APPENDIX D

GLOSSARY OF TERMS USED IN MEDICINAL CHEMISTRY

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Active transport: Active transport is the carriage of a solute across a biological membrane from low to high concentration that requires the expenditure of (metabolic) energy.

ADMET: Acronym referring to the absorption, distribution, metabolism, excretion, and toxicity profile or processes for a xenobiotic upon its administration *in vivo*. *Note*: ADME is also used to delineate these selected parameters within the context of a xenobiotics pharmacokinetic profile. Because any of the five characteristics may become hurdles during drug development, ADMET behaviour is typically studied and optimized among efficacious analogues during the early drug discovery stage by using *in vitro* models that attempt to predict such behaviors in clinical studies.

Adverse effect, adverse event, adverse drug event: (1) (In medicinal chemistry) Undesirable reaction in response to the administration of a drug or test compound. *Note*: In most instances such effects result from off-*target* interactions. (2) (In toxicokinetics) Change in biochemistry, morphology, physiology, growth, development, or lifespan of an organism, which results in impairment of functional capacity or impairment of capacity to compensate for additional stress or increase in susceptibility to other environmental influences.

Drug Discovery for the Treatment of Addiction: Medicinal Chemistry Strategies, First Edition. Brian S. Fulton.

Affinity: Affinity is the tendency of a molecule to associate with another. The affinity of a drug is its ability to bind to its biological target (receptor, enzyme, transport system, etc.). For pharmacological receptors, it can be thought of as the frequency with which the drug, when brought into the proximity of a receptor by diffusion, will reside at a position of minimum free energy within the force field of that receptor.

Agonist: An agonist is an endogenous substance or a drug that can interact with a receptor and initiate a physiological or a pharmacological response characteristic of that receptor (contraction, relaxation, secretion, enzyme activation, etc.).

Allosteric antagonist: Compound that binds to a receptor at a site separate from, but actively coupled to, that of the endogenous agonist to reduce actively receptor signals. *Note*: The terms "allosteric antagonist" and "noncompetitive antagonist" are often synonymous but not necessarily so. See also noncompetitive antagonist.

Allosteric enzyme: An allosteric enzyme is an enzyme that contains a region to which small, regulatory molecules ("effectors") may bind in addition to and separate from the substrate-binding site and thereby affect the catalytic activity. On binding the effector, the catalytic activity of the enzyme toward the substrate may be enhanced, in which case the effector is an activator, or reduced, in which case it is a deactivator or inhibitor.

Analogue, Analog: Chemical compound having structural similarity to a reference compound. *Note*: Despite the structural similarity, an analogue may display different chemical and/or biological properties, as is often intentionally the case during design and synthesis to optimize either efficacy or ADMET properties within a given series. See also analogue-based drug discovery, congener, follow-on drug.

Analog-based drug discovery: Strategy for drug discovery and/or optimization in which structural modification of an existing drug provides a new drug with improved chemical and/or biological properties. *Note*: Within the context of analogue-based drug discovery, three categories of drug analogues are recognized: Compounds possessing structural, chemical, and pharmacological similarities, termed "direct analogues" and sometimes referred to as "me-too" drugs; compounds possessing structural and often chemical but not pharmacological similarities, termed "structural analogues;" and structurally different compounds displaying similar pharmacological properties, termed "pharmacological analogues." See also ligand-based drug design.

Antagonist: An antagonist is a drug or a compound that opposes the physiological effects of another. At the receptor level, it is a chemical entity that opposes the receptor-associated responses normally induced by another bioactive agent.

ATP binding cassette protein, ABC protein: Large gene family of transporter proteins that bind ATP and use the energy to transport substrates (e.g., sugars, amino acids, metal ions, peptides, proteins, and a large number of hydrophobic compounds and metabolites) across lipid membranes. *Note*: These proteins have an important role in limiting oral absorption and brain penetration of xenobiotics. See also efflux pump, P-glycoprotein.

Atropisomer: Stereoisomer resulting from hindered rotation about a single bond in which steric hindrance to rotation is sufficient to allow isolation of individual isomers.

Attrition rate: Rate of loss of drug candidates during progression through the optimization and developmental stages while on route to the marketplace. *Note*: It has been estimated that for every 10,000 compounds examined during the early stages of biological testing just one reaches the market.

Autoinduction: Capacity of a drug to induce enzymes that mediate its own metabolism. *Note*: This often results in lower, often sub-therapeutic, drug exposure on prolonged or multiple dosing.

Autoreceptor: An autoreceptor, present at a nerve ending, is a receptor that regulates, via positive or negative feedback processes, the synthesis and/or release of its own physiological ligand.

Back-up compound: Molecule selected as a replacement for the lead drug candidate, should it subsequently fail during further preclinical evaluation or in clinical studies *Note*: Ideally, a back-up should be pharmacologically equivalent to the lead drug but have significant structural differences. Possession of a distinct core scaffold is optimal.

Best-in-class: Drug acting on a specific molecular target that provides the best balance between efficacy and adverse effects.

Bioassay: A bioassay is a procedure for determining the concentration, purity, and/or biological activity of a substance (e.g., vitamin, hormone, plant growth factor, antibiotic, enzyme) by measuring its effect on an organism, tissue, cell, and enzyme or receptor preparation compared with a standard preparation.

Bioinformatics: Discipline encompassing the development and utilization of computational tools to store, analyze, and interpret biological data. *Note*: Typically protein or DNA sequence or 3D information.

Bioisostere: A bioisostere is a compound resulting from the exchange of an atom or of a group of atoms with another, broadly similar, atom or group of atoms. The objective of a bioisosteric replacement is to create a new compound with similar biological properties to the parent compound. The bioisosteric replacement may be physicochemical or topologically based.

