# CHAPTER 6

# EVALUATION OF STACKING INTERACTION BY CHROMOPHORE OF 9-ANILINOACRIDINE WITH SEQUENCES OF DNA.


## SUMMARY

The stacking of anilino derivative of acridine has been investigated for few selected models. In order to assess the differences in the stacking of chromophore of this molecule with base pairs from that of acridine-4-carboxamides we explored some stacked structures. There are little variations between the stacking energies of this drug and acridine-4-carboxamide, and also such small variation may not be enough for demonstrating the contrasting biological property of this drug from other acridine carboxamides. The entry of this chromophore from minor and major grooves is well demonstrated.


## 6.1 INTRODUCTION

In exploring the sequence specificity of acridine-4-carboxamide, the nature and positioning of side chain carboxamide is one of the important factors with regard to anticancer property. A number of compounds having side chain at C4 position in chromophore have been reported, but there are few carboxamides having side chain at other positions. Some C1, C2, C3 and C9 substituted carboxamides are available ***[1-7]***. So the position of this cationic side chain in chromophore is also considered another important factor for sequence specific intercalation by chromophore of these drugs. In search of new acridine carboxamides, the C1, C2, C3, C4 and C9 substituted chromophore of carboxamides have been reported and the anticancer property of these drugs are found to be significantly different. Among these carboxamides acridine-4-carboxamides possess highest potency, and also serve as efficient DNA binding drug. Hence for these drugs the carboxamide side chain at C4 position in chromophore is the required condition. In further studies on these classes of acridinecarboxamides, the anilinoacridinecarboxamide compound acquires little antilukemic activities compared to the parent acridine-4-carboxamide, but the compound is known for its antimalarial activity ***[8-10]***. Hence the aim to explore the stacking ability by the chromophore of anilinoacridinecarboxamide for understanding the distinguished biological properties of this drug from the other acridine-4-carboxamides.

## 6.2 METHODOLOGY

(a) At the beginning the C9 substituted anilino acridine is placed at the opposite side of methyl groups representing the sugar backbone. Here the interaction energies with respect to $\pi$–$\pi$ interactions among the aromatic rings present in drug and base pairs are considered.

(b) Again we changed the orientation of anilino (C9) to other configuration, where the anilino (C9) was kept on the same side of the sugar backbone. Similarly the optimum interaction energies were obtained by changing the location of aromatic rings of drug along the sequences. In this case also we consider the $\pi$–$\pi$ interactions of aromatic rings present in drug and base pairs.

The stacked structures with large steric effect were arbitrarily ignored in the calculation. Both HF/6-31G** and B3LYP/6-31G** methods were used for calculating the stacking energies.

## 6.3 RESULTS AND DISCUSSION

Many acridine-4-carboxamides with side chain at position C4 have been reported to achieve high potency compared to other carboxamides having side chain at C2 and C3 positions. Then the position of side chain in the ring is very critical for acquiring high potency. Likewise attempts have been made to design another class of anilinoacridine with anilino at position C9. So we examined the stacking ability of anilinoacridine with AT and GC with different basis sets(**Table 6.1a-b**). Here the anilino group is placed on the opposite side of the methyl groups and again similar calculation have been carried out for the models with anilino in the same side of methyl group so that complete account for the entry of chromophore from the minor and major grooves can be examined (**Table 6.1a-b**, **Figure 6.1a-c**, **6.2a-c**). The plot between the various models versus interaction energies is shown in **Figure 6.3** and **6.4**, and the optimum stacked structure is obtained from the minimum energy. The stacked models of this drug corresponding to minimum energies are shown in **Figure 6.1c** and **6.2a**. The position of drug with respect to $\pi$–$\pi$ stacking of aromatic rings can be visualized from some of the structures (**Figure 6.1a-c** and **6.2a-c**). One of the approaches of finding the most favourable stacking between drug and sequence is the identification of various stacked structures of all aromatic rings contained in drug and

base pairs. Consequently, the structures corresponding to minimum energy appeared to be contributed from the stacking of aromatic ring as well as the heavy atoms contained in it. The interaction energies of these optimum stacked structures are computed by using different basis sets in the HF calculations, and also DFT method has been used for comparison of interaction energies obtained for the entire configurations (**Table 6.1a-b**).

