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Synthesis and In Vitro Cytotoxic Evaluation of Novel Indole-Based Hydrazone Derivatives Against Breast Cancer Cell Lines

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ABSTRACT

Background: Breast cancer remains the most commonly diagnosed malignancy in women worldwide, and the indole nucleus, functionalized as a hydrazone or hydrazide-hydrazone, has emerged as a synthetically accessible and biologically productive scaffold for anticancer drug discovery. Objective: This narrative review synthesizes published literature on the synthesis, structure-activity relationships, and in vitro cytotoxic evaluation of indole-based hydrazone and hydrazide-hydrazone derivatives against breast cancer cell lines. Methods: We reviewed synthetic, structure-activity, and mechanistic studies of indole-hydrazone chemotypes screened against MCF-7 and MDA-MB-231 breast cancer cells, focusing on condensation-based synthetic routes, substituent-driven potency trends, reported IC50 and selectivity data, and proposed molecular targets. Findings: Indole-hydrazones are consistently accessed by acid-catalyzed condensation of an indole carbaldehyde or carbohydrazide with acylhydrazides or sulfonohydrazides, often after N1-tosylation or N1-benzylation, and electron-withdrawing, halogenated, and appropriately positioned aryl substituents recur as determinants of potency. Reported activities span low-nanomolar to mid-micromolar IC50 values against MCF-7 and MDA-MB-231 cells, frequently accompanied by wide selectivity margins over normal breast epithelial or embryonic kidney cells, with kinase inhibition, histone deacetylase-2 inhibition, and computationally predicted target engagement each proposed as underlying mechanisms in different series. Conclusions: Indole-based hydrazone and hydrazide-hydrazone derivatives constitute a promising and chemically tractable class of breast cancer cytotoxic agents, though compound-specific mechanistic validation remains needed as the class advances toward more detailed pharmacological characterization.

Keywords: *indole hydrazone; hydrazide-hydrazone derivatives; breast cancer cytotoxicity; MCF-7 and MDA-MB-231 cell lines; structure-activity relationship*

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Introduction

Breast cancer remains the most commonly diagnosed malignancy in women worldwide and a leading cause of cancer-related mortality, with GLOBOCAN 2022 estimates placing its global incidence above two million new cases annually and underscoring the continued need for chemotherapeutic agents with improved potency and selectivity [1]. Among the heterocyclic scaffolds explored for this purpose, the indole nucleus occupies a privileged position in medicinal chemistry because it is both a naturally occurring pharmacophore, found in tryptophan, serotonin, and the vinca alkaloids, and a synthetically versatile platform whose substitution pattern can be tuned to engage diverse oncological targets, from tubulin and topoisomerases to kinases and epigenetic regulators [2,3]. Recent reviews of indole-based anticancer chemotypes have emphasized that the biological profile of an indole derivative is rarely dictated by the core ring system alone, but by the functional groups appended at the 2-, 3-, and N1-positions, which govern hydrogen-bonding capacity, planarity, and target engagement [4].

Hydrazone and hydrazide-hydrazone linkages, formed by condensation of a carbonyl-bearing indole intermediate with an acylhydrazide or sulfonohydrazide, have emerged as one of the most productive ways to decorate the indole scaffold for anticancer screening. The -C=N-NH-C(=O)- or -C=N-NH-SO2- linker introduces a rigid, hydrogen-bond-donating and -accepting motif that is synthetically accessible in a single condensation step, tolerant of extensive structural variation at the terminal aryl or heteroaryl group, and frequently associated with potent, selective cytotoxicity against breast cancer cell lines such as MCF-7 and MDA-MB-231 in the studies summarized below [5]. This narrative

review synthesizes the published literature on indole-based hydrazone and hydrazide-hydrazone derivatives evaluated against breast cancer cell lines, organizing the discussion around the synthetic strategies used to access these compounds, the structure-activity relationships that have emerged from systematic substituent variation, the in vitro cytotoxicity and selectivity data reported across studies, and the mechanistic and molecular-target insights that have accompanied the most thoroughly characterized series.

