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Computational assessments of sumanene-hydroxyurea conjugations for proposing a novel drug design and delivery platform

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ABSTRACT

Sumanene-hydroxyurea (SUM-HYD) conjugations were assessed based on the density functional theory (DFT) computational assessments for proposing a novel drug design and delivery platform. The structural geometry optimizations and electronic molecular orbital features evaluations were done to assess the investigated systems. The results indicated the existence of a semi-cup-like structure for the SUM counterpart, in which the in-side and out-side of the surface structure were participated in interactions with the HYD counterpart to yield the SH_i and SH_o complexes of SUM-HYD conjugation. The existence of interactions were analyzed and the models were assessed based on the involving interactions and the finally obtained configurations revealed a better suitability of the SH_o conjugation in comparison with the SH_i conjugation. Additionally, the electronic molecular orbital features indicated a lower hardness for the SH_i conjugation even in comparison with the singular HYD substance. Furthermore, the models were recognizable by the SUM sensing functions towards the HYD drug substance. Assessing the impacts of water and ethanol media on the Gibbs free energy of SUM-HYD conjugations indicated the stability of models in both media with a priority of water medium. As a result, the models were stabilized and their features indicated benefits of formations of such SUM-HYD conjugated systems for approaching a novel drug design and delivery platform.

Introduction

By modernizing the human life level, innovating novel drug design and delivery platforms is crucial for dealing with the diseases and enhancing the treatments to approach successful medications [1,2]. Indeed, either the appearance of new diseases or the wildness of earlier diseases leaded to unsuitability of the conventional treatments for so many diseases and disorders as seen by the complicated situation of recent COVID-19 pandemic era [3,4]. On the other hand, treating the earlier known diseases such as cancer has been still an unsolved problem with serious negative impacts on the human life levels all around the world [5,6]. The results of basic and clinical studies indicated that the unknown initiation of cancer and its rapid growing are main problems for dealing with this issue and many more studies are required for approaching successful medications [7,8]. In this regard, developing novel drug design and delivery platforms could be a possible method of medication enhancement for approaching a more successful treatment for both of earlier known diseases and newly appearing ones [9,10]. However, it is not an easy task and the drug-carrier conjugations should be customized for learning their details of communications as a first step of knowing their applicability for working in the drug delivery platforms [11,12]. This issue has been very widely investigated especially after the innovation of high-surface-area nanostructures to examine their features as possible drug carriers by providing a smart surface adsorbent [13,14]. Since many details are inside the drug-nanostructure conjugations, they should be learned carefully for developing their featured functions and

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applications [15,16]. Additionally, analyzing the complex systems in the smallest scales has been found as an appropriate method of approaching novel information for pushing forward the development of drug design and delivery platforms [17–20]. On the other hand, examining the properties of single-standing nano-flakes has been found as another important issue to manage a meaningful study on the drug-nanostructure conjugations [21,22]. As a result, a representative nano-flake was investigated in this work towards the drug design and delivery platform of an anticancer along with quantum chemical calculations of sumanene-hydroxyurea conjugations to provide details of a proposed systems for approaching a possible medication purpose.

Sumanene (SUM) (Fig. 1) is a single-standing structure representing a surface portion of the well-known fullerene nanostructure, in which the recognition of its features has been the target of several studies to this time [23,24]. The SUM-drug conjugations have been also investigated to learn the availability of this nano-flake for employing in the drug design and delivery platforms, in which the results indicated benefits of this nano-flake structure for making such conjugations regarding the medication purposes [25,26]. Indeed, the studies on nanostructures indicated so many features to be considered for customizing them towards a specific function and application [27–30]. To this point, the unique semi-cup-like geometrical conformation of SUM made it as a structure with inside and outside surfaces for working in a dual way of interaction with other substances [31,32]. Additionally, the small size of SUM made it also useful for interacting with small size drugs to make a conjugation along with the involving interactions between the counterparts [33,34]. Hydroxyurea; or hydroxycarbamide, (HYD) (Fig. 1) is a small size drug with significant roles for the treating different types of cancer such as leukemia and also other diseases such as sickle cell disease [35,36]. By the importance of medication by HYD, considerable efforts have been dedicated to enhance the efficacy of HYD and lowering its adverse effects; however, arising serious adverse effects limited its prescription to careful treatments [37,38]. Hence, it is an important issue to focus on the enhancement of HYD for approaching more successful medications [39,40]. To this aim, the SUM-HYD conjugations were assessed in this work for providing more insights into the drug design and delivery platforms along with computational studies. As shown in Fig. 1, the interactions between SUM and HYD counterparts were analyzed to learn the formation of SUM-HYD conjugations and their details. Accordingly, the required information was obtained by characterizing the models through structural geometry optimizations, electronic features evaluations, and media impacts examinations; the results were exhibited in Figs. 1–4 and Tables 1–4. To re-emphasize on the main goal of this work, it should be mentioned that the SUM-HYD conjugations were assessed to propose a novel drug design and delivery platform regarding the evaluated insights into the interacting counterparts and their corresponding structural and electronic features based on the quantum chemical computations.

