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Synthesis of a novel class of 1,ω-bis/(hydrazides), (hydrazones), (1,3,4-oxadiazoles) and (1,3,4-thiadiazoles) with potential antimicrobial activity

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ABSTRACT

A series of novel class of 1,ω-bis/ (carboxylic acids), (esters), (hydrazides), (hydrazones), (1,3,4-oxadiazoles) and (1,3,4-thiadiazoles) were synthesized. Of these novel compounds, some were seleced 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*, *Escherichia coli RCMB 103-001* and *Salmonella typhi RCMB B 008 001*), yeast (*Candida albicans RCMB 005003*) and fungi (*Aspergillus fumigatus RCMB 002008 (1)*, *Penicillium italicum RCMB 001018 (1)* and *Syncephalastrum racemosum RCMB 016001*). The screening results revealed that all the tested compounds exhibited broad spectrum inhibitory effects against different microbes. Some tested compounds showed remarkable higher activities against some test organisms, when compared to Chloramphenicol as commersial standard antibacterial agent and Terbinafin as commersial standard antifungal agent (at concentration 0.5 mg/mL).

KEYWORDS

1,ω-bis(carboxylic acid derivatives);
1,ω-bis(hydrazides);
1,ω-bis(hydrazones);
1,ω-bis(1,3,4-oxadiazoles);
1,ω-bis(1,3,4-thiadiazoles);
Antimicrobial activity.

INTRODUCTION

Hydrazides, the acylated derivatives[1] of hydrazine are usually encountered as the simple or monosubsituted ($RCONHNH_2$), or as sym-disubsituted (RCONHNH-COR) compounds. The latter have been referred to as sec-hydrazides. Besides being useful for a number of biological properties[2-18], hydrazides and related compounds are described as building blocks of various heterocyclic rings[19] and important starting materials for a wide range of derivatives utilizable in pharmaceutical products and as surfactants. Hydrazides have been known to be useful as medicaments especially in the treatment of inflammatory and autoimmune diseases, osteoarthritis, respiratory diseases, tumors, cachexia, cardiovascular diseases, fever, hemorrhage and sepsis[11]. Hydrazides and related compounds exhibited anthelmintic[17], antifungal[2], antiviral[14], bacteriostatic[2,7,9,14], antiparasite[2,10], antituberculous[3-6], antitumor[11,16], anticonvulsant[18], psychotropic[2], and insecticidal[15] activities. Some heterocyclic hydrazides are useful as antifertility agents in rats and pigeons[13].Other hydrazides are reported to be comprised in deodorant compositions that can be used for removal of offensive odor[20].

Hydrazones are well acknowledged to possess a diverse range of bioactivities in pharmaceutical[2,21-37]

and agrochemical field[38]. Hydrazones have been demonstrated to possess anticonvulsant[21-23], antidepressant[24], antinociceptive, ananalgesic, antiinflammatory, antiplatelet[25-29], antimalarial[30], antimicrobial[2,31], antimycobacterial[32], antitumoral[33], vasodilator[34], antiviral[35], antischistosomiasis[36,37] and insecticidal activities[38].

1,3,4-Oxadiazoles are a class of heterocycles which have attracted significant interest in medicinal and pesticide chemistry[39,40], and polymer and material science[41,42]. Thus, many of these compounds showed antibacterial, antifungal, hypnotic, sedative, analgesic, antimalarial, antiinflammatory, anticonvulsant, anticancer, diuretic, herbicidal and insecticidal activities[39,40,43,44]. Also, they found useful applications as dye stuffs fluorescent whiteners[43] and are of promising utilizaztion as Organic Light Emitting Diodes (OLED)[45].

1,3,4-Thiadiazoles exhibit broad spectrum of biological activities, possibly due to the presence of toxophoric N-C-S moiety[46]. They find applications as antibacterials, antitumor, antiinflammatory agents, pesticides, herbicides, dyes, lubricants and analytical reagents[47].

In view of these observations and in continuation of an ongoing research program on the synthesis of novel biologically active compounds[16,48-61], the current work reports the synthesis of some novel and potent 1,ω-bis/(hydrazides), (hydrazones), (1,3,4-oxadiazoles) and (1,3,4-thiadiazoles), which have been found to possess an interesting profile of antimicrobial activity.

RESULTS AND DISCUSSION

Synthesis

The synthetic strategies adopted to obtain the target compounds are depicted in Schemes 1, 2. The key intermediates in the present study are 1,ω-bis(4-methoxycarbonylphenoxy)alkanes **(6-8)**, they were synthesized, in 25-76% yields, from methyl 4-hydroxybenzoate **(1)** via its conversion into the corresponding potassium salt **(2)** followed by reaction with dihaloalkanes **(3-5)**. The structures of compounds **(6-8)** were assigned based on spectral and analytical data. Thus, the IR specra of compounds **(6-8)** revealed aromatic C-H stretching vibrations (C_6H_4) at 3017-3089 cm^{-1}, aliphatic C-H stretching vibrations (CH_3, OCH_2XOCH_2) at 2770-2959 cm^{-1}, ester carbonyl stretching vibrations at 1720-1724 cm^{-1}. The ^{1}HNMR spectra of compounds **(6-8)** showed the ester protons (OCH_3) at δ 3.88-3.89 (s, 6H) and aromatic protons at δ 6.90-8.01 (2d, 4H each, *J*= 8.9-9.0 Hz). Compound **(6)** showed an additional signal at δ 4.40 (s, 4H) due to oxymethylene protons (OCH_2CH_2O). Compounds **(7)**, **(8)** showed their methylene protons in two groups centered at δ 2.0-2.30 and 4.09-4.21. The group shifted higher upfield is due to secondary methylene protons C-CH_2C- (quint, 2H for compound **(7)**, 4H for compound **(8)**, *J*=5.4-6.0 Hz, OCH_2CH_2), and the group only lower shifted is due to primary methylene protons O-CH_2-C (t, 4H, *J*=5.4-6.0 Hz, OCH_2CH_2).

Reaction of compounds **(6-8)** with excess hydrazine monohydrate proceeded smoothly and afforded 1,ω-bis[4-(hydrazinecarbonyl)phenoxy]alkanes **(9-11)**, in 82-93% yields. The IR spectra of compounds **(9-11)** while revealed the absence of the ester carbonyl function at 1720-1724 cm^{-1}, exhibited the $NHNH_2$ and the carbonyl stretching vibrations at 3186-3321 cm^{-1} and 1651-1658 cm^{-1}, respectively. The NH_2 stretching vibrattions appeared as two bands at 3206-3321, while NH vibrations appeared as one band at 3186-3206 cm^{-1}. The ^{1}HNMR spectra of compounds **(9-11)** came in agreement with their IR spectra, thus, while revealing the absence of the ester protons (OCH_3) signal at δ 3.88-3.89 (s, 6H), they showed NH_2 (s, 4H, D_2O exchangeable) and NH (s, 2H, D_2O exchangeable) signals, at δ 4.39-4.42 and 9.52-9.59, respectively.

Compounds **(9-11)** were allowed to react with different aldehydes or ketones to give the corresponding 1,ω-bis[(4-[(arylideneamino/ alkylideneamino/ or arylalkylideneamino)carbamoyl]phenoxy]alkanes **(12-41)**, in 69-100% yields. The ^{1}HNMR spectra of compounds **(12-41)** showed the absence of NH_2 signal at δ 4.39-4.42 (s, 4H, D_2O exchangeable) and revealed the appearance of N=CH signal for compounds **(12-19)**, **(22-29)**, **(32-39)**, at δ 8.30-9.12 (s, 2H), CH_3 signals for compounds **(20)**, **(30)**, **(40)**, at δ 1.92-1.99 (2s, 6H each) and CH_3 signals for compounds **(21)**, **(31)**, **(41)** at δ 2.36 (s, 6H).

The synthesis of 1,ω-bis[4-(5-sulfanyl-1,3,4-oxadiazol-2-yl)phenoxy]alkanes **(42-44)** was achieved, in 69-95% yields, by adopting a simple procedure that

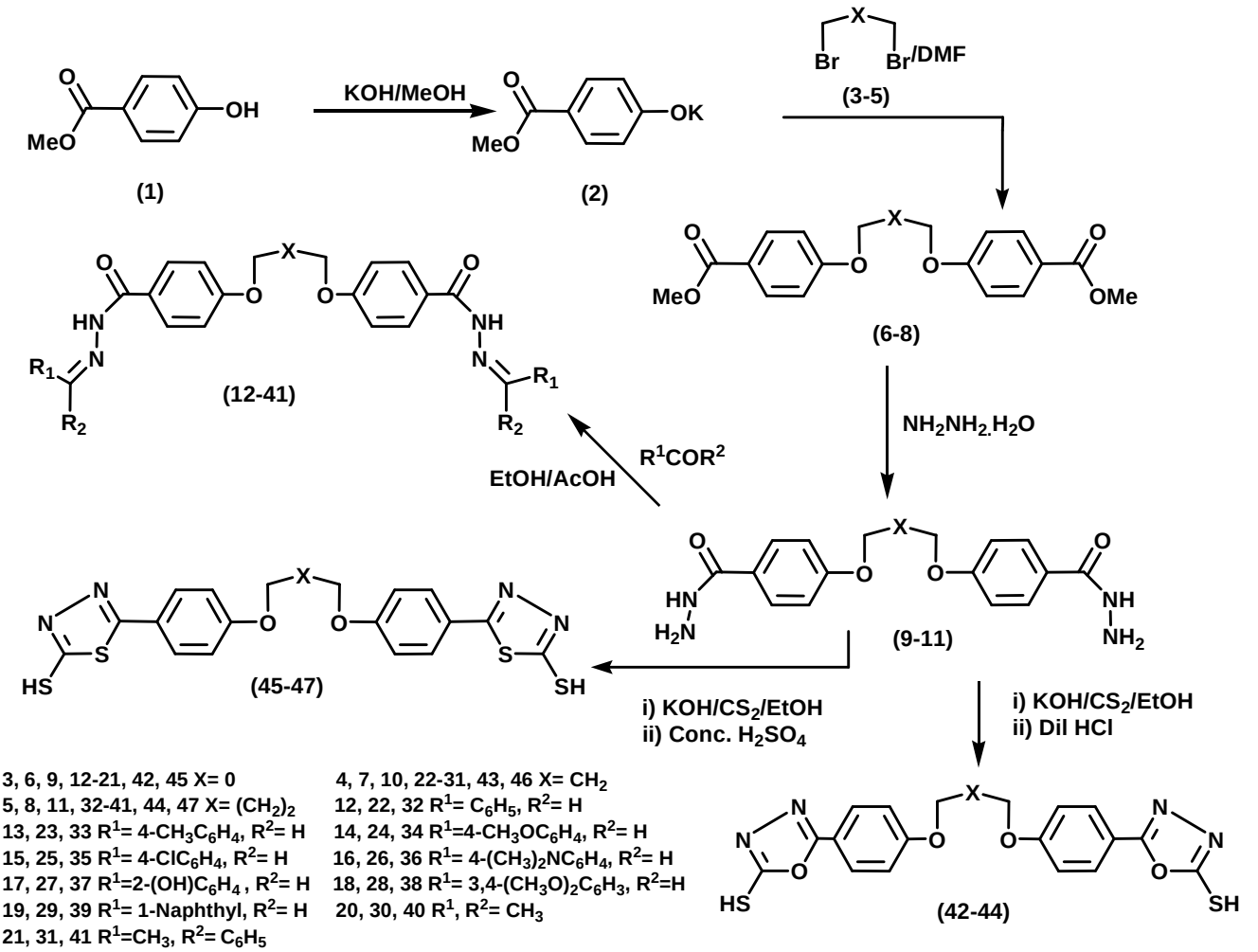
involves reaction of compounds **(9-11)** with carbon disulfide under basic conditions followed by acidification with dilute HCl. On the other hand, treatment of compounds **(9-11)** with carbon disulfide under basic conditions followed by treatment with concd sulfuric acid underwent smoothly to give 1,ω-bis[4-(5-sulfanyl-1,3,4-thiadiazol-2-yl)phenoxy]alkanes **(45-47)**, in 82-85% yields. While revealed the absence of the carbonyl and $NHNH_2$ vibrations, at 1651-1658 cm^{-1} and 3186-3321 cm^{-1}, respectively, the IR spectra of compounds **(42-47)**, moreover, revealed the appearance of the characteristic SH stretching vibrations at 2550-2573 cm^{-1}. Supporting this assignment, the ^{1}HNMR spectra of compounds **(42-47)** showed the absence of NH_2 and NH signals at δ 4.39-4.42 (s, 4H, D_2O exchangeable) and 9.52-9.59 (s, 2H, D_2O exchangeable), respectively, while revealed the SH proton signal furthest downfield, at δ 13.25-14.62 (s or br, 2H, D_2O exchangeable).

