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Interactions of anticancer drugs with usual and mismatch base pairs — Density functional theory studies

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ABSTRACT

The antitumor activity of a drug is associated with its molecular properties as well as its interactions with target molecules. The molecular structures of usual, mismatch base pairs and their drug (Hydroxyurea and 5-Fluorouracil) interacting complexes were studied using density functional theory methods. The two and three-body interaction energies have been used to analyze the influence of a drug on the stability of base pairs. The sharing of electron density between the interacting molecules is shown through electron density difference maps. The Atoms in Molecules theory and Natural Bond Orbital analysis have been performed to study the hydrogen bonds in the drug interacting complexes.

1. Introduction

Anticancer studies led to the discovery of the antitumor properties of some compounds and are found to be in the focus for many scientists [1]. Since then, substantial amount of work has been done to design and synthesize new drugs and to investigate their structure–activity relationships [2]. Further, in cancer chemotherapy, protocols with sub-optimal doses of drugs are frequently used, minimizing toxicity and patient suffering, but possibly resulting in an incomplete therapy with unsatisfactory prognosis (residual disease, tumor regrowth, drug resistance). Therefore, to improve the specificity of cancer therapy, drugs with tumor-targeting properties are essential and in clinical trials [3–5]. The antitumor activity of a drug is related to its molecular properties as well as to its interactions with different targets in cells [2].

Hydroxyurea (HU), a clinically established inhibitor of DNA plays an important role in the treatment for sickle cell disease and cancer chemotherapy [6–9]. It inhibits ribonucleotide diphosphate reductase, the enzyme that converts ribonucleotides into deoxyribonucleotides, which is essential for the DNA synthesis and repair [10]. Further, 5-fluorouracil (5FU) has been used over several decades in the treatment of various solid tumours namely colorectal cancer, colon cancer, rectal cancer, pancreatic cancer and metastatic oesophageal cancer [11–14]. It interferes with DNA synthesis by blocking the production of the pyrimidine nucleotide through inhibition of thymidylate synthase, as well as through incorporation of fluoro-nucleotides into DNA and RNA [11]. Besides their preclinical development, hydroxyurea and 5-fluorouracil are synergistic and they have been submitted to different phases of clinical trials and are introduced in clinical cancer chemotherapy [15–19]. These drugs would help in inhibiting DNA replication, and could induce cell death.

Mutations are believed to be an initial source of evolution as they change the content of the genetic blue-print in the DNA [20]. In the genome, during replication, base pair mismatches occur naturally as a result of either polymerase errors or by DNA damage due to ultraviolet radiation, ionizing radiation, and numerous genotoxic chemicals [21]. In most cases, the cell corrects these errors using a complex repair system. Failure of this repair mechanism can lead to serious consequences, as in the human hereditary diseases such as xeroderma pigmentosum, hereditary nonpolyposis colon cancer, and some forms of breast cancer [22]. The DNA is the primary intracellular target for antitumor drugs, because, the interaction of drug molecules with DNA can cause DNA damage in cancer cells, blocking the division of cancer cells and resulting in cell death [23]. The detection and targeting of single base pair mismatch in DNA will provide an avenue for the rational development of new diagnostics and chemotherapeutics [24]. Despite the efforts made to understand the mechanism of the action of 5-fluorouracil and hydroxyurea [15–19], as well as in the design of new anticancer drugs, a detailed structural and drug-DNA base pair interaction is still lacking. Hence, a theoretical study on drug binding with a single usual and mismatch base pairs is very important to understand the activity of drug molecules in DNA.

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Jiande Gue et al. [25a] have interacted platinum with base pair and Sponer et al. [25b] have interacted metal ions with unusual base pairs, and they have studied the influence of the metals on the neighbouring hydrogen bonds in the usual and mismatch base pairs. In the present investigation an attempt has been made to disrupt the Watson–Crick model and non-Watson–Crick hydrogen bonding model by interacting hydroxyurea and 5-fluorouracil drugs and to study the influence of these drugs on those base pairs. These drugs would preferentially target single usual base pairs GC, AT and mismatch base pairs AA, TT, GG, and CC which have already been confirmed by the NMR studies [26]. These mismatch base pairs occur both in DNA and RNA, but the present study is focused to inhibit DNA replication by the interaction of drugs sequentially to prevent redundant cell growth responsible for cancer cells. Further, the selection of the mismatch base pairs was based on their stability and interactions of purine–purine, pyrimidine–pyrimidine molecules. The clinically established drugs such as hydroxyurea and 5-fluorouracil were preferred based on their low toxicity.

The present study has been initiated to understand in detail the geometries of base pairs and drug interacting complexes. Specifically, the stability of the base pairs and the influence of drugs (HU and 5FU) on hydrogen bonding between nucleobases have been studied based on the interaction energy, many body analyses and the electron density analysis. The nature of hydrogen bonds formed between the drug and base pairs has also been analyzed through Atoms in Molecules (AIM) theory and Natural Bond Orbital (NBO) method which have proved to be an invaluable tool to characterize the hydrogen bond by a scheme through partitioning the molecular space into domains.

2. Computation details

The molecular structure of base pairs, mismatch base pairs and their respective drug interacting complexes have been optimized using Becke's three parameter exact exchange functional together with the gradient corrected correlation functional of Lee, Yang and Parr represented as B3LYP [27] of density functional theory (DFT) by employing the 6–31+G* basis set. Vibrational frequency analysis has been performed to confirm the minimum energy structure. The interaction energies for the optimized base pairs and drug interacting complexes have been corrected for the basis set superposition error (BSSE), through the counterpoise method of Boys and Bernardi [28]. The many body analysis [29] were performed for these drug interacting complexes, by partitioning the interaction energy into two and three body interactions,

$$\Delta E_{\mathrm{TOTAL}} = E_{(ABC)} - \left[E_{(A)} + E_{(B)} + E_{(C)}\right]$$
$$\Delta^3 E(ABC) = \Delta E_{\mathrm{TOTAL}} - \left[\Delta^2 E(AB) + \Delta^2 E(AC) + \Delta^2 E(BC)\right]$$
$$\Delta^2 E(AB) = E_{AB} - \left[E_{(A)} + E_{(B)}\right]$$

where $E_{(ABC)}$ is the total energy of drug interacting base pairs and E_A, E_B, E_C are the total energy of single base pair or drug and E_{AB} is the total energy of any two interacting molecules (base pairs or base pair with a drug). Note that, while calculating many body interaction energies, the BSSE was corrected. Wave function files were generated from the Gaussian output files at the B3LYP/6–31+G* level of theory to perform AIM calculations, and it was carried out using MORPHY 98 software [30]. The NBO analysis has also been carried out for the drug (HU and 5FU) interacting complexes using the same level of theory employing

