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FULL PAPER

Synthesis of Nucleobase di- and tetra-functionalized Porphyrins

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Abstract: A library composed of ten porphyrins bearing nucleobases is prepared, following two strategies: substitution or Sonogashira cross coupling reactions. The former strategy led to the synthesis of four porphyrins (**T_2-Po1**, **A_2-Po1**, **C_2-Po1** and **P_2-Po1**) bearing nucleobases (NBs) at two *trans meso*-positions. These 4 porphyrins were obtained by reacting 5,15-di(4-(bromomethyl)phenyl)-10,20-dimesitylporphyrin (**Po1**) with thymine (**T**), adenine (**A**), cytosine (**C**) and 2-amino-6-chloropurine (**P**), a precursor of guanine (**G**), respectively in the presence of a suitable base. A fifth porphyrin, 5,15-di(N9-methylphenylguanine)-10,20-dimesitylporphyrin (**G_2-Po1**) was obtained by hydrolysis of **P_2-Po1**. A thymine tetra-functionalized porphyrin was also synthesized following the same strategy starting from **T** and 5,10,15,20-tetrakis[4-(bromomethyl)phenyl]porphyrin (**Po2**). The second strategy based on Sonogashira cross coupling reactions between 5,15-dibromo-10,20-dipentylporphyrin (**Po3**) and ethynyl-substituted nucleobases resulted in four rigid porphyrins (**U_2-Po3**, **C_2-ZnPo3**, **A_2-ZnPo3** and **G_2-ZnPo3**).

Introduction

Porphyrins have been extensively studied due to their unique structure, biological properties and their vital role in several natural processes.[1] Their distinctive chemical and physical properties, in addition to their thermal stability and robustness, make them candidates of choice for the construction of conductive polymers, light-harvesting materials, chemical sensors, organic devices and others.[2] Furthermore, porphyrins are widely used in molecular tectonics due to the presence of their four *meso* and eight β-pyrrolic positions that can be functionalized by a variety of coordinating and H-bonding sites. Moreover, the tetra-aza core may bind various metal cations and self-assemble through π-π interactions.[3]

H-bonded porphyrin assemblies have attracted a considerable interest[4], especially in molecular tectonics[5]. However, concerning H-bonds as assembling nodes, the control and thus the prediction of the final architecture is a challenge because of their high reversibility and flexibility. Nature has provided nucleobases (NBs) that are known for their complementary base pairing properties in DNA and RNA as stable, reliable and predictable hydrogen bonding patterns, indeed thymine (**T**) (in DNA) or uracil (**U**) (in RNA) is complementary to adenine (**A**) whereas cytosine (**C**) is complementary to guanine (**G**) (in DNA and RNA) (**Figure 1**).[6] Therefore, several examples of nucleobase-functionalized porphyrin were reported in the past decade.[7-12]

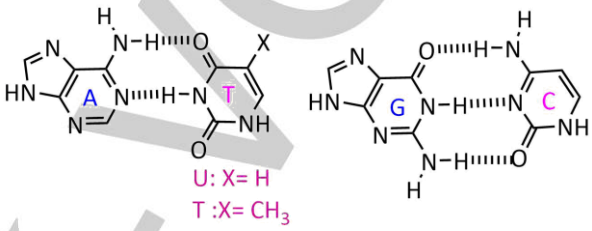


Figure 1. Nucleobases and their possible base paring

Both porphyrins and nucleobases (NBs) are naturally occurring molecules, and when linked together they lead to entities with a wide range of properties and applications. For example, Sessler *et al.*[7] described several dimeric assemblies based on porphyrin bearing guanine and cytosine forming photo antennas for photo-induced energy transfer[8,9] or for photo-induced electron transfer[10]. In addition, Champness et. *al.* recently reported the synthesis and the surface based assemblies of thymine and adenine bearing porphyrins.[11,12] Moreover, Balaz et. *al.*[13a-c] and Stulz et. *al.*[13d-e] described the synthesis, properties and applications of several DNA-templated porphyrin assemblies.

NB-Porphyrins were synthesized following different strategies, such as Sonogashira cross coupling reaction[10,13a] or by reacting aldehydes bearing the corresponding nucleobases with pyrrole[11,12] or dipyrromethanes[8,9]. Other synthetic approaches were also used to introduce NBs to the porphyrin scaffold. For instance, the uracil-functionalized porphyrins described by Drain *et al.*[14], the water-soluble NB-porphyrins reported by Maiya *et al.*[15] and the NB-porphyrin hybrid compounds described by Schneider *et al.*[16] were synthesized by an Adler synthesis[17], an alkylation reactions of NB's active amine sites and by a condensation reaction between corresponding NBs and porphyrin derivatives respectively. Furthermore, the synthesis of porphyrins bearing nucleobases *via* ethoxy and acetyl linkers[18] or *via* amide linkers[19] was also reported. Taking in consideration the previously followed synthetic pathways, we developed two new simple approaches to synthesize NB-porphyrins tectons. Herein, we describe the synthesis of 10 new NB-functionalized porphyrins *via* substitution reactions of porphyrin precursors bearing bromobenzyl groups by nucleobases or through Sonogashira cross coupling reactions between a *trans meso*-dibromoporphyrin and ethynyl-nucleobases. These new tectons are well suited for the formation of H-bonded porphyrin based networks either in the crystalline phase or on surface[20]. We describe here the formation of such a

H-bonded network in the crystals for the tecton bearing two cytosines in *trans* positions. Moreover, the complementarity of the tectons open the possibility to generate H-bonded networks based on complementary pairs such as **T_2Po/A_2Po** or **C_2Po/G_2Po**. Such networks have been investigated either in the solid state or on surface and will be reported elsewhere. Furthermore, the possibility to introduce metallic cations in the porphyrin cavity opens the way to molecular networks of higher dimensionality by taking advantage of the possibility of introducing additional ligands in the axial position of the metal cation present in the tetraaza core of the porphyrin cavity.

Results and Discussion

The targeted tectons are porphyrin molecules functionalized at their *meso*-positions by NBs *via* phenyl or ethynyl groups leading to flexible or rigid tectons respectively.

Synthesis of flexible NB-porphyrins tectons

Various examples in the literature proved that the substitution of N1 site of pyrimidines and N9 site of purines with different alkyl substituents can be easily achieved.[21] Therefore, we aimed to apply a similar procedure between nucleobases' active amino sites and porphyrins bearing either two (**Scheme 1A**) or four (**Scheme 2**) 4-(bromomethyl) phenyl groups at *meso* positions.

Di-functionalized NB-porphyrins

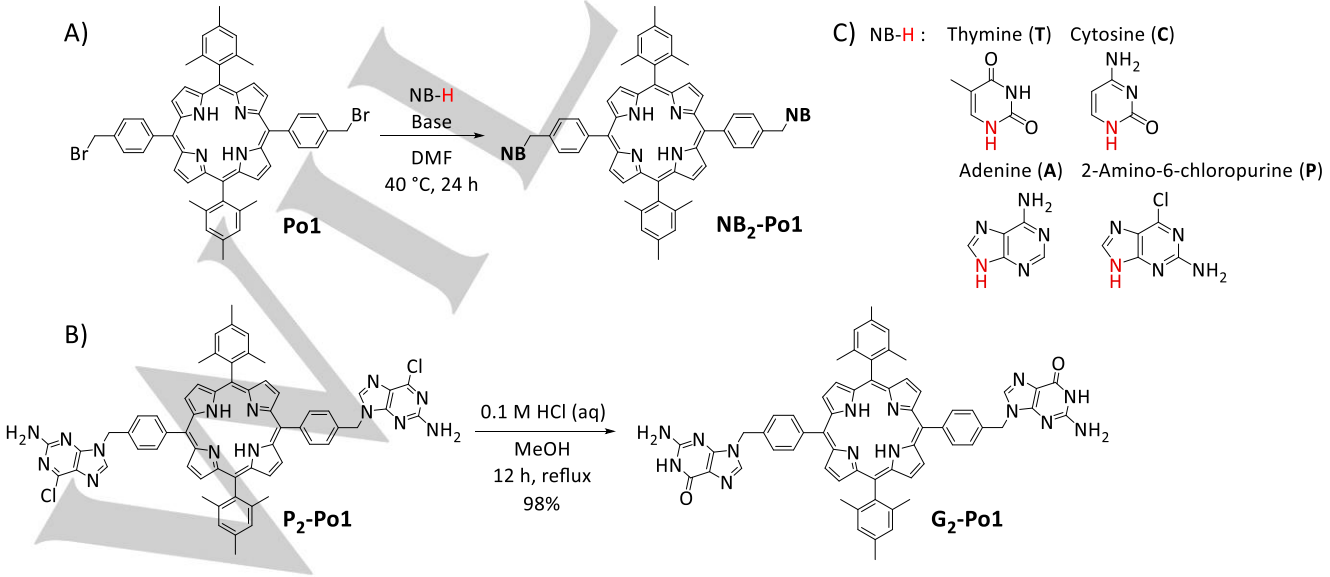
The 5,15-bis[4-(bromomethyl)phenyl]-10,20-bis(mesityl) porphyrin (**Po1**) was used as starting material. It was prepared as described by Jones *et al.*[22], from mesityl-dipyrromethane[23] and 4-(bromomethyl)benzaldehyde. The use of a sterically hindered dipyrromethane is crucial to avoid the formation of porphyrins mixtures due to scrambling.[23] **Po1** was then reacted with nucleobases in the presence of a suitable base (**Scheme 1**). The reaction conditions are summarized in **Table 1**.

