

Supporting Information

***De-novo* design of cereblon (CRBN) effectors guided by natural hydrolysis products of thalidomide derivatives**

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Figure S1. HPLC traces of tested compounds

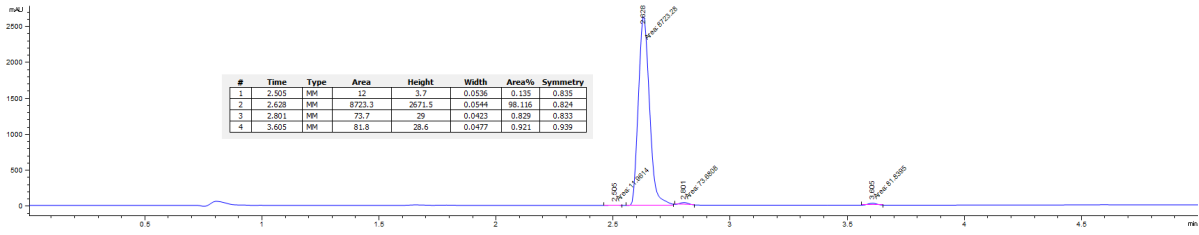
Figure S2. Western blot quantification and normalization IKZF3

Figure S3. Concentration response curve for IKZF3 mAb

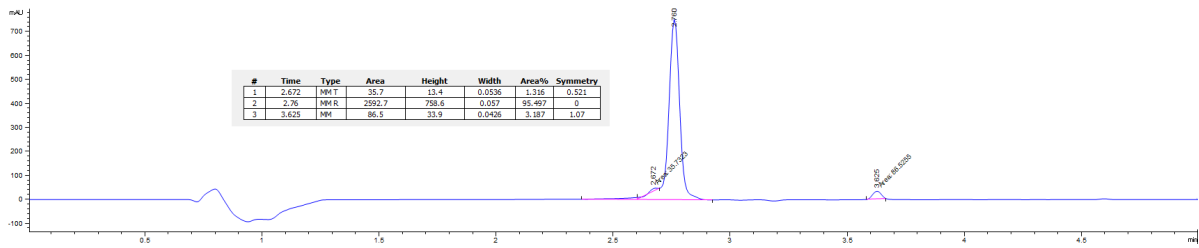
Table S1. Molecular formula strings and Ki values of tested compounds.

