Target-Specific Development of Pseudo Natural Products Through the Combination of Natural Product Fragments

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Natural products offer great promise as pharmaceuticals due to evolutionary optimization not seen in their synthetic counterparts, and because they exist beyond the reaches of most synthetic pharmaceuticals in the bioactive chemical space. Combining small natural product fragments to form pseudo natural products was previously shown to viably tap into regions of unexplored bioactive chemical space, but was not specific to individual targets. Herein, natural product fragments were computationally aligned to pharmacophores for specific protein targets and combined to make pseudo natural products with enhanced selectivity to a specific biological protein target and retained natural product characteristics. These pseudo natural products exhibited variable and slightly poorer pharmacokinetics than their synthetic counterparts (due to increased CYP metabolism) but remain toxicologically safe. The pseudo natural products herein created exhibited superb selectivity, but rather poor pharmacodynamic properties, which could likely be remedied with further optimization. Despite this, pseudo natural products offer great promise for accelerating and reducing the expenses of current drug discovery methods, which could allow for the expedited development of small molecule drugs for rare and emergent diseases or improvements on existing drugs.

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