

Through the Looking Glass a New World of Proteins Enabled by Chemistry

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Recent advances in synthetic methods enable the routine synthesis of protein enantiomorphs, unnatural protein molecules made up entirely of D-amino acids. These D-proteins have a tertiary structure that is the mirror image of the backbone fold of their counterparts found in nature. Such mirror image protein molecules have a variety of uses. More facile crystallization of racemic protein mixtures and the quantized phases of diffraction data from the resulting centrosymmetric racemic protein crystals enable the use of ab initio methods to solve novel protein Xray structures. These precise phases can be used to calculate electron density maps of unusually high quality from diffraction data of a given resolution. Protein enantiomorphs also enable discovery libraries. Select mirror image protein molecules themselves are good candidates for use in clinical applications: they are resistant to proteolytic digestion, are more stable in vivo, and are non-immunogenic. I will discuss the application of total synthesis to the creation of uniquely chemical analogues of a variety of protein targets including antifreeze proteins, venom-derived proteins, and enzymes. The design and synthesis of protein-derived molecules of novel topology will also be described.

mirror image drug', to identify unique therapeutic leads from chiral natural product

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