COMPUTACIONAL METHODS AS SCREENING TOOL FOR TRIAZOLE NATURAL PRODUCTS DERIVATIVES AS POTENCIAL β-TUBULIN INHIBITORS FOR *FUSARIUM GRAMINEARUM*

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SUPPLEMENTARY MATERIAL

SUMMARY

ANNEX I – QSAR-2D

Table 1 - Statistical results obtained in the Jamovi software for the other models obtained by QSAR-2D

QSAR-2D

Models	Descriptors present	R^2	Adjusted R^2	Durbin-Watson autocorrelation	VIF	Normality Test (Shapiro-Wilk)	r^2 test
1	JGI1 - VE3_D - RPCS	0.85	0.82	1.67	<1.09	0.92	0.6988
2	ETA_Psi_1 - JGI1 - xLogP	0.869	0.843	1.85	<3.2	1	0.5635
3	JGI1 - VE3_D - THSA	0.855	0.826	1.27	<1.21	0.421	0.7122

Table 2 - Equation of the QSAR-2D models by Jamovi software, used to predict the biological activities of the molecules in the test set and, subsequently, of new substances, which can be validated after experimental results.

Models	Descriptors	Equation of Model
1	JGI1 - VE3_D - RPCS	5.145+21.442***JG1I**+1.253* **VE3_D** +0.362* **RPCS**
2	ETA_Psi_1 - JGI1 - xLogP	16.43+25.09* **ETA_Psi_1** +54.91* **JGI1**-3.3* **xLogP**
3	JGI1 - VE3_D - THSA	6.75877+26.7844* **JGI1**+1.18045* **VE3_D** -0.00507* **THSA**

Table 3 - QSAR-2D models, with their respective descriptors, predicted biological activity and residues.

Model 1

COMPOUND	JGI1	VE3_D	RPCS	PEC_{50}	PEC_{50} PREDICT	RESIDUE
3	0.18	-3.93335	0.531565	5.271788	4.2685039	1.003284
5	0.16	-4.67614	1.577528	3.294955	3.28757886	0.007376
9	0.173077	-4.04609	1.69513	4.293783	4.40000778	-0.106225
10	0.192308	-4.86322	0.475926	4.226329	3.34713738	0.879192
13	0.206897	-3.98891	1.102393	5.161927	4.98224176	0.179685
17	0.189655	-4.64916	0.374966	3.190146	3.5219201	-0.331774
20	0.192308	-3.77015	1.547649	5.146248	5.10470831	0.041540
26	0.211538	-3.85575	1.648122	5.261102	5.44617155	-0.185069

Model 2

COMPOUND	ETA_PSI_1	JGI1	XLOGP	PEC_{50}	PEC_{50} PREDICT	RESIDUE
3	0.55128	0.18	0.897	5.271788	4.325315	0.946473
5	0.5186	0.16	0.436	3.294955	3.928474	-0.633519
9	0.53623	0.173077	0.56	4.293783	4.679665	-0.385882
10	0.56522	0.192308	1.315	4.226329	3.971485	0.254844
13	0.5215	0.206897	1.166	5.161927	4.167325	0.994602
17	0.5215	0.189655	1.166	3.190146	3.220601	-0.030455
20	0.55681	0.192308	1.078	5.146248	4.542578	0.603670
26	0.54895	0.211538	1.263	5.261102	4.790832	0.470270

Model 3

COMPOUND	JGI1	VE3_D	THSA	PEC_{50}	PEC_{50} PREDICT	RESIDUE
3	0.18	-3.93335	524.5432	5.271788	4.27741	0.994378
5	0.16	-4.67614	422.4313	3.294955	3.382595	-0.087640
9	0.173077	-4.04609	507.4085	4.293783	4.045769	0.248014
10	0.192308	-4.86322	503.376	4.226329	3.616717	0.609612
13	0.206897	-3.98891	551.9947	5.161927	4.793051	0.368875
17	0.189655	-4.64916	513.6962	3.190146	3.746023	-0.555878
20	0.192308	-3.77015	493.1303	5.146248	4.958968	0.187281
26	0.211538	-3.85575	506.5318	5.261102	5.305063	-0.043961

Compound	JGI1	VE3_D	pEC_{50} experimental	pEC_{50} predicted	Residue
3	0.180	-3.933	4.495	5.272	0.777
5	0.160	-4.676	3.030	3.295	0.265
9	0.173	-4.046	4.180	4.294	0.114
10	0.192	-4.863	3.552	4.226	0.674
13	0.207	-3.989	5.063	5.162	0.099
17	0.190	-4.649	3.774	3.190	-0.584
20	0.192	-3.770	5.006	5.146	0.140
26	0.212	-3.856	5.351	5.261	-0.090

Table 4 - Predicted biological activity (predicted pEC50) for the previously synthesized triazole compounds, showing the predictive capacity of these models with their respective molecular descriptors.

BIOLOGICAL ACTIVITY PREDICTED BY THE QSAR-2D MODEL

	Model 1	**Model 2**	**Model 3**
	r^2_{test} = 0.6988	r^2_{test} = 0.5635	r^2_{test}= 0.7122
Compound	**JGI - VE3_D - RPCS**	**ETA_PSI_1 - JGI1 - XLOGP**	**JGI1 - VE3_D - THSA**
1	0.736	-2.266	-0.800
2	-0.382	-1.919	-1.672
3	1.285	-1.307	-0.124
4	-0.694	-2.092	-2.129
5	-3.471	-2.266	-4.721
6	-4.497	0.769	-5.006
7	-0.588	0.016	-1.331
8	-6.993	-3.685	-7.024
9	1.168	-4.142	1.364
10	1.506	-1.031	1.330
11	-0.365	-2.087	-0.663
12	2.581	-1.528	2.166
13	-8.684	-2.499	-10.958
14	-5.833	-2.077	-5.996
15	0.590	-1.528	0.378
16	0.778	-0.434	0.293
17	-0.279	0.029	-0.652
18	**4.406**	3.770	3.042
19	-4.763	-2.545	-4.695
20	**5.066**	3.692	3.890
21	1.073	3.365	0.915
22	3.850	4.558	3.617
23	-20.640	**6.777**	-19.788
24	4.195	3.692	1.906
25	-4.437	2.081	-3.567
26	3.789	4.345	3.459
27	2.779	4.345	2.593
28	3.258	4.558	3.077
29	0.984	4.108	0.943
30	2.974	**5.720**	2.944
31	2.564	4.136	0.592
32	**5.645**	**9.890**	**4.065**

ANNEX II – CoMFA (QSAR-3D)

Table 5 - Construction of the CoMFA model (3D QSAR), using the PM7 semiempirical method.

PM7 MODEL

COMFA – WITH FOCUS – CHARGES FROM PM7													
LEAVE-ONE-OUT (q^2)	**Without Focus**	**W03D0.5**	**W03D1.0**	**W03D1.5**	**W05D0.5**	**W05D1.0**	**W05D1.5**	**W07D0.5**	**W07D1.0**	**W07D1.5**	**W09D05**	**W09D10**	**W09D15**
Standard Error of Prediction for 6 components:	0.428	0.443	0.339	0.451	0.371	0.272	0.430	0.336	**0.217**	0.490	0.326	0.208	0.243
Crossvalidated R^2 for 6 components:	0.772	0.775	0.857	0.747	0.815	0.901	0.771	0.871	**0.946**	0.724	0.878	0.951	0.932
N components	**5**	**6**	**5**	**5**	**4**	**4**	**5**	**6**	**6**	**6**	**6**	**6**	**6**
NO VALIDATION (r^2)													
Standard Error of Estimate	0.086	0.064	0.068	0.089	0.104	0.094	0.096	0.063	0.050	0.096	0.063	0.065	0.114
R squared	0.991	0.995	0.994	0.990	0.986	0.988	0.989	0.995	0.997	0.989	0.995	0.995	0.985
1 COMFA (Steric) FRACTION	0.493	0.494	0.503	0.473	0.475	0.464	0.411	0.407	0.412	0.433	0.409	0.423	0.578
2 COMFA (Electrostatic) FRACTION	0.507	0.506	0.497	0.527	0.525	0.536	0.589	0.593	0.588	0.567	0.591	0.577	0.422
# vars	990	7560	7560	2184	16744	16744	5168	38998	38998	12075	94300	94300	27621

Table 6 - Construction of the CoMFA model (3D QSAR), using the RM1 semiempirical method.

RM1 MODEL

COMFA – WITH FOCUS – CHARGES FROM RM1													
LEAVE-ONE-OUT (q^2)	**Without Focus**	**W03D0.5**	**W03D1.0**	**W03D1.5**	**W05D0.5**	**W05D1.0**	**W05D1.5**	**W07D0.5**	**W07D1.0**	**W07D1.5**	**W09D05**	**W09D10**	**W09D15**
Standard Error of Prediction for 6 components:	0.461	0.460	0.371	0.474	0.388	0.279	0.454	0.371	**0.227**	0.446	0.393	0.297	0.477
Crossvalidated R^2 for 6 components:	0.736	0.737	0.829	0.720	0.798	0.903	0.743	0.842	**0.941**	0.771	0.823	0.874	0.739
N components	**5**	**5**	**5**	**5**	**4**	**5**	**5**	**6**	**6**	**6**	**6**	**3**	**6**
NO VALIDATION (r^2)													
Standard Error of Estimate	0.088	0.083	0.069	0.083	0.104	0.087	0.114	0.070	0.054	0.077	0.070	0.153	0.178
R squared	0.990	0.992	0.994	0.991	0.985	0.990	0.984	0.994	0.997	0.993	0.994	0.966	0.964
1 COMFA (Steric) FRACTION	0.482	0.471	0.486	0.445	0.453	0.459	0.367	0.434	0.466	0.267	0.350	0.413	0.444
2 COMFA (Electrostatic) FRACTION	0.518	0.529	0.514	0.555	0.547	0.541	0.633	0.566	0.534	0.733	0.650	0.587	0.556
# vars	990	7560	7560	2184	16744	16744	5168	38998	38998	12075	94300	94300	27621

Table 7 - Construction of the CoMFA model (3D QSAR), using the empirical Gasteiger-Marsili method.

GASTEIGER-MARSILI MODEL

COMFA – WITH FOCUS – CHARGES FROM Gasteiger-Marsili													
LEAVE-ONE-OUT (q^2)	**Without Focus**	**W03D0.5**	**W03D1.0**	**W03D1.5**	**W05D0.5**	**W05D1.0**	**W05D1.5**	**W07D0.5**	**W07D1.0**	**W07D1.5**	**W09D05**	**W09D10**	**W09D15**
Standard Error of Prediction for 6 components:	0.628	0.555	0.497	0.617	0.497	0.375	0.418	0.302	**0.251**	0.333	0.348	0.332	0.390
Crossvalidated R^2 for 6 components:	0.510	0.587	0.670	0.563	0.670	0.798	0.800	0.869	**0.909**	0.831	0.815	0.831	0.767
N components	**5**	**4**	**4**	**6**	**4**	**3**	**6**	**3**	**3**	**2**	**2**	**2**	**2**
NO VALIDATION (r^2)													
Standard Error of Estimate	0.189	0.221	0.191	0.133	0.154	0.166	0.145	0.158	0.176	0.267	0.290	0.287	0.317
R squared	0.956	0.935	0.951	0.980	0.968	0.961	0.976	0.964	0.956	0.891	0.872	0.874	0.846
1 COMFA (Steric) FRACTION	0.485	0.516	0.485	0.308	0.391	0.471	0.415	0.504	0.534	0.518	0.503	0.517	0.563
2 COMFA (Electrostatic) FRACTION	0.515	0.484	0.515	0.692	0.609	0.529	0.585	0.496	0.466	0.482	0.497	0.483	0.437
# vars	990	6498	6498	2028	15600	15600	4624	35836	35836	11109	85050	85050	25200

Table 8 - Construction of the CoMFA model (3D QSAR), using the empirical Gasteiger-Hückel method.

GASTEIGER-HÜCKEL MODEL

COMFA – WITH FOCUS – CHARGES FROM Gasteiger-Hückel													
LEAVE-ONE-OUT (q^2)	**Without Focus**	**W03D0.5**	**W03D1.0**	**W03D1.5**	**W05D0.5**	**W05D1.0**	**W05D1.5**	**W07D0.5**	**W07D1.0**	**W07D1.5**	**W09D05**	**W09D10**	**W09D15**
Standard Error of Prediction for 6 components:	0.661	0.576	0.494	0.657	0.531	0.435	0.434	0.330	**0.272**	0.339	0.345	0.333	0.391
Crossvalidated R^2 for 6 components:	0.498	0.587	0.674	0.505	0.623	0.728	0.766	0.843	**0.894**	0.824	0.818	0.830	0.767
N components	**6**	**5**	**4**	**6**	**4**	**3**	**5**	**3**	**3**	**2**	**2**	**2**	**2**
NO VALIDATION (r^2)													
Standard Error of Estimate	0.123	0.141	0.173	0.139	0.150	0.151	0.152	0.156	0.165	0.260	0.282	0.287	0.319
R squared	0.983	0.975	0.960	0.978	0.970	0.967	0.971	0.965	0.961	0.896	0.878	0.874	0.844
1 COMFA (Steric) FRACTION	0.459	0.496	0.534	0.336	0.390	0.429	0.459	0.525	0.540	0.533	0.511	0.520	0.587
2 COMFA (Electrostatic) FRACTION	0.541	0.504	0.466	0.664	0.610	0.571	0.541	0.475	0.460	0.467	0.489	0.480	0.413
# vars	900	6498	6498	2028	15600	15600	4624	35836	35836	11109	85050	85050	25200

Table 9 - Construction of the CoMFA model (3D QSAR), using the MMFF-94 empirical method.

MMFF-94 MODEL

COMFA – WITH FOCUS – CHARGES FROM MMFF94													
LEAVE-ONE-OUT (q^2)	**Without Focus**	**W03D0.5**	**W03D1.0**	**W03D1.5**	**W05D0.5**	**W05D1.0**	**W05D1.5**	**W07D0.5**	**W07D1.0**	**W07D1.5**	**W09D05**	**W09D10**	**W09D15**
Standard Error of Prediction for 6 components:	0.467	0.471	0.401	0.470	0.399	0.315	0.487	0.405	**0.280**	0.393	0.370	0.346	0.333
Crossvalidated R^2 for 6 components:	0.729	0.724	0.800	0.746	0.787	0.877	0.682	0.812	**0.902**	0.779	0.803	0.851	0.873
N components	**5**	**5**	**5**	**6**	**4**	**5**	**4**	**6**	**5**	**3**	**3**	**5**	**6**
NO VALIDATION (r^2)													
Standard Error of Estimate	0.088	0.092	0.079	0.073	0.091	0.082	0.100	0.067	0.068	0.194	0.180	0.174	0.141
R squared	0.990	0.989	0.992	0.994	0.989	0.992	0.987	0.995	0.994	0.946	0.953	0.963	0.977
1 COMFA (Steric) FRACTION	0.445	0.419	0.422	0.355	0.351	0.374	0.319	0.360	0.406	0.344	0.351	0.314	0.503
2 COMFA (Electrostatic) FRACTION	0.555	0.581	0.578	0.645	0.649	0.626	0.681	0.640	0.594	0.656	0.649	0.686	0.497
# vars	900	7560	7560	2184	16744	16744	5168	38998	38998	12075	94300	94300	27621

Table 10 - Construction of the CoMFA model (3D QSAR), using the AM1-BCC semiempirical method.

