Structure-based Inhibitor Design for the Intrinsically Disordered Protein c-Myc

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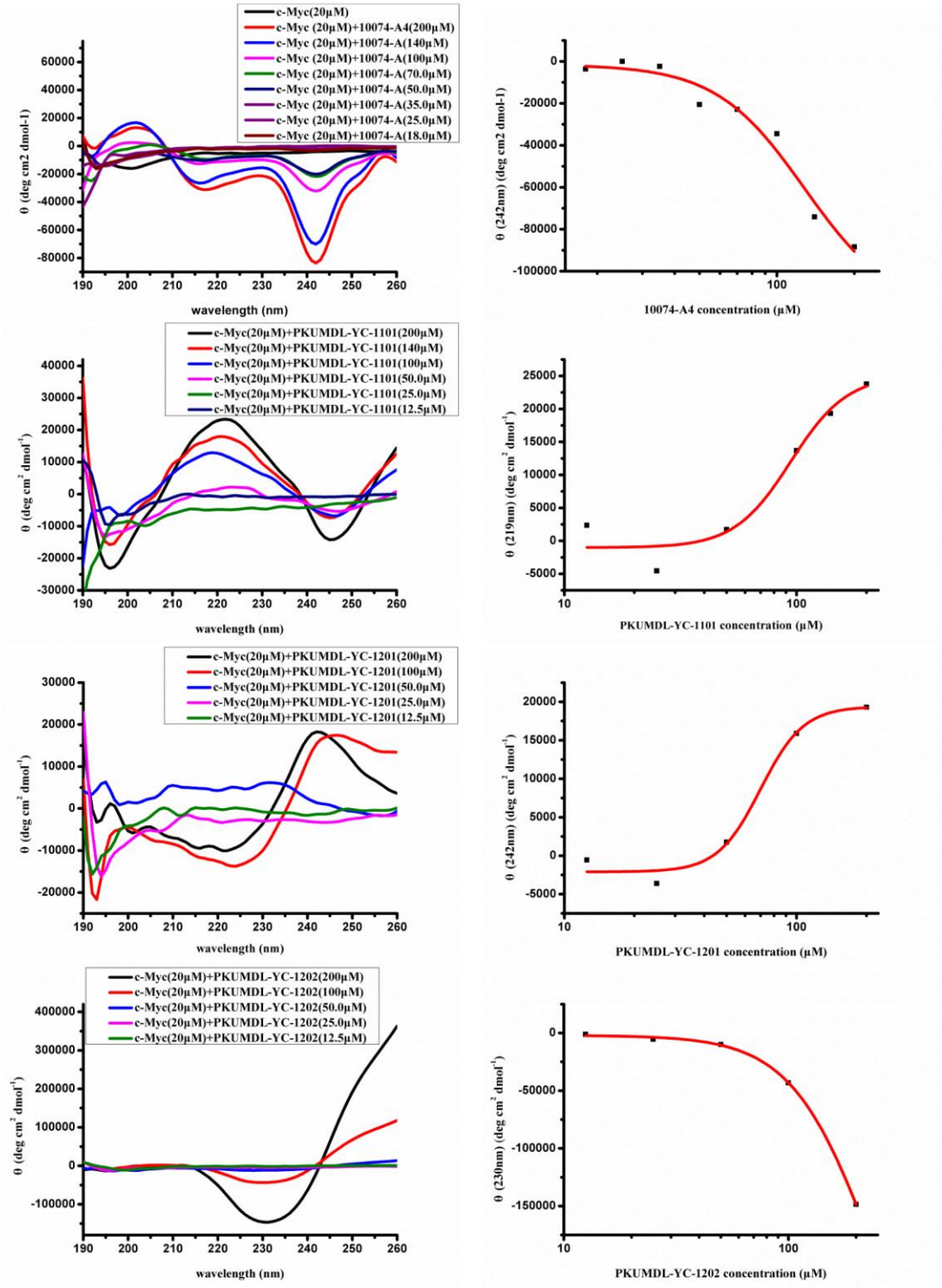
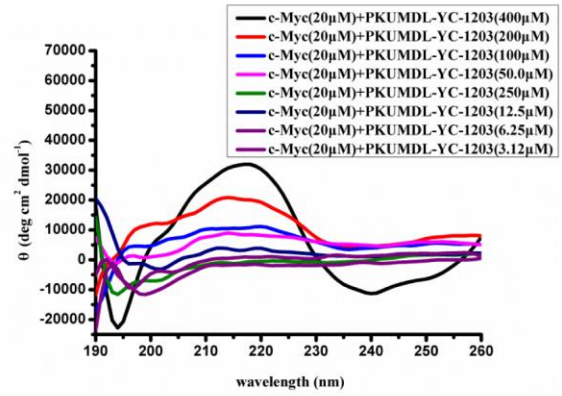
Supporting Information

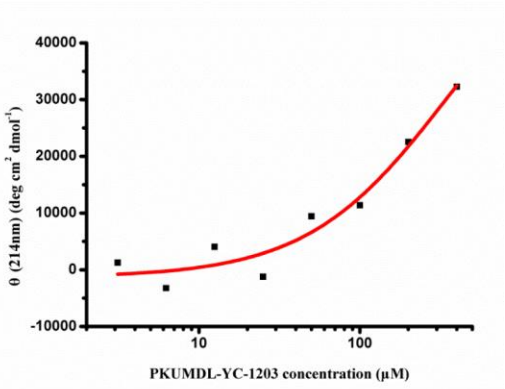
1. Supplementary Figures 1-9
2. Table S1 Ranks and library IDs of identified hits in virtual screening

