Supplementary file 1

Computational studies and structural insights for discovery of potential natural aromatase modulators for hormone-dependent breast cancer

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Table S1: List of the natural products virtually screened for aromatase binding affinity

Table S2. Natural flavonoids with aromatase inhibitory activity selected for QSAR studies and their actual Vs Predicted values

Table S1. List of the natural products virtually screened for aromatase binding affinity

Sr.no.	Compound
1.	1-acetoxy-3-methoxy-9,10-anthraquinone
2.	Ailanthinone
3.	Alizarin
4.	Aloe-emodin

5.	Anomanolide A
6.	Anomanolide B
7.	Anomanolide C
8.	Antcamphins A
9.	Antcamphins B
10.	Antcamphins C
11.	Antcamphins D
12.	Antcamphins E
13.	Antcamphins F
14.	Antcamphins G
15.	Antcamphins H
16.	Antcamphins I
17.	Antcamphins J
18.	Antcamphins K
19.	Antcamphins L
20.	Anthraquinone
21.	Antrocin
22.	Apigenin
23.	Arctigenin
24.	Ashwagandhanolide
25.	Astraodoric acid D
26.	Auristatin PE
27.	Berberine
28.	Brazilein
29.	Broussoflavanol B
30.	2-carbomethoxy-1,4- naphthoquinone
31.	2′-(R)-O-acetyl-glaucarubinone
32.	20(S)-dihydropanaxitriol
33.	20(s)-dihydroprotopanaxidiol
34.	20(S)-protopanaxadiol
35.	20-(s)-protopanaxatriol
36.	20(s)-protopanaxitriol
37.	20-hydroxytubocapsanolide A
38.	20-hydroxytubocapsanolide A
39.	20-α-dimethylamino-16β-hydroxy-3β-(3′α-isopropyl) lactam-5-pregn-4-one.
40.	23-hydroxytubocapsanolide A
41.	3, 3' bisbenzopyran
42.	3,5,7,3’,4’- pentahydroxyflavonol-3-O-*β*-D-glucopyranoside
43.	3,5,6,7,8,3′,4′-heptamethoxyflavone
44.	4-beta-hydroxywithanolide E
45.	4-methylene-5-oxovatodiolide
46.	5 beta, 6 beta- epoxy secocholestan-9-one
47.	6-gingerol
48.	6-shagol
49.	Isosclerone
50.	Nuapapuin b methyl ester

51.	7β-[(3'-ethylcrotonoyl)oxy]-1α-[(2'-methylbutanoyl)oxy]-3,14-dehydro-E-notonipetranone
52.	7-hydroxyflavone
53.	7,8-Dihydroxyflavone
54.	8-prenylnaringenin
55.	Calyflorenon B
56.	Cannabichromene
57.	Chrysin
58.	Chrysaphanol
59.	Cannabigerol
60.	Cannabinol
61.	Capsaicin
62.	Carbenoxolone
63.	Casticin
64.	Celastrol
65.	Centaureidin
66.	Chrysophanol
67.	Cimicifugic acid G
68.	Cis-(6ab,12ab)-hydroxyrotenone
69.	Cis-hydroxyrotenone
70.	Crassocolides A
71.	Crassocolides B
72.	Crassocolides D
73.	Crassocolides E
74.	Cryptotanshinlactone
75.	Curcumin
76.	Cyanidin
77.	Cynidin-3-glucoside
78.	Daidzein
79.	Delphidin-3-glucoside
80.	Delphinidin
81.	Delta-tetrahydrocannabinol
82.	Denbinobin
83.	D-limonene
84.	D-pinitol
85.	Emodin
86.	Ellagic acid
87.	Epicatechin
88.	Epigallocatechin 3-gallate
89.	Epipachysamine B
90.	Epipachysamine E
91.	Epoxymollugin
92.	E-salignone
93.	Eupatorin
94.	Excelsin
95.	Excisanin A

