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New hydrosoluble perylene and coronene derivatives

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Abstract—Several lipophilic perylene and coronene derivatives, employed mainly as liquid crystalline dyes are known and their synthesis has been widely studied. We have applied an analogue strategy using hydrophilic substituents to obtain highly water soluble perylene diimides (**4**) and a new hydrosoluble coronene derivative (CORON, **6**), whose molecular features appear particularly suitable for inducing G-quadruplex DNA structures and inhibiting human telomerase.

Perylene-3,4:9,10-tetracarboxydiimides with hydrophilic side chains have been widely studied as G-quadruplex interactive compounds and telomerase inhibitors.[1–3] G-quadruplexes are unusual DNA secondary structures based on planes of four guanines (G-tetrads) stabilized by Hoogsteen G–G pairings and monovalent cations[4] (Fig. 1). The central aromatic core of the perylene diimides is suitable for π–π stacking interactions with the terminal G-tetrad of DNA G-quadruplex, while the hydrophilic side chains interact with the DNA grooves.[2a] By means of these two kinds of interactions, these molecules are able to induce and stabilize G-quadruplex structures in G-rich single-stranded oligonucleotides.[1,2] This is of great pharmaceutical interest, since the terminal ends of eukaryotic chromosomes (telomeres) are characterized by the presence of a single-stranded G-rich overhang that represents the substrate of a reverse transcriptase enzyme, the ribonucleoprotein telomerase, which is involved in the maintenance of telomere length.[5] This enzyme is not active in most somatic cells but is active in most human tumours, and is therefore considered a potentially highly selective target for different anti-tumour strategies.[6] By means of the stabilization and/or induction of G-quadruplex structures, perylene diimides are able to inhibit human telomerase in cell-free systems, together with a wide series of other compounds.[7]

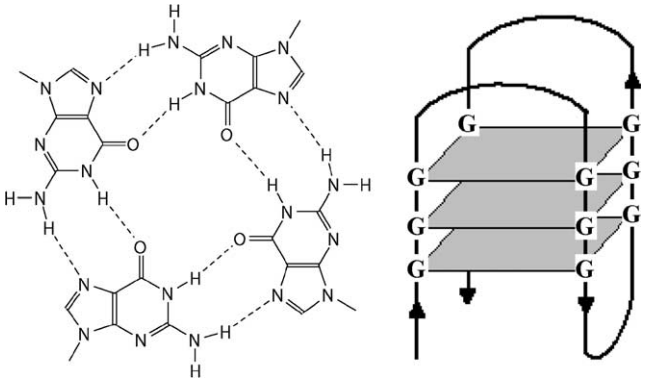

Figure 1. Schematic representation of a G-tetrad (left) and of a possible conformation of a monomeric G-quadruplex structure (right).

The tertiary amines, present in the hydrophilic side chains of this series of perylene diimides, can be transformed into the respective hydrochlorides, leading to a moderate water solubility of otherwise highly hydrophobic perylene core. Nevertheless, these compounds can undergo extensive 'self-aggregation'.[3] In order to achieve more water-soluble perylene diimides, as well as to obtain a new water soluble coronene derivative with molecular features designed to improve interactions with G-quadruplexes, a synthetic strategy already applied in the synthesis of lipophilic perylene derivatives used as liquid crystalline dyes[8] was used, obtaining the new compounds reported in Figure 2. Lipophilic perylene and coronene derivatives have been widely studied as chromophores in dye chemistry and used for many applications, such as photovoltaic cells, optical switches and lasers.[9] All these compounds have two or four

