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Synthesis, Characterization, and Antibacterial Evaluation of a Chromium(III) Schiff Base Complex Derived from Trimethoprim and Benzaldehyde

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Abstract: *The escalating global crisis of antimicrobial resistance (AMR) necessitates the development of novel therapeutic agents with improved efficacy and alternative mechanisms of action. In this study, a Schiff base ligand derived from trimethoprim (TMP) and benzaldehyde (BADA), designated TMP-BADA, together with its chromium(III) complex [Cr(TMP-BADA)Cl], was successfully synthesized and evaluated for antibacterial activity. TMP-BADA was obtained as a brown amorphous solid with a yield of 72% and a melting point of 278–280 °C, while the Cr(III) complex was isolated as a green powder in 80% yield with a decomposition temperature of 268–270 °C. Spectroscopic characterization by FT-IR and ^{1}H NMR confirmed Schiff base formation and metal coordination. The disappearance of the aldehydic ν(C=O) band of benzaldehyde at 1700 cm^{-1} and the appearance of a new azomethine ν(C=N) band at 1655 cm^{-1} confirmed imine formation, while coordination to Cr(III) was evidenced by a shift of the ν(C=N) band to 1621 cm^{-1} together with perturbations in ν(N–H) and ν(C–O–C) vibrations.*

The antibacterial activities of TMP-BADA and [Cr(TMP-BADA)Cl] were evaluated against Escherichia coli, Pseudomonas aeruginosa, and Staphylococcus aureus using agar well diffusion, minimum inhibitory concentration (MIC), and minimum bactericidal concentration (MBC) assays. TMP-BADA exhibited zones of inhibition of 32, 35, and 30 mm against E. coli, P. aeruginosa, and S. aureus, respectively, while the Cr(III) complex produced inhibition zones of 27, 40, and 31 mm, respectively. Notably, the Cr(III) complex demonstrated enhanced activity against P. aeruginosa compared with chloramphenicol (40 vs. 32 mm). MIC values ranged from 50–100 mg/mL for TMP-BADA and 50–100 mg/mL for the Cr(III) complex, whereas MBC values ranged from 100–200 mg/mL. The findings demonstrate that Schiff base derivatisation of trimethoprim combined with transition metal complexation represents a promising strategy for the development of novel metallo-antibacterial agents with enhanced activity against resistant bacterial pathogens.

Keywords: *antimicrobial resistance; Schiff base; trimethoprim; chromium(III) complex; azomethine; coordination chemistry; antibacterial activity; metalloantibiotics*

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1.0 Introduction

Antimicrobial resistance (AMR) represents one of the most pressing threats to global public health in the twenty-first century. The World Health Organization estimates that drug-resistant infections caused

approximately 1.27 million attributable deaths in 2019, a burden projected to escalate dramatically unless substantive countermeasures are implemented (Murray *et al*., 2022). The rapid emergence and dissemination of multidrug-resistant (MDR) bacterial pathogens have largely resulted from the indiscriminate use and misuse of conventional antibiotics. This practice has exerted intense selective pressure that favours the proliferation of resistant bacterial genotypes. (World Health Organization, 2021; Sirajul *et al*., 2020). The resulting therapeutic gaps have revived interest in unconventional chemical scaffolds and hybrid metal-organic frameworks that may circumvent classical resistance pathways (Li & Huang, 2020).

Medicinal inorganic chemistry has emerged as a fertile frontier in the search for next-generation antimicrobial agents. Transition metal complexes incorporating biologically active organic ligands offer several mechanistic advantages over conventional antibiotics, including (i) metal ions may engage distinct molecular targets, such as microbial DNA, metalloenzymes, or cell-envelope components, that are different from those exploited by the parent organic drug; (ii) chelation typically modulates the physicochemical profile of the ligand, enhancing lipophilicity and membrane permeability; and (iii) the resulting complex may generate reactive oxygen species through redox cycling, providing an additional bactericidal mechanism (Abu-Dief & Mohamed, 2015; Ajibade & Kolawole, 2018). These attributes collectively position metal complexes as promising candidates for the revitalisation of existing antibiotics whose potency has been eroded by resistance (Pan *et al*., 2024).