Scheme 2 outlines the synthetic routes followed for the synthesis of 1,ω-bis[4-(5-aryl-1,3,4-ozadizaol-2-yl)phenoxy]alkanes **(51-65)**. Thus, reaction of compounds **(9-11)** with aromatic acids/ or acid chlorides in phosphorous oxychloride afforded compounds **(51-65)**, in 57-89% yields. Compounds **(53)**, **(58)**, **(59)**, **(63)** were alternatively synthesized, in 64-82% yields, from 1,ω-bis(4-carboxyphenoxy)alkanes **(48-50)** (obtained from alkaline hydrolysis of compounds **(6-8)**), through their reaction with the aromatic acid hydrazides in phosphorous oxychloride. The absence of the carbonyl and $NHNH_2$ stretching vibrations at 1651-1658 cm^{-1} and 3186-3321 cm^{-1}, respectively, in the IR spectra of compounds **(51-65)** is an evidence of ring closure. Supporting their IR spectra, the ^{1}HNMR spectra of compounds **(51-65)**, showed the absence of NH_2 and NH signals at δ 4.39-4.42 (s, 4H, D_2O exchangeable) and 9.52-9.59 (s, 2H, D_2O exchangeable), respectively, while revealed additional aromatic protons at δ 7.16-8.44 as well as pyridyl protons for compounds **(55)**, **(60)**, **(65)** at δ 7.65-9.28 (spectral details are reported in the experimental section). Compounds **(48-50)** while revealed the absence of ester carbonyl stretching vibrations at 1720-1724 cm^{-1}, revealed the acid caronyl stretching vibrations at 1678-1686 cm^{-1} and the OH stretching vibration at 2361-3082 cm^{-1}. Confirming this assignment, ^{1}HNMR spectra of compounds **(48-50)** revealed the absence of ester protons (OCH_3) at δ 3.88-3.89 (s, 6H) and the appearance of OH proton signal (s, 2H, D_2O exchangeable) at δ 12.56-12.59.

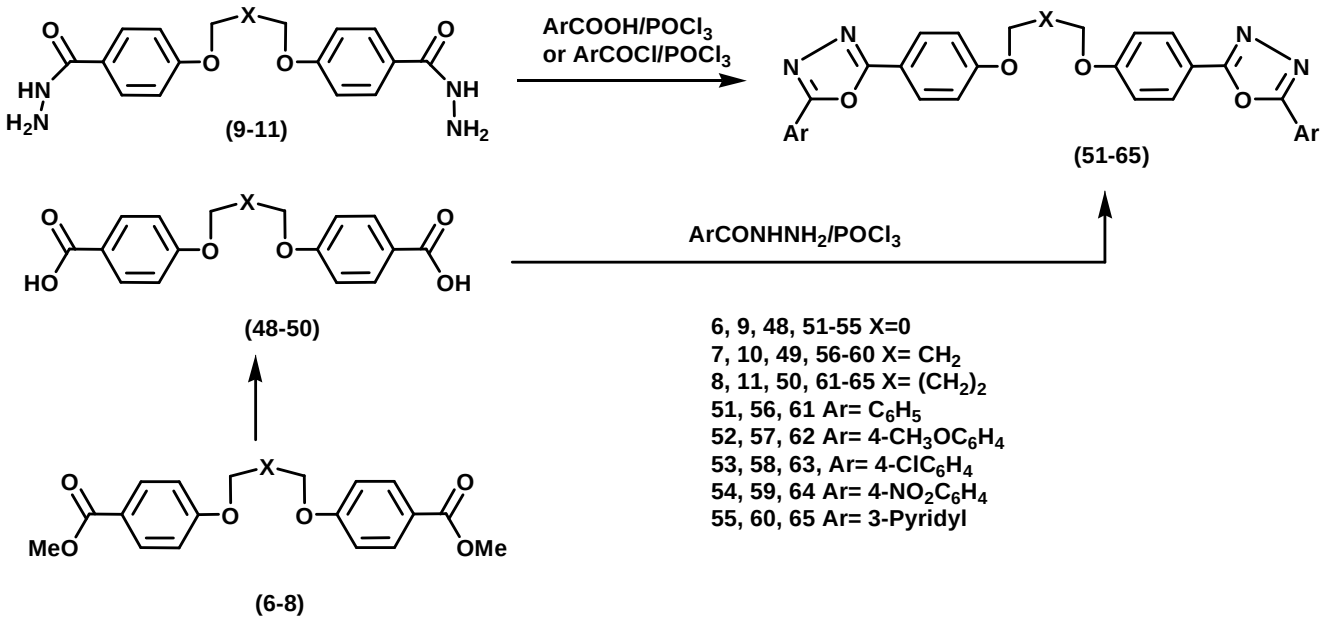
Antimicrobial activity and structure-activity relationship

Compounds **(8)**, **(11)**, **(32)**, **(34)**, **(38)**, **(41)**, **(44)**, **(50)**, **(62)** were evaluated for their antibacterial and antifungal activities against two Gram-positive bacterial strains (*Bacillus subtilis RCMB 101-001* and *Staphylococcus aureus RCMB 106-001 (1)*), three Gram-negative bacterial strains (*Pseudomonas aeruginosa RCMB 102-002*, *Escherichia coli RCMB 103-001* and *Salmonella typhi RCMB B 008 001*), one yeast strain (*Candida albicans RCMB 005003*) and three fungal strains (*Aspergillus fumigatus RCMB 002008 (1)*, *Penicillium italicum RCMB 001018 (1)* and *Syncephalastrum racemosum RCMB 016001*). The results of preliminary bioassays were compared with those obtained for commercial standard antimicrobial agents. As indicated in TABLE 1, all the tested compounds showed broad spectrum bioactivities against the test microbes. Compared to the commersial standard antifungal Terbinafin, compound **(11)**, having two hydrazide groups, showed higher inhibitory effect against *Candida albicans* (at concentration 5.0 mg/mL). On the other hand, compared to the commersial standard antibacterial Chloramphenicol, compound **(32)** showed higher inhibitory effect against *Staphylococcus aureus* (at concentration 5.0 mg/mL), while, compounds **(34)**, **(38)** showed higher inhibitory effects against *Staphylococcus aureus* and *Escherichia coli* (at concentration 5.0 mg/mL). The data provided in TABLE 1 indicate that conversion of the ester groups in compound **(8)** into hydrazide groups in compound **(11)**, increased the inhibitory effect against *Aspergillus fumigatus RCMB 002008 (1)* (at concentration 1.0 mg/mL), *Candida albicans RCMB 005003* (at concentrations 1.0-5.0 mg/mL) and *Pseudomonas aeruginosa RCMB 102-002* (at concentration 5.0 mg/mL), while, it decreased the inhibitory effect against *Penicillium italicum RCMB 001018 (1)* (at concentration 1.0 mg/mL), *Syncephalastrum racemosum RCMB 016001* (at concentrations 1.0, 5.0 mg/mL) and *Escherichia coli RCMB 103-001* (at concentration 5.0 mg/mL). Hydrolysis of the ester groups in compound **(8)** into car-

boxylic acid groups in compound **(50)** increased the inhibitory effect against *Aspergillus fumigatus RCMB 002008 (1)* (at concentrations 1.0, 5.0 mg/mL), *Pseudomonas aeruginosa RCMB 102-002* (at concentration 5.0 mg/mL) and *Salmonella typhi RCMB B 008 001* (at concentrations 2.5, 5.0 mg/mL), while, it decreased the inhibitory effect against *Penicillium italicum RCMB 001018 (1)* (at concentrations 1.0-5.0 mg/mL), *Candida albicans RCMB 005003* (at concentrations 1.0-5.0 mg/mL), *Staphylococcus aureus RCMB 106-001 (1)* (at concentration 2.5 mg/mL), *Bacillus subtilis RCMB 101-001* (at concentrations 1.0-5.0 mg/mL) and *Escherichia coli RCMB 103-001* (at concentrations 2.5, 5.0 mg/mL). Conversion of the hydrazide groups, in compound **(11)**, into hydrazone groups, in compound **(32)** (R^1= C_6H_5, R^2= H), increased the inhibitory effect against *Aspergillus fumigatus RCMB 002008 (1)* (at concentrations 1.0-5.0 mg/mL), *Penicillium italicum RCMB 001018 (1)* (at concentration 1.0 mg/mL), *Syncephalastrum racemosum RCMB 016001*) (at concentrations 1.0-5.0 mg/mL), *Staphylococcus aureus RCMB 106-001 (1)* (at concentrations 1.0-5.0 mg/mL) and *Salmonella typhi RCMB B 008 001*) (at concentrations 1.0-5.0 mg/mL), while, it deceased the inhibitory effect against *Candida albicans RCMB 005003* (at concentrations 1.0-5.0 mg/mL), *Bacillus subtilis RCMB 101-001* (at concentrations 1.0-5.0 mg/mL) and *Escherichia coli RCMB 103-001* (at concentration 2.5 mg/mL). Introduction of a methoxy group in the 4-position of each benzylideneamino(carbamoyl) moiety, enhanced the inhibitory effect of compound **(34)**, when compared with compound **(32)**, against *Candida albicans RCMB 005003* (at concentration 1.0 mg/mL), *Bacillus subtilis RCMB 101-001* (at concentrations 1.0-5.0 mg/mL) and *Escherichia coli RCMB 103-001* (at concentrations 1.0-5.0 mg/mL), while, it reduced the inhibitory effect against *Aspergillus fumigatus RCMB 002008 (1)* (at concentrations 1.0-5.0 mg/mL), *Penicillium italicum RCMB 001018 (1)* (at concentrations 1.0, 2.5 mg/mL), *Syncephalastrum racemosum RCMB 016001* (at concentrations 1.0-5.0 mg/mL), *Staphylococcus aureus RCMB 106-001 (1)* (at concentration 1.0 mg/mL), *Pseudomonas aeruginosa RCMB 102-002* (at concentration 5 mg/mL) and *Salmonella typhi RCMB B 008 001* (at concentrations 1.0, 2.5 mg/mL). Further introduction of a methoxy group, in the 3-position of each (4-methoxyphenyl)methyleneamino[carbamoyl] moiety, increased the inhibitory effect of compound **(38)**, when compared with compound **(34)**, against *Aspergillus fumigatus RCMB 002008 (1)* (at concentrations 2.5, 5.0 mg/mL), *Syncephalastrum racemosum RCMB 016001* (at concentration 5.0 mg/mL), *Candida albicans RCMB 005003* (at concentrations 2.5, 5.0 mg/mL) and *Pseudomonas aeruginosa RCMB 102-002* (at concentration 5.0 mg/mL), while, it decresed the inhibitory effect against *Bacillus subtilis RCMB 101-001* (at concentrations 1.0-5.0 mg/mL), *Escherichia coli RCMB 103-001* (at concentration 1.0 mg/mL) and *Salmonella typhi RCMB B 008 001* (at concentration 5.0 mg/mL). Conversion of the bis(hydrazide) **(11)** into the bis(chalcone) **(41)** increased the inhibitory effect against *Staphylococcus aureus RCMB 106-001 (1)* (at concentration 1.0 mg/mL) and *Salmonella typhi RCMB B 008 001* (at concentrations 1.0-5.0 mg/mL), while, it decreased the inhibitory effect against *Aspergillus fumigatus RCMB 002008 (1)* (at concentrations 1.0-5.0 mg/mL), *Syncephalastrum racemosum RCMB 016001* (at concentration 2.5 mg/mL), *Candida albicans RCMB 005003* (at concentrations 1.0-5.0 mg/mL), *Bacillus subtilis RCMB 101-001* (at concentration 1.0 mg/mL) and *Escherichia coli RCMB 103-001* (at concentration 2.5 mg/mL). Compared to the parent bis(hydrazide) **(11)**, compound **(44)**, having 5-sulfanyl-1,3,4-oxadiazol-2-yl moieties showed higher inhibitory effect against *Penicillium italicum RCMB 001018 (1)* (at concentrations 1.0, 5.0 mg/mL), *Syncephalastrum racemosum RCMB 016001* (at concentration 5.0 mg/mL), *Staphylococcus aureus RCMB 106-001 (1)* (at concentration 1.0 mg/mL) and *Salmonella typhi RCMB B 008 001*) (at concentrations 1.0-5.0 mg/mL), while, it exhibited lower inhibitory effect against *Aspergillus fumigatus RCMB 002008 (1)* (at concentrations 1.0-5.0 mg/mL), *Candida albicans RCMB 005003* (at concentrations 1.0-5.0 mg/mL), *Pseudomonas aeruginosa RCMB 102-002* (at concentration 5.0 mg/mL), *Bacillus subtilis RCMB 101-001* (at concentration 1.0 mg/mL) and *Escherichia coli RCMB 103-001* (at concentration 2.5 mg/mL). Conversion of the sylfanyl group at 5-position of each 1,3,4-ozadizaol-2-yl moity into 4-methoxyphenyl group, increased the inhibitory



Scheme 1: Synthetic routes towards novel 1,ω-bis/(esters), (hydrazides), (hydrazones), (5-sulfanyl-1,3,4-oxadiazoles) and (5-sulfanyl-1,3,4-thiadiazoles).



