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Review paper

Phosphoinositide 3-kinase-based dual-target inhibitors for cancer therapy: rational design, structure-activity relationships and biological evaluation

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Abstract

Background and purpose: The phosphoinositide 3-kinase (PI3K)/AKT/mTOR pathway is dysregulated in 30-50 % of human cancers. PI3K inhibition is clinically validated, yet of the seven PI3K pathway inhibitors approved by the US Food and Drug Administration, four have had indications withdrawn and two are no longer marketed, principally because narrow therapeutic windows and overall-survival detriments offset progression-free survival gains. Pathway reactivation and adaptive resistance further limit single-agent activity, motivating single-molecule dual-target inhibitors. **Experimental approach:** A structured search (January 2019 - July 2026) retained original medicinal-chemistry reports of single chemical entities engaging PI3K with a second oncology target, for which biochemical potency against both targets and an interpretable structure-activity relationship were reported. Five combinations dominated retrieval - PI3K/mTOR, PI3K/HDAC, PI3K/PARP, EGFR/PI3K and PI3K/BRD4 - and twenty representative leads are analysed. **Key results:** Each compound is assigned an explicit level of evidence for dual-target engagement, distinguishing measured biochemical and cellular target engagement from structural hypotheses generated by docking; nine of twenty leads reach the highest tier. *In vivo* pharmacokinetics are available for only seven leads and plasma protein binding for none, so a uniform *in silico* ADMET profile is reported for all compounds. Predictions reproduced the solubility-permeability trade-off and indicated near-complete plasma protein binding for the most lipophilic hybrids, but under-predicted clearance by up to two orders of magnitude and returned false-positive hERG calls for every compound in which the liability was measured. Solubilizing groups on the solvent-exposed vector improved solubility more than 100-fold without loss of dual potency, whereas carboxylic acids, hydroxamate zinc-binding groups and N-acylhydrazone linkers each improved one property at a cost in potency, permeability, oral bioavailability or chemical stability. **Conclusion:** Dual-target PI3K inhibition is now clinically validated: the pan-PI3K/mTORC1/2 inhibitor gedatolisib was approved in July 2026. The principal obstacles are not biochemical potency, which is routinely sub-nanomolar, but the 80- to 340-fold potency imbalance between the two targets of most hybrids, the lack of experimental DMPK data, low oral bioavailability of benzamide-based hybrids, and a regulatory environment now requiring randomized evidence of survival benefit.

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Keywords

Phosphoinositide 3-kinase; ADMET; molecular hybridization; structure-activity relationships; structure-based drug design

Introduction

Cancer is a multifactorial and heterogeneous disease characterized by uncontrolled cell proliferation resulting from the accumulation of genetic, epigenetic, and metabolic alterations that disrupt normal cellular homeostasis. It remains one of the leading causes of morbidity and mortality worldwide, with its incidence continuing to rise owing to population aging, environmental exposures, lifestyle factors, and inherited genetic susceptibility. As per the GLOBOCAN 2022 estimate [1], around 20 million new cancer cases and 9.7 million cancer-related deaths were recorded worldwide. Lung, breast, colorectal, prostate, and stomach cancers are the most prevalent types of cancer and lung cancer continues to be the deadliest type of cancer. The global burden of cancer is expected to rise to 35 million new cases every year in 2050 [2]. The gaps in cancer prevention programs, early detection and treatment indicate a critical need for better strategies. Tumour initiation and progression are driven by multiple interconnected hallmarks, including sustained proliferative signalling, metabolic reprogramming, genomic instability, evasion of apoptosis, angiogenesis, immune evasion, and metastatic dissemination, all of which contribute to disease progression and therapeutic failure [3,4].

Although substantial advances have been achieved through surgery, chemotherapy, radiotherapy, immunotherapy, and molecularly targeted therapies, their long-term clinical efficacy is frequently compromised by tumour heterogeneity, activation of compensatory signalling networks, and acquired drug resistance. [5] Dual-target inhibitors have consequently emerged as a promising pharmacological strategy. By simultaneously modulating two complementary oncogenic pathways, they enhance anticancer efficacy, reduce pathway crosstalk and address adaptive resistance, and may improve therapeutic outcomes relative to conventional single-target agents. This multitarget-directed approach has therefore become an important focus in contemporary anticancer drug discovery and medicinal chemistry for the development of more effective and durable therapeutic drugs [6-8].

Phosphoinositide 3-kinases signalling pathway and its aberrations in cancer

Phosphoinositide 3-kinases (PI3Ks) are a group of lipid kinases that are located in the plasma membrane and play a key role in the regulation of important cellular functions including growth, proliferation, survival, metabolism and angiogenesis [9]. PI3Ks can be categorized into three classes based on their structure, regulation and substrate specificity. Of these, class I PI3Ks are the best studied because of their major contribution to cancer development. Class I is further divided into Class IA and IB [10]. Class IA PI3Ks are composed of a regulatory subunit (p85) and a catalytic subunit (p110). Class IB contains the p110γ catalytic subunit encoded by the gene PIK3CG. Class IA catalytic isoforms, p110α, p110β, and p110δ, are encoded by the genes PIK3CA, PIK3CB and PIK3CD, respectively. The catalytic subunit of p110 has five functional domains: adaptor domain (ABD); helical domain; C2 domain; Ras-binding domain (RBD); and the ATP-binding site required for activity (kinase domain). PI3Kα and PI3Kβ are expressed in most tissues, while PI3Kδ and PI3Kγ are mainly expressed in hematopoietic cells. Unlike Class II PI3Ks, which are monomeric enzymes with no regulatory subunit, Class III PI3Ks are heterodimers of Vps34 and Vps15, the regulatory subunit [11]. PI3K/AKT signalling pathway is stimulated by extracellular signals like growth factors, receptor tyrosine kinases, cytokines, hormones, and non-receptor tyrosine kinases. In a resting state, the p85 subunit stabilizes and inhibits the p110 catalytic subunit. Once activated, PI3K phosphorylates phosphatidylinositol 4,5-bisphosphate (PIP2) to produce phosphatidylinositol 3,4,5-trisphosphate (PIP3). This second messenger recruits and activates downstream effectors such as AKT, thereby stimulating cell growth, proliferation and survival [12,13]. The pathway is negatively controlled by the tumour suppressor PTEN, which dephosphorylates PIP3 to PIP2 to prevent excessive activation of downstream signalling [14].

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The PI3K/AKT signalling pathway is one of the most commonly hyperactivated pathways in human cancers, including breast, lung, colon, prostate, ovarian, brain, gastric and endometrial cancers [15]. Its dysregulation occurs through several mechanisms, such as PI3K gene amplification, activating mutations in PIK3CA, PTEN loss or inactivation, and mutations in upstream or downstream signalling molecules [16]. Among the Class I PI3K isoforms, PIK3CA is the most commonly mutated gene. Two hotspot mutations predominate: E545K in the helical domain and H1047R in the kinase domain. The former reduces the inhibitory interaction of the p85 regulatory subunit with p110, whereas the latter enhances membrane binding; both increase catalytic activity [17,18]. On the other hand, PIK3CB, PIK3CD and PIK3CG are very rarely mutated, but tend to be overexpressed or amplified, leading to the progression of cancer. The tumour suppressor PTEN opposes this pathway by converting PIP3 back to PIP2, thereby limiting AKT activation [19-21]. Loss or mutation of PTEN therefore results in sustained PI3K signalling, uncontrolled cell growth, enhanced survival and therapeutic resistance [22]. PIK3CA mutations occur in approximately 14 % of tumours, and PTEN mutations or deletions in approximately 16 %. Overall, disturbances in the PI3K/AKT/mTOR pathway occur in 30 to 50 % of human cancers, which is why it has been a major focus of anticancer drug development [23].

Phosphoinositide 3-kinases inhibitors

Seven inhibitors acting on class I PI3K have received regulatory approval in the United States. The first was idelalisib (2014), a PI3Kδ-selective agent [24]. It was followed by the intravenous pan-class I inhibitor copanlisib (2017) [25], the PI3Kδ/γ inhibitor duvelisib (2018) [26] and the PI3Kα-selective inhibitor alpelisib (2019) [27]. Three further agents have since been approved: the dual PI3Kδ/casein kinase-1ε (CK1ε) inhibitor umbralisib (2021) [28], the PI3Kα-selective inhibitor and mutant-p110α degrader inavolisib (October 2024) [82] and, most recently, the pan-PI3K/mTORC1/2 inhibitor gedatolisib (July 2026) [83, 84]. Precise terminology is important when describing the status of this class, because the three outcomes that are often conflated are distinct: withdrawal of a single indication granted under accelerated approval; withdrawal of a product from the market; and conversion of an accelerated approval into regular approval following a confirmatory trial.

Four of these agents have had indications withdrawn, in every case an indication that had been granted under accelerated approval on the basis of single-arm response data (Table 1). The accelerated approvals of duvelisib for relapsed or refractory follicular lymphoma (FL), and of idelalisib for relapsed FL and small lymphocytic lymphoma (SLL), were voluntarily withdrawn with effect from December 2021 and February 2022, respectively. Both agents nevertheless retain the haematological indications granted regular approval: relapsed chronic lymphocytic leukaemia (CLL) with rituximab for idelalisib, and relapsed or refractory CLL/SLL after at least two prior therapies for duvelisib [29,30]. Umbralisib lost both of its accelerated approvals (marginal zone lymphoma and FL) with effect from May 2022 and was subsequently withdrawn from the United States market altogether, so that the only approved dual-target PI3K agent of its era is no longer available [31-32]. Copanlisib held a single accelerated approval for relapsed FL, and its withdrawal in March 2024 removed the product from the United States market as well [33]. It is therefore inaccurate to state, as is common in the literature, that these drugs were withdrawn because of toxicity alone. The proximate regulatory cause was the failure of postmarketing randomized trials to confirm clinical benefit. Several studies showed unfavourable overall-survival trends despite progression-free survival gains, an outcome the FDA attributed largely to treatment-related mortality.

Moreover, grade 3 or higher adverse events were reported in a majority of patients receiving these agents as monotherapy. Immune-mediated colitis, pneumonitis, hepatotoxicity and opportunistic infection predominated for the δ- and γ-directed agents, whereas on-target hyperglycaemia and rash predominated for the

α-selective agents. Pharmacovigilance analyses of postmarketing reports confirm these signals as class effects rather than compound-specific idiosyncrasies [29-31]. Following a 2022 advisory committee review of the class in haematological malignancies, randomized rather than single-arm evidence is now expected to support approval in these indications, and dose optimization is expected to be addressed prospectively rather than by using the maximum tolerated dose. Any new PI3K-based agent, including the dual-target compounds reviewed here, must therefore be designed from the outset with a therapeutic window wide enough to survive randomized comparison, reframing selectivity and ADMET optimization as efficacy-enabling rather than merely desirable objectives.

Table 1. Regulatory status of approved PI3K pathway inhibitors

Drug (brand)	Primary molecular target(s)	Approval year	Approval basis	Indication(s) withdrawn (effective date)	Current status
Idelalisib (Zydelig)	PI3Kδ	2014 [24]	Regular (CLL) + accelerated (FL, SLL)	Relapsed FL; relapsed SLL (18 Feb 2022)	Marketed; retains regular approval for relapsed CLL with rituximab; boxed warning (hepatotoxicity, diarrhoea/colitis, pneumonitis, intestinal perforation, infections)
Copanlisib (Aliqopa)	pan-class I PI3K (α/δ-preferring), i.v.	2017 [25]	Accelerated	Relapsed FL (18 Mar 2024)	No longer marketed in the United States; the withdrawn indication was its only one
Duvelisib (Copiktra)	PI3Kδ/γ	2018 [26]	Regular (CLL/SLL) + accelerated (FL)	Relapsed/refractory FL (17 Dec 2021)	Retains regular approval for relapsed/refractory CLL/SLL after >=2 prior therapies; an advisory committee advised against retention in 2022 and development has been refocused on T-cell lymphoma; boxed warning
Alpelisib (Piqray; Vijoice)	PI3Kα-selective	2019 [27]	Regular (breast cancer); accelerated (PROS)	None	Marketed; PIK3CA-mutated, HR+/HER2- advanced breast cancer with fulvestrant, and PIK3CA-related overgrowth spectrum
Umbralisib (Ukoniq)	dual PI3Kδ/CK1ε	2021 [28]	Accelerated	Relapsed/refractory MZL and FL (31 May 2022)	Withdrawn from the United States market; notable as the only approved dual-target PI3K agent before 2026
Inavolisib (Itovebi)	PI3Kα-selective inhibitor and mutant-p110α degrader	2024 [82]	Regular (randomized INAVO120)	None	Marketed; with palbociclib and fulvestrant for endocrine-resistant, PIK3CA-mutated, HR+/HER2- advanced breast cancer
Gedatolisib (Revtorpyk)	pan-class I PI3K + mTORC1/mTORC2 (dual PI3K/mTOR), i.v.	2026 [83,84]	Regular (randomized VIKTORIA-1)	None	Marketed; with fulvestrant +/- palbociclib for HR+/HER2-, PIK3CA wild-type advanced breast cancer; first approved dual PI3K/mTOR inhibitor

Against this background, the two most recent approvals are encouraging and are directly relevant to the subject of this review. Inavolisib, which both inhibits PIK3CA-mutant p110α and promotes its degradation, was approved in October 2024 in combination with palbociclib and fulvestrant for endocrine-resistant, PIK3CA-mutated, hormone receptor-positive, HER2-negative advanced breast cancer based on the randomized INAVO120 trial [28,83]. Gedatolisib, a pan-class I PI3K and mTORC1/2 inhibitor, was approved in July 2026 in combination with fulvestrant, with or without palbociclib, for hormone receptor-positive, HER2-negative, PIK3CA wild-type locally advanced or metastatic breast cancer progressing on or after a CDK4/6 inhibitor and an aromatase inhibitor. In the PIK3CA wild-type cohort of the randomized phase 3 VIKTORIA-1 trial, the triplet and doublet regimens produced median progression-free survival of 9.3 and 7.4 months, respectively, versus 2.0 months for fulvestrant alone (hazard ratios 0.24 and 0.33). Treatment-related discontinuation occurred in only 2.3 and 3.1 % of patients [84]. Gedatolisib is thus the first dual PI3K/mTOR inhibitor to reach the market, and its approval converts the central premise of this review from a design hypothesis into a clinically validated strategy.

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Two further observations deserve emphasis. First, the dominant toxicity of gedatolisib was stomatitis rather than the severe hyperglycaemia that has constrained PI3Kα-selective agents, with any-grade hyperglycaemia in only 9 to 12 % of patients, indicating that broad pathway inhibition does not necessarily produce a narrower window than isoform-selective inhibition. Second, gedatolisib is administered intravenously, so that oral bioavailability, a property on which many of the preclinical hybrids discussed below perform poorly, was not a prerequisite for approval [84].

Interest in PI3K inhibitors consequently remains strong rather than diminished. Recent studies describe renewed interest in targeting the PI3K/AKT/mTOR axis, driven by mutant-selective and allosteric chemotypes, degrader modalities, improved patient selection and rational combinations rather than by further pan-inhibitor optimization [22,24,37]. Multitarget PI3K inhibition and combination therapy are therefore best understood as two among several concurrent routes to a wider therapeutic index, and the remainder of this review assesses how far the dual-target route has progressed and what the medicinal chemistry has actually established (Figures 1 and 2) [34-38].

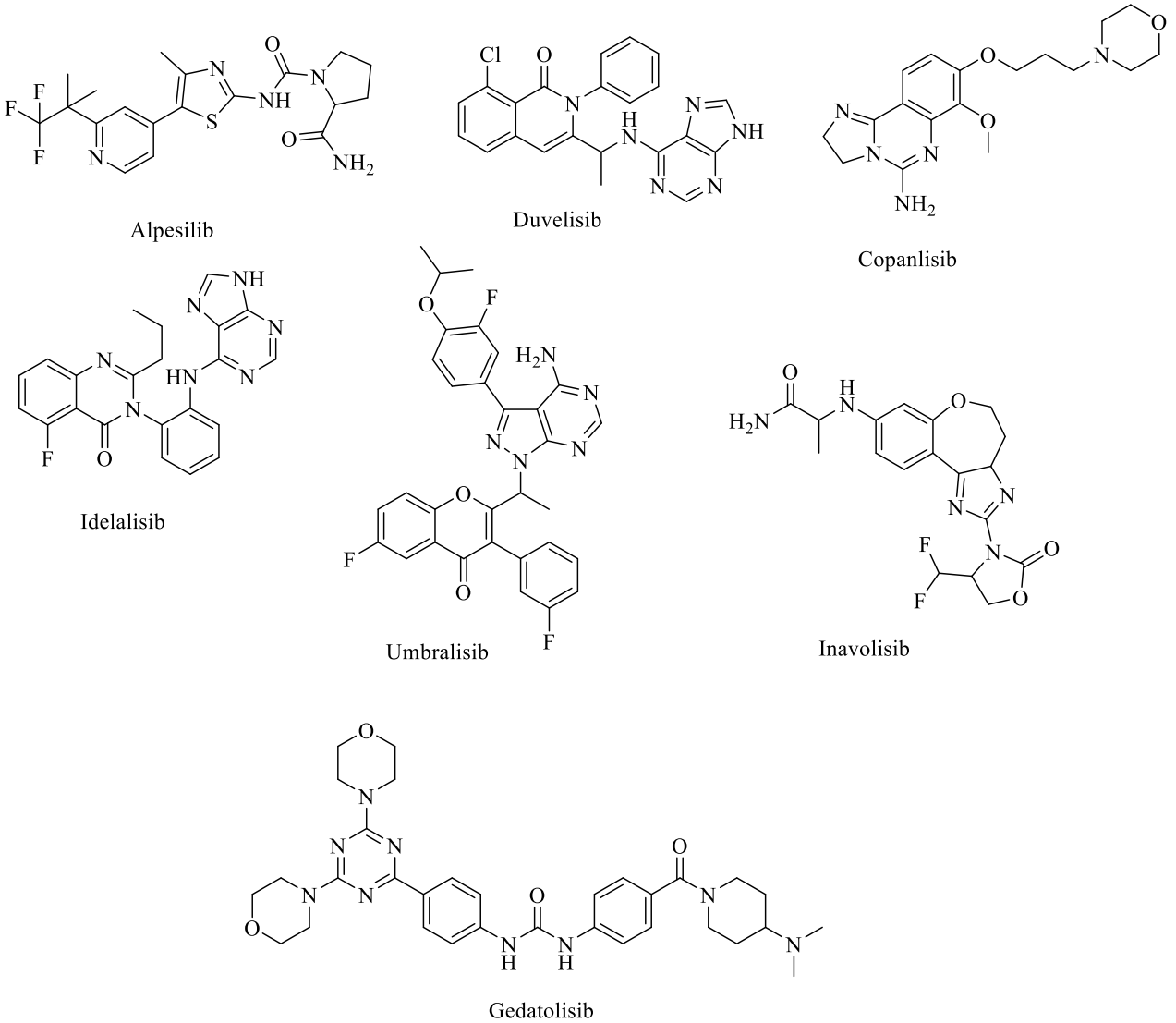


Figure 1. FDA-approved PI3K inhibitors for cancer therapy

Dual-target strategy

Selective PI3K inhibitors are limited by the activation of compensatory pathways, tumour heterogeneity and acquired resistance. These limitations have prompted dual-target strategies, in which PI3K is inhibited

together with a second molecular target critical for cancer progression and therapeutic resistance [36,37]. There is a large amount of cross-talk between the PI3K signalling pathway and other oncogenic pathways that justifies this strategy [38]. A few combinations of PI3K have recently been studied, including PI3K/mTOR, PI3K/HDAC, PI3K/PARP, EGFR/PI3K and PI3K/BRD4, all of which focus on pan pathway inhibition, improved antitumor activity and resistance mechanisms [39-42].

