Quanteon Quanteon SAMPLE REPORT

Covalent warhead electrophilicity triage

Ranking six Michael-acceptor warheads by first-principles reactivity — before a single flask comes out.

PREPARED FOR	METHOD	ENGINE	TURNAROUND
Illustrative example (public benchmark molecules)	B3LYP / 6-31G(d) gas phase, single point	Quanteon validated ~1×10^{-10} Ha	3–5 working days 6-molecule series

THE QUESTION

How reactive should the warhead be? A targeted covalent inhibitor must be electrophilic enough to engage its target cysteine, yet tame enough to spare the rest of the proteome. We rank a congeneric series by intrinsic electrophilicity so you know which warheads to make — and which to skip — **before synthesis**.

RECOMMENDATION

Acrylamide is the Goldilocks warhead (ω = 1.16 eV) — squarely mid-range, the same balance approved covalent drugs converged on (osimertinib, ibrutinib, sotorasib). The series spans **nearly 2× in electrophilicity**: esters/ketones/nitriles run hot, amides run mild, and α-methyl / N,N-dialkyl substitution cools them further. Two independent descriptors (LUMO energy and Parr ω) tell one consistent story.

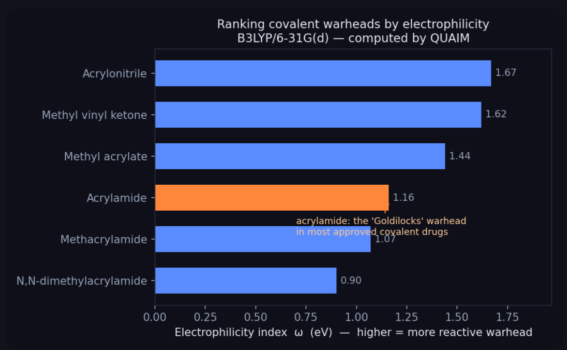

Figure 1 — Six Michael-acceptor warheads ranked by the Parr electrophilicity index ω (B3LYP/6-31G(d), Quanteon). Acrylamide (orange) sits in the centre of the range.

Computed descriptors, ranked by ω

WARHEAD	LUMO (EV)	Ω (EV)
Acrylonitrile	−1.44	1.67
Methyl vinyl ketone	−1.52	1.62
Methyl acrylate	−1.12	1.44
Acrylamide PICK	−0.76	1.16
Methacrylamide	−0.60	1.07
N,N-dimethylacrylamide	−0.30	0.90

$\omega = \mu^2/2\eta$, with $\mu = (\varepsilon_{HOMO}+\varepsilon_{LUMO})/2$ and $\eta = \varepsilon_{LUMO}-\varepsilon_{HOMO}$. The thiolate attacks the warhead LUMO — the lower it sits, the more electrophilic the warhead.

Interpretation

The ranking reproduces medicinal-chemistry intuition line for line. **Esters, ketones and nitriles** cluster at the top: with no donating heteroatom into the carbonyl, their π* (LUMO) sits low and accepts electron density eagerly. **Amides are milder** — the nitrogen lone pair donates into the carbonyl and raises the π*. Adding an α-methyl (methacrylamide) cools it further; capping the nitrogen with two methyls (N,N-dimethylacrylamide) drops it to the bottom.

Every substituent effect a chemist would predict by hand appears in the numbers, in the right order — which is exactly what makes the descriptor trustworthy as a triage. The practical signal is the **coarse ordering across chemotypes**, not a hair-splitting rank between near neighbours (the two hottest differ by only 0.05 eV in ω, within method noise).

The payoff: point this at *your* series and you learn where each candidate falls on the reactivity ladder in minutes, so synthesis effort goes to the warheads most likely to hit the therapeutic window.

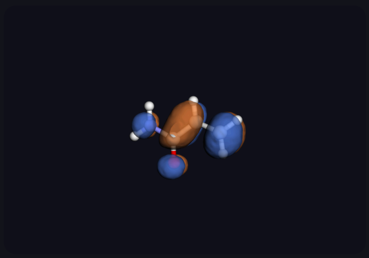

Figure 2 — The acrylamide LUMO (π*) computed by Quanteon and written to a Gaussian CUBE. This is the orbital the cysteine thiolate attacks in the Michael addition; blue/orange lobes are the two signs of the wavefunction.

Method & scope — what this is, and what it is not

What it is. An intrinsic-reactivity triage for ranking congeneric warheads from first principles. Descriptors: LUMO energy and the Parr electrophilicity index ω, both from a single ground-state calculation. Level of theory: B3LYP/6-31G(d), gas phase, single-point on RDKit ETKDG+MMFF geometries (not QM-reoptimised).

What it is not. Not an absolute rate constant, and not a binding affinity. Real cysteine labelling also depends on the cysteine pK_a (whether the thiolate even forms), the pocket microenvironment, sterics and orientation, and the actual addition barrier ΔG‡.

Natural next step. Promote the top candidates to an explicit thiolate-addition transition state (ΔG‡) and add implicit solvent — turning the ranking into quantitative, regiochemistry-aware rate guidance.

About this report

This is an **illustrative sample** built on public benchmark molecules to show the format, depth and honesty of a typical deliverable. Your project would carry your structures, run in a private environment (NDA on request), and include one round of follow-up questions plus all raw output and cube files. The underlying integral engine is Quanteon, a from-scratch implementation cross-checked against established quantum-chemistry codes to ~1×10^{-10} Hartree.