iJRASET
International Journal For Research in Applied Science and Engineering Technology



INTERNATIONAL JOURNAL FOR RESEARCH

IN APPLIED SCIENCE & ENGINEERING TECHNOLOGY

Volume: 14 **Issue:** XI **Month of publication:** November 2026

DOI: https://doi.org/10.22214/ijraset.2026.85887

www.ijraset.com

Call: 08813907089 | E-mail ID: ijraset@gmail.com

International Journal for Research in Applied Science & Engineering Technology (IJRASET)
ISSN: 2321-9653; IC Value: 45.98; SJ Impact Factor: 7.538
Volume 14 Issue XI Nov 2026- Available at www.ijraset.com

Modern Paradigms in Rational Drug Design: A Comprehensive Review

Rohit Malgunde[1], Dr. Nitin Gawai[2], Rekha Kolape[3]
Department of Pharmaceutical Chemistry, Mahadev Kanchan College of Pharmaceutical Education and Research, Uruli Kanchan, Pune, Maharashtra, India

Abstract: ***Pharmaceutical drug discovery has undergone a paradigm shift over the past century, evolving from phenotypic screening and serendipitous discovery to structural, computational, and molecularly targeted paradigms. Early drug discovery relied heavily on natural product isolation and empirical observation, which, while yielding foundational pharmacotherapies, lacked mechanistic precision and carried high failure rates. The modern era of rational drug design integrates high-resolution structural biology—specifically X-ray crystallography, nuclear magnetic resonance (NMR) spectroscopy, and cryo-electron microscopy (cryo-EM)—with computational modeling, quantitative structure-activity relationship (QSAR) analyses, and artificial intelligence (AI) to systematically engineer therapeutics with high affinity, exquisite selectivity, and optimal pharmacokinetic profiles. This comprehensive review synthesizes the methodological framework of contemporary drug discovery. We trace the continuum of target identification and validation across multi-omics platforms, functional genomics (CRISPR/Cas9), and chemical probes, detailing the physical and thermodynamic parameters that define druggable binding pockets. We examine lead discovery strategies, contrasting High-Throughput Screening (HTS) with Fragment-Based Drug Design (FBDD), and delineate structure-based (SBDD) and ligand-based (LBDD) approaches. Furthermore, we address the biophysical optimization of lead compounds through physicochemical parameterization, Lipinski's Rule of Five, in silico ADMET prediction, and targeted prodrug or nanoparticle delivery systems. Finally, we explore frontier therapeutic modalities, including proteolysis-targeting chimeras (PROTACs), covalent inhibitors, allosteric modulators, and deep generative AI models. Through detailed clinical case studies of imatinib, oseltamivir, and sofosbuvir, this manuscript demonstrates the real-world application of rational design, while providing a critical analysis of clinical attrition causes and future automated closed-loop discovery paradigms.***

Keywords: Rational Drug Design, Structure-Based Drug Design (SBDD), Quantitative Structure-Activity Relationship (QSAR), ADMET Optimization, PROTACs, Artificial Intelligence in Drug Discovery, Pharmacogenomics.

I. INTRODUCTION

A. Definition, Scope, and Economic Imperative

Rational drug design represents the logical, hypothesis-driven identification and optimization of bioactive chemical entities based on detailed mechanistic insights into macromolecular biological targets. Unlike traditional empirical screening—which evaluated candidate molecules based on observable phenotypic shifts in tissues or whole organisms without a prior understanding of the molecular target—rational drug design leverages chemical, physical, and biological principles to engineer molecules capable of modulating specific pathological pathways. The contemporary pharmaceutical landscape operates under an extraordinary economic and logistical imperative.

The research and development (R&D) cost to bring a single novel molecular entity (NME) to market is estimated at approximately $2.6 billion, inclusive of capital costs and the burden of clinical attrition [1]. The research timeline routinely spans 10 to 15 years from initial target discovery to regulatory approval. Consequently, the integration of computational chemistry, structural biology, high-performance computing, and machine learning into the R&D pipeline is no longer merely an academic exercise, but an operational necessity designed to compress timelines, reduce late-stage clinical failures, and maximize therapeutic efficacy.

B. Overview of Therapeutic Modalities

Fig. 1. Schematic workflow of the contemporary early-stage, preclinical, and clinical pharmaceutical development timeline.

Modern drug discovery spans a spectrum of molecular architectures. Historically dominated by small organic molecules capable of crossing cellular membranes to engage hydrophobic active sites, the drug discovery toolset has expanded to encompass diverse biophysical classes. Small molecules continue to offer advantages in oral bioavailability and intracellular accessibility.

©IJRASET: All Rights are Reserved

However, macromolecular biologics, peptides, nucleic acid therapies, and targeted protein degraders now provide options for engaging biological targets previously deemed "undruggable."

C. Historical Evolution of Drug Design Methodology

Table I: Overview Of Major Therapeutic Modalities And Design Characteristics

Modality	Molecular Weight (Da)	Typical Target Class	Primary Route of Administration	Key Advantages	Major Limitations
Small Molecules	150 – 800	Enzymes, Receptors, Ion Channels	Oral	High cell permeability, predictable stability, scalable synthesis	Limited capacity to modulate large, flat protein-protein interfaces
Peptides	500 – 5,000	Cell-surface Receptors, Modulators	Parenteral / Inhalation	High selectivity, low off-target toxicity, synthetic accessibility	Proteolytic susceptibility, rapid renal clearance, poor membrane permeability
Proteins & Biologics	> 40,000	Extracellular Ligands, Cell-Surface Receptors	Parenteral (IV/SC)	High specificity, long half-life, potent target neutralization	High manufacturing costs, immunogenicity risk, inability to cross cell membranes
Nucleic Acids	Variable (10,000 – 1,000,000)	mRNA, Non-coding RNA, Genomic DNA	Parenteral / LNP Delivery	Sequence-based design, precise gene silencing or expression	Systemic delivery barriers, enzymatic degradation, innate immune activation
Monoclonal Antibodies	~150,000	Transmembrane Receptors, Soluble Cytokines	Intravenous / Subcutaneous	Exquisite target specificity, extended elimination half-life via FcRn recycling	High production expense, lack of intracellular access, parenteral requirement

The history of pharmacology can be delineated into four epochal phases, spanning empirical natural product discovery, classical quantitative receptor theory, the structural biology revolution, and contemporary artificial intelligence paradigms.

1) *The Empirical and Serendipitous Era (1890s–1940s):* Early therapeutics were derived primarily from botanical extracts, synthetic dyestuffs, or unexpected biological observations. The synthesis of acetylsalicylic acid (Aspirin) by Felix Hoffmann at Bayer in 1897 represented a chemical modification of the natural product salicin to reduce gastric toxicity, though its molecular mechanism—inhibition of cyclooxygenase—remained unknown for over seven decades. Similarly, Alexander Fleming's discovery of penicillin in 1928 was a serendipitous observation of fungal inhibition on a bacterial culture, which was subsequently operationalized through industrial fermentation and validated structurally via X-ray crystallography by Dorothy Hodgkin in 1945 [2].

