Structure-Based Approach for the Study of Thyroid Hormone

Receptor Binding Affinity and Subtype Selectivity

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Table S1. Molecular structures of Indane Derivatives and their TR β binding affinity values (pK_i).

Compound	R ₁	R ₂	R ₃	R ₄	R ₅	pK _i
1	I	I	H	I		8.6402
2	Me	-CH ₂ CH ₂ CH ₂		H		5.7794
3	Me	-CH ₂ CH ₂ CH ₂		Et		7.2708
4	Me	-CH ₂ CH ₂ CH ₂		<i>i</i> Pr		8.1068
5	Me	-CH ₂ CH ₂ CH ₂				7.3990
6	Me	-CH ₂ CH ₂ CH ₂				7.4989
7 ^a	Me	-CH ₂ CH ₂ CH ₂				7.7696
8 ^a	Me	Me	H	4-F-C ₆ H ₄ CH(OH)		8.6635

9 ^a	Br	Br	H			6.6234
10 ^a	Me	-CH ₂ CH ₂ CH ₂		4-F-C ₆ H ₄ CH ₂		8.4318
11 ^a	Me	-CH ₂ CH ₂ CH ₂				7.8508
12	Me	-CH ₂ CH ₂ CH ₂		PhCH ₂ CH ₂		7.3958
13	Me	-CH ₂ CH ₂ CH ₂		4-F-C ₆ H ₄ CH ₂ CH ₂		8.0862
14 ^a	Me	-CH ₂ CH ₂ CH ₂		PhCH ₂ CH(OH)		6.9066
15 ^a	Me	-CH ₂ CH ₂ CH ₂		PhCH ₂ CO		6.3556
16	Me	-CH ₂ CH ₂ CH ₂		PhCH ₂ CH ₂ CH ₂		6.6517
25	Br	Br	H	<i>i</i> Pr		9.3665
26 ^a	Me	Me	H	<i>i</i> Pr		8.0000
27	CL	CL	CL	<i>i</i> Pr		8.8125
28	Me	Me	Me	<i>i</i> Pr		7.6925
29	Br	-CH ₂ CH ₂ CH ₂		<i>i</i> Pr		8.9245
30	Br	-CH ₂ (CH ₂) ₂ CH ₂		<i>i</i> Pr		6.5214
31	Me	-CH ₂ CH ₂ CH ₂		<i>i</i> Pr		8.5867
32	Me	-CH ₂ CH ₂ CH ₂		<i>i</i> Pr		7.821
33	Me	-CH ₂ CH ₂ CH ₂		<i>i</i> Pr		6.6716

Table S2. Summary of QSAR results based on superimposition I.

Table S2. Summary of QSAR results based on superimposition I.

	CoMFA	CoMSIA							
	SE	S	E	H	D	A	SE	SH	SD
R^2_{cv}	0.732	0.706	0.572	0.734	0.803	0.811	0.698	0.779	0.804
R^2_{ncv}	0.973	0.942	0.957	0.966	0.941	0.981	0.966	0.969	0.983
SEE	0.161	0.243	0.204	0.193	0.226	0.1433	0.182	0.179	0.128
F	102.781	37.408	62.613	53.144	75.203	98.93	79.564	71.033	164.513
R^2_{pred}	0.7054	0.5247	0.5758	0.086	0.7051	0.6163	0.581	0.133	0.6792
SEP	0.508	0.549	0.642	0.539	0.412	0.455	0.540	0.475	0.435
N _C	6	7	6	8	4	8	6	7	6
Field contribution									
S	0.302	0.652	-	-	-	-	0.165	0.236	0.104
E	0.374	-	0.661	-	-	-	0.486	-	-
H	-	-	-	0.730	-	-	-	0.476	-
D	-	-	-	-	0.524	-	-	-	0.472
A	-	-	-	-	-	0.684	-	-	-
L2 _p	0.190	0.239	0.165	0.140	0.283	0.128	0.187	0.168	0.252
MATS4 _p	0.134	0.109	0.174	0.130	0.194	0.188	0.162	0.120	0.171
CoMSIA									
	SA	EH	ED	EA	HD	HA	DA	SEH	SED
R^2_{cv}	0.739	0.708	0.877	0.644	0.794	0.820	0.863	0.769	0.870
R^2_{ncv}	0.986	0.970	0.996	0.931	0.983	0.992	0.969	0.984	0.998
SEE	0.126	0.176	0.068	0.250	0.129	0.096	0.167	0.132	0.053
F	127.602	73.28	397.284	48.738	160.718	197.776	113.463	116.125	641.592
R^2_{pred}	0.7798	0.4684	0.6065	0.6258	0.6578	0.5772	0.7179	0.4147	0.5868

