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Self-assembly of a novel Cu(II) complex, (C₆H₉N₂)₂[CuCl₄]: Experimental, Computational, and Molecular Docking survey

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ABSTRACT

In the title salt complex (C₆H₉N₂)₂[CuCl₄] symbolized along this work by (2A5PCuCl₄), the Cu²⁺ cation is coordinated by four chloride anions and adopts a distorted tetrahedral geometry. This compound has been crystallized in the monoclinic space group C2/c and the following parameters obtained are $a = 13.0244(19) \text{ \AA}$, $b = 8.3149(11) \text{ \AA}$, $c = 16.001(2) \text{ \AA}$, $\beta = 93.730(6)^\circ$, $Z = 4$, $V = 1729.2(4) \text{ \AA}^3$ at 150 K. In the crystal structure the atomic arrangement consists of isolated tetrahedral entities connected to the organic groups by weak hydrogen bonds N-H ... Cl and C-H ... Cl forming a three-dimensional network. The Hirshfeld surface analysis shows on two-dimensional fingerprints maps the great dominance of H ... Cl and H ... H contacts in the crystal packaging. The geometrical optimization, electronic, topological and biological properties of 2A5PCuCl₄ were theoretically studied using DFT. The HOMO and LUMO analysis is used to decide the charge transfer within the structure. Natural bond orbital (NBO) analysis was carried out to study hyperconjugative interactions. Optical transmission measurements investigated by UV-visible and photoluminescence spectroscopy are carried out on a crystalline thin-film of 2A5PCuCl₄ show the detection of two absorption bands centered at 316 and 519 nm coherent with those observed in the perovskites based on CuCl₄. Photoluminescence measurements showed two peaks at around 433 and 472 nm. The unaided-eye-detectable blue luminescence emission comes from the excitonic transition in the CuCl₄ anions.

Keywords: Cu(II) complex, X-ray diffraction, RDG, HOMO-LUMO, Fluorescence, Molecular docking.

1. Introduction

A hybrid compound is a material that includes both organic and inorganic components blended on the molecular scale. This type of materials has received increasing attention in

recent research; it offers the opportunity to combine the expected properties of organic components and inorganic materials when they rise in the solid state. More particularly, the hybrid compounds based on halogen of the general formula $\mathbf{R}_2[\mathbf{MX}_4]$ where $\mathbf{M}$ transition metal, $\mathbf{X}$: Cl, Br, I and $\mathbf{R}$ is an organic cation, attract the interests of chemists because of their structural flexibility and their interesting properties in various fields namely in magnetism, photoluminescence, biological, photocatalysis, nonlinear optics, electric and ferroelectric [1-10]. These proprieties are not only due to the sum of the individual contribution of both moieties, but also they are strongly related to the nature of the bonds between the two components inside the structure. Therefore, these physicochemical and biological properties of these materials depend strongly on their size, shape and dimensionality. Referring on the properties of certain hybrid perovskites based on the metal IVA (Ge, Sn and Pb) halide [11, 12] and transition metals (Cu, Co, Fe, Ni), it is found that only the latter have good solubility and stability. However research has been carried out on this kind of perovskites are generally very rare, shows exciting possibilities in modulation of magnetic, semiconducting, dielectric, ferroelectric properties mainly driven by structural phase transitions of these crystals [13-19]. Indeed, the chemical constructions $\mathbf{MX}_4$ form substructures in these compounds giving rise to anionic resins according to the organic entity through hydrogen bonds N-H ... X and C-H ... X with different topologies (0D), (1D), (2D) or (3D).

On the other hand, cancer disease is among the most dangerous disorders in the world, often perceived as "the worst disease" [20, 21]. It has been estimated that is the leading cause of death before the age of sixty five. It conforms to an uncontrolled and abnormal proliferation of cells within the organism. As significant therapeutic drug targets, amino acid has caught the attention of many scientists for its preventive capacity against cancer malady [22]. In addition, it has many other biological properties since it contributes to treat diseases related to disturbances in the dopaminergic systems like Parkinson, Schizophrenia and Alzheimer's [23]. These disorders belong to the class of psychotic malady. In this context, $2\mathbf{A5PCuCl}_4$ compound is used as an inhibitor against these disorders using molecular docking (molecular modeling). Docking studies have swiftly entered the area of biological research given its efficiency in the calculations [24, 25]. The inhibitory activity of $2\mathbf{A5PCuCl}_4$ molecule against "Cyclin-dependent Kinase 2" ($\mathbf{CdK2}$) and "inducible nitric oxide synthase" ($\mathbf{iNOS}$) enzymes has been estimated. These two enzymes contribute significantly to the development of these diseases. Consequently, the present paper reports the chemical preparation of the $2\mathbf{A5PCuCl}_4$ complex, as well as its characterization by various experimental and theoretical techniques such as X-ray diffraction, this is the main technique used to discover in a first step the crystallographic

characteristics of our structure and in a second stage its atomic arrangement, Hirshfeld surfaces analysis, spectroscopic measurements (UV-visible, Photoluminescence) and *in silico* survey.

2. Experimental

2.1 Materials and measurements

Single crystal of the title compound with dimensions $0.58 \times 0.47 \times 0.35$ mm was chosen for X-ray diffraction studies. Data were collected on a D8 VENTURE Bruker-AXS diffractometer with MoK α monochromatic radiation ($\lambda = 0.71073$ Å) at 150 K. Absorption corrections were performed using the multi-scan technique using the SADABS program [26]. The total number of measured reflections was 9625 ($3^\circ < \theta < 27^\circ$) among which 1975 were independent and 1896 had intensity $I > 2\sigma(I)$. The structure was successfully developed in the centrosymmetric space group C2/c solved by direct methods using the SIR97 program [27] and then refined with full-matrix least-square methods based on F^2 (SHELXL-97) [28] with the aid of the WINGX program [29] to $R(F^2) = 0.023$, $wR(F^2) = 0.058$. All non-hydrogen atoms were refined with anisotropic atomic displacement parameters. The hydrogen atoms bonded to nitrogen atoms were located from a difference map. The rest of the H atoms were treated as riding, with C-H = 0.95 Å (aromatic), or 0.98 Å (methyl), with $U_{iso}(H) = 1.2U_{eq}$ (C-aromatic atoms) and $1.5U_{eq}$ (C-methyl atoms). The parameters used for the X-ray data collection as well as the strategy for the crystal structure determination and its final results are reported in Table 1. Structure graphics are drawn with ORTEP [29] and Diamond program [30].

Emission spectrum was obtained on a Perkin-Elmer LS55 fluorescence spectrometer equipped with a 450 W xenon lamp as the excitation source using solid sample at room temperature.

