The human coronavirus, associated with severe acute respiratory syndrome (SARS-CoV), was identified and molecularly characterized in 2003. Sequence analysis of the virus indicates that there is only 20% amino acid (aa) identity with known coronaviruses. Previous studies indicate that protein-protein interactions amongst various coronavirus proteins are critical for viral assembly. Yet, little sequence homology between the newly identified SARS-CoV and those previously studied coronaviruses suggests that determination of protein-protein interaction and identification of amino acid sequences, responsible for such interaction in SARS-CoV, are necessary for the elucidation of the molecular mechanism of SARS-CoV replication and rationalization of anti-SARS therapeutic intervention. In this study, we employed mammalian two-hybrid system to investigate possible interactions between SARS-CoV nucleocapsid (N) and the membrane (M) proteins. We found that interaction of the N and M proteins takes place in vivo and identified that a stretch of amino acids (168-208) in the N protein may be critical for such protein-protein interactions. Importantly, the same region has been found to be required for multimerization of the N protein (He et al., 2004) suggesting this region may be crucial in maintaining correct conformation of the N protein for self-interaction and interaction with the M protein.