SUMMARY AND FUTURE PERSPECTIVE
Cancer is the second leading cause of death. Nowadays, discovery and development of anticancer drugs is the heart-throb of several pharmaceutical industries, research groups as well as government, non-government organizations. Nitrogen mustards (N-mustards) are considered as promising anticancer drugs since the beginning. N-mustard derivatives are excellent DNA-alkylators. This class of drug molecules inhibit cell growth by formation of intra- and interstrand cross-linking in all phases (G₀, G₁, S, G₂, and M) of the cell cycle. In last more than seventy years several hundreds of such molecules have been synthesized with potent anticancer activity. The major drawback of this class of drug is their high reactivity, toxicity because of non-target specificity. Discovery and development of target specific efficacious drugs necessitates understanding of the structure and reactivity/stability of drug molecules and the ways in which they interact with bio-targets. Structure based analysis is currently considered as the most fruitful approaches for new drug design. Mechanistic study of drug action is a subject matter of established investigations. Mechanistic understanding of drug action helps oncologists to predict which drugs are likely to work well.

Study of drugs at the molecular level is the central paradigms of anticancer drug discovery and development. Though mechanism of drug action of N-mustards has understood well, a molecular level study is of utmost important. Computational studies are extremely helpful for quantitative structure and reactivity/stability assessment at the molecular level. In comparison to a large number of experimental studies, only few computational studies have been performed on these drug molecules. In recent years DFT and DFRT have been successfully applied to understand the DNA alkylation mechanism, effect of
solvent on the alkylation process, stability of the chemical species involved in the reaction etc. In near future this kind of studies might be helpful in developing new more potent N-mustards.

In this research work, the structural variation of a few $Az^+$ ion intermediates has been countersigned during DNA alkylation. Our findings suggest that the structural variation in the drug intermediate facilitates DNA alkylation. Interaction energy in gas phase of the prototype drug intermediates with the GC base pair is found to be higher than in aqueous phase.

We also analysed the influence of solvent environments with different dielectric constants and temperatures on the reactivity/stability of $Az^+$ ion intermediates and thermodynamic feasibility of the $Az^+$ ion intermediate formation. It is found that the reactivity/stability of the drug-intermediates tremendously decreases from gas phase to solvent phases and continues from low to high dielectric constants. The decline in $\Delta G$ and $\Delta H$ with the increase of temperature and dielectric constant of the medium clearly indicates the effect of temperature and solvent polarity on the thermochemistry of $Az^+$ ion intermediate formation. A positive value of $\Delta G$ and $\Delta H$ indicates the absence of thermodynamic driving forces for $Az^+$ ion intermediate formation. Our observations suggest that in cytoplasm (polar environment) $Az^+$ ion intermediate formation is favoured at normal body temperature (310 K).

The influence of polar environment on the reactivity/stability of the $Az^+$ ion intermediate of mustine and mustine-guanine adduct has been analysed by means of external electric field. Our study confirms that for DNA alkylation by N-
mustards, presence of external electric field is must. Magnitude of external electric field strength and its direction of application also influences the thermochemistry of mustine-guanine adduct formation process, interaction energy between $AZ^+$ ion intermediate of mustine and guanine as well as stability of the mustine-guanine adduct.

It is found that the reactivity/stability pattern of $AZ^+/AZ^{2+}$ ion intermediates and their corresponding adducts is not uniform in gas and aqueous phases. The reactivity/stability of $AZ^+$ ion intermediates is different from that of $AZ^{2+}$ ion intermediates. Similarly the stability of the mono-adducts (drug-GC) is different from that of cross-linked adducts. It is established that LRDs are superior to explain the reactivity/stability pattern among the drug molecules than the GRDs. $\Delta G_{sol}$ shows that all the drug molecules are not equally solvated.

It is witnessed that internal coordinates effects the reactivity/stability of the drug-DNA (mustine-guanine) adduct. Thermodynamic parameters and the electrostatic nature of a molecular system are not significantly effected by change of internal coordinates while chemical behaviour of the system is highly effected.

A better understanding of the DNA alkylation by N-mustards is not only of academic interest but is relevant to cancer chemotherapy as well. The overall investigation of the DNA alkylation reaction shows that the structural variation, reaction environment, external electric field, solvation, internal coordinates; effects the reactivity/stability of the drug intermediates, as well as their corresponding drug-DNA adducts. Finally, we do hope that the results of our investigation would help in designing new drugs with enhanced potency, reactivity/stability, and site selectivity.