Carbohydrate Research 355 (2012) 79–86

Contents lists available at SciVerse ScienceDirect

Carbohydrate Research

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

Note

Synthesis of imidazo[2,1-*b*]thiazoles linked to an unprotected carbohydrate moiety

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ARTICLE INFO

Article history:
Received 25 February 2012
Received in revised form 10 April 2012
Accepted 12 April 2012
Available online 21 April 2012

Keywords:
Heterocycles
Carbohydrates
Protective groups
Imidazo[2,1-*b*]thiazoles

ABSTRACT

Two series of imidazo[2,1-*b*]thiazoles substituted on C-3 or C-5 with an unprotected carbohydrate moiety were synthesized. Different protective groups for position 3 of the carbohydrate moiety were tested (acetyl, *tert*-butyldimethylsilyl (TBDMS), and *p*-methoxybenzyl (PMB)) and the latter turn out to be the best strategy to obtain the desired products. Full deprotection of the carbohydrate was performed successfully in only one step.

Recently much interest has been focused on the chemistry and the biological activity of imidazo[2,1-*b*]thiazoles and their derivatives. Compounds containing this heterocycle in their structure have been reported as antihelmintic,[1] antiviral,[2] anti-hypertensives,[3] antiinflammatories,[4,5] fungicides,[6] herbicides,[7] antitumor,[8–13] and cardiotonic agents.[14] The broad spectrum of biological activities of imidazo[2,1-*b*]thiazoles, turn this heterocyclic nuclei in an interesting synthetic target for biological studies.[15]

Moreover, the attraction of including asymmetric centers in compounds when their biological activity is a focus of interest is also known. In that context, carbohydrates are especially attractive. They have many asymmetric carbons and depending on their protective group the hydrophilicity or lipophilicity of the final compounds can be easily controlled.

Taking into account the above discussion, in previous works we reported the synthesis and antiviral evaluation against the etiological agent of Argentine hemorrhagic fever (Junin virus (JUNV)), of two series of imidazo[2,1-*b*]thiazoles,[16,17] linked to a sugar residue.

Both series differed in the position of the heterocyclic ring substituent. Series 1 had the carbohydrate residue bonded to C-5 while in the series 2 the sugar was bonded to C-3 of the heterocyclic moiety (Fig. 1).

Argentine hemorrhagic fever is an important disease recognized as a major public health problem in the richest agriculture zones of our country.[18] We found that two of the investigated compounds (**2** and **3**), had an inhibitory activity against JUNV one order higher than ribavirin, the reference substance for this study. These results encourage us to extend the study of imidazo[2,1-*b*]thiazoles. Taking into account that the highest antiviral activity was detected when the phenyl group was *p*-substituted with either bromine or chloride,[17] the synthetic targets of the present work were their unprotected sugar analogous, for further analysis of the impact of this structural change in their antiviral activity.

The main challenge of this work was to find a suitable protective group for position 3 of the carbohydrate. Therefore, different protected groups were evaluated to achieve that goal.

Our selected approach to obtain the target compounds was based on the synthesis of a suitable 6-bromo-6-deoxy-1,2-*O*-isopropylidene-3-O-protected-α-D-*xylo*-hexofuranos-5-ulose using as the precursor 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (Scheme 1).[19–25] After testing different protective groups, the acetyl, the *tert*-butyldimethylsilyl (TBDMS), and the *p*-methoxybenzyl (PMB) group were selected for further transformation. Derivates **20**, **21**, **23** and **24**, are described here for the first time and were fully characterized by physical and spectroscopic techniques. Besides, since bibliographic data of the isopropylidene derivates **14** and **17** were incomplete, their spectroscopic characterization was also included in this paper (see Section 1).

Substituted imidazo[2,1-*b*]thiazoles were obtained by convergent synthetic pathways (Schemes 2 and 3).[26] Heterocycles **25**–**28** (series 1), were achieved by coupling one of the 6-bromo-6-deoxy-1,2-*O*-isopropylidene-3-O-protected-α-D-*xylo*-hexofuranos-5-ulose (**22**–**24**) with *N*′-(5-arylthiazol-2-yl)-*N*,*N*-dimethylimidoformamide (Scheme 2).[17,27] Reactions were not complete and starting

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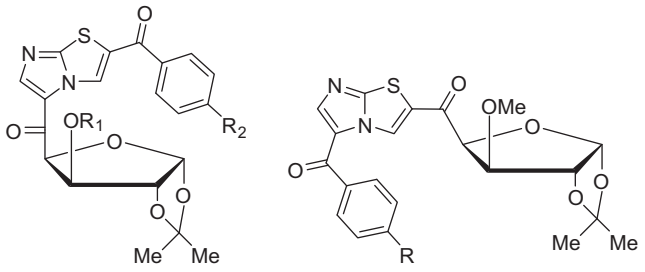
http://dx.doi.org/10.1016/j.carres.2012.04.011



Series 1

1. R1= CH3; R2= H
2. R1= CH3; R2= Br
3. R1= CH3; R2= Cl
4. R1= CH3; R2= F
5. R1= COCH3; R2= H
6. R1= COCH3; R2= Br
7. R1= COCH3; R2= Cl
8. R1= COCH3; R2= F

Series 2

9. R= H
10. R= Br
11. R= Cl
12. R= F

Figure 1. Substituted imidazo[2,1-*b*]thiazoles.

materials were detected in all of the cases. Higher yields of the PMB with respect to the TBDMS derivates could be attributed to the higher steric hindrance of the latter protective group.

Complete mechanism of the transformation was described by Landreau et al.,[27] but in our case the N-alkylation step was assisted by microwave radiation.

Imidazo[2,1-*b*]thiazoles belonging to series 2 were synthesized by coupling the thiazolylimidoformamides **29**–**31** with the commercially available 2-bromo-1-(4-chlorophenyl)ethanone or 2-bromo-1-(4-bromophenyl)ethanone (Scheme 3).

Although the methodology to synthesize the thiazolylimidoformamides **29**–**31** was previously reported,[17] particularly these derivates had not been published before and they were fully characterized here (see Section 1).

Even the synthetic strategy employed in this work allow us to obtain all the protected heterocyclic compounds belonging to series 1, in the case of series 2, the 3-O-acetylated sugar derivates could not be obtained (Scheme 3). During the coupling step of the thiazolylimidoformamides **29** with the corresponding *p*-halobenzoyl group, an elimination reaction occurred and, instead of the desired product, the dehydrated derivates **36** and **37** were obtained (Scheme 4).

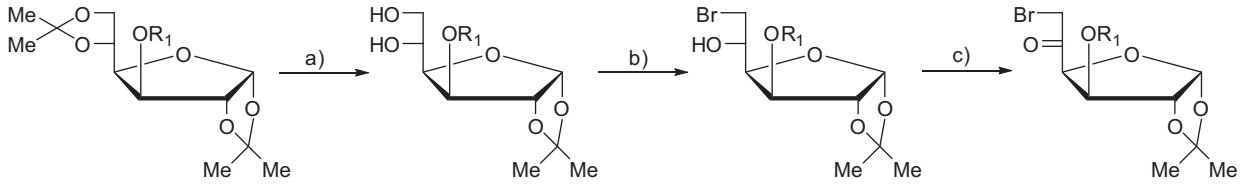
On the other hand, although the heterocycles belonging to both series could be obtained from the TBDMS or PMB derivates, in the case of TBDMS derivates, deprotection strategies failed, since many secondary products were obtained becoming the purification of the unprotected sugar derivate very difficult.

Deprotection of the PMB derivates was achieved by treatment with trifluoracetic acid (TFA) in dichloromethane (CH_2Cl_2) overnight (Scheme 5). In these conditions the isopropylidene group was also removed[28,29] affording compounds **38–41** as a mixture of the α and β anomers (50:50), as it was determined by ^1H NMR (see Section 1).

The one-pot deprotection reaction described here, allowed us to obtain the final product with moderate yield.

The new compounds were completely characterized by physical and spectroscopic methods as shown in Section 1.

In summary, in this work the synthesis and characterization of 21 new compounds is reported and the goal of obtaining imidazo[2,1-*b*]thiazoles linked to an unprotected carbohydrate residue was achieved.



