

## Figure S3. The SEW2871 bound S1PR1-Gi-scFv16 and siponimod bound S1PR5-Gi-scFv16 complex cryo-EM data collection, structure determination, and cryo-EM map quality.

(a) Flow chart of Cryo-EM single particle reconstruction of SEW2871 bound S1PR1-Gi complex. Single particle pipeline yields the final cryo-EM reconstruction with the FSC curve, corresponding angular distribution and local resolution map. FSC curve shows a 3.27 Å resolution according to the 0.143 cut-off.

(b) Flow chart of Cryo-EM single particle reconstruction of siponimod bound S1PR5-Gi complex. Single particle pipeline yields the final cryo-EM reconstruction with the FSC curve, corresponding angular distribution and local resolution map. FSC curve shows a 3.4 Å resolution according to the 0.143 cut-off.