

Answers to Chapter Problems

Chapter 1: Introduction

1. Having properties that produce acceptable ADME/Tox.
2. Pharmacology (efficacy, selectivity) and ADME/Tox (physicochemical, metabolic, and toxicity).
3. Biologists can optimize biological assays, dosing vehicles, and routes of administration to insure quality biological data.
4. a, b, c, d

Chapter 2: Advantages of Good Drug-like Properties

1. Structure modification.
2. Physicochemical properties: physical environment (e.g., pH, co-solutes); Biochemical properties: proteins (e.g., enzymes, transporters).
3. Exploration: use chemical libraries of compounds having drug-like properties. Lead selection: select leads that have acceptable properties. Lead optimization: optimize properties by structure modification. Development selection: advance compounds to development that meet or exceed established drug-like property criteria.
4. In vitro property assays and in vivo PK measurement.
5. Development: higher attrition, slower and more expensive development; Clinical: increased patient burden and lower compliance; Product lifetime: reduced patent life.
6. Precipitation or instability make compounds appear less active; low permeability limits cell penetration for intracellular targets; poor PK properties limit therapeutic target exposure in vivo and make compounds less active; poor penetration into the CNS.
7. Structure–property relationships. How different structures affect drug-like property values.
8. a, b, c, e

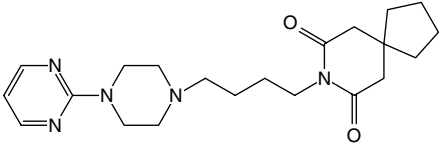
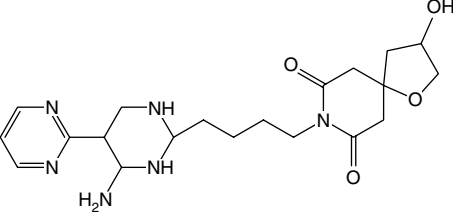
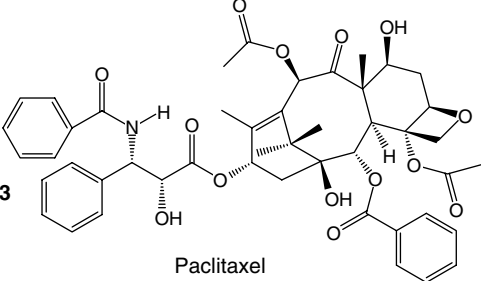
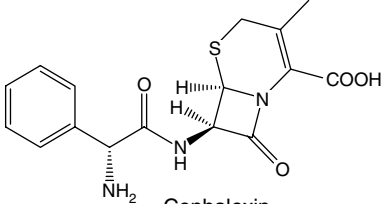
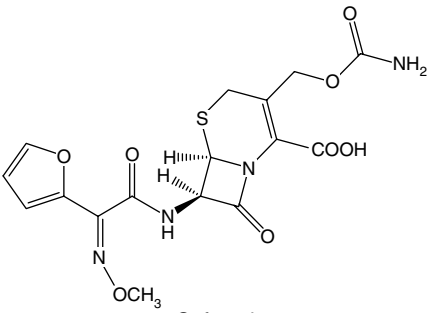
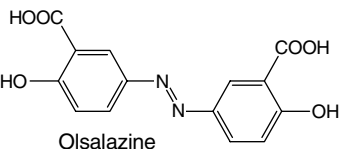
Chapter 3: Barriers to Drug Exposure in Living Systems

1. Inherent activity (target binding), exposure (drug-like properties that perform well at in vivo barriers).
2. Low dose, once per day oral tablet.
3. Property limitations for exposure include low solubility, low permeability, decomposition in the GI tract and plasma, low metabolic stability, high efflux transport, high plasma protein binding.
4. Increasing solubility results in increasing concentration at the surface of the membrane, which is favorable for higher absorption.
5. Increasing permeability results in increasing transfer of compound molecules through the membrane, resulting in higher absorption.
6. Stomach has lower surface area, shorter transit time, lower blood flow, and lower pH that can cause chemical instability.
7. pH is lower in the fasted state.
8. b, b
9. Bile, enhances solubility of lipophilic drugs. Pancreatic fluid, can catalyze hydrolysis.
10. b and c
11. b
12. Enzymatic hydrolysis, plasma protein binding, red blood cell binding.
13. e, f
14. Metabolism, biliary excretion.
15. Blood–brain barrier.
16. Metabolites are more polar and more readily extracted in the nephron.
17. d
18. a, b, c, d, f, g
19. a, c
20. all

Chapter 4: Rules for Rapid Property Profiling from Structure

1. a, d, e, h, j
2. H-bonds with water must be broken to permeate through the membrane.
3. High lipophilicity reduces solubility.
4. b
5. (a) HBD = 0, HBA = 2; (b) HBD = 1, HBA = 2

6.

Structure	#HBD	#HBA	MW	cLogP	PSA	Problem
<p>1</p>  <p>Buspirone</p>	0	7	385	1.7	70	none
<p>2</p> 	5	10	418	-3.3	143	PSA
<p>3</p>  <p>Paclitaxel</p>	4	15	852	4.5	209	HBA, MW, PSA
<p>4</p>  <p>Cephalexin</p>	4	7	347	0.5	138	none
<p>5</p>  <p>Cefuroxime</p>	4	12	424	-1.5	199	HBA, PSA
<p>6</p>  <p>Olsalazine</p>	4	8	302	3.2	141	PSA

7. a, c, e, f
8. b, d
9. a, c

Chapter 5: Lipophilicity

1. For Log P, all drug molecules are neutral in solution, whereas for Log D, anywhere from none to all molecules are ionized, depending on the compound pK_a and aqueous pH.
2. Molecular volume, dipolarity, hydrogen bonding acidity, hydrogen bond basicity.
3. $1 < \text{Log } D_{7.4} < 3$
4. Low Log P: low passive diffusion permeability. High Log P: low solubility.
5. b
6. a, c, e
7. b, c, d

Chapter 6: pK_a

1. b, d, e
2. a, c, f
3. a
- 4.

Location	pH	$[\text{HA}]/[\text{A}^-] = 10^{(pK_a - \text{pH})}$	Ionization
Stomach	1.5	$10^{(4.2-1.5)} = 10^{(2.7)}$	Neutral
Duodenum	$10^{(4.2-5.5)} = 10^{(-1.3)}$	(-) Ionized ~95%	
Blood	7.4		$10^{(4.2-7.4)} = 10^{(-3.2)}$
			(-) Ionized ~100%

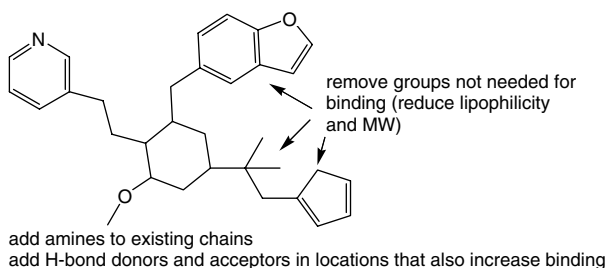
Location	pH	$[\text{BH}^+]/[\text{B}] = 10^{(pK_a - \text{pH})}$	Ionization
Stomach	1.5	$10^{(9.8-1.5)} = 10^{(8.3)}$	(+) Ionized
Duodenum	$10^{(9.8-5.5)} = 10^{(4.3)}$	(+) Ionized	
Blood	7.4	$10^{(9.8-7.4)} = 10^{(2.4)}$	(+) Ionized

5. b, d

Chapter 7: Solubility

1. The same. Both the free base and HCl salt will reach the same concentration in the buffered solution, thus, the IC_{50} will be the same.
2. No. In pure water the pH will change when the compound is added, and the sodium salt will be more soluble. Sodium salt. Yes.

3. Increase solubility: add an ionizable group, reduce Log P, add H-bonding, add polar group, out-of-plane substitution, reduce MW, prodrug, and formulation. Best: introduce ionizable groups. Increase dissolution rate: reduce particle size, formulate with surfactant, and salt form.
4. Solubility-limited absorption.
5. 2,000 $\mu\text{g/mL}$
6. In order to improve target binding, lipophilic groups are often added to the template, which reduces aqueous solubility.
7. pH, counter-ions, protein, lipid, surfactants, salts, co-solvents (types and concentrations), buffer, temperature, and incubation time.
8. Lipophilicity, molecular size, pK_a , charge, crystal lattice energy.
9. Solubility is the highest sustainable concentration; dissolution rate is how much of the compound dissolves per unit time.
10. Discovery compounds usually are amorphous solids whose thermodynamic solubility can change from batch to batch. Nearly all discovery experiments first dissolve compounds in DMSO solution.
11. (a) 10 $\mu\text{g/mL}$, (b) 100 $\mu\text{g/mL}$, (c) 520 $\mu\text{g/mL}$
12. Permeability by passive diffusion.
13. Add ionizable group.
14. b
- 15.

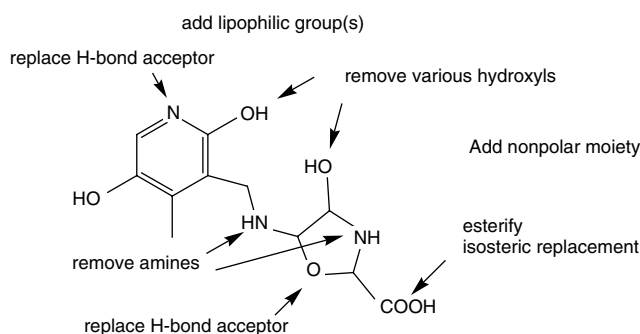


16. a, d
17. all
18. a, d
19. all

Chapter 8: Permeability

1. passive diffusion.
2. MW <180; polar.

3. (a) increase, (b) decrease.
4. Uptake into cells in cell-based assays, intestinal absorption, blood–brain and other organ barriers, therapeutic target cell penetration, entry and elimination from hepatocytes (liver), kidney nephron.
5. a, d, e
- 6.



7. a, c, e, f
8. d, b, c, a (H-bonding and polarity reduce permeability).
9. a, c, b (the lead compound already has high MW and lipophilicity, so adding more molecular mass is likely to reduce permeability).
10. a, c, b (the lead compound has low MW and lipophilicity, so adding more lipophilicity is likely to increase permeability).

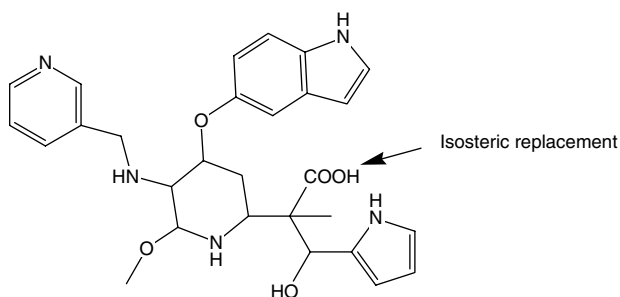
Chapter 9: Transporters

1. a, b, c, e, f, h, i
2. b
3. all
4. Pgp. It affects oral absorption, brain penetration, drug excretion, multidrug resistance tumor cells, and resistance to antibiotics. Pgp has broad substrate specificity and impacts PK profiles of many drug candidates.
5. B, D
6. Decrease H-bond acceptors, steric hindrance adjacent to H-bond acceptor, reduce lipophilicity, add groups that can disrupt Pgp binding.
7. Pgp knockout mice; Pgp inhibitor co-dosing (“chemical knockout”).
8. Efflux: b, e; Uptake: a, c, d, f.
9. c

10. all
11. a, b, c, d
12. a, b
13. C, A, B

Chapter 10: Blood–Brain Barrier

1. c
2. Drug concentration is much lower in the blood than in the GI lumen. Pgp can be saturated in the GI but not at the BBB.
3. e
4. B (MW, acid, total HB, PSA); C (MW); D (MW, acid, total HB, PSA).
- 5.



Remove unnecessary hydrogen bonders to get below 8 total (esp., donors)
 Remove unnecessary groups to get MW below 400
 Remove unnecessary polar and ionizable groups to increase cLogP

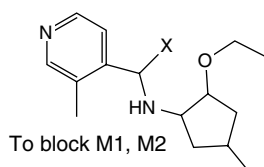
6. b, d, e, f
7. a, c, d, e, g
8. b, c, e, f
9. a, c, d, e, g

Chapter 11: Metabolic Stability

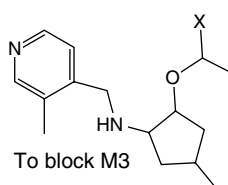
1. Intestinal decomposition (pH and enzymatic), intestinal metabolism, liver metabolism, plasma decomposition.
2. c
3. a, d
4. Change in metabolic reactions if one pathway is blocked.

5. Aliphatic and aromatic hydroxylation, *N*- and *O*-dealkylation, *N*-oxidation, *N*-hydroxylation, dehydrogenation, (others shown in Figure 11.5).
6. Glucuronidation, sulfation, *N*-acetylation, glutathione conjugation (others shown in Figure 11.6).
7. c, e
8. Possible structure modifications to investigate:

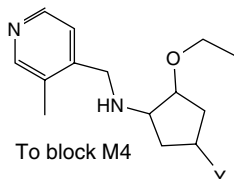
X = F, Cl, CN, CH₃, (CH₃)₂, =CH₂, CF₃, =O
Change NH to CH₂ if not necessary for activity



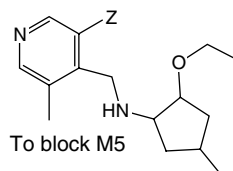
X = F, Cl, CN, CH₃, (CH₃)₂, =CH₂, CF₃, =O
Change ethyl to cyclopropyl
Remove entire ether if not necessary for activity
Change ether oxygen to CH₂ if not necessary



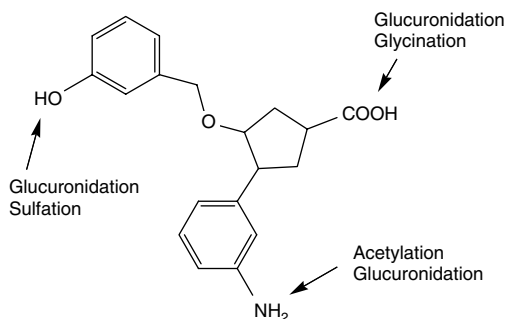
Y = CH₂F, CHF₂, CF₃, Cl, CN, cyclopropyl



Z = F, Cl, CN, CH₃, CH₂F, CHF₂, CF₃
Move N around ring or add second N



9. Potential sites of phase II metabolic reactions:

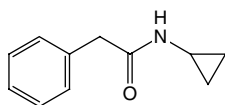


10. a, b, c, e

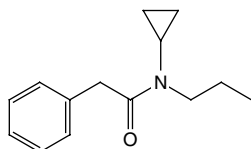
11. a, b, d, e, f

Chapter 12: Plasma Stability

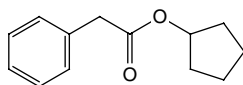
1. B, D, G, I, J, K
2. Anteddrugs, prodrugs.
3. The following are among the possible structural modifications:



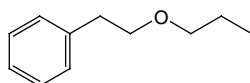
Change ester to amide



Change ester to amide,
Steric hindrance



Steric hindrance



Eliminate hydrolyzable group

4. No. The hydrolysis enzymes in microsomes and plasma are different and should be assessed separately.
5. c, d, f, g

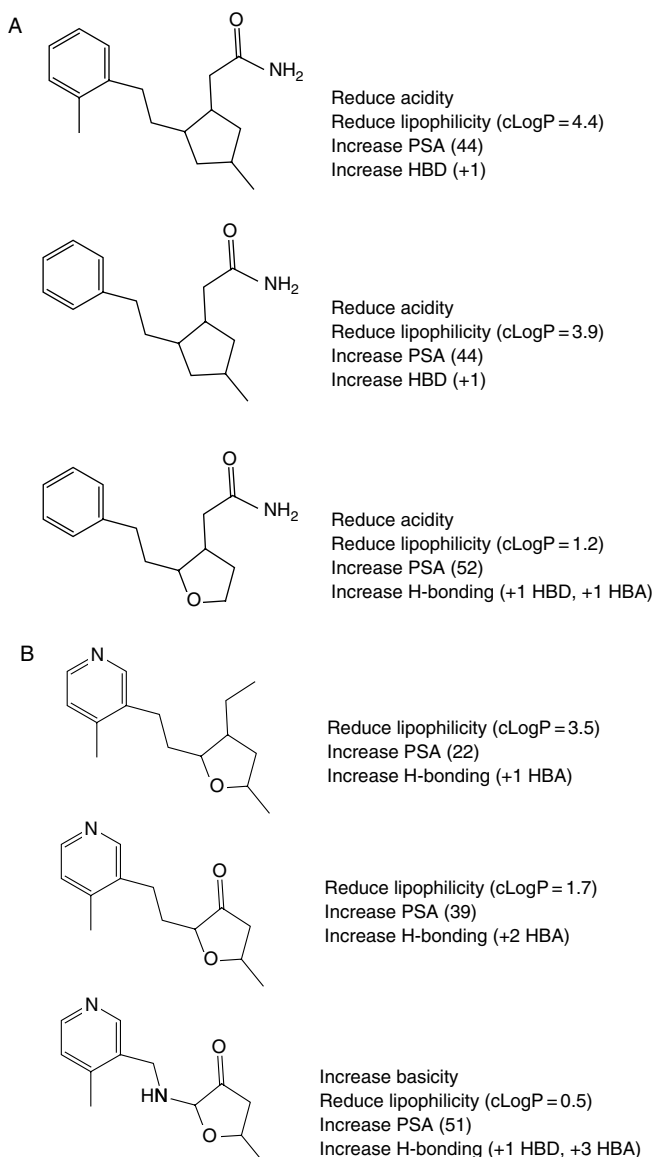
Chapter 13: Solution Stability

1. All
2. No. The stability might be improved without reducing activity by structural modification, thus allowing a valuable pharmacophore/series to continue optimization toward a quality clinical candidate.

