Tetrahedron Letters 53 (2012) 959–961

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

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

Synthesis of *N*-aryl spiro-sulfamides as potential glycogen phosphorylase inhibitors

Tony Tite [a], Loic Tomas [b], Tibor Docsa [c], Pal Gergely [c], José Kovensky [a], David Gueyrard [b,*], Anne Wadouachi [a,*]

[a] *Laboratoire des Glucides-UMR CNRS 6219, Université de Picardie Jules Verne, 33 rue Saint Leu, 80039 Amiens, France*
[b] *Université de Lyon, ICBMS, Laboratoire de Chimie Organique 2-Glycochimie, UMR CNRS 5246, Université Claude Bernard Lyon 1-CNRS, Bâtiment 308(CPE), 43 Boulevard du 11 novembre 1918, F-69622 Villeurbanne, France*
[c] *Department of Medical Chemistry, Medical and Health Science Centre, University of Debrecen, Egyetem tér 1, H-4032 Debrecen, Hungary*

ARTICLE INFO

Article history:
Received 2 November 2011
Revised 7 December 2011
Accepted 12 December 2011
Available online 17 December 2011

Keywords:
exo-glucal
Gluconolactone
Spiro-sulfamide
Burgess reagent

ABSTRACT

A new *C*-glucosylated spiro-sulfamide has been prepared and evaluated toward glycogen phosphorylase inhibition. The synthesis was carried out successfully by nucleophilic displacement of 1-*O*-tosyl or 1-deoxy-1-iodo-α-D-*gluco*-hept-2-ulopyranose tetra-*O*-benzylated derivative using aryl amines, followed by the formation of the corresponding cyclic sulfamide.

Glycogen phosphorylase (GP) is the enzyme in charge of the transformation of glycogen to glucose (glycogenolysis) in the liver. Because of its crucial role in the degradation of glycogen, the inhibition of GP has been considered a valuable and promising therapeutic approach[1] for the treatment of hyperglycemia.[2,3] Different classes of compounds have been designed for GP inhibition, competitive inhibitors of the catalytic site being generally D-glucose derivatives. Among them, spiro-isoxazolines[4,5] and spiro-oxathiazoles derivatives,[6,7] two families of spiro compounds bearing a heterocyclic ring, are the most active against GP (Fig. 1).

In our ongoing project devoted to the synthesis of original glycomimetics starting from exoglycals[8,9] using the Burgess reagent,[10,11] we were interested in the preparation of spiro-sulfamides bearing an aromatic substituent. The key structural characteristics of the glucose-based GP inhibitors are thus conserved: the presence of heteroatoms (sulfur, oxygen, and nitrogen atoms) in the heterocyclic ring that contributes to hydrogen bonding with amino-acids, the occurrence of an aromatic substituent that can be placed in the β-pocket of the enzyme, and the $^4C_1$ conformation of the sugar ring.[5] In this Letter, the synthesis of new *C*-glucosylated spiro-sulfamides is reported together with the inhibition results on GP.

Two synthetic approaches were considered, starting from methylene *exo*-glucal **1** and from gluconolactone **8**. D-*Gluco*-hept-2-ulopyranose derivatives with an activated primary carbon were first synthesized to obtain amino-alcohols precursors of the spiro-sulfamides. Osmylation[11,12] of the methylene *exo*-glucal **1**[8] into diol **2** and subsequent tosylation of the primary alcohol furnished the *O*-tosylate compound **3**. The tosylation reaction proceeded in a 90% yield, with the formation of a minor chlorinated side-product **4**, which could be easily separated from **3** (Scheme 1).

Microwave-assisted nucleophilic substitution of tosylate derivative **3** was conducted under pressure in a sealed vessel,[13] with

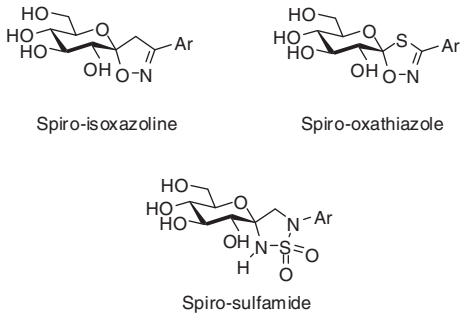
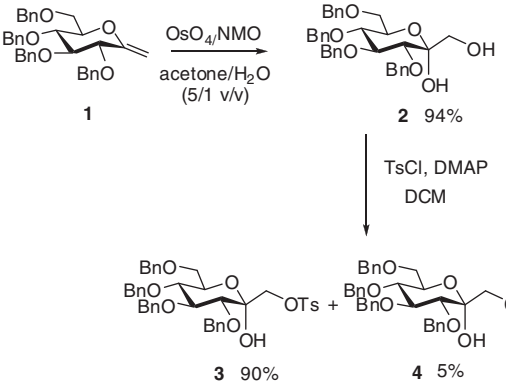


