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In Silico and In Vitro Screening of Hydrazone-Based Kinase Inhibitors for Anti-Proliferative Activity in Hormone Receptor-Positive Breast Cancer

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ABSTRACT

Background: Hormone receptor-positive (ER+/PR+) breast cancer accounts for the majority of the more than two million new breast cancer diagnoses made annually worldwide, and acquired resistance to endocrine therapy is frequently driven by compensatory activation of EGFR, PI3K/AKT/mTOR, and cyclin-dependent kinase (CDK) signaling that cross-talks with the estrogen receptor. Objective: This narrative review synthesizes the published literature on hydrazone-based kinase inhibitor chemotypes evaluated by molecular docking and in vitro anti-proliferative testing against hormone receptor-positive breast cancer models, principally the MCF-7 cell line. Methods: Peer-reviewed studies describing hydrazone or hydrazide-hydrazone derivatives designed against EGFR, CDK2, mTOR, or the estrogen receptor and profiled by in silico docking, ADMET prediction, and in vitro cytotoxicity were identified and narratively synthesized around synthetic strategy, kinase target rationale, in silico screening methodology, and structure-activity relationships. Findings: Hydrazone chemotypes built on indole, isatin, thiazole, benzimidazole, quinoline, and pyrazole cores have been docked against EGFR (including the T790M/L858R resistance mutant), CDK2, mTOR, and the estrogen receptor ligand-binding domain, with binding energies for lead compounds reaching approximately -11 to -12 kcal/mol. Reported anti-proliferative potencies against MCF-7 and related lines span single-digit nanomolar to double-digit micromolar concentrations, with several lead compounds achieving selectivity indices exceeding conventional cytotoxic reference agents and mechanistic evidence of apoptosis induction and cell-cycle arrest. Conclusions: Hydrazone-based kinase inhibitors represent a chemically versatile and pharmacologically promising class of candidate agents for hormone receptor-positive breast cancer, and further head-to-head structure-activity optimization against hormone receptor-positive and hormone receptor-negative models within single studies is warranted to advance this compound class toward more definitive preclinical validation.

Keywords: *hydrazone kinase inhibitors; hormone receptor-positive breast cancer; molecular docking; MCF-7 anti-proliferative activity; in silico ADMET screening*

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Introduction

Breast cancer remains the most frequently diagnosed cancer in women worldwide, with GLOBOCAN 2022 estimates reporting more than two million new cases and roughly 670,000 deaths annually, and hormone receptor-positive (estrogen receptor-positive/progesterone receptor-positive, ER+/PR+) tumors accounting for the large majority of these diagnoses [1]. Endocrine therapy with aromatase inhibitors or selective estrogen receptor modulators remains first-line management for this subtype, but resistance frequently emerges through compensatory activation of growth factor and kinase signaling pathways that cross-talk with the estrogen receptor, including the mitogen-activated protein kinase and phosphoinositide 3-kinase/AKT cascades, HER2, and cyclin-dependent kinases (CDKs) [2]. The clinical success of CDK4/6 inhibitors such as palbociclib, which combined with letrozole more than doubled median progression-free survival relative to letrozole alone in advanced HR-positive disease (24.8 versus 14.5 months), has firmly established kinase inhibition as a validated pharmacological strategy for augmenting or rescuing endocrine therapy in this population [3,4]. These clinical precedents have motivated an extensive medicinal chemistry effort to identify new

small-molecule kinase inhibitor chemotypes with improved selectivity, potency, and physicochemical tractability, and among the scaffolds explored for this purpose, the hydrazone functional group, formed by condensation of a carbonyl-bearing intermediate with a hydrazide or hydrazine, has proven exceptionally productive.

