Supporting information

Molecular dynamics simulations reveal the mechanism of the interactions between the inhibitors and SIRT2 at atom level

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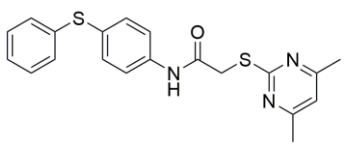
Supplementary Experimental Section

1H NMR assignment of TPN0_C7.

The 1H NMR (400 MHz, DMSO-d6) δ 10.03 (s, 1H), 7.60 (t, J = 7.6 Hz, 3H), 7.50 – 7.13 (m, 9H), 7.12 – 6.98 (m, 1H), 5.04 (s, 2H), 4.23 – 3.98 (m, 1H), 3.33 (d, J = 13.2 Hz, 4H), 1.77 – 1.56 (m, 2H), 1.54 – 1.39 (m, 4H), 1.37 – 1.08 (m, 10H), 0.85 (t, 3H). ESI-MS (m/z) = 513.56 [M+H] +

Supplementary Tables

Table S1. Chemical structure, IC_{50}, binding energy of 2-((4,6-dimethylpyrimidin-2-yl)thio)-N-phenylacetamide derivatives compounds.

Compound	Structural formula	IC_{50}	Binding energy (kcal/mol)
1a		1.32μM	-8.16

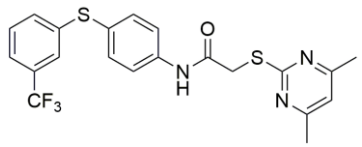
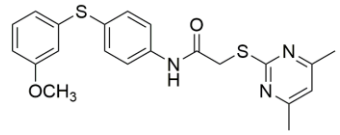
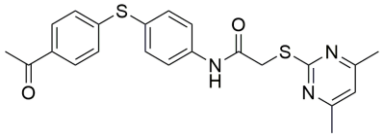
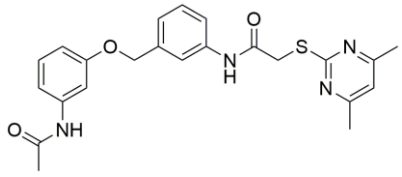
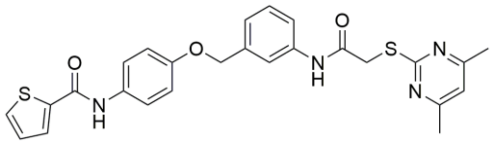
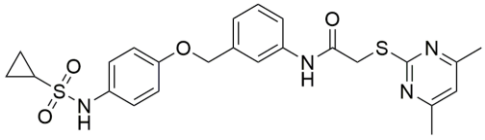
12f		0.85μM	-8.73
12g		0.70μM	-8.21
12l		NA	-9.03
28d		NA	-9.27
28e		42nM	-10.11
28f		NA	-8.7

Table S2. Chemical structure, IC_{50}, binding energy of compounds characterized with thiourea group and a long alkyl chain.

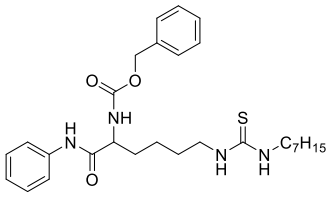
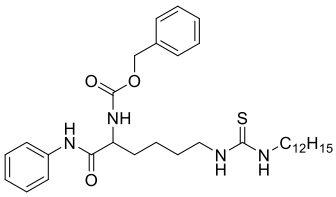
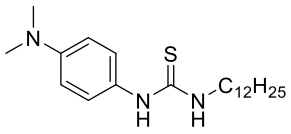
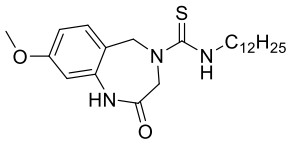
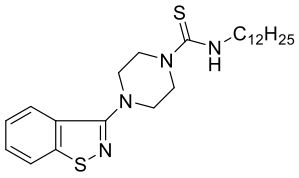
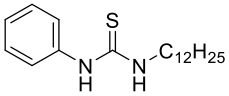
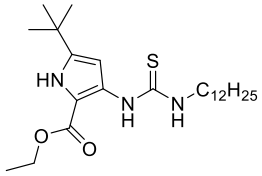
Compound	Structural formula	IC_{50}(μM)	Binding energy (kcal/mol)
TPN0_C7		1.52	-8.01
TPN0_C12		0.069	-6.56
TPN15050		NI	-7.14
TPN15049		NI	-9.18
TPN15063		30.58	-7.81
TPN15096		24.804	-7.23
TPN15082		NI	-5.61

Table S3. The contact probability (%) and binding energy (kJ/mol) between the residues of SIRT2 and TPN0_C7.

