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A density functional reactivity theory (DFRT) based approach to understand the interaction of cisplatin analogues with protecting agents

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Abstract In the present study some new insights are put into one of the major concern of cisplatin therapy and that is on the reduction of various cytotoxic and nephrotoxic side-effects of cisplatin analogues in cancer treatment. A better understanding of the interaction between different cisplatin analogues with various protecting agents can be achieved from the descriptors generated by density functional reactivity theory based comprehensive decomposition analysis of stabilization energy (Bagaria et al. in Phys Chem Chem Phys 11:8306–8315, 2009) scheme. Taking into account of three types of interactions i.e., of (1) Cisplatin analogues with DNA bases and base pairs (2) Cisplatin analogues with protecting agents and (3) Protecting agents with DNA bases, it is possible to develop a strategy (albeit qualitative) that suggests the best possible combinations of these drugs with protecting agents which can cause reduction in the toxic side-effects of cisplatin therapy. The sample set comprises of 96 pairs of cisplatin analogues and rescue agents and the generated data confirms the predictive power of the adopted strategy.

Keywords Cisplatin analogues · Protecting agents · Nucleobases · Reactivity descriptors · CDASE scheme · Kinetic and thermodynamic parameters

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Introduction

Cis-diamminedichloroplatinum(II), cisplatin [1], along with its analogues have the decade long series of major accomplishment on different types of cancer cell lines. Although, it is well known that the primary target of cisplatin analogues is genomic DNA [2–8], an ultimate mechanism of this platination process is not fully understood. Despite the excellent cure rate of up to 90 % [9, 10], severe toxic side-effects of cisplatins [11–13] are major disadvantages, raising a big question on their therapeutic exertion for cancer treatment. Because of the competitive protein binding of cisplatin analogues, toxic side-effects such as nephrotoxicity, ototoxicity, hematological toxicity and seizures [14–20] are prevalent among the patients undergoing cisplatin treatment. Thus, reducing the toxic side-effects of cisplatin has become a major concern among the worldwide scientific community and researchers throughout the last four decades. Medical research to eradicate the toxic side-effects of cisplatin analogues is boosted by the introduction of Pearson's hard soft acid base (HSAB) principle [21–23]. Platinum (Pt), being a soft metal center, prefers to bind with soft nucleophilic center such as sulfur ligand based compounds. It is the underlying perception behind the introduction of sulfur based cisplatin modulators, which are termed rescue or protecting agents [24–28]. There exist two customary protocols for the design and development of modulating agents. These are,

1. To protect the non-carcinogenic normal tissues from the effect of therapeutic agents.
2. Ameliorate (to make more satisfactory anticancer agent) the chemotherapeutic application of cisplatin analogues with the significant minimization of its toxic side-effect.

Keeping these two important aspects in mind, scientists proficiently venture the *HSAB principle*. They have successfully designed various sulfur ligand based rescue agents, which effectively diminished the toxic side-effects of cisplatin drug without reducing antineoplastic efficacy (i.e., relative ability to damage dividing cells than to resting cells) of these drugs much [29–34].

Interaction of cisplatin with genomic DNA has been the subject of extensive theoretical and computational investigation [35–45] over the years. However, reported literatures on the interaction of cisplatin analogues with sulfur based rescue agents are limited in terms of theoretical aspects (i.e., how to define the best possible protecting agent against a particular cisplatin analogue). So, to the best of authors' knowledge the present one may be the first theoretical study in this direction and that is also through an approach based on density functional reactivity theory (DFRT).

In the context of density functional reactivity theory, (DFRT) several local and global reactivity descriptors [46–59] have been developed in the last three decades. Fukui functions [$f(r)$], [60, 61] local softness (S_k^+, S_k^- and S_k^0), [62] local hardness, [63–66] relative electrophilicity (S_k^+/S_k^-) and relative nucleophilicity (S_k^-/S_k^+), [67, 68] local electrophilicity [69–71] etc. are some commonly used local reactivity descriptors. Global reactivity descriptors such as chemical potential [72] (i.e., the negative of electronegativity [73]), chemical hardness (η) [49], global electrophilicity index, [74, 75] nucleophilicity, [76–78] electrofugality and nucleofugality, [79, 80] etc. are mainly used for intermolecular reactivity study. Very recently Saha et al. [81] have proposed two new local reactivity descriptors (known as 'variants of hardness potential' or 'hardness potential derivatives') which have the prospect to be used as intermolecular reactivity descriptors. In a subsequent investigation the relative contribution of combined kinetic and exchange energy terms vs electronic component of molecular electrostatic potential in hardness potential derivatives are explored by Bhattacharjee et al. [82].

Utilizing the basic foundation of density functional reactivity theory (DFRT), Roy and collaborators recently formulated a new theoretical scheme [83] termed as "comprehensive decomposition analysis of stabilization energy" (CDASE) to rationalize the kinetics and thermodynamics of chemical reactions. They have introduced an useful correlation between the energy components (of the stabilization energy [49]) and the rate of a chemical reaction. The scheme is successfully used by Sarmah et al. [84] to explain the most stable binary non-covalently bonded complex formation between urea and *meta*-nitrobenzoic acid. The intrinsic complementary nature of CDASE scheme to conventional supermolecular approach was also highlighted in this study. Preferential binding interaction of aqua-cisplatins with DNA base guanine over adenine could also be explained by CDASE scheme [85]. The advantage of CDASE scheme as an alternative low cost computational methodology to study large molecular systems is elaborated through a recent study by Sarmah et al. [86] and Saha et al. [87] used this scheme to investigate the normal electron demand (NED) and inverse electron demand (IED) nature of Diels–Alder (DA) reaction between 108 pairs of dienes and dienophiles.

In the present study an effort is made to investigate the strength of interaction between different pairs comprising of cisplatin analogues and sulfur ligand based protecting agents. Also, the stability of the complexes formed by each pair will be evaluated using different energy components generated by CDASE scheme. These, together, will help to get an idea of the kinetics and thermodynamics of interaction between cisplatin analogues and rescue agents which can be extended further to develop a strategy of choosing a specific protecting agent against a particular type of cisplatin drug.

Normally, the major obstacles for theoretical studies in case of biological systems are the very high computational cost. However, use of the CDASE scheme has an advantage as the route which is taken here to reach the combined system [i.e., the drug + nucleobases (or base pairs) or drug + protecting agents] is from the corresponding isolated components which, to a significant extent, reduces the computational cost.

The article is structured in the following way: section "Theoretical background" carries a very brief theoretical background, where different energy components based on CDASE scheme are briefly discussed. Adopted computational methodology is elaborated in section "Computational methodology". In section "Strategy for choosing the best possible protecting agent against a particular cisplatin analogue" the strategic protocol to be used to define the best possible combination of cisplatin analogues and rescue agents (that may reduce the toxic side effects) is explained. Section "Interaction of different cisplatin analogues with DNA bases and base-pairs" and "Relative strength of interaction of protecting agents with cisplatin analogues as well as active biomolecules" contain discussion on the interaction of cisplatin analogues with nucleobases (plus base pairs) and protecting agents, respectively. Discussion on the strength of interaction between protecting agents and DNA bases is also included in section "Relative strength of interaction of protecting agents with cisplatin analogues as well as active biomolecules". In section "Synchronization of the data generated by different reactivity parameters and use of the strategy proposed in section "Results and discussion"" use of the proposed strategy ("Strategy for choosing the best possible protecting agent against a particular cisplatin analogue" section), by establishing a systematic correlation of the results obtained in the previous two subsections, is highlighted.

Finally, in section "Conclusions" we have summarized our entire work with a short note on some promising aspects of CDASE scheme and its advantages over other approaches where reactivity descriptors are mainly based on electron population.

Theoretical background

Parr and Pearson [49] developed the formalism for energy lowering, i.e., the stabilization energy (SE), due to electron transfer between two chemical species A and B in the formation of the complex AB. It was shown, from the definition of μ and η (i.e., chemical potential and chemical hardness), that when electron transfer (ΔN) is small, the total energy (after electron transfer stops) can be written as,

$$E_A + E_B = E_A^o + E_B^o + \left(\mu_A^o - \mu_B^o\right)\Delta\mathrm{N} + {}^1\!/_2(\eta_A + \eta_B)(\Delta\mathrm{N})^2 + \ldots \quad (1)$$

The corresponding stabilization energy can be written as,

$$\Delta E_{SE} = -\frac{\left(\mu_B^o - \mu_A^o\right)^2}{2(\eta_A + \eta_B)} \quad (2)$$

and the electron transfer (ΔN) as,

$$\Delta N = \frac{\mu_B^o - \mu_A^o}{(\eta_A + \eta_B)} \quad (3)$$

In another classic paper, Parr et al. [75] considered the interaction between an ideal donor and an electrophilic ligand (i.e., an acceptor) and argued that the ligand becomes saturated with electrons when electron transfer satisfy the condition,

$$\frac{\Delta E}{\Delta N} = 0 \quad (4)$$

In such a situation it was shown that,

$$\Delta E = -\frac{\mu^2}{2\eta} \quad (5)$$

and,

$$\Delta N_{\max} = -\frac{\mu}{\eta} \quad (6)$$

In this case μ and η refers to the chemical potential and chemical hardness, respectively of the electrophilic ligand only.

When, the charge transfer process is energetically favorable (i.e., $\eta > 0$, $\Delta E < 0$) negative of ΔE was defined as global electrophilicity (w) by Parr et al. [75]

$$\text{i.e., } w = \frac{\mu^2}{2\eta} \quad (7)$$

Several other global reactivity indices, e.g., nucleophilicity [76, 88], electrofugality and nucleofugality [77, 78] are also conceptually related to w.

