

PHARMACOLOGY OF RECEPTORS AND MOLECULAR MECHANISMS OF DRUG
SEARCHING: INTEGRATED CLINICAL PHARMACOLOGY, PHARMACODYNAMIC,
PHARMACOKINETIC, PHARMACOTHERAPEUTIC, PHARMACOGENOMIC,
THERAPEUTIC DRUG MONITORING, EVIDENCE-BASED, AND PRECISION MEDICINE
APPROACHES

DOI: <https://doi.org/10.52340/spectri.2026.13.01.05>

^{1,2,3,4,5,6}Nodar Sulashvili, MD, PhD, Professor; Tbilisi, Georgia. <https://orcid.org/0000-0002-9005-8577>

⁷Margarita Beglaryan ², MD, PhD, Academician, Professor; Yerevan, Armenia;
<https://orcid.org/0000-0003-3697-6390>

⁶Nana Gorgaslidze, MD, PhD Professor; Tbilisi, Georgia <https://orcid.org/0000-0002-4563-5224>

⁷Naira Chichoyan, MD, PhD, Professor; Yerevan, Armenia. <https://orcid.org/0000-0003-3905-3372>

⁸Vira Kravchenko, MD, PhD, Academician, Professor; Kharkiv, Ukraine.
<https://orcid.org/0000-0001-6335-2490>

^{6,3}Marika Sulashvili, MD, Invited Lecturer; Tbilisi, Georgia. <https://orcid.org/0000-0002-6338-4262>

⁹Nato Alavidze; Kutaisi, Georgia. <https://orcid.org/0000-0001-6695-5924>

¹Ia Egnatievi , MD, PhD, Professor; Tbilisi, Georgia.

¹Manana Giorgobiani, MD, PhD, Professor; Tbilisi, Georgia.

¹⁰Magda Davitashvili , PhD, Professor, Academician, Telavi, Georgia. <https://orcid.org/0009-0005-4213-6533>

⁴Irina Imerlishvili, PhD, Doctor of Law, Professor; Batumi, Georgia.

⁶Marina Giorgobiani, Academician, Professor; Tbilisi, Georgia. <https://orcid.org/0000-0003-0686-5227>

⁸Igor Seniuk, PhD, , Associate Professor, Kharkiv, Ukraine. <https://orcid.org/0000-0003-3819-7333>

^{5,11}Lali Patsia, MD, PhD, Professor; Tbilisi, Georgia.

⁸Olga Shapoval, Professor; Kharkiv, Ukraine <https://orcid.org/0000-0002-1971-2863>

⁶Natia Kvizhinadze , PhD, Professor; Tbilisi, Georgia.

⁶Lasha Tchelidze, MD, PhD student;

¹²David Aphkhazava, PhD, Professor, Tbilisi, Georgia. <https://orcid.org/0000-0001-6216-6477>

¹David Aghmashenebeli University of Georgia, ²Georgian International University GIU,

³Georgian National University SEU, ⁴BAU International University Batumi, ⁵Alte University,

⁶Tbilisi State Medical University; ⁷Yerevan State Medical University After Mkhitar Herats,

⁸National University of Pharmacy of Ukraine, Kharkiv, ⁹Akaki Tsereteli State University,

¹⁰Iakob Gogebashvili Telavi State University, ¹¹Ken Walker international

University, ¹²University of Georgia.

Corresponding Author: Dr. Professor Nodar Sulashvili

Mail: n.sulashvili@ug.edu.ge

Mob: +995-597-12-17-28

Abstract

Receptors are dynamic macromolecules that transduce chemical signals into biological responses and serve as the principal targets of modern therapeutics. This review surveys current concepts in receptor pharmacology and their application to drug discovery and development. Receptor-mediated signal transduction is examined across the major receptor families, including G protein-coupled receptors, ligand-gated and voltage-gated ion channels, nuclear receptors, and receptor tyrosine kinases, with emphasis on the second messengers, kinase cascades, and transcriptional programs that they engage. Classical receptor theory is reviewed alongside modern extensions that incorporate receptor efficacy, constitutive activity, receptor reserve, allosteric modulation, and biased agonism. Intracellular signal propagation is discussed as a network-level phenomenon shaped by cross-talk, feedback regulation, scaffold proteins, and compartmentalised signalling, providing the conceptual basis for network pharmacology. Drug-discovery strategies are then considered, from target identification and validation, high-throughput and phenotypic screening, and structure-based and fragment-based design to computational approaches, medicinal-chemistry optimisation, and the management of resistance, tolerance, and translational risk. Emerging modalities — allosteric modulators, agonists, targeted protein degraders (PROTACs), molecular glues, and covalent inhibitors — are discussed alongside the integration of receptor pharmacology with systems biology, biomarker-guided therapy, and personalised medicine. The review concludes that progress in receptor pharmacology will depend on controlling receptor conformational states, pathway selectivity, and tissue context rather than on maximising target affinity alone.

Keywords: Receptor pharmacology, drug discovery, G protein-coupled receptors, signal transduction, agonist, integrated pharmacology.

რეცეპტორების ფარმაკოლოგია და მედიკამენტების ძიების მოლეკულური მექანიზმები: კლინიკური ფარმაკოლოგიის, ფარმაკოდინამიკის, ფარმაკოკინეტიკის, ფარმაკოთერაპიის, ფარმაკოგენომიკის, სამკურნალო საშუალებების თერაპიული მონიტორინგის, მტკიცებულებებზე დაფუძნებული და პერსონალიზებული მედიცინის ინტეგრირებული მიდგომები

^{1,2,3,4,5,6}ნოდარ სულაშვილი, მედიცინის დოქტორი (MD, PhD), პროფესორი. თბილისი, საქართველო. <https://orcid.org/0000-0002-9005-8577>

⁷მარგარიტა ბეგლარიანი, მედიცინის დოქტორი (MD, PhD), აკადემიკოსი, პროფესორი. ერევანი, სომხეთი; <https://orcid.org/0000-0003-3697-6390>

⁸ნანა გორგასლიძე, მედიცინის დოქტორი (MD, PhD), პროფესორი. თბილისი, საქართველო. <https://orcid.org/0000-0002-4563-5224>

- ⁷ნაირა ჩიჩოიანი, მედიცინის დოქტორი (MD, PhD), პროფესორი. ერევანი, სომხეთი.
<https://orcid.org/0000-0003-3905-3372>
- ⁸ვირა კრავჩენკო, მედიცინის დოქტორი (MD, PhD), აკადემიკოსი, პროფესორი.
ხარკივი, უკრაინა. <https://orcid.org/0000-0001-6335-2490>
- ^{6,3}მარიკა სულაშვილი, მედიცინის დოქტორი (MD), მოწვეული ლექტორი. თბილისი, საქართველო. <https://orcid.org/0000-0002-6338-4262>
- ⁹ნატო ალავიძე, ქუთაისი, საქართველო. <https://orcid.org/0000-0001-6695-5924>
- ¹ია ეგნატიევი, მედიცინის დოქტორი (MD, PhD), პროფესორი
- ¹მანანა გიორგობიანი, მედიცინის დოქტორი (MD, PhD), პროფესორი, თბილისი, საქართველო.
- ¹⁰მაგდა დავითაშვილი, დოქტორი (PhD), პროფესორი, აკადემიკოსი, თელავი, საქართველო. <https://orcid.org/0009-0005-4213-6533>
- ⁴ირინა იმერლიშვილი, დოქტორი (PhD), სამართლის დოქტორი, პროფესორი; თბილისი, საქართველო.
- ⁶მარინა გიორგობიანი, აკადემიკოსი, პროფესორი; თბილისი, საქართველო.
<https://orcid.org/0000-0003-0686-5227>
- ⁸იგორ სენიუკი, დოქტორი, ასოცირებული პროფესორი, ხარკივი, უკრაინა.
<https://orcid.org/0000-0003-3819-7333>
- ^{5,11}ლალი ფაცია, მედიცინის დოქტორი, პროფესორი; თბილისი, საქართველო..
- ⁸ოლგა შაპოვალი, პროფესორი; ხარკივი, უკრაინა; <https://orcid.org/0000-0002-1971-2863>
- ⁶ნათია კვიფინაძე, დოქტორი, პროფესორი; თბილისი, საქართველო.
- ⁶ლამა ჭელიძე, დოქტორანტი; თბილისი, საქართველო.
- ¹²დავით აფხაზავა, დოქტორი, პროფესორი; თბილისი, საქართველო.
<https://orcid.org/0000-0001-6216-6477>

აბსტრაქტი

რეცეპტორები წარმოადგენს დინამიკურ მაკრომოლეკულებს, რომლებიც ქიმიურ სიგნალებს ბიოლოგიურ პასუხებად გარდაქმნიან და თანამედროვე ფარმაცოთერაპიის ძირითად სამიზნეებს წარმოადგენენ. სტატიაში განხილულია რეცეპტორული ფარმაცოლოგიის თანამედროვე კონცეფციები და მათი გამოყენება სამკურნალო საშუალებების აღმოჩენისა და განვითარების პროცესში. რეცეპტორებით ინდუცირებული სიგნალის ტრანსდუქცია გაანალიზებულია რეცეპტორების ძირითად ოჯახებში, მათ შორის G-ცილასთან შეწყვილებულ რეცეპტორებში, ლიგანდ-გააქტიურებად და ძაბვით-გააქტიურებად იონურ არხებში, ბირთვულ რეცეპტორებსა და რეცეპტორულ ტიროზინკინაზებში. განსაკუთრებული ყურადღებაა გამახვილებული მეორეულ მესენჯერებზე, კინაზურ კასკადებსა და მათ მიერ ინიცირებულ ტრანსკრიფციულ პროცესებზე. კლასიკური რეცეპტორული თეორია განხილულია თანამედროვე გაფართოებულ კონცეფციებთან ერთად, რომლებიც მოიცავს რეცეპტორის ეფექტურობას, კონსტიტუციურ აქტივობას, რეცეპტორულ რეზერვს, ალოსტერიულ მოდულაციასა და მიკერძოებულ აგონიზმს. უჯრედშიდა სიგნალის გავრცელება განხილულია როგორც ქსელური დონის ფენომენი, რომელსაც განსაზღვრავს სიგნალიზაციის გზებს შორის ურთიერთქმედება, უკუკავშირით რეგულაცია, სკაფოლდ-ცილები და კომპარტმენტალიზებული სიგნალიზაცია, რაც

ქმნის ქსელური ფარმაცოლოგიის კონცეპტუალურ საფუძველს. ასევე განხილულია პრეპარატების აღმოჩენის სტრატეგიები, დაწყებული სამიზნის იდენტიფიკაციითა და ვალიდაციით, მაღალი გამტარუნარიანობისა და ფენოტიპური სკრინინგით, სტრუქტურაზე დაფუძნებული და ფრაგმენტზე დაფუძნებული დიზაინით და დასრულებული კომპიუტაციური მიდგომებით, სამკურნალო ქიმიის ოპტიმიზაციითა და რეზისტენტობის, ტოლერანტობისა და ტრანსლაციური რისკის მართვით. განხილულია ახალი თაობის ფარმაცოლოგიური ჯგუფები — ალოსტერული მოდულატორები, აგონისტები, მიზანმიმართული ცილების დეგრადატორები (PROTACs), მოლეკულური „წებები“ (molecular glues) და კოვალენტური ინჰიბიტორები — აგრეთვე რეცეპტორული ფარმაცოლოგიის ინტეგრაცია სისტემურ ბიოლოგიასთან, ბიომარკერებზე ორიენტირებულ თერაპიასა და პერსონალიზებულ მედიცინასთან. მიმოხილვის დასკვნით, რეცეპტორული ფარმაცოლოგიის შემდგომი პროგრესი დამოკიდებული იქნება არა მხოლოდ სამიზნესთან მაქსიმალური აფინობის მიღწევაზე, არამედ რეცეპტორის კონფორმაციული მდგომარეობების, სიგნალიზაციის გზების სელექტიურობისა და ქსოვილოვანი კონტექსტის მიზანმიმართულ კონტროლზე.