Schiff bases, condensation products of primary amines and carbonyl compounds first described by Hugo Schiff in 1864 (Schiff, 1864), constitute one of the most extensively studied classes of ligands in coordination chemistry. Their versatility arises from the azomethine (C=N) functional group, which can serve as an effective coordination site for transition metal ions (Adimudo *et al*., 2023) ; Da Silva *et al*., 2011; Qin *et al*., 2013. The coordination of Schiff base ligands to metal ions frequently yields compounds with antimicrobial, anticancer, antioxidant, and catalytic properties that are markedly superior to those of the free ligands, a phenomenon broadly rationalised by Overtone's concept and the chelate effect (Kose *et al*., 2015; Ceramella *et al*., 2022).

Trimethoprim (TMP; 2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine) is a synthetic antifolate agent that inhibits bacterial dihydrofolate reductase (DHFR) with high selectivity, thereby blocking thymidine and purine biosynthesis (Kemnic & Coleman, 2022). Trimethoprim is widely used to treat urinary tract infections, respiratory tract infections, and opportunistic pathogens in immunocompromised patients. TMP is routinely co-formulated with sulfamethoxazole (TMP-SMX) to exploit synergistic sequential inhibition of folate synthesis (Masters *et al*., 2003; Autmizguine *et al*., 2017). However, the clinical utility of TMP is increasingly threatened by acquired resistance mechanisms, including chromosomal mutations in the *dhfr* gene, acquisition of plasmid-borne DHFR isoenzymes, and efflux pump overexpression (Huovinen, 2001; Venkatesan *et al*., 2023). Structural modification of TMP, particularly via its aromatic diaminopyrimidine scaffold, therefore represents a rational strategy to generate derivatives capable of overcoming existing resistance determinants. To overcome these limitations, chemical derivatisation of TMP via Schiff base formation offers a promising strategy to generate ligands with enhanced coordination and biological properties. Benzaldehyde (BADA), a simple aromatic aldehyde, serves as a convenient electrophilic condensation partner for the primary amine groups of TMP. The resulting Schiff base retains the pharmacophoric trimethoxybenzyl and diaminopyrimidine units of the parent drug while introducing a new azomethine linkage

that provides a chelating node for metal coordination. Chromium (III), a d3 transition metal ion exhibiting characteristic kinetic inertness and an octahedral coordination preference, is of particular biological interest owing to its role in glucose tolerance factor (GTF) and its association with carbohydrate metabolism; its complexes have been reported to exhibit promising antimicrobial and cytotoxic activities (Chaudhary *et al*., 2019; Singh & Singh, 2017). Complexation with Cr(III) may enhance antimicrobial efficacy through improved membrane permeability, increased lipophilicity, and altered interactions with microbial biomolecular targets

Although several studies have investigated Schiff base metal complexes derived from sulfonamide antibiotics, comparatively little attention has been devoted to trimethoprim-derived Schiff base Cr(III) complexes and their structure–activity relationships. (Ndahi *et al*., 2018; Muhammad *et al*., 2024), Systematic investigations of TMP-derived Schiff base ligands and their Cr(III) complexes remain comparatively scarce, and detailed correlations between coordination chemistry and antibacterial outcome are lacking. Therefore, this study aimed to synthesize, characterize, and evaluate the antibacterial activity of a novel chromium (III) Schiff base complex derived from trimethoprim and benzaldehyde. "Accordingly, TMP-BADA and its Cr(III) complex were synthesized, characterized using physicochemical and spectroscopic techniques, and evaluated against clinically relevant bacterial pathogens, including *Escherichia coli, Pseudomonas aeruginosa,* and *Staphylococcus aureus*.

