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Synthesis, antioxidant and antimicrobial activities for new 4,4'-methylenedianiline amide compounds

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Abstract

Free radicals are particles that have an unpaired electron. If they produced in high level in our bodies, they can cause damage to lipids, proteins, and DNA. Antioxidants are any compounds that can incorporate free radicals in a safe way, cease the reaction, and switch them to a risk-free molecule by donating a proton. The infectious diseases are among the chief causes of death worldwide, and antimicrobial resistance has been regularly reported globally. Thus, these complications necessitate the investigation for new therapies with potential antioxidant and antimicrobial activities. This study aims to design, synthesize and evaluate the antioxidant and antimicrobial activities of new N,N'-(dialkoyl/diaroyl)-4,4'-methylenedianiline compounds. These compounds were synthesized by the reaction of carboxylic acids with 4,4'-methylenedianiline in presence of N,N'-dicyclohexylcarbodiimide (DCC) as coupling agent. The structures of the synthesized compounds were characterized on the bases of the physical and spectral data. The antioxidant activity of these compounds was evaluated by testing their free radical scavenging activity of DPPH and H_2O_2 and their antimicrobial activity was evaluated via measuring the inhibition zones in the disk diffusion method. The synthesized compounds show varied antioxidant and antimicrobial activities. The hydroxyl and the amide moieties in the synthesized compound possess similar potent antioxidant activities. The fluoro-aromatic compound showed potent antibacterial and antifungal activities. While the chloro aliphatic and aromatic compounds showed only antibacterial activity. Whereas aromatic fluorine and the ether group exposed a potent antifungal activity if they incorporated in any organic compound.

Keywords: Antioxidants, antimicrobial, 4,4'-methylenedianiline, DPPH, amide.

1. Introduction:

Antioxidants are enzymes, synthetic or natural substances that considerably decline the toxicity of reactive oxygen and nitrogen species (superoxide, singlet oxygen, hydroxyl radical) that formed during normal physiological function in humanbody[1,2]. The antioxidants capable to interact with these radicals and prevent their chain reactions before essential vital molecules are damaged[3]. Free radicals are produced during normal cellular metabolism and they are recognized to be harmless when they are not excessive[2,3]. At elevated concentrations, free radicals can damage to cells structures, nucleic acids, lipids and proteins, leading to the age associated degenerative diseases, cancer and a wide range of different human diseases[4]. The development of new powerful antioxidant agents is a main goal for pharmaceutical and medicinal chemists, as a method of eliminating the excess of free radicals in food, pharmaceutical and agricultural industries[3,4].

Infectious diseases are among the chief causes of death worldwide, and antimicrobial resistance has been regularly reported globally [5].These complications necessitate the investigation for new therapies with potential antioxidant and antimicrobial activities[6]. In spite of the great works by various researchers over the years, emerging new antioxidant and antimicrobial agents that are effective, safe, and selective remains quite challenging[7,8].

Diamino diphenylmethane (4,4'-methylenedianiline) , is used as as a curing agent for epoxy resins, urethane elastomers, and a corrosion preventative for iron, antioxidant for lubricating oils, rubber processing and preparation of azodyes[8,9].

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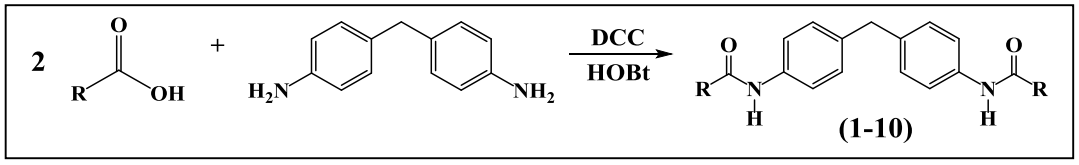
This study aims to design, synthesize and evaluate the antioxidant and antimicrobial activities of new amide compounds.

2. Experimental:

All employed chemicals were purchased from commercial sources and their suppliers are Fluka (Switzerland), Alpha (India), Scharlau (Spain), and Merck (Germany). Melting points were determined in open capillaries and are uncorrected. Infra-red (FTIR) spectra were recorded on a PerkinElmer infrared spectrophotometer, Nuclear Magnetic Resonance (^{1}H NMR and ^{13}C NMR) spectra were measured in Dimethyl Sulfoxide (DMSO-d*6*) on Bruker Avance DPX 400 and 100 MHz spectrometer respectively using tetramethylsilan (TMS) as an internal reference. All the products were synthesized by the method given in the literature and identified by ^{1}H NMR ^{13}C NMR and IR spectra and the results were in satisfactory agreement with their structures.

