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Noureddine Mhadhbi, Souad Dgachi, Soufienne Belgacem, Ali Ben Ahmed, Natacha Henry, et al.. Design, theoretical study, druggability, pharmacokinetics and properties evolution of a new organo-bromocadmate compound as prospective anticancer agent. *Journal of Molecular Structure*, 2023, *Journal of Molecular Structure*, pp.134439. 10.1016/j.molstruc.2022.134439 . hal-04313434

HAL Id: hal-04313434

<https://hal.univ-lille.fr/hal-04313434v1>

Submitted on 14 Dec 2023

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Design, theoretical study, druggability, pharmacokinetics and properties evolution of a new organo-bromocadmiate compound as prospective anticancer agent.

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Abstract

Crystals of the organic-inorganic hybrid complex $[\text{H}_3\text{NCH}_2(\text{C}_5\text{H}_4\text{NH})]_2\text{CdBr}_6 \cdot 2\text{H}_2\text{O}$ ($[\text{H}_3\text{NCH}_2(\text{C}_5\text{H}_4\text{NH})]$ = diprotonated 3-picolylamine or 3-ampH₂), were grown successfully by slow evaporation solution growth method at room temperature and characterized by single-crystal X-ray diffraction, infrared absorption, optical absorption and thermal analysis. The title compound belongs to the triclinic space group $P\bar{1}$, with a crystal structure consisting of inorganic layers built up from hexabromocadmate anions $[\text{CdBr}_6]^{4-}$ and free water molecules, linked together by O-H \cdots Br hydrogen bonds and halogen \cdots halogen interactions, along the *b* axis. The organic cations, 3-ampH₂, are intercalated between the mineral layers via N-H \cdots Br hydrogen bonds. The optimized molecular structure and the vibrational spectra were calculated thanks to the Density Functional Theory (DFT) method resorting to the B3LYP function with the LanL2DZ basis set. Infrared spectrum was used to gain more information of the title compound, with the assignment of the observed vibration modes. Good agreement has been found between the calculated results and the experimental data. Subsequently, the optical properties were diagnosed throughout optical absorption explaining the possible charge transfer interactions that happen within the molecules. The thermal behavior was studied by TG/DT analyses. In silico analyses showed that the synthesized compound bound several anticancer receptors (TNF- α , COX-2, VEGF...) with high affinities, which together with molecular interactions, druggability and pharmacokinetics satisfactory explain the anticancer potential of the compound.

Keywords: Organic-inorganic complex, X-ray diffraction, vibrational spectra, DFT calculations, optical absorption, Pharmacokinetics, Anticancer effect.

1. Introduction

In recent years, the chemistry of organo-metal halides has developed rapidly and become of significant importance. These compounds are now applied in a wide range of research fields, including catalysis, biochemistry, magnetism, luminescence, nonlinear optical (NLO) and materials science [1-6]. These properties emanate from their diverse structures that can be well predicted and designed under the guidance of coordination chemistry and crystal engineering [7-9]. Such materials have recently been the interest of many studies due to their attractive potential for application as insulators in the electronics industry. A very important class consists of organo-metal halides. In fact, many compounds of this type have been synthesized such as $([\text{H}_3\text{NCH}_2(\text{C}_5\text{H}_4\text{NH})]) [\text{ZnCl}_4]$ [10], $(\text{C}_6\text{N}_2\text{H}_{10}) [\text{CuCl}_4]$ [11], $(\text{C}_6\text{N}_2\text{H}_{10}) [\text{CuBr}_4]$ [11], $[\text{Bz-4-NH}_2\text{Py}]_4[\text{CdCl}_4]_2 \cdot \text{H}_2\text{O}$ [12], $(\text{C}_8\text{H}_{14}\text{N}_2)_2[\text{CdCl}_6]$ [13], $(\text{C}_5\text{H}_6\text{N}_2\text{Cl})_2[\text{CdBr}_4] \cdot \text{H}_2\text{O}$ [14], $(\text{C}_9\text{H}_{24}\text{N}_2)\text{CdCl}_4$ [15], $[\text{Bz-4-NH}_2\text{Py}]_2[\text{CdBr}_4]$ [16]. Hybrid compounds based on cadmium halide have constantly attracted much attention because the Cd^{2+} ion with a d^{10} configuration show a variety of coordination numbers, geometries and structural flexibility depending on crystal packing and ligands. Besides, the anionic sub-lattice of the crystal may consist of a simple discrete octahedral, one-dimensional chain, 2D or 3D anionic framework [17-19]. Although many organo-bromocadmiate compounds have been synthesized and characterized, by single-crystal X-ray diffraction, only some of them have been studied theoretically, even though computational analysis has become one of the effective methods to gain information about the electronic, reactivity and thermodynamic properties of this type of compounds. Due to the hybrid structure, these materials have resulted in exceptional intermolecular interactions. The energy difference between the frontier orbitals HOMO and LUMO can be used to predict the strength and stability of metal complexes transition [20].

