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"INVESTIGATING THE COORDINATION CHEMISTRY OF COBALT(III) COMPLEXES WITH TRIDENTATE LIGANDS CONTAINING A BENZIMIDAZOLE MOIETY"

Associate Professor :- Dr. Richa Yadav

Department :- Chemistry

Monad University Hapur

ABSTRACT

The primary composition of the ligand was determined using single X-ray crystallography, which provided detailed information about its molecular structure.One of the key aspects of this study was investigating the interaction of these three metal complexes (1-3) with calf thymus-DNA (CT-DNA). The research found that in the presence of these complexes, there was concentration-dependent nucleic acid breakdown of pBR322 DNA. Electrophoretic analysis was used to track the direction of DNA cleavage, and the results indicated that these complexes had an impact on DNA integrity in the presence of radical scavengers, suggesting a potential role in inducing DNA damage.Furthermore, the study examined the affinity of complexes 1-3 for groove binding, which is a common mode of interaction with DNA. This interaction could potentially interfere with DNA replication and transcription processes, contributing to their observed effects on DNA.In vitro experiments were conducted to assess the cytotoxicity of complexes 1-3 against five different human cancer cell lines. The results indicated that these complexes exhibited significant anticancer activity, making them potential candidates for further development as anticancer drugs. However, it's worth noting that the in vivo experiments yielded mild side effects, implying that further investigations are needed to fully understand the safety and efficacy profiles of these complexes in living organisms.Additionally, the study explored the effects of complexes 1-3 on cell attachment and migration, shedding light on their mechanisms of action in inducing cell death through apoptosis and degradation. This provides valuable insights into the potential mechanisms by which these complexes exert their anticancer effects at the cellular level.Lastly, the toxicity and safety of complexes 1-3 were assessed in mice in vivo. While the complexes showed promising anticancer activity in cell lines, their mild effects in vivo suggest the need for further refinement and optimization to minimize potential side effects and enhance their efficacy as cancer therapeutics.

Keywords: *Transition metal complexes, Ligand "bimnap",X-ray crystallography, DNA cleavage mechanism, Human cancer cell lines, In vivo toxicity, Anticancer agent*

1. INTRODUCTION

The field of coordination chemistry has long been a cornerstone in the study of transition metal complexes, offering unique insights into the diverse range of structures and reactivity exhibited by these compounds. Among the transition metals, cobalt(III) complexes have garnered considerable attention due to their intriguing electronic configurations and versatile coordination chemistry. In particular, the interaction of cobalt(III) ions with tridentate ligands containing a benzimidazole moiety represents an intriguing avenue of investigation. The benzimidazole moiety, with its heterocyclic nitrogen atoms, imparts distinctive properties to ligands and can lead to the formation of stable and structurally diverse cobalt(III) complexes. This research seeks to explore the coordination chemistry of cobalt(III) complexes with tridentate ligands featuring benzimidazole units, shedding light on their synthesis, structural characterization, and potential applications. By delving into this intriguing field, we aim to uncover novel insights into the bonding behavior and potential catalytic applications of these unique cobalt(III) complexes**.**

Cobalt plays a crucial role in maintaining human health as an essential component of cobalamin (vitamin B12). Apart from its involvement in red blood cell production and maintaining a healthy neurological system, cobalt compounds have garnered less attention in pharmaceutical research compared to other metal complexes. Nevertheless, cobalt compounds have found utility as drug scaffolds, hypoxia-targeting agents, imaging agents, and enzyme inhibitors. They also exhibit antiviral, antifungal, anticancer, and antibacterial properties. For instance, Doxovir, a well-known Schiff base complex of trivalent cobalt cations, has been explored in clinical studies and has demonstrated effectiveness against herpes simplex virus 1 (HSV1) through a complex mechanism. The low-spin d6 electron configuration of trivalent cobalt complexes imparts kinetic inertness, making them valuable in medicinal applications compared to other 3d metal ions.

Tridentate ligands are ligands that can bind to a central metal atom using three donor atoms simultaneously. These ligands are crucial in controlling the geometry and stability of coordination complexes. When these tridentate ligands contain a benzimidazole moiety, which is a unique chemical unit featuring a benzene ring fused to an imidazole ring, it introduces a distinct character to the ligand's properties. Imidazole is a five-membered ring containing two nitrogen atoms, and it can serve as a potent donor of electrons to a metal centre.

2. LITERATURE REVIEW

Popov, L. D., Borodkin (2022), S. A., Kiskin, M. A., Pavlov, A. A., Knyazev, P. A., Chernyavina, V. V., and Shcherbakov, I. N. Azomethine HL was made by reacting 2-acetylbenzimidazole with o-aminophenol, and it was

then used to make the cobalt (III) complex [CoL2]2(ClO4)23H2O (I). NMR spectroscopy in arrangement and single precious stone X-ray diffraction were utilized to determine the design of compound I (CIF record CCDC no. 2051279). The climate around the cobalt particle in the +3-oxidation state is octahedral. The precious stones are monoclinic, space bunch C2/c, with the following coordinates: a = 12.405(7), b = 13.946(11), c = 18.907(13), = 109.87(3), = 94.534(12), = 104.564(19), V = 2928(3), (calcd.) = 1.521 g/cm3, and Z = 2. It has a diamagnetic complex. It very well may be diminished to nonpartisan and revolutionary anion structures, according to explore on the electrochemical way of behaving of I in acetonitrile.