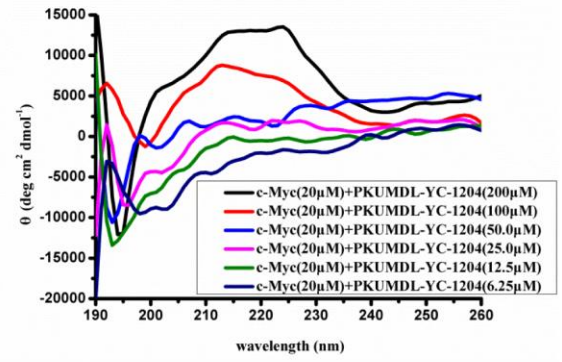
Supplementary Figures 1-9

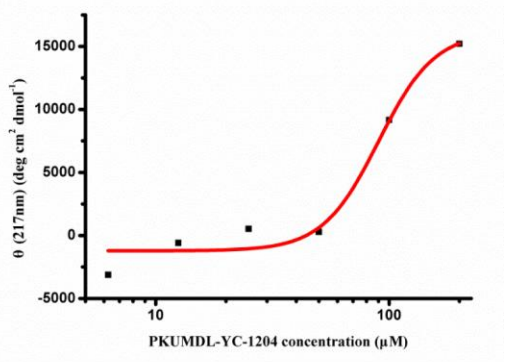
Figure S1 Circular dichroism (CD) spectra of c-Myc$_{370-409}$ with different compounds.

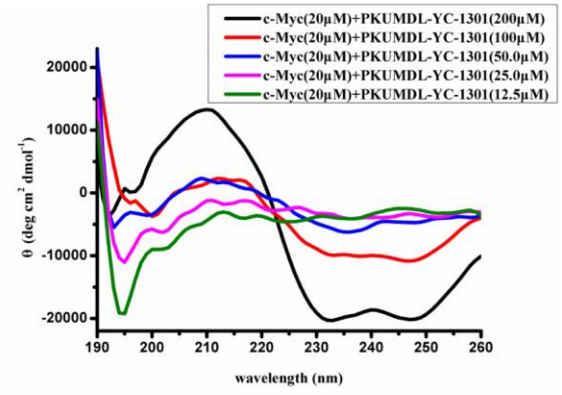



c-Myc(20μM)+PKUMDL-YC-1203(400μM)
c-Myc(20μM)+PKUMDL-YC-1203(200μM)
c-Myc(20μM)+PKUMDL-YC-1203(100μM)
c-Myc(20μM)+PKUMDL-YC-1203(50.0μM)
c-Myc(20μM)+PKUMDL-YC-1203(250μM)
c-Myc(20μM)+PKUMDL-YC-1203(12.5μM)
c-Myc(20μM)+PKUMDL-YC-1203(6.25μM)
c-Myc(20μM)+PKUMDL-YC-1203(3.12μM)
θ (deg cm² dmol⁻¹)
wavelength (nm)


θ (214nm) (deg cm² dmol⁻¹)
PKUMDL-YC-1203 concentration (μM)


c-Myc(20μM)+PKUMDL-YC-1204(200μM)
c-Myc(20μM)+PKUMDL-YC-1204(100μM)
c-Myc(20μM)+PKUMDL-YC-1204(50.0μM)
c-Myc(20μM)+PKUMDL-YC-1204(25.0μM)
c-Myc(20μM)+PKUMDL-YC-1204(12.5μM)
c-Myc(20μM)+PKUMDL-YC-1204(6.25μM)
θ (deg cm² dmol⁻¹)
wavelength (nm)


θ (217nm) (deg cm² dmol⁻¹)
PKUMDL-YC-1204 concentration (μM)


c-Myc(20μM)+PKUMDL-YC-1301(200μM)
c-Myc(20μM)+PKUMDL-YC-1301(100μM)
c-Myc(20μM)+PKUMDL-YC-1301(50.0μM)
c-Myc(20μM)+PKUMDL-YC-1301(25.0μM)
c-Myc(20μM)+PKUMDL-YC-1301(12.5μM)
θ (deg cm² dmol⁻¹)
wavelength (nm)