Materials and methods

To propose a novel drug design and delivery platform regarding the SUM-HYD conjugations, 3D molecular models of SUM and HYD counterparts were assigned as the parental models of this work for making the desired conjugations (Fig. 1). Quantum chemical density functional theory (DFT) calculations were performed for optimizing their geometries besides evaluating the corresponding structural and electronic features using the wB97XD/6-31G* level of computations as implemented in the Gaussian program [41]. It is known that the computational methods have been found as very suitable tools to solve the complicated systems in a pure state of excluding any external interferes or implementing the known interferers to recognize the original nature of investigating systems and their detected impacts [42,43]. The parental models were allowed for participating in interactions together

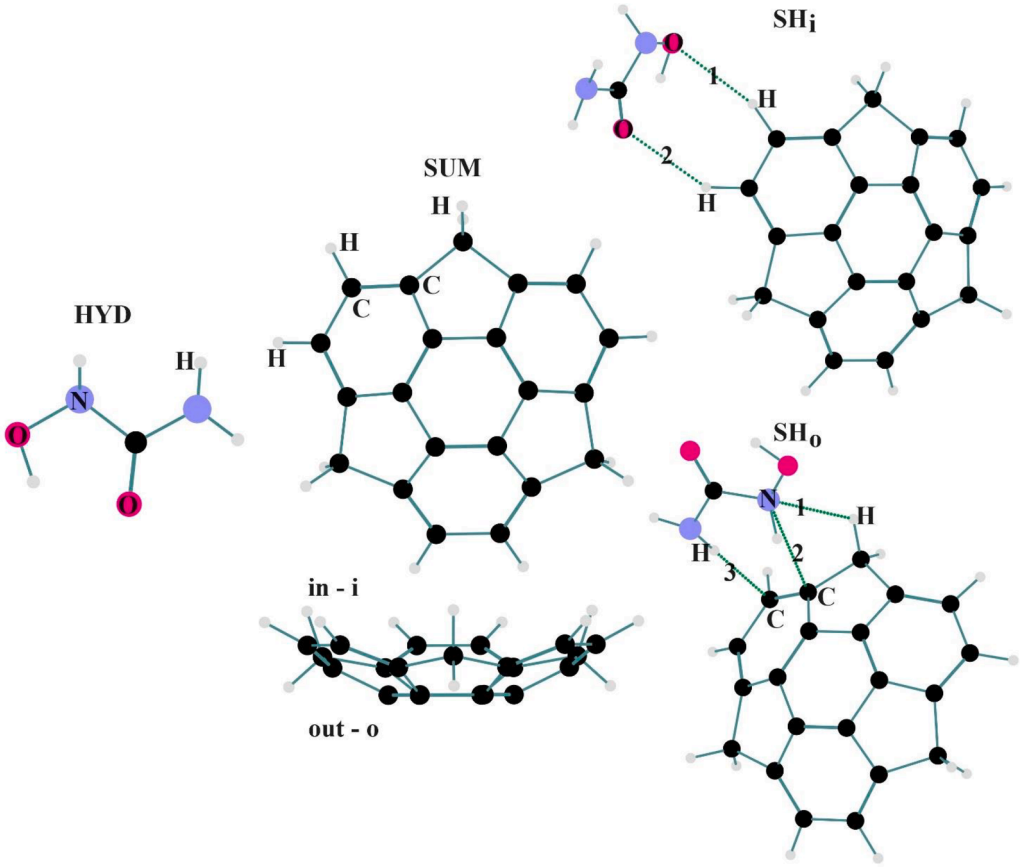

Fig. 1. The optimized parental HYD and SUM models and SUM-HYD conjugations.