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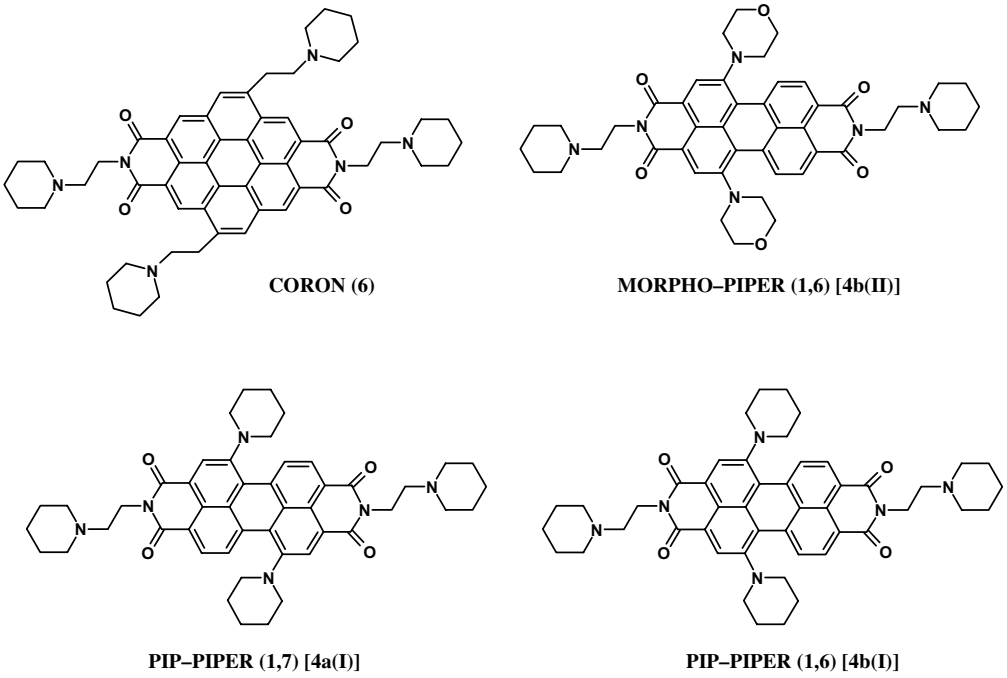
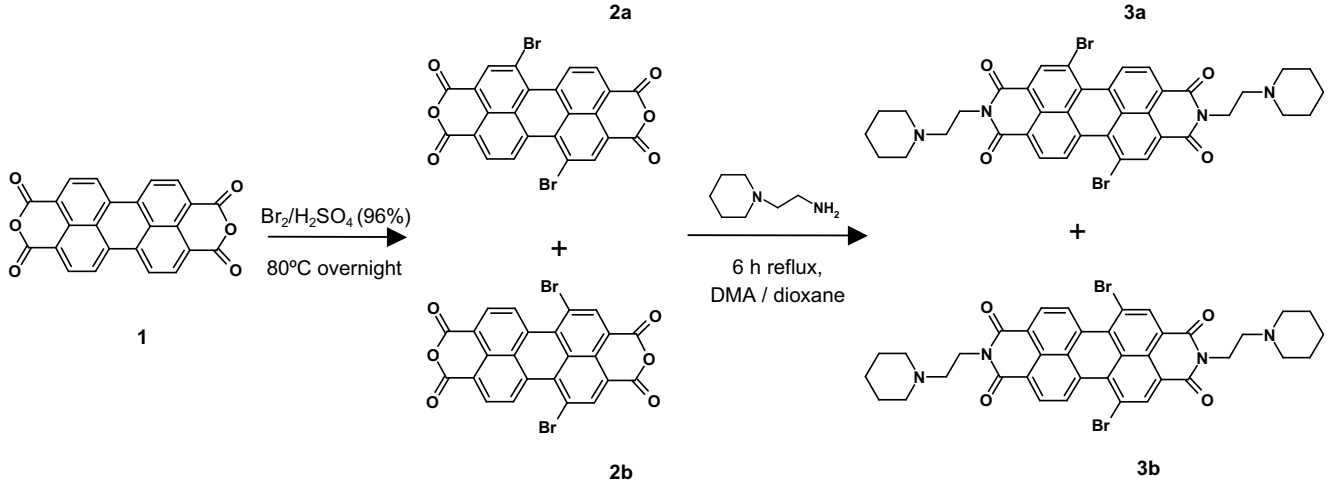