Scheme 2: Synthetic routes towards novel 1,ω-bis/(carboxylic acids) and (5-aryl-1,3,4-oxadiazoles).

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TABLE 1: Antimicrobial activity of compounds (8), (11), (32), (34), (38), (41), (44), (50) and (62) compared to standard antimicrobial agents.

Test Organisms	Compound														
	Compd 8[a]			Compd 11[a]			Compd 32[a]			Compd 34[a]			Compd 38[a]		
	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	0	+	+	+	+	+	++	++	+++	0	0	0	0	+	++
P. italicum	+	+	+	0	+	+	+	+	+	0	0	+	0	0	+
S. racemosum	+	+	++	0	+	+	++	++	+++	+	+	+	0	+	++
C. albicans	+	+	++	++	++	+++	0	+	+	+	+	+	+	++	++
S. aureus	0	+	+	0	+	+	++	++	+++	+	++	+++	+	++	+++
P. aeruginosa	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	+	++	++	+++	+	++	+++
S. typhi	0	0	0	0	0	0	+	+	+	0	0	+	0	0	0

Test Organisms	Compound														
	Compd 41[a]			Compd 44[a]			Compd 50[a]			Compd 62[a]			St.[b]		
	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	0	0	0	0	0	0	+	+	++	0	0	0	++	+++	+++
P. italicum	0	+	+	+	+	++	0	0	0	0	0	+	++	+++	+++
S. racemosum	0	0	+	0	+	++	+	+	++	+	++	++	+++	+++	+++
C. albicans	+	+	+	+	+	+	0	0	+	+	+	++	++	++	++
S. aureus	+	+	+	+	+	+	0	0	+	0	0	0	++	++	++
P. aeruginosa	0	0	+	0	0	0	0	0	+	0	+	+	++	+++	+++
B. subtilis	0	+	+	0	+	+	0	0	0	0	0	+	++	+++	+++
E.coli	0	0	+	0	0	+	0	0	+	+	+	++	++	++	++
S. typhi	+	+	+	+	+	+	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 = no inhibition detected.

[a]100 µL of each concentration was tested (5, 2.5, 1.0 mg/L); well diameter = 0.6 cm.

[b]St. = Reference standard; Chloramphenicol was used as a standard antibacterial agent and Terbinafin was used as a standard antifungal agent.

effect of compound **(62)**, when compared with compound **(44)**, against *Syncephalastrum racemosum RCMB 016001* (at concentrations 1.0, 2.5 mg/mL), *Candida albicans RCMB 005003* (at concentration 5.0 mg/mL), *Pseudomonas aeruginosa RCMB 102-002* (at concentrations 2.5, 5.0 mg/mL) and *Escherichia coli RCMB 103-001* (at concentrations 1.0 -5.0 mg/mL), while, it decreased the inhibitory effect against *Penicillium italicum RCMB 001018 (1)* (at concentrations 1.0-5.0 mg/mL), *Staphylococcus aureus RCMB 106-001 (1)* (at concentrations 1.0-5.0 mg/mL), *Bacillus subtilis RCMB 101-001* (at concentration 2.5 mg/mL) and *Salmonella typhi RCMB B 008 001* (at concentrations 1.0-5.0 mg/mL).

EXPERIMENTAL

Synthesis

1. General

All melting points are uncorrected and were determined using Stuart® meting point apparatus SMP3. IR spectra were recorded in KBr discs using FTIR spectrometer (Shimadzu 8201 PC). ^{1}H NMR spectra were measured with a Varian Mercury 300 spectrometer (300 MHz ^{1}H NMR). Mass spectra were measured on Shimadzu GCMS-QP2010 Plus spectrometer (with an

EI ionization mode and 70 eV electronic voltage) Elemental analyses were carried out at the Micro Analytical Center, Cairo University, Giza, Egypt.

2. Synthesis of the K salt (2)

A solution of each of compound **(1)** (15.215 g, 100 mmol) and KOH (5.6 g, 100 mmol) in MeOH(150 mL) was stirred at room temperature for 10 min. The solvent was then removed in vacuo and the remaining residue was washed with dry ether (3 x 50 mL), collected by filtration and dried. It was then used in the next steps without further purification.

3. Synthesis of 1,ω-bis(4-methoxycarbonylphenoxy)alkanes (6-8). General procedure

To a solution of the K-salt **(2)** (100 mmol) in dry DMF (75 mL) was added appropriate dihalo compound **(3-5)** (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.

A. 1,2-Bis(4-methoxycarbonylphenoxy)ethane (6)

Yield 4.13 g (25%); colorless crystals, mp 163-164 °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.

B. 1,3-Bis(4-methoxycarbonylphenoxy)propane (7)

Yield 8.95 g (52%); colorless crystals, mp 136-138 °C. IR: 3071, 3017, 2947, 2885, 2843, 2770, 1724, 1609, 1512, 1435, 1389, 1288, 1250, 1196, 1161, 1107, 1061, 984, 853, 810, 764, 694, 652, 517. ^{1}H NMR ($CDCl_3$) δ 2.30 (quint, 2H, *J*= 6.0 Hz, OCH_2CH_2), 3.88 (s, 6H, $COOCH_3$), 4.21 (t, 4H, *J*= 6.0 Hz, OCH_2CH_2), 6.92 (d, 4H, *J*= 8.9 Hz, ArH), 7.98 (d, 4H, *J*= 8.9 Hz, ArH). Anal. Calcd for $C_{19}H_{20}O_6$ (344.4): C, 66.27; H, 5.85. Found: C, 66.23; H, 5.91.

C. 1,4-Bis(4-methoxycarbonylphenoxy)butane (8)

Yield 13.62 g (76%); colorless crystals, mp 148-150 °C. IR: 3089, 3017, 2951, 2882, 2847, 1724, 1609, 1508, 1474, 1435, 1396, 1319, 1285, 1254, 1169, 1111, 1053, 1011, 957, 849, 768, 698, 656, 517, 440. ^{1}H NMR ($CDCl_3$) δ 2.00 (quint, 4H, *J*= 5.4 Hz, OCH_2CH_2), 3.88 (s, 6H, $COOCH_3$), 4.09 (t, 4H, *J*= 5.4 Hz, OCH_2CH_2), 6.90 (d, 4H, *J*= 8.9 Hz, ArH), 7.98 (d, 4H, *J*= 8.9 Hz, ArH). Anal. Calcd for $C_{20}H_{22}O_6$ (358.4): C, 67.03; H, 6.19. Found: C, 66.97; H, 6.23.

4. Synthesis of 1,ω-bis[4-(hydrazinecarbonyl) phenoxy]alkanes (9-11). General procedure

A mixture of the appropriate 1,ω-bis (ester) **(6-9)** (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.

A. 1,2-Bis[4-(hydrazinecarbonyl)phenoxy]ethane (9)

Yield 7.68 g (93%); colorless crystals, mp 263-265 °C (dec). IR: 3321, 3240, 3186, 3067, 3028, 2959, 2893, 1651, 1620, 1574, 1508, 1477, 1416, 1350, 1300, 1250, 1188, 1173, 1115, 1045, 984, 937, 883, 841, 806, 756, 718, 652, 640, 498, 440. ^{1}H NMR (DMSO-d_6) δ 4.39 (s, 8H, OCH_2CH_2O, D_2O exchangeable NH_2), 7.03 (d, 4H, *J*= 9.0 Hz, ArH), 7.80 (d, 4H, *J*= 9.0 Hz, ArH), 9.52 (s, 2H, D_2O exchangeable NH). Anal. Calcd for $C_{16}H_{18}N_4O_4$ (330.4): C, 58.17; H, 5.49; N, 16.96. Found: C, 58.19; H, 5.54; N, 17.12.

B. 1,3-Bis[4-(hydrazinecarbonyl)phenoxy]propane (10)

Yield 7.92 g (92%); colorless crystals, mp 246-247 °C. 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_2), 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.

C. 1,4-Bis[4-(hydrazinecarbonyl)phenoxy]butane (11)

Yield 7.35 g (82%); colorless crystals, mp 223-225 °C. IR: 3298, 3206, 3067, 3024, 2943, 2874, 2758, 1658, 1609, 1535, 1497, 1447, 1389, 1335, 1254, 1169, 1111, 1049, 1011, 968, 934, 841, 768, 702, 633, 513, 436. ^{1}H NMR (DMSO-d_6) δ 1.88 (s, 4H, OCH_2CH_2), 4.09 (s, 4H, OCH_2CH_2), 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), 9.58 (s, 2H, D_2O exchangeable NH). Anal. Calcd for $C_{18}H_{22}N_4O_4$ (358.4): C, 60.32; H, 6.19; N, 15.63. Found: C, 60.34; H, 6.12; N, 15.67.

5. Synthesis of 1,ω-bis[(4-[(arylideneamino/ alkylideneamino/ or arylalkylideneamino)carbamoyl]phenoxy]alkanes (12-41). General procedures

Procedure A: Synthesis of compounds (12-19), (21-29), (31-39), (41)

A mixture of each of comounds **(9-11)** (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 (20), (30), (40)

A mixture of each of 1,ω-bis(hydrazides) **(9-11)** (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.

A. 1,2-Bis[(4-[(benzylideneamino)carbamoyl] phenoxy]ethane (12)

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.

B. 1,2-Bis[4-[(p-tolylmethyleneamino)carbamoyl] phenoxy]ethane (13)

Yield 533.7 mg (100%, procedure A); olorless crystals, mp 312-314 °C. IR: 3252, 3044, 2943, 2882, 1647, 1609, 1547, 1504, 1366, 1300, 1250, 1177, 1119, 1053, 968, 918, 845, 810, 760, 652, 617, 509, 467. ^{1}H NMR (DMSO-d_6) δ 2.35 (s, 6H, CH_3), 4.45 (s, 4H, OCH_2CH_2O), 7.13 (d, 4H, *J*= 8.4 Hz, ArH of C_6H_4O), 7.27 (d, 4H, *J*= 7.8 Hz, ArH of 4-$CH_3C_6H_4$), 7.62 (d, 4H, *J*= 7.8 Hz, ArH of 4-$CH_3C_6H_4$), 7.93 (d, 4H, *J*= 8.4 Hz, ArH of C_6H_4O), 8.42 (s, 2H, CH = N), 11.65 (s, 2H, D_2O exchangeable NH). 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.

C. 1,2-Bis[4-[[(4-methoxyphenyl)methyleneamino]carbamoyl]phenoxy]ethane (14)

Yield 565.7 mg (100%, procedure A); colorless crystals, mp 314-315 °C. IR: 3252, 3044, 2943, 2843, 1647, 1609, 1543, 1508, 1454, 1420, 1362, 1285, 1246, 1177, 1146, 1115, 1061, 1030, 937, 841, 764, 664, 629, 529, 467, 424. ^{1}H NMR (DMSO-d_6) δ 3.81 (s, 6H, OCH_3), 4.45 (s, 4H, OCH_2CH_2O), 7.02 (d, 4H, *J*= 8.6 Hz, ArH of 4-$CH_3OC_6H_4$), 7.12 (d, 4H, *J*= 8.7 Hz, ArH of C_6H_4O), 7.67 (d, 4H, *J*= 8.6 Hz, ArH of 4-$CH_3OC_6H_4$), 7.92 (d, 4H, *J*= 8.7 Hz, ArH of C_6H_4O), 8.39 (s, 2H, CH = N), 11.58 (s, 2H, D_2O exchangeable NH). 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.

D. 1,2-Bis[4-[[(4-chlorophenyl)methyleneamino] carbamoyl]phenoxy]ethane (15)

Yield 574.8 mg (100%, procedure A); colorless crystals, mp 333-334 °C. IR: 3233, 3059, 2939, 1647, 1605, 1535, 1501, 1454, 1408, 1354, 1285, 1242, 1180, 1146, 1119, 1069, 1015, 937, 845, 764, 721, 664, 625, 505, 471, 421. ^{1}H NMR (DMSO-d_6) δ 4.45 (s, 4H, OCH_2CH_2O), 7.14 (d, 4H, *J*= 8.9 Hz, ArH of C_6H_4O), 7.52 (d, 4H, *J*= 8.1 Hz, ArH of 4-ClC_6H_4), 7.75 (d, 4H, *J*= 8.1 Hz, ArH of 4-ClC_6H_4), 7.93 (d, 4H, *J*= 8.9 Hz, ArH of C_6H_4O), 8.44 (s, 2H, CH = N), 11.79 (s, 2H, D_2O exchangeable NH) . 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.

