



Crystal structure, DFT studies, in silico evaluation of as a potential inhibitor against monkeypox virus, and ADMET properties of tetrachlorometallate salts of procaine

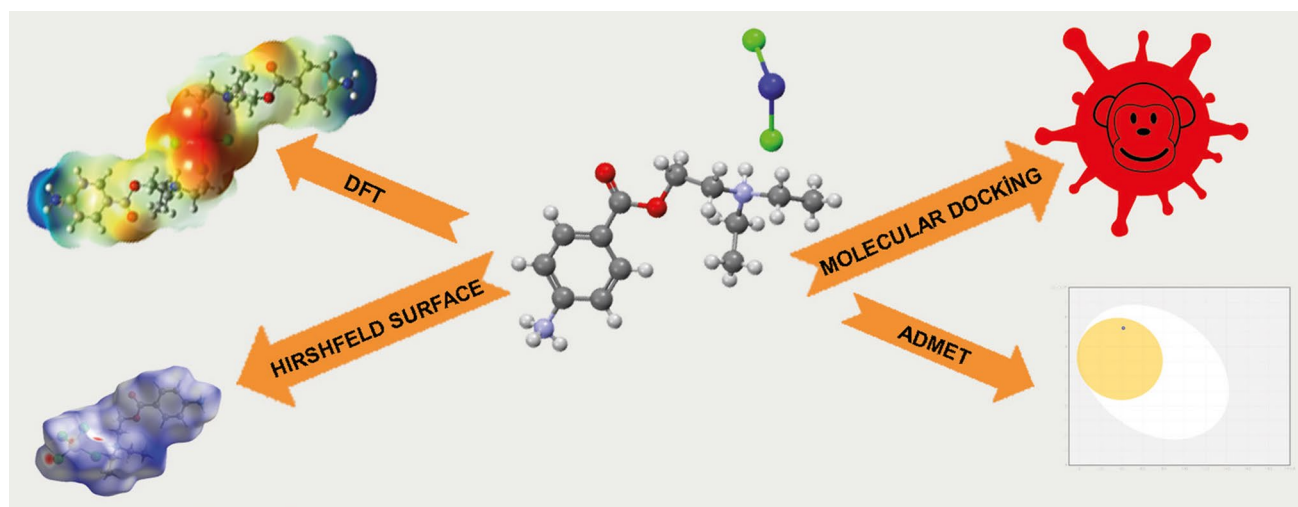
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Abstract

Two novel tetrachlorometallate salts of procaine have been designed and evaluated as potential antiviral drug candidates. Bis(procainium)tetrachlorido cadmium(II) (Complex 1) and bis(procainium)tetrachlorido cobalt(II) (Complex 2) were fully characterized via elemental analysis, FTIR spectroscopy, Mass Spectrometry, and single-crystal X-ray crystallography. The organic–inorganic hybrid complexes have an asymmetric unit that consists of one tetrachlorometallate anion and two protonated procainium cations. In order to analyze intermolecular interactions, Hirshfeld surfaces, and 2D fingerprint plots have been investigated. DFT calculations of the complexes were made and metal-to-ligand and ligand-to-metal charge transfer between metal and ligand were observed. Moreover, while the cadmium complex has a band gap of 3.63 eV, this value is greatly narrowed to 1.76 eV in the cobalt complex. The interactions of the complexes on the analgesic target, cyclooxygenase-2 enzyme, and A42R Profilin-like Protein, methyltransferase VP39 enzyme, and polymerase holoenzyme of monkeypox virus were investigated by molecular docking in order to predict its potential application as an effective antiviral drug. The interactions of the complexes with the selected targets and their binding affinity to the targets showed good inhibition performance when compared to the reference antiviral drugs. Moreover, the ADMET properties of the complexes were estimated with the help of online databases.

Graphical abstract



Keywords Novocaine · Monkeypox virus · Molecular docking · DFT · ADMET

Introduction

While the COVID-19 epidemic was still ongoing, monkeypox had raised new concerns around the world. Unlike COVID-19, which humanity suffered from in 2019, monkeypox is a previously known virus and was first reported in 1958. While the first monkeypox disease in humans was seen in Africa in 1970, its emergence in different continents in 2022 "Is it a new pandemic?" brought the question to mind (Ajmera et al. 2022; Lai et al. 2022; Singhal et al. 2022). The monkeypox outbreak of 2022 was depicted as a fast-spreading human outbreak with community transmission outside of Africa's endemic areas (Dou et al. 2022; Koenig et al. 2022). Again, the World Health Organization declared on May 11, 2023, that monkeypox is no longer a global health emergency. It is a zoonotic virus that is spread via droplets and exposure to infected skin lesions and/or infected materials, with an incubation period of 6–13 days (Velavan and Meyer 2022). Like many viral diseases (Avdeeva et al. 2022), there is no proven drug treatment for monkeypox infection. Smallpox vaccination is advised to prevent the disease and decrease the severity of symptoms such as high fever, headache, back pain, muscle aches, sore throat, swollen lymph nodes, and rash (Hraib et al. 2022; Velavan and Meyer 2022). Because variola, vaccinia, and monkeypox viruses are similar, smallpox vaccines and treatments are known to be effective in patients (Siegrist and Sassine 2022; Lam et al. 2022). Antivirals used in the treatment of smallpox are Brincidofovir, Cidofovir, and Tecovirimat, (Rizk et al. 2022; Chakraborty et al. 2022; Hung et al. 2022). After the first symptoms of the disease were detected, many countries started to use and stockpile smallpox vaccines and drugs to control the epidemic (Siegrist and Sassine 2022; Lam et al. 2022).

Procaine was synthesized by Alfred Einhorn in 1905. Procaine hydrochloride (Novocaine, 2-(diethylamino) ethyl-4-aminobenzoate hydrochloride) was first introduced to clinical practice as a local anesthetic in 1905 by Professor Heinrich Braun. It is commercially known not only as novocaine but also as procaine, neocaine, planocaine, kerokain, and etokaine. It is a local anesthetic that has been preferred for many years due to its low toxicity, water solubility, compatibility with adrenaline, and the ideal alternative to cocaine (Ball and Westhorpe 2004). New studies are being added every day on the research and design of more effective drugs. In addition to synthesizing new molecules, researchers are also investigating whether derivatives of known drugs are drug candidate molecules (Silverman and Holladay 2014; Borutinskaite et al. 2016). Based on this idea, many derivatives, co-crystals, and complexes of procaine HCl

have been synthesized and their anesthetic (Yin et al. 2022), antibacterial (Adam 2012), anticarcinogenic (Viale et al. 1996; Paşa et al. 2021; Bhol et al. 2022), and bovine serum albumin binding activities (MohdS and Al-Lohedan 2017) have been investigated. In addition to co-crystals, heavy metal complexes with intriguing structures (Hökelek et al. 2009) also exhibit promising biological activities (although many transition metals are known to be toxic) (Majumdar et al. 2020, 2021a, 2021b, 2022). Cobalt is an element that is essential for mammals in the form of cobalamin (vitamin B12). Bioavailability is possible from water-soluble inorganic cobalt compounds (Lison 2015). Although there is a lot of data on the toxicity of cadmium, another transition metal, studies on the biological activity of cadmium complexes, like other heavy metal complexes, continue to be carried out in recent years. Moreover, promising results of many *in vivo*, *in vitro* and *in silico* studies have been reported in the literature (Nordberg et al. 2015; Majumdar et al. 2023c). In this study, we synthesized two new metal complexes of procaine HCl and determined their crystal structures using single-crystal X-ray diffraction, FTIR spectroscopy, and Mass Spectrometry methods. We examined the interactions of these complexes with the A42R Profilin-like Protein, methyltransferase VP39 enzyme and polymerase holoenzyme of Monkeypox Virus, and cyclooxygenase-2 enzyme, which is an important analgesic target, *in silico* with the help of Molecular Docking. Furthermore, the physicochemical properties, lipophilicity, water solubility, pharmacokinetics, drug-likeness, and toxicity properties of the complexes were estimated with the help of online databases.

Materials and methods

Chemicals and instruments

Procaine HCl (Novocaine drug, Ukraine), CdCl₂ (Sigma Aldrich, Germany), and CoCl₂·6H₂O (Sigma Aldrich, Germany) were purchased commercially and used without any preliminary purification. The elemental analyzer LECO CNHS 932 was used to determine the C, H, and N percentages. FTIR spectra of the complexes were recorded with a PerkinElmer Frontier™ FTIR Spectrometer with a Diamond ATR accessory in the region 4000–600 cm⁻¹ from solid samples. Mass spectra were recorded on Bruker Microflex LT MALDI-TOF MS spectrometer using α -cyano-4-hydroxycinnamic acid (CHCA) as the MALDI matrix. The magnetic susceptibility measurements were obtained by using the Gouy balance at 298 K which was calibrated with Hg[Co(SCN)₄] as

standard. The effective magnetic moments were calculated from the expression: $\mu_{\text{eff}} = 2.83\sqrt{XMcd.T}$ B.M

Synthesis of Complex 1

For 1 g (3.66 mmol) Procaine HCl, 40 drug ampoules of 5 mg/mL concentration of the commercially available drug Novocaine were used. This solution, having a volume of 200 mL, was added to a solution of 0.33 g (1.83 mmol) of CdCl_2 dissolved in 100 mL of distilled water. The mixture was stirred by heating at 80 °C for 30 min. It was then kept at room temperature. After a week, the white crystals were filtered and washed with distilled water.

Anal. Calc. (%) for $\text{C}_{26}\text{H}_{44}\text{CdCl}_4\text{N}_4\text{O}_4$: C, 42.73; H, 6.07; N, 7.67. Found (%): C, 42.86; H, 6.01; N, 7.72. Yield: 82% (1.09 g), FTIR (cm^{-1}): $\nu(\text{N-H})_{\text{as}}$: 3548, $\nu(\text{N-H})_{\text{s}}$: 3365, $\nu(\text{C-H})_{\text{ring}}$: 3079, $\nu(\text{CH}_3)$: 3006, $\nu(\text{CH}_2)$: 2981, $\nu(\text{C=O})$: 1692, $\nu(\text{NH}_2)_{\text{scissoring}}$: 1618, $\nu(\text{C=C})$: 1590, $\nu(\text{CH}_3)_{\text{as}}$: 1512, $\nu(\text{CH}_2)_{\text{scissoring}}$: 1444. MALDI-TOF (m/z) calculated: 675.37, found 341.43 as $[\text{M} + 3\text{H}]^{2+}$ (Figure S1).

Synthesis of Complex 2

For 1 g (3.66 mmol) Procaine HCl, 40 drug ampoules of 5 mg/mL concentration of the commercially available drug Novocaine were used. This solution, having a volume of 200 mL, was added to a solution of 0.43 g (1.83 mmol) of $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ dissolved in 100 mL of distilled water. The mixture was stirred by heating at 80° for 30 min. It was then kept at room temperature. After ten days, the pink crystals were filtered and washed with distilled water.

