The prion protein PrPc is a glycosylated component of the extracellular surface of neurons, which appears to have an active role in signal transduction. Its misfolded isoform, PrPSc, is a β-sheet-rich, protease-resistant protein that causes fatal neurodegenerative disorders in humans and in other mammals, which can exhibit sporadic, inherited or infectious presentations. Despite remarkable differences in phenotypic expressions, these disorders share a similar pathogenic mechanism: a post-translational modification of the prion from the normal cellular isoform PrPc to disease-specific species PrPSc. The PrPc → PrPSc transition involves a profound conformational change with a decrease in α-helical secondary structure (from approximately 40% to 30%) and a consequent, remarkable increase in β-sheet content (from ~ 3% to 40%). This, in turn, is accompanied by the exhibition of abnormal physicochemical properties, including insolubility in typical non-denaturing detergents and partial resistance to proteinase K digestion.

In recent studies it has been found that residues 90-120 are antigenically accessible in PrPc but are encrypted in PrPSc. Further, experiments on mini-prions containing only residues 89-140 and 177-231 showed that one of these two regions is critical to the conformational changes but, since a peptide containing residues 90-144 carrying the P101L mutation folds into a β-rich structure that can cause a prion disease in transgenic mice and PrP(121-231) is not scrapie competent, residues 90-120 must be of paramount importance.

In this paper we present the results obtained from a detailed molecular modeling and dynamic simulation studies of the entire PrPc fragment (90-231) of the Syrian hamster above and below a pH that triggers conformational changes. Further, we report the evidence of possible binding sites of PrPc with several potential inhibitors, such as tetracyclines, Congo red and doxorubicin.