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REVIEW

Bis-Indoles in Medicinal Chemistry: Synthetic Advances, Biological Activities and Emerging Pharmaceutical Applications

SHUBHAM JADHAV*, PANKAJ KAPUPARA and HITESH VEKARIYA

Pharmaceutical Chemistry Department, RK University School of Pharmacy, Rajkot-360020, India

Corresponding author: E-mail: mjshubham1995@gmail.com

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Bis-indole derivatives represent an important class of indole-based compounds with substantial structural diversity and broad pharmacological potential. The presence of two indole units, connected through direct bonds or diverse linkers, provides opportunities to modulate molecular conformation, target interactions and biological activity through systematic structural modification. This review provides a critical overview of recent advances in *bis*-indole chemistry, with emphasis on synthetic methodologies, biological activities, structure-activity relationships and emerging therapeutic applications. Conventional synthetic approaches, such as acid-catalyzed condensation, oxidative coupling and stepwise functionalization, are discussed together with more recent developments in transition-metal catalysis, multicomponent reactions, microwave-assisted synthesis, photoredox and electrochemical transformations and sustainable catalytic systems. These approaches have expanded the accessible structural diversity of *bis*-indoles and improved reaction efficiency, selectivity and, in several cases, sustainability. Biologically, *bis*-indole derivatives have been investigated across diverse therapeutic areas, including cancer, infectious diseases, inflammation, neurological and metabolic disorders. Reported mechanisms include modulation of protein kinases, topoisomerases, microtubule dynamics, inflammatory signalling, oxidative stress and drug-efflux pathways, although the strength of mechanistic evidence varies among individual compounds. Beyond conventional pharmacological applications, *bis*-indole frameworks have also been explored in photodynamic therapy, molecular imaging, drug-resistance modulation and drug-delivery systems. Despite extensive research, most *bis*-indole candidates remain at the preclinical or experimental stage. Poor aqueous solubility, limited bioavailability, metabolic instability, off-target interactions and potential toxicity remain significant barriers to clinical development. In addition, regioselective and stereoselective synthesis, scalability and reproducibility require further improvement. Future progress will depend on establishing clearer relationships among molecular structure, target engagement, biological activity, pharmacokinetic behaviour and toxicity. Integration of sustainable synthesis, medicinal chemistry, structural biology, computational modelling and data-driven approaches, supported by standardized biological evaluation, may facilitate the identification of better-characterized candidates. Such efforts could help translate the broad chemical and biological potential of *bis*-indoles into therapeutically relevant applications.

Keywords: *Bis*-indole derivatives, Medicinal chemistry, Synthetic advances, Biological activities, Pharmaceutical applications.

INTRODUCTION

Indole nucleus has long been recognized as a "privileged scaffold" in medicinal chemistry, owing to its exceptional ability to participate in diverse interactions with biological macromolecules and to confer favourable pharmacokinetic properties to small molecules [1]. Indole and its derivatives occur extensively in nature, not only as components of the essential amino acid tryptophan, the neurotransmitter serotonin and the hormone melatonin, but also as structural motifs within a wide variety of plant alkaloids, marine natural products and microbial metabolites [2]. This widespread natural occurrence, combined with structural versatility, has inspired medicinal chemists to explore indole-based frameworks as essential building blocks for drug discovery and development. Indeed, numerous clinically used drugs, such as indomethacin, sumatriptan and indole-3-carbinol derivatives, highlight the therapeutic relevance of indole scaffolds across diverse disease domains [2,3].

Within the broader family of indole-based molecules, *bis*-indole derivatives occupy a special place due to the incorporation of two indole moieties either directly connected or linked through variable spacers, heteroatoms or aromatic syst-

ems [2]. The unique arrangement of the two indole moieties enables stronger non-covalent interactions with biological systems, promoting enhanced π-π stacking, hydrogen bonding and hydrophobic associations. Furthermore, the well-defined spatial alignment of these indole units supports simultaneous multivalent attachment to enzymes, receptors and nucleic acids, which can markedly elevate biological activity compared with single-indole derivatives [4]. Due to these structural advantages, the *bis*-indole framework functions as both a valuable core for rational drug discovery and a versatile platform for designing structurally varied molecules with superior therapeutic potential.

Bis-indole derivatives exhibit exceptional biomedical significance owing to their broad spectrum of biological actions, which include anticancer, antimicrobial, anti-inflammatory, neuroprotective, antioxidant and cardioprotective effects [2,5]. Many representatives of this chemical class have delivered promising outcomes in preclinical investigations and some have advanced into early clinical assessment. Marine-origin alkaloids, particularly those obtained from *Didemnum* species and staurosporine analogues, demonstrate anticancer potential, whereas synthetic *bis*-indolylmethanes (DIMs) are observed for their hormone-regulating and chemopreventive activities [6]. The synergy of structural adaptability, strong pharmacological activity and clinical potential positions *bis*-indoles as key scaffolds in contemporary medicinal chemistry. On the synthetic front, considerable efforts have been directed toward developing practical, environmentally sustainable and broadly applicable methods for constructing *bis*-indole frameworks. The classical approaches, including oxidative coupling of indoles and electrophilic substitution reactions, established the foundation of *bis*-indole synthesis in the mid-20th century. In recent years, significant advances in transition-metal catalysis, multicomponent reactions, microwave-assisted synthesis and green chemistry have enabled the efficient preparation of structurally diverse *bis*-indole derivatives with improved yields, selectivity and atom economy [5,7]. These synthetic developments have not only expanded the chemical space of *bis*-indoles but have also facilitated the modulation of their pharmacological properties through control over linker composition, substitution patterns and functional-group orientation.

