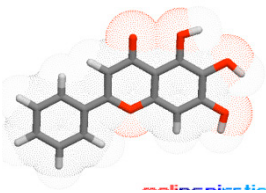

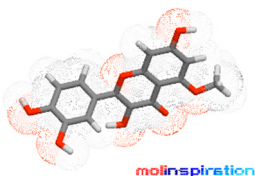
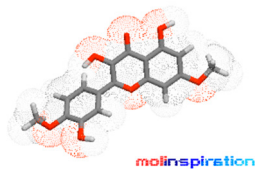
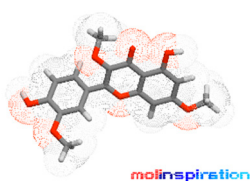
Compound	MW [g/mole]	Toxicity Risks <sup>[a]</sup>				Drug Score Calculations <sup>[b]</sup>			
		MUT	TUM	IRRI	REP	cLogP	cLogS	DL	DS
1	316.26					1.77	-2.8	1.7	0.49
2	332.26					1.42	-2.51	1.5	0.49
3	316.26					1.77	-2.8	1.17	0.47
4	316.26					1.77	-2.8	1.78	0.49
5	302.24					1.49	-2.49	1.6	0.3
6	332.26					1.42	-2.51	1.5	0.49
7	330.29					2.04	-3.12	3.0	0.5
8	418.40					2.45	-3.87	2.77	0.26
9	610.57					-0.81	-2.75	3.46	0.57
10	270.24					2.34	-2.86	0.75	0.75
11	344.32					2.47	-3.25	1.65	0.46
12	316.26					2.04	-3.12	2.0	0.48
13	330.29					2.04	-3.12	1.78	0.48
14	344.32					2.47	-3.25	1.03	0.43
15	358.35					2.75	-3.56	2.88	0.46
16	330.29					2.04	-3.12	1.17	0.45
17	346.29					1.7	-2.82	1.5	0.47

<sup>[a]</sup> Not toxic () , highly toxic: () , slightly toxic: () . REP: Reproductive effective, IRRIT: Irritant, TUM: Tumorigenic, MUT: Mutagenic. <sup>[b]</sup> DS: Drug-Score, DL: Drug Likeness, Sol: Solubility.

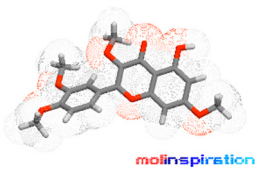

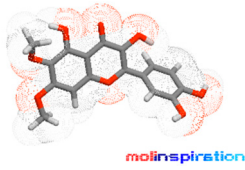
**Table S3** Molinspiration calculations for compounds **1-17**.

Co	3D Molecular Structure	Molecular properties	Drug scores	
1		<u>miLogP</u> 2.22	GPCR ligand	-0.11
		<u>TPSA</u> 120.36	Ion channel modulator	-0.27
		MW 316.26	Kinase inhibitor	0.21
		nOHNH 4	Nuclear receptor ligand	0.27
		nviolations 0	Protease inhibitor	-0.27
		<u>volume</u> 257.61	Enzyme inhibitor	0.20

