

Coordination Complexes of Cobalt with Pyrazole-Based Ligands and Potential Applications

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Abstract

Transition metals are one of the central aspects of modern coordination chemistry research. In addition to being well-studied, cobalt is a unique transition metal due to its presence in vitamin B₁₂. Pyrazole-based structures are common in nature and organic synthesis. Over the past decade, our research group has focused on synthesizing and characterizing novel cobalt, nickel, and copper organometallic complexes. To date, we have reported three cobalt complexes, five nickel complexes and one copper complex with pyrazole-derived ligands.

Based on the current scientific data, we are optimistic about potential applications of our coordination complexes with cobalt and pyrazole-based ligands. In this work we review applications of cobalt complexes with pyrazole-based ligands described in recent literature to explore possible applications of compounds synthesized and characterized by our research group.

Keywords: coordination chemistry, transition metals, cobalt, pyrazole-based ligands

1. Importance of Cobalt and Pyrazole-Based Structures in Chemistry and Biochemistry

1.1 Cobalt (Co) Metal

Element cobalt was first isolated and discovered by the Swedish scientist Georg Brandt in 1735 (Gusenius, 1967). Cobalt's discovery explained the blue color of pigments from cobalt-containing ores used in porcelain and glass production from the ancient times in Egypt, Middle East, and Renaissance Italy (Orna, 2022). In nature, cobalt is present in various minerals and is used as a component of alloys in metallurgy. Currently, about eighty percent of the world's cobalt output is employed in the metallic state (Gad, 2024). Naturally, cobalt occurs as an isotope cobalt-59. Radioactive isotope cobalt-60 has been used in various science experiments, for example the "Wu experiment" that led to the Nobel prize award in Physics in 1957 and was based on beta-decay of cobalt-60 (Dumancic & Enger, 2024; Lee & Yang, 1956). Isotope cobalt-60 is also one of the sources of radiation for cancer chemotherapy (Schreiner et al., 2009).

1.2 Cobalamin (Vitamin B₁₂)

Cobalt is one of the most famous transition metals due to its physiological role and appearance in the center of the chemical structure of vitamin B₁₂, also known as cobalamin (Marques, 2023). Dorothy Hodgkin determined the structure of vitamin B₁₂ by using X-ray diffraction methods in 1956 (Hodgkin et al., 1956) and was awarded the Nobel Prize in Chemistry in 1964 for this and other structure determinations. The basic vitamin B₁₂ structure has several chemical forms that differ by the substituent on the central cobalt atom (Marques, 2023). Cobalt plays a vital role in many biological processes (Genchi et al., 2023) and dietary vitamin B₁₂ has been associated with cognitive, cardiovascular, and ocular health benefits (Gharibzahedi et al., 2023). Vitamin B₁₂ is found in every cell in the body and has multiple functions, including acting as a cofactor in the synthesis of DNA (Combs & McClung, 2022).

Vitamin B₁₂ acts as the reserve for cobalt in the human body, allowing the various cobalt corrinoids and vitamin B₁₂ chemical forms to act in DNA, fatty acid, amino acid, and red blood cell synthesis (Genchi et al., 2023). Corrinoids are cyclic systems of pyrrole rings, a five-membered nitrogen-containing heterocyclic organic compound (Lambert et al., 2023). Though the diverse number of cobalt corrinoids can function in light-dependent gene regulation and human microbiomes in the stomach, vitamin B₁₂ specifically is needed for the body to make the enzymes required for tetrahydrofolate recycling and methionine synthesis in order to maintain the normal functions of DNA (Marques, 2023). Because of vitamin B₁₂'s essentiality to normal DNA function, deficiency of vitamin B₁₂ hinders cell division (Marques,

2023). The presence of adequate vitamin B₁₂ prevents accumulated methylmalonic acid from reaching toxic levels and interfering with DNA replication in rapidly dividing cells (Gharibzadeh et al., 2023). Most of the rapidly dividing cells that would be affected are found in the lining of the gastrointestinal tract, the bone marrow, and the skin. Though the effects on the skin and gastrointestinal tract are less noticeable, vitamin B₁₂ deficiency leads to anemia by effecting rapidly dividing cells in the bone marrow (Marques, 2023). Vitamin B₁₂ deficiency also has a detrimental effect on the maintenance of neurological functions (Pavlov et al., 2019). Lack of proper levels of dietary vitamin B₁₂ can lead to spinal cord degeneration (Pavlov et al., 2019) and the degradation of myelin sheaths surrounding nerves has been associated with progression of conditions such as dementia and Alzheimer's disease (Marques, 2023). Vitamin B₁₂'s role in DNA synthesis directly contributes to its role in overall immune system health; vitamin B₁₂ deficiency and subsequent decreases in protein and nucleic acid synthesis interfere with immune cell response time and efficacy, in some cases leading to systemic vascular inflammation (Genchi et al., 2023).

