The H2 histamine receptor (HRH2) belongs to a family of G–protein coupled receptors that are responsible for binding histamine, a biogenic amine which is known to play a key role in allergic responses. HRH2 has been shown to regulate muscle relaxation and intestinal secretion and has thus been utilized as a pharmacological target for treatment of anaphylaxis and acid peptic disorders. In this study, a computational model of the three-dimensional structure of HRH2 was generated from its amino acid sequence. A newly-developed docking procedure was then implemented to predict potential binding modes for a number of antagonists, as well as histamine itself, based on this structure. Our results help to explain the relative affinities of several known H2 ligands and are validated by comparison with experimental mutagenesis studies. It is hoped that further understanding of the binding properties of this receptor will aid in the design of more potent and specific pharmacological agents against it.