Fig. 2. Historical progression of pharmacological drug discovery paradigms from empirical screening to AI-driven targeted degradation.

2) *Receptor Theory and Quantitative Relationships (1940s–1970s):* The middle of the twentieth century established the theoretical foundation of modern pharmacology. Building upon Paul Ehrlich's concept of selective affinity ("corpora non agunt nisi fixata") and John L a n g l e y ' s receptive substances, quantitative receptor theory emerged through the mathematical formulations of A.J. Clark, E.J. Ariëns, and R.P. Stephenson. In 1964, Corwin Hansch and colleagues published foundational work linking chemical structure to biological activity through quantitative mathematical relationships (QSAR) [3]. This demonstrated that biological activity could be modeled as a function of lipophilic, electronic, and steric parameters.
3) *The Structural Biology and CADD Revolution (1970s–2000s):* The determination of high-resolution three-dimensional structures of biological macromolecules via X-ray crystallography and multi-dimensional NMR spectroscopy transformed drug discovery. Researchers moved from inferring active site topologies using active analog alignment to directly visualizing ligand-protein interactions at atomic resolution. Computer-Aided Drug Design (CADD) emerged as a central discipline during this period. Landmarks include the development of dorzolamide (Trusopt), a topically active carbonic anhydrase inhibitor approved in 1995 that was designed explicitly to fit the active site of carbonic anhydrase II [4], and the rapid design of human immunodeficiency virus (HIV) protease inhibitors (such as saquinavir and ritonavir), which transformed HIV infection into a manageable chronic condition.
4) *The AI-Driven and Degradation Era (2000s–Present):* Contemporary drug design leverages high-throughput genomic sequencing, high-resolution cryo-electron microscopy (cryo-EM), scalable cloud computing, and deep artificial neural networks. The focus has expanded from static occupancy-based inhibition to functional structural modulation, induced-proximity degradation (e.g., PROTACs), and automated multi-objective molecular generation via AI platforms.

D. Pharmacogenomics and Personalized Medicine Integration

Modern drug discovery increasingly incorporates pharmacogenomic data to identify patient sub-populations characterized by distinct genetic profiles, altered drug metabolizing enzymes, or unique target mutations. The traditional "one-size-fits-all" drug deployment model is being replaced by precision therapeutics engineered for distinct molecular subsets of disease.

For instance, the clinical efficacy of tyrosine kinase inhibitors is tightly linked to the presence of specific driver mutations, such as epidermal growth factor receptor (EGFR) mutations in non-small cell lung cancer or the BCR-ABL1 fusion gene in chronic myeloid leukemia. By integrating patient-derived genomic, transcriptomic, and metabolomic datasets early in the target selection process, rational drug design minimizes clinical non-response rates and reduces late-stage clinical trial attrition.

II. TARGET IDENTIFICATION AND VALIDATION

A. Criteria for Druggable Targets

Fig. 3. Multi-stage target identification, druggability assessment, and functional validation architecture.

The initial step in rational drug design is the selection and validation of a therapeutic target—typically a protein, enzyme, nuclear receptor, ion channel, or nucleic acid sequence whose functional modulation restores a physiological balance or halts disease progression. A candidate biological target must satisfy five critical parameters:

1) *Biological Relevance:* Clear mechanistic linkage between target activity and disease pathogenesis, validated in disease-relevant cell types or animal models.
2) *Druggability:* The presence of a well-defined, structurally accessible pocket or cleft with complementary charge, hydrogen-bonding capabilities, and hydrophobicity capable of binding a small molecule or therapeutic entity with high affinity (Kd < 10^-8 M).
3) *Synthetic Tractability:* The feasibility of synthesizing chemical modulators capable of engaging the target site with reasonable chemical yield and scalability.
4) *Tissue Selectivity and Safety:* Differential expression or function of the target in pathological tissues relative to vital healthy organs, minimizing mechanism-based on-target toxicities.
5) *Subcellular Accessibility:* Localization of the target within a compartment reachable by the chosen therapeutic modality (e.g., cell membrane vs. nucleus).

B. Multi-Omics Discovery Platforms

The identification of novel therapeutic targets relies on high-throughput, multi-omics profiling platforms including genomics, proteomics, and transcriptomics integrated through systems biology workflows.

©IJRASET: All Rights are Reserved | SJ Impact Factor 7.538 | ISRA Journal Impact Factor 7.894 |

1) *Genomics and Genome-Wide Association Studies (GWAS):* GWAS scan single-nucleotide polymorphisms (SNPs) across disease cohorts to identify susceptibility loci. Mendelian Randomization (MR) techniques are applied to leverage human genetic variants as instrumental variables, assessing causal relationships between target expression and disease risk, thereby prioritizing targets supported by human genetic validation [5].
2) *Proteomics and Mass Spectrometry:* Matrix-Assisted Laser Desorption/Ionization (MALDI) and Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) enable global quantification of cellular protein expression, post-translational modifications (phosphorylation, ubiquitination), and dynamic protein-protein interaction networks under pathological states.
3) *Transcriptomics and Single-Cell RNA Sequencing (scRNA-seq):* Bulk and single-cell RNA sequencing reveal differential gene expression patterns across pathological states. scRNA-seq resolves cell typeheterogeneity within tumor microenvironments or inflamed tissues, preventing the masking of therapeutic targets restricted to rare pathogenic cell sub-populations.

C. *Functional Genetic and Pharmacological Validation*

To establish that a candidate target is essential to disease progression, rigorous functional validation is required using orthogonal molecular techniques.

1) *CRISPR/Cas9 Gene Editing:* Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-Cas9 systems allow precise genomic deletion (CRISPRko), transcriptional activation (CRISPRa), or transcriptional repression (CRISPRi). Gene knockout models confirm whether complete removal of target function produces the desired therapeutic phenotype or generates unexpected cytotoxicity.
2) *RNA Interference (RNAi):* Small interfering RNA (siRNA) and short hairpin RNA (shRNA) post-transcriptionally silence target mRNA. RNAi provides a titratable, transient knock-down model that mimics incomplete pharmacological inhibition, serving as a biological control for small-molecule inhibition.
3) *Chemical Probes:* Small-molecule chemical probes—characterized by high selectivity (>30-fold against related family members), clear mechanism of action, and known cellular potencies (<100 nM)—are essential to validate target engagement in phenotypic assays before entering lead optimization.
4) *Key Validation Challenges:* Target validation can be complicated by several biological factors: genetic redundancy where paralogous genes upregulate; pathway crosstalk re-routing signaling; off-target liabilities of poorly validated tools; translational gaps between animal models and human biology; and undruggable interfaces lacking catalytic pockets.

