Molecular Modelling Analysis of the Metabolism of Bortezomib

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**Abstract:** Multiple myeloma [MM] is a malignant disorder characterized by the accumulation of neoplastic plasma cells in the bone marrow, osteolytic bone resorption and suppressed bone formation. The disease remains mostly incurable despite advances in conventional chemotherapy. Bortezomib (Velcade) is a potent first-in-class dipeptidyl boronic acid proteasome inhibitor that was approved in the United States in 2003 for the treatment of patients with relapsed MM. However, the use of bortezomib is associated with a number of side-effects including gastrointestinal disturbances, thrombocytopenia, asthenia and peripheral neuropathy. Molecular modelling analyses based on molecular mechanics, semi-empirical and DFT (at B3LYP/6-31G* level) calculations show that neither bortezomib nor any of its metabolites are extremely inert or extremely labile kinetically so that based on the kinetic consideration neither can be excluded from consideration as being responsible for adverse reactions due to the drug. However, the presence of significant electron-deficient regions on the molecular surfaces of M2, M27 and M28 indicates that the metabolites may be more be subject to nucleophilic attack. This means that M2, M27 and M28 may cause cellular toxicity though glutathione depletion and oxidative damage to DNA. Since reactive oxygen species (ROS) such as peroxide radical ion are believed to be formed in the oxidative deboronation of bortezomib, it is possible that the toxic side-effects due to bortezomib are mainly due to ROS.