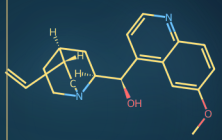
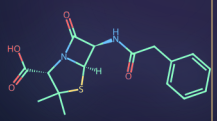
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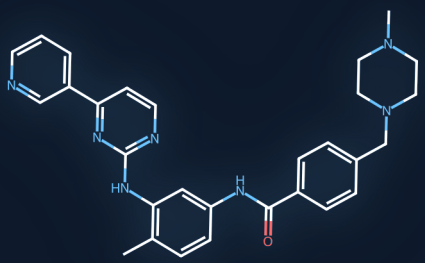
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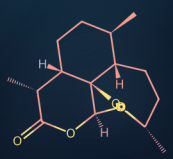
Foundations of Drug Design

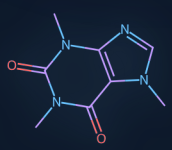
Molecular Recognition, Targets and Drug-like Properties











Twelve chapters on why molecules bind, what they bind to, and which properties decide whether a tight binder can ever become a medicine — with a 25-question self-assessment.

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About this book

Foundations of Drug Design is the first of four classes in the Kecudo Drug Design series. It is written for undergraduate and early graduate readers who have met basic chemistry and biology, and who want to understand *why* a drug works rather than only which drug treats what.

Each chapter is short by design. Concepts are introduced once, illustrated with a figure or a worked example, and then used. Where a number appears — a binding energy, a partition coefficient, a polar surface area — it has been calculated rather than quoted, and the method is stated so that you can repeat it.

MOLECULAR PROPERTIES

Molecular weight, clogP, hydrogen-bond counts, topological polar surface area, rotatable bonds and QED were computed with RDKit 2026.09 from published structures. Structure drawings are generated from the same structures.

NATURAL PRODUCT STATISTICS

Newman & Cragg, *J. Nat. Prod.* 2020 (1981–2019); Stone, Newman, Colletti & Tan, *Nat. Prod. Rep.* 2021; Newman, Cragg & Snader, *J. Nat. Prod.* 2003 (1981–2002).

THERMODYNAMIC CONSTANTS

Free energies computed at 310.15 K with R = 8.314 J $K^{-1}mol^{-1}$, giving RT = 2.579 kJ/mol.

WORKED EXAMPLES

Compounds designated *KC-* and the company *Kecudo Therapeutics* are fictional, created for teaching. Their data are internally consistent and recur across the series. All named drugs and natural products are real.

HOW TO USE THE QUIZ

Twenty-five questions in five parts. Each answer locks once chosen and is explained immediately; your running score appears in the header. A printed copy includes the answer key.

Educational content only. Nothing in this book is medical advice, a treatment recommendation, or guidance for the use of any medicine. Drug names appear as teaching examples. © 2026 Kecudo. For personal use only; please do not redistribute.

KECUDO · CLASS ONE

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Chapter One

The Design Problem ●○○ FOUNDATION

Drug design asks a question that sounds simple and is not: given a disease, can we build a molecule that changes its course, and nothing else?

A drug must do several things at once. It has to reach the tissue where the disease lives, survive the journey, recognise one protein out of roughly twenty thousand, bind it tightly enough to matter, change what that protein does in the right direction, and then leave again before it accumulates. Fail any one of these and the molecule is not a drug, however elegant its chemistry.

This is why drug design is a *multi-objective* problem. A chemist can almost always make a molecule bind harder. The difficulty is making it bind harder while staying soluble, staying permeable, staying off the other proteins, and staying out of the liver's way. Every improvement is paid for somewhere else. The craft lies in knowing the exchange rate.

> **The central exchange.** Adding greasy bulk usually buys affinity and costs solubility, metabolic stability and selectivity. Most of this book is about managing that single trade.

It is worth being clear about what "design" means here. Very few drugs are designed in the sense that a bridge is designed, from first principles to a finished object. What happens instead is iterative: a starting molecule is found, measured, modified, and measured again, hundreds of times, with each round guided by a hypothesis about why the last one behaved as it did. Good design is therefore less about invention than about asking the right question at each cycle — and the questions come from the physics and the properties set out in this book.

The chapters ahead build in three layers. First, the physics of why two molecules stick together at all. Then the biology of what they stick to, and how we measure the result. Finally the properties that decide whether a tight binder can ever become a medicine — and what nature, which has been at this far longer than we have, already knows.

Chapter Two

Molecular Recognition: The Forces ●○○ FOUNDATION

A drug binds its target through forces that are, individually, feeble. None of them is a chemical bond in the ordinary sense. Binding is the sum of many small terms, and the sum is what we design.

The energies below are the usable range for a single interaction inside a protein pocket in water. Compare them with a covalent bond and the scale of the problem becomes clear: a nanomolar drug is worth about 53 kJ/mol in total, which is less than a fifth of one carbon–carbon bond.