Biological agent: A biopolymer-based pharmaceutical, such as a protein, that is applicable to the prevention, treatment, or cure of diseases or injuries to man. *Note*: Biological agents may be any virus, therapeutic serum, toxin, antitoxin, vaccine, blood component or derivative, allergenic product, or analogous products.

Biomarker: Indicator signaling an event or condition in a biological system or sample and giving a measure of exposure, effect, or susceptibility.

Blockbuster drug: Drug that generates annual sales of USD 1 billion or more.

Blood–brain barrier (BBB): Layer of endothelial cells that line the small blood vessels of the brain. *Note 1*: These cells form "tight junctions" that restrict the free exchange of substances between the blood and the brain. Such cells are rich in P-glycoprotein, which serves to pump substrates back to the peripheral side of the

vasculature. *Note 2*: Passive diffusion across the BBB is highly dependent on drug lipophilicity, and very few orally active agents acting in the central nervous system have a polar surface area greater than 0.9 nm^2.

Carcinogen: Agent (chemical, physical, or biological) that is capable of increasing the incidence of malignant neoplasms, thus causing cancer.

Chemical biology: Application of chemistry to the study of molecular events in biological systems, often using tool compounds. *Note*: Distinguished from medicinal chemistry, which is focused on the design and optimization of compounds for specific molecular targets.

Chemical database: Specific electronic repository for storage and retrieval of chemical information. *Note 1*: Chemical structural information is sometimes stored in string notation such as the InChI or SMILES notations. *Note 2*: Such databases can be searched to retrieve structural information and data on specific or related molecules. *Note 3*: A free database of chemical structures of small organic molecules and information on their biological activities is available from PubChem.

Chemical library, compound library, compound collection: (1) Collection of samples (e.g., chemical compounds, natural products, over-expression library of a microbe) available for biological screening. (2) Set of compounds produced through combinatorial chemistry or other means, which expands around a single core structure or scaffold.

Chemical space: Set of all possible stable molecules based on a specific chemical entity that interacts at one or more specific molecular targets.

Cheminformatics, chemoinformatics: Use of computational, mathematical, statistical, and information techniques to address chemistry-related problems.

Chemogenomics, chemical genomics: Systematic screening of chemical libraries of congeneric compounds against members of a target family of proteins.

Chemokine: Member of a superfamily of proteins with the primary function to control leukocyte activity and trafficking through tissues.

CLOGP values: Calculated 1-octanol/water partition coefficients. *Note*: Frequently used in structure–property correlation or quantitative structure–activity relationship studies. See also log *P*, log *D*.

Cluster: Group of compounds that are related by structural, physicochemical, or biological properties. *Note*: Organizing a set of compounds into clusters is often used to assess the diversity of those compounds, or to develop structure–activity relationship models.

Co-drug, mutual prodrug: Two chemically linked synergistic drugs designed to improve the drug delivery properties of one or both drugs. *Note*: The constituent drugs are indicated for the same disease, but may exert different therapeutic effects via disparate mechanisms of action.

Comparative molecular field analysis (CoMFA): Comparative molecular field analysis (CoMFA) is a 3D-QSAR method that uses statistical correlation techniques for the analysis of the quantitative relationship between the biological activities of

a set of compounds with a specified alignment, and their three-dimensional electronic and steric properties. Other properties such as hydrophobicity and hydrogen bonding can also be incorporated into the analysis.

Congener: Substance structurally related to another and linked by origin or function. *Note*: Congeners may be analogues or vice versa but not necessarily. The term "congener," while most often a synonym for "homologue," has become somewhat more diffuse in meaning so that the terms "congener" and "analogue" are frequently used interchangeably in the literature. See also analogue, follow-on drug.

Constitutive activity: Receptor or enzymatic function displayed in the absence of an agonist or activator.

Contract research organization (CRO): Commercial organization that can be engaged to undertake specifically defined chemical, biological, safety, or clinical studies. *Note*: Typically, such studies are subject to confidentially agreements.

Covalent drug: Ligand that binds irreversibly to its molecular target through the formation of a new chemical bond.

Cytochrome P450 (CYP450): Member of a superfamily of heme-containing monooxygenases involved in xenobiotic metabolism, cholesterol biosynthesis, and steroidogenesis, in eukaryotic organisms found mainly in the endoplasmic reticulum and inner mitochondrial membrane of cells.

Designed multiple ligands: Compounds conceived and synthesized to act on two or more molecular targets.

Diversity: Unrelatedness of a set of molecules (e.g., building blocks or members of a compound library), as measured by properties such as atom connectivity, physical properties, or computationally generated descriptors. *Note*: Inverse of molecular similarity.

Diversity-oriented synthesis (DOS): Efficient production of a range of structures and templates with skeletal and stereochemical diversity as opposed to the synthesis of a specific target molecule.

Double-blind study: A double-blind study is a clinical study of potential and marketed drugs, where neither the investigators nor the subjects know which subjects will be treated with the active principle and which ones will receive a placebo.

Drug: A drug is any substance presented for treating, curing, or preventing disease in human beings or in animals. A drug may also be used for making a medical diagnosis or for restoring, correcting, or modifying physiological functions (e.g., the contraceptive pill).

Drug cocktail: (1) (In drug therapy) Administration of two or more distinct pharmacological agents to achieve a combination of their individual effects. *Note 1*: The combined effect may be additive, synergistic, or designed to reduce side effects. *Note 2*: This term is often used synonymously with that of "drug combination" but is preferred to avoid confusion with medications in which different drugs are included in a single formulation. (2) (In drug testing) Administration of two or more distinct compounds to test simultaneously their individual behaviors (e.g., pharmacological effects in high-throughput screens or drug metabolism.

Drug delivery: Process by which a drug is administered to its intended recipient. *Note*: Examples include administration orally, intravenously, or by inhalation. See also drug distribution, targeted drug delivery.

