CHAPTER 10

CONCLUSION

The investigation carried out on the stacking of drugs and sequences of DNA and other studies on physiochemical properties like proton affinities and pK_a can be summarized as followes -

Some stacked models of 9-aminoacridine with aromatic rings of base pairs are stable, but in optimum stacked models small portion of drug stacks with sequences. We have explored the different stacked models using MNDO and *ab initio* methods. In view of this it is rather difficult to come to the conclusion whether the chromophore actually intercalates itself with sequences of DNA or any other factor responsible for intercalation.

Consequently different azaacridine-4-carboxamides having additional nitrogen atom in the ring are found favorable for stacking with the aromatic rings of various sequences and the variation of the interaction energies of the optimum stacked models of different azaacridinecarboxamide having N atom at 5, 6, 7 and 8 positions in chromophore are found. Hence the contribution of N atom within the stacking region of aromatic rings cannot be ignored. The favorable stacking is observed in the stacked configuration when the N atoms are accommodated within the stacked region. It appears that the π–π and π–σ interactions contribute to the stability of stacked models of drug and base pairs. The drug acquires more specificity for GC sequences. In fact there indicates some differences in the stacking of this drug with AT and GC sequences, in spite of having steric effect from the side chain carboxamide.

Our findings on the variation of optimum stacked structures of 9-aminoacridine-4-carboxamide having nitrogen at 5, 6, 7 and 8 position in the ring with sequences prompt further study on the stacking of substituted azaacridine analogues. In addition to the π–π interaction for these molecules, we have considered the stacking of π-substituents in the stacked models. The efficacy of the molecules to stabilize the drug-sequence interaction have been observed in -C=O substituted drug, whereas the -Cl substituents produces less stacking with sequences. Here the -Cl, -C=O and $-NH_2$ group are not so insensitive to π–π stacking, the wide variations of the interaction energies sequence preference binding of this compound (AT or GC) clearly suggest some contribution from the substituents.

These drugs show GC specificity, however the small difference in the stacking energy renders specificity for AT or GC as not so remarkable.

A number of analogues of these drugs have been reported to acquire wide variation of pK_a and biological properties are known to be related to pK_a. As the concept of pK_a value is used in many biological reactions, we have computed values of pK_a of these drugs based on fundamental principles. The theoretically predicted pK_a values have been found to be within the range of 8-9, which are higher than the physiological pH (7.4). This variation in pK_a might be useful for exploring into the decrease in biological property of this drug from acridine-4-carboxamide. In fact this finding may be employed in understanding the concept of selectivity in binding with DNA rather than other molecules in biological system. In the sense that drugs of low pK_a may essentially acquire reversed behavior compared to azaacridinecarboxamides while entering the biological system. In addition to this the pK_a of the chromophore of some azaacridine carboxamide is less than that of carboxamide side chain. The results presented here suggest that the aza analogues may have similar structure with acridine-4-carboxamide, but azaacridine carboxamides have two basic sites in the chromophore. The shifting of pK_a based on the electronic properties of substituents appear to implicate some information how the pK_a value correlates with the nature of the substituents.

We have examined the intercalative ability of 9-anilinoacridine-4-carboxamide. There observed little differences between the stacking energies of 9-anilinoacridine and azaacridine-4-carboxamide, while the biological activity of these drugs is very much different.

The model studies on the intercalation of drug between two base pairs show reasonable improvement in the stacking energies. The chromophore of azaacridine is better stabilized within GC sequences than the AT sequences.

However the alternative strategy in enhancing the anticancer property may involve adjustment of pK_a rather than acquiring more DNA binding ability. In view of this both the DNA binding ability of drug and its pK_a should be taken into consideration in designing drugs with enhanced biological properties. From the accumulated results, the physiological nature of the chromophore that stabilizes the drug within the sequences of DNA might be important. Hence both protonated and unprotonated chromophore have been used to

assess the sequence specificity of this drug. The protonated form stacks with sequences less favorably than the unprotonated form and the chromophore nitrogen might be remarkably sensitive to pH of environment since the proton affinities of nitrogen atoms of chromophore are quite high. However we can hypothesized that the stabilization of the protonated form based on the pK_a values (pK_a >7). In view of this, the nature of the chromophore that goes into intercalation of these compounds might be different. In azaacridinecarboxamides two protonation sites in the chromophore are present, and thereby behaves as less efficient intercalator because stacking of protonated chromophore is less favorable than the free chromophore or the selectivity of drug for DNA might not be promising.

The computed pK_a value of aminoacridine is close to experimentally determined value, hence the theoretically predicted pK_a values of other azaacridinecarboxamide may be useful for understanding variation in the experimentally reported biological properties of this class of drugs.