Synthesis of the amides (1-10): [10]

The synthetic rout are represented in the following equation:



The rout of the synthesis

To an ice-cooled solution of corresponding carboxylic acids (4 mmol) in 20 ml DMF, a solution of DCC (0.84 g, 4 mmol) in 5 ml DMF was added with stirring in an ice bath and the stirring was continued for 30 min. Then a mixture of 4,4'-methylenedianiline (0.4 g 2 mmol) and HOBt (0.62 g, 4mmol) in 10 ml DMF was added in a drop wise manner at 0^{O}C. The reaction mixture was stirred at 0^{O}C for three hours and then overnight at RT. Precipitated DCU was filtered and the solvent was evaporated under reduced pressure[10]. The dried product was dissolved in 70ml DCM and filtered to remove the remaining of DCU or any unreacted compounds. The organic filtrate was washed twice with water (30 mL), saturated aqueous $NaHCO_3$ (30 mL) and finally with brine (30 mL). The organic layer was removed and dried over anhydrous Na_2SO_4, filtered and then the solvent evaporated to afford the amide products [10].

Antioxidant activity

The antioxidant activity of synthesized compounds was evaluated by testing their free radical scavenging activity of DPPH (1,1-diphenyl-2-picryl-hydrazyl) and H_2O_2. Seven serial diluted concentrations (1000, 500, 250, 125, 62.5, 31.25, 15.62 µM) were prepared from a standard methanolic solution (1 mM) of the tested compounds. Both methods were carried out in triplicate for each detected concentration and compared with well-known antioxidant ascorbic acid. The radical scavenging activity expressed as % was calculated using the following formula:

Scavenging activity(%) = (Ac – As/Ac) × 100

where Ac is the absorbance of positive control and As is the absorbance of the sample.

The SC_{50}, which is the required concentration of sample for scavenging 50% of free radicals for each of the synthesized compounds were graphically measured by plotting the scavenging % versus the log concentration using a nonlinear regression [11].

DPPH free radical scavenging method

Each concentration of the tested compound (1.5ml) was mixed in a test tube with (0.5ml) methanolic DPPH solution (0.1 mM) in ratio 3:1. After protection from light and incubation at RT for 30 min, the absorbance was measured at 517 nm using a positive control consisting of DPPH (0.5 ml) and MeOH (1.5 ml)[12].

H_2O_2 radicals scavenging assay

To test tube containing (3.4ml) of each concentration of the tested compound in (50 mM) phosphate buffer (pH 7.4), 0.6ml of (40 mM) H_2O_2 in the same buffer was added, and the resultant mixture shacked vigorously and then incubated at RT for 10 min. The absorbance was measured at 230 nm using a positive control consisting of phosphate buffer and H_2O_2 without samples [13].

Antimicrobial Activity

The Gram(+)ve *Staphylococcus aueus* (ATCC 43300) and the three of Gram(-)ve *Escherichia coli* (ATCC 25922), *Klebsiella pneumonia* (ATCC 700603) and *Pseudomonas aeroginosa* (ATCC 27853) along with the two fungi *Candida abicals* (ATCC 90028) and *Aspergillus niger* (ATCC 16404) were selected to evaluate the antibacterial and antifungal activities. Amoxicillin, cefotaxim and ciprofloxacin, also fluconazole and ketoconazole were used as standards for antibacterial and antifungal activity respectively. The antimicrobial activity of the synthesized compounds was evaluated via measuring the inhibition zones in the disk diffusion method. Each tested or standard compounds (20 mg/mL) were prepared as disks (5 µl/disk), then these disks were placed on Petri dish with Mueller–Hinton agar medium (previously inoculated with the tested microbial strain by sterile cotton swabs). After incubation at 37 °C for 24 h (bacteria)[14] and for 48 h (fungi)[15], the zones of microbial growth produced around the tested substances were measured and recorded. Antimicrobial activities were expressed as the diameter of the inhibition zone (IZ) in mm.

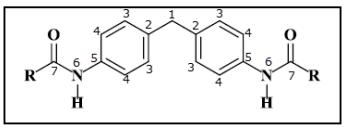
These experiments were carried out in triplicate and the average zone of inhibitions were calculated. DMSO was used as a solvent for the synthesized compounds with final concentration less than 2 % in order to ensure that it has no effect on the bacterial growth. DMSO served as negative control and the standards as positive controls[16].

