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Anomerically glycosylated zinc(II) naphthalocyanines

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ABSTRACT

In course of our work on sugar-substituted phthalocyanines (Pc's) for PDT applications, for the first time two macrocyclic Pc homologs, the anomerically tetraglucosylated Zn(II) naphthalocyanines **11** and **12** were synthesized and characterized.

The conjugation of carbohydrates with macrocycles, such as porphyrins, has been widely considered, mostly for use in photodynamic therapy (PDT). PDT uses photosensitizers as a source of singlet oxygen. Porphyrin-type compounds (e.g., porphyrins and/or phthalocyanines) photosensitize the formation of highly reactive singlet oxygen via transfer of energy from the triplet-excited state of the porphyrinoid to the triplet-ground state of oxygen. Singlet oxygen is a potent oxidant that reacts with several functional groups of biomolecules.[1] The drugs used in PDT still possess some drawbacks such as low chemical selectivity toward the intended targets and uptake by cells mostly arises from passive or diffusion processes.[2] Because the balance between hydrophobicity and hydrophilicity is acknowledged as a significant aspect for the design of new photosensitizers,[3,4] diverse research groups have synthesized a variety of new porphyrinoid–carbohydrate conjugates[5] assuming that the presence of the carbohydrate moiety could improve the membrane interaction, therefore increasing their tumor selectivity. Moreover, various types of glucose transporters are specific for different monosaccharides in cancer cells.[6]

Phthalocyanine (Pc)–carbohydrate conjugates contrary to porphyrin–carbohydrate systems are less common despite their great potential in PDT. To our knowledge only symmetrical[7–10] and unsymmetrical[11,12] phthalocyaninato zinc(II) compounds peripherally substituted with four glucose or galactose units and phthalocyaninato silicon(IV) complexes axially substituted with two galactose[13] or glucose[14] molecules have been reported; however, in none of these cases the Pc is linked to the carbohydrate through the anomeric carbon, like in most of the porphyrinoid–carbohydrate conjugates.[15,16]

We reported for the first time a series of peripherally tetraglycosylated Pc's with D-glucopyranose, 1-thio-β-D-glucopyranose, β-D-galactopyranose, 1-thio-β-D-cello- and lactobiose.[17]

A drawback of the tetraglycosylated Pc's which were prepared by tetramerization of monoglycosylated phthalonitriles, however, is the fact that these Pc's are obtained as mixtures of constitutional isomers which are difficult to separate.[18]

In order to circumvent the formation of isomers we recently prepared a symmetrically 4,5-diglycosylated phthalonitrile which afforded for the first time a constitutional uniform octaglycosylated Pc.[19] As sugar moiety, we chose 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose which was attached to the Pc macrocycle via its position 6.[19]

We have also been successful now to obtain anomerically octaglycosylated zinc(II) phthalocyanines in which the sugar part is protected as well as deprotected. The sugars glucose, galactose, lactose, cellobiose and maltose were anomerically attached either via oxygen or via sulfur to the Pc ring.[20]

In addition to porphyrins and Pc's also naphthalocyanines (Nc's) have been used as photosensitizers in PDT. Nc's are of particular interest due to their absorption maxima in the range of 750–800 nm, where light penetration through skin and tissues is approximately twice for that of Pc's~630 nm.[21] This would allow treatment of larger and more deeply lying tumors.[22] Several peripherally substituted metal naphthalocyanines have been synthesized and studied for their use in PDT by various research groups.[23]

We have extended our work on glycoconjugated Pc's to Nc's and report here about the first example of peripherally tetraglucose-substituted Zn(II) naphthalocyanines **11** and **12** linked via the anomeric carbon (Fig. 2).

