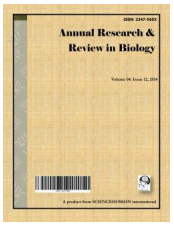

Annual Research & Review in Biology

15(1): 1-15, 2017; Article no.ARRB.34348
ISSN: 2347-565X, NLM ID: 101632869

Antimicrobial Evaluation and Structure Activity Relationship (SAR) of 1,ω-bis[4-[(arylideneamino/ alkylideneamino/ or arylalkylideneamino)carbamoyl]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.

Article Information

DOI: 10.9734/ARRB/2017/34348
Editor(s):
(1) Rajasekar Thirunavukkarasu, Centre for Drug Discovery & Development, Sathyabama University, Chennai, India.
(2) George Perry, Dean and Professor of Biology, University of Texas at San Antonio, USA.
Reviewers:
(1) Marjan Vracko, National Institute of Chemistry, Slovenia.
(2) K. Vijayakumar, Anna University, India.
(3) Chatrasal Singh Rajput, Lala Lajpat Rai Memorial Medical College, India.
Complete Peer review History: http://www.sciencedomain.org/review-history/20219

Original Research Article

Received 24th May 2017
Accepted 12th July 2017
Published 26th July 2017

ABSTRACT

Different 1,ω-bis[(4-[(arylideneamino/alkylideneamino/ or arylalkylideneamino)carbamoyl]phenoxy]alkanes **1-20**, **25** were synthesized and their inhibitory effects against different strains of Gram-positive bacteria (*Bacillus subtilis and Staphylococcus aureus*), Gram-negative bacteria (*Pseudomonas aeruginosa*, *Escherichia coli*), yeast (*Candida albicans*) and fungi (*Aspergillus fumigatus*, *Penicillium italicum* and *Syncephalastrum racemosum*) were evaluated using the diffusion agar technique. The screening results showed that most of the tested compounds exhibited wide spectrum activity against the test organisms and many of them revealed higher inhibitory effects against some organisms, when compared to standard antibacterial Chloramphenicol and antifungal Terbinafin. The structure activity relationship study was achieved via studying the effect of

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the aliphatic spacer length between the two ethereal oxygen atoms and the effect of functional groups attached to the terminal ends of the titled compounds. Thus, amomg compounds **1-10** that have short spacer between the phenoxy groups, at all concentrations, compound **5** with the dimethylaminophenyl group and compound **6** with the 2-hydroxyphenyl group exhibited the highest inhibitory effect. Among compounds **11-20** having medium spacer between the phenoxy groups, compound **12** having *p*-tolyl group, at all concentrations, exhibited the highest inhibitory effect. Among compounds **21-25** with long spacer between the phenoxy groups, compounds **21**, with the phenyl group and compound **22** with the 4-methoxyphenyl group, at all concentrations, exhibited the highest inhibitory effect.

Keywords: Antimicrobial evaluation; structure activity relationship (SAR); 1,ω-bis(hydrazones); 1,ω-bis(phenoxy)alkanes.

1. INTRODUCTION

A problem of ever-increasing significance that threats health worldwide is the dramatically rising prevalence of multi-drug resistant microbial infections [1-10]. An example of this fact is the emergence of multi-drug resistant strains of Gram-positive bacterial pathogens such as penicillin resistant *Staphylococcus aureus* [6], methicillin-resistant *Staphylococcus aureus* [7,9,10], oxacillin-resistant *Staphylococcus aureus* [10] and vancomycin-resistant *Enterococcus* [11]. Another example is the developed multiple resistance of *Candida* Spp. to azole antifungals [12,13]. For these reasons, there is a continuous demand for the discovery of novel more potent and less toxic therapeutics, especially, to control microbial infections by such multidrug-resistant strains, which are responsible for high morbidity and mortality. In order to gain new insights into the complexity of the disease, robust screening methods for evaluating different natural or synthetic drugs have been carried out from the science community. In this respect, the Hydrazones [14] are important molecules containing highly reactive azomethine group (-CO-NH-N=CH-) and are useful in drug development. Hydrazones are well acknowledged to possess a diverse range of bioactivities in pharmaceutical [15-33] and agrochemical field [33]. Hydrazones have been demonstrated to possess anticonvulsant [16-18], antidepressant [19], antinociceptive, analgesic, antiinflammatory, antiplatelet [20-24], antimalarial [25], antimicrobial [15,26], antimycobacterial [27], antitumoral [28], vasodilator [29], antiviral [30], antischistosomiasis [31,32] and insecticidal activities [33].

During the last years we have been working on the synthesis and biological properties of different novel organic compounds in order to establish a possible relationship between chemical structure and biological activity [34-54]. Following this research line, herein we complete our study and report the antimicrobial evaluation and structure activity relationship (SAR) of our previously synthesized 1,ω-bis[(4-[(arylideneamino/alkylideneamino/ or arylalkylideneamino)carbamoyl]phenoxy]alkanes which has not been previously reported.

2. MATERIALS AND METHODS

2.1 General

Compounds **1-20** and **25** (Fig. 1) were synthesized as reported [42] and identified by melting points (determined using Stuart® meting point apparatus SMP3), IR spectra (recorded on a Perkin-Elmer 1430 spectrometer), ^{1}H NMR spectra (recorded at 300 MHz with a Varian Mercury 300 spectrometer) and elemental analyses (carried out at the Micro Analytical Center, Cairo University, Giza, Egypt).

2.2 Synthesis of Compounds 1-20 and 25 [42]

*Synthesis of 1,ω-bis[4-[(arylideneamino/alkylideneamino/ or arylalkylideneamino)carbamoyl]phenoxy]alkanes **1-20, 25**. General procedures.*

*Procedure A. Synthesis of compounds **1-8, 10-18, 25** [42].*

A mixture of each of 1,ω-bis[4-(hydrazinecarbonyl)phenoxy]alkanes (1 mmol) and the appropriate aromatic aldehyde or acetophenone (2 mmol) in EtOH (50 mL) containing few drops of AcOH (3-7 drops) was heated ar reflux temperature for 24 h. After cooling, the product was filtered, washed with MeOH, dried and recrystallized from DMF.

*Procedure B. Synthesis of compounds **9**, **19**, **25** [42].*

A mixture of each of 1,ω-bis[4-(hydrazinecarbonyl)phenoxy]alkanes (1 mmol) and acetone (50 mL) containing few drops of AcOH (3-7 drops) was heated at reflux temperature for 24 h. After cooling, the product was filtered, washed with MeOH (3 x 20 mL), dried and recrystallized from DMF.