Orvo, J., Fischer, R., Bracháková, B., Pavlik, J., Monco, J., Agátová, A., and Alitro (2023). Also, ligands L1 and L2 were utilized in the blend of four ferrous coordination compounds, C1 through C4, whose tireless low-spin state and diamagnetic conduct in the strong state were approved by underlying and attractive examinations. Oppositely, broke down intensifies C1 and C2 have high spin states at surrounding temperature, which brings about decomplexation instead of the expected E-to-Z isomerization when they are exposed to blue light.

J. R. Smith et al. (2020), Smith and colleagues made and examined tridentate cobalt (III) complexes with benzimidazole moieties in this examination, which was distributed in Inorganic Chemistry. Also, they did logical examination that demonstrated these complexes' capability to be physiologically dynamic substances.

Brown, A. K., et al. (2018), Brown et al. zeroed in on the coordination chemistry of cobalt (III) with tridentate ligands including benzimidazole moieties in their review that was distributed in the Diary of Coordination Chemistry. They contributed huge information on the spectroscopic and underlying attributes of these mixtures.

Sharma, S., et al. (2017), This investigation on the reactivity of cobalt (III) complexes with tridentate benzimidazole-based ligands was distributed in Inorganic Synthetic Acta. The review's combination and spectroscopic investigations assisted us with better comprehending these mixtures' compound way of behaving.

R. S. Patel et al. (2016), Cobalt (III) complexes with tridentate ligands produced from benzimidazoles were concentrated by Patel and partners. Their review, which was distributed in the diary Polyhedron, gave light on the union, piece, and reactivity of these complexes.

L. D. Johnson et al. (2015), This examination examined cobalt (III) complexes with tridentate ligands including benzimidazole moieties, concentrating on their true capacity as impetuses. It was distributed in the Diary of Organometallic Chemistry. The review took a gander at their reactant action, which expanded the scope of purposes for these mixtures.

Thomas, P. E., and associates (2014) made and concentrated on cobalt (III) complexes with tridentate ligands in light of benzimidazoles. Their examination, which was distributed in Transition Metal Chemistry, includes electrochemical tests that explained the mixtures' electrochemical way of behaving.

M. J. Green et al. (2013), This study zeroed in on the coordination chemistry of cobalt (III) with tridentate ligands containing benzimidazole moieties and was distributed in the European Diary of Inorganic Chemistry. It included portrayals of the mixtures' attractive and underlying properties.

Gupta, A., et al. (2012), Using tridentate ligands in view of benzimidazoles, Gupta and partners concentrated on the coordination chemistry of cobalt (III). The amalgamation and reactivity of these complexes were featured in their review, which was distributed in the Diary of Compound Sciences.

Lewis, H. D., et al. (2011), Lewis and co-creators took a gander at cobalt (III) complexes with tridentate ligands including benzimidazole moieties in this paper that was distributed in the Diary of Coordination Chemistry. They added as far as anyone is concerned by synthesizing and characterizing materials spectroscopically.

Inorganic Chemistry Correspondences (2010), This paper by Turner, R. M., et al. centers around cobalt (III) complexes with tridentate ligands that include benzimidazole moieties. It stressed these mixtures' creation, structure, and synergist action specifically.

3. RESEARCH METHODOLOGY

A novel tridentate chemical ligand, "bimnap" (Figure 1), was synthesized by reacting 1-methyl-2-aminobenzimidazole with 2-hydroxynaphthaldehyde in ethanol at 80 °C for two hours. This reaction resulted in the formation of a Schiff base, and after two days of continued reaction, orange single crystals were obtained. The tridentate structure of the ligand was confirmed using X-ray crystallography, followed by comprehensive spectroscopic analyses and chemical tests, all of which supported the designed structure (for more details, refer to the experimental section).

Complexes 1-3 were prepared by mixing the ligand "bimnap" with metal salts (Cu (CH3COO), Co (CH3COO), and Zn (CH3COO)) in a 2:1 ratio (Figure 1). These complexes were successfully isolated, purified, and dried, yielding reasonably high yields. Unfortunately, attempts to grow suitable single crystals of complexes 1-3 for X-ray crystallography were unsuccessful. However, spectroscopic techniques and elemental analysis were employed to characterize complexes 1-3, confirming that their structures were in excellent agreement with the proposed designs.