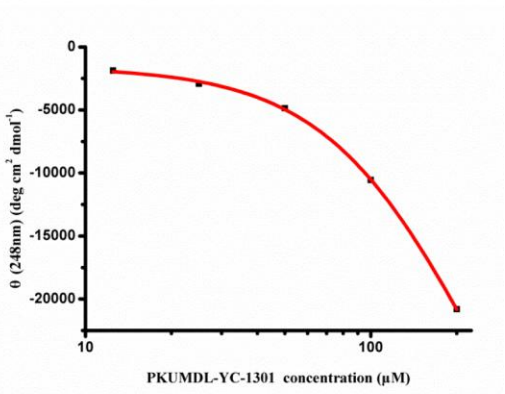
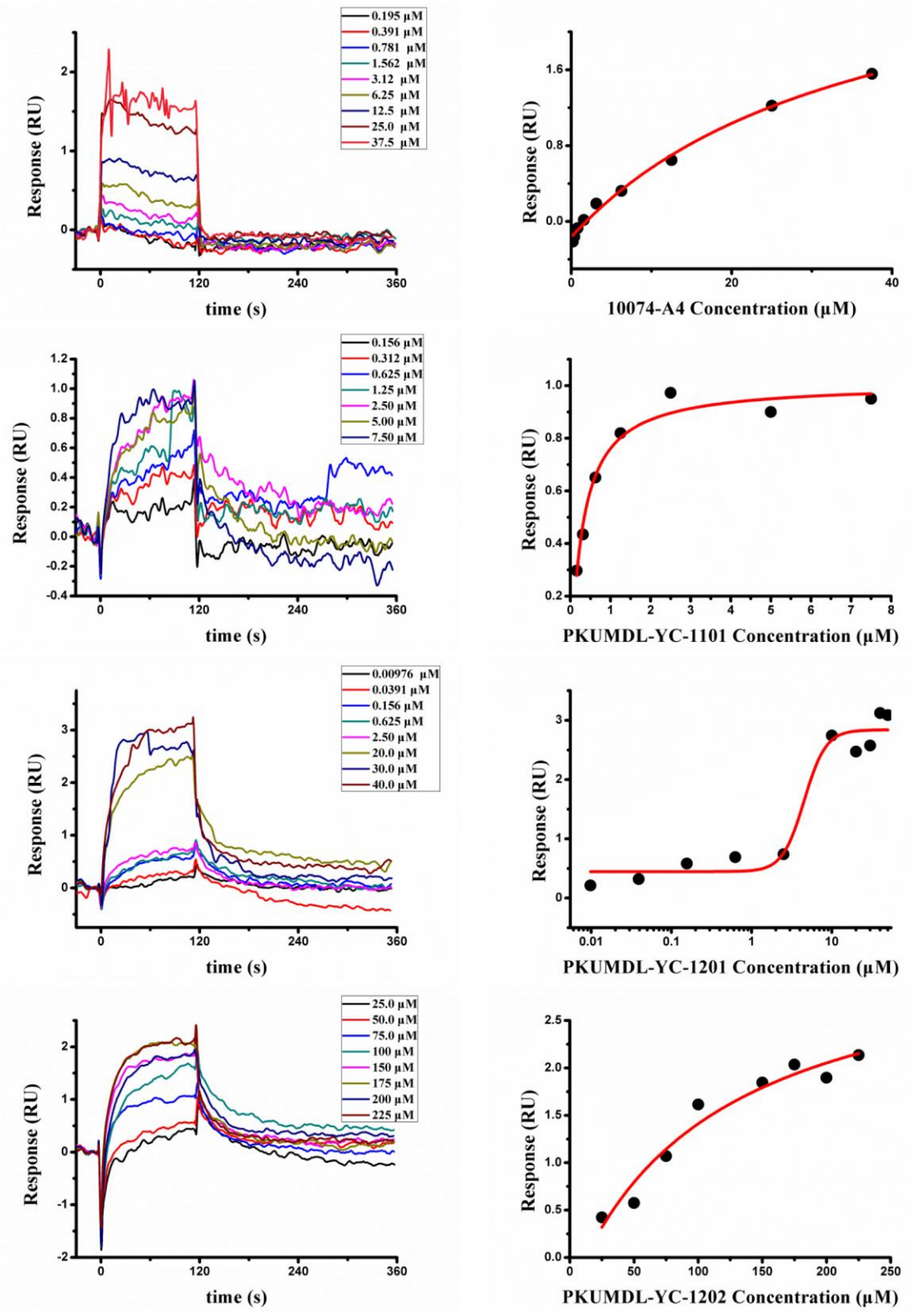
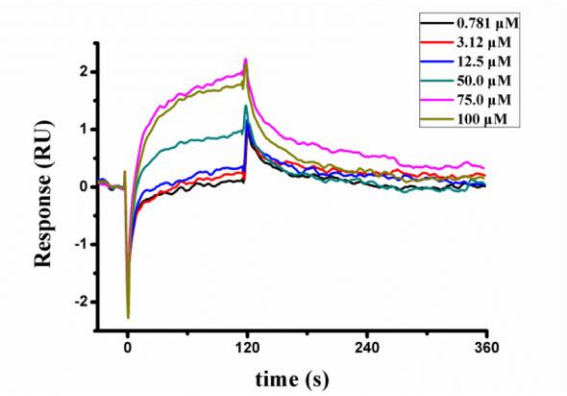
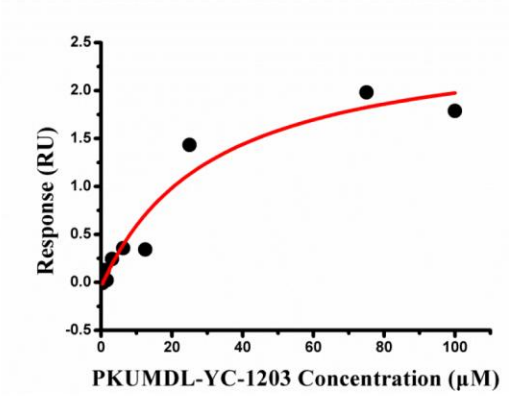
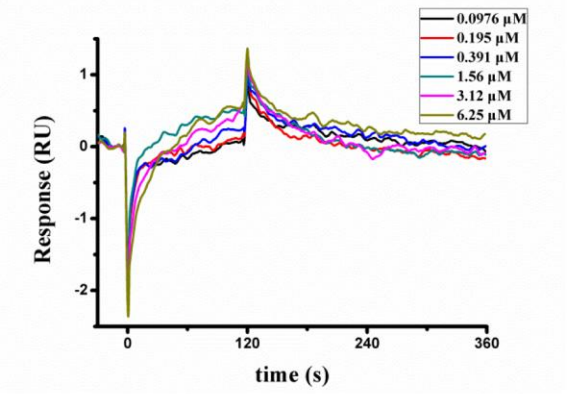

θ (248nm) (deg cm² dmol⁻¹)
PKUMDL-YC-1301 concentration (μM)

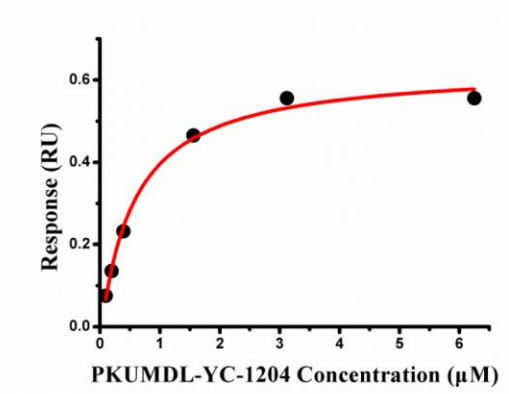
Figure S2 Surface plasmon resonance (SPR) assay results of different compounds.