SEP	0.534	0.547	0.379	0.569	0.445	0.459	0.353	0.502	0.390
N _C	8	7	9	5	6	9	5	8	9
Field contribution									
S	0.208	-	-	-	-	-	-	0.129	0.070
E	-	0.406	0.259	0.362	-	-	-	0.346	0.236
H	-	0.271	-	-	0.193	0.336	-	0.230	-
D	-	-	0.347	-	0.412	-	0.380	-	0.305
A	0.427	-	-	0.264	-	0.330	0.181	-	-
L2 _P	0.191	0.167	0.229	0.175	0.227	0.163	0.245	0.165	0.228
MATS4 _P	0.173	0.156	0.166	0.199	0.168	0.171	0.195	0.129	0.160
CoMSIA									
	SEA	SHD	SHA	SDA	EHD	EHA	EDA	HDA	SEHD
R ² _{cv}	0.718	0.810	0.802	0.848	0.858	0.753	0.890	0.846	0.867
R ² _{ncv}	0.989	0.972	0.991	0.971	0.995	0.986	0.996	0.982	0.999
SEE	0.107	0.160	0.100	0.163	0.075	0.124	0.066	0.133	0.040
F	176.463	123.864	180.022	119.555	364.58	130.579	411.521	152.426	1040.82
R ² _{pred}	0.6966	0.6862	0.601	0.7205	0.5908	0.5851	0.6356	0.7115	0.5149
SEP	0.555	0.428	0.481	0.372	0.394	0.520	0.359	0.385	0.410
N _C	8	5	9	5	8	8	9	6	10
Field contribution									
S	0.134	0.078	0.145	0.074	-	-	-	-	0.065
E	0.334	-	-	-	0.212	0.303	0.200	-	0.200
H	-	0.162	0.261	-	0.119	0.196	-	0.144	0.113
D	-	0.361	-	0.338	0.290	-	0.281	0.313	0.256
A	0.220	-	0.266	0.159	-	0.191	0.124	0.153	-
L2 _P	0.174	0.231	0.169	0.242	0.219	0.165	0.221	0.213	0.213
MATS4 _P	0.138	0.168	0.159	0.187	0.161	0.146	0.175	0.177	0.153
CoMSIA									
	SEHA	SEDA	SHDA	EHDA	SEHDA				
R ² _{cv}	0.783	0.881	0.853	0.873	0.875				
R ² _{ncv}	0.993	0.997	0.982	0.995	0.995				
SEE	0.088	0.059	0.132	0.077	0.075				
F	231.901	529.767	154.502	341.78	364.127				
R ² _{pred}	0.5868	0.6301	0.7129	0.6286	0.6336				
SEP	0.504	0.373	0.376	0.372	0.370				
N _C	9	9	6	8	8				
Field contribution									
S	0.106	0.059	0.062	-	0.051				
E	0.252	0.181	-	0.171	0.158				
H	0.174	-	0.131	0.099	0.093				
D	-	0.251	0.283	0.245	0.225				
A	0.164	0.115	0.138	0.109	0.100				
L2 _P	0.177	0.223	0.214	0.210	0.209				

MATS4 _P	0.127	0.171	0.173	0.167	0.164
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Table S3. Summary of QSAR results based on superimposition II .

