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Review paper

Recent advances in isatin-derived hybrids: promising multifunctional agents for drug development

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Abstract

Isatin-based hybrids have emerged as promising candidates in medicinal chemistry due to their broad biological activities and structural versatility. This review outlines recent developments (2020–2025) in the design of isatin hybrids targeting cancer, neurodegenerative diseases, bacterial and mycobacterial infections, diabetes, inflammation, and viral diseases. Rational hybridization strategies have led to compounds with enhanced potency, multitarget activity, and improved pharmacokinetic profiles. Key structural modifications, especially at the N-1, C-3, and C-5 positions of the isatin core, have been crucial in optimizing biological efficacy. Several hybrids demonstrated superior activity compared to standard drugs, alongside favorable safety and pharmacodynamic and pharmacokinetic profiles. This overview highlights the therapeutic potential of isatin hybrids as versatile scaffolds for the development of next-generation multifunctional agents across diverse clinical areas.

Key words: Isatin derivatives; drug discovery; pharmacological properties; anticancer activity; neuroprotective activity

Introduction

The persistent evolution of global health challenges, marked by the rise of multidrug-resistant pathogens, the growing burden of chronic illnesses, and the unmet needs in cancer and infectious disease therapeutics, highlight the urgent necessity for innovative pharmacological strategies (Barrenho et al., 2022; Hacker, 2024; Liang, 2020). In this landscape, the field of medicinal chemistry continues to evolve, embracing new methodologies to design compounds with improved efficacy, safety, and selectivity. One such promising strategy is molecular hybridization - a deliberate combination of two or more pharmacophores into a single framework to achieve enhanced therapeutic effects (Pinheiro et al., 2024). Among the many chemical scaffolds utilized in this approach, isatin (1*H*-indole-2,3-dione) stands out due to its structural versatility and rich pharmacological profile (Kumar et al., 2021).

Isatin, first isolated in the early 19th century from the oxidation of indigo, is an indole-based compound with a highly reactive core that allows for diverse structural modifications. It exists naturally in various plants and animal tissues, but its value lies not in its origin but in its chemical reactivity and wide-ranging biological activities (Singh and Desta, 2013). Over decades of study, isatin and its derivatives have exhibited noteworthy properties, including anticancer (Chowdhary et al., 2022),

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antibacterial (Hassan et al., 2023), antiviral (Elsaman et al., 2022), antifungal (Shu et al., 2025), anticonvulsant (Mathur and Nain, 2014), and anti-inflammatory (Cheke et al., 2022) activities. The molecular scaffold of isatin possesses several reactive centers, notably the keto groups at the C-2 and C-3 positions, the nitrogen atom at position N-1, and the aromatic ring system, all of which allow it to participate in a variety of synthetic transformations and bioactive interactions Cheke et al., 2022; (Chowdhary et al., 2022; Gandhi et al., 2021).

The pharmacological relevance of isatin is inherently tied to its ability to interact with multiple biological targets, including enzymes, receptors, and nucleic acids (Medvedev et al., 2007). These interactions are often driven by hydrogen bonding, π-π stacking, and van der Waals forces. Such a broad interaction profile is further enhanced when isatin is incorporated into hybrid molecules, where it can act either as a primary pharmacophore or as a synergistic component. This flexibility has led researchers to explore isatin-based hybrids across diverse therapeutic domains (Shu et al., 2025; Varpe et al., 2021).

The rationale behind hybridization involving isatin is both strategic and scientific. By linking isatin with other well-established pharmacophores - such as quinolines (Abdelrahman et al., 2022), triazoles (Mohite et al., 2024), thiazolidinones (Onali et al., 2025), chalcones (Ammar et al., 2017), or sulfonamides (Eldeeb et al., 2022) - the resulting hybrids often exhibit improved potency, selectivity, and even pharmacokinetic profiles (Bérubé, 2016). Importantly, these hybrids may act via dual or multi-target mechanisms, offering an advantage over single-target agents, particularly in the treatment of complex or resistant diseases (Meunier, 2008). Furthermore, hybrid molecules may reduce the likelihood of resistance development, a significant concern in antibacterial and antiviral therapy, by simultaneously interfering with multiple metabolic or replication pathways (Wang et al., 2016).

Structurally, the design of isatin hybrids depends heavily on the careful selection of linkers and the nature of the partner pharmacophores. Substituents at key positions of the isatin ring, especially N-1, C-3, and C-5, can modulate biological activity significantly (Chowdhary et al., 2022). For example, N-alkyl or N-aryl substitutions often enhance lipophilicity and membrane permeability (Cheke et al., 2022), whereas modifications at the C-3 position—such as hydrazones (Neganova et al., 2024), Schiff bases (Savitha et al., 2023), or spiro rings (Parakkal et al., 2023) - have been associated with potent activity against cancer cells and microbial pathogens. The presence of electron-withdrawing groups at the aromatic ring can further influence activity by altering electronic distribution and interaction potential with biological targets (Shu et al., 2025).

In addition to improving biological activity, hybridization may address other critical parameters in drug development. These include solubility, metabolic stability, and toxicity profiles. Many isatin hybrids have been reported to demonstrate not only enhanced in vitro activity but also favorable pharmacokinetics and reduced cytotoxicity in normal cell lines, making them strong candidates for further preclinical and clinical development (Ihmaid et al, 2021; Mancini et al., 2022; Singh and Agrawal, 2022).

The exploration of isatin-based hybrids is not merely an academic exercise, but a translational attempt aimed at addressing some of the most pressing clinical needs of our time. Whether in the realm of oncology, infectious diseases, or neurodegenerative disorders, these compounds are increasingly recognized as viable templates for next-generation therapeutics. The integration of isatin into hybrid molecules exemplifies a powerful intersection between natural product-inspired design and modern medicinal chemistry, offering a platform from which innovative and impactful drug candidates can emerge. Although several comprehensive reviews have explored the pharmacological potential of isatin derivatives, including the work of Shu et al., which primarily covers research up to 2022, there remains a need to update and refine the discussion with the latest advancements. This review aims to emphasize the most recent trends from 2020 to 2025, with a particular focus on literature published between 2023 and 2025. Special attention will be given to the development of isatin-based hybrids exhibiting anticancer, antibacterial, and antitubercular activities, as well as those targeting neurodegenerative disorders, highlighting emerging molecular designs, possible mechanisms of action, and therapeutic relevance in these critical domains.

