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Synthesis, biological evaluation, and docking studies of various β-substituted porphyrin conjugates embedded with N-containing heterocycles

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Abstract

A new methodology for the synthesis of some new β-porphyrin heterocyclic compounds containing nitrogen derivatives **10**, **12**, **13**, **15**, **17**, **19**, **21**, **22**, **25**, **27**, and **29** was screened for their cytotoxic activities. Both elemental and spectral analyses were used to confirm the structures of new compounds. Compounds **22**, **27**, and **21** exhibited very strong activity against the HepG2 cell line. Investigation of the binding between porphyrin **22** and the binding site of telomerase was performed by molecular docking.

1 | INTRODUCTION

Porphyrin derivatives are known as synthesizing drugs and are widely used as anticancer agents, especially their application for PDT "photodynamic therapy" [1] and BNCT "boron neutron capture therapy" [2]. Such therapies need activation of the tumor with light or low-energy neutrons, respectively.

Some porphyrin derivatives can selectively be localized in tumor tissues, this may be due to their ability for carrier biomolecules and/or biological members [3]. Some positively charged porphyrins showed strong interaction with negatively charged functions of proteins, DNA, and RNA to be active toward PDT [4–7].

Moreover, aromatic nitro compounds are found to be effective electron-affinity ratio sensitizers [8]. Also, compounds having nitro and amino groups can be conjugated with biologically active compounds [9–15].

Nitration of metallo porphyrinates by radical conditions gave mononitrate the macrocycle at the β-position by using a variety of oxidants [16,17]. Nitration by radical condition [18] and catalyzed by sulfuric acid [19] of free-base porphyrin are published to yield β and some meso substitution products. No nitration of phenyl group was observed in these studies.

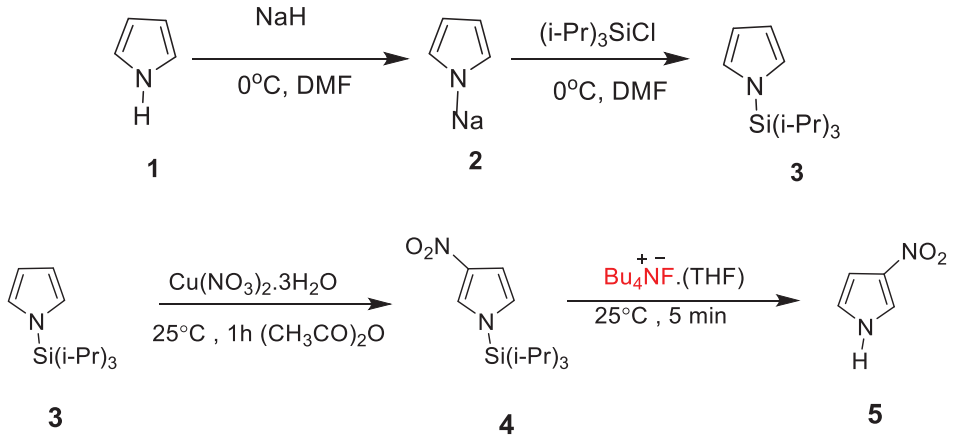
Moreover, cyanoacetamide derivatives are considered one of the most significant starting materials for the synthesis of different heterocyclic derivatives [20–22]. From these above facts and in continuation to our interest in developing an attractive, and alternative synthesis of mono(heteroaryl)tetraphenyl porphyrin through the reaction of β-cyanoacetamide moiety in compound **8** with bifunctional reagents and evaluation of their biological activity as antitumor reagents.

2 | RESULTS AND DISCUSSION

2.1 | Chemistry

Therefore, 3-nitropyrrole (**5**) was prepared by the following reaction sequence in which starting with the reaction of pyrrole (**1**) with sodium hydride in dimethylformamide (DMF) at 0°C to give N-sodium salt (**2**) [23]. Compound **2** was subjected to react with triisopropylsilyl chloride to give 1-(triisopropylsilyl) pyrrole (**3**) [23]. When compound **3** was reacted with cupric nitrate trihydrate in acetic anhydride at room temperature for 1 h afforded 3-nitro-1-(triisopropylsilyl) pyrrole (**4**) [23]. Compound **4** was converted to 3-nitropyrrole (**5**) by reaction with tetrabutylammonium fluoride in THF [23] (Scheme 1).

The main problem in porphyrin synthesis is its low yields (6%–20%) although different trials to enhance the yields of porphyrins are reported [24–26]. Recently,



SCHEME 1 Synthesis of 3-nitropyrrole from pyrrole

Fadda et al. [27,28] reported a new methodology, which yields 70%–80% yield. In this case, Fadda et al. used DMF "*N*,*N*-dimethylformamide" as a solvent and capping reagent. The capping mechanism prevents the pyrrole polymerization process. The intermediate DMF-pyrrole reacts with another pyrrole moiety to give the corresponding porphyrinogen. When each time pyrrole is added, loss of DMF molecule was appropriate as a good leaving group [27,28]. In this work, we report here the synthesis of free-base porphyrin **6** in high yields (75%). Therefore, it was found that 2,7,12,17-tetranitro-5,10,15,20-tetraphenylporphyrin (**6**) was synthesized from the reaction of 3-nitropyrrole (**5**) with benzaldehyde according to the reported method by Fadda et al. [27,28]. The synthesized porphyrin was well characterized by spectral data. The ^{1}H NMR spectra, porphyrin derivative 6 showed C_2-H, C_8-H, C_{13}-H, and C_{18}-H protons appeared at δ 6.61, 7.54, 7.74, and 9.14 ppm, respectively. The endocyclic NH showed two bands at δ 8.97 and 9.74, respectively, besides aromatic protons appeared at δ 7.17–7.74 ppm. Compound **6** displayed in its ^{13}C NMR characteristic signals at δ 119.2 for C-2, 152.1 for C-7 and C-17, and carbon atom attached to nitro group appeared at δ 142.4 ppm (Scheme 2).

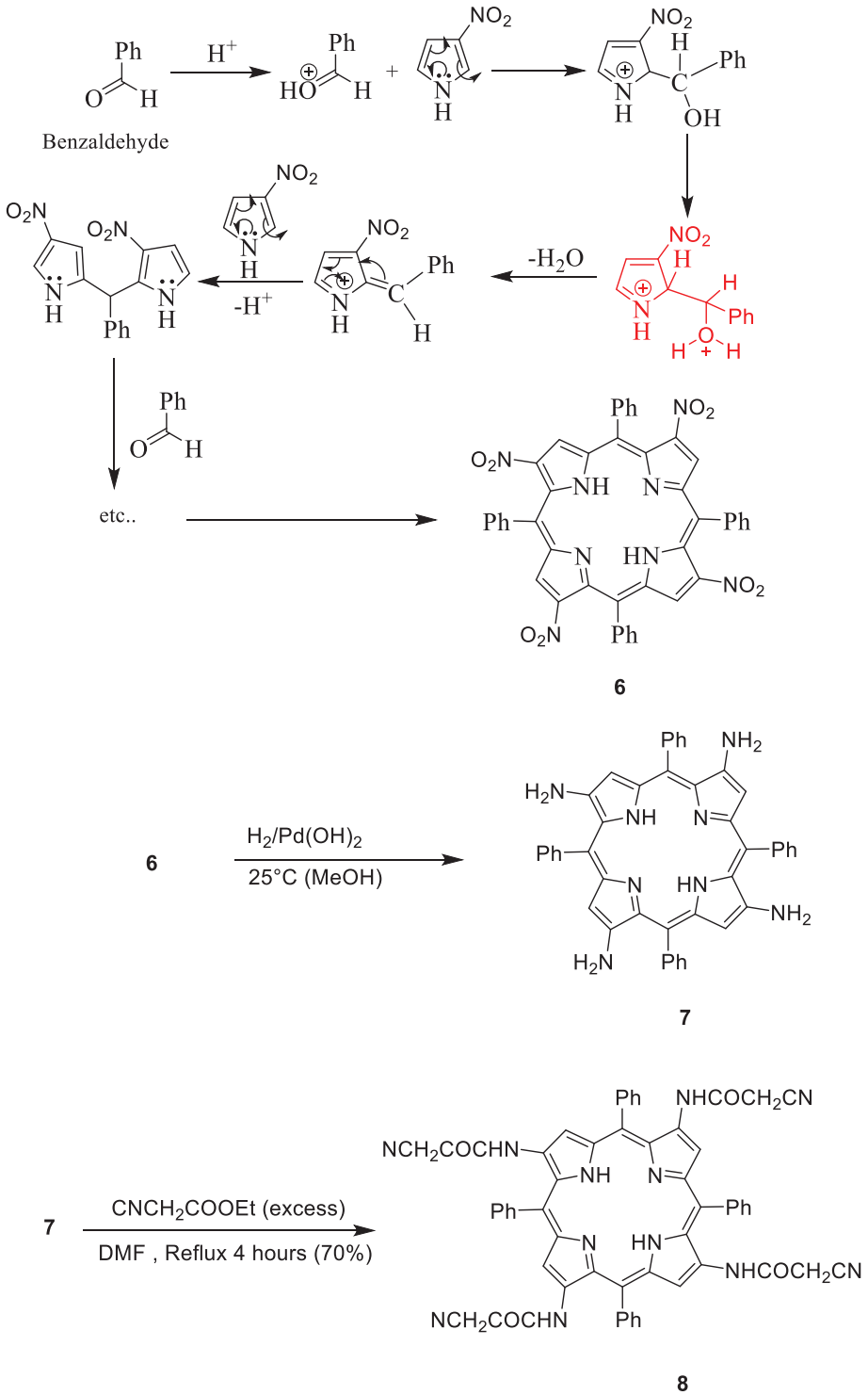
Regarding the low solubility of the nitro porphyrin (**6**), it was reduced into the corresponding amino porphyrin (**7**) by tin(II) chloride and HCl in yield 60%, according to the previously reported work [29,30]. ^{13}C NMR of compound **7** showed characteristic signals at δ 157.1 for C-2, 144.8 for C-7 and C-17, and at 129.2 for C-12, respectively. ^{1}H NMR of compound **7** displayed signals at δ 3.83 (C_2-NH_2), 4.79 (NH_2 protons at C_7 and -C_{17}), and at δ 6.79 for NH_2 protons at C_{12}, respectively. Moreover, four singlet signals at δ 6.35, 4.98, 5.18, and 6.58 appeared attributable to protons at C_3, C_8, C_{13}, and C_{18}, respectively (Scheme 2).