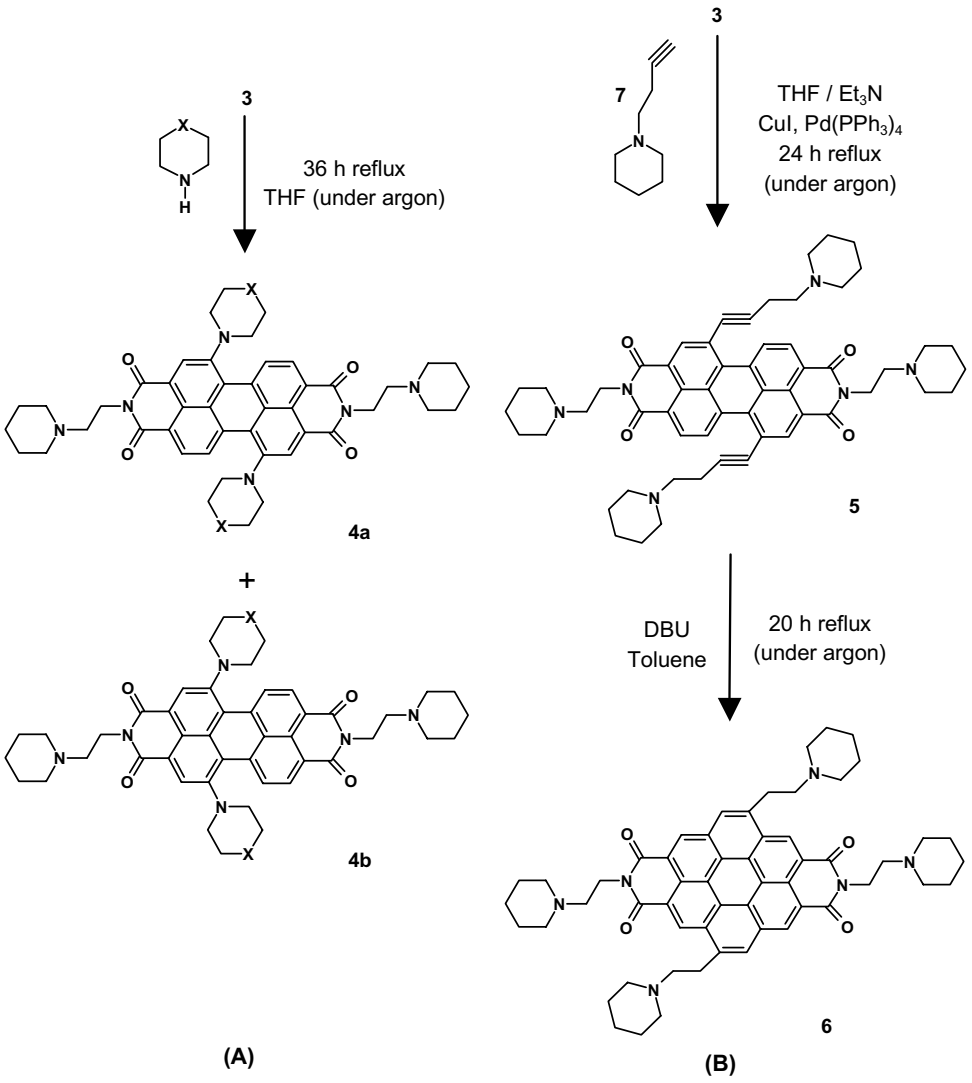
Figure 2.

lipophilic side chains. We have used the same strategy described by Mullen and co-workers[8] (bromination of the bay-area of 3,4,9,10-perylenetetracarboxylic dianhydride **1**), combined with the preparation of perylene diimides with hydrophilic side chains,[1] to obtain the brominated perylene diimide **3** PIPER-Br (Scheme 1), onto which two other hydrophilic substituents could be inserted (Scheme 2A and B). When bromine atoms on the perylene bay-area are substituted by piperidine or morpholine rings, new highly water-soluble perylene derivatives (**4**) are obtained (Scheme 2A). Upon replacement with the piperidine containing 1-alkyne **7** a two-step cyclization can occur, leading to the new hydrophilic coronene derivative **6** CORON (Scheme 2B).

The twofold bromination of the commercially available perylene-3,4:9,10-tetracarboxylic dianhydride (**1**) was easily carried out with elemental bromine in 96% sulfuric acid to give a mixture of the two isomers **2a** and **2b** in 98% yield (Scheme 1). The dianhydride **1** (9 g) was initially dissolved in 96% sulfuric acid (150 ml) and stirred for 4 h at room temperature. Elemental iodine (200 mg) was subsequently added and the mixture was heated. When a temperature of 80 °C was reached, elemental bromine (3 ml) was added drop wise, achieving a final excess of 20%. The reaction mixture was stirred at 80 °C overnight. After cooling, it was added drop wise to ice and then filtered and washed with a 5% sodium metabisulfite solution to provide a red solid, which was dried and characterized.[10] The two isomers (**2a** and



Scheme 1.