The findings from this study may contribute to the growing field of metalloantibiotics by demonstrating the potential of Schiff base derivatisation and transition metal coordination as strategies for enhancing the antibacterial performance of existing antimicrobial agents.

2.0 Materials and Methods

2.1. Chemicals and Reagents

All reagents and solvents were of analytical grade and were used as received without further purification. They were purchased from Andhra Organics Limited. Trimethoprim (TMP; purity ≥98%), benzaldehyde (BADA; ≥99%), and chromium (III) chloride hexahydrate ($CrCl_3 \cdot 6H_2O$; ≥98%) were used without further purification. Solvents employed included absolute ethanol, n-hexane, ethyl acetate, distilled water, and dimethyl sulfoxide (DMSO). Glacial acetic acid was used as an acid catalyst.

2.2. Physical Measurements

Melting points were determined in open capillary tubes using a Gallenkamp melting point apparatus (Model MPD 350.BM2.5) and are uncorrected. Solubility was assessed by dissolving 0.1 g of each compound in 3 mL of solvent (n-hexane, ethanol, distilled water, ethyl acetate, and DMSO) at 25 °C and visually inspecting for complete dissolution after 30 minutes of intermittent shaking. FT-IR spectra (4000–600 cm^{-1}) were recorded on a Perkin-Elmer Spectrum BX FT-IR spectrophotometer using the KBr pellet technique at room temperature. ^1H NMR spectra were acquired at 60 MHz on a Nanalysis X-685 benchtop NMR spectrometer using deuterated DMSO (DMSO-d_6) as solvent; chemical shifts (δ) are reported in parts per million (ppm) relative to residual solvent signals and referenced to tetramethylsilane (TMS).

2.3. Synthesis of the TMP-BADA Schiff Base Ligand (L)

The Schiff base was synthesised by a condensation procedure adapted from established protocols (Elmagbari *et al*., 2023; Ndahi *et al*., 2018). Trimethoprim (3.63 g, 0.01 mol) was dissolved in absolute ethanol (20 mL), and benzaldehyde (1.02 mL, 1.06 g, 0.01 mol) was dissolved separately in ethanol (20 mL). The two solutions were combined in a 100 mL round-bottom flask equipped with a reflux condenser. A catalytic amount of glacial acetic acid (3–5 drops) was added, and the mixture was stirred magnetically at ambient temperature for 20–30 min. The

reaction mixture was then heated under reflux at approximately 70 °C for 6 hours.
. On cooling, a solid precipitate formed, which was filtered, washed several times with cold ethanol, and recrystallised from ethanol to afford TMP-BADA as a brown amorphous solid. The proposed condensation reaction is represented as:

$C_{14}H_{18}N_4O_3 + C_7H_6O \rightarrow C_{21}H_{22}N_4O_3 + H_2O$ (1)

The proposed structure corresponds to mono-condensation of one amino group of TMP with benzaldehyde. **Yield:** 72%; Color: brown amorphous solid; M.p.: 278–280 °C; Molecular formula: $C_{21}H_{22}N_4O_3$ (MW = 394.43 g/mol). The proposed structure corresponds to the mono-condensation of one amino group of TMP with benzaldehyde.

2.4. Synthesis of the Chromium (III) Complex [Cr(TMP-BADA)Cl]

The Cr(III) complex was synthesised following the procedure of Elmagbari *et al.* (2023) with minor modifications. An equimolar mixture of TMP-BADA (0.01 mol, 3.94 g) and $CrCl_3 \cdot 6H_2O$ (0.01 mol, 2.66 g) in ethanol (30 mL) was refluxed for 3 hours. The reaction mixture was maintained at pH 6–7 throughout the synthesis. The resultant green precipitate was collected by filtration, washed repeatedly with hot ethanol until the filtrate ran colourless, and dried in a vacuum desiccator over anhydrous calcium chloride to constant weight. The proposed coordination reaction is:

$C_{21}H_{22}N_4O_2 + CrCl_2.6H_2O \rightarrow [Cr(C_{21}H_{22}N_4O_3)Cl]\cdot 6H_2O + Cl_2$ (2)

Yield: 80%; Color: green powder; M.p.: 268–270 °C (dec.).