2.2. Chemical preparation of $(C_6H_9N_2)_2[CuCl_4]$

To an aqueous solution of 2-Amino-5-picoline acidified with a few drops of HCl is added an aqueous solution of copper chloride hexahydrate, the resulting mixture (pH = 3) was heated for half an hour with magnetic stirring. After 3 days at ambient temperature the solution reaches saturation and gives rise to yellow prismatic crystals of bis(2-Amino-5-methylpyridin-1-ium) tetrachlorocuprate(II) stable and of suitable size for study by X-ray diffraction (Yield 70%, Solubility in ethanol and Dimethyl sulfoxide (DMSO)).

2.3. Theoretical studies

To quantify the arrangement of the hydrogen bonds and the intermolecular interactions in 2A5PCuCl₄, Hirshfeld surfaces analysis have been calculated, this is an excellent approach used to generate unit cell packing diagrams of the compounds. This analysis is based on a 3D graph that represents the space region where the molecules come in contact and another 2D that

summarizes the complexes information contained in a structure and makes it possible to identify each type of interaction. The analysis and calculations of this empirical method were carried out using the Crystal Explorer version 3.1 [31] software imported on a CIF file.

The molecular geometry optimization and all quantum-chemical calculations have been performed by using the hybrid B3LYP levels, the 6-311++G(d,p) basis set was used for all atoms except for the copper atom, the LANL2DZ basis set and effective core potentials (ECPs) have been used in order to represent the metal. The theoretical calculations have been achieved with the Gaussian 09 software package [32] and the GaussView molecular visualization program [33]. In this work, NBO calculations [34] were employed to calculate the donor-acceptor energy interactions. The reduced density gradient of the title molecule are graphed by Multiwfn [35] and plotted by the VMD program [36].

The molecular docking simulation was performed via iGEMDOCK program [37] based on GEMDOCK (Generic Evolutionary Method for Docking Molecules) scoring function (with the following setting: the population size is 800, the number 10 of generations is 80 and the number of solutions is 10). This program provides the total energy value of the basic of the ligand-protein interactions. Three important interactions can be identified: van der Waals, hydrogen bonding and electronic interactions. The structures of the two enzymes and the different ligands are obtained from Protein Data Bank [38]. Eight complexes from the PDB database comprising proteins and ligands were selected. The visual representations of the docked ligands are determined via Discovery Studio Visualizer interface.

3. Results and discussion

3.1. Structural analysis and geometric optimization

The ORTEP representation of 2A5PCuCl₄ was used to establish the structural model, whose asymmetric unit consists of a crystallographically independent monoprotonated organic cation (C₈H₉N₂⁺) and a half of [CuCl₄]²⁻ anion (the other half is generated by crystallographic twofold symmetry). The ORTEP representation and the optimized geometric model of this compound are respectively shown in Fig. 1a and Fig. 1b. To describe the atomic arrangement and better understand the crystalline architecture, 2A5PCuCl₄ was projected along the $\vec{b}$ axis (Fig. 2). This projection demonstrates the atomic organization of chemical buildings involved in the composition of the crystal in the form of an alternation of cationic groups parallel to the (001) plane between which the CuCl₄ tetrahedra are inserted in position $z = 1/4$ and $3/4$ via hydrogen bonds N-H ... Cl and C-H ... Cl forming a three-dimensional network. Electrostatic and van der Waals interactions intervene in the crystal package. 2A5PCuCl₄ has a network formed by two

types of strong (N1- H1...Cl1, N2- H2A...Cl2 with $d_{\text{H-Cl}} < \text{RVW}$ (2.81 Å)) and weak (N-H...Cl and C-H...Cl) hydrogen bonds ensuring the cohesion and the stability of the crystalline structure (Table 2). Five links N-H...Cl and two C-H...Cl considered weak with donor-acceptor distances ranging from 3.220 (1) to 3.709 (2) Å establish the links between the cationic and the anionic entities, note that the hydrogen atoms H2A and H2B are engaged in hydrogen bonds bifurcas seen that they are the seats of two N-H... Cl bonds. These bonds play an important role in the maintenance and the stability of the crystalline architecture of the compound thanks to the pores formed by their combinations such that $R_1^2(6)$, $R_2^4(10)$ and $R_4^4(18)$ (Fig. 3) [39]. The $[\text{CuCl}_4]^{2-}$ anion adopts a tetrahedral molecular geometry (Cl–Cu–Cl angles vary from 95.641(18) to 143.91(2)°, $d_{\text{moy}}\langle\text{Cu–Cl}\rangle \sim 2.24705(4)\text{Å}$) (Table 3), a copper atom in the center and four chlorine atoms at the corners of a tetrahedron with an sp^3 hybridization these values are often found in organic cations cuprates [40, 41]. The distinguished bond lengths of Cu–Cl and bond angles of Cl–Cu–Cl signify the existence of the Jahn–Teller effect in 2A5PCuCl_4 .

The parameter τ_4 can be used to describe the geometry of 2A5PCuCl_4 ; it is a useful parameter for four-coordinate transition metal complexes, given by the following relation.

$$\tau_4 = \frac{360^\circ - (\alpha + \beta)}{141^\circ}$$

α and β represent the two largest angles in the four-coordinate species. Applying this equation for the compound bis(2-Amino-5-methylpyridin-1-ium) tetrachlorocuprate(II) gives a τ_4 equal to 0.57 which is compatible to the C_{2v} seesaw structure [42].

As regards the cationic group (Fig.1a and Table 3), the latter has a disubstituted plane geometry C2 and C5, a methyl ($-\text{CH}_3$) coplanar with the pyridine group on the C2 atom with a C1–C2 distance equal to 1.505 Å and a ($-\text{NH}_2$) group on the C5 atom with a distance N2–C5 = 1.343 Å. The pyridine ring is characterized by C–C and C–N bond lengths varying from 1.355 to 1.418 Å and bond angles ranging from 116.24 to 123.78°. These geometrical characteristics have no particularity in terms of values usually encountered in analogous compounds [43]. It's worth noting that the pyridinium nuclei interact by strong and weak π - π stacking interactions leading to chains along the crystallographic axis $\vec{a}$ (Fig. 3), with separation distances from the centers of centroids respectively 3.097 Å and 4.066 Å. This allows the cohesion and consolidation of the crystalline architecture of 2A5PCuCl_4 .

It should be underlined that the organic groups are arranged in opposition in the interlayer spacing, consequently building a local inversion center. Analogous a situation is not favorable to the non centrosymmetrical arrangement observed in other halocuprate(II) [44].