Drug distribution: Measured amounts of an administered compound in various parts of the organism to which it is given. See also drug delivery.

Drug disposition: Drug disposition refers to all processes involved in the absorption, distribution metabolism, and excretion of drugs in a living organism.

Druggability: Capacity of a molecular target to be modulated in a favorable manner by a small-molecule drug. *Note*: It is estimated that only around 10% of the human genome affords druggable targets.

Drug-like(ness): Physical and chemical properties in a small molecule that makes it likely to perform efficiently as a drug.

Drug repurposing, drug repositioning, drug reprofiling: Strategy that seeks to discover new applications for an existing drug that was not previously referenced and not currently prescribed or investigated. *Note*: Various additional synonymous terms have been used to describe the process of drug repurposing. All appear to be used interchangeably.

Drug safety: Assessment of the nontolerable biological effects of a drug. *Note*: Because the nontolerable effects of a drug are directly related to its concentration or dose, safety is generally ranked relative to the dose required to obtain the desirable effect. See also therapeutic index.

Dual binding site: The presence of two distinct ligand-binding sites on the same molecular target.

Effective concentration (EC): Concentration of a substance that produces a defined magnitude of response in a given system. *Note 1*: EC_{50} is the median dose that causes 50% of the maximal response. *Note 2*: The term usually refers to an agonist in a receptor system effect and could represent either an increase or a decrease in a biological function. See also IC_{50}, effective dose.

Effective dose (ED): Dose of a substance that causes a defined magnitude of response in a given system. *Note*: ED_{50} is the median dose that causes 50% of the maximal response. See also IC_{50}, effective concentration.

Efficacy: Efficacy describes the relative intensity with which agonists vary in the response they produce even when they occupy the same number of receptors and with the same affinity. Efficacy *is not* synonymous to intrinsic activity. Efficacy is the property that enables drugs to produce responses. It is convenient to differentiate the properties of drugs into two groups, those that cause them to associate with the receptors (affinity) and those that produce stimulus (efficacy). This term is often used to characterize the level of maximal responses induced by agonists. In fact, not all agonists of a receptor are capable of inducing identical levels of maximal responses. Maximal response depends on the efficiency of receptor coupling, that is, from the cascade of events, which, from the binding of the drug to the receptor, leads to the observed biological effect.

Efflux pump: Transporter protein located in the membrane of cells that utilizes active transport to move a compound from the internal to the external environment.

Elimination: Elimination is the process achieving the reduction in the concentration of a xenobiotic including its metabolism.

Epigenetic(s): Phenotypic change(s) in an organism brought about by alteration in the expression of genetic information without any change in the genomic sequence itself. *Note*: Common examples include changes in nucleotide base methylation and changes in histone acetylation. Changes of this type may become heritable.

Equilibrium solubility: Analytical composition of a mixture or solution that is saturated with one of the components in the designated mixture or solution. *Note 1*: Solubility may be expressed in any units corresponding to quantities that denote relative composition, such as mass, amount concentration, molality, etc. *Note 2*: The mixture or solution may involve any physical state: solid, liquid, gas, vapor, supercritical fluid. *Note 3*: The term "solubility" is also often used in a more general sense to refer to processes and phenomena related to dissolution. See also intrinsic solubility, kinetic solubility, solubility, supersaturated solution.

Fast follower: Compound selected as a rapid successor to a lead drug candidate. *Note*: Fast followers usually possess a marked increase in one or more pharmacological/pharmaceutical characteristics such as potency, efficacy, therapeutic index, or physicochemical parameters (e.g., solubility).

Fingerprint: Representation of a compound or chemical library by attributes (descriptors) such as atom connectivity, 3D structure, or physical properties.

First-in-class: First drug acting on a hitherto unaddressed molecular target to reach the market.

Follow-on drug: Drug having a similar mechanism of action to an existing drug. *Note*: Compounds may be of the same or different chemical class. A therapeutic advantage over first-in-class drugs must be demonstrated for regulatory approval.

Fragment: Low-molar-mass ligand (typically smaller than 200 Da) that binds to a target with low affinity but high ligand efficiency. *Note*: Typically fragments have affinities in a concentration interval from 0.1 to 1.0 mM.

Fragment-based lead discovery: Screening libraries of low-molar-mass compounds (typically 120–250 Da) using sensitive biophysical techniques capable of detecting weakly binding lead compounds. *Note*: X-ray structures are frequently used to drive the optimization of fragment hits to leads. See also fragment, ligand efficiency.

Frequent hitter: Structural feature that regularly results in a positive response in a variety of high-throughput or primary screens. *Note*: Such compounds often exert their actions through nonspecific mechanisms and are therefore unreliable leads.

Genomics: Science of using DNA- and RNA-based technologies to demonstrate alterations in gene expression.

Good laboratory practice (GLP): Set of principles that provide a framework within which laboratory studies are planned, performed, monitored, recorded, reported, and archived. *Note*: These studies are undertaken to generate data by which the

hazards and risks to users, consumers, and third parties, including the environment, can be assessed for pharmaceuticals (only preclinical studies), agrochemicals, cosmetics, food additives, feed additives and contaminants, novel foods, biocides, detergents, etc. GLP helps assure regulatory authorities that the data submitted are a true reflection of the results obtained during the study and can therefore be relied upon when making risk/safety assessments.

Good manufacturing practice (GMP): Quality assurance process that ensures that medicinal products are consistently produced and controlled to the standards appropriate to their intended use. *Note*: Quality standards are those required under marketing authorization or product specification. GMP is concerned with both production and quality control.

G-protein, guanine binding protein: Member of a family of membrane-associated proteins that on activation by cellular receptors lead to signal transduction. See also G-protein-coupled receptor.

