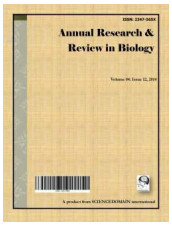

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Antimicrobial Evaluation and Structure-Activity Relationship (SAR) of Some 1,ω-bis[4-Carboxy/Methoxycarbonyl/(Hydrazinecarbonyl) /Phenoxy]Alkanes

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Authors' contributions

This work was carried out in collaboration between both authors. Author NSAMK designed the study, managed literature searches, performed and managed the chemical synthesis, wrote the protocol and wrote the first draft of the manuscript. Author NMM managed the elemental analyses, spectral data (IR data, [1]HNMR data) and antimicrobial evaluation of the study. Both authors read and approved the final manuscript.

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ABSTRACT

A series of some 1,ω-bis[4-carboxy/methoxycarbonyl/(hydrazinecarbonyl)/phenoxy]alkanes were synthesized and evaluated for their antimicrobial activity against different strains of Gram-positive bacteria (*Bacillus subtilis* RCMB 101-001 and *Staphylococcus aureus* RCMB 106-001 (1)), Gram-negative bacteria (*Pseudomonas aeruginosa* RCMB 102-002 and *Escherichia coli* RCMB 103-001), yeast (*Candida albicans* RCMB 005003) and fungi (*Aspergillus fumigates* RCMB 002008 (1), *Penicillium italicum* RCMB 001018 (1) and *Syncephalastrum racemosum RCMB 016001*). The screening results revealed that all the tested compounds exhibited different inhibitory effects against different organisms. Thus, compounds **1**, **4**, exhibited inhibitory effects against all the test organisms, compounds **5**, **7** exhibited inhibitory effects against seven of total eight test organisms, compound **2** exhibited inhibitory effect against six of total eight test organisms. Some tested

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compounds, at specific concentrations, showed the same or higher inhibitory effects against some test organisms, compared to standard antimicrobial agents, at the same concentrations. Thus, while compound **1** gave the same inhibitory effect against *Aspergillus fumigatus* RCMB 002008 (1) (at concentrations 1.0, 2.5 and 5.0 mg/mL) as Tebinafine (standard antifungal agent), it showed much higher inhibitory effect against *Syncephalastrum racemosum* RCMB 016001 (at concentrations 2.5 and 5.0 mg/mL) and *Candida albicans* RCMB 005003 (at concentrations 1, 2.5 and 5 mg/mL). Compound **7**, also, compared to Terbinafine, while revealed the same inhibitory effect, against *Penicillium italicum* RCMB 001018 (1) (at concentrations 1.0, 2.5 and 5.0 mg/mL), it revealed higher inhibitory effect against *Aspergillus fumigatus* RCMB 002008 (1) (at concentration 5.0 mg/mL), *Syncephalastrum racemosum* RCMB 016001 (at concentration 2.5 mg/mL) and *Candida albicans* RCMB 005003 (at concentration 5.0 mg/mL). Compared to the standard antibacterial Chloramphenicol, compound **7** revealed the same inhibitory effect against *Staphylococcus aureus* RCMB 106-001 (1) (at concentrations 1.0, 2.5 and 5 mg/mL) and *Escherichia coli* RCMB 103-001 (at concentrations 1.0, 2.5 and 5 mg/mL).The structure-activity relationship was investigated via studying the effect of the aliphatic spacer length between the two ethereal oxygen atoms as well as the effect of functional group attached to the two carbonyl groups (hydroxy/methoxy/hydrazine) on the inhibitory effect of the titled compounds**.**

Keywords: Antimicrobial activity; structure-activity relationship; 1,ω-bis(organic acids); 1,ω-bis(organic esters); 1,ω-bis(hydrazides); 1,ω-bis(phenoxyalkanes).

1. INTRODUCTION

Many Organic acids and esters that are existed by nature, at different concentrations, in many types of foods and beverages, are potent antimicrobial agents and used principally in acidic foods as inhibitors to yeasts, molds and bacteria at pH above 4.5 [1].

