http://dx.doi.org/10.5935/0103-5053.20130117
J. Braz. Chem. Soc., Vol. 24, No. 6, 914-921, 2013.
Printed in Brazil - ©2013 Sociedade Brasileira de Química
0103 - 5053 $6.00+0.00

Article

Ultrasound-Assisted Synthesis of 1-*N*-β-D-Glucopyranosyl-1*H*-1,2,3-triazole Benzoheterocycles and their Anti-Inflammatory Activities

Gilson B. da Silva,[a] Bruna M. Guimarães,[a] Shalom P. O. Assis,[b] Vera L. M. Lima[b] and Ronaldo N. de Oliveira*[,a]

[a]*Departamento de Ciências Moleculares, Universidade Federal Rural de Pernambuco, Rua Dom Manoel de Medeiros s/n, Dois Irmãos, 52171-900 Recife-PE, Brazil*

[b]*Departamento de Bioquímica, Laboratório de Química e Metabolismo de Lipídeos e Lipoproteínas, Universidade Federal Rural de Pernambuco, 50670-901 Recife-PE, Brazil*

Neste trabalho, a preparação de vários glicosídeos triazólicos a partir da reação entre a azida de 2,3,4,6-tetra-*O*-acetil-β-D-glicopiranosila e alcinos terminais foi desenvolvida em moderados a excelentes rendimentos (63-99%). Em todas as etapas de reação foi aplicada a energia de ultrassom para aumentar a reatividade química. Adicionalmente, os compostos conjugados com benzoeterociclos revelaram potente atividade anti-inflamatória.

In this work, the preparation of various glucosyl triazoles from a reaction between 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl azide and terminal alkynes was developed in moderate to excellent yields (63-99%). Ultrasound energy was applied at each step of the reaction to increase chemical reactivity. In addition, the compounds conjugated with benzoheterocycles moieties revealed potent anti-inflammatory activity.

Keywords: triazole, click chemistry, ultrasound, anti-inflammatory activity, carbohydrate, benzoheterocycle

Introduction

Much modern research in organic synthesis has promoted the development of new methodologies and their optimization. Over the past decade, one fast-growing area in organic chemistry has been the synthesis of compounds employing ultrasound irradiation.[1] In recent years, sonochemistry has been applied to accelerate a large number of organic reactions and enhance their chemical yields.[2] The use of this technology in organic synthesis has been reported in a variety of areas, for instance heterocycles[3] and carbohydrates,[4,5] and the latter represent a vast field for the exploration of chemical reactivity.

A research area in carbohydrate chemistry has been centered on the need to induce the formation of glycoside linkages towards the glycoconjugate mimics.[6] A diversity of carbohydrate structures is conjugated with heterocyclic moieties, e.g., via the aglycon part which promotes the formation of small molecules that show some biological activity. Hybrid compounds are often a prerequisite for biological activity and can influence drug design and discovery of new chemical entities (NCEs) based on sugar scaffolds.[7] Glucopyranosyl triazoles have shown biological activities such as enzyme inhibition,[8] and as antitumor,[9] antiviral[10] and anti-tuberculosis agents.[11] For anti-inflammatory activity, the literature describes a few examples based on carbohydrates.[12] In this context, glycocompounds with a benzoheterocyclic aglycon to evaluate their anti-inflammatory activities were selected.

The 1,2,3-triazoles linked to carbohydrate scaffolds have been synthesized employing a copper-based catalyst.[13] The effect of ultrasound on carbohydrate chemistry[4,5,14] and specifically on the click chemistry in the synthesis of 1,2,3-triazoles has been reported very recently.[15,16]

Motivated by our recent projects involving the synthesis[17] and biological activities [12,18] of a series of new 1,2,3-triazole derivatives, our group became interested in *N*-glycosyl-1,2,3-triazoles formed from 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl azide and terminal alkynes via 1,3-dipolar cycloaddition reaction using the application of

*e-mail: ronaldonoliveira@dcm.ufrpe.br

ultrasound energy. Our strategy to obtain these compounds containing a 1,2,3-triazole moiety was developed using only ultrasound irradiation in four steps, as shown in Scheme 1.