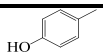
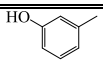
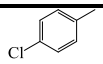
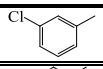
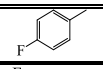
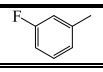
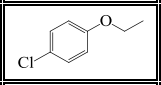
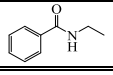
3. Results and discussion:

Chemistry:

The physical properties and the most characteristic IR absorption bands (ν cm^{-1}) of the FT-IR spectra for the amide compounds (1-10) were represented in table 1.

Table 1: The physical properties and the most characteristic absorption bands (ν cm^{-1}) of the FT-IR spectra for the amide compounds (1-10)



Compd. No.	R	m.p(°C)	Yield%	Color	IR (ν cm^{-1})			
					N-H	C=O	C-X	other
1		265-269	70	Brown	w 3316	m 1659	C-Cl m 1090	------
2		234-236	74	Dark Brown	w 3311	m 1658	C-Cl m 1087	------
3		182-184	77	Dark Yellow	w 3314	m 1662	------	O-H w 3476
4		177-180	86	Yellow	w 3314	m 1655	------	O-H w 3478
5		220-222	64	Dark Brown	w 3317	m 1663	C-Cl m 1087	------
6		232-235	74	Brown	w 3318	m 1651	C-Cl m 1094	------
7		158-160	83	Pale Brown	w 3312	m 1661	C-F m 1053	------
8		173-175	79	Brown	w 3320	m 1672	C-F m 1054	------
9		192-195	87	Brown	w 3316	m 1661	C-Cl m 1092	C-O-C s 1222, 1123
10		175-177	86	Pale Brown	w 3318	m 1671	------	------

The most characteristic observation of the FT-IR spectra for compounds (1-10) were the disappearance of the 1° amine NH_2 at 3363 cm^{-1} of the 4,4'-methylenedianiline and replaced by the 2° amide NH in the reign 3311-3320 cm^{-1}, and also the carbonyl

group C=O appears in the reign 1669-1674 cm^{-1} which indicate the amide bond formation.

Moreover, ^{1}H-NMR exposed chemical shifts at 8.66-9.94 ppm for single proton related to amide NH. On the other hand, the ^{13}C-NMR spectra showed chemical shifts at167.35-196.79 ppm related to carbonyl carbon of the amide moieties. These results confirmed the formation of the amides.

Chemical names and spectroscopic characterization of compounds 1-10:

Compound 1 [N,N'-(methylenebis(4,1-phenylene))bis(2,2-dichloroacetamide) **]**. **The ^{1}H-NMR of 1** (δ, ppm) (DMSO-d6): 9.94 (s, 2H, N 6), 7.91 (dt, 4H, C 4), 7.83 (m, 4H, C 3), 6.48 (s, 2H, C 8), 3.73 (s, 2H, C 1). **The ^{13}C-NMR of 1** (δ, ppm) (DMSO-d6): 182.75 (2C 7), 146.59 (2C 5), 145.57 (2C 2), 128.42 (4C 3), 122.81 (4C 4), 69.35 (2C 8), 46.65 (C1).

Compound 2 [N,N'-(methylenebis(4,1-phenylene))bis(2,3-dichloropropanamide) **]**. **The ^{1}H-NMR of 2** (δ, ppm) (DMSO-d6): 9.15 (s, 2H, N 6), 7.67 (dt, 4H, C 4), 7.70 (m, 4H, C 3), 5.95 (t, 2H, C 8), 3.80 (s, 2H, C 1), 3.71-3.78 (m, 4H, C 9). **The ^{13}C-NMR of 2** (δ, ppm) (DMSO-d6): 168.40 (2C 7), 137.92 (2C 5), 130.46 (2C 2), 127.65 (4C 3), 123.53 (4C 4), 67.51 (2C 8), 45.56 (2C 9), 41.69 (C1).