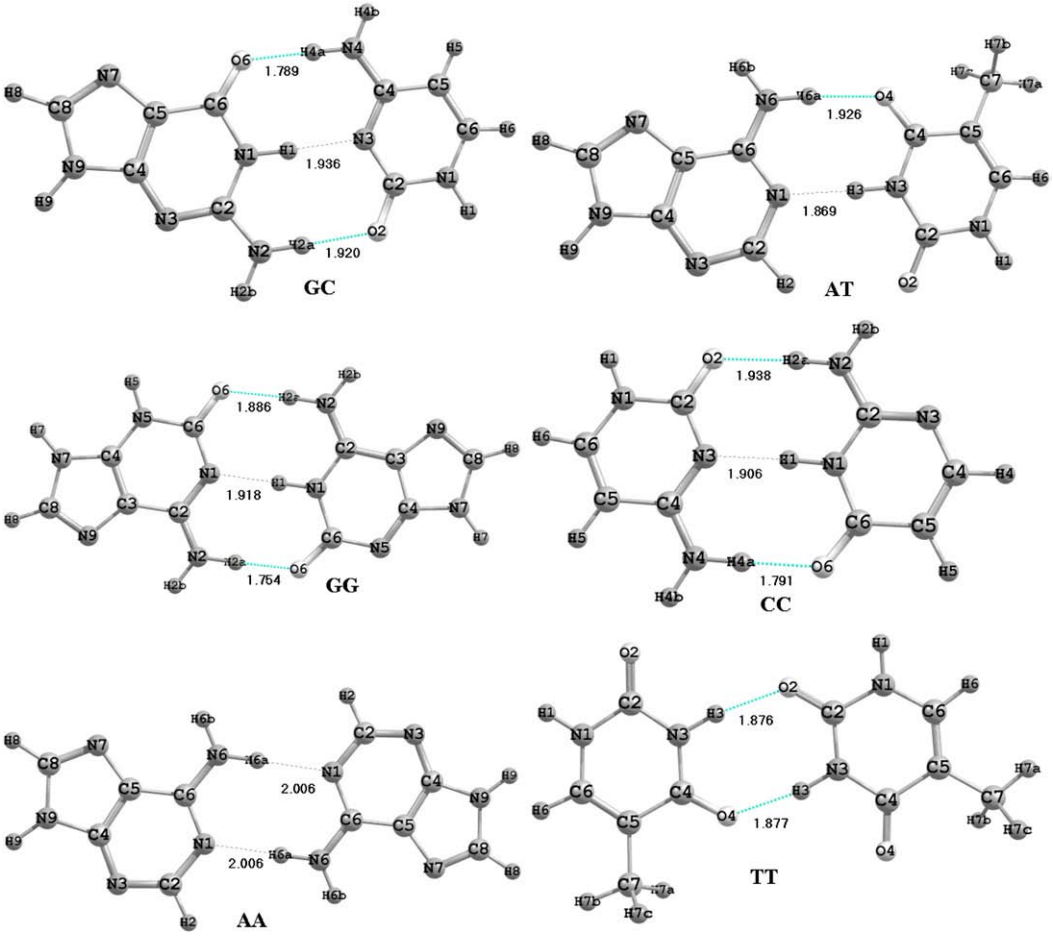

Fig. 1. Optimized structures of usual and mismatch base pairs at B3LYP/6–31+G* level of theory.

the NBO 3.1 Program [31]. It is used to derive information on the changes of electron densities in proton donor and acceptor as well as in the bonding and antibonding orbitals. For each donor NBO (i) and acceptor NBO (j), the stabilization energy $E^{(2)}$ associated with $i \rightarrow j$ delocalization is given by

$$E^{(2)} = \Delta E_{ij} = q_i \frac{F^2(i,j)}{\varepsilon_i - \varepsilon_j}$$

where q_i is the ith donor orbital occupancy, ε_i and ε_j, are the diagonal elements and $F(i,j)$ are the off-diagonal elements associated with the NBO Fock matrix. All the calculations were performed using the Gaussian 03W program [32].

3. Results and discussion

Two usual base pairs GC, AT and mismatch base pairs GG, CC, AA, TT and their respective drug interacting complexes have been optimized using the B3LYP method of density functional theory with the 6–31+G* basis set and the structures are shown in Figs. 1–3. The drugs, hydroxyurea (HU) and 5-fluorouracil (5FU) bind strongly with the usual and mismatch base pairs through the hydrogen bond interaction. Strong hydrogen bonds are formed between the drug and the base pairs and the hydrogen bond lengths are found to be within 2.1 Å. The optimized geometries of all the usual and mismatch base pairs are almost planar, whereas the geometries of drug interacting complexes deviate from planarity. The intrinsic non planarity and large flexibility of base pairs can influence DNA structure and its function [33]. The possible strand breaks caused due to interaction of drug molecules with the usual and mismatch base pairs will affect cell viability and the cell growth inhibition as suggested for camptothecin [34]. The binding of drug molecules will lead to a conformational change in DNA around the amine and amide group of the base pairs. The bond length of base pairs changes by 0.01 Å and bond angles by 1 to 3° upon the interaction with drug molecules. The distortions around the amine and amide bonds may reduce the π-electron conjugation and destabilize the DNA base pairs [35–37].