2		<u>miLogP</u>	1.70		
		<u>TPSA</u>	140.59	GPCR ligand	-0.14
		MW	332.26	Ion channel modulator	-0.34
		nOHNH	5	Kinase inhibitor	0.21
		nviolations	0	Nuclear receptor ligand	0.13
		nrotb	2	Protease inhibitor	-0.35
		<u>volume</u>	265.63	Enzyme inhibitor	0.17
3		<u>miLogP</u>	1.99	GPCR ligand	-0.10
		<u>TPSA</u>	120.36	Ion channel modulator	-0.26
		MW	316.26	Kinase inhibitor	0.25
		nOHNH	4	Nuclear receptor ligand	0.28
		nviolations	0	Protease inhibitor	-0.30
		<u>volume</u>	257.61	Enzyme inhibitor	0.22
4		<u>miLogP</u>	1.99	GPCR ligand	-0.10
		<u>TPSA</u>	120.36	Ion channel modulator	-0.26
		MW	316.26	Kinase inhibitor	0.25
		nOHNH	4	Nuclear receptor ligand	0.28
		nviolations	0	Protease inhibitor	-0.30
		<u>volume</u>	257.61	Enzyme inhibitor	0.22
5		<u>miLogP</u>	1.68	GPCR ligand	-0.06
		<u>TPSA</u>	131.35	Ion channel modulator	-0.19
		MW	302.24	Kinase inhibitor	0.28
		nOHNH	5	Nuclear receptor ligand	0.36
		nviolations	0	Protease inhibitor	-0.25
		<u>volume</u>	240.08	Enzyme inhibitor	0.28
6		<u>miLogP</u>	1.70	GPCR ligand	-0.15
		<u>TPSA</u>	140.59	Ion channel modulator	-0.12
		MW	332.26	Kinase inhibitor	0.17
		nOHNH	5	Nuclear receptor ligand	0.15
		nviolations	0	Protease inhibitor	-0.29
		<u>volume</u>	265.63	Enzyme inhibitor	0.22
7		<u>miLogP</u>	2.30	GPCR ligand	-0.10
		<u>TPSA</u>	109.36	Ion channel modulator	-0.26
		MW	330.29	Kinase inhibitor	0.23
		nOHNH	3	Nuclear receptor ligand	0.27
		nviolations	0	Protease inhibitor	-0.26
		<u>volume</u>	275.14	Enzyme inhibitor	0.19
8		<u>miLogP</u>	3.08	GPCR ligand	-0.15
		<u>TPSA</u>	105.84	Ion channel modulator	-0.10
		MW	418.40	Kinase inhibitor	0.11
		nOHNH	1	Nuclear receptor ligand	0.03
				Protease inhibitor	-0.26

		nviolations 0 volume 361.29	Enzyme inhibitor	0.15
9		miLogP -0.55 TPSA 234.30 MW 610.57 nOHNH 8 nviolations 3 volume 511.79	GPCR ligand Ion channel modulator Kinase inhibitor Nuclear receptor ligand Protease inhibitor Enzyme inhibitor	-0.01 -0.59 -0.36 -0.20 0.00 0.06
10		miLogP 2.68 TPSA 90.89 MW 270.24 nOHNH 3 nviolations 0 volume 224.05	GPCR ligand Ion channel modulator Kinase inhibitor Nuclear receptor ligand Protease inhibitor Enzyme inhibitor	-0.12 -0.18 0.19 0.17 -0.35 0.26
11		miLogP 2.80 TPSA 98.37 MW 344.32 nOHNH 2 nviolations 0 volume 292.67	GPCR ligand Ion channel modulator Kinase inhibitor Nuclear receptor ligand Protease inhibitor Enzyme inhibitor	-0.12 -0.22 0.14 0.14 -0.27 0.16
12		miLogP 1.96 TPSA 120.36 MW 316.26 nOHNH 4 nviolations 0 volume 275.61	GPCR ligand Ion channel modulator Kinase inhibitor Nuclear receptor ligand Protease inhibitor Enzyme inhibitor	-0.07 -0.24 0.24 0.29 -0.28 0.19
13		miLogP 2.53 TPSA 109.36 MW 330.29 nOHNH 3 nviolations 0 volume 275.14	GPCR ligand Ion channel modulator Kinase inhibitor Nuclear receptor ligand Protease inhibitor Enzyme inhibitor	-0.12 -0.28 0.21 0.23 -0.27 0.18
14		miLogP 2.80 TPSA 98.37 MW 344.32 nOHNH 2 nviolations 0 volume 292.67	GPCR ligand Ion channel modulator Kinase inhibitor Nuclear receptor ligand Protease inhibitor Enzyme inhibitor	-0.12 -0.22 0.14 0.14 -0.27 0.16



