

**Unlocking Tyrosinase Inhibition: Insights from Molecular Dynamics
and Binding Free Energy Studies of Novel Arylpiperidine and
Arylpiperazine-Based Inhibitors**

SUPPORTING INFORMATION

Table S1: Empirical parameters values for LIE calculations.

Inhibitor	α	β	γ
L02	0.18	0.43	0
L03	0.18	0.43	0
L04	0.18	0.39	0
L05	0.18	0.43	0
L06	0.18	0.43	0
L07	0.18	0.43	0
L08	0.18	0.39	0
L09	0.18	0.43	0
L10	0.18	0.43	0
L11	0.18	0.43	0
L12	0.18	0.43	0
L13	0.18	0.43	-2.75
L14	0.18	0.43	-2.75
L15	0.18	0.43	-2.75
L16	0.18	0.43	-2.75
L17	0.18	0.43	-2.75
L18	0.18	0.43	-2.75
L19	0.18	0.43	-2.75
L20	0.18	0.43	-2.75
L21	0.18	0.43	-2.75
L22	0.18	0.37	-2.75
L23	0.18	0.37	-2.75
L24	0.18	0.37	-2.75

9

10

Table S2: Residual decomposition analysis (in kcal/mol) for all TYR systems.

[illegible]

[illegible]

27	LE U	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
28	ILE	0 - 0.01	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
29	LE U	0 - 0.01	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 - 0.01	0 0	0 0	0 0	0 0	0 - 0.01	0 0	0 0	0 0	0 - 0.01	0 0
30	LY S	0 - 0.01	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0.0 1	0.0 1	0.0 1	0.0 1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
31	GL U	0 - 0.01	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 - 0.01	0 0	0 0	0 0	0 0	0 - 0.01	0 0	0 0	0 0	0 - 0.01	0 0	0 - 0.01
32	LY S	0 - 0.01	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 - 0.01	0 0	0 0	0 0	0 0	0 - 0.01	0 0	0 0	0 0	0 - 0.01	0 0	0 0
33	GL Y	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
34	ILE	0 0. 0.01	0 0. 0.01	0 0. 0.01	0 0. 0.01	0 0. 0.01	0 0. 0.01	0 0. 0.01	0 0. 0.01	0 0. 0.01	0 0. 0.01	0 0. 0.01	0 0. 0.01	0 0. 0.01	0 0. 0.01	0 0. 0.01	0 0. 0.01	0 0. 0.01	0 0. 0.01	0 0. 0.01	0 0. 0.01	0 0. 0.01	0 0. 0.01	0 0. 0.01	0 0. 0.01
35	TY R	- 0. 0.05 1	- 0. 0.02 1	- 0. 0.02 2	- 0. 0.02 1	- 0. 0.02 2	- 0. 0.02 1	- 0. 0.02 2	- 0. 0.02 1	- 0. 0.02 3	- 0. 0.02 1	- 0. 0.02 2	- 0. 0.02 3	- 0. 0.02 1	- 0. 0.02 2	- 0. 0.02 1	- 0. 0.02 2	- 0. 0.02 1	- 0. 0.02 2	- 0. 0.02 1	- 0. 0.02 2	- 0. 0.02 1	- 0. 0.02 2	- 0. 0.02 1	- 0. 0.02 2
36	AS P	0 0. 0.01	0 0. 0.01	0 0. 0.01	0 0. 0.01	0 0. 0.01	0 0. 0.01	0 0. 0.01	0 0. 0.01	0 0. 0.01	0 0. 0.01	0 0. 0.01	0 0. 0.01	0 0. 0.01	0 0. 0.01	0 0. 0.01	0 0. 0.01	0 0. 0.01	0 0. 0.01	0 0. 0.01	0 0. 0.01	0 0. 0.01	0 0. 0.01	0 0. 0.01	0 0. 0.01
37	AR G	0 - 0.01	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
38	TY R	- 0. 0.01	- 0. 0.02	- 0. 0.03	- 0. 0.02	- 0. 0.03	- 0. 0.02	- 0. 0.03	- 0. 0.02	- 0. 0.03	- 0. 0.04	- 0. 0.03	- 0. 0.05	- 0. 0.03	- 0. 0.02	- 0. 0.01	- 0. 0.02	- 0. 0.01	- 0. 0.02	- 0. 0.01	- 0. 0.02	- 0. 0.01	- 0. 0.02	- 0. 0.01	- 0. 0.02

[illegible]

78	AR G	0 - 0 0.03	0 - 0 0.01	0 - 0 0.02	0 - 0 0.01	0 - 0 0.01	0 - 0 0.01	0 - 0 0.01	0 - 0 0.02	0 - 0 0.02	0 - 0 0.02	0 - 0 0.02	0 - 0 0.02	0 - 0 0.01	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
79	AS P	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
80	LE U	0 - 0 0.01	0 0	0 - 0 0.01	0 0	0 0	0 0	0 0	0 - 0 0.01	0 - 0 0.01	0 - 0 0.01	0 - 0 0.01	0 0	0 0	0 - 0 0.01	0 0	0 0	0 - 0 0.01	0 - 0 0.01	0 - 0 0.01	0 - 0 0.01	0 0	0 - 0 0.01	0 - 0 0.01	- 0 0.01
81	GL N	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 - 0 0.01	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
82	SE R	0 - 0 0.01	0 0	0 - 0 0.01	0 0	0 0	0 0	0 0	0 - 0 0.01	0 - 0 0.01	0 - 0 0.01	0 - 0 0.01	0 0	0 - 0 0.01	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
83	ILE	0 - 0 0.01	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 - 0 0.01	0 0	0 0	0 0	0 0	0 0	0 - 0 0.01	0 0	0 0	0 - 0 0.01	0 0
84	AS N	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
85	PR O	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
86	GL U	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
87	VA L	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
88	TH R	0 - 0 0.01	0 - 0 0.01	0 - 0 0.01	0 - 0 0.01	0 - 0 0.01	0 - 0 0.01	0 - 0 0.01	0 - 0 0.01	0 - 0 0.01	0 - 0 0.01	0 - 0 0.01	0 0	0 - 0 0.01	0 0	0 - 0 0.01	0 - 0 0.01	0 - 0 0.01	0 - 0 0.01	0 - 0 0.01	0 - 0 0.01	0 0	0 - 0 0.01	0 - 0 0.01	- 0 0.01
89	LE U	0 - 0 0.01	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 - 0 0.01	0 - 0 0.01	0 0	0 0	0 0	0 0	0 - 0 0.01	0 - 0 0.01	0 - 0 0.01	0 - 0 0.01	0 - 0 0.01	0 0

