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Original article

Efficient synthesis of novel 1,2,4-triazole fused acyclic and 21–28 membered macrocyclic and/or lariat macrocyclic oxaazathia crown compounds with potential antimicrobial activity

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ABSTRACT

Versatile simple efficient routes with good to excellent yields towards different functionalized 1,ω-bis (1,2,4-triazoles), 21–28 membered 1,2,4-triazole fused macrocyclic and/or lariat macrocyclic oxaazathia crown Schiff bases and/or amines have been investigated. Antimicrobial screening of some selected compounds revealed different inhibitory effects against *Aspergillus fumigatus RCMB 002008* (*1*), *Penicillium italicum RCMB 001018* (*1*), *Syncephalastrum racemosum RCMB 016001 Candida albicans RCMB 005003*, *Staphylococcus aureus RCMB 106-001* (*1*), *Pseudomonas aeruginosa RCMB 102-002*, *Bacillus subtilis RCMB 101-001* and *Escherichia coli RCMB 103-001*.

1. Introduction

1,2,4-Tiazole moiety appears frequently in the structure of various natural products [1] and the synthesis of compounds incorporating this moiety has attracted widespread attention of chemists as well as biologists, mainly due to their diverse biological activities in pharmaceutical and agrochemical fields [2–18]. A large variety 1,2,4-triazole derivatives possess antibacterial [2,3], antifungal [2,4], antimycobacterial [5,10], antiviral [6], anti-inflammatory [7], anticonvulsant [8], antidepressant [9], antitubercular [10], antitumoral [11], antihypertensive [12], analgesic [13], enzyme inhibitor [14], hypoglycemic [15], sedative, hypnotic [16], antiparasitic, herbicidal, insecticidal and plant growth activities [17]. Thus, several potent drugs possessing triazole nucleus have been applied in medicine, like, Alprazolam (anxiolytic agent, tranquilizer), Anastrozole, Letrozole, Vorozole (antineoplastics, nonsteroidal competitive aromatase inhibitors), Estazolam (hypnotic, sedative, tranquilizer), Etoperidone (antidepressant), Fluconazole, Itraconazole, Terconazole (antifungal agents), Ribavirin (antiviral agent), Benatradin (diuretic), Rilmazafon (hypnotic, anxiolytic, used in the case of neurotic insomnia), Nefazodone (antidepressant, 5-HT_2 A-antagonist), Rizatriptan (antimigraine agent), Trapidil (hypotensive),Trazodone (antidepressant, anxiolytic, selectively inhibits central serotonin uptake) and Triazolam (sedative and hypnotic) [18].

Schiff bases are considered as a very important class of organic compounds which have wide applications in many biological aspects [19]. Many Schiff bases containing 1,2,4-triaole moiety exhibit antibacterial, antifungal [20] and antitumoral activities [21]. Metal complexes of some Schiff bases are used as model molecules for biological oxygen carrier systems [22]. Transition metal complexes of tetradentate Schiff base ligands find applications as model analogues of certain metal enzymes [23].

Mixed *N,O,S*-donor crowns form an interesting class of compounds, which have found use as selective extractants for soft metal cations [24] and as models for the active sites of some enzymes [25].

Pendant arm macrocycles have also attracted considerable attention, because of their unique coordination and structural properties [26] and their roles in bioinorganic chemistry as models of biomolecules and in modern chemical techniques such as magnetic resonance imaging [27].

Encouraged by these facts and in continuation of an ongoing program of research on the synthesis of some biologically active compounds [28–42] as well as the synthesis of macrocyclic crown compounds [43] the current work reports the synthesis and antimicrobial activity of some novel 1,2,4-triazole fused acyclic, macrocyclic and lariat macrocyclic oxaazathia crown Schiff bases and crown bis(amines).

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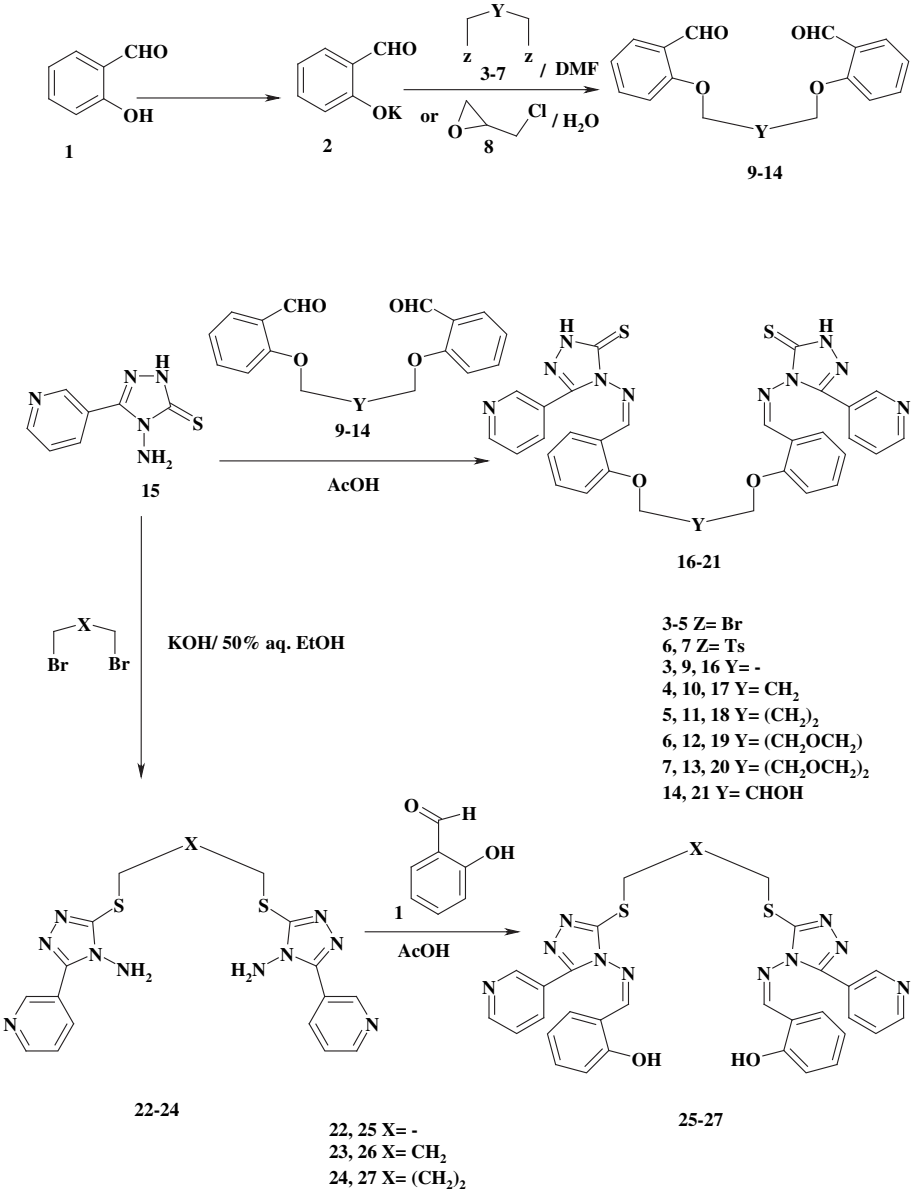
2. Results and discussion

2.1. Synthesis

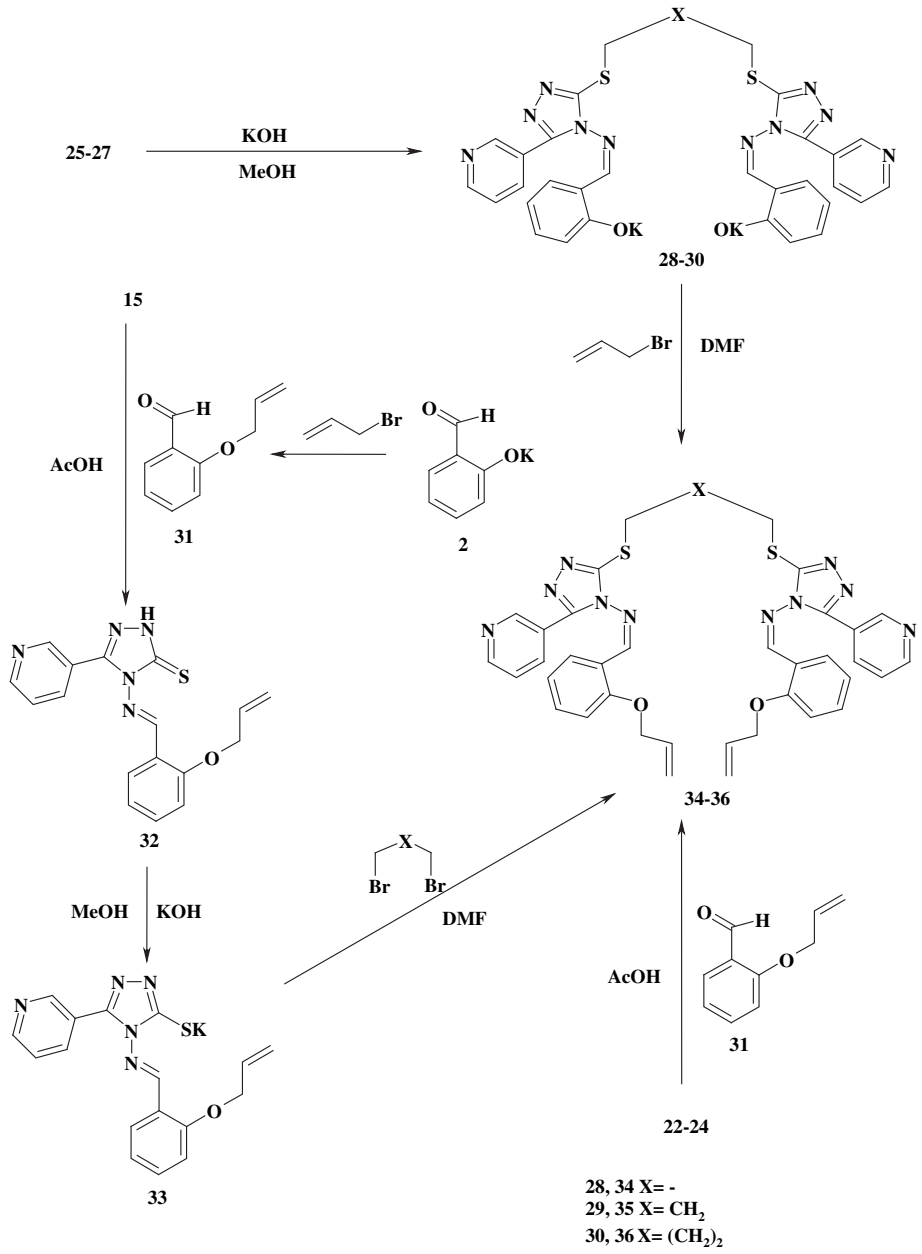
The precursors 1,ω-bisaldehydes **9**–**14** (Scheme 1) needed for the titled synthesis were synthesized starting with salislaldehyde. Thus, the latter compound was converted into its potassium salt **2**, which was then reacted with the appropriate 1,ω-bis functionalized alkanes **3**–**7**/or epichlorohydrin **8** to afford the corresponding 1,ω-bisaldehydes **9**–**13**/or **14**. Condensation of 5-pyridin-3-yl-4*H*-1,2,4-[triazole]-3-thione (**15**) with the appropriate 1,ω-bis(aldehyde) **9**–**14** gave the corresponding 1,ω-bis{[[5-(pyridin-3-yl)-3-thioxo-2,4-dihydro-[1,2,4]triazol-4-ylimino]methyl]phenoxy}alkanes **16**–**21**. On the other hand, reaction of compound **15** with dihaloalkanes in 50% aqueous ethanol containing sodium hydroxide gave the corresponding 1,ω-bis[4-amino-5-(pyridin-3-yl)-1,2,4-triazol-3-ylsulfanyl]alkanes **22**–**24** which were condensed with salisylaldehyde to give the corresponding 1,ω-bis[4-(2-hydroxybenzylideneamino)-5-(pyridin-3-yl)-1,2,4-triazol-3-ylsulfanyl]alkanes **25**–**27**.

Compounds **25**–**27** when converted into their potassium salts **28**–**30** (Scheme 2), followed by reaction with allyl bromide in dry DMF, afforded the corresponding 1,ω-bis[4-(2-allyloxybenzylideneamino)-5-(pyridin-3-yl)-1,2,4-triazol-3-ylsulfanyl]alkanes **34**–**36**. The latter compounds were alternatively prepared via condensation of compound **15** with 2-allyloxy-benzaldehyde (**31**) (obtained from reaction of the potassium salt **2** with allyl bromide) in refluxing acetic acid to give the corresponding 4-(2-allyloxybenzylideneamino)-5-(pyridin-3-yl)-2,4-dihydro-[1,2,4]-triazole-3-thione (**32**) followed by its conversion to the potassium salt **33** then reaction with dihaloalkanes. A third alternative route to prepare compounds **34**–**36** was achieved via condensation of compounds **22**–**24** with 2-allyloxybenzaldehyde **31** in refluxing acetic acid.

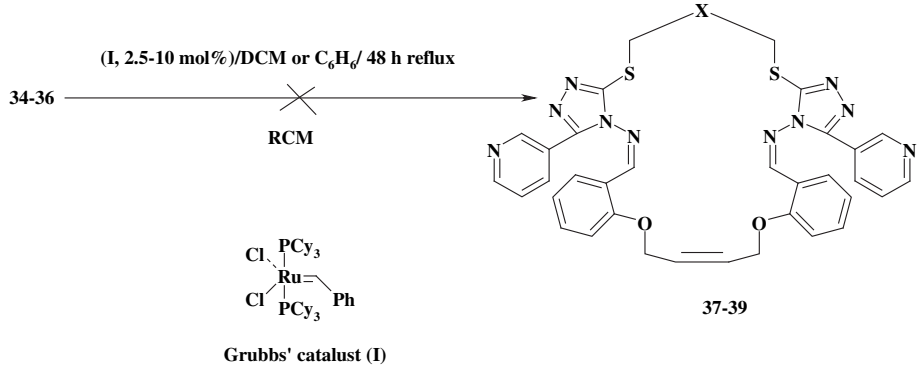
Compounds **16**–**24**, **28**–**30** and **34**–**36** were investigated as useful precursors for the synthesis of versatile 1,2,4-triazole fused macrocyclic and lariat macrocyclic oxaazathia crown compounds. Recently, ring clothing metathesis (RCM) [43] has found increasing application in the synthesis of macrocyclic compounds. Unfortunately, application of RCM on the dienes **34**–**36** (Scheme 3), using



Scheme 1. Versatile efficient synthetic routes towards novel 1,2,4-triazole fused acyclic azathia and/or oxaazathia crown compounds.



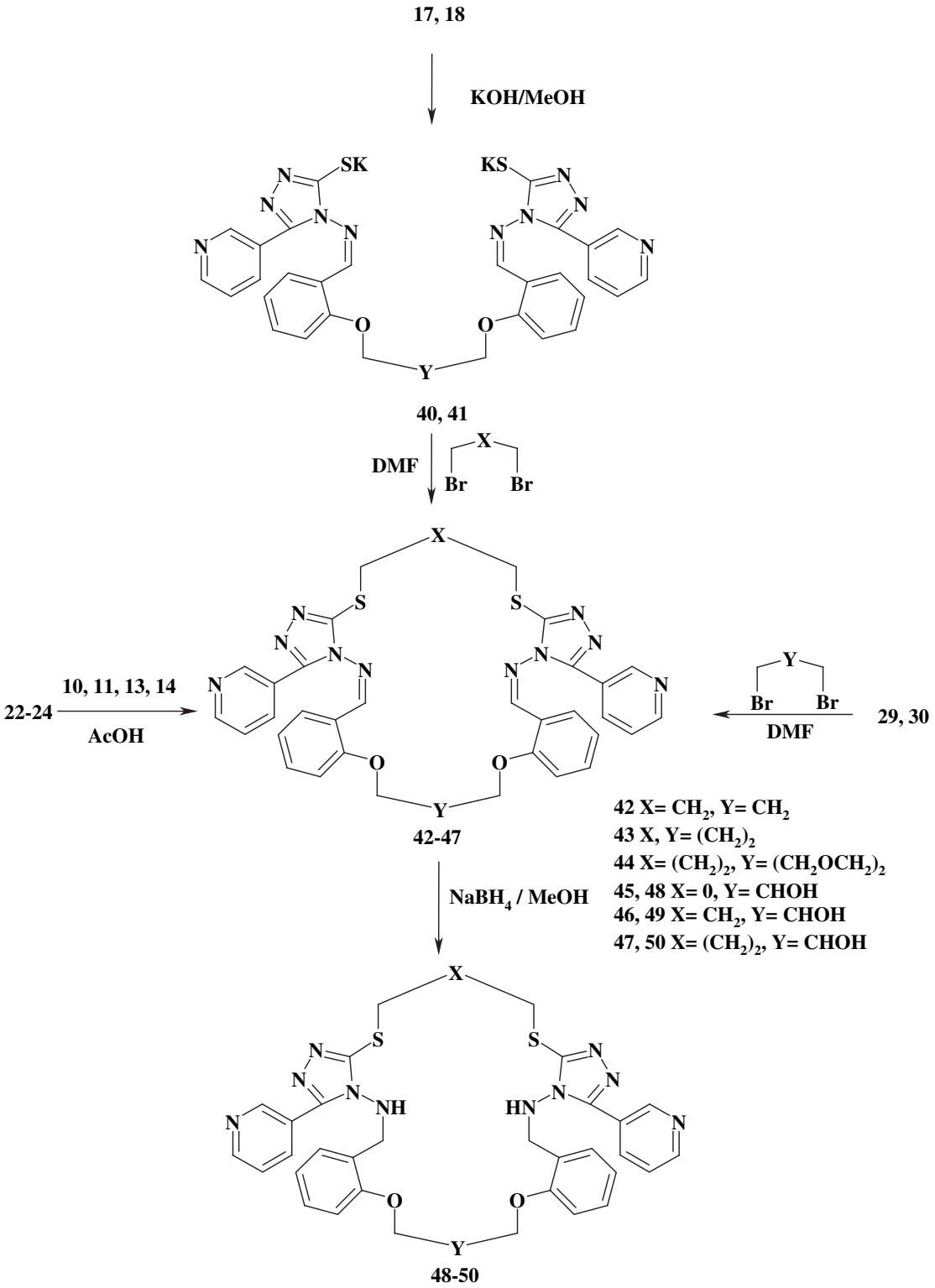
Scheme 2. Versatile efficient synthetic routes towards 1,2,4-triazole fused acyclic oxaazathia crown 1,ω-dienes.