Considering the attractive characteristics and attributes of halogenocadmate (II) and the new promising opportunities they may open with regard to the development of useful organic-inorganic hybrid materials, the present study reports the synthesis and structural characterization of the 3-ammoniumethyl-pyridinium hexabromocadmate (II) dihydrate with the general chemical formula $(C_6H_{10}N_2)_2[CdBr_6] \cdot 2H_2O$. The characterizations of the grown crystals were achieved throughout X-ray diffraction, spectroscopic techniques (infrared spectrum and optical properties) and thermal studies. The molecular geometry optimization was performed using DFT/B3LYP methods with the LanL2DZ basis set to assist the interpretation and the assignment of experimental IR spectrum. Good agreement has been found between the calculated results and the experimental data. The optical property reveals a noticeable band energy gap stating the stability of the resulting structure. In an attempt to rationalize the possible biological activity of the compound, its bioavailability, pharmacokinetics and molecular interactions with key receptors involved in cancer were also studied using computational modeling.

2. Experimental

2.1. Chemical materials and methods

In this experiment, the following ingredients were used in accordance with their analytical purity, purchased from Sigma Aldrich: $CdBr_2 \cdot 4H_2O$ (98 %), 3-picolyamine ($C_6H_8N_2$; 3-(aminoethyl)pyridine, noted 3-amp) (99%) and hydrobromic acid HBr (48%). The synthesis was carried out using distilled water.

The IR spectrum was measured using a PerkinElmer BX FT-IR spectrometer, in the 400-4000 cm^{-1} region at ambient temperature.

In order to measure the optical properties at room temperature, a Cary 4000 UV-Visible spectrophotometer will be used which covers a spectrum from 200 nm to 800 nm and uses a Xenon lamp for the UV-Visible range.

Thermal analyses were performed on raw powders with a TGA/DTA 'SETSYS Evolution' (Pt crucibles, Al₂O₃ as a reference) under air flow (100 ml/min) of (3-ampH₂)₂CdBr₆·2H₂O. The thermograms were gathered from 11 mg samples in the RT-600°C range (heating rate: 5°C·min⁻¹).

2.2. Synthesis of (3-ampH₂)₂CdBr₆·2H₂O

The title compound was synthesized by the reaction of 3-picolylamine (2 mmol: 0.216g), cadmium (II) bromide tetrahydrate (1 mmol: 0.344g) and 10 ml of distilled water. The mixture was acidified by concentrated hydrobromic acid (0.080g), under continuous stirring. The solution was slowly evaporated. After few days some transparent single crystals were carefully isolated under a polarizing microscope for analysis by X-ray diffraction. The yield of the reaction is 79 % (based on Cd). Anal. Calc. for (3-ampH₂)₂CdBr₆·2H₂O (M = 848.21): C, 8.52; H, 6.41; N, 3.96 (%). Found: C, 8.65; H, 5.93; N, 4.12 (%). MS (ESI): m/z: 336.12; IR (KBr): $\tilde{\nu}$ = 3443 [br, ν (H₂O)], 2925 [ν (NH)], 1612 [ν (C=N)] cm⁻¹.

2.3. X-ray Data Collection

A suitable crystal of (C₆H₁₀N₂)₂[CdBr₆]·2H₂O was glued to a glass fiber on an APEX II area detector 4-circle diffractometer. Intensity data sets were collected until a resolution of 0.8Å because the intensity beyond was too low using Ag K α radiation (λ = 0.56086Å) through the Bruker AXS APEX2 Software Suite. The crystal structure was solved in the triclinic system, space group $P\bar{1}$. Using Olex2 [21], the structure was solved with the olex2.solve [22] structure solution program using Charge Flipping and refined with the ShelXL [23] refinement package using Least Squares minimization with anisotropic thermal parameters for all non-H-atoms. H atoms bonded to C and N atoms were located in a difference map and

refined with C-H distance of 0.93(2) Å and N-H distance of 0.91(2) Å. The drawings were made with DIAMOND program [24].