15		<u>miLogP</u>	3.11	GPCR ligand	-0.13
		<u>TPSA</u>	87.38	Ion channel modulator	-0.22
		MW	358.35	Kinase inhibitor	0.12
		nOHNH	1	Nuclear receptor ligand	0.13
		nviolations	0	Protease inhibitor	-0.25
		<u>volume</u>	310.20	Enzyme inhibitor	0.14
16		<u>miLogP</u>	2.53	GPCR ligand	-0.12
		<u>TPSA</u>	109.36	Ion channel modulator	-0.28
		MW	330.29	Kinase inhibitor	0.21
		nOHNH	3	Nuclear receptor ligand	0.23
		nviolations	0	Protease inhibitor	-0.27
		<u>volume</u>	275.14	Enzyme inhibitor	0.18
17		<u>miLogP</u>	2.01	GPCR ligand	-0.15
		<u>TPSA</u>	129.59	Ion channel modulator	-0.34
		MW	346.29	Kinase inhibitor	0.21
		nOHNH	4	Nuclear receptor ligand	0.09
		nviolations	0	Protease inhibitor	-0.35
		<u>volume</u>	283.16	Enzyme inhibitor	0.15

Molecular weight in g/mol

Topological polar surface area in Å<sup>2</sup>

Volume in Å<sup>3</sup>

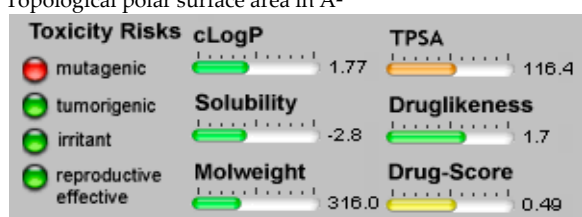
**Table S4** Comparison of Molinspiration data for compounds 1-17.

Compd	Lipinski parameters calculations <sup>[a]</sup>				Drug-likeness <sup>[b]</sup>					
	TPSA	NONH	NV	VOL	GPCRL	ICM	KI	NRL	PI	EI
1	120.36	4	0	257.61	-0.11	-0.27	0.21	0.27	-0.27	0.20
2	140.59	5	0	265.63	-0.14	-0.34	0.21	0.13	-0.35	0.17
3	120.36	4	0	257.61	-0.10	-0.26	0.25	0.28	-0.30	0.22
4	120.36	4	0	257.61	-0.10	-0.26	0.25	0.28	-0.30	0.22
5	131.35	5	0	240.08	-0.06	-0.19	0.28	0.36	-0.25	0.28
6	140.59	5	0	265.63	-0.15	-0.12	0.17	0.15	-0.29	0.22
7	109.36	3	0	275.14	0.10	-0.26	0.23	0.27	-0.26	0.19
8	105.84	1	0	361.29	-0.15	-0.10	0.11	0.03	-0.26	0.15
9	234.30	8	3	511.79	-0.01	-0.59	0.36	-0.20	0.00	0.06
10	90.89	3	0	224.05	-0.12	-0.18	0.19	0.17	-0.35	0.26

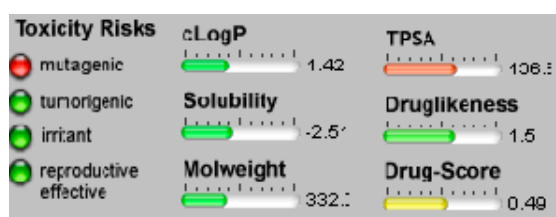
11	98.37	2	0	292.67	-0.12	-0.22	0.14	0.14	-0.27	0.16
12	120.36	4	0	275.61	-0.07	-0.24	0.24	0.29	-0.28	0.19
13	109.36	3	0	275.14	-0.12	-0.28	0.21	0.23	-0.27	0.18
14	98.37	2	0	292.67	-0.12	-0.22	0.14	0.14	-0.27	0.16
15	87.38	1	0	310.20	-0.13	-0.22	0.12	0.13	-0.25	0.14
16	109.36	3	0	275.14	-0.12	-0.28	0.21	0.23	-0.27	0.18
17	129.59	4	0	283.16	-0.15	-0.34	0.21	0.09	-0.35	0.15