საკვანძო სიტყვები: რეცეპტორების ფარმაცოლოგია, მედიკამენტების აღმოჩენა, G-ცილასთან დაკავშირებული რეცეპტორები, სიგნალის ტრანსდუქცია, აგონისტი, ინტეგრირებული ფარმაცოლოგია.

Introduction

Pharmacology has progressively evolved from a predominantly empirical science of drug effects into a highly integrated, molecularly informed discipline that seeks to explain, predict, and optimize the interactions between therapeutic agents and biological systems. Central to this transformation is receptor pharmacology, which provides a mechanistic framework for understanding how endogenous mediators and exogenous drugs produce cellular, tissue, and systemic effects. Receptors are not merely passive binding sites; they are dynamic molecular entities that translate chemical information into intracellular signals, regulate physiological processes, and determine, in substantial part, both therapeutic efficacy and adverse drug responses. Consequently, contemporary drug discovery and development increasingly depend on detailed characterization of receptor structure, ligand–receptor interactions, downstream signaling networks, receptor regulation, and the pharmacological determinants of selectivity. The integration of these concepts with clinical pharmacology, pharmacodynamics, pharmacokinetics, pharmacotherapeutics, pharmacogenomics, therapeutic drug monitoring, evidence-based medicine, and precision medicine has created a multidimensional framework for modern therapeutic development [1,57,59,62].

The molecular investigation of receptors has fundamentally changed the conceptual basis of drug searching and drug design. Classical pharmacology traditionally emphasized the relationship between drug concentration and biological response, whereas contemporary receptor pharmacology incorporates structural biology, molecular genetics, computational chemistry, systems biology, and quantitative pharmacology. Advances in cryo-electron microscopy, X-ray crystallography, nuclear magnetic resonance spectroscopy, molecular modeling, molecular dynamics simulations, and artificial-intelligence-assisted drug design have enabled increasingly precise characterization of receptor conformations and ligand-binding

sites. These technologies have contributed to a shift from phenotypic and serendipitous drug discovery toward target-based and structure-guided approaches. Nevertheless, successful drug development requires more than identifying a molecular target or demonstrating high-affinity binding. A pharmacologically promising molecule must also demonstrate appropriate selectivity, efficacy, exposure, distribution, metabolic stability, safety, and clinical relevance [63,68,74].

Receptor pharmacology encompasses several major receptor families, including G protein-coupled receptors (GPCRs), ligand-gated ion channels, voltage-regulated ion channels, enzyme-linked receptors, intracellular receptors, and other regulatory macromolecules. Each receptor class possesses distinctive structural and functional characteristics that influence pharmacological responses. GPCRs, for example, constitute one of the largest and most therapeutically important receptor superfamilies and participate in the regulation of neurotransmission, cardiovascular function, endocrine signaling, immune responses, metabolism, and sensory physiology. Ligand-gated ion channels rapidly convert ligand binding into changes in membrane permeability and electrical activity, making them critical targets for anesthetics, anticonvulsants, sedatives, analgesics, and other centrally acting agents. Enzyme-linked receptors frequently regulate cellular proliferation, differentiation, metabolism, and survival and therefore occupy a prominent position in therapeutic strategies for cancer, inflammatory disorders, and metabolic diseases. Nuclear receptors, in contrast, regulate gene transcription and contribute to delayed but sustained pharmacological effects [65,71,75].

A fundamental principle of receptor pharmacology is that drug response depends not simply on receptor occupancy but on the functional consequences of ligand binding. Agonists, antagonists, partial agonists, inverse agonists, allosteric modulators, and biased ligands can stabilize distinct receptor conformations and consequently generate different signaling outcomes. This concept has substantially expanded the pharmacological interpretation of drug action. A ligand may exhibit high affinity but limited efficacy, or it may preferentially activate one signaling pathway while minimizing another. Such functional selectivity, commonly described as biased agonism or biased signaling, has become an important strategy for designing therapeutics with improved efficacy and reduced adverse effects. Similarly, allosteric modulation offers opportunities to regulate receptor activity through sites that are distinct from endogenous ligand-binding domains, potentially providing greater subtype selectivity and preservation of physiological signaling [9,27,54,65].

The quantitative characterization of drug-receptor interactions constitutes another essential component of contemporary pharmacology. Concepts such as affinity, efficacy, potency, receptor occupancy, intrinsic activity, spare receptors, and concentration-response relationships provide the theoretical foundation for interpreting pharmacological effects. The distinction between potency and efficacy is particularly important in clinical pharmacology because a drug requiring a lower concentration to produce a given response is not necessarily more therapeutically effective. Furthermore, receptor density, tissue distribution, receptor coupling efficiency, downstream signaling capacity, and endogenous physiological conditions can substantially modify observed drug responses. Mathematical models of receptor activation and pharmacological response therefore contribute to more sophisticated predictions of drug behavior than simple binding measurements alone [41,48,68].

The integration of pharmacodynamics with receptor biology is essential for understanding the relationship between drug exposure and therapeutic or toxic effects. Pharmacodynamics

examines what a drug does to the organism, including its molecular mechanisms, physiological effects, biomarkers, dose–response relationships, and time-dependent responses. Pharmacokinetics, conversely, examines what the organism does to the drug through absorption, distribution, metabolism, and excretion. The interaction between these two domains establishes the exposure–response relationship that ultimately determines clinical outcomes. A drug possessing an excellent receptor profile may nevertheless fail therapeutically if it cannot achieve adequate concentrations at the site of action, undergoes excessive metabolism, exhibits unfavorable distribution, or produces unacceptable systemic toxicity. Thus, receptor pharmacology must be interpreted within the broader pharmacokinetic–pharmacodynamic framework [37,62].

Pharmacokinetic optimization is particularly important during drug searching because candidate molecules must possess physicochemical and biological properties compatible with clinical administration. Molecular weight, lipophilicity, ionization, aqueous solubility, membrane permeability, protein binding, metabolic stability, and transporter interactions influence systemic exposure and tissue concentrations. Drug metabolism, especially through hepatic and extrahepatic enzymatic systems, can generate active, inactive, or toxic metabolites. Cytochrome P450 enzymes and conjugative pathways may profoundly influence interindividual variability in drug exposure. Transport proteins can additionally affect intestinal absorption, hepatic elimination, renal clearance, and penetration into protected anatomical compartments such as the central nervous system. Consequently, modern drug discovery incorporates pharmacokinetic and drug-metabolism considerations at increasingly early stages of development [36,41,53,69].

Pharmacotherapeutics represents the translational dimension of pharmacology, connecting molecular mechanisms with therapeutic decision-making. The ultimate purpose of receptor-targeted drug discovery is not simply to develop molecules capable of modifying biological pathways but to improve clinically meaningful outcomes. Therapeutic selection must therefore consider disease pathophysiology, therapeutic objectives, patient characteristics, contraindications, drug interactions, treatment duration, adherence, and the balance between benefit and risk. A receptor that is biologically validated may not necessarily constitute an optimal therapeutic target if its modulation produces unacceptable systemic consequences or if compensatory biological pathways diminish clinical effectiveness. Modern pharmacotherapeutic development consequently emphasizes target validation, mechanistic plausibility, biomarkers, clinically relevant endpoints, and comparative therapeutic effectiveness [43,58,69].

Pharmacogenomics further demonstrates why receptor pharmacology cannot be separated from individual biological variability. Genetic variation can modify receptor expression, receptor structure, ligand affinity, intracellular signaling, drug metabolism, transporter activity, or downstream biological responses. Polymorphisms in genes encoding pharmacological targets and drug-metabolizing enzymes can contribute to differences in drug efficacy, toxicity, and optimal dosage. Pharmacogenomic information therefore provides an important mechanism for explaining why patients receiving the same drug at the same nominal dose may experience markedly different outcomes. The incorporation of genomic information into drug development and clinical decision-making supports a transition from population-based treatment strategies toward individualized therapeutic approaches [62,68,74].

Therapeutic drug monitoring (TDM) provides another important bridge between pharmacokinetic theory and clinical pharmacology. For drugs characterized by a narrow therapeutic index, substantial pharmacokinetic variability, or a strong concentration–effect relationship, measurement of circulating drug concentrations can assist in optimizing treatment. TDM is particularly valuable when clinical response cannot be reliably determined from symptoms alone or when toxicity is associated with excessive exposure. However, concentration measurements must be interpreted within the context of pharmacokinetic parameters, sampling time, active metabolites, protein binding, disease state, and pharmacodynamic response. Therefore, TDM is most effective when integrated into a broader pharmacological model rather than treated as an isolated laboratory measurement [16,23,42,71]. The principles of evidence-based medicine provide the clinical framework through which pharmacological discoveries are evaluated. Molecular mechanisms and preclinical observations are necessary but insufficient evidence for establishing therapeutic value. Clinical efficacy, safety, comparative effectiveness, quality of life, patient-reported outcomes, and long-term benefit–risk relationships must be demonstrated through appropriately designed clinical investigations. Randomized controlled trials, systematic reviews, meta-analyses, pharmacovigilance studies, and real-world evidence collectively contribute to the assessment of therapeutic interventions. Evidence-based pharmacology therefore requires continuous integration of molecular knowledge with clinical data and population-level outcomes.

Precision medicine represents a further evolution of this integrated approach. Rather than assuming that a single therapeutic strategy is equally appropriate for all patients with the same diagnostic classification, precision medicine seeks to identify clinically meaningful biological subgroups according to genetic, molecular, phenotypic, environmental, and behavioral characteristics. Receptor expression profiles, genomic alterations, signaling signatures, biomarkers, and pharmacokinetic phenotypes can potentially guide therapeutic selection. In oncology, for example, molecular characterization of tumors has enabled treatment strategies based on specific molecular abnormalities. Similar principles are increasingly being explored in cardiovascular, neurological, inflammatory, metabolic, and rare diseases [2,29,67].

The modern drug-searching process is consequently best understood as an iterative translational continuum rather than a linear sequence of isolated laboratory stages. Target identification is followed by target validation, ligand discovery, hit-to-lead optimization, receptor selectivity assessment, pharmacodynamic characterization, absorption–distribution–metabolism–excretion and toxicity evaluation, and clinical development. Computational approaches can accelerate several stages by predicting molecular interactions, identifying candidate binding sites, screening large chemical libraries, and estimating pharmacokinetic properties. Bioinformatics and systems pharmacology can additionally integrate genomic, transcriptomic, proteomic, metabolomic, and clinical datasets to identify disease-associated pathways and therapeutic vulnerabilities [36,61,63,68].

An important emerging concept is that drug action occurs within complex biological networks rather than through isolated molecular interactions. Although the traditional “one drug–one target” paradigm remains useful for certain pharmacological questions, many therapeutics influence multiple targets and interconnected signaling pathways. Polypharmacology can produce beneficial therapeutic effects but may also contribute to adverse reactions and drug–drug interactions. Network pharmacology therefore seeks to understand drug effects at the level

of interconnected molecular systems. This approach is particularly relevant for multifactorial diseases in which pathological processes involve numerous interacting pathways.

