Electronic Supplementary Material (ESI) for RSC Advances.

Computational Insights into Inhibitory Mechanism of Azole Compounds against Human Aromatase

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Table S1. Docking results of LTZ and IMZ to aromatase

	Cluster Number	Cluster Size	Chemscore	
			Top1	Average
LTZ	1	50	38.71	37.67
R-IMZ	1	10	41.58	40.79
	2	24	40.64	39.24
	3	10	40.40	39.23
	4	6	38.89	37.98
S-IMZ	1	20	40.18	39.05
	2	19	40.04	39.02
	3	8	38.60	38.11
	4	3	37.66	37.52

Table S2 Energy contributions of key residues to the binding free energies (kcal/mol)

Residue number	LTZ		*S*-IMZ		*R*-IMZ	
	Residue name	Δ*G*res bind ± std	Residue name	Δ*G*res bind ± std	Residue name	Δ*G*res bind ± std
115	Arg	-1.02±0.49	Arg	-0.57±0.32	Arg	-0.77±0.17
127	Met	-0.05±0.02	Met	-0.03±0.02	Met	-0.04±0.02
133	Ile	-1.3±0.33	Ile	-1.41±0.33	Ile	-1.27±0.33
134	Phe	-0.61±0.17	Phe	-1.2±0.33	Phe	-0.82±0.24
217	Ile	-0.04±0.02	Ile	-0.01±0	Ile	-0.02±0.01
221	Phe	-1.37±0.25	Phe	-0.32±0.21	Phe	-0.24±0.18
224	Trp	-0.92±0.24	Trp	-1.13±0.31	Trp	-0.71±0.27
305	Ile	-0.39±0.09	Ile	-0.34±0.09	Ile	-0.29±0.06
306	Ala	-0.69±0.35	Ala	-0.52±0.15	Ala	-0.54±0.14
307	Ala	-0.13±0.04	Ala	0.02±0.02	Ala	0±0.03
308	Pro	-0.06±0.02	Pro	-0.01±0.02	Pro	-0.01±0.02
309	Asp	-0.76±0.33	Asp	-0.32±0.19	Asp	-0.28±0.24
310	Thr	-1.81±0.53	Thr	-0.91±0.25	Thr	-0.91±0.29
369	Val	-0.62±0.2	Val	-0.19±0.06	Val	-0.23±0.08
370	Val	-0.98±0.2	Val	-0.97±0.25	Val	-1.63±0.26
371	Asp	-0.09±0.02	Asp	-0.15±0.05	Asp	-0.07±0.03
372	Leu	-0.35±0.15	Leu	0.14±0.23	Leu	-0.43±0.36
373	Val	-1.53±0.2	Val	-0.71±0.27	Val	-1.05±0.21
374	Met	-0.85±0.25	Met	-0.65±0.32	Met	-0.50±0.33
375	Arg	0.02±0.02	Arg	-0.13±0.04	Arg	-0.06±0.02
478	Ser	-0.21±0.27	Ser	-0.3±0.15	Ser	-0.22±0.19
479	Leu	-0.08±0.03	Leu	-0.01±0.01	Leu	-0.03±0.01
480	His	-0.16±0.08	His	0.02±0.01	His	0.01±0.01
437	Heme	-8.61±0.79	Heme	-5.2±0.57	Heme	-7.66±0.63

Table S3. The statistical results of the sum of force and maximum force for SMD simulations of LTZ and *R*-IMZ unbinding along Path S and Path 2a, respectively