III. LEAD IDENTIFICATION AND DE NOVO DISCOVERY STRATEGIES

A. *Hit-to-Lead Criteria*

Following target validation, hit discovery campaigns identify molecules displaying confirmed activity against the target. A "hit" is defined as a compound demonstrating reproducible target-specific activity in a biological assay, with a half-maximal inhibitory concentration (IC50) or effective concentration (EC50) typically below 100 µM. Hits are evaluated and optimized into "lead" series using quantitative biochemical, biophysical, and pharmacokinetic criteria.

1) *Potency:* Concentration dependence with IC50/EC50 < 10 µM (ideally < 1 µM) in primary biochemical assays.
2) *Selectivity:* > 100-fold selectivity against off-target screening panels, antitargets (e.g., hERG, CYP enzyme isoforms), and structural paralogs.
3) *Ligand Efficiency (LE):* A measure of binding energy per non-hydrogen (heavy) atom: LE = ΔG / N_heavy = (-RT ln Kd) / N_heavy. Acceptable lead molecules typically display an LE ≥ 0.3 kcal/mol/heavy atom.
4) *Absence of PAINS Features:* Elimination of Pan-Assay Interference Compounds—chemical structures containing reactive or promiscuous functional groups (e.g., rhodanines, quinones, curcumin-like structures) that cause false-positive assay readings through aggregation, fluorescence quenching, or covalent denaturation.

B. *High-Throughput Screening (HTS) vs. Fragment-Based Drug Design (FBDD)*

The two primary methodologies for hit identification are HTS and FBDD, which differ in library size, molecular weight of screening entries, hit rates, and biophysical detection requirements.

1) *High-Throughput Screening (HTS):* Involves automated biochemical or cell-based testing of chemical libraries containing 10^5 to 10^6 distinct small molecules (MW 300–500 Da). While HTS rapidly identifies high-affinity hits, it suffers from variable hit quality, higher rates of false positives, and lower overall efficiency relative to library size.

2) *Fragment-Based Drug Design (FBDD):* Screens lower-complexity, smaller molecular weight libraries (10^3–10^4 compounds) composed of "fragments" (MW 150–250 Da) conforming to the Rule of Three (MW ≤ 300 Da, LogP ≤ 3, H-bond donors ≤ 3, H-bond acceptors ≤ 3). Because fragments are small, they form high-quality, efficient interactions with specific sub-pockets of the target binding site, despite displaying weak affinity (Kd ~ 100 µM to 10 mM). These initial fragment hits are subsequently linked, merged, or grown using high-resolution structural guidance (X-ray or NMR) into potent lead molecules.

Notable successes of FBDD include vemurafenib (a BRAF V600E mutant inhibitor approved for melanoma), which was developed from a simple 7-azaindole fragment scaffold, and venetoclax (a BCL-2 inhibitor), derived from fragment assembly targeting protein-protein interactions.

C. Virtual Screening, Natural Products, and De Novo Molecular Design

Complementary lead generation platforms include:

1) *Virtual High-Throughput Screening (vHTS):* Computational evaluation of multi-million compound digital libraries using ligand-based molecular similarity algorithms or structure-based molecular docking into target crystal structures.
2) *Natural Product Isolation:* Natural products account for approximately 25% of all FDA-approved small-molecule drugs [6]. They provide complex, highly three-dimensional structural skeletons with structural diversity that often spans challenging biological targets. Modern platforms apply automated fractionated extraction, NMR dereplication, and semi-synthetic modification to optimize natural product hits.
3) *De Novo Design:* Automated computational algorithm assembly of novel molecular structures within a target binding site using fragment building blocks, constrained by geometric and chemical feasibility parameters.

IV. STRUCTURE-ACTIVITY RELATIONSHIPS (SAR) AND QUANTITATIVE MODELING (QSAR)

A. Classical SAR and Pharmacophore Principles

Structure-Activity Relationship (SAR) studies systematically map the relationship between specific chemical structural modifications on a core molecular framework and changes in observed biological activity.

SAR optimization maps functional groups to essential biological interactions:

1) *Hydrogen Bond Donors and Acceptors:* Directional electrostatic interactions (1.5–2.5 kcal/mol).
2) *Hydrophobic Contacts:* Entropically driven displacement of ordered water molecules (0.5–1.5 kcal/mol per methyl group).
3) *Aromatic Centers:* Parallel or edge-to-face pi-pi stacking interactions (1–3 kcal/mol).
4) *Electrostatic/Ionic Interactions:* Long-range charge-charge interactions (3–5 kcal/mol).

A pharmacophore is defined by the International Union of Pure and Applied Chemistry (IUPAC) as "an ensemble of steric and electronic features that is necessary to ensure the optimal supramolecular interactions with a specific biological target and to trigger (or block) its biological response." Pharmacophore features are represented geometrically as spatial arrays of vectors, spheres, or planes, independently of specific chemical scaffolds.

B. Quantitative SAR (QSAR) and Hansch Analysis

Quantitative Structure-Activity Relationships (QSAR) construct predictive mathematical models correlating quantified chemical descriptors (lipophilic, electronic, steric) with biological potency (IC50, EC50, or 1/C).

The classical Hansch Equation models biological response using linear or parabolic multilinear regression equations:

$$\log(1 / C) = -k1 (\log P)^2 + k2 (\log P) + \rho \sigma + \delta Es + c$$

Where C is the molar concentration of the compound required to produce a defined biological end-point (IC50); log P is the octanol-water partition coefficient, representing molecular lipophilicity (the negative quadratic term models the parabolic nature of drug absorption); σ is the Hammett substituent constant measuring electron-donating or electron-withdrawing effects; Es is Taft's steric substituent parameter; and c is the regression constant.

1) *Descriptor Dimensionality Hierarchy:* Descriptors used in QSAR modeling span multiple levels of spatial complexity: 1D (MW, formula), 2D (topological indices, fingerprints, log P), 3D (molecular volume, surface area, pharmacophores), and 4D–6D (conformational ensembles over time, solvation, induced-fit states).

C. Comparative Evaluation of 2D and 3D QSAR Methodologies

1) *3D QSAR Methodologies (CoMFA and CoMSIA):* Comparative Molecular Field Analysis (CoMFA) requires molecular alignment of bioactive conformations across a series of compounds mapped inside a 3D spatial grid. Steric and electrostatic interaction energies are calculated at grid points. Comparative Molecular Similarity Indices Analysis (CoMSIA) calculates similarity indices using Gaussian distance functions, incorporating hydrophobic and hydrogen bonding fields.

