Antitumor Activity of Tetra-Substituted Zinc Phthalocyanines Containing 4(3*H*)-Quinazolinone Derivatives

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*Series of tetra-substituted zinc(II)phthalocyanines (ZnPcs) bearing four 4(3H) quinazolinone ring system units (qz)$_4$ZnPcs **4a-c** have been synthesized and characterized. They were screened for their in-vitro antitumor activity on Human lung adenocarcinoma (A549), human breast adenocarcinoma (MCF-7) and Hepatocellular carcinoma (HEPG2). Preliminary study of the structure–activity relationship showed that electronic factors in the 4(3H)-quinazolinone moiety that attached to the ZnPc skeleton had a magnificent effect on the antitumor activity of the newly synthesized (qz)$_4$ZnPcs **4a-c**. They showed promising anticancer activity against the tested human cancer cell lines. The detailed synthesis, characterization and biological screening data were reported.*

Keywords: 4(3H)-quinazolinone, zinc(II)phthalocyanines, hetero-substituted phthalocyanines, anticancer activity, biological targeting agents.

Different series of Zinc phthalocyanines (ZnPcs) were used as valuable photosensitizers for photodynamic therapy of cancer (PDT) [1-5]. Until now, great variety of ZnPc derivatives functionalized with substituted heterocycles such as pyridyloxy, 4-pyridylmethyloxy [6] and oxyquinoline groups [7] have been offered potent PDT properties. Another derivatives of ZnPcs with multiple functional groups have been received attention as anticancer agents due to their photophysical and photochemical properties (e.g., tetracarboxy zinc phthalocyanine[8], pentalysine peptidyl moiety(ZnPc-(Lys)$_5$) [9], hexadecafluoro zinc phthalocyanine[10] and adamantylethoxy zinc phthalocyanines) [11].

Unfortunately, limitations of PDT of cancer have been found in previous studies [12] . It was shown that the ZnPc photosensitiser drugs require cellular oxygen to kill cancer cells *via* the formation of singlet oxygen. Moreover, they worked only on the area which was exposed to light. Therefore, when cancer spread in the body, it cannot be treated completely. In this regard, new hypoth has been studied in the present work dealing with the combinations of chemotherapy of ZnPcs and 4(3*H*)-quinazolinone derivatives (which will most likely result in the enhance of their anticancer efficiency for the treatment of metastasized and localized cancers).4(3*H*)-Quinazolinones are known to posses interesting drugs with diverse biological activities. They were used to modify the biological properties of several other compounds. The major effective biological activities and pharmacological properties of their derivatives include: anti-inflammatory activity [13-15], sedative [16], antimalarial [17], CNS depressant[18] analgesic [19], anticonvulsant [20], antidiabetic [21,22], antitubercular and antibacterial effects [23], antihypertensive[24], antiviral [25] and cancer chemotherapy [26-28]. The value of the 4(3*H*)-quinazolinone ring system derivatives as antitumor agents in drug design was also recognized [29-33]. Additionally, some researchers have reported the importance of different quinazolinone derivatives with potent antitumor activities such as, quinazolinones bearing thioureido[34] or thiazolidinone [35,36].

Earlier, Youssef et al. [37-42] have described novel symmetrically and asymmetrically Pcs with differently peripheral substitution and axial ligands for potential applications. The authors have also described the synthesis of NiPcs bearing heterocyclic moieties for pharmaceutical application [43]. In connection with a previous work and our current interest in the synthesis of organic compounds for biological evaluations [44-49]. We described herein a facile convenient synthesis of novel tetra substituted zinc phthalocyanines based on heterocyclic moiety (i.e 4(3*H*)-quinazolinone ring system, (qz)$_4$ZnPcs (**4a-c**). To the best of our knowledge, this is the first report which aims to modify the structural activity of zinc(II)phthalocyanines by combining them with four 4(3*H*)-quinazolinone units and evaluates their parameters required for the structure-function relationship for cancer therapy. The biological screening results obtained for the newly (qz)$_4$ZnPcs **4a-c** showed a promising anticancer activity *in vitro*.

