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BENZOPHENONE SCHIFF BASE METAL COMPLEXES: A REVIEW OF SYNTHESIS, CHARACTERISATION, AND BIOLOGICAL ACTIVITY

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ABSTRACT

Benzophenone-derived Schiff bases and their metal complexes have emerged as versatile pharmacophores with a wide range of biological activities, including antibacterial, antifungal, cytotoxic, and antioxidant effects that are frequently superior to those of the corresponding free ligands. Chelation with transition metals, such as Cu, Ni, Zn, and Mn, improves activity by enhancing lipophilicity, modifying charge distribution, and allowing for more effective interactions with microbial membranes and biomolecular targets. Antibacterial potency often outweighs antifungal effects, and some complexes exhibit significant cytotoxicity against cancer cell types as well as increased radical scavenging capacity. Lipophilicity, overall charge, coordination geometry, metal oxidation state/redox potential, and co-ligand planarity (phen > bipy > en) all play crucial roles in bioactivity. These patterns highlight the necessity for additional systematic, chemistry-driven research that includes complete spectroscopic and crystallographic characterisation in order to improve benzophenone Schiff base metal complexes as promising therapeutic candidates.

Keywords—Bidentate ligand; azomethine; BPSB; 1,10-phenanthroline; co-ligand; antimicrobial; antiproliferative; transition metals;

1.0 INTRODUCTION

The Schiff bases, which are distinguished by an azomethine (-C=N-) unit, are one of the most important families of ligands utilised in the study of coordination chemistry. As the name implies, Schiff bases are a class of chemicals named after Hugo Schiff, a German chemist who discovered them as byproducts of the reaction of a primary amine with an aldehyde/ketone (Raczuk et al.,2022). However, coordination chemistry using Schiff bases has evolved, from relatively simple organic imine molecules to extremely efficient chelators capable of generating strong and stable coordination complexes with a wide range of metal ions (Soroceanu et al.,2022;Aytac et al 2023). Because of their di-aryl ketone group, benzophenone Schiff bases (BPSBs) stand out among the several types of Schiff bases known today. The aromatic rings in BPSBs give longer π-conjugation, resonance stability of the imine linkage, and increased lipophilicity compared to simple Schiff bases produced from aldehydes (Surana et al.,2018). Furthermore, benzophenone derivatives belong to a class of clinically proven pharmacophores that are commonly represented by medications like ketoprofen. Thus, owing to their medicinal potential, BPSB-type ligands have become of great interest for further development in coordination chemistry (Kotnik et al.,2016)].

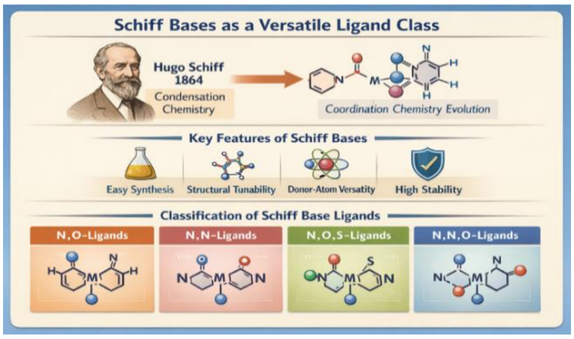

Figure 1: : History and Classifications of Schiff base ligands

1.2 Existing Strategies and Paper Purpose

In the last ten years, there has been an increase in publications about BPSB ligands and their coordination complexes. The current review aims to examine the literature on their synthesis, characterisation, and

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biological activity, identifying important trends, valid structure-activity relationship (SAR), and lingering challenges in BPSB-based coordination chemistry.

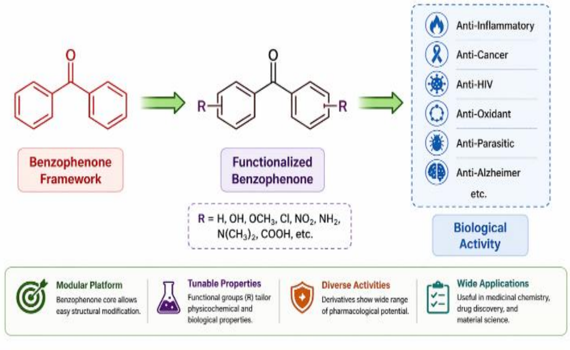

Figure 2: Benzophenone Functionalized Derivatives

2.0 SYNTHESIS OF BPSB LIGANDS

2.1 Condensation Chemistry of the Schiff Base

BPSB ligands are prepared via the well-known condensation process between ketone groups generated from benzophenone and primary amines. Because the ketone's carbonyl group is less electrophilic than that of aldehydes, an acid catalyst is required to speed up the reaction. Specifically, BPSB, a useful synthetic intermediate, is effectively produced under mild acid-catalyzed conditions, most typically using acetic acid. One-pot methods allow for the direct condensation of benzene and aromatic amines with high yields (Akhrem et al., 2020). Alternatively, a two-step technique of converting benzyl phenyl ketone into a hydrazone using hydrazine hydrate and acetic acid, followed by reflux with different aromatic aldehydes in methanol with catalytic acetic acid, gives high yields (≈79-87%) (Ahmad et al., 2023). Acid-promoted condensations provide BPSB glycine derivatives (]. Several recent investigations report novel BPSB produced primarily by conventional ketone-amine condensations, generally under simple conditions with high yields, as listed in Table 1. Each synthetic approach is consistent with the overall procedure, which involves the condensation of the ketone (benzophenone moiety) with amines or diamines under specific conditions.