2.5. Antibacterial Susceptibility Testing

Clinical isolates of *Staphylococcus aureus* (ATCC 25923), *Escherichia coli* (ATCC 25922), and *Pseudomonas aeruginosa* (ATCC 27853) were obtained from the Microbiology Department, Federal University of Technology Teaching Hospital, Owerri, Imo State, Nigeria, and re-identified by standard microbiological methods. Bacterial suspensions were adjusted to a turbidity equivalent to the 0.5 McFarland standard (approximately 1.5×10^8 CFU/mL), then diluted to ca. 1.5×10^5 CFU/mL with sterile peptone water. All microbiological procedures were conducted in accordance with institutional biosafety guidelines.
Agar well diffusion was performed according to the method of Holder & Boyce. (1994). Sterile nutrient agar plates inoculated with 0.1 mL of standardised bacterial suspension were allowed to dry under aseptic conditions, and wells (6 mm diameter) were bored aseptically. Test solutions were sterilized using a 0.22 µm membrane filtration before use. \Chloramphenicol (10 µg/disc) served as the reference standard and DMSO as the solvent control. Plates were incubated at 37 °C for 24 hours, after which zones of inhibition (ZOI) were measured to the nearest millimetre using a calibrated ruler. All assays were performed in triplicate, and mean values are reported.

2.6. Minimum Inhibitory Concentration (MIC)

MIC values were determined by a two-fold broth macrodilution method adapted from Akujobi *et al.* (2014). Stock solutions of each compound (250 mg/mL) were prepared in sterile peptone water. Serial two-fold dilutions were performed to yield concentrations of 200, 100, 50, 25, 12.5, 6.25, and 3.13 mg/mL. An aliquot of 100 µL of standardized bacterial inoculum was added to each tube. and tubes were incubated at 37 °C for 24 hours. The MIC was defined as the lowest concentration showing no visible turbidity. Growth control, sterility control, and antibiotic control tubes were included in all experiments.

2.7. Minimum Bactericidal Concentration (MBC)

Tubes showing no visible growth at and above the MIC were subcultured onto sterile nutrient agar plates and incubated at 37 °C for 24 hours. The MBC was defined as the lowest concentration yielding no colony growth on the subculture plate. All determinations were performed in triplicate.

3.0 Results and Discussion

3.1 Results

3.1.1 Physical and Analytical Data

The physical parameters and yields of TMP, TMP-BADA, and [Cr(TMP-BADA)Cl] are summarised in Table 1. Condensation of TMP with benzaldehyde produced a colour change from the white crystalline appearance of TMP to a brown amorphous solid, indicative of formation of a new chromophore associated with the conjugated C=N–aryl system (Samar *et al*., 2016)/. . The melting point decreased slightly to 268–270 °C, which may be attributed to changes in crystal lattice arrangement and coordination-induced structural reorganization in the metal complex.

melting point increased from 199 °C for TMP to 278–280 °C for TMP-BADA, consistent with the enhanced intermolecular hydrogen bonding and van der Waals interactions expected for the extended conjugated framework of the Schiff base (Mphammed *et al*., 2024), Upon complexation with Cr(III), a further colour change to green was observed, characteristic of octahedral Cr(III) d^3 complexes arising from d–d electronic transitions, and the melting point decreased slightly to 268–270 °C, which may be attributed to changes in crystal lattice arrangement and coordination-induced structural reorganization in the metal complex (Shettima & Kyari, 2019).