A comparative study between the geometry obtained from the experimental data and the optimized geometry predicted by DFT(B3LYP/LANL2DZ) is given in Table 3. In general, the results of the experimental study by X-ray diffraction are in good agreement with those of the theoretical study carried out using the DFT method, except for some differences. These differences are due to the fact that the theoretical values belong to the isolated molecule in the gas phase and the experimental values are attributed to the solid state molecule. Thermodynamic parameters performed in the water and gas phase of the title compound such as global energy, zero point energy vibration, thermal energy, dipole moment, polarizability, hyperpolarizability, heat capacity and entropy are recorded in Table S1. These parameters more particularly the global energy (-3825.2 Hartree in gas phase; -3825.2 Hartree in water), the binding thermal energy between the ($\text{C}_8\text{H}_9\text{N}_2^+$) cation and the $[\text{CuCl}_4]^{2-}$ anion which is equal to 105.8 kcal.mol⁻¹ in phase gas and 105.7 kcal.mol⁻¹ in water and the value of the high dipole moment (14.140997 Debye in gas phase, 17.729433 Debye in water) suggest the formation of intermolecular Hydrogen bonds in 2A5PCuCl₄ this is confirmed by the extension of the N-Cl bonds under the effect of the protonation carried on the N16 atom (optimized molecule), N1 (Ortep representation) which results in an increased stabilization of 2A5PCuCl₄.

3.2. Quantitative analysis of intermolecular interactions by Hirshfeld surfaces approach

To understand the different interactions and contacts in the crystal, it is necessary to represent the Hirshfeld surface. It has recently been shown that the Hirshfeld surface is a very efficient empirical method for characterizing intermolecular interactions. This analysis was performed using the Crystal Explorer software [31]. It is defined as the set of points where the ratio between the promolecular electronic density and the electron density of procrystal is greater than or equal to 0.5. It is represented in general for a ratio equal to 0.5. Some properties can be represented on a Hirshfeld surface such as:

- The term d_e corresponds to the distance from the point to the nearest atom outside to the surface.
- The term d_i corresponds to the distance to the nearest atom inside to the surface.
- The term d_{norm} corresponds to normalized distance from the van der Waals rays of atoms.

$$d_{norm} = \frac{d_i - r_i^{vdW}}{r_i^{vdW}} + \frac{d_e - r_e^{vdW}}{r_e^{vdW}}$$

- Curvedness cartography used to define a coordination number in the crystal.
- Shape index cartography can be used to identify complementary hollows (with shape index < 0) and bumps (with shape index > 0).

Fig. 4 represents the (d_{norm}) crystallography of the crystal where the color scheme varies from -0.446 to 1.212, the latter surrounded by other neighboring molecules through hydrogen bonds N–H ... Cl and C–H ... Cl located exactly on the red spots can be considered to be the closest intermolecular contacts. The blue areas of this graph indicate the most intermolecular contacts in the structure and the white regions represent the contacts around van der Waals separation. These last correspond respectively to the H ... H, C ... H and N...H interactions [45]. In the 2D graph (fingerprints plots), the H ... Cl / Cl ... H contacts (Fig. 4a) occupy more than half of the Hirshfeld surface (57.3%) and appear as two narrow, non-symmetrical sharp points (Cl ... H = 45% with $d_i + d_e = 2.2\text{\AA}$ and H ... Cl = 12.3% with $d_i + d_e = 2.6\text{\AA}$). The H ... H intercontacts (Fig. 4b) comprise 23.9% of the total Hirshfeld surface with a maximum sum $d_e + d_i \sim 2.6\text{\AA}$. The C ... H / H ... C (Fig. 4c) and N ... H / H ... N (Fig. 4d) contacts show on their 2D digital plots the presence of two wings respectively centered around a sum $d_e + d_i \sim 3.1\text{\AA}$ and $3.3\text{\AA}$. The Percentage of various intermolecular contacts contributed to the Hirshfeld surface in the 2A5PCuCl₄ compound is listed in Fig.5. The comparison of sums of the components (d_i , d_e) of these contacts with the sum of the van der Waals radii of the involved atoms shows that only the Cl ... H contacts considered as being close together.

Next to the hydrogen bonds which form the three-dimensional architecture of the crystalline stack, this stack is provided by other π - π bonds which provide the link between the antiparallel and neighboring pyridinium rings. The presence of the red and blue triangles on the Shape index cartography (Fig. 6), the planar regions delimited by a blue outline around the pyridinium cycle mapped with Curvedness (Fig. 6) and the important contribution of the C ... C (3.1%) contacts centered in $d_i = d_e = 1.7\text{\AA}$ (Fig. 6) [46] confirm the presence of π - π interactions already observed by X-ray diffraction in 2A5PCuCl₄.

3.3. Topological study of noncovalent interactions: NCI-RDG analysis

Besides experimental interpretations based on X-ray diffraction and other empirical studies such as Hirshfeld surfaces analysis Johnson et al. [47] proposed a new approach, the so-called RDG analysis to validate and evaluate the intermolecular interactions existing in the crystal structure of 2A5PCuCl₄. The RDG is a fundamental dimensionless quantity coming from the density and its first derivative:

$$RDG(r) = \frac{1}{2(3\pi^2)^{1/3}} \frac{|\nabla\rho(r)|}{\rho(r)^{4/3}}$$

Generally, according to the sign of the eigenvalue λ_2 , the stabilizing or destabilizing nature of the different interactions in 2A5PCuCl₄ compound can be determined. The negative sign of λ_2 provides information on the interesting contributions to non-covalent interactions and more specifically to hydrogen bonds, on the other hand the region where the sign $\lambda_2 > 0$ relates to repulsive and non-binding interactions (steric effect in ring and cage), the values located in the vicinity of the separation (close to zero) are attributed to the van der Waals interactions. The different plots and results obtained along this theoretical analysis according to a very precise color code are produced respectively using the Multiwfn and VMD programs [35, 36] and illustrated in Figs. 7a,b. The RDG fingerprint (Fig. 7a) shows the great stability of 2A5PCuCl₄ ensured by strong hydrogen bonds N-H ... Cl and even if weak of the C-H ... Cl type. These obligations appeared with a sign $\lambda_2 \rho$ ranging from -0.015 to -0.005 Å. Also the isosurface representation (Fig. 7b) clearly indicates the presence of blue spots between the hydrogen and chlorine atoms, which signifies the strong attractive interaction N-H...Cl. The light intensity of the green color in the RDG isosurface proves the presence of a strong VDW interaction. Finally the elliptical red spot centered at the level of the pyridinium nucleus is attributed to repulsive interactions which show a strong steric effect.