E. 1,2-Bis[4-[[(4-dimethylaminophenyl)methyleneamino]carbamoyl]phenoxy]ethane (16)

Yield 591.5 mg (100%, procedure A); pale yellow crystals, mp 312-314 °C. IR: 3294, 3089, 3044, 2939, 2882, 2808, 1647, 1605, 1535, 1501, 1362, 1309, 1246, 1180, 1111, 1045, 945, 914, 849, 814, 760, 652, 598, 529, 486, 448. ^{1}H NMR (DMSO-d_6) δ 2.98 (s, 12H, $N(CH_3)_2$), 4.44 (s, 4H, OCH_2CH_2O), 6.76 (d, 4H, *J*= 8.1 Hz, ArH of 4-$(CH_3)_2NC_6H_4$), 7.11 (d, 4H, *J*= 8.9 Hz, ArH of C_6H_4O), 7.54 (d, 4H, *J*= 8.1 Hz, ArH of 4-$(CH_3)_2NC_6H_4$), 7.90 (d, 4H, *J*= 8.9 Hz, ArH of C_6H_4O), 8.31 (s, 2H, CH = N), 11.42 (s, 2H, D_2O exchangeable NH). 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.

F. 1,2-Bis[4-[[(2-hydroxyphenyl)methyleneamino]carbamoyl]phenoxy]ethane (17)

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.

G. 1,2-Bis[4-[[(3,4-dimethoxyphenyl)methyleneamino]carbamoyl]phenoxy]ethane (18)

Yield 625.6 mg (100%, procedure A); colorless crystals, mp 277-278 °C. IR: 3248, 3078, 2939, 2839, 1647, 1609, 1547, 1508, 1462, 1423, 1373, 1272, 1242, 1177, 1142, 1061, 1022, 945, 899, 849, 810, 760, 667, 625, 471, 417. ^{1}H NMR (DMSO-d_6) δ 3.81, 3.82 (2s, 6H each, OCH_3), 4.45 (s, 4H, OCH_2CH_2O), 7.03 (d, 2H, *J*= 8.4 Hz, ArH of 3,4-$(OCH_3)_2C_6H_3$), 7.13 (d, 4H, *J*= 8.7 Hz, ArH of C_6H_4O), 7.20 (d, 2H, *J*= 8.4 Hz, ArH of 3,4-$(OCH_3)_2C_6H_3$), 7.34 (s, 2H, ArH of 3,4-$(OCH_3)_2C_6H_3$), 7.92 (d, 4H, *J*= 8.7 Hz, ArH of C_6H_4O), 8.39 (s, 2H, CH = N), 11.60 (s, 2H, D_2O exchangeable NH). 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.

H. 1,2-Bis[4-[(1-naphthylmethyleneamino)carbamoyl]phenoxy]ethane (19)

Yield 594.6 mg (98%, procedure A); colorless crystals, mp 285-287 °C. IR: 3217, 3047, 2939, 2882, 1647, 1605, 1578,1547, 1508, 1481, 1454, 1362, 1339, 1292, 1250, 1180, 1119, 1069, 1045, 1015, 945, 914, 837, 779, 667, 625, 475, 428. ^{1}H NMR (DMSO-d_6) δ 4.48 (s, 4H, OCH_2CH_2O), 7.18 (d, 4H, *J*= 8.9 Hz, ArH of C_6H_4O), 7.61 (t, 6H, *J*= 7.9 Hz, ArH of $C_{10}H_7$), 7.99 (d, 4H, *J*= 8.9 Hz, ArH of C_6H_4O), 8.02 (d, 6H, *J*= 7.9 Hz, ArH of $C_{10}H_7$), 8.87 (d, 2H, *J*= 7.9 Hz, ArH of $C_{10}H_7$), 9.12 (s, 2H, CH = N), 11.83 (s, 2H, D_2O exchangeable NH). 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.

I. 1,2-Bis[4-[(isopropylideneamino)carbamoyl]phenoxy]ethane (20)

Yield 299.7 mg (73%, procedure B); colorless crystals, mp 246-248 °C. IR: 3225, 2993, 2947, 2882, 1670, 1609, 1531, 1504, 1450, 1373, 1292, 1246, 1177, 1150, 1119, 1076, 1034, 949, 914, 845, 814, 764, 660, 610, 525, 482. ^{1}H NMR (DMSO-d_6) δ 1.93, 1.99 (2s, 6H each, $C(CH_3)_2$), 4.42 (s, 4H, OCH_2CH_2O), 7.06 (d, 4H, *J*= 8.9 Hz, ArH), 7.83 (d, 4H, *J*= 8.9 Hz, ArH), 10.21 (s, 2H, D_2O exchangeable NH). 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.

J. 1,2-Bis[4-[(1-phenylethylideneamino)carbamoyl]phenoxy]ethane (21)

Yield 368.9 mg (69%, procedure A); colorless crystals, mp 248-250 °C. IR: 3255, 3020, 2959, 2893, 1651, 1616, 1570, 1539, 1504, 1450, 1296, 1250, 1180, 1111, 1045, 980, 937, 891, 841, 806, 756, 671, 656, 563, 498, 428. ^{1}H NMR (DMSO-d_6) δ 2.36 (s, 6H, CH_3), 4.46 (s, 4H, OCH_2CH_2O), 7.12 (d, 4H, *J*= 8.7 Hz, ArH of C_6H_4O), 7.43 (m, 6H, ArH of C_6H_5), 7.80 (d, 4H, *J*= 9.0 Hz, ArH of C_6H_5), 7.91 (d, 4H, *J*= 8.7 Hz, ArH of C_6H_4O), 10.57 (s, 2H, D_2O exchangeable NH). 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.

K. 1,3-Bis[(4-[(benzylideneamino)carbamoyl] phenoxy]propane (22)

Yield 489.4 mg (94%, procedure A); colorless crystals, mp 253-255 °C. IR: 3248, 3059, 2874, 1651, 1605, 1547, 1508, 1366, 1312, 1250, 1177, 1115, 1053, 1011, 964, 914, 845, 756, 664, 482, 417. ^{1}H NMR (DMSO-d_6) δ 2.24 (quint, 2H, *J*= 6.2 Hz, OCH_2CH_2), 4.25 (t, 4H, *J*= 6.2 Hz, OCH_2CH_2), 7.10 (d, 4H, *J*= 8.9 Hz, ArH of C_6H_4O), 7.45 (m, 6H, ArH of C_6H_5), 7.72 (d, 4H, *J*= 6.6 Hz, ArH of C_6H_5), 7.92 (d, 4H, *J*= 8.9 Hz, ArH of C_6H_4O), 8.45 (s, 2H, CH = N), 11.71 (s, 2H, D_2O exchangeable NH). 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.

L. 1,3-Bis[4-[(p-tolylmethyleneamino)carbamoyl] phenoxy]propane (23)

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_2), 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.

M. 1,3-Bis[4-[[(4-methoxyphenyl)methyleneamino]carbamoyl]phenoxy]propane (24)

Yield 563.3 mg (97%, procedure A); colorless crystals, mp 285-286 °C. IR: 3260, 3074, 3040, 2939, 2839, 1647, 1605, 1543, 1508, 1462, 1420, 1366, 1312, 1250, 1173, 1146, 1119, 1057, 1026, 964, 914, 837, 764, 660, 621, 529, 494, 436. ^{1}H NMR (DMSO-d_6) δ 2.24 (quint, 2H, *J*= 6.2 Hz, OCH_2CH_2), 3.81 (s, 6H, OCH_3), 4.25 (t, 4H, *J*= 6.2 Hz, OCH_2CH_2), 7.02 (d, 4H, *J*= 8.6 Hz, ArH of 4-$CH_3OC_6H_4$), 7.08 (d, 4H, *J*= 8.7 Hz, ArH of C_6H_4O), 7.66 (d, 4H, *J*= 8.6 Hz, ArH of 4-$CH_3OC_6H_4$), 7.90 (d, 4H, *J*= 8.7 Hz, ArH of C_6H_4O), 8.39 (s, 2H, CH = N), 11.56 (s, 2H, D_2O exchangeable NH). 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.

N. 1,3-Bis[4-[[(4-chlorophenyl)methyleneamino] carbamoyl]phenoxy]proane (25)

Yield 542.3 mg (92%, procedure A); colorless crystals, mp 274-276 °C. IR: 3236, 3071, 2874, 1647, 1605, 1547, 1508, 1497, 1366, 1312, 1250, 1177, 1088, 1057, 1011, 968, 914, 829, 760, 660, 625, 509, 478, 421. ^{1}H NMR (DMSO-d_6) δ 2.24 (quint, 2H, *J*= 6.2 Hz, OCH_2CH_2), 4.25 (t, 4H, *J*= 6.2 Hz, OCH_2CH_2), 7.10 (d, 4H, *J*= 8.7 Hz, ArH of C_6H_4O), 7.52 (d, 4H, *J*= 8.3 Hz, ArH of 4-ClC_6H_4), 7.74 (d, 4H, *J*= 8.3 Hz, ArH of 4-ClC_6H_4), 7.91 (d, 4H, *J*= 8.7 Hz, ArH of C_6H_4O), 8.44 (s, 2H, CH = N), 11.77 (s, 2H, D_2O exchangeable NH). 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.

O. 1,3-Bis[4-[[(4-dimethylaminophenyl)methyleneamino]carbamoyl]phenoxy]propane (26)

Yield 588.5 mg (97%, procedure A); colorless crystals, mp 289-291 °C. IR: 3279, 3084, 3044, 2866, 2808, 1647, 1605, 1504, 1439, 1362, 1312, 1254, 1177, 1123, 1053, 957, 918, 837, 814, 760, 613, 525, 424. ^{1}H NMR (DMSO-d_6) δ 2.24 (quint, 2H, *J*= 6.0 Hz, OCH_2CH_2), 2.97 (s, 12H, $N(CH_3)_2$), 4.24 (t, 4H, *J*= 6.0 Hz, OCH_2CH_2), 6.76 (d, 4H, *J*= 8.4 Hz, ArH of 4-$(CH_3)_2NC_6H_4$), 7.07 (d, 4H, *J*= 8.7 Hz, ArH of C_6H_4O), 7.53 (d, 4H, *J*= 8.4 Hz, ArH of 4-$(CH_3)_2NC_6H_4$), 7.89 (d, 4H, *J*= 8.7 Hz, ArH of C_6H_4O), 8.30 (s, 2H, CH = N), 11.39 (s, 2H, D_2O exchangeable NH). 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.

P. 1,3-Bis[4-[[(2-hydroxyphenyl)methyleneamino] carbamoyl]phenoxy]propane (27)

Yield 551.9 mg (100%, procedure A); colorless crystals, mp 288-290 °C. IR: 3506, 3213, 3051, 2951, 2858, 1647, 1612, 1574, 1512, 1466, 1373, 1296, 1254, 1192, 1153, 1115, 1053, 968, 845, 752, 664, 475, 432. ^{1}H NMR (DMSO-d_6) δ 2.25 (quint, 2H, *J*= 6.2 Hz, OCH_2CH_2), 4.26 (t, 4H, *J*= 6.2 Hz, OCH_2CH_2), 6.93 (d, 4H, *J*= 7.9 Hz, ArH of 2-(OH)C_6H_4), 7.11 (d, 4H, *J*= 8.9 Hz, ArH of C_6H_4O), 7.30 (dt, 2H, *J*= 1.4, 7.9 Hz, ArH of 2-(OH)C_6H_4),

7.52 (dd, 2H, *J*= 1.4, 7.9 Hz, ArH of 2-(OH)C_6H_4), 7.93 (d, 4H, *J*= 8.9 Hz, ArH of C_6H_4O), 8.62 (s, 2H, CH = N), 11.37 (s, 2H, D_2O exchangeable NH), 11.98 (s, 2H, D_2O exchangeable OH). 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.

Q. 1,3-Bis[4-[[(3,4-dimethoxyphenyl)methyleneamino]carbamoyl]phenoxy]propane (28)

Yield 615.1 mg (96%, procedure A); colorless crystals, mp 239-241 °C. IR: 3248, 3084, 2961, 2849, 1647, 1609, 1543, 1508, 1466, 1423, 1373, 1275, 1242, 1177, 1138, 1061, 1022, 964, 899, 845, 810, 756, 664, 625, 471. ^{1}H NMR (DMSO-d_6) δ 2.24 (quint, 2H, *J*= 6.0 Hz, OCH_2CH_2), 3.81, 3.82 (2s, 6H each, OCH_3), 4.25 (t, 4H, *J*= 6.0 Hz, OCH_2CH_2), 7.02 (d, 2H, *J*= 8.4 Hz, ArH of 3,4-$(OCH_3)_2C_6H_3$), 7.09 (d, 4H, *J*= 8.7 Hz, ArH of C_6H_4O), 7.19 (d, 2H, *J*= 8.4 Hz, ArH of 3,4-$(OCH_3)_2C_6H_3$), 7.34 (s, 2H, ArH of 3,4-$(OCH_3)_2C_6H_3$), 7.90 (d, 4H, *J*= 8.7 Hz, ArH of C_6H_4O), 8.37 (s, 2H, CH = N), 11.58 (s, 2H, D_2O exchangeable NH). 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.

