Dyes and Pigments 191 (2021) 109008

Contents lists available at ScienceDirect

Dyes and Pigments

journal homepage: http://www.elsevier.com/locate/dyepig

Utility of dipyrromethane in the synthesis of some new A_2B_2 porphyrin and their related porphyrin like derivatives with their evaluation as antimicrobial and antioxidant agents

Ahmed A. Fadda [a], Eman El-Gendy [a,*], Hala M. Refat [b], Eman H. Tawfik [a,c,**]

[a] Chemistry Department, Faculty of Science, Mansoura University, 35516, Mansoura, Egypt
[b] Chemistry Department, Faculty of Science, Al-Arish University, Egypt
[c] Chemistry Department, Faculty of Science and Arts, Taibah University, Ulla, Saudi Arabia

ARTICLE INFO

Keywords:
Dipyrromethane
Porphyrin like and A_2B_2 Porphyrins
Antimicrobial
DNA damage
Hemolysis activities
Antioxidant

ABSTRACT

In this work, the dipyrromethane derivatives 2a,b were synthesized from an aldehyde and excess of pyrrole at room temperature in solvent-free conditions. The reaction of dipyrromethanes 2a,b with different aromatic aldehydes in the presence of hydrochloric acid or p-toluenesulfonic acid as a catalyst afforded some new porphyrin like and A_2B_2 porphyrin derivatives 4a-g and 5a-d, respectively. Biological evaluation of the newly synthesized compounds 4a-g and 5a-d showed promising activity as antimicrobial and antioxidant agents. Compounds 4c,4e,4g,5c, and 5d exhibited the highest antimicrobial activity, whereas, compounds 4a,4f,5a,5b, and 5d recorded the highest antioxidant activity.

1. Introduction

Porphyrins have received great attention as they serve as biomimetic material and are used in material chemistry [1–5]. Most synthesized porphyrins have potential applications in medicinal chemistry [6–8]. Many reported methods for the synthesis of porphyrin derivatives have previously been reported [9,10]. Traditional strategies described by Rothemund and Alder for porphyrin synthesis facilitated the synthesis of porphyrins with poor yields and long reaction times under drastic conditions [11]. In 1978, T. J. Doupherty was the first to utilize a hematoporphyrin derivative (HpD) for photodynamic cancer therapy [12,13]. Extensive research has been conducted to develop photosensitizer-based drugs in the last three decades [14–16]. It was reported a photosensitivity and photo-toxicity in a mice's skin that was administrated with hematoporphyrin [14]. The characteristic red fluorescence property of HpD is one essential indication of tumors and provides a means for endoscopic investigations [17]. Ultimately, partially purified heamatoporphyrin derivatives were approved in 1993 under the trade name Photofrin (porfimer sodium) as a first-generation photosensitizer for the treatment of bladder cancer [12]. Porphyrin derivatives have been tested as synthesizing drugs for application in tumor diagnosis and treatment using photodynamic therapy and boron neutron capture therapy [18–21].

Dipyrromethanes are important building blocks for the synthesis of different porphyrins, calixpyrrols, and corroles [22,23]. Although the stability of dipyrromethanes to oxidation is always a cause for concern during the synthetic procedure, isolation, and storage of such compounds, diversity conditions have been established allowing good to excellent yields of dipyrromethanes to be obtained in the case where adequate substituents are present on the pyrrole rings. For this, we are looking for a solvent-free conditions system for the preparation of dipyrromethanes which are then used to synthesize porphyrin. Different methods have been used in green chemistry including manual and mechanical grinding which able to induce mechanochemical transformation [24], and solvent-free synthesis [25,26]. The application of grinding had been assisted in the development of many pharmaceutical compounds [23,25,27].

2. Results and discussion

Most of the reported methodologies for the synthesis of porphyrin derivatives had been afforded symmetrical porphyrin (A_4) which is

* Corresponding author.
** Corresponding author. Chemistry Department, Faculty of Science, Mansoura University, 35516, Mansoura, Egypt.
E-mail addresses: afadda50@yahoo.com (A.A. Fadda), emanorganic@gmail.com (E. El-Gendy), hala7223530@hotmail.com (H.M. Refat), emanhelmy4@yahoo.com (E.H. Tawfik).

https://doi.org/10.1016/j.dyepig.2020.109008
Received 23 May 2020; Received in revised form 7 October 2020; Accepted 12 November 2020
Available online 29 March 2021

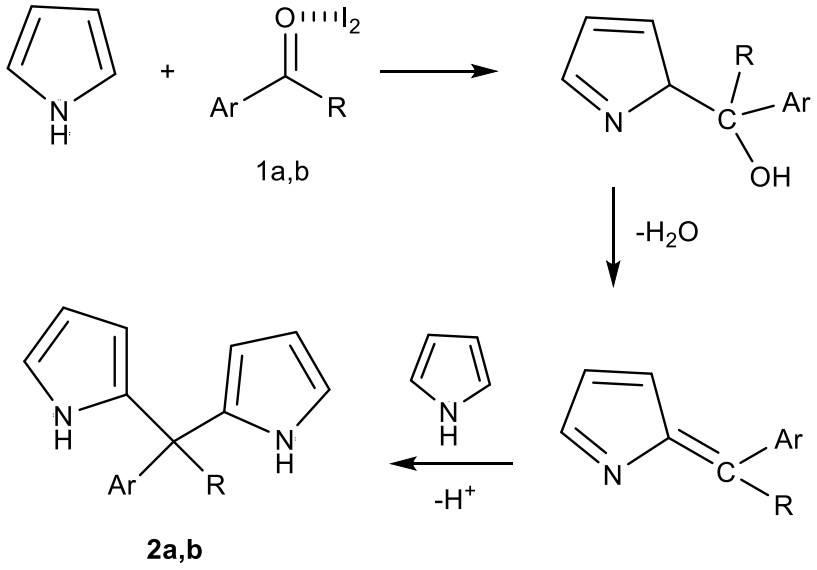
difficult to achieve excitation when irradiated to study energy transfer. So, our aim in the present work has been directed to synthesize unsymmetrical porphyrins like 4a-g and A_2B_2 porphyrin derivatives 5a-d, which can be easily achieved the selective excitation (Schemes 2 and 3). Many synthetic routes have been pointed out in the preparation of dipyrromethane [28,29] and porphyrin derivatives [30,31]. Substantially, all latest porphyrin synthesis depends on starting with pyrrole and all of them have the prospect to be used in combinatorial chemistry [32]. Compounds 4a-g are defined as porphyrin like derivatives due to the loss of aromaticity of the porphyrin ring.

Firstly, the desired dipyrromethanes 2a,b have been achieved by the reaction of pyrrole and carbonyl compounds (acetophenone and/or 3,4,5-trimethoxybenzaldehyde) by grinding at room temperature catalyzed by iodine (Scheme 1). By this method, we improved the previously reported methods to minimize the issues associated with the formation of by-products as N-confused dipyrromethane isomer and tripyrromethane [28]. On the other hand, we concerned with the environmentally harmless catalytic system. All previously reported works have many disadvantages, such as high price reagents, the use of excess pyrrole aldehyde ratio, and prolonged reaction time. Thus, in our method, we overcome all these problems and obtained the dipyrromethanes in high yield. ^{1}HNMR and TLC control of the formed dipyrromethanes showed very high purity during the reaction mentioned time (10–15 min), while the precipitate which formed after longer reaction times showed a gradual increase in tripyrromethane content. The obtainable dipyrromethanes 2a,b have been purified chromatographically in basic medium cyclohexane/chloroform 0.5% triethylamine (1:2) as eluent to prevent the decomposition of dipyrromethane on silica gel. It was preferred to store the resulted dipyrromethanes in the refrigerator in absence of light. In this method, we present simple and efficient procedures for the synthesis of dipyrromethane, mild reaction condition, absence of solvent, shorter reaction time, easy and quick purification of the product, and excellent yield are the main advantages of this procedure which make this method economically and environmentally attractive. The obtained dipyrromethanes 2a,b have been subjected to react with different aromatic aldehydes using HCl acid as an acid catalyst or p-toluenesulfonic acid to afford their corresponding new porphyrin like and/or A_2B_2 porphyrin derivatives 4a-g and 5a-d, respectively (Schemes 2 and 3).