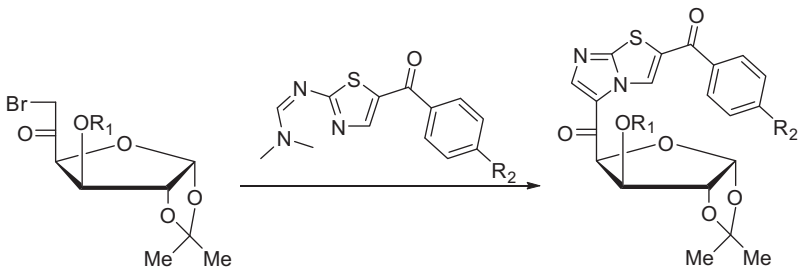
13.[16] R_1= Ac
14. R_1= TBDMS, 91%
15. R_1= PMB, 95%

16.[16] R_1= Ac
17. R_1= TBDMS, 21.2%
18. R_1= PMB, 95%

19.[16] R_1= Ac
20. R_1= TBDMS, 55.4%
21. R_1= PMB, 87.4%

22.[16] R_1= Ac
23. R_1= TBDMS, 99.3%
24. R_1= PMB, 82.5%

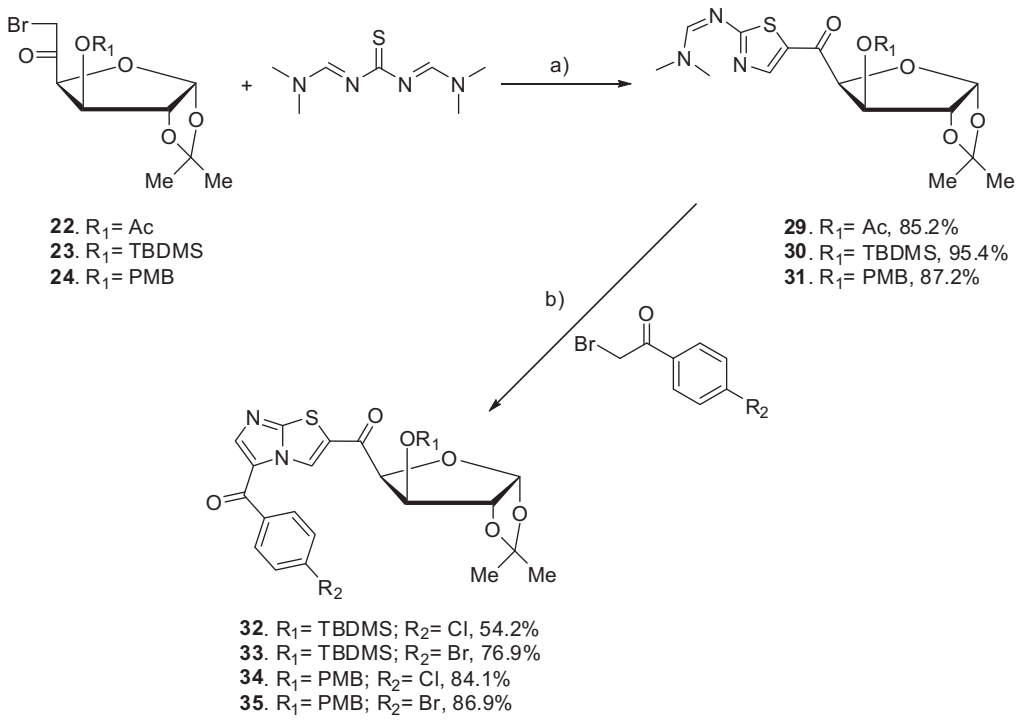
Scheme 1. Reagents and conditions: (a) **14**–**17**: $FeCl_3$ supported on Silicagel/$CHCl_3$ 48 h, **15**–**18**: H_2SO_4 (0.8%)/MeOH (1:1), 24 h; (b) (i) NBS, PPh_3, DMF, 8 h, (ii) MeOH 14 h; (c) IBX, CH_3CN reflux.



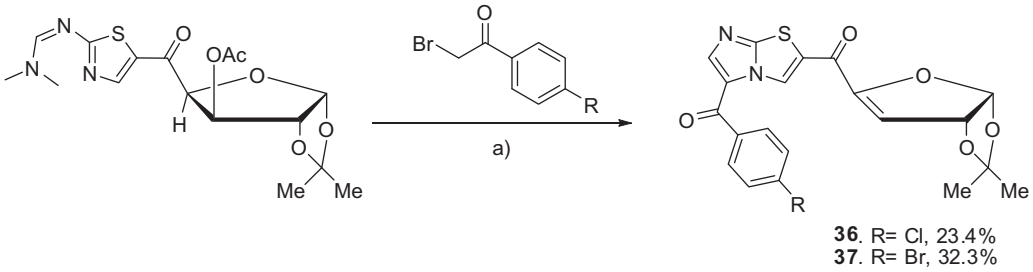
22. R_1= Ac
23. R_1= TBDMS
24. R_1= PMB

6.[16] R_1= Ac; R_2= Cl
7.[16] R_1= Ac; R_2= Br
25. R_1= TBDMS; R_2= Cl, 25.4%
26. R_1= TBDMS; R_2= Br, 16.4%
27. R_1= PMB; R_2= Cl, 47.7%
28. R_1= PMB; R_2= Br, 43.1%

Scheme 2. Reagents and conditions: (a) (i) THF (anhyd), MW (300 W, 105 °C, 150 min), (ii) Et_3N, rt, 16 h.



Scheme 3. Reagents and conditions: (a) (i) CH_2Cl_2 reflux, 3 h; (ii) Et_3N (1.5 equiv) rt, 12 h; (b) (i) THF (anhyd), MW (300 W, 100 °C, 90 min); (ii) Et_3N (1.5 equiv) rt, 16 h.



Scheme 4. Reagents and conditions: (a) (i) THF (anhyd), MW (300 W, 100 °C, 90 min); (ii) Et_3N (1.5 equiv) rt, 16 h.

Moreover, the deprotection of both a PMB and an isopropylidene group belonging to a sugar residue in a one-pot reaction was reported .

We are working now to extend the methodology described here to the synthesis of pirrolo[2,1-*b*]thiazoles in order to evaluate the impact of this change in the antiviral activity.

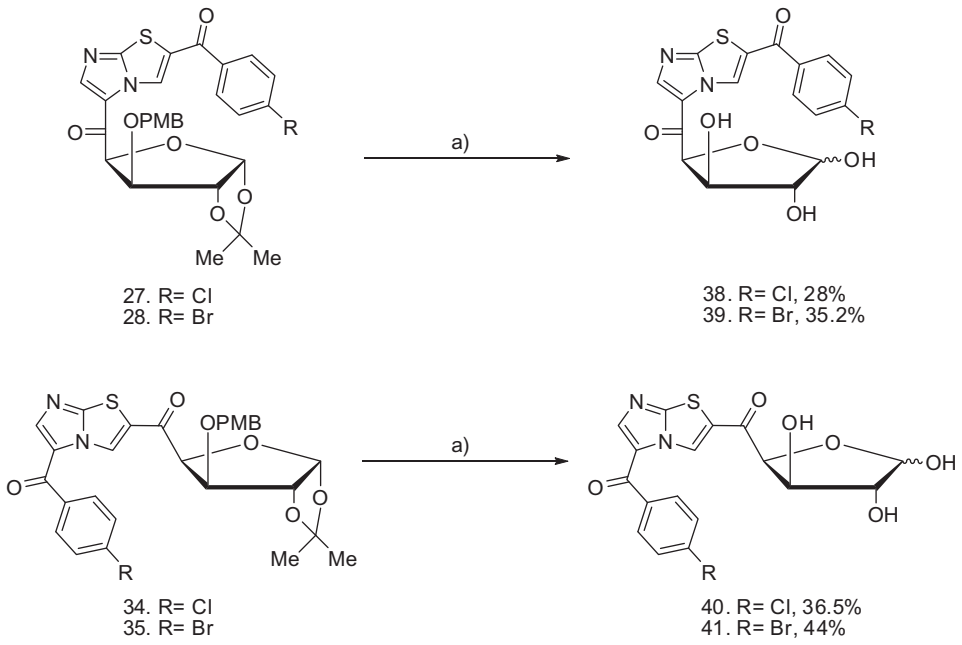
1. Experimental

1.1. General remarks

Syntheses were carried out using reagents as purchased, without further purification. Solvents were reagent grade and, in most cases, dried and distillated before use according to standard procedures. Analytical TLC was conducted on Silica Gel 60G (Merck) on precoated plates and visualization was made by UV light and ethanol/sulfuric acid (10:1) or cerium molybdate followed by heating. Column-chromatographic separations were performed on Silica Gel (240–400 mesh, Merck). Microwave reactions were carried out using an Anton-Paar Monowave 300 microwave reactor. Elemental analysis was performed on an Exeter Analytical CE-440 elemental analyzer. Optical rotations were recorded at 20 °C on a Perkin Elmer 343 polarimeter, and melting points were uncorrected. NMR spectra were recorded on either a Bruker AC-200 or a Bruker AMX-500 spectrometer. Assignments of the ^1H and ^{13}C NMR spectra were confirmed with the aid of two dimensional techniques (COSY, HSQC-DEPT, HMBC). Chemical shifts (δ) are reported in parts per million downfield from tetramethyl silane or solvent residual peak as internal standard. High-resolution mass spectra (HRMS) were obtained on a Bruker micrOTOF-Q II spectrometer using Electrospray Ionization (ESI) and a Q-TOF analyzer. Compounds **6**, **7**, **13**, **16**, **19**, and **22** were synthesized as we previously described,[16] meanwhile **15** and **18** were synthesized and spectroscopical characterized (^1H and ^{13}C NMR spectra) as described in literature.[17]

1.2. 3-*O*-(*tert*-Buthyldimethylsilyl)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (14)

1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose was obtained as described by Schmidt and col.[19] Silylation was carried out from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (758 mg, 2.99 mmol) using the procedure described by Corey and col.[20] affording compound **14** as colorless syrup (986 mg, 2.63 mmol, 91% yield). ^1H NMR (200 MHz, $CDCl_3$) δ: 5.87 (d, 1H, $J_{1,2}$ 3.6 Hz, H-1), 4.35 (br d,



Scheme 5. Reagents and conditions: (a) TFA 60% in CH_2Cl_2 (anhyd) rt 24 h.

