CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
SJIF Impact Factor: 7.187
https://doi.org/10.5281/zenodo.22015675

Available online at: http://www.iajps.com Review Article

DUAL-TARGET INHIBITORS IN DRUG-DISCOVERY: RATIONALE, ADVANCES, AND FUTURE PERSPECTIVES

Omkar Rai[1]* [0009-0003-1861-3753], Lakhan Kumar Soni[2] [0009-0008-8760-2536], Soma Sekhar Pulamarasetti[1]* [0009-0007-3552-1868], Deepshikha Dey[1]*[0009-0008-6882-9647], Vishesh Kumar Prajapati[3] [0009-0004-7657-581X]

[1]Faculty of Pharmacy, B. R. Nahata College of Pharmacy, Mandsaur University, Mandsaur, Madhya Pradesh, India (PIN: 458001), ORCID: 0009-0003-1861-3753
[2]Faculty of Pharmacy, Aman Pharmacy College, Dholakhera, Jhunjhunu, Rajasthan, India (PIN: 333307), ORCID: 0009-0008-8760-2536
[3]Faculty of Pharmacy, B. R. Nahata College of Pharmacy, Mandsaur University, Mandsaur, Madhya Pradesh, India (PIN: 458001), ORCID: 0009-0007-3552-1868
[4]Faculty of Pharmacy, B. R. Nahata College of Pharmacy, Mandsaur University, Mandsaur, Madhya Pradesh, India (PIN: 458001), ORCID: 0009-0008-6882-9647
[5]*Department of Pharmacy / Central University of Rajasthan (CURAJ), NH-8, Bandarsindri, Ajmer District, Rajasthan, India (PIN: 305817)*, ORCID: 0009-0004-7657-581X

Abstract:
Dual-target inhibitors are single small molecules intentionally designed to modulate two therapeutically relevant proteins, enzymes, receptors, or signaling nodes within one pharmacological intervention. The strategy extends the polypharmacology paradigm and is especially attractive for complex diseases in which pathway redundancy, compensatory signaling, disease heterogeneity, and acquired resistance weaken single-target therapy. A dual inhibitor can provide coordinated target coverage and synchronized exposure, while potentially simplifying pharmacokinetic management compared with two independent drugs. nevertheless, intentional duality is not equivalent to nonspecific promiscuity: both target interactions should contribute to efficacy at clinically achievable exposure while important antitargets remain controlled. Here, we examine examines the biological rationale for target pairing; pharmacophore fusion, linker-based hybridization, scaffold hopping, repurposing, and phenotypic screening; computational methods including docking, pharmacophore modeling, molecular dynamics, machine learning, and network analysis; and the medicinal-chemistry optimization of potency balance, selectivity, ADME, and safety. Representative programs are discussed in oncology, neurodegeneration, inflammation, infectious disease, and metabolic disorders, with emphasis on PI3K/mTOR, HDAC/PI3K, BET/kinase, PARP/HDAC, COX/LOX, and AChE/MAO-B strategies. The field has generated extensive preclinical evidence, but movement into clinical use remains comparatively limited. Future progress will depend on biologically justified target pairs, quantitative target-balance criteria, biomarker-led development, human-relevant models, chemical proteomics, and AI-assisted multi-objective design.
Keywords: dual-target inhibitor; multitarget drug-discovery; polypharmacology; multi-target-directed ligand; medicinal chemistry; target balance; pharmacophore hybridization; molecular docking; molecular dynamics; machine learning; ADME; drug resistance.

Corresponding author:
Omkar Rai,
Faculty of Pharmacy, B. R. Nahata College of Pharmacy, Mandsaur University, Mandsaur, Madhya Pradesh, India (PIN: 458001), ORCID: 0009-0003-1861-3753
Email: omkarrai274304@gmail.com
Mobile No.: +91-9792279812

Please cite this article in press Omkar Rai et al., Dual-Target Inhibitors In Drug-Discovery:Rationale, Advances, And Future Perspectives., Indo Am. J. P. Sci, 2026; 13(08).

1. INTRODUCTION:

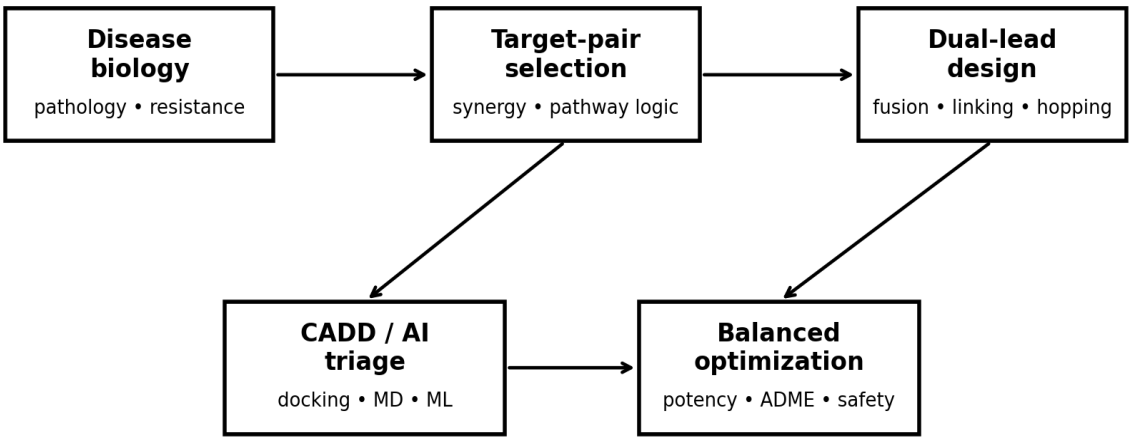

Figure 1. Conceptual workflow for discovery and optimization of dual-target inhibitors.