R. 1,3-Bis[4-[(1-naphthylmethyleneamino)carbamoyl]phenoxy]propane (29)

Yield 619.8 mg (100%, procedure A); colorless crystals, mp 260-261 °C. IR: 3221, 3047, 2916, 2874, 2750, 1647, 1609, 1547, 1508, 1470, 1369, 1315, 1254, 1177, 1119, 1065, 1011, 968, 914, 845, 768, 725, 667, 629, 544, 471, 428. ^{1}H NMR (DMSO-d_6) δ 2.27 (quint, 2H, *J*= 6.1 Hz, OCH_2CH_2), 4.28 (t, 4H, *J*= 6.1 Hz, OCH_2CH_2), 7.14 (d, 4H, *J*= 8.4 Hz, ArH of C_6H_4O), 7.61 (t, 6H, *J*= 8.0 Hz, ArH of $C_{10}H_7$), 7.97 (d, 4H, *J*= 8.4 Hz, ArH of C_6H_4O), 8.02 (d, 6H, *J*= 8.0 Hz, ArH of $C_{10}H_7$), 8.86 (d, 2H, *J*= 8.0 Hz, ArH of $C_{10}H_7$), 9.11 (s, 2H, CH = N), 11.81 (s, 2H, D_2O exchangeable NH). 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.

S. 1,3-Bis[4-[(isopropylideneamino)carbamoyl]phenoxy]propane (30)

Yield 331.1 mg (78%, procedure B); colorless crystals, mp 231-232 °C. IR: 3317, 3086, 2951, 2916, 2882, 1647, 1612, 1504, 1470, 1423, 1373, 1312, 1254, 1177, 1134, 1057, 1018, 907, 841, 760, 652, 579, 525, 459. ^{1}H NMR (DMSO-d_6) δ 1.92, 1.98 (2s, 6H each, $C(CH_3)_2$), 2.21 (quint, 2H, *J*= 6.2 Hz, OCH_2CH_2), 4.21 (t, 4H, *J*= 6.2 Hz, OCH_2CH_2), 7.03 (d, 4H, *J*= 8.7 Hz, ArH), 7.80 (d, 4H, *J*= 8.7 Hz, ArH), 10.24 (s, 2H, D_2O exchangeable NH). 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.

T. 1,3-Bis[4-[(1-phenylethylideneamino)carbamoyl]phenoxy]propane (31)

Yield 504.8 mg (92%, procedure A); colorless crystals, mp 252-254 °C. IR: 3206, 3059, 3020, 2939, 2885, 2824, 1643, 1609, 1578, 1547, 1504, 1466, 1420, 1377, 1285, 1258, 1188, 1138, 1111, 1080, 1053, 1007, 976, 899, 837, 760, 687, 625, 563, 505. ^{1}H NMR (DMSO-d_6) δ 2.24 (quint, 2H, *J*= 6.2 Hz, OCH_2CH_2), 2.36 (s, 6H, CH_3), 4.25 (t, 4H, *J*= 6.2 Hz, OCH_2CH_2), 7.08 (d, 4H, *J*= 8.7 Hz, ArH of C_6H_4O), 7.42 (m, 6H, ArH of C_6H_5), 7.82 (m, 4H, ArH of C_6H_5), 7.89 (d, 4H, *J*= 8.7 Hz, ArH of C_6H_4O), 10.59 (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, 72.19; H, 5.92; N, 10.24.

U. 1,4-Bis[(4-[(benzylideneamino)carbamoyl]phenoxy]butane (32)

Yield 502.5 mg (94%, procedure A); colorless crystals, mp 275-276 °C. IR: 3263, 3036, 2924, 2870, 1647, 1605, 1543, 1504, 1458, 1366, 1312, 1285, 1250, 1173, 1119, 1049, 968, 914, 841, 756, 691, 652, 486, 432. ^{1}H NMR (DMSO-d_6) δ 1.93 (quint, 4H, *J*= 5.0 Hz, OCH_2CH_2), 4.16 (t, 4H, *J*= 5.0 Hz, OCH_2CH_2), 7.06 (d, 4H, *J*= 8.7 Hz, ArH of C_6H_4O), 7.45 (m, 6H, ArH of C_6H_5), 7.72 (dd, 4H, *J*= 1.7, 7.8 Hz, ArH of C_6H_5), 7.91 (d, 4H, *J*= 8.7 Hz, ArH of C_6H_4O), 8.44 (s, 2H, CH = N), 11.60 (s, 2H, D_2O exchangeable NH). 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, 5.62; N, 10.41.

V. 1,4-Bis[4-[(p-tolylmethyleneamino)carbamoyl]phenoxy]butane (33)

Yield 512.1 mg (91%, procedure A); colorless crystals, mp 284-286 °C. IR: 3260, 3040, 2920, 2866, 1647, 1609, 1543, 1504, 1466, 1366, 1309, 1254, 1177, 1115, 1053, 1018, 972, 918, 841, 764, 656, 513, 471. ^{1}H NMR (DMSO-d_6) δ 1.92 (s, 4H, OCH_2CH_2), 2.34 (s, 6H, CH_3), 4.15 (s, 4H,

OC*H*$_2$CH$_2$), 7.06 (d, 4H, *J*= 8.6 Hz, ArH of C$_6$H$_4$O), 7.26 (d, 4H, *J*= 7.8 Hz, ArH of 4-CH$_3$C$_6$*H*$_4$), 7.60 (d, 4H, *J*= 7.8 Hz, ArH of 4-CH$_3$C$_6$*H*$_4$), 7.90 (d, 4H, *J*= 8.6 Hz, ArH of C$_6$H$_4$O), 8.40 (s, 2H, CH = N), 11.57 (s, 2H, D$_2$O exchangeable NH). Anal. Calcd for C$_{34}$H$_{34}$N$_4$O$_4$ (562.7): C, 72.58; H, 6.09; N, 9.96. Found: C, 72.64; H, 6.00; N, 10.03.

W. 1,4-Bis[4-[[(4-methoxyphenyl)methyleneamino]-carbamoyl]phenoxy]butane (34)

Yield 559.0 mg (94%, procedure A); colorless crystals, mp 286-287 °C. IR: 3267, 3089, 3049, 3009, 2924, 2878, 2839, 1647, 1609, 1543, 1504, 1466,1420, 1369, 1312, 1254, 1177, 1115, 1053, 1030, 972, 918, 837, 764, 652, 621, 532, 498, 424. ^{1}H NMR (DMSO-d$_6$) δ 1.92 (s, 4H, OCH$_2$C*H*$_2$), 3.81 (s, 6H, OCH$_3$), 4.14 (s, 4H, OC*H*$_2$CH$_2$), 7.02 (d, 4H, *J*= 8.4 Hz, ArH of 4-CH$_3$OC$_6$*H*$_4$), 7.05 (d, 4H, *J*= 8.6 Hz, ArH of C$_6$H$_4$O), 7.65 (d, 4H, *J*= 8.4 Hz, ArH of 4-CH$_3$OC$_6$*H*$_4$), 7.90 (d, 4H, *J*= 8.6 Hz, ArH of C$_6$H$_4$O), 8.39 (s, 2H, CH = N), 11.51 (s, 2H, D$_2$O exchangeable NH). Anal. Calcd for C$_{34}$H$_{34}$N$_4$O$_6$ (594.7): C, 68.67; H, 5.76; N, 9.42. Found: C, 68.71; H, 5.79; N, 9.29.

X. 1,4-Bis[4-[[(4-chlorophenyl)methyleneamino] carbamoyl]phenoxy]butane (35)

Yield 573.3 mg (95%, procedure A); colorless crystals, mp 303-304 °C. IR: 3229, 3047, 2939, 2870, 1647, 1605, 1547, 1501, 1481, 1362, 1308, 1250, 1177, 1080, 1057, 1011, 968, 914, 833, 756, 656, 625, 513, 478, 417. ^{1}H NMR (DMSO-d$_6$) δ 1.92 (s, 4H, OCH$_2$C*H*$_2$), 4.14 (s, 4H, OC*H*$_2$CH$_2$), 7.06 (d, 4H, *J*= 8.7 Hz, ArH of C$_6$H$_4$O), 7.51 (d, 4H, *J*= 8.3 Hz, ArH of 4-ClC$_6$*H*$_4$), 7.73 (d, 4H, *J*= 8.3 Hz, ArH of 4-ClC$_6$*H*$_4$), 7.91 (d, 4H, *J*= 8.7 Hz, ArH of C$_6$H$_4$O), 8.43 (s, 2H, CH = N), 11.73 (s, 2H, D$_2$O exchangeable NH). Anal. Calcd for C$_{32}$H$_{28}$Cl$_2$N$_4$O$_4$ (603.5): C, 63.69; H, 4.68; N, 9.28. Found: C, 63.78; H, 4.60; N, 9.32.

Y. 1,4-Bis[4-[[(4-dimethylaminophenyl)methyleneamino]carbamoyl]phenoxy]butane (36)

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$_2$C*H*$_2$), 2.97 (s, 12H, N(CH$_3$)$_2$), 4.14 (s, 4H, OC*H*$_2$CH$_2$), 6.76 (d, 4H, *J*= 8.6 Hz, ArH of 4-(CH$_3$)$_2$NC$_6$*H*$_4$), 7.05 (d, 4H, *J*= 8.9 Hz, ArH of C$_6$H$_4$O), 7.53 (d, 4H, *J*= 8.6 Hz, ArH of 4-(CH$_3$)$_2$NC$_6$*H*$_4$), 7.88 (d, 4H, *J*= 8.9 Hz, ArH of C$_6$H$_4$O), 8.30 (s, 2H, CH = N), 11.39 (s, 2H, D$_2$O exchangeable NH). Anal. Calcd for C$_{36}$H$_{40}$N$_6$O$_4$ (620.8): C, 69.66; H, 6.50; N, 13.54. Found: C, 69.71; H, 6.45; N, 13.48.

Z. 1,4-Bis[4-[[(2-hydroxyphenyl)methyleneamino] carbamoyl]phenoxy]butane (37)

Yield 564.9 mg (100%, procedure A); colorless crystals, mp 280-282 °C. IR: 3225, 3032, 2955, 2878, 1647, 1609, 1578, 1543, 1508, 1366, 1250, 1180, 1153, 1119, 1053, 1007, 972, 922, 876, 841, 752, 694, 664, 536, 475, 424. ^{1}H NMR (DMSO-d$_6$) δ 1.92 (s, 4H, OCH$_2$C*H*$_2$), 4.15 (s, 4H, OCH$_2$C*H*$_2$), 6.93 (d, 4H, *J*= 7.7 Hz, ArH of 2-(OH)C$_6$*H*$_4$), 7.08 (d, 4H, *J*= 8.4 Hz, ArH of C$_6$H$_4$O), 7.29 (t, 2H, *J*= 7.7 Hz, ArH of 2-(OH)C$_6$*H*$_4$), 7.51 (d, 2H, *J*= 7.7 Hz, ArH of 2-(OH)C$_6$*H*$_4$), 7.93 (d, 4H, *J*= 8.4 Hz, ArH of C$_6$H$_4$O), 8.61 (s, 2H, CH = N), 11.38 (s, 2H, D$_2$O exchangeable NH), 11.98 (s, 2H, D$_2$O exchangeable OH). Anal. Calcd for C$_{32}$H$_{30}$N$_4$O$_6$ (566.6): C, 67.83; H, 5.34; N, 9.89. Found: C, 67.92; H, 5.36; N, 9.78.

AA. 1,4-Bis[4-[[(3,4-dimethoxyphenyl)methyleneamino]carbamoyl]phenoxy]butane (38)

Yield 648.2 mg (99%, procedure A); colorless crystals, mp 267-268 °C. IR: 3179, 2997, 2951, 2878, 2839, 1647, 1605, 1570, 1508, 1458, 1420, 1366, 1261, 1173, 1138, 1061, 1022, 968, 899, 845, 814, 756, 660, 629, 544, 467. ^{1}H NMR (DMSO-d$_6$) δ 1.92 (s, 4H, OCH$_2$C*H*$_2$), 3.81, 3.82 (2s, 6H each, OCH$_3$), 4.14 (s, 4H, OC*H*$_2$CH$_2$), 7.02 (d, 2H, *J*= 8.3 Hz, ArH of 3,4-(OCH$_3$)$_2$C$_6$H$_3$), 7.06 (d, 4H, *J*= 8.9 Hz, ArH of C$_6$H$_4$O), 7.19 (d, 2H, *J*= 8.3 Hz, ArH of 3,4-(OCH$_3$)$_2$C$_6$H$_3$), 7.34 (s, 2H, ArH of 3,4-(OCH$_3$)$_2$C$_6$H$_3$), 7.90 (d, 4H, *J*= 8. 9 Hz, ArH of C$_6$H$_4$O), 8.37 (s, 2H, CH = N), 11.58 (s, 2H, D$_2$O exchangeable NH). Anal. Calcd for C$_{36}$H$_{38}$N$_4$O$_8$ (654.7): C, 66.04; H, 5.85; N, 8.56. Found: C, 66.00; H, 5.74; N, 8.63.