Scheme 3. Application of RCM on the 1,ω-dienes **34**–**36**, using Gubbs' Catalyst (I), failed to afford the expected oxaazathia macrocyclic Schiff bases **37**–**39**.

Grubbs' catalyst (I), at different molar ratios (2.5–10 mol%), in different refluxing solvents (CH_2Cl_2 and benzene), did not afford the expected macrocyclic Schiff bases **37**–**39**.

Scheme 4 outlines three successful efficient synthetic routes towards the desired 1,2,4-triazole fused macrocyclic and lariat macrocyclic oxaazathia crown compounds **42**–**47**. The first route is conversion of compounds **17** and **18** into their potaasium salts **40** and **41** followed by their reaction with the appropriate dihalo compounds to give the corresponding macrocyclic Schiff bases **42** and **43**, respectively. The second route is reaction of compounds **29** and **30** with the appropriate dihalo compounds to give the corresponding macrocycles **42** and **43**, respectively. The third route is condensation of the 1,ω-bis(amines) **22**–**24** with 1,ω-bis(aldehydes) **10**, **11**, **13**, **14** to give the corresponding macrocycles **42**–**47**.



Scheme 4. Versatile efficient synthetic routes towards novel 21–28 membered macrocylic and/or lariat macrocyclic crown compounds.

Table 1
Antimicrobial Activity of compounds **15**, **17**–**25**, **43**, **44**, **46**, **47** and **49** compared to standard antimicrobial agents.

Test Organisms	Compound								
	Compd **15**[a]			Compd **17**[a]			Compd **18**[a]		
	Concentration (mg/mL)								
	1.0	2.5	5.0	1.0	2.5	5.0	1.0	2.5	5.0
Aspergillus fumigatus	0	0	0	0	0	0	0	0	0
Penicillium italicum	0	0	+	0	0	0	+	+	+
Syncephalastrum racemosum	0	0	0	0	+	+	0	+	+
Candida albicans	0	0	0	0	0	0	0	0	+
Staphylococcus aureus	0	0	0	0	+	+	0	0	+
Pseudomonas aeruginosa	0	0	0	0	0	0	0	+	+
Bacillus subtilis	0	0	0	+	+	+	0	0	0
Escherichia coli	0	0	+	0	0	0	0	0	0

Test Organisms	Compd **19**[a]			Compd **20**[a]			Compd **21**[a]		
	Concentration (mg/mL)								
	1.0	2.5	5.0	1.0	2.5	5.0	1.0	2.5	5.0
Aspergillus fumigatus	0	+	+	0	0	0	0	0	+ (250)[c]
Penicillium italicum	+	+	+	+	+	++	++	++	++ (250)[c]
Syncephalastrum racemosum	0	0	+	0	0	0	0	+	+ (250)[c]
Candida albicans	0	0	0	0	0	+	0	0	0
Staphylococcus aureus	0	0	0	0	0	+	0	0	0
Pseudomonas aeruginosa	0	0	0	0	0	0	0	0	0
Bacillus subtilis	+	+	+	0	0	0	+	+	++ (250)[c]
Escherichia coli	0	0	0	0	0	0	0	+	+ (250)[c]

Test Organisms	Compd **22**[a]			Compd **23**[a]			Compd **24**[a]		
	Concentration (mg/mL)								
	1.0	2.5	5.0	1.0	2.5	5.0	1.0	2.5	5.0
Aspergillus fumigatus	0	0	0	0	+	+	0	0	0
Penicillium italicum	0	+	+	0	0	0	0	0	0
Syncephalastrum racemosum	0	0	0	0	0	+	+	+	+
Candida albicans	+	+	+	0	0	+	0	0	0
Staphylococcus aureus	0	0	+	0	0	0	0	+	+
Pseudomonas aeruginosa	0	0	0	0	0	0	0	0	0
Bacillus subtilis	0	0	0	0	0	0	0	+	+
Escherichia coli	0	0	+	0	0	0	0	0	0

Test Organisms	Compd **25**[a]			Compd **43**[a]			Compd **44**[a]		
	Concentration (mg/mL)								
	1.0	2.5	5.0	1.0	2.5	5.0	1.0	2.5	5.0
Aspergillus fumigatus	0	0	0	0	0	0	0	0	0
Penicillium italicum	0	0	+	0	0	+ (250)[c]	0	0	0
Syncephalastrum racemosum	0	+	+	0	0	0	0	0	+
Candida albicans	0	0	0	0	+	+ (250)[c]	0	0	0
Staphylococcus aureus	0	0	0	+	+	+ (250)[c]	0	0	+
Pseudomonas aeruginosa	0	0	0	0	0	+ (250)[c]	0	+	+
Bacillus subtilis	0	0	+	0	0	0	0	0	0
Escherichia coli	0	0	0	+	+	+ (250)[c]	0	+	+

Test Organisms	Compd **46**[a]			Compd **47**[a]			Compd **49**[a]		
	Concentration (mg/mL)								
	1.0	2.5	5.0	1.0	2.5	5.0	1.0	2.5	5.0
Aspergillus fumigatus	0	0	0	0	0	0	0	0	0
Penicillium italicum	0	+	+	0	0	0	0	0	0
Syncephalastrum racemosum	0	+	+	0	0	0	0	0	0
Candida albicans	0	+	+	0	0	0	0	0	0
Staphylococcus aureus	0	0	0	0	0	+	0	0	0
Pseudomonas aeruginosa	0	0	0	0	0	0	0	0	0
Bacillus subtilis	+	+	++	+	+	+	+	++	++
Escherichia coli	0	0	0	0	0	0	0	0	0

Test Organisms	**St.**[b]		
	Concentration (mg/mL)		
	1.0	2.5	5.0
Aspergillus fumigatus	++	+++	+++
Penicillium italicum	++	+++	+++
Syncephalastrum racemosum	+++	+++	+++
Candida albicans	++	++	++
Staphylococcus aureus	++	++	++

(*continued on next page*)

Table 1 (*continued*)

Test Organisms	**St.**[b]		
	Concentration (mg/mL)		
	1.0	2.5	5.0
Pseudomonas aeruginosa	++	+++	+++
Bacillus subtilis	++	+++	+++
Escherichia 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 = no inhibition detected.

[a] 100 μL of each concentration was tested (5.0, 2.5, 1.0 mg/mL); 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.

[c] MIC values are given in brackets MIC (μg/mL) = minimum inhibitory concentration, i.e., lowest concentration to completely inhibit microbial growth.

Reduction of compounds **45**–**47** with sodium borohydride in refluxing methanol proceeded smoothly to give the macrocyclic bis (amines) **48**–**50**.

2.2. Antimicrobial activity

Compounds **15**, **17**–**25**, **43**, **44**, **46**, **47** and **49** 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*)), two Gram-negative bacterial strains (*Pseudomonas aeruginosa RCMB 102-002* and *Escherichia coli RCMB 103-001*), one yeast (*Candida albicans RCMB 005003*) and three fungal strains (*Aspergillus fumigatus RCMB 002008* (*1*), *Penicillium italicum RCMB 001018* (*1*) and *Syncephalastrum racemosum RCMB 016001*). The screening results (Table 1) indicated that all the tested compounds exhibited different inhibitory effects against different test organisms. Compound **15** (at concentration 5.0 mg/mL) showed an inhibitory effect against *Penicillium italicum RCMB 001018* (*1*) and *Escherichia coli RCMB 103-001*. Conversion of this parent triazole into the corresponding acyclic 1,ω-bis(triazoles) **17**–**25**/macrocyclic crown compounds **43**, **44**/or lariat macrocycles **46**, **47**, **49** enhanced the inhibitory effect against one or more type of the test organisms. Thus, compared to compound **15**, compounds **19**, **21**, **23** (at concentrations 2.5–5.0 mg/mL) showed higher inhibitory effect against *Aspergillus fumigatus RCMB 002008* (*1*), compounds **18**, **19**–**22**, **46** (at concentrations 1.0–5.0 mg/mL) showed higher inhibitory effect against *Penicillium italicum RCMB 001018* (*1*), compounds **17**–**19**, **21**, **23**–**25**, **44**, **46** (at concentrations 1–5.0 mg/mL) showed higher inhibitory effect against *Syncephalastrum racemosum RCMB 016001*, compounds **18**, **20**, **22**, **23**, **43**, **46** (at concentrations 1.0–5.0 mg/mL) showed higher inhibitory effect against *Candida albicans RCMB 005003*, compounds **17**, **18**, **20**, **22**, **24**, **43**, **44**, **47** (at concentrations 1.0–5.0 mg/mL) showed higher inhibitory effect against *Staphylococcus aureus RCMB 106-001* (*1*), compounds **18**, **43**, **44** (at concentrations 2.5–5.0 mg/mL) showed higher inhibitory effect against *Pseudomonas aeruginosa RCMB 102-002*, compounds **17**, **19**, **21**, **24**, **25**, **46**, **47**, **49** (at concentrations 1–5.0 mg/mL) showed higher inhibitory effect against *Bacillus subtilis RCMB 101-001*, compounds **21**, **43**, **44** showed higher inhibitory effect against *Escherichia coli RCMB 103-001* (at concentrations 1.0–2.5 mg/mL). On the other hand, compounds **17**, **23**, **24**, **44**, **47**, **49** (at concentration 5.0 mg/mL) exhibited lower inhibitory effect against *Penicillium italicum RCMB 001018* (*1*), compounds **17**–**20**, **23**–**25**, **46**, **47**, **49** (at concentration 5.0 mg/mL) exhibited lower inhibitory effect against *Escherichia coli RCMB 103-001*, when compared to compound **15**.

The biological screening of the mentioned compounds revealed some similarity between compounds with comparable antimicrobial activity. Thus, compounds **18**, **19**, **20** and **21** are all active against *Penicillium italicum RCMB 001018* (*1*) and all have Schiff base and NHC(S)N moieties in their structure. Compounds **21**, **46**, **47**, **49** are all active against *Bacillus subtilis RCMB 101-001* and all are characterized by the presence of the CHOH group in the spacer between the triazole units. Compounds **17**, **19** are also active against *Bacillus subtilis RCMB 101-001* and both have two OCH_2CH_2 groups in their structure. While compound **22**, having two amino groups, with a short spacer between the triazole units (X = 0), is active against *Candida albicans RCMB 005003*, compound **24**, having the same amino groups, with a longer spacer between the triazole units (X = $(CH_2)_2$), is active against *Syncephalastrum racemosum RCMB 016001*. Compound **43**, with Schiff base motif as well as aliphatic methylene groups (X, Y = $(CH_2)_2$) groups in the spacer between triazole units is active against *Staphylococcus aureus RCMB 106-001* (*1*) and *Escherichia coli RCMB 103-001*.

The minimum inhibitory concentrations (MICs) of compounds **21** and **43** were determined and found to be 250 μg/mL.

3. Experimental

3.1. Synthesis

3.1.1. General

All melting points are uncorrected. IR spectra were recorded in KBr discs using Perkin–Elmer 1430 spectrometer. ^1H and ^{13}C NMR spectra were measured with a Varian Mercury 300 spectrometer (300 MHz ^1H NMR, 75 MHz ^{13}C NMR). Mass spectra were measured on Shimadzu GCMS-QP2010 Plus spectrometer (with an EI ionization mode and 70 eV electronic voltage) and with LCMS using Agilent 1100 series LC/MSD (with an API-ES/APCI ionization mode). Elemental analyses were carried out at the Micro Analytical Center, Cairo University, Giza, Egypt. TLC was performed on Fluka silica gel 60 F_{254} aluminum sheets, and products were detected using 254 nm light. Fluka silica gel 60 (70–230 mesh) was used for column chromatography.

*3.1.1.1. Synthesis of the K-salts **2**, **28**–**30**, **33**, **40**, **41**.* A solution of each of compounds **1**, **25**–**27**, **32**, **17**, **18** (10 mmol) and KOH [0.56 g (10 mmol) for compounds **2**, **32** and 1.12 g (20 mmol) for compounds **25**–**27**, **17**, **18**] in methanol (100 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 × 50 mL), collected and dried. It was then used in the next steps without further purification.

*3.1.1.2. Synthesis of 1,ω-bis(2-formylphenoxy)alkanes **9**–**13**. General procedure.* The K-salt **2** (30 mmol) was dissolved in dry DMF (75 mL) and the appropriate dihalide **3**–**5** (15 mmol)/or bis(tosyl) derivative **6**,**7** (15 mmol) was added. The reaction mixture was heated in water bath at 100 °C for 8–10 h, during which time KCl

was precipitated. Ice and water were added and the product was extracted with DCM (100 mL). The organic extract was washed two times with 10% aqueous KOH solution (2 × 100 mL), then water (3 × 100 mL) and dried (Na_2SO_4). After evaporation of DCM under reduced pressure, compounds **9**–**11** were recrystallized from ethanol while compounds **12** and **13** were obtained as oils and used without further purification.

*3.1.1.2.1. 1,2-Bis(2-formylphenoxy)ethane (**9**).* Yield 1.82 g (45%); colorless crystals, mp 128–130 °C. IR: 3076, 3004, 2934, 2872, 1668, 1600, 1490, 1442, 1390, 1253, 1191, 1160, 1099, 1063, 949, 865, 832, 760, 661. ^{1}H NMR ($CDCl_3$): δ 4.46 (s, 4H, OCH_2CH_2O), 7.00 (dd, 4H, J = 1.8, 7.9 Hz, ArH), 7.49 (dt, 2H, J = 1.8, 7.9 Hz, ArH), 7.74 (dd, 2H, J = 1.8, 7.9 Hz, ArH), 10.35 (s, 2H, CHO). Anal. Calcd for $C_{16}H_{14}O_4$ (270.3): C, 71.10; H, 5.22. Found: C, 70.98; H, 5.24.

*3.1.1.2.2. 1,3-Bis(2-formylphenoxy)propane (**10**).* Yield 3.33 g (78%); colorless crystals, mp 99–100 °C. IR: 3073, 3040, 3014, 2966, 2931, 2870, 2764, 1685, 1599, 1485, 1457, 1391, 1287, 1240, 1190, 1162, 1103, 1053, 1022, 953, 842, 818, 760, 654, 606, 533, 496, 438. ^{1}H NMR ($CDCl_3$): δ 2.42 (quint, 2H, J = 6.0 Hz, OCH_2CH_2), 4.32 (t, 4H, J = 6.0 Hz, OCH_2CH_2), 7.01 (d, 2H, J = 8.1 Hz, ArH), 7.03 (t, 2H, J = 8.1 Hz, ArH), 7.54 (dt, 2H, J = 1.8, 8.1 Hz, ArH), 7.82 (dd, 2H, J = 1.8, 8.1 Hz, ArH), 10.49 (s, 2H, CHO). Anal. Calcd for $C_{17}H_{16}O_4$ (284.3): C, 71.82; H, 5.67. Found: C, 71.66; H, 5.51.