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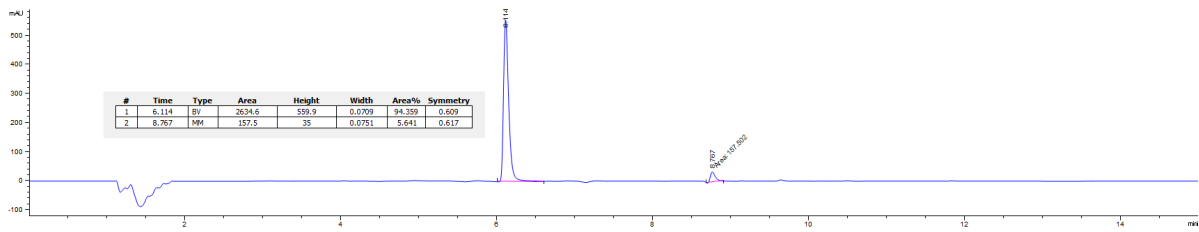
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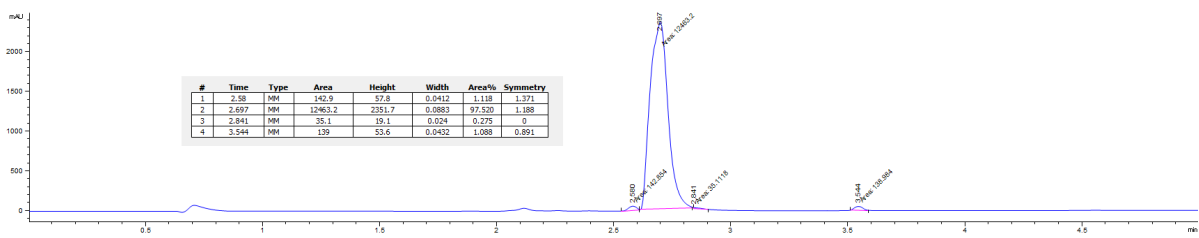
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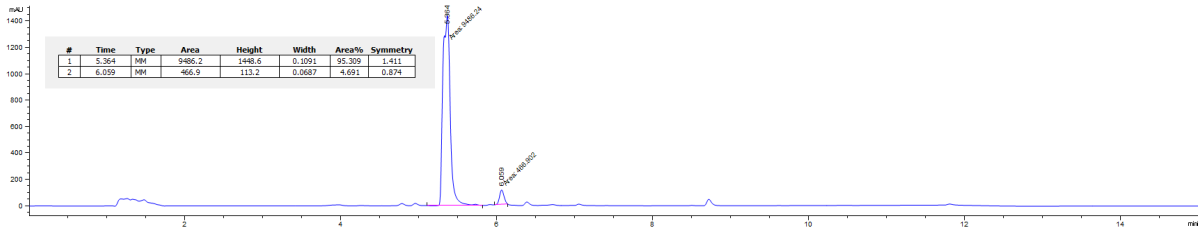
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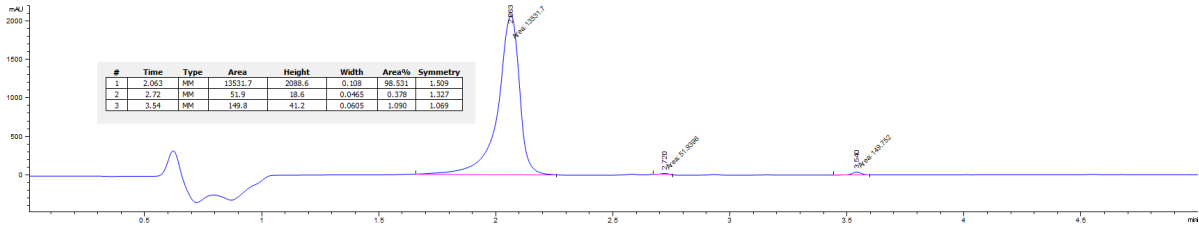
