Carbohydrate Research 402 (2015) 245–251

Contents lists available at ScienceDirect

Carbohydrate Research

journal homepage: www.elsevier.com/locate/carres

Synthesis of 4-amidomethyl-1-glucosyl-1,2,3-triazoles and evaluation as glycogen phosphorylase inhibitors

David Goyard [a], Tibor Docsa [b], Pál Gergely [b], Jean-Pierre Praly [a], Sébastien Vidal [a,*]

[a] Institut de Chimie et Biochimie Moléculaires et Supramoléculaires, Laboratoire de Chimie Organique 2—Glycochimie, UMR 5246, CNRS, Université Claude Bernard Lyon 1, 43 Boulevard du 11 Novembre 1918, F-69622 Villeurbanne, France

[b] Cell Biology and Signalling Research Group, Department of Medical Chemistry, Research Centre for Molecular Medicine, University of Debrecen, Nagyerdei krt. 98, H-4032 Debrecen, Hungary

ARTICLE INFO

Article history:
Received 25 September 2014
Accepted 18 October 2014
Available online 27 October 2014

Keywords:
Carbohydrate
Triazole
Click chemistry
Inhibitor
Glycogen phosphorylase

ABSTRACT

Glycogen phosphorylase (GP) appears as a key enzyme for the control of hyperglycemia in the context of type 2 diabetes. In order to gain additional data for structure–activity studies of the inhibition of this enzyme, a series of eight GP inhibitor candidates were prepared from peracetylglucopyranosyl azide **1** by click-chemistry. The need for a *N*-Boc-protected propargylamine was identified in the CuAAC with azide **1** under Meldal's conditions, while Sharpless' conditions were better adapted to the CuAAC of azide **1** with propargyl bromide. Cycloaddition of Boc-propargylamine with azide **1** afforded the *N*-Boc precursor of a 4-aminomethyl-1-glucosyl-1,2,3-triazole which gave access to a series of eight amide and sulfonamide derivatives. After deacetylation, enzymatic studies revealed poor to moderate inhibitions toward this enzyme. The *N*-Boc-protected amine was the best inhibitor (IC_{50} = 620 μM) unexpectedly slightly better than the 2-naphthylamido substituted analogue (IC_{50} = 650 μM).

1. Introduction

Glycogen phosphorylase[1,2] (GP) is an enzyme responsible for the depolymerization of glycogen and a contributor to hepatic glucose output to the blood stream. Hyperglycemia can be linked to the activity of this enzyme and the tight control of GP activity appears as a promising strategy in the context of type 2 diabetes.[3–6] Glucose-based derivatives have been intensively studied and provided the most populated family of GP inhibitors.[7–11] While the best candidates displaying sub-micromolar activities for inhibition of the enzyme are spiro-anomeric-bicyclic carbohydrates,[12–19] a large set of heteroaromatic glucosides have also been investigated providing inhibitions in the low micromolar range.[20–28]

N-Acyl-β-D-glucopyranosylamines[29] (Fig. 1, A) have been reported as good inhibitors of rabbit muscle glycogen phosphorylase *b* (RMGP*b*), the unphosphorylated isoenzyme typically used for inhibition studies. The bioisosterism between the amide bond and the 1,2,3-triazole[30,31] moiety prompted the synthesis of 1-glucopyranosyl-4-aryl-1,2,3-triazoles[32,33] (Fig. 1, B). The inhibition of both derivatives was in the micromolar range while in the case of *N*-acyl-*N*′-β-D-glucopyranosyl ureas with an additional amide bond (Fig. 1, C) the inhibition was largely improved to reach sub-micromolar K_i values.[34]

We therefore decided to synthesize analogues of such triazoles **B** or ureas **C** identified as potent GP inhibitors. The corresponding analogues (Fig. 1, D) can be constructed on a 1,2,3-triazole scaffold displaying a methylamino substituent for amidation with acyl or sulfonyl halides. Such molecular design provides a 1,2,3-triazole moiety as a surrogate of the first amide bond while the second amide bond is maintained. The methylene group between the triazole and amide functionalities can be seen as a flexible pivotal linkage providing a conformational mobility to the scaffold in order to better fit the binding pocket of the enzyme.