*3.1.1.2.3. 1,4-Bis(2-formylphenoxy)butane (**11**).* Yield 3.04 g (68%); colorless crystals, mp 146–148 °C. IR: 3108, 3076, 3047, 2950, 2877, 2758, 1680, 1651, 1599, 1488, 1458, 1387, 1288, 1239, 1193, 1168, 1104, 1058, 1042, 1002, 950, 868, 842, 810, 757, 654, 603, 524, 440. ^{1}H NMR ($CDCl_3$): δ 2.09 (quint, 4H, J = 2.7 Hz, OCH_2CH_2), 4.18 (t, 4H, J = 2.7 Hz, OCH_2CH_2), 6.98 (d, 2H, J = 8.2 Hz, ArH), 7.02 (t, 2H, J = 8.2 Hz, ArH), 7.53 (dt, 2H, J = 1.8, 8.2 Hz, ArH), 7.81 (dd, 2H, J = 1.8, 8.2 Hz, ArH), 10.49 (s, 2H, CHO). Anal. Calcd for $C_{18}H_{18}O_4$ (298.3): C, 72.47; H, 6.08. Found: C, 72.52; H, 6.12.

*3.1.1.2.4. 1,5-Bis(2-formylphenoxy)-3-oxapentane (**12**).* Yield 3.30 g (70%); colorless oil. IR: 3081, 2872, 2765, 1958, 1685, 1599, 1484, 1454, 1395, 1287, 1244, 1133, 1051, 928, 834, 759, 656, 440. ^{1}H NMR ($CDCl_3$): δ 3.95 (t, 4H, J = 4.6 Hz, OCH_2CH_2O), 4.23 (t, 4H, J = 4.6 Hz, OCH_2CH_2O), 6.95 (d, 2H, J = 8.0 Hz, ArH), 7.00 (t, 2H, J = 8.0 Hz, ArH), 7.48 (dt, 2H, J = 2.0, 8.0 Hz, ArH), 7.77 (dd, 2H, J = 2.0, 8.0 Hz, ArH), 10.45 (s, 2H, CHO). Anal. Calcd for $C_{18}H_{18}O_5$ (314.3): C, 68.78; H, 5.77. Found: C, 68.69; H, 5.88.

*3.1.1.2.5. 1,8-Bis(2-formylphenoxy)-3,6-dioxaoctane (**13**).* Yield 5.27 g (98%); colorless oil. IR: 3075, 2872, 1958, 1685, 1599, 1484, 1456, 1395, 1287, 1244, 1191, 1124, 1052, 929, 834, 761, 657, 606, 531, 441. ^{1}H NMR ($CDCl_3$): δ 3.71 (s, 4H, OCH_2CH_2O), 3.87 (t, 4H, J = 4.6 Hz, OCH_2CH_2O), 4.21 (t, 4H, J = 4.6 Hz, OCH_2CH_2O), 6.97 (m, 4H, ArH), 7.48 (dt, 2H, J = 1.8, 7.5 Hz, ArH), 7.77 (dd, 2H, J = 1.8, 7.5 Hz, ArH), 10.47 (s, 2H, CHO). Anal. Calcd for $C_{20}H_{22}O_6$ (358.4): C, 67.03; H, 6.19. Found: C, 66.94; H, 6.06.

*3.1.1.3. 1,3-Bis(2-formylphenoxy)-2-propanol (**14**).* Potassium salt **2** (100 mmol) was dissolved in boiling water (100 mL). The solution was cooled to 50 °C, epichlorohydrin (50 mmol) was added drop wise with stirring over a period of 3 h. The reaction mixture was stirred at 50 °C for an additional 4 h, cooled to room temperature and acidified with conc. HCl. The formed product was extracted with chloroform (150 mL) and washed with KOH solution (100 mL, 0.1 M) then water (3 × 100 mL). The organic layer was dried (anhydrous Na_2SO_4), the solvent was evaporated under reduced pressure and the formed residue was recrystallized from benzene. The resulting colorless crystals were collected by filtration and dried in a vacuum desiccator over P_4O_{10}. Yield 12.76 g (85%), mp 114 °C. IR: 3470, 3106, 2941, 2877, 2839, 2759, 1679, 1599, 1486, 1274, 1163, 1031, 844, 756, 662. ^{1}H NMR ($CDCl_3$): δ 2.11 (s, 1H, D_2O exchangeable OH), 4.258 (d, 2H, J = 5.7 Hz, OCH_2), 4.263 (d, 2H, J = 4.8 Hz, OCH_2), 4.49 (quint, 1H, J = 5.1 Hz, $CHOH$), 6.96 (d, 2H, J = 7.9 Hz, ArH), 6.97 (t, 2H, J = 7.9 Hz, ArH), 7.47 (m, 2H, ArH), 7.71 (dd, 2H, J = 1.6, 7.9 Hz, ArH), 10.37 (s, 2H, CHO). Anal. Calcd for $C_{17}H_{16}O_5$ (300.3): C, 67.99; H, 5.37. Found: C, 67.83; H, 5.49.

*3.1.1.4. Synthesis of 1,ω-Bis{[[5-(pyridin-3-yl)-3-thioxo-2H-3,4-dihydro-[1,2,4]triazol-4-ylimino]methyl]phenoxy}alkanes **16**–**21**. General procedure.* To a solution of compound **15** (2 mmol) in glacial acetic acid (100 mL), was added the appropriate bis(aldehyde) **9**–**14** (1 mmol) and the reaction mixture was heated at reflux temperature for 2 h. The excess AcOH was evaporated to be about 20 mL and the reaction mixture was left to cool. The product was collected by filtration, washed several times with methanol, dried and recrystallized from DMF/MeOH.

*3.1.1.4.1. 1,2-Bis{[[5-(pyridin-3-yl)-3-thioxo-2H-3,4-dihydro-[1,2,4]triazol-4-ylimino]methyl]phenoxy}ethane (**16**).* Yield 99.3 mg (16%); pale crystals, mp 295–297 °C (dec.). IR: 3424, 3229, 3099, 3068, 3017, 2964, 2927, 2900, 2819, 2756, 1598, 1536, 1489, 1453, 1417, 1360, 1254, 1160, 1109, 1047, 1026, 965, 932, 887, 810, 755, 698, 641, 615, 589, 507, 470. ^{1}H NMR (DMSO-d_6): δ 4.53 (s, 4H, OCH_2CH_2O), 7.03 (t, 2H, J = 7.6 Hz, ArH), 7.29 (d, 2H, J = 7.6 Hz, ArH), 7.51 (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.), 7.54 (dd, 2H, J = 1.2, 7.6 Hz, ArH), 7.82 (dd, 2H, J = 1.2, 7.6 Hz, ArH), 8.18 (td, 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.), 8.68 (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.), 8.98 (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.), 10.17 (s, 2H, CH=N), 14.13 (s, 2H, D_2O exchangeable NH). Anal. Calcd for $C_{30}H_{24}N_{10}O_2S_2$ (620.7): C, 58.05; H, 3.90; N, 22.57; S, 10.33. Found: C, 58.19; H, 4.09; N, 22.44; S, 10.29.

*3.1.1.4.2. 1,3-Bis{[[5-(pyridin-3-yl)-3-thioxo-2H-3,4-dihydro-[1,2,4]triazol-4-ylimino]methyl]phenoxy}propane (**17**).* Yield 399.9 mg (63%); pale crystals, mp 298–300 °C. IR: 3449, 3077, 3046, 3014, 2922, 2884, 2744, 1598, 1534, 1486, 1455, 1418, 1395, 1361, 1294, 1259, 1200, 1160, 1109, 1050, 1027, 993, 966, 887, 855, 809, 753, 698, 644, 617, 585, 536, 504, 467. ^{1}H NMR (DMSO-d_6): δ 2.25 (quint, 2H, J = 5.8 Hz, OCH_2CH_2), 4.38 (t, 4H, J = 5.8, OCH_2CH_2), 7.05 (t, 2H, J = 7.6 Hz, ArH), 7.21 (d, 2H, J = 8.4 Hz, ArH), 7.54 (m, 4H, ArH, H-5 pyrid.), 7.86 (dd, 2H, J = 1.5, 7.8 Hz, ArH), 8.23 (td, 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.), 8.69 (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.), 9.01 (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.), 10.28 (s, 2H, CH=N), 14.28 (s, 2H, D_2O exchangeable NH). Anal. Calcd for $C_{31}H_{26}N_{10}O_2S_2$ (634.7): C, 58.66; H, 4.13; N, 22.07; S, 10.10. Found: C, 58.54; H, 4.09; N, 21.99; S, 10.21.

*3.1.1.4.3. 1,4-Bis{[[5-(pyridin-3-yl)-3-thioxo-2H-3,4-dihydro-[1,2,4]triazol-4-ylimino]methyl]phenoxy}butane (**18**).* Yield 506.1 mg (78%); pale crystals, mp 301–303 °C (dec.). IR: 3423, 3070, 3038, 2928, 2875, 2827, 2675, 1598, 1516, 1486, 1453, 1418, 1355, 1291, 1254, 1193, 1161, 1131, 1106, 1041, 961, 921, 874, 808, 757, 700, 646, 582, 528, 488, 419. ^{1}H NMR (DMSO-d_6): δ 2.01 (s, 4H, OCH_2CH_2), 4.18 (s, 4H, OCH_2CH_2), 7.03 (t, 2H, J = 7.8 Hz, ArH), 7.18 (d, 2H, J = 7.8 Hz, ArH), 7.53 (dt, 2H, J = 1.5, 7.8, ArH), 7.57 (dd, 2H, $J_{\text{H-5 pyrid.–H-6 pyrid.}}$ = 4.8 Hz, $J_{\text{H-5 pyrid.–H-4 pyrid.}}$ = 8.1 Hz, H-5 pyrid.), 7.86 (dd, 2H, J = 1.5, 7.8 Hz, ArH), 8.24 (td, 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.), 8.71 (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.), 9.02 (d, 2H, $J_{\text{H-2 pyrid.–H-4 pyrid.}}$ = 2.1 Hz, H-2 pyrid.), 10.32 (s, 2H, CH=N), 14.24 (br, 2H, D_2O exchangeable NH). Anal. Calcd for $C_{32}H_{28}N_{10}O_2S_2$ (648.8): C, 59.24; H, 4.35; N, 21.59; S, 9.88. Found: C, 59.31; H, 4.29; N, 21.47; S, 9.76.

*3.1.1.4.4. 1,5-Bis{[[5-(pyridin-3-yl)-3-thioxo-2H-3,4-dihydro-[1,2,4]triazol-4-ylimino]methyl]phenoxy}-3-oxapentane (**19**).* Yield 372.3 mg (56%); pale crystals, mp 189–190 (resolidify at 204 °C and

melt again at 307–308 °C). IR: 3417, 3071, 3033, 2924, 2873, 2733, 1598, 1548, 1487, 1450, 1417, 1354, 1291, 1254, 1193, 1162, 1131, 1111, 1046, 959, 923, 875, 810, 755, 700, 648, 584, 524, 484. ^{1}H NMR ($CDCl_3$): δ 4.04 (t, 4H, J = 4.5 Hz, OCH_2CH_2O), 4.25 (t, 4H, J = 4.5 Hz, OCH_2CH_2O), 6.98 (t, 2H, J = 7.8 Hz, ArH), 7.02 (d, 2H, J = 7.8 Hz, ArH), 7.42 (m, 4H, ArH, H-5 pyrid.), 7.94 (dd, 2H, J = 1.5, 7.8 Hz, ArH), 8.26 (td, 2H, $J_{H\text{-}4\ pyrid.–H\text{-}6\ pyrid.}$ = 1.8 Hz, $J_{H\text{-}4\ pyrid.–H\text{-}2\ pyrid.}$ = 2.1 Hz, $J_{H\text{-}4\ pyrid.–H\text{-}5\ pyrid.}$ = 8.1 Hz, H-4 pyrid.), 8.73 (dd, 2H, $J_{H\text{-}6\ pyrid.–H\text{-}4\ pyrid.}$ = 1.8 Hz, $J_{H\text{-}6\ pyrid.–H\text{-}5\ pyrid.}$ = 4.8 Hz, H-6 pyrid.), 9.25 (d, 2H, $J_{H\text{-}2\ pyrid.–H\text{-}5\ pyrid.}$ = 0.9 Hz, H-2 pyrid.), 10.49 (s, 2H, CH=N), 12.73 (br, 2H, D_2O exchangeable NH). Anal. Calcd for $C_{32}H_{28}N_{10}O_3S_2$ (664.8): C, 57.82; H, 4.25; N, 21.07; S, 9.65. Found: C, 57.76; H, 4.36; N, 20.98; S, 9.62.

*3.1.1.4.5. 1,8-Bis{[[5-(pyridin-3-yl)-3-thioxo-2H-3,4-dihydro-[1,2,4]triazol-4-ylimino]methyl]phenoxy}-3,6-dioxaoctane (**20**).* Yield 439.5 mg (62%); pale crystals, mp 191–193 (resolidify at 204 °C and melt again at 263–265 °C). IR: 3447, 3078, 3039, 2924, 2872, 2729, 1597, 1487, 1451, 1418, 1353, 1296, 1253, 1193, 1164, 1105, 1046, 957, 922, 875, 813, 755, 699, 637, 584, 524, 478. ^{1}H NMR ($CDCl_3$): δ 3.77 (s, 4H, OCH_2CH_2O), 3.90 (t, 4H, J = 4.5 Hz, $ArOCH_2$-CH_2O), 4.22 (t, 4H, J = 4.5 Hz, OCH_2CH_2O), 6.97 (t, 2H, J = 7.8 Hz, ArH), 7.00 (d, 2H, J = 7.8 Hz, ArH), 7.43 (m, 4H, ArH, H-5 pyrid.), 7.99 (dd, 2H, J = 1.5, 7.8 Hz, ArH), 8.24 (td, 2H, $J_{H\text{-}4\ pyrid.–H\text{-}6\ pyrid.}$ = 1.8 Hz, $J_{H\text{-}4\ pyrid.–H\text{-}2\ pyrid.}$ = 2.1 Hz, $J_{H\text{-}4\ pyrid.–H\text{-}5\ pyrid.}$ = 8.1 Hz, H-4 pyrid.), 8.70 (dd, 2H, $J_{H\text{-}6\ pyrid.–H\text{-}4\ pyrid.}$ = 1.8 Hz, $J_{H\text{-}6\ pyrid.–H\text{-}5\ pyrid.}$ = 4.8 Hz, H-6 pyrid.), 9.22 (d, 2H, $J_{H\text{-}2\ pyrid.–H\text{-}5\ pyrid.}$ = 0.9 Hz, H-2 pyrid.), 10.50 (s, 2H, CH=N), 11.46 (br, 2H, D_2O exchangeable NH). Anal. Calcd for $C_{34}H_{32}N_{10}O_4S_2$ (708.8): C, 57.61; H, 4.55; N, 19.76; S, 9.05. Found: C, 57.55; H, 4.62; N, 19.61; S, 9.11.

*3.1.1.4.6. 1,3-Bis{[[5-(pyridin-3-yl)-3-thioxo-2H-3,4-dihydro-[1,2,4]triazol-4-ylimino]methyl]phenoxy}propan-2-ol (**21**).* Yield 292.8 mg (45%); pale crystals, mp 188–190 (resolidify at 204 °C and melt again at 294–296 °C). IR: 3381, 3072, 3039, 2927, 2882, 2736, 1598, 1548, 1489, 1450, 1417, 1354, 1291, 1250, 1162, 1108, 1028, 962, 875, 812, 754, 701, 647, 588, 524, 492. ^{1}H NMR ($CDCl_3$): δ 3.47 (s, 1H, D_2O exchangeable CHOH), 4.36 (d, 2H, J = 5.4 Hz, OCH_2), 4.50 (d, 2H, J = 5.1 Hz, OCH_2), 5.54 (quint, 1H, J = 5.1 Hz, C*H*OH), 7.02 (t, 2H, J = 7.5 Hz, ArH), 7.04 (d, 2H, J = 7.5 Hz, ArH), 7.45 (m, 4H, ArH, H-5 pyrid.), 7.91 (td, 2H, J = 1.8, 7.5 Hz, ArH), 8.24 (td, 2H, $J_{H\text{-}4\ pyrid.–H\text{-}6\ pyrid.}$ = 1.8 Hz, $J_{H\text{-}4\ pyrid.–H\text{-}2\ pyrid.}$ = 2.1 Hz, $J_{H\text{-}4\ pyrid.–H\text{-}5\ pyrid.}$ = 8.1 Hz, H-4 pyrid.), 8.72 (dd, 2H, $J_{H\text{-}6\ pyrid.–H\text{-}4\ pyrid.}$ = 1.8 Hz, $J_{H\text{-}6\ pyrid.–H\text{-}5\ pyrid.}$ = 4.8 Hz, H-6 pyrid.), 9.24 (dd, 2H, $J_{H\text{-}2\ pyrid.–H\text{-}5\ pyrid.}$ = 0.9 Hz, $J_{H\text{-}2\ pyrid.–H\text{-}4\ pyrid.}$ = 2.1-Hz, H-2 pyrid.), 10.52 (s, 2H, CH=N), 13.28 (br, 2H, D_2O exchangeable NH). Anal. Calcd for $C_{31}H_{26}N_{10}O_3S_2$ (650.7): C, 57.22; H, 4.03; N, 21.52; S, 9.85. Found: C, 57.31; H, 4.12; N, 21.37; S, 9.76.

