Effects of point mutation on BVDV RdRp:

An In-silico study

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Bovine viral diarrhea virus (BVDV) represents a major viral pathogen in cattle and other ruminants, responsible for heavy agronomic losses every year as well as a wide assortment of diseases manifestation including resorption, mummification and abortion of dead fetus. Recently our group has reported the most potent inhibitor of the BVDV RdRp, a benzimidazole class of compound, as well as the point mutation I261M in this protein, which confers resistance to BVDV RdRp against benzimidazole compounds. Here, we investigated the effect of the I261M mutation by using a non conventional approach that includes molecular dynamics, cluster analysis, flexible docking and metadynamics. We found that the mutation affects the structure and the dynamics of the protein, particularly in the region of binding of inhibitor and this results the two different binding sites in wild and mutated proteins. Moreover, while inhibitor closes the entrance for the template in the the wild protein, in presence of the mutation a channel leading to the catalytic site are available as the inhibitor moved away from its original position during dynamics. Our results furnishes a molecular explanation of the resistance mechanism that is in good agreement with experimental data.