Anal. Calc. (%) for $\text{C}_{26}\text{H}_{44}\text{Cl}_4\text{CoN}_4\text{O}_4$: C, 46.24; H, 6.27; N, 8.30. Found (%): C, 46.36; H, 6.41; N, 8.34. Yield: 84% (1.03 g), FTIR (cm^{-1}): $\nu(\text{N-H})_{\text{as}}$: 3469, $\nu(\text{N-H})_{\text{s}}$: 3351, $\nu(\text{C-H})_{\text{ring}}$: 3069, $\nu(\text{CH}_3)$: 2980, $\nu(\text{CH}_2)$: 2951, $\nu(\text{C=O})$: 1689, $\nu(\text{NH}_2)_{\text{scissoring}}$: 1620, $\nu(\text{C=C})$: 1570, $\nu(\text{CH}_3)_{\text{as}}$: 1518, $\nu(\text{CH}_2)_{\text{scissoring}}$: 1458. MALDI-TOF (m/z) calculated: 728.85, found 364.33 as $[\text{M}]^{2+}$ (Figure S1).

Single-crystal X-ray diffraction

Single-Crystal X-ray diffraction experiments were performed on the Bruker APEX II CCD. All crystal structures were solved using SHELXT (Sheldrick 2015a) and then refined with full matrix least squares corrections on F2 using SHELXL (Sheldrick 2015b) in the Olex2 Software Package (Dolomanov et al. 2009). Aromatic and aliphatic C-bonded H atoms are geometrically positioned and refined using a

smearing mode. Crystal structure verifications, geometric calculations, and drawings were performed using Mercury (Macrae et al. 2020) software. Additional crystallographic data with CCDC reference numbers 2215314 (Complex 1) and 2,215,315 (Complex 2) are deposited in the Cambridge Crystallographic Data Center at www.ccdc.cam.ac.uk/depot it.

Computational method

Density Functional Theory (DFT) (Kohn and Sham 1965) was used to investigate the molecular properties of the complexes. The 3D structures of the complexes were obtained from the crystal information file (CIF) and Gaussian 16, Revision C.01, et al. (2016) software. IQMol v2.14.0 (<http://iqmol.org/>) software was used for visualizations. B3LYP functionals (Becke 1988), (Becke 1993), (Lee et al. 1988) used with the SDD basis set in DFT calculations.

Crystal Explorer 21.5 (Spackman et al. 2021) was utilized to perform Hirshfeld surface analysis to provide more information and quantify the molecular crystal's intermolecular interactions.

In silico assays

Molecular docking is a technique used to calculate the binding energy of a protein–ligand interaction and determine potential ligand binding sites. The Molecular docking studies were carried out using the AutoDock Vina program. Protein crystallographic structures (A42R profilin-like protein of monkeypox virus (PDB Code: 4QWO (Minasov et al. 2022b)), monkeypox virus methyltransferase VP39 (PDB Code: 8CEQA (Silhan et al. 2023)), monkeypox virus DNA polymerase holoenzyme (PDB Code: 8HG1 (Peng et al. 2023)), and cyclooxygenase-2 (prostaglandin synthase-2) (PDB Code: 1CX2 (Kurumbail et al. 1996)) were obtained from the Protein Data Bank (<https://www.rcsb.org/>). To make the targeted protein receptor-free, the protein coordinates were first refined by removing all water and heteroatoms. The polar hydrogens and Kollman charges were then added to the protein with the Autodock tool 1.5.6 (Park et al. 2006). Autodock tool program is used to save the produced protein and ligand coordinates in pdbqt file format. After the cationic and anionic units were bonded to each other via N–H...Cl bonds, the ligand.pdbqt file was prepared. The grid box of the necessary volume is chosen so that the ligand can freely spin inside the active site of the proteins. The coordinates and dimensions of the grid box are used to generate the configuration files. The Vina Lamarckian genetic algorithm (Seeliger and de Groot 2010) creates output files that provide anticipated free energy for binding

areas. The outcome includes various stances with related energies that were examined. Discovery Studio 2021 Client BIOVIA, Dassault Systèmes, BIOVIA (2021) was used to visualize ligand interaction with the proteins.

The Pharmit web server (<http://pharmit.csb.pitt.edu/>) is an online tool for creating pharmacophores based on complicated inhibitor compounds and database screening. The Pharmit web application is free to use and has a very user-friendly interface for creating pharmacophore models, and by utilizing the produced model, one can quickly screen several built-in databases as well as user-made molecular databases (Sunseri and Koes 2016).

Estimates of the absorption, distribution, metabolism, and excretion (ADME) properties of the complexes were obtained using the <http://www.swissadme.ch/> online web server (Daina et al. 2017), and estimates of the toxicity properties were obtained using the https://tox-new.charite.de/protox_II/ online web server (Banerjee et al. 2018).

Results and discussion

Structural description

The asymmetric unit contains one protonated procainium cation and one half of a tetrachlorometallate $[\text{MCl}_4]^{2-}$ anion (Fig. 1a and b). The molecular unit of the organic–inorganic hybrid compounds is made up of one tetrachlorometallate $[\text{MCl}_4]^{2-}$ anion contains one M^{2+} ion, four Cl^- ions together with two protonated procainium cation $[\text{C}_{13}\text{H}_{21}\text{N}_2\text{O}_2]^+$ (Fig. 1c). Crystallographic information of Complexes **1** and **2** is given in Table 1.

The $[\text{MCl}_4]^{2-}$ anions represent a slightly distorted tetrahedron with C2 symmetry compressed along the twofold rotation axis. The coordination geometry about the metal atoms shows a tetrahedron formed by the Cl1, Cl2, Cl1ⁱ, and Cl2ⁱ atoms (i: 1-x, y, 3/2-z). In Complex **1** the Cl–Co–Cl bond angles are in the range 104.56(4)–119.28(6)° with an average angle Cl–Co–Cl of 109.53(5)°, and in Complex **2** Cl–Cd–Cl bond angles are in the range 101.82(4)–122.22(6)° with an average angle Cl–Cd–Cl of 109.60(5)°. The average angles Cl–M–Cl are very close to the ideal tetrahedral angle value of 109.28°. The Co–Cl bond length in Complex **1** ranges from 2.2497(10) to 2.2805(10) Å (average Co–Cl length 2.2651 Å), which is in the range of commonly observed distances between cobalt halides and is similar to the lengths which are usually found in analogous compounds containing tetrachlorocobaltate(II) anions (Bisht et al. 2012; Tounsi et al. 2016, 2017; Chaouachi et al. 2016; Mostafa et al. 2018; Issaoui et al. 2019; Dhouib et al. 2020). The Cd–Cl distances vary between 2.4282(11) Å and 2.4616(10) Å with an average value equal to 2.4449 Å, which is comparable to those found in other organic–inorganic hybrid

compounds containing isolated $[\text{CdCl}_4]^{2-}$ tetrahedral anions (Richardson et al. 1975; Oleksyn et al. 1978; Azumi et al. 1996; Neve et al. 2002; Jellibi et al. 2015; Boufas et al. 2015).

In both complexes, M–Cl2 and M–Cl2ⁱ bond lengths are approximately 0.03 Å longer than M–Cl1 and M–Cl1ⁱ bond lengths, in as much as the C2 and Cl2ⁱ atoms in $[\text{MCl}_4]^{2-}$ anions are connected symmetrically to two $[\text{C}_{13}\text{H}_{21}\text{N}_2\text{O}_2]^+$ cations by three-center hydrogen bonds of the N–H...Cl₂M type (Yap et al. 1995; Dadon and Bernstein 1997; Lewis 1998). In addition, the amino groups of two procainium cations with antiparallel aminobenzoic groups between the $[\text{MCl}_4]^{2-}$ anions form hydrogen bonds of the N–H...Cl type with symmetrical related Cl2 atoms. This leads to a weakening of the M–Cl2 and M–Cl2ⁱ bonds compared to the M–Cl1 and M–Cl1ⁱ bonds. Thus, two procainium cations between two anions form a ribbon along the [101] direction due to hydrogen bonds (Fig. 2a and b). The packing diagrams of Complexes **1** and **2** are given in Fig. 3a and b, respectively. All bond lengths and angles are given in Tables S1 and S2.

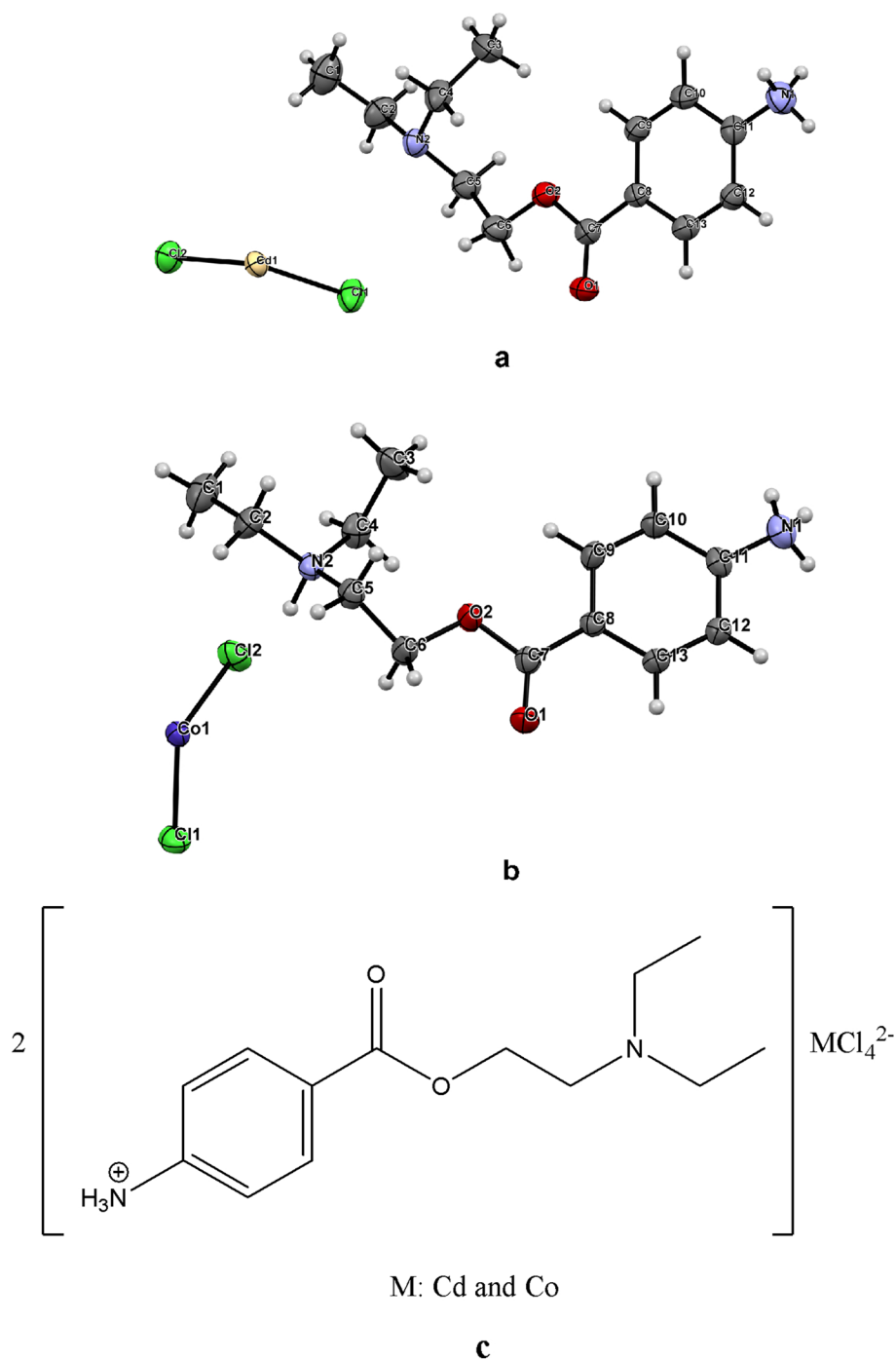
Each procainium cation is attached to two neighboring cations stacked "head to tail" by intermolecular hydrogen bonds between the amino and carbonyl groups. Parameter of hydrogen bonds: N...O 3.054 Å and 3.086 Å, H...O 2.292 Å and 2.233 Å, N–H...O 147.91° and 170.96° for complexes **1** and **2**, respectively.