*3.1.1.5. Synthesis of 1,ω-bis[4-amino-5-(pyridin-3-yl)-4H-1,2,4-triazol-3-ylsulfanyl]alkanes (**22**–**24**). General procedure.* To a solution of compound **15** (1.93 g, 10 mmol) in aqueous alcoholic NaOH solution [prepared by dissolving NaOH (0.40 g, 10 mmol) in 100 mL 50% aqueous EtOH] was added the appropriate dihalo compound (5 mmol) and the reaction mixture was heated at reflux temperature for 1–3 h, after which time the product is precipitated. The reaction mixture was allowed to cool and the product was collected by filtration, washed with 10% aqueous NaOH solution (2 × 50 mL), water (3 × 100 mL) and MeOH (2 × 10 mL), dried and recrystallized from DMF.

*3.1.1.5.1. 1,2-Bis[4-amino-5-(pyridin-3-yl)-4H-1,2,4-triazol-3-ylsulfanyl]ethane (**22**).* Yield 1.24 g (60%); colorless crystals, mp 230–232 °C. IR: 3308, 3180, 2922, 1629, 1593, 1569, 1480, 1451, 1414, 1394, 1327, 1280, 1253, 1188, 1126, 1019, 968, 813, 703, 620, 595, 439. ^{1}H NMR (DMSO-d_6): δ 3.59 (s, 4H, SCH_2CH_2S), 6.21 (s, 4H, D_2O exchangeable NH_2), 7.57 (ddd, 2H, $J_{H\text{-}5\ pyrid.–H\text{-}2\ pyrid.}$ = 0.9 Hz, $J_{H\text{-}5\ pyrid.–H\text{-}6\ pyrid.}$ = 4.8 Hz, $J_{H\text{-}5\ pyrid.–H\text{-}4\ pyrid.}$ = 8.1 Hz, H-5 pyrid.), 8.37 (td, 2H, $J_{H\text{-}4\ pyrid.–H\text{-}6\ pyrid.}$ = 1.8 Hz, $J_{H\text{-}4\ pyrid.–H\text{-}2\ pyrid.}$ = 2.1 Hz, $J_{H\text{-}4\ pyrid.–H\text{-}5\ pyrid.}$ = 8.1 Hz, H-4 pyrid.), 8.70 (dd, 2H, $J_{H\text{-}6\ pyrid.–H\text{-}4\ pyrid.}$ = 1.8 Hz, $J_{H\text{-}6\ pyrid.–H\text{-}5\ pyrid.}$ = 4.8 Hz, H-6 pyrid.), 9.16 (dd, 2H, $J_{H\text{-}2\ pyrid.–H\text{-}5\ pyrid.}$ = 0.9 Hz, $J_{H\text{-}2\ pyrid.–H\text{-}4\ pyrid.}$ = 2.1 Hz, H-2 pyrid.). Anal. Calcd for $C_{16}H_{16}N_{10}S_2$ (412.5): C, 46.59; H, 3.91; N, 33.96; S, 15.55. Found: C, 46.49; H, 4.00; N, 33.89; S, 15.52.

*3.1.1.5.2. 1,3-Bis[4-amino-5-(pyridin-3-yl)-4H-1,2,4-triazol-3-ylsulfanyl]propane (**23**).* Yield 1.09 g (51%); colorless crystals, mp 230–232 °C. IR: 3305, 3177, 3083, 2953, 2919, 1629, 1592, 1567, 1506, 1479, 1450, 1414, 1393, 1354, 1326, 1279, 1186, 1125, 1100, 1016, 967, 874, 813, 738, 704, 619, 593, 497, 437. ^{1}H NMR (DMSO-d_6): δ 2.17 (quint, 2H, J = 6.9 Hz, SCH_2CH_2), 3.34 (t, 4H, J = 6.9 Hz, SCH_2), 6.19 (s, 4H, D_2O exchangeable NH_2), 7.55 (ddd, 2H, $J_{H\text{-}5\ pyrid.–H\text{-}2\ pyrid.}$ = 0.9 Hz, $J_{H\text{-}5\ pyrid.–H\text{-}6\ pyrid.}$ = 4.8 Hz, $J_{H\text{-}5\ pyrid.–H\text{-}4\ pyrid.}$ = 8.1 Hz, H-5 pyrid.), 8.36 (td, 2H, $J_{H\text{-}4\ pyrid.–H\text{-}6\ pyrid.}$ = 1.8 Hz, $J_{H\text{-}4\ pyrid.–H\text{-}2\ pyrid.}$ = 2.1 Hz, $J_{H\text{-}4\ pyrid.–H\text{-}5\ pyrid.}$ = 8.1 Hz, H-4 pyrid.), 8.68 (dd, 2H, $J_{H\text{-}6\ pyrid.–H\text{-}4\ pyrid.}$ = 1.8 Hz, $J_{H\text{-}6\ pyrid.–H\text{-}5\ pyrid.}$ = 4.8 Hz, H-6 pyrid.), 9.15 (dd, 2H, $J_{H\text{-}2\ pyrid.–H\text{-}5\ pyrid.}$ = 0.9 Hz, $J_{H\text{-}2\ pyrid.–H\text{-}4\ pyrid.}$ = 2.1 Hz, H-2 pyrid.). Anal. Calcd for $C_{17}H_{18}N_{10}S_2$ (426.5): C, 47.87; H, 4.25; N, 32.84; S, 15.03. Found: C, 47.84; H, 4.29; N, 32.97; S, 15.12.

*3.1.1.5.3. 1,4-Bis[4-amino-5-(pyridin-3-yl)-4H-1,2,4-triazol-3-ylsulfanyl]butane (**24**).* Yield 1.52 g (69%); colorless crystals, mp 218–220 °C. IR: 3343, 3172, 2948, 1628, 1582, 1566, 1479, 1450, 1393, 1355, 1313, 1273, 1204, 1130, 1054, 966, 814, 780, 731, 700, 599, 450. ^{1}H NMR (DMSO-d_6): δ 1.89 (quint, 4H, J = 5.7 Hz, SCH_2CH_2), 3.23 (t, 4H, J = 5.7 Hz, SCH_2CH_2), 6.16 (s, 4H, D_2O exchangeable NH_2), 7.55 (ddd, 2H, $J_{H\text{-}5\ pyrid.–H\text{-}2\ pyrid.}$ = 0.9 Hz, $J_{H\text{-}5\ pyrid.–H\text{-}6\ pyrid.}$ = 4.8 Hz, $J_{H\text{-}5\ pyrid.–H\text{-}4\ pyrid.}$ = 8.1 Hz, H-5 pyrid.), 8.34 (qd, 2H, $J_{H\text{-}4\ pyrid.–H\text{-}6\ pyrid.}$ = 1.8 Hz, $J_{H\text{-}4\ pyrid.–H\text{-}2\ pyrid.}$ = 2.1 Hz, $J_{H\text{-}4\ pyrid.–H\text{-}5\ pyrid.}$ = 8.1 Hz, H-4 pyrid.), 8.67 (dd, 2H, $J_{H\text{-}6\ pyrid.–H\text{-}4\ pyrid.}$ = 1.8 Hz, $J_{H\text{-}6\ pyrid.–H\text{-}5\ pyrid.}$ = 4.8 Hz, H-6 pyrid.), 9.13 (dd, 2H, $J_{H\text{-}2\ pyrid.–H\text{-}5\ pyrid.}$ = 0.9 Hz, $J_{H\text{-}2\ pyrid.–H\text{-}4\ pyrid.}$ = 2.1 Hz, H-2 pyrid.). Anal. Calcd for $C_{18}H_{20}N_{10}S_2$ (440.6): C, 49.07; H, 4.58; N, 31.79; S, 14.56. Found: C, 49.14; H, 4.61; N, 31.69; S, 14.43.

*3.1.1.6. Synthesis of 1,ω-bis[4-(2-hydroxybenzylideneamino)-5-(pyridin-3-yl)-4H-1,2,4-triazol-3-ylsulfanyl]alkanes (**25**–**27**). General procedure.* To a solution of each of compounds **22**–**24** (1 mmol) in glacial acetic acid (75 mL) was added salicylaldehyde (**1**) (0.21 mL, 2 mmol). The reaction mixture was heated at reflux temperature for 3 h. The excess solvent was then evaporated to a small volume (about 10 mL) and the reaction mixture was allowed to cool to room temperature. The formed product was collected by filtration, washed with water (3 × 50 mL), followed by MeOH (2 × 10 mL) and recrystallized from acetic acid to give colorless crystals of compounds **25**–**27**.

*3.1.1.6.1. 1,2-Bis[4-(2-hydroxybenzylideneamino)-5-(pyridin-3-yl)-4H-1,2,4-triazol-3-ylsulfanyl]ethane (**25**).* Yield 571 mg (92%); colorless crystals, mp 244–246 °C. IR: 3440 (br), 2929, 1604, 1450, 1267, 1032, 970, 816, 756, 702, 596. ^{1}H NMR (DMSO-d_6): δ 3.59 (s, 4H, SCH_2CH_2), 6.89 (t, 2H, J = 7.8 Hz, ArH), 6.96 (d, 2H, J = 8.4 Hz, ArH), 7.45 (m, 2H, ArH), 7.53 (ddd, 2H, $J_{H\text{-}5\ pyrid.–H\text{-}2\ pyrid.}$ = 0.9 Hz, $J_{H\text{-}5\ pyrid.–H\text{-}6\ pyrid.}$ = 4.8 Hz, $J_{H\text{-}5\ pyrid.–H\text{-}4\ pyrid.}$ = 8.1 Hz, H-5 pyrid.), 7.76 (dd, 2H, J = 1.5, 7.8 Hz, ArH), 8.18 (td, 2H, $J_{H\text{-}4\ pyrid.–H\text{-}6\ pyrid.}$ = 1.8 Hz, $J_{H\text{-}4\ pyrid.–H\text{-}2\ pyrid.}$ = 2.1 Hz, $J_{H\text{-}4\ pyrid.–H\text{-}5\ pyrid.}$ = 8.1 Hz, H-4 pyrid.), 8.67 (d, 2H, $J_{H\text{-}6\ pyrid.–H\text{-}4\ pyrid.}$ = 4.8 Hz, $J_{H\text{-}6\ pyrid.–H\text{-}5\ pyrid.}$ = 4.8 Hz, H-6 pyrid.), 8.96 (s, 2H, CH=N), 8.99 (s, 2H, H-2 pyrid.), 10.57 (s, 2H, D_2O exchangeable OH). Anal. Calcd for $C_{30}H_{24}N_{10}O_2S_2$ (620.7): C, 58.05; H, 3.90; N, 22.57; S, 10.33. Found: C, 57.97; H, 3.88; N, 22.63; S, 10.27.

*3.1.1.6.2. 1,3-Bis[4-(2-hydroxybenzylideneamino)-5-(pyridin-3-yl)-4H-1,2,4-triazol-3-ylsulfanyl]propane (**26**).* Yield 603 mg (95%); colorless crystals, mp 198 °C. IR: 3420, 3059, 2922, 2852, 2714, 1654, 1602, 1571, 1456, 1347, 1307, 1259, 1186, 1154, 1120, 1097, 1027, 969,

887, 840, 811, 755, 701, 623, 590, 552, 475. ^{1}H NMR ($CDCl_3$): δ 2.34 (quint, 2H, J = 6.9 Hz, SCH_2CH_2), 3.45 (t, 4H, J = 6.9 Hz, SCH_2CH_2), 6.99 (t, 2H, J = 7.5 Hz, ArH), 7.05 (d, 2H, J = 8.4 Hz, ArH), 7.42 (m, 6H, ArH, H-5 pyrid.), 8.11 (td, 2H, $J_{H\text{-}4\ pyrid.–H\text{-}6\ pyrid.}$ = 1.8 Hz, $J_{H\text{-}4\ pyrid.–H\text{-}2\ pyrid.}$ = 2.1 Hz, $J_{H\text{-}4\ pyrid.–H\text{-}5\ pyrid.}$ = 8.1 Hz, H-4 pyrid.), 8.65 (dd, 2H, $J_{H\text{-}6\ pyrid.–H\text{-}4\ pyrid.}$ = 1.8 Hz, $J_{H\text{-}6\ pyrid.–H\text{-}5\ pyrid.}$ = 4.8 Hz, H-6 pyrid.), 8.78 (s, 2H, CH=N), 9.04 (d, 2H, $J_{H\text{-}2\ pyrid.–H\text{-}4\ pyrid.}$ = 2.1 Hz, H-2 pyrid.), 10.18 (br s, 2H, D_2O exchangeable OH). Anal. Calcd for $C_{31}H_{26}N_{10}O_2S_2$ (634.7): C, 58.66; H, 4.13; N, 22.07; S, 10.10. Found: C, 58.59; H, 4.17; N, 21.98; S, 10.01.

*3.1.1.6.3. 1,4-Bis[4-(2-hydroxybenzylideneamino)-5-(pyridin-3-yl)-4H-1,2,4-triazol-3-ylsulfanyl]butane (**27**).* Yield 623 mg (96%); colorless crystals, mp 252–253 °C (dec.). IR: 3053, 2930, 2855, 2710, 1602, 1573, 1457, 1375, 1348, 1307, 1261, 1188, 1155, 1121, 1096, 1026, 968, 914, 887, 838, 811, 756, 702, 621, 590, 551, 527, 479. ^{1}H NMR (DMSO-d_6): δ 1.85 (quint, 4H, J = 6.6 Hz, SCH_2CH_2), 3.28 (t, 4H, J = 6.6 Hz, SCH_2), 6.97 (t, 2H, J = 8.1 Hz, ArH), 6.99 (d, 2H, J = 8.1 Hz, ArH), 7.46 (m, 2H, ArH), 7.46 (ddd, 2H, $J_{H\text{-}5\ pyrid.–H\text{-}2\ pyrid.}$ = 0.9 Hz, $J_{H\text{-}5\ pyrid.–H\text{-}6\ pyrid.}$ = 4.8 Hz, $J_{H\text{-}5\ pyrid.–H\text{-}4\ pyrid.}$ = 8.1 Hz, H-5 pyrid.), 7.85 (m, 2H, ArH), 8.23 (td, 2H, $J_{H\text{-}4\ pyrid.–H\text{-}6\ pyrid.}$ = 1.8 Hz, $J_{H\text{-}4\ pyrid.–H\text{-}2\ pyrid.}$ = 2.1 Hz, $J_{H\text{-}4\ pyrid.–H\text{-}5\ pyrid.}$ = 8.1 Hz, H-4 pyrid.), 8.66 (dd, 2H, $J_{H\text{-}6\ pyrid.–H\text{-}4\ pyrid.}$ = 1.8 Hz, $J_{H\text{-}6\ pyrid.–H\text{-}5\ pyrid.}$ = 4.8 Hz, H-6 pyrid.), 8.99 (s, 2H, CH=N), 9.01 (s, 2H, H-2 pyrid.), 10.56 (s, 2H, D_2O exchangeable OH). Anal. Calcd for $C_{32}H_{28}N_{10}O_2S_2$ (648.8): C, 59.24; H, 4.35; N, 21.59; S, 9.88. Found: C, 59.19; H, 4.31; N, 21.63; S, 9.69.

*3.1.1.7. 2-Allyloxy-benzaldehyde (**31**).* A mixture of salicylaldehyde (5 mL, 47.7 mmol), allyl bromide (3.7 mL, 43.7 mmol) and anhydrous K_2CO_3 (7.22 g, 52.2 mmol) in dry acetone (100 mL) was heated at reflux temperature for 9 h. The solid precipitate was filtered off and the solvent was evaporated in vacuo. The remaining oil was dissolved in DCM (150 mL), washed with 10% aqueos KOH solution (2 × 150 mL) then water (3 × 150 mL), dried over anhydrous Na_2SO_4 and the solvent was then removed in vacuo and the remaining oil was purified by column chromatography over silica gel using EtOAc/pet ether (bp 40–60 °C) as an eluent to give 7.09 g (100%; based on allyl bromide) of colorless oil. R_f = 0.96 [EtOAc/pet ether (bp 40–60 °C) 3:2]. IR: 3080, 3040, 3018, 2991, 2923, 2867, 2765, 1688, 1599, 1486, 1456, 1422, 1396, 1363, 1289, 1240, 1192, 1162, 1105, 1068, 1045, 997, 932, 840, 812, 759, 658, 586, 531, 504, 466, 441. ^{1}H NMR ($CDCl_3$): δ 4.63 (td, 2H, J = 1.5, 5.1 Hz, CH_2CH=), 5.31 (dd, 1H, J = 1.5, 10.5 Hz, CH_2=), 5.43 (dd, 1H, J = 1.6, 17.2 Hz, CH_2=), 6.05 (m, 1H, CH=), 6.95 (d, 1H, J = 7.8 Hz, ArH), 6.99 (t, 1H, J = 7.8 Hz, ArH), 7.50 (dt, 1H, J = 1.8, 7.8 Hz, ArH), 7.81 (dd, 1H, J = 1.8, 7.8 Hz, ArH), 10.51 (s, 1H, CHO). Anal. Calcd for $C_{10}H_{10}O_2$ (162.2): C, 74.06; H, 6.21. Found: C, 74.12; H, 6.36.

