Reaction of monosaccharides with 2-pyridylcarboxamidrazone and determination of the nature of products

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Abstract

Reaction of 2-pyridylcarboxamidrazone with D-arabinose, D-xylose, D-galactose, D-glucose and D-mannose afforded the corresponding hydrazones in either the acyclic or cyclic structures depending on the nature of the sugar. Assignment of the sugar hydrazones structures were based on 1D and 2D NMR experiments. Vicinal coupling constants were used to deduce the favored conformations.

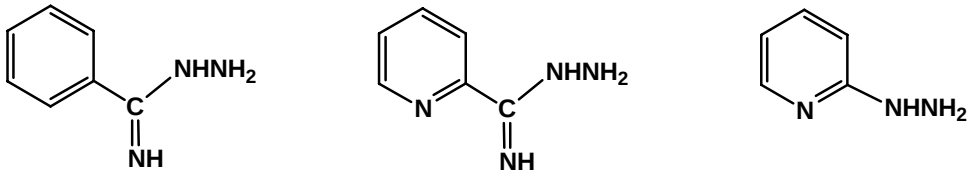
Keywords: Carbohydrates, sugar hydrazones, amidrazones, seco-nucleosides

Introduction

Amidrazones are important precursors for many useful compounds with industrial and medicinal applications.[1] 2-Pyridylcarboxamidrazone and its heterocyclic derivatives showed antimicrobacterial activity[2] and anticancer activity.[3] The phenylalanine derivative (*S*)-3-(4-amidrazonophenyl)-*N*-cyclopentyl-*N*-methyl-2-(naphthalene-2-sulfonyl)propionamide (LB30057) was identified as a potent selective and orally active thrombin inhibitor; several derivatives have also significant enhancing potency as thrombin inhibitors.[4] Carbohydrates have attracted much attention as starting material in organic synthesis.[5] Their role in the synthesis of naturally occurring nitrogen heterocycles[6] has been investigated in various laboratories.

Much work has been published from our laboratory on the synthesis and reactivity of hydrazones[7] derived from carbohydrates for the synthesis of heterocycles[6] and acyclic (*seco*)-nucleosides.[8] The reaction of sugars with benzamidrazone (**A**) has led to an interesting entry towards nucleoside analogues.[9] Moreover, their reaction with 2-pyridylhydrazine (**B**) has been recently investigated.[10] D-Glucose 2-pyridylhydrazone was isolated during a study on sequential removal of monosaccharides from the reducing end of oligosaccharides.[11] Consequently, it became interesting to investigate the reactions of the close analogue, 2-pyridylcarboxamidrazone (**1**), which has both features. The incorporation of alditolyl moieties on these pyridylamidrazones

may lead to an interesting improvement in their biological activity and/or enhancement of their bioavailability as a consequence of the hydrophilic nature of the alditolyl residue that may aid in their transportation into biological systems.