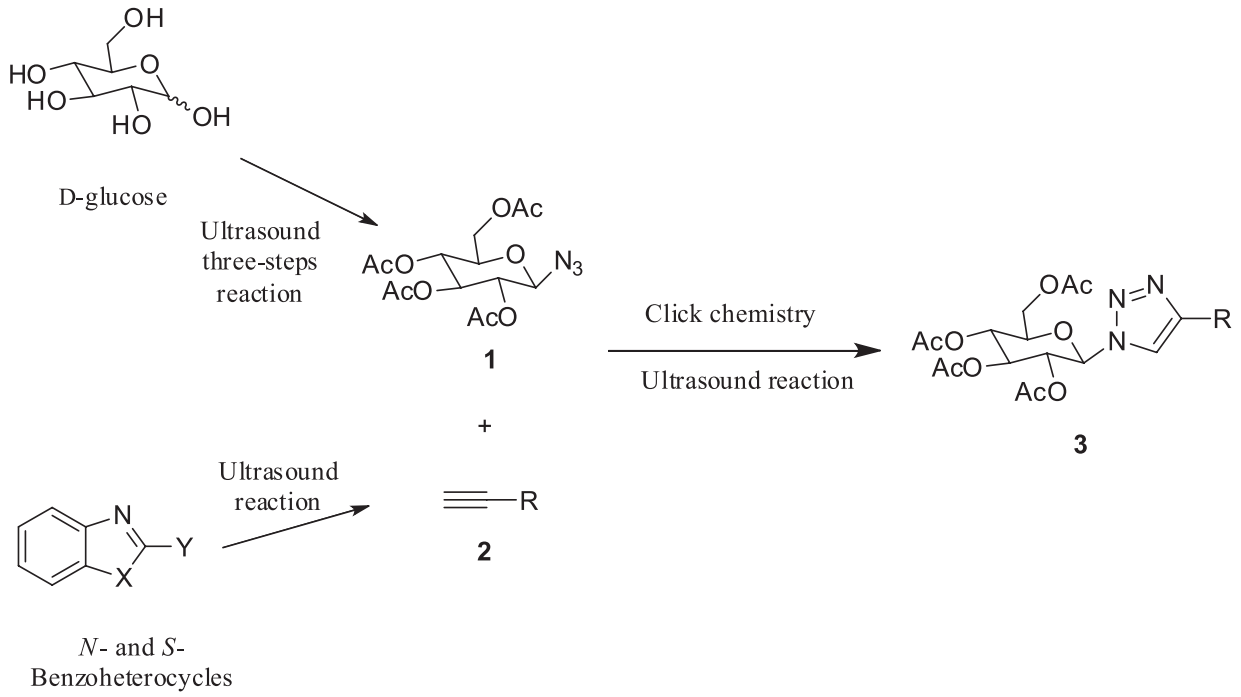
Results and Discussion

Firstly, our attention was focused on the preparation of the starting materials, namely 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl azide **1** and terminal alkynes **2c**-**g**. In order to simplify the synthesis of **1** a three-step procedure employing ultrasound irradiation was performed. Compound **1** was prepared from D-glucose under modified conditions using ultrasonic energy in the acetylation[19] (Ac_2O, 3.5 mol% I_2, ultrasound, 20 min), bromination[20] (HBr/AcOH, ultrasound, 50 min) and azidation[21] (acetone/H_2O/NaN_3, ultrasound, 40 min). After these three steps, compound **1** was obtained with overall yields of 61%. Comparatively, the results without ultrasound energy are overall lower yields and longer-time processes to obtain the azide-tagged sugar **1** (Table 1).

Our research group has been interested in the synthesis of benzoheterocyclic derivatives,[17,22] and recently, developed a stereoselective functionalization of unsaturated carbohydrates using palladium reagents that resulted in an efficient strategy for constructing allylic *N*- and *S*-benzoheterocycles linked to carbohydrate moieties.[22]

To continue along this line, compounds **2c**-**g** were prepared through a reaction between propargyl bromide and benzoheterocycles in the presence of K_2CO_3 under sonication conditions were synthesized, as shown in Table 2. This protocol furnished the desired compounds in 45-77%. In comparison, the reactions using the silent conditions afforded the same compounds **2c**-**g** with similar yields, albeit after 20-24 h.

To begin our study towards producing glucopyranosyl 1,2,3-triazoles (Scheme 2), the Sharpless protocol[28] was



Scheme 1. Strategy to obtain 1,2,3-triazolyl sugars in four-steps from D-glucose and benzoheterocycles using ultrasound irradiation

Table 1. Synthesis of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl azide (**1**)

Step	Method A - Ultrasound		Method B - Silent condition	
	time / min	Yield / %	time / min	Yield[b] / %
Acetylation	20	95[a]	60	82
Bromination	50	70[a]	240	63
Azidation	40	92[b]	360	91
Total (three steps)	110	61	660	47

[a]Yields of crude materials: no secondary spots were observed by TLC. [b]Isolated yield after column chromatography.

