

Supplementary Data

This supplementary data is a part of paper entitled “Ligand Based Pharmacophore Modeling, Virtual Screening, and Molecular Docking Studies of Asymmetrical Hexahydro-2H-Indazole Analogs of Curcumin (AIACs) to Discover Novel Estrogen Receptors Alpha (ER α) Inhibitor”.

Table S1.a. The intermediate of designed compound structures

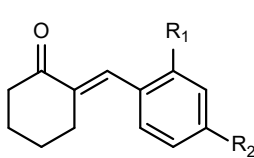
No	Compound code	Structure	R ₁	R ₂
1	1A		H	H
2	1B		H	CH ₃
3	1C		H	Cl
4	1D		H	F
5	1E		H	OCH ₃
6	1F		OCH ₃	OCH ₃

Table S1.b. The AMACs compound structures

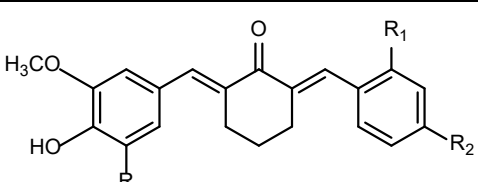
No	Compound code	Structure	R ₁	R ₂	R ₃
7	2A		H	H	H
8	2B		H	CH ₃	H
9	2C		H	Cl	H
10	2D		H	F	H
11	2E		H	OCH ₃	H
12	2F		OCH ₃	OCH ₃	H

Table S1.c. The AIACs compound structures I

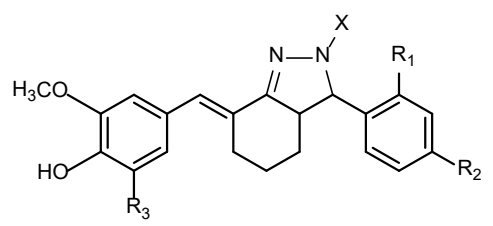
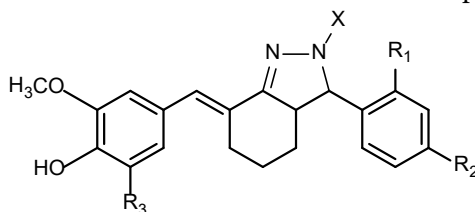
No	Compound code	Structure	R ₁	R ₂	R ₃	X
13	3A1		H	H	H	H
14	3A2		H	CH ₃	H	H
15	3A3		H	Cl	H	H
16	3A4		H	F	H	H
17	3A5		H	OCH ₃	H	H
18	3A6		OCH ₃	OCH ₃	H	H
19	3A7		H	H	H	phenyl
20	3A8		H	CH ₃	H	phenyl
21	3A9		H	Cl	H	phenyl
22	3A10		H	F	H	phenyl
23	3A11		H	OCH ₃	H	phenyl
24	3A12		OCH ₃	OCH ₃	H	phenyl

Table S1.d. The AIACs compound structures II

No	Compound code	Structure	R ₁	R ₂	R ₃	X
25	3B1		H	H	H	H
26	3B2		H	CH ₃	H	H
27	3B3		H	Cl	H	H
28	3B4		H	F	H	H
29	3B5		H	OCH ₃	H	H
30	3B6		OCH ₃	OCH ₃	H	H
31	3B7		H	H	H	phenyl
32	3B8		H	CH ₃	H	phenyl
33	3B9		H	Cl	H	phenyl
34	3B10		H	F	H	phenyl
35	3B11		H	OCH ₃	H	phenyl
36	3B12		OCH ₃	OCH ₃	H	phenyl

Table S1.e. The Mannich base derivative of AIACs compound structures I

No	Compound code	R ₁	R ₂	R ₃ ')	X
37	4A1A	H	H	CH ₂ -(A)	H
38	4A1B	H	H	CH ₂ -(B)	H
39	4A1C	H	H	CH ₂ -(C)	H
40	4A1D	H	H	CH ₂ -(D)	H
41	4A1E	H	H	CH ₂ -(E)	H
42	4A2A	H	CH ₃	CH ₂ -(A)	H
43	4A2B	H	CH ₃	CH ₂ -(B)	H
44	4A2C	H	CH ₃	CH ₂ -(C)	H
45	4A2D	H	CH ₃	CH ₂ -(D)	H
46	4A2E	H	CH ₃	CH ₂ -(E)	H
47	4A3A	H	Cl	CH ₂ -(A)	H
48	4A3B	H	Cl	CH ₂ -(B)	H
49	4A3C	H	Cl	CH ₂ -(C)	H
50	4A3D	H	Cl	CH ₂ -(D)	H
51	4A3E	H	Cl	CH ₂ -(E)	H
52	4A4A	H	F	CH ₂ -(A)	H
53	4A4B	H	F	CH ₂ -(B)	H
54	4A4C	H	F	CH ₂ -(C)	H
55	4A4D	H	F	CH ₂ -(D)	H
56	4A4E	H	F	CH ₂ -(E)	H
57	4A5A	H	OCH ₃	CH ₂ -(A)	H

Table S1.e. The Mannich base derivative of AIACs compound structures I (*Continued*)