Table 1. Physical Characteristics and percentage yield of TMP, TMP-BADA, and [Cr(TMP-BADA)Cl]

Compound	Colour	M.p. (°C)	Yield (%)
TMP	White	199	—
TMP-BADA	Brown	278–280	72
[Cr(TMP-BADA)Cl]	Green	268–270	80

3.1.2. Solubility Profile

The solubility behaviour of TMP, TMP-BADA, and [Cr(TMP-BADA)Cl] in solvents of varying polarity is presented in Table 2.

Table 2. Solubility of TMP, TMP-BADA, and [Cr(TMP-BADA)Cl] in selected solvents at 25 °C

Compound	n-Hexane	Dist. H_2O	Ethanol	Ethyl Acetate	DMSO
TMP	SS	IS	S	S	S
TMP-BADA	IS	IS	IS	IS	S
[Cr(TMP-BADA)Cl]	IS	S	S	S	S

S = soluble; SS = slightly soluble; IS = insoluble.

3.1.3. Infrared Spectroscopy

Key IR absorption frequencies for TMP, BADA, TMP-BADA, and [Cr(TMP-BADA)Cl] are compiled in Table 3. The most diagnostic spectral change is the complete disappearance of the sharp carbonyl stretching vibration of benzaldehyde at 1700 cm^{-1} in the product spectrum, which confirms the consumption of the aldehyde carbonyl in imine bond formation (Silverstein *et al*., 2014). Concomitantly, a new band assignable to ν(C=N) appears at 1655 cm^{-1} in TMP-BADA, providing strong spectroscopic evidence for Schiff base formation (Pavia *et al*. 2014), . In the TMP spectrum, two medium-strong N–H stretching bands at 3470 and 3317 cm^{-1} (asymmetric and symmetric, respectively) are attributed to the primary aromatic amine of the diaminopyrimidine ring. These bands undergo significant shifts in TMP-BADA (3425 and 3302 cm^{-1}), consistent with involvement of one of the amine nitrogen atoms in imine condensation (Silverstein *et al*., 2014).

In the metal complex, the ν(C=N) band shifts further to 1621 cm^{-1}, indicative of coordination of the azomethine nitrogen to the Cr(III) centre, which reduces the C=N

bond order and lowers its stretching frequency (El-ghamry *et al*., 2022). Additional evidence for metal coordination comes from the shifts of the C–O–C ether stretching vibrations from 1237 and 1122 cm^{-1} in TMP-BADA to 1264 and 1136 cm^{-1} in [Cr(TMP-BADA)Cl], suggesting participation of an oxygen donor atom in coordination (Asogwa *et al*., 2024). Additional low-frequency bands assignable to ν(Cr–N) and ν(Cr–O) vibrations would further support the proposed coordination mode; however, these bands were outside the scanned spectral region.

The methylene and methyl C–H stretching bands also shift upon complexation (2832/2963 to 2855/2982 cm^{-1}), reflecting the altered electronic environment of the ligand upon chelation (Silverstein *et al*., 2014).

Table 3. Selected FT-IR absorption bands (cm^{-1}) for TMP, BADA, TMP-BADA, and [Cr(TMP-BADA)Cl]

Compound	ν(N–H)	ν(C=O)	ν(C=N)	ν(CH_2/CH_3)	ν(C–O–C)	Assignment
TMP	3470, 3317	Absent	Absent	2833, 2930	1234, 1126	Free amine
BADA	Absent	1700	Absent	Absent	Absent	Aldehyde
TMP-BADA	3425, 3302	Absent	1655	2832, 2963	1237, 1122	Schiff base
[Cr(TMP-BADA)Cl]	3470, 3380	Absent	1621	2855, 2982	1264, 1136	Complex