As a continuation of our interest in the chemistry of cyanoacetamide [20–22,31–37], *N*,*N*′,*N*″,*N*‴-(5,10,15,20-tetraphenylporphyrin-2,7,12,17-tetrayl)tetrakis (2-cyanoacetamide) (**8**) was achieved by heating compound **7** with cyanoacetic acid in presence of drops of acetic anhydride. The structure of **8** was elucidated by spectroscopic data. The IR spectrum revealed the disappearance of the band due to NH_2 groups, instead showed bands at 3300, 3150, 2220, and 1685 cm^{-1} corresponding to NH, C≡N, and CO amidic functions, respectively. ^{1}H NMR showed a characteristic signal at δ 3.50 ppm due to CH_2 protons (Scheme 2).

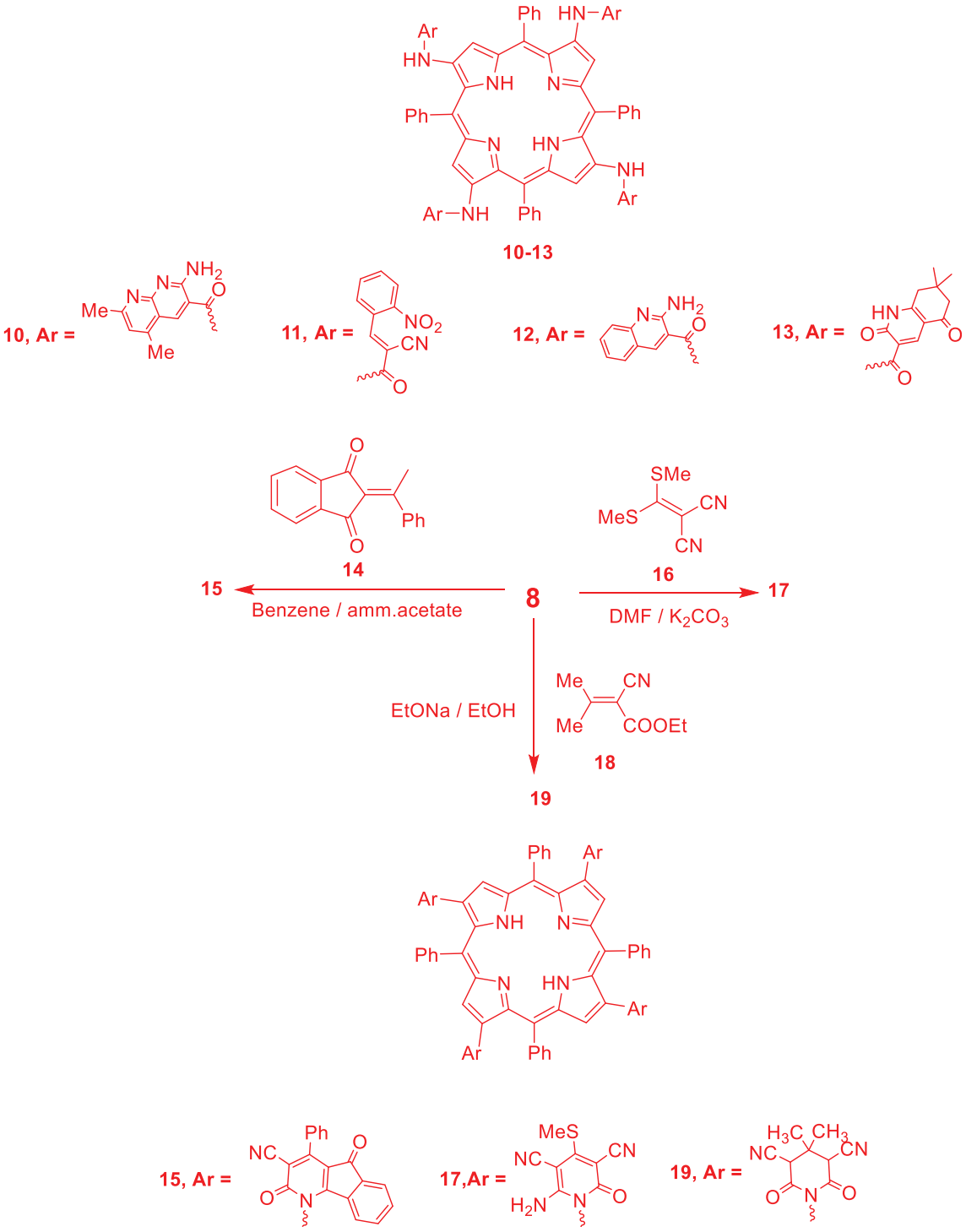
1,8-Naphthyridine derivatives showed mild activity toward murine p388 leukemia when changes were carried out at N-1 and N-7 positions [38,39]. These above facts and in continuation of previous work from our lab in 1,8-naphthyridine derivative [40], we synthesized new 1,8-naphthyridine derivative **10** by Friedlander cyclocondensation of **8** with nicotine aldehyde **9** in refluxing ethanol containing piperidine as a catalyst. ^{1}H NMR of **10** displayed signals at δ 2.48, 2.88, 5.51, 5.77, 6.27, 6.51, 7.24–7.45, 8.11, 8.48, 8.88, 9.55, 9.65, and 11.00 ppm corresponding to naphthyridine two methyl protons, C_8-H, C_{13}-H, (pyrrole protons), NH_2 protons, C_3-H pyrrole, aromatic protons, C_5-H naphthyridine proton, NH endocyclic, NH exocyclic, 2NH exocyclic, NH endocyclic, and exocyclic NH proton, respectively (Scheme 3).

Many reported works showed that quinoline derivatives had been evaluated for their antibacterial and antifungal activities and were found active against *Vibrio cholerae* and *Escherichia coli* [41]. Therefore, these facts prompted us to synthesize new porphyrin containing quinoline moiety. So it has been found that cyanoacrylamide derivative **11** was obtained by condensation of **8** with o-nitrobenzaldehyde in refluxing ethanol with piperidine as a catalyst, which on reductive cyclization of **11** with iron in boiling acetic acid furnished quinoline **12**. Structures of **11** and **12** were established by spectral data. IR spectrum of **11**

SCHEME 2 Synthesis of 3-nitropyrrole from pyrrole



displayed stretching vibration bands at 3310, 3120, 2220, 1685, 1620, 1600, 1530, and 1350 cm^{-1} corresponding NH, CN, CO, C=N, C=C, symmetric and asymmetric NO_2 function groups. The ^1H NMR spectrum showed a characteristic singlet signal at δ 8.85 due to olefinic protons. The IR spectrum of compound **12** showed the NH_2 absorption band at 3370–3300 cm^{-1}. The ^1H NMR spectrum displayed a singlet signal at δ 8.31 ppm due to the C_4-H quinoline ring. In a two-step reaction mechanism using microwave irradiation, three-components condensation of dimedone, Dimethylformamide/Dimethylacetal (DMF/DMA), and compound **8** gave the corresponding 2-pyridone derivative **13**. ^1H NMR of compound **13** displayed, some selected singlet, signals at δ 1.11, 2.27,2.85, 7.27, 7.85, 10.75, and 12.58 corresponding to two methyl protons of dimedone ring, CO-CH_2, CH_2, C_{17}-H, C_4-H



SCHEME 3 Synthesis of 3-nitropyrrole from pyrrole

pyridine ring, exocyclic NH, and NH pyridine ring, respectively (Scheme 3).