Table 1: Recently Reported BPSB and Syntheses

BPSB	Preparation method	Citations
BPN photoinitiator (4-aminobenzophenone–4-(dimethylamino)-2-hydroxybenzaldehyde)	One-step "one-spot" Schiff base condensation of 4-aminobenzophenone with 4-(dimethylamino)-2-hydroxybenzaldehyde to give BPN, characterized spectroscopically	(Xue et al.,2021)
Tetradentate benzophenone Schiff base (ONNO)	Condensation of (3,4-diaminophenyl)(phenyl)methanone (a benzophenone diamine) with 4-(diethylamino)-2-hydroxybenzaldehyde in methanol, reflux 48 h, then solvent removal and drying	(Bal et al.,2023)
Symmetric benzophenone Schiff base in lyotropic media	Condensation of a diamine with a benzophenone-type ketone in THF; both amine termini converted to imines, giving a symmetric ONNO Schiff base in high yield	(Suhta et al.,2024)
Tetradentate benzophenone derivative Schiff base (octyloxy phenol arms)	New tetradentate benzophenone-based ligand 6,6′-(1Z,1′Z)-(butane-1,4-diylbis(azanylyidene))bis(phenylmethanylylidene))bis(3-octyloxy)phenol synthesized and fully characterized; abstract notes standard Schiff condensation but no detailed conditions	(Suhta et al.,2024)
N1-(diphenylmethylene) naphthalene-1,8-diamine	Condensation of benzophenone with 1,8-naphthylenediamine (1:1) in hot EtOH/DMF, reflux 3 h, workup and recrystallization to give 82% of the benzophenone–diamine Schiff base	(Khalil et al.,2023)
Bidentate NO benzophenone Schiff base (HL)	Condensation of 2-hydroxy-4-methoxyphenyl)phenylmethanone (a hydroxybenzophenone) with aniline to form an NO-type Schiff base ligand, then complexation with Mn(II), Co(II), Ni(II), Cu(II), Zn(II)	(Subbaraj et al.,2014)
Azo–benzophenone Schiff base	Multicomponent condensation of 3,4-diamino benzophenone, 2-aminoacetophenone, and 3,5-dihydroxy toluene to form an extended Azo–Schiff base ligand used for Co(II), Ni(II), Cu(II), Zn(II), Cd(II), Pt(II), Au(III) complexes	(Hadi et al.,2020)
Thiocarbohydrazone benzophenone Schiff bases (L1–L5)	Condensation of substituted 2-hydroxybenzophenones with thiocarbohydrazide to yield ONS donor Schiff bases L1–L5, then complexation with MoO_2^{2+} to give [$MoO_2L(ROH)$]	(Kaya et al.,2018)
BPB chiral benzophenone Schiff base	$SOCl_2$-promoted condensation of (S)-N-benzylproline with 2-aminobenzophenone, giving (S)-2-[N-(N′-benzylprolyl)amino]benzophenone (BPB) in 82% yield	(Belokon et al.,1998)

2.2. Structural Variations and Reactions of BPSB Ligands

BPSB exhibits wide structural diversity depending on the position and type of substituents on the benzophenone analogue. Substituted benzophenone monodentate/bidentate ligands contain a simple NO bidentate motif derived from 2-hydroxy-4-methoxyphenyl phenylmethanone and aniline. The benzophenone carries a phenolic OH and methoxy group, and coordination occurs via deprotonated phenolate O and azomethine N to bind Mn(II), Co(II), Ni(II), Cu(II), and Zn(II) in tetrahedral or octahedral metal complexes. Condensation of benzophenone with 1,8-naphthylenediamine produces a NN bidentate ligand, N1-(diphenylmethylene) naphthalene-1,8-diamine, which coordinates with Mn (II), Ni (II), Zn (II), and lanthanides in octahedral metal complexes . When benzophenone condenses with 1,8-naphthylenediamine for mixed-ligand complexes with o-aminophenol, it forms a similar NN ligand that acts as a NN bidentate donor. (Khalil et al.,2023).