Synthesis of T_2-Po1

Po1 was reacted with an excess of thymine in the presence of K_2CO_3 in dry DMF at 40 °C to yield 72% of the targeted 5,15-di(N1-methylphenylthymine)-10,20-dimesitylporphyrin (**T_2-Po1**), bearing thymine in the two *trans meso*-positions.
The ^{1}H-NMR spectrum of **T_2-Po1** confirmed the presence of two thymine moieties. Interestingly, it also showed that the peaks corresponding to the CH_2 protons are affected by the nature of the deuterated solvent, which suggest that the two protons of the CH_2 site are diastereotopic. In $CDCl_3$, the signals of the methylene protons appeared as two peaks each integrating for two protons with a $\Delta\delta$ of 0.25 ppm. Upon addition of drops of deuterated methanol, these peaks shifted closer to each other with a $\Delta\delta$ of 0.07 ppm (**Figure ESI 1**). Moreover, in d_6-DMSO (containing water) the signal corresponding to the CH_2 appeared as a singlet integrating for four protons. The presence of two singlets in a non-protic solvent such as $CDCl_3$ could indicate the formation of intermolecular H-bonds between thymine that lead to two non-equivalent signals for the CH_2 protons.

Table 1. Reaction conditions and yields of **NB_2-Po1** synthesis from **Po1**

NB (nb eq)	Base (nb eq)	Product (Yield)
T (5)	K_2CO_3 (3)	**T_2-Po1** (72%)
C (5)	NaH (3)	**C_2-Po1** (37%)
A (5)	K_2CO_3 (3)	**A_2-Po1** (54%) + **A-Po1-A'** (5%)
P (5)	K_2CO_3 (3)	**P_2-Po1** (80%) **+ P-Po1-P'** (8%)



Scheme 1. A) Synthetic route of **NB_2-Po1**. B) Synthetic route of **G_2-Po1**. C) Chemical Structure of the nucleobases and their active amino site shown in red.

Synthesis of C_2-Po1

The pKa value of cytosine (**C**) is higher than that of thymine, therefore a stronger base was used to deprotonate its N1 site.[6(b)] **Po1** was reacted with an excess of **C** in the presence of NaH resulting in **C_2-Po1** with a 37% yield. The low yield of the reaction is due to the low solubility and high polarity of **C_2-Po1**, which affect the purification process, decreasing the yield compared to the previous substitution reaction with thymine.

The ^{1}H-NMR spectrum of **C_2-Po1** showed two broad peaks at 7.13 and 7.23 ppm integrating each for two protons (**Figure ESI 4**). These signals are the fingerprint of the tautomeric form of cytosine displaying two NH sites (**Figure 2**).[6, 24]

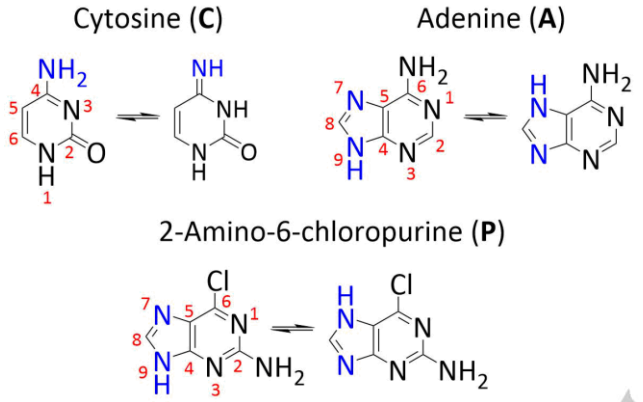


Figure 2. The tautomeric forms of **C**, **A** and **P**

Synthesis of A_2-Po1

The 5,15-di(N1-methylphenyladenine)-10,20-dimesityl porphyrin (**A_2-Po1**) was synthesized following the same procedure, where **Po1** was reacted with an excess of adenine and K_2CO_3 in dry DMF leading to the targeted porphyrin in 54% yield. In addition, a minor by-product **A-Po1-A'** was isolated in 5% yield.

The mass spectrum of this by-product **A-Po1-A'** showed the same mass as **A_2-Po1** however, the ^{1}H-NMR and ^{13}C-NMR spectra of the isomers were found to be different. The ^{1}H-NMR of **A_2-Po1** showed a C2 symmetry for the molecule, whereas the ^{1}H-NMR of **A-Po1-A'** in 1% of CD_3OD in $CDCl_3$ showed two sets of peaks for the protons of the CH_2 linker, the adenine protons at the C8 position, the mesityl protons and the β-pyrrolic hydrogens indicating that the C2 symmetry is broken in **A-Po1-A'** (**Figure 3**). This could be explained by the connection of both adenine molecules to the porphyrin *via* their N9 position in **A_2-Po1**, whereas in **A-Po1-A'** one adenine molecule is connected *via* its N9 and the other *via* its N7, which is possible because of the tautomeric forms of adenine (**Figure 2**). Moreover, **A-Po1-A'** is more soluble and less polar than **A_2-Po1**, these differences could be explained by less favored intermolecular H-bonds between adenines in **A-Po1-A'** compared to **A_2-Po1**.

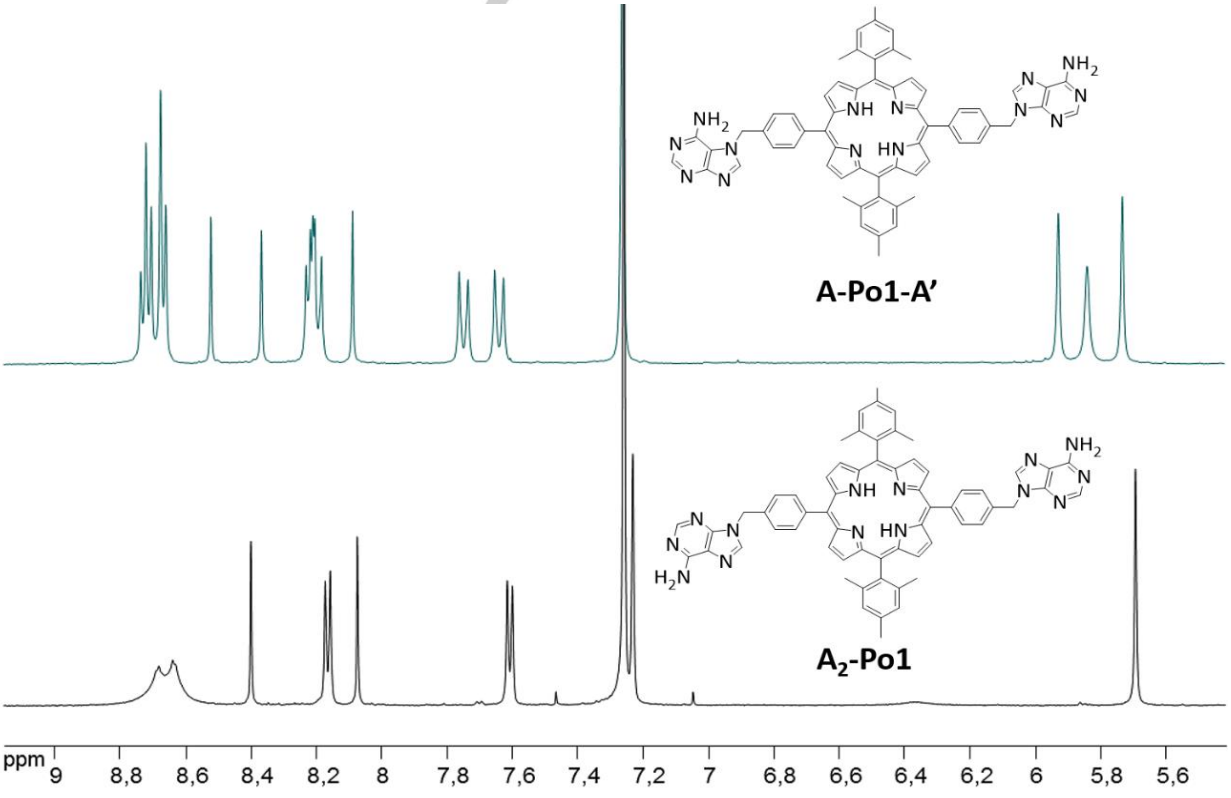


Figure 3. Portion of ^{1}H-NMR spectra of **A_2-Po1** (500 M Hz) and **A-Po1-A'** (300 MHz) in $CDCl_3$ + CD_3OD

Synthesis of G_2-Po1

The use of guanine to reach the targeted tecton 5,15-di(N9-methylphenylguanine)-10,20-dimesityl porphyrin (**G_2-Po1**) was unsuccessful, due to its low solubility and high polarity, making its purification unfeasible. Therefore, a two-step procedure was followed. 2-amino-6-chloropurine (**P**) was used as a precursor of guanine (**G**) given its higher solubility and its possible hydrolysis into **G** under acidic conditions.[25]

An excess of **P** was reacted with **Po1** and K_2CO_3 resulting in 80% yield of **P_2-Po1** and 8% of a minor product **P-Po1-P'**. By comparing the ^{1}H-NMR spectrum of both products, the latter was identified as an isomer bearing two non-equivalent tautomeric forms of **P** connected in *trans meso*-positions of the porphyrin, one *via* its N9 site and another *via* its N7 site (**Figure 4**).

P_2-Po1 was then hydrolyzed using an aqueous HCl solution (**Scheme 1B**), and the target porphyrin **G_2-Po1** was obtained in 98% yield by precipitation at neutral pH. The hydrolysis of **P** to **G** was confirmed with the IR spectroscopy of **G_2-Po1** by the appearance of a peak at 1682 cm^{-1} which corresponds to the C=O stretching of **G.**

Tetra functionalized NB-porphyrin

The porphyrin bearing four NBs could lead to higher complexity networks. To prepare such molecules, 5,10,15,20-tetrakis[4-(bromomethyl)phenyl] porphyrin (**Po2**)[26] was reacted with an excess of thymine in the presence of K_2CO_3 affording the targeted **T_4-Po2** in 93% yield (**Scheme 2**). We tried to apply this strategy with **C**, **A** and **P**. Unfortunately, it led to the formation of mixtures of partially substituted porphyrins which were impossible to purify due to their low solubility.