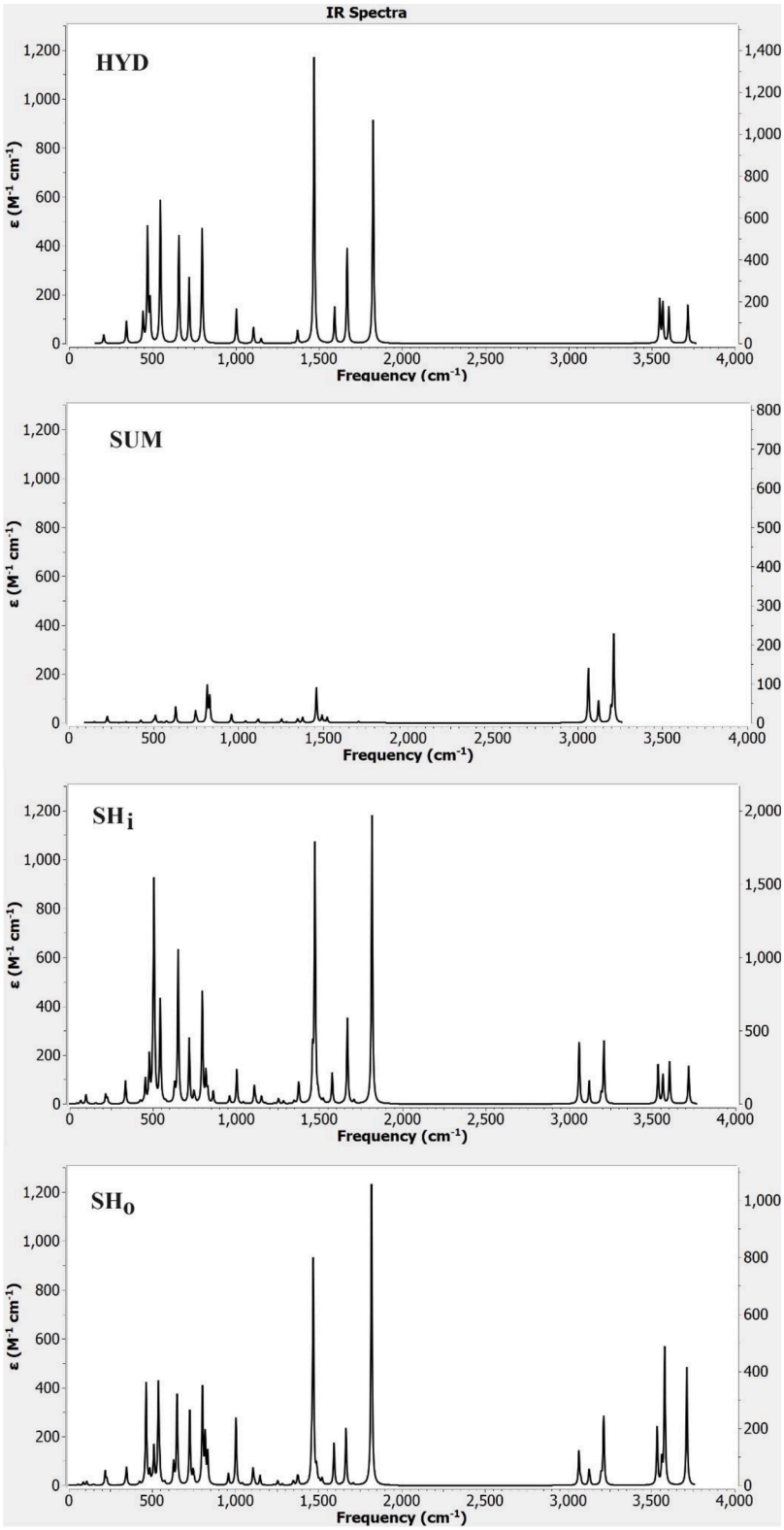

Fig. 2. The IR spectra of parental HYD and SUM models and SUM-HYD conjugations.