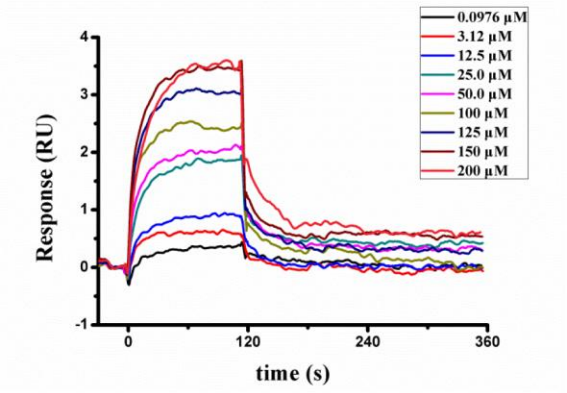



0.781 μM
3.12 μM
12.5 μM
50.0 μM
75.0 μM
100 μM
Response (RU)
time (s)


Response (RU)
PKUMDL-YC-1203 Concentration (μM)


0.0976 μM
0.195 μM
0.391 μM
1.56 μM
3.12 μM
6.25 μM
Response (RU)
time (s)


Response (RU)
PKUMDL-YC-1204 Concentration (μM)


0.0976 μM
3.12 μM
12.5 μM
25.0 μM
50.0 μM
100 μM
125 μM
150 μM
200 μM
Response (RU)
time (s)

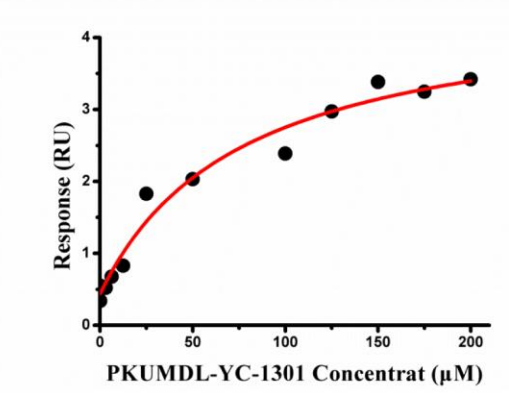

Response (RU)
PKUMDL-YC-1301 Concentrat (μM)

Figure S3 HL-60 cells growth inhibition of different compounds. Data represent the mean ± standard deviation of three independent experiments.