Our synthesis of the tetraglucose Zn(II) naphthalocyanines in high yield via template reaction of the glucosylated naphthalodinitrile **5** (Fig. 1) is based on the possibility to obtain glucosyloxyphthalonitriles, in high yields by nucleophilic substitution of 4-nitrophthalonitrile with protected glycopyranoses.[24]

To synthesize the glucosylated naphthalodinitrile **5** (Fig. 1) the same S_NAr displacement of nitrite in 6-nitronaphthalodinitrile **6a**[24] by anomerically deprotected glucose **7** in various polar aprotic solvents such as DMF, DMSO and HMPA at room temperature,

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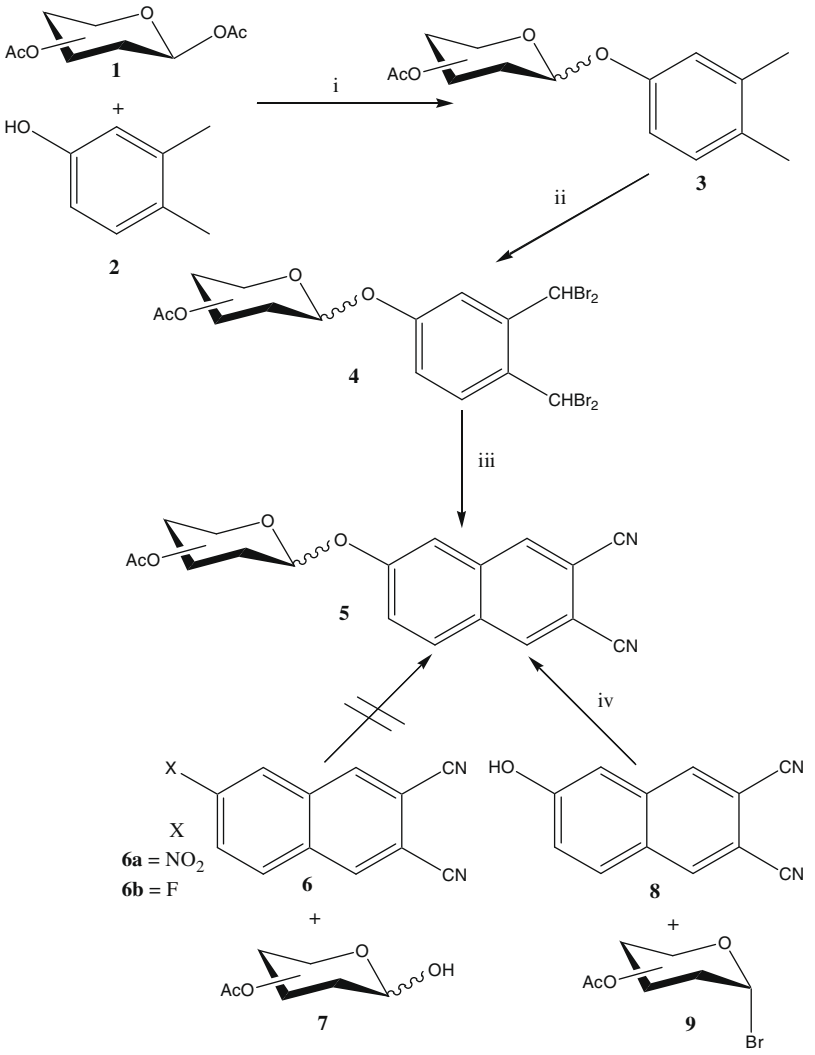

Figure 1. Synthesis of glucosylated naphthalodinitrile **5**. Reagents and conditions: (i) **1** + **2**, BF_3:etherate, benzene, rt, 48 h, 94% **3**; (ii) **3**, NBS, benzoyl peroxide, CCl_4, reflux, 48 h, 91% **4**; (iii) **4**, fumaronitrile, NaI, DMF, 75–80 °C, 24 h, 65% **5**; (iv) **8** + **9**, Ag_2O, CH_3CN, 50 °C, 24 h, 71% **5**.

with NaH and K_2CO_3 as bases was followed. In spite of different conditions which were applied, no sugar nitrite exchange was observed. Increasing the temperature mostly led to the degradation of the sugar part. To increase the reactivity of the leaving group X in the naphthalodinitrile **6**, instead of the nitro- the corresponding fluoronaphthalodinitrile **6b** was reacted with sugar **7**. However, also the fluoronaphthalodinitrile **6b** using different conditions did not react with the sugar **7** to form the expected substitution product **5**.