	CoMFA	CoMSIA							
	SE	S	E	H	D	A	SE	SH	SD
R^2_{cv}	0.467	0.473	0.445	0.455	0.457	0.433	0.447	0.461	0.457
R^2_{ncv}	0.663	0.710	0.622	0.610	0.630	0.605	0.633	0.620	0.641
SEE	0.513	0.487	0.543	0.552	0.537	0.555	0.535	0.544	0.529
F	20.658	16.349	78.362	16.424	17.874	16.077	18.106	17.150	18.749
R^2_{pred}	0.7262	0.6268	0.7192	0.7465	0.7583	0.7299	0.7165	0.7417	0.7521
SEP	0.645	0.657	0.658	0.652	0.651	0.665	0.657	0.649	0.651
N _C	2	3	2	2	2	2	2	2	2
Field contribution									
S	0.113	0.433	-	-	-	-	0.045	0.044	0.044
E	0.190	-	0.148	-	-	-	0.150	-	-
H	-	-	-	0.083	-	-	-	0.085	-
D	-	-	-	-	0.169	-	-	-	0.173
A	-	-	-	-	-	0.068	-	-	-
GATS8e	0.572	0.380	0.658	0.697	0.650	0.692	0.634	0.676	0.626
Mor29m	0.125	0.187	0.194	0.220	0.181	0.240	0.171	0.194	0.157
CoMSIA									
	SA	EH	ED	EA	HD	HA	DA	SEH	SED
R^2_{cv}	0.438	0.439	0.433	0.425	0.445	0.431	0.429	0.440	0.433
R^2_{ncv}	0.615	0.638	0.612	0.601	0.646	0.620	0.607	0.648	0.615
SEE	0.548	0.532	0.538	0.545	0.526	0.545	0.541	0.524	0.536
F	16.785	18.484	34.723	33.153	19.132	17.131	33.934	19.371	35.075
R^2_{pred}	0.7293	0.7290	0.6535	0.6348	0.7571	0.7405	0.6675	0.7230	0.6546
SEP	0.662	0.662	0.650	0.655	0.658	0.666	0.652	0.661	0.650
N _C	2	2	1	1	2	2	1	2	1
Field contribution									
S	0.043	-	-	-	-	-	-	0.045	0.017
E	-	0.149	0.078	0.082	-	-	-	0.147	0.077
H	-	0.085	-	-	0.083	0.085	-	0.084	-
D	-	-	0.085	-	0.170	-	0.088	-	0.084
A	0.072	-	-	0.040	-	0.072	0.040	-	-
GATS8e	0.677	0.614	0.540	0.566	0.607	0.658	0.562	0.586	0.531
Mor29m	0.209	0.153	0.297	0.312	0.140	0.185	0.310	0.139	0.293
CoMSIA									
	SEA	SHD	SHA	SDA	EHD	EHA	EDA	HDA	SEHD
R^2_{cv}	0.425	0.444	0.432	0.429	0.430	0.422	0.427	0.426	0.430
R^2_{ncv}	0.604	0.657	0.631	0.609	0.613	0.603	0.614	0.608	0.615
SEE	0.543	0.518	0.537	0.540	0.537	0.544	0.536	0.540	0.535
F	33.519	20.087	17.964	34.299	34.836	33.357	34.998	34.100	35.167

R ² _{pred}	0.6360	0.7478	0.7320	0.6687	0.6601	0.6421	0.6466	0.6744	0.6610
SEP	0.655	0.659	0.666	0.652	0.652	0.656	0.653	0.654	0.652
N _C	1	2	2	1	1	1	1	1	1
Field contribution									
S	0.017	0.045	0.045	0.017	-	-	-	-	0.016
E	0.080	-	-	-	0.074	0.078	0.075	-	0.073
H	-	0.082	0.086	-	0.046	0.048	-	0.048	0.045
D	-	0.168	-	0.087	0.081	-	0.082	0.084	0.080
A	0.039	-	0.073	0.039	-	0.038	0.037	0.038	-
GATS8e	0.556	0.580	0.632	0.552	0.515	0.539	0.520	0.535	0.507
Mor29m	0.307	0.126	0.163	0.304	0.284	0.297	0.287	0.295	0.279
CoMSIA									
	SEHA	SEDA	SHDA	EHDA			SEHDA		
R ² _{cv}	0.422	0.427	0.426	0.424			0.424		
R ² _{ncv}	0.605	0.616	0.610	0.615			0.617		
SEE	0.542	0.535	0.539	0.536			0.534		
F	33.700	35.336	34.442	35.093			35.411		
R ² _{pred}	0.6431	0.6485	0.6755	0.6539			0.6553		
SEP	0.656	0.653	0.654	0.655			0.655		
N _C	1	1	1	1			1		
Field contribution									
S	0.017	0.016	0.017	-			0.015		
E	0.076	0.074	-	0.072			0.071		
H	0.047	-	0.047	0.044			0.044		
D	-	0.081	0.083	0.078			0.077		
A	0.038	0.036	0.037	0.035			0.035		
GATS8e	0.530	0.511	0.526	0.497			0.489		
Mor29m	0.292	0.282	0.290	0.274			0.270		

Table S4. Summary of QSAR results based on superimposition III.