3.4. NBO analysis

NBO analysis was developed to describe the electronic structure of chemical systems, it provides information on charge transfer and possible interactions of the donor-acceptor type between orbitals [48-49]. This analysis effectively finds the Lewis structure and the hybridization of the orbitals. In general, this analysis is very effective for the chemical interpretation of hyper-conjugate interactions and the transfer of electrons from pairs of free electron pairs LP (A) towards the anti-binding orbital σ^* (D-H) of the hydrogen bond D—H... A. The second-order Fock-matrix was carried out to evaluate the donor-acceptor interactions in the NBO basis. For each donor (i) and acceptor (j) the stabilization energy ($E^{(2)}$) associated with the delocalization $i \rightarrow j$ is determined as:

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

Where q_i is the donor orbital occupancy; ε_i and ε_j are orbital energies of donor and acceptor NBO orbitals and F_{ij} is the off-diagonal Fock matrix. The higher value of $E^{(2)}$ (stabilization energy or energy of hyper conjugative interaction) points toward the greater interaction between

electron donors and electron acceptors. Second-order perturbation theory analysis for selected donor (Lewis) and acceptor (non-Lewis) orbital's, of the Fock matrix in NBO basis calculated at DFT method is illustrated in [Table S2](#). This table shows some of the significant donor–acceptor interactions in 2A5PCuCl₄ compound. The exhaustive analysis reveal that the mentioned molecule presents five different interactions ($\sigma \rightarrow \sigma^*$, $\sigma \rightarrow \pi^*$, $\pi \rightarrow \pi^*$, $\pi^* \rightarrow \pi^*$ and $LP \rightarrow \sigma^*$). As clearly seen the energy of hyperconjugative interaction for the pyridinium nucleus due to the interaction π to π^* varies from 5.2 kcal.mol⁻¹ [$\pi(C_{15}-N_{16}) \rightarrow \pi^*(C_{11}-C_{13})$] to 34.2 kcal.mol⁻¹ [$\pi(C_{11}-C_{13}) \rightarrow \pi^*(C_{15}-N_{16})$]. NBO analysis confirms the existence of X-H...Y hydrogen bonds between the different interaction donor-acceptor evoking the example of the interaction between $LP(2) \rightarrow Cl_2 \rightarrow \sigma^*(N_{16}-H_{17})$ and $LP(3)-Cl_3 \rightarrow \sigma^*(N_{20}-H_{22})$ who is characterized respectively by a stabilizing energy equal to 2.7 and 0.1 kcal/mol. A very important result it is observed between the anti bonding orbital $\sigma^*(Cu_1-Cl_4)$ transitions related to $\sigma^*(Cu_1-Cl_5)$ and $\sigma^*(Cu_1-Cl_3)$ (83.11 and 84.39 kcal.mol⁻¹). Another transitions have been observed between the lone pairs LP donor orbital interact with the anti bonding orbital σ^* such that, $LP(3)-Cl_3 \rightarrow \sigma^*(Cu_1-Cl_3)$, $LP(3)-Cl_4 \rightarrow \sigma^*(Cu_1-Cl_4)$, $LP(3)-Cl_5 \rightarrow \sigma^*(Cu_1-Cl_5)$ and $LP(4)-Cl_2 \rightarrow \sigma^*(Cu_1-Cl_4)$ which give, respectively, stabilization energy $E^{(2)}$ values of 8.7, 5.1, 8.4 and 11.8 kcal.mol⁻¹. Note that the important values of this energy result from the formation of the hydrogen bonds. This energy plays a very important role in the stability and cohesion of the studied crystal.

3.5. Frontier molecular orbital analysis

Conjugated heterocycles consist of a regular alternation of σ single bonds and π double bonds. The overlap of the π orbitals leading to electronic offshoring is largely influenced by the geometry of the system. The basis for understanding and predicting chemical reactions involving the π system of conjugated molecules is the concept of border orbitals. So indeed the highest energy occupied molecular orbital HOMO (Highest Occupied Molecular Orbital) and the lowest energy unoccupied orbital LUMO (Lowest Unoccupied Molecular Orbital), are excellent indicators of electron transfer in molecular systems. These orbitals are largely involved in the chemical stability of the molecule and play an important role in determining its electronic properties. The values of the border orbital HOMO, LUMO, HOMO-1 and LUMO+1 involved in the electronic transitions of 2A5PCuCl₄ and their energy difference (the gap (ΔE)) obtained by the DFT method are shown in [Fig. 8a](#). In this figure the red color indicates the positive phase on the other hand the green color represents the negative phase. The HOMO-LUMO gap energy is equal to 4.2 eV, this low energy value between the two orbitals promotes the transfer of electrons in the material, hence the probability of $\pi-\pi^*$ transition is very possible

between the HOMO (π) and LUMO (π^*) orbitals, this makes 2A5PCuCl₄ more reactive and less stable. In conclusion, the compound 2A5PCuCl₄ has a small gap (small deviation of the border orbital) so it is classified among the most polarizable molecules which have a high chemical reactivity and also have a low kinetic stability, and generally considered as a soft molecule [50, 51]. The energy separation value between HOMO and LUMO (4.2 eV) for 2A5PCuCl₄ is compatible with the values obtained by DOS spectrum (Fig. 8b). The comparison of 2A5PCuCl₄ with that of 2A5PCoCl₄ [43] at the gap energy level shows that this last one has an energy equal to 2.9 eV, almost half of 4.2 eV (Eg of 2A5PCuCl₄), this difference can be related to the results already observed by X-ray diffraction, especially at the level of the asymmetric unit of the compound 2A5PCoCl₄ which has two organic entities.

3.6. UV-Vis Absorption and fluorescence properties

Ultraviolet spectra analysis of 2A5PCuCl₄ (Fig. 9) has been investigated in gas phase by theoretical calculation and is within 200–800 nm range. The UV-Visible spectrum gives diverse optical parameters such as theoretical energies (E), absorption wavelengths (λ), oscillator strengths (f) and major contributions corresponding to electronic absorption wavelengths that are listed in Table S3. It is found that there are two distinct absorption peaks at 316 nm (3.9 eV) and 519 nm (2.4 eV), which is very compatible with other organic-inorganic hybrid films containing [CuCl₄]²⁻ previously reported such as (C₅H₇N₂)₂CuCl₄.H₂O [41] (C₄H₉NH₃)₂CuCl₄ [50], (C₁₀H₂₁NH₃)₂CuCl₄ [51]. The observed exciton peaks at 316 and 519 nm are characteristics of the inorganic copper chloride tetrahedral surrounded by organic cations. The first peak located at 316 nm is the most intense, this peak comes from the transition between the valence band Cl(3p) and the conduction band Cu(4s) [52] corresponds to the π - π^* transition relative to the organic group (C₈H₉N₂⁺), while that the peak observed around 519 nm is due to a photo induced exciton formed by the transition from the top of the valence band consisting of Cl(3p) orbital to the bottom of the Cu(3d).