The *p*-aminobenzoate group has a quinonoid character. The average values of C9–C10 and C12–C13 bond distance in the phenyl rings of **1** and **2**, respectively, are shortened to 1.373 Å and 1.372 Å compared with the mean of the remaining ring C–C distances 1.392 Å and 1.391 Å. The average values of the two endocyclic angles at the carbon atoms defining the para positions 118.2 and 118.55, in **1** and **2** respectively, compared with mean values of 120.7° and 120.9° for the other four endocyclic angles. In the Zn complex (Sokolova et al. 1991) the corresponding values are 117.5 and 121.25°, in the free *p*-aminobenzoic acid the mean values are 118.8 and 120.6° (Lai and Marsh 1967), showing an equally small but significant contribution from the quinoid structure.

The torsion angles in the chains from the C8 atom to C4 indicate that the C8–C7–O2–C6–C5–N2–C4 fragment in both complexes has trans–trans–gauche–gauche conformation, which is observed in procaine (Kashino et al. 1982), its salts (Beall and Sass 1970; Dexter 1972; Freeman and Bugg 1975) and its Zn complex (Sokolova et al. 1991). The torsion angles at C7–C8 indicate that the carboxyl groups in both complexes are not in the same plane as the phenyl rings (Table S3).

Since the proximity of the ammonium nitrogen atom to the ether oxygen atom and the orientation of ammonium substituents relative to the ether oxygen are important features necessary for effective effector–receptor interaction,

Fig. 1 Asymmetric unit of Complex **1** **a** and Complex **2** **b** and molecular unit of the complexes **c**

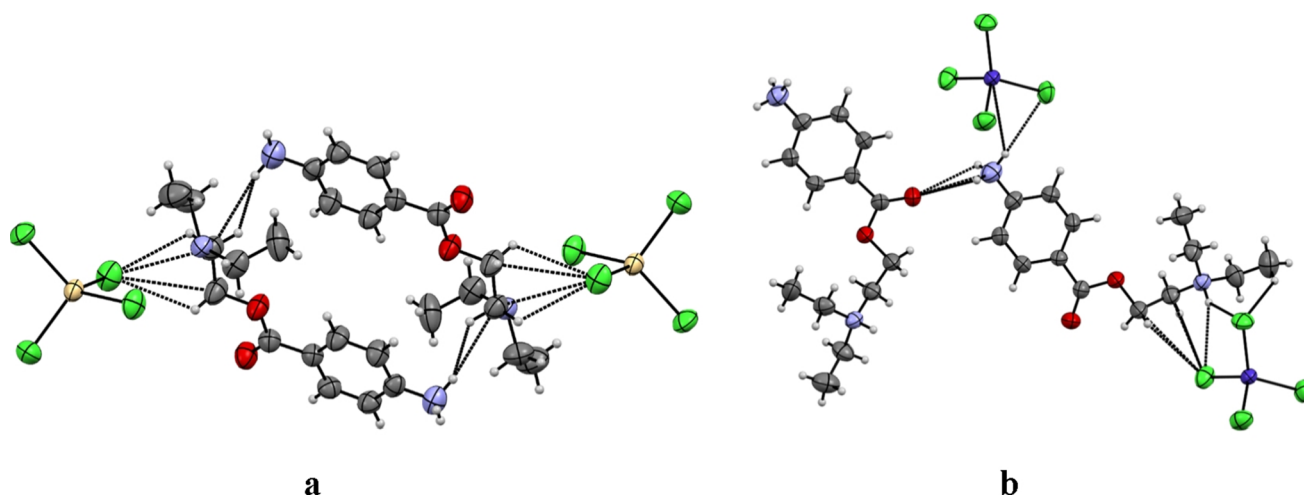


N2...O1 distances are 3.170 and 3.65 Å, as well as O2...C4 distances are 3.049 and 3.065 Å in Complexes **1** and **2**, respectively, these distances are consistent with the average values of similar distances in compounds related to procaine hydrochloride (3.17 and 3.00 Å, respectively) (Beall and Sass 1970).

In the trialkyl ammonium group, the average C–N bond lengths of 1.502 Å (Complex **1**) and 1.509 Å (Complex **2**) exceed the commonly observed C–N single bond length of 1.469 (Allen et al. 1987), which is probably related to the increased coordination number of the nitrogen upon protonation. The C–N–C average angles in the trialkyl

Table 1 Crystallographic information of Complexes **1** and **2**

Identification code	hacali70	hacali75
Empirical formula	C ₂₆ H ₄₂ CdCl ₄ N ₄ O ₄	C ₂₆ H ₄₄ Cl ₄ CoN ₄ O ₄
Formula weight	728.83	677.38
Temperature/K	293(2)	293(2)
Crystal system	Monoclinic	Monoclinic
Space group	C2/c	C2/c
a/Å	18.842(2)	18.675(4)
b/Å	14.968(2)	14.890(3)
c/Å	14.764(2)	14.578(3)
$\alpha/^\circ$	90	90
$\beta/^\circ$	125.620(7)	125.571(5)
$\gamma/^\circ$	90	90
Volume/Å ³	3384.9(9)	3297.5(11)
Z	4	4
$\rho_{\text{calc}}/\text{cm}^3$	1.430	1.364
μ/mm^{-1}	0.996	0.880
F(000)	1496.0	1420.0
Crystal size/mm ³	0.12×0.11×0.1	0.10×0.07×0.06
Radiation	MoK α (λ =0.71073)	MoK α (λ =0.71073)
2 θ range for data collection/ $^\circ$	5.32 to 49.996	5.364 to 50
Index ranges	−22 ≤ h ≤ 22, −17 ≤ k ≤ 17, −17 ≤ l ≤ 17	−20 ≤ h ≤ 22, −17 ≤ k ≤ 17, −17 ≤ l ≤ 17
Reflections collected	51,002	29,361
Independent reflections	2988 [R _{int} =0.0644, R _{sigma} =0.0279]	2903 [R _{int} =0.0821, R _{sigma} =0.0532]
Data/restraints/parameters	2988/0/177	2903/0/180
Goodness-of-fit on F ²	1.046	1.060
Final R indexes [I > 2 σ (I)]	R ₁ =0.0404, wR ₂ =0.0928	R ₁ =0.0501, wR ₂ =0.1006
Final R indexes [all data]	R ₁ =0.0557, wR ₂ =0.0984	R ₁ =0.0929, wR ₂ =0.1103
Largest diff. peak/hole / e Å ^{−3}	0.54/−0.38	0.30/−0.36

**Fig. 2** Non-covalent intermolecular interactions in the crystal structure of Complex **1 a** and Complex **2 b**

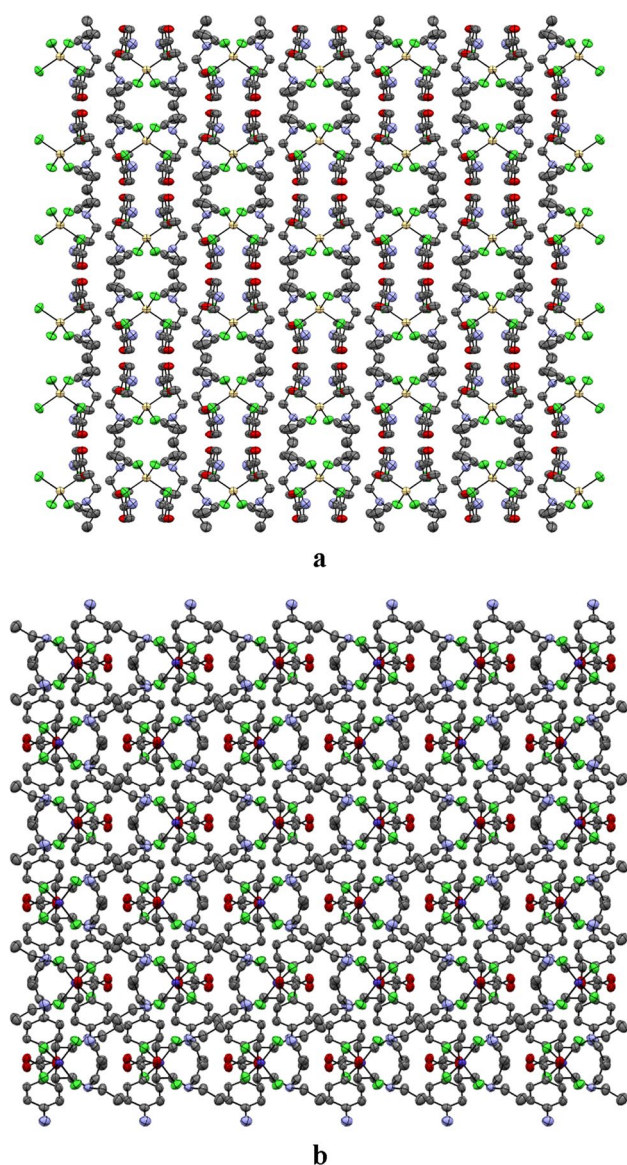


Fig. 3 A partial packing diagram of Complex **1** **a** and Complex **2** **b**

ammonium group in Complexes **1** and **2** are 112.3 and 112.0°, respectively.

