International Journal for Rapid Research in Engineering Technology & Applied Science (IJRRETAS)

(Peer-Reviewed, Open Access, Fully Refereed International Journal)

Volume 11 issue 03 March 2025 OPEN ACCESS E-ISSN: 2455-4723 Impact Factor 7.95

Synthesis and Structure–Activity Relationship Studies of Novel Schiff Base Derivatives and Their Biological Applications: A Review

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Abstract

Schiff bases, characterised by the azomethine (–C=N–) linkage formed through the condensation of a primary amine with an aldehyde or ketone, occupy a privileged position in contemporary medicinal and coordination chemistry. Since Hugo Schiff first described their formation in the nineteenth century, this deceptively simple functional group has proven remarkably adaptable, tolerating an enormous range of aliphatic, aromatic and heterocyclic substituents while retaining a stable, planar and electronically polarisable core. The present review consolidates the literature published between 2015 and 2021 on the synthesis of novel Schiff base derivatives, the structural determinants that govern their pharmacological behaviour, and the breadth of their biological applications. Conventional acid-catalysed condensation in refluxing alcohol remains the workhorse preparation, but the last decade has seen a decisive shift towards greener protocols including microwave irradiation, ultrasonication, mechanochemical grinding, natural-acid catalysis and solvent-free solid-state reactions, all of which shorten reaction times, improve atom economy and simplify purification. Against this synthetic backdrop, structure–activity relationship (SAR) analysis has matured from qualitative substituent commentary into a quantitative, computationally supported design discipline. Recurring SAR themes emerge consistently across therapeutic areas: electron-withdrawing halogens and nitro groups on the aldehyde-derived aromatic ring generally enhance antimicrobial and enzyme-inhibitory potency, ortho-hydroxyl functionality supports intramolecular hydrogen bonding and radical scavenging, extended conjugation and planarity favour DNA intercalation and antiproliferative activity, and chelation with transition metals frequently amplifies potency by increasing lipophilicity and membrane permeation. Reported activities encompass antibacterial, antifungal, antiviral, anticancer, antioxidant, antidiabetic, anti-inflammatory, antitubercular and antimalarial effects, together with enzyme inhibition against urease, α-glucosidase, carbonic anhydrase and cholinesterases. This review summarises representative structural series in three comparative tables, evaluates the mechanistic rationale underpinning observed trends, and identifies the hydrolytic instability, selectivity deficits and translational gaps that continue to limit clinical progression of this compound class.

Keywords: Schiff base; azomethine; structure–activity relationship; green synthesis; metal complexes; antimicrobial; anticancer; enzyme inhibition

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1. Introduction

1.1 Chemistry and Structural Features of the Azomethine Linkage

Schiff bases are compounds bearing the general formula $R_1R_2C=NR_3$, in which the nitrogen atom is attached to an alkyl or aryl group rather than to hydrogen. They arise from the nucleophilic addition of a primary amine to a carbonyl carbon, producing a tetrahedral carbinolamine intermediate that subsequently dehydrates to furnish the imine. The reaction is reversible and pH-dependent, proceeding optimally under mildly acidic conditions in which the carbonyl is activated by protonation yet the amine remains substantially unprotonated and nucleophilic (Raczuk et al., 2022). This equilibrium sensitivity is simultaneously the greatest synthetic convenience and the principal pharmaceutical liability of the class.

The azomethine group is more than a passive connector. The carbon–nitrogen double bond is polarised, with appreciable partial positive charge at carbon and a lone pair localised on nitrogen that is available for hydrogen bonding and metal coordination. When an ortho-hydroxyl group is present on an aldehyde-derived aromatic ring, as in salicylaldehyde-based derivatives, a six-membered intramolecular hydrogen-bonded pseudo-ring forms, imposing near-planarity on the molecule and enabling keto–enol and enol–imine/keto–amine tautomerism. This conformational rigidity has direct pharmacological consequences: planar systems intercalate into DNA more effectively, and the phenolic proton participates in hydrogen atom transfer relevant to antioxidant behaviour (Boulechfar et al., 2023).

Structural classification is generally made on denticity and donor-atom composition. Monodentate imines are comparatively rare in biological studies; bidentate N,O and N,N systems dominate, while tridentate ONO, ONS and NNO ligands and tetradentate salen-type frameworks derived from diamines such as ethylenediamine or 1,2-phenylenediamine are widely exploited for metal complexation (Abu-Dief & Mohamed, 2015). Bis-Schiff bases, or azines, containing two azomethine functions, have attracted particular attention because the doubled pharmacophore often produces superadditive activity relative to the corresponding monomer (Gul et al., 2021).

