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Exploring the Potential of a Cobalt(II) Metal Complex as an Anticancer Agent: An *In Silico* Investigation

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Abstract

In the field of medicine, transition metals have captivated researchers due to their versatility in creating unique metal complexes. Cobalt, known for its safety, holds promise in healthcare. Our research aims to unlock the potential of 4,4,4-trifluoro-1-(thiophen-2-yl)butane-1,3-dione cobalt (II) complex [TTB-Co]. Cobalt, known for its safety compared to other metals, has become a focal point for potential anticancer agents. Our study seeks to uncover the hidden power of cobalt complexes, a relatively unexplored area, by combining cobalt's strengths with the medicinal properties of β-diketones. This research article presents a comprehensive study on the synthesis and potential anticancer properties of a cobalt-based metal complex via *in silico* studies. The investigation utilizes molecular docking and dynamic simulations to reveal the profound potential of the complex as an agent against oncogenes. The study demonstrates that the cobalt(II) complex exhibits capabilities that may offer a valuable potential replacement for platinum-based drugs in anticancer therapy. However, further research is needed to confirm the complex's effectiveness and safety as an anticancer inhibitor. Overall, this investigation lays the groundwork for exploring new cobalt-diketone-based treatments for mutated cancers, opening doors to potential novel therapies for cancer patients.

Keywords: Beta-diketone, Co(II) complex, molecular docking, dynamic simulation, *in silico*

1. Introduction

In medicine, inorganic chemistry plays a significant role, with metals, especially transition metals, having diverse clinical applications. Scientists and researchers have been captivated by metal complexes for their distinct properties and versatile uses [1]. The unexpected discovery of Platinol's anticancer properties marked the beginning of promising therapeutic agents based on metal complexes [2-4]. Transition metal complexes, such as platinum, ruthenium, lanthanum, and gallium, have undergone comprehensive preclinical and clinical research, highlighting their critical involvement in antitumor therapy. These agents involve metal ions as their active components, possessing unique chemical properties that allow them to be employed in a broad spectrum of medicinal applications, ranging from diagnostic imaging to the treatment of cancer and various diseases [5-7]. However, the use of these platinum based drugs has been restricted due to their detrimental side effects, including toxicity, acquired resistance and reduced efficiency against certain cancerous cells which fueled to focus on advancement of non-platinum based drug which containing non-plainum metals [8-10]. Over the years, complexes incorporating elements such as Ru, Ir, Cu, Ni, Zn, Co, and more have consistently demonstrated superior anticancer efficacy compared to cis-platin in multiple studies [11-14]. Budotitane, cis-diethoxy(1-phenylbutane-1,3-diomato) titanium(IV), marked a groundbreaking milestone as the first non-platinum metal-

based anticancer compound to undergo clinical trials [15]. Within the realm of 3-d transition metals cobalt stands as an indispensable trace element having crucial role in numerous biological processes comprising fatty acids and metabolism, haematopoiesis and it exists in extremely small quantities within the human body, primarily in the form of vitamin B12(cobalamin), humans have developed mechanisms to counteract cobalt overload, making it less toxic compared to non-essential metals like platinum. This intriguing aspect has sparked researchers interest in investigating cobalt containing compounds as alternatives to platinum based anticancer drugs [16-18]. The pioneering investigation of cobalt complexes in biological studies was conducted by Dwyer et al. in 1952. Various in vitro studies revealed that cobalt complex shows promising anti-cancer activity [19-20]. Cobalt based complexes have wide range of medical applications, incorporating their utilization as antimicrobial [21], antiviral [22], anti-inflammatory [23], antiprotozoal [24], antioxidant [25], antiproliferative[26-27] and also as anticancer[28-30] agents.

β-diketones have emerged as valuable components in drug discovery and delivery, displaying potential as antiviral, antimicrobial, and treatments for neuro degenerative disease treatments like Alzheimer's and Parkinson's and as anticancer agents [31-37]. At present, the anticancer potential of β-diketones based cobalt complexes has not been thoroughly investigated. These gaps in knowledge have inspired our research focus, which involves the synthesis of a novel cobalt complex incorporating beta-diketone moiety. By exploring potential synergetic effects of cobalt complex, our study aims to pave a new avenue for the development of promising anticancer agents based on cobalt based complex. This study including synthesis, structural cauterization and *in silico* analysis with targeted protein unveil the pharmalogical activity of the compound which can enhance the human health by conducting further studies through other techniques. Specifically, we targeted a protein bovine serum albumin (PDB ID-4F5S) that has been previously studied [38], aiming to enhance our understanding of how cobalt-based complexes interact with this protein and potentially uncover novel therapeutic opportunities in the fight against cancer.