2.2.1 1,2-Bis[(4-[(benzylideneamino)carbamoyl]phenoxy]ethane (1) [42]

Yield 505.5 mg (100%, procedure A); colorless crystals, mp 283-285°C. IR: 3244, 3071, 2939, 2827, 1651, 1609, 1547, 1508, 1450, 1423, 1369, 1288, 1242, 1180, 1146, 1115, 1057, 968, 930, 849, 756, 656, 513, 428. ^{1}H NMR (DMSO-d_6) δ 4.45 (s, 4H, OCH_2CH_2O), 7.13 (d, 4H, *J*= 8.7 Hz, ArH of C_6H_4O), 7.45 (m, 6H, ArH of C_6H_5), 7.71 (br s, 4H, ArH of C_6H_5), 7.93 (d, 4H, *J*= 8.7 Hz, ArH of C_6H_4O), 8.45 (s, 2H, CH = N), 11.72 (s, 2H, D_2O exchangeable NH). Anal. Calcd for $C_{30}H_{26}N_4O_4$ (506.6): C, 71.13; H, 5.17; N, 11.06. Found: C, 71.22; H, 5.18; N, 10.98.

2.2.2 1,2-Bis[4-[(p-tolylmethyleneamino)carbamoyl]phenoxy]ethane (2) [42]

Yield 533.7 mg (100%, procedure A); colorless crystals, mp 312-314°C. Anal. Calcd for $C_{32}H_{30}N_4O_4$ (534.6): C, 71.89; H, 5.66; N, 10.48. Found: C, 71.81; H, 5.60; N, 10.52.

2.2.3 1,2-Bis[4-[[(4-methoxyphenyl)methyleneamino]carbamoyl]phenoxy]ethane (3)

Yield 565.7 mg (100%, procedure A); colorless crystals, mp 314-315°C. Anal. Calcd for $C_{32}H_{30}N_4O_6$ (566.6): C, 67.83; H, 5.34; N, 9.89. Found: C, 67.76; H, 5.30; N, 9.77.

2.2.4 1,2-Bis[4-[[(4-chlorophenyl)methyleneamino]carbamoyl]phenoxy]ethane (4) [42]

Yield 574.8 mg (100%, procedure A); colorless crystals, mp 333-334°C. Anal. Calcd for $C_{30}H_{24}Cl_2N_4O_4$ (575.5): C, 62.62; H, 4.20; N, 9.74. Found: C, 62.61; H, 4.24; N, 9.69.

2.2.5 1,2-Bis[4-[[(4-dimethylaminophenyl)-methyleneamino]carbamoyl]phenoxy]ethane (5) [42]

Yield 591.5 mg (100%, procedure A); pale yellow crystals, mp 312-314°C. Anal. Calcd for $C_{34}H_{36}N_6O_4$ (592.7): C, 68.90; H, 6.12; N, 14.18. Found: C, 68.86; H, 6.23; N, 14.21.

2.2.6 1,2-Bis[4-[[(2-hydroxyphenyl)methyleneamino]carbamoyl]phenoxy]ethane (6) [42]

Yield 538.0 mg (100%, procedure A); pale yellow crystals, mp 320-321°C. IR: 3221, 3044, 2961, 2885, 1635, 1613, 1574, 1508, 1481, 1369, 1300, 1254, 1184, 1150, 1119, 1083, 1042, 972, 876, 837, 752, 687, 656, 471. ^{1}H NMR (DMSO-d_6) δ 4.46 (s, 4H, OCH_2CH_2O), 6.94 (d, 4H, *J*= 7.8 Hz, ArH of 2-(OH)C_6H_4), 7.15 (d, 4H, *J*= 8.4 Hz, ArH of C_6H_4O), 7.30 (t, 2H, *J*= 7.8 Hz, ArH of 2-(OH)C_6H_4), 7.52 (d, 2H, *J*= 7.8 Hz, ArH of 2-(OH)C_6H_4), 7.95 (d, 4H, *J*= 8.4 Hz, ArH of C_6H_4O), 8.62 (s, 2H, CH = N), 11.36 (s, 2H, D_2O exchangeable NH), 11.99 (s, 2H, D_2O exchangeable OH). Anal. Calcd for $C_{30}H_{26}N_4O_6$ (538.6): C, 66.91; H, 4.87; N, 10.40. Found: C, 66.82; H, 4.94; N, 10.29.

2.2.7 1,2-Bis[4-[[(3,4-dimethoxyphenyl)methyleneamino]carbamoyl]phenoxy]ethane (7) [42]

Yield 625.6 mg (100%, procedure A); colorless crystals, mp 277-278°C. Anal. Calcd for $C_{34}H_{34}N_4O_8$ (626.7): C, 65.17; H, 5.47; N, 8.94. Found: C, 65.11; H, 5.32; N, 9.19.

2.2.8 1,2-Bis[4-[(1-naphthylmethyleneamino)carbamoyl]phenoxy]ethane (8) [42]

Yield 594.6 mg (98%, procedure A); colorless crystals, mp 285-287°C. Anal. Calcd for $C_{38}H_{30}N_4O_4$ (606.7): C, 75.23; H, 4.98; N, 9.23. Found: C, 75.21; H, 4.86; N, 9.19.

2.2.9 1,2-Bis[4-[(isopropylideneamino)carbamoyl]phenoxy]ethane (9) [42]

Yield 299.7 mg (73%, procedure B); colorless crystals, mp 246-248°C. Anal. Calcd for $C_{22}H_{26}N_4O_4$ (410.5): C, 64.38; H, 6.38; N, 13.65. Found: C, 64.19; H, 6.29; N, 13.49.

2.2.10 1,2-Bis[4-[(1-phenylethylideneamino)carbamoyl]phenoxy]ethane (10) [42]

Yield 368.9 mg (69%, procedure A); colorless crystals, mp 248-250°C. Anal. Calcd for $C_{32}H_{30}N_4O_4$ (534.6): C, 71.89; H, 5.66; N, 10.48. Found: C, 71.97; H, 5.71; N, 10.34.

2.2.11 1,3-Bis[(4-[(benzylideneamino)carbamoyl]phenoxy]propane (11) [42]

Yield 489.4 mg (94%, procedure A); colorless crystals, mp 253-255°C. Anal. Calcd for

$C_{31}H_{28}N_4O_4$ (520.6): C, 71.52; H, 5.42; N, 10.76. Found: C, 71.53; H, 5.35; N, 10.63.

2.2.12 1,3-Bis[4-[(p-tolylmethyleneamino)carbamoyl]phenoxy]propane (12) [42]

Yield 515.8 mg (94%, procedure A); colorless crystals, mp 282-283°C. IR: 3244, 3047, 2916, 2874, 1647, 1605, 1547, 1504, 1470, 1366, 1312, 1250, 1177, 1150, 1115,1057, 1011, 968, 914, 841, 814, 760, 660, 625, 513, 467, 421. ^{1}H NMR (DMSO-d_6) δ 2.24 (quint, 2H, *J*= 6.1 Hz, OCH_2CH_2), 2.35 (s, 6H, CH_3), 4.25 (t, 4H, *J*= 6.1 Hz, OCH_2CH_2O), 7.09 (d, 4H, *J*= 7.8 Hz, ArH of C_6H_4O), 7.27 (d, 4H, *J*= 7.5 Hz, ArH of 4-$CH_3C_6H_4$), 7.61 (d, 4H, *J*= 7.5 Hz, ArH of 4-$CH_3C_6H_4$), 7.91 (d, 4H, *J*= 7.8 Hz, ArH of C_6H_4O), 8.41 (s, 2H, CH = N), 11.63 (s, 2H, D_2O exchangeable NH). Anal. Calcd for $C_{33}H_{32}N_4O_4$ (548.7): C, 72.24; H, 5.88; N, 10.21. Found: C, 72.30; H, 5.84; N, 10.15.