The total interaction energy and many body interaction energies have been calculated for the isolated base pairs and drug interacting complexes, after eliminating basis set superposition error (BSSE), and are summarized in the Table 1. The calculated interaction energy for the isolated base pairs is found to be comparable with the reported values [33]. In the case of isolated (without drug) usual base pairs and mismatch base pairs GG have the largest interaction energy (ΔE_{iso}) of −30.08 kcal/mol and TT with the smallest interaction energy of −9.39 kcal/mol. The largest and smallest interaction energies calculated for the GG and TT base pairs reflect the presence of three and two strongest hydrogen bonds in these base pairs. For the isolated base pairs

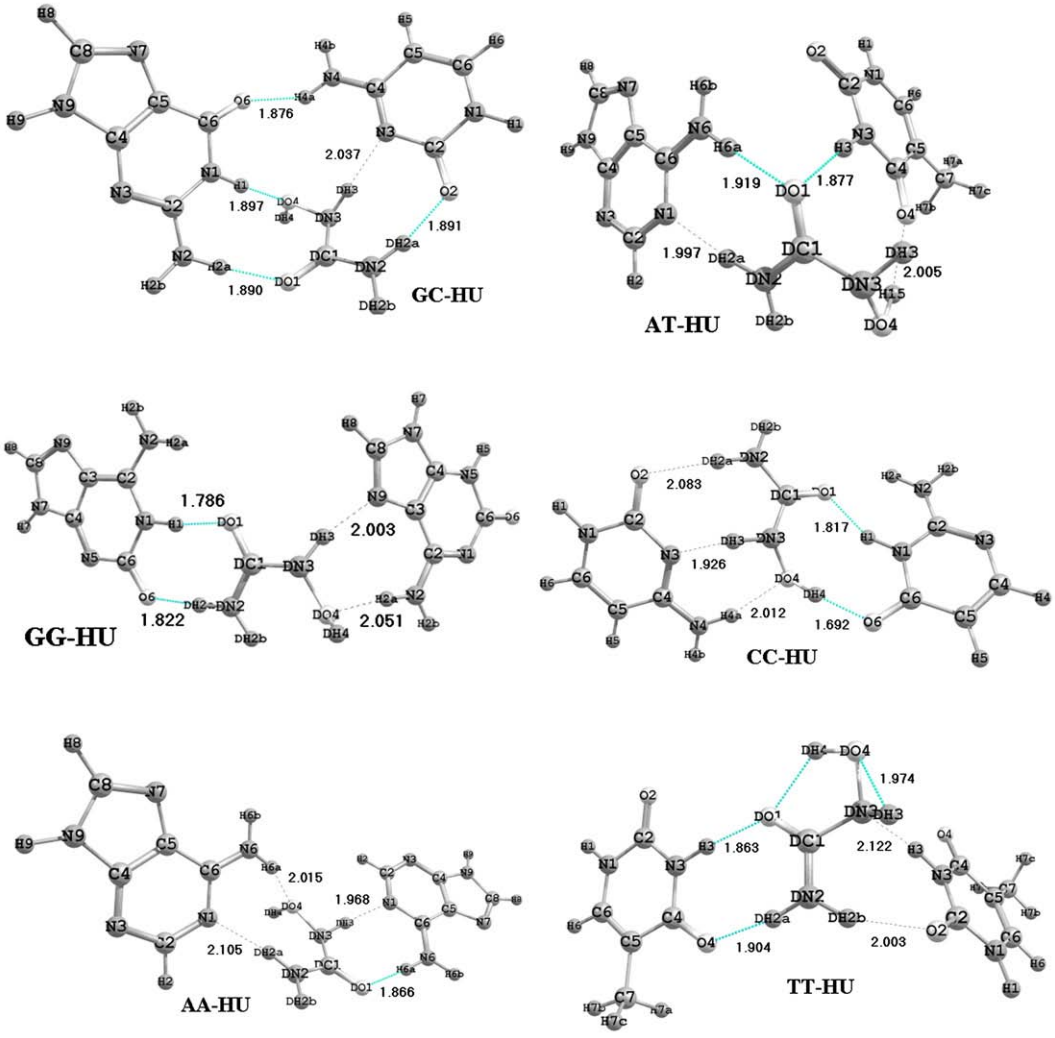

Fig. 2. Optimized structures of Hydroxyurea (HU) interacting complexes at B3LYP/6–31+G* level of theory. (IUPAC number has been followed for labeling of atoms and for drug molecules 'D' has been added along with the atom number).