A more detailed investigation concerning the reactivity of both the 6-nitro- and the 6-fluoronaphthalodinitriles **6a**, **b** not only with the sugar **7** but also, for example, with *n*-hexanol as the alcohol part in solvents such as DMF, DMSO and HMPA, respectively, and K_2CO_3 or NaH as bases gave no indication for a substitution reaction at room temperature or slightly elevated temperatures. At higher temperatures (80–100 °C) only degradation products were found.

Nucleophilic substitution of **6a** has only been reported with sterically hindered phenols.[25] Even in these cases the yields of substitution products are low and side products of unknown structure are formed. These and our own experiments also demonstrate that the nucleophilic reactivity of the nitro- and fluoro-substituted naphthalodinitriles **6** is much lower and less clear than the well investigated reactivity of the 4-substituted phthalonitriles.

Therefore the synthesis of glucosylated naphthalodinitrile **5** was carried out using the well known route for the preparation of substituted naphthalodinitriles[26] (Fig. 1): first the glucose part was introduced by a Koenigs–Knorr type glycosidation reaction of 3,4-dimethylphenol **2** with penta-*O*-acetyl-β-D-glucose **1** under activation with BF_3–etherate leading to compound **3**.[27] **3** could be brominated with NBS in CCl_4 to form tetrabromide **4** in good yield[28] which was reacted with fumaronitrile and NaI in DMF in a Diels–Alder process to obtain the glucosylated naphthalodinitrile **5** (Fig. 1).[29]

Naphthalodinitrile **5** was also obtained by reacting 6-hydroxy naphthalodinitrile[30] (**8**) with the acetylated bromoglucose **9**.[29]

The sugar part of naphthalodinitrile **5** was deprotected with Na in methanol while passing gaseous NH_3 through the solution to form the corresponding diiminoisoindoline[31] **10** which was subsequently reacted with $Zn(OAc)_2{\cdot}2H_2O$ in DMAE as solvent, after which the tetraglucosylated NcZn **12** was obtained as a mixture of structural isomers.[32]

Naphthalocyanine **11** was formed by direct tetramerization of naphthalodinitrile **5** with hexamethyldisilazan, *p*-TsOH and $Zn(OAc)_2{\cdot}2H_2O$ in refluxing DMF.[33] Treating **11** with CH_3ONa in a

