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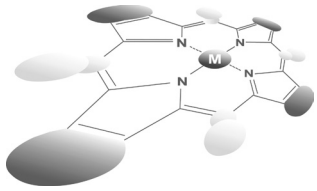

Synthesis, antiviral, cytotoxicity and antitumor evaluations of A_4 type of porphyrin derivatives

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ABSTRACT: This manuscript describes the synthesis of a new series of porphyrin structures **4a–4m**, **7**, **9**, **12** and **14.** These structures were investigated against two types of viruses such as HIV-1 and HSV-1. Also they were screened for their antitumor activity. Among all tested compounds, it was found that compound **4b** showed a high activity against HIV-1 and HSV-1 and against four different tumor cell lines. Most of the tested compounds showed a moderate degree of a potent antimicrobial activity. The structure of these compounds was confirmed on the basis of their analytical and spectral data such as UV-vis, IR, ^{13}C NMR, ^{1}H NMR spectroscopy and mass spectral data.

KEYWORDS: antiviral activity, antitumor activity, porphyrin structures.

INTRODUCTION

The search for new biologically active agents is an important task for medicinal chemists. It has long been known that porphyrin is a representative π-functional skeleton that has been actively investigated in many research areas. [1–5]. Porphyrins have received a great deal of interest because they show unique properties in electronics [6], photosynthesis [7], optical memories [8], photocatalysis [9], photodynamic therapy [10], and solar cells [11]. The structural flexibility and well-developed synthetic chemistry of porphyrins allow their physical, biological and chemical properties to be tailored by choosing from a wide library of macrocycle substituents at the β- or *meso*-positions and central metal atoms. *Meso*-Tetraarylporphyrins offer attractive features in this context and have been used in a wide variety of model systems owing to their ease of synthesis and facile functionalization. However, the reports on porphyrins having *meso* substituents like five-membered heterocycles such as pyrrole, thiophene, furan *etc*. are scarce.

In recent times, there have been a few reports on *meso*-tetrathienylporphyrins because of their unique energy transfer and electrochemical properties [12]. To the best of our knowledge, there are no reports on the synthesis of porphyrins containing pyrazolyl groups at the *meso* carbons. On the other hand, the chemistry of 1*H*-pyrazole containing compounds is particularly interesting because of their potential application in medicinal chemistry as analgesic [13, 14], anti-inflammatory [15], antitumor [16, 17], antimicrobial [18–21] and therapeutic agents [22] and as potent insecticides [23] and herbicides [24] although they are scarcely found in nature [25]. Due to many promising pharmacological, agrochemical and analytical applications, a number of substituted pyrazoles is being used as inhibitors of heat-shock protein 90 (Hsp90) and as therapeutics of cancer and therefore they have been the focus of many synthetic targets over the past decades [26]. 1*H*-Pyrazole based heterocyclic structures have also attracted a synthetic interest for being essential moieties in many chemotherapeutic agents with potential antiparasitic [27], antimalarial [28] and antiviral activities [29, 30]. As far as the anticancer activity is concerned, literature citation revealed that a wide range of pyrazole

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derivatives was reported to contribute to a variety of antineoplastic potentials against a wide range of cancer cell lines [31, 32]. In this research work, we report for the first time the synthesis and characterization of novel *meso*-tetrapyrazolylporphyrins and their pharmaceutical screening as antiviral and antitumor agents.

RESULTS AND DISCUSSION

Chemistry

As a continuation of our recent publishing work [33], some new substituted 3-aryl-1-phenyl-1*H*-pyrazole-4-carbaldehydes (**3a–3m**) were prepared by Vilsmeier–Haack reaction of their corresponding hydrazone derivatives **4a–4m** [34].

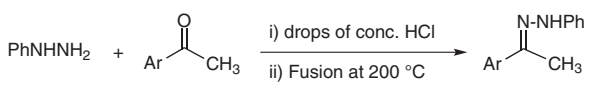
Moreover, porphyrin shows a broad spectrum of biological and pharmaceutical activity. Thus, compounds having a combination of such pyrazole and porphyrin moities might afford less toxic and more potent drugs in the field of medicinal chemistry. In continuation of our study on the chemistry of heterocyclic compounds and the synthesis of heterocyclic substituted porphyrin of pharmaceutical importance, we report herein on the use of pyrazole derivatives **3a–3m** as a key intermediate for the synthesis of new series of A_4 type of *meso*-substituted porphyrin.

Thus, the arylhydrazone derivatives **2a–2m** were prepared by condensing the acetyl derivatives **1a–1m** with phenylhydrazine in the presence of a few drops of concentrated hydrochloric acid according to the following reaction (Scheme 1).

Consequently, the obtained hydrazones **2a–2m** were subjected to react with Vilsmeier–Haak reagent to give the corresponding pyrazole derivatives **3a–3m** according to the following proposed mechanism (Schemes 2 and 3).

Porphyrins **4a–4m** were synthesized according to (Scheme 4). The precursors **3a–3m** were condensed with pyrrole in the presence of *p*-toluenesulfonic acid and *N,N*-dimethylformamide as a solvent under nitrogen gas to obtain the free-base porphyrins **4a–4m** which provided a high yield (80–90%). We suggested that this reaction was proceded *via* a capping mechanism to prevent the formation of polymeric pyrrole [35, 36].

The ^{1}H NMR spectra were also consistent with the structure of the synthesized compounds. Particularly, the



1a-m **2a-m**

2a; Ar = Ph, **2b**; Ar = pyrrol-2-yl, **2c**; Ar = Indol-3-yl, **2d**; Ar = 4-tol-1-yl, **2e**; Ar = 4-hydroxy phenyl, **2f**; Ar = pyridin-2-yl, **2g**; Ar = 1-biphenyl, **2h**; Ar = pyridin-4-yl, **2i**; Ar = 2-hydroxyphenyl, **2j**; Ar = 3-hydroxyphenyl, **2k**; Ar = 3-aminophenyl, **2l**; Ar = 4-acetylphenyl, **2m**; Ar = cyclohexen-1-yl

Scheme 1. simple and convenient method for the synthesis of different arylhydrazones **2a–2m**

2a-m **3a-m**

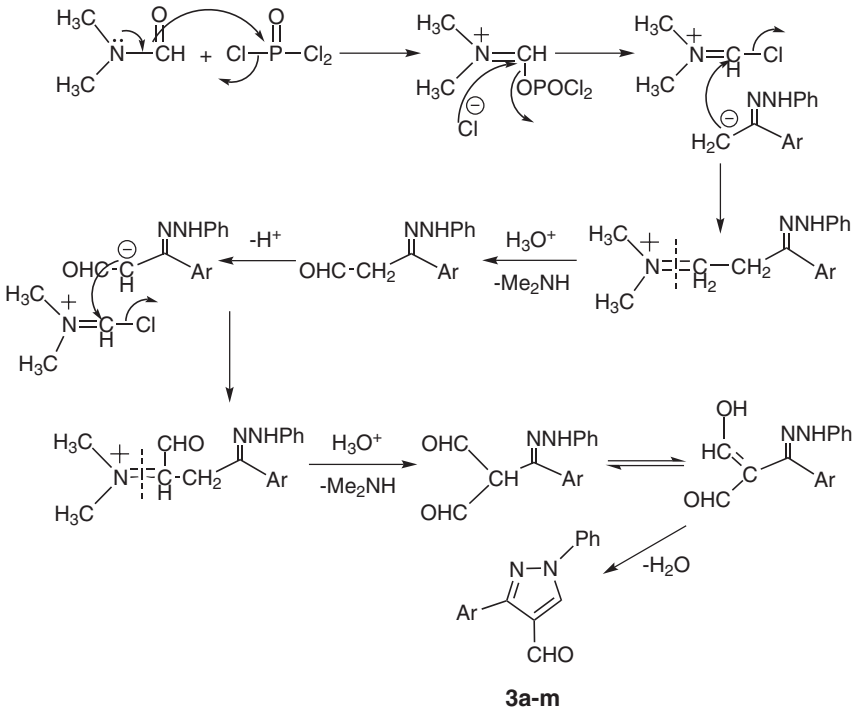
3a; Ar = Ph,3**b**; Ar = pyrrol-2-yl, **3c**; Ar = Indol-3-yl, **3d**; Ar = 4-tol-1-yl, **3e**; Ar = 4-hydroxy phenyl, **3f**; Ar = pyridin-2-yl, **3g**; Ar = 1-biphenyl, **3h**; Ar = pyridin-4-yl, **3i**; Ar = 2-hydroxyphenyl, **3j**; Ar = 3-hydroxyphenyl, **3k**; Ar = 3-aminophenyl, **3l**; Ar = 4-acetylphenyl, **3m**; Ar = cyclohexen-1-yl

Scheme 2. Vilsmeier–Haack reaction for the synthesis of different formyl pyrazoles **3a–3m**

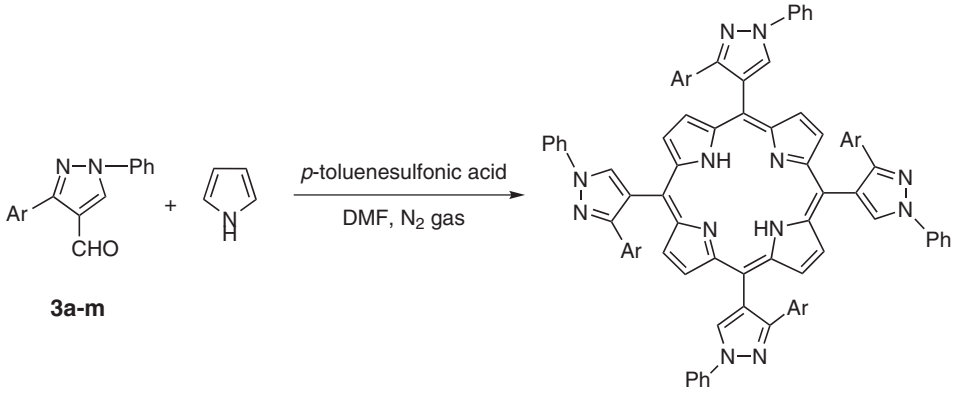
^{1}H NMR spectra have appeared very interesting due to the anisotropic effect of porphyrin ring (Fig. 1), resulting from circulation of electrons making up the conjugated π-bonding system, two shielded zones were formed over and under the macrocycle plane. The chemical shift assigned to protons falling within the conical areas was shielded and those falling outside the conical areas were deshielded. In this way, it was possible to justify the chemical shifts measured in the case of **4b** were shielded for 0.1–1.2 ppm relatively to **4b**.

In addition to the above results, it was interesting to prepare 5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazole-3-carbaldehyde (**6**) by the reaction of 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (**5**) [37-41] with selenium dioxide in dioxane to give a good yield of compound **6**. When 5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazole-3-carbaldehyde (**6**) reacted with pyrrole, according to the above mentioned procedure, they afforded the corresponding porphyrin **7**. Structure **7** was elucidated from its correct elemental and spectral data. The IR spectrum showed absorption bands at ν 3418, 1675 and 1615 cm^{-1} corresponding to vibrational frequencies of NH, C=O and C=N groups. Its UV-vis spectrum showed λ_{max} at 423 nm (**soret band**). The ^{1}H NMR spectrum showed a characteristic band at δ 3.8 ppm due to CH_2 protons and the absence of singlet signals at δ 9.75 ppm indicating that the CHO group was involved in the formation of porphyrin molecule. ^{13}C NMR gave a more confirmation for this structure (Scheme 5).