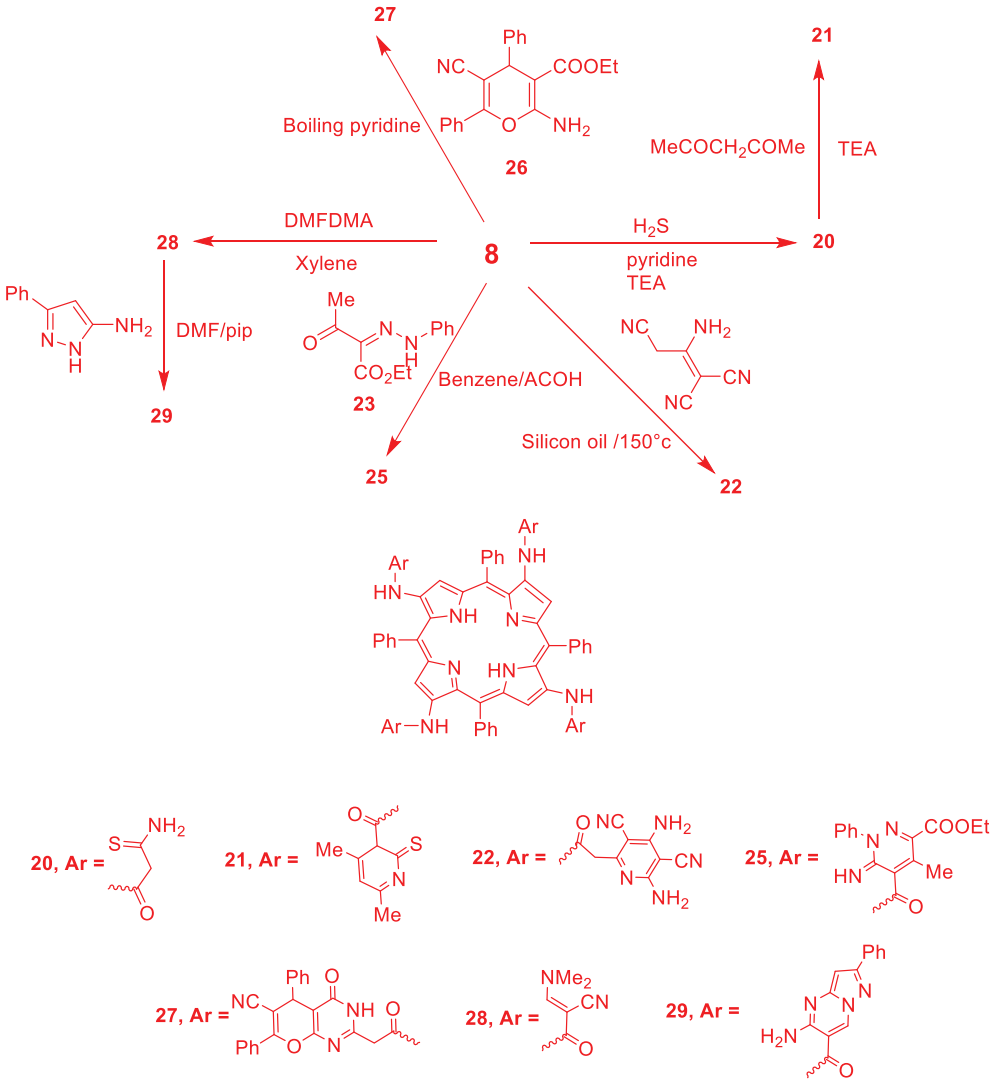
Due to the importance of pyridine derivatives as antifungal, antiviral, antioxidant, antidiabetic, anticancer, antimalarial, anti-inflammatory, and antiamoebic agents [42–46], we decided to synthesize some new porphyrin carrying pyridine moiety. So, a convenient and simple route for 2-pyridone derivative was achieved by reaction of cyanoacetamide **8** with 2-arylmethyleneindan-1,-3-dione (**14**) in refluxing benzene in the presence of ammonium acetate afforded 2-pyridone derivative **15**. ^{13}C NMR of **15** showed signals at 115.8, 136.0, and 162.9 ppm characteristic for CN, CO, and N-CO carbon atoms, respectively (Scheme 3).

Compound **8** reacts with ketene dithioacetal **16** in refluxing DMF catalyzed by anhydrous potassium carbonate gave pyridine-2-one derivative **17**. ^{1}H NMR of compound **17** displayed signals at δ 2.80 and 6.58 due to S-CH_3 and NH_2 protons (Scheme 3).

On the other hand, the reaction of **8** with ethyl 3-cyano-2-methyl-but-2-enate **18** in presence of sodium ethoxide furnished pyridine derivative **19**. ^{1}H NMR of compound **19** showed a characteristic three singlet signals at δ 0.99 and 3.11 ppm due to two methyl protons and two CH protons, respectively (Scheme 3). Reaction of compound **8** with hydrogen sulfide afforded 3-amino-N-(5-cyano-2-phenyl-6-[p-tolyl]pyrimidine-4-yl)-3-thioxopropanamide (**20**). ^{1}H NMR of compound **20** displayed two singlet signals at δ 3.77 and 6.85 ppm referred to CH_2 and NH_2 protons, respectively. The ^{13}C NMR showed signals at 53.2 corresponding to CH_2 carbon atom. Treatment of **20** with acetylacetone in boiling ethanol in presence of triethylamine as catalyst affords pyridine-2-thione derivative **21**. ^{1}H NMR referred signals at δ 1.77, 2.27, 3.11, 5.95, and 10.85 ppm corresponding to C_4-CH_3, C_2-CH_3, C_5-H pyridine, C_3-H pyridine, and NH, respectively (Scheme 4).

Heating of **8** with malononitrile dimer in pressure tube in silicon oil furnished pyridine derivative **22**. The same product was obtained when **8** was boiled with two moles of malononitrile in refluxing ethanol containing a catalytic amount of piperidine. Moreover, a reaction of **8** with ethyl-2-arylhydrazono-3-buterate (**23**) in boiling benzene-acetic acid mixture yielded pyridazine **25**. The reaction proceeded via the intermediate **24**. ^{1}H NMR of **25** displayed a characteristic triplet and quartet signals at δ 1.25 and 4.11 due to ethyl protons of the ester group (Scheme 4).

Reaction of cyanoacetamide **8** with 2-amino-3-carboxy-5-cyano-4,6-diphenyl-4*H*-pyran (**26**) in boiling pyridine affords dihydropyrano-[2,3-*d*]-pyrimidinone (**27**). Also, the reaction of **8** with DMF/DMA in refluxing dry xylene gives enaminonitrile **28**. Treatment of **28** with 5-phenyl-3-amino pyrazole in DMF and few drops of



SCHEME 4 Synthesis of 3-nitropyrrole from pyrrole

piperidine furnished pyrazolo-[1,5-*a*]pyrimidine (**29**). IR spectrum of **29** showed absorption band at 3360, 3100, 1675, and 1610 cm^{-1} due to NH_2, NH, CO, and C=N function groups (Scheme 4).

2.2 | Biological evaluation

2.2.1 | Evaluation of antitumor and cytotoxicity

Anti-cancer activity in vitro against three cell lines, "hepatocellular carcinoma (HePG-2), colon cancer HCT-116, and mammary gland breast cancer (MCF-7)" were tested for all the new porphyrin derivatives. Growth inhibitory concentration values (IC_{50}) were used to reflect the anticancer activity (Table 1). Compound **22** displayed very strong activity toward all tested cell lines with an IC_{50} value of 9.62 ± 0.9, 5.16 ± 1.4, and 5.05 ± 1.6 μg/ml.

Compound **27** showed the optimal result (high activity) with an IC_{50} value 10.13 ± 0.8, 7.49 ± 0.6, and 7.13 ± 0.6 μg/ml for the three cell lines. Compound **10** displayed very high activity against HCT-116 cell line with an IC_{50} value of 9.16 ± 1.5 μg/ml. Compound **21** showed very high activity toward MCF-7 with an IC_{50} value of 9.91 ± 0.9 μg/ml. Compound **10** showed very high activity toward HCT-116 cell line, compounds **12** and **13** displayed high activity toward HePG-2 cell line with IC_{50} values 17.08 ± 1.6 and 16.73 ± 1.4 μg/ml, compound **20** exhibited high activity toward the three cell lines. Derivative **21** displayed very high activity toward the MCF-7 cell line and high activity against the two other cell lines with IC_{50} values 9.91 ± 0.9, 11.64 ± 1.2, and 16.44 ± 1.6 μg/ml, respectively. Compound **25** showed very strong activity against the HePG-2 cell line with an IC_{50} 16.06 ± 1.5 μg/ml, while compound **29** displayed strong activity against both HePG-2 and HCT-116. The other rest of the compounds displayed moderate-weak activity toward the tested cell lines.

TABLE 1 Cytotoxicity (IC_{50}) of the tested compounds on different cell lines

	IC_{50} (μg/ml)[a]		
Compound no.	**HePG2**	**HCT-116**	**MCF-7**
6	64.13 ± 3.6	70.46 ± 3.8	67.16 ± 3.9
7	44.89 ± 3.1	28.44 ± 1.6	40.53 ± 2.8
8	31.12 ± 2.3	21.87 ± 1.7	39.5 ± 2.7
10	13.78 ± 1.1	9.16 ± 1.5	12.78 ± 1.2
11	23.85 ± 1.9	50.92 ± 2.9	43.88 ± 3.1
12	17.08 ± 1.6	29.42 ± 2.3	28.13 ± 2.2
13	16.73 ± 1.4	28.46 ± 1.8	28.07 ± 1.5
15	44.89 ± 3.1	38.46 ± 2.3	53.2 ± 3.6
17	47.34 ± 3.3	33.42 ± 2.3	41.53 ± 2.8
19	25.94 ± 2.2	35.19 ± 2.4	51.32 ± 3.5
20	13.78 ± 1.1	19.55 ± 1.5	12.98 ± 1.2
21	11.64 ± 1.2	16.44 ± 1.6	9.91 ± 0.9
22	9.62 ± 0.9	5.16 ± 1.4	5.05 ± 1.6
25	16.06 ± 1.5	21.87 ± 1.7	26.33 ± 2.0
27	10.13 ± 0.8	7.49 ± 0.6	7.13 ± 0.6
28	31.12 ± 2.3	28.46 ± 1.8	33.88 ± 3.1
29	14.88 ± 1.3	11.24 ± 1.1	28.13 ± 2.2
DOX	4.50 ± 0.2	5.23 ± 0.3	4.17 ± 0.2

Abbreviation: DOX, doxorubicin.

[a]IC_{50} (μg/ml): 1–10 (very strong); 11–20 (strong); 21–50 (moderate); 51–100 (weak); above 100 (noncytotoxic).