System		LTZ				*R*-IMZ			
Pathway		S		2a		S		2a	
SMD No.	N total	Sum	Max	Sum	Max	Sum	Max	Sum	Max
1	3000	13357.454	17.573	17579.186	17.635	14790.226	17.025	12824.046	13.907
2	3000	14982.776	16.596	16388.277	18.879	13894.311	17.421	15607.797	15.481
3	3000	13110.256	16.184	15402.860	19.593	12584.528	12.774	10313.273	13.177
4	3000	11655.123	14.637	19999.746	18.364	11527.608	12.772	9203.774	12.424
5	3000	18084.637	17.219	16238.282	18.476	16189.459	18.646	13204.665	11.631
6	3000	14810.889	20.230	20546.259	19.647	12549.917	16.240	12599.378	12.842
7	3000	13296.400	17.231	16856.471	17.093	13288.799	15.623	11364.522	12.257
8	3000	10442.141	17.428	15151.019	16.102	10529.601	15.090	8446.294	11.380
9	3000	18077.092	19.939	18783.951	23.956	15729.953	15.620	9353.919	12.127
10	3000	10435.520	15.227	17098.329	16.847	12456.373	14.072	12772.416	13.025
11	3000	13838.192	15.934	20237.268	19.411	15664.501	19.253	9265.059	11.390
12	3000	16831.441	20.648	17800.449	21.640	14773.350	17.581	9807.546	11.737
13	3000	15654.356	16.509	18130.690	17.480	14353.196	17.782	13035.432	16.168
14	3000	12335.439	15.920	18284.943	17.124	13450.187	19.063	13989.245	15.925
15	3000	15589.484	17.900	16503.568	18.933	13545.959	13.079	9412.949	15.749
16	3000	15589.484	17.900	22764.364	19.852	16131.638	18.226	9116.495	12.215
17	3000	11364.746	14.443	16561.446	18.127	13250.535	15.568	11242.851	12.504
18	3000	14695.676	15.803	16077.820	18.649	13735.520	13.604	9470.844	12.811
19	3000	15115.895	16.787	19039.541	19.912	11246.991	15.556	12184.717	12.590
20	3000	12243.893	15.756	17319.321	17.983	13976.208	15.817	13137.605	12.183