These porphyrins like and/or porphyrin derivatives 4a-g and 5a-d were achieved by two pathways: A) dipyrromethanes 2a,b have been firstly dissolved in HCl acid and reacted with the proper aldehyde derivatives 3a-j under nitrogen gas condition and heated in a silicon oil bath for 15–35 min. The obtainable porphyrin like and/or porphyrin derivatives 4a-g and 5a-d have been established their structures based on their correct elemental and spectral analyses, B) dipyrromethanes 2a, b were dissolved in DMF (as solvent and capping agent [29]) and added to a solution of the proper aldehydes 3a-j in DMF. To this reaction mixture, p-toluenesulfonic acid in DMF was added. The reaction mixture was then heated in a silicon oil bath for 15–40 min, which then chromatographed on silica gel to afford the corresponding porphyrin like and/or porphyrin derivatives 4a-g and 5a-d, respectively in good yield [29]. The newly obtainable porphyrins like and/or porphyrin derivatives 4a-g and 5a-d, in this case, showed identical spectral data to that acquired by method A. The reaction product for porphyrins 5a-d has been monitored by UV spectra; which showed after 5–10 min in the first cut of the reaction mixture to absorb at 504 nm due to the reacting compounds. On continuing heating at 150 °C the λ_{max} of porphyrins 5a-d peak continued to grow in the range of 424–429 nm with the corresponding decrease in the reacting compounds having λ_{max} at 504 nm. On the other hand, the UV–vis spectra of porphyrin like compounds 4a-g in different solvents, in general, displayed two λ_{max} at 276–294 and 389–398 nm due to π-π* and n-π* as broad bands.

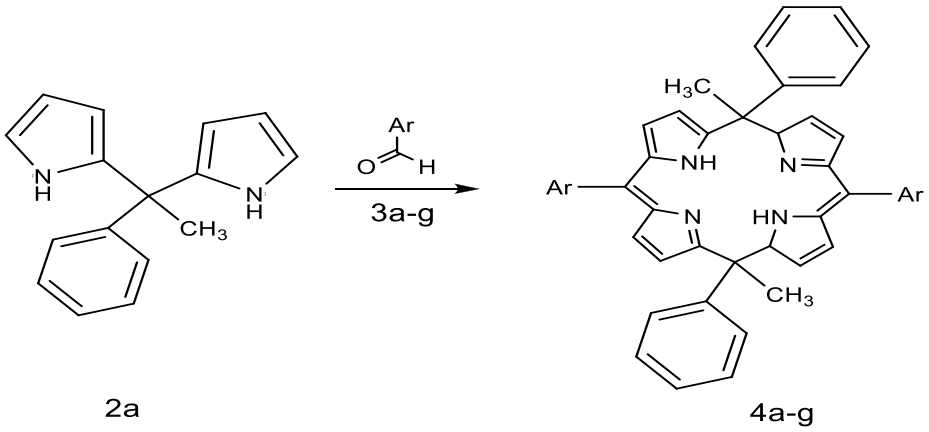
The infrared spectra of porphyrin like 4a-g and porphyrin derivatives 5a-d, in general, showed absorption bands at 3315-3317 cm^{-1} indicates the presence of NH. Also, the band at 3504 cm^{-1} in compounds 4a and 4f indicates the presence of OH groups. IR spectra showed also absorption bands of 2925 cm^{-1} due to the C–H group. ^{1}HNMR exhibited, in general, two doublets for pyrrolic C–H proton in the region at δ 5.0–7.0 ppm.

In conclusion, our reported results expand the scoop of the synthesis of porphyrin like and A_2B_2 porphyrin derivatives using dipyrromethane and aldehydes. Our developed methods increase the yield of the resulted products, in general, in comparison with the binary mixed aldehyde condensation method. P-Toluenesulfonicacid, an alternative catalyst of these reactions instead of many other acid catalysts, could decrease the acidolysis of dipyrromethanes and the number of oligomers formed.



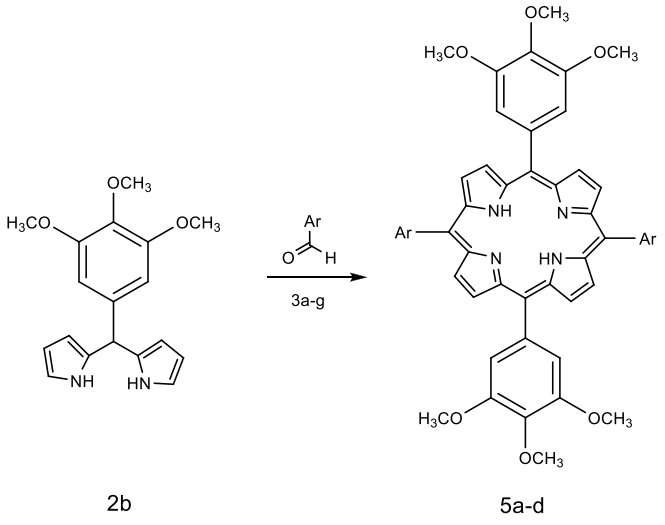
1a,2a, R=CH_3, Ar=C_6H_5; 1b,2b, R=H, Ar=C_6H_2-OCH_3-m,p,m

Scheme 1. Synthesis of dipyrromethane derivatives 2a,b.



3a, 4a, Ar = C_6H_4-OH-p; 3b, 4b, Ar = C_6H_2-OCH_3-p;
3c, 4c, Ar = C_6H_4-Cl-p; 3d, 4d, Ar = C_6H_2-OCH_3-m,p,m;
3e, 4e, Ar = C_6H_4-NO_2-p; 3f, 4f, Ar = C_6H_3-OH-o,OCH_3-m;
3g, 4g, Ar = C_6H_4-Br-p

Scheme 2. Synthesis of porphyrin like derivatives 4a-g from dipyrromethane 2a.



3a, 5a, Ar=C_6H_2-OCH_3-o,p,m; 3b, 5b, Ar = C_6H_2-OCH_3-p;
3c, 5c, Ar = C_6H_4-Cl-p; 3d, 5d, Ar = C_6H_4-Br-p;

Scheme 3. Synthesis of porphyrin derivatives 5a-d from dipyrromethane 2b

2.1. Biological investigation

I) Antimicrobial evaluation:

A series of the newly unsymmetric synthesized targeted porphyrin like and porphyrin derivatives 4a-g, 5a-d has been prepared to expand the spectrum of activity of this class of antibiotics to include *Gram*-negative and positive organisms and have been estimated versus *Gram*-positive bacteria (*Bacillus subtilis* and *Bacillus thuringienesis*) and *Gram*-negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*), to detect the *in vitro* antimicrobial activity of the synthesized porphyrins (see Table 1). The newly synthesized compounds were evaluated against *Fusarium oxysporum* and *Botrytis fabae* fungal strains to estimate the *in vitro* antifungal activity. For the report, both antibacterial and antifungal activity agar-diffusion method [33] has been used. We choose Cephalothin, Chloramphenicol, and Cycloheximide to indicate the antimicrobial activity of the tested porphyrins. The antibacterial and antifungal activity of the synthesized porphyrins has been listed as rated inhibition zone diameter (IZ) of the development of bacteria or fungi. The lowest concentrations of tested compounds that suppress the development of bacteria or fungi were recorded as minimum inhibitory concentration (MIC) and IZ in Table 2. The outcomes detect that most porphyrins have satisfied activity against *Gram-positive* and *Gram-negative* bacterial and fungal strains. Compounds 4c, 4e and 4g showed suppressor activity to *Gram*-positive bacteria (*B. subtilis*) with the MICs in the range of 3.125–6.25 μg/mL, while compounds 4c and 4e displayed high activity against *B. thuringienesis* with MICs 6.25 μg/mL. The activity against *Gram*-negative bacteria (*E. coli* and *P. aeruginosa*) was found to be 12.5–50.0 μg/mL. Among the observed results of *Gram*-negative bacteria, the highest activity of compounds 4c, 4e and 4g have been noted for *E.coli* with MIC values of 25.0 μg/mL, followed by *P. aeruginosa* with MICs range 25.0–50.0 μg/mL. Additionally, the *F. oxyporum* and *B. fabae* were highly inhibited by the compounds 4c, 4e and 4g with the MICs 25.0 μg/mL. The halogenated porphyrins 4c,4g, 5c and 5d inhibited *Gram*-positive bacteria with the MIC range of 3.125–25.00 μg/mL, and inhibition zone range of 29–44 mm. Whereas, compounds 5a-c showed moderate antimicrobial activity (MIC≤ 50 μg/mL) against most of the bacterial strains.

The consequences of antimicrobial activity of the tested compounds exhibited the following presumptions for the structure-activity relationships (SAR's): (1) it noticed that all compounds (4c,4e,4g,5c, and 5d) having electron-withdrawing groups such as NO_2, Cl and Br recorded higher antibacterial activity. (2) The substitution of benzene ring by methoxy groups (compounds 5a-d) showed the lowest antimicrobial activity than compounds 4a-g. (3) it is clear from the results that the tested compounds 4a-g and 5a-d are more active against *Gram-positive* than *Gram-negative* bacteria, these results can be illustrated due to the differences in the cell wall thickness of both type of bacteria due to the peptidoglycan layer in which the *Gram-positive* bacteria have a thick peptidoglycan layer and no outer lipid membrane, on the other hand, the *negative Gram* bacteria have thin peptidoglycan and outer lipid membrane. These distinctions in the cell wall structure can create contrasts in the antibacterial sensibility of synthesized compounds 4a-g and

Table 1
Minimum inhibitory concentration (MIC, μg/mL) and inhibition zone (mm) of some new compounds.

Compound No.	MIC[a] in μg/mL, and inhibition zone (mm)					
	Bacteria				Fungi	
	Gram-positive Bacteria		Gram-negative Bacteria			
	B. Subtilis	*B. Thuringiensis*	*E. Coli*	*P. Aeruginosa*	*F. Oxysporum*	*B. Fabae*
4a	6.25 (40)	6.25 (34)	50.0 (15)	50.0 (14)	50.0 (15)	50.0 (22)
4b	6.25 (44)	12.5 (29)	50.0 (16)	50.0 (17)	50.0 (12)	50.0 (26)
4c	3.125 (57)	6.25 (29)	25.0 (22)	50.0 (20)	50.0 (19)	25.0 (32)
4d	50.0 (18)	50.0 (18)	50.0 (19)	50.0 (19)	100.0 (13)	50.0 (20)
4e	3.125 (61)	6.25 (39)	25.0 (24)	50.0 (16)	100.0 (11)	25.0 (26)
4f	25.0 (29)	12.5 (22)	25.0 (26)	50.0 (19)	50.0 (19)	50.0 (15)
4g	3.125 (52)	6.25 (33)	25.0 (30)	25.0 (24)	50.0 (18)	25.0 (36)
5a	25.0 (32)	25.0 (35)	25.0 (32)	50.0 (17)	50.5 (21)	25.0 (34)
5b	50.0 (18)	50.0 (21)	50.0 (19)	50.0 (23)	50.0 (19)	100.0 (10)
5c	12.5 (32)	25.0 (38)	50.0 (21)	25.0 (32)	50.5 (22)	50.0 (17)
5d	12.5 (36)	25.0 (26)	25.0 (26)	50.0 (24)	25.0 (24)	50.0 (14)
Chloramphenil	3.125 (44)	3.125 (44)	6.25 (37)	6.25 (38)	B	B
Cephalothin	6.25 (36)	6.25 (37)	6.25 (38)	6.25 (37)	B	B
Cycloheximide	B	B	b	b	3.125 (43)	3.125 (42)

MIC[a]: Minimum inhibitory concentration values with SEM = 0.02 (The lowest concentration that inhibited the bacterial growth). [b]NT: Not tested.

II) Antioxidant evaluation:

a) Bleomycin-dependent DNA damage

Table 2
Results of bleomycin-dependent DNA damage assay of isolated compounds and antioxidant assay for the newly prepared compounds.

Compound no.	Absorbance	ABTS inhibition (%)	Erythrocyte hemolysis (%)
4a	0.00882	86.25	0.84
4b	0.00899	73.70	0.88
4c	0.00913	60.25	0.94
4d	0.00895	74.38	0.92
4e	0.00911	60.18	0.91
4f	0.00884	83.24	0.80
4g	0.00981	53.28	0.94
5a	0.00886	81.44	0.85
5b	0.00888	79.22	0.86
5c	0.00890	73.54	0.87
5d	0.00893	74.24	0.89
L-Ascorbic acid	0.00881	88.61	0.85

ABTS + scavenging activity (%) = [(Ac − As)/Ac] × 100, where Ac is the absorbance value of the control and As is the absorbance value of the added samples test solution. The concentration of the pure compounds was 2 mM. The concentration shows 50% inhibition is expressed in mM. The positive control was vitamin C and showed 88.61%, absorbance 0.00881 at the same concentration of the tested compounds.

5a-d [34].

One of the important members of the huge family of antitumor antibiotics is bleomycin. The role of bleomycin is to evaluate the pro-oxidant of antioxidants and the restriction of iron and DNA. The formed bleomycin-iron complex decays DNA by heating with thiobarbituric acid (TBA) due to the formation of a pink chromogen. Additions of antioxidants create a competition with DNA which leads to minify the formation of chromogen. Between different synthetic compounds 4a-g and 5a-d, compounds 4a, 4f, 5a, and 5b exhibited elevated protection level against DNA damage stimulated by the complex. Whereas, compounds 5c, 5d, 4d and 4b showed low to moderate activity, and compound 4e, 4c and 4g displayed low activity, these results summarized in Table 2.