TABLE II: Comparative Evaluation OF 2D AND 3D QSAR Methodologies

Characteristic	2D QSAR	3D QSAR (e.g., CoMFA, CoMSIA)
Input Data Required	Biological activity, 2D structural graphs	Biological activity, explicit 3D conformations, rigid alignment
Characteristic	2D QSAR	3D QSAR (e.g., CoMFA, CoMSIA)
Alignment Dependency	Fully independent (No molecular alignment needed)	Highly dependent on accurate molecular superposition
Predictive Power	Moderate; ideal for congeneric series	High for novel spatial modifications, low if alignment is inaccurate
Mechanistic Interpretation	Abstract statistical correlations	Intuitive 3D steric and electrostatic contour maps
Computational Overhead	Very low (seconds per thousands of compounds)	High (requires conformational sampling and grid sampling)
Primary Applications	Rapid screening of large compound libraries	Fine structural tuning of defined lead series within known binding sites

2) *QSAR Validation and Limitations:* QSAR models must be validated using external test sets, cross-validation metrics ($q^2 > 0.5$, $R^2_{pred} > 0.6$), and Y-randomization tests to rule out chance correlations. Limitations include the applicability domain—models cannot reliably predict biological activity for chemical scaffolds outside the training set space—and the activity cliff phenomenon, where minor chemical modifications yield non-linear changes in biological activity.

V. STRUCTURE-BASED AND LIGAND-BASED DRUG DESIGN PARADIGMS

A. Structure-Based Drug Design (SBDD)

Fig. 4. Decision tree illustrating structure-based (SBDD) versus ligand-based (LBDD) drug design selection strategies.

1) *Target Determination Methods:* SBDD relies on obtaining high-resolution three-dimensional atomic coordinates of target biological macromolecules via X-ray crystallography (< 1.5 Å resolution), NMR spectroscopy (capturing solution dynamics), Cryo-EM (< 2.0 Å resolution for large complex assemblies), or homology modeling when experimental coordinates are unavailable.
2) *Binding Site Characterization:* Computational identification of binding pockets uses grid-based algorithms or surface topology mapping to locate deep, hydrophobic cavities. "Hot spots"—sub-regions within binding pockets that contribute disproportionately to the total free energy of binding (ΔG_{bind})—are identified using computational solvent mapping or molecular dynamics with organic probe solutions.
3) *Molecular Docking and Scoring Functions:* Molecular docking algorithms sample the conformational space of a small-molecule ligand within a designated target binding site to predict the binding pose and calculate relative binding affinity via force field, empirical, or knowledge-based scoring functions.
4) *Molecular Dynamics (MD) Simulations:* Static crystal structures do not capture dynamic protein motions or solvent-mediated thermodynamic effects. MD simulations calculate force trajectories using Newton's second law over nanosecond-to-microsecond timespans. MD validates docking stability, quantifies target structural reorganization (induced-fit mechanisms), evaluates key water molecule bridges, and calculates binding free energies using MM-PBSA or MM-GBSA methodologies: $\Delta G_{bind} = \langle G_{complex} \rangle - \langle G_{protein} \rangle - \langle G_{ligand} \rangle$.

©IJRASET: All Rights are Reserved | SJ Impact Factor 7.538 | ISRA Journal Impact Factor 7.894 |

B. Ligand-Based Drug Design (LBDD)

When high-resolution three-dimensional target structures are unavailable, LBDD uses structural and physical properties derived from ensembles of known active and inactive small-molecule ligands.

1) *Pharmacophore Modeling:* Overlaying dynamic structural ensembles of known active compounds isolates key shared 3D spatial arrangements of chemical functionalities (e.g., two hydrophobic aromatic rings separated by 5.2 Å from a hydrogen-bond acceptor) required for biological activity, generating an abstract quantitative query for database screening.
2) *Molecular Fingerprints and Similarity Metrics:* Chemical structures are translated into binary bit strings (fingerprints) representing structural paths or circular atom environments (ECFP4/ECFP6). Molecular similarity is quantified using the Tanimoto Coefficient (ST = c / (a + b - c)), where a and b are set bits in compounds A and B, and c is shared bits. A threshold of ST ≥ 0.85 indicates high structural similarity and likely shared biological target activity.

VI. PHYSICOCHEMICAL OPTIMIZATION, ADMET PROFILING, AND ADVANCED DELIVERY

A. Drug-Likeness and Lipinski's Rule of Five

The translation of a potent enzyme inhibitor into an orally bioavailable therapeutic requires balancing binding affinity with suitable physicochemical parameters. Christopher Lipinski's empirical Rule of Five (Ro5) defines property guidelines for poor absorption or permeability.

B. Physicochemical Relationships, In Silico ADMET Prediction, and Oral Bioavailability Enhancement

Table III: Lipinski's Rule Of Five And Extended Oral Bioavailability Parameters

Physicochemical Parameter	Lipinski Criteria	Extended Bioavailability Threshold	Physical/Biological Significance
Molecular Weight (MW)	≤ 500 Da	≤ 500 Da	Larger molecules exhibit reduced passive membrane diffusion rates
Octanol-Water Partition (log P)	≤ 5.0	-0.5 to 3.5	Excess lipophilicity drives poor aqueous solubility and non-specific binding
Hydrogen Bond Donors (HBD)	≤ 5 (O-H and N-H groups)	≤ 5	Desolvation penalty increases as HBD count rises, reducing membrane transfer
Hydrogen Bond Acceptors (HBA)	≤ 10 (O and N atoms)	≤ 10	High HBA density creates a large polar solvation shell
Topological Polar Surface Area	Not in original Ro5	≤ 140 Å² (≤ 60 Å² for CNS)	High polar area hinders passive lipid membrane permeability
Rotatable Bond Count (NROT)	Not in original Ro5	≤ 10	Conformational entropy loss upon binding limits oral exposure
Ro5 Rule Violations	≤ 1 violation allowed	0 violations preferred	Multiple violations increase preclinical development failure rates

1) *Physicochemical Interrelationships:* Lipophilicity (log P / log D_7.4) dictates partition equilibrium between aqueous biological fluids and lipid membranes. While higher lipophilicity promotes passive membrane permeability, excessive lipophilicity (log P > 5) reduces aqueous solubility, increases hepatic CYP450 clearance, and elevates off-target toxicity liabilities. Ionization constant (pKa) dictates whether species are neutral (permeable) or ionized (soluble). CNS penetration requires stricter parameterization: MW < 400 Da, log P ~ 2.0–3.0, TPSA < 60–90 Å², HBD ≤ 1, and non-substrate selectivity for P-glycoprotein efflux pumps.
Fig. 5. Optimization window of lipophilicity (log P) balancing membrane permeability and aqueous solubility.

2) *In Silico ADMET Profiling:* Predictive machine learning models evaluate early lead structures against absorption (Caco-2 permeability), distribution (plasma protein binding, log BB), metabolism (CYP450 site-of-metabolism prediction), excretion (renal clearance), and toxicity endpoints prior to synthetic execution.

