Perylenediimide-based glycoclusters as high affinity ligands of bacterial lectins: synthesis, binding studies and anti-adhesive properties

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The synthesis of eight perylenediimide-based glycoclusters was readily performed from hexa- and tetra-propargylated cores through azide-alkyne "click" conjugation. Variations on the carbohydrate epitope (Glc, Gal, Man, Fuc) and the linker arm provided molecular diversity. Interactions with LecA and LecB, two proteins involved in the adhesion of *Pseudomonas aeruginosa* to host tissues, was evaluated by microcalorimetry (ITC). In both cases high affinities were obtained with K_d values in the nanomolar range. The further evaluation of their anti-adhesive properties using cultured epithelial cells demonstrated their potent anti-adhesive activities against *Pseudomonas aeruginosa* with only 30-40% residual adhesion observed. The fluorescence properties of the PDI core were then investigated by confocal microscopy on cell-bacteria cultures. However, the red fluorescence signal of the PDI-based glycocluster was too weak to provide significant data. The present study provides another type of anti-adhesive glycocluster against bacterial infection with a large aromatic PDI core.

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Introduction

Perylenediimide-based organic dyes are now widely studied[1] due to their π-π stacking aggregation properties[2-4] that led to application in field effect transistors[5-9] or other biologically relevant systems.[10-14] Nevertheless, applications are sometimes troublesome due to their specific prone to poor solubility in water and aggregation. The introduction of carbohydrate moiety onto the PDI scaffold was reported[15-23] as a method to provide water-soluble PDI-based glycomaterials for further applications in biology. Several other approaches for the conjugation of carbohydrates to aromatic cores[24] or fluorescent dyes[18, 19, 25-32] have also been reported in this context.

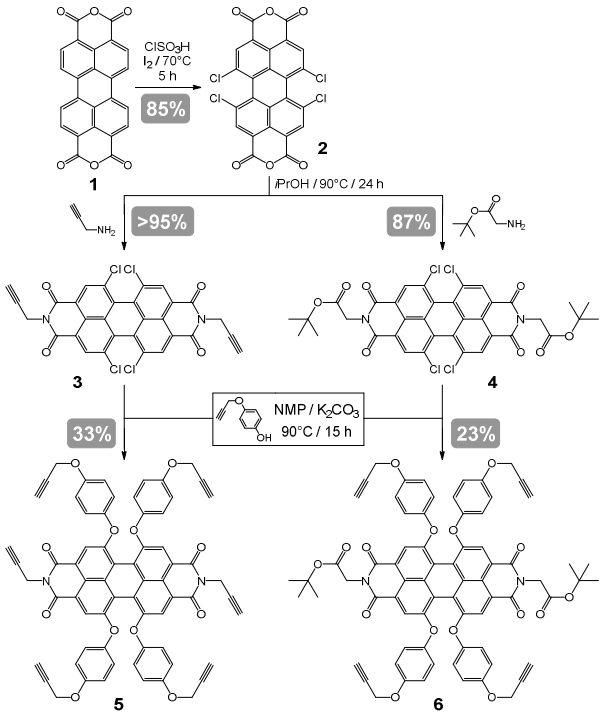
We and other described that the multivalent glycoclusters with high affinity for bacterial lectins could represent a new way to treat bacterial infection especially infection due to the bacteria *Pseudomonas aeruginosa*.[33, 34] *P. aeruginosa* is a pathogenic bacterium involved in acute and chronic lung infection especially in immune-compromised patients or patients suffering from cystic fibrosis. Two lectins have been identified as implicated in the adhesion of the bacteria to the host cells, namely the galactose-specific LecA and the fucose-specific LecB.[35, 36] We have also previously designed a large series of glycoclusters for applications in anti-adhesive strategies against *P. aeruginosa* infection.[37-53] We have especially demonstrated the excellent anti-adhesive properties of calixarene-based glycoclusters in animal models of lung infection leading to protection of mice against *P. aeruginosa* infection.[45]

In the present study, we designed a series of PDI-based glycoclusters with different and complementary properties towards the (1) multivalent binding to bacterial lectins and also (2) their anti-adhesive properties against bacterial infection. The goal was to take advantage of the intrinsic fluorescence properties of the PDI core for diagnostic tools or a better understanding at the biomolecular level of the anti-adhesive mechanism.

