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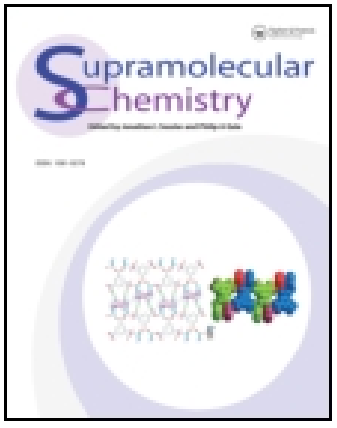

Supramolecular Chemistry
Publication details, including instructions for authors and subscription information:
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Published online: 29 Aug 2013.

To cite this article: Andrea Taladriz-Sender & Cristina Vicent (2013) Synthesis of cationic glyco-oligoamide for DNA-carbohydrate interaction studies, Supramolecular Chemistry, 25:9-11, 656-664, DOI: 10.1080/10610278.2013.814776

To link to this article: http://dx.doi.org/10.1080/10610278.2013.814776

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*Supramolecular Chemistry*, 2013
Vol. 25, Nos. 9–11, 656–664, http://dx.doi.org/10.1080/10610278.2013.814776

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# Synthesis of cationic glyco-oligoamide for DNA–carbohydrate interaction studies

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(*Received 8 May 2013; final version received 5 June 2013*)

We are using carbohydrate-based ligands, glyco-oligoamides, as a strategy to obtain structural and thermodynamic information on carbohydrate–minor groove DNA binding. In order to improve the solubility of the first generation of neutral ligands type **1** in aqueous solution and the stability of the complexes formed with DNA as well as their sequence selectivity towards AT/TA base pairs, a new cationic vector β-D-Xyl-Py-γ[3(*R*)$NH_3^+$]-Py-Ind **2** has been designed. Here, we present an efficient convergent solution-phase synthesis of the xylose cationic glyco-oligoamide **2**, evidence of improvement of water solubility and the binding to polymers of DNA when compared with the xylose neutral ligand **1**. This synthetic work paves the way to the synthesis of glyco-oligoamides with carbohydrates which contain in their structure cooperative hydrogen bonding centres based on our previous studies on carbohydrate cooperativity in apolar media and the use of the new design to achieve multivalency with calixaren-based platforms.

**Keywords:** molecular recognition; carbohydrate interactions; carbohydrate–DNA binding

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## Introduction

The study, at molecular level, of interaction of carbohydrates with the grooves of DNA is a relevant field because sugars take part in relevant drugs as Calicheamicine or mitramicine that binds DNA, and the sugar residue is responsible for the sequences selectivity of the ligand (*1*). In addition, they take part in the structure of nuclear glycoproteins which act as a transcription factor, and in some cases there is a correlation between glycosylation and DNA complex formation (*2*, *3*). The interactions at the origin of neutral carbohydrates recognition processes are hydrogen bonding and CH–π interactions as proposed initially by Lemieux and Quiocho after inspection of the crystalline structure of lectine–carbohydrate complexes (*4*, *5*). However, quantification in water of their contribution to binding in different recognition processes is at the moment a question of current debate (*6–8*). We want to learn to control these interactions in the context of DNA groove binding.

Thus, sugar-oligoamides have been designed and synthesised as structurally simple carbohydrate-based ligands to study the carbohydrate–minor groove DNA interactions (*9–14*).

The ligand designed for this purpose has a neutral oligoamide type structure, which resembles the structures of the naturally occurring antibiotics distamycin A and netropsin (two minor groove binders), and was based on the 'DNA recognition code' of Dervan (*15–19*).

As an example, Figure 1 shows the structure of xylose neutral ligand (β-D-Xyl-Py-γ-Py-Ind) which has been deeply studied. Even though we have succeeded in the initial study of carbohydrate–DNA binding with the neutral vector (**1**), the need to obtain the thermodynamic parameters of the interaction with oligonucleotides arises. Thus, in order to improve the solubility of these neutral ligands in aqueous solution and the stability of the complexes formed with DNA as well as their sequence selectivity towards AT/TA base pairs, the new cationic vector has been designed (Figure 1).

According to several studies by Dervan (*20*, *21*) and Sugiyama (*22*, *23*), selective chiral substitution on the γ-aminobutyric acid linker with a cationic group ($NH_3^+$) enhances the properties of the polyamide hairpins with regard to DNA affinity and sequence specificity. Thus, we have selected the side-by-side pairing of pyrrole amino acids (Py) covalently joined head-to-tail by an (*R*)-3,4-diaminobutyric acid linker (**6**) which results in a β-amine residue at the γ-turn unit (γ[3(*R*)$NH_3^+$]). Consequently, the core of the molecule keeps a design comparable to our neutral vector analogue (Figure 1, compound **2**). Again, the carbohydrate for study was placed at C-terminal and an indole ring (Ind) was included at the N-terminal, with the aim to drive the conformational equilibrium towards the folded conformation through CH–π interactions, as already achieved in our previous design.

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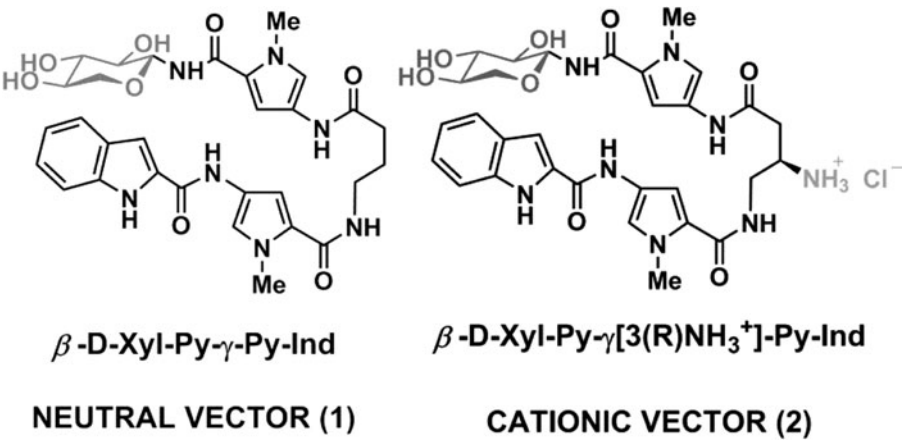


Figure 1. Structure of xylose neutral vector (β-D-Xyl-Py-γ-Py-Ind) (**1**) and cationic vector β-D-Xyl-Py-γ[3(*R*)$NH_3^+$]-Py-Ind (**2**).

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Most of the synthesis of oligoamides involves the formation of amide bonds in solid phase, whereas the solution-phase strategy is less well developed due to purification problems (*22*, *24*–*28*). However, these techniques intrinsically limit the scale of synthesis. Our synthetic efforts are focused on developing an efficient solution-phase synthesis, avoiding arduous purifications that would allow us access to diverse families of glyco-oligoamides.

Regarding our previous synthetic work, we have explored and developed two solution-phase synthesis methods that allowed access to neutral glyco-oligoamides (*9*, *14*). Our first synthesis (*9*) was planned as a convergent approach. The key step was the coupling of the sugar strand (Xyl-Py) with the indole moiety which contained the gamma fragment (HO-γ-Py-Ind). This pathway allowed us to obtain a first generation of neutral glyco-oligoamides with structural diversity in the carbohydrate residue. Later, our interest to study multivalent sugar-oligoamide systems brought us the opportunity to improve the synthetic methodology. Then a new linear synthesis allowed us to introduce a wild structural diversity in the sugar as well as in the pyrrole B (*14*). The skeleton of the oligoamide was obtained by a linear synthesis, incorporating the sugar at the last stage.