Scheme 2.

2b) could not be separated and the isomeric mixture was used in the following step, in which the commercially available 1-(2-aminoethyl)piperidine was added to give a mixture of the two isomers **3a** and **3b** (Scheme 1). Six grams of **2**, obtained in the previous reaction and 3.6 ml of 1-(2-aminoethyl)piperidine were stirred in a refluxing mixture of *N*,*N*-dimethylacetamide (DMA, 60 ml) and 1,4-dioxane (60 ml) for 6 h. After cooling, water was added and a red solid was separated by filtration (71% yield).[11] This mixture of isomers (**3**) was used in the following steps (Schemes 2A and B).

When reacting **3** with piperidine (X = CH_2 in Scheme 2A) two isomers [**4a(I)** and **4b(I)**] were separated and characterized.[12] Two hundred and fifty milligrams of **3** were stirred under argon in a refluxing mixture of tetrahydrofuran (THF, 20 ml) and piperidine (20 ml) for 36 h. After cooling, water was added and the crude product was extracted with ethyl acetate. The organic layer was extracted with water until the aqueous layer was neutral. The two isomers [**4a(I)** (30%) and **4b(I)** (5%), PIP-PIPER(1,7) and (1,6) respectively] were isolated by column chromatography on silica gel ($CHCl_3$). A standard commercial silica gel had been previously washed with 1 N HCl, followed by water until the chlorine test was negative, activated at 120 °C for 48 h and finally equilibrated with 10% water.[13] In order to obtain the water soluble hydrochlorides, these compounds were dissolved in 0.2 M HCl and after filtration, the solution was concentrated under vacuum, adding repeatedly an equal volume of chloroform until water had been eliminated completely. When repeating the same experimental conditions using morpholine (X = O in Scheme 2A) only the isomer **4b(II)** [MORPHO-PIPER(1,6)] was isolated from the chromatographic column (5% yield).[14] With reaction times under 12 h, monosubstituted derivatives can be obtained. In particular, it was possible to purify and characterize the compound **10** (30% yield)[15] (Fig. 3).

According to the model of threading intercalation proposed by Hurley and co-workers[2a] for the perylene

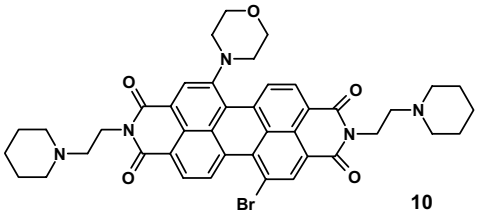


Figure 3.

diimides interacting with a G-quadruplex structure, it is possible to suppose that a wider aromatic core and four positively charged side chains should improve the interactions between these ligands and the G-quadruplex, leading to higher binding constants and consequently to increased telomerase inhibition. In order to obtain a new molecule with these two molecular features, the synthesis of the new hydrosoluble coronene derivative CORON (**6**) was carried out. **3** was reacted with the previously prepared **7** to give the intermediate **5**, using the conditions previously described by Sonogashira et al.;[16] **5** was found to be already partially closed to coronene and provided **6** in the following cyclization step (Scheme 2B). In this case, the minor isomer due to the initial presence of 1,6-dibromoperylene diimide **3b** cannot be separated from the major isomer, which is the only one reported in Scheme 2B. Compound **7** was prepared from the commercially available 3-butyn-1-ol by a mesylate conversion.[17] Two grams of **3** were dissolved in anhydrous THF (80 ml) and triethylamine (80 ml), then CuI (50 mg) and $Pd(PPh_3)_4$ (240 mg) were added. After adding 1.45 g of **7**, argon was bubbled into the reaction mixture that was then refluxed with stirring under argon for 24 h. After cooling, 150 ml of diluted HCl ($HCl:H_2O$ 1:3) were added and the product was extracted with dichloromethane, after neutralization with NaOH 2 M. The organic layer was extracted with water until the aqueous layer was neutral. The crude product was purified by column chromatography on a silica gel ($CHCl_3$:MeOH 100:0, 98:2, 95:5, 90:10) to give 510 mg (22% yield) of intermediate **5**, together with a small amount of **6**. Separation and better characterization were not possible at this stage, and the entire mixture was used in the following cyclization step. The mixture was poured into 50 ml of toluene and 0.17 ml of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were added. The reaction mixture was refluxed with stirring under argon for 20 h. After cooling, water was added and the crude product was extracted with dichloromethane. The organic layer was extracted with water until the aqueous layer was neutral. The crude product was purified by column chromatography on a silica gel ($CHCl_3$:MeOH 100:0, 98:2, 95:5, 90:10, 80:20) to give 160 mg (31% yield) of compound **6**. It was then purified by dissolving in 0.2 M HCl and precipitating the respective hydrochloride with acetone (64% yield).[18]

