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Ward et al.

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[54] MODIFIED POLYNUCLEOTIDES AND METHODS OF PREPARING SAME

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[73] Assignee: **Yale University**, New Haven, Conn.

[*] Notice: The portion of the term of this patent subsequent to Dec. 8, 2004 has been disclaimed.

[21] Appl. No.: **886,660**

[22] Filed: **May 20, 1992**

Related U.S. Application Data

[60] Continuation of Ser. No. 130,002, Dec. 8, 1987, abandoned, which is a division of Ser. No. 496,915, May 23, 1983, Pat. No. 4,711,955, which is a continuation-in-part of Ser. No. 255,223, Apr. 17, 1981, abandoned.

[51] **Int. Cl.**[6] **C07H 21/00**

[52] **U.S. Cl.** **536/24.3**; 536/25.32; 536/25.6; 536/26.6

[58] **Field of Search** 536/24.3, 25.32, 25.6, 536/26.6; 435/6

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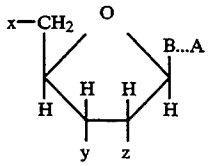
Primary Examiner—Che S. Chereskin
Attorney, Agent, or Firm—Ronald C. Fedus; John L. Santalone

[57] **ABSTRACT**

Compounds having the structure:

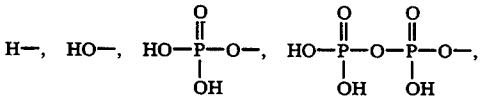


wherein B represents 7-deazapurine, or pyrimidine moiety covalently bonded to the $C^{1'}$-position of the sugar moiety, provided that when B is 7-deazapurine, it is attached at the N^9-position of the 7-deazapurine and when B is pyrimidine, it is attached at the N^1-position;

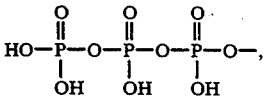
wherein A represents a moiety consisting of at least three carbon atoms which is capable of forming a detectable complex with a polypeptide when the compound is incorporated into a double-stranded ribonucleic acid, deoxyribonucleic acid duplex, or DNA-RNA hybrid;

wherein the dotted line represents a chemical linkage joining B and A, provided that if B is 7-deazapurine, the linkage is attached to the 7-position of the deazapurine, and if B is pyrimidine, the linkage is attached to the 5-position of the pyrimidine; and

wherein each of x, y and z represents



or



either directly, or when incorporated into oligo- and polynucleotides, provide probes which are widely useful.

71 Claims, No Drawings

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MODIFIED POLYNUCLEOTIDES AND METHODS OF PREPARING SAME

The invention disclosed and/or claimed in this application was made in the course of work carried out under grants from the Public Health Service, National Institute of General Medical Research Grant No. P50-GM20124; Public Health Service, National Cancer Institute Training Grant No. T32-CA09159; and Public Health Service, National Institute of General Medical Science Grant No. T32-GM07499. The Government has certain rights in the invention.

This is continuation of application Ser. No. 07/130,002, filed Dec. 8, 1987, now abandoned, which is in turn a division of application Ser. No. 06/496,915, filed May 23, 1983, issued Dec. 8, 1987 as U.S. Pat. No. 4,711,955. Application Ser. No. 06/496,915 is in turn a continuation of application Ser. No. 06/255,223, filed Apr. 17, 1981, now abandoned.

BACKGROUND OF THE INVENTION

Many procedures employed in biomedical research and recombinant DNA technology rely heavily on the use of nucleotide or polynucleotide derivatives radioactively labeled with isotopes of hydrogen (^{3}H), phosphorous (^{32}p), carbon (^{14}C), or iodine (^{125}I). Such radioactive compounds provide useful indicator probes that permit the user to detect, monitor, localize, or isolate nucleic acids and other molecules of scientific or clinical interest, even when present in only extremely small amounts. To date, radioactive materials have provided the most sensitive, and in many cases the only, means to perform many important experimental or analytical tests. There are, however, serious limitations and drawbacks associated with the use of radioactive compounds. First, since personnel who handle radioactive material can be exposed to potentially hazardous levels of radiation, elaborate safety precautions must be maintained during the preparation, utilization, and disposal of the radioisotopes. Secondly, radioactive nucleotides are extremely expensive to purchase and use, in large part due to the cost of equipment and manpower necessary to provide the appropriate safeguards, producer-/user health monitoring services, and waste-disposal programs. Thirdly, radioactive materials are often very unstable and have a limited shelf-life, which further increases usage costs. This instability results from radiolytic decomposition, due to the destructive effects associated with the decay of the radioisotope itself, and from the fact that many isotopes (e.g. ^{32}p and ^{125}I) have half-lives of only a few days

It is known that haptens can combine with antibodies, but can initiate an immune response only if bound to a carrier. This property can be exploited in detection and identification testing.