Experimental part

Materials and methods

All reagents and solvents were commercial reagent grade and used without further purification. The following chemicals were purchased commercially from Aldrich and used as received: 4-nitrophthalonitrile, 2-Methyl-4(3*H*)-quinazolinone, 2-phenyl-4(3*H*)-quinazolinone and 2-mercapto-4(3*H*)-quinazolinone. Solvents (GR grade) from Merck (Darmstadt, Germany) were distilled. Silica gel thin-layer chromatography (TLC) plates 250 microns from Analtech (Newark, DE, USA) were used.

Physical characterizations

Melting points were determined by the open capillary method and were uncorrected. Infrared spectra were recorded on a Nicolet Magna 560 spectrophotometer in the spectral range 4000–400 cm^{-1} using KBr pellets. ^{1}H NMR

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spectra were recorded using a BVT 3000 Bruker Spectro spin instrument operating at 300.13 MHz. Spectra were referenced internally to residual solvent (DMSO). UV- Vis spectra were recorded using an Agilent 8453 UV-Vis spectrophotometer with Dimethyl sulfoxide (DMSO) used as solvent. Field depolarization mass spectroscopy technique (FDMS) mass spectra were recorded using a Varian MAT 711A spectrometer, operated at 70 eV for using the electron ionization technique (EIMS) and reported in mass/charge (m/z). Elementary analyses were performed on Carlo Erba Elemental Analyzer 1106.Purity of all synthesized compounds were checked by TLC on precoated silica gel plates utilizing chloroform/methanol in different ratios (8:2 / 7:3 v/v) as developing solvent system and spots were detected on exposure to UV lamp.

*Typical procedure for synthesis of 4(3H)-quinazolinone-phthalonitrile precursors **3a-c***

A mixture of quinazolinone derivative **1a-c** (4 mg, 2.50 mmol) **1a**, (5.5 mg, 2.5 mmol) **1b**, (4.4 mg, 2.5 mmol) **1c** and 4-nitrophthalonitrile **2** (4.3 mg, 2.5 mmol) was dissolved in dry DMF (100 mL). After stirring for 20 min at room temperature, a finely grounded anhydrous K_2CO_3 (excess) was added portion wise over 2 h, with efficient stirring for 24 h at 70-80°C. After cooling to room temperature, the reaction mixture was poured into ice-water. The crude product was held at 2 h and filtered off. The mixture washed with water and dried under vacuum. The crude products were purified by column chromatography (silica gel, chloroform/*n*-hexane) in different ratios (8:2 / 7:3 v/v) yielding 5.5 mg (76%) of the pure phthalonitrile **3a**, 6.3 mg (73%) of **3b** and 5.4 mg (72%) of **3c**.

Synthesis of 2-Methyl-4(3H)-quinazolinone- phthalonitrile **3a**

Prepared from 2-*M*ethyl-4(3*H*)-quinazolinone (**1a**) as a white solid; m.p. 290-292 °C; IR (KBr): ν= 3070-3068 (Ar-H_{str}), 2965, 2870 (C-H_{str}, CH_3), 2232 (CN_{str}), 1677 (C=O_{str}, qz ring), 1655 (C-N; C-C); 1584, 1571, 1479 (C–CH); 1422 mPh, 1418, 856, 740, 745 d(C–C), 640, 520 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ= 1.50 (3H, s, CH_3-qz), 7.6-7.8 (4H, m, Ar-H, quinazolinone moiety), 8.20 (1H, dd, 5-H), 8.33 (1H, d, 6-H), 8.41 (1H, s, 3-H) ppm. MS (EI): m/z = 286.29 (M^+). Elemental analysis: $C_{17}H_{10}N_4O$ found C 70.97, H 3.17, N 19.11, Calcd. C 71.32, H 3.52, N 19.57.