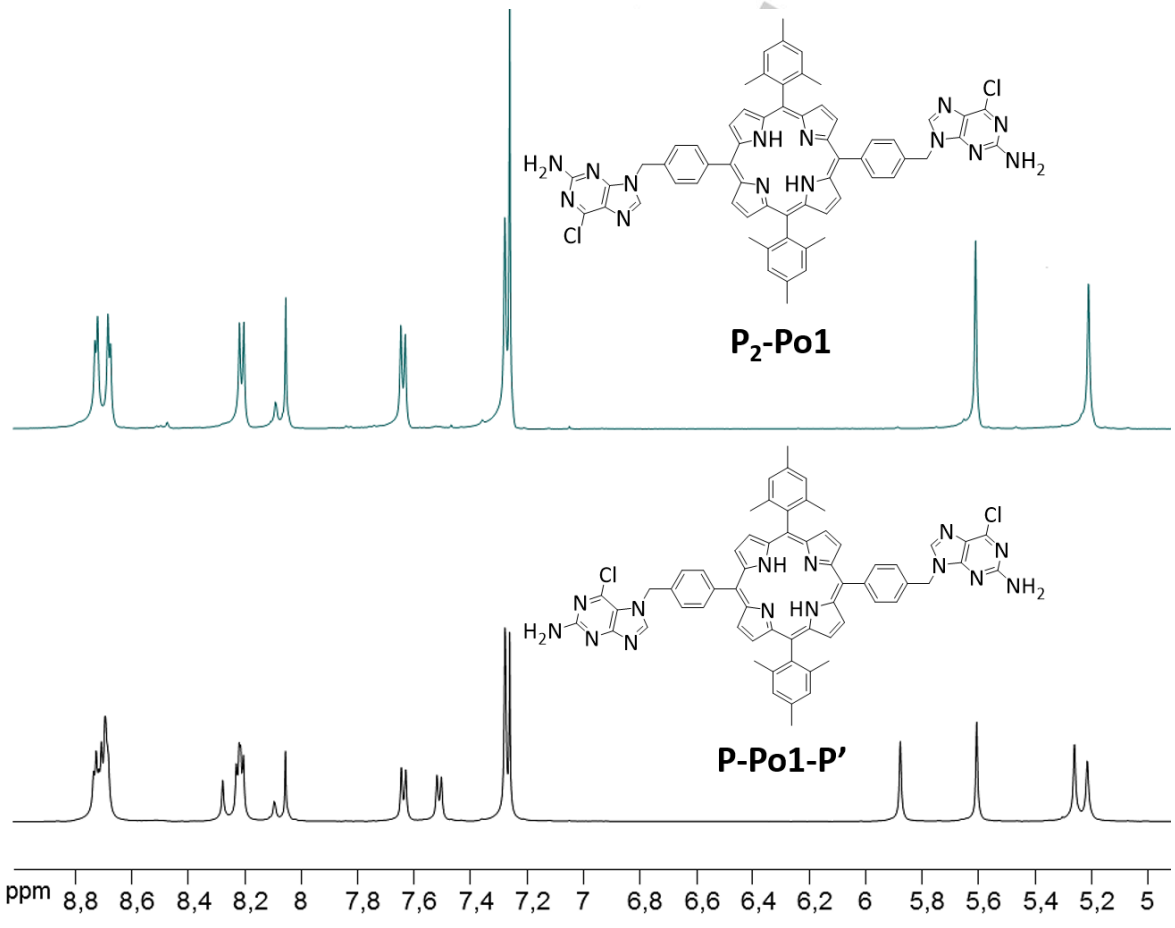
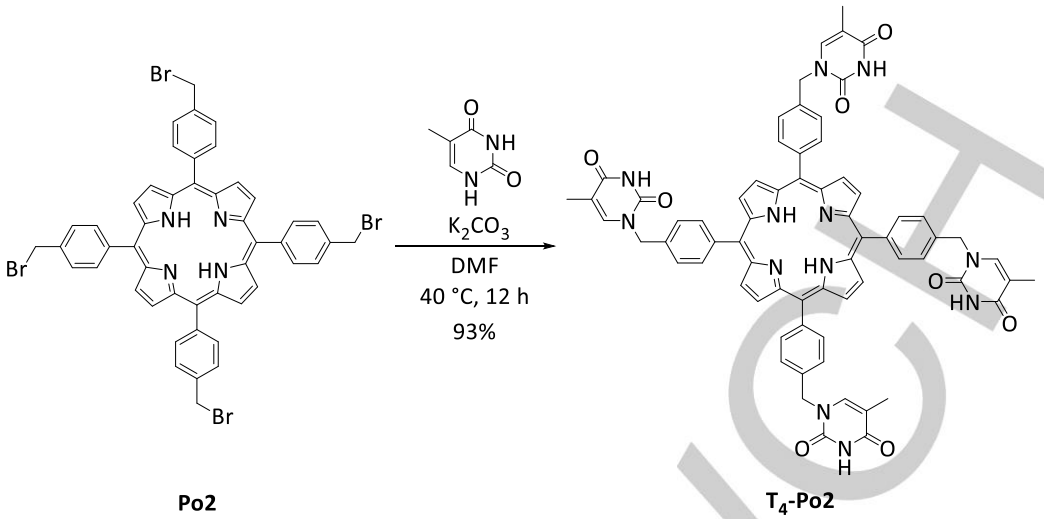


Figure 4. A portion of ^{1}H-NMR spectra of **P_2-Po1** and **P-Po1-P'** ($CDCl_3$ + CD_3OD, 500 MHz)

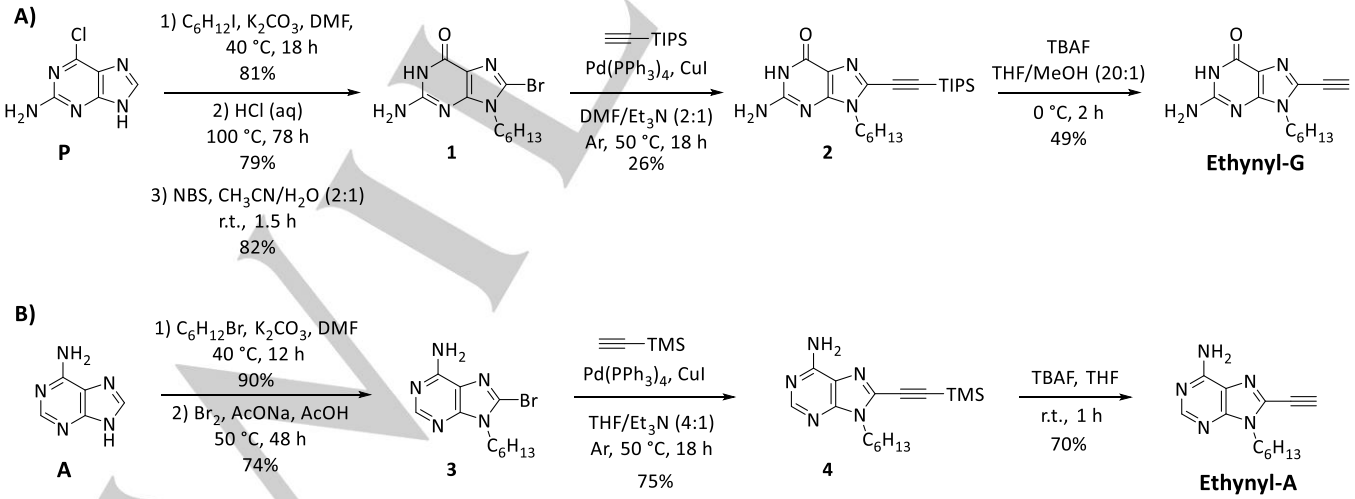


Scheme 2. Synthesis of **T_4-Po2**

Synthesis of Rigid NB-porphyrins based tectons

Our second objective was to replace the flexible methylene linker by a more rigid one, the ultimate goal of such tectons being to favour and master their organization on surface. In order to generate rigid frameworks based on porphyrins and NBs, we first envisioned to introduce the NBs directly on the porphyrin scaffold through a Suzuki cross coupling reaction between a porphyrin boronic ester and halogenated NBs. Unfortunately, this strategy led to insoluble mixtures whose purification and characterization were difficult. We then focused on the introduction of NBs *via* rigid ethynyl linkers.

Our targeted tectons are porphyrin molecules bearing NBs on two *trans meso*-positions connected *via* ethynyl linker, which will allow coplanarity of the H-bonding sites and the porphyrin main plane. In addition, pentyl side chains were introduced on the other two remaining *trans meso*-positions to increase solubility of the final tectons and further enhance their affinity for the surface. The first strategy to synthesize the rigid tectons was to introduce the ethynyl group on the porphyrin and then to perform a Sonogashira cross coupling reaction between the porphyrin and halogenated nucleobases. However, this strategy was not successful. Therefore, we proceeded in synthesizing ethynyl-functionalized nucleobases and then coupling them with brominated porphyrins using a strategy that has proven to be successful for porphyrin bearing ethynylpyridine groups at the *meso* positions.[20b]



Scheme 3. Synthetic route to A) **Ethynyl-G** and B) **Ethynyl-A**.

In order to increase the solubility of the nucleobases bearing ethynyl groups, a hexyl chain was introduced on the N1 position of pyrimidine derivatives and on the N9 site of purine derivatives. The targeted C5-ethynyl-functionalized pyrimidines, **Ethynyl-U** and **Ethynyl-C**, have been prepared following a methodology described by González-Rodríguez *et al*.[27]

The synthesis of **Ethynyl-G** (Fehler! Verweisquelle konnte nicht gefunden werden. **3A**) was inspired by a five-step procedure described by Wasielewski *et al*.[25] for a N9-octyl substituted guanine derivative using 2-amino-6-chloropurine (**P**) as starting material. The alkylation of the N9 position of **P** was performed using 1-iodohexane and K_2CO_3 in dry DMF. The resulting intermediate 2-amino-6-chloro-N9-hexylpurine was then hydrolyzed in aqueous hydrochloric acid yielding 79 % of N9-hexylguanine**.** The C8 position of the latter was then brominated with NBS in a water/acetonitrile mixture, giving rise to compound **1** with a yield of 82 %.