In a recent study Bagaria et al. [83] extended the above concept of stabilization energy to explain the thermodynamics and kinetics of chemical interactions. They argued that when the donor and acceptor systems are of comparable size the mutual effect of interacting species on each other cannot be avoided. Then, the modified form of the expression for overall stabilization energy can better be represented as,

$$\Delta E_{SE(AB)} = \Delta E_{A(B)} + \Delta E_{B(A)} = -\frac{\left(\mu_B^o - \mu_A^o\right)^2}{2(\eta_A + \eta_B)} \quad (8)$$

Thus the expression for individual energy components as given by Parr et al. [49] has to be re-denoted when both the donor and the acceptor are of ordinary sized molecules. As those energy components are not completely independent entities the changes in energy of B i.e., $\Delta E_{B(A)}$, due to transfer of ΔN electrons to A, can be written as,

$$\Delta E_{B(A)} = \frac{\mu_B^o - \mu_A^o}{\eta_A + \eta_B}\left[-\mu_B^o + \frac{1}{2}\eta_B\left(\frac{\mu_B^o - \mu_A^o}{\eta_A + \eta_B}\right)\right] \quad (9)$$

Similarly, for change of energy of A (i.e., $\Delta E_{A(B)}$) can be written as,

$$\Delta E_{A(B)} = \frac{\mu_B^o - \mu_A^o}{\eta_A + \eta_B}\left[\mu_A^o + \frac{1}{2}\eta_A\left(\frac{\mu_B^o - \mu_A^o}{\eta_A + \eta_B}\right)\right] \quad (10)$$

Based on the understanding as discussed above Roy and collaborators proposed a new scheme, named as CDASE [83] (comprehensive decomposition analysis of stabilization energy), which correlates $\Delta E_{B(A)}$ and $\Delta E_{A(B)}$ to the kinetic and thermodynamic aspects of a particular reactive interaction. The proposed scheme defined $\Delta E_{B(A)}$ as a new reactivity parameter, 'internal assistance' (or more appropriately be termed as 'kinetic assistance') because it solely depends on the electronic and structural properties of the two reacting species and helps in overcoming the activation barrier. This newly proposed reactivity parameter plays a major role in determining the reaction rate. Different energy components (of the proposed CDASE scheme) along with the global electrophilicity descriptor have shown to be very promising in exploring and understanding different types of chemical interactions [83–87].

Computational methodology

Altogether, twelve different cisplatin analogues (Fig. 1) and eight promising cisplatin modulators (Fig. 2) have been included in the present study. Model cisplatin analogues consist of both Pt(II) and Pt(IV) metal centers. It is

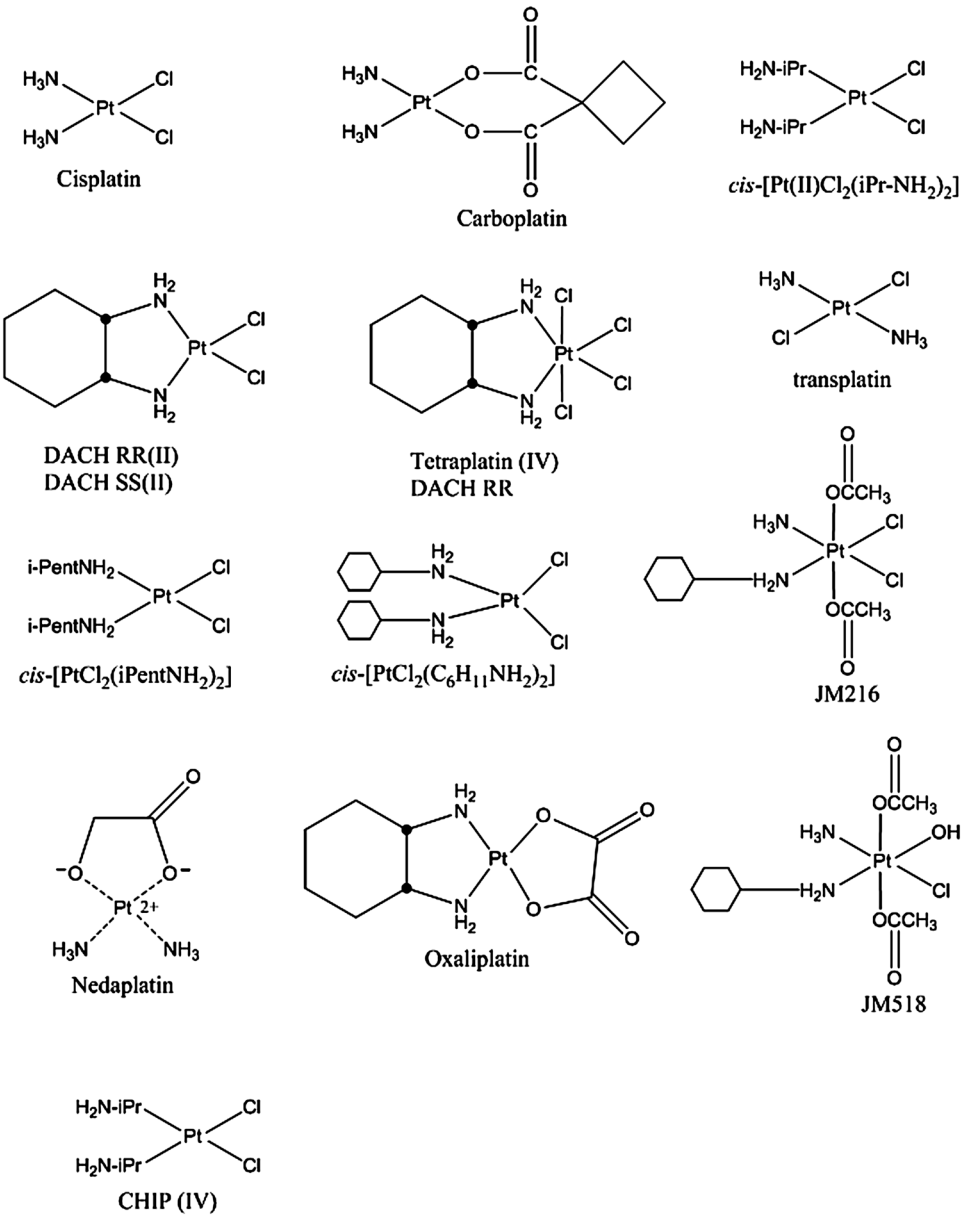


Fig. 1 Names and structures of different cisplatin analogues chosen in the present study

worth mentioning here that, in the treatment of cancer both the oxidation states of Pt play significant roles. The protecting agents chosen here are of moderate size, recently developed as well as known to be very effective. A study on the relative rate of interaction of cisplatin analogues with the DNA is also carried out.

Initial crude structures of cisplatin analogues, DNA bases as well as protecting agents are generated using Gauss View [89] visualization program. Full geometry optimization as well as relevant single point calculations of protecting agents and DNA bases are performed at B3LYP [90–92]/6-31G(d,p) [93–96] method. Subsequent frequency analysis has been performed for every structure to ensure no imaginary frequency is present (i.e., minimum energy state has been achieved in potential energy surface).

Geometries of cisplatin analogues are also optimized at the same level of theory (i.e., B3LYP) but the basis set used here is LanL2DZ (with effective core potential, ECP) [97–99]. The reason for choosing the LanL2DZ basis set for the whole cisplatin analogue (not just the Pt atom) is to reduce the computational cost (i.e., to take care of the computational limitations) and also because of the fact that the Pt atom is mainly responsible for the whole process of cisplatin–nucleobase interaction and it is the primary concern in our present study. Vertical ionization potential (IP) and electron affinity (EA) values are considered in the

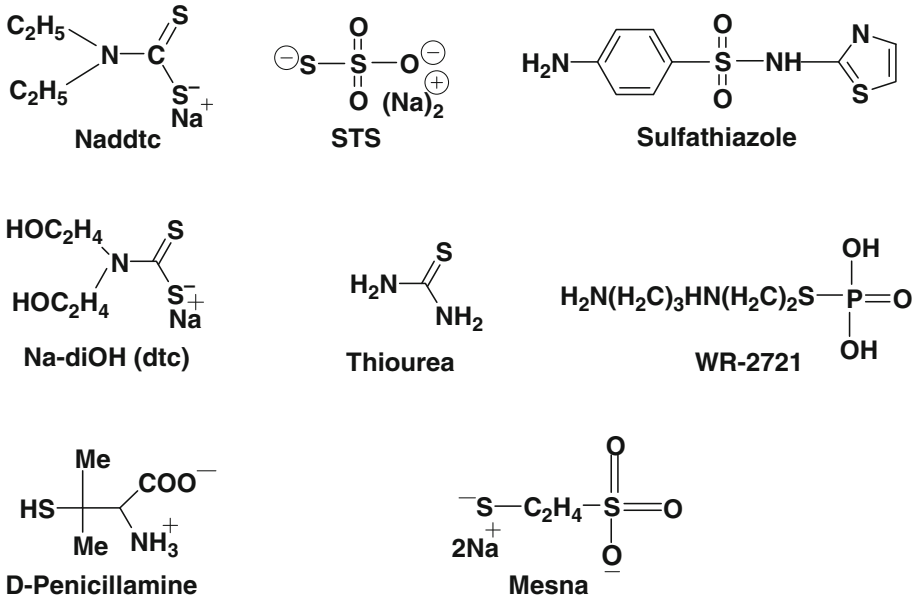


Fig. 2 Names and structures of different protecting agents chosen in the present study

present study to evaluate η, μ, ΔN etc. These quantities were generated after performing single point calculations for neutral, cationic and anionic systems using the geometry of the optimized neutral structures only. While restricted level of theory (RB3LYP) was used for neutral systems, unrestricted level of the same theory (UB3LYP) was used for calculations of ionic systems. Gaussian 03 [100] program suit has been used for the entire computational calculations.

Some of the calculations for protecting agents are also carried out using higher level basis sets such as 6-311G(2d,2p), 6-311++G(d,p) (results are not shown here). The observation is that optimizations with these higher level basis sets hardly make any change to the sequence of the values of the reactivity descriptors generated by CDASE scheme using 6-31G (d,p) basis sets for the protecting agents.

Results and discussion

Strategy for choosing the best possible protecting agent against a particular cisplatin analogue

It is believed that the anticancer activity of the cisplatin drug originates from the intrastrand adduct formation with DNA base pairs [7]. More specifically, attachment of cisplatin analogues to DNA takes place through the N-7 positions of purine bases [20]. One of the factors which decide the anticancer activity of cisplatin analogues is the strength of interaction of these drugs with DNA bases (but this does not ensure the analogue to be an efficient anticancer drug). This is because stronger the interaction of cisplatin analogues with DNA bases, the DNA replication process is inhibited, thus stopping the cell division as well as cell growth. However, another important factor which needs to be considered here is the binding ability of the drug with other biomolecules. If a drug interacts strongly with DNA then it is expected that the extent of interaction of the drug with other biomolecules, such as proteins and amino acids, will also be significantly high. This is because the basic inorganic chemistry knowledge refers Pt as a soft metal center and it is natural that it has higher affinity towards soft nucleophilic centers present in sulfur containing compounds. There is a significant abundance of sulfur containing biomolecules in the cytosol as well as in the nucleus of human cell. Indeed, the most reasonable implication is the possibility of a strong interaction between the highly active platinum anticancer drugs and biomolecules present inside the cell. So, it can be argued that the toxic side-effects will be more for a strongly active drug.