Modern medicinal chemistry has traditionally emphasized high selectivity for a single target. Such a strategy has yielded major therapeutic successes, but many diseases are governed by interconnected networks rather than isolated molecular switches. Polypharmacology redefines therapeutic selectivity as the controlled modulation of a biologically meaningful set of targets. The dual-target inhibitors are the conscious realization of this concept, in which two selected targets are attacked by a single chemical entity [1–9].

Fundamental is the distinction between intentional dual targeting and incidental off-target activity. A useful dual inhibitor is not a promiscuous ligand. The two desired interactions should be mechanistically linked to efficacy, have an experimentally validated exposure window and be separable from unwanted anti-target activity [1–5].

Dual targeting can be vertically acting at two nodes in a single pathway; horizontally acting on parallel or compensatory pathways; or mechanistically complementary, combining distinct disease processes.These models are exemplified by PI3K/mTOR, HDAC/PI3K, BET/kinase, PARP/HDAC, COX/LOX, and AChE/MAO-B programs [10–18].

2. Biological Rationale for Dual Targeting

A strong target pair should be chosen from disease biology, not from chemical convenience. The combination is most compelling when combined

modulation leads to greater pathway suppression than either target alone, blocks a known escape route, exploits synthetic lethality or targets two pathological mechanisms that are difficult to control with one target. The biology may be similar with combination therapy, but the individual drugs may have different absorption, distribution, metabolism, clearance, tissue penetration, and dose-limiting toxicities [2,3,19–24].

The fixed-ratio nature of the dual inhibitor is both an advantage and a limitation. It coordinates the two activities, but it loses the flexibility that one has with two independent drugs. Therefore, the desired potency ratio should be defined based on cellular and PK/PD data and not assumed to be 1:1.

Table 1. Framework for assessing the biological rationale of a candidate target pair.

Target-pair criterion	Evidence to seek	Typical failure mode
Mechanistic complementarity	Genetics, pathway maps, perturbation studies	Targets are individually valid but not jointly useful
Synergy / synthetic lethality	Bliss, Loewe, HSA, genetic interaction	In-vitro synergy fails in vivo
Compensatory signaling	Time-course phosphoproteomics	Escape mechanism is transient or tissue-specific
Co-localization	Subcellular localization, tissue exposure	Targets occur in different compartments
Therapeutic window	Cellular and animal dose-response	Second target needs excessive exposure
Chemical tractability	Structures, ligands, fragments	Potency balance is chemically incompatible
Biomarker feasibility	Target-engagement and PD assays	Mechanism cannot be verified in humans

3. Discovery and Design Strategies

3.1 Pharmacophore fusion and molecular hybridization

Pharmacophore fusion merges important recognition features from two ligands into a common framework. This strategy can reduce size relative to a long linked construct and generate new binding modes but may also require compromises regarding geometry, solvation and conformational freedom. Thus medicinal chemistry must be able to distinguish essential interactions from displaceable substituents and must apply structure-guided vector analysis [25–30].

3.2 Linker-based connected ligands

Two identifiable pharmacophores may be joined by a linker when maintaining both original binding modes is beneficial. The design of linkers significantly affects potency, permeability, metabolic stability, and conformational entropy. Systematic evaluations of length, polarity, stiffness, and attachment vectors often provide more insights than singular linker optimization efforts [25,31–34].

3.3 Scaffold hopping and privileged chemotypes

Scaffold hopping aims to identify compact chemotypes that can replicate binding characteristics at both targets while enhancing solubility, stability, and selectivity. Privileged heterocycles and prevalent interaction motifs may serve as advantageous foundations, although the structural compatibility of the two binding sites is the determining element.

3.4 Repurposing and target deconvolution

Bioactive ligands and well-known medications may disclose beneficial secondary actions. An observed polypharmacological profile may be converted into a deliberate dual-target hypothesis using chemical-proteomics, target-profiling, transcriptomics, and network analysis [35–38].

3.5 Phenotypic screening

When the optimal target pair is unclear, phenotypic screening is useful. Resistance mapping, CRISPR perturbation, chemoproteomics, and pathway profiling may deconvolute hits, and the identified target pair can then serve as the foundation for logical optimization.

4. Computational and AI-Assisted Dual-Target Discovery

Discovering two targets at once is inherently multi-objective. Network pharmacology ranks target pairs in disease-specific systems, docking and pharmacophore methods aid in establishing binding hypotheses at each target, free-energy approaches rank close analogs, QSAR and machine learning predict activity and ADME, and molecular dynamics tests conformational stability [39–48].

Table 2. Computational and AI-assisted methods used in dual-target discovery.

Method	Primary role	Dual-target value	Main limitation
Docking	Binding-pose prediction	Compare poses at both targets	Scoring functions can mis-rank affinity
Pharmacophore modeling	Interaction abstraction	Define shared or dual pharmacophores	Sensitive to training-set quality
Molecular dynamics	Conformational sampling	Test stability of both complexes	Sampling/force-field dependence
Free-energy methods	Relative affinity	Prioritize balanced analogues	Computationally demanding
QSAR / ML	Prediction	Multi-task activity and ADME modeling	Dataset bias and extrapolation
Generative AI	Chemical-space exploration	Joint potency/property optimization	Synthetic feasibility needs validation
Network pharmacology	Systems rationale	Target-pair prioritization	Association is not causation
Chemical proteomics	Target deconvolution	Separate intentional duality from promiscuity	Specialized assays required

5. Quantitative Target Balance

A molecule that is active at 10 nM against Target A and 10 µM against Target B is usually a single target inhibitor functionally. However, the need for equal biochemical potency is not always warranted because of differences in target abundance, pathway position, residence time, signal amplification and tissue exposure. The design goal should therefore be a biologically defined window of potency and not a universal ratio.