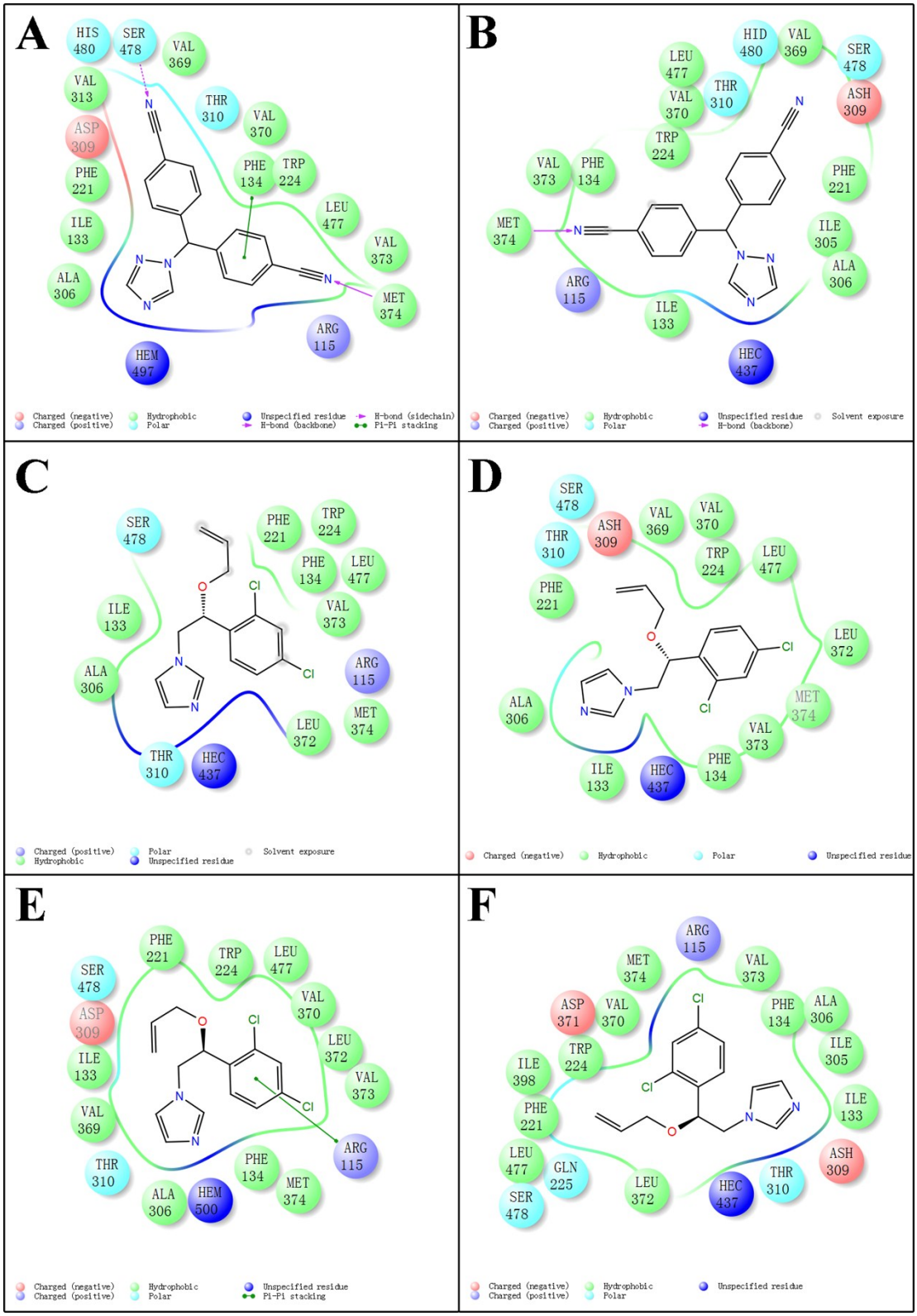

Figure S1. The 2D diagrams of the interactions between aromatase and LTZ (A), *R*-IMZ (C) and *S*-IMZ (E) from docking poses and MD refined poses of LTZ (B), *R*-IMZ (D) and *S*-IMZ (F)

