The posttranslational modification of histones has proven to be critical for gene regulation, repair and cell cycle progression. The increased risk of onset of several diseases such as cancer, obesity, diabetes, and cardiovascular disease have more recently shown to be related to such modifications. One class of enzymes responsible for carrying out such modifications is the methyltransferases (MTs), which can add methyl groups to lysine, arginine, and serine residues of histones. These modifications, known as histone methylation, can result in various epigenetic changes (Esteller, 2006, Jirtel et al., 2007). Several classes of enzymes are responsible for carrying out such modifications. One of these classes is the histone methyltransferases (HMTs), which add methyl groups to histone tails. This modification can result in changes to chromatin structure, leading to changes in gene expression. The EC80 concentration for the methyltransferase (MT) reaction product S-adenosylhomocysteine in a dual head of the liquid handling instrument. During determination of the EC80 of the HMT, the assay was carried out in 384-well plates using the MultiFlo ™ Microplate Dispenser and the Precision ™ Microplate Pipetting. The unique XY transport design offers a choice of either peristaltic pump or gravity dispensing for automated 96-/384-well microplate liquid transfers with the same pipette mechanism. The 8-channel head of the liquid handling instrument was used to automate addition of the histone methyltransferase (HMT) G9a and transfer of the inhibitor across a 96-well plate, as well as all assay components were also automated during determination of the IC50 value of a HMT inhibitor. The IC50 value was 14.5 µM. The G9a enzyme reaction progressed to ~10% conversion. A dose response curve was generated for G9a methyltransferase sensitivity with the known IC50 value of 14.5 µM shows excellent correlation with published values (Reactions et al., 2001). A combination of labeled and single channel liquid handling was used to automate addition of the 96-well plate background homocysteine S-adenosylmethionine, and all assay components were also automated during determination of the IC50 value of a HMT inhibitor. The IC50 value was 14.5 µM. The G9a enzyme reaction progressed to ~10% conversion. A dose response curve was generated for G9a methyltransferase sensitivity with the known IC50 value of 14.5 µM shows excellent correlation with published values (Reactions et al., 2001).