Hydrazides and related compounds are described as building blocks of various heterocyclic rings [2] and important starting materials for a wide range of derivatives utilizable in pharmaceutical products and surfactants, so, they are useful medicaments, especially, in the treatment of inflammatory and autoimmune diseases, osteoarthritis, respiratory diseases, tumors, cachexia, cardiovascular diseases, fever, hemorrhage and sepsis [3]. Hydrazide derivatives exhibited anthelmintic [4], antifungal [5], antiviral [6], bacteriostatic [5-8], antiparasite [5,9], antituberculous [10-13], antitumor [3,14], anticonvulsant [15], psychotropic [5], and insecticidal [16] activities. While some heterocyclic hydrazides are useful as antifertility agents in rats and pigeons [17], others, find useful applications, as active ingredients, in deodorant compositions that can be used for removal of offensive odor [18].

Development of antibiotic-resistant bacterial and fungal strains over recent decades resulted in substantial need of new classes of antimicrobial agents. So, herein, and in continuation of our program [14,19-38] directed to synthesize and biologically evaluate some promising candidates of new organic compounds, the antimicrobial evaluation and structure-activity relationship of an interesting new class of 1,ω-bis[4-carboxy/methoxycarbonyl/(hydrazinecarbonyl)/p-henoxy]alkanes are studied.

2. MATERIALS AND METHODS

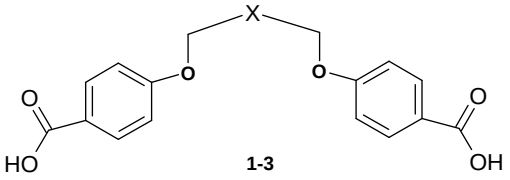
2.1 Synthesis

2.1.1 General

Compounds **1**, **2**, **4**, **5**, **7** (Fig. 1) were synthesized as reported [27] and identified by melting points (determined using Stuart® meting point apparatus SMP3 and are uncorrected), IR spectra (recorded in KBr discs using Perkin-Elmer 1430 spectrometer), ^{1}H NMR spectra (recorded at 300 MHz with a Varian Mercury 300 spectrometer), mass spectra (measured on Shimadzu GCMS-QP2010 Plus spectrometer, with an EI ionization mode and 70 eV electronic voltage) and elemental analyses (carried out at the Micro Analytical Center, Cairo University, Giza, Egypt).

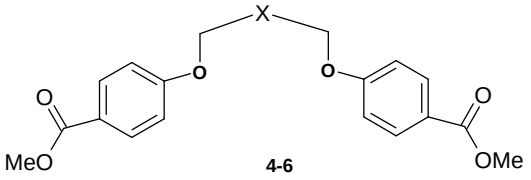
2.1.2 Synthesis of 1,ω-bis(4-carboxyphenoxy)alkanes 1, 2. General procedure [27]

A mixture of each of compounds **4**, **5** (5 mmol) in aq KOH (10%, 20 mL) was heated at reflux temperature for 24 h and left to cool. The non reacted bis(ester) was extracted with DCM (3 x 20 mL) and discarded. The aq phase was diluted with concd HCL (3-7 mL) and the



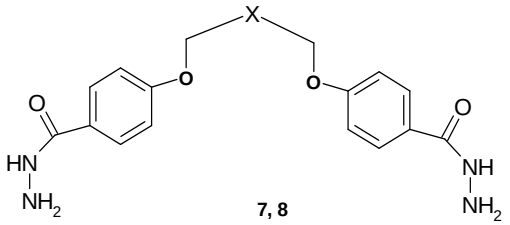
1-3

1,ω-Bis(4-carboxyphenoxy)alkanes



4-6

1,ω-Bis(4-methoxycarbonylphenoxy)alkanes



7, 8

1,ω-Bis[4-(hydrazinecarbonyl)phenoxy]alkanes

1, 4 X= 0
2, 5, 7 X= (CH_2)
3, 6, 8 X= $(CH_2)_2$

Fig. 1. 1,ω-bis[4-carboxy/methoxycarbonyl/(hydrazinecarbonyl)/phenoxy]alkanes

obtained solid was collected by filtration and washed successively with water (3 x 100 mL) and MeOH (3 x 10 mL). The product was dried and recrystallized from DMF/MeOH.

