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Artificial Intelligence-Based Halogenated Chalcone Drug Discovery: An Integrated Framework for Rational Anticancer Lead Optimization

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ABSTRACT: Halogenated chalcones are emerging as an exciting class of potential anticancer scaffolds with respect to medicinal chemistry; they exhibit structural flexibility, multitarget pharmacology, and allow for rapid medicinal chemistry optimization. The biological activity associated with halogen substitutions on the scaffold is influenced by numerous non-linear SARs. As a result, traditional trial-and-error optimization approaches are typically very time-consuming and reduce the ability to find clinically relevant lead structures. Recent advancements in artificial intelligence (AI), however, now provide a means to optimize various aspects of drug discovery through the use of predictive models derived from large amounts of data, including the development of anticancer leads. This review will present a complete framework for designing optimized halogenated chalcone derivatives using AI, which assesses the role of molecular descriptor selection, QSAR modeling, molecular docking, molecular dynamics simulations, machine learning, deep learning, graph neural network technology, explainable AI, and generative AI to accelerate anticancer lead discovery. Furthermore, this review aims to integrate all these computational tools into one cohesive medicinal chemistry approach while providing an evaluation of their advantages and disadvantages and their translational relevance compared to previous reviews that assessed each individually. Finally, this review also addresses the potential of multimodal learning and next-generation generative AI methods along with some challenges currently facing researchers, i.e., the lack of integration among existing computational workflows, limited availability of quality datasets, and limited experimental validation.

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Figure 1: graphical abstract

1. INTRODUCTION

"Although progress has been made in targeted therapy and precision medicine, the clinical success of many cancer therapies continues to be limited by treatment failure, drug resistance, toxic side effects, and poor absorption. [1] Thus, finding structurally diverse small molecule drugs that are better than current drugs in terms of both their ability to kill cancer cells effectively and safely remains an important goal for medicinal chemists. [2]

Chalcones have been extensively investigated as anticancer scaffolds because of their simple structure, synthetic accessibility, and diverse biological activities [3] Chalcones are also one of the anticancer scaffold types which have been extensively studied. The presence of an α, β-unsaturated carbonyl group allows the potential interaction of chalcones with numerous molecular targets related to tumor growth such as beta-tubulin, EGFR, VEGFR-2, PI3K, HDACs, and topoisomerase. Therefore, they represent very promising candidate drugs for multitarget anticancer therapies. [4] Halogenation on chalcones is particularly interesting as it creates significant variations in physicochemical properties, including lipophilicity, electron density, metabolic stability, molecular recognition, and target binding affinity compared to non-halogenated counterparts. [5] Although halogens exhibit highly structure-dependent effects on biological activities, identification of ideal positions for halogen substitutions using traditional medicinal chemistry is costly, time-consuming and largely based upon empiricism. [6]

The use of artificial intelligence (AI), however, has transformed this process into a data driven predictive model of the biological activity, target interaction, pharmacokinetics, and molecular design prior to experimental synthesis. [7] This represents a paradigm shift in drug discovery where iterative trial and error has been replaced by rational lead optimization through the integration of QSAR models, molecular docking, MD simulations, ML algorithms, GNNs, XAI and GM designs. [7] Unfortunately, at present there is no all-encompassing methodology or approach that combines medicinal chemistry strategies with AI techniques and the applications of these methodologies to halogenated chalcone derivatives appear to be fragmented. [2] This review examines how artificial intelligence can speed up the rational design of new anticancer agents based on halogenated chalcones using a combination of computational predictions with experimental medicinal chemistry. The review describes modern AI methods, highlights their benefits, limitations, and translational potential, and proposes a unified framework to improve the developability, pharmacokinetic properties, efficacy, and specificity of novel halogenated chalcone derivatives.

