



**Original Research Article**

## **Fullerene (C<sub>20</sub>) as a Nanocarrier for the Drug delivery of Dacarbazine: DFT Studies**

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### **ABSTRACT**

Upon conducting an investigation, the functionality of the smallest fullerene (C<sub>20</sub>) as a nano-carrier for the dacarbazine anticancer drug was thoroughly examined using density functional theory simulations. The adsorption energies obtained from the simulations indicate that the interaction of dacarbazine with C<sub>20</sub> is indeed feasible under experimental conditions. Furthermore, the Natural Bond Orbital (NBO) analysis revealed that no chemical bond is formed between dacarbazine and the nanostructure, indicating that the interaction is purely a result of physisorption. Additionally, the results from the frontier molecular orbital analysis demonstrated a significant decrease in the bandgap of the fullerene by 44.469% to 4.967 eV. This reduction in bandgap suggests that C<sub>20</sub> has the potential to serve as an ideal nanocarrier for the delivery of dacarbazine. Moreover, the values obtained for the dipole moment and chemical hardness further support the suitability of C<sub>20</sub> as a nano-carrier for the delivery of dacarbazine. In conclusion, the findings from the density functional theory simulations provide compelling evidence for the potential use of C<sub>20</sub> as an effective nano-carrier for the delivery of the dacarbazine anticancer drug. These results pave the way for further exploration and development of C<sub>20</sub>-based nanomaterials for drug delivery applications.

