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Graphical Abstract

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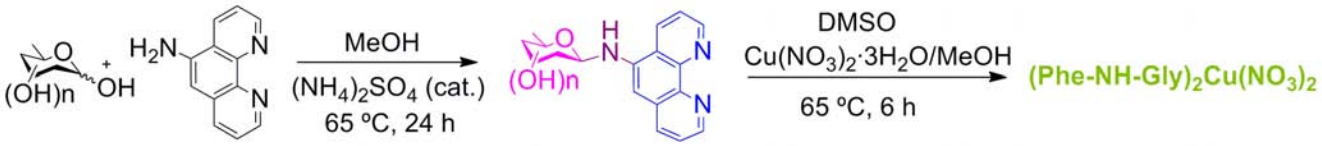

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ABSTRACT

A series of novel *N*-(1,10-phenanthrolin-5-yl)-β-glycopyranosylamines was obtained with excellent stereoselectivity and synthetically useful yields by treatment of 5-amino-1,10-phenanthroline with different unprotected monosaccharides, using $(NH_4)_2SO_4$ as an efficient promoter. Copper(II) complexes having a 2:1 mole ratio of the bidentate ligand phenanthroline *N*-glycoside and the metal were also prepared.

1. Introduction

Glycosylamines are important in carbohydrate enzymology and some of them are considered to be inhibitors of glycosidases.[1] Inhibition of glycosidase enzymes is at the heart of the therapy of numerous diseases, since they are involved in varied and essential biological processes. Thus, rebeccamycin analogues are indolocarbazole *N*-glycosides with antitumor activity that can inhibit topoisomerase I, kinases and/or bind to DNA according to their chemical structure.[2] Many carbohydrates, both neutral and positively charged, are known to be generally good binders for nucleic acids, and the interaction occurs mainly throughout the minor groove because of their hydrogen-bonding ability and large hydrophobic patches. On the other hand, heterocyclic compounds such as 1,10-phenanthroline and 2,2'-bipyridine are powerful bidentate metal chelators with applications in diverse areas, and different metal complexes have been extensively studied for their nuclease-like activity.[3,4]

The development of novel chemical compounds capable of modulating human telomerase activity is currently a very active and competitive area of research, mainly because of its potential applications in the treatment of cancer and age-related diseases.[5,6] The enzymatic activity of this ribonucleoprotein, encharged of telomere length maintenance in humans, is overexpressed in 85-90% of cancer patients,[7] which has led to the recognition of telomerase as a feasible drug target.[8] Among the different approaches for the design of telomerase inhibitors, selective G-quadruplex ligands are currently attracting much attention,[9] due to the prevalence of DNA G-quadruplex folding architectures in many genomic regions of biological interest, such as gene promoters and human telomeres.[9,10]

We are interested in the preparation of metallo-organic molecules that can selectively bind and stabilize the G-quadruplex DNA structures,[11] as they can act as human telomerase inhibitors.[12,13] Some common structural features of the designed compounds have been shown to contribute to binding: they are water-soluble metal complexes containing flat aromatic surfaces -to favour π stacking interactions with the DNA G-tetrads-,[11] they incorporate lateral side-chains that can act as groove binding moieties by electrostatic interactions and/or H-bonds, and they contain positively charged metal atoms to simulate the role of potassium or sodium ions at stabilizing the quadruplex structure under physiological conditions.[12] Phenanthroline serves as the scaffold for several potent stabilizers of DNA G-quadruplexes,[13] which can act as human telomerase inhibitors and are currently receiving much attention as potential targets for anticancer drug development.

Based on the hypothesis that sugars add important features to the shape and the stereoelectronic properties of a molecule and often play an essential role in the biological activity, we wished to explore the DNA-binding properties of metal complexes of *N*-heteroaryl glycosylamines including two structural components: a heteroaromatic system –DNA intercalating moiety- and a carbohydrate unit- minor/major groove-binding moiety- (Scheme 1). Although few data have been reported about the interactions

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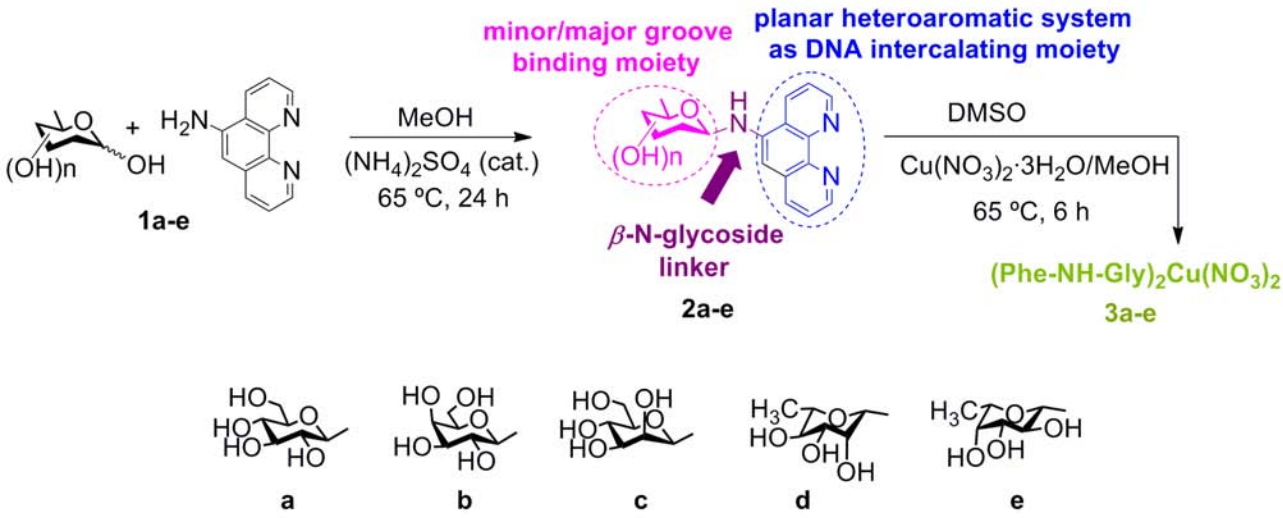


