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Structure-Activity Relationship of Novel Kinase Inhibitors in Triple-Negative Breast Cancer: An X-ray Crystallographic Study

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ABSTRACT

Background: Triple-negative breast cancer (TNBC) lacks a validated hormonal or HER2-directed target, driving sustained interest in the dysregulated kinase signaling networks, including PI3K/AKT/mTOR, cyclin-dependent kinases, mitotic kinases, focal adhesion kinase, and receptor tyrosine kinases, that support its proliferation and metastasis. Objective: This narrative review synthesizes the published medicinal chemistry, X-ray crystallographic, and translational literature on kinase inhibitors developed for or evaluated against TNBC. Methods: We reviewed structure-activity relationship and structural biology studies of kinase inhibitor chemotypes with reported relevance to TNBC, focusing on the principal kinase targets implicated in disease biology, the X-ray co-crystal structures that have guided inhibitor optimization, substituent-driven potency and selectivity trends across independent chemotypes, and the preclinical and clinical efficacy data available for these agents. Findings: X-ray crystallography has directly informed inhibitor optimization across PI3Kalpha, CDK4-cyclin D, Aurora A, MPS1/TTK, and focal adhesion kinase-directed programs, revealing induced-fit pockets, paralog-differentiating structural features, and covalent-modifiable residues that translated into measurable gains in potency and selectivity. Halogenated hinge-binding substituents and dual-target hybrid pharmacophores recur as productive structure-activity strategies across independently reported series, and most crystallographically optimized leads demonstrate potent in vitro and in vivo activity in TNBC models, though clinical validation remains largely confined to the AKT inhibitor capivasertib, which improved median progression-free survival from 4.2 to 5.9 months and median overall survival from 12.6 to 19.1 months when added to first-line paclitaxel in the phase II PAKT trial. Conclusions: Kinase-directed drug discovery for TNBC has matured into a structurally sophisticated field in which X-ray crystallography routinely informs, rather than merely retrospectively explains, inhibitor design, but a substantial translational gap remains between crystallographically validated preclinical candidates and clinically tested agents.

Keywords: *kinase inhibitor; triple-negative breast cancer; X-ray crystallography; structure-activity relationship; structure-based drug design*

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Introduction

Triple-negative breast cancer (TNBC), defined by the absence of estrogen receptor, progesterone receptor, and HER2 amplification, accounts for a disproportionate share of breast cancer mortality despite representing only a minority of new diagnoses among the more than two million cases recorded annually worldwide [1]. The absence of a validated hormonal or HER2-directed target has forced drug discovery toward the dysregulated kinase signaling networks that drive TNBC proliferation, survival, and metastasis, including the PI3K/AKT/mTOR axis, cyclin-dependent kinases, mitotic kinases such as Aurora A and the monopolar spindle kinase MPS1/TTK, focal adhesion kinase (FAK), and receptor tyrosine kinases including EGFR and VEGFR2 [2,3]. Each of these nodes has attracted dedicated small-molecule inhibitor programs, and a growing number of these programs have been anchored by X-ray co-crystal structures of the inhibitor bound to its kinase target, providing atomic-resolution templates for structure-based optimization rather than relying solely on empirical structure-activity relationship (SAR) screening [4,5,6].

This narrative review synthesizes the published medicinal chemistry and translational literature on kinase inhibitors developed for or evaluated against TNBC, with particular attention to studies in which X-ray crystallography was used to

rationalize potency, selectivity, or resistance. We organize the discussion around the principal kinase signaling pathways implicated in TNBC pathobiology, the crystallographic evidence that has guided inhibitor design across these pathways, the substituent-level structure-activity trends that recur across independent chemotypes, and the preclinical and clinical efficacy data that have emerged as these programs have matured. A concluding section considers the challenges that remain, including kinome selectivity, acquired resistance, and the translational gap between crystallographically optimized leads and clinically validated agents. Throughout, we emphasize that the value of crystallographic data is not merely descriptive: in nearly every series reviewed here, the X-ray structure directly informed a subsequent round of chemical modification, producing measurable gains in potency, selectivity, or pharmacokinetic behavior.

