

# Medicinal Chemistry in Precision Oncology: Molecular Design, Targeted Therapies, and Emerging Strategies for Anticancer Drug Discovery

*A Narrative Review*

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## Abstract

Cancer remains a major therapeutic challenge because malignant cells evolve, diversify, and develop resistance under treatment pressure. Medicinal chemistry contributes to cancer therapy by translating molecular knowledge into compounds with defined target engagement, selectivity, exposure, and safety profiles. This narrative review summarizes core principles that connect chemical structure to anticancer activity, including target validation, structure–activity relationships (SAR), physicochemical optimization, covalent and non-covalent inhibition, targeted protein degradation, antibody–drug conjugates, and drug repurposing. It also discusses why promising biochemical potency does not automatically produce clinical benefit: tumor heterogeneity, pathway redundancy, pharmacokinetics, toxicity, and acquired resistance can limit efficacy. Examples from kinase inhibition, DNA-damage response, epigenetic modulation, and immune-oncology illustrate how modern drug discovery increasingly combines structural biology, cellular pharmacology, biomarkers, and computational methods. The review emphasizes that candidate evaluation should integrate potency, selectivity, exposure, mechanism, and translational evidence rather than relying on a single assay. Finally, it outlines practical opportunities for student-led research, including evidence mapping, comparative analysis of approved agents, and reproducible computational projects. This article is a narrative synthesis of published literature, not a report of new experimental results or a systematic review.

**Keywords:** Medicinal chemistry; cancer; anticancer agents; precision oncology; structure–activity relationship; targeted therapy; drug resistance; targeted protein degradation

## 1. Introduction

Cancer is not one disease but a collection of disorders in which cells acquire alterations that enable uncontrolled growth, survival, invasion, and, in some cases, metastasis. The molecular diversity of tumors creates a central therapeutic problem: a drug that is effective against one molecular subtype may be ineffective in another, and an initially responsive tumor may later evolve resistance. Modern oncology therefore increasingly seeks treatments matched to tumor biology, while retaining the need to demonstrate meaningful clinical benefit and acceptable toxicity. Medicinal chemistry is the discipline that designs, synthesizes, and optimizes biologically active molecules. In oncology, it links a molecular target to a drug candidate by iteratively improving binding, selectivity, solubility, permeability, metabolic stability, and exposure. The objective is not simply to create a compound with strong activity in a test tube; it is to develop a molecule whose properties collectively support a useful therapeutic window in humans. Recent reviews describe the expansion of anticancer drug design from classical cytotoxic agents toward targeted therapies, immunotherapies, radiotheranostics, antibody–drug conjugates, and targeted protein degradation [1,2].

## 2. From biological target to chemical candidate

A discovery program often begins with a biological hypothesis: a protein or pathway is sufficiently important to tumor survival that its modulation may produce a therapeutic effect. Target validation draws on genetic evidence, disease biology, patient data, and pharmacological experiments. Yet biological relevance alone is insufficient. A target must also be chemically tractable, reachable by a drug at tolerable exposure, and sufficiently differentiated from normal-tissue functions. Small molecules can act through several mechanisms. Reversible inhibitors bind through non-covalent interactions such as hydrogen bonding, hydrophobic contacts, electrostatic interactions, and van der Waals forces. Covalent inhibitors form a chemical bond with a target residue; this can prolong target engagement but requires careful assessment of reactivity and off-target effects. Other approaches include disrupting protein–protein interactions, modulating nucleic-acid-associated processes, or recruiting cellular machinery to alter the abundance of a disease-associated protein. A useful development chain is: target hypothesis → chemical starting point → confirmed mechanism → structure–activity relationship → optimization of drug-like properties → cellular and in-vivo evaluation → translational biomarkers → clinical testing. Each stage can expose weaknesses that were invisible in an earlier assay. A compound may bind a purified protein yet fail to enter cells, or inhibit a target in cells but show inadequate exposure or unacceptable toxicity in an organism.