AM1-BCC MODEL

COMFA – WITH FOCUS – CHARGES FROM AM1-BCC													
LEAVE-ONE-OUT (q^2)	**Without Focus**	**W03D0.5**	**W03D1.0**	**W03D1.5**	**W05D0.5**	**W05D1.0**	**W05D1.5**	**W07D0.5**	**W07D1.0**	**W07D1.5**	**W09D05**	**W09D10**	**W09D15**
Standard Error of Prediction for 6 components:	0.377	0.403	0.341	0.386	0.317	0.215	0.311	0.228	**0.134**	0.162	0.141	0.140	0.268
Crossvalidated R^2 for 6 components:	0.823	0.799	0.855	0.829	0.884	0.943	0.889	0.940	**0.980**	0.962	0.971	0.975	0.910
N components	**5**	**5**	**5**	**6**	**6**	**5**	**6**	**6**	**6**	**3**	**3**	**5**	**5**
NO VALIDATION (r^2)													
Standard Error of Estimate	0.088	0.081	0.074	0.075	0.064	0.063	0.065	0.058	0.048	0.085	0.087	0.089	0.137
R squared	0.990	0.992	0.993	0.994	0.995	0.995	0.995	0.996	0.997	0.990	0.989	0.990	0.977
1 COMFA (Steric) FRACTION	0.486	0.496	0.502	0.358	0.359	0.331	0.382	0.394	0.384	0.344	0.372	0.398	0.225
2 COMFA (Electrostatic) FRACTION	0.514	0.504	0.498	0.642	0.641	0.669	0.618	0.606	0.616	0.656	0.628	0.602	0.775
# vars	990	7560	7560	2184	16744	16744	5472	40145	40145	12075	92414	92414	27621

Table 11 - Construction of the CoMFA model (3D QSAR), using the HF 3-21G method.

HF 3-21G MODEL

COMFA – WITH FOCUS – CHARGES FROM HF3-21G													
LEAVE-ONE-OUT (q^2)	**Without Focus**	**W03D0.5**	**W03D1.0**	**W03D1.5**	**W05D0.5**	**W05D1.0**	**W05D1.5**	**W07D0.5**	**W07D1.0**	**W07D1.5**	**W09D05**	**W09D10**	**W09D15**
Standard Error of Prediction for 6 components:	0.617	0.556	0.535	0.702	0.560	0.517	0.475	0.432	**0.332**	0.404	0.386	0.350	0.394
Crossvalidated R^2 for 6 components:	0.417	0.527	0.563	0.434	0.580	0.643	0.676	0.732	**0.841**	0.750	0.772	0.813	0.762
N components	**2**	**2**	**2**	**6**	**4**	**4**	**3**	**3**	**3**	**2**	**2**	**2**	**2**
NO VALIDATION (r^2)													
Standard Error of Estimate	0.365	0.346	0.310	0.152	0.140	0.126	0.198	0.194	0.187	0.268	0.275	0.286	0.310
R squared	0.797	0.816	0.853	0.973	0.974	0.979	0.944	0.946	0.950	0.890	0.884	0.875	0.853
1 COMFA (Steric) FRACTION	0.400	0.402	0.449	0.248	0.320	0.345	0.451	0.447	0.505	0.508	0.484	0.490	0.545
2 COMFA (Electrostatic) FRACTION	0.600	0.598	0.551	0.752	0.680	0.655	0.549	0.553	0.495	0.492	0.516	0.510	0.455
# vars	900	6498	6498	2028	15600	15600	4624	35836	35836	11109	85050	85050	25200

Table 12 - Construction of the CoMFA model (3D QSAR), using the HF 6-311G method.

HF 6-311G MODEL

COMFA – WITH FOCUS – CHARGES FROM HF6-311G													
LEAVE-ONE-OUT (q^2)	**Without Focus**	**W03D0.5**	**W03D1.0**	**W03D1.5**	**W05D0.5**	**W05D1.0**	**W05D1.5**	**W07D0.5**	**W07D1.0**	**W07D1.5**	**W09D05**	**W09D10**	**W09D15**
Standard Error of Prediction for 6 components:	0.589	0.538	0.525	0.590	0.538	0.621	0.472	0.477	**0.348**	0.443	0.438	0.408	0.443
Crossvalidated R^2 for 6 components:	0.469	0.556	0.578	0.467	0.529	0.557	0.680	0.695	**0.826**	0.682	0.706	0.745	0.681
N components	**2**	**2**	**2**	**2**	**1**	**6**	**3**	**4**	**3**	**1**	**2**	**2**	**1**
NO VALIDATION (r^2)													
Standard Error of Estimate	0.341	0.320	0.299	0.374	0.451	0.171	0.237	0.157	**0.169**	0.342	0.284	0.291	0.394
R squared	0.822	0.844	0.863	0.786	0.669	0.967	0.920	0.967	**0.959**	0.810	0.877	0.871	0.748
1 COMFA (Steric) FRACTION	0.389	0.394	0.440	0.380	0.179	0.253	0.446	0.398	**0.479**	0.334	0.476	0.460	0.349
2 COMFA (Electrostatic) FRACTION	0.611	0.606	0.560	0.620	0.821	0.747	0.554	0.602	**0.521**	0.666	0.524	0.540	0.651
# vars	900	6498	6498	2028	15600	15600	4624	35836	**35836**	11109	85050	85050	25200

Table 13 - Construction of the CoMFA model (3D QSAR), using the DFT 6-311G method.

DFT HF 6-311G MODEL

COMFA – WITH FOCUS – CHARGES FROM DFT B3LYP - HF6-311G													
LEAVE-ONE-OUT (q^2)	**Without Focus**	**W03D0.5**	**W03D1.0**	**W03D1.5**	**W05D0.5**	**W05D1.0**	**W05D1.5**	**W07D0.5**	**W07D1.0**	**W07D1.5**	**W09D05**	**W09D10**	**W09D15**
Standard Error of Prediction for 6 components:	0.607	0.545	**0.531**	0.601	0.539	0.531	0.544	0.559	0.556	0.603	0.579	0.577	0.605
Crossvalidated R^2 for 6 components:	0.436	0.545	**0.569**	0.447	0.527	0.541	0.519	0.491	0.498	0.409	0.455	0.459	0.405
N components	**2**	**2**	**2**	**2**	**1**	**1**	**1**	**1**	1	**1**	**1**	**1**	**1**
NO VALIDATION (r^2)													
Standard Error of Estimate	0.358	0.340	**0.307**	0.386	0.447	0.449	0.466	0.482	0.488	0.524	0.512	0.519	0.532
R squared	0.803	0.823	**0.855**	0.772	0.676	0.672	0.647	0.623	0.613	0.554	0.574	0.562	0.540
1 COMFA (Steric) FRACTION	0.391	0.388	**0.439**	0.386	0.198	0.238	0.214	0.200	0.186	0.197	0.159	0.143	0.173
2 COMFA (Electrostatic) FRACTION	0.609	0.612	**0.561**	0.614	0.802	0.762	0.786	0.800	0.814	0.803	0.841	0.857	0.827
# vars	900	6498	**6498**	2028	15600	15600	4624	35836	35836	11109	85050	85050	25200

Table 14 - Construction of the CoMFA model (3D QSAR), using the RESP HF 6-311G method.

RESP HF 6-311G MODEL

COMFA – WITH FOCUS – CHARGES FROM RESP HF6-311G													
LEAVE-ONE-OUT (q^2)	**Without Focus**	**W03D0.5**	**W03D1.0**	**W03D1.5**	**W05D0.5**	**W05D1.0**	**W05D1.5**	**W07D0.5**	**W07D1.0**	**W07D1.5**	**W09D05**	**W09D10**	**W09D15**
Standard Error of Prediction for 6 components:	0.585	0.535	0.523	0.588	0.536	0.620	0.462	0.484	**0.340**	0.443	0.383	0.357	0.514
Crossvalidated R^2 for 6 components:	0.476	0.562	0.582	0.471	0.534	0.559	0.694	0.686	**0.834**	0.681	0.775	0.805	0.570
N components	**2**	**2**	**2**	**2**	**1**	**6**	**3**	**4**	**3**	**1**	**2**	**2**	**1**
NO VALIDATION (r^2)													
Standard Error of Estimate	0.342	0.320	0.299	0.373	0.449	0.165	0.233	0.155	**0.171**	0.343	0.220	0.232	0.366
R squared	0.821	0.843	0.863	0.787	0.673	0.969	0.922	0.968	**0.958**	0.808	0.926	0.917	0.782
1 COMFA (Steric) FRACTION	0.382	0.389	0.433	0.380	0.178	0.237	0.436	0.403	**0.481**	0.333	0.490	0.470	0.462
2 COMFA (Electrostatic) FRACTION	0.618	0.611	0.567	0.620	0.822	0.763	0.564	0.597	**0.519**	0.667	0.510	0.530	0.538
# vars	900	6498	6498	2028	15600	15600	4624	35836	**35836**	11109	278318	278318	85050

ANNEX III – CoMSIA (QSAR-3D)

Table 15 - Construction of the CoMSIA model (3D QSAR), using the PM7 semiempirical method.

PM7 MODEL

COMSIA - SEM FOCAGEM - COM SEPARAÇÃO - TODOS OS DESCRITORES - PM7					
PM7	S/E/H/D/A	S/E/H/D	S/E/D	E/D	**S/E/D - W09D15**
		LEAVE-ONE-OUT (q^2)			
q^2	0,465	0,500	0,533	0,514	0,22
Erro padrão da Predição	0,656	0,634	0,613	0,625	0,945
N componentes	5	5	5	5	6
		NO VALIDATION (r^2)			
r^2	0,982	0,984	0,969	0,967	0,980
Erro padrão da Estimativa	0,122	0,115	0,158	0,162	0,133
doador	0,242	0,254	0,258	0,279	0,255
aceptor	0,047	-	-	-	-
hidrofóbico	0,255	0,266	-	-	-
estérico	0,077	0,081	0,121	-	0,211
eletrostático	0,380	0,399	0,620	0,721	0,535

C/ 4 tipos de descritores	S/E/H/A	S/E/H/D	S/E/D/A	E/H/D/A	S/H/D/A
	LEAVE-ONE-OUT (q2)				
q2 LOO	0,328	0,500	0,491	0,449	0,241
SEP	0,663	0,634	0,666	0,666	0,814
N components	2	5	6	5	6
	NO VALIDATION (r2)				
r2	0,874	0,984	0,980	0,982	0,985
SEE	0,287	0,115	0,133	0,120	0,116
donor		0,254	0,249	0,247	0,314
acceptor	0,076		0,071	0,051	0,089
hydrophobic	0,354	0,266		0,280	0,448
steric	0,086	0,081	0,119		0,148
eletrostatic	0,484	0,399	0,561	0,423	

CoMSIA – Without Focus – PM7

C/ 3 tipos de descritores	H/D/A	S/D/A	E/D/A	S/H/D	E/H/D	S/E/D	S/H/A	E/H/A	S/E/A	S/E/H
LEAVE-ONE-OUT (q2)										
q2 LOO	0,164	0,156	0,454	0,201	0,482	**0,533**	-0,026	0,318	0,364	0,373
SEP	0,717	0,721	0,663	0,802	0,646	**0,613**	0,795	0,668	0,752	0,739
N components	1	1	5	5	5	**5**	1	2	2	6
NO VALIDATION (r2)										
r2	0,496	0,472	0,962	0,978	0,984	**0,969**	0,513	0,862	0,827	0,983
SEE	0,557	0,570	0,174	0,132	0,113	**0,158**	0,547	0,301	0,336	0,120
donor	0,688	0,845	0,265	0,346	0,261	**0,258**				
acceptor	0,070	0,086	0,076				0,189	0,088	0,124	
hydrophobic	0,243			0,486	0,293		0,658	0,382		0,344
steric		0,070		0,168		**0,121**	0,153		0,142	0,104
eletrostatic			0,659		0,446	**0,620**		0,530	0,734	0,552

C/ 2 tipos de descritores	D/A	S/D	E/D	H/D	H/A	S/A	E/A	S/H	E/H	S/E
LEAVE-ONE-OUT (q2)										
q2 LOO	0,171	0,235	**0,514**	0,173	-0,024	-0,217	0,327	0,005	0,356	0,501
SEP	0,719	0,730	**0,625**	0,713	0,794	0,865	0,685	0,782	0,670	0,571
N components	2	3	**5**	1	1	1	3	1	3	2
NO VALIDATION (r2)										
r2	0,485	0,685	**0,967**	0,481	0,497	0,370	0,921	0,508	0,936	0,833
SEE	0,580	0,468	**0,162**	0,565	0,556	0,622	0,235	0,550	0,211	0,331
donor	0,866	0,596	**0,279**	0,739						
acceptor	0,134				0,223	0,552	0,141			
hydrophobic				0,261	0,777			0,811	0,410	
steric		0,404				0,448		0,189		0,169
eletrostatic			**0,721**				0,859		0,590	0,831

C/ 1 tipo de descritor	S	E	H	D	A
LEAVE-ONE-OUT (q2)					
q2 LOO	0,039	0,457	0,001	0,262	-0,231
SEP	0,793	0,596	0,784	0,695	0,870
N components	2	2	1	2	1
NO VALIDATION (r2)					
r2	0,498	0,810	0,472	0,464	0,667
SEE	0,573	0,352	0,570	0,592	0,277
donor				1,000	
acceptor					1,000
hydrophobic			1		
steric	1				
eletrostatic		1			

CoMSIA MODEL – With Focus – PM7

COMSIA - COM SEPARAÇÃO - COM FOCAGEM - PM7													
PM7	**Sem focagem**	S/E/D - W03D05	S/E/D - W03D10	S/E/D - W03D15	S/E/D -W05D05	S/E/D - W05D10	S/E/D - W05D15	S/E/D -W07D05	S/E/D - W07D10	**S/E/D - W07D15**	S/E/D -W09D05	S/E/D - W09D10	**S/E/D - W09D15**
LEAVE-ONE-OUT (q2)													
SEP	**0,533**	0,549	0,437	0,416	0,395	0,344	0,299	0,326	0,23	**0,224**	0,251	0,232	**0,22**
q2 LOO	**0,613**	0,654	0,745	0,768	0,791	0,841	0,88	0,878	0,934	**0,933**	0,928	0,938	**0,945**
N components	**5**	6	4	4	4	4	4	6	5	**4**	6	6	**6**
NO VALIDATION (r2)													
r2	**0,969**	0,977	0,966	0,963	0,956	0,956	0,960	0,976	0,975	**0,975**	0,98	0,98	**0,980**
SEE	**0,158**	0,141	0,159	0,166	0,181	0,182	0,172	0,144	0,14	**0,137**	0,132	0,13	**0,133**
doador	**0,258**	0,245	0,240	0,226	0,243	0,243	0,274	0,274	0,277	**0,278**	0,263	0,264	**0,255**
steric	**0,121**	0,154	0,148	0,167	0,185	0,189	0,215	0,258	0,256	**0,217**	0,238	0,235	**0,211**
eletrostático	**0,620**	0,601	0,613	0,607	0,572	0,568	0,51	0,469	0,467	**0,504**	0,5	0,501	**0,535**

CoMSIA – Without Focus – RM1

Table 16 - Construction of the CoMSIA model (3D QSAR), using the RM1 semiempirical method.