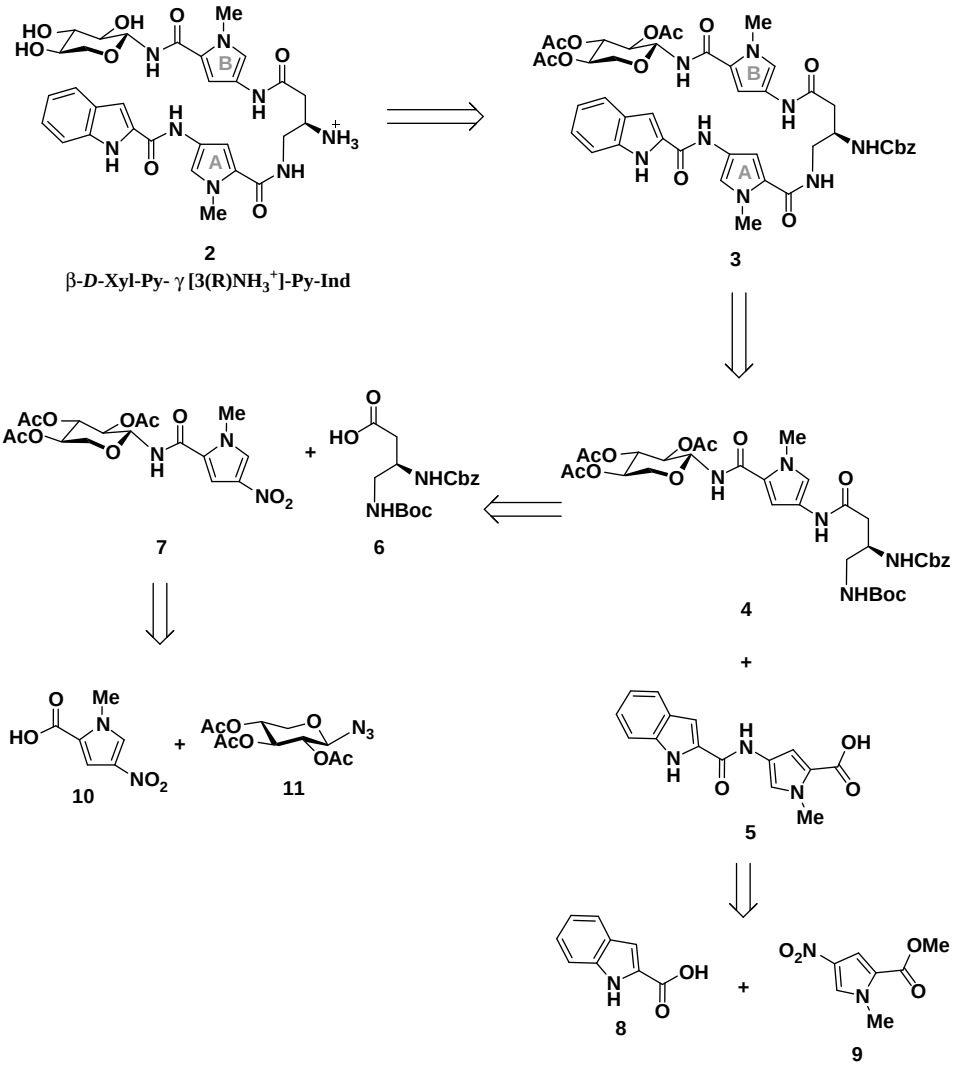
To synthesise the new cationic vector β-D-Xyl-Py-γ[3(*R*)$NH_3^+$]-Py-Ind (**2**), we need to reconsider the synthetic strategy. Here, we present a convergent solution-phase synthesis in which indole strand (OH-Py-Ind) was synthesised first, next the sugar strand (β-Xyl-Py-$NO_2$) was synthesised and finally the γ-diaminobutyric fragment was introduced. Incorporation of γ-diaminobutyric part in the last moment was crucial to avoid premature deprotection of the amino group or β-elimination. Here we show that this new pathway allows getting a new family of cationic glyco-oligoamides with the additional advantage of allowing introducing structural diversity in the γ-turn unit. Furthermore, an optimised synthesis has been developed, avoiding in several steps the use of column chromatography. Finally, evidence of enhancement of either solubility in water or qualitative binding affinity to poly(dA–dT)$_2$ of cationic ligand (**2**) compared with that of the corresponding neutral analogue β-D-Xyl-Py-γ-Py-Ind (**1**) is shown.

## Results and discussion

The new convergent solution-phase synthesis of β-D-Xyl-Py-γ[3(*R*)$NH_3^+$]-Py-Ind (**2**) was designed according to retrosynthetic analysis shown in Scheme 1. Coupling of the two subchains (β-Xyl-Py-γ[3(*R*)NHCbz]NHBoc) **4** and (HOPy-Ind) **5** will result in a convergent synthesis with fewer linear steps. The chains were built up from two separate suitably protected strands, incorporating γ-diaminobutyric building block at the last stage. Late introduction of this chiral fragment was crucial to avoid premature deprotection of the amino group in the γ-fragment or a β-elimination process. The key step of the synthesis is the final coupling of both strands.

Following the retrosynthetic pathway shown in Figure 1, preparation of cationic glyco-oligoamide, Xyl-Py-γ[3(*R*)$NH_3^+$]-Py-Ind (**2**) was achieved. Sequential couplings of Ind **8** to Py **9**, followed by ester saponification and coupling to Boc-deprotected sugar strand **4**, afford protected xylose-oligoamide **3** in a convergent manner. Sugar moiety **7** was prepared from building blocks **10** and **11,** which have been previously synthesised in our laboratory and by others (*14*, *24*).

The synthesis of the sugar strand **7** (β-Xyl-Py-$NO_2$) (Scheme 2) begins with the catalytic hydrogenation (10% Pd/C, MeOH) of xylose azide **11** to obtain amine **12**. The xylose azide compound was synthesised from commercially available xylose using a described procedure (*14*). 1-Methyl-4-nitropyrrole-2-carboxylic acid **10** (*24*) was prepared for coupling with protected amine **12**. The amido glycosidic bond formation to afford **7** is one of the key




Scheme 1. Retrosynthetic strategy for the convergent solution-phase synthesis of Xyl-Py-γ[3(*R*)$NH_3^+$]-Py-Ind **2**.

steps in the synthetic strategy. The choice of coupling reagents is always critical. In contrast to our previous convergent approach, amide **7** was reached by the activation of acid **10** with O-(Benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HBTU) and Hunig's base. A side reaction can often take place when using this coupling reagent. The amine reacting with the coupling agent can form a guanidinium by-product (*29*), thus the order of addition and timing are relevant. However, HBTU gave the best results affording amide **7** in 72% yield. Furthermore, a major fraction of the β-anomer was isolated by precipitation in EtOH with no need of chromatographic purification. Nitro group from **7** was converted into amine **13** by catalytic hydrogenation (10% Pd/C, DCM/MeOH) and used without further purification in the next amide bond formation. This time, the activation of commercially available acid **6** was carried out with (Benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP). The advantage of phosphonium salts over the aminium/uranium salts was to avoid the guanidinium side reaction (*30*). Therefore, introduction of gamma moiety was successfully achieved to obtain sugar fragment **4** (β-Xyl-Py-γ[3(*R*)NHCbz]NHBoc) in 70% yield.