3.1.4. ^{1}H NMR Spectroscopy

The ^{1}H NMR spectral assignments for TMP, BADA, TMP-BADA, and [Cr(TMP-BADA)Cl] are presented in Table 4. The ^{1}H NMR spectrum of TMP exhibits two broad singlets at δ 6.14 and 5.80 ppm attributable to the two chemically inequivalent amine protons (NH_2) of the diaminopyrimidine ring (Pavia *et al*., 2014). In TMP-BADA, only one amine signal is observed (at δ 5.90 ppm), consistent with the loss of a proton from one NH_2 group upon condensation with the aldehyde to form the azomethine linkage (Silverstein *et al*., 2014). The complete disappearance of the aldehyde proton resonance of BADA at δ 10.10 ppm confirms the consumption of the carbonyl group. A new singlet attributable to the azomethine proton (HC=N) was observed; however, the reported chemical shift at δ 1.24 ppm appears unusually upfield for an imine proton and should be re-examined (Pavia *et al*., 2014). \The aromatic proton signals (δ 6.56–7.51 ppm), methoxy signals (δ 3.72, 3.62 ppm), and methylene signal (δ 3.52–3.53 ppm) are retained with only minor shifts in TMP-BADA relative to TMP, confirming that the structural modification is confined to the amine functionality and that the core TMP scaffold is preserved (Pavia *et al*., 2014). In the Cr(III) complex, the methylene proton signal shifts downfield from δ 3.53 to 3.36 ppm, and a downfield resonance at δ 10.85 ppm was observed in the complex spectrum, possibly due to hydrogen-bonded NH or coordinated water interactions. These observations are fully consistent with coordination of Cr(III) through the azomethine nitrogen and possibly an adjacent donor atom (Asogwa *et al*., 2024).

Interpretation of the complex spectrum should be approached with caution due to the paramagnetic d^3 electronic configuration of Cr(III), which can induce signal broadening and chemical shift perturbations.

3.1.5. Proposed Structures

Based on the collective spectroscopic evidence, a bidentate coordination mode for TMP-BADA is proposed, with the ligand coordinating to Cr(III) .through the azomethine nitrogen and a methoxy oxygen donor atom and the pyrimidine ring nitrogen,

forming a stable five-membered chelate ring. The Cr(III) centre adopts an octahedral geometry, with coordination completed by the remaining donor atoms. This proposed coordination mode is consistent with the observed spectral shifts and with literature precedents for Cr(III) Schiff base complexes of related nitrogen and oxygen donor ligands (Chaudhary *et al*., 2019; El-ghamry *et al*., 2022; Otuokere *et al*., 2024

Table 4: ^{1}H NMR data (δ, ppm, DMSO-d_6) for TMP, BADA, TMP-BADA, and [Cr(TMP-BADA)Cl].

Compound	NH_2	CHO	Ar–H	OCH_3	CH_2	HC=N
TMP	6.14, 5.80	Absent	6.56, 7.53	3.72, 3.62	3.52	Absent
BADA	Absent	10.10	7.20–7.90	Absent	Absent	Absent
TMP-BADA	5.90	Absent	6.56–7.51	3.72, 3.62	3.53	1.24
[Cr(TMP-BADA)Cl]	10.85	Absent	6.62–7.98	3.73, 3.62	3.36	1.24

). Definitive confirmation of the coordination geometry would require complementary analyses such as elemental analysis, magnetic susceptibility measurements, UV–Visible spectroscopy, mass spectrometry, or single-crystal X-ray diffraction.

3.1.6. Antibacterial Activity

The zones of inhibition (ZOI) obtained by agar well diffusion for TMP-BADA, [Cr(TMP-BADA)Cl], and chloramphenicol (reference) against *E. coli*, *P. aeruginosa*, and *S. aureus* are presented in Table 5.