COMSIA - SEM FOCAGEM - COM SEPARAÇÃO - TODOS OS DESCRITORES - RM1					
RM1	S/E/H/D/A	S/E/H/D	S/E/D	E/D	**E/D - W09D10**
LEAVE-ONE-OUT (q^2)					
q^2	0,459	0,482	0,513	0,514	**0,737**
Erro padrão da Predição	0,687	0,672	0,626	0,582	**0,415**
N componentes	6	6	5	3	**2**
NO VALIDATION (r^2)					
r^2	0,987	0,988	0,967	0,881	**0,864**
Erro padrão da Estimativa	0,104	0,102	0,163	0,288	**0,298**
doador	0,255	0,265	0,266	0,350	**0,291**
aceptor	0,044				-
hidrofóbico	0,253	0,264			-
estérico	0,075	0,079	0,123		-
eletrostático	0,374	0,392	0,611	0,650	**0,709**

C/ 4 tipos de descritores	S/E/H/A	S/E/H/D	S/E/D/A	E/H/D/A	S/H/D/A
LEAVE-ONE-OUT (q2)					
q2 LOO	0,328	0,482	0,478	0,439	0,241
SEP	0,663	0,672	0,648	0,699	0,814
N components	2	6	5	6	6
NO VALIDATION (r2)					
r2	0,859	0,988	0,966	0,987	0,985
SEE	0,304	0,102	0,164	0,106	0,116
donor		0,265	0,254	0,259	0,314
acceptor	0,081		0,064	0,048	0,089
hydrophobic	0,326	0,264		0,280	0,448
steric	0,086	0,079	0,112		0,148
eletrostatic	0,507	0,392	0,570	0,413	

C/ 3 tipos de descritores	H/D/A	S/D/A	E/D/A	S/H/D	E/H/D	S/E/D	S/H/A	E/H/A	S/E/A	S/E/H
LEAVE-ONE-OUT (q2)										
q2 LOO	0,164	0,156	0,443	0,201	0,462	**0,513**	-0,026	0,303	0,355	0,371
SEP	0,717	0,721	0,645	0,802	0,684	**0,626**	0,795	0,675	0,670	0,662
N components	1	1	4	5	6	**5**	1	2	3	3
NO VALIDATION (r2)										
r2	0,496	0,472	0,929	0,978	0,988	**0,967**	0,513	0,849	0,927	0,941
SEE	0,557	0,570	0,230	0,132	0,104	**0,163**	0,547	0,314	0,226	0,203
donor	0,688	0,845	0,301	0,346	0,272	**0,266**				
acceptor	0,070	0,086	0,064				0,189	0,094	0,115	
hydrophobic	0,243			0,486	0,293		0,658	0,357		0,344
steric		0,070		0,168		**0,123**	0,153		0,135	0,103
eletrostatic			0,635		0,435	**0,611**		0,549	0,750	0,553

C/ 2 tipos de descritores	D/A	S/D	E/D	H/D	H/A	S/A	E/A	S/H	E/H	S/E
LEAVE-ONE-OUT (q2)										
q2 LOO	0,171	0,235	**0,514**	0,173	-0,024	-0,217	0,311	0,005	0,355	0,451
SEP	0,736	0,730	**0,582**	0,713	0,794	0,865	0,693	0,782	0,670	0,599
N components	2	3	**3**	1	1	1	3	1	3	2
NO VALIDATION (r2)										
r2	0,485	0,685	**0,881**	0,481	0,497	0,370	0,907	0,508	0,942	0,862
SEE	0,580	0,468	**0,288**	0,565	0,556	0,622	0,255	0,550	0,201	0,300
donor	0,866	0,596	**0,350**	0,739						
acceptor	0,134				0,223	0,552	0,146			
hydrophobic				0,261	0,777			0,811	0,383	
steric		0,404				0,448		0,189		0,159
eletrostatic			**0,650**				0,854		0,617	0,841

C/ 1 tipo de descritor	S	E	H	D	A
LEAVE-ONE-OUT (q2)					
q2 LOO	0,039	0,370	0,001	0,262	-0,231
SEP	0,793	0,642	0,784	0,695	0,870
N components	2	2	1	2	1
NO VALIDATION (r2)					
r2	0,498	0,840	0,472	0,464	0,277
SEE	0,573	0,323	0,570	0,592	0,667
donor				1,000	
acceptor					1,000
hydrophobic			1		
steric	1				
eletrostatic		1			

CoMSIA – With Focus – RM1

COMSIA - COM SEPARAÇÃO - COM FOCAGEM - RM1													
RM1	**Without Focus**	E/D - W03D05	E/D - W03D10	E/D - W03D15	E/D -W05D05	E/D - W05D10	E/D - W05D15	E/D -W07D05	E/D - W07D10	E/D - W07D15	E/D -W09D05	E/D - W09D10	E/D - W09D15
LEAVE-ONE-OUT (q2)													
SEP	**0,582**	0,51	0,451	0,485	0,518	0,461	0,523	0,509	0,479	0,532	0,462	**0,415**	0,479
q2 LOO	**0,514**	0,627	0,688	0,64	0,615	0,674	0,686	0,628	0,649	0,621	0,714	**0,737**	0,671
N components	**3**	3	2	2	3	2	6	3	2	4	4	**2**	3
NO VALIDATION (r2)													
r2	**0,881**	0,910	0,871	0,838	0,882	0,855	0,958	0,859	0,832	0,900	0,89	**0,864**	0,846
SEE	**0,288**	0,251	0,290	0,325	0,286	0,308	0,191	0,313	0,331	0,273	0,287	**0,298**	0,328
donor	**0,350**	0,294	0,357	0,351	0,246	0,279	0,249	0,19	0,242	0,23	0,247	**0,291**	0,246
eletrostatic	**0,650**	0,706	0,643	0,649	0,754	0,721	0,751	0,810	0,758	0,770	0,753	**0,709**	0,754

CoMSIA MODEL – Without Focus – AM1-BCC

Table 17 - Construction of the CoMSIA model (3D QSAR), using the AM1-BCC semiempirical method.

COMSIA - SEM FOCAGEM - COM SEPARAÇÃO - TODOS OS DESCRITORES -					
AM1-BCC	S/E/H/D/A	E/H/D/A	E/H/D	E/D	E/H/D/A - W07D10
		LEAVE-ONE-OUT (q^2)			
q^2	0,836	0,840	0,812	0,773	**0,95**
Erro padrão da Predição	0,378	0,373	0,405	0,427	**0,209**
N componentes	6	6	6	5	**6**
		NO VALIDATION (r^2)			
r^2	0,990	0,991	0,988	0,971	**0,991**
Erro padrão da Estimativa	0,092	0,091	0,103	0,152	**0,088**
doador	0,085	0,087	0,089	0,191	**0,053**
aceptor	0,047	0,049			**0,059**
hidrofóbico	0,322	0,341	0,359		**0,355**
estérico	0,057				-
eletrostático	0,490	0,523	0,552	0,809	0,533

C/ 4 tipos de descritores	S/E/H/A	S/E/H/D	S/E/D/A	E/H/D/A	S/H/D/A
LEAVE-ONE-OUT (q2)					
q2 LOO	0,784	0,810	0,810	0,840	0,613
SEP	0,434	0,407	0,391	0,373	0,581
N components	6	6	5	6	6
NO VALIDATION (r2)					
r2	0,987	0,988	0,980	0,991	0,922
SEE	0,108	0,103	0,126	0,091	0,261
donor		0,087	0,136	0,087	0,117
acceptor	0,053		0,076	0,049	0,110
hydrophobic	0,375	0,340		0,341	0,644
steric	0,057	0,058	0,101		0,129
eletrostatic	0,514	0,515	0,686	0,523	

C/ 3 tipos de descritores	H/D/A	S/D/A	E/D/A	S/H/D	E/H/D	S/E/D	S/H/A	E/H/A	S/E/A	S/E/H
LEAVE-ONE-OUT (q2)										
q2 LOO	0,618	0,626	0,810	0,434	0,812	**0,769**	0,566	0,788	0,728	0,750
SEP	0,554	0,549	0,391	0,675	0,405	**0,431**	0,615	0,430	0,487	0,466
N components	5	5	5	5	6	**5**	6	6	6	6
NO VALIDATION (r2)										
r2	0,909	0,894	0,977	0,876	0,988	**0,977**	0,907	0,987	0,991	0,983
SEE	0,270	0,291	0,136	0,316	0,103	**0,136**	0,284	0,106	0,089	0,120
donor	0,109	0,311	0,163	0,113	0,089	**0,153**				
acceptor	0,124	0,293	0,089				0,127	0,056	0,11	
hydrophobic	0,767			0,718	0,359		0,755	0,399		0,402
steric		0,396		0,168		**0,113**	0,118		0,126	0,061
eletrostatic			0,748		0,552	**0,734**		0,545	0,764	0,537

C/ 2 tipos de descritores	D/A	S/D	E/D	H/D	H/A	S/A	E/A	S/H	E/H	S/E
LEAVE-ONE-OUT (q2)										
q2 LOO	0,542	0,241	**0,773**	0,425	0,531	0,702	0,736	0,413	0,750	0,652
SEP	0,565	0,813	**0,427**	0,680	0,640	0,490	0,480	0,716	0,467	0,550
N components	3	6	**5**	5	6	5	6	6	6	6
NO VALIDATION (r2)										
r2	0,764	0,844	**0,971**	0,883	0,906	0,894	0,985	0,874	0,984	0,986
SEE	0,406	0,369	**0,152**	0,307	0,287	0,292	0,116	0,331	0,120	0,110
donor	0,482	0,384	**0,191**	0,122						
acceptor	0,518				0,141	0,442	0,133			
hydrophobic				0,878	0,859			0,838	0,430	
steric		0,616				0,558		0,162		0,136
eletrostatic			**0,809**				0,867		0,570	0,864

C/ 1 tipo de descritor	S	E	H	D	A
LEAVE-ONE-OUT (q2)					
q2 LOO	0,622	0,663	0,398	0,170	0,686
SEP	0,574	0,542	0,671	0,761	0,468
N components	6	6	4	3	3
NO VALIDATION (r2)					
r2	0,915	0,979	0,823	0,524	0,800
SEE	0,272	0,137	0,364	0,576	0,374
donor				1,000	
acceptor					1,000
hydrophobic			1		
steric	1				
eletrostatic		1			

CoMSIA – With Focus – AM1-BCC

COMSIA - COM SEPARAÇÃO - COM FOCAGEM													
AM1BCC	**Sem focagem**	E/H/D/A - W03D05	E/H/D/A - W03D10	E/H/D/A - W03D15	E/H/D/A -W05D05	E/H/D/A - W05D10	E/H/D/A - W05D15	E/H/D/A-W07D05	E/H/D/A - W07D10	E/H/D/A - W07D15	E/H/D/A -W09D05	E/H/D/A- W09D10	E/H/D/A - W09D15
LEAVE-ONE-OUT (q2)													
SEP	**0,840**	0,821	0,855	0,857	0,871	0,919	0,924	0,939	**0,95**	0,944	**0,954**	0,95	**0,966**
q2 LOO	**0,373**	0,395	0,356	0,353	0,336	0,266	0,247	0,23	**0,209**	0,221	**0,2**	0,209	**0,171**
N components	**6**	6	6	6	6	6	5	6	**6**	6	**6**	6	**6**
NO VALIDATION (r2)													
r2	**0,991**	0,992	0,992	0,992	0,992	0,991	0,990	0,991	**0,991**	0,991	0,991	0,992	0,991
SEE	**0,091**	0,082	0,083	0,085	0,085	0,087	0,089	0,09	**0,088**	0,087	0,087	0,086	0,087
donor	**0,087**	0,070	0,065	0,055	0,061	0,061	0,053	0,055	**0,053**	0,058	0,068	0,073	0,065
aceptor	**0,049**	0,037	0,044	0,038	0,042	0,049	0,037	0,048	**0,059**	0,060	0,065	0,069	0,083
hydrophobic	**0,341**	0,362	0,355	0,368	0,354	0,35	0,359	0,359	**0,355**	0,35	0,338	0,335	0,281
eletrostatic	0,523	0,531	0,536	0,54	0,542	0,54	0,551	0,538	0,533	0,532	0,53	0,522	0,572

CoMSIA MODEL – Without Focus – Gasteiger Marsili

Table 18 - Construction of the CoMSIA model (3D QSAR), using the Gasteiger Marsili empirical method.

COMSIA - SEM FOCAGEM - COM SEPARAÇÃO - TODOS OS DESCRITORES - GASTEIGER MARSILI					
GASTEIGER- MARSILI	S/E/H/D/A	S/E/H/A	E/H/A	E/H	**E/H - W09D15**
		LEAVE-ONE-OUT (q^2)			
q^2	0,674	0,807	0,806	0,769	**0,956**
Erro padrão da Predição	0,533	0,410	0,411	0,448	**0,195**
N componentes	6	6	6	6	**6**
		NO VALIDATION (r^2)			
r^2	0,984	0,990	0,990	0,987	**0,987**
Erro padrão da Estimativa	0,117	0,095	0,092	0,106	**0,106**
donor	0,238				**-**
aceptor	0,031	0,066	0,071		**-**
hydrophobic	0,406	0,523	0,561	0,612	**0,585**
steric	0,072	0,066			**-**
eletrostatic	0,253	0,344	0,368	0,388	**0,415**

C/ 4 tipos de descritores	S/E/H/A	S/E/H/D	S/E/D/A	E/H/D/A	S/H/D/A
LEAVE-ONE-OUT (q2)					
q2 LOO	0,807	0,654	0,431	0,686	0,525
SEP	0,410	0,549	0,704	0,523	0,643
N components	6	6	6	6	6
NO VALIDATION (r2)					
r2	0,990	0,984	0,938	0,986	0,910
SEE	0,095	0,117	0,232	0,112	0,280
donor		0,248	0,304	0,238	0,343
acceptor	0,066		0,077	0,034	0,043
hydrophobic	0,523	0,419		0,442	0,513
steric	0,066	0,074	0,162		0,101
eletrostatic	0,344	0,259	0,457	0,286	

C/ 3 tipos de descritores	H/D/A	S/D/A	E/D/A	S/H/D	E/H/D	S/E/D	S/H/A	E/H/A	S/E/A	S/E/H
LEAVE-ONE-OUT (q2)										
q2 LOO	0,596	0,352	0,420	0,493	0,664	0,318	0,583	0,806	0,723	0,772
SEP	0,593	0,751	0,683	0,665	0,541	0,771	0,603	0,411	0,439	0,446
N components	6	6	5	6	6	6	6	6	3	6
NO VALIDATION (r2)										
r2	0,919	0,877	0,272	0,906	0,985	0,925	0,907	0,990	0,911	0,987
SEE	0,265	0,327	0,908	0,286	0,113	0,255	0,285	0,092	0,249	0,108
donor	0,375	0,493	0,339	0,366	0,249	0,332				
acceptor	0,049	0,166	0,083				0,109	0,071	0,137	
hydrophobic	0,576			0,531	0,457		0,776	0,561		0,566
steric		0,341		0,103		0,182	0,115		0,209	0,071
eletrostatic			0,579		0,293	0,487		0,368	0,655	0,363

C/ 2 tipos de descritores	D/A	S/D	E/D	H/D	H/A	S/A	E/A	S/H	E/H	S/E
LEAVE-ONE-OUT (q2)										
q2 LOO	0,200	-0,074	0,298	0,560	0,567	0,686	0,700	0,469	0,769	0,655
SEP	0,802	0,967	0,752	0,619	0,590	0,502	0,473	0,681	0,448	0,490
N components	5	6	5	6	5	5	4	6	6	3
NO VALIDATION (r2)										
r2	0,723	0,810	0,887	0,914	0,893	0,888	0,925	0,895	0,987	0,878
SEE	0,472	0,406	0,301	0,274	0,294	0,300	0,237	0,303	0,106	0,292
donor	0,730	0,598	0,384	0,397						
acceptor	0,270				0,115	0,435	0,241			
hydrophobic				0,603	0,885			0,852	0,612	
steric		0,402				0,565		0,148		0,254
eletrostatic			0,616				0,759		0,388	0,746

C/ 1 tipo de descritor	S	E	H	D	A
LEAVE-ONE-OUT (q2)					
q2 LOO	0,554	0,533	0,474	-0,298	0,691
SEP	0,623	0,591	0,650	1,022	0,450
N components	6	4	5	5	2
NO VALIDATION (r2)					
r2	0,903	0,884	0,870	0,492	0,753
SEE	0,290	0,295	0,323	0,639	0,402
donor				1,000	
acceptor					1,000
hydrophobic			1		
steric	1				
eletrostatic		1			

CoMSIA – With Focus – Gasteiger Marsili

COMSIA - COM SEPARAÇÃO - COM FOCAGEM - GASTEIGER MARSILI													
MARSILI	**Sem focagem**	E/H- W03D05	E/H - W03D10	E/H - W03D15	E/H -W05D05	E/H - W05D10	E/H - W05D15	E/H -W07D05	E/H - W07D10	E/H - W07D15	E/H -W09D05	E/H - W09D10	E/H - W09D15
LEAVE-ONE-OUT (q2)													
SEP	**0,769**	0,773	0,76	0,761	0,789	0,821	0,819	0,891	0,899	0,916	0,926	0,941	**0,956**
q2 LOO	**0,448**	0,412	0,423	0,422	0,397	0,365	0,381	0,296	0,285	0,242	0,253	0,228	**0,195**
N components	**6**	4	4	4	4	4	5	5	5	3	6	6	**6**
NO VALIDATION (r2)													
r2	**0,987**	0,984	0,981	0,982	0,985	0,985	0,986	0,984	0,983	0,970	0,989	0,988	**0,987**
SEE	**0,106**	0,109	0,118	0,115	0,105	0,106	0,107	0,112	0,119	0,144	0,1	0,101	**0,106**
hydrophobic	**0,612**	0,585	0,585	0,574	0,586	0,577	0,575	0,613	0,623	0,617	0,473	0,482	**0,585**
eletrostatic	**0,388**	0,415	0,415	0,426	0,414	0,423	0,425	0,387	0,377	0,383	0,527	0,518	**0,415**

CoMSIA – Without Focus – Gasteiger Hückel

Table 19 - Construction of the CoMSIA model (3D QSAR), using the empirical Gasteiger Hückel method.

