# 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

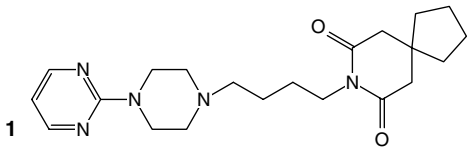
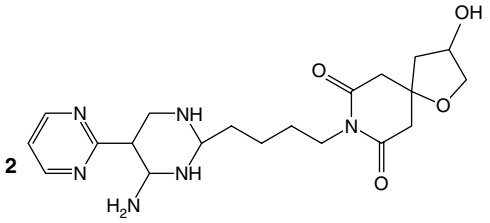
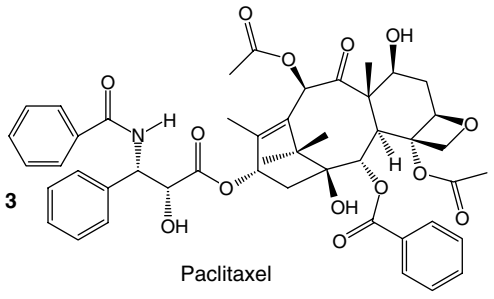
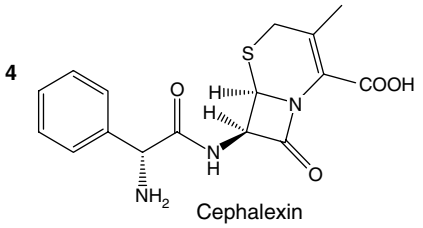
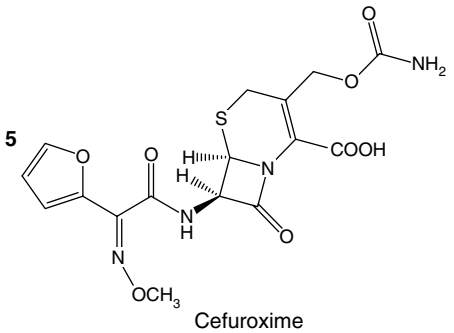
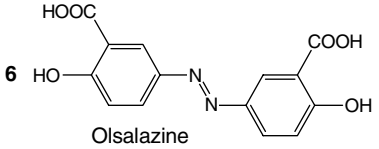
## Chapter 3: Barriers to Drug Exposure in Living Systems

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 |
|---|---|---|---|---|---|---|
| **1**  Buspirone | 0 | 7 | 385 | 1.7 | 70 | none |
| **2**  | 5 | 10 | 418 | −3.3 | 143 | PSA |
| **3**  Paclitaxel | 4 | 15 | 852 | 4.5 | 209 | HBA, MW, PSA |
| **4**  Cephalexin | 4 | 7 | 347 | 0.5 | 138 | none |
| **5**  Cefuroxime | 4 | 12 | 424 | −1.5 | 199 | HBA, PSA |
| **6**  Olsalazine | 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 p$K_a$ 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: p$K_a$

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

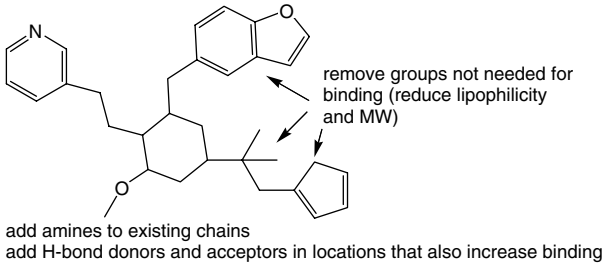
| Location | pH | $[HA]/[A^-] = 10(pK_a - pH)$ | Ionization |
|---|---|---|---|
| Stomach | 1.5 | $10^{(4.2-1.5)} = 10^{(2.7)}$ | Neutral |
| Duodenum | $10^{(4.2-5.5)} = 10^{(-1.3)}$ | (−) Ionized ~95% | |
| Blood | | 7.4 | $10^{(4.2-7.4)} = 10^{(-3.2)}$ |
| (−) Ionized ~100% | | | |

| Location | pH | $[BH+]/[B] = 10^{(pK_a-pH)}$ | 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