No	Compound code	R ₁	R ₂	R ₃ ^{*)}	X
58	4A5B	H	OCH ₃	CH ₂ -(B)	H
59	4A5C	H	OCH ₃	CH ₂ -(C)	H
60	4A5D	H	OCH ₃	CH ₂ -(D)	H
61	4A5E	H	OCH ₃	CH ₂ -(E)	H
62	4A6A	OCH ₃	OCH ₃	CH ₂ -(A)	H
63	4A6B	OCH ₃	OCH ₃	CH ₂ -(B)	H
64	4A6C	OCH ₃	OCH ₃	CH ₂ -(C)	H
65	4A6D	OCH ₃	OCH ₃	CH ₂ -(D)	H
66	4A6E	OCH ₃	OCH ₃	CH ₂ -(E)	H
67	4A7A	H	H	CH ₂ -(A)	phenyl
68	4A7B	H	H	CH ₂ -(B)	phenyl
69	4A7C	H	H	CH ₂ -(C)	phenyl
70	4A7D	H	H	CH ₂ -(D)	phenyl
71	4A7E	H	H	CH ₂ -(E)	phenyl
72	4A8A	H	CH ₃	CH ₂ -(A)	phenyl
73	4A8B	H	CH ₃	CH ₂ -(B)	phenyl
74	4A8C	H	CH ₃	CH ₂ -(C)	phenyl
75	4A8D	H	CH ₃	CH ₂ -(D)	phenyl
76	4A8E	H	CH ₃	CH ₂ -(E)	phenyl
77	4A9A	H	Cl	CH ₂ -(A)	phenyl
78	4A9B	H	Cl	CH ₂ -(B)	phenyl
79	4A9C	H	Cl	CH ₂ -(C)	phenyl
80	4A9D	H	Cl	CH ₂ -(D)	phenyl
81	4A9E	H	Cl	CH ₂ -(E)	phenyl
82	4A10A	H	F	CH ₂ -(A)	phenyl
83	4A10B	H	F	CH ₂ -(B)	phenyl
84	4A10C	H	F	CH ₂ -(C)	phenyl
85	4A10D	H	F	CH ₂ -(D)	phenyl
86	4A10E	H	F	CH ₂ -(E)	phenyl
87	4A11A	H	OCH ₃	CH ₂ -(A)	phenyl
88	4A11B	H	OCH ₃	CH ₂ -(B)	phenyl
89	4A11C	H	OCH ₃	CH ₂ -(C)	phenyl
90	4A11D	H	OCH ₃	CH ₂ -(D)	phenyl
91	4A11E	H	OCH ₃	CH ₂ -(E)	phenyl
92	4A12A	OCH ₃	OCH ₃	CH ₂ -(A)	phenyl
93	4A12B	OCH ₃	OCH ₃	CH ₂ -(B)	phenyl
94	4A12C	OCH ₃	OCH ₃	CH ₂ -(C)	phenyl
95	4A12D	OCH ₃	OCH ₃	CH ₂ -(D)	phenyl
96	4A12E	OCH ₃	OCH ₃	CH ₂ -(E)	phenyl

*) R₃ = CH₂-(..) = Mannich bases group




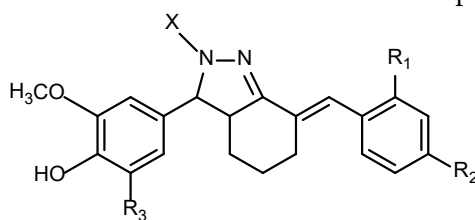
(..)	Structure	(..)	Structure	(..)	Structure
A	-N(CH ₃) ₂	C		E	
B	-N(C ₂ H ₅) ₂	D			

Table S1.f. The Mannich base derivative of AIACs compound structures II

No	Compound code	R ₁	R ₂	R ₃ ^{a)}	X
97	4B1A	H	H	CH ₂ -(A)	H
98	4B1B	H	H	CH ₂ -(B)	H
99	4B1C	H	H	CH ₂ -(C)	H
100	4B1D	H	H	CH ₂ -(D)	H
101	4B1E	H	H	CH ₂ -(E)	H
102	4B2A	H	CH ₃	CH ₂ -(A)	H
103	4B2B	H	CH ₃	CH ₂ -(B)	H
104	4B2C	H	CH ₃	CH ₂ -(C)	H
105	4B2D	H	CH ₃	CH ₂ -(D)	H
106	4B2E	H	CH ₃	CH ₂ -(E)	H
107	4B3A	H	Cl	CH ₂ -(A)	H
108	4B3B	H	Cl	CH ₂ -(B)	H
109	4B3C	H	Cl	CH ₂ -(C)	H
110	4B3D	H	Cl	CH ₂ -(D)	H
111	4B3E	H	Cl	CH ₂ -(E)	H
112	4B4A	H	F	CH ₂ -(A)	H
113	4B4B	H	F	CH ₂ -(B)	H
114	4B4C	H	F	CH ₂ -(C)	H
115	4B4D	H	F	CH ₂ -(D)	H
116	4B4E	H	F	CH ₂ -(E)	H
117	4B5A	H	OCH ₃	CH ₂ -(A)	H
118	4B5B	H	OCH ₃	CH ₂ -(B)	H
119	4B5C	H	OCH ₃	CH ₂ -(C)	H
120	4B5D	H	OCH ₃	CH ₂ -(D)	H
121	4B5E	H	OCH ₃	CH ₂ -(E)	H
122	4B6A	OCH ₃	OCH ₃	CH ₂ -(A)	H
123	4B6B	OCH ₃	OCH ₃	CH ₂ -(B)	H
124	4B6C	OCH ₃	OCH ₃	CH ₂ -(C)	H
125	4B6D	OCH ₃	OCH ₃	CH ₂ -(D)	H
126	4B6E	OCH ₃	OCH ₃	CH ₂ -(E)	H
127	4B7A	H	H	CH ₂ -(A)	phenyl
128	4B7B	H	H	CH ₂ -(B)	phenyl
129	4B7C	H	H	CH ₂ -(C)	phenyl
130	4B7D	H	H	CH ₂ -(D)	phenyl
131	4B7E	H	H	CH ₂ -(E)	phenyl
132	4B8A	H	CH ₃	CH ₂ -(A)	phenyl
133	4B8B	H	CH ₃	CH ₂ -(B)	phenyl