applied to promote the reaction between 1 equiv. of **1** and 1.2 equiv. of **2a** using 20 mol% $CuSO_4 \cdot H_2O$, 40 mol% sodium ascorbate in 50% *tert*-BuOH:H_2O at ambient temperature, but a very low level of conversion was observed (thin layer chromatography (TLC) analysis), even after 12 h stirring. Field and co-workers[13] also described similar results when employing this protocol in the synthesis of α- and β-D-glucopyranosyl triazoles via CuAAC click chemistry. Based on our recent results,[17] however, the protocol was changed to 10 mol% CuI in dichloromethane, and a partial conversion (examined by TLC) was observed after 24 h. Fortunately, after adding 10 mol% of triethylamine, the reaction was completed in 20 h. The total conversion obtained by using a base (Et_3N) can be explained via deprotonation of the transient π-complex ($RC{\equiv}CH|CuL_n$) to form the copper-acetylide, as reported in the literature.[29] In order to obtain a shorter reaction time, the ultrasound energy at room temperature was applied, and 1,2,3-triazole-sugars **3a** were obtained in 20 min in 79% yield (Table 3, entry 1). This shorter time, under these conditions, can be accounted for by the sonocatalysis in 1,3-dipolar cycloaddition reaction.[3,15,30] Driowya *et al.*[16] recently described the synthesis of **3a** in 77% yield, for 20 min under ultrasound irradiation using 2 equiv. of CuI and 2 equiv. of DIEA (*N*,*N*-diisopropylethylamine). Hence, comparatively, our procedure appeared more efficient because employing catalytic amounts of copper(I) iodide and triethylamine.

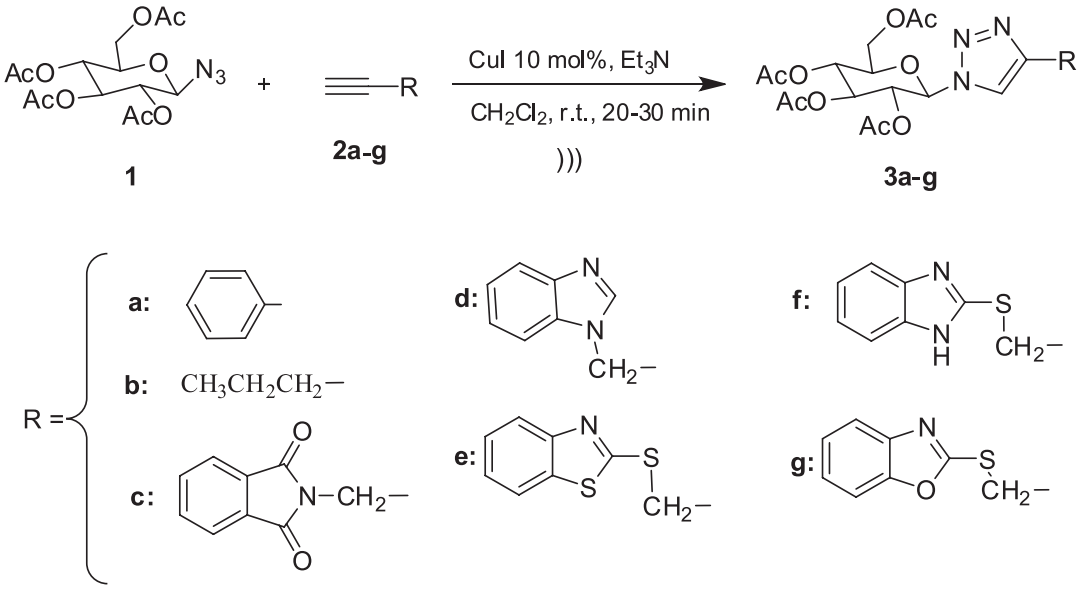
After optimization of the conditions, our group decided to apply our protocol to obtain *N*-glycosyl-1,2,3-triazoles **3a**-**g** using various terminal alkynes (Scheme 2). Ultrasound-assisted reaction of **1** with various functionalized alkynes **2a**-**g** afforded the corresponding β-glucopyranosyl triazole derivatives **3a**-**g** in moderate to excellent yields (63-96%) within short reaction times (Scheme 2 and Table 3).

Compounds **3a**,[31] **3c**[32] and **3d**[33] were recently reported in the literature. Compounds **3a** and **3c** were prepared via the click chemistry procedure under conventional conditions.[31,32]

Table 2. Synthesis of propargyl *N*- and *S*-benzoheterocycles (**2c**-**g**)

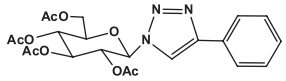
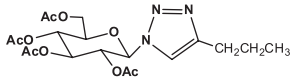
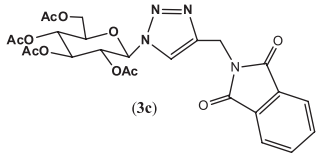
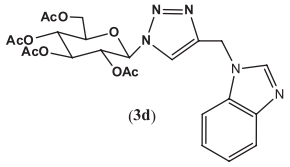
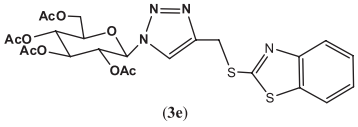
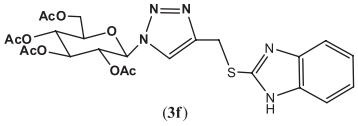
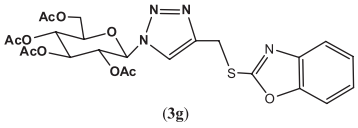
Product	Method A - Ultrasound		Method B - Silent condition		Melting point / °C (from Reference)
	time / min	Yield[a] / %	time / min	Yield[a] / %	
2c[b]	10	55	1440 (24 h)	55	141-43 (149)[23]
2d	20	76	1200 (20 h)	79	oil (38-40)[24]
2e	60	77	1380 (23 h)	83	40-42 (46)[25]
2f	60	45	1440 (24 h)	71	128-131 (153)[26]
2g	60	60	1320 (22 h)	51	47-48 (51)[27]

[a]Isolated yield after column chromatography. [b]In this case, the reaction was performed without addition of K_2CO_3.