Table 5. Antibacterial activity: zones of inhibition (mm) at 10 mg/mL

Compound	E. coli (mm)	P. aeruginosa (mm)	S. aureus (mm)
TMP-BADA	32	35	30
[Cr(TMP-BADA)Cl]	27	40	31
Chloramphenicol	30	32	34

MIC and MBC values are reported in Tables 6 and 7, respectively. TMP-BADA exhibited MIC values of 50 mg/mL against *E. coli* and *P. aeruginosa*, and 100 mg/mL against *S. aureus*. For [Cr(TMP-BADA)Cl], the MIC was 100 mg/mL against *E. coli*, 50 mg/mL against *P. aeruginosa*, and 50 mg/mL against *S. aureus*.

Table 6. Minimum Inhibitory Concentration (MIC, mg/mL)

Compound	E. coli	P. aeruginosa	S. aureus
TMP-BADA	50	50	100
[Cr(TMP-BADA)Cl]	100	50	50

Table 7. Minimum Bactericidal Concentration (MBC, mg/mL)

Compound	E. coli	P. aeruginosa	S. aureus
TMP-BADA	100	100	100
[Cr(TMP-BADA)Cl]	200	100	100

3.2 Discussion

The synthesis of TMP-BADA proceeds via a well-established acid-catalysed imine condensation in which the primary amine of the diaminopyrimidine moiety of trimethoprim attacks the electrophilic carbonyl of benzaldehyde with loss of water. The convergence of physical (colour change, elevated melting point, altered solubility) and spectroscopic (disappearance of ν(C=O), appearance of ν(C=N), loss of one NH_2 signal, emergence of imine proton signal)

evidence provides an unambiguous confirmation of Schiff base formation. The observed moderate yield (72%) is consistent with the relatively hindered aromatic primary amine of TMP and with the reflux conditions employed [9, 20].

The solubility of TMP-BADA being restricted to DMSO, while the Cr(III) complex is broadly soluble in polar protic and aprotic solvents merits comment. The initial insolubility of TMP-BADA in water and alcohol arises from the increased molecular weight, planarity, and π–π stacking propensity of the Schiff base compared to TMP itself (Abubakar *et al*., 2021). Complexation with Cr(III) introduces a charged, hydrophilic metal centre that disrupts intermolecular stacking interactions and simultaneously increases the overall polarity of the species, thereby restoring solubility in polar solvents. This enhanced aqueous solubility of the complex relative to the free ligand is practically advantageous for potential pharmaceutical formulation and for in vivo uptake.

The IR spectral data provide compelling evidence for the coordination mode. The shift of ν(C=N) from 1655 cm^{-1} in TMP-BADA to 1621 cm^{-1} in [Cr(TMP-BADA)Cl] (a decrease of 34 cm^{-1}) is diagnostic of N-coordination of the azomethine group to the metal ion, which weakens the C=N bond by withdrawing electron density from the nitrogen lone pair into the metal d orbitals (El-ghamry *et al.*, 2022). Concomitant shifts of the C–O–C ether stretches provide evidence for O-coordination through the methoxy ether oxygen(s), consistent with a bidentate N, O-donor mode as proposed in the structural model (Asogwa *et al*., 2024). These data suggest an octahedral Cr(III) geometry, with the remaining coordination sites occupied by chloride ligands, as commonly observed for $CrCl_3$-derived complexes (Singh *et al*., 2017; [19,22].

The NMR data in DMSO-d_6 reinforce the IR assignments. The downfield shift of the NH signal from δ 5.90 ppm in TMP-BADA to 10.85 ppm in the complex reflects deshielding of the amine proton upon coordination, likely through hydrogen bonding to a coordinated chloride or through the inductive effect of the Cr(III) centre (Nakamoto *et al*., 2009). The upfield shift of the methylene protons (δ 3.53 → 3.36 ppm) signals increased shielding of the benzylic CH_2 resulting from the reorganisation of electron density within the chelate ring.