Similarly, selection of an effective protecting agent against a particular cisplatin drug is decided by testing the interaction of that protecting agent with cisplatin analogues. The basic requisite of protecting agents is to restrain the higher activity of cisplatin analogues to such an extent that without compromising the anti-cancer property of the drug the undesired binding affinity of the drug towards other biomolecules (like proteins) is restricted. However, for an explicit understanding of the activity of a protecting agent it is also important to take into account the interaction between protecting agents and other active biomolecules. An effective protecting agent must have the low reactive interaction with the active biomolecules so that it can restore its maximum ability to provide protection against the cisplatin drug.

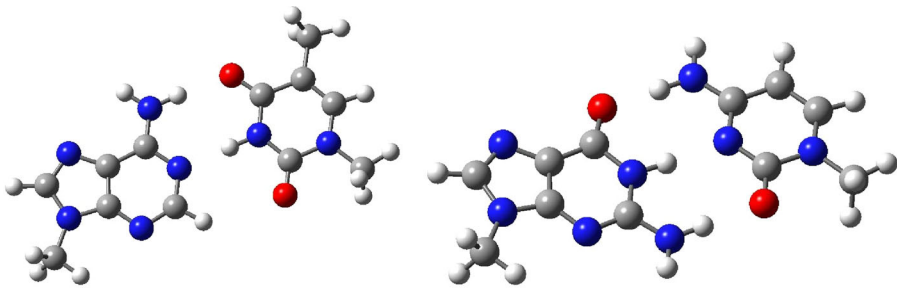
Table 1 Computed CDASE scheme based parameters namely, ΔW, $\Delta E_{B(A)}$, ΔN, $\Delta E_{A(B)}$, and $\Delta E_{SE(AB)}$ for the interaction between cisplatin analogues and individual purine bases adenine (A) and guanine (G)

Combinations	Δw (kcal mol^{-1})	$\Delta E_{B(A)}$ (kcal mol^{-1})	ΔN	$\Delta E_{A(B)}$ (kcal mol^{-1})	$\Delta E_{SE(AB)}$ (kcal mol^{-1})
Nedaplatin: Adenine	4.66	1.98	0.0265	−2.05	−0.07
Nedaplatin: Guanine	9.06	4.10	0.0589	−4.47	−0.37
Oxaliplatin: Adenine	9.99	3.55	0.0468	−3.78	−0.23
Oxaliplatin: Guanine	14.39	5.69	0.0804	−6.35	−0.67
DACH RR II: Adenine	13.26	4.95	0.0644	−5.38	−0.43
DACH RR II: Guanine	17.65	7.04	0.0981	−8.03	−0.99
Cis-[$PtCl_2(C_6H_{11}NH_2)_2$]: Adenine	14.57	5.04	0.0656	−5.48	−0.44
Cis-[$PtCl_2(C_6H_{11}NH_2)_2$]: Guanine	18.97	7.17	0.0998	−8.18	−1.00
Cis-[$PtCl_2(iPentNH_2)_2$]: Adenine	15.37	5.55	0.0718	−6.07	−0.53
Cis-[$PtCl_2(iPentNH_2)_2$]: Guanine	19.76	7.64	0.1059	−8.78	−1.14
Carboplatin: Adenine	17.53	7.05	0.0901	−7.90	−0.85
Carboplatin: Guanine	21.92	9.04	0.1236	−10.63	−1.59
Cis-[$Pt(II)Cl_2(iPrNH_2)_2$: Adenine	18.88	7.86	0.0998	−8.91	−1.04
Cis-[$Pt(II)Cl_2(iPrNH_2)_2$: Guanine	23.28	9.80	0.1331	−11.65	−1.85
Transplatin: Adenine	25.65	12.90	0.1576	−15.69	−2.79
Transplatin: Guanine	30.05	14.45	0.1886	−18.44	−3.99
CHIP-IV: Adenine	48.03	18.29	0.2153	−22.95	−4.66
CHIP-IV: Guanine	52.42	19.98	0.2501	−26.26	−6.28
JM 518: Adenine	65.04	19.38	0.2265	−24.01	−4.63
JM 518: Guanine	69.43	21.42	0.2654	−27.76	−6.34
JM216: Adenine	68.96	24.25	0.2745	−31.54	−7.29
JM216: Guanine	73.35	25.90	0.3114	−35.24	−9.34
Tetraplatin: Adenine	75.50	25.96	0.2914	−34.06	−8.10
Tetraplatin: Guanine	79.88	27.62	0.3284	−37.87	−10.26

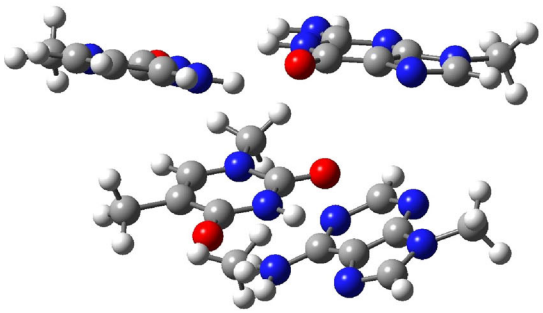
Method used for cisplatin analogues is B3LYP/LanL2DZ, whereas for nucleobases it is B3LYP/6-31 G(d,p)

A = Cisplatin analogue: B = Adenine (A)/Guanine (G)

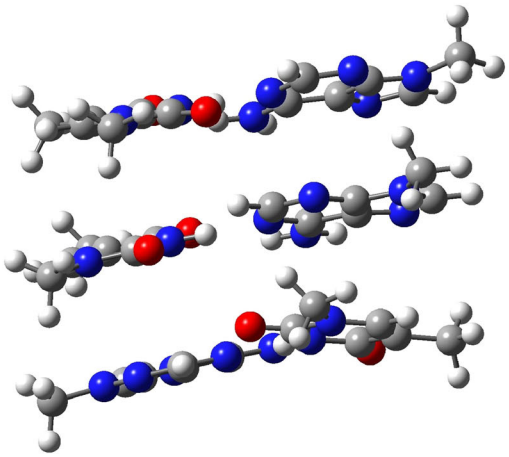
The ongoing discussion on three types of possible interactions (i.e., the interaction of a particular cisplatin drug with genomic DNA, the effect of protecting agents on that particular drug as well as on other active biomolecules) leads the way to develop a strategy of choosing suitable combination of cisplatin drugs and protecting agents that minimize toxic side effects. If the activity of a particular drug is low towards DNA bases, application of a strong protecting agent (distinction between weak and strong protecting agents can be made on the basis of the strength of interaction with drugs) reduce the activity of the drug to such an extent that the drug might lose its anti-cancer activity in the presence of that particular protecting agent. In another situation, may be the drug is highly active towards DNA bases. In such a case, it is obvious that the toxic side-effects of the drug will be more because of its higher binding ability with other biomolecules. So, to diminish the toxic side effects of the highly active cisplatin analogue the required protecting agent should also have strong affinity for the drug (i.e., a strong protecting agent). Also, if the strength of interaction of the protecting agent with biomolecules is much lower when compared to those between drugs and protecting agents as well as between drugs and biomolecules, then the first factor should play negligible role in the choice of protecting agents. However, if in a particular case the reactive interaction between a protecting agent and biomolecules are comparable to the other two types of interactions then it may also play a critical role in the choice of protecting agents. After a thorough analysis of three types of interactions (as discussed above) in different sections of "Interaction of different cisplatin analogues with DNA bases and base-pairs" and "Relative strength of interaction of protecting agents with cisplatin analogues as well as active biomolecules" the results are synchronized in section "Synchronization of the data generated by different reactivity parameters and use of the strategy proposed in section "Results and discussion"" to implement the adopted strategy.



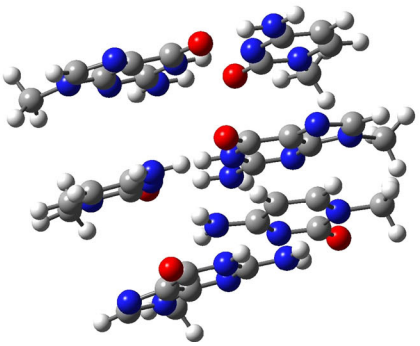
AT base pair GC base pair



GA-CT double base pair



AAT-TTA triple base pair unit



GCC-CGG triple base pair unit

Fig. 3 Structures of the methyl capped DNA base pairs optimized at B3LYP/6-31G(d,p) level of theory

Table 2 Computed CDASE scheme based parameters for the interaction between cisplatin analogues and W–C single base pair unit

Combinations	ΔW (kcal mol^{-1})	$\Delta E_{B(A)}$ (kcal mol^{-1})	ΔN	$\Delta E_{A(B)}$ (kcal mol^{-1})	$\Delta E_{SE(AB)}$ (kcal mol^{-1})
Nedaplatin: AT	0.32	1.66	0.022	−1.71	−0.05
Nedaplatin: GC	11.39	3.78	0.0534	−4.05	−0.27
Oxaliplatin: AT	22.64	3.33	0.0436	−3.52	−0.18
Oxaliplatin: GC	33.71	5.52	0.0768	−6.07	−0.55
DACH RR II: AT	36.30	4.83	0.0625	−5.21	−0.38
DACH RR II: GC	47.37	7.01	0.0965	−7.88	−0.86
Cis-[$PtCl_2(C_6H_{11}NH_2)_2$]: AT	41.80	4.93	0.0637	−5.21	−0.39
Cis-[$PtCl_2(C_6H_{11}NH_2)_2$]: GC	52.86	7.16	0.0983	−8.04	−0.88
Cis-[$PtCl_2(iPentNH_2)_2$]: AT	45.13	5.47	0.0704	−5.94	−0.47
Cis-[$PtCl_2(iPentNH_2)_2$]: GC	56.20	7.68	0.1050	−8.69	−1.01
Carboplatin: AT	54.17	7.08	0.0906	−7.87	−0.79
Carboplatin: GC	65.24	9.22	0.1247	−10.67	−1.46
Cis-[$Pt(II)Cl_2(iPrNH_2)_2$]: AT	59.84	7.95	0.1005	−8.93	−0.98
Cis-[$Pt(II)Cl_2(iPrNH_2)_2$]: GC	70.91	10.05	0.1352	−11.78	−1.72
Transplatin: AT	88.20	13.27	0.1619	−16.03	−2.76
Transplatin: GC	99.26	15.09	0.1959	−19.00	−3.92
CHIP-IV: AT	181.83	19.04	0.2243	−23.74	−4.70
CHIP-IV: GC	192.90	21.22	0.2650	−27.55	−6.34
JM 518: AT	253.04	20.31	0.2375	−25.00	−4.71
JM 518: GC	264.11	22.98	0.2840	−29.42	−6.45
JM216: AT	269.44	25.40	0.2889	−32.87	−7.46
JM216: AT	280.51	27.74	0.3339	−37.35	−9.61
Tetraplatin: AT	296.78	27.24	0.3068	−35.55	−8.31
Tetraplatin: GC	307.85	29.64	0.3532	−40.25	−10.60