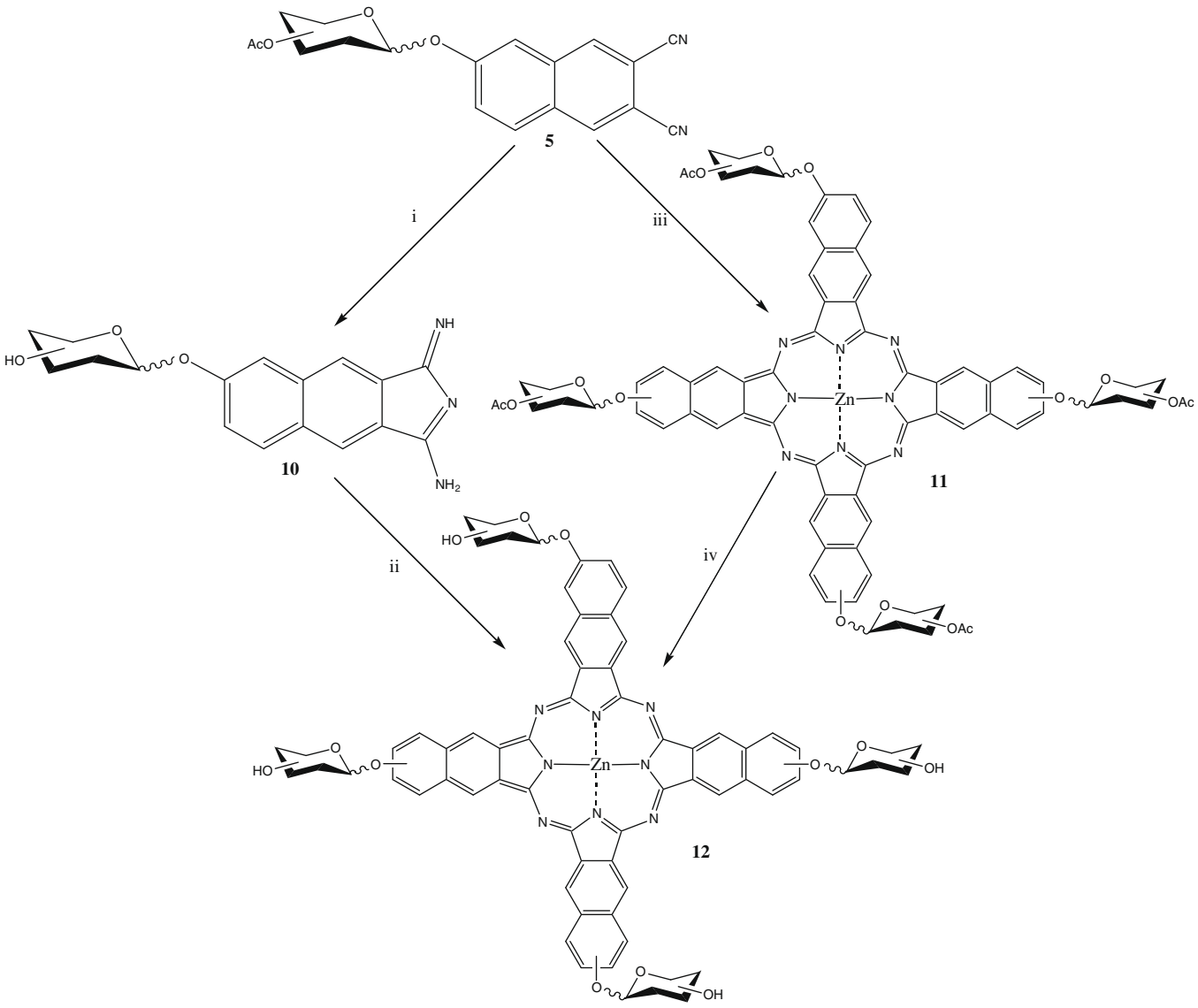

Figure 2. Synthesis of tetraglucosylated zinc(II) naphthalocyanines. Reagents and conditions: (i) **5**, Na, NH_3, methanol, rt-reflux, 2 h, 99% **10**; (ii) **10**, $Zn(OAc)_2{\cdot}2H_2O$, DBU, DMAE, reflux, 24 h, 29% **12**; (iii) **5**, $Zn(OAc)_2{\cdot}2H_2O$, HMDS, *p*-TsOH, DMF, reflux, 15 h, 45% **11**; (iv) **11**, CH_3ONa, MeOH, DMSO, rt, 12 h, 93% **12**.

DMSO/methanol mixture (2:1) the acetyl groups were removed and the deprotected NcZn **12** was formed.[32]

Contrary to the completely water soluble tetraglucose substituted PcZn[17] the corresponding NcZn **12** is much less soluble in water at room temperature, but soluble in DMF, DMSO and hot water. The lower solubility of **12** in water is a result of the larger hydrophobic Nc-macrocycle for which the four hydrophilic substituents are not sufficient enough to allow water solubility. NcZn **11** is soluble in organic solvents such as $CHCl_3$ and THF.