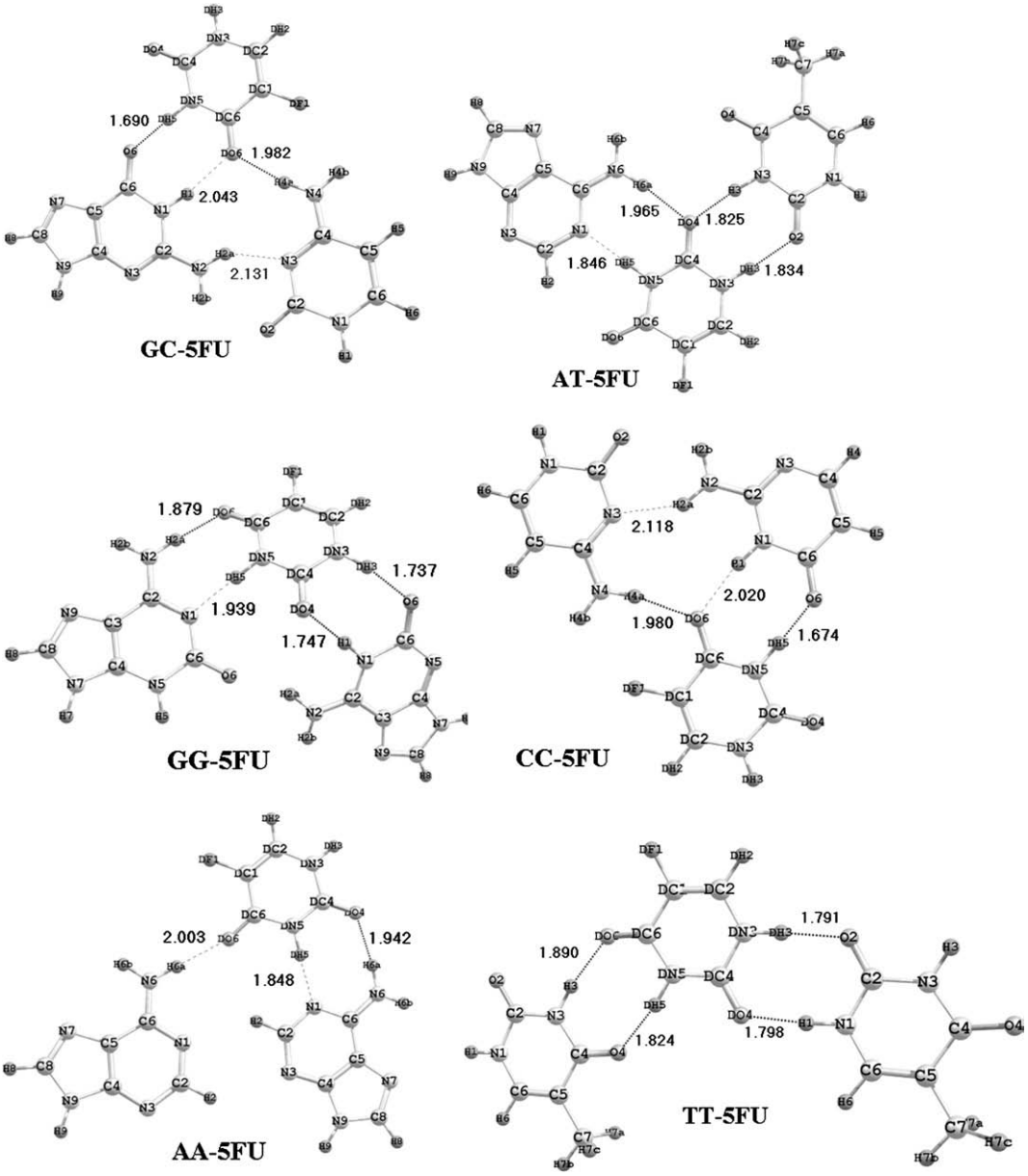

Fig. 3. Optimized structures of 5-Fluorouracil (5FU) interacting complexes at B3LYP/6–31+G* level of theory. (IUPAC number has been followed for labeling of atoms and for drug molecules 'D' has been added along with the atom number).

the interaction energy order is as follows GG>CC>GC>AT>AA>TT. It is observed that the two body interaction energy calculated for the isolated base pairs (ΔE_{iso}) is found to be higher than that of the isolated same base pair in drug interacting complexes (see Table 1), which shows that the interaction between the base pairs is decreased due to the influence of the drug molecules.

Among the HU interacting complexes, CC–HU mismatch base pair is found to have the largest interaction energy of −43.82 kcal/mol, whereas the complex formed between TT and HU is observed with the smallest interaction energy of −17.8 kcal/mol and the interaction energy order is CC–HU>GC–HU>GG–HU>AT–HU>AA–HU>TT–HU. The two body interaction energy (Δ^2E) corresponding to Cytosine base and HU (C1–HU, C2–HU) interaction in CC–HU and Guanine–HU (G–HU), Cytosine–HU (C–HU) interactions in GC–HU are found to be maximum compared with any other two body interactions, which is the reason for maximum stability of CC–HU and GC–HU. Notably, it is observed that in the case of TT–HU and GG–HU the interaction energy between the two bases in the absence of drug is found to be positive and the total many body interaction energy (Δ^3E) is also positive. This indicates the absence of interaction between the bases, suggests that the complexes are less stable. In the case of complexes AT–HU, AA–HU, GG–HU and TT–HU the interaction energy between the drug and their respective bases are found to be very minimum, and in case of AT–HU the total many body interaction energy (Δ^3E) is zero.

In the case of 5FU interacting complexes the total interaction energy for GG–5FU complex is found to be high (−41.19 kcal/mol) and next stable complex is CC–5FU with interaction energy of −32.73 kcal/mol. The stability order is GG–5FU>CC–5FU>GC–5FU>TT–5FU>AT–5FU>AA–5FU. The least stable 5FU interacting complex is AA–5FU with interaction energy of −18.38 kcal/mol. It is observed that the two body interaction energy in 5FU interacting guanine base (G1–5FU, G2–5FU) in GG–5FU and cytosine base (C1–5FU, C2–5FU) in CC–5FU is found to be maximum which leads to the highest interaction energy for GG–5FU and CC–5FU. Whereas in the case of AT–5FU, GC–5FU, AA–5FU and TT–5FU the two body interaction energy is minimum, indicating less stability. It is observed that the many body interaction

Table 1
Interaction energies (in kcal/mol) of hydroxyurea (HU), 5-fluorouracil (5FU) interacting complexes and their respective base pairs