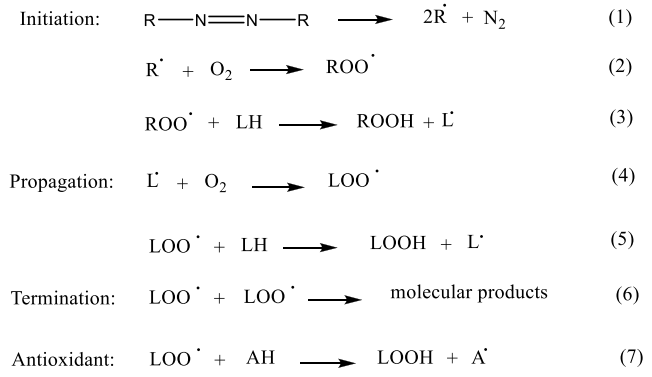
All compounds have been tested to bleomycin DNA damage. The results indicated that they may have some protective activity to DNA by a certain mechanism. A series of compounds 4a, 4f, 5a, 5b, 4d, and 5d exhibited a high antioxidant activity. On the other hand, all compounds show a potent protective effect on the DNA from the induced damage by bleomycin concerning ascorbic acid (Table 2). Synthetic compounds 4a-g and 5a-d which have pyrrole ring systems have found their way into such diverse applications as pharmaceuticals, oxidation inhibitors, and metal complexing agents. Pyrrole derivatives have antimicrobial, anti-inflammatory, anti-cancer, and many other biological activities. From the obtained results, it can be concluded that pyrrole moiety is essential for the protection activity against DNA damage induced by bleomycin-iron complex, and pyrrole ring is also required for the activity and an unsubstituted benzene ring (compounds 4a-g) exhibited better activity than those substituted derivatives (compounds 5a-d). The pro-oxidant activities of the aforementioned derivatives have been assisted by their effects on the bleomycin-induced DNA damage and their corresponding absorbencies. From Table 2 we noticed that as λ_{max} decreased the activity of the tested compounds increased. The positive control was vitamin C and showed 88.61%, absorbance 0.00881 at the same concentration of the tested compounds.

b) ABTS inhibition and erythrocyte hemolysis to evaluate Antioxidant activity

The antioxidant activity has been evaluated for the synthesized porphyrins using ABTS assay which mirrors the capacity of peroxidation inhibition in rat brain and specific kidney enzyme and the rate of hemolysis of erythrocyte. From Table 2 it was found that porphyrin derivatives 4a, 4f, 5a and 5b exhibited antioxidant activity, where derivatives 4d, 5d, 4b and 5c displayed moderate activity, while derivatives 4c, 4e and 4g displayed weak activity.

c) Induction of RBC hemolysis by AAPH assay

Decomposition of AAPH thermally in aq. suspension of RBCs leads to the formation of starting free radical (R•) which reacts with the lipid in RBC membranes to give lipid peroxidation (Eqs. 1-6). The starting rate of AAPH is 1.3×10^{-6} [AAPH]/s. The free radical chain reaction of lipid peroxidation and the starting radical create reaction up to 50 propagation reactions which lead to fast damage of RBCs membrane leading to hemolysis. From the other side, if antioxidant (AH) is present or added to RBCs, it was reacting with propagation radical to stop peroxidation and inhibit hemolysis (Eq. 7).



3. Conclusions

The porphyrin like 4a-g and porphyrin derivatives 5a-d (A_2B_2) are novel, they have been synthesized from the reaction of their corresponding dipyrromethanes 2a,b with different aldehydes. With significant high yield and screened for antimicrobial and antioxidant activity in which all compounds 4c,4e,4g, 5c and 5d having electron-withdrawing groups have been exhibited markedly higher antimicrobial activity, whereas compounds 4a,4f,5a,5b, 4d and 5d have been recorded higher antioxidant activity than the other derivatives.

4. Experimental

4.1. Instruments

All of the spectroscopic data and elemental analysis were executed as formerly reported [31].

4.2. Synthesis of dipyrromethane derivatives 2a,b

General procedure: Grinding a mixture of pyrrole (0.02 mol), appropriate aldehydes 1a,b (0.01 mol) and iodine crystals (0.001 mol) in a morter was continued for 10–15 min afforded dipyrromethanes 2a,b. The crude reaction product was washed with water and dried (Na_2SO_4). The obtained dipyrromethanes 2a,b was purified by flash chromatography silica gel using (2:1) chloroform/cyclohexane as eluent.

4.3. Synthesis of 2-(1-phenyl-1-(2H-pyrrol-2-yl)ethyl)-1H-pyrrole (2a)

Yield (86%); m.p. 250°C; IR (KBr): ν_{max} (cm^{-1}): 3213 (NH stretching), 1610 (C═C). ^{1}H NMR (DMSO-d_6): δ (ppm): 1.83 (s, 3H, CH_3), 2.94 (d, $J = 9.5$ Hz, 1H, pyrrolic-H), 5.17 (d, $J = 10$ Hz, 1H, pyrrolic-H), 5.56 (t, $J = 9$ Hz, 1H, pyrrolic-H), 5.71 (d, 1H, pyrrolic-H), 6.25 (t, 1H, Ar–H), 6.54 (d, 1H, pyrrolic-H), 7.25–7.58 (m, 5H, Ar–H), 7.79 (d, 1H, pyrrolic-H), 12.03 (s, 1H, NH); Anal. calcd. For $C_{16}H_{16}N_2$ (236.32): C, 81.32; H, 6.82; N, 11.85%. Found: C, 81.11; H, 6.69; N, 11.99%.

4.4. Synthesis of 2-((2H-pyrrol-2-ylidene) (3,4,5-trimethoxyphenyl) methyl)-1H-pyrrole (2b)

Yield (79%); m.p. 238°C; IR (KBr): ν_{max} (cm^{-1}): 3223 (NH), 1600 (C═C), 1256 (ph-O-C); ^{1}H NMR (DMSO-d_6): δ (ppm): 3.61 (s, 3H, OCH_3), 3.85 (d, 6H, $2OCH_3$), 5.82 (d, 1H, pyrrolic-H), 6.20 (t, 1H, pyrrolic-H), 6.39 (d, 1H, pyrrolic-H), 6.54 (s, 2H, Ar–H), 7.12 (d, 1H, pyrrolic-H), 7.85 (d, 1H, pyrrolic-H), 8.81 (d, 1H, pyrrolic-H), 11.52 (s, 1H, NH); Anal. calcd. For $C_{18}H_{18}N_2O_3$ (310.35): C, 69.66; H, 5.85; N, 9.03%. Found: C, 69.53; H, 5.79; N, 8.91%.

4.5. Synthesis of unsymmetric porphyrin derivatives (4a-g and 5a-d)

4.5.1. General procedure

4.5.1.1. Method A. Dipyrromethanes 2a,b (0.01 mol), was dissolved in dil. HCl acid (2 mL), aldehydes (3a-j) (0.1 mol) were combined in a three-neck round bottom flask equipped with a reflux condenser and N_2 (g) inlet. The mixture was flushed with N_2 gas for 5 min, then heated to 100°c and kept at this temperature for 10 min and then heated was continued to 150°c for 15–35 min. The color changed to deep blood-red, greenish and reddish black color within a few minutes. The ultraviolet spectra were used to follow up the reaction product via the reaction progress. So, when heated the reaction mixture up to 150°c, we found λ_{max} in compounds 5a-d 424–429 nm due to the soret band is appeared with continuous disappearing of λ_{max} at 504 nm due to Q band whereas the UV–vis spectra of compounds 4a-g exhibited two λ_{max} at 276–294 and 389–398 nm due to π-π* and n-π* transitions as broad bands. The solid material that was obtained when the reaction mixture was poured onto ice cold water was collected by filtration and purified chromatography (silica gel, chloroform/hexane: 1.5/1 eluent).