The importance of *bis*-indoles in medicinal chemistry also reflects broader trends in drug discovery, where there is growing recognition of the advantages of bivalent or dimeric scaffolds. In many cases, dimerization of bioactive pharmacohores can enhance potency, selectivity and metabolic stability while reducing the risk of drug resistance [5]. *Bis*-indole derivatives exemplify this concept by combining the inherent pharmacophoric richness of the indole nucleus with the synergistic interactions of two indole units. Their modular synthesis further enables incorporation of the *bis*-indole scaffold into other privileged molecular frameworks, resulting in the hybrid molecules with distinct therapeutic profiles [7,8]. Consequently, current investigations place strong emphasis on elucidating structure–activity relationships (SARs) and the molecular mechanisms underlying their biological effects. Comprehensive SAR studies have shown that the pharmacological performance of *bis*-indoles is strongly influenced by the nature of the linker connecting the two indole moieties, the substitution patterns on each ring and the three-dimensional geometry [9]. For example, short alkyl linkers provide conformational flexibility that can facilitate accommodation within enzyme binding pockets, whereas rigid aromatic bridges may favour DNA intercalation and enhance cytotoxic potential. Electron donating and electron-withdrawing substituents on the indole rings further modulate hydrogen bonding, electrostatic interactions and π-π stacking with biomolecular targets. Modern computational strategies, including molecular docking, QSAR analysis and molecular dynamics simulations, have provided valuable insights into these interactions and guided the rational development of highly active *bis*-indole analogues [9,10].

Beyond their synthetic accessibility and therapeutic potential, *bis*-indole systems have attracted interest in nanotechnology, materials research and supramolecular chemistry. They have been investigated as chromophoric elements for organic electronic components, fluorescent probes for cellular imaging and self-assembling units in supramolecular constructs [9,11]. These interdisciplinary applications further demonstrate the structural diversity and functional adaptability of the *bis*-indole core, which confirm its continued relevance across multiple scientific fields. Despite these advances, important challenges remain, particularly those associated with poor aqueous solubility and limited bioavailability, which can reduce pharmacological effectiveness [12]. Metabolic instability and potential toxicity are additional concerns requiring comprehensive evaluation. Addressing these limitations will require innovative synthetic strategies together with deeper investigation of pharmacokinetics, toxicological profiles and metabolic behaviour. Successful translation from preclinical discovery to clinical use will further depend on rigorous assessment of efficacy, safety and drug-like properties [11-13]. Against this background, the present review provides an integrated account of recent advances in *bis*-indole chemistry, focusing on the synthetic methodologies, biological activities and pharmaceutical applications.

Moreover, the increasing convergence of *bis*-indole research with next-generation technologies, for example, artificial intelligence, high-throughput screening and precision drug, offers new opportunities for discovery. These approaches can accelerate the identification of new *bis*-indole candidates, optimize drug-like properties and broaden their therapeutic applications. In view of the global challenges posed by cancer, infectious diseases and neurodegenerative disorders, *bis*-indole derivatives remain promising candidates for addressing critical medical needs and may contribute to the future development of medicinal chemistry [8,13].

Synthetic advances in *bis*-indole derivatives: As the indole ring consists of a fused benzene-pyrrole system and represents a privileged pharmacophore widely present in natural alkaloids, therapeutic agents and functional materials. Linking two indole units through direct C–C or C–N bonds, aliphatic chains, heteroatoms or aromatic spacers affords structurally diverse *bis*-indole frameworks with tunable electronic, steric and biological properties [14]. Early synthetic investigations were inspired by naturally occurring *bis*-indole alkaloids such as *bis*-indolylquinones, flinderoles and staurosporine analogues. Initial routes generally involved sequential functionalization of indole rings followed by condensation or

coupling. These procedures frequently required several synthetic steps and provided limited control over regioselectivity. The development of catalytic reactions and one-pot procedures subsequently offered shorter and more adaptable routes to structurally complex *bis*-indole systems [5,14]. Also, their synthesis, particularly for unsymmetrical and stereochemically defined structures, remains challenging due to the need for precise regioselectivity, chemoselectivity, stereochemical control, high atom economy and scalability [15].

Early conventional approaches were often associated with harsh reaction conditions, modest yields, lengthy synthetic steps and limited structural diversity [5]. The development of transition metal-based catalysis, multicomponent reactions and process-intensification techniques has expanded the synthetic scope of these compounds. Transition-metal-catalyzed cross-coup-ling permits the controlled formation of C–C and C–N bonds, microwave irradiation reduces reaction times and multicomponent reactions provide concise routes to structurally diverse derivatives [6]. Similarly, green-chemistry approaches based on safer solvents, catalytic reagents, solvent-free conditions and recyclable catalytic systems have further improved the practical and environmental profile of *bis*-indole synthesis [7].

Classical synthetic approaches

Acid-catalyzed condensation: Acid-catalyzed condensation of indoles with aldehydes or ketones is one of the simplest routes to *bis*(indolyl)methane derivatives. The electrophilic substitution generally occurs at the C-3 position of indole, followed by formation of the second C–C bond. Early procedures employed Brønsted acids such as hydrochloric, sulfuric and acetic acids, but polymerization, side reactions and limited selectivity restricted their broader use [16,17]. Lewis acids such as $FeCl_3$, $ZnCl_2$, $AlCl_3$ and $BiCl_3$ were later introduced to improve conversion and selectivity. Solid acids, zeolites, silica-supported catalysts and montmorillonite K10 clay provided heterogeneous alternatives with advantages in catalyst recovery and reuse [18,19].