The substituents attached at the amine functionality were chosen in connection with the properties of the so-called β-channel.[1] This pocket is in close vicinity to the catalytic site of GP and capable of hydrophobic interactions with the heteroaromatic moieties attached at the β-anomeric position of the glucose residue. Amide bonds were therefore generated with hydrophobic derivatives such as *t*-butyloxycarbamate (Boc), acetyl, and phenyl substituents but also with tyrosine, tosyl, and hydrophilic phosphonate moieties.

2. Results and discussion

2.1. Synthesis

The synthesis of the target glucose-based inhibitors of GP was performed by 1,3-dipolar cycloaddition of a propargylamine derivative with peracetylglucopyranosyl azide **1** (Scheme 1). The

* Corresponding author. Tel.: +33 472 448 349; fax: +33 472 448 109.
E-mail address: sebastien.vidal@univ-lyon1.fr (S. Vidal).

http://dx.doi.org/10.1016/j.carres.2014.10.009
0008-6215/

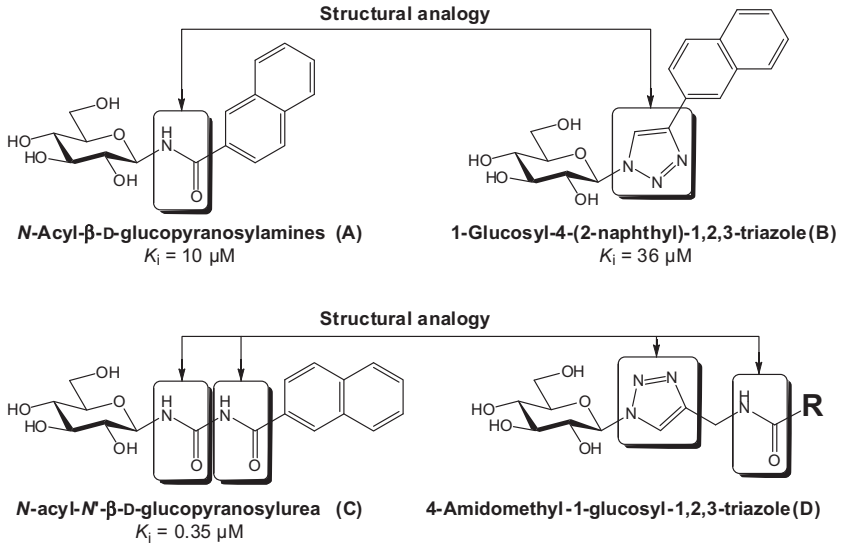
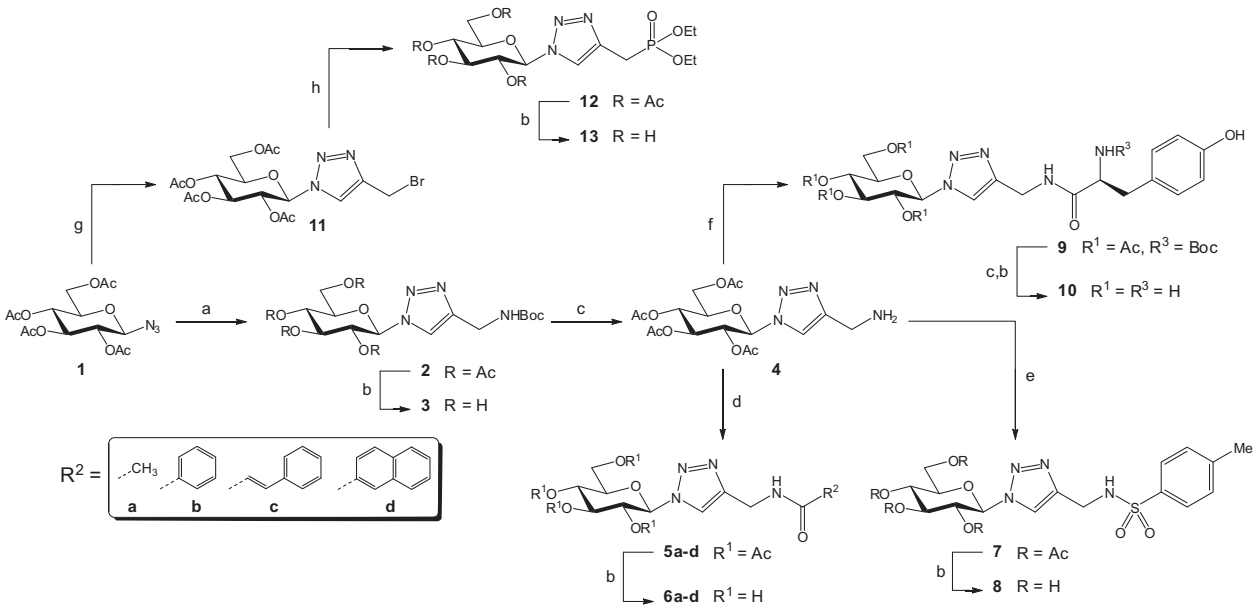