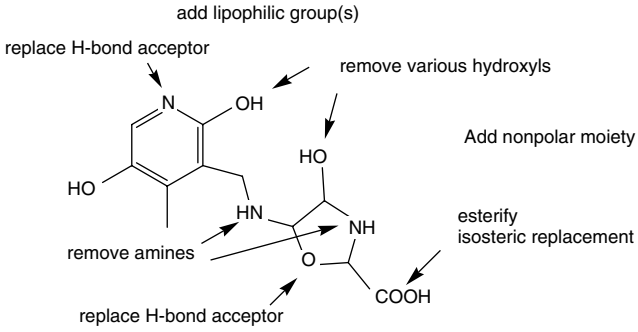
1. The same. Both the free base and HCl salt will reach the same concentration in the buffered solution, thus, the $IC_{50}$ will be the same.
2. No. In pure water the pH will change when the compound is added, and the sodium salt will be more soluble. Sodium salt. Yes.

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 μg/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, p$K_a$, 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 μg/mL, (b) 100 μg/mL, (c) 520 μg/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).

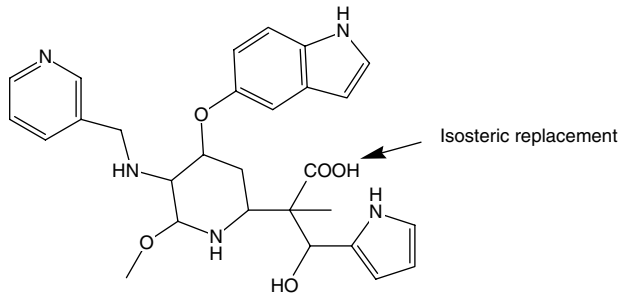
## Chapter 9: Transporters

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

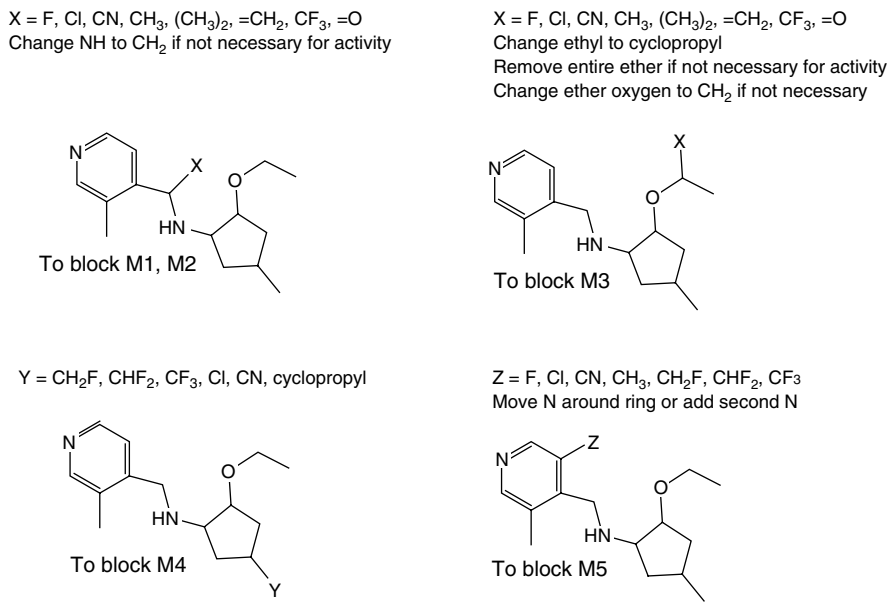
1. Intestinal decomposition (pH and enzymatic), intestinal metabolism, liver metabolism, plasma decomposition.
2. c
3. a, d
4. Change in metabolic reactions if one pathway is blocked.

5. Aliphatic and aromatic hydroxylation, *N*- and *O*-dealkylation, *N*-oxidation, *N*-hydroxylation, dehydrogenation, (others shown in Figure 11.5).