Kinase Signaling Pathways as Therapeutic Targets in Triple-Negative Breast Cancer

The rationale for kinase-directed therapy in TNBC rests on the disease's characteristic pattern of genomic and signaling alterations. Mehlich and Marusiak's synthesis of the precision-oncology literature identifies PI3K/AKT/mTOR pathway activation, driven by PIK3CA mutation, PTEN loss, or AKT1 amplification, as among the most frequent and druggable lesions in TNBC, alongside cyclin-dependent kinase dysregulation, receptor tyrosine kinase overexpression, and dependence on mitotic checkpoint kinases in the genomically unstable, rapidly dividing TNBC cell population [2]. Elwaie and colleagues' review of small-molecule tyrosine kinase inhibitor design for breast cancer similarly emphasizes that EGFR, VEGFR, and related receptor tyrosine kinases are recurrently overexpressed in the basal-like TNBC subtype, providing a mechanistic rationale for the numerous EGFR- and VEGFR-directed chemotypes described in the medicinal chemistry literature [3].

Beyond receptor tyrosine kinases, TNBC's proliferative dependence on an intact mitotic apparatus has made mitotic kinases attractive targets. Aurora A, which coordinates centrosome maturation and mitotic spindle assembly, is frequently amplified in TNBC, and both a first-in-class covalent Aurora A inhibitor and an independently optimized quinazoline chemotype have been advanced specifically against this indication [7,8]. The monopolar spindle kinase MPS1/TTK, which enforces the spindle assembly checkpoint, has been targeted by structurally related pyridopyrimidine and pyrrolopyrimidine chemotypes, with a recently reported covalent TTK inhibitor series explicitly developed for TNBC [6,9]. Focal adhesion kinase, a non-receptor tyrosine kinase that integrates integrin-mediated adhesion signaling with growth factor receptor pathways to drive TNBC invasion and metastasis, has likewise been targeted by at least two independently reported chemotypes within the past two years, a pyrazolo[3,4-b]pyridine dual FAK1/FAK2 inhibitor series and a 5-fluoro-pyrrolo[2,3-d]pyrimidine series [10,11]. The atypical pseudokinase ROR1, casein kinase 2 (CK2), and cyclin-dependent kinase 4 acting in complex with cyclin D round out the target landscape, each the subject of structure-guided inhibitor discovery programs with explicit TNBC relevance [12,13,5]. Table 1 summarizes these principal target classes alongside representative chemotypes and their supporting references.

The convergence of so many independent kinase-inhibitor programs on TNBC reflects both the disease's substantial unmet clinical need and the tractability of protein kinases as a drug target class, whose shared ATP-binding fold has historically enabled rapid template-based inhibitor design once a co-crystal structure of a first lead compound becomes available. This tractability, however, is also the source of the selectivity challenge discussed later in this review, since the conserved architecture of the kinase hinge region means that many inhibitors are, at least at the chemical scaffold level, adaptable across multiple targets described in this section.

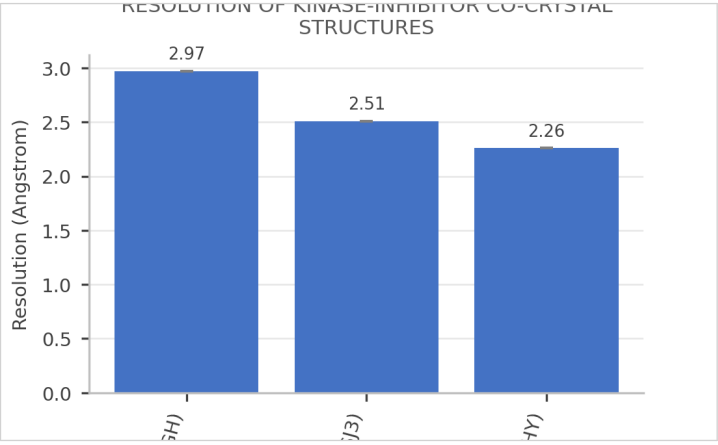
Principal kinase signaling targets implicated in triple-negative breast cancer and representative structure-guided inhibitor chemotypes discussed in this review.