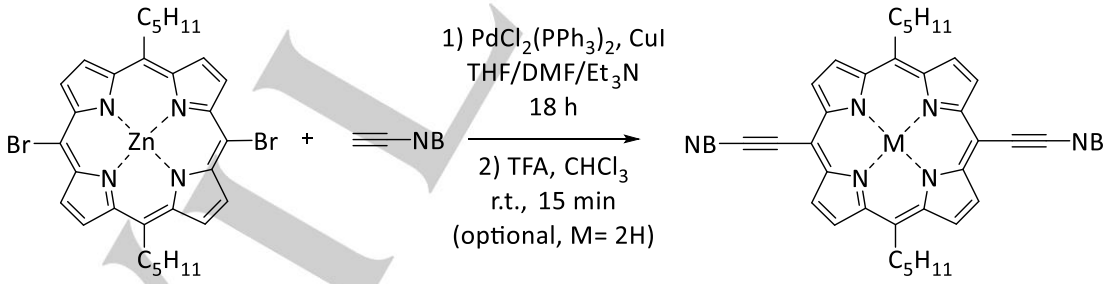
Compound **1** was subjected to a Sonogashira cross coupling reaction using TIPS-acetylene in a DMF/triethylamine mixture resulting in compound **2**, which was followed by a final desilylation step with TBAF resulting in the **Ethynyl-G**. The yields (26% and 49%) corresponding to the two last steps described hereby are relatively low and is probably due to the low solubility of the final molecule causing loss of product during the purification process (Fehler! Verweisquelle konnte nicht gefunden werden.**A**).

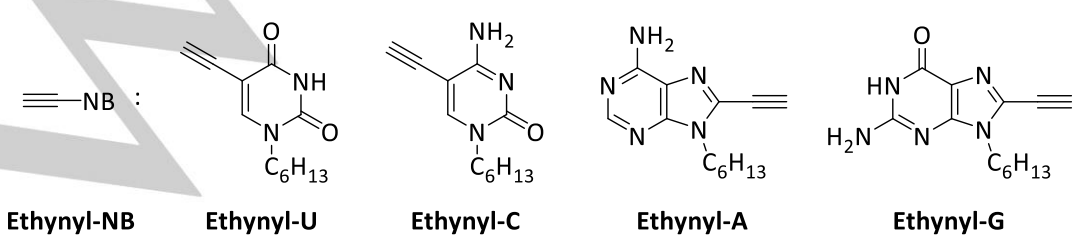
The C8-ethynyl-functionalized adenine moiety **Ethynyl-A** was prepared in four steps from the commercially available adenine. The first step consists in an alkylation of the N9 position of the purine **A** using 1-bromohexane and K_2CO_3 in dry DMF, following a modified procedure for the synthesis described by Verma *et al.*[28], which resulted in 90 % of N9-hexyladenine. The bromination step of the later was adapted from a procedure described by Raptopoulou *et al*[29]. The resulting 8-bromo-9-hexyladenine **3** was then reacted in a standard Sonogashira cross coupling reaction with TMS-acetylene yielding molecule **4**, which was deprotected in a final step using TBAF. **Ethynyl-A** was obtained with an overall yield of 35% (Fehler! Verweisquelle konnte nicht gefunden werden. **3B**).

Synthesis of NB_2-Po3

The ethynyl-funtionalized nucleobases (**Ethynyl-C**, **Ethynyl-U**, **Ethynyl-A** and **Ethynyl-G**) were reacted with zinc 5,15-dibromo-10,20-dipentylporphyrin **ZnPo3**[27] (Fehler! Verweisquelle konnte nicht gefunden werden. **4**) in a mixture of THF and triethylamine or a mixture of THF, DMF and trimethylamine in the presence of bis(triphenylphosphine)palladium dichloride and copper iodide as catalysts.

Rigid porphyrin-nucleobases derivatives **U_2-Po3**, **C_2-Po3**, **A_2-ZnPo3** and **G_2-ZnPo3** were obtained. Unfortunately, only **U_2-Po3** has been obtained as pure compound and has been fully characterized. The low solubility of **C_2-Po3**, **A_2-ZnPo3** and **G_2-ZnPo3** prevented efficient purifications. Nevertheless, the purity of these three tectons is estimate to be higher than 90%. The conditions used for the cross coupling reactions and their yields are summarized in **Table 2**. The targeted bis-pyrimidine-porphyrins **U_2-Po3** and **C_2-Po3** were found to be easier to purify when the porphyrin core was demetallated. Thus, TFA was added to the crude material before the purification step. However, the two bis-purine-porphyrin derivatives **A_2-ZnPo3** and **G_2-ZnPo3** have shown a lower solubility than **U_2-ZnPo3** and **C_2-ZnPo3**, and they were almost insoluble when demetallated. Therefore, purification by multiple washings of the crude metallated product with various solvents were followed and no demetallation step was performed.





Scheme 4. Synthetic route to the **NB$_2$-Po3** (NB = **U** and **C**) and **NB$_2$-ZnPo3** (NB = **U**, **C**, **A**, **G**) tectons

Table 2. Reaction conditions and yields of **NB$_2$-Po3** and **NB$_2$-ZnPo3** synthesis

Ethynyl-NB (nb eq)	$PdCl_2(PPh_3)_2$ (mol%)	CuI (mol%)	THF/DMF/Et_3N (ratio)	T (°C)	Product (Yd)
Ethynyl-U (3)	20	10	4:0:1	40	**U$_2$-Po3** (70%)[a]
Ethynyl-C (3)	8	4	4:0:1	40	**C$_2$-Po3** (<64%)[a][b]
Ethynyl-A (3)	10	10	4:0:1	40	**A$_2$-ZnPo3** (<23%) [b]
Ethynyl-G (3)	10	4	2:2:1	50	**G$_2$-ZnPo3** (<30%) [b]

[a] The yield of Sonogashira coupling step and the demetallation step. [b] The yields were calculated assuming a 100% purity, and is thus overestimated.

Hydrogen bonded Molecular Network of C$_2$-ZnPo3

Dark green single crystals suitable for XRD have been obtained for **C$_2$-ZnPo3** by slow evaporation of a 10 mM solution in 9:1 DMSO/THF. The compound crystallized as [**C$_2$-ZnPo3**$(DMSO)_3(H_2O)$] in the triclinic space group (**Figure 5**). Two DMSO molecules are coordinated in the axial positions of the zinc ion present in the porphyrin cavity with a Zn-O distance of 2.57 Å (**Figure 5A**). Cytosine of two adjacent porphyrins are H-bonded thus leading to a 1D staircase H-bonded network (**Figure 5B**). Hydrogen bonding between the cytosine moieties involves amine and the N3 pyrimidyl nitrogen atom in a complementary fashion (d_{N-N} = 3.00 Å).

Moreover, water molecules are H-bonded to the carbonyl oxygen atom and the amine group of two adjacent cytosines with distances in the range of 2.70 – 2.77 Å (**Figure 5B**). In the 1D staircase sequence, the porphyrins are parallel. The planes formed by two successive macrocycles are separated by 2.87 Å, while two porphyrins of two adjacent 1D sequences are π stacked and their mean planes are separated by 3.22 Å. The distance between two zinc ions is 20.18 Å within the 1D arrangement and 9.14 Å between 2 layers. An additional interaction between a water molecule and the carbonyl group of the cytosine in the adjacent layer (d_{O-O} = 2.84 Å) leads to the formation of a 2D hydrogen bonded network (**Figure 5B**).

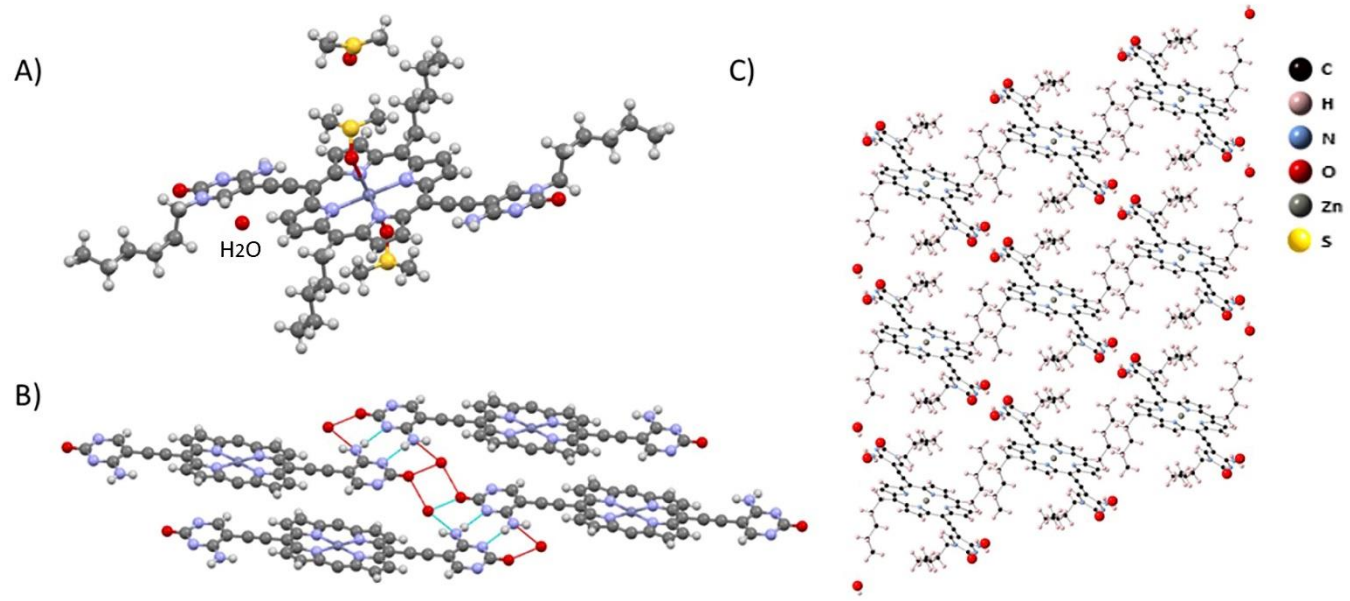


Figure 5. A) Portion of the crystal structure of [**C$_2$-ZnPo3**$(DMSO)_3(H_2O)$], B) Portion of the crystal structure showing the intermolecular H-bonding interactions (DMSO molecules, hydrogen of the water molecules and alkyl side chains of cytosine molecules have been omitted for clarity), C) Portion of the structure view along the a axis (DMSO molecules have been omitted for clarity).