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2. EVOLUTION FROM CONVENTIONAL MEDICINAL CHEMISTRY TO AI-ASSISTED DRUG DISCOVERY

Traditionally, the identification of anticancer compounds has relied on repeated chemical synthesis, molecular design, and biological evaluation procedures. [8] Although this empirical approach has produced many effective treatments, it is costly, time-consuming, and characterized by a high attrition rate as many candidates fail due to poor potency, poor selectivity, unfavourable pharmacokinetics, or severe toxicity. [8] These difficulties are especially noticeable when optimizing halogenated chalcone derivatives. Subtle variations in halogen properties or substitution patterns may have a substantial impact on pharmacological characteristics and biological efficacy, making exhaustive experimental evaluation impractical. [6]

The first step toward rational lead optimization was the development of computer-aided drug design (CADD), which made it possible to virtually predict protein-ligand interactions and molecular activity before synthesis. [9] However, because conventional computational approaches rely on predefined descriptors and basic mathematical models, they are still limited in their ability to depict the complex and nonlinear structure–activity relationships typical of halogenated chalcones. [9] The new paradigm is evolving because of an explosion of chemical and biological data combined with developments by researchers using artificial intelligence (AI), allowing for direct learning of experimental data from computational models at the same time as optimizing many drugs discovery-related parameters. AI has evolved from being an important tool in computational chemistry to becoming one of the most important tools in current medicinal chemistry, offering a way to develop rationally designed and developed halogenated chalcone-based anticancer drugs through a data-driven approach. [10]

3. HALOGENATED CHALCONE DERIVATIVES: AN IDEAL SCAFFOLD FOR AI-GUIDED ANTICANCER DRUG DISCOVERY

Halogenated chalcone derivatives offer an appealing basis for AI-driven anticancer drug discovery due to their combination of a synthetically obtainable framework and numerous possibilities for structural variation. [4] Lipophilicity, electronic distribution, molecular polarity, metabolic stability, and non-covalent interactions can be significantly influenced by the introduction of fluorine, chlorine, bromine, or iodine. This frequently leads to enhanced target affinity, selectivity, and pharmacological effectiveness. [10] Moreover, the type, position, and combination of halogen substituents generate complex and often nonlinear structure–activity relationships that are difficult to resolve by conventional medicinal chemistry alone. [10] Artificial intelligence offers an effective approach to predict anticancer activity, prioritize promising analogues, and reduce unnecessary synthesis by integrating structural, physicochemical, and biological data to identify optimal substitution patterns. As a result, the broad chemical diversity, multitarget biological activities, and complex structure–activity relationships of halogenated chalcone derivatives make these compounds an ideal model for applying AI-driven strategies to rational anticancer drug design. [11]

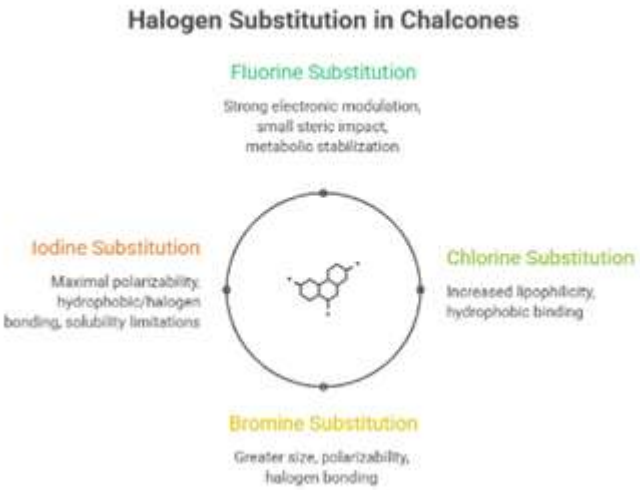

Figure 2. Halogen-dependent physicochemical and biological effects governing the AI-assisted optimization of chalcone derivatives.