2.2.13 1,3-Bis[4-[[(4-methoxyphenyl)methyleneamino]carbamoyl]phenoxy]propane (13)[42]

Yield 563.3 mg (97%, procedure A); colorless crystals, mp 285-286°C. Anal. Calcd for $C_{33}H_{32}N_4O_6$ (580.7): C, 68.26; H, 5.56; N, 9.65. Found: C, 68.34; H, 5.54; N, 9.70.

2.2.14 1,3-Bis[4-[[(4-chlorophenyl)methyleneamino]carbamoyl]phenoxy]proane (14) [42]

Yield 542.3 mg (92%, procedure A); colorless crystals, mp 274-276°C. Anal. Calcd for $C_{31}H_{26}Cl_2N_4O_4$ (589.5): C, 63.16; H, 4.45; N, 9.50. Found: C, 63.24; H, 4.34; N, 9.55.

2.2.15 1,3-Bis[4-[[(4-dimethylaminophenyl)methyleneamino]carbamoyl]phenoxy]propane (15) [42]

Yield 588.5 mg (97%, procedure A); colorless crystals, mp 289-291°C. Anal. Calcd for $C_{35}H_{38}N_6O_4$ (606.7): C, 69.29; H, 6.31; N, 13.85. Found: C, 69.22; H, 6.29; N, 14.00.

2.2.16 1,3-Bis[4-[[(2-hydroxyphenyl)methyleneamino]carbamoyl]phenoxy]propane (16) [42]

Yield 551.9 mg (100%, procedure A); colorless crystals, mp 288-290°C. Anal. Calcd for $C_{31}H_{28}N_4O_6$ (552.6): C, 67.38; H, 5.11; N, 10.14. Found: C, 67.36; H, 4.15; N, 10.00.

2.2.17 1,3-Bis[4-[[(3,4-dimethoxyphenyl)methyleneamino]carbamoyl]phenoxy]propane (17) [42]

Yield 615.1 mg (96%, procedure A); colorless crystals, mp 239-241°C. Anal. Calcd for $C_{35}H_{36}N_4O_8$ (640.7): C, 65.61; H, 5.66; N, 8.74. Found: C, 65.53; H, 5.49; N, 8.76.

2.2.18 1,3-Bis[4-[(1-naphthylmethyleneamino)carbamoyl]phenoxy]propane (18) [42]

Yield 619.8 mg (100%, procedure A); colorless crystals, mp 260-261°C. Anal. Calcd for $C_{39}H_{32}N_4O_4$ (620.7): C, 75.47; H, 5.20; N, 9.03. Found: C, 75.42; H, 5.18; N, 9.0.

2.2.19 1,3-Bis[4-[(isopropylideneamino)carbamoyl]phenoxy]propane (19) [42]

Yield 331.1 mg (78%, procedure B); colorless crystals, mp 231-232°C. Anal. Calcd for $C_{23}H_{28}N_4O_4$ (424.5): C, 65.08; H, 6.65; N, 13.20. Found: C, 65.02; H, 6.74; N, 13.18.

2.2.20 1,3-Bis[4-[(1-phenylethylideneamino)-carbamoyl]phenoxy]propane (20) [42]

Yield 504.8 mg (92%, procedure A); colorless crystals, mp 252-254°C. Anal. Calcd for $C_{33}H_{32}N_4O_4$ (548.7): C, 72.24; H, 5.88; N, 10.21. Found: C, 72.19; H, 5.92; N, 10.24.

2.2.21 1,4-Bis[4-[[(4-dimethylaminophenyl)methyleneamino]carbamoyl]phenoxy]butane (25) [42]

Yield 571.1 mg (92%, procedure A); colorless crystals, mp 314-316°C. IR: 3252, 3040, 2928, 2866, 2808, 1643, 1605, 1512, 1474, 1362, 1288, 1254, 1180, 1115, 1049, 972, 918, 845, 814, 760, 652, 525, 428. ^{1}H NMR (DMSO-d_6) δ 1.92 (s, 4H, OCH_2CH_2), 2.97 (s, 12H, $N(CH_3)_2$), 4.14 (s, 4H, OCH_2CH_2O), 6.76 (d, 4H, *J*= 8.6 Hz, ArH of 4-$(CH_3)_2NC_6H_4$), 7.05 (d, 4H, *J*= 8.9 Hz, ArH of C_6H_4O), 7.53 (d, 4H, *J*= 8.6 Hz, ArH of 4-$(CH_3)_2NC_6H_4$), 7.88 (d, 4H, *J*= 8.9 Hz, ArH of C_6H_4O), 8.30 (s, 2H, CH = N), 11.39 (s, 2H, D_2O exchangeable NH). Anal. Calcd for $C_{36}H_{40}N_6O_4$ (620.8): C, 69.66; H, 6.50; N, 13.54. Found: C, 69.71; H, 6.45; N, 13.48.

2.3 Antimicrobial Evaluation of Compounds 1-20 and 25

The *in vitro* antimicrobial screening of compounds **1-20** and **25** was carried out using

the diffusion agar technique [55,56]. 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 **1-20** and **25** 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* and *Staphylococcus aureus*), two Gram-negative bacterial strains (*Pseudomonas aeruginosa* and *Escherichia coli*), one yeast strain (*Candida albicans*) and three mould strains (*Aspergillus fumigatus*, *Penicillium italicum* and *Syncephalastrum racemosum*). The antimicrobial activities were expressed as the diameter of the inhibition zones (Table 1).

3. RESULTS AND DISCUSSION

Compound **1**, namely, 1,2-bis[4-[(benzylideneamino)carbamoyl]phenoxy]ethane, showed inhibitory effect against all the test organisms. Thus, it revealed inhibitory effects against *Aspergillus fumigatus* (at concentration 5.0 mg/mL), *Penicillium italicum* (at concentration 5.0 mg/mL), *Syncephalastrum racemosum* (at concentrations 1.0, 2.5 and 5.0 mg/mL), *Candida albicans* (at concentrations 1.0, 2.5 and 5.0 mg/mL), *Staphylococcus aureus* (at concentrations 2.5 and 5.0 mg/mL), *Pseudomonas aeruginosa* (at concentration 5.0 mg/mL), *Bacillus subtilis* (at concentrations 2.5 and 5.0 mg/mL) and *Escherichia coli* (at concentration 5.0 mg/mL).