A practical project metric is the potency ratio R = IC50(A)/IC50(B) interpreted together with free drug exposure and cellular target engagement. Target-B potency Selectivity ADME Safety Conceptually, a multi-objective score can combine target-A potency, target-B potency, selectivity, ADME and safety. The weights should reflect the intended therapeutic mechanism rather than biochemical potency alone.

Table 3. Optimization axes for balancing potency, selectivity, and developability.

Optimization axis	Preferred direction	Reason
Target-A potency	Increase to disease-relevant range	Ensures meaningful first mechanism
Target-B potency	Increase to disease-relevant range	Prevents functional monotherapy
Potency ratio	Keep in a biologically justified window	Maintains intended mechanism
Antitarget selectivity	Increase	Limits off-target toxicity
Solubility	Increase	Supports exposure and formulation
Permeability	Context dependent	Required for CNS/intracellular targets
Metabolic stability	Optimize	Controls duration and clearance
CYP/hERG liability	Decrease	Improves safety and DDI profile

6. Oncology: Major Area of Development

Cancer is especially well suited for dual targeting because tumors frequently activate parallel survival pathways, use feedback loops and acquire resistance thru pathway rewiring. Dual PI3K/mTOR inhibitors aim to inhibit two levels of one signaling axis, HDAC/PI3K inhibitors combine epigenetic and survival-pathway inhibition, BET/kinase programs target transcriptional dependence plus kinase signaling, and PARP/HDAC concepts exploit crosstalk between DNA repair and chromatin regulation [10–18,49–60].

Table 4. Representative target pairs and design concepts in oncology.

Target pair	Rationale	Representative concept	Key challenge
PI3K/mTOR	Vertical pathway suppression	Dual catalytic-site inhibitors	Class-related toxicity
HDAC/PI3K	Epigenetic + survival signaling	CUDC-907 and related hybrids	Balance isoform activity and PI3K selectivity
BET/kinase	Transcription + kinase dependency	BET/PLK1, BET/CDK, BET/PARP concepts	PK and molecular complexity
PARP/HDAC	DNA repair + chromatin	Hybrid PARP/HDAC inhibitors	Therapeutic window
COX/LOX	Two inflammatory branches	Dual eicosanoid inhibitors	Cardiovascular/GI safety
BRAF + escape target	MAPK + compensatory signaling	Dual kinase/other-target designs	Tumor-genotype dependence

6.1 Clinical Translation: Approved and Ongoing Dual-Target Inhibitors

movement into clinical use is an important test of the dual-target inhibitor concept because the benefits of simultaneous target engagement must be showed within a clinically acceptable therapeutic window. Unlike combination therapy, a dual-target inhibitor is a single chemical entity intentionally designed to engage two molecular targets or two closely related pathway nodes. Examples that have progressed into clinical development include PI3K/mTOR, HDAC/PI3K, EZH1/EZH2, ATM/DNA-PK and PDE3/PDE4 inhibitors, illustrating that the strategy is not restricted to one therapeutic area [1,2,3,4].

Gedatolisib (Revtorpyk; PF-05212384/PKI-587) is currently the most important regulatory example. It is a pan-class-I PI3K and mTORC1/mTORC2 inhibitor and accordingly provides simultaneous inhibition of multiple PI3K pathway nodes. The U.S. Food and Drug Administration approved gedatolisib on July 14, 2026, in combination with fulvestrant, with or without palbociclib, for adults with HR-positive/HER2-negative locally advanced or metastatic breast cancer without a detected PIK3CA mutation after progression on or after at least one line of endocrine therapy in the metastatic setting [5]. The VIKTORIA-1 study reported median progression-free survival of 9.3 months for gedatolisib plus fulvestrant and palbociclib, 7.4 months for gedatolisib plus fulvestrant, and 2.0 months for fulvestrant alone [5,6]. The clinical development of gedatolisib is especially informative because the dual inhibitor is not used as a substitute for all other mechanisms. Instead, the PI3K/mTOR dual inhibitor forms the pathway-directed component of a rational combination regimen, while fulvestrant suppresses estrogen-receptor signaling and palbociclib inhibits CDK4/6 when included. This model shows how single-molecule dual targeting can be integrated with complementary pharmacology to increase pathway coverage without simply administering two separate drugs against the same pathway [5,6].

Other clinically investigated dual-target inhibitors further show the breadth of the approach. HH2853 is an EZH1/EZH2 dual inhibitor being investigated in relapsed/refractory malignancies; XRD-0394 simultaneously inhibits ATM and DNA-PK and is being evaluated with radiotherapy in high-grade glioma; and AN01 is an early clinical PDE3/PDE4 dual inhibitor program [7,8,9]. Fimepinostat (CUDC-907), an HDAC/PI3K dual inhibitor, represents an earlier and extensively studied example of pharmacophore fusion designed to combine epigenetic modulation with inhibition of a major cancer-survival pathway [10,11].

Several PI3K/mTOR dual inhibitors—including dactolisib (BEZ235), bimiralisib (PQR309), voxtalisib (XL765/SAR245409) and samotolisib (LY3023414)—also reached clinical evaluation but did not become approved therapies. These programs are important because they show that strong biochemical dual-target activity does not automatically translate into clinical success; dose-limiting toxicity, pathway complexity, insufficient therapeutic index, pharmacokinetic limitations and patient-selection issues can all constrain development [1,12–15].

