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AQUANODUS: A THEORETICAL FRAMEWORK FOR COMPUTATIONAL PHARMACEUTICAL ANALYSIS OF NSAIDS

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Relevance. Non-steroidal anti-inflammatory drugs (NSAIDs), while effective, present a clinical paradox: their therapeutic efficacy is often inseparable from significant toxicity. Traditional development pipelines struggle to preemptively balance cyclooxygenase (COX) selectivity with gastrointestinal, renal, and cardiovascular risks. Furthermore, conventional computational models frequently oversimplify complex biological realities, neglecting the dynamic role of water networks, the entropic costs of binding, and the nuanced interplay between drug structure and isoform selectivity. This leads to high late-stage attrition rates and unforeseen safety issues.

Aim: to establish Aquanodus, a theoretical framework for the computational pharmaceutical analysis of NSAIDs.

Materials and methods. The theoretical foundation of Aquanodus is built upon a tiered computational pipeline. The base tier employs molecular docking for high-throughput screening of NSAIDs against COX-1 and COX-2 isoforms. The second tier utilizes MM/PBSA (Molecular Mechanics/Poisson-Boltzmann Surface Area) calculations to decompose binding free energies, quantifying the contributions of individual amino acid residues and, critically, explicit water molecules modeled with TIP3P force fields. The third tier incorporates explicit-solvent molecular dynamics (MD) simulations using AMBER and CHARMM force fields to assess complex stability, calculate residence times for key water bridges, and evaluate conformational entropy changes upon binding. The framework integrates a hydration analysis module that identifies stable water networks and quantifies their energetic contribution (ΔGhydration) to the overall binding affinity. (QED), and machine learning-based toxicity prediction models trained on curated datasets.

Results and their discussion. The application of the Aquanodus framework to ADMET (Absorption, Distribution, Metabolism, Excretion, Toxicity) and drug-likeness are assessed using a composite score that includes Lipinski's Rule of Five, the Quantitative Estimate of Drug-likeness model NSAIDs, including piroxicam and meloxicam, yielded several key insights. The hydration module consistently demonstrated that explicit water molecules are not passive solvents but active participants in the binding mechanism. For piroxicam, water-mediated hydrogen bonds with key residues (ARG120 in COX-1 and ARG513 in COX-2) contributed significantly to complex stability, explaining its non-selective profile. For meloxicam, the framework identified three stable water bridges with an average residence time of ~142 picoseconds, contributing an additional +1.5 kcal/mol to binding affinity when compared to implicit solvent models. MM/PBSA calculations confirmed similar total binding energies for piroxicam across both COX isoforms, correlating with its clinical non-selectivity, while revealing distinct energy decomposition patterns. MD simulations highlighted differences in conformational mobility within the active sites, providing a theoretical basis for the subtle selectivity profiles of various NSAIDs.

Conclusions. The Aquanodus framework provides a comprehensive, physically grounded approach to computational pharmaceutical analysis. By integrating hydration thermodynamics, dynamic simulations, and multi-scale binding energy calculations, it offers a more predictive model for NSAID behavior than traditional methods. This theoretical construct addresses the critical gap between static molecular models and dynamic clinical reality. Aquanodus demonstrates that by systematically accounting for water networks and conformational entropy, we can better rationalize COX selectivity, predict binding stability, and anticipate safety profiles.