Compound **2**, namely, 1,2-bis[4-[(*p*-tolylmethyleneamino)carbamoyl]phenoxy]ethane, showed inhibitory effect against all the test organisms. Thus, it revealed inhibitory effects against *Aspergillus fumigatus* (at concentration 5.0 mg/mL), *Penicillium italicum* (at concentration 5.0 mg/mL), *Syncephalastrum racemosum* (at concentrations 2.5 and 5.0 mg/mL), *Candida albicans* (at concentration 5.0 mg/mL), *Staphylococcus aureus* (at concentrations 2.5 and 5.0 mg/mL), *Pseudomonas aeruginosa* (at concentration 5.0 mg/mL), *Bacillus subtilis* (at concentrations 1.0, 2.5 and 5.0 mg/mL) and *Escherichia coli* (at concentration 5.0 mg/mL).

Compound **3**, namely, 1,2-bis[4-[[(4-methoxyphenyl)methyleneamino]carbamoyl]phenoxy]ethane, exhibited inhibitory effect against seven from total eight test organisms. Thus, it revealed inhibitory effects against *Aspergillus fumigatus* (at concentration 5.0 mg/mL), *Syncephalastrum racemosum* (at concentrations 1.0, 2.5 and 5.0 mg/mL), *Candida albicans* (at concentration 5.0 mg/mL), *Staphylococcus aureus* (at concentrations 2.5 and 5.0 mg/mL), *Pseudomonas aeruginosa* (at concentration 5.0 mg/mL), *Bacillus subtilis* (at concentration 5.0 mg/mL) and *Escherichia coli* (at concentrations 2.5 and 5.0 mg/mL), while, it revealed no inhibitory effect against *Penicillium italicum*.

Compound **4**, namely, 1,2-bis[4-[[(4-chlorophenyl)methyleneamino]carbamoyl]phenoxy]ethane, revealed inhibitory effect against six from total eight test organisms. Thus, it revealed inhibitory effects against *Aspergillus fumigatus* (at concentration 5.0 mg/mL), *Penicillium italicum* (at concentration 5.0 mg/mL), *Syncephalastrum racemosum* (at concentration 5.0 mg/mL), *Staphylococcus aureus* (at concentration 5.0 mg/mL), *Pseudomonas aeruginosa* (at concentrations 2.5 and 5.0 mg/mL) and *Escherichia coli* (at concentration 5.0 mg/mL), while, it revealed no inhibitory effect against *Candida albicans* and *Bacillus subtilis*.

Compound **5**, namely, 1,2-bis[4-[[(4-dimethylaminophenyl)methyleneamino]carbamoyl]phenoxy]ethane, showed inhibitory effect against all the test organisms. Thus, it revealed inhibitory effects against *Aspergillus fumigatus* (at concentrations 1.0, 2.5 and 5.0 mg/mL), *Penicillium italicum* (at concentrations 2.5 and 5.0 mg/mL), *Syncephalastrum racemosum* (at concentration 5.0 mg/mL), *Candida albicans* (at concentrations 1.0, 2.5 and 5.0 mg/mL), *Staphylococcus aureus* (at concentration 5.0 mg/mL), *Pseudomonas aeruginosa* (at concentration 5.0 mg/mL), *Bacillus subtilis* (at concentrations 1.0, 2.5 and 5.0 mg/mL) and *Escherichia coli* (at concentrations 1.0, 2.5 and 5.0 mg/mL).

Compound **6**, namely, 1,2-bis[4-[[(2-hydroxyphenyl)methyleneamino]carbamoyl]phenoxy]ethane, exhibited inhibitory effect against six from total eight test organisms. Thus, it revealed inhibitory effects against *Aspergillus fumigatus* (at concentrations 1.0, 2.5 and 5.0 mg/mL), *Syncephalastrum racemosum* (at concentrations 1.0, 2.5 and 5.0 mg/mL), *Candida albicans* (at concentration 5.0 mg/mL), *Staphylococcus*

aureus (at concentrations 1.0, 2.5 and 5.0 mg/mL), *Bacillus subtilis* (at concentrations 2.5 and 5.0 mg/mL) and *Escherichia coli* (at concentrations 1.0, 2.5 and 5.0 mg/mL), while, it revealed no inhibitory effect against *Penicillium italicum* and *Pseudomonas aeruginosa*.

Compound **7**, namely, 1,2-bis[4-[[(3,4-dimethoxyphenyl)methyleneamino]carbamoyl]phenoxy]ethane, showed inhibitory effect against seven from total eight test organisms. Thus, it revealed inhibitory effects against *Aspergillus fumigatus* (at concentration 5.0 mg/mL), *Syncephalastrum racemosum* (at concentrations 1.0, 2.5 and 5.0 mg/mL), *Candida albicans* (at concentrations 1.0, 2.5 and 5.0 mg/mL), *Staphylococcus aureus* (at concentrations 1.0, 2.5 and 5.0 mg/mL), *Pseudomonas aeruginosa* (at concentration 5.0 mg/mL), *Bacillus subtilis* (at concentration 5.0 mg/mL) and *Escherichia coli* (at concentrations 2.5 and 5.0 mg/mL), while, it revealed no inhibitory effect against *Penicillium italicum*.

Compound **8**, namely, 1,2-bis[4-[(1-naphthylmethyleneamino)carbamoyl]phenoxy]ethane, revealed inhibitory effect against four from total eight test organisms. Thus, it revealed inhibitory effects against *Penicillium italicum* (at concentrations 2.5 and 5.0 mg/mL), *Candida albicans* (at concentrations 2.5 and 5.0 mg/mL), *Staphylococcus aureus* (at concentrations 1.0, 2.5 and 5.0 mg/mL) and *Pseudomonas aeruginosa* (at concentration 5.0 mg/mL), while, it revealed no inhibitory effect against *Aspergillus fumigatus, Syncephalastrum racemosum, Bacillus subtilis* and *Escherichia coli.*

Compound **9**, namely, 1,2-bis[4-[(isopropylideneamino)carbamoyl]phenoxy]ethane, exhibited inhibitory effect against seven from total eight test organisms. Thus, it revealed inhibitory effects against *Aspergillus fumigatus* (at concentrations 1.0, 2.5 and 5.0 mg/mL), *Penicillium italicum* (at concentration 5.0 mg/mL), *Syncephalastrum racemosum* (at concentration 5.0 mg/mL), *Candida albicans* (at concentration 5.0 mg/mL), *Staphylococcus aureus* (at concentration 5.0 mg/mL), *Bacillus subtilis* (at concentration 5.0 mg/mL) and *Escherichia coli* (at concentration 5.0 mg/mL), while, it revealed no inhibitory effect against *Pseudomonas aeruginosa*.