Hirshfeld surface analysis

A technique that provides information about the interactions of crystal structures between molecules is called Hirshfeld surface analysis. On a graph known as the Hirshfeld surface, this analysis presents a value for the electron density within and outside the molecule of each point on the surface (Hirshfeld 1977; Spackman and Jayatilaka 2009; Venkatesan et al. 2016). The different types of interactions between molecules are provided through Hirshfeld surface analysis using

colored graphs. D_{norm} maps (Figs. 4a, 5a), shape indexes (Figs. 4b, 5b), curvedness maps (Figs. 4c, 5c), and Void analysis (Figs. 4d, 5d) of isostructure Complexes **1** and **2** show significant similarity. In the d_{norm} map, the red color represents short distances from the sum of the vdW radii and therefore strong interactions. In the d_{norm} map of Complexes **1** and **2**, 3D Hirshfeld surfaces were determined in the range of -0.3969 – 1.6378 a.u. and -0.2248 – 1.6523 a.u., respectively. White-to-blue interactions represent distances equal to or greater than the sum of the vdW radii. The red and blue triangles in the shape indexes show the π - π stacking; while, the regions of the aromatic ring in the structure of the complexes are represented by large green areas in the curvedness maps.

If there are large voids in the crystal package, the packing of the molecules can be easily affected by external mechanical forces. To determine the mechanical stability of the crystal package, a void analysis was performed. Calculated for the unit cell, the void surface is identified as the isosurface of the procrystalline electron density. The crystal voids' volumes are given in Figs. 7d and 8d. The volumes of the voids in the unit cells for Complexes **1** and **2** were calculated as $491.00 \text{ \AA}^3$ with percentage voids of 14.50% and $420.30 \text{ \AA}^3$ with percentage voids of 12.75%, respectively.

When Table 2 is examined, it was determined that the $\text{H}\cdots\text{H}$ and $\text{H}\cdots\text{Cl}/\text{Cl}\cdots\text{H}$ interactions made the greatest contribution to the two-dimensional fingerprint graphics of both complexes. The fact that the hydrogen–all element interactions determined by two-dimensional fingerprint graphics are over 80% and the most important contribution is the $\text{H}\cdots\text{H}$ interactions are attributed to the hydrogen abundance in the structure of the complexes. The blue color spikes in the 2D fingerprint plots represent the strong repulsion steric effect. On the Hirshfeld surface of Complex **1**, it has been determined that there are $\text{H}\cdots\text{C}/\text{C}\cdots\text{H}$, $\text{H}\cdots\text{O}/\text{O}\cdots\text{H}$, $\text{H}\cdots\text{N}/\text{N}\cdots\text{H}$, $\text{C}\cdots\text{C}$, $\text{C}\cdots\text{O}/\text{O}\cdots\text{C}$, $\text{Cd}\cdots\text{H}/\text{H}\cdots\text{Cd}$, and $\text{N}\cdots\text{Cl}/\text{Cl}\cdots\text{N}$ interactions. On the Hirshfeld surface of Complex **2**, there are $\text{H}\cdots\text{C}/\text{C}\cdots\text{H}$, $\text{H}\cdots\text{O}/\text{O}\cdots\text{H}$, $\text{C}\cdots\text{C}$, $\text{C}\cdots\text{O}/\text{O}\cdots\text{C}$, and $\text{Co}\cdots\text{H}/\text{H}\cdots\text{Co}$ interactions. All interaction percentages are given in Table 4. 2D fingerprint plots of Complexes **1** and **2** are given in Figures S2 and S3, respectively.

FTIR spectra and magnetic properties

FTIR spectra of Complexes **1** and **2** are given in Figures S4 and S5. As can be seen in Figures S4 and S5, the spectra of the isostructure cadmium and cobalt complexes are very similar. Asymmetric N–H stretching vibrations of the complexes are observed at 3458 cm^{-1} (for Complex **1**) and 3469 cm^{-1} (for Complex **2**); while, symmetrical N–H stretching vibrations are observed at 3365 cm^{-1} (for Complex **1**) and 3351 cm^{-1} (for Complex **2**) was observed. When the FTIR

Fig. 4 d_{norm} map **a**, shape index **b** and curvedness map **c**, and graphical views of voids **d** in the crystal packings of Complex **1**

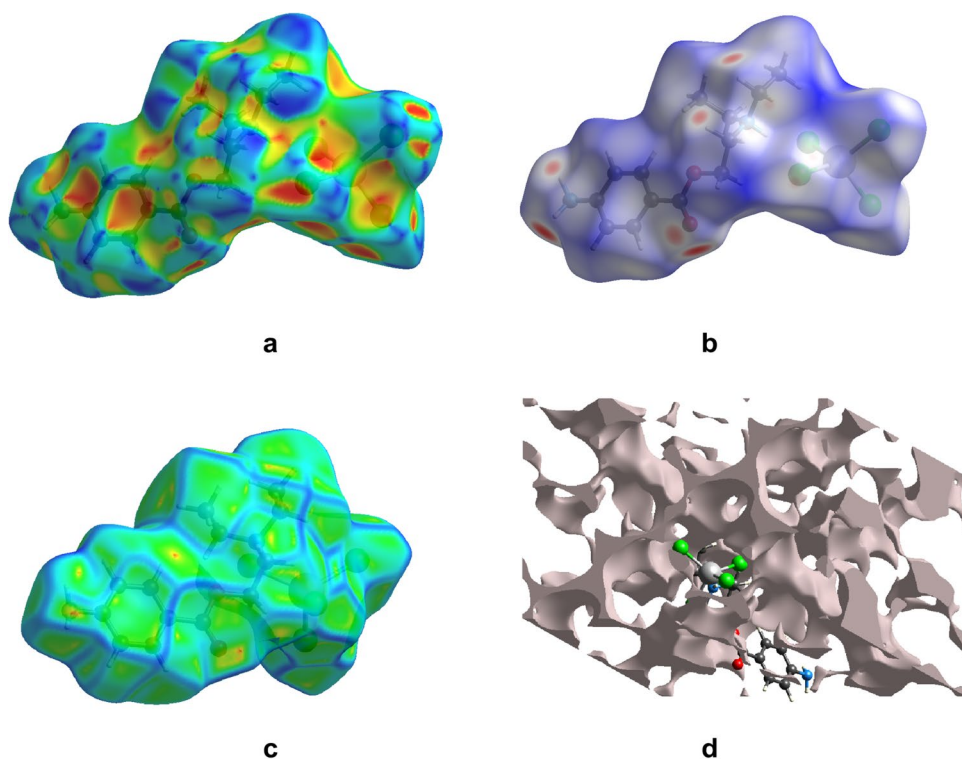
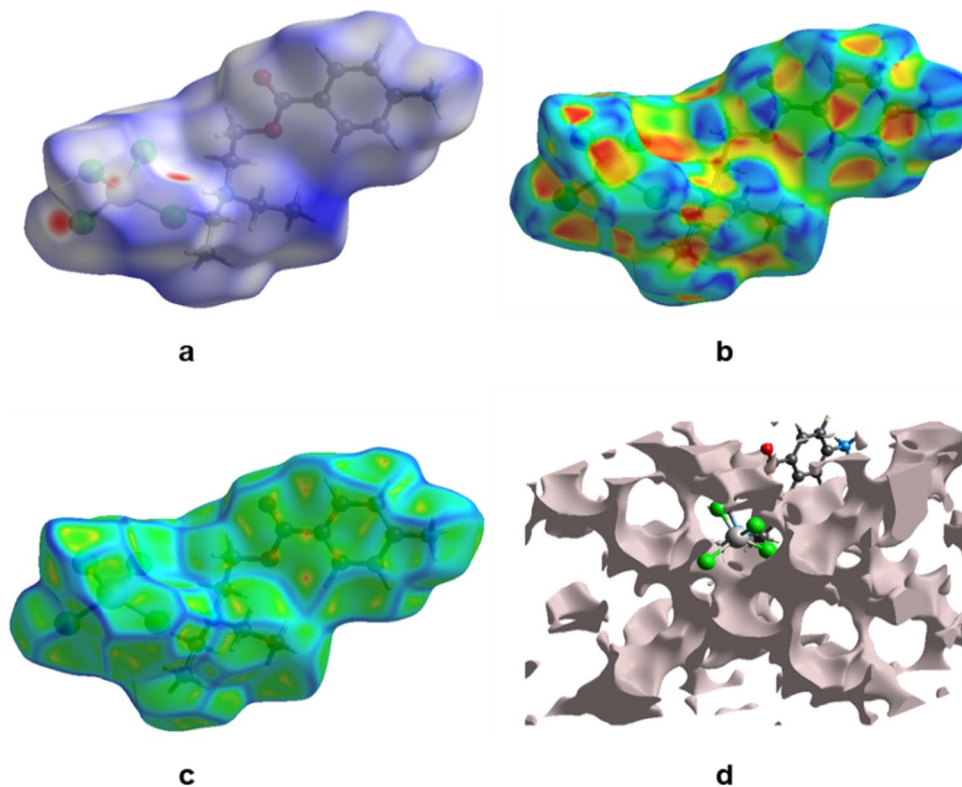


Fig. 5 d_{norm} map **a**, shape index **b** curvedness map **c**, and graphical views of voids **d** in the crystal packings of Complex **2**



spectrum of Procaine HCl was examined, it was reported that these peaks were observed at 3353 cm^{-1} and 3206 cm^{-1} (Sherlin et al. 2015). Aromatic C-H stretching vibrations

reported in the literature in the range of $3073\text{--}3055\text{ cm}^{-1}$ (Sherlin et al. 2015) were observed at 3079 cm^{-1} and 3069 cm^{-1} for complexes **1** and **2**, respectively. Moreover,

Table 2 Intermolecular Interactions of the Complexes **1** and **2**

Interaction Type	Percentage (%)		Interaction Type	Percentage (%)	
	Complex 1	Complex 2		Complex 1	Complex 2
H...H	39.6	43.7	All-M (M = Cd, Co)	0.3	0.3
H...Cl/Cl...H	37.4	36.9	All-Cl	7.7	7.2
H...C/C...H	9.0	8.6	All-O	3.6	3.7
H...O/O...H	6.2	6.4	All-N	1.8	–
H...N/N...H	2.3	–	All-H	80.1	82.3
C...C	1.9	2.0	All-C	6.7	6.6
C...O/O...C	1.5	1.5			
Cd...H/H...Cd	1.2	0.9			
N...Cl/Cl...N	1.0	–			

CH₃ asymmetrical stretching vibrations, CH₂ asymmetrical stretching vibrations, CH₃ symmetric stretching vibrations, and CH₂ symmetric stretching vibrations belonging to the ethyl group were seen between 3000–2850 cm⁻¹. Vibrations involving N–H stretching and overtones or combination bands in Fermi resonance cause the intense multi-vibrations of tertiary amine hydrochloride salts in the 2700–2330 cm⁻¹ range. In the study by Sherlin et al., N–H...Cl tensile bands of procaine hydrochloride were reported at 2870 cm⁻¹ (Sherlin et al. 2015). However, no band is seen in this region in the FTIR spectra of the complexes. This confirms the crystal structures characterized by X-ray diffraction. In the same study, while C=O stretch bands were reported at 1692 cm⁻¹, they were detected at 1689 cm⁻¹ in the spectra of Complexes **1** and **2**. NH₂ scissoring vibrations for both complexes were found at 1644 cm⁻¹. For the complexes, these vibrations were seen at 1618 cm⁻¹ and 1620 cm⁻¹, respectively. C=C vibrations were seen at 1590 cm⁻¹ and 1570 cm⁻¹ for Complexes **1** and **2**. According to the literature, CH₃ asymmetric deformation and CH₂ scissoring bands were observed at 1520 cm⁻¹ and 1464 cm⁻¹, respectively. The vibrations of these groups were detected at 1512 cm⁻¹ and 1444 cm⁻¹ for Complex **1**, and at 1518 cm⁻¹ and 1458 cm⁻¹ for Complex **2**, respectively. When all these data are evaluated in general, it is seen that the spectra of both complexes are similar and the slight shifts are seen as evidence that new complexes are obtained.