Base pair	Interaction energies	Base pair	Interaction energies	Base pair	Interaction energies	Base pair	Interaction energies
GC–HU		**CC–HU**		**GC–5FU**		**CC–5FU**	
Δ^2E_{iso}	−27.92	Δ^2E_{iso}	−28.06	Δ^2E_{iso}	−27.92	Δ^2E_{iso}	−28.06
ΔE_{Tot}	−40.37	ΔE_{Tot}	−43.82	ΔE_{Tot}	−31.84	ΔE_{Tot}	−32.73
$\Delta^2E^{com}_{(G+HU)}$	−23.06	$\Delta^2E^{com}_{(C1+H)}$	−23.06	$\Delta^2E^{com}_{(G+HU)}$	−3.48	$\Delta^2E^{com}_{(C1+HU)}$	−3.55
$\Delta^2E^{com}_{(C+HU)}$	−16.55	$\Delta^2E^{com}_{(C2+H)}$	−16.55	$\Delta^2E^{com}_{(C+HU)}$	−16.45	$\Delta^2E^{com}_{(C2+HU)}$	−17.12
Δ^2E_{GC}	−8.83	Δ^2E_{CC}	−2.07	Δ^2E_{GC}	−9.63	Δ^2E_{CC}	−9.65
Δ^3E	−7.08	Δ^3E	−2.14	Δ^3E	−2.28	Δ^3E	−2.41
AT–HU		**AA–HU**		**AT–5FU**		**AA–5FU**	
Δ^2E_{iso}	−12.86	Δ^2E_{iso}	−11.31	Δ^2E_{iso}	−12.86	Δ^2E_{iso}	−11.31
ΔE_{Tot}	−25.58	ΔE_{Tot}	−19.86	ΔE_{Tot}	−28.26	ΔE_{Tot}	−18.38
$\Delta^2E^{com}_{(A+HU)}$	−12.51	$\Delta^2E^{com}_{(A1+H)}$	−12.19	$\Delta^2E^{com}_{(A+HU)}$	−0.31	$\Delta^2E^{com}_{(A1+HU)}$	−13.3
$\Delta^2E^{com}_{(T+HU)}$	−12.71	$\Delta^2E^{com}_{(A2+H)}$	−7.07	$\Delta^2E^{com}_{(T+HU)}$	−14.26	$\Delta^2E^{com}_{(A2+HU)}$	−3.37
Δ^2E_{AT}	−0.36	Δ^2E_{AA}	−0.32	Δ^2E_{AT}	−13.48	Δ^2E_{AA}	−0.82
Δ^3E	0	Δ^3E	−0.28	Δ^3E	−0.21	Δ^3E	−0.89
GG–HU		**TT–HU**		**GG–5FU**		**TT–5FU**	
Δ^2E_{iso}	−30.08	Δ^2E_{iso}	−9.39	Δ^2E_{iso}	−30.08	Δ^2E_{iso}	−9.39
ΔE_{Tot}	−28.29	ΔE_{Tot}	−17.84	ΔE_{Tot}	−41.19	ΔE_{Tot}	−30.04
$\Delta^2E^{com}_{(G1+HU)}$	−21.13	$\Delta^2E^{com}_{(T1+H)}$	−12.48	$\Delta^2E^{com}_{(G1+HU)}$	−11.22	$\Delta^2E^{com}_{(T1+HU)}$	−18.15
$\Delta^2E^{com}_{(G2+HU)}$	−7.74	$\Delta^2E^{com}_{(T2+H)}$	−9.7	$\Delta^2E^{com}_{(G2+HU)}$	−20.88	$\Delta^2E^{com}_{(T2+HU)}$	−11.25
Δ^2E_{GG}	0.31	Δ^2E_{TT}	0.44	Δ^2E_{GC}	−10.44	Δ^2E_{TT}	−0.76
Δ^3E	0.27	Δ^3E	3.19	Δ^3E	1.35	Δ^3E	0.12

Δ^2E_{iso} is for isolated base pair, $\Delta E\Delta E_{Tot}$ is the total interaction energy of drug interacting complex, $\Delta^2E^{com}_{(G+HU)}$ is the interaction energy of Guanine base with drug and similarly for other cases, Δ^2E_{GG} is the interaction energy between guanine bases in the drug interacting complex and similarly for other cases and Δ^3E is the many body interaction energy.

energy (Δ^3E) in GG–5FU and TT–5FU is positive which shows the strongest two body interaction in these complexes.

From the results, it is observed that the drugs HU and 5FU have bonded well with the usual and mismatch base pairs, but the interaction energy order for these two drug interacting complexes is found to be different. The drug HU interacts strongly with the mismatch base pair CC, whereas the drug 5FU interacts strongly with the mismatch base pair GG. The drug hydroxyurea is a non-cyclic compound with the presence of carbonyl group (C═O), amine group, imine group and oxime group, whereas 5-fluorouracil is a cyclic compound with the presence of alkene, halogen, carbonyl group and imine group. These dissimilarities and different orientation of atoms in drug interacting complexes lead to the different interaction energy order in the drug interacting complexes. Moreover, the stability of the hydrogen bonded complexes depends not only by the number of hydrogen-bonds but also its strength and mutual orientation of molecular dipole moments [33]. The electron density difference maps have been plotted for the strong drug interacting complexes CC–HU and GG–5FU and weak drug interacting complexes TT–HU and AA–5FU and are shown in the Fig. 4. This gives a pictorial representation of the electron density distribution corresponding to the interactions. It has been observed that the concentration of electron density arises between the proton and the proton acceptor with a corresponding electron density deficiency at the vicinity of a proton and the acceptor lone pairs. The maximum amount of electron density is gained by the proton acceptor and minimum amount of electron density is lost by the proton donor in the CC–HU and GG–5FU complexes. But in the case of weak drug interacting complexes comparatively less amount of electron density is gained and lost by their respective proton acceptors and donors.

To obtain further insight into the nature of the hydrogen bond in the drug interacting complexes, we studied the electron density based