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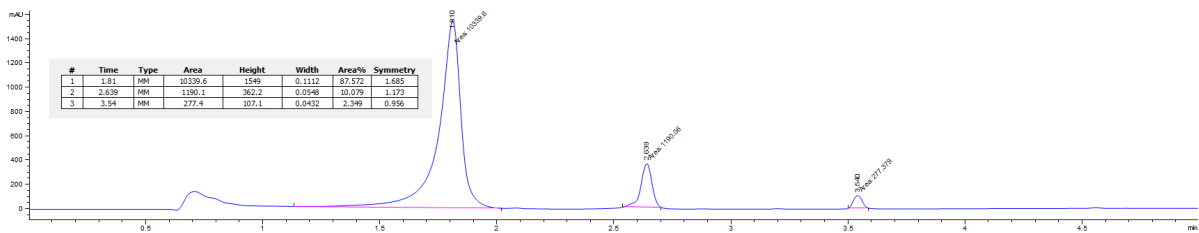
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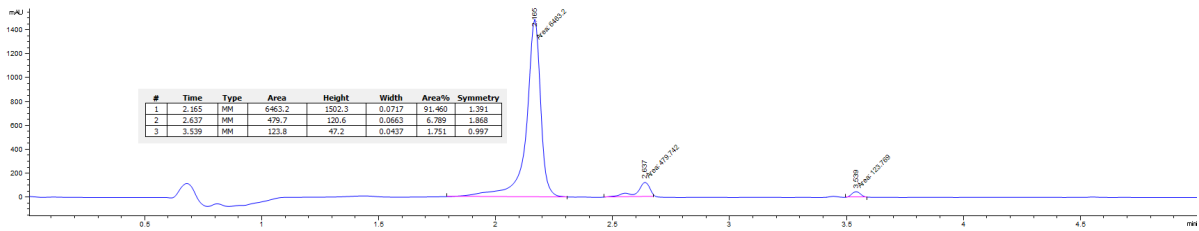
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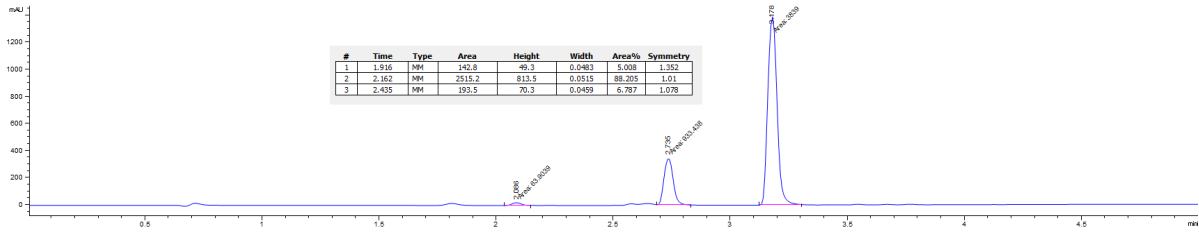
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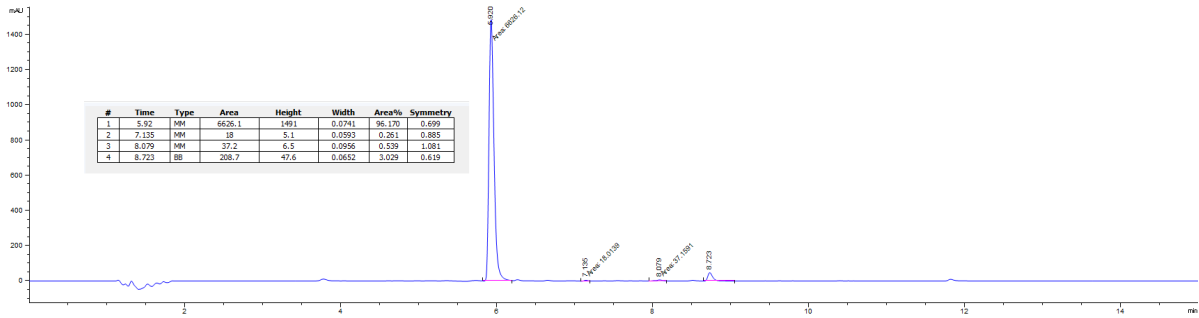
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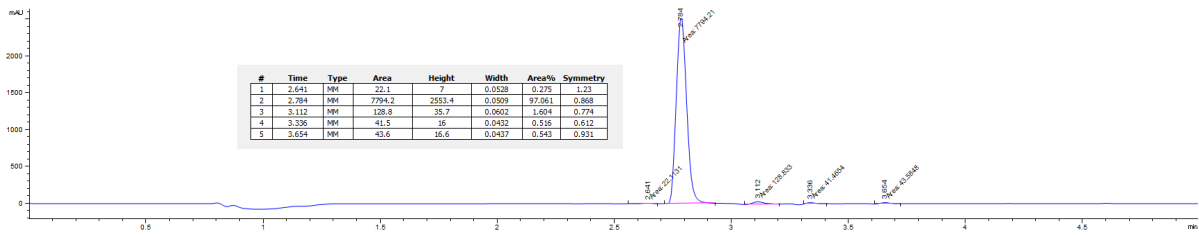