The most common form of vitamin B₁₂ seen in dietary supplements is cyanocobalamin, which is the most stable form of vitamin B₁₂ and does not directly act as a cofactor in cellular processes (Genchi et al., 2023). Proper vitamin B₁₂ intake must be achieved through consuming animal products, so the primary cause of vitamin B₁₂ deficiency is typically inadequate animal product intake (Pavlov et al., 2019). Vitamin B₁₂ can be found in animal meat, milk, and other animal products, meaning that people on vegetarian or vegan diets are recommended to obtain their vitamin B₁₂ through fortified foods and dietary supplementation (Gharibzadeh et al., 2023).

1.3 Pyrazole-based Structures and Their Coordination with Metal Ions

Pyrazole-based structures are prevalent in nature, commonly synthesized, and have a variety of applications. Pyrazole is a heterocyclic organic structure with a five-membered ring system containing two nitrogen atoms adjacent to each other (Yet, 2022). Kumar and others in their paper described thirteen natural products containing pyrazole moiety (Kumar et al., 2013). Notably, pyrazole structure ranks the forty-fourth out of one hundred most common heterocyclic rings in FDA approved drugs (Taylor et al., 2014). The family of pyrazole-based drugs is characterized by anti-cancer, antiglycemic, anti-inflammatory, and antimicrobial with the range of applications rapidly expanding (Ma & Yu, 2022). Pyrazole's nitrogen atoms serve as donor sites for metal ions, resulting in coordination complexes. Parshad et al. described three ways of coordination of a metal ion by pyrazole ring or rings (Parshad et al., 2024).

1.4 Purpose of This Review

This brief review focuses on potential applications of cobalt complexes with pyrazole-based ligands recently reported in literature. We hope to find similar applications of cobalt containing complexes, which our research group synthesized and characterized over the past decade.

2. Overview of Coordination Chemistry with Transition Metals and Pyrazole-based Ligands: Lyubartseva Research Group (2009-2024)

When GL started teaching at Southern Arkansas University (SAU), a primarily teaching undergraduate regional university, in 2009 she had a goal of involving students in research and maintaining an active and publication producing research group.

To encourage students to join her group, she designed research projects, which were aligned with undergraduate students' expectations. Typically, undergraduate students prioritize coursework to research with respect to effort and time, contrasting with graduate students, who are primarily focused on doing research required for their thesis or/and dissertation. It is true that in most cases, research is not the major requirement for B.S. in science graduation from four-year universities. With the recommended fifteen credit hours per semester for a full-time enrollment, undergraduate students often work part-time and sometimes full-time, while completing online courses. As a result, undergraduate students can commit only a limited number of hours towards research, if any. All these considerations came gradually to GL over the course of fifteen years of teaching at SAU and helped her to shape research projects for her students.

In the collaboration with Professor Sean Parkin from the University of Kentucky, who provided invaluable assistance with crystal structures of the organic compounds synthesized at Southern Arkansas University, we were fortunate to produce and report several transition metal complexes with pyrazole-based ligands (Lyubartseva et al., 2016; Lyubartseva et al., 2013b, 2013a, 2020; Lyubartseva, Parkin, & Mallik, 2012; Lyubartseva, Parkin, Mallik, et al., 2012; Lyubartseva & Parkin, 2009) including three novel cobalt complexes (Lyubartseva et al., 2020; Lyubartseva & Parkin, 2010a, 2010b) with active participation of SAU undergraduate students.

3. Cobalt Complexes with Pyrazole-based Ligands Synthesized and Characterized by Lyubartseva Research Group (2009-2024)

To date, we reported three organo-metallic complexes of cobalt with organic ligands based on pyrazole. For illustrative purposes, chemical and crystal structures of dichloridobis(3,4,5-trimethyl-1*H*-pyrazole- κ N²)cobalt(II) are shown in

Figures 1 and 2, correspondingly; chemical and crystal structures of tetra-ethyl-ammonium (2,2'-bipyridine)tetra-cyanidocobaltate(III) sesquihydrate acetonitrile solvate are shown in Figures 3 and 4, correspondingly, and chemical and crystal structures of bis[1-methoxy-2,2,2-tris-(pyrazol-1-yl- κN^2) ethane]-cobalt (II) bis-perchlorate are shown in Figures 5 and 6, correspondingly.