Receptor dynamics and cellular adaptation further complicate the interpretation of drug responses. Chronic exposure to receptor agonists or antagonists can produce receptor desensitization, internalization, downregulation, or compensatory signaling. Conversely, prolonged receptor blockade may induce receptor upregulation or changes in downstream sensitivity. Such adaptive processes can influence tolerance, withdrawal phenomena, therapeutic resistance, and long-term treatment effectiveness. Understanding receptor regulation is therefore essential not only for identifying new drug targets but also for determining optimal dosing schedules and anticipating changes in therapeutic response [15,18,23,47].

Drug safety represents an equally important component of modern pharmacological research. Off-target interactions, reactive metabolites, mitochondrial dysfunction, ion-channel inhibition, immune-mediated reactions, and organ-specific toxicity can limit the clinical utility of otherwise promising candidates. Early identification of safety liabilities is therefore increasingly integrated into drug discovery. Pharmacovigilance subsequently extends safety assessment beyond clinical trials by monitoring adverse drug reactions in broader and more heterogeneous patient populations. The combination of molecular toxicology, pharmacogenomics, real-world evidence, and post-marketing surveillance provides a more comprehensive understanding of drug safety throughout the therapeutic life cycle [9,17,24,57,62].

The convergence of receptor pharmacology, pharmacodynamics, pharmacokinetics, pharmacotherapeutics, pharmacogenomics, TDM, evidence-based medicine, and precision medicine thus represents a defining characteristic of contemporary drug development. Each discipline addresses a different dimension of therapeutic optimization, but their greatest value emerges when they are integrated into a coherent translational framework. Molecular pharmacology identifies mechanisms and therapeutic targets; structural and computational approaches facilitate ligand discovery and optimization; pharmacodynamics defines exposure–response relationships; pharmacokinetics determines drug disposition; pharmacotherapeutics translates these properties into clinical use; pharmacogenomics explains interindividual variability; TDM assists individualized dosing; evidence-based medicine establishes clinical effectiveness and safety; and precision medicine seeks to align treatment with the biological characteristics of individual patients.

Accordingly, modern receptor pharmacology should be regarded as a foundational component of an increasingly predictive, quantitative, and individualized discipline of therapeutic science. The future of drug searching will depend on the ability to integrate molecular and structural information with computational modeling, multi-omics data, quantitative pharmacology, clinical evidence, and patient-specific characteristics. Such integration has the potential to improve target validation, reduce late-stage drug-development failure, identify therapeutically meaningful biomarkers, optimize dosing, minimize adverse effects, and accelerate the translation of molecular discoveries into clinically effective interventions. The central challenge is therefore no longer merely to discover molecules capable of interacting with receptors, but to understand how those interactions propagate through biological systems and ultimately influence therapeutic outcomes in individual patients. This integrated perspective provides the conceptual foundation for a modern pharmacological paradigm in which receptor

mechanisms, drug disposition, clinical evidence, genetic variability, and precision therapeutics are considered interconnected components of rational and evidence-based drug development [37,45,56,68,74].

Results and Discussion

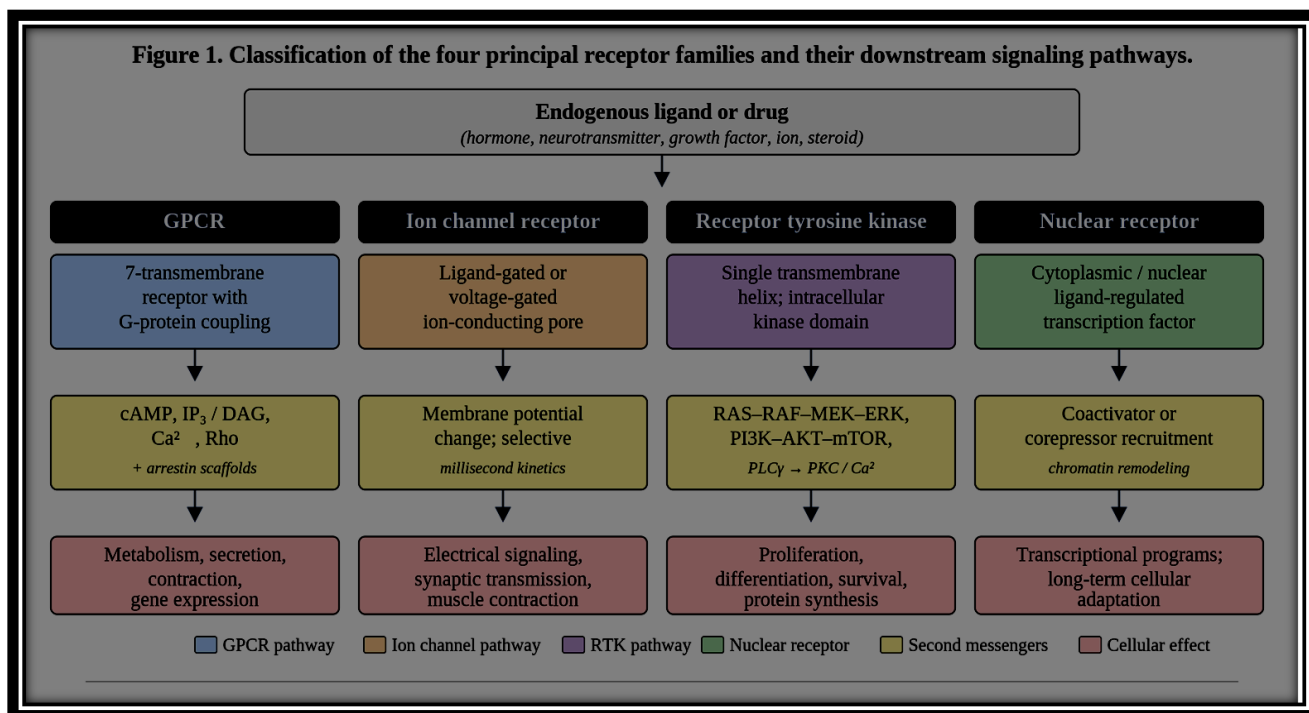
Receptor Pharmacology and Drug Discovery

Receptor pharmacology examines how chemical signals interact with cellular receptors to produce biological responses. Receptors are specialized macromolecules, usually proteins that recognize endogenous mediators such as hormones, neurotransmitters, growth factors, cytokines, and extracellular metabolites. Drugs influence these systems by mimicking endogenous ligands, blocking receptor activation, modifying receptor conformation, changing receptor abundance, or altering downstream signaling. The receptor is therefore not simply an inactive docking site. It is a dynamic molecular machine whose structural states determine the intensity, duration, and direction of cellular responses [1-2].

The classical concept of receptor pharmacology was developed from the observation that drug effects depend on concentration and that structurally related compounds may produce different levels of response. Occupancy theory proposed that biological activity increases as receptors become occupied, whereas later models incorporated receptor efficacy, spare receptors, constitutive activity, and multiple receptor conformations. These developments established the distinction between affinity and efficacy. Affinity describes the tendency of a ligand to bind to a receptor, while efficacy describes its ability to stabilize an active receptor state and initiate signaling [3-4].

Agonists activate receptors, antagonists prevent activation, inverse agonists reduce constitutive receptor activity, and partial agonists activate receptors without producing the maximal response of a full agonist. Modern pharmacology has expanded this classification to include allosteric modulators, bitopic ligands, biased agonists, and molecular glues. These categories reflect the structural complexity of receptor signaling and the increasing ability of drug discovery programs to target specific receptor states or signaling pathways [5-7].

Drug discovery begins with a therapeutic hypothesis. Researchers identify a disease-associated biological process, select a potential molecular target, determine whether the target is causally related to disease, and search for chemical or biological agents that modify its function. Successful discovery requires the integration of molecular pharmacology, structural biology,



medicinal chemistry, computational chemistry, cell biology, pharmacokinetics, toxicology, and clinical science. The most effective programs do not merely search for compounds that bind a protein. They seek compounds that produce a useful biological effect with acceptable selectivity, exposure, safety, and durability (Fig.1).

Figure 1. Receptor-mediated signal transduction. An extracellular ligand and an allosteric modulator interact with a transmembrane receptor, initiating G-protein/effector coupling, second-messenger generation, kinase signaling, feedback regulation, and downstream cellular responses.

Receptor Theory, Affinity, Efficacy, and Signal Amplification

The interaction between a drug and receptor is often represented by a reversible equilibrium: $D + R \rightleftharpoons DR$. The equilibrium dissociation constant, K_d , expresses the concentration of drug required to occupy half of the available receptors under defined conditions. A lower K_d indicates higher binding affinity. In functional assays, however, the concentration producing half-maximal effect is often expressed as EC_{50} for agonists or IC_{50} for inhibitors. These parameters are not identical to K_d because receptor reserve, signal amplification, ligand depletion, assay duration, and coupling efficiency can influence functional potency [8-10].

The operational model of agonism introduced efficacy as a property that depends on both the ligand and the receptor system. A full agonist has sufficient efficacy to produce the maximum response in a particular preparation, whereas a partial agonist produces a lower maximum response even when all receptors are occupied. The same ligand may behave as a full agonist in a system with strong receptor-effector coupling and as a partial agonist in a system with weak

coupling. Thus, pharmacological activity is a property of the ligand–receptor–cellular context rather than of the ligand alone [11-13].

Receptor reserve occurs when a maximal response can be generated without occupation of all receptors. This phenomenon results from amplification between receptor activation and the final measurable response. It is important clinically because irreversible receptor loss may not reduce drug efficacy until the reserve is substantially depleted. Conversely, antagonist potency can appear higher in tissues with receptor reserve because small levels of receptor blockade may have little effect on the maximum response [14-15].

Constitutive receptor activity refers to signaling in the absence of an added agonist. Receptors with spontaneous activity may be inhibited by inverse agonists, whereas neutral antagonists prevent agonist binding without changing basal activity. Desensitization occurs when continued stimulation produces a declining response. Mechanisms include receptor phosphorylation, arrestin recruitment, uncoupling from intracellular effectors, internalization, degradation, and transcriptional adaptation. Understanding these processes is essential for predicting tolerance, withdrawal, rebound phenomena, and differences between acute and chronic drug administration [16-18].

G Protein-Coupled Receptors

G protein-coupled receptors, or GPCRs, constitute one of the largest families of human signaling proteins and are targets for a substantial proportion of approved medicines. They generally contain seven transmembrane alpha-helices connected by extracellular and intracellular loops. GPCRs respond to neurotransmitters, hormones, lipids, peptides, nucleotides, ions, odorants, and sensory stimuli [20].

Ligand binding changes the relative orientation of transmembrane helices, particularly within the intracellular receptor cavity. The activated receptor promotes exchange of GDP for GTP on the alpha subunit of a heterotrimeric G protein. G alpha-GTP and G beta-gamma then regulate downstream enzymes and ion channels. Gs stimulates adenylyl cyclase and increases cyclic AMP, Gi inhibits adenylyl cyclase, Gq activates phospholipase C beta, and G12/13 regulates Rho-family signaling [21].

The cyclic AMP pathway activates protein kinase A and exchange proteins directly activated by cyclic AMP. The phospholipase C pathway generates inositol trisphosphate and diacylglycerol. Inositol trisphosphate releases calcium from intracellular stores, while diacylglycerol activates protein kinase C. These pathways regulate ion conductance, metabolism, contraction, secretion, gene expression, and cell survival.