2. Materials and methods

Synthesis and crystal structure

4,4,4-trifluoro-1-(thiophen-2-yl)butane-1,3-dione Co(II) complex is synthesized as shown in Scheme 1. Firstly, dissolving two equivalents of TTBD in dimethyl sulfoxide (DMSO) and Separately dissolved one equivalent of nickel chloride in distilled water. Afterward, combined both the solutions and stirred the mixture for approximately half an hour. To this reaction mixture, we added a small amount of trimethylamine as a catalyst. The temperature was then raised to 60 ºC and kept at this level for 30 minutes. Subsequently, we cooled the mixture using an ice bath, resulting in the formation of a green precipitate. We carefully filtered the precipitate, washed it with distilled water, and then dried it in an oven at 90 ºC. With the dried precipitate in hand, we proceeded to grow single crystals of the complex. This was achieved by using DMSO as the solvent and employing a gradual evaporation technique. Three-dimensional (3D) dimensional electronic structure was determined using Rigaku XtaLAB mini CCD diffractometer [39], which provided precise 3D information, enabling a comprehensive understanding of the molecular structure [40-49]. Figure 1 represents the molecular structure of the of the 4,4,4-trifluoro-1-(thiophen-2-yl)butane-1,3-dione)-cobalt(II) complex.

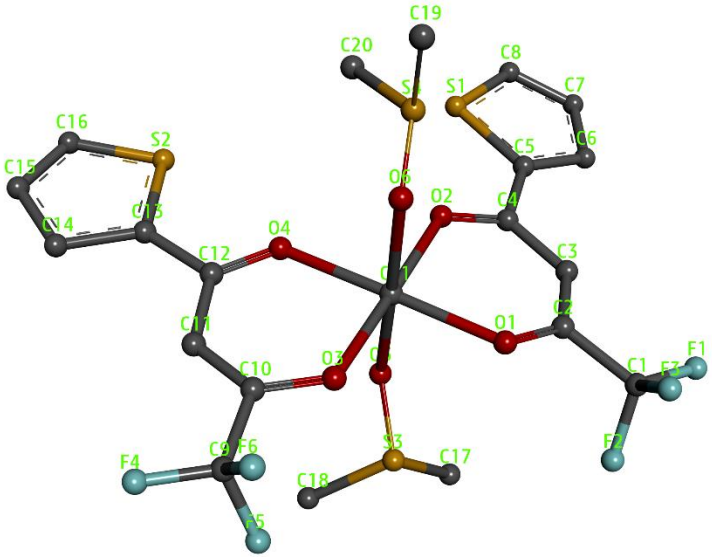


Figure 1: Molecular structure of the 4,4,4-trifluoro-1-(thiophen-2-yl)butane-1,3-dione)-cobalt(II) complex.

Molecular docking

We conducted a molecular docking analysis to explore the interaction between the [TTB-Co] complex and the target protein. We used MGL Tools 1.5.6 along with AutoDock Vina [50-52] for this investigation. Starting with the three-dimensional structure of the target protein [PDB ID: 4F5S] from the Protein Data Bank, we obtained the protein in PDB format and separated the bound ligands from the protein using Biovia Discovery Studio Visualize [53].

We then introduced a novel Cobalt complex into the active site of the chosen protein through AutoDock tools, yielding a negative binding affinity for the docked complex in kcal/mol units. The resultant protein-ligand complex was visualized, and we analyzed the interactions between the ligand and the binding sites using Biovia Discovery Studio Visualizer.

Molecular dynamic simulations.

Subsequently, we embarked on molecular dynamic simulations to gauge the stability of the protein-metal complex [TTB-Co] using the academic version of Desmond modules within the Schrodinger 2020-2 suite [54]. Building upon the promising docking results, we initiated MD simulations by immersing the complex in a cubic box filled with TIP3P water molecules. The system was appropriately solvated, and we employed the OPLS3 force field to prepare and evaluate the complex.