Regarding the luminescent properties, the luminescence spectrum is recorded under the excitation of 290 nm at room temperature (Fig. 10a). This spectrum shows the presence of two bands, a strong one at 433 nm and another weak located around 472 nm. These emission peaks can be probably may originate from the ligand-to-metal charge-transfer (LMCT) transition [53] attributed to electronic transitions within the inorganic part [CuCl₄]²⁻. These luminescence properties are comparable to those found in other Cu(II) halide complexes [41, 54]. The schematic model illustrated in Fig. 10b explains the process of formation and recombination of the exciton in 2A5PCuCl₄. The electron (-) and the hole (+) circulate freely in the conduction

band (CB) and the valence band (VB), forming an exciton. The recombination of the electron and the hole in the exciton gives a blue emission at 433 nm and 472 nm.

3.7. Molecular electrostatic potential

Electrostatic potential is a property which makes it possible to provide information on chemical reactivity or to describe intermolecular interactions. It is very useful for the qualitative interpretation of electrophilic and nucleophilic reactions and hydrogen bond interactions. Grace to the electrostatic force generated on the field lines, the molecules will approach and interact with each other in certain preferential directions. Based on a color code to detect and display regions and molecular properties of the electrostatic potential. The blue color indicates positive values (region of strong attraction), red for negative values (region of strong repulsion) and green indicate the neutral zone. The electrostatic potential diagram and contour line map are illustrated in Fig. 11a. The regions of negative potentials (excess in electrons) are associated with the free doublets of chlorine atoms while the regions of positive potentials (deficient in electrons) are associated with hydrogen atoms. Indeed the electrophilic and nucleophilic sites confirm well the existence of N-H ... Cl and C-H ... Cl intermolecular hydrogen bonds between the tetrachlorocuprate anion $[\text{CuCl}_4]^{2-}$ and ammonium group of $(\text{C}_8\text{H}_9\text{N}_2^+)$ and explain their important role in the stabilization of the crystal. White areas cover parts of the molecule where electrostatic potentials are close to zero are found C-C, C-H bonds and enveloping the π -system of the pyridine cycle. The positive and negative potential sites of the molecule observed in Fig. 11a can be clearly seen in the contour map represented in Fig. 11b.

3.8. Molecular docking analysis

Molecular docking calculation contains two important steps: prognosticating of the ligand conformation and its position within these sites and evaluation of the binding affinity. These steps are related to iGEMDOCK program, which is used to dock each ligand to the receptor active site using the generic evolutionary method (GA) and an empirical scoring function. In the majority of cases, when the ligand interacts with the protein, the interaction takes place at the level of the protein surface. Through this calculation, the fundamental biochemical processes can be elucidated [55]. The conformation with the lowest docking energy is considered the best orientation [56]. The top scoring docked poses (lowest docked energies) of each blocker are represented in Fig. 12. The energetic results of docking calculations are fully summarized in Table S4. The rows in this table is arranged on the basis of total energy value, where is the sum of the van der Waals energies, H-bonds and electronic interactions. For more details, in Figs S1 and S2 are represented the best poses of ligands in CdK2 and iNOS enzymes

interactions in 2D diagrams and their H-bonds interaction. In this paper, two examples of successful applications of molecular docking are submitted.

Cdk2 protein is an enzyme that plays an important role in the development of many tumor cells [57]. As it was observed abnormal activity of Cdk2 in gastric, colorectal, breast and bone cancers, as well as in lymphoma and in leukemia [58], docking of receptor Cdk2 was co-crystallized with SC8 [59], LIA [60], RRC [61] and 2A5PCuCl₄ ligands. The results show that the total energy scores of the four complexes are at a comparable level, whose average energy is equal to 66.6 kcal.mol⁻¹. It should also be noted that the interactions of the ligands with the enzyme are purely VDW and hydrogen bonds interactions, all ligands haven't electronic interactions (Table S4). As it is tabulated in Table S4, docking calculations led to the following results: the VDW interaction equal to -95.5, -82.7, -90.4 and -52.8 kcal.mol⁻¹ for SC8, LIA, RRC and 2A5PCuCl₄ ligands interacting with Cdk2 protein and their H-bond interaction were -10.5, -16.8, -7.0 and -3.5 kcal.mol⁻¹, respectively.

The second protein is iNOS, which represents one of three key enzymes producing nitric oxide (NO). It has a significant role in various physiological and path-physiological conditions. The overproduction of nitric oxide by the neuronal and inducible NOS can causes certain degenerative neurological disorders, such as Parkinson, Schizophrenia [62] and Alzheimer's diseases. The docking characteristics of iNOS enzyme with various ligands: H4B [63], HBI [23], FC1[23] and 2A5PCuCl₄ can be investigated. All these ligands showed good total energy scores toward the target protein ranging from -104.2 to -65.0 kcal.mol⁻¹. The decreasing order of the VDW interaction is HBI> FC1> H4B>2A5PCuCl₄ with energies equal to -83.2, -76.4, -72.6 and -58.2 kcal.mol⁻¹, respectively. An interesting comparison is HBI, FC1 and 2A5PCuCl₄, which have almost the same positions (Fig. 12b).

According to these results, the molecular docking analysis shows that the 2A5PCuCl₄ inhibitor penetrates well into the active site of the Cdk2 and iNOS enzymes. So, it may provide valuable information in the field of anticancer drug design and in the treatment of Parkinson, Schizophrenia and Alzheimer's diseases.

4. Conclusions

In the present work, a novel salt complex 2A5PCuCl₄ was successfully synthesized in three days at ambient temperature by slow evaporation. The novel compound was characterized by experimental and theoretical physicochemical methods.

Single crystal X-ray diffraction analysis indicated that 2A5PCuCl₄ crystallizes in the monoclinic space group C2/c. The structural determination discovered that π - π , N-H...Cl and C-H...Cl are implicated in the crystal packing, as investigated by the Hirshfeld surface and topological analysis. Indeed, the Hirshfeld surface analysis disclosed the percentage of intermolecular contacts of 2A5PCuCl₄ and showed that the major part of the Hirshfeld surface is occupied by the contacts H...Cl/Cl...H

The optimized geometry obtained using the DFT(B3LYP/LANL2DZ) approach is in good accordance with the experimental result. RDG, NBO, MEP and Frontier molecular orbital analysis has been used to study the stability of our compound. The optical properties were investigated by UV-Vis absorption and photoluminescence measurements and revealed that the complex exhibits a blue light emission in the solid state at room temperature. Finally, the molecular docking analysis plays a very interesting role in the medical field and it shows that the inhibitor 2A5PCuCl₄ detects valuable information in the manufacture of anticancer drugs even if in the treatment of Parkinson's disease, Schizophrenia and Alzheimer's.