As a continuation of the above work, the ((*z*)-4(4-(dimethylamino)benzylidene)-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazole-3-carbaldehyde (**8**) was obtained by the reaction of compound **6** with *p-N,N*-dimethyl-aminobenzaldehyde. Its ^{1}H NMR spectrum showed two singlet signals at δ 3.07 and 3.12 ppm due to N-Me_2 protons while the =CH proton appeared at δ 7.1 ppm and the formyl proton at δ 9.85 ppm in addition to the aromatic protons at δ 7.2–7.45 ppm. When compound **8** was subjected to react with pyrrole in DMF, it afforded the corresponding porphyrin structure **9**. The IR spectrum showed absorption bands at ν 3350, 1680, 1610 and 1590 corresponding to stretching vibration of NH, C=O, C=N and C=C functions. Its ^{1}H NMR spectrum showed a characteristic band due to =CH proton at δ 7.08 ppm and *N*-Me_2 protons appeared at δ 3.61 ppm as a singlet signal



Scheme 3. Proposed mechanism of Vilsmeier–Haack reaction



4a; Ar = Ph,**4b**; Ar = pyrrol-2-yl, **4c**; Ar = Indol-3-yl, **4d**; Ar = 4-tol-1-yl,
4e; Ar = 4-hydroxy phenyl, **4f**; Ar = pyridin-2-yl, **4g**; Ar = 1-biphenyl,
4h; Ar = pyridin-4-yl,**4i**; Ar = 2-hydroxyphenyl, **4j**; Ar = 3-hydroxyphenyl,
4k; Ar = 3-aminophenyl, **4l**; Ar = 4-acetylphenyl, **4m**; Ar = cyclohexen-1-yl

Scheme 4. New class of porphyrin derivatives **4a–4m**

plus the normal characteristic protons of a porphyrin molecule. Its UV-vis spectrum showed λ_{max} at 424 nm (Scheme 6).

4-Formylphenazone (1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carbaldehyde) (**11**) was obtained by the reaction of phenazone (**10**) with Vilsmeier–Haak reagent. Its IR spectrum showed stretching frequencies at ν 1710, 1680 and 1610 cm^{-1} corresponding to formyl, amidic carbonyl and C=N function groups. The mass spectrum showed a molecular ion peak at *m/z* = 216 corresponding to a molecular formula $C_{12}H_{12}N_2O_2$. When compound **11** was subjected to react with pyrrole, according to the previously mentioned procedure, it afforded the corresponding porphyrin **12.** The IR spectrum of porphyrin **12** showed stretching vibrations due to NH, C=O and C=N at ν 3310, 1683 and 1610 cm^{-1}. The ^1H NMR of **12** revealed four characteristic singlet signals at δ 1.77, 3.25, 3.51 and 10.56 ppm attributable to CH_3, NH, N-CH_3 and NH protons, respectively. Its UV-vis spectrum showed λ_{max} at 425 nm (Scheme 7).

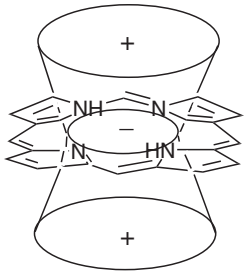
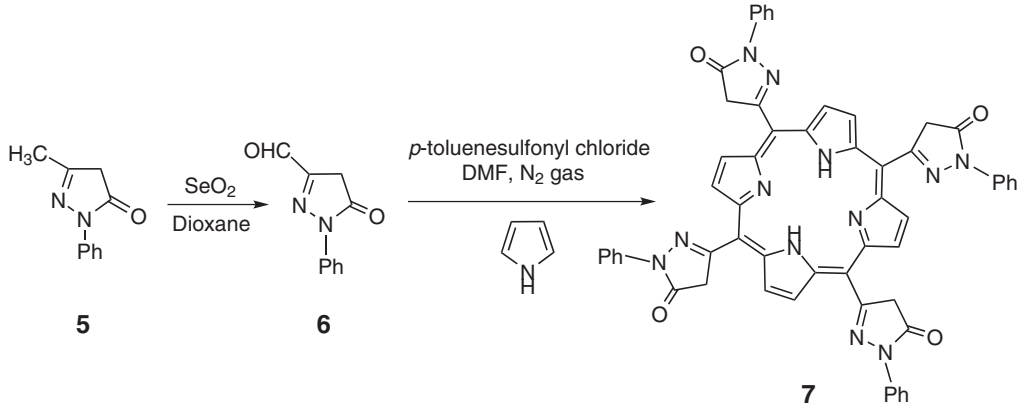


Fig. 1. The anisotropic effect of the porphyrin ring

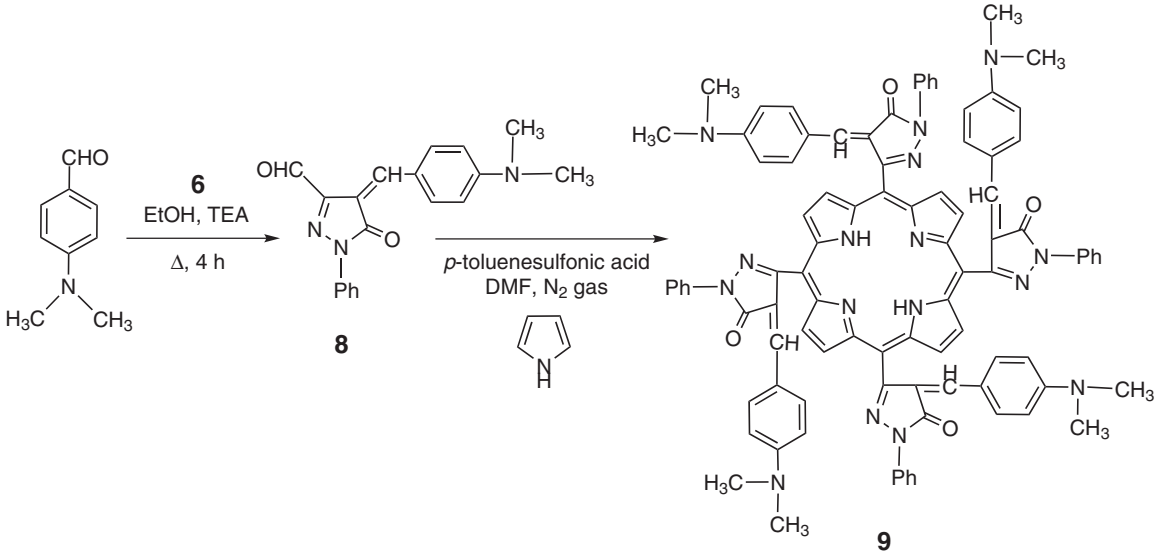
An interesting feature of the pyrrole is the possibility for the synthesis of 2,3,5-triformylpyrrole (**13**) by Vilsmeier–Haack reaction which was confirmed by analytical tools such as the IR spectrum that revealed absorption bands at ν 3316 and 1709 cm^{-1} due to NH and CHO groups. Mass spectroscopy showed a molecular ion peak *m/z* = 150 ($[M + 1]^+$, 95%). When compound **13** was treated with an excess amount of pyrrole in *N,N*-dimethylformamide as a solvent in an acid catalyzed reaction, it was found that all formyl groups were consumed in the preparation of porphyrin polymer **14** as depicted in Scheme 8. The IR spectrum showed no absorption band at ν 1709 cm^{-1} due to a C=O function. The UV-vis spectrum showed an absorption band at λ_{max} = 420 nm. The electronic absorption data was collected in Table 1. This data is well consistent with the molecular structure of the synthesized porphyrins.

In fact, one may note some slight spectral shifts by comparing the corresponding porphyrins which contain a heterocyclic moiety with porphyrins **4a–4m**, **7**, **9**, **12** and **14,** especially for both **4a**, **4b** species. The **4a** showed a band centered at λ_{max} = 423 (**Soret band**) after 1 h and Q-bands absorptions, respectively at 519, 556, 593 and 649 nm which have a strong Einstein shift compared with **4b.** The UV-vis spectrum consists of a **Soret band** at 419 nm and Q-bands at 514, 548, 589 and 644 nm.



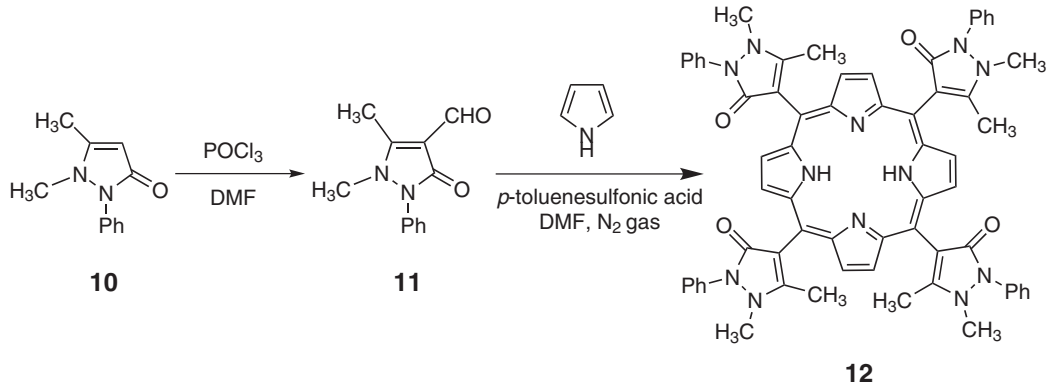
5 **6** **7**

Scheme 5. Formyl pyrazolone 6 in porphyrin synthesis **7**



8 **9**

Scheme 6. Novel porphyrin structure **9**



Scheme 7. Antipyrin used as key intermediate for the synthesis of porphyrin **12**