After activation, GPCR kinases phosphorylate intracellular receptor sites. Arrestins bind to the phosphorylated receptor, terminate interaction with G proteins, and promote receptor internalization through clathrin-coated pits. Arrestins may also scaffold extracellular signal-regulated kinase, c-Jun N-terminal kinase, and other pathways. High-resolution structures have demonstrated that GPCRs are flexible proteins capable of adopting multiple conformations. Agonists, antagonists, and allosteric ligands stabilize different ensembles of conformations, transforming drug discovery into a search for ligands that control defined receptor states [22-23].

Ionotropic and Voltage-Gated Ion Channel Receptors

Ion channels regulate movement of ions across biological membranes. Ligand-gated ion channels include nicotinic acetylcholine, GABA-A, glycine, 5-HT₃, NMDA, AMPA, and kainate receptors. These receptors open or close rapidly after ligand binding, often within milliseconds. Their architecture generally contains multiple subunits surrounding a central pore. Ligand binding shifts the receptor from a closed state to an open state, allowing selective ion flux. Continued exposure can produce desensitization, in which the receptor becomes nonconducting despite continued ligand occupancy [24-26].

The direction and magnitude of current depend on ion selectivity and the electrochemical gradient. Cation-permeable channels may depolarize membranes, whereas chloride-permeable channels often stabilize neurons. NMDA receptors require ligand binding and membrane depolarization to remove magnesium block from the pore, allowing them to function as coincidence detectors in synaptic plasticity.

Voltage-gated sodium, calcium, and potassium channels contain voltage-sensing domains and pore-forming regions. Depolarization moves positively charged residues within the voltage sensor, initiating conformational changes that open the pore. Sodium channel inactivation limits action-potential duration, potassium channels restore membrane potential, and calcium channels couple electrical activity to secretion and contraction [28-30].

Drugs may bind extracellular ligand sites, pores, voltage-sensor regions, or allosteric sites. Local anesthetics block voltage-gated sodium channels preferentially in open or inactivated states, producing use-dependent inhibition. Calcium-channel blockers reduce vascular contraction or cardiac conduction. The rapid kinetics and tissue-specific subunit composition of ion channels provide opportunities for selective therapy but require functional assays that measure opening, closing, conductance, inactivation, and recovery under physiologically relevant conditions.

Nuclear Receptors and Intracellular Signal Control

Nuclear receptors are ligand-regulated transcription factors that translate chemical signals into changes in gene expression. Their ligands include steroid hormones, thyroid hormones, retinoids, vitamin D metabolites, bile acids, fatty acids, and synthetic endocrine compounds. Most nuclear receptors contain an N-terminal transcriptional activation domain, a central DNA-binding domain with zinc-finger motifs, a hinge region, and a C-terminal ligand-binding domain. The DNA-binding domain recognizes hormone-response elements, while the ligand-binding domain recruits coactivators or corepressors [31-33].

In the absence of ligand, some nuclear receptors associate with corepressor complexes that promote chromatin condensation and transcriptional repression. Agonist binding changes the conformation of the ligand-binding domain and creates a surface that recruits coactivators. These proteins may possess histone acetyltransferase activity or recruit chromatin-remodeling complexes.

Selective receptor modulation is possible because receptor actions depend on ligand structure, response-element sequence, cell type, cofactor abundance, chromatin context, and post-translational modification. Selective estrogen receptor modulators illustrate this principle: a compound may act as an antagonist in breast tissue but as a partial agonist in bone because the balance of coactivators and corepressors differs between tissues [35-36]. Nuclear receptors also participate in rapid nontranscriptional signaling through cytoplasmic and membrane-associated complexes.

Drug discovery programs combine ligand-binding assays, transcriptional reporters, structural biology, genome-wide expression analysis, and chromatin profiling. Important risks include endocrine disruption, tissue accumulation, delayed toxicity, and long-lasting changes in gene networks (Fig. 2).

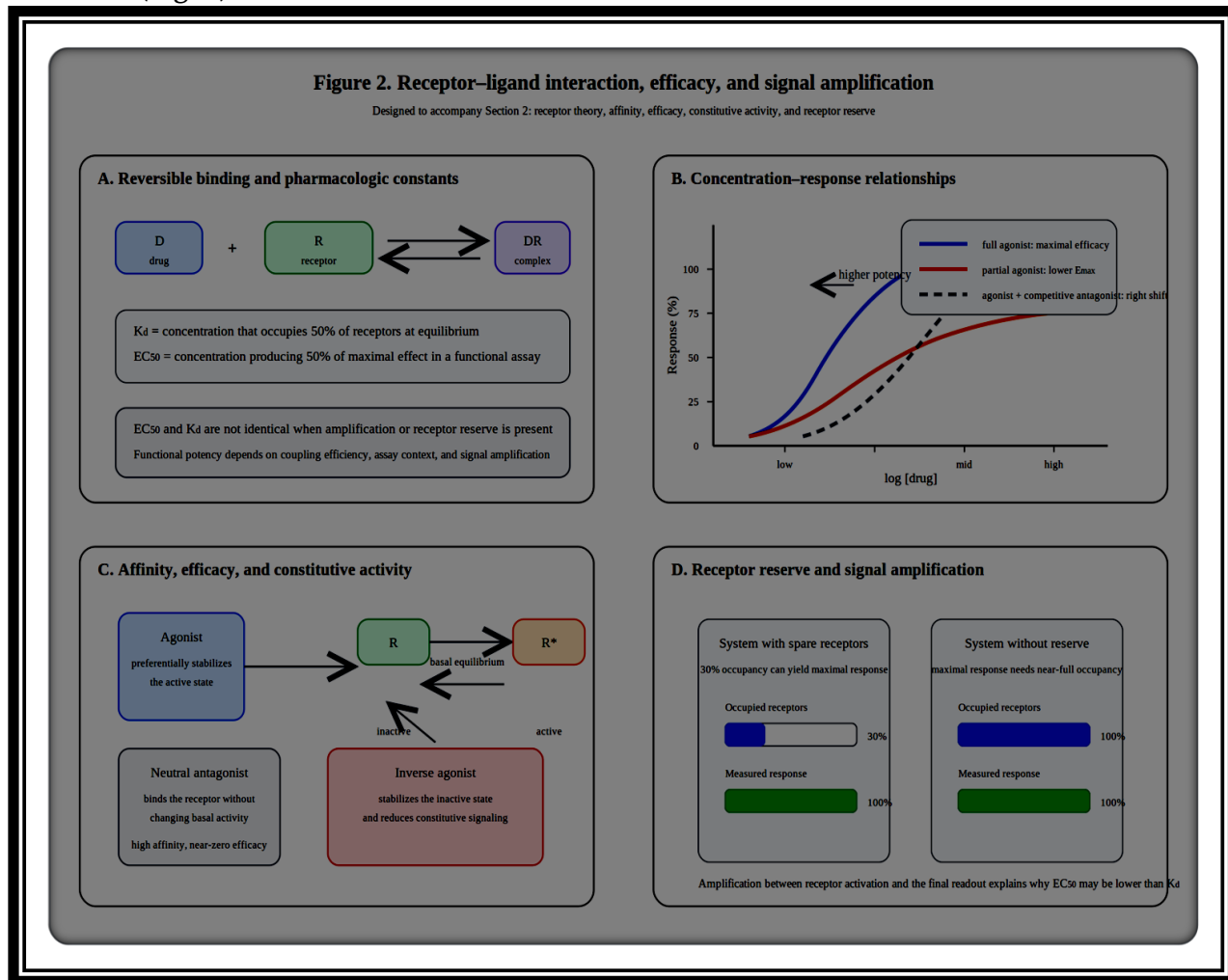


Figure 2. Receptor–ligand interaction, efficacy, and signal amplification.

Panel A shows reversible drug–receptor binding and the distinction between equilibrium affinity (K_d) and functional potency (EC_{50}). Panel B compares concentration–response behavior of a full agonist, a partial agonist, and agonist response in the presence of a competitive antagonist. Panel C summarizes how ligands differ in efficacy by stabilizing inactive or active receptor states, including agonists, neutral antagonists, and inverse agonists. Panel D illustrates **receptor reserve**, where maximal response can occur at submaximal receptor occupancy because of downstream signal amplification.

Receptor Tyrosine Kinases and Growth-Factor Signaling

Receptor tyrosine kinases are transmembrane receptors that regulate growth, differentiation, metabolism, migration, and survival. The family includes receptors for epidermal growth factor, insulin, platelet-derived growth factor, vascular endothelial growth factor, fibroblast growth factor, and nerve growth factor. RTKs generally possess an extracellular ligand-binding domain, a single transmembrane helix, and an intracellular kinase domain [37–39].

Ligand binding promotes receptor dimerization or rearrangement of pre-existing receptor dimers. Intracellular kinase domains phosphorylate tyrosine residues on one another. These

phosphotyrosines recruit adaptor proteins and enzymes containing Src homology 2 or phosphotyrosine-binding domains.

The Ras–RAF–MEK–ERK pathway regulates proliferation and differentiation. The phosphatidylinositol-3-kinase–AKT–mammalian target of rapamycin pathway controls survival, growth, metabolism, and protein synthesis. Phospholipase C gamma generates diacylglycerol and inositol trisphosphate, linking RTKs to protein kinase C and calcium signaling. Signal transducers and activators of transcription may also be recruited directly or activated indirectly [15].

Aberrant RTK activation may result from gene amplification, activating mutations, chromosomal rearrangements, ligand overproduction, or loss of negative regulators. Small-molecule kinase inhibitors often bind the ATP site, while antibodies may block ligand binding, prevent dimerization, promote receptor degradation, or recruit immune effector mechanisms. Resistance can emerge through secondary mutations, bypass pathways, increased receptor expression, altered drug metabolism, or phenotypic changes in tumor cells. Molecular profiling and pharmacodynamic biomarkers are therefore essential [40-43].

Intracellular Signal Transduction and Network Pharmacology

Receptors operate within interconnected signaling networks containing feedback loops, redundant pathways, scaffold proteins, organelle-specific signaling domains, and transcriptional programs. The same receptor can produce different responses depending on cell type, receptor density, interacting proteins, and the duration or location of signaling.

Second messengers such as cyclic AMP, calcium, diacylglycerol, inositol trisphosphate, cyclic GMP, nitric oxide, and phosphoinositides distribute receptor information inside cells. Their concentrations are controlled by synthesis, degradation, buffering, sequestration, and transport. Localized signaling is particularly important because a second-messenger signal near the plasma membrane may regulate ion channels while a nuclear signal may alter transcription [16].

Protein kinases and phosphatases create reversible phosphorylation networks. Scaffold proteins organize enzymes and substrates into functional complexes. Cross-talk occurs when one receptor regulates another pathway. GPCRs can transactivate RTKs, RTKs can influence GPCR phosphorylation, and cytokine receptors can modify nuclear receptor activity [44-46].

Network pharmacology approaches drug action as a systems-level intervention. A drug may bind one principal target but influence a broader network through pathway effects, transcriptional adaptation, metabolite changes, and cell–cell communication. Quantitative pharmacology connects molecular interactions with clinical outcomes through concentration–response relationships, time-course analysis, receptor occupancy, and pathway biomarkers [17]. Maximal inhibition is not always desirable; partial or intermittent modulation may avoid feedback activation and toxicity.