*2.1.2.1 1,2-Bis(4-carboxyphenoxy)ethane (**1**) [27]*

Yield 1.36 g (90%); colorless crystals, mp 350℃. IR: 3082-2557 (br), 3082, 2951, 2885, 2827, 2678, 2557, 1682, 1605, 1578, 1512, 1481, 1435, 1304, 1254, 1165, 1119, 1045, 945, 845, 768, 691, 644, 629, 552, 505, 478, 421. ^{1}H NMR (DMSO-d_6) δ 4.41 (s, 4H, OCH_2CH_2), 7.07 (d, 4H, *J*= 8.9 Hz, ArH), 7.90 (d, 4H, *J*= 8.9 Hz, ArH), 12.59 (br, 2H, D_2O exchangeable OH) Anal. Calcd for $C_{16}H_{14}O_6$ (302.3): C, 63.57; H, 4.67. Found: C, 63.59; H, 4.65.

*2.1.2.2 1,3-Bis(4-carboxyphenoxy)propane (**2**) [27]*

Yield 1.38 g (87%); colorless crystals, mp 327-328℃. Anal. Calcd for $C_{17}H_{16}O_6$ (316.3): C, 64.55; H, 5.10. Found: C, 64.51; H, 5.18.

2.1.3 Synthesis of 1,ω-bis(4-methoxycarbonylphenoxy)alkanes 4, 5. General procedure [27]

To a solution of the K-salt of methylparaben (100 mmol) in dry DMF (75 mL) was added appropriate dihalo compound (50 mmol). The reaction mixture was then heated at reflux temperature for 15 min (during which time KCl was separated) and poured over cold water containing cruched ice (150 mL). The formed precipitate was collected by filtration, washed with cold water (3 x 150 mL) followed by MeOH (3 x 50 mL), dried and recrystallized from DMF/MeOH.

*2.1.3.1 1,2-Bis(4-methoxycarbonylphenoxy)ethane (**4**) [27]*

Yield 4.13 g (25%); colorless crystals, mp 163-164^{o}C. IR: 3055, 3017, 2959, 2893, 2843, 1720, 1609, 1508, 1481, 1435, 1346, 1315, 1254, 1215, 1192, 1169, 1111, 1042, 1011, 953, 856, 768, 698, 644, 517, 471, 421. ^{1}H NMR ($CDCl_3$) δ 3.89 (s, 6H, $COOCH_3$), 4.40 (s, 4H, OCH_2CH_2O), 6.97 (d, 4H, *J*= 9.0 Hz, ArH), 8.01 (d, 4H, *J*= 9.0 Hz, ArH). Ms: m/z= 330 (M+). Anal. Calcd for $C_{18}H_{18}O_6$ (330.3): C, 65.45; H, 5.49. Found: C, 65.49; H, 5.38.

*2.1.3.2 1,3-Bis(4-methoxycarbonylphenoxy)propane (**5**) [27]*

Yield 8.95 g (52%); colorless crystals, mp 136-138℃. Anal. Calcd for $C_{19}H_{20}O_6$ (344.4): C, 66.27; H, 5.85. Found: C, 66.23; H, 5.91

2.1.4 Synthesis of 1,3-bis[4-(hydrazinecarbonyl)phenoxy]propane (7) [27]

A mixture of the 1,3-bis(ester) **5** (25 mmol) and hydrazine monohydrate (100 mL) was heated at reflux temperature for 4 h during which time the product precipitated from the mixture. After cooling to room temperature, water was added

(100 mL) and the formed precipitate was collected by filtration, washed succisively with water (3 x 100 mL), MeOH (3 x 25 mL) and chloroform (3 x 25 mL), dried and recrystallized from DMF. Yield 7.92 g (92%); colorless crystals, mp 246-247℃. IR: 3298, 3275, 3186, 3071, 2951, 2882, 1655, 1635, 1609, 1574, 1539, 1504, 1466, 1423, 1385, 1335, 1304, 1250, 1196, 1173, 1119, 1053, 968, 883, 849, 775, 721, 664, 625, 521, 482, 421. ^{1}H NMR (DMSO-d_6) δ 1.88 (quint, 2H, *J*= 5.3 Hz, OCH_2CH_2), 4.08 (t, 4H, *J*= 5.3 Hz, OCH_2CH_2O), 4.42 (s, 4H, D_2O exchangeable NH_2), 6.97 (d, 4H, *J*= 8.9 Hz, ArH), 7.79 (d, 4H, *J*= 8.9 Hz, ArH), 9.59 (s, 2H, D_2O exchangeable NH). Anal. Calcd for $C_{17}H_{20}N_4O_4$ (344.4): C, 59.29; H, 5.85; N, 16.27. Found: C, 59.22; H, 5.79; N, 16.22.