Indole strand (OH-Py-Ind) was synthesised in two steps from the reduced methyl-4-nitropyrrole-2-carboxylate **9** by coupling PyBOP-activated indole-2-carboxylic acid **8**, yielding ester **15** in 90% yield. Saponification of the ester with 10% $NaOH_{(aq)}$ in dioxane yielded product **5**. Remarkably, chromatographic purifications were not required for the synthesis of this strand.

With both strands in hand (**4** and **5**), the assembly of core cationic xylose-oligoamide **2** was initiated (Scheme 3). Carbamate protecting group from sugar moiety **4** was removed with Trifluoroacetic acid (TFA) in Dichloromethane (DCM), yielding amine **16** in 95% yield. PyBOP-mediated coupling of indole fragment **5** to a small excess of

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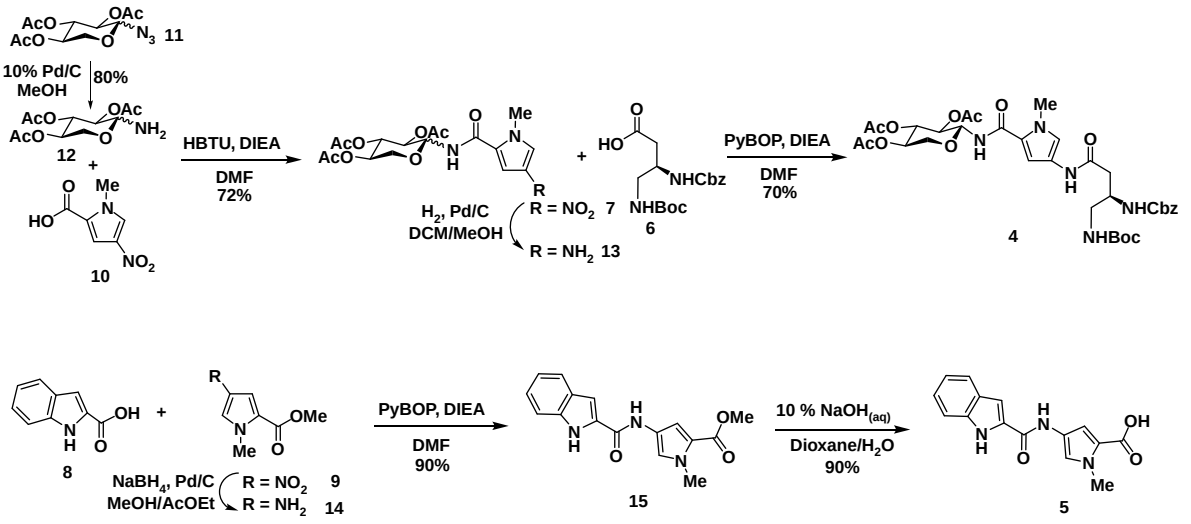


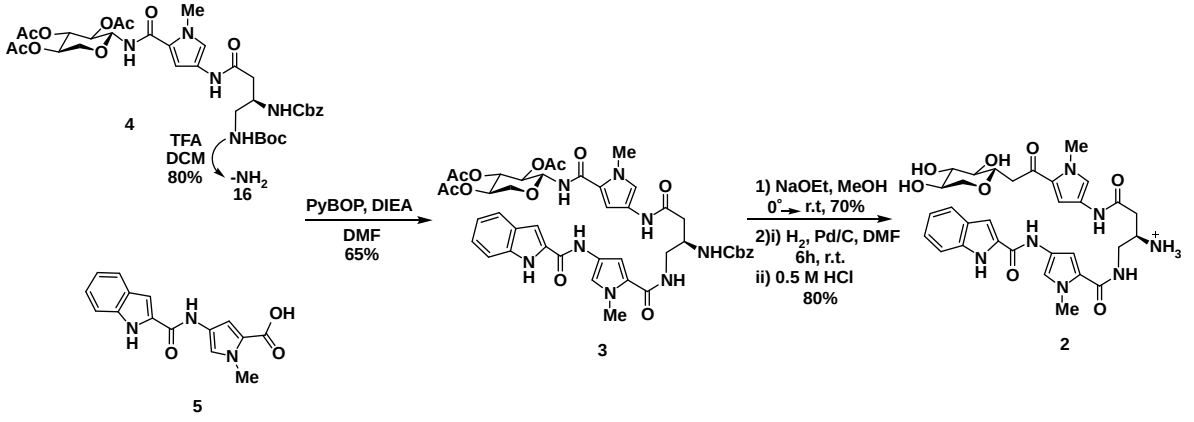

Scheme 2. Synthesis of sugar strand (β-Xyl-Py-γ[3(*R*)NHCbz]NHBoc) **4** and indole strand (OH-Py-Ind) **5**.

amine **16** delivered the desired protected xylose-oligoamide **3** in 65% yield. Acetate cleavage of the hydroxyl group from the sugar with sodium methoxide followed by Cbz deprotection by hydrogenation (Pd/C, 40 psi $H_2$) for 6–8 h affords free amine Xyl-Py-γ[3(*R*)$NH_2$]-Py-Ind. Subsequent treatment with HCl 0.5 M gives the target final product **2** which was purified by reverse-phase HPLC.

Solubility of both ligands **1** and **2** in phosphate buffer (pH 7.2) was analysed by UV–vis spectroscopy. Saturated solutions of both glyco-oligoamides were prepared, let to stabilise and filtered. Concentration of the resulting filtrate was measured by UV–vis spectroscopy using their respective molar extinction coefficients [$\varepsilon_{302} = 24{,}745\,M^{-1}\,cm^{-1}$ (**1**) and $\varepsilon_{302} = 24{,}938\,M^{-1}\,cm^{-1}$ (**2**)]. As was expected, concentration value obtained for the cationic xylose glyco-oligoamide (854 μM) was higher than for its neutral analogue (478 μM).

Preliminary interaction studies with poly(dA–dT)$_2$ were carried out to qualitatively evaluate the binding affinity of the new cationic glyco-oligoamide (**2**) which was compared with that of its neutral analogue (**1**). $^1$H NMR titrations with both glyco-oligoamides were carried out. Increasing amounts of poly(dA–dT)$_2$ were added to a constant concentration solution of cationic xylose glyco-oligoamide (**2**) and neutral xylose glyco-oligoamide (**1**), respectively, in phosphate buffer/$D_2O$. Differences in the kinetics of the free/bound exchange process could affect the chemical shifts, line intensities and/or the line widths of the ligand resonances. These perturbations enable monitoring of the DNA binding. In this qualitative $^1$H NMR binding experiment (*9*) with polymers of DNA, we follow the line broadening of resonances from compounds **1** and **2**, which eventually disappeared below the noise level upon addition of DNA. Complete disappearance of the $^1$H-signals indicates formation of the complex (Figure 2).