Synthesis of 2-Phenyl-4(3H)-quinazolinone- phthalonitrile **3b**

Prepared from 2-phenyl-4(3*H*)-quinazolinone (**1b**) as a white solid; m.p. 310-322 °C; IR (KBr): ν= 3072-3065 (Ar-H_{str}), 2961, 2873 (C-H_{str}, CH_3), 2235 (CN_{str}), 1678 (C=O_{str}, qz ring), 1665 (C-N; C-C); 1580, 1570, 1482 (C–CH); 1420 mPh, 1420, 853, 742, 749 d(C–C), 643, 522 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 7.3-7.6 (4H, m, Ar-H, quinazolinone moiety), 8.00 (1H, dd, 5-H), 8.21 (1H, d, 6-H), 8.35 (1H, s, 3-H), 8.50 (5H, m, ph-qz) ppm. MS (EI): m/z = 348.36 (M^+). Elemental analysis: $C_{22}H_{12}N_4O$, found C 70.97, H 3.87, N 18.98, Calcd. C 71.32, H 3.52, N 19.57.

Synthesis of 2-Mercapto-4(3H)-quinazolinone- phthalonitrile **3c**

Prepared from 2-mercapto-4(3H)-quinazolinone (**1c**), as a white solid; m.p. 288-291 °C; IR (KBr): ν= 3068-3071 (Ar-H_{str}), 2969, 2870 (C-H_{str}, CH_3), 2598 (SH_{str}), 2229 (CN_{str}), 1675 (C=O_{str}, qz ring), 1665 (C-N; C-C); 1580, 1574, 1471 (C–CH); 1426 mPh, 1410, 852, 744, 746 d(C–C), 647, 528 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ= 3.30 (1H, s, SH-qz) , 7.2-7.5 (4H, m, Ar-H, quinazolinone moiety), 8.40 (1H, dd, 5-H) , 8.53 (1H, d, 6-H), 8.62 (1H, s, 3-H) ppm. MS (EI): m/z = 304.33 (M^+). Elemental analysis:$C_{16}H_8N_4OS$, found C 62.87, H 2.07, N 19.11, Calcd. C 63.15, H 2.65, N 18.41.

*Typical procedure for synthesis of tetra [4(3H)-quinazolinone]phthalocyaninatozinc(II), [(qz)$_4$ZnPcs] (**4a-c**)*

A solution of 4(3*H*)-quinazolinone-phthalonitrile derivative **3a-c** (5.7 mg, 2.00 mmol) **3a**, (6.9 mg, 2.00 mmol) **3b**, (6.0 mg, 2.00 mmol) **3c** and zinc(II) acetate dihydrate (0.1 g, 0.05 mmol) in 10 mL of *n*-pentanol was stirred for 10 min under argon atmosphere. Then, DBU (5 mL, 0.05 mmol) was added and the mixture was refluxed for 20 h at 130-135 °C. The reaction mixture was cooled at room temperature and precipitated with methanol (25 mL). The solid was filtered and washed with water and dried under vacuum. The crude products were purified by column chromatography (silica gel, ethyl acetate/ *n*-hexane) in different ratios (7:3 / 8:2 v/v) yielding 18 mg (74%) of the pure PcZn **4a**, 21 mg (72%) of **4b**, and 18 mg (71%) of **4c**.

*Synthesis of Tetra [2-methyl-4(3H)-quinazolinone] phthalocyaninatozinc(II), [(Me-qz)$_4$ZnPc] (**4a**)*

IR (KBr): ν= 3075-3066 (Ar-H_{str}), 2975, 2870 (C-H_{str}, CH_3), 1672 (C=O_{str}, qz ring), 1658 (C-N; C-C); 1580, 1577, 1471 (C–CH); 1411 mPh, 1410, 855, 743, 745 d(C–C), 643, 522 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ= 1.30-1.6 (12H, m, CH_3-qz), 7.3-7.6 (16H, m, Ar-H, quinazolinone moiety), 8.25 (4H, dd, 5-H), 8.53 (4H, d, 6-H), 8.60 (4H, s, 3-H) ppm. UV–Vis (DMSO): λ_{max} (nm): 692,621, 358 sh, 290 nm. MS (FD): m/z = 1210.55 (M^+). Elemental analysis: $C_{68}H_{40}N_{16}O_4Zn$, found C 66.97, H 2.87, N 18.87, Calcd. C 67.47, H 3.33, N 18.51.