2.4. Computational details

Gaussian 09 software was used to perform optimizations and calculations of vibrational wavenumbers using molecular geometry and DFT [25]. The geometry optimizations and frequency calculations of (3-ampH₂)₂CdBr₆·2H₂O were carried out using the Becke's three-parameter hybrid exchange functional (B3) [26] combined with the Lee-Yang-Parr correlation functional (LYP) [27] in conjunction with the LanL2DZ basis set [28]. DFT is used to optimize a molecule's geometry by rearranging its atoms in order to obtain a structure that is most stable and with the lowest possible ground state energy. The calculated vibrational wavenumbers were assigned with the aid of the GaussView 05 program [29] employed to generate visual presentations and verify the normal mode assignments. These properties were determined as highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO).

2.5. Druggability, pharmacokinetics and anticancer biological activity

Prediction of druggability and pharmacokinetics of the synthesized and characterized compounds was performed based on the absorption, distribution, metabolism, excretion and toxicity (ADMET) properties as previously reported [30-32] (Badraoui et al., 2021; Hchicha et al., 2021; Mhadhbi et al., 2022). Likewise, the oral bioavailability was studied based on the physicochemical structure of the complex [31-33] (Badraoui et al., 2021, 2022).

The anticancer potential was carried out by measuring both binding scores and molecular interactions of the synthesized compound using some key receptors. For this end, TNF α , COX-2, CDK6, VEGF and KRAS were targeted as receptors. Both chemical compound and receptors were processed then subjected to a CHARMM force field for the complex formations as previously published reports [31,34] (Hchicha et al., 2021; Zammel 2021).

3. Results and Discussion

3.1. X-ray diffraction and geometric optimization

The (3-ampH₂)₂CdBr₆·2H₂O compound crystallizes in the triclinic $P\bar{1}$ space group with four formula units in unit cell ($Z = 1$) with the following lattice parameters: $a = 7.993(3)$ Å, $b = 8.139(3)$, $c = 10.092(4)$ Å, $\alpha = 90.735(14)^\circ$, $\beta = 95.964(3)^\circ$ and $\gamma = 112.451(12)^\circ$. Table 1 best summarizes the key crystallographic information for the title compound. The basic unit of the studied material, Fig.1(a), is made up of one inorganic [CdBr₆]⁴⁻ anion, one diprotonated cation, 3-ammoniummethyl-pyridinium, [C₆H₁₀N₂]²⁺ or (3-ampH₂)²⁺ and one uncoordinated water molecule, all of which lie in general positions. The cohesion of this structure is established by N/C-H ... Br hydrogen bonds, giving rise to a three-dimensional network (Fig.1(a)). The [CdBr₆]⁴⁻ anions exhibit a slightly distorted octahedral arrangement around the Cd²⁺ center, with Cd-Br bond lengths in the range 2.7464(9) - 2.9002(9) Å. The Br-Cd-Br angles fall in the range 88.99(3) to 180° (Table 2). Within the deprotonated amine molecule, the C-C and N-C distances range from 1.358(4) to 1.494(5) Å and from 1.334(4) to 1.481(4) Å, respectively. The C-N-C angle is equal to 123.2 (3) °. Pyridinium cations typically possess an expanded C-N-C angle in comparison with the parent pyridine [119°], which confirms well that protonation also takes place on the pyridine ring N atom [35-39]. The selected bond distances and angles are illustrated in Table 2. As observed, the calculated geometric parameters represent a good approximation and can be used as a base to calculate the other parameters for the title compound. The structure shows various hydrogen bonds, as given in Fig.2. Indeed, the [CdBr₆]⁴⁻ anionic species are strongly attached to organic molecules. The N-H...Br hydrogen bonds link organic cations and inorganic anions to give alternatively arranged organic-inorganic layers parallel to the (*ac*) plane (Fig.2). Therefore, the water molecules are located above and below the [CdBr₆]⁴⁻ octahedral and tied between organic and inorganic molecules via hydrogen bonds. In addition, the presence of hydrogen

bonds between organic and inorganic parts plays an important role in the stability of the structure. In these hydrogen-bonded interactions, the N \cdots Br distances vary from 3.362(3) to 3.607(3) Å and the angles range from 126° to 172° (Table 3). The optimized geometry of the title compound model is presented in (Fig.1(b)). The calculated geometrical parameters of the title compound are reported and compared with the experimental ones in Table 2, in which the average relative error of almost 1.82% for the inorganic structural parameters while it does not exceed 0.9% for the organic parameters. These discrepancies can be explained by the fact that the calculation relates to the isolated molecule where the intermolecular Coulombic interaction with the neighboring molecules is absent, whereas the experimental result corresponds to interacting molecules in the crystal lattice. This result does not only support our cluster choice and calculation results, but also indicates that the calculation precision is satisfactory and the B3LYP/LanL2DZ level is suitable for the complex.