Results and discussion

Synthesis of the PDI-based glycoclusters

The regioselective 1,6,7,12-tetrachlorination of 3,4,9,10-perylene tetracarboxylic dianhydride **1** to the corresponding 1,6,7,12-tetrachloroperylene-3,4,9,10-tetracarboxylic dianhydride **2** were mostly adapted from chlorination of perylenediimide scaffolds using chlorosulfonic acid and iodine under heating and during 20 h.[54] The reaction conditions required refluxing in chlorosulfonic acid as a solvent for 20 h.[54-58] Nevertheless, reducing the heating to 15 h was not detrimental.[59] A methodology study indicated that the reaction performed during 5 h afforded the desired tetrachlorinated compound while longer reaction times of 10 h and 20 h provided the penta- and hexa-chlorinated derivatives as by-products.[60] We therefore decided to use these conditions (5 h reflux) for the preparation of compound **2** which provided the best reproducible results in our hands (**Scheme 1**). The isolated yield of 85% required a long soxhlet extraction (11 days) due to the poor solubility of compound **2**.



Scheme 1. Synthesis of tetra- and hexa-propargylated PDI-based cores

Formation of the perylenediimide (PDI) moiety was then performed using either propargylamine or *t*-butyl glycinate[61-65] to afford the desired diimides **3** and **4** (**Scheme 1**). Condensation[16] with *p*-propargyloxyphenol[66] provided the hexa-propargylated core **5**[17, 18] and tetra-propargylated core **6**. The introduction of two glycine residues was used to provide improved water solubility to the glycocluster through the carboxylic acid moieties.[67]

Six azido-functionalized carbohydrates **7a-f** were then used for the conjugation to the alkynylated PDI-based cores. The azido-triethyleneglycol-based linkers have been largely reported as good spacer arms for the design of high affinity lectin ligands.[34, 37-39, 43, 45] Glycosides **7a-d** were synthesized according to revisited and robust large scale (> 5 g) procedures.[42, 68-70] A more hydrophobic linker was also investigated to take advantage of a hydrophobic group in the periphery of the anomeric position which improved the binding properties to LecA[42, 43, 46, 71-73] and LecB.[74] The synthesis was performed both in the galactose and fucose series for this study. The glucoside **7a** will be used to prepare glucosylated glycoclusters as negative control in ITC experiments. The mannose derivative **7c** was used to provide a further glycocluster with potential applications with other lectins. The mono-cycloadducts **7e-f** were obtained from the corresponding propargyl glycosides using a large excess of 1,5-diazido-3-oxapentane (25 equivalents) and the glycoside was added slowly with a syringe pump (~ 16 h) in a heated (90°C) and diluted solution of reagents. Selective mono-functionalization was readily achieved in high isolated yields (> 90%).