**Keywords:** Dacarbazine, Density functional theory, Adsorption, Nanocarrier, Drug delivery

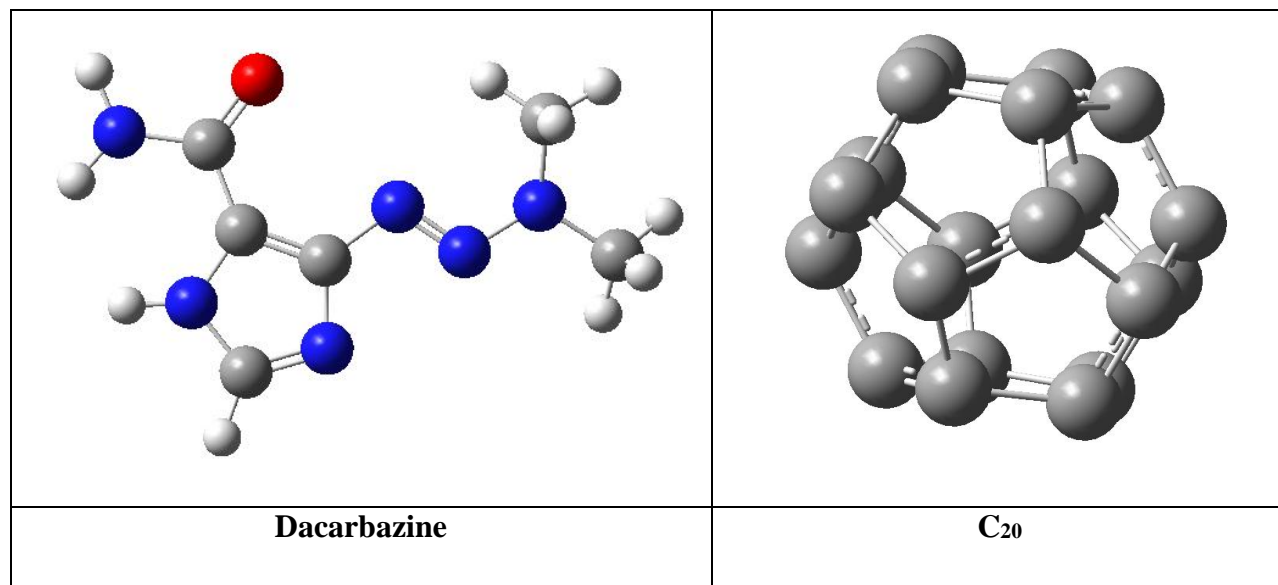
## Introduction

Dacarbazine (Fig. 1) is an anticancer drug that is commonly used in the treatment of various types of cancer, including melanoma, Hodgkin's lymphoma, and soft tissue sarcoma. It belongs to a class of medications known as alkylating agents, which work by interfering with the DNA synthesis of cancer cells, ultimately leading to their destruction [1]. While Dacarbazine has shown to be effective in treating cancer, it also comes with a range of potential side effects that patients and healthcare providers should be aware of. Some of the most common side effects of Dacarbazine include nausea, vomiting, loss of appetite, and temporary hair loss [2]. These side effects are often manageable and tend to improve once the treatment is completed. In addition to these common side effects, Dacarbazine can also cause more serious adverse reactions that require immediate medical attention [3]. These may include severe allergic reactions, such as difficulty breathing, swelling of the face, lips, or tongue, as well as symptoms of infection such as fever, chills, or persistent sore throat [4]. Patients may also experience unusual bruising or bleeding, severe stomach or abdominal pain, and yellowing of the eyes or skin, which could indicate liver problems [5]. It is important for patients receiving Dacarbazine to be closely monitored by their healthcare providers for any signs of these serious side effects. In some cases, the dosage of the medication may need to be adjusted or the treatment may need to be discontinued altogether if the side effects become too severe [6]. Patients should also be aware that Dacarbazine can have long-term effects on the body, including an increased risk of developing other types of cancer later in life [7]. It is important for patients to discuss these potential risks with their healthcare providers and to undergo regular screenings for other types of cancer following treatment with Dacarbazine [8]. Drug delivery systems play a crucial role in the field of medicine, allowing for targeted and controlled release of pharmaceutical compounds within the body [9]. Nanostructures, particularly nanoparticles, have emerged as promising candidates for drug delivery due to their unique properties and potential applications [10]. These nanostructures, with sizes ranging from 1 to 100 nanometers, offer advantages such as high surface area to volume ratio, tunable surface properties, and the ability to encapsulate a variety of drugs [11]. One of the key advantages of utilizing nanostructures for drug delivery is their ability to overcome biological barriers and deliver drugs to specific target sites within the body [12]. For instance, nanoparticles can be engineered to bypass the blood-brain barrier, allowing for the treatment of neurological disorders that were previously difficult to target [13]. Additionally,

nanostructures can be designed to selectively accumulate in tumor tissues through the enhanced permeability and retention effect, offering a promising approach for cancer therapy [14]. Furthermore, nanostructures can be functionalized with targeting ligands to enhance their specificity towards diseased tissues or cells. This targeted drug delivery approach minimizes off-target effects and reduces systemic toxicity, thereby improving the therapeutic index of the administered drugs [15]. Moreover, nanostructures can be designed to respond to specific stimuli, such as changes in pH or temperature, enabling controlled release of drugs at the desired location within the body. In addition to their role in improving drug delivery, nanostructures also offer opportunities for personalized medicine [16]. By tailoring the properties of nanostructures based on individual patient characteristics, it is possible to optimize drug efficacy and minimize adverse effects. This personalized approach holds great promise for the treatment of various diseases, including cancer, cardiovascular disorders, and infectious diseases [17]. Despite their potential benefits, the development of nanostructure-based drug delivery systems also presents challenges. These include concerns regarding the biocompatibility and long-term safety of nanostructures, as well as the scalability and reproducibility of manufacturing processes. Addressing these challenges requires interdisciplinary collaboration among scientists, engineers, and clinicians to ensure the translation of nanostructure-based drug delivery systems from bench to bedside [18]. In conclusion, nanostructures have emerged as promising tools for drug delivery, offering opportunities to enhance therapeutic outcomes and minimize adverse effects. Their unique properties and potential for targeted drug delivery make them attractive candidates for addressing unmet medical needs [19]. Continued research and development in this field hold the potential to revolutionize the way drugs are delivered and personalized medicine is practiced.