Method used for cisplatin analogues is B3LYP/LanL2DZ, whereas for base pairs it is B3LYP/6-31 G(d,p)

A = Cisplatin Analogue: B = A-T/G-C Base pair

Interaction of different cisplatin analogues with DNA bases and base-pairs

It is well accepted that N-7 position of the purine bases is the most active site for platination [7, 10]. It is also well established that the binding interaction of cisplatin with guanine is preferred to that with adenine [28, 41, 45, 85]. So, to make the observation broader, to the extent that it will help to apply the adopted strategy as discussed in the section "Strategy for choosing the best possible protecting agent against a particular cisplatin analogue" above, 12 different cisplatin analogues have been included in the present one. The strength of interaction is evaluated on the basis of different kinetic and thermodynamic parameters derived in the CDASE scheme ("Theoretical background" section). The values of these parameters are summarized in Table 1. Here, higher values for Δw and $\Delta E_{B(A)}$ predict faster rate of interaction, whereas those of ΔN, $\Delta E_{A(B)}$ and $\Delta E_{SE(AB)}$ talk about the stability of adducts. It is worth observing here that all the 12 different cisplatin analogues show a greater affinity for the nucleobase guanine, both from kinetic and thermodynamic aspects.

As the anti-tumor activity of these platinum drugs mainly depends on their preferential binding ability to DNA bases, more effectively they bind to DNA, more actively they will inhibit the process of DNA replication and thus the cell growth will stop. The DNA damaging activity of different cisplatin analogues have been systematically analyzed by Murray et al. [101]. They have studied the rate of interaction of a number of cisplatin drugs with DNA and based on their experimental results proposed an order of activity for a series of cisplatin analogues. Significantly, higher degrees of DNA damaging activity have been reported for Tetraplatin [i.e., tetrachloro(1,2-diaminocyclohexane)platinum(IV)] (Fig. 1). It is encouraging to notice here that CDASE scheme based theoretical results (in Table 1) also clearly reproduce the experimental evidence. The values generated for all the five parameters (i.e., Δw, $\Delta E_{B(A)}$ ΔN $\Delta E_{A(B)}$, and $\Delta E_{SE(AB)}$) are significantly high for Tetraplatin. So, it can be argued that among the series of chosen model cisplatin analogues Tetraplatin will be the most effective antineoplastic agent according to our observations.

Table 3 Computed CDASE scheme based parameters for the interaction between cisplatin analogues and double base pair units

Combinations	Δw (kcal mol^{-1})	$\Delta E_{B(A)}$ (kcal mol^{-1})	ΔN	$\Delta E_{A(B)}$ (kcal mol^{-1})	$\Delta E_{SE(AB)}$ (kcal mol^{-1})
Nedaplatin: GA-CT	10.37	3.65	0.0511	−3.89	−0.24
Oxaliplatin: GA-CT	11.95	5.51	0.0762	−6.02	−0.51
DACH RR II: GA-CT	25.61	7.12	0.0971	−7.93	−0.82
Cis-[$PtCl_2(C_6H_{11}NH_2)_2$]: GA-CT	31.10	7.26	0.0991	−8.10	−0.84
Cis-[$PtCl_2(iPentNH_2)_2$]: GA-CT	34.44	7.82	0.1063	−8.79	−0.97
Carboplatin: GA-AT	43.48	9.46	0.1273	−10.88	−1.42
Cis-[$Pt(II)Cl_2(iPrNH_2)_2$]: GA-CT	49.15	10.35	0.1384	−12.04	−1.69
Transplatin: GA-CT	77.50	15.64	0.2026	−19.58	−3.95
CHIP-IV: GA-CT	171.14	22.21	0.2776	−28.70	−6.49
JM 518: GA-CT	242.35	25.70	0.3280	−33.46	−7.76
JM216: GA-CT	258.75	31.22	0.3523	−39.14	−9.96
Tetraplatin: GA-CT	286.09	29.18	0.3733	−42.23	−11.02

Method used for cisplatin analogues is B3LYP/LanL2DZ, whereas for double base pairs it is B3LYP/6-31 G(d,p)

A = Cisplatin Analogue: B = GA-CT Base pairs

Also, a comprehensive study on the anti-cancer activity of four of the chosen cisplatin analogues [e.g., Oxaliplatin (*trans*-L-Diaminocyclohexane)oxalatoplatinum(II), Tetraplatin, Carboplatin (*cis*-diammine (1,1-Cyclobutanedicarboxylato) platinum(II)) and Cisplatin] has been reported by Rixe et al. [102]. According to their observation, interaction of DACH [i.e., dichloro(1,2-diaminocyclohexane)platinum(IV)] group of compounds (such as Tetraplatin, etc.) with DNA is far more active than cisplatin group of compounds (like Carboplatin, etc.).

To obtain some more realistic features of the interaction between cisplatin analogues and DNA, the study has been extended from individual nucleobases to relatively large DNA clusters i.e., to the single, double and triple base pair units of Watson–Crick DNA double helix. Optimized structures of the base pairs are provided in the Fig. 3. Model DNA structures are generated by trimming the reported crystal structure of DNA having PDB ID 2VAH [103] up to the specific base pair units (one, two or three base pair). For computational simplicity the sugar and phosphate units are replaced with methyl groups in their respective positions. Different CDASE scheme based parameters have been evaluated for the interaction between 12 cisplatin analogues and single base pair units A-T (adenine–thymine) and G-C (guanine–cytosine) followed by double base pair unit AG-TC as well as the triple base pair units AAT-TTA and GCG-CGC and the corresponding values are reported in Tables 2, 3 and 4, respectively.

In case of single base pair units, all the 12 cisplatin analogues have shown kinetic as well as thermodynamic preference for GC pair over AT (Table 2). The higher activity of cisplatin analogues toward guanine is already justified from CDASE scheme based calculations (Table 1). This seems to be logical as the presence of nucleobase guanine enhances the strength of interaction of GC pair with cisplatin analogues compared to that of the AT pair. The relative order of interaction for the 12 cisplatin analogues with single base pair unit is found to be consistent with that of the individual purine bases. Cisplatin analogue Nedaplatin shows the lowest and Tetraplatin shows the highest activity against W–C complementary base pairs AT and GC.

In Table 3 we have reported the values of the CDASE scheme based parameters for the interaction between cisplatin analogues and higher order DNA cluster having two base pair units (GA-CT). The trend of interaction with double base pair units is similar to that obtained for individual bases as well as the single base pair units. Except, again the JM 518, no major discrepancy is observed in the CDASE scheme based calculations for the extended DNA sequence and the relative order is consistent with the former predictions on the DNA binding activity of cisplatin analogues.

To justify the preferential binding affinity of cisplatin analogues for GC base pair over AT, we have further calculated the CDASE scheme based parameters for the larger DNA clusters containing triple base pair units. The two model systems are containing the standard W–C double helix sequence CGG-GCC and ATT-TAA, where letters represent the individual nucleobases. The incorporation of more base pair units in the model system enhances the reliability of theoretical calculation and approaching closer to the real situation. The numerical values of the generated CDASE-scheme based parameters are reported in Table 4. The results with triple base pair systems also confirm the claim that cisplatin analogues interact more strongly with extended GC pair in comparison to that of the extended AT pair. It is worth mentioning here that the

Table 4 Computed CDASE scheme based parameters for the interaction between cisplatin analogues and triple base pair units

Combinations	Δw (kcal mol^{-1})	$\Delta E_{B(A)}$ (kcal mol^{-1})	ΔN	$\Delta E_{A(B)}$ (kcal mol^{-1})	$\Delta E_{SE(AB)}$ (kcal mol^{-1})
Nedaplatin: $(AT)^t$	0.38	1.99	0.0266	−2.06	−0.07
Nedaplatin: $(GC)^t$	5.45	4.76	0.0689	−5.18	−0.42
Oxaliplatin: $(AT)^t$	0.96	3.79	0.0500	−4.02	−0.22
Oxaliplatin: $(GC)^t$	16.87	6.66	0.0952	−7.43	−0.77
DACH RR II: $(AT)^t$	4.22	5.39	0.0704	−5.84	−0.44
DACH RR II: $(GC)^t$	30.53	8.25	0.1167	−9.41	−1.16
Cis-$[PtCl_2(C_6H_{11}NH_2)_2]$: $(AT)^t$	5.53	5.51	0.0718	−5.96	−0.45
Cis-$[PtCl_2(C_6H_{11}NH_2)_2]$: $(GC)^t$	36.02	8.44	0.1191	−9.61	−1.19
Cis-$[PtCl_2(iPentNH_2)_2]$: $(AT)^t$	6.33	6.08	0.0790	−6.63	−0.55
Cis-$[PtCl_2(iPentNH_2)_2]$: $(GC)^t$	39.06	8.97	0.1063	−10.32	−1.34
Carboplatin: $(AT)^t$	8.49	7.78	0.0999	−8.68	−0.90
Carboplatin: $(GC)^t$	48.43	10.58	0.1473	−12.44	−1.86
Cis-$[Pt(II)Cl_2(iPrNH_2)_2]$: $(AT)^t$	9.84	8.69	0.1110	−9.81	−1.12
Cis-$[Pt(II)Cl_2(iPrNH_2)_2]$: $(GC)^t$	54.07	11.45	0.1585	−13.62	−2.17
Transplatin: $(AT)^t$	16.62	14.22	0.1758	−17.26	−3.04
Transplatin: $(GC)^t$	82.42	16.57	0.2223	−21.23	−4.66
CHIP-IV: $(AT)^t$	38.99	20.50	0.2450	−25.70	−5.20
CHIP-IV: $(GC)^t$	176.06	23.35	0.3017	−30.86	−7.50
JM 518: $(AT)^t$	56.00	22.12	0.2622	−27.37	−5.25
JM 518: $(GC)^t$	247.15	25.70	0.3280	−33.46	−7.76
JM216: $(AT)^t$	59.92	27.33	0.3159	−35.58	−8.25
JM216: $(GC)^t$	263.67	30.43	0.3794	−41.71	−11.28
Tetraplatin: $(AT)^t$	66.45	29.32	0.3357	−38.50	−9.18
Tetraplatin: $(GC)^t$	291.00	32.50	0.3733	−44.94	−12.44

Method used for cisplatin analogues is B3LYP/LanL2DZ, whereas for Triple base pairs it is B3LYP/6-31 G(d,p)

A = Cisplatin Analogue: B = GCG-CGC/ATT-TAA Base pairs

$(AT)^t$ = ATT-TAA, and $(GC)^t$ = CGC-GCG

Table 5 Earlier reported experimental as well as theoretical studies which are relevant to understand the mode of interaction of some promising protecting agents (chosen in the present study) against platinum based anticancer drugs

Protecting agent	Method	Ref.
Penicillamine	Experimental	[32, 107]
Thiourea	Experimental	[30, 32]
DDTC	Experimental	[32–34]
STS	Exp. + theoretical	[29–31, 104]
Mesna	Exp + theoretical	[105, 106]
WR-2721	Experimental	[24, 26, 28]

observed trend of interaction for the cisplatin analogues is exactly similar and consistent throughout the calculations and is not altered with the change of the size of the DNA clusters. The overall CDASE scheme based kinetic and thermodynamic predictions on the interaction of cisplatin analogues with DNA is well justified and is also supported by the earlier experimental as well as theoretical evidences [41–45].