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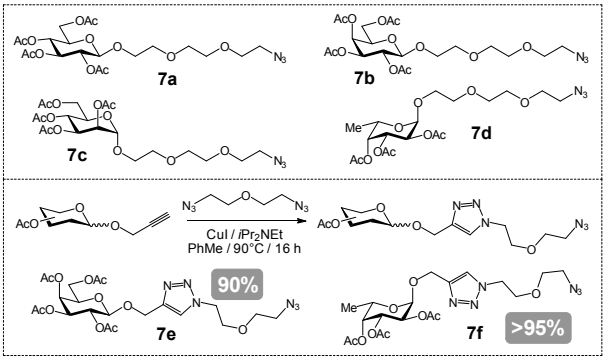
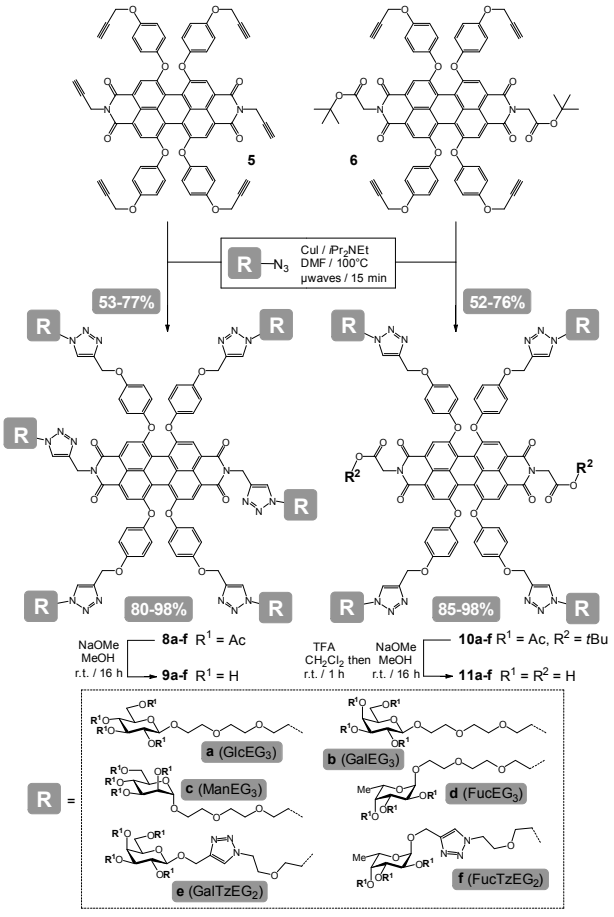


Scheme 2. Synthesis of the azido-functionalized glycosides

Conjugation of the glycosides **7a-f** to the propargylated cores **5-6** was then performed under Meldal's conditions[75, 76] (CuI, *i*Pr_2NEt) under microwaves activation. The corresponding acetylated PDI-based glycoclusters were **8a-f** and **10a-f** obtained from cores **5** and **6** respectively. Deacetylation afforded the desired glycoclusters **9a-f** and **11a-f** in good isolated yields.



Scheme 3. Synthesis of the PDI-based glycoclusters

ITC binding studies

The glycoclusters were then evaluated as multivalent ligands of LecA and LecB by isothermal titration microcalorimetry (ITC), a bioanalytical technique providing the thermodynamics parameters for the interactions such as the stoichiometry (*N*) of the complex, the enthalpy (ΔH) and also the association constant ($K_a = 1/K_d$) in a single measurement.[77, 78]

The binding properties toward LecA were evaluated for the galactosylated glycoclusters **9b**, **9e**, **11b** and **11e** (Table 1). The glucosylated PDI-based glycocluster **11a** was first evaluated as a negative control. No binding could be detected with this ligand indicating that no nonspecific binding occurred with the lectin due to the PDI-based core. The tetravalent compounds **11b** and **11e** displayed the same binding toward LecA with K_d values of nearly 200 nM. The stoichiometry for compounds **11b** and **11e** indicated the binding of three lectin monomers to each cluster. The four galactosides are therefore not all involved in lectin binding suggesting that steric hindrance would occur around the PDI-based core for a maximal binding of lectins. This steric hindrance was further observed with PDI-based glycoclusters **9b** and **9e** for which four contacts were evidenced ($N = 0.25$) while six galactose were available. The binding properties (K_d values in the 150 nM range) were only barely improved in comparison to the tetravalent glycoclusters **11b** and **11e** (K_d values in the 200 nM range). The increase in galactose valency resulted in higher enthalpy of binding, but the entropy cost is also stronger, resulting in equivalent affinity. These galactosylated glycoclusters are good candidates for further applications in anti-adhesive strategies against *Pseudomonas aeruginosa*.[34]

Titration curves obtained with LecB are more complex (Figure 1) and, except for glycocluster **9d**, they could not be fitted with a single site model (Table 2). For tetravalent compounds **11d** and **11f**, a two-binding site model was used, resulting in determination of low affinity (K_d ~ 500 nM) and high affinity (K_d ~ 100 nM) binding sites. Hexavalent glycoclusters **9d** and **9f** also displayed affinity in the 300-500 nM range. The low affinity binding site displays affinity in the same range as methyl α-L-fucopyranoside (α-FucOMe) used as the monovalent ligand reference. The second binding site may result from change in lectin conformation (allosteric effect) or contact with aglycon of already bound ligand. This second binding site has higher affinity, which may be promising and should be further investigated. The glucosylated glycocluster **11a** did not display any binding toward LecB as expected.