Chapter 14: Plasma Protein Binding

1. (a) metabolic clearance decrease, (b) tissue concentration decrease, (c) tissue distribution decrease, (d) blood concentration increase, (e) renal clearance decrease, (f) PK half-life increase, (g) pharmacological effect decrease, (h) brain penetration decrease.
2. Albumin, α_1 -acid glycoprotein, lipoprotein.
3. Compound binds to albumin and is restricted from interacting with the target protein.

4.

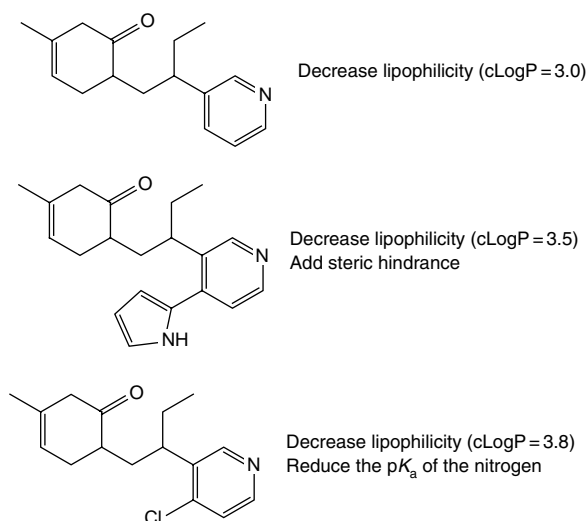


(For Example 4B, increasing basicity will likely increase binding to AGP.)

Chapter 15: Cytochrome P450 Inhibition

- 10 μM
- Greater than 10 times C_{max} . When concentration is greater than K_i .
- Seldane (terfenadine) was removed from the market because its metabolism at CYP3A4 was inhibited by 3A4 inhibitors, such as erythromycin. The resulting higher concentrations of Seldane led to hERG blocking and TdP arrhythmia in some patients.

4. In reversible inhibition, the inhibitor binds and releases from the enzyme. In mechanism-based inhibition, the inhibitor binds to the enzyme by a covalent reaction or strong complexation interaction. Dialyzing the inhibitor away from the enzyme can reduce reversible inhibition and inhibition does not increase with incubation time. Mechanism-based inhibition is not reduced by dialysis and inhibition increases with incubation time.
5. Among the possible structural modifications are the following:



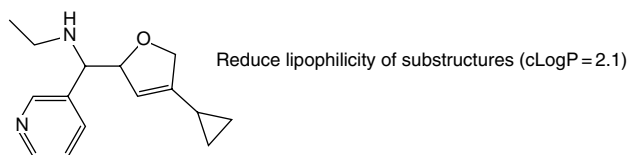
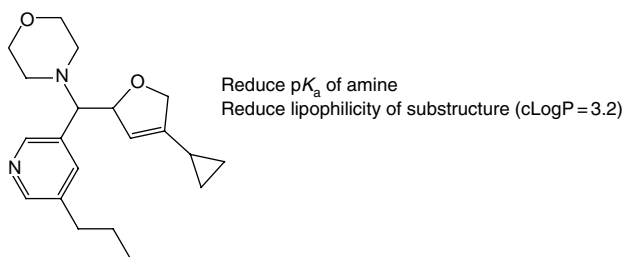
6. c

7. No. CYP inhibition involves competitive binding to a specific CYP isozyme when two compounds are present. A metabolic reaction does not need to occur to the inhibitor; it only needs to bind. In CYP inhibition, the reaction occurs to the substrate (not necessarily to the inhibitor). Metabolic stability involves one compound that (1) binds to any of the CYP isozymes and (2) reacts to form a metabolite.

Chapter 16: hERG Blocking

- Potassium ion channel in heart muscle.
- Outflow of K^+ ions from the cell is part of the action potential and reestablishes the internal negative potential of the cells.
- Lengthened QT interval on electrocardiogram (ECG).
- Torsades de pointes arrhythmia, which can be triggered by LQT.
- 1 in 10^5 to 10^6 patients for antihistamines, 1 in 5×10^4 patients for terfenadine.
- $hERG IC_{50}/C_{max, unbound} > 30$, or < 5 seconds lengthening of QT interval.
- c
- c, d

9. Among possible structural modifications are the following:



10. c

Chapter 17: Toxicity

- Ratio (or range) of compound concentrations at which it is toxic versus efficacious. Large.
- Reactive metabolites undergo covalent reactions with protein, DNA. They can be detected using glutathione or another trapping reagent.
- a, b, e
- Redox cycling by some structures (e.g., quinines) deplete the reducing capacity of the cell (e.g., glutathione), allowing free radicals and peroxides to increase.
- Higher levels of metabolizing enzymes are induced, resulting in greater chance of forming reactive metabolites or increasing the clearance of a co-administered drug.
- Antagonism or agonism of another biochemical target can cause side effects, which can be toxic.

Chapter 18: Integrity and Purity

- Activity could be due to the impurity; measured property could be inaccurate due to interference by impurity; impurity may cause a toxic effect; erroneous SAR conclusions from wrong structure.
- Mishandling, mislabeling, decomposition as a solid or in solution, inaccurate original structural assignment.
- All
- b

Chapter 19: Pharmacokinetics

1.

PK parameter	Definition choices
CL	b. rate a compound is removed from systemic circulation
C_{\max}	f. highest concentration reached in the blood
V_d	e. apparent volume into which the compound is dissolved
$t_{1/2}$	c. time for the compound's concentration in systemic circulation to decrease by half
C_0	g. initial concentration after IV dosing
AUC	d. compound's exposure as determined by blood concentration over time
%F	a. percentage of the oral dose that reaches systemic circulation unchanged

2. IV introduces the entire dose of a compound directly into the bloodstream. PO involves a delay for stomach residence, dissolution (if a solid), intestinal absorption over a couple of hours, and first-pass metabolism, which reduces the amount of compound that reaches the bloodstream.

3. (a) high nonspecific tissue binding, higher lipophilicity, lower PPB; (b) higher plasma protein binding, lower lipophilicity, higher hydrophilicity, lower nonspecific tissue binding.

4. b

5. Liver, kidney

6. 0.1: highly bloodstream restricted; 1: evenly distributed throughout the body; 100: highly tissue bound.

7. b

8. a

9. b

10.

IV dose (mg/kg)	PO dose (mg/kg)	AUC _{PO} (ng•h/mL)	AUC _{IV} (ng•h/mL)	Bioavailability
1	10	500	500	10%
2	10	1000	500	40%
5	10	300	200	75%

11. b

Chapter 20: Lead-like Compounds

1. Optimization typically synthesizes new compounds by adding moieties that increase the MW, hydrogen bonds, and lipophilicity. Such new compounds can exceed the rule of 5 and be at greater risk for poor solubility, permeability, and absorption.

2. (a) not lead-like: MW, PSA, HBD, and HBA; (b) not lead-like: PSA, HBD, HBA; (c) just over the guidelines for lead-like: MW, HBA; (d) not lead-like: MW, PSA, HBD, HBA.

3. a, c

Chapter 21: Strategies for Integrating Drug-like Properties into Drug Discovery

1. Performing target-binding optimization first can lock the project into substructures that reduce drug-like properties. There is great reluctance to eliminate structural features and reduce binding to achieve good properties. When planning structural modifications to improve target binding, an alternative is to consider the effects of the changes on the drug-like properties.
2. Faster decision-making. More new structures can be planned and synthesized to increase the chances of finding a successful structure modification that improves a property.
3. With multiple property assays, medicinal chemists do not receive specific guidance on how to modify the structure to improve the property. For example, Caco-2 permeability may have permeability components from passive diffusion, paracellular, active uptake, and efflux mechanisms. PAMPA permeability only has passive diffusion, and medicinal chemists can readily identify the structural modifications that will increase passive diffusion (e.g., increase lipophilicity, decrease hydrogen bonds, decrease polarity, change pK_a).

Chapter 22: Methods for Profiling Drug-like Properties: General Concepts

1. No. The pH 7.4 conditions of the generic solubility assay are very different than the low pH conditions of the intestine.
2. No. The Caco-2 assay is too expensive at this level. Most of the HTS hits can be deprioritized using other, less expensive data or calculated properties. After less expensive triage, a smaller number of HTS hits can be run on Caco-2 for the final decisions on leads.
3. No. Clinical candidate nomination should have a more rigorous data package that includes Caco-2 for permeability assessment.
4. No. Hydrolysis can occur in the plasma and intestine and be catalyzed by numerous enzymes, which have different substrate specificity than microsomal hydrolysis enzymes.
5. Yes. Metabolic stability varies among species. Therefore, it is useful to have data for metabolic stability in rat (often used as the toxicology species), the project's pharmacology/efficacy species (e.g., stability in transgenic mice can help with decisions on in vivo dosing and data interpretation if the pharmacology/efficacy species is transgenic), and human (assists predictions for clinical studies).

Chapter 23: Lipophilicity Methods

1. Drug discovery compounds may contain substructures not covered adequately in the training set for the software. Also, they generally have fewer drug-like properties than the commercial drugs on which the in silico models were built and behave more poorly.
2. Yes. Log P has been studied for many more years, so the underlying mechanisms are better understood. High-quality measurements of Log P, which are used to build the in silico models, are more available than for other properties.

- a, b, d, e, f, g
- Standards, whose Log D values were previously measured using an in-depth method, are run on the same system. Their retention times are plotted versus their Log D values.
- A factor of 10 or 1 Log unit.
- a, d, e

Chapter 24: pK_a Methods

- As the ionizable group is titrated from neutral to charged (or vice versa), the following can be detected: (1) change in the UV absorbance of a group near the ionizable group, (2) change in pH of the solution, or (3) change in electrophoretic mobility.
- Throughput: *in silico* > SGA > CE > pH metric.
- Features: high throughput; pK_a is calculated for different tautomers; the software labels each ionization center with its pK_a on the structure.
- Yes. As with *all* assays, low solubility can affect the measurement. Either no data should be reported for very-low-solubility compounds, or methods should be modified and validated to work accurately for low solubility compounds.

Chapter 25: Solubility Methods

- $\text{Log } S = 0.8 - \text{Log } P - 0.01$ (MP-25)

Compound	Melting point (°C)	Log P	Estimated solubility (mol/L)
1	125	0.8	0.1
2	125	1.8	0.01
3	225	1.8	0.001
4	225	3.8	0.00001

- $S_{\text{tot}} = S_{\text{HA}} (1 + 10^{(\text{pH} - \text{p}K_a)})$

Compound	Intrinsic solubility (g/mL)	pK_a	pH	Total solubility (g/mL)
1	0.001	4.4	7.4	1
2	0.001	4.4	4.4	0.002
3	0.001	4.4	8.4	10
4	0.00001	4.4	7.4	0.01

- Nephelometric: light scattering by precipitated particles. Direct UV: dissolved compound in aqueous solution.
- Customized solubility methods use the same solution conditions as the experiment in a discovery team experiment (e.g., bioassay buffer) in order to better estimate the solubility of a compound under the conditions of interest.
- Compound form: kinetic solubility uses a DMSO solution, whereas equilibrium solubility uses solid. Compound addition: kinetic solubility adds a small volume of DMSO solution

to an aqueous buffer, whereas equilibrium solubility adds buffer to solid compound. Time: kinetic solubility uses 1 to 18 hours of incubation, whereas equilibrium solubility uses 24 to 72 hours of incubation.

6. a, d, e

Chapter 26: Permeability Methods

1.

Method	Passive diffusion	Active uptake	Efflux	Paracellular
IAM	X			
PAMPA	X			
Caco-2	X	X	X	X

2. IAM uses HPLC instrumentation, which is widely available in drug discovery laboratories.

3. (a) 21 days of cell culture prior to use; (b) LC/MS quantitation; (c) Caco-2 is often run in both A>B and B>A directions; (d) more expensive supplies; (e) more scientists' time.

4. Active uptake transport, efflux transport, paracellular.

5. IAM uses phospholipids bonded to the solid support, whereas reversed phases commonly use bonded octadecane.

6. Bases appear to be effluxed. Acids appear to be actively taken up.

7.

Compound's permeability mechanism(s)	PAMPA relatively higher than Caco-2	Caco-2 relatively higher than PAMPA	PAMPA and Caco-2 relatively the same
Passive diffusion only			X
Passive diffusion and active uptake		X	
Passive diffusion and efflux	X		
Passive diffusion and paracellular		X	

Chapter 27: Transporter Methods

1. $ER = P_{B>A}/P_{A>B}$. $ER > 2$ indicates significant compound efflux.

2. (a) Measure $P_{A>B}$ with and without an efflux transporter-specific inhibitor. If $P_{A>B}$ is greater in the presence of the inhibitor, the compound is an efflux substrate. (b) Measure $P_{A>B}$ with a cell line (e.g., MDCKII) transfected with the gene of one specific efflux transporter (e.g., MDR1) and with the wild-type cell line. If $P_{A>B}$ is greater in the wild type, the compound is likely to be an efflux substrate.

3. Uptake is useful when (a) the cell line does not form a confluent monolayer with tight junctions that allow for a transwell experiment, (b) the discovery project team is interested in a specific cell line.

4. Binding of a test compound to an ABC transporter (e.g., Pgp). The ATP hydrolyzes to form ADP and Pi. The Pi is detected colorimetrically.
5. Inhibition of Pgp, which limits efflux of a known Pgp substrate (calcein-AM).
6. In vivo Pgp assay (Pgp knockout mouse) demonstrates proof-of-concept that Pgp affects the ADME characteristics of the compound.
7. Genetic knockout is a permanent condition in which no Pgp gene is present and none is expressed, thus no Pgp efflux can occur. The chemical knockout experiment involves the co-administration of a Pgp inhibitor with the test compound or saturation with test compound to reduce efflux. Chemical knockout can be used in the efficacy/pharmacology species model to test biological effects of Pgp substrates.

Chapter 28: Blood–Brain Barrier Methods

1. BBB permeation is the velocity of compound transfer across the BBB into the brain; brain distribution is the partitioning of compound between blood and brain tissue.
2. Hydrogen bonding, PSA, lipophilicity, MW, basicity/acidity.
3. Classification of passive BBB permeability (CNS +, CNS –)
4. Plasma and buffer; brain homogenate and buffer. It is a brain distribution method. The method indicates free drug concentration in the brain, free drug concentration in plasma, and predicted B/P.
5. Hydrogen bonding capacity.
6. BBB permeability by passive diffusion.
7. The isolation process is difficult and time consuming. Cells do not form tight junctions. Transporters may be overexpressed or underexpressed.
8. MDR1-MDCKII is primarily used for Pgp efflux and, occasionally, as a model of total BBB permeability. MDCK (without MDR1) is used for passive diffusion.
9. B/P limitations are it is resource intensive, B/P is a distribution ratio that is heavily affected by plasma protein and brain tissue binding but not necessarily by free drug.
10. BBB permeability (unaffected by brain tissue binding, plasma binding, or metabolism).

Chapter 29: Metabolic Stability Methods

1. S9 and hepatocytes contain more metabolizing enzymes than microsomes; thus, they survey a broader number of potential metabolic reactions. Hepatocytes also involve cell membrane permeability.
2. When the compound has a phenol, carboxylic acid, or other hydroxyl that might be susceptible to glucuronidation. In other compounds, glucuronidation may be observed as a minor metabolite but is not likely to be the rate-determining reaction for metabolic stability. Sulfation is rapid but is saturable and has limited capacity.
3. CYP-containing materials: rhCYP, microsomes, S9, hepatocytes, and liver slices contain CYPs. S9, hepatocytes, and liver slices contain sulfotransferases.

4. NADPH.
5. CYP enzymes can be saturated at higher concentration and give a falsely high metabolic stability value.
6. Metabolic stability usually varies among species, which may be important to the project.
7. The relationship between log (% remaining) and time is linear, so two points define the line. Additional time points add precision and accuracy but require additional resources.
8. Activity varies with each batch. If a project team is rank ordering compounds that were measured for metabolic stability using different microsomes batches, it is important that the activity be consistent or the rank ordering, or the structure–metabolism relationships, will be erroneous.
9. Uridine diphosphate glucuronic acid (UDPGA), 3'-phosphoadenosine-5'-phosphosulfate (PAPS).
10. None. Hepatocytes generate their own co-factors.
11. (a) guiding structure modification for improvement of metabolic stability, (b) anticipating potential DDI.
12. Determine specifically where the metabolism occurred on the structure, to guide structural modification of a compound to block metabolism.
13. LC/MS/MS provides a profile of major metabolites and unambiguously identifies some metabolites (e.g., dealkylations). NMR provides regiospecific identifications of sites of hydroxylation and other metabolic reactions (e.g., position of the hydroxyl on a phenyl ring).

Chapter 30: Plasma Stability Methods

1. Hydrolytic enzymes of widely different binding specificity, e.g., esterases, lipases, and phosphatases.
2. Check the activity for comparison to previous batches; adjust the method conditions for consistent activity on QC compounds. Activity of different plasma batches can vary significantly.
3. (a) false (as long as you stay within the ranges discussed in the chapter); (b) true; (c) true; (d) true; (e) false.