Compound 3 [N,N'-(methylenebis(4,1-phenylene))bis(4-hydroxybenzamide) **]**. **The ^{1}H-NMR of 3** (δ, ppm) (DMSO-d6): 9.28 (s, 2H, N 6), 8.56 (s, 2H, O 12), 7.97-7.99 (dt, 4H, C 9), 7.61-7.63 (dt, 4H, C 4), 7.33-7.35 (dt, 4H, C 3), 6.81-6.83 (dt, 4H, C 10) , 3.65 (s, 2H, C 1). **The ^{13}C-NMR of 3** (δ, ppm) (DMSO-d6): 167.35 (2C 7), 161.92 (2C 8), 139.48 (2C 5), 137.53 (2C 2), 128.47 (4C 3), 128.32 (4C 9), 125.07 (2C 8), 121.38 (4C 4), 116.52 (4C 10), 41.61 (C1).

Compound 4 [N,N'-(methylenebis(4,1-phenylene))bis(3-hydroxybenzamide) **]**. **The ^{1}H-NMR of 4** (δ, ppm) (DMSO-d6): 9.79 (s, 2H, O 14), 8.68 (s, 2H, N 6), 7.62-7.64 (m, 6H, C 4, 12, 13), 7.38 (t, 2H, C 8), 7.15-7.18 (t, 2H, C 11), 7.03-7.05 (m, 4H, C 3) , 6.71-6.74 (dt, 2H, C 9), 3.85 (s, 2H, C 1). **The ^{13}C-NMR of 4** (δ, ppm) (DMSO-d6): 176.80 (2C 7), 166.58 (2C 10), 139.39 (2C 5), 145.72 (2C 2), 138.12 (C 8), 129.80 (2C 11), 128.47 (4C 3), 124.95 (4C 4), 119.89 (2C 12), 118.80 (2C 13), 112.32 (2C 9), 45.75 (C1).

Compound 5 [N,N'-(methylenebis(4,1-phenylene))bis(4-chlorobenzamide) **]**. **The ^{1}H-NMR of 5** (δ, ppm) (DMSO-d6): 9.15 (s, 2H, N 6), 7.86-7.89 (dt, 4H, C 9), 7.63-7.66 (dt, 4H, C 4), 7.37-7.40 (dt, 4H, C 10), 7.24 (dt, 4H, C 3), 4.05 (s, 2H, C 1). **The ^{13}C-NMR of 5** (δ, ppm) (DMSO-d6): 187.79 (2C 7), 147.59 (2C 5), 135.69 (2C 9), 133.69 (2C 2), 131.69 (2C 8), 122.55 (4C 9), 122.47 (4C 3), 122.08 (4C 10), 120.38 (4C 4), 47.76 (C1).

Compound 6 [N,N'-(methylenebis(4,1-phenylene))bis(3-chlorobenzamide) **]**. **The ^{1}H-NMR of 6** (δ, ppm) (DMSO-d6): 8.73 (s, 2H, N 6), 7.85 (q, 2H, C 9), 7.79-7.81 (m, 2H, C 11), 7.51-7.53 (dt, 4H, C 4), 7.36-7.20 (m, 2H, C 12, 13) , 7.03-7.05 (dt, 4H, C 3), 4.04 (s, 2H, C 1). **The ^{13}C-NMR of 6** (δ, ppm) (DMSO-d6): 196.26 (2C 7), 148.45 (2C 5), 145.53 (2C 2), 143.34 (2C 8), 142.63 (2C 9), 140.99 (2C 10), 130.96 (2C 11), 129.47 (4C 3), 125.64 (2C 12), 125.57 (2C 13), 121.38 (4C 4), 43.69 (C1).

Compound 7 [N,N'-(methylenebis(4,1-phenylene))bis(4-fluorobenzamide) **]**. **The ^{1}H-NMR of 7** (δ, ppm) (DMSO-d6): 9.17 (s, 2H, N 6), 8.70 (dt, 4H, C 9), 7.62 (dt, 4H, C 4), 7.35-7.38 (dt, 4H, C 10), 7.06 (dt, 4H, C 3), 4.06 (s, 2H, C 1). **The ^{13}C-NMR of 7** (δ, ppm) (DMSO-d6): 186.34 (2C 7), 165.82 (2C 5), 139.48 (2C 9), 138.53 (2C 2), 132.45 (2C 8), 129.84 (4C 9), 127.57 (4C 3), 121.48 (4C 10), 116.97 (4C 4), 44.69 (C1).