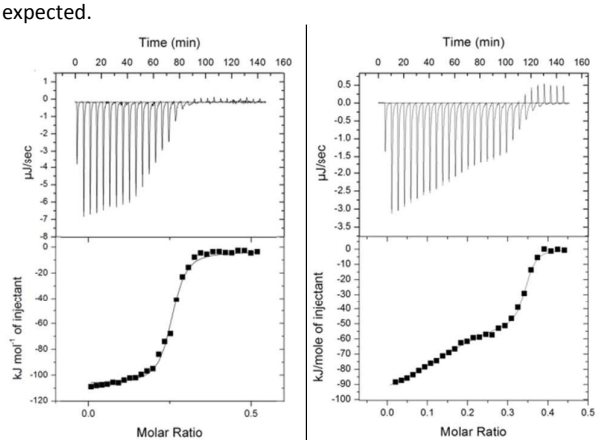


Figure 1. ITC binding studies. **Left:** Raw ITC data (top) for LecA (0.1 mM) obtained by injections of glycocluster **9b**: **PDI-(EG$_3$-Gal)$_6$** (0.24 mM) and the corresponding integrated titration curve (bottom) obtained with a one-site model. **Right:** Raw ITC data (top) for LecB (0.1 mM) obtained by

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injections of glycocluster **11f**: **PDI-(TzEGTz-Fuc)$_4$** (0.2 mM) and the corresponding integrated curve obtained by a two-site model.

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Table 1. ITC measurements for binding of PDI-based glycoclusters **9b**, **9e**, **11a**, **11b** and **11e** to LecA.

Ligand	N[a]	$-\Delta H$ (kJ/mol)	$-T\Delta S$ (kJ/mol)	K_d (nM)	β[b]
PDI-$(EG_3Glc)_4$ (11a)	No binding observed (see Supporting Information Figure S9)				
PDI-$(EG_3Gal)_4$ (11b)	0.34±0.03	71.2±1.6	31.1	202±68	346
PDI-$(TzEGTzGal)_4$ (11e)	0.41±0.02	79.2±0.6	41.0	208±19	336
PDI-$(EG_3Gal)_6$ (9b)	0.25±0.01	113.9±0.7	75.3	172±5	406
PDI-$(TzEGTzGal)_6$ (9e)	0.26±0.01	104.7±2.7	65.6	143±3	489

[a] Stoichiometry of binding defined as the number of glycoclusters per monomer of LecA. [b] Calculated using methyl β-D-galactopyranoside (β-GalOMe) as a monovalent reference with K_d = 70 μM.[37]

Table 2. ITC measurements for binding of PDI-based glycoclusters **9d**, **9f**, **11a**, **11d** and **11f** to LecB.

Ligand	$N1$[a]	$-\Delta H1$ (kJ/mol)	$-T\Delta S1$ (kJ/mol)	K_{d1} (nM)	β1[b]	$N2$[a]	$-\Delta H2$ (kJ/mol)	$-T\Delta S2$ (kJ/mol)	K_{d2} (nM)	β2[b]
PDI-$(EG_3Glc)_4$ (11a)	No binding observed (see Supporting Information Figure S10)									
PDI-$(EG_3Fuc)_4$ (11d)	0.18±0.01	29.2±1.5	-12.4	527±122	0.8	0.14±0.01	103.2±2.4	59	137±47	3.1
PDI-$(TzEGTzFuc)_4$ (11f)	0.23±0.03	45.6±2.2	4	534±9	0.8	0.12±0.01	98.4±7.6	52.2	88±26	4.9
PDI-$(EG_3Fuc)_6$ (9d)	0.19±0.01	79±3	43	473±2	0.9	Single site binding observed on titration curve				
PDI-$(TzEGTzFuc)_6$ (9f)	0.25±0.01	44.5±2.8	5.2	325±141	1.3	Two sites binding observed on titration curve. Fitting with 2-site model could not provide 2 K_d values. Fitting with 1-site model was used.				