3.2. Infrared spectroscopy

Fig.3 focuses on the calculated (blue) and experimental (red) IR spectra of the title compound. The most intense IR absorption bands were dealt with in Table 4. Asymmetric and symmetric O-H (H₂O) stretching are observed at 3424 and 3409 cm⁻¹, respectively. The observed band corresponding to the N-H bending vibration is observed at 3064 cm⁻¹. The corresponding calculated value appear at 3076 cm⁻¹. The bands appearing at 3043 and 2925 cm⁻¹ are assignable to asymmetric and symmetric CH₂ stretching modes, respectively. The corresponding theoretical value is situated at 3079 and 3019 cm⁻¹. The bands identified at 1729 cm⁻¹ can be assigned to ring deformation and the H-N-H in-plane bending appeared at 1627 cm⁻¹. They are theoretically predictable at 1739 and 1651 cm⁻¹, respectively. The band appeared at 1549 cm⁻¹ results from the deformation CH₂. As it can be seen in Fig.3, the bands observed at 1467 cm⁻¹ and 1425 cm⁻¹ are assigned to the in-plane bending of H-C-C and H-N-C as well as torsion of H-N-H-Cl, respectively. Their calculated frequencies are found in

the range from 1481 to 1443 cm^{-1} . The H–C–N torsion is reported also experimentally, at 1390 cm^{-1} and theoretically, at 1406 cm^{-1} . The vibrations modes between 1379 and 1317 cm^{-1} in the experimental spectrum refer to N–C stretching, in plane bending H–C–N which are modes predicted at 1261 cm^{-1} in the calculated spectrum. The stretching vibrations C–C are also observed within the range of 1225 and 1070 cm^{-1} for the experimental spectra. The calculated frequencies between 1239 and 1087 cm^{-1} are assigned to the last mode. The H–C–C–H torsion appears in the experimental spectrum as a peak located at 1050 cm^{-1} . This mode was provided theoretically at 1063 cm^{-1} . The band identified at 793 cm^{-1} can be assigned to the torsion H–C–C–H. Its theoretical value is located at 805 cm^{-1} . The band appearing at 494 cm^{-1} is allocated to the H–C–C–C torsion. Finally, the band that appears at 406 cm^{-1} is attributed to the C–C–C–C torsion. The DFT calculation provides this mode at 417 cm^{-1} . A detailed assignment of the observed bands is displayed in Table 4.

3.3. Mulliken atomic charges

The charge distribution of the title compound (Fig.4) shows that the cadmium atom attached with bromide atoms and the carbon atoms attached with nitrogen atoms are positive. The Bromide atoms have more negative charges whereas all hydrogen atoms have a positive charge. The maximum atomic charge is obtained for Cd when compared with other atoms. This is due to the attachment of negatively charged on bromide (Br) atoms. Negatively charged bromide atoms shows that charge is transferred from Cd to Br. The calculated Mulliken charges for Cd (0.565) and Br (-0.289 / -0.010 / -0.508483 / -0.492544 / -0.443283 / -0.25847) taking part in the intramolecular charge transfer is revealed in the optical absorption. Nitrogen atoms are positively charged which shows the charge transfer from Br to N through the hydrogen bridge.

3.4. Optical characteristics

3.4.1. UV-visible spectra analysis

The measured and simulated optical UV-Vis absorption spectra of the (3-ampH₂)₂CdBr₆·2H₂O compound are shown in Fig.5. The UV-Vis spectrum exhibits four distinct absorption bands centered at 242 nm (5.12 eV), 227 nm (5.46 eV), 215 nm (5.76 eV) and 200 nm (6.2 eV). The strong absorption band centered at 242 nm should be allocated to the $\pi \rightarrow \pi^*$ transitions with the ring in the organic cation. This peak appears in the spectrum of the cation alone at 292 nm (4.24 eV). While, the average absorption band centered at 227 nm should be assigned to the charge transferred from organic cation to inorganic anion, this band appears in the simulated spectrum at 237 nm (5.23 eV). The calculated electronic transition (TDDFT) is in very good agreement with the experimental findings. The absorption bands centered at 215 nm and 200 nm should be accredited to the $n \rightarrow \pi^*$ transitions with the ring in the organic cation.