1.2 Synthetic Methodologies and the Green Chemistry Transition

Classical Schiff base preparation involves refluxing equimolar quantities of amine and carbonyl compound in ethanol or methanol with a catalytic quantity of glacial acetic acid, typically for two to eight hours, followed by cooling, filtration and recrystallisation. The method is robust and delivers acceptable yields for reactive aromatic aldehydes, but consumes substantial volumes of volatile organic solvent, demands prolonged heating and performs poorly with sterically hindered ketones or weakly nucleophilic amines such as those bearing strong electron-withdrawing substituents.

The past decade has therefore witnessed sustained methodological innovation. Microwave-assisted synthesis has emerged as the most broadly adopted alternative, reducing reaction times from hours to minutes while frequently improving yields and suppressing side-product formation through uniform dielectric heating (Nagar et al., 2023). Ultrasonication achieves comparable acceleration through acoustic cavitation. Mechanochemical grinding, in which

solid reagents are ground together in a mortar with or without a trace of catalyst, eliminates solvent entirely and is particularly well suited to substrates that crystallise readily. Natural acid catalysts — lemon juice, lime juice, tamarind extract, cashew shell extract and calcined eggshell — have replaced mineral acids in numerous protocols, offering biodegradability alongside genuine catalytic competence.

Water-mediated and ionic-liquid-mediated syntheses, ball milling, and heterogeneous nanocatalysis using magnetic Fe_3O_4-supported systems complete the current green toolkit (Nagar et al., 2023). Purification has correspondingly simplified: many solvent-free reactions deliver products of sufficient purity that a single recrystallisation suffices, avoiding column chromatography. Characterisation is routinely accomplished through FT-IR spectroscopy, where the diagnostic azomethine stretch appears near 1600–1640 cm^{-1} accompanied by the disappearance of carbonyl absorption around 1700 cm^{-1}; ^1H NMR, in which the imine proton resonates characteristically between δ 8.2 and δ 8.9; ^{13}C NMR; mass spectrometry; elemental analysis; and, increasingly, single-crystal X-ray diffraction supplemented by Hirshfeld surface analysis and density functional theory calculations (Oladipo et al., 2021).

1.3 Structure–Activity Relationship as a Design Framework

Structure–activity relationship analysis correlates systematic structural variation with measured biological response, converting empirical screening data into transferable design principles. For Schiff bases, the modular nature of the condensation reaction makes SAR study unusually tractable: a single amine can be condensed with twenty substituted benzaldehydes in parallel, generating a congeneric series in which only one variable changes across the set.

Four structural regions are conventionally interrogated. The first is the aldehyde-derived aromatic ring, where substituent electronics and position exert the dominant influence on potency. The second is the amine-derived fragment, which frequently carries the heterocyclic pharmacophore — thiazole, benzimidazole, triazole, quinoline, indole or sulfonamide — responsible for target recognition. The third is the azomethine bridge itself, which may be extended, reduced to the secondary amine, or doubled as in bis-Schiff bases. The fourth is the coordination sphere, where complexation with copper, zinc, nickel, cobalt or palladium introduces an entirely additional dimension of activity modulation (Uddin et al., 2020).

Modern SAR work is rarely purely empirical. Molecular docking against defined protein targets, molecular dynamics simulation, DFT-derived electronic descriptors such as HOMO–LUMO gap and molecular electrostatic potential, and in silico ADMET prediction are now standard companions to in vitro assay data, allowing observed potency trends to be rationalised in terms of specific binding interactions and electronic distributions (Gul et al., 2021).

1.4 Scope of Biological and Applied Significance

The pharmacological range of Schiff bases is exceptionally broad. Reported activities include antibacterial and antifungal action against both susceptible and multidrug-resistant pathogens (Ceramella et al., 2022), antiproliferative effects across diverse carcinoma cell lines (Majid et al., 2022), radical scavenging and antioxidant capacity (Al Zoubi et al., 2016), antidiabetic activity through α-amylase and α-glucosidase inhibition (Oladipo et al., 2021), anti-

inflammatory, antiviral, antimalarial and antitubercular effects, and inhibition of clinically relevant enzymes including urease and carbonic anhydrase (Rafiq et al., 2021).