As can be observed in Figure 2, for equal ligand concentration, a significant difference (fivefold) in the ligand/polymer ratio is needed for complete disappearance




Scheme 3. Final coupling and global deprotection for the synthesis of Xyl-Py-γ[3(*R*)$NH_3^+$]-Py-Ind (**2**).

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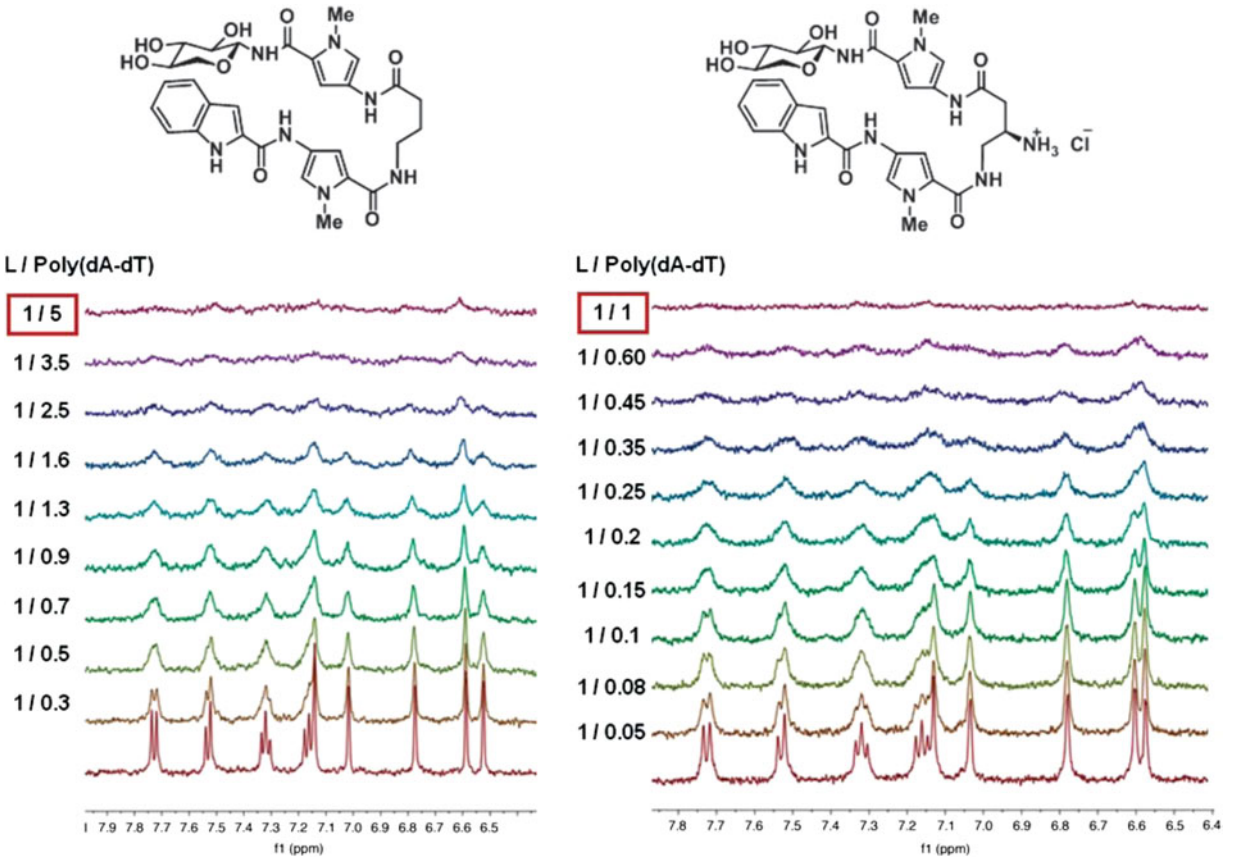


Figure 2. $^{1}$H NMR spectra of the aromatic region of neutral xylose glyco-oligoamide **1** and cationic xylose glyco-oligoamide **2** at different ratios ligand/poly(dA–dT)$_2$ in phosphate buffer/$D_2O$.

of the signals from cationic vector compared with the neutral vector, suggesting an improvement in the binding affinity.

## Conclusions

In conclusion, an efficient convergent solution-phase synthetic route to cationic glyco-oligoamides has been described. The xylose cationic glyco-oligoamide **2** was synthesised, and the solubility and preliminary binding studies to polymers of DNA suggested that either the solubility in aqueous solution or the binding to poly(dA–dT)$_2$ has been improved when compared with the neutral ligand **1**. This synthetic work paves the way to the synthesis of glyco-oligoamides with carbohydrates which contain in their structure cooperative hydrogen bonding centres based on our previous studies on carbohydrate cooperativity in apolar media (*31–35*), and the use of the new design to achieve multivalency with calixaren-based platforms (*36–38*) has already been successfully used for cell penetration and DNA delivery by the Parma group (*39*).

## Experimental

Chemicals were purchased from Sigma-Aldrich (Schnelldorf/Germany) and were used without further purification. (*R*)-3,4-Cbz-Dbu(Boc)-OH was purchased from Sigma-Aldrich CAS 108919-51-3 (code number 17974). Poly (dA–dT)$_2$, 25 μm, was purchased from Sigma-Aldrich (code number PO883) and used without further purification. Solvents were purified according to the standard procedures. Flash column chromatography was carried out by using silica gel (60 Å pore size, 40–63 μm, Merck, Darmstadt, Hesse, Germany). The reactions were monitored by thin layer chromatography on silica gel-coated plates (Merck 60 F254). NMR measurements were recorded on a Varian Inova-300 (300 MHz), Varian Inova-400 (400 MHz), Mercury-400 (400 MHz), Varian Unity-500 (500 MHz) and Bruker AVANCE 500 MHz spectrometers which were calibrated by using the residual undeuterated solvent as an internal reference. The abbreviations used to explain multiplicities are s, singlet; d, doublet; t, triplet; appt, apparent triplet; q, quartet; m, multiplet; br., broad. Mass spectrometry analyses were carried out with an HP series 1100 MSD by electrospray ionisation (ESI). High-resolution

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mass spectra (HR-MS) were recorded with an Agilent 6520-Accurate-Mass LC/MS Q-TOF mass spectrometer. IR experiments were recorded with a PerkinElmer Spectrum One FT-IR spectrometer (Shelton, CT, USA). Optical rotations were measured on a PerkinElmer 241MC polarimeter (Shelton, CT, USA) in a 1-dm cell. Elemental analyses were measured on a Carla Erba CHNS-O EA1108 chromatography system. Semi-preparative HPLC–MS was run with a SunFire Prep. C18, (50 mm × 4.6 mm × 5 μm) column on a Waters separation module (Waters 2545/SFO/2767) coupled to a Waters 3100 mass detector using ESI+. The fractions were collected with a Waters 2767 sampler manager. The following HPLC conditions were used: $H_2O$: $CH_3CN$ (98:2 → 5:95), $HCO_2H$ (0.1%), flow rate of 1 ml/min and UV detection using diode array ($\lambda = 190 - 400$ nm). The UV absorption spectra of the samples were recorded using a double-beam PerkinElmer Lambda 35 UV–vis spectrophotometer, with standard 10-mm path length cuvettes. The interval of measured wavelengths is between 200 and 600 nm. For all the cases, the scanning speed was fixed at 240 nm $min^{-1}$ and the width of the slits at 2 nm. The 0.2 μm nylon filters were provided by Symta (Madrid, Spain). Water was purified using a Milli-Q system. Melting points of solid compounds **2**–**5**, **7** and **15** are not reported because decomposition was observed below the melting temperature.