Molecular weight in g/mol

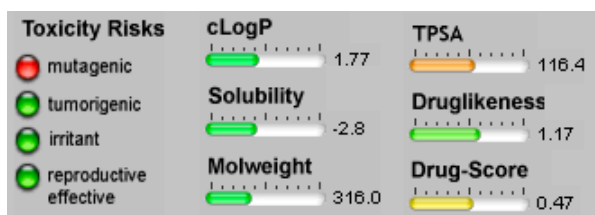
Topological polar surface area in Å<sup>2</sup>



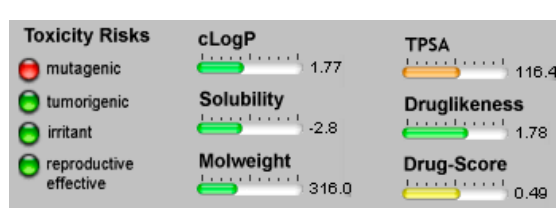
Compound 1



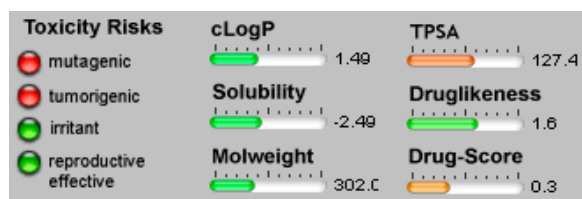
Compound 2



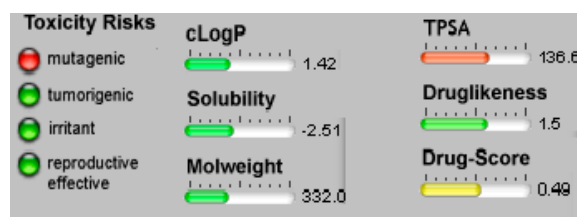
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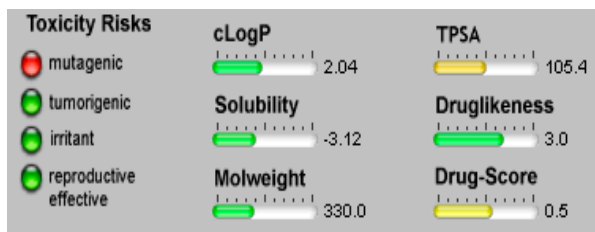
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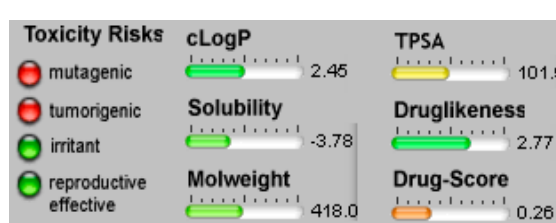
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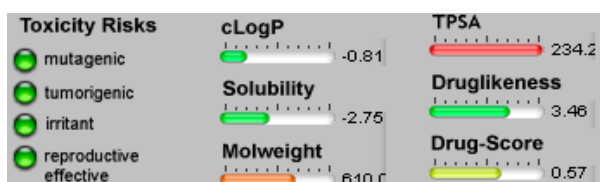
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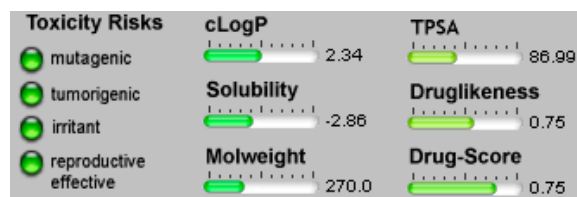
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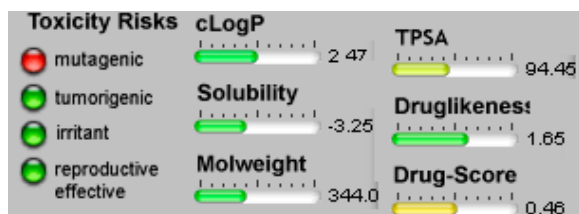
Compound 8



