Model study on the sequence specific stacking by chromophore of an anticancer drug, acridine carboxamide with base pairs of DNA

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The study on the sequence specific binding of acridine-4-carboxamides with DNA has been an important topic in the design of new drugs. It has been known that the anticancer properties of acridine-2, acridine-3 and acridine-4-carboxamides are significantly different. So the sequence specific binding of these drugs can be monitored from the intercalative mode of binding by chromophores within DNA. The stacking energies obtained from ab initio, MP2 and DFT methods have been used to understand the sequence preference intercalation by chromophore. Among these drugs, the acridine-4-carboxamide shows maximum stacking with GC base pair in spite of acquiring high potency, but the stacking energy of this drug with AT base pair is not so small. The conformation of carboxamide side chain in acridine-4-carboxamide does not lie in the same plane of chromophore, and also the orientation of side chain in acridine-2 and acridine-3 carboxamides is different from that of acridine-4-carboxamide.

Keywords: Stacking, ab initio, MP2, DFT, DNA

A number of acridine-4-carboxamides have been known as anticancer drugs, and this class of drugs acquires intercalative as well as covalent binding ability with DNA. These drugs contain intercalative molecular fragment (chromophore) and a carboxamide side chain that may act as primary or secondary binding fragment with DNA. Perhaps little has been analysed to know how the interactions contributed from these different parts of this drug control the overall binding ability. In this context a variety of structurally similar chromophore substituted acridine-4-carboxamides are reported, and many studies on structure-activity relationships have been explored to trap the factor for enhancing anticancer property. The binding of these two distinguished parts, the chromophore and the carboxamide side chain cannot be separately estimated because the chromophore intercalates in between the sequences of DNA and at the same time carboxamide side chain binds covalently within the grooves. However the change in the electronic properties of chromophores due to substituents, and also positioning of side chain at different positions of chromophore affects the DNA binding abilities of drugs that consequently produce wide variation of anticancer properties. In addition, drastic change in anticancer property with the change in carboxamide side chain position of drug might be considered for demonstrating the dependence of side chain in DNA binding of this drug. Herein the additional effect incorporated in the intercalative binding with the change in side chain position is an intuitive question, and such change in the position of carboxamide side chain may affect the intercalative ability. At most, it should acquire some special geometrical features for easy access within the sequences of DNA, and also the side chain must possess affinity for binding along the grooves of DNA. But, the features of such covalent binding by side chain can be studied from the interaction of drug with fragments of DNA sequences. Hence the stacked models of carboxamides with side chain at 2, 3 and 4 positions in the chromophore are taken up for understanding only the sequence preference intercalation within DNA.

Generally new drugs with enhanced anticancer properties are designed by modifying substituents at different positions in chromophore. As an example, 7-chloroacridine-4-carboxamide is found to be more potent than acridine-4-carboxamide. Then the biological activity may depend on the intercalative ability of the molecular fragment 7-chloroacridine, but in some cases increasing intercalative ability does not produce better biological activity. However the position of carboxamide side chain in the
chromophore is critical and positioning of this side chain at 4 position is must for having high potency. The anticancer properties of acridine-2 and acridine-3-carboxamides are significantly less than acridine-4-carboxamide. Then it is important to investigate the variation of intercalative ability of these drugs having side chain position at 2, 3 and 4 positions because anticancer property may depend on the intercalative ability of chromophore (Figure 1).

On the other hand the physiochemical properties of these drugs are significantly different, and the $pK_a$ of acridine-4-carboxamide is much more than acridine-2 and acridine-3-carboxamides. There is no direct indication why low $pK_a$ values are observed in acridine-2 and acridine-3-carboxamides, and if the anticancer property depend on the $pK_a$ value, then its consequent role in DNA binding may be important. In acridine-2, acridine-3 and acridine-4-carboxamides, the variation of intercalative mode binding must be necessary because these drugs possess common carboxamide side chain and the contribution of side chain in binding DNA may not vary. The requirement of side chain center separated from the acridine nitrogen (chromophore) by fixed distance (approximately 8Å) is noted for acquiring high potency. Again the biological properties of these carboxamides have been studied by increasing side chain length and the requirement of definite side chain length for attaining potency is found. However no concrete conclusion could be obtained from these evidences how the anticancer property of this drug is correlated with the position of carboxamide in chromophore and on its length, while both the side chains binding and the chromophore intercalation may contribute to the biological activity of these drugs. At the beginning it may be necessary to examine the differences in intercalative abilities among these drugs from the study on various stacked models of chromophore and base pairs.