through both of inside and outside surfaces of the SUM nano-flake, in which two SUM-HYD conjugations were recognized; SH_i and SH_o. It should be mentioned here that the finalized configurations of converged SUM-HYD conjugations were assigned by SH_i and SH_o in this work. The evaluated energy features including the total energy (E_{tot}) and interaction energy (E_{int}) were summarized in Table 1 in addition to the basis set superposition error (BSSE) correction [44]. To learn details of conjugations, the involving interactions were analyzed by the quantum theory of atoms in molecules (QTAIM) [45]. Next, energy levels of the highest occupied and the lowest unoccupied molecular orbitals (E_{HOMO} and E_{LUMO}), energy gap (E_{gap}), chemical hardness (η), and chemical potential (μ), were summarized in Table 3 as the frontier molecular orbitals

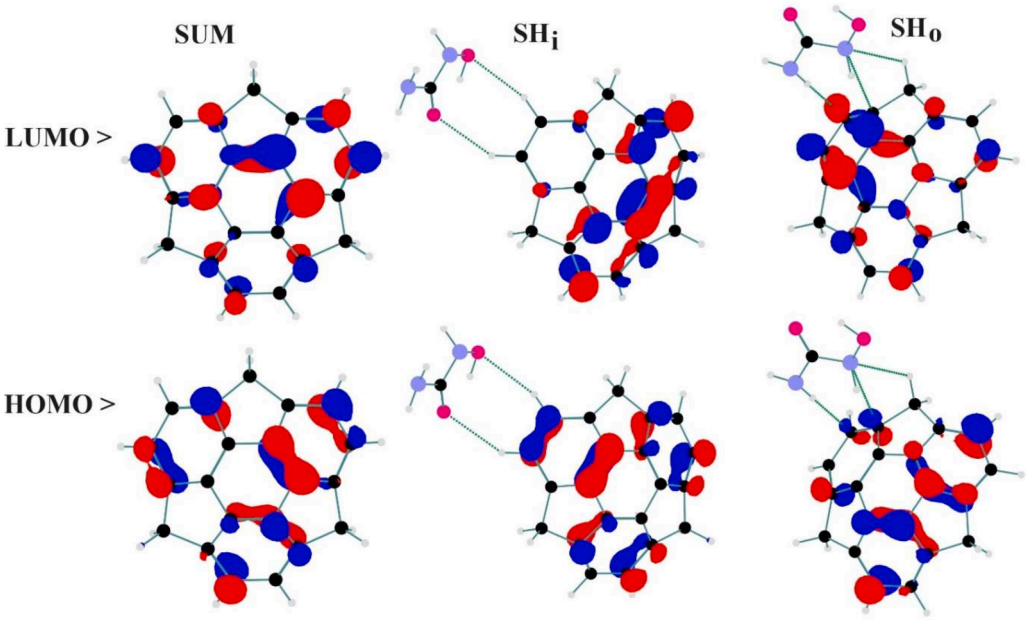

Fig. 3. The HOMO-LUMO distribution patterns of parental SUM model and SUM-HYD conjugations.

electronic features [46]. Additionally, thermochemistry features were evaluated to show the impacts of water and ethanol media on the Gibbs free energy variations (ΔG) features of SH_i and SH_o conjugations using the polarizable continuum model (PCM) approach [47]. Besides the quantitative analyses, the models were exhibited through the optimized configurations of Fig. 1, the vibrational infrared (IR) spectra of Fig. 2, the HOMO-LUMO distribution patterns of Fig. 3, and the illustrated density of states (DOS) diagrams of Fig. 4. All the required information was evaluated to assess the SUM-HYD conjugations for proposing a novel drug design and delivery platform.