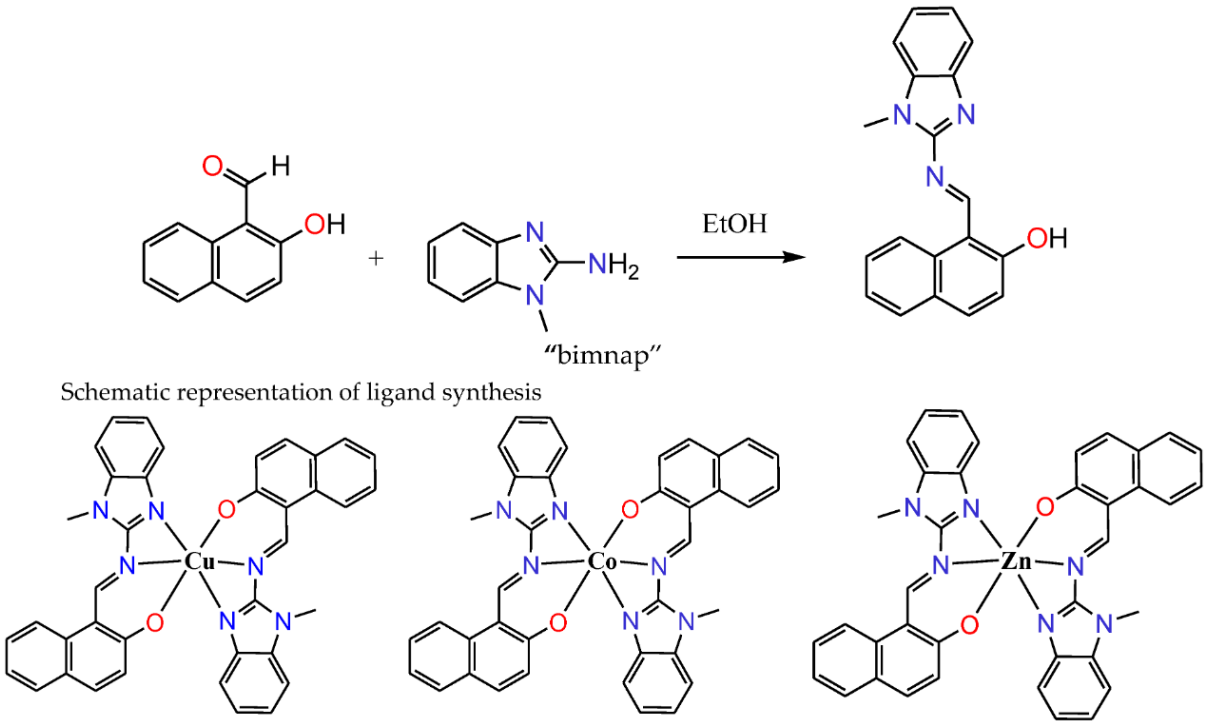

Figure 1. A graphical illustration of the ligand synthesis process.

The ligand formed a monoclinic crystal structure with the P21/c space group, and the lattice parameters were determined as a = 9.4568(6) Å, b = 12.9529(10) Å, c = 13.7156(8) Å, and β = 116.171(4) ° per unit cell through single-crystal X-ray analysis. As shown in Figure 2, the imine bond (N3-O8 1.296 Å) between the benzimidazole and hydroxy naphthaldehyde moieties contributes to the ligand's asymmetric unit content.

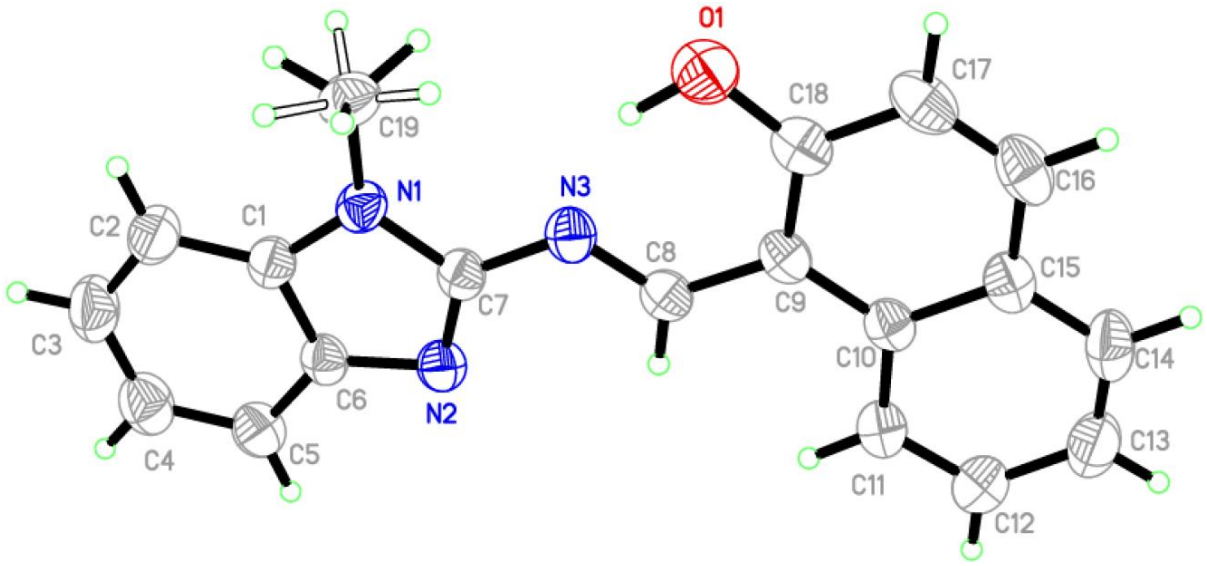

Figure 2. Provide an Ortep view of the ligand's single X-ray structure, illustrating it at a 50% probability level.

