3D-QSAR、 Molecular docking and Molecular dynamics Studies of a series of ROR γ t inhibitors

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Table S1. Molecular structures of thiazole/thiophene ketone amides and their ROR γ t binding affinity values (pIC₅₀).

Compound	R ₁	R ₂	R ₃	X	pIC ₅₀ (μ M)
1		Me	H	N	4.6
2			H	N	4.6
3 ^a			H	N	4.4
4			H	N	5.0

5 ^a			H	N	5.1
6			H	N	5.3
7			H	N	5.4
8			H	N	6.0
9 ^a			H	N	5.8
10			H	N	5.3
11			H	N	4.2
12			H	N	5.9
13 ^a			H	N	4.9
14	H		H	N	4.3
15 ^a	Me		H	N	4.1
16			H	N	5.8

17			H	N	5.1
18			H	N	5.7
19 ^a			H	N	5.4
20			H	N	5.4
21			H	N	6.1
22			H	N	5.9
23 ^a			H	N	5.2
24			Me	N	5.0
25			Et	N	5.3
26				N	5.7
27				N	6.2

28 ^a				N	6.4
29				N	5.0
30 ^a				N	5.2
31				N	5.6
32				N	7.6
33 ^a				N	7.5
34				N	7.4
35				N	7.9
36 ^a				N	7.4
37				N	7.5
38				N	6.1

39 ^a				N	5.1
40				N	7.8
41				N	8.0
42 ^a				N	7.9
43				N	7.7
44				N	7.6
45 ^a				CH	8.0
46				CH	7.9
47				CH	7.8
48				CH	8.0

49				CH	8.1
50				CH	8.2
51				CH	7.9
52 ^a				CH	8.0

^a represents the test set.

Table S2. Summary of QSAR results of ligand-based model for thiazole/thiophene ketone amides.

	CoMFA	CoMSIA							
	SE	S	E	H	D	A	SE	SH	SD
R^2_{cv}	0.859	0.746	0.811	0.899	0.161	0.835	0.860	0.906	0.787
R^2_{ncv}	0.993	0.929	0.902	0.980	0.369	0.928	0.965	0.983	0.941
SEE	0.120	0.360	0.422	0.195	1.106	0.363	0.255	0.179	0.334
F	689.96	143.888	101.717	388.446	3.620	141.263	222.121	369.421	126.995
R^2_{pred}	0.7317	0.7375	0.7095	0.7554	0.1484	0.6912	0.741	0.766	0.7335
SEP	0.531	0.680	0.587	0.436	1.275	0.549	0.512	0.427	0.633
N _C	6	3	3	4	5	3	4	6	4
Field contribution									
S	0.757	1.000	-	-	-	-	0.548	0.256	0.840
E	0.243	-	1.000	-	-	-	0.452	-	-
H	-	-	-	1.000	-	-	-	0.744	-
D	-	-	-	-	1.000	-	-	-	0.160
A	-	-	-	-	-	1.000	-	-	-
CoMSIA									
	SA	EH	ED	EA	HD	HA	DA	SEH	SED
R^2_{cv}	0.858	0.904	0.805	0.832	0.900	0.905	0.846	0.906	0.875
R^2_{ncv}	0.967	0.991	0.920	0.935	0.986	0.990	0.935	0.991	0.965
SEE	0.251	0.135	0.386	0.351	0.164	0.142	0.350	0.136	0.256
F	184.057	542.745	92.548	114.169	365.208	586.530	114.464	536.664	221.614
R^2_{pred}	0.7516	0.7573	0.7097	0.7263	0.7561	0.7636	0.6933	0.7639	0.7267
SEP	0.524	0.438	0.606	0.562	0.447	0.429	0.538	0.434	0.484
N _C	5	6	4	4	6	5	4	6	4

Field contribution									
S	0.396	-	-	-	-	-	-	0.224	0.498
E	-	0.213	0.891	0.304	-	-	-	0.178	0.385
H	-	0.787	-	-	0.963	0.683	-	0.599	-
D	-	-	0.109	-	0.037	-	0.111	-	0.117
A	0.604	-	-	0.696	-	0.317	0.889	-	-
CoMSIA									
	SEA	SHD	SHA	SDA	EHD	EHA	EDA	HDA	SEHD
R^2_{cv}	0.868	0.905	0.910	0.877	0.900	0.889	0.835	0.903	0.911
R^2_{ncv}	0.958	0.983	0.988	0.970	0.990	0.991	0.938	0.990	0.989
SEE	0.281	0.183	0.152	0.242	0.139	0.137	0.341	0.143	0.144
F	182.229	350.736	514.903	96.059	515.664	526.736	120.958	486.508	569.786
R^2_{pred}	0.7452	0.7677	0.7742	0.7300	0.7591	0.7653	0.7139	0.7575	0.7634
SEP	0.497	0.430	0.419	0.489	0.447	0.472	0.557	0.441	0.415
N_C	4	5	5	5	6	6	4	6	5
Field contribution									
S	0.323	0.251	0.189	0.358	-	-	-	-	0.212
E	0.213	-	-	-	0.205	0.122	0.264	-	0.172
H	-	0.715	0.532	-	0.754	0.619	-	0.653	0.570
D	-	0.034	-	0.116	0.042	-	0.103	0.036	0.046
A	0.464	-	0.280	0.526	-	0.259	0.633	0.310	-
CoMSIA									
	SEHA	SEDA	SHDA	EHDA	SEHDA				
R^2_{cv}	0.900	0.878	0.909	0.890	0.902				
R^2_{ncv}	0.988	0.962	0.986	0.990	0.987				
SEE	0.151	0.268	0.163	0.143	0.159				
F	518.311	201.204	445.293	487.837	466.465				
R^2_{pred}	0.7747	0.7352	0.7658	0.7614	0.7664				
SEP	0.440	0.480	0.421	0.469	0.436				
N_C	5	4	5	6	5				
Field contribution									
S	0.177	0.299	0.182	-	0.169				
E	0.110	0.191	-	0.118	0.105				
H	0.483	-	0.495	0.583	0.447				
D	-	0.084	0.052	0.047	0.058				
A	0.230	0.426	0.271	0.252	0.221				