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

216	GL Y	- 0.833	- 0.14	- 1.311	- 0.39	- 0.326	- 0.322	- 1.228	- 0.287	- 1.334	- 0.429	- 1.375	- 0.356	- 1.225	- 0.311	- 1.478	- 0.384	- 1.548	- 0.435	- 1.789	- 0.467	- 1.833	- 0.538	- 1.931	- 0.672
217	VA L	- 1.199	0.04	- 1.938	0.1	- 1.037	0.0	- 2.043	- 0.28	- 1.034	0.0	- 1.069	0.1	- 1.056	0.0	- 1.085	0.1	- 2.013	- 0.08	- 1.088	0.04	- 2.011	- 0.14	- 1.049	- 0.08
218	VA L	- 2.334	0.07	- 3.144	0.2	- 3.055	0.1	- 2.099	- 0.23	- 3.099	0.4	- 3.034	0.2	- 2.051	0.5	- 3.066	0.3	- 3.071	- 0.06	- 3.066	0.19	- 3.094	- 0.18	- 4.001	- 0.3
219	PR O	- 0.18	0.03	- 0.27	0.0	- 0.06	0.0	- 0.09	0.04	- 0.03	0.0	- 0.04	0.0	- 0.06	0.0	- 0.05	0.0	- 0.04	0.0	- 0.07	0.0	- 0.05	0.0	- 0.07	0.17
220	TH R	- 0.08	0.02	- 0.11	0.0	- 0.05	0.0	- 0.01	0.05	- 0.01	0.0	- 0.01	0.0	- 0.01	0.0	- 0.03	0.0	- 0.01	0.0	- 0.01	0.0	- 0.01	0.0	- 0.01	0.01
221	AL A	- 0.95	0.15	- 0.81	0.22	- 0.155	0.0	- 0.065	- 0.23	- 0.177	0.0	- 0.073	0.1	- 0.069	0.0	- 0.075	0.1	- 0.073	0.1	- 0.049	0.0	- 0.056	0.12	- 0.051	- 0.03
222	PR O	- 0.23	0.02	- 0.22	0.0	- 0.04	0.0	- 0.02	0.01	- 0.06	0.0	- 0.01	0.0	- 0.02	0.0	- 0.01	0.0	- 0.03	0.0	- 0.01	0.0	- 0.02	0.0	- 0.04	- 0.0
223	AS N	- 0.03	0.06	- 0.00	0.05	- 0.01	0.0	- 0.02	0.09	- 0.03	0.0	- 0.02	0.0	- 0.03	0.0	- 0.01	0.0	- 0.03	0.0	- 0.02	0.0	- 0.03	0.07	- 0.03	- 0.04
224	AS P	- 0.03	0.04	- 0.03	0.04	- 0.01	0.05	- 0.03	- 0.23	- 0.03	0.0	- 0.03	0.04	- 0.03	0.06	- 0.02	0.03	- 0.02	0.04	- 0.03	0.03	- 0.03	0.04	- 0.03	- 0.13
225	PR O	- 0.01	0.04	- 0.01	0.02	- 0.00	0.01	- 0.00	0.02	- 0.00	0.0	- 0.00	0.02	- 0.00	0.01	- 0.00	0.0	- 0.00	0.0	- 0.00	0.0	- 0.00	0.02	- 0.00	- 0.02

[illegible]

28 4	TY R	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
28 5	VA L	0	0. 01	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
28 6	TY R	0	0	0	0	0	0	0	0	0.01	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
28 7	AS P	0	- 0. 01	0	0	0	- 0. 01	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
28 8	ILE	0	- 0. 01	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
28 9	GL U	0	0. 01	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
29 0	LE U	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
29 1	CU A	- 6. 75	- 5. 96	- 1. 91	- 7. 19	- 1. 23	- 9. 97	- 1. 26	- 6. 22	- 1. 29	- 6. 88	- 3. 29	- 10. 22	- 1. 24	- 7. 26	- 1. 13	- 3. 13	- 7. 13	- 1. 81	- 3. 07	- 0. 41	- 5. 63	- 0. 27	- - 33	- 0. 12	- 2. 76	- 0. 63	- 0. 24	- 0. 26	- 0. 33	- 0. 45	- 0. 41
29 2	CU B	- 3. 99	- 13. 33	- 3. 57	- 5. 44	- 0. 29	- 2. 95	- 3. 63	- 5. 82	- 0. 67	- 2. 11	- - 44	- - 7. 95	- 4. 15	- 6. 10	- 3. 46	- 3. 56	- 3. 82	- 3. 52	- 0. 27	- 0. 31	- 0. 26	- 0. 49	- 0. 44	- 2. 75	- 0. 47	- 2. 95	- 0. 42	- 0. 44	- 1. 65	- 2. 81	- 0. 38