Chapter 31: Solution Stability Methods

1. Bioassay media components, pH buffers, intestinal fluid, gastric fluid, enzymes, light, oxygen, temperature.
2. Quenching the reaction.
3. Use a programmable HPLC autosampler that can add reagents, mix, inject at predetermined time points, and perform these functions for multiple samples.
4. Use the same conditions and protocol that are relevant to the project's experiment in question.

5. Reaction kinetics (used to predict long-term stability); structures of decomposition products (used to modify structures for improved stability).
6. Diagnose unexplained results from in vivo or in vitro experiments; rank ordering compounds for stability; apply kinetics for planning other experiments or clinical studies; predict how much compound remains at various times; determine which moiety is unstable; guide structural modifications to improve stability.

Chapter 32: CYP Inhibition Methods

1. Recombinant human CYP isozymes (rhCYP); human liver microsomes.
2. High substrate turnover; high test compound metabolism; protein binding.
3. Fluorogenic; drug compounds; luminogenic; radioactive.
4. b
5. Fluorescent test compound or metabolites will interfere with the results.
6. Multiple CYP isozymes are simultaneously assayed, thus increasing throughput.
7. High substrate and test compound metabolism (turnover), for some isozymes, and protein binding increase the apparent IC_{50} of CYP inhibition, making the test compound appear less inhibitory. Conditions are not optimal for enzyme kinetics of most of the isoforms.
8. The concentrations of each isozyme and substrate can be set up independently from the other isozymes, thus allowing optimum enzymatic conditions for accurate initial enzyme kinetic rates.

Chapter 33: Plasma Protein Binding Methods

1. Equilibrium dialysis.
2. The equilibrium concentration of the chamber containing buffer without plasma protein.
3. The compound will appear to have higher clearance because it is not detected in the plasma.
4. The membrane filter prevents plasma proteins from passing, thus allowing the unbound compound concentration to be independently measured.

Chapter 34: hERG Methods

1. Alerting the project team early to potential hERG blocking problems. This allows the team to investigate further before major investment in synthesis of analogs for a lead series that may later fail.
2. Patch clamp.
3. Human ECG studies.
4. a, c
5. High IC_{50} values compared to patch clamp.
6. b, c

7. K^+ ; Rubidium (Rb) is the same size and charge as K^+ and can permeate through the K^+ channel. Rb can be sensitively detected using radioactivity with ^{86}Rb or atomic absorption spectroscopy with stable Rb.
8. c, d
9. The current required to hold the transmembrane potential at a constant voltage.
10. The standard patch clamp method is manual and time consuming, and requires highly skilled scientists to perform accurately.
11. a, c, d

Chapter 35: Toxicity Methods

1. Structural rules decided by expert committees and QSAR models.
2. An indication or alert to potential toxicity problems that can be followed up experimentally.
3. CYP3A4 induction.
4. Test the activity of each isozyme before and after incubation with the test compound. If the activity increases with test compound treatment, the compound induced the enzyme.
5. c, d
- 6.

Assay	DNA fragments move faster in gel electrophoresis than normal DNA	Abnormally divided DNA is observed by microscope	Reversion mutations allow colonies to grow without histidine	Unusually shaped chromosomes	Normal mammalian cells mutate so TMP does not kill them
Micronucleus Chromosomal aberration		X		X	
Comet	X				
Ames			X		
TK mouse lymphoma					X

7. c
8. Microscopic examination of embryos from rodents or zebrafish.
9. Glutathione
10. Animal dosing studies to determine maximum tolerable dose, such as acute dose, chronic dose (e.g., 2 weeks), safety pharmacology with full microscopic histology. In vitro genotoxicity/mutagenicity studies, such as Ames, micronucleus, and chromosome aberration.
11. Toxicometabonomics (measures changes in normal endogenous biochemical intermediates); toxicoproteomics (measures changes in protein expression); toxicogenomics (measures changes in mRNA expression).

Chapter 36: Integrity and Purity Methods

1. To increase throughput and deliver data to teams sooner. For example, 1,000 samples require 42 days to complete at 30 minutes per analysis versus 3.5 days at 5 minutes per analysis.
2. NMR spectral interpretation makes the time per sample too long. Also, impurities can be observed in NMR, but the number of impurities and their relative amounts are hard to determine because there is no chromatographic separation.
3. The undissolved material may be a different compound. If it is the putative compound, impurities will appear to be a higher relative concentration.
4. The small-particle columns enhance resolution and allow short analysis times (1–1.5 minutes per sample).
5. No HPLC detector responds on a molar basis for all compounds. Response per number of molecules varies with compound. Therefore, purity is a relative response versus the more desirable relative number of moles. Furthermore, no detector produces a response for all compounds. Some compounds do not respond to the detector and remain undetected.
6. No MS interfaces produces ions for all compounds. Nor do they produce the same types of ions for all compounds. For example, the commonly used electrospray interface makes positive $(M + 1)^+$ ions for basic compounds, negative $(M - 1)^-$ ions for acidic compounds, adduct ions (e.g., $M + \text{NH}_4$)⁺ ions for neutral compounds, and no ions for some compounds. A trained scientist should examine the data for consistency with expected ionization.

Chapter 37: Pharmacokinetic Methods

1. Co-dosing multiple compounds reduces the number of animals used in PK experimentation. It also shortens the experimental time, so the project team receives the data faster. It is useful for initial PK screening of many compounds and can be later followed up with more detailed studies of selected compounds.
2. The criticism of cassette dosing is that compounds may interact and affect each other's PK parameters, especially with regard to metabolizing enzymes and transporters. This has been addressed by reducing the dosing level (mg/kg) to reduce interaction. Also, a compound with known PK parameters is added to the cocktail, and, if its PK parameters are affected, the study is repeated with individual compounds.
3. Samples are obtained unattended around the clock, thus allowing fewer scientist hours and improving scheduling.
4. In CARRS, the compounds are individually dosed. The samples from two animals, dosed with the same compound, are pooled to reduce the analyses by half.
5. Matrix suppression is the co-elution of plasma matrix material from the HPLC column into the mass spectrometer along with the test compound. This material suppresses the ion signal from the test compound and causes a falsely low or variable signal.
6. The team wants to know the concentration of a compound in the disease target tissue, in order to correlate in vivo concentration to pharmacological effects or to determine if the compound is penetrating into the tissue (e.g., brain, tumor) to a sufficient concentration.

7.

cpd	Dose [IV, PO] (mg/kg)	AUC _{PO} (ng•h/mL)	C ₀ (ng/mL)	AUC _{IV} (ng•h/mL)	CL (mL/min/kg)	V _d (L/kg)	%F
1	1, 10	2,000	1,000	4,000	4.2	1	5%
2	1, 10	2,000	2,000	1,000	17	0.5	20%
3	5, 10	200	1,000	8,000	10	5	1.3%
4	1, 10	500	1,000	200	83	1	25%
5	5, 30	305	2,000	1,900	44	2.5	2.7%

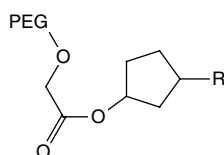
Chapter 38: Diagnosing and Improving Pharmacokinetic Performance

1. Alternate formulation; salt forms; prodrugs; different dosing route (e.g., IV, IP, SC, IM).
2. Structure modifications that improve the limiting property.
3. Solubility, permeability, first-pass metabolism (GI and liver); intestinal solution stability.
4. a, c, f, g, m
5. a, c, j, k, o, p, q
6. b, d

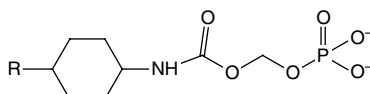
Chapter 39: Prodrugs

1. b, c, e, g
2. Among the possible prodrug analogs are the following:

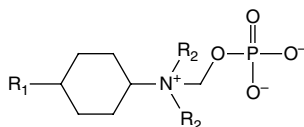
A.



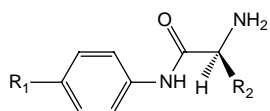
B.



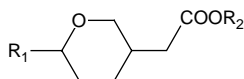
C.



D.



3. Ester prodrug:



4. Alkaline phosphatase.

5. Hydrolyzed by esterase in blood

Chapter 40: Effects of Properties on Biological Assays

- Solubility in cell assay media, stability in cell assay media, permeability through the cell membrane, and toxicity to the cell.
- If the property limitation can be diagnosed, structural modifications might improve the property without losing a valuable pharmacophore. If the assay characteristics are improved (e.g., to better solubilize or maintain the stability of a series), more accurate SAR may be derived. When multiple variables (i.e., properties, target binding) contribute to the final activity, discovery project teams are left without clear guidance for decision making and planning structural modifications to improve activity or properties.
- Class 1: lower MW, rigid, hydrophilic (e.g., organic salts); Class 2: high MW, high Log P, many rotatable bonds.
- Higher concentrations: if precipitate is carried from the DMSO stock solution into the aqueous solution and dissolves. Lower concentrations: if only the solution portion of the DMSO is carried into the aqueous solution; if both solution portion and particulate is carried into the aqueous solution and the precipitate does not dissolve.
- Cooling of the solution can enhance crystallization and crystals are harder to redissolve. Condensation of water in the DMSO stock solution can lower the solubility of the compound.
- (1) Class 1 may better dissolve in 1:1 aqueous/DMSO solution. (2) Another solvent can be substituted for DMSO. (3) Use the DMSO solution for a minimum time or a single time. (4) Store DMSO solutions at room temperature for a short term use (e.g., 2 weeks). (5) Make DMSO solution at a lower concentration. (6) Sonication.
- Higher IC_{50} .
- (1) Modify the dilution protocol. (2) Optimize the solutions to better solubilize compounds.
- c
- c, d
- DMSO, other organic co-solvents, protein, excipients.

12. Molecular properties (H-bond donors, H-bond acceptors, MW, PSA, acidity), PAMPA, Caco-2.
13. IC₅₀ right shift is caused when the concentrations of each point in the dilution curve are actually lower than intended. This is caused when the concentration of the initial (highest) concentration point is low because of compound precipitation or another error.
14. Often lower DMSO concentration and other co-solutes are used in cell-based assays, resulting in precipitation of low-solubility compounds. During method development, the tolerance of the assay for higher DMSO or other co-solvents can be tested and the DMSO concentration can be maximized for the final assay. The assay may also tolerate higher concentrations of other co-solvents, which can be used instead of DMSO.

Chapter 41: Formulation

1. Oral (PO). This route is limited by low solubility, low permeability, or high first-pass metabolism.
2. Rapid onset, bioavailability of the entire dose.
3. a, d, e, g
4. An in situ salt is a solution of the compound in a buffer that fully ionizes the compound and provides a counter-ion to keep it solubilized. For a basic compound of pK_a 9.5, HCl could be added to adjust the pH to <7.5 and provide the counter-ion.
5. Co-solvents: ethanol, propylene glycol, PEG400. Function: increase solubility of the compound.
6. a, c, d
7. Tween 80/Methocel. Tween 80 is a surfactant that wets the surface of the compound particles. Methocel helps keep the particles in suspension so that they do not settle.
8. Pure oil (100% oil dissolves a highly lipophilic compound), emulsion (a compound is dissolved in oil and dispersed as droplets into aqueous buffer with the aid of surfactant or emulsifier), micelle (spherical monolayer with hydrophilic shell and lipophilic core with which the lipophilic compound associates), liposome (spherical bilayer in which hydrophilic compounds are held in the central core or lipophilic compounds are associated with the lipophilic portion of the bilayer).
9. The hydrophilic outer shell interacts with water and the lipophilic compound is held in the central core, which is more lipophilic.
10. Small compound particle size, amorphous particles are more soluble than crystals, the particles are released directly into an aqueous environment.
11. Increases surface area for faster dissolution.
12. Eliminates the effects of solubility and solid-state properties.
13. Provides maximal exposure to study the pharmacological effects rather than being confused by delivery effects.
14. c, d, e

General References

1. Avdeef, A. (2003). *Absorption and drug development: solubility, permeability, and charge state*. New York: John Wiley & Sons.
2. Berg, J. M., Tymoczko, J. L., & Stryer, L. (2002). *Biochemistry*. New York: WH Freeman and Company, New York.
3. Birkett, D. J. (2002). *Pharmacokinetics made easy*. North Ryde, Australia: McGraw-Hill Australia.
4. Borhardt, R. T., Kerns, E. H., Lipinski, C. A., Thakker, D. R., & Wang, B. (Eds.). (2004). *Pharmaceutical profiling in drug discovery for lead selection*. Arlington, Virginia: AAPS Press.
5. Borhardt, R. T., Kerns, E. H., Hageman, M. J., Thakker, H. R., & Stevens, J. L. (Eds.). (2006). *Optimizing the "drug-like" properties of leads in drug discovery*. Arlington, Virginia: AAPS Press and Springer.
6. Kwon, Y. (2001). *Handbook of essential pharmacokinetics, pharmacodynamics and drug metabolism for industrial scientists*. New York: Springer.
7. Martin, A. (1993) *Physical pharmacy*. Philadelphia: Lea & Febiger.
8. Rodrigues, A. D. (Ed). (2002). *Drug-drug interactions*. New York: Marcel Dekker.
9. Silverman, R. B. (2004) *The organic chemistry of drug design and drug action* (2nd ed.). San Diego: Elsevier Academic Press.
10. Smith, D. A., Van de Waterbeemd, H., & Walker, D. K. (2001). *Pharmacokinetics and metabolism in drug design*. Weinheim, Germany: Wiley-VCH.
11. Testa, B., van de Waterbeemd, H., Folkers, G., & Guy, R. (Eds.). (2002). *Pharmacokinetic optimization in drug research, biological, physicochemical and computational strategies*. Postfach, Switzerland: Verlag Helvetica Chimica Acta.
12. Testa, B., Krämer, S. D., Wunderli-Allenspach, H., & Folkers, G. (Eds.). (2006). *Pharmacokinetic profiling in drug research*. Zurich, Switzerland: Verlag Helvetica Chimica Acta.
13. Testa, B., & van de Waterbeemd, H. (Eds.). (2007). *Comprehensive medicinal chemistry II, vol. 5, ADME-Tox approaches*. Amsterdam: Elsevier.
14. Van de Waterbeemd, H., Linnernäs, H., & Artursson, P. (Eds.). (2003). *Drug bioavailability*. Weinheim, Germany: Wiley-VCH.
15. Wermuth, C. G. (Ed.). (2003). *The practice of medicinal chemistry*. San Diego: Elsevier-Academic Press.
16. Yan, Z., Caldwell, & Gary W. (2004). *Optimization in drug discovery; in vitro methods*. Totowa: Humana Press.

Glossary

Term	Acronym	Definition
absorptive direction		having the tendency to absorb; moving in the direction of absorption or uptake (e.g., from intestinal lumen into bloodstream, or from apical to basolateral faces of cells)
absorption		process of absorbing
acidity		level of hydrogen ion concentration in solution as measured on the negative logarithmic pH scale (1 is highly acidic [10^{-1} M] and 14 [10^{-14} M] is highly basic or alkaline); the more readily a compound gives up a proton, the more acidic it is
action potential		change in voltage across a cell membrane with the opening and closing of ion channels (e.g., in a muscle or nerve cell)
active transport		facilitated movement of a molecule across a cellular membrane from a point of lower concentration to a point of higher concentration; requires energy
activity		capacity to produce physiological or chemical effects by the binding of the molecule to a biological macromolecule
acute		occurring with rapid onset, in a short time, after a single dose, or lasting a short time
ADME	ADME	absorption, distribution, metabolism, and excretion
ADME/Tox	ADME/Tox	absorption, distribution, metabolism, excretion, and toxicity
administer		dose a compound
advance		select a compound to move forward in the discovery and development pipeline
albumin (serum)		major plasma protein (60% of total); involved in regulating osmotic pressure and transporting large organic anions (e.g., fatty acids, bilirubin, many drugs, hormones)

Term	Acronym	Definition
Ames assay		procedure for testing a compound's ability to cause DNA mutation, which may cause cancer
amorphous solid		solid in which atoms or ions are not arranged in a definite crystal structure
amphipathic		molecules that have both hydrophilic and hydrophobic parts
amphiphilic		molecule that combines hydrophilic and lipophilic properties
amylase		digestive enzyme that catalyzes the hydrolysis of starch (carbohydrate)
analog		structural derivative of a parent compound whose chemical and biological properties may be quite different
anion		negatively charged ion (e.g., chloride)
antdrug		locally active synthetic derivative of a drug that undergoes biotransformation to a readily excretable inactive form upon entry into the systemic circulation, thus minimizing systemic side effects; also called a <i>soft drug</i>
apical	A	initial face of a cell encountered by compound moving in the absorptive direction (e.g., top side of Caco-2 cells)
area under the curve	AUC	pharmacokinetic term for the integrated area under a plot of compound plasma concentration (y-axis, ordinate) vs time (x-axis, abscissa) from a dosed test animal; used to evaluate total exposure to the compound over time
barrier		obstacle to the access of molecules to the therapeutic target which results in reduced compound concentration at the target or delayed access (e.g., membrane, metabolism, pH)
basicity		level of hydrogen ion concentration in solution as measured on the negative logarithmic pH scale (1 is highly acidic [10^{-1} M] and 14 [10^{-14} M] is highly basic or alkaline); the more readily a compound accepts a proton, the more basic it is
basolateral	B	exiting face of a cell for molecules moving in the absorptive direction (e.g., bottom side of Caco-2 cells)
bilayer membrane		dual layer of phospholipids having the nonpolar side chains oriented inward and polar head groups toward the aqueous solutions
bile canaliculus		capillaries between hepatocytes for collection of bile and solutes (e.g., bile salts, drugs, metabolites), which merge to form bile ductules, which merge into the bile duct
bile salts		steroid acids that form micelles in the intestinal lumen and assist solubilization of lipophilic compounds (e.g., lipids, fatty acids, lipophilic drugs) by emulsification