The -C=N-NH-C(=O)- hydrazone linkage combines synthetic accessibility, typically a single acid- or base-catalyzed condensation step, with a rigid, hydrogen-bond-donating and -accepting geometry that mimics the adenine-mimetic hinge-binding motifs recognized by ATP-competitive kinase inhibitors. This has made hydrazones a recurring feature of rationally designed inhibitors of EGFR, CDK2, mTOR, and other kinases implicated in hormone receptor-positive breast cancer proliferation and endocrine resistance, frequently evaluated head-to-head with in silico docking against the corresponding kinase active sites and estrogen receptor ligand-binding domain [5,6,7,8]. Complementary in vitro cytotoxicity screening against the MCF-7 cell line, the most widely used hormone receptor-positive breast cancer model, has generated a substantial and rapidly growing body of structure-activity data that has not yet been synthesized specifically through the lens of hormone receptor-positive disease. This narrative review addresses that gap, organizing the literature around the kinase targets most relevant to hormone receptor-positive breast cancer biology, the synthetic strategies used to access hydrazone-based inhibitor chemotypes, the in silico docking and absorption-distribution-metabolism-excretion (ADME) methods used to prioritize candidates, and the in vitro anti-proliferative and mechanistic data that have emerged from testing against MCF-7 and related cell lines.

Kinase Signaling Targets in Hormone Receptor-Positive Breast Cancer

Rational design of kinase-directed hydrazones for hormone receptor-positive breast cancer draws on a well-characterized set of oncogenic signaling nodes that intersect with estrogen receptor function. The epidermal growth factor receptor (EGFR) and its family member HER2, although more classically associated with triple-negative and HER2-amplified disease, contribute to ligand-independent estrogen receptor activation and are implicated in acquired resistance to tamoxifen and aromatase inhibitors, providing a mechanistic rationale for EGFR-directed hydrazones tested against ER-positive lines even when their primary evaluation used triple-negative models [2,6,9]. The phosphoinositide 3-kinase/AKT/mammalian target of rapamycin (PI3K/AKT/mTOR) axis is similarly central to hormone receptor-positive breast cancer, both as a driver of proliferation downstream of growth factor receptors and as a clinically validated co-target with endocrine therapy, a rationale reflected in docking studies that screen hydrazone hits against mTOR kinase alongside the estrogen receptor ligand-binding domain itself [5].

Cyclin-dependent kinase 2 (CDK2) has emerged as an especially prominent target within the hydrazone literature. CDK2 partners with cyclin E to drive the G1/S transition and has been proposed as a mechanism of acquired resistance to CDK4/6 inhibitors in hormone receptor-positive breast cancer, making it a rational next-generation target alongside the now-standard CDK4/6 inhibitor class [4]. Multiple independent hydrazone series have been explicitly designed as CDK2 inhibitors and profiled by enzymatic assay in parallel with cellular cytotoxicity: isatin-hydrazone derivatives reported by Tao and colleagues, indole-pyrazole hybrids from Eldehna and colleagues benchmarked against the reference inhibitor roscovitine, and coumarin/thiazole congeners evaluated with molecular dynamics simulation by Bondock and colleagues [7,8,10]. Because CDK2, EGFR/HER2, and PI3K/AKT/mTOR signaling all converge functionally on estrogen receptor transcriptional activity and cell-cycle progression, hydrazone chemotypes designed against any of these nodes are directly relevant to the pharmacology of hormone receptor-positive disease even when the reporting studies used mixed cell-line panels that include hormone receptor-negative comparators.

The functional rationale for targeting these kinases in ER-positive breast cancer is reinforced by the observation that estrogen receptor and growth factor kinase pathways are reciprocally regulated: kinase activation can phosphorylate and activate the estrogen receptor in a ligand-independent manner, while estrogen receptor signaling can in turn upregulate components of the growth factor cascade, creating a self-reinforcing signaling network that endocrine therapy alone frequently fails to fully suppress [2]. This bidirectional crosstalk is the central pharmacological argument for combining, or replacing, endocrine agents with small-molecule kinase inhibitors, and it is the argument that the hydrazone-based inhibitor literature surveyed in this review implicitly or explicitly invokes when selecting EGFR, mTOR, and CDK2 as docking and enzymatic targets for compounds subsequently tested against MCF-7 cells.