C. *Preclinical Safety and Toxicity De-Risking*

Early toxicity testing includes evaluating hERG potassium ion channel inhibition to prevent fatal cardiac QT prolongation, avoiding structural alerts (e.g., unsubstituted anilines, furans) that undergo CYP bioactivation to reactive electrophilic species causing hepatotoxicity, and running broad off-target panel profiling (Eurofins SafetyScreen44) to establish therapeutic indices.

D. *Prodrug Strategies and Nanoparticle-Based Drug Delivery*

1) *Prodrug Strategies:* A prodrug is a pharmacologically inactive chemical entity that undergoes predictable enzymatic or chemical transformation in vivo to release the active parent drug moiety.
Fig. 6. Structural classification of carrier-based versus bioprecursor prodrug chemical delivery systems.

2) *Advanced Nanoparticle-Based Delivery Architecture:* When optimization of small-molecule structures compromises target binding affinity, nano-formulation methodologies can address pharmacokinetic barriers. Lipid Nanoparticles (LNPs) utilize ionizable cationic lipids, helper phospholipids, cholesterol, and PEGylated lipids to deliver nucleic acids (e.g., Patisiran). Polymeric nanoparticles (PLGA/PEG) provide controlled release via ester erosion, while liposomes and micelles encapsulate hydrophobic payloads (e.g., liposomal doxorubicin) to reduce systemic toxicity.

Table IV: Prodrug Classifications, Activation Mechanisms, And Clinical Examples

Prodrug Class	Activation Mechanism	Chemical Modification	Primary Rationale / Advantage	Clinical Example
Ester Carrier Prodrug	Cleavage by intestinal or hepatic carboxylesterases (CES1/CES2)	Esterification of carboxylic acid or hydroxyl group	Increases lipophilicity and passive intestinal absorption	Oseltamivir carboxylate (administered as ethyl ester prodrug)
Phosphate Prodrug	Rapid hydrolysis by membrane-bound Alkaline Phosphatase	Attachment of phosphate moiety to hydroxyl/amine group	Dramatically increases aqueous solubility for parenteral delivery	Fosamprenavir (phosphate prodrug of amprenavir)
Amino Acid Conjugate	Active transport via peptide transporters (PEPT1/ PEPT2)	L-valine amino acid conjugation to active hydroxyl	Enhances active intestinal absorption via transporter targeting	Valacyclovir (prodrug of acyclovir)
Bioprecursor Prodrug	Oxidative or reductive hepatic P450 metabolism	Molecular transformation without transient carrier group	Modifies metabolic activation kinetics and systemic clearance	Codeine (O-demethylated by CYP2D6 to form morphine)
Mutual Prodrug	Enzymatic cleavage of covalent linker	Covalent coupling of two synergistic therapeutic drugs	Ensures synchronized spatial and temporal drug delivery	Sultamicillin (ampicillin covalently linked to sulbactam)

VII. EMERGING THERAPEUTIC MODALITIES AND NEXT-GENERATION DESIGN

A. *Peptide, Protein, and Nucleic Acid Therapeutics*

Fig. 7. Overview of next-generation therapeutic modalities: PROTAC degraders, targeted covalent modulators, and pathway-biased GPCR agonists.

1) *Peptide Therapeutics:* Synthetic peptides bridge the gap between small molecules and biologics. Unmodified linear peptides suffer from rapid proteolytic degradation (half-life < 5 min) and renal clearance. Optimization includes N-methyl substitution, backbone cyclization, D-amino acid incorporation, and hydrocarbon stapling of alpha-helical peptides to confer protease resistance.
2) *Nucleic Acid Therapeutics:* Includes Antisense Oligonucleotides (ASOs), siRNAs, and miRNA mimics. Sequence-specific Watson-Crick base pairing drives target mRNA degradation via RNase H or RISC complex loading. Chemical modifications (2'-O-methyl, 2'-MOE, phosphorothioate backbones) and GalNAc conjugation enhance stability and tissue targeting.

B. *Targeted Protein Degradation (PROTACs) and Covalent Inhibitors*

1) *Proteolysis-Targeting Chimeras (PROTACs):* PROTACs are heterobifunctional molecules engineered with three distinct domains: a ligand that selectively binds a Protein of Interest (POI), a flexible linker domain, and a ligand recruiting an E3 ubiquitin ligase (VHL or CRBN). Recruiting the ligase into close proximity forms a transient ternary complex, inducing K48-linked polyubiquitination and 26S proteasomal degradation. Unlike classic occupancy-driven pharmacology, PROTACs operate via event-driven catalytic pharmacology, permitting sub-stoichiometric dosing and targeting non-enzymatic scaffold proteins.
   Fig. 8. Mechanism of PROTAC-mediated ternary complex formation and proteasomal degradation.
2) *Covalent Inhibitors:* Targeted covalent inhibitors (TCIs) pair a non-covalent binding scaffold with a mildly reactive electrophilic warhead that reacts with a specific nucleophilic residue (Cys, Lys, Ser) in the active site. Potency is defined by Ki (non-covalent affinity) and k_react (covalent reaction rate), giving inactivation efficiency k_react / Ki. TCIs offer sustained pharmacodynamics lasting until de novo protein synthesis occurs, high isoform selectivity (e.g., ibrutinib targeting Cys481 in BTK), and enhanced therapeutic indices.

C. *Allosteric Modulators, Biased Agonists, and Polypharmacology*

1) *Allosteric Modulators:* Engage topographically distinct binding sites away from the conserved orthosteric catalytic pocket. Positive Allosteric Modulators (PAMs) enhance endogenous agonist efficacy, while Negative Allosteric Modulators (NAMs) decrease signal transduction, providing higher subtype selectivity and reduced receptor desensitization.
2) *Biased Agonism (Functional Selectivity):* Biased GPCR agonists stabilize specific active conformations that selectively activate G-protein pathways while avoiding beta-arrestin recruitment, reducing side effects such as desensitization and arrestin-mediated toxicity.
3) *Polypharmacology:* Rationally designs single chemical entities to modulate multiple defined biological targets simultaneously, avoiding complex drug-drug interactions in multi-factorial diseases such as neurodegeneration and cancer.

VIII. ARTIFICIAL INTELLIGENCE AND MACHINE LEARNING IN MODERN DRUG DISCOVERY

A. *Cheminformatics Infrastructure and Predictive Machine Learning*

Fig. 9. End-to-end artificial intelligence and machine learning pipeline for predictive screening and generative molecular design.

The integration of computational platforms and chemical databases (PubChem, ChEMBL, PDB) enables automated molecular modeling workflows. Standard software packages include AMBER/GROMACS for molecular dynamics, Glide/AutoDock for docking, and RDKit for cheminformatics.

Classical machine learning algorithms (Random Forests, SVM, XGBoost) and deep learning architectures like Convolutional Neural Networks (CNNs for 3D active sites) and Graph Neural Networks (GNNs/MPNNs operating directly on molecular graphs) accurately predict bioactivity and ADMET profiles without manual descriptor engineering.