Scheme 2. Synthesis of *N*-glucosyl-1,2,3-triazoles under ultrasound activation.

Table 3. Ultrasound-assisted synthesis of *N*-glucosyl-1,2,3-triazoles (**3a**-**g**)

entry	Product	Reaction time / min	Melting point / °C (from Reference)	$[\alpha]_D$ [a]	Yield[b] / % (from Reference)
1	 (**3a**)	20	189-193 (195-198)[30]	–19.0	79
2	 (**3b**)	30	153-155	–32.8	96
3	 (**3c**)	20	204-205 (203-204)[31]	–22.0	63
4	 (**3d**)	30	182-184	–21.5	88 (78)[c]
5	 (**3e**)	25	152-153	–17.7	69
6	 (**3f**)	20	156-158	–20.8	95
7	 (**3g**)	20	161-162	–25.7	88

[a] c = 0.01 g mL^{-1} in CH_2Cl_2. [b] After chromatography column. [c] Two isomers: 1,4 and 1,5.[33]

The compound **3d** was obtained via a thermal cycloaddition reaction along with its 1,5-isomer and separated by column chromatography.[33] When applying our click protocol, compound **3d** was synthesized in 88% isolated yield (Table 3, entry 4). To our knowledge, compounds **3b**, **3e**, **3f** and **3g** have not been previously described.

The structures of the compounds **3a**-**g** were analyzed using ^{1}H and ^{13}C nuclear magnetic resonance (NMR) and high-resolution mass spectrometry (HRMS) or elemental analysis. The appearance of a singlet in ^{1}H NMR spectrum data in the region between 7.5 and 7.9 ppm was assigned to $H_{5'}$ (methine proton) of the triazolyl ring. In order to ascertain the preferential conformations in the 1,2,3-triazole-sugars **3a**-**g**, our study was decided on the base of the proton coupling constants (J) in the glucopyranose ring. The ^{1}H and ^{13}C NMR spectra were in concordance with the proposed structure. The methylene protons (–CH_2–Het) in **3c**, **3e**-**g** do not appear as a singlet, but as a double doublet, the non-equivalence between hydrogen atoms is a case of diastereotopic geminal protons. The ^{1}H NMR spectra of compounds **3a**-**g** showed the anomeric proton (H_1) as a doublet in the range δ 5.81-5.93 ppm and $J_{H1,H2}$ 8.8-9.2 Hz. This vicinal coupling indicates a 1,2-*trans* relationship and a β-anomeric configuration. Large vicinal coupling constants were observed for protons H_2, H_3 and H_4 (9.2-10.0 Hz) that appeared in the δ 5.17-5.55 ppm region. These results are in agreement with a *trans* diaxial relationship between H_1/H_2, H_2/H_3, H_3/H_4 and H_4/H_5, suggesting that all hydrogens are in axial position in a $^4C_1$ conformation

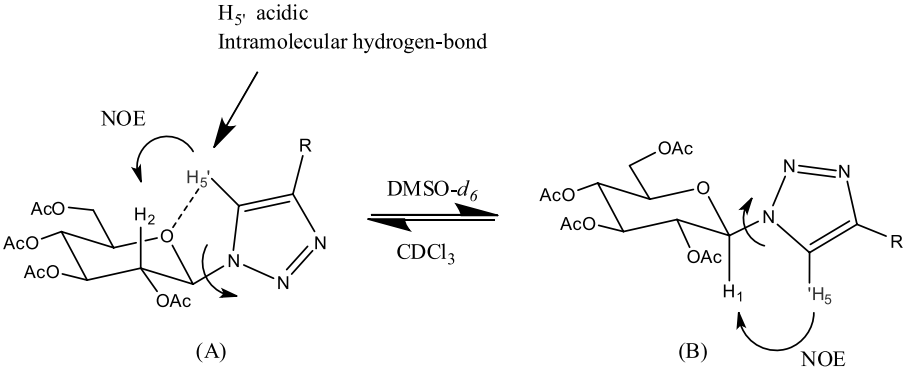
for the β-D-glucopyranosyl ring. The proton H_5 is located upfield (ca 4 ppm) and the multiplicity appears as ddd due to H_5 coupling with protons H_4 ($J_{5,4}$ 8.4-10.0 Hz), H_6 ($J_{5,6}$ 3.6-5.0 Hz) and $H_{6'}$ ($J_{5,6'}$ 1.6-2.8 Hz), as expected for D-series sugar compounds **3a**-**g**. The relations between H_1, H_2, H_3 and H_4 were shown using a H,H-correlation spectrum (COSY). Nuclear Overhauser effect (NOE) contact between H_{1ax} with H_{3ax} and H_{5ax} was observed employing H,H-nuclear Overhauser effect spectroscopy (NOESY) experiment.