*Synthesis of Tetra [2-phenyl-4(3H)-quinazolinone] phthalocyaninatozinc(II), [(Ph-qz)$_4$ZnPc] (**4b**)*

IR (KBr): ν= 3073-3069 (Ar-H_{str}), 2973, 2870 (C-H_{str}, CH_3), 1678 (C=O_{str}, qz ring), 1655 (C-N; C-C); 1577, 1572, 1473 (C–CH); 1441 mPh, 1409, 859, 744, 747 d(C–C), 645, 520 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 7.1-7.3 (16H, m, Ar-H, quinazolinone moiety), 8.00 (4H, dd, 5-H) , 8.13 (4H, d, 6-H), 8.32 (4H, s, 3-H), 8.4-8.7 (20H, m, ph-qz) ppm. UV–Vis (DMSO): λ_{max} (nm): 687,619, 355 sh, 256 nm. MS (FD): m/z = 1458.83 (M^+). Elemental analysis: $C_{88}H_{48}N_{16}O_4Zn$, found C 66.90, H 3.67, N 19.01, Calcd. C 67.47, H 3.33, N 18.51.

*Synthesis of Tetra [2-mercapto-4(3H)-quinazolinone] phthalocyaninatozinc(II), [(SH-qz)$_4$ZnPc] (**4c**)*

IR (KBr): ν= 3073-3069 (Ar-H_{str}), 2973, 2870 (C-H_{str}, CH_3), 1678 (C=O_{str}, qz ring), 1655 (C-N; C-C); 1577, 1572, 1473 (C–CH); 1441 mPh, 1409, 859, 744, 747 d(C–C), 645, 520 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ= 3.35 (4H, s, SH-qz), 7.3-7.6 (16H, m, Ar-H, quinazolinone moiety), 8.20 (4H, dd, 5-H), 8.33 (4H, d, 6-H), 8.52 (4H, s, 3-H) ppm. UV–Vis (DMSO): λ_{max} (nm): 679, 610, 351 sh, 289 nm. MS (FD): m/z = 1282.68 (M^+). Elemental analysis: $C_{64}H_{32}N_{16}O_4S_4Zn$, Found C 59.04, H 2.07, N 16.98, Calcd. C 59.93, H 2.51, N 17.47.

Biological screening

n-vitro assay for anti-cancer activity

The synthesized ZnPcs were supplied to the Bioassay-Cell Culture Laboratory, National Research Centre, Cairo-Egypt for *in-vitro* antitumor screening on Lung adenocarcinoma (A549), hepatocellular carcinoma (HePG2) and caucasian breast adenocarcinoma (MCF7) (American Type Culture Collection). Cell viability was assessed by the mitochondrial dependent reduction of

yellow MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) to purple formazan [50,51] .

Procedure: All the following procedures were done in a sterile area using a Laminar flow cabinet biosafety class II level (Baker, SG403INT, and Sanford, ME, USA). HePG2 cell line was cultured in RPMI-1640 and MCF7 cell line was cultured in DMEM. Cells were plated in 96-well plates (having about 10000 cells /well). The plates are then incubated for 24 h in 37°C incubation and 5% CO_2 atmosphere before treatment with the compounds to allow attachment of cell to the wall of the plate. Tested compounds were dissolved in DMSO and different concentrations of the compounds under test were added to the cell monolayer. Triplicate wells were prepared for each individual concentration. Then the plate was incubated for 48 h in 37 °C incubator. After the completion of compound exposure, 40 μL of MTT solution (2.5 mg/mL) was added into each well for an additional 4h. Formazan was dissolved in 200 μL (10 %) Sodium Dodecyl Sulphate and the absorbance at λ= 495 nm was measured. The concentration of DMSO as a solvent for the different compounds was 0.1% in the culture medium used and was without any effect on cell growth. Cell viability at given compound concentration was calculated as the percentage of absorbance in wells with the compound-treated cells to that of vehicle control cells (100 %).