Using 3,4-diaminobenzophenone enables the formation of higher-dentate ligands. A tetradentate ONNO ligand is synthesised by condensing 3,4-diaminobenzophenone with 4-(diethylamino)-2-hydroxybenzaldehyde. The two imine nitrogens and two phenolic oxygens bind Co(II), Ni(II), and Cu(II) (Bal,2023). The Azo-Schiff base, composed of 3,4-diaminobenzophenone, 2,2-aminoacetophenone, and 3,5-dihydroxytoluene, coordinates with Co(II), Ni(II), Cu(II), Zn(II), Cd(II), Pt(II), and Au(III) to form octahedral complexes (square-planar for Pt(II) and Au(III)) . Another 3,4-diaminobenzophenone-pyridoxal system provides an ONN polyfunctional ligand (two azomethine Ns and a phenolic O) that forms octahedral complexes with Co(II), Ni(II), Cu(II), Zn(II), Cd(II), and square-planar Au(III) (Salih et al.,2022). Thiosemicarbazone-type benzophenone Schiff bases utilise sulphur donors. Crystal structures confirm tridentate or bidentate binding via azomethine N, hydrazinic N, and thione S to Co(II), Ni(II), Cu(II), and Zn(II). This variation uses benzophenone N(4), methyl N(4), and a related thiocarbonohydrazide derivative as NS, NNO, or SNO donors (Sangeetha et al.,2017). ONS tridentate ligands L1-L5 chelate cis-MoO_2^{2+} in [$MoO_2L(ROH)$] complexes where the ligand binds via phenolate O, azomethine N, and thioamide S, as supported by X-ray and spectroscopy (Kaya et al.,2018). One may compare the binding of bidentate (O,S) thiourea derivatives to the metal center in N-di(pyridin-2-yl) thiourea metal complexes (Fayomi et al.,2018). Bis-benzophenone frameworks and amino-acid derivatives offer additional versatility. The tetradentate benzophenone derivative, 6,6′-(butane-1,4-diylbis(azanylylidene))bis(phenylmethanylylidene)bis(3-octyloxy)phenol, has two salicylidene-type arms on a flexible spacer, giving a N_2O_2 pocket ideal for metal binding. It has been examined in lyotropic and DFT settings (Suhta et al.,2024). Benzophenone Schiff bases of glycine derivatives (classical O'Donnell "BP-glycine" imines) function as N, O, O tridentate chiral ligands upon metal binding. They are extensively used as masked glycine equivalents in phase-transfer-catalyzed alkylations and related reactions to build α-mono- and α-disubstituted amino acids (O’Donnell,2019). Crystallographic analysis of Ni(II) complexes of amino-acid benzophenone Schiff bases reveals that aromatic π-π interactions between the o-aminobenzophenone ring and N-benzylproline ring have a significant impact on stereochemistry and thermodynamic stability across various amino acids (Nian et al.,2017).

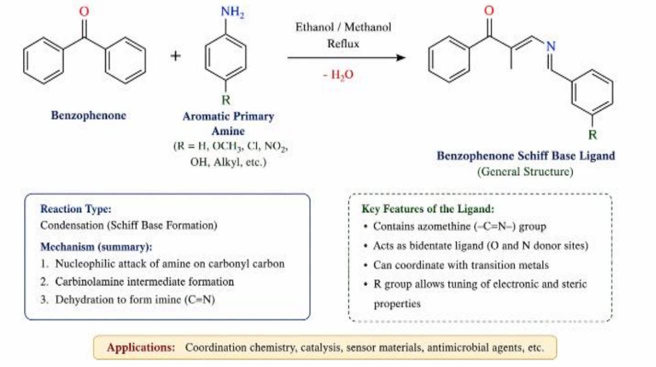

Figure 3: Synthesis of Benzophenone Schiff Bases

3.0 SYNTHESIS OF METAL COMPLEXES

3.1 General Synthetic Methods

Metal complexes of BPSB ligands are typically produced using two major synthetic methods. The metal ion is present in the template (in situ) technique while the carbonyl and amine components condense, allowing imine synthesis and metal coordination to occur in the same pot, often yielding metal complexes and ligand connectivities that are unreachable without the metal center (Mazzoni et al.,2021;Fabbrizzi,2020). BPSB ligands can be synthesised into metal complexes using a step-by-step reaction with metal salts, similar to the "preformed ligand" approach used in salicylaldehyde systems. To create complexes with Cu(II), Zn(II), and Cd(II) acetates in DMF under reflux, a Schiff base is formed by combining 5\chloro~2~hydroxybenzophenone and 4~chloro~3~(trifluoromethyl)aniline(Sahare,2024). Benzophenone-derived hydrazone/benzohydrazide ligands are preformed and then treated with Cu(II), La(III), and other metal salts such as Cu(II) and Fe(II) complexes of isoniazid to show how pre-formed metal-ligand drug complexes can be further developed (Gosu et al.,2025).

Benzophenone-based Schiff base ligands are typically well characterised using several spectroscopic approaches before complexing with metals. Azo-Schiff and tetradentate benzophenone ligands derived from 3,4-diaminobenzophenone are analysed using FT-IR, UV-Vis, 1H NMR, 13C NMR, and mass spectrometry before and after reaction with Co(II), Ni(II), and Cu(II) salts to ensure accurate structural assignment of the free ligand and subsequent complexes (Tella et al.,2024). Studies on benzophenone-derived NO-type and thiosemicarbazone ligands follow similar workflows: IR, UV-Vis, 1H NMR, and mass spectra are recorded for the ligand alone and then repeated for the complexes to detect shifts in diagnostic bands and signals indicating coordination(Hadi et al.,2020). High-resolution mass spectrometry and chromatographic methods, such as HPLC or LC-MS, are used in benzophenone chemistry and related ligand systems to separate, verify purity, and analyse benzophenone derivatives in complex matrices. This highlights the importance of chromatographic-mass spectrometric coupling as a complementary characterisation tool (Elaaraj et al.,2025;Xu et al.,2018;Yang et al.,2025).