Term	Acronym	Definition
biliary excretion		elimination of compound via bile
binding		energetic association of compound with a macromolecule (e.g., therapeutic target protein)
bioactivity		degree of response produced when a compound is administered to a living system, living tissue, or biochemical assay
bioassay		procedure for testing if a compound produces a biochemical or biological response compared to a standard
bioavailability	F	fraction of administered compound that is detected in systemic circulation after administration; losses result from lack of absorption into the systemic circulation and/or metabolic clearance; oral bioavailability is associated with oral administration
bioequivalence	BE	degree to which one compound formulation acts in the body with the same strength and bioavailability as a standard formulation
bioequivalent		formulations are bioequivalent if the nature and extent of therapeutic and toxic effects are equal following the administration of equal doses
bioisosteric		compound resulting from exchange of a moiety with another in order to have similar biological properties to the parent compound, but modified properties
biomarker		endogenous biochemical compound whose concentration indicates the progress of a disease or the effects of treatment
Biopharmaceutics Classification System	BCS	method of evaluating compound solubility, permeability, and dose for the purpose of granting waivers by regulatory agencies for bioequivalence and bioavailability studies
biotransformation		chemical alteration of a molecule by enzymes
blockbuster		drug product with sales greater than \$1 billion (U.S.) per year
blocking (ion channel)		partial or complete obstruction of an ion channel so that ions cannot pass at a normal rate
blood flow to organ	Q	flow rate of blood to an organ (e.g., liver)
blood–brain barrier	BBB	endothelial cell layer of the brain microvessels between blood and brain; restricts passage of some compounds into brain tissue, depending on the compound structure
blood–cerebrospinal fluid barrier	BCSFB	barrier located at the tight junctions that surround and connect the cuboidal epithelial cells on the surface of the choroid plexus
bound drug	C_{bound}	compound molecules bound to a protein or lipid
brain microvessel endothelial cells	C_B BMEC	endothelial cells removed from microcapillary blood vessels of brain and cultured for BBB permeability studies

Term	Acronym	Definition
brain/plasma ratio	B/P	ratio of compound in brain to plasma, which is variously calculated using AUC, C_{max} , or concentration at a time point
breast cancer resistance protein	BCRP	membrane efflux transporter family
brush border		specialization of the free surface of a cell to have microvilli that increase the surface area (e.g., on epithelial cells lining the intestine)
buccal		inner lining of cheeks or lips
buffer		solution of ionic compound(s) that resists changes in pH
Caco-2	Caco-2	human colon carcinoma cell line for which one use is intestinal permeability studies
candidate		compound considered for approval of entry into drug development; compound undergoing studies from preclinical through phase I–IV clinical trials until NDA approval
cannulation		insertion of a tube into a body cavity, duct, or vessel for the drainage of fluid or administration of medication
capillary electrophoresis	CE	separation technique using a capillary tube filled with buffer and forming a circuit across a high voltage
carcinogenic		compound that causes cancer
cassette dosing		co-administration of multiple compounds for simultaneous assessment of pharmacokinetic parameters using a single test animal
cation		positively charged ion
central nervous system	CNS	brain and spinal cord
cerebrospinal fluid	CSF	fluid that is continuously produced by the brain's choroid plexus, flows in the ventricles and around the surface of the brain and spinal cord, and is absorbed into the venous system; it absorbs shock and maintains constant pressure
chiral		having asymmetric centers that are not superimposable
chiral center		tetrahedral carbon atom having four different attached groups
chromosome		assembly in the cell nucleus consisting of a single long thread of DNA (containing many genes) and associated proteins, which tightens up into a defined structure for cell division; occurs in pairs with one from the father and one from the mother
chronic		occurring over a long duration, frequently reoccurring, being long lasting, or continual regular dosing or exposure
classification		categorization of things into classes or categories of the same type
clearance	Cl	volume of blood from which the drug is completely removed per unit time by the various elimination processes; amount eliminated is proportional to the concentration of the drug in the blood
cLogP	cLogP	Log P calculated using structure

Term	Acronym	Definition
CNS–	CNS–	compound does not penetrate appreciably into brain tissue after dosing, as determined by absence of a measurable concentration or lack of the expected pharmacological response
CNS+	CNS+	compound penetrates appreciably into brain tissue after dosing as determined by a measurable concentration or positive pharmacological response
co-administer		dose at the same time
cocktail		mixture of compounds used for in vivo PK cassette dosing or for in vitro assays that simultaneously assess multiple compounds or properties (e.g., cocktail CYP450 inhibition assay of multiple isozymes)
cost/benefit ratio		resources required to obtain a certain measurement vs the benefit that data have for a project team
counter-ion		ion with an opposite charge to that of another ion in the solution or salt
crystal form		geometric configuration in which a compound forms a crystal (often two or more polymorphs of a compound have different crystal energies)
cytochrome	CYP	enzyme family containing a heme porphyrin to which an iron atom is attached; important in cell respiration as catalysts of oxidation–reduction reactions
cytochrome P450	CYP450	family of cytochrome isozymes that absorb light at 450 nm and oxidize compounds in many tissues; found in high abundance in the liver
cytotoxicity		degree of a compound's ability to damage or kill cells
Dalton	Da	unit of mass used for molecules, equal to one twelfth of the atomic mass of ^{12}C
degradation product		chemical product of an undesired reaction of a compound owing to its environment (e.g., oxidation of a compound caused by air O_2)
delta Log P	$\Delta\text{Log P}$	difference in Log P values for partitioning between aqueous and organic solvents [e.g., $\text{Log P}_{(\text{octanol-water})}$ minus $\text{Log P}_{(\text{cyclohexane-water})}$]
development		studies following discovery that takes a compound with desired biological effects in animal models and prepares and tests it as a drug product that can be used in humans; includes formulation, stability, chemical process, human pharmacokinetics, toxicity, and clinical efficacy

Term	Acronym	Definition
dialysis		separation of smaller molecules (e.g., drugs) from larger molecules (e.g., proteins) in solution by selective diffusion through a semipermeable membrane
discovery		research that finds compounds with desirable biological effects in animal models, which have potential to become new drugs in humans
disposition		what happens to a compound after it is administered to an organism; fate
dissolution		dissolving in a solution
distribution	D	movement of compound molecules into tissues of an organism
DMSO	DMSO	dimethylsulfoxide
dosage form		physical combination of a compound (e.g., drug) with additives (e.g., excipients, encapsulation) for administration to the test animal or human (e.g., tablet, lotion, solution)
dosing regimen		systematic plan of dosing (i.e., dosage, route, frequency)
dosing solution		solution of compound for administration to a test animal which may include additives to solubilize the compound
drug product		dosage form that is dispensed to patients
drug substance		pharmacologically active component of a drug product
drug–drug interaction	DDI	interference of molecules of one drug with the normal disposition of molecules of another drug when they are co-administered
drug-like		having properties that are consistent with most commercial drugs and lead to acceptable pharmacokinetics and toxicity in humans
DTT	DTT	dithiothreitol
duodenum		first segment of the small intestine following the stomach
EC ₅₀	EC ₅₀	median effective concentration (concentration that induces a 50% effect in a functional in vitro assay)
ED ₅₀	ED ₅₀	median efficacious dose (dose that produces the desired effect in 50% of population in an in vivo assay)
efficacy		ability to produce the desired pharmacological effect (control or cure) on the test animal or human
efflux		transport of a molecule out of a cell by a transporter with the expenditure of energy
efflux ratio	ER	permeability in the secretory direction (basolateral to apical) divided by permeability in the absorptive direction (apical to basolateral) using an in vitro cell layer assay (e.g., Caco-2)
electrocardiogram	ECG	graphic record from measurement of voltage changes on the surface of the heart resulting from conductance of action potentials across the muscle

Term	Acronym	Definition
elimination		disappearance of a dosed compound from a living organism, usually by metabolic biotransformation and/or excretion by intestine, kidneys, lungs, skin, or any other bodily fluid
elimination rate constant	k	first-order kinetics indicating the rate of compound elimination; used in pharmacokinetics studies
endogenous		compound that naturally occurs within the organism
endothelial		layer of epithelial cells lining heart cavities, blood vessels, and serum cavities of the body
enterohepatic circulation		recurring movement of molecules from intestine to bloodstream (via absorption), then to the liver, intestine (via biliary excretion), then back into the bloodstream (via absorption)
enzyme		protein that catalyzes a specific biochemical reaction
epithelial		layer of cells that line the inner and outer surfaces of organs, vessels, and cavities
equilibrium dialysis		performing dialysis until equilibrium is established across the membrane
equilibrium solubility		solubility assay in which buffer is added to solid compound and the solution is stirred for an extended time (e.g., 72 hours) until equilibrium is established between the solution and the excess solid
esophagus		tube that leads from the throat to the stomach
excipients		substances added to drug to produce a dosing vehicle or drug product to enhance solubility, dissolution, stability, taste, consistency, or other properties
excretion	E	removal of dosed compound molecules or metabolites from the body, usually via the urine or feces
exposure		concentration and/or duration of compound molecules in the body, tissue, or in vitro assay that can interact with the therapeutic target
extracellular fluid	ECF	body fluid excluding that in cells; includes plasma and fluid between cells (interstitial fluid)
extraction ratio	E	fraction of compound in blood that is removed with each pass through the organ of elimination (i.e., kidney, liver)
fasted state		condition (e.g., pH, bile salts) of fluids in gastrointestinal tract when no ingestion of food has occurred for several hours
First-pass metabolism (or effect)		metabolism occurring to compound molecules, mostly in intestine and liver, prior to reaching systemic circulation
FLIPR	FLIPR	fluorometric imaging plate reader method; uses fluorescent reagents for assay end point/quantitation
fluorogenic		production of a fluorescent product from a nonfluorescent starting substance for quantitation in an assay
flux		rate of flow of molecules across a membrane

Term	Acronym	Definition
Food and Drug Administration	FDA	U.S. Food and Drug Administration, regulatory agency that approves and monitors commercial drugs (and foods) in the United States
formulation		mixture of excipients (vehicle) and compound solid to make a dosage form
fragment		molecule with lower MW, fewer H-bonds, and more moderate Log P than typical drugs; for use in screening for ligands to a therapeutic target using NMR or x-ray crystallography
free drug	C_{unbound} , C_U	concentration of compound in blood that is unbound to plasma proteins (e.g., albumin) or lipids, or in tissues that is unbound to proteins or lipids
gallbladder		organ in which bile is stored prior to release into duodenum during stomach emptying
gastric		associated with the stomach
gastrointestinal	GI	system consisting of stomach, small intestine, and large intestine
genomics		study of the complement of genes and other genetic material present in the cell, animal, or human
genotoxicity		degree of a compound's ability to cause DNA or chromosomal damage
glomerular filtration rate	GFR	flow rate of fluid passing by filtration from the glomerulus into the Bowman's capsule of all the nephrons in the kidney
glomerulus		cluster of blood capillaries surrounded by the Bowman's capsule in the nephron of the kidney
glucuronide		product of reaction of glucuronic acid with a hydroxyl (e.g., phenol, carboxylic acid, alcohol) or amine, catalyzed by UDP-glucuronosyltransferase
glutathione		endogenous compound that reacts with reactive metabolites of compounds for detoxification
G-protein-coupled receptor	GPCR	transmembrane protein family that binds a signaling compound on the extracellular side, which induces a change on the intracellular side, initiating biochemical reactions within the cell
half-life	$t_{1/2}$	time for half the quantity of a compound in a living organism to be metabolized or eliminated by normal biological processes
heme group		protoporphyrin ring with a central iron atom
hepatic		pertaining to the liver
hepatic portal vein	HPV	blood vessel that carries blood to the liver from the stomach and intestine
hepatocytes		liver cells in which a large portion of metabolism of xenobiotic compounds occurs; many other endogenous biochemical reactions also occur here

Term	Acronym	Definition
high-performance liquid chromatography	HPLC	technique for mixture separation, compound identification or quantitation in which compounds partition between stationary and mobile phases within a tube
hERG	hERG	human ether-a-go-go-related gene that encodes a subunit of the potassium channel, which contributes to cardiac repolarization
high throughput	HT	techniques that allow for fast testing of a large number of compounds
high-throughput chemistry		synthesizing compounds at a high rate compared to conventional one-at-a-time compound synthesis; sometimes called <i>combi chem</i>
high-throughput screening	HTS	performing assays at a high rate using large compound libraries
hit		compound that is active in HTS or in initial screens following virtual screening
hit selection		process of choosing the most favorable hits for further study during the hit-to-lead stage of drug discovery
hit-to-lead		time period in which a large number of hits are studied and structurally modified to select a few leads for the optimization phase
HLM	HLM	human liver microsomes
human serum albumin		a plasma protein; important in maintaining fluid balance in blood, maintaining blood pressure, regulating fatty acids, and transporting hormones
hydrogen bond		bond that exists between an electronegative atom (e.g., O, N, F) and a hydrogen atom bonded to another electronegative atom
hydrogen-bond acceptor	HBA	electronegative atom (e.g., O, N, F) that may accept a hydrogen bond
hydrogen-bond donor	HBD	hydrogen atom attached to a relatively electronegative atom that may form a hydrogen bond
hydrolysis		chemical reaction in which a compound reacts with water
hydrophilicity		tendency of a molecule to be solvated by water
IC ₅₀	IC ₅₀	median inhibition concentration (concentration that reduces the effect by 50%)
idiosyncratic toxicity		unpredicted toxicity observed occasionally in large populations and is theorized to be triggered by reaction of a drug metabolite with a protein
ileum		final section of the small intestine
immobilized artificial membrane	IAM	HPLC stationary phase in which phospholipid is bonded to the stationary phase and used to predict membrane permeation
immunotoxicity		toxicity caused by a mechanism of the immune system following compound administration (e.g., immune reaction resulting from reaction of a drug metabolite with a protein)
in silico		performed using a computer and specially developed software
in situ		performed in the natural position (e.g., in the living organism)

Term	Acronym	Definition
in vitro		performed in a laboratory vessel (e.g., test tube, well of a titer plate) outside the living system
in vivo		performed in a living organism
induction		increase in enzyme concentration, caused by dosing a compound that triggers a nuclear receptor, leading to production of mRNA and synthesis of more copies of the enzyme
influx		transport of a molecule into a cell by a transporter with the expenditure of energy (i.e., uptake)
inhibitor		compound that binds to an enzyme and prevents the normal enzyme-substrate binding and subsequent catalytic reaction
initial concentration	C_0	initial concentration in blood following intravenous compound administration
insoluble		having a solubility that is very low
integrity		condition in which the analytical data for a compound are consistent with the putative structure
intestinal epithelium		monolayer of cells that form the inner surface of the gastrointestinal lumen
intramuscular	IM	administered by needle into the muscle
intraperitoneal	IP	administered within the peritoneum (lining of intestinal cavity)
intravenous	IV	administered directly into the bloodstream via a vein as a bolus injection or infusion
intrinsic solubility		solubility of the neutral form of the compound
inverted vesicle		vesicle that is turned inside out
investigational new drug application	IND	application to FDA to begin phase I trials
ion channel		transmembrane protein complex that serves as a gate for the entrance or exit of ions from the cell
ionic strength		measure of the average electrostatic interactions among ions in an electrolyte
irreversible inhibition		covalent or coordination binding of an inhibitor to a protein rendering it permanently inactive
irreversible inhibitor		compound that irreversibly modifies and deactivates an enzyme (covalent or coordination); often contains reactive functional groups (e.g., nitrogen mustards, aldehydes, haloalkanes, or alkenes)
isosteric		similar electronic arrangements in chemical compounds
isozyme		member of a family of enzymes that catalyze the same type of reaction but differ from each other in primary structure and/or electrophoretic mobility
jejunum		longest part of the small intestine extending from the duodenum to the ileum
K_i	K_i	dissociation constant of an inhibitor (enzyme kinetics)
kinetic solubility		solubility assay in which a small volume of organic solvent (e.g., DMSO) containing concentrated test compound is added to aqueous buffer, followed by measurement of the concentration after an established incubation period