Compound **10**, namely, 1,2-bis[4-[(1-phenylethylideneamino)carbamoyl]phenoxy]ethane, revealed inhibitory effect against seven from total eight test organisms. Thus, it revealed inhibitory effects against *Aspergillus fumigatus* (at concentration 5.0 mg/mL), *Penicillium italicum* (at concentrations 1.0, 2.5 and 5.0 mg/mL), *Syncephalastrum racemosum* (at concentration 5.0 mg/mL), *Staphylococcus aureus* (at concentration 5.0 mg/mL), *Pseudomonas aeruginosa* (at concentration 5.0 mg/mL), *Bacillus subtilis* (at concentration 5.0 mg/mL) and *Escherichia coli* (at concentration 5.0 mg/mL), while, it revealed no inhibitory effect against *Candida albicans.*

Studying the structure activity relationship of compounds **1-10** having the same short spacer between the phenoxy groups with different substituents at the terminal aromatic/aliphatic groups led to valuable scientific findings. Thus, compound **1**, having two terminal phenyl groups, showed its highest inhibitory effect, at all concentrations, against *Syncephalastrum racemosum* and *Candida albicans*. Compound **2**, having two terminal *p*-tolyl groups, revealed its highest inhibitory effect, at all concentrations, against *Bacillus subtilis*. Compound **3**, having two terminal 4-methoxyphenyl groups, exhibited its highest inhibitory effect, at all concentrations, against *Syncephalastrum racemosum*. Compound **5**, having two terminal 4-dimethylaminophenyl groups, showed its highest inhibitory effect, at all concentrations, against *Aspergillus fumigates*, *Candida albicans*, *Bacillus subtilis* and *Escherichia coli*. Compound **6**, having two terminal 2-hydroxyphenyl groups, revealed its highest inhibitory effect, at all concentrations, against *Aspergillus fumigates*, *Syncephalastrum racemosum*, *Staphylococcus aureus* and *Escherichia coli*. Compound **7**, having two terminal 3,4-dimethoxyphenyl groups, revealed its highest inhibitory effect, at all concentrations, against *Syncephalastrum racemosum*, *Candida albicans* and *Staphylococcus aureus*. Compound **8**, having two terminal 1-naphthyl groups, revealed its highest inhibitory effect, at all concentrations, against *Staphylococcus aureus*. Compound **9**, having two terminal isopropylideneamino groups, revealed its highest inhibitory effect, at all concentrations, against *Aspergillus fumigates*. Compound **10**, having two terminal 1-phenylethylideneamino groups, revealed its highest inhibitory effect, at all concentrations, against *Penicillium italicum*.

Compound **11**, namely, 1,3-bis[4-[(benzylideneamino)carbamoyl]phenoxy]propane, showed inhibitory effect against six from total

eight test organisms. Thus, it revealed inhibitory effects against *Aspergillus fumigatus* (at concentrations 2.5 and 5.0 mg/mL), *Penicillium italicum* (at concentrations 1.0, 2.5 and 5.0 mg/mL), *Candida albicans* (at concentration 5.0 mg/mL), *Staphylococcus aureus* (at concentration 5.0 mg/mL), *Pseudomonas aeruginosa* (at concentration 5.0 mg/mL) and *Bacillus subtilis* (at concentrations 1.0, 2.5 and 5.0 mg/mL), while, it revealed no inhibitory effect against *Syncephalastrum racemosum* and *Escherichia coli*.

Compound **12**, namely, 1,3-bis[4-[(*p*-tolylmethyleneamino)carbamoyl]phenoxy]propane, revealed inhibitory effect against seven from total eight test organisms. Thus, it revealed inhibitory effects against *Aspergillus fumigatus* (at concentrations 1.0, 2.5 and 5.0 mg/mL), *Penicillium italicum* (at concentrations 1.0, 2.5 and 5.0 mg/mL), *Syncephalastrum racemosum* (at concentrations 2.5 and 5.0 mg/mL), *Candida albicans* (at concentrations 1.0, 2.5 and 5.0 mg/mL), *Staphylococcus aureus* (at concentrations 2.5 and 5.0 mg/mL), *Pseudomonas aeruginosa* (at concentrations 1.0, 2.5 and 5.0 mg/mL) and *Bacillus subtilis* (at concentrations 1.0, 2.5 and 5.0 mg/mL), while, it revealed no inhibitory effect against *Escherichia coli*.

Compound **13**, namely, 1,3-bis[4-[[(4-methoxyphenyl)methyleneamino]carbamoyl]phenoxy]propane, exhibited inhibitory effect against six from total eight test organisms. Thus, it revealed inhibitory effects against *Aspergillus fumigatus* (at concentration 5.0 mg/mL), *Syncephalastrum racemosum* (at concentration 5.0 mg/mL), *Staphylococcus aureus* (at concentration 5.0 mg/mL), *Pseudomonas aeruginosa* (at concentration 5.0 mg/mL), *Bacillus subtilis* (at concentrations 2.5 and 5.0 mg/mL) and *Escherichia coli* (at concentration 5.0 mg/mL), while, it revealed no inhibitory effect against *Penicillium italicum* and *Candida albicans*.

Compound **14**, namely, 1,3-bis[4-[[(4-chlorophenyl)methyleneamino]carbamoyl]phenoxy]propane, showed inhibitory effect against five from total eight test organisms. Thus, it revealed inhibitory effects against *Aspergillus fumigatus* (at concentrations 1.0, 2.5 and 5.0 mg/mL), *Penicillium italicum* (at concentrations 1.0, 2.5 and 5.0 mg/mL), *Candida albicans* (at concentrations 2.5 and 5.0 mg/mL), *Pseudomonas aeruginosa* (at concentration 5.0 mg/mL) and *Escherichia coli* (at concentrations 1.0, 2.5 and 5.0 mg/mL), while, it revealed no inhibitory effect against *Syncephalastrum racemosum, Staphylococcus aureus* and *Bacillus subtilis*.

Compound **15**, namely, 1,3-bis[4-[[(4-dimethylaminophenyl)methyleneamino]carbamoyl]phenoxy]propane, revealed inhibitory effect against five from total eight test organisms. Thus, it revealed inhibitory effects against *Penicillium italicum* (at concentrations 2.5 and 5.0 mg/mL), *Candida albicans* (at concentration 5.0 mg/mL), *Staphylococcus aureus* (at concentrations 2.5 and 5.0 mg/mL), *Pseudomonas aeruginosa* (at concentration 5.0 mg/mL) and *Bacillus subtilis* (at concentrations 2.5 and 5.0 mg/mL), while, it revealed no inhibitory effect against *Aspergillus fumigatus, Syncephalastrum racemosum* and *Escherichia coli.*

Compound **16**, namely, 1,3-bis[4-[[(2-hydroxyphenyl)methyleneamino]carbamoyl]phenoxy]propane, exhibited inhibitory effect against seven from total eight test organisms. Thus, it revealed inhibitory effects against *Aspergillus fumigatus* (at concentrations 2.5 and 5.0 mg/mL), *Penicillium italicum* (at concentrations 2.5 and 5.0 mg/mL), *Syncephalastrum racemosum* (at concentrations 1.0, 2.5 and 5.0 mg/mL), *Candida albicans* (at concentrations 1.0, 2.5 and 5.0 mg/mL), *Staphylococcus aureus* (at concentration 5.0 mg/mL), *Bacillus subtilis* (at concentration 5.0 mg/mL) and *Escherichia coli* (at concentrations 1.0, 2.5 and 5.0 mg/mL), while, it revealed no inhibitory effect against *Pseudomonas aeruginosa*.