Compound 9



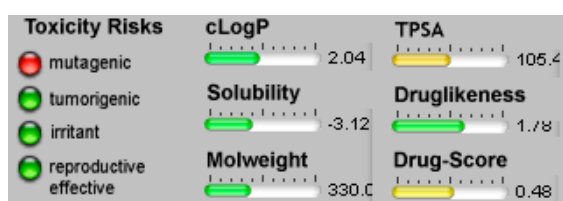
Compound 10



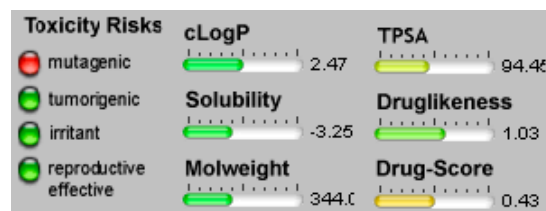
Compound 11



Compound 12



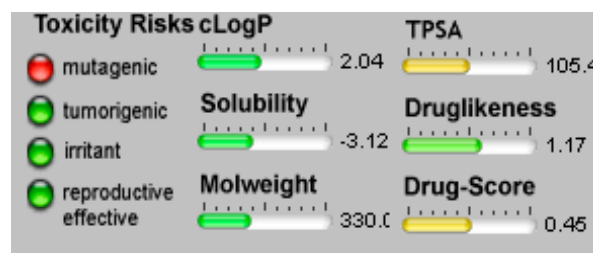
Compound 13



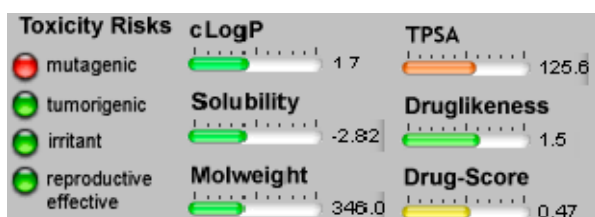