## 3. Structure–activity relationships and optimization

Structure–activity relationship (SAR) analysis examines how chemical changes affect biological activity and related properties. Medicinal chemists may modify substituents, ring systems, stereochemistry, hydrogen-bond donors and acceptors, ionization, or conformational flexibility. A reliable SAR conclusion requires comparable measurements and adequate controls; apparent differences

can be caused by assay variability, solubility limits, aggregation, or changes in intracellular exposure rather than target affinity alone. Optimization is inherently multi-objective. Increasing lipophilicity can improve membrane permeability in some contexts but may reduce solubility, increase nonspecific binding, or alter metabolic clearance. Strong biochemical potency can be offset by rapid metabolism, poor oral bioavailability, or limited penetration into a tumor. Selectivity is also context-dependent: a molecule may discriminate between closely related proteins in a biochemical assay but show a broader profile across the proteome in cells. Consequently, compound selection should integrate biochemical potency, cellular target engagement, selectivity, pharmacokinetics, tolerability, and evidence that the proposed mechanism explains the observed phenotype. Computational approaches—including molecular docking, molecular dynamics, quantitative SAR, and machine-learning models—can help prioritize hypotheses and compounds. They do not replace experimental validation. Predictions are limited by training-data quality, assay inconsistency, protein flexibility, and the fact that biological systems contain interactions not represented in simplified models.

## **4. Major therapeutic strategies in contemporary oncology**

4.1 Targeted small-molecule inhibitors. Many cancers depend on altered signaling networks, including receptor tyrosine kinases and downstream pathways. Small-molecule inhibitors can suppress a driver pathway when the tumor is dependent on it. Clinical utility generally depends on molecular context, drug exposure, target engagement, and the availability of a biomarker that identifies patients likely to benefit. Resistance may arise through target mutation, pathway reactivation, bypass signaling, or changes in drug transport and metabolism. 4.2 DNA-damage response and cell-cycle targets. Tumor cells may rely on DNA repair pathways because of pre-existing genomic instability. In selected molecular contexts, inhibiting a compensatory repair mechanism can create a therapeutic vulnerability, often described as synthetic lethality. PARP inhibitors are a well-known example in defined settings, but the concept must be applied carefully: the presence of a pathway alteration does not guarantee response, and resistance can emerge through restoration of repair or changes in the relevant biological state. 4.3 Epigenetic modulators. DNA methylation, histone modifications, and chromatin-associated proteins influence gene expression without changing the underlying DNA sequence. Drugs that modulate epigenetic machinery can alter malignant cell states, although effects may be broad and context-dependent. The key medicinal-chemistry challenge is to achieve adequate target modulation while avoiding toxic disruption of normal tissues. 4.4 Antibody–drug conjugates (ADCs). ADCs combine an antibody that recognizes a cell-surface antigen with a cytotoxic payload linked through a chemical linker. Their performance depends on antigen expression and internalization, linker stability, payload potency, drug-to-antibody ratio, distribution, and the possibility of bystander effects. ADC design is therefore a multidisciplinary problem spanning antibody engineering, linker chemistry, payload chemistry, and pharmacology. 4.5 Targeted protein degradation. Proteolysis-targeting chimeras (PROTACs) and related approaches aim to recruit a target protein to cellular degradation machinery rather than simply inhibit its activity. These compounds can act catalytically in favorable circumstances, but their larger molecular size and complex ternary-complex behavior create challenges in permeability, oral exposure, selectivity, and pharmacokinetic optimization. Molecular glues offer a related strategy by stabilizing or creating protein–protein interactions that trigger a biological effect [1,2].

## **5. Drug repurposing: opportunity and limitations**

Drug repurposing evaluates whether an existing medicine may have a new therapeutic use. Existing pharmacokinetic, manufacturing, and safety information can sometimes reduce early development uncertainty. However, a plausible mechanism or activity in cultured cells is not evidence that a drug treats cancer in patients. Concentrations effective in vitro may be unattainable or unsafe in humans; laboratory models may not reproduce tumor microenvironments; and observational associations can be distorted by confounding. A credible repurposing study should specify a testable hypothesis, compare relevant concentrations with clinically achievable exposure, use appropriate positive and negative controls, distinguish cytostatic from cytotoxic effects, and examine selectivity between malignant and non-malignant cells. Computational predictions should be treated as hypothesis-generating. Any claim of clinical efficacy requires appropriately designed clinical evidence. A recent open-access review surveys drug repurposing strategies and their translational challenges in cancer therapy [3].