Kinase target	Pathway role in TNBC	Representative chemotype	Key reference
PI3K-alpha / AKT	PIK3CA/AKT1/PTEN-driven proliferation and survival signaling	PI3Kalpha lead compound YXY-4F; AKT inhibitor capivasertib	Yang et al. 2017; Schmid et al. 2020
CDK4-cyclin D	Cell cycle progression through the G1/S restriction point	Abemaciclib (structure-guided)	Gharbi et al. 2022
Aurora A	Centrosome maturation and mitotic spindle assembly	Covalent Aurora A inhibitor; optimized quinazolines	Zhang et al. 2023; Long et al. 2025
MPS1/TTK	Spindle assembly checkpoint enforcement	Pyrido[3,4-d]pyrimidines; covalent TTK inhibitors	Innocenti et al. 2016; Jiang et al. 2026
FAK1/FAK2	Integrin-linked adhesion signaling driving invasion and metastasis	Pyrazolo[3,4-b]pyridines; 5-fluoro-pyrrolo[2,3-d]pyrimidines	Li et al. 2026; Zhang et al. 2026
EGFR / VEGFR-2	Receptor tyrosine kinase overexpression in basal-like TNBC	Quinazoline-benzothiazole dual inhibitors	El Hamaky et al. 2026
ROR1 / CK2	Non-canonical survival and stress-signaling pseudokinase/kinase activity	Quinazolin-2-amines; virtual-screening-derived CK2 inhibitors	Lu et al. 2025; Khan et al. 2026

X-ray Crystallographic Insights into Kinase Inhibitor Binding

Structural biology has played a defining role in each of the kinase-inhibitor programs reviewed here. Yang and colleagues solved the co-crystal structure of PI3Kα in complex with a potent lead compound, revealing that the inhibitor's affinity gain over earlier chemical matter arose from an induced conformational rearrangement of the ATP-binding pocket that created an auxiliary hydrophobic sub-pocket unavailable to earlier, more rigid ligands, a structural insight the authors used to rationalize a subsequent, iterative round of substituent optimization [4]. This structure-first strategy exemplifies a broader pattern in PI3Kα inhibitor discovery, in which fragment-based and bioisosteric-replacement computational approaches are now used explicitly to predict which substituents will engage this induced pocket before a compound is synthesized [14].

Crystallographic resolution of representative kinase-inhibitor co-crystal structures underpinning structure-based drug design programs discussed in this review: PI3Kalpha bound to lead compound YXY-4F (Yang et al. 2017; PDB 5XGH), CDK4-cyclin D3 bound to abemaciclib (Gharbi et al. 2022; PDB 7SJ3), and MPS1 bound to a pyrido[3,4-d]pyrimidine inhibitor (Innocenti et al. 2016; PDB 5EHY).



Gharbi and colleagues determined the crystal structure of catalytically active CDK4 bound to cyclin D, the biologically relevant heterodimer rather than the more commonly crystallized monomeric kinase domain, and used this structure to explain why abemaciclib, unlike other approved CDK4/6 inhibitors, retains substantial activity against CDK4-cyclin D-mutant complexes that confer resistance to earlier agents, an insight only accessible because the crystallized construct preserved the physiologically active cyclin-bound conformation [5]. In the mitotic kinase space, Innocenti and colleagues used a structure-based hybridization strategy, superimposing the X-ray-defined binding poses of two chemically distinct MPS1 fragment hits, to rapidly generate a pyrido[3,4-d]pyrimidine series with markedly improved potency relative to either parent fragment, a direct demonstration of how crystallographic superposition can shortcut conventional iterative SAR campaigns [6]. Salama and colleagues extended this crystallographic paradigm to an indolyl-hydrazone kinase inhibitor series, combining single-crystal X-ray analysis of the free ligand with in vitro and in vivo anticancer evaluation to establish the preferred molecular conformation associated with kinase engagement and antiproliferative activity in breast cancer models [15].