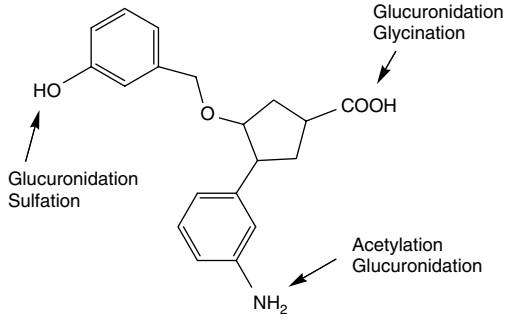
6. Glucuronidation, sulfation, *N*-acetylation, glutathione conjugation (others shown in Figure 11.6).

7. c, e

8. Possible structure modifications to investigate:




9. Potential sites of phase II metabolic reactions:

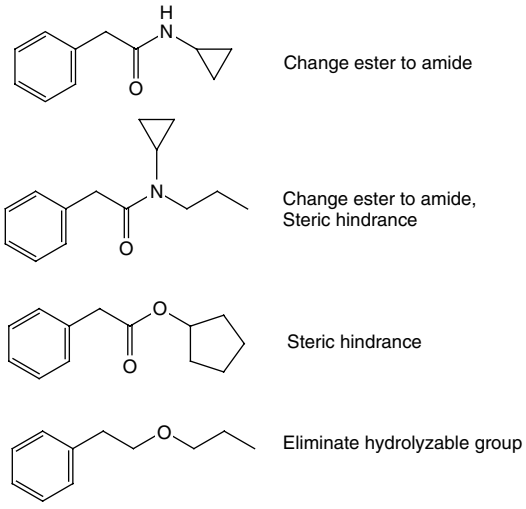



10. a, b, c, e

11. a, b, d, e, f

## Chapter 12: Plasma Stability

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




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

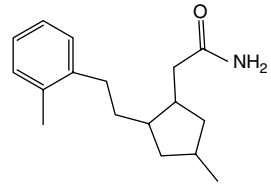
1. All
2. No. The stability might be improved without reducing activity by structural modification, thus allowing a valuable pharmacophore/series to continue optimization toward a quality clinical candidate.

## Chapter 14: Plasma Protein Binding

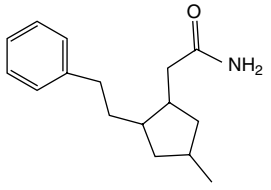
1. (a) metabolic clearance decrease, (b) tissue concentration decrease, (c) tissue distribution decrease, (d) blood concentration increase, (e) renal clearance decrease, (f) PK half-life increase, (g) pharmacological effect decrease, (h) brain penetration decrease.
2. Albumin, $\alpha_1$-acid glycoprotein, lipoprotein.
3. Compound binds to albumin and is restricted from interacting with the target protein.

4.

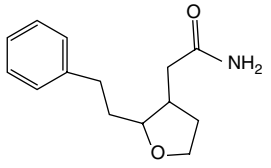
A



Reduce acidity
Reduce lipophilicity (cLogP = 4.4)
Increase PSA (44)
Increase HBD (+1)

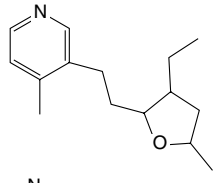


Reduce acidity
Reduce lipophilicity (cLogP = 3.9)
Increase PSA (44)
Increase HBD (+1)

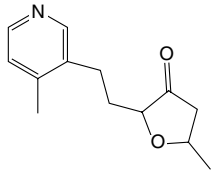


Reduce acidity
Reduce lipophilicity (cLogP = 1.2)
Increase PSA (52)
Increase H-bonding (+1 HBD, +1 HBA)

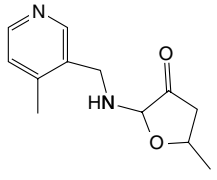
B



Reduce lipophilicity (cLogP = 3.5)
Increase PSA (22)
Increase H-bonding (+1 HBA)