In solution both Nc's **11** and **12** depending upon the solvent are aggregated. This was directly demonstrated through the UV/Vis spectra of the acetyl protected tetraglucosylated NcZn **11**: Its UV/Vis spectrum in DCM shows a strong broad band with the maximum at 696 nm typical for strong aggregation. The Q-band of **11** only appears as shoulder at 769 nm. Traces of pyridine added to the DCM solution of **11** led to an interruption of the aggregation shown in the UV/Vis spectrum by a now strong narrow Q-band with the maximum at 763 nm and a broad band of low intensity at 704 nm. In DMSO as solvent **11** and **12** show less aggregation as shown by strong Q-bands at 769 and 773 nm, respectively (Fig. 3).

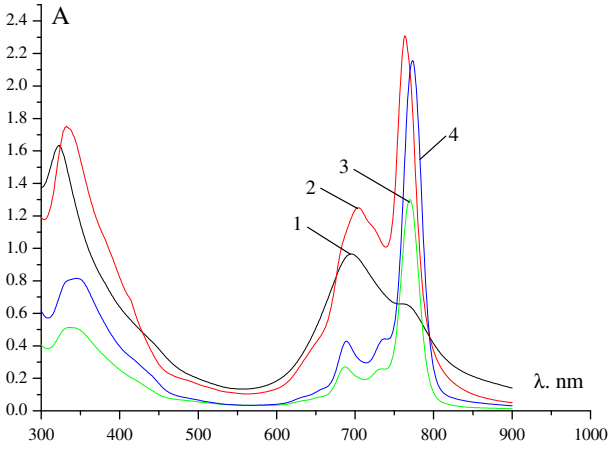

Figure 3. UV–vis spectra of NcZn's **11** and **12**. (1) NcZn **11** in DCM ($c = 0.16 \times 10^{-7}$ M). (2) NcZn **11** in DCM with traces of pyridine. (3) NcZn **11** in DMSO ($c = 0.14 \times 10^{-7}$ M). (4) NcZn **12** in DMSO ($c = 0.6 \times 10^{-7}$ M).

The ^{1}H NMR spectra of **11** and **12** were recorded in Methanol-d_4 and DMSO-d_6, respectively. Both NMR spectra depend very much upon the temperature of the solution which for both compounds has been increased from 20 to 100 °C. Only at higher temperatures very well resolved spectra were obtained indicating aggregation of **11** and **12** even in coordinating solvents such as DMSO-d_6 and methanol-d_4. In non-coordinating solvents, for example, $CDCl_3$, the spectra especially in the aromatic region were of very low intensity. Even the addition of pyridine-d_5 did not change the spectra very much at ambient temperature.

Work is now in progress to synthesize NcZn's containing more than four glucose substituents thereby increasing the hydrophilicity of such Nc-derivatives and making them water soluble.