## **6. Resistance, tumor heterogeneity, and combination design**

Resistance is an expected evolutionary challenge in cancer treatment. It can be intrinsic, when a tumor is unresponsive before therapy, or acquired, when a previously responsive tumor progresses. Mechanisms include target-site mutations, amplification or loss of relevant genes, activation of bypass pathways, altered apoptosis, drug efflux, changes in tumor-cell state, and microenvironmental effects. A single biopsy may not capture the full diversity of a tumor, and different metastatic sites may contain distinct resistant populations. Combination therapy can delay resistance when agents act on complementary vulnerabilities, but combinations can also increase toxicity, complicate dosing, and make causal interpretation difficult. Rational combinations should be based on a mechanistic hypothesis, evidence of non-redundant activity, compatible pharmacology, and a feasible safety profile. Biomarkers and longitudinal sampling can help determine whether a treatment is engaging its target and whether resistance mechanisms are emerging. The objective is not simply to combine more drugs, but to match treatment to tumor biology and adapt as that biology changes.

## **7. Translational evidence: what makes a promising compound credible?**

A strong preclinical package should connect chemical identity and quality to a reproducible biological effect. Important elements include compound characterization, assay validation, concentration–response data, independent replication, selectivity testing, mechanistic confirmation, and transparent reporting of limitations. Where relevant, studies should assess exposure, metabolism,

tolerability, and efficacy in suitable models, while recognizing that no model fully predicts human outcomes. Biomarkers can strengthen the link between mechanism and clinical application. Predictive biomarkers estimate the likelihood of benefit from a treatment; pharmacodynamic biomarkers indicate that a biological process has changed after exposure. These roles should not be conflated. A marker associated with poor prognosis is not automatically predictive of response to a particular drug. Similarly, statistical association does not establish causation, and exploratory findings require independent validation. Clinical translation also depends on formulation, manufacturing feasibility, intellectual property, patient selection, trial design, and regulatory evaluation. Medicinal chemistry is therefore essential but not sufficient by itself: successful cancer medicines emerge from coordinated chemistry, biology, pharmacology, toxicology, clinical research, and patient-centered evidence.

## 8. Research opportunities suitable for undergraduate chemists

Undergraduate researchers can contribute meaningfully without claiming to have discovered a new anticancer drug. Feasible projects include: (i) a structured comparison of approved inhibitors targeting one protein family; (ii) a literature-based analysis of how selected structural features relate to potency and selectivity, with careful attention to assay comparability; (iii) a reproducible computational screening exercise with explicit limitations and no claim of clinical efficacy; (iv) a mapping of resistance mechanisms for one drug class; or (v) a systematic evidence table of ADC linker and payload design principles. A rigorous student project should define a focused question, preregister or clearly state inclusion criteria when appropriate, document search databases and dates, use primary studies alongside reviews, and distinguish established evidence from speculation. For a true systematic review, the methods should be sufficiently detailed to permit reproduction, including search strings, screening procedures, and reasons for exclusions. For computational work, software versions, input structures, parameters, and validation steps should be reported. For experimental work, laboratory safety, institutional oversight, and appropriate supervision are essential. This manuscript is a narrative review draft. It does not report new experiments, original datasets, or a systematic search. Before submission to a journal, the author should verify every reference, update the literature search, refine the scope, and ensure that the final manuscript complies with the target journal's requirements.

## 9. Conclusion

Medicinal chemistry has become central to precision oncology by transforming molecular insights into agents designed for defined targets and biological contexts. The field now encompasses reversible and covalent inhibitors, DNA-damage response modulators, epigenetic agents, ADCs, targeted protein degradation, and repurposing strategies. Across these modalities, the same principle holds: potency alone is not enough. Selectivity, exposure, mechanism, resistance, safety, biomarkers, and clinical evidence must be considered together. For students entering this field, the strongest starting point is a focused, transparent, evidence-based question rather than an exaggerated claim of novelty. A carefully documented review or reproducible computational analysis can build the skills needed for future laboratory research and drug discovery. The ultimate standard remains whether a proposed strategy is supported by reliable evidence and can improve outcomes for patients safely.

## Declarations

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