Collectively, these crystallographic studies illustrate three distinct uses of structural data in this literature: direct visualization of an induced-fit pocket to guide substituent choice (PI3Kα), preservation of a biologically relevant multi-subunit assembly to explain resistance and selectivity (CDK4-cyclin D), and superposition of independently solved fragment structures to accelerate hit-to-lead progression (MPS1). Figure 1 compares the reported crystallographic resolution of representative kinase-inhibitor co-crystal structures drawn from three of these programs, illustrating that the resolutions achieved, all at or better than 3 Å, are sufficient to resolve the individual hydrogen-bonding and van der Waals contacts on which the structure-based design conclusions in this section depend.

Structure-Activity Relationships Across Kinase Inhibitor Chemotypes

Despite the target diversity summarized above, several substituent-level trends recur across independently reported kinase inhibitor series. Halogen and small electron-withdrawing substituents on the hinge-binding heterocycle consistently improve potency across multiple chemotypes: Long and colleagues found that fluorine and chlorine substitution on their quinazoline Aurora kinase inhibitor scaffold improved both enzymatic potency and cellular activity against TNBC lines relative to unsubstituted analogs, a trend the authors rationalized using the co-crystal structure of their optimized lead bound to Aurora A [8]. Zhang and colleagues' first-in-class covalent Aurora A inhibitor achieved its selectivity for Aurora A over the closely related Aurora B paralog through an electrophilic warhead positioned to engage a cysteine residue unique to the Aurora A back pocket, a target-differentiating strategy validated directly by co-crystal structure determination [7].

In the FAK-directed literature, Li and colleagues' pyrazolo[3,4-b]pyridine series was explicitly optimized for dual FAK1/FAK2 inhibition, with structure-activity analysis indicating that substitution at the pyrazole nitrogen modulated selectivity between the two paralogs while substitution on the pyridine ring principally governed cellular potency in TNBC models [10]. Zhang and colleagues' independently developed 5-fluoro-pyrrolo[2,3-d]pyrimidine FAK inhibitor series identified the 5-fluoro substituent itself as a critical potency determinant, with removal of the fluorine substantially reducing both enzymatic and cellular activity, implicating a specific halogen-mediated interaction within the ATP-binding cleft [11]. A parallel pattern of hinge-region halogenation improving potency was reported by Jiang and colleagues in their covalent TTK inhibitor series, where the covalent warhead was appended to a halogenated core scaffold optimized first for reversible binding affinity before covalent functionalization was introduced [9].