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27. Sokolov, V. M.; Zakharov, V. I.; Studentsov, E. P. Russian J. General Chemistry (Translation of *Zhurnal Obshchei Khimii*) **2002**, *72*, 806–811; (b) 3,4-Dimethylphenyl-2,3,4,6-tetra-*O*-acetyl-D-glucopyranoside (**3**): To a solution of (11.71 g, 30 mmol) of penta-*O*-acetyl-β-D-glucopyranose (**1**) and (4 g, 33 mmol.) of 3,4-dimethylphenol (**2**) in dry benzene (100 mL) was added boron trifluoride etherate (0.4 mL). The reaction mixture was stirred at room temperature for 48 h. After completion, the reaction was terminated by dilution with benzene (100 mL). The benzene solution was washed with water, sodium hydroxide (1 N), and water to neutral washings, dried with sodium sulfate and evaporated in vacuo to obtain syrup-like product which was recrystallized from hot ethanol to get white solid. Yield 12.76 g (94%). Mp: 113–115 °C. $[\alpha]_D^{20} = -7.1$ (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.00 (d, ^3J = 8.1 Hz, 1H, H-5′), 6.76 (d, *J* = 2.3 Hz, 1H, H-2′), 6.70 (dd, ^3J = 8.1 Hz, *J* = 2.3 Hz, 1H, H-6′), 5.28–5.19 (m, 2H, H-1, H-3), 5.12 (t, 1H, H-2), 5.01 (d, ^3J = 7.4 Hz, 1H, H-4), 4.27 (dd, *J6a,6b* = 12.4, *J6a,5* = 5.4, 1H, H-6a), 4.15 (dd, *J6b,6a* = 12.4, *J5,6b* = 2.5, 1H, H-6b), 3.84–3.78 (m, 1H, H-5), 2.20, 2.17 (2s, 6H, H–CH_3), 2.06, 2.03, 2.01, 2.00 (4s, 12H, H(Ac)); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0, 170.6, 169.8, 169.7 (4C, C=O), 155.4 (1C, C1′), 138.3 (1C, C-2′), 131.9 (1C, C-6′), 130.7 (1C, C-5′), 118.9 (1C, C-3′), 114.4 (1C, C-4′), 99.8 (1C, C-1), 73.1 (1C, C-2), 72.3 (1C, C-3), 71.6 (1C, C-5), 68.7 (1C, C-4), 62.4 (1C, C-6), 21.2, 21.0, 20.9, 20.8, 20.3, 10.3 (6C, CH_3): FTICR MS *m*/*z* 475.15747 $[M+Na]^+$. IR (KBr): 2957, 1755, 1607, 1503, 1429, 1368, 1213, 1169, 1095, 1077, 1045, 908, 817, 600 cm^{-1}.
28. 3,4-Bis(dibromomethyl)phenyl-2,3,4,6-tetra-*O*-acetyl-D-glucopyranoside (**4**): 3,4-dimethylphenyl-2,3,4,6-tetra-*O*-acetyl-D-glucopyranoside **3** (9 g, 20 mmol), NBS (14.24 g, 80 mmol), and benzoyl peroxide (0.15 g) were stirred in dry CCl_4 (100 mL) at reflux for 48 h, while illuminating the mixture with 250 W tungsten lamp. The warm solution was filtered and the precipitate was washed with warm CCl_4 (50 mL). After removal of bromine traces with $NaHSO_3$, the filtrate was dried and concentrated to yield a white solid. Crude product was purified by column chromatography using *n*-hexane:ethylacetate (3:1) mixture. Yield 14 g (91%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58 (d, ^3J = 8.1 Hz, 1H, H-5′), 7.05 (d, *J* = 2.3 Hz, 1H, H-2′), 6.93 (dd, ^3J = 8.1 Hz, *J* = 2.3 Hz, 1H, H-6′), 6.90 (s, 1H, H–$CHBr_2$), 6.88 (s, 1H, H–$CHBr_2$), 5.31–5.01 (m, 2H, H-1, H-3), 4.54 (s, 1H, H-2), 4.40–4.29 (m, 2H, H-4, H-6a), 4.05–3.80 (m, 2H, H-5, H-6b), 2.09–1.83 (m, 12H, H–CH_3); IR (KBr): 3050, 2960, 1759, 1606, 1576, 1498, 1429, 1368, 1240, 1042, 907, 702, 639, 599 cm^{-1}; MS (FT-ICR): *m*/*z*: 788.794 $[M+Na]^+$, 802.773 $[M+K]^+$.