3.2 Mixed-Ligand Metal Complexes of BPSB

Mixed-ligand complexes based on benzophenone-derived Schiff bases combine the stiff, π-rich core with auxiliary co-ligands to tune geometry, electronics, and bioactivity. N1-(diphenylmethylene)naphthalene-1,8-diamine, a prototype benzophenone Schiff base, is produced by condensing benzophenone with 1,8-naphthalenediamine. It behaves as a NN bidentate ligand L around Mn(II), Ni(II), Zn(II), La(III), Er(III), and Yb(III) in octahedral complexes (Khalil et al., 2021). Using this ligand as a main chelate, mixed complexes with o-aminophenol as a secondary N-O donor provide octahedral transition and inner transition metal species, where L occupies two sites and o-aminophenol completes the coordination sphere (Khalil et al 2023). A comparable mixed system has been described in zinc(II) coordination polymers, where [Zn(nba)2(tmdp)]n and [Zn(biphen)2(tmdp)]n are synthesised (Tella et al., 2020). This synthesis substantially resembles the benzophenone-derived L with 1,10-phenanthroline, yielding $[M(L)(Phen)Cl_2]$-type octahedral complexes for Mn(II), Ni(II), Zn(II), La(III), Er(III), and Yb(III) (Khalil et al.,2022). The co-ligand promotes octahedral coordination, transitioning from the $[M(L)(H_2O)_3Cl]Cl$ type in simple benzophenone complexes (Raczuk et al.,2022) to $[M(L)(Phen)Cl_2]$, with Phen providing a stiff N_2 chelate (Subbaraj et al.,2014).

Another benzophenone framework combines 2,4-dihydroxybenzophenone and aniline to generate a bidentate N, O ligand; mixed complexes of type MAB with 2-aminophenol or 2-aminobenzoic acid provide octahedral M(II) environments through combined N, O chelation from both ligands. The inclusion of any of these co-ligands increases the coordination number to six, stabilising octahedral complexes (Subbaraj et al.,2014).. Mixed systems of 2,2,4,4-tetrahydroxybenzophenone and 1-naphthylamine with 8-hydroxyquinoline produce [M(A)(Q)] and $[M(A)(Q)(H_2O)_2]$ species, with both ligands binding through azomethine N and deprotonated phenolic O donors. The addition of 8-hydroxyquinoline (another N, O chelate) to metal complexes results in 4 and 6 coordinate formulations [M(A)(Q)] and $[M(A)(Q)(H_2O)_2]$, demonstrating how the co-ligand affects hydration and coordination number (Atiyah et al.,2021).Biological activity in the benzophenone naphthalenediamine system, mixed metal complexes with o-aminophenol demonstrate higher antibacterial and anticancer activity compared to ligand or metals alone, indicating cooperative effects of dual chelation and increased lipophilicity (Rana et al.,2024). The addition of Phen as a co-ligand with the identical benzophenone core results in strong antibacterial and antifungal characteristics, as well as promising cytotoxic activity against MCF-7, exceeding the free Schiff base(Kazemi et al.,2025). Benzophenone-type N,O ligands generated from 2,4-dihydroxybenzophenone increase antibacterial and DNA cleavage activity in complexes with 2-aminophenol/2-aminobenzoic acid, indicating a positive co-ligand effect. Tetrahydroxybenzophenone/8-hydroxyquinoline complexes exhibit stronger antibacterial activity than their parent ligands (Atiyah et al.,2021).. Co-ligands such 1,10-phenanthroline and 2,2′-bipyridyl improve DNA binding, protein affinity, and cytotoxicity, providing a consistent molecular basis for the effects reported in benzophenone systems (Ibrahim et al.,2023;Fathima et al.,2024).

Table 2: Some Mixed-Ligand Metal Complexes of BPSB

Mixed-ligand complex (generic)	Primary benzophenone Schiff base	Co-ligand (X)	Key features/outcomes	Citations
[M(L)(o-AP)]	N1-(diphenylmethylene)naphthalene-1,8-diamine (NN)	o-aminophenol (N,O)	Octahedral mixed chelates of Mn(II), Ni(II), Zn(II), La(III), Er(III), Yb(III); improved antimicrobial/anticancer activity vs. ligand	(Tella et al.,2020)
$[M(L)(Phen)Cl_2]$	Same NN benzophenone ligand L	1,10-Phenanthroline	Octahedral Mn(II), Ni(II), Zn(II), La(III), Er(III), Yb(III); strong antibacterial, antifungal and MCF-7 cytotoxicity	(Khalil et al2022)
[M(HA)(B)] (MAB type)	(E)-4-(phenyl(phenylimino)methyl)benzene-1,3-diol from 2,4-dihydroxybenzophenone + aniline	2-aminophenol or 2-aminobenzoic acid	Octahedral Mn(II), Co(II), Ni(II), Cu(II), Zn(II); significant DNA binding and nuclease, enhanced antimicrobial activity	(ubbaraj et al.,2014)
[M(A)(Q)], $[M(A)(Q)(H_2O)_2]$	Schiff base from 2,2,4,4-tetrahydroxybenzophenone + 1-naphthylamine	8-hydroxyquinoline	4- and 6-coordinate complexes for Mn(II), Co(II), Cu(II), Zn(II), Cd(II), Hg(II); higher antibacterial activity than free ligands	(Atiyah et al.,2021)

4.0 CHARACTERISATION OF METAL COMPLEXES DERIVED FROM BPSB

Metal complexes of benzophenone-derived Schiff bases are frequently investigated using a multi-technique approach that focuses on their composition, coordination mode, and geometry.