The magnetic moment of complex **2** was measured as 4.53 B.M. These data obtained are compatible with that of tetrahedral cobalt complexes (Cotton and Holm 2002).

DFT

Density functional theory (DFT) in computational chemistry has contributed greatly to experimental processes with the developing technology, and accelerated the acquisition and comparison of physical, chemical, and electronic data of molecules, thus developing a targeted study approach. Gaussian16 software was used for all these calculations

and IQMol software was used for visualizations. B3LYP/SDD was used as the basis set. DFT calculations of some cobalt and cadmium complexes have been performed in the literature, and the results are positively correlated (Abdel-Rahman et al. 2017; Konakanchi et al. 2018; Majumdar et al. 2023c). As a result of DFT calculations of metallic novocaine compounds, the electronic energy of Complex **1** molecule is -96,449.84 eV, and the electronic energy of Complex **2** molecules is -95,882.81 eV. The HOMO (highest occupied molecular orbital) and LUMO (lowest occupied molecular orbital) orbitals are the two most important orbitals for determining the reactivity and stability of complexes.

In the HOMO-1, HOMO, LUMO, and LUMO + 1 energy levels of Complex **1**, the electron density is on the novocaine ligand, and at the HOMO-2 energy level, electrons migrated to the cadmium metal via ligand-to-metal charge transfer (LMCT). The HOMO value is -5.77 eV, the LUMO value is -2.14 eV, and the band gap is 3.63 eV. In the HOMO-2, HOMO-1, and HOMO energy levels of Complex **2**, the electron density is on the cobalt metal, and at the LUMO and LUMO + 1 energy levels, the electron density migrated to the novocaine ligand via metal-to-ligand charge transfer (MLCT). The HOMO value is -2.96 eV, the LUMO value is -1.20 eV, and it has a band gap of 1.76 eV (Fig. 6).

Because cobalt metal's 3d orbitals have electrons that are placed at higher energy levels, the electronic transition bands of cobalt complexes typically shift to lower energies and have narrower band gaps. Since cadmium metal's 4d orbitals are located at lower energy levels, the electronic transition bands of cadmium complexes typically shift to higher energies and therefore have wider band gaps. Molecules with lower energy and narrower band gaps are more reactive because molecules with low energy and narrow band gap have electrons that are more loosely bound. This means that they are more likely to give or receive electrons from molecules with higher energy and wider band gap. According to DFT results, the cobalt complex is more reactive than the cadmium complex due to its lower energy and narrower band gap.

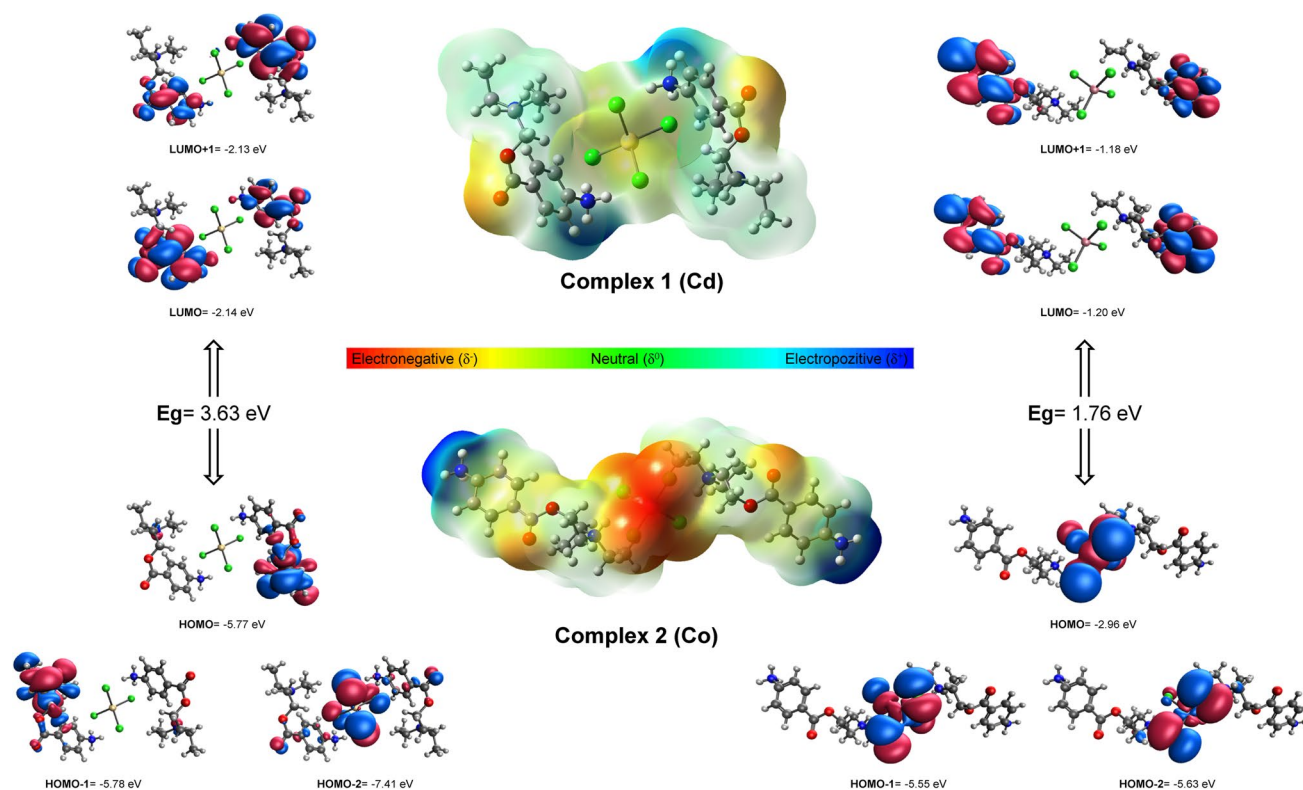
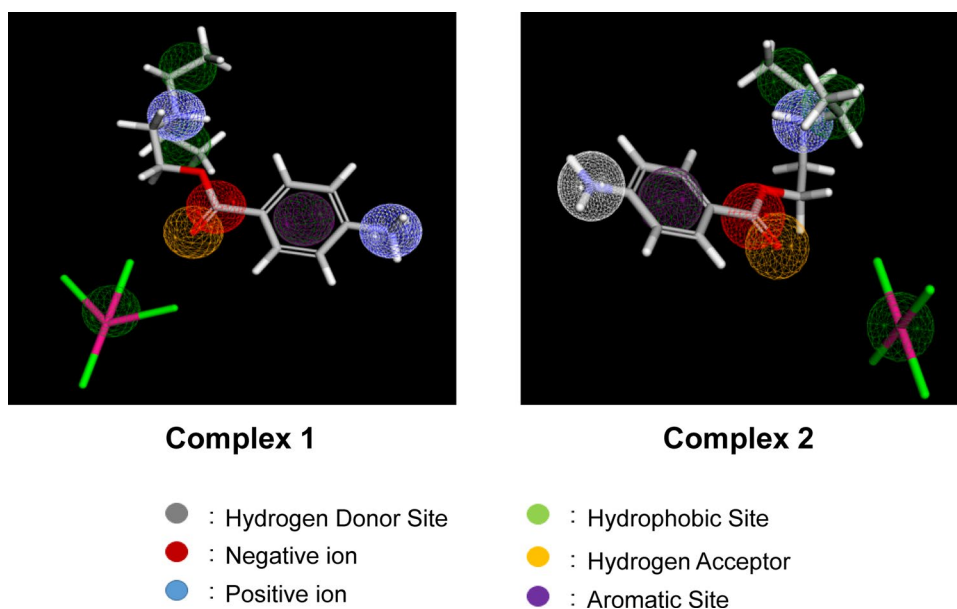


Fig. 6 DFT calculated molecular energy levels and orbitals of Complexes **1** and **2**

In the electron density maps of the complexes, the carbonyl oxygen, the oxygen atoms adjacent to the carbonyl are electronegative. The positively charged terminal amine group attached to the trimethyl is strongly

electropositive. In addition to the novocaine ligand, tetrachlorocadmium and tetrachlorocobalt are electropositive. The electron map is denser in the cobalt complex **2** than cadmium complex **1**. The diethylamino groups are

Fig. 7 Pharmacophore sites of the Complexes **1** and **2**



slightly electropositive due to their electron donor group nature.

Pharmacophore modeling

Pharmacophore regions where complexes can interact with proteins were obtained with the help of the Pharmit online database. As seen in Fig. 7, hydrogen donor and acceptor sites, positive and negative ion sites, aromatic group, and hydrophobic sites were determined as pharmacophore sites of the complexes. Hydrogen bonding and hydrophobic and electrostatic interactions between these pharmacophore regions of the complexes and target proteins are confirmed by the results of molecular docking studies.