Furthermore, a spatial NOE contact between $H_{5'}$ and H_2 or H_1 was detected, these results confirmed the exclusive formation of 1,4-regioisomer. For the experiment of nuclear Overhauser effect difference spectroscopy (NOE DIFF), the proton $H_{5'}$ ($H_{triazole}$) for irradiation in compounds **3b** and **3e**, such as representative sampling, was chosen. These experiments can be monitored by increasing the H_1 or H_2 signals. When performing the experiments in $CDCl_3$ or DMSO-d_6, a more accurate analysis of the NOE DIFF spectrum revealed solvent effects on the population distribution of rotamers of the *N*-glucosyl-1,2,3-triazole series, as shown in Figure 1.

Srivastava and co-workers[34] described *ab initio* (HF/6-31G* method) molecular orbital calculations in vacuum of a glucosyl-triazole linked to 1,2,4-oxadiazole moiety, indicating a more stable B-type conformer. Through H_1 irradiations, the authors also observed a NOE contact of 6% between H_1 and $H_{5'}$ in DMSO-d_6. In our case, the NOE-DIFF experiment indicates that the conformer A-type is preferred in $CDCl_3$ for compound **3b** (ca. 5% to H_2 and < 1.0% to H_1, Figure 1). On the other hand, in DMSO-d_6, the experiments revealed a substantial increase of conformer B-type, displaying a rotational equilibrium of *N*-glucosyl-1,2,3-triazoles between the conformer A- and B-types. These results are consistent with polarity parameters involving hydrogen-bond donating solvents.[35] Probably, this tendency can be explained in terms of $H_{5'}$ acidity[36] allowing an intramolecular CH–O hydrogen bond formation between $H_{5'}$ and the endocyclic oxygen of glucopyranose, as shown in Figure 1 (structure A-type). In this case, as expected, the less polar $CDCl_3$ favored the conformer A-type, whereas the more polar DMSO-d_6 destabilized the intramolecular hydrogen-bond, thus increasing the conformer B-type. These are interesting results that can play important roles in biological activities through conformational stabilization. Further investigation of the correlation of conformational behavior and biological activity of 1,2,3-triazole-carbohydrates is currently under way in our laboratory.

Having synthesized and characterized 1,2,3-triazole-sugars **3a**-**g**, and considering the results of Shafi *et al.*[37] related to the anti-inflammatory activity of benzothiazole-2-thio-linked 1,2,3-triazoles, the benzoheterocyclic series **3d**-**g** was selected to have studies their acute anti-inflammatory activity profiles, the results are summarized in Table 4 and Figure 2. The above compounds exhibited moderate to good anti-inflammatory activity with the percentage inhibition of edema formation ranging from 49.2 to 64.7%, while the reference drug ASA and ibuprofen both showed 77% inhibition (Table 4).

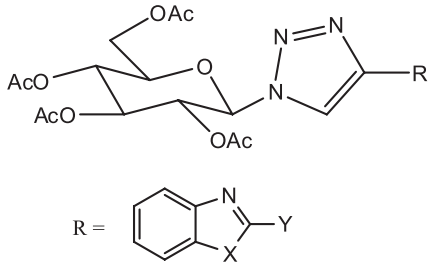
Compound **3d** showed moderate activity (49.2%). It was observed that when the thiomethyl group (Y=SCH_2–) was introduced in the structure, the activity increased from 55 to 65% (Figure 2). Our results are in agreement with the



	NOE of $H_{5'}$ in $CDCl_3$	
R	NOE with H_2	NOE with H_1
3b	5.3%	< 1.0%
3e	3.0%	< 1.0%

	NOE of $H_{5'}$ in DMSO-d_6	
R	NOE with H_2	NOE with H_1
3b	1.7%	< 1.0%
3e	< 1.0%	< 1.0%

Figure 1. Solvent effect observed on the conformational equilibrium of **3b** and **3e**.



X	Y	Edema inhibition / %
NCH_2–	H	49.2 (**3d**)
S	SCH_2–	55.8 (**3e**)
NH	SCH_2–	58.0 (**3f**)
O	SCH_2–	64.7 (**3g**)

Figure 2. Structure and anti-inflammatory activity of 1-*N*-β-D-glucopyranosyl-1*H*-1,2,3-triazole benzoheterocycles **3d**-**g**.