Isatin hybrids targeting neurodegenerative diseases

In recent years, isatin-based hybrid molecules have gained considerable attention as promising candidates for the treatment of neurodegenerative disorders (NDD). By combining isatin with complementary pharmacophores, these hybrids are designed to exert synergistic or additive effects across multiple pathological pathways, including cholinesterase inhibition (Thanh et al., 2023), reduction of oxidative stress (Aftab et al., 2017), prevention of amyloid-β (Aβ) aggregation (Sagnou et al., 2020), metal ion chelation (Tamaddon-Abibigloo et al., 2024) and modulation of neuroinflammation (Wang et al., 2025). Such a multitarget-directed approach offers significant advantages over conventional single-target therapies, particularly in the context of complex neurodegenerative diseases where multiple mechanisms contribute to disease progression. Many of these hybrids also demonstrate favorable pharmacokinetic profiles, including blood–brain barrier permeability and drug-like properties, making them attractive for central nervous system (CNS) applications (Maliyakkal et al., 2024). Given their therapeutic potential, research on isatin-based hybrids has intensified, with a

growing number of studies reporting new structures with improved efficacy, selectivity, and neuroprotective effects. In the following section, we discuss the most recent examples of isatin-containing hybrids that have been developed as multifunctional agents for NDDs, highlighting their biological activities and relevance in modern drug discovery.

Recent investigations into isatin-triazoles and 3-hydroxyindole–triazole hybrids have highlighted their multifunctional potential as inhibitors of cholinesterases and Aβ aggregation. Among the isatin-based derivatives, compound 1a demonstrated remarkable potency and selectivity toward butyrylcholinesterase (BChE), exhibiting submicromolar IC_{50} values (460 nM for equine BChE and 510 nM for human BChE). Notably, compound 1b showed the most pronounced activity in inhibiting $A\beta_{42}$ self-aggregation. In comparison, the 3-hydroxyindole analogues displayed generally reduced activity; however, compound 1c retained notable BChE inhibition (IC_{50} = 2.20 μM). Molecular docking studies revealed that these hybrid molecules engage critical residues within the peripheral anionic site (PAS) of both AChE and BChE. While anti-Aβ plaque formation activity was modest, the compounds demonstrated a favorable safety profile, with no observed hepatotoxicity and minimal neurotoxicity in rat primary neurons—supporting their potential as neuroprotective cholinesterase inhibitors (Marques et al., 2020).

A series of 15 novel multi-target-directed ligands (MTDLs) incorporating s-triazine, isatin, and aniline scaffolds were synthesized as potential anti-Alzheimer's agents. Designed to combine cholinesterase inhibition, antioxidant activity, and metal chelation, these hybrids exhibited potent in vitro inhibition of AChE (IC_{50} = 0.2–734.5 nM) and BChE (IC_{50} = 0.02–1.92 μM). Compounds 2a and 2b showed the highest potency, with IC_{50} values of 0.2 and 0.7 nM for AChE and 0.03 and 0.09 μM for BChE respectively. Molecules bearing hydroxyl-substituted aniline rings also demonstrated antioxidant effects (EC_{50} = 64.2–103.6 μM). Furthermore, UV–Vis spectroscopy confirmed that compound 2b effectively chelates biologically relevant metal ions (Zn^{2+}, Cu^{2+}, Fe^{2+}). In silico studies supported the experimental findings, highlighting key interactions within enzyme active sites. These results suggest that the synthesized hybrids are promising candidates for further development as multifunctional agents in Alzheimer's disease (AD) therapy (Tamaddon-Abibigloo et al., 2024).

A novel series of isatin-linked 4,4-dimethyl-5-methylene-4,5-dihydrothiazole-2-thiol hybrids was synthesized and evaluated for AChE inhibition. Designed to interact with both the catalytic active site (CAS) and the PAS, compounds 3a and 3b emerged as the most potent (IC_{50} = 18.2 and 27.5 μM, respectively), showing activity comparable to galantamine and superior to rivastigmine. Kinetic analysis revealed that 3b acts via a non-competitive inhibition mechanism. Molecular docking confirmed its dual binding to CAS and PAS, supporting its multitarget engagement. Additionally, in silico ADME predictions highlighted favorable drug-like properties (Davis and Eckroat, 2021).

In a newly conducted study, benzylpiperidine–isatin hybrids were designed as dual-acting agents targeting two critical enzymes implicated in NDD pathology: AChE and monoamine oxidases (MAO-A/B). The rational design involved the hybridization of piperidine, known for its presence in clinically used drugs like donepezil, and isatin, a privileged scaffold with neuroprotective potential and blood–brain barrier permeability. Among the synthesized compounds, compound 4b demonstrated potent dual inhibition of AChE (IC_{50} = 0.034) and MAO-A (IC_{50} = 0.108 μM). Notably, its AChE inhibition surpassed that of donepezil. The inhibition was characterized as reversible and mixed-type for AChE, and competitive for MAO-A. Another compound, 4a, exhibited selective and competitive inhibition of MAO-B with an IC_{50} of 0.057 μM. Structure–activity relationship (SAR) analysis highlighted the influence of electron-withdrawing groups and linker length on potency and selectivity. Molecular docking and molecular dynamics (MD) simulations revealed key stabilizing interactions within the active sites of target enzymes. Furthermore, lead compounds showed no neurotoxicity in neuronal cell assays, exhibited notable antioxidant activity, and had favorable ADMET profiles in silico. The findings underscore benzylpiperidine–isatin hybrids as strong candidates for further development in the treatment of NDDs (Negi et al., 2025).

Tamaddon-Abibigloo et al. have also developed a novel series of isatin–1,3,5-triazine–benzylamine hybrids and assessed for their potential in Alzheimer's disease (AD) therapy. These compounds showed potent inhibitory activity against AChE, with IC_{50} values ranging from 0.86 to 36.30 nM, and moderate inhibition of BChE, with IC_{50} values between 0.66 and 3.88 μM. Among them, compound 5a exhibited the strongest dual inhibition, acting non-competitively on AChE and competitively on BChE. Additionally, 6c effectively inhibited amyloid β aggregation and chelated Cu^{2+} ions, a biometal implicated in AD pathogenesis. In silico studies confirmed favorable interactions with key residues in both cholinesterases, supporting their multitarget-directed potential. Overall, these hybrids represent promising candidates for further development as MTDLs targeting key aspects of AD, including cholinesterase inhibition, metal chelation, and anti-amyloid activity (Tamaddon-Abibigloo et al., 2025)

In another recent study, three series of newly designed isatin–chalcone hybrid derivatives were synthesized and evaluated for their anti-neuroinflammatory activity using BV2 microglial cells. Among them, compound 6a emerged as the most promising candidate, exhibiting strong anti-inflammatory effects with an IC_{50} of 1.6 μM and a therapeutic index of 21.6. Treatment with 6a significantly reduced the levels of pro-inflammatory cytokines TNF-α and IL-6. Molecular docking studies suggested that 6a could interact with key inflammatory targets, including

TLR4/MD2 and p38 MAP kinase. According to in silico predictions, compound 6a has a Log P value of 3.36 and a Log BB of −0.32, suggesting moderate lipophilicity and limited blood–brain barrier penetration. The results of the study emphasize the potential of isatin–chalcone hybrids as anti-inflammatory agents for NDDs (Wang et al., 2025).