The absorption spectra of compounds **4a(I)**, **4b(I)** and **4b(II)**, performed in chloroform and reported in Figure 4A, show a broad band between 500 and 800 nm that is not present in the spectrum of PIPER-Br (**3**). This is due to the conjugation of the N atom of the piperidine or morpholine ring and the aromatic core of perylene, to which it is directly linked. This leads to an interesting chromatic change from the typical red colour of PIPER-Br (**3**) (analogous to that of 3,4,9,10-perylenetetracarboxylic dianhydride and previously derived perylene diimides[1–3]) to the green colour of **4a(I)** and the blue of **4b(I)** and **4b(II)**. It is also interesting to note that the colour of each compound depends on the relative positions of the two nitrogen atoms directly linked to the aromatic core: the (1,7) isomer is green, while the (1,6) isomers are blue, regardless of the different kind of cyclic ammine. The UV–vis spectrum ($CHCl_3$) of CORON (**6**) shows the characteristic five bands between 350 and 550 nm of coronene[8] (Fig. 4B). In the same figure, the spectrum of the hydrochloride of **6** performed in water solution is reported: a minor resolution of the bands and a slight hypochromic effect with respect to the $CHCl_3$ spectrum can be observed.

In this paper, the synthesis and characterization of the highly water soluble perylene derivatives (**4**) and of the new hydrosoluble coronene derivative CORON (**6**) are reported (Fig. 2). These compounds show very interesting spectroscopic properties, combining their different

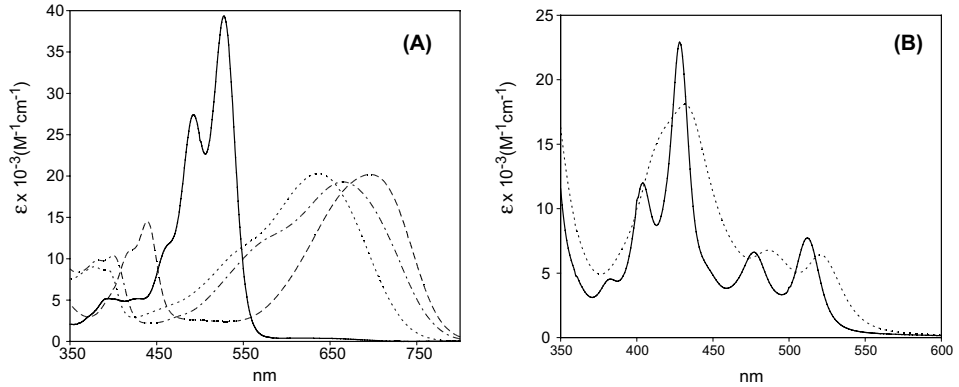


Figure 4. UV–vis absorption spectra in $CHCl_3$ of PIPER-Br (**3**) (——), MORPHO-PIPER(1,6) [**4b(II)**] (····), PIP-PIPER(1,6) [**4b(I)**] (–·–·–) and PIP-PIPER(1,7) [**4a(I)**] (– – –) (A). UV–vis absorption spectra in $CHCl_3$ of CORON (**6**) (——) and in aqueous solution of the respective hydrochloride (····) (B). All the spectra were performed at 300 K using a JASCO V-530 spectrophotometer.