Table S1.f. The Mannich base derivative of AIACs compound structures II (*Continued*)

No	Compound code	R ₁	R ₂	R ₃ ^{*)}	X
134	4B8C	H	CH ₃	CH ₂ -(C)	phenyl
135	4B8D	H	CH ₃	CH ₂ -(D)	phenyl
136	4B8E	H	CH ₃	CH ₂ -(E)	phenyl
137	4B9A	H	Cl	CH ₂ -(A)	phenyl
138	4B9B	H	Cl	CH ₂ -(B)	phenyl
139	4B9C	H	Cl	CH ₂ -(C)	phenyl
140	4B9D	H	Cl	CH ₂ -(D)	phenyl
141	4B9E	H	Cl	CH ₂ -(E)	phenyl
142	4B10A	H	F	CH ₂ -(A)	phenyl
143	4B10B	H	F	CH ₂ -(B)	phenyl
144	4B10C	H	F	CH ₂ -(C)	phenyl
145	4B10D	H	F	CH ₂ -(D)	phenyl
146	4B10E	H	F	CH ₂ -(E)	phenyl
147	4B11A	H	OCH ₃	CH ₂ -(A)	phenyl
148	4B11B	H	OCH ₃	CH ₂ -(B)	phenyl
149	4B11C	H	OCH ₃	CH ₂ -(C)	phenyl
150	4B11D	H	OCH ₃	CH ₂ -(D)	phenyl
151	4B11E	H	OCH ₃	CH ₂ -(E)	phenyl
152	4B12A	OCH ₃	OCH ₃	CH ₂ -(A)	phenyl
153	4B12B	OCH ₃	OCH ₃	CH ₂ -(B)	phenyl
154	4B12C	OCH ₃	OCH ₃	CH ₂ -(C)	phenyl
155	4B12D	OCH ₃	OCH ₃	CH ₂ -(D)	phenyl
156	4B12E	OCH ₃	OCH ₃	CH ₂ -(E)	phenyl

*) R₃ = CH₂-(..) = Mannich bases group




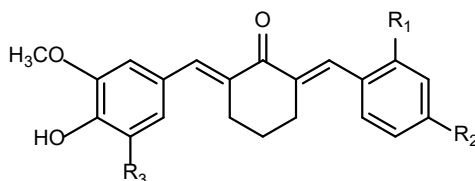
(..)	Structure	(..)	Structure	(..)	Structure
A	-N(CH ₃) ₂	C		E	
B	-N(C ₂ H ₅) ₂	D			

Table S1.g. The Mannich base derivative of AMACs compound structures

No	Compound code	R ₁	R ₂	R ₃
157	2AA	H	H	CH ₂ -(A)
158	2AB	H	H	CH ₂ -(B)
159	2AC	H	H	CH ₂ -(C)
160	2AD	H	H	CH ₂ -(D)
161	2AE	H	H	CH ₂ -(E)
162	2BA	H	CH ₃	CH ₂ -(A)
163	2BB	H	CH ₃	CH ₂ -(B)
164	2BC	H	CH ₃	CH ₂ -(C)
165	2BD	H	CH ₃	CH ₂ -(D)
166	2BE	H	CH ₃	CH ₂ -(E)
167	2CA	H	Cl	CH ₂ -(A)
168	2CB	H	Cl	CH ₂ -(B)
169	2CC	H	Cl	CH ₂ -(C)
170	2CD	H	Cl	CH ₂ -(D)
171	2CE	H	Cl	CH ₂ -(E)
172	2CA	H	F	CH ₂ -(A)
173	2DB	H	F	CH ₂ -(B)
174	2DC	H	F	CH ₂ -(C)
175	2DD	H	F	CH ₂ -(D)
176	2DE	H	F	CH ₂ -(E)
177	2EA	H	OCH ₃	CH ₂ -(A)
178	2EB	H	OCH ₃	CH ₂ -(B)
179	2EC	H	OCH ₃	CH ₂ -(C)
180	2ED	H	OCH ₃	CH ₂ -(D)
181	2EE	H	OCH ₃	CH ₂ -(E)
182	2FA	OCH ₃	OCH ₃	CH ₂ -(A)
183	2FB	OCH ₃	OCH ₃	CH ₂ -(B)
184	2FC	OCH ₃	OCH ₃	CH ₂ -(C)
185	2FD	OCH ₃	OCH ₃	CH ₂ -(D)
186	2FE	OCH ₃	OCH ₃	CH ₂ -(E)