Table 1. Effects of Halogen Substitution on Chalcone Drug-Design Properties

Halogen	Key physicochemical effect	Potential medicinal-chemistry advantage	Possible limitation	Relevance to AI-guided optimization
Fluorine	High electronegativity, small atomic radius, altered electronic distribution	May enhance metabolic stability, membrane permeability, and target recognition with limited steric disruption	Biological effects are strongly position-dependent; fluorine does not always improve potency	Models should capture local electronic effects and ortho/meta/para substitution rather than treating fluorine as a simple categorical feature
Chlorine	Increases lipophilicity, molecular size, and hydrophobic contact area	May improve binding within hydrophobic protein pockets and enhance cellular permeability	May reduce aqueous solubility and increase nonspecific binding	Multi-objective models should balance target affinity against solubility and pharmacokinetic liabilities
Bromine	Greater size and polarizability than chlorine; may support directional halogen bonding	Can strengthen hydrophobic and dispersion interactions and improve binding affinity	Increased molecular weight, lipophilicity, and possible metabolic or plasma-protein-binding liabilities	Docking and MD require appropriate treatment of bromine-specific electrostatic anisotropy and halogen bonding
Iodine	Largest atomic radius and highest polarizability among common halogens	May produce strong hydrophobic and halogen-bond interactions in suitable binding pockets	Frequently associated with increased molecular weight, poor solubility, and reduced developability	Generative and ADMET models should prevent excessive optimization of binding affinity at the expense of drug-like properties

4. AN INTEGRATED AI-DRIVEN FRAMEWORK FOR RATIONAL OPTIMIZATION OF HALOGENATED CHALCONE DERIVATIVES

Halogenated chalcone derivative discovery has transitioned from sequential experimental screening to an integrated framework that uses both computational and experimental approaches for optimization of lead compounds, rather than in isolation. [12] Modern AI platforms are designed to identify those lead compounds with the highest probability of therapeutic effectiveness by simultaneously integrating structural, biological, pharmacokinetic and physicochemical data, which enables iterative prediction, validation and optimization of patterns of halogen substitution via lowering experimental burden and improving decision-making throughout the drug development process.[13] Additionally, the integration of molecular representation, activity prediction, structure-based analysis, pharmacokinetic assessment and generative molecular design into a unified medicinal chemistry pipeline strengthens this conceptual framework, provides the fundamental basis for the AI technologies discussed below and represents a major step toward rational development of clinically translatable halogenated chalcone-based anticancer agents. [14]

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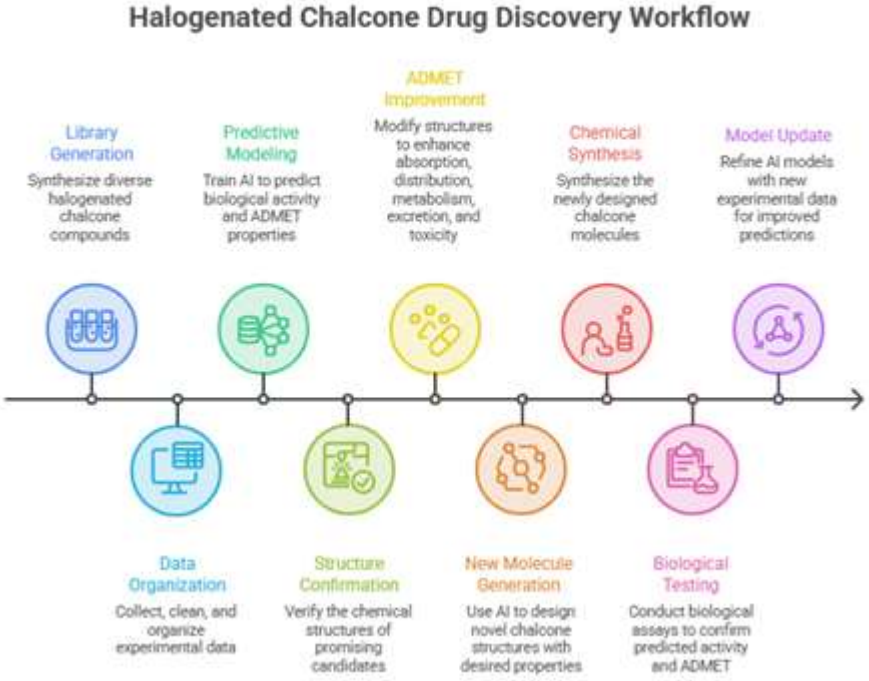

Figure 3. Incorporated AI-driven processes for the systematic identification and enhancement of halogenated chalcone-derived anticancer compounds.