Results and discussion

Developing the drug design and delivery issues is indeed a non-stop process requiring many types of information to learn the mechanism of this complicated process and its improvements [48]. In this regard, it is crucial to recognize the features of the main counterparts of drug design and delivery platforms; including carrier and drug substances [49]. Besides, the sensing functions of carrier could make it a responsible of managing a targeted drug delivery process to carry the uploaded drug up to a correct destination among several other unwanted destinations and receptors [50]. To this aim, a customization of carrier-drug conjugation is needed how to proceed such a vital function through the medicinal functions and applications [51]. Accordingly, the current work was done by the aim of customizing the sumanene (SUM) carrier substance towards the hydroxyurea (HYD) anticancer drug through the formation of SUM-HYD conjugated complexes in complementary to the results of earlier works for nano-enhancement of HYD anticancer [52–55]. As shown in Fig. 1, the models of this work were optimized and their 3D conformations and interacting configurations were found and exhibited. The initiating part of a computational study is the preparation of optimized 3D structures to yield the minimized energy geometries in both of singular and complex states. Hence, the current work were intimated by optimizing the molecular models and the results were shown as HYD, SUM, and two configurations of SUM-HYD conjugations including SH_i and SH_o. To explain the i and o indices, it should be mentioned that the pre-optimized models were placed towards each other regarding the in - i and out - o sides of SUM; as it was found as a semi-cup-like structure not a planar one, yielding SH_i and SH_o configurations and the optimized models were found as the resulting complex models. Indeed, it was an advantage of SUM with two inside and outside surfaces to be examined in both sides regarding the adsorption of external drug. Hence, two configurations were found accordingly to emphasize on the importance of such semi-cup-like surfaces to be examined within both of surfaces. It is known that the structural stabilizations of bimolecular models are somehow challenging regarding the possibility of many available configurations; therefore, all possible configurations should be examined. Within this work, such an important challenge was implemented and the results of various configurations of models indicated the formation of one configuration in each side as indicated by SH_i and SH_o configurations. As a consequence, these two configurations were assigned as the reference bimolecular structures of SUM-HYD conjugations to be investigated in this work.

As exhibited in Fig. 1, the models were optimized in the singular and conjugated complex states, in which the main point was that the parental SUM was found as a semi-cup-like surface and the occurrence of interactions between SUM and HYD counterparts were possible from both of in - i and out - o sides of the SUM resulting two configurations including SH_i and SH_o. It was amazing that HYD substance was moved to the edge of SUM in both of in and out initiating configurations and making interactions with the surface edging atoms. To examine the stabilities of conjugated systems, the energy features were evaluated for the models (Table 1) to show the levels of total energy (E_{tot}) and interaction energy (E_{int}). The values of −694,402.70 and −694,405.36 kcal/mol were found for the E_{tot} of SH_i and SH_o configurations showing a better stability level for the out-side interaction (SH_o) in comparison with the in-side interaction (SH_i) of HYD and SUM counterparts. As could be found by these energy values, the formation of SH_o configuration could be known more favorable than the formation of SH_i configuration. The repulsive forces from the surface edges might ban the formation of a favorable in-side conjugation, in which such repulsive force are absent in the adosorption processes of out-side configuration. To learn the strength of interactions between the conjugated system counterparts, the values of −4.52 kcal/mol and −8.18 kcal/mol were found for the E_{int} of SH_i and SH_o showing a significance of favorability of the formation of SH_o configuration versus the formation of SH_i configuration. The employed BSSE correction did not change the comparative results of complexes and the strength of interacting models were confirmed accordingly. The evaluated IR spectra of models (Fig. 2) also indicated the variations of vibrational strengths in the investigating