Residue name	Binding energy (kJ/mol)	Contact probability (%)
PHE96	-4.17	71.67
PHE119	-7.85	99.99
PHE131	-0.91	95.33
LEU134	-1.29	86.72
ALA135	-1.08	86.59
LEU138	-1.91	99.62
ILE169	-4.57	99.99
PHE190	-1.83	95.91
ILE232	-3.58	99.97
VAL233	-6.74	84.93
PHE234	-0.97	86.39
PHE235	-11.12	99.21
LEU239	-6.48	64.72

Supplementary Figures

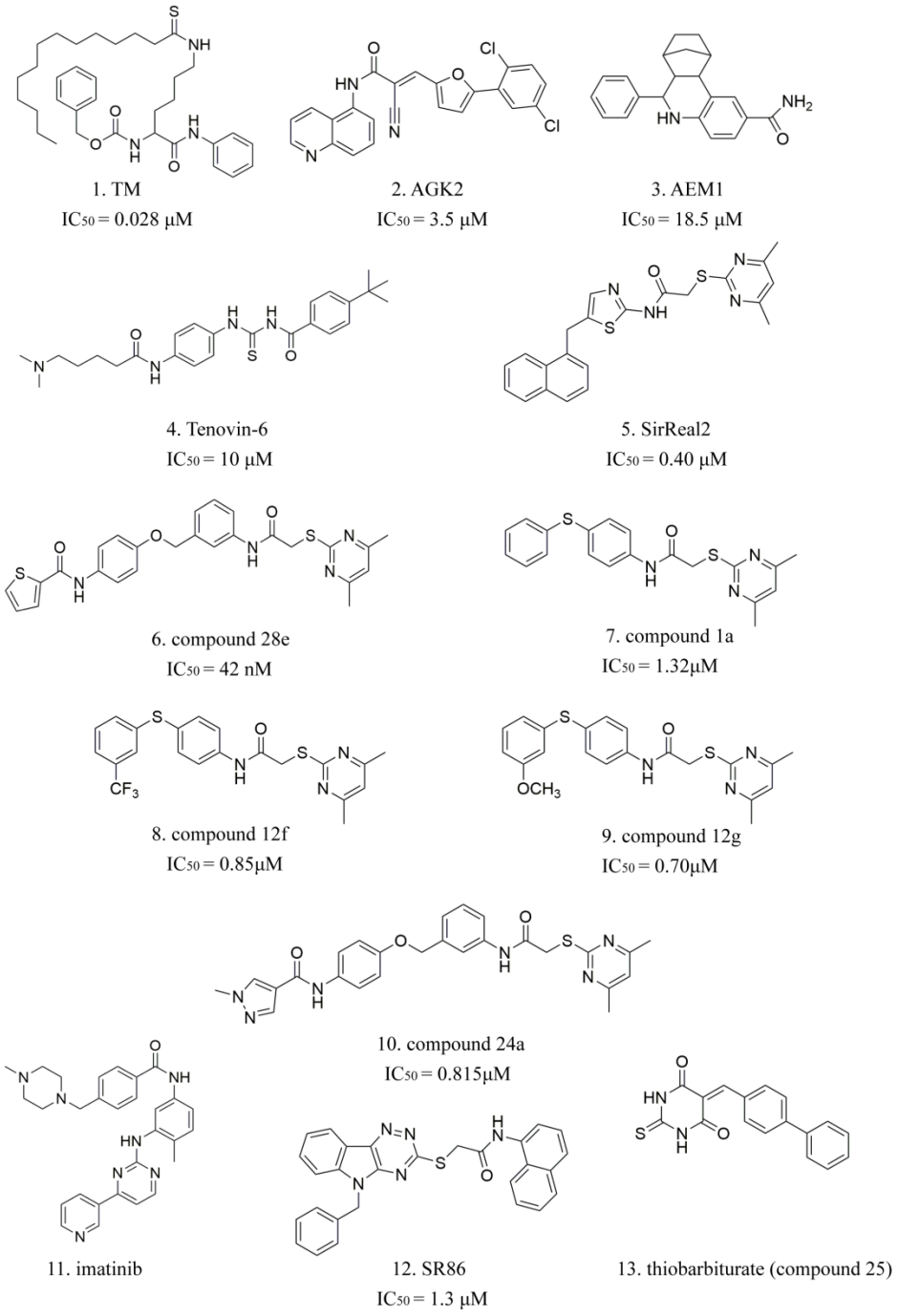


Figure S1. Chemical structure and IC_{50} of reported SIRT2 inhibitors.