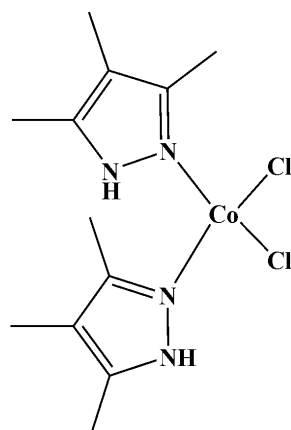


Figure 1. Chemical Structure of Dichloridobis(3,4,5-trimethyl-1*H*-pyrazole- κN^2)cobalt(II) (Lyubartseva & Parkin, 2010a)

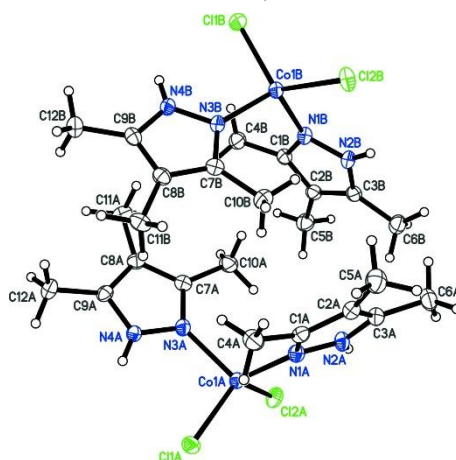


Figure 2. Crystal Structure of Dichloridobis(3,4,5-trimethyl-1*H*-pyrazole- κN^2)cobalt(II) (Lyubartseva & Parkin, 2010a)

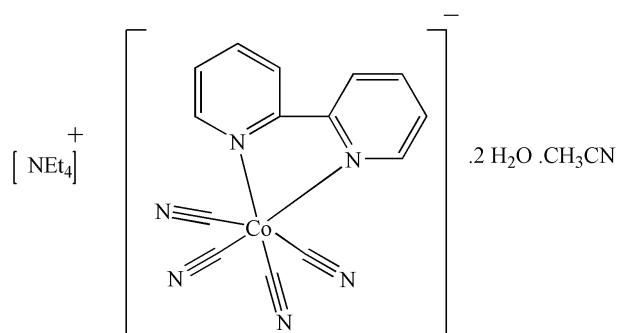


Figure 3. Chemical Structure of Tetra-ethyl-ammonium (2,2'-bipyridine)tetra-cyanidocobaltate(III) sesquihydrate acetonitrile solvate, NEt_4 = tetra-ethyl-ammonium (Lyubartseva & Parkin, 2010b)

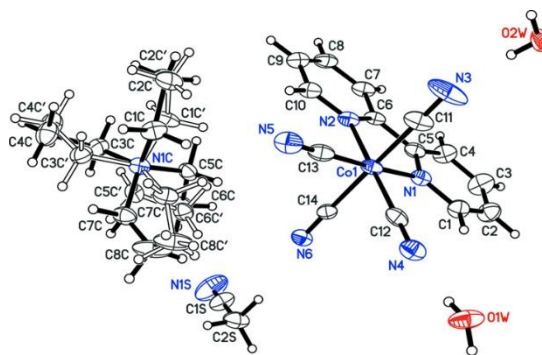


Figure 4. Crystal Structure of Tetra-ethyl-ammonium (2,2'-bipyridine)tetra-cyanidocobaltate(III) sesquihydrate acetonitrile solvate (Lyubartseva & Parkin, 2010b)

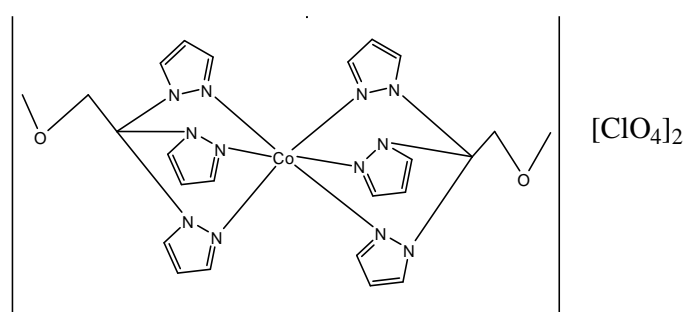


Figure 5. Chemical Structure of Bis[1-methoxy-2,2,2-tris-(pyrazol-1-yl- κN^2) ethane]-cobalt (II) bis-perchlorate (Lyubartseva et al., 2020)