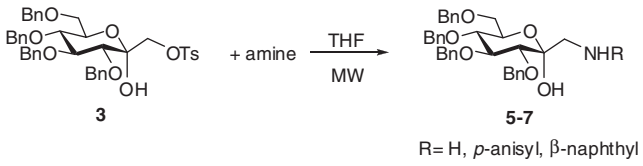
Figure 1. Structure of two representative families of GP inhibitors and similarity with the spiro-sulfamide.

* Corresponding authors. Tel.: +33 3 22 82 75 63; fax: +33 3 22 82 75 60 (A.W.), tel.: +33 4 72 44 83 49; fax: +33 4 72 44 81 09 (D.G.).
E-mail addresses: david.gueyrard@univ-lyon1.fr (D. Gueyrard), anne.wadouachi@sc.u-picardie.fr, anne.wadouachi@u-picardie.fr (A. Wadouachi).

0040-4039/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.12.049



Scheme 1. Preparation of the tosylated compound **3**.



Scheme 2. Substitution reaction on the tosylated compound **3**.

several amines (aqueous ammonia, *p*-anisidine, and β-naphthylamine) to afford the corresponding amino compounds **5**, **6**, and **7**, respectively (Scheme 2). Microwave-assisted reactions gave shortened reaction times comparatively to the aminolysis of primary tosylates reported in the literature (100 °C for 24 h).[13] The addition of a non nucleophilic base as K_2CO_3 was essential to obtain these two aryl amines (Table 1).

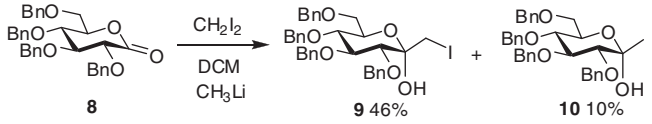
In the second synthetic approach, 1-deoxy-1-iodo compound **9**[14] was synthesized via iodomethylenation[15] of an easily available tetrabenzylated gluconolactone **8**. In these conditions, 1-deoxy-1-iodo compound **9** was provided as a single anomer (β) but together with the β-1-deoxy-1-methyl derivative **10**[16] (Scheme 3).

Under the above mentioned microwave conditions, the β-1-deoxy-1-iodo derivative **9** was proved to be unstable, and much degradation was observed. So, the aminolysis of **9** was realized using conventional conditions. The nucleophilic substitution of **9** furnished the corresponding 1-deoxy-1-amino-hept-2-ulopyranose derivatives with higher yields (Table 2).

At room temperature, ammonium hydroxide provided without the addition of base, the desired amino alcohol **5** in a good yield (73%). In the case of aromatic amines, sodium hydride was necessary to generate the corresponding anion and to carry out the reaction (Scheme 4, Table 2). In such conditions, the β-naphthylamino and tryptamino alcohols were provided, respectively, in 70% and 75% yields. Surprisingly, for the 2-aminopyridine reagent, the corresponding amino alcohol was not obtained. By HRMS, compound **12** shows a $[M+H]^+$ ion at *m/z* 629.2992. The full assignment of the protons has been performed using the combination of standard 2D experiments such as COSY, HSQC, and HMBC. In the ^1H NMR spectrum of **12**, no adjacent methylene proton appears in the 2.5–3.5 ppm range as seen for the amino-alcohols derivatives **5**–**7** and **11**. In the ^{13}C NMR spectrum, a signal corresponding to an enamine carbon appeared at 111 ppm. The structure of **12** in accordance with these data is depicted in Scheme 4.