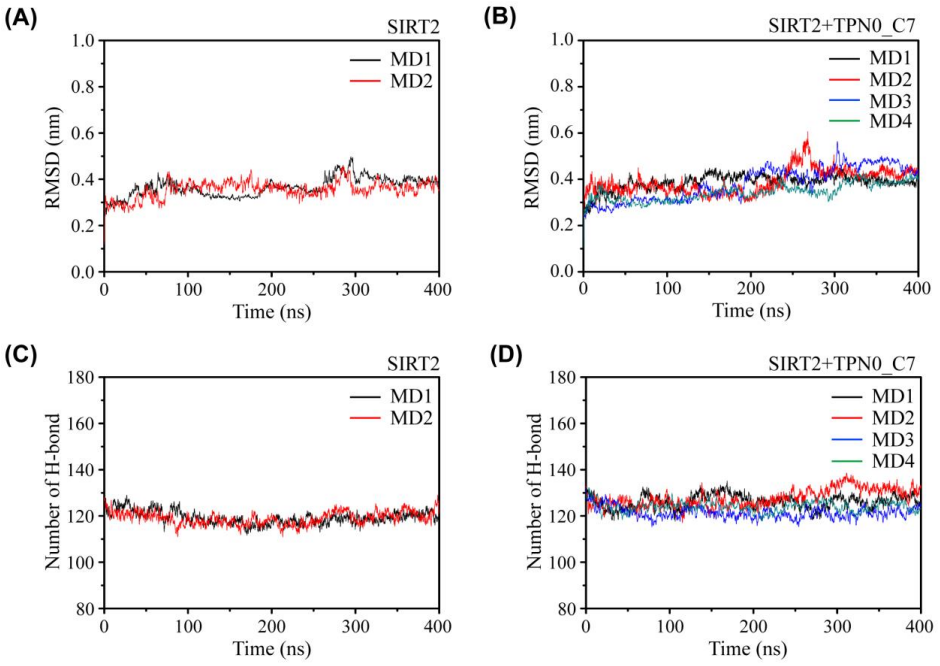


Figure S2. Time evolution of Cα RMSD and H-bond numbers of the SIRT2 in SIRT2 system (A) (C) and SIRT2+TPN0_C7 system (B) (D).

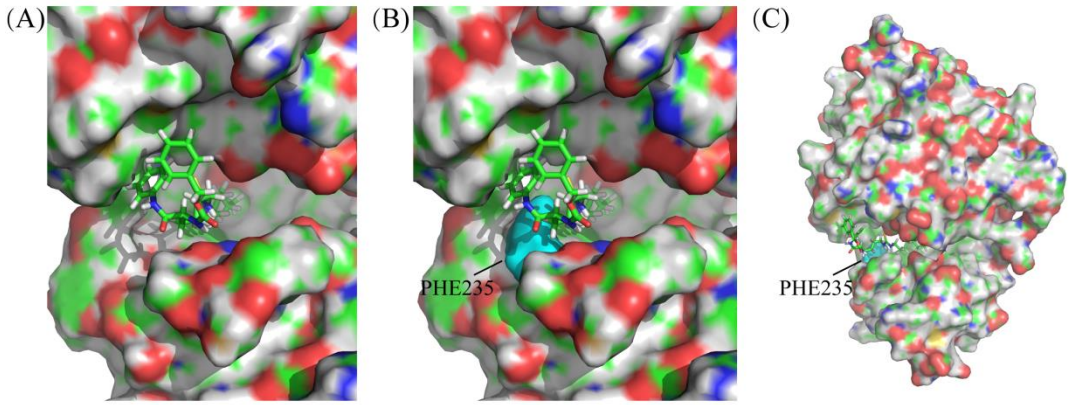


Figure S3. The representation of Phe235 as a gate keeper of hydrophobic pocket. (A) The SIRT2+TPN0_C7 system without Phe235. (B) The SIRT2+TPN0_C7 with Phe235. SIRT2 is shown in surface mode, TPN0_C7 is shown in green and stick mode.