4.5.1.2. Method B. This method was carried out according to the previously reported work [31].

4.6. Synthesis of 4,4'-((4,6,15,19)-10,20-dimethyl-10,20-diphenyl-1H,9H,10H,20H-porphyrin-5,15-diyl)diphenol (4a)

Yield (86%); m.p. 234°C; IR (KBr): ν_{max} (cm^{-1}): 3410 (OH), 3352 (NH); ^{1}H NMR (DMSO-d_6): δ (ppm): 1.44 (s, 3H, CH_3), 1.85 (s, 3H, CH_3), 2.95 (d, 1H, pyrrolic-H), 3.78 (d, 1H, pyrrolic-H), 5.11 (d, 1H, pyrrolic-H), 5.29 (d, 1H, pyrrolic-H), 5.31 (d, 1H, pyrrolic-H), 5.59 (d, 1H, pyrrolic-H), 6.24 (d, 1H, pyrrolic-H), 6.25 (d, 1H, pyrrolic-H), 6.54 (s, 1H, NH), 6.68–7.84 (m, 18H, Ar–H), 7.84 (d, 1H, pyrrolic-H), 9.55 (s, 2H, 2OH), 12.00 (s, 1H, NH); ^{13}CNMR (DMSO-d_6): δ (ppm): 19.4, 25.4, 46.9, 51.3, 66.5, 76.4, 108.2, 112.4, 115.6 (4C), 117.6, 119.9 (2C), 122.2, 125.8 (2C), 126.4 (4C), 128.6 (5C), 130.0 (3C), 131.1 (2C), 134.7 (2C), 135.2, 142.5, 143.7, 144.8 (2C), 147.8 (2C), 148.9, 151.7, 157.6 (2C), 164.5; UV–Vis spectrum: (λ_{max}), 283,398 nm. Anal. calcd. For $C_{46}H_{38}N_4O_2$ (678.84): C, 81.39; H, 5.64; N, 8.25%. Found: C, 81.46; H, 5.71; N, 8.36%.

4.7. Synthesis of (4,6,15,19)-5,15-bis(4-methoxyphenyl)-10,20-dimethyl-10,20-diphenyl-1H,9H,10H,20H-porphyrin (4b)

Yield (95%); m.p. 321°C; IR (KBr): ν_{max} (cm^{-1}): 3347 (NH); ^{1}H NMR (DMSO-d_6): δ (ppm): 1.45 (s, 3H, CH_3), 1.86 (s, 3H, CH_3), 2.95 (d, 1H, pyrrolic-H), 3.62 (d, 1H, pyrrolic-H), 3.90 (s, 6H, $2OCH_3$), 5.13 (d, 1H, pyrrolic-H), 5.59 (d, 1H, pyrrolic-H), 5.66 (t, 1H, pyrrolic-H), 5.81 (t, 1H, pyrrolic-H), 6.27 (d, 1H, pyrrolic-H), 6.29 (d, 1H, pyrrolic-H), 6.66 (s, 1H, NH), 6.68 (d, 1H, pyrrolic-H), 7.08–7.47 (m, 18H, Ar–H), 7.86 (d, 1H, pyrrolic-H), 12.04 (s, 1H, NH); ^{13}CNMR (DMSO-d_6): δ (ppm): 19.7, 25.1, 46.2, 50.3, 56.1 (2C), 67.5, 76.6, 107.9, 112.2, 114.4 (4C), 117.3, 119.1, 119.8, 121.8, 125.8 (2C), 126.3 (4C), 127.9, 128.5 (4C), 130.1, 134.7 (2C), 136.2 (5C), 142.5, 144.3, 145.1, 146.2, 146.8, 149.0, 150.9, 159.6 (2C), 164.4 (2C); UV–Vis spectrum: (λ_{max}), 288,389 nm. Anal. calcd. For $C_{48}H_{42}N_4O_2$ (706.89): C, 81.56; H, 5.99; N, 7.93%. Found: C, 81.47; H, 6.09; N, 7.81%.

4.8. Synthesis of (4,6,15,19)-5,15-bis(4-chlorophenyl)-10,20-dimethyl-10,20-diphenyl-1H,9H,10H,20H-porphyrin (4c)

Yield (88%); m.p. 281°C; IR (KBr): ν_{max} (cm^{-1}): 3338 (NH), 750 (C–Cl); ^{1}H NMR (DMSO-d_6): δ (ppm): 1.44 (s, 3H, CH_3), 1.89 (s, 3H, CH_3), 2.95 (d, 1H, pyrrolic-H), 3.78 (d, 1H, pyrrolic-H), 5.12 (d, 1H, pyrrolic-H), 5.29 (t, 1H, pyrrolic-H), 5.34 (d, 1H, pyrrolic-H), 5.55 (t,

1H, pyrrolic-H), 6.25 (d, 1H, pyrrolic-H), 6.26 (d, 1H, pyrrolic-H), 6.43 (d, 1H, pyrrolic-H), 6.54 (s, 1H, NH), 7.06–7.62 (m, 18H, Ar–H), 7.84 (d, 1H, pyrrolic-H), 12.02 (s, 1H, NH). ^{13}CNMR (DMSO-d_6): δ (ppm): 19.3, 24.7, 46.4, 50.6, 67.5, 76.6, 107.5, 112.1, 117.5, 119.3, 119.9, 122.2, 126.2 (6C), 127.9 (2C), 128.2, 128.5 (4C), 128.9 (4C), 129.7, 130.2 (2C), 133.6 (2C), 135.6, 140.6 (2C), 142.8, 144.3, 145.2, 146.5 (2C), 149.1, 151.6, 164.7 (2C); UV–Vis spectrum: (λ_{max}), 294,390 nm. Anal. calcd. For $C_{46}H_{36}Cl_2N_4$ (715.72): C, 77.20; H, 5.07; N, 7.83%. Found: C, 77.27; H, 5.19; N, 7.71%.

4.9. Synthesis of (4,6,15,19)-10,20-dimethyl-10,20-diphenyl-5,15-bis (3,4,5-trimethoxyphenyl)-1H,9H,10H,20H-porphyrin (4d)

Yield (91%); m.p. 271° C; IR (KBr): ν_{max} (cm^{-1}): 3319 (NH), 1252 (ph-O-C); ^{1}H NMR (DMSO-d_6): δ (ppm): 1.45 (s, 3H, CH_3), 1.87 (s, 3H, CH_3), 2.90 (d, 1H, pyrrolic-H), 3.60 (d, 1H, pyrrolic-H), 3.77 (s, 6H, 2OCH_3), 3.92 (s, 12H, 4OCH_3), 5.12 (d, 1H, pyrrolic-H), 5.53 (d, 1H, pyrrolic-H), 5.62 (t, 1H, pyrrolic-H), 6.81 (d, 1H, pyrrolic-H), 6.24 (d, 1H, pyrrolic-H), 6.27 (d, 1H, pyrrolic-H), 6.45 (d, 1H, pyrrolic-H), 6.68 (s, 1H, NH), 6.73 (d, 1H, pyrrolic-H), 7.18–7.53 (m, 14H, Ar–H), 12.05 (s, 1H, NH); ^{13}CNMR (DMSO-d_6): δ (ppm): 19.5, 24.7, 46.4, 50.6, 56.3 (4C), 60.9 (2C), 67.5, 76.8, 101.2 (2C), 104.8 (2C), 107.8, 112.2, 117.3, 119.3, 119.8, 122.3, 126.0 (6C), 126.9, 128.2, 128.6 (4C), 130.0, 134.4, 135.5, 138.2 (2C), 142.9, 144.3, 145.0, 146.4, 146.8, 148.6, 151.9, 153.2 (4C), 164.7 (2C); UV–Vis spectrum: (λ_{max}), 276,391 nm. Anal. calcd. For $C_{52}H_{50}N_4O_6$ (826.99): C, 75.52; H, 6.09; N, 6.77%. Found: C, 75.47; H, 6.19; N, 6.82%.