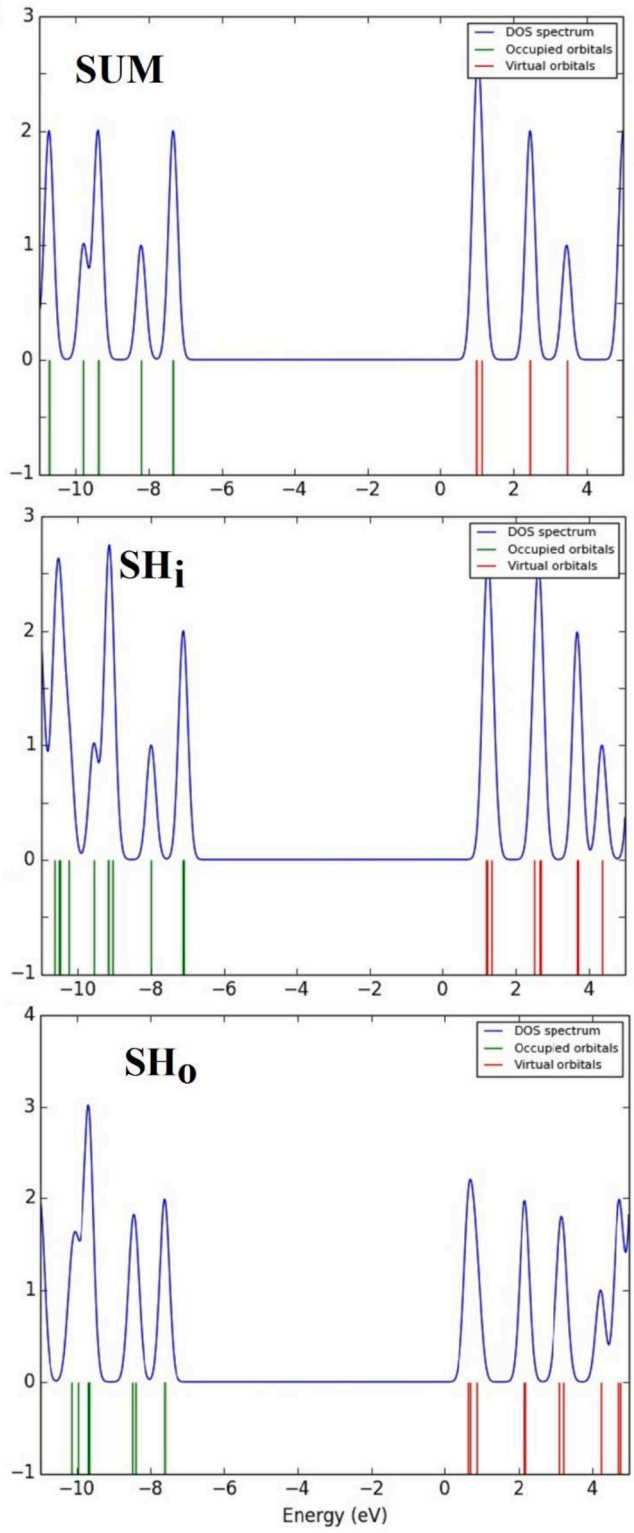

Fig. 4. The DOS diagrams of parental SUM model and SUM-HYD conjugations.

Table 1
Energy features of SUM-HYD conjugations.

SUM-HYD	E_{tot} kcal/mol	E_{int} kcal/mol	BSSE kcal/mol	BSSE+E_{int} kcal/mol
SH_i	−694,402.70	−4.52	1.86	−2.66
SH_o	−694,405.36	−8.18	1.40	−6.78

Table 2
Interaction features of SUM-HYD conjugations.

SUM-HYD	Interaction	Distance Å	ρ au	H au
SH_i	1: H…O	2.58	0.0076	0.0088
	2: H…O	2.55	0.0081	0.0068
SH_o	1: H…N	2.93	0.0050	0.0075
	2: C…N	3.54	0.0041	0.0061
	3: C…N	2.59	0.0091	0.0117

Table 3
HOMO-LUMO features of parental HYD and SUM models and SUM-HYD conjugations.

SUM-HYD	E_{HOMO} eV	E_{LUMO} eV	E_{gap} eV	η eV	μ eV
SH_i	−7.11	1.19	8.29	4.15	−2.96
SH_o	−7.60	0.62	8.22	4.11	−3.49
SUM	−7.33	0.99	8.32	4.16	−3.17
HYD	−8.74	2.78	11.51	5.76	−2.98

Table 4
Media impacts on the Gibbs free energy of SUM-HYD conjugations.

SUM-HYD	ΔG(Water-Gas) kcal/mol	ΔG(Ethanol-Gas) kcal/mol	ΔG(Water-Ethanol) kcal/mol
SH_i	−11.81	−11.21	−0.60
SH_o	−9.86	−9.36	−0.50

models from the singular state to the conjugated complex state, in which the obtained non-imaginary frequencies affirmed the stability of conjugated systems. Especially in the SH_o spectra, the highlighted changes of 3000–3750 cm^{-1} region for the conjugated system in comparison with both of singular HYD and SUM counteracts indicated a higher contribution of HYD for interacting with the SUM substance in comparison with the SH_i complex. As a result, the formation of SH_o conjugation was found as the typical interacting configuration of SUM-HYD conjugated systems, but the formation of SH_i was still meaningful to be considered.

