Is it drug-like?

Chem2Cure

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The rules of thumb on one sheet, what each number means, and where the rules stop working.

The six numbers, in plain words

Number	What it is	Why it matters
Molecular weight (MW)	The mass of one molecule, in g/mol.	Bigger molecules are usually absorbed less well and are harder to make. Most oral drugs are under 500.
cLogP	A calculated measure of how much a molecule prefers oil over water.	Too low and it will not cross cell membranes. Too high and it dissolves badly and sticks to everything, which raises the risk of toxicity.
TPSA (Å²)	The surface covered by polar atoms: nitrogen, oxygen and the hydrogens on them.	A high value means poor passage through membranes. About 140 is a common ceiling for oral drugs, and about 90 for drugs that must reach the brain.
H-bond donors (HBD)	Count of N–H and O–H groups.	Each one holds on to water, and that has to be given up before the molecule can enter a membrane.
H-bond acceptors (HBA)	Count of nitrogen and oxygen atoms that can accept a hydrogen bond.	Same idea as donors. Many acceptors make a molecule polar and hard to absorb.
Rotatable bonds (RotB)	Single bonds that can spin freely.	Floppy molecules lose freedom when they bind a target and tend to be absorbed less well.

The rule sets, side by side

Rule set	MW	cLogP	TPSA	HBD	HBA	RotB	Use it for
Rule of five Lipinski 1997	≤ 500	≤ 5	n/a	≤ 5	≤ 10	n/a	Oral drugs. Poor absorption is more likely when **more than one** limit is broken.
Veber limits Veber 2002	n/a	n/a	≤ 140	n/a	n/a	≤ 10	Oral bioavailability. Added to the rule of five, not instead of it.
Rule of three Congreve 2003	< 300	≤ 3	≤ 60	≤ 3	≤ 3	≤ 3	Fragment libraries: small, simple starting points that can be grown.
Lead-like rule of thumb, as in our screener	200 to 350	−1 to 3.5	≤ 120	≤ 4	≤ 8	≤ 7	Room to grow during optimisation.
Brain-penetrant rule of thumb, as in our screener	≤ 450	1 to 5	≤ 90	≤ 3	≤ 7	≤ 8	A rough guide for molecules that must cross the blood–brain barrier.

The rule of three and the Veber limits are shown with the usual cut-offs. The screener starts from the same numbers and lets you change every one.

Groups that often cause trouble

These are reasons to look twice, not reasons to throw a molecule away.

Group	Why it is flagged	Group	Why it is flagged
Michael acceptor (enone)	Reacts with protein thiols, giving false positives in many assays.	**Aldehyde**	Reacts with amines and thiols, and is quickly oxidised.
Catechol and hydroquinone	Oxidise easily to quinones and grab metals, so they hit many unrelated targets.	**Acyl and sulfonyl halides**	Too reactive to survive water or reach a target.
Quinone	Redox-active and thiol-reactive. A classic cause of assay artefacts.	**Free thiol, disulfide**	Oxidise, bind metals, and swap with protein cysteines.
Ene-rhodanine	A scaffold that shows up as a hit against almost anything.	**Peroxide**	Unstable and oxidising (but see artemisinin below).
Aromatic nitro	Can be reduced in the body to reactive, toxic species.	**Epoxide, aziridine**	Strained rings that can alkylate DNA and proteins.

Real drugs, measured

Numbers worked out with RDKit. “Over” counts how many rule-of-five limits each one breaks.

Drug	MW	cLogP	TPSA	HBD	HBA	Over	What it teaches
Aspirin	180.2	1.3	64	1	3	0	A textbook pass.
Paracetamol	151.2	1.4	49	2	2	0	Small and polar, and still a very good oral drug.
Metformin	129.2	−1.0	89	4	2	0	Passes easily, yet very polar (negative cLogP). It enters cells through transporter proteins.
Artemisinin	282.3	2.4	54	0	5	0	Passes every limit, but its key peroxide bridge is a flagged group.
Imatinib	493.6	4.6	86	2	7	0	Right at the edge of 500, like many kinase inhibitors that fill a deep pocket.
Atorvastatin	558.7	6.3	112	4	4	2	Breaks two limits and is one of the best-selling drugs ever.
Venetoclax	868.5	8.7	172	3	11	3	Far outside the rules, yet taken as a tablet. Large drugs can work when they are designed with care.

When the rules stop working

- **Natural products and antibiotics.** Many are large and have many oxygen atoms, yet are absorbed or work where they are needed. Rifampicin weighs about 823.
- **Cyclic peptides and designed large molecules.** Ciclosporin (about 1,203) is taken by mouth. Venetoclax is a tablet. These sit in the region chemists call “beyond the rule of five”.
- **Transporters.** Some drugs, like metformin, are carried into cells by proteins, so the usual picture of passing through the membrane does not apply.
- **Drugs given another way.** Injected, inhaled and topical medicines face different barriers, so the oral limits are the wrong yardstick.

How to use this sheet

1. Work out the six numbers for your molecule (the Compound screener does it for a whole list).

2. Look at **which** limit is broken, not just how many. Two broken limits for size are different from two for polarity.

3. Ask whether there is a reason. A flagged group or a broken limit is a question to answer, not a verdict.

References

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