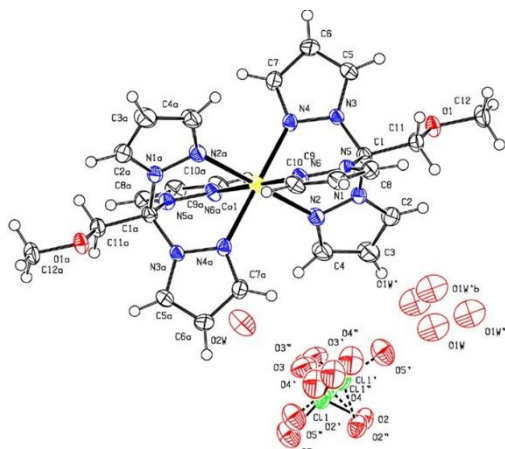


Figure 6. Crystal Structure of Bis[1-methoxy-2,2,2-tris-(pyrazol-1-yl- κN^2) ethane]-cobalt (II) bis-perchlorate (Lyubartseva et al., 2020)

For the synthesis of dichloridobis(3,4,5-trimethyl-1*H*-pyrazole- κN^2)cobalt(II), we used commercially available cobalt (II) chloride hexahydrate as a cobalt source to react with the ligand, 3,4,5-trimethylpyrazole in tetrahydrofuran. Crystals suitable for crystal structure determination were obtained from methylene chloride solution of the product layered with hexane (Lyubartseva & Parkin, 2010a).

For the synthesis of tetra-ethyl-ammonium (2,2'-bipyridine)tetra-cyanidocobaltate(III) sesquihydrate acetonitrile solvate, $[Co(bpy)_3]Cl_2 \cdot 2H_2O \cdot CH_3CH_2OH$ complex where $bpy = 2,2'$ -bipyridine was prepared by following the previously published procedure by Szalda et al. (Szalda et al., 1983). Then the complex was dissolved in methanol and acetonitrile mixture and treated with tetraethylammonium cyanide. The resulting crystals were suitable for crystal structure determination (Lyubartseva & Parkin, 2010b).

For the preparation of bis[1-methoxy-2,2,2-tris-(pyrazol-1-yl- κ N²) ethane]-cobalt (II) bis-perchlorate, commercially available cobalt (II) perchlorate hexahydrate and the ligand, 1-methoxy-2,2,2-tris(pyrazol-1-yl) ethane produced crystals suitable for crystal structure determination from methanol/acetonitrile mixture (Lyubartseva et al., 2020).

All three complexes were characterized by elemental analysis, IR, and X-ray crystallography (Lyubartseva et al., 2020; Lyubartseva & Parkin, 2010a, 2010b).

In all the above crystal structures, cobalt ions of various valencies are coordinated by nitrogen atoms of pyrazole rings, however, the geometry of each complex is different.

In dichloridobis(3,4,5-trimethyl-1*H*-pyrazole- κ N²)cobalt(II), two 3,4,5-trimethylpyrazole ligands function as monodentate ligands. In addition, two chloride anions form direct bonds with cobalt (II) resulting in a slightly distorted tetrahedral geometry (Lyubartseva & Parkin, 2010a).

Tetra-ethyl-ammonium (2,2'-bipyridine)tetra-cyanidocobaltate(III) sesquihydrate acetonitrile solvate has the most intricate coordination of the transition metal cobalt of the three structures discussed. Here, cobalt (III) atom is six-coordinated with two nitrogen atoms from 2,2'-bipyridine and four carbon atoms from cyanide ions in a distorted octahedral geometry, producing cyano-linked metalloorganic compound (Lyubartseva & Parkin, 2010b).