Scheme 1

Table 1. *N*-Glycosylation reactions of 5-amino-1,10-phenanthroline

Entry	Monosaccharide	Method[a]	Reaction medium	Temperature (ºC)	Reaction time (h)	Glycopyranosylamine, yield (%)[c]
1	D-glucose	A	Methanol	65	72	**2a**, 20-26
2		B	Aqueous phosphate buffer[b]	40	5	12
3		C	Methanol-aqueous phosphate buffer (1:1)	65	74	72
4		D	Methanol/$(NH_4)_2SO_4$	65	24	88
5				65	48	79
6	D-galactose	D	Methanol/$(NH_4)_2SO_4$	65	24	**2b**, 68
7	D-mannose	D	Methanol/$(NH_4)_2SO_4$	65	24	**2c**, 90
8				65	48	80
9	L-rhamnose	D	Methanol/$(NH_4)_2SO_4$	65	24	**2d**, 90
10				65	48	81
11	L-fucose	D	Methanol/$(NH_4)_2SO_4$	65	24	**2e**, 67

[a] Molar ratio monosaccharide:amine 3:1 for entries 1 (yield 20%), 3-11 and 4:1 for entries 1 (yield 26%) and 2. [amine] = 0.06 M except for entry 2 0.13 M.
[b] Aqueous phosphate buffer Na_2HPO_4/NaH_2PO_4, 50 mM, pH 6.5.
[c] Yields of isolated products except for entries 1-3 in which cases these values correspond to the conversion of starting amine and were determined by ^{1}H-NMR (± 1%).

between carbohydrates and G-quadruplexes, recent studies on sugar-DNA conjugates have shown that favourable interactions occur between the carbohydrate and the DNA G-tetrad through stacking interactions as well as hydrogen bonding or hydrophobic contacts, when they are available.[14] Moreover, it has been shown that carbohydrates can give rise to significant differences in the affinity for a quadruplex target and they are promising motifs for selective G-quadruplex recognition and the design of new G-quadruplexes ligands.[14,15]

In this paper we describe the synthesis and characterization of a series of *N*-(1,10-phenanthrolin-5-yl)-β-glycopyranosylamines **2a-e** and their copper(II) complexes (Scheme 1). *N*-glycosylation reactions were accomplished by treatment of 5-amino-1,10-phenanthroline with different unprotected monosaccharides using $(NH_4)_2SO_4$ as a convenient promoter. To the best of our knowledge, these phenanthroline *N*-glycosides and their complexes have been not reported previously.

2. Results and discussion

Few synthetic methods have been reported for the direct *N*-glycosylation of aromatic compounds and carbohydrates without hydroxyl protection or activation.[16-23] Usually, the reaction can be accomplished by heating at reflux in protic solvents and, in some cases, better results can be achieved under mildly acidic conditions.[16-23] It is known that the reaction is strongly influenced by the reactivity of the starting amine and the best preparative yields were obtained for aromatic amines of moderate basicity.[18-20] An increase of the amine basicity seems to be related with lesser stability of the *N*-glycoside, which undergoes side reactions more easily.[18] Hydrolysis, Amadori rearrangement or melanoidine formation were described mainly in water, at high temperature and in acid media.[18,21,22] Moreover, the steric features of the amine and the sugar as well as the reaction conditions exert a strong influence on the stereoselectivity of the *N*-glycosylation. Frequently, mixtures of the α and β anomers are obtained.[19,23]

As a first step toward the synthesis of the *N*-phenanthroline glycosylamines, we decided to study the *N*-glycosylation of 5-amino-1,10-phenanthroline and D-glucose in order to optimize the reaction conditions in terms of yield, reaction time and stereoselectivity of the *N*-glycosidic linkage. According to a coupling strategy developed for the glycosylation of indolines and applied for the synthesis of some indolo[2,3-a]carbazol glycosides,[20] the *N*-glycosylation reactions were performed using a large excess of sugar (3-4 equiv.). Heating in methanol resulted in low conversion even after 72 h (20-26%, Table 1, entry 1). In aqueous phosphate buffer at pH 6.5[22] during 5 h at 40 ºC lesser conversion was observed (12% Table 1, entry 2). Using a 1:1 mixture of methanol and aqueous phosphate buffer to work in homogeneous medium at 65 ºC for 74 h the yield could be increased to 72%. (Table 1, entry 3). With 3 equiv. of monosaccharide and a catalytic amount of $(NH_4)_2SO_4$ as activator[20] in methanol at 65 ºC for 24 h the starting 5-amino-1,10-phenanthroline was exhausted and the *N*-glycosylation occurred stereoselectively leading to the *N*-β-glycoside.

By using this procedure 5-amino-1,10-phenanthroline could be glycosylated stereoselectively and the conversion was nearly quantitative for all monosaccharides tested: D-glucose, D-galacto se, D-mannose, L-rhamnose and L-fucose. The *N*-β-glycopyranosylamines **2a-e** (Scheme 1) could be obtained in synthetically useful yields. α- Anomers and/or other by-products were not detectable in yields higher than 2%. The products were isolated in yields ranging from 67% to 90% (Table 1, entries 4, 6, 7, 9 and 11); the lower yields being due to the fact that derivatives **2b** and **2e** were more difficult to purify. Longer reaction times led to lower yields (Table 1, entries 5, 8 and 10) probably because the resulting *N*-glycosides underwent slow transformations (decomposition, hydrolysis, Amadori rearrangement, etc.) in the reaction conditions. This trend suggests that the yield is ultimately limited by the stability of the *N*-β-glycopyranosylamine.