Generally the stacking between base pair and chromophore is contributed from the $\sigma-\pi$ and $\pi-\pi$ interactions between chromophore and base pair. For studying such stacking energies proper inclusion of electron correlation in the $ab\ initio$ calculation is must. An extensive use of $ab\ initio$ methods is known in many of the hydrogen bonded van der Waals complexes and small biological molecules. The intercalation of DNA within sequences by chromophore may be analysed from the stacked models of drug and sequences where the total intermolecular energy is due to the various energy components such as exchange repulsion, dispersion, charge transfer and polarization energies etc. The $ab\ initio$ methods have been used for interpreting the sequence specificity of various sequences in nucleic acid, and the stacking of acridine-4-carboxamide with sequence. This work focuses on the study of various stacked models of sequences of DNA and drug having carboxamide side chain at different positions of chromophore for understanding the sole factor responsible for the sequence specificity with respect to side chain position.
Methodology

Complete geometry optimisation of drugs and base pairs were carried out before constructing the stacked models (Figures 2-4). The stacked models of base pairs and drugs are constructed by changing the orientation of drug with respect to base pairs, and stacking energies were computed using various levels of theories (Figures 5-10). The 6-31G/HF route is used for geometry optimisation, and each rigid configuration of base pair so obtained is allowed to stack with chromophore. In this case the methyl groups representing sugar in the base pair and the carboxamide side chain were placed on the same side so that in each stacked model, sugar and carboxamide side chain should fall on the periphery of helix circle. Again, the other configurations where the carboxamide side chain lies on the opposite side of -CH₃ groups of base pair are also studied (Table I, Figures 11 and 12). These constructed stacked structures were taken for computing interaction energies of chromophore and base pair. Initially the optimum vertical separation (rise) of all stacked structures was obtained from the minimum stacking interaction energies.

As in all minimization procedures used, there is no way to be sure that all the local minima are completely identified. So the orientation of drug is changed by small degrees along the plane of the base pair without changing the optimum rise. The stacked models of acridine-2, acridine-3 and acridine-4-carboxamides and base pair are constructed, and the corresponding interaction energies are obtained. The optimum stacked models were taken for computing interaction energies at MP2/6-31G level; herein the stacked portion of molecules is only taken. Both DFT/6-31G and \textit{ab initio} (HF/6-31G**) methods were used to analyse the fundamental differences between the electrostatic energies computed with DFT method and those of \textit{ab initio} method. As it is known that the DFT method calculates the electrostatic interaction energies obtained from the \textit{ab initio} charge densities of base pair and drug molecule, but the electrostatic interaction energies due to intermolecular electron correlation (dispersion term) are not included. On the other hand in HF/6-31G** total interaction energies cannot well estimate the electrostatic interaction energies due to dispersion, that is the prerequisite factor in stabilization of stacked structures. So interaction energies using MP2/6-31G route for each stacked structure in their optimum rise and twist angles have been computed. It is beyond the computational facility available to use higher basis sets in the calculation for such large stacked models (~72 atoms). In fact, only the
chromophore and portion of the stacked base pair for computing interaction energies at MP2/6-31G level have been taken. The interaction energies obtained from these methods are compared. All the calculations were carried out in Pentium IV machines by using Gaussian programme code\textsuperscript{31}, and a program has been developed, JoinMolecule\textsuperscript{32} for constructing the stacked models of acridine-2, acridine-3 and acridine-4 carboxamides with sequences of DNA.

In addition to this interaction energies of stacked small aromatic molecules such as benzene-benzene and benzene-pyridine for checking the level of theories used in large molecular system have been computed. For both these systems the interaction
Table I — Computed interaction energies (DFT and HF) at optimum stacked structures of drug and base-pair with the methyl groups on the other side of the carboxamide side chain.