Table 4. Acute anti-inflammatory activity for the benzoheterocyclic glucosyl 1,2,3-triazoles **3d**-**g**

Compound	Dose / (mg kg^{-1})	Mean ± standard deviation / g	Edema inhibition / %
Control (saline 0.9%)	–	0.1512	–
ASA	250	0.0347^a ± 0.001	77.0
Ibuprofen	250	0.0347^b ± 0.007	77.0
CMC	–	0.1412^b ± 0.040	6.7
3d	250	0.0767^a ± 0.001	49.2
3e	250	0.0667^a ± 0.001	55.8
3f	250	0.0633^a ± 0.002	58.0
3g	250	0.0533^a ± 0.002	64.7

Significant differences: $^a p < 0.001$; $^b p < 0.05$.

literature, that recently related that the anti-inflammatory activity was increased when 2-mercapto benzothiazole was linked to 1,2,3-triazole.[37]

In particular, the substitution at the third position of benzoheterocyclic, when X = S, NH or O, shows growth in anti-inflammatory activity for **3e** (55.8%), **3f** (58.0%) and **3g** (64.7%), respectively (Figure 2). The potency for acute anti-inflammatory activity was optimized in compound **3g**, which exhibited a higher diversity of atoms (N, S and O) at the benzoheterocyclic site and showed a relativity similar profile when compared with the positive controls, ibuprofen and acetylsalicylic acid.

Conclusion

In summary, regioselectively 1,4-disubstituted *N*-β-D-glucopyranosyl-1,2,3-triazoles **3a-g** were synthesized under ultrasound irradiation in moderate to excellent yields of 63 to 99% at short reaction time of 20-30 min using catalytic amounts of CuI and Et_3N at room temperature. The compounds containing the benzoheterocyclic moieties showed moderate to good acute anti-inflammatory activity. The current results demonstrate that these glycoconjugates represent a promising starting point for further design of potential anti-inflammatory drugs.

Experimental

All organic solvents were analytical grade (Vetec, Brazil). All reactions were monitored by TLC analysis on GF-254 (Merck-Darmstadt, Germany). Reactions were carried out in a USC-1400A Ultracleaner ultrasound cleaning bath with an operating frequency of 40 kHz. Column chromatography was performed on Merck silica gel 60 (Darmstadt, Germany). Melting points were determined in a PFM II BioSan apparatus and are uncorrected. Optical rotations were measured in a Krüss Model P1000 polarimeter. ^1H (300 or 400 MHz), ^{13}C NMR (75 or 100 MHz), COSY, NOESY and NOE-DIFF spectra were obtained with Varian Unity Plus spectrometers in $CDCl_3$ or DMSO-d_6. Elemental analysis were carried out in a CA EA1110 CHNS-O analyzer, and HRMS analysis were recorded with a Shimadzu Liquid Chrom MS LCMS-IT-TOF using acetonitrile or methanol as the solvent. IR spectra were recorded on a IFS66 Bruker spectrophotometer using KBr discs.

Acute anti-inflammatory activity

Bio-activity tests were performed by the following procedure of Winter *et al.*,[38] on groups of 10 Swiss white mice. The acute anti-inflammatory activity used 250 mg kg^{-1} of the compounds which had been evaluated by the carrageenan-induced paw edema method. The control group received 1% carboxymethylcellulose. Two positive and negative anti-inflammatory tests were performed on three animal groups by oral administration of aspirin, ibuprofen and aqueous saline solution, respectively. The results for the compounds are expressed as mean ± standard deviation using the paired student-*t* test. In all cases, $p < 0.001$ was used as the criterion for statistical significance.

Supplementary Information

Supplementary information (spectral data and figures containing IR, ^1H and ^{13}C NMR) are available free of charge at http://jbcs.sbq.org.br as a PDF file.

Acknowledgements

The authors are grateful to FACEPE (PPP-0776.1.06/08), FACEPE-PRONEM (1232.1.06/10) and INCT_if for financial support. Our thanks are also to Analytical Centers CENAPESQ-UFRPE for facilities installation and DQF-UFPE for obtaining the spectral data. We also thank Professor Patrick Rollin (ICOA-Université d'Orleans) for his kind suggestions.