Relative strength of interaction of protecting agents with cisplatin analogues as well as active biomolecules

In this section we have implemented the CDASE scheme to evaluate the reliability of different kinetic and thermodynamic parameters in explaining the interaction between platinum anticancer drugs and sulfur containing protecting agents. Table 5 includes some earlier experimental and theoretical reports on the sulfur based compounds (protecting agents) which behave as effective chemoprotector against different platinum anticancer drugs. It is to be seen whether the reactivity parameters, based on the CDASE scheme can reproduce the relative strength of interaction between cisplatin drugs and protecting agents (Tables 6, 7, 8, 9, 10; Figs. 4, 5, 6, 7, 8), whichever are available in the literature (Table 5).

The last row in Tables 6, 7, 8, 9 and 10 are the values for the five CDASE scheme based parameters corresponding to the interaction of protecting agents with the active biomolecule (we have considered guanine as the prototype of active biomolecule for the present study). Analysis of these

Table 6 The difference between global electrophilicity (Δw) values (in kcal mol^{-1}) for different combinations of cisplatin analogues (acceptor, A) and protecting agents (donor, B)

Protecting agents / Cisplatin analogues	D-penicillamine	Thiourea	STS	WR-1065	S-thioazole	Na-diOH	NaDDTC	Mesna
Nedaplatin	0.09	2.78	4.55	5.16	6.16	6.19	6.86	7.35
Oxaliplatin	5.34	8.11	9.88	10.49	11.49	11.52	12.19	12.69
DACH RR(II)	8.69	11.37	13.15	13.75	14.76	14.78	14.46	15.95
Cis-[$PtCl_2(C_6H_{11}NH_2)_2$]	10.00	15.69	14.46	15.07	16.07	16.09	16.76	17.26
Cis-[$PtCl_2(iPentNH_2)_2$]	10.80	13.48	15.25	15.86	16.86	16.89	17.57	18.06
Carboplatin	12.96	15.64	17.41	18.02	19.03	19.05	19.73	20.21
Cis-[$Pt(II)Cl_2(iPrNH_2)_2$	14.13	17.00	18.76	19.37	20.38	20.41	21.08	21.57
Transplatin	21.03	23.77	25.54	26.15	27.15	27.18	27.85	28.34
CHIP-IV	43.46	46.14	47.91	48.52	49.52	49.55	50.23	50.71
JM 518	60.47	63.15	64.92	65.53	66.53	66.56	67.24	67.73
JM 216	64.39	67.07	68.84	69.45	70.45	70.48	71.16	71.64
Tetraplatin	70.92	73.61	75.37	75.98	76.99	77.01	77.68	78.18
Guanine	8.97	6.28	4.51	3.90	2.90	2.87	2.20	1.70

While in a particular row the number in a box represents the Δw value for the interaction between the corresponding cisplatin analogue and the protecting agent the values in the last row are for interaction between guanine (i.e., the biomolecule here) and the corresponding protecting agent

Table 7 The values of the positive energy component, $\Delta E_{B(A)}$, (in kcal mol^{-1}) for different combinations of cisplatin analogues (considered as A) and protecting agents (considered as B)

Protecting agents / Cisplatin analogues	D-penicillamine	Thiourea	STS	WR-1065	S-thioazole	Na-diOH	NaDDTC	Mesna
Nedaplatin	-0.57	0.92	1.86	2.33	2.52	3.56	3.66	4.40
Oxaliplatin	0.96	2.42	3.35	3.83	4.11	5.21	5.31	6.19
DACH RR(II)	2.41	3.79	4.69	5.17	5.52	6.62	6.72	7.07
Cis-[$PtCl_2(C_6H_{11}NH_2)_2$]	2.46	3.87	4.77	5.27	5.62	6.75	6.85	7.86
Cis-[$PtCl_2(iPentNH_2)_2$]	2.98	4.36	5.25	5.75	6.12	7.24	7.34	8.38
Carboplatin	4.60	5.87	6.67	7.18	7.62	8.78	8.81	9.92
Cis-[$Pt(II)Cl_2(iPrNH_2)_2$	5.4	6.67	7.48	7.96	8.43	9.51	9.61	10.76
Transplatin	10.88	11.74	12.35	12.79	13.41	14.38	14.48	15.75
CHIP-IV	16.05	16.87	17.45	18.00	18.90	20.08	20.28	22.07
JM 518	16.59	17.67	18.31	18.97	20.12	21.55	21.71	24.05
JM 216	21.99	22.57	23.11	23.67	24.93	26.22	26.37	28.75
Tetraplatin	23.68	24.22	24.73	25.31	26.66	28.00	28.15	30.69
Guanine	4.19	2.94	2.13	1.69	1.36	0.37	0.28	0.61

While in a particular row the number in a box represents the $\Delta E_{B(A)}$ value for the interaction between the corresponding cisplatin analogue and the protecting agent the values in the last row are for interaction between guanine (i.e., the biomolecule here) and the corresponding protecting agent

values together with those demonstrated in Tables 1, 2, 3, 4 and use of the strategy as outlined in section "Strategy for choosing the best possible protecting agent against a particular cisplatin analogue" will assist to predict the most preferable protecting agent against a specific drug.

Relative strength of interaction between cisplatin analogues and protecting agents on the basis of the difference in global electrophilicity values i.e., Δw

The numbers in each box in Table 6 demonstrate the difference in global electrophilicity values ($\Delta w = w_A - w_B$) between cisplatin analogues (behaving as an electron acceptor, $w_A = \frac{(\mu_A^0)^2}{2\eta}$) and protecting agents (behaving as an electron donor, $w_B = \frac{(\mu_B^0)^2}{2\eta}$) (see also Fig. 4). Higher the difference between w_A and w_B (i.e., $\Delta w = w_A - w_B$) stronger is the interaction for that particular combination of cisplatin analogue and protecting agent. This is also demonstrated through the change in the color sequence of Table 6. As the Δw values increase downwards as well as rightwards, the color also shifts from lower to higher intensity indicating the increase in the strength of interaction between cisplatin analogues and protecting agents.

Table 8 The charge transfer (ΔN) values for different combinations of chosen cisplatin analogues (considered as A) and protecting agents (considered as B)

Protecting agents / Cisplatin analogues	D-penicillamine	Thiourea	STS	WR-1065	S-thioazole	Na-diOH	NaDDTC	Mesna
Nedaplatin	-0.0072	0.0119	0.0248	0.0315	0.0343	0.0503	0.0516	0.0632
Oxaliplatin	0.0119	0.0310	0.0441	0.0511	0.0551	0.0721	0.0736	0.0875
DACH RR(II)	0.0293	0.0479	0.0608	0.0681	0.0729	0.0905	0.0920	0.1076
Cis-[$PtCl_2(C_6H_{11}NH_2)_2$]	0.0299	0.0488	0.0619	0.0693	0.0743	0.0921	0.0937	0.1097
Cis-[$PtCl_2(iPentNH_2)_2$]	0.0362	0.0549	0.0678	0.0752	0.0805	0.0984	0.1000	0.1165
Carboplatin	0.0550	0.0728	0.0853	0.0928	0.0989	0.1169	0.1186	0.1364
Cis-[$Pt(II)Cl_2(iPrNH_2)_2$	0.0649	0.0822	0.0946	0.1021	0.1087	0.1267	0.1285	0.1470
Transplatin	0.1245	0.1390	0.1500	0.1575	0.1665	0.1845	0.1863	0.2079
CHIP-IV	0.1777	0.1923	0.2039	0.2128	0.2259	0.2476	0.2499	0.2802
JM518	0.1846	0.2005	0.2133	0.2232	0.2386	0.2631	0.2658	0.3018
JM216	0.2352	0.2485	0.2600	0.2698	0.2868	0.3109	0.3137	0.3515
Tetraplatin	0.2410	0.2640	0.2755	0.2855	0.3037	0.3286	0.3314	0.3715
Guanine	0.0637	0.0465	0.0346	0.0279	0.0232	0.0071	0.0056	0.0088

While in a particular row the number in a box represents the ΔN value for the interaction between the corresponding cisplatin analogue and the protecting agent the values in the last row are for interaction between guanine (i.e., the biomolecule here) and the corresponding protecting agent

Table 9 The values of the negative energy component, $\Delta E_{A(B)}$ (in kcal mol^{-1}), for different combinations of cisplatin analogues (considered as A) and protecting agents (considered as B)

Protecting agents / Cisplatin analogues	D-penicillamine	Thiourea	STS	WR-1065	S-thioazole	Na-diOH	NaDDTC	Mesna
Nedaplatin	0.58	-0.94	-1.93	-2.44	-2.65	-3.84	-3.93	-4.78
Oxaliplatin	-0.99	-2.53	-3.56	-4.12	-4.42	-5.73	-5.84	-6.89
DACH RR(II)	-2.50	-4.04	-5.09	-5.67	-6.06	-7.43	-7.56	-8.56
Cis-[$PtCl_2(C_6H_{11}NH_2)_2$]	-2.55	-4.12	-5.81	-5.78	-6.18	-7.57	-7.70	-8.94
Cis-[$PtCl_2(iPentNH_2)_2$]	-3.12	-4.68	-5.75	-6.35	-6.78	-8.19	-8.32	-9.60
Carboplatin	-4.92	-6.44	-7.49	-8.11	-8.63	-10.08	-10.22	-11.63
Cis-[$Pt(II)Cl_2(iPrNH_2)_2$	-5.90	-7.14	-8.46	-9.09	-9.65	-11.13	-11.27	-12.76
Transplatin	-12.64	-14.00	-15.00	-15.70	-16.49	-18.08	-18.24	-20.09
CHIP-IV	-19.26	-20.65	-21.85	-22.70	-23.98	-26.03	-26.24	-29.03
JM518	-19.85	-21.44	-22.73	-23.69	-25.18	-27.55	-27.80	-31.17
JM216	-27.38	-28.80	-30.00	-31.00	-32.76	-35.20	-35.47	-39.18
Tetraplatin	-29.76	-31.20	-32.38	-33.40	-35.34	-37.90	-38.18	-42.19
Guanine	-5.14	-3.71	-3.50	-2.19	-1.82	-0.55	-0.43	-0.67