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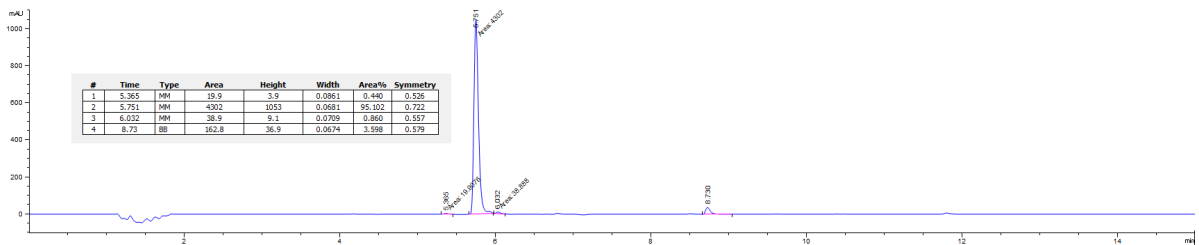
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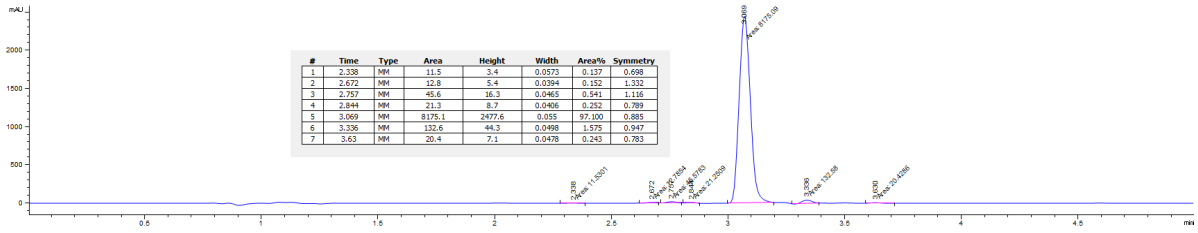
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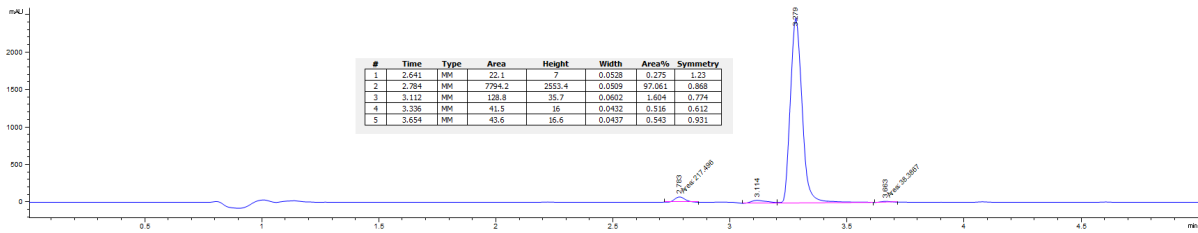
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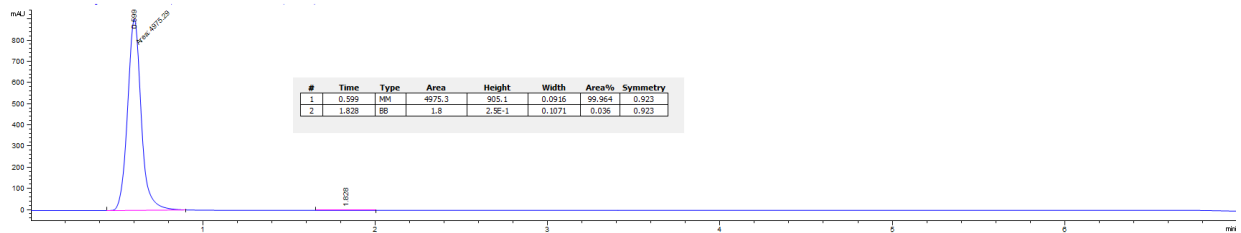