Synthetic Strategies for Indole-Based Hydrazone and Hydrazide Derivatives

The dominant synthetic route to indole-based hydrazones begins with an indole carbaldehyde or carbohydrazide precursor, most often indole-3-carbaldehyde or its N1-functionalized analogs, which is condensed with an acylhydrazide, arylsulfonohydrazide, or heteroarylhydrazide under mild acid catalysis. Hassan and colleagues exemplified this classical approach, condensing indole-3-carbaldehyde with a series of acid hydrazides in refluxing ethanol for four hours to obtain indole-hydrazone derivatives in 61-81% yield after recrystallization, a protocol that has been repeated with only minor modification across much of the subsequent literature [6]. Mahdi and colleagues instead built the hydrazone from the carbohydrazide end, converting 1H-indole-3-carbohydrazide into a family of hydrazone and triazole-fused derivatives for anti-breast cancer screening [7].

A recurring refinement of this strategy is prior N1-functionalization of the indole nitrogen to modulate lipophilicity and steric bulk before hydrazone formation. Ghaffar and colleagues first N-tosylated indole-3-carbaldehyde and then condensed the resulting sulfonated aldehyde with substituted hydrazides under reflux in methanol with acetic acid catalysis to generate a 21-compound N-tosyl-indole hydrazone library [8]. Farooq and colleagues pursued an analogous two-step sequence, first N-benzylating indole-3-carboxaldehyde with benzyl bromide and potassium carbonate, then coupling the N-benzylated aldehyde with diverse hydrazides in refluxing methanol with acetic acid to yield compounds 5a-5v [9]. The same research group extended this platform to the isatin series, N-benzylating isatin and condensing it with hydrazides to access N-benzyl isatin hydrazones, formally indole-2,3-dione hydrazones that retain the bicyclic indole-derived core while introducing a second carbonyl for hydrogen bonding [10].

Sulfonohydrazone chemistry represents a parallel and prolific line of synthesis. Angelova and colleagues generated arylsulfonylhydrazones by condensing aromatic aldehydes, including indole-3-carbaldehyde, with benzenesulfonohydrazide or 4-methylbenzenesulfonohydrazide in a 1:1 molar ratio in absolute ethanol, a mild, catalyst-free protocol requiring only one to three hours at reflux [11]. A follow-up study from the same group extended this chemistry with an additional preparatory step, converting sulfonyl chlorides to hydrazides before coupling with indole-3-carbaldehyde, and separately assembling a bis-indole derivative through direct hydrazine-mediated double condensation [12]. More architecturally complex indolyl-hydrazones have also been reported: Salama and colleagues condensed ethyl 3-formyl-1H-indole-2-carboxylate with various amine and hydrazide partners under fusion conditions to generate six structurally distinct classes bearing ester and azomethine functionalities on a single indole core, while Sreenivasulu and colleagues linked an indole and an indazole ring through a hydrazide-hydrazone bridge to create hybrid heterocyclic architectures explicitly designed for dual-pharmacophore engagement [13,14]. Nanocatalyzed variants of this chemistry have also appeared, with Feizi-Dehnayebi and colleagues employing a sulfonic-acid-functionalized silica nanocatalyst to accelerate condensation of an isatin hydrazone with aryl aldehydes to only minutes at reflux [15].

Representative synthetic routes to indole-based hydrazone and hydrazide-hydrazone derivatives evaluated against breast cancer cell lines.

Study	Indole-derived precursor	Coupling partner	Conditions
Hassan et al. 2023	Indole-3-carbaldehyde	Acid hydrazides	EtOH, reflux, 4 h
Ghaffar et al. 2025	N-Tosyl-indole-3-carbaldehyde	Substituted hydrazides	MeOH/AcOH, reflux
Farooq et al. 2025	N-Benzyl-indole-3-carboxaldehyde	Hydrazides	MeOH/AcOH, reflux
Munira et al. 2025	N-Benzyl isatin	Hydrazides	MeOH/AcOH, reflux
Angelova et al. 2023/2025	Indole-3-carbaldehyde	Aryl/tosyl-sulfonohydrazides	Absolute EtOH, reflux, 1-3 h
Feizi-Dehnayebi et al. 2025	Isatin hydrazone	Aryl aldehydes	EtOH, nanocatalyst, reflux, ~5 min

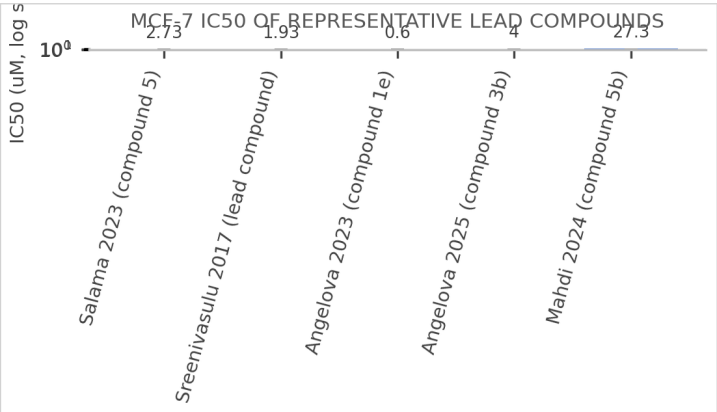
Structure-Activity Relationships Against Breast Cancer Cell Lines