29. 6-(2,3,4,6-Tetra-*O*-acetyl-D-glucopyranosyl)naphthalodinitrile **5**: Method A: compound **4** (7.68 g, 10 mmol) was stirred with fumaronitrile (780 mg, 10 mmol) and NaI (10 g) in dry DMF (100 mL) at 75–80 °C for 24 h. Afterwards additional fumaronitrile (780 mg, 10 mmol) was added, the reaction mixture was stirred for another 24 h. The cold solution was poured into a solution of $NaHSO_3$ in water. Precipitates formed were filtered, dried, and purified by column chromatography with acetonitrile: DCM (1:9). Yield 3.4 g (65%).Method B: 6-hydroxynaphthalodinitrile **8** (1.36 g, 7 mmol) and acetobromoglucose **9** were suspended in acetonitrile (100 mL). Silver(I) oxide (2.32 g, 10 mmol) was added and the reaction mixture was heated at 50 °C for 24 h. The reaction mixture was cooled and filtered to remove inorganic salts and the solvent was evaporated by rotary evaporator. The solid obtained was purified by column chromatography using toluene acetone (4:1) mixture as solvent. Yield 2.53 g (71%). Mp: 190–192 °C. $[\alpha]_D^{20} = -19$ (*c* 0.8, $CHCl_3$). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.68 (s, 1H, H-1′), 8.59 (s, 1H, H-4′), 8.23 (d, *J* = 9.2 Hz, 1H, H-8′), 7.84 (d, *J* = 2.3, 1H, H-5′), 7.64 (dd, *J* = 9.2 Hz, *J* = 2.3 Hz, 1H, H-7′), 5.79 (d, *J* = 7.9 Hz, 1H, H-1), 5.46 (t, *J* = 9.6 Hz, 1H, H-3), 5.31 (t, *J* = 7.9 Hz, 1H, H-2), 5.21 (t, *J* = 9.6, 1H, H-4), 4.37–4.25 (m, 3H, H-5, H-6a,b), 2.03–2.01 (m, 12H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.1, 170.7, 170.4, 170.1 (4C, C=O), 159.3 (1C, C6′), 137.3 (1C, C-7′), 137.2 (1C, C-5′), 135.6 (1C, C-8′), 131.0 (1C, C-4′), 124.4 (1C, C-1′), 117.4 (1C, C-2′), 117.3 (1C, C-3′), 113.1 (1C, C-CN),111.6 (1C, C-CN), 99.1 (1C, C-1), 73.6 (1C, C-2), 73.3 (1C, C-3), 72.6 (1C, C-5), 72.0 (1C, C-4), 68.9 (1C, C-6), 21.1, 21.0, 20.9, 20.8, 20.3 (4C, CH_3): IR (KBr): 2958, 2234 (C ≡ N), 1755, 1623, 1597, 1500, 1465, 1369, 1233, 1040, 908, 822, 700 cm^{-1}; MS (FT-ICR): *m*/*z*: 547.132 $[M+Na]^+$, 563.106 $[M+K]^+$.
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31. *Synthesis of* **10**: Naphthalodinitrile **5** (1.0 g, 1.9 mmol) was suspended in dry methanol (10 mL), cooled in ice bath while bubbling gaseous ammonia through the suspension. At 0 °C Na metal (46 mg, 2 mmol) was added. After some time the solid dissolved in methanol indicating the deprotection of acetyl groups of sugar part. The reaction mixture now warmed slowly to room temperature and then refluxed for 2 h while bubbling gaseous ammonia through the solution. After completion of the reaction, the solution was cooled, ammonia gas removed, and mixture was bubbled with air to remove excess of ammonia. Precipitate formed was separated and dried to get the crude product, which was used without further purification for the next step. Yield: 1.2 g (99%). ^{1}H NMR (400 MHz, DMSO-d_6, significant signals): δ = 8.28 (s, 1H, H-1′), 8.23 (s, 1H, H-4′), 8.02 (d, *J* = 9.2 Hz, 1H, H-8′), 7.61 (s, 1H, H-5′), 7.40 (dd, *J* = 9.2 Hz, *J* = 2.3 Hz, 1H, H-7′), 5.10 (d, *J* = 7.1 Hz, 1H, H-1), 3.80–3.72 (m, 2H), 3.55–3.41 (m, 4H), 3.37–3.28 (m, 4H), 3.24–3.18 (m, 2H, H-5), 1.22 (s, 1H), 0.89–0.75 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 156.9 (1C, C6′), 135.5 (1C, C-7′), 131.9 (1C, C-5′), 131.2 (1C, C-8′), 129.7 (1C, C-4′), 121.1 (1C, C-1′), 120.4 (1C, C–NH_2), 112.6 (1C, C–NH), 100.7 (1C, C-1), 77.5 (1C, C-2), 76.9 (1C, C-3), 73.6 (1C, C-5),