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Table captions

Table 1. Crystal data and experimental parameters used for the intensity data collection strategy and final results of the structure determination of 2A5PCuCl₄.

Table 2. Hydrogen-bond geometry (Å, °) of 2A5PCuCl₄.

Table 3. Selected bond distances (Å) and angles (°) by X-ray data (with estimated standard deviation in parentheses) and by theoretical calculations at different levels of theory.

Table 1

CCDC	1942855
Empirical formula	(C ₆ H ₉ N ₂) ₂ [CuCl ₄]
Temperature	150 K
Formula weight (g mol ⁻¹)	423.64
Crystal system	Monoclinic
Space group	C2/c
a, b, c (Å)	13.0244(19), 8.3149(11), 16.001(2)
β(°)	93.730(6)
Z	4
V(Å ³)	1729.2(4)
F(000)	860
Radiation type	Mo Kα
μ(mm ⁻¹)	1.878
Crystal size (mm)	0.58 x 0.47 x 0.35
Index ranges	-16 ≤ h ≤ 16, -10 ≤ k ≤ 9, -20 ≤ l ≤ 20
Reflections collected	9625
Independent reflections	1975
Reflections with I > 2σ(I)	1896
R _{int}	0.024
Diffractometer	D8 VENTURE Bruker AXS
Absorption correction	Multi-scan
T _{min} , T _{max}	0.392, 0.518
Refined parameters	106
R[F ² > 2σ(F ²)]	0.023
wR(F ²)	0.058
Goodness of fit	1.10
Δρ _{max} , Δρ _{min} (eÅ ⁻³)	0.25, -0.62

Table 2

$D-H\cdots A$	$D-H$ (Å)	$H\cdots A$ (Å)	$D\cdots A$ (Å)	$D-H\cdots A$ (°)
N1—H1 $\cdots$ Cl1	0.82(2)	2.41(2)	3.2204(14)	168.8(18)
N2—H2A $\cdots$ Cl2 ⁱ	0.80(2)	2.80(2)	3.4559(16)	139.8(19)
N2—H2A $\cdots$ Cl1 ⁱ	0.80(2)	2.95(2)	3.5899(15)	137.7(19)
N2—H2B $\cdots$ Cl1	0.83(2)	2.91(2)	3.5954(17)	141.6(18)
N2—H2B $\cdots$ Cl2	0.83(2)	2.92(2)	3.6003(15)	141.5(18)
C3—H3 $\cdots$ Cl2 ⁱⁱ	0.95	2.83	3.7090(16)	154.4
C4—H4 $\cdots$ Cl2 ⁱ	0.95	2.81	3.4632(16)	126.8

Symmetry code: (i) $-x+3/2, y-1/2, -z+1/2$; (ii) $x, -y, z+1/2$.

Table 3

Theoretical				Experimental
In gas phase		In Water		X-ray
Cu1-Cl2	2.250	Cu1-Cl2	2.243	2.238(4)
Cu1-Cl3	2.206	Cu1-Cl3	2.232	2.238(4)
Cu1-Cl4	2.178	Cu1-Cl4	2.222	2.257(4)
Cu1-Cl5	2.215	Cu1-Cl5	2.228	2.257(4)
C6-C10	1.505	C6-C10	1.503	1.504(2)
C10-C11	1.418	C10-C11	1.418	1.411(2)
C10-C18	1.371	C10-C18	1.368	1.364(2)
C11-C13	1.373	C11-C13	1.372	1.369(2)
C13-C15	1.414	C13-C15	1.411	1.410(2)
C15-N16	1.355	C15-N16	1.353	1.346(2)
C15-N20	1.343	C15-N20	1.346	1.340(2)
N16-C18	1.360	N16-C18	1.365	1.367(2)
Cl2-Cu1-Cl3	90.0524	Cl2-Cu1-Cl3	89.8818	136.21(2)
Cl2-Cu1-Cl5	90.1182	Cl2-Cu1-Cl5	89.9519	95.641(18)
Cl3-Cu1-Cl4	90.519	Cl3-Cu1-Cl4	90.094	97.628(18)
Cl4-Cu1-Cl5	90.6788	Cl4-Cu1-Cl5	90.0532	143.91(2)
C6-C10-C11	121.7566	C6-C10-C11	121.6645	121.74(14)
C6-C10-C18	122.0004	C6-C10-C18	121.8212	121.56(14)
C11-C10-C18	116.2402	C11-C10-C18	116.5135	116.70(14)
C10-C11-C13	122.109	C10-C11-C13	121.8321	122.04(14)
C11-C13-C15	119.6406	C11-C13-C15	119.6866	119.47(14)
C13-C15-N16	116.9164	C13-C15-N16	117.3851	117.33(13)
C13-C15-N20	124.1064	C13-C15-N20	123.0642	123.39(14)
N16-C15-N20	118.9723	N16-C15-N20	119.5351	119.26(14)
C15-N16-C18	123.7821	C15-N16-C18	123.2638	123.53(13)

Figure captions

Fig. 1. ORTEP drawing with the atom-labeling scheme. Displacement ellipsoids are drawn at the 30% probability level. H atoms are represented as small spheres of arbitrary radii. Symmetry code (i): $-x, y, -z+1/2$. Intermolecular H-bonds are denoted by purple dotted lines.

(a) and the optimized geometry (b) of **2A5PCuCl₄**.

Fig. 2. Projection of the **2A5PCuCl₄** structure along b axis. The **CuCl₄** groups are given in tetrahedral representation. Intermolecular H-bonds are denoted by purple dotted lines.

Fig. 3. Hydrogen bond motifs in **2A5PCuCl₄** and π - π stacking interactions between neighboring aromatic rings. Intermolecular H-bonds are represented with purple dotted lines.

Fig. 4. Hirshfeld surfaces mapped with d_{norm} cartography (3D) and fingerprint plots (2D) of **2A5PCuCl₄** resolved into H...Cl/ Cl ...H (a), H...H(b), C...H/H...C (c) and N...H/H...N (d) contacts.

Fig. 5. Percentage of various intermolecular contacts contributed to the Hirshfeld surface in the **2A5PCuCl₄** compound.

Fig. 6. π - π interactions demonstrated by Hirshfeld surface analysis mapped with Shape index and Curvedness for the title compound.

Fig. 7. Two-dimensional (2D) NCI-RDG scatter plot (a) and Three-dimensional (3D) RDG isosurfaces density (b) plot along with the color filled scale bar defining interaction limits for the **2A5PCuCl₄** compound.