1H, $J_{2,1}$ 3.6 Hz, H-2), 4.24 (d, 1H, $J_{3,4}$ 2.8 Hz, H-3), 4.22 (dt, 1H, $J_{5,4}$ 7.9 Hz, $J_{5,6a}$ 5.9 Hz, $J_{5,6b}$ 5.6 Hz, H-5), 4.11 (dd, 1H, $J_{6a,5}$ 6.0 Hz, $J_{6a,6b}$ 8.3 Hz, H-6a), 4.02 (dd, 1H, $J_{4,3}$ 2.7 Hz, $J_{4,5}$ 8.1 Hz, H-4), 3.95 (dd, 1H, $J_{6b,5}$ 5.9 Hz, $J_{6b,6a}$ 8.3 Hz, H-6b), 1.49 (s, 3H, CMe_2), 1.40 (s, 3H, CMe_2), 1.32 (s, 3H, CMe_2), 1.31 (s, 3H, CMe_2), 0.90 (s, 9H, CMe_3Si), 0.13 (s, 3H, *Me*Si), 0.12 (s, 3H, *Me*Si). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 111.8 (*C* Me_2), 108.9 (*C* Me_2), 105.3 (C-1), 85.6 (C-2), 82.3 (C-4), 75.5 (C-3), 72.2 (C-5), 67.7 (C-6), 27.0 (CMe_2), 26.8 (CMe_2), 26.4 (CMe_3Si), 25.7 (CMe_2), 25.3 (CMe_2), 18.1 (*C*Me_3Si), −5.0 (*Me*Si), −5.2 (*Me*Si).

1.3. 3-*O*-(*tert*-Buthyldimethylsilyl)-1,2-*O*-isopropylidene-α-D-glucofuranose (17)

Deprotection of 3-*O*-(*tert*-buthyldimethylsilyl)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (850 mg, 2.27 mmol) was carried out following the procedure described by Kim and col.[22] Compound **17** was afforded as a white solid (313 mg, 0.93 mmol, after two deprotection steps, 41.2% yield). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 5.89 (d, 1H, $J_{1,2}$ 3.7 Hz, H-1), 4.37 (d, 1H, $J_{2,1}$ 3.7 Hz, H-2), 4.32 (d, 1H, $J_{3,4}$ 2.6 Hz, H-3), 4.08 (dd, 1H, $J_{4,3}$ 2.7 Hz, $J_{4,5}$ 7.9 Hz, H-4), 3.93 (ddd, 1H, $J_{5,4}$ 8.1 Hz, $J_{5,6a}$ 5.1 Hz, $J_{5,6b}$ 3.3 Hz, H-5), 3.84 (dd, 1H, $J_{6a,5}$ 3.3 Hz, $J_{6a,6b}$ 11.4 Hz, H-6a), 3.76 (dd, 1H, $J_{6b,5}$ 5.1 Hz, $J_{6b,6a}$ 11.4 Hz, H-6b), 1.49 (s, 3H, CMe_2), 1.32 (s, 3H, CMe_2), 0.91 (s, 9H, CMe_3Si), 0.16 (s, 3H, *Me*Si); 0.14 (s, 3H, *Me*Si). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 111.8 (*C* Me_2), 105.0 (C-1), 85.3 (C-2), 80.9 (C-4), 75.9 (C-3), 68.9 (C-5), 64.6 (C-6), 26.9 (CMe_2), 26.3 (CMe_2), 25.7 (CMe_3Si), 18.0 (*C*Me_3Si), −4.7 (C*Me*Si), −5.0 (C*Me*Si).

1.4. 6-Bromo-6-deoxy-1,2-*O*-isopropylidene-3-*O*-(*tert*-buthyldimethylsilyl)-α-D-glucofuranose (20)

NBS (208 mg, 1.17 mmol) in dry DMF (5 mL) was added dropwise to a cooled (ice bath) solution of compound **17** (196 mg, 0.59 mmol) and triphenylphosphine (306 mg, 1.17 mmol) in dry DMF (15 mL) under argon atmosphere.[16,23] The mixture was stirred for 3.5 h at room temperature and quenched by addition of MeOH. The solvent was evaporated and the residue extracted with CH_2Cl_2 and dried (Na_2SO_4). The crude product was purified by column chromatography on silica gel using mixtures of cyclohexane/acetone (90:10–75:25) as eluents. The 6-bromo derivative (**20**) was afforded as pallid yellow oil (124 mg, 0.312 mmol, 55.4% yield); $[\alpha]_D^{25}$ −19.5 (*c* 2.8, chloroform). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 5.87 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 4.36 (dd, 1H, $J_{2,1}$ 3.5 Hz, $J_{2,3}$ 0.5 Hz, H-2), 4.33 (dd, 1H, $J_{3,2}$ 0.5 Hz, $J_{3,4}$ 2.5 Hz, H-3), 4.07 (dd, 1H, $J_{4,3}$ 2.5 Hz, $J_{4,5}$ 8.4 Hz, H-4), 3.92–4.09 (ddd, 1H, $J_{5,4}$ 8.6 Hz, $J_{5,6a}$ 5.9 Hz; $J_{5,6b}$ 2.7 Hz, H-5), 3.78 (dd, 1H, $J_{6a,5}$ 2.7 Hz, $J_{6a,6b}$ 10.5 Hz, H-6a), 3.65 (dd, 1H, $J_{6b,5}$ 6.0 Hz, $J_{6b,6a}$ 10.5 Hz, H-6b), 2.20 (broad signal, *HO*), 1.49 (s, 3H, CMe_2), 1.33 (s, 3H, CMe_2), 0.91 (s, 9H, CMe_3Si), 0.16 (s, 3H, *Me*Si); 0.14 (s, 3H, *Me*Si). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 112.1 (*C* Me_2), 105.1 (C-1), 85.4 (C-2), 81.5 (C-4), 75.4 (C-3), 67.8 (C-5), 39.5 (C-6), 27.0 (CMe_2), 26.5 (CMe_2), 25.0 (CMe_3Si), 18.1 (*C*Me_3Si), −4.8 (*Me*Si), −5.1 (*Me*Si). Anal. Calcd for $C_{15}H_{29}BrO_5Si$: C, 45.34; H, 7.36. Found: C, 45.35; H, 7.75.

1.5. 6-Bromo-6-deoxy-1,2-*O*-isopropylidene-3-*O*-(*p*-methoxybenzyl)-α-D-glucofuranose (21)

NBS (400.8 mg, 2.65 mmol) in DMF (5 mL) was added dropwise to a stirred cooled (ice bath) solution of triphenylphosphine (693.9 mg, 2.65 mmol) and compound **18** (455 mg, 1.32 mmol) in dry DMF (15 mL) under argon atmosphere. Compound **21** was obtained by the same procedure applied for compound **20**, as colorless oil (466.4 mg, 1.15 mmol, 87.4% yield); $[\alpha]_D^{25}$ −39.6 (*c* 1.5, chloroform). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.28 (d, 2H, *J* 8.8 Hz, aromatic protons), 6.90 (d, 2H, *J* 8.8 Hz, aromatic protons), 5.92 (d, 1H, $J_{1,2}$ 3.7 Hz, H-1), 4.67 (d, 1H, *J* 14.4 Hz, methylene proton), 4.61 (d, 1H, $J_{2,1}$ 3.8 Hz, H-2), 4.49 (d, 1H, *J* 14.4 Hz, methylene proton), 4.04–4.17 (m, 3H, H-3, H-4, H-5), 3.81 (s, 3H, O*Me*), 3.71 (dd, 1H, $J_{6a,5}$ 2.7 Hz, $J_{6a,6b}$ 10.7 Hz, H-6a), 3.57 (dd, 1H, $J_{6b,5}$ 5.4 Hz, $J_{6b,6a}$ 10.4 Hz, H-6b), 2.20 (broad signal, *HO*), 1.49 (s, 3H, CMe_2), 1.32 (s, 3H, CMe_2). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 159.6, 129.6, 129.1, 114.1 (aromatic carbons), 112.1 (*C* Me_2), 105.2 (C-1), 82.3 (C-4), 81.0 (C-2), 80.7 (C-3), 72.0 (methylene carbon), 67.2 (C-5), 55.3 (*C*H_3O), 38.0 (C-6), 26.9 (CMe_2), 26.4 (CMe_2). Anal. Calcd for $C_{17}H_{23}BrO_6$: C, 50.63; H, 5.75. Found: C, 50.55; H, 5.71.

1.6. 6-Bromo-6-deoxy-1,2-*O*-isopropylidene-3-*O*-(*tert*-buthyldimethylsilyl)-α-D-*xylo*-hexofuranos-5-ulose (23)

1-Hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide (IBX) (370,8 mg, 1.32 mmol) was added to a solution of **20** (105.2 mg, 0.26 mmol) in acetonitrile (15 mL) and the mixture was refluxed for 2.5 h. The reaction mixture was filtered to remove the excess of IBX and the solution evaporated. The residue was purified by column chromatography on silica gel using mixtures of cyclohexane/acetone (95:5–80:20) as eluents. Compound **23** was afforded as a white solid (104 mg, 0.26 mmol, 99.3% yield): mp: 53–54 °C; $[\alpha]_D^{25}$ −125.3 (*c* 1.1, chloroform). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 6.07 (d, 1H, $J_{1,2}$ 3.4 Hz, H-1), 4.76 (d, 1H, $J_{2,1}$ 3.2 Hz, H-2), 4.50 (d, 1H, $J_{3,4}$ 3.2 Hz, H-3), 4.44 (d, 1H, $J_{6a,6b}$ 16.4 Hz, H-6a), 4.38 (d, 1H, $J_{4,3}$ 3.5 Hz, H-4), 4.26 (d, 1H, $J_{6b,6a}$ 16.4 Hz, H-6b), 1.47 (s, 3H, C*Me*$_2$), 1.33 (s, 3H, C*Me*$_2$), 0.85 (s, 9H, C*Me*$_3$Si), 0.10 (s, 3H, *Me*Si); 0.03 (s, 3H, *Me*Si). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 199.4 (C=O), 112.8 (*C*Me$_2$), 106.1 (C-1), 86.0 (C-4), 84.7 (C-2), 78.0 (C-3), 36.9 (C-6), 27.1 (C*Me*$_2$), 26.5 (C*Me*$_2$), 25.6 (C*Me*$_3$Si), 17.8 (*C*Me$_3$Si), −5.1 (*Me*Si), −5.1 (*Me*Si). Anal. Calcd for $C_{15}H_{27}BrO_5Si$: C, 45.57; H, 6.88. Found: C, 45.72; H, 6.99.