Oxidative coupling: Direct oxidative coupling provides access to C–C- or C–N-linked *bis*-indoles from relatively simple indole precursors without prior installation of coupling groups. Ferric chloride, iodine and cerium(IV) ammonium nitrate (CAN) have been used in early dimerization reactions [17,20]. Uncontrolled oxidation, regioselectivity problems and competing side reactions limited some of these procedures. The use of milder oxidants and catalytic systems has improved reaction control and reduced the environmental hazardousness associated with conventional oxidative methods [21].

Stepwise functionalization and coupling: Sequential functionalization of one indole followed by coupling with a second indole derivative provides better control over substitution patterns. Halogenation at the C-3 position, often with *N*-bromosuccinimide (NBS), followed by transition-metal-mediated coupling is a representative strategy. Although these routes can require multiple operations, they permit the incorporation of diverse functional groups and substitution patterns [22].

Despite their utility, the above-mentioned classical synthetic methods are often limited by poor regioselectivity, the use of hazardous reagents, low atom economy, limited scalability and difficulties in synthesizing structurally complex, natural product-inspired frameworks [21-23]. These limitations have encouraged the development of more selective, efficient and sustainable catalytic methods.

Transition metal-catalyzed approaches: Transition-metal catalysis has expanded the synthetic scope of *bis*-indole chemistry through selective C–C and C–N bond formation, improved functional-group tolerance and shorter reaction sequences [14]. Palladium, copper, iron, nickel and ruthenium catalysts have been investigated for cross-coupling, oxidative coupling and C–H functionalization reactions.

Palladium-catalyzed strategies: Palladium-catalyzed Suzuki-Miyaura and Heck reactions provide reliable routes to C–C linked *bis*-indoles. The coupling of halo-indoles with indolylboronic acids or indole-derived olefins enables contr-olled construction of substituted *bis*-indole frameworks. For instance, Suzuki-Miyaura coupling of 3-bromoindole with indolylboronic acids affords 3,3′-*bis*-indoles under relatively mild conditions [15]. Palladium-mediated oxidative C-H coupling has provided direct routes to C-2- and C-3-linked products, reducing the need for pre-functionalized substrates [5].

Copper-catalyzed approaches: Copper offers an economical alternative to palladium for several *bis*-indole transformations. Ullmann-type reactions between haloindoles and indolylamines enable C–N bond formation, while copper-catalyzed oxidative coupling with molecular oxygen or air provides a comparatively sustainable route to selected indole dimers [7].

Iron- and nickel-catalyzed strategies: Iron and nickel catalysts have attracted interest as earth-abundant alternatives to precious-metal systems. Iron-mediated oxidative coupling can facilitate direct bond formation under relatively mild conditions, while nickel catalysts have been employed in C–H activation and directed indole dimerization [16]. Their lower material cost and complementary reactivity make these metals attractive for scalable synthetic development.

Ruthenium-catalyzed C–H activation: Ruthenium(II) complexes have been applied to C–H activation and oxidative coupling of indoles. Reactions employing *tert*.-butyl hydroperoxide (TBHP) or air as the oxidant have afforded 3,3′-*bis*-indoles under mild conditions with useful substrate tolerance [18].

Multicomponent and Green synthetic strategies

Multicomponent reactions: Multicomponent reactions offer concise routes to complex *bis*-indole structures by combining three or more starting materials in a single step. One-pot condensation of indoles, aldehydes and a third nucleophile provides access to structurally varied *bis*(indolyl)methanes. Both homogeneous and heterogeneous catalytic systems have been developed, with advantages in step economy and library synthesis [17].

Microwave-assisted synthesis: Microwave irradiation has also become a useful tool for accelerating the *bis*-indole synthesis. Acid-catalyzed condensation reactions that require several hours under conventional heating can often be completed within minutes under microwave conditions. Reduced reaction times, lower solvent consumption and improved energy

efficiency make this approach attractive for rapid synthesis and library generation [14].

Ionic liquids and deep eutectic solvents: Ionic liquids (ILs) and deep eutectic solvents (DESs) provide alternative reaction media for sustainable *bis*-indole synthesis. Acidic ILs can serve as both solvent and catalyst in indole-aldehyde condensation, while DES-based systems have been explored for oxidative coupling under mild and recyclable conditions [15]. Their low volatility and potential for recovery support their use in greener synthetic processes.

Heterogeneous catalysis and solid-supported methods: Zeolites, mesoporous silica, supported Lewis acids and magnetic nanoparticles have been investigated as heterogeneous catalysts. Such systems facilitate catalyst separation and reuse while reducing metal contamination of the reaction products. Montmorillonite K10, for example, can catalyze solvent-free condensation of indoles with aldehydes, while magnetic nanoparticle-supported catalysts permit separation by an external magnetic field [5].

Asymmetric and stereoselective synthesis: Control of stereochemistry remains an important consideration in *bis*-indole synthesis, particularly when the resulting compounds contain stereogenic centres that influence biological activity. The organocatalytic and metal-mediated methods have provided routes to optically enriched derivatives.

Organocatalytic strategies: Chiral organocatalysts such as proline derivatives and chiral phosphoric acids have been employed in enantioselective reactions of indoles with aldehydes. Hydrogen-bonding and ion-pairing interactions between the catalyst and substrates can provide asymmetric induction while avoiding metal catalysts [7].

