Supporting Information

Discovery of M-808 as a Highly Potent, Covalent, Small-Molecule Inhibitor of the Menin-MLL Interaction with Strong *in vivo* Antitumor Activity

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Table S1. Crystallography Data Collection and Refinement Statistics for Co-Crystal Structure of M-808 in complex with Menin

Data Collection	**Menin:M-808**
PDB ID	6MN9
Space Group	$I4_1$
Unit Cell (Å)	a = b =153.549
	c = 81.283
	$\alpha = \beta = \gamma = 90°$
Wavelength (Å)	0.9787
Resolution (Å)[1]	2.10 (2.10-2.14)
Rmerge[2]	0.102 (2.55)
$\langle I/\sigma I \rangle$[3]	3 (1)
Completeness (%)[4]	99.9 (99.0)
Redundancy	6.9 (4.9)
Refinement	
Resolution (Å)	2.10
R-Factor [5]	0.191
Rfree [6]	0.228
Protein atoms	3701
Ligands	1
Water Molecules	252
Unique Reflections	36178
R.m.s.d.[7]	
Bonds	0.009
Angles	1.00
MolProbity Score[8]	1.24
Clash Score[8]	2.15
RSCC[9]	0.92
RSR[9]	0.19

[1]Statistics for highest resolution bin of reflections in parentheses.

[2]$R_{merge} = \Sigma_h \Sigma_j | I_{hj} - \langle I_h \rangle | / \Sigma_h \Sigma_j I_{hj}$, where I_{hj} is the intensity of observation j of reflection h and $\langle I_h \rangle$ is the mean intensity for multiply recorded reflections.

[3]Intensity signal-to-noise ratio.

[4]Completeness of the unique diffraction data.

[5]R-factor = $\Sigma_h | IF_oI - IF_cI | / \Sigma_h |F_o|$, where F_o and F_c are the observed and calculated structure factor amplitudes for reflection h.

[6]R_{free} is calculated against a 5% random sampling of the reflections that were removed before structure refinement.

[7]Root mean square deviation of bond lengths and bond angles.

[8]Chen et al. (2010) MolProbity: all-atom structure validation for macromolecular crystallography. Acta Crystallographica D66:12-21.

[9]wwPDB Validation Server.

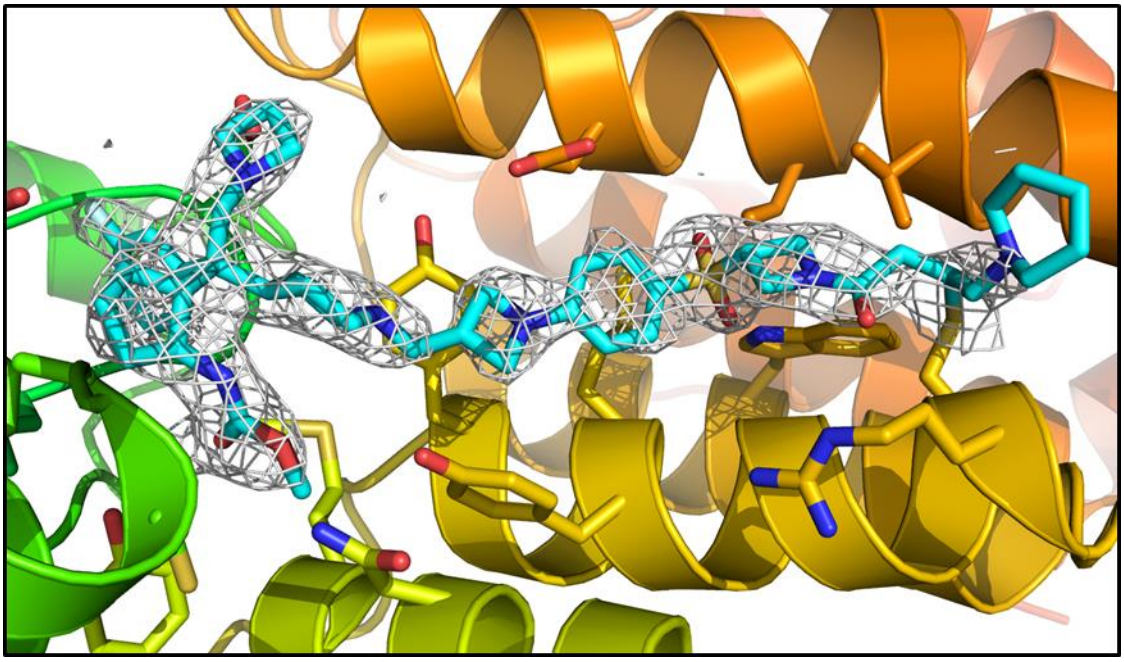

Figure S1. Omit map shows that M-808 covalently binds to Sγ atom of C329 of menin protein. M-808 is shown with cyan carbons. Fo-Fc electron density maps are shown as grey grids contoured at 3σ.

Purity of the Final Compounds Determined by UPLC

Table S2. Purity and retention time of compounds **7**-**20** determined by UPLC

Compd.	Retention time (min)	Purity (%)
7	3.24	97.8
8	3.62	99.2
9	2.82	98.1
10	2.79	96.4
11	2.93	97.5
12	3.15	97.8
13	3.20	99.2
14	2.87	97.6
15	2.95	99.8
16 (M-808)	3.09	98.5
17	2.89	98.8
18	3.01	99.1
19	3.07	98.2
20	3.20	97.1