Conclusion

The synthesis of ten new porphyrins bearing nucleobases was achieved following different synthetic strategies. **Po1** (5,15-di(4-(bromomethyl)phenyl)-10,20-diphenylporphyrin) was used as a starting material to introduce two NBs in trans *meso*-positions of the porphyrin scaffold *via* a substitution reaction of the N1 site of thymine and cytosine in the presence of K_2CO_3 and NaH respectively, and to the N9 site of adenine and 2-amino-6-chloropurine using K_2CO_3. The substitution reaction between guanine and **Po1** was unsuccessful. However, the porphyrin bearing guanines (**G_2-Po1**) was obtained by the hydrolysis of the porphyrin bearing 2-amino-6-chloropurine (**P_2-Po1**). In addition, it was possible to synthesize a porphyrin bearing four thymine moieties at its four *meso*-positions by reacting 5,10,15,20-tetrakis(4-(bromomethyl)phenyl)porphyrin (**Po2**) with thymine in the presence of K_2CO_3. The substitution reactions of the other nucleobases with **Po2** was not successful due to the low solubility of the final products. Furthermore, four rigid tectons bearing two NBs in *trans* positions (**U_2-Po3**, **C_2-Po3**, **A_2-ZnPo3** and **G_2-ZnPo3**) have been synthesized using the Sonogashira cross coupling methodology with **ZnPo3** and the corresponding **NB-Ethynyl** derivatives. Moreover, **C_2-ZnPo3** has been characterized in the solid state by X-ray diffraction. The self-complementarity of the cytosine leads to the formation of a hydrogen bonded network. The next step is to use this library of NB-porphyrin based tectons in order to generate H-bonded networks based on complementary pairs and also to take advantage of the porphyrin cavity as an additional coordinating site to design more complex assemblies bearing hydrogen bonding donor/acceptor groups as well as coordinating units.

Experimental Section

Experimental Details. All the starting reagents were obtained from commercial sources and used as received. The starting porphyrins: 5,15-bis(4-(bromomethyl)phenyl)-10,20-dimesitylporphyrin[23] (**Po1**), 5,10,15,20-tetrakis[4-(bromomethyl)phenyl]porphyrin[26] (**Po2**) and zinc 5,15-dibromo-10,20-dipentylporphyrin[27] (**ZnPo3**) were obtained following the described procedures. Brucker AC or AV-300, AV-400 or AV-500 spectrometer was used to record NMR spectra at room temperature with the deuterated solvent as the internal reference. NMR chemical shifts and J values are given in parts per million (ppm) and in Hertz respectively. Mass spectrometry was performed at the Common Analysis Service of the University of Strasbourg. X-ray crystallography data were collected on a Bruker SMART CCD diffractometer with Mo-Kα radiation at 173 K for all compounds. The structures were solved using SHELXS-97 and refined by full matrix least-squares on F2 using SHELXL-2014 with anisotropic thermal parameters for all non-hydrogen 01448[30] Hydrogen atoms were introduced at calculated positions and refined using the riding model. CCDC 2026828 contains the supplementary crystallographic data for [**C2-ZnPo3** $(DMSO)_3(H_2O)$]. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

T_2-Po1

5,15-bis(4-(bromomethyl)phenyl)-10,20-dimesityl porphyrin (132 mg, 0.1497 mmol, 1 eq) and thymine (94 mg, 0.748 mmol, 5 eq) were dissolved in dry degassed DMF (8 mL). K_2CO_3 (62 mg, 0.449 mmol, 3 eq) was added to the suspension and stirred for 24 hours at 40 °C. The reaction was followed by TLC and stopped when all starting porphyrin was consumed. The solvent was evaporated and the resulting solid was washed with water (10 mL) to remove the excess of thymine and salt. The crude product was purified by column chromatography (Silica gel, 5% methanol in DCM) to give a purple solid (106 mg, 72 %).

^{1}H NMR (400 MHz, $CDCl_3$ + MeOD): δ=8.70-8.64 (m, 8H), 8.18-8.16 (d, ^3J=7.8 Hz, 4H), 7.61-7.59 (d, $^3J_{H,H}$=8.0 Hz, 4H), 7.30 (s, 2H), 7.22 (s, 4H), 5.25 (s, 2H), 5.18(s, 2H), 2.57 (s, 6H), 1.96 (s, 6H), 1.76 ppm (s, 12H); ^{13}C NMR (126 MHz, $CDCl_3$ + MeOD): δ=164.9, 151.6, 142.1, 140.4, 139.4, 138.3, 137.9, 135.1, 135.0, 127.8, 126.1, 123.8, 118.5, 111.5, 53.5, 51.1, 21.6, 21.4, 12.4 ppm; IR: $\tilde{\nu}$=419.3, 470.9, 558.2, 738.4, 756.5, 810.5, 830.2, 933.7, 981.9, 1027.6, 1201.1, 1243.2, 1380.4, 1423.7, 1445.3, 1477.9, 1666.6, 1715.8, 2928.8, 3028.3 cm^{-1}; UV/Vis (DMF): λ_{max} (εx10^3)= 644 (2.38), 589 (2.99), 549 (3.85), 515 (9.69), 419 nm (227.97 mol^{-1}.L.cm^{-1}), HRMS (ESI): *m/z* calcd for $C_{62}H_{54}N_8O_4$+H$^+$: 975.4323 [*M*+H]$^+$; found: 975.4322.

C_2-Po1

5,15-bis(4-(bromomethyl)phenyl)-10,20-dimesitylporphyrin (130 mg, 0.156 mmol, 1 eq) and cytosine (86 mg, 0.779 mmol, 5 eq) were dissolved in dry degassed DMF (12 mL). NaH (11.20 mg, 0.467 mmol, 3 eq) was added to the suspension and stirred for 24 hours at 40 °C. The reaction was followed by TLC and stopped when all starting porphyrins were consumed. The reaction was dried under vacuum, and then washed with water to remove the excess of salt and cytosine. The crude was purified by column chromatography (Silica gel, 5% Methanol in DCM) to give a purple solid (55 mg, 37 %).

^{1}H NMR (400 MHz, DMSO-d_6): δ=8.78 (d, $^3J_{H,H}$=4.7 Hz, 4H), 8.62 (d, $^3J_{H,H}$=4.6 Hz, 4H), 8.21-8.20 (d, $^3J_{H,H}$=7.9 Hz, 4H), 7.99-7.98 (d, $^3J_{H,H}$=7.2 Hz, 2H), 7.68-7.66 (d, $^3J_{H,H}$=7.9 Hz, 4H), 7.35(s, 4H), 7.23 (s, brd, 2H), 7.13 (s, brd, 2H), 5.84-5.82 (d, $^3J_{H,H}$=7.3 Hz, 2H), 5.21 (s, 4H), 2.58 (s, 6H), 1.75 (s, 12H), -2.78 ppm (s, 2H); ^{13}C NMR (126 MHz, DMSO-d_6): δ=166.2. 156.2, 146.5, 139.9, 138.5, 137.8, 137.7, 134.4, 127.9, 126.0, 117.8, 94.0, 65.0, 51.5, 21.3, 21.1 ppm; IR: $\tilde{\nu}$=410.7, 606.2, 726.3, 787.3, 1077.7, 1264.7, 1384.9, 1489.3, 1644.5, 3320.8 cm^{-1}; UV/Vis (DMF): λ_{max} (εx10^3)= 647 (2.85), 591 (3.21), 548 (4.87), 514 (9.50), 418 nm (190.49 mol^{-1}.L.cm^{-1}); HRMS (ESI): *m/z* calcd for $C_{60}H_{52}N_{10}O_2$: 945.4347 [*M*+H]$^+$; found: 945.4354.

A_2-Po1

5,15-bis(4-(bromomethyl)phenyl)-10,20-dimesitylporphyrin (150 mg, 0.170 mmol, 1 eq) and adenine (114.5 mg, 0.848 mmol, 5 eq) were dissolved in dry degassed DMF (10 mL). K_2CO_3 (70.1 mg, 0.508 mmol, 3 eq) was added to the suspension and stirred for 24 hours at 40 °C. The reaction was followed by TLC and stopped when all starting porphyrin was consumed. The mixture was dried under vacuum, and then washed with water (10 mL) to remove the excess of salt and adenine. The crude was purified by column chromatography (Silica gel, 5% methanol in DCM) to give **A_2-Po1** (90 mg, 54%) and **A-Po1-A'** (8 mg, 5%) as purple solids.

A_2-Po1:^{1}H NMR (500 MHz, $CDCl_3$ + MeOD): δ=8.68-8.63 (m, 8H), 8.40 (s, 2H), 8.17-8.16 (d, $^3J_{H,H}$= 7.9 Hz, 4H), 8.07 (s, 2H), 7.62-7.60 (d, $^3J_{H,H}$=7.9 Hz, 4H), 7.23 (s, 4H), 5.69 (s, 4H), 2.58 (s, 6H), 1.76 (s, 12H), -2.74 ppm (br s, 2H); ^{13}C NMR (126MHz, $CDCl_3$ + MeOD): δ=155.7, 153.3, 150.0, 142.3, 140.6, 139.4, 138.3, 137.9, 135.1, 134.9, 127.8, 126.1, 119.1, 118.6, 118.3, 47.4, 21.6, 21.5 ppm; IR: $\tilde{\nu}$= 407.7, 544.1, 727.7, 745.1, 771.8, 791.6, 825.1, 967.5, 1021.5, 1076.1, 1076.1, 1245.9, 1308.8, 1332.1, 1431.3, 1468.4, 1580.9, 1603.7, 1681.2, 2851.8, 2922.1, 3076.5 cm^{-1}; UV/Vis (DMF): λ_{max} (εx10^3)= 648 (2.22). 591 (2.30), 551 (2.68), 516 (3.19),

418 nm (283.28 $mol^{-1}.L.cm^{-1}$); HRMS (ESI): *m/z* calcd for $C_{62}H_{52}N_{14}$: 993.4575 $[M+H]^+$; found : 993.4516.