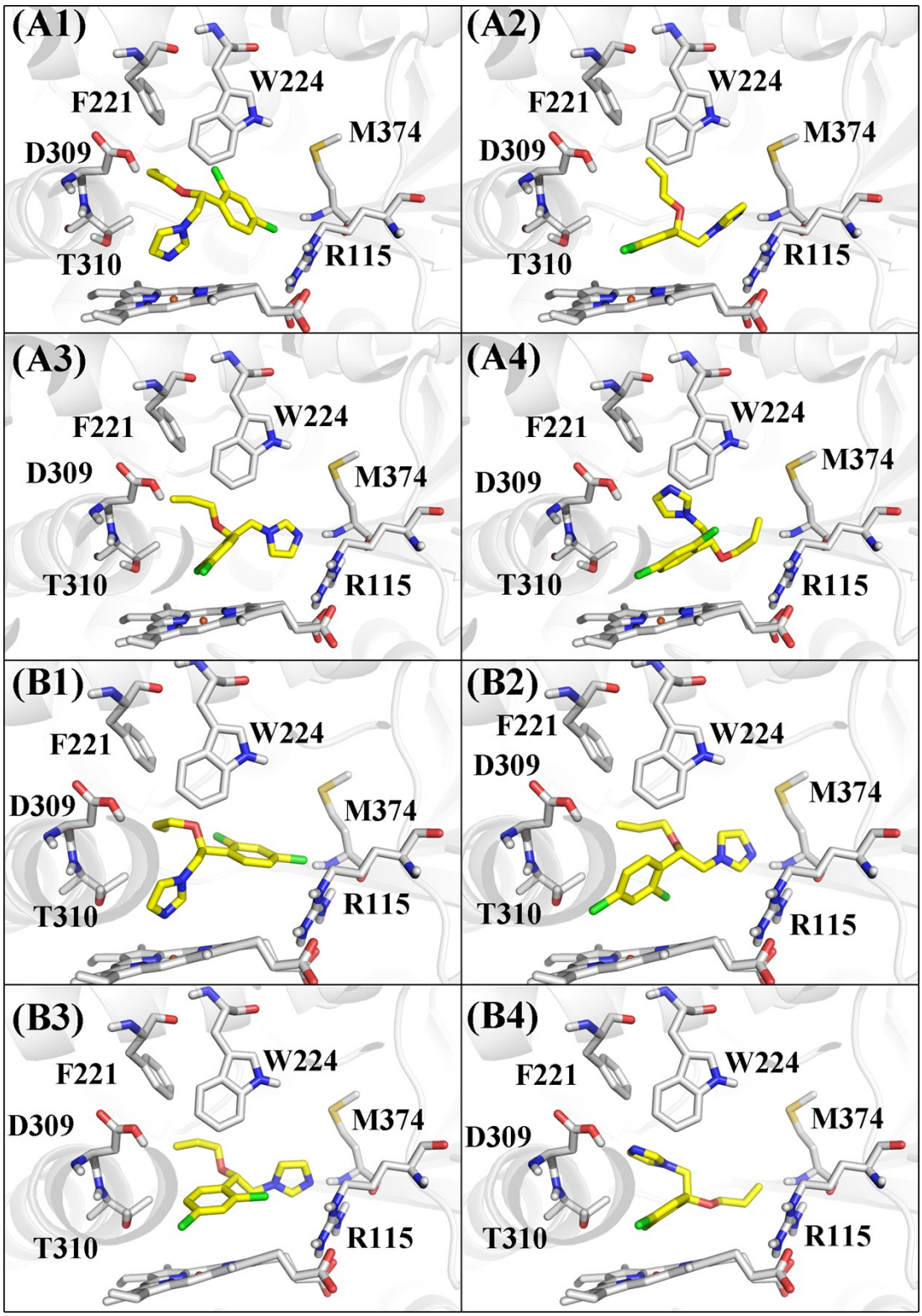

Figure S2. The representative docking poses of *R*-IMZ (A) and *S*-IMZ (B). (A1-A4): the highest scored poses of *R*-IMZ in clusters 1 to 4, respectively. (B1-B4): the highest scored poses of *S*-IMZ in clusters 1-4, respectively

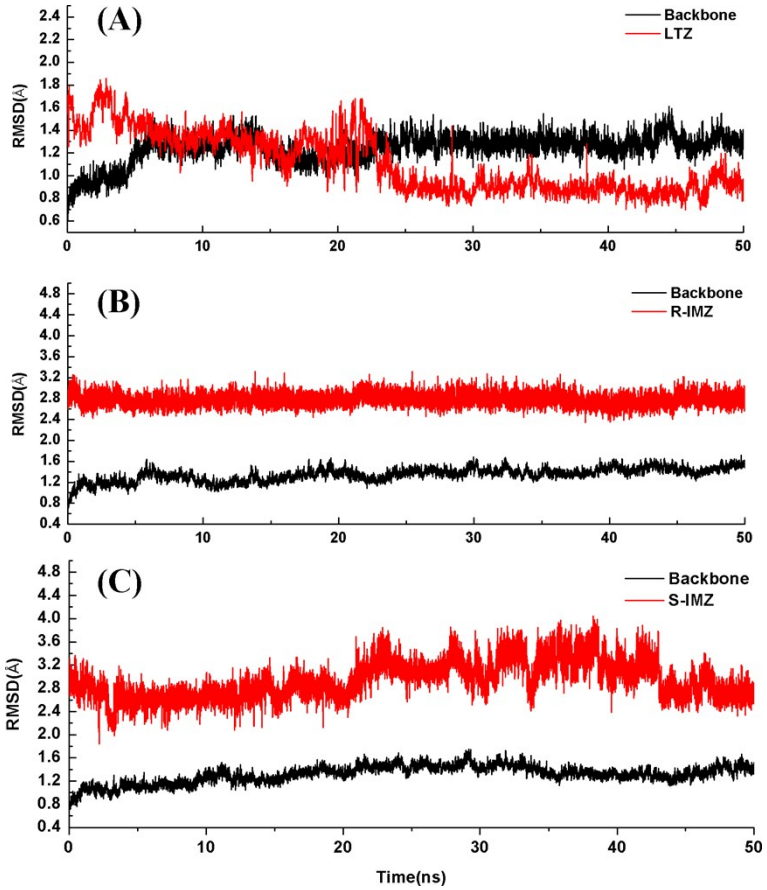

Figure S3. RMSD variation of LTZ (A), *R*-IMZ (B) and *S*-IMZ(C) with respect to simulation time