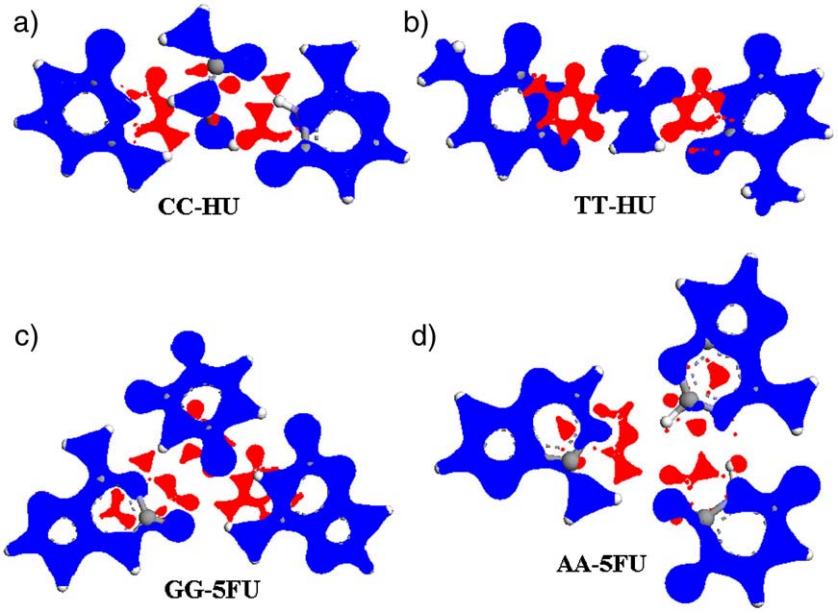

Fig. 4. Electron density difference maps for most interacting complexes a).CC-HU, b)TT–HU and least interacting complexes c)GG-5FU, d) AA-5FU. Here, blue regions represent the gain in electron density as a result of formation of the drug interacting complex relative to non-interacting nucleobases and drug molecule; red regions refer to loss of electron density. The contour shown is 0.2 e/au^3.

Table 2
Electron density ρ (in a.u.) and Laplacian of electron density $\nabla^2\rho$ (in a.u.) and bond ellipticity (ε) corresponds to hydrogen bonds in drug interacting complexes calculated through topological analysis at B3LYP/6–31+G* level of theory

	ρ	$\nabla^2\rho$	ε		ρ	$\nabla^2\rho$	ε
GC–HU				**AT–HU**			
$DH_{2a}...O_2$	0.029	0.094	0.028	$DH_{2a}...N_1$	0.028	0.077	0.059
$DH_3...N_3$	0.025	0.071	0.065	$H_{6a}...DO_1$	0.028	0.088	0.048
$H_{4a}...O_6$	0.028	0.102	0.054	$H_{15}...O_4$	0.021	0.077	0.068
$H_{2a}...DO_1$	0.027	0.094	0.046	$H_3...DO_1$	0.030	0.095	0.055
$H_1...DO_4$	0.028	0.093	0.076	–	–	–	–
GG–HU				**CC–HU**			
H_{2a} ...DO_4	0.020	0.066	0.067	H_1 ...DO_1	0.036	0.113	0.039
$DH_3...N_9$	0.027	0.078	0.047	$DH_4...O_6$	0.047	0.144	0.016
$DH_{2a}...O_6$	0.034	0.108	0.028	$DH_{2a}...O_2$	0.019	0.060	0.042
$H_1...DO_1$	0.038	0.120	0.032	$DH_3...N_3$	0.033	0.095	0.074
–	–	–	–	H_{4a} ...DO_4	0.023	0.070	0.072
–	–	–	–	H_1 ...DO_1	0.013	0.053	0.121
AA–HU				**TT–HU**			
$H_{6a}...DO_1$	0.031	0.099	0.035	$H_3...DN_3$	0.021	0.061	0.039
$DH_3...N_1$	0.030	0.081	0.061	$DH_{2b}...O_2$	0.022	0.075	0.041
$DH_{2a}...N_1$	0.022	0.063	0.058	$H_3...DO_1$	0.030	0.098	0.029
$H_{6a}...DO_4$	0.021	0.072	0.090	$DH_{2a}...O_4$	0.028	0.091	0.195
GC–5FU				**C–C–5FU**			
$H_{2a}...N_3$	0.020	0.062	0.047	H_1 ...DO_6	0.022	0.070	0.024
$H_1...DO_6$	0.021	0.066	0.025	$DH_5...O_6$	0.047	0.153	0.014
$H_{4a}...DO_6$	0.023	0.076	0.033	$H_{4a}...DO_6$	0.023	0.076	0.032
$DH_5...O_6$	0.045	0.148	0.012	$H_{2a}...N_3$	0.020	0.063	0.050
AT–5FU				**A–A–5FU**			
$H_3...DO_4$	0.034	0.109	0.026	$DH_5...N_1$	0.039	0.099	0.053
$DH_3...O_2$	0.033	0.106	0.027	$H_{6a}...DO_4$	0.025	0.084	0.031
$H_{6a}...DO_4$	0.024	0.079	0.037	$H_{6a}...DO_6$	0.019	0.074	0.021
$DH_5...N_1$	0.038	0.101	0.053	–	–	–	–
GG–5FU				**T–T–5FU**			
H_{2a} ...O_6	0.018	0.071	0.026	$DH_5...O_4$	0.033	0.108	0.013
$DH_5...N_1$	0.031	0.085	0.062	$H_3...DO_6$	0.028	0.093	0.015
$H_{2a}...DO_5$	0.030	0.095	0.026	$H_1...DO_4$	0.036	0.116	0.026
$H_1...DO_4$	0.041	0.134	0.036	$DH_3...O_2$	0.037	0.118	0.028
$DH_3...O_6$	0.042	0.131	0.026	–	–	–	–

topological parameters within the framework of Bader's Atoms in Molecule theory [30]. The interactions are studied by considering the values of electron density and its Laplacian at the bond critical points (BCP) of the N–H…O, N–H…N and O–H…O bonds. A BCP point corresponding to zero gradient of electron density is found between each pair of nuclei, which are considered to be linked by a chemical bond with two negative curvatures (λ_1 and λ_2) and one positive curvature (λ_3) denoted as the (3, −1) critical point. The bond ellipticity defined in terms of the two negative curvatures as $\varepsilon=(\lambda_1/\lambda_2-1)$ reflects the deviation of the charge distribution in bond path from axial symmetry, thus providing a sensitive measure of the susceptibility of a system to undergo a structural change. The calculated values of the electron density (ρ), Laplacian of electron density ($\nabla^2\rho$) and bond ellipticity (ε) at the BCP for O–H…O, N–H…O and N–H…N bonds in the drug interacting complexes are summarized in the Table 2. The strong hydrogen bonds are found to be associated with maximum electron density at BCPs and higher stability, which is observed for the complexes CC–HU, GC–HU, GG–5FU and CC–5FU. Thus the electron density values calculated at the BCPs augment the stability order predicted through the interaction energy. Generally, for hydrogen bonded complexes, the electron density (ρ) and Laplacian of electron density ($\nabla^2\rho$) are in the range of 0.0002–0.34 a.u. and 0.016–0.1 3 a.u., respectively. In the present study, the value of ρ and $\nabla^2\rho$ for HU interacting complexes varies from 0.013–0.047 a.u. and 0.060–0.144 a.u., respectively and for 5FU interacting complexes the values of ρ and $\nabla^2\rho$ varies from 0.019–0.047 a.u. and 0.062–0.153 a.u., respectively. So, the above values indicate that the drug interacting complexes are having strong hydrogen bonds.