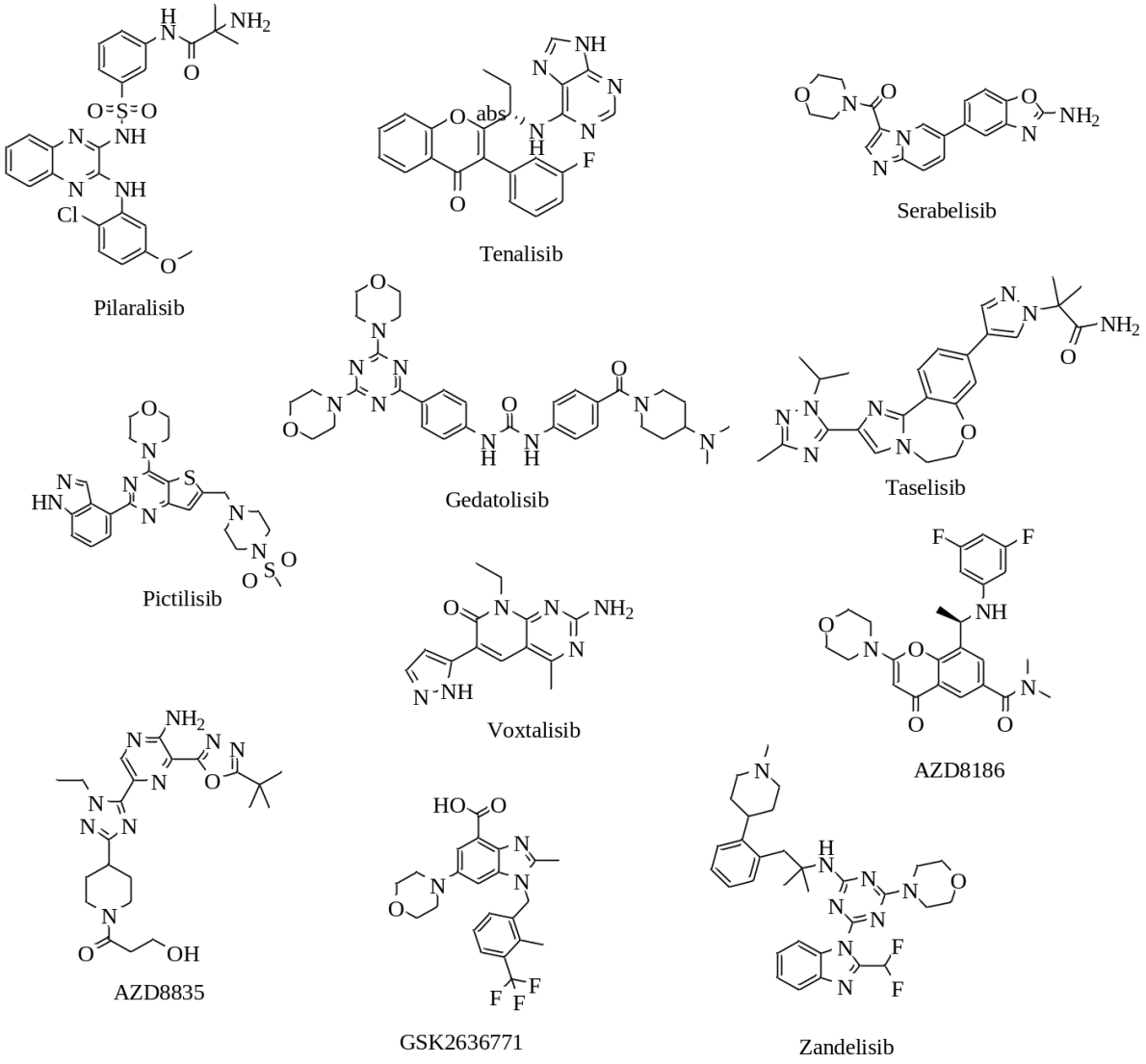


Figure 2. PI3K inhibitors currently under clinical investigation for cancer therapy

Compared with conventional combination therapy using two separate inhibitors, single-molecule dual inhibitors may provide synchronized target engagement and more predictable pharmacological exposure [43]. In addition, new techniques such as scaffold hopping, molecular hybridization, pharmacophore fusion, bioisosteric replacement and structure-based drug design have enabled the design of compounds that can simultaneously target two complementary targets. Thus, dual-target inhibitors targeting PI3Ks have become a promising approach toward the enhancement of therapeutic efficiency and the establishment of more effective and long-lasting anticancer treatment [44,45].

The present review highlights the recent progress of the newly developed PI3K-based dual-target inhibitors, including the most important combinations of PI3K/mTOR, PI3K/HDAC, PI3K/PARP, EGFR/PI3K and PI3K/BRD4. The compounds reported are discussed in terms of their structural scaffolds, synthetic approach, key structural modifications, target interactions, SAR, biological activity, pharmacokinetic properties, and *in vivo* activity. The importance of how changes in substituents, heterocyclic systems, linkers, and

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pharmacophoric groups affect dual-target potency and selectivity is emphasized. This review compares the structural and biological properties of various target combinations to identify key trends that govern the activity of PI3K-based dual-target inhibitors, their limitations, and future directions for developing and optimizing them to generate more potent anticancer agents.

Scope, literature search strategy and selection criteria

Because the volume of literature on PI3K inhibition is large and heterogeneous, the boundaries of this review were defined prospectively. PubMed/MEDLINE, Scopus, Web of Science and SciFinder were searched for records published between January 2019 and July 2026 using combinations of the terms ("PI3K" OR "phosphoinositide 3-kinase" OR "phosphatidylinositol 3-kinase" OR PIK3CA) AND ("dual inhibitor" OR "dual-target" OR "dual-targeting" OR multitarget OR multi-target OR hybrid OR bifunctional OR "degrader") AND (design OR synthesis OR "structure-activity"). Reference lists of the retrieved primary papers and of recent reviews of the field were screened manually to capture records missed by the database queries. Searches were last updated in July 2026.

Records were retained when they met all of the following criteria: (i) an original medicinal-chemistry report describing the design and chemical synthesis of a single chemical entity, or a bifunctional degrader, intended to engage PI3K together with one defined second target, (ii) quantitative biochemical, biophysical or degradation potency reported against both targets for at least one compound in the series, (iii) a congeneric series large enough to support an interpretable SAR analysis. Records were excluded when they described coadministration of two separate agents or fixed-dose combinations rather than a single molecule; when the dual-target claim rested exclusively on computational predictions without any experimental potency measurement. When they concerned repurposing or re-profiling of known agents without new synthetic chemistry. When they reported natural-product extracts or mixtures without defined SAR and when they were conference abstracts, patents or theses without accessible experimental data. Papers that reported only cellular antiproliferative potency, with no enzymatic or target-engagement data for either target, were also excluded.

Applying these criteria, the retrieved primary literature partitions unevenly across target pairs. PI3K/mTOR is by a wide margin the most heavily populated combination, followed by PI3K/HDAC, PI3K/PARP, EGFR/PI3K and PI3K/BRD4, which form a second tier in which a small number of well-characterized congeneric series have been reported. These five combinations accounted for the great majority of the records meeting our inclusion criteria and, on that basis, are treated here as the major and most extensively investigated PI3K-based dual-target approaches. They are also the combinations for which independent research groups have reproduced the design concept, which is a precondition for extracting generalisable SAR lessons. Each is, in addition, supported by a specific and testable mechanistic argument rather than by the general observation that two pathways interact.

Demonstrated versus predicted dual-target activity

A review of dual-target agents must be explicit about what has been measured and what has been inferred, because the two are easily conflated in the primary literature. Molecular docking, and to a lesser extent molecular dynamics simulation, recurs in almost every paper discussed below, and in several of them the dual-target claim is supported for one of the two targets principally by a favourable binding interaction. Docking generates a structural hypothesis about how a ligand might occupy a binding site, and is useful for rationalizing an observed SAR, for prioritising synthetic effort and for explaining why a substituent is tolerated at one vector but not another. However, docking alone does not demonstrate enzyme inhibition, and its scoring functions correlate only weakly with measured affinity. A favourable docking score is therefore not evidence of biochemical activity, still less of target engagement in cells, and it cannot establish that the two

activities occur at comparable concentrations - which is the only form of dual-target activity with pharmacological meaning.

Throughout this review we therefore distinguish three kinds of statements. Biochemical inhibition refers to a measured IC_{50}, *K*i or percentage inhibition in a cell-free enzymatic or binding assay, or a measured DC_{50} for a degrader. Cellular target engagement refers to a pharmacodynamic readout specific to the target concerned in intact cells. Examples include suppression of AKT phosphorylation at Ser473 and Thr308 for PI3K; of p70S6K, S6 or 4E-BP1 phosphorylation for mTOR, accumulation of acetylated histone H3 for class I HDACs, or of acetylated α-tubulin for HDAC6, downregulation of BRCA1/2 with loss of RAD51 foci and accumulation of γH2AX for PARP-mediated repair, loss of EGFR autophosphorylation for EGFR and downregulation of MYC for BRD4. Predicted or putative engagement refers to activity supported by docking, pharmacophore mapping or a phenotype consistent with inhibition, but not by direct measurement at that target.

Table 2 summarizes the twenty lead compounds discussed in this review and assigns each to one of four evidence tiers. Tier A denotes quantified biochemical potency against both targets, together with target-specific cellular pharmacodynamic evidence for both and demonstrated *in vivo* antitumor efficacy. Tier B denotes biochemical potency and cellular pharmacodynamic evidence for both targets without *in vivo* efficacy data. Tier C denotes biochemical potency against both targets but incomplete cellular confirmation for one of them. Tier D denotes compounds for which biochemical data exist for only one target, the second being supported by computational or phenotypic argument alone. On this analysis, nine of the twenty leads reach tier A, which is a credible standard for a preclinical literature, and no compound in the selected set falls into tier D-a direct consequence of our inclusion criterion that biochemical potency be reported against both targets. The residual weaknesses are concentrated in tier C and are of two kinds: cellular pharmacodynamic confirmation is sometimes provided for the PI3K arm only, with the second target represented solely by an enzymatic IC_{50} and a docking pose, and in one instance the compound selected for cellular characterization was not the compound with the best dual enzymatic profile, because the latter proved chemically unstable.

Table 2. Comparative biochemical, cellular and *in vivo* evidence for dual-target inhibitors

Com-pounds	Target	Biochemical potency	Potency ratio	Cellular pharmacodynamic evidence	*In vivo* efficacy	Evidence tier	Ref.
1	PI3Kα/mTOR	PI3Kα 0.12 nM; mTOR 3.7 nM	~31×	p-AKT suppression; pan-class I isoform profiling	HCT116 and HT-29 xenografts	A	[53]
2	PI3Kα/δ + mTOR	PI3Kα 0.16 nM; PI3Kδ 0.25 nM; mTOR 3.8 nM	~24×	p-AKT and p-p70S6K (mTORC1 substrate) suppression	HCT116 xenograft, 72.7-82.3 % TGI	A	[54]
3	PI3Kα/mTOR	PI3Kα 0.91 nM; mTOR 15.2 nM	~17×	p-AKT suppression	HCT116 and HT-29 xenografts	A	[55]
4	PI3Kα/mTOR	PI3Kα 2.3 nM; mTOR 10.1 nM	~4×	Reduced PI3K expression, p-AKT and p-mTOR	Not reported (toxicity study only)	B	[56]
5	PI3Kα/mTOR	PI3Kα 0.22 nM; mTOR 23 nM	~105×	p-AKT suppression; G0/G1 arrest; apoptosis	Not reported	B	[57]
6	PI3Kδ/mTOR	PI3Kδ 0.042 μM; mTOR 0.059 μM	~1.4×	p-AKT (S473, T308) and p-RPS6 suppression	Not reported	B	[58]
7	PI3Kδ/mTOR	PI3Kδ 0.034 μM; mTOR 0.047 μM	~1.4×	p-PI3K, p-AKT and p-RPS6 suppression	Not reported	B	[59]
8	PI3K/mTOR (PROTAC degrader)	DC_{50}: PI3Kα 227.4 nM; PI3Kγ 42.2 nM; mTOR 45.4 nM	~5× (α *vs.* mTOR)	Proteasome-dependent degradation of both proteins; p-AKT, p-GSK3β, p-4EBP1 loss; RNA-seq and DIA proteomics	MDA-MB-231 xenograft, >70 % TGI	A	[60]
9	pan-PI3K/mTOR	PI3K isoforms 0.3 to 5.8 μM; mTOR 0.3 μM	~1 to 19×	Not demonstrated for this analogue (reported for the parent hit at 50 μM)	Not reported	C	[61]

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Com-pounds	Target	Biochemical potency	Potency ratio	Cellular pharmacodynamic evidence	*In vivo* efficacy	Evidence tier	Ref.
10	PI3Kα/HDAC6	PI3Kα 8.34 nM; potent HDAC6 inhibition	n.d.	Cellular work performed on a more chemically stable con-gener, not on this compound	Not reported	C	[69]
11	PI3Kα/HDAC6	PI3Kα 373 nM; HDAC6 4.5 nM	~83× (HDAC-favoured)	Acetylated α-tubulin accumulation; p-AKT suppression; G2/M arrest	Not reported	B	[70]
12	PI3Kα/HDAC3	PI3Kα 20.3 nM; HDAC3 24.5 nM	~1.2×	Acetylated histone H3 and α-tubulin accumulation; p-AKT suppression; cleaved PARP/caspase-3	Not reported (PK and safety reported)	B	[71]
]13	PI3Kα/HDAC1	PI3Kα <0.5 nM; HDAC1 172 nM	>340×	p-AKT (S473, T308) suppression; acetylated H3 and p53 accumulation	MV4-11 xenograft, 75.0 % TGI at 20 mg kg^{-1}	A	[72]
14	PI3Kα/HDAC1	PI3Kα sub-nanomolar; HDAC1 nanomolar	>100×	As for compound 13	MV4-11 xenograft, dose-dependent	A	[72]
15	pan-PI3K/HDAC1	PI3Kα 0.59 nM; PI3Kδ 0.59 nM; PI3Kγ 2.02 nM; PI3Kβ 12.69 nM; HDAC1 114 nM	~193×	p-AKT (T308) suppression; histone H3 acetylation; G2/M arrest	Not reported	B	[73]
16	PARP-1/PI3Kα	PARP-1 pIC50 8.22; PI3Kα pIC_{50} 8.25	~1×	BRCA1/2 downregulation; loss of RAD51 foci; γH2AX induction; p-AKT suppression	MDA-MB-468 xenograft, 73.4 % TGI	A	[77]
17	PARP-1/PI3Kα	Balanced nanomolar inhibition of both	~1x	BRCA1/2 downregulation; RAD51 inhibition; γH2AX induction; p-AKT suppression	MDA-MB-468 xenograft, 54.6 % TGI	A	[78]
18	PARP-1/PI3Kα	PARP-1 0.91 nM; PI3Kα 1.5 nM	~1.6×	Pathway suppression; selectivity confirmed across 374 kinases	MDA-MB-468 xenograft, 48.8 % TGI	A	[79]
19	EGFR/PI3Kα	EGFR 3.6 nM; PI3Kα 30.0 nM	~8×	p-EGFR and p-AKT suppres-sion; G0/G1 arrest; apoptosis	Not reported	B	[80]
20	PI3Kα/BRD4	PI3Kα <1 nM; BRD4 173-204 nM	>170×	p-AKT suppression; MYC downregulation; AMPK-p27 senescence programme	KYSE450 xenograft	A	[81]

PI3K/mTOR dual inhibitors

The phosphoinositide 3-kinase (PI3K)/AKT/mTOR signalling pathway regulates cell survival, angiogenesis, proliferation, metabolism and apoptosis. It is dysregulated in cancer initiation, progression, metastasis and resistance [46,47]. The upregulation of PI3K results in the phosphorylation of PIP2 to PIP3, which in turn activates AKT and stimulates the activation of mTORC1/mTORC2, which stimulate tumour growth and survival [48]. While the specific PI3K and mTOR inhibitors have demonstrated clinical benefit, their effectiveness is frequently restricted by incomplete pathway inhibition, compensatory feedback activation and acquired resistance. These drawbacks prompted the development of dual PI3K/mTOR inhibitors, which suppress the pathway more completely, are less prone to resistance, and induce apoptosis and inhibit tumour growth more effectively [49,50]. With the advent of structure-based drug design, scaffold hopping and molecular hybridization techniques, powerful dual PI3K/mTOR inhibitors are also being developed that have improved pharmacological properties and therapeutic potential (Figure 3) [51,52].

In 2020, Yu *et al.* [53] developed and optimized a new series of imidazo[1,2-*a*]pyridine derivatives as promising dual inhibitors of PI3K/mTOR based on the lead compound (1). The modifications were the replacement of the amide with 1,3,4-oxadiazole or 1,2,3-triazole with the addition of sulphonamide methoxypyridine side chains to optimize interactions in affinity-, hinge- and ribose-binding pockets. The target compounds were prepared by a multistep synthetic process including Suzuki cross-coupling, cyclization, amidation and click chemistry, which

provided structurally diverse analogues. The molecular docking results indicated that lead compound (1) bound favourably in the ATP-binding sites of both PI3Kα and mTOR, making an H-bond network with the hinge region and forming further interactions in the affinity- and ribose-binding sites.

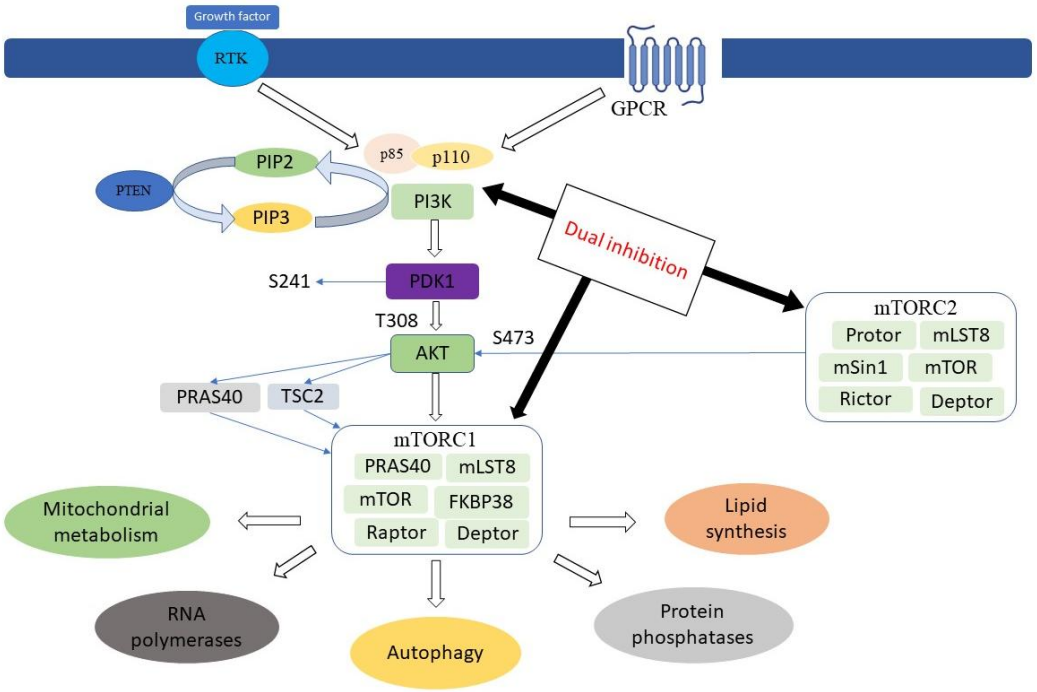


Figure 3. Dual inhibition of PI3K and mTOR by a single drug

This binding interaction offers a structural rationale for, but does not by itself establish, the dual kinase inhibition subsequently measured in enzymatic assays. Across the series, compound (1) combined the highest potency at both kinases. It inhibited PI3Kα with an IC_{50} of 0.12 nM and mTOR with an IC_{50} of 3.7 nM, inhibited all class I PI3K isoforms, and reduced HCT116 cell proliferation with an IC_{50} of 0.01 μM, comparable to or lower than the value obtained for copanlisib. Through SAR studies, it was found that the 1,3,4-oxadiazole linker improved kinase potency over triazole analogues and 1-methyl-4-ethylpiperazine improved PI3Kα inhibition. The 2,4-difluorophenyl and methoxy groups were essential for maintaining activity, while changing the substitution pattern and moving side chains in either direction significantly lowered kinase inhibition, underscoring the importance of the C-3 and C-6 substitution pattern for optimal dual PI3K/mTOR inhibitory activity. Taken together, the synthetic optimization, molecular docking studies, biological evaluation and SAR studies led to compound (1) as a promising candidate for developing PI3K/mTOR targeted anticancer agents (Figure 4).