A-Po1-A': ^{1}H NMR (500 MHz, $CDCl_3$ + MeOD): δ=8.73-8.66 (m, 8H), 8.52 (s, 1H), 8.45 (s, 1H), 8.27 (s, 1H), 8.25- 8.23 (d, $^3J_{H,H}$=7.9 Hz, 2H), 8.21-8.19 (d, $^3J_{H,H}$=7.8 Hz, 2H), 8.09 (s, 1H), 7.78-7.76 (d, $^3J_{H,H}$=7.9 Hz, 2H), 7.65-7.63 (d, $^3J_{H,H}$=7.9 Hz, 4H), 7.27 (s, 4H), 5.74 (s, 2H), 5.67 (s, 2H), 2.62 (s, 6H), 1.81 (s, 12H), -2.66 ppm (s, 2H).

P_2-Po1

5,15-bis(4-(bromomethyl)phenyl)-10,20-dimesitylporphyrin (100 mg, 0.113 mmol, 1 eq) and 2-amino-6-chloropurine (95.81 mg, 0.565 mmol, 5 eq) were dissolved in dry degassed DMF (15 mL). K_2CO_3 (46.85 mg, 0.339 mmol, 3 eq) was added to the suspension and stirred for 24 hours at 50°C. The reaction was followed by TLC and stopped when all starting porphyrin was consumed. The reaction was dried under vacuum then washed with water (5 mL) to remove the excess of 4-chloro-1-aminopurine and salt. The crude product was purified by Column Chromatography (Silica gel, 5% Methanol in DCM) to give **P_2-Po1** (96 mg, 80%) and **P-Po1-P'** (10 mg, 8%) as purple solids.

P_2-Po1: ^{1}H NMR (500 MHz, $CDCl_3$): δ=8.73-8.72 (d, $^3J_{H,H}$=4.7 Hz, 4H), 8.68 (d, $^3J_{H,H}$=4.7 Hz, 4H), 8.22-8.20 (d, $^3J_{H,H}$=8.0 Hz, 4H), 8.05 (s, 2H), 7.65-7.63 (d, $^3J_{H,H}$=7.9 Hz, 4H), 7.28 (s, 4H), 5.61 (s, 4H), 5.21 (s, 4H), 2.63 (s, 6H), 1.81 (1s, 12H), -2.68 ppm (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$ + MeOD) δ=159.4, 154.2, 151.8, 142.5, 142.4, 139.5, 138.4, 137.9, 135.2, 134.8, 129.9, 127.9, 126.2, 125.5, 118.7, 118.4, 47.3, 21.8, 21.6 ppm; IR: $\tilde{\nu}$=437.9, 496.2, 528.4, 605.9, 638.8, 734.1, 755.9, 782.7, 819.2, 914.2, 991.9, 1119.3, 1165.8, 1210.9, 1348.0, 1391.8, 1407.6, 1469.1, 1518.0, 1559.1, 1628.7, 1699.9, 3073.9, 33313.1, 3458.8 cm^{-1}; UV/Vis (DMF): λ_{max} (εx10^3)= 647 (4.43). 591 (5.07), 548 (7.33), 514 (16.15), 418 nm (348.60 $mol^{-1}.L.cm^{-1}$), HRMS (ESI): *m/z* calcd for $C_{62}H_{50}N_{14}Cl_2$: 1061.3793 $[M+H]^+$; found: 1061.3782.

P-Po1-P': ^{1}H NMR (500 MHz, $CDCl_3$): δ=8.69 (m, 8H), 8.28 (s, 1H), 8.21 (m, 4H), 8.05 (s, 1H), 7.64-7.63 (d, $^3J_{H,H}$=7.9 Hz, 2H), 7.52-7.50 (d, $^3J_{H,H}$=7.9 Hz, 2H), 7.28 (s, 4H), 5.88 (s, 2H), 5.60 (s, 2H), 5.26 (s, 2H), 5.21 (s, 2H), 2.63 (s, 6H), 1.82 (s, 12H), -2.67 ppm (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$ + MeOD): δ=164.6, 159.7, 159.5, 154.2, 151.8, 149.0, 144.1, 142.5, 139.4, 138.3, 137.9, 135.2, 134.9-134.8, 127.9, 126.2, 125.5, 125.3, 118.7, 118.4, 118.2, 116.8, 50.7, 47.3, 21.8, 21.6 ppm; MS: *m/z* calcd for $C_{62}H_{50}N_{14}Cl_2$: 1061.38 $[M+H]^+$; found : 1061.38.

G_2-Po1

5,15-bis(N_9-methylphenyl-2-amino-6-chloropurine)-10,20-dimesityl porphyrin (60 mg, 0.0565 mmol, 1 eq) was dissolved in 20 mL of MeOH. 0.1 M of HCl aqueous solution was added to the mixture (4 mL, 0.4 mmol, 7 eq). Upon addition of HCl, the color of the solution changed from purple to green. The mixture was stirred overnight under reflux, and the reaction was followed by TLC. When all starting material was consumed, 0.1 M NaOH solution was added drop wise to neutralize the solution (*ca.* 3 mL). The resulting purple precipitate was filtered, washed with water (10 mL) and acetone (10 mL) and dried under reduced pressure to give the final product (56 mg, 98 %).

^{1}H NMR (500 MHz, DMSO-d_6): δ=10.87 (br s, 2H), 8.75-8.74 (d, $^3J_{H,H}$=4.2 Hz, 4H), 8.63-8.62 (d, $^3J_{H,H}$=4.2 Hz, 4H), 8.22-8.21 (d, $^3J_{H,H}$=8.0 Hz, 4H), 8.04 (s, 2H), 7.64-7.62 (d, $^3J_{H,H}$=7.8 Hz, 4H), 7.34 (s, 4H), 6.77 (br s, 4H), 5.55 (s, 4H), 2.58 (s, 6H), 1.74 (s, 12H), -2.80 ppm (s, 2H); IR: $\tilde{\nu}$=477.9, 688.9, 757.1, 797.8, 1017.1, 1093.7, 1167.7, 1213.1, 1260.0, 1409.3, 1480.3, 153.5, 1606.8, 1682.8, 2852.0, 2923.1, 3113.9 cm^{-1}; UV/Vis (DMF): λ_{max} (εx10^3)= 647 (1.34), 591 (1.44), 548 (2.09), 514 (4.00), 418 nm (76.94 $mol^{-1}.L.cm^{-1}$); HRMS (ESI): *m/z* calcd for $C_{62}H_{52}N_{14}O_2$: 513.2272 $[M/2+H]^+$; found: 513.2272.

T_4-Po2

5,10,15,20-tetrakis(4-(bromomethyl)phenyl)porphyrin (200 mg, 0.203 mmol, 1 eq), thymine (255 mg, 2.03 mmol, 10 eq) and K_2CO_3 (141 mg, 1.02 mmol, 5 eq) were dissolved in 10 mL of degassed DMF. The mixture was stirred overnight at 40 °C under argon. The reaction was followed by TLC. After the disappearance of the starting porphyrin, the reaction was dried under vacuum and then triturated with water (10 mL). The purple precipitate was filtered over a frit and washed with water (20 mL), then dried under vacuum to give a purple solid (220 mg, 93 %).

^{1}H NMR (400 MHz, DMSO-d_6): δ=11.50 (br s, 4H), 8.82-8.81 (s, 8H), 8.22-8.21 (d, $^3J_{H,H}$= 7.7 Hz, 8H), 7.96 (s, 4H), 7.73-7.72 (d, $^3J_{H,H}$=7.7 Hz, 8H), 5.22 (s, 8H), 1.88 (s, 12H), -2.97 ppm (s, 2H); ^{13}C NMR (126 MHz, DMF-d_7): δ=165.4, 164.8, 152.0, 141.8, 141.4, 138.1, 137.6, 135.2, 126.7, 120.2, 110.0, 108.3, 73.4, 50.7, 12.0, 11.7 ppm; IR $\tilde{\nu}$=411.8, 477.6, 558.6, 798.8, 966.1, 982.2, 1212.8, 1349.1, 1382.2, 1661.0, 2925.5 cm^{-1}; UV/Vis (DMF): λ_{max} (εx10^3)= 646 (4.08). 593 (4.42), 550 (6.69), 515(11.20), 419 nm (231.96 $mol^{-1}Lcm^{-1}$); HRMS (ESI): *m/z* calcd for $C_{68}H_{54}N_{12}O_8$: 1167.4260$[M+H]^+$; found: 1167.4257.

2-amino-6-chloro-N9-hexylpurine

To a solution of 6-chloro-N_9-hexylpurine **P** (2.28 g, 13.4 mmol) in dry DMF (50 mL) potassium carbonate (2.8 g, 20.2 mmol) was added. The mixture was heated at 40 °C for 30 min and 1-iodohexane (2 mL, 13.4 mmol) was then added. The resulting mixture was allowed to stir at 40 °C for 18 h. After completion of the reaction, the solvents were evaporated under vacuum and the crude product was dissolved in dichloromethane and washed with water. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The crude material was subjected to a chromatography column over silica gel using CH_2Cl_2/MeOH (97:3) as eluent to provide a pure product (2.77 g, 81%).

^{1}H NMR (500 MHz, d_6-DMSO): δ=8.14 (s, 1H), 6.90 (br s, 2H), 4.02 (t, $^3J_{H,H}$=7.2 Hz, 2H), 1.75 (quint, $^3J_{H,H}$=7.2 Hz, 2H), 1.28-1.17 (m, 6H), 0.82 ppm (t, $^3J_{H,H}$=6.7 Hz, 3H); ^{13}C NMR (125 MHz, d_6-DMSO): δ=159.7, 154.1, 149.3, 143.3, 123.3, 43.0, 30.7, 28.9, 25.7, 22.0, 13.9 ppm; HRMS (ESI): *m/z* calcd for $C_{11}H_{17}N_5Cl$: 254.1167 $[M+H]^+$; found: 254.1173.