B. *Deep Generative Models, Active Learning, and Multi-Objective Optimization*

Generative AI frameworks sample vast chemical space (> 10^60 feasible molecules) using Generative Adversarial Networks (GANs), Variational Autoencoders (VAEs), SMILES Transformers, and 3D Diffusion Models to generate novel molecular structures optimized for multi-parameter requirements.

1) *Multi-Objective Pareto Optimization and Active Learning:* Generative models incorporate reinforcement learning to balance multiple properties simultaneously (potency, selectivity, log P, synthetic accessibility). Active learning integrates these computational designs into automated robotic synthesis platforms, creating a closed loop where assay data retrains AI models in real time.

Fig. 10. Closed-loop active learning cycle integrating generative AI, automated synthesis, and high-throughput screening.

2) *Current Machine Learning Bottlenecks:* Key bottlenecks include data quality and negative reporting bias in public databases, lack of interpretability in black-box deep networks, synthetic accessibility challenges of generated molecules, and dataset bias limiting out-of-distribution scaffold predictions.

IX. CLINICAL CASE STUDIES IN RATIONAL DRUG DESIGN

A. *Imatinib (Gleevec): Structure-Based Targeting of the BCR-ABL Inactive Conformation*

Fig. 11. Summary of key structural mechanisms for clinical case studies: imatinib, oseltamivir, and sofosbuvir.

Chronic Myeloid Leukemia (CML) is driven by the reciprocal translocation t(9;22), forming the Philadelphia chromosome and constitutively active BCR-ABL1 tyrosine kinase. Optimization of an initial PKC-inhibiting 2-phenylaminopyrimidine hit involved inserting a 3-pyridyl group to boost kinase affinity, adding an ortho-methyl group on the phenyl ring to restrict rotation and abolish PKC activity, and introducing an N-methylpiperazine group to enhance solubility.

Crystallographic analysis confirmed that imatinib binds the inactive kinase domain, stabilizing the "DFG-out" loop conformation [7]. Approved in 2001, imatinib transformed CML 5-year survival rates from <30% to >90%.

B. *Oseltamivir (Tamiflu): Structure-Guided Design of Influenza Neuraminidase Inhibitors*

Influenza neuraminidase cleaves terminal sialic acid to release budding virions. Structure-guided design replaced the oxocarbenium transition-state mimic (DANA) 4-hydroxyl with a basic guanidino group to yield zanamivir (IC50 ~ 1 nM), which lacked oral bioavailability. Replacing the glycerol side chain with a 3-pentyl ether induced a structural shift in Glu276, and converting the carboxylate to an ethyl ester prodrug yielded oseltamivir phosphate, an effective oral antiviral.

C. *Sofosbuvir (Sovaldi): Structure-Guided Nucleoside Analog and Prodrug Engineering for HCV*

Hepatitis C Virus (HCV) NS5B RNA-dependent RNA polymerase is essential for viral replication. Designing 2'-deoxy-2'-alpha-fluoro-2'-beta-C-methyluridine provided metabolic stability (2'-F) and chain termination via steric clash (2'-beta-C-methyl). Applying McGuigan Aryl Phosphoramidate Prodrug technology masked the 5'-monophosphate with phenol and L-alanine isopropyl ester motifs, overcoming the rate-limiting initial intracellular phosphorylation step and achieving sustained virologic response cure rates >95%.

X. TRANSLATIONAL CHALLENGES, FUTURE PERSPECTIVES, AND CONCLUSION

A. *Clinical Attrition Analysis and Translational Gaps*

Fig. 12. Breakdown of major causes of Phase I-III clinical trial drug attrition (~90% failure rate).

Despite technological advancements, ~90% of candidate small molecules entering Phase I clinical trials fail. Clinical attrition causes include lack of clinical efficacy (~30%), unforeseen toxicity liabilities (~25%), unfavorable ADMET/PK profiles (~20%), and commercial factors (~25%). Animal models often fail due to species differences in CYP450 metabolism and immune pathways, driving the adoption of microfluidic human organs-on-chips and patient-derived organoids.

B. *Addressing Undruggable Targets, Multi-Omics Systems Pharmacology, and Regulatory Evolution*

Undruggable Targets and Systems Pharmacology: Targets lacking catalytic pockets (transcription factors, IDPs, flat PPIs) are engaged using covalent modulators, macrocycles, and PROTACs. Systems pharmacology integrates multi-omics network models to evaluate systemic polypharmacology. Regulatory frameworks (FDA Modernization Act 2.0) increasingly accept AI models and non-animal testing data.

C. *Future Outlook: Closed-Loop Automated Discovery, Digital Twins, and Quantum Computing*

Future paradigms rely on self-driving laboratories combining AI generative models and autonomous synthesis, multiscale digital twin patient models for virtual in silico trials, and quantum computing to solve the Electronic Schrödinger Equation directly for precise metalloenzyme dynamic modeling.

©IJRASET: All Rights are Reserved | SJ Impact Factor 7.538 | ISRA Journal Impact Factor 7.894 |

D. Conclusion

Rational drug design has evolved from early empirical screening into a multi-disciplinary, computation-driven discipline. Modern drug discovery integrates high-resolution structural biology, quantitative physical chemistry, multi-omics systems biology, and advanced artificial intelligence to design safer, more target-specific therapies. While challenges remain in clinical translation and engaging historically "undruggable" targets, emerging modalities—such as targeted protein degradation, covalent modifiers, generative AI, and automated discovery platforms—continue to transform the discovery pipeline. By maintaining biophysical rigor and leveraging advanced computational methods, rational drug design remains central to developing next-generation therapeutics for complex human diseases.

XI. ACKNOWLEDGMENT

The author acknowledges the Department of Pharmaceutical Chemistry at Mahadev Kanchan College of Pharmaceutical Education and Research for providing research facilities. The author declares no competing financial or professional conflicts of interest.