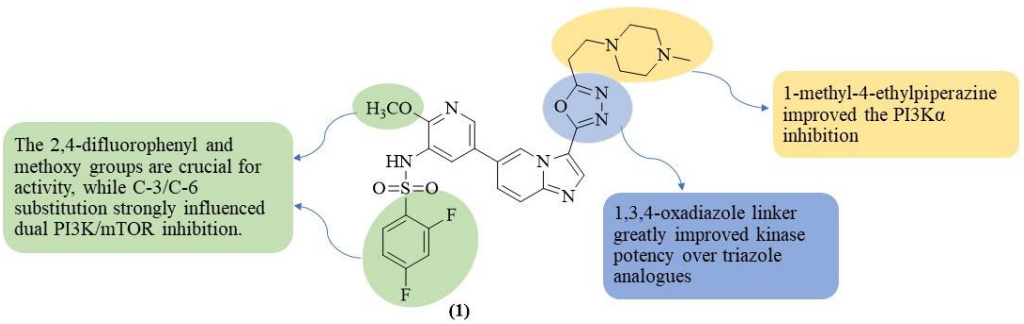


Figure 4. SAR of imidazo[1,2-a]pyridine based PI3K/mTOR dual inhibitors

In 2020, Wu *et al.* [54] rationally designed and synthesized a novel series of benzimidazole-1,3,5-triazine derivatives as dual PI3K/mTOR inhibitors by replacing the C-2 side chain of recently approved gedatolisib with substituted benzimidazole amide fragments to improve kinase selectivity, metabolic stability, and antitumor efficacy while preserving the dimorpholino-triazine pharmacophore. The synthesis proceeded through a multistep

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sequence that included benzimidazole ring construction, sequential triazine substitution, and amide coupling to afford the target compounds in good yield. The molecular docking studies with PI3Kα (PDB: 6OAC), PI3Kδ (PDB: 2WXP) and mTOR (PDB: 4JT6) showed that the lead compound (2) has the same hinge-binding interactions with PI3Ks with conserved morpholine and has a number of additional H-bonding and hydrophobic interactions within the ATP-binding pocket, a binding hypothesis consistent with the dual kinase inhibition measured biochemically, although the docking itself provides no evidence of enzyme inhibition. Biological evaluation revealed that compound (2) showed potent inhibition of PI3Kα (IC_{50} = 0.16 nM), PI3Kδ (IC_{50} = 0.25 nM) and mTOR (IC_{50} = 3.8 nM) as well as antiproliferative activity against various human cancer cell lines, such as HCT116, HeLa, MDA-MB-231, HepG2, MCF-7and CNE2. Mechanistically, compound (2) was effective in inhibiting the phosphorylation of Akt and p70S6K, which supports the hypothesis that compound (2) is an inhibitor of the PI3K/Akt/mTOR signalling pathway, and that it was more stable in simulated gastrointestinal fluids and rat liver microsomes than was gedatolisib. Compound (2) showed efficacy against tumour growth in HCT116 xenograft mice, providing 72.7 and 82.3 % tumour growth inhibition (TGI) at doses of 17.7 and 35.4 mg kg^{-1}, respectively, while remaining tolerable with minimal body-weight loss. SAR showed that attachment of the benzimidazole skeleton with optimization of the cyclic amide side chain significantly improved the PI3K/mTOR inhibitory activity, whereas the position and type of the substituents were critical factors in their kinase potency, antiproliferative activity and metabolic stability. Collectively, the synthetic work, molecular docking, biological evaluation, mechanistic investigation, *in vivo* antitumor studies and SAR analysis led to the identification of a lead compound (2) as a candidate compound for developing anticancer agents targeting both PI3K and mTOR (Figure 5).

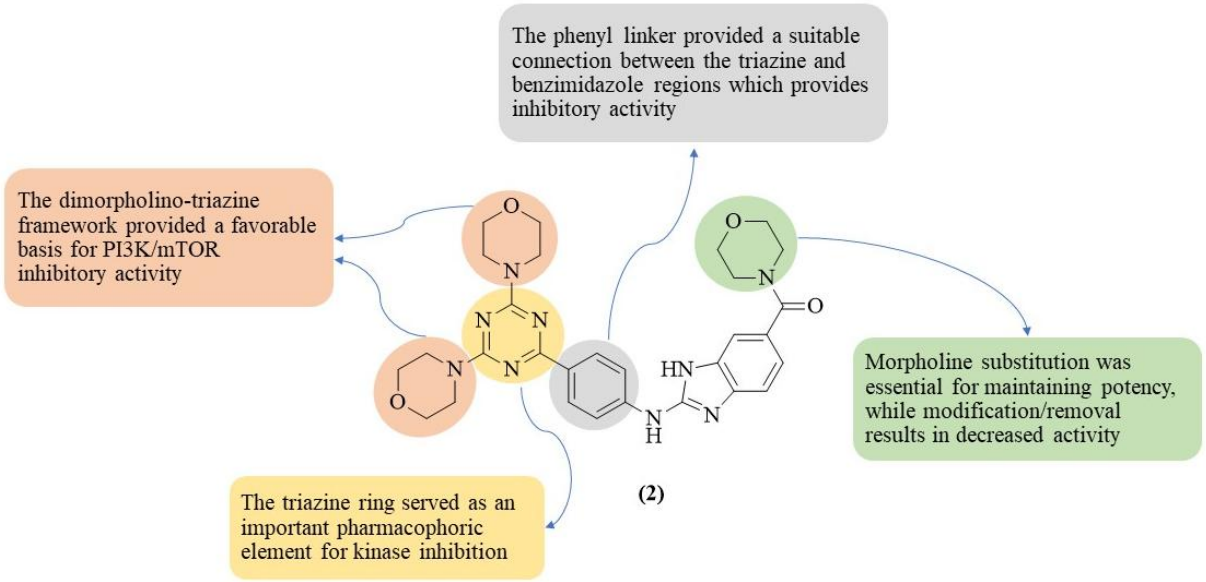


Figure 5. SAR of benzimidazole-1,3,5-triazine based PI3K/mTOR dual inhibitors

Li *et al.* [55] used a scaffold-hopping strategy to design and synthesize a novel series of imidazo[1,2-b]pyridazine- and imidazo[1,2-a]pyrazine-based sulphonamide derivatives as dual PI3K/mTOR inhibitors derived from copanlisib. The design strategy involved replacing the purine backbone with imidazo-fused heterocycles and incorporating 1,2,3-triazole-linked morpholine and various amide substituents to improve kinase potency, pharmacokinetic profile, and safety. The target compounds were prepared by multi-step reactions including amide coupling, Cu(I)-catalysed azide-alkyne cycloaddition (click chemistry) and Suzuki cross-coupling reactions for the desired amide and click products in moderate to good yield. The molecular docking experiments of lead compound (3) with PI3Kα showed that the triazole group assumed a favourable orientation in the ATP-binding pocket, while the morpholine and sulphonamide groups formed H-bonding and hydrophobic interactions with the enzyme, respectively. Compound (3) was the strongest analogue and

showed very high inhibitory activity for the PI3Kα and mTOR enzymes, with IC_{50} values of 0.91 and 15.2 nM, respectively, as well as very good antiproliferative activity against the HCT116 and HT-29 cancerous cell lines (IC_{50} = 21 and 34 nM, respectively). Mechanistic studies additionally showed that compound (3) can effectively inhibit the PI3K/AKT/mTOR signalling pathway through inhibition of Akt phosphorylation. Moreover, compound (3) showed improved oral pharmacokinetics and strong antitumor activity in HCT116 and HT-29 xenografts at 20 mg kg^{-1}, resulting in a TGI similar to copanlisib without significant body-weight loss and only low levels of serum ALT, AST, urea, and uric acid. The SAR data indicated that the introduction of the imidazo[1,2-b]pyridazine scaffold, along with the 2,4-difluorophenylsulfonamide pharmacophore and the introduction of a triazole-linked morpholine side chain, gave significant improvements in dual PI3K/mTOR inhibitory activity, while changes in the length of the linker and terminal amine substituents showed marked changes in kinase potency, antiproliferative activity, and pharmacokinetic behaviour. The collective studies of the synthetic optimization, molecular docking, biological evaluation, pharmacokinetic studies, *in vivo* antitumor investigations and SAR analysis led to the identification of lead compound (3) as a potential lead for further development as orally active dual PI3K/mTOR-targeted anticancer agents (Figure 6).

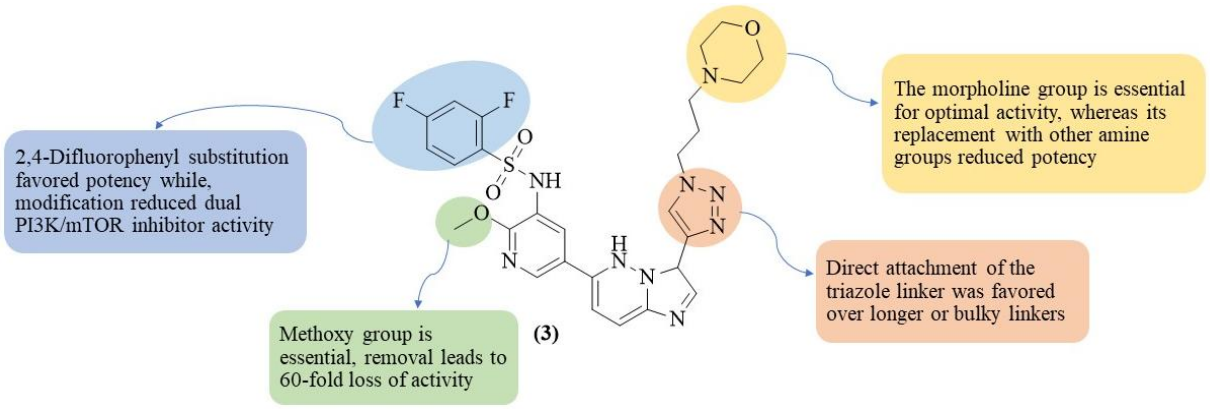


Figure 6. SAR of imidazo[1,2-a/b]pyrazine-based sulfonamide derivatives as dual PI3K/mTOR inhibitors

In 2023, Yang *et al.* [56] developed and synthesized a novel series of triazine-thiophene urea derivatives as dual PI3Kα/mTOR inhibitors using a scaffold-hopping approach starting from GDC-0941, GDC-0980 and ZSTK474. The target compounds were prepared by two-step sequential substitution of the triazine, followed by addition of various heterocyclic urea groups to improve dual-target activity without losing the morpholine-triazine scaffold. The molecular docking studies indicated that the lead compound (4) bound to the ATP-binding pockets of PI3Kα and mTOR with the conserved morpholine-mediated hinge interactions, with the urea linker forming hydrogen-bonding interactions to improve the ligand-protein interactions and dual kinase inhibition. The greatest dual potency within this series was obtained with compound (4), which inhibited PI3Kα with an IC_{50} of 2.3 nM and mTOR with an IC_{50} of 10.1 nM. It was also antiproliferative against a panel of cancer cell lines, including A549, MCF-7, HeLa, HeLa-MDR, NCI-H460, NCI-H1975, Ovcar-3, H2228 and U87MG. Mechanistic studies also revealed that compound (4) promoted apoptosis, blocked cell proliferation, migration and colony formation, enhanced ROS levels in the cells, decreased the mitochondrial membrane potential, and inhibited the PI3K/AKT/mTOR signalling pathway by suppressing the expression of PI3K and blocking activation of AKT and mTOR, and it did not show significant hepatorenal toxicity and had limited haemolytic toxicity in mice. The SAR indicated that the addition of the urea moiety was beneficial for increasing the mTOR selectivity, while the incorporation of a methyl group on the 5-membered heterocycle was found to be very beneficial for the antiproliferative activity, while the attachment of triazole/tetrazole analogues and the excessive flexibility of the linker were generally deleterious for potency. Overall, integrated synthetic optimization, molecular docking, biological evaluation, mechanistic studies, and SAR analysis provided a lead toward developing dual PI3Kα/mTOR-targeted anticancer agents (Figure 7).

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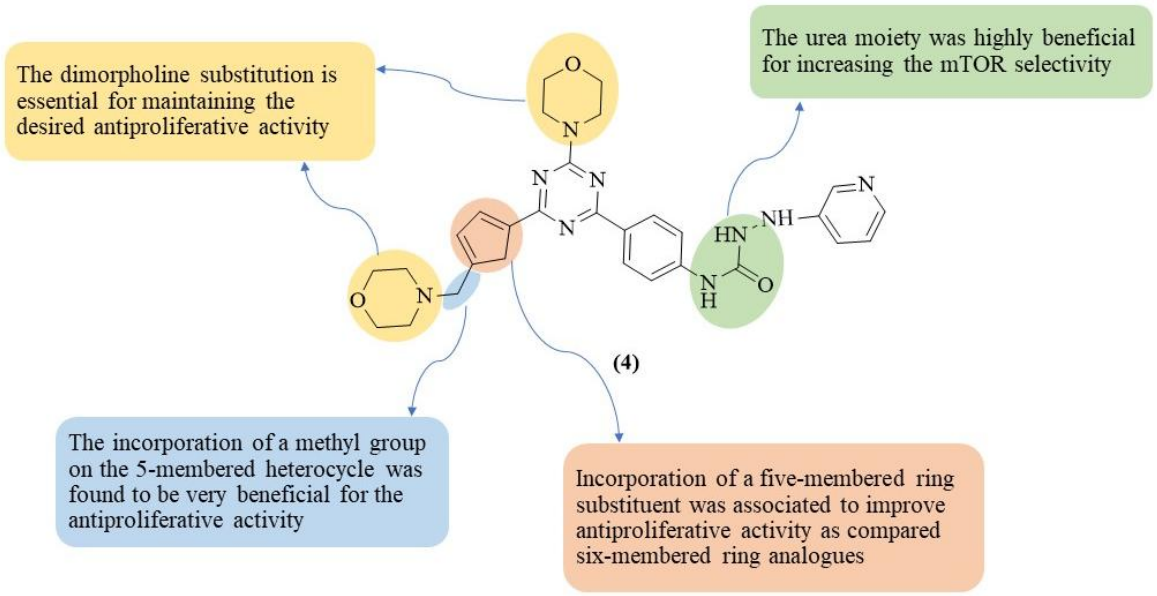


Figure 7. SAR of triazine-thiophene urea derivatives as dual PI3Kα/mTOR inhibitors.

In 2023, Gao *et al.* [57] described a novel series of sulphonamide methoxypyridine derivatives using a scaffold-hopping approach to improve the hinge- and ribose-binding regions of known PI3K inhibitors for dual inhibition of PI3Kα and mTOR. Structure-based optimization included the addition of a quinoline core, an oxazole linker, a sulphonamide group and an amide group to enhance receptor binding and kinase inhibition. The target compounds were obtained by a multi-step synthetic route for structural diversity to be evaluated by biological testing. Molecular docking against PI3Kα (PDB: 4JPS) and mTOR (PDB: 4JT6) showed that the lead compound (5) made a number of important hydrogen bonds with Lys802, Asp933, Asp810 and Val851 in the active site of PI3Kα, whereas the quinoline nucleus formed a conserved hydrogen bond with Val2240 in the mTOR active site. Moreover, π-π interactions between the quinoline and oxazole groups further strengthened the ligand-protein complexes, providing a structural hypothesis consistent with the dual kinase inhibition that was subsequently measured. Compound (5) was the most active compound in the series, inhibiting PI3Kα with an IC_{50} of 0.22 nM and mTOR with an IC_{50} of 23 nM, compared with the reference inhibitors HS-173 and omipalisib, respectively. Compound (5) also showed a good antiproliferative activity against HCT-116 (IC_{50} = 20 nM) and MCF-7 (IC_{50} = 130 nM) cancer cell lines. In cellular assays, compound (5) could effectively inhibit the PI3K/AKT/mTOR signalling pathway by significantly decreasing AKT phosphorylation, inducing G0/G1 cell cycle arrest, and promoting apoptosis in HCT-116 cells, as evidenced by Annexin V-FITC/PI flow cytometry and Hoechst 33342/PI staining. SAR studies revealed that the quinoline scaffold was more active than the benzo[4,5]thio-phenopyrimidine and pyridopyrimidine scaffolds, and that the oxazole-amide fragment was well placed in the ribose-binding pocket, providing additional H-bonding and π-π interactions that improved potency and metabolic stability of the ligand-receptor interaction. The integrated synthetic optimization, molecular docking, biological assessment, mechanistic studies, and SAR analysis have led to compound (5) as a favourable lead for the development of dual PI3Kα/mTOR-targeted anticancer drugs (Figure 8).

In 2024, Yevale *et al.* [58] developed and prepared a new series of 6-methoxy-2-(1H-1,2,4-triazol-1-yl)quinoline aminomethyl derivatives to function as selective dual inhibitors of PI3Kδ/mTOR for therapeutic use in cancer. The lead compounds were prepared by a multistep synthetic process consisting of Vilsmeier-Haack formylation, nucleophilic substitution with 1,2,4-triazole and reductive amination to provide the desired analogues. Molecular docking analysis revealed that the lead compound (6) binds to the ATP-binding pocket of PI3Kδ and mTOR in a favourable binding mode with important hydrogen bond interactions with Val828 and Asp911 of PI3Kδ, and Ser2165 and Gln2167 of mTOR.

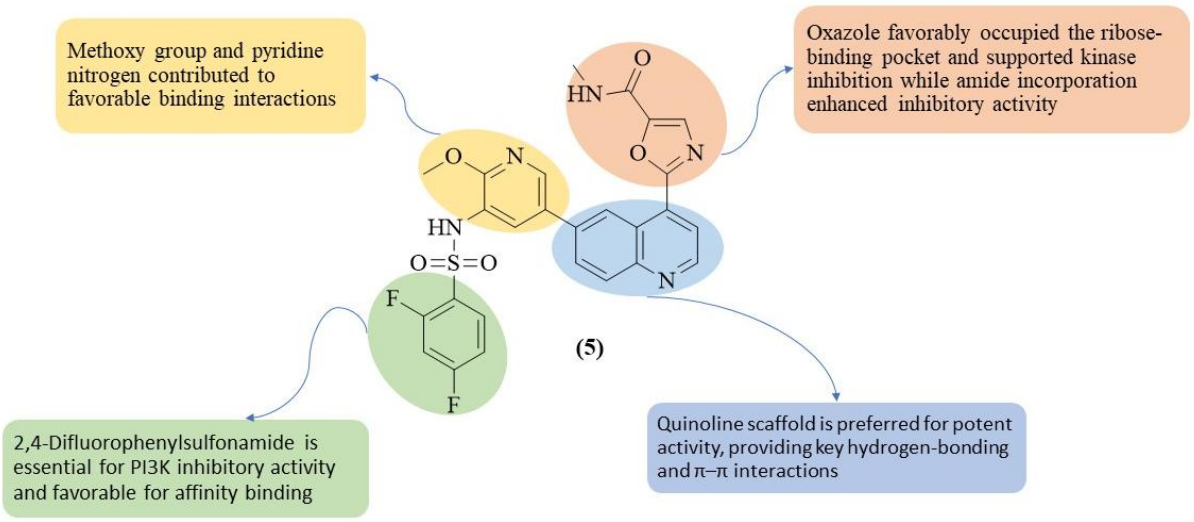


Figure 8. SAR of sulfonamide methoxy pyridine derivatives as PI3K/mTOR dual inhibitors.

Multiple hydrophobic interactions were also predicted, with Met752, Ile825, Trp2239, Leu2185 and Met2345, in a pose similar to that computed for dactolisib. The predicted binding mode supports the design rationale, whereas the dual-target activity is established by the enzymatic data below. Among the analogues evaluated, compound (6) gave the lowest IC_{50} values, inhibiting PI3Kδ with an IC_{50} of 0.042 µM and mTOR with an IC_{50} of 0.059 µM. Compound (6) also exhibited good antiproliferative activity against Ramos lymphoma cells (IC_{50} = 0.26 µM), better than that of dactolisib (IC_{50} = 0.76 µM), and exhibited broad-spectrum anticancer activity against A549, HCT-116, PC-3, Raji, and other cancer cell lines with minimal toxicity toward normal Vero cells (IC_{50} >100 µM). Mechanistic studies showed that compound (6) effectively suppressed the PI3K/Akt/mTOR signalling pathway by decreasing Akt (Ser473 and Thr308) and RPS6 phosphorylation, while promoting mitochondrial apoptosis by increasing cytochrome c, p53, Bax, caspase-3, and caspase-9, and decreasing Bcl-2. Moreover, compound (6) showed 15-16-fold selectivity for PI3Kδ over other PI3K isoforms, with in silico ADMET properties superior to dactolisib, including good oral absorption, low hERG liability, improved metabolic stability, and a longer liver microsomal half-life. Exploration of the SAR revealed that bulky aromatic benzylamine and phenylamine substituents were found to be more cytotoxic and dual kinase inhibitors than their aliphatic counterparts, especially when carrying chloro, bromo and methoxy groups. All of the integrated synthetic optimization, molecular docking, biological evaluation, mechanistic studies, ADMET and SAR analysis led to the selection of compound (6) as a promising lead for selective PI3Kδ/mTOR inhibitors in anticancer drug development (Figure 9) [58].

In 2025, Yevale *et al.* [59] designed and synthesized a novel series of 6-methoxy-2-(1H-1,2,4-triazol-1-yl)quinoline-3-carboxamide derivatives as selective dual PI3Kδ/mTOR inhibitors through bioisosteric optimization of previously reported quinoline-triazole scaffolds to simultaneously target two key components of the PI3K/Akt/mTOR signalling pathway. Sequential construction of quinoline, substitution of triazole, oxidation and amide coupling with HATU/DIPEA were performed to obtain the target compounds. The molecular docking studies showed that the lead compound (7) was able to bind to PI3Kδ and mTOR with binding affinities of -10.41 and -9.70 kJ mol^{-1}, respectively, within their ATP-binding pockets with a favourable binding mode. The ligand interacted with multiple hydrogen bonds, hydrophobic interactions, and π-cation interactions and the carboxamide linker interacted with additional hydrogen-bonding interactions, which were predicted to stabilise the ligand-protein complexes. In addition, 100 ns molecular dynamics simulations showed the stability of the ligand-protein complexes for the entire simulation time.