A **1** **B**

Figure 1

Results and Discussion

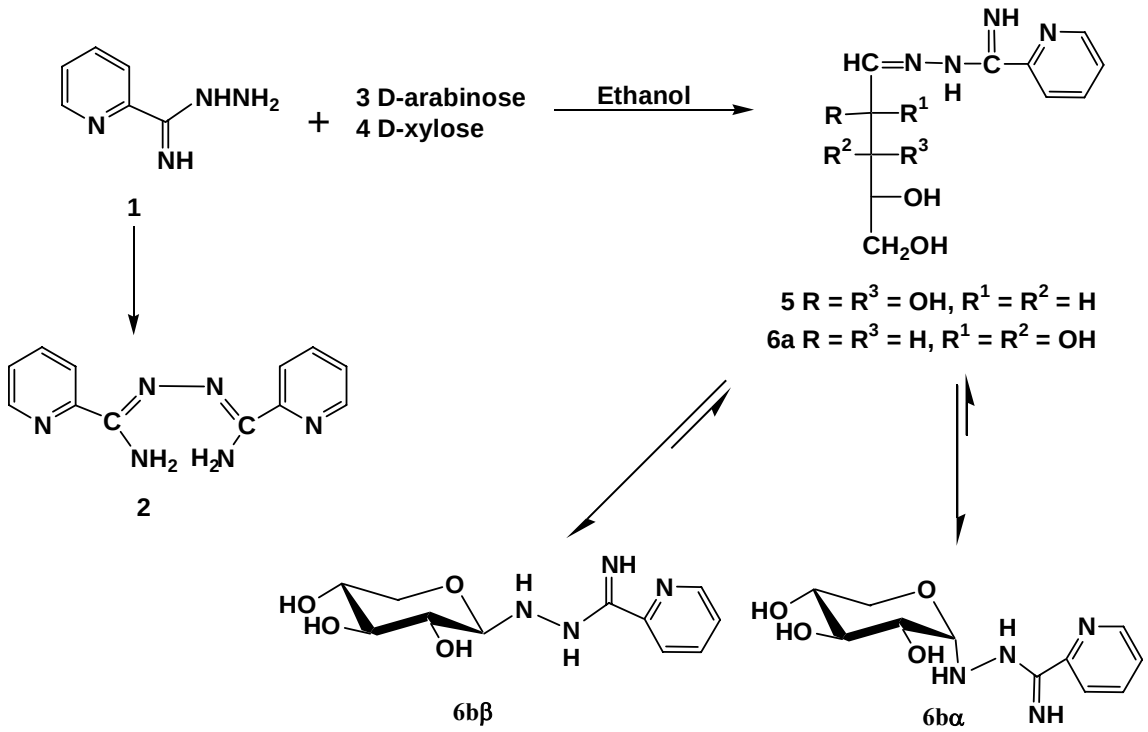
Condensation of an equimolar amount of 2-pyridylcarboxamidrazone (**1**) with aldoses was carried out in refluxing ethanol to give the respective hydrazone derivatives **5, 6, 10, 11** and **12** accompanied with a yellow crystalline by-product, which was separated by fractional crystallization and identified from its spectral data; FABMS showed a molecular ion peak at m/z 240 as the dihydrazidine 2.[12] Moreover, the dihydrazidine **2** was formed when the amidrazone **1** was heated in a solution of ethanol and in the presence of oxygen.

Sugar hydrazones can exist in solution as acyclic Schiff's base or as cyclic glycosylhydrazine[10,13,14] and are often present as equilibrium mixtures that are strongly dependent on the pH of the solution as well as on the nature of the sugar and the basicity of the hydrazine derivative. The characterization and assignment of the acyclic-cyclic nature of the newly prepared sugar hydrazones were investigated based on the study of their ^{1}H and ^{13}C NMR spectra, while ^{1}H-^{1}H DQFCOSY and ^{1}H-^{13}C HMQC NMR experiments helped in the assignment of both proton and carbon signals.

Examination of ^{1}H and ^{13}C NMR spectra of the D-arabinose derivative **5** in a solution of DMSO-d_6 and D_2O showed that it existed exclusively in the acyclic structure; based on the presence of a doublet corresponding to H-1' at the downfield region at δ 7.77 that correlated with C-1' at δ_C 159.7. The presence of only four signals corresponding to the sugar carbons at δ_C 63.8, 70.8, 71.5, 73.1 (C-5', 2', 4' and 3') was also in agreement of such acyclic structure.

Conversely, D-xylose (**4**) afforded a product whose NMR spectral data (DMSO-d_6+D_2O) indicated the presence of more than one component with the most prominent being the two anomers N^2-(α,β-D-xylopyranosyl)-N^1-2-pyridylcarboxamidrazone (**6b**α and **6b**β), present in a 1:1.6 ratio. Identification of both anomers was performed by assignment of the signals at the downfield region corresponding to H-1'-α (δ 4.86) and H-1'-β (δ 4.23) which appeared as doublets with vicinal coupling constants, $J_{1',2'}$ = 3.5 Hz for the α anomer compatible with a cis relationship with H-2', whereas that of the β-anomer, $J_{1',2'}$ = 7.7 Hz, agreed with a trans relationship for H-1', H-2'. A HMQC experiment correlated H-1'α