^{*)} R₃ = CH₂-(..) = Mannich bases group

(..)	Structure	(..)	Structure	(..)	Structure
A	-N(CH ₃) ₂	C		E	
B	-N(C ₂ H ₅) ₂	D			

Table S2.a. Four native ligands of ER α receptor

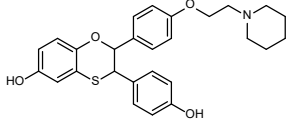
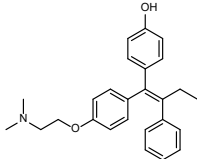
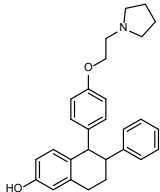
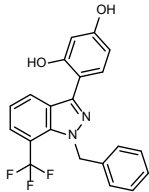
No	Native Ligand Name	PDB ID	Molecular Formula	Molecular Weight
1	E4D600	1SJ0	C ₂₇ H ₂₉ N ₁ O ₄ S ₁	463.60
				
2	OHT201	2OUZ	C ₂₆ H ₃₀ N ₁ O ₂	388.53
				
3	C3D999	2P7Z	C ₂₈ H ₃₁ N ₁ O ₂	413.56
				
4	KN01	3OS8	C ₂₁ H ₁₅ N ₂ O ₂ F ₃	384.36
				

Table S2.b. Data of 30 ER α inhibitor compounds

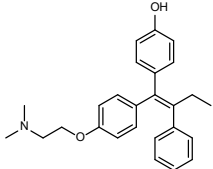
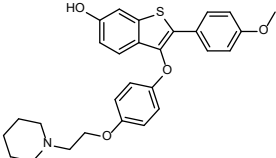
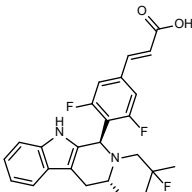
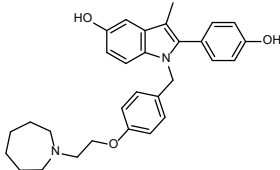
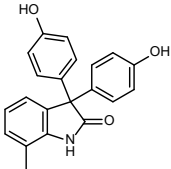
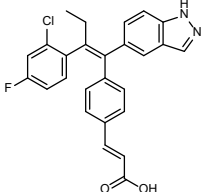
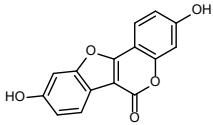
No	ER α inhibitor compounds	Pubchem CID	Molecular Formula	Molecular Weight	pIC ₅₀ (M)
1	4-OH-Tamoxifene/Afimoxifene 	449459	C ₂₆ H ₂₉ NO ₂	387.5	9.30
2	Arzoxifene 	179337	C ₂₈ H ₂₉ NO ₄ S	475.6	7.67
3	AZD9496 	86287635	C ₂₅ H ₂₅ F ₃ N ₂ O ₂	442.5	9.86
4	Bazedoxifene 	154257	C ₃₀ H ₃₄ N ₂ O ₃	470.6	9.22
5	BHPI 	3860640	C ₂₁ H ₁₇ NO ₃	331.4	7.57
6	Brilanestrant/GDC-0810 	56941241	C ₂₆ H ₂₀ ClFN ₂ O ₂	446.9	8.21
7	Coumestrol 	5281707	C ₁₅ H ₈ O ₅	268.22	7.96

Table S2.b. Data of 30 ER α inhibitor compounds (*Continued*)

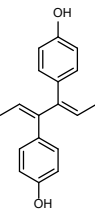
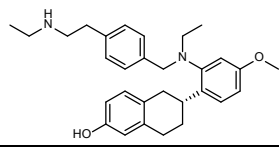
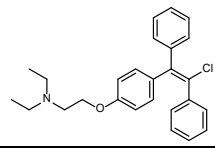
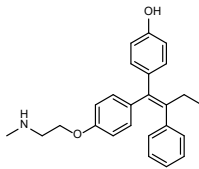
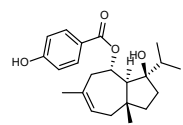
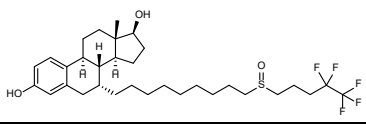
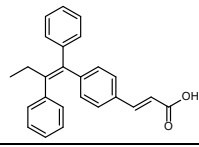
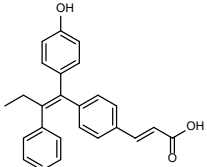
No	ER α inhibitor compounds	Pubchem CID	Molecular Formula	Molecular Weight	pIC ₅₀ (M)
8	Dienestrol 	667476	C ₁₈ H ₁₈ O ₂	266.3	7.82
9	Elacestrant 	23642301	C ₃₀ H ₃₈ N ₂ O ₂	458.6	7.32
10	Enclomiphene 	1548953	C ₂₆ H ₂₈ ClNO	406	7.11
11	Endoxifen 	10090750	C ₂₅ H ₂₇ NO ₂	373.5	7.82
12	Ferutinin 	354654	C ₂₂ H ₃₀ O ₄	358.5	7.48
13	Fulvestran = Faslodex 	104741	C ₃₂ H ₄₇ F ₅ O ₃ S	606.8	9.09
14	GW 5638 	5288494	C ₂₅ H ₂₂ O ₂	354.4	8.49
15	GW 7604 	9799518	C ₂₅ H ₂₂ O ₃	370.4	6.89