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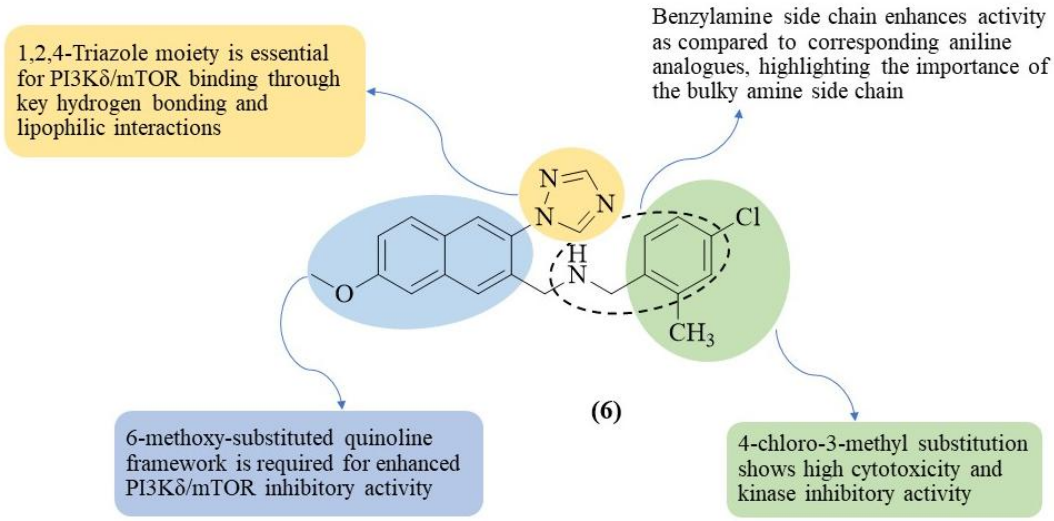


Figure 9. SAR of 6-methoxy-2-(1H-1,2,4-triazol-1-yl)quinoline aminomethyl derivatives as dual PI3K/mTOR inhibitors.

The highest dual potency was exhibited for compound (7), which inhibited PI3Kδ with an IC_{50} of 0.034 μM and mTOR with an IC_{50} of 0.047 μM. It inhibited the proliferation of Raji (IC_{50} = 0.18 μM), HeLa (IC_{50} = 0.39 μM), K562, PC-3, Ramos, and HCT-116 cancer cell lines, while showing low toxicity toward normal Vero cells (IC_{50} = 84.09 μM), indicating good cancer selectivity. Biochemical analysis confirmed that compound (7) could successfully inhibit the PI3K/Akt/mTOR signalling pathway by decreasing the level of phosphorylated PI3K, Akt and RPS6, arresting cells in the G0/G1 phase, increasing ROS production in cells, depolarizing the mitochondrial membrane, releasing cytochrome-c, Bax/Bcl-2 ratio, activating caspase-3/-9, and cleaving PARP, leading to mitochondrial-mediated apoptosis. Furthermore, cardiac safety studies of hERG inhibition (>30 μM) showed a favourable preliminary cardiac safety profile. SAR studies indicated that the isobutyl carboxamide has a significant boost in biological activity, while the quinoline core, 1,2,4-triazole ring, methoxy group and carboxamide linkage have complementary hydrogen bonding and hydrophobic interactions that resulted in better binding affinity and kinase inhibition. In summary, integrated synthetic optimization, molecular docking, biological evaluation, mechanistic investigations, molecular dynamics simulations, and SAR analysis point to compound (7) as a lead candidate for developing selective dual PI3Kδ/mTOR-targeted anticancer agents (Figure 10).

In 2025, Zhu *et al.* [60] developed and synthesized the first family of dual PI3K/mTOR-targeting PROTAC degraders using the targeted protein degradation approach with the dual PI3K/mTOR inhibitor gedatolisib (PKI587). A total of 24 bifunctional PROTACs were synthesized by sequential amide condensation, linker installation, deprotection, and coupling reactions of the PKI587 warhead with the E3 ligase ligands VH032 or pomalidomide, each linked to the warhead through PEG, alkyl, piperidine, and piperazine linkers. Biological evaluation identified compound (8) as the lead degrader, exhibiting potent degradation of PI3Kα (DC_{50} = 227.4 nM), PI3Kγ (DC_{50} = 42.23 nM) and mTOR (DC_{50} = 45.4 nM), together with antiproliferative activity against MDA-MB-231 (IC_{50} = 68.0 nM), MDA-MB-361 (IC_{50} = 124.2 nM), MCF-7 (IC_{50} = 161.6 nM), OCI-AML3 (IC_{50} = 44.3 nM), and THP-1 (IC_{50} = 48.3 nM) cancer cell lines. Mechanistic studies showed that compound (8) simultaneously degrades PI3K and mTOR by the ubiquitin-proteasome system (UPS), strongly reduces the phosphorylation of AKT, GSK3β, and 4EBP1, induces apoptosis, blocks the ability to form colonies and is effective in inhibiting the PI3K/AKT/mTOR pathway. Furthermore, RNA-seq, DIA proteomics, and kinase selectivity profiling confirmed selective on-target pathway inhibition, and *in vivo* studies showed over 70 % inhibition of tumour growth with favourable pharmacokinetic properties and tolerable systemic toxicity in an MDA-MB-231 xenograft model.

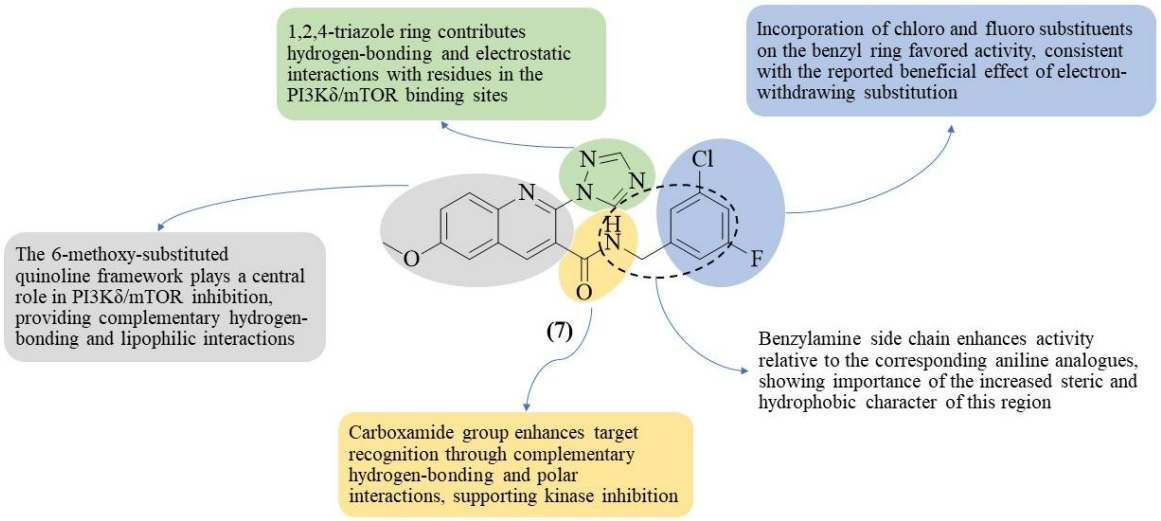


Figure 10. SAR of 6-methoxy-2-(1H-1,2,4-triazol-1-yl)quinoline-3-carboxamide derivatives as selective dual PI3Kδ/mTOR inhibitors

SAR studies showed that the main factor that influenced the degradation efficiency were linker length and conformational flexibility: flexible PEG or alkyl linkers were more efficient in ternary complex formation and better for degradation of mTOR, while PROTACs based on VHL showed higher degradation efficiency. In addition, removing the dimethylaminopiperidine warhead further enhanced the degradation efficiency, leading to the identification of compound (8) as the first potent dual PI3K/mTOR PROTAC degrader and a promising lead molecule for breast cancer and leukemia treatment (Figure 11).

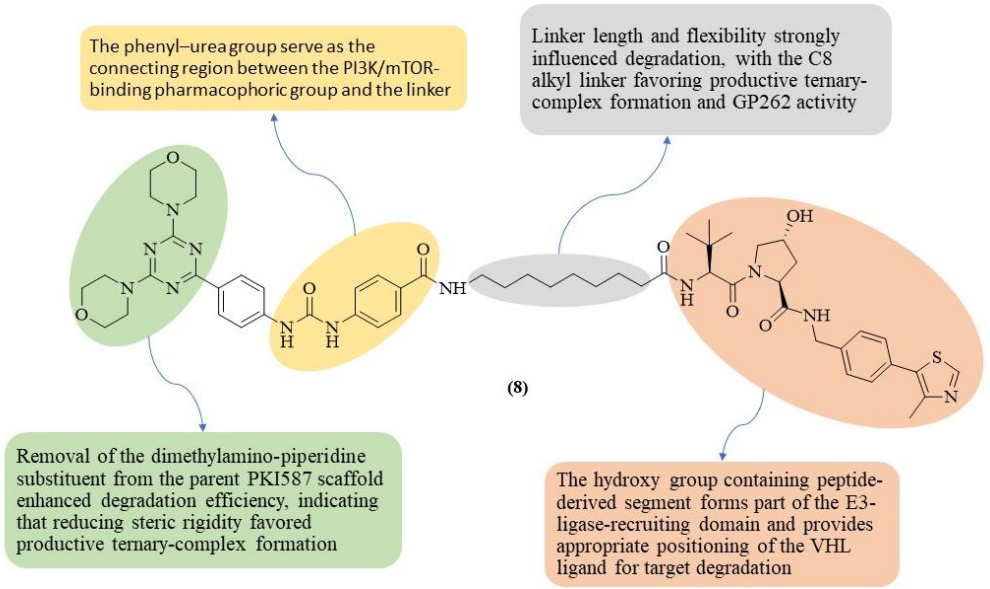


Figure 11. SAR of dual PI3K/mTOR-targeting PROTAC based on the PKI587 pharmacophore

In 2026, Silva *et al.* [61] rationally developed and synthesized new members of morpholino-triazine derivatives as dual inhibitors of pan-PI3K/mTOR, which are derived from the simplified gedatolisib analogue. The target compounds were prepared by sequential nucleophilic substitution of cyanuric chloride followed by a Suzuki reaction, providing structurally diverse phenyl and aza-phenyl groups that feature the morpholine-triazine pharmacophore required for kinase inhibition. The lead compound (9) (LASSBio-2337) showed a favourable binding mode to the ATP-binding pocket of both kinases PI3Kα (PDB: 4L23) and mTOR (PDB: 4JT6), with a conserved binding mode with the conserved morpholine-Val851 hinge interaction, as well as additional H-bonding and hydrophobic interactions, which were predicted to stabilise the ligand-protein complexes and supported its dual inhibitory profile. Compound (9) was the most active compound in the series, inhibiting all

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class I PI3K isoforms with IC_{50} values of 0.3-5.8 μM and mTOR with an IC_{50} of 0.3 μM. It was cytotoxic to CCRF-CEM (CC_{50} = 4.37 μM) and MOLT-4 (CC_{50} = 8.05 μM) leukaemia cells, showed lower toxicity towards normal human peripheral blood mononuclear cells, and retained activity against multidrug-resistant Lucena cells. Moreover, compound (9) showed moderate gastrointestinal permeability in the PAMPA assay but low metabolic stability in rat liver microsomes, indicating potential for further pharmacokinetic optimization. Structure-activity comparison showed that a meta-hydroxyl-substituted compound (9) had the best kinase inhibition/cellular activity profile, aza-homologation had a slight decrease in PI3Kα/β and mTOR inhibition; carboxylic acid analogues showed an improvement in aqueous solubility but a significant decrease in PI3K inhibitory activity (due to decreased membrane permeability) and amide substitution showed an improvement in PI3Kα selectivity while maintaining dual PI3Kα/mTOR inhibition. The integrated synthetic approach, docking studies, biological evaluation, pharmacokinetic studies and SAR analysis led to compound (9) (LASSBio-2337) as a potential lead for the development of dual PI3K/mTOR targeted anticancer agents (Figure 12).

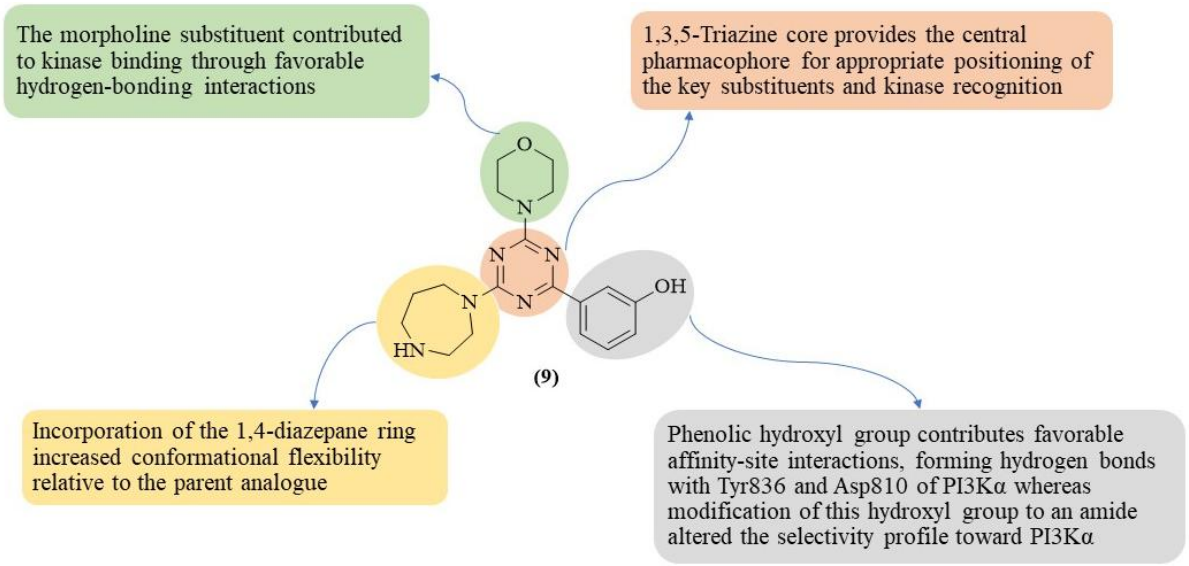


Figure 12. SAR of morpholino-triazine derivatives as dual inhibitors of pan-PI3K/mTOR

PI3K/HDAC dual inhibitors

The phosphoinositide 3-kinase (PI3K) signalling pathway and histone deacetylases (HDACs) play critical roles in cancer cell proliferation, survival, apoptosis, angiogenesis, metabolism and epigenetic gene expression [62-64]. PI3K signalling dysregulation, due to mutations in PIK3CA, loss of PTEN, or activating mutations in receptor tyrosine kinases, in combination with the overexpression of HDACs, increases oncogenic signalling and the repression of tumour suppressor genes to drive tumour progression and therapeutic resistance. Selective PI3K or HDAC inhibitors, which have been demonstrated to possess anticancer activity, often have to be used in combination with other therapies because they have relatively limited efficacy in the clinic, due to compensatory signalling and acquired resistance [65,66]. Thus, dual PI3K/HDAC inhibitors have become a promising pharmacological approach to simultaneously inhibit oncogenic signalling and epigenetic dysregulation, leading to synergistic antitumor effects including increased apoptosis, cell cycle arrest, reactivation of tumour suppressors and increased therapeutic efficacy, with reduced acquisition of drug resistance (Figure 13) [67,68].

In 2020, Rodrigues *et al.* [69] developed and synthesized a novel series of morpholinopyrimidine-N-acylhydrazone hydroxamate derivatives which were developed using a molecular hybridization approach, by merging the PI3K inhibitor PI-103/GDC-0941 pharmacophore with the motif of the hydroxamic acid, which is recognized by HDACs.

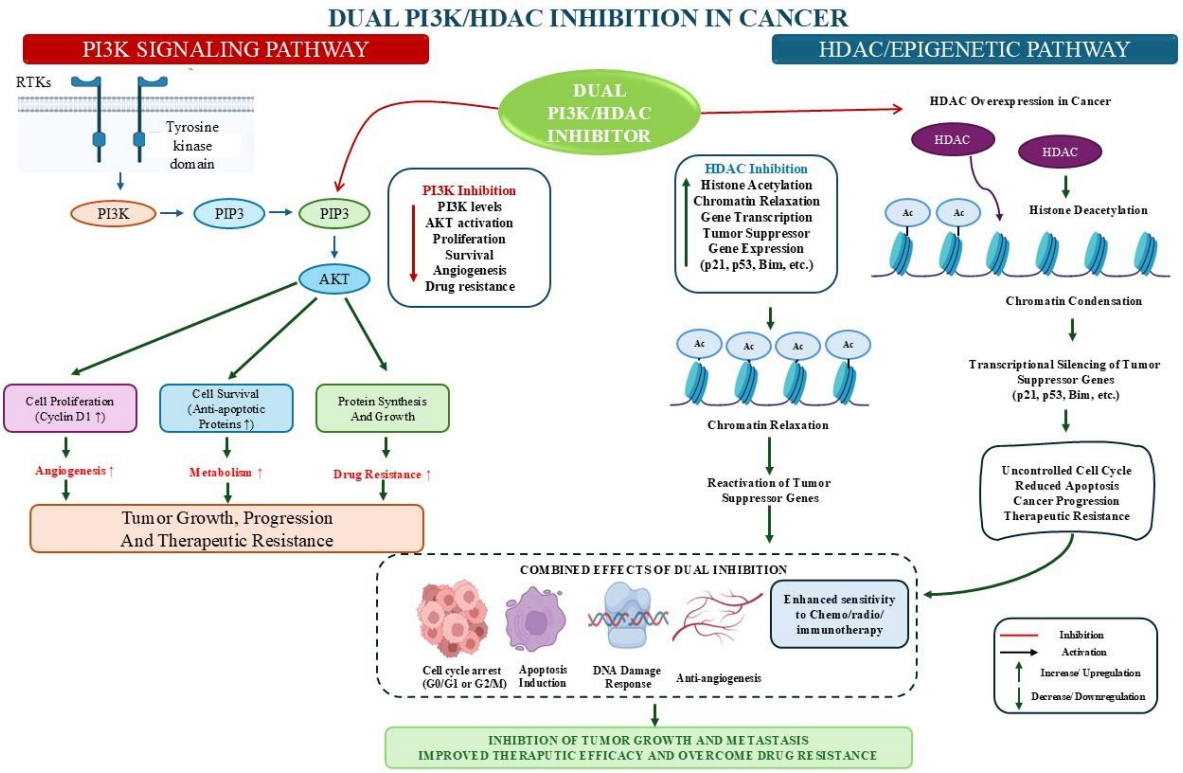


Figure 13. Schematic representation of the dual PI3K/HDAC inhibitory mechanism of a single drug

The derivatives were prepared via a multi-step synthetic procedure that included the formation of substituted morpholinopyrimidine intermediates, their conversion into hydrazide intermediates and finally condensation with hydroxamic acid-containing aldehydes to give the final derivatives. Molecular docking studies showed that the lead compound (10) (LASSBio-2235) fit into the ATP-binding pocket of the PI3Kα kinase in a favourable orientation, retaining the hydrogen bond interaction with Val851 present in the hinge region, and forming additional H-bonds with Tyr836 and Asp810 in the affinity pocket, interactions that offer a structural explanation for the measured kinase inhibition and isoform selectivity. Compound (10) (LASSBio-2235) showed the highest PI3Kα potency in the series, with an IC_{50} of 8.34 nM, along with HDAC6 inhibition. It should be noted that the subsequent cellular characterization of HDAC6 and PI3K/AKT/mTOR pathway inhibition was performed not on compound (10) but on a closely related congener that proved more chemically stable at neutral pH, so that cellular dual-target engagement was not established for compound (10) itself. Compound (10) showed only weak CYP3A4 inhibition (IC_{50} >10 µM), compared with an IC_{50} of 3.6 µM for its congener LASSBio-2208, and neither compound produced significant hERG blockade at 10 µM. Both compounds nevertheless underwent substantial hydrolysis at pH 2.0, with less than 30 % recovery after 4 h compared with more than 60 % at pH 7.4. This chemical-stability liability is intrinsic to the N-acylhydrazone linker, is independent of metabolic clearance, and has direct implications for oral delivery. The SAR study revealed that the morpholine ring was crucial for binding to PI3Kα, that the 3-hydroxyphenyl group significantly improved the PI3Kα potency, that O-methylation decreased the kinase activity, and that incorporation of N-containing heteroaryl rings progressively increased the kinase potency due to additional H-bonding interactions, while the introduction of a 1H-indazol-4-yl moiety at the 3-position of the 3-benzoylbenzoyl group (10) resulted in the most potent dual inhibitor with beneficial bioisosteric interactions. The synthetic optimization, molecular docking, biological evaluation and SAR data together suggested compound (10) (LASSBio-2235) as a promising lead for the further development of dual PI3Kα/HDAC6 targeted anticancer agents (Figure 14).