Synthetic Chemistry and Structural Diversity of Hydrazone-Based Kinase Inhibitor Chemotypes

The dominant synthetic route across this literature condenses an aldehyde- or ketone-bearing heterocyclic core with an acylhydrazide, sulfonohydrazide, or hydrazine derivative under mild acid catalysis, typically in refluxing ethanol or methanol for one to several hours. Ghaffar and colleagues exemplified this approach by first N-tosylating indole-3-carbaldehyde and then condensing the sulfonated aldehyde with a panel of substituted hydrazides to generate an indole hydrazone library subsequently screened against EGFR and breast cancer cell lines [11]. Farghaly and colleagues pursued a parallel sulfonyl-thiazolyl hydrazone strategy explicitly designed around the EGFR pharmacophore, coupling thiazole-based hydrazide intermediates with aromatic aldehydes to generate a focused EGFR-inhibitor series evaluated by both enzymatic assay and molecular docking [6]. Isatin, or indolin-2,3-dione, has proven an especially versatile hydrazone precursor because its 3-keto group condenses readily with hydrazides while the retained 2-oxindole carbonyl provides an additional hydrogen-bond acceptor; Munir and colleagues exploited this bis-carbonyl architecture to build isatin-hybrid hydrazones for triple-negative breast cancer, while Tao and colleagues used the same core to access isatin-hydrazone CDK2 inhibitors [12,7].

Heteroaryl hybridization strategies that fuse two or more pharmacophoric ring systems through the hydrazone or a closely related hydrazone/thiosemicarbazone linkage represent a second major synthetic theme. Aljuhani and colleagues linked a benzothiazole and a 1,2,3-triazole through hydrazone and thiosemicarbazone bridges in a single synthetic platform, generating dual-warhead EGFR inhibitors with confirmed cytotoxicity against breast cancer cells [9]. Eldehna and colleagues built indole-pyrazole hybrid hydrazones as CDK2-directed agents, while Lu and colleagues assembled

quinoline-based dihydrazones bearing two hydrazone linkages on a single quinoline scaffold to maximize hydrogen-bonding contacts within the kinase active site [8,13]. Bondock and colleagues instead paired a coumarin chromophore with a thiazole ring through hydrazone-type connectivity to generate CDK2-targeted congeners subsequently validated by molecular dynamics simulation [10]. Demirci and colleagues and Özil and colleagues both employed benzimidazole- and arylthiazole-based aldehydes, respectively, condensed with substituted acylhydrazides to generate structurally compact hydrazones optimized for MCF-7 potency and favorable drug-likeness [14,5].

Representative hydrazone-based chemotypes evaluated as kinase inhibitors against hormone receptor-positive or related breast cancer cell models, with principal target and reference.

Hydrazone chemotype	Primary kinase/target	Cell line(s) tested	Key reference
N-tosyl-indole hydrazone	EGFR (incl. T790M/L858R)	MDA-MB-231, MCF-10A	Ghaffar et al. 2025
Isatin-hybrid hydrazone	Not specified (TNBC-focused)	Triple-negative breast cancer lines	Munir et al. 2025
Sulfonyl thiazolyl -hydrazone	EGFR	Cancer cell panel	Farghaly et al. 2022
Benzothiazole-1,2,3-triazole hydrazone/thiosemicarbazone	EGFR	Breast cancer cells	Aljuhani et al. 2025
Trifluoromethyl-benzimidazole-hydrazone	ERalpha, BRD4, mTOR	MCF-7, hTERT (normal)	Ozil et al. 2026
4-Arylthiazole-hydrazone	Caspase-3 (apoptosis)	MCF-7	Demirci et al. 2026
Isatin-hydrazone	CDK2	A549, HeLa, HepG2	Tao et al. 2026
Indole-pyrazole hydrazone hybrid	CDK2	HepG2, HCT-116, MCF-7	Eldehna et al. 2026
Coumarin/thiazole hydrazone	CDK2	Cancer cell panel	Bondock et al. 2024
Quinoline-based dihydrazone	Not specified	Cancer cell panel	Lu et al. 2025

A broader historical thread, reviewed by Verma and colleagues for the quinoline hydrazide/hydrazone chemotype and exemplified earlier by Kumar and colleagues' bis(indolyl)hydrazide-hydrazones, establishes that electron-withdrawing aryl substituents, extended aromatic conjugation, and bis-heterocyclic hybridization are recurring structural levers used across this chemical space to tune both kinase engagement and cellular potency, independent of which specific heterocyclic core is chosen as the hydrazone-bearing scaffold [15,16]. Collectively, these synthetic strategies demonstrate that hydrazone chemistry offers a modular, low-step platform for generating structurally diverse kinase-inhibitor candidates from a common set of well-precedented heterocyclic building blocks, a property that has facilitated the parallel in silico and in vitro screening approach that characterizes nearly every study surveyed in this review.

