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Drug-Likeness Rules Cheatsheet

Lipinski to PROTACs. The classic rules, the modern ones, and when to break them. Free, no signup.

Drug-likeness is a set of empirical rules that flag compounds with high oral-absorption risk. The thresholds emerged from statistical analysis of marketed drugs, they are heuristics, not biology. Use them as triage signals, not pass/fail gates.

CONTENTS

Rules at a glance

The full landscape of drug-likeness rules in one view. Each rule is detailed on its own page that follows.

RULE	YEAR	PARAMETERS
Lipinski's Rule of 5	1997	MW ≤500 · LogP ≤5 · HBD ≤5 · HBA ≤10
Veber's Rules	2002	Rotatable bonds ≤10 · TPSA ≤140 Å² · (or HBD + HBA ≤12)
Egan's Rules	2000	LogP -1 to 5.88 · TPSA ≤131.6 Å²
Ghose's Rules	1999	MW 160-480 · LogP -0.4 to 5.6 · MR 40-130 · Atoms 20-70
QED	2012	Continuous score 0 to 1 · Higher = more drug-like · 8 weighted properties
Lead-Likeness	2004	MW ≤350 · LogP ≤3 · RotB ≤7
CNS MPO	2010	MW ≤360 · ClogP ≤3 · cLogD7.4 ≤2 · TPSA 40-90 Å² · HBD ≤1 · pKa ≤8.0

1997

Lipinski's Rule of 5

MW ≤500 | LogP ≤5 | HBD ≤5 | HBA ≤10

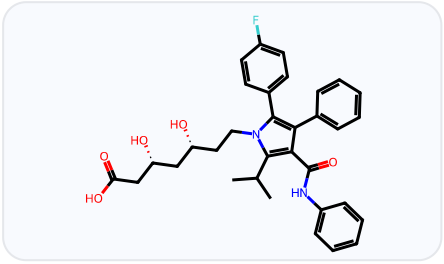
WHY IT EXISTS

Pfizer's analysis of ~2,250 drugs that had entered Phase II trials. The Rule of 5 emerged as a pattern: orally bioavailable drugs tended to satisfy these four limits. The thresholds are heuristics, not biology. Lipinski's classic convention: HBD = count of N-H and O-H bonds; HBA = total count of N + O atoms. Modern SMARTS-based implementations (e.g. RDKit NumHAcceptors) refine this by excluding pyrrole NH, amide N, nitro N, and most guanidine-type N — reported HBA can therefore differ substantially from the strict N+O count, particularly for amide- or guanidine-rich molecules.

WHAT VIOLATION ACTUALLY MEANS

A violation is a flag, not a disqualifier. ~35-40% of post-2000 oral approvals violate at least one Ro5 criterion and still get to market — closer to 40% in the 2013-2019 cohort, driven by MW inflation in oncology and antivirals (Stegemann 2023, Shultz 2019). The genuine red flag is two or more violations, which remains rare among approved orals (~3%).

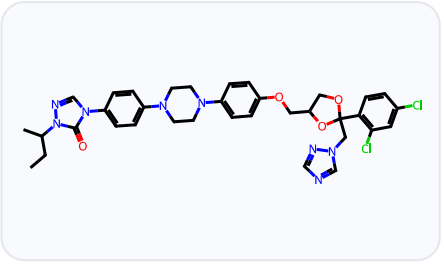
FAMOUS VIOLATORS



Atorvastatin

Atorvastatin

MW 558 and ALogP ~5.0-5.4 — two violations, the supposed red flag. Yet among the top-selling oral drugs in history. The dihydroxy-heptanoic-acid tail is essential for HMG-CoA reductase binding.



Itraconazole

Itraconazole

MW 705 and cLogP > 5. Oral antifungal, demonstrates that highly lipophilic compounds can still work given the right formulation.

Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. *Adv Drug Deliv Rev* 23: 3-25 (1997). DOI: 10.1016/S0169-409X(96)00423-1

2002

Veber's Rules

Rotatable bonds ≤10 | TPSA ≤140 Å² | (or HBD + HBA ≤12)

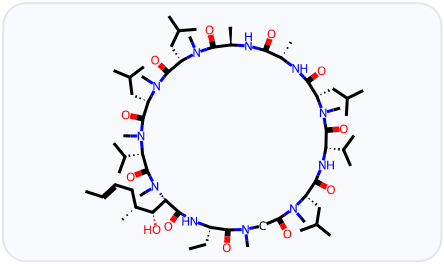
WHY IT EXISTS

GSK analysis of rat oral bioavailability for 1,100 compounds. Veber and colleagues found that rotatable bond count and polar surface area predicted oral absorption better than Lipinski's parameters in this dataset.

WHAT VIOLATION ACTUALLY MEANS

Conformational flexibility (high RotB) and polarity (high TPSA) both raise the entropic and energetic cost of crossing membranes. Compounds breaching both limits are the highest-risk category.

FAMOUS VIOLATORS



Cyclosporin A

Cyclosporin A

TPSA 279 Å², well over Veber's limit. Orally bioavailable through chameleonic conformational shielding (covered in the bRo5 section below).

Veber DF, Johnson SR, Cheng HY, Smith BR, Ward KW, Kopple KD. *J Med Chem* 45: 2615-2623 (2002). DOI: 10.1021/jm020017n

2000

Egan's Rules

LogP -1 to 5.88 | TPSA ≤131.6 Å²

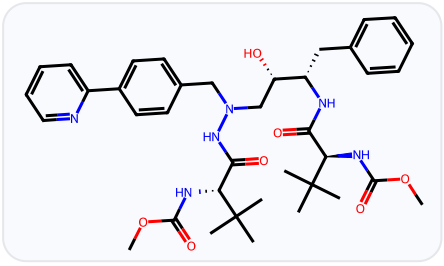
WHY IT EXISTS

Pharmacopeia, Inc. statistical analysis of human intestinal absorption (HIA) data. Egan, Merz, and Baldwin originally used AlogP98 (≈ LogP) and 3D PSA (Cerius2, single low-energy conformer); modern implementations substitute Ertl's 2D TPSA, which correlates r ≈ 0.99 with 3D PSA, so the 131.6 Å² cutoff is applied to TPSA in practice.

WHAT VIOLATION ACTUALLY MEANS

Compounds outside the Egan ellipse have a higher probability of poor passive absorption. Useful as an early-stage triage filter.

FAMOUS VIOLATORS



Atazanavir

Atazanavir

TPSA ~171 Å², exceeds Egan's 131.6 limit. Oral HIV protease inhibitor; absorption rescued by once-daily ritonavir boosting and pH-dependent solubility.

Egan WJ, Merz KM Jr, Baldwin JJ. *J Med Chem* 43: 3867-3877 (2000). DOI: 10.1021/jm000292e

1999

Ghose's Rules

MW 160-480 | LogP -0.4 to 5.6 | MR 40-130 | Atoms 20-70

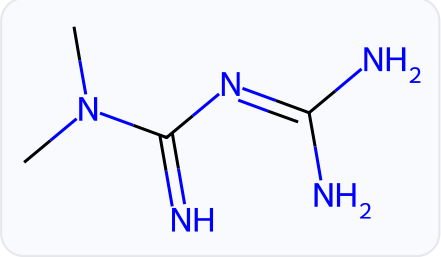
WHY IT EXISTS

Knowledge-based filter derived from analysis of CMC drug database compounds. Ghose, Viswanadhan, and Wendoloski derived bounds capturing the qualifying-drug property space.

WHAT VIOLATION ACTUALLY MEANS

Tighter than Lipinski. Useful when designing combinatorial libraries where you want to enrich for drug-like starting points rather than rule out terminal candidates.

FAMOUS VIOLATORS



Metformin

Metformin

MW 129, MR ~37, ALogP ~ -1.2 — violates three of Ghose's four lower bounds (MW, MR, ALogP). Total atom count = 20 sits exactly at the lower bound (Ghose 1999 counts hydrogens). The canonical small-molecule example: drug-likeness filters can reject compounds for being too small or too polar, not just too large.