Molecular docking

The docking scores and the list of interacting residues of 1CX2, 4QWO, 8CEQ, and 8HG1 proteins with Complexes **1** and **2** and novocaine are given in Table 3. The A42R profilin-like protein of the Monkeypox virus is the first protein whose structure has been determined after it was perceived as a threat by the World Health Organization, and it has been reported to have a role in the viral replication of the virus (Minasov et al. 2022a). The binding energies between the A42R Profilin-like protein of monkeypox virus and procaine HCl, Complexes **1** and **2** were determined as -6.2 kcal/mol, -7.1 kcal/mol, and -7.1 kcal/mol, respectively. The binding scores between the A42R Profilin-like protein of the monkeypox virus and the antiviral drugs brincidofovir,

Table 3 Docking scores and the list of interacting residues of 1CX2, 4QWO, 8CEQ, and 8HG1 proteins with the Complexes **1** and **2** and procaine hydrochloride

Target	Ligand	Interaction Type			Docking Score (kcal/mol)
		Hydrogen Bond	Hydrophobic	Electrostatic	
4QWO	1	◆ : Tyr118, Try80	◆ : Ala125, Ile104 ◆ : Arg119, Arg122	◆ : Arg115, Arg114 ◆ : Tyr118	-7.1
	2	◆ : Tyr118, Arg122, Tyr80	◆ : Arg119, Arg122		-7.1
	Novocaine	◆ : Tyr80	◆ : His100, Arg119	◆ : Asp123 ◆ : Asp122	-6.2
8CEQ	1		◆ : Arg140	◆ : Asp95	-6.0
	2	◆ : Arg140		◆ : Phe115	-5.6
	Novocaine	◆ : Val116 ◆ : Gly68, Val139	◆ : Val139 ◆ : Phe115 ◆ : Arg140		-5.7
8HG1	1		◆ : His307, Arg497	◆ : Lys337	-6.7
	2		◆ : DA3		-6.7
	Novocaine	◆ : Lys901, Gual1 ◆ : Ade20			-6.0
1CX2	1	◆ : Leu408 ◆ : His207, Leu408	◆ : Lys405 ◆ : Val295	◆ : His207	-7.6
	2	◆ : His388	◆ : His388	◆ : His207	-7.8
	Novocaine	◆ : Pro512, Pro514 ◆ : Gly437	◆ : Pro512 ◆ : Ile188 ◆ : Lys511		-4.2
◆ : Hydrogen Bond, ◆ : Carbon Hydrogen Bond, ◆ : π -Alkyl, ◆ : Alkyl, ◆ : π -Anion, ◆ : π -Sigma, ◆ : π -Cation, ◆ : π - π Stacked, ◆ : Attractive Charge, and ◆ : π - π T-shaped interactions					

cidofovir, and tecovirimat were found to be -6.0 kcal/mol, -6.7 kcal/mol, and -8.9 kcal/mol, respectively. These results show that Complexes **1** and **2** have stronger binding affinity to the A42R Profilin-like protein of the monkeypox virus compared to the procaine HCl and reference drugs brincidofovir, and cidofovir. However, Complexes **1** and **2** show less binding affinity compared to tecovirimat. There are carbon–hydrogen bond interactions between Complex **1** and amino acid residues Tyr118 and Tyr80 in the active site of the A42R Profilin-like protein of monkeypox virus. These hydrogen bond lengths between amino acids Tyr118 and Tyr80 with Complex **1** were found as 3.05 Å and 3.53 Å, respectively. In addition, it was determined that complex **1** made π -anion interactions with the Tyr118 amino acid, alkyl interactions with the Ala125, and Ile104 amino acids, and π -alkyl interactions with the Arg119, Arg122 amino acids,

and attractive charges with Arg115 and Arg114 amino acid residues in the active site of the A42R Profilin-like protein of monkeypox virus (Fig. 8a and c). Complex **2** interacts through a carbon–hydrogen bond with Tyr118, Arg122, and Tyr80, and π -alkyl interactions with Arg119 and Arg122 amino acid residues in the active region of A42R Profilin-like protein of monkeypox virus (Fig. 8b and d).

Since the VP39 enzyme has an important role in the viral life cycle of the monkeypox virus, it is thought that inhibiting it will reduce or even destroy the effects of the disease (Silhan et al. 2023). The binding energies between the monkeypox virus methyltransferase VP39 enzyme and procaine HCl, Complexes **1** and **2** are -5.7 kcal/mol, -6.0 kcal/mol, and -5.6 kcal/mol, respectively. The binding energy between the monkeypox virus methyltransferase VP39 enzyme and the antiviral drugs brincidofovir, cidofovir, and

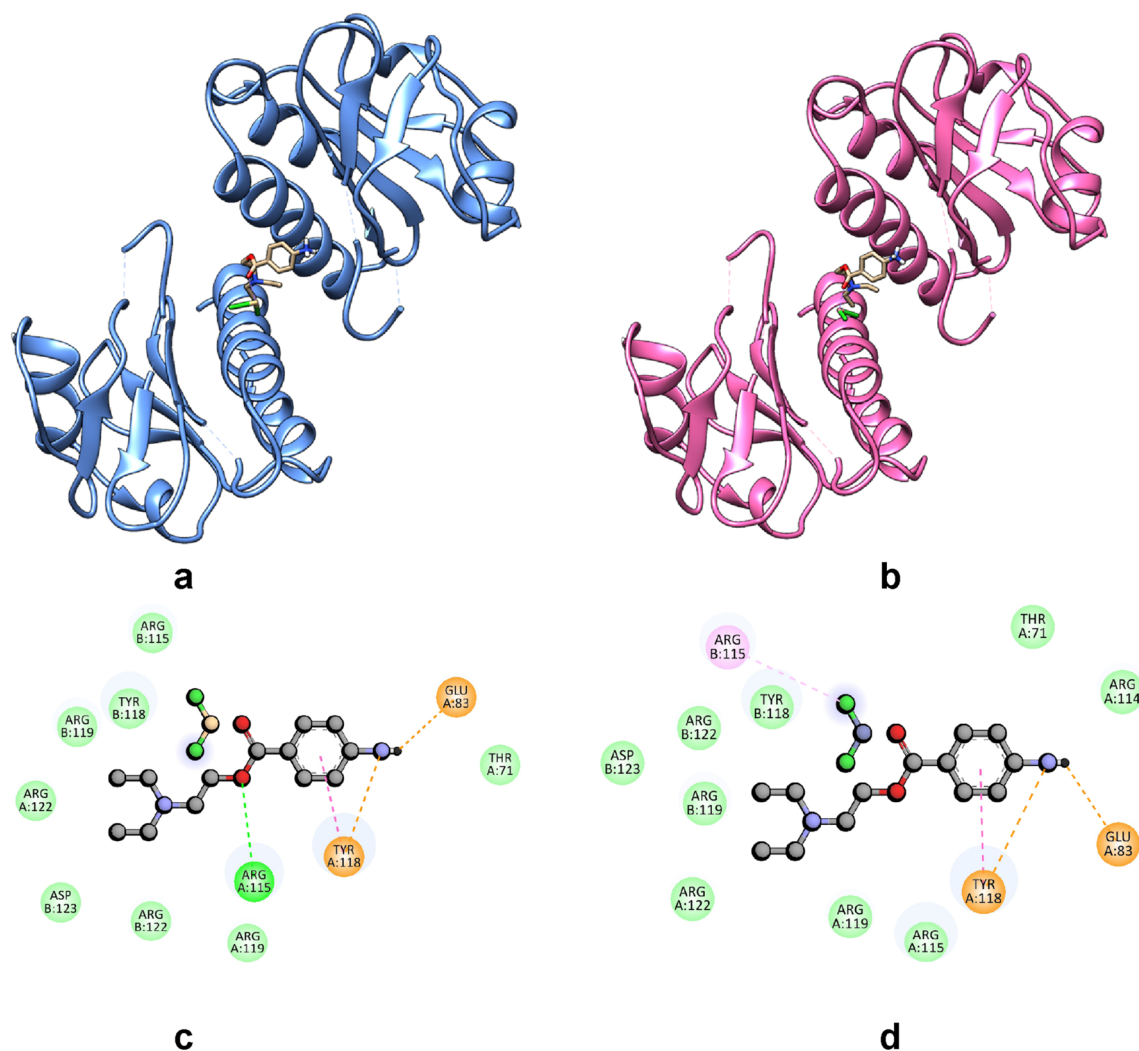


Fig. 8 Molecular docking of Complexes **1** and **2** with the active site of A42R profilin-like protein of monkeypox virus **a** and **b**, respectively, 2D view of the interactions between Complex **1** and active site

of A42R profilin-like protein of monkeypox virus **c** and 2D view of the interactions between Complex **2** and active site of A42R profilin-like protein of monkeypox virus **d**

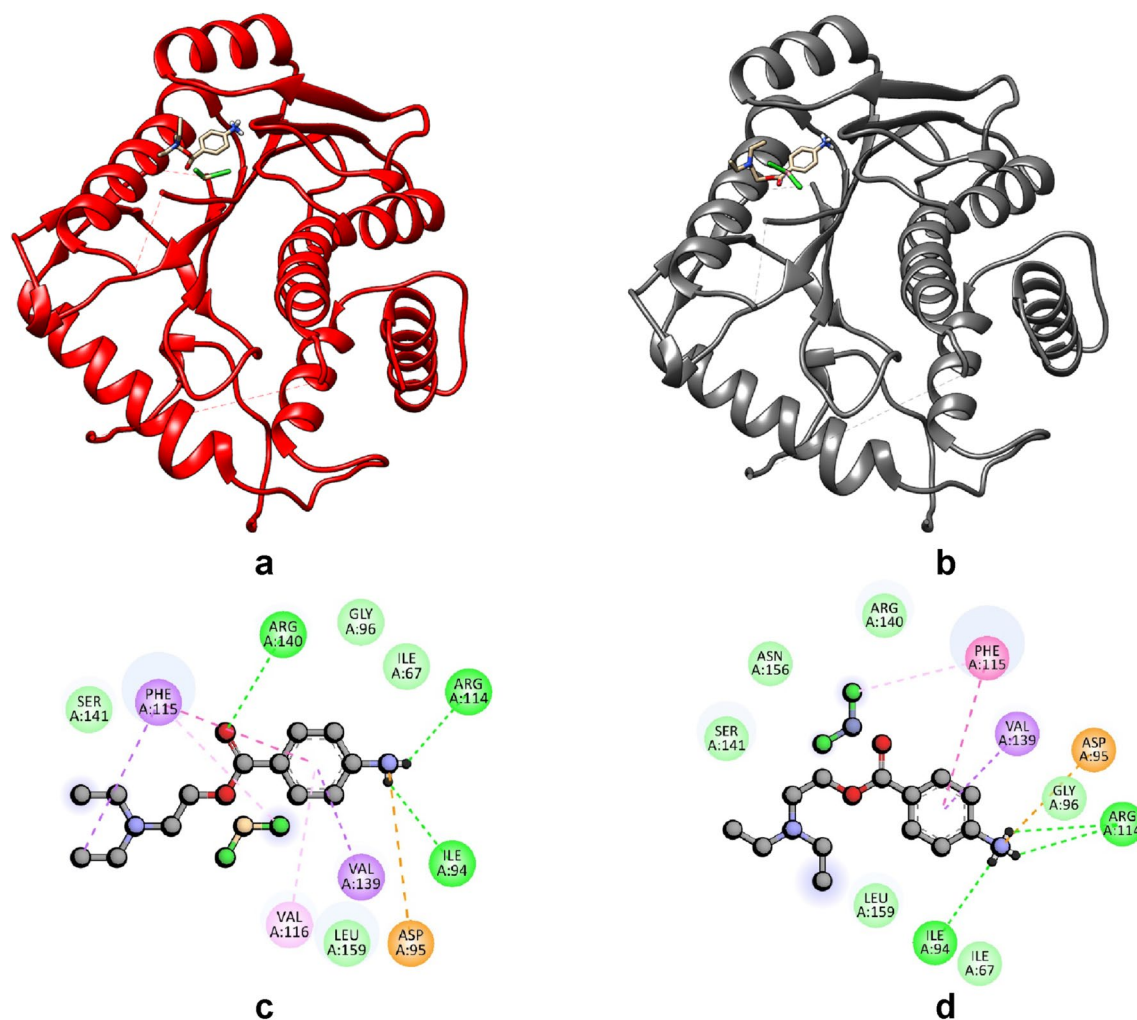


Fig. 9 Molecular docking of Complexes **1** and **2** with the active site of monkeypox virus methyltransferase VP39 **a** and **b**, respectively, 2D view of the interactions between Complex **1** and active site of

monkeypox virus methyltransferase VP39 **c** and 2D view of the interactions between Complex **2** and active site of monkeypox virus methyltransferase VP39 **d**

tecovirimat were found to be -5.4 kcal/mol, -5.9 kcal/mol, and -8.4 kcal/mol, respectively. Complex **1** contacts via π -alkyl interactions with Arg140 amino acid, attractive charge with Asp95 amino acid residue in the active site of monkeypox virus methyltransferase VP39 (Fig. 9a and c). There are conventional hydrogen bonds (with Arg140 (2.44 Å)) and π -anion (Phe115) interactions between Complex **2** and amino acid residues in the active site of monkeypox virus methyltransferase VP39 (Fig. 9b and d).