2.2.2 | Structure–activity relationship (SAR)

1. Compound **22** with IC_{50} (9.62 ± 0.9 and 5.05 ± 1.6) against HePG2 and MCF-7, respectively, showed the presence of four sets of disubstituted amino groups meta to each other exposed out to the celling of the DNA groove enhanced the hydrophilic recognition.
2. Compound **27** with IC_{50} (10.13 ± 0.8 and 7.13 ± 0.6) against HePG2 and MCF-7, respectively, showed four well-distributed pyrimidine-one fused rings that showed considerable hydrophilic interaction with the backbone. However, the diphenyl rings substitution on the pyrane fused ring performed high hydrophobic interactions with the out-pocket surface.
3. Compound **21** with IC_{50} (11.64 ± 1.2 and 9.91 ± 0.9) against HePG2 and MCF-7, respectively, showed the presence of function 2-thiopyridine showed proper electrostatic balance with the two methyl functions. However, shrinking the linker by using amido function instead of acetamido spacer dwindles the overall biological effect.
4. Compound **10** with IC_{50} (13.78 ± 1.1 and 12.78 ± 1.2) against HePG2 and MCF-7, respectively, has key functions including the dimethyl-substituted pyrido-pyridine in addition to the free amino function that present neighbor to the amido linkage augmenting the electrostatic filed showed a proper biological effect.
5. Compound **20** with IC_{50} (13.78 ± 1.1 and 12.98 ± 1.2) against HePG2 and MCF-7, respectively, has a significant donating open chain; thiocarbamoyl acetamide that enhances the biological effect.
6. Compound **29** with IC_{50} (14.88 ± 1.3 and 28.13 ± 2.2) against HePG2 and MCF-7, respectively, amido and amino substitutions of the pyrazolopyrimidine

enhance the electron donor interaction with the surrounding DNA base pairs. While the outer phenyl function balances the lipophilic interaction.

7. Compound **25** with IC_{50} (16.06 ± 1.5 and 26.33 ± 2.0) against HePG2 and MCF-7, respectively, that has both of ethyl carboxylate side chain of the pyridazine ring and the imino-function are performing proper donor–acceptor.
8. Compound **7** with IC_{50} (44.89 ± 3.1 and 40.53 ± 2.8) against HePG2 and MCF-7, respectively, which contains amino group, in comparison with compound **6** that has nitro substitution, compound **7** showed a more proper biological effect that may correlate with the enriched amino electrostatic field.
9. Compound **15** with IC_{50} (44.89 ± 3.1 and 53.2 ± 3.6) against HePG2 and MCF-7, respectively, showed rigidity of the indenopyridinone fused ring decline the recognition and inturn drop the biological effect.
10. Compound **6** with IC_{50} (64.13 ± 3.6 and 67.16 ± 3.9) against HePG2 and MCF-7, respectively, which contains nitro electron-withdrawing group showed mini electrostatic recognition within the DNA groove.

2.2.3 | Docking antitumor active porphyrin **22**

Molecular docking of compound **22** into the binding site of telomerase was expressed using Discovery Studio 2020 [47]. The three-dimensional structures of compound **22** were designed using Chem. Draw 3D Ultra 11.0 software. Using compute module to perform Gasteiger–Hückel, charges of ligands were assigned. The molecular charged structure was energetically minimized by using AMBER with 100 iterations and a minimum RMS gradient of 0.10. The template (PDB code: 2A5R) was obtained from the RCSB protein data bank.

2.2.4 | Preparation of the telomerase protein

The starting coordinates of the X-ray crystal structure of a complex tetra(4-*n*-methylpyridyl) porphyrin with monomeric parallel-stranded DNA Tetraplex (PDB code 2A5R: in complex with the POH 25A) that retrieved from the RCSB protein data bank of Brookhaven National Laboratory (Figure 1).

2.2.5 | Porphyrin interaction with telomerase

The availability of a high-resolution crystallographic structure of the human telomerase enzyme facilitated the research considering the small molecules with potential telomerase inhibition. In this study, we aimed to find efficient G-quartets ligands that would be able at the same time to discriminate between different forms of nucleic acids to be selective as telomeric DNA.

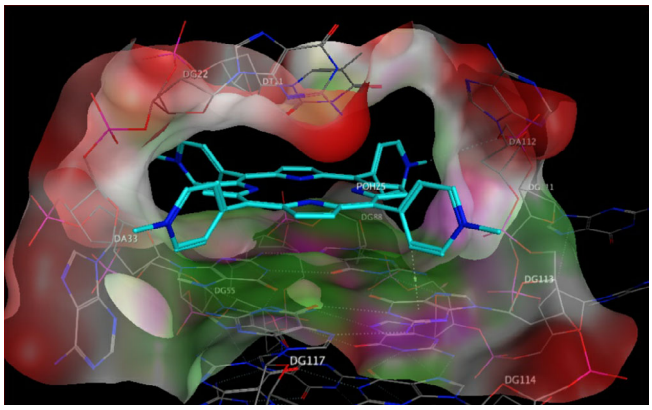


FIGURE 1 Putative docking interaction of ligand POH 25A that was in complex of G-quartet DNA (PDB code 2A5R)

Large porphyrin ligand **22** perfectly overlaps with G-quartets and professionally capped the quadruplex groove.

2.2.6 | Docking studies of compound **22**

Telomerase and compound **22** have strong complementarities as it sandwiched between the inside the major groove of telomeric DNA as the reference ligand **POH 25A** in addition to the two of the phenyl groups and two the substituted pyridines merged out to seal off the groove entry (Figure 2).

3 | CONCLUSION

A series of new β-substituted porphyrin conjugates embedded with N-containing heterocycles derivatives were synthesized from condensation reaction of 3-nitropyrrole with benzaldehyde in good yield, which followed by reduction to its corresponding amino derivative (**7**). Cyanoacetamide (**8**) was achieved by heating compound **7** with cyanoacetic acid in presence of drops of acetic anhydride with the hope of discovering a new structure that leads to serving as potent antitumor agents. Some β-substituted porphyrins were screened for them in vitro biological activities showed good antitumor activities. Compound **22** displayed very strong activity toward all tested cell lines with an IC_{50} value of 9.62 ± 0.9, 5.16 ± 1.4, and 5.05 ± 1.6 μg/ml. The obtained results may be related to the presence of four sets of disubstituted amino

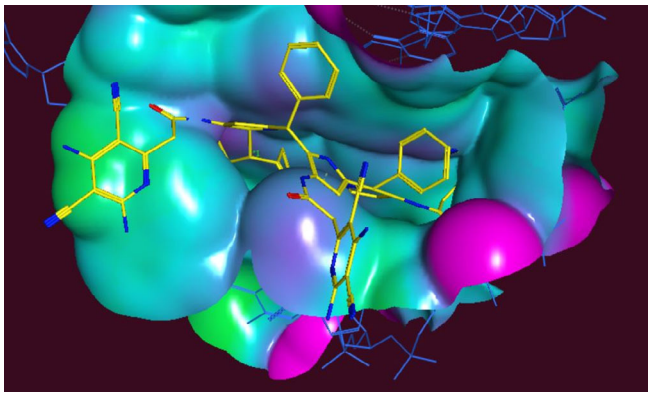


FIGURE 2 Top view of the docked compound **22** where two of the phenyl groups and two the substituted pyridines merged out to seal off the groove entry

groups meta to each other exposed out to the celling of the DNA groove enhanced the hydrophilic recognition.

4 | EXPERIMENTAL

4.1 | Chemistry

Preparation of 1-(triisopropylsilyl) pyrrole (3)

Compound **3** was obtained as previously reported [23], boiling point (120)°C/10 mm. (Lit. (125)°C/11 mm, mp. (5)°C [23]).

Preparation of 3-nitro-1-(triisopropylsilyl) pyrrole (4)

Compound **4** was obtained as previously reported, mp. (50)°C (Lit. 52–54°C [23]).

Preparation of 3-nitro pyrrole (5)

It was prepared by desilylation of compound **4** as described in previous work mp. (100)°C, in 70% yield (Lit. 95–96°C [23]).

Synthesis of 2,7,12,17-tetranitro-5,10,15,20-tetraphenylporphyrin (6)

It was prepared according to Fadda et al. [27,28] method.

Yield 72%; mp. < (300)°C; IR (KBr): ν/cm^{-1} = 3150 (NH), 1610 (C=N), 1590 (C=C), 1530, 1350 (symm., asymm. NO_2); ^1H NMR (DMSO-d_6): δ (ppm): 6.61 (s, 1H, C_3-H),7.15–7.70 (m, 20 H, Ar-H), 7.54 (s, 1H, C_8-H), 7.74 (s, 1H, C_{13}-H), 8.97 (s, 1H, N-H), 9.14 (s, 1H, C_{18}-H), 9.74 (s, 1H, N-H); ^{13}C NMR (DMSO-d_6): δ (ppm): 103.1, 109.1, 116.7, 119.2 (C_2), 125.5, 127.8, 128.6, 129.2, 132.1, 134.6, 135.7, 136.7, 138.5, 142.4 (C_{12}), 150.1, 152.1 (C_7 and C_{17}), 156.8, 161.1. MS (EI, 70 eV) m/z (%) = 794 (M^+, 100), 795 ($M^+ + 1$, 50). Anal calcd for $C_{44}H_{26}N_8O_8$ (794.74): C, 66.50; H, 3.30; N, 14.10%. Found: C, 66.22; H, 3.16; N, 13.95%.

Synthesis of 2,7,12,17-tetraamino-5,10,15,20-tetraphenylporphyrin (7)

The reduction of compound **6** was conducted according to the reported work [29,30].

62% yield; mp. < (300)°C; IR (KBr): ν/cm^{-1} = 3410 (NH_2), 3100 (NH); ^1H NMR (DMSO-d_6): δ (ppm): 3.83 (s, 2H, C_2-NH_2), 4.79 (s, 4H, C_7-NH_2, C_{17}-NH_2), 4.98 (s, 1H, C_8-H), 5.19 (s, 1H, C_{13}-H), 6.35 (s, 1H, C_3-NH_2), 6.58 (s, 1H, C_{18}-H), 6.79 (s, 2H, C_{12}-NH_2), 7.17–7.41 (m, 20H, Ar-H). ^{13}C NMR (DMSO-d_6): δ (ppm): 101.5, 103.1, 104.8, 105.1, 124.2, 127.8, 127.9, 128.6, 129.2, 132.1, 134.4, 135.7, 136.7, 137.5, 142.4, 144.8, 150.1, 155.7, 157.1, 161.1. MS (EI, 70 eV) m/z (%) = 674 (M^+, 100), 675 ($M^+ + 1$, 47). Anal calcd for $C_{44}H_{34}N_8$ (674.81): C, 78.32; H, 5.08; N, 16.61%. Found: C, 78.11; H, 4.98; N, 16.55%.