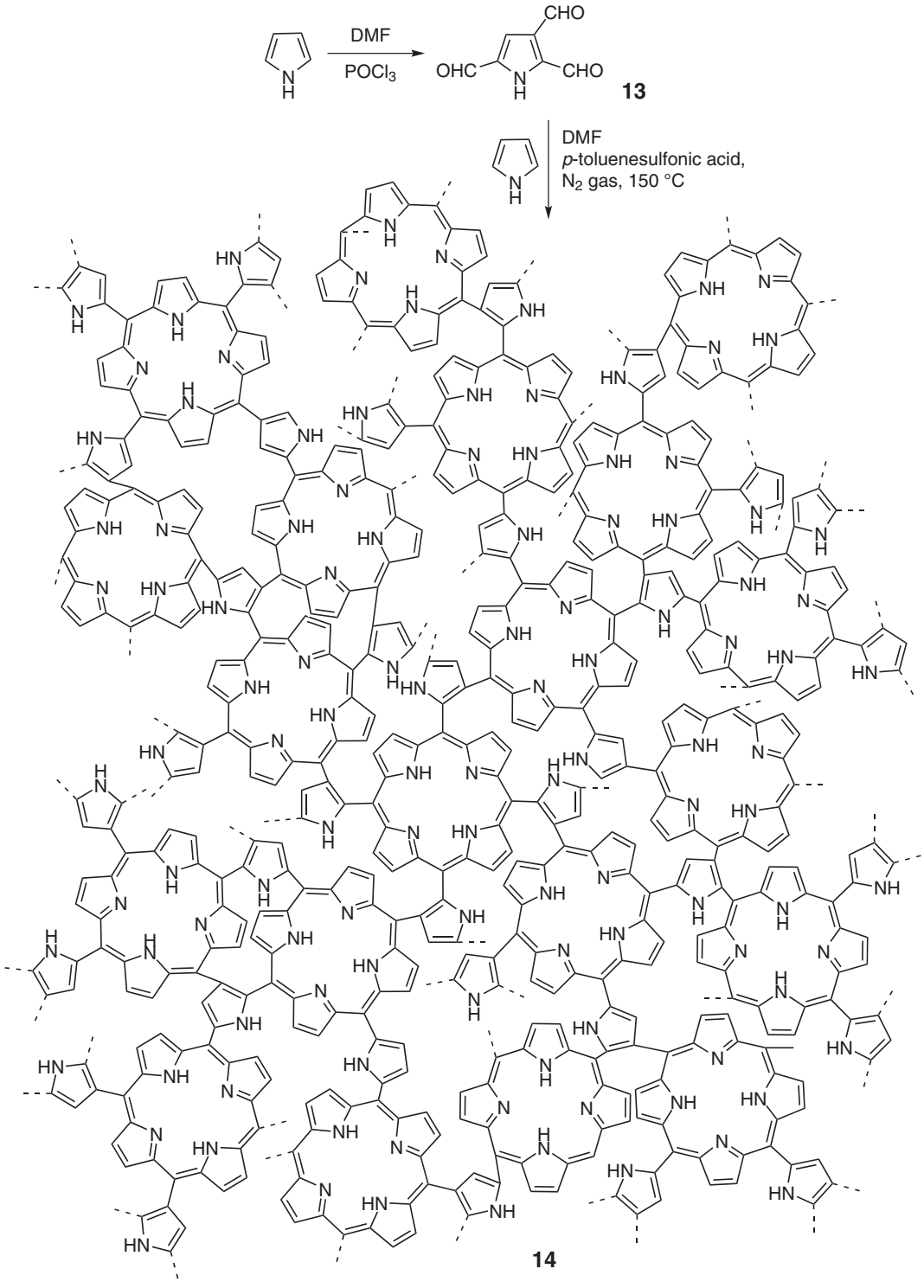
Biological screening

Antiviral activity. Viruses with high infection rates and rapid propagation can cause worldwide human and animal disease pandemics. With the emergence of previously unknown viruses and new virus variants in recent years, viral infection remains a major cause of human health problems. Moreover, the existing antiviral agents mainly target the key viral enzymes that are involved in the process of replication. Combination therapy by drugs with different modes of action and resistance profiles could be beneficial for a number of viral infections. There is a crucial need for developing new agents with novel antiviral mechanisms and broad antiviral activities. To this end, 17 new porphyrin compounds **4a**, **4b**, **4c**, **4d**, **4e**, **4f**, **4j**, **4h**, **4i**, **4j**, **4k**, **4l**, **4m**, **7**, **9**, **12** and **14** were screened and evaluated for their *in vitro* activity against Herpes Simplex Virus-1 (HSV-1) and Human Immunodeficiency Virus-1 (HIV-1). Regarding the HSV-1 which was grown on Vero African green monkey kidney cells, the antiviral antimitotic antibiotic Aphidicolin was used as a positive control [42]. Antiviral activity is defined as relatively confluent unaltered monolayers of stained Vero cells treated with HSV-1. The cytotoxicity of the tested porphyrin derivatives was performed using Vero cell culture [43]. Cytotoxicity was estimated as the concentration that caused approximately 50% inhibition of cell proliferation or cell viability. An improved plaque reduction assay for antiviral activity was used to test the targeted compounds. Among the 17 tested compounds, compound **4b** revealed a marginal activity as it reduced the number of the plaques by 45% at a minimum antiviral concentration (MAC) of 0.03 μ.M/L with cytotoxicity (IC_{50} = 0.03 μ.M/L). On the other hand, compounds **4h**, **4c**, **4e**, **4i and 4j** showed a moderate activity against HSV-1. Also, the rest of compounds exhibited from low to no inhibitory effect against HSV-1. The obtained results showed that the synthesized compounds showed various levels of cytotoxicity. The highest cytotoxicity was observed in compounds **4b**, **4h**, **4c**, **4e, 4i and 4j** (IC_{50} < 0.1 μ.M/L). However, the rest porphyrin derivatives were found to possess the lowest cytotoxic effect (IC_{50} > 1.5 μ.M/L) as outlined in Table 2.

HIV-1 is a causative agent for the transmission and development of the acquired immunodeficiency syndrome (AIDS). Being the leading cause of death in Africa and the fourth world wide [44], AIDS remains one of the most urgent world health problems. Therefore, this matter should be taken into account. Subsequently, the procedure used to evaluate the anti-HIV-1 potency is designed to detect agents acting at any stage of the virus reproductive cycle [45]. The assay involves the killing of T4 lymphocytes by HIV-1. Compounds that interfere with viral activities will protect cells from cytolysis. The median effective concentration (EC_{50}) of the tested compounds using infected cells was compared with their cytotoxic effect (IC_{50}) on uninfected cultures. Infected and uninfected cultures were incubated without test compounds to serve as controls. Zidovudine or Azidothymidine (AZT) treated cultures were also used as positive controls. The *in vitro* assessment against HIV-1 revealed that some of the tested compounds displayed a high inhibition activity while other compounds displayed a moderate or little activity according to the obtained results outlined in Table 3.

Therefore, compound **4b** has the most potent cytotoxic activity against HIV-1, whereas, compounds **4h**, **4g**, **4c**, **4e**, **4j** and **4i** have a moderate activity. Finally, the rest of compounds exhibited the lowest activity.

Antitumor activity. Cancer continues to present the largest cause of mortality in the world and claims over six million lives each year [46]. Prevention is the sensible maneuver towards the ultimate goal of cancer control [47]. Several methods exist for the treatment of cancer in modern medicine. These include chemotherapy, radiotherapy and surgery. Chemotherapy is now considered as the most effective method of cancer treatment. Intervention with chemopreventive agents at the early stage in carcinogenesis is theoretically more rational than attempting to eradicate fully developed



Scheme 8. High functionalized porphyrin polymer **14**

tumor with chemotherapeutic drugs. However, most cancer chemotherapeutic agents severely affect the most normal cells [48]. So, it is very important to find some new anticancer chemical entities which have less toxicity to host cell [49, 50]. The use of heterocyclic compounds played an important role in the control of cancer and its eradication program. Heterocyclic compounds are commonly used as scaffolds on which pharmacophores are arranged to provide potent and selective drugs. This is especially true for five member ring heterocyclic compounds [51], which serve as the core components of a large number of substances that possess a wide interesting range of the biological activity. Taking all of the above mentioned evidence into account, the aim of

Table 1. UV-vis spectra of porphyrin derivatives **4a–4m**, **7**, **9**, **12** and **14**

Compound	λ_{max}		
	After 1 min (Q-bands)	After 30 min (Q-bands)	After 60 min (soret band)
4a	649, 593, 556	519	423
4b	644, 589, 548	514	419
4c	526, 521	511	423
4d	640, 556, 524	513	425
4e	540	500	422
4f	525, 512	502	420
4g	536	499	425
4h	620, 587, 542	506	422
4i	525	495	425
4j	630, 590, 540	510	423
4k	554, 530	501	422
4l	543	512	426
4m	589, 530	500	425
7	562	495	423
9	546, 530	506	424
12	632, 582	496	425
14	590	512	420

Table 2. The cytotoxicity, anti-HSV-1 activities of compounds **4a–4m**, **7**, **9**, **12** and **14** and the antiviral antibiotic aphidicolin

Entry	Compound	Reduction in number in plaques, %	Minimum Antiviral Conc. (MAC), μM/L	Cytotoxicity (IC_{50}) [a]
1	**Aphidicolin**	100	0.02	0.58
2	**4a**	B	C	0.32
3	**4b**	45	0.03	0.03
4	**4c**	29	0.08	0.09
5	**4d**	B	C	0.15
6	**4e**	28.6	0.10	0.08
7	**4f**	30	0.09	0.07
8	**4g**	B	C	0.24
9	**4h**	32	0.06	0.06
10	**4i**	26	0.15	0.098
11	**4j**	26.2	0.12	0.094
12	**4k**	25	0.18	0.10
13	**4l**	12	0.20	0.19
14	**4m**	B	C	>1.74
15	**7**	11	0.23	0.128
16	**9**	B	0.31	0.125
17	**12**	9	0.24	0.199
18	**14**	B	C	0.15

[a] IC_{50}: the concentration of drug that caused 50% loss of the monolayer present around the plaques. [b] B: 0% reduction in number of viral plaques. [c] C: inactive compound.

Table 3. The cytotoxicity, anti-HIV-1 activities of compounds **4a–4m**, **7**, **9**, **12** and **14** and the antiviral drug Zidovudine (AZT)

Entry	Compound	Cytotoxicity (IC_{50}), μM/L[a]	Effective concentration (EC_{50}), μM/L[b]	SI_{50} (IC_{50}/EC_{50})[c]
1	**AZT**	35.60	0.70	50.86
2	**4a**	C	>100	C
3	**4b**	>100	0.82	>100
4	**4c**	>75	>100	>0.75
5	**4d**	55.21	>100	>0.55
6	**4e**	>75	>100	>0.75
7	**4f**	80	>100	>0.80
8	**4g**	35.62	>100	>0.35
9	**4h**	>85	>100	>0.85
10	**4i**	>70	>100	>0.70
11	**4j**	>70	>100	>0.70
12	**4k**	>69	>100	>0.69
13	**4l**	25.5	>100	>0.255
14	**4m**	C	C	C
15	**7**	30.25	>100	>0.30
16	**9**	22.5	>100	>0.22
17	**12**	11.00	>100	>0.11
18	**14**	C	>100	C

[a] IC_{50}: 50% inhibitory concentration (the molar concentration of drug that caused 50% inhibition of cell growth). [b] 50% effective concentration (the molar concentration of drug that caused 50% protection against HIV-1 cytopathic effect); C: inactive compound. [c] SI: selectivity index: ratio IC_{50}/EC_{50}.

this research was to synthesize novel drugs for anticancer evaluation as a trial to obtain new antitumor agents of a higher activity and lower side effects. In the present work, the selected compounds related to porphyrin derivatives were evaluated and screened *in-vitro* as inhibitors of the growth of Vero (an African green monkey kidney cell line), WI-38 (lung fibroblast cell line), HepG2 (hepatoma cells or human liver hepatocellular carcinoma cell line) and MCF-7 (human breast adenocarcinoma cell line) in comparison to the known anticancer drug: 5-fluorouracil (5-Fu) and as a trial to get more effective and less toxic agents. The results were expressed in the form of the concentration of compounds that caused 50% inhibition of cells growth.

The *in vitro* evaluation revealed that some of the tested compounds revealed a high inhibition activity while other compounds displayed a moderate or little activity according to the obtained results outlined in Table 4.

Therefore, compounds **4b** and **4h** have the most potent cytotoxic activity against HepG2 cell lines. Whereas, compounds **4f**, **4c**, **4e**, **4i** and **4j** have a moderate activity against HepG2 cell lines. Finally, the rest of compounds exhibited the lowest activity against HepG2 cell lines.

Additionally, compound **4b** showed the highest cytotoxic activity against WI-38 cell line while, compounds **4f**, **4c**, **4e** and **4j** revealed a moderate cytotoxic activity against WI-38 cell lines. On the other hand, compounds **4k** and **4l** exhibited a lower activity against WI-38 cell lines. Furthermore, compound **4b** displayed a broad spectrum of activity against MCF-7 cell lines. However, compounds **4f**, **4c, 4c**, **4e** and **4j** revealed a moderate cytotoxic activity against MCF-7 cell lines. The rest of compounds exhibited a lower cytotoxic activity against MCF-7 cell lines.