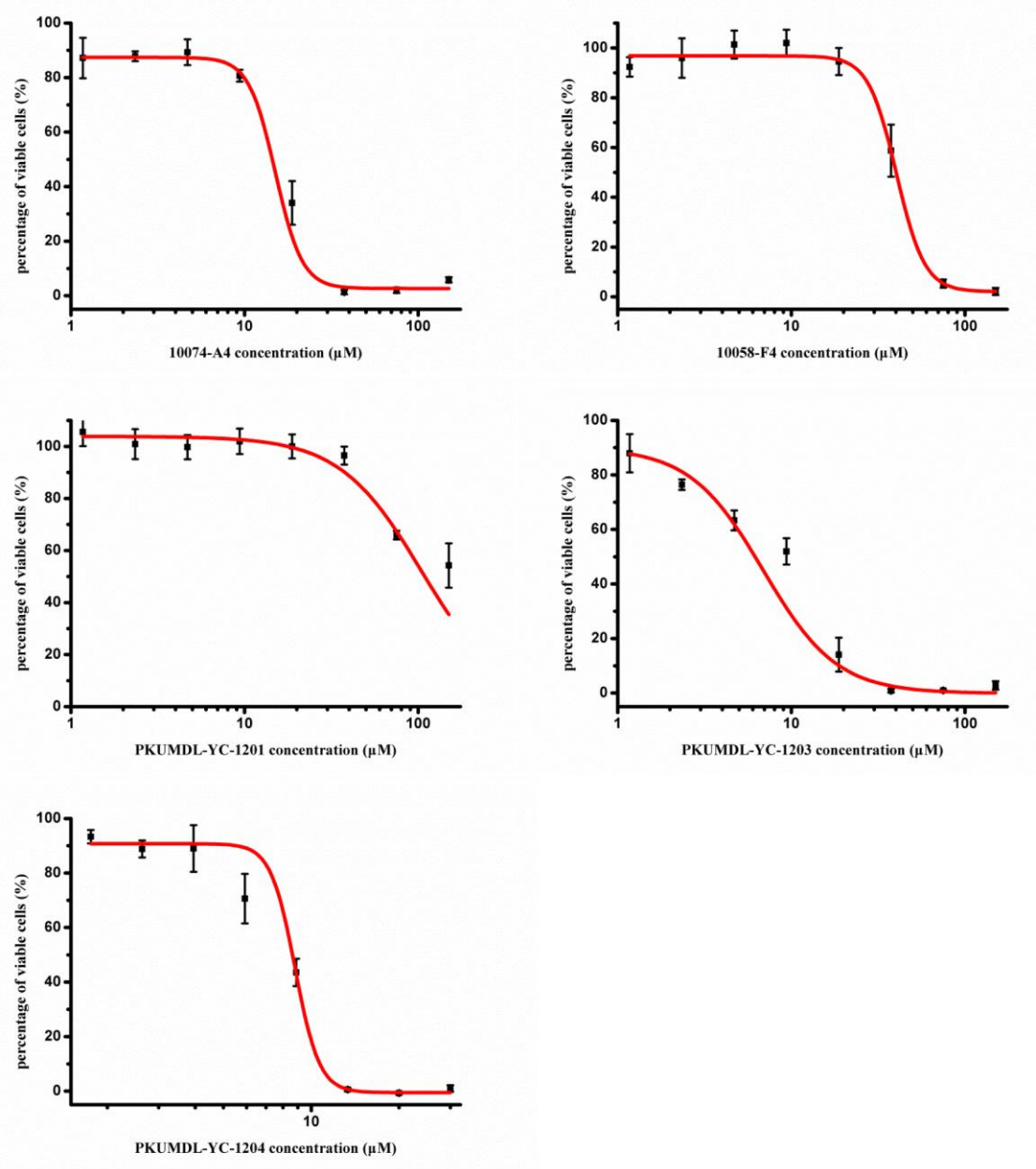


Figure S4 Compounds changed HL-60 cell cycle. Data represent the mean ± standard deviation of three independent experiments. *$p < 0.05$, **$p < 0.01$.

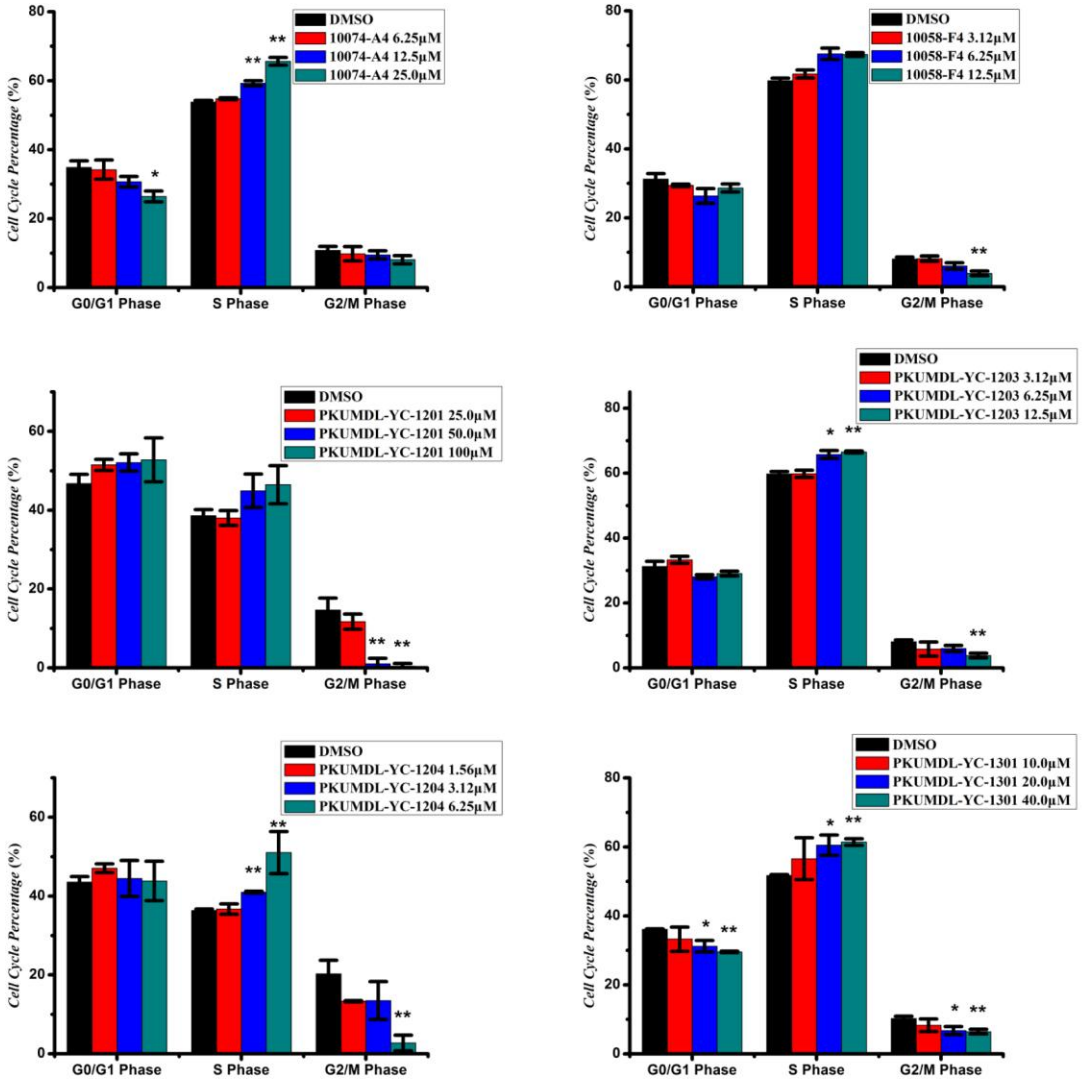


Figure S5 PKUMDL-YC-1205's non-specific binding to GST-Max.