Beyond therapeutics, Schiff bases and their metal complexes serve as homogeneous catalysts for oxidation, epoxidation and polymerisation, as corrosion inhibitors for mild steel in acidic media, as fluorescent chemosensors for heavy metal ions, as polymer stabilisers and dye intermediates, and as diagnostic imaging agents when complexed with lanthanides (Kaczmarek et al., 2018). Chitosan-based Schiff bases occupy a distinctive niche, combining the biocompatibility and film-forming capacity of the polysaccharide with the bioactivity of the imine function to yield antimicrobial wound dressings, food-packaging materials and drug delivery matrices (Antony et al., 2019). Patent activity across the period confirms sustained commercial as well as academic interest (Hameed et al., 2017).

2. Literature Review

2.1 Antimicrobial Schiff Base Derivatives and Their Structure–Activity Relationships

Antimicrobial evaluation constitutes the single largest body of Schiff base literature, driven substantially by the accelerating global crisis of antimicrobial resistance. The mechanistic rationale most commonly advanced is Overtone's concept of cell permeability combined with Tweedy's chelation theory: the lipophilic azomethine core facilitates passage across the lipid bilayer, while the nitrogen lone pair disrupts bacterial enzyme function by coordinating essential metal cofactors or interfering with cell-wall biosynthesis (Ceramella et al., 2022).

Substituent effects on the aldehyde-derived ring follow a reasonably consistent pattern. Halogen substitution — particularly chlorine and bromine at the para or meta position — reliably enhances activity, an effect attributed to increased lipophilicity improving membrane transit combined with the electron-withdrawing inductive effect that raises the electrophilicity of the imine carbon. Nitro groups produce similar or greater enhancement, and derivatives bearing both a halogen and a hydroxyl group frequently rank among the most potent members of a series. Methoxy and other electron-donating groups generally reduce antibacterial potency relative to halogenated analogues, though they often improve antifungal selectivity and antioxidant behaviour, illustrating the trade-offs inherent in single-scaffold optimisation (Yuldasheva et al., 2022).

Heterocyclic amine fragments contribute decisively. Janowska et al. (2023) prepared Schiff bases from 4-amino-5-(3-fluorophenyl)-1,2,4-triazole-3-thione and a panel of substituted aldehydes, reporting selective activity against Gram-positive strains with the triazole-thione moiety serving as the recognition element and aldehyde-ring substitution tuning potency. Benzimidazole-derived Schiff bases prepared by Beč et al. (2023) demonstrated combined antibacterial, antiviral and antiproliferative activity, with N-substitution on the benzimidazole nitrogen modulating the balance between the three activities. Quinoline-based systems have proven especially valuable for dual antimalarial–antimicrobial targeting, since the 7-chloroquinoline pharmacophore retains its heme-polymerisation-inhibiting function while the appended imine confers additional antibacterial character.

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Metal complexation is a recurrent amplifier. Comparative studies almost uniformly report that copper(II), zinc(II), nickel(II) and cobalt(II) complexes exceed the potency of the parent ligand, sometimes by an order of magnitude. Chelation reduces the polarity of the metal ion through partial sharing of its positive charge with donor atoms and through π-electron delocalisation across the chelate ring, increasing lipophilicity and consequently membrane penetration. Copper complexes additionally generate reactive oxygen species through redox cycling, adding an oxidative-damage mechanism to the primary mode of action (Malik et al., 2018).

Table 1. Representative antimicrobial Schiff base systems and associated SAR observations (2015–2021)

Scaffold / amine fragment	Key structural variation	Principal activity reported	SAR observation
1,2,4-Triazole-3-thione	Substituted benzaldehydes	Gram-positive bacteria, Candida spp.	Halogen on aldehyde ring improves potency; thione tautomer essential for activity
N-Substituted benzimidazole	Alkyl chain length on benzimidazole N	Antibacterial, antiviral, antiproliferative	Longer lipophilic N-alkyl chains favour antiproliferative over antibacterial action
7-Chloroquinoline	Aryl aldehyde substitution	Antimalarial and antibacterial	Electron-withdrawing groups enhance dual activity; retained quinoline nitrogen essential
Sulfonamide	Position of aryl substituent	Antibacterial, urease inhibition	Combined halogen plus hydroxyl gives greatest inhibition
Chitosan (polymeric)	Degree of imine substitution	Broad-spectrum antibacterial, antifungal	Higher substitution improves activity until solubility becomes limiting
Salicylaldehyde-derived ONO ligands	Cu(II), Zn(II), Ni(II), Co(II) complexation	Enhanced antibacterial vs free ligand	Chelation increases lipophilicity; Cu(II) generally most potent