REFERENCES

[1] J. A. DiMasi, H. G. Grabowski, and R. W. Hansen, "Innovation in the pharmaceutical industry: New estimates of R&D costs,"
[2] Journal of Health Economics, vol. 47, pp. 20–33, 2016.
[3] D. Hodgkin, C. Crowfoot, B. W. Rogers, and B. W. Durnford, "X-ray crystallographic investigation of the structure of penicillin,"
[4] Nature, vol. 156, no. 3966, pp. 509–510, 1945.
[5] C. Hansch and T. Fujita, "p-σ-π Analysis. A method for the correlation of biological activity and chemical structure," Journal of the American Chemical Society, vol. 86, no. 8, pp. 1616–1626, 1964.
[6] J. Greer, J. W. Erickson, J. J. Baldwin, and M. D. Varney, "Application of structural biology to drug discovery," Journal of Medicinal Chemistry, vol. 37, no. 8, pp. 1035–1054, 1994.
[7] G. Davey Smith and G. Hemani, "Mendelian randomization: genetic anchors for causal inference in epidemiological studies,"
[8] Human Molecular Genetics, vol. 23, no. R1, pp. R89–R98, 2014.
[9] D. J. Newman and G. M. Cragg, "Natural products as sources of new drugs over the nearly four decades from 01/1981 to 09/2019,"
[10] Journal of Natural Products, vol. 83, no. 3, pp. 770–803, 2020.
[11] T. Schindler, W. Bornmann, P. Pellicena, W. T. Miller, B. Clarkson, and J. Kuriyan, "Structural mechanism for STI-571 inhibition of abelson tyrosine kinase," Science, vol. 289, no. 5486, pp. 1938–1942, 2000.
[12] M. Von Itzstein, W. Y. Wu, G. B. Kok, M. S. Pegg, J. C. Dyason, and B. Jin, et al., "Rational design of potent sialidase-based inhibitors of influenza virus replication," Nature, vol. 363, no. 6428, pp. 418–423, 1993.
[13] M. J. Sofia, D. Bao, W. Chang, J. Du, D. Nagarathnam, and S. Wang, et al., "Discovery of a β-D-2'-deoxy-2'-α-fluoro-2'-β-C-methyluridine nucleotide prodrug (PSI-7977) for the treatment of hepatitis C virus," Journal of Medicinal Chemistry, vol. 53, no. 19, pp. 7202–7218, 2010.
[14] A. L. Hopkins and C. R. Groom, "The druggable genome," Nature Reviews Drug Discovery, vol. 1, no. 9, pp. 727–730, 2002.
[15] C. A. Lipinski, F. Lombardo, B. W. Dominy, and P. J. Feeney, "Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings," Advanced Drug Delivery Reviews, vol. 23, no. 1-3, pp. 3–25, 1997.
[16] D. F. Veber, S. R. Johnson, H. Y. Cheng, B. R. Smith, K. W. Ward, and K. D. Kopple, "Molecular properties that influence the oral bioavailability of drug candidates," Journal of Medicinal Chemistry, vol. 45, no. 12, pp. 2615–2623, 2002.
[17] D. A. Erlanson, S. W. Fesik, R. E. Hubbard, W. Jahnke, and H. Jhoti, "Twenty years on: the impact of fragment-based drug discovery," Nature Reviews Drug Discovery, vol. 15, no. 9, pp. 605–619, 2016.
[18] D. P. Bondeson, A. Mares, I. E. Smith, E. Ko, S. Campos, and A. H. Miah, et al., "Catalytic in vivo protein knockdown by small-molecule PROTACs," Nature Chemical Biology, vol. 11, no. 8, pp. 611–617, 2015.
[19] K. M. Sakamoto, K. B. Kim, A. Kumagai, F. Mercurio, C. M. Crews, and R. J. Deshaies, "Protacs: chimeric molecules that target proteins to the Skp1-Cullin-F-box complex for ubiquitination and degradation," Proceedings of the National Academy of Sciences, vol. 98, no. 15, pp. 8554–8559, 2001.
[20] J. Singh, R. C. Petter, T. A. Baillie, and A. Whitty, "The resurgence of covalent drugs," Nature Reviews Drug Discovery, vol. 10, no. 4, pp. 307–317, 2011.
[21] J. Jumper, R. Evans, A. Pritzel, T. Green, M. Figurnov, and O. Ronneberger, et al., "Highly accurate protein structure prediction with AlphaFold," Nature, vol. 596, no. 7873, pp. 583–589, 2021.
[22] J. M. Stokes, K. Yang, K. Swanson, W. Jin, A. Cubillos-Ruiz, and N. M. Donghia, et al., "A deep learning approach to antibiotic discovery," Cell, vol. 180, no. 4, pp. 688–702, 2020.
[23] R. D. Cramer, D. E. Patterson, and J. D. Bunce, "Comparative molecular field analysis (CoMFA). 1. Effect of shape on binding of steroids to carrier proteins," Journal of the American Chemical Society, vol. 110, no. 18, pp. 5959–5967, 1988.
[24] G. Klebe, U. Abraham, and T. Mietzner, "Molecular similarity indices analysis (CoMSIA) to devise 3D QSAR models and define pharmacophore features," Journal of Medicinal Chemistry, vol. 37, no. 24, pp. 4130–4146, 1994.
[25] G. Sliwoski, S. Kothiwale, J. Meiler, and E. W. Lowe, "Computational methods in drug discovery," Pharmacological Reviews, vol. 66, no. 1, pp. 334–395, 2014.
[26] W. L. Jorgensen, "The many roles of computation in drug discovery," Science, vol. 303, no. 5665, pp. 1813–1818, 2004.
[27] B. K. Shoichet, "Virtual screening of chemical libraries," Nature, vol. 432, no. 7019, pp. 862–865, 2004.
[28] D. B. Kitchen, H. Decornez, J. R. Furr, and J. Bajorath, "Docking and scoring in virtual screening for drug discovery: methods and applications," Nature Reviews Drug Discovery, vol. 3, no. 11, pp. 935–949, 2004.
[29] P. Ferrara, H. Gohlke, D. J. Price, G. Klebe, and C. L. Brooks, "Assessing scoring functions for protein-ligand interactions,"

[30] Journal of Medicinal Chemistry, vol. 47, no. 12, pp. 3032–3047, 2004.
[31] P. A. Kollman, I. Massova, C. Reyes, B. Kuhn, S. Huo, and L. Chong, et al., "Calculating structures and free energies of complex molecules: combining molecular mechanics and continuum electrostatics," Accounts of Chemical Research, vol. 33, no. 12, pp. 889–897, 2000.
[32] G. Schneider and U. Fechner, "Computer-based de novo design of drug-like molecules," Nature Reviews Drug Discovery, vol. 4, no. 8, pp. 649–663, 2005.
[33] P. Willett, "Similarity-based virtual screening using 2D fingerprints," Drug Discovery Today, vol. 11, no. 23-24, pp. 1046–1052,
[34] 2006.
[35] D. Rogers and M. Hahn, "Extended-connectivity fingerprints," Journal of Chemical Information and Modeling, vol. 50, no. 5, pp.
[36] 742–754, 2010.
[37] J. P. Hughes, S. Rees, S. B. Kalindjian, and K. L. Philpott, "Principles of early drug discovery," British Journal of Pharmacology, vol. 162, no. 6, pp. 1239–1249, 2011.
[38] J. B. Baell and G. A. Holloway, "New substructure filters for removal of pan-assay interference compounds (PAINS) from screening libraries and for their alert in drug discovery," Journal of Medicinal Chemistry, vol. 53, no. 7, pp. 2719–2740, 2010.
[39] A. L. Hopkins, "Network pharmacology: the next paradigm in drug discovery," Nature Chemical Biology, vol. 4, no. 11, pp. 682–690, 2008.
[40] T. Kenakin, "Biased agonism," PLoS Biology, vol. 7, no. 3, p. e1000059, 2009.
[41] P. J. Conn, A. Christopoulos, and C. W. Lindsley, "Allosteric modulators of GPCRs: a novel approach to chemotherapy," Nature Reviews Drug Discovery, vol. 8, no. 1, pp. 41–54, 2009.
[42] J. Rautio, H. Kumpulainen, T. Heimbach, R. Oliyai, D. Oh, and T. Järvinen, et al., "Prodrugs when and why?" Nature Reviews Drug Discovery, vol. 7, no. 3, pp. 255–270, 2008.
[43] C. McGuigan, A. Gilles, K. Madela, M. Alajah, A. Powell, and Y. Lad, et al., "Application of phosphoramidate ProTide technology to potent nucleoside antiviral agents," Journal of Medicinal Chemistry, vol. 53, no. 5, pp. 2136–2145, 2010.
[44] M. J. Mitchell, M. M. Billingsley, R. M. Haley, M. E. Wechsler, N. A. Peppas, and R. Langer, "Engineering precision nanoparticles for drug delivery," Nature Reviews Drug Discovery, vol. 20, no. 2, pp. 101–124, 2021.