N9-hexylguanine

A suspension of 2-amino-6-chloro-N_9-hexylpurine (2.77 g, 10.9 mmol) in aqueous hydrochloric acid (0.5 M, 200 mL) was stirred under reflux for 18 h. The resulting solution was neutralized with a concentrated aqueous solution of sodium hydroxide and the resulting white precipitate was filtered, washed with water and dried under vacuum to provide N9-hexylguanine as a pure white solid (2.2 g, 79%).

^{1}H NMR (500 MHz, d_6-DMSO): δ=10.52 (s, 1H), 7.67 (s, 1H), 6.42 (br s, 2H), 3.91 (t, $^3J_{H,H}$=7.1 Hz, 2H), 1.70 (quint, $^3J_{H,H}$=7.1 Hz, 2H), 1.30 – 1.16 (m, 6H), 0.83 ppm (t, $^3J_{H,H}$=6.8 Hz, 3H); ^{13}C NMR (125 MHz, d_6-DMSO): δ=156.9, 153.4, 151.2, 137.5, 116.6, 42.6, 30.7, 29.4, 25.7, 22.0, 13.9 ppm; HRMS (ESI): *m/z* calcd for $C_{11}H_{18}N_5O$ 236.1506, $[M+H]^+$; found: 236.1515.

8-bromo-N9-hexylguanine (1)

N-bromosuccinimide (753 mg, 4.2 mmol) was added in small portions to a suspension of N_9-hexylguanine (664 mg, 2.8 mmol) in water (15 mL) and acetonitrile (30 mL). The mixture was allowed to stir at room temperature for 1.5 h. Acetonitrile was evaporated under vacuum and the resulting yellowish precipitate was filtered, washed with water and dried under vacuum to provide **1** as a pure solid (726 mg, 82%).

^{1}H NMR (500 MHz, d_6-DMSO): δ=10.66 (s, 1H), 6.57 (br s, 2H), 3.90 (t, $^3J_{H,H}$= 7.3 Hz, 2H), 1.66 (tt, $^3J_{H,H}$=7.3 Hz and 6.7 Hz, 2H), 1.30 – 1.21 (m, 6H), 0.84 ppm (t, $^3J_{H,H}$=6.5 Hz, 3H); ^{13}C NMR (125 MHz, d_6-DMSO): δ=155.6, 153.8, 152.4, 120.7, 116.8, 43.4, 30.7, 28.8, 25.6, 22.0, 13.8 ppm; HRMS (ESI): *m/z* calcd for $C_{11}H_{17}N_5OBr$: 314.0611 $[M+H]^+$; found: 314.0611.

9-hexyl-8-[2-(triisopropylsilyl)ethynyl]guanine (2)

To a degassed solution of 8-bromo-N9-hexylguanine (**1**) (366 mg, 1.16 mmol) in DMF/Et_3N (2:1, 30 mL) was added tetrakis(triphenylphosphine)palladium (67 mg, 58 µmol), copper iodide (22 mg, 116 µmol) and (triisopropylsilyl)acetylene (1.0 mL, 4.7 mmol). The resulting mixture was allowed to stir under an argon atmosphere at 50 °C for 40 h. After completion of the reaction, the solvents were evaporated and the crude material was subjected to a short chromatography column over silica gel using CH_2Cl_2/MeOH (96:4) as eluent to provide **2** as a pure product (125 mg, 26%).
^{1}H NMR (500 MHz, d_7-DMF): δ=10.75 (s, 1H), 6.80 (br s, 2H), 4.10 (t, $^3J_{H,H}$=7.3 Hz, 2H), 1.82 (quint, $^3J_{H,H}$=7.3 Hz, 2H), 1.37-1.26 (m, 6H), 0.86 ppm (t, $^3J_{H,H}$=6.8 Hz, 3H); ^{13}CNMR (125 MHz, d_7-DMF): δ= 157.6, 155.9, 152.4, 131.1, 118.4, 97.8, 96.6, 44.2, 32.3, 27.3, 23.4, 19.3, 14.6, 12.1 ppm; HRMS (ESI): *m*/*z* calcd for $C_{22}H_{38}N_5OSi$: 416.2840 [*M*+H]$^+$; found: 416.2843.

8-ethynyl-9-hexylguanine (Ethynyl-G)

Tetrabutylammonium fluoride (1 M in THF, 0.6 mL, 0.6 mmol) was added to a solution of 9-hexyl-8-[2-(triisopropylsilyl)ethynyl]-guanine **2** (125 mg, 0.30 mmol) in THF (6 mL) and methanol (0.3 mL) at 0 °C and the mixture was allowed to stir at room temperature for 2 h. After completion of the reaction, the solvents were evaporated and the crude material was subjected to a short chromatography column over silica gel using CH_2Cl_2/MeOH (94:6) as eluent to provide **Ethynyl-G** as a pure product (38 mg, 49%).
^{1}H-NMR (500 MHz, d_7-DMF): δ=10.77 (s, 1H), 6.80 (br s, 2H), 4.70 (s, 1H), 4.08 (t, $^3J_{H,H}$= 7.1 Hz, 2H), 1.80 (quint, $^3J_{H,H}$=7.1 Hz, 2H), 1.33–1.25 (m, 6H), 0.86 ppm (t, $^3J_{H,H}$=6.9 Hz, 3H); ^{13}C NMR (125 MHz, d_7-DMF): δ=157.6, 155.9, 152.5, 130.7, 118.3, 85.0, 75.1, 44.0, 32.2, 30.2, 27.0, 23.4, 14.6 ppm; HRMS (ESI): *m*/*z* calcd for $C_{13}H_{18}N_5O$: 260.1506 [*M*+H]$^+$; found: 260.1510.

N9-hexyladenine

Adenine **A** (100 mg, 0.74 mmol, 1 eq) and K_2CO_3 (121 mg, 0.88 mmol, 1.2 eq) were dissolved in 20 mL of degassed DMF. 1-bromohexane (146 mg, 0.12 mmol, 0.88 mmol, 1 eq) was added drop wise to the suspension. The reaction was stirred for 12 hours at 40 ºC under argon. After completion of the reaction, the mixture was evaporated to dryness, solubilized in DCM (50 mL) and washed with 20 mL of water and then with 20 mL of brine solution. The organic phase was dried over $MgSO_4$, filtered and dried under reduced pressure. The crude product was purified by column chromatography (silica gel, 2% MeOH in DCM) to give N9-hexyladenine as a white solid (250 mg, 90 %).
^{1}H NMR (300 MHz, $CDCl_3$): δ=8.36 (s, 1H), 7.78 (s, 1H), 5.58 (s, brd, 2H), 4.18 (t, $^3J_{H,H}$=7.3 Hz, 2H), 1.88 (tt, $^3J_{H,H}$=7.5 Hz and 7.3 Hz, 2H), 1.30 (m, 6H), 0.86 ppm (t, $^3J_{H,H}$=7.0 Hz, 3H);^{13}C NMR (126 MHz, $CDCl_3$): δ=156.1, 153.2, 150.3, 140.6, 120.0, 44.2, 31.5, 30.3, 26.6, 22.7, 14.2 ppm.

8-bromo-N9-hexyladenine (3)

To a solution of N9-hexyladenine (1.17 g, 5.3 mmol) in glacial acetic acid (16 mL) was added sodium acetate (1.96 g, 23.9 mmol) and bromine (820 µL, 16 mmol). The resulting mixture was protected from light and stirred at 50 °C for 48 h. A saturated aqueous solution of sodium metabisulfite was added and the mixture was extracted with ethyl acetate. The organic layer was washed twice with a saturated aqueous solution of sodium bicarbonate, dried over anhydrous sodium sulfate, filtered and evaporated under vacuum. The crude material was subjected to a chromatography column over silica gel using ethyl acetate as eluent to provide **3** as a pure product (1.18 g, 74%).
^{1}H NMR (500 MHz, d_6-DMSO): δ=8.13 (s, 1H), 7.38 (br s, 2H), 4.10 (t, $^3J_{H,H}$=7.1 Hz, 2H), 1.73 (quint, $^3J_{H,H}$=7.1 Hz, 2H), 1.28-1.21 (m, 6H), 0.82 ppm (t, $^3J_{H,H}$=6.8 Hz, 3H); ^{13}C NMR (125 MHz, d_6-DMSO): δ=154.8, 152.8, 150.7, 126.3, 119.0, 43.7, 30.7, 28.7, 25.6, 21.9, 13.8 ppm; HRMS (ESI): *m*/*z* calcd for $C_{11}H_{17}N_5Br$: 298.0662 [*M*+H]$^+$; found: 298.0666.

9-hexyl-8-[2-(trimethylsilyl)ethynyl]-adenine (4)

To a degassed solution of 8-bromo-N_9-hexyladenine (**3**) (389 mg, 1.30 mmol) in THF/Et_3N (4:1, 10 mL) was added tetrakis(triphenylphosphine)palladium (75 mg, 65 µmol), copper iodide (25 mg, 130 µmol) and ethynyltrimethylsilane (720 µL, 5.2 mmol). The resulting mixture was allowed to stir under an argon atmosphere at 50 °C for 18 h. After completion of the reaction, the solvents were evaporated and the crude material was subjected to a chromatography column over silica gel using ethyl acetate as eluent to provide **4** as a pure product (310 mg, 75%).
^{1}H NMR (500 MHz, d_6-DMSO): δ=8.17 (s, 1H), 7.46 (br s, 2H), 4.16 (t, $^3J_{H,H}$=7.0 Hz, 2H), 1.78 (quint, $^3J_{H,H}$=7.0 Hz, 2H), 1.29-1.20 (m, 6H), 0.83 (t, $^3J_{H,H}$=6.8 Hz, 3H), 0.29 ppm (s, 9H); ^{13}C NMR (125 MHz, d_6-DMSO): δ=155.9, 153.8, 149.0, 132.6, 118.6, 101.4, 93.8, 42.9, 30.5, 28.8, 25.5, 21.9, 13.8, -0.7 ppm; HRMS (ESI): *m*/*z* calcd for $C_{16}H_{26}N_5Si$: 316.1952 [*M*+H]$^+$; found: 316.1960.