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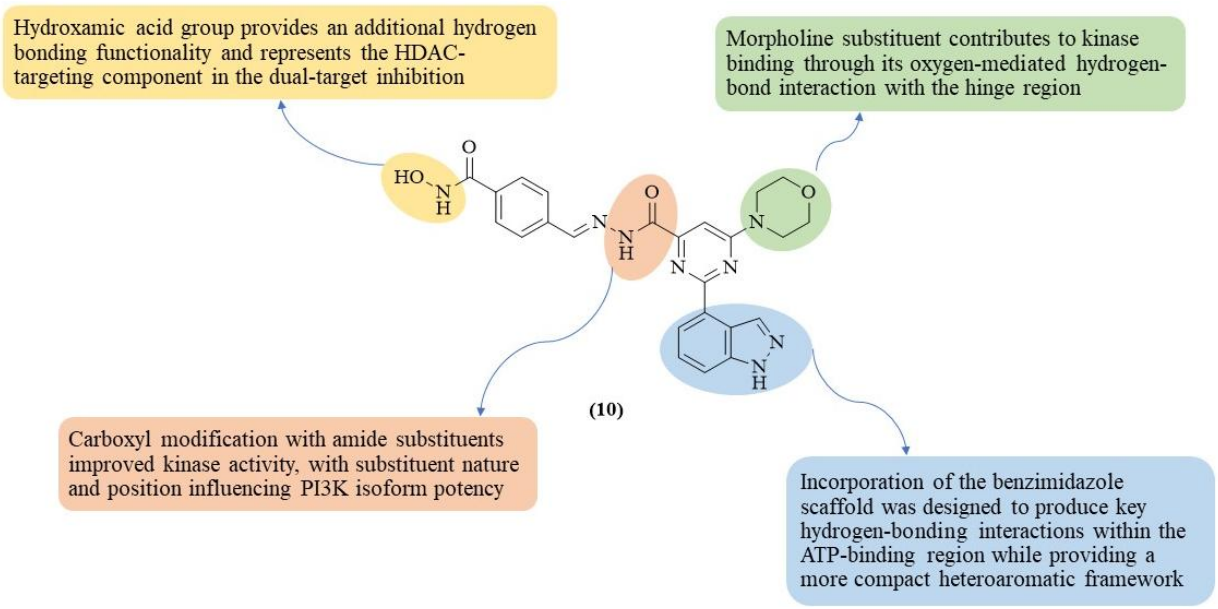


Figure 14. SAR of morpholinopyrimidine-N-acylhydrazone hydroxamate derivatives as PI3K/HDAC dual inhibitors

In 2022, Wang *et al.* [70] *de*veloped and synthesized a novel series of pyrazin-2(1H)-one-based hydroxamic acid derivatives, which were obtained by a scaffold-replacement and molecular hybridization approach, coupling the pharmacophoric features of the PI3K inhibitor, BKM120, and the HDAC inhibitor, SAHA, to provide concurrent and synergistic inhibition of both targets. The target compounds were synthesized in a multistep synthetic route; the pyrazinone core was first constructed and then hydroxamic acid and various heteroaryls were added to achieve optimum dual-target activity. Molecular docking experiments with PI3Kα (PDB: 3P2B) and HDAC6 (PDB: 5EDU) revealed that the lead compound (11) adopted optimal binding poses in the catalytic pockets of both enzymes, with favourable predicted hydrogen-bonding and hydrophobic interactions and the dual inhibitory activity measured in the enzymatic assays. Compound (11) was the most active compound in the series, inhibiting PI3Kα with an IC_{50} of 373 nM and HDAC6 with an IC_{50} of 4.5 nM. It was antiproliferative against MV4-11 (IC_{50} = 0.09 μM), HL-60 (IC_{50} = 0.35 μM), K562 (IC_{50} = 0.12 μM), HGC-27 (IC_{50} = 0.88 μM), HepG2 (IC_{50} = 1.19 μM), and MCF-7 (IC_{50} = 0.40 μM) cancer cell lines. Further investigation showed that compound (11) caused G2/M cell cycle arrest, apoptosis in MV4-11 cells, a significant increase in acetylated α-tubulin and repression of the PI3K/AKT/mTOR signalling pathway by downregulation of Akt phosphorylation. SAR studies showed that meta-hydroxyl and benzyl-hydroxyl substituents significantly increased PI3Kα inhibitory activity, while five-membered heterocycles reduced PI3Kα inhibitory activity to zero. Morpholine was also critical for retaining PI3Kα binding and dual-target activity; replacing it with piperidine or other amines substantially reduced activity. Overall, synthetic optimization, molecular docking, biological evaluation, mechanistic studies, and SAR indicated that compound (11) is a promising lead compound for advancing dual PI3Kα/HDAC6 inhibitors (Figure 15).

In 2023, Deng *et al.* [71] developed and synthesized a novel series of dual PI3K/HDAC inhibitors by hybridizing a morpholinotriazine-based PI3K pharmacophore with a benzamide HDAC zinc-binding pharmacophore to simultaneously inhibit PI3K signalling and HDAC-mediated epigenetic regulation. Synthetic optimization of the known structures of the target compounds was carried out systematically to preserve the ATP-binding interactions necessary for the inhibition of PI3K enzymes and add a benzamide group that can coordinate with the catalytic Zn^{2+} ion of HDAC enzymes.

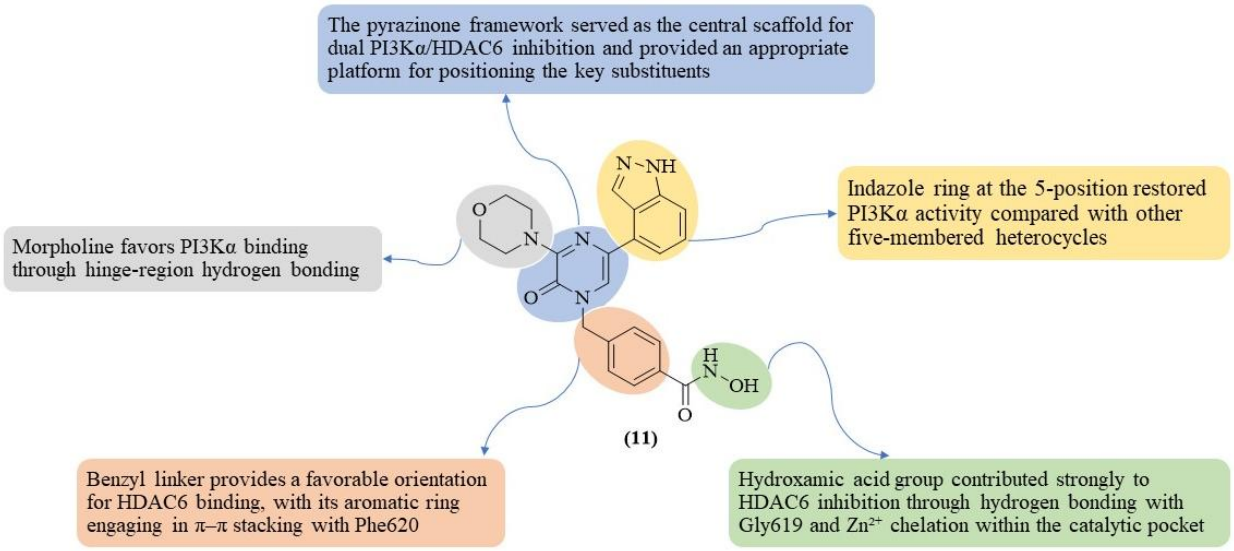


Figure 15. SAR of pyrazin-2(1H)-one-based hydroxamic acid derivatives as dual PI3K/HDAC inhibitors.

Molecular docking revealed that (12) was found to have favourable binding conformations in both PI3Kα and HDAC3, with the morpholinotriazine part of the molecule binding in the ATP pocket of PI3Kα with multiple H-bonds and hydrophobic interactions, and the benzamide part predicted to coordinate the catalytic Zn^{2+} of HDAC3. Consistent with these hypotheses, both activities were confirmed biochemically and by target-specific cellular pharmacodynamic markers. Compound (12) was the most active compound in the series, inhibiting PI3Kα with an IC_{50} of 20.3 nM and HDAC3 with an IC_{50} of 24.5 nM. It was antiproliferative against Jeko-1 mantle cell lymphoma cells and other human cancer cell lines, with lower cytotoxicity towards normal cells. Mechanistic evaluation revealed that (12) significantly suppressed the PI3K/AKT/mTOR signalling pathway by decreasing AKT phosphorylation, led to an increase in acetylated histone H3, acetylated α-tubulin, and G0/G1 cell cycle arrest, promoted cancer cell apoptosis by activation of cleaved PARP and caspase-3, and inhibited cancer cell proliferation by simultaneously targeting oncogenic signalling and epigenetic regulation. Furthermore, the drug-like properties of (12) were favourable, with low hERG inhibition, weak CYP450 inhibition, and good liver microsomal stability, and with desirable pharmacokinetic parameters in mice such as an intravenous half-life of around 10 h. The structure-activity data indicated that the benzamide zinc-binding group in the solvent-exposed area of the morpholino-triazine backbone maintained the parent's potent PI3K inhibitory activity while increasing HDAC inhibitory activity. Moreover, the length of the linker and the terminal aromatic groups played an important role in dual-target potency, further attesting to the importance of balancing interactions with both the PI3K and HDAC active sites for optimal biological activity. Molecular docking, biological evaluation, mechanistic studies, pharmacokinetics, and SAR analysis indicated that compound (12) is a potential lead for developing dual PI3K/HDAC-targeted anticancer agents (Figure 16).

In 2023, Zhang *et al.* [72] developed and synthesized a novel series of 4-methyl quinazoline-based PI3K/HDAC dual inhibitors by attaching a benzamide zinc-binding group to a PI3K pharmacophore of quinazoline derivatives to circumvent the lack of isoform selectivity and potential toxicity of hydroxamate-based HDAC inhibitors. Structurally diverse target compounds were prepared by systematic medicinal chemistry optimization by varying the length of the alkyl and benzoyl linkers to give structurally diverse analogues for dual target inhibition. Molecular docking experiments showed that both the lead compounds (13) and (14) were found to have good binding conformations in both the PI3K and HDAC active sites. In the PI3K structure, the quinazoline scaffold formed a conserved H-bond with Val851, a water-mediated hydrogen bond with Asp810 and Tyr836, and a charged interaction with Lys802.

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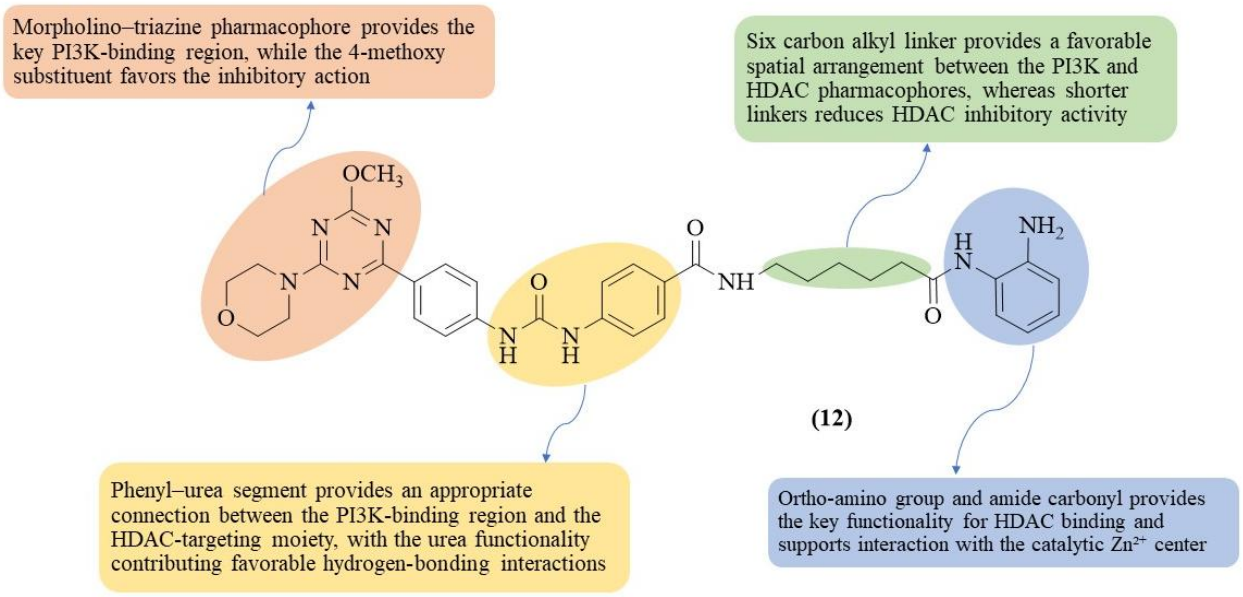


Figure 16. SAR of morpholinotriazine-based dual PI3K/HDAC inhibitors.

The benzamide scaffold coordinated the catalytic Zn^{2+} ion in the HDAC active site. These poses provide a structural hypothesis for the dual inhibitory properties, which were then established by enzymatic assay and by target-specific cellular pharmacodynamic markers for both targets. Biological evaluation identified compounds (13) and (14) as having the most favourable combination of PI3K and HDAC inhibitory activity within the series; it should be noted, however, that the two activities were not balanced, PI3Kα inhibition being sub-nanomolar while HDAC1 inhibition was in the 100 to 200 nM range (compound 13: PI3Kα IC_{50} <0.5 nM, HDAC1 IC_{50} = 172 nM). Biochemical studies also showed that both compounds potently suppressed the PI3K/AKT/HDAC signalling pathway by inhibiting AKT phosphorylation (Ser473 and Thr308), enhancing acetylation of histone H3 and p53, inhibiting cell cycle progression at the G0/G1 phase and inducing apoptosis by increasing cleaved PARP and cleaved caspase-3 expression. Pharmacokinetic evaluations were reported as favourable, with a half-life of 2.30 h for compound (13) and 2.43 h for compound (14). Moreover, both compounds showed notable dose-dependent *in vivo* antitumor activity in MV4-11 xenografts, with compound (13) showing 75 % inhibition of tumour growth at 20 mg kg^{-1} without any significant body weight loss and western blot of tumour tissue showed *in vivo* inhibition of both PI3K and HDAC signalling. The SAR revealed that the benzamide zinc-binding pharmacophore was vital for the HDAC inhibitor activity, while optimizing the length of the linker and the scaffold of the quinazoline significantly boosted the dual-target HDAC inhibitor activity, selectivity, and overall biological activity. In summary, the integrated synthetic optimization, molecular docking, biological evaluation, mechanistic studies, pharmacokinetic studies, *in vivo* antitumor evaluation and SAR analysis led to the identification of compounds (13) and (14) as novel benzamide-based dual PI3K/HDAC inhibitors that are potentially suitable for further development as anticancer drugs (Figure 17).

In 2025, Sun *et al.* [73] reported a novel series of quinoline-linked sulphonamide-pyridine derivatives as dual PI3K/HDAC inhibitors by combining the GSK2126458-derived quinoline sulphonamide PI3K pharmacophore with an o-aminobenzamide zinc-binding group to improve the pharmacokinetic limitations and genotoxicity associated with hydroxamate-based HDAC inhibitors. Target compounds were prepared by sequential nucleophilic substitution, reduction, sulphonylation, Suzuki coupling, hydrolysis, and amidation using EDCI-HOBt. Flexible, semi-rigid, and hybrid linkers were used to optimize the dual-target binding.

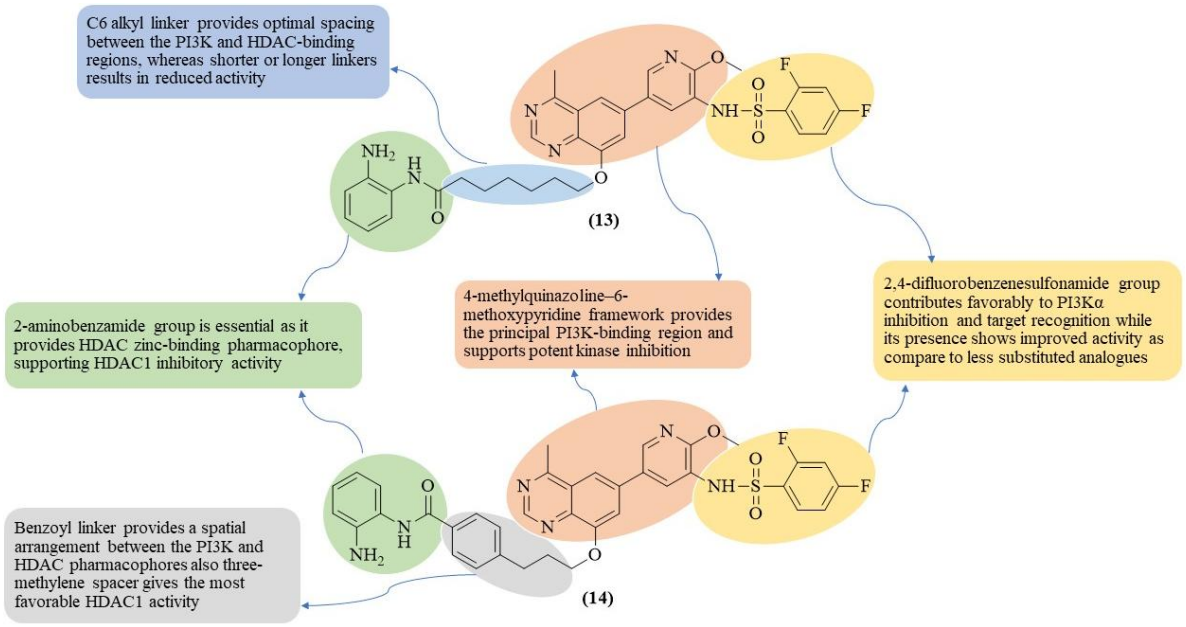


Figure 17. SAR of 4-methyl quinazoline-based PI3K/HDAC dual inhibitors incorporating a benzamide zinc binding group

The molecular docking study revealed that the lead compound (15) exhibited suitable binding conformations in both HDAC1 (PDB: 1C3S) and PI3Kα (PDB: 5DXT), with the sulphonamide oxygen forming an important H-bond with Ser275 in PI3Kα and the quinoline nitrogen making H-bond interactions with Tyr17 and Phe141 in HDAC1. The predicted binding mode is consistent with the dual inhibitory activity measured in the enzymatic assays. The biological evaluation revealed that (15) had potent inhibitory activity against PI3Kα (IC_{50} = 0.59 nM), PI3Kβ (IC_{50} = 12.69 nM), PI3Kδ (IC_{50} = 0.59 nM), PI3Kγ (IC_{50} = 2.02 nM) and moderate inhibitory activity against HDAC1 (IC_{50} = 114 nM), with antiproliferative activity against Jurkat, MCF-7, K562 and PC9R cancer cell lines. Cellular studies demonstrated that (15) effectively suppressed cell migration in the PC9R cell and caused cell cycle arrest at the G2/M phase, initiated dose-dependent cell death and decreased the levels of phosphorylated AKT (Thr308) and increased the levels of histone H3 acetylation, suggesting that it could inhibit both the PI3K/AKT signalling and HDAC activity simultaneously. SAR comparison showed that substitution at the quinoline C-3 position was more favourable than substitution at the quinoline-4 position; flexible linkers with appropriate length were most effective in achieving dual-target activity and antiproliferative activity, with a 6-carbon linker being most active against MCF-7 cells (Figure 18).

PI3K/PARP dual inhibitors

PI3K signalling is a therapeutic target associated with oncogenic signalling, and poly(ADP-ribose) polymerase (PARP) is a therapeutic target involved in DNA damage repair. PI3K signalling supports the growth, survival and proliferation of tumour cells, whereas PARP1/2 is required for the repair of single-strand DNA breaks (SSBs) through the base excision repair (BER) pathway [74]. Although PARP inhibitors are clinically effective, their therapeutic benefit is limited by restoration of homologous recombination (HR) repair and by other resistance mechanisms. Adaptive signalling resistance is a comparable problem for PI3K inhibitors [75]. Importantly, inhibition of PI3K causes a 'BRCAness' phenotype, characterized by downregulation of BRCA1/2 and RAD51, which renders tumour cells sensitive to PARP inhibitors. Hence, dual PI3K/PARP inhibitors are emerging as a pharmacological option with the ability to simultaneously inhibit the growth of oncogenic signalling and DNA repair, achieving enhanced DNA damage, apoptosis and better antitumor activity and overcoming resistance found with single-agent treatments [76] (Figure 19).