2.2 Antimicrobial Evaluation of Compounds 1, 2, 4, 5, 7

The *in vitro* antimicrobial screening of compounds **1**, **2**, **4**, **5**, **7** was carried out using the diffusion agar technique [39,40]. The test organisms were obtained from the culture of the Regional Center for Mycology and Biotechnology (RCMB), Faculty of Science, Al-Azhar University, Cairo, Egypt. Compounds **1**, **2**, **4**, **5**, **7** as well as standard antimicrobial agents (Chloramphenicol and Terbinafine were used as standard antibacterial and antifungal agents, respectively) were dissolved in DMSO (5 mg/mL). Further dilutions of the tested compounds and standard agents were prepared at the required quantities of 5, 2.5 and 1 mg/mL concentrations. All the compounds were tested for their *in vitro* growth inhibitory activity against two Gram-positive bacterial strains (*Bacillus subtilis* RCMB 101-001 and *Staphylococcus aureus* RCMB 106-001 (1)), two Gram-negative bacterial strains (*Pseudomonas aeruginosa* RCMB 102-002 and *Escherichia coli* RCMB 103-001), one yeast strain (*Candida albicans* RCMB 005003) and three mould strains (*Aspergillus fumigatus* RCMB 002008 (1), *Penicillium italicum* RCMB 001018 (1) and *Syncephalastrum racemosum* RCMB 016001). The antimicrobial activities were expressed as the diameter of the inhibition zones (Tables 1-3).

3. RESULTS AND DISCUSSION

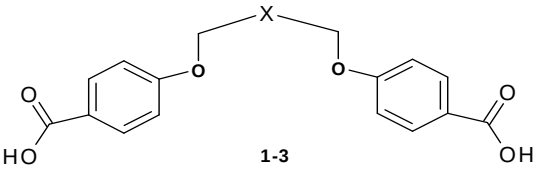
Table (1) illustrates the antimicrobial activity 1,ω-bis(4-carboxyphenoxy) alkanes (**1-3**). Compound **1**, namely, 1,2-bis(4-carboxyphenoxy)ethane, exhibited inhibitory effect against all the test organisms. Thus, it revealed inhibitory effects against *Aspergillus fumigatus* RCMB 002008 (1) (at concentrations 1.0, 2.5 and 5.0 mg/mL), *Penicillium italicum* RCMB 001018 (1) (at concentration 5.0 mg/mL), *Syncephalastrum racemosum* RCMB 016001 (at concentrations 2.5 and 5.0 mg/mL), *Candida albicans* RCMB 005003 (at concentrations 1.0, 2.5 and 5.0 mg/mL), *Staphylococcus aureus* RCMB 106-001 (1) (at concentration 5.0 mg/mL), *Pseudomonas aeruginosa* RCMB 102-002 (at concentrations 2.5 and 5.0 mg/mL), *Bacillus subtilis* RCMB 101-001 (at concentration 5.0 mg/mL) and *Escherichia coli* RCMB 103-001 (at concentrations 2.5 and 5.0 mg/mL).

Compound **2**, namely, 1,3-bis(4-carboxyphenoxy)propane (Table 1), revealed inhibitory effect against six of total eight test organisms. Thus, it revealed inhibitory effects against *Aspergillus fumigatus* RCMB 002008 (1) (at concentrations 1.0, 2.5 and 5.0 mg/mL), *Penicillium italicum* RCMB 001018 (1) (at concentration 5.0 mg/mL), *Candida albicans* RCMB 005003 (at concentration 5.0 mg/mL), *Staphylococcus aureus* RCMB 106-001 (1) (at concentrations 1.0, 2.5 and 5.0 mg/mL), *Pseudomonas aeruginosa* RCMB 102-002 (at concentration 5.0 mg/mL) and *Bacillus subtilis* RCMB 101-001 (at concentrations 2.5 and 5.0 mg/mL), while, it revealed no inhibitory effect against *Syncephalastrum racemosum* RCMB 016001 and *Escherichia coli* RCMB 103-001.