COMSIA - SEM FOCAGEM - COM SEPARAÇÃO - TODOS OS DESCRITORES - GASTEIGER-HÜCKEL					
GASTEIGER-HÜCKEL	S/E/H/D/A	S/E/H/A	E/H/A	E/H	**E/H - W09D15**
		LEAVE-ONE-OUT (q^2)			
q^2	0,697	0,831	0,828	0,793	**0,931**
Erro padrão da Predição	0,514	0,384	0,388	0,425	**0,219**
N componentes	6	6	6	6	**3**
		NO VALIDATION (r^2)			
r^2	0,982	0,989	0,093	0,987	**0,973**
Erro padrão da Estimativa	0,124	0,098	0,990	0,105	**0,137**
donor	0,235				**-**
aceptor	0,030	0,063	0,068		**-**
hydrophobic	0,386	0,464	0,496	0,536	**0,619**
steric	0,069	0,062			**-**
eletrostatic	0,279	0,411	0,437	0,464	**0,381**

C/ 4 tipos de descritores	S/E/H/A	S/E/H/D	S/E/D/A	E/H/D/A	S/H/D/A
LEAVE-ONE-OUT (q2)					
q2 LOO	0,831	0,682	0,539	0,702	0,525
SEP	0,384	0,527	0,634	0,509	0,643
N components	6	6	6	6	6
NO VALIDATION (r2)					
r2	0,989	0,982	0,956	0,984	0,910
SEE	0,098	0,126	0,197	0,118	0,280
donor		0,245	0,268	0,234	0,343
acceptor	0,063		0,068	0,033	0,043
hydrophobic	0,464	0,399		0,423	0,513
steric	0,062	0,072	0,151		0,101
eletrostatic	0,411	0,284	0,513	0,310	

C/ 3 tipos de descritores	H/D/A	S/D/A	E/D/A	S/H/D	E/H/D	S/E/D	S/H/A	E/H/A	S/E/A	S/E/H
LEAVE-ONE-OUT (q2)										
q2 LOO	0,596	0,352	0,513	0,493	0,682	0,455	0,583	0,828	0,777	0,798
SEP	0,593	0,751	0,651	0,665	0,526	0,689	0,603	0,388	0,408	0,419
N components	6	6	6	6	6	6	6	6	4	6
NO VALIDATION (r2)										
r2	0,919	0,877	0,952	0,906	0,983	**0,947**	0,907	0,093	0,939	0,986
SEE	0,265	0,327	0,204	0,286	0,120	**0,214**	0,285	0,990	0,214	0,110
donor	0,375	0,493	0,299	0,366	0,245	**0,291**				
acceptor	0,049	0,166	0,089				0,109	0,068	0,122	
hydrophobic	0,576			0,531	0,438		0,776	0,496		0,498
steric		0,341		0,103		**0,164**	0,115		0,162	0,066
eletrostatic			0,612		0,317	**0,544**		0,437	0,716	0,436

C/ 2 tipos de descritores	D/A	S/D	E/D	H/D	H/A	S/A	E/A	S/H	E/H	S/E
LEAVE-ONE-OUT (q2)										
q2 LOO	0,200	-0,074	0,396	0,560	0,567	0,686	0,743	0,469	0,793	0,711
SEP	0,802	0,967	0,726	0,619	0,590	0,502	0,423	0,681	0,425	0,464
N components	5	6	6	6	5	5	3	6	6	4
NO VALIDATION (r2)										
r2	0,723	0,810	0,941	0,914	0,893	0,888	0,924	0,895	0,987	0,920
SEE	0,472	0,406	0,228	0,274	0,294	0,300	0,230	0,303	0,105	0,245
donor	0,730	0,598	0,330	0,397						
acceptor	0,270				0,115	0,435	0,141			
hydrophobic				0,603	0,885			0,852	0,536	
steric		0,402				0,565		0,148		0,189
eletrostatic			0,670				0,859		0,464	0,811

C/ 1 tipo de descritor	S	E	H	D	A
LEAVE-ONE-OUT (q2)					
q2 LOO	0,554	0,687	0,474	-0,298	0,691
SEP	0,623	0,467	0,650	1,022	0,450
N components	6	3	5	5	2
NO VALIDATION (r2)					
r2	0,903	0,899	0,870	0,492	0,753
SEE	0,290	0,265	0,323	0,639	0,402
donor				1,000	
acceptor					1,000
hydrophobic			1		
steric	1				
eletrostatic		1			

CoMSIA – With Focus – Gasteiger-Hückel

COMSIA - COM SEPARAÇÃO - COM FOCAGEM - GASTEIGER-HÜCKEL													
GASTEIGER-HÜCKEL	**Sem focagem**	E/H - W03D05	E/H - W03D10	E/H - W03D15	E/H -W05D05	E/H - W05D10	E/H - W05D15	E/H -W07D05	E/H - W07D10	E/H - W07D15	E/H -W09D05	E/H - W09D10	**E/H - W09D15**
LEAVE-ONE-OUT (q2)													
SEP	**0,793**	0,819	0,824	0,839	0,831	0,839	0,857	0,886	0,897	0,913	0,908	0,907	**0,931**
q2 LOO	**0,425**	0,381	0,377	0,36	0,344	0,347	0,327	0,292	0,277	0,247	0,262	0,264	**0,219**
N components	**6**	5	5	5	3	4	4	4	4	3	4	4	**3**
NO VALIDATION (r2)													
r2	**0,987**	0,987	0,987	0,987	0,982	0,983	0,982	0,98	0,98	0,973	0,977	0,978	**0,973**
SEE	**0,105**	0,102	0,103	0,102	0,111	0,113	0,115	0,121	0,123	0,136	0,131	0,129	**0,137**
hydrophobic	**0,536**	0,556	0,554	0,558	0,558	0,561	0,555	0,59	0,615	0,607	0,592	0,613	**0,619**
eletrostatic	**0,464**	0,444	0,446	0,442	0,442	0,439	0,445	0,410	0,385	0,393	0,408	0,387	**0,381**

CoMSIA MODEL – Without Focus – MMFF94

Table 20 - Construction of the CoMSIA model (3D QSAR), using the MMFF-94 empirical method.

COMSIA - SEM FOCAGEM - COM SEPARAÇÃO - TODOS OS DESCRITORES - MMFF94					
MMFF94	S/E/H/D/A	S/E/H/A	**E/H/A**	S/A	**E/H/A - W09D15**
		LEAVE-ONE-OUT (q^2)			
q^2	0,590	0,691	0,697	0,686	**0,94**
Erro padrão da Predição	0,598	0,519	0,514	0,502	**0,205**
N componentes	6	6	6	5	**3**
		NO VALIDATION (r^2)			
r^2	0,986	0,984	0,984	0,888	**0,974**
Erro padrão da Estimativa	0,111	0,119	0,118	0,300	**0,134**
doador	0,241				-
aceptor	0,024	0,046	0,049	0,435	**0,072**
hidrofóbico	0,247	0,329	0,352		**0,482**
estérico	0,055	0,055		0,565	**-**
eletrostático	0,432	0,569	0,599		**0,446**

COMSIA - SEM FOCAGEM - COM SEPARAÇÃO - TODOS OS DESCRITORES - MMFF94					
MMFF94	S/E/H/D/A	S/E/H/A	**E/H/A**	S/A	**E/H/A - W09D15**
		LEAVE-ONE-OUT (q^2)			
q^2	0,590	0,691	0,697	0,686	**0,94**
Erro padrão da Predição	0,598	0,519	0,514	0,502	**0,205**
N componentes	6	6	6	5	**3**
		NO VALIDATION (r^2)			
r^2	0,986	0,984	0,984	0,888	**0,974**
Erro padrão da Estimativa	0,111	0,119	0,118	0,300	**0,134**
donor	0,241				-
aceptor	0,024	0,046	0,049	0,435	**0,072**
hydrophobic	0,247	0,329	0,352		**0,482**
steric	0,055	0,055		0,565	**-**
eletrostatic	0,432	0,569	0,599		**0,446**

C/ 4 tipos de descritores	S/E/H/A	S/E/H/D	S/E/D/A	E/H/D/A	S/H/D/A
LEAVE-ONE-OUT (q2)					
q2 LOO	0,691	0,570	0,439	0,582	0,525
SEP	0,519	0,612	0,699	0,603	0,643
N components	6	6	6	6	6
NO VALIDATION (r2)					
r2	0,984	0,984	0,975	0,983	0,910
SEE	0,119	0,117	0,147	0,120	0,280
donor		0,248	0,254	0,243	0,343
acceptor	0,046		0,035	0,025	0,043
hydrophobic	0,329	0,255		0,269	0,513
steric	0,055	0,056	0,092		0,101
eletrostatic	0,569	0,441	0,618	0,463	

C/ 3 tipos de descritores	H/D/A	S/D/A	E/D/A	S/H/D	E/H/D	S/E/D	S/H/A	E/H/A	S/E/A	S/E/H
LEAVE-ONE-OUT (q2)										
q2 LOO	0,596	0,352	0,451	0,493	0,557	0,387	0,583	0,697	0,594	0,657
SEP	0,593	0,751	0,691	0,665	0,621	0,731	0,603	0,514	0,571	0,547
N components	6	6	6	6	6	6	6	6	5	6
NO VALIDATION (r2)										
r2	0,919	0,877	0,975	0,906	0,983	0,973	0,907	0,984	0,956	0,980
SEE	0,265	0,327	0,149	0,286	0,123	0,153	0,285	0,118	0,189	0,131
donor	0,375	0,493	0,260	0,366	0,251	0,267				
acceptor	0,049	0,166	0,039				0,109	0,049	0,075	
hydrophobic	0,576			0,531	0,277		0,776	0,352		0,350
steric		0,341		0,103		0,097	0,115		0,116	0,058
eletrostatic			0,700		0,471	0,636		0,599	0,809	0,592

C/ 2 tipos de descritores	D/A	S/D	E/D	H/D	H/A	S/A	E/A	S/H	E/H	S/E
LEAVE-ONE-OUT (q2)										
q2 LOO	0,200	-0,074	0,389	0,560	0,567	0,686	0,598	0,469	0,662	0,528
SEP	0,802	0,967	0,729	0,619	0,590	0,502	0,569	0,681	0,543	0,616
N components	5	6	6	6	5	5	5	6	6	5
NO VALIDATION (r2)										
r2	0,723	0,810	0,972	0,914	0,893	0,888	0,962	0,895	0,980	0,945
SEE	0,472	0,406	0,157	0,274	0,294	0,300	0,175	0,303	0,131	0,211
donor	0,730	0,598	0,278	0,397						
acceptor	0,270				0,115	0,435	0,096			
hydrophobic				0,603	0,885			0,852	0,378	
steric		0,402				0,565		0,148		0,130
eletrostatic			0,722				0,904		0,622	0,870

C/ 1 tipo de descritor	S	E	H	D	A
LEAVE-ONE-OUT (q2)					
q2 LOO	0,554	0,515	0,474	-0,298	0,691
SEP	0,623	0,624	0,650	1,022	0,450
N components	6	5	5	5	2
NO VALIDATION (r2)					
r2	0,903	0,948	0,870	0,492	0,753
SEE	0,290	0,204	0,323	0,639	0,402
donor				1,000	
acceptor					1,000
hydrophobic			1		
steric	1				
eletrostatic		1			

CoMSIA – With Focus – MMFF94

COMSIA - COM SEPARAÇÃO - COM FOCAGEM - MMFF94													
MMFF94	**Sem focagem**	E/H/A - W03D05	E/H - W03D10	E/H - W03D15	E/H -W05D05	E/H - W05D10	E/H - W05D15	E/H -W07D05	E/H - W07D10	E/H - W07D15	E/H -W09D05	E/H - W09D10	**E/H/A - W09D15**
LEAVE-ONE-OUT (q2)													
SEP	**0,697**	0,729	0,762	0,795	0,819	0,824	0,834	0,868	0,91	0,909	0,911	0,916	**0,94**
q2 LOO	**0,514**	0,486	0,437	0,423	0,368	0,351	0,34	0,293	0,243	0,244	0,242	0,243	**0,205**
N components	**6**	6	5	6	4	3	3	2	2	2	2	3	**3**
NO VALIDATION (r2)													
r2	**0,984**	0,988	0,987	0,989	0,984	0,979	0,979	0,957	0,942	0,937	0,934	0,965	**0,974**
SEE	**0,118**	0,101	0,101	0,096	0,110	0,122	0,122	0,168	0,195	0,203	0,207	0,156	**0,134**
aceptor	**0,049**	0,039	0,034	0,034	0,026	0,027	0,021	0,017	0,022	0,018	0,017	0,115	**0,072**
hydrophobic	**0,352**	0,404	0,408	0,409	0,384	0,360	0,389	0,412	0,437	0,430	0,455	0,420	**0,482**
eletrostatic	**0,599**	0,557	0,558	0,557	0,59	0,614	0,591	0,571	0,541	0,552	0,528	0,465	**0,446**

CoMSIA MODEL – Without Focus – HF 3-21G

Table 21 - Construction of the CoMSIA model (3D QSAR), using the HF 3-21G method.