Compound 8 [N,N'-(methylenebis(4,1-phenylene))bis(3-fluorobenzamide) **]**. **The ^{1}H-NMR of 8** (δ, ppm) (DMSO-d6): 8.66 (s, 2H, N 6), 7.91-7.93 (m, 2H, C 9), 7.81 (t, 2H, C 11), 7.71-7.73 (dt, 4H, C 4), 7.60 (t, 1H, C 12), 7.36 (m, 1H, C 13) , 7.24 (dt, 4H, C 3), 3.94 (s, 2H, C 1). **The ^{13}C-NMR of 8** (δ, ppm) (DMSO-d6): 196.79 (2C 7), 160.95 (2C 5), 148.48 (2C 2), 145.69 (2C 8), 145.53 (2C 9), 141.45 (2C 5), 129.96 (2C 11), 127.02 (4C 3), 121.38 (2C 12), 119.14 (2C 13), 116.28 (4C 4), 41.69 (C1).

Compound 9 [N,N'-(methylenebis(4,1-phenylene))bis(2-(4-chlorophenoxy)acetamide) **]**. **The ^{1}H-NMR of 9** (δ, ppm) (DMSO-d6): 9.69 (s, 2H, N 6), 7.16 (dt, 4H, C 4), 7.13-7.17 (dt, 4H, C 10), 7.03 (m, 4H, C 3), 6.84-6.87 (dt, 4H, C 11), 4. 94 (s, 2H, C 8), 3.55 (s, 2H, C 1). **The ^{13}C-NMR of 9** (δ, ppm) (DMSO-d6): 178.04 (2C 7), 167.21 (2C 10), 146.54 (2C 5), 145.53 (2C2), 129.54 (4C 11), 128.42 (4C 3), 127.29 (2C 9), 121.43 (4C 4), 117.05 (2C 12), 77.49 (2C 8), 44.83 (C1).

Compound 10 [N,N'-(((methylenebis(4,1-phenylene))bis(azanediyl))bis(carbonyl))dibenzamide **]**. **The ^{1}H-NMR of 10** (δ, ppm) (DMSO-d6): 10.60 (s, 2H, N 9), 9.65 (s, 2H, N 6), 7.72 (dt, 4H, C 12), 7.52

(tt, 2H, C 14), 7.43-7.47 (m, 4H, C 13), 7.33 (dt, 4H, C 4) , 7.13-7.14 (dt, 4H, C 3), 3.55 (s, 2H, C 1). **The ^{13}C-NMR of 10** (δ, ppm) (DMSO-d6): 169.19 (2C 10), 155.48 (2C 7), 139.27 (2C 5), 136.65 (2C 2), 135.03 (2C 11), 131.15 (2C 14), 128.41 (4C 3), 127.42 (4C 12), 127.13 (4C 13), 118.96 (4C 8), 45.69 (C1).

Antioxidant activity results:

The antioxidant activity of the synthesized compounds was evaluated by testing their free radical scavenging activity of DPPH (1,1-diphenyl-2-picryl-hydrazyl) and H_2O_2. The results were illustrated in table 2.

Table 2: The antioxidant activity for the amide compounds (1-10)

Compounds	Antioxidant activity SC_{50} (µM) ± SD (n = 3)		Compounds	Antioxidant activity SC_{50} (µM) ± SD (n = 3)	
	DPPH	H_2O_2		DPPH	H_2O_2
1	51.830 ± 0.38	37.540 ± 0.01	7	33.820 ± 0.21	21.530 ± 0.21
2	31.520 ± 0.28	26.130 ± 0.21	8	41.730 ± 0.24	27.550 ± 0.11
3	592.02 ± 0.11	190.43 ± 0.43	9	21.540 ± 0.48	36.130 ± 0.31
4	570.53 ± 0.19	185.17 ± 0.23	10	543.80 ± 0.09	95.320 ± 0.32
5	25.330 ± 0.28	22.350 ± 0.31	Ascorbic acid	38.520 ± 0.27	24.010 ± 0.50
6	32.560 ± 0.43	35.130 ± 0.36			

It is well known that the antioxidant is any compound that can incorporate free radicals in a safe way and switch them to a riskless molecule by offering a proton[2]. So that any attempt to increase the number of such protons in the designated compounds with maintaining their superficial hydrogen atom transfer and resonance stabilization, would create a potent antioxidant compounds.

As it was expected, the compounds 3 and 4 that contain the hydroxyl group showed excellent antioxidant activity compared with the control compound (ascorbic acid). Compound 10 with the amide proton showed an antioxidant activity similar to that of the hydroxyl group. This activity may be related to the stabilization via the proton-shift (resonance) of the amide proton with the carbonyl group[2]. The other compounds, which showed antioxidant activity, their results were similar and all were weak and could be related to the proton of the developed amide bond.