Accordingly, the clinical record supports a balanced interpretation of dual-target inhibition. Successful development requires not only simultaneous target engagement but also appropriate target biology, exposure, selectivity, biomarker-defined patient populations and a therapeutic window that is superior

to, or meaningfully different from, single-target inhibition or conventional combination therapy [1,2,12].

Table 5. Selected approved and clinically investigated dual-target inhibitors in the clinical pipeline.

Compound	Dual target(s)	Clinical area	Status	Trial / regulatory record	Key reference(s)
Gedatolisib (Revtorpyk)	PI3K + mTOR	HR+/HER2− advanced/metastatic breast cancer	FDA approved; ongoing development	VIKTORIA-1; NCT05501886	[5,6]
HH2853	EZH1 + EZH2	Relapsed/refractory lymphoma and solid tumors	Clinical development	NCT04390737	[7]
XRD-0394	ATM + DNA-PK	High-grade glioma with radiotherapy	Early clinical development	NCT06829173	[8]
AN01	PDE3 + PDE4	Pulmonary/COPD development	Phase 1 development	NCT07554365	[9]
Fimepinostat (CUDC-907)	HDAC + PI3K	Lymphoma and solid-tumor programs	Clinical studies; not approved	NCT02674750; NCT03893487	[10,11]
Dactolisib (BEZ235)	PI3K + mTOR	Advanced solid tumors	Historical/discontinued	Early-phase studies	[12]
Bimiralisib (PQR309)	PI3K + mTOR	Advanced cancers/lymphoma	Historical/discontinued	Early-phase studies	[13]
Voxtalisib (XL765/SAR245409)	PI3K + mTOR	Advanced solid tumors	Historical/discontinued	Early-phase studies	[14]
Samotolisib (LY3023414)	PI3K + mTOR	Advanced cancers	Historical/discontinued	Early-phase studies	[15]

6.2 PI3K/mTOR

The PI3K–AKT–mTOR pathway contains feedback relationships that can permit pathway recovery after single-node inhibition. Reviews describe extensive medicinal-chemistry work on dual PI3K/mTOR inhibitors, including SAR, selectivity, pharmacokinetics, and clinical development [11–14,49–54]. The key lesson is that vertical pathway inhibition can be biologically attractive, but broad pathway suppression can also amplify metabolic and systemic toxicity.

6.3 HDAC/PI3K and HDAC-containing dual inhibitors

Epigenetic regulation and a major pro-survival signaling pathway targeted by HDAC/PI3K dual inhibitors. CUDC-907 is a leading proof-of-concept and newer studies continue to explore PI3K-isoform and HDAC-isoform selectivity [15,16,55,82,87]. Dual strategies related and containing HDAC are BET/HDAC, EGFR/HDAC, PARP/HDAC, LSD1/HDAC and DNA/HDAC [16,18,55].

7. Neurodegenerative Diseases

Multi-target approaches are appealing for example in neurodegeneration. Alzheimer's disease is a complicated combination of cholinergic, amyloid, tau, oxidative, inflammatory and synaptic processes. Thus, MTDLs have been designed to combine cholinesterase inhibition with MAO-B inhibition, antioxidant effects, anti-aggregation activity, metal chelation, or other disease-relevant mechanisms [17,56–63].

Table 6. Target pairs under investigation for neurodegenerative disease.

Target pair	Therapeutic hypothesis	Design focus	persistent challenge
AChE/MAO-B	Cholinergic support + oxidative-stress control	Balanced AChE and MAO-B activity	CNS exposure and selectivity
AChE/BChE	Broader cholinesterase inhibition	Dual-site or hybrid ligands	Peripheral cholinergic effects
AChE/amyloid	Symptomatic + aggregation control	PAS interactions plus anti-aggregation motif	Proof of disease modification
MAO-B/antioxidant	Neurotransmission + redox control	Non-toxic redox-active motifs	Redox liabilities

8. Inflammation and Pain

The arachidonic acid cascade offers a classic rationale for dual inhibition. COX enzymes make prostanoids and LOX enzymes make leukotrienes and related lipid mediators. The goal of dual COX/LOX inhibition is to have a wider suppression of inflammatory signaling and to overcome some of the liabilities with selective COX inhibition [64–69]. Recent reviews continue to review COX-2/5-LOX and COX-2/15-LOX chemotypes, but cardiovascular, gastrointestinal, hepatic and metabolic safety issues remain key translational challenges.

Table 7. Dual COX/LOX inhibition strategies for inflammation and pain.

Strategy	Main rationale	Potential advantage	Main concern
COX-2/5-LOX	Block prostaglandin + leukotriene pathways	Broad anti-inflammatory coverage	Safety and tissue selectivity
COX-2/15-LOX	Suppress two lipid mediator branches	Potential anti-inflammatory/anticancer benefit	Limited clinical validation
COX/LOX hybrids	Single fixed-ratio agent	Simplified exposure relationship	Property optimization

9. Other Therapeutic Opportunities

The rationale for infectious disease is different: simultaneous inhibition of two essential pathogen processes can increase the genetic barrier to resistance. Dual activity in two signaling axs that together control disease phenotype might be useful in metabolic and cardiovascular disease. Systemic dual activity, however, might increase toxicity. In each area, the choice of target pair should be supported by causal biology and an exposure compatible therapeutic window.

Dual inhibitors can also be relevant to protein-protein interaction biology, epigenetic targets, receptor/kinase combinations and emerging target classes where resistance is driven by network adaptation rather than a single point mutation.

10. ADME, Safety, and Developability

The central tension in developability is that the molecule has to be complex enough to hit two targets, but simple enough to still look like a drug. Increased molecular weight, lipophilicity, aromaticity, and rotatable bonds may result in reduced permeability, increased nonspecific binding, and increased liability toward CYP or ion-channel. The properties have to be optimized already in the first design cycle [70–73].