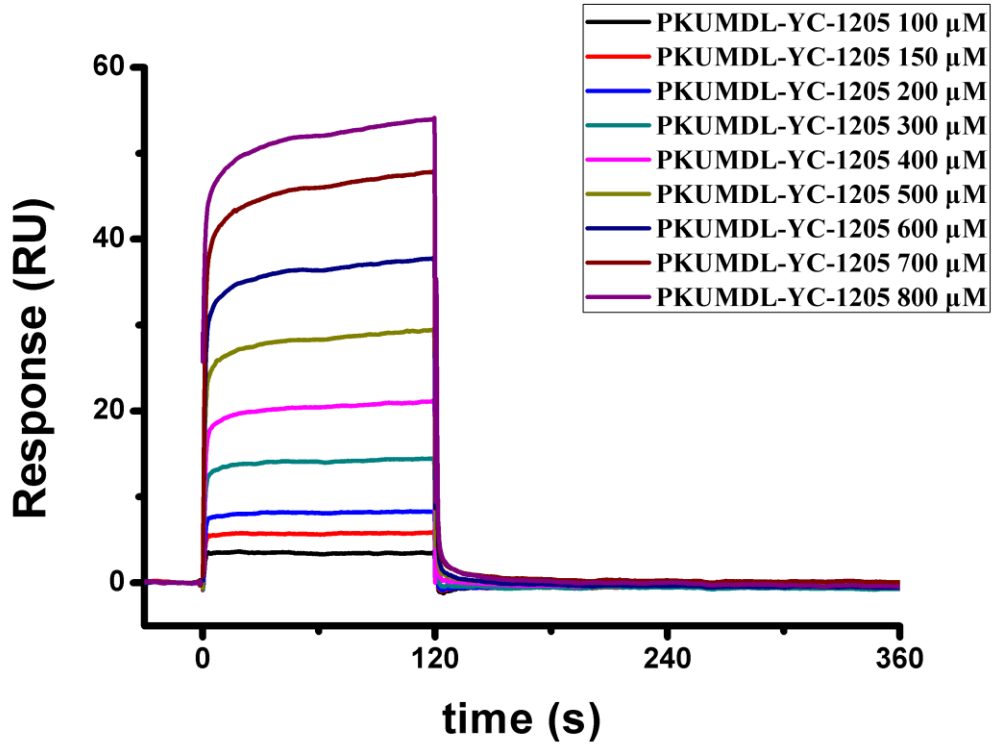


Figure S6 PKUMDL-YC-1205 had no effect on GST dimerization equilibrium. (A) Chemical cross-linking and anti-GST western blot results. (B) Blackness integrals of GST homodimer percentage are shown as a histogram. Data represent the mean ± standard deviation of two independent experiments.

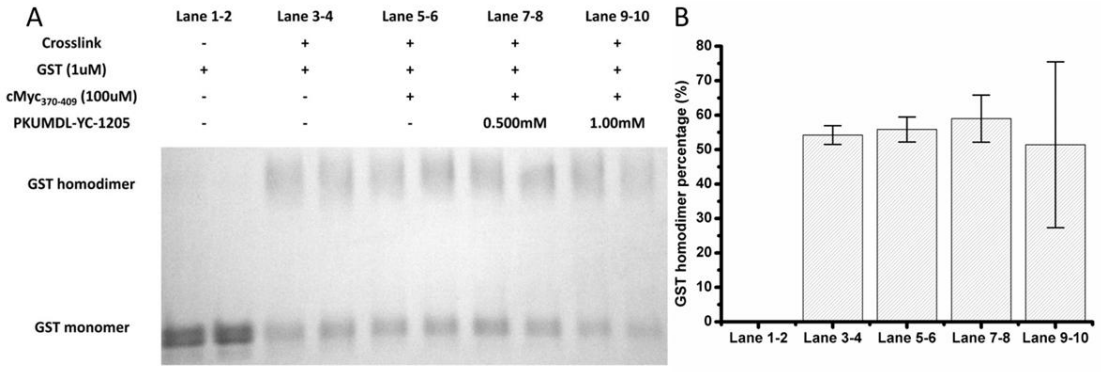


Figure S7 Overlapped ^{1}H-^{1}H TOCSY spectrum of c-Myc$_{370-409}$ with (green) and without (red) PKUMDL-YC-1205.

