Supporting information

Insights into anti-tuberculosis drug design on the scaffold of nitroimidazole derivatives using the structure-based computer-aided approaches

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Table S1. Summary of QSAR results based on template ligand-based alignment.

	CoMFA	CoMSIA							
	SE	S	E	H	D	A	SE	SH	SD
R^2_{cv}	0.732	0.845	0.657	0.742	0.634	0.618	0.778	0.752	0.833
R^2_{ncv}	0.991	0.988	0.942	0.996	0.713	0.726	0.994	0.996	0.986
SEE	0.122	0.148	0.304	0.089	0.657	0.642	0.099	0.086	0.159
F	654.454	295.482	119.749	734.014	32.223	34.364	656.21	788.819	227.988
R^2_{pred}	0.7212	0.5979	0.7160	0.6547	0.8487	0.3930	0.7337	0.6605	0.6887
SEP	0.660	0.525	0.737	0.688	0.741	0.758	0.627	0.674	0.553
N_C	6	9	5	10	3	3	9	10	10
Field contribution									
S	0.899	1.000	-	-	-	-	0.620	0.325	0.538
E	0.101	-	1.000	-	-	-	0.380	-	-
H	-	-	-	1.000	-	-	-	0.675	-
D	-	-	-	-	1.000	-	-	-	0.462
A	-	-	-	-	-	1.000	-	-	-
CoMSIA									
	SA	EH	ED	EA	HD	HA	DA	SEH	SED
R^2_{cv}	0.782	0.713	0.698	0.759	0.751	0.713	0.648	0.728	0.809
R^2_{ncv}	0.986	0.987	0.953	0.982	0.957	0.971	0.793	0.991	0.993
SEE	0.162	0.150	0.280	0.181	0.264	0.222	0.565	0.122	0.113
F	219.443	367.357	102.004	195.233	134.386	165.548	36.351	485.811	456.734
R^2_{pred}	0.3180	0.7384	0.7941	0.4070	0.8302	0.6783	0.6901	0.7211	0.7597
SEP	0.632	0.694	0.712	0.655	0.637	0.693	0.737	0.685	0.591
N_C	10	7	7	9	6	7	4	8	10
Field contribution									
S	0.586	-	-	-	-	-	-	0.280	0.381
E	-	0.249	0.452	0.476	-	-	-	0.183	0.254
H	-	0.751	-	-	0.625	0.704	-	0.537	-
D	-	-	0.548	-	0.375	-	0.509	-	0.365
A	0.414	-	-	0.524	-	0.296	0.491	-	-
CoMSIA									
	SEA	SHD	SHA	SDA	EHD	EHA	EDA	HDA	SEHD
R^2_{cv}	0.775	0.766	0.725	0.781	0.742	0.715	0.702	0.717	0.757
R^2_{ncv}	0.994	0.993	0.971	0.983	0.966	0.933	0.980	0.946	0.970
SEE	0.104	0.110	0.222	0.176	0.236	0.323	0.193	0.298	0.220
F	538.982	482.597	164.537	185.702	169.774	131.329	154.016	104.194	196.483
R^2_{pred}	0.4327	0.7354	0.6825	0.6440	0.8292	0.7146	0.7031	0.7803	0.8048
SEP	0.643	0.655	0.679	0.633	0.649	0.663	0.739	0.678	0.630
N_C	10	10	7	10	6	4	10	6	6
Field contribution									

S	0.371	0.229	0.226	0.379	-	-	-	-	0.190
E	0.273	-	-	-	0.158	0.144	0.356	-	0.127
H	-	0.504	0.514	-	0.509	0.510	-	0.515	0.398
D	-	0.267	-	0.341	0.333	-	0.301	0.278	0.285
A	0.356	-	0.260	0.280	-	0.346	0.343	0.208	-