Similarly we have taken various stacked structures of drug with GC base pairs, where the minimum stacked structures are located from the plot of various stacked models versus interaction energies (**Figure 6.4**). In this case also we have found a number of configurations where the stabilization of stacked model with base pairs are contributed due to stacking of some portion of drug and base pair. Among these configurations, the most stable stacked structure are shown in **Figure 6.2a**. As we can see that the stacked structure correspond to the minimum energy arises from the stacking of specific regions that can accommodate heavy atoms present within it. This situation contrasts to those of aromatic ring stacking of other models where heavy atom are not found within stacked region (**Figure 6.1a-c** and **6.2a-c**). Hence the interaction energies of the optimum models correspond to $\pi$–$\pi$ and non bonded electron pair interactions. The binding model has been viewed for both orientation of anilino group in the minor and major grooves (**Figures 6.1a-c** and **6.2a-c**). The variations of Mulliken net charges on the heavy atoms present in the optimum stacked structures are shown in **Table 6.3a-b**. The involvement of heavy atom may be justified from the variation of net charge on heavy atoms.

It is found that the optimum model with side chain position in the major groove is more stable than the structure with side chain in minor groove for AT sequence. The interaction energy of major groove binding is 1-3 kcal/mol lower than that of minor groove binding. However the electrostatic potential within the minor groove of DNA is more than the major groove. So the intercalative binding should prefer major groove of DNA. However in the optimum stacked model of this drug with GC, the entry of chromophore through minor group is favoured.

If we compare the stacking energy of this drug with aminoacridine, there observed no significant differences (**Table 3.3a-b**, **3.4a-b** of **Chapter 3**). Hence the role of anilino group in the intercalative mode of binding may not be so important in distinguishing the

DNA finding ability of these drugs. Hence there might be other factors for acquiring contrasting biological properties of this drug from other azaacridine-4-carboxamides.

## 6.4 CONCLUSION

The sequence preference stacking of this class of molecules does not vary much from that of azaacridinecarboxamides. Hence there may be another factor for explaining the contrasting biological property of this drug from azaacridinecarboxamides.

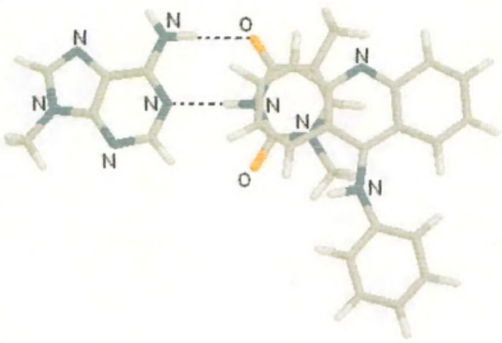

Figure 6.1a- Optimum stacking (AT-AZNL-8).

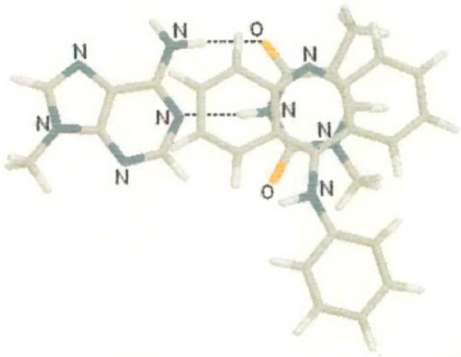

Figure 6.1b- Optimum stacking (AT-AZNL-10).

