The flaviviruses are emerging arthropod-borne viruses that are important human pathogens and represent an immense global health problem. These enveloped, positive-stranded ribonucleic acid viruses can cause significant human diseases in the form of encephalitis or haemorrhagic fever. Some of the medically important flaviviruses are Dengue Virus (DEV), West Niles Virus (WNV), Japanese Encephalitis Virus (JEV), Yellow Fever Virus (YFV) and Hepatitis C Virus (HCV). There are no effective antiviral therapies available to date and the main approach to disease control is via vaccination and vector control. Therefore focus on the development of anti viral target for drug development is crucial to treat the infection of flaviviruses. The viral protease and, NS3 and its cofactor, NS2B plays a major role in the cleavage of polyprotein during viral replication. Therefore, the understanding of residues interaction in flaviviruses protease has the potential to lead to drug discovery of flaviviruses infection.