Synthesis of *N*,*N*′,*N*″,*N*‴-(5,10,15,20-tetraphenylporphyrin-2,7,12,17-tetrayl)tetrakis (2-cyanoacetamide) (8)

78% yield; mp. < (300)°C; IR (KBr): ν/cm^{-1} = 3300, 3150 (NH), 2220 (CN), 1685 (CO), 1615 (C=N), 1595 (C=C); ^1H NMR (DMSO-d_6): δ (ppm): 3.50 (s, 8H, CH_2), 5.50 (s, 1H, C_8-H), 5.77 (s, 1H, C_{13}-H), 6.38 (s, 1H, C_3-H), 7.24–7.48 (m, 20H, Ar-H + 1H, C_{18}-H), 8.38 (s, 1H, C_2-NH), 8.88 (s, 1H, endocyclic NH), 9.38 (s, 2H, C_7-NH + C_{17}-NH), 9.50 (s, 1H, endocyclic NH), 10.58 (s, 1H, C_{12}-NH). ^{13}C NMR (DMSO-d_6): δ (ppm): 25.3, 25.5, 100.9, 101.1, 103.5, 103.7, 119.1, 122.5, 125.7, 127.9, 128.6, 129.7, 131.8, 132.1, 133.6, 134.4, 135.6, 136.7, 142.4, 150.1, 151.9, 157.5, 161.1, 167.3, 167.5. MS (EI, 70 eV) m/z (%) = 942 (M^+, 100), 943 ($M^+ + 1$, 60). Anal calcd for $C_{56}H_{38}N_{12}O_4$ (943): C, 71.33; H, 4.06; N, 17.82%. Found: C, 71.21; H, 3.98; N, 17.66%.

Synthesis of *N*,*N*′,*N*″,*N*‴-(5,10,15,20-tetraphenylporphyrin-2,7,12,17-tetrayl)tetrakis (2-amino-5,7-dimethyl-1,8-naphthyridine-3-carboxamide) (10)

Refluxing compound **8** (0.01 mol) with 2-amino-4,-6-dimethylnicotenaldehyde (**9**) (0.04 mol) in dry ethanol

(20 ml) and piperdine as a catalyst for 8 h. The reaction was coole and the obtained solid product was collected and recrystallized from ethanol to give **10**.

68% yield; mp. < (300)°C; IR (KBr): ν/cm^{-1} = 3410 (NH_2), 3300 (NH br.), 1680 (CO), 1620 (C=N), 1600 (C=C); ^{1}H NMR (DMSO-d_6): δ (ppm): 2.48 (s, 12H, $4CH_3$), 2.88 (s, 12H, $4CH_3$), 5.51 (s, 1H, C_8-H pyrrole), 5.77 (s, 1H, C_{13}-H pyrrole), 6.27 (s, 8H, $4NH_2$), 6.51 (s, 1H, C_3-H pyrrole), 7.24–7.27 (m, 24H, 20Ar-H + $4C_3$-H naphthyridine), 7.45 (s, 1H, C_{18}-H pyrrole), 8.11 (s, 4H, $4C_5$-H naphthyridine), 8.48 (s, 1H, C_2-NH), 8.88 (s, 1H, endocyclic NH), 9.55 (s, 2H, C_7-NH + C_{17}-NH), 9.65 (s, 1H, endocyclic NH), 11.00 (s, 1H, C_{12}-NH). ^{13}C NMR (DMSO-d_6): δ (ppm): 19.5, 24.2, 103.5, 106.1, 111.2, 115.2, 122.5, 124.4, 127.8, 128.6, 131.9, 134.4, 135.7, 136.7, 137.4, 139.4, 142.4, 145.8, 150.5, 155.7, 156.1, 158.5, 161.4, 164.1. Anal calcd for $C_{88}H_{70}N_{20}O_4$ (1471.66): C, 71.82; H, 4.79; N, 19.04%. Found: C, 71.71; H, 4.72; N, 18.95%.

Synthesis of (2E,2′E,2″E,2‴E)-*N*,*N*′,*N*″,*N*‴-(5,10,15,20-tetraphenylporphyrin-2,7,12,17-tetrayl) tetrakis(2-cyano-3-[2-nitrophenyl] acrylamide) (**11**)

Heating of compound **8** (0.01 mol) and 2-nitrobenzaldehyde (0.04 mol) in absolute ethanol (20 ml) and piperdine as catalyst (4 drops) for 6 h. The reaction was cooled, collected, and recrystallized from ethanol to give **11**.

78% yield; mp. (295)°C; IR (KBr): ν/cm^{-1} = 3310 (NH), 2218 (CN), 1678 (CO), 1535, 1350 (symm., asymm. NO_2); ^{1}H NMR (DMSO-d_6): δ (ppm): 5.63 (s, 1H, C_8-H pyrrole), 5.85 (s, 1H, C_{13}-H pyrrole), 6.38 (s, 1H, C_3-H pyrrole), 7.11–7.95 (m, 36H, Ar-H), 7.57 (s, 1H, C_{18}-H pyrrole), 8.38 (s, 1H, C_2-NH), 8.77 (s, 1H, 4C-H olefinic), 8.85 (s, 1H, endocyclic NH), 9.25 (s, 2H, C_7-NH + C_{17}-NH), 9.77 (s, 1H, endocyclic NH), 10.75 (s, 1H, C_{12}-NH). ^{13}C NMR (DMSO-d_6): δ (ppm): 103.1, 103.7, 105.9, 106.1, 106.9, 115.8, 122.8, 123.8, 124.3, 127.9, 128.6, 128.8, 130.9, 131.8, 132.1, 134.4, 134.7, 135.6, 136.7, 137.4, 142.3, 147.7, 150.1, 150.6, 153.4, 155.7, 161.1, 162.9, 163.3. Anal calcd for $C_{84}H_{50}N_{16}O_{12}$ (1475.42): C, 68.38; H, 3.42; N, 15.19%. Found: C, 68.24; H, 3.13; N, 15.01%.

Synthesis of *N*,*N*′,*N*″,*N*‴-(5,10,15,20-tetraphenylporphyrin-2,7,12,17-tetrayl)tetrakis (2-aminoquinoline-3-carboxamide) (**12**)

Heating of compound **11** (0.01 mol) and Fe (catalytic amount) in presence of glacial acetic acid (20 ml) for 5 h, The reaction was cooled, collected, and recrystallized from ethanol to give **12**.

58% yield; mp. < (300)°C; IR (KBr): ν/cm^{-1} = 3420 (NH_2), 3250 (NH br.), 1682 (CO); ^{1}H NMR (DMSO-d_6): δ (ppm): 5.63 (s, 1H, C_8-H pyrrole), 5.85 (s, 1H, C_{13}-H pyrrole), 6.25 (s, 8H, $4NH_2$), 6.38 (s, 1H, C_3-H pyrrole), 7.11–7.38 (m, 36H, Ar-H), 7.55 (s, 1H, C_{18}-H pyrrole), 8.09 (d, 4H, Ar-H), 8.31 (s, 4H, C_4-H quinoline), 8.63 (s, 1H, C_2-NH), 8.85 (s, 1H, endocyclic NH), 9.25 (s, 2H, C_7-NH + C_{17}-NH), 9.77 (s, 1H, endocyclic NH), 10.75 (s, 1H, C_{12}-NH). ^{13}C NMR (DMSO-d_6): δ (ppm): 103.5, 103.8, 105.8, 106.1, 120.2, 122.8, 122.9, 124.3, 125.0, 127.6, 128.8, 131.3, 131.6, 132.0, 134.4, 135.8, 136.8, 137.4, 137.5, 142.5, 146.6, 150.2, 150.8, 155.5, 161.3, 163.8, 164.2, 164.5. Anal calcd for $C_{84}H_{58}N_{16}O_4$ (1355.50): C, 74.43; H, 4.31; N, 16.53%. Found: C, 74.15; H, 4.27; N, 16.45%.

Synthesis of *N*,*N*′,*N*″,*N*‴-(5,10,15,20-tetraphenylporphyrin-2,7,12,17-tetrayl)tetrakis (7,7-dimethyl-2,5-dioxo-1,2,5,6,7,8-hexahydroquinoline-3-carboxamide) (**13**)

A mixture of compound **8** (0.01 mol) and ([2-dimethylamino] methylene)-5,5-dimethylcyclohexane-1,3-dione (0.04 mol) was heated under microwave condition for 12 min (100 °C). The reaction was cooled, collected, and recrystallized from ethanol to give **13**.

71% yield; mp. < (300)°C; IR (KBr): ν/cm^{-1} = 3330 (NH br.), 1725 (CO ketonic), 1687 (CO amidic); ^{1}H NMR (DMSO-d_6): δ (ppm): 1.11 (s, 24H, 8 CH_3), 2.27 (s, 8H, 4 CH_2),2.85 (s, 8H, 4 CH_2), 5.63 (s, 1H, C_8-H pyrrole), 5.85 (s, 1H, C_{13}-H pyrrole), 6.38 (s, 1H, C_3-H pyrrole), 7.11–7.27 (m, 20H, Ar-H), 7.38 (s, 1H, C_{18}-H pyrrole), 7.85 (s, 4H, C_4-H tetrahydro quinoline), 8.38 (s, 1H, C_2-NH), 8.85 (s, 1H, endocyclic NH), 9.25 (s, 2H, C_7-NH + C_{17}-NH), 9.77 (s, 1H, endocyclic NH), 10.75 (s, 1H, C_{12}-NH), 12.58 (s, 4H, 4 NH). ^{13}C NMR (DMSO-d_6): δ (ppm): 27.2 ($8CH_3$), 32.5, 41.7 ($4CH_2$), 42.6 ($4CH_2$), 103.1, 103.5, 105.7, 106.2, 117.1, 122.8, 124.3, 127.6, 127.7, 128.6, 131.4, 131.6, 132.1, 134.3, 135.6, 136.6, 137.4, 142.3, 150.1, 150.3, 150.6, 153.7, 155.7, 161.1, 161.5, 162.5, 162.9, 163.3, 194.4. Anal calcd for $C_{92}H_{78}N_{12}O_{12}$ (1543.71): C, 71.58; H, 5.09; N, 10.89%. Found: C, 71.44; H, 4.98; N, 10.76%.