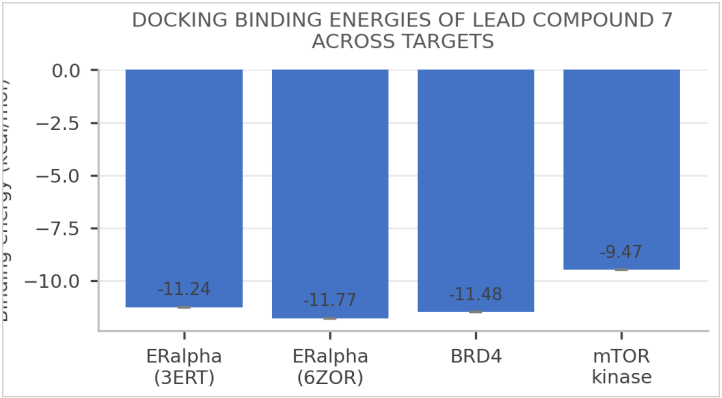
In Silico Screening: Molecular Docking and ADMET Profiling of Hydrazone Chemotypes

Structure-based molecular docking has become a near-universal component of hydrazone kinase-inhibitor discovery, used both to rationalize observed cytotoxicity and to prioritize compounds for synthesis or further testing. Docking exercises in this literature typically target the ATP-binding pocket of the relevant kinase, most often EGFR or CDK2, and increasingly extend to secondary targets relevant to hormone receptor-positive biology. Özil and colleagues docked their lead trifluoromethyl-benzimidazole-hydrazone (compound 7) against four targets simultaneously, obtaining binding energies of -11.24 and -11.77 kcal/mol against two estrogen receptor-alpha crystal structures (PDB 3ERT and 6ZOR, respectively), -11.48 kcal/mol against BRD4, and -9.47 kcal/mol against mTOR kinase, directly connecting the compound's cellular potency in MCF-7 cells to plausible engagement of the estrogen receptor ligand-binding domain and a validated kinase target in the same molecule [5]. Ghaffar and colleagues reported a binding energy of -11.533 kcal/mol for their lead N-tosyl-indole hydrazone (5q) against the clinically relevant EGFR T790M/L858R double mutant, illustrating that docking in this literature is increasingly used to probe resistance-associated kinase variants rather than wild-type enzyme alone [11]. Farghaly and colleagues similarly combined molecular docking with EGFR enzymatic inhibition assays to confirm that their sulfonyl thiazolyl-hydrazones occupied the ATP-competitive binding site in a pose consistent with the hinge-binding interactions expected of a kinase inhibitor [6].

Comparative CDK2-directed potency of three hydrazone-based chemotypes discussed in this review, spanning enzymatic and cellular assay formats.

Compound / series	Assay	Reported potency	Reference
Isatin-hydrazone 2e	Cellular IC50 (A549)	5 nM	Tao et al. 2026
Isatin-hydrazone 2f	Cellular IC50 (HeLa)	6 nM	Tao et al. 2026
Isatin-hydrazone 2h	Cellular IC50 (A549 / HepG2)	8 nM / 13 nM	Tao et al. 2026
Indole-pyrazole hybrid 5d	Enzymatic CDK2 IC50	0.536 uM (vs roscovitine 0.716 uM)	Eldehna et al. 2026
Coumarin/thiazole CDK2 series	Docking + molecular dynamics	Stable active-site occupancy over MD trajectory	Bondock et al. 2024

Molecular docking binding energies of lead compound 7 against the estrogen receptor-alpha ligand-binding domain (two crystal structures, PDB 3ERT and 6ZOR), BRD4, and mTOR kinase, illustrating simultaneous predicted engagement of the hormone receptor and a kinase target by a single hydrazone chemotype (Ozil et al., 2026).



