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Design and synthesis of novel phthalocyanines as potential antioxidant and antitumor agents starting with new synthesized phthalonitrile derivatives†

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New phthalonitrile derivatives formed from reactions of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) were considered as the key intermediates for the synthesis of new phthalocyanines. Moreover, new phthalonitrile derivatives **2**, **5**, **9**, **10**, **15** and **16** reacted with 1,4-diazabicyclo[2.2.2]octane (DBO) or hydroquinone to afford the corresponding new phthalocyanine dyes **3**, **6**, **11**, **12**, **17** and **18**. In addition, the cyclotetramerization of phthalic anhydride derivative **20** afforded new phthalocyanine dye **22**. Spectral and elemental investigations revealed the structures of the newly synthesized phthalocyanines. The antioxidant and cytotoxic properties of the novel compounds were investigated, and it has been established that compounds **17** and **18** have very strong anticancer and antioxidant action against all cell lines.

Introduction

There is permanent interest in phthalocyanines (Pcs), which are essential heterocyclic nitrogen conjugated compounds in the field of dyes and pigments, due to their optical properties.[1] There are many pharmaceutical and biological applications using phthalocyanines (Pcs) or metallo-phthalocyanines (M-Pcs).[2–4] There is great interest in phthalocyanines and metallo-phthalocyanines in the photodynamic therapy (PDT), wherein the first photosensitizers, namely, hematoporphyrin derivatives and Photofrin[5] were used. Cancer can be treated by the formation and accumulation of photosensitizers within tumor tissue after activation by light using photodynamic therapy.[6] In recent years, novel generations of photosensitizers have been developed for use as better tumor agents.[7]

In general, phthalocyanine derivatives can be synthesized starting with phthalic anhydride, phthalimide, or phthalonitrile to enable the synthesis of phthalocyanines in a single-step reaction.[8,9] Methoxy groups may show a strong antioxidant effect when they are combined with phthalocyanines. There is great interest in studying the development of the structure–activity relationships (SARs) of novel phthalocyanine derivatives.[10]

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A major problem in the development of novel phthalocyanine compounds containing peripherally functionalized fused heterocyclic systems is low solubility, which prevents their use in medical applications. Our main objective is to synthesize new phthalocyanines in high yields with different substituents, which enhance their use in a broad spectrum of medical applications.

Results and discussion

Synthesis and characterization

The synthesis, characterisation, and structural analysis of novel phthalocyanine derivatives have been discussed in this study. The amino groups in *o*-phenylenediamine were protected by reaction with bromopropane to realize highly reactive $N1,N2$-dipropylbenzene-1,2-diamine **1**. This reaction was followed by refluxing of compound **1** with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in the presence of dry ethanol containing a catalytic amount of pyridine at room temperature under N_2 gas to realize the corresponding 1,4-dioxo-5,10-dipropyl-1,4,5,10-tetrahydrophenazine-2,3-dicarbonitrile **2** in 72% yield.
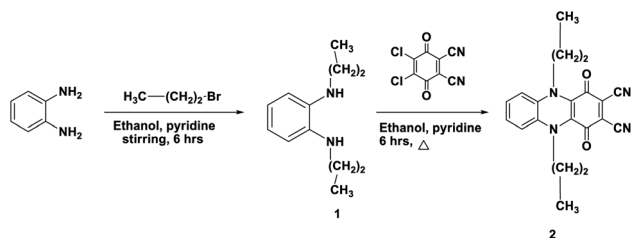
The IR spectrum of compound **1** showed an absorption band at ν 3220 cm^{-1} corresponding to the NH stretching vibration. The ^{1}H-NMR spectrum of compound **1** showed two triplet signals at δ 0.91 and 3.61 ppm due to the protons of two CH_3 groups and two CH_2–N, multiplet signals at δ 1.60 ppm due to CH_2 (middle), a singlet signal at δ 6.88 ppm due to the protons of two NH groups and multiplet aromatic protons at δ 6.46–6.66 ppm. Achievement of the cyclization process can be confirmed from the analytical and spectroscopic data of

Scheme 1 Synthesis of dicarbonitrile derivative 2.

Scheme 3 Two synthesis routes of phthalocyanine derivative 3.

dinitrile derivative 2. The removal of the C–Cl band of DDQ at ν 680 cm^{-1} and the NH band of compound 1 at ν 3220 cm^{-1} clearly showed the synthesis of compound 2 in addition to the appearance of a new absorption band at ν 2218 cm^{-1} corresponding to C≡N besides the absorption band at ν 1700 cm^{-1} corresponding to C=O. The ^{1}H-NMR spectrum of dinitrile 2 also indicates its correct structure by the disappearance of the singlet signal at δ 6.88 due to the NH proton. The ^{13}C-NMR spectrum of 2 revealed characteristic signals at δ 110.7 ppm due to (CN), 128.0 ppm due to (C–CN) and δ 187.0 ppm due to (CO quinone), in addition to the other expected signals (Scheme 1).[11] Compound 2 may be formed according to the proposed mechanism in Scheme 2.

Phthalocyanine 3 can be formed in two ways. Route (A): compound 2 and hydroquinone were fused together at 200 °C under N$_2$ gas for about 10 h and afforded the corresponding deep green product, which was analyzed as C$_{80}$H$_{74}$N$_{16}$O$_8$ and confirmed to be phthalocyanine structure 3 (shown in Scheme 3). The IR spectrum of Pc 3 displayed an absorption band at 3250 cm^{-1} due to the presence of the two NH groups; moreover, the missing band of the cyano group in the IR spectrum confirmed the formation of phthalocyanine 3. The ^{1}H-NMR spectrum of compound 3 showed two triplet signals at δ 1.05 and 2.87 ppm due to the protons of eight CH$_3$ and eight CH$_2$, a multiplet signal at δ 1.69 ppm due to eight CH$_2$ (middle), a singlet signal at δ 3.45 ppm due to the protons of the two NH groups, a triplet signal at δ 7.18 due to eight aromatic protons, and a doublet signal at δ 7.37 ppm due to eight other aromatic

protons. Also, the structure of Pc 3 was established by the ^{13}C-NMR spectrum, which showed that the signal at δ 110.7 ppm had disappeared due to absence of the C≡N group. The UV-vis spectrum exhibited λ_{max} at 602 and 668 nm, corresponding to the Q-bands. The identical reaction was repeated using route (B), where DBO (1,4-diazobicyclo[2.2.2]octane) was fused with ethylene glycol at 200 °C under N$_2$ gas for 30 min. After that, phthalonitrile derivative 2 was added to the reaction, and refluxing was sustained for about 10 h to afford
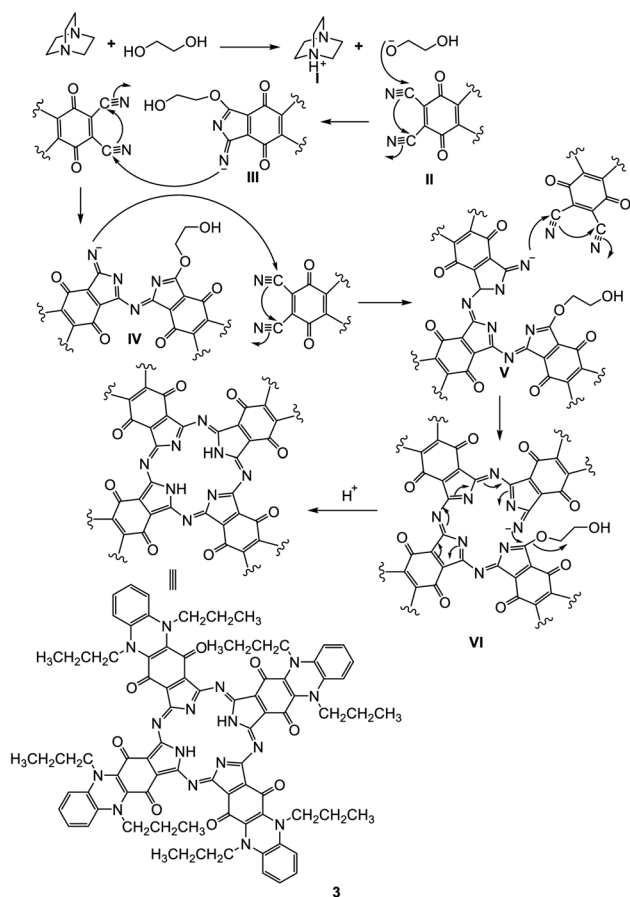
Scheme 4 Expected mechanism for the formation of phthalocyanine 3.