4.1 Spectroscopic and magnetic characterisation

FTIR spectroscopy is essential for identifying donor sites in benzophenone Schiff base metal complexes. Coordination of the benzophenone NN ligand N1 (diphenylmethylene)naphthalene-1,8-diamine to Mn(II), Ni(II), Zn(II), La(III), Er(III), and Yb(III) is demonstrated by a shift of ν(C=N) and the emergence of new ν(M-N) bands, consistent with N,N-bidentate binding in octahedral complexes (Khalil et al.,2021). When Mn(II), Co(II), Ni(II), Cu(II), and Zn(II) are complexed with aniline in substituted benzophenone NO-type ligands, the azomethine and phenolic ν(OH) bands shift and ν(M-O)/ν(M-N) bands arise, indicating N,O chelation (Al-Saif et al.,2018). The weak bands at 652 and 473 cm^{-1} for Cu-N and Cu-O, as well as 552 and 495 cm^{-1} for Co-N and Co-O vibrations, have been confirmed (Tella et al.,2021).”Chloro-substituted hydroxybenzophenone-propylene diamine systems exhibit similar ν(C=N)/ν(OH) shifts upon metal binding, enabling N,O coordination in Co(II), Ni(II), Cu(II), Zn(II), and Cd(II) complexes”. 1H/13C NMR of benzophenone-based ligands (e.g.3,4-diaminobenzophenone tetradentate and pyridoxal/benzophenone systems) verifies imine production and coordination through azomethine and phenolic sites via distinctive signal shifts between free ligand and diamagnetic complexes (Hadi et al.,2020). [39UV-Vis spectra and room-temperature magnetic moments show octahedral high-spin geometries for Mn(II), Co(II), Ni(II), Cu(II), and lanthanide benzophenone complexes. However, some Zn(II) benzophenone complexes are diamagnetic, indicating tetrahedral or distorted octahedral environments (Oladipo et al.,2021). Magnetic and electronic data in benzophenone-derived azo-Schiff bases indicate octahedral complexes of Co(II), Ni(II), Cu(II), Zn(II), and Cd(II), with square-planar geometries for Pt(II) and Au(III) (Hadi et al.,2020).EPR investigations on benzophenone-thiosemicarbazone and similar benzophenone Schiff base Cu(II) complexes show axial spectra indicative of elongated octahedral or distorted square-planar coordination, which confirms ligand field assignments from UV-Vis and magnetic studies (El-Asmy et al.,2009).

Elemental (C,H,N,metal) analysis determines stoichiometry in benzophenone Schiff base complexes, allowing formulations like $[M(L)(H_2O)_3Cl]Cl\cdot nH_2O$ (M = Mn(II), Ni(II)) and $[Zn(L)(H_2O)_2Cl_2]$ for the N1-(diphenylmethylene)naphthalene-1,8-diamine ligand, and $[ML_2]$ for 2,2-dihydroxy-4,4-dime. Molar conductance in DMF/DMSO differs between electrolytic and neutral benzophenone complexes: N1-(diphenylmethylene)naphthalene-1,8-diamine complexes of Mn(II), Ni(II), La(III), Er(III), and Yb(III) behave as 1:1 electrolytes, but the Zn(II) analogue is non-electrolytic (Raman et al.,2007). Substituted benzophenone NO complexes are normally non-electrolytes with 1:2 (M:L) stoichiometry(Al-Saif et al.,2018;Asha et al.,2014). Azo-benzophenone Schiff base complexes, such as octahedral Co(II), Ni(II), Cu(II), Zn(II), and Cd(II), are non-electrolytes, unlike ionic Pt(II)/Au(III) benzophenone systems (Oladipo et al.,2022;Adeyemi et al.,2020). Thermogravimetric (TG/DTG or TGA/DTA) analysis is commonly used on benzophenone Schiff base complexes. Stepwise mass loss in the N1 (diphenylmethylene)naphthalene-1,8-diamine series identifies lattice water, coordinated water, chloride, and organic ligand breakdown, validating hypothesised hydration states and producing metal oxides as residues [1]. Substituted hydroxybenzophenone NO complexes of Co(II), Ni(II), Cu(II), Zn(II), and Cd(II) exhibit an early loss of coordinated water followed by ligand breakdown, consistent with octahedral formulations from spectroscopy and magnetism (Asha et al.,2014). Benzophenone-derived thiosemicarbazone complexes exhibit multistep TG patterns with loss of coordinated groups, indicating $[ML_2]$ stoichiometry and octahedral geometry (Kareem et al.,2019).

PXRD has been used directly for benzophenone Schiff base systems. PXRD analysis of substituted 2-hydroxy-4-methoxybenzophenone-aniline NO ligands and their complexes with Mn(II), Co(II), Ni(II), Cu(II), and Zn(II) reveals microcrystalline phases and coordinated water, supporting thermal data (Subbbaraj et al.,2015). PXRD, thermal, and spectroscopic findings reveal hydrated octahedral formulations and microcrystalline nature in N1 (diphenylmethylene)naphthalene-1,8-diamine complexes(Raman et al.,2007). Benzophenone-based thiosemicarbazone compounds exhibit patterns similar to polycrystalline materials, with octahedral $[ML_2]$ assignments Pandian et al.,2013).. SEM has been explicitly described for benzophenone Schiff base ligands and complexes. N1-(diphenylmethylene)naphthalene-1,8-diamine has a rod-like nanomorphology (~77 nm), while its $[Mn(L)(H_2O)_3Cl]Cl\cdot4H_2O$ complex generates non-uniform platelet/rod aggregates (~58 nm), showing a clear morphological shift upon complexation [47]. Mixed ligand benzophenone-1,10-phenanthroline complexes of Mn(II), Ni(II), Zn(II), La(III), Er(III), and Yb(III) exhibit unique surface characteristics compared to the free benzophenone ligand, with Ni(II) complexes displaying platelets with distributed rods (~54 nm) [40]sssssssssssssssssssss. SEM analysis of substituted benzophenone NO complexes reveals micro- to nano-sized particles, confirming PXRD findings of microcrystallinity and establishing connections between morphology, thermal stability, and biological activity (Al-Saif et al.,2018;Asha et al.,2014). In various benzophenone-based azo-Schiff systems, EDX coupled with SEM validates the presence and distribution of Co(II), Ni(II), Cu(II), Zn(II), and Cd(II) within observed particles, supporting formulations based on analytical data [40] [54].