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Scaffold / amine fragment	Key structural variation	Principal activity reported	SAR observation
p-Vanillin derivatives	Reduction of C=N to secondary amine	Antimicrobial, antioxidant, antidiabetic	Reduction improves hydrolytic stability but can reduce antimicrobial potency
Bis-Schiff bases (azines)	Symmetric vs asymmetric substitution	Antibacterial, antifungal	Symmetric halogenated azines outperform monomeric analogues

The comparative data assembled in Table 1 illustrate a broader point: no single substituent pattern is universally optimal. Potency against Gram-negative organisms, which possess an additional outer membrane and efficient efflux machinery, generally requires greater lipophilicity than activity against Gram-positive organisms, and derivatives optimised for one frequently underperform against the other. Selectivity against mammalian cells is inconsistently reported, and where cytotoxicity data are available the therapeutic windows are often narrower than the antimicrobial figures alone would suggest (Ceramella et al., 2022).

2.2 Anticancer and Antiproliferative Schiff Base Derivatives

Interest in Schiff bases as antineoplastic agents was catalysed by the clinical success and simultaneous limitations of cisplatin. The search for platinum alternatives with reduced nephrotoxicity and activity against resistant tumours led naturally to nitrogen-donor ligands capable of stabilising a wide range of transition metal centres (Matela, 2020).

Several mechanisms have been documented. DNA binding is the most extensively characterised: planar, extended-conjugation Schiff bases and their square-planar complexes intercalate between base pairs or bind in the minor groove, disrupting replication and transcription. Topoisomerase inhibition, tubulin polymerisation interference, generation of reactive oxygen species leading to mitochondrial membrane depolarisation, caspase-dependent apoptosis induction, and cell-cycle arrest at G1 or G2/M checkpoints have all been reported for specific series (Catalano et al., 2021).

SAR trends in this therapeutic area diverge somewhat from the antimicrobial pattern. Planarity and conjugation length assume primary importance, since intercalative binding requires an extended aromatic surface. Naphthalene, anthracene, pyrene and quinoline-derived aldehydes therefore outperform simple benzaldehyde analogues in DNA-binding assays. Electron-donating substituents such as methoxy and dimethylamino, which raise the HOMO energy and increase electron density on the aromatic system, frequently improve intercalation affinity — the reverse of the antimicrobial trend. Hydroxyl groups positioned ortho to the imine enable both intramolecular hydrogen bonding and metal chelation, and their removal typically abolishes activity in salicylaldehyde-derived series.

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Metal complexation again modulates potency substantially. Copper(II) complexes are frequently the most cytotoxic, reflecting the redox accessibility of the Cu(II)/Cu(I) couple and consequent Fenton-type radical generation within the tumour microenvironment. Palladium(II) complexes, structurally analogous to platinum systems, have shown activity against cisplatin-resistant lines, while ruthenium and zinc complexes have been explored for improved selectivity profiles. Lanthanide complexes occupy a distinctive position, offering simultaneous therapeutic and diagnostic potential through their luminescent and magnetic properties (Kaczmarek et al., 2018).

Selectivity remains the central unresolved difficulty. Many reported series display cytotoxicity against normal fibroblast lines that is only two- to fivefold lower than against the target carcinoma, a margin insufficient for therapeutic development. The studies that report the most encouraging selectivity indices generally involve derivatives designed against a defined molecular target rather than screened for general cytotoxicity (Majid et al., 2022).

Table 2. Anticancer Schiff base derivatives: structural class, target and SAR trend

Structural class	Metal centre	Cell lines commonly evaluated	Proposed mechanism	SAR trend
Salicylaldehyde ONO tridentate	Cu(II), Ni(II), Zn(II)	MCF-7, HeLa, HCT-116	DNA binding, ROS generation	ortho-OH essential; Cu(II) most potent
Salen-type tetradentate	Cu(II), Mn(III), VO(IV)	MCF-7, A549	DNA cleavage, topoisomerase inhibition	Diamine bridge rigidity improves potency
Naphthaldehyde-derived imines	Free ligand and Pd(II)	A549, MCF-7	Intercalation, cell-cycle arrest	Extended conjugation increases binding constant
Isatin/indole hybrids	Free ligand	HeLa, LS174T, HCT-116	Apoptosis induction, kinase inhibition	5-Halo substitution on isatin enhances potency
Benzimidazole Schiff bases	Free ligand	Panel of solid-tumour lines	Antiproliferative, antiviral dual action	N-Alkylation modulates potency and selectivity