Scheme 2 Mechanism of formation of dicarbonitrile derivative 2.
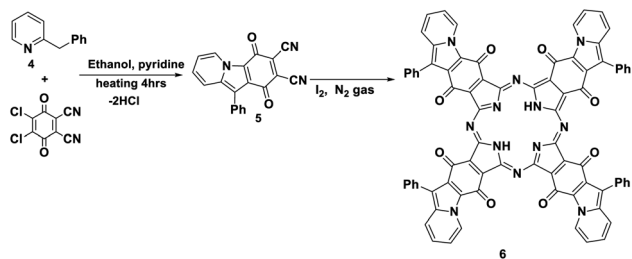
Scheme 5 Formation of phthalonitrile derivative **5** and novel phthalocyanine **6**.

indistinguishable Pc **3**. The yield was improved and almost reached 68% in the case of using route (B), compared to 35% in the case of using route (A). The reaction may proceed by the previously reported mechanism in Scheme 4.[12,13]

Furthermore, the reaction of DDQ with 2-benzylpyridine **4** by refluxing in the presence of ethanol and a catalytic amount of pyridine afforded the corresponding phthalonitrile, 1,4-dioxo-10-phenyl-1,4-dihydropyrido [1,2-*a*] indole-2,3-dicarbonitrile (**5**). Its IR spectrum showed the stretching vibrational band of the C≡N group at ν 2220 cm^{-1} due to two cyano groups and an absorption band at ν 1730 cm^{-1} in accordance with an α,β-unsaturated ketone. The ^{13}C-NMR spectrum displayed an excellent illustration of compound **5** (Schemes 5 and 6).[11] The new phthalonitrile **5** was heated under N$_2$ gas in boiling dry *n*-propanol for 3 h; after that, for the initiation of the reaction, to produce new Pc **6** with a deep red colour, a few crystals of iodine were added to the reaction mixture, which was heated for around 10 h (Scheme 5).[14] Phthalocyanine **6** was established by its correct spectral analysis, in which the IR spectrum exposed absorption bands at ν 3150, 1730, 1620 and 1560 cm^{-1} due to the two NH groups, C=O groups, C=N groups and C=C groups, respectively. The ^{13}C-NMR spectrum displayed an excellent illustration of phthalocyanine **6**. The UV spectrum of Pc **6** exhibited bands at λ_{max} = 611 and 673 nm (Q bands).

Similarly, we report here that the same procedure is an efficient method to synthesize 2,5,8-trioxo-2,3,5,8-

tetrahydrobenzofuro [2,3-*d*]thiazole-6,7-dicarbonitrile (**9**) and 5,8-dioxo-5,8-dihydrobenzofuro [3,2-*d*]thiazole-6,7-dicarbonitrile (**10**) by the reaction of DDQ with thiazolidinedione **7** and/or thiazolone **8**. The structures of **9** and **10** were determined using accurate analytical and spectroscopic data (*cf.* the Experimental section). Refluxing hydroquinone with compounds **9** and **10** at 200 °C under nitrogen gas afforded the corresponding phthalocyanine products **11** and **12**, respectively, in 39–44% yield. In general, the IR spectra of Pcs **11** and **12** displayed the disappearance of the band of cyano groups at 2220 cm^{-1}, and this confirms that the dinitrile compounds **9** and **10** underwent cyclotetramerization. Also, the IR spectrum of compound **11** displayed the expected absorption bands, and the most important of them at ν 3100, 3150, 1700, 1685 and 1595 cm^{-1} correspond to the six NH groups, α,β-unsaturated ketone, C=O-amidic and C=N functional groups, respectively. Similarly, the IR spectrum of the phthalocyanine **12** gives almost the same picture without the C=O-amidic band. The ^{1}H-NMR spectrum of phthalocyanine **11** displays two singlet signals at δ 3.45 and 9.87 ppm due to the two pyrrolic NH groups in addition to the four NH-amidic groups, respectively. The ^{13}C-NMR spectrum displayed an excellent illustration of phthalocyanine **12**. The absorption data of the Q bands were obtained for the illustrative compounds **11** and **12** in DMF and gave the same λ_{max} at 618 and 680 nm, respectively (Schemes 7 and 8).[15]

Moreover, *p*-acetylaminophenylrhodanine **13** and its 2-phenylimino derivative **14** were refluxed with DDQ in the presence of EtOH containing a catalytic amount of piperidine and heated for 4 h; this reaction afforded the corresponding dicarbonitrile derivatives **15** and **16**, respectively. The structures of novel phthalonitriles **15** and **16** were confirmed by their correct
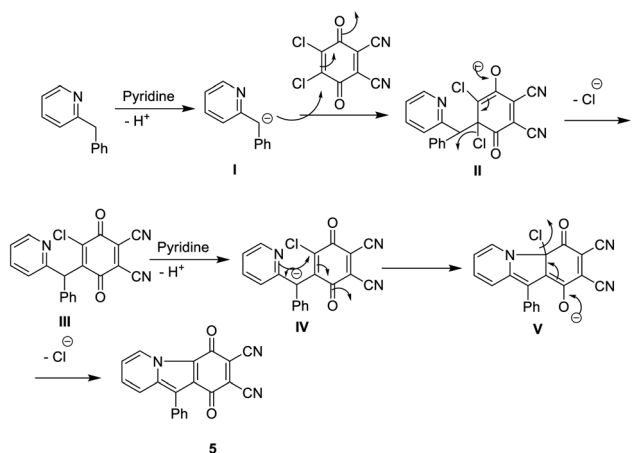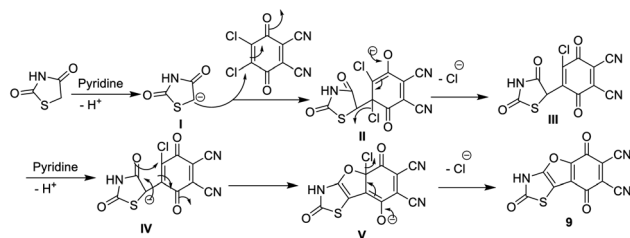

Scheme 6 Mechanism formation of compound **5**.
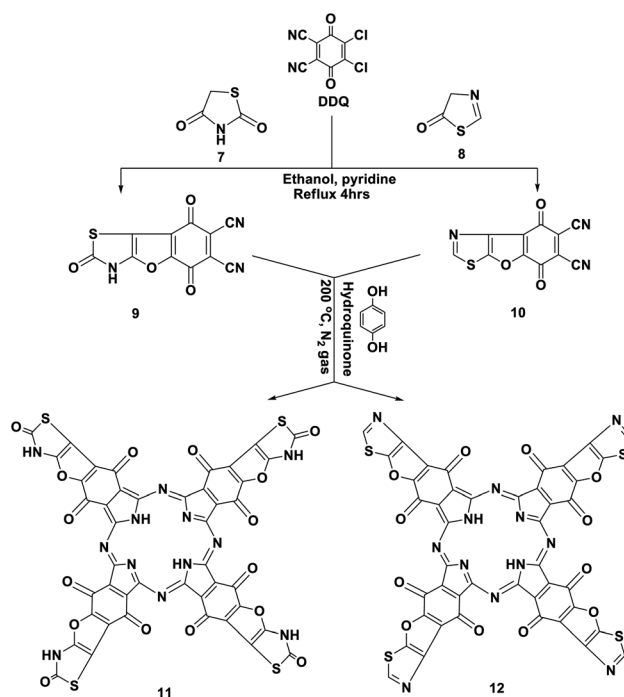
Scheme 7 Synthesis of novel phthalocyanines **11** and **12**.