G-protein-coupled receptor (GPCR): Large family of cell surface receptors in which seven portions of the protein cross the cellular membrane and are linked to internal G-proteins. *Note 1*: Interaction of these receptors with extracellular ligands activates signal transduction pathways and, ultimately, cellular responses. *Note 2*: G-protein-coupled receptors are found only in eukaryotes. See also G-protein.

Green chemistry: Invention, design, and application of chemical products and processes to reduce or eliminate the use and generation of hazardous substances.

Hydrogen-bond acceptor (HBA): Typically N or O with a free lone pair of electrons.

Hydrogen-bond donor (HBD): A N-H or O-H functional group.

High-throughput screening (HTS): Method for the rapid assessment of the activity of samples from large compound collections. *Note 1*: Typically, these assays are carried out in microplates of at least 96 wells using automated or robotic techniques *Note 2*: The rate of at least 10^5 assays per day has been termed "ultra-high-throughput screening" (UHTS).

Hit: Molecule that produces reproducible activity above a defined threshold in a biological assay and whose structural identity has been established. *Note*: Hits typically derive from high-throughput screening initiatives or other relatively extensive primary assays and do not become true hits until fully validated.

Hit expansion: Generation of additional compound sets that contain chemical motifs and scaffolds that have activity in the primary screen. *Note*: This methodology permits the identification of additional hits and new scaffolds and develops structure–activity relationships around existing hits.

Hit-to-lead chemistry: Process by which a proven molecule or series derived from high-throughput screening or primary screens is chemically optimized to a viable lead or series.

Homology model: Computational representation of a protein built from the 3D structure of a similar protein or proteins using alignment techniques and homology arguments.

Hydrophilicity: Hydrophilicity is the tendency of a molecule to be solvated by water.

Hydrophobic fragmental constant: Representation of the lipophilicity contribution of a constituent part of a structure to the total lipophilicity.

Hydrophobic interaction: Entropically driven favorable interaction between nonpolar substructures or surfaces in aqueous solution.

Hydrophobicity: Hydrophobicity is the association of nonpolar groups or molecules in an aqueous environment that arises from the tendency of water to exclude nonpolar molecules.

IC_{50} (inhibitory concentration 50): The concentration of an enzyme inhibitor or receptor antagonist that reduces the enzyme activity or agonist response by 50%. *Note*: IC_{50} values are influenced by experimental conditions (e.g., substrate or agonist concentration, which should be specified). Related terms: inhibition constant, K_i.

Inhibition constant, K_i: (1) Equilibrium dissociation constant of an enzyme-inhibitor complex: $K_i = [E][I]/[EI]$. (2) The equilibrium dissociation constant of a receptor-ligand complex. *Note*: This value is usually obtained through competition binding experiments, where the K_i is determined after the IC_{50} obtained in a competition assay performed in the presence of a known concentration of labeled reference ligand. Related term: IC_{50}.

International chemical identifier (InChI): Nonproprietary identifier for chemical substances that can be used in printed and electronic data sources to enable easier linking of diverse data compilations. *Note*: This IUPAC notation frequently replaces the earlier SMILES notation.

Intercalation: Thermodynamically favorable, reversible inclusion of a molecule (or group) between two other molecules (or groups). Examples include DNA intercalation.

Intrinsic activity: Intrinsic activity is the maximal stimulatory response induced by a compound in relation to that of a given reference compound (see also partial agonist). This term has evolved with common usage. It was introduced by Ariëns as a proportionality factor between tissue response and receptor occupancy. The numerical value of intrinsic activity (alpha) could range from unity (for full agonists, i.e., agonist inducing the tissue maximal response) to zero (for antagonists), the fractional values within this range denoting partial agonists. Ariëns' original definition equates the molecular nature of alpha to maximal response only when response is a linear function of receptor occupancy. This function has been verified. Thus, intrinsic activity, which is a drug and tissue parameter, cannot be used as a characteristic drug parameter for classification of drugs or drug receptors. For this purpose, a proportionality factor derived by null methods, namely, relative efficacy, should be used. Finally, "intrinsic activity" should not be used instead of "intrinsic efficacy." A "partial agonist" should be termed "agonist with intermediate intrinsic efficacy" in a given tissue.

Intrinsic solubility: Equilibrium solubility of the uncharged form of an ionizable compound at a pH where it is fully unionized.

$$HA(s) = HA(aq)$$
$$HA(aq) = H^+ + A^-$$

The intrinsic solubility can be determined from the analytical composition at a pH, where [HA] is very much greater than [A^-]. See also equilibrium solubility, kinetic solubility, solubility, supersaturated solution.

Inverse agonist: An inverse agonist is a drug which acts at the same receptor as that of an agonist, yet produces an opposite effect. Also called negative antagonists.

Investigational new drug (IND): Drug not yet approved for general use by the national authority, such as the Food and Drug Administration of the United States of America, but undergoing clinical investigation to assess its safety and efficacy.

Ionotropic receptor: Transmembrane ion channel that opens or closes in response to the binding of a ligand.

Kinetic solubility, turbidimetric solubility: Composition of a solution with respect to a compound when it's induced precipitate first appears. See also equilibrium solubility, intrinsic solubility, solubility, supersaturated solution.

Lead: Compound (or compound series) that satisfies predefined minimum criteria for further structure and activity optimization. *Note*: Typically, a lead will demonstrate appropriate activity, selectivity, and tractable structure–activity relationship and have confirmed activity in a relevant cell-based assay. See lead validation.

Lead discovery: Lead discovery is the process of identifying active new chemical entities, which by subsequent modification may be transformed into a clinically useful drug.

Lead generation: Lead generation is the term applied to strategies developed to identify compounds that possess a desired but non-optimized biological activity.

Lead optimization: Lead optimization is the synthetic modification of a biologically active compound, to fulfill all stereoelectronic, physicochemical, pharmacokinetic, and toxicologic requirements for clinical usefulness.