Kumar et al. synthetized sixteen isatin-based hydrazone derivatives and evaluated their inhibitory activity MAOs. Most compounds showed selectivity toward MAO-B over MAO-A. Notably, 7a was the most potent MAO-B inhibitor (IC_{50} = 0.082 µM), while 7b exhibited the highest MAO-A inhibition (IC_{50} = 1.852 µM). PAMPA (Parallel Artificial Membrane Permeability Assay) assay confirmed CNS permeability. In vitro studies in LPS-treated SH-SY5Y neuroblastoma cells revealed that lead compounds reduced oxidative stress and inflammatory cytokines while enhancing antioxidant defenses. Molecular docking, dynamics, and MM-GBSA calculations supported the strong binding affinity of 7a to MAO-B. These results suggest that isatin-hydrazone derivatives, 7a represent promising candidates for the treatment of NDD such as Parkinson's disease.

Taken together, these findings position isatin-based hybrids at the forefront of next-generation neurotherapeutic research.

Isatin hybrids as antineoplastic agents

The search for novel anticancer therapies has increasingly focused on the rational design of MTDLs to address the complexity of cancer pathogenesis. Among the diverse strategies explored, isatin-based hybrid molecules have emerged as promising candidates for drug development. By combining the structural versatility of the isatin scaffold with various biologically active moieties, these hybrids can modulate multiple oncogenic pathways simultaneously. They aim to enhance antiproliferative potency, improve tumor selectivity, and reduce off-target toxicity, a major drawback of conventional chemotherapy. Structural hybridization allows these compounds to interfere with apoptosis regulation, kinase signaling and enzymatic activity, offering a comprehensive therapeutic approach. Moreover, many isatin hybrids exhibit favorable pharmacokinetic properties, supporting their progression toward advanced stages of preclinical development and highlighting their potential in modern oncology (Chowdhary et al., 2022).

Wang et al. synthetized a series of two-carbon tethered artemisinin–isatin hybrids and evaluated their antiproliferative activity against MCF-7, MDA-MB-231, and MDA-MB-231/ADR breast cancer cell lines. SAR analysis revealed that shorter linkers favored activity, and modifications at the C-3 and C-5 positions of the isatin moiety significantly influenced potency. Among the compounds, hybrid 8a demonstrated the strongest antiproliferative effect (IC_{50} = 2.49–12.6 µM), outperforming adriamycin across tested models while maintaining a favorable safety profile. In silico studies suggested that 8a targets multiple proteins, including EGFR, PIK3CA, and MAPK8, and modulates key pathways such as PI3K-Akt and MAPK signaling. Molecular docking and dynamics simulations further supported its strong interactions with critical oncogenic targets. These findings highlight hybrid 8a as a promising candidate for further development in breast cancer therapy (Wang et al., 2023).

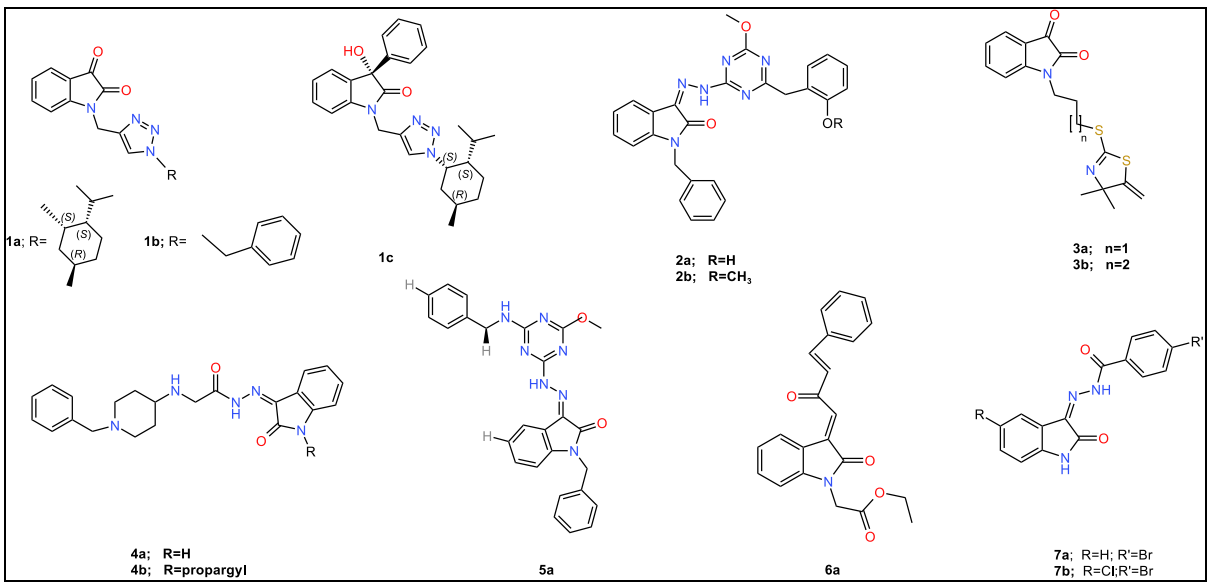

Fig. 1. Isatin derived hybrid molecules targeting neurodegenerative diseases.