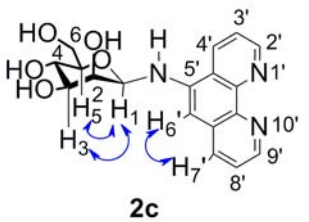
The copper(II) complexes **3a-e** were prepared by adding an ethanolic solution of $Cu(NO_3)_2{\cdot}3H_2O$ to the corresponding *N*-phenanthroline glycosylamine **2a-e** (Phe-NH-Gly) in dimethylsulfoxide and heating the mixture at 65 ºC for 6 h. A 2:1 molar ratio ligand:copper salt was employed and the complexes were isolated in good yields (ranging from 64 to 80%). Interestingly, Cu complexation improved the solubility properties of the *N*-glycopyranosylamines. This behaviour is particularly important for the potential applications of these metallo-organic derivatives.

The *N*-glycopyranosylamines **2a-e** were studied in depth by ^1H and ^{13}C NMR in $(CD_3)_2SO$. 2D-NMR techniques (^1H-^1H gCOSY, TOCSY, ROESYAD, gC2HSQCSE, gCH2MBC) were used for the identification and unambiguous assignment of the proton and carbon resonances. At 300 and 500 MHz the ^1H NMR spectra of **2a-e** in $(CD_3)_2SO$ exhibited high complexity in the region around 3.2-5.2 ppm corresponding to the saccharide moieties, due to the observation of the vicinal coupling constants with OH and NH protons. Changes observed after D_2O addition facilitated the identification of acidic OH and NH proton resonances and the analysis of the remaining signals. The interpretation of the ^1H-^1H COSY and TOCSY spectra was based on the unequivocal assignment of the signals corresponding to the anomeric protons (H-1) and the 6-OH protons (apparent triplet) in **2a-c** or CH_3-6 groups in **2d**,**e** owing to their shape and chemical shifts. In all cases, the NH proton appeared as a doublet about 6.3-6.9 ppm. Aromatic protons resonate around 9.1-7.0 ppm and the introduction of carbohydrate moieties only slightly affected their chemical shifts. From COSY and TOCSY correla tions two groups of aromatic signals could be differentiated. The assignment of these sets of signals to the two pyridine rings of the phenanthroline system was based on the NOE correlations found in the 2D ROESY spectra (Scheme 2). Thus, in the case of **2a** the correlation between the singlet due to H-6' at 7.00 ppm and the doublet of doublets centred at 8.12 ppm allowed the assignment of this signal to H-7' while H-4' resonates at 8.84 ppm. The analysis of the direct and long-range ^1H-^{13}C correlated spectra (gC2HSQCSE and gCH2MBC) allowed the assignment of carbon resonances, once the signals of the respective protons were established. Data are given in Table 2 and in the experimental section.

Table 2. Selected NMR parameters of the *N*-β-glycopyranosylamines **2a-e**

	1	2a	2b	2c	2d	2e
δ(ppm)						
H-1	-	4.64	4.62	5.01	5.02	4.62
NH	6.14	6.89	6.90	6.27	6.24	6.86
H-6'	6.84	7.00	7.01	7.07	7.03	6.97
H-7'	8.03	8.12	8.11	8.13	8.20	8.17
H-4'	8.66	8.84	8.87	8.60	8.59	8.86
C-1	-	84.7	85.2	81.4	81.0	84.8
J (Hz)						
$^3J_{H1\text{-}H2}$	-	8.4	8.5	-	-	8.5
$^3J_{H1\text{-}NH}$	-	7.7	7.6	9.0	9.0	7.9
$^1J_{C1\text{-}H1}$	-	151	151	158	157	151

The β-anomeric configuration was assigned on the basis of NOE experiments (2D ROESY spectra). The NOE cross-peaks observed between H-1 and H-3/H-5 protons in all cases and between H-1 and H-2 protons in **2c**,**d** (Scheme 2) indicate an axial disposition of the anomeric proton. In **2a**,**b**,**e** the large vicinal coupling constant of 7.6-7.9 Hz between anomeric H-1 and H-2 shows their *trans*-diaxial orientation and corroborates β-configuration.[17,19,23,24] Moreover, anomeric proton and carbon chemical shifts[17,19,23,24] as well as the value of the ^{13}C-^1H direct coupling constant for the C-1 carbon ($^1J_{CH}$ = 151-158 Hz, Table 2)[25] also support this statement. The experimental values of the vicinal coupling constants for the protons of the pyranoside ring indicate that these derivatives are almost completely in the $^4C_1$ conformation (**2a**,**b**,**c**) or $^1C_4$ form (**2d**,**e**). The large values of coupling constants $^3J_{NH\text{-}H1}$ (7.6-9.0 Hz, Table 2) are consistent with an *anti* relationship between NH and H-1 in $(CD_3)_2SO$ solution and may be rationalized in terms of a conformation around C1-N bond that exhibits stabilizing exo-anomeric interactions,[25] greater for β-manno and β-rhamno derivatives



2c

Scheme 2

(**2c**,**d**). The comparison of the aromatic and NH proton chemical shifts of the *N*-glycopyranosilamines **2a-e** with those of the parent amine **1** indicates a deshielding of NH (ca. 0.7 ppm) and aromatic H-4' and H-6' protons (ca. 0.2 ppm) when 2-OH adopts an equatorial position (**2a**,**b**,**e**, Table 2). The different values of $^{3}J_{NH-H1}$ seem to be also influenced by the spatial disposition of the 2-OH. These findings might be related to a small dependence of these parameters on the conformation around the C1-N bond and/or the hydrogen bonding pattern, influenced by the 2-OH spatial orientation.