Reduce lipophilicity (cLogP = 1.7)
Increase PSA (39)
Increase H-bonding (+2 HBA)



Increase basicity
Reduce lipophilicity (cLogP = 0.5)
Increase PSA (51)
Increase H-bonding (+1 HBD, +3 HBA)

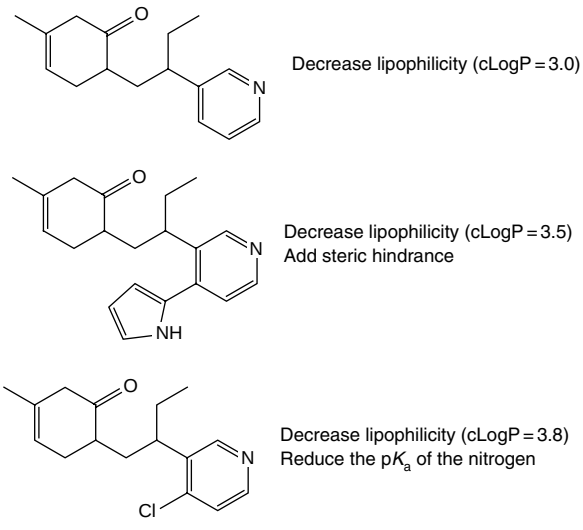
(For Example 4B, increasing basicity will likely increase binding to AGP.)

## Chapter 15: Cytochrome P450 Inhibition

1. 10 μM
2. Greater than 10 times $C_{max}$. When concentration is greater than $K_i$.
3. 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

1. Potassium ion channel in heart muscle.

2. Outflow of $K^+$ ions from the cell is part of the action potential and reestablishes the internal negative potential of the cells.

3. Lengthened QT interval on electrocardiogram (ECG).

4. Torsades de pointes arrhythmia, which can be triggered by LQT.

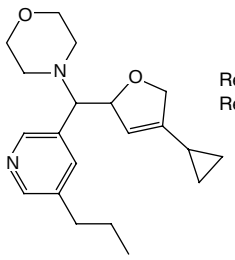
5. 1 in $10^5$ to $10^6$ patients for antihistamines, 1 in $5 \times 10^4$ patients for terfenadine.

6. hERG $IC_{50}/C_{max,unbound} > 30$, or $< 5$ seconds lengthening of QT interval.

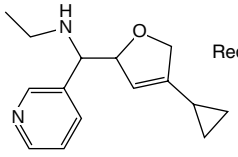
7. c

8. c, d

9. Among possible structural modifications are the following:



Reduce p$K_a$ of amine
Reduce lipophilicity of substructure (cLogP = 3.2)



Reduce lipophilicity of substructures (cLogP = 2.1)

10. c

## Chapter 17: Toxicity

1. Ratio (or range) of compound concentrations at which it is toxic versus efficacious. Large.
2. Reactive metabolites undergo covalent reactions with protein, DNA. They can be detected using glutathione or another trapping reagent.
3. a, b, e
4. 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.
5. Higher levels of metabolizing enzymes are induced, resulting in greater chance of forming reactive metabolites or increasing the clearance of a co-administered drug.
6. Antagonism or agonism of another biochemical target can cause side effects, which can be toxic.

## Chapter 18: Integrity and Purity

1. 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.
2. Mishandling, mislabeling, decomposition as a solid or in solution, inaccurate original structural assignment.
3. All
4. 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 |
| $t_{½}$ | 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 p$K_a$).