Novel niclosamide–isatin hybrids were synthesized and assessed for their cytotoxicity against HepG-2, HCT-116, and MCF-7 cancer cell lines. Hybrid 9a emerged as the most potent analogue, demonstrating strong cytotoxicity and selectivity toward HCT-116 cells. Mechanistic studies indicated that 9a induces apoptosis by modulating the expression of BAX, Bcl-2, BCL-xL, and PAR-4, causing G1 phase cell cycle arrest and activating mitochondria-dependent apoptotic pathways. Molecular docking revealed that 9a binds with high affinity to the XIAP BIR2 domain, promoting caspase-3 activation. Compared to other isatin hybrids discussed, 9a notably combines strong cytotoxicity with a clear mechanistic pathway targeting intrinsic apoptotic signaling, positioning it as a particularly promising scaffold for the development of apoptosis-based anticancer therapeutics (Omran et al., 2024).

Recent progress in cancer therapy has emphasized the importance of targeting cell cycle regulation, with novel strategies including small-molecule inhibitors. In this context, a series of *N*-benzyl isatin-based hydrazones were synthesized and their antiproliferative activity against the triple-negative MDA-MB-231 breast cancer cell line and normal MCF-10A breast epithelial cells was accessed. All compounds demonstrated notable anticancer activity, with compound 10a, bearing a nitro group at the para-position, showing the most potent effect (IC_{50} = 15.8 μM). SAR analysis indicated that electron-withdrawing groups enhanced antiproliferative efficacy. Molecular docking studies revealed that compound 10a formed a key hydrogen bond with the M769 residue of the EGFR kinase domain, contributing to its strong binding affinity and superior biological activity. Molecular dynamics simulations further supported the potential of these hydrazones as promising candidates for the development of new breast cancer therapeutics (Munir et al., 2025).

The synthesized isatin-based analogues, comprising hydrazone–isatin hybrids, spiro-heterocyclic isatin derivatives, and *N*-substituted isatin conjugates incorporating bioactive moieties such as thiophene, benzothiazole, and purine rings, demonstrated notable antiproliferative activity against a range of human cancer cell lines. Compounds 11a, 11b, 11c, 11d, and 11e exhibited strong growth inhibition, particularly against the renal cancer UO-31 cell line, with compound 11c showing additional potency against leukemia and CNS cancer models. The presence of thiophene, benzothiazole, and oxathiino moieties appeared to enhance cytotoxicity, while purine-fused derivatives like compound 11f showed selective activity against CNS cancer cells. SAR analysis indicated that electron-withdrawing groups and spiro-heterocyclic systems contributed significantly to biological activity. The findings highlight the promising potential of isatin hybrids as scaffolds for developing new anticancer agents with improved efficacy profiles (Altamimi et al., 2023).

Recently, a novel series of isatin–gallate hybrids was synthesized and evaluated for their antioxidant and anticancer potential. These hybrids were constructed by coupling gallic hydrazide with various substituted isatins, aiming to harness synergistic biological activities. In vitro studies demonstrated that the hybrids exhibited moderate to strong antioxidant activity in the DPPH assay, with compound 12a (bearing a methoxy group) showing the highest potency. Cytotoxic evaluation against MCF-7, HeLa, and HCT116 cancer cell lines revealed promising antiproliferative effects, particularly for 12a, while maintaining selectivity over normal WRL-68 cells. SAR analysis suggested that electron-donating groups enhanced antioxidant capacity, while halogen substitutions influenced anticancer activity. Additionally, molecular docking studies indicated that hybrids, especially 12b and 12c, displayed favorable binding affinities toward EGFR, and moderate activity against RNA-dependent RNA polymerase, suggesting potential anticancer and antiviral applications. The results emphasize isatin–gallate hybrids as promising candidates for further optimization (Al-Mudhafar and Wadi, 2024).

Mohite et al. synthetized a series of ten isatin–1,2,3-triazole hybrids in high yields using Copper(I)-catalyzed Azide–Alkyne Cycloaddition (CuAAC). The compounds were tested against sixty human cancer cell lines. Hybrids 13a, 13b, and 13c showed significant growth inhibition (PGI > 70%) across breast, leukemia, and melanoma models, achieving mortality rates ranging from 6% to 99%. Molecular docking against cyclin-dependent kinase 2 (CDK2) supported the proposed antitumor mechanism (Mohite et al., 2024).

MARK4 is a serine/threonine kinase implicated in cancer, diabetes, and neurodegenerative diseases due to its role in cytoskeletal dynamics. In a recent study, a series of vanillin–isatin hybrids were synthesized and evaluated as MARK4 inhibitors. Among them, compound 14a demonstrated the strongest binding affinity, potent enzyme inhibition (IC_{50} = 7.16 μM), and significant antiproliferative effects against SNU-475 and C3A hepatocellular carcinoma cell lines (IC_{50} = 4.35 μM and 6.96 μM, respectively). Molecular docking and 100 ns MD simulations confirmed stable binding within the MARK4 active site, supported by strong hydrogen bonding with key residues. 14a also inhibited tau phosphorylation and reduced cell migration and induced apoptosis in HCC cells. These findings stress 14a as a potential MARK4-targeted anticancer agent (Ahmed et al., 2024).

A novel series of dihydropyrazole–isatin–dihydrothiazole hybrids was synthesized and assessed for anticancer activity. Initial MTT assays at 10 μM revealed that 2-naphthyl-substituted compounds exhibited superior antiproliferative activity across nine cancer cell lines compared to 2-thiophenyl analogs. 15a showed the most potent effects, with EC_{50} values ranging from 0.01 to 0.38 μM, particularly against H1299 lung carcinoma cells. Mechanistic studies demonstrated that 15a and 15b induced apoptosis (13.5–27% apoptotic cells) with

minimal necrosis (<1%). The results suggest that hybridization of 5-chloroisatin with diaryldihydropyrazoles through a dihydrothiazole linker offers a encouraging strategy for developing targeted anticancer agents. Further optimization is warranted to enhance their pharmacokinetic properties (Meleddu et al., 2019).

A new library of thiazolidinone–isatin hybrids was designed, synthesized, and evaluated for selective inhibition of tumor-associated carbonic anhydrase isoforms IX and XII. Using a hybridization approach, a sulfonamide Zn-binding group was combined with diverse isatin derivatives to optimize hydrophilic/lipophilic balance. Biological assays demonstrated that several compounds exhibited potent, selective inhibition of hCA IX and XII, with minimal off-target effects on hCA I and II. Notably, compound 16a, featuring a 7-fluoro-isatin moiety, displayed Ki values of 57.8 nM (hCA IX) and 44.3 nM (hCA XII), achieving high selectivity indices. Molecular docking confirmed the preferential binding of 16a to the active sites of hCA IX and XII while failing to coordinate Zn in hCA II. The study underlines thiazolidinone–isatin hybrids as promising candidates for selective cancer therapy targeting CA isoforms, although additional structural optimization is recommended to enhance potency and drug-like properties (Onali et al., 2025).