CoMSIA					
	SEHA	SEDA	SHDA	EHDA	SEHDA
R^2_{cv}	0.717	0.773	0.730	0.718	0.726
R^2_{ncv}	0.988	0.988	0.972	0.935	0.939
SEE	0.143	0.149	0.217	0.321	0.312
F	354.666	291.239	172.331	106.057	113.388
R^2_{pred}	0.5999	0.6579	0.7251	0.7508	0.7787
SEP	0.699	0.644	0.673	0.669	0.659
N_C	8	9	7	5	5
Field contribution					
S	0.202	0.272	0.185	-	0.153
E	0.148	0.222	-	0.118	0.098
H	0.419	-	0.426	0.406	0.336
D	-	0.253	0.212	0.255	0.225
A	0.231	0.253	0.177	0.222	0.189

Table S2. The docking scores of all the prepared NOS compounds. Total score is exponential to the binding affinity (μM) of the compounds.

Name	Total_Score	Crash	Polar	FragRMSD	Name	Total_Score	Crash	Polar	FragRMSD
1	6.454	-0.979	1.314	1.583	30.000	8.350	-2.455	0.000	4.479
2	6.617	-0.945	1.303	1.563	31.000	8.234	-3.360	1.603	3.208
3	6.364	-0.942	1.238	1.618	32.000	8.444	-2.268	1.707	3.371
4	6.873	-0.846	0.220	2.005	33.000	8.169	-2.404	1.666	3.295
5	6.331	-1.128	1.196	1.733	34.000	8.354	-1.751	1.760	3.296
6	6.119	-1.201	1.324	1.683	35.000	9.165	-2.354	2.019	3.229
7	7.012	-1.154	1.290	1.505	36.000	8.562	-2.444	1.789	3.380
8	6.520	-1.047	1.361	1.496	37.000	8.050	-2.368	1.749	3.385
9	7.841	-0.736	0.089	1.594	38.000	9.143	-2.701	1.657	3.321
10	7.493	-1.154	1.375	1.570	39.000	9.241	-2.235	1.690	3.378
11	6.237	-2.265	1.521	3.395	40.000	9.597	-2.397	1.643	3.208
12	6.505	-0.722	2.369	3.833	41.000	5.118	-1.503	1.830	3.221
13	5.945	-0.641	0.000	8.009	42.000	5.147	-1.355	2.603	3.129
14	6.021	-3.802	1.799	3.251	43.000	5.583	-1.093	1.850	3.183

15	7.623	-1.630	1.354	2.097	44.000	6.674	-1.476	1.755	3.122
16	7.417	-1.149	1.747	3.178	45.000	6.447	-1.744	1.706	3.125
17	5.902	-1.136	1.563	4.159	46.000	5.844	-0.865	0.975	6.746
18	6.676	-0.691	0.000	4.710	47.000	6.548	-1.521	2.400	5.640
19	6.005	-0.398	2.396	3.254	48.000	4.576	-1.085	1.623	2.898
20	6.066	-1.291	1.429	2.725	49.000	5.817	-1.838	1.691	2.918
21	6.362	-1.879	2.715	2.804	50.000	6.736	-2.208	1.675	3.186
22	6.567	-0.725	0.305	2.376	51.000	6.788	-1.383	1.588	3.031
23	7.159	-1.119	1.171	12.172	52.000	7.272	-1.576	1.600	3.190
24	8.136	-0.906	1.508	12.270	53.000	6.554	-1.282	2.997	3.186
25	8.482	-0.998	1.662	12.360	54.000	5.909	-0.717	3.346	3.836
26	7.319	-0.777	0.099	1.562	55.000	7.232	-1.207	1.662	3.284
27	7.983	-1.250	1.012	1.543	56.000	6.031	-2.123	1.583	2.895
28	8.267	-1.158	0.512	3.635	57.000	7.626	-1.269	1.590	3.153
29	8.518	-1.930	1.453	3.280	58.000	6.359	-1.426	2.109	3.286

*The fregRMSD refers to the molecular displacement between the nitroimidazodiazine moiety of the compound and the redocked PA-824. The unit is in Å.