Compound 14



Compound 15



Compound 16



Compound 17

Not toxic ( ), highly toxic: ( ),

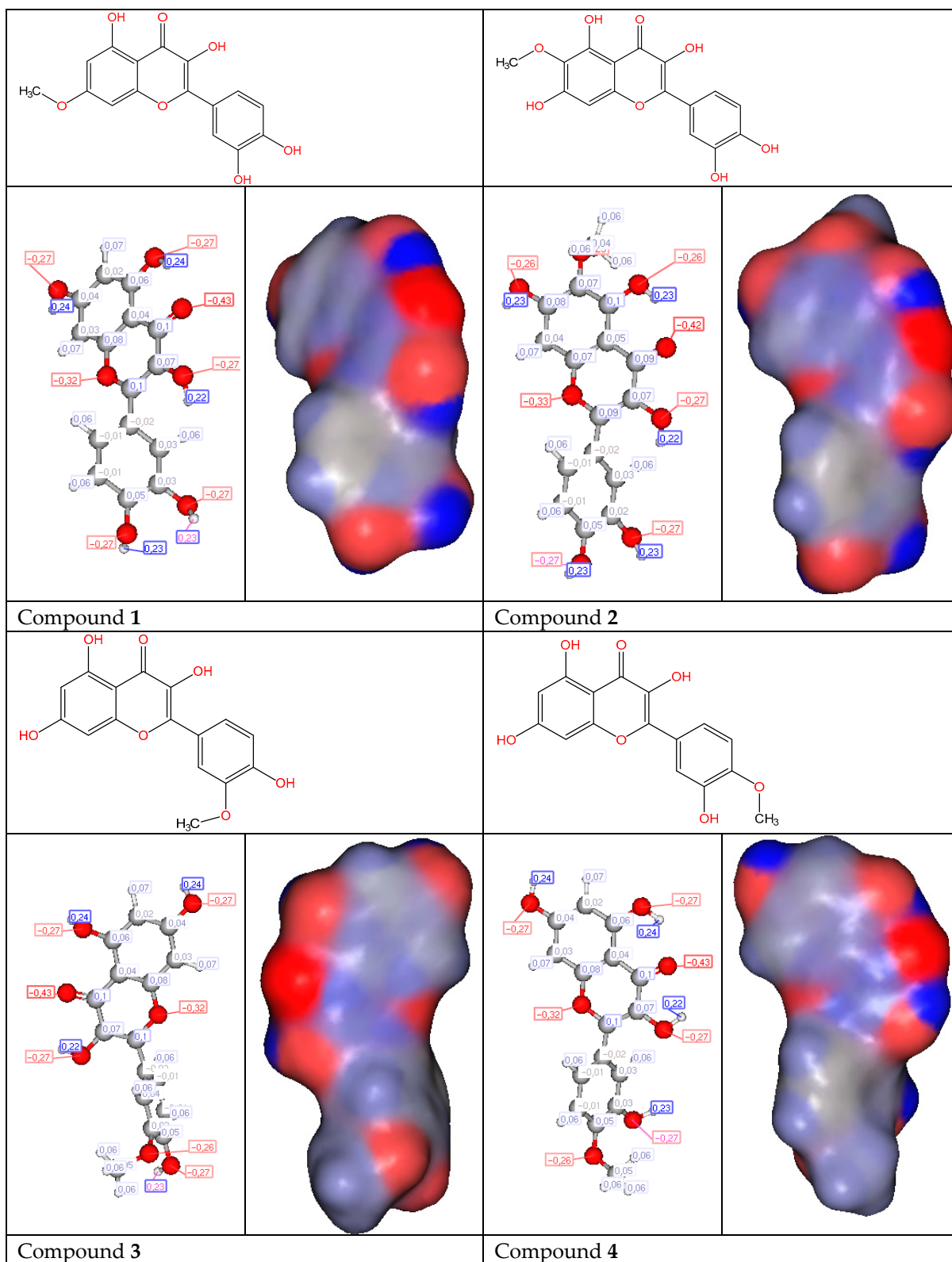
slightly toxic: ( ). REP: Reproductive effective, IRRIT: Irritant, TUM: Tumorigenic, MUT: Mutagenic.