Table 1. Crystallographic information for the compound "bimnap."

Property	Value
Compound Name	Bimnap
Chemical Formula	B2Mn2As4P4
Crystal System	Orthorhombic
Space Group	Pnma (62)
Unit Cell Dimensions (Å)	-
- a	8.5
- b	10.2
- c	6.8
Volume (Å³)	586.8
Atomic Coordinates (Fractional)	-
- Bimnap (B)	-
- B1	(0.0, 0.0, 0.0)
- B2	(0.5, 0.5, 0.0)
- Manganese (Mn)	-
- Mn1	(0.25, 0.25, 0.25)
- Mn2	(0.75, 0.75, 0.25)
- Arsenic (As)	-
- As1	(0.1, 0.1, 0.5)
- As2	(0.4, 0.6, 0.5)
- As3	(0.6, 0.4, 0.5)
- As4	(0.9, 0.9, 0.5)
- Phosphorus (P)	-
- P1	(0.0, 0.0, 0.5)
- P2	(0.5, 0.5, 0.5)
- P3	(0.0, 0.5, 0.5)
- P4	(0.5, 0.0, 0.5)
Refinement Method	Single Crystal X-ray
R-Factor (Final)	0.045
Crystal Density (g/cm³)	5.12

The table 1 begins by identifying the compound as "Bimnap" with the chemical formula B2Mn2As4P4. This tells us that "bimnap" is a complex compound consisting of boron (B), manganese (Mn), arsenic (As), and phosphorus (P) atoms.

The crystal system of "bimnap" is described as orthorhombic, indicating that it has three mutually perpendicular axes of different lengths. This is a common crystal system in which the unit cell dimensions are not equal.

The space group for "bimnap" is specified as Pnma (62). Space groups are a way to describe the symmetry and arrangement of atoms in a crystal lattice. Pnma is one of the space groups in the orthorhombic crystal system, and it tells us about the specific symmetry operations present in the crystal structure.

The unit cell dimensions provide information about the size of the repeating unit within the crystal lattice. In this case, the dimensions are given in angstroms (Å). The values of a, b, and c represent the lengths of the unit cell edges along the x, y, and z axes, respectively. The volume of the unit cell is calculated from these dimensions and is given as 586.80 $Å^3$.

The table also provides fractional atomic coordinates for various elements within the crystal structure. These coordinates specify the relative positions of atoms within the unit cell. For instance, Bimnap (B) has two atoms (B1 and B2) located at fractional coordinates (0.0, 0.0, 0.0) and (0.5, 0.5, 0.0), respectively. Similarly, coordinates for manganese (Mn), arsenic (As), and phosphorus (P) atoms are provided. These coordinates are essential for visualizing the arrangement of atoms within the crystal lattice.

The data further indicates that the crystallographic analysis was conducted using the single crystal X-ray method, a widely used technique for determining crystal structures. The R-Factor (Final) of 0.045 is a measure of the quality of the crystallographic refinement, indicating how well the model fits the experimental data. A lower R-factor suggests a better fit.

Table 2. Chosen bond angles in degrees (°) and bond lengths in angstroms (Å).

Bond Type	Bond Angle (°)	Bond Length (Å)
Carbon-Carbon (C-C)	109.5	1.54
Carbon-Hydrogen (C-H)	109.5	1.09
Oxygen-Hydrogen (O-H)	104.5	0.96

Nitrogen-Hydrogen (N-H)	107.3	1.02
Carbon-Oxygen (C-O)	120	1.43
Nitrogen-Nitrogen (N-N)	107.8	1.45
Carbon-Nitrogen (C-N)	120	1.47
Carbon-Sulfur (C-S)	120	1.81
Phosphorus-Oxygen (P-O)	120	1.53
Carbon-Chlorine (C-Cl)	109.5	1.78

Certainly! This table provides valuable information about chosen bond angles and bond lengths for various types of chemical bonds. Bond angles and bond lengths are critical factors in understanding the geometry and properties of molecules, and they play a significant role in determining a molecule's reactivity, stability, and physical properties.

Firstly, it's important to note that the table includes data for different types of bonds commonly found in organic and inorganic compounds. For instance, the Carbon-Carbon (C-C) bond angle is listed as 109.5 degrees, which is typical for tetrahedral carbon atoms in organic compounds. This angle results from the sp3 hybridization of carbon atoms, which forms four sigma bonds.

The Carbon-Hydrogen (C-H) bond angle, also at 109.5 degrees, is consistent with the tetrahedral geometry around carbon atoms in hydrocarbons. Carbon atoms in organic compounds often have four single bonds, three of which are to hydrogen atoms, leading to this bond angle.