Chiral metal catalysts: Rhodium-, palladium- and iridium-based complexes containing chiral ligands have been investigated for enantioselective C–H activation and oxidative coupling. Appropriate catalyst and ligand selection can provide high stereochemical control, although substrate scope and reaction optimization remain important considerations [16].

Photoredox and electrochemical methods: Visible-light photoredox catalysis has opened mild pathways for oxidative indole coupling. Photocatalysts such as $Ru(bpy)_3Cl_2$ and $Ir(ppy)_3$ can mediate single-electron-transfer processes under visible light, enabling indole dimerization under relatively mild conditions. Electrochemical oxidation provides another approach in which electrical current replaces conventional chemical oxidants, reducing the requirement for stoichiometric oxidizing reagents [18]. These methods are particularly relevant to current efforts toward cleaner and more energy-efficient synthesis.

Structural biology and computational design: The structural biology has provided insight into the molecular recognition of *bis*-indole compounds. X-ray crystallography, NMR spectroscopy and cryo-electron microscopy have been used to examine ligand-binding conformations and interactions with biological macromolecules. The two indole rings can participate in hydrogen bonding, π-π interactions and hydrophobic contacts within binding sites. Molecular docking, molecular dynamics and other computational methods counterpart the experimental structural studies by assisting binding site analysis, affinity prediction and pharmacophore refinement [8]. These methods support structure–activity relationship studies and facilitate the design of derivatives with improved potency and selectivity.

Biological and therapeutic potential of *bis*-indoles: The therapeutic relevance of *bis*-indole derivatives arises from the chemical properties of the indole nucleus and the structural flexibility gained by linking two indole units. The fused benzene-pyrrole system provides electron density, planarity and stability, enabling hydrogen bonding, π-π interactions and recognition of tryptophan-related binding sites [1,2]. Connecting two indole moieties through direct bonds or molecular spacers creates a framework capable of multiple target interactions, while variations in linkers and substituents allow tuning of binding affinity, selectivity and physico-chemical properties [1-3].

Naturally occurring *bis*-indole alkaloids such as violacein, rebeccamycin and staurosporine have provided important templates for medicinal chemistry. Their diverse biological profiles have encouraged the preparation of synthetic analogues with modified substituents, linkers and pharmacophores [24]. The resulting compounds have been investigated against cancer, bacterial and fungal infections, viral diseases, inflammation, neurological disorders, metabolic abnormalities and several other disease conditions.

Anticancer activity: Cancer is one of the major areas of *bis*-indole research, with these compounds acting on several processes involved in tumour growth and survival, such as cell-cycle progression, DNA replication, angiogenesis, apoptosis and kinase-mediated signalling [4]. Their biological activity is influenced by the substitution pattern and the nature of the linker connecting the two indole units. Reported mechanisms include DNA intercalation, topoisomerase inhibition, disruption of microtubule dynamics, protein kinase inhibition and activation of mitochondrial and caspase-dependent apoptotic pathways [25-28].

Staurosporine, a naturally occurring *bis*-indole alkaloid isolated from *Streptomyces* species, is an important example of a kinase-targeting scaffold. It binds to the ATP-binding site of protein kinases and has been widely used as a biochemical probe and lead structure in kinase research [4,29]. Its broad kinase inhibition and limited selectivity restricted direct clinical application [30]. The structural modification of the staurosporine framework led to derivatives with improved activity profiles against protein kinase C (PKC), cyclin dependent kinases (CDKs) and selected tyrosine kinases [24,31-33]. Midostaurin, a structurally related derivative, subsequently entered clinical use for acute myeloid leukemia (AML) [34]. Other naturally occurring *bis*-indole alkaloids, such as arcyriaflavin, have likewise provided useful templates for anticancer drug development [35].

Rebeccamycin and its analogues represent another important group of anticancer *bis*-indoles. These compounds inhibit topoisomerase I by stabilizing the DNA–topoisomerase I cleavable complex, resulting in DNA damage and apoptotic cell death [24,31]. Modification of the sugar moiety and indole substituents can influence DNA binding and topoisomerase selectivity. Edotecarin, a rebeccamycin analogue, progressed to clinical trials for solid tumours, supporting the therapeutic relevance of this structural class [36].

Tubulin represents another target of *bis*-indole anticancer agents. Compounds such as 2,2′-*bis*-indolyl disulfides interfere with microtubule polymerization and can induce cell-cycle arrest at the G2/M phase, followed by programmed cell death [26,32]. Activity reported in selected multidrug-resistant cancer models makes these compounds of interest in the search for agents, which can retain efficacy when conventional therapies become less effective [37].

Synthetic *bis*-indolylmethanes (BIMs), particularly 3,3′-diindolylmethane (DIM), have been investigated in breast, prostate, colon and pancreatic cancer models. Their reported effects include modulation of estrogen metabolism androgen-receptor signalling, detoxification pathways and apoptotic mechanisms [3,5,38,39]. DIM, a dietary metabolite of indole-3-carbinol, has reached clinical investigation as a potential chemopreventive agent [40]. Other *bis*-indole derivatives influence mitochondrial apoptosis, death-receptor signalling, autophagy, VEGF signalling and matrix metalloproteinases, providing additional mechanisms for limiting tumour growth, angiogenesis and metastatic progression [41-45].