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Structural class	Metal centre	Cell lines commonly evaluated	Proposed mechanism	SAR trend
Thiosemicarbazone-derived ONS	Cu(II), Fe(III)	MCF-7, HepG2	Ribonucleotide reductase inhibition	Sulfur donor critical; N-terminal substitution tunes activity
Lanthanide complexes	La(III), Ce(III), Eu(III)	Various carcinoma lines	DNA binding plus imaging capability	Larger ionic radius favours higher coordination and activity
Bis-Schiff bases (azines)	Free ligand	HeLa, A549	DNA damage, G1 arrest	Symmetric aryl substitution maximises antiproliferative effect

2.3 Antioxidant, Antidiabetic and Enzyme-Inhibitory Activity

Oxidative stress underlies a wide spectrum of pathologies, and Schiff bases bearing phenolic hydroxyl groups are effective radical scavengers. Activity is typically assessed by DPPH and ABTS radical scavenging, ferric reducing antioxidant power and hydrogen peroxide scavenging assays. The dominant SAR determinant is the number and position of hydroxyl substituents: ortho-dihydroxy (catechol) arrangements outperform single hydroxyls, and para-hydroxy derivatives generally exceed meta-substituted analogues because of superior radical stabilisation through resonance. Methoxy groups adjacent to a phenolic hydroxyl, as in vanillin-derived Schiff bases, enhance activity through electron donation that stabilises the resulting phenoxyl radical (Al Zoubi et al., 2016; Yuldasheva et al., 2022).

Antidiabetic evaluation has focused principally on inhibition of α-amylase and α-glucosidase, enzymes that hydrolyse dietary carbohydrates and whose inhibition blunts postprandial hyperglycaemia. Oladipo et al. (2021) synthesised Schiff bases from 2-naphthaldehyde and substituted aromatic amines, combining crystallographic characterisation, Hirshfeld surface analysis and computational modelling with in vitro enzyme assays. The naphthalene system provided a hydrophobic anchor within the enzyme active site, while amine-ring substitution modulated potency, with several derivatives outperforming the clinical reference acarbose. This inversion of the usual reference-standard hierarchy is a recurring and encouraging feature of the Schiff base α-glucosidase literature.

Urease inhibition represents a further well-developed application. The enzyme, which contains a dinuclear nickel active site, contributes to Helicobacter pylori colonisation and to agricultural

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nitrogen loss. Rafiq et al. (2021) prepared amino-acid-conjugated Schiff bases and evaluated them against carbonic anhydrase II, α-glucosidase and urease, establishing that the amino acid side chain governs selectivity between the three targets while the aldehyde-derived aromatic substitution controls absolute potency. Sulfonamide-based Schiff bases have proven especially effective urease inhibitors, with derivatives combining halogen and hydroxyl substitution reaching submicromolar to low-micromolar inhibition well below thiourea reference values.

Bis-Schiff bases have attracted particular attention in enzyme inhibition. Gul et al. (2021) reported novel bis-Schiff base derivatives characterised through combined theoretical and experimental analysis, demonstrating that the second azomethine unit provides additional hydrogen-bonding contacts within extended active sites, and that DFT-derived electronic descriptors correlate meaningfully with measured inhibition constants.

Table 3. Antioxidant, antidiabetic and enzyme-inhibitory Schiff bases: structural determinants of activity

Activity	Assay system	Favourable structural features	Unfavourable features
Radical scavenging	DPPH, ABTS, FRAP	ortho-Dihydroxy or hydroxy-methoxy aryl; extended conjugation	Halogen-only substitution; absence of phenolic OH
α-Glucosidase inhibition	p-Nitrophenyl-α-D-glucopyranoside hydrolysis	Naphthyl or indolyl hydrophobic anchor; meta-bromo aryl	Bulky ortho substituents causing steric clash
α-Amylase inhibition	Starch–iodine method	Planar aromatic core; hydroxyl for hydrogen bonding	Excessive lipophilicity reducing solubility
Urease inhibition	Indophenol ammonia assay	Sulfonamide fragment; combined halogen and hydroxyl	Electron-donating alkyl groups alone
Carbonic anhydrase II	Esterase (p-nitrophenyl acetate)	Amino-acid conjugation; zinc-binding sulfonamide	Neutral non-coordinating substituents
Cholinesterase inhibition	Ellman method	Aromatic stacking surface; tertiary amine side chain	Rigid unsubstituted imines
Anti-inflammatory (COX/LOX)	In vitro enzyme and in vivo oedema	Coumarin or chalcone-derived fragment	Highly polar substituents limiting penetration

