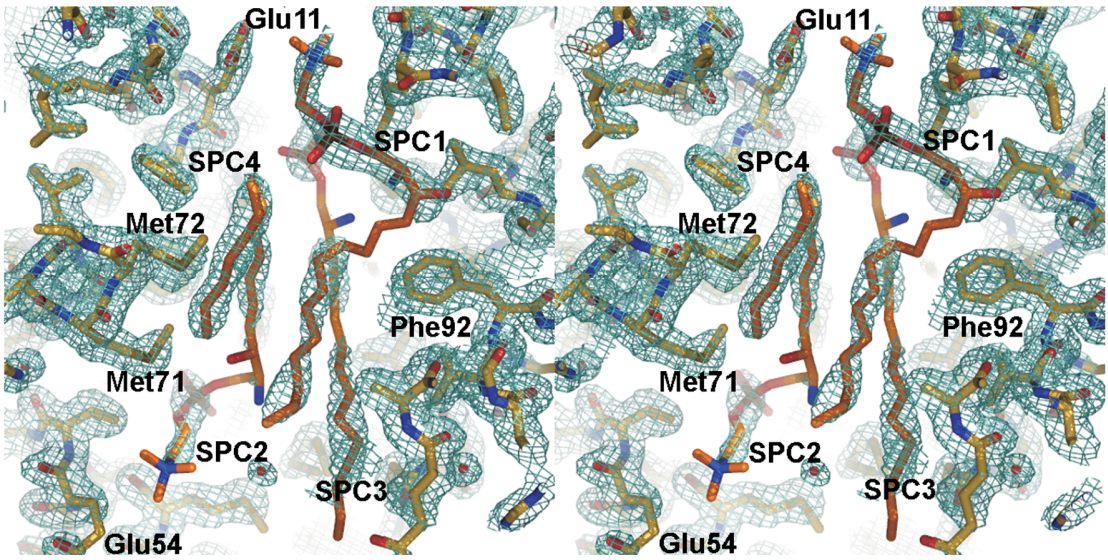
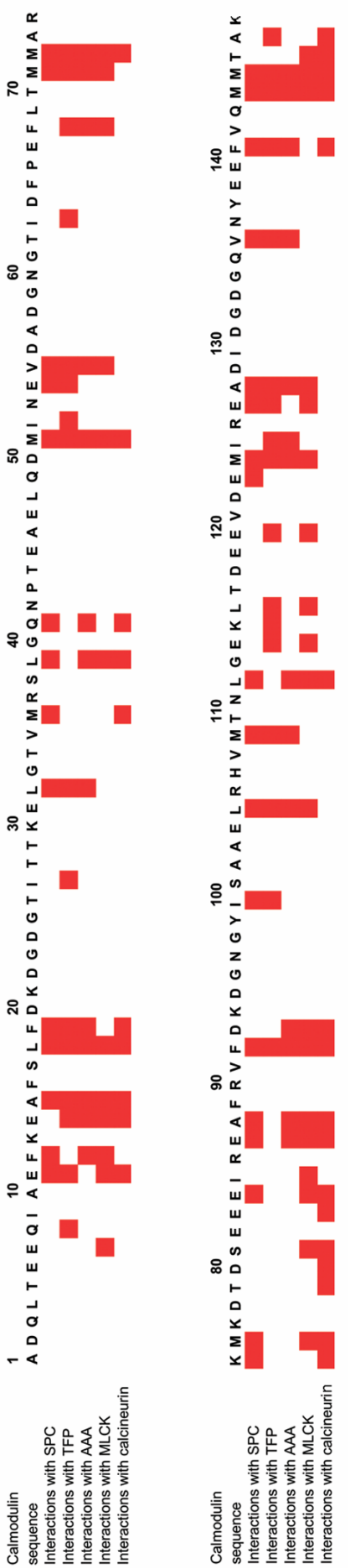
Supplemental Figure S1. Stereo view of the electron density map contoured at 1.0 σ level in the SPC binding region. Note that segments of the SPC molecules outside the hydrophobic binding region are disordered.



Supplemental Figure S2. Comparison of the binding site of SPC and other small molecule competitive inhibitors as well as target peptides of CaM. Residues of the CaM sequence within 4.0 Å distance from the ligand/peptide are colored red. Intermolecular contacts were collected from PDB structures 3IF7 (present structure, Ca^{2+}CaM / 4 SPC), 1LIN (Ca^{2+}CaM / 4 TFP), 1QIV (Ca^{2+}CaM / 2 arylalkylamine), 2K0F (Ca^{2+}CaM / myosin light chain kinase target peptide), 2R28 (Ca^{2+}CaM / calcineurin target peptide 2:2 complex), respectively.



Supplemental Figure S3. Isothermal titration calorimetry of the SPC – apoCaM interaction (A) 200 µM SPC in the cell was titrated with 300 µM apoCaM in a wide concentration range (■). The result indicated a complex process with two binding reactions at low molar ratios. We observed an additional endothermic heat reaction which gradually decreased during the whole experiment. We interpreted this third process as micelle rearrangement or dilution effect and fitted an exponential decay to it in the larger molar ratio range with good agreement (— — —). The extrapolated curve was subtracted from the original profile resulting in a curve of clearly two binding steps (□) that could be fitted with a two-site model provided by Origin for ITC software (----). The first binding occurs at very low apoCaM concentrations represented by only two points in this titration. (B) For a more detailed and accurate investigation of the two binding processes, we repeated the experiments in the lower molar ratio range using only 75 µM apoCaM in the syringe and injecting lower volumes into the cell. The symbols are identical to those in panel a. The resulting thermodynamic parameters are listed in Table 1 of the manuscript.