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 = $R^2_{ncv}/(1-R^2_{ncv})$;

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=H-bond donor, A= H-bond acceptor.

Table S3. Summary of QSAR results of receptor-based model for thiazole/thiophene ketone amides.

	CoMFA	CoMSIA							
	SE	S	E	H	D	A	SE	SH	SD
R^2_{cv}	0.731	0.673	0.596	0.762	0.268	0.653	0.656	0.749	0.686
R^2_{ncv}	0.953	0.880	0.877	0.970	0.469	0.851	0.908	0.951	0.897
SEE	0.293	0.467	0.473	0.237	0.998	0.520	0.410	0.298	0.439
F	222.484	80.685	78.362	260.171	7.069	62.984	108.247	214.997	69.929
R^2_{pred}	0.5521	0.5606	0.3835	0.7126	0.1739	0.4444	0.4834	0.6778	0.5455
SEP	0.700	0.772	0.858	0.668	1.173	0.794	0.792	0.676	0.768
N_C	3	3	3	4	4	3	3	3	4
Field contribution									
S	0.514	1.000	-	-	-	-	0.417	0.344	0.828
E	0.486	-	1.000	-	-	-	0.583	-	-
H	-	-	-	1.000	-	-	-	0.656	-
D	-	-	-	-	1.000	-	-	-	0.172
A	-	-	-	-	-	1.000	-	-	-
CoMSIA									
	SA	EH	ED	EA	HD	HA	DA	SEH	SED
R^2_{cv}	0.680	0.731	0.557	0.632	0.788	0.734	0.647	0.739	0.645
R^2_{ncv}	0.873	0.968	0.888	0.870	0.971	0.975	0.840	0.955	0.916
SEE	0.481	0.244	0.459	0.487	0.233	0.222	0.539	0.287	0.397
F	75.394	243.875	63.355	73.545	269.189	237.411	57.847	231.334	87.179
R^2_{pred}	0.5504	0.5994	0.3654	0.4657	0.6976	0.5939	0.4895	0.5770	0.4476
SEP	0.763	0.710	0.912	0.819	0.631	0.718	0.801	0.689	0.816
N_C	3	4	4	3	4	5	3	3	4
Field contribution									
S	0.417	-	-	-	-	-	-	0.236	0.397
E	-	0.420	0.897	0.496	-	-	-	0.324	0.533
H	-	0.580	-	-	0.925	0.590	-	0.440	-
D	-	-	0.103	-	0.075	-	0.129	-	0.070
A	0.583	-	-	0.504	-	0.410	0.871	-	-
CoMSIA									
	SEA	SHD	SHA	SDA	EHD	EHA	EDA	HDA	SEHD
R^2_{cv}	0.658	0.773	0.730	0.688	0.720	0.716	0.633	0.753	0.725
R^2_{ncv}	0.882	0.9837	0.922	0.882	0.966	0.943	0.890	0.974	0.945
SEE	0.464	0.212	0.376	0.463	0.252	0.323	0.454	0.223	0.316
F	82.102	260.187	130.896	82.354	228.529	181.130	64.921	236.436	189.416
R^2_{pred}	0.5347	0.6706	0.6641	0.5761	0.5930	0.5568	0.3729	0.5905	0.5673
SEP	0.790	0.663	0.701	0.753	0.724	0.719	0.830	0.692	0.708
N_C	3	5	3	3	4	3	4	5	3
Field contribution									
S	0.259	0.312	0.226	0.379	-	-	-	-	0.229