Table 3: Characterisation Techniques for Metal Complexes of BPSB

Technique / Method	**Assignments**	Example
FT-IR	Identifies Schiff base formation via the ν(C=N) band and confirms coordination through shifts of ν(C=N), O–H, N–H and other donor groups.	In Ni(II) and Cu(II) complexes of 3,4-diamino-benzophenone Schiff bases, ν(C=N) shifts from ~1620 cm^{-1} in the free ligand to ~1600 cm^{-1} on coordination, while phenolic O–H disappears or shifts, supporting imine formation and metal binding (Subbaraj et al.,2015).
UV–Vis / electronic spectra	Diagnose *d–d* and charge-transfer bands, providing ligand-field parameters and supporting octahedral, tetrahedral or square-planar geometries in NO/NN benzophenone systems and mixed-ligand complexes.	Substituted benzophenone–naphthylenediamine Cu(II) complexes show broad bands around 13,000–15,000 cm^{-1} assigned to $^2E_g \rightarrow {}^2T_{2g}$ transitions, consistent with distorted octahedral geometry; higher-energy bands are attributed to LMCTAsha et al.,2014).
NMR (^1H, ^{13}C)	Confirms imine formation and ligand framework; donor atoms and coordination are inferred from downfield or upfield shifts of imine-H and C=N signals after complexation.	For tetradentate 3,4-diamino-benzophenone Schiff bases, the imine proton appears at δ ~8.5–9.0 ppm and C=N carbon at δ ~160–170 ppm in the free ligand; both signals broaden and shift on complexation with Ni(II)/Cu(II), indicating coordination through azomethine N (Bal,2023).
Mass spectrometry	Confirms molecular ion peaks, molecular weight and stoichiometry of benzophenone ligands and selected complexes.	ESI-MS of a benzophenone-derived Cu(II) complex gives a peak corresponding to $[Cu(L)Cl]^+$, matching the calculated m/z and confirming 1:1 metal:ligand stoichiometry (Karem,2025)].
EPR/ESR	Probes geometry and metal–ligand bonding in paramagnetic complexes; axial g‖ > g⊥ values support octahedral Cu(II) environments.	A Cu(II) Schiff base complex related to benzophenone analogues exhibits g‖ ≈ 2.22, g⊥ ≈ 2.05 (g‖ > g⊥) and an axial symmetry parameter (G > 4), diagnostic of elongated octahedral geometry with strong in-plane bonding (Gosu et al., 2025).
Elemental (CHN, metal) analysis	Defines empirical formulae and verifies M:L stoichiometry; typical formulations include $[M(L)(Phen)Cl_2]Cl\cdot xH_2O$ for mixed-ligand benzophenone–phen complexes.	Cu(II)/diiminic complexes based on 2-hydroxybenzophenones, with phenanthroline adduct and full CHN/HRMS data (Rodrigues et al.,2023)
Molar conductance	Distinguishes non-electrolytes (inner-sphere anions) from electrolytes (outer-sphere anions) in DMF/DMSO; widely used for benzophenone NN/NO and mixed-ligand chelates.	Substituted benzophenone Cu(II) complexes from chloride salts show low molar conductance (<20 S cm^2 mol^{-1}) in DMF, indicating non-electrolytic neutral species, whereas nitrate analogues display higher values consistent with 1:1 electrolytes (Hadi et al.,2020).
Magnetic susceptibility	Determines the number of unpaired electrons and supports assignment of octahedral, tetrahedral or square-planar geometries for Mn(II), Co(II), Ni(II), Cu(II), lanthanide benzophenone complexes.	High-spin Co(II) benzophenone Schiff base complexes exhibit μ_{eff} ≈ 4.7–5.2 B.M., characteristic of octahedral Co(II); square-planar Ni(II) analogues show μ_{eff} ≈ 0 B.M. (diamagnetic)
Thermal analysis (TG/DTG, DTA)	Tracks loss of lattice/coordination water, anions and ligand fragments; provides thermal stability and nature of final metal oxide residue.	A benzophenone NO Cu(II) complex shows initial mass loss below 150 °C corresponding to lattice water, followed by decomposition of organic ligands to yield CuO above 600 °C, in agreement with calculated residue (Yaul et al., 2014).