Series of isatin–pyrimidine hybrids was synthesized and evaluated for their anticancer potential. The most active compound, 17a, exhibited significant cytotoxicity against MCF-7 breast cancer cells with an IC_{50} of 12.47 μM and improved survival in a DAL mouse model. Molecular docking studies showed that 17a binds to the ATP-binding site of Heat shock protein 90 (Hsp90), forming crucial hydrogen bonds with Asn106 and Gly97 residues, thereby disrupting Hsp90's chaperone function, which is critical for cancer cell growth and survival. In silico ADME predictions indicated good drug-likeness and oral absorption properties. These results suggest that inhibition of Hsp90 is the primary mechanism of action of isatin–pyrimidine hybrids (Raju et al., 2023).

The promising preclinical outcomes of isatin-based hybrids underline their potential to overcome limitations of conventional chemotherapy and pave the way for innovative, more effective cancer treatments.

Isatin hybrids as antibacterial and antitubercular agents

The increasing emergence of antibiotic-resistant bacteria and the ongoing challenge of effective tuberculosis treatment have prompted renewed efforts to discover more efficient antimicrobial agents. Isatin-derived hybrids have attracted considerable interest in this field due to their capacity to interact with diverse microbial targets and disrupt essential biological processes. Through careful hybridization with other pharmacologically active motifs, isatin-containing molecules have demonstrated the ability to inhibit bacterial growth, impair biofilm formation, and interfere with key enzymes critical for pathogen survival. Modifications at specific positions of the isatin core often enhance spectrum of activity and selectivity, offering opportunities to address both Gram-positive and Gram-negative pathogens, as well as Mycobacterium tuberculosis. These promising results highlight the relevance of isatin hybrids in the ongoing development of new anti-infective therapeutics (Hassan et al., 2023).

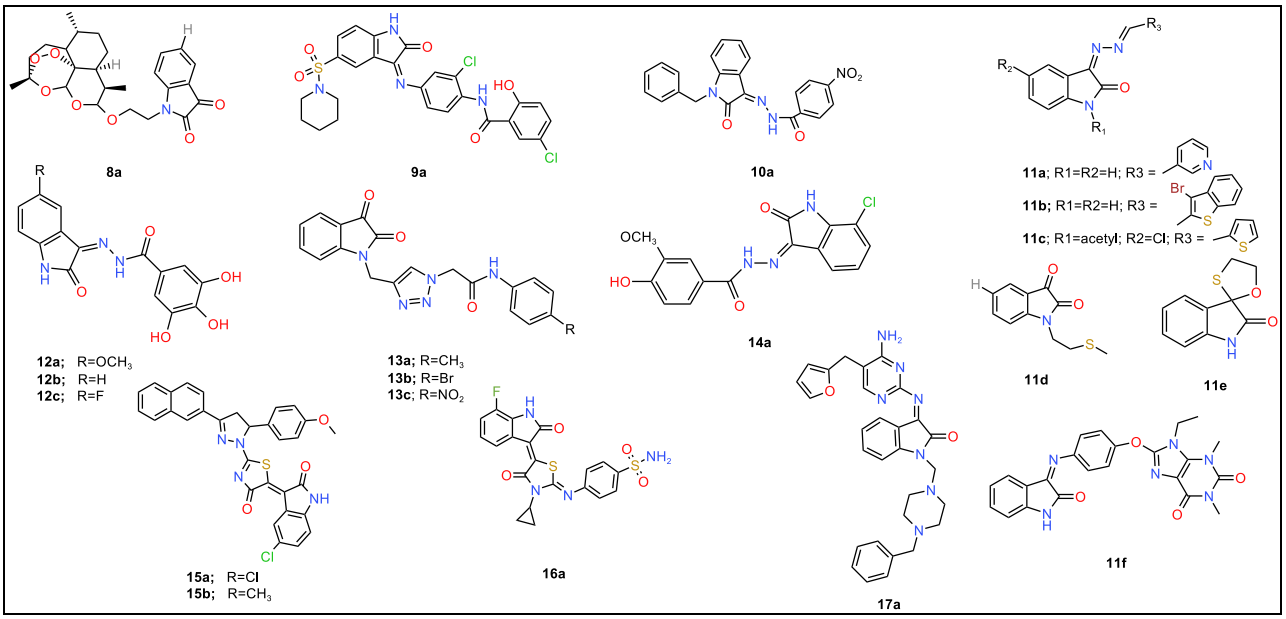

Fig. 2. Structures of isatin hybrids as anticancer agents.

A series of isatin derivatives, modified at N-1, C-3, and C-5 positions, was designed to target bacterial peptidoglycan glycosyltransferase (PGT). These modifications allowed optimized interactions with key amino acids in the PGT binding pocket. Compounds were evaluated for antimicrobial activity against *Staphylococcus aureus, Escherichia coli* and Methicillin-Resistant *S. aureus* (MRSA) strains, and for inhibition of *E. coli* PBP 1b enzymatic activity. The most potent compounds, 18a and 18b, showed MIC values of 3 μg/mL against *S. aureus* and MRSA, and strong inhibition of PBP 1b (IC_{50} = 2.4 and 3.2 μM respectively). Molecular docking confirmed favorable interactions, including hydrogen bonding and hydrophobic contacts, supporting their mechanism of action. Cytotoxicity assays on BJ normal human cells indicated selective antibacterial activity. These results underline isatin-based PGT inhibitors as promising scaffolds for the development of new antibacterial agents (Wang et al., 2021).

Recently, isatin-derived 1,2,4-triazole hybrid 19a was developed as a promising new antimicrobial agent. It exhibited excellent activity against *E. coli*, with a Minimal Inhibitory Concentration (MIC) value of 1 μg/mL, showing 8-fold greater potency than norfloxacin. Hybrid 19a demonstrated broad-spectrum antibacterial and antifungal effects and a low propensity to induce resistance. Preliminary studies indicated that 19a may inhibit bacterial growth by intercalating with DNA and potentially interacting with DNA polymerase III, thereby blocking DNA replication and exerting its antimicrobial action (Tangadanchu et al., 2021).