4.10. Synthesis of (4,6,15,19)-10,20-dimethyl-5,15-bis(3-nitrophenyl)-10,20-diphenyl-1H,9H,10H,20H-porphyrin (4e)

Yield (92%); m.p. 261° C; IR (KBr): ν_{max} (cm^{-1}): 3335 (NH), 1530 (symm. NO_2), 1350 (asymm. NO_2); ^{1}H NMR (DMSO-d_6): δ (ppm): 1.47 (s, 3H, CH_3), 1.82 (s, 3H, CH_3), 2.97 (d, 1H, pyrrolic-H), 3.78 (d, 1H, pyrrolic-H), 5.13 (d, 1H, pyrrolic-H), 5.29 (t, 1H, pyrrolic-H), 5.33 (d, 1H, pyrrolic-H), 5.55 (t, 1H, pyrrolic-H), 6.23 (d, 1H, pyrrolic-H), 6.25 (d, 1H, pyrrolic-H), 6.45 (d, 1H, pyrrolic-H), 6.55 (s, 1H, NH), 7.35–7.86 (m, 18H, Ar–H), 8.12 (d, 1H, pyrrolic-H), 12.05 (s, 1H, NH); ^{13}CNMR (DMSO-d_6): δ (ppm): 19.2, 24.7, 46.6, 50.3, 67.5, 76.9, 107.5, 112.2, 117.6, 119.3, 119.6, 120.1 (2C), 122.3, 122.9 (2C), 126.3 (2C), 126.3 (2C), 127.9, 128.2, 128.6 (4C), 129.6 (2C), 130.0, 133.3, 134.3, 134.4, 135.1, 135.5, 141.0, 142.5, 144.2, 145.2, 146.4, 146.8, 148.1 (2C), 148.7, 164.5 (2C); UV–Vis spectrum: (λ_{max}), 279,391 nm. Anal. calcd. For $C_{46}H_{36}N_6O_4$ (736.83): C, 74.98; H, 4.92; N, 11.41%. Found: C, 74.87; H, 4.89; N, 11.51%.

4.11. Synthesis of 6,6'-((4,6,15,19)-10,20-dimethyl-10,20-diphenyl-1H,9H,10H,20H-porphyrin-5,15-diyl)bis(2-methoxyphenol) (4f)

Yield (95%); m.p. 321° C; IR (KBr): ν_{max} (cm^{-1}): 3400 (OH), 3347 (NH), 1260 (ph-O-C); ^{1}H NMR (DMSO-d_6): δ (ppm): 1.41 (s, 3H, CH_3), 1.86 (s, 3H, CH_3), 2.96 (d, 1H, pyrrolic-H), 3.62 (d, 1H, pyrrolic-H), 3.93 (s, 6H, 2OCH_3), 5.12 (d, 1H, pyrrolic-H), 5.50 (d, 1H, pyrrolic-H), 5.66 (t, 1H, pyrrolic-H), 5.85 (t, 1H, pyrrolic-H), 6.24 (d, 1H, pyrrolic-H), 6.26 (d, 1H, pyrrolic-H), 6.66 (s, 1H, NH), 6.68 (d, 1H, pyrrolic-H), 7.01–7.48 (m, 16H, Ar–H), 7.86 (d, 1H, pyrrolic-H), 12.01 (s, 1H, NH), 13.29 (s, 2H, 2OH); ^{13}CNMR (DMSO-d_6): δ (ppm): 19.2, 24.7, 46.3, 50.7, 55.8 (2C), 67.5, 76.6, 107.6, 111.8 (2C), 115.7, 115.9, 117.3, 119.3, 119.5, 122.2, 122.3, 125.6, 125.7 (2C), 125.9 (4C), 127.9, 128.5 (4C), 129.9, 135.3, 142.6, 144.3, 145.2, 146.2, 146.4, 146.7, 147.5 (2C), 149.0 (3C), 150.6, 164.5 (2C); UV–Vis spectrum: (λ_{max}), 278,389 nm. Anal. calcd. For $C_{48}H_{42}N_4O_4$ (738.89): C, 78.03; H, 5.73; N, 7.58%. Found: C, 78.21; H, 5.59; N, 7.41%.

4.12. Synthesis of (4,6,15,19)-5,15-bis(4-bromophenyl)-10,20-dimethyl-10,20-diphenyl-1H,9H,10H,20H-porphyrin (4g)

Yield (88%); m.p. 281° C; IR (KBr): ν_{max} (cm^{-1}): 3338 (NH), 759 (C–Br); ^{1}H NMR (DMSO-d_6): δ (ppm): 1.42 (s, 3H, CH_3), 1.81 (s, 3H, CH_3), 2.92 (d, 1H, pyrrolic-H), 3.71 (d, 1H, pyrrolic-H), 5.12 (d, 1H, pyrrolic-H), 5.29 (t, 1H, pyrrolic-H), 5.34 (t, 1H, pyrrolic-H), 5.57 (d, 1H, pyrrolic-H), 6.25 (d, 1H, pyrrolic-H), 6.29 (d, 1H, pyrrolic-H), 6.43 (d, 1H, pyrrolic-H), 6.54 (s, 1H, NH), 7.15–7.67 (m, 18H, Ar–H), 7.79 (d, 1H, pyrrolic-H), 12.01 (s, 1H, NH). ^{13}CNMR (DMSO-d_6): δ (ppm): 19.3, 24.7, 46.6, 50.7, 67.5, 76.6, 107.5, 112.2, 117.3, 119.3, 119.6, 122.2, 122.4 (2C), 126.1 (2C), 126.3 (4C), 128.2, 128.5 (4C), 128.7 (2C), 129.9, 130.2 (2C), 131.3 (4C), 135.3, 141.2 (2C), 142.5, 144.2, 145.3, 146.4, 146.5, 148.7, 151.7, 164.6 (2C); UV–Vis spectrum: (λ_{max}), 288,392 nm. Anal. calcd. For $C_{46}H_{36}Br_2N_4$ (804.63): C, 68.67; H, 4.51; N, 6.96%. Found: C, 68.46; H, 4.39; N, 6.75%.

4.13. Synthesis of 5,15-bis(2,4,5-trimethoxyphenyl)-10,20-bis(3,4,5-trimethoxyphenyl)porphyrin (5a)

Yield (85%); m.p. 311° C; IR (KBr): ν_{max} (cm^{-1}): 3310 (NH), 1254 (ph-O-C); ^{1}H NMR (DMSO-d_6): δ (ppm): 3.62 (s, 6H, 2OCH_3), 3.85 (s, 24H, 8OCH_3), 3.98 (s, 6H, 2OCH_3), 6.31 (d, 2H, pyrrolic-H), 6.42 (d, 2H, pyrrolic-H), 6.51 (d, 2H, pyrrolic-H), 6.61–6.88 (m, 8H, Ar–H), 7.90 (d, 2H, pyrrolic-H), 8.71 (s, 1H, NH), 9.52 (s, 1H, NH). ^{13}CNMR (DMSO-d_6): δ (ppm): 56.3 (8C), 56.4 (2C), 60.7 (2C), 98.6 (2C), 99.4, 101.2 (2C), 103.3, 104.9 (2C), 106.3, 111.1, 112.7, 113.0, 119.7 (2C), 120.6 (2C), 126.7, 131.8 (2C), 134.4, 136.6 (2C), 137.6 (2C), 138.3 (2C), 141.2 (2C), 142.3 (2C), 142.4 (2C), 150.1 (2C), 150.8, 152.7, 153.2 (4C), 155.8 (2C), 161.3 (2C); UV–Vis spectrum: (λ_{max}), 427 nm. Anal. calcd. For $C_{56}H_{54}N_4O_{12}$ (974.37): C, 68.98; H, 5.58; N, 5.75%. Found: C, 68.97; H, 5.56; N, 5.73%.