*3.1.1.8. 4-(2-allyloxybenzylideneamino)-5-(pyridin-3-yl)-2,4-dihydro-[1,2,4]-triazole-3-thione (**32**).* To a solution of compound **15** (1.93 g, 10 mmol) in glacial acetic acid (75 mL) was added 2-allyloxybenzaldehyde (**31**) (1.62 g, 10 mmol). The reaction mixture was heated at reflux temperature for 3 h. The excess AcOH was evaporated to a small volume (about 10 mL) and the reaction mixture was allowed to cool to room temperature. The formed product was collected by filtration, washed with water (3 × 100 mL) followed by MeOH (3 × 10 mL) and recrystallized from AcOH/MeOH to give yellow crystals of compound **32**. Yield 3.07 g (91%). IR: 3448, 3105, 3071, 3022, 2862, 2820, 2700, 1597, 1548, 1515, 1483, 1447, 1415, 1353, 1331, 1297, 1260, 1189, 1163, 1125, 1024, 990, 962, 912, 876, 812, 751, 698, 647, 630, 585, 524, 491, 468. ^{1}H NMR (DMSO-d_6): δ 4.70 (td, 2H, J = 1.5, 4.5 Hz, CH_2CH=), 5.27 (td, 1H, J = 1.5, 10.8 Hz, CH_2=), 5.52 (td, 1H, J = 1.5, 17.3 Hz, CH_2=), 6.05 (m, 1H, CH=), 7.08 (t, 1H, J = 8.1 Hz, ArH), 7.19 (d, 1H, J = 8.1 Hz, ArH), 7.57 (t, 1H, J = 8.1 Hz, ArH), 7.58 (d, 1H, J = 8.1 Hz, ArH), 7.91 (d, 1H, $J_{H\text{-}5\ pyrid.–H\text{-}4\ pyrid.}$ = 7.8 Hz, H-5 pyrid.), 8.26 (td, 1H, $J_{H\text{-}4\ pyrid.–H\text{-}6\ pyrid.}$ = 1.5 Hz, $J_{H\text{-}4\ pyrid.–H\text{-}2\ pyrid.}$ = 1.8 Hz, $J_{H\text{-}4\ pyrid.–H\text{-}5\ pyrid.}$ = 7.8 Hz, H-4 pyrid.), 8.71 (dd, 1H, $J_{H\text{-}6\ pyrid.–H\text{-}4\ pyrid.}$ = 1.5 Hz, $J_{H\text{-}6\ pyrid.–H\text{-}5\ pyrid.}$ = 4.8 Hz, H-6 pyrid.), 9.03 (s, 1H, H-2 pyrid.), 10.32 (s, 1H, CH=N), 14.30 (s, 1H, D_2O exchangeable NH). Anal. Calcd for $C_{17}H_{15}N_5OS$ (337.4): C, 60.52; H, 4.48; N, 20.76; S, 9.50. Found: C, 60.42; H, 4.39; N, 20.61; S, 9.41.

*3.1.1.9. 1,ω-Bis[4-(2-allyloxybenzylideneamino)-5-(pyridin-3-yl)-4H-1,2,4-triazol-3-ylsulfanyl]alkanes (**34**–**36**). General procedures. Procedure A.* To a solution of each of the K-salts **28**–**30** (1.0 mmol) in dry DMF (2.5 mL) was added allyl bromide (0.17 mL, 2.01 mmol). The reaction mixture was then heated at reflux temperature for 5 min during which time KCl was separated. The mixture was then cooled, diluted with water (50 mL) and the precipitate was collected by filtration, washed with cold water (3 × 50 mL) and dried at room temperature. The product was purified by column chromatography over silica gel using MeOH/$CHCl_3$ as an eluent.

Procedure B. The K-salt **33** (375.5 mg, 1.0 mmol) was dissolved in dry DMF (2.5 mL) and to the formed solution was added the appropriate dihalo compound (0.5 mmol). The reaction mixture was then worked up as in procedure A.

Procedure C. To a solution of the appropriate bis(amines) **22**–**24** (1.0 mmol) in AcOH (40 mL) was added a solution of 2-allyloxybenzaldehyde (**31**) (324.4 mg, 2.0 mmol) in AcOH (10 mL). The reaction mixture was heated at reflux temperature for 2 h. The solvent was then evaporated and the remaining residue was purified by column chromatography over silica gel using MeOH/$CHCl_3$ as an eluent.

*3.1.1.9.1. 1,2-Bis[4-(2-allyloxybenzylideneamino)-5-(pyridin-3-yl)-4H-1,2,4-triazol-3-ylsulfanyl]ethane (**34**).* Yield 476.5 (68%, procedure A), 504.6 mg (72%, procedure B), 203.2 mg (29%, procedure C), colorless crystals, mp 180–182 °C. R_f = 0.72 (MeOH/$CHCl_3$ 1:9). IR: 3039, 2924, 2868, 1742, 1649, 1614, 1595, 1572, 1485, 1454, 1436, 1423, 1362, 1346, 1328, 1292, 1252, 1194, 1165, 1141, 1117, 1093, 1018, 997, 971, 930, 881, 831, 816, 757, 729, 716, 680, 649, 628, 611, 595, 529, 485. ^{1}H NMR ($CDCl_3$): δ 3.77 (s, 4H, SCH_2CH_2S), 4.57 (td, 4H, J = 1.5, 5.2 Hz, CH_2CH=), 5.26 (Qd, 2H, J = 1.5, 10.5 Hz, CH_2=), 5.34 (Qd, 2H, J = 1.5, 17.2 Hz, CH_2=), 5.96 (m, 2H, J = 1.5, 5.2, 10.5, 17.2 Hz, CH=), 6.93 (d, 2H, J = 7.9 Hz, ArH), 7.01 (t, 2H, J = 7.9 Hz, ArH), 7.36 (dd, 2H, $J_{H\text{-}5\ pyrid.–H\text{-}4\ pyrid.}$ = 8.1 Hz, $J_{H\text{-}5\ pyrid.–H\text{-}6\ pyrid.}$ = 4.8 Hz, H-5 pyrid.), 7.48 (m, 2H, J = 1.8, 7.9 Hz, ArH), 8.01 (dd, 2H, J = 1.8, 7.9 Hz, ArH), 8.26 (td, 2H, $J_{H\text{-}4\ pyrid.–H\text{-}6\ pyrid.}$ = 1.8 Hz, $J_{H\text{-}4\ pyrid.–H\text{-}2\ pyrid.}$ = 2.1 Hz, $J_{H\text{-}4\ pyrid.–H\text{-}5\ pyrid.}$ = 8.1 Hz, H-4 pyrid.), 8.62 (br d, 2H, $J_{H\text{-}6\ pyrid.–H\text{-}5\ pyrid.}$ = 4.8 Hz, H-6 pyrid.), 9.02 (s, 2H, CH=N), 9.18 (br s, 2H, H-2 pyrid.). Anal. Calcd for $C_{36}H_{32}N_{10}O_2S_2$ (700.8): C, 61.70; H, 4.60; N, 19.99; S, 9.15. Found: C, 61.68; H, 4.53; N, 20.12; S, 8.98.

*3.1.1.9.2. 1,3-Bis[4-(2-allyloxybenzylideneamino)-5-(pyridin-3-yl)-4H-1,2,4-triazol-3-ylsulfanyl]propane (**35**).* Yield 493.3 (69%, procedure A), 521.9 mg (73%, procedure B), 536.2 mg (75%, procedure C), colorless crystals, mp 144–146 °C. R_f = 0.69 (MeOH/$CHCl_3$ 1:9). IR: 3075, 3002, 2924, 1937, 1645, 1595, 1573, 1486, 1441, 1424, 1413, 1369, 1347, 1325, 1293, 1253, 1190, 1163, 1104, 1044, 1016, 994, 965, 940, 916, 884, 850, 832, 804, 750, 707, 679, 664, 638, 617, 585, 529, 511, 484. ^{1}H NMR ($CDCl_3$): δ 2.30 (quint, 2H, J = 7.0 Hz, SCH_2CH_2), 3.39 (t, 4H, J = 7.0 Hz, SCH_2CH_2), 4.55 (td, 4H, J = 1.5, 5.2 Hz, CH_2CH=), 5.23 (dd, 2H, J = 1.5, 10.5 Hz, CH_2=), 5.32 (dd, 2H, J = 1.5, 17.2 Hz, CH_2=), 5.93 (m, 2H, J = 1.5, 5.2, 10.5, 17.2 Hz, CH=), 6.90 (d, 2H, J = 7.9 Hz, ArH), 6.98 (t, 2H, J = 7.9 Hz, ArH), 7.32 (dd, 2H, $J_{H\text{-}5\ pyrid.–H\text{-}4\ pyrid.}$ = 8.1 Hz, $J_{H\text{-}5\ pyrid.–H\text{-}6\ pyrid.}$ = 4.8 Hz, H-5 pyrid.), 7.44 (dt, 2H, J = 1.4, 7.9 Hz, ArH), 8.00 (dd, 2H, J = 1.4, 7.9 Hz, ArH), 8.24 (td, 2H, $J_{H\text{-}4\ pyrid.–H\text{-}6\ pyrid.}$ = 1.8 Hz, $J_{H\text{-}4\ pyrid.–H\text{-}2\ pyrid.}$ = 2.1 Hz, $J_{H\text{-}4\ pyrid.–H\text{-}5\ pyrid.}$ = 8.1 Hz, H-4 pyrid.), 8.58 (dd, 2H, $J_{H\text{-}6\ pyrid.–H\text{-}4\ pyrid.}$ = 1.8 Hz, $J_{H\text{-}6\ pyrid.–H\text{-}5\ pyrid.}$ = 4.8 Hz, H-6 pyrid.), 9.01 (s, 2H, CH=N), 9.15 (d, 2H, $J_{H\text{-}2\ pyrid.–H\text{-}4\ pyrid.}$ = 2.1 Hz, H-2 pyrid.). Anal.

Calcd for $C_{37}H_{34}N_{10}O_2S_2$ (714.9): C, 62.17; H, 4.79; N, 19.59; S, 8.97. Found: C, 62.02; H, 4.85; N, 19.63; S, 8.89.

*3.1.1.9.3. 1,4-Bis[4-(2-allyloxybenzylideneamino)-5-(pyridin-3-yl)-4H-1,2,4-triazol-3-ylsulfanyl]butane (**36**).* Yield 510.2 mg (70%, procedure A), 539.4 mg (74%, procedure B), 328 mg (45%, procedure C), colorless crystals, mp 155–157 °C. $R_f = 0.73$ (MeOH/$CHCl_3$ 1:9). IR: 2922, 2869, 1596, 1569, 1479, 1452, 1434, 1376, 1350, 1296, 1242, 1186, 1159, 1103, 1046, 996, 966, 939, 910, 883, 817, 767, 753, 701, 668, 621, 584, 479. ^{1}H NMR ($CDCl_3$): δ 1.97 (quint, 4H, $J = 6.3$ Hz, SCH_2CH_2), 3.32 (t, 4H, $J = 6.3$ Hz, SCH_2CH_2), 4.60 (td, 4H, $J = 1.3$, 5.1 Hz, CH_2CH=), 5.29 (dd, 2H, $J = 1.3$, 10.5 Hz, CH_2=), 5.38 (dd, 2H, $J = 1.3$, 17.2 Hz, CH_2=), 5.99 (m, 2H, $J = 1.3$, 5.1, 10.5, 17.2 Hz, CH=), 6.95 (d, 2H, $J = 7.8$ Hz, ArH), 7.05 (t, 2H, $J = 7.8$ Hz, ArH), 7.38 (dd, 2H, $J_{\text{H-5 pyrid.–H-4 pyrid.}} = 8.1$ Hz, $J_{\text{H-5 pyrid.–H-6 pyrid.}} = 4.8$ Hz, H-5 pyrid.), 7.50 (dt, 2H, $J = 1.7$, 7.8 Hz, ArH), 8.06 (dd, 2H, $J = 1.7$, 7.8 Hz, ArH), 8.31 (td, 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.), 8.64 (br d, 2H, $J_{\text{H-6 pyrid.–H-5 pyrid.}} = 4.8$ Hz, H-6 pyrid.), 9.05 (s, 2H, CH=N), 9.21 (br s, 2H, H-2 pyrid.). Anal. Calcd for $C_{38}H_{36}N_{10}O_2S_2$ (728.9): C, 62.62; H, 4.98; N, 19.22; S, 8.80. Found: C, 62.54; H, 5.02; N, 19.09; S, 8.77.

*3.1.1.10. Synthesis of the macrocyclic Schiff bases **42**–**47**. General procedures. Procedure A.* To a solution of each of the K-salts **40** and **41** (1.0 mmol) in dry DMF (2.5 mL) was added the appropriate 1,ω-dihaloalkane (1.0 mmol). After heating the reaction mixture at reflux temperature for 5 min (during which time KCl was separated), it was cooled, diluted with water (20 mL) and the precipitate was collected by filtration, washed with cold water (3 × 50 mL), dried at room temperature and the remaining residue was purified by column chromatography over silica gel using MeOH/$CHCl_3$ as an eluent and recrystallized from MeOH.

Procedure B. Each of the K-salts **29** and **30** (1.0 mmol) was dissolved in dry DMF (2.5 mL) and to the formed solution was added the appropriate 1,ω-dihaloalkane (1.0 mmol). The reaction mixture was then worked up as described in procedure A.

Procedure C. A solution of each of the appropriate 1,ω-bis(aldehydes) **10**, **11**, **13**, **14** (1 mmol) in AcOH (10 mL) was added to a solution of the appropriate 1,ω-bis(amine) **22**–**24** (1 mmol) in AcOH (90 mL). The reaction mixture was heated at reflux temperature for 3 h. The excess AcOH was evaporated to a small volume (ca. 10 mL) and the reaction mixture was allowed to cool to room temperature. The formed product was collected by filtration, washed successively with water (3 × 100 mL) and MeOH (2 × 20 mL) then dried at room temperature. Compounds **42**, **43** were purified as described in procedure A, compound **44** was recrystallized from AcOH/MeOH, Compounds **45**–**47** were recrystallized from $CHCl_3$/pet ether (bp 40–60 °C).

*3.1.1.10.1. 3,23-Di(pyridin-3-yl)-12,13,28,29-tetrahydro-14H,30H-bis[1,2,4]triazolo[4,3-f:3,4-m]dibenzo[b,q][1,19,5,6,14,15,8,12]dioxatetrazadithiacyclodocosine (**42**).* Yield 499.3 mg (74%, B), 587.1 mg (87%, C) colorless crystals, mp 238–240 °C. $R_f = 0.22$ (MeOH/$CHCl_3$ 0.5:9.5). IR: 3057, 2924, 2876, 2361, 1597, 1436, 1404, 1369, 1349, 1255, 1157, 1099, 1033, 1000, 959, 876, 821, 751, 699, 617, 582, 485. ^{1}H NMR ($CDCl_3$): δ 2.50 (quint, 2H, $J = 6.3$ Hz, SCH_2CH_2), 2.52 (quint, 2H, $J = 7.2$ Hz, OCH_2CH_2), 3.56 (t, 4H, $J = 6.3$ Hz, SCH_2CH_2), 4.30 (t, 4H, $J = 7.2$ Hz, OCH_2CH_2), 7.00 (dd, 2H, $J = 1.5$, 7.7 Hz, ArH), 7.09 (t, 2H, $J = 7.7$ Hz, ArH), 7.47 (ddd, 2H, $J_{\text{H-5 pyrid.–H-4 pyrid.}} = 8.1$ Hz, $J_{\text{H-5 pyrid.–H-6 pyrid.}} = 4.8$ Hz, $J_{\text{H-5 pyrid.–H-2 pyrid.}} = 0.9$ Hz, H-5 pyrid.), 7.53 (m, 2H, $J = 1.5$, 7.7 Hz, ArH), 8.03 (dd, 2H, $J = 1.5$, 7.7 Hz, ArH), 8.43 (td, 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.), 8.69 (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.), 9.29 (dd, 2H, $J_{\text{H-2 pyrid.–H-4 pyrid.}} = 2.1$ Hz, $J_{\text{H-2 pyrid.–H-5 pyrid.}} = 0.9$ Hz, H-2 pyrid.), 9.30 (s, 2H, CH=N). ^{13}C NMR ($CDCl_3$): δ 26.58, 29.62, 32.55, 65.18, 112.52, 120.39, 121.82, 123.60, 127.43, 134.79, 136.15, 146.46, 148.39, 149.95, 150.72, 158.73, 159.33. LCMS: $m/z = 675$ (M + 1). GCMS: m/z (relative intensity); 578 [M − ($O_2 + S_2$), 9%], 577 (22%), 551 (20%), 516 (30%), 415 (18%), 368 (5%), 354 (7%), 335 (5%), 313 (23%), 307 (5%), 264 (23%), 239 (22%), 236 (6%), 219 (6%), 185 (7.5%), 162 (11%), 149 (23%), 135 (21%), 121 (26%), 105 (89%), 85 (46%), 77 (87%), 57 (100%), 55 (84%), 50 (7%). Anal. Calcd for $C_{34}H_{30}N_{10}O_2S_2$ (674.8): C, 60.52; H, 4.48; N, 20.76; S, 9.50. Found: C, 60.44; H, 4.52; N, 20.83; S, 9.49.