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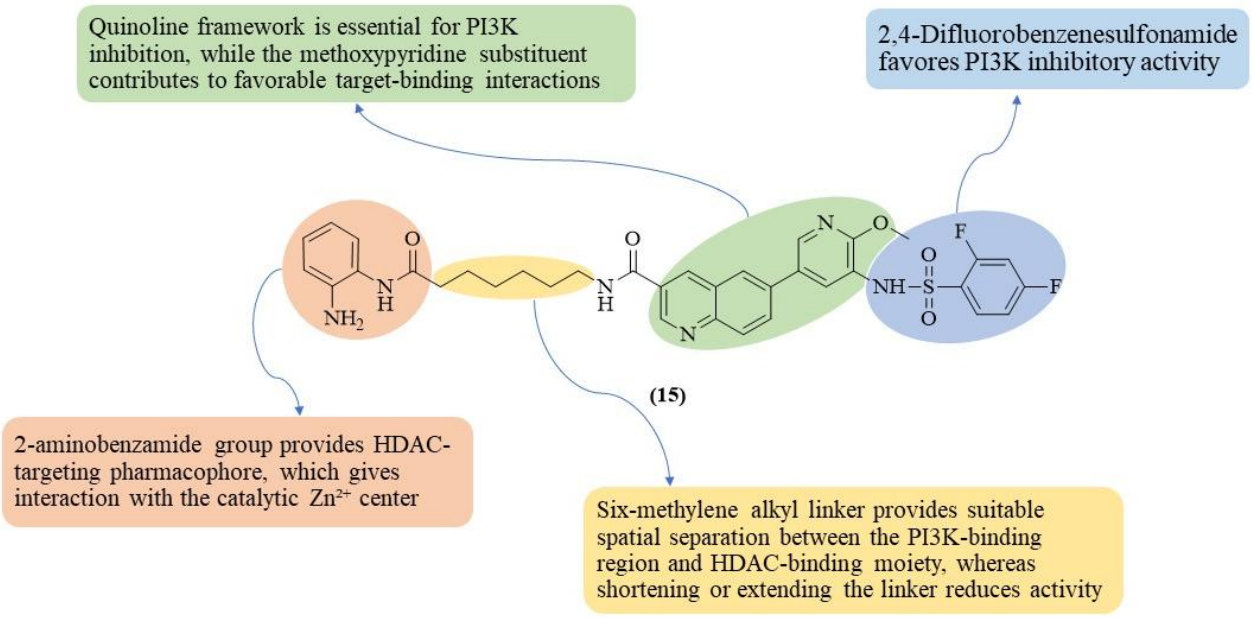


Figure 18. SAR of quinoline-linked sulfonamide-pyridine derivatives as dual PI3K/HDAC inhibitors

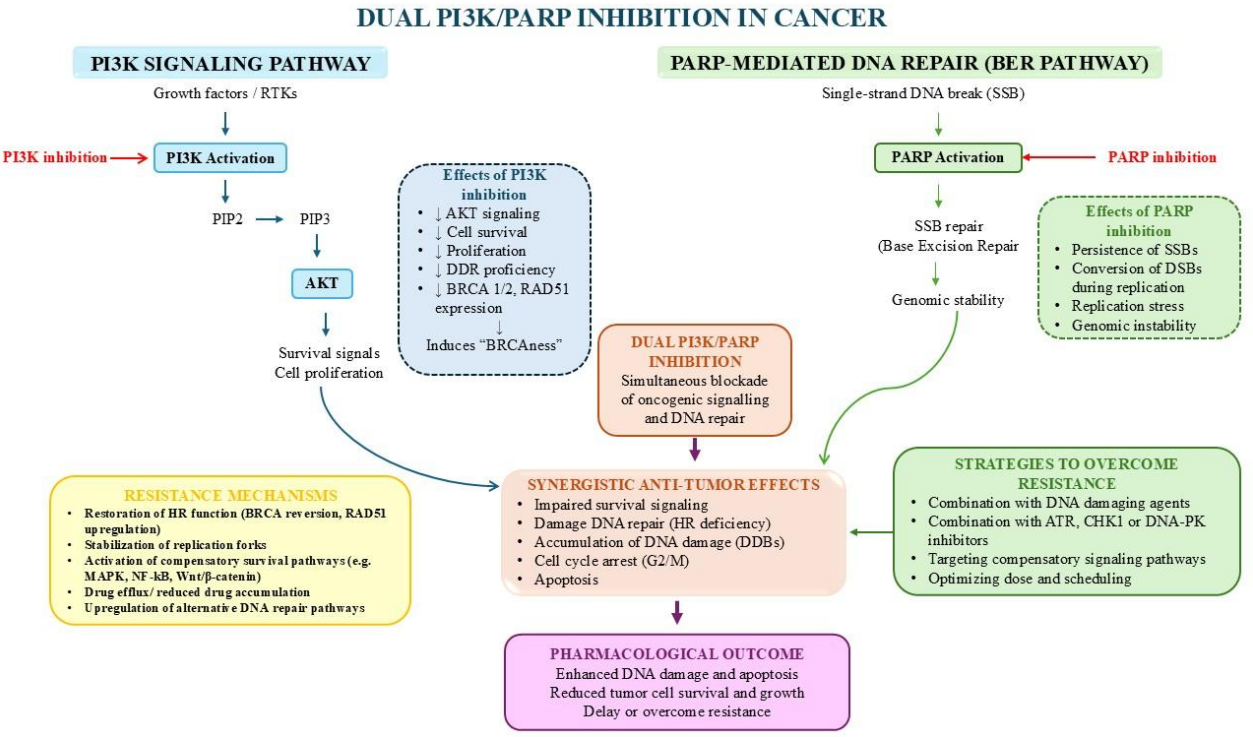


Figure 19. Dual inhibition of PI3K signaling and PARP-dependent DNA repair with a single agent

In 2020, Wang *et al.* [77] developed and developed a novel series of dual PARP/PI3K inhibitors that were rationally designed by combining the pharmacophores of the PI3K inhibitor BKM120 with the PARP inhibitor olaparib, to achieve simultaneous inhibition of DNA repair and PI3K/AKT signalling. The compounds were prepared through systematic scaffold optimization by replacing the pyrimidine scaffold with a 1,3,5-triazine scaffold and modifying the central linker to increase dual-target potency. The molecular docking analysis of PI3Kα (PDB: 4JPS) and PARP-1 (PDB: 5DS3) revealed that the lead compound (16) maintained the crucial H-bonding interactions with the catalytic residues in the active site of both PARP-1 and PI3Kα, a result consistent with the dual-target design strategy, which was then established experimentally by the enzymatic and cellular assays. Compound (16) was the most active compound in the series. It inhibited PARP-1 and PI3Kα with pIC_{50} values of 8.22 and 8.25, respectively, and also inhibited PARP-2 and PI3Kδ. Compound (16) also showed

antiproliferative activity against both BRCA-deficient (HCT116 and HCC1937) and BRCA-proficient (MDA-MB-231, BxPC-3, MDA-MB-468, DU145, A2780, A549, Caki-1, Ramos and SW620) cancer cell lines, surpassing the activity of olaparib, BKM120 and their combination. Mechanistic characterization indicated that compound (16) was able to inhibit the PI3K/AKT pathway, downregulate the expression of BRCA1/2, inhibit RAD51 foci formation, promote γH2AX DNA damage and induce significant apoptosis. *In vivo*, compound (16) demonstrated greater efficacy than olaparib, BKM120, or the combination in an MDA-MB-468 xenograft mouse model, with 73.4 % tumour growth inhibition at 50 mg/kg and no observable toxicity. From SAR studies, it emerged that a 1,3,5-triazine scaffold, tetrahydropyrido[3,4-d]pyrimidine linker, and electron-deficient heteroaromatic groups were indispensable to achieve the desired balanced dual PARP/PI3K inhibition. Overall, integrated synthetic optimization, molecular docking, biological evaluation, mechanistic investigations, in vivo antitumor studies, and SAR analysis revealed compound (16) as the first potent, balanced dual PARP/PI3K inhibitor reported with activity against both BRCA-deficient and proficient cancers (Figure 20).

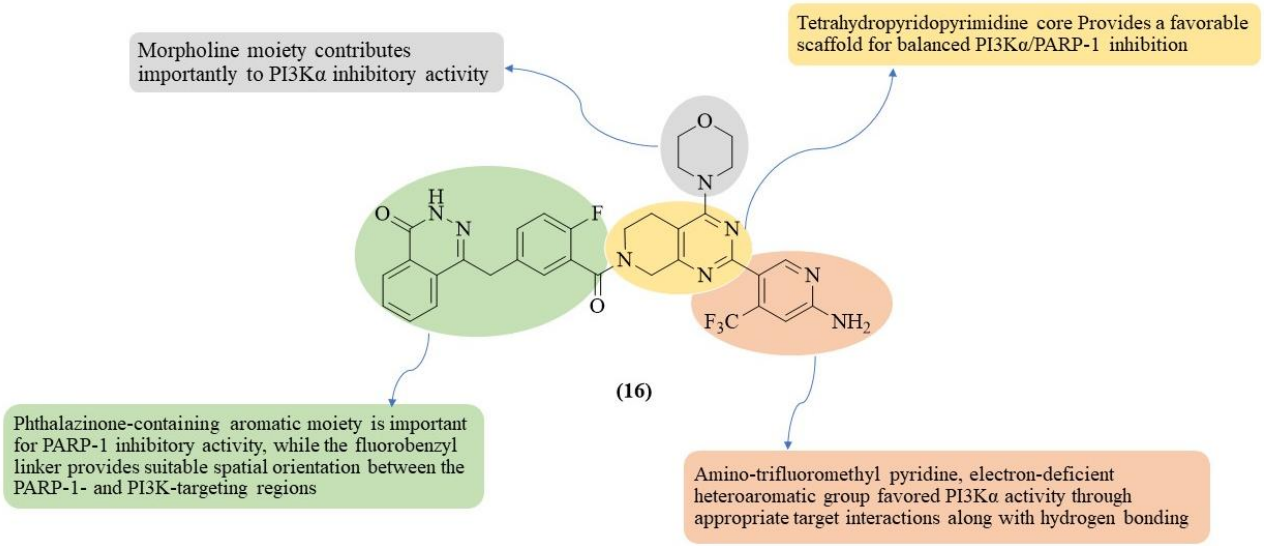


Figure 20. SAR of tetrahydropyridopyrimidine based dual PI3Kα/PARP1 inhibitors

In 2020, Wang *et al.* [78] developed and synthesized a novel series of dual PARP/PI3K inhibitors by structurally optimizing their previously reported lead compounds, which possessed highly desirable aqueous solubility, pharmacokinetic properties and *in vivo* antitumor efficacy, coupled with balanced inhibition of PARP-1 and PI3Kα. Based on the structural considerations, the target compounds were synthesized by systematic modification of the scaffold, introducing a hydrophilic N-acetyl morpholine group into the lead structure, from which compound (17) was selected. Molecular docking studies against PI3Kα (PDB: 4JPS) and PARP-1 (PDB: 5DS3) confirmed that compound (17) maintained the representative binding modes of both parent inhibitors via crucial H-bonding interactions with key catalytic residues in the active site of both PARP-1 and PI3Kα, as predicted by a dual-target approach followed by experimental validation through enzymatic, cellular and *in vivo* studies. A biological evaluation identified compound (17) as a good candidate, showing potent dual PARP-1 and PI3Kα inhibitory activity against several cancer cell lines, notably MDA-MB-468 triple-negative breast cancer cells (IC_{50} = 1.40 μM), which is lower than that of the previously reported most potent compound (IC_{50} = 4.06 μM) and olaparib (IC_{50} = 13.72 μM). In mechanistic experiments, compound (17) was a potent suppressor of the PI3K/AKT pathway, a potent downregulator of BRCA1 and BRCA2 expression, an inhibitor of RAD51-mediated homologous recombination repair, a stimulator of γH2AX expression and formation of DNA double-strand breaks and was found to induce a much higher level of apoptosis than either olaparib or BKM120 or their combination. Pharmacokinetic evaluation showed metabolic stability, good permeability in the Caco-2 cell, very low hERG liability (IC_{50} >29.4 μM) and MCI >1000 mg kg^{-1}. *In vivo*, compound (17) showed 54.6 percent TGI at

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50 mg/kg in the MDA-MB468 xenograft mouse model with no body weight loss and no significant toxicity. The SAR analysis showed that the N-acetyl morpholine substituent significantly enhanced aqueous solubility, metabolic stability and overall pharmacokinetic properties of the dual PARP/PI3K inhibitors. Overall, the synthetic work, molecular docking, biological evaluation, mechanistic studies, drug metabolism and distribution (DMPK) analyses, and *in vivo* antitumor evaluation, along with the SAR studies, finally led to compound (17) as a potential candidate with improved drug-like properties and promising therapeutic potential as a next-generation dual PARP/PI3K inhibitor (Figure 21).

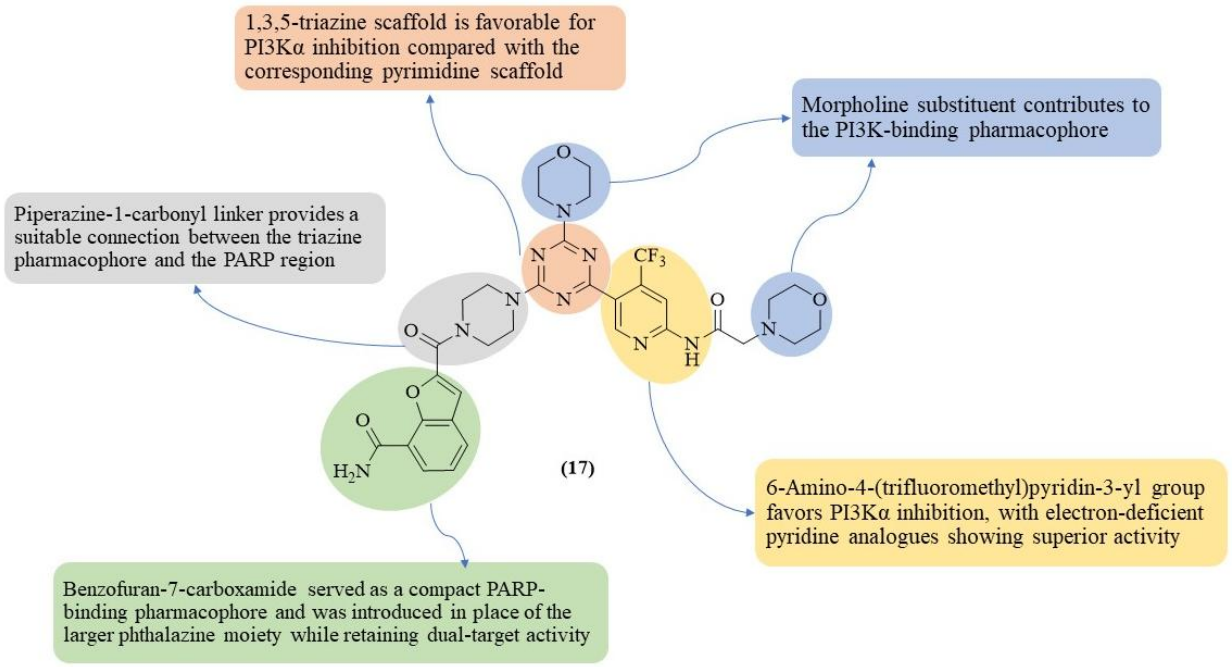


Figure 21. SAR of 1,3,5-triazine based dual PI3K/PARP inhibitors

In 2021, Wu *et al.* [79] developed a novel series of benzofuran-based dual PARP/PI3K inhibitors via a pharmacophore hybridization approach that simultaneously targets DNA damage repair and the PI3K/AKT signalling pathway. To enhance the physicochemical characteristics of their previously reported lead, the phthalazinone moiety was replaced by a benzofuran-7-carboxamide scaffold, and target compounds were synthesized by systematic scaffold optimization and compound (18) was identified as the optimized lead. Molecular docking experiments against PI3Kα (PDB: 4JPS) and PARP-1 (PDB: 5DS3) confirmed that compound (18) bound in a favourable manner to the catalytic pockets of both enzymes, with several predicted H-bonding and hydrophobic interactions with essential residues validating the dual-target design approach. Compound (18) exhibited the lowest IC_{50} values at both enzymes. It inhibited PARP-1 with an IC_{50} of 0.91 nM and PI3Kα with an IC_{50} of 1.5 nM, and also inhibited PARP-2 and PI3Kδ. Compound (18) further displayed antiproliferative activity against SW620 (IC_{50} = 0.88 μM), HCT116 (IC_{50} = 0.28 μM), HCC1937 (IC_{50} = 0.29 μM), MDA-MB-468 (IC_{50} = 1.02 μM) and MDA-MB-231 (IC_{50} = 0.92 μM), cancer cell lines, outperforming the reference drugs olaparib and GDC-0980 in most models. Additionally, enzyme selectivity profiling revealed selectivity for PARP-1/2 and PI3Kα/δ and low activity against PI3Kβ, PI3Kγ, mTOR and AKT and pharmacokinetic testing showed improved drug-like properties compared with the parent compound. *In vivo*, compound (18) inhibited the growth of tumours in an MDA-MB-468 xenograft model with 48.77 % growth inhibition and showed no toxicity or significant body weight loss. SAR analysis indicated that 2-aminopyrimidine-substituted thienopyrimidine derivatives were critical for potent, balanced dual PARP/PI3K inhibition, whereas substitution with pyridine, benzene, indazole, or indole rings significantly reduced PI3K inhibitory activity, underscoring the importance of the heteroaromatic pharmacophore. In silico synthetic optimization, molecular docking, biological evaluation, pharmacokinetic studies, *in vivo* antitumor

evaluation, and SAR analysis identified compound (18) as a promising next-generation dual PARP/PI3K inhibitor with improved drug-like characteristics and significant therapeutic potential (Figure 22).

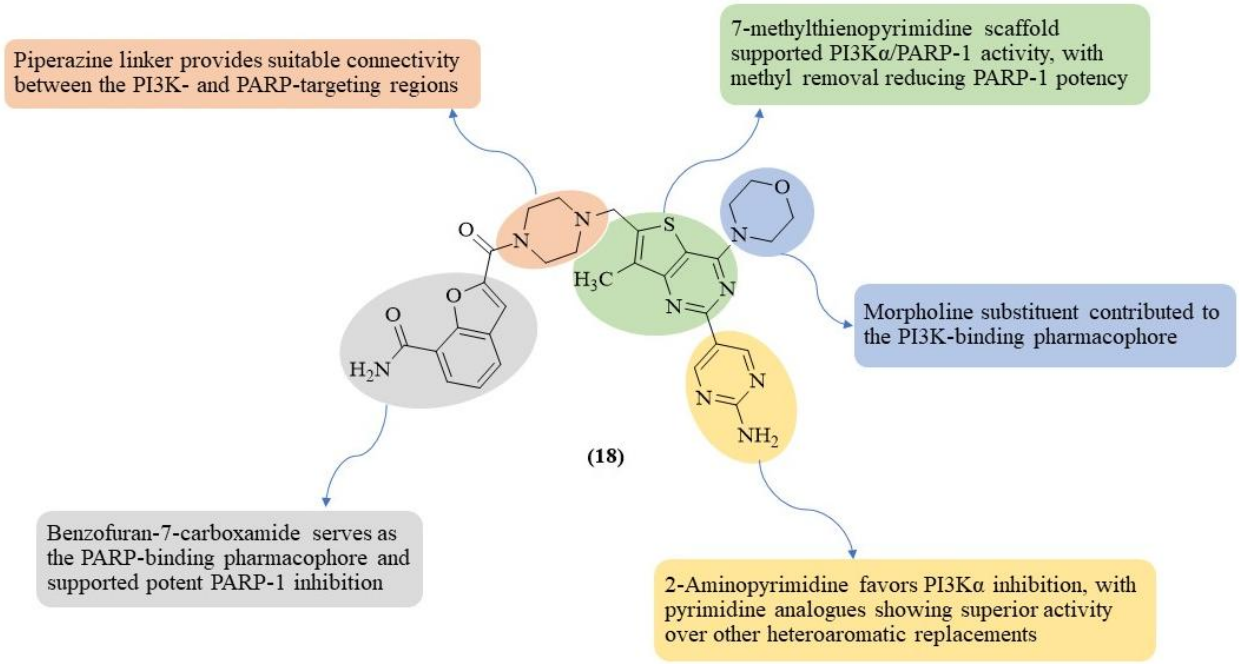


Figure 22. SAR of benzofuran-based dual PARP/PI3K inhibitors

Miscellaneous PI3K-based dual inhibitors (EGFR/PI3K and PI3K/BRD4)

In 2024, Wang *et al.* [80] developed a novel series of olmutinib-TAK-117 hybrid derivatives using a molecular hybridization strategy to address both EGFR-TKI resistance and PI3K signalling, replacing olmutinib's solvent-exposed methylpiperazine moiety with TAK-117's PI3K pharmacophore. The target compounds were synthesized via a multistep route involving cyclization, Suzuki-Miyaura coupling, amide bond formation, Boc deprotection, and nucleophilic substitution to afford the desired hybrids. The molecular docking results against PI3Kα (PDB: 4JPS) and EGFR revealed that the lead compound (19) has a good binding conformation with both receptors by making favourable H-bond interactions with Val851 and Ser919 of PI3Kα and retaining the covalent interaction with Cys797 of EGFR. These binding interactions are consistent with the dual inhibitory activity, which was established by enzymatic assay against both kinases (EGFR IC_{50} = 3.6 nM; PI3Kα IC_{50} = 30.0 nM) and by suppression of both EGFR and AKT phosphorylation in cells. The most potent hybrid of the series was compound (19). It inhibited the proliferation of EGFR L858R/T790M mutant NCI-H1975 cells with an IC_{50} of 0.48 µM and was more selective than olmutinib. Biochemical analysis showed that compound (19) could suppress the EGFR/PI3K/AKT signalling pathway by inhibiting EGFR and Akt phosphorylation, markedly inhibit the colony formation and cell migration of NCI-H1975 cells, and induce cell cycle arrest at the G0/G1 phase and cell death by apoptosis, thus demonstrating its potent inhibitory effect on drug-resistant NSCLC. SAR analysis showed that the olmutinib scaffold must be hybridized with the PI3Kα pharmacophore from TAK-117 to achieve balanced dual-target inhibition in cells; optimizing linker length and terminal substituents significantly affected kinase potency, cellular activity, and selectivity. Synthetic optimization, molecular docking, biological evaluation, mechanistic studies, and SAR analysis identified compound (19) as a promising dual EGFR/PI3Kα-targeted anticancer agent (Figure 23).