Allosteric Modulation and Biased Signaling

Allosteric ligands bind to receptor sites distinct from the endogenous ligand-binding site. Positive allosteric modulators enhance receptor responses, negative allosteric modulators reduce them, and silent allosteric modulators occupy the site without changing receptor function. Allosteric sites are often less conserved than orthosteric sites, which can improve subtype selectivity. Modulators may also preserve the timing and spatial distribution of endogenous signaling [3].

Biased signaling occurs when different ligands stabilize receptor conformations that preferentially activate distinct downstream pathways. At a GPCR, one ligand may favor G protein signaling while another favors arrestin recruitment. Bias can also occur among G protein subtypes or downstream kinase pathways [18]. The potential value is the possibility of separating beneficial effects from adverse effects.

Demonstrating genuine bias requires multiple ligands, pathways, concentration–response curves, reference agonists, and operational models. Apparent bias may instead result from differences in receptor expression, ligand depletion, pathway amplification, assay sensitivity, or signaling kinetics. A ligand may appear biased at one time point but not another because phosphorylation, desensitization, or internalization changes the system [47–50].

Allosteric modulation and biased agonism can be combined. An allosteric ligand may stabilize a receptor conformation that changes the signaling preference of an orthosteric agonist. This creates opportunities for precision pharmacology but increases the need for characterization across receptor states, pathways, tissues, and exposure conditions.

Target Identification and Target Validation

Target identification selects a biological molecule whose modulation may alter disease. Targets may be discovered through human genetics, disease-associated mutations, transcriptomics, proteomics, metabolomics, pathogen biology, phenotypic screening, clinical observations, or analysis of existing medicines. A target is especially attractive when human genetic evidence supports a causal relationship with disease risk [19].

Target validation determines whether changing the target produces a reproducible and therapeutically relevant phenotype. Genetic approaches include gene knockout, knockdown, CRISPR interference, CRISPR activation, base editing, and rescue experiments. Pharmacological approaches use selective ligands, antibodies, degraders, or chemical probes. Concordance between genetic and pharmacological results strengthens confidence, although drugs may produce partial, transient, tissue-specific, or state-dependent modulation.

A validated target should be associated with disease biology, produce meaningful effects in relevant models, be accessible to a drug or biologic, and possess a measurable pharmacodynamic biomarker. Target validation is weakened by inadequate models, overexpression systems, immortalized cells, and species differences in receptor pharmacology [51–53].

Chemical probes should be selective, potent, cell-active, and well characterized. Orthogonal probes with different structures provide stronger evidence than one compound. Human evidence from biomarkers, natural experiments, patient-derived cells, clinical genetics, and early pharmacodynamic data can confirm or challenge the original hypothesis. Failed trials may reflect inadequate exposure, inappropriate patient selection, insufficient target modulation, poor disease timing, or unsuitable endpoints rather than an invalid target [20].

High-Throughput and Phenotypic Screening

High-throughput screening evaluates large compound collections in automated biochemical, cellular, or binding assays. Technologies include fluorescence polarization, luminescence, absorbance, radioligand binding, surface plasmon resonance, thermal-shift assays, mass spectrometry, and cell-based reporters [21].

A successful campaign depends on assay quality. Important parameters include signal-to-background ratio, signal-to-noise ratio, reproducibility, coefficient of variation, plate uniformity, solvent tolerance, and the Z-prime factor. Screening assays must minimize aggregation, fluorescence interference, redox activity, nonspecific membrane disruption, and other forms of assay interference.

Primary hits require concentration–response confirmation using fresh samples. Counterscreens identify nonspecific or promiscuous compounds, and orthogonal assays measure the same mechanism through a different physical principle. Cellular assays establish cell entry and pathway modulation.

Phenotypic screening begins with a cellular or organismal phenotype rather than a predetermined target. It can reveal unexpected mechanisms and compounds that act through multiple targets, but target deconvolution may require resistance selection, affinity methods, proteomics, genetic screening, or chemical biology [22]. Target-based and phenotypic screening are complementary. A good hit has a credible mechanism, acceptable stability, reproducible activity, suitable physicochemical properties, and a scaffold that can be optimized.

Structure-Based and Fragment-Based Drug Discovery

Structure-based drug discovery uses three-dimensional information about a target to guide ligand design. Structures may be obtained by X-ray crystallography, nuclear magnetic resonance, cryo-electron microscopy, homology modeling, or computational prediction. Structural data reveal binding pockets, hydrogen-bonding networks, hydrophobic cavities, water molecules, and conformational states [23].

Virtual screening ranks compounds according to predicted binding modes and interaction energies. Experimental testing determines whether selected compounds bind and modulate the target. Fragment-based drug discovery begins with small compounds that bind weakly but efficiently. Fragment hits are detected by nuclear magnetic resonance, surface plasmon resonance, thermal-shift analysis, X-ray crystallography, or biophysical mass spectrometry [24]. Fragments are developed through growing, linking, or merging. Growing adds groups that extend into adjacent pockets. Linking connects fragments that bind nearby sites. Merging combines favorable elements from related fragments. Ligand efficiency and lipophilic ligand efficiency help determine whether potency is being improved through productive interactions rather than increased hydrophobicity.

Modern structural approaches increasingly capture multiple receptor states, which is important for GPCRs, ion channels, kinases, and other proteins with large conformational changes. Docking scores may be inaccurate, protein structures may represent nonphysiological states, and water-mediated interactions can be difficult to predict. Successful programs combine computation with biochemical testing, cellular pharmacology, medicinal chemistry, and repeated structural determination [54-57].

Computational Drug Discovery and Artificial Intelligence

Computational methods support molecular property prediction, docking, molecular dynamics, quantitative structure–activity relationships, pharmacophore modeling, synthesis planning, and toxicity assessment [25]. Virtual screening can reduce the number of compounds requiring experimental testing. Structure-based methods use protein structures, while ligand-based methods search for molecules similar to known active compounds.

Artificial intelligence and machine learning are used for de novo design, target identification, patient stratification, and analysis of biological data. Deep-learning models learn relationships among molecular graphs, protein sequences, structures, assay conditions, and phenotypes. Generative models can propose molecules optimized for potency, selectivity, solubility, permeability, metabolic stability, and synthetic accessibility [26].

Protein-structure prediction has expanded the number of targets that can be approached structurally. However, predicted structures may be less reliable for disordered regions, alternative conformations, complexes, ligand-induced states, and membrane proteins. A major limitation of machine learning is data quality. Assay measurements may differ between laboratories, inactive results may be underreported, and models may learn experimental artifacts.

Active learning allows models to select experiments that provide the greatest expected information. Results are then used to update the model and refine compound selection. Artificial intelligence is most useful when integrated with expert medicinal chemistry and pharmacology. It accelerates hypothesis generation but does not eliminate the need to establish mechanism, selectivity, target engagement, efficacy, manufacturability, and clinical benefit.

Medicinal Chemistry, Selectivity, and Pharmacokinetics

Medicinal chemistry transforms a hit into a candidate with a balanced profile. Chemists modify substituents, stereochemistry, ring systems, linkers, heteroatoms, and ionization properties to determine which features control potency and selectivity.

Absorption depends on solubility, permeability, formulation, and intestinal stability. Distribution is influenced by lipophilicity, plasma protein binding, tissue binding, transporter activity, and access to biological barriers. Metabolism includes oxidation, reduction, hydrolysis, conjugation, and sometimes bioactivation. Elimination occurs through renal, biliary, pulmonary, and other routes.

A drug may be potent in a biochemical assay but ineffective in vivo because it is poorly absorbed, rapidly metabolized, highly protein bound, or unable to reach the target compartment. Selectivity may be achieved through differences in binding-site residues, receptor conformations, tissue expression, signaling context, or exposure. Allosteric sites, covalent pockets, protein-protein interfaces, and tissue-restricted delivery can provide alternative strategies [61-67].

Safety liabilities include off-target receptor binding, ion-channel inhibition, mitochondrial toxicity, reactive metabolites, immune activation, genotoxicity, and disruption of physiological signaling. Inhibition of the human ether-à-go-go-related gene potassium channel can prolong cardiac repolarization and increase arrhythmia risk [27]. Multiparameter optimization is therefore necessary. The final candidate is not necessarily the most potent compound but the molecule with the best relationship between target modulation, exposure, therapeutic effect, and risk.

Resistance, Tolerance, and Translational Challenges

Drug resistance is the loss of therapeutic response despite continued treatment. In infectious diseases, resistance may result from mutations in the target, increased drug efflux, enzymatic inactivation, or metabolic changes. In cancer, resistant cells may acquire secondary target

mutations, activate bypass signaling, amplify alternative receptors, alter apoptotic programs, or undergo phenotypic transition [28].

Receptor adaptation can also produce pharmacological tolerance. Repeated agonist exposure may cause receptor phosphorylation, arrestin recruitment, internalization, degradation, and reduced gene expression. Chronic antagonist treatment may increase receptor abundance or signaling capacity, producing rebound effects when therapy stops.

Translational failure may occur because preclinical models do not reproduce human disease. Receptor expression and ligand pharmacology can differ between species. Drug exposure may be inadequate at the human target even when plasma concentrations appear sufficient. Biomarkers may measure downstream change without confirming target engagement.

Clinical trials should incorporate receptor occupancy, pharmacodynamic effects, biomarker development, and patient selection. Combination therapy may improve efficacy by blocking parallel pathways or preventing resistance but can increase toxicity and pharmacokinetic interactions. Real-world treatment is also affected by adherence, formulation, route of administration, comorbidities, age, organ function, genetic variation, and concomitant drugs [58-60].

The translational process is strongest when the same target, pathway, and pharmacodynamic marker can be traced from molecular assays through animal studies and clinical trials. This continuity helps distinguish failure of the molecule from failure of the biological hypothesis (Fig 3).