COMSIA - SEM FOCAGEM - COM SEPARAÇÃO - TODOS OS DESCRITORES - ORCA					
HF 3-21G	S/E/H/D/A	S/E/H/A	S/E/H	E/H	E/H W0.9D1.5
LEAVE-ONE-OUT (q^2)					
q^2	0,474	0,545	0,548	0,546	**0,865**
Erro padrão da Predição	0,677	0,545	0,544	0,562	**0,343**
N componentes	6	2	2	3	**6**
NO VALIDATION (r^2)					
r^2	0,989	0,862	0,863	0,902	**0,972**
Erro padrão da Estimativa	0,100	0,300	0,299	0,262	**0,157**
donor	0,291				
aceptor	0,001	0,003			
hydrophobic	0,197	0,360	0,361	0,372	**0,352**
steric	0,051	0,055	0,055		
eletrostatic	0,461	0,582	0,584	0,628	**0,648**

C/ 4 tipos de descritores	S/E/H/A	S/E/H/D	S/E/D/A	E/H/D/A	S/H/D/A
LEAVE-ONE-OUT (q2)					
q2 LOO	**0,545**	0,477	0,500	0,467	0,369
SEP	**0,545**	0,675	0,660	0,682	0,742
N components	**2**	6	6	6	6
NO VALIDATION (r2)					
r2	**0,862**	0,989	0,989	0,988	0,937
SEE	**0,300**	0,100	0,097	0,101	0,234
donor		0,291	0,354	0,288	0,494
acceptor	**0,003**		0,001	0,001	0,004
hydrophobic	**0,360**	0,197		0,216	0,401
steric	**0,055**	0,051	0,079		0,102
eletrostatic	**0,582**	0,461	0,566	0,495	

C/ 3 tipos de descritores	H/D/A	S/D/A	E/D/A	S/H/D	E/H/D	S/E/D	S/H/A	E/H/A	S/E/A	S/E/H
LEAVE-ONE-OUT (q2)										
q2 LOO	0,345	0,360	0,495	0,386	0,470	0,502	0,34	0,541	0,479	**0,548**
SEP	0,756	0,747	0,664	0,732	0,679	0,659	0,679	0,565	0,584	**0,544**
N components	6	6	6	6	6	6	3	3	2	**2**
NO VALIDATION (r2)										
r2	0,944	0,835	0,989	0,938	0,988	0,989	0,703	0,901	0,808	**0,863**
SEE	0,220	0,380	0,100	0,233	0,101	0,097	0,455	0,262	0,354	**0,299**
donor	0,501	0,533	0,359	0,497	0,288	0,355				
acceptor	0,004	0,007	0,001				0,009	0,002	0,005	
hydrophobic	0,495			0,401	0,216		0,838	0,371		**0,361**
steric		0,460		0,101		0,079	0,153		0,082	**0,055**
eletrostatic			0,640		0,496	0,566		0,626	0,913	**0,584**

C/ 2 tipos de descritores	D/A	S/D	E/D	H/D	H/A	S/A	E/A	S/H	E/H	S/E
LEAVE-ONE-OUT (q2)										
q2 LOO	-0,016	0,340	0,497	0,358	0,307	0,036	0,482	0,350	**0,546**	0,482
SEP	0,842	0,758	0,662	0,748	0,695	0,820	0,582	0,673	**0,562**	0,582
N components	3	6	6	6	3	3	2	3	**3**	2
NO VALIDATION (r2)										
r2	0,443	0,834	0,989	0,945	0,688	0,469	0,848	0,702	**0,902**	0,808
SEE	0,623	0,380	0,100	0,218	0,466	0,609	0,316	0,455	**0,262**	0,354
donor	0,991	0,540	0,359	0,506						
acceptor	0,009				0,012	0,107	0,005			
hydrophobic				0,494	0,988			0,845	**0,372**	
steric		0,460				0,893		0,155		0,082
eletrostatic			0,641				0,995		**0,628**	0,918

C/ 1 tipo de descritor	S	E	H	D	A
LEAVE-ONE-OUT (q2)					
q2 LOO	0,053	0,486	0,318	-0,017	0,031
SEP	0,813	0,580	0,689	0,842	0,772
N components	3	2	3	3	1
NO VALIDATION (r2)					
r2	0,472	0,847	0,686	0,443	0,276
SEE	0,607	0,317	0,468	0,623	0,667
donor				1,000	
acceptor					1,000
hydrophobic			1		
steric	1				
eletrostatic		1			

CoMSIA – With Focus – HF 3-21G

COMSIA - COM SEPARAÇÃO - COM FOCAGEM - ORCA													
HF3-21	**Sem focagem**	E/H - W03D05	E/H - W03D10	E/H - W03D15	E/H -W05D05	E/H - W05D10	E/H - W05D15	E/H -W07D05	E/H - W07D10	E/H - W07D15	E/H -W09D05	E/H - W09D10	E/H - W09D15
LEAVE-ONE-OUT (q2)													
SEP	0,562	0,532	0,499	0,499	0,491	0,456	0,426	0,473	0,381	0,351	0,376	0,382	**0,343**
q2 LOO	0,546	0,593	0,643	0,643	0,655	0,702	0,74	0,743	0,806	0,824	0,824	0,832	**0,865**
N components	3	3	3	3	3	3	3	6	4	3	5	6	**6**
NO VALIDATION (r2)													
r2	0,902	0,927	0,945	0,941	0,964	0,959	0,955	0,982	**0,973**	0,941	0,958	0,966	**0,972**
SEE	0,262	0,226	0,196	0,202	0,158	0,170	0,177	0,123	**0,141**	0,204	0,185	0,171	**0,157**
hydrophobic	0,372	0,373	0,357	0,388	0,347	0,375	0,366	0,342	0,371	0,459	0,360	0,277	**0,352**
eletrostatic	0,628	0,627	0,643	0,612	0,653	0,625	0,634	0,658	0,629	0,541	0,64	0,723	**0,648**

CoMSIA MODEL – Without Focus – HF 6-311G

Table 22 - Construction of the CoMSIA model (3D QSAR), using the HF 6-311G method.

COMSIA - SEM FOCAGEM - COM SEPARAÇÃO - TODOS OS DESCRITORES - ORCA					
HF 6-311G	S/E/H/D/A	S/E/H/A	S/E/H	E/H	E/H - W09D15
LEAVE-ONE-OUT (q^2)					
q^2	0,476	0,565	0,570	0,552	**0,749**
Erro padrão da Predição	0,676	0,551	0,547	0,559	**0,418**
N componentes	6	3	3	3	**3**
NO VALIDATION (r^2)					
r^2	0,988	0,898	0,898	0,904	0,927
Erro padrão da Estimativa	0,103	0,267	0,267	0,259	0,226
donor	0,295				
aceptor	0,001	0,002			
hydrophobic	0,183	0,356	0,357	0,367	0,364
steric	0,052	0,053	0,053		
eletrostatic	0,470	0,589	0,590	0,633	0,636

C/ 4 tipos de descritores	S/E/H/A	S/E/H/D	S/E/D/A	E/H/D/A	S/H/D/A
LEAVE-ONE-OUT (q2)					
q2 LOO	**0,565**	0,479	0,521	0,471	0,369
SEP	**0,551**	0,674	0,646	0,679	0,742
N components	**3**	6	6	6	6
NO VALIDATION (r2)					
r2	**0,898**	0,988	0,988	0,988	0,937
SEE	**0,267**	0,103	0,102	0,104	0,234
donor		0,295	0,348	0,291	0,494
acceptor	**0,002**		0,001	0,001	0,004
hydrophobic	**0,356**	0,183		0,204	0,401
steric	**0,053**	0,052	0,083		0,102
eletrostatic	**0,589**	0,470	0,569	0,504	

C/ 3 tipos de descritores	H/D/A	S/D/A	E/D/A	S/H/D	E/H/D	S/E/D	S/H/A	E/H/A	S/E/A	S/E/H
LEAVE-ONE-OUT (q2)										
q2 LOO	0,345	0,360	0,518	0,386	0,474	0,524	0,34	0,548	0,516	**0,570**
SEP	0,756	0,747	0,648	0,732	0,677	0,644	0,679	0,561	0,650	**0,547**
N components	6	6	6	6	6	6	3	3	6	**3**
NO VALIDATION (r2)										
r2	0,944	0,835	0,987	0,938	0,988	0,988	0,703	0,903	0,983	**0,898**
SEE	0,220	0,380	0,105	0,233	0,104	0,102	0,455	0,259	0,122	**0,267**
donor	0,501	0,533	0,353	0,497	0,291	0,348				
acceptor	0,004	0,007	0,001				0,009	0,002	0,002	
hydrophobic	0,495			0,401	0,204		0,838	0,366		**0,357**
steric		0,460		0,101		0,083	0,153		0,065	**0,053**
eletrostatic			0,647		0,505	0,569		0,632	0,933	**0,590**

C/ 2 tipos de descritores	D/A	S/D	E/D	H/D	H/A	S/A	E/A	S/H	E/H	S/E
LEAVE-ONE-OUT (q2)										
q2 LOO	-0,016	0,340	0,520	0,358	0,307	0,036	0,513	0,350	**0,552**	0,521
SEP	0,842	0,758	0,647	0,748	0,695	0,820	0,652	0,673	**0,559**	0,646
N components	3	6	6	6	3	3	6	3	**3**	6
NO VALIDATION (r2)										
r2	0,443	0,834	0,987	0,945	0,688	0,469	0,984	0,702	**0,904**	0,983
SEE	0,623	0,380	0,105	0,218	0,466	0,609	0,120	0,455	**0,259**	0,121
donor	0,991	0,540	0,353	0,506						
acceptor	0,009				0,012	0,107	0,002			
hydrophobic				0,494	0,988			0,845	**0,367**	
steric		0,460				0,893		0,155		0,064
eletrostatic			0,647				0,998		**0,633**	0,936

C/ 1 tipo de descritor	S	E	H	D	A
LEAVE-ONE-OUT (q2)					
q2 LOO	0,053	0,518	0,318	-0,017	0,031
SEP	0,813	0,648	0,689	0,842	0,772
N components	3	6	3	3	1
NO VALIDATION (r2)					
r2	0,472	0,984	0,686	0,443	0,276
SEE	0,607	0,120	0,468	0,623	0,667
donor				1,000	
acceptor					1,000
hydrophobic			1		
steric	1				
eletrostatic		1			

CoMSIA – With Focus – HF 6-311G

COMSIA - COM SEPARAÇÃO - COM FOCAGEM - HF 6-311G													
HF 6-311G	**Sem focagem**	E/H - W03D05	E/H - W03D10	E/H - W03D15	E/H -W05D05	E/H - W05D10	E/H - W05D15	E/H -W07D05	E/H - W07D10	E/H - W07D15	E/H -W09D05	E/H - W09D10	E/H - W09D15
LEAVE-ONE-OUT (q2)													
SEP	**0,559**	0,518	0,489	0,485	0,466	0,464	0,436	0,451	0,46	0,468	0,435	0,423	**0,418**
q2 LOO	**0,552**	0,615	0,657	0,662	0,668	0,67	0,71	0,689	0,677	0,685	0,729	0,743	**0,749**
N components	**3**	3	3	3	2	2	2	2	2	3	3	3	**3**
NO VALIDATION (r2)													
r2	**0,904**	0,930	0,945	0,945	0,909	0,892	0,897	0,882	0,876	0,917	0,911	0,903	**0,927**
SEE	**0,259**	0,221	0,195	0,196	0,244	0,266	0,259	0,278	0,285	0,24	0,249	0,26	**0,226**
hydrophobic	**0,367**	0,358	0,358	0,382	0,423	0,453	0,404	0,447	0,465	0,308	0,325	0,312	**0,364**
eletrostatic	**0,633**	0,642	0,642	0,618	0,577	0,547	0,596	0,553	0,535	0,692	0,675	0,688	**0,636**

CoMSIA MODEL – Without Focus – DFT HF 6-311G

Table 23 - Construction of the CoMSIA model (3D QSAR), using the HF 6-311G DFT method.

COMSIA - SEM FOCAGEM - COM SEPARAÇÃO - TODOS OS DESCRITORES - DFT					
DFT 6-311G	S/E/H/D/A	S/E/H/A	S/E/H	E/H	**E/H - W09D10**
LEAVE-ONE-OUT (q^2)					
q^2	0,465	0,536	0,540	0,527	**0,915**
Erro padrão da Predição	0,683	0,569	0,566	0,574	**0,272**
N componentes	6	3	3	3	**2**
NO VALIDATION (r^2)					
r^2	0,988	0,892	0,892	0,899	**0,91**
Erro padrão da Estimativa	0,101	0,275	0,275	0,266	**0,242**
donor	0,291				
aceptor	0,001	0,002			
hydrophobic	0,187	0,354	0,355	0,365	**0,439**
steric	0,052	0,053	0,053		
eletrostatic	0,470	0,591	0,592	0,635	**0,561**

C/ 4 tipos de descritores	S/E/H/A	S/E/H/D	S/E/D/A	E/H/D/A	S/H/D/A
LEAVE-ONE-OUT (q2)					
q2 LOO	**0,536**	0,468	0,508	0,459	0,369
SEP	**0,569**	0,681	0,655	0,687	0,742
N components	**3**	6	6	6	6
NO VALIDATION (r2)					
r2	**0,892**	0,988	0,989	0,988	0,937
SEE	**0,275**	0,101	0,099	0,102	0,234
donor		0,291	0,343	0,287	0,494
acceptor	**0,002**		0,001	0,001	0,004
hydrophobic	**0,354**	0,187		0,208	0,401
steric	**0,053**	0,052	0,082		0,102
eletrostatic	**0,591**	0,470	0,575	0,505	

C/ 3 tipos de descritores	H/D/A	S/D/A	E/D/A	S/H/D	E/H/D	S/E/D	S/H/A	E/H/A	S/E/A	**S/E/H**
LEAVE-ONE-OUT (q2)										
q2 LOO	0,345	0,360	0,499	0,386	0,462	0,510	0,34	0,523	0,499	**0,540**
SEP	0,756	0,747	0,660	0,732	0,685	0,654	0,679	0,577	0,572	**0,566**
N components	6	6	6	6	6	6	3	3	2	**3**
NO VALIDATION (r2)										
r2	0,944	0,835	0,988	0,938	0,988	0,989	0,703	0,899	0,847	**0,892**
SEE	0,220	0,380	0,101	0,233	0,102	0,099	0,455	0,266	0,316	**0,275**
donor	0,501	0,533	0,346	0,497	0,287	0,343				
acceptor	0,004	0,007	0,001				0,009	0,002	0,004	
hydrophobic	0,495			0,401	0,208		0,838	0,365		**0,355**
steric		0,460		0,101		0,082	0,153		0,076	**0,053**
eletrostatic			0,653		0,505	0,575		0,633	0,920	**0,592**

C/ 2 tipos de descritores	D/A	S/D	E/D	H/D	H/A	S/A	E/A	S/H	**E/H**	S/E
LEAVE-ONE-OUT (q2)										
q2 LOO	-0,016	0,340	0,502	0,358	0,307	0,036	0,490	0,350	**0,527**	0,503
SEP	0,842	0,758	0,659	0,748	0,695	0,820	0,577	0,673	**0,574**	0,570
N components	3	6	6	6	3	3	2	3	**3**	2
NO VALIDATION (r2)										
r2	0,443	0,834	0,988	0,945	0,688	0,469	0,877	0,702	**0,899**	**0,847**
SEE	0,623	0,380	0,101	0,218	0,466	0,609	0,283	0,455	**0,266**	**0,316**
donor	0,991	0,540	0,346	0,506						
acceptor	0,009				0,012	0,107	0,005			
hydrophobic				0,494	0,988			0,845	**0,365**	
steric		0,460				0,893		0,155		**0,076**
eletrostatic			0,654				0,995		**0,635**	**0,924**

C/ 1 tipo de descritor	S	E	H	D	A
LEAVE-ONE-OUT (q2)					
q2 LOO	0,053	0,495	0,318	-0,017	0,031
SEP	0,813	0,663	0,689	0,842	0,772
N components	3	6	3	3	1
NO VALIDATION (r2)					
r2	0,472	0,983	0,686	0,443	0,276
SEE	0,607	0,122	0,468	0,623	0,667
donor				1,000	
acceptor					1,000
hydrophobic			1		
steric	1				
eletrostatic		1			

CoMSIA – With Focus – DFT HF 6-311G

COMSIA - COM SEPARAÇÃO - COM FOCAGEM - DFT													
DFT 6-311G	**Sem focagem**	E/H - W03D05	E/H - W03D10	E/H - W03D15	E/H -W05D05	E/H - W05D10	E/H - W05D15	E/H - W07D05	E/H - W07D10	E/H - W07D15	E/H -W09D05	**E/H - W09D10**	E/H - W09D15
LEAVE-ONE-OUT (q2)													
SEP	**0,574**	0,539	0,501	0,5	0,479	0,475	0,449	0,508	0,463	0,413	0,306	**0,272**	0,322
q2 LOO	**0,527**	0,583	0,639	0,641	0,649	0,655	0,691	0,679	0,754	0,805	0,893	**0,915**	0,881
N components	**3**	3	3	3	2	2	2	5	6	6	6	**2**	6
NO VALIDATION (r2)													
r2	**0,899**	0,932	0,954	0,952	0,902	0,888	0,893	0,984	0,984	0,986	0,986	**0,91**	0,984
SEE	**0,266**	0,217	0,180	0,183	0,254	0,271	0,265	0,113	0,118	0,111	0,109	**0,242**	0,118
hydrophobic	**0,365**	0,359	0,360	0,378	0,430	0,454	0,407	0,479	0,413	0,340	0,343	**0,439**	0,410
eletrostatic	**0,635**	0,641	0,640	0,622	0,570	0,546	0,593	0,521	0,587	0,660	0,657	**0,561**	0,590

CoMSIA MODEL – Without Focus – RESP HF 6-311G

Table 24 - Construction of the CoMSIA model (3D QSAR), using the RESP HF 6-311G method.