While in a particular row the number in a box represents the $\Delta E_{A(B)}$ value for the interaction between the corresponding cisplatin analogue and the protecting agent the values in the last row are for interaction between guanine (i.e., the biomolecule here) and the corresponding protecting agent

To predict the most suitable protecting agent for a cisplatin drug it is also necessary to focus on the extent of interaction between protecting agent and active biomolecules. The numbers in the last row of Table 6 represent the differences in global electrophilicity values (i.e., Δw) between the corresponding protecting agent (behaving as an acceptor) and the nucleobase guanine (behaving as donor). An effective protecting agent should have low strength of interaction with biomolecules. Otherwise, higher degree of interaction between a protecting agent and biomolecules results in a significant decrease in the activity of that particular protecting agent. An ideal protecting agent should sustain its activity to inhibit the toxic side-effect of cisplatin analogues. Simply, we can argue that a protecting agent is said to be more capable of modulating the activity of drugs if the Δw values in each box of Table 6 is larger (and positive) than the ones in the corresponding boxes in the last row of Table 6.

The general observation from Table 6 and Fig. 4 is that as we move towards right the values of Δw in each row go on increasing while the ones in the last row go on decreasing and thus indicating higher efficiency of the protecting agents in the same direction. Also, the most common observation about Δw values presented in Table 6

Table 10 The values of the overall stabilization energy, $\Delta E_{SE(AB)}$ (in kcal mol^{-1}) for different combinations of cisplatin analogues (considered as A) and the protecting agents (considered as B)

Protecting agents / Cisplatin analogues	D-penicillamine	Thiourea	STS	WR-1065	S-thioazole	Na-diOH	NaDDTC	Mesna
Nedaplatin	-0.01	-0.02	-0.07	-0.11	-0.12	-0.26	-0.27	-0.38
Oxaliplatin	-0.02	-0.103	-0.21	-0.28	-0.31	-0.52	-0.54	-0.70
DACH RR(II)	-0.10	-0.25	-0.40	-0.50	-0.54	-0.81	-0.84	-1.05
Cis-[$PtCl_2(C_6H_{11}NH_2)_2$]	-0.09	-0.25	-0.41	-0.51	-0.55	-0.83	-0.86	-1.08
Cis-[$PtCl_2(iPentNH_2)_2$]	-0.14	-0.32	-0.49	-0.60	-0.65	-0.95	-0.98	-1.22
Carboplatin	-0.32	-0.57	-0.80	-0.93	-1.01	-1.37	-1.40	-1.71
Cis-[Pt(II)$Cl_2(iPrNH_2)_2$	-0.45	-0.74	-0.98	-1.14	-1.22	-1.62	-1.66	-2.00
Transplatin	-1.76	-2.26	-2.65	-2.90	-3.08	-3.70	-3.76	-4.34
CHIP-IV	-3.21	-3.78	-4.41	-4.70	-5.07	-5.94	-6.03	-6.95
JM518	-3.26	-3.80	-4.42	-4.71	-5.06	-5.99	-6.09	-7.12
JM216	-5.40	-6.22	-6.89	-7.34	-7.84	-8.98	-9.09	-10.44
Tetraplatin	-6.07	-6.94	-7.64	-8.13	-8.68	-9.90	-10.03	-11.50
Guanine	-0.95	-0.77	-0.61	-0.50	-0.46	-0.18	-0.15	-0.06

While in a particular row the number in a box represents the $\Delta E_{SE(AB)}$ value for the interaction between the corresponding cisplatin analogue and the protecting agent the values in the last row are for interaction between guanine (i.e., the biomolecule here) and the corresponding protecting agent

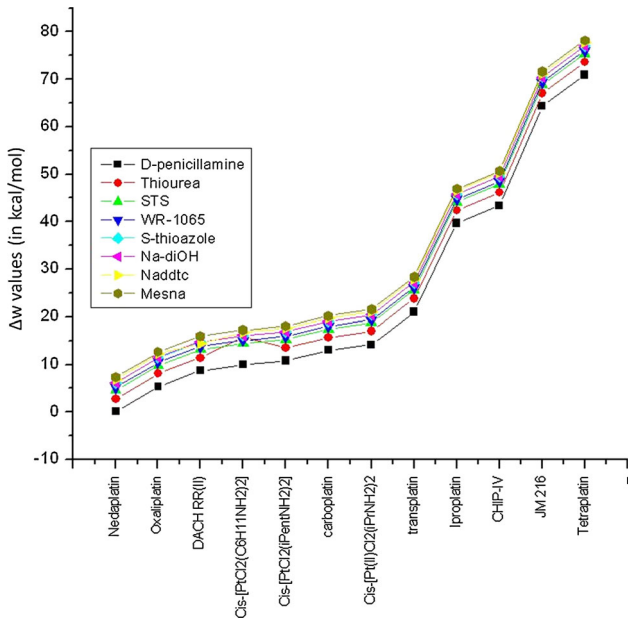


Fig. 4 Graphical representation of the difference of global electrophilicity (Δw) values for different combinations of cisplatin analogues and protecting agents

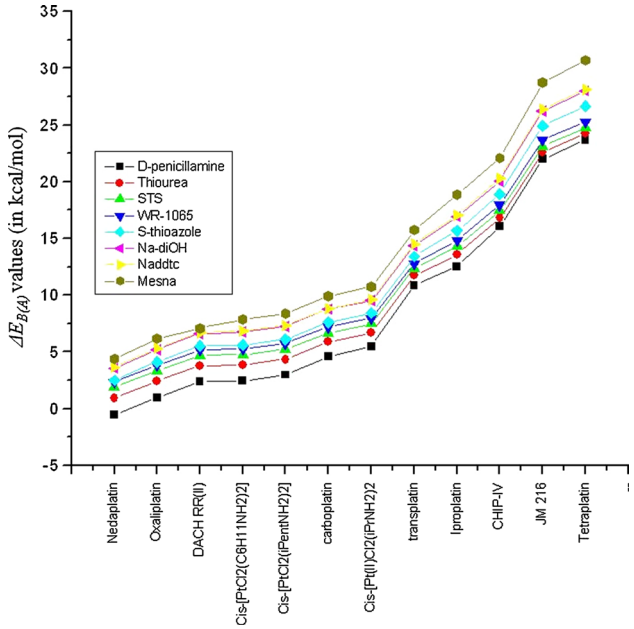


Fig. 5 Graphical representation of the values of positive energy component ($\Delta E_{B(A)}$) for different combinations of cisplatin analogues and protecting agents

is that strong sulfur nucleophiles such as NaDDTC (sodium diethyldithiocarbamate) and Mesna (sodium 2-mercaptoethanesulfonate) show significantly higher rate of interaction with all the cisplatin analogues. Thus considering the Δw values generated from the interaction between cisplatin drugs and nucleobases (in Tables 1, 2, 3, 4) and the Δw values generated from interaction between cisplatin drugs and protecting agents as well as protecting agents and the biomolecule (here guanine) a prescription can be made for choosing a suitable protecting agent against a particular drug. As one moves down the Tables 1, 2, 3 and 4 (or Table 6) to use a cisplatin drug he has to move towards the right of Table 6 to choose the suitable protecting agent. Some earlier reported studies (Table 5) also agree to the just proposed prescription. Boelrijk et al. [30] extensively studied the action of Sodium diethyldithiocarbamate

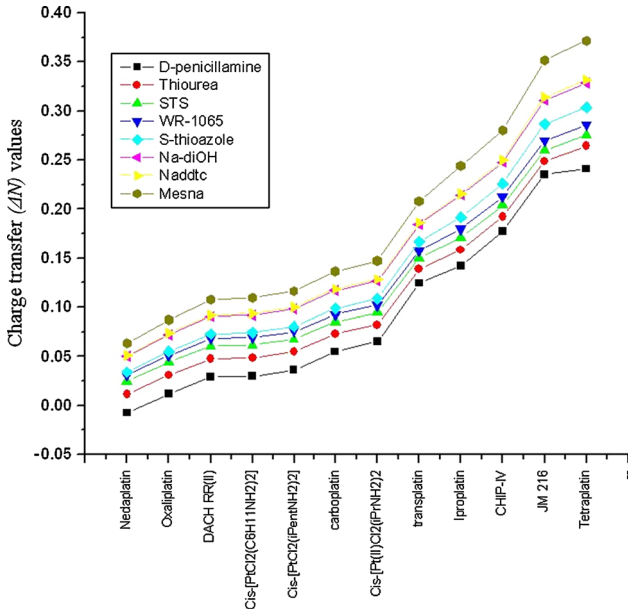


Fig. 6 Graphical representation of the charge transfer (ΔN) values for different combinations of cisplatin analogues and rescue agents

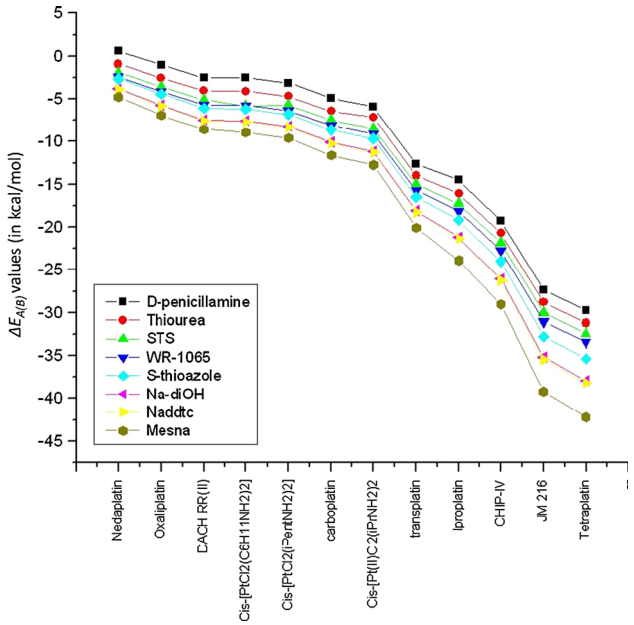


Fig. 7 Graphical representation of the values of negative energy component ($\Delta E_{A(B)}$) (in kcal mol^{-1}) for different combinations of cisplatin analogues and rescue agents

(NaDDTC), thiourea and sodium thiosulfate (STS) as promising protecting agents against cisplatin drug. They have concluded that the protecting agents NaDDTC and thiourea are capable of breaking the Pt-methionine type binding, whereas, the protecting agent STS is able only to inhibit the nephrotoxicity by inactivating unbound Pt compounds in the cell. Thus, the study by Boelrijk et al.