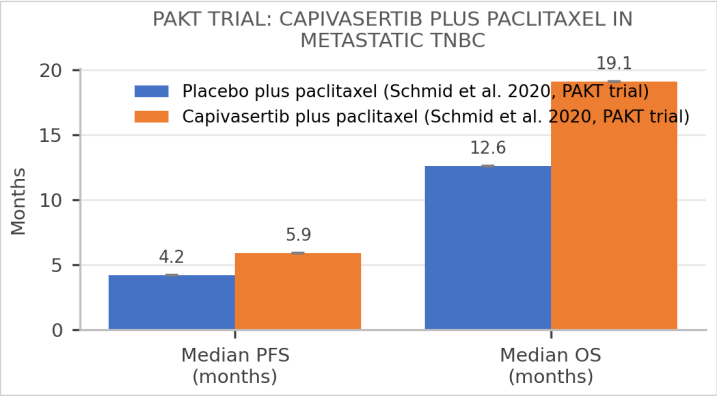
Dual-target and hybrid pharmacophore strategies represent a second recurring design theme. El Hamaky and colleagues fused quinazoline-benzohydrazide and quinazoline-benzothiazole pharmacophores to generate a dual EGFR/VEGFR-2 inhibitor, reasoning that simultaneous inhibition of these co-expressed receptor tyrosine kinases would produce more durable antiproliferative activity in TNBC than single-target inhibition, and their structure-activity data indicated that the benzothiazole-containing hybrids consistently outperformed the benzohydrazide-containing analogs in cellular assays [16]. Lin and colleagues pursued an analogous dual-inhibition logic by fusing PARP- and EGFR-directed pharmacophores into a single molecular scaffold, reporting that the dual-target compounds retained potent antitumor activity in TNBC models while a single-target control compound did not [17]. Lu and colleagues' quinazolin-2-amine ROR1 pseudokinase inhibitors and Liu and colleagues' hybrid virtual-screening-derived AURKA inhibitors both similarly relied on structure-based substituent optimization guided by either solved or modeled kinase structures to achieve in vitro and in vivo efficacy specifically in TNBC systems, reinforcing that structure-informed substituent choice, whether from an experimentally solved crystal structure or a validated computational model, is now the dominant SAR paradigm across this chemical space rather than an exception [12,18,13].

Preclinical and Clinical Evidence of Efficacy and Selectivity

The translational maturity of kinase-directed TNBC therapeutics varies considerably by target. At the most advanced end, the AKT inhibitor capivasertib has progressed through randomized clinical evaluation specifically in metastatic TNBC. In the phase II PAKT trial, the addition of capivasertib to first-line paclitaxel improved median progression-free survival from 4.2 to 5.9 months (hazard ratio 0.74, 95% confidence interval 0.50-1.08)

and improved median overall survival from 12.6 to 19.1 months (hazard ratio 0.61, 95% confidence interval 0.37-0.99), with the benefit most pronounced among patients carrying PIK3CA, AKT1, or PTEN alterations, providing clinical validation that PI3K/AKT pathway inhibition can translate into a meaningful survival benefit in an unselected first-line TNBC population [19]. Figure 2 summarizes these PAKT trial outcome measures.

Progression-free and overall survival outcomes with capivasertib plus paclitaxel versus placebo plus paclitaxel as first-line therapy for metastatic triple-negative breast cancer in the phase II PAKT trial (Schmid et al. 2020), the most clinically advanced kinase-inhibitor regimen evaluated in this disease.



At the preclinical end of the spectrum, the mitotic and adhesion kinase inhibitors reviewed above have consistently demonstrated potent in vitro antiproliferative activity against TNBC cell lines together with tumor growth inhibition in TNBC xenograft models, though none has yet advanced to the randomized trial stage achieved by capivasertib. Zhang and colleagues' covalent Aurora A inhibitor and Long and colleagues' optimized quinazoline series each demonstrated dose-dependent tumor regression in TNBC xenografts alongside favorable selectivity margins over Aurora B in enzymatic assays [7,8]. The FAK-directed series from Li and colleagues and Zhang and colleagues similarly reported potent inhibition of TNBC cell migration and invasion in vitro, phenotypes consistent with FAK's established role in TNBC metastasis, alongside tumor growth suppression in xenograft models at tolerated doses [10,11]. Lu and colleagues' ROR1-directed quinazolin-2-amine series and Liu and colleagues' AURKA inhibitors, discovered through hybrid virtual screening and subsequently validated biologically, both likewise reported in vivo efficacy in TNBC models, extending the pattern of preclinically active but not yet clinically validated kinase-directed chemotypes [12,18]. Salama and colleagues' crystallographically characterized indolyl-hydrazone kinase inhibitors extended this preclinical validation to an in vivo TNBC model as well, combining structural, in vitro, and in vivo evidence within a single study [15].