The Cu(II) complexes **3a-e** were characterized by elemental analysis, MS spectrometry and FTIR-spectroscopy. A common structural feature in these derivatives is the presence of a 2:1 mole ratio of the bidentate ligand and the metal. In order to avoid interferences, ESI-MS spectra were recorded using water as mobile phase. When the spectra were obtained in aqueous acetic acid higher fragmentation and partial interchange of NO_3^- anion for CH_3COO^- was observed leading to a superposition of sets of peaks with *m/z* differences of 3 units. Thus, for **3a** [Cu(Phe-NH-Gly)$_2$NO$_3$]$^+$/ [Cu(Phe-NH-Gly)$_2$CH$_3$COO]$^+$ and [Cu(Phe-NH-Gly)NO$_3$]$^+$/ [Cu(Phe-NH-Gly)CH$_3$COO]$^+$ species were found in the spectrum. In these conditions the divalent fragment [Cu(Phe-NH-Gly)$_2$]$^{2+}$ was also detected. In general, the complexes exhibited very comparable IR features, suggesting that they are of similar structure. A sharp band at ca. 1384 cm^{-1} appeared after complex formation which was assigned to NO_3^- vibration. The strong broad band in the region of 3300-3400 cm^{-1} corresponding to O-H and N-H stretching vibrations showed a shift of 40 cm^{-1} towards lower frequency in **3b** while it was shifted to higher frequency in **3c** (50 cm^{-1}), **3d** (72 cm^{-1}) and **3e** (20 cm^{-1}) compared to the ligands. These changes might be related to the existence of different hydrogen bond networks in complexes and in the free *N*-glycopyranosylamines.

The same coordination environments around copper centre can be assumed for the Cu(II) complexes **3a-e** bearing in mind the similar behaviour observed. However, detailed structure studies by X-ray analysis were not possible because of the difficulties in obtaining suitable crystals, and exact coordination geometry and spatial disposition of the non-symmetrical substituted *N*-phenanthroline glycosylamine ligands could not be established. Structure studies on related Cu(II) complexes indicate that the copper atom is usually pentacoordinate and that geometries ranging from distorted trigonal bipyramidal to square pyramidal are typical of them.[26]

3. Conclusion

Treatment of 5-amino-1,10-phenanthroline with different unprotected monosaccharides under optimized conditions led to *N*-(1,10-phenanthrolin-5-yl)-β-glycopyranosylamines with excellent stereoselectivity and synthetically useful yields. Cu(II) complexes having a 2:1 mole ratio of the bidentate ligand phenanthroline *N*-glycoside and the metal were also prepared with good yields. Regarding the potential applications, the high solubility of these metallo-organic compounds may be particularly important for an efficient activity. In addition, the introduction of chirality via the carbohydrate unit might confer selectivity and good binding affinity towards the chiral DNA biomolecule. Further experiments designed to confirm these hypotheses are currently underway.

4. Experimental

4.1. General methods

All reagents were commercially available (Sigma-Aldrich) in high purity and used as received. The *N*-glycosylation reactions were monitored by thin-layer chromatography (TLC) and their composition was determined by ^{1}H-NMR spectroscopy. TLC was performed on precoated Kieselgel 60 F_{254} aluminium sheets; plates were eluted with methanol, dried and then eluted with methanol-NH_4OH (30%) 10:1; detection was first by UV and then by charring with sulphuric acid in ethanol (1:4, v/v). Flash chromatography was performed on Fluka Silica Gel 60 (230-400 mesh) enriched with approx. 0.1% Ca, using methanol as eluent. Melting points were taken on an Electrothermal Digital IA9100 apparatus and were uncorrected. Optical rotations were measured in HPLC grade dimethylsulfoxide on a Perkin-Elmer 341 polarimeter; $[\alpha]_D$ values are given in 10^{-1} deg·cm^2·g^{-1}; concentration is given in mg·mL^{-1}. FAB mass spectra were obtained on a V. G. Autoexpec spectrometer using 3-nitrobenzyl alcohol as the matrix. ESI mass (+ mode) spectra were performed on a Thermo Scientific TSQ Quantum LC/MS or an Agilent 6210 LC/MS/TOF instruments. IR spectra (KBr disks) were recorded on a FT-IR Perkin-Elmer Spectrum 2000 spectrophotometer. All NMR spectra (^{1}H, ^{13}C, 2D ^{1}H-^{1}H gCOSY, TOCSY, ROESYAD, gC2HSQCSE, gCH2MBC) were recorded on a Varian 300 UNITY-Plus or VNMRS-500 spectrometer in $(CD_3)_2SO$ at 298 K using standard pulse sequences. Chemical shifts are reported relative to the residual $(CHD_2)_2SO$ (δ_H 2.50 ppm), or $(CD_3)_2SO$ (δ_C 39.5 ppm); resonance patterns are reported with the notations s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet); in addition, the notations ap and br are used to indicate an apparent multiplicity and a broad signal; geminal H-6 protons at the sugar moieties resonating at low and high frequency were assigned as H-6a and H-6b, respectively. Lorentz-Gauss transformation was used to improve the resolution of the ^{1}H NMR spectra. Errors: ^{1}H, $\delta \pm 0.01$ ppm, $J \pm 0.1$ Hz; ^{13}C, $\delta \pm 0.1$ ppm.

5-Amino-1,10-phenanthroline (1) was prepared from 5-nitro-1,10-phenanthroline as previously described[27] by reduction with hydrazine hydrate using Pd/C 10% as catalyst. δ_H (500 MHz; $(CD_3)_2SO$) 6.14 (2H, br s, NH_2), 6.84 (1H, s, H-6), 7.49 (1H, dd, *J* 8.1, 4.3 Hz, H-8), 7.72 (1H, dd, *J* 8.4, 4.3 Hz, H-3), 8.03 (1H, dd, *J* 8.1, 1.7 Hz, H-7), 8.66 (1H, dd, *J* 8.4, 1.7 Hz, H-4), 8.67 (1H, dd, *J* 4.3, 1.7 Hz, H-9), 9.04 (1H, dd, *J* 4.3, 1.7 Hz, H-2). δ_C (125 MHz; $(CD_3)_2SO$) 101.8 (C-6), 121.8 (C-4a), 122.0 (C-3), 123.2 (C-8), 130.6 (C-6a), 130.8 (C-4), 132.7 (C-7), 140.5, 142.7 (C-5, C-10a), 144.8 C-9), 146.2 (C-10b), 149.3 (C-2).