A series of isatin-Schiff base linked 1,2,3-triazole hybrids was synthesized using CuAAC approach. In vitro antimicrobial evaluation showed that several compounds exhibited promising activity. Among them, compound 20a demonstrated notable antibacterial potency against *Pseudomonas aeruginosa* and *Bacillus subtilis* (MIC = 0.0062 μmol/mL), and significant antifungal activity against *Aspergillus niger* (MIC = 0.0123 μmol/mL). Molecular docking studies revealed strong binding interactions of hybrids 20b and 20c with bacterial and fungal targets and molecular dynamics simulations further confirmed the stability of the ligand–protein complexes (Kumar et al., 2024).

Novel series composed of isatin–nicotinohydrazide hybrids was developed and assessed for anti-tubercular and antibacterial activity. Several compounds, particularly 5g and 5h, exhibited excellent potency against drug-susceptible and drug-resistant *M. tuberculosis* strains, with MIC values as low as 0.24 μg/mL. These hybrids also demonstrated strong antibacterial activity against bronchitis-causing bacteria, notably *Klebsiella pneumoniae*. Molecular docking studies suggested DprE1 as a likely target, with compounds 5g and 5h showing favorable binding interactions and higher docking scores compared to the co-crystallized ligand. Cytotoxicity studies revealed low toxicity against normal lung fibroblast cells, supporting their potential for further development as selective antimicrobial agents and highlighting the promise of isatin–nicotinohydrazide hybrids in combating resistant infections (Elsayed et al., 2021).

Isatin–pyrazole hydrazone conjugates were obtained and evaluated for their inhibitory activity against bacterial methionine aminopeptidases (MetAPs). Compound 22a demonstrated potent and selective inhibition of *M. tuberculosis* and *Streptococcus pneumoniae* MetAPs with nanomolar Ki values, while sparing the human counterpart. 22a also exhibited strong bactericidal activity against standard and multidrug-resistant bacterial strains, showing synergy with antibiotics and reduced MIC values compared to conventional drugs. Importantly, 22a demonstrated excellent selectivity, being non-toxic to mammalian cells, human red blood cells, and *Galleria mellonella* larvae. These findings support 22a as a promising lead for antibacterial drug development (Irfan et al., 2022).

A series of novel isatin–isoniazid hybrids was synthesized and their antimycobacterial activity against *M. tuberculosis* was examined. Several compounds exhibited potent bactericidal effects, with MIC values between 0.195 and 0.39 μg/mL, outperforming isoniazid in both in vitro and intracellular models. Lead hybrids demonstrated inhibition of mycolic acid biosynthesis by targeting InhA, requiring activation by KatG. Resistant mutant selection confirmed the same mechanism of action as isoniazid. Importantly, the hybrids displayed excellent selectivity indices and low cytotoxicity towards Vero cells and macrophages. These findings suggest that isatin–isoniazid hybrids are promising candidates for further preclinical evaluation against tuberculosis (Johansen et al., 2021).

In an effort to develop novel therapies against drug-resistant tuberculosis, a series of isatin-tethered quinoline hybrids was synthesized and biologically evaluated. Most of the synthesized compounds showed promising to potent activity against drug-susceptible, multidrug-resistant (MDR), and extensively drug-resistant (XDR) *M. tuberculosis* strains. Among them, compound 23a emerged as the most potent analogue, demonstrating MIC values of 0.06, 0.24, and 1.95 μg/mL against drug-susceptible, MDR and XDR strains, respectively. SAR analysis highlighted the significance of N-substitution and maintaining an unsubstituted C-5 position on the isatin scaffold for enhanced antimycobacterial potency. Moreover, compound 23a exhibited favorable cytotoxicity profiles, with IC_{50} values exceeding 36 μM against WI-38 non-tumorigenic lung fibroblast cells. These results suggest that isatin–quinoline hybrids, particularly 23a, represent promising leads for the development of new antitubercular agents capable of overcoming resistance mechanisms associated with current therapies.

Recent efforts have also led to the development of triazole-tethered thymol–isatin hybrids as promising antibacterial agents. Compound 24a exhibited remarkable potency against MRSA, achieving MIC of 1.9 μM. Beyond

inhibiting bacterial growth, 24a suppressed biofilm formation and attenuated virulence by targeting dehydrosqualene synthase (CrtM), thereby reducing staphyloxanthin production, as supported by molecular docking and molecular dynamics simulations. In vivo evaluation using a *G. mellonella* infection model demonstrated that 24a provided 90% survival at 10 mg/kg without detectable toxicity. The findings further underscore the therapeutic promise of isatin-based hybrids against multidrug-resistant bacterial infections.

The continuous emergence of resistant pathogens highlights the critical role of isatin-based hybrids as innovative tools in the future development of antibacterial and antitubercular therapies.

Miscellaneous pharmacological activities of isatin hybrids

Beyond their well-established anticancer and antimicrobial effects, isatin-based hybrids have been increasingly recognized for a broad range of other pharmacological activities. Recent studies have highlighted their potential as antioxidants, anti-inflammatory agents, antiviral candidates, and enzyme inhibitors targeting metabolic and inflammatory pathways. Their flexible structure, combined with rational hybridization strategies, enables them to interact with diverse biological targets, often resulting in compounds with favorable safety profiles and promising efficacy. In this section, we explore the expanding pharmacological potential of isatin-based hybrids across a variety of emerging therapeutic areas (Cheke et al., 2022; Mathur and Nain, 2014).

Diabetes mellitus remains one of the leading causes of morbidity worldwide, and the inhibition of carbohydrate-hydrolyzing enzymes such as α-amylase and α-glucosidase offers an effective therapeutic strategy for managing postprandial hyperglycemia. In vitro evaluations of isatin–hydrazide hybrids revealed significant inhibitory activities, with α-amylase IC_{50} values typically ranging from 12 to 20 µg/mL and α-glucosidase IC_{50} values between 13 and 26 µg/mL. These activities were notably superior compared to the standard drug acarbose, which demonstrated an IC_{50} value of 36.2 µg/mL for α-amylase inhibition. Several derivatives exhibited dual inhibitory profiles, achieving approximately two-fold greater potency in comparison to acarbose. Collectively, these findings suggest that isatin–hydrazide hybrids represent promising candidates for the development of new antidiabetic agents targeting enzymatic regulation of glucose metabolism (Abbasi et al., 2021).