BB. 1,4-Bis[4-[(1-naphthylmethyleneamino) carbamoyl]phenoxy]butane (39)

Yield 620.7 mg (98%, procedure A); colorless crystals, mp 265-266 °C. IR: 3221, 3079, 3047, 2947,

2909, 2870, 1651, 1609, 1578, 1547, 1508, 1578, 1474, 1393, 1362, 1288, 1312, 1254, 1177, 1150, 1115, 1061, 1015, 976, 914, 872, 841, 799, 764, 733, 664, 629, 540, 467, 421. ^{1}H NMR (DMSO-d_6) δ 1.95 (s, 4H, OCH_2CH_2), 4.17 (s, 4H, OCH_2CH_2), 7.11 (d, 4H, *J*= 8.7 Hz, ArH of C_6H_4O), 7.61 (t, 6H, *J*= 8.0 Hz, ArH of $C_{10}H_7$), 7.97 (d, 4H, *J*= 8.7 Hz, ArH of C_6H_4O), 8.02 (d, 6H, *J*= 8.0 Hz, ArH of $C_{10}H_7$), 8.86 (d, 2H, *J*= 8.0 Hz, ArH of $C_{10}H_7$), 9.10 (s, 2H, CH = N), 11.80 (s, 2H, D_2O exchangeable NH). Anal. Calcd for $C_{40}H_{34}N_4O_4$ (634.7): C, 75.69; H, 5.40; N, 8.83. Found: C, 75.73; H, 5.34; N, 8.87.

CC. 1,4-Bis[4-[(isopropylideneamino)carbamoyl] phenoxy]butane (40)

Yield 307.0 mg (70%, procedure B); colorless crystals, mp 230-231 °C. IR: 3290, 2959, 2924, 2882, 2785, 2735, 1639, 1605, 1501, 1431, 1373, 1308, 1254, 1177, 1119, 1057, 1003, 903, 837, 760, 648, 598, 529, 475. ^{1}H NMR (DMSO-d_6) δ 1.90 (s, 4H, OCH_2CH_2), 1.93, 1.99 (2s, 6H each, $C(CH_3)_2$, 4.11 (s, 4H, OCH_2CH_2), 7.00 (d, 4H, *J*= 8.9 Hz, ArH), 7.80 (d, 4H, *J*= 8.9 Hz, ArH), 10.24 (s, 2H, D_2O exchangeable NH). Anal. Calcd for $C_{24}H_{30}N_4O_4$ (438.5): C, 65.73; H, 6.90; N, 12.78. Found: C, 65.66; H, 6.93; N, 12.84.

DD. 1,4-Bis[4-[(1-phenylethylideneamino)carbamoyl]phenoxy]butane (41)

Yield 510.4 mg (91%, procedure A); colorless crystals, mp 266-268 °C. IR: 3213, 3059, 3020, 2924, 2870, 1643, 1609, 1578, 1543, 1501, 1447, 1420, 1389, 1281, 1254, 1192, 1138, 1107, 1053, 1022, 972, 945, 895, 837, 760, 687, 656, 625, 563, 509, 475, 424. ^{1}H NMR (DMSO-d_6) δ 1.93 (s, 4H, OCH_2CH_2), 2.36 (s, 6H, CH_3), 4.15 (s, 4H, OCH_2CH_2), 7.05 (d, 4H, *J*= 8.7 Hz, ArH of C_6H_4O), 7.42 (m, 6H, ArH of C_6H_5), 7.83 (m, 4H, ArH of C_6H_5), 7.88 (d, 4H, *J*= 8.7 Hz, ArH of C_6H_4O), 10.58 (s, 2H, D_2O exchangeable NH). Anal. Calcd for $C_{34}H_{34}N_4O_4$ (562.7): C, 72.58; H, 6.09; N, 9.96. Found: C, 72.49; H, 6.00; N, 10.01.

6. Synthesis of 1,ω-bis[4-(5-sulfanyl-1,3,4-oxadiazol-2-yl)phenoxy]alkanes (42-44). General procedure

A mixture of each of compounds **(9-11)** (3 mmol), KOH (533.1 mg, 9.5 mmol) and carbon disulfide [0.54 mL (685.3 mg), 9 mmol)] in 75 mL of absolute EtOH was heated at reflux temperature for 8 h. After the solvent was evaporated in vacuo, the residue was dissolved in ice-cold water (100 mL) and acidified with concd HCl (3-5 mL). The precipitate was collected by filtration, washed with water (3 x 100 mL) followed by MeOH (3 x 25 mL) and dried. Compounds **(42)**, **(43)** were recrystallized from DMF/MeOH and compound **(44)** was recrystallized from DMF.

A. 1,2-Bis[4-(5-sulfanyl-1,3,4-oxadiazol-2-yl) phenoxy]ethane (42)

Yield 858.0 mg (69%); colorless crystals, mp 298-299 °C (dec). IR: 3090, 2951, 2889, 2762, 2573, 1609, 1508, 1477, 1423, 1354, 1308, 1258, 1173, 1123, 1072, 1038, 968, 937, 829, 810, 729, 694, 664, 629, 559, 521, 467. ^{1}H NMR (DMSO-d_6) δ 4.45 (s, 4H, OCH_2CH_2), 7.19 (d, 4H, *J*= 8.9 Hz, ArH), 7.83 (d, 4H, *J*= 8.9 Hz, ArH), 13.25 (br, 2H, D_2O exchangeable SH). Anal. Calcd for $C_{18}H_{14}N_4O_4S_2$ (414.5): C, 52.16; H, 3.40; N, 13.52; S, 15.47. Found: C, 52.15; H, 3.44; N, 13.49; S, 15.45.

B. 1,3-Bis[4-(5-sulfanyl-1,3,4-oxadiazol-2-yl) phenoxy]propane (43)

Yield 989.8 mg (77%); colorless crystals, mp 279-280 °C (dec). IR: 3067, 2951, 2882, 2758, 2565, 1616, 1512, 1489, 1423, 1385, 1354, 1312, 1254, 1165, 1123, 1072, 988, 964, 937, 837, 768, 729, 694, 660, 629, 556, 521, 502, 444, 413. ^{1}H NMR (DMSO-d_6) δ 2.23 (quint, 2H, *J*= 6.1 Hz, OCH_2CH_2), 4.24 (t, 4H, *J*= 6.1 Hz, OCH_2CH_2), 7.15 (d, 4H, *J*= 9.0 Hz, ArH), 7.81 (d, 4H, *J*= 9.0 Hz, ArH), 14.62 (br, 2H, D_2O exchangeable SH). Anal. Calcd for $C_{19}H_{16}N_4O_4S_2$ (428.5): C, 53.26; H, 3.76; N, 13.08; S, 14.97. Found: C, 53.18; H, 3.79; N, 13.03; S, 15.02.

C. 1,4-Bis[4-(5-sulfanyl-1,3,4-oxadiazol-2-yl) phenoxy]butane (44)

Yield 1.26 g (95%); colorless crystals, mp 276-277 °C (dec). IR: 3086, 2947, 2878, 2770, 2592, 2565, 1612, 1512, 1458, 1423, 1393, 1354, 1312, 1254, 1177, 1126, 1072, 1049, 1011, 968, 937, 841, 729, 694, 664, 629, 548, 529, 444, 421. ^{1}H NMR (DMSO-d_6) δ 1.91 (quint, 4H, *J*= 4.8 Hz, OCH_2CH_2), 4.13 (t,

4H, *J*= 4.8 Hz, OC*H*$_2$CH$_2$), 7.12 (d, 4H, *J*= 8.9 Hz, ArH), 7.80 (d, 4H, *J*= 8.9 Hz, ArH), 14.54 (br, 2H, D$_2$O exchangeable SH). Anal. Calcd for $C_{20}H_{18}N_4O_4S_2$ (442.5): C, 54.29; H, 4.10; N, 12.66; S, 14.49. Found: C, 54.19; H, 4.16; N, 12.74; S, 14.39.

7. Synthesis of 1,ω-bis[4-(5-sulfanyl-1,3,4-thiadiazol-2-yl)phenoxy]alkanes (45-47). General procedure

A mixture of each of compounds **(9-11)** (3 mmol), KOH (533.1 mg, 9.5 mmol) and carbon disulfide [0.54 mL (685.3 mg), 9 mmol)] in 75 mL of absolute EtOH was heated at reflux temperature for 1 h and kept stirred at room temperature overnight. After the solvent was evaporated in vacuo and the obtained solid was dried, ice cold concd sulphuric acid (25 mL) was added gradually while stirring and cooling (0-5 °C) and the reaction mixture was further stirred for 4 h in an ice bath. The mixture was then poured over crushed ice and the obtained solid was collected by filtration, washed with water (5 x 100 mL) followed by MeOH (3 x 25 mL) and dried. Compound **(45)** was recrystallized from DMF and compounds **(46)**, **(47)** were recrystallized from DMF/MeOH.

A. 1,2-Bis[4-(5-sulfanyl-1,3,4-thiadiazol-2-yl) phenoxy]ethane (45)

Yield 1.10 g (82%); Pale yellow crystals, mp 305-307 (dec). IR: 3078, 2947, 2885, 2573, 1605, 1578, 1516, 1477, 1439, 1412, 1373, 1304, 1250, 1173, 1119, 1045, 976, 941, 833, 810, 768, 671, 621, 567, 517, 467. ^{1}H NMR (DMSO-d$_6$) δ 4.43 (s, 4H, OCH$_2$CH$_2$), 7.08 (d, 4H, *J*= 8.7 Hz, ArH), 7.90 (d, 4H, *J*= 8.7 Hz, ArH), 14.60 (s, 2H, D$_2$O exchangeable SH). Anal. Calcd for $C_{18}H_{14}N_4O_2S_4$ (446.6): C, 48.41; H, 3.16; N, 12.55; S, 28.72. Found: C, 48.49; H, 3.08; N, 12.59; S, 28.69.

B. 1,3-Bis[4-(5-sulfanyl-1,3,4-thiadiazol-2-yl) phenoxy]propane (46)

Yield 1.15 g (83%); Pale yellow crystals, mp 274-276 (dec). IR: 3094, 2951, 2882, 2770, 2565, 1612, 1512, 1466, 1423, 1385, 1354, 1308, 1254, 1173, 1123, 1057, 968, 937, 837, 733, 694, 629, 556, 521, 413. ^{1}H NMR (DMSO-d$_6$) δ ^{1}H NMR (DMSO-d$_6$) δ 2.23 (quint, 2H, *J*= 5.4 Hz, OCH$_2$C*H*$_2$), 4.23 (t, 4H, *J*= 5.4 Hz, OC*H*$_2$CH$_2$), 7.14 (d, 4H, *J*= 8.3 Hz, ArH), 7.80 (d, 4H, *J*= 8.3 Hz, ArH), 14.59 (s, 2H, D$_2$O exchangeable SH). Anal. Calcd for $C_{19}H_{16}N_4O_2S_4$ (460.6): C, 49.54; H, 3.50; N, 12.16; S, 27.84. Found: C, 49.47; H, 3.56; N, 12.09; S, 27.87.

C. 1,4-bis[4-(5-sulfanyl-1,3,4-thiadiazol-2-yl) phenoxy]butane (47)

Yield 1.21 g (85%); yellow crystals, mp 283-284 °C (dec). IR: 3084, 2939, 2878, 2550, 1605, 1512, 1423, 1254, 1169, 1119, 1045, 968, 837, 768, 617, 509, 417. ^{1}H NMR (DMSO-d$_6$) δ 1.90 (s, 4H, OCH$_2$C*H*$_2$), 4.12 (s, 4H, OC*H*$_2$CH$_2$), 7.01 (d, 4H, *J*= 7.7 Hz, ArH), 7.88 (d, 4H, *J*= 7.7 Hz, ArH), 14.55 (br, 2H, D$_2$O exchangeable SH). Anal. Calcd for $C_{20}H_{18}N_4O_2S_4$ (474.7): C, 50.61; H, 3.82; N, 11.80; S, 27.02. Found: C, 50.64; H, 3.77; N, 11.78; S, 27.16.

8. Synthesis of 1,ω-Bis(4-carboxyphenoxy)alkanes (48-50). General procedure

A mixture of each of compounds **(6-8)** (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 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.

A. 1,2-Bis(4-carboxyphenoxy)ethane (48)

Yield 1.36 g (90%); colorless crystals, mp 350 °C. 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$_2$CH$_2$), 7.07 (d, 4H, *J*= 8.9 Hz, ArH), 7.90 (d, 4H, *J*= 8.9 Hz, ArH), 12.59 (br, 2H, D$_2$O 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.