### *(AcO)$_3$-β-Xyl-Py-NO$_2$ (7)*

2,3,4-Tri-*O*-acetyl-β-D-xylopyranosylamine (**12**) obtained in 80% yield by hydrogenation (10% Pd/C, MeOH) (*14*) of the corresponding azide **11** (1.00 g, 3.32 mmol) was added to a mixture of HO-Py-$NO_2$ (**10**) (565 mg, 3.32 mmol), HBTU (1.38 g, 3.65 mmol) and DIEA (1.16 ml, 6.64 mmol) dissolved in DMF (2.0 ml) previously stirred at room temperature (rt) for 30 min. After 16 h, a white precipitate was formed in the reaction mixture. The precipitate was isolated by vacuum filtration, and cold ethanol was added to the residual filtrate yielding a white precipitate. Both precipitates were crystallised in pure ethanol to provide (AcO)3-Xyl-Py-$NO_2$ in 72% yield, as a white crystalline solid containing just a pure β-anomer (*9*). $R_f = 0.39$ ($CH_2Cl_2$:EtOAc, 8:2, v/v). $[\alpha]_D^{20} = -53.9$ ($c = 1$ in chloroform). $^1$H NMR (400 MHz, DMSO): $\delta$ 1.93 (s, 3H, $CH_3$), 1.98 (s, 3H, $CH_3$), 2.00 (s, 3H, $CH_3$), 3.61 (appt, $J = 10.9$ Hz, 1H, $H_5$ ax), 3.89 (s, 3H, $CH_3$), 3.91 (dd, $J = 5.5$ Hz, 11.2 Hz, 1H, $H_5$ ec), 4.82 (ddd, $J = 10.5$ Hz, 9.6, 5.5 Hz, 1H, $H_4$), 5.01 (appt, $J = 9.3$ Hz, 1H, $H_2$), 5.31 (appt, $J = 9.6$ Hz, 1H, $H_3$), 5.35 (appt, $J = 9.2$ Hz, 1H, $H_1$), 7.49 (d, $J = 2.0$ Hz, 1H, CH Py-3$^B$), 8.19 (d, $J = 2.0$ Hz, 1H, CH Py-5$^B$), 9.07 (d, $J = 9.3$ Hz, 1H, NH 5). $^{13}$C NMR (101 MHz, DMSO) $\delta$ 20.4 ($CH_3$), 20.5 ($CH_3$), 20.5 ($CH_3$), 37.5 ($NCH_3$), 63.3 ($CH_5$), 68.6 ($CH_4$), 70.6 ($CH_2$), 72.7 ($CH_3$), 77.7 ($CH_1$), 108.8 (CH Py-3$^B$), 125.1 (C Py), 128.8 (CH Py-5$^B$), 133.8 ($CNO_2$), 160.0 (CONH), 169.2 ($COCH_3$), 169.7 ($COCH_3$), 170.1 ($COCH_3$). MS (ES+) *m/z*: 450.0 $[M + Na]^+$, 428.0 $[M + H]^+$. Elemental analysis calcd (%) for $C_{17}H_{21}O_{10}N_3$ (427.36): C, 47.78; H, 4.95; N, 9.83. Found: C, 48.00; H, 5.02; N, 10.08. HR-MS-ESI: $m/z = 427.1227$, calcd for $C_{17}H_{21}O_{10}N_3$ $[M + H]^+$: 427.1223. IR (KBr) $\nu$ ($cm^{-1}$): 3375, 1739, 1531,1313, 1224, 1067 and 1036.

### *β-(OAc)$_3$Xyl-Py-γ[3(R)NHCbz]NHBoc (4)*

$(AcO)_3$-Xyl-Py-$NO_2$ (**7**) (375.0 mg, 0.90 mmol) dissolved in MeOH (5 ml) and DCM (5 ml) was treated with 10% Pd/C (68.5 mg, 20 mol%) and hydrogenated overnight. The mixture was filtered over a pad of Celite, and the solvent was removed under reduced pressure to afford amine (AcO) 3-Xyl-Py-$NH_2$ (**13**) which was used without further purification. In the meantime, a solution of (*R*)-3,4-Cbz-Dbu(Boc)-OH (**6**) (275.0 mg, 0.78 mmol) and PyBOP (447.5 mg, 0.86 mmol) in DMF (2 ml) and DIEA (367 μl, 2.11 mmol) was stirred at rt for 40 min. This solution was then added to amine **13** and stirred overnight at rt. Evaporation of the solvent and purification by column chromatography (Hex:EtOAc, gradient 1:2 to 1:10) afforded the title compound as yellowish solid (392 mg, 70%). $R_f = 0.37$ (Hex:EtOAc, 1:3, v/v). $[\alpha]_D^{20} = -7.2$ ($c = 0.95$ in DMSO). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 1.36 (s, 9H, *t*-Bu), 1.90 (s, 3H, $CH_3$), 1.97 (s, 3H, $CH_3$), 2.00 (s, 3H, $CH_3$), 2.35–2.41 (m, 2H, $CH_2$ $\gamma_c$), 3.03 (t, $J = 5.9$ Hz, 2H, $CH_2$ $\gamma_a$), 3.56 (appt, $J = 10.9$ Hz, 1H, $H_5$ ax), 3.77 (s, 3H, $NCH_3$), 3.90 (dd, $J = 10.9$ Hz, 5.6, 1H, $H_5$ ec), 3.93–3.97 (m, 1H, CH $\gamma_b$), 4.80 (ddd, $J = 10.1$, 10.1, 5.5 Hz, 1H, $H_4$), 4.98 (d, $J = 3.3$ Hz, 2H, $CH_2$ Cbz), 5.06 (appt, $J = 9.3$ Hz, 1H, $H_2$), 5.30 (appt, $J = 9.5$ Hz, 1H, $H_3$), 5.33 (appt, $J = 9.3$ Hz, 1H, $H_1$), 6.73 (d, $J = 1.6$ Hz, 1H, CH Py-3$^B$), 6.81 (t, $J = 5.9$ Hz, 1H, NHBoc), 7.06 (d, $J = 8.4$ Hz, 1H, NHCbz), 7.19 (d, $J = 1.6$ Hz, 1H, CH Py-5$^B$), 7.29–7.36 (m, 5H, Cbz), 8.60 (d, $J = 9.4$ Hz, 1H, $NH_5$), 9.82 (s, 1H, $NH_4$). $^{13}$C NMR (101 MHz, DMSO) $\delta$ 20.4 ($CH_3$), 20.5 ($CH_3$), 20.5 ($CH_3$), 28.2 (*t*-Bu), 36.1 ($CH_3$), 38.3 (CH $\gamma_a$), 43.4 (CH $\gamma_c$) 48.7 (CH $\gamma_b$), 63.3 ($CH_5$), 65.1 ($CH_2$Cbz), 68.7 ($CH_4$), 70.6 ($CH_2$), 72.8 ($CH_3$), 77.7 ($CH_1$), 77.8 (C *t*-Bu), 104.8 (CH Py-3$^B$), 119.0 (CH Py-5$^B$), 121.6 (C Py), 122.1 (C Py), 127.6 (CH ar), 127.7 (CH ar), 128.3 (CH ar), 137.1 (Cbz), 155.5 (CO Cbz), 155.8 (CO BOC), 161.0 (CONH), 167.0 (CONH), 169.1 ($COCH_3$), 169.6 ($COCH_3$) and 169.7 ($COCH_3$). MS (ES + ) *m/z*: 754.3 $[M + Na]^+$, 732.3 $[M + H]^+$. HR-MS-ESI: $m/z = 731.3034$, calcd for $C_{34}H_{45}O_{13}N_5$ $[M + H]^+$, 731.3034. IR (KBr) $\nu$($cm^{-1}$): 3418, 1754, 1714, 1521, 1231 and 852.