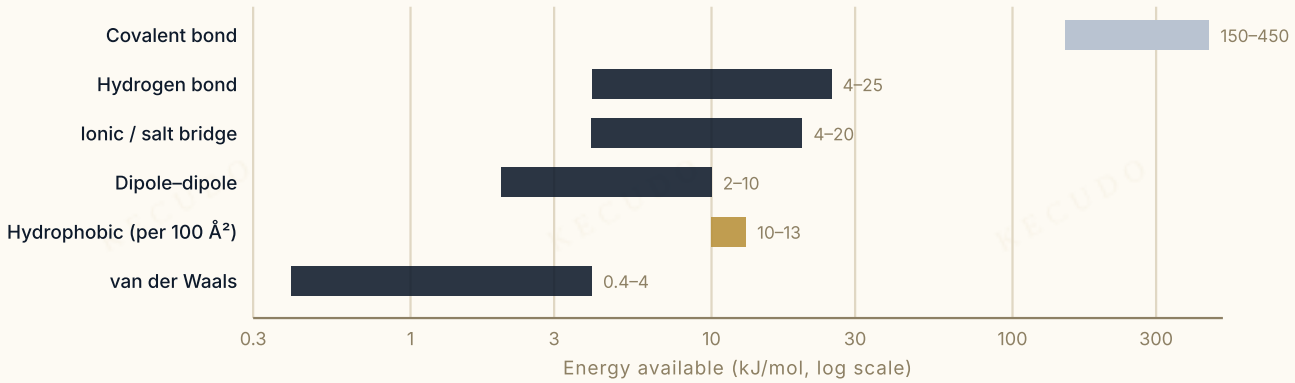


FIG 2.1 — Typical energy available from a single interaction in an aqueous protein site. The hydrophobic effect is shown per 100 Å² of apolar surface buried, since it scales with area rather than with a discrete contact.

Three consequences follow. Because each term is small, **many contacts are needed**, which is why ligands are molecules rather than atoms. Because the terms are comparable to thermal energy ($RT \approx 2.6$ kJ/mol at 37 °C), **binding is reversible** and described by an equilibrium. And because water competes for every polar contact, **the apparent strength of a hydrogen bond in a drug–protein complex is far below its strength in vacuum**.

Chapter Four

Measuring Affinity ●●○ CORE

Every design decision rests on a number, and the numbers are easy to confuse. This chapter makes them precise.

The dissociation constant

For the equilibrium L + P ⇌ LP,

$$K_d = [L][P] / [LP] \qquad \Delta G° = RT \ln K_d$$

K_d has units of concentration and a useful physical meaning: it is the ligand concentration at which half the target is occupied. Smaller is tighter. Because the relationship to energy is logarithmic, affinity is usually quoted as $pK_d = -\log_{10} K_d$, which is additive and therefore easier to reason with.

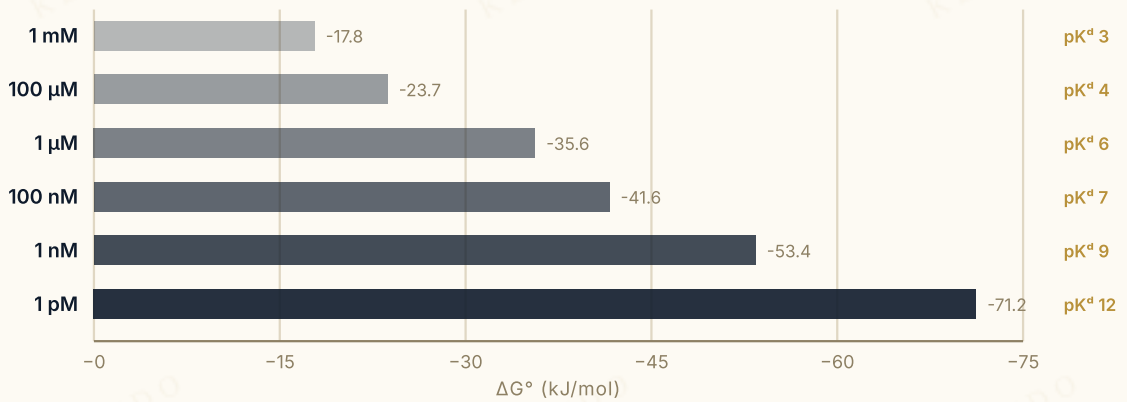


FIG 4.1 — The affinity ladder at 37 °C. Each factor of ten in K_d is worth 5.94 kJ/mol (1.42 kcal/mol). Computed from $\Delta G° = RT \ln K_d$, RT = 2.579 kJ/mol.

> **The most useful number in medicinal chemistry.** One order of magnitude of potency costs about 6 kJ/mol — roughly one well-placed hydrogen bond, or 60 Å² of buried apolar surface. Keep it in mind and you can estimate whether a proposed modification is worth making before you make it.

PART A · BASICS

01 For most drug–protein complexes, which term contributes the most binding energy?

- **A** A single strong hydrogen bond
- **B** Burial of apolar surface area (the hydrophobic effect)
- **C** A covalent bond to the protein
- **D** Ion–ion attraction at the protein surface

02 K_d is best described as...

- **A** the ligand concentration at which half the target is occupied
- **B** the rate at which the complex falls apart
- **C** the maximum response a ligand can produce
- **D** the fraction of dose reaching the circulation

03 Which of these is *not* one of Lipinski's four rule-of-five criteria?

- **A** Molecular weight below 500
- **B** clogP below 5
- **C** Rotatable bonds no more than 10
- **D** Hydrogen-bond donors no more than 5

04 Which kind of binding site is generally most tractable for a small molecule?

- **A** A flat protein–protein interface
- **B** A shallow surface groove
- **C** An extended RNA loop
- **D** A deep, enclosed, partly polar cavity

05 A partial agonist differs from a full agonist because it...

- **A** binds more weakly
- **B** cannot produce the full response at any concentration
- **C** blocks the receptor completely
- **D** only works below the K_d

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Thank you for learning with Kecudo.

NEXT IN THE SERIES

Class 2 · Design Methods. Ligand-based design and pharmacophores, structure-based design and docking, biostructure and mechanism-based inhibition, and the peptide, macrocycle and protein modalities that begin where cyclosporin A leaves off.

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