The monkeypox virus's DNA polymerase holoenzyme is required for viral genome replication and is a potential target for antiviral drug studies (Peng et al. 2023; Li et al. 2023). The binding scores between polymerase holoenzyme of monkeypox virus and procaine HCl, Complexes **1** and **2** are -6.0 kcal/mol, -6.7 kcal/mol, and -6.7 kcal/mol, respectively. The docking scores between the polymerase holoenzyme of the monkeypox virus and the antiviral drugs

brincidofovir, cidofovir, and tecovirimat were found to be -6.3 kcal/mol, -6.8 kcal/mol, and -8.9 kcal/mol, respectively. It was determined that Complex **1** interacts with His307 and Arg497 amino acids by forming alkyl interactions and with Lys337 amino acid by forming an attractive charge (Fig. 10a and c). Complex **2** interacts with DA3 residue in the active site of the polymerase holoenzyme of the monkeypox virus via conventional π -alkyl interactions (Fig. 10b and d).

The docking scores between procaine HCl, Complexes **1** and **2**, and the cyclooxygenase-2 enzyme, an analgesic target (Kurumbail et al. 1996), were found to be -4.2 kcal/mol, -7.6 kcal/mol, and -7.8 kcal/mol, respectively. Complex **1** binds through a conventional hydrogen bond with Leu408 amino acid residue (2.40 Å), through alkyl interactions with Lys405 and carbon–hydrogen bond with His207 and Leu408 amino acid residues, through π -alkyl

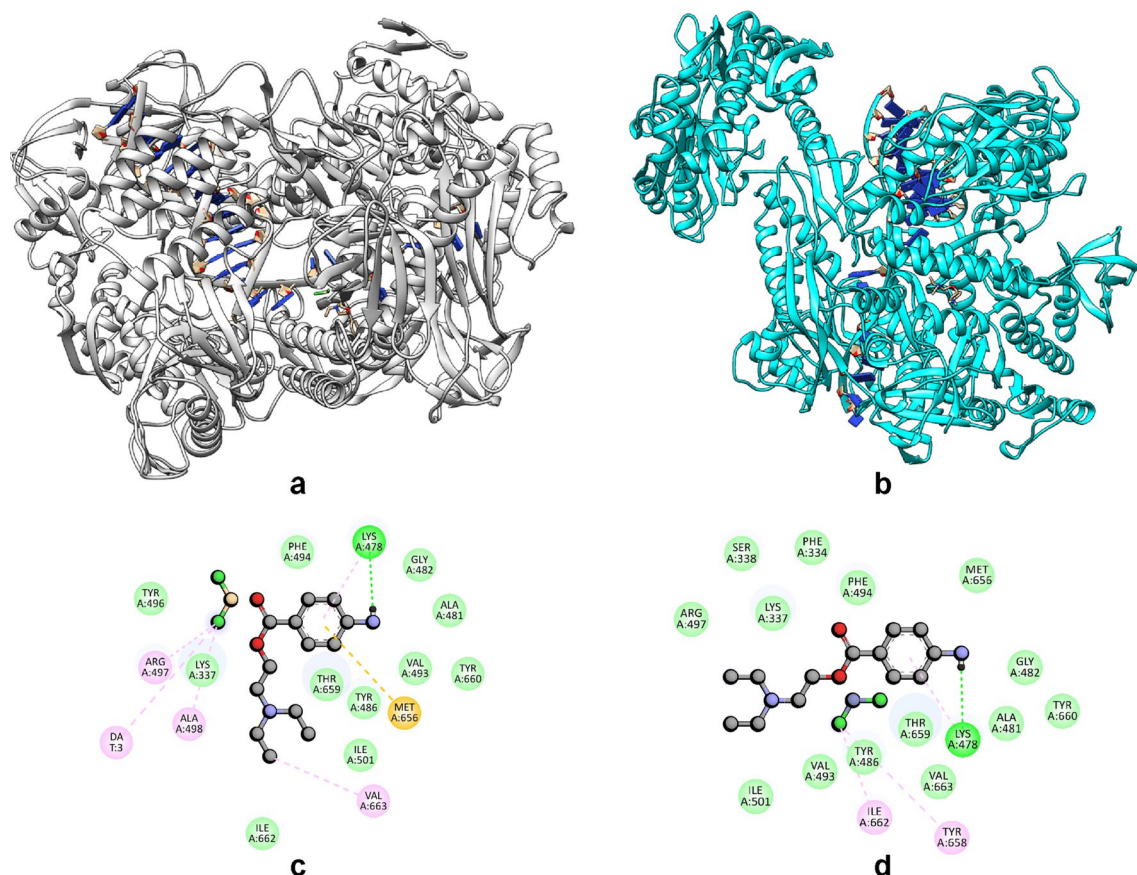


Fig. 10 Molecular docking of complexes **1** and **2** with the active site of monkeypox virus DNA polymerase holoenzyme **a** and **b**, respectively, 2D view of the interactions between Complex **1** and active site

of monkeypox virus DNA polymerase holoenzyme **c** and 2D view of the interactions between Complex **2** and active site of monkeypox virus DNA polymerase holoenzyme **d**

interactions with Val295 amino acid residue and attractive charge with His207 amino acid residue in the active site of the cyclooxygenase-2 enzyme (Fig. 11a and c). Complex **2** interacts via a conventional hydrogen bond ($d = 2.71 \text{ \AA}$) and π -sigma interactions with His388 amino acid residue and attractive charges with His207 amino acid in the active site of the cyclooxygenase-2 enzyme (Fig. 11b and d). In a previous study, it was reported that the substrate region of the cyclooxygenase enzyme has an affinity for making hydrogen bonds (Gurevich et al. 2023).

ADMET properties

It is crucial to ascertain the pharmacokinetic characteristics of chemical compounds or therapeutic candidate molecules, such as absorption, distribution, metabolism, and excretion (ADME) when selecting candidates. These features can improve the likelihood that these compounds will succeed in clinical trials and become promising medicinal candidates. Based on Lipinski's rule of five (Lipinski et al. 1997), in

silico ADMET comprises the properties of absorption, distribution, metabolism, excretion, and toxicity, which are used to predict the drug-likeness behavior of substances. The rule declared that $\text{Log } P_{\text{o/w}}$ values of compounds should be less than 5, molecular weight should be less than 500, H-bond acceptors should be less than 10, H-bond donors should be less than 5, and bioactive scores should be less than one. All estimated data on physicochemical properties, lipophilicity, water solubility, pharmacokinetics, drug-likeness, and toxicity properties of the complexes are given in Table 4. According to the results obtained, except for the deviation in molecular weight > 500 rule, both complexes are compatible with Lipinski's five rules. The novocaine compound complies with the rules of Lipinski, Ghose, Veber, Egan, and Muegge. Both complexes and procaine have high gastrointestinal (GI) absorption. Both complexes can cross the blood–brain barrier and is a *P*-glycoprotein substrate. These properties are also presented in the boiled egg model (Daina and Zoete 2016) obtained for the complexes (Fig. 12). Although Complexes **1** and **2** are not inhibitors of the cytochrome P450 enzymes CYP1A2, CYP2D6, and CYP3A4, it has been