Antimicrobial activity results:

The antimicrobial activity of the synthesized compounds was evaluated via measuring the inhibition zones in the disk diffusion method. The results were illustrated in table 3.

Table 3: The antimicrobial activity of the amide compounds (1-10)

Compounds	Zone of growth inhibition (IZ) (mm) ± SD (n = 3)					
	Staph. aureus	*E. coli*	*K. pneumonia*	*P. aeroginosa*	*C. abicals*	*A. niger*
1	29.23 ± 0.41	30.15 ± 0.29	32.02 ± 0.11	27.52 ± 0.28	-----	-----
2	26.52 ± 0.27	31.80 ± 0.47	30.53 ± 0.19	25.02 ± 0.11	-----	-----
3	6.300 ± 0.27	10.80 ± 0.37	12.33 ± 0.28	7.530 ± 0.19	20.54 ± 0.25	23.54 ± 0.25
4	12.53 ± 0.33	17.25 ± 0.28	7.560 ± 0.43	9.350 ± 0.31	-----	-----
5	25.93 ± 0.32	24.44 ± 0.34	17.82 ± 0.21	15.13 ± 0.36	-----	-----
6	20.72 ± 0.23	28.39 ± 0.42	14.73 ± 0.24	10.53 ± 0.21	-----	-----
7	30.52 ± 0.27	32.15 ± 0.29	27.54 ± 0.48	29.55 ± 0.11	33.54 ± 0.25	30.53 ± 0.19
8	29.30 ± 0.27	30.80 ± 0.47	25.80 ± 0.09	26.13 ± 0.31	32.03 ± 0.20	28.33 ± 0.28
9	-----	-----	-----	-----	27.82 ± 0.34	25.56 ± 0.43
10	-----	-----	-----	-----	-----	-----
Amoxicillin	30.73 ± 0.25	27.61 ± 0.14	25.41 ± 0.13	28.77 ± 0.30	-----	-----
Cefotaxim	20.04 ± 0.31	30.37 ± 0.46	28.92 ± 0.27	27.65 ± 0.41	-----	-----
Ciprofloxacin	28.64 ± 0.29	30.58 ± 0.35	29.55 ± 0.40	30.76 ± 0.30	-----	-----
Fluconazole	-----	-----	-----	-----	32.54 ± 0.21	30.50 ± 0.35
Ketoconazole	-----	-----	-----	-----	31.64 ± 0.43	28.83 ± 0.22

(-----): inactive (Zone of inhibition > 5 mm)

The antibacterial and antifungal activity could be related to the presence of halogen atoms in any organic compound, and their potency will depend on their selectivity toward the bacterial or fungal targets. This will cause the variety of the activities for different antimicrobial compounds[17].

Compounds 1 and 2 with aliphatic chlorine substituents exposed potent antibacterial activity comparing to the standard antibacterial agents, which could be related to the multiple chlorine atoms in their structures. The halo-aromatic compounds 5-8 showed similar antibacterial activities; here the fluro-compounds provide stronger effect than the chloro-compounds. The substitution at meta- and para-positions do not affect their antibacterial activities. From this we can conduct that the aliphatic or aromatic halogen substitution has no effect on the antibacterial activities and that both gives similar potency[17].

The antifungal activity results showed different picture. Compounds 7 and 8 with the aromatic fluorine substitutions possess excellent antifungal activities comparing to the standard antifungal agents[18, 19]. While compound 9 offered lower antifungal activity, which could be attributed to the oxygen atom of the ether [20,21]. Whereas the hydroxyl moiety of the compound 3 could be the cause of its antifungal effect[22].

4. Conclusion:

There are an urgent need to emerge a new antioxidant and antimicrobial agents that are effective, safe, and selective. The synthesized compounds showed varied antioxidant and antimicrobial activities. The hydroxyl and the amide moiety in any organic compound could possess similar potent antioxidant activities. The fluoro-aromatic compounds exposed potent antibacterial and antifungal activities. While the chloro-aliphatic and aromatic compounds showed only antibacterial activity. The substitution at meta- and para- positions with halogens do not affect the antimicrobial activities. On the other hand, any fluoro-aromatic and ether organic compounds can exhibited a potent antifungal activity.

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