©IJRASET: All Rights are Reserved | SJ Impact Factor 7.538 | ISRA Journal Impact Factor 7.894 |

[1] P. R. Cullis and M. J. Hope, "Lipid nanoparticle systems for enabling gene therapies," *Molecular Therapy*, vol. 25, no. 7, pp. 1467–1475, 2017.

[2] M. J. Waring, J. Arrowsmith, A. R. Leach, P. D. Leeson, S. Mandrell, and R. M. Owen, et al., "An analysis of the attrition of drug candidates from four major pharmaceutical companies," *Nature Reviews Drug Discovery*, vol. 14, no. 7, pp. 475–486, 2015.

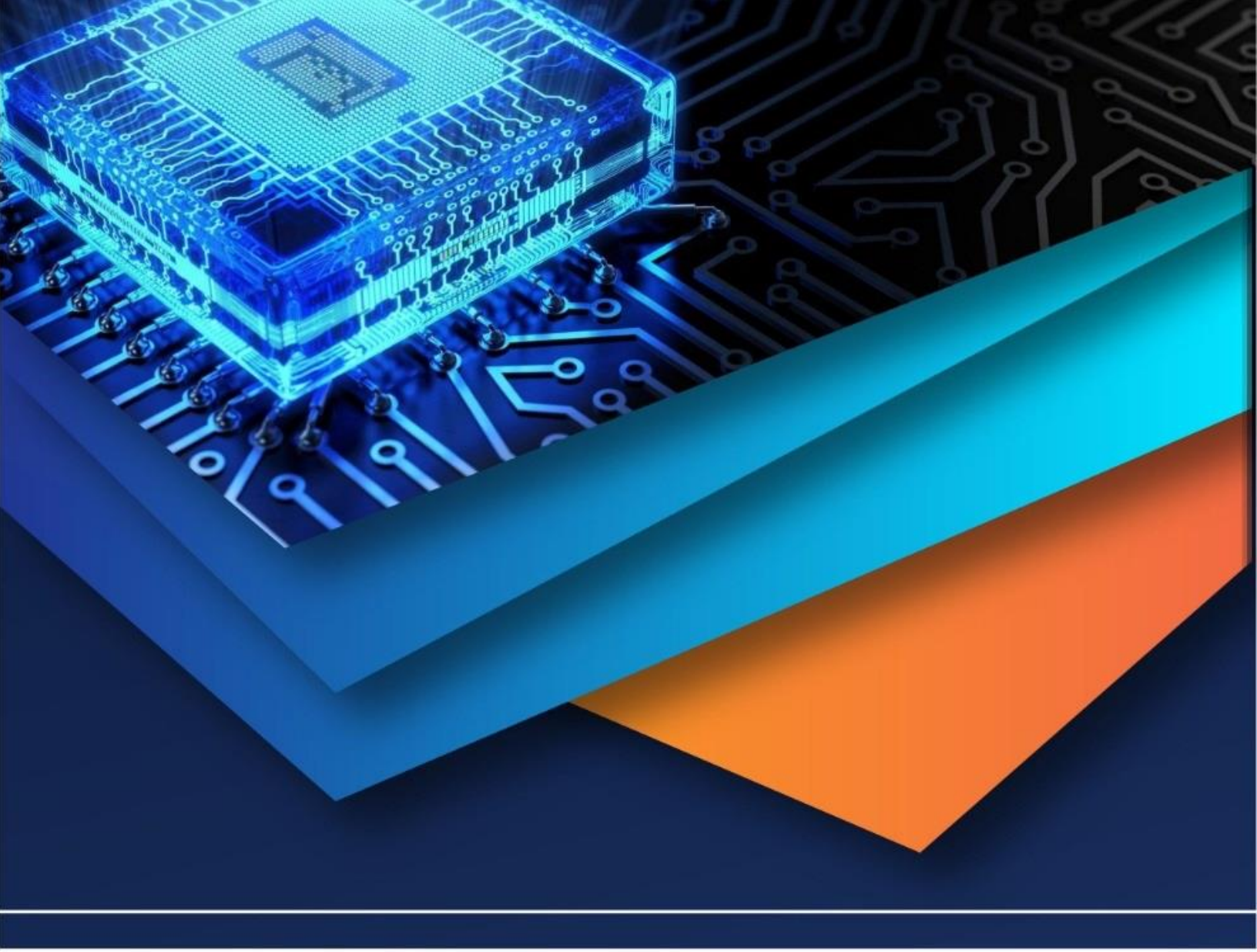
[3] D. Sun, W. Gao, H. Hu, and S. Zhou, "Why 90% of clinical drug development fails and how to improve it?" *Acta Pharmaceutica Sinica B*, vol. 12, no. 7, pp. 3049–3062, 2022.

[4] G. Schneider, "Automating drug discovery," *Nature Reviews Drug Discovery*, vol. 17, no. 2, pp. 97–113, 2018.

[5] M. H. S. Segler, M. Preuss, and M. P. Waller, "Planning chemical syntheses with deep neural networks and symbolic AI," *Nature*, vol. 555, no. 7698, pp. 604–610, 2018.

[6] Y. Cao and T. N. Kipf, "MolGAN: An implicit generative model for small molecular graphs," *arXiv preprint arXiv:1805.11973*, 2018.

©IJRASET: All Rights are Reserved | SJ Impact Factor 7.538 | ISRA Journal Impact Factor 7.894 |



10.22214/IJRASET

45.98

IMPACT FACTOR: 7.129

IMPACT FACTOR: 7.429

INTERNATIONAL JOURNAL FOR RESEARCH

IN APPLIED SCIENCE & ENGINEERING TECHNOLOGY

Call : 08813907089 (24*7 Support on Whatsapp)