COMSIA - SEM FOCAGEM - COM SEPARAÇÃO - TODOS OS DESCRITORES - RESP					
RESP HF 6-311G	S/E/H/D/A	S/E/H/A	S/E/H	E/H	**E/H - W09D10**
LEAVE-ONE-OUT (q^2)					
q^2	0,480	0,551	0,555	0,558	**0,78**
Erro padrão da Predição	0,673	0,560	0,557	0,555	**0,392**
N componentes	6	3	3	3	**3**
NO VALIDATION (r^2)					
r^2	0,987	0,895	0,895	0,903	**0,924**
Erro padrão da Estimativa	0,105	0,270	0,270	0,260	**0,229**
doador	0,302				
aceptor	0,001	0,002			
hidrofóbico	0,178	0,353	0,354	0,361	**0,489**
estérico	0,051	0,053	0,053		
eletrostático	0,468	0,592	0,593	0,639	**0,511**

C/ 4 tipos de descritores	S/E/H/A	S/E/H/D	S/E/D/A	E/H/D/A	S/H/D/A
LEAVE-ONE-OUT (q2)					
q2 LOO	**0,551**	0,484	0,531	0,476	0,369
SEP	**0,560**	0,671	0,639	0,676	0,742
N components	**3**	6	6	6	6
NO VALIDATION (r2)					
r2	**0,895**	0,987	0,988	0,987	0,937
SEE	**0,270**	0,105	0,104	0,105	0,234
donor		0,302	0,351	0,298	0,494
acceptor	**0,002**		0,001	0,001	0,004
hydrophobic	**0,353**	0,178		0,200	0,401
steric	**0,053**	0,051	0,083		0,102
eletrostatic	**0,592**	0,469	0,565	0,501	

C/ 3 tipos de descritores	H/D/A	S/D/A	E/D/A	S/H/D	E/H/D	S/E/D	S/H/A	E/H/A	S/E/A	**S/E/H**
LEAVE-ONE-OUT (q2)										
q2 LOO	0,345	0,360	0,528	0,386	0,480	0,533	0,34	0,553	0,534	**0,555**
SEP	0,756	0,747	0,641	0,732	0,673	0,638	0,679	0,558	0,637	**0,557**
N components	6	6	6	6	6	6	3	3	6	**3**
NO VALIDATION (r2)										
r2	0,944	0,835	0,987	0,938	0,987	0,988	0,703	0,903	0,983	**0,895**
SEE	0,220	0,380	0,107	0,233	0,105	0,104	0,455	0,260	0,122	**0,270**
donor	0,501	0,533	0,356	0,497	0,298	0,351				
acceptor	0,004	0,007	0,001				0,009	0,002	0,002	
hydrophobic	0,495			0,401	0,200		0,838	0,360		**0,354**
steric		0,460		0,101		0,084	0,153		0,073	**0,053**
eletrostatic			0,644		0,502	0,565		0,638	0,924	**0,593**

C/ 2 tipos de descritores	D/A	S/D	E/D	H/D	H/A	S/A	E/A	S/H	**E/H**	S/E
LEAVE-ONE-OUT (q2)										
q2 LOO	-0,016	0,340	0,531	0,358	0,307	0,036	0,533	0,350	**0,558**	0,538
SEP	0,842	0,758	0,640	0,748	0,695	0,820	0,638	0,673	**0,555**	0,634
N components	3	6	6	6	3	3	6	3	**3**	6
NO VALIDATION (r2)										
r2	0,443	0,834	0,987	0,945	0,688	0,469	0,984	0,702	**0,903**	**0,983**
SEE	0,623	0,380	0,107	0,218	0,466	0,609	0,118	0,455	**0,260**	**0,121**
donor	0,991	0,540	0,356	0,506						
acceptor	0,009				0,012	0,107	0,003			
hydrophobic				0,494	0,988			0,845	**0,361**	
steric		0,460				0,893		0,155		**0,073**
eletrostatic			0,644				0,997		**0,639**	**0,927**

C/ 1 tipo de descritor	S	E	H	D	A
LEAVE-ONE-OUT (q2)					
q2 LOO	0,053	0,538	0,318	-0,017	0,031
SEP	0,813	0,634	0,689	0,842	0,772
N components	3	6	3	3	1
NO VALIDATION (r2)					
r2	0,472	0,984	0,686	0,443	0,276
SEE	0,607	0,118	0,468	0,623	0,667
donor				1,000	
acceptor					1,000
hydrophobic			1		
steric	1				
eletrostatic		1			

CoMSIA – With Focus – RESP HF 6-311G

COMSIA - COM SEPARAÇÃO - COM FOCAGEM - RESP													
RESP HF 6-311G	**Sem focagem**	E/H - W03D05	E/H - W03D10	E/H - W03D15	E/H -W05D05	E/H - W05D10	E/H - W05D15	E/H - W07D05	E/H - W07D10	E/H - W07D15	E/H -W09D05	**E/H - W09D10**	E/H - W09D15
LEAVE-ONE-OUT (q2)													
q2 LOO	**0,558**	0,611	0,655	0,656	0,663	0,659	0,701	0,694	0,749	0,764	0,752	**0,78**	0,78
SEP	**0,555**	0,521	0,49	0,49	0,469	0,472	0,442	0,496	0,45	0,405	0,43	**0,392**	0,405
N components	**3**	3	3	3	2	2	2	5	5	3	4	**3**	4
NO VALIDATION (r2)													
r2	**0,903**	0,930	0,947	0,944	0,904	0,888	0,894	0,982	0,976	0,922	0,938	**0,924**	0,924
SEE	**0,260**	0,221	0,192	0,197	0,250	0,270	0,263	0,12	0,138	0,233	0,215	**0,229**	0,238
hydrophobic	**0,361**	0,359	0,356	0,381	0,423	0,450	0,398	0,489	0,463	0,475	0,476	**0,489**	0,474
eletrostático	**0,639**	0,641	0,644	0,619	0,577	0,550	0,602	0,511	0,537	0,525	0,524	**0,511**	0,526

ANNEX IV - INPUT FILES FOR PERFORMING CHELPG PARTIAL ATOMIC CHARGE CALCULATIONS USING ORCA QUANTUM CHEMISTRY SOFTWARE

The molecules must first be converted from '.mol2' to '.xyz', using the **obabel *.mol2 –O .xyz –m**

From this, all the files will be '.xyz', which will be used to run the "model.inp" file

model.inp file:

! HF 6-311G sp - "HF": Indicates that the Hartree-Fock method will be used for the calculation.
"6-311G": Specifies the molecular basis set that will be used to represent the wave functions.
"sp": Indicates that the calculation will be a single-point calculation.

! tightscf soscf – "tightscf": Configures a stricter criterion for the convergence of self-consistency.
"soscf": Indicates that the Self-Consistent Field (SCF) method will be used.

! slowconv largeprint allpop aim cpcm chelpg "slowconv": Sets a slower criterion for convergence.
"largeprint": Requests a more detailed output.
"allpop": Requests the printing of detailed atomic populations.
"aim": Requests AIM (Atoms In Molecules) analysis.
"cpcm": Activates the solvation model CPCM (Conductor-like Screening Model for Real Solvents).
"chelpg": Requests the atomic charge derived from the population

%PAL NPROCS 12 END – "%PAL": Indicates the start of a parallelism section.
"NPROCS 12": Specifies the number of processors that can be used for the calculation (12 in this case).
"END": Indicates the end of the parallelism section.

%cpcm - Specific configurations for the CPCM model.
    smd true - Activates the solvation model SMD (Solvation Model Density).
    smdsolvent "water" - Specifies the solvent (water, in this case).
end

%geom - Settings related to geometric optimization.
  maxiter 9999 - Specifies the maximum number of iterations for the optimization.
    end

%scf - Configurations related to the Self-Consistent Field.
    maxiter 9999 - Maximum number of SCF iterations
    cnvdiis 1 - Activates the DIIS (Direct Inversion in Iterative Space) method.
    cnvsoscf 1 - Activates slow convergence for SOSCF.
end

%output - Settings for outputting results.
    print[p_mos] true - It asks you to print out the molecular orbitals.
    print[p_basis] 5 - Sets the level of detail for printing the molecular basis.
end

*xyzfile 0 1 4a.xyz - Specifies the format of the input file, which contains the atomic coordinates of the molecule in XYZ format.
"0" and "1" indicate multiplicity and charge of the molecule, respectively.
"4a.xyz" is the name of the file containing the atomic coordinates.

Source: OpenAI. (2022). ChatGPT: Conversational Agent [Computer software]. Available at: https://www.openai.com. Accessed on 08 Aug. 2023.

It can be done manually, one by one, or use another script to automate the process. The script *create_inp_from_xyz.py* creates several '.inp' files using an .inp model and replaces the reference to the '.xyz' file in the last line of the model for each '.xyz' file found in the directory, generating corresponding '.inp' files. The template is supplied as "**model.inp**", and the output files have the same name as the '.xyz' file, but with the extension '.inp'.

```
import os

def create_inp_files(template_file):
    # Read the contents of the template file
    with open(template_file, "r") as file:
        template_content = file.readlines()

    # List all .xyz files in the folder
    xyz_files = [f for f in os.listdir(".") if f.endswith('.xyz')]

    for xyz_file in xyz_files:
        # Change the last line of the template to reference the current .xyz file
        template_content[-1] = f"*xyzfile 0 1 {xyz_file}\n"

        # Create the .inp file name based on the .xyz file name
        inp_filename = xyz_file.replace(".xyz", ".inp")

        # Write the changed content to the new .inp file
        with open(inp_filename, "w") as out_file:
            out_file.writelines(template_content)

if __name__ == "__main__":
    create_inp_files("model.inp")
```

The ./**runtodos.sh** script automates the execution of the orca program for all '.inp' files in the current directory, generating corresponding output files with a '.out' extension. The command runs in the background (nohup), which allows it to continue even if the terminal session is closed. The '.out' files will be responsible for storing the chelpg loads from the chosen method, which in this case was done using HF 3-21G, HF 6-31G, HF 6-311G and DFT 6-311G.**runtodos.sh:**

```
#!/bin/bash
export LD_LIBRARY_PATH=~/orca5

# Iterate over all .inp files in the current directory
for inp_file in *.inp; do
    # Get the base name of the file (without extension)
    base_name="${inp_file%.*}"
```

```
    # Print the name of the file being executed on the screen
    echo " Running $inp_file..."

    # Run the nohup command for the current .inp file
    ~/orca5/orca $inp_file > $base_name.out
done
```

Calculation of RESP loads using the ORCA program

They were calculated using multiwfn v.3.8 (.wfn) (http://sobereva.com/multiwfn) (LU; CHEN, 2012), where the output generated are '.chg' files, which contain the calculated loads.

ANNEX V - COMMANDS AFTER MOLECULAR DYNAMICS SIMULATION

To make the cluster:

- gmx cluster -f fitado2.gro -s sistema_md.tpr -n index2.ndx -method gromos -o -g -dist -ev -sz -tr -ntr -clid -cl -tu ns

It generates the cluster.pdb file. You must select the flag that contains the entire complex.

Calculate the RMSD between the frames in the cluster:

- gmx rms -s sistema_md.tpr -f clusters.pdb -o rmsd_clusters.xvg

Perform a cut-off to select the frames with the lowest RMSD. At this stage, the values were modified in order to achieve this cut-off.

- gmx cluster -cutoff 0.01 -f fitado2.gro -s sistema_md.tpr -n index2.ndx -method gromos -o -g -dist -ev -sz -tr -ntr -clid -cl -tu ns

Keep the RMSD value column next to the frame indexes in the selected_frames.txt file, and you can modify the awk command as follows:

- awk '$1 > 0 && $2 <= 50 {print $1, $2}' rmsd_clusters.xvg > quadros_selecionados.txt

Sort the selected_frames.txt file based on the RMSD value:

- sort -k2 -n quadros_selecionados.txt > quadros_selecionados_ordenados.txt

The 50 smallest RMSD were then selected and placed in a separate .txt file to run the script to separate the clusters: **quadros.sh**

SCRIPT TO SEPARATE CLUSTERS INTO MULTIPLE '.pdb' FILES

Script based on argument, so it is necessary to have separated all the selected clusters in a text file. So **./frames.sh frames_selected.txt**

The file named **frames.sh** contains the Bash script below:

```
#!/bin/bash - Indicates that the script will be interpreted by Bash.

#  Checks if a file was passed as an argument
if [ "$#" -ne 1 ]; then   - Checks if the number of arguments passed is different from 1.

    echo "Uso: $0 <arquivo_de_numeros>" - Displays a message indicating how to use the script.
    exit 1
fi

# Defining the file with the numbers from the argument
ARQUIVO_NUMEROS="$1" - Assigns the first argument (name of the numbers file) to the
ARQUIVO_NUMEROS variable.

# Checks if the file exists
if [ ! -f "$ARQUIVO_NUMEROS" ]; then - Checks if the number file doesn't exist.
    echo "Erro: Arquivo '$ARQUIVO_NUMEROS' não encontrado!" -  Displays an error message.
exit 1
fi

# Reading each line of the file
while IFS= read -r numero  -  Starts a loop to read each line of the numbers file.
do
    #  Running the gmx trjconv command with the current number
    echo -e "23/n" | gmx trjconv -s sistema_md.tpr -f fitado2.gro –dump "$numero" -o "cluster${numero}.pdb"
-n index2.ndx
done < "$ARQUIVO_NUMEROS" - Run the gmx trjconv command for each number in the file,
using specific parameters. The number is used to name the output files.
```

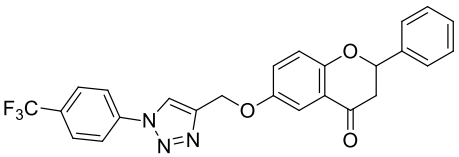
Table 25: Result obtained after ensemble docking, carried out in the Gold 2022.3.0 program. Redocking done with the 50 clusters with the lowest RMSD after molecular dynamics simulation on a 100 ns trajectory.