Ghose AK, Viswanadhan VN, Wendoloski JJ. *J Comb Chem* 1: 55-68 (1999). DOI: 10.1021/cc9800071

2012

QED

Continuous score 0 to 1 | Higher = more drug-like | 8 weighted properties

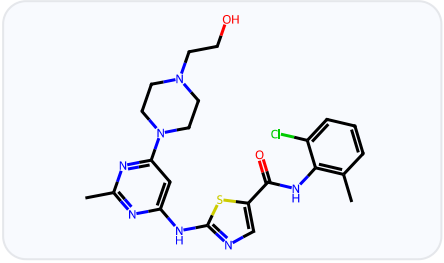
WHY IT EXISTS

Bickerton, Paolini, Besnard, Muresan, and Hopkins replaced binary cutoffs with a continuous 0-1 score. Eight property distributions (MW, ALogP, HBD, HBA, PSA, RotB, aromatic rings, structural alerts) across 771 approved oral drugs are fit to asymmetric double-sigmoidal desirability functions; the QED score is their weighted geometric mean. Three weighting schemes are published; QED_w,mo (mean of optimal weight combinations) is the typical default in Bickerton 2012 and standard implementations (RDKit, silicos-it/qed).

WHAT VIOLATION ACTUALLY MEANS

QED is a continuous score, not pass/fail. The instruction is "aim higher," not "clear a fixed threshold." For context, the paper ran a chemical-beauty survey where medicinal chemists rated compounds on attractiveness; QED on the chemist-rated attractive set averaged noticeably higher than on the unattractive set, confirming the score tracks expert intuition without supplying a universal cutoff. Caveats: trained on small-molecule oral drugs to 2012, so PROTACs, macrocycles, and oligonucleotides score artificially low; the aromatic-ring penalty is contested in fragment work; the structural-alerts list is heuristic.

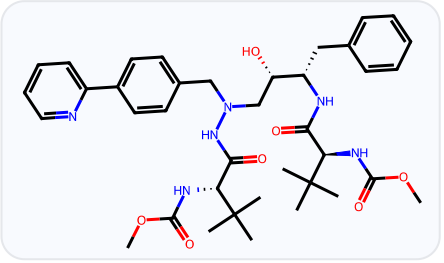
FAMOUS VIOLATORS



Dasatinib

Dasatinib

QED 0.47, moderate. BCR-Abl / Src inhibitor; three aromatic rings (phenyl, pyrimidine, thiazole) plus an aliphatic piperazine, combined with high HBA load — drag the unweighted score below the approved-drug average despite blockbuster clinical use.



Atazanavir

Atazanavir

QED 0.15, very low. The same properties that violate Egan (MW 705, TPSA 171, RotB 18) collapse the geometric mean. Marketed only via once-daily ritonavir boosting.

Bickerton GR, Paolini GV, Besnard J, Muresan S, Hopkins AL. *Nat Chem* 4(2): 90-98 (2012). DOI: 10.1038/nchem.1243

2004

Lead-Likeness

MW ≤350 | LogP ≤3 | RotB ≤7

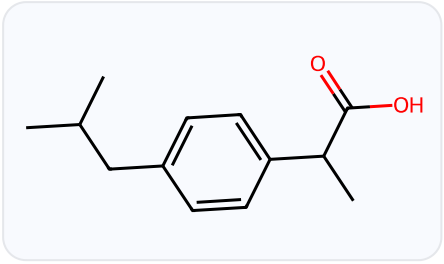
WHY IT EXISTS

Originally proposed by Teague, Davis, Leeson, and Oprea (1999) and elaborated by Hann and Oprea (2004): fragments and hits used as starting points for medicinal chemistry should be smaller and less lipophilic than final drugs, since optimisation tends to add MW and LogP.

WHAT VIOLATION ACTUALLY MEANS

Lead-like is for screening libraries and starting points, not for end candidates. Filtering an HTS deck against lead-likeness keeps the optimisation runway open.

