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TITLE

METHOD OF SYNTHESIZING DIVERSE COLLECTIONS OF OLIGOMERS

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PATENT

METHOD OF SYNTHESIZING DIVERSE COLLECTIONS OF OLIGOMERS

FIELD OF THE INVENTION

The present invention relates generally to a general stochastic method for synthesizing random oligomers on particles. A further aspect of the invention relates to the use of identification tags on the particles to facilitate identification of the oligomer sequence.

BACKGROUND OF THE INVENTION

The relationship between structure and activity of molecules is a fundamental issue in the study of biological systems. Structure-activity relationships are important in understanding, for example, the function of enzymes, the ways in which cells communicate with each other, as well as cellular control and feedback systems. Certain macromolecules are known to interact and bind to other molecules having a very specific three-dimensional spatial and electronic distribution. Any large molecule having such specificity can be considered a receptor, whether it is an enzyme catalyzing hydrolysis of a metabolic intermediate, a cell-surface protein mediating membrane transport of ions, a glycoprotein serving to identify a particular cell to its neighbors, an IgG-class antibody circulating in the plasma, an oligonucleotide sequence of DNA in the nucleus, or the like. The various molecules which receptors selectively bind are known as ligands.

Many assays are available for measuring the binding affinity of known receptors and ligands, but the information which can be gained from such experiments is often limited by the number and type of ligands which are available. Novel ligands are sometimes discovered by chance or by application of new techniques for the elucidation of molecular structure, including x-ray crystallographic analysis and recombinant genetic techniques for proteins.

Small peptides are an exemplary system for exploring the relationship between structure and function in biology. A peptide is a sequence of amino acids. When the twenty naturally occurring amino acids are condensed into polymeric molecules they form a wide variety of three-dimensional configurations, each resulting from a particular amino acid sequence and solvent condition. The number of possible pentapeptides of the 20 naturally occurring amino acids, for example, is 20^5 or 3.2 million different peptides. The likelihood that molecules of this size might be useful in receptor-binding studies is supported by epitope analysis studies showing that some antibodies recognize sequences as short as a few amino acids with high specificity. Furthermore, the average molecular weight of amino acids puts small peptides in the size range of many currently useful pharmaceutical products. Of course, larger peptides may be necessary for many purposes; and polypeptides having changes in only a small number of residues may also be useful for such purposes the analysis of structure-activity relationships.

Pharmaceutical drug discovery is one type of research which relies on such a study of structure-activity relationships. In most cases contemporary pharmaceutical research can be described as the process of discovering novel ligands with desirable patterns of specificity for biologically important receptors. Another example is research to discover new compounds for use in agriculture, such as pesticides and herbicides.

Prior methods of preparing large numbers of different oligomers have been painstakingly slow when used at a scale sufficient to permit effective rational ~~or random screening~~. For example, the "Merrifield" method (J. Am. Chem. Soc. (1963) 85:2149-2154, which is incorporated herein by reference) has been used to synthesize peptides on a solid support. In the Merrifield method, an amino acid is covalently bonded to a support made of an insoluble polymer. Another amino acid with an alpha protected group is reacted with the covalently bonded amino acid to form a dipeptide. After washing, the protective group is removed and a third amino acid with an alpha

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