Lead validation: Process by which a lead compound is authenticated by the confirmation of its expected pharmacological properties. *Note*: Usually, a cluster of structurally similar compounds showing discernable structure–activity relationships will support the validation process.

Ligand: Ion or molecule that binds to a molecular target to elicit, block, or attenuate a biological response.

Ligand-based drug design: Method of drug discovery and/or optimization in which the pursuit of new structures and/or structural modifications is based upon one or more ligands known to interact with the molecular target of interest. *Note*: This approach is applicable even when no structural detail of the target is known. In such cases, a series of analogues is usually prepared and tested to produce structure–activity relationship data that can be extrapolated to indirectly derive a

topographical map of the biological surface. See also analogue-based drug discovery, structure-based drug design.

Ligand efficiency (LE): Measure of the free energy of binding per heavy atom count (i.e., non-hydrogen) of a molecule. *Note 1*: It is used to rank the quality of molecules in drug discovery, particularly in fragment-based lead discovery. *Note 2*: An LE value of 1.25 kJ mol^{-1} (non-hydrogen atom)$^{-1}$ is the minimum requirement of a good lead or fragment.

Ligand lipophilic efficiency (LLE), lipophilic efficiency: Parameter used to identify ligands with a high degree of specific interaction toward the desired molecular target. *Note 1*: The potency of a ligand toward a molecular target may be dominated by nonspecific partitioning from the aqueous phase. It can be advantageous to separate out the nonspecific component of the potency to identify more specific interactions; typically using an equation such as: LLE, symbol E_{LL}, is defined by the logarithm of the potency minus a lipophilicity measure, where a typical example would be

$$E_{LL} = -\log(IC_{50}) - \log\ P.$$

Note 2: E_{LL} can be regarded as part of a thermodynamic cycle used as a complementary measure to potency in the search for specific target interactions. In this case, the dissociation constant, K_d, is a more appropriate measure than IC50 since it refers to the Gibbs energy of the binding process

$$E_{LL} = -\log\ K_d - \log\ P.$$

Lipophilicity: Lipophilicity represents the affinity of a molecule or a moiety for a lipophilic environment. It is commonly measured by its distribution behavior in a biphasic system, either liquid-liquid (e.g., partition coefficient in octanol/water) or solid/liquid (retention on reversed-phase high performance liquid chromatography (RP-HPLC) or thin-layer chromatography (TLC) system).

log *D*, lg *D*: Logarithm of the apparent partition coefficient at a specified pH. See CLOGP, log *P*.

log *P*, lg *P*: Measure of the lipophilicity of a compound by its partition coefficient between an apolar solvent (e.g., 1-octanol) and an aqueous buffer. Thus, *P* is the quotient of the concentration of non-ionized drug in the solvent divided by the respective concentration in buffer. See CLOGP, log *D*.

Markush structure: Generalized formula or description for a related set of chemical compounds used in patent applications and chemical papers.

Metabotropic receptor: Receptor that modulates electric potential-gated channels via G-proteins. *Note*: The interaction can occur entirely within the membrane or by the generation of diffusible second messengers. The involvement of G-proteins causes the activation of these receptors to last tens of seconds to minutes, in contrast with the brief effect of ionotropic receptors.

Microarray: Planar surface where assay reagents and samples are distributed as sub-microliter drops. *Note*: This screening format is a direct offshoot of genomic microarray technologies and makes use of ultra-low-volume miniaturization provided by nanodispensing technologies.

microRNA (miRNA): Small single-stranded RNA molecules that play a significant role in the post-transcriptional regulation of gene expression. *Note*: MicroRNA usually comprises approximately 22 nucleotides.

Molecular descriptor: Parameter that characterizes a specific structural or physicochemical aspect of a molecule.

Molecular dynamics: Computational simulation of the motion of atoms in a molecule or of individual atoms or molecules in solids, liquids, and gases, according to Newton's laws of motion. *Note*: The forces acting on the atoms, required to simulate their motions, are generally calculated using molecular mechanics force fields.

Molecular similarity: Measure of the coincidence or overlap between the structural and physicochemical profiles of compounds.

Molecular target: Protein (e.g., receptor, enzyme, or ion channel), RNA, or DNA that is implicated in a clinical disorder or the propagation of any untoward event. *Note*: Usually, biochemical, pharmacological, or genomic information supporting the role of such a target in disease will be available.

Multidrug resistance (MDR): Characteristic of cells that confers resistance to the effects of several different classes of drugs. *Note*: There are several forms of drug resistance of which each is determined by genes that govern how cells will respond to chemical agents. One type of multidrug resistance involves the ability to eject several drugs out of cells (e.g., efflux pumps such as P-glycoprotein).

Multiparameter optimization (MPO): Drug-likeness penetrability algorithm derived from CLOGP, clogD, molar mass, topological polar surface area, number of hydrogen-bond donors, and pK_a. *Note*: The MPO desirability score is larger or equal to 4 on a scale of 0-6.

Multi-target-directed ligand (MTDL), multi-target drug: Ligand acting on more than one distinct molecular target. Targets may be of the same or different mechanistic classes.

Multi-target drug discovery (MTDD): Deliberate design of compounds that act on more than one molecular target.

Murcko assembly: Core scaffold of a molecule that remains after all chain substituents that do not terminate in a ring are removed. Single atoms connected by a double bond are typically also retained.

Neural network: A statistical analysis procedure based on models of nervous system learning in animals. *Note*: Neural networks have the ability to "learn" from a collection of examples to discover patterns and trends. These data-mining techniques can be used in forecasting or prediction.