Compound **17**, namely, 1,3-bis[4-[[(3,4-dimethoxyphenyl)methyleneamino]carbamoyl]phenoxy]propane, revealed inhibitory effect against five from total eight test organisms. Thus, it revealed inhibitory effects against *Aspergillus fumigatus* (at concentration 5.0 mg/mL), (*Candida albicans* (at concentration 5.0 mg/mL), *Staphylococcus aureus* (at concentration 5.0 mg/mL), *Bacillus subtilis* (at concentrations 1.0, 2.5 and 5.0 mg/mL) and *Escherichia coli* (at concentration 5.0 mg/mL), while, it revealed no inhibitory effect against *Penicillium italicum*, *Syncephalastrum racemosum* and *Pseudomonas aeruginosa*.

Compound **18**, namely, 1,3-bis[4-[(1-naphthylmethyleneamino)carbamoyl]phenoxy]propane, exhibited inhibitory effect against five from total eight test organisms. Thus, it revealed

inhibitory effects against *Aspergillus fumigatus* (at concentration 5.0 mg/mL), *Syncephalastrum racemosum* (at concentration 5.0 mg/mL), *Candida albicans* (at concentrations 2.5 and 5.0 mg/mL), *Bacillus subtilis* (at concentrations 1.0, 2.5 and 5.0 mg/mL) and *Escherichia coli* (at concentrations 1.0, 2.5 and 5.0 mg/mL), while, it revealed no inhibitory effect against *Penicillium italicum, Staphylococcus aureus,* and *Pseudomonas aeruginosa*.

Compound **19**, namely, 1,3-bis[4-[(isopropylideneamino)carbamoyl]phenoxy]propane, showed inhibitory effect against five from total eight test organisms. Thus, it revealed inhibitory effects against *Penicillium italicum* (at concentration 5.0 mg/mL), *Syncephalastrum racemosum* (at concentrations 2.5 and 5.0 mg/mL), *Candida albicans* (at concentrations 1.0, 2.5 and 5.0 mg/mL), *Staphylococcus aureus* (at concentrations 2.5 and 5.0 mg/mL) and *Bacillus subtilis* (at concentrations 2.5 and 5.0 mg/mL), while, it revealed no inhibitory effect against *Aspergillus fumigatus, Pseudomonas aeruginosa* and *Escherichia coli*.

Compound **20**, namely, 1,3-bis[4-[(1-phenylethylideneamino)carbamoyl]phenoxy]propane, revealed inhibitory effect against five from total eight test organisms. Thus, it revealed inhibitory effects against *Aspergillus fumigatus* (at concentrations 2.5 and 5.0 mg/mL), *Penicillium italicum* (at concentration 5.0 mg/mL), *Candida albicans* (at concentrations 1.0, 2.5 and 5.0 mg/mL), *Staphylococcus aureus* (at concentrations 1.0, 2.5 and 5.0 mg/mL) and *Escherichia coli* (at concentrations 1.0, 2.5 and 5.0 mg/mL), while, it revealed no inhibitory effect against *Syncephalastrum racemosum, Pseudomonas aeruginosa,* and *Bacillus subtilis*.

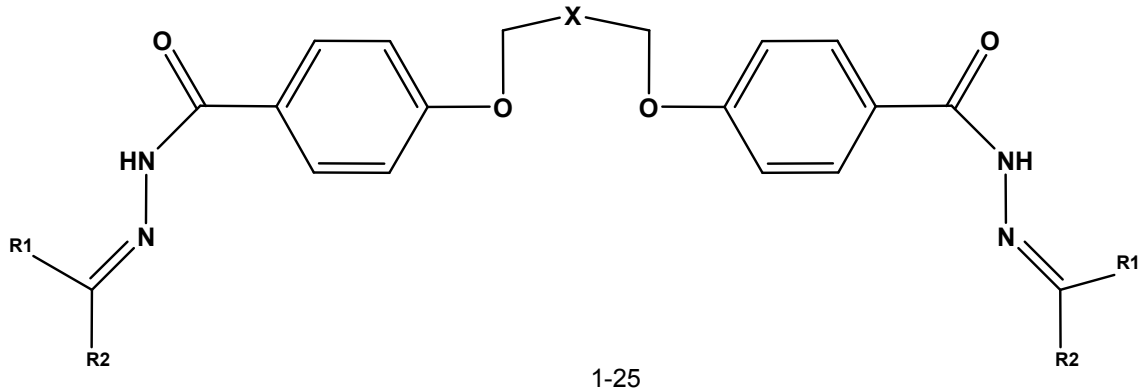
Studying the Stucture activity relationship of compounds **11-20** having the same medium spacer between the phenoxy groups with different substituents at the terminal aromatic/aliphatic groups revealed interesting facts. Thus, compound **11**, having two terminal phenyl groups, exhibited its highest activity, at all concentrations, against *Penicillium italicum* and *Bacillus subtilis*. Compound **12**, having two terminal *p*-tolyl groups, revealed its highest inhibitory effect, at all concentrations, against *Aspergillus fumigates, Penicillium italicum*, *Candida albicans*, *Pseudomonas aeruginosa* and *Bacillus subtilis*. Compound **14**, having two terminal 4-chlorophenyl groups, showed its highest inhibitory effect, at all concentrations, against *Aspergillus fumigates*, *Penicillium italicum* and *Escherichia coli*. Compound **16**, having two terminal 2-hydroxyphenyl groups, revealed its highest inhibitory effect, at all concentrations, against *Syncephalastrum racemosum*, *Candida albicans* and *Escherichia coli*. Compound **17**, having two terminal 3,4-dimethoxyphenyl groups, exhibited its highest inhibitory effect, at all concentrations, against *Bacillus subtilis*. Compound **18**, having two terminal 1-naphthyl groups, showed its highest inhibitory effect, at all concentrations, against *Bacillus subtilis* and *Escherichia coli*. Compound **19**, having two terminal isopropylideneamino groups, revealed its highest inhibitory effect, at all concentrations, against *Candida albicans*. Compound **20**, having two terminal 1-phenylethylideneamino groups, exhibited its highest inhibitory effect, at all concentrations, against *Candida albicans*, *Staphylococcus aureus* and *Escherichia coli*.