The antimicrobial inhibitory effect of compound **3**, namely, 1,4-bis(4-carboxyphenoxy)butane, was reported [27]. Thus, Compound **3**, as previously reported [27], against the current test organisms, revealed inhibitory effect against six of eight (it was also reported to give inhibitory effect against *salmonella typhi* at concentrations 2.5, 5.0 mg/mL). Compound **3** revealed inhibitory effects against *Aspergillus fumigatus* RCMB 002008 (1) (at concentrations 1.0, 2.5 and 5.0 mg/mL), *Syncephalastrum racemosum* RCMB 016001 (at concentrations 1.0, 2.5 and 5.0 mg/mL), *Candida albicans* RCMB 005003 (at concentration 5.0 mg/mL), *Staphylococcus aureus* RCMB 106-001 (1) (at concentration 5.0 mg/mL), *Pseudomonas aeruginosa* RCMB 102-002 (at concentration 5.0 mg/mL), *Escherichia coli* RCMB 103-001 (at concentration 5.0 mg/mL), while, it revealed no inhibitory effect against *Penicillium italicum* RCMB 001018 (1) and *Bacillus subtilis* RCMB 101-001.

Having shorter spacer between the aromatic rings, compound **1** showed much broad spectrum, than those of compounds **2** and **3**, as it

Table 1. Antimicrobial activity of 1,ω-bis(4-carboxyphenoxy)alkanes (1-3) compared to standard antimicrobial agents



1-3

Test Organisms	Compound														
	1[a]			**2**[a]			**3**[a, d]			**St.**[b]			**St.**[c]		
	Concentration (mg/mL)														
	1	2.5	5	1	2.5	5	1	2.5	5	1	2.5	5	1	2.5	5
A. fumigatus RCMB 002008 (1)	+	+	+	+	+	+	+	+	++	0	0	0	+	+	+
P. italicum RCMB 001018 (1)	0	0	+	0	0	+	0	0	0	0	+	+	+	+	+
S. racemosum RCMB 016001	0	+	++	0	0	0	+	+	++	+	+	+	0	0	+
C. albicans RCMB 005003	+	+	+	0	0	+	0	0	+	0	+	+	0	0	0
S.aureus RCMB 106-001 (1)	0	0	+	+	+	+	0	0	+	+	+	+	+	+	++
P. aeruginosa RCMB 102-002	0	+	+	0	0	+	0	0	+	+	+	+	0	0	0
B. subtilis RCMB 101-001	0	0	+	0	+	+	0	0	0	++	++	++	0	0	+
E. coli RCMB 103-001	0	+	+	0	0	0	0	0	+	+	+	+	+	+	+

Note: The test was done using the diffusion agar technique. Inhibition values = 0.1-0.5 cm beyond control = +; Inhibition values = 0.6-1.0 cm beyond control = ++; Inhibition values = 1.0-1.5 cm beyond control = +++; 0 = Not detected.

[a]100 µL of each conc. was tested (1.0, 2.5, 5.0 mg/mL); Well diameter = 0.6 cm.

[b]St.: Reference standard; Chloramphenicol was used as a standard antibacterial agent.

[c]St.: Reference standard; Terbinafine was used as a standard antifungal agent.

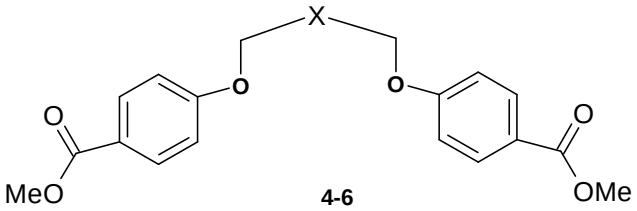
*[d]Activity of compound **3** was reported [27]*

showed inhibitory effect against all the test organisms at concentration 5.0 mg/mL, while, compounds **2** and **3**, with longer spacer, revealed inhibitory effect against six of total eight test organisms, at the same concentration. On the other hand, compound **3**, with longer spacer, exhibited higher inhibitory effect against *Aspergillus fumigatus* RCMB 002008 (1) (at concentration 5.0 mg/mL) and *Syncephalastrum racemosum* RCMB 016001 (at concentration 1.0 mg/mL).