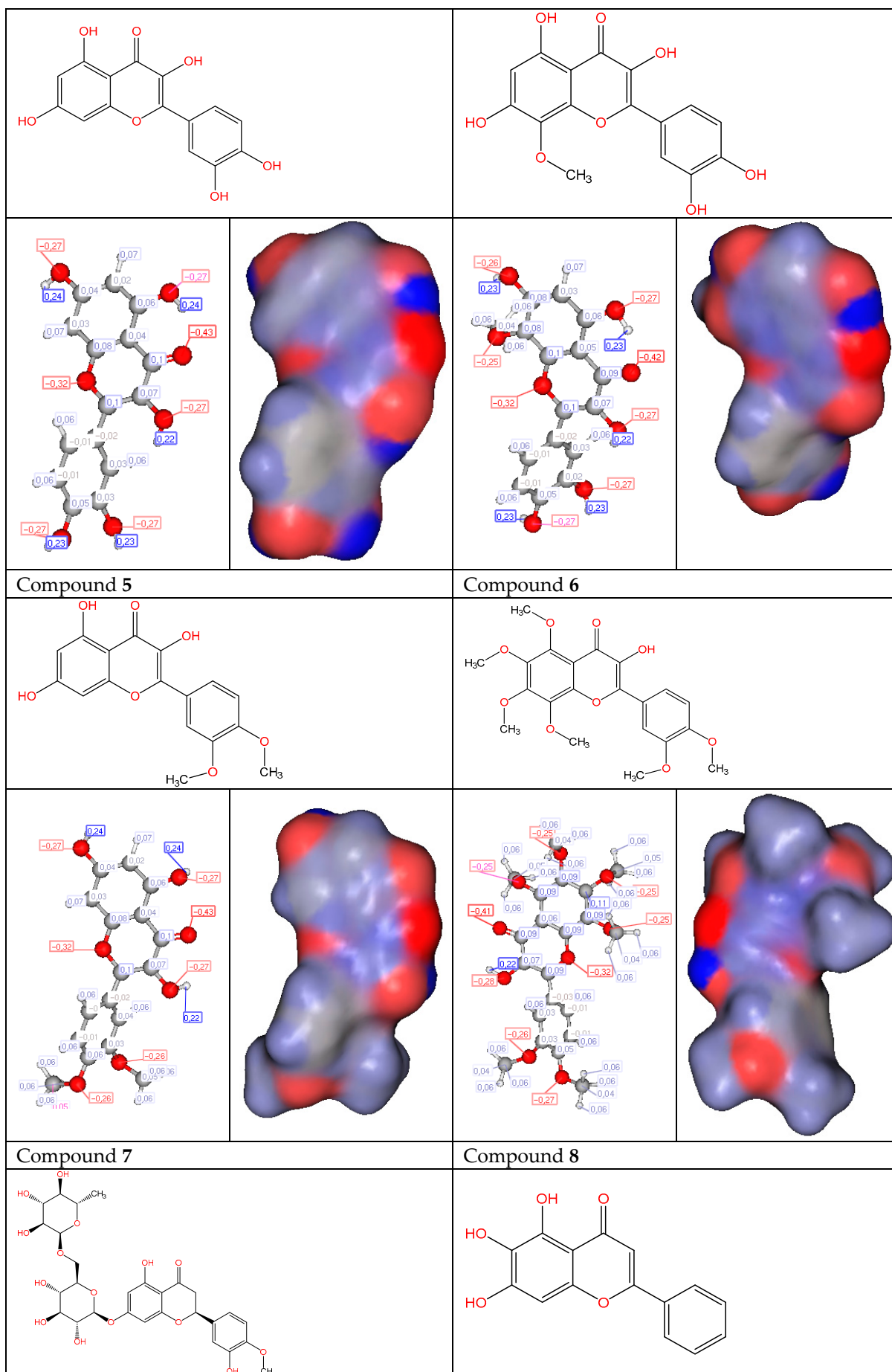
**Drug-Scores:**

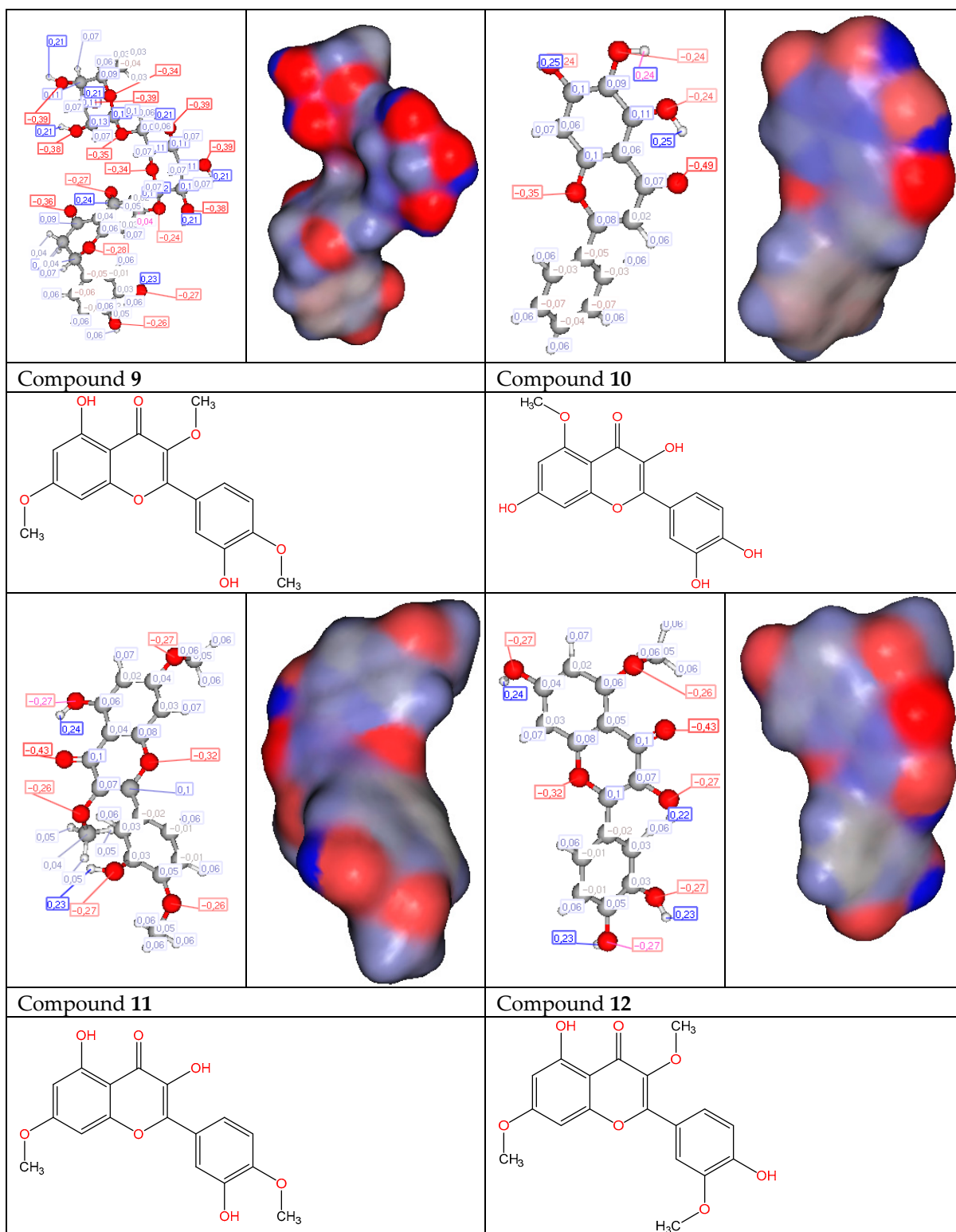
DS: Drug-Score, DL: Drug Likeness, Sol: Solubility.

**Toxicity Risks**

Figure S1. Osiris calculations of likeness and drug-score of compounds (1-17).

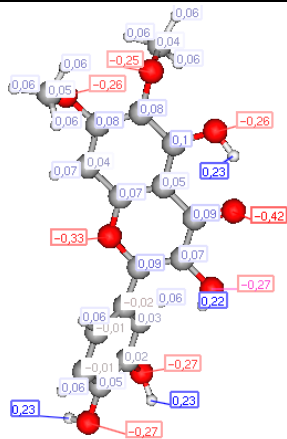
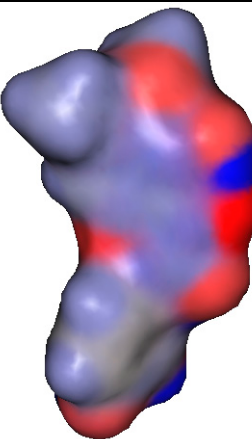










		<p> <math>O \delta^-</math>  <math>O' \delta^-</math> : Antiviral Pharmacophore Site  <math>d(O \cdots O') = 2.8-3.2 \text{ \AA}</math>  <math>d(O' \cdots O'') = 2.8-3.2 \text{ \AA}</math>  <math>O'' \delta^-</math> </p>
Compound 17	Topology of antiviral pharmacophore site of 1-17	

**Figure S2.** Atomic charge calculations for compounds 1-17.