5. ARTIFICIAL INTELLIGENCE TECHNOLOGIES DRIVING THE RATIONAL DESIGN OF HALOGENATED CHALCONE DERIVATIVES

5.1 Molecular Representation of Halogenated Chalcone Derivatives

Predictive performance of AI-assisted optimization of halogenated chalcone derivatives will be much more dependent upon the representation of molecular structure rather than the complexity of learning algorithms. [15] Reliable structure-activity relationships require descriptors which can describe physiochemically relevant changes such as: modification of lipophilicity, electronic dispersion, steric character, polarizability and molecular flexibility resulting from halogen substitution. Feature engineering has become an important tool in reducing irrelevant variables and maintaining descriptors controlling target recognition and anticancer activity. [16] Moreover, recent graph neural network architectures can improve molecular representation by learning directly from atomic connectivity. Therefore, robust molecular representation forms the basis of AI-guided design by giving the chemical information needed for reliable prediction, rational optimization, and prioritization of biologically promising halogenated chalcone derivatives. [17]

5.2 AI-Driven QSAR Modelling for Halogenated Chalcone Optimization

Quantitative structure–activity relationship (QSAR) modelling is one of the most effective AI-driven strategies for prioritizing biologically active analogues before synthesis and the diversity of halogenated chalcone derivatives make this approach particularly available. QSAR determines the physicochemical properties that control potency and selectivity by linking molecular descriptors with empirically measured anticancer activity, allowing halogen substitution patterns to be rationally optimized. [18] capturing the nonlinear effects of fluorine, chlorine, bromine, and iodine on lipophilicity, electronic distribution, steric interactions, and molecular polarity in halogenated chalcones, machine learning-based QSAR models go beyond conventional linear approaches.[19] However, a significant limitation of current halogenated chalcone research is that dataset quality, standardized IC_{50} measurements, external validation, and well-defined applicability domains are more important for prediction performance than algorithm selection.[20] Explainable AI boosts QSAR by identifying descriptors linked to biological activity.

This converts predictive models into applicable structures for the logical advancement of future halogenated chalcone-derived anticancer compounds. [21]

5.3 AI-Guided Structure-Based Design of Halogenated Chalcone Derivatives

Halogenated chalcones have an extremely large range of chemical structure; therefore, it's necessary to determine what structural features are most important for maximal interaction with the therapeutic target and at the same time maintaining "drug-like" characteristics. [22] Consequently, molecular docking has been identified as one of the primary forms of Artificial Intelligence (AI) assisted prediction of interactions between fluorinated, chlorinated, brominated, and iodinated chalcones and therapeutically relevant targets such as β-tubulin, EGFR, VEGFR-2, HDACs, PI3K and topoisomerase. [23] In addition to the ability to predict binding affinity, docking also offers a mechanistic explanation of the effects of halogen substitution on hydrophobic interactions, π–π stacking, hydrogen bonding and directed halogen bonding in addition to explaining experimental variability in anticancer activity. [24] However, when using docking alone to predict biologic efficacy or target engagement, even highly favourable docking scores will not be able to accurately do so due to its reliance upon relatively rigid protein structures and simplistic scoring schemes. [25]