4.14. Synthesis of 5,15-bis(4-methoxyphenyl)-10,20-bis(3,4,5-trimethoxyphenyl) porphyrin (5b)

Yield (91%); m.p. 319° C; IR (KBr): ν_{max} (cm^{-1}): 3312 (NH), 1261 (ph-O-C); ^{1}H NMR (DMSO-d_6): δ (ppm): 3.62 (s, 6H, 2OCH_3), 3.68 (s, 6H, 2OCH_3), 3.82 (s, 12H, 4OCH_3), 5.98 (d, 2H, pyrrolic-H), 6.38 (d, 2H, pyrrolic-H), 6.55 (d, 2H, pyrrolic-H), 6.71–7.03 (m, 12H, Ar–H), 7.92 (d, 2H, pyrrolic-H), 10.12 (s, 1H, NH), 12.25 (s, 1H, NH). ^{13}CNMR (DMSO-d_6): δ (ppm): 55.8 (2C), 56.3 (4C), 60.6 (2C), 101.2 (2C), 103.2 (2C), 105.0 (2C), 114.0 (4C), 120.1 (2C), 120.7 (2C), 126.7, 132.3 (2C), 134.2, 134.5 (2C), 136.1 (4C), 136.8 (2C), 137.5 (2C), 138.3 (2C), 141.1 (2C), 142.3 (2C), 153.2 (4C), 155.6 (2C), 159.7 (2C), 161.2 (2C); UV–Vis spectrum: (λ_{max}), 429 nm. Anal. calcd. For $C_{52}H_{46}N_4O_8$ (854.33): C, 73.05; H, 5.42; N, 6.55%. Found: C, 73.07; H, 5.40; N, 6.54%.

4.15. Synthesis of 5,15-bis(4-chlorophenyl)-10,20-bis(3,4,5-trimethoxyphenyl) porphyrin (5c)

Yield (86%); m.p. 284° C; IR (KBr): ν_{max} (cm^{-1}): 3350 (NH), 762 (C–Cl); ^{1}H NMR (DMSO-d_6): δ (ppm): 3.55 (s, 6H, 2OCH_3), 3.85 (s, 12H, 4OCH_3), 6.29 (d, 2H, pyrrolic-H), 6.39 (d, 2H, pyrrolic-H), 6.41 (d, 2H, pyrrolic-H), 6.54 (s, 2H, Ar–H), 6.59 (s, 2H, Ar–H), 7.22–7.78 (m, 8H, Ar–H), 7.85 (d, 2H, pyrrolic-H), 9.03 (s, 1H, NH), 9.81 (s, 1H, NH). ^{13}CNMR (DMSO-d_6): δ (ppm): 56.0 (4C), 60.7 (2C), 101.3 (2C), 105.2 (2C), 119.7 (2C), 120.6 (2C), 126.7, 127.6 (2C), 128.2 (4C), 130.2 (2C), 132.3 (2C), 133.4 (2C), 134.2, 136.5 (2C), 137.5 (2C), 138.3 (2C), 140.5 (2C), 141.2 (2C), 142.3 (2C), 153.1 (4C), 155.8 (2C), 161.2 (2C); UV–Vis spectrum: (λ_{max}), 424 nm. Anal. calcd. For $C_{50}H_{40}Cl_2N_4O_6$ (862.23): C, 69.52; H, 6.49; N, 6.52%. Found: C, 69.50; H, 6.47; N, 6.53%.

4.16. Synthesis of 5,15-bis(4-bromophenyl)-10,20-bis(3,4,5-trimethoxyphenyl)porphyrin (5d)

Yield (86%); m.p. 284 °C; IR (KBr): ν_{max} (cm^{-1}): 3348 (NH), 751 (C–Br); ^{1}H NMR (DMSO-d_6): δ (ppm): 3.53 (s, 6H, $2OCH_3$), 3.82 (s, 12H, $4OCH_3$), 6.23 (d, 2H, pyrrolic-H), 6.39 (d, 2H, pyrrolic-H), 6.42 (d, 2H, pyrrolic-H), 6.53 (s, 4H, Ar–H), 7.24–7.78 (m, 8H, Ar–H), 7.88 (d, 2H, pyrrolic-H), 9.11 (s, 1H, NH), 10.22 (s, 1H, NH). ^{13}CNMR (DMSO-d_6): δ (ppm): 56.2 (4C), 60.6 (2C), 101.3 (2C), 102.9 (2C), 105.3 (2C), 119.7 (2C), 120.6 (2C), 122.2 (2C), 126.7, 128.8 (2C), 130.3 (2C), 131.7 (4C), 131.8 (2C), 134.4, 136.6 (2C), 137.3 (2C), 138.5 (2C), 141.4 (4C), 142.3 (2C), 153.2 (4C), 155.8 (2C), 161.3 (2Cd); UV–Vis spectrum: (λ_{max}), 426 nm. Anal. calcd. For $C_{50}H_{40}Br_2N_4O_6$ (950.13): C, 63.04; H, 4.23; N, 5.88%. Found: C, 63.05; H, 4.21; N, 5.86%.

4.16.1. Biochemical assays

(I) Antimicrobial assay:

Standard sterilized filter paper disks (5 mm diameter) impregnated with a solution of the tested compound in DMF (1 mg/mL) was placed on an agar plate seeded with the appropriate test organism in triplicates. The utilized test organisms were: Bacillus Subtilis and Bacillus Thuringiensis as examples of Gram-positive bacteria and Escherichia Coli and Pseudomonas Aeruginosa as examples of Gram-negative bacteria. We have been estimated the synthesized compounds for their *in vitro* antifungal potential against Fusarium Oxysporum and Botrytis Fabae fungal strains. Chloramphenicol, cephalothin, and cycloheximide were used as standard antibacterial and antifungal agents, respectively [33]. DMF alone was used as control at the same above-mentioned concentration. The plates were incubated at 37 °C for 24 h for bacteria and 48 days for fungi. Compounds that showed significant growth inhibition zones (>14 mm) using the twofold serial dilution technique, were further evaluated for their minimal inhibitory concentrations (MICs).

4.16.2. Minimal inhibitory concentration (MIC) measurement

The minimum inhibitory concentrations (MICs) were determined using 96-well microtitre plates. The microdilution susceptibility test in Müller-Hinton Broth (Oxoid) and Sabouraud Liquid Medium (Oxoid) was used for the determination of antibacterial and antifungal activity, respectively. Stock solutions of the tested compounds, chloramphenicol, cephalothin, and cycloheximide were prepared in DMF at a concentration of 1000 μg/mL followed by twofold dilution at concentrations of (500, 250, 3.125 μg/mL). The microorganism suspensions at 106 CFU/mL (Colony Forming U/mL) concentrations were inoculated to the corresponding wells. Plates were incubated at 36 °C for 24–48 h and the minimal inhibitory concentrations (MIC) were determined. Control experiments were also done. The MIC values were expressed in μg/ml [34].

(II) Antioxidant assay:

4.16.3. Antioxidant activity screening assay for erythrocyte hemolysis

Blood was obtained from rats by cardiac puncture and collected in heparinized tubes. Erythrocytes were separated from plasma and the buffy coat and washed three times with 10 vol of 0.15 M NaCl. During the last washing, the erythrocytes were centrifuged at 2500 rpm for 10 min to obtain a constantly packed cell preparation. Erythrocyte hemolysis was mediated by peroxyl radicals in this assay system. A 10% suspension of erythrocytes in phosphate-buffered saline pH 7.4 (PBS) was added to the same volume of 200 mM 2,20-azobis (2-amidinopropane) dihydrochloride (AAPH) solution (in PBS) containing samples to be tested at different concentrations. We used L-Ascorbic acid as a positive control. The solution was shaken gently while being incubated at 378C for 2 h, diluted with eight volumes of PBS, and centrifuged at 1500g for 10 min. The absorbance A of the supernatant was measured at 540 nm. Similarly, the reaction mixture was treated with eight volumes of distilled water to achieve complete hemolysis, and the absorbance B of the supernatant obtained after centrifugation was measured at 540 nm [35].