Scheme 8 Mechanism of the formation of compound 9.

elemental and spectral data (*cf.* the Experimental section). Compounds 15 and 16 were proposed to be formed by a similar mechanism to that of the formation of compound 9 (Scheme 8).

After that, when hydroquinone was refluxed with compounds 15 and 16 at 200 °C under nitrogen gas, it afforded the corresponding Pcs 17 and 18, respectively, in 41–43% yield. In general, the IR spectra of phthalocyanines 17 and 18 gave an indication of the cyclotetramerization process of the dinitrile compounds 15 and 16 through the vanishing of the cyano absorption bands in the range of 2220 cm^{-1}. Also, the IR spectra of the two Pcs 17 and 18 gave almost the same picture, except that compound 17 was differentiated by the presence of an intense absorption band at ν 1350 cm^{-1} due to the presence of the C=S functional group. Meanwhile, Pc 18 was characterized by the presence of an intense absorption band at ν 1620 cm^{-1} due to the presence of the imino functional group (=C=N–Ph). The ^{13}C-NMR spectra of phthalocyanines 17 and 18 displayed the expected signals which confirmed their structures. The Q

band absorption data were obtained for the illustrative phthalocyanines 17 and 18 in DMF at λ_{max} = 622, 688 nm and 622, 691 nm, respectively (Scheme 9).[15]

In this study, we report the fusion process of ethanolamine and picolinic anhydride in a pressure tube in the presence of NaOAc in a silicon oil bath at 150 °C for two hours, which afforded the corresponding imide 19. The structure of imide 19 was confirmed by both elemental and spectral data (*cf.* the Experimental section). After that, the refluxing of imide 19 with 4-nitrophthalic anhydride in the presence of DMF as solvent containing an amount of KOH pellets under N$_2$ gas led to the formation of the corresponding phthalic anhydride 20. Compound 20 was also established by its correct elemental and spectral data (*cf.* the Experimental section). Finally, the phthalic anhydride 20 was heated with disilazane derivative 21 at 150 °C in the presence of DMF as solvent containing an equivalent amount of urea as a source of nitrogen and afforded the corresponding phthalocyanine 22 (Scheme 10). The IR spectrum of Pc 22 showed the absence of the band which corresponds to the C=O groups of anhydride 20 at ν 1720 cm^{-1}, which confirmed the phthalocyanine structure 22, in addition to the attendance of new absorption bands at ν 3145, 2195 and 1605 cm^{-1}, corresponding to the NH, Ar-CH and C=N functional groups, respectively. The ^{13}C-NMR spectrum of phthalocyanine 22 displayed the expected signals, which confirmed its structure. The UV spectrum exhibited the characteristic Q bands in the regions of λ_{max} of 625 and 694 nm.

Electronic study of our novel phthalocyanines

Phthalocyanines have been reported as unique compounds which have a good chemical stability and absorb light at λ_{max} = 690 nm.[16] Phthalocyanines 3, 6, 11, 12, 17, 18 and 22 displayed typical UV spectra, with two distinct zones of high absorption. Firstly, the Soret band (B band) appeared in the electronic spectra in the range of 340–500 nm,[17] which arises from the transition of π-levels → LUMO. After that, the Q-band appeared in the visible region in the range of λ_{max} = 600–750 nm, and a green color appeared; this band appeared due to the transition
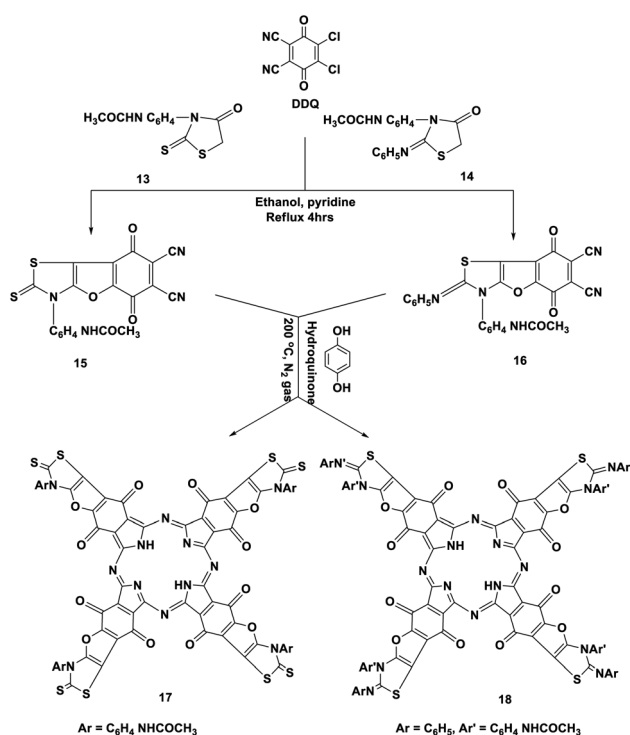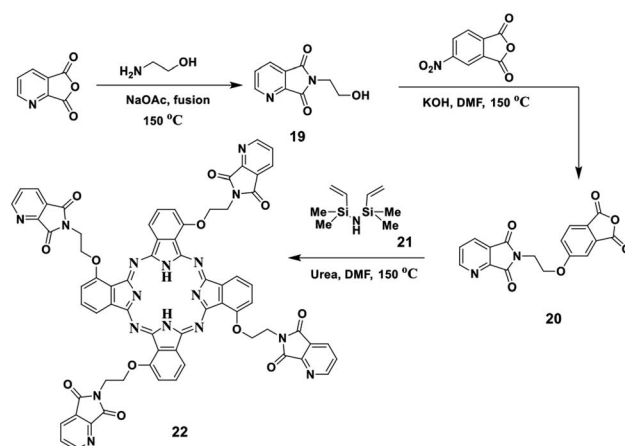

Scheme 9 Synthesis of phthalonitriles 15 and 16 and their novel phthalocyanines 17 and 18.

Scheme 10 Synthesis of compound 20 and the novel phthalocyanine derivative 22.

Table 1 B and Q bands of the new synthesized phthalocyanines

Compound	B bands λ_{max} (nm)	Q bands λ_{max} (nm)
3	—, —	602, 668
6	—, —	611, 673
11	458, 500	618, 680
12	458, 500	618, 680
17	465, 500	620, 688
18	465, 500	622, 691
22	460, 500	625, 694

Table 2 Antioxidant assay comparing the studied compounds to commercially available BHA and BHT[a]

Compound	DPPH (IC$_{50}$, mM/1 h)	HO (IC$_{50}$, mM)	LP (IC$_{50}$, mM)
3	1.860	4.630	na[a]
6	1.670	4.120	na[a]
11	0.091	0.216	0.051
12	0.097	0.722	0.190
17	0.067	0.133	0.034
18	0.061	0.120	0.030
22	1.620	2.830	na[a]
BHA	0.012	2.130	0.048
BHT	0.040	1.940	0.210

[a] na[a] means 50% inhibition not achieved. BHA, butylated hydroxyanizol; BHT, butylated toluene; DPPH, 2, 2-diphenyl-1-picrylhydrazyl; HO, hydroxyl; LP, lipid peroxidation.

between the π–π* orbitals from the HUMO to the LUMO.[18] The separation of the Q-band at the far-red end of the UV spectrum caused the purity and depth of color of the phthalocyanines using DMF as solvent at room temperature and showed the collection of the characteristic Q bands and B bands for all synthesized phthalocyanines (Table 1 and Fig. 1). From Table 1, the two compounds 3 and 6 did not show any bands in the UV region and only showed bands in the visible region at λ_{max} = 688 and 673 nm, respectively. On the other hand, compounds 11 and 12 are very similar to each other and were characterized by peaks at λ_{max} = 500 for the B bands and at λ_{max} = 680 for the Q bands. For the remaining compounds, 17, 18 and 22, all of them showed both B bands and Q bands; the Q bands appeared as intense peaks at λ_{max} = 688, 691 and 694 nm, respectively.

