**Supplementary Materials**

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**Structural and functional insights into the 2'-O-methyltransferase of SARS-CoV-2**

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**Supplementary data**

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**Supplementary Fig. S1.** Recombinant protein expression and purification. **A** The elution chromatogram (λ280, mAU) of SARS-CoV-2 nsp16 (blue) or nsp10 (orange) showed a main peak. The corresponding elution column volumes of nsp16 and nsp10 were 12.86 mL and 13.36 mL, respectively. **B** The purified proteins were separated using SDS-PAGE and stained with Coomassie blue. MW, molecular mass markers.

**Supplementary Fig. S2.** Multiple sequence alignment and structural analysis. **A, B** Multiple-sequence alignment of nsp16 amino acid sequences (**A**) and nsp10 amino acid sequences (**B**) across diverse coronaviruses. The K-D-K-E catalytic tetrad was highlighted in a black box. The nsp16/nsp10 interface of SARS-CoV-2 was highlighted in a gray circle, while that of MERS-CoV was highlighted in a yellow circle. **C** Superimposition of the nsp16/nsp10 structure of SARS-CoV-2 (PDB 6WKS, cartoon, gray) onto those of MERS-CoV (PDB 5YN5, cartoon, yellow). **D**–**F**The schematic summary of nsp16 and nsp10 residues of SARS-CoV-2 (**D**), MERS-CoV (**E**), and MERS-CoV/SARS-CoV-2 (**F**), directly interacting within a 3.5 Å range, was presented. Distinct residues were denoted in red. **G** The overall structure of nsp16/nsp10 complex was shown as surface and cartoon with 40% transparency. Lys-46, Asp-130, Lys-170 and Glu-203 were both shown as sticks and colored in red. SAM and 7MeGpppA were depicted as stick colored by atoms (C: white, H: white, N: blue, O: red, S: yellow).