Table S2.b. Data of 30 ER α inhibitor compounds (*Continued*)

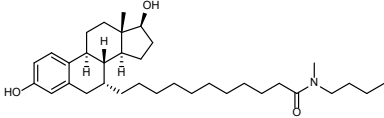
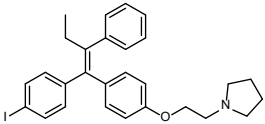
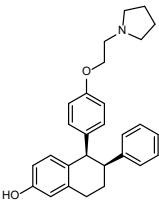
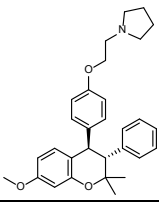
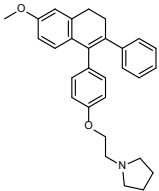
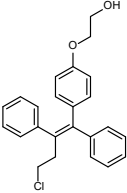
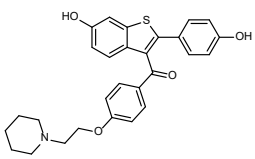
No	ER α inhibitor compounds	Pubchem CID	Molecular Formula	Molecular Weight	pIC ₅₀ (M)
16	ICI-164384 	104772	C ₃₄ H ₅₅ NO ₃	525.8	8.52
17	Idoxifene 	3034011	C ₂₈ H ₃₀ INO	523.4	6.47
18	Lasofloxifene 	3081919	C ₃₂ H ₃₇ NO ₈	563.6	8.82
19	Levormeloxifene 	35805	C ₃₀ H ₃₅ NO ₃	457.6	8.14
20	Nafoxidine 	4416	C ₂₉ H ₃₁ NO ₂	425.6	5.13
21	Ospemiphene 	3036505	C ₂₄ H ₂₃ ClO ₂	378.9	6.10
22	Raloxifene 	5035	C ₂₈ H ₂₇ NO ₄ S	473.6	8.40

Table S2.b. Data of 30 ER α inhibitor compounds (*Continued*)

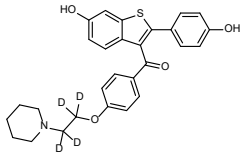
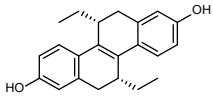
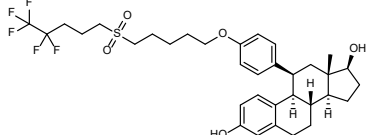
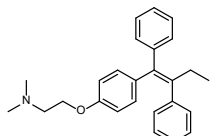
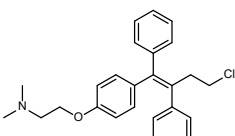
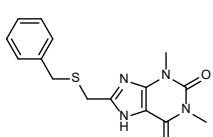
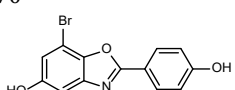
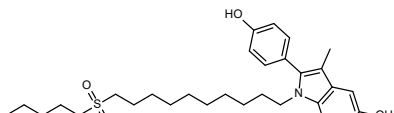
No	ER α inhibitor compounds	Pubchem CID	Molecular Formula	Molecular Weight	pIC ₅₀ (M)
23	Raloxifene d4 	25217190	C ₂₈ H ₂₇ NO ₄ S	477.6	9.43
24	(R,R)-THC 	446849	C ₂₂ H ₂₄ O ₂	320.4	4.98
25	RU58668 	6918261	C ₃₄ H ₄₃ F ₅ O ₅ S	658.8	4.40
26	Tamoxifene 	2733526	C ₂₆ H ₂₉ NO	371.5	6.76
27	Toremifene 	3005573	C ₂₆ H ₂₈ ClNO	406	6.00
28	TPBM 	262425	C ₁₅ H ₁₆ N ₄ O ₂ S	316.4	5.30
29	WAY 200070 	135418373	C ₁₃ H ₈ BrNO ₃	306.11	7.20
30	ZK 164015 	9806489	C ₃₀ H ₄₃ NO ₄ S	513.7	4.60