Pharmacology of the new phthalocyanines

Antioxidant activities. The new synthesized compounds 3, 6, 11, 12, 17, 18 and 22 were estimated in a chain of *in vitro* tests for their antioxidant properties. In the DPPH assay, which is mentioned in Table 2, a spectrophotometric technique[19] was used to measure the conversion of DPPH˙ to its reduced form, DPPH (the color of the compound changed from purple to yellow). Commercial synthetic antioxidants such as butylated toluene (BHT) and butylated hydroxyanisole (BHA) were used as positive controls. Compounds 18 and 17 have the strongest radical scavenging activity, owing to their distinct structures and many nitrogen atoms in the hetero-aryl moiety in addition to the presence of the keto–enol form, which enhances the antioxidant activity.[20] As also reported in Table 2, the deoxyribose assay was used to measure the hydroxyl radical scavenging activity of our synthesized compounds. The synthesized

compounds can inhibit the degradation by removing the hydroxyl radicals from the tested solution, which helps us to monitor the protective effect of these compounds. All tested compounds demonstrated high prevention of degradation, especially compounds 18 and 17. Because of the highly powerful OH˙ scavengers created during Fenton's reaction, compounds 18 and 17 had the highest IC$_{50}$ values. Based on the discovery of MDA production, using liposomes as an oxidizable material can avoid LP.[19] The tested derivatives 18 and 17, which displayed the highest inhibition, showed a distinguished decrease of Fe^{2+}/ascorbate-induced LP in the liposomes. Compounds 18 and 17 could be categorized as good inhibitors of LP based on their IC$_{50}$ values for BHT and BHA. Generally, from Table 2, it can be said that compounds 18 and 17 showed the highest activity in this assay compared to BHT and BHA. These results were found to be similar to those of previously reported compounds that have quinone moieties, which were reported to be good antioxidant agents at lower concentrations.[20]

Cytotoxicity (anticancer screening). There are two factors that can be relied upon to study the cytotoxicity activity of synthesized compounds towards any cell line:[21,22] (1) the formation of an intramolecular H-bond with any of one of the nucleotides in DNA; (2) the attraction force between the positive charge on the tested derivatives and the negative charge on the wall of the cell. The following SAR study was concluded by making a comparison between the Experimental results of the cytotoxicity of the tested compounds and their structures. As shown in Table 3, the obtainable derivatives were estimated and tested for their cytotoxic activity against different cell lines, such as HepG2, WI-38, Vero and MCF-7, which were obtained from The Regional Center for Mycology and Biotechnology, Al Azhar University, Cairo Governorate, Egypt. The highest cytotoxic activity against the HepG2 cell line was shown by compounds 17 and 18 (with IC$_{50}$ values of 9.6 and 9.8 μg mL^{-1}, respectively). Meanwhile, compounds 3, 6, 11, 12 and 22 exhibited strong cytotoxic activities against the target cell line. All of these compounds contain more than one NH group in their structure, which can form intramolecular H-bonds with one of the
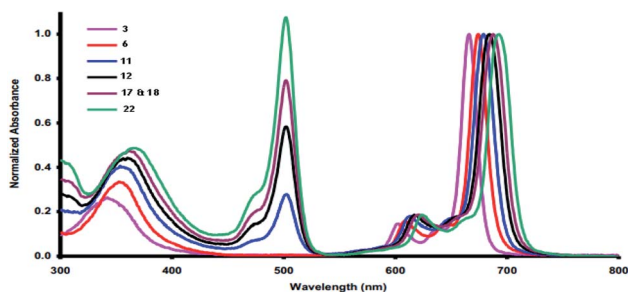

Fig. 1 UV-vis absorption spectra of the novel phthalocyanines 3, 6, 11, 12, 17, 18 and 22.

Table 3 Cytotoxicity (IC$_{50}$) of the tested compounds on different cancer cell lines[a]

| Compound | IC$_{50}$, µg mL^{-1} | | | |
	HepG2	WI-38	VERO	MCF-7
3	10.6 ± 0.22	48 ± 0.07	45 ± 0.05	17 ± 0.06
6	11.5 ± 0.13	62 ± 0.04	50 ± 0.05	21 ± 0.19
11	10.1 ± 0.22	36 ± 0.31	49 ± 0.02	15 ± 0.01
12	12 ± 0.13	68 ± 0.21	57 ± 0.19	26 ± 0.04
17	9.6 ± 0.22	10 ± 0.04	15 ± 0.05	4 ± 0.04
18	9.8 ± 0.11	24 ± 0.01	17 ± 0.06	9 ± 0.18
22	24 ± 0.22	70 ± 0.03	70 ± 0.02	27 ± 0.23
5-Flu	8.80 ± 0.03	3.10 ± 0.0	6.60 ± 0.04	2.30 ± 0.02

[a] IC$_{50}$ (µg mL^{-1}): 1–10 (very strong), 11–25 (strong), 26–50 (moderate), 51–100 (weak), 100–200 (very weak), 200 (noncytotoxicity), 5-Flu = 5-fluorouracil.

nucleobases of DNA and cause harm. Also, in addition to the presence of NH groups, compound **11** contains amidic carbonyl groups which act as strong electron withdrawing groups and lead to electrostatic attractions with DNA nucleobases, thus causing DNA damage. Correspondingly, compounds **17** and **18** displayed the maximum cytotoxic activity against the WI-38 cell line (with IC$_{50}$ values of 10 and 24 µg mL^{-1}, respectively) because of the presence of many NH groups, of which some can undergo keto–enol tautomerization; thus, they exposed more potent activity. Similarly, compound **11** displayed strong cytotoxicity due to the presence of many NH groups present in keto–enol tautomer form, while the rest of the compounds showed a range of moderate to weak cytotoxic activity. Using the same approach, compounds **17** and **18** exhibited strong cytotoxic activity against the Vero cell line (with IC$_{50}$ values of 15 and 17 µg mL^{-1}, respectively). Moreover, compounds **3**, **6** and **11** showed mild activities toward the same tumor cells, while the other derivatives revealed less activity. Furthermore, compounds **17** and **18** displayed the maximum activity against the MCF-7 cell line (with IC$_{50}$ values of 4 and 9 µg mL^{-1}, respectively), and this is due to the formation of the keto–enol form and many N atoms. Meanwhile, derivatives **3**, **6**, **11**, **12** and **22** displayed mild activity towards the same tumor cells.

Experimental

General remarks

The experiments were carried out according to previously reported work.[23]

Synthesis of novel phthalocyanine derivatives using different methods

Synthesis of N1,N2-dipropylbenzene-1,2-diamine (1). The reaction mixture of the bimolar ratio of 1-bromopropane (2.46 g, 0.02 mol) and o-phenylinediamine (1.92 g, 0.01 mol) was stirred in the presence of EtOH (15 mL)/pyridine for six h. At the end of the stirring time, the color of the reaction mixture was altered from pale red to dark red. The solvent was evaporated to

afford colorless needle crystals. Colorless needle crystals; yield 57%; mp 173 °C; IR (KBr) v/cm^{-1}: 3320 (2NH); ^{1}H NMR (DMSO-d_6): δ (ppm): δ 0.91 (t, 6H, 2 CH$_3$), 1.60 (m, 4H, 2CH$_2$), 3.61 (t, 4H, J = 10 Hz, 2CH$_2$), 6.46–6.66 (m, 4H, Ar-H), 6.88 (s, 2H, 2NH). ^{13}C NMR (DMSO-d_6) δ (ppm): 11.5, 23.2, 47.2, 109.4, 117.9, 137.4; MS: m/z (%): 192 (M+, 42%); anal. calcd for C$_{12}$H$_{20}$N$_2$ (192.31): C, 74.95; H, 10.48; N, 14.57%. Found: C, 74.88; H, 10.36; N, 14.44%.