Across these chemical series, several consistent structure-activity trends have emerged from systematic substituent screening against MCF-7 and MDA-MB-231 cells. Electron-withdrawing and halogenated substituents on the terminal aryl ring of the hydrazone consistently enhance potency relative to unsubstituted or electron-donating analogs. In the N-tosyl-indole hydrazone series, Ghaffar and colleagues found that bicyclic naphthyl substituents outperformed monocyclic and simple heteroaryl groups, that trifluoromethyl-substituted analogs were among the most potent compounds tested, and that para-substitution on phenyl rings was systematically favored over ortho-substitution, while nitro substituents reduced activity, attributed to unfavorable steric interactions at the binding site [8]. A related pattern was observed by Munira and colleagues in the N-benzyl isatin hydrazone series, where a 4-nitrophenyl derivative nonetheless proved the most potent compound against MDA-MB-231 cells, ahead of a pyridyl-bearing analog and a 2,4-difluorobenzyl-substituted congener, indicating that the optimal electronic profile is sensitive to the specific scaffold and linker geometry rather than universally transferable [10].

Salama and colleagues similarly linked potency to electron-withdrawing character, reporting that a bis-hydrazino derivative, a Schiff base, and a dinitrophenylhydrazone each outperformed the reference agent staurosporine against MCF-7 cells, with structure-activity analysis pointing to the electron-withdrawing substituents as the principal driver of the improved activity relative to simpler analogs [13]. In the arylsulfonylhydrazone series, Angelova and colleagues found that unsubstituted or minimally substituted benzenesulfonohydrazide condensation products achieved sub-micromolar potency against MCF-7 cells, while bulkier or more polar substitutions on the sulfonyl aryl ring generally reduced activity, and only the most potent compound retained comparable sub-micromolar activity against the triple-negative MDA-MB-231 line, highlighting that

selectivity for hormone-receptor-positive over triple-negative breast cancer cells is a common feature of this chemotype [11]. Their subsequent QSAR-guided sulfonylhydrazone series similarly identified a lead compound with markedly greater potency and a favorable in silico selectivity index relative to its analogs, reinforcing the role of aryl ring geometry and sulfonyl substitution in tuning both potency and selectivity [12]. Sreenivasulu and colleagues, working with the indole-indazolyl hydrazide-hydrazone hybrids, found that only three of ten synthesized compounds achieved sub-25-micromolar activity against a panel of four cancer cell lines, with the most active compound approaching the potency of doxorubicin against MCF-7 cells while showing no measurable cytotoxicity toward normal HEK-293 cells, illustrating that hybridization of two heterocyclic pharmacophores through the hydrazone linker can preserve a favorable therapeutic window even when overall potency remains submaximal [14].

Reported IC50 values against MCF-7 breast cancer cells for representative lead compounds from five indole-based hydrazone/hydrazide-hydrazone series (log scale). Values: bis-hydrazino indolyl-hydrazone compound 5 (Salama et al., 2023), indole-indazolyl hydrazide-hydrazone (Sreenivasulu et al., 2017), arylsulfonylhydrazone compound 1e (Angelova et al., 2023), indole-based sulfonylhydrazone compound 3b (Angelova et al., 2025), and indole-3-carbohydrazide derivative 5b (Mahdi et al., 2024).



In Vitro Cytotoxicity and Selectivity Profiles

Considered together, the reported in vitro cytotoxicity values span nearly three orders of magnitude, reflecting the breadth of chemotypes captured under the indole-hydrazone umbrella. At the most potent end, Farooq and colleagues reported nanomolar activity against the triple-negative MDA-MB-231 line, with the lead N-benzyl indole hydrazone achieving an IC50 of 17.2 nanomolar, more than three orders of magnitude below the greater-than-50-micromolar threshold observed against normal MCF-10A epithelial cells, yielding a very wide selectivity margin [9]. In the arylsulfonylhydrazone series, Angelova and colleagues reported four compounds with sub-micromolar activity against MCF-7 cells, the most potent reaching 0.6 micromolar, while activity against MDA-MB-231 cells was generally weaker except for the same lead compound, which retained sub-micromolar potency against both lines [11]. The follow-up sulfonylhydrazone series from the same group reported a best-in-class MCF-7 IC50 of 4.0 micromolar with a calculated selectivity index exceeding twenty, alongside somewhat higher, though still low-micromolar, activity against MDA-MB-231 cells for two structurally related compounds [12].