For CDK2-directed series, docking has been paired with molecular

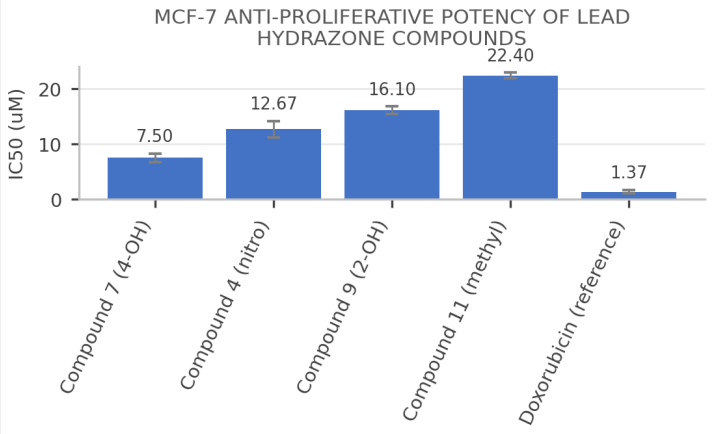
dynamics simulation to assess pose stability beyond a single static structure. Bondock and colleagues ran molecular dynamics trajectories on their coumarin/thiazole CDK2 inhibitor complexes to confirm sustained active-site occupancy over simulation time, while Eldehna and colleagues combined docking with ADMET prediction to support the developability of their lead indole-pyrazole hybrid (5d), which achieved a CDK2 IC50 of 0.536 micromolar, more potent than the reference inhibitor roscovitine at 0.716 micromolar [10,8]. Tao and colleagues confirmed that their most potent isatin-hydrazone CDK2 inhibitors, active at single-digit-to-low-double-digit nanomolar concentrations in cellular assays, engaged in stable interactions with key CDK2 active-site residues by docking analysis [7]. Demirci and colleagues extended the computational toolkit further, combining docking and molecular dynamics with density functional theory calculations to show that carboxylate substituents on their 4-arylthiazole-hydrazones formed persistent electrostatic contacts with Arg64 and Arg207 of caspase-3, linking the compounds' apoptosis-inducing activity in MCF-7 cells to a specific, structurally rationalized protein interaction rather than kinase inhibition alone [14].

Physicochemical and pharmacokinetic prediction is the second pillar of the in silico workflow used throughout this literature. Lipinski's rule of five, which flags departures from drug-like molecular weight, lipophilicity, and hydrogen-bonding capacity associated with poor oral absorption, remains the baseline filter applied across nearly every hydrazone series before or alongside cytotoxicity testing [17], while the freely available SwissADME platform has become the standard tool for generating these predictions alongside gastrointestinal absorption, cytochrome P450 interaction, and synthetic accessibility estimates [18]. Reviews of the broader molecular docking field caution, however, that docking scores correlate imperfectly with true binding affinity because scoring functions inadequately capture solvation, entropy, and protein flexibility, underscoring why the studies summarized here treat docking as a hypothesis-generating and rank-ordering tool to be corroborated by molecular dynamics and, ultimately, cellular and enzymatic assay rather than as a standalone measure of drug-likeness [19].

In Vitro Anti-Proliferative Activity and Structure-Activity Relationships

Cellular cytotoxicity testing against MCF-7 and related breast cancer cell lines has generated a wide potency range across the hydrazone chemotypes surveyed, spanning single-digit nanomolar enzymatic and cellular activity to double-digit micromolar cytotoxicity, generally tracking the electronic and steric properties of the terminal aryl or heteroaryl substituent. Özil and colleagues reported the clearest structure-activity trend against MCF-7 cells among the trifluoromethyl-benzimidazole-hydrazones: the para-hydroxy-substituted compound 7 was most potent at 7.5 ± 0.8 micromolar, followed by the nitro-substituted compound 4 at 12.67 ± 1.5 micromolar, the ortho-hydroxy isomer (compound 9) at 16.1 ± 0.7 micromolar, and the methyl-substituted compound 11 at 22.4 ± 0.5 micromolar, against a doxorubicin reference of 1.37 ± 0.3 micromolar [5]. Despite falling short of doxorubicin's absolute potency, compound 7 achieved a markedly superior selectivity index of 12.66 against normal hTERT cells, compared with approximately 1.09 for doxorubicin, illustrating that this hydrazone chemotype favorably decouples cytotoxic potency from off-target toxicity relative to a conventional cytotoxic reference [5].

Anti-proliferative potency (IC50, MCF-7 cells) of a lead trifluoromethyl-benzimidazole-hydrazone series relative to doxorubicin, showing that the para-hydroxy-substituted compound 7 was the most potent analog while remaining an order of magnitude less potent than the doxorubicin reference (Ozil et al., 2026).