E	0.366	-	-	-	0.393	0.287	0.459	-	0.307
H	-	0.613	0.432	-	0.552	0.405	-	0.548	0.417
D	-	0.075	-	0.094	0.056	-	0.059	0.067	0.047
A	0.375	-	0.342	0.527	-	0.308	0.482	0.385	-
CoMSIA									
	SEHA		SEDA		SHDA		EHDA		SEHDA
R ² _{cv}	0.712		0.656		0.741		0.707		0.713
R ² _{ncv}	0.930		0.890		0.932		0.970		0.935
SEE	0.358		0.447		0.353		0.241		0.343
F	145.294		89.288		150.065		201.336		158.864
R ² _{pred}	0.6118		0.5262		0.6606		0.5174		0.5886
SEP	0.724		0.791		0.687		0.754		0.723
N _C	3		3		3		5		3
Field contribution									
S	0.170		0.249		0.215		-		0.166
E	0.244		0.339		-		0.258		0.230
H	0.330		-		0.406		0.424		0.317
D	-		0.055		0.058		0.047		0.039
A	0.256		0.357		0.321		0.271		0.248

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 = $R^2_{ncv}/(1-R^2_{ncv})$;

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=H-bond donor, A= H-bond acceptor.

Table S4. Actual and Optimal CoMFA predicted pIC₅₀ of training and test sets.

Compound	Observed	Predicted	Residual
1	4.600	4.622	0.022
2	4.600	4.593	-0.007
3	4.400	4.759	0.359
4	5.000	5.139	0.139
5	5.100	5.276	0.176
6	5.300	5.152	-0.148
7	5.400	5.529	0.129
8	6.000	5.985	-0.015
9	5.800	5.401	-0.399
10	5.300	5.577	0.277
11	4.200	4.264	0.064
12	5.900	5.651	-0.249
13	4.900	5.565	0.665
14	4.300	4.217	-0.083
15	4.100	4.638	0.538

16	5.800	5.902	0.102
17	5.100	5.199	0.099
18	5.700	5.502	-0.198
19	5.400	5.554	0.154
20	5.400	5.500	0.100
21	6.100	5.938	-0.162
22	5.900	5.843	-0.057
23	5.200	5.854	0.654
24	5.000	4.998	-0.002
25	5.300	5.130	-0.170
26	5.700	5.839	0.139
27	6.200	6.262	0.062
28	6.400	5.601	-0.799
29	5.000	5.027	0.027
30	5.200	5.257	0.057
31	5.600	5.643	0.043
32	7.600	7.560	-0.040
33	7.500	6.937	-0.563
34	7.400	7.505	0.105
35	7.900	7.933	0.033
36	7.400	7.029	-0.371
37	7.500	7.465	-0.035
38	6.100	6.026	-0.074
39	5.100	7.233	2.133
40	7.800	7.836	0.036
41	8.000	7.920	-0.080
42	7.900	7.735	-0.165
43	7.700	7.671	-0.029
44	7.600	7.506	-0.094
45	8.000	7.717	-0.283
46	7.900	7.935	0.035
47	7.800	7.8633	0.063
48	8.000	7.977	-0.023
49	8.100	8.220	0.120
50	8.200	8.178	-0.022
51	7.900	7.791	-0.109
52	8.000	7.576	-0.424

Table S5. Actual and Optimal CoMSIA predicted pIC₅₀ of training and test sets.

Compound	Observed	Predicted	Residual
1	4.600	4.659	0.059
2	4.600	4.398	-0.202
3	4.400	4.664	0.264

4	5.000	5.078	0.078
5	5.100	5.076	-0.024
6	5.300	5.025	-0.275
7	5.400	5.740	0.340
8	6.000	5.508	-0.492
9	5.800	5.609	-0.191
10	5.300	5.584	0.284
11	4.200	4.182	-0.018
12	5.900	5.909	0.009
13	4.900	5.603	0.703
14	4.300	5.184	0.884
15	4.100	5.010	0.910
16	5.800	5.581	-0.219
17	5.100	5.797	0.697
18	5.700	5.569	-0.131
19	5.400	5.673	0.273
20	5.400	5.776	0.376
21	6.100	5.596	-0.504
22	5.900	5.609	-0.291
23	5.200	5.556	0.356
24	5.000	5.495	0.495
25	5.300	5.507	0.207
26	5.700	5.479	-0.221
27	6.200	5.260	-0.940
28	6.400	5.972	-0.428
29	5.000	5.687	0.687
30	5.200	4.978	-0.222
31	5.600	5.162	-0.438
32	7.600	7.427	-0.173
33	7.500	7.062	-0.438
34	7.400	7.663	0.263
35	7.900	7.76	-0.140
36	7.400	7.031	-0.369
37	7.500	7.634	0.134
38	6.100	6.146	0.046
39	5.100	7.369	2.269
40	7.800	7.706	-0.094
41	8.000	7.633	-0.367
42	7.900	7.749	-0.151
43	7.700	7.94	0.240
44	7.600	7.78	0.180
45	8.000	7.298	-0.702
46	7.900	7.723	-0.177

47	7.800	7.852	0.052
48	8.000	7.911	-0.089
49	8.100	7.788	-0.312
50	8.200	8.175	-0.025
51	7.900	7.780	0.080
52	8.000	8.224	0.224

Figure S1. Present the alignments from the superimposition II .

Figure S2. Structural superposition of ROR γ t-50 and the crystal structure 4NIE. The projection highlights the structure of the active site with compound 50(cyan) and NBH (green), which is displayed in sticks.