Efficiently Screening the Most Abundant Bioactive Molecular Moiety: In silico Structure Property Relationships of Primary Amide Bioisosteres

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Poor aqueous solubility is an increasing problem for achieving effective formulation and pharmacokinetic properties for novel small molecule oral therapies. This problem could be potentially avoided by screening leads for a secondary solubility parameter alongside potency in high throughput screening. An effective, linear algorithm has herein been developed to model the predicted aqueous kinetic solubilities of 87 common bioisosteric replacements for primary amides, the most abundant terminal molecular moiety. Using computed physical properties of these bioisosteres has afforded a fast and statistically significant (p=0.0003) in silico approach for estimating aqueous kinetic solubility. By including this algorithm as a constraint in de novo drug design, or by using this algorithm to add a solubility constraint to high throughput screening assays, expeditious and less expensive drug development is possible preventing costly and time-consuming setbacks from late-stage failure of poorly soluble small molecules.

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