Synthesis of 1,4-dioxo-5,10-dipropyl-1,4,5,10-tetrahydrophenazine-2,3-dicarbonitrile (2). A mixture of compound **1** (0.58 g, 0.003 mol) and an equivalent amount of DDQ (0.68 g, 0.003 mol) was refluxed in the presence of absolute EtOH (20 mL)/pyridine for 6 h under N$_2$ gas. At the end of refluxing, the colour of the reaction mixture changed from pale red to dark brown. Then, the unreacted materials were removed by filtration of the reaction mixture, where the hot mixture was poured onto ice-cold H$_2$O. The solid product was filtrated, dried, recrystallized with EtOH and finally collected. Brown powder; yield 52%; mp 286 °C; IR (KBr) v/cm^{-1}: 2218 (2 C≡N), 1700 (2 C=O); ^{1}H-NMR (DMSO-d_6) δ (ppm): 0.93 (t, 6H, J = 6.5 Hz, 2 CH$_3$), 1.67 (m, 4H, 2CH$_2$), 3.77 (t, 4H, J = 7.5 Hz, 2CH$_2$), 7.17–7.37 (m, 4H, Ar-H); ^{13}C-NMR (DMSO-d_6) δ (ppm): 11.9, 21.1, 48.3, 110.7, 117.9, 118.6, 128.0, 129.5, 141.5, 187.0; MS: m/z (%) 346 (M$^+$, 35%); anal. calcd For C$_{20}$H$_{18}$N$_4$O$_2$ (346.39): C, 69.35; H, 5.24; N, 16.17%. Found: C, 69.22; H, 5.18; N, 16.10%.

Synthesis of 5,11,16,22,27,33,38,44-octapropyl-5,11,16,22,27,33,38,44-octahydro-7,42:20,29-di(azeno)-9,18:31,40-diepimino [1,6,11,16]tetraazacycloicosino[3,4-b:8,9-b′:13,14-b″:18,19-b‴] tetraphenazin-6,10,17,21,28,32,39,43-octaone; phthalocyanine (3).

Route A. Dinitrile compound **2** (1 g, 0.003 mol) was gently refluxed with hydroquinone (0.22 g, 0.002 mol) (purified by sublimation) at 200 °C under N$_2$ gas and maintained at this temperature for three hours. The reaction mixture was left to cool at r.t. and then washed several times with ethanol (2 × 100 mL) and ethyl acetate (2 × 100 mL). The extraction method was performed using chloroform, and after that, the reaction mixture was filtered to remove the unreacted organic material. Under vacuum, the filtrate was evaporated and the green product was washed with hot EtOH, then dried to afford the corresponding Pc **3** in high yield.

Route B. A mixture of dinitrile compound **2** (2.99 g, 0.002 mol) and a suitable amount of DBO (0.29 g, 0.0026 mol) was flushed using N$_2$ gas and refluxed at 200 °C for 30 minutes; then, 25 mL of ethylene glycol was added. Heating of the reaction mixture was continued with stirring under N$_2$ gas at 150 °C for 10 h. The dark green product was obtained after removal of the solvent and disposal of the residue by the chromatographic process using silica gel and an eluent, CH$_2$Cl$_2$: CHCl$_3$ (2 : 1.5). Dark green powder; yield 68%; mp >300 °C; IR (KBr) v/cm^{-1}: 3250 (NH), 1700 (C=O), 1620 (C=N); ^{1}H NMR (DMSO-d_6) δ (ppm): 1.05 (t, 24H, J = 8.5 Hz, 8CH$_3$), 1.69 (m, 16H, 8CH$_2$), 2.87 (t, 16H, J = 9.5 Hz, 8CH$_2$), 3.45 (s, 2H, 2NH), 7.18 (m, 8H, Ar-H), 7.37 (d, 8H, J = 11.0 Hz, Ar-H). ^{13}C NMR (DMSO-d_6) δ (ppm): 12.1, 20.8, 47.8, 116.7, 118.0, 129.2, 140.7, 151.7, 153.2, 160.3, 173.8; UV-vis spectrum: λ_{max} (nm) 602, 668 nm. Anal. calcd for C$_{80}$H$_{74}$N$_{16}$O$_8$

(1387.58): C, 29.25; H, 5.38; N, 16.15%. Found: C, 29.23; H, 5.40; N, 16.17%.

Synthesis of 1,4-dioxo-10-phenyl-1,4-dihydropyrido [1,2-a] indole-2,3-dicarbonitrile (5). An equimolar ratio of 2-benzyl-pyridine compound **4** (0.51 g, 0.003 mol) and DDQ (0.68 g, 0.003 mol) was refluxed in the presence of 15 mL EtOH/pyridine for four hours until the color of the reaction mixture changed from dark green to deep brown at the end of refluxing. The unreacted materials were removed during filtration of the reaction mixture while hot. Then, the reaction mixture was allowed to cool at r.t. and poured onto ice cold H_2O. The solid product was filtered and dried after being washed several times with cold H_2O. Finally, the brown product was obtained from recrystallization using a mixture of acetone and EtOH (0.5 : 10 mL) as the eluent. Brown powder; yield 59%; mp 172 °C; IR (KBr) ν/cm^{-1}: 2220 (2 C≡N), 1730 (2 C=O); ^{1}H NMR (DMSO-d_6) δ (ppm): 6.41 (t, 1H, J = 7.5 Hz, Ar-H), 7.11 (t, 1H, J = 7.5 Hz, Ar-H), 7.33–7.69 (m, 6H, Ar-H), 9.83 (t, 1H, J = 7.5 Hz, Py-H); ^{13}C NMR (DMSO-d_6) δ (ppm): 112.1, 115.8, 117.2, 122.1, 124.4, 124.5, 124.7, 127.5, 128.7, 129.2, 132.7, 138.0, 138.4, 145.8, 175.2, 177.0; MS: m/z (%): 323 (M$^+$, 20); anal. calcd for $C_{20}H_9N_3O_2$ (323.31): C, 74.30; H, 2.81; N, 13.00%. Found: C, 74.22; H, 2.79; N, 12.88%.

Synthesis of 5,15,25,35-tetraphenyl-6H,10H-7,39:19,27-di(azeno)-9,17:29,37-diepimino-10b,20b,30b,40b-tetraza-tetrafluoreno[2,3-c:2′,3′-h:2″,3″-m:2‴,3‴-r] [1,6,11,16]tetraazacycloicosin-6,10, 16, 20,26,30,36,40(10bH,20bH,30bH,40bH)-octaone; phthalocyanine (6). In the reaction mixture, dinitrile compound **5** (0.65 g, 0.002 mol) was refluxed with *n*-propanol (0.12 mL, 0.002 mol) for 3 h under N_2 gas in the presence of ethanol as solvent containing a few crystals of I_2 which were used for the initiation of the reaction. The reaction mixture was then heated at 130 °C for 15 hours with stirring. The reaction mixture was filtered and washed with chloroform while it was still hot. The organic layer was evaporated using a vacuum and chromatographed using (CHCl$_3$: MeOH : NH$_4$OH) (3 : 1.5 : 0.5) to obtain the corresponding product. Dark red powder; yield 59%; mp >300 °C; IR (KBr) ν/cm^{-1}: 3150 (NH), 1730 (C=O), 1620 (C=N), 1560 (C=O); ^{1}H NMR (DMSO-d_6) δ (ppm): 6.41 (t, 4H, J = 7.5 Hz, Ar-H), 7.11 (t, 4H, J = 7.5 Hz, Ar-H), 7.33–7.69 (m, 24H, Ar-H), 9.83 (t, 4H, J = 7.0 Hz, Py-H), 12.43 (s, 2H, 2NH); ^{13}C NMR (DMSO-d_6) δ (ppm): 112.1, 117.2, 122.1, 124.4, 124.5, 124.7, 127.5, 128.7, 129.2, 132.7, 138.0, 138.2, 145.8, 155.1, 160.8, 170.9, 177.5, 182.1; UV-vis spectrum: λ_{max} (nm): 611, 673 nm. Anal. calcd for $C_{80}H_{38}N_{12}O_8$ (1295.26): C, 74.18; H, 2.96; N, 12.98%. Found: C, 74.00; H, 2.88; N, 12.83%.