Table S3 Summary of QSAR results based on docking-based alignment.

	CoMFA	CoMSIA							
	SE	S	E	H	D	A	SE	SH	SD
R^2_{cv}	0.695	0.675	0.638	0.580	0.644	0.554	0.718	0.676	0.662
R^2_{ncv}	0.964	0.938	0.888	0.891	0.815	0.700	0.989	0.898	0.783
SEE	0.243	0.331	0.415	0.411	0.583	0.671	0.144	0.398	0.564
F	158.883	55.772	75.426	77.287	14.076	30.401	279.589	83.211	72.309
R^2_{pred}	0.0932	0.0032	0.7216	0.3001	0.2282	0.6230	0.0552	0.3530	0.2793
SEP	0.705	0.759	0.747	0.805	0.808	0.819	0.687	0.707	0.704
N_C	6	9	4	4	10	3	7	4	2
Field contribution									
S	0.823	1.000	-	-	-	-	0.460	0.356	0.395
E	0.177	-	1.000	-	-	-	0.540	-	-
H	-	-	-	1.000	-	-	-	0.644	-
D	-	-	-	-	1.000	-	-	-	0.605
A	-	-	-	-	-	1.000	-	-	-
CoMSIA									
	SA	EH	ED	EA	HD	HA	DA	SEH	SED
R^2_{cv}	0.697	0.653	0.635	0.691	0.600	0.634	0.606	0.698	0.679
R^2_{ncv}	0.816	0.928	0.971	0.868	0.989	0.843	0.786	0.914	0.800
SEE	0.525	0.334	0.230	0.451	0.145	0.486	0.567	0.365	0.541
F	57.805	121.677	107.56	62.585	275.807	69.596	47.731	100.654	80.160

R^2_{pred}	0.4746	0.4101	0.2201	0.7537	0.2463	0.4690	0.4595	0.3933	0.2636
SEP	0.675	0.731	0.818	0.690	0.856	0.742	0.770	0.682	0.686
N_C	3	4	10	4	10	3	3	4	2
Field contribution									
S	0.557	-	-	-	-	-	-	0.270	0.303
E	-	0.286	0.405	0.514	-	-	-	0.199	0.197
H	-	0.714	-	-	0.594	0.661	-	0.530	-
D	-	-	0.595	-	0.406	-	0.657	-	0.500
A	0.443	-	-	0.486	-	0.339	0.343	-	-
CoMSIA									
	SEA	SHD	SHA	SDA	EHD	EHA	EDA	HDA	SEHD
R^2_{cv}	0.703	0.683	0.694	0.674	0.645	0.664	0.608	0.623	0.696
R^2_{ncv}	0.830	0.993	0.857	0.815	0.991	0.922	0.759	0.988	0.995
SEE	0.506	0.116	0.464	0.527	0.129	0.347	0.594	0.146	0.094
F	63.450	431.066	77.876	57.343	388.283	112.425	63.111	272.876	665.667
R^2_{pred}	0.5216	0.1219	0.4249	0.4198	0.2386	0.5257	0.4099	0.3889	0.1359
SEP	0.668	0.762	0.678	0.700	0.794	0.720	0.758	0.831	0.747
N_C	3	10	3	3	9	4	2	10	10
Field contribution									
S	0.445	0.204	0.299	0.282	-	-	-	-	0.169
E	0.206	-	-	-	0.177	0.210	0.180	-	0.142
H	-	0.463	0.440	-	0.455	0.586	-	0.502	0.387
D	-	0.332	-	0.466	0.367	-	0.576	0.357	0.302
A	0.348	-	0.261	0.252	-	0.204	0.244	0.141	-