Term	Acronym	Definition
knockout		when an protein's activity (e.g., efflux transport) is eliminated by deleting the gene that codes for it (genetic knockout) or co-administering an inhibitor (chemical knockout)
knowledge-based expert system		experts decide on rules for classifying a substructure as conferring a likelihood of having certain property behavior and for constructing software that evaluates new compounds based on these rules (e.g., nitroso confers likelihood of mutagenicity)
labeling		required information included with prescription drugs that describes vital information for patients and physicians, such as indications, precautions, warnings, and side effects
LD ₅₀	LD ₅₀	median lethal dose (i.e., lethal to 50% of the population of test animals in a prescribed time)
lead		compound that is currently most favorable in a discovery project and serves as a template for the design of analogs during lead optimization
lead optimization		time period in which a few leads are structurally modified and assayed to study the structure–activity and structure–property relationships in order to obtain the optimum structure as a clinical candidate
lead-like		having properties that are consistent with leads that will undergo structural augmentation during lead optimization to result in a clinical candidate that stays within drug-like property space
library		assembly of compounds, often analogs made by parallel synthesis (compound library) or assembled from multiple sources for HTS (screening library)
ligand		molecule that binds to another chemical entity to form a larger complex (e.g., substrate to enzyme)
lipase		member of a family of enzymes that catalyze the hydrolysis of fats (e.g., monoglycerides, triglycerides) to fatty acids and glycerol
Lipinski rules	Rule of 5	set of structural characteristic guidelines for drug-like structures
lipophilicity		affinity of a molecule or a moiety for a lipid (nonpolar) environment
loading dose		initial high dose of a compound, given to bring the compound in the body to the steady-state amount
Log BB	Log BB	log ₁₀ value of brain to plasma concentration ratio; a blood–brain partition coefficient
Log D	Log D	log ₁₀ of the distribution coefficient of the equilibrium concentrations of all species (unionized and ionized) of a molecule in octanol to the same species in the water phase under given solution conditions; differs from Log P in that ionized species are considered as well as the neutral form of the molecule

Term	Acronym	Definition
Log P	Log P	\log_{10} of the partition coefficient; measure of differential solubility of a compound in two solvents; most commonly partitioning is between 1-octanol and water, a measure of the hydrophobicity or hydrophilicity of a substance
LQT	LQT	lengthening of the QT interval on an electrocardiogram
lumen		inner open space of a tubular organ (i.e., of a blood vessel or the intestine)
luminogenic		produces a luminescent product for quantitation from a nonluminescent starting substance
lyse		break the cell membrane, destroy, or disorganize cells using chemicals, enzymes, or viruses
maximum concentration	C_{\max}	maximum plasma concentration of compound reached after administration in vivo
maximum tolerated dose	MTD	maximum daily (chronic) dose that an animal species can tolerate for a major portion of its lifetime without significant impairment or toxic effect other than carcinogenicity; can be determined by extrapolating a 90 day study
MDCK	MDCK	Madin Darby Canine Kidney cell line
MDR1-MDCKII	MDR1-MDCKII	Madin Darby Canine Kidney cell line transfected with human MDR1 gene, which codes for Pgp
mechanism-based inhibition	MBI	irreversible inhibition owing to formation of a covalent or quasi-irreversible bond between the inhibitor or inhibitor metabolite and the enzyme (e.g., CYP450) that inactivates the enzyme
metabolic phenotyping		determination of which metabolic enzymes and isozymes metabolize a particular compound
metabolic switching		if the primary scheme of metabolism (e.g., isozyme, site of metabolism) is blocked by DDI or chemical modification of the structure, other routes of metabolism can increase
metabolism		enzymatic structure modification of a compound in an organism
metabonomics		study of the identities and concentrations of endogenous small molecules present in the cell or organism (i.e., metabolite pool) during normal life and following a stimulus (e.g., compound dose)
metastable crystal		crystal form that is not the most thermodynamically stable
micelle		aggregate of amphipathic molecules in water with the nonpolar portions in the interior and the polar portions on the exterior exposed to water
microdialysis		technique in which a dialysis membrane capillary or probe is implanted into a tissue or fluid compartment, through which compounds in the extracellular fluid are collected for analysis
micronucleus		vesicle smaller than nucleus that contains chromosomal material that was cleaved from a chromosome

Term	Acronym	Definition
microsome		vesicles prepared from tissue (e.g., liver) by homogenization and differential centrifugation, which contain enzymes and ribosomes attached to the endoplasmic reticulum
microtiter plates		flat plate with multiple “wells” (4–3,456) used as small test tubes; has become a standard tool in biomedical research and clinical diagnostic testing laboratories; as called a <i>microplate</i>
microvessels		capillary blood vessels (e.g., in brain)
molecular weight	MW	sum of the atomic weights of all the atoms in a molecule
mRNA	mRNA	messenger RNA that is transcribed from DNA by RNA polymerase and translated into a protein sequence on the ribosome
multidrug resistance protein	MRP	family of efflux transporters whose existence was first indicated as a mechanism for resistance to drug therapy, such as in cancer
mutation		permanent change (i.e., structural alteration) in DNA or RNA
NADPH	NADPH	reduced form of nicotinamide adenine dinucleotide phosphate (NADP), a coenzyme involved in numerous enzymatic reactions (e.g., metabolism by CYP450), in which it serves as an electron carrier by being alternately oxidized (NADP ⁺) and reduced (NADPH)
nanoparticles		microscopic particle with at least one dimension <100 nm
natural products		compounds produced by a living organism (e.g., plants, microorganisms) that have pharmacological or biological activity and may be used as drugs or in drug design
nephelometry		technique used to measure the size and concentration of particles in a liquid by analysis of light scattered by the liquid (e.g., for solubility assays)
nephron		unit of the kidney that removes waste materials (e.g., drug, metabolites) from the blood and excretes them via the urine
new drug application	NDA	new drug application to FDA; to market a new drug
NMR	NMR	nuclear magnetic resonance spectroscopy; used for structural studies
no observable adverse effect level	NOAEL	highest dose or exposure that causes no detectable <i>adverse</i> effect (no adverse alterations compared to control organisms of morphology, functional capacity, growth, development, or life span) in test animals, in which higher doses or concentrations resulted in an adverse effect; any nonadverse affects are manageable

Term	Acronym	Definition
no observable effect level	NOEL	highest dose or exposure that causes no detectable effect (no alterations compared to control organisms of morphology, functional capacity, growth, development, or life span) in test animals, in which higher doses or concentrations resulted in an effect
nonspecific binding		binding of compound to lipid or protein in tissue other than at the active site
NSAID	NSAID	nonsteroidal antiinflammatory drug (e.g., aspirin, ibuprofen)
off-target		interaction of compound with a biochemical material (e.g., receptor) other than the intended therapeutic target
oocyte		developing female gamete before completion and fertilization
optimization		process of synthesizing chemical analogs of a lead compound with the goal of creating compounds with improved pharmacological properties
oral	PO	dosing by mouth
oxidative stress		increased oxidant production in animal cells characterized by the release of free radicals and peroxides resulting in cellular degeneration
PAMPA-BBB	PAMPA-BBB	variation of PAMPA permeability technique to predict passive diffusion through the blood–brain barrier
paracellular		movement of molecules across a cell membrane via pores between the epithelial cells
parallel artificial membrane permeability assay	PAMPA	in vitro permeability method using phospholipid dissolved in organic solvent and placed in the pores of a filter membrane held between two aqueous compartments
parallel synthesis		reaction of an intermediate with a number of different reagents to produce a library of analogs
passive diffusion		movement of molecules across a cell membrane from the region of higher concentration to the region of lower concentration without the expenditure of energy; different compounds have different rates of passive diffusion owing to the selective permeability of the membrane
patch clamp		in vitro assay in which an electrical circuit is established across a cell membrane to study the current changes produced by movement of ions through ion channels
perfusion		bathing a vessel (e.g., intestine, brain blood vessels) with a solution; often used to study the permeation of compound through the vessel wall
peripheral tissue		tissue situated away from the central tissue being considered; on the outer part of an organ or body
permeability	P_e , P_{app}	ability of a compound to penetrate or pass through a membrane; velocity of flow

Term	Acronym	Definition
permeability surface area coefficient	PS	Permeability times surface area of brain capillary endothelium, which is approximately 100 cm ² /g of brain (see Chapter 28, Tanaka and Mizojiri ^[50])
perpetrator		enzyme inhibitor or inducer that alters the pharmacokinetics of co-administered drugs
Pgp	Pgp	P-glycoprotein, an ABC family transporter of the MDR subfamily; extensively expressed in some normal cells (e.g., intestinal epithelium, liver, renal proximal tubule, BBB endothelial cells) also called ABCB1, MDR1, and PGY1
pH	pH	negative log ₁₀ of the hydrogen ion concentration; measure of the acidity or alkalinity of a solution; neutral solutions are pH 7, alkaline solutions have pH >7, and acidic solutions have pH <7
pharmaceutics		science of preparing and dispensing drugs; includes formulation, stability, and salt form selection
pharmacodynamics	PD	study of the biochemical and physiological effects, duration, mechanisms of action, and concentration effects of a compound on an organism; what a drug does to the body
pharmacokinetics	PK	study of the concentration–time course fate of a compound and its metabolites in an organism, which is affected by absorption, distribution, metabolism, and excretion (ADME); what the body does to the drug
pharmacology		study of the action of compounds on organisms, including the biochemical interactions, biological effects, and applications in treating disease; includes drug composition and properties, interactions, toxicology, PK, PD, therapy, and medical applications
pharmacophore		structure (ensemble of steric and electronic features) that effectively binds to the specific therapeutic target to produce the desired effect by triggering or blocking its biological response; serves as a template for the synthesis of analogs during optimization
Phase 0 clinical trials		human clinical studies in which single doses (usually subtherapeutic) of an investigational drug are administered to a small number of human volunteers (10–15) to obtain initial data on the compound's PK, PD, and mechanism of action; assesses whether the compound behaves in human subjects as predicted by preclinical studies; reduces time and cost for decisions on continued development

Term	Acronym	Definition
Phase I development (clinical trials)		human clinical studies in which an investigational drug is administered to a small group of healthy volunteers (20–80) who do not have the subject medical condition; assesses the human safety, tolerability, and PK
Phase I metabolism		enzymatic modifications of the molecular structure of the compound (e.g., oxidation, dealkylation); polar groups are either introduced or unmasked, resulting in more polar metabolites; can lead either to activation or inactivation of the drug; produces sites to which polar molecules are more readily conjugated (see <i>phase II metabolism</i>)
Phase II development (clinical trials)		human clinical studies in which an investigational drug is administered to a larger group of human volunteers (20–300) who have the subject medical condition; assesses the human efficacy and continues the safety assessments in a larger group
Phase II metabolism		enzymatic addition (conjugation) of a polar moiety to the compound's structure (e.g., glucuronic acid, sulfate); the metabolite has increased polarity
Phase III development (clinical trials)		human clinical trials in which an investigational drug is administered to a large group of volunteer patients (300–3,000 or more) who have the subject medical condition as randomized controlled trials in multiple clinics; provides a definitive assessment of human efficacy in comparison with the current best drug treatment for the condition ("gold standard") that can be extrapolated to the general population; provides information for product labeling
phospholipid		lipid containing phosphorus, including those with glycerol or sphingosine backbones; the primary lipids in cell membranes
physicochemical		physical and chemical properties of a compound
pinocytosis		type of endocytosis in which molecules are taken up from outside the cell through invagination of the cell membrane to form vesicles
pK_a	pK_a	acid dissociation constant; equilibrium constant for the dissociation of a weak acid (or negative logarithm of the ionization constant K of an acid); pH of a solution in which half of the acid molecules are ionized
plasma		liquid component of blood in which blood cells are suspended
plasma clearance		clearance of compound from the blood (plasma)
plasma protein		proteins found in blood plasma; various proteins serve different functions, including circulatory transport (for lipids, hormones, vitamins, metals), enzymes, and complement components
plasma protein binding	PPB	degree to which a compound binds to the proteins in blood plasma

Term	Acronym	Definition
polar surface area	PSA	surface sum over all polar atoms (e.g., oxygen, nitrogen) and attached hydrogens
polymorph		solid that shares chemical composition with another material but is composed of a different crystal lattice or form
potentiometric titration	pH-metric	technique using two electrodes (neutral and standard reference); voltage across the compound in solution is measured as titrant is added; graph of voltage vs volume of added titrant indicates the end point of the reaction as halfway between the increase in voltage
preclinical predevelopment		research conducted prior to clinical studies development activities conducted prior to clinical studies, especially just before phase I
primary cells		cultured cells derived directly from living tissue; typically lack the ability to remain viable for many further passages; certain genes may be up-regulated or down-regulated compared to tissue from which they were obtained
prodrug		compound with low activity that, once administered, is metabolized in vivo into an active compound
proof of concept	POC	short experiment whose purpose is to verify a theory
property		physical, chemical, metabolic, or biochemical characteristic of a compound that affects compound pharmacokinetics, exposure to the therapeutic target, or toxicity
property-based design		structure design for the purpose of improving physicochemical, pharmacokinetic, and toxicity properties
protease		any enzyme that catalyzes proteolysis by hydrolysis of peptide bonds linking amino acids together in a polypeptide chain
proteomics		study of the identities, concentrations, and locations of endogenous proteins present in the cell or organism during normal life or following a stimulus (e.g., compound exposure)
QT prolongation		lengthening of the QT interval on an electrocardiogram (see <i>LQT</i>)
quantitative structure–activity relationships	QSAR	process by which chemical structure is quantitatively correlated with biological activity
quantitative structure–property relationships	QSPR	process by which chemical structure is quantitatively correlated with properties
racemate		mixture of equal amounts of left-handed and right-handed enantiomers of a chiral molecule

Term	Acronym	Definition
reactive metabolite		compound metabolite that reacts covalently with an endogenous macromolecule (e.g., protein, DNA) to form a stable conjugate; usually disrupts normal function
receptor		protein in the cell membrane, cytoplasm, or nucleus to which a specific ligand (e.g., neurotransmitter, hormone) binding initiates a cellular biochemical response
recombinant human cytochrome proteins	rhCYP	human CYP450 isozymes prepared by recombinant DNA technology
renal		pertaining to the kidney
repolarization		change in membrane potential that returns it to a negative value (after depolarization of an action potential changed it to a positive value) by movement of potassium ions out of the cell through ion channels
reversed-phase HPLC	RP HPLC	high-performance liquid chromatography in which the solid chromatographic particles are derivatized to form a nonpolar stationary phase (e.g., bonding of octadecylsilane on silica or polymer particle surface) and an aqueous/organic mixed mobile phase is used
reversible inhibition		binding to enzyme with noncovalent interaction
reversible inhibitor		compound that binds reversibly to an enzyme with noncovalent interactions (e.g., hydrogen bonds, hydrophobic interactions, ionic bonds) to produce multiple weak bonds between the inhibitor and the active site to provide strong and specific binding; inhibits normal ligand–enzyme binding
rotatable bond	RB	single non-ring bond, on a nonterminal heavy atom (not hydrogen)
S9	S9	material prepared from liver tissue by homogenization and differential centrifugation at 9,000g; contains metabolizing enzymes attached to membranes from the endoplasmic reticulum (microsomes) and cytosol; used for some in vitro metabolism studies
safety		study of toxicity risk
safety window		range between the concentration that is predicted to cause human toxicity and the concentration that is predicted to produce human efficacy
salt form		material in which ionized molecules of a compound are paired with ions of the opposite polarity to enhance solubility or another physical property (e.g., buspirone hydrochloride)
scaffold		central structure (lead) that binds to the therapeutic target and is modified during lead optimization to improve activity, selectivity, and drug-like properties (see <i>template</i>)

Term	Acronym	Definition
scale-up		make a larger batch of compound for studies requiring large amounts
secretory		in the direction of elimination in intestine (e.g., from blood into intestinal lumen)
selectivity		degree to which a compound produces the desired result compared to adverse side effects; ratio between the IC ₅₀ at another target for which binding is possibly deleterious to the IC ₅₀ at the therapeutic target
selectivity screen		measurement of IC ₅₀ of a compound in a large number of biochemical assays to check for activity at other biological targets to avoid causing side effects
serum		aqueous fluid of blood, containing dissolved compounds and proteins, from which blood cells and clotting factors have been removed
shake flask		laboratory vessel in which partitioning (e.g., Log P) or equilibrium solubility experiments are performed (i.e., capped vials, sealable tube, separatory funnel)
simulated gastric fluid	SGF	artificial solution whose recipe is prescribed by the United States Pharmacopeia to mimic gastric fluid contents
simulated intestinal bile salts–lecithin mixture	SIBLM	artificial solution to mimic intestinal fluid contents
simulated intestinal fluid	SIF	artificial solution whose recipe is prescribed by the United States Pharmacopeia to mimic intestinal fluid contents
soft drug		see <i>antedrug</i>
solid dispersion		dispersing one or more active ingredients in an inert matrix in the solid state in order to achieve increased dissolution rate, sustained release of drugs, altered solid-state properties, enhanced release of drugs from ointment and suppository bases, or improved solubility and stability
solubility	S	measure of how much of a compound will dissolve in a specific liquid; usually measured in weight per unit volume
solubilizer		material added to enhance a compound's solubility
steric hindrance		diminished reactivity of a site in a molecule owing to the presence of adjacent moiety (s)
stock		concentrated chemical solution that is diluted before use
structure alert		substructure in compound has been reported as causing toxicity
structure elucidation		determination of the structure of an unknown compound using analytical techniques (e.g., spectroscopy)