FAMOUS VIOLATORS



Ibuprofen

Ibuprofen

MW 206, LogP 3.97, already an optimised drug rather than a lead, useful as a marketed reference for where final compounds tend to land.

Hann MM, Oprea TI. *Curr Opin Chem Biol* 8: 255-263 (2004). DOI: 10.1016/j.cbpa.2004.04.003

2010

CNS MPO

MW ≤360 | ClogP ≤3 | cLogD7.4 ≤2 | TPSA 40-90 Å² | HBD ≤1 | pKa ≤8.0

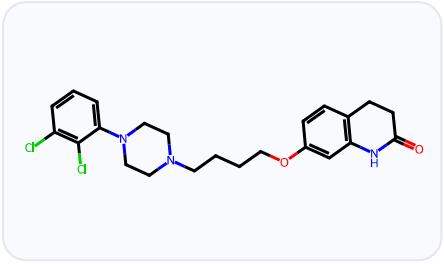
WHY IT EXISTS

Pfizer's multi-parameter optimisation framework for CNS drug candidates, derived from analysis of marketed CNS vs non-CNS drugs. Each parameter scores 0-1; the sum (max 6) ranks candidates.

WHAT VIOLATION ACTUALLY MEANS

CNS exposure depends on passive permeability across the BBB and on minimising P-gp efflux. Higher MPO scores correlate with lower clinical attrition for CNS targets. Wager 2010 recommends MPO ≥ 4 (out of 6) as the desirable cut-off; ~74% of marketed CNS drugs clear that bar versus ~60% of CNS clinical candidates.

FAMOUS VIOLATORS



Aripiprazole

Aripiprazole

Calculated MPO ≈ 3.6 (RDKit-based); published values cluster 3.6-4.0 across implementations depending on cLogP/cLogD predictor — borderline against the ≥ 4 threshold. Clinically successful atypical antipsychotic. CNS rules are a probabilistic ranking, not pass/fail gates.

Wager TT, Hou X, Verhoest PR, Villalobos A. *ACS Chem Neurosci* 1: 435-449 (2010). DOI: 10.1021/cn100008c

Beyond Rule of 5: where Lipinski stops, three concepts pick up

Lipinski reads the 2D structure. Big molecules need a 3D view. What the donors do in solution, what polarity the molecule actually shows, and how it reshapes between water and lipid. These decide whether a compound outside Ro5 still goes oral.

eHBD

EXPOSED DONORS

The H-bond donors solvent actually sees. Counted from solution NMR conformations, not from the 2D structure. Donors locked into intramolecular H-bonds do not count.

ePSA

MEASURED POLAR SURFACE

The polarity the molecule presents in solution, read by SFC chromatography. Often disagrees with the Ertl sum from 2D atoms, especially for macrocycles and PROTACs.

Chameleonic

ADAPTS TO ENVIRONMENT

Big molecules can fold polar groups inward in lipid and expose them in water. One structure, two faces. This is how cyclosporin crosses membranes despite huge calculated TPSA.

Recent work puts numbers on chameleonic behavior: David 2021 uses molecular dynamics on 24 FDA-approved drugs plus a PROTAC to predict experimental chromatographic apparent polarity, defining "chameleonic efficiency indices" that flag bRo5 candidates likely to fold favourably in lipid environments. Matsson 2016 frames the broader cell-permeability landscape outside Ro5.

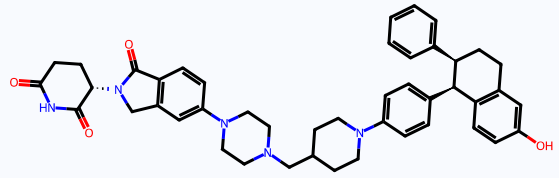
Matsson P, Doak BC, Over B, Kihlberg J. *Adv Drug Deliv Rev* 101: 42-61 (2016). DOI: 10.1016/j.addr.2016.03.013

David L, Wenlock M, Barton P, Ritzén A. *ChemMedChem* 16(17): 2669-2685 (2021). DOI: 10.1002/cmdc.202100306

For oral PROTACs, the rule is eHBD ≤2

AstraZeneca's NMR-based analysis of clinical oral PROTACs (Schade 2024) derives eHBD ≤ 2 as the operational rule. The Arvinas dataset of ~1,800 rat-PK-profiled compounds (Pike 2023) independently shows that exposed donors dominate the absorption signal. Each exposed donor costs energy to strip on entry into the bilayer.