### *MeO-Py-Ind (15)*

A mixture of $NaBH_4$ (92 mg, 2.44 mmol) in water (2 ml) was added dropwise to a solution of MeO-Py-$NO_2$ (**9**) (150 mg, 0.82 mmol) and Pd/C (10%) (30 mg) in EtOAc:

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MeOH (3:3) at 0°C. The reaction mixture was allowed to warm up to rt and was stirred for 30 min. The catalyst was removed by vacuum filtration through Celite, and the solvent was evaporated to afford amine (**14**), which was used without further purification. A solution of 2-indole carboxylic acid (**8**) (120 mg, 0.75 mmol), PyBOP (429 mg, 0.83 mmol) and DIEA (261 μl, 1.5 mmol) in DCM (2 ml) was stirred at rt for 30 min. Next, a solution of amine (**14**) in DCM (2 ml) was added to the previous activated acid and was stirred at rt overnight. The reaction mixture was washed with HCl (1 M), extracted with DCM, washed with brine, dried over $Na_2SO_4$, then filtered and the solvent was evaporated in vacuo. A white solid was obtained in 90% yield. $R_f = 0.57$ (Hex:EtOAc, 1:1, v/v). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 3.76 (s, 3H, $OCH_3$), 3.88 (s, 3H, $NCH_3$), 6.97 (d, $J = 1.9$ Hz, 1H, CH Py-3$^A$), 7.05 (ddd, $J = 8.0$ Hz, 7.0, 1.0, 1H, CH Ind-6), 7.20 (ddd, $J = 8.0$ Hz, 7.0, 1.0, 1H, CH Ind-5), 7.27 (dd, $J = 2.2$ Hz, 1.0, 1H, CH Ind-3), 7.46 (dd, $J = 8.0$ Hz, 1.0, 1H, CH Ind-7), 7.51 (d, $J = 1.9$ Hz, 1H, CH Py-5$^A$), 7.65 (d, $J = 8.0$ Hz, 1H, CH Ind-4), 10.35 (s, 1H, $NH_2$), 11.68 (s, 1H, $NH_1$). $^{13}$C NMR (101 MHz, DMSO) $\delta$ 36.3 ($NCH_3$), 51.1 ($OCH_3$), 102.9 (CH Ind-3), 108.4 (CH Py-3$^A$), 112.4 (CH Ind-4), 118.9 (C Py), 119.9 (CH Ind-6), 120.9 (CH Py-5$^A$), 121.6 (CH Ind-7), 122.6 (C Ind), 123.5 (CH Ind-5), 127.1 (C Py), 131.5 (C Ind), 136.7 (C Ind), 158.3 (CONH) and 160.8 ($COCH_3$). MS (ES −) *m/z*: 296.0 $[M - H]^-$. Elemental analysis calcd (%) for $C_{16}H_{15}O_3N_3$ (297.31): C, 64.64; H, 5.09; N, 14.13. Found: C, 64.51; H, 5.02; N, 14.22. HR-MS-ESI: *m/z* = 297.1113, calcd for $C_{16}H_{15}O_3N_3$ $[M + H]^+$, 297.1118. IR (KBr) $\nu$ (cm$^{-1}$): 3359, 3271, 1681, 1644, 1566, 1451 and 1250.

### *HO-Py-Ind (5)*

An aqueous solution of 1 N NaOH (13 ml) was added to a solution of MeO-Py-Ind (**15**) (200 mg, 0.67 mmol) in dioxane (13 ml). The reaction mixture was stirred for 3 h at rt. The solution was then cooled to 0°C and pH was adjusted to 4–5 with an aqueous solution of 1 M HCl. The precipitate was filtered yielding a white powder and dried in vacuo (170 mg, 90% yield). $R_f = 0.19$ (DCM:MeOH, 9:1, v/v). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 3.86 (s, 3H, $NCH_3$), 6.91 (d, $J = 1.9$ Hz, 1H, CH Py-3$^A$), 7.05 (t, $J = 7.5$ Hz, 1H, CH Ind-6), 7.19 (t, $J = 7.7$ Hz, 1H, CH Ind-5), 7.26 (d, $J = 1.9$ Hz, 1H, CH Ind-3), 7.43–7.48 (m, 2H, CH Ind-7, CH Py-5$^A$), 7.65 (d, $J = 8.0$ Hz, 1H, CH Ind-4), 10.33 (s, 1H, $NH_2$), 11.67 (d, $J = 2.3$ Hz, 1H, $NH_1$) and 12.26 (s, 1H, OH). $^{13}$C NMR (101 MHz, DMSO) $\delta$ 36.3 ($NCH_3$), 102.8 (CH–3 Ind), 108.3 (CH Py-3$^A$), 112.3 (CH Ind-4), 119.8 (CH Ind-6), 120.3 (CH Py-5$^A$), 121.6 (CH Ind-7), 122.2 (C Py), 123.4 (CH Ind-5), 127.1 (C Ind), 131.5 (C Ind), 136.6 (C Ind), 158.2 (CONH), 162.0 ($COCH_3$). MS (ES +) *m/z*: 284.0 $[M + H]^+$, 306.0 $[M + Na]^+$. Elemental analysis calcd (%) for $C_{15}H_{13}O_3N_3$ (283.09): C, 63.60; H, 4.63; N, 14.83. Found: C, 63.31; H, 4.80; N, 14.62. HR-MS-ESI: *m/z* = 283.0957 calcd for $C_{15}H_{13}O_3N_3$ $[M + H]^+$, 283.0966. IR (KBr) $\nu$ (cm$^{-1}$): 3437, 1653, 1558, 1457 and 748.

### *β-(OAc)$_3$Xyl-Py-γ[3(R)NHCbz]-Py-Ind (3)*

Compound β-(OAc)$_3$Xyl-Py-γ[3(*R*)NHCbz]NHBoc (**4**) (151 mg, 0.21 mmol) was dissolved in TFA:DCM (1:5) and stirred for 1 h and 30 min at rt. The mixture was diluted with DCM, evaporated and washed with sodium bicarbonate solution, the organic layer was separated, dried over $MgSO_4$, filtered and evaporated under vacuum to yield compound (**15**) β-(OAc)$_3$Xyl-Py-γ[3(*R*)NHCbz] $NH_2$ (126 mg, 95%). Amine (**16**) was pure enough to be used without further purification.