The limitations of docking predictions are especially relevant to the use of halogenated chalcones. Larger halogens (iodine and bromine) typically increase predicted binding affinity because larger halogens can create stronger dispersion forces and expand hydrophobic surface area for contact. [26] Nevertheless, molecular weight, lipophilicity, plasma-protein binding, and metabolic liabilities may all rise concurrently with these same structural alterations. As a result, derivatives that are iodinated or brominated may have lower cellular activity or worse pharmacokinetic characteristics but have better docking scores. As a result, only one aspect of the multidimensional optimization problem that arises during the search for anticancer drugs is evaluated by docking. [27] Docking's advantages and disadvantages are demonstrated by recent original research covered in this study. Docking predictions for the α-fluorinated chalcone series targeting β-tubulin were validated by cell-cycle analysis, apoptosis investigations, immunofluorescence microscopy, and direct tubulin polymerization assays. [28] Similar to how brominated chalcones suggested to target PCNA integrated docking with molecular dynamics simulations and cellular evaluation, iodinated chalcones assessed against VEGFR-2 combined docking with enzyme inhibition experiments. [29] Because computational predictions were validated thru experiments, these studies serve as examples of effective practices. [29] In contrast, numerous published reports assign molecular targets solely on the basis of docking without biochemical confirmation. Such target assignments should be interpreted as hypotheses rather than experimentally established mechanisms. [30] Therefore, molecular docking should be considered as a structure-guided prioritization tool that directs the synthesis of the most promising halogenated chalcone derivatives while need complementary computational and experimental validation before mechanistic conclusions can be established. [31]

5.4 Dynamic Validation of Halogenated Chalcone–Target Interactions

Molecular dynamics (MD) simulations are now a crucial part of AI-guided optimization of halogenated chalcone derivatives since minute modifications in halogen substitution can affect the stability of protein–ligand interactions. [32] MD evaluates the temporal stability of halogenated chalcone–target interactions under near-physiological conditions by monitoring conformational flexibility, interaction persistence, and binding stability throughout the simulation rather than a single static binding pose provided by molecular docking. [33] Analyses based on RMSD, RMSF, radius of gyration, solvent-accessible surface area, and MM-PBSA/MM-GBSA free-energy calculations improve confidence in computational lead selection by enabling the distinction between transient and stable binding modes.[26] Force-field quality, adequate sampling, and proper handling of halogen-specific interactions—especially for brominated and iodinated derivatives—remain critical to simulation accuracy.[27] Therefore, by confirming structurally stable halogenated chalcone prospects prior to biochemical characterization and experimental evaluation, MD should be viewed as a refinement method that enhances AI-driven lead optimization. Therefore, MD should be seen as a refinement technique that improves AI-driven lead optimization by verifying structurally stable halogenated chalcone prospects before biochemical characterization and experimental evaluation.[26]

MD simulations have been used more frequently in recent original studies of halogenated chalcone derivatives. A 100-ns molecular dynamics simulation showed that the predicted ligand–protein combination in the brominated chalcone derivative 2D, which is proposed to target proliferating cell nuclear antigen (PCNA), remained structurally stable during the simulation. While interaction analyses revealed persistent interactions with important residues inside the predicted binding site, RMSD

analysis revealed persistence of the binding orientation predicted by docking. [34]. The docking pose was more likely to be a physically plausible binding mode, based on these finding. However, MD should be considered supporting structural evidence rather than experimental proof of target interaction because no direct biochemical PCNA inhibition assay was performed. [35] For several of iodinated chalcone derivatives tested against VEGFR-2, a comparable integrated approach was used. After molecular docking, MD simulations were used to evaluate the persistence of hydrophobic contacts and hydrogen bonds within the ATP-binding pocket as well as the temporal stability of ligand-kinase interactions. Crucially, direct enzyme inhibition tests were used to supplement these computational analyses. [36] As a result, rather than serving as the primary evidence for target assignment, MD explained the structural underpinnings of experimentally observed VEGFR-2 inhibition. This is a suitable combination of biological and computational approaches. [37]