In few drug interacting complexes, the proton acceptor of drug molecule interacts with the two proton donor of nucleobases i.e. (H_{6a} … DO_1, H_3 …DO_1) in AT–HU and (H_{2a} …DO_1, H_1 …DO_1) in CC–HU, (H_1 … DO_6, H_{4a} …DO_6) in GC–5FU, (H_{6a} …DO_4, H_3 …DO_4) in AT–5FU and (DO_6 …H_1, H_{4a} …DO_6) in CC–5FU, which reflect in the calculated electron density and stabilization energy obtained from NBO analysis. It is observed that the calculated electron density for the cases in which proton acceptor interacts with two proton donor is lower than that of the case, where proton acceptor interacts with single proton donor. Hence, the value of electron density at BCPs can be taken as a measure of the strength of bonding interaction. Further, a correlation has been found between the hydrogen bond distance, electron density and Laplacian of electron density of drug interacting complexes and is shown in Figs. 5 and 6 for CC–HU and GG–5FU. Electron density and Laplacian of the electron density are decreases with increasing hydrogen bond length and a better linear correlation (~0.97) has been found for the drug interacting complexes.

The occupation numbers for the proton donor antibonds, σ^*(X–H) and for the proton acceptor lone pair's, $n(y)$ and the stabilization energy $E^{(2)}$ calculated from NBO method are summarized in Table 3. The charge is transferred between the interacting orbitals and hence the X–H antibond occupation values (X=N, O) and bond length r(X–H) of proton donor are comparably elongated for all the bonds in HU and 5FU interacting complexes. Specifically for the complexes CC–HU and GG–FU the bond length r(X–H) is elongated more when drug molecules interact with the base pairs. The stabilization energy $E^{(2)}$ corresponding to hydrogen bond interactions can be considered as the total charge transfer energy. It is expected that the hydrogen bond length and stabilization energy $E^{(2)}$ are directly proportional but in the case of interactions (N_3- –H_3…DO_6 and N_6–H_{6a}…DO_1) in AT–HU (N_4–H_{4a}…DO_6 and N_1–H_1…DO_6) in GC–5FU, (N_1–H_1…DO_6 and N_4–H_{4a}…

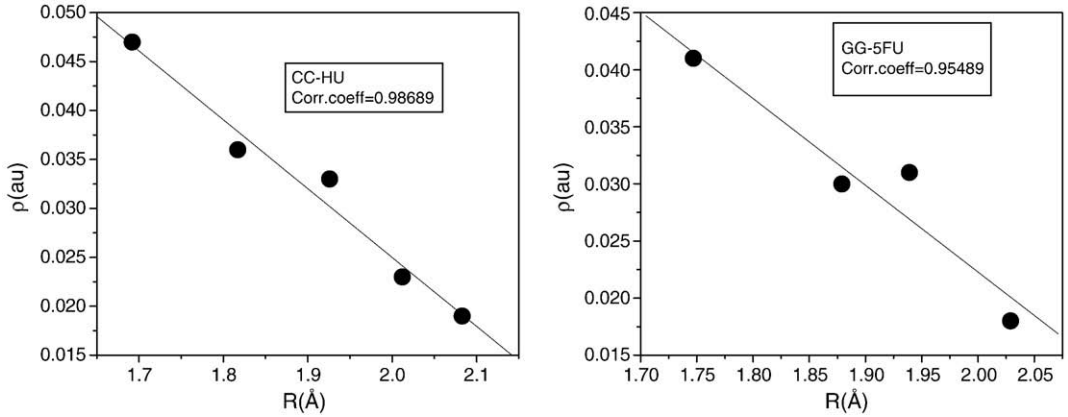

Fig. 5. The correlation between electron density, ρ (in a.u.) and the Hydrogen-bond distance at the bond critical point calculated at B3LYP level of theory for drug interacting complexes: CC–HU and GG–5FU.

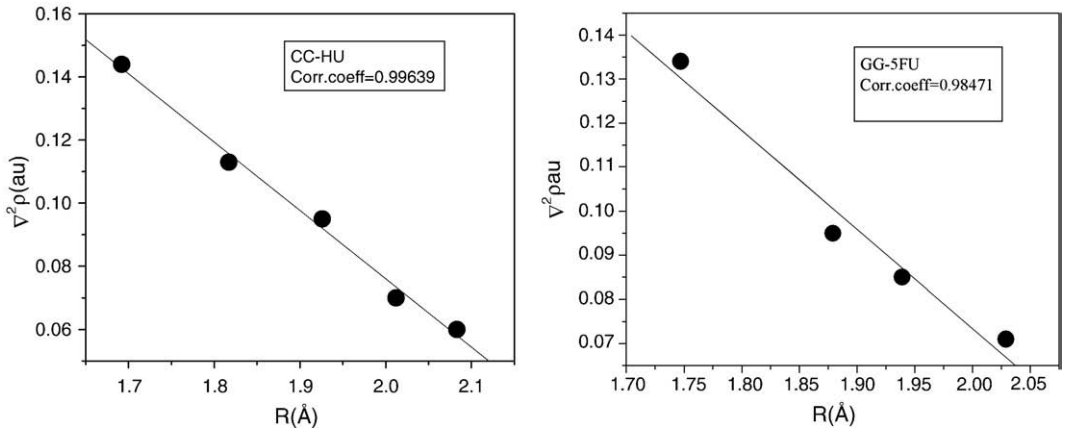

Fig. 6. The correlation between Laplacian of the electron density, $\nabla^2\rho$ (in a.u.) and the Hydrogen–bond distance, R(Å) at the bond critical point calculated at B3LYP level of theory for drug interacting complexes: CC–HU and GG–5FU.