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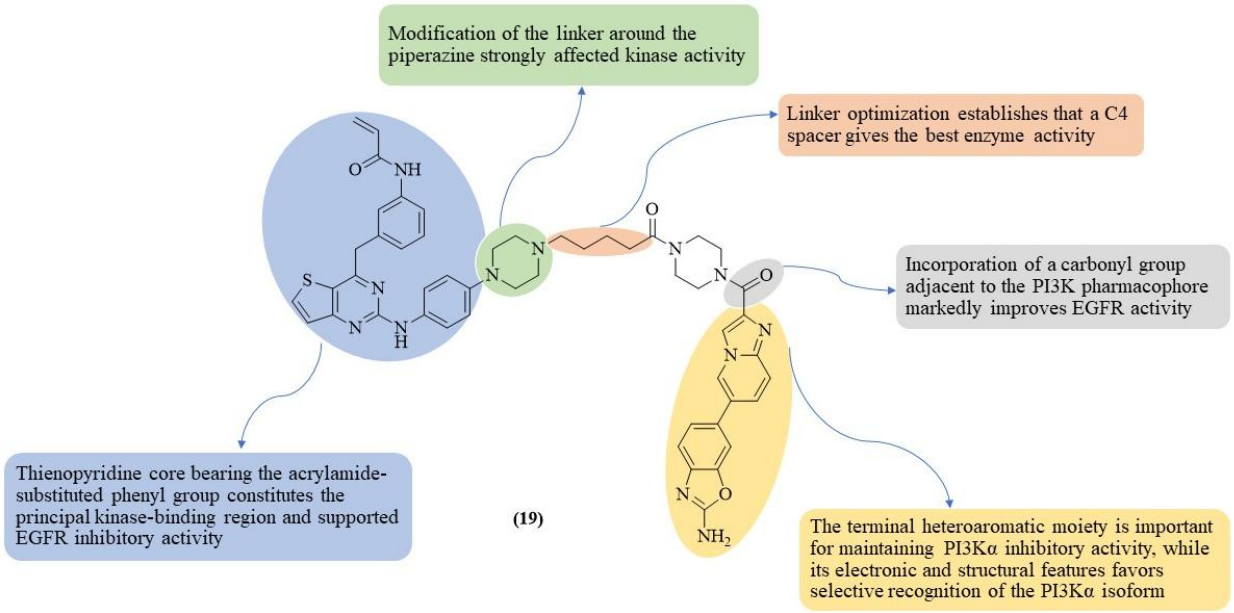


Figure 23. SAR of olmutinib-TAK-117 hybrid derivatives as PI3Kα/EGFR dual inhibitors.

In 2025, Peng *et al.* [81] produced a novel series of PI3K/BRD4 dual inhibitors by a rational molecular hybridization strategy of two compounds with different chemical structures, a 4-methylquinazoline-based PI3K inhibitor and the BRD4 inhibitor JQ1, linked by various alkyl, ethylene glycol and heterocyclic linkers to achieve concurrent inhibition of both targets. The targeted compounds were prepared by a multistep synthesis strategy comprising etherification, amide coupling, Suzuki cross-coupling, Boc deprotection, and condensation using HATU to introduce the dual-target activity and then optimized systematically to enhance the dual-target activity. The molecular docking analysis revealed that the binding interaction of the lead compound (20) was favourable for both PI3Kα (PDB: 4JPS) and BRD4 (PDB: 3MXF) with the 4-methyl-quinazoline scaffold occupying the ATP binding pocket of PI3Kα, forming a conserved H-bond with Val851, and a water mediated hydrogen bond with Trp836 and Asp810, whereas the triazole was predicted to form H-bond with Asn140 in the BRD4 bromodomain. Both activities were confirmed biochemically, although with a marked imbalance: PI3Kα inhibition was sub-nanomolar whereas BRD4 inhibition was in the 173 to 204 nM range, so that full BRD4 engagement requires concentrations more than two orders of magnitude above those needed for PI3K inhibition. Compound (20) was the most active compound in the series, with sub-nanomolar PI3Kα inhibition (IC_{50} <1 nM) and moderate BRD4 inhibition (IC_{50} = 173-204 nM). It was selective for PIK3CA across an 80-kinase panel and antiproliferative against KYSE180 (IC_{50} = 0.55 µM) and KYSE450 (IC_{50} = 0.39 µM) esophageal cancer cells, while showing minimal cytotoxicity against normal esophageal epithelial cells. Biochemical studies indicated that compound (20) was able to inhibit AKT phosphorylation, to downregulate the expression of c-Myc, inhibit cell proliferation, migration, invasion, colony formation and growth in 3D tumour cell culture, and to induce AMPK-p27-mediated cellular senescence. Compound (20) (2.5 to 5 mg kg^{-1}) demonstrated comparable tumour inhibition activity in an *in vivo* KYSE450 xenograft model to that of the combination of BKM120/JQ1; co-dosing with the senolytic ABT737 further increased the tumour inhibitory activity of compound (20) without major toxicity. SAR analysis indicated that linker composition and length were key factors in determining the dual-target activity, with medium-length alkyl or heterocyclic linkers showing the optimal balance between PI3Kα and BRD4 inhibition, while excessively long, rigid, or improperly oriented linkers showed strong PI3K inhibition but significantly diminished BRD4 potency. All the integrated synthetic optimization, molecular docking, biological evaluation, mechanistic studies, *in vivo* anticancer studies and SAR analysis show that compound (20) is a good lead for anticancer drug development by targeting PI3K and BRD4 (Figure 24).

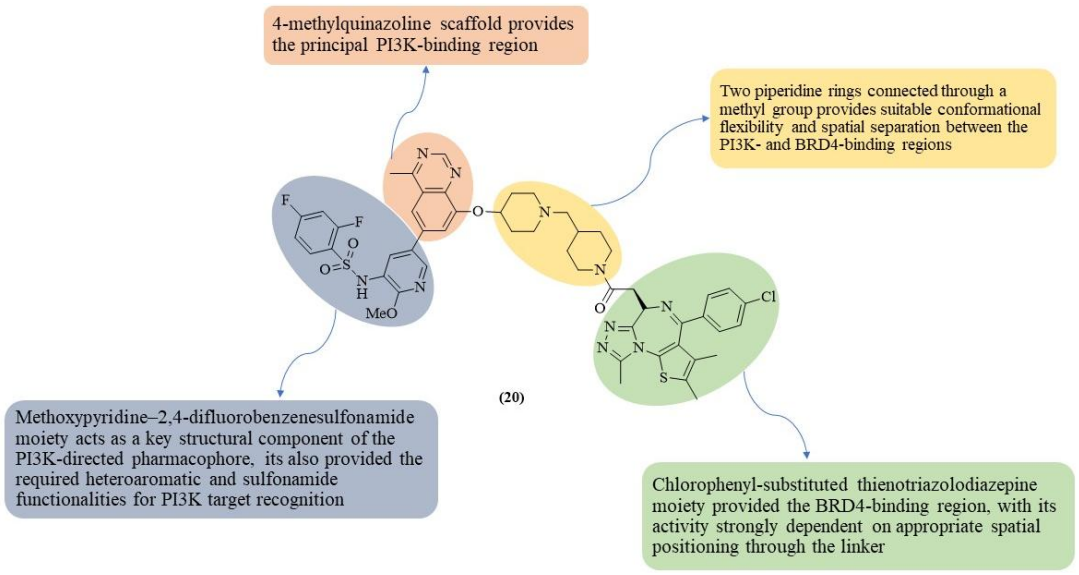


Figure 24. SAR of 4-methylquinazoline-based PI3K/BRD4 dual inhibitors.

ADMET and DMPK profiles of PI3K-based dual-target inhibitors

The clinical history of the PI3K inhibitor class, summarized in Table 1, indicates that attrition has been driven less by insufficient target potency than by narrow therapeutic windows, unfavourable exposure-response relationships and dose-limiting toxicity. For dual-target agents, the problem is compounded, because hybridization of two pharmacophores almost always increases molecular weight, polar surface area, H-bond count and rotatable-bond count, and because the structural element most often used to reach the second target, a flexible linker terminating in a zinc-binding group, a hydroxamate, a phthalazinone or an acetyl-lysine mimetic, is frequently also the element most vulnerable to metabolism, conjugation or chemical hydrolysis. Physicochemical and DMPK optimization of these molecules is therefore not a late-stage activity that follows potency optimization, but a parallel design constraint. This section therefore assembles the ADMET and DMPK data reported for the compounds in Tables 3 and 4 and then interprets those data against the structural modifications and SAR that produced them.

The predicted absorption data recover the solubility-permeability trade-off that constrains this chemotype (Table 3). Predicted aqueous solubility spans two orders of magnitude, from approximately 8 µM for the two low-molecular-weight quinoline PI3Kδ/mTOR inhibitors (6) and (7) to 855 to 1033 µM for the more polar compounds (9), (19), (8) and (20). Permeability moves in the opposite direction: compounds (6) and (7) were the only members of the series to exceed the pkCSM threshold for high Caco-2 permeability, at 16.1 and 13.9×10^{-6} cm s^{-1}, whereas the remaining eighteen compounds were predicted at or below 2.4×10^{-6} cm s^{-1}. Predicted human intestinal absorption remained high across the set, between 62.0 % for the PROTAC degrader compound (8) and 100 % for the PI3K/BRD4 hybrid compound (20), but this endpoint proved a poor guide to oral exposure, as discussed below. All twenty compounds were predicted to be P-glycoprotein substrates and nineteen to be P-glycoprotein inhibitors, so efflux is likely to limit both absorption and tissue penetration throughout the series and is an obvious candidate for experimental follow-up, since no transporter data have been reported for any compound reviewed here. The distribution predictions contain the single most consequential finding of this analysis. Plasma protein binding has not been measured experimentally for any compound in this review, yet it determines the free concentration available to engage either target. pkCSM predicts fractions unbound of 0.000, 0.002 and 0.014 for the three benzamide-based PI3K/HDAC lead compounds (13), (15) and (14), corresponding to essentially complete plasma protein binding, against 0.526, 0.494 and 0.446 for the comparatively polar compounds (1), (2) and (9) (Table 3).

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Table 3. Predicted absorption and distribution properties of the twenty PI3K-based dual-target lead compounds

Com-pound	Target	log (WS, mol L^{-1}) (WS, μM)	Caco-2 permeability log (Papp, 10^{-6} cm s^{-1})	HIA, %	log (V_{Dss}, L kg^{-1}) (V_{Dss}, L kg^{-1})	Fu	Predicted plasma protein binding, %	BBB log BB	CNS log PS
1	PI3K/mTOR	-3.179 (662)	-0.054 (0.88)	86.64	0.88 (7.59)	0.526	47.4	-2.13	-3.43
2	PI3K/mTOR	-3.203 (627)	0.378 (2.39)	83.03	0.828 (6.73)	0.494	50.6	-1.53	-3.41
3	PI3K/mTOR	-4.178 (66)	-0.159 (0.69)	80.89	-0.855 (0.14)	0.303	69.7	-2.05	-3.79
4	PI3K/mTOR	-4.151 (71)	0.339 (2.18)	80.55	-0.371 (0.43)	0.292	70.8	-1.50	-3.39
5	PI3K/mTOR	-4.752 (18)	0.036 (1.09)	93.06	-1.733 (0.02)	0.052	94.8	-1.80	-3.02
6	PI3K/mTOR	-5.086 (8)	1.207 (16.11)	94.88	-0.028 (0.94)	0.067	93.3	0.07	-1.81
7	PI3K/mTOR	-5.098 (8)	1.142 (13.87)	94.98	-1.252 (0.06)	0.08	92.0	-0.99	-2.79
8	PI3K/mTOR (PROTAC)	-3.018 (959)	-0.006 (0.99)	61.98	-0.999 (0.10)	0.191	80.9	-2.45	-3.68
9	PI3K/mTOR	-3.068 (855)	0.352 (2.25)	77.04	-0.041 (0.91)	0.446	55.4	-0.77	-2.81
10	PI3K/HDAC	-4.094 (81)	-0.17 (0.68)	70.24	-1.344 (0.05)	0.207	79.3	-1.38	-3.44
11	PI3K/HDAC	-4.04 (91)	-0.19 (0.65)	77.32	-1.161 (0.07)	0.191	80.9	-1.08	-3.22
12	PI3K/HDAC	-4.448 (36)	-0.128 (0.74)	71.57	-1.269 (0.05)	0.041	95.9	-1.75	-3.29
13	PI3K/HDAC	-4.477 (33)	-0.327 (0.47)	90.23	-1.372 (0.04)	0	100.0	-2.22	-3.01
14	PI3K/HDAC	-3.907 (124)	-0.248 (0.56)	94.75	-1.378 (0.04)	0.014	98.6	-2.05	-2.76
15	PI3K/HDAC	-4.379 (42)	-0.222 (0.60)	83.58	-1.309 (0.05)	0.002	99.8	-2.02	-3.01
16	PI3K/PARP	-4.082 (83)	-0.04 (0.91)	87.18	-1.487 (0.03)	0.059	94.1	-1.60	-2.99
17	PI3K/PARP	-3.713 (194)	-0.065 (0.86)	73.01	-1.16 (0.07)	0.263	73.7	-2.01	-3.82
18	PI3K/PARP	-3.863 (137)	-0.027 (0.94)	81.40	-0.889 (0.13)	0.199	80.1	-1.49	-3.30
19	EGFR/PI3K	-2.986 (1033)	0.302 (2.00)	91.36	0.051 (1.12)	0.339	66.1	-1.72	-2.72
20	PI3K/BRD4	-3.044 (904)	-0.102 (0.79)	100	-0.769 (0.17)	0.181	81.9	-2.65	-2.68

BBB - blood-brain barrier; BB - brain-to-blood partition coefficient; CNS - central nervous system; PS - permeability-surface area product; Fu - predicted fraction unbound in plasma; HIA - human intestinal absorption; Papp - apparent permeability coefficient; VDss - steady-state volume of distribution; WS - water solubility; Caco-2 permeability is high when log Papp > 0.90 (i.*e.* >8×10^{-6} cm s^{-1}); intestinal absorption below 30 % is considered poor; VDss is low when log VDss < -0.15 and high when > 0.45; log BB < -1 indicates poor brain distribution and log PS < -3 indicates inability to penetrate the CNS. All values are computational predictions and are presented separately from the experimental data

Predicted binding tracks lipophilicity closely across the series, and for compounds (13) to (15), whose calculated cLogP values lie between 6.3 and 6.9, it compounds two liabilities already established experimentally: an oral bioavailability of 3.17 % for compound (13) and HDAC1 inhibition in the 114 to 172 nM range against sub-nanomolar PI3Kα inhibition. If free plasma concentrations approach these predicted values, the unbound exposure attainable at a tolerated dose would be insufficient to engage the HDAC component, and these compounds would function *in vivo* predominantly as PI3K inhibitors. This remains a hypothesis rather than a conclusion, but it converts the potency imbalance identified in Table 2 from a comparison of biochemical IC_{50} values into a specific and readily testable pharmacokinetic question, and it makes the measurement of plasma protein binding the highest-priority experimental gap in this series. Predicted central nervous system exposure was negligible throughout, with log BB below -1 for seventeen of the twenty compounds, which is consistent with the intended peripheral application but indicates that none of these leads would address the brain metastases that frequently complicate the breast and lung cancers in which PI3K pathway inhibitors are used.

The metabolism, excretion and toxicity predictions are summarized in Table 4. Nine of the sixteen categorical endpoints returned an identical call for all twenty compounds, including CYP3A4 substrate status and P-glycoprotein substrate status (positive for every compound) and hERG I inhibition, hepatotoxicity and skin sensitization. CYP3A4 inhibition was predicted for seventeen of twenty compounds, the exceptions being the three least lipophilic compounds (9), (10) and (11), while inhibition of CYP1A2, CYP2C9 and CYP2C19 was confined almost entirely to the small, lipophilic quinoline compounds (5), (6) and (7). Moreover, the same compounds showed the highest predicted permeability and the highest predicted maximum tolerated dose. Predicted total clearance varied approximately thirty-fold across the series, from 0.27 (mL min^{-1}) kg^{-1} for

compound (20) to 7.78 (mL min^{-1}) kg^{-1} for compound (2), and the Ames test was predicted negative for nineteen of twenty compounds.

Table 4. Predicted metabolism, excretion and toxicity profile of the twenty PI3K-based dual-target lead compounds

Compound	log (CL, (mL min^{-1}) kg^{-1}) (CL, (mL min^{-1}) kg^{-1})	log (MTD, (mg kg^{-1}) day^{-1} (MTD, (mg kg^{-1}) day^{-1})	Rat LD_{50}, mol kg^{-1}	Rat log (LOAEL, (mg kg^{-1}) day^{-1} (LOAEL, (mg kg^{-1}) day^{-1})	T. pyriformis log (IGC_{50}/ µg L^{-1})
1	-0.005 (0.99)	0.22 (1.66)	2.47	1.408 (25.6)	0.286
2	0.891 (7.78)	-0.086 (0.82)	2.521	1.942 (87.5)	0.286
3	0.103 (1.27)	-0.162 (0.69)	2.393	1.425 (26.6)	0.287
4	0.728 (5.35)	-0.271 (0.54)	2.722	1.502 (31.8)	0.293
5	0.182 (1.52)	0.413 (2.59)	2.569	1.732 (54.0)	0.29
6	0.884 (7.66)	0.885 (7.67)	2.806	1.964 (92.0)	0.725
7	-0.011 (0.97)	0.755 (5.69)	2.698	1.846 (70.1)	0.485
8	0.442 (2.77)	0.167 (1.47)	1.9	3.109 (1285.3)	0.285
9	0.56 (3.63)	0.128 (1.34)	2.577	1.499 (31.6)	0.625
10	0.335 (2.16)	0.336 (2.17)	2.464	1.935 (86.1)	0.289
11	0.451 (2.82)	0.383 (2.42)	2.484	1.993 (98.4)	0.3
12	-0.367 (0.43)	0.385 (2.43)	2.493	2.6 (398.1)	0.285
13	-0.31 (0.49)	0.429 (2.69)	2.559	2.339 (218.3)	0.285
14	-0.119 (0.76)	0.383 (2.42)	2.545	2.668 (465.6)	0.285
15	-0.117 (0.76)	0.429 (2.69)	2.55	2.547 (352.4)	0.285
16	-0.152 (0.70)	0.113 (1.30)	2.538	2.08 (120.2)	0.285
17	0.204 (1.60)	-0.171 (0.67)	2.068	1.448 (28.1)	0.285
18	0.721 (5.26)	-0.069 (0.85)	2.49	1.821 (66.2)	0.285
19	0.793 (6.21)	0.252 (1.79)	2.551	2.752 (564.9)	0.285
20	-0.571 (0.27)	0.179 (1.51)	2.191	1.983 (96.2)	0.285

CL - total clearance; LD_{50} - median lethal dose; LOAEL - lowest observed adverse effect level; MTD - maximum tolerated dose; ≤0.477 log (mL min^{-1}) kg^{-1} is considered low; OCT2 - organic cation transporter 2; IGC_{50} - concentration producing 50 % inhibition of growth of Tetrahymena pyriformis; log (IGC_{50}, µg L^{-1}) above -0.5 is considered toxic. Nine of the sixteen categorical endpoints returned an identical call for all twenty compounds and are therefore uninformative for ranking within this series.

In vivo pharmacokinetic characterization has been reported for only seven of the twenty lead compounds, and Table 5 compiles every parameter disclosed for them alongside the corresponding antitumor efficacy. Intravenous terminal half-life varies over seventeen-fold, from 0.60 h for the imidazopyridazine sulphonamide (3) to 10.0 h for the benzamide-based PI3K/HDAC inhibitor (12), and plasma clearance varies over a comparable range, from 339.6 (mL h^{-1}) $kg^{-1}$for compound (1) and 361 (mL h^{-1}) $kg^{-1}$for compound (12) to 1428 and 1689 (mL h^{-1}) kg^{-1} for compounds (3) and (20). Volume of distribution is modest for the conventional ATP-site binders, at 690 and 528 mL kg^{-1} for compounds (1) and (3), but reaches 6.96 L kg^{-1} for the PROTAC degrader (8), consistent with the extensive tissue distribution expected of a bifunctional molecule of this size. Compound (12) has the most favourable exposure profile in the series, combining a 10 h half-life with low clearance and an AUC of 2772 h·ng mL^{-1} after a 1 mg kg^{-1} intravenous dose, parameters the original authors noted to be comparable to those of gedatolisib and markedly better than those of hydroxamate-based HDAC inhibitors such as vorinostat.