<table>
<thead>
<tr>
<th>Models</th>
<th>Rise (Å)</th>
<th>DFT (6-31G/B3LYP)</th>
<th>HF/6-31G**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Twist angles (degree)</td>
<td>Interaction energies (kcal/mol)</td>
</tr>
<tr>
<td>AT-S1</td>
<td>3.6</td>
<td>140</td>
<td>-5.4656</td>
</tr>
<tr>
<td>AT-S2</td>
<td>3.6</td>
<td>120</td>
<td>-5.4724</td>
</tr>
<tr>
<td>AT-S3</td>
<td>3.6</td>
<td>90</td>
<td>-3.0111</td>
</tr>
<tr>
<td>GC-S1</td>
<td>3.6</td>
<td>110</td>
<td>-6.6571</td>
</tr>
<tr>
<td>GC-S2</td>
<td>3.6</td>
<td>140</td>
<td>-7.0344</td>
</tr>
<tr>
<td>GC-S3</td>
<td>3.6</td>
<td>70</td>
<td>-3.8835</td>
</tr>
</tbody>
</table>

Figure 11 — Optimum AT-S3 stacked structure with methyl groups of base pair opposite to the carboxamide side chain.

E\text{int} = E_S - (E_D + E_B)

Where \( E_{int} \), \( E_S \), \( E_D \) and \( E_B \) are the interaction energies, energies of stacked models, drugs and base pairs respectively.

Hence, the applicability of HF/6-31G** route for studying the stacking of chromophore with base pairs by considering the results of benzene-benzene and benzene-pyridine stacked models is checked. **Figures 13-16** shows the trend in the variation of stacking energies of benzene-benzene and benzene-pyridine systems obtained from these two levels of theories, where the optimum stacked structures from these two routes are located at the same configurations. The orientations of benzene-benzene and benzene-pyridine by small degree (1°) have been
Results and Discussion

The interaction energies for various stacked structures of acridine-2, acridine-3 and acridine-4-carboxamides with AT base pair are shown (Tables III and IV). Initially the optimum vertical separation (R) between acridine chromophore and base pair are optimised by changing the vertical separation, and the minimum interaction energy in plot of rise (R) versus interaction energies correspond to optimum rise (Figure 17). In all stacked models the optimum rise is found to be at 3.6Å, and also both HF/6-31G** and DFT calculations are used in each calculation (Tables III and IV). It is found that the interaction energies obtained from DFT calculation gives negative values whereas those of HF/6-31G** calculations are positive, and this might be attributed because of the inclusion of some intramolecular electron correlations in DFT method. The constructed stacked structures are sensitive to the steric repulsion from the methyl groups representing sugars. In order to avoid such steric factor, initially the carboxamide side chain is placed at the least steric configuration so that the low energy barrier in stacking should not be affected. Hence the optimum stacking distances (rise) of base pairs and chromophores are obtained at 90°-twist angle. Again the unwinding angles of the base pair after stacking with chromophores are also

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Table II — Minimum interaction energies (HF/6-31G** and MP2/6-31G**) for benzene-benzene and benzene-pyridine stacking

<table>
<thead>
<tr>
<th>Stacked systems</th>
<th>Twist angles (degree)</th>
<th>Interaction energies (HF/6-31G**) (kcal/mol)</th>
<th>Twist angles (degree)</th>
<th>Interaction energies (MP2/6-31G**) (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzene-Benzene</td>
<td>150</td>
<td>5.0893</td>
<td>150</td>
<td>-2.2052</td>
</tr>
<tr>
<td>Benzene-Pyridine</td>
<td>174</td>
<td>3.9179</td>
<td>174</td>
<td>-2.9142</td>
</tr>
</tbody>
</table>
calculated for all optimum drug-AT complexes. In this case, the twist angles (\(\phi\)) of optimum stacked structures of base pair are taken, and the difference between the twist angles of drug-base pair and base pair-base pair combinations gives the unwinding angles (Table IV).