A series of novel (*Z*)-isatin aroylhydrazones was synthesized and evaluated for anticonvulsant potential. In vivo studies using maximal electroshock (MES) and pentylenetetrazole (PTZ) models in mice demonstrated that while most compounds were ineffective against chemically induced seizures at 100 mg/kg, several showed significant protection against electrically induced seizures at 5 mg/kg. Notably, *N*-methyl analogs 25a and 25b provided 100% protection at the lower dose. Molecular docking and distance mapping suggested their potential interaction with VGSCs and $GABA_A$ receptors. Additionally, cytotoxicity assays confirmed that compounds 25a and 25b were non-toxic toward SH-SY5Y neuronal and Hep-G2 hepatic cells at conventional doses, highlighting their promise as safe and potent anticonvulsant candidates (Emami et al., 2021).

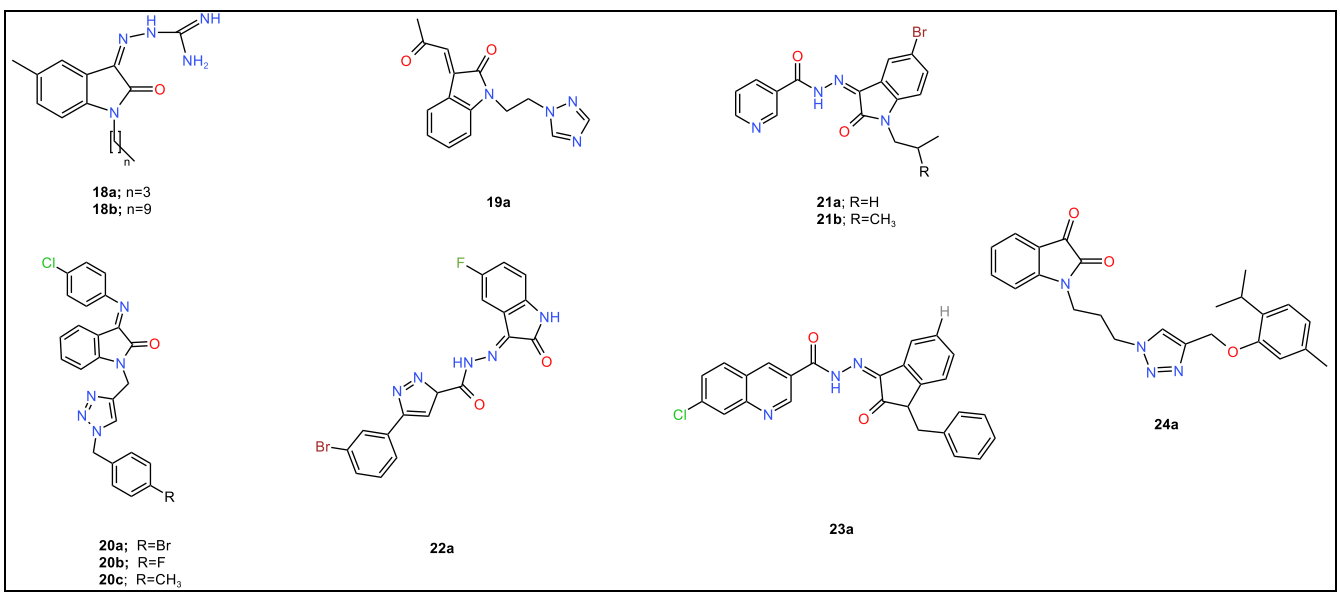

Fig. 3. Structures of isatin hybrids as antibacterial or antitubercular agents.

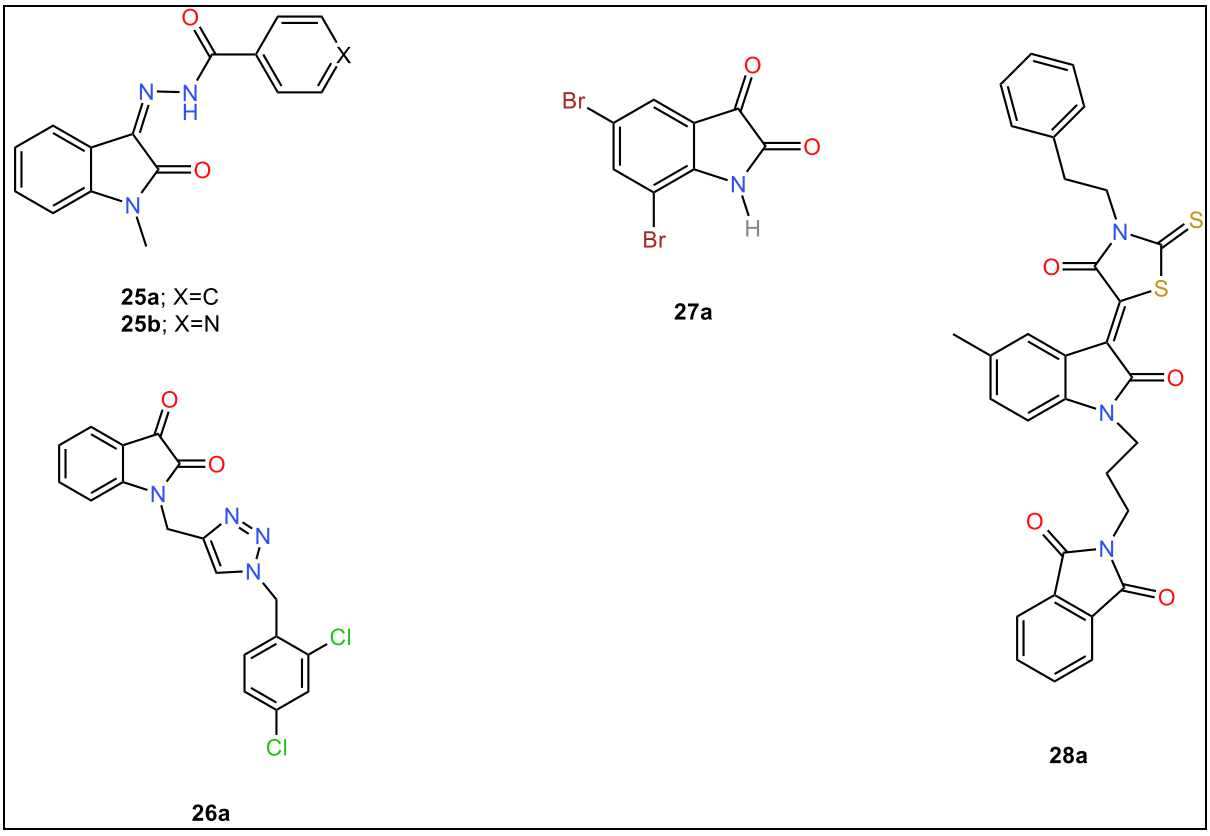

Fig. 4. Isatin hybrids with miscellaneous activities.