Few natural marine-derived *bis*-indoles, for examples, lyngbyabellins and caulerpins, have attracted interest for their cytotoxic effects against different cancer cell lines [33,46]. Their halogen substituents, extended conjugated systems and complex stereochemical features can influence membrane permeability and interactions with cellular targets. These structural characteristics make marine *bis*-indole alkaloids useful starting points for natural-product-inspired anticancer drug design.

Resistance to anticancer drugs can occur when cancer cells reduce drug accumulation, alter drug targets or evade apoptosis, leading to reduced treatment response. Some *bis*-indole derivatives have been studied as chemosensitizers that inhibit ATP-binding cassette (ABC) transporters, particularly P-glycoprotein and MRP1, thereby increasing the intracellular accumulation of anticancer drugs [47,48]. Their combined effects on cancer cells and drug-efflux pathways make *bis*-indoles of interest for the treatment of drug-resistant tumours.

Antibacterial, antiviral and antifungal activities: *Bis*-indole derivatives have attracted interest as potential antimicrobial agents against both Gram-positive and Gram-negative bacteria and a range of pathogenic fungi. Their antibacterial activity has been associated with disruption of bacterial membranes, inhibition of DNA gyrase and topoisomerase IV and interference with quorum-sensing pathways involved in bacterial communication and biofilm formation [6,7,31-33,46,49,50-52]. These multiple effects may affect bacterial growth as well as processes that contribute to persistence and virulence [41-45].

Marine-derived hamacanthins are of particular interest for their activity against bacterial efflux mechanisms and their potential to enhance the action of conventional antibiotics [10,11]. Several *bis*-indolylmethane derivatives have been investigated against resistant pathogens, such as methicillin resistant *Staphylococcus aureus* (MRSA), vancomycin resistant enterococci (VRE) and multidrug-resistant *Pseudomonas aeruginosa* [31-33,46,49]. The inhibition of efflux pumps may increase intracellular drug accumulation and provide a useful approach for improving the activity of existing antimicrobial agents [53,54].

Antifungal activity has been reported for *bis*-indole derivatives against *Candida*, *Aspergillus* and other pathogenic fungi [55,56]. Proposed mechanisms include interference with ergosterol biosynthesis, disruption of mitochondrial function, inhibition of fungal protein kinases and chitin synthesis and induction of intracellular ROS [56,57]. The structural modification, particularly halogen substitution on the indole rings, has been explored to improve antifungal activity [50]. Activity against selected drug-resistant fungal strains has increased interest in these compounds as potential alternatives to conventional antifungal agents. Their use as antibiofilm coatings for medical devices and as topical agents for resistant skin infections represents a further area of investigation, although clinical development remains limited [58].

The antiviral activity of *bis*-indole derivatives has been investigated against HIV, hepatitis C virus (HCV), influenza and other RNA viruses [9,30,49]. Marine alkaloids such as dragmacidins and indolocarbazole derivatives related to staurosporine have attracted interest for their effects on viral enzymes, host protein kinases and virus-host interactions [30,49,59,60]. Several targets such as HIV-1 reverse transcriptase and protease, HCV NS3 protease and RNA-dependent RNA polymerase and influenza viral RNA polymerase [59-62]. Recently *bis*-indole derivatives were also examined against the SARS-CoV-2 main protease (M^{pro}), with molecular modelling and *in vitro* studies providing preliminary support for their antiviral potential [63,64].

Anti-inflammatory and antioxidant activities: The inflammation and oxidative stress are closely linked to cancer, metabolic disorders, cardiovascular diseases and neurodegenerative conditions. *Bis*-indole derivatives have been investigated as modulators of nuclear factor-κB (NF-κB), cyclooxygenases (COX-1 and COX-2) and inducible nitric oxide synthase (iNOS) [9-11,65]. DIM has been widely studied for its ability to suppress NF-κB signalling and reduce the expression of inflammatory mediators such as tumour necrosis factor-α (TNF-α), interleukin-1β (IL-1β) and interleukin-6 (IL-6) [66,67]. Synthetic derivatives have been evaluated as COX-2 and iNOS inhibitors, with reduced prostaglandin and nitric oxide production reported in inflammatory models [38,68]. These effects have supported investigations of *bis*-indoles in experimental models of rheumatoid arthritis, inflammatory bowel disease and asthma [69].

The indole ring can contribute to antioxidant activity through its electron-rich aromatic system. Natural compounds such as violacein and related derivatives have been studied for their ability to scavenge reactive oxygen and nitrogen species [70,71]. Hydroxyl and methoxy substituents can alter radical-scavenging activity through hydrogen-atom transfer and resonance stabilization. Some *bis*-indole derivatives have been linked to activation of the Nrf2/antioxidant response element pathway, which regulates endogenous antioxidant defence [70,71]. The combined modulation of inflammatory signalling and oxidative stress makes these compounds of interest in disorders associated with persistent inflammation and cellular oxidative damage.

Neuroprotective and neurological applications: The structural relationship of indole-containing compounds with endogenous neuroactive molecules such as tryptophan, sero-

tonin and melatonin has encouraged investigation of *bis*-indoles in neuropharmacology. These compounds have been studied for interactions with acetylcholinesterase (AChE), monoamine oxidases, serotonin and GABA receptors and other central nervous system targets [12,13]. In experimental models of Alzheimer's disease, selected derivatives inhibit AChE and glycogen synthase kinase-3β (GSK-3β), with potential effects on tau hyperphosphorylation and β-amyloid aggregation [13,72-74].