	CoMFA	CoMSIA							
	SE	S	E	H	D	A	SE	SH	SD
R^2_{cv}	0.464	0.493	0.454	0.488	0.479	0.466	0.461	0.495	0.486
R^2_{ncv}	0.663	0.703	0.641	0.630	0.654	0.625	0.650	0.638	0.663
SEE	0.513	0.494	0.530	0.537	0.519	0.541	0.522	0.531	0.512
F	20.631	15.756	18.713	17.912	19.881	17.497	19.527	18.521	20.701
R^2_{pred}	0.7173	0.6081	0.7236	0.7592	0.7473	0.7511	0.7237	0.7615	0.7478
SEP	0.647	0.645	0.653	0.632	0.638	0.645	0.649	0.628	0.634
N_C	2	3	2	2	2	2	2	2	2
Field contribution									
S	0.117	0.4390	-	-	-	-	0.038	0.035	0.038
E	0.178	-	0.200	-	-	-	0.199	-	-
H	-	-	-	0.147	-	-	-	0.145	-

D	-	-	-	-	0.221	-	-	-	0.217
A	-	-	-	-	-	0.128	-	-	-
GATS8e	0.583	0.390	0.632	0.647	0.635	0.653	0.609	0.626	0.611
Mor29m	0.122	0.220	0.168	0.205	0.144	0.219	0.154	0.193	0.133
CoMSIA									
	SA	EH	ED	EA	HD	HA	DA	SEH	SED
R^2_{cv}	0.474	0.471	0.449	0.449	0.489	0.477	0.467	0.474	0.454
R^2_{ncv}	0.633	0.671	0.693	0.666	0.681	0.651	0.678	0.678	0.700
SEE	0.535	0.506	0.490	0.510	0.499	0.522	0.501	0.501	0.484
F	18.137	21.447	23.672	20.970	22.390	19.599	22.157	22.106	24.516
R^2_{pred}	0.7541	0.7443	0.7392	0.7264	0.7688	0.7700	0.7681	0.7439	0.7401
SEP	0.641	0.643	0.656	0.656	0.632	0.639	0.645	0.641	0.653
N _C	2	2	2	2	2	2	2	2	2
Field contribution									
S	0.035	-	-	-	-	-	-	0.033	0.033
E	-	0.184	0.179	0.186	-	-	-	0.178	0.173
H	-	0.135	-	-	0.132	0.132	-	0.130	-
D	-	-	0.195	-	0.197	-	0.203	-	0.189
A	0.129	-	-	0.121	-	0.117	0.122	-	-
GATS8e	0.634	0.537	0.522	0.542	0.542	0.568	0.546	0.519	0.503
Mor29m	0.202	0.143	0.105	0.150	0.129	0.184	0.128	0.139	0.102
CoMSIA									
	SEA	SHD	SHA	SDA	EHD	EHA	EDA	HDA	SEHD
R^2_{cv}	0.453	0.491	0.479	0.470	0.455	0.445	0.451	0.455	0.455
R^2_{ncv}	0.674	0.687	0.658	0.686	0.640	0.631	0.641	0.638	0.641
SEE	0.504	0.494	0.517	0.495	0.518	0.524	0.517	0.519	0.517
F	21.717	23.042	20.177	22.919	39.037	37.649	39.236	38.831	39.330
R^2_{pred}	0.7253	0.7697	0.7707	0.7686	0.6777	0.6704	0.6761	0.6910	0.6788
SEP	0.653	0.630	0.638	0.643	0.637	0.643	0.640	0.637	0.637
N _C	2	2	2	2	1	1	1	1	1
Field contribution									
S	0.034	0.033	0.032	0.034	-	-	-	-	0.013
E	0.182	-	-	-	0.076	0.079	0.077	-	0.075
H	-	0.127	0.128	-	0.062	0.064	-	0.063	0.061
D	-	0.190	-	0.198	0.085	-	0.086	0.087	0.084
A	0.118	-	0.114	0.118	-	0.052	0.051	0.051	-
GATS8e	0.523	0.523	0.549	0.526	0.501	0.519	0.507	0.515	0.495
Mor29m	0.143	0.126	0.176	0.123	0.276	0.286	0.280	0.294	0.273
CoMSIA									
	SEHA	SEDA	SHDA	EHDA	SEHDA				
R^2_{cv}	0.445	0.451	0.455	0.455	0.455				
R^2_{ncv}	0.633	0.643	0.640	0.649	0.650				
SEE	0.523	0.516	0.518	0.511	0.510				

F	37.937	39.539	39.117	40.660	40.923
R^2_{pred}	0.6712	0.6773	0.6916	0.6843	0.6846
SEP	0.643	0.640	0.637	0.637	0.637
N _C	1	1	1	1	1
Field contribution					
S	0.013	0.013	0.013	-	0.012
E	0.078	0.076	-	0.072	0.072
H	0.063	-	0.063	0.059	0.058
D	-	0.085	0.086	0.081	0.080
A	0.051	0.050	0.051	0.048	0.047
GATS8e	0.512	0.501	0.508	0.477	0.471
Mor29m	0.282	0.276	0.280	0.263	0.260

R^2_{cv} = cross-validated correlation coefficient using the leave-one-out methods;

R^2_{ncv} = Non-cross-validated correlation coefficient; SEE = Standard error of estimate; F= Ratio of R^2_{ncv} explained to unexplained = $R^2_{\text{ncv}}/(1-R^2_{\text{ncv}})$;

R^2_{pred} = Predicted correlation coefficient for the test set of compounds; SEP= Standard error of prediction; N_C= Optimal number of principal components; S=steric, E=electrostatic, H=hydrophobic, D=hydrogen bond donor, A= hydrogen bond acceptor.