[a] Stoichiometry of binding defined as the number of glycoclusters per monomer of LecB. [b] Calculated using methyl α-L-fucopyranoside (α-FucOMe) as a monovalent reference with K_d = 0.43 μM.[79]

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Fluorescence assays

The UV-vis absorption and fluorescence emission properties of representative **PDI**-based glycoclusters were tested in different solvents. Typical absorbance band of **PDI** monomer with multiple absorbance peaks was observed for all glyco-**PDI**s,[80] suggesting the successful introduction of the carbohydrate moieties to the perylene diimide scaffold (Figure 2a). A red shift in absorbance was observed for the glyco-**PDI**s in EtOH and water with respect to that in other solvents. This might be a result of aggregation (forming micelle-like architectures due to their amphiphilic property) of the compounds in these solvents to increase the intermolecular interactions of the hydrophobic perylene molecules. Typical **PDI** fluorescence emission was observed for the glyco-**PDI**s in DMF, DMSO and MeOH upon excitation at 410 nm (Figure 2b). However, the fluorescence emission was largely quenched in EtOH and H_2O (the emission maxima also slightly red-shifted in EtOH), probably because of an aggregation-induced-quenching in these two solvents. This solvent effect is similar to that observed in the UV-vis spectra of the glyco-**PDI**s. The UV-vis absorption and fluorescence emission for all tested glyco-**PDI**s appeared to be similar irrespective of the valency and carbohydrate units clicked to **PDI**.

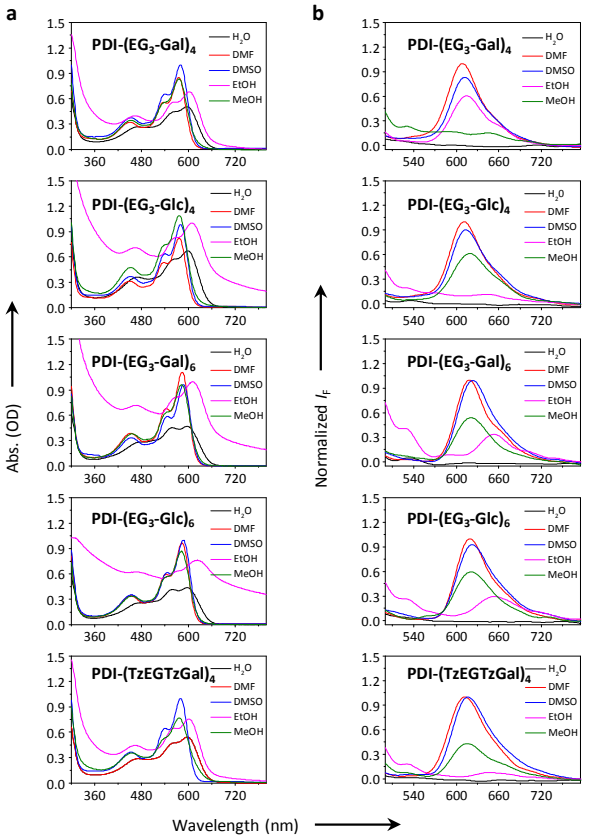

Figure 2. (a) UV-vis absorption spectra of glyco-**PDI**s (50 µM) in different solvents. (b) Fluorescence emission spectra of glyco-**PDI**s (12.5 µM) in different solvents with excitation of 410 nm. All experiments have been repeated at least three times, and representative data are shown.