B. 1,3-Bis(4-carboxyphenoxy)propane (49)

Yield 1.38 g (87%); colorless crystals, mp 327-328 °C. IR: 3078-2361 (br), 3078, 2955, 2889, 2824, 2767, 2557, 2361, 1678, 1605, 1578, 1512, 1470, 1431, 1300, 1250, 1169, 1115, 1057, 991, 937, 849, 768, 694, 640, 548, 505, 471. ^{1}H NMR (DMSO-d$_6$) δ 2.21 (quint, 2H, *J*= 6.2 Hz, OCH$_2$C*H*$_2$), 4.20 (t, 4H, *J*= 6.2 Hz, OC*H*$_2$CH$_2$), 7.02 (d, 4H, *J*= 8.9 Hz, ArH),

7.89 (d, 4H, *J*= 8.9 Hz, ArH), 12.57 (br, 2H, D_2O exchangeable OH). Anal. Calcd for $C_{17}H_{16}O_6$ (316.3): C, 64.55; H, 5.10. Found: C, 64.51; H, 5.18.

C. 1,4-Bis(4-carboxyphenoxy)butane (50)

Yield 1.21 g (73%); colorless crystals, mp 342-344 °C. IR: 3072-2361 (br), 3072, 2951, 2890, 2866, 2824, 2665, 2557, 2361, 1686, 1605, 1578, 1512, 1466, 1427, 1396, 1323, 1300, 1254, 1173, 1123, 1049, 972, 945, 849, 772, 694, 644, 552, 505, 471, 444. ^{1}H NMR (DMSO-d_6) δ 1.89 (s, 4H, OCH_2CH_2), 4.10 (s, 4H, OCH_2CH_2), 7.00 (d, 4H, *J*= 8.7 Hz, ArH), 7.88 (d, 4H, *J*= 8.7 Hz, ArH), 12.56 (br, 2H, D_2O exchangeable OH). Anal. Calcd for $C_{18}H_{18}O_6$ (330.3): C, 65.45; H, 5.49. Found: C, 65.40; H, 5.52.

9. 1,ω-Bis[4-(5-aryl-1,3,4-ozadizaol-2-yl)phenoxy] alkanes (51-65). General procedures

Procedure A: A mixture of each of compounds **(9-11)** (1.5 mmol) and the appropriate aromatic acid or 4-chlorobenzoyl chloride (3 mmol) in phosphorus oxychloride (10 mL) was heated at reflux temperature for 6 h. The reaction mixture was slowly poured over crushed ice (100 g) and kept stirred till all ice had been went into solution. The formed solid was collected by filtration, washed successively with 5% aq KOH (3 x 25 mL, except for compounds **(55)**, **(60)**, **(65)**), water (3 x 100 mL), MeOH (3 x 10 mL) and dried. Compounds **(51)**, **(52)**, **(56)**, **(57)**, **(61)**, **(62)**, **(65)** were recrystallized from DMF and compounds **(53-55)**, **(58-60)**, **(63)**, **(64)** were recrystallized from DMF/MeOH.

Procedure B: A mixture of each of compounds **(48-50)** (1.5 mmol) and the appropriate aromatic acid hydrazide (3 mmol) in phosphorus oxychloride (10 mL) was heated at reflux temperature for 6 h. The reaction mixture was slowly poured over crushed ice (100 g) and kept stirred for 15 min. The formed solid was collected by filtration, washed successively with 5% aq KOH (3 x 25 mL), water (3 x 100 mL), MeOH (3 x 10 mL), dried and recrystallized from DMF/MeOH.

A. 1,2-Bis[4-(5-phenyl-1,3,4-ozadizaol-2-yl) phenoxy]ethane (51)

Yield 610.5 mg (81%, procedure A); colorless crystals, mp 221-223 °C. IR: 3067, 2928, 2889, 1612, 1551, 1497, 1427, 1373, 1308, 1250, 1177, 1103, 1061, 964, 926, 837, 775, 737, 698, 664, 613, 490, 525. ^{1}H NMR (DMSO-d_6) δ 4.51 (s, 4H, OCH_2CH_2O), 7.25 (d, 4H, *J*= 8.7 Hz, ArH of C_6H_4O), 7.64 (dd, 6H, *J*= 2.0, 7.5 Hz, ArH of C_6H_5), 8.09 (d, 4H, *J*= 8.7 Hz, ArH of C_6H_4O), 8.12 (m, 4H, ArH of C_6H_5). Anal. Calcd for $C_{30}H_{22}N_4O_4$ (502.5): C, 71.70; H, 4.41; N, 11.15. Found: C, 71.67; H, 4.46; N, 10.99.

B. 1,2-Bis[4-[5-(4-methoxyphenyl)-1,3,4-ozadizaol-2-yl]phenoxy]ethane (52)

Yield 666.7 mg (79%, procedure A); colorless crystals, mp 258-260 °C. IR: 3071, 2943, 2893, 2839, 1612, 1493, 1423, 1304, 1254, 1177, 1111, 1026, 961, 930, 833, 741, 702, 664, 617, 517. ^{1}H NMR (DMSO-d_6) δ 3.87 (s, 6H, OCH_3), 4.50 (s, 4H, OCH_2CH_2O), 7.17 (d, 4H, *J*= 9.0 Hz, ArH of C_6H_4O), 7.24 (d, 4H, *J*= 8.7 Hz, ArH of 4-$CH_3OC_6H_4$), 8.05 (d, 4H, *J*= 8.7 Hz, ArH of 4-$CH_3OC_6H_4$), 8.07 (d, 4H, *J*= 9.0 Hz, ArH of C_6H_4O). Anal. Calcd for $C_{32}H_{26}N_4O_6$ (562.6): C, 68.32; H, 4.66; N, 9.96. Found: C, 68.42; H, 4.59; N, 10.02.

C. 1,2-Bis[4-[5-(4-chlorophenyl)-1,3,4-ozadizaol-2-yl]phenoxy]ethane (53)

Yield 531.4 mg (62%, procedure A), 548.5 mg (64%, procedure B); colorless crystals, mp 221-223 °C. IR: 3076, 2947, 2882, 1609, 1493, 1423, 1404, 1304, 1250, 1173, 1092, 1053, 1011, 934, 837, 741, 660, 629, 586, 517, 421. ^{1}H NMR (DMSO-d_6) δ 4.50 (s, 4H, OCH_2CH_2O), 7.25 (d, 4H, *J*= 8.3 Hz, ArH), 7.69 (d, 4H, *J*= 8.3 Hz, ArH), 8.09 (d, 4H, *J*= 8.3 Hz, ArH), 8.13 (d, 4H, *J*= 8.3 Hz, ArH). Anal. Calcd for $C_{30}H_{20}Cl_2N_4O_4$ (571.4): C, 63.06; H, 3.53; N, 9.80. Found: C, 63.02; H, 3.58; N, 9.75.

D. 1,2-Bis[4-[5-(4-nitrophenyl)-1,3,4-ozadizaol-2-yl]phenoxy]ethane (54)

Yield 791.0 mg (89%, procedure A); pale yellow crystals, mp 248-250 °C. ^{1}H NMR (DMSO-d_6) δ 4.51 (s, 4H, OCH_2CH_2O), 7.26 (d, 4H, *J*= 9.2 Hz, ArH of C_6H_4O), 8.12 (d, 4H, *J*= 8.7 Hz, ArH of 4-$NO_2C_6H_4$), 8.37 (d, 4H, *J*= 8.7 Hz, ArH of 4-$NO_2C_6H_4$), 8.44 (d, 4H, *J*= 9.2 Hz, ArH of C_6H_4O). Anal. Calcd for $C_{30}H_{20}N_6O_8$ (592.5): C, 60.81; H, 3.40; N, 14.18. Found: C, 60.77; H, 3.48; N, 14.23.

E. 1,2-Bis[4-[5-(3-pyridyl)-1,3,4-ozadizaol-2-yl]phenoxy]ethane (55)

Yield 605.4 mg (80%, procedure A); pale yellow

crystals, mp 236-238 °C. IR: 3067, 2928, 2882, 2793, 1609, 1489, 1412, 1304, 1254, 1177, 1115, 1057, 957, 918, 837, 737, 702, 664, 617, 521. ^{1}H NMR (DMSO-d_6) δ 4.49 (s, 4H, OCH_2CH_2O), 7.24 (d, 4H, *J*= 9.0 Hz, ArH of C_6H_4O), 7.65 (ddd, 2H, $J_{H\text{-}5\ pyrid.\text{-}H\text{-}2\ pyrid.}$= 0.9 Hz $J_{H\text{-}5\ pyrid.\text{-}H\text{-}6\ pyrid.}$= 4.8 Hz, $J_{H\text{-}5\ pyrid.\text{-}H\text{-}4\ pyrid.}$= 8.1 Hz, H-5 pyrid.), 8.09 (d, 4H, *J*= 9.0 Hz, ArH of C_6H_4O), 8.46 (td, 2H, $J_{H\text{-}4\ pyrid.\text{-}H\text{-}6\ pyrid.}$= 1.8 Hz, $J_{H\text{-}4\ pyrid.\text{-}H\text{-}2\ pyrid.}$= 2.1 Hz, $J_{H\text{-}4\ pyrid.\text{-}H\text{-}5\ pyrid.}$= 8.1 Hz, H-4 pyrid.), 8.80 (dd, 2H, $J_{H\text{-}6\ pyrid.\text{-}H\text{-}4\ pyrid.}$= 1.8 Hz, $J_{H\text{-}6\ pyrid.\text{-}H\text{-}5\ pyrid.}$= 4.8 Hz, H-6 pyrid.), 9.27 (dd, 2H, $J_{H\text{-}2\ pyrid.\text{-}H\text{-}5\ pyrid.}$= 0.9 Hz, $J_{H\text{-}2\ pyrid.\text{-}H\text{-}4\ pyrid.}$= 2.1 Hz, H-2 pyrid.). Anal. Calcd for $C_{28}H_{20}N_6O_4$ (504.5): C, 66.66; H, 4.00; N, 16.66. Found: C, 66.52; H, 3.91; N, 16.59.

F. 1,3-Bis[4-(5-phenyl-1,3,4-ozadizaol-2-yl) phenoxy]propane (56)

Yield 619.9 mg (80%, procedure A); colorless crystals, mp 237-239 °C. IR: 3059, 2959, 2928, 2882, 2781, 1609, 1551, 1493, 1416, 1308, 1250, 1173, 1107, 1065, 1003, 961, 837, 775, 737, 698, 490, 521. ^{1}H NMR (DMSO-d_6) δ 2.26 (br s, 2H, OCH_2CH_2), 4.29 (br s, 4H, OCH_2CH_2), 7.21 (d, 4H, *J*= 8.9 Hz, ArH of C_6H_4O), 7.63 (dd, 6H, *J*= 2.0, 7.5 Hz, ArH of C_6H_5), 8.06 (d, 4H, *J*= 8.9 Hz, ArH of C_6H_4O), 8.09 (m, 4H, ArH of C_6H_5). Anal. Calcd for $C_{31}H_{24}N_4O_4$ (516.6): C, 72.08; H, 5.68; N, 10.85. Found: C, 71.98; H, 5.73; N, 10.84

G. 1,3-Bis[4-[5-(4-methoxyphenyl)-1,3,4-ozadizaol-2-yl]phenoxy]propane (57)

Yield 700.6 mg (81%, procedure A); pale colorless crystals, mp 258-260 °C. IR: 3079, 3017, 2961, 2894, 2839, 1612, 1497, 1416, 1308, 1254, 1173, 1103, 1069, 1007, 961, 837, 741, 702, 671, 625, 517. ^{1}H NMR (DMSO-d_6) δ 2.27 (quint, 2H, *J*= 6.2 Hz, OCH_2CH_2), 3.87 (s, 6H, OCH_3), 4.30 (t, 4H, *J*= 6.2 Hz, OCH_2CH_2), 7.16 (d, 4H, *J*= 8.7 Hz, ArH), 7.20 (d, 4H, *J*= 8.7 Hz, ArH), 8.04 (d, 8H, *J*= 8.7 Hz, ArH). Anal. Calcd for $C_{33}H_{28}N_4O_6$ (576.6): C, 68.74; H, 4.89; N, 9.72. Found: C, 68.69; H, 4.90; N, 9.69.

H. 1,3-Bis[4-[5-(4-chlorophenyl)-1,3,4-ozadizaol-2-yl]phenoxy]propane (58)

Yield 535.7 mg (61%, procedure A), 579.7 mg (66%, procedure B); pale colorless crystals, mp 222-224 °C (dec). IR: 3071, 2955, 2882, 1609, 1541, 1497, 1469, 1419, 1396, 1308, 1250, 1173, 1092, 1053, 1011, 961, 837, 745, 637, 521. ^{1}H NMR (DMSO-d_6) δ 2.25 (quint, 2H, *J*= 6.3 Hz, OCH_2CH_2), 4.25 (t, 4H, *J*= 6.3 Hz, OCH_2CH_2), 7.18 (d, 4H, *J*= 8.5 Hz, ArH), 7.19 (d, 4H, *J*= 8.5 Hz, ArH), 8.04 (d, 4H, *J*= 8. 5 Hz, ArH), 8.12 (d, 4H, *J*= 8.5 Hz, ArH). Anal. Calcd for $C_{31}H_{22}Cl_2N_4O_4$ (585.5): C, 63.60; H, 3.79; N, 9.57. Found: C, 63.56; H, 3.83; N, 9.64.