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Activity	Assay system	Favourable structural features	Unfavourable features
Antiglycation	Bovine serum albumin–glucose model	Bis-Schiff base architecture; free imine nitrogen	Reduced (amine) analogues showing lower activity

2.4 Coordination Chemistry, Emerging Applications and Methodological Considerations

The capacity of Schiff bases to act as versatile chelating ligands underlies much of their applied significance. Depending on donor-atom arrangement they stabilise metal centres in unusual oxidation states and geometries, and the resulting complexes serve in catalysis, materials science and sensing as well as in medicine (Abu-Dief & Mohamed, 2015). Salen-type complexes catalyse asymmetric epoxidation, aziridination and Diels–Alder reactions; copper and vanadium complexes catalyse alcohol oxidation; and Schiff base-functionalised nanoparticles and covalent organic frameworks have found application in heterogeneous catalysis and gas storage.

In biological contexts, coordination alters pharmacological behaviour along several axes simultaneously. Lipophilicity increases, improving membrane permeation. Molecular geometry becomes constrained, which can either enhance or diminish target complementarity. Redox chemistry becomes available, particularly for copper and iron. Hydrolytic stability of the imine typically improves, since coordination of the nitrogen lone pair reduces its basicity and impedes the protonation step that initiates hydrolysis. This last point deserves emphasis: the hydrolytic lability of free Schiff bases under gastric conditions is arguably the most serious obstacle to their oral development, and complexation is among the more effective mitigation strategies alongside imine reduction and steric shielding (Uddin et al., 2020).

Anti-inflammatory applications have developed steadily, with coumarin-derived and chalcone-derived Schiff bases demonstrating cyclooxygenase and lipoxygenase inhibition supported by docking evidence of binding within the enzyme hydrophobic channel. Antiviral activity has been documented against a range of DNA and RNA viruses, with benzimidazole and thiosemicarbazone derivatives among the more promising classes (Beč et al., 2023). Neuroprotective activity through cholinesterase inhibition and antidepressant effects have been reported for vanillin-derived systems and their reduced amine analogues (Yuldasheva et al., 2022).

Polymeric and macromolecular Schiff bases constitute a distinct area. Chitosan Schiff bases, formed by condensation of the polysaccharide amino groups with aldehydes, retain biodegradability and low toxicity while gaining enhanced antimicrobial activity, and have been developed as wound dressings, antimicrobial food packaging and controlled-release matrices. The degree of substitution emerges as the critical variable: activity rises with substitution until aqueous solubility becomes limiting (Antony et al., 2019).

Several methodological cautions recur across this literature and merit explicit statement. Antimicrobial results are reported variously as zone-of-inhibition diameters, minimum

inhibitory concentrations and percentage inhibition, at concentrations and against strains that differ between laboratories, making cross-study comparison hazardous. Cytotoxicity assays vary in exposure duration and readout. Reference standards differ, and some reported "superior to standard" claims reflect an unusually weak reference rather than exceptional test-compound potency. Purity and hydrolytic stability under assay conditions are seldom verified, raising the possibility that measured activity derives partly from hydrolysis products — free aldehyde or amine — rather than the intact Schiff base. Systematic dose–response characterisation with proper controls, and stability verification in the assay medium, would substantially strengthen the evidential base of this field (Boulechfar et al., 2023).

3. Conclusion

Schiff bases have sustained more than a century of research attention because they combine synthetic accessibility with structural adaptability and genuine biological relevance. The condensation reaction that produces them is among the most economical transformations in organic chemistry, requiring no protecting groups, no expensive reagents and, increasingly, no organic solvent. This synthetic tractability has enabled the construction of very large congeneric libraries and, consequently, an unusually rich SAR literature.