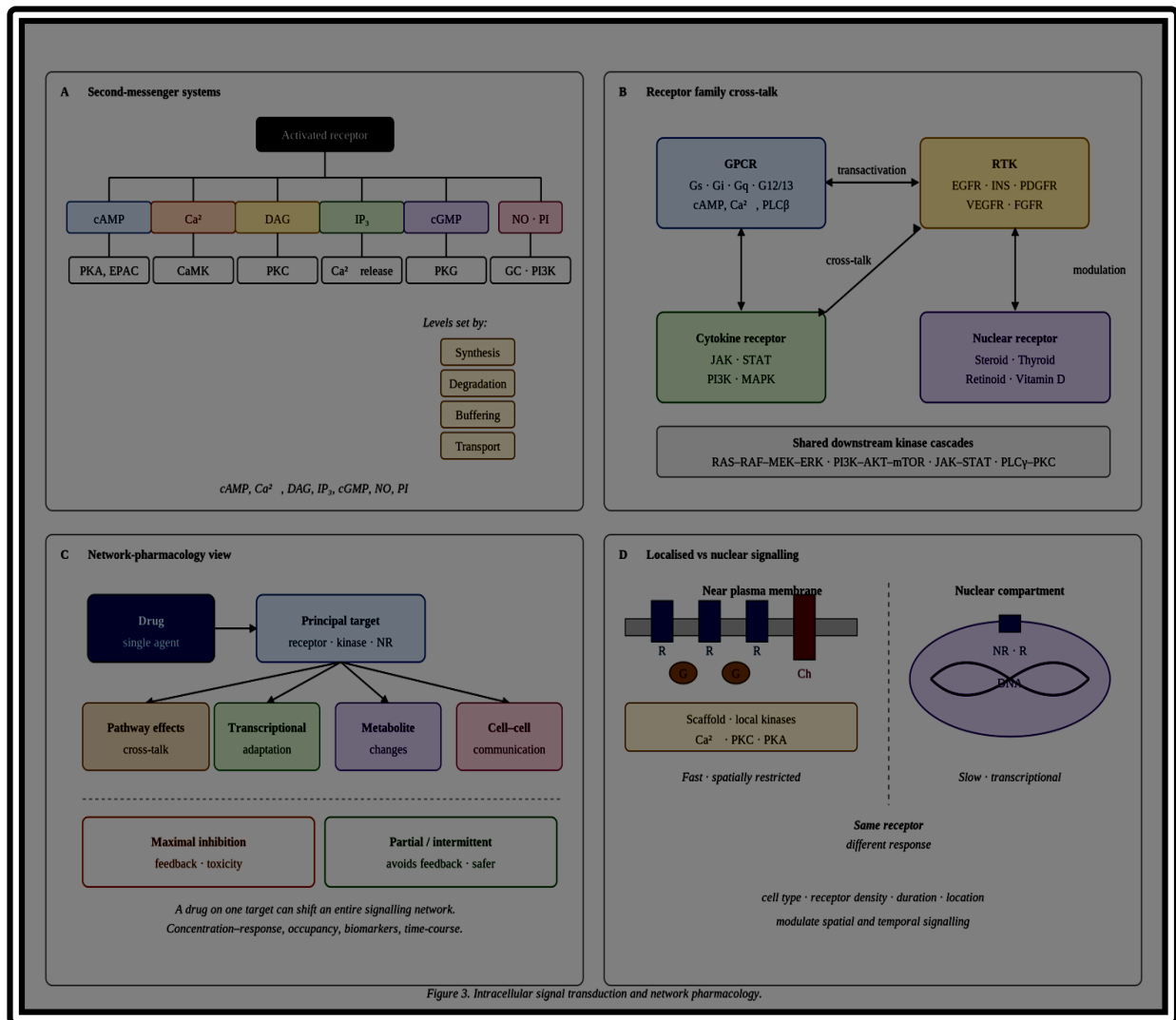


Figure 3. Intracellular signal transduction and network pharmacology.

(A) Schematic of the principal receptor-generated second messengers. The activated receptor (grey) is coupled to six downstream effectors: cAMP (activating PKA/EPAC); Ca^{2+} (activating CaMK); diacylglycerol (DAG, activating PKC); inositol 1,4,5-trisphosphate (IP_3 , mobilising intracellular Ca^{2+}); cyclic GMP (cGMP, activating PKG); and nitric oxide/phosphoinositide-derived signals (activating guanylyl cyclase and PI3K). Steady-state messenger concentrations are governed by synthesis, degradation, buffering/sequestration, and transport (right panel).

(B) Receptor-family cross-talk. Bidirectional arrows depict transactivation between GPCRs and receptor tyrosine kinases (RTKs), GPCR-cytokine-receptor cross-talk, and RTK-nuclear-receptor modulation, with convergence on shared downstream kinase cascades (RAS-RAF-MEK-ERK; PI3K-AKT-mTOR; JAK-STAT; PLC γ -PKC).

(C) Network-pharmacology model. A single drug acting on a principal target (receptor, kinase, or nuclear receptor) redistributes the pharmacological response across pathway effects, transcriptional adaptation, metabolite changes, and cell-cell communication. The lower comparison contrasts maximal inhibition (associated with feedback activation and toxicity) with partial or intermittent modulation.

(D) Compartmentalised signalling from the same receptor. Left: near the plasma membrane, receptors couple to G proteins, ion channels, scaffolds, and local kinases (Ca^{2+} , PKC, PKA),

producing fast, spatially restricted responses. Right: in the nuclear compartment, the same receptor or a translocated signalling complex engages DNA, producing slow transcriptional responses. Modifying factors include cell type, receptor density, signal duration, and subcellular localisation.

Future Directions

Future drug discovery will increasingly focus on controlling receptor states, signaling duration, cellular location, and tissue specificity. Rather than treating receptors as simple on–off switches, researchers are developing models in which receptors occupy ensembles of conformations. Drugs may stabilize one state, promote a particular effector interaction, or alter transitions between active and inactive forms [68-71].

Cryo-electron microscopy, time-resolved structural methods, single-molecule studies, and advanced spectroscopy are improving understanding of receptor complexes. These techniques can reveal interactions with G proteins, arrestins, ion channels, lipids, scaffolds, and intracellular membranes [29]. Covalent and reversible-covalent drugs, protein degraders, molecular glues, RNA-targeting drugs, and gene-editing approaches are expanding the range of biological mechanisms that can be therapeutically controlled.

Artificial intelligence will become increasingly integrated with automated experimentation. Robotic platforms can synthesize compounds, perform assays, analyze results, and update design models. Precision pharmacology will combine receptor biology with patient genetics, spatial transcriptomics, proteomics, imaging, and real-world data. This may identify patients whose disease depends on a particular receptor state or signaling network.

The central challenge remains biological validation. A compound can be chemically elegant, structurally characterized, and computationally optimized yet fail if the target is not causally important, the disease stage is inappropriate, or the therapeutic window is too narrow. Future success will depend on integrating molecular mechanisms with human evidence from the earliest stages of discovery [72-75].

Receptor Pharmacology in Personalized Medicine and Biomarker-Guided Therapy

Personalized medicine applies receptor pharmacology to match patients with therapies based on the molecular features of disease. Inter-individual variation in receptor expression, receptor sequence, downstream coupling efficiency, and compensatory signaling shapes how a patient will respond to a given drug. Germline and somatic alterations can change ligand affinity, constitutive receptor activity, desensitization kinetics, internalization rates, and the spectrum of biased outputs that a single ligand produces. Because drug response is essentially the product of the ligand, the receptor system, and the surrounding signaling network, understanding patient biology is necessary for rational drug selection. Pharmacogenomics studies how genetic variation influences drug response. Polymorphisms in receptors and downstream signaling proteins can shift concentration-response curves, alter clearance pathways, or change the balance of efficacy and adverse effects. Examples include well-characterized variants in drug-metabolizing enzymes that modify systemic exposure, as well as variants in drug targets themselves that alter binding pocket geometry or coupling preference. Haplotype-level analysis is often more informative than single-variant testing because receptor phenotypes can depend on combinations of polymorphisms acting together. Population-specific reference databases guide interpretation and reduce ambiguity in clinical reporting. Receptor-driven biomarker

strategies stratify patients for clinical trials. Receptor occupancy can be measured with positron emission tomography ligands that bind the same site as the therapeutic agent. Downstream pharmacodynamic biomarkers can be measured in blood, in skin biopsies, in circulating tumor cells, or in patient-derived tissue samples. Genomic and transcriptomic profiles can be used to infer pathway activity, while proteomic and phosphoproteomic assays reveal post-translational events that integrate signaling across many receptor classes. Biomarker selection must be biologically grounded, technically reproducible, and economically feasible for the health-care setting in which the drug will be used. Companion diagnostic tests link a drug to a measurable molecular feature. These tests may rely on polymerase chain reaction, immunohistochemistry, fluorescence in situ hybridization, next-generation sequencing, or ligand-binding assays. Test development must occur in parallel with drug development so that clinical decisions are supported at the time of regulatory approval. Analytical validation confirms assay reliability under defined conditions. Clinical validation confirms the relationship between biomarker status and clinical outcome. Clinical utility confirms that biomarker-guided treatment improves patient outcomes relative to standard approaches. All three layers should be documented to regulatory standards and revisited whenever new evidence emerges. Receptor pharmacology therefore becomes the bridge between molecular biology and individualized therapy, giving clinicians a mechanistic framework for choosing among available drugs.

Emerging Modalities: PROTACs, Molecular Glues, and Covalent Inhibitors

Targeted protein degradation has expanded pharmacology beyond classical inhibition. Proteolysis-targeting chimeras are bifunctional molecules that present a target-binding element on one end and a ligand for an E3 ubiquitin ligase on the other end. The induced proximity brings the target into the geometry required for ubiquitination and subsequent proteasomal recognition. Once polyubiquitin chains are deposited, the target is degraded by the 26S proteasome. A degrader removes the protein entirely rather than blocking a single functional surface, which can be useful when biology depends on scaffolding interactions, on protein-protein interfaces, or on non-catalytic roles of the target. Molecular glues are small molecules that stabilize a natural interaction between a target and a ligase, leading to degradation without requiring a bifunctional linker. These molecules have been discovered serendipitously through cellular screens and have also been designed using structural insight into ligase-substrate pockets. Both PROTACs and glues widen the target space beyond what is druggable by classical inhibitors, making previously intractable proteins accessible to medicinal chemistry. Degradation is catalytic. A single degrader molecule can promote multiple rounds of target turnover, which distinguishes this modality from stoichiometric inhibitors and may permit lower exposures for a given pharmacodynamic effect. Pharmacokinetic and absorption profiles are more challenging for bifunctional molecules because their physicochemical properties differ from typical oral drugs. Lipophilicity, molecular weight, and rotatable-bond counts often exceed the rule-of-five ceiling, so formulation strategies become essential. Covalent inhibitors form a stable bond between the drug and a target residue, often a nucleophilic cysteine, serine, lysine, or threonine. Covalent engagement can yield prolonged pharmacodynamics, increased selectivity against closely related paralogs, and the ability to engage shallow binding sites that are difficult to inhibit with reversible ligands. Irreversible covalent inhibitors commit the target fully. Reversible covalent inhibitors combine a degree of selectivity with reduced risk of long-lived protein adducts. Designing covalent inhibitors requires careful tuning of electrophile

reactivity, geometric orientation relative to the nucleophile, and the kinetics of bond formation under physiological conditions. Glutathione, cysteine residues on off-target proteins, and other biological thiols compete for the electrophile, so the warhead must be matched to the cellular context. Covalent pharmacology also creates regulatory considerations related to long-lived metabolites, hapten formation, and the possibility of off-target modification. The pharmacology of covalent inhibitors must therefore be characterized at the level of the intact protein, the modified residue, and the downstream signaling consequence. Together, degraders, molecular glues, and covalent ligands demonstrate that receptor pharmacology keeps evolving alongside chemistry, and that the principles of selectivity, efficacy, and safety described elsewhere in this review remain essential when new modalities are introduced.