Single Crystal X-ray diffraction (**SC**XRD)	shows how metal centre is coordinated (square planar, square pyramidal, octahedral) and which atoms (N, O) bind to the metal.	Cu(II) ONO Schiff base ligand complex is shown to be mononuclear, tetracoordinate, with two tridentate NO_2 ligands and an overall square-planar geometry, with Cu–N and Cu–O distances ~1.93 and ~1.90 Å (Salehi et al., 2018)
Electrochemical (CV) & conductivity (solid-state)	Cyclic voltammetry probes redox couples (M(II)/M(III), ligand-centred processes); solid-state conductivity reveals semiconducting behaviour applicable to benzophenone systems by analogy.	Amino-acid Schiff base metal complexes show quasi-reversible M(III)/M(II) waves in CV and p-type semiconductivity with σ increasing on heating, behaviour expected for π-conjugated benzophenone Schiff base frameworks (Buran .,2025;Hassan et al.,2022).
SEM	Visualizes particle morphology, size and surface texture of ligands and complexes; applied directly to benzophenone NN systems and mixed-ligand benzophenone–Phen complexes.	SEM images of a benzophenone NN Schiff base ligand show rod-like nanostructures (~77 nm), whereas its Ni(II) complex forms platelet/rod aggregates (~54 nm), indicating metal-induced morphological reorganisation (Elaaraj et al.,2025).
SEM/EDX, TEM (broader Schiff base work)	SEM/EDX provides surface composition and metal distribution; TEM offers higher-resolution particle size and shape, approaches transferrable to benzophenone frameworks.	In hybrid Schiff base–triphenylphosphine complexes, SEM/EDX confirms homogeneous metal and P distribution, while TEM reveals discrete nanocrystallites, a strategy equally applicable to benzophenone-derived complexes (Chaudhary et al.,2017).

5.0 BIOLOGICAL ACTIVITIES OF METAL COMPLEXES OF BPSB

Metal complexes formed from benzophenone-type Schiff bases exhibit enhanced biological activity compared to their ligands, particularly in benzophenone-3 (2-hydroxy-4-methoxybenzophenone)-based systems(Firdaus et al.,2026)

5.1 Antimicrobial and antifungal activity

A benzophenone Schiff base ligand derived from 2-hydroxy-4-methoxybenzophenone and aniline, together with its Mn(II), Co(II), Ni(II), Cu(II), and Zn(II) complexes, was evaluated against bacterial and fungal strains. Metal complexes and their ligands have high bioefficacy against pathogenic bacterial and fungal strains (Sharma et al., 2022).Antimicrobial testing of H_2L and its mixed ligands (Mn(II), Co(II), Ni(II), Cu(II), and Zn(II) complexes with phenanthroline revealed a clear order of activity against bacteria and fungi: MLB complexes > phenanthroline > free Schiff base H_2. This directly reveals that metal coordination significantly improves antibacterial and antifungal activity when compared to the benzophenone Schiff base ligand alone.

5.2 Antioxidant activity

The antioxidant activity of benzophenone-3-derived heteroleptic complexes was investigated in vitro using DPPH and ABTS assays. Free Schiff base (H_2L), phen (B) ligands, and their hetero ligand MLB complexes (Mn(II), Ni(II), and Cu(II) complexes) have shown remarkable antioxidant activity (Sridev et al.,2025). Metal complexes outperformed benzophenone Schiff base in terms of radical scavenging.

5.3 Behaviour related to cytotoxicity or antiproliferation.

Benzophenone Schiff bases, like imidazoles, exhibit dose-dependent cytotoxicity through extended aromatic frameworks and tunable electron-donating/withdrawing groups, leading to ROS overproduction and impaired mitochondrial membrane potential (MMP), among other effects (Adeyemi et al.,2020). Water-soluble metal complexes of a N_2O_2 benzophenone Schiff base (N,N′-bis(5-sulfosalicyliden)-3,4-diaminobenzophenone) with Zn, Cu, Ni, and Mn were synthesised and evaluated for their growth inhibitory activities against the K562 cancer cell line (Asadi et al., 2014)]. Schiff base metal complexes based on benzophenone have been shown to have antiproliferative properties (Uddin et al.,2020). In the benzophenone-3 mixed ligand series, Mn(II), Ni(II), and Cu(II) complexes exhibit significant activity, implying that complexation enhances biologically relevant interactions (DNA binding, redox behaviour) beyond free BPSB (Ejidike et al.,2015).

5.4 Other biological interactions

The benzophenone-3-based heteroleptic complexes exhibit significant DNA interaction through intercalation, with binding constants of $4.86\text{-}7.21\times10^5\ M^{-1}$ and spontaneous binding (negative ΔG) (Hemalatha et al.,2019) Similarly, the simpler benzophenone-aniline Schiff base complexes exhibit effective DNA binding and cleavage [69]. These features support their antibacterial and cytotoxic activities, which are significantly amplified in metal complexes compared to benzophenone Schiff base ligands alone.

Table 4: Reviewed Biological Activities of Metal Complexes of BPSB

Biological activity / theme	**Key findings for benzophenone Schiff base metal complexes**	**Citations**
Antimicrobial (antibacterial) activity	A benzoin-tryptamine Schiff base Cu(II), Co(II), Ni(II), Cd(II) series showed much stronger antibacterial activity than the free ligand; for Cu(II), MIC against S. aureus dropped to 37.11 µg/mL vs. 97.7 µg/mL for the ligand. Complexes with Mn(II), Zn(II), La(III), Er(III), Yb(III) also gave larger inhibition zones against B. subtilis and E. coli; Zn(II) complexes were often the most active.	(Karem ,2025)
Antifungal activity	Antifungal effects are generally moderate but can be notable depending on metal and ligand design. Ni(II) complexes derived from N1-(diphenylmethylene)naphthalene-1, 8-diamine showed good activity against Candida albicans, surpassing both the free ligand and other metal complexes in the same series.	(Khalil et al.,2021)
Antiproliferative / cytotoxic (anticancer) activity	Many benzophenone Schiff base metal complexes exhibit promising anticancer properties. In MCF-7 breast cancer cells, Zn(II), Cu(II), Fe(III) complexes were more cytotoxic than the parent ligand, with Zn(II) particularly potent (IC_{50} = 61.47 µM). Docking studies indicate	(Ateq et al.,2025)