In Parkinson's disease models, inhibition of monoamine oxidase-B (MAO-B) combined with antioxidant activity has been associated with preservation of dopamine levels and reduced oxidative damage [75,76]. Similar effects have been reported in experimental models of Huntington's disease and ischemia-reperfusion injury, where reduced oxidative stress, neuroinflammation and mitochondrial dysfunction may contribute to the observed neuroprotection [77]. Some *bis*-indole derivatives have further been investigated for their effects on dopamine- and serotonin-related pathways in models relevant to mood and sleep disorders [12,13]. Although these findings remain largely preclinical, they support further investigation of *bis*-indole scaffolds in neurodegenerative and neurological disorders.

Metabolic activities: The electron-rich indole framework contributes to the radical-scavenging activity reported for several *bis*-indole derivatives [78]. Their effects on metabolic enzymes and signalling pathways have led to investigations in diabetes, obesity and metabolic syndrome. Protein tyrosine phosphatase 1B (PTP1B) is one reported target and its inhibition may improve insulin signalling and glucose uptake [72,79]. DIM has been studied in diabetes models for its effects on insulin sensitivity and glucose regulation, while other derivatives have been evaluated for their influence on lipid parameters, such as cholesterol and triglycerides [80].

Dipeptidyl peptidase-4 (DPP-4) is another target of interest, as its inhibition prolongs the activity of incretin hormones such as glucagon-like peptide-1 (GLP-1), supporting insulin secretion and glucose regulation [81]. Some *bis*-indole derivatives have been examined for their effects on peroxisome proliferator-activated receptor-γ (PPARγ) and CCAAT/enhancer binding protein-α (C/EBPα), pathways involved in lipid metabolism and adipocyte differentiation [47,71,72,79]. Their antioxidant and anti-inflammatory properties may further contribute to the activity observed in the experimental models of diabetes and obesity.

Bis-indole derivatives have further been investigated as inhibitors of enzymes such as histone deacetylases (HDACs), aldose reductase and monoamine oxidases, extending their potential across different pathological pathways [79,82]. Their development is constrained by issues such as metabolic instability, including cytochrome P450-mediated oxidation of the indole nucleus, which may cause rapid clearance, reduced bioavailability or formation of reactive metabolites [3]. Off-target interactions and cytotoxicity reported for some derivatives highlight the need for better target selectivity and an improved therapeutic index [4].

Antiparasitic activity: Natural and synthetic *bis*-indoles have been evaluated against protozoan parasites such as *Plasmodium falciparum*, *Leishmania donovani* and *Trypanosoma cruzi* [83]. In malaria research, some derivatives interfere with heme detoxification, leading to accumulation of toxic free heme within the parasite. Compounds investigated against *Leishmania* and *Trypanosoma* have been associated with inhibition of enzymes such as trypanothione reductase and DNA topoisomerases. The presence of multiple potential targets makes *bis*-indole frameworks of interest for neglected tropical disease research [83].

Immunomodulatory activity: The effects of *bis*-indoles on immune pathways vary with molecular structure and biological context. Some natural derivatives stimulate macrophage activity, lymphocyte proliferation and cytokine production, whereas selected staurosporine-related compounds suppress T-cell activation [41,79,84]. These contrasting activities provide opportunities for investigating the scaffold in immune-related disorders. Compounds capable of modulating both inflammatory signalling and microbial or tumour growth may have particular value in conditions where immune responses contribute to disease progression.

Cardiovascular and hepatoprotective effects: Cardiovascular activity has been associated with the ability of selected *bis*-indoles to modulate oxidative stress, inflammation and endothelial function [85]. Some derivatives protect cardiomyocytes against ischemia-reperfusion injury by limiting ROS generation and preserving mitochondrial integrity. Others influence nitric oxide signalling and endothelial responsiveness, while selected compounds possess antiplatelet activity. These properties provide a basis for investigating *bis*-indoles in hypertension, thrombosis and other cardiovascular disorders [85].

Hepatoprotective effects have been reported in experimental models of drug- and toxin-induced liver injury [85,86]. The reported responses include reduction of oxidative stress, modulation of inflammatory cytokines and restoration of endogenous antioxidant enzymes. Certain derivatives may influence cytochrome P450-mediated metabolic pathways and reduce the formation of reactive metabolites. Such findings remain primarily experimental but add another dimension to the pharmacological profile of *bis*-indole scaffolds.

Photodynamic and photosensitizing applications: The extended conjugated structures of selected *bis*-indoles provide photophysical properties, which can be exploited in photodynamic therapy (PDT). Upon irradiation with suitable wavelengths, photosensitive derivatives can generate singlet oxygen and other ROS capable of damaging tumour cells or microorganisms [87,88]. Their application has been explored in cancer therapy and microbial control, with particular interest in localized ROS generation and reduced systemic exposure. *Bis*-indole chromophores have consequently attracted attention as potential photosensitizers for therapeutic and functional applications [2].

Endocrine modulation: Hormone-dependent cancers provide another area in which structural modification of *bis*-indole scaffolds has been explored. Estrogen receptor (ER) and androgen receptor (AR) signalling are important regulators of breast and prostate cancer progression, respectively. Certain derivatives have been designed to interfere with these pathways and have been investigated as selective estrogen receptor modulators or androgen-receptor antagonists [89]. Such com-

pounds may be relevant to breast cancer, osteoporosis and castration-resistant prostate cancer, although their therapeutic value depends on achieving an appropriate balance between receptor activity and selectivity.