Cell adhesion assays

We have evaluated the ability of PDI-based glycoclusters to counteract *P. aeruginosa* infection in an *in vitro* model using the human pulmonary cell lines A549 as previously described.[45] A significant decrease of the cytotoxicity mediated by *P. aeruginosa* was observed with **PDI-$(EG_3Gal)_4$** (Figure 3A), **PDI-$(TzEGTzFuc)_4$**, **PDI-$(TzEGTzFuc)_6$** and **PDI-$(EG_3Fuc)_4$** (Figure 3C). This decrease of the cytotoxicity was not dependent on the linker arm or carbohydrate moieties, but rather on the valency of the glycoclusters. Moreover, an important decrease of bacterial adhesion in a range between 50-60% was observed with **PDI-$(TzEGTzGal)_4$**, **PDI-$(TzEGTzGal)_6$**, **PDI-$(EG_3Gal)_4$**, **PDI-$(EG_3Gal)_6$** (Figure 3B). This phenomenon was even more pronounced for the fucosylated glycoclusters in a range of 40-80% with **PDI-$(TzEGTzFuc)_4$**, **PDI-$(TzEGTzFuc)_6$** or **PDI-$(EG_3Fuc)_4$** and **PDI-$(EG_3Fuc)_6$** (Figure 3D). The low adherence of the bacteria resulting from the presence of the PDI-based glycoclusters was not dependent on the

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linker arm or valency but rather on the carbohydrate moiety with a preference for the fucoside residues.

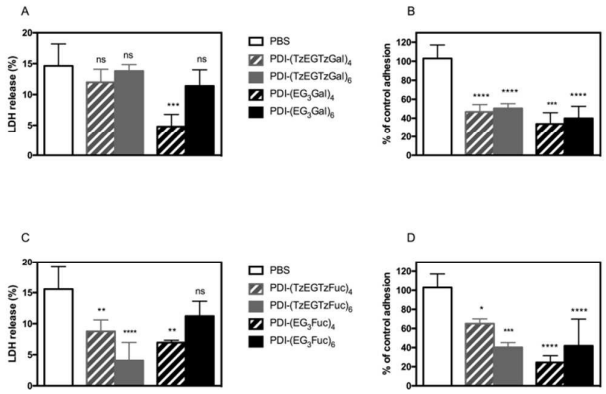

Figure 3. Bacterial adhesion to A549 cells in the presence or absence of different PDI-based glycoclusters. All results are compared to the first column without adhesion inhibitors (PAO1, positive control): (A,B) galactosylated glycoclusters and (C,D) fucosylated glycoclusters. (A,C) LDH release following cell death, (B,D) inhibition of adhesion of wild-type PAO1. All experiments were performed in triplicate. Results are mean ± SEM (*p < 0.05). NS: not significant. * P < 0.05; ** P < 0.01; *** P < 0.001 compared to control.

The tetra-fucosylated PDI-based glycocluster **PDI-$(EG_3Fuc)_4$** appeared as the most potent anti-adhesive candidate against *P. aeruginosa*. Its fluorescence properties have been used in a confocal microscopy experiment to investigate if the glycocluster would colocalize at the cell-bacteria interface or around swimming bacteria. Nevertheless, the fluorescence emission of GFP overlapped the fluorescence emission of **PDI-$(EG_3Fuc)_4$.** This characteristic of the compound does not allow to establish definitely if the **PDI-$(EG_3Fuc)_4$** colocalized with *P. aeruginosa* (Figure 4). While bacteria and A549 cells can be readily identified through their green and blue fluorescence respectively, the red fluorescence of the **PDI-$(EG_3Fuc)_4$** was rather weak but could still be colocalized with bacteria when noticeable (top right hand corner), thus demonstrating the actual interaction of the glycoclusters with the bacteria in the cell culture medium.