Table S5. Actual and Optimal CoMFA predicted pK_i of training and test sets.

Compound	Observed	Predicted	Residual
1	8.6402	8.615	-0.0252
2	5.7794	5.781	0.0016
3	7.2708	7.15	-0.1208
4	8.1068	8.007	-0.0998
5	7.3990	7.406	0.007
6	7.4989	7.417	-0.0819
7	7.7696	7.476	-0.2936
8	8.6635	8.768	0.1045
9	6.6234	7.307	0.6836
10	8.4318	7.83	-0.6018
11	7.8508	7.727	-0.1238
12	7.3958	7.35	-0.0458
13	8.0862	7.752	-0.3342
14	6.9066	7.583	0.6764
15	6.3556	6.767	0.4114
16	6.6517	6.67	0.0183
17	7.9208	7.781	-0.1398
18	8.2218	8.179	-0.0428
19	7.5229	7.278	-0.2449
20	7.3872	7.367	-0.0202
21	7.3979	7.39	-0.0079
22	7.2716	7.285	0.0134

23	7.0899	7.461	0.3711
24	7.2396	7.553	0.3134
25	9.3665	9.489	0.1225
26	8.0000	7.97	-0.03
27	8.8125	8.733	-0.0795
28	7.6925	7.715	0.0225
29	8.9245	8.96	0.0355
30	6.5214	6.596	0.0746
31	8.5867	8.653	0.0663
32	7.8210	7.765	-0.056
33	6.6716	6.678	0.0064

Table S6. Actual and Optimal CoMSIA predicted pK_i of training and test sets.

Compound	Observed	Predicted	Residual
1	8.6402	8.747	0.1068
2	5.7794	5.747	-0.0324
3	7.2708	7.116	-0.1548
4	8.1068	7.876	-0.2308
5	7.3990	7.43	0.031
6	7.4989	7.493	-0.0059
7	7.7696	7.638	-0.1316
8	8.6635	8.98	0.3165
9	6.6234	7.226	0.6026
10	8.4318	7.778	-0.6538
11	7.8508	7.574	-0.2768
12	7.3958	7.507	0.1112
13	8.0862	7.816	-0.2702
14	6.9066	7.48	0.5734
15	6.3556	6.903	0.5474
16	6.6517	6.7	0.0483
17	7.9208	7.822	-0.0988
18	8.2218	8.069	-0.1528
19	7.5229	7.531	0.0081
20	7.3872	7.561	0.1738
21	7.3979	7.551	0.1531
22	7.2716	7.361	0.0894
23	7.0899	7.142	0.0521
24	7.2396	7.332	0.0924
25	9.3665	9.422	0.0555
26	8.0000	7.929	-0.071
27	8.8125	8.784	-0.0285
28	7.6925	7.64	-0.0525
29	8.9245	8.931	0.0065

30	6.5214	6.536	0.0146
31	8.5867	8.623	0.0363
32	7.8210	7.868	0.0470
33	6.6716	6.678	0.0064

Table S7. Descriptors used in model construction.

Symbol	Class	Meaning
L2 _p	WHIM	2nd component size directional WHIM index/weighted by atomic polarizabilities
MATS4 _p	2D autocorrelations	Moran autocorrelation-lag 4/weighted by atomic polarizabilities
GATS8e	2D autocorrelations	Geary autocorrelation-lag 8/weighted by atomic masses
Mor29m	3D-MoRSE	3D-MoRSE-signal 29/weighted by atomic masses

Figure S1. Graphs of the predicted versus the experimental pK_i values of the optimal models. (A) CoMFA model. (B) CoMSIA model.

Figure S2. The structure of the most active molecule used in the contour analyses.

Figure S3. The enlargement for compound 2 in the binding site after molecular docking, which is displayed in stick, H-bonds are shown as dotted black lines, and the nonpolar hydrogens were removed for clarity.

Figure S4. The enlargement for compound 1 in the binding site after molecular docking, which is displayed in stick, H-bonds are shown as dotted black lines, and the nonpolar hydrogens were removed for clarity.