and H-1'β with the carbons resonating at δ_C 91.3 and 96.6, respectively, in agreement with the expected cyclic structure. The presence of the cyclic structure in the pyranose form rather than the furanose form was confirmed by the signal of C-4' which appeared at a lower frequency region at δ_C 69.0 and 68.6 for **6b**α and **6b**β, respectively, in agreement with those established for pyranosides;[15] expected values for furanosides were δ_C 77.4 and 72.7.[16] The assignment of the signals at δ_C 60.3 and 64.5 for C-5' of both anomers **6b**α and **6b**β, respectively, was based on DEPT-135° experiments. These anomers were the two forms existing in solution and no signals corresponding to the acyclic structure **6a** were observed, although **6b**α and **6b**β need to be formed via the open chain hydrazone **6a**. However, it seems that the cyclic structures are readily formed and consequently **6a** can not be detected.



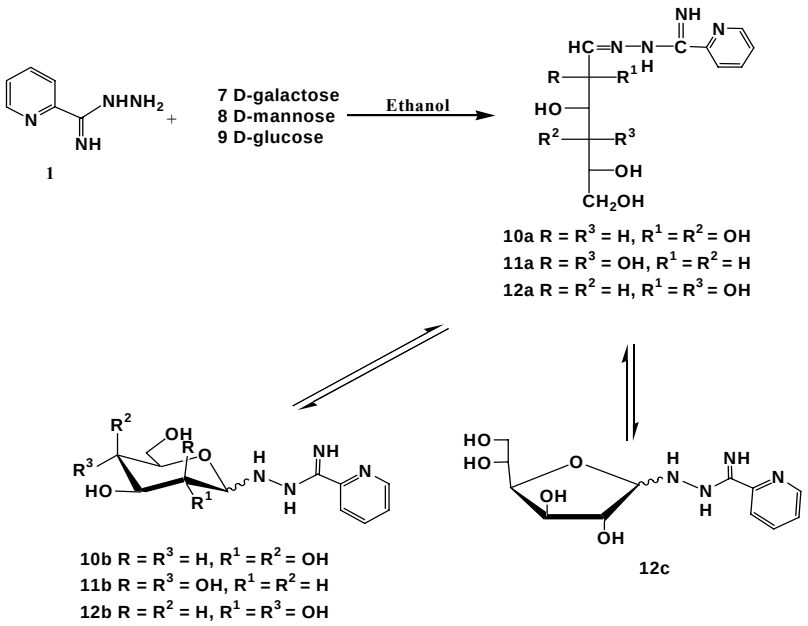
Scheme 1

Spectral analysis of the product from D-galactose (**7**) showed that it existed as a mixture of the acyclic **10a** and cyclic **10b** structure, in a ratio of 4:1, respectively, in which the acyclic structure was the main one. The presence of a doublet corresponding to H-1' in the downfield region at δ 7.80 that correlated with C-1' at δ_C 159.9 confirmed the presence of the acyclic structure. The pyranosyl ring structure in **10b** was assigned based on the signal corresponding to C-5' that resonated at δ_C 76.4. The presence of only one signal corresponding to H-1' at δ 4.20, correlated with C-1' at δc 91.7, indicated the presence of only a single anomer **10b**. The assignment of the anomeric configuration of **10b** as β was based on the value of $J_{1',2'}$ = 8.9 Hz, confirming a trans relationship with H-2'.

The D-mannose derivative **11** also existed in the acyclic and cyclic structures in a ratio of 4:1, respectively. Thus, H-1' in the acyclic structure **11a** appeared as a doublet at δ 7.84, correlated with C-1' at δ_C 159.9, while the cyclic pyranosyl structure **11b** was based on the assignment of C-5' at δ_C 78.7. Its H-1' was observed at δ 4.48, correlated with C-1' at δ_C 88.0, and showed a coupling constant $J_{1',2'}$ = 8.6 Hz which was not fully decisive for assigning the α or β-anomeric configuration for **11b**.