3.4.2. Global reactivity descriptors and energy gap analysis

Analysis of density functional theory descriptors gives additional information about the characteristics of stability, electrophilicity, and nucleophilicity. Therefore, the global reactivity descriptors were calculated based on the DFT method with the B3LYP/LAN2DZ basis set. The quantum chemical parameters calculated using TDDFT with B3LYP/LAN2DZ functional, molecular orbital energies (HOMO and LUMO), energy gap (ΔE_{H-L}), Electron Affinity (E_A), Ionization Potential (I_P), global hardness (η), chemical potential (μ), global softness (σ), electronegativity (χ) and electrophilicity index (ω) are listed in Table 5. All relationships connecting these parameters with HOMO and LUMO energies, termed as global reactivity descriptors are given by the following equations [40]:

$$\Delta E_{H-L} = E_{LUMO} - E_{HOMO} \quad (1)$$

$$I_P = -E_{HOMO} \quad (2)$$

$$E_A = -E_{LUMO} \quad (3)$$

$$\chi = -\frac{E_{LUMO} + E_{HOMO}}{2} \quad (4)$$

$$\mu = \frac{E_{LUMO} + E_{HOMO}}{2} \quad (5)$$

$$\eta = \frac{E_{LUMO} - E_{HOMO}}{2} \quad (6)$$

$$\sigma = \frac{1}{\eta} \quad (7)$$

$$\omega = \frac{\mu^2}{2\eta} \quad (8)$$

The chemical hardness and softness is related to the stability of a given compound. Molecules having low energy gap are called as soft molecules which are polarizable, whereas those having high energy gap are called as hard molecules which are less polarizable (non-polar). From the Table 5, it is clear that $(3\text{-ampH}_2)_2\text{CdBr}_6 \cdot 2\text{H}_2\text{O}$ exhibits a larger energy gap (3.56 eV). Its value denoted as hard and less polarizable (non-polar) molecule. For atoms, electrons include atomic orbitals, but for molecules they occupy similar molecular orbitals which are surrounded by the molecule, called frontier molecular orbitals (FMOs). The chemical activity of the molecule is reflected through the energies of the FMOs. The electron donating nature is expressed by the highest occupied molecular orbital (HOMO) which has a physical significance, which means that it has an energy value equal to the first ionization potential and the electron withdrawing nature is expressed by the lowest unoccupied molecular orbitals (LUMO) with the energy (completely or partly vacant) of a molecular entity, and has a tendency to attract electrons. These orbitals play a fundamental role in determining electric and optical properties of the compound. The molecular orbitals mapped surface with charged electron densities of HOMO and LUMO are observed in the CdBr_6 anion. The bandgap obtained from the frontier molecular orbital calculation is 3.56 eV, which is the distance between the HOMO (-0.12 eV) and LUMO (-3.68 eV), respectively. The HOMO and LUMO plots of $(3\text{-ampH}_2)_2\text{CdBr}_6 \cdot 2\text{H}_2\text{O}$ are shown in Fig.6. The transition of electrons from ground state to first excited state due to the absorption by means of one

electron excitation from the HOMO to LUMO has been known from the wave function analysis. The DOS diagram of $(3\text{-ampH}_2)_2\text{CdBr}_6 \cdot 2\text{H}_2\text{O}$ is shown in Fig.6. It is well known that chemical stability of a molecule is largely affected by the frontier orbitals. The electron donating capability of a molecule can be explained by HOMO–LUMO energy. Thus, it is assumed that the energy gap between the HOMO and LUMO reveals the reactivity of the molecule. The NLO responses can be understood by examining the energies of frontier molecular orbitals. There is an inverse relationship between hyperpolarizability and HOMO–LUMO.