In bis[1-methoxy-2,2,2-tris-(pyrazol-1-yl- κ N²) ethane]-cobalt (II) bis-perchlorate, the organic ligand is a tridentate 1-methoxy-2,2,2-tris(pyrazol-1-yl) ethane. Our group was the first to report the crystal structure of this ligand (Lyubartseva et al., 2014). Up to date, we synthesized and obtained crystal structures of coordination complexes of 1-methoxy-2,2,2-tris(pyrazol-1-yl) ethane with three different transition metals: nickel (Lyubartseva et al., 2013a; Lyubartseva et al., 2013b), copper (Lyubartseva et al., 2016) and most recently cobalt compounds (Lyubartseva et al., 2020). Bis[1-methoxy-2,2,2-tris-(pyrazol-1-yl- κ N²) ethane]-cobalt (II) bis-perchlorate contains cobalt (II) atom, which is coordinated by two ligand molecules producing distorted octahedral geometry, resulting in the crystal structure similar to the one with copper (II) (Lyubartseva et al., 2016).

4. Discussion of Potential Applications of Previously Reported Similar Complexes of Transition Metals with Pyrazole-based Organic Ligands

4.1 Catalysis

Complexes of cobalt with pyrazole-based ligands demonstrated high potential in catalysis. For example, they were used as catalyst precursors for the peroxidative oxidation of cyclohexane (Silva et al., 2014), the reaction used for the industrial production of nylon-6 and polyamide-6 intermediates (Reis Conceição et al., 2023). Cobalt(II) complexes which formed metal-organic frameworks (MOF), were useful in heterogeneous catalytic oxidation reactions with molecular oxygen at ambient temperatures (Tonigold et al., 2011). Recently, another MOF constructed from clusters of cobalt with pyrazole-based ligands showed high catalytic activity in the oxygen evolution reaction (Li et al., 2024). Cobalt complexes with bis(benzimidazole)pyrazolide ligands were effective in electrochemical water oxidation, the reaction which enables to use hydrogen as a renewable energy source, a potential alternative to conventional fossil fuels (Wu et al., 2024). Cobalt-based catalysts are associated with a lower cost, greater natural abundance, and catalytic performance comparable to that of noble metal catalysts such as platinum and palladium. In addition, cobalt-based catalysts are typically characterized by structural stability and are promising substitutes for costlier noble metals, which are in short supply in environment (Huang et al., 2022).

Cobalt (III) complex with pyrazole-based ligand, 5-methyl-3-formylpyrazole-N(4)-isopropyl-thiosemicarbazone, was reported to display a photocatalytic activity towards degradation of methylene blue under UV radiation (Saha et al., 2024). Photocatalytic activity refers to the ability of a photocatalyst to initiate a reaction under specific conditions when exposed to light (Ohtani, 2011). Methylene blue has been used in a treatment for malaria and other diseases, most recently including Alzheimer's disease (Silva et al., 2020).

4.2 Magnetism Studies

Cobalt complexes with pyrazole-based ligands have potential applications as room temperature magnets and single-molecule magnets. Previously reported by Oki and others, cobalt(3,5-dimethylpyrazole) dichloride, which is similar to dichloridobis(3,4,5-trimethyl-1*H*-pyrazole- κ N²)cobalt(II), showed magnetic properties (Oki et al., 1995). Magnetic studies of cobalt (II) coordination polymers with pyrazole-3,5-dicarboxylate and pyrazine (Hou et al., 2023), which is similar to pyrazole present in our complexes, exhibit the antiferromagnetic interaction between cobalt ions (Klongdee et al., 2023).

In several recent studies cobalt-based complexes with pyrazole-derived ligands demonstrated potential as single-molecule magnets. A single molecule magnet is different from traditional bulk magnets (Pedersen et al., 2014). It is a molecule which can be magnetized in a magnetic field, and that will remain magnetized even after switching off the magnetic field (Madhu et al., 2005).

Single molecule magnets have a promising potential for spintronics, the study of the intrinsic spin of the electron and its associated magnetic moment, and device applications (Yin et al., 2023). A novel coordination polymer containing cobalt (II), a pyrazole-based ligand and 4,4-bipyridine as a spacer was reported to display a single-ion magnet behavior (Soares et al., 2020). Recently, Kumar Sahu et al. described six complexes with cobalt and pyrazole-based ligands which showed potential as cobalt(II) based single-ion magnets (Kumar Sahu et al., 2023).