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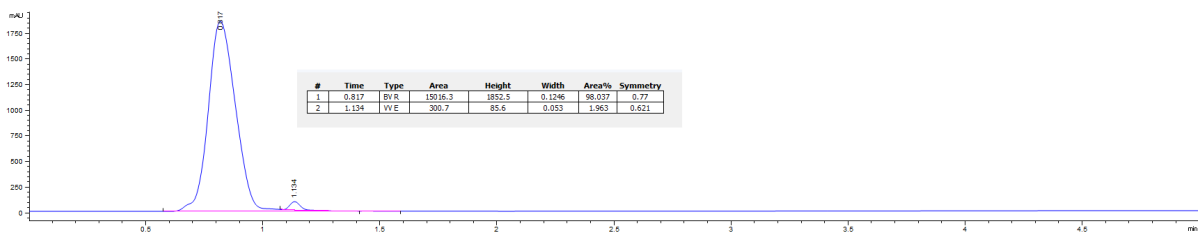
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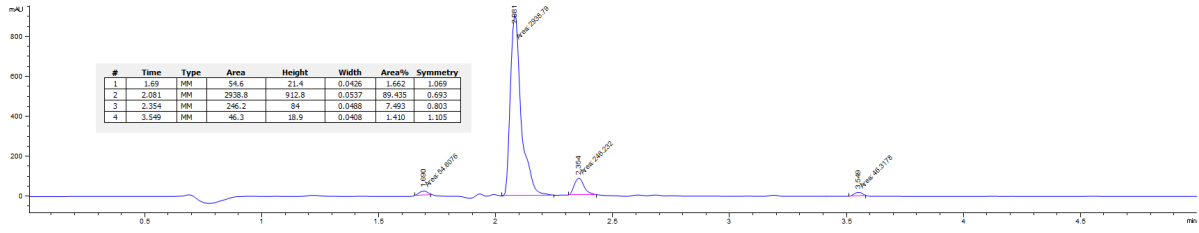
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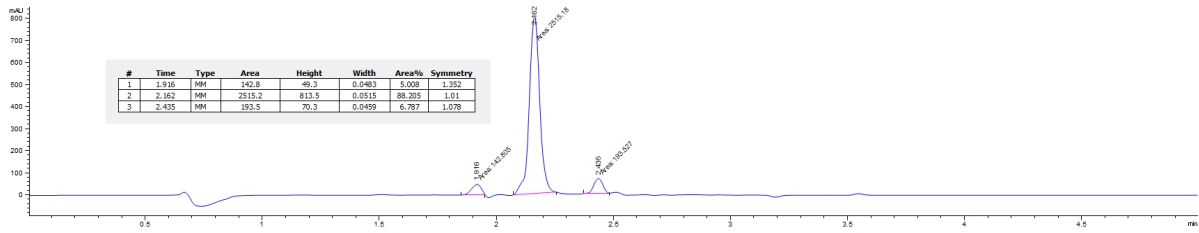
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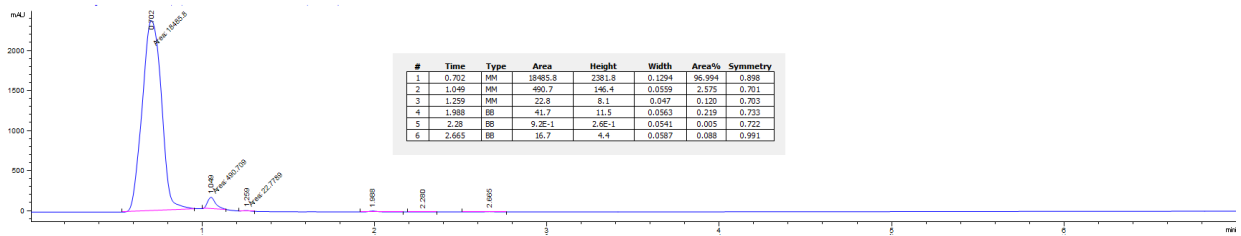
12a