hydrophobic chromophores with the possibility of further use in aqueous solution. Many useful applications can thus be envisaged, ranging from dyes for microscopic techniques to the quantization of biological macromolecules.[19] We are mainly interested in the ability of these compounds to induce G-quadruplex DNA structures and thereby inhibit human telomerase: preliminary results look promising and a deeper study is being carried out in our group. It is worth noting that the synthetic strategies used to obtain these compounds result in a great versatility: different side chains can be added to the new coronene moiety, with the possibility of achieving selectivity towards different G-quadruplex structures, as has been shown previously for perylene diimides.[1] Moreover, it is possible to add two different kinds of side chains (one type on the imidic nitrogen atoms and a different one directly linked to the aromatic moiety), since they are added in two different steps. This is very interesting since some G-quadruplex structures have four identical grooves (where the side chains mainly interact), while others have grooves of different dimensions.[4] Finally, by means of intermediate compounds (such as **10**), it will be possible to obtain asymmetric compounds.

Acknowledgements

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10. *1,7-Dibromoperylene-3,4:9,10-tetracarboxylic dianhydride* (**2a**): ^{1}H NMR (200 MHz, D_2SO_4): δ 10.42 (d, $J = 8$ Hz, 2H, aromatic H), 9.75 (s, 2H, aromatic H), 9.53 (d, $J = 8$ Hz, 2H, aromatic H). The signals of the minor (1,6) isomer (**2b**) are mainly superimposed with those reported for **2a**, a part from the doublet centred at 10.34 ppm, that is sufficiently separated from the other signals to be integrated, giving a ratio between **2a** and **2b** of 6:1. $C_{24}H_6O_6Br_2$: calcd C 52.4, H 1.1; found C 51.6, H 1.1.
11. *N,N′-Bis[2-(1-piperidino)-ethyl]-1,7-dibromoperylene-3,4:9,10-tetracarboxylic diimide* (PIPER-Br,**3a**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.44 (d, $J = 8$ Hz, 2H, aromatic H), 8.89 (s, 2H, aromatic H), 8.67 (d, $J = 8$ Hz, 2H, aromatic H), 4.41 (t, $J = 7$ Hz, 4H, N_{imidic}–CH), 2.8–2.6 (broad, 12H, $N_{piperidine}$–CH), 1.8–1.4 (br, 12H, $CH_{piperidine}$); ^{13}C NMR APT (200 MHz, $CDCl_3$): δ 162.14 (C=O), 161.64 (C=O), 137.31 ($CH_{ar.}$), 132.17 ($C_{ar.}$), 132.02 ($C_{ar.}$), 129.29 ($CH_{ar.}$), 128.50 ($C_{ar.}$), 127.78 ($CH_{ar.}$), 126.28 ($C_{ar.}$), 122.55 ($C_{ar.}$), 122.12 ($C_{ar.}$), 120.18 ($C_{ar.}$), 55.74, 54.24, 37.41, 25.48, 23.81. MS (ESI) *m/z*: 771.10 [$(M + 1)^+$] (calcd for $C_{38}H_{34}N_4O_4Br_2$ $M = 770.09$). In this case, all ^{1}H NMR signals of the two isomers are superimposed and it is not possible to obtain the isomeric ratio.