Compound **4**, namely, 1,2-bis(4-methoxycarbonylphenoxy)ethane (Table 2), showed inhibitory effect against all the test organisms. Thus, it revealed inhibitory effects against *Aspergillus fumigatus* RCMB 002008 (1) (at concentration 5.0 mg/mL), *Penicillium italicum* RCMB 001018 (1) (at concentration 5.0 mg/mL), *Syncephalastrum racemosum* RCMB 016001 (at concentration 5.0 mg/mL), *Candida albicans* RCMB 005003 (at concentration 5.0 mg/mL), *Staphylococcus aureus* RCMB 106-001 (1) (at concentrations 2.5 and 5.0 mg/mL), *Pseudomonas aeruginosa* RCMB 102-002 (at concentrations 2.5 and 5.0 mg/mL), *Bacillus subtilis* RCMB 101-001 (at concentrations 1.0, 2.5 and 5.0 mg/mL) and *Escherichia coli* RCMB 103-001 (at concentrations 2.5 and 5.0 mg/mL).

Compound **5**, namely, 1,3-bis(4-methoxycarbonylphenoxy)propane (Table 2), revealed inhibitory effect against seven of total eight test organisms. Thus, it revealed inhibitory effects against *Aspergillus fumigatus* RCMB 002008 (1) (at concentration 5.0 mg/mL), *Penicillium italicum* RCMB 001018 (1) (at

Table 2. Antimicrobial activity of 1,ω-bis(4-methoxycarbonylphenoxy)alkanes (4-6) compared to standard antimicrobial agents



4-6

Test Organisms	Compound														
	Compound 4[a]			Compound 5[a]			Compound 6[a,d]			St.[b]			St.[c]		
	Concentration (mg/mL)														
	1	2.5	5	1	2.5	5	1	2.5	5	1	2.5	5	1	2.5	5
A. fumigatus RCMB 002008 (1)	0	0	+	0	0	+	0	+	+	0	0	0	+	+	+
P. italicum RCMB 001018 (1)	0	0	+	0	+	+	+	+	+	0	+	+	+	+	+
S. racemosum RCMB 016001	0	0	+	+	+	+	+	+	++	+	+	+	0	0	+
C. albicans RCMB 005003	0	0	+	+	+	++	+	+	++	0	+	+	0	0	0
S. aureus RCMB 106-001 (1)	0	+	+	+	+	+	0	+	+	+	+	+	+	+	++
P. aeruginosa RCMB 102-002	0	+	+	+	+	+	0	0	0	+	+	+	0	0	0
B. subtilis RCMB 101-001	+	+	++	0	0	0	+	+	+	++	++	++	0	0	+
E. coli RCMB 103-001	0	+	+	+	+	+	0	+	++	+	+	+	+	+	+

Note: The test was done using the diffusion agar technique. Inhibition values = 0.1-0.5 cm beyond control = +; Inhibition values = 0.6-1.0 cm beyond control = ++; Inhibition values = 1.0-1.5 cm beyond control = +++; 0 = Not detected.

[a]100 µL of each conc. was tested (1.0, 2.5, 5.0 mg/mL); Well diameter = 0.6 cm.

[b]St.: Reference standard; Chloramphenicol was used as a standard antibacterial agent.

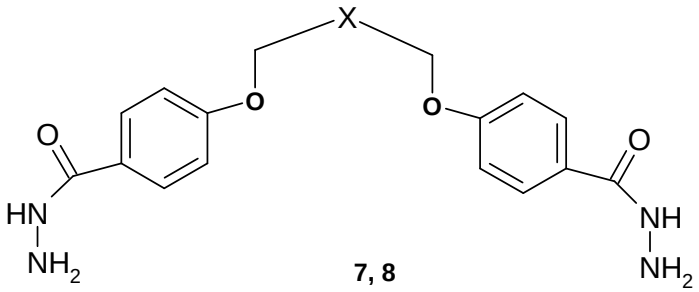
[c]St.: Reference standard; Terbinafine was used as a standard antifungal agent.