*3.1.1.10.2. 3,24-Di(pyridin-3-yl)-12,13,14,29,30,31-hexahydro-15H,32H-bis[1,2,4]triazolo[4,3-f:3,4-n]dibenzo[b,r][1,20,5,6,15,16,8,13]dioxatetrazadithiacyclotetracosine (**43**).* Yield 527.2 mg (75%, A), 555.3 mg (79%, B), 569.3 mg (81%, C), colorless crystals, mp 226–228 °C. $R_f = 0.20$ (MeOH/$CHCl_3$ 0.5:9.5). IR: 3070, 2944, 2858, 1596, 1571, 1477, 1454, 1434, 1410, 1376, 1349, 1298, 1252, 1191, 1163, 1105, 1044, 1023, 986, 965, 882, 813, 758, 703, 669, 636, 618, 582, 484. ^{1}H NMR ($CDCl_3$): δ 2.04 (quint, 4H, $J = 5.8$ Hz, SCH_2CH_2), 2.11 (quint, 4H, $J = 5.7$ Hz, OCH_2CH_2), 3.43 (t, 4H, $J = 5.8$ Hz, SCH_2CH_2), 4.16 (t, 4H, $J = 5.7$ Hz, OCH_2CH_2), 6.99 (d, 2H, $J = 7.9$ Hz, ArH), 7.05 (t, 2H, $J = 7.9$ Hz, ArH),7.48 (dd, 2H, $J_{\text{H-5 pyrid.–H-4 pyrid.}} = 8.1$ Hz, $J_{\text{H-5 pyrid.–H-6 pyrid.}} = 4.8$ Hz, H-5 pyrid.), 7.53 (dt, 2H, $J = 1.5$, 7.9 Hz, ArH), 8.08 (dd, 2H, $J = 1.5$, 7.9 Hz, ArH), 8.47 (td, 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.), 8.67 (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.), 9.21 (s, 2H, CH=N), 9.28 (d, 2H, $J_{\text{H-2 pyrid.–H-4 pyrid.}} = 2.1$ Hz, H-2 pyrid.). LCMS: $m/z = 703$ (M + 1). GCMS: m/z (relative intensity); 579 [M − ($O_2 + S_2 + C_2H_4$) + 1, 4%], 578 [M − ($O_2 + S_2 + C_2H_4$), 10%], 577 [M − ($O_2 + S_2 + C_2H_4$) − 1, 22%], 551 (22%), 415 (4%), 367 (5%), 339 (9%), 313 (26%), 264 (24%), 239 (24%), 236 (7%), 213 (5%), 185 (6%), 171 (7%), 158 (7%), 149 (17%), 129 (17%), 121 (24%), 98 (45%), 97 (52%), 83 (63%), 55 (100%), 51 (7%). Anal. Calcd for $C_{36}H_{34}N_{10}O_2S_2$ (702.9): C, 61.52; H, 4.88; N, 19.93; S, 9.12. Found: C, 61.56; H, 4.75; N, 20.09; S, 8.97.

*3.1.1.10.3. 3,28-Di(pyridin-3-yl)-12,13,15,16,18,33,34,35-octahydro-19H,36H-bis[1,2,4]triazolo[4,3-f:3,4-n]dibenzo[b,r][1,20,23,26,5,6,15,16,8,13]tetraoxatetrazadithiacycloocatacosine (**44**).* Yield 442.5 mg (58%, C), colorless crystals, mp 200–202 °C. ^{1}H NMR ($CDCl_3$): δ 2.13 (quint, 4H, $J = 6.3$ Hz, SCH_2CH_2), 3.43 (t, 4H, $J = 6.3$ Hz, SCH_2CH_2), 3.78 (s, 4H, OCH_2CH_2O), 3.90 (t, 4H, $J = 4.5$ Hz, $ArOCH_2CH_2O$), 4.22 (t, 4H, $J = 4.5$ Hz, OCH_2CH_2O) 6.96 (d, 2H, $J = 7.8$ Hz, ArH), 7.07 (t, 2H, $J = 7.8$ Hz, ArH), 7.43 (dd, 2H, $J_{\text{H-5 pyrid.–H-4 pyrid.}} = 8.1$ Hz, $J_{\text{H-5 pyrid.–H-6 pyrid.}} = 4.8$ Hz, H-5 pyrid.), 7.51 (dt, 2H, $J = 1.7$, 7.8 Hz, ArH), 8.05 (dd, 2H, $J = 1.7$, 7.8 Hz, ArH), 8.39 (td, 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.), 8.67 (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.), 9.17 (s, 2H, CH=N), 9.26 (d, 2H $J_{\text{H-2 pyrid.–H-4 pyrid.}} = 2.1$ Hz, H-2 pyrid.). Anal. Calcd for $C_{38}H_{38}N_{10}O_4S_2$ (762.9): C, 59.83; H, 5.02; N, 18.36; S, 8.41. Found: C, 59.77; H, 5.07; N, 18.34; S, 8.43

*3.1.1.10.4. 13-Hydroxy-3,23-di(pyridin-3-yl)-12,13,28-trihydro-14H,29H-bis[1,2,4]triazolo[4,3-f:3,4-l]dibenzo[b,p][1,18,5,6,13,14,8,11]dioxatetrazadithiacyclohenicosine (**45**).* Yield 541.4 mg (80%, C); colorless crystals, mp 291–293 °C (resolidify after melting and melt again at >350 °C). IR: 3390 (br), 3071, 2930, 2876, 1599, 1572, 1484, 1452, 1376, 1351, 1324, 1293, 1255, 1191, 1163, 1106, 1026, 967, 886, 813, 758, 704, 619, 587, 476. ^{1}H NMR ($CDCl_3$): δ 2.02 (s, 1H, D_2O exchangeable OH), 3.47 (s, 4H, SCH_2CH_2S), 4.27 (d, 2H, $J = 5.4$ Hz, $ArOCH_2$), 4.31 (m, 1H, CHOH), 4.40 (d, 2H, $J = 5.4$ Hz, $ArOCH_2$), 7.04 (d, 2H, $J = 7.7$ Hz, ArH), 7.09 (t, 2H, $J = 7.7$ Hz, ArH), 7.37 (dd, 2H, $J_{\text{H-5 pyrid.–H-4 pyrid.}} = 8.1$ Hz, $J_{\text{H-5 pyrid.–H-6 pyrid.}} = 4.8$ Hz, H-5 pyrid.), 7.53 (dt, 2H, $J = 1.4$, 7.7 Hz, ArH), 7.97 (dd, 2H, $J = 1.4$, 7.7 Hz, ArH), 8.29 (td, 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.), 8.63 (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.), 9.20 (s, 2H, CH=N), 9.24 (s, 2H, H-2 pyrid.). Anal. Calcd for $C_{33}H_{28}N_{10}O_3S_2$ (676.8): C, 58.57; H, 4.17; N, 20.70; S, 9.48. Found: C, 58.49; H, 4.09; N, 20.62; S, 9.57.

3.1.1.10.5. 13-Hydroxy-3,23-di(pyridin-3-yl)-12,13,28,29-tetrahydro-14H,30H-bis[1,2,4]triazolo[4,3-f:3,4-m]dibenzo[b,q]

*[1,19,5,6,14,15,8,12]dioxatetrazadithiacyclodocosine (**46**).* Yield 594.1 mg (86%, C); colorless crystals, mp 281–282 °C (resolidify after melting and melt again at >350 °C). IR: 3380, 3071, 2913, 2878, 1599, 1572, 1485, 1452, 1377, 1350, 1325, 1293, 1254, 1190, 1162, 1105, 1026, 966, 888, 813, 757, 704, 618, 586, 476. ^{1}H NMR ($CDCl_3$): δ 2.03 (s, 1H, D_2O exchangeable OH), 2.16 (s, 2H, SCH_2CH_2), 3.47 (s, 4H, SCH_2CH_2), 4.29 (d, 4H, J = 5.4 Hz, $ArOCH_2$), 4.70 (q, 1H J = 5.1 $CHOH$), 7.02 (d, 2H, J = 7.8 Hz, ArH), 7.09 (t, 2H, J = 7.8 Hz, ArH), 7.40 (dd, 2H, $J_{H\text{-}5\ pyrid.–H\text{-}4\ pyrid.}$ = 8.1 Hz, $J_{H\text{-}5\ pyrid.–H\text{-}6\ pyrid.}$ = 4.8 Hz, H-5 pyrid.), 7.53 (dt, 2H, J = 1.4, 7.7 Hz, ArH), 7.92 (dd, 2H, J = 1.4, 7.7 Hz, ArH), 8.35 (td, 2H, $J_{H\text{-}4\ pyrid.–H\text{-}6\ pyrid.}$ = 1.8 Hz, $J_{H\text{-}4\ pyrid.–H\text{-}2\ pyrid.}$ = 2.1 Hz, $J_{H\text{-}4\ pyrid.–H\text{-}5\ pyrid.}$ = 8.1 Hz, H-4 pyrid.), 8.64 (d, 2H, $J_{H\text{-}6\ pyrid.–H\text{-}5\ pyrid.}$ = 4.8 Hz, H-6 pyrid.), 9.23 (s, 2H, CH=N), 9.31 (s, 2H, H-2 pyrid.). Anal. Calcd for $C_{34}H_{30}N_{10}O_3S_2$ (690.8): C, 59.12; H, 4.38; N, 20.28; S, 9.28. Found: C, 59.00; H, 4.47; N, 20.32; S, 9.19.

*3.1.1.10.6. 13-Hydroxy-3,23-di(pyridin-3-yl)-12,13,28,29,30-pentahydro-14H,31H-bis-[1,2,4]triazolo[4,3-f:3,4-n]dibenzo[b,r][1,20,5,6,15,16,8,13]dioxatetrazadithiacyclotricosine (**47**).* Yield 606.1 mg (86%, C); colorless crystals, mp 286–287 °C (resolidify after melting and melt again at >350 °C). IR: 3403, 3105, 3040, 2929, 2867, 1599, 1569, 1486, 1439, 1410, 1377, 1352, 1299, 1552, 1189, 1160, 1106, 1044, 1006, 966, 894, 814, 764, 704, 670, 628, 618, 578, 483. ^{1}H NMR (DMSO-d_6): δ 1.92 (quint, 2H, J = 5.2 Hz, SCH_2CH_2), 3.26 (t, 4H, J = 5.2 Hz, SCH_2CH_2), 4.16 (dd, 2H, J = 7.2, 9.0 Hz, $ArOCH_2$), 4.29 (br s, 1H, $CHOH$), 4.31 (d, 2H, J = 9.0 Hz, $ArOCH_2$), 5.45 (d, 1H, J = 4.2 Hz, D_2O, exchangeable OH), 7.14 (t, 2H, J = 7.8 Hz, ArH), 7.24 (d, 2H, J = 7.8 Hz, ArH), 7.58 (tdd, 2H, $J_{H\text{-}5\ pyrid.–H\text{-}4\ pyrid.}$ = 8.1 Hz, $J_{H\text{-}5\ pyrid.–H\text{-}6\ pyrid.}$ = 4.8 Hz, $J_{H\text{-}5\ pyrid.–H\text{-}2\ pyrid.}$ = 0.9 Hz, H-5 pyrid.), 7.64 (tt, 2H, J = 0.8, 7.8 Hz, ArH), 7.98 (dd, 2H, J = 1.2, 7.8 Hz, ArH), 7.20 (dd, 2H, $J_{H\text{-}5\ pyrid.–H\text{-}4\ pyrid.}$ = 8.1 Hz, $J_{H\text{-}5\ pyrid.–H\text{-}6\ pyrid.}$ = 4.8 Hz, H-5 pyrid.), 8.29 (m, 2H, $J_{H\text{-}4\ pyrid.–H\text{-}6\ pyrid.}$ = 1.8 Hz, $J_{H\text{-}4\ pyrid.–H\text{-}2\ pyrid.}$ = 2.1 Hz, $J_{H\text{-}4\ pyrid.–H\text{-}5\ pyrid.}$ = 8.1 Hz, H-4 pyrid.), 8.69 (ddd, 2H, $J_{H\text{-}6\ pyrid.–H\text{-}2\ pyrid.}$ = 0.9 Hz, $J_{H\text{-}6\ pyrid.–H\text{-}4\ pyrid.}$ = 1.8 Hz, $J_{H\text{-}6\ pyrid.–H\text{-}5\ pyrid.}$ = 4.8 Hz, H-6 pyrid.), 9.08 (dd, 2H, $J_{H\text{-}2\ pyrid.–H\text{-}5\ pyrid.}$ = $J_{H\text{-}2\ pyrid.–H\text{-}6\ pyrid.}$ = 0.9 Hz, $J_{H\text{-}2\ pyrid.–H\text{-}4\ pyrid.}$ = 1.8 Hz, H-2 pyrid.), 9.42 (s, 2H, CH=N). Anal. Calcd for $C_{35}H_{32}N_{10}O_3S_2$ (704.8): C, 59.64; H, 4.58; N, 19.87; S, 9.10. Found: C, 59.69; H, 4.48; N, 19.82; S, 9.04.

*3.1.1.11. General procedure for the synthesis of macrocyclic amines **48**–**50**.* To a stirred boiling solution of each of **45**–**47** (0.23 mmol) in methanol (10 mL) was added sodium borohydride (0.20 g, 5.29 mmol) in incremental amounts over a period of 15 min. After the effervescence had stopped, the reaction mixture was heated at reflux temperature for 1 h. The solvent was then removed in vacuo and the remaining residue was extracted into DCM (50 mL). The extract was washed with water (2 × 50 mL), dried (Na_2SO_4), reduced by rotary evaporator (to ca. 10 mL) and pet ether (bp 40–60 °C) (10 mL) was added. The solid obtained upon cooling was collected by filtration and recrystallized from DCM/pet ether (bp 40–60 °C) to give colorless crystals of **48**–**50**.

*3.1.1.11.1. 13-Hydroxy-3,23-di(pyridin-3-yl)-5,6,12,13,20,21,28-heptahydro-14H,29H-bis[1,2,4]triazolo[4,3-f:3,4-l]dibenzo[b,p][1,18,5,6,13,14,8,11]dioxatetrazadithiacyclohenicosine (**48**).* Yield 150.3 mg (96%); colorless crystals, mp 278–280 °C (dec.). IR: 3228, 3065, 2927, 2872, 1598, 1548, 1493, 1452, 1417, 1293, 1244, 1191, 1163, 1121, 1029, 961, 894, 813, 754, 703, 627, 525, 488. ^{1}H NMR (DMSO-d_6): δ 3.39 (s, 4H, SCH_2CH_2S), 3.91 (s, 1H, D_2O exchangeable OH), 3.93 (d, 4H, J = 4.6 Hz, $ArCH_2$), 4.02 (dd, 4H, J = 6.0, 10.2 Hz, $ArOCH_2$), 4.52 (quint, 1H J = 5.1 Hz, $CHOH$), 6.61 (t, 2H, J = 4.6 Hz, D_2O exchangeable NH), 6.73 (d, 2H, J = 7.7 Hz, ArH), 6.75 (t, 2H, J = 7.7 Hz, ArH), 6.98 (dd, 2H, J = 1.4, 7.7 Hz, ArH), 7.23 (dt, 2H, J = 1.4, 7.7 Hz, ArH), 7.52 (dd, 2H, $J_{H\text{-}5\ pyrid.–H\text{-}4\ pyrid.}$ = 8.1 Hz, $J_{H\text{-}5\ pyrid.–H\text{-}6\ pyrid.}$ = 4.8 Hz, H-5 pyrid.), 8.29 (td, 2H, $J_{H\text{-}4\ pyrid.–H\text{-}6\ pyrid.}$ = 1.8 Hz, $J_{H\text{-}4\ pyrid.–H\text{-}2\ pyrid.}$ = 2.1 Hz, $J_{H\text{-}4\ pyrid.–H\text{-}5\ pyrid.}$ = 8.1 Hz, H-4 pyrid.), 8.66 (dd, 2H, $J_{H\text{-}6\ pyrid.–H\text{-}4\ pyrid.}$ = 1.8 Hz, $J_{H\text{-}6\ pyrid.–H\text{-}5\ pyrid.}$ = 4.8 Hz, H-6 pyrid.), 9.09 (d, 2H $J_{H\text{-}2\ pyrid.–H\text{-}4\ pyrid.}$ = 2.1 Hz, H-2 pyrid.). Anal. Calcd for $C_{33}H_{32}N_{10}O_3S_2$ (680.8): C, 58.22; H, 4.74; N, 20.57; S, 9.42. Found: C, 58.23; H, 4.62; N, 20.56; S, 9.39.