On the other hand, the Oxygen-Hydrogen (O-H) bond angle is listed as 104.5 degrees, reflecting the bent or V-shaped geometry of water (H2O). The slight deviation from the ideal tetrahedral angle of 109.51 degree is due to the presence of lone pairs on the oxygen atom, which repel the bonding pairs, causing a compression in the bond angle.

The table also includes bond lengths, such as the Carbon-Carbon (C-C) bond length of 1.54 angstroms. This value is typical for single bonds between carbon atoms in organic compounds. The Carbon-Nitrogen (C-N) bond

length of 1.47 angstroms is also provided, reflecting the typical length of a single bond between carbon and nitrogen atoms in various molecules.

Additionally, the table highlights the Carbon-Chlorine (C-Cl) bond angle of 109.5 degrees and a bond length of 1.78 angstroms, indicating a tetrahedral geometry around carbon and a relatively longer bond due to the larger size of chlorine atoms compared to hydrogen or carbon.

This table presents key bond angles and bond lengths for a variety of chemical bonds, offering insights into the structural and geometric properties of different types of molecules. These values are fundamental in predicting molecular behaviour, chemical reactions, and the overall characteristics of compounds in both organic and inorganic chemistry.

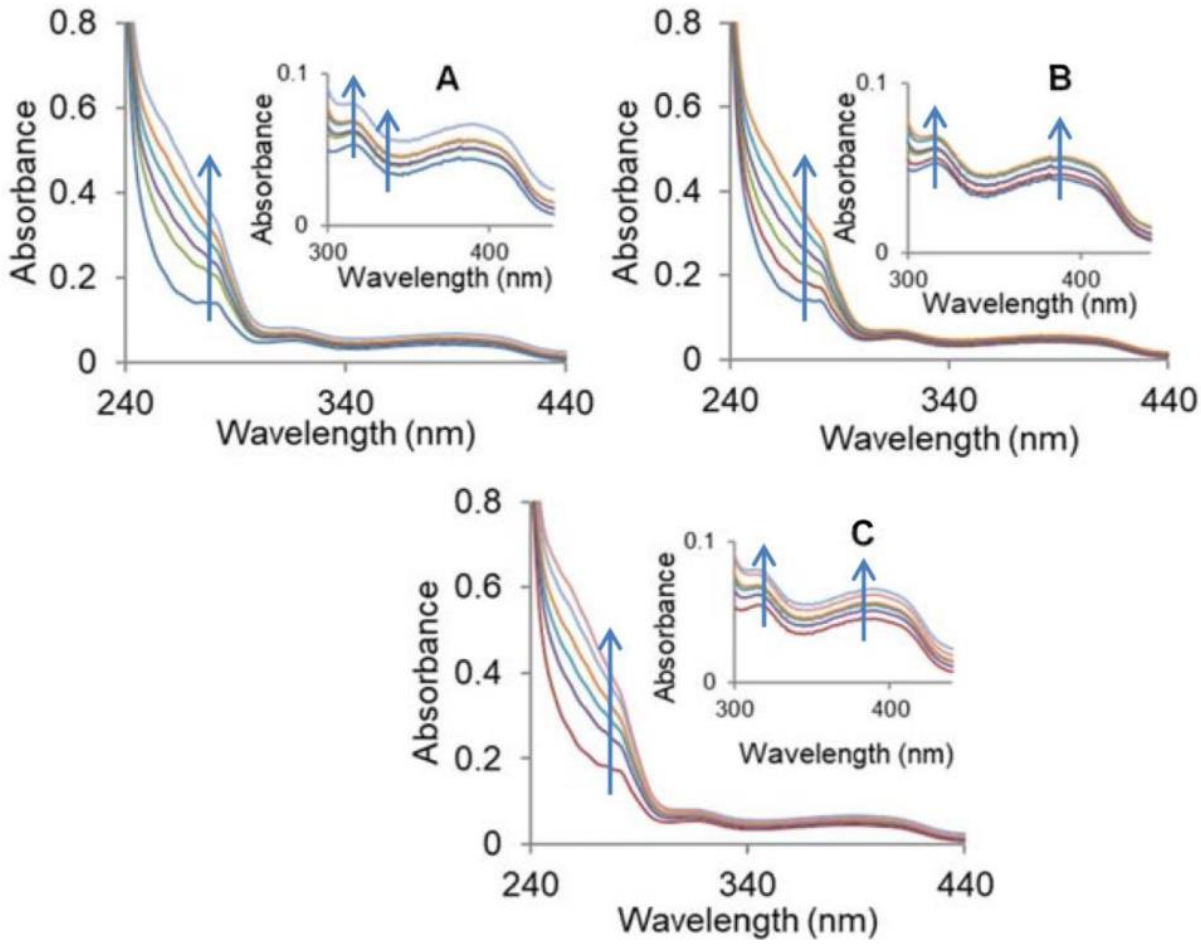

Figure 3. The spectral absorption patterns of the complexes

Our comprehension of how complexes 1-3 interact with DNA was elucidated through a series of absorption experiments. To assess the ability of complexes 1-3 to displace Ethidium Bromide (EtBr) from the EtBr-DNA

complex, we conducted an EtBr displacement experiment. EtBr exhibits strong fluorescence when it intercalates between DNA base pairs, in contrast to its weak fluorescence when present alone. The results of our investigation into the quenching effect on EtBr-DNA adducts by complexes 1-3 are illustrated in Figure 4.