The adduct from D-glucose (**9**) and **1** was found to be the acyclic structure **12a,** the α,β-pyranosyl **12b** and the α,β-furanosyl **12c** ring structure, in which the cyclic structure was the main one as deduced from their ^{1}H and ^{13}C NMR spectra in DMSO-d_6 and D_2O. At the higher frequency region the azomethine carbon (C-1'=N) of the acyclic form **12a** was observed at δ_C 162.9. The presence of more than one cyclic structure was deduced from the presence of four anomeric signals; assigned at δ_C 90.9, 91.4, 92.6 (lower intensities) and 97.2 (higher intensity). In addition, the DEPT-135° experiment showed the presence of five negative signals at δ_C 61.4, 61.5, 61.7, 63.1, 63.8 corresponding to C-6' in agreement with the presence of five species. Complete assignment of either sugar protons or carbons was not possible due to the overlap of their signals. The doublet of the β-anomeric proton of the pyranosyl isomer **12b** was assigned at δ 4.28 with $J_{1',2'}$ = 7.6 Hz, correlating with the triplet of H-2' at δ 2.89 that consequently correlated with H-3' at δ 3.01. The pyranosyl ring structure was confirmed from the downfield assignment of C-5' at δ_C 78.1. ^{1}H-^{13}C-HMQC experiment showed that the signals corresponding to C-1', C-2', C-3' and C-4' resonated at δ_C 97.2, 75.1, 70.6 and 77.1, respectively. The anomeric α-proton was observed at δ 4.90 which correlated with the doublet of doublets of H-2'α at δ 3.14 with $J_{1',2'}$ = 3.6 Hz, whereas their corresponding carbons resonated at δ_C 92.6 and 70.9, respectively.

Signals corresponding to protons and carbons of the pyridyl moiety for all products were similar and were assigned based on 1D and 2D NMR experiments. The ^{1}H NMR spectra of all products typically showed H-6 as the most downfield shift at δ_H 8.59, as a doublet correlating to H-5' (δ_H 7.49), appearing as a dd, which in turn was correlating to H-4 (δ_H 7.86), appearing as a ddd which correlated to H-3 (δ_H 8.08) that appeared as a doublet. Signals for the respective carbons were assigned based on ^{13}C, DEPT-135º and ^{1}HMQC experiments; observed at δ_C 149.2 (C-6), 126.2 (C-5), 137.8 (C-4), 121.6 (C-3) while C-2 showed as quaternary carbon in the region δ_C 150.5 ppm. The C=NH amidrazone carbon was assigned at δ_C 156.7.



Scheme 2

Reaction of D-xylose and D-glucose with amidrazone **1**, gave products in which the pyranose ring structure was predominant whereas the acyclic structure was found to be more favorable for the products from D-arabinose, D-mannose and D-galactose. The carbohydrate structure and the nature of the amidrazone determines the ratio of the acyclic and/or cyclic compounds in solution.[9]

Experimental Section

General Procedures. Melting points were determined on a Mel-temp apparatus and are uncorrected. Mass spectra were recorded using Electron Impact (EI) on a Finnian MAT 312 spectrometer and Fast-Atom bombardment (FAB) on a Kratos MS 50 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DRX 600 MHz or a Bruker Avance 300 MHz spectrometer. The chemical shifts are expressed on the δ-scale using Me_4Si as a standard, and coupling–constant values are given in Hz. The assignments of ^{1}H NMR spectra were based on chemical-shift correlation DQFCOSY spectra, while the assignment of ^{13}C NMR spectra were based on heteronuclear multiple quantum coherence (HMQC) experiments. TLC was preformed on Merck Silica Gel 60F254 with detection by charring in sulfuric acid and by UV light. Microanalyses were preformed in the Microanalysis Unit at the Faculty of Science, Cairo University.

General procedure for reaction of 2-pyridylcarboxamidrazone with aldoses

A mixture of the aldose (10 mmol) and 2-pyridylcarboxamidrazone **1** (10 mmol) in ethanol (50 ml) was heated under reflux for 2-5 hours. The reaction mixture was then concentrated and left to cool. Fractional crystallization of the product gave the amidrazones and dihydrazidine.