Term	Acronym	Definition
structure–activity relationship structure-based design	SAR	relationship linking chemical structure and pharmacological activity structure design for the purpose of enhancing pharmacological activity
structure–property relationship	SPR	relationship linking chemical structure and an ADME/Tox properties
subcutaneous	SC	administered using a needle just under the skin into the subcutaneous tissues; after injection the compound moves into the small blood vessels and bloodstream
sublingual		administered beneath or on the underside of the tongue, where the tablet dissolves and the drug is absorbed through the sublingual gland
substrate		compound on which an enzyme acts
surfactant		material that in small quantity markedly affects the surface characteristics of a system; also called a <i>surface-active agent</i>
tandem mass spectrometry	MS/MS	instrument consisting of two mass spectrometers in series connected by a collision chamber; molecular ions are sorted in the first mass spectrometer, broken into fragments (product ions) in the collision chamber, and fragments are sorted in the second mass spectrometer; used for structure elucidation and quantitative analysis
target		endogenous enzyme, receptor, ion channel, or other protein in the body that may be affected by a compound to produce a therapeutic effect
template		core structure that serves as a pattern for the synthesis of other molecules; also called a <i>scaffold</i>
teratogenicity		degree of a compound's ability to damage, kill, or morphologically alter a fetus
therapeutic index		ratio between the toxic dose and the therapeutic dose of a drug, used as a measure of the relative safety of the drug for a particular treatment
therapeutic target		see <i>target</i>
time of maximum drug concentration	t_{\max}	time after dosing to reach the peak concentration
tissue uptake		absorption of compound molecules into a tissue
torsades de pointes	TdP	sudden ventricular tachycardia in which the ECG shows a steady undulation in the QRS axis in runs of 5–20 beats and with progressive changes in direction
toxicity	TOX	extent, quality, or degree of being poisonous
transepithelial electrical resistance	TEER	electrical resistance across a membrane layer in an in vitro permeability experiment
transfect		introduction of DNA into a recipient eukaryote cell and its subsequent integration into the chromosomal DNA
transport		movement of a compound across a membrane barrier

Term	Acronym	Definition
transporter		type of protein that actively transports molecules across a cell membrane that would not otherwise allow such compounds across
turbidimetry		method for determining the concentration of a compound in solution by measuring the loss in intensity of a light beam through a solution that contains suspended particulate matter
turbidity		cloudiness or opacity in a liquid caused by suspended particulate matter
UDP-glucuronosyltransferase	UGT	class of metabolic enzymes that catalyze addition of glucuronic acid to drugs and metabolites, a phase II process that increases their solubility in water and enhances their excretion
ultrafiltration		technique for separation of low-MW compounds from high-MW proteins using centrifugation and a membrane that excludes proteins
unbound “free” drug	C_{unbound} , C_U	fraction of compound not bound to carrier proteins in blood or nonspecifically to protein or lipid in tissue
uptake		movement of compound into a cell or tissue
vehicle		additives and solvents used to solubilize a compound for dosing
venous sinusoid		capillary blood vessel (branching from the portal vein) from which drug molecules permeate into hepatocytes
victim drug		compound that is metabolized by enzymes whose activities are inhibited or induced by a co-administered perpetrator drug
virtual screening		selection of compounds that may bind to the target using a computational model; also called <i>in silico screening</i>
volume of distribution	V_d	apparent volume in which the compound is dissolved in the living organism; indicates how widely the compound is distributed in the body
withdraw		remove a commercial drug from the market
xenobiotic		compound that is not naturally found in the organism (e.g., drug); also called a <i>foreign</i> or <i>exogenous substance</i>
zwitterion		dipolar ion containing ionic groups of opposite charge

Index

- ABC. *See* ATP binding cassette
- ABCB1, 111–116
- ABCC2, 116
- ABCG2, 116
- Absorption
- enhancement, 26–27
 - human oral, 65
 - intestinal, 434–435
 - oral, 435t
 - physiology, 68–70
 - salt forms, 80–81
 - solubility, 62–63
 - species dependence, 69f
- Absorptive transport, 89
- Acetonitrile crash, 410
- α_1 -acid glycoprotein (AGP), 187
- Active uptake, permeability, 89
- ADME/Tox, 3–4, 6, 10, 45, 104, 106, 110, 190, 216, 224, 249, 277, 386
- Administration routes, 454–455
- comparison, 454t
- Adsorption, distribution, metabolism, excretion, and toxicity. *See* ADME/Tox
- AGP. *See* α_1 -acid glycoprotein
- AhR assay. *See* Aryl hydrocarbon receptor assay
- Albumin, 187
- Aldehyde oxidation metabolism, 141f
- Aliphatic oxidation metabolism, 141f
- American Type Culture Collection (ATCC), 288
- Ames assay, 390–391
- Aniline toxicity, 219
- Anions, 81t–82t
- Antedugs, 170, 437
- Apical, 22
- Aqueous buffers, 292, 443–449
- Area under the curve (AUC), 421
- PK, 231
- Aromatic oxidation metabolism, 141f
- Artificial membrane permeability assay, 292–293
- Aryl hydrocarbon receptor (AhR) assay, 389
- ATCC. *See* American Type Culture Collection
- ATP binding cassette (ABC), 89, 111, 305
- ATPase assay, 305–306
- Attrition during development, 9–10
- AUC. *See* Area under the curve
- Barriers, 17–19, 440f
- bloodstream, 27–28
 - blood-tissue, 30
 - chiral effect, 31
 - GI tract, 20–27
 - kidney, 29
 - liver, 28–29
 - mouth, 19–20
 - properties, 31
 - stomach, 19–20
 - in vivo, 31–32
- Basolateral, 22
- Batch-to-batch variation of reagents, 339f
- BBB. *See* Blood-brain barrier
- BCRP. *See* Breast cancer resistance protein
- BCS. *See* Biopharmaceutics Classification System
- BCSFB. *See* Brain-CSF barrier
- BDDCS. *See* Biopharmaceutics Drug Disposition Classification System
- Bile, 21, 26
- Bilayer membrane, 23
- Bile canaliculus, 28
- Bile salt export pump (BSEP), 118
- Biliary excretion, 29, 232
- Bioassay buffers
- chemical instability, 179, 448–449
- Bioavailability, 234
- Biochemical properties, 7
- Bioisosteric replacement, 94f

- Biological assay optimization, 439–449
aqueous buffer insolubility, 443–448
DMSO insolubility, 441–443
IC₅₀ shift, 444
instability in assay media, 448
media, 355–356
optimizing assay buffer, 447–448
permeability in cell-based assays, 447–448
SARs, 440–441
serial dilution scheme, 443–446
solubility limitations, 441t
- Biopharmaceutics Classification System (BCS), 66–67
- Biopharmaceutics Drug Disposition Classification System (BDDCS), 67
- Biotransformation, 138
- Biphasic dose responses, 149
- Blocking groups, 149–150
- Blood-brain barrier (BBB), 46t, 90, 108t, 122–135, 191–192, 303, 311–325
acids, 131f
amines, 131f
bases, 131f
basic drugs, 53f
B/P and Log BB in vivo method, 319–320
brain microvessel endothelial cell (BMEC) method, 317
brain uptake index, 320
Caco-2 method, 318
capillary microvessels, 123
carboxylic acid group reduction, 133
cell-based in vitro methods, 317–319
cerebrospinal fluid method, 324
classification models, 312
CNS therapy, 123f
 $\Delta \log P$ method, 316
effects, 129
efflux transporters, 116–117
equilibrium dialysis method, 316
fundamentals, 123–129
hydrogen bond reduction, 132
immobilized artificial membrane HPLC method, 317
lipophilicity, 133, 315
Log P, 316
mouse brain uptake assay (MBUA), 322–323
MDR1-MDCKII method, 318–319
metabolism, 125
microdialysis method, 323–324
MW, 133
nonspecific binding, 127
PAMPA-BBB method, 314–315
penetration, 129, 130–131
permeability, 39, 123, 124–125, 129, 311
permeability prediction, 313t
Pgp efflux reduction, 122, 132
physicochemical methods, 314–317
plasma protein binding, 126f
rules, 130
schematic diagram, 123f
in silico methods, 312–314
in situ perfusion, 321–322
structure-BBB relationships, 130–131
structure modification strategies, 131–134
surface activity method, 317
TM-BBB and TR-BBB methods, 319
transporters, 110
uptake transporters, 119, 133–134
in vitro methods, 314–319
in vivo methods, 319–324
- Bloodstream, 27–28
- Blood-tissue barriers, 30
- BMEC. *See* Brain microvessel endothelial cell permeability
- Bovine serum albumin (BSA), 282, 445
- Bowman's capsule, 29
- B/P, 128–129, 319–320
- Brain distribution mechanisms, 123, 125–126
extent, 128–129
- Brain penetration, 123
assessment strategy, 324–325
effects, 129
- Brain uptake index, BBB permeability, 320
- Brain-CSF barrier (BCSFB), 127
- Breast cancer resistance protein (BCRP), 89, 116, 124, 289, 302
- Brush border, 22
- BSA. *See* Bovine serum albumin
- BSEP. *See* Bile salt export pump
- Caco-2 permeability method, 289, 291–292, 301–302
BBB, 318
PAMPA comparison, 293–294, 295f
- Calcein AM assay, 306, 307f
- Capillary electrophoresis (CE), 264
lipophilicity, 267f
pK_a, 273–274
- Carboxylic acids, 71, 220
ester prodrugs, 431–432
esterifying, 93
isosteric replacement, 94f, 133
- Carcinogenicity, 217
- Cardiac output, 232
- CARRS. *See* Cassette-accelerated rapid rat screen
- Cassette dosing, 409–410
- Cassette-accelerated rapid rat screen (CARRS), 411
- CAT1. *See* Cationic amino acid transporter

- Cations, 88
 salt formation, 81t–82t
- Cationic amino acid transporter (CAT1), 134
- Cationic nucleoside transporter (CNT2), 134
- CE. *See* Capillary electrophoresis
- Cell culture insert for Caco-2, 289
- Cell layer assays
 efflux, 301f
 pH values, 291
- Cell monolayer efflux assays, 290
- Cell monolayer permeability methods, 300–301
- Cell-based activity assays, 445f
 permeability effect, 91–92, 448
- Central nervous system (CNS), 12
 disorders, 122
- Cerebrospinal fluid (CSF), 125, 127
 BBB, 324
- Chemical decomposition, 137
- Chemical instability, 20
 bioassays, 448–449
- Chemical knockout experiments, 308
- Chirality
 barriers, 31
 CYP inhibition, 202–203
 metabolic stability, 152, 160–161
 plasma stability, 170
 PPB, 189
 solubility, 61–62
 transporters, 110
- Chromosomal aberration assay, 390
- Cl. *See* Clearance
- Clearance (Cl), 145. *See also* Renal clearance;
 Systemic clearance
 intrinsic, 159–160
 IV injection, 420–421
 PK, 160t, 231–233
 PPB, 192
- Cl_s. *See* Systemic clearance
- CNS. *See* Central nervous system
- CNT2. *See* Cationic nucleoside transporter
- Cocktail substrate HLM assay for CYP
 inhibition, 363, 365–367
- Comet assay, 390
- Compound assessment, 39–40
- Compound purification, conditions, 183
- Compound structure and properties, 8f
- Co-solvent, 456
 toxicity, 457t
- Cost-benefit analysis of methods, 257–258
- Covalent protein binding, 393
- Crystal lattice energy, 58
- CSF. *See* Cerebrospinal fluid
- Customized assays, 252
- Customized kinetic solubility method, 282–283
- Cyclic peptides, 96f
- Cyclic urea, 155
- Cyclization to improve stability, 151
- Cyclodextrins, 460
 pharmaceutical products, 461t
 structure, 460f
- CYP. *See* Cytochrome P450
- CYP inhibition, 197–207, 225, 388–389
 assessment strategy, 367–368
 case studies, 201–203
 chirality, 202–203
 cocktail substrate HLM method, 365–367
 commercial suppliers of materials for
 methods, 361
 determination, 364t
 double cocktail method, 367
 drug substrates, 367t
 drug withdrawals due to, 201t
 effects, 199–201
 fluorescent assay, 364–365
 fundamentals, 197–198
 irreversible, 204–205
 mechanism-dependent, 204
 methods, 360–368
 reducing, 204t
 reversible, 204–205
 in silico methods, 360
 single substrate HLM assay, 365
 structure modification strategies, 203–204
 toxicity, 388
- CYP isozymes, 162–165
- CYP phenotyping, 157
- CYP1A2, 162
- CYP2C9, 164
 SAR/active site, 164f
- CYP2D6, 149, 163, 202, 203, 204f
- CYP3A4, 24, 147, 199, 202, 204, 366t
- Cytochrome P450 (CYP), 139, 216, 219,
 360, 422
 isoforms, 198f, 199f
 isozymes, 199t
 structure, 140f
 substrate specificity, 162–165
- Cytotoxicity, 217, 391
- DDI. *See* Drug-drug interactions
- Dealkylation metabolism, 142f, 143
- Deamination, oxidative metabolism, 142f
- Decomposition
 chemical, 137
 intestinal, 137
 plasma, 137
- Degradation products, 357
- Dehydrogenation metabolism, 141f
- Delivery routes, 187

- DEREK toxicity software, 387
- Detection methods used in CYP inhibition assays, 362
- Development process, 8–9
attrition, 9
- Diagnosing limitations, 252
- DiBAC₄(3), 380
- Diffusion, passive, 23, 87–88, 88f
- Dilution protocol and insolubility in bioassays, 445–446
- Dimethylsulfoxide (DMSO), 44, 60–61, 180, 265, 274, 277, 279, 280, 335, 337, 348, 354, 402, 405, 440
dilutions, 445–446
dispensing, 281
insolubility, 441–443
- Discrete dosing, 409
- Dissolution rate, 19, 25t, 25f, 57
improving, 77–78
oral solution, 78
surfactants, 78
salt form, 78
particle size, 77–78
- Distal tubule, 30
- Distribution, 228
- DMSO. *See* Dimethylsulfoxide
- Donors, hydrogen bond, 292
- Dopamine, 436
- Dosing, 18–19
- Dosing routes, 19t, 454
- Double cocktail assay for CYP inhibition, 363
- Drug complexation, 460–461
- Drug Development, 8–9
- Drug discovery, 4
drug-like properties, 6–12
emphasis on properties, 12–13
inefficiencies, 9–11
introduction/overview, 8–9
PK, 235–240
property optimization, 15
property profiling, 14
stages, 9f
- Drug-drug interactions (DDI), 105, 197, 201, 205–206, 218, 388–389
- Drug-like properties, 3–4, 7
assessing, 249
biochemical, 7
biological assays, 439–449
chirality, 31
concepts related, 4
drug discovery, 6–12
emphasis, 12–13
optimization, 15
pharmacokinetics, 7
physicochemical, 7
poor, 9–10, 11–12
profiling, 14
rapid profiling, 37–42, 250
structural, 7
- Duodenum, 20, 21
- ECF. *See* Extracellular fluid
- ECG. *See* Electrocardiogram
- Efflux, 89
- Efflux ratio (ER), 124
- Efflux substrates, Pgp, 112–113
- Efflux transporters, 22–23, 104f, 111–117
BBB, 116–117
BCRP, 116
MRP2, 116
Pgp, 111–116
- Electrocardiogram (ECG), 211, 212f, 378
- Electron-withdrawing groups, 154–155
adding, 181
antedrugs, 173–174
- Emulsions, 458
- Endocytosis permeability, 22, 89
- Endoplasmic reticulum (ER), 139
- Endothelial cells, 109–110
- Enterohepatic circulation, 29
- Enzymatic hydrolysis, 24–25
- Epithelial cells, 107t
transporters, 108–109
- Epoxidation metabolism, 141f
- Equilibrium dialysis, 316
PPB, 373
- Equilibrium shake flask thermodynamic solubility method, 283
- ER. *See* Efflux ratio; Endoplasmic reticulum
- Erythrocyte binding, 187
- Escherichia coli* lipid A transporter (MsbA), 299
- Extracellular fluid (ECF), 125, 127
- FDA. *See* Food and Drug Administration
- FIA. *See* Flow injection analysis
- Filtration, glomerular, 29
- First pass metabolism, 24
- Flavine monooxygenase (FMO), 139
- Flow injection analysis (FIA), 402
- Fluorescent assay
CYP inhibition, 363–365
- Fluorine substitution for metabolic stability, 147–149
- Fluorogenic substrates for CYP inhibition assays, 362t
- FMO. *See* Flavine monooxygenase
- Food and Drug Administration (FDA), 8, 66, 197, 209, 216, 378
- Food effect, 69–70