I. 1,3-Bis[4-[5-(4-nitrophenyl)-1,3,4-ozadizaol-2-yl]phenoxy]propane (59)

Yield 691.5 mg (76%, procedure A), 673.3 mg (74%, procedure B); pale yellow crystals, mp 226-228 °C (dec). IR: 3074, 2951, 2882, 1609, 1555, 1524, 1493, 1466, 1420, 1396, 1342, 1308, 1250, 1173, 1103, 1053, 1007, 964, 837, 764, 741, 710, 652, 525. ^{1}H NMR (DMSO-d_6) δ 2.24 (quint, 2H, *J*= 6.2 Hz, OCH_2CH_2), 4.26 (t, 4H, *J*= 6.2 Hz, OCH_2CH_2), 7.20 (d, 4H, *J*= 8.5 Hz, ArH), 8.07 (d, 4H, *J*= 8.5 Hz, ArH), 8.36 (d, 4H, *J*= 8.5 Hz, ArH), 8.41 (d, 4H, *J*= 8.5 Hz, ArH). Anal. Calcd for $C_{31}H_{22}N_6O_8$ (606.6): C, 61.39; H, 3.66; N, 13.86. Found: C, 61.42; H, 3.65; N, 13.95.

J. 1,3-Bis[4-[5-(3-pyridyl)-1,3,4-ozadizaol-2-yl]phenoxy]propane (60)

Yield 443.3 mg (57%, procedure A); pale yellow crystals, mp 253-255 °C. IR: 3067, 2972, 2932, 2882, 1609, 1547, 1497, 1466, 1412, 1304, 1254, 1177, 1115, 1053, 1007, 961, 837, 741, 702, 664, 621, 525. ^{1}H NMR (DMSO-d_6) δ 2.28 (quint, 2H, *J*= 6.2 Hz, OCH_2CH_2), 4.31 (t, 4H, *J*= 6.2 Hz, OCH_2CH_2), 7.22 (d, 4H, *J*= 9.0 Hz, ArH of C_6H_4O), 7.65 (ddd, 2H, $J_{H\text{-}5\ pyrid.\text{-}H\text{-}2\ pyrid.}$= 0.9 Hz $J_{H\text{-}5\ pyrid.\text{-}H\text{-}6\ pyrid.}$= 4.8 Hz, $J_{H\text{-}5\ pyrid.\text{-}H\text{-}4\ pyrid.}$= 8.1 Hz, H-5 pyrid.), 8.09 (d, 4H, *J*= 9.0 Hz, ArH of C_6H_4O), 8.46 (td, 2H, $J_{H\text{-}4\ pyrid.\text{-}H\text{-}6\ pyrid.}$= 1.8 Hz, $J_{H\text{-}4\ pyrid.\text{-}H\text{-}2\ pyrid.}$= 2.1 Hz, $J_{H\text{-}4\ pyrid.\text{-}H\text{-}5\ pyrid.}$= 8.1 Hz, H-4 pyrid.), 8.81 (dd, 2H, $J_{H\text{-}6\ pyrid.\text{-}H\text{-}4\ pyrid.}$= 1.8 Hz, $J_{H\text{-}6\ pyrid.\text{-}H\text{-}5\ pyrid.}$= 4.8 Hz, H-6 pyrid.), 9.28 (dd, 2H, $J_{H\text{-}2\ pyrid.\text{-}H\text{-}5\ pyrid.}$= 0.9 Hz, $J_{H\text{-}2\ pyrid.\text{-}H\text{-}4\ pyrid.}$= 2.1 Hz, H-2 pyrid.). Anal. Calcd for $C_{29}H_{22}N_6O_4$ (518.5): C, 67.17; H, 4.28; N, 16.21. Found: C, 61.24; H, 4.22; N, 16.17.

K. 1,4-Bis[4-(5-phenyl-1,3,4-ozadizaol-2-yl) phenoxy]butane (61)

Yield 660.6 mg (83%, procedure A); colorless crystals, mp 198-200 °C. IR: 3067, 2947, 2878, 1612, 1551, 1489, 1412, 1304, 1254, 1177, 1107, 1065, 1003, 968, 930, 833, 775, 737, 698, 525, 486. ^{1}H

NMR (DMSO-d_6) δ 1.96 (quint, 4H, *J*= 5.4 Hz, OCH_2CH_2), 4.20 (t, 4H, *J*= 5.4 Hz, OCH_2CH_2), 7.18 (d, 4H, *J*= 8.9 Hz, ArH of C_6H_4O), 7.63 (dd, 6H, *J*= 2.0, 7.5 Hz, ArH of C_6H_5), 8.06 (d, 4H, *J*= 8.9 Hz, ArH of C_6H_4O), 8.11 (m, 4H, ArH of C_6H_5). Anal. Calcd for $C_{32}H_{26}N_4O_4$ (530.6): C, 72.44; H, 4.94; N, 10.56. Found: C, 72.47; H, 4.84; N, 10.42.

L. 1,4-Bis[4-[5-(4-methoxyphenyl)-1,3,4-ozadizaol-2-yl]phenoxy]butane (62)

Yield 682.1 mg (77%, procedure A); colorless crystals, mp 235-237 °C. IR: 3056, 2951, 2885, 2843, 1612, 1551, 1493, 1412, 1308, 1254, 1177, 1111, 1069, 1015, 964, 833, 802, 745, 702, 671, 613, 517, 467, 417. ^{1}H NMR (DMSO-d_6) δ 1.95 (quint, 4H, *J*= 5.3 Hz, OCH_2CH_2), 3.87 (s, 6H, OCH_3), 4.19 (t, 4H, *J*= 5.3 Hz, OCH_2CH_2), 7.16 (d, 4H, *J*= 8.9 Hz, ArH), 7.17 (d, 4H, *J*= 8.6 Hz, ArH), 8.035 (d, 4H, *J*= 8.9 Hz, ArH), 8.041 (d, 4H, *J*= 8.6 Hz, ArH). Anal. Calcd for $C_{34}H_{30}N_4O_6$ (590.6): C, 69.14; H, 5.12; N, 9.49. Found: C, 69.09; H, 4.90; N, 9.58.

M. 1,4-Bis[4-[5-(4-chlorophenyl)-1,3,4-ozadizaol-2-yl]phenoxy]butane (63)

Yield 764.4 mg (85%, procedure A), 737.4 mg (82%, procedure B); colorless crystals, mp 238-240 °C (dec). IR: 3074, 2951, 2878, 2781, 1609, 1497, 1423, 1396, 1308, 1254, 1177, 1092, 1045, 1011, 972, 914, 837, 745, 702, 671, 640, 590, 521, 421. ^{1}H NMR (DMSO-d_6) δ 1.94 (quint, 4H, *J*= 5.4 Hz, OCH_2CH_2), 4.18 (t, 4H, *J*= 5.4 Hz, OCH_2CH_2), 7.16 (d, 4H, *J*= 8.6 Hz, ArH), 7.17 (d, 4H, *J*= 8.6 Hz, ArH), 8.05 (d, 4H, *J*= 8. 6 Hz, ArH), 8.12 (d, 4H, *J*= 8.6 Hz, ArH). Anal. Calcd for $C_{32}H_{24}Cl_2N_4O_4$ (599.5): C, 64.12; H, 4.04; N, 9.35. Found: C, 64.09; H, 4.00; N, 9.46.

N. 1,4-Bis[4-[5-(4-nitrophenyl)-1,3,4-ozadizaol-2-yl]phenoxy]butane (64)

Yield 763.3 mg (82%, procedure A); pale yellow crystals, mp 258-260 °C (dec). IR: 3073, 2955, 2878, 1609, 1524, 1493, 1423, 1342, 1308, 1254, 1177, 1107, 1065, 1007, 841, 741, 706, 667, 521. ^{1}H NMR (DMSO-d_6) δ 1.95 (br s, 4H, OCH_2CH_2), 4.20 (br s, 4H, *J*= OCH_2CH_2), 7.19 (d, 4H, *J*= 8.6 Hz, ArH), 8.09 (d, 4H, *J*= 8.6 Hz, ArH), 8.36 (d, 4H, *J*= 8.6 Hz, ArH), 8.43 (d, 4H, *J*= 8.6 Hz, ArH). Anal. Calcd for $C_{32}H_{24}N_6O_8$ (620.6): C, 61.93; H, 3.90; N, 13.54. Found: C, 61.92; H, 3.77; N, 13.66.

O. 1,4-Bis[4-[5-(3-pyridyl)-1,3,4-ozadizaol-2-yl]phenoxy]butane (65)

Yield 647.1 mg (81%, procedure A); pale yellow crystals, mp 223-225 °C. IR: 3063, 2928, 2870, 2778,1609, 1493, 1416, 1308, 1250, 1173, 1111, 1049, 1015, 972, 833, 741, 706, 652, 621, 521. ^{1}H NMR (DMSO-d_6) δ 1.96 (quint, 4H, *J*= 5.6 Hz, OCH_2CH_2), 4.19 (t, 4H, *J*= 5.6 Hz, OCH_2CH_2), 7.19 (d, 4H, *J*= 9.0 Hz, ArH), 7.65 (ddd, 2H, $J_{\text{H-5 pyrid.-H-2 pyrid.}}$= 0.9 Hz $J_{\text{H-5 pyrid.-H-6 pyrid.}}$= 4.8 Hz, $J_{\text{H-5 pyrid.-H-4 pyrid.}}$= 8.1 Hz, H-5 pyrid.), 8.08 (d, 4H, *J*= 9.0 Hz, ArH), 8.47 (ddd, 2H, $J_{\text{H-4 pyrid.-H-6 pyrid.}}$= 1.8 Hz, $J_{\text{H-4 pyrid.-H-2 pyrid.}}$= 2.1 Hz, $J_{\text{H-4 pyrid.-H-5 pyrid.}}$= 8.1 Hz, H-4 pyrid.), 8.81 (dd, 2H, $J_{\text{H-6 pyrid.-H-4 pyrid.}}$= 1.8 Hz, $J_{\text{H-6 pyrid.-H-5 pyrid.}}$= 4.8 Hz, H-6 pyrid.), 9.28 (dd, 2H, $J_{\text{H-2 pyrid.-H-5 pyrid.}}$= 0.9 Hz, $J_{\text{H-2 pyrid.-H-4 pyrid.}}$= 2.1 Hz, H-2 pyrid.). Anal. Calcd for $C_{30}H_{24}N_6O_4$ (532.6): C, 67.66; H, 4.54; N, 15.78. Found: C, 67.53; H, 4.61; N, 15.79.

Antimicrobial activity

Antimicrobial screening of compounds **(8)**, **(11)**, **(32)**, **(34)**, **(38)**, **(41)**, **(44)**, **(50)**, **(62)** was carried out using the diffusion agar technique[62]. 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, **(8)**, **(11)**, **(32)**, **(34)**, **(38)**, **(41)**, **(44)**, **(50)**, **(62)** and standard antimicrobial agents (Chloramphenicol and Terbinafin were used as standard antibacterial and antifungal agents, repectively) were dissolved in DMF (5 mg/mL). Further dilutions of the compounds and standard drugs were prepared at the required quantities of 5.0, 2.5 and 1.0 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)*), three Gram-negative bacterial strains (*Pseudomonas aeruginosa RCMB 102-002*, *Escherichia coli RCMB 103-001* and *Salmonella typhi RCMB B 008 001*), one yeast strain (*Candida albicans RCMB 005003*) and three fungal 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 (TABLE 1).

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CONCLUSIONS

Many novel 1,ω-bis/ (carboxylic acids), (esters), (hydrazides), (hydrazones), (1,3,4-oxadiazoles) and (1,3,4-thiadiazoles) were synthesized and their structure was assigned based on analytical and spectral data. Some selected compounds were screened for their antimicrobial activity against different strains of Gram-positive bacteria (*Bacillus subtilis* and *Staphylococcus aureus*), Gram-negative bacteria *(Pseudomonas aeruginosa*, *Escherichia coli*, *Salmonella typhi*), yeast (*Candida albicans*) and fungi (*Aspergillus fumigatus, Penicillium italicum* and *Syncephalastrum racemosum*). and exhibited promising antimicrobial activity. Compounds **(11)**, **(32)**, **(34)**, **(38)** exhibited higher inhibitory effect against some test organisms, when compared to commersial standard antimicrobial agents (at concentration 5.0 mg/mL).

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