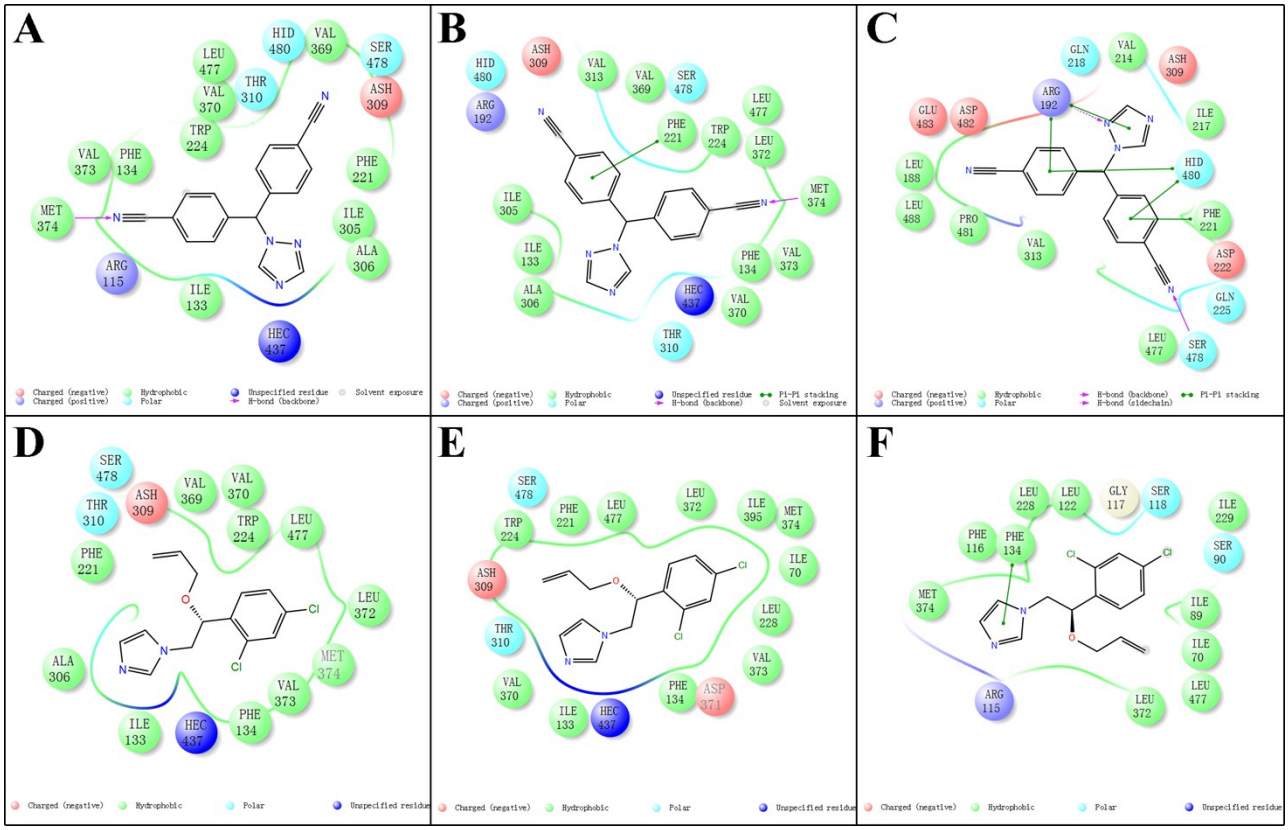

Figure S4. The 2D diagrams of snapshots of LTZ unbinding from aromatase along Path S (A, 0 ps; B, 460 ps; C, 1700 ps), and of *R*-IMZ along Path 2a (D, 0 ps; E, 330 ps; F, 1330 ps)