- Formulation, 26, 453–464
administration routes, 454–455
applications, 453–454
buffers, 456
co-solvents, 456–457
complexation, 460
efficacy studies, 464t
lipid-based, 458–460
particle size, 461
pH adjustment, 456
potency, 455, 456f
PK studies, 463
practical guide, 462–464
solid dispersion, 461
solubilizing excipients used, 458t
strategies, 456–462
surfactants, 457
toxicity studies, 464
- Fosphenytoin, prodrug example, 76
- Fragment-based screening, 245–246
- Free drug, 27
- Freeze-thaw cycles, 442
- GADD45a-GFP (Greenscreen) genotoxicity assay, 391
- Gastric emptying time, 69t
- Gastrointestinal fluids, 356–357
- Gastrointestinal (GI) tract, 19, 107t
absorption enhancement, 26–27, 434–435
barriers, 20–27
cellular membrane, 22
drug barriers, 25t
enzymatic hydrolysis, 24–25
pH values, 20t
physiology, 68
species differences, 68–69
transit times, 20t
transporters, 103t, 109
villus, 22f
- Gene induction in toxicity, 221
- Genetic knockout animal experiments, 307
- Genotoxicity, 217, 389–390
- GFR. *See* Glomerular filtration rate
- GI tract. *See* Gastrointestinal tract
- Glomerular filtration rate (GFR), 233
- Glomerulus, 29
- GLP. *See* Good Laboratory Practice
- Glucose transporter (GLUT1), 118
- Glucuronic acid, 143
- Glucuronidation metabolism, 341
- GLUT1. *See* Glucose transporter
- Glutathione, 143
conjugation, 145f
trapping, 393
- GMP. *See* Good Manufacturing Practice
- Good Laboratory Practice (GLP), 409
- Good Manufacturing Practice (GMP), 409
- Half-life, 233–234
metabolic stability, 146, 335, 336
pharmacokinetic PK, 145, 145f, 233–234
- HBA. *See* H-bond acceptors
- HBD. *See* H-bond donors
- H-bond acceptors (HBA), 38
- H-bond donors (HBD), 38
- HDL. *See* High-density lipoprotein
- Henderson-Hasselbalch equation, 49, 59
- Hepatic metabolism, 137
stereospecific, 160t
- Hepatocytes, 28t, 333–334, 340
transporters, 109–110
- hERG blocking, 209–214, 389
cardiac action potential, 210f
commercial instrument methods, 384t
ECG, 210f
effects, 211–212
fundamentals, 209–210
high-throughput patch-clamp method, 383
in silico, 379
in vitro methods, 379t, 379–384
in vivo methods, 384
ligand binding method, 381
long QT interval (LQT), 211, 211f
membrane potential-sensitive dye method, 379–380
methods, 378–384
patch-clamp method, 381–383
potassium channel, 211f
rubidium efflux method, 381
screening, 379t
structure-activity relationship, 212–213
structure modification strategies, 213
Torsades de Pointe (TdP) arrhythmia, 211, 212f
withdrawn drugs due to, 210f
- High-density lipoprotein (HDL), 188, 399
- High-performance liquid chromatography (HPLC), 224, 264, 266–267, 279, 348, 353, 363, 446, 449
IAM, 288, 317
immobilized protein, 375
- High-throughput screening (HTS), 12, 39, 224–225, 249, 399, 444
- HLM. *See* Human liver microsomes
- ¹H-NMR spectra, 343f, 344f
- Hockey stick PK profiles, 422
- HPBEC. *See* Human primary brain endothelial cells
- HPLC. *See* High-performance liquid chromatography

- HPRT Chinese hamster ovary cell assay, 391
HSA. *See* Human serum albumin
HTS. *See* High-throughput screening
Human liver microsomes (HLM), 198, 361
Human oral absorption, 65
Human primary brain endothelial cells (HPBEC), 317
Human serum albumin (HSA), 188
 drug classification, 189t
Hydrogen bonding, 73
 intramolecular, 133
 permeability, 94, 95f
 reducing, 94, 132
Hydrolysis, 179
 intestinal enzymatic, 24–25
 plasma enzyme, 27
 rates, 170f
 stomach acidic, 20
Hydrolytic enzymes, 20
Hydrophilic compounds, 230
Hydroxylation metabolism, 142f
- Idiosyncratic reactions, 217
Ileum, 20
IM. *See* Intramuscular
Immobilized artificial membrane HPLC method, 288, 317
Immobilized protein HPLC method, 375
Immunotoxicity, 217
In situ perfusion, 321–322
In vitro hepatocyte stability assay, 340
In vitro phase II stability assay, 340–341
In vitro S9 stability assay, 338–340
In-depth profiling, 401
Integrity and Purity, 224–226
 applications, 226
 case study, 226
 criteria for assays, 399–400
 effects, 224–226
 example method, 405–406
 fundamentals, 224
 identity characterization, 404–405
 method case studies, 406–407
 methods, 399–407
 profiling, 400–401
 techniques incorporated, 402t
Intestinal decomposition, 137, 240
Intestinal lumen, 21
Intestinal metabolism, 24, 137
Intramuscular (IM), 187, 455
Intraperitoneal (IP), 187, 455
Intravenous (IV), 187, 455
Inverted vesicle transporter assay, 305
Ionizable groups, 71–72
 non-ionizable groups, 92
IP. *See* Intraperitoneal
Isoteric replacement, 155f, 182
 polar groups, 93
Isozymes, CYP, 162–165
Iterative parallel optimization, 251
IV. *See* Intravenous
IV formulation, solubility, 63
- Jejunum, 20
- Kidney, 107t
 barriers, 29
 transporters, 110
Kinetic solubility, 60–61
 customized method, 282–283
 direct UV method, 278
 methods, 278–283
 nephelometric method, 280–281
 turbidimetric method, 281
- Labile groups, 150–151
 isoteric replacement, 182
Lactate dehydrogenase (LDH) toxicity
 assay, 392
Large neutral amino acid transporter (LAT1), 106f, 118
LAT1. *See* Large neutral amino acid transporters
LC/MS/MS. *See* Liquid chromatography/mass spectrometry/mass spectrometry
LDH. *See* Lactate dehydrogenase
LDL. *See* Low-density lipoprotein
Lead optimization, 9, 244f
Lead-like compounds, 242–247
 criteria, 243
 fragment based screening, 245
 template conservation, 244
 rules, 243, 246
 trriage, 245
Lead-like properties, 243
Lead selection, 9
Liabilities, 183
 plasma stability, 174
Lipid-based formulation, 458–460
Lipinski rules, 37–38, 242
Lipophilic compounds, 230
Lipophilicity, 43, 58
 BBB, 315
 capillary electrophoresis method, 267f
 case studies, 46
 effects, 45–46
 fundamentals, 43–44
 in-depth methods, 267–268
 methods, 260–268
 permeability, 92–93
 pH-metric method, 268

- Lipophilicity (*Continued*)
reversed-phase HPLC method, 266–267
scaled-down shake flask method, 265
shake flask method, 267–268
in silico, 260–264
structure modification, 46
- Lipoproteins, 27. *See also* High-density lipoprotein; Low-density lipoprotein; Very-high-density lipoprotein; Very-low-density lipoprotein
- Liposomes, 459
- Liquid chromatography/mass spectrometry/mass spectrometry (LC/MS/MS), 290, 348, 350, 355, 362, 410–411
- Liver, 107t
barriers, 28–29
metabolism, 29
microsomes, 332
transporters, 109–110
- LLC-PK1 cells, 302
- Log BB, 128–129, 319–320
- Log D, 44, 45–46, 423f
calculated values, 262–263t
commercial instruments for measurement, 266t
literature values, 262–263t, 264f
software for calculating, 261t
- Log P, 44, 45, 58, 260
BBB, 316
commercial instruments for measurement, 266t
software for calculating, 261t
solubility effects, 73
- Low-density lipoprotein (LDL), 188
- Luciferase, 362
- Luminal membrane, 87
- Luminogenic substrates, 361
- MAD. *See* Maximum absorbable dose
- Madin Darby Canine Kidney (MDCK) cells, 288, 302
- Mass spectrometry (MS), 224, 225–226, 282
- Maximum absorbable dose (MAD), 64
- Maximum tolerated dose (MTD), 216
- MBUA. *See* Mouse brain uptake assay
- MCT1. *See* Monocarboxylic acid transporter1
- MDCK. *See* Madin Darby Canine Kidney
- MDR1, multidrug resistance transporter 1, 111–116
- MDR1-MDCKII cells, 303, 312
BBB permeability, 318–319
- MEEKC technique. *See* Microemulsion electrokinetic chromatographic
- Membrane potential-sensitive dye method for hERG, 379–380
- Metabolic enzyme induction, 206
- Metabolic phenotyping, 206, 341–342
- Metabolic stability, 137–165
applications, 156–160
blocking groups, 149–150
chirality, 152, 160–161
cyclization, 151
CYP substrate specificity, 162–165
detection methods for assays, 334–335
determination, 330t
effects, 145–146
electron-withdrawing groups, 154–155
fluorine, 147–149
fundamentals, 138–145
general aspects of methods, 331–334
intrinsic clearance, 159
labile groups, 150–151
materials for assays, 331–334
methods, 329–331
oral bioavailability, 146t
ring size, 151–152
in silico methods, 331
steric hindrance, 154–155
structure modification for phase I, 146–154
structure modification for phase II, 147f, 154–156
unstable groups, 153
in vitro hepatocytes assay, 340
in vitro microsomal assay, 335–338
in vitro phase II assay, 340–341
in vitro S9 assay, 338–340
- Metabolism. *See also* Hepatic metabolism; Stereoselective metabolism
intestinal, 24, 137
liver, 29
phase I, 139–143
phase II, 143–145
prodrugs, 435–436
- Metabolites, 218–221
structure identification, 342–344
- Micelles, 459
- Microdialysis method, 323–324, 375–376
- Microemulsion electrokinetic chromatographic (MEEKC) method for lipophilicity, 267
- Micronucleus assay, 390
- Microsomal stability, 159f
assay, 329
assay setup, 338f
automation scheme, 338f
- Microvessel endothelial cell permeability (BMEC), 317
- Microvilli, 22

- Molecular weight (MW), 38, 243
 cutoff, 373
 reduction, 74–75, 133
- Monocarboxylic acid transporter1 (MCT1),
 106f, 118
- Monooxygenase metabolism, 139
- Mouse brain uptake assay (MBUA), 322–323
- Mouth, barriers, 19–20
- MRP2. *See* Multidrug resistance protein 2
- MS. *See* Mass spectrometry
- MsbA. *See* *Escherichia coli* lipid A transporter
- MTD. *See* Maximum tolerated dose
- MTT human hepatotoxicity assay, 392
- Multidrug resistance protein 2 (MRP2), 116,
 124, 289, 302
- Mutagenicity, 389–390
- MW. *See* Molecular weight
- N*-acetyl-*p*-benzoquinoneimine (NAPQI), 221
- NAPQI. *See* *N*-acetyl-*p*-benzoquinoneimine
- NCTP. *See* Sodium dependent taurocholate
 co-transporting polypeptide
- Nephelometric kinetic solubility method,
 280–281
- Nephron, 29, 30f
- Netherlands Cancer Institute, 303t
- Neutral red assay, 392
- Nitroaromatics toxicity, 220
- NMR. *See* Nuclear magnetic resonance
- No adverse effect level (NOAEL), 394
- No effect level (NOEL), 394
- NOAEL. *See* No adverse effect level
- NOEL, no effect level, 394
- Non-ionized drugs, 189t
- Nonspecific binding, 127
- Nuclear magnetic resonance (NMR), 224,
 225–226
 proton, 405
- OATP1. *See* Organic anion transporter
 polypeptide1
- OCT. *See* Organic cation transporter
- Off-target, 217, 218
- Oil-in-water (O/W) emulsions, 458
- Oligopeptide transporter1 (PEPT1), 105t,
 117–118
- Oocyte uptake method, 304–305
- Oral administration, 454
- Oral bioavailability, 145
 metabolic stability effects, 146t
 permeability effects, 91t
 salt forms effects, 80–81
 solubility effects, 62–63
- Oral solutions, 78
- Organ toxicity, 217
- Organic anion transporter polypeptide1
 (OATP1), 106f, 117, 118
- Organic cation transporter (OCT), 118
- Out-of-plane substitution, 75–76
- O/W emulsions. *See* Oil-in-water emulsions
- Oxidation metabolic, 142f
 aldehyde, 141f
 aliphatic, 141f
 aromatic, 141f
- Oxidative deamination metabolism, 142f
- Oxidative stress toxicity, 221
- PAMPA. *See* Parallel artificial membrane
 permeability assay
- Pancreatic fluid, 21
- Paracellular permeability, 89
- Parallel artificial membrane permeability assay
 (PAMPA), 53, 87f, 90–91, 95f, 288,
 292–293, 448
 BBB method, 314–315
 Caco-2, 293–294, 295f
- Partial least squares discriminant (PLSD)
 analysis, 299
- Particle size
 dissolution, 77
 reduction, 461–462
- Passive diffusion, 23
 permeability, 87–88
 pH, 88f
- Patch-clamp method, 381–383
 diagram, 382f
 high-throughput, 383
- PEPT1. *See* Oligopeptide transporter1
- PEPT1, 302, 434
- PEPT2, 302, 434
- Permeability, 19, 86–96, 287–293
 absorption, 93f
 active uptake, 89
 artificial membrane method, 292
 BBB, 39, 123, 124–125, 311
 bioavailability, 90–91
 Caco-2 method, 288
 cell layer method, 288–291
 cell-based assays, 91–92, 448
 determination, 287–294
 effective, 292
 effects, 90–92
 efflux, 89, 288
 endocytosis, 89
 fundamentals, 86–90
 hydrogen bonding, 94, 95f
 IAM HPLC method, 288

- Permeability (*Continued*)
- in-depth methods, 294–295
 - ionizable groups, 92
 - lipophilicity, 92
 - mechanisms, 86f
 - methods, 287–294
 - molecular properties, 67
 - molecular weight and size, 94
 - nonpolar side chains, 96
 - oral absorption, 93f
 - oral bioavailability, 91t
 - PAMPA method, 292
 - polar groups, 93
 - paracellular, 89, 125
 - passive diffusion, 87–88
 - prodrugs, 93, 96, 97f, 430–433
 - in silico, 287–288
 - solubility versus permeability, 64f
 - structure modification strategies, 92–96
 - substitutions, 95f
 - in vitro, 288–294
- Perpetrators of CYP inhibition, 198, 205–206
- P-glycoprotein (Pgp), 22, 89, 104, 111–116, 289, 299, 302, 321
- case studies, 113–114
 - efflux, 305t
 - efflux substrates, 112–113
 - reducing efflux, 114–115, 132
 - schematic diagram, 111f
 - steric hindrance, 115f
 - structure modification strategies, 114–116
 - substitutions, 113f
- Pgp. *See* P-glycoprotein
- pH values, 49f, 87–88
- adjusting, 456
 - cell layer assays, 291
 - across lipid membranes, 88f
 - passive diffusion, 88f
 - physiological fluids, 30t
 - solubility, 59t
 - solution stability, 356
- Pharmacokinetics (PK), 3, 7, 9, 10, 17, 145, 228–241, 252, 312, 331, 426
- area under curve (AUC), 231
 - applications in discovery, 235–240
 - bioavailability, 234, 421
 - case studies, 421–424
 - cassette dosing, 409
 - clearance, 160t, 231–233, 420
 - commercial suppliers of products for PK methods, 410t
 - diagnosing poor PK, 252, 419–424
 - dosing, 409–410
 - example data, 412–413
 - formulation, 463–464
 - fundamentals, 228–229
 - goals, 236t
 - half-life, 233–234
 - instrumental analysis, 411–412
 - methods, 409–414
 - parameters, 229–234, 235–236t
 - performance, 419–424
 - property limitations, 420–421, 420f
 - PPB, 234
 - sampling, 410–411
 - selected compounds, 237–239t
 - single-compound (discrete) dosing, 412t
 - tissue uptake, 234, 413–414
 - unusual, 421–423
 - volume of distribution (V_d), 229–231
- Phase I stability assay, 335–338
- Phase II stability assay, 329
- Phenol prodrugs, 432, 433t
- Phenotyping
- CYP, 157
 - metabolic, 206, 341–342
- pH-metric method, 268
- Phosphatidylcholine, 23
- Phospholipids, 23, 217
- structures, 24f
- Phospholipidosis, 217
- Physicochemical properties, 7
- Physiology
- absorption, 68–70
 - gastrointestinal tract, 68
 - solubility, 68–70
- PK. *See* Pharmacokinetics
- pK_a , 21, 48–55, 58, 87–88
- acidic substructures, 51t
 - activity, 52t
 - basic substructures, 51t
 - capillary electrophoresis method, 273–274
 - case studies, 50–54
 - effects, 50
 - example drugs, 51t
 - fundamentals, 48–49
 - in silico, 271–274
 - methods, 271–274
 - pH-metric method, 274–275
 - SGA method, 273
 - structure modification strategies, 54
 - titration curves, 60f
- Plasma decomposition, 137
- Plasma enzyme hydrolysis, 27
- Plasma protein binding (PPB), 27, 187–195, 230
- BBB, 126f
 - case studies, 193
 - chirality, 189
 - clearance, 192