Neutral antagonist (in pharmacology)**:** Ligand that blocks the responses of a receptor to both agonists and inverse agonists with the same intensity. It binds to the

receptor without evoking any change of conformation or change to the ratio of activated to inactivated conformations. *Note*: Perfect neutral antagonism is difficult to achieve.

New chemical entity: Drug that contains no active moiety previously approved for use by the national authority, such as the US Food and Drug Administration. See also new molecular entity.

New molecular entity: Active ingredient that has never before been approved in any form by the national authority, such as the US Food and Drug Administration.

Noncompetitive antagonist: Functional antagonist that either binds irreversibly to a receptor or to a site distinct from that of the natural agonist. See allosteric antagonist.

Nuclear hormone receptor, nuclear receptor: Ligand-activated transcription factor that regulates gene expression by interacting with specific DNA sequences upstream of its target gene(s).

Obviousness: Term associated with intellectual property wherein the latter's patentability is assessed relative to the combination of more than one item of "prior art." *Note*: To be patentable within the context of medicinal chemistry, a given compound must be: (1) novel, in that its specific arrangement of atoms has never been previously disclosed; (2) non-obvious, in that its specific arrangement of atoms is not readily suggested to be of benefit by a person having ordinary skill in the art upon considering two or more other, previously disclosed structures; and (iii) useful, in that it should have some benefit, the disclosure of the latter encompassing a valid "reduction to practice."

Off-target effect: Pharmacological action induced by any molecule at molecular/biological sites distinct from that for which it was designed. *Note*: Such effects are dose-dependent and may be beneficial, adverse, or neutral.

Orphan disease: Disease for which drug research, development, and marketing is economically unfavorable. *Note 1*: The poor commercial environment could be due to a lack of economic incentives or a lack of understanding of the diseases or a combination of both. *Note 2*: Sometimes the term "rare disease" is used synonymously with orphan disease, although there is a slight difference. For example, a rare disease is so uncommon that there is no drug development effort. *Note 3*: Which diseases are classified as orphan depends strongly on the country that classifies it. In the United States, for example, any disease affecting less than 200,000 people is considered an orphan or rare disease. Europe and countries such as Japan, Australia, and Singapore have a different definition.

Orphan drug: Pharmaceutical agent that has been approved specifically to treat a rare and commercially unfavorable medical condition.

Orphan receptor: Receptor for which an endogenous ligand has yet to be identified.

Parallel synthesis: Simultaneous preparation of sets of discrete compounds in arrays of physically separate reaction vessels or microcompartments without interchange of intermediates during the assembly process.

Partial agonist: A partial agonist is an agonist that is unable to induce maximal activation of a receptor population, regardless of the amount of drug applied.

Patentability: Set of criteria that must be satisfied to achieve commercial exclusivity for an invention. *Note*: These criteria are essentially the same in all major countries and include: suitability, novelty, inventiveness, utility, and the provision of an adequate description.

P-glycoprotein (Pgp) ATP-binding cassette transporter is responsible for the efflux of small molecules from cells. *Note*: P-glycoproteins can play a major role in limiting brain penetration and restricting the intestinal absorption of drugs. Their over-expression in cancer cells becomes a common mechanism of multidrug resistance. See also blood–brain barrier, efflux pump.

Pharmacodynamics: Relates to the specific interaction of a drug with its target.

Pharmacogenetics: Study of inherited differences (variation) in drug metabolism and response.

Pharmacogenomics: General study of all of the many different genes that determine drug behaviour. *Note*: The distinction between the terms pharmacogenetics and pharmacogenomics has blurred with time and they are now frequently used interchangeably.

Pharmacokinetics: The pattern of absorption, distribution, and excretion of a drug over time.

Pharmacophore: A pharmacophore is the ensemble of steric and electronic features that is necessary to ensure the optimal supramolecular interactions with a specific biological target structure and to trigger (or to block) its biological response. A pharmacophore does not represent a real molecule or a real association of functional groups, but a purely abstract concept that accounts for the common molecular interaction capacities of a group of compounds toward their target structure. The pharmacophore can be considered as the largest common denominator shared by a set of active molecules. This definition discards a misuse often found in the medicinal chemistry literature that consists of naming as pharmacophores simple chemical functionalities such as guanidines, sulfonamides or dihydroimidazoles (formerly imidazolines), or typical structural skeletons such as flavones, phenothiazines, prostaglandins, or steroids.

Pharmacophoric descriptors: Pharmacophoric descriptors are used to define a pharmacophore, including H-bonding, hydrophobic and electrostatic interaction sites, defined by atoms, ring centers, and virtual points.

Phase 0 clinical studies, exploratory investigational new drug: Exploratory first-in-human trials that involve microdosing of drug to allow the assessment of pharmacokinetic parameters with limited drug exposure. *Note*: These trials have no therapeutic or diagnostic intent but are designed to assist decision making by providing bioavailability, metabolism, and other limited data from a small number of patients.

Phase I clinical studies: Initial introduction of an investigational new drug into humans. *Note*: These studies are designed to determine the metabolic and

pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness.

Phase II clinical studies: Controlled clinical studies conducted in a limited number of individuals to obtain some preliminary data on the effectiveness of an investigational new drug for a particular indication or indications in patients with the disease or condition. *Note*: Phase II clinical trials have two subclasses, II(a) and II(b). Phase II(a) trials are essentially pilot clinical trials designed to evaluate efficacy (and safety) in selected populations of patients with the disease or condition to be treated, diagnosed, or prevented. Phase II(b) trials extend those of Phase II(a) to well-controlled trials that evaluate the same parameters in similar patient populations.

Phase III clinical studies: Expanded controlled and uncontrolled trials in humans. *Note*: These trials are performed after preliminary evidence suggesting effectiveness of the drug has been obtained in Phase II, and are intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit/risk relationship of the drug.

Phase IV clinical studies: Extended post-marketing studies in humans. *Note*: These trials are designed to broaden information concerning treatment risks, benefits, and optimal drug use.