Synthesis of new phthalonitrile derivatives (9), (10), (15) and (16)

General procedure. The reaction mixture of DDQ (0.68 g, 0.003 mol) and thiazolidine-2,4-dione (**7**), mp 124 °C (0.35 g, 0.003 mol) and/or thiazol-5(4H)-one (**8**) (0.30 g, 0.003 mol) and/or N-(p-acetylaminophenyl)rhodanine (**13**), mp 240 °C (0.80 g, 0.003 mol), and/or N-(4-(4-oxo-2-(phenylimino)thiazolidin-3-yl) phenyl) acetamide (**14**), mp 265 °C (0.98 g, 0.003 mol) was refluxed in the presence of 15 mL EtOH/pyridine for four hours until the reaction mixture had changed colour from dark green to dark brown at the end of the refluxing. We eliminated the unreacted elements by filtering the reaction mixture while it was still hot and allowing it to cool at room temperature before

pouring it into ice cold H_2O. Each crude product was filtered and recrystallized using acetone : EtOH (0.5 : 10) as the eluent after washing it several times with cold H_2O, then dried and collected to afford the corresponding products.

2,5,8-Trioxo-2,3,5,8-tetrahydrobenzofuro[2,3-d]thiazole-6,7-dicarbonitrile (9). Reddish brown powder; yield 75%; mp 163 °C; IR (KBr) ν/cm^{-1}: 3250 (NH), 2219 (C≡N), 1725 (C=O), 1682 (C=O-amidic), 1110 (C–O–C); ^{13}C NMR (DMSO-d_6) δ (ppm): 110.0, 115.8, 137.0, 138.4, 151.9, 160.7, 169.6, 170.0, and 175.0. MS: m/z (%): 271 (M$^+$, 18). Anal. calcd for $C_{11}HN_3O_4S$ (271.21): C, 48.72; H, 0.37; N, 15.49%. Found: C, 48.66; H, 0.28; N, 15.36%.

5, 8-Dioxo-5,8-dihydrobenzofuro [3,2-d] thiazole-6,7-dicarbonitrile (10). Brown powder; yield 77%; mp 173 °C; IR (KBr) ν/cm^{-1}: 2220 (2 C≡N), 1730 (C=O), 1620 (C=N), 1110 (C–O–C). ^{1}H NMR (DMSO-d_6) δ (ppm): 8.89 (s, 1 H, CH); ^{13}C NMR (DMSO-d_6) δ (ppm): 115.8, 118.6, 138.4, 140.5, 143.2, 153.6, 161.6, 169.6, 175.0; MS: m/z (%): 255 (M$^+$, 26). Anal. calcd for $C_{11}HN_3O_3S$ (255.21): C, 51.77; H, 0.39; N, 16.47%. Found: C, 51.65; H, 0.31; N, 16.32%.

N-(4-(6, 7-Dicyano-5, 8-dioxo-2-thioxo-5, 8-dihydrobenzofuro [2, 3-d] thiazol-3(2H)-yl) phenyl) acetamide (15). Dark brown powder; yield 77%; mp 179 °C; IR (KBr) ν/cm^{-1}: 3300 (NH), 2218 (C≡N), 1718 (C=O), 1678 (C=O), 1350 (C=S); ^{1}H NMR (DMSO-d_6) δ (ppm): 2.01 (s, 3H, CH$_3$), 7.46 (d, 2H, J = 8.5 Hz, Ar-H), 7.66 (d, 2H, J = 9.5 Hz, Ar-H), 9.88 (s, 1H, NH); MS: m/z (%): 420 (M$^+$, 31); anal. calcd for $C_{19}H_8N_4O_4S_2$ (420.42): C, 54.28; H, 1.92; N, 13.33%. Found: C, 54.11; H, 1.88; N, 13.21%.

N-(4-(6,7-Dicyano-5,8-dioxo-2-(phenylimino)-5,8-dihydro benzofuro[2,3-d]thiazol-3(2H)-yl)phenyl)acetamide (16). Brown powder; yield 61%; mp 181 °C; IR (KBr) ν/cm^{-1}: 3310 (NH), 2220 (C≡N), 1720 (C=O), 1680 (C=O-amidic), 1615 (C=N); ^{1}H NMR (DMSO-d_6) δ (ppm): 2.53 (s, 3H, CH$_3$), 7.19 (d, 2H, J = 9.0 Hz, Ar-H), 7.27 (d, 2H, J = 8.0 Hz, Ar-H), 7.56–7.82 (m, 5H, Ar-H), 9.89 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ (ppm): 24.0, 110.0, 115.8, 118.7, 122.3, 122.4, 127.2, 128.5, 130.0, 137.0, 138.4, 141.0, 151.5, 151.9, 158.9, 160.7, 168.9, 169.8, 175.0; MS: m/z (%): 479 (M$^+$, 43). Anal. calcd for $C_{25}H_{13}N_5O_4S$ (479.47): C, 62.63; H, 2.73; N, 14.61%. Found: C, 62.55; H, 2.64; N, 14.58%.

Synthesis of novel phthalocyanines (11), (12), (17) and (18)

General procedure. The reaction mixture of dinitrile compound **9** (0.81 g, 0.003 mol) and/or compound **10** (0.77 g, 0.003 mol) and/or compound **15** (1.26 g, 0.003 mol) and/or compound **16** (1.44 g, 0.003 mol) was refluxed with hydroquinone (0.22 g, 0.002 mol) (purified by sublimation) at 200 °C under N_2 gas and held at this temperature for 3 h. After cooling the reaction mixture to r.t., it was washed several times with EtOH (2 × 100 mL) and ethyl acetate (2 × 100 mL). The product was extracted with chloroform and filtered to remove the unreacted organic material. Under vacuum, the filtrate was evaporated and the green solid product was washed with hot EtOH and then allowed dry to afford the corresponding phthalocyanines **11**, **12**, **27** and **18**, respectively, in high yields.

2,30-Dihydro-8,15:26,33-di(azeno)-6,35:17,24-diepiminothiazolo [4′,5′:2,3] benzofuro [5,6-c]thiazolo[4′,5′:2,3]benzofuro[5,6-h]thiazolo

[4′,5′:2,3] benzofuro [5,6-*m*] thiazolo [4′,5′:2,3] benzofuro[5,6-*r*] [1,6,11,16]tetraazacycloicosine-2,5,9,11, 14, 18, 20,23,27,29, 32,36(3*H*,12*H*,21*H*)-dodecaone; phthalocyanine (11). Dark green powder; yield 44%; mp >300 °C; IR (KBr) ν/cm^{-1}: 3100, 3150 (NH), 1700 (C=O), 1685 (C=O-amidic), 1595 (C=N); ^{1}H NMR (DMSO-d_6) δ (ppm): 3.45 (s, 2H, 2NH), 9.87 (s, 4H, 4NH). ^{13}C-NMR (DMSO-d_6) δ (ppm): 110.0, 137.0, 138.2, 151.9, 152.6, 160.7, 160.8, 170.1, 171.9, 175.4; UV-vis spectrum: λ_{max} (nm): 618, 680 nm; anal. calcd for C$_{44}$H$_6$N$_{12}$O$_{16}$S$_4$ (1086.84): C, 48.63; H, 0.56; N, 15.47%. Found: C, 48.61; H, 0.59; N, 15.46%.

5*H*-8,15:26,33-Di(azeno)-6,35:17,24-diepiminothiazolo [4′,5′:2,3] benzofuro[5,6-*c*] thiazolo [4′,5′:2,3] benzofuro[5,6-*h*]thiazolo [4′,5′:2,3]benzofuro [5,6-*m*] thiazolo [4′,5′:2,3] benzofuro[5,6-*r*] [1,6,11,16]tetraazacycloicosin-5,9,14,18,23,27,32,36(31*H*)-octaone; phthalocyanine (12). Dark green powder; yield 39%; mp >300 °C; IR (KBr) ν/cm^{-1}: 3130 (NH), 1710 (C=O), 1600 (C=N); ^{1}H NMR (DMSO-d_6) δ (ppm): 6.95 (s, 4H, thiazole-H), 9.11 (s, 2H, 2NH); ^{13}C NMR (DMSO-d_6) δ (ppm): 118.6, 138.2, 140.5, 143.2, 152.6, 153.6, 160.8, 161.6, 171.9, 175.0; UV-vis spectrum: λ_{max} (nm): 618, 680 nm. Anal. calcd for C$_{44}$H$_6$N$_{12}$O$_{12}$S$_4$ (1022.84): C, 51.67; H, 0.59; N, 16.43%. Found: C, 51.66; H, 0.56; N, 16.45%.