The variation of stacking energies at different rises between AT base pair and acridine-2 (S1), acridine-3 (S2) and acridine-4-carboxamides (S3) are respectively shown in Figure 17. The acridine-2-carboxamide (S1) stacks favorably with AT base pair at the optimum rise of 3.6 Å and 90° twist angle (the least steric orientation of drug from methyl groups). Keeping the stacking distance 3.6 Å, the chromophore is orientated by changing the twist angles in the stacked model to cover most of the favorable structures, and the interaction energies at different twist angles of stacked models are computed. The variation of interaction energies with the change in twist angles is shown in Figure 18. The minimum interaction energies in the plots are taken for comparing the AT specific stacking of acridine-2, acridine-3 and acridine-4-carboxamides. Again studies have been carried out at different levels of theories for comparing the interaction energies (Tables III and IV). The interaction energies of S1, S2 and S3 with AT obtained by using MP2/6-31G level of theory range from -9.2641 kcal/mol to
Table III — Computed interaction energies (DFT and MP2) at the optimum rise and twist angles with the methyl groups on the same side of the carboxamide side chain

<table>
<thead>
<tr>
<th>Stacked Models</th>
<th>Rises (Å)</th>
<th>Twist angles ($\theta_1$)</th>
<th>DFT (6-31G/B3LYP)</th>
<th>Unwinding angles* (degree)</th>
<th>MP2/6-31G (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AT-S1</td>
<td>3.6</td>
<td>77</td>
<td>-7.1462</td>
<td>28</td>
<td>-12.5149</td>
</tr>
<tr>
<td>AT-S2</td>
<td>3.6</td>
<td>70</td>
<td>-5.7544</td>
<td>35</td>
<td>-11.0561</td>
</tr>
<tr>
<td>AT-S3</td>
<td>3.6</td>
<td>50</td>
<td>-3.7592</td>
<td>55</td>
<td>-9.2641</td>
</tr>
<tr>
<td>GC-S1</td>
<td>3.6</td>
<td>100</td>
<td>-7.0218</td>
<td>15</td>
<td>-11.1489</td>
</tr>
<tr>
<td>GC-S2</td>
<td>3.6</td>
<td>130</td>
<td>-8.6291</td>
<td>-15</td>
<td>-13.3259</td>
</tr>
<tr>
<td>GC-S3</td>
<td>3.6</td>
<td>51</td>
<td>-8.8516</td>
<td>64</td>
<td>-13.5051</td>
</tr>
</tbody>
</table>

Table IV — Computed interaction energies (HF/6-31G**) in the optimum rise and twist angles with the methyl groups on the same side of the carboxamide side chain

<table>
<thead>
<tr>
<th>Stacked Models</th>
<th>Rises (Å)</th>
<th>Twist angles ($\theta_1$)</th>
<th>HF (6-31G**)</th>
<th>Unwinding angles* (degree)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AT-S1</td>
<td>3.6</td>
<td>77</td>
<td>9.5526</td>
<td>28</td>
</tr>
<tr>
<td>AT-S2</td>
<td>3.6</td>
<td>102</td>
<td>11.8263</td>
<td>3</td>
</tr>
<tr>
<td>AT-S3</td>
<td>3.6</td>
<td>50</td>
<td>14.2285</td>
<td>55</td>
</tr>
<tr>
<td>GC-S1</td>
<td>3.6</td>
<td>98</td>
<td>9.9166</td>
<td>17</td>
</tr>
<tr>
<td>GC-S2</td>
<td>3.6</td>
<td>124</td>
<td>7.4772</td>
<td>-9</td>
</tr>
<tr>
<td>GC-S3</td>
<td>3.6</td>
<td>53</td>
<td>3.9858</td>
<td>62</td>
</tr>
</tbody>
</table>

S1: 9-aminoacridine-2-carboxamide, S2: 9-aminoacridine-3-carboxamide
S3: 9-aminoacridine-4-carboxamide

*Unwinding angle=Optimum twist angle for stacked base pairs (i.e. AT-AT, GC-GC)-$\theta_1$
Optimum twist angle (both for 6-31G/B3LYP and HF/6-31G**) for AT-AT= 105˚
Optimum twist angle (both for 6-31G/B3LYP and HF/6-31G**) for GC-GC= 115˚