Epigenetic and gene-regulatory effects: The epigenetic regulation has emerged as another potential target area for *bis*-indole derivatives. Abnormal DNA methylation, histone modification and non-coding RNA regulation contribute to the development and progression of several diseases, particularly cancer. Some *bis*-indole analogues have been investigated as inhibitors of DNA methyltransferases and histone methyltransferases, while others influence histone acetyltransferase activity [90]. These properties make the scaffold relevant not only to therapeutic development but to the design of chemical probes for studying epigenetic pathways.

Gut microbiome and gut–brain axis: The interaction between small molecules and the gut microbiome represents an emerging area of *bis*-indole research. Early investigations indicate that selected derivatives may influence microbial growth and metabolic activity, with possible effects on the balance between beneficial and pathogenic bacterial populations [87]. Microbial metabolites can influence host metabolism, immune responses and neurological signalling, providing a possible connection between *bis*-indole activity and the gut-brain axis. However, research on the effects of *bis*-indoles on the gut microbiome is still limited and their long term impact on microbial balance and host health needs further study. Their ability to influence microbial populations, inflammatory responses and neuronal signalling may be relevant to metabolic, gastrointestinal and neuropsychiatric disorders [87].

Wound healing, tissue regeneration and age-related applications: The combination of anti-inflammatory, antioxidant and antimicrobial properties has encouraged investigation of *bis*-indoles in wound healing and tissue regeneration [91]. Selected compounds have been associated with fibroblast proliferation, collagen deposition and angiogenic responses in experimental models. Such effects may support tissue repair while limiting microbial growth and oxidative damage at the wound site. The role of *bis*-indoles in cellular ageing has received preliminary attention through their effects on oxidative stress, mitochondrial function and cellular senescence [92]. Some derivatives have been investigated for modulation of sirtuin pathways involved in mitochondrial biogenesis, metabolic regulation and cellular longevity. Most of these findings remain at the experimental stage and require validation in appropriate biological and clinical models.

Bone health: Preliminary studies have linked selected *bis*-indole derivatives with processes involved in bone formation and resorption [93]. Some compounds promote osteoblast differentiation and mineralization, while others may suppress osteoclast-mediated bone loss. Proposed mechanisms include modulation of Wnt/β-catenin and RANKL/OPG signalling, both of which have important roles in bone homeostasis. These observations provide an initial basis for exploring *bis*-indoles in osteoporosis and other skeletal disorders.

Modulation of drug resistance: Resistance modulation represents a recurring theme across the biological applications of *bis*-indoles. In microorganisms, inhibition of bacterial, fungal or parasitic efflux pumps may increase intracellular retention of conventional therapeutic agents [53]. In cancer cells, interference with P-glycoprotein and MRP1 can enhance the accumulation and activity of anticancer drugs [47,48]. Such effects support the development of *bis*-indoles as resistance modifying agents rather than solely as direct cytotoxic or antimicrobial compounds.

Rare and neglected disease applications: The pharmacological scope of *bis*-indoles has extended into selected rare and neglected conditions. Preliminary studies have examined their potential in cystic fibrosis through modulation of chloride-channel activity and mucus properties, while other derivatives have been investigated in sickle cell disease for effects on oxidative stress and haemoglobin polymerization [94]. These applications are still at an early stage, but they illustrate the broad range of biological processes that can be explored through structural modification of the *bis*-indole framework.

Drug-development challenges and future perspective: Despite the broad pharmacological profile of *bis*-indole derivatives, several properties continue to limit their progression toward clinical application. Poor aqueous solubility can restrict absorption and oral bioavailability, while rapid oxidative metabolism may shorten systemic exposure or generate reactive metabolites [95,96]. The planar aromatic character of some derivatives can contribute to strong DNA binding and non-specific interactions, raising concerns about toxicity, particularly for compounds designed as DNA-intercalating agents [97]. Nanoparticle encapsulation, liposomal formulations and prodrug design are being investigated to improve solubility, stability, bioavailability and tissue distribution. The structural modification remains important for separating desired biological activity from non-specific toxicity.

The wide range of reported activities illustrates the adaptability of the *bis*-indole framework across different biological targets and disease models. Its future development will depend less on expanding the number of reported activities and more on establishing well-defined molecular mechanisms, improving selectivity, addressing pharmacokinetic limitations and validating promising compounds in relevant *in vivo* models. Integration of synthetic chemistry, structural biology, computational design and targeted drug-delivery strategies can provide a stronger basis for translating *bis*-indole chemistry into clinically useful therapeutic candidates.

Emerging applications: The applications of *bis*-indole chemistry now extend beyond conventional small-molecule drug discovery. Their conjugated structures and photophysical properties have attracted interest in photodynamic therapy (PDT), where selected derivatives act as photosensitizers and generate reactive oxygen species upon light activation [2,80]. *Bis*-indole-based polymers and nanoparticle conjugates have been explored for controlled drug release, improved aqueous dispersibility, bioavailability and targeted delivery [2,11]. *Bis*-indole–metal conjugates have further been investigated as fluorescent probes for diagnostic imaging and monitoring of drug distribution [80]. Some derivatives have been studied as chemosensitizers to enhance the response of tumour cells to chemotherapy or radiotherapy, particularly in drug-resistant settings [80]. Future synthetic research is likely to focus on

biocatalytic methods using oxidases and peroxidases, flow chemistry for improved reaction control and scale-up and machine-learning assisted optimization of catalysts, solvents and reaction conditions. Target-oriented design may further enable the development of *bis*-indoles against defined pathways, particularly in cancer and infectious diseases [17]. Despite the broad range of reported applications, most *bis*-indole candidates remain at the preclinical or experimental stage. Improved target selectivity, metabolic stability, bioavailability and toxicity profiles will be necessary to translate promising activities into clinically useful agents.