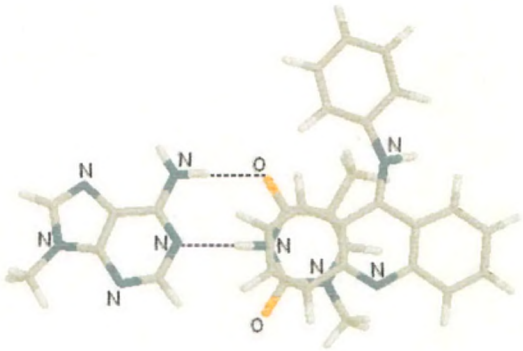

Figure 6.1c- Optimum stacking (AT-AZNL-11).

**Figure 6.1a-c-** Optimum stacking structure of 9-anilinoacridine (AZNL) and AT base pair.

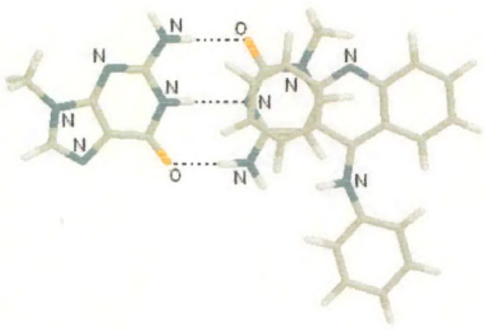

Figure 6.2a- Optimum stacking (GC-AZNL-8).

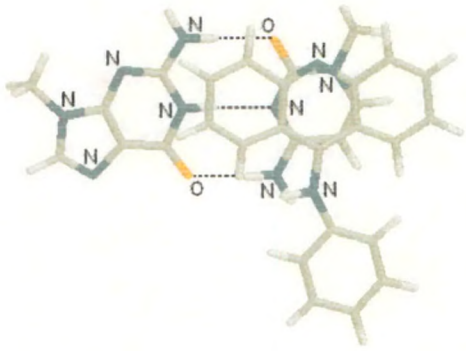

Figure 6.2b- Optimum stacking (GC-AZNL-10).

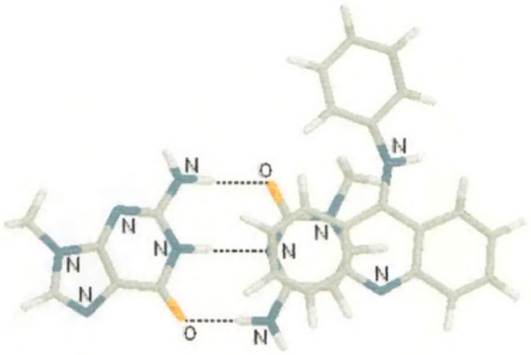


**Figure 6.2c-** Optimum stacking (GC-AZNL-11).
**Figure 6.2a-c-** Optimum stacking structure of 9-anilinoacridine AZNL and GC base pair.

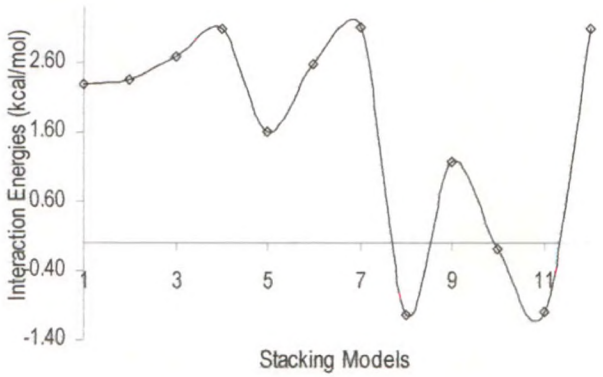


**Figure 6.3-** Plot of stacking models versus variation of Interaction Energies AT and 9-anilinoacridine (AZNL). (HF/6-31G)