Phenotypic screening: Evaluation of compounds (small molecules, peptides, siRNA, etc.) in cells, tissues, or organisms for their ability to modify the system in a measurable manner. *Note*: Phenotypic screening differs from target-based screens in that it assesses the overall response of the compound under investigation rather than its specific response on a purified molecular target. Advances in molecular biology resulted in a marked shift away from phenotypic screening, although the latter is now regaining popularity.

Pipeline: Discovery and development compound portfolio of a pharmaceutical company or research organization.

Pivotal study: Experiment that provides strong support for or against the drug or molecular target under investigation. See also proof of concept.

Placebo: A placebo is an inert substance or dosage form that is identical in appearance, flavor, and odor to the active substance or dosage form. It is used as a negative control in a bioassay or in a clinical study.

Polar surface area (PSA), topological polar surface area: Surface area over all polar atoms (usually oxygen and nitrogen), including any attached hydrogen atoms, of a molecule. *Note*: Polar surface area is a commonly used metric (c.f. molecular descriptor) for the optimization of cell permeability. Molecules with a PSA of greater than 1.4 nm^2 are usually poor at permeating cell membranes. For molecules to penetrate the blood–brain barrier, the polar surface area should normally be smaller than 0.6 nm^2, although values up to 0.9 nm^2 can be tolerated. See also blood–brain barrier.

Polymorphism: Ability of a compound to exist in more than one crystalline form (polymorph) with each having a different arrangement or conformation of the

molecules within the crystal lattice. *Note*: Polymorphs generally differ in their melting points, solubility, and relative intestinal absorption such that optimal polymorphs can markedly enhance the attractiveness of some drugs.

Positron emission tomography (PET): Imaging technique used to visualize small amounts of a compound in biological tissues by the use of radionuclide labels. These radionuclide's, such as ^{11}C, ^{18}F, ^{13}N, and ^{15}O, are positron emitters.

Potency: Potency is the dose of drug required to produce a specific effect of given intensity as compared to a standard reference. Potency is a comparative rather than an absolute expression of drug activity. Drug potency depends on both affinity and efficacy. Thus, two agonists can be equipotent, but have different intrinsic efficacies with compensating differences in affinity.

Preclinical candidate (PCC), safety assessment candidate: Optimized lead compound successfully passing key screening, selectivity, and physicochemical criteria sufficient to warrant further detailed pharmacological and pharmacokinetic evaluation in animal models. *Note*: Critical studies usually include bioavailability, therapeutic efficacy in an appropriate disease model, and side effect profiling.

Privileged structure: Substructural feature that confers desirable (often drug-like) properties on compounds containing that feature. They often consist of a semirigid scaffold that presents multiple hydrophobic residues without undergoing hydrophobic collapse. *Note 1*: Such structures are commonly found to confer activity against different targets belonging to the same receptor family.

Prodrug: A prodrug is any compound that undergoes biotransformation before exhibiting its pharmacological effects. Prodrugs can thus be viewed as drugs containing specialized non-toxic protective groups used in a transient manner to alter or to eliminate undesirable properties in the parent molecule.

Proof of concept (in pharmacology)**:** Procedure by which a specific therapeutic mechanism or treatment/diagnostic paradigm is shown to be beneficial. *Note*: Similar to, and often simultaneously associated with, that for a new drug candidate. This process usually involves an early supporting step prior to clinical testing and final validation within human studies. See also lead validation, pivotal study.

Protein data bank (PDB): Repository for the 3D structural data of large biological molecules including proteins and nucleic acids. *Note*: These high-resolution structures, generated predominantly by X-ray or NMR spectroscopic techniques, provide a major resource for structural biology.

Protein–protein interaction (PPI): Association of one protein with one or more other proteins to form either homo- or heteromeric proteins. *Note*: Such associations are common in biological systems and are responsible for the regulation of numerous cellular functions in addition to the mediation of disease morphology where aberrant interactions play a significant role.

Prototype drug: Early compound that has biological properties suitable for target validation but may not necessarily be adequate for clinical studies.

QTc interval: Time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. When corrected for individual heart rate it becomes

known as the corrected QT, or QTc interval. *Note*: Significant prolongation of the QTc interval by pharmaceutical agents can induce life-threatening ventricular arrhythmia (Torsades de Pointes), typically by interacting with the hERG channel.

Quantitative structure-activity relationships (QSAR): Quantitative structure-activity relationships are mathematical relationships linking chemical structure and pharmacological activity in a quantitative manner for a series of compounds. Methods that can be used in QSAR include various regression and pattern recognition techniques.

Receptor: A receptor is a molecule or a polymeric structure in or on a cell that specifically recognizes and binds a compound acting as a molecular messenger (neurotransmitter, hormone, lymphokine, lectin, drug, etc.).

Retrosynthesis: Process of conceptually deconstructing complex molecules into simpler fragments capable of chemical manipulation to reform the parent compound.

Rule of five: Set of molecular descriptors used to assess the potential oral bioavailability of a compound. *Note 1*: Characterized by a mass of less than 500 Da, less than or equal to 5 hydrogen-bond donors, less than or equal to 10 hydrogen-bond acceptors (usually using the N+O count as a surrogate for the number of hydrogen-bond acceptors), and a CLOGP less than or equal to 5. *Note 2*: Frequently used to profile a chemical library or virtual chemical library with respect to the proportion of drug-like members that it contains. Often used as a surrogate for "drug-likeness." *Note 3*: While these criteria are frequently referred to as Lipinski's rules, the depersonalized term "rule of five" is preferred.