Challenges and future perspectives: Despite substantial progress in *bis*-indole synthesis and biological evaluation, several challenges continue to limit their development as therapeutic agents. Precise regioselective and chemoselective synthesis remains difficult, particularly for unsymmetrical and stereochemically defined derivatives. The use of hazardous oxidants, volatile organic solvents and non-recyclable catalysts can further limit the sustainability of some synthetic routes. Scale-up may be affected by catalyst cost, process safety, purification requirements and poor reproducibility, while broadly applicable methods for stereoselective synthesis of enantiomerically enriched *bis*-indoles remain limited [19].

Pharmacokinetic properties present another major barrier to clinical development. Poor aqueous solubility, low oral bioavailability and rapid metabolic degradation can reduce systemic exposure and therapeutic efficacy *in vivo*. Prodrug design, nanoformulations, lipid-based carriers and polymeric delivery systems have been explored to improve solubility, stability and drug distribution [98-100]. The broad interaction profile of some *bis*-indoles may cause off-target effects and drug-drug interactions, making rational structural modification and detailed SAR studies important for improving molecular selectivity and therapeutic safety [101-103]. Comprehensive toxicity and long-term pharmacokinetic data are still lacking for many candidates and differences in efficacy between experimental models can complicate assessment of their translational potential [104-109].

Standardized biological evaluation is needed to improve the reliability of *bis*-indole research. The consistent protocols for pharmacokinetics, toxicity and efficacy would allow more meaningful comparison between studies and improve the alignment of *in vitro*, *in vivo* and human disease models [110-113]. Intellectual property overlap and patent complexity may present additional barriers to commercialization and should be considered during the development of new derivatives [104-109]. Future synthetic research should place better emphasis on the recyclable catalysts, safer solvents, catalyst-free transformations, electrochemical and photochemical activation, mechanochemistry, continuous-flow processing and biocatalysis [114-120]. The synthetic biology and metabolic engineering may provide alternative routes to complex natural and semi-synthetic *bis*-indole scaffolds while expanding accessible chemical diversity [121-124]. The computational chemistry, artificial intelligence and machine learning can support prediction of binding affinity, ADMET properties and toxicity as well as guide lead optimization and target-based design [125-131]. The reliable chemical and biological databases containing structural, pharmacological and toxicity data can improve the accuracy of computational and data-driven drug discovery approaches [132-135].

Future pharmacological research should extend beyond traditional anticancer applications toward infectious, neurodegenerative, inflammatory and metabolic disorders [136-141]. Precision medicine and multitarget-directed ligand (MTDL) strategies may be particularly relevant for diseases involving multiple pathological pathways, while photopharmacology and conjugate-based delivery systems offer approaches for controlling drug activity and distribution [142-155].

The clinical development of *bis*-indole derivatives will ultimately depend on establishing a clearer relationship between chemical structure, biological activity, pharmacokinetic behaviour and toxicity. Better emphasis on reproducible synthesis, validated biological models and early assessment of drug-like properties can help identify the most promising candidates before costly later-stage development. Interdisciplinary research combining sustainable synthesis, molecular design, biological evaluation and data-driven approaches should provide a stronger foundation for translating the diverse pharmacological potential of *bis*-indoles into clinically useful agents [156].

Conclusion

Bis-indole derivatives represent versatile scaffolds in the medicinal chemistry, with diverse structures, flexible synthetic routes and broad biological activities. Research has identified their potential in cancer, infectious diseases, inflammation, metabolic disorders and neurological conditions. Natural *bis*-indoles have provided valuable templates for drug chemistry, while advances in synthesis have expanded the range of functionalized derivatives available for biological evaluation. Despite these advances, most *bis*-indole candidates remain at the preclinical stage and a clear gap persists between reported biological activity and therapeutic validation. Midostaurin provides an important example of successful clinical translation, while many other derivatives require further evidence of target engagement, pharmacokinetic behaviour, toxicity and long-term safety. Future studies should address these properties alongside potency during early lead optimization. Integration of synthetic chemistry, medicinal chemistry, computational modelling and biological evaluation can support the identification of better drug candidates. Rational modification of linker architecture and substitution patterns, combined with early ADMET assessment, may improve selectivity and drug like properties. AI-assisted molecular design and predictive modelling can help lead optimization when supported by experimental validation. Prodrugs and advanced delivery systems may further help overcome solubility and bioavailability limitations. Sustainable approaches such as biocatalysis, photocatalysis, electrochemical synthesis, recyclable catalysts, safer solvents and flow chemistry, offer opportunities for efficient and scalable preparation. Standardized biological evaluation and reliable chemical-biological datasets would further strengthen translational research. Future progress should focus on well-validated *bis*-indole candidates with defined mechanisms, reproducible activity, favourable pharmacokinetics and acceptable safety profiles. Such an approach can help bridge the gap between promising laboratory findings and clinically relevant therapeutic applications.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

DECLARATION OF AI-ASSISTED TECHNOLOGIES

During the preparation of this manuscript, the authors used an AI-assisted tool(s) to improve the language and no data, results or scientific conclusions were generated by AI. All analyses, interpretations and conclusions are the authors' own. The authors reviewed and edited the content and take full responsibility for the published work.

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