1.7. 6-Bromo-6-deoxy-1,2-*O*-isopropylidene-3-*O*-(*p*-methoxybenzyl)-α-D-*xylo*-hexofuranos-5-ulose (24)

Compound **24** was obtained from compound **21** (445.3 mg, 1.10 mmol) by the same procedure applied for compound **23**, but, in this case, 4 h of reflux were needed to achieve the product as white crystals (440.1 mg, 1.09 mmol, 82.5% yield): mp: 88–89 °C; $[\alpha]_D^{25}$ −95.9 (*c* 1.4, chloroform). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.15 (d, 2H, *J* 8.8 Hz, aromatic protons), 6.87 (d, 2H, *J* 8.6 Hz, aromatic protons), 6.06 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 4.82 (d, 1H, $J_{2,1}$ 3.7 Hz, H-2), 4.59 (d, 1H, *J* 3.6 Hz, H-3), 4.51 (d, 1H, *J* 11.3 Hz, methylene proton), 4.39 (d, 1H, *J* 11.3 Hz, methylene proton), 4.36 (d, 1H, $J_{6a,6b}$ 15.9 Hz, H-6a), 4.29 (d, 1 H, $J_{4,3}$ 3.6 Hz, H-4), 4.25 (d, 1H, $J_{6b,6a}$ 15.9 Hz, H-6b), 3.80 (s, 3H, O*Me*), 1.47 (s, 3H, C*Me*$_2$), 1.33 (s, 3H, C*Me*$_2$). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 199.0 (C=O), 159.6, 129.6, 128.5, 114.0 (aromatic carbons), 112.7 (*C*Me$_2$), 106.2 (C-1), 84.9 (C-4), 83.3 (C-2), 81.8 (C-3), 72.5 (methylene carbon), 55.3 (*C*H$_3$O), 35.9 (C-6), 27.0 (C*Me*$_2$), 26.4 (C*Me*$_2$). Anal. Calcd for $C_{17}H_{21}BrO_6$: C, 50.89; H, 5.28. Found: C, 50.72; H, 5.09.

1.8. General procedure to synthesize compounds 25–28

Compounds **25**–**28** were obtained by reaction of one of the 3-O-protected sugar derivates **20** or **21** with the corresponding *N*′-[5-(4-halobenzoyl)-1,3-thiazol-2-yl]-*N*,*N*-dimethylimidoformamide in a molar relation of (1:1.5) in anhydrous THF (7 mL) under microwave radiation (300 W, 105 °C, 150 min). A solution of triethylamine (molar relation 1.5:1 amine/sugar) in 15 mL of anhydrous THF was added and the mixture was stirred at room temperature overnight.[17] The crude products were purified by column chromatography on silica gel using mixtures of cyclohexane/acetone (90:10–75:25) as eluents.

1.8.1. 3-(*p*-Chlorobenzoyl)-5-(1,2-*O*-isopropylidene-3-*O*-*tert*-buthyldimethylsilyl-α-D-xylofuranos-5-ulo-5-yl)imidazo[2,1-*b*]thiazole (25)

Compound **25** was obtained from **23** (260.4 mg, 0.66 mmol) and *p*-chlorobenzoyl-thiazolylimidoformamide (293.2 mg, 0.99 mmol) as yellow amorphous solid (141.5 mg, 0.25 mmol, 25.4% yield): mp 77–78 °C; $[\alpha]_D^{25}$ −154.6 (*c* 1.5, chloroform). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 8.88 (s, 1H, imidazo[2,1-*b*]thiazole proton), 8.52 (s, 1H, imidazo[2,1-*b*]thiazole proton), 7.81 (d, 2H, *J* 8.5 Hz, aromatic protons), 7.53 (d, 2H, *J* 8.5 Hz, aromatic protons), 6.20 (d, 1H, $J_{1,2}$ 3.4 Hz, H-1), 5.00 (d, 1H, $J_{4,3}$ 3.1 Hz, H-4), 4.60 (d, 1H, $J_{3,4}$ 3.1 Hz, H-3), 4.42 (d, 1H, $J_{2,1}$ 3.5 Hz, H-2), 1.53 (s, 3H, C*Me*$_2$), 1.37 (s, 3H, C*Me*$_2$), 0.59 (s, 9H, C*Me*$_3$Si), 0.04 (s, 3H, *Me*Si); −0.19 (s, 3H, *Me*Si). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 186.0 (C=O), 185.9 (C=O); 155.9, 147.1, 140.0, 127.8, 127.4 (imidazo[2,1-*b*]thiazole carbons), 140.0, 134.7, 130.3, 127.4 (aromatic carbons), 112.8 (*C*Me$_2$), 106.0 (C-1), 86.3 (C-4), 84.6 (C-2), 78.1 (C-3), 26.9 (C*Me*$_2$), 26.5 (C*Me*$_2$), 25.2 (C*Me*$_3$Si), 17.7 (*C*Me$_3$Si), −4.8 (C*Me*Si), −5.5 (C*Me*Si). Anal. Calcd for $C_{26}H_{31}ClN_2O_6SSi$: C, 55.45; H, 5.55; N, 4.97. Found: C, 55.72; H, 5.29; N, 4.83.

1.8.2. 3-(*p*-Bromobenzoyl)-5-(1,2-*O*-isopropylidene-3-*O*-*tert*-buthyldimethylsilyl-α-D-xylofuranos-5-ulo-5-yl)imidazo[2,1-*b*]thiazole (26)

Compound **26** was obtained from **23** (215.3 mg, 0.54 mmol) and *p*-bromobenzoyl-thiazolylimidoformamide (280.3 mg, 0.83 mmol) as yellow amorphous solid (53.9 mg, 0.08 mmol, 16.4% yield): mp 72–75 °C; $[\alpha]_D^{25}$ −119.0 (*c* 1.5, chloroform). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 8.88 (s, 1H, imidazo[2,1-*b*]thiazole proton), 8.53 (s, 1H, imidazo[2,1-*b*]thiazole proton), 7.71 (m, 4H, aromatic protons), 6.20 (d, 1H, $J_{1,2}$ 3.4 Hz, H-1), 5.01 (d, 1H, $J_{4,3}$ 3.1 Hz, H-4), 4.60 (d, 1H, $J_{3,4}$ 3.0 Hz, H-3), 4.42 (d, 1H, $J_{2,1}$ 3.3 Hz, H-2), 1.53 (s, 3H, C*Me*$_2$), 1.37 (s, 3H, C*Me*$_2$), 0.59 (s, 9H, C*Me*$_3$Si), 0.04 (s, 3H, *Me*Si); −0.19 (s, 3H, *Me*Si). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 186.1 (C=O), 186.0 (C=O); 156.0, 147.1, 134.1, 128.7, 127.8 (imidazo[2,1-*b*]thiazole carbons), 135.1, 132.3, 130.4, 130.1 (aromatic carbons), 112.8 (*C*Me$_2$), 106.0 (C-1), 86.3 (C-4), 84.6 (C-2), 78.1 (C-3), 27.1 (C*Me*$_2$), 26.5 (C*Me*$_2$), 25.2 (C*Me*$_3$Si), 17.7 (*C*Me$_3$Si), −4.8 (C*Me*Si), −5.5 (C*Me*-Si). Anal. Calcd for $C_{26}H_{31}BrN_2O_6SSi$: C, 51.40; H, 5.14; N, 4.61. Found: C, 51.72; H, 5.09; N, 4.49.