Table 8. Key ADME, safety, and developability assays for dual-target inhibitors.

Assay/property	Why important	Interpretation
Solubility	Controls achievable free exposure	Measure kinetic and thermodynamic solubility
Microsomal stability	Dual molecules may have several metabolic soft spots	Identify clearance drivers early
CYP inhibition	Promiscuity can create DDIs	Profile major CYPs before nomination
hERG/ion channels	Lipophilic compounds may bind channels	Early counter-screening
Protein binding	Changes free target exposure	Interpret PK/PD using unbound concentrations
Permeability/efflux	Critical for CNS and intracellular targets	Measure permeability with efflux
Genotoxicity	Relevant for DNA-reactive or electrophilic chemotypes	Use structural alerts and assays
Broad target panel	Defines selectivity landscape	Avoid treating two-target potency as the whole profile

11. Experimental Validation Pipeline

Table 9. Experimental validation pipeline for dual-target inhibitor programs.

Stage	Experiments	Decision
Target validation	Genetic perturbation; selective reference inhibitors; rescue	Are both targets causally relevant?
Biochemical potency	IC50, Ki, kinetics at both targets	Is dual activity genuine?
Selectivity	Target-family and antitarget panels	Is duality distinct from promiscuity?
Cellular mechanism	Pathway biomarkers, phosphoproteomics, acetylation	Are both targets engaged in cells?
Synergy	Bliss/Loewe/HSA; comparison with two-drug combination	Is the dual molecule mechanistically advantageous?
PK/PD	Free exposure + both target biomarkers	Can both targets be engaged simultaneously?
In vivo efficacy	Disease-relevant models	Does mechanism translate?
Safety	Organ toxicity, QT, CNS, etc.	Is the therapeutic window adequate?

12. Dual Inhibitor versus Combination Therapy

The standard comparator for a dual inhibitor is a rational combination therapy, not a single-target drug. The dual molecule synchronizes the two activities and may allow for simpler adherence and formulation, but also fixes the exposure ratio and prevents independent dose adjustment. However, combination therapy may be preferred when target requirements differ between tissue/patients or when one target has a narrow therapeutic window. The dual molecule approach is especially attractive when dual target engagement is mechanistically important and the fixed ratio is advantageous.

Table 10. Comparison of dual inhibitors and two-drug combination therapy.

Feature	Dual inhibitor	Two-drug combination
PK relationship	Fixed	Independently adjustable
Dose flexibility	Lower	Higher
Adherence	Potentially simpler	Potentially more complex
Target ratio	Intrinsic	Clinically adjustable
Optimization	One molecule	Two programs
Toxicity management	Activities are linked	One component can be reduced/stopped
Resistance	Can raise barrier when both targets are essential	Can be equally flexible or superior
Regulatory strategy	Single entity	Combination development may be more complex

13. AI, Systems Pharmacology, and Precision Medicine

Dual-target optimization is multi-dimensional, so AI-assisted discovery is particularly important. Multi-task learning can predict activity at both targets, graph models can explore chemical space, generative systems may optimize potency and ADME, network models can rank target pairs from disease-specific omics. But AI is still a tool for prioritization: dataset bias, assay heterogeneity, target imbalance, and extrapolation outside the training distribution can give false confidence [39,44–48,74–78].

Precision medicine may be the next big advance. Biomarkers can identify patients where both targets are simultaneously activated, are essential or are associated with resistance, rather than developing a dual inhibitor for an average disease population. This sharpens the biological hypothesis and may enhance the clinical effect size.

14. Future Perspectives

- **Quantitative target-balance engineering:** Define target ratios based on free-drug exposure and PD biomarker data.
- **Disease network directed target pairing:** Integration of genetics, transcriptomics, proteomics and phosphoproteomics.
- **Structure-aware generative design:** Generate compounds conditioned on binding pocket geometry at both targets.
- **Closed loop optimization:** Cycle synthesis, assay data and models for optimizing dual potency and ADME.
- **Chemical proteomics:** standard global profiling in an effort to distinguish between intended duality and promiscuity.
- **Duality of patient-specific:** Identification of subpopulations that rely on both targets using biomarkers.
- **Resistance studies in longitudinal samples:** Use resistance under dual inhibition to measure the genetic barrier.
- **Human-relevant models:** use organoids, patient derived models and translation PK/PD.
- **Regulatory-ready mechanism packages:** Develop dual-target PD biomarkers prior to late clinical development.

15. CONCLUSIONS:

Dual-target inhibitors represent a logical step forward in polypharmacology, integrating two biological relevant activities into a single chemical entity. The most suitable diseases for their use are those with pathway redundancy, compensatory signaling, multifactorial pathology or predictable resistance to single target treatment. The field has evolved from empirical hybrid molecules to target-pair validation, structural biology, computational design, balanced SAR, systems pharmacology, and biomarker-led translation. But the amount of preclinical literature is not the same as clinical maturity. The key question is if engaging both targets at the same time gives a reproducible therapeutic benefit which justifies the developability cost of the dual molecule. Success in the future will depend on disciplined target selection, quantitative potency balancing, early ADME/Tox

optimization, mechanistic cellular validation, translational PK/PD, and patient stratification.

16. Summary Table of Representative Strategies

Table 11. Summary of representative dual-target strategies by therapeutic area.