4.3 Optoelectronic Properties

Optoelectronics is the study and application of electronic devices that source, detect, and control light based on the quantum mechanical effects of light on electronic materials such as semiconductors (Adams & Barbante, 2015). In 2020, Chenab's research group introduced a cobalt metal complex as a novel class of sensitizer for more efficient dye sensitized solar cells (Chenab et al., 2020). Hegde et al. in their recent report described series of (pyrazolyl)methane supported cobalt (II) complexes similar to our complex, dichloridobis(3,4,5-trimethyl-1*H*-pyrazole- κ N²)cobalt(II), that exhibited significant sensitization capacity and therefore could be potentially used in dye-sensitized solar cells, thus providing a safer and more environmentally-friendly alternative to ruthenium-based compounds typically used for this purpose (Hegde et al., 2024).

4.4 Anti-microbial Properties

Reported in 2024 by Saha et al., cobalt (III) complex with the pyrazole-based thiosemicarbazone ligand, 5-methyl-3-formylpyrazole-N(4)-isopropylthiosemicarbazone, showed potential antimicrobial activities against both the gram-positive bacteria, *Bacillus subtilis* MTCC 7193 and gram-negative bacteria, *E. coli* MTCC 1610 (Saha et al., 2024). The other study by Sangwan and Singh, showed that another macrocyclic Schiff base complex with cobalt (II) could be potentially used as an antimicrobial agent (Sangwan & Singh, 2019). A Schiff base is a nitrogen-containing compound made by condensing a carbonyl-containing aldehyde or ketone with a nitrogen-based counterpart (Pervaiz et al., 2024). Pyrazole bridged binuclear cobalt (II) complex, described by Kulkarni et al., was found to have anti-microbial properties against a gram negative bacterium, *E. coli*, by intercalating ability with *E. coli*'s DNA (Kulkarni et al., 2011).

4.5 Anti-cancer Properties

Transition metal complexes are gaining increased attention in cancer chemotherapy which is defined as the drug therapy that targets at destroying cancerous cells or stopping their propagation (Dasmahapatra et al., 2024). There is a need for novel non-platinum based metallodrugs to use in anti-cancer therapeutics. As described earlier, cobalt, and other transition metals are important for the structure and function of biological molecules. In addition, transition metal complexes can interact with nitrogen- and oxygen-containing terminals of protein and DNA molecules and act as enzymatic inhibitors due to selective binding to active sites of various enzymes (Dasmahapatra et al., 2024; Saha et al., 2024). In organometallic complexes the metal ion may have been protected by the organic ligands, thus preventing or reducing negative side effects of the medication. The combined effects of the metal and ligands could lead to an increase in biological activities or alternatively trigger new action pathways, making metallodrugs even more effective (Erkkila et al., 1999). The drug named *Doxovir*, a cobalt (III) complex with nitrogen-containing ligand [Co(acacen)(2-methylimidazole)₂]⁺Br⁻ where acacen is bis(acetylaceton)ethylenediamine, was found effective against drug-resistant herpes simplex virus type I during the second phase of clinical trials. *Doxovir*, a Schiff base complex, inhibits the membrane fusion events to prevent viral entry (Schwartz et al., 2001). Cobalt (III)-Schiff-base complexes with acacen ligand was reported to selectively disrupt the structure and function of zinc fingers, structures that mediate sequence recognition for a large number of DNA-binding proteins (Louie & Meade, 1998). Previously described cobalt (III) complex, which exhibited antimicrobial and photocatalytic activities, also showed efficient anticancer activity against HeLa (human cervical cancer cell line) and A549 cell cultures (lung cancer cell line), and was found to be more efficient in its anticancer activity compared to ligand alone and similar complex with nickel (II) (Saha et al., 2024). Therefore, cobalt containing complexes with organic nitrogen-containing ligands which are based on heterocycles like pyrazole have a potential to target pathways related to cancer as they can aim precisely for several transcription factors involved in progression of cancer and metastasis.

5. Conclusions

In summary, cobalt complexes have been shown to have a variety of applications including but not limited to catalysis, magnetism, optoelectrical and anti-microbial utilities, and anti-cancer therapeutics over the past three decades. Recently reported applications of cobalt complexes with nitrogen-containing organic ligands are keeping us motivated to explore additional derivatives of the ligand based on pyrazole and their complexes with transition metals such as cobalt. We are planning to use our synthetic methodologies to produce similar complexes by introducing new transition metals and changing functional groups of the ligand and generating a library of compounds for potential application studies.

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Authors contributions

Both authors contributed to the present work.

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Competing interests

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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Obtained.

Ethics approval

The Publication Ethics Committee of the Canadian Center of Science and Education.

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Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Data sharing statement

No additional data are available.

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