4.2. Synthesis of N-(1,10-phenanthrolin-5-yl)-β-glycopyranosyl amines

General Procedures

Method A. 5-Amino-1,10-phenanthroline (49 mg, 0.25 mmol) was dissolved in 4 mL of MeOH. D-glucose monohydrate (0.75 or 1.00 mmol) was then added and the mixture was stirred at 65 ºC. After 72 h, the reaction was allowed to cool to room temperature and concentrated.

Method B. A stirred suspension of 5-amino-1,10-phenanthroline (49 mg, 0.25 mmol) and D-glucose monohydrate (198 mg, 1.00 mmol) in 2 mL of aqueous Na_2HPO_4/NaH_2PO_4, (50 mM, pH 6.5) was heated at 40 ºC for 5 h. The reaction mixture was worked up as described above.

Method C. This procedure is analogous to method B using a 1:1 mixture of MeOH (2 mL, to dissolve the amine) and aqueous

phosphate buffer (2 mL) and a molar ratio monosaccharide: amine 3:1 at 65 ºC for 74 h.

Method D. A stirred solution of the 5-amino-1,10-phenanthroline (195 mg, 1 mmol), the monosaccharide (3 mmol) and ca. 4 mg of $(NH_4)_2SO_4$ in 16 mL of MeOH was heated at 65 ºC for 24 or 48 h. During this time a pale yellow precipitate was accumulated. The reaction mixture was cooled and the solid obtained was separated by filtration and washed with MeOH (2x10 mL) and H_2O (2x10 mL) to eliminate excess of sugar and possible traces of the starting amine and/or other by-products as well to remove the $(NH_4)_2SO_4$ salt, followed by Et_2O. This protocol provided pure *N*-(1,10-phenanthrolin-5-yl)-β-glycopyranosyl amines 2a, 2c and 2d. For derivatives 2b and 2e the starting sugar could not be completely removed and a subsequent purification was required. The product was preadsorbed on silica gel and purified by flash chromatography. After drying in vacuum the purity of the products was checked by TLC, ^{1}H-NMR and analytical data. Derivatives 2a-e were obtained as monohydrates and exhibited poor solubility in water and organic solvents.

***N*-(1,10-phenanthrolin-5-yl)-β-*D*-glucopyranosylamine (2a)**. Pale yellow powder; yield: 332 mg (88%); R_f = 0.51; mp 214-216 ºC (decomposition); [Found: C, 57.2; H, 5.6; N, 11.4. $C_{18}H_{19}N_3O_5{\cdot}H_2O$ requires C, 57.6; H, 5.6; N, 11.2%]; $[\alpha]_D^{22}$ -130 (*c* 3.03 in DMSO); IR (KBr) ν_{max} 3355 br (NH and OH), 1621 s (δ NH), 1548 s (C=C), 1077 s, 1028 s, 737 cm^{-1}; δ_H (500 MHz; $(CD_3)_2SO$) 3.21 (1H, tdap, *J* 9.6, 8.7, 5.1 Hz, H-4), 3.34 (1H, tdap, *J* 8.7, 8.1, 4.4 Hz, H-3), 3.39 (1H, ddd, *J* 9.6, 5.6, 2.2 Hz, H-5), 3.49 (2H, m, H-2, H-6a), 3.73(1H, ddd, *J* -11.8, 5.7, 2.2 Hz, H-6b), 4.48 (1H, tap, *J* 5.7 Hz, 6-OH), 4.64 (1H, tap, *J* 8.4, 7.7 Hz, H-1), 4.97 (1H, d, *J* 5.1 Hz, 4-OH), 5.05 (2H, dap, *J* 4.4 Hz, 2-OH, 3-OH), 6.89 (1H, d, *J* 7.7 Hz, NH), 7.00 (1H, s, H-6´), 7.55 (1H, dd, *J* 8.1, 4.3 Hz, H-8'), 7.75 (1H, dd, *J* 8.4, 4.3 Hz, H-3'), 8.12 (1H, dd, *J* 8.1, 1.6 Hz, H-7'), 8.74 (1H, dd, *J* 4.3, 1.6 Hz, H-9'), 8.84 (1H, dd, *J* 8.4, 1.6 Hz, H-4'), 9.05 (1H, dd, *J* 4.3, 1.6 Hz, H-2'); δ_C (125 MHz; $(CD_3)_2SO$) 60.4 (C-6), 69.7 (C-4), 72.1 (C-2), 77.1, 77.2 (C-3, C-5), 84.7 (C-1, $^1J_{C1\text{-}H1}$=151 Hz), 101.3 (C-6'), 121.5, 121.6 (C-3', C-4'a), 122.8 (C-8'), 129.6, 130.1 (C-4', C-6'a), 133.3 (C-7'), 139.90, 140.5 (C-5', C-10'a), 145.2, 145.4 (C-9', C-10'b), 148.9 (C-2'); LRMS (ESI) *m/z* 358 $(M + H)^+$.