With a neutral system, we employed the complex algorithm, and subsequently, we moved on to relax the system using the Marlyna-Tobias-Klein method. The relaxed system was then subjected to 100 ns simulations under NPT ensembles, with a pressure of 1 bar and a Nose-Hoover thermostat set at 300 K. We delved into investigating the potential stability of the protein-metal complex energy by analyzing parameters such as root mean square deviation (RMSD), root mean square fluctuations (RMSF), and hydrogen bond fingerprint profiles. These analyses provided insights into the stability of the protein-metal complex throughout the simulation period.

3. Results and discussion

Molecular docking: The molecular docking is a computational procedure used to the study of ligand protein docking to predict the predominant binding mode and affinity ligand with a protein of three dimensional structure by creating optimal conformation of protein and ligand.

Through molecular docking, the interaction between the complex and protein with PDB ID: 4F5S, was analyzed. Docking analysis unveiled a highly favorable binding site, showcasing a good binding affinity score of -8.8 kcal/mol. The distinct bonding interaction patterns of newly synthesized cobalt complex towards the catalytic region of the targeted protein is summarized in table 3 displaying the strong attraction towards the distinct amino acids such as ARG-185, PRO-117, GLU-182 located in the binding site of the targeted protein which are characterized through variety of bonding patterns, comprising hydrogen bonding, π – anion, π - alkyl, and THR-518, ARG-427, PRO-516, GLU-519, ASP-517 AND LEU-115 are attracted through Van der Waals type of

interactions as showcased in diagram. Furthermore, the hydrogen bond interactions between the coordinated atoms and ARG-185 catalytic amino acid of protein with bond distance of 6.58 and 6.33Å, respectively involves the oxygen atoms of DMSO and ketonated ligand that are engaged in intermolecular hydrogen bond interactions (table 2 and fig 4) having major role in the formation of supramolecular architectures within the crystal structure of the complex. Moreover, the π electron cloud of thiophene ring interacts with PRO-117 and GLU-182 binding pocket amino acids through π...alkyl and π...anion type of interaction having donor acceptor distance of 6.71 and 4.44Å, respectively. Additionally, other amino acids in the catalytic sites interacts through Van der Waals types of interactions.