Structure activity relationship. From the antiviral and antitumor activity results obtained for the selected porphyrin derivatives, the activity of the tested compounds could be correlated with structure variation and modification. Therefore, it was noticed that compound **4b** has a more potent activity. This may be attributed to the presence of five pyrrolyl rings besides a pyrazolyl ring as a number of heterocyclic ring increase especially a five membered ring which contains one heteroatom and possess a high potency and activity increase. It seems that compounds **4h**, **4f**, **4c** exhibited a moderate activity owing to the large size of heterocyclic ring. Also fused heterocyclic ring decreased the activity. On the other hand, compounds **4e**, **4j** and **4i** revealed a moderate activity due to the introducing of OH group in different positions of phenyl group according to the

Table 4. *In vitro* antitumor activities of tested compounds on different cell lines

Compound	IC_{50}, μg/mL			
	HepG2	WI-38	VERO	MCF-7
4a	89.20 ± 0.13	79.60 ± 0.07	100 ± 0.05	120 ± 0.19
4b	12.40 ± 0.03	20.10 ± 0.02	9.32 ± 0.04	12.50 ± 0.03
4c	29.50 ± 0.09	27.60 ± 0.19	36.50 ± 0.33	29.90 ± 0.14
4d	33.10 ± 0.06	39.80 ± 0.16	42.60 ± 0.16	45.60 ± 0.01
4e	33.02 ± 0.01	55.30 ± 0.21	41.90 ± 0.08	65.60 ± 0.23
4f	26.00 ± 0.11	40.30 ± 0.13	38.10 ± 0.19	45.90 ± 0.18
4g	89.20 ± 0.26	71.10 ± 0.15	85.20 ± 0.07	88.2 ± 0.22
4h	23.20 ± 0.03	33.70 ± 0.31	30.3 ± 0.19	26.1 ± 0.06
4i	44.10 ± 0.09	41.00 ± 0.07	49.25 ± 0.05	42.65 ± 0.01
4j	42.02 ± 0.06	46.18 ± 0.02	43.12 ± 0.01	42.12 ± 0.02
4k	88.20 ± 0.22	74.02 ± 0.06	90.01 ± 0.03	85.50 ± 0.04
4l	85.20 ± 0.09	75.32 ± 0.21	86.05 ± 0.02	71.60 ± 0.05
4m	102.00 ± 0.40	120.00 ± 0.07	100.85 ± 0.23	200.00 ± 0.3
7	79.60 ± 0.07	65.41 ± 0.12	74.92 ± 0.20	88.20 ± 0.22
9	79.30 ± 0.16	64.00 ± 0.02	79.12 ± 0.06	73.10 ± 0.11
12	71.10 ± 0.15	75.00 ± 0.023	85.03 ± 0.31	93.85 ± 0.14
14	92.00 ± 0.05	99.32 ± 0.04	75.24 ± 0.03	94.32 ± 0.03
5-Fu	8.60 ± 0.03	3.20 ± 0.01	6.50 ± 0.04	2.30 ± 0.02

[a] IC_{50} (μg/mL): 1–10 (very strong), 11–25 (strong), 26–50 (moderate), 51–100 (weak), 100–200 (very weak), 200 (noncytotoxicity).

following sequence **4e (*p*-OH) > 4j (m-OH) > 4i (o-OH).** This may be attributed to a steric hindrance around linkage between aryl substituent in *meso*-position and porphyrin skeleton. It is remarkable that this variation of activity spectrum between these derivatives indicates the importance of one nitrogen containing a heterocyclic ring, especially a five membered ring, as size of ring increases, the activity decreases. Aromaticity and steric hindrance of aryl derivatives in *meso*-position of porphrin skeleton reduces conformational freedom of the skeleton and consequently it decreases activity and increases twist angle around linkage between aryl substituent in *meso*-position and porphyrin skeleton. Moreover, electronegativity of introducing heteroatom in derivatives increases and stability decreased. The activity has the following order **4b > 4h > 4f > 4c > 4e > 4j > 4i > 4k > 4l > 7 > 12 > 9 > 4a > 4d > 4g > 14 > 4m.**

EXPERIMENTAL

General

All melting points are uncorrected and determined on Gallenkamp electric apparatus. The IR spectra were recorded (KBr disk) on a Mattson 5000 FTIR spectrometer at Mansoura University, Egypt. The ^{1}H NMR spectra were determined on a Bruker WPSY 200 M.Hz spectrometer with tetramethylsilane and the chemical shifts are in δ ppm using (DMSO-d_6) as a solvent. The mass spectra were recorded at 70 eV with a Varian MAT 311 at the Microanalytical Center, Cairo University. Elemental analyses (C, H and N) were carried out at the Faculty of Science, Cairo University. The results were found to be in a good agreement (± 0.03) with the calculated values.

Synthesis of arylhydrazone derivatives 2a–2m

General procedure. A mixture of acetyl derivatives **1a–1m** (0.01 mol) and phenylhydrazine (1.08 g, 0.01 mol) was fused in silicon oil bath at 150 °C for about 5–10 min in the presence of a few drops of concentrated HCl. The reaction mixture was washed with dil. ethanol, filtered off, dried well, then recrystallized from dil. ethanol.

1-Phenyl-2-(1-phenylethylidene)hydrazine (2a). Beige crystal, yield 60%, mp 170 °C. Anal. data for $C_{14}H_{14}N_2$ (210). Calcd. C; 79.97 H; 6.71 N; 13.32%. Found C; 79.99 H; 6.72 N; 13.30%. IR (KBr): ν, cm^{-1} 3440 (NH), 1615 (C=N), 1608 (C=C). ^{1}H NMR

(DMSO-d_6): δ ppm 2.1 (s, 3H, CH_3), 6.96–7.90 (m, 10H, Ar-H), 10.94 (s, 1H, NH). MS: *m/z* 210 ([M]$^+$, 25%), 133 (81%), 70 (100%), 156 (75%).

2-(1-(2-Phenylhydrazono)ethyl)-1H-pyrrole (2b). Beige cotton crystal, yield 82%, mp 160 °C. Anal. data for $C_{12}H_{13}N_3$ (199). Calcd. C; 72.33 H; 6.58 N; 21.09%. Found C; 72.34 H; 6.59 N; 21.09%. IR (KBr): ν, cm^{-1} 3343, 3399 (2 NH), 1625 (C=N), 1600 (C=C). ^{1}H NMR (DMSO-d_6): δ ppm 2.1 (s, 3H, CH_3), 6.03 (d, 1H, pyrrolic CH), 6.3 (d, 1H, pyrrolic CH), 6.69 (d.d, 1H, pyrrolic CH), 7.10–7.40 (m, 5H, Ar-H), 10.64 (s, 1H, NH), 10.94 (s, 1H, NH). MS: *m/z* 199 ([M]$^+$, 100%), 184 (18%), 118 (32%), 92 (75%), 80 (75.5%), 53 (45%).

3-(1-(2-Phenylhydrazono)ethyl)-1H-indole (2c). Yellow cotton crystal, yield 86%, mp 148 °C. Anal. data for $C_{16}H_{15}N_3$ (249). Calcd. C; 77.08 H; 6.06 N; 16.85%. Found C; 77.10 H; 6.10 N; 16.85%. IR (KBr): ν, cm^{-1} 3442, 3413 (2 NH), 1625 (C=N), 1600 (C=C).^{1}H NMR (DMSO-d_6): δ ppm 2.00 (s, 3H, CH_3), 7.32 (s, 1H, CH), 6.89–8.20 (m, 9H, Ar-H), 10.64 (s, 1H, NH), 10.94 (s, 1H, NH). MS: *m/z* 249 ([M]$^+$, 37%), 172 (65%), 144 (10%), 117 (35%), 90 (100%).

1-Phenyl-2-(1-p-tolylethylidene)hydrazine (2d). Buff powder, yield 86%, mp 214 °C. Anal. data for $C_{15}H_{16}N_2$ (224). Calcd. C; 80.32 H; 7.19 N; 12.49%. Found C; 80.30 H; 7.10 N; 12.50%. IR (KBr): ν, cm^{-1} 3455, 3439 (2 NH), 296 (CH_3), 1620 (C=N), 1587 (C=C). ^{1}H NMR (DMSO-d_6): δ ppm 2.1 (s, 3H, CH_3), 2.3 (s, 1H,CH_3), 6.91–7.56 (m, 7H, Ar-H), 7.62 (d, 2H, Ar-H), 11.01 (s, 1H, NH). MS: *m/z* 224 ([M]$^+$, 25%), 208 (52%), 130 (17%), 103 (100%), 74 (52%), 49 (25%).

4-(1-(2-Phenylhydrazono)ethyl)phenol (2e). Buff powder, yield 65%, mp 220 °C. Anal. data for $C_{14}H_{14}N_2O$ (226). Calcd. C; 74.31 H; 6.24 N; 12.38%. Found C; 74.30 H; 6.25 N; 12.37%. IR (KBr): ν, cm^{-1} 3451 (OH), 3431 (NH), 1622 (C=N), 1587 (C=C). ^{1}H NMR (DMSO-d_6): δ ppm 2.1 (s, 3H, CH_3), 6.93–7.45 (m, 7H, Ar-H), 7.72 (d, 2H, Ar-H), 11.21 (s, 1H, NH), 11.34 (s, 1H, OH). MS: *m/z* 226 ([M]$^+$, 73%), 210 (86%), 132 (15%), 105 (100%), 64 (45.5%), 50 (55%).

2-(1-(2-Phenylhydrazono)ethyl)pyridine (2f). Buff powder, yield 65%, mp 216–218 °C. Anal. data for $C_{13}H_{13}N_3$ (211). Calcd. C; 73.91 H; 6.20 N; 19.89%. Found C; 73.99 H; 6.25 N; 19.89%. IR (KBr): ν, cm^{-1} 3431 (NH), 1619 (C=N), 1600 (C=C). ^{1}H NMR (DMSO-d_6): δ ppm 2.1 (s, 3H, CH_3), 7.09–7.55 (m, 9H, Ar-H), 11.00 (s, 1H, NH). MS: *m/z* 211 ([M]$^+$, 52%), 196 (74%), 143 (66%), 118 (100%), 92 (44%), 65 (78%).

1-(1-Biphenyl-4-ylethylidene)-2-phenylhydrazine (2g). Beige cotton crystal, yield 75%, mp 165–168 °C. Anal. data for $C_{20}H_{18}N_2$ (286). Calcd. C; 83.88 H; 6.34 N; 9.78%. Found C; 83.90 H; 6.35 N; 9.78%. IR (KBr): ν, cm^{-1} 3343 (NH), 1625 (C=N), 1598 (C=C). ^{1}H NMR (DMSO-d_6): δ ppm 2.1 (s, 3H, CH_3), 6.89–7.33 (m, 14H, Ar-H), 10.89 (s, 1H, NH). MS: *m/z* 286 ([M]$^+$, 83%), 209 (66%), 133 (74%), 106 (34%), 77 (100%), 53 (51%).