Redocking of Clusters after Molecular Dynamics - ASP 7A		
Cluster	**RMSD**	**Solução**
700	0.5779	3
500	0.5972	2
7060	0.7805	2
960	0.8919	3
4920	0.8926	4
1100	0.9167	8
1220	0.9205	1
280	0.9298	2
5040	0.9446	3
30560	0.9872	5
1540	1.0187	8
9480	1.0452	9
60	1.0558	9
3680	1.0597	1
4660	1.0875	7
620	1.0927	9
38340	1.0948	2

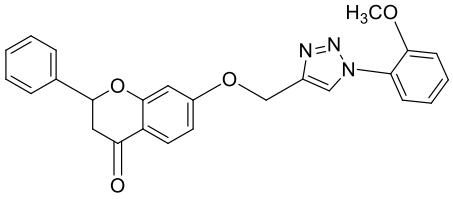
7080	1.0967	1
16740	1.0989	1
8860	1.1077	7
4000	1.1294	1
1020	1.1313	6
1280	1.1365	5
3940	1.1514	1
3840	1.2433	4
1380	1.2449	3
2880	1.2544	1
8520	1.2599	2
2840	1.2651	6
11240	1.2872	5
6920	1.3262	3
760	1.3333	1
42140	1.4073	10
1400	1.412	1
4160	1.4274	8
4600	1.4607	3
20	1.5501	5
400	1.6282	2
780	1.654	7
8560	1.6773	3
4340	1.7561	8
4480	1.8507	8
200	2.0607	1
240	2.1279	5
3740	2.1318	1
600	2.1652	9
140	2.2051	1
840	2.2054	3
40	2.3949	6
5080	2.6937	10

ANNEX VI - LIBRARY OF TRIAZOLE DERIVATIVE COMPOUNDS

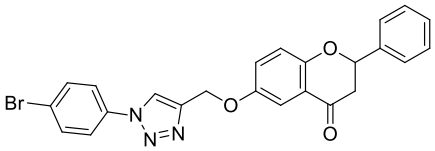
Table 26: Triazole derivatives used to predict their respective biological activities using the QSAR models constructed..



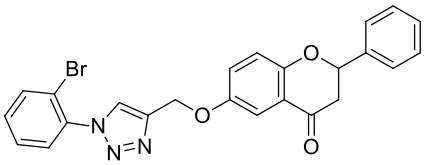
Flavonone – 1



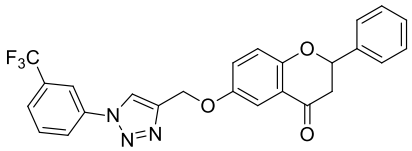
Flavonone – 2



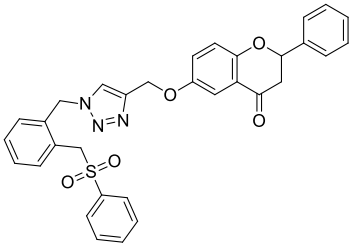
Flavonone – 3



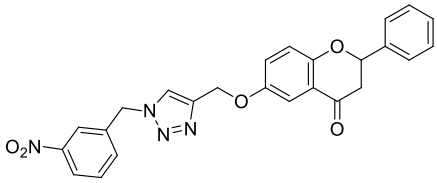
Flavonone – 4



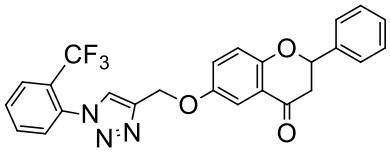
Flavonone – 5



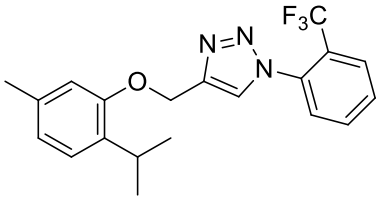
Flavonone – 6



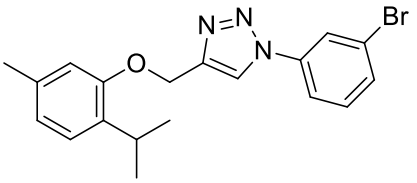
Flavonone – 7



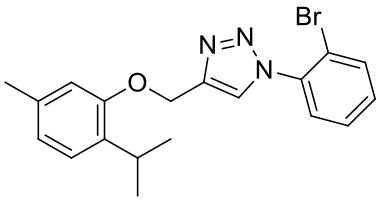
Flavonone – 8



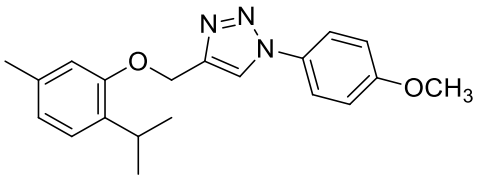
Thymol – 9



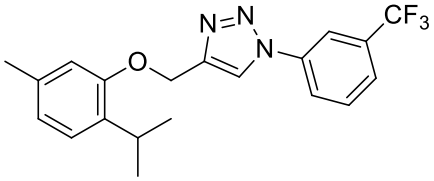
Thymol – 10



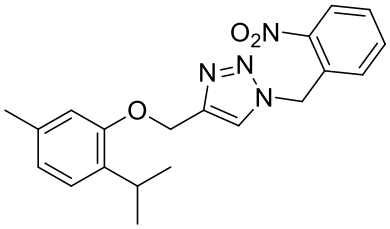
Thymol – 11



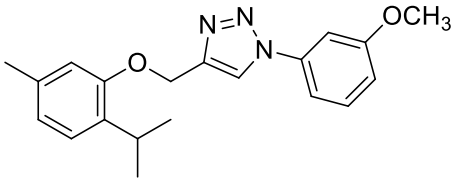
Thymol – 12



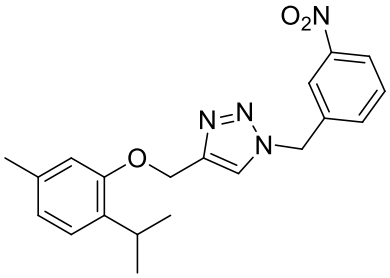
Thymol – 13



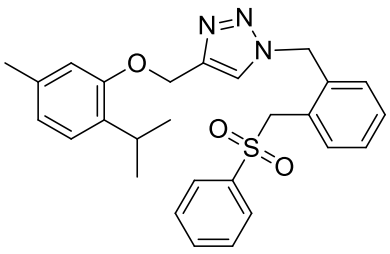
Thymol – 14



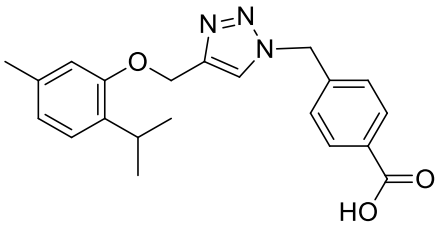
Thymol – 15



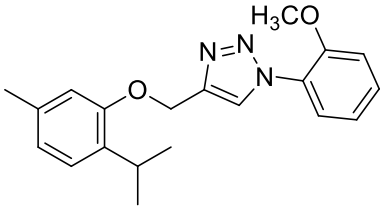
Thymol – 16



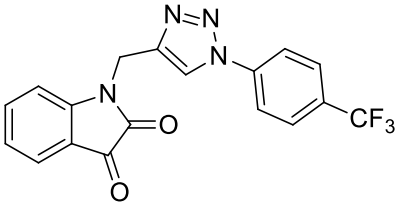
Thymol – 17



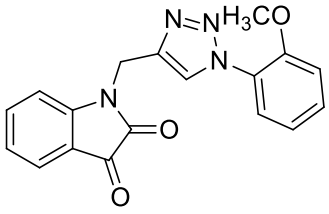
Thymol – 18



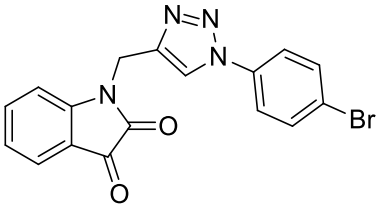
Thymol – 19



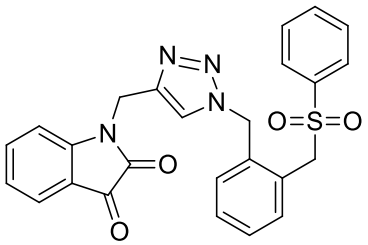
Isatin - 20



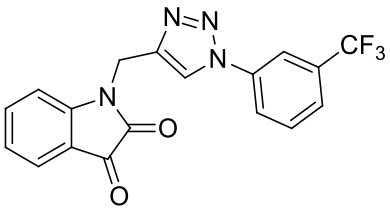
Isatin - 21



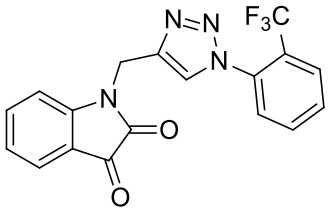
Isatin - 22



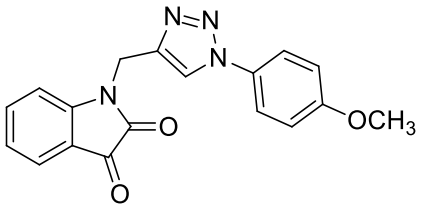
Isatin - 23



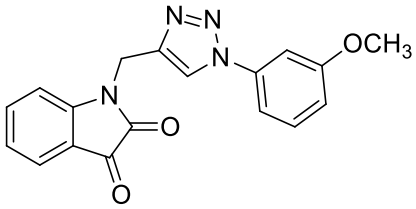
Isatin - 24



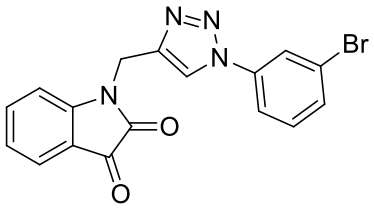
Isatin - 25



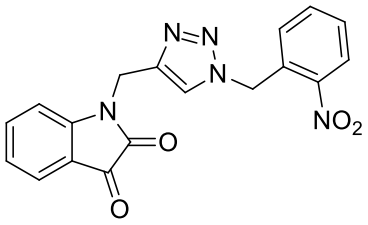
Isatin - 26



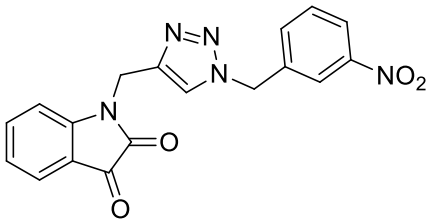
Isatin - 27



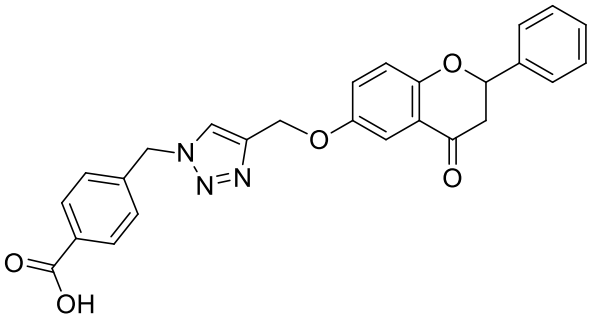
Isatin - 28



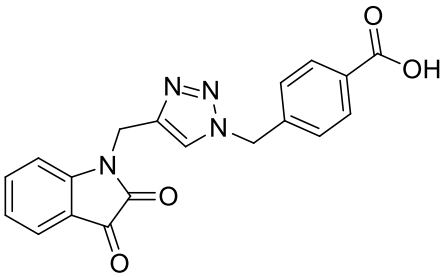
Isatin - 29



Isatin - 30



Flavonone - 31



Isatin - 32

Table 27 - Triazole derivatives whose biological activity was predicted by the QSAR-2D models validated with a r^2_{test} = 0.764, QSAR-3D validated with a r^2_{test} = 0.834 (CoMFA) and a r^2_{test} = 0.858 (CoMSIA). The activities highlighted in bold were the highest.

PREDICTED BIOLOGICAL ACTIVITY			
QSAR-2D		**QSAR-3D**	
	Model 4	**CoMFA S + E**	**CoMSIA E + H**
Compound		**$pEC_{50\ predicted}$**	
1	*	4.595	5.104
2	*	**4.639**	5.247
3	0.685	**4.639**	5.248
4	*	4.572	5.217
5	1.225	4.449	5.341
6	*	3.965	5.329
7	*	4.174	5.363
8	*	4.602	5.223
9	*	4.204	3.780
10	1.477	4.357	5.023
11	1.672	**4.624**	4.930
12	*	4.557	3.942
13	2.819	4.539	5.054
14	*	4.170	5.291
15	*	**4.727**	5.095
16	0.711	3.982	3.801
17	0.879	4.234	5.123
18	*	3.938	3.985
19	3.180	3.850	4.232
20	*	**4.743**	4.316
21	**3.907**	3.979	5.427
22	0.918	4.122	**5.539**
23	3.832	3.952	**5.462**
24	*	4.408	5.363
25	**4.172**	3.934	5.179
26	1.747	4.411	5.014
27	*	4.273	**5.509**
28	**3.801**	4.496	5.237
29	2.730	4.051	**5.466**
30	3.204	3.832	4.454
31	0.930	4.035	5.310

32	2.982	4.510	**5.468**

Fractions S+E (steric and electrostatic); E+H (electrostatic and hydrophobic). Biological activity (pEC50).

*: The model was unable to predict the activity of this compound.

When analyzing the predictions for QSAR-2D, it was not possible to predict the possible biological activity of certain compounds. The structural diversity of these compounds, which deviates slightly from the quinazoline skeleton utilized to construct the model itself, is most likely what caused these results. This was not the case with the QSAR-3D models, which showed that these models are more robust than the QSAR-2D model (CRUZ, 2012).

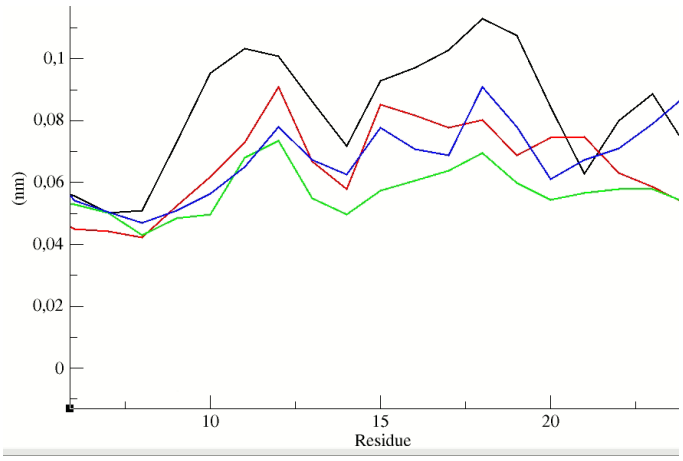
Tabela 28. Triazole derivatives from the library of compounds that obtained the best results in the prediction of biological activity, by QSAR-2D and 3D.

BEST CANDIDATES COMPOUNDS					
QSAR-2D		**3D-QSAR**			
Model 4		**CoMFA**		**CoMSIA**	
Compound	**$pEC_{50(predicted)}$**	**Compound**	**$pEC_{50(predicted)}$**	**Compound**	**$pEC_{50\ (predicted)}$**
21	3.907	20	4.743	22	5.539
25	4.172	15	4.727	27	5.509

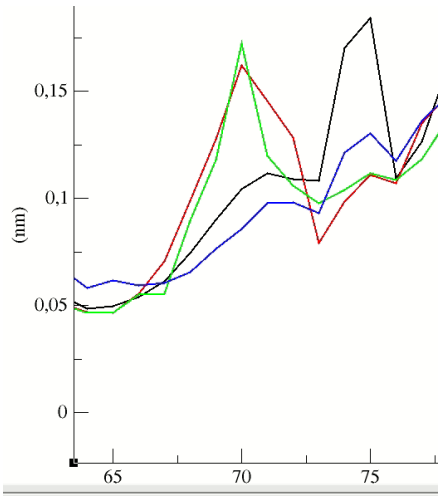
ANNEX VII - RMSF GRAPH ZOOMED IN ON ACTIVE SITE REGIONS

Figure 1 - Amplified RMSF graph in each region of Cluster 700's active site.