1.8.3. 3-(*p*-Chlorobenzoyl)-5-(1,2-*O*-isopropylidene-3-*O*-*p*-methoxybenzyl-α-D-xylofuranos-5-ulo-5-yl)imidazo[2,1-*b*]thiazole (27)

Compound **27** was obtained from **24** (250 mg, 0.62 mmol) and *p*-chlorobenzoyl-thiazolylimidoformamide (274.5 mg, 0.93 mmol) as yellow amorphous solid (169.1 mg, 0.30 mmol, 47.7% yield): mp 80–82 °C; $[\alpha]_D^{25}$ −120.5 (*c* 1.3, chloroform). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 8.82 (s, 1H, imidazo[2,1-*b*]thiazole proton), 8.40 (s, 1H, imidazo[2,1-*b*]thiazole proton), 7.83 (d, 2H, *J* 8.6 Hz, aromatic protons), 7.55 (d, 2H, *J* 8.6 Hz, aromatic protons), 6.91 (d, 2H, *J* 8.6 Hz, aromatic protons), 6.66 (d, 2H, *J* 8.6 Hz, aromatic protons), 6.19 (d, 1H, $J_{1,2}$ 3.6 Hz, H-1), 5.07 (d, 1H, $J_{4,3}$ 3.5 Hz, H-4), 4.61 (d, 1H, $J_{2,1}$ 3.6 Hz, H-2), 4.51 (d, 2H, *J* 11.8 Hz, methylene proton), 4.39 (d, 1H, $J_{3,4}$ 3.6 Hz, H-3), 4.32 (d, 2H, *J* 11.8 Hz, methylene proton), 3.72 (s, 3H, O*Me*), 1.52 (s, 3H, C*Me*$_2$), 1.36 (s, 3H, C*Me*$_2$). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 185.9 (C=O), 185.0 (C=O); 156.1, 146.4, 134.2, 128.0 (imidazo[2,1-*b*]thiazole carbons), 140.0, 134.7, 130.3, 129.4, 128.8, 127.9, 113.6 (aromatic carbons), 112.7 (*C*Me$_2$), 106.0 (C-1), 84.8 (C-4), 83.7 (C-2), 82.0 (C-3), 72.4 (methylene carbon), 55.2 (*C*H$_3$O), 26.9 (C*Me*$_2$), 26.3 (C*Me*$_2$). Anal. Calcd for $C_{28}H_{25}ClN_2O_7S$: C, 59.10; H, 4.43; N, 4.92. Found: C, 58.97; H, 4.35; N, 4.77.

1.8.4. 3-(*p*-Bromobenzoyl)-5-(1,2-*O*-isopropylidene-3-*O*-*p*-methoxybenzyl-α-D-xylofuranos-5-ulo-5-yl)imidazo[2,1-b]thiazole (28)

Compound **28** was obtained from **24** (215.3 mg, 0.54 mmol) and *p*-bromobenzoyl-thiazolylimidoformamide (280.3 mg, 0.83 mmol) as yellow amorphous solid (141.8 mg, 0.23 mmol, 43.1% yield): mp 87–90 °C; $[\alpha]_D^{25}$ −113.0 (*c* 1.4, chloroform). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 8.81 (s, 1H, imidazo[2,1-*b*]thiazole proton), 8.40 (s, 1H, imidazo[2,1-*b*]thiazole proton), 7.73 (m, 4H, aromatic protons), 6.91 (d, 2H, *J* 8.6 Hz, aromatic protons), 6.65 (d, 2H, *J* 8.6 Hz, aromatic protons), 6.18 (d, 1H, $J_{1,2}$ 3.6 Hz, H-1), 5.06 (d, 1H, $J_{4,3}$ 3.5 Hz, H-4), 4.61 (d, 1H, $J_{2,1}$ 3.7 Hz, H-2), 4.50 (d, 2H, *J* 11.8 Hz, methylene proton), 4.38 (d, 1H, $J_{3,4}$ 3.6 Hz, H-3), 4.31 (d, 2H, *J*

11.8 Hz, methylene proton), 3.74 (s, 3H, O*Me*), 1.52 (s, 3H, C*Me*$_2$), 1.35 (s, 3H, C*Me*$_2$). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 186.1 (C═O), 185.0 (C═O); 156.1, 146.4, 134.1, 128.0 (imidazo[2,1-*b*]thiazole carbons), 159.3, 135.1, 132.4, 130.2, 128.9, 113.6 (aromatic carbons), 112.7 (*C*Me$_2$), 106.0 (C-1), 84.9 (C-4), 83.7 (C-2), 82.0 (C-3), 72.4 (methylene carbon), 55.2 (*C*H$_3$O), 27.0 (C*Me*$_2$), 26.3 (C*Me*$_2$). Anal. Calcd for $C_{28}H_{25}BrN_2O_7S$: C, 54.82; H, 4.11; N, 4.57. Found: C, 54.87; H, 4.25; N, 4.77.

1.9. General procedure to synthesize compounds 29–31

6-Bromo-6-deoxy-1,2-*O*-isopropylidene-3-O-protected-α-D-*xylo*-hexofuranos-5-ulose **22**–**24** was added to a solution of *N*,*N*′-bis(dimethylaminomethylene)thiourea (1.2 equiv) in anhydrous dicloromethane (25 mL), and refluxed for 3 h under argon atmosphere. Et_3N (1.5 equiv) was added and the mixture was stirred for 12 h at room temperature. The crude product was purified by flash column chromatography, using cyclohexane/acetone as eluent.

1.9.1. *N*,*N*-Dimethylformamidyl-5-(1,2-*O*-isopropylidene-3-*O*-acetyl-α-D-xylofuranos-5-ulo-5-yl)-1,3-thiazole (29)

Compound **29** was obtained from **22** (526.7 mg, 1.62 mmol) as a waxy yellow solid (532.5 mg, 1.38 mmol, 85.2% yield) using the procedure previously described:[17] $[\alpha]_D^{25}$ −80.5 (*c* 0.9, chloroform). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 8.36 (s, 1H, –HC═N), 8.31 (s, 1H, thiazole proton), 6.14 (d, 1H, $J_{1,2}$ 3.6 Hz, H-1), 5.57 (d, 1H, $J_{3,4}$ 3.4 Hz, H-3), 5.16 (d, 1H, $J_{3,4}$ 3.4 Hz, H-4), 4.58 (d, 1H, $J_{2,1}$ 3.6 Hz, H-2), 3.16 (s, 3H, *Me*$_2$N), 3.12 (s, 3H, *Me*$_2$N), 1.89 (s, 3H, *Me*CO), 1.54 (s, 3H, C*Me*$_2$), 1.34 (s, 3H, C*Me*$_2$). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 186.1 (C═O), 181.4, 149.2, 130.2 (thiazole carbons), 156.6 (–*C*═N), 169.3 (Me*C*O), 112.9 (*C*Me$_2$), 105.4 (C-1), 83.2 (C-3), 82.6 (C-4), 77.7 (C-2), 41.2 (*Me*$_2$N), 35.3 (*Me*$_2$N), 26.9 (C*Me*$_2$), 26.3 (C*Me*$_2$), 20.6 (*C*H$_3$CO). Anal. Calcd for $C_{16}H_{21}N_3O_6S$: C, 50.12; H, 5.52; N, 10.96. Found: C, 50.17; H, 5.52; N, 10.87.

1.9.2. *N*,*N*-Dimethylformamidyl-5-(1,2-*O*-isopropylidene-3-*O*-(*tert*-buthyldimethylsilyl)-α-D-xylofuranos-5-ulo-5-yl)-1,3-thiazole (30)

Compound **30** was obtained from **23** (180.2 mg, 0.46 mmol) as it was previously described[17,26] as a waxy yellow solid (198.4 mg, 0.44 mmol, 95.4%, yield): $[\alpha]_D^{25}$ −143.5 (*c* 0.7, chloroform). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 8.37 (s, 1H, –HC═N), 8.32 (s, 1H, thiazole proton), 6.14 (d, 1H, $J_{1,2}$ 3.4 Hz, H-1), 4.96 (d, 1H, $J_{3,4}$ 3.1 Hz, H-3), 4.57 (d, 1H, $J_{3,4}$ 3.1 Hz, H-4), 4.39 (d, 1H, $J_{2,1}$ 3.3 Hz H-2), 3.14 (s, 3H, *Me*$_2$N), 3.11 (s, 3H, *Me*$_2$N), 1.49 (s, 3H, C*Me*$_2$), 1.34 (s, 3H, C*Me*$_2$), 0.70 (s, 9H, C*Me*$_3$Si), 0.02 (s, 3H, *Me*Si); −0.14 (s, 3H, *Me*Si). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 188.5 (C═O), 180.9, 148.9, 131.0 (thiazole carbons), 156.5 (–*C*═N), 112.6 (*C*Me$_2$), 105.8 (C-1), 86.5 (C-4), 84.8 (C-2), 78.1 (C-3), 41.2 (*Me*$_2$N), 35.2 (*Me*$_2$N), 27.1 (C*Me*$_2$), 26.6 (C*Me*$_2$), 25.4 (C*Me*$_3$Si), 17.8 (*C*Me$_3$Si), −5.0 (*Me*Si), −5.4 (*Me*Si). Anal. Calcd for $C_{20}H_{33}N_3O_5SSi$: C, 52.72; H, 7.30; N, 9.22. Found: C, 52.87; H, 7.25; N, 9.27.