A solution of acid (**5**) OH-Py-Ind (51 mg, 0.18 mmol), PyBOP (103 mg, 0.20 mmol) and DIEA (85 μM, 0.49 mmol) in 2 ml of DMF was stirred at rt. for 1 h. Then, a solution of amine **16** (120 mg, 0.19 mmol) in DMF, 1 ml, was added to the reaction mixture and stirred overnight. Next, the solvent was evaporated and the product was purified by column chromatography (toluene: MeOH, 10:1), yielding a yellow solid (105 mg, 65%). $R_f = 0.16$ (toluene:MeOH, 5:1, v/v). $[\alpha]_D^{20} = -2.8$ ($c = 0.93$ in DMSO). $^1$H NMR (500 MHz, DMSO-$d_6$): 1.90 (s, 3H, $CH_3$), 1.97 (s, 3H, $CH_3$), 2.00 (s, 3H, $CH_3$), 2.44–2.47 (m, 2H, $CH_2$ $\gamma_c$), 3.33–3.36 (m, 2H, $CH_2$ $\gamma_a$), 3.56 (appt, $J = 10.9$ Hz, 1H, CH, $H_5$ ax), 3.77 (s, 3H, $CH_3$), 3.82 (s, 3H, $CH_3$), 3.90 (dd, $J = 10.9$ Hz, 5.6, 1H, CH, $H_5$ ec), 4.08–4.12 (m, 1H, CH $\gamma_c$), 4.81 (ddd, $J = 10.1$ Hz, 10.1, 5.6, 1H, CH, $H_4$), 5.01 (d, $J = 6.8$ Hz, 2H, $CH_2$ Cbz), 5.06 (appt, $J = 9.3$ Hz, 1H, CH, $H_2$), 5.25–5.37 (m, 2H, 2CH, $H_3$, $H_1$), 6.74 (d, $J = 1.9$ Hz, 1H, CH Py-3$^B$), 6.90 (d, $J = 1.9$ Hz, 1H, CH Py-3$^A$), 7.05 (t, $J = 7.4$ Hz, 1H, CH Ind-5), 7.16–7.22 (m, 3H, 2CH Ind-6, CH Py-5$^B$, NHCbz), 7.25–7.33 (m, 7H, CH Cbz, CH Py-5$^A$, CH Ind-3), 7.46 (d, $J = 8.2$ Hz, 1H, CH Ind-7), 7.65 (d, $J = 8.0$ Hz, 1H, CH Ind-4), 8.06 (t, $J = 6.1$ Hz, 1H, $NH_3$), 8.59 (d, $J = 9.5$ Hz, 1H, $NH_5$), 9.85 (s, 1H, $NH_4$), 10.30 (s, 1H, $NH_2$), 11.60 (s, 1H, $NH_1$). $^{13}$C NMR (126 MHz, DMSO) $\delta$ 20.8 ($CH_3$), 20.9 ($CH_3$), 21.0 ($CH_3$), 36.5 ($NCH_3$), 36.6 ($NCH_3$), 42.6 (CH $\gamma_a$), 49.1 (CH $\gamma_c$), 56.3 (CH $\gamma_b$), 63.7 ($CH_5$), 65.6 ($CH_2$ Cbz), 69.1 ($CH_4$), 71.0 ($CH_2$), 73.2 ($CH_3$), 78.2 ($CH_1$), 103.2 (CH Ind-3), 104. 7 (CH Py-3$^A$), 105.2 (CH Py-3$^B$), 112.7 (CH Ind-7), 118.7 (CH Py-5$^A$), 119.5 (CH Py-5$^B$), 120.22 (CH Ind-5), 122.0 (CH Ind-4), 122.0 (C Py), 122.1 (C Py), 122.5 (C Py), 123.5 (CH Ind-6), 123.8 (C Ind), 127.6 (C Ind), 128.1 (Cbz), 128.1 (Cbz), 128.7 (Cbz), 132.1 (C Py), 137.0 (C Ind), 137.5 (Cbz), 156.1 (CONH Cbz), 158.6 (CONH), 161. 5 (CONH), 161.9 (CONH), 167.5 (CONH), 169.6 ($COCH_3$), 170.0 ($COCH_3$), 170.1 ($COCH_3$) MS (ES +) *m/z*: 919.3 $[M + Na]^+$, 897.3 $[M + H]^+$. HR-MS-ESI: *m/*

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$z = 896.3345$ calcd for $C_{44}H_{48}O_{13}N_8$ $[M + H]^+$, 896.3317.

### *β-Xyl-Py-γ[3(R)NH$_2$]-Py-Ind (2)*

A solution of β-(OAc)$_3$Xyl-Py-γ[3(*R*)NHCbz]-Py-Ind (**3**) (80 mg, 0.09 mmol) in MeOH (8 ml) was treated with a solution of sodium (67 mg, 1.25 mmol) in MeOH (8 ml) to produce an immediate deeper yellow colour, indicative of completion of the reaction. The solution was acidified to pH 6 with Amberlite IR-120 ion-exchange resin (strongly acidic), and the resin was removed by filtration. Evaporation of the solvent under reduced pressure afforded the title compound as an off-white solid (48 mg, 70%).

Subsequently, a solution of sugar-deprotected β-Xyl-Py-γ[3(*R*)NHCbz]-Py-Ind (60 mg, 0.078 mmol) and Pd/C (10% dry, 30 mg) in DMF (3 ml) was stirred at room temperature for 8 h under $H_2$ atmosphere at 40 psi. When the reaction was complete, the catalyst was removed by filtration, washed with DMF and MeOH and the solvent evaporated in vacuo, providing the free amine as a yellow solid. $[\alpha]_D = -2.09$. $^1$H NMR (500 MHz, DMSO-$d_6$): 2.19 (dd, $J = 14.6$, 8.3 Hz, 1H, CH $\gamma_c$), 2.32–2.34 (m, 1H, CH $\gamma_c$), 3.05 (appt, $J = 10.8$ Hz, 1H, $H_5$ ax), 3.13–3.17 (m, 2H, CH $\gamma_a$, $H_3$), 3.20–3.30 (m, 4H, CH $\gamma_a$, CH $\gamma_b$, $H_4$, $H_2$), 3.66 (dd, $J = 10.8$ Hz, 5.3, 1H, $H_5$ ec), 3.78 (s, 3H, $CH_3$), 3.84 (s, 3H, $CH_3$), 4.77 (appt, $J = 8.9$ Hz, 1H, $H_1$), 4.84 (d, $J = 5.7$ Hz, 1H, OH), 4.93 (d, $J = 5.7$ Hz, 1H, OH), 5.01 (d, $J = 5.7$ Hz, 1H, OH), 6.84 (d, $J = 1.8$ Hz, 1H, CH Py-P3$^B$), 6.92 (d, $J = 1.9$ Hz, 1H, CH Py-3$^A$), 7.05 (ddd, $J = 7.9$ Hz, 7.0, 1.0, 1H, CH Ind-5), 7.17–7.21 (m, 2H, CH Ind-6, CH Py-5$^B$), 7.28 (dd, $J = 2.1$ Hz, 0.7, 1H, CH Ind-3), 7.29 (d, $J = 1.8$ Hz, 1H, CH Py-5$^A$), 7.46 (dd, $J = 8.2$ Hz, 0.9, 1H, CH Ind-7), 7.65 (dd, $J = 8.1$ Hz, 0.9, 1H, CH Ind-4), 8.06 (t, $J = 5.5$ Hz, 1H, $NH_3$), 8.32 (d, $J = 8.7$ Hz, 1H, $NH_5$), 10.03 (s, 1H, $NH_4$), 10.29 (s, 1H, $NH_2$), 11.61 (d, $J = 1.5$ Hz, 1H, $NH_1$). $^{13}$C NMR (126 MHz, DMSO) δ 36.5 ($NCH_3$), 36.6 ($NCH_3$), 42.0 ($CH_2$ $\gamma_c$), 45.7 ($CH_2$ $\gamma_a$) 49.3 (CH $\gamma_b$), 67.8 ($CH_5$), 70.2 ($CH_4$), 72.1 ($CH_2$), 78.2 ($CH_3$), 81.0 ($CH_1$), 103.3 (CH Ind-3), 104.7 (CH Py-3$^A$), 105.0 (CH Py-3$^B$), 112.7 (CH Ind-7), 118.6 (CH Py-5$^A$), 119.0 (CH Py-5$^B$), 120.2 (CH Ind-5), 122.0 (CH Ind-4), 122.1 (C Py), 122.3 (C Py), 122.6 (C Py), 123.6 (CH Ind-6), 123.8 (C Ind), 127.6 (C Ind), 132.09 (C Py), 137.02 (C Ind), 158.6 (CONH), 161.8 (CONH), 161.8 (CONH), 168.8 (CONH). MS (ES + ) *m/z*: 637.3 $[M + H]^+$. HR-MS-ESI: $m/z = 636.2656$ calcd for $C_{30}H_{36}O_8N_8$ $[M + H]^+$, 636.2657.