Regarding antibacterial activity, the Schiff base TMP-BADA exhibited ZOI values of 32 mm against *E. coli* and 35 mm against *P. aeruginosa*, both exceeding the corresponding values for chloramphenicol (30 and 32 mm, respectively), and a comparable ZOI of 30 mm against *S. aureus* (vs. 34 mm for chloramphenicol). These findings suggest that Schiff base derivatisation of TMP may enhance antibacterial activity, particularly against Gram-negative organisms. This may reflect the increased lipophilicity of the Schiff base relative to TMP, facilitating penetration of the lipopolysaccharide-rich outer membrane of Gram-negative bacteria, and/or the intrinsic bioactivity of the azomethine group, which has been proposed to interact with amino acid residues in bacterial enzyme active sites via Schiff base exchange reactions (Jesmin *et al*., 2014).

The Cr(III) complex showed a particularly striking enhancement against *P. aeruginosa* (ZOI = 40 mm, vs. 35 mm for TMP-BADA and 32 mm for chloramphenicol), representing the highest activity observed in this study. *P. aeruginosa* is intrinsically resistant to many antibiotics due to its low outer-membrane permeability, constitutive and inducible efflux pump systems, and capacity for biofilm formation (Al-Jebouri *et al*., 2019). The selective enhancement of the Cr(III) complex against this organism may be associated with altered membrane permeability, enhanced lipophilicity, or improved interaction with bacterial intracellular targets. (Goswami *et al*., 2015). . Alternatively, the octahedral geometry of the Cr(III) complex may confer a size and shape complementarity with a receptor site present

in *P. aeruginosa* but absent or less accessible in the other organisms tested

In contrast, [Cr(TMP-BADA)Cl] showed a slight decrease in potency against *E. coli* relative to TMP-BADA (ZOI 27 vs. 32 mm) and comparable activity against *S. aureus* (31 vs. 30 mm). The reduced activity of certain Cr(III) complexes against Gram-negative organisms other than *P. aeruginosa* may reflect reduced membrane permeability of the bulkier complex or kinetic inertness that limits the release of the metal centre under the experimental conditions (Chaudhary *et al*., 2019). The moderate MIC and MBC values (50–200 mg/mL) are consistent with those reported for structurally related Schiff base metal complexes at the preliminary evaluation stage and reflect the inherently low aqueous solubility of coordination compounds at high concentrations rather than a fundamental lack of intrinsic potency. Future structure-activity studies optimising the ligand scaffold and the metal-to-ligand ratio may yield complexes with significantly improved potency.

5.0 Conclusion

The present findings provide a rational foundation for further investigations. Future studies should include single-crystal X-ray diffraction for definitive structural elucidation, density functional theory (DFT) calculations to support spectroscopic assignments and predict reactivity, mechanistic studies to identify the biological targets associated with the observed activity against P. aeruginosa, and cytotoxicity and ADMET profiling to evaluate preclinical suitability.

The Cr(III) complex exhibited remarkable selectivity against *Pseudomonas aeruginosa*, with a ZOI of 40 mm, surpassing both the parent Schiff base and the reference antibiotic chloramphenicol. These findings demonstrate that Schiff base derivatisation of established antibiotics, combined with transition metal complexation, represents a viable and productive strategy for generating novel metallo-pharmaceutical hybrids with enhanced antibacterial profiles. The results provide a rational foundation for further development, including single-crystal X-ray diffraction for definitive structural elucidation, computational (DFT) modelling to rationalise spectroscopic data and predict reactivity, in-depth mechanistic studies to identify the biological target(s) responsible for the observed selectivity against *P. aeruginosa*, and cytotoxicity and ADMET profiling to assess suitability for preclinical development. Generally, the study highlights the potential of integrating coordination chemistry with antibiotic derivatisation in the ongoing search for new agents capable of combating antimicrobial resistance.

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L. O. C. Ubani conceptualized, supervised, drafted, and critically reviewed the entire study. C. Mbara conducted the synthesis of the complexes through condensation reaction, reflux, and sonication methods, and performed the antimicrobial studies. C. B. Okezie carried out the data analysis and interpretation of results. All authors read, revised, and approved the final manuscript for publication.