5.5 Machine Learning for Predicting the Anticancer Activity of Halogenated Chalcone Derivatives

The complexity of the structure–activity relationships of halogenated chalcone derivatives surpasses the prediction capacity of traditional statistical models, making machine learning (ML) a crucial tool for rational lead optimization. By combining multidimensional molecular descriptors with experimental bioactivity data, machine learning algorithms—such as Random Forest, Support Vector Machine, Gradient Boosting, and XGBoost—identify nonlinear relationships between halogen substitution patterns and anticancer activity that cannot be readily detected using conventional QSAR techniques. [38.39] Beyond predicting activity — machine learning (ML) allows for compound prioritization, virtual screening and multi-parameter optimization by simultaneously considering potency, selectivity and physico-chemical properties of halogenated chalcone derivatives. However, existent applications are still limited by small, heterogenous and poorly standardized datasets of experimentally obtained halogenated chalcones, therefore indicating that the quality of a dataset rather than the complexity of an algorithm is still the primary factor determining the performance of a predictive model. [40] thus, development of reliable machine learning models which will accelerate discovery of therapeutically important halogenated chalcone derivative depends on well curated experimental databases.

5.6 Deep Learning and Graph Neural Networks for Halogenated Chalcone Design

Through directly understanding molecular representations from chemical structures rather than relying only on hand-crafted descriptors, deep learning has transformed the computational enhancement of halogenated chalcone derivatives. By preserving atomic connectivity and local chemical environments, graph neural networks (GNNs) are particularly helpful for precisely differentiating between minute variations in halogen identity and substitution location, which typically impact biological activity. [41] This capacity is particularly useful for halogenated chalcones since, despite subtle structural variations, para-, meta-, and ortho-substitution patterns frequently result in noticeably distinct pharmacological characteristics. The successful use of deep learning is constrained by the limited number of experimentally validated halogenated chalcone datasets, as well as the increased risk of overfitting and poor external generalization. [6]

This graph-based representation is particularly beneficial for derivatives of halogenated chalcones. Fluorine, chlorine, bromine, and iodine can be regarded as categorical variables or factors influencing global physicochemical characteristics such as molecular weight or lipophilicity in conventional descriptor-based models. [42] In contrast, graph neural networks precisely preserve local substitution patterns and atomic connections. Consequently, the model is capable of recognizing adjacent methoxy or hydroxy groups, distinguishing between para-fluorinated and ortho-fluorinated chalcones, and evaluating how surrounding chemical conditions influence expected biological activity. Experimental SAR studies consistently demonstrate that the position of substitution often has a greater impact on anticancer effectiveness than the identity of the halogen by itself, making this structural sensitivity very valuable. [43] Consequently, transfer learning, self-supervised learning, and multimodal chemical representations are anticipated to be progressively combined to significantly enhance predictive accuracy and broaden the use of deep learning for the rational optimization of halogenated chalcones.

5.7 Explainable AI for Reasoned SAR Structure-Activity Relationships

High-performance predictions are achievable with advanced AI models; however, these models may provide limited understanding of how they make predictions. This lack of understanding limits the utility of AI in drug discovery. Explainable Artificial Intelligence (XAI), addresses this limitation through identification of the specific chemical structure elements that contribute to predicted biological activity. By converting the complex computer model into an understandable design principle, XAI aids medicinal chemists in translating the findings of AI models into actionable design principles. [44] The relative

contributions of individual descriptor characteristics including halogen identity, substitution position, lipophilicity, electronic effects, steric effects and/or interaction among a combination of molecular descriptor characteristics contributing to predicted anticancer activity can be determined using XAI techniques, i.e., SHAP and LIME [45] (figure 4). XAI represents a tool beyond traditional SAR that enables medicinal chemist's to rationally optimize scaffolds based on the knowledge gained about the structural basis of bioactivity. For example, whereas SAR would indicate that fluorine-substituted compounds were generally more active than chloro-substituted analogs, XAI enables determination of what portion(s) of the observed increase in activity contributed most significantly to that increase - e.g., was due to increased lipophilicity, changes in molecular polarity, increased polarizability, steric effects, etc.?, as well as any potential synergy/interactions resulting from combinations of multiple descriptor characteristics. [46]. While informative regarding empirical activity trends, such information is far more valuable to medicinal chemists since it describes characteristics of molecules that can be modified versus providing solely descriptive data regarding the relationship between structure and bioactivity**.** As a result, XAI represents a strong bridge between computational prediction and experimental medicinal chemistry by improving confidence in AI-guided design while facilitating the development of more potent and selective halogenated chalcone-based anticancer agents. [34]