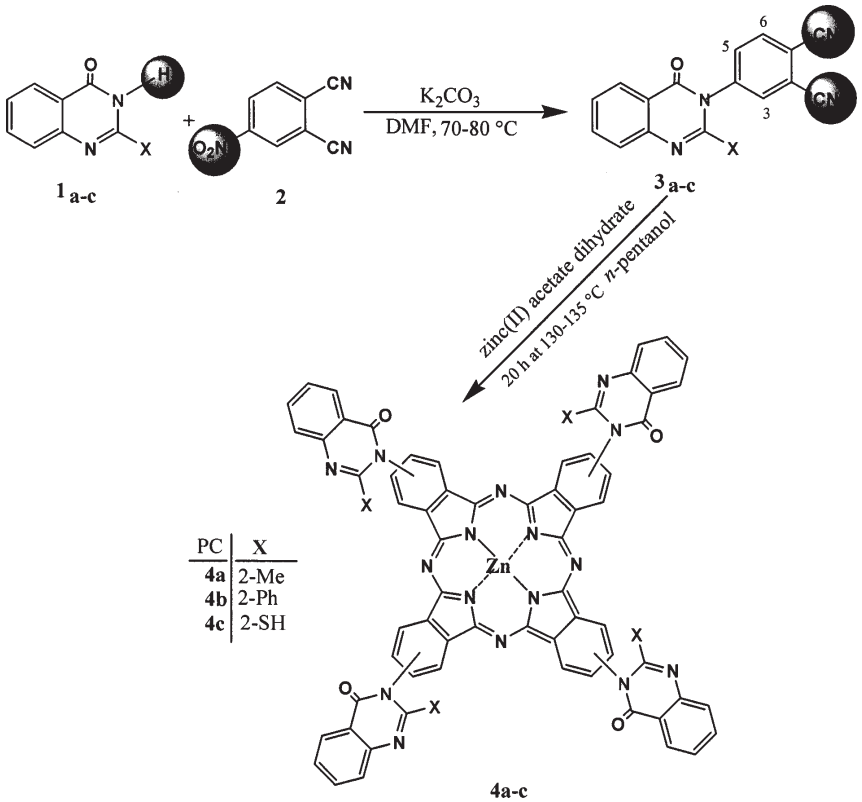
Results and discussions

Chemistry

Improved synthetic procedure for the newly Zn(II) phthalocyanines $(qz)_4$ZnPc **4a-c** substituted by 4(3*H*)-quinazolinone units has been described. They synthesized from their phthalonitrile derivatives **3a- c** by a two-step reaction procedure depicted in scheme1. First, a nucleophilic ipso-nitro substitution reaction of 4-nitrophthalonitrile 2 with 4(3*H*)-quinazolinone derivatives **1a-c** in dry DMF for 24 h at 70-80°C. Second, the cyclotetramerization reaction of 4(3*H*)-quinazolinone-phtalonitriles precursors **3a-c** with Zn(II)acetate in the presence of organic base DBU in *n*-pentanol for 20 h at 130-135°C, afforded the corresponding $(qz)_4$ZnPcs (**4a-c**) with 71-74% yield. The desired phthalocyanines were separated chromatographically as a mixture of regioisomers from the reaction mixture (scheme 1). The structures of the target compounds were confirmed using IR, ^{1}H NMR spectroscopy and mass spectra. The analyses are consistent with the predicted structures as shown in the experimental section.

The described synthetic method produced a mixture of four regioisomers with a 4(3*H*)-quinazolinone units at the 2- or 3-positions of each benzene ring in the $(qz)_4$ZnPc molecule. The formation of constitutional isomers [52] and the high-dipole moment that results from the 4(3*H*)-quinazolinone units at the periphery positions leads to increase the solubility of the obtained products **4a-c**.The IR spectra clearly indicated the formation of 4(3*H*)-quinazolinone-phtalonitriles precursors **3a-c** with the appearance of absorption bands at ν= 2235-2229 cm^{-1} (CN) and 1678-1675 (C=O_{str}, qz ring) and the appearance of (SH stretch) at 2598 cm^{-1} in case of **3c**. In the ^{1}H NMR spectrum of phtalonitrile **3a** the methyl protons appeared at δ= 1.50 (m) ppm, but for phtalonitrile **3a** the phenyl protons appeared at 8.50 (m) and for phtalonitrile **3c** the thiol protons appeared at δ= 3.30 (s) ppm, in addition to their mass spectra were consistent with the proposed structure.