[14]. Fullerene ( $C_{20}$ , Fig. 1), the smallest nanomaterial with a dodecahedral cage structure, possesses unique characteristics that make it an excellent candidate as both a sensing material and nanocarrier [15-17]. Its highly curved structure consists of pentagonal rings and offers high conductance, a large surface area-to-volume ratio, and exceptional reactivity [18-20]. Therefore, this study aims to evaluate the performance of  $C_{20}$  as a nanocarrier for the delivery of Dacarbazine through density functional theory simulations. By exploring the potential of  $C_{20}$  in drug delivery and sensing applications, we hope to contribute to the development of more effective and efficient therapies while minimizing unwanted side effects. In conclusion, the utilization of nanocarriers holds great promise in improving drug delivery systems. Through the

evaluation of  $C_{20}$  as a potential nanocarrier, this study aims to advance our understanding of these applications and pave the way for future advancements in pharmaceutical research.



**Figure 1.** The optimized structures of Dacarbazine and  $C_{20}$

### Computational Methods

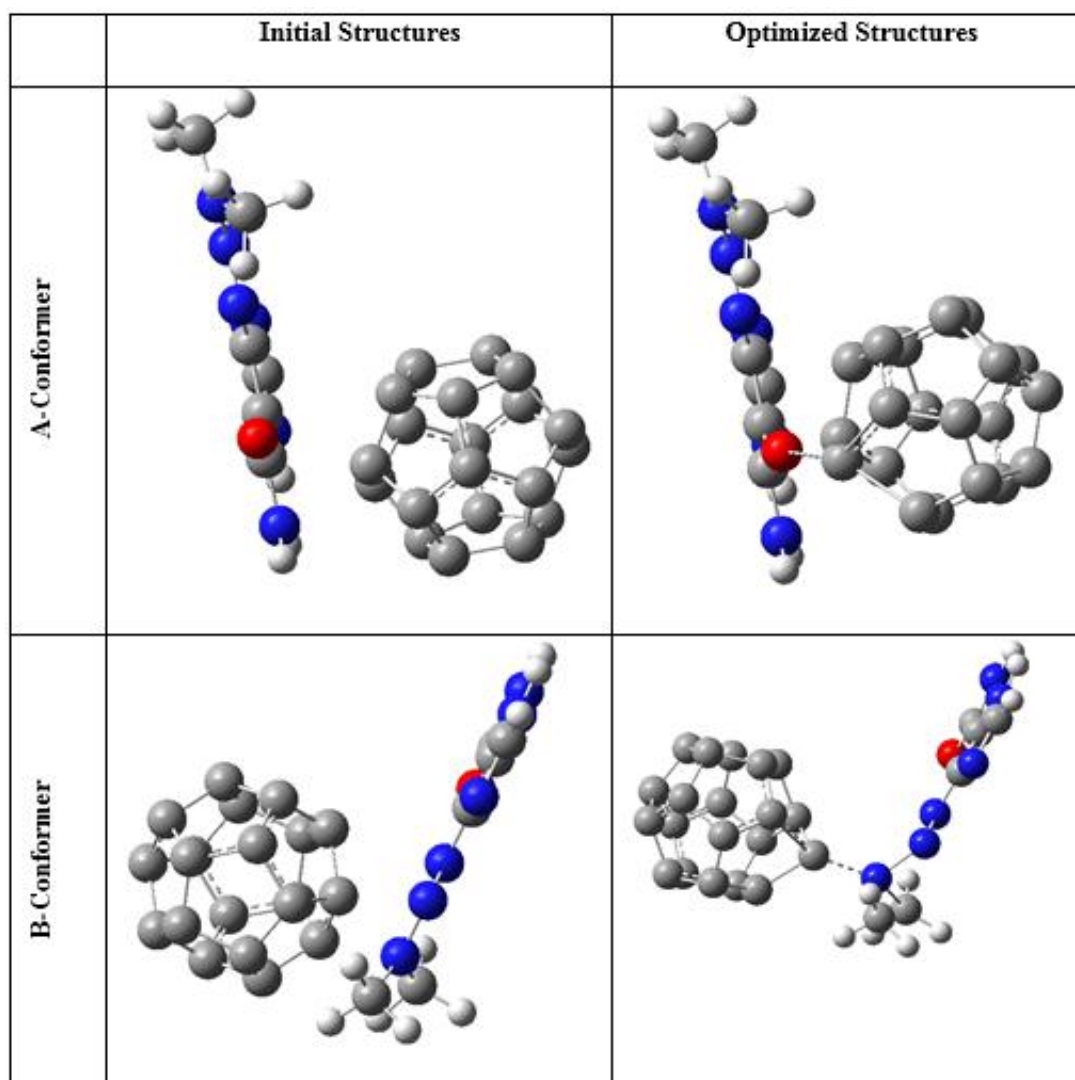
The structures of  $C_{20}$ , Dacarbazine, and their complexes were created using GaussView 6 [21] and Nanotube Modeler 1.3.0.3 [22]. The calculations were performed with the density functional theory (DFT) method in Gaussian 16 [23] software at the B3LYP/6-31G (d) level of theory [23]. The parameters were determined following a method outlined in [20].