In vitro cytotoxicity and selectivity of representative indole-based hydrazone/hydrazide-hydrazone lead compounds against breast cancer cell lines versus normal cells.

Study	Lead compound	Cancer cell line (IC50)	Normal cell comparator
Salama et al. 2023	Compound 5	MCF-7, 2.73 uM	Staurosporine ref. 8.32 uM
Sreenivasulu et al. 2017	Lead hydrazide-hydrazone	MCF-7, 1.93 uM	HEK-293, no cytotoxicity
Angelova et al. 2023	Compound 1e	MCF-7, 0.6 uM; MDA-MB-231, 0.9 uM	Not reported
Ghaffar et al. 2025	Compound 5p	MDA-MB-231, 12.2 uM	MCF-10A, reduced viability only
Farooq et al. 2025	Compound 5b	MDA-MB-231, 0.0172 uM	MCF-10A, >50 uM
Munira et al. 2025	Compound 23	MDA-MB-231, 15.8 uM	MCF-10A, >50 uM
Angelova et al. 2025	Compound 3b	MCF-7, 4.0 uM	Selectivity index 20.975

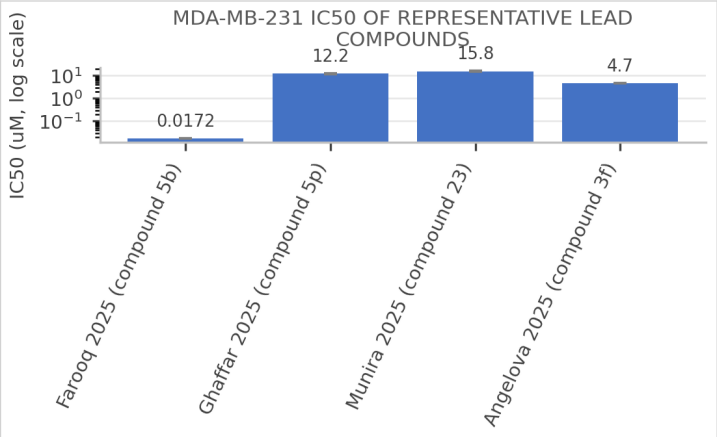
In the mid-micromolar range, Salama and colleagues identified three lead indolyl-hydrazone compounds active against MCF-7 cells between 2.73 and 7.03 micromolar, each more potent than the staurosporine reference standard [13], while Ghaffar and colleagues reported their most active N-tosyl-indole hydrazones inhibiting MDA-MB-231 cells between 12.2 and 18.1 micromolar with negligible effect on normal MCF-10A cells [8], and Munira and colleagues reported comparable potency, 15.8 to 22.2 micromolar against MDA-MB-231 cells, for their leading N-benzyl isatin hydrazones, again with selective sparing of normal breast epithelial cells [10]. Feizi-Dehnayebi and colleagues, using nanocatalyst-accelerated synthesis, reported an arylidene isatin hydrazone active at approximately 10 micrograms per milliliter against both MCF-7 and MDA-MB-231 cells in a time- and concentration-dependent manner [15]. At the higher end of the potency range, Sreenivasulu and colleagues reported an indole-indazolyl hydrazide-hydrazone active at 1.93 micromolar against MCF-7 cells [14], while Mahdi and colleagues reported indole-3-carbohydrazide-derived hydrazones active between 27.3 and 42.6 micromolar against the same cell line [7]. Across nearly every series in which a normal-cell comparator was included, whether HEK-293, MCF-10A, or an unspecified normal line, the indole-hydrazone and indole-hydrazide-hydrazone compounds showed markedly reduced or negligible cytotoxicity toward non-malignant cells, a selectivity pattern that recurs across otherwise structurally diverse chemotypes and supports the general tolerability of this pharmacophore class in cell-based assays.