***N*^{2}-(D-Arabinose)-*N*^{1}-2-pyridylcarboxamidrazone (5).** Pale yellow crystals (78 %), m.p. 168-170 °C, ^{1}H NMR (600 MHz, DMSO-d$_6$ + D$_2$O) δ (ppm) 3.43 (dd, 1 H, H-5', $J_{4',5'}$ = 5.9 Hz, $J_{5',5''}$ = 11.2 Hz), 3.50 (dd, 1 H, H-3', $J_{2',3'}$ = 2.4 Hz, $J_{3',4'}$ = 8.4 Hz), 3.54-3.57 (m, 1 H, H-4'), 3.62 (dd, 1 H, H-5", $J_{4',5''}$ = 3.3 Hz, $J_{5',5''}$ = 11.2 Hz), 4.46 (dd, 1 H, H-2', $J_{1',2'}$ = 4.2 Hz, $J_{2',3'}$ = 2.4 Hz), 7.49 (dd, 1 H, H-5, $J_{5,6}$ = 4.9 Hz, $J_{4,5}$ = 7.6 Hz), 7.77 (d, 1 H, H-1', $J_{1',2'}$ = 4.2 Hz), 7.86 (ddd, 1 H, H-4, $J_{4,3}$ = 7.8 Hz, $J_{4,5}$ = 7.6 Hz, $J_{4,6}$ = 1.4 Hz), 8.08 (d, 1 H, H-3, $J_{3,4}$ = 7.9 Hz), 8.59 (d, 1 H, H-6, $J_{5,6}$ = 4.9 Hz). ^{13}C NMR (150.8 MHz, DMSO-d$_6$ +D$_2$O) δ (ppm) 63.8 (C-5'), 70.8 (C-2'), 73.1 (C-3'), 71.5 (C-4'), 121.6 (C-3), 126.2 (C-5), 137.8 (C-4), 149.2 (C-6), 150.5 (C-2), 156.7 (NC=N), 159.7 (C-1'); FABMS *m/z* = 269 (MH$^{+\cdot}$). Analylsis for $C_{11}H_{16}N_4O_4$ (268.27), calcd: C, 49.25; H, 6.01; N, 20.88; Found: C, 49.12; H, 6.05; N, 20.71 %.

***N*^{2}-(α-D-Xylopyranosyl)-*N*^{1}-2-pyridylcarboxamidrazone and *N*^{2}-(β-D-xylopyranosyl)-*N*^{1}-2-pyridylcarboxamidrazone (6bα and 6bβ).** Hygroscopic glassy product (78 %), α:β (2:3), ^{1}H NMR (300 MHz, DMSO-d$_6$ + D$_2$O) for α-anomer **6b**α δ (ppm) 3.16 (d, 0.4 H, H-2', $J_{1',2'}$ = 3.5 Hz), 3.27-3.31 (m, 0.4 H, Hz, H-4'), 3.38 (dd, 0.4 H, H-3', $J_{3',4'}$ = 7.6 Hz), 3.35-3.42 (m, 0.8 H, H-5',5"), 4.86 (d, 0.4 H, H-1'- α, $J_{1',2'}$ = 3.5 Hz). ^{13}C NMR (DMSO-d$_6$) δ (ppm) 60.3 (C-5'), 69.0 (C-4'), 71.1 (C-2'), 71.9 (C-3'), 91.3 (C-1'- α), FABMS *m/z* = 268(M$^{+\cdot}$).

^{1}H NMR (DMSO-d$_6$+ D$_2$O) for β-anomer **6b**β δ (ppm) 2.89 (t, 0.6 H, H-2', $J_{1',2'}$ = $J_{2',3'}$ = 8.9 Hz), 3.09 (dd, 0.6 H, H-5', $J_{5',4'}$ = 8.9 Hz, $J_{5',5''}$ = 11.3 Hz), 3.12 (m, 0.6 H, H-3'), 3.30 (m, 0.6 H, H-4'), 3.65 (dd, 0.6 H, H-5", $J_{4',5''}$ = 5.4 Hz, $J_{5',5''}$ = 11.3 Hz), 4.23 (d, 0.6 H, H-1'- β, $J_{1',2'}$ = 7.7 Hz). ^{13}C NMR (DMSO-d$_6$) δ (ppm) 64.5 (C-5'), 68.6 (C-4'), 73.5 (C-2'), 75.5 (C-3'), 96.6 (C-1'- β).