4-(1-(2-Phenylhydrazono)ethyl)pyridine (2h). Orange powder, yield 65%, mp 214–216 °C. Anal. data for $C_{13}H_{13}N_3$ (211). Calcd. C; 73.91 H; 6.20 N; 19.89%. Found C; 73.99 H; 6.25 N; 19.89%. IR (KBr): ν, cm^{-1} 3331 (NH), 1623 (C=N), 1590 (C=C). ^{1}H NMR (DMSO-d_6): δ ppm 1.95 (s, 3H, CH_3), 7.11–7.65 (m, 9H, Ar-H), 10.90 (s, 1H, NH); MS: *m/z* 211 ([M]$^+$, 62%), 196 (54%), 143 (64%), 118 (100%), 92 (77%), 65 (74%). MS: *m/z* 211 ([M]$^+$, 62%), 196 (54%), 143 (64%), 118 (100%), 92 (77%), 65 (74%).

2-(1-(2-Phenylhydrazono)ethyl)phenol (2i). Pale yellow cotton crystal, yield 88%, mp 233–234 °C. Anal. data for $C_{14}H_{14}N_2O$ (226). Calcd. C; 74.31 H; 6.24 N; 12.38%. Found C; 74.30 H; 6.25 N; 12.37%. IR (KBr): ν, cm^{-1} 3450 (OH), 3431 (NH), 1624 (C=N), 1587 (C=C). ^{1}H NMR (DMSO-d_6): δ ppm 2.11 (s, 3H, CH_3), 7.09–7.45 (m, 9H, Ar-H), 10.98 (s, 1H, NH), 11.00 (s, 1H, OH). MS: *m/z* 228 ([M + 2]$^+$, 84%), 211 (36%), 132 (33%), 105 (100%), 63 (45.5%), 51 (55%).

3-(1-(2-Phenylhydrazono)ethyl)phenol (2j). Silver cotton crystal, yield 82%, mp 230–232 °C. Anal. data for $C_{14}H_{14}N_2O$ (226). Calcd. C; 74.31 H; 6.24 N; 12.38%. Found C; 74.30 H; 6.25 N; 12.37%. IR (KBr): ν, cm^{-1} 3455 (OH), 3433 (NH), 1618 (C=N), 1597 (C=C). ^{1}H NMR (DMSO-d_6): δ ppm 1.99 (s, 3H, CH_3), 7.19–7.65 (m, 9H, Ar-H), 10.65 (s, 1H, NH), 11.30 (s, 1H, OH). MS: *m/z* 228 ([M + 2]$^+$, 24%), 209 (41%), 130 (13%), 104 (100%), 63 (42%), 50 (15%).

3-(1-(2-Phenylhydrazono)ethyl)aniline (2k). Buff cotton crystal, yield 80%, mp 220–222 °C. Anal. data for $C_{14}H_{15}N_3$ (225). Calcd. C; 74.64 H; 6.71 N; 18.65%. Found C; 74.60 H; 6.75 N; 18.67%. IR (KBr): ν, cm^{-1} 3450 (NH), 3425 (NH_2), 1625 (C=N), 1597 (C=C). ^{1}H NMR (DMSO-d_6): δ ppm 1.98 (s, 3H, CH_3), 7.09–7.65 (m, 9H, Ar-H), 6.20 (s, 2H, NH_2), 10.65 (s, 1H, NH). MS: *m/z* 225 ([M]$^+$, 27%), 209 (19%), 132 (62%), 104 (18%), 92 (100%), 76 (32%).

1-(4-(1-Phenylhydrazono)ethyl)phenyl)ethanone (2l). Pale yellow crystal, yield 72%, mp 228–230 °C. Anal. data for $C_{16}H_{16}N_2O$ (252). Calcd. C; 76.16 H; 6.39 N; 11.10%. Found C; 76.20 H; 6.40 N; 11.19%. IR (KBr): ν, cm^{-1} 3433 (NH), 1725 (C=O), 1615 (C=N), 1599 (C=C). ^{1}H NMR (DMSO-d_6): δ ppm 2.1 (s, 3H, CH_3), 3.23 (s, 3H, CH_3), 7.19–7.71 (m, 9H, Ar-H), 10.78 (s, 1H, NH). MS: *m/z* 252 ([M]$^+$, 45%), 237 (86%), 160 (100%), 145 (75%), 104 (75.5%), 64 (55%).

1-(-Cyclohexenylethylidene)-2-phenylhydrazine (2m). Orange crystal, yield 62%, mp 171–174 °C. Anal. data for $C_{14}H_{15}N_3$ (214). Calcd. C; 78.46 H; 8.47 N; 13.07%. Found C; 78.47 H; 8.50 N; 13.10%. IR (KBr): ν, cm^{-1} 3452 (NH), 1624 (C=N), 1597 (C=C). ^{1}H NMR (DMSO-d_6): δ ppm 2.1 (s, 3H, CH_3), 1.6 (m, 4H, 2 CH_2), 2.0 (m, 4H, 2 CH_2), 5.3 (t, 1H, CH), 7.19–7.35 (m, 5H, Ar-H), 10.89 (s, 1H, NH). MS: *m/z* 215 ([M + 1]$^+$, 37%), 199 (9%), 122 (53%), 94 (90%), 82 (100%), 58 (42%).

Synthesis of 3-aryl-1-phenyl-1H- pyrazole-4-carbaldehydes 3a–3m

General procedure. At 0 °C, phosphorous oxychloride (5.37 g, 0.035 mol) was added dropwise with stirring to DMF (1.095 g, 0.015 mol) in an ice bath during 0.5 h, then a solution of arylhydrazone derivatives **2a–2m** (0.005 mol) in DMF (10 mL) was added to the Vilsmeier–Haak reagent and continued being stirred for about 0.5 h, then the reaction mixture was refluxed on water bath for 1–2 h. The reaction mixture was cooled, poured onto ice-water, then a solution of potassium carbonate was added until effervesence ceased and the precipitated solid material was filtered off, washed with cold water, dried well and recrystallized from absolute ethanol.

1,3-Diphenyl-1H-pyrazole-4-carbaldehyde (3a). Beige cotton crystal, yield 75%, mp 147–150 °C. Anal. data for $C_{16}H_{12}N_2O$ (248). Calcd. C; 77.40 H; 4.87 N; 11.28%. Found C; 77.45 H; 4.88 N; 11.30%. IR (KBr): ν, cm^{-1} 1669 (C=O), 1625 (C=N), 1698 (C=C). MS: *m/z* 248 ($[M]^+$, 45%), 247 (100%), 246 (90%), 219 (25%), 218 (75.5%), 143 (10%), 98 (11%), 94 (20%), 76 (50%).

1-Phenyl-3-(1H-pyrrol-2-yl)-1H-pyrazole-4-carbaldehyde (3b). Black crystal, yield 75%, mp 169–170 °C. Anal. data for $C_{14}H_{11}N_3O$ (237). Calcd. C; 70.87 H; 4.67 N; 17.71%. Found C; 70.88 H; 4.70 N; 17.70%. IR (KBr): ν, cm^{-1} 3424 (NH), 1670 (C=O), 1625 (C=N), 1694 (C=C). MS: *m/z* 237 ($[M]^+$, 45%), 208 (44%), 183 (36%), 161 (57%), 132 (100%), 104 (32%), 67 (26%).

3-(1H-Indol-3-yl)-1-phenyl-1H-pyrazole-4-carbaldehyde (3c). Buff crystal, yield 72%, mp > 300 °C. Anal. data for $C_{18}H_{13}N_3O$ (287). Calcd. C; 75.25 H; 4.56 N; 14.63%. Found C; 75.26 H; 4.57 N; 14.63%. IR (KBr): ν, cm^{-1} 3438 (NH), 1650 (C=O), 1625 (C=N), 1684 (C=C). MS: *m/z* 287 ($[M]^+$, 78%), 276 (50%), 258 (64%), 252 (48%), 211 (53%), 200 (45%), 188 (79%), 173 (53%), 156 (46%), 139 (62%), 110 (65%), 94 (60%), 78 (78%), 55 (100%).

1-Phenyl-3-p-tolyl-1H-4-carbaldehyde (3d). Bege crystal, yield 55%, mp 110–112 °C. Anal. data for $C_{17}H_{14}N_2O$ (262). Calcd. C; 77.84 H; 5.38 N; 10.68%. Found C; 77.85 H; 5.39 N; 10.68%. IR (KBr): ν, cm^{-1} 1670 (C=O), 1635 (C=N), 1690 (C=C). ^{1}H NMR (DMSO-d_6): δ ppm 2.38 (s, 3H, CH_3), 7.31–7.60 (m, 5H, Ar-H), 7.80 (d, 2H, Ar-H), 8.00 (d, 2H, Ar-H), 9.28 (s, 1H, CH), 9.98 (s, 1H, CHO). MS: *m/z* 262 ($[M]^+$, 40%), 261 (100%), 260 (65%), 246 (50%), 233 (20%), 129 (10%), 76 (23%).

3-(4-Hydroxyphenyl)-1-phenyl-1H-pyrazole-4-carbaldehyde (3e). Pale brown crystal, yield 88%, mp > 300 °C. Anal. data for $C_{16}H_{12}N_2O_2$ (264). Calcd. C; 72.72 H; 4.58 N; 10.60%. Found C; 72.75 H; 4.60 N; 10.68%. IR (KBr): ν, cm^{-1} 3412 (OH), 1687 (C=O), 1622 (C=N), 1600 (C=C). MS: *m/z* 271 (M^+ + 7, 42%), 178 (50%), 165 (36%), 149 (100%), 135 (36%), 111 (51%), 146 (51%), 97 (61%), 83 (55%).

1-Phenyl-3-(pyridin-2-yl)-1H-pyrazole-4-carbaldehyde (3f). Green crystal, yield 88%, mp > 300 °C. Anal. data for $C_{15}H_{11}N_3O$ (249). Calcd. C; 72.28 H; 4.45 N; 16.86%. Found C; 72.30 H; 4.50 N; 16.88%. IR (KBr): ν, cm^{-1} 1676 (C=O), 1630 (C=N), 1615 (C=C). MS: *m/z* 249 ($[M]^+$, 42%), 218 (40%), 208 (40%), 185 (54%), 181 (43%), 160 (40%), 146 (51%), 117 (53%), 99 (54%), 85 (75%), 61 (85%), 55 (100%).

3-(Biphenyl-4-yl)-1-phenyl-1H-pyrazole-4-carbaldehyde (3g). Deep yellow crystal, yield 81%, mp 168–170 °C. Anal. data for $C_{24}H_{18}N_2O$ (324). Calcd. C; 78.67 H; 4.95 N; 7.65%. Found C; 78.70 H; 4.99 N; 7.65%. IR (KBr): ν, cm^{-1} 1675 (C=O), 1620 (C=N), 1610 (C=C). MS: *m/z* 325 ($[M + 1]^+$, 1.45%), 295 (8.37%), 247 (100%), 219 (7.87%), 189 (8.13%), 152 (18.33%), 104 (7.71%), 77 (38.19%).

1-Phenyl-3-(pyridin-4-yl)-1H-pyrazole-4-carbaldehyde (3h). Pale brown crystal, yield 70%, mp > 300 °C. Anal. data for $C_{15}H_{11}N_3O$ (249). Calcd. C; 72.28 H; 4.45 N; 16.86%. Found C; 72.30 H; 4.50 N; 16.88%. IR (KBr): ν, cm^{-1} 1680 (C=O), 1632 (C=N), 1601 (C=C). MS: *m/z* 250 ($[M + 1]^+$, 18.1%), 248 (100%), 247 (70%), 246 (36.9%), 219 (17.8%), 102 (26.1%), 95 (16.3%), 76 (61.9%).