***N*-(1,10-phenanthrolin-5-yl)-β-*D*-galactopyranosylamine (2b).** Pale yellow powder; yield: 254 mg (68%); R_f = 0.45; mp 225-228 ºC (decomposition); [Found: C, 57.3; H, 5.3; N, 11.5. $C_{18}H_{19}N_3O_5{\cdot}H_2O$ requires C, 57.6; H, 5.6; N, 11.2%]; $[\alpha]_D^{22}$ -95 (*c* 2.54 in DMSO); IR (KBr) ν_{max} 3402 br (NH and OH), 1616 s (δ NH), 1538 s (C=C), 1075 s, 1042 s, 737 cm^{-1}; δ_H (500 MHz; $(CD_3)_2SO$) 3.48 (1H, ddd, *J* 9.3, 5.0, 3.3 Hz, H-3), 3.52 (1H, ddd, *J* -11.3, 5.5, 4.0 Hz, H-6a), 3.57 (1H, ddd, *J* -11.3, 6.1, 4.5 Hz, H-6b), 3.66 (1H, tap, *J* 6.1, 5.5 Hz, H-5), 3.80 (1H, dd, *J 3.9*, 3.3 Hz, H-4), 3.82 (1H, ddd, *J* 9.3, 8.5, 5.0 Hz, H-2), 4.46 (1H, d, *J* 3.9 Hz, 4-OH), 4.61 (1H, tap, *J* 4.5, 4.0 Hz, 6-OH), 4.62 (1H, tap, *J* 8.5, 7.6 Hz, H-1), 4.86 (1H, d, *J* 5.0 Hz, 3-OH), 4.92 (1H, d, *J* 5.0 Hz, 2-OH), 6.90 (1H, d, *J* 7.6 Hz, NH), 7.01 (1H, s, H-6'), 7.56 (1H, dd, *J* 8.1, 4.2 Hz, H-8'), 7.75(1H, dd, *J* 8.5, 4.2 Hz, H-3'), 8.11 (1H, dd, *J* 8.1, 1.7 Hz, H-7'), 8.75 (1H, dd, *J* 4.2, 1.7 Hz, H-9'), 8.87 (1H, dd, *J* 8.5, 1.6 Hz, H-4'), 9.06 (1H, dd, *J* 4.2, 1.6 Hz, H-2'); δ_C (125 MHz; $(CD_3)_2SO$) 60.1 (C-6), 67.9 (C-4), 69.2 (C-2), 73.7 (C-3), 75.4 (C-5), 85.2 (C-1, $^1J_{C1\text{-}H1}$ 151 Hz), 101.2 (C-6'), 121.5 (C-3', C-4'a), 122.8 (C-8'), 129.6, 130.2 (C-4', C-6'a), 133.2 (C-7'), 139.9, 140.5 (C-5', C-10'a), 145.2, 145.4 (C-9', C-10'b), 148.8 (C-2'); LRMS (ESI) *m/z* 358 $(M + H)^+$.

***N*-(1,10-phenanthrolin-5-yl)-β-*D*-mannopyranosylamine (2c).** Slightly yellowish solid; yield: 336 mg (90%)**;** R_f = 0.42; mp 239-242 ºC (decomposition); [Found: C, 57.7; H, 5.5; N, 11.4. $C_{18}H_{19}N_3O_5{\cdot}H_2O$ requires C, 57.6; H, 5.6; N, 11.2%]; $[\alpha]_D^{22}$ -149 (*c* 1.70 in DMSO); IR (KBr) ν_{max} 3307 br (NH and OH), 1617 s (δ NH), 1520 s (C=C), 1086 s, 1058 s, 741 cm^{-1}; δ_H (500 MHz; $(CD_3)_2SO$) 3.34 (1H, ddd, *J* 9.4, 5.9, 2.1 Hz, H-5), 3.45 (1H, ddd, *J* 9.4, 9.1, 4.9 Hz, H-4), 3.47 (1H, ddd, *J* -11.7, 6.3, 5.9 Hz, H-6a), 3.50 (1H, ddd, *J* 9.1, 6.1, 3.2 Hz, H-3), 3.73 (1H, ddd, *J* -11.7,5.4, 2.1 Hz, H-6b), 3.93 (1H, dd, *J* 4.9, 3.2 Hz, H-2), 4.40 (1H, dd, *J* 6.3, 5.4 Hz, 6-OH), 4.74 (1H, d, *J* 6.1 Hz, 3-OH), 4.80 (1H, d, *J* 4.9 Hz, 4-OH), 5.01 (1H, d, *J* 9.0 Hz, H-1), 5.20 (1H, d, *J* 4.9 Hz, 2-OH), 6.27 (1H, d, *J* 9.0 Hz, NH), 7.07 (1H, s, H-6'), 7.58 (1H, dd, *J* 8.1, 4.2 Hz, H-8'), 7.78(1H, dd, *J* 8.6, 4.2 Hz, H-3'), 8.13 (1H, dd, *J* 8.1, 1.6 Hz, H-7'), 8.60 (1H, dd, *J* 8.8, 1.6 Hz, H-4'), 8.7 7 (1H, dd, *J* 4.2, 1.6 Hz, H-9'), 9.08 (1H, dd, *J* 4.2, 1.6 Hz, H-2'); δ_C (125 MHz; $(CD_3)_2SO$) 60.7 (C-6), 66.7 (C-4), 70.6 (C-2), 73.8 (C-3), 77.7 (C-5), 81.4 (C-1, $^1J_{C1\text{-}H1}$ 158 Hz), 102.5 (C-6'), 121.4 , 121.9(C-3', C-4'a), 122.8 (C-8'), 129.2, 129.5 (C-4', C-6'a), 133.4 (C-7'), 138.7, 140.7 (C-5', C-10'a), 145.4, 145.5 (C-9', C-10'b), 149.0 (C-2'); LRMS (ESI) *m/z* 358 $(M + H)^+$.