*3.1.1.11.2. 13-Hydroxy-3,23-di(pyridin-3-yl)-5,6,12,13,20,21,28,29-octahydro-14H,30H-bis[1,2,4]triazolo[4,3-f:3,4-m]dibenzo[b,q][1,19,5,6,14,15,8,12]dioxatetrazadithiacyclodocosine (**49**).* Yield 149.3 mg (93%); colorless crystals, mp 274–276 °C (dec.). IR: 3221, 3067, 2927, 2872, 1599, 1530, 1493, 1451, 1292, 1244, 1192, 1162, 1121, 1029, 963, 898, 813, 754, 704, 664, 625, 532. ^{1}H NMR ($CDCl_3$): δ 2.25 (quint, 2H, J = 6.4 Hz, SCH_2CH_2), 3.38 (t, 4H, J = 6.4 Hz, SCH_2CH_2), 3.90 (s, 1H, D_2O exchangeable OH), 4.00 (d, 4H, J = 5.5 Hz, $ArCH_2$), 4.07 (dd, 4H, J = 6.3, 11.4 Hz, $ArOCH_2$), 4.61 (quint, 1H J = 5.1 Hz, $CHOH$), 6.08 (t, 2H, J = 5.5 Hz, D_2O exchangeable NH), 6.73 (d, 2H, J = 7.7 Hz, ArH), 6.74 (t, 2H, J = 7.7 Hz, ArH), 6.99 (dd, 2H, J = 1.4, 7.7 Hz, ArH), 7.13 (dt, 2H, J = 1.4, 7.7 Hz, ArH), 7.20 (dd, 2H, $J_{H\text{-}5\ pyrid.–H\text{-}4\ pyrid.}$ = 8.1 Hz, $J_{H\text{-}5\ pyrid.–H\text{-}6\ pyrid.}$ = 4.8 Hz, H-5 pyrid.), 8.18 (td, 2H, $J_{H\text{-}4\ pyrid.–H\text{-}6\ pyrid.}$ = 1.8 Hz, $J_{H\text{-}4\ pyrid.–H\text{-}2\ pyrid.}$ = 2.1 Hz, $J_{H\text{-}4\ pyrid.–H\text{-}5\ pyrid.}$ = 8.1 Hz, H-4 pyrid.), 8.50 (dd, 2H, $J_{H\text{-}6\ pyrid.–H\text{-}4\ pyrid.}$ = 1.8 Hz, $J_{H\text{-}6\ pyrid.–H\text{-}5\ pyrid.}$ = 4.8 Hz, H-6 pyrid.), 9.16 (d, 2H, $J_{H\text{-}2\ pyrid.–H\text{-}4\ pyrid.}$ = 2.1 Hz, H-2 pyrid.). Anal. Calcd for $C_{34}H_{34}N_{10}O_3S_2$ (694.8): C, 58.77; H, 4.93; N, 20.16; S, 9.23. Found: C, 58.66; H, 4.81; N, 19.99; S, 9.21.

*3.1.1.11.3. 13-Hydroxy-3,23-di(pyridin-3-yl)-5,6,12,13,20,21,28,29,30-nonahydro-14H,31H-bis[1,2,4]triazolo[4,3-f:3,4-n]dibenzo[b,r][1,20,5,6,15,16,8,13]dioxatetrazadithiacyclotricosine (**50**).* Yield 127.2 mg (78%); colorless crystals, mp 271–273 °C (dec.). IR: 3220, 3066, 2925, 2855, 1599, 1493, 1452, 1417, 1378, 1290, 1245, 1191, 1162, 1120, 1045, 963, 895, 834, 812, 753, 704, 624, 600, 479, 434. ^{1}H NMR ($CDCl_3$): δ 1.95 (quint, 4H, J = 4.6 Hz, SCH_2CH_2), 3.21 (t, 4H, J = 4.6 Hz, SCH_2CH_2), 4.08 (s, 1H, D_2O exchangeable OH), 4.11 (d, 4H, J = 5.8, $ArCH_2$), 4.23 (dd, 4H, J = 4.6, 10.6 Hz, $ArOCH_2$), 4.52 (quint, 1H, J = 5.5 Hz, $CHOH$), 6.23 (t, 2H, J = 5.8 Hz, D_2O exchangeable NH), 6.77 (d, 2H, J = 7.8 Hz, ArH), 6.80 (dt, 2H, J = 1.3, 7.8 Hz, ArH), 6.98 (dd, 2H, J = 1.3, 7.8 Hz, ArH), 7.17 (dt, 2H, J = 1.3, 7.8 Hz, ArH), 7.52 (dd, 2H, $J_{H\text{-}5\ pyrid.–H\text{-}4\ pyrid.}$ = 8.1 Hz, $J_{H\text{-}5\ pyrid.–H\text{-}6\ pyrid.}$ = 4.8 Hz, H-5 pyrid.), 8.56 (td, 2H, $J_{H\text{-}4\ pyrid.–H\text{-}6\ pyrid.}$ = 1.8 Hz, $J_{H\text{-}4\ pyrid.–H\text{-}2\ pyrid.}$ = 2.1 Hz, $J_{H\text{-}4\ pyrid.–H\text{-}5\ pyrid.}$ = 8.1 Hz, H-4 pyrid.), 8.63 (dd, 2H, $J_{H\text{-}6\ pyrid.–H\text{-}4\ pyrid.}$ = 1.8 Hz, $J_{H\text{-}6\ pyrid.–H\text{-}5\ pyrid.}$ = 4.8 Hz, H-6 pyrid.), 9.46 (d, 2H, $J_{H\text{-}2\ pyrid.–H\text{-}4\ pyrid.}$ = 2.1 Hz, H-2 pyrid.). Anal. Calcd for $C_{35}H_{36}N_{10}O_3S_2$ (708.9): C, 59.30; H, 5.12; N, 19.76; S, 9.05. Found: C, 59.23; H, 5.01; N, 19.68; S, 9.00.

3.2. Antimicrobial activity

Antimicrobial screening of compounds **15**, **17**–**25**, **43**, **44**, **46**, **47** and **49** was carried out using the diffusion agar technique [44]. The test organisms were obtained from the culture of the Regional Center for Mycology and Biotechnology, Faculty of Science, Al-Azhar University, Cairo, Egypt. Compounds, **15**, **17**–**25**, **43**, **44**, **46**, **47**, **49** and standard antimicrobial agents (chloramphenicol and terbinafin were used as standard antibacterial and antifungal agents, respectively) were dissolved in DMF (5.0 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 bacteria (*Bacillus subtilis* RCMB 101-001 and *Staphylococcus aureus* RCMB 106-001 (1)), two Gram-negative bacteria (*Pseudomonas aeruginosa* RCMB 102-002 and *Escherichia coli* RCMB 103-001), one yeast (*Candida albicans* RCMB 005003) and three fungal strains (*Aspergillus fumigatus* RCMB 002008 (1), *Penicillium italicum* RCMB 001018 (1) and *Syncephalastrum racemosum* RCMB 016001). The minimum inhibitory

concentrations (MICs) of compounds **21** and **43** were determined via further twofold serial dilutions to prepare the required quantities of 1000, 500, 250, 125, 62.50, 31.25, 15.63, 7.81, 3.91, 1.95, 0.98, 0.49 μg/mL concentrations. The antimicrobial activities were expressed as the diameter of the inhibition zones (Table 1).

References

[1] T. Asami, Y.K. Min, N. Nagata, K.Y. amagishi, S. Takatsuto, S. Fujioka, N. Murofushi, I. Yamaguchi, S. Yoshida, Characterization of brassinazole, a triazole-type brassinosteroid biosynthesis inhibitor, Plant Physiol. 123 (1) (2000) 93–100.

[2] (a) V.J. Ram, L. Mishra, N.H. Pandey, D.S. Kushwaha, L.A.C. Pieters, A.J. Vlietinck, Bis heterocycles as potential chemotherapeutic agents X. Synthesis of bis(4-arylthiosemicarbazido)-, bis(2-arylamino-1,3,4-thiadiazol-5-yl) and bis (4-aryl-1,2,4-triazolin-3-thione-5-yl)pentanes and related compounds, J. Heterocycl. Chem. 27 (1990) 351;
(b) P.S. Upadhyay, R.N. Vansdadia, A.J. Baxi, Studies on sulphone derivatives: preparation and antimicrobial activity of thiosemicarbazides, thiazolidones, triazoles, oxadiazoles and thiadiazoles, Indian J. Chem. Sect. B. 29 (1990) 793;
(c) N. Ergenç, E. İlhan, G. Ötük, Synthese und biologische Wirkungeiniger 1,4-disubstituierter thiosemicarbazide und deren 1,2,4-triazol-5-thion-derivate, Pharmazie 47 (1992) 59.

[3] (a) Z. Muhi-Eldeen, M. Nadir, N.R. Aljobory, F. Husseen, S.J. Stohs, Synthesis and antimicrobial evaluation of 3-(4-*tert*-amino-2-butynyl)thio and alkyl/alkenylthio-4,5-disubstituted-4*H*-1,2,4-triazoles, Eur. J. Med. Chem. 26 (1991) 237;
(b) F.A. Ashour, S.A. Almazroa, Synthesis of certain thiosemicarbazide and triazole derivatives as potential antimicrobial agents, Il Farmaco 45 (1990) 1207;
(c) S.P. Hiremath, K. Shivaramayya, K.R. Sekhar, M.G. Purohit, Synthesis of substituted 2,5-bis(1,3,4-oxadiazolyl/thiadiazolyl/1,2,4-triazolyl)indoles and study of their biological activities, Indian J. Chem. Sect. B. 29 (1990) 1118;
(d) A. Gürsoy, Ş. Demirayak, Z. Cesur, J. Reisch, G. Ötük, Synthesis of some new hydrazidehydrazones, thiosemicarbazides, thiadiazoles, triazoles and their derivatives as possible antimicrobials, Pharmazie 45 (1990) 246;
(e) N.S. Habib, S. Abdel-Hamid, M. El-Hawash, Synthesis of benzimidazole derivatives as potential antimicrobial agents, Il Farmaco 44 (1989) 1225;
(f) I.M. Labouta, A.M.M. Hassan, O.M. Aboulwafa, O. Kader, Synthesis of some substituted benzimidazoles with potential antimicrobial activity, Monatsh. Chem. 120 (1989) 571;
(g) S.M. El-Khawass, N.S. Habib, Synthesis of 1,2,4-triazole, 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole and 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazine derivatives of benzotriazole, J. Heterocycl. Chem. 26 (1989) 177;
(h) N. Ergenç, E. İlhan, A. Salman, S. Salman, Synthesis of some new 5-carboxymethylthio-3,4-disubstituted-triazoles as possible antimicrobial and antiinflammatory agents, J. Fac. Pharm. İstanbul 24 (1988) 37;
(i) B.S. Holla, B. Kalluraya, K.R. Sridhar, Synthesis of 4-(5-nitro-2-furfurylidene) amino-3-mercapto-5-(substituted)-1,2,4-triazoles as possible antibacterial agents, Curr. Sci. 56 (1987) 236;
Chem. Abstr. 107 (1987) 74080a;
(j) B.N. Goswami, J.C.S. Kataky, J.N. Baruah, Synthesis and antibacterial activity of 1-(2,4-dichlorobenzoyl)-4-substituted thiosemicarbazides, 1,2,4-triazoles and their methyl derivatives, J. Heterocycl. Chem. 21 (1984) 1225;
(k) E. Hassan, M.I. Al-Ashmawi, B. Abdel-Fattah, Synthesis and antimicrobial testing of certain oxadiazoline and triazole derivatives, Pharmazie 38 (1983) 833;
(l) S.M. El-Khawass, A.A.B. Hazzaa, Sh.A.S. El-Din, Synthesis of 3,4-disubstituted-5-carboxy/carbethoxymethylthio-1,2,4-(4*H*)-triazoles, as potential antimicrobial agents, Sci. Pharm. 47 (1979) 314.

[4] (a) V.J. Ram, H.N. Pandey, Synthesis of 5-membered heterocycles and related compounds, Chem. Pharm. Bull. 22 (1974) 2778;
(b) K.R. Reddy, K. Mogilaiah, B. Swamy, Synthesis of some 1,8-naphthyridinylthiosemicarbazides, triazoles and thiadiazoles, Acta Chim. Hung. 127 (1990) 45;
(c) S.P. Hiremath, V.N. Sonar, K.R. Sekhar, M.G. Purohit, Synthesis of oxadiazolyl-, thiadiazolyl- and triazolylindoles and indolylthiazolidinones, Indian J. Chem. Sect. B. 28 (1989) 626;
(d) B.K. Bhattacharya, V.D. Dirk, G. Hoornaert, S. Sawant, Synthesis and antifungal activity of some new 2-[2-(4′-aryl-5′-methoxystyryl)-1′,2′,4′-triazol-3′-thio]pyridines [4-aryl-5-[2-[2-(2-pyridyl)vinyl]phenoxy]methyl-1,2,4-triazole-3-thiones], Bokin Bobai 12 (1984) 383;
Chem. Abstr. 102 (1985) 24441v.

[5] (a) S.C. Bennur, V.B. Jigajinni, V.V. Badiger, Pyrimidines. VI. Synthesis of 2-methylthio-5-bromopyrimidine-4-carboxylic acid thiosemicarbazides, 3-pyrimidyl-1,2,4-4*H*-triazoles and 2-arylamino-1,3,4-thiadiazoles, Rev. Roum. Chim. 21 (1976) 757;
Chem. Abstr. 85 (1976) 94306j;
(b) C.S. Andotra, S.K. Sharma, Synthesis and biocidal activity of some substituted oxadiazoles, thiadiazoles and triazoles, Indian J. Pharm. Sci. 51 (1989) 107;
(c) Z. Zhang, X. Feng, L. Chen, Q. Meng, D. Gao, Studies on acylthiosemicarbazides and related heterocyclic compounds X. Cyclization of 1-(4′-pyridinoyl)-4-aroylthiosemicarbazide derivatives, Gaodeng Xuexiao Huaxue Xuebao 10 (1989) 471;
Chem. Abstr. 112 (1990) 158149w;
(d) W. Rudnicka, H. Foks, M. Janowiec, Z. Zwolska-Kwiek, Pyrazine derivatives. XXI. Synthesis and tuberculostatic activity of 4-aryl-1-pyrazinoylthiosemicarbazides and of the products of their cyclization to the derivatives of 1,2,4-triazol-3-thione, Acta Pol. Pharm. 43 (1986) 523;
Chem. Abstr. 108 (1988) 131695b;
(e) W. Rudnicka, J. Sawlewicz, Reaction of 1,2,4-triazolo-3-thione and some derivatives thereof with isocyanates and isothiocyanates, Acta Pol. Pharm. 35 (1978) 135;
Chem. Abstr. 89 (1978) 215308e.

[6] M. Kritsanida, A. Mouroutsou, P. Marakos, N. Pouli, S. Papakonstantinou-Garoufalias, C. Pannecouque, M. Witvouw, E. De Clercq, Synthesis and antiviral activity evaluation of some new 6-substituted 3-(1-adamantyl)-1,2,4-triazolo [3,4-*b*][1,3,4]thiadiazoles, Il Farmaco 57 (2002) 253–257.

[7] (a) V. Mathew, J. Keshavayya, V.P. Vaidya, D. Giles, Studies on synthesis and pharmacological activities of 3,6-disubstituted-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazoles and their dihydro analogues, Eur. J. Med. Chem. 42 (2007) 823–840;
(b) B. Tozkoparan, N. Gökhan, G. Aktay, E. Yeşilada, M. Ertan, 6-Benzylidene-thiazolo[3,2-*b*]-1,2,4-triazole-5(6*H*)-ones substituted with ibuprofen: synthesis, characterization and evaluation of anti-inflammatory activity, Eur. J. Med. Chem. 35 (2000) 743–750;
(c) B. Tozkoparan, E. Küpeli, E. Yeşilada, M. Ertan, Preparation of 5-aryl-3-alkylthio-l,2,4-triazoles and corresponding sulfones with antiinflammatory–analgesic activity, Bioorg. Med. Chem. 15 (2007) 1808–1814;
(d) M. Amir, S. Kumar, Synthesis and evaluation of anti-inflammatory, analgesic, ulcerogenic and lipid peroxidation properties of ibuprofen derivatives, Acta Pharm. 57 (2007) 31–45.