***N*^{2}-(D-Galactose)-*N*^{1}-2-pyridylcarboxamidrazone and *N*^{2}-(β-D-galactopyranosyl)-*N*^{1}-2-pyridylcarboxamidrazone (10a,b).** Pale yellow crystals (65 %), m.p. 124-126 °C, ^{1}H NMR (600 MHz, DMSO-d$_6$ + D$_2$O) for **10a** δ (ppm) 3.38 (dd, 1.6 H, H-6', 6", $J_{6',5'}$ = 5.2 Hz, $J_{6'',5'}$ = 6.6 Hz, $J_{6',6''}$ = 9.5 Hz), 3.56 (d, 0.8 H, H-4', $J_{4',3'}$ = 9.2 Hz), 3.76 (under DMSO, H-3'), 4.49 (d, 0.8 H, H-2', $J_{2',3'}$ = 2.3 Hz), 7.49 (dd, 0.8 H, H-5', $J_{5',6'}$ = 5.2 Hz, $J_{5',4'}$ = 6.7 Hz), 7.80 (d, 0.8 H, H-1', $J_{1',2'}$ = 4.1 Hz), 7.86 (ddd, 0.8 H, H-4, $J_{3,4}$ = 7.9 Hz, $J_{4,5}$ = 1.30 Hz), 8.10 (d, 0.8 H, H-3, $J_{3,4}$ = 7.9 Hz), 8.60 (d, 0.8 H, H-6, $J_{5,6}$ = 4.5 Hz).

^{13}C NMR (150.8 MHz, DMSO-d$_6$) δ (ppm) 63.3 (C-6'), 69.6 (C-4'), 70.1 (C-5'), 70.8 (C-2'), 71.9 (C-3'), 121.7 (C-3), 125.9 (C-5), 137.5 (C-4), 148.9 (C-6), 150.5 (C-2), 156.4 (NC=N), 159.9 (C-1').

^{1}H NMR (600 MHz, DMSO-d$_6$+ D$_2$O) for **10b** δ (ppm) 3.40 (d, 0.2 H, H-3', $J_{3',4'}$ = 3.6 Hz), 3.41 (under DMSO, H-5'), 3.47 (dd, 0.4 H, H-6',6", $J_{6',5'}$ = 4.7 Hz, $J_{6'',5''}$ = 6.3 Hz, $J_{6',6''}$ = 11.8 Hz), 3.63 (dd, 0.2 H, H-2', $J_{1',2'}$ = 8.9 Hz, $J_{2',3'}$ = 8.2 Hz), 3.76 (under DMSO, H-4'), 4.20 (d, 0.2 H, H-1', $J_{1',2'}$ = 8.9 Hz). ^{13}C NMR (150.8 MHz, DMSO-d$_6$) δ (ppm) 61.2 (C-6'), 68.9 (C-4'), 71.9 (C-2'), 74.5 (C-3'), 76.4 (C-5'), 91.7 (C-1'); FABMS *m/z* = 299 (MH$^{+\cdot}$). Analysis for $C_{12}H_{18}N_4O_5$ (298.30): Calcd: C, 48.32; H, 6.08; N, 18.78. Found: C, 48.11; H, 5.91; N, 18.59 %.