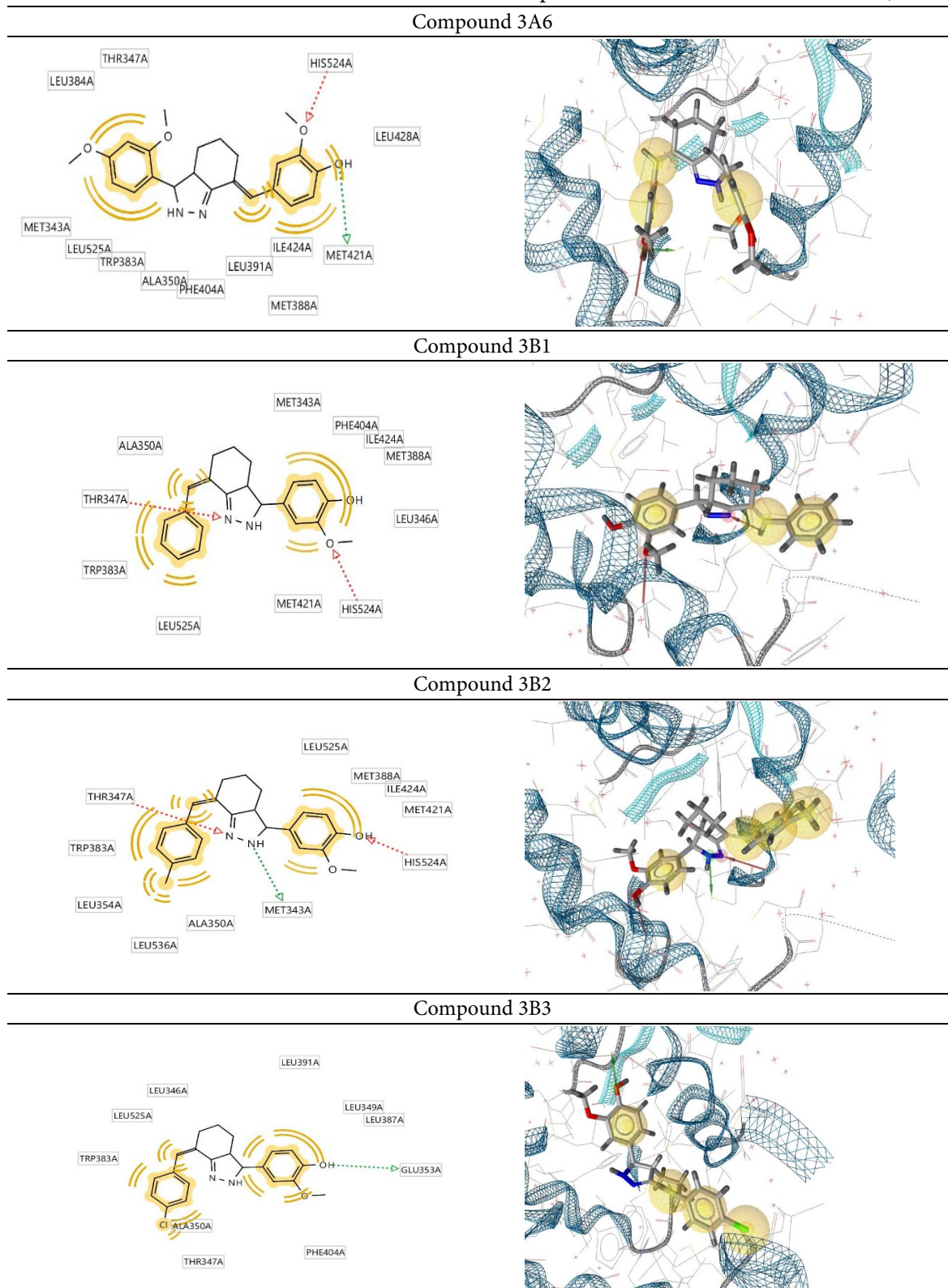
Table S3. 2D and 3D visualization results of 10 selected compounds and Tamoxifen docked at 1SJ0 receptors

Table S3. 2D and 3D visualization results of 10 selected compounds and Tamoxifen docked at 1SJ0 receptors (Continued)