Demirci and colleagues reported a complementary mechanistic angle on MCF-7 activity, showing that three 4-arylthiazole-hydrazones (2c, 2d, and 2h) each induced apoptosis in more than 24% of treated MCF-7 cells, with compound 2c activating caspase-3 to a degree comparable with the cytotoxic reference agent cisplatin, directly implicating the intrinsic apoptotic pathway rather than a purely cytostatic mechanism [14]. In the EGFR-targeted series, Ghaffar and colleagues reported nanomolar-to-low-micromolar potency against the triple-negative MDA-MB-231 line for their two leading N-tosyl-indole hydrazones, 5p at 12.2 ± 0.4 micromolar and 5q at 16.4 ± 0.2 micromolar, with negligible cytotoxicity toward normal MCF-10A epithelial cells, a selectivity pattern recurring across nearly every series with a normal-cell comparator in this literature [11]. Munir and colleagues similarly reported favorable in vitro and in silico profiles for their isatin-hybrid hydrazones against triple-negative breast cancer models, extending the same chemotype's applicability beyond hormone receptor-positive disease and suggesting that the underlying pharmacophore is not intrinsically subtype-selective, but rather that selectivity for hormone receptor-positive over triple-negative or normal cells depends on the specific substitution pattern realized in a given series [12].

At the CDK2-targeted end of the spectrum, potency values were substantially more potent in absolute terms. Tao and colleagues reported cellular IC50 values as low as 5 nanomolar (compound 2e, A549 cells) and 6 nanomolar (compound 2f, HeLa cells), with a dual-active compound 2h reaching 8 nanomolar against A549 and 13 nanomolar against HepG2 cells [7], while Eldehna and colleagues reported that their lead indole-pyrazole hybrid, active at sub-micromolar concentration against isolated CDK2 enzyme, also produced antiproliferative activity against HepG2, HCT-116, and MCF-7 cells accompanied by G1/G2 cell-cycle arrest and apoptosis induction, directly linking enzymatic CDK2 inhibition to a hormone receptor-positive-relevant cellular phenotype [8]. Aljuhani and colleagues confirmed that their benzothiazole-triazole hydrazone/thiosemicarbazone hybrids retained EGFR-inhibitory potency together with cytotoxicity specifically against breast cancer cells, reinforcing that EGFR remains a productive target for hydrazone chemotypes even outside the CDK2-focused series that currently dominate the most potent end of this literature [9]. Taken together, these structure-activity patterns indicate that terminal aryl

electron-withdrawing character, heterocyclic hybridization, and specific hydrogen-bond-donor placement each contribute, often synergistically, to the anti-proliferative potency and selectivity of hydrazone-based kinase inhibitors against hormone receptor-positive breast cancer models.

Conclusion

The literature reviewed here demonstrates that hydrazone-based kinase inhibitors constitute a chemically versatile and pharmacologically active class of candidate agents against hormone receptor-positive breast cancer, built around a synthetically accessible linkage that has been fused to indole, isatin, thiazole, benzimidazole, quinoline, and pyrazole cores to target EGFR, CDK2, mTOR, and the estrogen receptor ligand-binding domain itself. In silico molecular docking, increasingly supplemented by molecular dynamics simulation and ADMET prediction, has become a standard companion to in vitro cytotoxicity screening across nearly every series summarized, and the reported anti-proliferative potencies against MCF-7 and related cell lines span from single-digit nanomolar to double-digit micromolar concentrations, with several compounds achieving selectivity indices well in excess of conventional cytotoxic reference agents. Mechanistic characterization, though not yet uniform across the field, has begun to converge on apoptosis induction, cell-cycle arrest, and direct kinase or estrogen receptor engagement as the operative modes of action for the most thoroughly studied compounds. Given the established clinical precedent for kinase-directed adjuncts to endocrine therapy in hormone receptor-positive disease, continued structure-activity optimization of hydrazone-based chemotypes, coupled with more systematic head-to-head profiling against hormone receptor-positive and hormone receptor-negative models in the same study, represents a promising direction for advancing this compound class toward more definitive preclinical validation.

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Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

Diego Romero conceived the review, conducted the literature search, and drafted the manuscript. Anete Krumins contributed to the in silico methodology framing and critically revised the manuscript for important intellectual content. Eva Kral contributed additional oncological and pharmacological context and approved the final version for submission.

Ethics Statement

Not applicable. This is a narrative review of previously published in silico and 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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