WORKED EXAMPLE: VEPDEGESTRANT



Vepdegestrant

Sits exactly at the eHBD = 2 boundary: the phenol OH (warhead) and the glutarimide NH (E3 ligand handle), both solvent-exposed. The rule is permissive at the edge, the molecule passes despite being well outside Ro5 on every other axis.

PROTAC VS RO5, TYPICAL RANGES

	RO5	ORAL PROTAC
MW	≤500	700-1000
LogP	≤5	2-7
HBA	≤10	≤16
eHBD	(N/A)	≤2

Ranges from analyses of orally-dosed PROTACs in rat PK datasets. eHBD is the high-signal parameter. Lipophilicity, conformational rigidity, transporters, and formulation still matter.

RECENT UPDATES (2024)

Schade 2024 established eHBD ≤2 as the dominant oral-bioavailability predictor in clinical oral PROTACs across mouse, rat, and dog, and introduced eHBD / eHBA as experimental NMR-derived descriptors that capture solution behaviour better than the 2D Ertl sum. The same study placed the oral-PROTAC ePSA upper bound at ~170 Å² (much narrower than calculated tPSA). Scott 2024 reinforces that CRBN-engaging warheads (low MW, single HBD in the binding pharmacophore) consistently outperform VHL-engaging ones for oral PK. Linker rigidity, ring-rich and conformationally constrained, helps both degradation potency and metabolic stability.

Edmondson SD, Yang B, Fallan C. *Bioorg Med Chem Lett* 29: 1555-1564 (2019). DOI: 10.1016/j.bmcl.2019.04.030

Pike A, Williamson B, Harlfinger S, Martin S, McGinnity DF. *Drug Discov Today* 25: 1793-1800 (2020). DOI: 10.1016/j.drudis.2020.07.013

Schade M, Scott JS, Hayhow TG, Pike A, Terstiege I, Ahlqvist M, Johansson JR, Diene CR, Fallan C, Balazs AYS, Chiarparin E, Wilson D. *J Med Chem* 67(15): 13106-13116 (2024). DOI: 10.1021/acs.jmedchem.4c01017

Scott JS, Michaelides IN, Schade M. *RSC Med Chem* 16(2): 449-456 (2024). DOI: 10.1039/d4md00769g

When to break the rules

The Rule of 5 was fitted to small-molecule oral drugs in 1997. Plenty of marketed drugs since then violate it and work anyway. The pattern is consistent: violations are tolerable when the chemistry is dictated by mechanism, the formulation can rescue exposure, or a different framework (bRo5, PROTAC) governs the chemotype.

Atorvastatin. MW 558 + ALogP ~5.0-5.4 — two violations. The dihydroxy-heptanoate tail is mechanistically required for HMG-CoA reductase inhibition; cannot be trimmed without losing potency.

Cyclosporin A. MW 1202, TPSA 279 Å². Chameleonic conformer hides polar groups intramolecularly during membrane crossing — the textbook bRo5 case.

Lopinavir. MW 628, ALogP ~5.9, 14 rotatable bonds (over Veber). Boosted with ritonavir to inhibit CYP3A4 and rescue oral exposure.

Vepdegestrant. Oral PROTAC, MW > 700. Passes eHBD ≤2, the parameter that actually correlates with PROTAC PK.

Sources & citations

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12. Schade M, Scott JS, Hayhow TG, Pike A, Terstiege I, Ahlqvist M, Johansson JR, Diene CR, Fallan C, Balazs AYS, Chiarparin E, Wilson D. *J Med Chem* 67(15): 13106-13116 (2024). DOI: 10.1021/acs.jmedchem.4c01017

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