***N*-(1,10-phenanthrolin-5-yl)-β-*L*-rhamnopyranosylamine (2d)** Slightly yellowish solid; yield: 324 mg (90%); R_f = 0.58; mp 216-218 ºC (decomposition); [Found: C, 60.5; H, 5.7; N, 11.4. $C_{18}H_{19}N_3O_4{\cdot}H_2O$ requires C, 60.2; H, 5.9; N, 11.7%]; $[\alpha]_D^{22}$ +119 (*c* 2.80 in DMSO); IR (KBr) ν_{max} 3308 br (NH and OH), 1617 s (δ NH), 1519 s (C=C), 1091 s, 1066 s, 739 cm^{-1}; δ_H (500 MHz; $(CD_3)_2SO$) 1.19 (3H, d, *J* 6.2 Hz, CH_3-6), 3.23 (1H, tdap, *J* 9.3, 5.4 Hz, H-4), 3.42 (1H, dq, *J* 9.3, 6.2 Hz, H-5), 3.46 (1H, ddd, *J* 9.3, 6.0, 3.4 Hz, H-3), 3.92 (1H, dd, *J* 5.0, 3.4 Hz, H-2), 4.73 (1H, d, *J* 6.0 Hz, 3-OH), 4.84 (1H, d, *J* 5.4 Hz, 4-OH), 5.02 (1H, d, *J* 9.0 Hz, H-1), 5.23 (1H, d, *J* 5.0 Hz, 2-OH), 6.24 (1H, d, *J* 9.0 Hz, NH), 7.03 (1H, s, H-6'), 7.57 (1H, dd, *J* 8.1, 4.2 Hz, H-8'), 7.78 (1H, dd, *J* 8.4, 4.2 Hz, H-3'), 8.20 (1H, dd, *J* 8.1, 1.8 Hz, H-7'), 8.59 (1H, dd, *J* 8.4, 1.6 Hz, H-4'), 8.77 (1H, dd, *J* 4.2, 1.8 Hz, H-9'), 9.08 (1H, dd, *J* 4.2, 1.6 Hz, H-2'); δ_C (125 MHz; $(CD_3)_2SO$) 17.6 (C-6), 70.7, 71.6 (C-2, C-4), 72.3, 73.5 (C-3, C-5), 81.0 (C-1, $^1J_{C1\text{-}H1}$ 157 Hz), 102.0 (C-6'), 121.3, 121.9(C-3', C-4'a), 122.8 (C-8'), 129.2, 129.4 (C-4', C-6'a), 133.4 (C-7'), 138.6, 140.7 (C-5', C-10'a), 145.4, 145.6 (C-9', C-10'b), 149.0 (C-2'); LRMS (ESI) *m/z* 342 $(M + H)^+$.

***N*-(1,10-phenanthrolin-5-yl)-β-L-fucopyranosylamine (2e).** Pale yellow powder; yield: 239 mg (67%); R_f = 0.55; mp 230-232 ºC (decomposition); [Found: C, 60.4; H, 6.2; N, 12.0. $C_{18}H_{19}N_3O_4{\cdot}H_2O$ requires C, 60.2; H, 5.9; N, 11.7%]; $[\alpha]_D^{22}$ +82 (*c* 2.01 in DMSO); IR (KBr) ν_{max} 3384 br (NH and OH), 1618 s (δ NH), 1542 s (C=C), 1081 s, 1069 s, 735 cm^{-1}; δ_H (500 MHz; $(CD_3)_2SO$) 1.18 (3H, d, *J* 6.3, CH_3-6), 3.49 (1H, ddd, *J* 9.4, 5.4, 3.3, H-3), 3.57 (1H, tap, *J* 4.3, 3.3, H-4), 3.79 (1H, ddd, *J* 9.4, 8.5, 5.1, H-2), 3846 (1H, q, *J* 6.3, H-5), 3.80 (1H, dd, *J 3.9*, 3.3m, H-4), 3.82 (1H, ddd, *J* 9.3, 8.5, 5.0, H-2), 4.46 (1H, d, *J 3.9*, 4-OH), 4.50 (1H, d, *J* 4.3, 4-OH), 4.62 (1H, tap, *J* 8.5, 7.9, H-1), 4.82 (1H, d, *J* 5.4, 3-OH), 4.86 (1H, d, *J* 5.1, 2-OH), 6.86 (1H, d, *J* 7.9, NH), 6.97 (1H, s, H-6'), 7.56 (1H, dd, *J* 8.2, 4.2, H-8'), 7.76 (1H, dd, *J* 8.6, 4.2 Hz, H-3'), 8.17 (1H, dd, *J* 8.2, 1.7, H-7'), 8.75 (1H, dd, *J* 4.2, 1.7, H-9'), 8.86 (1H, dd, *J* 8.6, 1.6, H-4'), 9.07 (1H, dd, *J* 4.2, 1.6, H-2'); δ_C (125 MHz; $(CD_3)_2SO$) 16.5 (C-6), 68.9 (C-2), 70.2 (C-5), 70.8 (C-4), 73.8 (C-3), 84.8 (C-1, $^1J_{C1\text{-}H1}$ 151 Hz), 100.8 (C-6'), 121.5, 121.6 (C-3', C-4'a), 122.8 (C-8'), 129.7, 130.3 (C-4', C-6'a), 133.3 (C-7'), 140.1, 140.5 (C-5', C-10'a), 145.2, 145.4 (C-9', C-10'b), 148.9 (C-2'); LRMS (ESI) *m/z* 342 $(M + H)^+$.

Synthesis of copper(II) complexes.

General method. A stirred suspension of the *N*-phenanthroline glycopyranosylamine **2a-e** (0.1 mmol) in DMSO (1 mL) was heated at 65 ºC for 30 min (a clear solution was obtained for **2a**, **2b** and **2e**) and then an ethanol solution of $Cu(NO_3)_2{\cdot}3H_2O$ (0.052 M, 0.052 mmol) was added. The colour changed immediately to dark green and after heating for 6 h at this temperature the solution obtained was allowed to stand overnight at room temperature. Solvents were removed and the residue dissolved in the minimum amount of MeOH and treated with acetonitrile. The precipitate was separated out, washed with acetonitrile and dried in vacuum, affording the pure Cu(II) complexes **3a-e** as green powders. Single crystals suitable for X-ray analysis could not be obtained in the different conditions assayed. While the *N*-phenanthroline glycopyranosylamines **2a-e** have disappointing solubility, their Cu complexes exhibited better solubility properties.