CoMSIA					
	SEHA	SEDA	SHDA	EHDA	SEHDA
R^2_{cv}	0.698	0.674	0.692	0.633	0.692
R^2_{ncv}	0.868	0.797	0.992	0.990	0.995
SEE	0.446	0.546	0.122	0.136	0.099
F	85.306	78.297	389.534	346.747	595.716
R^2_{pred}	0.4587	0.3803	0.2415	0.3831	0.2527
SEP	0.673	0.691	0.751	0.688	0.752
N_C	3	2	10	9	10
Field contribution					
S	0.266	0.237	0.172	-	0.150
E	0.131	0.143	-	0.144	0.123
H	0.392	-	0.423	0.417	0.363
D	-	0.430	0.299	0.331	0.276
A	0.211	0.191	0.107	0.108	0.088

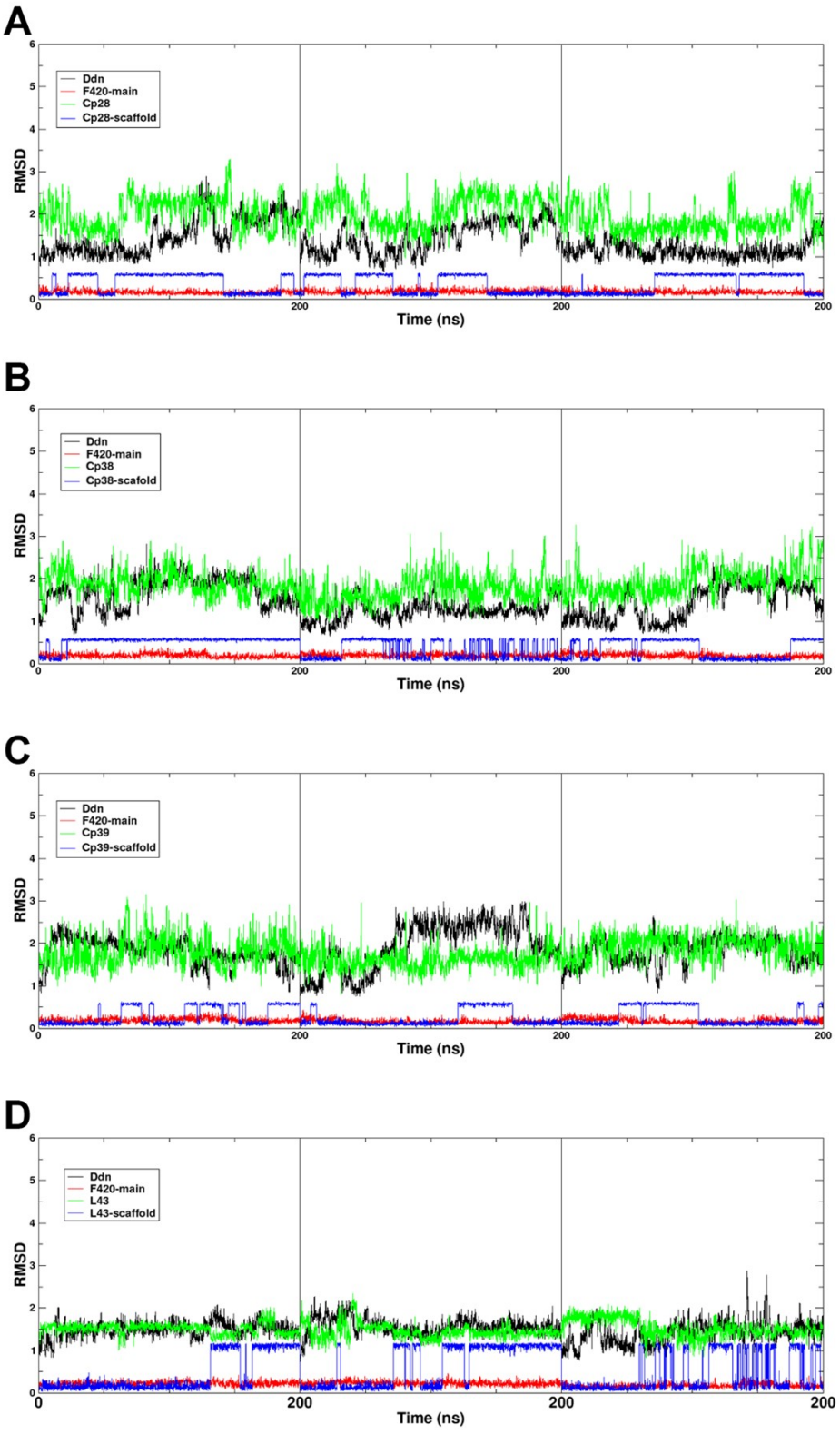

Fig. S1. The RMSD plot of the four MD systems. (A) Ddn-F420-L28 MD system; (B) Ddn-F420-L38 MD

system; (C) Ddn-F420-L39 MD system; (D) Ddn-F420-L43 MD system. The black line is the RMSD of the backbone atoms of Ddn. The F420-main is in red, while the NOS part and R tail moiety of the compounds are in green and blue lines, respectively.

S.Video 1: allnoHPC1-CP28.mp4. The PC1 movement of the overall PCA on Cp28 system.

S.Video 2: localPC1-Cp28.mp4. The PC1 movement of the local PCA on Cp28 system.

S.Video 3: allnoHPC1-CP38.mp4. The PC1 movement of the overall PCA on Cp38 system.

S.Video 4: localPC1-Cp38.mp4. The PC1 movement of the local PCA on Cp38 system.

S.Video 5: allnoHPC1-CP39.mp4. The PC1 movement of the overall PCA on Cp39 system.

S.Video 6: localPC1-Cp39.mp4. The PC1 movement of the local PCA on Cp39 system.