Cyclotetramerization of the 4(3*H*)-quinazolinone-phtalonitriles precursors **3a-c** to the zinc(II)phthalocyanines $(qz)_4$ZnPcs **4a-c** were confirmed by the disappearance of the sharp (CN) vibration in their IR spectra. The ^{1}H NMR spectra of tetra-substituted zinc (II)phthalocyanines **4a-c** were obtained as expected. The ^{1}H NMR spectrum of $(Me\text{-}qz)_4$ZnPc **4a** indicated the methyl protons at δ= 1.30-1.6 ppm and the aromatic protons of Pc skeleton at 7.36 ppm. Also, the ^{1}HNMR spectrum of $(Ph\text{-}qz)_4$ZnPc **4b** indicated the aromatic protons of phenyl group at β= 8.4-8.7 ppm. In case of $(SH\text{-}qz)_4$ZnPc **4c**, thiol proton appeared at δ= 3.35 ppm (see experimental part).The electronic spectra of the studied zinc(II)phthalocyanines $(qz)_4$ZnPcs **4a-c** showed characteristic absorption bands in the Q band region at around 692, 687, and 679 nm, respectively, in



Scheme 1. The synthetic pathway for the preparation of zinc(II)phthalocyanines (**4a-c**)

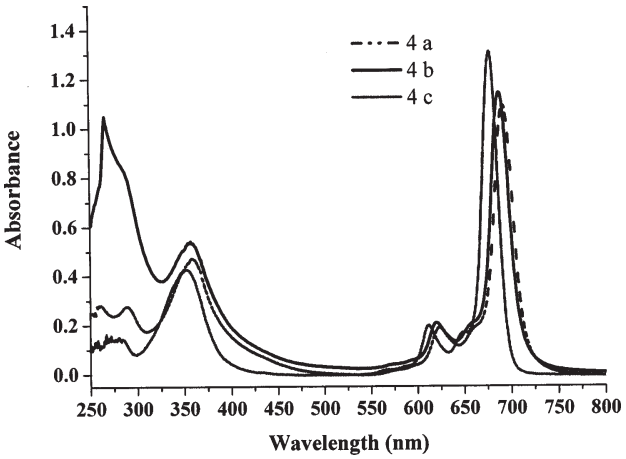


Fig. 1. The absorption spectra of (qz)4ZnPcs **4a-c** in DMSO

as LC50 (μM) which is the lethal concentration of the ZnPc which cause death of 50% of the cells in 24 h.

In case of human breast adenocarcinoma (MCF-7), the studied zinc(II)phthalocyanine (SH-qz)$_4$ZnPc **4c** (IC50= 3.65 μM) more potent than Doxorubicin (IC_{50}= 3.78 μM), while **4a** (IC50= 5.22 μM) and **4b** (IC50= 4.53 μM) found to be slightly less effective than the reference drug. In case of hepatocellular carcinoma (HEPG2), the studied zinc(II)phthalocyanine (SH-qz)$_4$ ZnPc **4c** exhibited an excellent activity with IC_{50} values 3.21 μM, respectively more potent than the reference drug (Doxorubicin, IC50 value 4.61 μM), while compounds **4a** and **4b** were found to be less effective than the reference drug with IC50 values (5.21 and 21.6 μM), respectively (table 1). The newly synthesized zinc(II) phthalocyanines (qz)$_4$ZnPcs **4a–c** showed activity against human lung adenocarcinoma (A549) with IC_{50} values 25.6, 31.5 and 6.05 μM, respectively (table 1), less potent than the reference drug (Doxorubicin, IC50 value 2.61 μM) (fig. 2).

Compound NO.	Cytotoxicity [a,b] (IC_{50}, μM)		
	MCF7	HEPG2	A549
(Me-qz)$_4$ZnPc **4a**	5.22	5.21	25.6
(Ph-qz)$_4$ZnPc **4b**	4.53	21.6	31.5
(SH-qz)$_4$ZnPc **4c**	3.65	3.21	6.05
Doxorubicin	3.78	4.61	2.61

[a] IC_{50}, compound concentration required to inhibit tumor cell proliferation by 50%.
[b] Values are means of three experiments.