Compound **25**, namely, 1,4-bis[4-[(isopropylideneamino)carbamoyl]phenoxy]butane, exhibited inhibitory effect against four from total eight test organisms. Thus, it revealed inhibitory effects against *Syncephalastrum racemosum* (at concentration 5.0 mg/mL), *Candida albicans* (at concentration 5.0 mg/mL), *Staphylococcus aureus* (at concentrations 2.5 and 5.0 mg/mL) and *Bacillus subtilis* (at concentration 5.0 mg/mL), while, it revealed no inhibitory effect against *Aspergillus fumigatus, Penicillium italicum, Pseudomonas aeruginosa,* and *Escherichia coli*.

The antimicrobial activity of other 1,4-bis[4-[(arylidene/phenylethylideneamino)carbamoyl]phenoxy]butanes was reported [42]. Compound **21**, namely, 1,4-bis[4-[(benzylideneamino)carbamoyl]phenoxy]butane, was reported [42] to exhibit inhibitory effect against seven from the eight test organisms mentioned in the current study. Thus, it revealed inhibitory effects against *Aspergillus fumigatus* (at concentrations 1.0, 2.5 and 5.0 mg/mL), *Penicillium italicum* (at concentrations 1.0, 2.5, 5.0 mg/mL), *Syncephalastrum racemosum* (at concentrations 1.0, 2.5 and 5.0 mg/mL), *Candida albicans* (at concentrations 2.5 and 5.0 mg/mL), *Staphylococcus aureus* (at concentrations 1.0, 2.5 and 5.0 mg/mL), *Pseudomonas aeruginosa* (at concentration 5.0 mg/mL), and *Escherichia coli* (at concentration 5.0 mg/mL), while, it revealed no inhibitory effect against *Bacillus subtilis*. Compound **21** was also reported [42] to possess inhibitory effect against *Salmonella typhi* at concentrations 1.0, 2.5 and 5.0 mg/mL.

Compound **22**, namely, 1,4-bis[4-[[(4-methoxyphenyl)methyleneamino]carbamoyl]phenoxy]butane, was reported [42] to exhibit inhibitory effect against six from the eight test organisms mentioned in the current study. Thus, it revealed inhibitory effects against *Penicillium italicum* (at concentration 5.0 mg/mL), *Syncephalastrum racemosum* (at concentrations 1.0, 2.5 and 5.0 mg/mL), *Candida albicans* (at concentrations 1.0, 2.5 and 5.0 mg/mL), *Staphylococcus aureus* (at concentrations 1.0, 2.5 and 5.0 mg/mL), *Bacillus subtilis* (at concentrations 1.0, 2.5 and 5.0 mg/mL) and *Escherichia coli* (at concentrations 1.0, 2.5 and 5.0 mg/mL), while, it revealed no inhibitory effect against *Aspergillus fumigates* and *Pseudomonas aeruginosa*. Compound **22** was also reported [42] to possess inhibitory effect against *Salmonella typhi* (at concentration 5.0 mg/mL).

Compound **23**, namely, 1,4-bis[4-[[(3,4-dimethoxyphenyl)methyleneamino]carbamoyl]phenoxy]butane, was reported [42] to exhibit inhibitory effect against seven from the eight test organisms mentioned in the current study. Thus, it revealed inhibitory effects against *Aspergillus fumigates* (at concentrations 2.5 and 5.0 mg/mL), *Penicillium italicum* (at concentration 5.0 mg/mL), *Syncephalastrum racemosum* (at concentrations 2.5 and 5.0 mg/mL), *Candida albicans* (at concentrations 1.0, 2.5 and 5.0 mg/mL), *Staphylococcus aureus* (at concentrations 1.0, 2.5 and 5.0 mg/mL), *Pseudomonas aeruginosa* (at concentration 5.0 mg/mL) and *Escherichia coli* (at concentrations 1.0, 2.5 and 5.0 mg/mL), while, it revealed no inhibitory effect against *Bacillus subtilis*. Compound **23** was also reported [42] to possess no inhibitory effect against *Salmonella typhi*.



1-25

1-10 X= 0
11-20 X= CH_2
21-25 X= $(CH_2)_2$
1, 11, 21 R^1= C_6H_5, R^2= H
2, 12 R^1= 4-$CH_3C_6H_4$, R^2= H
3, 13, 22 R^1=4-$CH_3OC_6H_4$, R^2= H
4, 14 R^1= 4-ClC_6H_4, R^2= H
5, 15 R^1= 4-$(CH_3)_2NC_6H_4$, R^2= H
6, 16 R^1=2-$(OH)C_6H_4$, R^2= H
7, 17, 23 R^1= 3,4-$(OCH_3)_2C_6H_3$
8, 18 R^1= 1-Naphthyl, R^2= H
9, 19, 25 R^1, R^2= CH_3
10, 20, 24 R^1=CH_3, R^2= C_6H_5

Fig. 1. 1,ω-bis[4-[(arylideneamino/ alkylideneamino/ or arylalkylideneamino)carbamoyl]phenoxy]alkanes

Table 1. Antimicrobial activity of 1,ω-bis[4-[(arylideneamino/ alkylideneamino/ or arylalkylideneamino)carbamoyl]phenoxy]alkanes1-25 compared to standard antimicrobial agents

	Compound														
	1[a]			2[a]			3[a]			4[a]			5[a]		
	Concentration (mg/mL)														
Test Organisms	1	2.5	5	1	2.5	5	1	2.5	5	1	2.5	5	1	2.5	5
A. fumigatus	0	0	+	0	0	+	0	0	+	0	0	+	+	+	+
P. italicum	0	0	+	0	0	+	0	0	0	0	0	+	0	+	+
S. racemosum	+	+	++	0	+	+	+	+	+	0	0	+	0	0	+
C.albicans	+	+	+	0	0	+	0	0	+	0	0	0	+	+	+
S.aureus	0	+	++	0	+	+	0	+	+	0	0	+	0	0	+
P. aeruginosa	0	0	+	0	0	+	0	0	+	0	+	+	0	0	+
B. subtilis	0	+	+	+	+	+	0	0	+	0	0	0	+	+	+
E. coli	0	0	+	0	0	+	0	+	++	0	0	+	+	+	++
	Compound														
	6[a]			7[a]			8[a]			9[a]			10[a]		
	Concentration (mg/mL)														
Test Organisms	1	2.5	5	1	2.5	5	1	2.5	5	1	2.5	5	1	2.5	5
A. fumigatus	+	+	+	0	0	+	0	0	0	+	+	+	0	0	+
P. italicum	0	0	0	0	0	0	0	+	+	0	0	+	+	+	+
S. racemosum	+	+	+	+	+	+	0	0	0	0	0	+	0	0	+
C.albicans	0	0	+	+	+	++	0	+	+	0	0	+	0	0	0
S.aureus	+	+	+	+	++	++	+	+	+	0	0	+	0	0	+
P. aeruginosa	0	0	0	0	0	+	0	0	+	0	0	0	0	0	+
B. subtilis	0	+	++	0	0	+	0	0	0	0	0	+	0	0	+
E. coli	+	+	+	0	+	+	0	0	0	0	0	+	0	0	+
	Compound														
	11[a]			12[a]			13[a]			14[a]			15[a]		
	Concentration (mg/mL)														
Test Organisms	1	2.5	5	1	2.5	5	1	2.5	5	1	2.5	5	1	2.5	5
A. fumigatus	0	+	+	+	+	+	0	0	+	+	+	+	0	0	0
P. italicum	+	+	++	+	+	+	0	0	0	+	+	+	0	+	+
S. racemosum	0	0	0	0	+	+	0	0	+	0	0	0	0	0	0
C.albicans	0	0	+	+	+	+	0	0	0	0	+	+	0	0	+
S.aureus	0	0	+	0	+	+	0	0	+	0	0	0	0	+	+
P. aeruginosa	0	0	+	+	+	+	0	0	+	0	0	+	0	0	+
B. subtilis	+	+	+	+	+	+	0	+	+	0	0	0	0	+	+
E. coli	0	0	0	0	0	0	0	0	+	+	+	+	0	0	0
	Compound														
	16[a]			17[a]			18[a]			19[a]			20[a]		
	Concentration (mg/mL)														
Test Organisms	1	2.5	5	1	2.5	5	1	2.5	5	1	2.5	5	1	2.5	5
A. fumigatus	0	+	+	0	0	+	0	0	+	0	0	0	0	+	+
P. italicum	0	+	++	0	0	0	0	0	0	0	0	+	0	0	+
S. racemosum	+	+	+	0	0	0	0	0	+	0	+	+	0	0	0
C.albicans	+	+	+	0	0	+	0	+	+	+	+	+	+	+	+
S.aureus	0	0	+	0	0	+	0	0	0	0	+	++	+	+	+
P. aeruginosa	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
B. subtilis	0	0	+	+	+	+	+	+	+	0	+	+	0	0	0
E. coli	+	+	+	0	0	+	+	+	+	0	0	0	+	+	+