### Results and Discussion

#### Structural Analysis

The investigation of the interaction between Dacarbazine and  $C_{20}$  was conducted to determine the most stable conformer. Two different configurations, A-Conformer and B-Conformer, were studied. In A-Conformer, the drug approached  $C_{20}$  through its ring, while in B-Conformer, the nanostructure was located near the aliphatic chain of the drug molecule. The optimized structures

showed no significant structural deformations, indicating that no chemical bonds were formed between the adsorbate and adsorbent molecules [15]. Table 1 presents the calculated total electronic energies and adsorption energies. The total electronic energies for B-Conformer were more negative than those for A-Conformer in both vacuum and aqueous phases, indicating that the formation of B-Conformer was more energetically favorable [16]. The negative adsorption energies suggest that the interaction between Dacarbazine and  $C_{20}$  is experimentally possible in both phases. In addition to geometric optimizations, IR calculations were performed on the structures, and no negative frequencies were observed, confirming that all structures were true local minimums [17].



**Figure 2.** Initial and optimized structures of Dacarbazine- $C_{20}$  complexes

The dipole moment of Dacarbazine increased significantly after its adsorption on the surface of C<sub>20</sub>, suggesting that Dacarbazine-C<sub>20</sub> complexes are more soluble in polar solvents compared to the pure drug without the nanostructure [18]. Furthermore, the reactivity and bioavailability of Dacarbazine improved noticeably after its interaction with fullerene, indicating that C<sub>20</sub> can serve as a suitable nanocarrier for this drug. NBO computations were also conducted to gain further insights into the adsorption mechanism, and the results showed that no bonds were formed between the adsorbate and adsorbent, confirming that the adsorption mechanism is physisorption [29].

**Table 1.** The calculated structural properties of Dacarbazine, C<sub>20</sub> and their complexes in both vacuum and aqueous phases

NO	Total electronic energy (a.u)	Adsorption energy (kcal/mol)	ZPE (kcal/mol)	$\nu_{\min}$ (cm <sup>-1</sup> )	$\nu_{\max}$ (cm <sup>-1</sup> )	Dipole Moment (Debye)
Dacarbazine-Vacuum	-794.716	---	85.249	88.606	3735.678	2.832
C <sub>20</sub> -Vacuum	-748.615	---	130.789	310.485	1434.865	0.000
A-Conformer-Vacuum	-1541.821	-88.599	166.432	99.116	2063.366	4.371
B-Conformer-Vacuum	-1541.831	-115.639	167.203	189.736	2054.396	4.689
DACARBAZINE-Water	-794.724	---	167.565	201.186	2050.806	2.888
C <sub>20</sub> -Water	-748.612	---	128.025	228.236	1434.848	0.000
A-Conformer-Water	-1541.812	-50.943	163.562	118.926	2047.476	4.728
B-Conformer-Water	-1541.818	-66.543	164.223	190.946	2045.416	4.552

### FMO Analysis

The bandgap, which refers to the energy difference between the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO), plays a crucial role in

determining the reactivity of a compound [18]. A narrower bandgap indicates higher reactivity, while a wider bandgap implies lower reactivity. The data presented in Table 3 clearly demonstrate that the bandgap of C<sub>20</sub> is initially 6.097 eV. However, when Dacarbazine adsorbs onto the surface of C<sub>20</sub>, this parameter decreases by 44.469% and 32.998% for the A and B conformers, respectively. Consequently, the bandgap values for the A and B conformers become 5.482 eV and 4.967 eV, respectively.