1.9.3. *N*,*N*-Dimethylformamidyl-5-(1,2-*O*-isopropylidene-3-*O*-(*p*-methoxybenzyl)-α-D-xylofuranos-5-ulo-5-yl)-1,3-thiazole (31)

Compound **31** was obtained from **24** (443.7 mg, 1.11 mmol) as it was previously reported in literature[17] as a waxy yellow solid (386.9 mg, 0.84 mmol, 87.2% yield): $[\alpha]_D^{25}$ −25.9 (*c* 4.1, chloroform). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 8.30 (s, 1H, –HC═N), 8.24 (s, 1H, thiazole proton), 7.01 (d, 2H, *J* 8.6 Hz, aromatic protons), 6.73 (d, 2H, *J* 8.6 Hz, aromatic protons), 6.12 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 5.04 (d, 1H, $J_{3,4}$ 3.7 Hz, H-4), 4.57 (d, 1H, $J_{2,1}$ 3.7 Hz, H-2), 4.45 (d, 1H, *J* 11.5 Hz, methylene proton), 4.34 (d, 1H, *J* 11.5 Hz, methylene proton), 4.33 (d, 1H, $J_{3,4}$ 3.7 Hz, H-3), 3.72 (s, 3H, O*Me*), 3.11 (s, 3H, *Me*$_2$N), 3.08 (s, 3H, *Me*$_2$N), 1.48 (s, 3H, C*Me*$_2$), 1.31 (s, 3H, C*Me*$_2$). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 187.6 (C═O), 181.0, 148.8, 130.7 (thiazole carbons), 156.5 (–*C*═N), 159.3, 129.3, 129.0, 113.7 (aromatic carbons), 112.4 (*C*Me$_2$), 105.8 (C-1), 85.0 (C-4), 83.3 (C-2), 82.2 (C-3), 72.2 (methylene carbon), 55.2 (*C*H$_3$O), 41.1 (*Me*$_2$N), 35.2 (*Me*$_2$N), 27.0 (C*Me*$_2$), 26.4 (C*Me*$_2$). Anal. Calcd for $C_{22}H_{27}N_3O_6S$: C, 52.25; H, 5.90; N, 9.10. Found: C, 52.37; H, 5.95; N, 8.97.

1.10. General procedure to synthesize compounds 32–35

Compounds **32**–**35** were obtained by reaction of **30** or **31** with the corresponding 2-bromo-1-(4-chlorophenyl)ethanone or 2-bromo-1-(4-bromophenyl)ethanone in anhydrous THF (7 mL) under microwave radiation (300 W, 90 min, 100 °C). Then 15 mL of THF and triethylamine (molar relation 1.5:1 amine/sugar) was added and the mixture was kept stirring at room temperature overnight. Solvent was evaporated and the crude products were purified by column chromatography on silica gel using mixtures of cyclohexane/acetone (90:10–75:25) as eluents.

1.10.1. 3-(1,2-*O*-Isopropylidene-3-*O*-*tert*-buthyldimethylsilyl-α-D-xylofuranos-5-ulo-5-yl)-5-(*p*-chlorobenzoyl)imidazo[2,1-b]thiazole (32)

Compound **32** was obtained from **30** (157.6 mg, 0.35 mmol) and 2-bromo-1-(4-chlorophenyl)ethanone (121.1 mg, 0.52 mmol) as a waxy yellow solid (105.6 mg, 0.19 mmol, 54.2% yield): $[\alpha]_D^{25}$ −74.6 (*c* 2.1, chloroform). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 9.45 (s, 1H, imidazo[2,1-*b*]thiazole proton), 7.96 (s, 1H, imidazo[2,1-*b*] thiazole proton), 7.85 (d, 2H, *J* 8.4 Hz, aromatic protons), 7.51 (d, 2H, *J* 8.4 Hz, aromatic protons), 6.29 (d, 1H, $J_{1,2}$ 3.1 Hz, H-1), 5.05 (d, 1H, $J_{4,3}$ 3.1 Hz, H-4), 4.64 (d, 1H, $J_{3,4}$ 3.4 Hz, H-3), 4.45 (d, 1H, $J_{2,1}$ 3.5 Hz, H-2), 1.52 (s, 3H, C*Me*$_2$), 1.37 (s, 3H, C*Me*$_2$), 0.66 (s, 9H, C*Me*$_3$Si), 0.07 (s, 3H, *Me*Si); −0.10 (s, 3H, *Me*Si). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 190.4 (C═O), 181.5 (C═O); 156.9, 145.6, 133.4, 129.8, 129.1 (imidazo[2,1-*b*]thiazole carbons), 139.1, 136.0, 130.0, 129.8 (aromatic carbons), 112.9 (*C*Me$_2$), 106.1 (C-1), 86.9 (C-4), 84.6 (C-2), 77.7 (C-3), 27.1 (C*Me*$_2$), 26.5 (C*Me*$_2$), 25.3 (C*Me*$_3$Si), 17.8 (*C*Me$_3$Si), −5.0 (C*Me*Si), −5.3 (C*Me*Si). Anal. Calcd for $C_{26}H_{31}ClN_2O_6SSi$: C, 55.45; H, 5.55; N, 4.97. Found: C, 55.17; H, 5.25; N, 4.77.

1.10.2. 3-(1,2-*O*-Isopropylidene-3-*O*-*tert*-buthyldimethylsilyl-α-D-xylofuranos-5-ulo-5-yl)-5-(*p*-bromobenzoyl)imidazo[2,1-*b*]thiazole (33)

Compound **33** was obtained from **30** (151.2 mg, 0.33 mmol) and 2-bromo-1-(4-bromophenyl)ethanone (113.7 mg, 0.49 mmol) as a waxy yellow solid (155.4 mg, 0.26 mmol, 76.9% yield): $[\alpha]_D^{25}$ −67.5 (*c* 1.8, chloroform). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 9.43 (s, 1H, imidazo[2,1-*b*]thiazole proton), 7.94 (s, 1H, imidazo[2,1-*b*] thiazole proton), 7.76 (d, 2H, *J* 8.0 Hz, aromatic protons), 7.65 (d, 2H, *J* 8.0 Hz, aromatic protons), 6.27 (d, 1H, $J_{1,2}$ 3.3 Hz, H-1), 5.03 (d, 1H, $J_{4,3}$ 3.1 Hz, H-4), 4.62 (d, 1H, $J_{3,4}$ 3.0 Hz, H-3), 4.44 (d, 1H, $J_{2,1}$ 3.4 Hz, H-2), 1.52 (s, 3H, C*Me*$_2$), 1.37 (s, 3H, C*Me*$_2$), 0.65 (s, 9H, C*Me*$_3$Si), 0.05 (s, 3H, *Me*Si); −0.11 (s, 3H, *Me*Si). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 190.4 (C═O), 181.6 (C═O); 156.9, 145.6, 133.4, 129.5, 127.4 (imidazo[2,1-*b*]thiazole carbons), 136.4, 132.1, 130.1, 127.6 (aromatic carbons), 112.9 (*C*Me$_2$), 106.1 (C-1), 86.9 (C-4), 84.6 (C-2), 78.4 (C-3), 27.1 (C*Me*$_2$), 26.4 (C*Me*$_2$), 25.3 (C*Me*$_3$Si), 17.7 (*C*Me$_3$Si), −5.0 (C*Me*Si), −5.3 (C*Me*Si). Anal. Calcd for $C_{26}H_{31}BrN_2O_6SSi$: C, 51.40; H, 5.14; N, 4.61. Found: C, 51.47; H, 5.15; N, 4.57.

1.10.3. 3-(1,2-*O*-Isopropylidene-3-*O*-*p*-methoxybenzyl-α-D-xylofuranos-5-ulo-5-yl)-5-(*p*-chlorobenzoyl)imidazo[2,1-b]thiazole (34)

Compound **34** was obtained from **31** (406.5 mg, 0.88 mmol) and 2-bromo-1-(4-chlorophenyl)ethanone (312.5 mg, 1.32 mmol) as a waxy yellow solid (422.1 mg, 0.74 mmol, 84.1% yield): $[\alpha]_D^{25}$ −64.8 (*c* 0.9, chloroform). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 9.52 (s,

1H, imidazo[2,1-*b*]thiazole proton), 9.19 (s, 1H, imidazo[2,1-*b*]thiazole proton), 7.84 (d, 2H, *J* 8.8 Hz, aromatic protons), 7.52 (d, 2H, *J* 8.6 Hz, aromatic protons), 7.01 (d, 2H, *J* 8.6 Hz, aromatic protons), 6.65 (d, 2H, *J* 8.8 Hz, aromatic protons), 6.26 (d, 1H, $J_{1,2}$ 3.6 Hz, H-1), 5.14 (d, 1H, $J_{4,3}$ 3.7 Hz, H-4), 4.66 (d, 1H, $J_{2,1}$ 3.7 Hz, H-2,), 4.53 (d, 2H, *J* 11.6 Hz, methylene proton), 4.42 (d, 1H, $J_{3,4}$ 3.7 Hz, H-3), 4.31 (d, 2H, *J* 11.7 Hz, methylene proton), 3.66 (s, 3H, O*Me*), 1.53 (s, 3H, CMe_2), 1.37 (s, 3H, CMe_2). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 190.6 (C═O), 180.1 (C═O); 156.7, 145.5, 133.1, 128.8 (imidazo[2,1-*b*]thiazole carbons), 159.4, 139.1, 136.0, 130.1, 129.7, 129.1, 128.7, 128.3, 113.6 (aromatic carbons), 112.9 (*C*Me_2), 106.1 (C-1), 85.3 (C-4), 83.1 (C-2), 81.9 (C-3), 72.2 (methylene carbon), 55.1 (O*C*H_3), 27.0 (CMe_2), 26.3 (CMe_2). Anal. Calcd for $C_{28}H_{25}ClN_2O_7S$: C, 59.10; H, 4.43; N, 4.92. Found: C, 59.17; H, 4.35; N, 4.77.