References

1. Mason, T. J.; Lorimer, J. P.; *Applied Sonochemistry: Uses of Power Ultrasound in Chemistry and Processing*; Wiley-VCH Verlag GmbH: Weinheim, Germany, 2002.
2. Barros, C. J. P.; de Freitas, J. J. R.; de Oliveira, R. N.; de Freitas Filho, J. R.; *J. Chil. Chem. Soc.* **2011**, *56*, 721; Duarte, A.; Cunico, W.; Pereira, C. M. P.; Flores, A. F. C.; Freitag, R. A.; *Ultrason. Sonochem.* **2010**, *17*, 281; Lepore, S. D.; He, Y.; *J. Org. Chem.* **2003**, *68*, 8261; Li, J.-T.; Meng, X.-T.; Zhai, X.-L.; *Ultrason. Sonochem.* **2009**, *16*, 590.
3. Cella, R.; Stefani, H. A.; *Tetrahedron* **2009**, *65,* 2619.
4. Kardos, N.; Luche, J.-L.; *Carbohydr. Res.* **2001**, *332*, 115.
5. Neves Filho, R. A. W.; de Oliveira, R. N.; *Application of Ultrasound Irradiation in Carbohydrate Synthesis*; Org. Chem. Highlights 2009, July 25, http://www.organic-chemistry.org/Highlights/2009/25July.shtm, accessed in November 2012.
6. Wang, P. G.; Bertozzi, C. R.; *Glycochemistry: Principles, Synthesis, and Applications*; Marcel Dekker, Inc.: New York, USA, 2001.
7. Le, G. T.; Abbenante, G.; Becker, B.; Grathwohl, M.; Halliday, J.; Tometzki, G.; Zuegg, J.; Meutermans, W.; *Drug Discovery Today* **2003**, *8*, 701.
8. Goyard, D.; Baron, M.; Skourti, P. V.; Chajistamatiou, A. S.; Docsa, T.; Gergely, P.; Chrysina, E. D.; Praly, J.-P.; Vidal, S.; *Carbohydr. Res.* **2012**, *364*, 28; Anand, N.; Jaiswal, N.; Pandey, S. K.; Srivastava, A. K.; Tripathi, R. P.; *Carbohydr. Res.* **2011**, *346*, 16.
9. Hager, C.; Miethchen, R.; Reinke, H.; *J. Fluorine Chem.* **2000**, *104*, 135.
10. da Silva, F. C.; Cecília, M. B. V. S.; Frugulhetti, I. I. P.; Castro, H. C.; Souza, S. L. O.; Souza, T. M. L.; Rodrigues, D. I. Q.; Souza, A. M. T.; Abreu, P. A.; Passamani, F.; Rodrigues, C. R.; Ferreira, V. F.; *Eur. J. Med. Chem.* **2009**, *44*, 373.
11. Kumar, K. K.; Seenivasan, S. P.; Kumar, V.; Das, T. M.; *Carbohydr. Res.* **2011**, *346* 2084.
12. Assis, S. P. O.; da Silva, M. T.; de Oliveira, R. N.; Lima, V. L. M.; *The Scientific World Journal* **2012**, ID 925925, DOI: 10.1100/2012/925925; El-Gazzar, A.-R. B. A.; Hafez, H. N.; Abbas, H.-A. S.; *Eur. J. Med. Chem.* **2009**, *44*, 4249.
13. Goyard, D.; Praly, J.-P.; Vidal, S.; *Carbohydr. Res.* **2012**, *362*, 79; Hradilová, L.; Polákova, M.; Dvořáková, B.; Hajdúch, M.; Petruš, L.; *Carbohydr. Res.* **2012**, *361*, 1; Dedola, S.; Hughes, D. L.; Nepogodiev, S. A.; Rejzek, M.; Field, R. A.; *Carbohydr. Res.* **2010**, *345*, 1123; Kumar, R.; Maulik, P. R.; Misra, A. K.; *Glycoconjugate J.* **2008**, *25*, 595; Dedola, S.; Nepogodiev, S. A.; Field, R. A.; *Org. Biomol. Chem.* **2007**, *5*, 1006; de Oliveira, R. N.; Sinou, D.; Srivastava, R. M.; *Synthesis* **2006**, 467.
14. Deng, S.; Gangadharmath, U.; Chang, C.-W. T.; *J. Org. Chem.* **2006**, *71*, 5179; Parvathy, K. S.; Srinivas, P.; *Ultrason. Sonochem.* **2008**, 15, 571.
15. For reviews click chemistry combined with ultrasound, see: da Silva, M. T.; de Oliveira, R. N.; Valença, W. O.; Barbosa, F. C. G.; da Silva, M. G.; Camara, C. A.; *J. Braz. Chem. Soc.* **2012**, *23*, 1839; Sreedhar, B.; Reddy, P. S.; *Synth. Commun.* **2007**, *37*, 805; Cintas, P.; Palmisano, G.; Cravotto, G.; *Ultrason. Sonochem.* **2011**, *18*, 836; Jiang, Y.; Chen, X.; Qu, L.; Wang, J.; Yuan, J.; Chen, S.; Li, X.; Qu, C.; *Ultrason. Sonochem.* **2011**, *18*, 527; Cravotto, G.; Fokin, V. V.; Garella, D.; Binello, A.; Boffa, L.; Barge, A.; *J. Comb. Chem.* **2010**, *12*, 13; Dondoni, A.; *Chem. Asian J.* **2007**, *2*, 700; Santoyo-Gonzalez, F.; Hernandez-Mateo, F.; *Chem. Soc. Rev.* **2009**, *38*, 3449; Aragão-Leoneti, V.; Campo, V. L.; Gomes, A. S.; Field, R. A.; Carvalho, I.; *Tetrahedron* **2010**, *66*, 9475; Dondoni, A.; *Org. Biomol. Chem.* **2010**, *8*, 3366.
16. Stefani, H. A.; Silva, N. C. S.; Manarin, F.; Lüdtke, D. S.; Zukerman-Schpector, J.; Madureira, L. S.; Tiekink, E. R. T. *Tetrahedron Lett.* **2012**, *53*, 1742; Driowya, M.; Puissant, A.; Robert, G.; Auberger, P.; Benhida, R.; Bougrin, K.; *Ultrason. Sonochem.* **2012**, *19*, 1132.
17. Nascimento, W. S.; Camara, C. A.; de Oliveira, R. N.; Synthesis **2011**, *20,* 3220; Barbosa, F. C. G.; de Oliveira, R. N.; *J. Braz. Chem. Soc.* **2011**, *22*, 592.
18. da Silva Jr., E. N.; de Melo, I. M. M.; Diogo, E. B. T.; Costa, V. A.; de Souza Filho, J. D.; Valença, W. O.; Camara, C. A.; de Oliveira, R. N.; Araújo, A. S.; Emery, F. S.; Santos, M. R.; Simone, C. A.; Menna-Barreto, R. F. S.; Castro, S. L.; *Eur. J. Med. Chem.* **2012**, *52,* 304.
19. Mukhopadhyay, B.; Kartha, K. P.; Russel, D.A.; Field, R. A.; *J. Org. Chem.* **2004**, *69*, 7758.
20. Misra, A. K.; Tiwari, P.; Kamlesh, S.; Madhusudan, S. K.; *Carbohydr. Res.* **2005**, *340*, 325.
21. Butera, A. P.; de Souza Filho, J. D.; Carvalho, D. T.; Figueiredo, R. C.; de Faria, L. C. A.; Nunes, M. A.; Prado, M. A. F.; Alves, R. J.; de Andrade, M. H. G.; Silva, K. T. S.; *Quim. Nova* **2007,** *30*, 1267; Sureshbabu, V. V.; Venkataramanarao, R.; Hemantha, H. P.; *Int. J. Pept. Res. Ther.* **2008**, *14*, 34.
22. de Oliveira, R. N.; Mendonça Jr., F. J. B.; Sinou, D.; de Melo, S. J.; Srivastava, R. M.; *Synlett* **2006**, 3049; de Oliveira, R. N.; do Nascimento, W. S.; da Silva, G. R.; Silva, T. M. S.; *Orbital Elec. J. Chem.* **2012**, *4*, 118.
23. Asano, K.; Matsubara, S.; *Heterocycles* **2010**, *80*, 989.