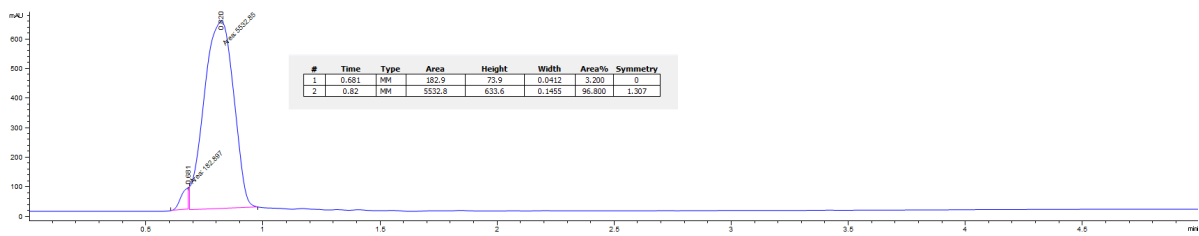
12b



16a



16b



20b

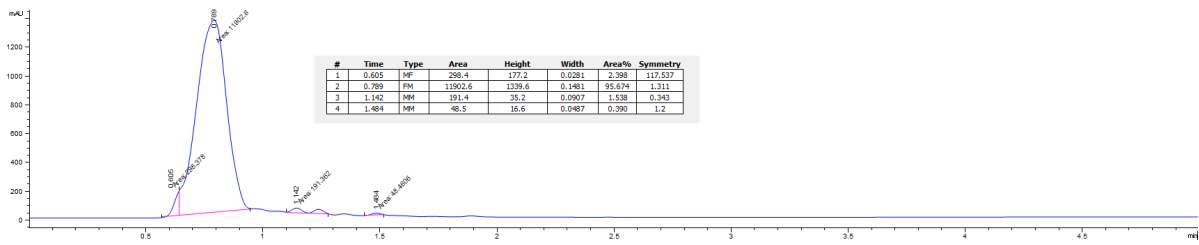


Figure S1. HPLC traces of tested compounds

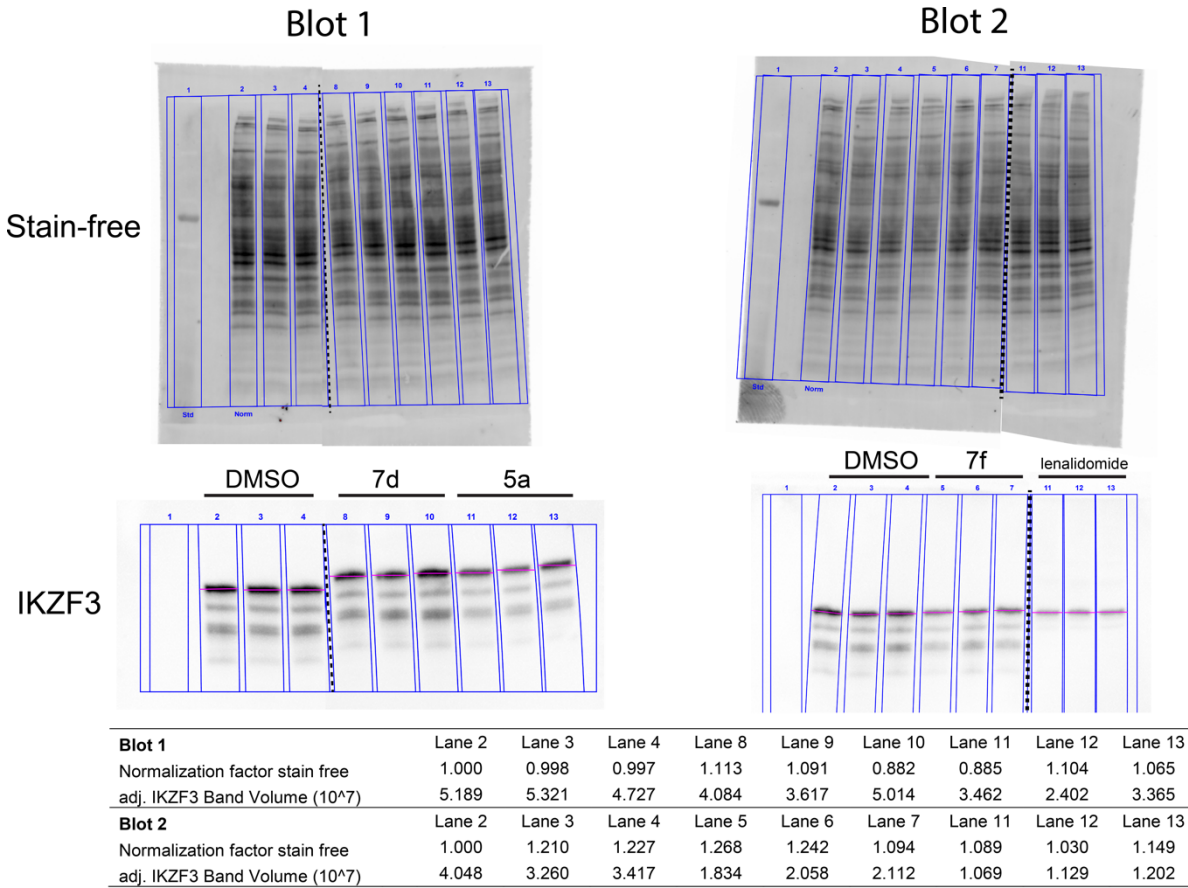


Figure S2. Quantification of IKZF3 from treated OPM2 cells by western blotting. Upper panels show stain-free images of PVDF-membranes; the same immunoblots stained with anti-IKZF3 mAb are depicted in the lower panels. Blots were cropped at indicated lines. The table shows the normalization factors and the adjusted (adj.) band volumes for IKZF3.

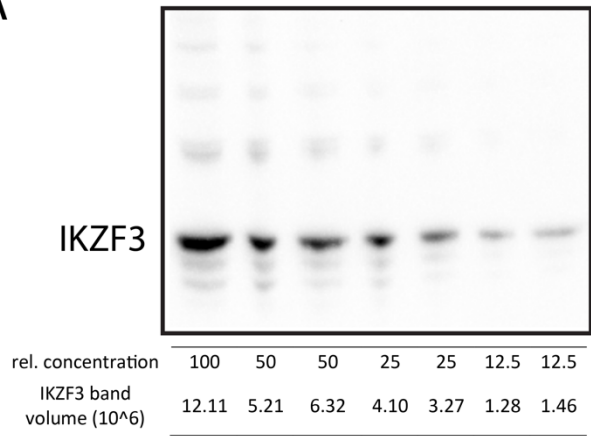
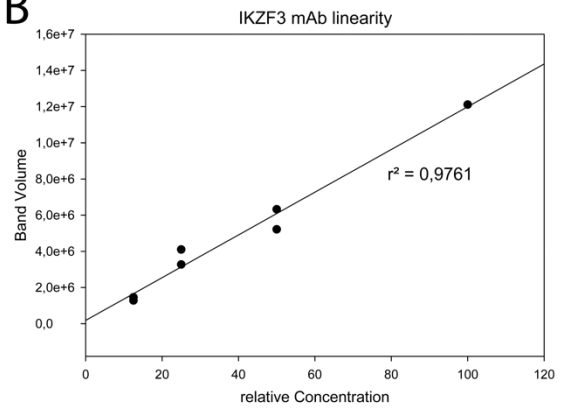
A**B**