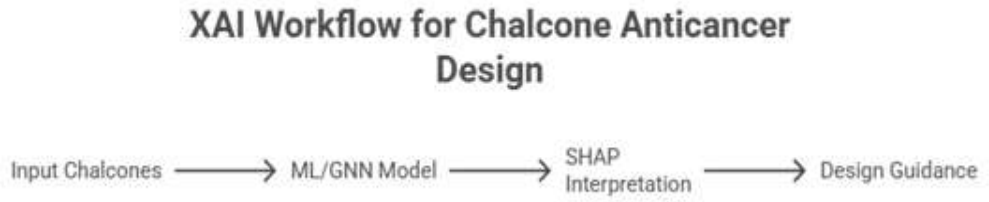

Figure 4. Explainable AI framework for translating predictions of halogenated chalcone activity into actionable structure–activity relationships.

5.8 Generative Artificial Intelligence for Designing Next-Generation Halogenated Chalcone Derivatives

Transforming computational drug discovery from molecular prediction to molecular creation is the main purpose of generative artificial intelligence which is the most advanced stage of AI-assisted medicinal chemistry. [47] Rather than screening existing halogenated chalcone derivatives, generative models—including variational autoencoders, diffusion models, graph-based generators, and transformer architectures—design entirely new analogues optimized for multiple objectives, including anticancer potency, pharmacokinetic behaviour, synthetic accessibility, and safety and target selectivity as these systems condition molecular generation on characteristics of the binding pocket, enabling target-specific optimization, this evolution is particularly relevant for halogenated chalcones because experimentally validated targets—including β-tubulin, VEGFR-2, HDACs, and Topoisomerases—possess well-characterized three-dimensional binding sites that may guide structure-aware molecular design. Because it is impractical to experimentally investigate the vast array of potential halogen substitution patterns, this capacity is especially useful for halogenated chalcones. [48] Generative AI minimizes unnecessary synthesis while facilitating effective exploration of hitherto unreachable chemical space through the integration of experimentally validated structure–activity relationships with molecular docking, ADMET prediction, and reinforcement learning. For instance, bromination can enhance hydrophobic interactions with targets while also raising lipophilicity and decreasing water solubility. Fluorination could enhance metabolic stability without necessarily increasing target affinity. Generative AI has the capability to assess these conflicting goals at once using reinforcement-learning techniques or multi-objective optimization methods, thereby identifying molecular designs located on the Pareto-optimal frontier instead of maximizing a single pharmacological endpoint. [49]

The use of high-quality experimental data sets along with strong biological validation (and thus, the potential for "success") has been shown to support recent developments in both modern diffusion models and graph-based architecture designs which are designed to include structural biology information about proteins from crystallization experiments, cryo-EM experiments, or from computational predictions. In addition to being able to generate molecules independent of their biologic targets. [50]

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6. CURRENT BARRIERS TO SUCCESS AND POTENTIAL PATHS FORWARD FOR AI-DRIVEN DEVELOPMENT OF NEW HALOGENATED CHALCONES

While there have been many advances in AI-assisted drug development through medicinal chemistry, developing new halogenated chalcones continues to be impeded by poor quality data as opposed to insufficient computing capabilities. The most significant barrier to creating universally-applicable and robust predictive models from available literature has been the dependence upon small, heterogenous datasets; varying biological outcomes; and unvalidated docking assignments with respect to biochemical target assignment. [51] Furthermore, pharmacokinetics, toxicity, selectivity, and synthetic accessibility are not sufficiently integrated into unified predictive frameworks by existing AI procedures, which primarily maximize specific characteristics like cytotoxic potency and binding affinity (Table 2). To overcome these constraints, explainable AI, multimodal learning, transfer learning, generative molecular design, and standardized, experimentally validated databases devoted to halogenated chalcone derivatives will be needed in order to simultaneously optimize several drug-development goals. Halogenated chalcones from scaffolds that have promise in testing may become anticancer candidates that can be applied in clinical settings because of these integrated, data-driven methodologies.