Integration of Receptor Pharmacology with Systems Biology and Translational Pipelines

Modern pharmacology views receptors as nodes in larger signaling networks rather than as isolated switches. Systems biology provides quantitative frameworks that connect receptor engagement to cellular phenotypes and, ultimately, to clinical outcomes. Ordinary differential equation models, constraint-based metabolic models, and logic-based signaling models describe how a perturbation of a single receptor propagates through the cell, and how feedback, redundancy, and crosstalk shape the eventual biological response. Each modeling framework carries assumptions about reversibility, stoichiometry, and spatial compartmentalization, and the choice of framework should be matched to the biological question under study rather than applied uniformly. Multi-omics data refine these models and turn them into patient-relevant predictive tools. Transcriptomics captures downstream transcriptional changes, proteomics and phosphoproteomics capture post-translational signaling, and metabolomics captures biochemical consequences that reflect integrated cellular state. Integration of these layers allows inference of which receptor pathways are active in a given sample and how those pathways change with treatment, with resistance, or with disease progression. Public repositories, standardized ontologies, and reproducible analysis pipelines are essential foundations for this work because they allow independent verification of results across laboratories. Translational pipelines benefit from continuous feedback between clinical trial phases. Phase I data on receptor occupancy, pharmacokinetics, and pharmacodynamics should inform dose selection for phase II. Phase II biomarker and response data should refine dose, schedule, and patient selection for phase III. Centralized data warehouses, digital twins, and standardized electronic case-report forms support that feedback loop and shorten the time between observation and action. Adaptive trial designs, when properly justified, can use early-response data to redirect resources toward the most promising arms without compromising statistical integrity. Patient-derived models, including organoids, induced pluripotent stem cell-derived tissues, and microfluidic tissue chips, reflect human receptor biology more faithfully than immortalized cell lines and may improve the predictive value of preclinical studies. These models are not a replacement for in vivo work, but they can refine hypothesis generation, prioritize candidates before animal studies, and reduce the number of dead-end programs that reach clinical development. CRISPR-based screening clarifies which receptors and downstream effectors control specific phenotypes and provides orthogonal evidence that complements pharmacology. Genome-wide association studies connect natural variation in receptor loci to disease risk, and these loci can nominate targets that are already validated by human genetics. Education and collaboration remain essential. Receptor pharmacology must be taught alongside

structural biology, bioinformatics, and clinical science so that future scientists can navigate the full pipeline from molecule to medicine. When receptor mechanisms, computational methods, and clinical pharmacology are integrated, drug discovery becomes a more predictable and patient-centered discipline, capable of producing safer and more effective therapies for the populations who need them.

References

1. Rang HP, Dale MM, Ritter JM, Flower RJ, Henderson G. Rang and Dale's Pharmacology. 9th ed. London: Elsevier; 2019.
2. Kenakin T. Pharmacology in Drug Discovery and Development: Understanding Drug Response. 2nd ed. London: Academic Press; 2017.
3. Changeux JP, Christopoulos A. Allosteric modulation as a unifying mechanism for receptor function and regulation. *Cell*. 2016;166(5):1084-1102.
4. Black JW, Leff P. Operational models of pharmacological agonism. *Proc R Soc Lond B Biol Sci*. 1983;220(1219):141-162.
5. Stephenson RP. A modification of receptor theory. *Br J Pharmacol Chemother*. 1956;11(4):379-393.
6. Gainetdinov RR, Premont RT, Bohn LM, Lefkowitz RJ, Caron MG. Desensitization of G protein-coupled receptors and neuronal functions. *Annu Rev Neurosci*. 2004;27:107-144.
7. Hauser AS, Attwood MM, Rask-Andersen M, Schiöth HB, Gloriam DE. Trends in GPCR drug discovery: new agents, targets and indications. *Nat Rev Drug Discov*. 2017;16(12):829-842.
8. Pierce KL, Premont RT, Lefkowitz RJ. Seven-transmembrane receptors. *Nat Rev Mol Cell Biol*. 2002;3(9):639-650.
9. Wootten D, Christopoulos A, Marti-Solano M, Babu MM, Sexton PM. Mechanisms of signalling and biased agonism in G protein-coupled receptors. *Nat Rev Mol Cell Biol*. 2018;19(10):638-658.
10. Changeux JP. The nicotinic acetylcholine receptor: a typical allosteric protein. *Cold Spring Harb Symp Quant Biol*. 1986;51 Pt 1:343-353.
11. Catterall WA. Voltage-gated sodium channels at the forefront of neurological research. *J Physiol*. 2012;590(11):2577-2589.
12. Evans RM. The steroid and thyroid hormone receptor superfamily. *Science*. 1988;240(4854):889-895.
13. Mangelsdorf DJ, Thummel C, Beato M, Herrlich P, Schütz G, Umesono K, et al. The nuclear receptor superfamily: the second decade. *Cell*. 1995;83(6):835-839.
14. Lemmon MA, Schlessinger J. Cell signaling by receptor tyrosine kinases. *Cell*. 2010;141(7):1117-1134.
15. Schlessinger J. Cell signaling by receptor tyrosine kinases. *Cell*. 2000;103(2):211-225.
16. Saucerman JJ, Brunton LL. Mechanisms of muscarinic receptor regulation of cardiac function. *Nat Rev Cardiol*. 2016;13(9):549-560.
17. Hopkins AL. Network pharmacology: the next paradigm in drug discovery. *Nat Chem Biol*. 2008;4(11):682-690.
18. Smith JS, Lefkowitz RJ, Rajagopal S. Biased signalling: from simple switches to allosteric microprocessors. *Nat Rev Drug Discov*. 2018;17(4):243-260.
19. Cook D, Brown D, Alexander R, March R, Morgan P, Satterthwaite G, et al. Lessons learned from the fate of AstraZeneca's drug pipeline: a five-dimensional framework. *Nat Rev Drug Discov*. 2014;13(6):419-431.

20. Hughes JP, Rees S, Kalindjian SB, Philpott KL. Principles of early drug discovery. *Br J Pharmacol*. 2011;162(6):1239-1249.
21. Macarron R, Banks MN, Bojanic D, Burns DJ, Cirović DA, Garyantes T, et al. Impact of high-throughput screening in biomedical research. *Nat Rev Drug Discov*. 2011;10(3):188-195.
22. Moffat JG, Vincent F, Lee JA, Eder J, Prunotto M. Opportunities and challenges in phenotypic drug discovery: an industry perspective. *Nat Rev Drug Discov*. 2017;16(8):531-543.
23. Blundell TL, Jhoti H, Abell C. High-throughput crystallography for lead discovery in drug design. *Nat Rev Drug Discov*. 2002;1(1):45-54.
24. Erlanson DA, McDowell RS, O'Brien T. Fragment-based drug discovery. *J Med Chem*. 2004;47(14):3463-3482.
25. Sadybekov AV, Katritch V. Computational approaches streamlining drug discovery. *Nature*. 2023;616(7958):673-685.
26. Vamathevan J, Clark D, Czodrowski P, Dunham I, Ferran E, Lee G, et al. Applications of machine learning in drug discovery and development. *Nat Rev Drug Discov*. 2019;18(6):463-477.
27. Roden DM. Drug-induced prolongation of the QT interval. *N Engl J Med*. 2004;350(10):1013-1022.
28. Holohan C, Van Schaeybroeck S, Longley DB, Johnston PG. Cancer drug resistance: an evolving paradigm. *Nat Rev Cancer*. 2013;13(10):714-726.
29. Cheng Y. Single-particle cryo-EM at crystallographic resolution. *Cell*. 2015;161(3):450-457.
30. Jumper J, Evans R, Pritzel A, Green T, Figurnov M, Ronneberger O, et al. Highly accurate protein structure prediction with AlphaFold. *Nature*. 2021;596(7873):583-589.
31. Sulashvili N, Beglaryan M, Gorgaslidze N, Gabunia L. The manifestation of key issue aspects of features of influence of medications on the living organisms, including humans and their physical environment. *The Caucasus Economic & Social Analysis Journal of Southern Caucasus*. 2024;61(04):37-60.
32. Sulashvili N, Gorgaslidze N, Gabunia L, Alavidze N, Giorgobiani M, Topchiyeva S. The key issue aspects of features of influence of medications on the living organisms, including humans and their physical environment. In: *Proceedings of the Second International Scientific-Practical Conference in Health Innovations & Research: Prognosis, Achievement, and Challenges*. Tallinn, Estonia; 2024 Apr 6-7. p. 29-30.
33. Gorgaslidze N, Sulashvili N, Gabunia L, Topchiyeva S, Kravchenko V, Giorgobiani M, et al. The scientific discussion of key issue aspects of features of influence of medications on the living organisms, including humans and their physical environment. In: *Proceedings of the II International Scientific and Practical Conference "Modern aspects of the achievements of fundamental and applied medical and biological areas of medical and pharmaceutical education and science"*. Kharkiv, Ukraine; 2023 Nov 17. p. 119-141.
34. Sulashvili N, Beglaryan M, Gorgaslidze N, Gabunia L, Alavidze N, Abuladze N, et al. The key issue aspects of features of age-related use of medicines, side effects of drugs and pharmacoeconomic aspects in general. In: *Proceedings of the III International Scientific and Practical Conference "Fundamental and Applied Research in the Field of Pharmaceutical Technology"*. Kharkiv, Ukraine; 2023 Nov 24. p. 43-64.
35. Sulashvili N, Gorgaslidze N, Gabunia L, Beglaryan M, Alavidze N, Abuladze N, et al. The manifestation of features of some key issue aspects of anti-tumor remedy temozolomide use in cancer chemotherapy. In: *Materials of the VII International Scientific and Practical Conference "Medicines for Humans"*. Kharkiv, Ukraine; 2024 Mar 21-22. p. 89-95.

36. Sulashvili N, Gorgaslidze N, Gabunia L, Beglaryan M, Alavidze N, Abuladze N, et al. The manifestation of features of modern problems of pharmacotherapy of human diseases in general. In: Materials of the VII International Scientific and Practical Conference "Medicines for Humans". Kharkiv, Ukraine; 2024 Mar 21-22. p. 30-36.
37. Sulashvili N, Beglaryan M, Gabunia L, Gorgaslidze N, Alavidze N, Abuladze N, et al. The scientific discussion of the manifestation of the topical issues aspects of characteristics of some up-to-date considerations repercussion on patients' dental health care and pharmacotherapy challenges in general. In: Materials of the International Scientific and Practical Conference "Topical Issues of Clinical Pharmacology and Clinical Pharmacy". Kharkiv, Ukraine; 2024 Oct 29-30. p. 230-249.
38. Sulashvili N, Gorgaslidze N, Gabunia L, Beglaryan M, Alavidze N, Abuladze N, et al. The manifestation of key issue aspects of features of treatment of acute periodontitis by using plasma irradiation and plasma flow. In: Materials of the VII International Scientific and Practical Conference "Medicines for Humans". Kharkiv, Ukraine; 2024 Mar 21-22. p. 49-55.
39. Sulashvili N, Gorgaslidze N, Gabunia L, Beglaryan M, Alavidze N, Abuladze N, et al. The scientific discussion of the key issue aspects of the features of pharmacotherapeutic treatment of COVID-19 pandemic before vaccination. Tbilisi State Medical University, Faculty of Public Health; 2021.
40. Sulashvili N, Gorgaslidze N, Beglaryan M, Gabunia L, Alavidze N, Abuladze N, et al. The scientific discussion of characteristics of some key issue aspects of pharmacists' profession, vocational achievements, enhancement, challenges, inclination and perspectives in pharmaceutics and medicine based on the sunlight of social pharmacy at local and global level in general. In: Conference Proceedings of the First International Scientific-Practical Conference in Health Innovations & Research: Prognosis, Achievement and Challenges. Tallinn, Estonia; 2023 Dec 15-16. p. 22-23.
41. Sulashvili N, Gabunia L, Beglaryan M, Gorgaslidze N, Ghambashidze K, Sulashvili M, et al. The peculiarities of pharmacodynamics and pharmacokinetics of some antiarrhythmic medicines. In: Full Text Book Volume - 2 of 11th International European Congress on Scientific Research. Roma, Italy; 2024 Nov 11-13. p. 665-683.
42. Sulashvili N, Gabunia L, Beglaryan M, Gorgaslidze N, Ghambashidze K, Sulashvili M, et al. The scientific talks of manifestation of topical issue aspects of features of pharmacology of the antiarrhythmic drugs in general. In: Materials of the International Scientific and Practical Conference "Topical Issues of Clinical Pharmacology and Clinical Pharmacy". Kharkiv, Ukraine; 2024 Oct 29-30. p. 70-84.
43. Sulashvili N, Gabunia L, Beglaryan M, Gorgaslidze N, Sulashvili M, Patsia L, et al. The scientific talks of features of effects of some antiarrhythmic remedies in general. In: Proceedings of the IV International Scientific and Practical Conference "Fundamental and Applied Research in the Field of Pharmaceutical Technology". Kharkiv, Ukraine; 2024 Oct 25. p. 25-41.
44. Sulashvili N, Gorgaslidze N, Gabunia L, Beglaryan M, Alavidze N, Abuladze N, et al. The manifestation of the key issue aspects of features of treatment of acute periodontitis by using plasma irradiation and plasma flow. In: Materials of the VII International Scientific and Practical Conference "Medicines for Humans". Kharkiv, Ukraine; 2024 Mar 21-22. p. 49-55.
45. Sulashvili N, Gorgaslidze N, Gabunia L, Alavidze N, Giorgobiani M, Abuladze N, et al. The manifestation of peculiarities of pharmacological effects of the medicinal product -- "Phenomenon" on liver biochemical and functionality options results, in CCL4- provoked tentative liver cirrhosis on lab rats. In: Proceedings of the First International Scientific-Practical