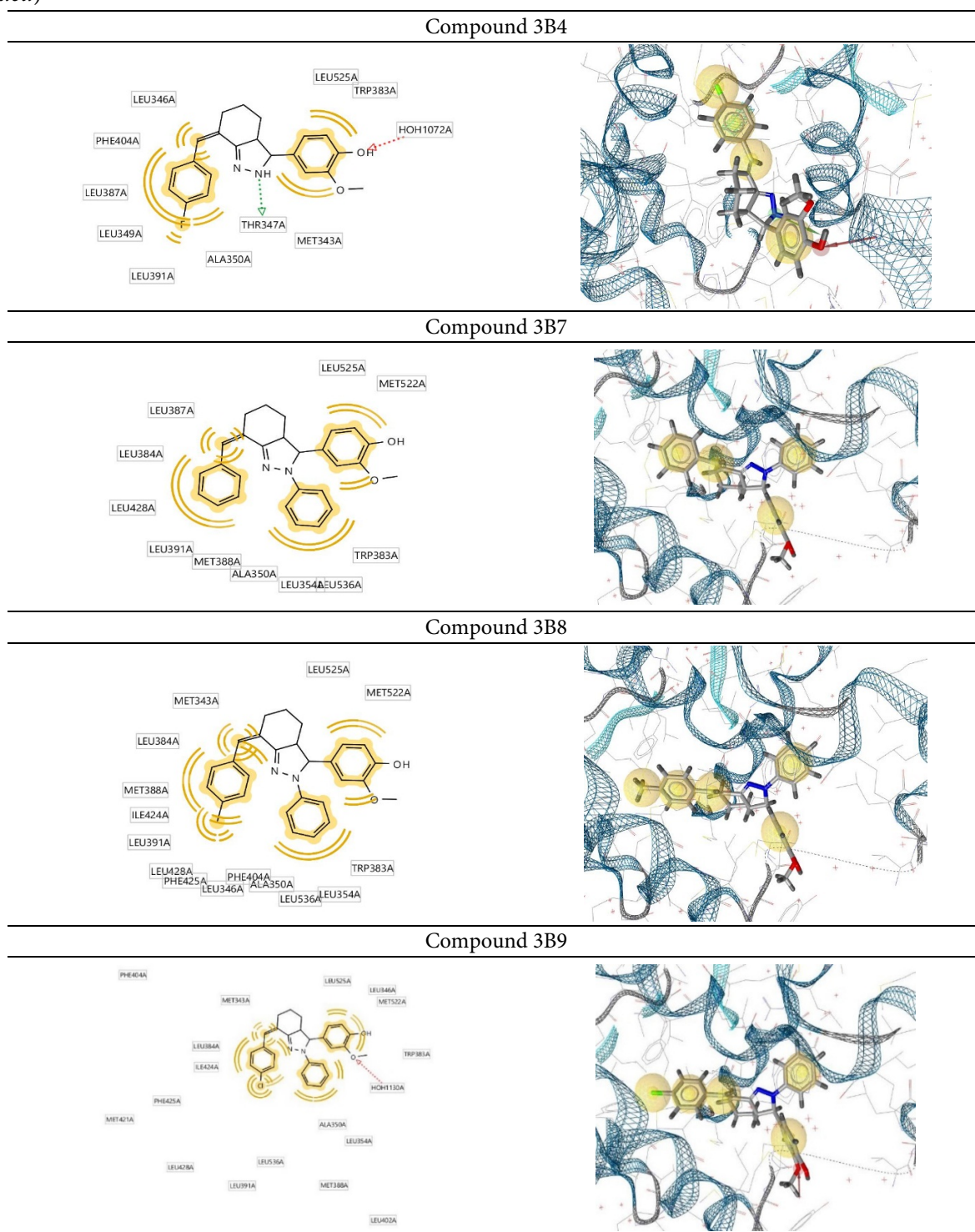


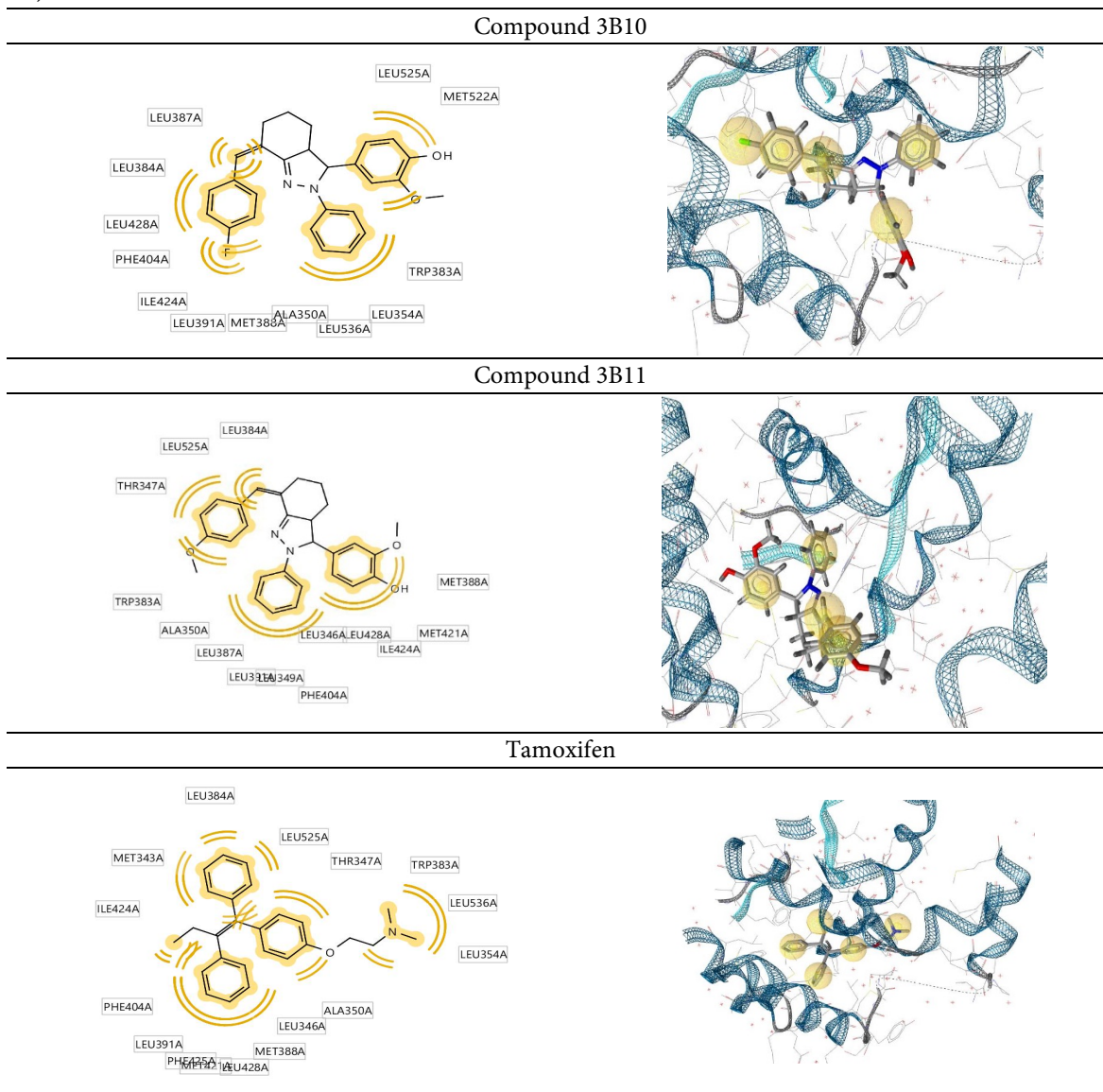
Table S3. 2D and 3D visualization results of 10 selected compounds and Tamoxifen docked at 1SJ0 receptors (Continued)