[8] (a) M.S. Langley, S.P. Clissold, in: Adis International (Ed.), Brotizolam: a Review of Its Pharmacodynamic and Pharmacokinetic Properties, and Therapeutic Efficacy as an Hypnotic, Drugs (1988), pp. 104–122;
(b) J.L. Kelley, C.S. Koble, R.G. Davis, E.W. McLean, F.E. Soroko, B.R. Cooper, 1-(Fluorobenzyl)-4-amino-1*H*-1,2,3-triazolo[4,5-*c*]pyridines: synthesis and anticonvulsant activity, J. Med. Chem. 38 (1995) 4131–4134.

[9] E. Przegalinski, A. Lewandowska, J. Neural Transm. 46 (1979) 303–312.

[10] I. Küçükgüzel, S.G. Küçükgüzel, S. Rollas, M. Kiraz, Some 3-thioxo/alkylthio-1,2,4-triazoles with a substituted thiourea moiety as possible antimycobacterials, Bioorg. Med. Chem. Lett. 11 (2001) 1703–1707.

[11] (a) N. Demirbaş, R. Uğurluoğlu, A. Demirbaş, Synthesis of 3-alkyl(aryl)-4-alkylidenamino-4,5-dihydro-1*H*-1,2,4-triazol-5-ones and 3-alkyl-4-alkylamino-4,5-dihydro-1*H*-1,2,4-triazol-5-ones as antitumor agents, Bioorg. Med. Chem. 10 (2002) 3717–3723;
(b) A. Howell, J. Cuzick, M. Baum, A. Buzdar, M. Dowsett, J.F. Forbes, G. Hoctin-Boes, J. Houghton, G.Y. Locker, J.S. Tobias, ATAC Trialists Group, Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer, Lancet 365 (2005) 60–62.

[12] H. Emilsson, H. Salender, J. Gaarder, Eur. J. Med. Chem. Chim. Ther. 21 (1985) 333–338.

[13] G. Turan-Zitouni, Z.A. Kaplancikli, K. Erol, F.S. Killic, Synthesis and analgesic activity of some triazoles and triazolothiadiazines, Il Farmaco 54 (1999) 218–223.

[14] M. Ghannoum, L.B. Rice, Antifungal agents: mode of action, mechanism of resistance, and correlation of these mechanisms with bacterial resistance, Clin. Microbiol. Rev. 12 (1999) 501–517.

[15] M.Y. Mhasalkar, M.H. Shah, S.T. Nikam, Further studies in substituted 4*H*-1,2,4-triazoles for possible hypoglycemic activity, J. Med. Chem. 14 (3) (1971) 260–262.

[16] J.N. Delgado, W.A. Remers, Text Book of Organic, Medicinal and Pharmaceutical Chemistry, tenth ed. J.B., Lippincott Company, Philadelphia, 1998, 189.

[17] (a) M. Moreno-Manas, Y. Arredondo, R. Pleixats, M. Teixido, M.M. Haga, C. Palacin, J.M. Castello, J.A. Oritizz, J. Hetero. Chem. 29 (1992) 1557;
(b) L. Czollner, G. Sxilagli, J. Janaky, Arch. Pharm. (Weinheim, Ger.) 323 (1990) 225;
(c) C.H. Chu, X.W. Sun, L. Sun, Z.Y. Zhang, Z.C. Li, R.A. Liao, J. Chin. Chem. Soc. 46 (1999) 229;
(d) A. Er-Rhaimini, R. Mornet, Indian J. Hetero. Chem. 29 (1992) 1561;
(e) H.L. Elbe, K.H. Buechel, W. Brandes, S. Dutzmann, K. Luerssen, Ger. offen, 4, 803,883. Chem. Abstr. 124 (1996) 261076;
(f) B. Wolfgan, R. Wolfgan, P. Arbold, S. Bartel, Ger. Offen DE. 4,425,660. Chem. Abstr. 124 (1996) 261076;
(g) Y. Liu, A. Gangguly, F. Bennet, JP 10: 231,296. Chem. Abstr. 129 (1998) 260464.

[18] (a) A.M. Isloor, B. Kalluraya, M. Rao, A.M. Rahiman, J. Saudi Chem. Soc. 4 (2000) 265–270;
(b) B. Kalluraya, A.M. Isloor, S. Shenoy, Indian J. Heterocycl. Chem. 11 (2001) 159–162;
(c) B. Kalluraya, A.M. Isloor, F.V. Priya, R.L. Jagadeesha, Indian J. Heterocycl. Chem. 13 (3) (2004) 245–248;
(d) The Merck Index & Co. Inc., Whitehouse Station, NJ, USA, 3737, 2001;
(e) M. Zając, E. Pawełczyk, Chemia Leków, AM Poznan (2000) 188;
(f) The Merck Index & Co. Inc., Whitehouse Station, NJ, USA, 320, 2001;
(g) The Merck Index & Co. Inc., Whitehouse Station, NJ, USA, 8324, 2001;
(h) A. Kleemann, J. Engel, Pharmaceutical Substances. Thieme, Stuttgart, New York, 1999.

[19] (a) B. Witkop, L.K. Ramachandran, Progress in non-enzymatic selective modification and cleavage of proteins, Metabolism 13 (10) (1964) 1016–1025;
(b) R.A. Morton, G.A.J. Pitt, Studies on rhodopsin. 9. pH and the hydrolysis of indicator yellow, J. Biochem. 59 (1955) 128–134;
(c) E. Grazi, P.T. Rowley, T. Cheng, O. Tchola, B.L. Horecker, The mechanism of action of aldolases. III. Schiff base formation with lysine, Biochem. Biophys. Res. Commun. 9 (1962) 38–43;
(d) I. Fridovich, F.H. Westheimer, On the mechanism of the enzymatic decarboxylation of acetoacetate. II, J. Am. Chem. Soc. 84 (16) (1962) 3208–3209;
(e) G.G. Hammes, P. Fasella, A kinetic study of glutamic-aspartic transaminase, J. Am. Chem. Soc. 84 (24) (1962) 4644–4650;
(f) B.S. Tovrog, D.J. Kitko, R.S. Drago, Nature of the bound oxygen in a series of cobalt dioxygen adducts, J. Am. Chem. Soc. 98 (17) (1976) 5144–5153.

[20] (a) G. Rao, S. Rajasekaran, M. Attimarad, Synthesis and antimicrobial activity of some 5-phenyl-4-substituted amino-3-mercapto (4*H*)-1,2,4-triazoles, Indian J. Pharm. Sci. 62 (6) (2000) 475–477;
(b) K.D. Patel, B.D. Mistry, K.R. Desai, Synthesis and antimicrobial activity of 1,2,4-triazoles, J. Indian Chem. Soc. 79 (2002) 964–965 Dec.;
(c) N.F. Eweiss, A.A. Bahajaj, E.A. Elsherbini, Synthesis of heterocycles. Part VI. Synthesis and antimicrobial activity of some 4-amino-5-aryl-1,2,4-triazole-3-thiones and their derivatives, J. Heterocyclic Chem. 23 (5) (1986) 1451–1458;
(d) R.H. Udupi, A. Kushnoor, A.R. Bhatt, J. Indian Chem. Soc. 76 (1999) 461–462.

[21] J.M. Kane, B.M. Baron, M.W. Dudley, S.M. Sorensen, M.A. Staeger, F.P. Miller, 2,4-Dihydro-3*H*-1,2,4-triazol-3-ones as anticonvulsant agents, J. Med. Chem. 33 (10) (1990) 2772–2777.

[22] R.E. Hester, E.M. Nour, Resonance Raman studies of transition metal peroxo complexes: 5-The oxygen carrier cobalt(II)-salen and its μ-peroxo complexes, $[(L)(salen)Co]_2O_2$; L = DMSO, py, DMF, pyO and no L, J. Raman Spectrosc. 11 (1981) 49–58.

[23] (a) H. Sigel, D.B. McCormick, Discriminating behavior of metal ions and ligands with regard to their biological significance, Acc. Chem. Res. 3 (1970) 201–208;
(b) A. Bigotto, G. Costa, G. Mestroni, G. Pellizer, A. Puxeddu, E. Reisenhofer, L. Stefani, G. Tauzher, Extension of the "model" approach to the study of coordination chemistry of vit. B12 group compounds, Inorg. Chim. Acta, Rev. 4 (1970) 41–49.

[24] (a) A.S. Craig, R. Kataky, R.C. Matthews, D. Parker, G. Ferguson, A. Lough, H. Adams, N. Bailey, H. Schneider, Synthesis of 1,10-dithia-4,7,13,16-tetraazacyclo-octadecane, 1-aza-4,7-dithiacyclononane, and *N*, *N*′-1,2-bis(1-aza-4,7-dithia-cyclononyl)ethane. Structural and solution studies of their silver complexes, J. Chem. Soc., Perkin Trans. 2 (1990) 1523–1531;
(b) J.S. Bradshaw, R.M. Izatt, Crown ethers: the search for selective ion ligating agents, Acc. Chem. Res. 30 (8) (1997) 338–345.

[25] K. Krylova, C.P. Kulatilleke, M.J. Heeg, C.A. Salhi, L.A. Ochrymowycz, D.B. Rorabacher, A Structural strategy for generating rapid electron-transfer kinetics in copper(II/I) systems, Inorg. Chem. 38 (19) (1999) 4322–4328.

[26] (a) A.A. Khandar, S.A. Hosseini-Yazdi, Synthesis, X-ray crystal structure, and solution properties of nickel(II) complexes of new 16-membered mixed-donor macrocyclic Schiff base ligand incorporating a pendant alcohol function, Polyhedron 22 (11) (2003) 1481–1487;
(b) A.A. Khandar, S.A. Hosseini-Yazdi, Synthesis and characterization of the nickel(II) complex of a macrocyclic Schiff base ligand with a single pendant coordinating hydroxyl arm, Aust. J. Chem. 56 (12) (2003) 1255–1257;
(c) M. Vicente, R. Bastida, A. Macias, L. Valencia, C.F.G.C. Geraldes, C.D. Bronidino, Copper complexes with new oxaaza-pendant-armed macrocyclic ligands: X-ray crystal structure of a macrocyclic copper(II) complex, Inorg. Chim. Acta 358 (4) (2005) 1141–1150;
(d) M. Vicente, C. Lodeiro, H. Adams, R. Bastida, A. Blas, D.E. Fenton, A. Macias, A. Rodríguez, T. Rodríguez-Blas, Synthesis and characterization of some metal complexes with new nitrogen-oxygen donor macrocyclic ligands – X-ray crystal structures of a 26-membered reduced monoprotonated macrocycle and a 20-membered pendant Schiff-base macrocyclic cadmium(II) complex, Eur. J. Inorg. Chem. 2000 (5) (2000) 1015–1024;
(e) M. Vicente, R. Bastida, C. Lodeiro, A. Macías, A.J. Parola, L. Valencia, S.E. Spey, Metal complexes with a new N_4O_3 amine pendant-armed macrocyclic ligand: synthesis, characterization, crystal Structures, and fluorescence studies, Inorg. Chem. 42 (21) (2003) 6768–6779.

[27] (a) V. Artero, M. Fontecave, Some general principles for designing electrocatalysts with hydrogenase activity, Coord. Chem. Rev. 249 (15–16) (2005) 1518–1535;
(b) S. Li, J. Xia, D. Yang, Y. Xu, D. Li, M. Wu, W. Tang, Carboxyester hydrolysis catalyzed by a novel dicopper(II) complex with an alcohol-pendant macrocycle, Inorg. Chem. 41 (7) (2002) 1807–1815;
(c) L. Siegfried, A. Comparone, M. Neuburger, T.A. Kaden, Selective metal promoted hydrolysis of nitrile groups in the side chain of tetraazamacrocyclic Cu^{2+} complexes, Dalton Trans. (2005) 30–36;
(d) K.P. Wainwright, Applications of polyazamacrocycles with nitrogen-attached pendant arms. in: A.G. Sykes (Ed.), Advances in Inorganic Chemistry, 52. AcademicPress, San Diego, 2001, pp. 293–334;
(e) J. Costamagna, G. Ferraudi, B. Matsuhiro, M. Campos-Vallette, J. Canales, M. Villagrán, J. Vargas, M.J. Aguirre, Complexes of macrocycles with pendant arms as models for biological molecules, Coord. Chem. Rev. 196 (1) (2000) 125–164.

[28] N.S.A.M. Khalil, A facile synthesis, structure, and antimicrobial evaluation of novel 4-arylhydrazono-5-trifluoromethyl-2,4-dihydropyrazol-3-ones, their *N*- and *N*, *O*-bis-β-D-glucosides, Carbohydr. Res. 344 (2009) 1654–1659.

[29] N.S.A.M. Khalil, G.A.M.A. Darwish, F.A.A. Mostafa, N.I. Bassuony, Antimicrobial evaluation and structure-activity relationship (SAR) of 4-amino-4*H*-[1,2,4]-triazole-3,5-dithiol and some related 6-substituted-2*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole-3-thiones, Az. J. Pharm. Sci. 37 (2008) 34–48.

[30] N.S.A.M. Khalil, Novel simple efficient synthetic approach toward 6-substituted-2*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole-3-thiones and first synthesis and biological evaluation of *N*-and *S*-β-D-glucosides of the[1,2,4] triazolo [3,4-*b*][1,3,4]thiadiazole ring system, Nucleosides, Nucleotides Nucleic Acids 26 (2007) 347–359.

[31] N.S.A.M. Khalil, First synthesis and antimicrobial activity of *N*- and *S*-α-L-arabinopyranosyl-1,2,4-triazoles, Nucleosides, Nucleotides Nucleic Acids 26 (2007) 361–377.

[32] N.S.A.M. Khalil, *N*- and *S*-α-L-Arabinopyranosyl[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles. First synthesis and biological evaluation, Eur. J. Med. Chem. 42 (2007) 1193–1199.

[33] N.S.A.M. Khalil, Efficient synthesis, structure, and antimicrobial activity of some novel *N*- and *S*-β-D-glucosides of 5-pyridin-3-yl-1,2,4-triazoles, Carbohydr. Res. 341 (2006) 2187–2199.

[34] A.A. Abbas, N.S.A.M. Khalil, Synthesis of some new 1,3/ or 1,4-bis(glucopyranosyl-1,2,4-triazol-5-ylthio)propanes/or butanes as potential antimicrobial agents, Nucleosides, Nucleotides Nucleic Acids 24 (2005) 1353–1372.

[35] N.S.A.M. Khalil, Synthesis of some novel *N*-ribosyl-1,2,4-triazin-6(1*H*)-/ones or thiones as potential antibacterial and antifungal chemotherapeutics, Nucleosides, Nucleotides Nucleic acids 24 (2005) 111–120.

[36] N.S.A.M. Khalil, Synthesis of novel α-L-arabinopyranosides of β-lactams with potential antimicrobial activity, Nucleosides, Nucleotides Nucleic Acids 24 (2005) 1277–1287.

[37] N.S.A.M. Khalil, A.K. Mansour, M.M. Eid, Synthesis of some novel 6-benzyl(or substituted benzyl)-2-β-D-glucopyranosyl-1,2,4-triazolo[4,3-*b*][1,2,4]triazines as potential antimicrobial chemotherapeutics, Nucleosides, Nucleotides Nucleic Acids 23 (2004) 1889–1910.

[38] A.K. Mansour, M.M. Eid, N.S.A.M. Khalil, Selective synthesis and reactions of 6-substituted-2-β-galactosyl-1,2,4-triazines of potential anticancer activity, Nucleosides, Nucleotides Nucleic Acids 22 (2003) 21–44.

[39] A.K. Mansour, M.M. Eid, N.S.A.M. Khalil, Synthesis of some new 2-α-L-arabinopyranosyl-1,2,4-triazines as potential antitumor chemotherapeutics, Nucleosides, Nucleotides Nucleic Acids 22 (2003) 1805–1823.

[40] A.K. Mansour, M.M. Eid, N.S.A.M. Khalil, Synthesis of some *N*-galactosides of 3-aryl-5-benzyl(or substituted benzyl)-1,2,4-triazin-6(1*H*)-/ones or thiones of expected biological activity, Nucleosides, Nucleotides Nucleic Acids 22 (2003) 1825–1833.

[41] A.K. Mansour, M.M. Eid, N.S.A.M. Khalil, Synthesis and reactions of some new heterocyclic carbohydrazides and related compounds as potential anticancer agents, Molecules 8 (2003) 744–755.

[42] A.K. Mansour, Y.A. Ibrahim, N.S.A.M. Khalil, Selective synthesis and structure of 6-arylvinyl-2- and 4-glucosyl-1,2,4-triazines of expected interesting biological activity, Nucleosides Nucleotides 18 (1999) 2265–2283.

[43] Y.A. Ibrahim, H. Behbehani, N.S. Khalil, Efficient route to 20–32 membered macrocyclic crown diamides via ring closing metathesis, Tetrahedron 60 (2004) 8429–8436.

[44] (a) R.M. Atlas, A.E. Brown, L.C. Parks, Laboratory Manual of Experimental Microbiology. Mosby-Year Book, Inc., New York, NY, 1995;
(b) R.M. Atlas, Handbook of Microbiology Media. Paks, CRC Press, 1993.