3-(2-Hydroxyphenyl)-1-phenyl-1H-pyrazole-4-carbaldehyde (3i). Pale brown crystal, yield 88%, mp > 300 °C. Anal. data for $C_{16}H_{12}N_2O_2$ (264). Calcd. C; 72.72 H; 4.58 N; 10.60%. Found C; 72.75 H; 4.60 N; 10.68%. IR (KBr): ν, cm^{-1} 3430 (OH), 1678 (C=O), 1622 (C=N), 1600 (C=C). MS: *m/z* 264 ($[M]^+$, 46%), 236 (100%), 131 (45%), 104 (42%), 77 (66%).

3-(3-Hydroxyphenyl)-1-phenyl-1H-pyrazole-4-carbaldehyde (3j). Beige crystal, yield 56%, mp > 300 °C. Anal. data for $C_{16}H_{12}N_2O_2$ (264). Calcd. C; 72.72 H; 4.58 N; 10.60%. Found C; 72.75 H; 4.60 N; 10.68%. IR (KBr): ν, cm^{-1} 3422 (OH), 1678 (C=O), 1632 (C=N), 1610 (C=C). MS: *m/z* 265 ($[M + 1]^+$, 17.6%), 264 (100%), 236 (32.8%), 208 (27%), 76 (32.6%).

3-(3-Aminophenyl)-1-phenyl-1H-pyrazole-4-carbaldehyde (3k). Beige crystal, yield 66%, mp > 300 °C. Anal. data for $C_{16}H_{11}N_2O_2$ (263). Calcd. C; 72.99 H; 4.98 N; 15.96%. Found C; 73.00 H; 4.90 N; 15.98%. IR (KBr): ν, cm^{-1} 3422 (NH_2), 1675 (C=O), 1610 (C=N), 1600 (C=C). ^{1}H NMR (DMSO-d_6): δ ppm 7.44–7.76 (m, 5H, Ar-H), 7.76 (d, 2H, 2 Ar-H), 8.02 (d, 2H, 2 Ar-H), 8.40 (s, 2H, NH_2), 9.33 (s, 1H, CH), 10.01 (s, 1H, CHO). MS: *m/z* 263 ($[M]^+$, 51%), 248 (28%), 170 (27%), 15 (91%), 107 (100%), 77 (32%).

3-(4-Acetylphenyl)-1-phenyl-1H-pyrazole-4-carbaldehyde (3l). Yellow crystal, yield 60%, mp > 300 °C. Anal. data for $C_{16}H_{11}N_2O_2$ (290). Calcd. C; 74.47 H; 4.86 N; 9.65%. Found C; 74.50 H; 4.88 N; 9.70%. IR (KBr): ν, cm^{-1} 1702, 1675 (2 C=O), 1623 (C=N), 1601 (C=C). MS: *m/z* 292 ($[M + 2]^+$, 82%), 291(68%), 170 (88%), 153 (69%), 145 (100%), 105 (67%).

3-Cyclohexenyl-1-phenyl-1H-pyrazole-4-carbaldehyde (3m). Beige crystal, yield 52%, mp >300 °C; Anal. data for $C_{16}H_{15}N_2O$ (251). Calcd. C; 76.16 H; 6.39 N; 11.10%. Found C; 76.20 H; 6.40 N; 11.10%. IR (KBr): ν, cm^{-1} 1755 (C=O), 1626 (C=N), 1597 (C=C). ^1H NMR (DMSO-d_6): δ ppm 1.65 (m, 4H, 2 CH_2), 1.96 (m, 4H, 2 CH_2), 5.95 (t, 1H, CH), 7.44–7.76 (m, 5H, Ar-H), 8.05 (s, 1H, CH), 10.01 (s, 1H, CHO). MS: *m/z* 251 ([M]$^+$, 89%), 208 (31%), 132 (41%), 106 (100%).

Synthesis of porphyrin derivatives 4a–4m

General procedure. A mixture of the appropriate aromatic aldehyde (1.44 mmol) and pyrrole (1.44 mmol, 0.0967 g) in DMF (10 mL) was placed into 100 mL three necked round-bottom flask fitted with a magnetic stirrer, a condenser equipped with a Dean–Stark trap, a thermometer and a nitrogen gas bubbler inlet tube. The reaction mixture was flushed with nitrogen gas for 5 min and then heated to 100 °C for 10 min, then *p*-toluene sulfonic acid (1.44 mmol, dissolved in 5 mL DMF) was added to the reaction mixture using a syringe. The clear, colorless reaction mixture turned into various shades of red over the next 1–2 min, was heated to 150 °C and held at this temperature for 1 h. The reaction mixture was monitored by UV.vis spectrum. Thus, when heating was continued at 150 °C, the **Soret band** of porphyrins at λ_{max} 415–430 nm started to appear with continuous disappearing one of the Q-band intensity at 504 nm (Table 1). After 1 h at 150 °C, the reaction mixture was cooled in an ice bath for 20 min. The mixture was then poured onto ice-cold water. The precipitate was collected by filtration and dried under a vacuum at an ambient temperature and the residue was purified by column chromatograghy (silica gel, chloroform/hexane: 1.5/1: eluent).

5,10,15,20-*Meso*tetrakis[1,3-diphenyl-1H-pyrazole-4-yl]-21H,23H-porphyrin (4a). Black crystal, yield 81%, mp 280–282 °C. Anal. data for $C_{80}H_{54}N_{12}$ (1182). Calcd. C; 81.21 H; 4.20 N; 14.21%. Found C; 81.20 H; 4.22 N; 14.22%. IR (KBr): ν, cm^{-1} 3419 (NH), 1632 (C=N), 1591 (C=C). UV-vis: λ_{max}, nm 423 nm. ^1H NMR (DMSO-d_6): δ ppm 2.28 (s, 1H, NH), 5.40 (d, 2H, 2 pyrrolic CH), 5.80 (d, 2H, 2 pyrrolic CH), 6.00 (d, 2H, 2 pyrrolic CH), 6.60 (d, 2H, 2 pyrrolic CH), 7.10–7.85 (m, 40H, Ar-H), 7.92 (s, 4H, 4 CH), 10.59 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ ppm 103.066, 106.236, 119.946, 120.587, 122.656, 123.374, 125.007, 126.303, 127.514, 128.976, 130.564, 133.130, 135.004, 136.524, 139.786, 140.723, 150.226, 157.166, 164.176.

5,10,15,20-*Meso*tetrakis[1-phenyl-3-(1H-pyrrol-2-yl)-1H-pyrazole-4-yl]-21H,23H-porphyrin (4b). Brown powder, yield 84%, mp 230–232 °C. Anal. data for $C_{72}H_{50}N_{16}$ (1138). Calcd. C; 75.92 H; 4.39 N; 19.66%. Found C; 75.93 H; 4.40 N; 19.69%. IR (KBr): ν, cm^{-1} 3443 (NH), 1625 (C=N), 1561 (C=C). UV-vis: λ_{max}, nm 419. ^1H NMR (DMSO-d_6): δ ppm 2.3 (s, 1H, NH), 5.30 (d, 2H, 2 pyrrolic CH), 5.99 (d, 2H, 2 pyrrolic CH), 6.10 (d, 4H, 4 pyrrolic CH), 6.21 (d.d, 4H, 4 pyrrolic CH), 6.40 (d, 2H, 2 pyrrolic CH), 6.60 (d, 2H, 2 pyrrolic CH), 6.69 (d, 4H, 4 pyrrolic CH), 7.53–7.68 (m, 20H, Ar-H), 7.98 (s, 4H, 4 CH), 10.59 (s, 1H, NH), 11.01 (s, 1H, NH).

5,10,15,20-*Meso*tetrakis[3-(1H-indol-3-yl)-1-phenyl-1H-pyrazole-4-yl]-21H,23H-porphyrin (4c). Reddish brown powder, yield 90%, mp 232–234 °C. Anal. data for $C_{88}H_{54}N_{16}$ (1334). Calcd. C; 79.16 H; 4.04 N; 16.79%. Found C; 79.21 H; 4.06 N; 16.81%. IR (KBr): ν, cm^{-1} 3433–3440 (NH), 1630 (C=N), 1561 (C=C). UV-vis: λ_{max}, nm 423. ^1H NMR (DMSO-d_6): δ ppm 2.3 (s, 1H, NH), 5.20 (d, 2H, 2 pyrrolic CH), 6.19 (d, 2H, 2 pyrrolic CH), 6.44 (d, 2H, 2 pyrrolic CH), 6.69 (d, 2H, 2 pyrrolic CH), 7.32 (s, 4H, 4 CH), 7.53–7.68 (m, 36H, Ar-H), 10.09 (s, 1H, NH), 11.91 (s, 1H, NH).

5,10,15,20-*Meso*tetrakis[1-phenyl-3-p-tolyl-1H-4-yl-21H,23H-porphyrin (4d). Intense reddish brown crystal, yield 88%, mp 240–242 °C. Anal. data for $C_{84}H_{62}N_{12}$ (1238). Calcd. C; 81.42 H; 5.00 N; 13.57%. Found C; 81.43 H; 54.01 N; 13.60%. IR (KBr): ν, cm^{-1} 3433 (NH), 1633 (C=N), 1567 (C=C). UV-vis: λ_{max}, nm 425. ^1H NMR (DMSO-d_6): δ ppm 2.17 (s, 1H, NH), 2.33 (s, 3H, CH_3), 5.17 (d, 2H, 2 pyrrolic CH), 5.85 (d, 2H, 2 pyrrolic CH), 6.20 (d, 2H, 2 pyrrolic CH), 6.60 (d, 2H, 2 pyrrolic CH), 7.27 (s, 4H, 4 CH), 7.09–7.48 (m, 20H, Ar-H), 7.70 (d, 4H, 4 CH), 7.95 (d, 41H, 4 CH), 10.79 (s, 1H, NH).

5,10,15,20-*Meso*tetrakis[3-(4-hydroxyphenyl)-1-phenyl-1H-pyrazole-4-yl]-21H,23H-porphyrin (4e). Reddish brown powder, yield 81.5%, mp >300 °C. Anal. data for $C_{80}H_{54}N_{12}O_4$ (1246). Calcd. C; 77.04 H; 4.33 N; 13.48%. Found C; 77.05 H; 4.33 N; 13.48%. IR (KBr): ν, cm^{-1} 3442 (OH), 3433 (NH), 1635 (C=N), 1587 (C=C). UV-vis: λ_{max}, nm 422. ^1H NMR (DMSO-d_6): δ ppm 2.23 (s, 1H, NH), 5.27 (d, 2H, 2 pyrrolic CH), 5.95 (d, 2H, 2 pyrrolic CH), 6.40 (d, 2H, 2 pyrrolic CH), 6.70 (d, 2H, 2 pyrrolic CH), 7.09–7.48 (m, 20H, Ar-H), 7.73 (d, 8H, 8 CH), 7.95 (d, 8H, 8 CH), 7.97 (s, 4H, 4 CH), 10.77 (s, 1H, NH), 11.34 (s, 1H, OH).