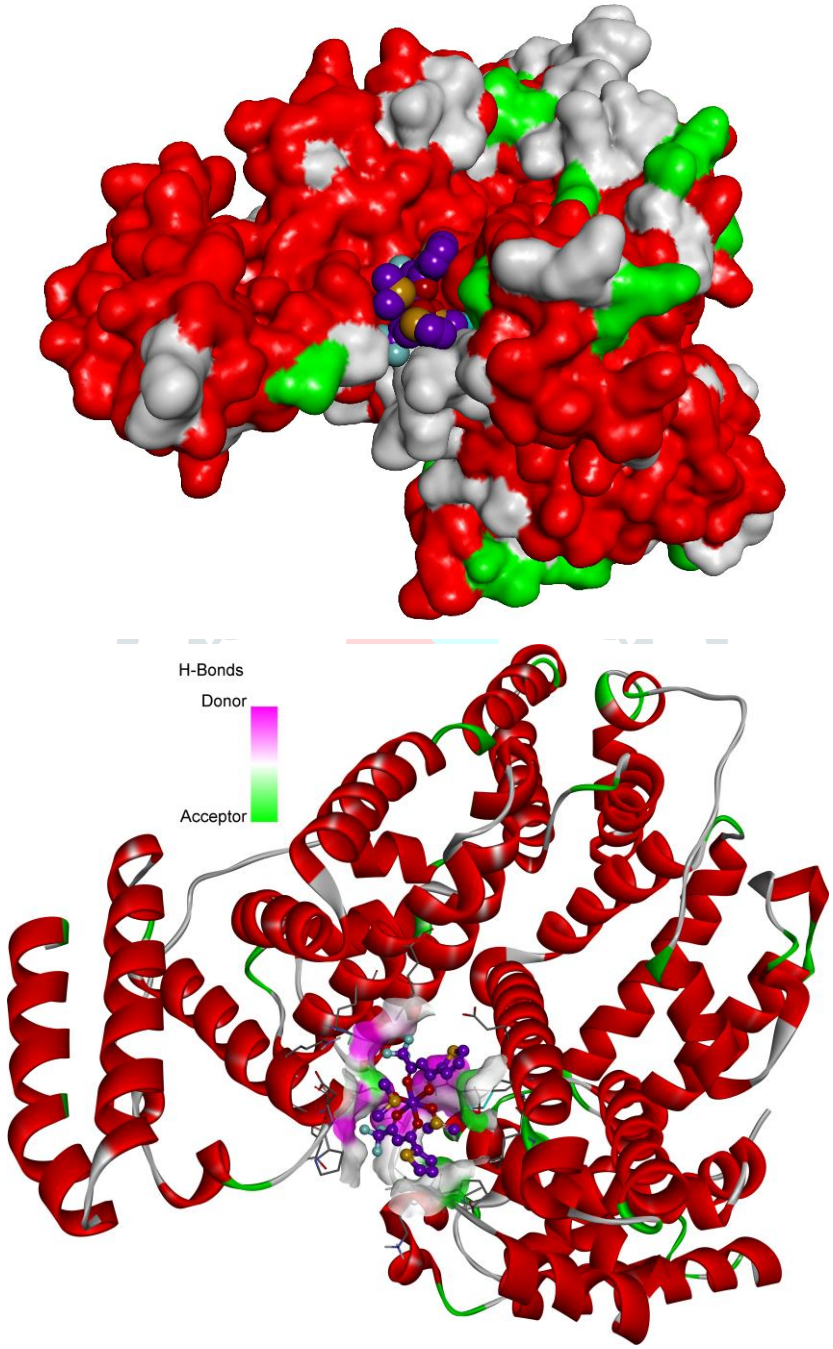


Figure 2: Molecular docking: Binding poses of [TTB-Co] with 4F5S protein: surface model representation (top) and cartoon model representation (bottom).