**Table 3.** The calculated FMO parameters

NO	E <sub>HOMO</sub> (eV)	E <sub>LUMO</sub> (eV)	E <sub>g</sub> (eV)	%ΔE <sub>g</sub>	η (eV)	μ (eV)	ω (eV)	ΔN <sub>max</sub> (eV)
<b>Dacarbazine</b>	-5.294	-1.008	4.286	---	2.143	-3.151	2.317	1.470
<b>C<sub>20</sub></b>	-7.955	-1.859	6.097	---	3.048	-4.907	3.949	1.610
<b>A-Conformer</b>	-5.313	-1.928	3.386	-44.469	1.693	-3.621	3.872	2.139
<b>B-Conformer</b>	-6.009	-1.924	4.085	-32.998	2.042	-3.967	3.852	1.942

This significant decrease in bandgap indicates a substantial enhancement in the electrochemical conductivity of C<sub>20</sub> during the adsorption process of Dacarbazine [19]. Therefore, C<sub>20</sub> can be considered an excellent sensing material for detecting Dacarbazine. The chemical hardness of Dacarbazine was found to be 6.021 eV. However, when Dacarbazine interacts with the nanostructure (A and B conformers), its chemical hardness decreases to 3.386 eV and 4.085 eV, respectively. This decrease suggests an improvement in the chemical reactivity of Dacarbazine upon interaction with the nanostructure [20]. Furthermore, the negative values of the chemical potential for all studied structures indicate that these structures are thermodynamically stable [22]. Additionally, the electrophilicity and maximum transferred charge capacity of Dacarbazine were found to be 2.317 and 1.470 eV, respectively. However, when Dacarbazine is adsorbed onto the fullerene surface, both indices experience a significant increase [23]. This suggests that Dacarbazine-C<sub>20</sub> complexes are more electrophilic and have a higher tendency to absorb electrons compared to pure Dacarbazine without the nanostructure. In conclusion, the findings of this study indicate that fullerene (C<sub>20</sub>) can serve as an excellent nanocarrier for drug delivery of

Dacarbazine. The adsorption of Dacarbazine onto  $C_{20}$  leads to an increase in the chemical reactivity of Dacarbazine improves upon interaction with the nanostructure.

## Conclusion

Following the investigation, thorough density functional theory simulations were utilized to carefully analyze the potential of using the smallest fullerene ( $C_{20}$ ) as a nano-carrier for the dacarbazine anticancer drug. The adsorption energies obtained from the simulations clearly demonstrate that under experimental conditions, the interaction between dacarbazine and  $C_{20}$  is indeed feasible. Moreover, the Natural Bond Orbital (NBO) analysis indicates that there is no chemical bond formation between dacarbazine and the nanostructure, suggesting that the interaction is purely due to physisorption. Furthermore, the results from the frontier molecular orbital analysis show a significant 44.469% decrease in the bandgap of the fullerene to 4.967 eV. This reduction in bandgap strongly implies that  $C_{20}$  has the potential to serve as an outstanding nanocarrier for delivering dacarbazine. Additionally, the obtained values for the dipole moment and chemical hardness further support the suitability of  $C_{20}$  as a nano-carrier for dacarbazine delivery. In summary, the insights gained from the density functional theory simulations provide compelling evidence for the potential of utilizing  $C_{20}$  as an efficient nano-carrier for dacarbazine delivery. These findings set the stage for further exploration and development of  $C_{20}$ -based nanomaterials for drug delivery purposes.

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