Table 2. AI Technologies for Rational Optimization of Halogenated Chalcone Derivatives

Technology	Role in halogenated chalcone discovery	Halogen-specific value	Principal limitation	Required validation
Molecular descriptors and feature engineering	Convert chalcone structures into numerical inputs	Capture lipophilicity, polarity, volume, electronic effects, and polarizability caused by halogen substitution	Descriptor redundancy and dependence on manually selected features	Feature-selection analysis and standardized biological data
QSAR	Predict anticancer activity before synthesis	Identifies relationships between halogen type, position, physicochemical properties, and potency	Small datasets, overfitting, weak applicability domains	External test sets, cross-validation, and matched halogen series
Machine learning	Models nonlinear structure–activity relationships	Captures interactions among halogen identity, substitution position, and neighboring functional groups	Dataset heterogeneity and class imbalance	Independent validation and prospective experimental testing
Molecular docking	Predicts binding orientation and target interactions	Evaluates hydrophobic contacts and possible halogen bonding	Rigid receptor approximation and unreliable scoring functions	Biochemical target assays and comparison with experimental activity
Molecular dynamics	Tests stability of chalcone–target complexes over time	Evaluates persistence of interactions involving chlorine, bromine, or iodine	Force-field limitations and inadequate conformational sampling	Replicate simulations, suitable parameters, and experimental target confirmation
ADMET prediction	Prioritizes compounds with balanced developability	Assesses whether halogen-driven potency gains compromise solubility, metabolism, or toxicity	Reduced reliability outside the training domain	Experimental solubility, permeability, metabolism, and toxicity studies

Graph neural networks	Learn structural features directly from molecular graphs	Distinguish local substitution environments and positional isomers	Data-intensive and frequently difficult to interpret	External datasets and explainability analysis
Explainable AI	Reveals features driving model predictions	Determines whether activity arises from halogen identity, position, polarity, steric effects, or correlated features	Explanations may not establish causality	Medicinal-chemistry interpretation and experimental SAR testing
Generative AI	Designs new chalcone derivatives with predefined objectives	Explores untested fluorinated, chlorinated, brominated, and iodinated substitution patterns	Unrealistic structures and dependence on limited training data	Synthetic feasibility assessment, synthesis, and biological evaluation

7. CONCLUSION

Halogenated chalcone derivatives represent a promising class of small-molecule anticancer agents owing to their structural versatility, synthetic accessibility, and capacity for extensive medicinal chemistry optimization. Artificial intelligence has reshaped this optimization process by integrating molecular representation, QSAR, structure-based modeling, molecular dynamics, ADMET prediction, machine learning, explainable AI, and generative molecular design into a unified framework for rational drug discovery[52] Ultimately, Artificial Intelligence (AI) should not be seen as a substitute for Experimental Drug Discovery, but rather as an effective Catalyst for the Rational Design of Next Generation Halogenated Chalcone Anticancer Therapies. " (14), The Future Development of Multimodal AI, Graph Neural Networks, Foundation Models, and Generative Molecular Design are expected to accelerate the identification of novel halogenated chalcone derivatives that have enhanced Potency, Selectivity, Pharmacokinetics, and Translational Therapeutic Potential. [53]

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AUTHOR CONTRIBUTIONS

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ETHICS STATEMENT

Ethical approval was not required for this review because it did not involve human participants, animals, patient data, or the collection of any new experimental or clinical data.

DATA AVAILABILITY STATEMENT

No new data were generated or analyzed in this review

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