Mechanistic Insights and Molecular Targets

Beyond raw potency, several studies have sought to define the molecular basis for the observed cytotoxicity. Salama and colleagues framed their indolyl-hydrazones explicitly as kinase inhibitors, combining X-ray single-crystal structural analysis with in vitro and in vivo anticancer activity evaluation to support a kinase-directed mechanism of action in breast cancer models [13]. Naghi-Ganji and colleagues pursued a distinct epigenetic target, designing indole-acylhydrazone derivatives of 4-pyridinone as candidate histone deacetylase-2 inhibitors and evaluating their cytotoxicity alongside enzyme-level activity, illustrating that the indole-hydrazone scaffold can be repurposed away from classical DNA- or tubulin-directed mechanisms toward chromatin-modifying targets [16]. Reviews of the broader

hydrazide-hydrazone and hydrazone chemotype have similarly emphasized that this linker functions as a versatile molecular hinge capable of engaging diverse anticancer targets, including tubulin, topoisomerases, kinases, and metal-chelation-dependent redox pathways, depending on the flanking pharmacophores attached to it, which helps explain why structurally similar indole-hydrazones described in this review have been variously proposed as kinase inhibitors, epigenetic modulators, or generalized apoptosis inducers [5].

Reported IC50 values against the triple-negative MDA-MB-231 breast cancer cell line for representative lead compounds from four indole-hydrazone series (log scale, micromolar). N-benzyl indole-derived hydrazone compound 5b (Farooq et al., 2025) is active in the low-nanomolar range; N-tosyl-indole hydrazone compound 5p (Ghaffar et al., 2025), N-benzyl isatin hydrazone compound 23 (Munira et al., 2025), and indole-based sulfonylhydrazone compound 3f (Angelova et al., 2025) are active in the low-micromolar range.



Several of the studies summarized above complemented in vitro cytotoxicity screening with in silico target engagement analysis. Ghaffar, Farooq, and Munira and their colleagues each paired molecular docking of their lead compounds against relevant oncology targets with ADME and quantitative structure-activity relationship modeling, and consistently found that their most cytotoxic derivatives also achieved the most favorable predicted binding poses and drug-likeness profiles, supporting a plausible mechanistic link between the substituent patterns favored in the empirical structure-activity relationships and stable target engagement [8,9,10]. Angelova and colleagues extended this computational layer furthest, building quantitative structure-activity relationship models from their arylsulfonylhydrazone dataset specifically to guide the design of their second-generation, more selective compounds, an iterative design-test-refine cycle that exemplifies how mechanistic and computational insight is increasingly integrated with synthetic and cytotoxicity work in this chemical space [11,12]. Broader reviews of indole pharmacology in oncology reinforce that this scaffold engages an unusually wide range of validated cancer targets, providing a rationale for why the hydrazone-functionalized indoles surveyed here have been pursued against such a varied set of proposed mechanisms rather than converging on a single molecular target [3,4].

Conclusion

The literature reviewed here demonstrates that indole-based hydrazone and hydrazide-hydrazone derivatives constitute a chemically accessible and biologically productive class of anticancer candidates against breast cancer cell lines. Synthetic access is consistently achieved through acid-catalyzed condensation of an indole carbaldehyde or carbohydrazide, frequently after N1-functionalization by tosylation or benzylation, with acylhydrazides or sulfonohydrazides, and this synthetic tractability has enabled the systematic structure-activity studies that have identified electron-withdrawing, halogenated, and appropriately positioned aryl substituents as recurring determinants of potency. Reported cytotoxicity values span from low-nanomolar to mid-micromolar concentrations against MCF-7 and MDA-MB-231 cells, and a striking majority of the most potent compounds also display wide selectivity margins over normal breast epithelial or embryonic kidney cell lines, a favorable pharmacological signature for early-stage anticancer candidates. Mechanistic work remains comparatively less mature than the synthetic and cytotoxicity literature, with kinase inhibition, histone deacetylase-2 inhibition, and computationally predicted target engagement each proposed for different series, suggesting that the indole-hydrazone pharmacophore is target-promiscuous in a manner that will require compound-specific mechanistic validation as this chemical class advances toward more detailed pharmacological characterization.

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Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

Ida Jensen conceived the review, conducted the literature search, and drafted the manuscript. Panagiotis Vasileiou contributed to the literature screening and pharmacological framing and critically revised the manuscript for important intellectual content. Conor Byrne contributed additional oncological context and approved the final version for submission.

Ethics Statement

Not applicable. This is a narrative review of previously published in vitro literature and did not involve new experimental data, human participants, or animal subjects.

Data Availability

No new data were generated or analyzed for this review. All sources synthesized are cited in the reference list and are available through their original publishers.

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