5,10,15,20-*Meso*tetrakis[1-phenyl-3-(pyridin-2-yl)-1H-pyrazole-4-yl]-21H,23H-porphyrin (4f). Brown powder, yield 81.5%, mp >300 °C. Anal. data for $C_{80}H_{50}N_{16}$ (1074). Calcd. C; 84.91 H; 4.66 N; 10.43%. Found C; 85.00 H; 4.63 N; 10.44%. IR (KBr): ν, cm^{-1} 3418 (NH), 1631 (C=N), 1590 (C=C). UV-vis: λ_{max}, nm 420. ^1H NMR (DMSO-d_6): δ ppm 2.30 (s, 1H, NH), 5.20 (d, 2H, 2 pyrrolic CH), 6.15 (d, 2H, 2 pyrrolic CH), 6.45 (d, 2H, 2 pyrrolic CH), 6.57 (d, 2H, 2 pyrrolic CH), 6.99 (d, 4H, 4 CH), 7.09–7.48 (m, 28H, Ar-H), 8.43 (d, 1H, CH), 8.32 (s, 4H, 4 CH), 10.07 (s, 1H, NH).

5,10,15,20-*Meso*tetrakis[1-phenyl-3-(pyridin-4-yl)-1H-pyrazole-4-yl]-21H,23H-porphyrin (4g). Blackish brown powder, yield 85%, mp 224–226 °C. Anal. data for $C_{80}H_{50}N_{16}$ (1074). Calcd. C; 84.91 H; 4.66 N; 10.43%. Found C; 85.00 H; 4.63 N; 10.44%. IR (KBr): ν, cm^{-1}

3418 (NH), 1625 (C=N), 1590 (C=C). UV-vis: λ_{max}, nm 420. ^{1}H NMR (DMSO-d_6): δ ppm 2.31 (s, 1H, NH), 5.21 (d, 2H, 2 pyrrolic CH), 6.19 (d, 2H, 2 pyrrolic CH), 6.45 (d, 2H, 2 pyrrolic CH), 6.77 (d, 2H, 2 pyrrolic CH), 6.89 (d, 1H, CH), 7.02–7.58 (m, 20H, Ar-H).

5,10,15,20-*Meso*tetrakis[1-phenyl-3-(pyridin-4-yl)-1H-pyrazole-4-yl]-21H,23H-porphyrin (4h). Brown powder, yield 85.5%; mp >300 °C. Anal. data for $C_{104}H_{70}N_{12}$ (1480). Calcd. C; 84.32 H; 4.72 N; 11.35%. Found C; 84.33 H; 4.72 N; 11.35%. IR (KBr): ν, cm^{-1} 3418 (NH), 1635 (C=N), 1587 (C=C). UV-vis: λ_{max}, nm 424. ^{1}H NMR ($CDCl_3$): δ ppm 2.64 (s, 1H, NH), 5.20 (d, 2H, 2 pyrrolic CH), 5.85 (d, 2H, 2 pyrrolic CH), 6.10 (d, 2H, 2 pyrrolic CH), 6.23 (d, 2H, 2 pyrrolic CH), 6.80 (s, 4H, 4 CH), 7.26–7.97 (m, 40H, Ar-H), 8.08 (d, 8H, 8 CH), 8.53 (d, 8H, 8 CH), 10.42 (s, 1H, NH).

5,10,15,20-*Meso*tetrakis[3-(2-hydroxyphenyl)-1-phenyl-1H-pyrazole-4-yl]-21H,23H-porphyrin (4i). Brown powder, yield 89%, mp >300 °C. Anal. data for $C_{80}H_{54}N_{12}O_4$ (1246). Calcd. C; 77.04 H; 4.33 N; 13.48%. Found C; 77.05 H; 4.33 N; 13.48%. IR (KBr): ν, cm^{-1} 3440 (OH), 3423 (NH), 1626 (C=N), 1601 (C=C). UV-vis: λ_{max}, nm 425. ^{1}H NMR (DMSO-d_6): δ ppm 2.28 (s, 1H, NH), 5.25 (d, 2H, 2 pyrrolic CH), 5.96 (d, 2H, 2 pyrrolic CH), 6.46 (d, 2H, 2 pyrrolic CH), 6.70 (d, 2H, 2 pyrrolic CH), 6.95 (d, 4H, 4 CH), 7.19–7.62 (m, 28H, Ar-H), 7.73 (d, 1H, 4 CH), 7.97 (s, 4H, 4 CH), 10.72 (s, 1H, NH), 11.34 (s, 4H, 4 OH).

5,10,15,20-*Meso*tetrakis[3-(3-hydroxyphenyl)-1-phenyl-1H-pyrazole-4-yl]-21H,23H-porphyrin (4j). Deep brown crystal, yield 89%, mp 266–268 °C. Anal. data for $C_{80}H_{54}N_{12}O_4$ (1246). Calcd. C; 77.04 H; 4.33 N; 13.48%. Found C; 77.05 H; 4.33 N; 13.48%. IR (KBr): ν, cm^{-1} 3439 (OH), 3423 (NH), 1626 (C=N), 1605 (C=C). UV-vis: λ_{max}, nm 423. ^{1}H NMR (DMSO-d_6): δ ppm 2.34 (s, 1H, NH), 5.20 (d, 2H, 2 pyrrolic CH), 6.06 (d, 2H, 2 pyrrolic CH), 6.44 (d, 2H, 2 pyrrolic CH), 6.55 (d, 2H, 2 pyrrolic CH), 6.95 (d, 4H, 4 CH), 7.09–7.48 (m, 20H, Ar-H), 7.43 (d, 4H, 4 CH), 7.74 (d.d, 1H, CH), 7.89 (s, 4H, 4 CH), 8.07 (s, 4H, 4 CH), 10.51 (s, 1H, NH), 11.32 (s, 4H, 4 OH). ^{13}C NMR (DMSO-d_6): δ ppm 106.236, 111.079, 112.149, 114.719, 115.904, 119.946, 120.587, 126.303, 129.476, 130.564, 131.164, 134.430, 135.786, 139.786, 146.623, 150.226, 159.546.

5,10,15,20-*Meso*tetrakis[3-(4-acetylphenyl)-1-phenyl-1H-pyrazole-4-yl]-21H,23H-porphyrin (4k). Brown powder, yield 90%, mp >300 °C. Anal. data for $C_{88}H_{62}N_{12}O_4$ (1350). Calcd. C; 78.22 H; 4.59 N; 12.44%. Found C; 78.25 H; 4.56 N; 12.48%. IR (KBr): ν, cm^{-1} 1712 (C=O), 3433 (NH), 1631 (C=N), 1587 (C=C). UV-vis: λ_{max}, nm 426. ^{1}H NMR (DMSO-d_6): δ ppm 2.28 (s, 1H, NH), 3.01 (s, 3H, CH_3), 5.40 (d, 2H, 2 pyrrolic CH), 5.80 (d, 2H, 2 pyrrolic CH), 6.02 (d, 2H, 2 pyrrolic CH), 6.60 (s, 4H, 4 CH), 7.12 (d, 2H, 2 pyrrolic CH), 7.19–7.50 (m, 20H, Ar-H), 7.73 (d, 8H, 8 CH), 7.82 (d, 8H, 8 CH), 10.59 (s, 1H, NH).

5,10,15,20-*Meso*tetrakis[3-(3-aminophenyl)-1-phenyl-1H-pyrazole-4-yl]-21H,23H-porphyrin (4l). Blackish brown powder, yield 89%, mp 247–250 °C. Anal. data for $C_{80}H_{58}N_{16}$ (1082). Calcd. C; 88.72 H; 5.36 N; 20.70%. Found C; 88.70 H; 5.40 N; 20.74%. IR (KBr): ν, cm^{-1} 3418 (NH), 3385 (NH_2), 1635 (C=N), 1580 (C=C). UV-vis: λ_{max}, nm 422. ^{1}H NMR (DMSO-d_6): δ ppm 2.26 (s, 1H, NH), 5.25 (d, 2H, 2 pyrrolic CH), 5.71 (s, 1H, NH_2), 5.89 (d, 2H, 2 pyrrolic CH), 6.11 (d, 2H, 2 pyrrolic CH), 6.22 (d, 2H, 2 pyrrolic CH), 6.34 (s, 4H, 4 CH), 6.4 (s, 4H, 4 CH), 6.59–6.67 (m, 20H, Ar-H), 6.78 (d.d, 4 H, 4 CH), 7.01 (d, 4H, 4 CH), 7.11 (d, 4H, 4 CH), 10.50 (s, 1H, NH).

5,10,15,20-*Meso*tetrakis[3-cyclohexenyl-1-phenyl-1H-pyrazole-4-yl]-21H,23H-porphyrin (4m). Deep violet crystal, yield 89.5%, mp 250–252 °C. Anal. data for $C_{80}H_{70}N_{16}$ (1254). Calcd. C; 76.55 H; 5.62 N; 17.99%. Found C; 76.56 H; 5.60 N; 17.99%. IR (KBr): ν, cm^{-1} 3418 (NH), 1631 (C=N), 1587 (C=C). UV-vis: λ_{max}, nm 425. ^{1}H NMR (DMSO-d_6): δ ppm 1.61–2.78 (m, 24H, 12 CH_2), 2.00 (t, 24H, 12 CH_2), 3.37 (s, 1H, NH), 5.30 (d, 2H, 2 pyrrolic CH), 5.80 (t, 4H, 4 =CH), 6.11 (d, 2H, 2 pyrrolic CH), 6.62 (s, 4H, 4 CH), 7.11 (d, 2H, 2 pyrrolic CH), 7.19 (d, 2H, 2 pyrrolic CH), 7.30–7.73 (m, 20H, Ar-H), 10.58 (s, 1H, NH).

Synthesis of 6–14

Synthesis of 5-oxo-1-phenyl-4,5-dihydro-1H-pyrazole-3-carbaldehyde (6). A pure sample of 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (**5**) (0.87 g, 0.005 mol) was refluxed in dioxane (25 mL) containing selenium dioxide (0.56 g, 0.005 mol) for 4–5 h. The reaction mixture was filtered while hot to remove selenium metal, concentrated, cooled and precipitated by adding cold water. The precipitated product **6** was filtered off, dried, collected and recrystallized from ethanol. Brown crystal, yield 72%, mp 153–155 °C. Anal. data for $C_{10}H_8N_2O_2$ (188). Calcd. C; 74.16 H; 4.25 N; 14.89%. Found C; 74.17 H; 4.26 N; 14.91%. IR (KBr): ν, cm^{-1} 1722 (CHO), 1650 (amidic C=O), 1610 (C=N), 1597 (C=C). ^{1}H NMR ($CDCl_3$): δ ppm 3.7 (s, 2H, CH_2), 7.20–8.00 (m, 5H, Ar-H), 9.75 (s, 1H, CHO). MS: *m/z* 188 ([M]$^+$, 90%), 159 (42%), 131 (100%), 55 (65%).

Synthesis of 5,10,15,20-*meso*tetrakis[5-oxo-1-phenyl-4,5-dihydro-1H-pyrazole-3-yl]-21H,23H-porphyrin (7). Dark violet crystal, yield 85.5%, mp 211–212 °C. Anal. data for $C_{56}H_{38}N_{12}O_4$ (942). Calcd. C; 71.33 H; 4.03 N; 17.83%. Found C; 71.30 H; 4.10 N; 17.84%. IR (KBr): ν, cm^{-1} 3418 (NH), 1675 (C=O), 1615 (C=N), 1587 (C=C). UV-vis: λ_{max}, nm 423. ^{1}H NMR ($CDCl_3$): δ ppm 2.41 (s, 1H, NH), 3.80 (s, 8H, 4 CH_2), 5.21 (d, 2H, 2 pyrrolic CH), 6.05 (d, 2H, 2 pyrrolic CH), 6.40 (d, 2H, 2 pyrrolic CH), 6.60 (d, 2H, 2 pyrrolic CH), 7.08–7.94 (m, 20H, Ar-H), 11.41 (s, 1H, NH). ^{13}C NMR δ (ppm): 30.297, 31.340, 109.435, 109.999, 113.843, 120.355,

121.655, 122.973, 124.473, 125.073, 132.229, 137.629, 140.347, 142.262, 151.007, 155.689, 172.827.