Table 1
Optimization of the synthesis of aminoalcohols **5**–**7** from tosyl **3**

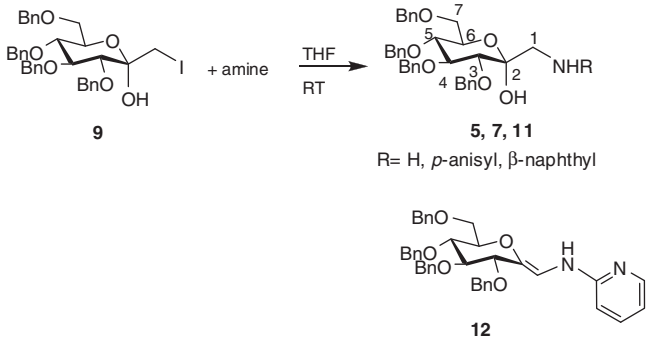
Amine	Compound	R	100 °C 60 psi 20 W 1 h	100 °C 20 psi 60 W K_2CO_3 1 h (%)
NH_4OH	**5**	H	60%	—
Anisidine	**6**	*p*-Anisyl	Inert	52
β-Naphthylamine	**7**	β−Naphthyl	Inert	52



Scheme 3. Iodomethylenation reaction.

Table 2
Synthesis of amino-alcohols from iodo compound **9**

Amine	Base	Time	Compound	Yield (%)
NH_4OH	—	4 h 30 min	**5**	73
β-Naphthylamine	NaH	35 min	**7**	70
Tryptamine	NaH	45 min	**11**	75
2-Aminopyridine	NaH	2 h	**12**	69



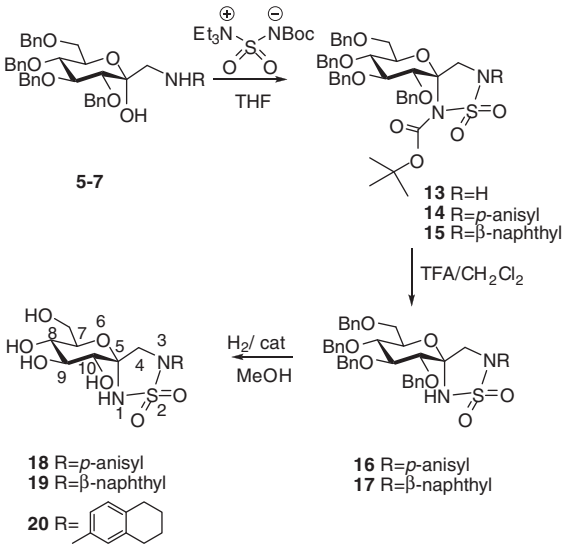
Scheme 4. Substitution reaction of the iodo derivative **9**.

To synthesize cyclic sulfamide derivatives, the Burgess-type reagent *tert*-butyl *N*-(triethylammoniumsulfonyl)-carbamate[17,18] was used. We have previously described a synthesis of sulfamide-type indolizidines from 5-amino-5-deoxy D-gluco and D-mannofuranose compounds used as precursors.[10] In an analogous strategy we managed to synthesize the *N*-(Boc)-sulfamide derivatives from the compounds **5**, 6, and **7**, the spiro-sulfamides **13**–**15** were obtained in satisfactory yields (Table 3, Scheme 5).

The spiro formation of compounds **13**–**16** and **17**, **18**, and **20** was confirmed by the NMR chemical shift of the C-5 (Table 4), and as example a NOESY experiment for compound **18** showed the correlation between the H-4 and H-10 which is presented in Figure 2.

Table 3
Synthesis of spiro-sulfamides compounds from aminoalcohols **5**–**7**

Amino-alcohols	R	Compounds	Yield (%)
5	H	**13**	68
6	*p*-Anisyl	**14**	73
7	β-Naphthyl	**15**	85



Scheme 5. Preparation of the spiro-sulfamides.

Table 4
NMR chemical shifts of spiro-carbon of compounds **13**–**16** and **17**, **18**, and **20**

Compounds	δ C-5 (ppm)
13	93.7[a]
14	90.3[a]
16	88.8[a]
17	88.5[a]
18	90.2[b]
20	89.9[c]

[a] NMR 75 MHz in $CDCl_3$.
[b] NMR 150 MHz in $CDCl_3$.
[c] NMR 150 MHz in CD_3OD.

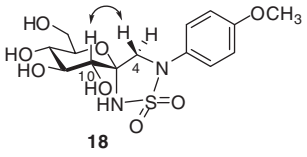


Figure 2. Noesy correlation of spiro compound **18**.

Subsequent classical triflic acid deprotection of the carbamate protecting group for **14** and **15** provided the corresponding spiro-sulfamides **16** and **17**. Compound **16** was then debenzylated by catalytic hydrogenation at rt in the presence of $PdCl_2$ to afford the final derivative **18** in an 83% yield. Under the same conditions with the naphthyl compound **17**, the debenzylation reaction was accompanied by a partial reduction of the naphthyl part and gave an inseparable mixture of **19** and **20**. Compound **20** was obtained as a sole product (75%) when spiro-sulfamide **17** was hydrogenated in the presence of Pd/C 10% at 50 °C under pressure (11 bar) on a H-Cube.