Rule of three: Set of molecular descriptors used to assess the quality of hit or lead molecules. *Note 1*: Most commonly applied to fragments that ideally are characterized by a mass of less than 300 Da, less than or equal to three hydrogen-bond donors, less than or equal to three hydrogen-bond acceptors, and a CLOGP of less than or equal to 3. In addition, the number of rotatable bonds should average or be less than 3 and the polar surface area about 0.6 nm^2. *Note 2*: Often used to distinguish "lead-like" from "drug-like" molecules. See fragment-based lead discovery.

Scaffold, template: Core portion of a molecule common to all members of a chemical library or compound series.

Scaffold hopping: Exchange of one scaffold for another while maintaining molecular features that are important for biological properties.

Second messenger: A second messenger is an intracellular metabolite or ion increasing or decreasing as a response to the stimulation of receptors by agonists, considered as the "first messenger." This generic term usually does not prejudge the rank order of intracellular biochemical events.

Site-directed mutagenesis: Molecular biology technique in which mutations are created at one or more defined sites in a DNA molecule. *Note*: Typically used in molecular target validation and to determine whether specific amino acids are involved at ligand or substrate interaction sites.

SMILES (simplified molecular input line entry system) notation: String notation used to describe the atom type and connectivity of molecular structures. *Note*: Primarily used to input chemical structures into electronic databases and now frequently replaced by the InChI notation.

Solubility: Analytical composition of a mixture or solution that is saturated with one of the components of the mixture or solution, expressed in terms of the proportion of the designated component in the designated mixture or solution. *Note 1*: Solubility may be expressed in any units corresponding to quantities that denote relative composition, such as mass, amount concentration, molality, etc. *Note 2*: The mixture or solution may involve any physical state: solid, liquid, gas, vapor, supercritical fluid. *Note 3*: The term "solubility" is also often used in a more general sense to refer to processes and phenomena related to dissolution. See equilibrium solubility, intrinsic solubility, kinetic solubility, supersaturated solution.

Spare receptor, receptor reserve: Residual binding site still available to an endogenous ligand after sufficient sites have already been filled to elicit the maximal response possible for that particular biological system. *Note*: Xenobiotics such as drugs may similarly interact with such receptors, but by definition, their identification and quantification occur via use of the natural ligand.

Stem cell: Multipotent cell with mitotic potential that may serve as a precursor for many kinds of differentiated cells. *Note*: Unipotent stem cells can differentiate into one mature cell type only.

Structural alert: Chemical features present in a hit or lead molecule indicative of potential toxicity. *Note*: Typically, such features include chemically reactive functionality and components known to metabolize to chemically reactive entities. Examples include anhydrides, aromatic amines, and epoxides.

Structure-activity relationship (SAR): Structure-activity relationship is the relationship between chemical structure and pharmacological activity for a series of compounds.

Structure-based design: Structure-based design is a drug design strategy based on the 3D structure of the target obtained by X-ray or NMR.

Structure-property correlations (SPC): Structure-property correlations refer to all statistical mathematical methods used to correlate any structural property to any other property (intrinsic, chemical, or biological), using statistical regression and pattern recognition techniques.

Supersaturated solution: Solution that has a greater composition of a solute than one that is in equilibrium with undissolved solute at specified values of temperature and pressure. See also equilibrium solubility, intrinsic solubility, kinetic solubility.

Systems biology: Integration of high-throughput biology measurements with computational models that study the projection of the mechanistic characteristics of metabolic and signaling pathways onto physiological and pathological phenotypes.

Targeted drug delivery: Approach to target a drug to a specific tissue or molecular target using a prodrug or antibody recognition systems.

Target validation: Process by which a protein, RNA, or DNA is implicated in a biological pathway thought to be of relevance to a disease or adverse pathology. *Note*: Typically, validation will involve location of the molecular target in relevant cells, organs, or tissues, evidence for its up-regulation/activation in the disorder, and the ability to attenuate adverse responses by agents known to interfere with the target.

Tautomer: Structural isomer that can readily convert to another form that differs only by the attachment position of a hydrogen atom and the location of double bond(s). *Note*: In most cases, these isomers are formed by a proton shift to or from heteroatoms such as O, N, or S as typified by the enol and keto forms of carbonyl compounds. Tautomers rapidly interconvert by proton transfer and are usually in equilibrium with one another.

Tautomerism: Reversible interconversion of two different tautomers.

Therapeutic index, therapeutic ratio: Ratio of the exposure/concentration of a therapeutic agent that causes beneficial effects to that which causes the first observed adverse effect. *Note*: A commonly used measure of therapeutic index is the toxic dose of a drug for 50% of a population divided by the minimum effective dose for 50% of a population.

Three-dimensional quantitative structure-activity relationship (3D-QSAR): A three-dimensional quantitative structure-activity relationship is the analysis of the quantitative relationship between the biological activity of a set of compounds and their spatial properties using statistical methods.

Training set: Specific group of compounds selected for characterization of both the molecular descriptors and the measured values of the targeted property. *Note*: Statistical methods applied to the set are used to derive a function between the molecular descriptors and the targeted property.

Unmet medical need: Term used for diseases or other disorders for which no optimal therapeutic options exist.

Virtual chemical library: Collection of chemical structures constructed solely in electronic form or on paper. *Note*: The building blocks required for such a library may not exist, and the chemical steps for such a library may not have been tested. These libraries are used in the design and evaluation of possible libraries.

Virtual screening, in silico screening: Evaluation of compounds using computational methods. *Note*: The source of the model could be a macromolecular structure or based on physicochemical parameters or ligand structure–activity relationships.

Volume of distribution (V_d): Apparent (hypothetical) volume of fluid required to contain the total amount of a substance in the body at the same concentration as that present in the plasma assuming equilibrium has been attained.

Wild-type receptor: Receptor that occurs naturally in human and other species.

Xenobiotic: A xenobiotic is a compound foreign to an organism (xenos [Greek] = foreign).