Figure 17 — Plot of rise versus interaction energies (6-31G/B3LYP) values for drug-AT and drug-GC structures
Similarly the calculation of the stacking energies of acridine-2, acridine-3 and acridine-4-carboxamides with GC base pair are carried out. The optimum stacking distance is shown in the plot of stacking energies versus rises where favorable stacking occurs at 3.6 Å (Figure 17). Subsequently the interaction energies are calculated at various levels of theories for identifying the component of energies contributed to the stabilization of stacked structures (Tables III and IV). As it is observed in Table III and IV, acridine-1-carboxamide (S1) is more AT specific than other acridine carboxamides whereas acridine-4-carboxamide acquires maximum specificity for GC base pair. Hence acridine chromophore may intercalate between AT or GC sequences depending on the electronic property of chromophore due to side chin position. The stacked structures at optimum twist angles and 3.6 Å rise are located from the minimum interaction energies in the plot shown in Figure 18 where the stacking of these drugs with GC base pair are found to be more favorable for acridine-3 and acridine-4-carboxamides and the stacking energies (MP2/6-31G) range from -11.149 kcal/mol to -13.505 kcal/mol.

In this work the optimum twist angles (φ) and optimum rises of drugs stacked with AT and GC sequences by using both HF/6-31G** and 6-31G/DFT methods are required. Then the stacking structures from the minimum energies in the plots are compared (Tables I and II). Here the plots obtained from DFT method are shown because HF/6-31G** route gives positive values of interaction energies in spite of showing minimum energy at optimum rise. The discrepancy of DFT method for studying stacking energies is already known but some intramolecular electron correlations included in this method appears to be useful. Also the applicability of DFT method for medium sized biological molecules, which cannot be handled by accurate ab initio calculations with more electron correlation, has been demonstrated. Moreover in earlier studies, DFT method has been used for qualitative interpretation of sequence specificity of DNA sequences. Likewise the optimum stacked structures of drugs with base pairs by using DFT and HF/6-31G** methods has been explored. The stacked portions in the optimum structures are taken for calculating interaction energies at MP2/6-31G level of theory. The correlation between interaction energies and optimum twist angles obtained from DFT and HF/6-31G** are shown in Figures 19 and 20.

From the studies of various stacked structures of acridine-2, acridine-3 and acridine-4-carboxamides and base pairs, it appears that the position of carboxamide side chain affect the stacking of drug with base pairs. It is distinctly indicated that in the stacked model of GC and acridine-3-carboxamide (S2), the acridine-3 chromophore is twisted to an
The twist angle of 130°, whereas in other stacked acridine-2 (S1) and acridine-4-carboxamides (S3) with GC and AT base pairs the twist angles are less (Tables III and IV). It is known that acridine-4-carboxamide is the most potent drug among these carboxamides, and also it has been reported that DNA binding ability of acridine-4-carboxamide is relatively more than acridine-2 and acridine-3-carboxamides. On the other hand the present study indicates better stacking by the chromophore of acridine-4-carboxamide with GC base pair than those of other carboxamides (Tables III and IV). Generally the stabilization of these molecules is known from the stacking of aromatic rings occurred in the system. Thus the chromophore is oriented to all possible positions so that the stacking abilities of different regions, aromatic rings and groups should be covered in the analysis. However in the optimum structures, the stacking of heavy atoms of base pair and chromophore appears to stabilize the stacked models (Figures 5-10).

Again the structural disposition of the carboxamide side chain with respect to chromophore in the stacked structures is explored so that any steric bulk of side chain leading to hindrance during intercalation may be analyzed. As it is observed that the configuration of side chain appears to be different in all the optimised geometries of drugs (S1, S2 and S3). Unlike acridine-2-carboxamide (S1), the carboxamide side chain in acridine-4-carboxamide projects more towards the plane perpendicular to the chromophore (Figures 2-4). In this case, the optimum stacked structure may be taken as a model for intercalation with carboxamide side chain in the opposite side of sugar. Alternatively, the carboxamide side chain can be put on the same side of sugar. There has been lots of confusion in the binding of side chains within minor and major grooves. So, the entry of chromophore is checked from the same side or opposite side of sugar. Tables III and IV indicate the stacking energies of these drugs with carboxamide on the same side of methyl groups. But, these drugs intercalate preferably from the opposite side of sugar.

There are abundant crystallography studies of intercalated molecules and some theoretical studies are also available. As a rule, the structures obtained from theoretical studies are in good agreement with crystal structures. In this study it should be noted that the most potent acridine-4-carboxamide acquires high stacking energy, whereas relatively less potent drugs, acridine-2-carboxamide (S1) interacts with AT base pair better than GC and also the computed stacking energies obtained from MP2/6-31G level of theory demonstrates more interaction energy for acridine-4-carboxamide than acridine-2 and acridine-3-carboxamides with GC base pairs. Hence the binding mode of relatively potent drug acridine-4-carboxamide might be different from acridine-2 and acridine-3-carboxamide.