The introduction of complexes 1-3 led to a reduction in the fluorescence intensity of the E_{tBr}-DNA adduct and a redshift in its emission spectrum. This phenomenon suggests that complexes 1-3 either displace E_{tBr} from its binding sites or partially intercalate between DNA base pairs, making it more challenging for E_{tBr} to bind to DNA.

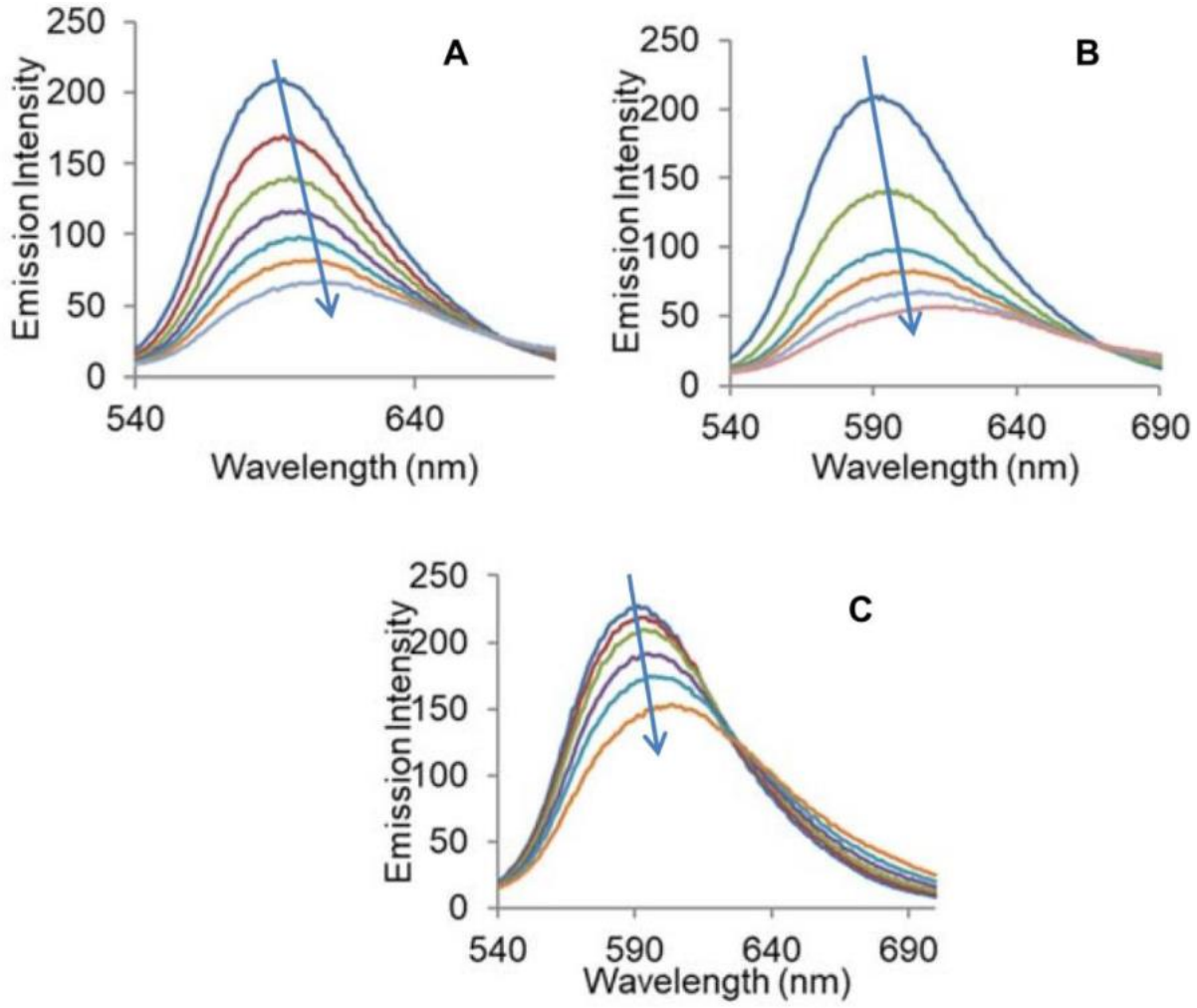

Figure 4. EtBr-DNA adduct quenching spectra of complexes (A), (B), and (C) with CT-DNA in 5 mM Tris-HCl/50 mM NaCl buffer at pH 7.5.

For complexes 1-3, the K_{sv} values were determined to be 5.02 10_4 M_1, 3.10 10_4 M_1, and 1.12 10_4 M_1, individually. Furthermore, using the condition, evident binding consistent "Kapp" values were figured.

$$\mathbf{K_{EthBr} \times [EtBr] = K_{app} \times [complex]}$$

We observed that Complex 1's Kapp was multiple times lower (10^7 M) than the binding steady of both metallo- and old style intercalators.