Details of involving interactions in the formation of SUM-HYD conjugated complexes were found by performing QTAIM analyses on the optimized structures. As shown by the dot-lines in Fig. 1, there were two interactions in SH_i and there interaction in SH_o between the interacting counterparts. Additional results were summarized in Table 2 to show the quantitative interaction details of conjugated models including the interaction distance, electron density (ρ), and energy density (H) of each interaction. As could be learned by the obtained results, two H…O interactions were found from the SUM side to the HYD side in the SH_i configuration showing the importance of this single-standing structure for working in a successful interaction system even by the assistance of surrounding hydrogen atoms. Indeed, such a single-standing mode of stability could make the SUM substance as a nano-flake for working in various purposes and processes especially in the formation of conjugated systems with the small sized molecules such as HYD. For the case of SH_o, three interactions in two types of H…N and C…N were found. An important achievement of these analyses is the contribution of different atoms of HYD to interactions with the SUM substance, in which the starting pre-optimizing configuration was playing a dominant role for the generation of such a remarkable configuration state. The oxygen atoms of HYD were dominant in the case of in-side interactions whereas the nitrogen atoms were dominant in the case of out-side interactions. As a consequence, all possibilities of interactions were almost examined for approaching the purpose of interacting conjugation formations.

To assess the electronic features of investigated models including the singular SUM and HYD counterparts and their conjugated SUM-HYD complexes, the frontier molecular orbitals analyses were done in both of quantitative and qualitative terms. As shown in Fig. 3, the distribution

patterns of HOMO and LUMO were localized at the SUM counterpart in both of SH_i and SH_o conjugated complexes. In this regard, an important role of SUM for the formation of SUM-HYD hybrids was learned by conducting the interactions and adsorbing the electronic patterns. Referring to the expected sensing functions of a carrier towards the delivery of an uploaded drug, the evaluated molecular orbital features could lead to such achievements. Within the current results, the role of SUM was significant for detecting the molecular orbitals variations before and after the conjugation formations. Indeed, the localization of HOMO and LUMO patterns could be related to the next electronic-dependent behaviors of the structures, in which the models were found to work regarding the role of SUM surface adsorbent. This dominant role could be also very helpful for releasing the uploaded drug to a correct destination based on the customized electronic features of DUH-HYD complex and the corresponding electronic features of destination. This is indeed another description of sensor function of SUM for managing the future reactions and interactions of HYD drug substance.

Additionally, analyzing the illustrated DOS diagrams (Fig. 4) could reveal insights into the measurements of molecular orbitals features variation during the conjugation formations to provide the required elements of approaching a sensing function for the investigating models. The results showed a significance of conjugated SUM-HYD complex formations based on the obtained electronic features and variations. Indeed, the exact levels of HOMO and LUMO and their energy distances are crucial to assess the electronic features of chemical systems. In the case of DOS diagrams, even the pre-HOMO and post-LUMO orbitals could be recognized and the energy gap distances could be determined regarding the sensing functions issues. Accordingly, measuring such variations could lead to an identification of adsorption process or even the type of complex formation. In this case, the models could be recognized from each other in both of complex states or between the singular and complex states. Additionally, a corresponding response to such an observed variation could lead to an identification of a significant model and the results could be affirmed based on the recorded changes and variations. For the investigated models, the DOS diagrams indicated shifting of HOMO and LUMO levels by the formation of SUM-HYD complexes, and also their variations were recorded to confirm the formation of the type of SUM-HYD complex system. As a consequence, the expected sensor role of SUM was affirmed.

For making a quantitative analyses of investigating models, the results of HOMO and LUMO related features were summarized in Table 3. The results included the exact energy values of HOMO and LUMO levels and their derived features as energy gap (E_{gap}), chemical hardness (η), and chemical potential (μ) for both of singular and complex states of the investigated models. As the HOMO refers to the electron-containing orbitals and LUMO refers to the electron-vacant orbitals, the results of these parameters could help to recognize the electronic sensitivity especially in the case of electron transferring ability of a molecular system. For the case of conjugated complex formation, such electronic variations could lead to a detection point of drug uploading and also assigning a time of drug releasing. Based on such features, the values of E_{gap} were found to be 8.29 eV for the SH_i conjugation and 8.22 eV for the SH_o conjugation in comparison with the singular SUM counterpart with a value of 8.32 eV. The results indicated a shorter energy distance between the HOMO-LUMO levels of conjugations in comparison with the singular SUM counterpart revealing the shortest distance for the SH_o conjugation. On the other hand, the values of η revealed the lowest hardness or the highest softness for the SH_o conjugation for participating in further reaction and interactions even more significant than the singular HYD substance. In this case, the models could be learned by their enhanced features in the conjugation state for working in the future processes. As a result, the SUM-HYD conjugations could lead to the generation of a new model system based on the evaluated structural and electronic features to propose a system for working in the novel drug design and delivery platforms for keeping the uploaded drug and making the sensing functions.