96.	Fangchinoline
97.	Fenretinide
98.	Filiasparoside A
99.	Filiasparoside B
100.	Filiasparoside C
101.	Filiasparoside D
102.	Flavopiridol
103.	Flemingin A
104.	Flemingin B
105.	Flemingin C
106.	Fokihodgins I
107.	Formononetin
108.	Frondoside A
109.	Furanodiene
110.	Furomollugin
111.	Gallic acid
112.	Genipin
113.	Genistein
114.	Glaucarubinone
115.	Glycyrrhetinic acid
116.	Hantupeptin A
117.	Honokiol
118.	Hypophyllanthin
119.	Ilelic acid A
120.	Ilelic acid B
121.	Indole-3-carbinol
122.	Isoliquiritigenin
123.	Isosinestin
124.	Isoxanthohumol
125.	Jaborosalactol
126.	Jaborosalactol 20
127.	Jaborosalactol 24
128.	Jaborosalactone
129.	Jaborosalactone 38
130.	Jaborosalactone 46
131.	Jaborosalactone P
132.	Kaempferol
133.	Kurarinone
134.	Lineariifolianoids E
135.	Lupeol
136.	Lycopene
137.	Malvidin
138.	Mollugin
139.	Napthoquinone
140.	Naringin
141.	Nemorosone

142.	Neo-tanshinlactone
143.	Neocalycopteron
144.	Nobiletin
145.	Odyendene
146.	Oleuropein
147.	Oridonin
148.	Ovatodiolide
149.	Pachystermine A
150.	Pachystermine B
151.	Pelargonidin-3-O-glucoside
152.	Petunidin
153.	Phyllanthin
154.	Physcion
155.	Piperine
156.	Prolifenone acid
157.	Prolifenone B
158.	Prolificin A
159.	Protoapigenone
160.	Quercetin
161.	Quercetin 3,5,7,3′,4′- pentamethyl ether
162.	Quercetin 3,7,3′,4′- tetramethyl ether
163.	Rhein
164.	Rhein glucoside
165.	Salpichrolide A
166.	Salpichrolide C
167.	Salpichrolide D
168.	Salpichrolide G
169.	Sasanquasaponin I
170.	Sauchinone
171.	Scutellarintetramethyl ether
172.	Sceptrin
173.	Secocholestan-9-one
174.	Secocholestan-9-one
175.	Secocholestan-9-one (3)
176.	Secocholestan-9-one (4)
177.	Silibinin
178.	Sinensetin
179.	Sodwanones V
180.	Songaricalarins A
181.	Songaricalarins C
182.	Songaricalarins D
183.	Songaricalarins E
184.	Soranjidiol
185.	Spicatolide D
186.	Spicatolide F
187.	Spicatolide G

188.	Spiropachysine-20-one
189.	Tangeretin
190.	Tanshinlactone
191.	Tanshinlactone I
192.	Tanshinlactone IIA
193.	Tanshinone I
194.	Tanshinone IIA
195.	Tauranin
196.	Taxifolin
197.	Terminaline
198.	Terminamine B
199.	Terminamine C
200.	Terminamine D
201.	Terminamine E
202.	Terminamine F
203.	Terminamine G
204.	THC- acid
205.	Thymoquinone
206.	Tubocapsanolide A
207.	Tubocapsanolide D
208.	Tubocapsanolide F
209.	Tubocapsenolide A
210.	Tubocapsenolide F
211.	Tubonolide A
212.	Ursolic acid
213.	Vinblastine
214.	Vincristine
215.	Withanolide D
216.	Withanolide E
217.	Xanthohumol
218.	Z-salignone
219.	Acacetin
220.	Biochanin A
221.	Chrysin
222.	Fisetin
223.	Flavanone
224.	Flavone
225.	Hesperetin
226.	Hesperidine
227.	Isoflavanone
228.	isolicoflavonol
229.	pinocembrin
230.	Prunetin
231.	Robinetine
232.	S4-Flavanol
233.	Silymarin

234.	2-Hydroxyisoflavanone
235.	3',4'-Dihydroxyflavanone
236.	3',4'-Dihydroxyflavone
237.	3,4,5, 7-Tetrahydroxyflavone
238.	3-Hydroxyflavone
239.	4',5-Dihydroxyflavone
240.	4'-Hydroxyflavanone
241.	4'-Hydroxyisoflavanone
242.	4'-hydroxy flavone
243.	5 hydroxyflavone
244.	6-Hydroxyflavone
245.	7,4'-Dihydroxyflavone
246.	7-Hydroxyflavone