- comparison of methods, 375t
- complementary factors, 190
- discovery strategy, 194
- distribution, 191–192
- effects, 190–193
- equilibrium dialysis method, 373
- free drug, 27
- fundamentals, 187–189
- immobilized protein HPLC method, 375
- instruments and supplies for methods, 374
- in vitro methods, 373–376
- in vitro vs in vivo, 126f
- methods, 372–376
- microdialysis method, 375–376
- permissive effects, 191t
- pharmacology, 192–193
- PK parameters, 234
- reduction, 194
- restrictive effects, 191t
- in silico methods, 372
- stereoselectivity, 189t
- structure modification strategies, 193–194
- ultracentrifugation method, 375
- ultrafiltration method, 374
- unbound drug, 280
- Plasma stability, 169–177, 348–351
 - applications of data, 174–176
 - chirality, 170
 - commercial suppliers of plasma, 349t
 - effects, 170–171
 - fundamentals, 169–170
 - prodrug screening, 175–176
 - species difference, 171f
 - steric hindrance, 173
 - structure modification strategies, 172–174
- PLSD analysis. *See* Partial least squares discriminant analysis
- Polar group, 74
 - isoteric replacement, 93
- Polar surface area (PSA), 39, 130, 448
- Pooling samples for PK assays, 411
- Poor drug properties, 9–10, 11–12
- Potency, 455, 456f
- Potentiometric in vitro thermodynamic solubility method, 283–284
- PPB. *See* Plasma protein binding
- Precipitation in bioassays, 447
- Pregnane X-receptor (PXR), 221, 389
- Presystemic metabolism, 139
- Prodrugs, 25, 170, 426–437
 - alcohols, 432, 433t
 - amino-acid type, 429f
 - barriers overcome with prodrugs, 427
 - blockbuster, 427f
 - carboxylic acids, 431–432
 - commercially available, 428t
 - constructing, 76
 - ester of carboxylic acid, 431–432
 - hydrolysis in intestine, 25
 - metabolism, 435–436
 - nitrogen-containing functional groups, 433
 - oral absorption, 435t
 - permeability, 96, 97f, 430, 433
 - phenols, 432, 433t
 - phosphate-acid type, 429f, 430f
 - screening, 175–176
 - solubility, 428–430
 - structures, 428f
 - targeting specific tissues, 436
 - transporter-mediated, 434–435
- Property-based design, 15, 18
- Property optimization, 140
- Property profiling, 14
- Property-related concepts, 4
- Proximal tubule, 30
- PSA. *See* Polar surface area
- Purity, *see* Integrity and Purity
- PXR. *See* Pregnane X-receptor
- QC. *See* Quality control
- QSAR. *See* Quantitative structure-activity relationships
- QT interval, 211
- Quality control (QC), 349, 350
- Quantitative structure-activity relationships (QSAR), 299, 387
 - BBB, 312–313
- Rapid property profiling, 37–42, 250
- Reabsorption, renal, 29
- Reactive metabolites, 218–221
- Reactivity screens, 392
- Red blood cell binding, 28, 194, 376
- Renal clearance, 231
 - stereoselectivity, 31
- Reproductive toxicity, 217
- Reverse-phase HPLC lipophilicity method, 266–267
- rhCYP enzymes, 332
- Ring size and metabolism, 151–152
- Risk management, 400
- Rubidium efflux method for hERG, 381
- Rules for structure-property prediction
 - BBB, 130
 - Jorgensen rules, 277
 - lead-likeness rules, 243
 - rule of 5 (Lipinski rules), 37
 - rule of 3, 246
 - Veber rules, 39

- S9, 333
S9 stability assay, 329
Safety pharmacology, 217
Salt forms, 78–82
 absorption, 80–81
 anions, 81t–82t
 cations, 81t–82t
 dissolution rate, 78
 oral bioavailability, 80–81
 precautions, 82
 selection, 81–82
 solubility, 78–80
Sample preparation for purity and integrity method, 402
SARs. *See* Structure-activity relationships
SC. *See* Subcutaneous
Scaled-down shake flask lipophilicity method, 265
Secretory transport, 90
Selectivity screens, 392
Serial dilution schemes in bioassays, 444f
Serum albumin, 27
SGA. *See* Spectral gradient analysis
SGF. *See* Simulated gastric fluid
Shake flask lipophilicity method, 267–268
Shift assays and plasma protein binding, 193
SIF. *See* Simulated intestinal fluid
Simulated gastric fluid (SGF), 421
Simulated intestinal fluid (SIF), 421
Single substrate HLM CYP inhibition assay, 363, 365
Single time point HT microsomal stability assay, 337t
Single-compound dosing, 409
Sink conditions, 291
Sink effect, 88
Sodium dependent taurocholate co-transporting polypeptide (NCTP), 118
Soft drugs. *See* Antedrgs
Solid dispersion formulation, 461
 products, 462t
Solubility, 26, 56–82. *See also* Dissolution rate;
 Kinetic solubility; Thermodynamic solubility
 acceptance criteria, 63–66
 aqueous buffers, 443–449
 assessment, 446–447
 basicity, 72f
 BCS, 66
 bile salts, 260
 bioavailability, 62
 calculation methods, 276
 chirality, 61–62
 classifications, 63–66
 commercial instruments and products for methods, 280t
 commercial software, 277
 crystal lattice energy, 58
 customized methods, 282
 determination, 279t
 direct UV method, 278
 DMSO, 441–443
 effects, 62–68
 equilibrium shake flask method, 283
 estimating, 65f
 food effect, 69
 IV formulation, 63
 formulary solvents, 284
 fundamentals, 57–60
 given pH, 59t
 Henderson-Haselbach equation, 59
 hydrogen bonding, 73
 intrinsic solubility, 59
 ionizable groups, 71
 kinetic solubility, 60
 kinetic solubility methods, 278–282
 lipophilicity, 57–58, 73
 Log P, 73
 in silico methods, 277
 melting point, 57
 methods, 276–284
 minimal acceptable, 64t
 molecular weight, 58, 74
 nephelometric method, 280
 oral bioavailability, 62–63
 out-of-plane substitution, 75–76
 permeability versus solubility, 64f, 67
 physical conditions, 57
 physiology of GI tract, 68–70
 potentiometric method, 283
 pKa, 58
 polar groups, 74
 potentiometric titration method, 283
 prodrugs, 428–430
 salts, 78–80
 solvent effects, 284
 species dependence, 69f
 structural properties affecting, 57–58
 structure effects, 57
 structure modification strategies, 70–75
 structure-solubility relationships, 57–59
 thermodynamic solubility, 60–61
 thermodynamic solubility methods, 283–284
 turbidimetric method, 281
Solubilizers, 291
Solution stability, 178–185
 applications, 183–185
 biological assay media, 355–356
 data, 183–185

- degradation products from, 357
 - effects, 180
 - electron-withdrawing groups, 181
 - fundamentals, 178–180
 - general method, 353–355
 - pH stability, 356
 - simulated gastrointestinal fluids, 356–357
 - steric hindrance, 182
 - structure elucidation of products, 185
 - structure modification, 180–185
 - unstable groups modification, 180–181
- Spectral gradient analysis (SGA), 273, 274
- SPRs. *See* Structure-property relationships
- Stereoselective metabolism, 160
- Steric hindrance
- metabolic stability, 154–155
 - Pgp efflux, 115f
 - plasma stability, 173
 - solution stability, 182–183
- Stomach barriers, 19–20
- Structural properties, 7
- Structure modification
- BBB penetration, 131–133
 - CYP inhibition, 203–204
 - hERG, 213
 - lipophilicity, 46
 - permeability, 92–96
 - Pgp efflux, 114–115
 - phase I metabolic stability, 146–153
 - phase II metabolic stability, 154–156
 - pKa, 54
 - plasma stability, 172–174
 - PPB, 193–194
 - solubility, 70–76
 - solution stability, 180–185
 - toxicity, 222
 - uptake transporters, 119
- Structure-activity relationships (SARs), 3, 18, 137, 224, 250, 399. *See also* Quantitative structure-activity relationships
- biological assays, 440–441
 - CYP2C9, 164f
 - hERG blocking, 212–213
- Structure-based design, 18
- Structure-property relationships (SPRs), 15, 18, 225, 250
- developing, 250–251
- Structure-stability relationships, 184
- Subcutaneous (SC), 187, 455
- Substitutions to improve properties
- fluorine atoms for metabolic stability, 148
 - permeability, 95f
 - Pgp transport, 113f
 - use amides for esters in plasma stability, 172–173
- Substrate compounds for CYP inhibition
- methods, 361
- Sulfation metabolism, 144f
- Sulfide oxidation metabolism, 143
- Sulfotransferase metabolism, 220
- Sulfoxide metabolism, 143
- Surface activity BBB method, 317
- Surfactants, 457
- formulating, 78
 - products containing, 458t
- Synthetic efforts, prioritizing, 175
- Systemic clearance (Cl_s), 232
- TEER. *See* Transepithelial electrical resistance
- Template conservation, 244
- Teratogenicity, 217, 392
- Tethering fragments, 246
- Therapeutic index, 216
- Thermodynamic solubility, 60–61, 283–284
- equilibrium shake flask method, 283
 - potentiometric method, 283–284
 - testing, 284t
 - various solutions, 284
- Thiophene toxicity, 221f
- Thiourea substitution, 155
- Thymidine kinase (TK) mouse lymphoma cell
- mutagenicity assay, 391
- Tissue distribution barriers, 30–31
- Tissue uptake, 234, 413–414
- Toxicity, 215–223. *See also* types
- acute, 217
 - AhR method, 389
 - Ames assay, 390
 - biomarkers, 395
 - case studies, 221
 - chromosomal aberration method, 390
 - comet method, 390
 - commercial vendors of products assays, 387t
 - co-solvents, 457t
 - covalent protein binding method, 393
 - CYP inhibition, 388
 - CYP induction, 389
 - development studies, 393–394
 - drug-drug interaction, 388–389
 - formulation, 464
 - fundamentals, 216–217
 - glutathione method, 393
 - Greenscreen method, 391
 - HRPT method, 391
 - knowledge-based expert system, 387–388
 - LDH method, 392
 - LDsubscript50, 216
 - mechanisms, 217–221
 - mechanism-based, 217–218

- Toxicity (*Continued*)
 methods, 386–395
 micronucleus method, 390
 MTT method, 392
 mutagenicity methods, 389
 Neutral red method, 392
 off target, 217
 organ, 217
 preclinical studies, 393–394
 reactivity screens, 392
 reproductive, 217
 selectivity screens, 393
 in silico, 387–388
 safety window, 215
 selectivity screens, 392
 statistically-based methods, 388
 structure modification strategies, 222
 substructures initiating, 219t
 terms, 218
 therapeutic index, 215
 therapeutic target effects, 217–218
 TK mouse method, 391
 toxic alerts, 219
 in vitro assays, 388–393
 in vivo assays, 393–395
 zebrafish method, 392
- Toxicogenomics, 395
- Toxicokinetics, 394, 457
- Toxicometabonomics, 395
- Toxicoproteomics, 395
- Transdermal, 187
- Transepithelial electrical resistance (TEER), 291, 303
- Transfected cell line permeability method, 302–304
- Transporters, 103–119, 299–307, 434–435.
 See also specific types
 ADME functions, 107t–108t
 ATPase method, 305–306
 blood-brain barrier, 110
 Caco-2 permeability method, 301–302
 Calcein AM method, 306–307
 cell layer permeability methods, 300–304
 cell uptake assay, 304
 chemical knockout method, 307–308
 chirality, 110–111
 commercial suppliers of products assays, 300t
 compilation, 107t–108t
 diagrams, 109f
 effects, 104–109
 efflux, 104f, 111–117
 fundamentals, 103–104
 genetic knockout method, 307
 GI tract, 103
 intestinal epithelial cells, 108
 inverted vesicle assay, 305
 kidney epithelial cells, 110
 liver hepatocytes, 108–110
 methods, 299–307
 oocyte uptake method, 304–305
 in silico methods, 299–300
 stereoselectivity, 110, 111t
 structure-modification strategies for efflux, 111–116
 transfected cell line permeability method, 302–304
 uptake transport, 104f, 105t–106t, 117–119
 uptake method, 304
 in vitro methods, 300–307
 in vivo methods, 307–308
- Triacylglycerols, 27
- Triage in hit-to-lead, 245
- Turbidimetric in vitro solubility method, 281
- UDP-glucuronosyltransferases (UGTs), 143, 341
- UGTs. *See* UDP-glucuronosyltransferases
- Ultracentrifugation PPB method, 375
- Ultrafiltration PPB method, 374
- Ultraperformance liquid chromatography, 403
- Unstable (metabolically) groups, 153
 eliminating, 180–185
- Uptake transporters, 22–23, 104f, 117–119, 133–134, 304
 BBB, 119, 133
 examples, 105t–106t
 structure modification, 119
- Veber rules, 39
- Vendor-to-vendor variation of reagents, 339f
- Venous sinusoid vessels, 28
- Very-high-density lipoprotein (VHDL), 188
- Very-low-density lipoprotein (VLDL), 188
- VHDL. *See* Very-high-density lipoprotein
- Victims in CYP inhibition, 198, 205–206
- Villi, 21–22
- VLDL. *See* Very-low-density lipoprotein
- Volume of distribution, 145
 commercial drugs, 30t
 diagnosing compound binding locations using, 230
 PK, 229–231
- Wallach rule of solubility, 61
- Water-in-oil (W/O) emulsions, 458
- W/O emulsions. *See* Water-in-oil emulsions
- Zebrafish toxicity models, 392

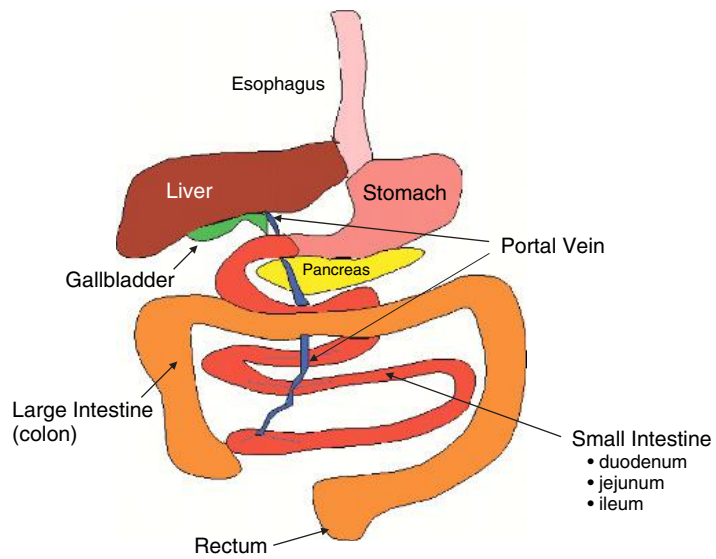


Plate 1 ► Diagram of the gastrointestinal tract. (see Figure 3.2 on p. 20)

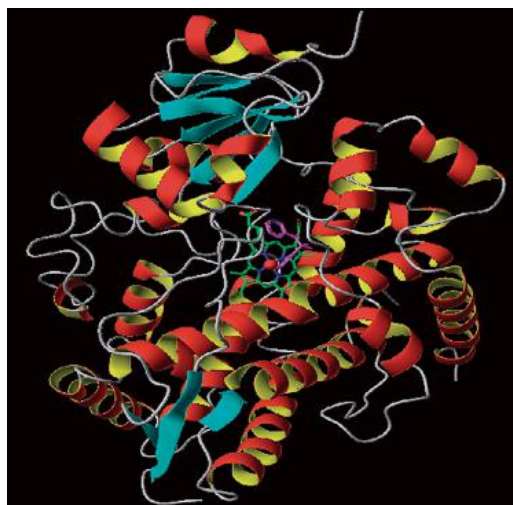


Plate 2 ► Structure of human cytochrome P450 3A4 with heme and inhibitor metyrapone. (Drawing courtesy Kristi Fan.) (see Figure 11.3 on p. 140)

	Lead	Analog	Desired Profile
MW	330	445	<450
clogP	1.9	5.19	<4.0
IC50 (μM)	4.2	>20	<1.0 μM
Binding to target (STD, FP, Trp-Fl.)	X-ray		Yes (NMR, FP)
MIC			
<i>B. subtilis</i>	>200 μM	50 μM	<200 μM
<i>S. aureus</i> MRSA	>200 μM	25 μM	<200 μM
<i>S. aureus</i> ATCC	>200 μM	200 μM	<200 μM
<i>S. pneumo</i> +	>200 μM	25 μM	<200 μM
Selectivity: <i>C. albicans</i> (MIC μg/mL)	>200	>200	>10 fold
Aqueous Solubility (μg/ml @ pH 7.4)	>100	26.5	>60
Permeability (10 ⁻⁶ m/s @ pH 7.4)	0	0.15	>1
CYP 3A4 (% inhibition @ 3 μM)	11	7	<15
CYP 2D6 (% inhibition @ 3 μM)	0	1	<15
CYP 2C9 (% inhibition @ 3 μM)	NT	23	<15
Microsome stability (% remaining @ 30 min)	NT	NT	>80
Definable Series	Yes	Yes	Yes
Definable SAR	Yes	Yes	Yes

Plate 3 ► Example of goals used by Wyeth Research exploratory medicinal chemists for hit selection, initial structural modification, and lead selection in an acyl carrier protein synthase (AcpS) inhibitor project. (see Figure 20.2 on p. 245)

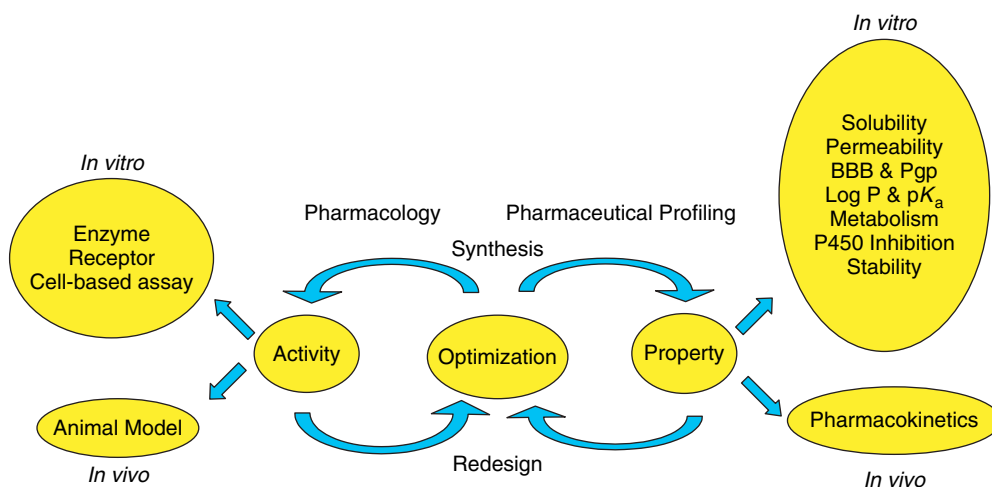


Plate 4 ► Iterative parallel optimization by simultaneous assessment of both activity and properties. (Reprinted with permission from [2].) (see Figure 21.3 on p. 251)