70.0 (1C, C-4), 61.0 (1C, C-6): IR (KBr): 3381 (N–H, O–H), 2957, 1614, 1549, 1517, 1398, 1290, 1079, 1049 cm^{-1}; MS (FT-ICR): *m*/*z*: 374.13466 $[M+Na]^+$.

32. *Synthesis of* **12**: Method A: isoindoline **10** (373 mg, 1 mmol.) and DBU 2–3 drops were refluxed in 1 mL DMAE for 24 h. Reaction mixture was cooled to room temperature and washed with methanol. Precipitate formed was separated by centrifugation. Crude product was extracted with methanol in Soxhlet apparatus. Yield 108 mg (29%).Method B: naphthalocyanine **11** (400 mg,) was dissolved in 2:1 mixture of DMSO/MeOH (15 mL). Catalytic amount of CH_3ONa was added and the reaction mixture was stirred at room temperature overnight. Ion exchange resin amberlite IR-120H was added to neutralize the solution. The solution was filtered to remove the resins. Precipitation of the product was carried out by excess of acetone. Precipitates formed were filtered and dissolved in small amount of water and reprecipitated with acetone. The crude product was dried and purified with reverse phase HPLC using water acetonitrile as eluent. Yield 257 mg (93%).^{1}H NMR (250 MHz, DMSO-d_6, significant signals): δ = 9.75 (s, 4H), 8.70 (s, 4H), 8.61 (d, J = 9.2, 4H), 8.24 (s, 4H),7.68 (d, J = 9.2, 4H), 5.38 (s, 4H), 3.98–3.94 (m, 12H), 3.77–3.42 (m, 28H); UV/Vis (DMSO): λ_{max} (log ε) = 773 (7.55), 688 (6.85), 344 (7.13) nm; MALDI–TOF MS: *m*/*z* 1488.325 $[M]^+$.

33. *Synthesis of* **11**: a mixture of naphthalodinitrile **5** (1.57 g, 3 mmol), *p*-toluenesulfonic acid monohydrate (57 mg, 0.3 mmol), hexamethyldisilazane (HMDS) (0.21 mL, 1 mmol), DMF (2 mL), and $Zn(OAc)_2{\cdot}2H_2O$ (330 mg, 1.5 mmol) in a sealed glass tube was stirred and heated at 150 °C overnight. The semisolid obtained was cooled and precipitated with methanol–water (1:2) mixture. The precipitates obtained were dried and chromatographed first with ethylacetate to remove unreacted naphthalodinitrile **5** and then side products with ethylacetate containing 2–5% methanol. Yield 730 mg (45%).^{1}H NMR (250 MHz, CD_3OD-d_4, significant signals): δ = 9.38 (br s, 8H), 8.38 (br s, 4H), 8.11 (br s, 4H), 7.45 (br s, 4H),5.91–5.68 (m, 4H), 5.39–5.29 (m, 4H), 5.23–5.06 (m, 12H), 4.85–4.48 (m, 8H), 2.25–2.06 (m, 48H); UV/Vis (DMSO): λ_{max} (log ε) = 769 (5.46), 336 (5.05) nm; MALDI–TOF MS: *m*/*z* 2160.475 $[M]^+$.