*[d]Activity of compound **6** was reported [27]*

concentrations 2.5 and 5.0 mg/mL), *Syncephalastrum racemosum* RCMB 016001 (at concentrations 1.0, 2.5 and 5.0 mg/mL), *Candida albicans* RCMB 005003 (at concentrations 1.0, 2.5 and 5.0 mg/mL), *Staphylococcus aureus* RCMB 106-001 (1) (at concentrations 1.0, 2.5 and 5.0 mg/mL), *Pseudomonas aeruginosa* RCMB 102-002 (at concentrations 1.0, 2.5 and 5.0 mg/mL) and *Escherichia coli* RCMB 103-001 (at concentrations 1.0, 2.5 and 5.0 mg/mL), while, it revealed no inhibitory effect against *Bacillus subtilis* RCMB 101-001.

The antimicrobial inhibitory effect of compound **6**, namely, 1,4-bis(4-methoxycarbonylphenoxy)butane, was reported [27]. Thus, Compound **6**, as previously reported [27], versus the current eight test organisms, revealed inhibitory effect against seven of them (it also exhibited no inhibitory effect against *Salmonella typhi* at concentrations

Table 3. Antimicrobial activity of 1,ω-bis[4-(hydrazinecarbonyl)phenoxy]alkanes (7, 8) compared to standard antimicrobial agents



7, 8

Test organisms	Compound											
	Compound 7[a]			Compound 8[a, d]			St.[b]			St.[c]		
	Concentration (mg/mL)											
	1	2.5	5	1	2.5	5	1	2.5	5	1	2.5	5
A. fumigatus RCMB 002008 (1)	+	+	++	+	+	+	0	0	0	+	+	+
P. italicum RCMB 001018 (1)	+	+	+	0	+	+	0	+	+	+	+	+
S. racemosum RCMB 016001	0	+	+	0	+	+	+	+	+	0	0	+
C. albicans RCMB 005003	0	0	+	++	++	+++	0	+	+	0	0	0
S. aureus RCMB 106-001 (1)	+	+	+	0	+	+	+	+	+	+	+	++
P. aeruginosa RCMB 102-002	0	0	0	0	0	+	+	+	+	0	0	0
B. subtilis RCMB 101-001	0	+	+	+	+	+	++	++	++	0	0	+
E. coli RCMB 103-001	+	+	+	0	+	+	+	+	+	+	+	+

Note: The test was done using the diffusion agar technique. Inhibition values = 0.1-0.5 cm beyond control = +; Inhibition values = 0.6-1.0 cm beyond control = ++; Inhibition values = 1.0-1.5 cm beyond control = +++; 0 = Not detected.

[a]100 µL of each conc. was tested (1.0, 2.5, 5.0 mg/mL); Well diameter = 0.6 cm.
[b]St.: Reference standard; Chloramphenicol was used as a standard antibacterial agent.
[c]St.: Reference standard; Terbinafine was used as a standard antifungal agent.
*[d]Activity of compound **8** was reported [27]*

1.0, 2.5 and 5.0 mg/mL). Compound **6** revealed inhibitory effects against *Aspergillus fumigatus* RCMB 002008 (1) (at concentrations 2.5 and 5.0 mg/mL), *Penicillium italicum* RCMB 001018 (1) (at concentrations 1.0, 2.5 and 5.0 mg/mL), *Syncephalastrum racemosum* RCMB 016001 (at concentrations 1.0, 2.5 and 5.0 mg/mL), *Candida albicans* RCMB 005003 (at concentrations 1.0, 2.5 and 5.0 mg/mL), *Staphylococcus aureus* RCMB 106-001 (1) (at concentrations 2.5 and 5.0 mg/mL), *Bacillus subtilis* RCMB 101-001 at concentrations (1.0, 2.5 and 5.0 mg/mL) and *Escherichia coli* RCMB 103-001 (at concentrations 2.5 and 5.0 mg/mL), while, it revealed no inhibitory effect against *Pseudomonas aeruginosa* RCMB 102-002.

It could be noted that, compound **4**, with short spacer, showed much broad spectrum, than those of compounds **5** and **6**, as it showed inhibitory effect against all the test organisms at concentration 5.0 mg/mL, while, compounds **5** and **6**, with longer spacer, revealed inhibitory effect against seven of total eight test organisms. At concentration 5 mg/mL, compound **4**, with short spacer, revealed its most inhibitory effect against *Bacillus subtilis* RCMB 101-001, compound **5**, with medium spacer revealed its

most potent inhibitory effect against *Candida albicans* RCMB 005003, compound **6** with longer spacer revealed its most potent inhibitory effect against *Syncephalastrum racemosum RCMB 016001*, *Candida albicans* RCMB 005003 and *Escherichia coli* RCMB 103-001.