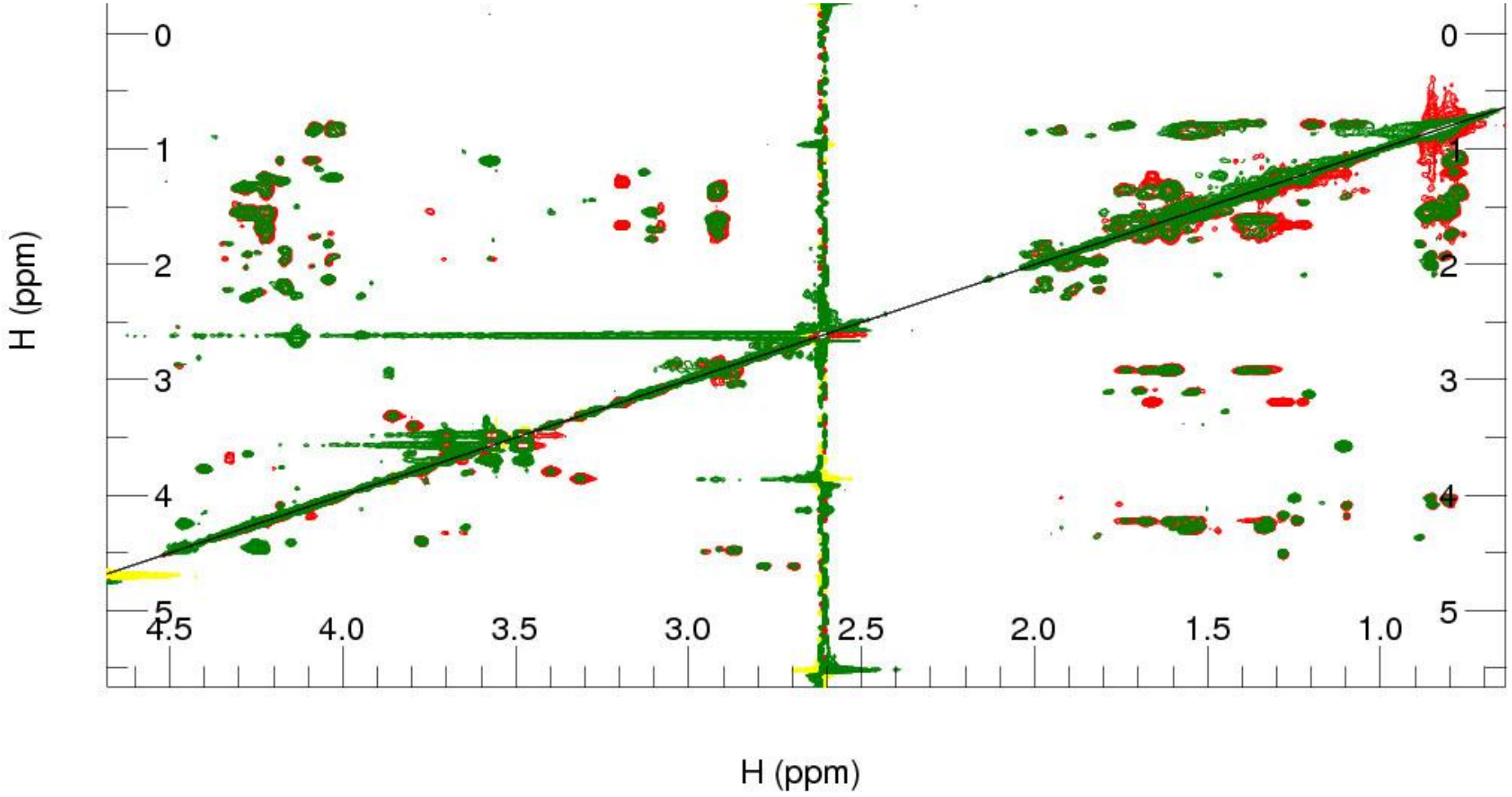


Figure S8 Interactions between compounds and c-Myc$_{370\text{-}409}$ in molecular dynamic simulations. Black squares represent the interactions between PKUMDL-YC-1205 (A), 10074-A4 (S form, B), AJ-292/41944612 (C) and the residues of c-Myc$_{370\text{-}409}$. Five independent 100-nanosecond simulations are represented.

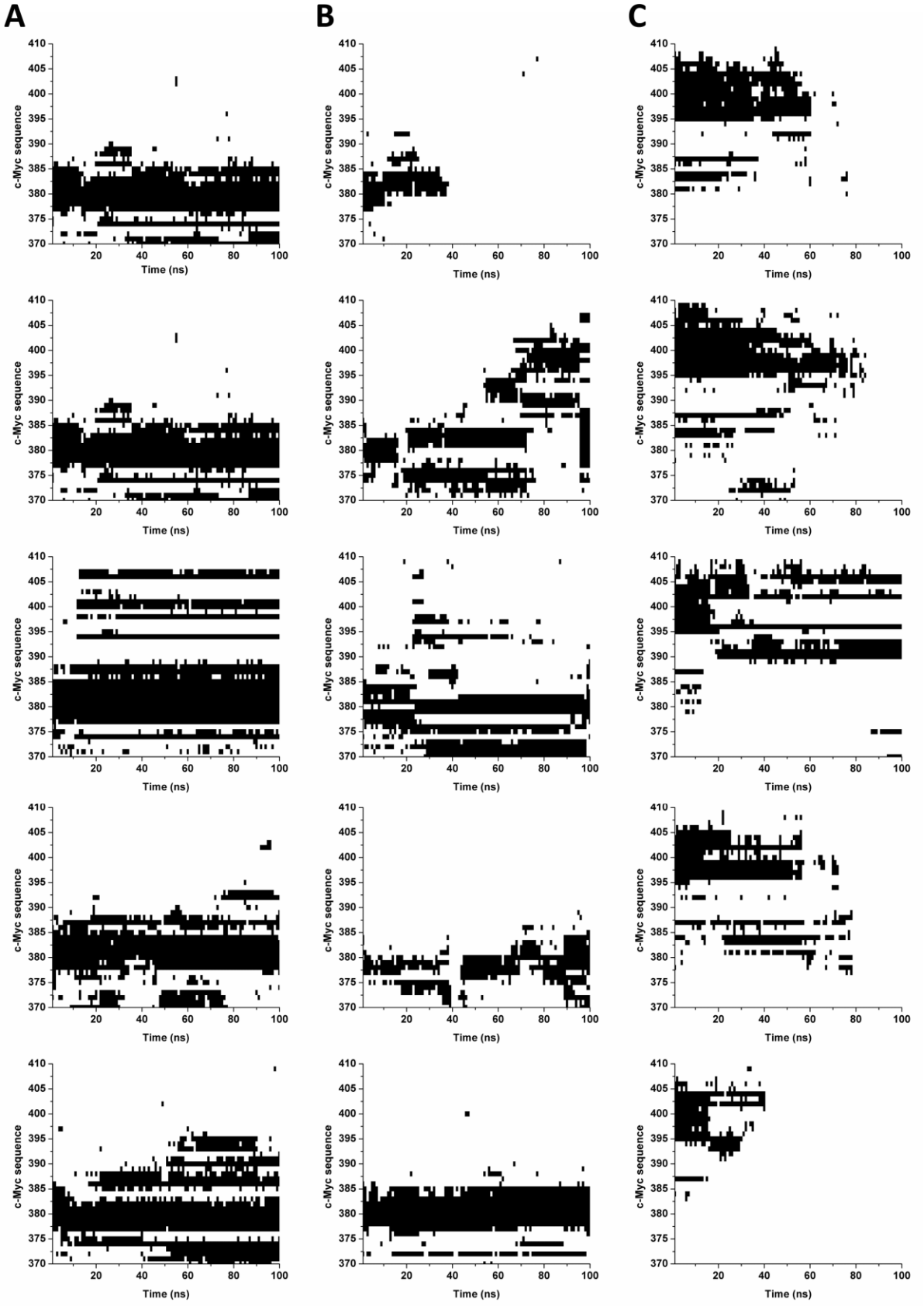

A
B
C
c-Myc sequence
Time (ns)