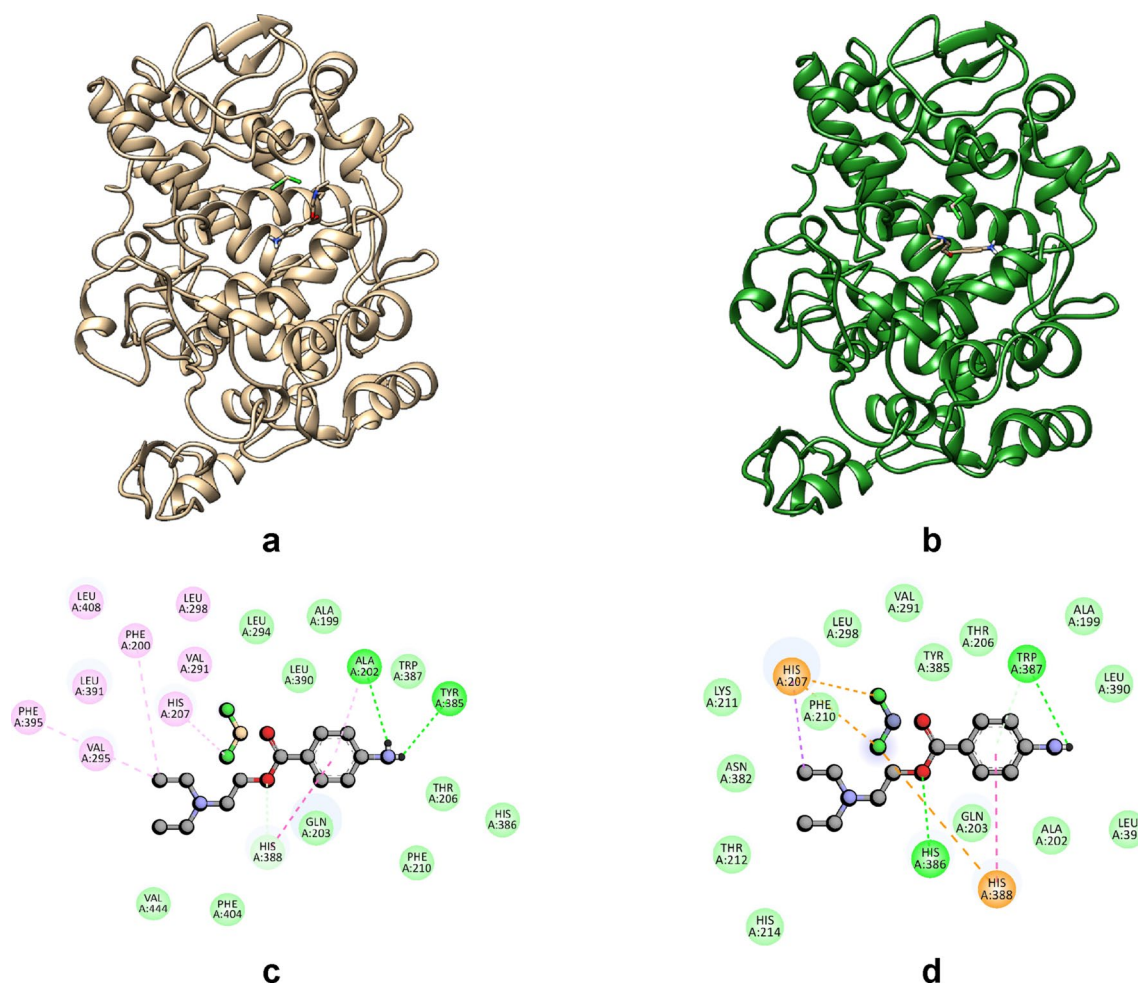


Fig. 11 Molecular docking of Complexes **1** and **2** with the active site of cyclooxygenase-2 (prostaglandin synthase-2) **a** and **b**, respectively, 2D view of the interactions between Complex **1** and active site of

cyclooxygenase-2 (prostaglandin synthase-2) **c** and 2D view of the interactions between Complex **2** and active site of cyclooxygenase-2 (prostaglandin synthase-2) **d**

determined that they may be inhibitors of the cytochrome P450 enzymes CYP2C19 and CYP2C9. Skin permeation of Complexes **1** and **2** was estimated as -5.67 cm/s and -5.34 cm/s, respectively. When the toxicity properties of the complexes and novocaine were evaluated, the toxicity class was determined as 3 (1 = toxic, 6 = non-toxic). Both complexes were found inactive in terms of hepatotoxicity, carcinogenicity, immunotoxicity, mutagenicity, and cytotoxicity. According to the data obtained from Pro-Tox II, the procaine compound was found to be active in terms of carcinogenicity and inactive in terms of hepatotoxicity, immunotoxicity, mutagenicity, and cytotoxicity. Although cadmium is known for its toxic properties, in previous studies the toxicity of heavy metal complexes such as cadmium, lead, and mercury was calculated with the help of online databases and it was suggested that they could be drug candidate molecules (Majumdar et al. 2023b, 2023a). Further in vivo/in vitro studies are needed to evaluate toxicity.

Conclusion

Tetrachlorocadmate and tetrachlorocobaltate salts of procaine have been synthesized and characterized by elemental analysis, FTIR spectroscopy, Mass Spectrometry, and single-crystal X-ray crystallography. Two protonated procainium cations $[\text{C}_{13}\text{H}_{21}\text{N}_2\text{O}_2]^+$ and one tetrachlorometallate $[\text{MCl}_4]^{2-}$ anion form the asymmetric unit of the organic–inorganic hybrid complexes. The M^{2+} center is tetracoordinated with four chlorine atoms. The average lengths of the Cd–Cl and Co–Cl bonds were calculated to be 2.27 Å and 2.45 Å, respectively. These values are similar to those seen in other organic–inorganic hybrid compounds that include isolated $[\text{MCl}_4]^{2-}$ tetrahedral anions. Based on the DFT calculations of metallic novocaine compounds, the electronic energies of the Complex **1** and **2** are $-96,449.84$ and $-95,882.81$ eV, respectively. The band gaps are 3.63 eV for Complex **1** and 1.76 eV for Complex

Table 4 Pharmacokinetics and toxicity properties of the Complexes **1** and **2**

	Complex 1	Complex 2	Novocaine
<i>Physicochemical Properties</i>			
Molecular weight	728.85 g/mol	677.38 g/mol	272.77
Num. heavy atoms	22	22	18
Num. aromatic heavy atoms	6	6	6
Num. rotatable bonds	7	7	7
Num. H-bond acceptors	3	3	3
Num. H-bond donors	1	2	1
Molar Refractivity	94.43	94.39	76.02
TPSA	55.56 Å ²	41.57 Å ²	55.56
<i>Lipophilicity</i>			
Log P_{ow} (iLOGP)	0.00	0.00	0.00
Log P_{ow} (XLOGP3)	5.92	5.12	2.27
Log P_{ow} (WLOGP)	5.33	5.27	2.58
Log P_{ow} (MLOGP)	3.18	2.95	2.20
Log P_{ow} (SILICOS-IT)	1.61	0.92	1.61
Consensus Log P_{ow}	3.21	2.85	1.82
<i>Water Solubility</i>			
Class	Moderately soluble	Moderately soluble	Soluble
<i>Pharmacokinetics</i>			
GI absorption	High	High	High
BBB permeant	Yes	Yes	Yes
P-gp substrate	Yes	Yes	No
CYP1A2 inhibitor	No	No	No
CYP2C19 inhibitor	Yes	Yes	No
CYP2C9 inhibitor	Yes	Yes	No
CYP2D6 inhibitor	No	No	No
CYP3A4 inhibitor	No	No	No
Log K_p (skin permeation)	−5.67 cm/s	−5.34 cm/s	−6.03
<i>Druglikeness</i>			
Lipinski	Yes; 1 violation MW > 500	Yes; 1 violation MW > 500	Yes; 0 violation
Ghose	No; 1 violation: MW > 480	No; 1 violation: MW > 480	Yes
Veber	Yes	Yes	Yes
Egan	Yes	Yes	Yes
Muegge	No; 1 violation: XLOGP3 > 5	No; 1 violation: XLOGP3 > 5	Yes
Bioavailability Score	0.55	0.55	0.55
<i>Toxicity</i>			
Hepatotoxicity	Inactive	Inactive	Inactive
Carcinogenicity	Inactive	Inactive	Active
Immunotoxicity	Inactive	Inactive	Inactive
Mutagenicity	Inactive	Inactive	Inactive
Cytotoxicity	Inactive	Inactive	Inactive
Toxicity Class	3	3	3
Predicted LD ₅₀	156 mg/kg	156 mg/kg	175 mg/kg

2. According to DFT results, the cobalt complex is more reactive than the cadmium complex due to its lower energy and narrower band gap. To gain insights into the potent Monkeypox virus inhibitory properties of the synthesized complexes, we docked the complexes into active sites of

A42R profilin-like protein of monkeypox virus, monkeypox virus methyltransferase VP39, and monkeypox virus DNA polymerase holoenzyme, which are responsible for the viral life cycle and replication of the virus, with the help of molecular docking studies. Since the initial

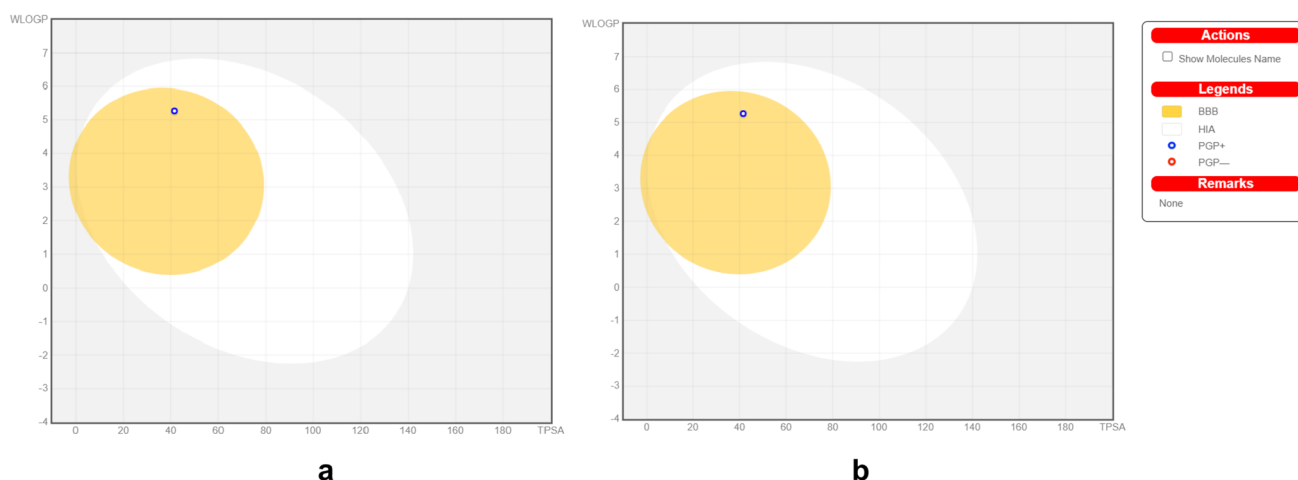


Fig. 12 Boiled-Egg Models of Complexes **1 a** and **2 b**

compound, procaine hydrochloride is an analgesic drug, the interactions of the complexes with the analgesic target cyclooxygenase-2 enzyme were also investigated by molecular docking studies. The binding energies between the Complex **1** and cyclooxygenase-2 enzyme, and A42R Profilin-like Protein, methyltransferase VP39 enzyme, and polymerase holoenzyme of monkeypox virus were found as 7.6 kcal/mol, -7.1 kcal/mol, -6.0 kcal/mol, and 6.7 kcal/mol, respectively. The binding energies between the Complex **2** and cyclooxygenase-2 enzyme, and A42R Profilin-like Protein, methyltransferase VP39 enzyme, and polymerase holoenzyme of monkeypox virus were found as 7.8 kcal/mol, -7.1 kcal/mol, -5.6 kcal/mol, and 6.7 kcal/mol, respectively. The binding energies between the novocaine and A42R Profilin-like Protein, methyltransferase VP39 enzyme, and polymerase holoenzyme of monkeypox virus were found as 4.2 kcal/mol, -6.2 kcal/mol, -5.7 kcal/mol, and 6.0 kcal/mol, respectively. Accordingly, these two synthesized compounds exhibit stronger binding affinity to monkeypox target proteins compared to novocaine. Promising results were obtained when the binding affinity of the complexes to these target proteins was compared with the reference drugs brincidofovir, cidofovir, and tecovirimat. Additionally, in silico ADMET was investigated for predicting the drug-like behavior and pharmacokinetic behavior of the two novel complexes. Overall, the results of the study point to tetrachlorocadmate and tetrachlorocobaltate salts of procaine as possible therapeutic agents against the Monkeypox target proteins. Therefore, advanced in vitro/in vivo studies are recommended to determine the potential antiviral drug properties of the complexes.

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Declarations

Conflict of 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.

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