Compound **7**, namely, 1,3-bis[4-(hydrazinecarbonyl)phenoxy]propane (Table 3), exhibited inhibitory effect against seven of total eight test organisms. Thus, it revealed inhibitory effects against *Aspergillus fumigatus* RCMB 002008 (1) (at concentrations 1.0, 2.5 and 5.0 mg/mL), *Penicillium italicum* RCMB 001018 (1) (at concentrations 1.0, 2.5 and 5.0 mg/mL), *Syncephalastrum racemosum* RCMB 016001 (at concentrations 2.5 and 5.0 mg/mL), *Candida albicans* RCMB 005003 (at concentration 5.0 mg/mL), *Staphylococcus aureus* RCMB 106-001 (1) (at concentrations 1.0, 2.5 and 5.0 mg/mL), *Bacillus subtilis* RCMB 101-001 (at concentrations 2.5 and 5.0 mg/mL) and *Escherichia coli* RCMB 103-001 (at concentrations 1.0, 2.5 and 5.0 mg/mL), while, it revealed no inhibitory effect against *Pseudomonas aeruginosa* RCMB 102-002.

Compared to the previously reported activity of 1,4-bis[4-(hydrazinecarbonyl)phenoxy]butane **8** [27], compound **7**, with shorter spacer showed lower inhibitory effect against *Candida albicans* RCMB 005003 (at concentrations 1.0, 2.5 and 5.0 mg/mL), *Pseudomonas aeruginosa* RCMB 102-002 (at concentration 5.0 mg/mL) and *Bacillus subtilis* RCMB 101-001 (at concentration 1 mg/mL). On the other hand, compound **7** gave higher inhibitory effect against *Aspergillus fumigates* RCMB 002008 (at concentration 5.0 mg/mL), *Penicillium italicum* RCMB 001018 (1) (at concentration 1.0 mg/mL), *Staphylococcus* aureus RCMB 106-001 (1) (at concentration 1.0 mg/mL) and *Escherichia coli* RCMB 103-001 (at concentration 1.0 mg/mL), compared to compound **8**.

Compared to standard antimicrobial agents, while some compounds, at specific concentrations showed the same inhibitory effect against some organisms, at other concentrations, they revealed higher inhibitory effect against other organisms. For example, while compound **1** gave the same inhibitory effect against *Aspergillus fumigatus* RCMB 002008 (1) (at concentrations 1.0, 2.5 and 5.0 mg/mL) as Tebinafine (standard antifungal agent), it showed much higher inhibitory effect against *Syncephalastrum racemosum* RCMB 016001 (at concentrations 2.5 and 5.0 mg/mL) and *Candida albicans* RCMB 005003 (at concentrations 1, 2.5 and 5 mg/mL). Compound **7**, also, compared to Terbinafine, while revealed the same inhibitory effect, against *Penicillium italicum* RCMB 001018 (1) (at concentrations 1.0, 2.5 and 5.0 mg/mL), it revealed higher inhibitory effect against *Aspergillus fumigatus* RCMB 002008 (1) (at concentration 5.0 mg/mL), *Syncephalastrum racemosum* RCMB 016001 (at concentration 2.5 mg/mL) and *Candida albicans* RCMB 005003 (at concentration 5.0 mg/mL). Compared to the standard antibacterial Chloramphenicol, compound **7** revealed the same inhibitory effect against *Staphylococcus aureus* RCMB 106-001 (1) (at concentrations 1.0, 2.5 and 5 mg/mL) and *Escherichia coli* RCMB 103-001 (at concentrations 1.0, 2.5 and 5 mg/mL).

4. CONCLUSION

The biologically evaluated 1,ω-bis[4-carboxy/methoxycarbonyl/(hydrazinecarbonyl)/phenoxy]alkanes **1**, **2**, **4**, **5**, **7** were found to possess antimicrobial activity against wide spread microorganisms (Gram-postive bacteria, Gram-negative bacteria, yeast and fungi). The potency of the evaluated compounds depends on the functional group attached to the carbonyl ring as well as the spacer length between the two aromatic rings. Some of the evaluated compounds, versus some organisms, were found to be either as potent as or more potent than the standard antimicrobial agents, at specific concentrations.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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