## 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.

3. a, b, d, e, f, g
4. 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.
5. A factor of 10 or 1 Log unit.
6. a, d, e

## Chapter 24: p$K_a$ Methods

1. 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.
2. Throughput: in silico > SGA > CE > pH metric.
3. Features: high throughput; p$K_a$ is calculated for different tautomers; the software labels each ionization center with its p$K_a$ on the structure.
4. 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

1. $\text{Log S} = 0.8 - \text{Log P} - 0.01$ (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 |

2. $S_{tot} = S_{HA}\ (1 + 10^{(pH - pK_a)})$

| Compound | Intrinsic solubility (g/mL) | p$K_a$ | 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 |

3. Nephelometric: light scattering by precipitated particles. Direct UV: dissolved compound in aqueous solution.
4. 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.
5. 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 microsome 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′-phosphoadenoside-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 | | X | | | |
| Chromosomal aberration | | | | 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., $M+NH_4)^+$ 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% |

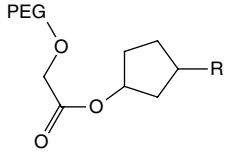
## Chapter 38: Diagnosing and Improving Pharmacokinetic Performance

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

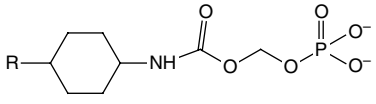
## Chapter 39: Prodrugs

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

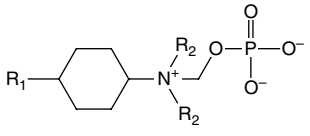
A.



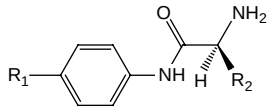

B.



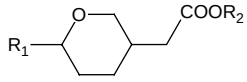

C.



D.




3. Ester prodrug:




4. Alkaline phosphatase.

5. Hydrolyzed by esterase in blood

## Chapter 40: Effects of Properties on Biological Assays

1. Solubility in cell assay media, stability in cell assay media, permeability through the cell membrane, and toxicity to the cell.

2. 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.

3. Class 1: lower MW, rigid, hydrophilic (e.g., organic salts); Class 2: high MW, high Log P, many rotatable bonds.

4. 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.

5. 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.

6. (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.

7. Higher $IC_{50}$.

8. (1) Modify the dilution protocol. (2) Optimize the solutions to better solubilize compounds.

9. c

10. c, d

11. DMSO, other organic co-solvents, protein, excipients.

12. Molecular properties (H-bond donors, H-bond acceptors, MW, PSA, acidity), PAMPA, Caco-2.

13. $IC_{50}$ 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 p$K_a$ 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

Appendix II

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Appendix III

# 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) |
| antedrug | | 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 *soft drug* |
| 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 nopolar 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 | $C_{bound}$, $C_B$ | compound molecules bound to a protein or lipid |
| brain microvessel endothelial cells | 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 | ΔLog P | difference in Log P values for partitioning between aqueous and organic solvents [e.g., Log $P_{(octanol-water)}$ minus Log $P_{(cyclohexane-water)}$] |
| 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 *combichem* |
| 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 *microplate* |
| 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 *adverse* 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 *phase II metabolism*) |
| 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 |
| p$K_a$ | p$K_a$ | 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 | | research conducted prior to clinical studies |
| predevelopment | | 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 toxicicity 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 *LQT*) |
| 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 9,000*g*; 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 *template*) |

| 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 *antedrug* |
| 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 | SAR | relationship linking chemical structure and pharmacological activity |
| structure-based design | | 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 *surface-active agent* |
| 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 *scaffold* |
| 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 *target* |
| 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 *in silico screening* |
| 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 *foreign* or *exogenous substance* |
| zwitterion | | dipolar ion containing ionic groups of opposite charge |