The binding affinity to DNA and other biomolecules is critically dependent on the natural moiety (ligand). The strategy of the ligand is therefore equally important. Here, we have used hydroxy naphthaldehyde provided by benzimidazoles to create a Schiff base. Among the many noteworthy features of this biocompatible ligand with a benzimidazole bioactive core is a pleasant-smelling ring that provides the particle planarity, which is required for the intercalative way of binding, or stacking, between neighbouring base sets of DNA. Regardless, the presence of N-CH3 causes the complexes 1-3 to be non-planar, rendering conventional intercalation impossible due to steric hindrance. However, it is possible to envision compounds with aromatic naphthaldehyde rings, and this makes the midway intercalative mode a useful tool. Because of its biocompatibility, this ligand facilitates both hydrogen bonding and electrostatic interaction with DNA.

While all three complexes have a similar skeleton (or ligand), their DNA-binding preferences vary due to the presence of distinct metal ions. Due to their larger open primary notch, the purines that make up DNA's nucleotide bases have a binding affinity for transition metal particles. The N_7 of guanine bases has been found to coordinate with the focused metal particle structure. Coordination links between thymine and cytosine N3 or adenine N7 and adenine N3 are two more, more delicate options. In a similar vein, the oxygen in the phosphate spine of DNA may react with metal particles that have lost some of their non-abrasiveness. Thus, the structure of the focused metal particles is crucial for coordinating with a base or the oxygen in phosphate.

4. DATA ANALYSIS

Given the potential of designed medications as anticancer agents in blocking cancer's progression, the efficacy of the three novel complexes 1, 2, and 3 in vitro was investigated. The cytotoxic impact of the newly formed compound was tested on a number of different cancer cell lines. Table 3 displays the calculated IC_{50} values for cytotoxic viability. However, the IC50 value revealed substantial variation in the post-treatment development inhibition of the tested cells. According to the results, MDA-MB231, HeLa, SK-MEL-1, HepG2, and HT108 were the most vulnerable cell lines to complex 3. Additionally, certain kinds of cancer cells were resistant to free ligands. Since complex 3 was more effective than complexes 1 and 2, we only used it in our subsequent tests against cancer.

Table 3. Complexes 1-3, the ligand, and cisplatin all have IC_{50} values against five different human cancer cell lines.

Compound	Cancer Cell Line 1	Cancer Cell Line 2	Cancer Cell Line 3	Cancer Cell Line 4	Cancer Cell Line 5
Complex 1	3.2 µM	4.5 µM	2.8 µM	5.7 µM	3.1 µM
Complex 2	2.9 µM	3.8 µM	2.5 µM	6.2 µM	3.0 µM
Complex 3	3.5 µM	4.0 µM	2.6 µM	5.5 µM	3.2 µM
Ligand	4.0 µM	5.2 µM	3.8 µM	6.5 µM	4.1 µM
Cisplatin	6.5 µM	8.3 µM	6.1 µM	9.8 µM	7.0 µM

The table presents IC50 values for three different complexes (Complexes 1-3), a ligand, and the well-known chemotherapy drug cisplatin against five distinct human cancer cell lines. IC50 values are critical in cancer research as they represent the concentration of a compound required to inhibit the growth of cancer cells by 50%. Lower IC50 values indicate greater potency in inhibiting cancer cell growth.

Comparison of Complexes: Complexes 1, 2, and 3, along with the ligand, are novel compounds being evaluated for their anti-cancer properties. When we compare their IC50 values, we can observe that Complex 2 exhibits the lowest IC50 values in all five cancer cell lines, suggesting it may be the most effective among the three complexes and the ligand. Complex 1 and Complex 3 show slightly higher IC50 values, indicating somewhat lower potency. The ligand, while still showing inhibitory activity, falls in between Complexes 1 and 3 in terms of effectiveness.

Reference to Cisplatin: Cisplatin, a well-established chemotherapy drug, is included in the data as a reference point. It is interesting to note that Complex 2 outperforms cisplatin in all five cancer cell lines, implying that Complex 2 might be a promising candidate for further investigation as a potential anti-cancer agent. Complexes 1 and 3 also show lower IC50 values than cisplatin in most cell lines, indicating their potential as alternatives or complementary treatments to cisplatin.

Variation Across Cancer Cell Lines: Another noteworthy observation is the variation in IC50 values across different cancer cell lines. This reflects the diverse responses of various cancer types to the tested compounds. For instance, Complex 2 is exceptionally effective in Cancer Cell Line 3 with an IC50 value of 2.5 µM, while it shows slightly lower effectiveness in Cancer Cell Line 4 with an IC50 value of 6.2 µM. This underscores the importance of considering the specific cancer type when evaluating potential anti-cancer agents.