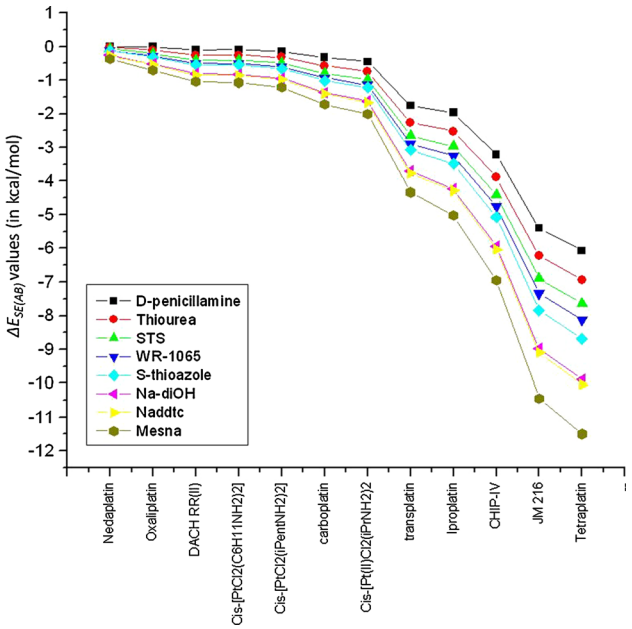


Fig. 8 Graphical representation of the values of overall stabilization energy ($\Delta E_{SE(AB))}$ (in kcal mol^{-1}) for different combinations of cisplatin analogues and rescue agents

suggests NaDDTC to be the most effective protecting agent against Pt-compounds. The mode of interaction of different sulfur-containing biologic and nonbilogic nucleophiles with cisplatin drugs was explored by Dedon et al. [32]. Their experimental study suggest a relatively more favorable interaction between cisplatin drugs and diethyldithiocarbamate (DDTC) compared to that of the cisplatin drugs and thiosulfate. The potential application of amifostine (Ethyol^{R}; WR 2721) and its main metabolites (WR 1065) as an effective chemoprotective agent was explored by Korst et al. [26]. The experimental findings by Korst et al. reveals short initial half-life of WR-1065. A suitable explanation for this observation is the process of faster uptake of WR-1065 in cellular environment and the formation of disulphides. The relatively high affinity of moderately active protecting agent WR 1065 towards active biomolecules suggests that it will be a suitable protecting agent against moderately active cisplatin analogues (i.e., the ones near the midway of Table 6 while moving from top to bottom). It is encouraging to notice that the CDASE scheme based Δw values also predict the same.

Relative strength of interaction between cisplatin analogues and protecting agents on the basis of positive energy components, i.e., $\Delta E_{B(A)}$

From section "Theoretical background" (i.e., Theoretical Background) $\Delta E_{B(A)}$ is expected to be a positive quantity. Earlier $\Delta E_{B(A)}$ was correlated to the kinetic aspect (i.e.,

rate) of a reactive interaction [83–87]. Thus, higher the value of $\Delta E_{B(A)}$ higher should be the rate of interaction between the cisplatin analogue and the protecting agent.

The $\Delta E_{B(A)}$ values for 96 pairs of cisplatin analogues and protecting agents (12 cisplatin analogues and 8 protecting agents) are presented in Table 7 and Fig. 5. Each box in Table 7 carries the $\Delta E_{B(A)}$ value for the interaction between the corresponding cisplatin analogue and the protecting agent. Analysis of these values of $\Delta E_{B(A)}$ reveals a periodic variation in the trends of kinetically favorable interaction for different combinations of cisplatin analogues and protecting agents. As one moves along Table 7 (or Fig. 4) from left to right the interaction between cisplatin analogues and protecting agents seems to be more and more kinetically favorable and that is obvious from the gradual increase in the $\Delta E_{B(A)}$ values in each successive box. The similar trend of $\Delta E_{B(A)}$ values (for interaction between cisplatin analogues and protecting agents) has been observed if someone is moving from lower to higher ordinates in Fig. 4. On the other hand the $\Delta E_{B(A)}$ values in the boxes of the last row are decreasing as one moves from left to right. Thus, the interaction between protecting agents and the active biomolecule gradually decreases as we go from left to right along the Table 7. So, it is logical to define an effective protecting agent from the higher value of $\Delta E_{B(A)}$ for the interaction between a drug and a protecting agent with a much smaller value of $\Delta E_{B(A)}$ for the interaction between a protecting agent and a biomolecule (i.e., values in each box of the last row of Table 7).

An extensive study by Treskes et al. [24] provide worthy evidence regarding the change in reversibility of binding interaction between cisplatin drugs and proteins with the variation in applied protecting agents. Eventually, a reasonable correlation can be obtained for the experimental observations made by Treskes et al. [24] and the calculated CDASE scheme based $\Delta E_{B(A)}$ values.

Experimental observation		Theoretical $\Delta E_{B(A)}$ values (in kcal mol^{-1})	
Protecting agent	Drug-protein reversal activity (experimental rate constant)	For interaction between drug and protecting agent	For interaction between protecting agent and biomolecule
WR1065	$k_2 = 0.142$ M^{-1} s^{-1} (slow)	5.17	1.69
DDTC	$k_2 = 3.66$ M^{-1} s^{-1} (fast)	6.72	0.28

The outcome of the experimental study by Treskes et al. [24] establish a comparatively slow rate for the drug-protein reversal activity in presence of protecting agent WR-1065 [*S*-2-(3-(aminopropyl)amino)ethyl-phosphorothioic acid] (rate constant $k_2 = 0.142$ M^{-1} s^{-1}) in comparison to the reversal ability of the same reaction by DDTC (rate constant $k_2 = 3.66$ M^{-1} s^{-1}). It is possible to offer a logical explanation for the kinetic preference of DDTC over WR-1065 to revert the drug-protein interaction using the corresponding $\Delta E_{B(A)}$ values. Here, the calculated value of $\Delta E_{B(A)}$ for the combination of cisplatin analogue DACH RR (II) [dichloro(1,2-diaminocyclohexane)platinum(II) RR isomer] and protecting agent WR-1065 is found to be 5.17 kcal mol^{-1}. The $\Delta E_{B(A)}$ value for the interaction between WR-1065 and guanine is 1.69 kcal mol^{-1}. Similarly, for the combination of the protecting agent DDTC, cisplatin analogue DACH RR (II) and the biomolecule guanine the $\Delta E_{B(A)}$ values are 6.72 and 0.28 kcal mol^{-1}, respectively. These results clearly indicate that the interaction of WR-1065 with guanine is stronger than that between DDTC and guanine and so the ability of WR-1065 to revert the drug-protein interaction to an effective drug-protecting agent interaction is lower than the same by DDTC. So, as argued earlier ("Relative strength of interaction between cisplatin analogues and protecting agents on the basis of the difference in global electrophilicity values i.e., Δw" section) a significant amount of activity of DDTC is retained after interaction with biomolecules and it can more efficiently reverse the drug-protein interaction into an active drug-protecting agent interaction.

Relative stability of the adducts formed between cisplatin analogues and protecting agents on the basis of electron transfer values i.e., ΔN

In the present study cisplatin analogues are considered as electron acceptors (i.e., A) and protecting agents as electron donors (i.e., *B*). The logic behind this consideration is that cisplatin analogues, having electropositive metal center (i.e., Pt metal with vacant d-orbitals), can better act as an electron acceptors and the protecting agents having the lone pair of electrons on the sulfur atom behave as electron donors. From Eq. 3 in section "Theoretical background", the charge transfer component ΔN will be positive when $\mu_B^o \rangle \mu_A^o$ (or $\chi_A^o > \chi_B^o$). This also supports our consideration about donor and acceptor systems (i.e., chemical potential values of protecting agents will be higher than those of cisplatin analogues). Thus, for a favorable interaction process, electrons will be transferred from donor to acceptor until an equilibrium has been established (i.e., $\mu_B \approx \mu_A$ or $\chi_B \approx \chi_A$).

The process of electron transfer plays a vital role in chemical interactions. As discussed before, a larger amount of electron exchange between the interacting donor and

acceptor system demonstrates a higher extent of stabilization of the resultant adduct. So, it can be argued that a higher value of ΔN is the indication of a thermodynamically favorable interaction between that particular pair of cisplatin analogue and protecting agent. Table 8 (and Fig. 6) represent the charge transfer (i.e., ΔN) values for all the possible combinations of cisplatin analogues (considered as acceptor A) and protecting agents (considered as donor B) included in the present study. Each box in Table 8 contains charge transfer value for the interaction between cisplatin analogue and the protecting agent. The values in the last row are for interaction between the biomolecule (guanine) and the corresponding protecting agent.

The periodic changes in color intensity of Table 8 indicate the extent of charge transfer interaction between different cisplatin analogues and protecting agents. Thus, higher the color intensity greater will be the amount of charge transfer that results to a more thermodynamically favorable interaction between the drug and the protecting agent. The exceptional case of negative value of charge transfer (ΔN) in the combination of *cis*-diammine-glycolloato-*O*,*O*-platinum(II), Nedaplatin and D-penicillamine only shows that electron transfer is taking place in the reverse direction. The qualitative interpretation for this kind of observation is that such interactions will be no longer a thermodynamically favorable process.

Here also the logic to choose a suitable protecting agent against a particular cisplatin analogue is similar to that outlined in section "Relative strength of interaction between cisplatin analogues and protecting agents on the basis of the difference in global electrophilicity values i.e., Δw". It can be easily noticed that as one moves down the Table 8 to select a cisplatin analogue the suitable protecting agents will be more and more right side of the Table.

