Fluorinated Glucosamine Analogs Useful for Modulating Post-Translational Glycosylation of Cells

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Summary:
The invention provides compositions and methods for inhibiting cell migration, e.g., lymphocytes and inflammation. The invention also provides an improved process for preparing fluorinated N-acetylglucosamines.

The invention features methods of inhibiting cell migration, cell proliferation or cell differentiation by contacting a cell with a fluorinated N-acetylglucosamine (F-GlcNAc), e.g., 2-acetamido-2-deoxy-1,3,6-tri-O-acetyl-4-deoxy-4-fluoro-D-glucopyranose or 2-acetamido-2-deoxy-1,4,6-tri-O-acetyl-3-deoxy-3-fluoro-D-glucopyranose in an amount sufficient to inhibit cell migration, proliferation or differentiation.

Also provide by the invention is a method of decreasing an amount of HECA-452 epitope on a glycoprotein, e.g., PSGL-1 or CD44 on a cell, by contacting the cell with a fluorinated N-acetylglucosamine. The amount of the glycoprotein on the cell in the presence of the fluorinated N-acetylglucosamine as compared to in the absence of the fluorinated N-acetylglucosamine differs by less than 10%, 5% or 1%.

In another aspect the invention features a method of inhibiting inflammation in a tissue, e.g., dermal tissue of a subject by administering to the subject a fluorinated N-acetylglucosamine.

The inflammation is for example, chronic inflammation, e.g., DTH, acute inflammation, cutaneous inflammation, psoriasis, inflammatory bowel disease, colitis or Crohn's disease. The fluorinated N-acetylglucosamine is administered prior to an inflammatory event. Alternatively, the fluorinated N-acetylglucosamine is administered after an inflammatory event. Administration is, intraperitoneal, subcutaneous, nasal, intravenous, oral, topical and transdermal delivery.

The cell is a leukocyte such as a lymphoid cell, e.g., T-cell or a hematopoietic cell. Alternatively, the cell is a cancerous cell such a leukemic cell or a lymphoma, e.g., cutaneous lymphoma. The cell is further contacted with a chemotherapeutic agent such as daunorubicin (DNR), cytarabine (ara-C), idarubicin, thioguanine, etoposide, and mitoxantrone or an anti-inflammatory agent such as aspirin, ibuprofen, naproxen sodium, celecoxib, prednisone, prednisolone, and dexamethasone.

The invention provides an improved method for preparing fluorinated N-acetylglucosamine which comprises the intermediate step of preparing benzyl 2-acetamido-2-
deoxy-3,6-di-O-benzyl-D-glucopyranoside from benzyl 2-acetamido-3-O-benzyl-4,6-benzylidene-2-deoxy-D-glucopyranoside, the improvement comprising (i) hydrolyzing benzyl 2-acetamido-3-O-benzyl-4,6-benzylidene-2-deoxy-D-glucopyranoside under appropriate conditions to form benzyl 2-acetamido-3-O-benzyl-2-deoxy-D-glucopyranoside; (ii) reacting benzyl 2-acetamido-3-O-benzyl-2-deoxy-D-glucopyranoside with a tin compound to form a tin complex comprising benzyl 2-acetamido-3-O-benzyl-2-deoxy-D-glucopyranoside; and (iii) reacting the tin complex with a benzylating agent under appropriate conditions to form benzyl 2-acetamido-3,6-benzyl-2-deoxy-D-glucopyranoside.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are hereby incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.