The structure–activity relationships that emerge from the 2015–2021 literature are internally coherent and mechanistically interpretable. Electron-withdrawing halogen and nitro substituents on the aldehyde-derived aromatic ring enhance antimicrobial and enzyme-inhibitory potency by increasing lipophilicity and imine electrophilicity. Phenolic hydroxyl groups, particularly in ortho-dihydroxy or hydroxy-methoxy arrangements, govern antioxidant capacity through radical stabilisation. Extended conjugation and molecular planarity favour DNA intercalation and antiproliferative activity, where electron-donating substituents that raise HOMO energy paradoxically outperform the electron-withdrawing groups favoured in antimicrobial series. Heterocyclic amine fragments supply target-specific recognition. Bis-Schiff architectures frequently deliver superadditive activity through additional binding contacts. Transition metal complexation amplifies potency across nearly every therapeutic category, with copper(II) most consistently effective owing to combined lipophilicity enhancement and redox-mediated oxidative damage.

The transition to green synthetic methodology has been one of the clearest advances of the review period. Microwave irradiation, ultrasonication, mechanochemical grinding, natural-acid catalysis and solvent-free conditions now constitute a mature and widely validated alternative to conventional reflux, delivering shorter reaction times, higher yields, simpler workup and markedly reduced environmental burden without sacrificing product quality.

Nevertheless, the field's translational record remains disappointing relative to the volume of published activity data. Three deficits are principally responsible. First, hydrolytic instability of the free azomethine under physiological and especially gastric conditions compromises oral bioavailability and confounds interpretation of in vitro results. Second, selectivity margins between target activity and mammalian cytotoxicity are frequently too narrow for development, reflecting the reality that many reported mechanisms — membrane disruption,

reactive oxygen species generation, DNA intercalation — are inherently non-selective. Third, the overwhelming majority of studies terminate at in vitro screening, with pharmacokinetic, toxicological and in vivo efficacy data almost entirely absent. Closing these gaps, rather than further expanding the already vast catalogue of screened derivatives, represents the more valuable direction for the field.

4. Future Work

Several priorities follow directly from the limitations identified above.

Stability engineering. Systematic investigation of strategies to stabilise the azomethine linkage should take precedence. Reduction to the corresponding secondary amine, steric shielding through ortho substitution, conformational locking via intramolecular hydrogen bonding, incorporation of the C=N bond into a heterocyclic ring, and metal coordination each offer partial solutions with differing pharmacological consequences. Comparative studies quantifying the stability–activity trade-off across a matched series would be genuinely informative and are currently lacking.

Target-directed design. The field would benefit from a decisive shift away from phenotypic screening towards rational design against defined molecular targets with available structural data. Docking-guided optimisation, structure-based design using co-crystal structures where obtainable, and confirmatory biophysical binding measurement — surface plasmon resonance, isothermal titration calorimetry, thermal shift assay — would place mechanistic claims on considerably firmer ground than docking scores alone currently permit.

Selectivity and safety profiling. Routine inclusion of non-malignant control cell lines, calculation and reporting of selectivity indices, and haemolysis assays for compounds intended for systemic use should become standard practice rather than occasional additions. Early ADMET assessment, both computational and experimental, would allow unpromising series to be discontinued before further synthetic investment.

In vivo translation. Progression of the most promising derivatives into animal models is the most consequential outstanding requirement. Pharmacokinetic characterisation, acute and subchronic toxicity evaluation, and efficacy testing in relevant disease models would establish whether the in vitro promise of this class is genuinely translatable.

Computational and data-driven approaches. The accumulated Schiff base activity literature is now sufficiently large to support machine learning approaches. Curated datasets combining structural descriptors with standardised activity measurements could yield quantitative SAR models with genuine predictive power, accelerating design and reducing synthetic effort. Realising this potential depends on improved reporting standardisation, which the community should pursue collectively.

Hybrid and delivery strategies. Molecular hybridisation, in which the Schiff base pharmacophore is conjugated to a second bioactive fragment, offers a route to multi-target agents suited to complex diseases. Complementarily, nanoparticle encapsulation, liposomal formulation and polymer conjugation could address both the stability and the selectivity limitations simultaneously, delivering intact Schiff bases preferentially to target tissues.

Sustainable scale-up. Green synthetic methods validated at milligram scale require demonstration at preparative and pilot scale, with life-cycle assessment quantifying the environmental benefit relative to conventional routes. Continuous-flow implementation of microwave and ultrasonic protocols appears a particularly promising direction.

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