Table S4. 2D and 3D visualization of chemical features with triangular patterns

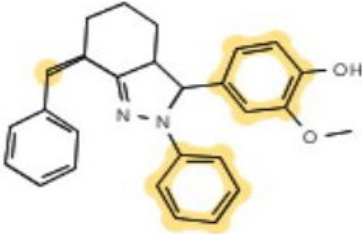
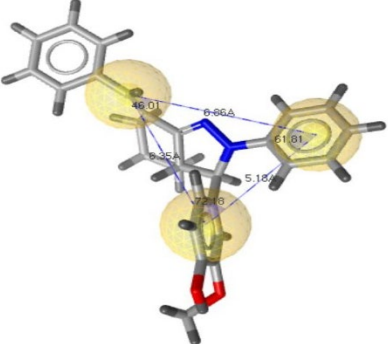
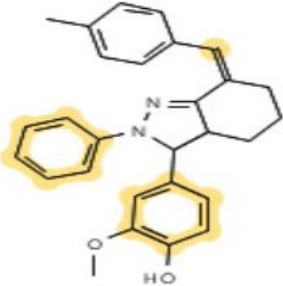
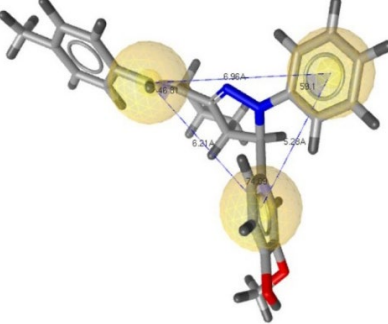
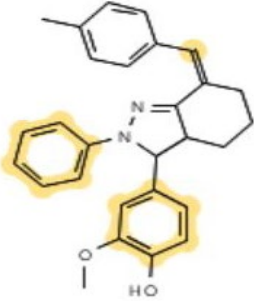
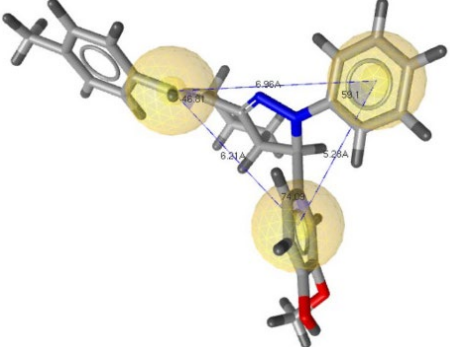
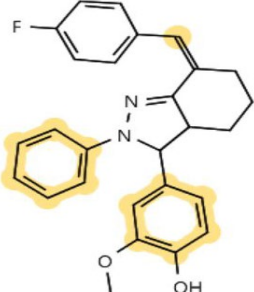
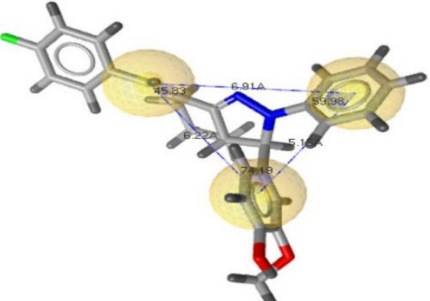
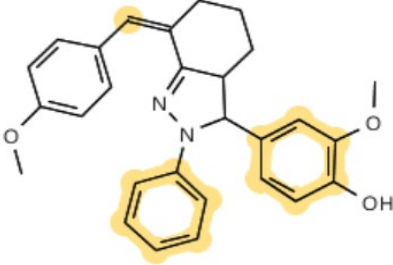
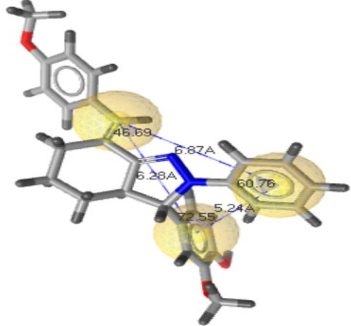
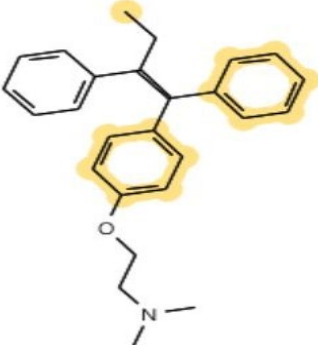
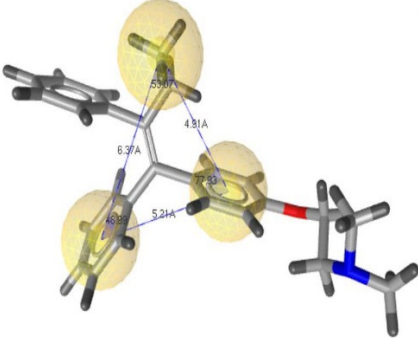
Ligands	2D feature image	3D feature image
3B7		
3B8		
3B9		
3B10		

Table S4. 2D and 3D visualization of chemical features with triangular patterns (*Continued*)

Ligands	2D feature image	3D feature image
3B11		
Tamoxifen		
Feature Model 2	