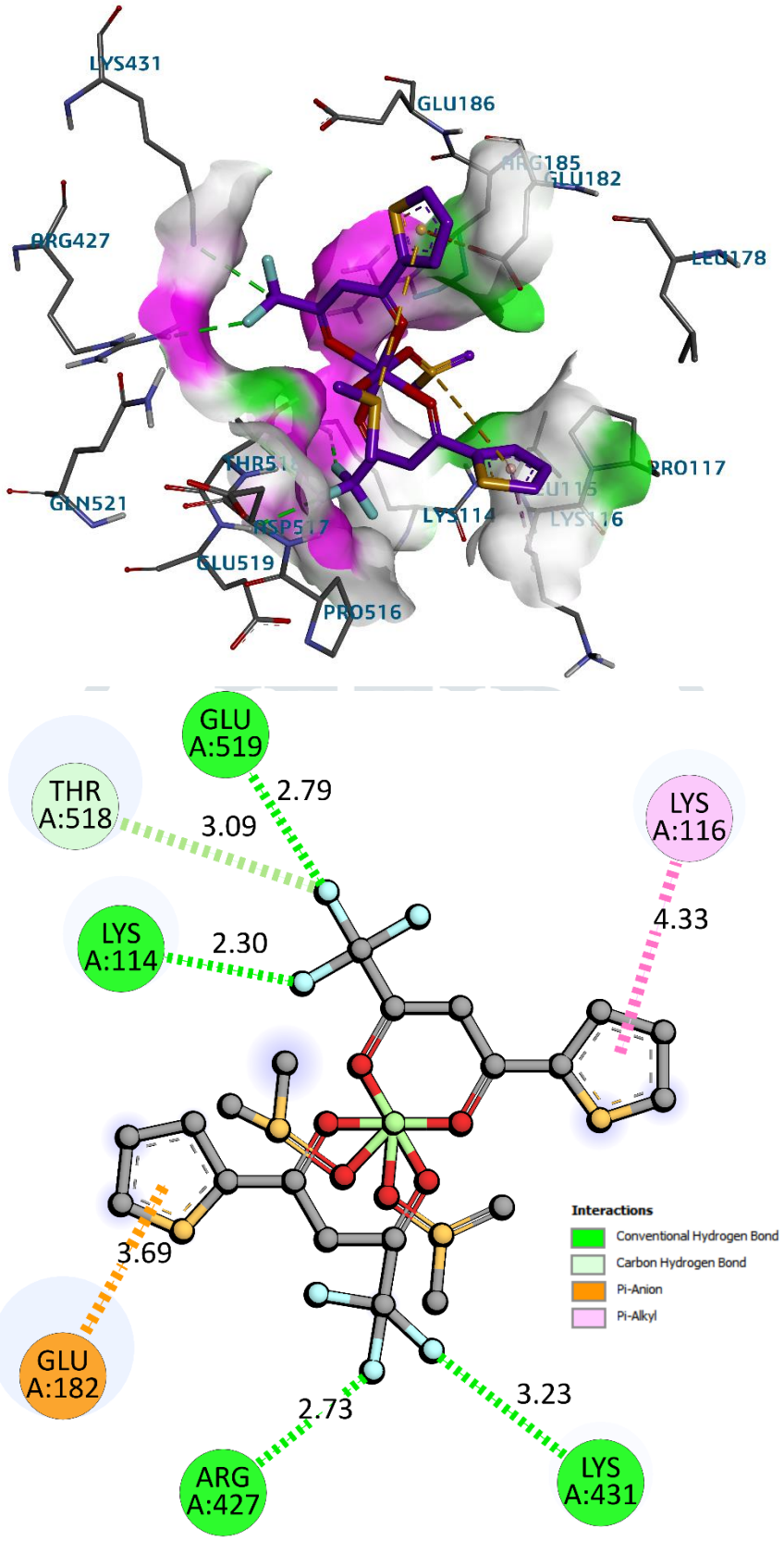


Figure 3: Interactions between [TTB-Co] between 4F5S protein, 3D view (top) and 2D view (bottom).

Table 3: Interaction of $[Co(TTBD)_2(DMSO)_2]$ with protein through binding domain.

PDB ID	Protein (Amino acids)	Ligand	Interaction type	Bond distance (Å)
	LYS-114	Fluorine (F6)	Conventional hydrogen bond	2.30
	ARG-427	Fluorine (F1)	Conventional hydrogen bond	2.73

4F5S	LYS-431	Fluorine (F2)	Conventional hydrogen bond	3.23
	GLU-519	Fluorine (F5)	Conventional hydrogen bond	2.79
	THR-518	Fluorine (F5)	Conventional hydrogen bond	3.09
	PRO-117	π of Thiophene	π - Alkyl	6.71
	GLU-182	π of Thiophene	π - Anion	4.44
	LYS-116	π of Thiophene	π - Alkyl	4.33

Molecular Dynamic simulations: It serves as a powerful tool for understanding the stability and behaviour of the protein-ligand complex system by analysing the outputs obtained from molecular docking. This also gives the comprehensive information about the ability of the protein-ligand complex to retain its conformation and adaptability assessed using the parameters such as root mean square deviation (RMSD) and root mean square fluctuation (RMSF) during the certain period of simulation. The complex was allowed to run over a simulation period of 100ns.

RMSD Root mean square deviation serves as a valuable metric, providing crucial details about the average distance and dynamic fluctuations of molecules within the complex. This information assessing the stability and structural conformation shifts of the complex that occurs throughout the simulation period. The RMSD plot of novel cobalt complex showcases that the complex demonstrated significant stability in the initial stage of simulation, spanning upto ~22 nanoseconds(ns). However, complex deviated in a range approximately 1.5 to 2Å between 22ns to 40ns. After 40ns the complex again reached a state of stabilization, maintaining a range approximately 1 to 2.5 Å throughout the remaining time of simulation. As the simulation approached its conclusion, the deviation of the complex reduced, leading to the emergence of its most stable state.

On the other hand, the targeted protein exhibited higher deviation compared to the cobalt complex. In the initial span of simulation, the deviation slowly increased upto 4Å till 25ns and displayed moderate fluctuations of ~1.5 Å between the 25 to 78ns time frame. However, in the latter half of the simulation period, the protein attained stability by deviating within ~1Å and maintaining this consistency until the end of the simulation, except for a slightly larger deviation of around 1.2Å at approximately 85ns. This suggests that the protein-ligand complex remained relatively stable for almost three fourth of the simulation period, which is an indicative of effective binding interaction between the protein and cobalt TTBD complex.