Table 1 (Cont'd)

	Compound														
	21[a, d]			**22**[a, d]			**23**[a, d]			**24**[a, d]			**25**[a]		
	Concentration (mg/mL)														
Test Organisms	1	2.5	5	1	2.5	5	1	2.5	5	1	2.5	5	1	2.5	5
A. fumigatus	++	++	+++	0	0	0	0	+	++	0	0	0	0	0	0
P. italicum	+	+	+	0	0	+	0	0	+	0	+	+	0	0	0
S. racemosum	++	++	+++	+	+	+	0	+	++	0	0	+	0	0	+
C.albicans	0	+	+	+	+	+	+	++	+++	+	+	+	0	0	+
S.aureus	++	++	+++	+	++	+++	+	++	+++	+	+	+	0	+	+
P. aeruginosa	0	0	+	0	0	0	0	0	+	0	0	+	0	0	0
B. subtilis	0	0	0	+	+	+	0	0	0	0	+	+	0	0	+
E. coli	0	0	+	++	++	+++	+	++	+++	0	0	+	0	0	0

	Compound					
	St.[b]			**St.**[c]		
Test Organisms	1	2.5	5	1	2.5	5
A. fumigatus	0	0	0	+	+	+
P. italicum	0	+	+	+	+	+
S. racemosum	+	+	+	0	0	+
C.albicans	0	+	+	0	0	0
S.aureus	+	+	+	+	+	++
P. aeruginosa	+	+	+	0	0	0
B. subtilis	++	++	++	0	0	+
E. coli	+	+	+	+	+	+

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 **21-24** was previously reported [42]*

Compound **24**, namely, 1,4-bis[4-[(1-phenylethylideneamino)carbamoyl]phenoxy]butane, was reported [42] to exhibit inhibitory effect against seven from the eight test organisms mentioned in the current study. Thus, it revealed inhibitory effects against *Penicillium italicum* (at concentrations 2.5 and 5.0 mg/mL), *Syncephalastrum racemosum* (at concentration 5.0 mg/mL), *Candida albicans* (at concentrations 1.0, 2.5 and 5.0 mg/mL), *Staphylococcus aureus* (at concentrations 1.0, 2.5 and 5.0 mg/mL), *Pseudomonas aeruginosa* (at concentration 5.0 mg/mL), *Bacillus subtilis* (at concentrations 2.5 and 5.0 mg/mL) and *Escherichia coli* (at concentration 5.0 mg/mL), while, it revealed no inhibitory effect against *Aspergillus fumigates*. Compound **24** was also reported [42] to possess inhibitory effect against *Salmonella typhi* (at concentrations 1.0, 2.5 and 5.0 mg/mL).

Studying the structure activity relationship of compounds **21-25** having the same long spacer between the phenoxy groups with different substituents at the terminal aromatic/aliphatic groups led to valuable scientific findings. Thus, compound **21**, having two terminal phenyl groups, showed its highest inhibitory effect, at all concentrations, against *Aspergillus fumigates*, *Penicillium italicum, Syncephalastrum racemosum* and *Staphylococcus aureus*. Compound **22**, having two terminal 4-methoxyphenyl groups, revealed its highest inhibitory effect, at all concentrations, against *Syncephalastrum racemosum*, *Candida albicans*, *Staphylococcus aureus*, *Bacillus subtilis* and *Escherichia coli*. Compound 2**3**, having two terminal 3,4-dimethoxyphenyl groups, exhibited its highest inhibitory effect, at all concentrations, against *Candida albicans, Staphylococcus aureus* and *Escherichia coli*. Compound **24**, having two terminal 1-phenylethylideneamino groups, exhibited its highest inhibitory effect, at all concentrations, against *Candida albicans* and *Staphylococcus aureus*.

4. CONCLUSION

Antimicrobial evaluation of our previously synthesized 1,ω-bis[(4-[(arylideneamino/ alkylideneamino/ or arylalkylideneamino)carbamoyl]phenoxy]alkanes **1-20**, **25** emphasized possible application of an important new class of broad spectrum antimicrobial compounds against wide spread microorganisms (Gram-postive

bacteria Gram-negative bacteria, yeast and fungi). Many of the synthesized compounds revealed higher inhibitory effect than standard antimicrobial agents (Chloramphenicol as a standard antibacterial agent and Terbinafin as a standard antifungal agent) against the test organisms. Structure activity relationship revealed the dependence of the potency of the evaluated compounds on the functional groups attached to the terminal sides of the compound and the spacer length between its two aromatic rings. Thus, among compounds **1-10** that have short spacer between the phenoxy groups, at all concentrations, compound **5** with the dimethylaminophenyl group and compound **6** with the 2-hydroxyphenyl group exhibited the highest inhibitory effect. Among compounds **11-20** having medium spacer between the phenoxy groups, compound **12** having *p*-tolyl group, at all concentrations, exhibited the highest inhibitory effect. Among compounds **21-25** with long spacer between the phenoxy groups, compound **21**, with the phenyl group and compound **22** with the 4-methoxyphenyl group, at all concentrations, exhibited the highest inhibitory effect.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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