- Conference in Health Innovations & Research: Prognosis, Achievement and Challenges. Tallinn, Estonia; 2023 Dec 15-16. p. 18-19.
46. Sulashvili N, Beglaryan M, Gorgaslidze N, Gabunia L, Alavidze N, Abuladze N, et al. The scientific discussion of manifestation of modern achievements of characteristics, pharmacotherapeutic action, clinical use and adverse effects of cisplatin. In: Book of publications of I International Scientific and Practical Conference "Modern achievements of experimental, clinical, environmental biochemistry and molecular biology". Kharkiv, Ukraine; 2024 Mar 7. p. 73-112.
 47. Sulashvili N, Gorgaslidze N, Gabunia L, Beglaryan M, Alavidze N, Abuladze N, et al. The scientific discussion of manifestation of the key issue aspects of features of genetic views of carbohydrate metabolism disorder in glycogen storage disease and treatment strategy summons. The Caucasus Economic & Social Analysis Journal of Southern Caucasus. 2024;61(04):15-36.
 48. Sulashvili N, Gorgaslidze N, Gabunia L, Sulashvili M, Alavidze N, Abuladze N, et al. The manifestation of key issue aspects of some features of genetic views of carbohydrate metabolism disorder in glycogen storage disease and treatment strategy summons. In: Proceedings of the Second International Scientific-Practical Conference in Health Innovations & Research: Prognosis, Achievement, and Challenges. Tallinn, Estonia; 2024 Apr 6-7. p. 27-29.
 49. Sulashvili N, Gorgaslidze N, Gabunia L, Beglaryan M, Alavidze N, Abuladze N, et al. The scholarly discourse on the main pathways underlying glycogen accumulation illnesses, various clinical facets and the in-managing drug treatment strategic issues. In: Proceedings of the 6th International Congress on Contemporary Scientific Research. Paris, France; 2024 Oct 25-28. p. 707-738.
 50. Sulashvili N, Beglaryan M, Gorgaslidze N, Gabunia L, Alavidze N, Abuladze N, et al. The scientific discussion of key issue aspects of features of new immunotherapy challenges and perspectives by CAR-T cell therapy. Experimental and Clinical Medicine. 2024;(4):119-122.
 51. Sulashvili N, Gorgaslidze N, Gabunia L, Beglaryan M, Alavidze N, Abuladze N, et al. The manifestation of key issue features of novel lectin-rich protein fractions and their antimicrobial activities. In: Materials of the III Scientific and Practical International Conference "Microbiological and Immunological Research in Modern Medicine". Kharkiv, Ukraine; 2025 Mar 21. p. 30-33.
 52. Sulashvili N, Gorgaslidze N, Gabunia L, Beglaryan M, Alavidze N, Abuladze N, et al. The manifestation of key issue aspects of broadening the spectrum of degradable triazole polymers for cutting-edge of biomedical applications. In: Materials of the III Scientific and Practical International Conference "Microbiological and Immunological Research in Modern Medicine". Kharkiv, Ukraine; 2025 Mar 21. p. 38-41.
 53. Sulashvili N, Gorgaslidze N, Gabunia L, Beglaryan M, Alavidze N, Abuladze N, et al. The scientific discussion of key issue aspects of potential features of applications of zeolite-containing Geomin Forte in physical and rehabilitation medicine as food supplement. In: Proceedings of the All-Ukrainian International Scientific Conference "Multidisciplinary Approach in Physical Rehabilitation Medicine". Kharkiv, Ukraine; 2025 Mar 28. p. 251-259.
 54. Sulashvili N, Gorgaslidze N, Gabunia L, Beglaryan M, Alavidze N, Abuladze N, et al. The manifestation of peculiarities, side effects and toxicities of drugs and their summons features in clinical application at different ages. In: Proceedings of the III International Scientific and Practical Conference "Fundamental and Applied Research in the Field of Pharmaceutical Technology". Kharkiv, Ukraine; 2023 Nov 24. p. 64-92.

55. Sulashvili N, Gorgaslidze N, Gabunia L, Beglaryan M, Alavidze N, Abuladze N, et al. The scientific discussion of key issue aspects of manifestation of non-conventional mummification, self-mummification and mollification in general according with some correlation of ancient medicine and ancient pharmacy in general. In: Materials of the III International Scientific and Practical Conference "Training of Pharmacy Specialists within the framework of the concept of 'Life Long Learning': Science, Education, Practice". Kharkiv, Ukraine; 2024 Oct 23-24. p. 114-127.
56. Sulashvili N, Gorgaslidze N, Beglaryan M, Gabunia L, Alavidze N, Abuladze N, et al. The key issues related to features and perspectives of antioxidants in asthma and allergy pharmacotherapy. Georgian Biomedical News. 2023;1(2):64-67.
57. Gorgaslidze N, Sulashvili N, Gabunia L, Beglaryan M, Alavidze N, Abuladze N, et al. The manifestation of role of antioxidants in maintaining cellular redox homeostasis during various pathological processes. PIRETC Journal of Social Research & Behavioral Sciences. 2023;25(04):20-57.
58. Sulashvili N, Gorgaslidze N, Gabunia L, Beglaryan M, Alavidze N, Abuladze N, et al. The manifestation of features of advances and challenges in COVID-19 vaccine development, efficacy, safety, and global deployment in general. Experimental and Clinical Medicine. 2025;(4):55-58.
59. Sulashvili N, Gorgaslidze N, Gabunia L, Beglaryan M, Alavidze N, Abuladze N, et al. The scientific discussion of key issue aspects of immunopathogenesis and pharmacological properties and profiles in relation to adverse drug reactions challenges, focus on multidimensional drug-induced eosinophilia and systemic syndrome. Georgian Scientists. 2025;7(3):141-179.
60. Gorgaslidze N, Sulashvili N, Gabunia L, Advadze M, Tskitishvili L, Topchiyeva S, et al. Exploring the profound environmental contamination by pharmaceutical residues, their action on ecosystems: health risks, complex interactions, assessing risks, comprehensive mitigation strategies and the imperative for enhanced risk evaluation. PIRETC Journal of Social Research & Behavioral Sciences. 2025;34(01):67-99.
61. Dundua K, Taboridze I, Kvanchakhadze R, Abesadze I, Jashi L. CORRELATIONS BETWEEN HOMOCYSTEINE AND VITAMIN B12 IN TYPE 2 DIABETES TREATED WITH METFORMIN. Georgian Med News. 2026;(3-4):6-12.
62. Shervashidze T, Kvanchakhadze R, Abuladze D, Jashi L, Shervashidze M, Taboridze I, et al. THE IMPACT OF BARIATRIC SURGERY ON TYPE 2 DIABETES MELLITUS REMISSION IN THE GEORGIAN POPULATION. Georgian Med News. 2025 Jan;(358):106-112.
63. Arabidze K, Gogokhia I, Sokhadze K, Kintsurashvili N, Tsiklauri M, Taboridze I, et al. THE EVALUATION OF THE RISK OF COMPLICATIONS DURING MULTIMODAL AND OPIOID ANESTHESIA IN BARIATRIC SURGERY AND ABDOMINOPLASTY. Georgian Med News. 2023 Dec;(345):67-76.
64. Kacharava T, Giorgadze E, Janjgava S, Lomtadze N, Taboridze I. Correlation between vitamin B12 deficiency and autoimmune thyroid diseases. Endocr Metab Immune Disord Drug Targets. 2023;23(10).
65. Lomtadze N, Giorgadze E, Janjgava S, Kacharava T, Taboridze I. The relationship between insulin resistance and thyroid volume in Georgia. Endocr Metab Immune Disord Drug Targets. 2023;23(11).
66. Chigogidze M, Sharashidze N, Pagava Z, Taboridze I. The Correlation of Collateral Circulation and Age during Acute Ischemic Heart Disease. Eur Sci J. 2020;16(18):335-346.

67. Gujejiani L, Sharashidze N, Mamatsashvili M, Tvalchrelidze S, Taboridze I, et al. GENDER DIFFERENCES OF STENT IMPLANTATION COMPLICATIONS. ASSESSMENT OF ACUTE CORONARY SYNDROME WITH ST ELEVATION. Eur Sci J. 2014;10(9).
68. Janashia G, Beselia K, Taboridze I. Complications and In-Hospital Mortality After On-Pump Vs Off-Pump Coronary Artery Bypass Grafting. Eur Sci J. 2018;14(14).
69. Taboridze I, Aladashvili L, Vardzukashvili I. Surgical Treatment of Scoliosis in Marfan Syndrome: A Case Report. In: 5th Eurasian Multidisciplinary Forum; 2017.
70. Tsiklauri MV, Taboridze II, Aladashvili LT. [Use of Lazegrin in the complex treatment of post-traumatic osteomyelitis in patients with hepatitis C]. Allergol Immunol. 2008;7(5). (Russian).
71. Beselia L, Tsintsadze M, Taboridze I. Evaluation of some diagnostic features of covid-19 in patients with comorbidities. Scientific Journal Spectri. 2024;9(1).
72. Beselia L, Tsintsadze M, Sakvarelidze I, Tsiklauri M, Gorgodze T, Taboridze I, et al. MORTALITY RISK ASSESSMENT AMONG PATIENTS, HOSPITALIZED FOR COVID-19. Georgian Med News. 2024;(3-4):60-67.
73. Rekhviashvili D, Chakhunashvili G, Megrelishvili N, Taboridze I. Type 1 Diabetes and Cardiovascular Diseases in Children (Literature Review). Scientific Journal Spectri. 2024;10(2).
74. Makharadze M, Sulukhia R, Megrelishvili N, Melia L, Taboridze I. Correlations between spontaneous abortions and patient's history, social-biological and environmental factors. Experimental and Clinical Medicine Georgia. 2019(2):17-9.
75. Gagoshidze M, Antelava M, Zedginidze A, Manjavidze N, Aladashvili L, Taboridze I. Evaluation of morbidity risk in school age children living under arsenic influence conditions and significance of micronuclei assays. ANNALS OF BIOMEDICAL RESEARCH AND EDUCATION. 2005 Oct;5(4).