Thermochemistry features of the investigated SUM-HYD conjugations in different media were investigated by evaluating the Gibbs free energy of models in gas phase as the default set of calculations of this work, in water phase, and in ethanol phase (Table 4). The obtained results of ΔG indicated changes of the energy level in comparing media, in which the results of ΔG(Water-Gas) and ΔG(Ethanol-Gas) indicated the advantage of both of water and gas media for providing even more stable conjugations. However, it should be mentioned that the SH_i conjugation showed even better situation than the SH_o conjugation in both of water and ethanol media in comparison with the gas phase. Additionally, the values of ΔG(Water-Ethanol) indicated a higher suitability of water medium than the ethanol medium to obtain the conjugated systems. As a result, it could be mentioned that the investigated SUM-HYD conjugations could work in both of water and ethanol media with a priority of choice for the water medium in comparison with the ethanol medium. Additionally, because of easier penetrations of medium between the counterparts of out-side surface conjugation, the formation of SH_i was found even better than SH_o. As a final remark, not only the medium did not have an instability impact on the conjugations, but the impacts were even for making stronger complexes revealing the working function and applications of the conjugated models in all the gas, water, and ethanol media.

Conclusions

Computational assessments of sumanene-hydroxyurea (SUM-HYD) conjugations were done for proposing a novel drug design and delivery platform. DFT calculations were performed to stabilize the geometries of models in the singular state and their conjugated complex state. Two SUM-HYD conjugations were obtained including SH_i and SH_o, in which the in-side and out-side of semi-cup-like SUM for initiating the interactions with the HYD substance were assigned by i and o indices. The results of energy features indicated a higher stability of the SH_o conjugation in compassion with the SH_i conjugation, in which the results indicated the existence of three interactions in the former conjugation and two interactions in the latter conjugation. Additionally, the non-imaginary IR spectra indicated stronger vibrations of HYD counterpart in the SH_o conjugation in compassion with the SH_i conjugation. Next, the electronic features were assessed by analyzing the frontier molecular orbitals for HOMO and LUMO levels and their derivatives. A shorter energy distance of HOMO and LUMO levels was found for the SH_o conjugation and its hardness was accordingly lower making it a suitable substance for participating in further reactions and interactions even better that the singular HYD substance. Additionally, the HOMO and LUMO distribution patterns indicated a significant role of SUM substance for managing the conjugated system in terms of sensing functions. As a conclusion, the results of investigated SUM-HYD conjugations indicated highlighted benefits of these models for proposing to be employed in the novel drug delivery platforms. The evaluated impacts of media on the Gibbs free energy of SUM-HYD conjugations indicated the stability of models even in water and ethanol media in addition to the default gas phase of study. Moreover, the results indicated that the better stability of models in water medium than the ethanol medium. As a concluding remark, it should be mentioned that the investigated SUM-HYD conjugations could be proposed for working in drug design and delivery related functions, as the structures were found stable and their electronic features indicated possible sensing functions for making the whole process in a customized platform.

Research data

Research data will be provided on a request.

CRediT authorship contribution statement

M.J. Saadh: Project administration, Conceptualization, Writing –

original draft. **M. Mirzaei:** Formal analysis, Investigation, Methodology. **H.H. Ahmed:** Formal analysis, Investigation. **W.M. Taher:** Investigation, Writing – review & editing. **M. Alwan:** Data curation, Writing – review & editing. **H. Meliyev:** Validation, Writing – review & editing. **R. R. Maaliw III:** Data curation, Visualization, Software. **M. Da'i:** Conceptualization, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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