A novel approach adopted for studying the intercalation model of acridine carboxamides appears to be suitable for qualitative interpretation of molecular stacking at 3.6Å. However the approach is inadequate for quantitative interpretation of stacking energies of drug-base pair. Earlier it is noted that both HF/6-31G** and B3LYP methods are applicable in determining optimum stacked structures of various base pairs where the use of MP2 calculation with large basis set is not possible. So, these observations are interesting even though the stacking energies obtained from these methods are very different. The
calculations are extended with 6-31G/MP2 routes to cover some description of electrostatic energies from the intermolecular electron correlation (dispersion energy), (Table III). In general highly accurate interaction energy of super molecules is computed with large basis set and electron correlation. It has been known that the basis set inconsistency in the calculations lead to BSSE in evaluating interaction energies. However at the correlated level (MP2) the full counterpoise method such basis set error is taken into account to some extent in most cases, but sometimes overestimates BSSE\textsuperscript{14-19}. Therefore the MP2 interaction energies for evaluating stacking energies of chromophores and sequences at their optimum stacked structures are used. Intra-system correlation is the correction to the columbic and exchange part of the energies whereas the inter-system correlation is the dispersion energy. In this case some of the inter-system and intra-system electron correlations and coupling between these correlation terms computed in MP2 method might be useful for demonstrating sequence preference binding of chromophores with base pairs.

In the present calculation the optimum twist angle in the intercalation model of acridine-2, acridine-3 and acridine-4-carboxamides is determined over these sequences. Among the carboxamides, acridine-4-carboxamide is comparatively more potent than acridine-2 and acridine-3-carboxamides, but the stacking ability of acridine-4-carboxamide with GC is not much different than that of acridine-3-carboxamide. So there is no overlapping between the intercalative ability and the experimentally observed biological property like potency. All these drugs in fact produce different helix unwinding angles. The unwinding angles after stacking with sequences are computed, and the values are shown in Table III. Alternatively, the biological potency may be due to additional stabilization due to hydrogen bond between ring nitrogen and carboxamide oxygen other than intercalation by the equally accessible portion of chromophore of acridine-2, acridine-3 and acridine-4-carboxamides. In acridine-2 and acridine-3-carboxamides, since the side chain bending with respect to the chromophore is less and the contribution of side chain binding during chromophore intercalation may not be possible. In this case DNA binding may be suitable either by chromophore or by side chain binding. It has not been explored which group initiates DNA binding, either by chromophore intercalation or by side chain binding. These observations imply that both intercalation and side chain binding might occur simultaneously in acridine-4-carboxamide in the process of DNA binding. But the exact feature of having more potency in acridine-4-carboxamide might not be from the intercalating ability since GC specificity of this drug is not much different from that of acridine-3-carboxamide. Again the absolute requirement of suitably placed side chain in the drugs in DNA binding has been emphasized by Denny, and positioning of carboxamide side chain at 4-position in designing new carboxamides with enhanced potency is must\textsuperscript{13}. In this case the capability of DNA binding by side chain as well as chromophore might be important in determining potency of acridine-4-carboxamide. The stacked models of drugs with base pairs demonstrate certain description of sequence preference of various acridine carboxamides during intercalation.

**Conclusion**

The results obtained from the simple models of stacked chromophore of acridine-2, acridine-3 and acridine-4-carboxamides with sequence of DNA are useful for understanding the sequence specific intercalation. The interaction energies of the optimum stacked models obtained from \textit{ab initio}, DFT and MP2 methods distinctly show GC sequence specificity by the chromophores of acridine-3 and acridine-4-carboxamides. Among these carboxamides the most potent drug, acridine-4-carboxamide stacks favorably with GC but less potent acridine-3-carboxamide also stacks quite efficiently with GC. Again the results obtained from MP2/6-31G distinctly indicate GC specificity of acridine-3 and acridine-4 chromophores, and these findings agree with the intercalation of acridine-4-carboxamide with GC rich region of DNA.

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**References**