DO_6) in CC–5FU the hydrogen bond length is smaller in comparison with the other hydrogen bonds as shown in the Figs. 2 and 3 and Table 2, but the stabilization energy is relatively small. As explained earlier, this can be attributed to the multiple hydrogen bonds formed by oxygen atom of drug molecules. It is observed that the most drug interacting complexes do not have multiple hydrogen bonds and their second order stabilization energies are found to be high.

4. Conclusion

We have investigated the usual, mismatch base pairs and their hydroxyurea (HU) and 5-fluorouracil (5FU) interacting complexes using density functional theory methods. It is observed that the drugs HU and 5FU binds strongly with the base pairs through hydrogen bond interactions and alters the geometry of base pairs. The optimized geometries of the usual and mismatch base pairs are almost planar whereas the geometries of drug interacting complexes deviate from planarity. The presence of hydrogen bonds has been identified and studied through the interaction energy and many body interaction energy, topological and NBO analysis. The electron density difference maps illustrate the delocalization of the electron density in the drug interacting complexes. In the case of isolated (without drug) usual and mismatch base pairs, GG base pair has the largest interaction energy and TT with the smallest interaction energy. It is observed that the two body interaction energy calculated for the isolated base pairs (ΔE_{iso}) is found to be higher than that of the isolated same base pair in drug interacting complexes, which shows that the interaction between base pairs is decreased due to the interaction of the drug molecule.

Among the HU interacting complexes, CC mismatch base pair is found to have the largest interaction energy, whereas the complex formed between TT and HU is observed with the smallest interaction energy. In the 5-fluorouracil interacting complex GG–5FU is found to have the largest interaction energy and AA–5FU with the smallest interaction energy. In the drug interacting complexes the many body

Table 3
Occupation number of the proton donor, σ^*(X–H) and the acceptor lone pairs, $n(y)(y)$ and the hydrogen bond stabilization energy E^2 (in kcal/mol) calculated for drug interacting complexes at B3LYP/6–31+G*

Bonding	Donor	Acceptor	$E^{(2)}$	Bonding	Donor	Acceptor	$E^{(2)}$
	σ^*(X–H)	$n(y)$			σ^*(X–H)	$n(y)$	
GC–HU				**CC–HU**			
DN_3–DH_3…N_2	0.050	1.873	14.09	N_1–H_1… DO_1	0.064	1.856	15.76
DN_2–DH_{2a}…O_2	0.040	1.859	9.53	DO_4–DH_4…O_6	0.069	1.850	24.69
N_1–H_1…DO_4	0.045	1.961	15.11	DN_2–DH_{2a}… O_2	0.031	1.855	6.55
N_2–H_{2a}…DO_1	0.036	1.960	9.27	DN_3–DH_3…N_3	0.058	1.864	19.18
N_4–H_{4a}…O_6	0.040	1.960	9.24	N_4–H_{4a}… DO_4	0.036	1.949	11.28
GG–HU				**GC–5FU**			
N_1–H_1…DO_1	0.066	1.841	19.00	N_{20}–H_{29}…N_{23}	0.030	1.882	9.24
DN_2–DH_{2a}…O_6	0.052	1.849	14.68	N_{16}–H_{31}…O_7	0.037	1.958	5.5
DN_3–DH_3…N_9	0.050	1.897	16.29	N_{28}–H_{38}…O_7	0.033	1.864	5.95
N_2–H_{2a}…DO_4	0.026	1.965	8.62	N_5–H_{39}…O_{10}	0.081	1.849	23.72
AA–HU				**CC–5FU**			
N_6–H_{6a}…DO_1	0.044	1.849	10.23	N_{16}–H_{23}… N_2	0.032	1.881	9.78
DN_3–DH_3…N_1	0.059	1.876	19.10	O_{11}–H_{22}…O_{34}	0.040	1.957	5.90
DN_2–DH_{2a}…N_1	0.039	1.890	11.27	N_8–H_{18}… O_{34}	0.033	1.957	6.25
N_6–H_{6a}…DO_4	0.027	1.971	7.33	DN_5–DH_5… O_6	0.085	1.854	27.07
TT–HU				**GG–5FU**			
DN_2–DH_{2b}…O_2	0.028	1.966	5.33	N_{33}–H_{41}…N_{18}	0.064	1.861	19.62
N_3–H_{23}…N_{33}	0.042	1.838	10.24	N_{12}–H_{23}…O_{40}	0.046	1.856	11.93
N_{32}–H_{38}…O_{10}	0.038	1.869	8.63	N_7–H_{32}… O_{39}	0.064	1.848	12.12
N_{12}–H_{25}…O_{39}	0.051	1.845	9.93	N_{36}–H_{42}…O_{11}	0.074	1.849	20.06
–	–	–	–	N_{10}–H_{30}… O_{22}	0.023	1.964	7.57
AT–HU				**TT–5FU**			
N_3–H_3…DO_1	0.051	1.951	6.57	N_5–H_{41}… O_{19}	0.057	1.867	12.75
DO_4–H_{15}…O_4	0.023	1.880	6.36	N_{21}–H_{34}… O_8	0.048	1.857	9.56
N_6–H_{6a}…DO_1	0.039	1.862	9.21	N_{12}–H_{33}…O_7	0.058	1.845	15.75
DN_2–DH_{2a}…N_1	0.047	1.881	16.18	N_3–H_{40}…O_{10}	0.060	1.847	16.60

*NBO analysis for AT–5FU and AA–5FU has not been achieved due to the linear dependency of basis set used.

interaction energy values shows that the two-body interactions are stronger than the three body interactions. The strong binding nature of the drug hydroxyurea and 5-fluorouracil with the usual and mismatch base pairs reveals that, these drugs are suitable to inhibit the replication of DNA base pairs, sequentially to prevent the redundant cell growth responsible for cancer cells.

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