Table S2. Natural flavonoids with aromatase inhibitory activity seleceted for QSAR studies and their actual Vs Predicted values

Compounds	**Pub Chem. ID**	**Actual activity**	**Predicted activity**	
			2d QSAR	**3d QSAR**
2-Hydroxyisoflavanone	13257279	3.7696	2.4926	3.7651
3',4'-Dihydroxyflavanone	462700	3.7959	4.1484	3.7744
3',4'-Dihydroxyflavone	145726	4.0458	4.1269	4.5547
3,4,5, 7-Tetrahydroxyflavone*	5280863	5.4815	-	-
3-Hydroxyflavone	11349	3.8539	3.9737	4.1812
4',5-Dihydroxyflavone	165521	3.9208	3.7340	3.9436
4'-Hydroxyflavanone	165506	5.0000	3.7741	5.0019
4'-Hydroxyisoflavanone	69198620	3.7959	3.7022	3.8444
4'-hydroxy flavone	-	3.7447	3.9462	3.7062
5 hydroxyflavone	68112	4.0000	3.7601	4.0198
6-Hydroxyflavone	72279	4.0969	4.0697	4.2201
7,4'-Dihydroxyflavone	5282073	4.6990	4.4456	4.9274
7-Hydroxyflavone*	5281894	6.3010	-	-
Acacetin	5280442	4.7235	4.8146	4.6088

Apigenin*	5280443	6.0458	-	-
Biochanin A	5280373	4.9914	4.8297	5.0444
chrysin*	5281607	5.9586	-	-
Fisetin	5281614	5.0706	4.9944	5.0905
Flavanone	10251	5.0605	4.9820	5.0534
Flavone	10680	5.0000	4.9319	4.5398
Hesperetin*	72281	6.0000	-	-
Hesperidine	10621	4.3883	3.4930	4.2469
Isoflavanone	160767	3.9208	4.4047	3.8813
isolicoflavonol*	5318585	7.000	-	-
kaempferol	5280863	4.2147	4.5098	4.1974
Luteolin	5280445	4.6021	4.5668	4.5764
Myricetin*	5281672	5.2518	5.2224	-
Naringin*	442428	5.7447	-	-
pinocembrin	68071	4.7282	4.5924	4.7386
Prunetin	5281804	5.1079	5.0614	4.9629
Robinetine	5281692	4.3401	4.386617	4.3771
S4-Flavanol	253959	3.9208	3.985422	4.0571
Silymarin	5213	5.1739	4.647453	5.1062

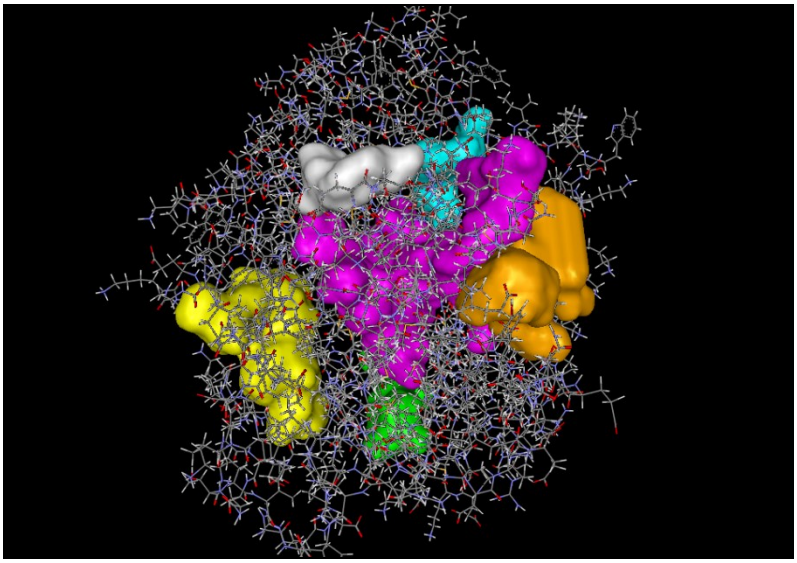
* Outliers in QSAR study

Supplementary figures:

Figure S1. Cavities present in aromatase enzyme. (Pink color-binding cavity)

Figure S2. Ramachandran plot analyses for the 3S7S

Figure S3. Natural product hit compounds having binding affinity for 3S7S



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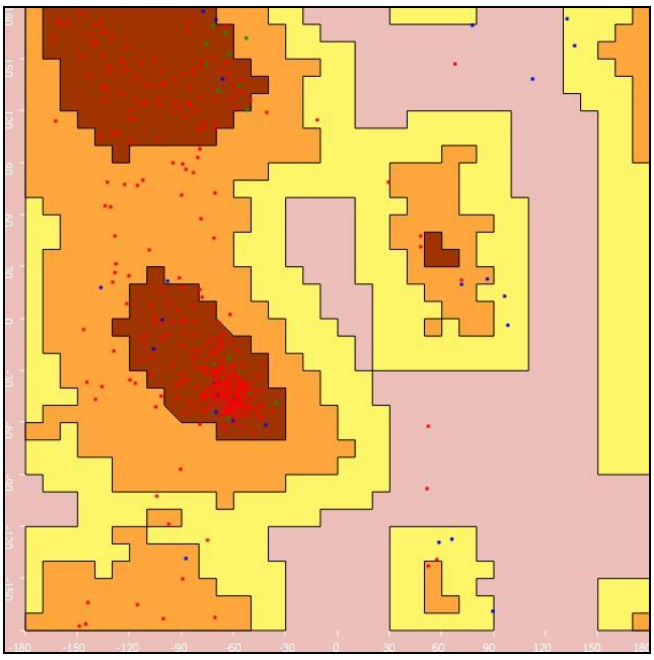

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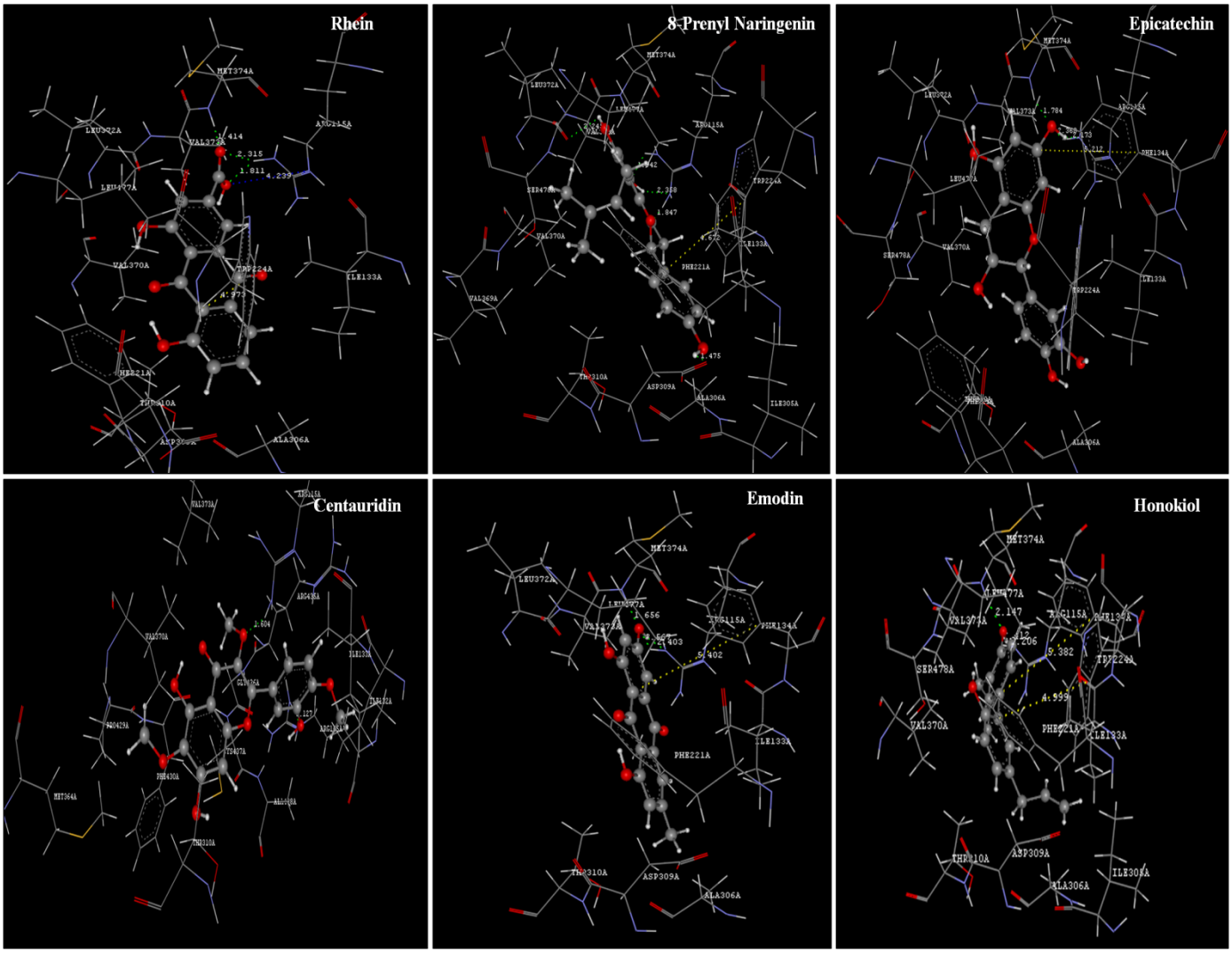

