



**Detailed interactions of SETD3 and  $\beta$ -actin peptide (66-88).** The  $\beta$ -actin peptide mainly contacts N-terminal lobe of SETD3, with its N-terminal and C-terminal sides contact SET and iSET domains, respectively. In the top panel, SETD3 are shown in ribbon and colored in the same way as shown in Figure 2A.  $\beta$ -actin peptide is shown in yellow sticks. Detailed interactions between SETD3 and Leu67-Glu72, and between SETD3 and Gly74 and Glu83, are shown in the left bottom and right bottom panels, respectively. The SETD3 residues involved in  $\beta$ -actin binding are shown in sticks.

**Figure 2–figure supplement 1**