N,*N*′,*N*″,*N*‴-((4,8,13,17,22,26,31,35-Octaoxo-2,10,20,28-tetra thioxo 8,13,17,18,22,30,31,35-octahydro-4*H*,26*H*-5, 34:16,23-di(azeno)-7,14:25,32-diepiminothiazolo [4′,5′:2,3] benzofuro [5,6-*c*]thiazolo[4′,5′:2,3]benzofuro[6,5-*r*]thiazolo [5′,4′:1,2] benzofuro [5,6-*h*]thiazolo [5′,4′:1,2] benzofuro [6,5-*m*][1,6,11,16] tetraazacycloicosine-1,11,19,29 (2*H*,10*H*,20*H*,28*H*) tetrayl) tetrakis(benzene-4,1-diyl))tetraacetamide; phthalocyanine (17). Dark green powder; yield 41%; mp >300 °C; IR (KBr) ν/cm^{-1}: 3210, 3124 (NH), 1712 (C=O), 1683 (C=O-amidic), 1596 (C=N), 1350 (C=S); ^{1}H NMR (DMSO-d_6) δ (ppm): 2.01 (s, 12H, 4CH$_3$), 7.46–7.66 (dd, J = 8.5 Hz, 16H, Ar-H), 9.88 (s, 4H, 4NH), 11.49 (s, 2H, 2NH);^{13}C NMR (DMSO-d_6) δ (ppm): 24.0, 110.0, 121.9, 128.6, 133.7, 134.5, 137.0, 138.2, 151.9, 152.6, 160.7, 160.8, 168.9, 171.9, 175.0, 189.7; UV-vis spectrum: λ_{max} (nm) 620, 688 nm; anal. calcd for C$_{76}$H$_{34}$N$_{16}$O$_{16}$S$_8$ (1683.68): C, 54.22; H, 2.04; N, 13.31%. Found: C, 54.20; H, 2.07; N, 13.33%.

N,*N*′,*N*″,*N*‴-(((2*E*,10*E*,20*Z*,28*Z*)-4,8,13,17,22,26,31,35-Octaoxo-2,10,20,28-tetrakis (phenylimino)-8,13,17,18,22,30,31,35-octahydro-4*H*,26*H*-5,34:16,23-di(azeno)-7,14:25,32-diepiminothiazolo [4′,5′:2,3]benzofuro[5,6-*c*]thiazolo[4′,5′:2,3] benzofuro[6,5-*r*]thiazolo[5′,4′:1,2]benzofuro[5,6-*h*]thiazolo [5′,4′:1,2]benzofuro[6,5-*m*] [1,6,11,16]tetraazacycloicosine-1,11, 19,29(2*H*,10*H*,20*H*,28*H*)-tetrayl) tetrakis (benzene-4,1-diyl)) tetraacetamide; phthalocyanine (18). Yield 43%; mp >300 °C; IR (KBr) ν/cm^{-1}: 3201, 3175 (NH), 1715 (C=O), 1692 (C=O-amidic), 1620,1599 (C=N); ^{1}H NMR (DMSO-d_6) δ (ppm): 2.13 (s, 12H, 4CH$_3$), 6.75–7.53 (dd, J = 8.5 Hz, 16H, Ar-H), 7.71–7.91 (m, 20H, Ar-H), 9.83 (s, 4H, 4NH), 11.99 (s, 2H, 2NH);^{13}C NMR (DMSO-d_6) δ (ppm): 24.0, 110.0, 118.7, 122.3, 122.4, 127.2, 128.5, 130.0, 137.0, 138.2, 141.0, 151.5, 151.9, 152.6, 156.9, 160.7, 160.8, 168.9, 171.9, 175.0; UV-vis spectrum: λ_{max} (nm): 622, 691 nm; anal. calcd for C$_{100}$H$_{54}$N$_{20}$O$_{16}$S$_4$ (1919.90): C, 62.56; H, 2.84; N, 14.59%. Found: C, 62.53; H, 2.86; N, 14.58%.

Synthesis of 6-(2-hydroxyethyl)-5*H*-pyrrolo [3,4-*b*] pyridine-5,7(6*H*)-dione (19). The reaction mixture of ethanolamine (0.488 g, 0.008 mol) was heated with picolinic anhydride (0.60 g, 0.004 mol) and NaOAc (0.5 g) in a pressure tube in a silicon oil bath at 150 °C for two hours. The reaction mixture was left to cool at r.t. and finally afforded the corresponding product **19** after recrystallization from a mixture of EtOH : DMF (2 : 1) as solvent. Buff powder; yield 74%; mp 179 °C; IR (KBr) ν/cm^{-1}: 3400 (OH), 1700 (C=O), 1620 (C=N); ^{1}H NMR (DMSO-d_6) δ (ppm): 3.62 (t, 2H, J = 10.0 Hz, CH$_2$), 3.69 (m, 2H, CH$_2$), 4.91 (br s, 1H, OH), 8.02 (d, 1H, J = 8.5 Hz, C$_4$–H pr), 8.66 (t, 1H, J = 9.2 Hz, C$_5$–H pr), 9.02 (d, 1H, J = 10.5 Hz, C$_6$–H pr).; MS: m/z (%): 192 (M$^+$, 36%). Anal. calcd for C$_9$H$_8$N$_2$O$_3$ (192.17): C, 56.25; H, 4.20; N, 14.58%. Found: C, 56.11; H, 4.09; N, 14.56%.

Synthesis of 6-(2-((1,3-dioxo-1,3-dihydroisobenzofuran-5-yl) oxy) ethyl)-5*H*-pyrrolo [3,4-*b*] pyridine-5,7(6*H*)-dione (20). In the reaction mixture, 6-(2-hydroxyethyl)-5*H*-pyrrolo[3,4-*b*]pyridine-5,7(6*H*)-dione compound (**19**) (0.96 g, 0.005 mol) was refluxed with stirring with 4-nitrophthalic anhydride (0.97 g, 0.005 mol) in dry DMF (20 mL) as solvent containing anhydrous KOH pellets (0.45 g, 0.008 mol) under N$_2$ gas at 150 °C. At the end of reflux, the color of the reaction mixture changed to brown. The reaction mixture was left to cool at r.t., then poured onto ice cold H$_2$O and neutralized with conc. HCl to obtain the corresponding ppt., which was filtered, collected after washing with H$_2$O, and dried. The solid product was purified by recrystallization using CH$_2$Cl$_2$: EtOH (5 : 20) to obtain the corresponding brown compound **20**. Brown powder, yield 69%; mp 188 °C; IR (KBr) ν/cm^{-1}: 1720 (C=O), 1680 (C=O-amidic); ^{1}H NMR (DMSO-d_6) δ (ppm): 3.62 (t, 2H, J = 9.8 Hz, CH$_2$), 4.27 (t, 2H, J = 10.0 Hz, CH$_2$), 7.48 (q, 1H, Ar-H), 7.88 (m, 1H, Ar-H), 7.91 (m, 1H, Ar-H), 8.02 (d, 1H, J = 9.0 Hz, C$_4$H-pr), 8.66 (t, 1H, J = 10.0 Hz, C$_5$H-pr), 9.02 (d, 1H, J = 8.2 Hz, C$_6$H-pr); ^{13}C NMR (DMSO-d_6) δ (ppm): 50.9, 64.7, 116.4, 116.8, 119.5, 120.0, 122.7, 128.4, 130.2, 135.2, 146.1, 152.6, 162.3, 165.9, 167.9, 169.6. MS: m/z (%): 338 (M$^+$, 37%). Anal. calcd for C$_{17}$H$_{10}$N$_2$O$_6$ (338.28): C, 60.36; H, 2.98; N, 8.28%. Found: C, 60.28; H, 2.87; N, 8.11%.