Cu(Phe-NH-Glucopyranosylamine)$_2$(NO$_3$)$_2$·4H$_2$O (3a). Green powder; yield: 41 mg (84%); [Found: C, 43.9; H, 4.6; N, 11.4. $C_{36}H_{38}CuN_8O_{16}{\cdot}4H_2O$ requires C, 44.4; H, 4.8; N, 11.5%]; IR (KBr) ν_{max} 3355 br (NH and OH), 1625 (δ NH), 1600, 1542 (C=C), 1384 s (NO_3^-), 1074, 1015, 724 cm^{-1}; FAB-MS (m-NBA) *m/z* 839 (M –NO_3)$^+$; LRMS (ESI, H_2O-CH_3COOH) *m/z* 839 (2) (M – NO_3)$^+$ [Cu(Phe-NH-Gly)$_2$NO$_3$]$^+$, 836 (10) [Cu(Phe-NH-Gly)$_2$CH$_3$COO]$^+$, 482 (35) Cu(Phe-NH-Gly)NO$_3$]$^+$, 479 (68) [Cu(Phe-NH-Gly)CH$_3$COO]$^+$, 388.5 (47) [Cu(Phe-NH-Gly)$_2$]$^{+2}$, 358 (100%) [(Phe-NH-Gly) + H]$^+$; HRMS (ESI-TOF, H_2O): (M – NO_3)$^+$ [Cu(Phe-NH-Gly)$_2$NO$_3$]$^+$, found 839.1820 $C_{36}H_{38}CuN_7O_{13}$ requires 839.1824.

Cu(Phe-NH-Galactopyranosylamine)$_2$(NO$_3$)$_2$·4H$_2$O (3b). Dark green powder; yield: 39 mg (80%); [Found: C, 44.0; H, 4.7; N, 11.7. $C_{36}H_{38}CuN_8O_{16}{\cdot}4H_2O$ requires C, 44.4; H, 4.8; N, 11.5%]; IR (KBr) ν_{max} 3365 br (NH and OH), 1623 (δ NH), 1535 (C=C), 1384 s (NO_3^-), 1082 br, 724 cm^{-1}; LRMS (ESI, H_2O) *m/z* 839 (M – NO_3)$^+$ [Cu(Phe-NH-Gly)$_2$NO$_3$]$^+$.

Cu(Phe-NH-Mannopyranosylamine)$_2$(NO$_3$)$_2$·4H$_2$O (3c). Green powder; yield: 46 mg (86%); [Found: C, 44.1; H, 4.5; N, 11.9. $C_{36}H_{38}CuN_8O_{16}{\cdot}4H_2O$ requires C, 44.4; H, 4.8; N, 11.5%];. IR (KBr) ν_{max} 3351 br (NH and OH), 1624 (δ NH), 1528 (C=C), 1384 s (NO_3^-), 1104 br, 721 cm^{-1}; LRMS (ESI, H_2O) *m/z* 839 (M – NO_3)$^+$ [Cu(Phe-NH-Gly)$_2$NO$_3$]$^+$.

Cu(Phe-NH-Rhamnopyranosylamine)$_2$NO$_3$)$_2$·4H$_2$O (3d). Green powder; yield: 30 mg (64%); [Found: C, 45.5; H, 4.5; N, 12.3. $C_{36}H_{38}CuN_8O_{14}{\cdot}4H_2O$ requires C, 45.9; H, 4.9; N, 11.9%]; IR (KBr) ν_{max} 3380 br (NH and OH), 1623 (δ NH), 1528 (C=C), 1384 s (NO_3^-), 1107 br, 1056 br, 721 cm^{-1}; LRMS (ESI, H_2O) *m/z* 807 (M – NO_3)$^+$ [Cu(Phe-NH-Gly)$_2$NO$_3$]$^+$.

Cu(Phe-NH-Fucopyranosylamine)$_2$(NO$_3$)$_2$·4H$_2$O (3e). Green powder; yield: 33 mg (70%); [Found: C, 45.4; H, 4.6; N, 11.6. $C_{36}H_{38}CuN_8O_{14}{\cdot}4H_2O$ requires C, 45.9; H, 4.9; N, 11.9%]; IR (KBr) ν_{max} 3406 br (NH and OH), 1623 (δ NH), 1536 (C=C), 1383 s (NO_3^-), 1085 br, 726 cm^{-1}; LRMS (ESI, H_2O) *m/z* 807 (M – NO_3)$^+$ [Cu(Phe-NH-Gly)$_2$NO$_3$]$^+$.

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Supplementary Material

^{1}H and ^{13}C NMR spectra of *N*-(1,10-phenanthrolin-5-yl)-β-glycopyranosylamines **2a-e,** 2D-NMR spectra of **2a** and MS spectra of Cu(II) complex **3a**. Supplementary data associated with this article can be found at…

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Figure Captions

Scheme 1. Synthesis of *N*-(1,10-phenanthrolin-5-yl) β-glycopyranosylamines **2a-e** and their copper(II) complexes

Scheme 2. Glycopyranosylamine **2c** showing the atomic numbering and NOE contacts.

Table(s)

Table 1. *N*-Glycosylation reactions of 5-amino-1,10-phenanthroline

Entry	Monosaccharide	Method[a]	Reaction medium	Temperature (ºC)	Reaction time (h)	Glycopyranosylamine, yield (%)[c]
1	D-glucose	A	Methanol	65	72	**2a**, 20-26
2		B	Aqueous phosphate buffer[b]	40	5	12
3		C	Methanol-aqueous phosphate buffer (1:1)	65	74	72
4		D	Methanol/$(NH_4)_2SO_4$	65	24	88
5				65	48	79
6	D-galactose	D	Methanol/$(NH_4)_2SO_4$	65	24	**2b**, 68
7	D-mannose	D	Methanol/$(NH_4)_2SO_4$	65	24	**2c**, 90
8				65	48	80
9	L-rhamnose	D	Methanol/$(NH_4)_2SO_4$	65	24	**2d**, 90
10				65	48	81
11	L-fucose	D	Methanol/$(NH_4)_2SO_4$	65	24	**2e**, 67

[a] Molar ratio monosaccharide:amine 3:1 for entries 1 (yield 20%), 3-11 and 4:1 for entries 1 (yield 26%) and 2. [amine] = 0.06 M except for entry 2 0.13 M.
[b] Aqueous phosphate buffer Na_2HPO_4/NaH_2PO_4, 50 mM, pH 6.5.
[c] Yields of isolated products except for entries 1-3 in which cases these values correspond to the conversion of starting amine and were determined by ^{1}H-NMR (± 1%).