3.4.3. Hyperpolarizability calculations

The NLO effect is extremely important since it plays a crucial role in various signals conditioning processes such as frequency shifting, optical modulation, optical switching, and optical interactions [41-44]. The calculation of the second-order hyperpolarizability and its components are very informative in expressing the charge delocalization and a measure of nonlinear optical effects in a compound. In this study, the total dipole moment, average linear polarizability, and the second molecular hyperpolarizability are given by using the following equations [45-48]:

$$\mu_{tot} = \sqrt{\mu_x^2 + \mu_y^2 + \mu_z^2} \quad (9)$$

$$\alpha_{tot} = \frac{\alpha_{xx} + \alpha_{yy} + \alpha_{zz}}{3} \quad (10)$$

$$\langle \gamma \rangle = \frac{1}{5} (\gamma_{xxxx} + \gamma_{yyyy} + \gamma_{zzzz} + 2(\gamma_{xxyy} + \gamma_{xxzz} + \gamma_{yyzz})) \quad (11)$$

Since the values of the Polarizability α_{tot} , and the second Hyperpolarizability $\langle \gamma \rangle$ of Gaussian 09 output are reported in atomic units (*au*), the calculated values have been converted in to electrostatic units (*esu*): $\alpha_{tot}: 1 \text{ au} = 0.1482 \times 10^{-24} \text{ esu}$, $\langle \gamma \rangle: 1 \text{ au} = 0.50367 \times 10^{-39} \text{ esu}$. As can be see Table 6, the calculated dipole moment is equal to 19.6 D (Debye). The highest value of dipole moment is observed for component μ_y . In this direction, this

value is equal to 17.14 D. For direction x and z , these values are equal to 8.40 D and 1.58 D respectively. The calculated Polarizability α_{tot} , is equal to 23.56×10^{-24} esu. The calculated Polarizability α_{ij} have non-zero values and was dominated by the diagonal components. The second Hyperpolarizability value $\langle \gamma \rangle$ of our compound is equal to 2.06×10^{-36} esu. The second Hyperpolarizability is dominated by the diagonal components of γ_{xxxx} and γ_{yyyy} . The intensive presence of particular components reveals a substantial delocalization of charges in these directions. In directions of γ_{zzzz} , γ_{xxyy} , γ_{xxzz} and γ_{yyzz} , the values of components are relatively medium. In directions of γ_{xxxy} , γ_{yyyz} and γ_{xxzx} the components values are weak. In other directions, the particular components are practically low. The non-zero $\langle \gamma \rangle$ value is probably due to the charge transfer between the organic cation and the CdBr_6 anion which facilitates the delocalization of the electronic charge density. Based on the above facts, it could be proposed that this material can be better placed for nonlinear optical applications.

3.5. Thermal behavior of $(3\text{-ampH}_2)_2[\text{CdBr}_6] \cdot 2\text{H}_2\text{O}$

The thermal stability of the examined crystal was studied by means of a simultaneous thermogravimetric analysis (TGA) and differential thermal analysis (DTA), carried out with a heating rate of $5 \text{ }^\circ\text{C} \cdot \text{min}^{-1}$ between 25 and $600 \text{ }^\circ\text{C}$ (Fig.7). The first endotherm peak at $77 \text{ }^\circ\text{C}$, starts at $35 \text{ }^\circ\text{C}$ and ends at $110 \text{ }^\circ\text{C}$, and is accompanied by a weight loss of about 4.06%. The experimental loss in mass corresponds to a value which is calculated for the removal of two water molecules (theoretical 4.24%), thus leading to the anhydrous phase $(3\text{-ampH}_2)_2[\text{CdBr}_6]$. The crystal seems to be stable up to about $250 \text{ }^\circ\text{C}$ and above this temperature a continuous decomposition of the sample takes place. The endothermic peak characterized by a weight loss of 69.77% observed on the TGA curve in the range $250\text{--}470 \text{ }^\circ\text{C}$, which can be attributed to the destruction of the organic entities (weight loss: calculated 69.77%, experimental 71.14%). $(3\text{-ampH}_2)_2[\text{CdBr}_6]$ is not stable and decompose, probably, to CdBr_2 and the

bromine derivatives. The ultimate change starts at about 500 °C and corresponds to the formation of cadmium oxide CdO.

3.6. Druggability, pharmacokinetics and anticancer biological activity

Table 7 exhibits the major criteria, which are commonly used for screening new drugs to avoid any possible failure, particularly during the clinical phase [30-31] (Badraoui et al., 2021, Hchicha et al., 2021; Zammel et al., 2021). It showed the druggability and the pharmacokinetic properties of the synthesized compound. It was predicted that both compound units obey Lipinski rule of five as they showed no violations. While presenting low to moderate skin permeability (as assessed by Log Kp), they possessed good bioavailability scores (0.55) that was confirmed further by the bioavailability radars (Fig. 8).