Relative stability of the adducts formed between cisplatin analogues and protecting agents on the basis of negative energy components, i.e., $\Delta E_{A(B)}$

Values of $\Delta E_{A(B)}$ generated from CDASE scheme are presented in Table 9 and the relative trends of these values are shown graphically in Fig. 7. In section "Theoretical Background" it is already discussed that $\Delta E_{A(B)}$ is the negative energy component of the overall stabilization energy. As it is an energy lowering term it can be correlated to the thermodynamic stability of the adduct formed. Mathematically $\Delta E_{A(B)}$ can be expressed as,

$$\left|\Delta E_{A(B)}\right| = \left|\Delta E_{B(A)}\right| + \left|\Delta E_{SE(AB)}\right| \quad (10)$$

Thus, it can be argued that larger the negative value of $\Delta E_{A(B)}$ higher will be the interaction between that particular pair of cisplatin analogue and protecting agent, causing higher stability of the resultant adduct. The gradual change in the color intensity from light to a highly intense one represents the increasing stability of adducts formed between the cisplatin analogues and protecting agents. Interestingly, the observed trend for $\Delta E_{A(B)}$ values on the basis of the color code of Table 9 appeared to be exactly similar to that of $\Delta E_{B(A)}$ values presented in Table 7, indicating identical trend of interaction from both kinetic and thermodynamic point of view.

It is to be noted here that similar to Tables 6, 7 and 8, in Table 9 also the $\Delta E_{A(B)}$ values are reported for two different types of interactions. All the $\Delta E_{A(B)}$ values (except the last row) of these tables represent the interaction between cisplatin analogue and protecting agent. The last row represents the $\Delta E_{A(B)}$ values for the interaction between the protecting agent and the active biomolecule (i.e., guanine).

The observed values of $\Delta E_{A(B)}$ for the drug Tetraplatin are significantly high against all protecting agents chosen in the present study. This means that interaction of all the protecting agents with Tetraplatin is highly favorable thermodynamically when compared to other cisplatin analogues. An ideal protecting agent must have highly negative $\Delta E_{A(B)}$ value for the interaction with the drug along with a low negative value of $\Delta E_{A(B)}$ for the interaction with the bio-molecule. Then only the protecting agent can form a more stable adduct (i.e., thermodynamically favorable) with the cisplatin analogues than that with active biomolecules. It is to be noted here that when it comes to the choice of protecting agents prescription here will also be similar to those made on the basis of Tables 6, 7 and 8.

Relative stability of the adducts formed between cisplatin analogues and protecting agents on the basis of the overall stabilization energy, (i.e., $\Delta E_{SE(AB)}$) values

The overall stabilization energy, $\Delta E_{SE(AB)}$, is an indicator of the overall stability of the adduct formed in a particular interaction. The more negative is the value of $\Delta E_{SE(AB)}$ higher will be the stability of the adduct formed in the course of an interaction. The $\Delta E_{SE(AB)}$ values are shown in Table 10 and the relative trends are demonstrated in Fig. 8.

In Table 10 the interaction energies between the drugs and the protecting agents are presented in different rows, whereas the stabilities of the adducts formed between the protecting agents and the biomolecule are presented in the last row. A trend of increasing relative stability for the adducts formed between cisplatin drugs and protecting agents is observed as one moves along the Table 10 from left to right as well as from top to bottom. This is more obvious from Fig. 7. The color intensity changes (from a lighter zone to a more intense one) according to the variation of adduct stability.

One important outcome of the analysis of the stabilization energy values is that none of the protecting agents is able to produce reasonably large amount of $\Delta E_{SE(AB)}$. Most of the values are in between the range of −0.5 to −10 kcal mol^{-1}. The physical interpretation is that these types of interactions are not stable enough to sustain for a long period. This is what it should be if these chemical systems qualify as rescue agents because they are used only to eliminate the higher probability of interaction of cisplatin analogues with sulfur donors in protein chain. And this unwanted interaction is the origin for the toxic side-effects of cisplatin drugs. The data in the present study also support the argument that these rescue agents produce some weak interactions with the drugs so that the activity of drugs reduces to a certain extent. Consequently, a protecting agent does not hinder the antitumor activity of a cisplatin drug. The relevance of the $\Delta E_{SE(AB)}$ values generated by CDASE scheme is also supported by the experimental observations [104–108].

Synchronization of the data generated by different reactivity parameters and use of the strategy proposed in section "Results and discussion"

The ongoing discussion in the last three sub-sections helps to understand the action of different protecting agents to minimize the toxic side-effects of cisplatin analogues. Here, one needs to focus on three types of possible interactions. These are interaction

(i) of a particular cisplatin drug with genomic DNA.
(ii) between rescue agent and that particular drug.
(iii) of rescue agent with active biomolecules.

To determine the most suitable protecting agent against a particular cisplatin analogue a systematic correlation among the above three interactions is warranted for.

The study on the strength of relative interaction between cisplatin analogues and nucleobases ascertain the difference in their ability to interact. We can justify our terminology for 'strong' and 'weak' cisplatin drugs on the basis of the data presented in Tables 1, 2, 3 and 4. The relevance of the interpretation of this information in defining a specific protecting agent for a particular cisplatin analogue will be clear if it is explained with examples. In Tables 1, 2, 3 and 4 the values of both kinetic [Δw, $\Delta E_{B(A)}$] and thermodynamic [ΔN, $\Delta E_{A(B)}$, $\Delta E_{SE(AB)}$] descriptors predict that interaction of Carboplatin with adenine and guanine is moderate (as these values are in the middle of Tables 1, 2, 3 and 4 and the strength of interaction increases as someone moves towards bottom from top). Thus, the theoretical calculation predicts moderate tumor inhibition activity of Carboplatin. So, if a highly active rescue agent (ranking of the rescue agents in terms of strength of their interaction with cisplatin analogues is discussed in different sub-sections of section "Relative strength of interaction of protecting agents with cisplatin analogues as well as active biomolecules"), such as NaDDTC, is selected in cancer therapy with Carboplatin as anti-cancer drug it will probably reduce the anti-tumor activity of Carboplatin to a large extent. As a result, Carboplatin might lose its activity toward cancer cells in the presence of protecting agent NaDDTC. To avoid this, chemotherapeutic application of Carboplatin should be accompanied by a moderately active protecting agent such as D-penicillamine or WR-1065, which will result in a minor decrease of the activity of Carboplatin. Again, as per the values of the reactivity descriptors, amminediacetatodichloro(cyclohexylamine)platinium(IV), JM-216 shows significantly high interaction with nucleobases (Tables 1, 2, 3, 4). So, in case of a treatment with JM-216 we can go for a rescue agent with higher activity so that it can effectively modulate the undesirable protein binding affinity of the drug. Some earlier reported experimental and theoretical studies, as summarized in Table 5 and described in different sections of "Relative strength of interaction of protecting agents with cisplatin analogues as well as active biomolecules", also support the above claim.

Conclusions

Basically, selection of a protecting agent that could be the potential modulator for a specific cisplatin analogue depends on three critical factors. The first one is how strongly a particular drug interacts with nucleobases (guanine N-7 position is the most active site) of DNA. The second one is the activity of that particular drug towards that protecting agent. The third factor is how strongly the protecting agent interacts with other biomolecules. All these three factors complement each other in the process of deciding the most effective combination of drugs and protecting agents in cancer therapy. The present study uses the density functional theory based reactivity descriptors in framing up a qualitative strategy to aid such a selection process.

It is encouraging to note that the trend of Δw values (i.e., difference of global electrophilicity values between cisplatin analogues and rescue agents, Table 6) generated by this scheme is quite similar to the experimental trend of activity observed by Boelrijk et al. [30]. Also, the findings by Elferink et al. [31] on the rate of interaction of cisplatin analogues with the protecting agent STS is also correlated well with our CDASE scheme based results. The stronger interaction between cisplatin drugs with protecting agent diethyldithiocarbamate (DDTC) as compared to that with thiosulfate compound was experimentally explored by

Dedon et al. [32]. This experimental observation is correlated well with our reported CDASE scheme based theoretical findings in the present study ["Relative strength of interaction between cisplatin analogues and protecting agents on the basis of the difference in global electrophilicity values i.e., Δw" section]. An extensive experimental study by Korst et al. [26] strongly supports the CDASE scheme based prediction on WR-1065 as a moderately active chemoprotective agent. Relatively higher degree of interactions between WR-1065 with active biomolecules, to some extent, inhibits the chemoprotective activity of WR-1065. Treskes et al. [24] experimentally analyzed the reversal of drug-protein binding interaction to an effective drug-DNA interaction in presence of two different protecting agents WR-1065 and DDTC. The CDASE scheme based positive energy component ($\Delta E_{B(A)}$) values are able to provide a logical explanation for the kinetic aspect (experimentally obtained rate constant values) of these interactions (as discussed in "Relative strength of interaction between cisplatin analogues and protecting agents on the basis of positive energy components, i.e., $\Delta E_{B(A)}$" section). Analysis of different reactivity descriptor values from Tables 6, 7, 8, 9 and 10 prescribes that as one moves down these Tables to select a drug he has to move more and more right in these tables to select the corresponding protecting agent.

Understanding of the interaction behavior of cisplatin analogues with protecting agents using density functional reactivity theory (DFRT) based descriptors through the CDASE-scheme is an ongoing initiative in the research group of the authors to develop an alternative and computationally cost-effective approach to explore interesting biological phenomena. To the best of author's knowledge, the present one may be the very first theoretical attempt in this direction as there is no such study reported in the literature to understand the interaction of cisplatin analogues with various protecting agents using DFRT based descriptors. The explicit interaction protocol for cisplatin analogues and protecting agents will hopefully lay the foundation for an extensive theoretical as well as experimental research work to verify all the emerging aspects of the present study.

The authors are more hopeful because the qualitative prediction made here are based on the direction of electron transfer which is generated from different energy based parameters (i.e., $\Delta E_{A(B)}$ and $\Delta E_{B(A)}$). High sensitivity of reactivity descriptors generated from electronic population is well documented in the literature.

Finally, there is increasing evidence that systematic analysis of the data generated from ab initio quantum chemistry based simulation is an important tool in the field of discovery and development of new anti-cancer drugs [104]. Rapid advancement in the computational power along with some sophisticated software programs makes it possible to outplay the primary limitations in the accuracy of theoretical chemistry based approaches. Multidisciplinary research applications like the combination of quantum chemistry, computer programming and clever modeling techniques constantly endeavor to reduce the possibility of unsuccessful attempts in different phases of clinical trials for a newly developed drug. The present study may be perceived as an attempt to develop a computationally cost-effective and reliable theoretical technique in this direction.

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