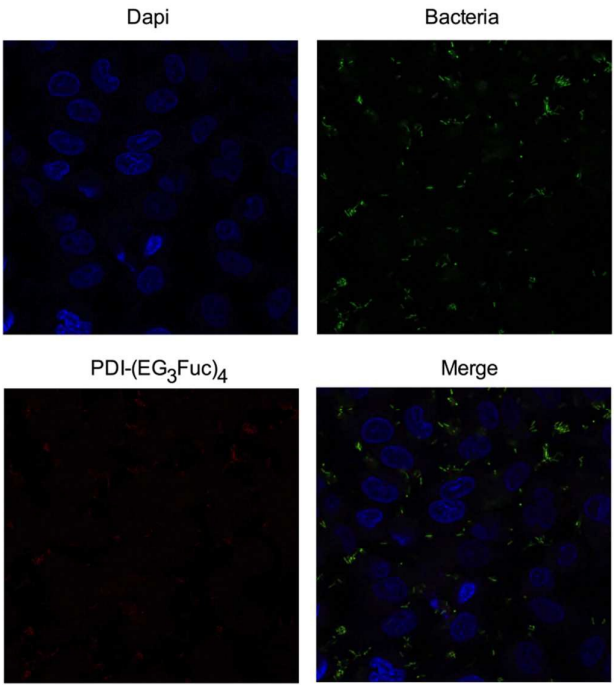

Figure 4. Confocal microscopy of A549 alveolar epithelial cells. Nuclei stained with 4',6'-diamidino-2-phenylindole (DAPI) infected by PAO1 strain with a GFP plasmid at MOI 10 in the presence of **PDI-$(EG_3Fuc)_4$** at 20 mM concentrations.

Conclusions

The synthesis of PDI-based glycoclusters was readily performed from hexa- and tetra-propargylated cores through azide-alkyne "click" conjugation. These multivalent macromolecules were then evaluated as lectin ligands against LecA and LecB as the two proteins involved in the adhesion of *Pseudomonas aeruginosa* to host cells. A high affinity was measured by microcalorimetry (ITC) in both cases with K_d values in the nanomolar range for both lectins. Although two valencies (4 or 6) and several linker arms were combined, the 8 glycoclusters performed almost equally as lectin ligands. These encouraging nanomolar affinities prompted for the evaluation of their anti-adhesive properties in a cell-based assay for adhesion to human epithelial cells. The PDI-based glycoclusters were demonstrated as potent anti-adhesive agents against *Pseudomonas aeruginosa* with only 30-40% residual adhesion observed with such glycoclusters. The fluorescence properties of the PDI core were then investigated by confocal microscopy on cell-bacteria cultures. However, the red fluorescence signal of the tetravalent fucosylated PDI-based glycocluster selected for the confocal study was too weak to provide significant data. Altogether, the present study provides interesting data for another type of anti-adhesive glycocluster against bacterial infection with a large aromatic PDI core.

Conflicts of interest

There are no conflicts to declare.

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Acknowledgements

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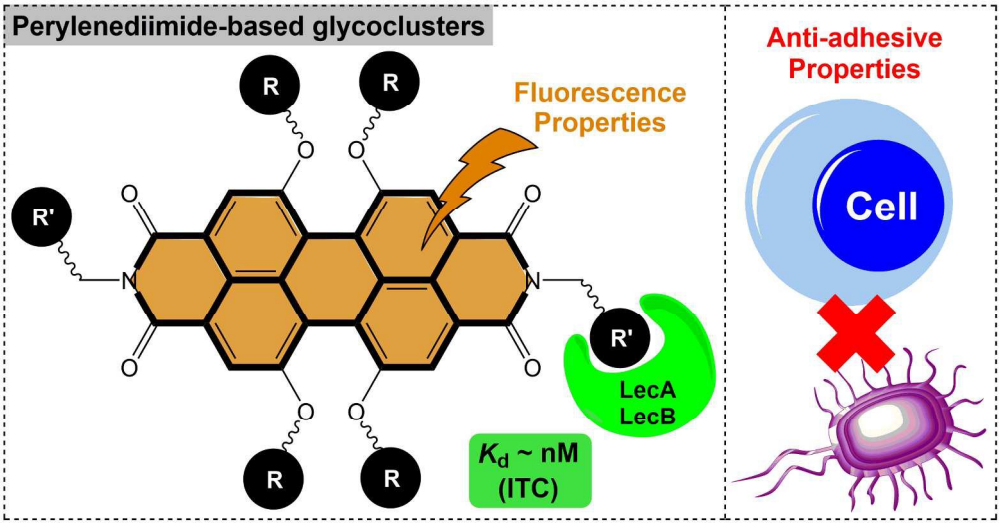

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