None of the subunits was found to be blood-brain-barrier permeant or P-glycoprotein substrate (P-gp), which permit to deduce not only the absence of any disruptions regarding the physiological drug transportation but also the safety on nervous tissues, as confirmed by previous similar results [30,49] (Badraoui et al., 2022; Zammel et al., 2022). Regarding cytochrome P450 (CYP), the major isoforms were investigated to check the compound metabolism within the body. In this context, only CYP3A4 was found to be inhibited, but no inhibition was predicted to the CYP1A2, CYP2C9, CYP2C19 and CYP2D6, which have been reported to interfere with more than 80% of the drugs and toxicants [49-51] (Zammel et al., 2022; Allouche et al., 2022; Akacha et al., 2020).

In this study, five major macromolecules, which are commonly involved in the pathogenesis of cancer, its development and metastatic process [33] (Badraoui et al., 2022), were targeted and simulated. Hence, the network of bonds of interactions were studied. As shown in table 8, the compound subunits exhibited negative binding energies with all the selected macromolecules. The obtained energies ranged between -6.0 and -3.2 kcal.mol⁻¹. Thus, the anticancer effect of the (3-ampH₂)₂[CdBr₆].2H₂O compound sounds thermodynamically

possible, as previously reported by similar docking scores [31,33,34] (Zammel et al., 2021; Hchicha et al., 2021; Badraoui et al., 2022). The best docking score was predicted for COX-2 and CDK6 with unit 1 and unit 2 of the compound, respectively (Fig. 9). Nevertheless, interaction types with COX-2 were much better. In fact, the latter established one electrostatic bond with Glu465 and four conventional H-bonds with Asn39, Cys41, Asn39 and Gln461, which were additionally, enforced by one carbon H-bond and three hydrophobic (alkyl) bonds. Furthermore, the compound was found to be deeply embedded within the pocket region of each selected receptor. Here again, the deeper embedding distance was found in the compound complexed to COX-2. Taken together, these molecular interactions contribute certainly to the stability of the complex and satisfy the possible anticancer effect of the (3-ampH₂)₂[CdBr₆]·2H₂O compound.

4. Conclusion

In a nutshell, a new organic-inorganic hybrid compound (C₆H₁₀N₂)₂[CdBr₆]·2H₂O has been successfully synthesized at room temperature by slow evaporation. This compound belongs to the triclinic system with the $P\bar{1}$ space group. The atomic arrangement can be described as an alternation of organic/inorganic layers. The cohesion and the stability of the atomic arrangement of the title compound stem from the establishment of N-H···Br and O-H···Br hydrogen bonds between the [C₆H₁₀N₂]²⁺ cations, the water molecules and the [CdBr₆]⁴⁻ anions. The vibrational FT-IR spectrum of (C₆H₁₀N₂)₂[CdBr₆]·2H₂O was recorded and the vibrational frequencies were precisely assigned with the aid of the theoretical calculations at B3LYP/LanL2DZ level. The experimental and theoretical results were found to support each other. The optical properties were investigated by optical absorption, showing four bands at 200, 215, 227 and 242 nm. The HOMO and LUMO energy gap value explain the eventual charge transfer interactions that took place in the molecule. The Mulliken atomic charges describe the charge distribution of every atom in the molecule. Moreover, the thermal analysis

results confirm the presence of two water molecules per formula in addition to an absence of any phase transition in the studied range of temperature. The physico-chemical characteristics and the properties evolution of the compound may explain the potential anticancer effect, which may result from the bioavailability, pharmacokinetics and the established molecular interactions with some cancer targeted receptors.

Acknowledgements

The authors extend their appreciation to the Deanship of Scientific Research at King Khalid University for funding this work through a research groups program under Grant Number R.G.P. 2/213/43.

Appendix

Supplementary crystallographic data for this article in CIF format are available as Electronic Supplementary Publication from Cambridge Crystallographic Data Centre (CCDC 2168558). This data can be obtained free of charge via <http://www.ccdc.cam.ac.uk/conts/retrieving.html>, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: (international): +44 1223/336 033; e-mail: deposit@ccdc.cam.ac.uk).

Conflicts of Interest

The authors declare no competing financial interest.

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