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EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION**

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NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

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(54) Title: AMINOALKYL GLUCOSAMINE PHOSPHATE COMPOUNDS AND THEIR USE AS ADJUVANTS AND IMMUNOEFFECTORS

(57) **Abstract**

Aminoalkyl glucosamine phosphate compounds that are adjuvants and immunoeffectors are described and claimed. The compounds have a 2–deoxy–2–amino glucose in glycosidic linkage with an aminoalkyl (aglycon) group. Compounds are phosphorylated at the 4 or 6 carbon on the glucosamine ring and comprise three 3–alkanoyloxyalkanoyl residues. The compounds augment antibody production in immunized animals as well as stimulate cytokine production and activate macrophages. Methods for using the compounds as adjuvants and immunoeffectors are also disclosed.

or negative controls. The precise dosage of the compounds of the subject invention to be administered to a patient will depend upon the particular AGP used, the route of administration, the pharmaceutical composition, and the patient. For example, when administered subcutaneously to enhance an antibody response, the amount of AGP used is from 1 to about 250 micrograms, preferably from about 25 to about 50 micrograms based upon administration to a typical 70 kg adult patient.

In vaccine compositions, the AGPs of the subject invention are administered to a warm-blooded animal, including humans, with an antigen. The amount of antigen administered to elicit a desired response can be readily determined by one skilled in the art and will vary with the type of antigen administered, route of administration and immunization schedule. For example, 0.2 μg of tetanus toxoid administered with the claimed compounds subcutaneously to a mouse in two immunization 21 days apart elicited a humoral immune response to that antigen.

The compounds of the subject invention are synthesized by coupling an *N*-acyloxyacylated or *N*-protected aminoalkanol or aminoalkanethiol (aglycon unit) with a suitably protected and/or 3-*O*-acyloxyacylated glucosamine unit. In one preferred method for preparing the compounds of the subject invention (Scheme 1), an *N*-(2,2,2-trichloroethoxycarbonyl (Troc))-protected glycosyl halide **1** (Z = F, Cl, Br) is coupled with an *N*-[(*R*)-3-*n*-alkanoyloxytetradecanoyl]aminoalkanol or thiol **2** (possessing R_6 and R_7 in suitably protected form) via a Koenigs-Knorr type reaction in the presence of mercury or silver salts to give glycoside intermediate **3**. Preferably, the glucosamine unit **1** possesses an anomeric chloride atom (Z = Cl), and the coupling catalyst is silver trifluoromethanesulfonate. Intermediate **3** can also be prepared by coupling the aglycon unit **2** with an *N*-Troc-protected glycosyl acetate (Z = OAc) or related activated derivative in the presence of a Lewis acid such as boron trifluoride etherate. By "activated" is meant having an appropriate displaceable leaving group "Z" attached to the anomeric center of the glucosamine unit. Glucosamine unit **1** bears an (*R*)-3-*n*-alkanoyloxytetradecanoyl residue on the 3-position, and suitable protecting groups on the 6-hydroxyl and 4-phosphate moieties. Typical protecting groups for the phosphate group include, but are not limited to, phenyl, benzyl, and *o*-xylyl. The phosphate group is protected preferably with two phenyl groups. The 6-position can be temporarily

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[54] **ADJUVANT**

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[57] **ABSTRACT**

The present invention relates generally to adjuvants which comprise a combination of at least two cytokines or functional derivatives thereof. More particularly, the present invention is directed to an adjuvant such as a vaccine adjuvant comprising at least two cytokines or functional derivatives thereof wherein the cytokines are selected from IL-1β and TNFα or IL-1β and GM-CSF. The present invention is farther directed to genetic adjuvants encoding at least two cytokines or derivatives thereof either separately or fused together. The present invention also contemplates a method for enhancing an immune response to an antigen comprising the administration of at least two cytokines which act in synergy to enhance an immune response to said antigen. The present invention is particularly useful in pharmaceutical vaccines and genetic vaccines in humans and livestock animals.

14 Claims, 15 Drawing Sheets