Area	Target pair	Rationale	Maturity*	Primary risk
Oncology	PI3K/mTOR	Vertical pathway suppression	High preclinical/clinical activity	Class toxicity
Oncology	HDAC/PI3K	Epigenetic + survival signaling	Clinical/preclinical	Dose balance
Oncology	BET/kinase	Transcription + kinase	Preclinical	PK/complexity
Oncology	PARP/HDAC	DNA repair + chromatin	Preclinical	Therapeutic window
Neurodegeneration	AChE/MAO-B	Cholinergic + oxidative stress	Preclinical	CNS safety
Inflammation	COX/5-LOX	Two eicosanoid branches	Long-standing preclinical	CV/GI safety
Inflammation/cancer	COX-2/15-LOX	Eicosanoid pathway coverage	Preclinical	Translation

*Development maturity is a qualitative literature assessment and is not a regulatory classification.

List of Symbols and Abbreviations

Abbreviation	Full Form
AI	Artificial intelligence
ADME	Absorption, distribution, metabolism, and excretion
AChE	Acetylcholinesterase
BChE	Butyrylcholinesterase
BET	Bromodomain and extra-terminal (protein family)
CADD	Computer-aided drug design
CNS	Central nervous system
COX	Cyclooxygenase
EZH1/EZH2	Enhancer of zeste homolog 1/2
FDA	U.S. Food and Drug Administration
HDAC	Histone deacetylase
HR+/HER2−	Hormone-receptor-positive, HER2-negative (breast cancer subtype)
IC50	Half-maximal inhibitory concentration
Ki	Inhibition constant
LOX	Lipoxygenase
MAO-B	Monoamine oxidase B
MD	Molecular dynamics
ML	Machine learning
mTOR	Mechanistic (mammalian) target of rapamycin
NCT	National Clinical Trial (identifier, ClinicalTrials.gov)
PARP	Poly(ADP-ribose) polymerase
PI3K	Phosphoinositide 3-kinase
PK/PD	Pharmacokinetics/pharmacodynamics

REFERENCES:

1. Anighoro A, Bajorath J, Rastelli G. Polypharmacology: challenges and opportunities in drug discovery. J Med Chem. 2014;57:7874–7887. doi:10.1021/jm5006463.

2. Bolognesi ML, Cavalli A. Multitarget drug discovery and poly pharmacology. Chem Med Chem. 2016;11:1190–1192. doi:10.1002/cmdc.201600161.
3. Proschak E, Stark H, Merk D. Poly pharmacology by design: a medicinal chemist's perspective on multitarget drugs. J Med Chem. 2019;62:420–444.
4. Ryszkiewicz P, Malinowska B, Schlicker E. Polypharmacology: promises and new drugs in 2022. Pharmacol Rep. 2023;75:755–770.
5. Hopkins AL. Network pharmacology: the next paradigm in drug discovery. Nat Chem Biol. 2008;4:682–690.
6. Hopkins AL. Pharmacology: the network pharmacology revolution. Nat Rev Drug Discov. 2008;7:727–738.
7. Morphy R, Rankovic Z. Fragments, network biology and designing multi-target drugs. J Med Chem. 2005;48:6523–6537.
8. Morphy R, Kay C, Rankovic Z. From magic bullets to designed multiple ligands. Drug Discov Today. 2004;9:641–651.
9. Medina-Franco JL, Giulianotti MA, Welmaker GS, Houghten RA. Shifting from the single to the multi-target paradigm in drug discovery. Drug Discov Today. 2013;18:495–501.
10. Raghavendra NM, Pingili D, Kadasi S, Mettu A, Prasad SVUM. Dual or multi-targeting inhibitors: the next generation anticancer agents. Eur J Med Chem. 2018;143:1277–1300. doi:10.1016/j.ejmech.2017.10.021.
11. Liu P, Cheng H, Roberts TM, Zhao JJ. Targeting the phosphoinositide 3-kinase pathway in cancer. Nat Rev Drug Discov. 2009;8:627–644.
12. Lliu YN, Wan RZ, Liu ZP. Recent developments of small molecule PI3K/mTOR dual inhibitors. Mini Rev Med Chem. 2013;13(14):2047-2059. doi:10.2174/13895575113136660105. PMID:24195664.
13. Shi F, Wang M, Wang Z, et al. Recent advances in dual PI3K/mTOR inhibitors for tumour treatment. Front Pharmacol. 2022;13:875372. doi:10.3389/fphar.2022.875372. PMID:35614940.
14. Janku F, Yap TA, Meric-Bernstam F. Targeting the PI3K pathway in cancer: are we making headway? Nat Rev Clin Oncol. 2018;15:273–291.
15. Caner A, et al. Dual-target inhibitors based on HDACs: novel antitumor agents for cancer therapy. J Med Chem. 2020. doi:10.1021/acs.jmedchem.0c00491.
16. Peng X, Sun Z, Kuang P, Chen J. Recent progress on HDAC inhibitors with dual targeting capabilities for cancer treatment. Eur J Med Chem. 2020;208:112831.
17. Feng L, Wang G, Chen Y, et al. Dual-target inhibitors of bromodomain and extra-terminal proteins in cancer: a review from medicinal chemistry perspectives. Med Res Rev. 2022;42:710–743. doi:10.1002/med.21859.
18. Haque S, et al. Dual inhibitors of histone deacetylases and other cancer-related targets: a pharmacological perspective. Biochem Pharmacol. 2020.
19. Morphy R, Rankovic Z. Designed multiple ligands. J Med Chem. 2005;48:6523–6537.
20. Peters JU. Polypharmacology—foes or friends? J Med Chem. 2013;56:8955–8971.
21. Talevi A. Multi-target pharmacology: possibilities and limitations of the “skeleton key approach”. Front Pharmacol. 2015;6:205.
22. Csermely P, Ágoston V, Pongor S. The efficiency of multi-target drugs: the network approach might help. Trends Pharmacol Sci. 2005;26:178–182.
23. Mestres J, Gregori-Puigjané E. Conciliating binding efficiency and polypharmacology. Trends Pharmacol Sci. 2009;30:470–476.
24. Berenstein A, et al. Improving the efficacy-safety balance of polypharmacology in multi-target drug discovery. Expert Opin Drug Discov. 2018.
25. Lavecchia A, Cerchia C. In silico methods to address the challenges related to polypharmacology and drug repurposing. Front Pharmacol. 2016;7:298.
26. Bolognesi ML. Harnessing polypharmacology with medicinal chemistry. ACS Med Chem Lett. 2013;4:968–969.
27. Royo M, et al. Multi-target-directed ligands: a strategy for the treatment of multifactorial diseases. Curr Med Chem. 2017.
28. Geldenhuys WJ, et al. Rational design of multitarget-directed ligands for neurodegenerative diseases. Future Med Chem. 2014.
29. Borisy AA, Elliott PJ, Hurst NW, et al. Systematic discovery of multicomponent therapeutics. Proc Natl Acad Sci USA. 2003;100:7977–7982.
30. Keiser MJ, Setola V, Irwin JJ, et al. Predicting new molecular targets for known drugs. Nature. 2009;462:175–181.
31. Lounkine E, Keiser MJ, Whitebread S, et al. Large-scale prediction and testing of drug activity on side-effect targets. Nature. 2012;486:361–367.
32. Yildirim MA, Goh KI, Cusick ME, Barabási AL, Vidal M. Drug-target network. Nat Biotechnol. 2007;25:1119–1126.
33. Frantz S. Drug discovery: playing dirty. Nature. 2005;437:942–943.