12. (a) *N,N′-Bis[2-(1-piperidino)-ethyl]-1,7-bis(1-piperidinyl)perylene-3,4:9,10-tetracarboxylic diimide* [PIP-PIPER(1,7), **4a(I)**]: ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.46 (d, $J = 8$ Hz, 2H, aromatic H), 8.33 (s, 2H, aromatic H), 8.30 (d, $J = 8$ Hz, 2H, aromatic H), 4.32 (t, $J = 7$ Hz, 4H, N_{imidic}–CH), 3.38 (m, 4H, $C_{ar.}$–$N_{piperidine}$–CH), 2.81 (m, 4H, $C_{ar.}$–$N_{piperidine}$–CH), 2.7–2.4 (br, 12H, $N_{piperidine}$–CH), 1.8–1.5 (broad, 24H, $CH_{piperidine}$); ^{13}C NMR APT (200 MHz, $CDCl_3$): δ 163.05 (C=O), 162.91 (C=O), 150.20 ($C_{ar.}$), 134.90 ($C_{ar.}$), 129.36 ($C_{ar.}$), 127.50 ($CH_{ar.}$), 123.70 ($C_{ar.}$), 123.17 ($CH_{ar.}$), 122.64 ($CH_{ar.}$), 122.34 ($C_{ar.}$), 121.85 ($C_{ar.}$), 120.30 ($C_{ar.}$), 55.87, 54.21, 52.27, 37.15, 25.50, 25.21, 23.88, 23.27. MS (ESI) *m/z*: 779.41 [$(M + 1)^+$] (calcd. for $C_{48}H_{54}N_6O_4$ $M = 778.42$). (b) *N,N′-Bis[2-(1-piperidino)-ethyl]-1,6-bis(1-piperidinyl)perylene-3,4:9,10-tetracarboxylic diimide* [PIP-PIPER(1,6), **4b(I)**]: ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.63 (d, $J = 8$ Hz, 2H, aromatic H), 8.53 (d, $J = 8$ Hz, 2H, aromatic H), 8.31 (s, 2H, aromatic H), 4.30 (m, 4H, N_{imidic}–CH), 3.29 (m, 4H, $C_{ar.}$–$N_{piperidine}$–CH), 2.79 (m, 4H, $C_{ar.}$–$N_{piperidine}$–CH), 2.7–2.4 (broad, 12H, $N_{piperidine}$–CH), 1.9–1.5 (br, 24H, $CH_{piperidine}$); ^{13}C NMR (200 MHz, $CDCl_3$): δ 163.23 (C=O), 163.10, (C=O), 152.76 (ar.), 135.60 (ar.), 131.24 (ar.), 130.21 (ar.), 128.34 (ar.), 127.51 (ar.), 123.26 (ar.), 122.69 (ar.), 122.61 (ar.), 121.85 (ar.), 120.20 (ar.), 119.68 (ar.), 55.91, 54.22, 52.63, 37.24, 37.06, 25.51, 25.28, 23.84, 23.27. MS (ESI) *m/z*: 779.43 [$(M + 1)^+$] (calcd for $C_{48}H_{54}N_6O_4$ $M = 778.42$).
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14. *N,N′-Bis[2-(1-piperidino)-ethyl]-1,6-bis(4-orpholinyl)perylene-3,4:9,10-tetracarboxylic diimide* [MORPHO-PIPER(1,6), **4b(II)**]: ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.80 (d, $J = 8$ Hz, 2H, aromatic H), 8.55 (d, $J = 8$ Hz, 2H, aromatic H), 8.32 (s, 2H, aromatic H), 4.31 (m, 4H, N_{imidic}–CH), 3.87 (m, 8H, $CH_{morpholine}$), 3.19 (m, 4H, $CH_{morpholine}$), 3.03 (m, 4H, $CH_{morpholine}$), 2.6–2.4 (br, 12H, $N_{piperidine}$–CH), 1.6–1.3 (br, 12H, $CH_{piperidine}$); ^{13}C NMR (200 MHz, $CDCl_3$): δ 162.45 (C=O), 162.41 (C=O), 151.07 (ar.), 134.44 (ar.), 130.81 (ar.), 129.68 (ar.), 127.84 (ar.), 127.29 (ar.), 123.35 (ar.), 122.70 (ar.),