S.Video 7: allnoHPC1-CP43.mp4. The PC1 movement of the overall PCA on Cp43 system.

S.Video 8: localPC1-Cp43.mp4. The PC1 movement of the local PCA on Cp43 system.

Table S4. The MMPBSA results of the Cp28/38/39/43 systems.

	Terms	Cp28 system			Cp38 system			Cp39 system			Cp43 system		
	VDWAALS	-46.89	3.57	0.21	-46.24	7.84	0.45	-53.07	5.86	0.34	-33.56	2.97	0.17
	EEL	-14.63	3.52	0.20	-12.77	7.80	0.45	-14.67	5.47	0.32	-9.08	3.47	0.20
	EPB	35.37	3.56	0.21	32.30	9.82	0.57	38.55	6.31	0.36	26.43	3.74	0.22
	ENPOLAR	-4.20	0.21	0.01	-4.47	0.44	0.03	-4.59	0.34	0.02	-3.06	0.12	0.01
PBSA	EDISPER	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	DELTA G gas	-61.52	5.02	0.29	-59.01	13.86	0.80	-67.74	8.69	0.50	-42.64	4.00	0.23
	DELTA G solv	31.17	3.50	0.20	27.83	9.53	0.55	33.96	6.16	0.36	23.38	3.73	0.22
	DELTA TOTAL	-30.35	4.39	0.25	-31.18	5.96	0.34	-33.78	5.69	0.33	-19.27	3.35	0.19
	Translational	-13.05	0.00	0.00	-12.32	0.00	0.00	-18.32	0.00	0.00	-12.70	0.00	0.00
T*Delta	Rotational	-11.13	0.06	0.01	-11.70	0.03	0.01	-11.75	0.03	0.00	-10.16	0.00	0.00
S	Vibrational	1.06	3.10	0.46	-0.34	4.01	0.60	0.94	4.44	0.66	4.02	3.00	0.45
	DELTA S total	-23.12	3.10	0.46	-24.36	4.01	0.60	-29.14	4.44	0.66	-18.84	3.00	0.45
Binding affinity		-7.24	1.29	-0.21	-6.82	1.95	-0.25	-4.64	1.25	-0.33	-0.43	0.35	-0.25