34. Leeson PD, Springthorpe B. The influence of drug-like concepts on decision-making in medicinal chemistry. Nat Rev Drug Discov. 2007;6:881–890.
35. Gaulton A, Hersey A, Nowotka M, et al. The ChEMBL database in 2017. Nucleic Acids Res. 2017;45:D945–D954.
36. Wang Y, Bryant SH, Cheng T, et al. PubChem BioAssay: 2017 update. Nucleic Acids Res. 2017;45:D955–D963.
37. Szklarczyk D, Gable AL, Lyon D, et al. STRING v11: protein–protein association networks with increased coverage. Nucleic Acids Res. 2019;47:D607–D613.
38. Vogt I, Mestres J. Drug-target identification through drug effects on the transcriptome. Curr Opin Pharmacol. 2010;10:633–638.
39. Cereto-Massagué A, Guasch L, Valls C, et al. Decoding molecular polypharmacology across chemical space. Nat Commun. 2017;8.
40. Vamathevan J, Clark D, Czodrowski P, et al. Applications of machine learning in drug discovery and development. Nat Rev Drug Discov. 2019;18:463–477.
41. Schneider G. Automating drug discovery. Nat Rev Drug Discov. 2018;17:97–113.
42. Bender A, Cortes-Ciriano I. Artificial intelligence in drug discovery: what is realistic, what are illusions? Drug Discov Today. 2021;26:2017–2020.
43. Stokes JM, Yang K, Swanson K, et al. A deep learning approach to antibiotic discovery. Cell. 2020;180:688–702.e13.
44. Zhavoronkov A, Ivanenkov YA, Aliper A, et al. Deep learning enables rapid identification of potent DDR1 kinase inhibitors. Nat Biotechnol. 2019;37:1038–1040.
45. Jiménez-Luna J, Grisoni F, Schneider G. Drug discovery with explainable artificial intelligence. Nat Mach Intell. 2020;2:573–584.
46. Ertl P, Schuffenhauer A. Estimation of synthetic accessibility score of drug-like molecules based on molecular complexity and fragment contributions. J Cheminform. 2009;1:8.
47. Engelman JA. Targeting PI3K signalling in cancer: opportunities, challenges and limitations. Nat Rev Cancer. 2009;9:550–562.
48. Fruman DA, Chiu H, Hopkins BD, Bagrodia S, Cantley LC, Abraham RT. The PI3K pathway in human disease. Cell. 2017;170:605–635.
49. Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. Nat Rev Cancer. 2015;15:7–24.
50. Yap TA, Bjerke L, Clarke PA, Workman P. Drugging PI3K in cancer: refining targets and therapeutic strategies. Curr Opin Pharmacol. 2015;23:98–107.
51. Sabbah DA, Brattain MG, Zhong H. Dual inhibitors of PI3K/mTOR or mTOR-selective inhibitors: which way shall we go? Curr Med Chem. 2011;18(36):5528-5544. doi:10.2174/092986711798347298. PMID:22172063.
52. Lliu YN, Wan RZ, Liu ZP. Recent developments of small molecule PI3K/mTOR dual inhibitors. Mini Rev Med Chem. 2013;13(14):2047-2059. doi:10.2174/13895575113136660105. PMID:24195664.
53. Recent advances in PI3K/PKB/mTOR inhibitors as new anticancer agents. Eur J Med Chem. 2022.
54. Zeng W, Zhang Z, Li K, Yin Y, Dong S, Ma M. HDAC and PI3K dual inhibitors in the treatment of cancers: current status, trends, and solutions. Eur J Med Chem. 2026;304:118511. doi:10.1016/j.ejmech.2025.118511. PMID:41453303.
55. Discovery of (S)-N1-(thiazol-2-yl)pyrrolidine-1,2-dicarboxamide derivatives targeting PI3Kα/HDAC6. Bioorg Med Chem Lett. 2023;129462. doi:10.1016/j.bmcl.2023.129462.
56. Pathak C, Kabra UD. A comprehensive review of multi-target directed ligands in the treatment of Alzheimer's disease. Bioorg Chem. 2024;144:107152. doi:10.1016/j.bioorg.2024.107152.
57. Advancements in the development of multi-target directed ligands for the treatment of Alzheimer's disease. Bioorg Med Chem. 2022;66:116742. doi:10.1016/j.bmc.2022.116742.
58. Multi-target-directed ligands in Alzheimer's disease treatment. Curr Med Chem. 2012.
59. Cavalli A, Bolognesi ML, Minarini A, et al. Multi-target-directed ligands to combat neurodegenerative diseases. J Med Chem. 2008;51:347–372.
60. León R, García AG, Marco-Contelles J. Recent advances in the multitarget-directed ligands approach for the treatment of Alzheimer's disease. Med Res Rev. 2013;33:139–189.
61. Youdim MBH, Buccafusco JJ. Multi-target strategies in Alzheimer's and Parkinson's diseases. J Neural Transm. 2005;112:519–537.
62. Kumar A, Singh A, Ekavali. A review on Alzheimer’s disease pathophysiology and its management: an update. Pharmacol Rep. 2015;67:195–203.