It is also known that biotin and iminobiotin strongly interact with avidin, a 68,000 dalton glycoprotein from egg white. This interaction exhibits one of the tightest, non-covalent binding constants ($K_{dis}=10^{-15}$) seen in nature. If avidin is coupled to potentially demonstrable indicator molecules, including fluorescent dyes, e.g. fluorescein or rhodamine; electron-dense reagents, e.g. ferritin, hemocyanin, or colloidal gold; or enzymes capable of depositing insoluble reaction products, e.g. peroxidase or alkaline phosphatase, the presence, location, or quantity of a biotin probe can be established. Although iminobiotin binds avidin less tightly than biotin, similar reactions can be used for its detection. Moreover, the reversibility of the iminobiotin-avidin interaction, by decreasing solution pH, offers significant advantages in certain applications.

The specificity and tenacity of the biotin-avidin complex has been used in recent years to develop methods for visually localizing specific proteins, lipids, or carbohydrates on or within cells (reviewed by E. A. Bayer and M. Wilchek in Methods of Biochemical Analysis, 26, 1, 1980). Chromosomal location of RNA has been determined by electron microscopy using a biotinized protein, cytochrome C, chemically crosslinked to RNA as a hybridization probe. The site of hybridization was visualized through the binding of avidin-ferritin or avidin-methacrylate spheres mediated by the avidin-biotin interaction. (J. E. Manning, N. D. Hershey, T. R. Broker, M. Pellegrini, H. K. Mitchell, and N. Davidson, Chromosoma, 53, 107, 1975; J. E. Manning, M. Pellegrini, and N. Davidson, Biochemistry, 61, 1364, 1977; T. R. Broker, L. M. Angerer, P. H. Yen, N. D. Hersey, and N. Davidson, Nucleic Acid Res., 5, 363, 1978; A Sodja and N. Davidson, Nucleic Acid Res., 5, 383, 1978.) This approach to the detection of polynucleotide sequences, although successful in the specialized cases examined which were highly reitterated sequences, is not of general utility for analysis of polynucleotides present in single or low copy number.

Moreover, methods for attaching chemical moieties to pyrimidine and purine rings are known. Several years ago a simple and rapid acetoxymercuration reaction was developed for introducing covalently bound mercury atoms into the 5-position of the pyrimidine ring, the C-8 position of the purine ring or the C-7 position of a 7-deazapurine ring, both in nucleotides and polynucleotides. (R. M. K. Dale, D. C. Livingston and D. C. Ward, Proc. Natl. Acad. Sci. U.S.A., 70, 2238, 1973; R. M. K. Dale, E. Martin, D. C. Livingston and D. C. Ward, Biochemistry, 14, 2447, 1975.) It was also shown several years ago that organomercurial compounds would react with olefinic compounds in the presence of palladium catalysts to form carbon-carbon bonds (R. F. Heck, J. Am. Chem. Soc., 90, 5518, 1968; R. F. Heck, Ibid., 90, 5526, 1968; R. F. Heck, Ibid., 90, 5531, 1968; R. F. Heck, Ibid., 90, 5535, 1968; and R. F. Heck, J. Am. Chem. Soc. 91, 6707, 1969.) Bergstrom and associates (J. L. Ruth and D. E. Berstrom, J. Org. Chem., 43, 2870, 1978; and D. E. Bergstrom and M. K. Ogawa, J. Am. Chem. Soc., 100, 8106, 1978) and Bigge, et al. (C. F. Bigge, P. Kalaritis, J. R. Deck and M. P. Mertes, J. Am. Chem. Soc., 102, 2033, 1980) have recently applied this reaction scheme in the synthesis of C-5 substituted pyrimidine nucleotide compounds.

Finally, it is known that antibodies specific for modified nucleotides can be prepared and used for isolating and characterizing specific constituents of the modified nucleotides. (T. W. Munns and M. K. Liszewski, Progress in Nucleic Acid Research and Molecular Biology, 24, 109, 1980.) However, none of the antibodies prepared to date against naturally occurring nucleotides have been shown to react with their nucleotide determinant when it exists in a double-stranded RNA or DNA duplex or when in DNA-RNA hybrid molecules.

To circumvent the limitations of radioactively labeled probes or previously utilized chemical and biological probes, a series of novel nucleotide derivatives that contain biotin, iminobiotin, lipoic acid, and other determinants attached covalently to the pyrimidine or purine ring have been synthesized. These nucleotide deriva-

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