Isatin-1,2,3-triazole conjugates were evaluated for their anti-inflammatory potential in an in vitro model using LPS-stimulated THP-1 cells. Among the tested compounds, 26a significantly reduced the secretion of proinflammatory cytokines TNF-α, IL-6, and MCP-1. In gene expression studies, 26a substantially downregulated the transcription of TNF-α, IL-6, and MCP-1 genes relative to LPS-induced cells. The most pronounced effects were observed at the lower tested concentration (4 mM), suggesting that 26a effectively inhibits both cytokine secretion and gene expression linked to inflammation. These findings propose compound 26a as a promising anti-inflammatory agent with potential for further development (Niranjana Kumar et al., 2025).

A library of 27 isatin-based derivatives, including newly synthesized 3-hydroxy bis-oxindoles and isoindigos, was assessed for antiviral activity against SARS-CoV-2 using a phenotypic assay in Vero CCL-81 cells. Initial screening identified compound 27a (not a true hybrid molecule, but rather a 5- and 7-bromo-substituted isatin) as most active (EC_{50} = 3.6 μM), although it exhibited cytotoxicity (CC_{50} = 4.1 μM), leading to a low selectivity index. Overall, simple halogenated and acetylated isatin structures demonstrated superior antiviral profiles compared to more complex bis-oxindole derivatives (Lima et al., 2023).

The design of novel molecular hybrids combining isatin, rhodanine, and phthalimide scaffolds has led to promising advances in anti-inflammatory and analgesic drug discovery. Among a synthesized series compound 28a demonstrated remarkable pharmacological performance, exhibiting potent COX-2 inhibition and significant suppression of pro-inflammatory cytokines IL-6 and TNF-α. Notably, 28a showed a superior selectivity index (SI = 1.11) compared to indomethacin (SI = 0.67), indicating preferential COX-2 targeting and reduced gastrointestinal toxicity, as evidenced by a markedly lower ulcer index. In vivo toxicological studies confirmed its favorable safety profile, with no mortality or adverse effects observed at therapeutic doses. Overall, compound 28a emerges as a robust lead candidate as a therapeutic agent for pain and inflammation management (Brown et al., 2025).

Schiff bases incorporating isatin and nonsteroidal anti-inflammatory drugs (NSAIDs) represent an important class of hybrid molecules designed to achieve dual or enhanced biological activity. By linking isatin, to NSAID derivatives such as ibuprofen and mefenamic acid, researchers have successfully generated multifunctional compounds targeting key enzymes involved in metabolic and infectious diseases. These hybrids typically employ an imine bond to combine the structural features of both pharmacophores into a single framework, enabling synergistic effects. Recent studies demonstrate that such Schiff base hybrids exhibit potent dual inhibitory activity against α-glucosidase and urease, enzymes implicated in diabetes and gastrointestinal disorders, respectively. In

addition to their enzymatic inhibition, several derivatives show favorable cytocompatibility profiles, underscoring their therapeutic potential (Daud et al., 2024).

These diverse findings underscore the broad therapeutic versatility of isatin-based hybrids, establishing them as valuable platforms for the future development of multifunctional drug candidates across various disease domains.

Conclusion

Over the past few decades, the isatin scaffold has proven itself as a versatile and privileged structure in medicinal chemistry, offering significant promise across a wide range of therapeutic domains. By leveraging molecular hybridization strategies, researchers have successfully expanded the biological potential of isatin derivatives, creating multifunctional agents with improved efficacy, selectivity, and pharmacokinetic profiles. Recent studies from 2020 to 2025 demonstrate that isatin-based hybrids exhibit remarkable activities in oncology, neurodegenerative disease management, antibacterial and antitubercular therapy, as well as in various emerging fields such as antidiabetic, anti-inflammatory, and antiviral drug development.

The modularity of the isatin core, has allowed fine-tuning of biological properties and target engagement. Notably, isatin hybrids consistently show the capacity to modulate multiple disease pathways, offering dual or multitarget-directed mechanisms that are highly advantageous for addressing complex and resistant diseases. Furthermore, many hybrids demonstrate favorable cytotoxicity profiles, metabolic stability, and promising in vivo efficacy, supporting their potential for translation into clinical candidates.

Despite these encouraging advances, challenges remain, including the need for deeper mechanistic studies, improved selectivity in vivo, and comprehensive toxicity assessments. Nevertheless, the collective data strongly suggest that isatin-based hybrids represent an exceptional foundation for next-generation drug discovery efforts. Continued innovation in structural design, combined with advanced pharmacological evaluations, is expected to further expand the therapeutic applications of these compounds.

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Резиме

Хибридни молекули кои го содржат изатинското јадро – преглед на најновите достигнувања во дизајнот и фармаколошките дејства

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Клучни зборови: деривати на изатин; откривање на лекови; фармаколошки карактеристика; антиканцерогени дејства; невропротективна активност

Концептот на рационално дизајнирање на нови кандидати за лекови преку инкорпорирањето на два или повеќе фармакофори во еден лиганд и создавање на т.н. хибридни молекули претставува современ тренд во медицинската хемија. Хибридните соединенија во чија основа се наоѓа изатинското јадро се од особен интерес во медицинската хемија заради различните можности за структурни модификации на изатинот, особено на позициите N-1, C-3 и C-5 од хетероцикличниот нуклеус, како и широкиот фармаколошки профил на самиот фармакофор. Овој преглед ги резимира неодамнешните достигнувања (2020–2025) во дизајнот на хибриди на изатин насочени кон невродегенеративните заболувања, онколошките болести, бактериските и микобактериски инфекции, дијабетесот и инфламаторните состојби. Примената на оваа стратегија доведува до создавање на соединенија со полифармаколошко дејство со што се овозможува активност на еден молекул врз различни таргети и патофизиолошки патеки на сложените мултифакторијални заболувања. Некои хибридни молекули покажале подобрена биолошка ефикасност во споредба со референтните лекови, дополнети со намалена токсичност и оптимизиран фармакокинетички профил. Овој преглед го истакнува терапевтскиот потенцијал на изатинските хибриди во развојот на мултифункционални агенси во различни клинички области.