	favorable binding to relevant protein targets. La(III), Er(III), Yb(III) complexes show enhanced apoptosis induction and associated antioxidant effects after coordination.	
Antioxidant activity	Complexation typically enhances antioxidant capacity. Dioxomolybdenum(VI) complexes from substituted benzophenones showed higher TEAC values in DPPH assays than reference antioxidants. Both ligands and their Mo(VI) complexes outperformed standard compounds, indicating a strong metal-dependent improvement in radical scavenging.	
Other biological activities	Benzophenone Schiff base metal complexes have been explored for anti-inflammatory, antimalarial, antituberculosis, anti-Alzheimer's activities, DNA binding/cleavage and enzyme inhibition, reinforcing their value as versatile pharmacophores for drug development.	[73,76–78]

6.0 STRUCTURE–ACTIVITY RELATIONSHIPS

Chelation of benzophenone-Schiff bases with transition metals often increases the lipophilicity of the complexes formed. This increased lipophilicity allows for better penetration through microbial cell lipid membranes, contributing to their improved antibacterial action as compared to free ligands. For example, studies consistently show that metal complexes have greater antibacterial and antifungal activity than their parent Schiff bases, with the increased lipophilicity attributed to electron delocalisation over the chelate ring and partial sharing of the metal's positive charge with donor atoms in the ligand (Buran et al., 2025)]. The charge on the metal complex also plays a role: non-electrolytic (neutral) complexes frequently show better membrane permeability and consequently more bioactivity than electrolytic (charged) ones (Ateq et al.,2025). Coordination geometry also influences activity; these complexes typically have octahedral or distorted octahedral geometries, which are associated with high stability and effective biological interactions (Subbaraj et al., 2015). Tetrahedral or square planar geometries have been seen in some systems (for example, Zn(II) or Cu(II), which can alter DNA binding modes and enzyme interactions(Khalil et al.,2021).

The nature of the central metal ion is critical in distinguishing biological activity amongst metal complexes. For example, Fe(III) complexes have been demonstrated to have the strongest antibacterial activity among a series that includes Zn(II), Cu(II), Ni(II), and Fe(III), most likely due to their higher redox potential, which facilitates reactive oxygen species (ROS) formation or other redox-mediated mechanisms (Ateq et al.,2025). Zn(II) complexes have high cytotoxicity against cancer cells (IC_{50} = 61.47 μM for MCF-7 cells), presumably due to disrupting zinc-dependent enzymes or protein structures. The order of biological activity varies depending on the assay type and target organism; nonetheless, it is usual to see trends such as Cu(II) > Ni(II) > Co(II) > Mn(II) in antibacterial potency [64], although Fe(III) may shine in redox-related bioassays. The redox characteristics of each metal centre influence not only direct cytotoxicity, but also DNA cleavage ability and enzyme inhibition profiles (Khalil et al., 2021)]. The planarity of co-ligands has a significant effect on bioactivity. 1,10-phenanthroline (phen) is a highly planar co-ligand that improves π-π stacking interactions with biomolecules including DNA and proteins. Mixed-ligand benzophenone-Schiff base complexes with phenanthroline exhibit significantly stronger antibacterial and anticancer activity than those with less planar co-ligands such as bipyridine (bipy) or ethylenediamine (en). This is due to better intercalative binding to DNA and more favourable hydrophobic interactions within biological targets . Mixed-ligand systems containing phenanthroline, for example, demonstrated greater inhibitory zones against both Gram-positive and Gram-negative bacteria, as well as increased cytotoxic effects in breast cancer cell lines, when compared to equivalent bipy or en systems (Khalil et al.,2021). Thus, planarity not only helps in target recognition but also stabilises complicated biomolecule adducts.

7.0 CONCLUSION

This work shows that benzophenone-derived Schiff base ligands are easily synthesised via condensation processes and serve as diverse chelating platforms for a variety of transition and inner-transition metal ions, as well as mixed-ligand complex formation. Comprehensive spectroscopic (UV-Vis, IR, NMR, EPR, MS), thermal, and, where available, crystallographic and morphological (SEM/TEM, SC-XRD) studies consistently confirm well-defined coordination modes and geometries, resulting in neutral or cationic complexes that are more stable than free ligands. Metal complexation generally enhances biological activity in antimicrobial, antifungal, antioxidant, and anticancer assays compared to uncoordinated benzophenone Schiff bases, owing to increased lipophilicity, modified charge distribution, and accessible redox behaviour that favour membrane permeation and biomolecular interactions. Structure activity relationships indicate that ligand electronic effects, metal identity and oxidation state, overall geometry, and co-ligand planarity (e.g., phen > bipy > en) act as key determinants of potency and selectivity, underscoring benzophenone Schiff base metal complexes and their mixed-ligand analogues as promising, tunable scaffolds for future bioactive coordination compounds.

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