Figure S3. Concentration response curve for IKZF3 mAb. **A** Immunoblot for detection of IKZF3 in a dilution series of OPM2 cell extracts and integrated band volumes. **B** Resulting concentration response curve of the IKZF3 mAb.

Compound	SMILES	K _i (μM)
4a	<chem>O=C3CC(n2c(=O)c1cccc(N(=O)=O)c1c2=O)C(=O)N3</chem>	>40
4b	<chem>O=C3CC(n2c(=O)c1ccc(N(=O)=O)cc1c2=O)C(=O)N3</chem>	11 ± 1.8
4c	<chem>O=C3CCC(n2c(=O)c1cccc(N(=O)=O)c1c2=O)C(=O)N3</chem>	>40
4d	<chem>O=C3CCC(n2c(=O)c1ccc(N(=O)=O)cc1c2=O)C(=O)N3</chem>	9.0 ± 1.6
5a	<chem>Nc2cccc3c(=O)n(C1CC(=O)NC1=O)c(=O)c23</chem>	>40
5b	<chem>Nc3ccc2c(=O)n(C1CC(=O)NC1=O)c(=O)c2c3</chem>	12 ± 0.7
7a	<chem>C/C(C)=C\C(=O)NC1CC(=O)NC1=O</chem>	>40
7b	<chem>O=C(Cc1cccc1)NC2CC(=O)NC2=O</chem>	>40
7c	<chem>O=C2CC(NC(=O)c1c(Cl)cc(Cl)cc1Cl)C(=O)N2</chem>	9.0 ± 1.5
7d	<chem>O=C2CC(NC(=O)OCc1cccc1)C(=O)N2</chem>	4 ± 0.4
7e	<chem>O=C2CC(NC(=O)c1cc(N(=O)=O)cc(N(=O)=O)c1)C(=O)N2</chem>	>99
7f	<chem>O=C(/C=C/c1cccc1)NC2CC(=O)NC2=O</chem>	20 ± 2.6
7g	<chem>O=C3CC(NC(=O)c2sc1cccc1c2Cl)C(=O)N3</chem>	>40
7h	<chem>O=C3CC(NC(=O)c2sc1cccc(Cl)c1c2Cl)C(=O)N3</chem>	20 ± 5.8
11a	<chem>[NH3+]Cc2ccc(COC(=O)NC1CC(=O)NC1=O)cc2</chem>	12 ± 1.7
11b	<chem>[NH3+]Cc2ccc(COC(=O)NC1CCC(=O)NC1=O)cc2</chem>	10 ± 0.8
12a	<chem>O=C(O)CCC(=O)NCc2ccc(COC(=O)NC1CC(=O)NC1=O)cc2</chem>	12 ± 2.0
12b	<chem>O=C(O)CCC(=O)NCc2ccc(COC(=O)NC1CCC(=O)NC1=O)cc2</chem>	36 ± 10.5
16a	<chem>[NH3+][C@@H]2CC[C@H](COC(=O)NC1CC(=O)NC1=O)CC2</chem>	20 ± 2.0
16b	<chem>[NH3+][C@@H]2CC[C@H](COC(=O)NC1CCC(=O)NC1=O)CC2</chem>	5.0 ± 0.5
20a	<chem>O=C2CC(NC(=O)OC[C@@H]1CCC[NH2+])C(=O)N2</chem>	insufficient purity
20b	<chem>O=C2CCC(NC(=O)OC[C@@H]1CCC[NH2+])C(=O)N2</chem>	45 ± 15.7

Table S1. Molecular formula strings and K_i values of all compounds.