Synthesis of 6,6′,6″,6‴-((phthalocyanine-1,8,15,22-tetrayltetrakis (oxy))tetrakis(ethane-2,1-diyl))tetrakis(5*H*-pyrrolo[3,4-*b*]pyridine-5,7(6*H*)-dione); phthalocyanine (22). In the reaction mixture, compound **20** (1.69 g, 0.005 mol) was refluxed with 1,3-divinyl-1,1,3,3-tetramethyldisilazane (**21**) (0.93 g, 0.005 mol) in the presence of dry DMF as a solvent containing an amount of urea (0.244 g, 0.004 mol) at 150 °C under N$_2$ gas. A deep colored product instantaneously appeared and was then filtered. The product was washed with MeOH and dissolved in conc. H$_2$SO$_4$ (in the range of 4–5 mL), and then the solution was poured into H$_2$O. Then the precipitate was filtered and washed with dil. H$_2$SO$_4$ followed by H$_2$O and MeOH. The purification process involved using CHCl$_3$: hexane : MeOH (2 : 1.5 : 0.5) as the solvent (on silica gel). Deep red crystals; yield 63%; mp >300 °C; IR (KBr) ν/cm^{-1}: 3145(NH), 2195 (Ar-CH), 1682 (C=O-amidic), 1605 (C=N); ^{1}H NMR (DMSO-d_6) δ (ppm): 3.91 (t, 8H, J = 8.0 Hz, 4CH$_2$), 4.20 (t, J = 8.0 Hz, 8H, 4CH$_2$), 7.02–7.75 (m, 12H, Ar-H), 7.94 (s, 1H, NH), 8.02–9.01 (dd, J = 9.0 Hz, 12H, Py-H), 9.61 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ (ppm): 50.9, 64.7, 103.9, 104.5, 111.8, 112.0, 115.1, 116.8, 116.9, 119.3, 120.0, 120.9, 121.2, 128.4, 130.0, 131.7, 132.3, 135.0, 146.1, 152.6, 154.3, 155.4, 157.3, 165.9, 167.9, 168.2, 169.7, 171.4; UV-vis spectrum: λ_{max} (nm): 625, 694 nm; anal. calcd for C$_{68}$H$_{42}$N$_{16}$O$_{12}$ (1275.18): C, 64.05; H, 3.32; N, 17.57%. Found: C, 64.02; H, 3.30; N, 17.60%.

Biochemical assays

Antioxidant properties. The capacity of our tested compounds to neutralize DPPH and OH radicals was used to assess their free radical scavenging activity.

DPPH assay. DPPH was purchased from Sigma-Aldrich (St. Louis, MO, USA). The DPPH assay was applied according to the reported literature.[24]

Hydroxyl-radical scavenging assay. The (HO· RSA) assay by applying the degradation of 2-deoxy-D-ribose by OH radicals generated *in situ* by Fenton's reaction was used to assess the quality of the tested samples.[10,24]

Cytotoxicity and antitumor assay for phthalocyanines. This assay was carried out according to previous work.[25,26]

Conclusions

The purpose of this study was to develop new phthalonitrile derivatives as a starting material for high-yield production of new phthalocyanine colours. In the current work, the newly synthesized compounds were screened and tested for antioxidant and cytotoxicity properties, and they showed extremely good activity due to distinct functionalized heterocycles, which could be useful in the development of novel antioxidant and anticancer drugs. These findings revealed that the novel phthalocyanine compounds **17** and **18** could be useful in the creation of new antioxidant and anticancer agents.

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 N. B. McKeown, *The Porphyrin Handbook: Phthalocyanines: Synthesis*, 2002, vol. 15, p. 61.
2 Y. B. Platonova, A. N. Volov and L. G. Tomilova, *Bioorg. Med. Chem. Lett.*, 2020, **30**(16), 127351.
3 M. J. Naim, O. Alam, M. Farah Nawaz, J. Alam and P. Alam, *J. Pharm. BioAllied Sci.*, 2016, **8**(1), 2.
4 A. Chwiłkowska, J. Saczko, T. Modrzycka, A. Marcinkowska, A. Malarska, J. Bielewicz, D. Patalas and T. Banaś, *Acta Biochim. Pol.*, 2003, **50**(2), 509.
5 X. Jia and L. Jia, *Curr. Drug Metab.*, 2012, **13**(8), 1119.
6 A. F. Dos Santos, D. R. O. De Almeida, L. F. Terra, M. S. Baptista and L. Labriola, *J. Cancer Metastasis Treat.*, 2019, **5**, DOI: 10.20517/2394-4722.2018.83.
7 P. Xu, J. Chen, Z. Chen, S. Zhou, P. Hu, X. Chen and M. Huang, *PLoS One*, 2012, **7**(5), e37051.
8 H. Kantekin, Z. Bıyıklıoğlu and E. Çelenk, *Inorg. Chem. Commun.*, 2008, **11**(6), 633.
9 A. Staicu, A. Pascu, A. Nuta, A. Sorescu, V. Raditoiu and M. L. Pascu, *Rom. Rep. Phys.*, 2013, **65**(3), 1032.
10 M. S. Ağırtaş, B. Cabir and S. Özdemir, *Dyes Pigm.*, 2013, **96**(1), 152.
11 H. Shy, P. Mackin, A. S. Orvieto, D. Gharbharan, G. R. Peterson, N. Bampos and T. D. Hamilton, *Faraday Discuss.*, 2014, **170**, 59.
12 Z. Odabaş, A. Altındal, A. R. Özkaya, M. Bulut, B. Salih and Ö. Bekaroğlu, *Polyhedron*, 2007, **26**(3), 695.
13 C. J. P. Monteiro, M. M. Pereira, S. M. A. Pinto, A. V. C. Simões, G. F. F. Sá, L. G. Arnaut, S. J. Formosinho, S. Simões and M. F. Wyatt, *Tetrahedron*, 2008, **64**, 5132.
14 V. Z. Yuriy, I. S. Liliya and N. N. Victor, *J. Org. Chem.*, 2021, **86**(6), 4733.
15 S. Abid, S. Ben Hassine, N. Richy, F. Camerel, B. Jamoussi, M. Blanchard-Desce, O. Mongin, F. Paul and C. O. Paul-Roth, *Molecules*, 2020, **25**, 239.
16 Y. M. Shaker, A. M. Sweed, C. Moylan, L. Rogers, A. A. Ryan, R. Petitdemange and M. O. Senge, *Handbook of Photodynamic Therapy: Updates on Recent Applications of Porphyrin-Based Compounds*, 2016, vol. 95.
17 A. M. El-badrawy, N. Nagy, E. Abdel-Latif and A. A. Fadda, *Biointerface Res. Appl. Chem.*, 2021, **11**(5), 12937.
18 J. Leclaire, R. Dagiral, S. Fery-Forgues, Y. Coppel, B. Donnadieu, A. M. Caminade and J. P. Majoral, *J. Am. Chem. Soc.*, 2005, **127**(45), 15762.
19 A. Nakano, A. Osuka, I. Yamazaki, T. Yamazaki and Y. Nishimura, *Angew. Chem., Int. Ed.*, 1998, **37**(21), 3023.
20 S. Abu-Melha, *Arch. Pharm.*, 2019, **352**(2), 1800221.
21 G. Bischoff and S. Hoffmann, *Curr. Med. Chem.*, 2002, **9**(3), 321.
22 R. Martinez and L. Chacon-Garcia, *Curr. Med. Chem.*, 2005, **12**(2), 127.
23 A. A. Fadda, R. E. El-Mekawy, N. N. Soliman, A. M. Allam and M. T. Abdelaal, *Dyes Pigm.*, 2018, **155**, 300.
24 E. Klein and V. Lukeš, *J. Phys. Chem. A*, 2006, **110**(44), 12312.
25 A. A. Fadda, R. E. El-Mekawy, A. I. El-Shafei and H. Freeman, *Arch. Pharm.*, 2013, **346**(1), 53.
26 A. A. H. Abdel-Rahman, W. A. El-Sayed, E. S. G. Zaki, A. A. Mohamed and A. A. Fadda, *J. Heterocycl. Chem.*, 2012, **49**(1), 93.