Figure 1. Structural analogy between amide- and triazole-containing GP inhibitors (K_i values are given against RMGP*b*).



Scheme 1. Reagents and conditions: (a) HC≡CCH_2NHBoc, CuI, *i*$PrNEt_2$, DMF, 70 °C, 4 h; (b) MeONa, MeOH, rt, 16 h; (c) CH_2Cl_2/TFA (10:1), rt, 4 h; (d) R^2COCl, Et_3N, CH_2Cl_2, rt, 4 h; (e) TsCl, Et_3N, CH_2Cl_2, rt, 4 h; (f) BocTyrOH, EDCI, HOBt, CH_2Cl_2/DMF (2:1), −10 °C, 2 h then rt, 16 h; (g) HC≡CCH_2Br, $CuSO_4$, sodium ascorbate, *t*BuOH/H_2O (1:1), rt, 16 h; (h) $P(OEt)_3$, 140 °C (μW), 1 h.

development of Cu(I)-catalyzed azide-alkyne cycloaddition[35] (CuAAC) reactions in organic chemistry was boosted after the discovery of reliable and powerful catalysis with Cu(I) species by Meldal[36] and Sharpless[37] following the pioneering discovery on such 1,3-dipolar cycloadditions by Huisgen.[38] Although this reaction is now intensively used, its outcome sometimes differs from the typical result expected, leading to 5-halogenated 1,2,3-triazoles or even 5,5′-bis-triazoles under certain conditions.[39,27]

In various investigations,[40–44] propargylamine has been used as a dipolarophile affording in good to excellent yields 4-aminomethyl-triazoles of interest. Attempted cycloaddition performed with propargylamine and the azido derivative **1** did not afford cleanly the expected triazole but instead a complex mixture containing partially deacetylated compounds most probably through aminolysis of the acetate protecting groups in **1** by propargylamine. Even though reacetylation of the crude mixture could be envisaged for the recovery of the target compound, this strategy was not further investigated. Fortunately, carbamoylation of propargylamine as the *t*-butyloxycarbamate (Boc) derivative allowed for a clean and high yielding (95%) cycloaddition with azide **1** to afford the desired Boc-protected amine **2**[45] (Scheme 1). This compound was deacetylated under Zemplén conditions to afford compound **3** as a GP inhibitor candidate.

The Boc-protected amine **2** was converted quantitatively by acidic cleavage to the free amine **4** suitable for further functionalization with acyl chlorides (Scheme 1, R^2COCl) affording the acetylated amides **5a**–**d** which were deprotected to the GP inhibitors candidates **6a**–**d**. The amine **4** was also converted to the sulfonamide derivative **7** using *p*-toluenesulfonyl chloride TsCl and subsequent deacetylation afforded derivative **8**. The sulfonamide **8** was synthesized in order to take advantage of hydrophobic contact in the β-channel of GP and also to have potential additional contacts with the sulfonamide group and the side chain amino acids of the enzyme. Finally, the Boc-protected tyrosine