1.10.4. 3-(1,2-*O*-Isopropylidene-3-*O*-*p*-methoxybenzyl-α-D-xylofuranos-5-ulo-5-yl)-5-(*p*-bromobenzoyl)imidazo[2,1-b]thiazole (35)

Compound **35** was obtained from **31** (350.1 mg, 0.76 mmol) and 2-bromo-1-(4-bromophenyl)ethanone (321.5 mg, 1.14 mmol) as a waxy yellow solid (404.5 mg, 0.66 mmol, 86.9% yield): $[\alpha]_D^{25}$ −50.1 (*c* 0.7, chloroform). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 9.52 (s, 1H, imidazo[2,1-*b*]thiazole proton), 9.19 (s, 1H, imidazo[2,1-*b*]thiazole proton), 7.85 (d, 2H, *J* 8.8 Hz, aromatic protons), 7.52 (d, 2H, *J* 8.6 Hz, aromatic protons), 7.01 (d, 2H, *J* 8.6 Hz, aromatic protons), 6.65 (d, 2H, *J* 8.8 Hz, aromatic protons), 6.26 (d, 1H, $J_{1,2}$ 3.6 Hz, H-1), 5.14 (d, 1H, $J_{4,3}$ 3.7 Hz, H-4), 4.66 (d, 1H, $J_{2,1}$ 3.7 Hz, H-2), 4.53 (d, 2H, *J* 11.6 Hz, methylene proton), 4.42 (d, 1H, $J_{3,4}$ 3.7 Hz, H-3), 4.31 (d, 2H, *J* 11.8 Hz, methylene proton), 3.66 (s, 3H, O*Me*), 1.53 (s, 3H, CMe_2), 1.37 (s, 3H, CMe_2). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 189.1 (C═O), 181.6 (C═O); 156.7, 145.5, 133.1, 128.7, 126.8 (imidazo[2,1-*b*]thiazole carbons), 159.4, 139.1, 136.0, 130.1, 129.8, 129.5, 128.7, 128.3, 113.6 (aromatic carbons), 112.9 (*C*Me_2), 106.1 (C-1), 85.3 (C-4), 83.1 (C-2), 81.9 (C-3), 72.2 (methylene carbon), 55.1 (O*C*H_3), 26.9 (CMe_2), 25.8 (CMe_2). Anal. Calcd for $C_{28}H_{25}BrN_2O_7S$: C, 54.82; H, 4.11; N, 4.57. Found: C, 54.87; H, 4.25; N, 4.63.

1.11. General procedure to synthesize compounds 36–37

A mixture of *N,N*-dimethylformamidyl-5-(1,2-*O*-isopropylidene-3-*O*-acetyl-α-D-xylofuranos-5-ulo-5-yl)-1,3-thiazole and the corresponding 2-bromo-(4-halophenyl)etanone (1.2 equiv) in anhydrous THF (6 mL) was heated under microwave irradiation (300 W, 100 °C), for 90 min. The reaction mixture was diluted with anhydrous THF (20 mL) and Et_3N (1.5 equiv) was added under argon atmosphere and the mixture was stirred for 12 h at room temperature. The crude product was purified by flash column chromatography, using cyclohexane/acetone (90:10) as eluent.

1.11.1. 3-(3-Deoxy-1,2-*O*-isopropylidene-α−D-*glycero*-pent-3-enofuranosid-5-ulo-5-yl)-5-(*p*-chlorobenzoyl)imidazo[2,1-*b*]thiazole (36)

Compounds **36** was obtained from **29** (130.3 mg, 0.34 mmol) and 2-bromo-1-(4-chlorophenyl)ethanone (114.2 mg, 0.50 mmol) as a waxy yellow solid (34.2 mg, 0.08 mmol, 23.4% yield): $[\alpha]_D^{25}$ −96.9 (*c* 1.8, chloroform). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 8.81 (s, 1H, imidazo[2,1-*b*] proton), 8.48 (s, 1H, imidazo[2,1-*b*] proton), 7.87 (d, *J* 8.5 Hz, aromatic proton), 7.53 (d, *J* 8.5 Hz, aromatic proton), 6.39 (d, 1H, $J_{1,2}$ 5.4 Hz, H-3), 6.32 (d, 1H, $J_{3,2}$ 2.6 Hz, H-1), 5.46 (dd, 1H, $J_{2,1}$ 2.6 Hz, $J_{2,3}$ 5.3 Hz, H-2), 1.50 (s, 3H, CMe_2), 1.49 (s, 3H, CMe_2). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 181.7 (C═O), 176.2 (C═O), 156.7, 145.6, 133.4, 129.7, 129.1 (imidazo[2,1-*b*] carbons), 154.7 (C-4), 139.3, 135.8, 130.0, 129.2 (aromatic carbons), 113.5 (*C*Me_2), 111.4 (C-3), 107.6 (C-1), 82.1 (C-2), 28.1 (CMe_2), 27.7 (CMe_2). HR ESI MS found *m/z* $[M+H]^+$ 431.0472, $C_{20}H_{16}ClN_2O_5S^+$ requires *m/z* 431.0468.

1.11.2. 3-(3-Deoxy-1,2-*O*-isopropylidene-α-D-*glycero*-pent-3-enofuranosid-5-ulo-5-yl)-5-(*p*-bromobenzoyl)imidazo[2,1-*b*]thiazole (37)

Compound 37 was obtained from **29** (92.1 mg, 0.24 mmol) and 2-bromo-1-(4-bromophenyl)ethanone (102.8 mg, 0.36 mmol) as a waxy yellow solid (36.8 mg, 0.08 mmol, 32.3% yield): $[\alpha]_D^{25}$ −23.9 (*c* 2.0, chloroform). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 9.56 (s, 1H, imidazo[2,1-*b*] proton), 7.99 (s, 1H, imidazo[2,1-*b*] proton), 7.80 (d, *J* 8.8 Hz, aromatic proton), 7.70 (d, *J* 8.8 Hz, aromatic proton), 6.39 (d, 1H, $J_{3,2}$ 5.4 Hz, H-3), 6.33 (d, 1H, $J_{1,2}$ 2.7 Hz, H-1), 5.46 (dd, 1H, $J_{2,1}$ 2.7 Hz, $J_{2,3}$ 5.4 Hz, H-2), 1.50 (s, 3H, CMe_2), 1.49 (s, 3H, CMe_2). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 181.8 (C═O), 176.2 (C═O), 156.7, 145.7, 133.4, 129.7, 127.0 (imidazo[2,1-*b*] carbons), 154.8 (C-4), 136.3, 132.2, 130.1, 127.9 (aromatic carbons), 113.5 (*C*Me_2), 111.4 (C-3), 107.6 (C-1), 82.1 (C-2), 28.0 (CMe_2), 27.7 (CMe_2). HR ESI MS found *m/z* $[M+H]^+$ 474.9967, $C_{20}H_{16}BrN_2O_5S^+$ requires *m/z* 474.9963.

1.12. General procedure for carbohydrate deprotection

Compounds **27**, **28**, **34,** and **35** were dissolved in anhydrous CH_2Cl_2 (5 mL) and the solutions were cooled to 0 °C in an ice bath and then TFA (7 mL) was added stepwise up to 60% (v/v) final concentration. Reaction was kept stirring for 24 h at room temperature and quenched by addition of water and $NaHCO_3$ to pH 7. The solution was extracted with CH_2Cl_2/water and AcOEt/water, the combined organic layers were dried (Na_2SO_4) and evaporated. The crude product was purified by column chromatography on silica gel using mixtures of toluene/ethanol (95:5–80:20) as eluents.

1.12.1. 3-(*p*-Chlorobenzoyl)-5-((α/β)-D-xylofuranos-5-ulo-5-yl)imidazo[2,1-*b*]thiazole (38)

Deprotection of compound **27** (100 mg, 0.18 mmol) gave a white solid product **38** which was characterized as a mixture of α and β anomers (20.1 mg, 0.05 mmol, 28% yield, α/β = 52:48): mp 118–120 °C (dec.); $[\alpha]_D^{25}$ −53.7 (*c* 0.4, DMSO). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.80 (s, 1H, imidazo[2,1-*b*]thiazole proton), 8.77 (s, 1H, imidazo[2,1-*b*]thiazole proton), 8.73 (s, 1H, imidazo[2,1-*b*]thiazole proton), 8.46 (s, 1H, imidazo[2,1-*b*]thiazole proton), 7.98–7.96 (m, 4H, aromatic protons), 7.75–7.74 (m, 4H, aromatic protons), 6.48 (d, 1H, *J* 6.5 Hz, *H*OC-1 β-anomer), 6.35 (d, 1H, *J* 7.8 Hz, *H*OC-1 α-anomer), 5.52 (dd, 1H, $J_{1,HO}$ 7.3 Hz, $J_{1,2}$ 3.5 Hz, H-1 α-anomer), 5.49 (d, 1H, *J* 3.7 Hz, *H*OC-2 β-anomer), 5.45 (d, 1H, *J* 4.8 Hz, *H*OC-3 α-anomer), 5.21 (t, 3H, *J* 5.2 Hz, *H*OC-2 α-anomer, *H*OC-3 β-anomer, H-1 β-anomer), 5.08 (d, 1H, $J_{4,3}$ 5.2 Hz, H-4 α-anomer), 4.93 (d, 1H, $J_{4,3}$ 4.8 Hz, H-4 β-anomer), 4.37 (dd, 1H, $J_{3,HO}$ 8.2 Hz, $J_{3,4}$ 4.9 Hz, H-3 α-anomer), 4.25 (t, 1H, *J* 4.1 Hz, H-3 β-anomer), 3.90 (s, 1H, H-2 β-anomer), 3.84 (d, 1H, $J_{2,1}$ 3.1 Hz, H-2 α-anomer). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 188.0 (C═O), 186.6 (C═O), 154.9, 146.7, 145.3, 133.5, 133.4, 129.3, 129.1, 127.7, 127.6 (imidazo[2,1-*b*]thiazole carbons), 138.8, 135.4, 131.2, 129.7 (aromatic carbons), 105.0 (C-1 β-anomer), 98.4 (C-1 α-anomer), 86.4 (C-4 β-anomer), 82.6 (C-4 α-anomer), 80.7 (C-2 β-anomer), 78.0 (C-3 β-anomer), 77.9 (C-3 α-anomer), 76.1 (C-2 α-anomer). HR ESI MS found *m/z* $[M+H]^+$ 409.0266, $C_{17}H_{14}ClN_2O_6S^+$ requires *m/z* 409.0261.