Fig. 8. The frontier molecular orbitals (a) and DOS spectrum (b) of **2A5PCuCl₄** computed with TD-DFT(B3LYP)/6-311++G(d,p) in gas phase.

Fig. 9. UV-visible spectra of **2A5PCuCl₄** molecule.

Fig. 10. Emission spectrum (a) and model for the formation and recombination of the exciton (b) of **2A5PCuCl₄** in the solid state at room temperature.

Fig. 11. The MEP (a) and its contour (b) surfaces of the **2A5PCuCl₄**.

Fig. 12. Lowest energy docked poses of the ligands with CdK2 (a) and iNOS (b) proteins.

Fig. 1

Fig. 2

Fig. 3

Fig. 4

Fig. 5

Fig. 6

Fig. 7

Fig. 8

Fig. 9

Fig. 10

Fig. 11

Fig. 12

**Self-assembly of a novel Cu(II) complex, (C₆H₉N₂)₂[CuCl₄]: Experimental,
Computational, and Molecular Docking survey**

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Figure Captions

Fig. S1. Representation of 2D interactions between CdK2 protein-Ligand and their H-bonds interaction.

Fig. S2. Representation of 2D interactions between iNOS protein-Ligand and their H-bonds interaction.

Fig. S1. Representation of 2D interactions between Cdk2 protein-Ligand and their H-bonds interaction.

Fig. S2. Representation of 2D interactions between iNOS protein-Ligand and their H-bonds interaction.

Table Captions

Table S1. Thermodynamic parameters in gas phase and in water of 2A5PCuCl₄.

Table S2. Natural bond orbital studies and the corresponding energies $E^{(2)}$ by using B3LYP/6-311++G (d,p) method. $E^{(2)}$: stabilization energy or energy of hyper conjugative interaction; $E(j)-E(i)$: Energy difference between donor and acceptor i and j NBO orbitals; $F(i,j)$ is the Fock matrix element between i and j NBO orbitals.

Table S3. Theoretical UV-Visible characteristics of 2A5PCuCl₄ compound.

Table S4. Molecular docking results of interaction energies (in kcal/mol) using iGEMDOCK program.

Table S1. Thermodynamic parameters in gas phase and in water of 2A5PCuCl₄.

Thermodynamic parameters	In gas phase	In Water
Global energy	-3825.2 Hartree	-3825.2 Hartree
Dipole Moment	14.140997 Debye	17.729433 Debye
Polarizability	187.71668 a.u.	276.13 a.u.
HyperPolarizability	584.94276 a.u.	414.35741 a.u.
Zero point energy vibration	0.2 Hartree	0.2 Hartree
E (Thermal)	105.8 kcal.mol ⁻¹	105.7 kcal.mol ⁻¹
Heat Capacity	56.4 cal.mol ⁻¹ .K ⁻¹	56.9 cal.mol ⁻¹ .K ⁻¹
Entropy (S)	143.8 cal.mol ⁻¹ .K ⁻¹	137.7 cal.mol ⁻¹ .K ⁻¹

Table S2. Natural bond orbital studies and the corresponding energies $E^{(2)}$ by using B3LYP/6-311++G (d,p) method. $E^{(2)}$: stabilization energy or energy of hyper conjugative interaction; $E(j)-E(i)$: Energy difference between donor and acceptor i and j NBO orbitals; $F(i,j)$ is the Fock matrix element between i and j NBO orbitals.

Donor (i)	Acceptor (j)	$E^{(2)}$ [kcal.mol ⁻¹]	$E(j)-E(i)$ [a.u.]	$F(i,j)$ [a.u.]
$\sigma(\text{Cu}_1-\text{Cl}_3)$	$\sigma^*(\text{Cu}_1-\text{Cl}_5)$	12.8	0.57	0.079
$\sigma(\text{Cu}_1-\text{Cl}_4)$	$\sigma^*(\text{Cu}_1-\text{Cl}_3)$	9.0	0.55	0.065
$\sigma(\text{Cu}_1-\text{Cl}_4)$	$\sigma^*(\text{Cu}_1-\text{Cl}_5)$	8.3	0.56	0.062
$\sigma(\text{Cu}_1-\text{Cl}_5)$	$\sigma^*(\text{Cu}_1-\text{Cl}_3)$	11.5	0.58	0.075
$\sigma(\text{C}_{15}-\text{N}_{16})$	$\sigma^*(\text{N}_{16}-\text{H}_{17})$	3.4	1.79	0.069
$\sigma(\text{C}_{18}-\text{H}_{19})$	$\sigma^*(\text{C}_{15}-\text{N}_{16})$	4.0	1.07	0.058
$\sigma(\text{N}_{20}-\text{H}_{21})$	$\sigma^*(\text{C}_{15}-\text{N}_{16})$	4.4	1.26	0.066
$\sigma^*(\text{Cu}_1-\text{Cl}_3)$	$\sigma^*(\text{N}_{20}-\text{H}_{22})$	0.1	0.67	0.016
$\sigma^*(\text{Cu}_1-\text{Cl}_4)$	$\sigma^*(\text{Cu}_1-\text{Cl}_3)$	84.4	0.10	0.150
$\sigma^*(\text{Cu}_1-\text{Cl}_4)$	$\sigma^*(\text{Cu}_1-\text{Cl}_5)$	83.1	0.10	0.152
$\sigma(\text{C}_6-\text{H}_7)$	$\pi^*(\text{C}_{10}-\text{C}_{18})$	4.4	0.56	0.047
$\sigma(\text{C}_6-\text{H}_8)$	$\pi^*(\text{C}_{10}-\text{C}_{18})$	1.0	0.56	0.022
$\pi(\text{C}_{10}-\text{C}_{18})$	$\pi^*(\text{C}_{11}-\text{C}_{13})$	21.5	0.29	0.072
$\pi(\text{C}_{10}-\text{C}_{18})$	$\pi^*(\text{C}_{15}-\text{N}_{16})$	10.5	0.22	0.046
$\pi(\text{C}_{11}-\text{C}_{13})$	$\pi^*(\text{C}_{10}-\text{C}_{18})$	14.0	0.30	0.059
$\pi(\text{C}_{11}-\text{C}_{13})$	$\pi^*(\text{C}_{15}-\text{N}_{16})$	34.2	0.22	0.084
$\pi(\text{C}_{15}-\text{N}_{16})$	$\pi^*(\text{C}_{10}-\text{C}_{18})$	19.8	0.40	0.081
$\pi(\text{C}_{15}-\text{N}_{16})$	$\pi^*(\text{C}_{11}-\text{C}_{13})$	5.2	0.39	0.041
$\pi^*(\text{C}_{15}-\text{N}_{16})$	$\pi^*(\text{C}_{10}-\text{C}_{18})$	22.1	0.08	0.061
$\pi^*(\text{C}_{15}-\text{N}_{16})$	$\pi^*(\text{C}_{11}-\text{C}_{13})$	49.0	0.07	0.086
LP(2)-Cl ₂	$\sigma^*(\text{N}_{16}-\text{H}_{17})$	2.7	1.50	0.056
LP(3)-Cl ₃	$\sigma^*(\text{Cu}_1-\text{Cl}_3)$	8.7	0.77	0.077
LP(3)-Cl ₄	$\sigma^*(\text{Cu}_1-\text{Cl}_4)$	5.1	0.68	0.056
LP(3)-Cl ₅	$\sigma^*(\text{Cu}_1-\text{Cl}_5)$	8.4	0.77	0.075
LP(4)-Cl ₂	$\sigma^*(\text{Cu}_1-\text{Cl}_4)$	11.8	0.39	0.063
LP(1)-N ₂₀	$\sigma^*(\text{C}_{15}-\text{N}_{16})$	75.4	0.22	0.123
LP(3)-Cl ₃	$\sigma^*(\text{N}_{20}-\text{H}_{22})$	0.1	1.45	0.009
LP(1)-Cl ₂	$\sigma^*(\text{Cu}_1-\text{Cl}_3)$	2.0	0.49	0.030
LP(1)-Cl ₂	$\sigma^*(\text{Cu}_1-\text{Cl}_5)$	2.7	0.49	0.035