Oral bioavailability is where the series divides most sharply, and the division follows the chemistry rather than the target pair. The sulphonamide-bearing PI3K/mTOR inhibitors compound (1) and (3) achieved 26.8 % and 33.1 % in rats, whereas the benzamide-based PI3K/HDAC inhibitor compound (13) reached only 3.17 % in mice and its congener compound (14) was lower still, so that the dose-dependent efficacy demonstrated for both compounds in MV4-11 xenografts required oral administration at 60 mg kg^{-1}. The same structural feature that resolved the metabolic and genotoxic liabilities of hydroxamate zinc-binding groups, and that gave compound (12) its 10 h half-life, therefore imposes a severe absorption penalty, and the calculated profiles in Table 5 attribute this to the lipophilicity and conformational flexibility introduced by the benzamide and its linker. For the two largest molecules in the set, the problem was circumvented rather than solved:

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the PROTAC compound (8) and the PI3K/BRD4 hybrid (20) were advanced by the intraperitoneal route, achieving 51.5 and 20 % bioavailability, respectively, which is an appropriate development strategy for compounds of this size but one that constrains their eventual clinical application.

Table 5. *In vivo* pharmacokinetic parameters and antitumor efficacy reported for PI3K-based dual-target lead compounds

Com-pound	Species	Route (Dose, mg kg $^{-1}$)	$t_{½}$ / h	CL, (mL h^{-1}) kg^{-1}	V / mL kg^{-1}	AUC, h·ng mL^{-1}	C_{max} / ng mL^{-1}	F / %	*In vivo* efficacy
1	SD rat	i.v. (1)	4.71	339.6	V_{ss} 690	2958	-	-	HCT116 and HT-29 xenografts, significant TGI without body-weight loss
1	SD rat	p.o. (5)	7.94	-	-	3965	553	26.8	HCT116 and HT-29 xenografts, significant TGI without body-weight loss
3	Rat	i.v. (1)	0.60	1428	V_{dss} 528	760	-	-	HCT116 and HT-29 xenografts at 20 mg kg^{-1}, TGI comparable to copanlisib without body-weight loss
3	Rat	p.o. (5)	2.33	-	-	1356	1218	33.1	HCT116 and HT-29 xenografts at 20 mg/kg, TGI comparable to copanlisib without body-weight loss
8	SD rat	i.v. (5)	-	10.5	V_d 6960	-	993	-	MDA-MB-231 xenograft, >70 % TGI at 15 and 25 mg/kg i.p.
8	SD rat	i.p. (15)	8.25	-	-	-	816	51.5	MDA-MB-231 xenograft, > 70 % TGI at 15 and 25 mg kg^{-1} i.p.
12	ICR mouse	i.v. (1)	10.0 ± 1.5	361 ± 20	V_{ss} 719 ± 20	2772 ± 152	603	-	Not reported; marked pro-apoptotic activity in Jeko-1 lymphoma cells
13	ICR mouse	i.v. (6)	2.30	-	-	1605	-	-	MV4-11 xenograft, 75.0 % TGI at 20 mg kg^{-1} without body-weight loss
13	ICR mouse	p.o. (60)	1.38	-	-	5042	776	3.17	MV4-11 xenograft, 75.0 % TGI at 20 mg kg^{-1} without body-weight loss
14	ICR mouse	i.v. (6)	2.43	-	-	-	-	-	MV4-11 xenograft, dose-dependent TGI
14	ICR mouse	p.o. (60)	4.46	-	-	-	306	low	MV4-11 xenograft, dose-dependent TGI
16	Mouse	not reported in detail	-	-	-	-	-	-	MDA-MB-468 xenograft, 73.4 % TGI at 50 mg kg^{-1}, no observable toxicity
17	Mouse / rat	not reported in detail	-	-	-	-	-	-	MDA-MB-468 xenograft, 54.6 % TGI at 50 mg kg^{-1}; maximum tolerated dose >1000 mg kg^{-1}
18	Mouse	not reported in detail	-	-	-	-	-	-	MDA-MB-468 xenograft, 48.8 % TGI, no body-weight loss
20	Mouse	i.v. (2)	1.02 ± 0.04	1689 ± 200	V_z 2480 ± 376	AUC(0-t) 1140 ± 129	-	-	KYSE450 xenograft at 2.5 to 5 mg kg^{-1}, efficacy comparable to the BKM120/JQ1 combination; enhanced by the senolytic ABT737
20	Mouse	i.p. (20)	2.66	-	-	AUC(0-t) 2225	-	20	KYSE450 xenograft at 2.5-5 mg kg^{-1}, efficacy comparable to the BKM120/JQ1 combination; enhanced by the senolytic ABT737

i.v. - intravenous; p.o. - oral; i.p. - intraperitoneal; F - absolute bioavailability; TGI - tumour growth inhibition

Antitumor efficacy, by contrast, is markedly consistent across the series and across target combinations. Tumour growth inhibition of 48.8 to 75.0 % was achieved in xenograft models by compounds drawn from the PI3K/mTOR, PI3K/HDAC, PI3K/PARP and PI3K/BRD4 classes, and tolerability was uniformly good, with no significant body-weight loss reported in any study and a maximum tolerated dose above 1000 mg kg^{-1} for compound (17). Two observations temper this. First, the efficacy of compounds (16), (17) and (18) was established without any accompanying pharmacokinetic characterization, so the exposure at which that efficacy was obtained is unknown and no exposure-response relationship can be constructed; the same applies to compound (12), for which pharmacokinetics was reported but efficacy was not. Second, the narrow range of tumour growth inhibition achieved across chemically and mechanistically diverse agents suggests that these models may discriminate poorly between them, and that comparative efficacy claims based on

such data should be made cautiously. Reporting plasma concentrations at the efficacious dose, alongside the biochemical potencies at both targets, would do more to establish the value of a dual-target agent than a further increment in tumour growth inhibition.

Structure-property relationships: how structural modification governs ADMET

Solubilising substituents on the solvent-exposed vector are the most reliably successful property-driven modification in this literature. In the dual PARP/PI3K series, the parent leads combined potent inhibition of both targets with aqueous solubility below 100 μg mL^{-1} and attempts to solve the problem by salt formation, hydrochloride, tartrate and others, failed. Adding a basic, hydrophilic N-acetyl morpholine group to the aminopyrimidine nitrogen raised solubility to more than 10 mg mL^{-1}, a gain of over two orders of magnitude, while leaving the dual-target pharmacophore unchanged. The resulting compound (17) showed a human liver microsomal half-life ($t_{½}$) of 107 min, an intrinsic clearance of 14.7 (μL min^{-1}) mg^{-1}, Caco-2 permeability above 10^{-6} cm s^{-1}, weak hERG inhibition (IC_{50} = 29.4 μM) and a maximum tolerated dose above 1000 mg kg^{-1}. It achieved 54.6 % tumour growth inhibition in a triple-negative breast cancer xenograft. [78] This is the clearest demonstration in the set that solubility, metabolic stability and safety can be engineered into a dual-target hybrid without sacrificing dual potency, and the structural reason is instructive: the modification was made at a vector that projects into solvent in both binding sites and is therefore insensitive to the steric and electronic requirements of either.

Ionisable acidic groups, by contrast, trade potency for solubility. In the morpholino-triazine pan-PI3K/mTOR series, replacing the meta-hydroxyl of compound (9) with a carboxylic acid raised kinetic solubility at pH 7.4 more than 80-fold, from below 1 to 82.8 μM, but sharply reduced PI3K inhibitory activity, an effect the authors attributed to reduced membrane permeability of the ionized species. Replacement with a non-ionized primary amide gave a more modest 9-fold solubility gain, while improving PI3Kα selectivity and retaining dual PI3Kα/mTOR inhibition [61]. The practical conclusion for this chemotype is that neutral polar groups and weakly basic amines are preferable to carboxylic acids when solubility must be improved without loss of cell-based activity. The same series also illustrates how incomplete a single solubility measurement can be: solubility measured at 4 h and at 24 h diverged, with two analogues precipitating over time, so that thermodynamic rather than kinetic solubility is the parameter that should be reported.

Lipophilicity and polar surface area define a narrow operating window for these hybrids, and the PARP/PI3K work provides a rare direct comparison. Two closely related leads of comparable enzymatic potency differed in their *in vivo* performance: the analogue with cLog*P* 2.7 and tPSA 1.53 nm^2achieved 56.4 % tumour growth inhibition, against 48.8 % for the analogue with cLog*P* 1.8 and tPSA 1.64 nm^2. The authors attributed this difference to permeability, noting that a cLog*P* near 3 is advantageous and that large tPSA values predict poor membrane permeation. They also cautioned that further increases in lipophilicity produced instability in mouse liver microsomes [79]. Because pharmacophore fusion inevitably pushes molecular weight and TPSA upward, the PARP and HDAC pharmacophores each contribute substantial polarity on top of a morpholino-heteroaryl PI3K binder, lipophilicity cannot simply be raised to compensate without incurring metabolic liability. The authors of the EGFR/PI3K hybrid series reached the same conclusion independently, identifying molecular weight, solubility and permeability rather than potency as the limiting factors for further development of compound (19), despite its rat liver microsomal $t_{½}$ of 87.72 min, stability in simulated gastrointestinal fluids and 72.3 % recovery after 3 h in rat plasma [80].

The choice of zinc-binding group in the PI3K/HDAC series is the most consequential single ADMET decision in this review, and it is a genuine trade-off rather than a straightforward improvement. Hydroxamic acids such as that in compound (11) confer sub-10 nM HDAC6 inhibition. However, the class is associated with rapid metabolic clearance, poor oral bioavailability and a genotoxicity risk arising from Lossen rearrange-

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ment. No DMPK data were reported for compound (11) [70]. Deliberate replacement by an o-aminobenzamide in compounds (12) to (15) achieved its intended safety and exposure objectives. Compound (12) inhibited six cytochrome P450 isoforms only weakly, 2D6 being the most affected at 48.8 % inhibition and 1A2 essentially unaffected at 2.5 % and showed a low likelihood of hERG inhibition. It displayed consistent microsomal stability across mouse, rat and human ($t_{½}$ 26.9-37.5 min), and achieved an intravenous half-life of 10.0 h in mice with a clearance of 361 mL/h/kg and an AUC of 2772 h·ng mL^{-1} at 1 mg kg^{-1}. The authors noted these parameters to be comparable to those of gedatolisib and better than those of hydroxamate HDAC inhibitors such as vorinostat [71]. The cost, however, appears at the absorption step and in the balance of potencies. Compound (13) showed an oral bioavailability of only 3.17 % in mice, with compound (14) similarly low, so that the favourable oral exposure relative to hydroxamate comparators was achieved only at a 60 mg/kg oral dose, and the *in vivo* efficacy studies relied on high oral dosing rather than on efficient absorption. In parallel, benzamide zinc-binding groups are intrinsically less potent at HDACs than hydroxamates, so HDAC inhibition in compounds (13) to (15) falls into the 114 to 172 nM range while PI3K inhibition remains sub-nanomolar, widening the potency gap between the two targets to more than two orders of magnitude. The benzamide strategy therefore resolves a safety and half-life problem while creating an absorption problem and aggravating the potency-imbalance problem.

Linker group/chain governs ADMET as directly as it governs potency. In compound (13), a six-methylene chain was optimal for HDAC1 inhibition, with shorter and longer chains both being markedly less active. In the PI3K/BRD4 series, medium-length alkyl or heterocyclic linkers gave the best balance, whereas excessively long or rigid linkers retained PI3K inhibition but abolished BRD4 activity, in one case raising the BRD4 IC_{50} above 10 μM. In the PROTAC series, flexible polyethylene glycol or alkyl linkers favoured productive ternary complex formation and mTOR degradation [72,81]. Each of these optimizations also changes rotatable-bond count, polar surface area and molecular weight, and therefore solubility, permeability and metabolic exposure. The N-acylhydrazone linker of compound (10) illustrates the extreme case: it provided the conformational properties required for dual HDAC6/PI3Kα engagement but hydrolysed extensively at pH 2.0, with less than 30 % of compound recovered after 4 h against more than 60 % at pH 7.4, a chemical rather than enzymatic instability that would compromise oral delivery irrespective of metabolic stability and that argues for bioisosteric replacement of the C=N bond [69].

Targeted protein degradation introduces a distinct and more favourable DMPK profile. The dual PI3K/mTOR PROTAC compound (8), built from the gedatolisib scaffold and a VHL ligand, lies well outside conventional oral drug-like space, yet achieved 51.5 % bioavailability and an 8.25 h half-life after intraperitoneal dosing in rats, with sustained local exposure [60]. After intravenous dosing, however, its clearance of 10.5 (mL^{-1} min) kg^{-1} and volume of distribution of 6.96 L kg^{-1} indicate rapid distribution and elimination from plasma, despite a high initial concentration (Cmax 50,993 ng mL^{-1} at 5 mg kg^{-1}). The intraperitoneal route was therefore selected for efficacy studies [84].

In terms of metabolic stability, compound (20) showed liver microsomal half-lives ranging from 30.5 min in rat to 232.7 min in monkey, a 7.6-fold span, with human at 69.8 min and mouse at 109.4 min, so that a stability assessment based on mouse microsomes alone would have been optimistic by more than 50 % relative to human [81]. Compound (17) displayed the opposite rank order, being most stable in human liver microsomes ($t_{½}$ 107 min) and least stable in mouse (17.4 min), a 6-fold span in the other direction [78]. At minimum, microsomal stability should be determined in human microsomes and in those of the efficacy species, and preferably across at least three species, as was done for compounds (17) and (20).

Finally, the reported off-target safety data are reassuring as far as they go. Measured hERG IC_{50} values exceeded 29 µM for compound (17) and 30 µM for compounds (7) and (18), and no significant blockade was seen at 10 µM for compound (10). Cytochrome P450 inhibition was weak for compounds (10) and (12), and the maximum tolerated dose of compound (17) exceeded 1000 mg kg^{-1} in rats. [69,71,78,79,59] Kinase selectivity, where profiled broadly, was good: compounds (13) and (14) inhibited only class I and class II PI3Ks among 97 kinases screened, and compound (18) was inactive against most of a 374-kinase panel [72,79]. These results indicate that the hybrid chemotypes do not inherently display broad off-target activity. However, address the on-target toxicities that have actually limited this drug class in patients: hyperglycemia arising from inhibition of wild-type PI3Kα in insulin-responsive tissues, and the immune-mediated colitis, pneumonitis and infection risk associated with PI3Kδ and PI3Kγ inhibition. Several of the compounds reviewed here are deliberately PI3Kδ-directed, with compound (6) showing 15- to 16-fold selectivity for PI3Kδ, and several others are pan-class I inhibitors; neither profile has been evaluated against the immune and metabolic endpoints that matter clinically. Glucose and insulin measurements in repeat-dose studies, and assessment of effects on lymphocyte and regulatory T-cell populations, would be considerably more informative for this class than further hERG and cytochrome P450 screening [29,31].

Development status: preclinical leads, clinical candidates and approved agents

All twenty compounds discussed are preclinical leads. None has entered clinical investigation; none has an assigned international non-proprietary name and for most, the available data comprise enzymatic potency, cellular pharmacology and, in several cases, a mouse xenograft study, with the DMPK characterization summarized in Tables 3 to 5. They are appropriately described as lead compounds or, where *in vivo* efficacy and pharmacokinetics have been demonstrated, as advanced leads or preclinical candidates.

Within the PI3K/mTOR class, numerous agents have entered clinical trials, including dactolisib, apitolisib, voxtalisib, samotolisib, bimiralisib, paxalisib and gedatolisib, and until recently none had been approved, with development of several having been curtailed by toxicity and narrow therapeutic windows [51,52]. That changed in July 2026 with the approval of gedatolisib, a pan-class I PI3K and mTORC1/2 inhibitor, for hormone receptor-positive, HER2-negative, PIK3CA wild-type advanced breast cancer, based on the randomized phase 3 VIKTORIA-1 trial [84]. Gedatolisib is consequently the first approved dual PI3K/mTOR inhibitor, and its approval is relevant here because two of the preclinical series reviewed above - the benzimidazole-triazines of compound (2) and the PROTAC degraders of compound (8) - were derived directly from its dimorpholino-triazine pharmacophore [54,60].

Within the PI3K/HDAC class, two agents have reached clinical trials. Fimepinostat (CUDC-907) was the first dual HDAC/PI3K inhibitor to enter clinical evaluation and has been granted fast-track and orphan-drug designations. It was well tolerated without dose-limiting toxicity in a phase I lymphoma study, and showed pharmacodynamic evidence of engagement of both targets, with increased acetylated tubulin, histone H3 and p21 and reduced phosphorylated AKT. It remains investigational and has also been examined preclinically in pleural mesothelioma, where activity depended on cisplatin sensitivity and MYC expression [65]. Ifupinostat (BEBT-908), a fimepinostat analogue, received conditional approval from the Chinese regulatory authority in July 2025 for relapsed or refractory diffuse large B-cell lymphoma, with a reported phase IIb overall response rate of 54.6 % and median overall survival of 8.8 months. Its enzymatic potency data have not been publicly disclosed [35]. Finally, umbralisib should be noted as a dual PI3Kδ/CK1ε inhibitor that was approved in the United States in 2021 and subsequently withdrawn, and which therefore constitutes the one completed regulatory cycle for a dual-target PI3K agent to date [82]. No dual PI3K/PARP, EGFR/PI3K or

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PI3K/BRD4 single molecule has yet entered clinical development, although the corresponding free-drug combinations have been evaluated clinically.

Conclusion

The PI3K/AKT/mTOR pathway plays a key role in regulating cancer cell growth, survival, metabolism and progression and thus represents a promising target for anticancer drug development. Single-target PI3K inhibitors, however, may be clinically limited by pathway reactivation, compensatory signalling, acquired resistance, and toxicity. The development of dual-target inhibitors is thus a promising approach to more potent and persistent antitumor activity. The compounds in this review highlight the concept that simultaneous inhibition of PI3K and other targets in the same pathways, such as mTOR, HDAC, EGFR, PARP, and other oncogenic pathways, may increase anticancer activity and potentially overcome resistance mechanisms.

Several structural features improve dual potency reproducibly. A morpholine oxygen hydrogen-bonding to Val851 in PI3Kα and Val2240 in mTOR is nearly obligatory, and replacing it with piperidine abolishes activity; this shared hinge interaction is why PI3K/mTOR is the most tractable pair. A 2,4-difluoro-phenylsulfonamide engaging Lys802 delivered sub-nanomolar PI3Kα inhibition in four unrelated series, and rigid azoles used as amide surrogates improve potency and solubility together.

Other strategies improve one property at a measurable cost. Carboxylic acids raised solubility more than eighty-fold but collapsed PI3K potency and permeability, whereas neutral amides did not. Replacing hydroxamate zinc-binding groups with o-aminobenzamides resolved genotoxicity and gave a 10 h intravenous half-life but reduced oral bioavailability to 3.17 % and widened the PI3K-to-HDAC potency gap beyond three hundred-fold. N-Acylhydrazone linkers hydrolyse at gastric pH, and raising lipophilicity to recover permeability produces metabolic instability; the usable window appears to be cLog*P* 2-3 with polar surface area below 155 Å².

The target combinations differ in mechanistic strength. PI3K/PARP is the best founded, since PI3K inhibition generates a measurable homologous-recombination defect and may extend PARP inhibitor sensitivity to BRCA-proficient tumours; it is also the only pair in which balanced dual potency was consistently achieved. EGFR/PI3K follows, blocking a validated resistance route in a biomarker-defined population. PI3K/mTOR is the most tractable and now the only approved combination, though complete pathway blockade carries an inherent risk to the therapeutic window. PI3K/HDAC is clinically more advanced but mechanistically least specific.

Four barriers now limit translation, and none concerns potency. First, the second-target IC_{50} exceeds the PI3K IC_{50} by 80- to 340-fold in most hybrids, so the second target may be only fractionally engaged; because a single molecule fixes that ratio at synthesis, it must be designed correctly from the outset. Second, *in vivo* pharmacokinetics exist for only seven of twenty leads and plasma protein binding for none, so dual engagement at tolerated exposure remains unverified. Third, oral bioavailability is low or unmeasured for most hybrids. Fourth, randomized evidence of survival benefit is now expected of PI3K-directed agents, and no biomarker exists for the second target. With the first dual PI3K/mTOR inhibitor now approved, the question facing the field is no longer whether dual-target PI3K inhibition can work, but which combinations, in which populations, and at what cost in therapeutic window.

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