63. Anand R, Gill KD, Mahdi AA. Therapeutics of Alzheimer's disease: past, present and future. Neuropharmacology. 2014;76:27–50.
64. Latest advances in dual inhibitors of acetylcholinesterase and monoamine oxidase B against Alzheimer's disease. Expert Opin Ther Pat. 2023. doi:10.1080/14756366.2023.2270781.
65. Dual inhibitors of acetylcholinesterase and monoamine oxidase-B for the treatment of Alzheimer's disease. Review. 2025.
66. Patrignani P, Tacconelli S. Is selective inhibition of cyclooxygenase-2 all that we need to spare the heart? Trends Pharmacol Sci. 2002;23:250–255.
67. Marnett LJ. Aspirin and the potential role of prostaglandins in cancer prevention. J Natl Cancer Inst. 2002;94:252–253.
68. Charlier C, Michaux C. Dual inhibition of cyclooxygenase-2 and 5-lipoxygenase as a new strategy to provide safer non-steroidal anti-inflammatory drugs. Eur J Med Chem. 2003;38:645–659. doi:10.1016/S0223-5234(03)00115-6.
69. Cuzzolin L, et al. New trends in dual 5-LOX/COX inhibition. Curr Med Chem. 2002. doi:10.2174/0929867024606713.
70. Safer anti-inflammatory therapy through dual COX-2/5-LOX inhibitors: a structure-based approach. Eur J Med Chem. 2018.
71. Aliabadi A, Khanniri E, Mahboubi-Rabbani M, Bayanati M. Dual COX-2/15-LOX inhibitors: a new avenue in the prevention of cancer. Eur J Med Chem. 2023;261:115866. doi:10.1016/j.ejmech.2023.115866.
72. Agrawal N. A comprehensive review on the advancements of dual COX-2/5-LOX inhibitors as anti-inflammatory drugs. Chem Biol Drug Des. 2025;105:e70114. doi:10.1111/cbdd.70114.
73. Recent advances in dual COX/LOX inhibitor design (2020–2024). Review. 2026.
74. Waring MJ. Defining optimum lipophilicity and molecular weight for drug design. Bioorg Med Chem Lett. 2009;19:2844–2851.
75. Veber DF, Johnson SR, Cheng HY, Smith BR, Ward KW, Kopple KD. Molecular properties that influence the oral bioavailability of drug candidates. J Med Chem. 2002;45:2615–2623.
76. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv Drug Deliv Rev. 2001;46:3–26.
77. Leeson PD. Molecular inflation, attrition and the rule of five. Adv Drug Deliv Rev. 2016;101:22–33.
78. Yang Y, et al. Rethinking therapeutic strategies of dual-target drugs: an update on pharmacological small-molecule compounds in cancer. Med Res Rev. 2024. doi:10.1002/med.22057.
79. Dual inhibitors of human DNA topoisomerase II and other cancer-related targets. J Med Chem. 2019. doi:10.1021/acs.jmedchem.9b00726.
80. Dual kinase-bromodomain inhibitors in anticancer drug discovery: a structural and pharmacological perspective. J Med Chem. 2016. doi:10.1021/acs.jmedchem.6b00438.
81. Dual inhibitors of histone deacetylases and other cancer-related targets: a pharmacological perspective. Biochem Pharmacol. 2020.
82. Hybrids from farnesylthiosalicylic acid and hydroxamic acid as dual Ras-related signaling and HDAC inhibitors. ChemMedChem. 2015. doi:10.1002/cmdc.201500019.
83. Dual-targeting strategy in cancer therapy: emerging role of pyrrolopyrimidine scaffolds. ChemMedChem. 2026.
84. Strategies for multi-target drug discovery. In: Polypharmacology. Wiley. 2025. doi:10.1002/9781394182862.ch16.
85. Improving the efficacy-safety balance of polypharmacology in multi-target drug discovery. Expert Opin Drug Discov. 2018.
86. Talevi A, Bellera CL. Challenges and opportunities in multitarget drug design. Future Med Chem. 2012.
87. Delmas F, et al. Dual-target drug design: medicinal chemistry and pharmacology perspectives. Drug Discov Today. 2019.
88. Berenstein A, et al. Polypharmacology and the efficacy-toxicity balance in anticancer drug discovery. Expert Opin Drug Discov. 2018.
89. Peters JU. Polypharmacology: implications for drug discovery and development. J Med Chem. 2013.
90. Shi D, Li X. Strategies for multi-target drug discovery. Polypharmacology. Wiley. 2025.
91. Shi F, Wang M, Wang Z, et al. Recent advances in dual PI3K/mTOR inhibitors for tumour treatment. Front Pharmacol. 2022;13:875372. doi:10.3389/fphar.2022.875372. PMID:35614940.