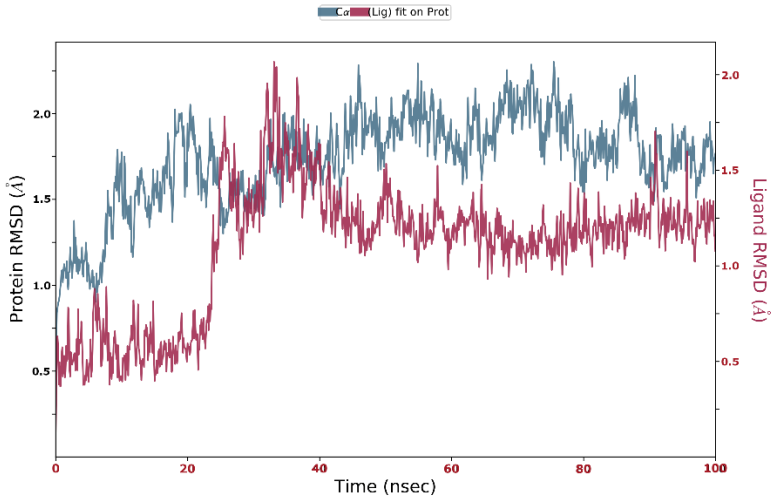


Figure 4: RMSD plot of [TTB-Co] and 4F5S protein during the 100ns simulations.

RMSF Using Root mean square fluctuations (RMSF), we examined the magnitude of fluctuation and dynamic behaviour exhibited by individual amino acids within the protein structure throughout the simulation period. The average RMSF values for each amino acid of the PKB protein with the presence of cobalt complex was calculated in order to evaluate the protein's flexibility. The RMSF plot depicted a consistent binding interaction with the receptor, with minimal impact on the protein's flexibility observed throughout the entire span of simulation.

In the RMSF plot, residue ALA-568 stood out for exhibiting the highest fluctuation of 5.41Å. Notably, LYS-116, PRO-179, PRO-515 and PRO-516 fluctuated with magnitude >2Å displaying major variability. In contrast,

residues showed in the molecular docking within the binding pocket of the protein, including ARG-185, PRO-117, GLU-182 showed deviations <2Å. Whereas, other amino acids comprising GLU-186, LYS-431 and ARG-427 showed minimal deviation of 0.99, 1.03 and 1.10Å which were involved in interaction with ligand during the simulation time frame. To highlight their significance in the protein-ligand binding, these specific residues were identified and marked with green coloured lines.

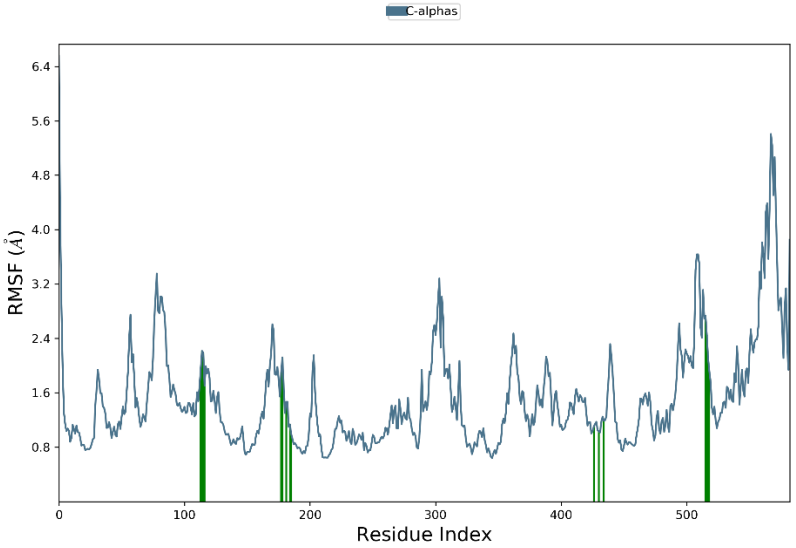
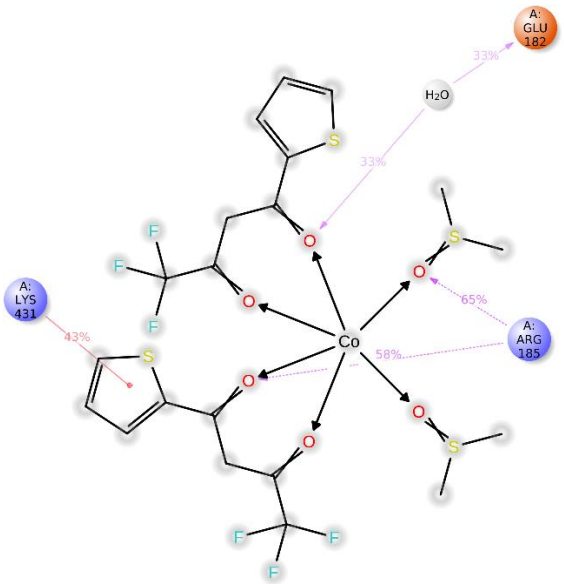