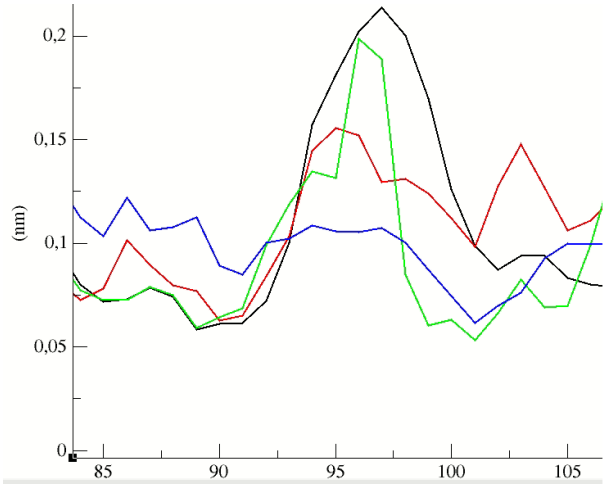
Region 8-16



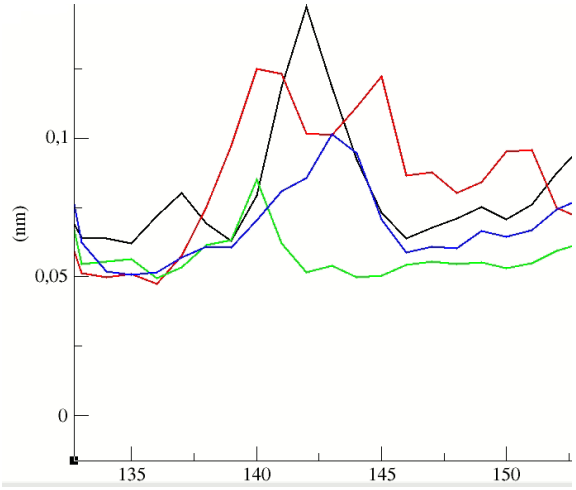
Region 67-69, 72



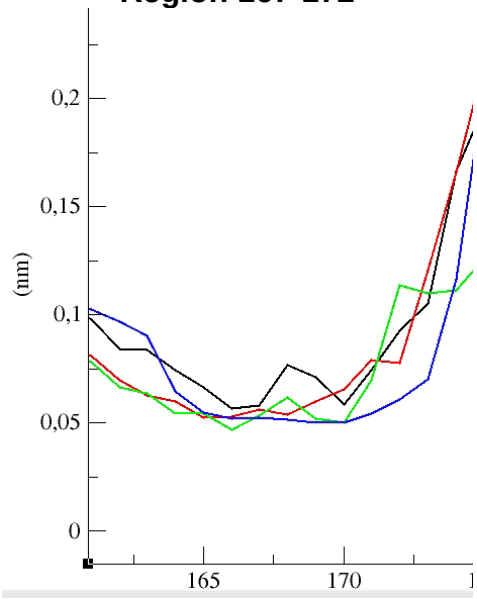
Region 96-101, 104



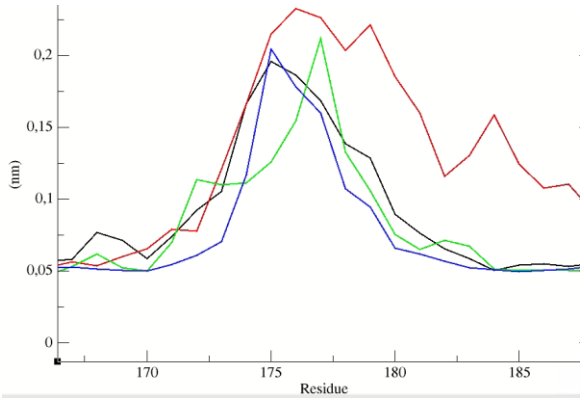
Region 136-148



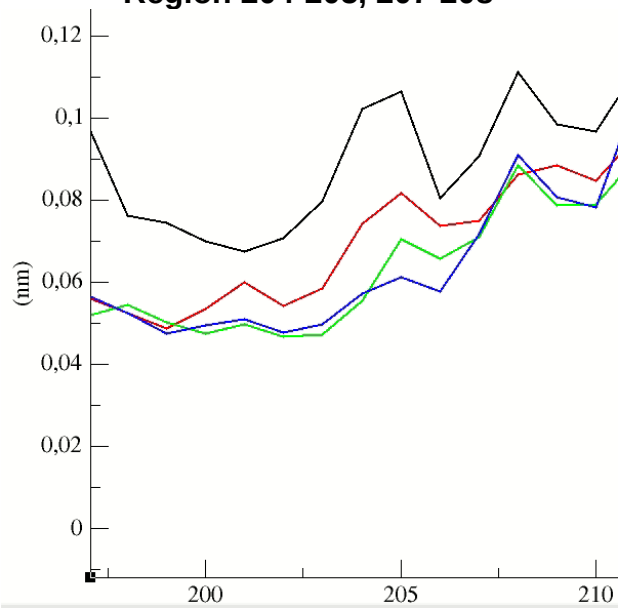
Region 167-172



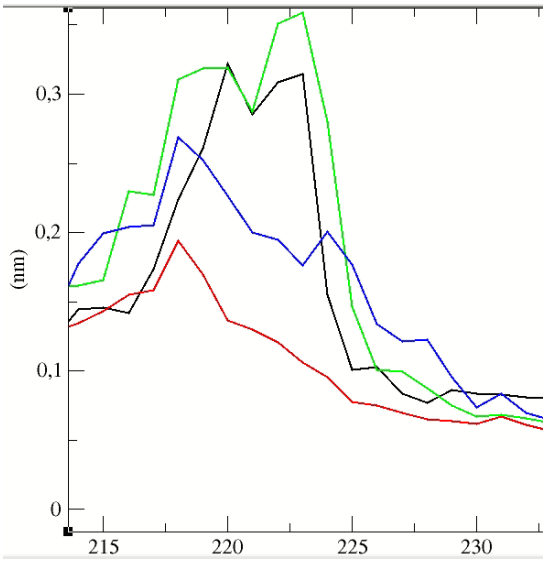
Region 175-178, 181, 185



Region 204-205, 207-208



Region 221-226, 229



The peak with the most variance in the 96–101 range of the RMSF graph indicates that the CBZ had less prominent interactions in this region. Regarding residues 136–148, it was shown that T15 started to oscillate more intensively and eventually passed CBZ, while CBZ started out with less evident interactions and then enhanced them. These findings point to a dynamic oscillation in this particular area between these two ligands.It is evident that CBZ first interacts with residues 167–169 the least in the range of residues 167–172, but that it eventually increases

its connections with them. On the other hand, T15 interacts with residues 169–171 the least. With the crystallographic ligand G2P, amino acid 172 exhibits the largest peak, suggesting that CBZ and T15 both help to stabilize the protein at these positions.

T15 interacts with residues 175–178, 181–185 less than the other ligands. This observation clarifies why, in this location, T15 has the most pronounced peak of all the others.

The G2P ligand exhibits further alterations in the range of amino acids 221-226 and 229, altering its orientation with the protein following amino acid 224. The T15 and CBZ ligands have more interactions in this area of the graph, which explains why their peaks are smaller. It is evident that the interactions with Tyr222 and Asn226—which are carried out by both ligands—contribute to the stabilization of the protein. T15 and CBZ both stay below the line that denotes G2P and the separated protein in this area.

Figure 2 - Hydrogen bonds of the CBZ, T15 and G2P complexes over 200 ns of trajectory.

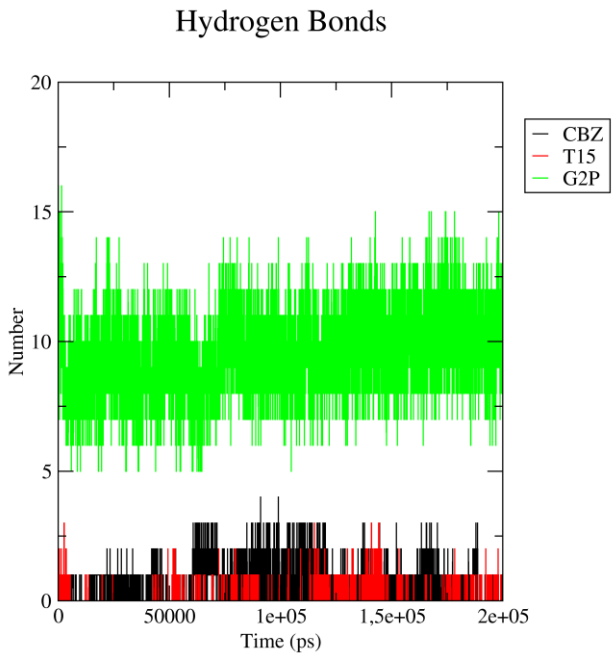
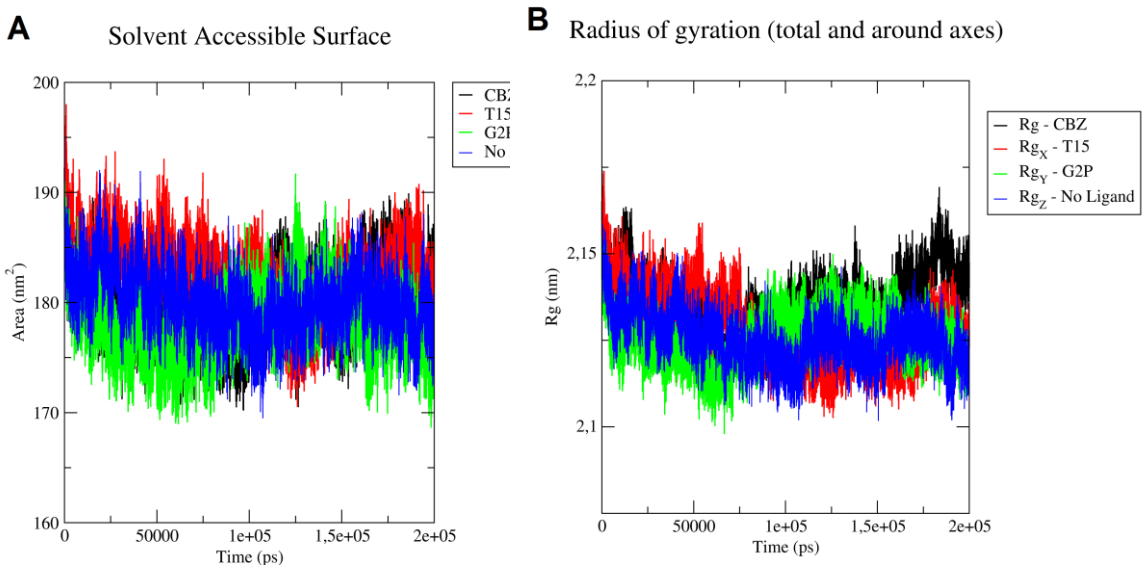


Figure 3. Image A represents the SASA (Solvent Accessible Surface Area) analysis while in B is the turning radius showing the compaction of the protein. All refer to complexes involving the ligands CBZ, T15, G2P.



ANNEX VIII - REDOCKING

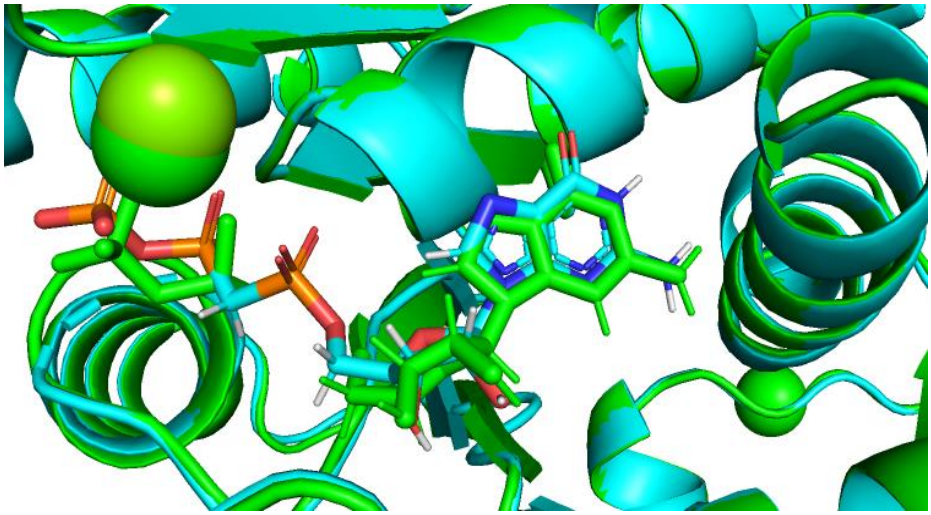
Table 29. Results of the scoring functions for the redocking of the crystallographic ligand of the 7ZCW protein.

REDOCKING PROTEIN 7ZCW - G2P LIGAND						
	RMSD			Solution		
	5A	7A	10A	5A	7A	10A
GoldScore	1,0823	1,2783	1,229	9	29	29
ChemPLP	3,2981	3,1438	4,281	47	63	69
ASP	1,2201	1,0851	1,1014	20	11	4
ChemScore	1,9633	1,7989	2,1279	67	47	98

The ASP scoring function at 7 Å (RMSD = 1.0851) and GoldScore at 5 Å (RMSD = 1.0823) thus reflected the best RMSDs. A close overlap between the crystallographic and predicted ligands is indicated by a reduced RMSD, indicating a better prediction of the molecular fit. Since they are very similar, the modeled proteins were docked in both configurations to determine whether the interactions were the same as those of the crystallographic protein. The interactions between the amino acids found in the modeled protein 7ZCW.1. G could be detected using

solutions 11 (ASP 7 Å) and 9 (GoldScore 5 Å). To determine potential ligand–protein interactions, the complexes in '.pdb' from these solutions were exported from the Gold program and added to Discovery Studio Visualizer. After all, the ASP 7 Å function was selected because it was possible to obtain eight of the twelve interactions that the crystallographic ligand makes with the original protein. The fact that the modeled protein had identical van der Waals and hydrogen bond interactions indicates that the comparison modeling was effectively validated. On this basis, this scoring function was selected as the standard for the next ensemble docking procedure.

Figure 4. Redocking of the modeled protein (in cyan blue) in superposition with the crystallographic ligand in the ASP 7 Å function (green color). An RMSD = 0.208 was obtained by aligning the proteins in PyMOL.



ANNEX IX - TOXICITY PREDICTION

Table 30. Results obtained by the ProTox II server for the six best triazoles obtained from the 2D QSAR (2 and 31), CoMFA (21 and 26) and CoMSIA (28 and 33) systems.

TOXICITY PREDICTION							
Compound	**LD_{50}**	**Predicted Toxicity Class**	**Average similarity**	**Prediction accuracy**	**Target**	**Probability**	**Lipinski**
15	400 mg/kg	4	51.74%	67.38%	**Inactive**		zero
20	500 mg/kg	4	54.68%	67.38%	Carcinogenicity	50%	zero
					Mutagenicity	50%	
21	500 mg/kg	4	52.05%	67.38%	Immunotoxicity	52%	zero
					Mutagenicity	60%	
22	500 mg/kg	4	54.68%	67.38%	Mutagenicity	52%	zero
25	500 mg/kg	4	45.39%	54.26%	Mutagenicity	61%	zero
27	500 mg/kg	4	52.61%	67.38%	Mutagenicity	60%	zero
CBZ	6000 mg/kg	6	48.35%	54.26%	Hepatotoxicity	63%	zero
					Mutagenicity	77%	
					Nuclear receptor signaling pathways: Aryl hydrocarbon Receptor (AhR)	100%	
					Stress response pathways: Phosphoprotein (Tumor Supressor) p53	100%	

CBZ: Carbendazim fungicide.

Table 31. Results of the physicochemical descriptors obtained by the Swiss ADME server for the six triazoles that obtained the best antifungal activity predicted according to the QSAR models.

Compound	MW	LogP	HBA	HBD	RB	arR
15	337.42	3.14	4	0	6	3
20	372.3	2.47	7	0	4	4
21	334.33	2.05	5	0	4	4
22	383.2	2.24	4	0	3	4
25	372.3	2.74	7	0	4	4
27	334.33	1.33	5	0	4	4
Carbendazim	191.19	0.81	3	2	3	2

MW: molecular weight; LogP: hydrophobicity; HBD: number of donors and acceptors of hydrogen bonds; RB: number of rotatable bonds; and arR: number of aromatic bonds.