***N*^{2}-(D-Mannose)-*N*^{1}-2-pyridylcarboxamidrazone and *N*^{2}-(α-D-mannopyranosyl)-*N*^{1}-2-pyridylcarboxamidrazone (11a,b).** Pale yellow crystals (80%), m.p. 164-166 °C, ^{1}H NMR (600 MHz, DMSO-d$_6$ + D$_2$O) for **11a** δ (ppm) 3.42 (dd, 0.8 H, H-6', $J_{5',6'}$ = 6.1 Hz, $J_{6',6''}$ =11.7 Hz),

3.48-3.50 (m, 0.8 H, H-5'), 3.60 (t, 0.8 H, H-4', $J_{4',3'}$ = $J_{4',5'}$ = 8.5 Hz), 3.63 (dd, 0.8 H, H-6'', $J_{5',6''}$ = 2.9 Hz, $J_{6',6''}$ = 11.7 Hz), 3.69 (t, 0.8 H, H-3', $J_{3',4'}$ = $J_{2',3'}$ = 8.5 Hz), 4.21 (dd, 0.8 H, H-2', $J_{1',2'}$ = 4.8 Hz, $J_{2',3'}$ = 8.5 Hz), 7.49 (dd, 0.8 H, H-5, $J_{5,6}$ = 5.3 Hz, $J_{4,5}$ = 6.8 Hz), 7.84 (d, 0.8 H, H-1', $J_{1',2'}$ = 4.9 Hz), 7.88 (dd, 0.8 H, H-4, $J_{3,4}$ = 7.9 Hz, $J_{4,5}$ = 6.8 Hz), 8.09 (d, 0.8 H, H-3, $J_{3,4}$ = 7.9 Hz), 8.59 (d, 0.8 H, H-6, $J_{5,6}$ = 4.21 Hz). ^{13}C NMR (150.8 MHz, DMSO-d_6) δ (ppm) 64.2 (C-6'), 70.1 (C-4'), 70.8 (C-2'), 71.5 (C-5'), 71.8 (C-3'), 121.6 (C-3), 126.2 (C-5), 137.8 (C-4), 149.2 (C-6), 151.1 (C-2), 156.6 (NC=N), 159.9 (C-1'). ^{1}H NMR for **11b** δ (ppm) 3.14 (m, 0.2 H, H-5'), 3.33 (t, 0.2 H, H-4'), 3.37 (bd, 0.2 H, H-6', $J_{6',5'}$ = 2.9 Hz), 3.48 (m, 0.2 H, H-6''), 3.60 (d, 0.2 H, H-2', $J_{1',2'}$ = 8.6 Hz), 3.8 (d, 0.2 H, H-3'), 4.48 (bs, 0.2 H, H-1'). ^{13}C NMR (DMSO-d_6) δ (ppm) 61.9 (C-6'), 67.6 (C-4'), 71.3 (C-3'), 74.6 (C-2'), 78.7 (C-5'), 88.0 (C-1'); FABMS *m/z* = 299 (MH^{+-}). Analylsis for $C_{12}H_{18}N_4O_5$ (298.30) calcd: C, 48.32; H, 6.08; N, 18.78; Found: C, 48.17; H, 6.01; N, 18.69 %.

***N*^{2}-(D-Glucose)-*N*^{1}-2-pyridylcarboxamidrazone and *N*^{2}-(α,β-D-glucopyranosyl and α,β-D-glucofuranosyl)-*N*^{1}-2-pyridylcarboxamidrazone (12a,b,c).** Hygroscopic glassy product (75 %), ^{1}H NMR (300 MHz, DMSO-d_6 + D_2O) δ (ppm) 2.89 (t, H-2' β py, $J_{1',2'}$ = 7.6 Hz), 3.01 (m, H-3' β py), 3.14 (dd, H-2'α, $J_{1',2'}$ = 3.6 Hz, $J_{2',3'}$ = 9.2 Hz), 4.28 (d, H-1' β, $J_{1',2'}$ = 7.6 Hz), 4.90 (d, H-1' α, $J_{1',2'}$ = 3.6 Hz).

^{13}C NMR (DMSO-d_6) δ (ppm) 61.7 (C-6'), 61.5 (C-6' β py), 70.6 (C-3' β py), 70.9 (C-2' α), 75.1 (C-2' β py), 77.1 (C-4' β py), 78.1 (C-5' β py), 92.6 (C-1' α), 97.2 (C-1' β py), 162.9 (C-1'=N).

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