1.12.2. 3-(*p*-Bromo)-5-((α/β)-D-xylofuranos-5-ulo-5-yl)imidazo[2,1-*b*]thiazole (39)

Deprotection of compound **28** (151.5 mg, 0.25 mmol) gave a white solid product **39** which was characterized as a mixture of α and β anomers (39.4 mg, 0.09 mmol, 35.2% yield, α/β = 47:53): mp 127–130 °C (dec.); $[\alpha]_D^{25}$ −34.5 (*c* 0.8, DMSO). ^{1}H NMR

(500 MHz, DMSO-d_6) δ: 8.80 (s, 1H, imidazo[2,1-*b*]thiazole proton), 8.77 (s, 1H, imidazo[2,1-*b*]thiazole proton), 8.73 (s, 1H, imidazo[2,1-*b*]thiazole proton), 8.46 (s, 1H, imidazo[2,1-*b*]thiazole proton), 7.89, 7.88 (s, 8H, aromatic protons), 6.47 (br s, 1H, *H*OC-1β-anomer), 6.35 (br s, 1H, *H*OC-1 α-anomer), 5.52 (br s, 1H, H-1 α-anomer), 5.49 (br s, 1H, *H*OC-2 β-anomer), 5.45 (d, 1H, *J* 4.3 Hz, *H*OC-3 α-anomer), 5.22 (s, 3H, *H*OC-2 α-anomer, *H*OC-3 β-anomer, H-1 β-anomer), 5.08 (d, 1H, $J_{4,3}$ 5.2 Hz, H-4 α-anomer), 4.93 (d, 1H, $J_{4,3}$ 4.8 Hz, H-4 β-anomer), 4.38 (d, 1H, $J_{3,4}$ 3.2 Hz, H-3 α-anomer), 4.25 (s, 1H, H-3 β-anomer), 3.90 (s, 1H, H-2 β-anomer), 3.84 (t, 1H, *J* 3.3 Hz, H-2 α-anomer). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 188.0 (C═O), 186.7 (C═O), 154.8, 146.7, 145.3, 134.4, 133.3, 129.3, 129.1, 127.7, 127.6 (imidazo[2,1-*b*]thiazole carbons), 135.7, 132.6, 131.2, 127.9 (aromatic carbons), 105.0 (C-1 β-anomer), 98.4 (C-1 α-anomer), 86.4 (C-4 β-anomer), 82.6 (C-4 α-anomer), 80.7 (C-2 β-anomer), 78.0 (C-3 β-anomer), 77.9 (C-3 α-anomer), 76.1 (C-2 α-anomer). HR ESI MS found *m/z* $[M+H]^+$ 454.9759, $C_{17}H_{14}BrN_2O_6S^+$ requires *m/z* 454.9756.

1.12.3. 5-(*p*-Chlorobenzoyl)-3-((α/β)-D-xylofuranos-5-ulo-5-yl)imidazo[2,1-*b*]thiazole (40)

Deprotection of compound **34** (104.6 mg, 0.18 mmol) gave a white solid product **40** which was characterized as a mixture of α and β anomers (27.4 mg, 0.07 mmol, 36.5% yield, α/β = 48:52): mp 97 °C (dec.); $[\alpha]_D^{25}$ −31.4 (*c* 0.5, DMSO). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 9.77 (s, 1H, imidazo[2,1-*b*]thiazole proton), 9.32 (s, 1H, imidazo[2,1-*b*]thiazole proton), 8.23 (s, 1H, imidazo[2,1-*b*]thiazole proton), 8.21 (s, 1H, imidazo[2,1-*b*]thiazole proton), 7.96–7.95 (m, 4H, aromatic protons), 7.68–7.66 (m, 4H, aromatic protons), 6.67 (d, 1H, *J* 6.4 Hz, *H*OC-1 β-anomer), 6.48 (d, 1H, *J* 7.9 Hz, *H*OC-1 α-anomer), 5.70 (d, 1H, *J* 3.1 Hz, *H*OC-3 α-anomer), 5.59 (d, 1H, *J* 3.0 Hz, H-1 α-anomer), 5.56 (s, 1H, *H*OC-2 β-anomer), 5.51 (d, 1H, *J* 3.8 Hz, *H*OC-3 β-anomer), 5.39 (s, 1H, *H*OC-2 α-anomer), 5.28 (s, 1H, H-1 β-anomer), 5.21 (d, 1H, *J* 4.8 Hz, H-4 α-anomer), 5.08 (d, 1H, *J* 4.7 Hz, H-4 β-anomer), 4.41 (s, 1H, H-3 α-anomer), 4.30 (s, 1H, H-3 β-anomer), 3.92 (s, 1H, H-2 β-anomer), 3.86 (d, 1H, *J* 2.8 Hz, H-2 α-anomer). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 192.7 (C═O), 181.5 (C═O), 181.3 (C═O), 156.0, 155.8, 146.3, 133.7, 133.2, 130.0, 128.3, 127.1, 127.0 (imidazo[2,1-*b*]thiazole carbons), 138.1, 138.0, 136.3, 136.2, 131.1, 131.0, 129.5 (aromatic carbons), 105.5 (C-1 β-anomer), 99.2 (C-1 α-anomer), 87.0 (C-4 β-anomer), 83.9 (C-4 α-anomer), 80.9 (C-2 β-anomer), 78.4 (C-3 α-anomer and β-anomer), 76.0 (C-2 α-anomer). HR ESI MS found *m/z* $[M+H]^+$ 409.0258, $C_{17}H_{14}ClN_2O_6S^+$ requires *m/z* 409.0261.

1.12.4. 5-(*p*-Bromobenzoyl)-3-((α/β)-D-xylofuranos-5-ulo-5-yl)imidazo[2,1-*b*]thiazole (41)

Deprotection of compound **35** (112.4 mg, 0.18 mmol) gave a white solid product **41** which was characterized as a mixture of α and β anomers (36.5 mg, 0.08 mmol, 44% yield, α/β = 52:48): mp 103 °C (dec.); $[\alpha]_D^{25}$ −31.6 (*c* 0.7, DMSO). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 9.71 (s, 1H, imidazo[2,1-*b*]thiazole proton), 9.31 (s, 1H, imidazo[2,1-*b*]thiazole proton), 8.21 (s, 1H, imidazo[2,1-*b*]thiazole proton), 8.20 (s, 1H, imidazo[2,1-*b*]thiazole proton), 7.87–7.79 (m, 8H, aromatic protons), 6.68 (d, 1H, *J* 6.4 Hz, *H*OC-1 β-anomer), 6.49 (d, 1H, *J* 7.5 Hz, *H*OC-1 α-anomer), 5.71 (d, 1H, *J* 3.8 Hz *H*OC-3 α-anomer), 5.60 (s, 1H, H-1 α-anomer), 5.56 (s, 1H, *H*OC-2 β-anomer), 5.52 (d, 1H, *J* 3.8 Hz, *H*OC-3 β-anomer), 5.39 (br s, 1H, *H*OC-2 α-anomer), 5.29 (d, 1H, *J* 5.2 Hz, H-1 β-anomer), 5.21 (d, 1H, *J* 4.8 Hz, H-4 α-anomer), 5.09 (d, 1H, *J* 4.7 Hz, H-4 β-anomer), 4.42 (m, 1H, H-3 α-anomer), 4.31 (m, 1H, H-3 β-anomer), 3.93 (s, 1H, H-2 β-anomer), 3.86 (d, 1H, *J* 2.8 Hz, H-2 α-anomer). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 192.7 (C═O), 192.7 (C═O), 181.6 (C═O), 181.5 (C═O), 156.0, 155.8, 146.3, 133.7, 133.2, 129.9, 128.3, 127.1, 127.0 (imidazo[2,1-*b*]thiazole carbons), 136.6, 136.5, 132.4, 131.2, 131.1, 127.2, 127.1 (aromatic carbons), 105.5 (C-1 β-anomer), 99.2 (C-1 α-anomer), 87.0 (C-4 β-anomer), 83.9 (C-4 α-anomer), 80.9 (C-2 β-anomer), 78.4 (C-3 α-anomer and β-anomer), 76.0 (C-2 α-anomer). HR ESI MS found *m/z* $[M+H]^+$ 454.9751, $C_{17}H_{14}BrN_2O_6S^+$ requires *m/z* 454.9756.

Acknowledgments

The authors acknowledge Agencia Nacional de Promoción Científica y Tecnológica, Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET) and Universidad de Buenos Aires (UBA) from Argentina for financial support. N.B.D. is member of Research Career from CONICET and J.S.B. has a fellowship from CONICET.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.carres.2012.04.011.

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