Figure S3. Natural product hit compounds having binding affinity for 3S7S

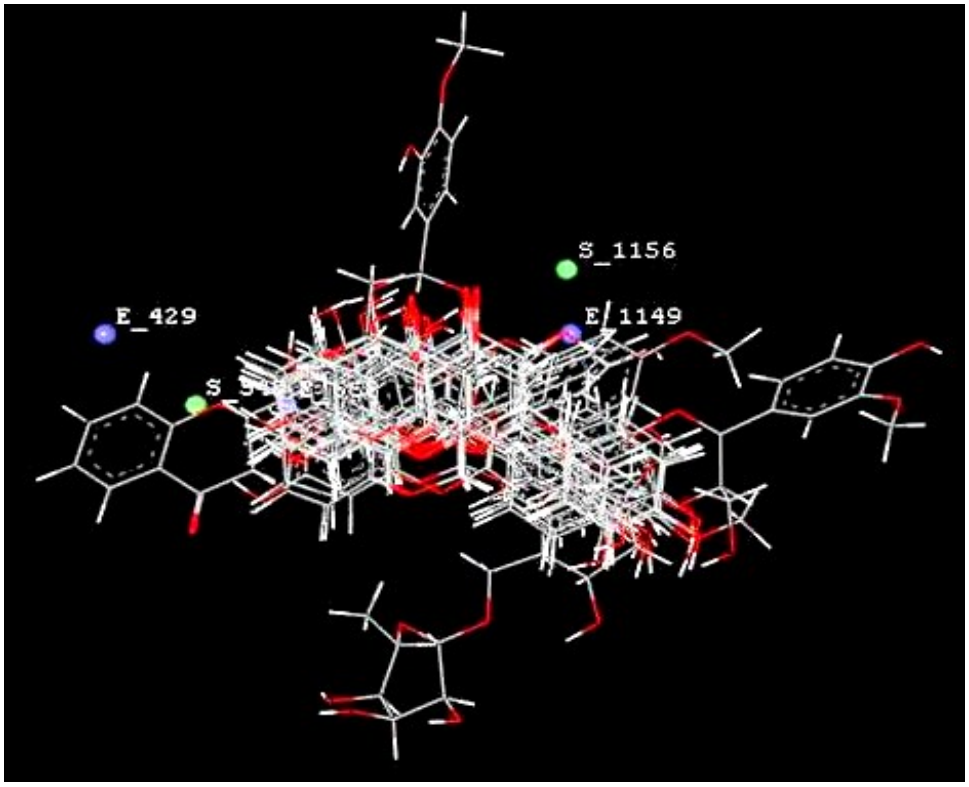

Figure S4. 3D QSAR model of all aligned flavonoids as aromatase inhibitors