Synthesis of 1,1′,1″,1‴-(5,10,15,20-tetraphenylporphyrin-2,7,12,17-tetrayl)tetrakis (2,5-dioxo-4-phenyl-2,5-dihydro-1*H*-indeno [1,2-*b*]pyridine-3-carbonitrile) (**15**)

To a stirred solution of compound **8** (0.01 mol) and 2-(1-phyenylethylidene)-indane-1,3-dione (**14**) (0.04 mol) in presence of benzene (20 ml) and ammonium acetate (0.5 g) were refluxed for 8 h. The reaction was cooled, collected, and recrystallized from ethanol to give **15**.

62% yield; mp. < (300)°C; IR (KBr): ν/cm^{-1} = 3100 (NH), 2215 (CN), 1729 (CO ketone), 1680 (CO amidic); ^{1}H NMR (DMSO-d_6): 5.63 (s, 1H, C_8-H pyrrole), 5.85 (s, 1H, C_{13}-H pyrrole), 6.38 (s, 1H, C_3-H pyrrole), 7.11–7.38 (m, 56H, Ar-H), 7.55 (s, 1H, C_{18}-H pyrrole), 8.85 (s, 1H, endocyclic NH), 9.77 (s, 1H, endocyclic NH). ^{13}C NMR (DMSO-d_6): δ (ppm): 99.5, 103.1, 103.8, 106.9, 109.0, 115.3, 115.8, 123.4, 124.0, 124.2, 126.2, 127.8, 127.9, 128.6, 128.4, 128.9, 132.3, 132.5, 134.2, 134.4, 135.6, 135.7, 136.5, 136.7, 137.4, 142.3, 145.0, 146.2, 150.1, 151.9, 155.7, 157.5, 157.9, 161.3, 169.4, 190.4. Anal calcd for $C_{120}H_{62}N_{12}O_8$ (1799.89): C, 80.08; H, 3.47; N, 9.34%. Found: C, 79.98; H, 3.21; N, 9.27%.

Synthesis of 1,1′,1″,1‴-(5,10,15,20-tetraphenylporphyrin-2,7,12,17-tetrayl)tetrakis (6-amino-4-[methylthio]-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile) (**17**)

A mixture of compound **8** (0.01 mol) and 2-(bis(methylthio)methylene malononitrile (**16**) (0.04 mol) in dry DMF (25 ml) in presence of anhydrous potassium carbonate (0.5 g) was refluxed for 8 h. The reaction was cooled, collected, and recrystallized from ethanol to give **17**.

67% yield; mp. < (300)°C; IR (KBr): ν/cm^{-1} = 3440 (NH_2), 3200 (NH), 2219 (CN), 2217 (CN), 1685 (CO); ^{1}H NMR (DMSO-d_6): 2.80 (s, 12H, 4 SMe), 5.63 (s, 1H, C_8-H pyrrole), 5.85 (s, 1H, C_{13}-H pyrrole), 6.38 (s, 1H, C_3-H pyrrole), 6.58 (s, 8H, 4 NH_2), 7.11–7.27 (m, 20H, Ar-H), 7.38 (s, 1H, C_{18}-H pyrrole), 8.77 (s, 1H, endocyclic NH), 9.77 (s, 1H, endocyclic NH). ^{13}C NMR (DMSO-d_6): δ (ppm): 14.4 (4CH_3-S), 61.8, 63.9, 89.2, 99.5, 103.1, 104.0, 115.8, 124.0, 124.3, 127.5, 127.9, 128.6, 132.4, 134.2, 134.4, 135.6, 136.7, 137.4, 142.3, 149.9, 150.3, 155.7, 157.5, 157.9, 160.7, 161.9, 175.9. Anal calcd for $C_{76}H_{46}N_{20}O_4S_4$ (1431.58): C, 63.76; H, 3.24; N, 19.57%. Found: C, 63.65; H, 3.17; N, 19.44%.

Synthesis of 1,1′,1″,1‴-(5,10,15,20-tetraphenylporphyrin-2,7,12,17-tetrayl)tetrakis (4,4-dimethyl-2,6-dioxopiperidine-3,5-dicarbonitrile) (**19**)

Heating a mixture of **8** (0.01 mol) and ethyl 3-cyano-2-methyl-but-2-enate (**18**) (0.04 mol) in dry ethanol (25 ml) and sodium ethoxide (1.36 g, 0.02 mol) for 7 h. The reaction was cooled, collected, and recrystallized from ethanol to give **19**.

73% yield; mp. < (300)°C; IR (KBr): ν/cm^{-1} = 3150 (NH br.), 2218 (CN), 1680 (CO); ^{1}H NMR (DMSO-d_6): 0.99 (s, 24H, 8 CH_3), 3.11 (s, 8H, 8 CH), 5.63 (s, 1H, C_8-H pyrrole), 5.85 (s, 1H, C_{13}-H pyrrole), 6.38 (s, 1H, C_3-H pyrrole), 7.11–7.27 (m, 20H, Ar-H), 7.38 (s, 1H, C_{18}-H pyrrole), 8.77 (s, 1H, endocyclic NH), 9.77 (s, 1H, endocyclic NH). ^{13}C NMR (DMSO-d_6): 18.2, 18.3, 22.7 (8CH_3), 43.6, 43.9, 100.9, 101.1, 103.1, 103.7, 116.8, 119.0, 122.5, 127.9, 128.8, 129.7, 131.9, 132.4, 133.6, 134.4, 135.5, 136.9, 142.5, 150.1, 151.9, 157.5, 161.1, 169.1, 169.5. Anal calcd for $C_{80}H_{58}N_{16}O_8$ (1371.45): C, 70.06; H, 4.26; N, 16.34%. Found: C, 69.95; H, 4.14; N, 16.22%.

Synthesis of *N*,*N*′,*N*″,*N*‴-(5,10,15,20-tetraphenylporphyrin-2,7,12,17-tetrayl)tetrakis (3-amino-3-thioxopropanamide) (**20**)

To compound **8** (0.001 mol) in pyridine (25 ml) and in presence of a catalytic amount of triethylamine (4 drops), H_2S gas is bubbled through with stirring until the weight increased by (1.3 g). The reaction was cooled, collected, and recrystallized from ethanol to give **20**.

61% yield; mp. < (300)°C; IR (KBr): ν/cm^{-1} = 3380 (NH_2), 3160 (NH br.), 1680 (CO), 1350 (C=S); ^{1}H NMR (DMSO-d_6): 3.77 (s, 8H, 4 CH_2), 5.63 (s, 1H, C_8-H pyrrole), 5.85 (s, 1H, C_{13}-H pyrrole), 6.38 (s, 1H, C_3-H pyrrole), 6.85 (s, 8H, 4 NH_2), 7.11–7.28 (m, 20H, Ar-H), 7.37 (s, 1H, C_{18}-H pyrrole), 8.50 (s, 1H, C_2-NH), 8.85 (s, 1H, endocyclic NH), 9.38 (s, 2H, C_7-NH + C_{17}-NH), 9.77 (s, 1H, endocyclic NH), 10.85 (s, 1H, C_{12}-NH). ^{13}C NMR (DMSO-d_6): δ (ppm): 53.2, 101.1, 103.5, 119.2, 122.5, 127.8, 128.6, 129.6, 131.9, 133.4, 134.4, 135.7, 136.7, 142.4, 150.1, 151.9, 157.5, 161.1, 163.5, 167.5, 201.5. Anal calcd for $C_{56}H_{46}N_{12}O_4S_4$ (1079.30): C, 62.32; H, 4.30; N, 15.57%. Found: C, 62.26; H, 4.14; N, 15.44%.

Synthesis of *N*,*N*′,*N*″,*N*‴-(5,10,15,20-tetraphenylporphyrin-2,7,12,17-tetrayl)tetrakis (4,6-dimethyl-2-thioxo-2,3-dihydropyridine-3-carboxamide) (**21**)

A solution of compound **20** (0.01 mol) and pentane-2,-4-dione (1 g, 0.04 mol) in absolute ethanol (30 ml) were refluxed for 8 h in presence of a catalytic amount of triethylamine (4 drops). The reaction was cooled, collected, and recrystallized from ethanol to give **21**.

73% yield; mp. < (300)°C; IR (KBr): ν/cm^{-1} = 3170 (NH br.), 1679 (CO), 1354 (C=S); ^{1}H NMR (DMSO-d_6): 1.77 (s, 12H, 4 CH_3), 2.27 (s, 12H, 4 CH_3), 3.11 (s, 4H, 4 CH), 5.63 (s, 1H, C_8-H pyrrole), 5.85 (s, 1H, C_{13}-H pyrrole), 5.95 (s, 4H, C_3-H pyridine), 6.38 (s, 1H, C_3-H pyrrole), 7.11–7.27 (m, 20H, Ar-H), 7.38 (s, 1H, C_{18}-H pyrrole), 8.50 (s, 1H, C_2-NH), 8.85 (s, 1H, endocyclic

NH), 9.38 (s, 2H, C_7-NH + C_{17}-NH), 9.77 (s, 1H, endocyclic NH), 10.85 (s, 1H, C_{12}-NH). ^{13}C NMR (DMSO-d_6): 18.4 (4CH_3), 19.9 (4CH_3), 66.8, 67.7, 101.4, 103.2, 103.7, 109.2, 119.2, 122.2, 127.7, 128.6, 129.5, 131.9, 132.2, 133.6, 134.4, 135.6, 136.3, 136.7, 142.2, 150.4, 151.7, 157.5, 161.3, 167.3, 167.7, 174.0, 242.2 (4C=S). Anal calcd for $C_{76}H_{62}N_{12}O_4S_4$ (1335.65): C, 68.34; H, 4.68; N, 12.58%. Found: C, 68.27; H, 4.57; N, 12.46%.