Figure S9 Docking Modes of Compounds to c-Myc$_{370-409}$. PKUMDL-YC-1201 (A), PKUMDL-YC-1202 (B), PKUMDL-YC-1203 (C), PKUMDL-YC-1204 (D) are represented in pink and Holo conformation of the c-Myc$_{370-409}$ is represented in green.

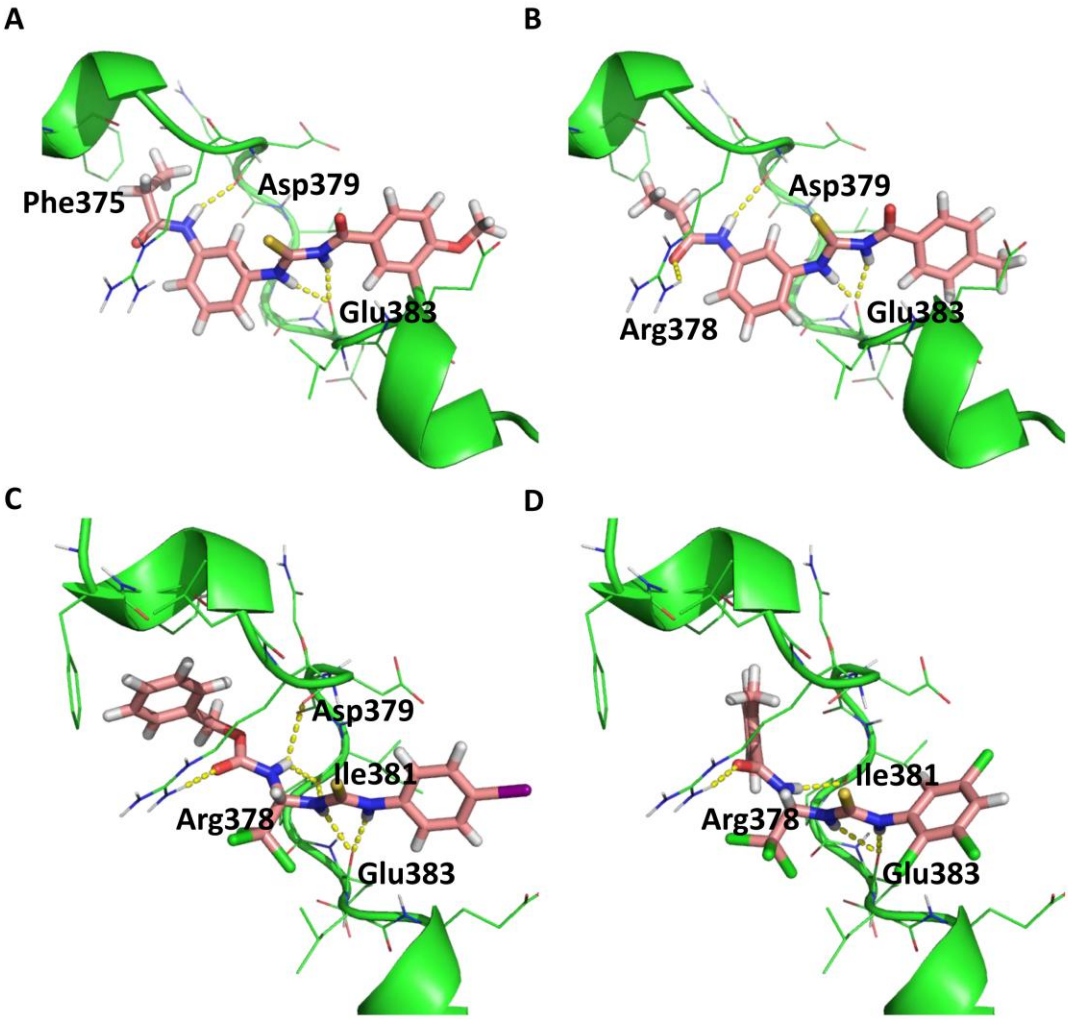


Table S1 Ranks and library IDs of identified hits in virtual screening

SPECS libarary: 197,211 compounds

DCSD libarary: 4,728 compounds

Total: 201,939 compounds

Compound	Cavity	Rank	Library ID
PKUMDL-YC-1101	**Apo1**	**6**	**AG-205/36494016**
PKUMDL-YC-1201	**Holo1**	**19**	**AG-690/15430337**
PKUMDL-YC-1202	**Holo1**	**5**	**AG-690/15430703**
PKUMDL-YC-1203	**Holo1**	**63**	**AG-690/33250021**
PKUMDL-YC-1204	**Holo1**	**51**	**AH-034/07821020**
PKUMDL-YC-1205	**Holo1**	**32**	**DCSD002857**
PKUMDL-YC-1301	**Analog of 10074-A4**	**9**	**AH-487/41976595**