Synthesis of ((z)-4(4-(dimethylamino)benzylidene)-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazole-3-carbaldehyde (8). A mixture of compound **6** (0.56 g, 0.003 mol) with *p-N,N*-dimethylaminobenzaldehyde (0.45gm, 0.003 mol) was refluxed in 25 mL of absolute ethanol containing a catalytic amount of triethylamine for 2 h. The reaction mixture was concentrated and cooled. The precipitated product **10** was collected by filtration, dried and recrystallized from ethanol.

Beige cotton crystal, yield 69%, mp 196–198 °C. Anal. data for $C_{19}H_{17}N_3O_2$ (319). Calcd. C; 71.47 H; 5.32 N; 13.16%. Found C; 71.47 H; 5.33 N; 13.17%. ^{1}H NMR (DMSO-d_6): δ ppm 3.07 (s, 3H, CH_3), 3.12 (s, 3H, CH_3), 7.1 (s, 1H, CH), 7.20–7.45 (m, 9H, Ar-H), 9.85 (s, 1H, CHO); IR (KBr): ν, cm^{-1} 1720, 1662 (2 C=O), 1610 (C=N), 1597 (C=C). MS: *m/z* 319 ([M]$^+$, 35%), 275 (66%), 199 (19%), 145 (75%), 174 (71%), 146 (55%), 105 (65%), 77 (100%).

Synthesis of 5,10,15,20-*meso*tetrakis[((z)-4(4-(dimethylamino)benzylidene)-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazole-3-yl]-21H,23H-porphyrin (9). Dark red crystal, yield 82%, mp 193–195 °C. Anal. data for $C_{92}H_{98}N_{16}O_4$ (1490). Calcd. C; 74.09 H; 6.57 N; 15.03%. Found C; 74.12 H; 6.60 N; 15.06%. IR (KBr): ν, cm^{-1} 3350 (NH), 1680 (C=O), 1610 (C=N), 1590 (C=C). UV-vis: λ_{max}, nm 424. ^{1}H NMR ($CDCl_3$): δ ppm 2.29 (s, 1H, NH), 3.62 (s, 24H, 8 CH_3), 5.49 (d, 2H, 2 pyrrolic CH), 6.05 (d, 2H, 2 pyrrolic CH), 6.41 (d, 2H, 2 pyrrolic CH), 6.56 (d, 2H, 2 pyrrolic CH), 6.77 (d, 8H, Ar-H), 7.08 (s, 4H, 4 CH), 7.08–7.94 (m, 20H, Ar-H), 8.29 (d, 8H, Ar-H), 11.41 (s, 1H, NH).

Synthesis of 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carbaldehyde (11). At 0 °C, phosphorous oxychloride (5.37 g, 0.035 mol) was added dropwise with stirring in DMF (1.095 g, 0.015 mol) in an ice bath for about 0.5 h, then a solution of phenazone (**10**) (0.94 g, 0.005 mol) in DMF was added to the Vilsmeier–Haack reagent and continued being stirred for further 0.5 h, then the reaction mixture was refluxed on water bath for 1–2 h. The reaction mixture was cooled, poured into ice-water, then a solution of potassium carbonate was added until effervesence ceased and the precipitated product **11** was filtered off, washed with cold water, dried well, then recrystallized from absolute ethanol. Beige cotton crystal, yield 69%, mp >300 °C. Anal. data for $C_{12}H_{12}N_2O_2$ (216). Calcd. C; 66.67 H; 5.56 N; 12.96%. Found C; 66.66 H; 5.55 N; 12.99%. IR (KBr): ν, cm^{-1} 1710, 1680 (2 C=O), 1610 (C=N), 1597 (C=C). MS: *m/z* 216 ([M]$^+$, 52%), 188 (98%), 159 (15%), 121 (100%), 97 (18%), 77 (22%).

Synthesis of 5,10,15,20-*meso*tetrakis[1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-y]-21H,23H-porphyrin (12). Reddish brown crystal, yield 82%, mp 193–195 °C. Anal. data for $C_{64}H_{54}N_{12}O_4$ (1054). Calcd. C; 72.86 H; 5.10 N; 15.94%. Found C; 72.88 H; 5.12 N; 15.99%. IR (KBr): ν, cm^{-1} 3310 (NH), 1683 (C=O), 1610 (C=N), 1587 (C=C). UV-vis: λ_{max}, nm 425. ^{1}H NMR (DMSO-d_6): δ ppm 1.77 (s, 12H, 4 CH_3), 3.25 (s, 1H, NH), 3.51 (s, 12H, 4 CH_3), 5.29 (d, 2H, 2 pyrrolic CH), 5.90 (d, 2H, 2 pyrrolic CH), 6.04 (d, 2H, 2 pyrrolic CH), 6.43 (d, 2H, 2 pyrrolic CH), 7.30–7.50 (m, 20H, Ar-H), 10.56 (s, 1H, NH)

Synthesis of 1H-pyrrole-2,3,5-tricarbaldehyde (13). At 0 °C, phosphorous oxychloride (5.37 g, 0.035 mol) was added dropwise with stirring in DMF (1.095 g, 0.015 mol) in an ice bath for about 0.5 h then pyrrole (0.33 g, 0.005 mol) in DMF was added to Vilsmeier–Haack reagent and continued being stirred for about 0.5 h, then the reaction mixture was refluxed on water bath for 1–2 h. The reaction mixture was cooled, then poured onto ice-water, then a solution of potassium carbonate was added until effervesence ceased and the precipitated solid material was filtered off, washed with cold water, dried well, then recrystallized from absolute ethanol. Beige crystal, yield 72%, mp >300 °C. Anal. data for $C_4H_5NO_3$ (150). Calcd. C; 55.63 H; 3.33 N; 9.27 5%. Found C; 55.64 H; 3.34 N; 9.28%. IR (KBr): ν, cm^{-1} 3353 (NH), 1709 (C=O), 1612 (C=N), 1554 (C=C). ^{1}H NMR ($CDCl_3$): δ ppm 7.94 (d, 1H, CH), 9.62 (d, 3H, CHO), 11.23 (s, 1H, NH). MS: *m/z* 150 (95%), 149 (100%), 135 (65%), 119 (82%), 105 (90%), 97 (98%), 83 (98%), 71 (45%).

Synthesis of porphyrin polymer (14). Porphyrin polymer derivative **27** was synthesized from the reaction of compound **13** (1.44 mmol) with an excess amount of pyrrole by the previous capping method. Brown crystal, yield 70%, mp >300 °C. IR (KBr): ν, cm^{-1} 3409 (NH), 1622 (C=N), 1594 (C=C). UV-vis: λ_{max}, nm 420.

Biological screening

***In vitro* Anti-Herpes Simplex-1 Virus (HSV-1).** Samples were prepared by dissolving in DMSO and diluting aliquots into a sterile culture medium before preparing a serial dilution and placed in microtiter trays. Microtiter trays with confluent monolayer cultures of Vero cells were inverted. The medium was shaken out and replaced with serial dilutions of sterile extracts in a triplicate in 100 µL medium followed by a tittered virus in 100 µL medium containing 10% (v/v) of calf serum in each cell. In each tray, the last row of cells was reserved for controls that were not treated with compounds or treated with a virus. The trays were cultured and incubated at 37 °C in 5% CO_2 atmosphere for 6 h. The trays were inverted into a pad of paper towels. The remaining cells rinsed carefully with a medium, and fixed with 3.7% (v/v) formaldehyde in a saline for 20 min. The fine cells were rinsed with water, and examined visually. Antiviral activity is identified as relatively-confluent unaltered monolayers of stained *Vero* cells treated with HSV-1. Cytotoxicity was estimated as the concentration that caused approximately 50% loss of the monolayer present around the plaques caused by HSV-1 (Table 2).

In vitro Anti-Human Immunodeficiency Virus-1 (HIV-1). Compounds were prepared for assay by dissolving in DMSO then diluted 1:100 in a cell culture medium before preparing a serial dilution and placed in microtiter trays. T4 lymphocytes (CEM cell line) were added and after a brief interval (1 min or more) HIV-1 was added resulting in a 1:200 final dilution of each of the tested compounds. Cultures were incubated at 37 °C in 5% CO_2 atmosphere for six days. Tetrazolium salt XTT was added to all cells and cultures were incubated to allow formazan color development by virally infected cells. Individual cells were analyzed spectrophotometrically to a quantitative formazan production and, in addition, were viewed microscopically for detection of viable cells. Results were compared with controls and Zidovudine (AZT) treated cells as a positive control and a determination about activity was made as a percentage protection of T4 cells against HIV-1 cytopathic effect (Table 3).

***Antitumor activity* [52–54].** RPMI-1640 medium (Sigma Co., St. Louis, USA), Foetal Bovine serum (GIBCO, UK), and the cell lines from ATCC were used.

The cytotoxic activity of the synthesized compounds was tested against human heptacellular liver carcinoma cell line (HepG2), human lung fibroblast cell line (WI-38), human causcasian breast adenocarcinoma cell line (MCF-7), and normal adult African green monkey kidney cell line (VERO). The stock samples of the compounds were diluted with RPMI-1640 medium to desired concentrations ranging from 10 to 1000 µg/mL. The final concentration of DMSO in each sample did not exceed 1% v/v.

The cells were bath-cultured for 10 d, then seeded in 96 well plates of 10×10^3 cells/well in fresh complete growth medium in 96-well microtiter plastic plates at 37 °C for 24 h. Under 5% CO_2 using a water jacketed carbon dioxide incubator (Shedon. TC2323. Carnelius, OR, USA). The medium was added with 10% (v/v) calf serum (Hyclone Laboratories, Ogden, UT) and cells were incubated either alone (negative control) or with different concentrations of sample to give a final concentrations of (1000, 500, 200, 50, 20, 10 µg/mL). Cells were suspended in RPMI-1640 medium, 1% antibiotic-antimycotic mixture (10^4 µ/mL) potassium penicillin, 10^4 µg/mL streptomycin sulfate and 25 µg/mL Amphotericin B) and 1% L-glutamin in 96-well flat bottom microplates at 37 °C under 5% CO_2. After 96 h of incubation, the medium was again aspirated, trays were inverted onto a pad of paper towels, the remaining cells rinsed carefully with medium, and fixed with 3.7% (v/v) formaldehyde in saline for at least 20 min. The fixed cells were rinsed with water. The % viability of cells was examined visually as described previously [55–57].

CONCLUSION

A series of novel *meso*-tetraarylporphyrin derivatives **4a–4m**, **7**, **9**, **12** and **14** was obtained from condensation reaction of pyrrole with different aldehydes in good to excellent yields with hope of discovering a new structure which leads to serving as potent antiviral and antitumor agents. Some compounds were screened for their *in vitro* biological activities showing good antiviral and antitumor activities. Compounds **4b** and **4h** showed the best antiviral and antitumor activities. The obtained results may be related to the importance of one nitrogen containing a heterocyclic ring, especially five membered ring, aromaticity, steric hindrance of aryl derivatives in *meso*-position of porphyrin skeleton and electronegativity of the heteroatom.

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