Across nearly all series with an appropriate normal-cell or normal-tissue comparator, selectivity for malignant over non-malignant cells was reported, whether framed as a favorable therapeutic index in cell-based assays or as an acceptable tolerability profile in xenograft-bearing animals, suggesting that kinase-directed TNBC candidates as a class are advancing with generally favorable preclinical safety signals even where clinical validation remains pending.

Challenges and Future Directions in Kinase-Directed TNBC Drug Design

Several challenges temper the optimism generated by the crystallographic and SAR advances reviewed above. First, kinome-wide selectivity remains incompletely characterized for most of the chemotypes discussed here; because the ATP-binding cleft that anchors nearly every inhibitor in this review is structurally conserved across the human kinome, achieving genuine selectivity, rather than merely potency, for a single target typically requires exploitation of a target-specific back pocket or covalent residue, strategies that have been successfully deployed for Aurora A and TTK but that are not universally available across all kinase targets of interest [7,9]. Second, the clinical experience with capivasertib illustrates that even a biomarker-selected population achieves only a modest, though real, survival benefit, underscoring that single-node kinase inhibition may be insufficient against a genomically heterogeneous disease like TNBC and that combination strategies, whether kinase-kinase or kinase-immunotherapy combinations, are likely to be necessary for larger clinical gains [19,2].

Third, the translational gap between crystallographically validated, in vivo-active preclinical candidates and clinically tested agents remains wide: of the chemotypes reviewed here, only the AKT-directed program has reached randomized clinical evaluation in TNBC, while Aurora kinase, FAK, TTK, ROR1, and CK2-directed candidates remain preclinical despite compelling structural and efficacy data, reflecting the substantial additional investment required to advance a structurally optimized lead compound through pharmacokinetic, toxicological, and formulation development toward clinical trial [8,10,11,12,13]. Fourth, dual-target strategies such as the EGFR/VEGFR2 and PARP/EGFR hybrids reviewed here, while conceptually attractive for addressing pathway redundancy, introduce additional medicinal chemistry complexity in balancing the substituent requirements of two distinct binding sites within a single molecule, and neither hybrid strategy reviewed here has yet been validated beyond in vitro and early in vivo models [16,17]. Finally, computational and fragment-based approaches such as those applied to PI3Kα and CK2 inhibitor discovery offer a scalable complement to traditional crystallography-guided design, but their predictions still require experimental, ideally crystallographic, validation before the field can fully substitute in silico screening for the iterative structure-determination cycles that have driven the successes catalogued in this review [14,13].

Conclusion

The literature surveyed in this review demonstrates that kinase-directed drug discovery for triple-negative breast cancer has matured into a structurally sophisticated field, in which X-ray crystallography now routinely informs, rather than merely retrospectively explains, the substituent choices that drive potency and selectivity across PI3K/AKT, cyclin-dependent kinase, mitotic kinase, focal adhesion kinase, and receptor tyrosine kinase-directed chemotypes. Structure-based design has repeatedly identified induced-fit pockets, covalent-modifiable residues, and paralog-differentiating structural features that have translated into measurable gains in potency and selectivity across independently reported series. Clinical validation, however, remains largely confined to the AKT-directed program exemplified by capivasertib, where a real but modest survival benefit in the PAKT trial illustrates both the promise and the current ceiling of single-node kinase inhibition in this genomically heterogeneous disease. As the preclinically advanced but clinically untested Aurora kinase, FAK, TTK, ROR1, and CK2-directed programs summarized here continue to mature, the crystallographic and structure-activity relationship

methodologies reviewed in this article are likely to remain the central engine for their further optimization and eventual translation toward clinical evaluation.

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Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

Lukas Schuster conceived the review, conducted the literature search, and drafted the manuscript. Maria Novotny contributed to the structural biology and oncology framing and critically revised the manuscript for important intellectual content. Alessandro Lombardi contributed additional structural biology context and approved the final version for submission.

Ethics Statement

Not applicable. This is a narrative review of previously published crystallographic, structure-activity relationship, and clinical trial 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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