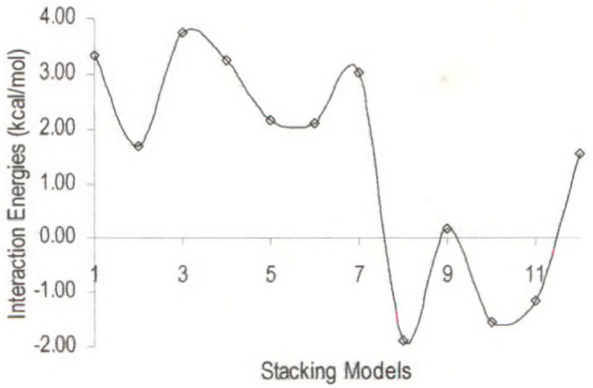


**Figure 6.4-** Plot of stacking models versus variation of Interaction Energies GC and 9-anilinoacridine (AZNL). (HF/6-31G)

**Table 6.1a** – The computed Interaction Energies of the optimum stacked models of 9-anilinoacridine (ANLI) with AT base pair.

| Stacked Models | Interaction energies ( in k cal/mol) | | | |
|---|---|---|---|---|
| (AT-ANLI-n) | HF/6-31G | HF/6-31G* | HF/6-31G** | B3LYP/6-31G** |
| AT-ANLI-8 | -1.051 | -0.961 | -0.986 | -1.517 |
| AT-ANLI-10 | -0.097 | -0.355 | -0.397 | -1.219 |
| **AT-ANLI-11** | **-1.012** | **-1.046** | **-1.111** | **-1.999** |

n = stacking location.

**Table 6.1b** – The computed Interaction Energies of the optimum stacked models of 9-anilinoacridine (ANLI) with GC base pair.

| Stacked Models | Interaction energies ( in k cal/mol) | | | |
|---|---|---|---|---|
| (AT-ANLI-n) | HF/6-31G | HF/6-31G* | HF/6-31G** | B3LYP/6-31G** |
| **GC-ANLI-8** | **-1.886** | **-1.698** | **-1.707** | **-1.909** |
| GC-ANLI-10 | -1.552 | -1.617 | -1.634 | -2.284 |
| GC-ANLI-11 | -1.157 | -1.022 | -1.033 | -1.430 |

n= stacking location.

**Table 6.2** – The computed Interaction Energies of the optimum stacked models of 9-anilinoacridine (ANLI) with AT and GC base pair for the aniline group staying towards minor and major grooves.

| Stacked models (XX-ANLI-n) | Observed binding direction | HF/6-31G |
|---|---|---|
| AT-ANLI-8 | Major groove | -1.051 |
| AT-ANLI-11 | Minor groove | -1.011 |
| GC-ANLI-8 | Minor groove | -1.886 |
| GC-ANLI-11 | Major groove | -1.157 |

XX = AT or GC, n= stacking location.

**Table 6.3a** – Variation of Mulliken net charges on heavy atoms of 9-anilinoacridine (ANLI) in optimum stacked structure with AT base pair.

| Stacked Models | Net charge on N7 | | Net charge on N10 | |
|---|---|---|---|---|
| (AT-ANLI-n) | Free | Interacted | Free | Interacted |
| AT-ANLI-8 | | -.686 | | -.974 |
| AT-ANLI-10 | -.687 | -.688 | -.640 | -.980 |
| AT-ANLI-11 | | -.693 | | -.979 |

n = stacking location.

**Table 6.3b** – Variation of Mulliken net charges on heavy atoms of 9-anilinoacridine (ANLI) in optimum stacked structure with GC base pair.

| Stacked Models | Net charge on N7 | | Net charge on N10 | |
|---|---|---|---|---|
| (AT-ANLI-n) | Free | Interacted | Free | Interacted |
| GC-ANLI-8 | | -.690 | | -.979 |
| GC-ANLI-10 | -.687 | -.689 | -.640 | -.979 |
| GC-ANLI-11 | | -.689 | | -.980 |

n= stacking location.

**Reference:**


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