# Index

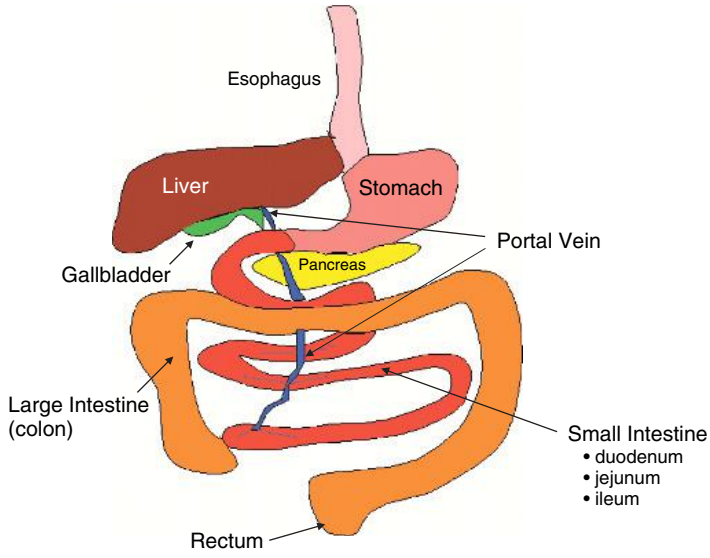


**Plate 1** ► Diagram of the gastrointestinal tract. (see Figure 3.2 on p. 20)

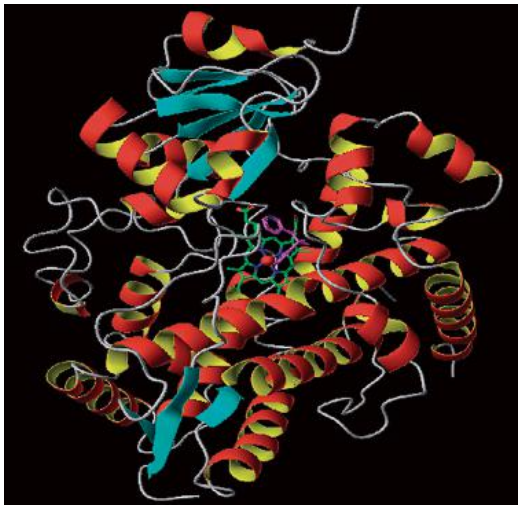

**Plate 2** ► Structure of human cytochrome P450 3A4 with heme and inhibitor metyrapone. (Drawing courtesy Kristi Fan.) (see Figure 11.3 on p. 140)

| | 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 | | | |
| *B. subtilus* | >200 μM | 50 μM | **<200 μM** |
| *S. aureus MRSA* | >200 μM | 25 μM | **<200 μM** |
| *S. aureus ATCC* | >200 μM | 200 μM | **<200 μM** |
| *S. pneumo +* | >200 μM | 25 μM | **<200 μM** |
| | | | |
| Selectivity: *C. albicans* (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)

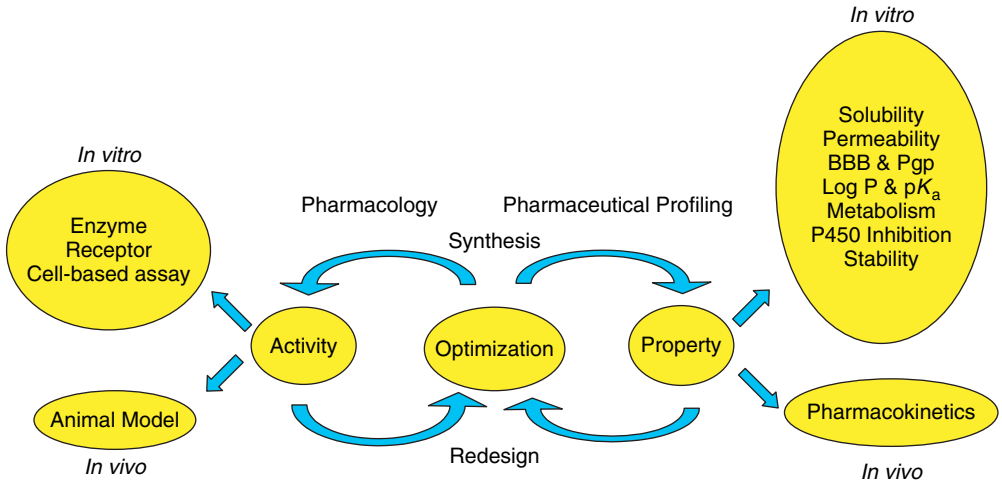


**Plate 4** ► Iterative parallel optimization by simultaneous assessment of both activity and properties. (Reprinted with permission from [2].) (see Figure 21.3 on p. 251)