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Synthesis of novel sugar diamino acids

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Synthesis of novel sugar diamino acids

Abstract

Sugar amino acids (SAAs) are found in nature as good construction elements for the preparation of peptide mimetics and oiigosaccharides in drug design and development. The synthesis of SAAs is readily accomplished in few steps and more than 40 SAAs have been synthesised to date.2 Sugar amino acids with an additional amino group, the sugar diamino acid (SDAs) would represent a useful expansion to the library of SAAs available because one of the amino group and carboxylic acid is available for peptide coupling and the another amino/azide group allow to do further derivatisation via peptide or click chemistry such as labelling. However, the synthesis of SDAs is challenging and only three general type have been reported to date.2 As part of a project involving the synthesiso f novel integrin antagonists, we require a new series of SDAs to be developed. Herein, the synthesis of the novel SDAs type 1 and 2 and their applications will be presented. Reference: (1) Gruner, S. A.; Locardi, E.; Lohof, E.; Kessler, H. Chemical Reviews 2002, 102, 491-514. (2) Risseeuw, M. D. P.; Overhand, M.; Fleet,G . W J.; Simone. M. I. Tetrahedron: Asymmetry 2007, 18, 2001-2010.

Keywords

synthesis, acids, novel, sugar, diamino

Disciplines

Life Sciences | Physical Sciences and Mathematics | Social and Behavioral Sciences

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391: Synthesis of novel sugar diamino acids

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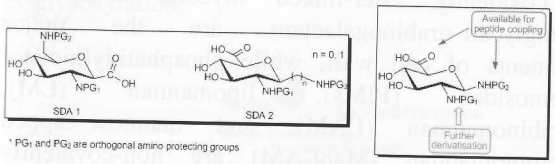
Sugar amino acids (SAAs) are found in nature as good construction elements[1] for the preparation of peptide mimetics and oligosaccharides in drug design and development. The synthesis of SAAs is readily accomplished in few steps and more than 40 SAAs have been synthesised to date.[2] Sugar amino acids with an additional amino group, the sugar diamino acid (SDAs) would represent a useful expansion to the library of SAAs available because one of the amino group and carboxylic acid is available for peptide coupling and the another amino/azide group allow to do further derivatisation via peptide or click chemistry such as labelling. However, the synthesis of SDAs is challenging and only three general type have been reported to date.[2] As part of a project involving the synthesis of novel integrin antagonists, we require a new series of SDAs to be developed. Herein, the synthesis of the novel SDAs type 1 and 2 and their applications will be presented.



* PG_1 and PG_2 are orthogonal amino protecting groups

Reference: (1) Gruner, S. A.; Locardi, E.; Lohof, E.; Kessler, H. Chemical Reviews 2002, 102, 491-514. (2) Risseeuw, M. D. P.; Overhand, M.; Fleet, G. W. J.; Simone, M. I. Tetrahedron: Asymmetry 2007, 18, 2001-2010.

392: Detection of N-acetylgalactosamine-containing glycosylphosphatidylinositol molecules in mammalian cells using an azide-labeled sugar analog

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Many eukaryotic cell surface proteins are post-translationally modified by a glycosylphosphatidylinositol (GPI) glycolipid that anchors the protein to the cell membrane. The biosynthesis and attachment of GPI precursors to proteins in the endoplasmic reticulum has been well defined, whereas subsequent carbohydrate side-chain modifications of protein-bound GPIs are still largely uncharacterized. N-acetylgalactosamine (GalNAc) linked to the first mannose of the core GPI glycan has been previously reported to be heterogeneously present on certain mammalian GPI-anchored proteins. However, nothing is known about the timing and mechanisms of GalNAc addition, due in part to the lack of an effective method to visualize GalNAc-containing GPIs.

Here we present a method for profiling GalNAc-containing GPIs in mammalian cells by metabolic labeling with N-azidoacetylgalactosamine (GalNAz) followed by Staudinger ligation to a biotinylated phosphine probe. This approach was validated by GalNAz labeling of endogenous and recombinant GPI-anchored proteins, followed by methodical characterization of GPIs containing the azide-activated sugar. GPI labeling with GalNAz confirms the identity of the HexNAc residue identified by mass spectrometry in GPI moieties of analyzed mammalian cells. To our knowledge, this is the first direct labeling of the GPI glycan with an azide-labeled sugar. This method permits the detection of GPIs present in the cells under normal physiological conditions, including GPI structures that are difficult to study using conventional labeling techniques. The use of this method for specific enrichment of GalNAc-containing GPIs and GPI-anchored proteins will be discussed.

393: 2-DG: Is it a 2-Deoxy-D-glucose or 2-deoxy-D-mannose? Inhibition of N-glycosylation in glioblastoma-derived cancer stem cells

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Deoxygenation of D-glucose and D-mannose at C-2 leads to structurally identical compounds known for historical reasons as 2-deoxy-D-glucose (2-DG). 2-DG is a known inhibitor of glycolysis and has been shown to interfere with the metabolism of D-glucose. Because 2-DG is also a 2-deoxy-D-mannose, we would expect that it would also interefere with mannose biosynthetic processes. Thus, we hypothesized that the 2-DG-mediated inhibition of glioma-derived stem cells (GSC11) grown under normoxic conditions results from the ability of 2-DG to affect D-glucose and D-mannose bioenergetic and biosynthetic processes. In our approach we have used mass spectrometry to analyze in detail the effects of 2-DG on the formation of N-glycans and its abillity to substitute for D-mannose in