Synthesis of *N*,*N*′,*N*″,*N*‴-(5,10,15,20-tetraphenylporphyrin-2,7,12,17-tetrayl)tetrakis (2-[4,6-diamino-3,5-dicyanopyridin-2-yl] acetamide) (**22**)

A mixture of compound **8** (0.01 mol) and 2-aminoprop-1-ene-1,1,3-tricarbonitrile (malononitrile dimer) (0.04 mol) was heated in a pressure tube at 150 °C in a silicon oil bath. The reaction was cooled, collected, and recrystallized from ethanol to give **22**.

76% yield; mp. < (300)°C; IR (KBr): ν/cm^{-1} = 3370 (NH_2), 3300 (NH br.), 2220 (CN), 2218 (CN), 1680 (CO); ^{1}H NMR (DMSO-d_6): 3.98 (s, 8H, 4 CH_2), 5.63 (s, 1H, C_8-H pyrrole), 5.85 (s, 1H, C_{13}-H pyrrole), 6.38 (s, 9H, C_3-H pyrrole +4 NH_2), 6.85 (s, 8H, 4 NH_2), 7.11–7.27 (m, 20H, Ar-H), 7.38 (s, 1H, C_{18}-H pyrrole), 8.50 (s, 1H, C_2-NH), 8.85 (s, 1H, endocyclic NH), 9.38 (s, 2H, C_7-NH + C_{17}-NH), 9.77 (s, 1H, endocyclic NH), 10.85 (s, 1H, C_{12}-NH). Anal calcd for $C_{80}H_{54}N_{28}O_4$ (1471.50): C, 65.30; H, 3.70; N, 26.65%. Found: C, 65.27; H, 3.56; N, 26.49%.

Synthesis of tetraethyl 5,5′,5″,5‴-(((5,10,15,20-tetraphenylporphyrin-2,7,12,17-tetrayl)tetrakis (azanediyl))tetrakis(carbonyl))tetrakis(6-imino-4-methyl-1-phenyl-1,6-dihydropyridazine-3-carboxylate) (**25**)

A solution of compound **8** (0.01 mol) and ethyl(z)-3-oxo-2-(2-phenylhydrazono)butanoate (**23**) (0.04 mol) was refluxed in benzene-acetic acid mixture (20 ml, 1:1) for 8 h. The reaction was cooled, collected, and recrystallized from ethanol to give **25**.

69% yield; mp. < (300)°C; IR (KBr): ν/cm^{-1} = 3150 (NH), 3100 (NH br.), 1700 (CO); ^{1}H NMR (DMSO-d_6): 1.25 (t, 12H, 4CH_3), 2.38 (s, 12H, 4 CH_3), 4.11 (q, 8H, 4 CH_2), 5.63 (s, 1H, C_8-H pyrrole), 5.85 (s, 1H, C_{13}-H pyrrole), 6.38 (s, 1H, C_3-H pyrrole), 7.11–7.38 (m, 40H, Ar-H), 7.57 (s, 1H, C_{18}-H pyrrole), 8.50 (s, 1H, C_2-NH), 8.85 (s, 1H, endocyclic NH), 9.27 (s, 4H, 4 C=NH), 9.38 (s, 2H, C_7-NH + C_{17}-NH), 9.77 (s, 1H, endocyclic NH), 10.85 (s, 1H, C_{12}-NH). ^{13}C NMR (DMSO-d_6): δ (ppm): 10.8, 13.8, 61.5, 103.5, 106.1, 122.5, 123.6, 124.4, 127.8, 128.6, 129.6, 131.9, 134.4, 135.7, 136.7, 137.4, 138.6, 139.2, 141.9, 142.4, 150.5, 155.5, 158.9, 161.5, 162.5, 163.5. Anal calcd for $C_{104}H_{86}N_{20}O_{12}$ (1807.96): C, 69.09; H, 4.79; N, 15.49%. Found: C, 68.95; H, 4.66; N, 15.37%.

Synthesis of *N*,*N*′,*N*″,*N*‴-(5,10,15,20-tetraphenylporphyrin-2,7,12,17-tetrayl)tetrakis (2-(6-cyano-4-oxo-5,7-diphenyl-3,5-dihydro-4*H*-pyrano[2,3-*d*]pyrimidin-2-yl)acetamide) (**27**)

Heating a mixture of compound **8** (0.01 mol) and 2-amino-3-carbethoxy-5-cyno-4,6-diphenyl-4*H*-pyran (**26**) (3.46 g, 0.01 mol) in presence of pyridine (25 ml) for 7 h. The reaction was cooled, collected, and recrystallized from ethanol to give **27**.

71% yield; mp. < (300)°C; IR (KBr): ν/cm^{-1} = 3200 (NH), 3150 (NH br.), 2218 (CN), 1685 (2 CO), 1620 (C=N), 1110 (C-O-C); ^{1}H NMR (DMSO-d_6): 3.11 (s, 8H, 4 CH_2), 4.38 (s, 4H, 4 CH), 5.63 (s, 1H, NH endocyclic), 5.77 (s, 1H, C_8-H pyrrole), 5.85 (s, 1H, C_{13}-H pyrrole), 6.36 (s, 1H, C_3-H pyrrole), 7.11–7.38 (m, 60H, Ar-H), 7.55 (s, 1H, C_{18}-H pyrrole), 9.28 (s, 2H, C_7-NH + C_{17}-NH), 9.77 (s, 1H, C_2-NH), 12.58 (s, 4H, NH), 12.85 (s, 1H, NH endocyclic). ^{13}C NMR (DMSO-d_6): 33.5, 38.8, 39.5, 39.7, 92.3, 93.4, 98.0, 100.7, 104.1, 108.0, 114.0, 117.3, 119.7, 120.1, 121.5, 125.7, 127.6, 127.9, 128.8, 130.3, 133.5, 134.4, 135.6, 137.9, 139.0, 142.1, 142.3, 144.1, 146.6, 149.4, 156.4, 159.8, 161.9, 162.2, 164.0, 164.9, 167.3. Anal calcd for $C_{132}H_{86}N_{20}O_{12}$ (2144.27): C, 73.74; H, 4.04; N, 13.06%. Found: C, 73.88; H, 3.97; N, 12.98%.

Synthesis of (2E,2′E,2″E,2‴E)-*N*,*N*′,*N*″,*N*‴-(5,10,15,20-tetraphenylporphyrin-2,7,12,17-tetrayl)tetrakis(2-cyano-3-[dimethylamino]acrylamide) (**28**)

A mixture of compound **8** (0.01 mol) and dimethylformamide-dimethyl acetal (4.76 g, 0.04 mol) was refluxed for 8 h in presence of dry xylene. The reaction was cooled, collected, and recrystallized from ethanol to give **28**.

78% yield; mp. < (300)°C; IR (KBr): ν/cm^{-1} = 3150 (NH br.), 2220 (CN), 1675 (CO amidic); ^{1}H NMR (DMSO-d_6): 3.11 (s, 24H, 8 CH_3), 5.63 (s, 1H, C_8-H pyrrole), 5.85 (s, 1H, C_{13}-H pyrrole), 6.38 (s, 1H, C_3-H pyrrole), 7.11–7.27 (m, 20H, Ar-H), 7.38 (s, 1H, C_{18}-H pyrrole), 7.58 (s, 4H, =CH), 8.50 (s, 1H, C_2-NH), 8.77 (s, 1H, endocyclic NH), 9.38 (s, 2H, C_7-NH + C_{17}-NH), 9.66 (s, 1H, NH endocyclic), 10.85 (s, 1H, C_{12}-NH). ^{13}C NMR (DMSO-d_6): 43.5, 98.8, 103.1, 103.7, 105.9, 106.1, 114.6, 122.8, 124.3, 127.8, 127.9, 128.6, 131.8, 132.0, 134.4, 135.6, 136.4, 137.4,

142.3, 150.1, 150.6, 155.7, 156.0, 161.1, 162.9, 163.3. Anal calcd for $C_{68}H_{58}N_{16}O_4$ (1163.32): C, 70.21; H, 5.03; N, 19.26%. Found: C, 70.11; H, 4.93; N, 19.12%.

Synthesis of *N*,*N*′,*N*″,*N*‴-(5,10,15,20-tetraphenylporphyrin-2,7,12,17-tetrayl)tetrakis (5-amino-2-phenylpyrazolo[1,5-*a*]pyrimidine-6-carboxamide) (**29**)

A mixture of compound **28** (0.01 mol) was heated with 3-phenyl-1*H*-pyrazol-5-amine (6.36 g, 0.04 mol) in presence of DMF (25 ml) and 4 drops of piperdine for 8 h. The reaction was cooled, collected, and recrystallized from ethanol to give **29**.