24. Bognar, B.; Kalai, T.; Hideg, K.; *Synthesis* **2008**, *15*, 2439.
25. Ueno, Y.; Okawara, M.; *J. Am. Chem. Soc.*, **1979**, *101*, 1893.
26. Sasaki, T.; Shimizu, I.; *Heterocycles* **1984**, *22*, 1225.
27. Ray, S.; Ghosh, S.; Ganguly, N.; *Synth. Commun.* **2006**, *36*, 1447.
28. Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B.; *Angew. Chem., Int. Ed.* **2002**, *41*, 2596.
29. Meldal, M.; Tornøe, C. W.; *Chem. Rev.* **2008**, *108*, 2952; Himo, F.; Lovell, T.; Hilgraf, R.; Rostvtsev, V. V.; Noodleman, L.; Sharpless, K. B.; Folkin, V. V.; *J. Am. Chem. Soc.* **2005**, *127*, 210.
30. Thompson, L. H.; Doraiswamy, L. K.; *Ind. Eng. Chem. Res.* **1999**, *38*, 1215.
31. Kumar, R.; Maulik, P. R.; Misra, A. K.; *Glycoconjugate J.* **2008**, *25*, 595.
32. Sirion, U.; Lee, J. H.; Bae, Y. J.; Kim, H. J.; Lee, B. S.; Chi, D. Y.; *Bull. Korean Chem. Soc.* **2010**, *31*, 1843.
33. El Moncef, A.; El Hadrami, E. M.; Ben-Tama, A.; de Arellano, C. R.; Zaballos-Garcia, E.; Stiriba, S.-E.; *J. Mol. Struct.* **2009**, *929*, 6.
34. dos Anjos, J. V. ; Neves Filho, R. A. W.; Nascimento, S. C.; Srivastava, R.M.; de Melo, S. J.; Sinou, D.; *Eur. J. Med. Chem.* **2009**, *44*, 3571.
35. Testoni, F. M.; Ribeiro, E. A.; Giusti, L. A.; Machado, V. G.; *Spectrochim. Acta, Part A* **2009**, *71*, 1704.
36. Horne, W. S.; Yadav, M. K.; Stout, C. D.; Ghadiri, M. R.; *J. Am. Chem. Soc.* **2004**, *126*, 15366.
37. Shafi, S.; Alam, M. M.; Mulakayala, N.; Mulakayala, C.; Vanaja, G.; Kalle, A. M.; Pallu, R.; Alam, M. S.; *Eur. J. Med. Chem.* **2012**, *49*, 324.
38. Winter, C. A.; Risley, E. A.; Nuss, G. W.; *Proc. Soc. Exp. Biol. Med.* **1962**, *111*, 544.

Submitted: December 5, 2012
Published online: May 21, 2013