8-ethynyl-9-hexyladenine (Etynyl-A)

Tetrabutylammonium fluoride (1 M in THF, 2.4 mL, 2.4 mmol) was added to a solution of 9-hexyl-8-[2-(trimethylsilyl)ethynyl]-adenine **4** (309 mg, 0.98 mmol) in dry THF (25 mL). The mixture was allowed to stir at room temperature for 1 h. After completion of the reaction, the solvents were evaporated and the crude material was subjected to a chromatography column over silica gel using ethyl acetate as eluent to provide **Ethynyl-A** as a pure product (166 mg, 70%).
^{1}H NMR (500 MHz, d_6-DMSO): δ= 8.18 (s, 1H), 7.47 (br s, 2H), 4.93 (s, 1H), 4.18 (t, $^3J_{H,H}$=7.1 Hz, 2H), 1.78 (quint, $^3J_{H,H}$=7.1 Hz, 2H), 1.32 – 1.18 (m, 6H), 0.82 PPM (t, $^3J_{H,H}$=6.7 Hz, 3H);^{13}C NMR (125 MHz, d_6-DMSO): δ=155.9, 153.8, 149.2, 132.4, 118.4, 86.5, 73.2, 42.9, 30.6, 28.9, 25.6, 21.9, 13.8 ppm; HRMS (ESI): *m*/*z* calcd for $C_{13}H_{18}N_5$: 244.1557 [*M*+H]$^+$, found: 244.1562.

U_2-Po3

Bis(triphenylphosphine)palladium(II) dichloride (6 mg, 9 µmol) and copper(I) iodide (1 mg, 4.5 µmol) were added to a degassed solution of zinc porphyrin **ZnPo3** (30 mg, 45 µmol) and **Ethynyl-U** (29.5 mg, 1.3 mmol) in a 4:1 mixture of THF and triethylamine (4 mL) and the solution was allowed to stir at 40 °C for 18 h. The solvents were evaporated and the crude product was dissolved in chloroform (30 mL) and TFA (0.5 mL) was added. The mixture was allowed to stir for 15 min at room temperature and a saturated aqueous solution of sodium carbonate was added. The organic phase was dried over anhydrous sodium sulfate, evaporated and subjected to a chromatography column using CH_2Cl_2/MeOH (99.5:0.5 to 99:1) as eluent to give **U_2-Po3** as a pure green product (28 mg, 70%).
^{1}H NMR (500 MHz, d_6-DMSO: δ=11.96 (s, 2H), 9.83 (d, $^3J_{H,H}$=4.5 Hz, 4H), 9.66 (d, $^3J_{H,H}$=4.5 Hz, 4H), 8.88 (s, 2H), 4.90 (t, $^3J_{H,H}$=6.8 Hz, 4H), 3.90 (t, $^3J_{H,H}$=7.0 Hz, 4H), 2.41-2.29 (m, 4H), 1.80 (quint, $^3J_{H,H}$=6.7 Hz, 4H), 1.69 (quint, $^3J_{H,H}$=7.6 Hz, 4H), 1.51-1.32 (m, 14 H), 0.93 (t, $^3J_{H,H}$=6.9 Hz, 6H), 0.89 (t, $^3J_{H,H}$=7.3 Hz, 6H), -2.0 ppm (br s, 2H); HRMS (ESI): *m*/*z* calcd for $C_{54}H_{63}N_8O_4$: 887.4967 [*M*+H]$^+$; found: 887.4973.

C_2-Po3

Bis(triphenylphosphine)palladium(II) dichloride (3.6 mg, 5.1 µmol) and copper(I) iodide (0.5 mg, 2.6 µmol) were added to a degassed solution of zinc porphyrin **ZnPo3** (43 mg, 64 µmol) and **Ethynyl-C** (42.1 mg, 0.19 mmol) in a 4:1 mixture of THF and triethylamine (6 mL) and the solution was allowed to stir at 40 °C for 18 h. The solvents were evaporated and the crude product was dissolved in $CHCl_3$ (30 mL) and TFA (0.5 mL) was added. The mixture was allowed to stir for 15 min at room temperature and a saturated aqueous solution of sodium carbonate was added. The organic

phase was dried over anhydrous sodium sulfate, evaporated and subjected to a chromatography column using CH_2Cl_2/MeOH (94:6) as eluent. Eventually a size exclusion chromatography column over lipophilic Sephadex gel was performed using $CHCl_3$/MeOH (65:35) providing **C_2-Po3** with an enhanced purity (36 mg, < 64%). Once dry, the solubility of the target product was too low in common solvents to perform satisfying characterization analysis. HRMS (ESI): *m/z* calcd for $C_{54}H_{66}N_{10}O_2$:443.2680 $[M+2H]^{2+}$; found: 443.2678.

C_2-ZnPo3

C_2-Po3 was dissolved in a $CHCl_3$/MeOH mixture (9:1) and a large excess of zinc acetate (a saturated solution in MeOH) was added. The mixture was stirred at room temperature overnight and was washed with water prior to evaporation of the solvents providing **C_2-ZnPo3** in quantitative yields.
^{1}H NMR (500 MHz, d_6-DMSO/d_8-THF 9 :1): δ=9.67 (d, $^3J_{H,H}$=4.5 Hz, 4H), 9.58 (d, $^3J_{H,H}$=4.5 Hz, 4H), 8.75 (s, 2H), 7.94 (br s, 2H), 7.14 (br s, 2H), 4.94 (t, $^3J_{H,H}$=6.9 Hz, 4H), 3.91 (t, $^3J_{H,H}$=6.9 Hz, 4H), 2.42 (quint, $^3J_{H,H}$=7.4 Hz, 4H), 1.77-1.67 (m, 8H), 1.50 (sext, $^3J_{H,H}$=7.4 Hz, 4H), 1.42-1.33 (m, 12H), 0.96-0.88 ppm (m, 12H); HRMS (ESI) calcd for $C_{54}H_{63}N_{10}O_2Zn$ 947.4421 $[M+H]^+$; found: 947.4415.

A_2-ZnPo3

Bis(triphenylphosphine)palladium(II) dichloride (6.3 mg, 9 µmol) and copper(I) iodide (1.7 mg, 9 µmol) were added to a degassed solution of zinc porphyrin **ZnPo3** (59 mg, 90 µmol) and **Ethynyl-A** (64 mg, 0.26 mmol) in a 4:1 mixture of THF and triethylamine (8 mL) and the solution was allowed to stir at 50 °C for 18 h. The solvents were evaporated and the crude product was sonicated in methanol, filtered over a fritted funnel and washed with CH_2Cl_2, THF and warm pyridine to give **A_2-ZnPo3** (20 mg, < 23%) as a pure green product with an enhanced purity.
HRMS (ESI) calcd for $C_{56}H_{63}N_{14}Zn$: 995.4646 $[M+H]^+$;found : 995.4649.

G_2-ZnPo3

Bis(triphenylphosphine)palladium(II) dichloride (5 mg, 7 µmol) and copper(I) iodide (0.6 mg, 3.1 µmol) were added to a degassed solution of zinc porphyrin **ZnPo3** (50 mg, 74 µmol) and **Ethynyl-G** (58 mg, 0.22 mmol) in a 2:2:1 mixture of THF/DMF/triethylamine (6 mL) and the solution was allowed to stir at 50 °C for 18 h. The solvents were evaporated and the crude product was sonicated in a CH_2Cl_2/methanol (3:1) mixture, filtered over a fritted funnel and washed with warm pyridine to give **G_2-ZnPo3** (23 mg, < 30%) as a pure green product with an enhanced purity.
^{1}H NMR (500 MHz, d_6-DMSO/d_8-THF 9 :1): δ=10.84 (s, 2H), 9.59-9.65 (m, 8H), 6.74 (s, br, 4H), 4.92 (t, $^3J_{H,H}$=7.4 Hz, 4H), 4.55 (t, $^3J_{H,H}$=7.1 Hz, 4H), 2.42 (quint, $^3J_{H,H}$=7.4 Hz, 4H), 2.15 (quint, $^3J_{H,H}$=7.4 Hz, 4H), 1.76 (quint, $^3J_{H,H}$=7.6 Hz, 4H), 1.60 (quint, $^3J_{H,H}$=7.5 Hz, 4H), 1.51 (sext, $^3J_{H,H}$=7.4 Hz, 4H), 1.43 (quint, $^3J_{H,H}$=7.4 Hz, 4H), 1.31 (sext, $^3J_{H,H}$=7.3 Hz, 4H), 0.94 (t, $^3J_{H,H}$=7.3 Hz, 6H), 0.77 (t, $^3J_{H,H}$=7.3 Hz, 6H).

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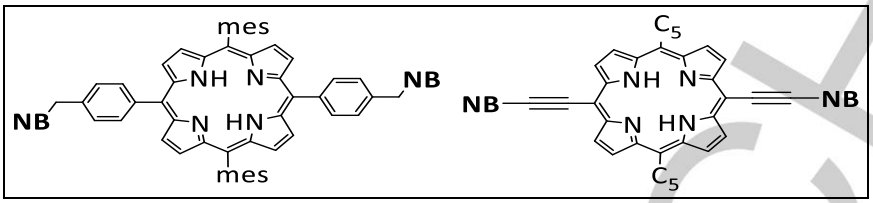

The synthesis of nucleobase-functionalized porphyrins was achieved *via* two strategies: substitution and Sonogashira cross coupling reactions, which resulted in five porphyrins having two nucleobases (NBs) at *trans meso*-positions linked by flexible methylene linkers and four porphyrins bearing two NBs at *trans meso*-positions linked by ridged ethynyl linkers respectively.