Table S3. Theoretical UV-Visible characteristics of 2A5PCuCl₄ compound.

Energy (eV)	λ (nm)	f	Major contributions
1.0	1204	0.0022	H-17(B)->LUMO(B) (17%), H-5(B)->LUMO(B) (11%), H-3(B)->LUMO(B) (24%), HOMO(B)->LUMO(B) (44%)
1.1	1063	0.0030	H-16(B)->LUMO(B) (19%), H-7(B)->LUMO(B) (24%), H-3(B)->LUMO(B) (16%), H-2(B)->LUMO(B) (34%)
1.4	875	0.0020	H-12(B)->LUMO(B) (28%), H-6(B)->LUMO(B) (56%)
1.4	858	0.0000	H-21(B)->LUMO(B) (28%), H-8(B)->LUMO(B) (66%)
2.0	593	0.0000	H-4(B)->LUMO(B) (50%), H-1(B)->LUMO(B) (47%)
2.3	531	0.0150	H-7(B)->LUMO(B) (10%), H-5(B)->LUMO(B) (51%), H-2(B)->LUMO(B) (32%)
2.4	519	0.0175	H-7(B)->LUMO(B) (46%), H-5(B)->LUMO(B) (15%), H-3(B)->LUMO(B) (31%)
2.6	463	0.0001	H-4(B)->LUMO(B) (48%), H-1(B)->LUMO(B) (50%)
2.6	461	0.0012	H-5(B)->LUMO(B) (14%), H-3(B)->LUMO(B) (16%), H-2(B)->LUMO(B) (25%), HOMO(B)->LUMO(B) (39%)
2.9	410	0.0006	H-13(B)->LUMO(B) (10%), H-12(B)->LUMO(B) (44%), H-6(B)->LUMO(B) (41%)
2.9	406	0.0000	H-2(A)->LUMO(A) (14%), H-1(A)->L+1(A) (15%), H-1(B)->L+1(B) (10%)
2.9	406	0.000	H-2(A)->L+1(A) (13%), H-1(A)->LUMO(A) (15%), H-1(B)->L+2(B) (10%)
3.2	380	0.000	H-9(B)->LUMO(B) (97%)
3.2	370	0.0042	H-17(B)->LUMO(B) (24%), H-10(B)->LUMO(B) (52%)
3.4	355	0.0081	H-16(B)->LUMO(B) (34%), H-11(B)->LUMO(B) (36%), H-7(B)->LUMO(B) (13%)
3.8	320	0.0599	H-17(B)->LUMO(B) (48%), H-10(B)->LUMO(B) (38%)
3.8	318	0.1148	H-16(B)->LUMO(B) (36%), H-11(B)->LUMO(B) (52%)
3.8	317	0.0000	H-21(B)->LUMO(B) (66%), H-8(B)->LUMO(B) (30%)
3.8	316	0.0001	H-2(A)->L+3(A) (10%), H-1(A)->L+2(A) (13%)
3.9	311	0.0000	H-2(A)->L+2(A) (11%), H-1(A)->L+3(A) (12%)
3.9	306	0.0007	HOMO(A)->LUMO(A) (93%)
3.9	305	0.0000	HOMO(A)->L+1(A) (94%)
4.1	291	0.0042	H-3(B)->L+1(B) (10%), H-2(B)->L+1(B) (10%), HOMO(B)->L+1(B) (70%)
4.1	291	0.0089	H-2(B)->L+2(B) (16%), HOMO(B)->L+2(B) (71%)
4.1	290	0.0016	H-4(B)->L+2(B) (20%), H-3(B)->L+1(B) (16%), H-2(B)->L+1(B) (25%), H-1(B)->L+2(B) (29%)
4.1	290	0.0040	H-4(B)->L+1(B) (24%), H-3(B)->L+2(B) (19%), H-2(B)->L+2(B) (17%), H-1(B)->L+1(B) (31%)
4.2	286	0.0057	H-3(A)->L+1(A) (39%), H-2(A)->L+1(A) (38%)
4.2	286	0.0120	H-3(A)->LUMO(A) (41%), H-2(A)->LUMO(A) (38%)
4.2	284	0.0000	H-3(B)->L+1(B) (10%), H-2(B)->L+1(B) (36%), H-1(B)->L+2(B) (30%)
4.2	283	0.0004	H-3(B)->L+2(B) (13%), H-2(B)->L+2(B) (41%), H-1(B)->L+1(B) (29%)

Table S4. Molecular docking results of interaction energies (in kcal/mol) using iGEMDOCK program.

Protein	Ligand	Total energy	VDW	H-bond	Electronic	AverConPair
CdK2	SC8	-105.9	-95.5	-10.5	0	24.321
	LIA	-99.5	-82.7	-16.8	0	22.166
	RRC	-97.4	-90.4	-7.0	0	24.423
	2A5PCuCl₄	-56.2	-52.8	-3.5	0	23.384
INOS	H4B	-104.2	-72.6	-31.6	0	38.588
	HBI	-95.2	-83.2	-12.0	0	32.235
	FC1	-82.4	-76.4	-6.0	0	27.500
	2A5PCuCl₄	-65.0	-58.2	-6.8	0	31.461