Subsequently, treatment with 0.5 M HCl afforded the final compound (**2**) which was purified by reverse-phase HPLC and lyophilised to dryness (32 mg, 80%). $^1$H NMR (500 MHz, DMSO-$d_6$): 2.60 (dd, $J = 16.7$ Hz, 7.8, 1H, CH $\gamma_c$), 2.67–2.76 (m, 1H, CH $\gamma_c$), 3.05 (appt, $J = 10.8$ Hz, 1H, $H_5$ ax), 3.16 (t, $J = 8.7$ Hz, 1H, $H_3$), 3.30–3.33 (m, 2H, $H_4$, $H_2$), 3.47 (ddd, $J = 20.0$ Hz, 13.9, 7.7, 2H, CH $\gamma_a$), 3.66 (m, 1H, $H_5$ ec, CH $\gamma_b$), 3.79 (s, 3H, $CH_3$), 3.86 (s, 3H, $CH_3$), 4.78 (appt, $J = 8.9$ Hz, 1H, $H_1$), 4.80–5.14 (m, 3H, OH), 6.83 (d, $J = 2.1$, 1H, CH Py-P3$^B$), 7.01 (d, $J = 2$ Hz, 1H, CH Py-3$^A$), 7.05 (appt, $J = 7.5$ Hz, 1H, CH Ind-5), 7.18–7.22 (m, 2H, CH Ind-6, CH Py-5$^B$), 7.29 (dd, $J = 2.1$ Hz, 0.7, 1H, CH Ind-3), 7.31 (d, $J = 1.9$ Hz, 1H, CH Py-5$^A$), 7.46 (d, $J = 8.2$ Hz, 1H, CH Ind-7), 7.65 (d, $J = 8.1$ Hz, 1H, CH Ind-4), 7.96 (d, $J = 5.5$ Hz, 3H, $NH_3$), 8.30 (t, $J = 5.9$ Hz, 1H, $NH_3$), 8.37 (d, $J = 8.8$ Hz, 1H, $NH_5$), 10.17 (s, 1H, $NH_4$), 10.35 (s, 1H, $NH_2$), 11.62 (d, $J = 2.3$ Hz, 1H, $NH_1$). $^{13}$C NMR (126 MHz, DMSO) δ 36.2 ($NCH_3$), 36.3 ($NCH_3$), 35.1 ($CH_2$ $\gamma_c$), 40.0 ($CH_2$ $\gamma_a$), 48.4 (CH $\gamma_b$), 67.4 ($CH_5$), 69.7 ($CH_4$), 71.6 ($CH_2$), 77.7 ($CH_3$), 80.5 ($CH_1$), 102.9 (CH Ind-3), 104.4 (CH Py-3$^A$), 104.8 (CH Py-3$^B$), 112.3 (CH Ind-7), 118.7 (CH Py-5$^A$), 119.8 (CH Py-5$^B$), 121.4 (CH Ind-5), 121.5 (CH Ind-4), 121.9 (C Py), 122.4 (C Py), 122.5 (C Py), 123.4 (CH Ind-6), 127.1 (C Ind), 131.6 (C Py), 136.6 (C Ind), 158.3 (CONH), 161.2 (CONH), 162.0 (CONH), 166.1 (CONH). MS (ES + ) *m/z*: 638.3 $[M + H]^+$.

### *Interaction NMR studies with poly(dA–dT)$_2$*

All NMR interaction experiments were carried out in phosphate buffer (10 mM, pH 7.2) with TSP 20 μM as an internal reference. The binding affinity of sugar oligoamides **1** and **2** to poly(dA–dT) was investigated by $^1$H NMR titration experiments. Ligand samples were prepared at a constant concentration of 175 μM for cationic xylose-oligoamide **2** and 130 μM neutral xylose-oligoamide **1**. Poly(dA–dT)$_2$ stock solution was prepared by dissolving 25 unites of the oligonucleotide in 1 ml of a solution phosphate buffer/$D_2O$ with TSP 20 μM. Under these conditions, the concentration of poly(dA–dT) was calculated by UV–vis spectroscopy using $\varepsilon_{258} = 13\,200\ M^{-1}\,cm^{-1}$ ($c = 3.02$ mM bp) (*40*). Poly(dA–dT)$_2$ titrant samples were prepared by diluting 250 μl of poly(dA–dT)$_2$ stock solution with 250 μl of ligand solution (350 μM for cationic xylose-oligoamide **2** and 260 μM neutral xylose-oligoamide **1**). Then, 0.5 ml of the ligand solution was introduced into the NMR tube, and increasing amounts of the titrant DNA solution were added while keeping the ligand concentration constant. $^1$H NMR spectrum was recorded in the same conditions after each addition of poly(dA–dT)$_2$ (500 MHz, 64 scans, $d_1 = 5$ s, 25°C).

### *Solubility assay in aqueous media*

Saturation ligand solutions were freshly prepared by dissolving $5 \times 10^{-4}$ mM of each compound in 0.5 ml of phosphate buffer solution, stirred for 2 h and filtered through

a 0.2-μm nylon filter before the spectra were recorded. The concentrations of the ligands were determined optically by using the molar extinction coefficient, $\varepsilon_{302} = 24{,}745\,M^{-1}\,cm^{-1}$ for neutral xylose glyco-oligoamide (**1**) and $\varepsilon_{302} = 24{,}938\,M^{-1}\,cm^{-1}$ cationic xylose (**2**) glyco-oligoamide. Molar extinction coefficients for compounds **1** and **2** were calculated in the phosphate buffer solution according to the Lambert–Beer law.

## Supporting Information Available

$^1$H NMR spectra for synthesized compounds.

## Acknowledgements

The authors thank the Spanish Ministry of Economy and Competitivity (Project Nos CTQ2009-10547 and CTQ2012-32025) and the EU (COST-CM 1102) for financial support. A.T. is grateful to the MINECO for FPI pre-doctoral fellowship (BES-2010-034877).

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