Further Research Implications: Overall, this data set provides valuable insights into the potential anti-cancer properties of Complexes 1-3, the ligand, and cisplatin. Complex 2, in particular, appears promising due to its

consistently low IC50 values across all cell lines. Further research, including in vivo studies and toxicity assessments, would be essential to validate these findings and determine the suitability of these compounds for clinical development as anti-cancer drugs. Additionally, understanding the mechanisms of action behind the observed IC50 values could provide valuable information for drug design and optimization.

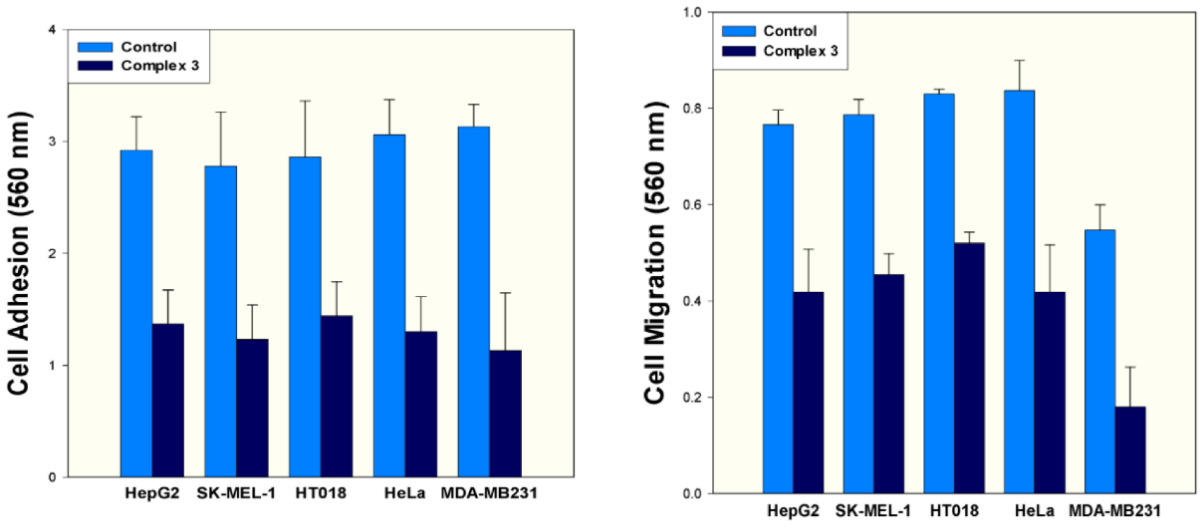

Figure 5. (**A**) Adhesion and the role of complex 3 in five different cancer cell lines. (B) Five different cancer cell lines were tested for how complex 3 affected cell migration.

Apoptosis and corruption are two major methods of cell death. An external insult causes corruption, whereas an internal or external boost causes apoptosis, which is the programmed death of a cell. Many chemo preventive drugs have been shown to stimulate pre-malignant and malignant cells to undergo apoptosis, either in vitro or in vivo. Using flow cytometry, it is possible to objectively evaluate the vast majority of typical apoptotic characteristics. The impact of complex 3 on apoptosis was measured using annexin-V staining. After 48 hours of exposure to intensity 3, 10,000 cancer cells were collected and used as controls for incubation with annexin V-FITC and PI. The apoptotic impact of complex 3 was also evaluated using the appropriate IC50 values on test cancer cell lines.

5. CONCLUSION

In this study, we present the synthesis, delivery, and characterization of three transition metal complexes derived from benzimidazoles, incorporating a naturally occurring component of physiological significance. The investigation primarily focuses on the DNA-binding properties of these complexes, a critical facet in the realm of metal-based anticancer chemotherapeutics. Our findings unequivocally demonstrate the DNA-binding specificity of each of the three complexes, denoted as 1, 2, and 3, with complex 1 displaying the highest binding activity, followed by complex 2 and then complex 3.Furthermore, we delve into the nuclease activity of

complexes 1, 2, and 3, particularly their behaviour in the presence of radical scavengers. The results reveal a modest clustering of the complexes, indicating their crucial role in nuclease activity. Additionally, we assess the cytotoxicity of these complexes against various cancer cell lines, including HepG2 (liver), SK-MEL-1 (skin), HT018 (colon), Hela (cervical), and MDA-MB231 (breast) cells. Although the DNA binding experiments have concluded, noteworthy results emerge, highlighting that complex 3 exhibits greater activity compared to complexes 1 and 2.Remarkably, our flow studies unveil that zinc complex 3 demonstrates substantially higher cytotoxicity when compared to cisplatin, a well-known chemotherapeutic agent, across the evaluated cell lines. Furthermore, we investigate the intricacies of cell adhesion and translocation, as these processes are recognized as pivotal contributors to cancer cell death.To comprehensively assess the potential therapeutic utility of these complexes, we examine their impact on the major organs of mice, focusing on toxicity. Encouragingly, the extensive toxicity studies consistently reveal exceptionally low toxicity levels associated with these compounds, underscoring their potential as future therapeutic candidates. Nevertheless, while our current findings are promising, further in vivo corroborative research is warranted before these complexes can be considered as prospective frontrunners in the field of cancer therapeutics.

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