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Sol-Moiety: Discovery of a Water-Soluble Prodrug Technology for Enhanced Oral Bioavailability of Insoluble Therapeutics
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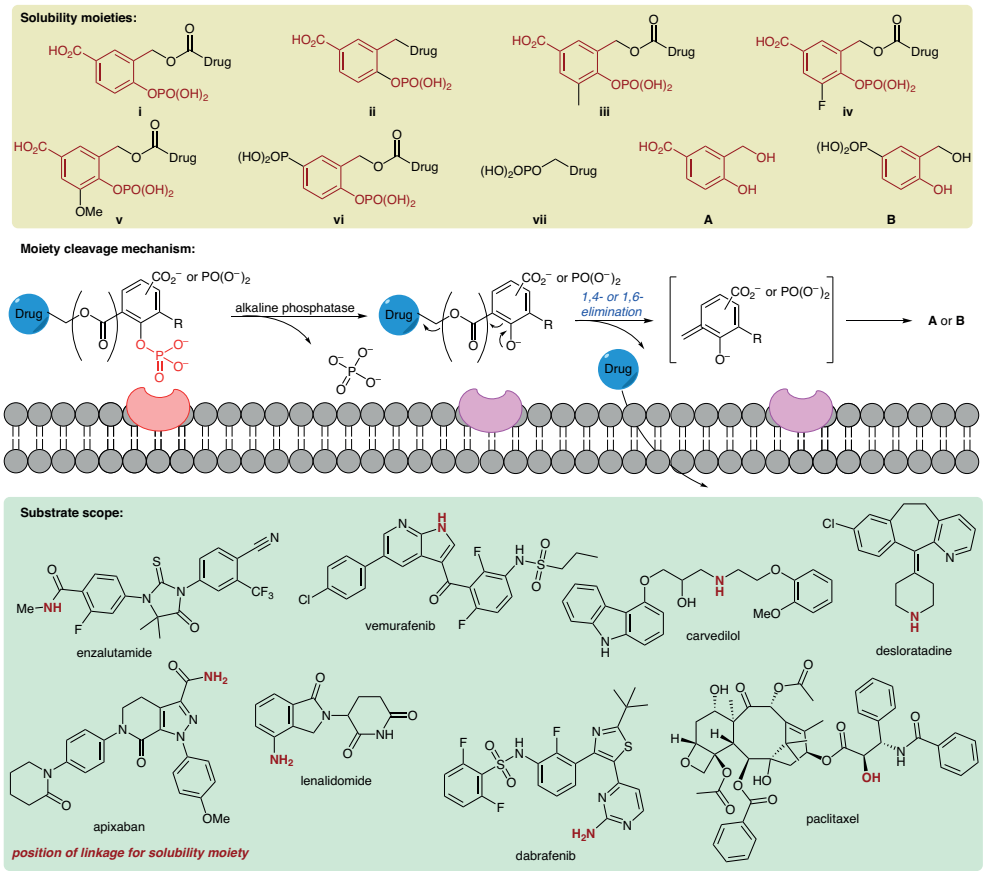
Cleavable Linker Delivers Increased Solubility of Highly Insoluble Small-Molecule Therapeutics



Significance: Solubility is a problem that plagues many small-molecule therapeutics. Few moieties have been able to provide solubility enhancement while maintaining pH stability (ranging from 1.2 to 6.5), lack of permeable, toxic byproducts, or suitable hydrolysis pathways not resulting in immediate drug precipitation or multiple enzymatic interactions. The scope of this paper is broad, and the authors were able to show significant improvement in drug administration without specialty formulation. This technology could strongly influence the ability to administer water-insoluble drugs orally.

Comment: The authors incorporate a cleavable solubility tag to a variety of clinical therapeutics with poor solubility. The moieties can be linked to primary and secondary amides, sulfonamides, alcohols, amines, anilines, and NH-containing heterocycles. The carboxylate or phosphonate groups of **i**–**vii** are then hydrolyzed by alkaline phosphatase, a critical enzyme in human intestines, to promote the 1,4– or 1,6-eliminations of the solubility group. This then yields byproducts **1** or **2** and the free, released drug. Their compounds showed marked improvement in oral availability in mice and no permeation of the byproducts across the epithelial cells in vitro.

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Category
Innovative Drug Discovery and Development

Key words
solubility
prodrugs
small-molecule therapeutics

Synfact of the Month