Figure 5: RMSF plot of 4F5S protein during the 100ns simulations.

Protein-ligand interactions

The investigation of protein-ligand interactions holds immense importance in comprehending drug specificity, metabolism, and absorption. These interactions are vividly illustrated through a fingerprint image, providing insights into the molecular associations at the protein's active site. Throughout the 100ns simulation, key amino acids, including LYS-114, LYS-116, PRO-179, GLU-182, ARG-185 and LYS-431 demonstrate consistent involvement in various interactions such as hydrogen bond, hydrophobic and water bridges, signifying their indispensable role in stabilizing the protein-ligand complex (Figure 10a). Notably, the coordinated oxygen atoms of cobalt complex establish significant interactions with active site residues ARG185 of protein, accounting for approximately 65% and 58% of the total simulation time, respectively (Figure 10b). Furthermore, a compelling 33% hydrogen bond interaction through water bridges between the ligand's carbonyl group and GLU-182 of the protein. Additionally, 43% of π – anion interaction between elctron cloud of thiophene and LYS-431 amino acid provides substantial support to the complex's stability during the MD simulations.



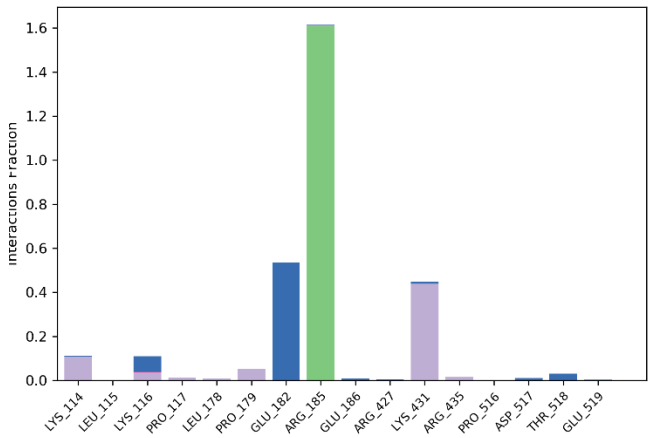


Figure 5: 2D representation of ligand-protein contacts (top)
Fingerprints of protein-ligand interactions (bottom) during the 100ns simulations.

5. Conclusion

In essence, this study concentrated on the synthesis and analysis of a cobalt 4,4,4-trifluoro-1-(thiophen-2-yl)butane-1,3-dione Co(II) complex. Moreover, using X-ray diffraction analysis, the 3D electronic structure of the novel compound was conformed. By employing computational techniques such as molecular docking and dynamic simulations, the investigation unveiled its profound possible use of complex as an agent against oncogene. The docking results showed that the cobalt complex bided into the protein with greater binding score 8.8 kcl/mol through hydrogen, pi-alkyl and pi-anion interactions. This protein-ligand complex greatly stabilized in 100ns of molecular dynamic simulation with a very lesser RMSD and greater protein-ligand interactions. These results signifies that, [TTB-Co] could be potential replacement for platinum based drugs as an anticancer warrior. Further research is necessary to confirm its effectiveness and safety as an inhibitor for cancer therapy. Overall, this study lays a foundation for exploring new cobalt-diketone based treatments for mutated cancers.

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