4.16.4. Antioxidant activity screening assay ABTS method

For each of the investigated dyes, 2 mL of ABTS solution (60 mM) was added to 3 mL MnO_2 solution (25 mg/mL) all prepared in 5 mL aqueous phosphate buffer solution (pH 7, 0.1 M). The mixture was shaken, centrifuged, filtered, and the absorbance (A control) of the resulting green-blue solution (ABTS radical solution) at λ_{max} 734 nm was adjusted at approx. 0.5. Then, 50 mL of 2 mL solution of the test compound in spectroscopic grade MeOH/phosphate buffer (1:1) was added. The absorbance (A test) was measured and the reduction in color intensity was expressed as % inhibition percentage. L-Ascorbic acid (vitamin C) was used as a standard antioxidant (positive control), and a blank sample was run without ABTS and using MeOH/phosphate buffer (1:1) instead of the tested compounds [36].

4.16.5. Bleomycin-dependent DNA damage assay

The reaction mixtures contained, in a final volume of 1.0 mL, the following reagents at the final concentrations stated: DNA (0.2 mg/mL), bleomycin (0.05 mg/mL), $FeCl_3$ (0.025 mM), MgCl (5 mM), KH_2PO_4–KOH buffer pH 7.0 (30 mM), and ascorbic acid (0.24 Mm) or the dyes tested in MeOH to give a concentration of (0.1 mg/mL). The reaction mixtures were incubated in a water bath at 378C for 1 h. At the end of the incubation period, 0.1 mL of 0.1 M EDTA was added to stop the reaction (the iron–EDTA complex is unreactive in the bleomycin assay). DNA damage was assessed by adding 1 mL 1% w/v TBA and 1 mL 25% v/v hydrochloric acid (HCl) followed by heating in a water bath maintained at 808C for 15 min. The chromogen formed was extracted into butan-1-ol and the absorbance was measured at 532 nm [37–39].

CRediT authorship contribution statement

Ahmed A. Fadda: Supervision, Principle supervisor, suggesting the point of research, Continuous help, continuous advice, Formal analysis, check up the analysis, Writing – review & editing. **Eman El-Gendy:** Responsible for practical work, Writing – review & editing. **Hala M. Refat:** Supervision, Co-supervisor. **Eman H. Tawfik:** Continuous help.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dyepig.2020.109008.

References

[1] Chou Jun-hong, Kosal Margaret E. Hari singh nalwa, neal A. Rakow. Chem.Inform. 2003;34:17.
[2] MonginO SchuweyA, Vallot MAand Gossauer A. Tetrahedron Lett 1999;40:8347–50.
[3] Tabushi I, Kugimiyua S, Kinnaird MG, Sasaki T. J Am Chem Soc 1985;107:4192.
[4] Hotten D, Bocian DF, Lindsey JS. Acc Chem Res 2002;35:57–69.
[5] Barnham KJ, Masters CL, Bush AI. Nat Rev Drug Discov 2004;3:205–14.
[6] Kadish KM, Smith KM, Guilard R. New York, NY, US. Academic press, vol. 14; 2000. p. 55–63. 1.
[7] Egger NG, Motamedi M, Pow-Sang M, Orihuela E, Anderson KE. Pharmacology 1996;52:362–70.
[8] Nakjima S, Sokaka I, Takemura T. Drug Deliv Syst 1996;11:105–10.
[9] Rai S, Ravicanth M. J Org Chem 2008;73:8364–75.
[10] Tang H, Dong Z, Merican Z, Margetic D, Marinic Z, David Officer MJG, Butler DN, Warrener RN. Tetrahedron Lett 2009;50:667–70.
[11] Xiaoquan Lu, Zaixin G, Jingwan K, Zhihua W, Jinzhang G. Synth Commun 2000;30:2213–21.

[12] Levy J, Levy E. Hndbook of photodynamic therapy. World Scientific 2016:531–48.
[13] Doupherty TJ, Kaufman JE, Goldfarb A, Weishaupt KR, Boyle D, Mittleman A. Canc Res 1978;38:2628–35.
[14] Dolmans DE, Fukumura D, Jain RK. Nat Rev Canc 2003;3:380–7.
[15] Yoon IL, Z J, Shim YK. Clinical Endoscopy 2013;46:7–23.
[16] Mitton D, Ackroyd R. Photodiagnosis Photodyn Ther 2008;5:103–11.
[17] Zheng L, Li Y. IFMBE Proceedings 2013:1604–7.
[18] Fakayode OJ, Kruger CA, Songca SP, Abrahamse H, Oluwafemi OS. Mater Sci. Eng. C. Mater Biol. Appl. 2018;92:737–44.
[19] Newman DK. Eye 2016;2:202–10.
[20] Yang Guosheng, Tang Yunyu, Li Xin, Agren Hans, Xie Yongshu. ACS Appl Mater Interfaces 2017;42:36875–85.
[21] Krishna Jonnadula VS. Madoori mrinalini, seelam prasanthkumar. Academic press; 2019. p. 231–84.
[22] Temelli B, Unaleroglu C. Tetrahedron 2009;65:2043–50.
[23] Zhan H-Y, Liu H-Y, Chen H-J, Jiang H-F. Tetrahedron Lett 2009;50:2196.
[24] Colombo I, Grassi G, Grassi M. J. Pharm. Sci. 2009;398:3961–86.
[25] Hernández JG, Bolm C. J Org Chem 2017;82:4007–19.
[26] Friščić. T. Chem. Soc. Rev. 2012;41:3493–510.
[27] Bikiaris DN. Expet Opin Drug Deliv 2011;8:1501–19.
[28] Sobral Abilio JF N, Rebanda Nuno GC L, Melo da Silva, Sandra H, Lampreia, Ramos Silva M, Beja A Matos, Paixao JA, Antonio MA. Rosha Consalves *Tetrahedron Lett* 2003;44:3971–3.
[29] Fadda AA, El-Mekawey RE, El-Shafei A. Int Arch Pharmacol 2013;346:53–61.
[30] Jonathan S. Lindsey *Accounts of Chemical Research* 2010;43.
[31] Fadda AA, El-Mekawey RE, El-Shafei AI. J Porphyr Phthalocyanines 2015;19: 753–68.
[32] Michael Drain Charles, Gong Xianchang, Ruta Vanessa, Soll Clifford E, Chicoineau Philippe F. J Comb Chem 1999;1(4):286–90.
[33] Baker CN, Banerjee SN, Tenover FC. J *Clin Microbiol* 1994;32(5):1261–7.
[34] Martinez de Tejada Guillermo, Sánchez-Gómez Susana, Kowalski Ina, Kaconis Yani, Andrä Jörg, Tobias Schürholz, Hornef Mathias, Dupont Aline, Garidel Patrick, Gutsmann Thomas, David Sunil A, Brandenburg Klaus. Curr Drug Targets 2012;13(9):1121–30.
[35] Morimoto Y, Tanaka K, Iwakiri Y, Tokuhiro S, Fukushima S, Takeuchi Y. Biol Pharm Bull 1995;18:1417–22.
[36] El-Gazzar ABA, Youssef AMS, Youssef MM, Abu-Hashem AA, Badria FA. Eur J Med Chem 2009;44:609–24.
[37] Gutteridge J, Rowley D, Halliwel B. Biochem J 1981;199:263–5.
[38] Abdel-Wahab BF, El-Ahl A-AS, Badria FA. Chem Pharm Bull 2009;57:1348–51.
[39] Fadda Ahmed A, El-Mekawy Rasha E, Ahmed I. El-shafei and harold freeman *Arch*. Pharm. Chem. Life Sci. 2013;346:53–61.