Table 1
ANTICANCER ACTIVITY (IC_{50}, μM) OF THE SYNTHESIZED ZINC(II)PHTHALOCYANINES (qz)$_4$ZnPcs **4a–c** AGAINST HUMAN CANCER CELL LINES (MCF7, HEPG2 AND A549)

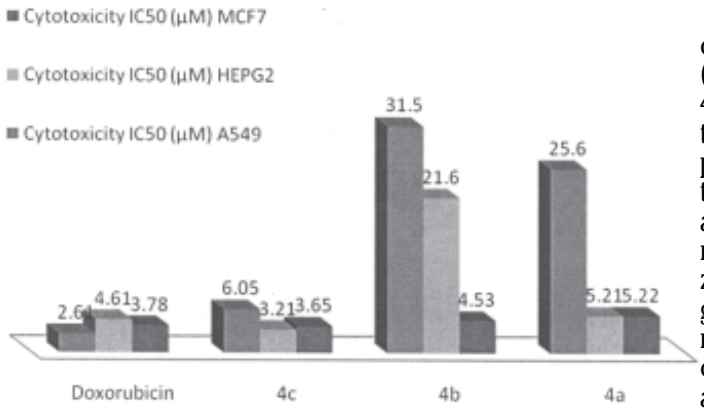


Fig. 2. Anticancer activity (IC_{50}, μM) of the synthesized zinc(II)phthalocyanines (qz)$_4$ZnPcs 4a–c against human cancer cell lines (MCF7, HEPG2 and A549)

DMSO. The B-bands were observed at around 358, 355, and 351 nm, respectively, (fig. 1). The spectra showed monomeric behavior evidenced by a single (narrow) Q band, typical of metallated phthalocyanine complexes in DMSO [53].

In-vitro anticancer screening

Three ZnPc derivatives namely; **4a–c,** were selected to be evaluated for their *in vitro* cytotoxic effect via the standard Doxorubicin HCl as a reference drug against a panel of three human tumor cell lines namely; hepatocellular carcinoma (HePG2), lung adenocarcinoma (A549), and breast adenocarcinoma (MCF7) using MTT assy method [62,63].The results are presented in table 1

Detailed interpretation of the obtained results and considering preliminary structure– activity relationship (SAR) showed that, zinc(II)phthalocyanine (SH-qz)4ZnPc **4c** that contains four mercapto groups (SH) attached to the 4(3*H*)-quinazolinone ring system at position 2 in its phthalocyanine skeleton, was the most active member in this study which revealed antitumor activity against MCF-7 and HEPG2 human tumor cell line (3.65 and 3.21μM, respectively). Replacement of mercapto groups in zinc(II)phthalocyanine (qz)4ZnPc **4c** with methyl or phenyl groups as in case of **4a**& **4b** are associated with remarkable decrease in the potency against the two tumors cell lines. So, compound **4c** showed promising anticancer activity.

Conclusions

The present study reports the successful synthesis of the title zinc(II)phthalocyanine (qz)$_4$ZnPcs **4a-c** in good yields via cyclotetramerization reactions of 4(3H)-quinazolinone-phtalonitriles precursors **3a-c**. The results indicated that the studied (qz)$_4$ZnPcs **4a-c** possessed a broad spectrum of activity against liver and breast cancer. Preliminary study of the structure–activity relationship revealed that electronic factors in the 4(3*H*)-quinazolinone moiety that attached to the phthalocyanine molecule have a great effect on the antitumor activity of these Zinc(II) phtalocyanines. This proves the novelty of biological efficiency of our new (qz)$_4$ZnPcs **4a-c** series. In MTT cytotoxicity studies, the (SH-qz)$_4$ZnPc **4c** that contains 2-mercapto-4(3*H*)-quinazolinone group attached to the phthalocyanine molecule were found to possess potent activity against the two tested cancer cell lines. In HEPG2 and MCF-7 cell linnets the antitumor effect showed in the

order **4c > 4b> 4a**.The resulted ZnPcs **4a-c** will be subject to further study on the DNA level to know their mode of actions.In the light of above considerations and from preliminary results the future work will be focused on the synthesis of zinc(II)phtalocyanine derivatives with 4(3*H*)-quinazolinone units. In addition, their application in the photodynamic therapy of cancer will be studied.

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