Preliminary biological evaluation on glycogen phosphorylase was performed on spiro-sulfamide with the *p*-anisyl derivative **18** which inhibited the GP with a 15 μM K_i value. This result showed that this novel family inhibits the rabbit muscle glycogen phosphorylase (RMGP)b and strongly suggests that the rigid spiro-bicyclic structure oriented properly the large apolar aromatic group in the β-pocket to bind strongly the catalytic site of GP.

In conclusion, we designed and synthesized a novel family of N-arylated spirosulfamides. Preliminary biological test on GP shows that the *p*-anisyl derivative is an active inhibitor of GP. Further works are in progress to synthesize several members of this family and to prepare more potent inhibitors of glycogen phosphorylase.

Acknowledgements

The authors thank the MESR for a grant (L.T.) and David Lesur for HRMS experiments.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.12.049.

References and notes

1. Moller, D. E. *Nature* **2001**, *414*, 821–827.
2. Zimmet, P.; Alberti, K. G. M. M.; Shaw, J. *Nature* **2001**, *414*, 782–861.
3. Treadway, J. L.; Mendys, P.; Hoover, D. J. *Exp. Opin. Invest. Drugs* **2001**, *10*, 439–454.
4. Benltifa, M.; Vidal, S.; Gueyrard, D.; Goekjian, P. G.; Msaddek, M.; Praly, J.-P. *Tetrahedron Lett.* **2006**, *47*, 6143–6147.
5. Benltifa, M.; Hayes, J. M.; Vidal, S.; Gueyrard, D.; Goekjian, P. G.; Praly, J.-P.; Kizilis, G.; Tiraidis, C.; Alexacou, K.-M.; Chrysina, E. D.; Zographos, S. E.; Leonidas, D. D.; Archontis, G.; Oikonomakos, N. G. *Bioorg. Med. Chem.* **2009**, *17*, 7368–7380.
6. Somsák, L.; Nagy, V.; Vidal, S.; Czifrák, K.; Berzsényi, E.; Praly, J.-P. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5680–5683.
7. Nagy, V.; Benltifa, M.; Vidal, S.; Berzsényi, E.; Teilhet, C.; Czifrák, K.; Batta, G.; Docsa, T.; Gergely, P.; Somsák, L.; Praly, J.-P. *Bioorg. Med. Chem.* **2009**, *17*, 5696–5707.
8. Gueyrard, D.; Haddoub, R.; Salem, A.; Said Bacar, N.; Goekjian, P. G. *Synlett* **2005**, 520–522.
9. Bourdon, B.; Corbet, M.; Fontaine, P.; Goekjian, P. G.; Gueyrard, D. *Tetrahedron Lett.* **2008**, *49*, 747–749.
10. Benltifa, M.; Garcia-Moreno, M. I.; Ortiz Mellet, C.; Garcia Fernandez, J. M.; Wadouachi, A. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2805–2808.
11. Benltifa, M.; De Kiss, M.; Garcia-Moreno, M. I.; Ortiz Mellet, C.; Gueyrard, D.; Wadouachi, A. *Tetrahedron: Asymmetry* **2009**, *20*, 1817–1823.
12. Li, X.; Takahashi, H.; Ohtake, H.; Shiro, M.; Ikegami, S. *Tetrahedron* **2001**, *57*, 8053–8066.
13. Neimert-Andersson, K.; Blomberg, E.; Somfai, P. *J. Org. Chem.* **2004**, *69*, 3746–3752.
14. Noort, D.; Veeneman, G. H.; Boons, G.-J. P. H.; Van der Marel, G. A.; Mulder, G. J.; Van Boom, J. H. *Synlett* **1990**, 205–206.
15. Bessieres, B.; Morin, C. *Synlett* **2000**, 1691–1693.
16. Li, X.; Ohtake, H.; Takahashi, H.; Ikegami, S. *Tetrahedron* **2001**, *57*, 4283–4295.
17. Nicolaou, K. C.; Huang, X.; Snyder, S. A.; Rao, P. B.; Bella, M.; Reddy, M. V. *Angew. Chem., Int. Ed.* **2002**, *41*, 834–838.
18. Nicolaou, K. C.; Snyder, S. A.; Nalbandian, A. Z.; Longbottom, D. A. *J. Am. Chem. Soc.* **2004**, *126*, 6234–6235.