In this paper, the potential of adaptive neuro fuzzy inference system (ANFIS) was appraised for investigation of thermal performances of a minichannel heat sink for cooling of electronics using nanofluid coolant instead of pure water. The process, which simulates the thermal performances with ANFIS network, was constructed. The developed ANFIS network was with three neurons in the input layer, and one neuron (thermal performances) in the output layer. Since there are three thermal performances investigated, three ANFIS networks are created. The inputs were flow rate, as well as the Reynolds number. The third input represents the nanofluid concentration. The Al2O3–H2O nanofluid including the volume fraction was used as a coolant. Obtained experimental results showed the higher improvement of the thermal performances using nanofluid instead of pure distilled water. ANFIS results show that an improvement in predictive accuracy and capability of generalization can be achieved by the ANFIS approach for heat sink base temperature prediction.