68% yield; mp. < (300)°C; IR (KBr): ν/cm^{-1} = 3360 (NH_2), 3120 (NH br.), 1681 (CO amidic), 1615 (C=N), 1595 (C=C); ^{1}H NMR (DMSO-d_6): 5.63 (s, 1H, C_8-H pyrrole), 5.85 (s, 1H, C_{13}-H pyrrole), 6.38 (s, 1H, C_3-H pyrrole), 6.77 (s, 4H, C_3-H pyrazole), 6.85 (s, 8H, 4 NH_2), 7.25–7.38 (m, 40H, Ar-H), 7.57 (s, 1H, C_{18}-H pyrrole), 8.66 (s, 4H, 4 C_7-H pyrazolopyrimidine), 8.77 (s, 1H, endocyclic NH), 9.58 (s, 2H, C_7-NH + C_{17}-NH), 9.66 (s, 1H, NH endocyclic), 10.58 (s, 1H, C_{12}-NH). ^{13}C-NMR (DMSO-d_6): 92.5, 103.1, 103.7, 105.6, 106.0, 112.7, 122.8, 124.2, 127.5, 127.8, 127.9, 128.6, 128.7, 129.2, 131.4, 132.3, 133.1, 134.2, 135.6, 136.9, 137.7, 140.3, 142.2, 149.4, 150.1, 150.7, 154.8, 155.5, 161.5, 163.9, 164.2. Anal calcd for $C_{96}H_{66}N_{24}O_4$ (1619.75): C, 71.19; H, 4.11; N, 20.75%. Found: C, 70.98; H, 3.96; N, 20.56%.

4.2 | Biological activity

4.2.1 | Cytotoxicity assay

It was carried out according to the work reported before [27,28].

4.2.2 | Preparation of tested compound

Molecular docking of compound **22** into the binding site of telomerase inhibitor enzyme was investigated using the Biovia *Discovery Studio*. The three-dimensional structures of **22** were constructed using a building module. Gasteiger–Hückel charges of ligands were assigned. They were energetically minimized by using AMBER with 100 iterations conformer with the lowest energy, the "global-minima," was pre-adjusted using the crystal structure ligand "POH 25A" as a template at the major groove-binding pocket.

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DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

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REFERENCES

[1] T. J. Dougherty, C. J. Gomer, B. W. Henderson, G. Jori, D. Kessel, M. Korbelike, J. Moan, Q. J. Peng, *Natl Cancer Inst* **1998**, *90*, 889.
[2] (a) R. F. Barth, A. H. Soloway, J. H. Goodman, R. A. Gahbauer, N. Gupta, T. E. Blue, W. Yang, W. Tjarks, *Neurosurgery* **1999**, *44*, 433. (b) R. F. Barth, *Neurosurgery* **2003**, *62*, 1.
[3] J. Osterloh, M. G. H. Vicente, *J Porphyr Phthalocya* **2002**, *6*, 305.
[4] M. G. H. Vicente, *Curr Med Chem: Anti-Cancer Agents* **2001**, *1*, 175.
[5] (a) L. G. Marzilli, *New J Chem* **1990**, *14*, 409. (b) G. Pratviel, J. Bernadou, B. Meunier, *Angew Chem, Int Ed Engl* **1995**, *34*, 746.
[6] (a) C. Bustamante, S. Gurrieri, R. F. Pasternack, R. Purrello, E. Rizzarelli, *Biopolymers* **1994**, *34*, 1099. (b) D. Magda, M. Wright, S. Crofts, A. Lin, J. L. Sessler, *J Am Chem Soc* **1997**, *119*, 6947.
[7] (a) A. Villanueva, G. Jory, *Cancer Lett* **1993**, *73*, 59. (b) A. Villanueva, *J Photochem Photobiol B: Biol* **1994**, *23*, 49.
[8] E. M. Lord, L. Harwell, C. J. Koch, *Cancer Res* **1993**, *53*, 5721.
[9] D. Kessel, R. Luguya, M. G. H. Vicente, *Photochem Photobiol* **2003**, *78*, 431.
[10] L. Jaquinod, in *The Porphyrin Handbook*, Vol. 1 (Eds: K. M. Kadish, K. M. Smith, R. Guilard), Academic, Boston **2000**, p. 201.
[11] K. P. S. Dancil, L. F. Hilario, R. G. Khoury, K. U. Mai, C. K. Nguyen, K. S. Weddle, A. M. Schachter, *J Heterocycl Chem* **1997**, *34*, 749.
[12] D. Schmidt, H. Steffen, *Eur Patent Appl* **1948**, *127*, 797.
[13] A. Maderna, R. Huertas, M. F. Hawthorne, R. Luguya, M. G. H. Vicente, *Chem Commun* **2002**, *16*, 1784.
[14] (a) E. Hasegawa, J. Nemoto, T. Kanayama, E. Tsuchida, *Eur Polym J* **1978**, *14*, 123. (b) E. J. Tsuchida, *J Macromol Sci: Pure Appl Chem* **1979**, *A13*, 545.
[15] M. C. Gonzales, A. C. Weedon, *Can J Chem* **1985**, *63*, 602.
[16] J. H. Fuhrhop, in *In The Porphyrins*, Vol. 2 (Ed: D. Dolphin), Academic Press, New York **1978**, p. 131.
[17] (a) J. E. Baldwin, M. J. Crossley, J. Bernardis, *Tetrahedron* **1982**, *38*, 685. (b) M. M. Catallano, M. J. Crossley, M. M. Harding, L. G. King, *J Chem Soc Chem Commun* **1984**, *22*, 1535.
[18] B. Evans, K. M. Smith, J. A. S. Calvaleiro, *J Chem Soc Perkin Trans 1* **1978**, *7*, 768.

[19] W. J. Kruper Jr, T. A. Chamberlin, M. Kochanny, *The Journal of Organic Chemistry* **1989**, *54*, 2753.
[20] A. A. Fadda, M. Abd El Salam, E. H. Tawfik, E. M. Anwar, H. A. Etman, *RSC Adv* **2017**, *763*, 39773.
[21] A. El-Mekabaty, A. Mesbah, A. A. Fadda, *J Heterocycl Chem* **2017**, *54*, 916.
[22] A. A. Fadda, R. Rabie, H. A. Etman, *J Heterocycl Chem* **2017**, *54*, 1015.
[23] B. L. Bray, P. H. Mathies, R. Naef, D. R. Solas, T. T. Tidwell, D. R. Artis, J. M. Muchowski, *J Org Chem* **1990**, *55*, 6317.
[24] S. Mondal, K. Sahu, B. Patra, S. Jena, H. S. Biswal, S. Kar, *Dalton Trans* **2020**, *49*, 1424.
[25] S. M. A. Pinto, C. Henrique, V. A. Tome, C. S. Vinagreiro, M. J. F. Calvete, J. M. Dabrowski, et al., *J Porphyr Phthalocya* **2016**, *20*, 45.
[26] Q. Su, T. D. Hamilton, *J Org Chem* **2019**, *15*, 1149.
[27] (a) A. A. Fadda, R. E. El-Mekawy, A. L. I. El-Shafei, H. Freeman, *Arch Pharm* **2013**, *346*, 53. (b) A. A. Fadda, R. E. El-Mekawy, A. El-Shafei, H. S. Freeman, D. Hinks, M. El-Fedawy, *J Chem* **2013**, *2013*, 340230.
[28] A. Ahmed, W. A. Omar, H. A. El-Asmy, L. Abou-Zeid, A. A. Fadda, *Dyes Pigments* **2020**, *183*, 108728.
[29] W. J. Kruper, A. T. Chamberlin, M. J. Kochanny, *Org Chem* **1989**, *54*, 2753.
[30] J. P. Collman, R. R. Gagne, C. A. Reed, T. R. Halbert, G. Lang, W. T. Robinson, *J Am Chem Soc* **1975**, *97*, 1427.
[31] A. A. Fadda, R. Rabie, *Res Chem Intermed* **2016**, *42*, 771.
[32] H. M. Refat, A. A. Fadda, S. Kamal, *J Iran Chem Soc* **2015**, *12*, 845.
[33] A. A. Fadda, R. Rabie, H. A. Etman, A. A. S. Fouda, *Res Chem Intermed* **2015**, *41*, 7883.
[34] A. A. Fadda, M. M. Mukhtar, H. M. Refat, *Am J Org Chem* **2012**, *2*, 32.
[35] A. A. Fadda, H. A. Etman, A. A. Sarhan, S. A. El-Hadidy, *Phosphorus Sulfur Silicon* **2010**, *185*, 526.
[36] A. A. Fadda, F. M. Abdelrazek, K. S. Mohamed, H. M. M. Ghieth, H. A. Etman, *Eur J Chem* **2010**, *1*, 90.
[37] A. A. Fadda, N. M. Bayoumy, N. N. Soliman, D. M. Eldiasty, *J Heterocycl Chem* **2019**, *56*, 597.
[38] C. S. Cooper, P. L. Klock, D. T. W. Chu, D. J. Hardy, R. N. Swanson, J. J. Plattner, *J Med Chem* **1992**, *35*, 1392.
[39] K. Tomita, Y. Tsuzuki, K. Shibamori, M. Tshima, F. Kajikawa, Y. Sato, S. Kashimoto, K. Chiba, K. Hino, *J Med Chem* **2002**, *45*, 5564.
[40] A. A. Fadda, A. M. El-Defrawy, S. A. El-Hadidy, *Am J Org Chem* **2012**, *2*, 87.
[41] J. A. Makawana, M. P. Patel, R. G. Patel, *Med Chem Res* **2012**, *21*, 616.
[42] V. Chavan, S. Sonawane, M. Shingare, B. Karale, *Chem Heterocycl Compds* **2006**, *42*, 625.
[43] S. Firke, B. Firake, V. Patil, *Asian J Res Chem* **2009**, *2*, 157.
[44] X. T. Yang, H. Wu, S. J. Ma, J. J. Hu, Y. Wang, *Transit Met Chem* **2011**, *36*, 403.
[45] B. Narayan Acharya, D. Thavaselvam, M. Parshad Kaushik, *Med Chem Res* **2008**, *17*, 487.
[46] S. M. Sondhi, M. Dinodia, A. Kumar, *Bioorg Med Chem* **2006**, *14*, 4657.
[47] Dassault Systems BIOVIA, *Discovery Studio Modeling Environment, Release 2020*, Dassault Systems, San Diego **2020**.

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