122.57 (ar.), 120.98 (ar.), 120.54 (ar.), 119.93 (ar.), 65.52, 55.29, 53.70, 50.79, 36.80, 36.57, 24.92, 23.31. MS (ESI) *m/z*: 783.39 [(M + 1)$^+$] (calcd for $C_{46}H_{50}N_6O_6$ *M* = 782.38).

15. *N,N′-Bis[2-(1-piperidino)-ethyl]-1-bromo-7-(4-morpholinyl)perylene-3,4:9,10-tetracarboxylic diimide* **(10)**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.61 (d, *J* = 8 Hz, 1H, aromatic H), 9.30 (d, *J* = 8 Hz, 1H, aromatic H), 8.73 (s, 1H, aromatic H), 8.51 (d, *J* = 8 Hz, 1H, aromatic H), 8.44 (d, *J* = 8 Hz, 1H, aromatic H), 8.39 (s, 1H, aromatic H), 4.31 (m, 4H, N_{imidic}–CH), 3.86 (m, 4H, $CH_{morpholine}$), 3.28 (m, 2H, $CH_{morpholine}$), 3.10 (m, 2H, $CH_{morpholine}$), 2.7–2.4 (broad, 12H, $N_{piperidine}$–CH), 1.6–1.3 (broad, 12H, $CH_{piperidine}$). MS (ESI) *m/z*: 776.31 [(M + 1)$^+$] (calcd for $C_{42}H_{42}N_5O_5Br$ *M* = 775.24).
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17. 3-Butyn-1-ol was converted into its mesylate,[20] 1 g of which, without purification, was stirred with piperidine (1.35 ml) in refluxing absolute ethanol overnight under nitrogen. After cooling, solvent was evaporated under vacuum, then dichloromethane was added and the organic layer was repeatedly washed with saturated NaCl solution. Finally the organic layer was dried under vacuum to give 390 mg of liquid **7** (42% yield). 1-(3-butynyl)-piperidine (**7**): ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.49 (m, 2H, ≡C–CH), 2.4–2.2 (br, 6H, N–CH), 1.90 (t, *J* = 3 Hz, 1H, C≡C–H), 1.53 (m, 4H, $CH_{piperidine}$), 1.37 (m, 2H, $CH_{piperidine}$); ^{13}C NMR (200 MHz, $CDCl_3$): δ 82.50 (≡C), 68.30 (≡CH), 57.29, 53.64, 25.36, 23.74, 16.10.
18. *N,N′-Bis[2-(1-piperidino)-ethyl]-5,11-bis[2-(1-piperidino)-ethyl]-coronene-2,3:8,9-tetracarboxylic diimide* (CORON, **6**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.22 (s, 2H, aromatic H), 9.02 (s, 2H, aromatic H), 8.25 (s, 2H, aromatic H), 4.61 (t, *J* = 7 Hz, 4H, N_{imidic}–CH), 3.66 (m, 4H, $C_{ar.}$–CH), 3.1–2.5 (broad, 24H, $N_{piperidine}$–CH), 1.9–1.4 (br, 24H, $CH_{piperidine}$). ^{13}C NMR (300 MHz, $CDCl_3$): δ 163.66 (C═O), 163.50 (C═O), 138.63 (ar.), 130.77 (ar.), 128.70 (ar.), 127.98 (ar.), 127.72 (ar.), 127.40 (ar.), 124.75 (ar.), 121.26 (ar.), 120.80 (ar.), 120.35 (ar.), 120.12 (ar.), 118.62 (ar.), 60.23, 56.55, 54.92, 54.81, 38.20, 30.86, 26.24, 24.57. Aromatic ^{1}H NMR singlets due to the minor (5,10) isomer can be detected at 9.28 and 8.92 ppm. Integration of the signals shows that the ratio of the two isomers is about 5:1. It is worth noting that the strong ring-current effect of the coronene system leads to unusually high deshielding of about 1–2 ppm, in comparison with a benzenic system, both of the aromatic and benzilic-like protons. ^{1}H NMR (300 MHz, CF_3COOD, hydrochloride): δ 10.74 (s, 2H, aromatic H), 10.51 (s, 2H, aromatic H), 9.64 (s, 2H, aromatic H), 5.38 (m, 2H, N_{imidic}–CH), 4.88 (m, 2H, N_{imidic}–CH), 4.5–4.1 (br, 16H, $N_{piperidine}$–CH + $C_{ar.}$–CH), 3.7–3.4 (br, 12H, $N_{piperidine}$–CH), 2.6–1.9 (br, 24H, $CH_{piperidine}$); ^{13}C NMR (300 MHz, CF_3 COOD, hydrochloride): δ 163.51 (C═O), 163.07 (C═O), 131.35 (ar.), 128.94 (ar.), 127.27 (ar.), 126.84 (ar.), 125.55 (ar.), 123.87 (ar.), 121.48 (ar.), 120.39 (ar.), 119.42 (ar.), 118.03 (ar.), 116.95 (ar.), 116.71 (ar.), 54.53, 52.73, 51.47, 51.21, 32.35, 24.37, 19.35, 19.22, 17.14. MS (ESI) *m/z*: 883.49 [(M + 1)$^+$] (calcd for $C_{56}H_{62}N_6O_4$ *M* = 882.48).
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