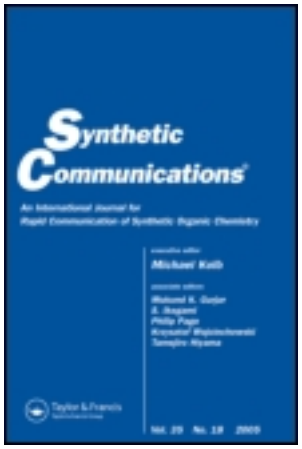

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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SOME NOVEL QUINOXALINES

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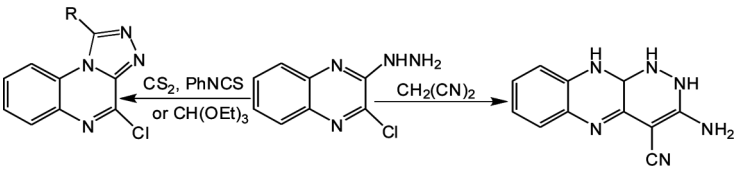
GRAPHICAL ABSTRACT



Abstract *2-Hydrazino-3-chloroquinoxaline* ***2*** *was prepared and reacted with active methylene compounds, potassium thiocyanate, carbon disulfide, phenylisothiocyanate, acetic acid, ethyl chloroformate, triethyl orthoformate, and Lawessen's reagent (LR) to give a new class of fused quinoxalines* ***4–16****, respectively. Also, 2,3-dihydrazinoquinoxaline* ***3*** *was prepared and reacted with carbon disulfide, phenyl isothiocyanate, and triethyl orthoformate to give the corresponding di[1,2,4] triazolo-[4,3-a:3′,4′-c]-quinoxalines* ***17–19****, respectively. Reaction of* ***3*** *with LR gave the corresponding di[1,2,4,3]triazophospholo[4,5-a:5′,4′-c]quinoxaline-1,6-dithione (****20****). It was found that all synthesized compounds exhibit antimicrobial activity and that compound* ***20*** *had a broad spectrum of activity.*

Keywords Antimicrobial activity; polyfused; pyrazoles; quinoxalines; synthesis; triazoles

INTRODUCTION

Quinoxalines can act as glutamate receptors[1] or serine protease inhibitors,[1] and have shown a broad spectrum of biological activities such as anticancer,[2] antimicrobial,[2,3] antibacterial,[4,5] and antitumor[5] activities, which have made them privileged structures in combinatorial drug discovery libraries.[6,7] Moreover, some quinoxaline derivatives served as DNA photocleavers[8] and act as dyes.[9,10] Furthermore, they act as useful rigid subunits in macrocyclic receptors for molecular recognition[11,12] and chemically controllable switches.[13] Hence, they are an important class of nitrogen-containing heterocycles and useful intermediates in organic synthesis.[14]

In the light of these facts, we have synthesized some new families of fused and polyfused heterocyclic compounds incorporating quinoxaline moiety with the hope

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that they will possess better antimicrobial activity. All the synthesized compounds were screened for their antibacterial and antifungal activities against some selected microbes.

RESULTS AND DISCUSSIONS

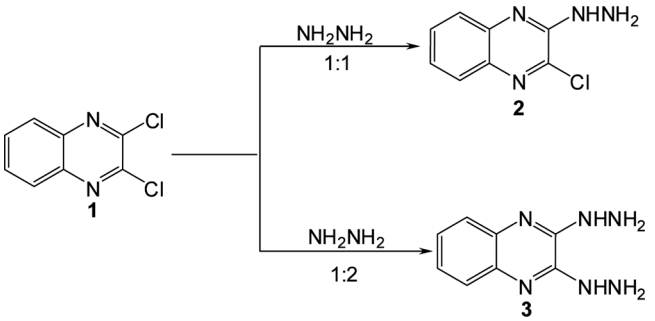
Chemistry

The chemical synthesis commences with the preparation of 2-hydrazino-3-chloroquinoxaline[15,16] **(2)** and 2,3-dihydrazinoquinoxaline[17] **(3)** by treating 2,3-dichloroquinoxaline **(1)** with hydrazine hydrate in 1:1 or 1:2 molar ratios (Scheme 1).

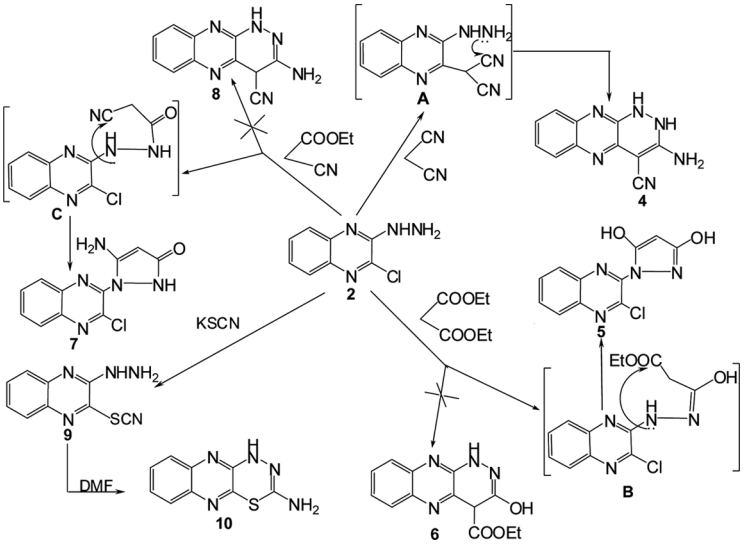
Compound **2** was allowed to react with malononitrile in the presence of triethylamine (TEA) as a basic catalyst to give the corresponding pyridazinoquinoxalin derivative **4**, while its reaction with other active methylene compounds (namely, ethyl cyanoacetate or diethylmalonate) in the same reaction conditions furnished the pyrazoloquinoxaline derivatives **5** and **7**, respectively. The expected fused products **6** and **8** were not obtained, perhaps because of the lesser reactivity of the methylene group in these reagents than in the malononitrile. The formation of compound **4** was assumed to proceed via substitution of the chloro atom in compound **2** with malononitrile to give the intermediate **A** followed by intermolecular cyclization through nucleophilic attack of the NH_2 group at CN group (Scheme 2). The first step of the formation of compounds **5** and **7** was assumed to be the addition of an NH_2 group of compound **1** at the C=O group with elimination of ethanol molecule to yield intermediates **B** and **C**, which then undergo intermolecular cyclization to give the desired compounds **5** and **7** respectively.

Treatment of compound **2** with potassium thiocyanate in refluxing ethanol led to the formation of quinoxaline derivative **9** and in turn refluxed in dimethyl formamide (DMF) for 18 h to give the cyclized compound **10**. Infrared (IR) spectrum of compound **10** showed absorption peaks at 3395, 3320, and 3198 cm^{-1}, which correspond to the presence of NH and NH_2 groups, respectively, whereas its ^1H NMR showed a broad singlet signal at δ 9.2 for the NH group, multiplet signals at 7.5–7.0 for the aromatic protons, and a broad signal at 5.2–4.6 for the NH_2 group (Scheme 2).

The biological activity of fused azoles has led to intensive research on their synthesise.[18,19] Hence, in this work, we have tried to synthesize a new family of fused



Scheme 1. Reaction of 2,3-dichloroquinoxaline with hydrazine hydrate.



Scheme 2. Reaction of compound **2** with some active methylene compounds.

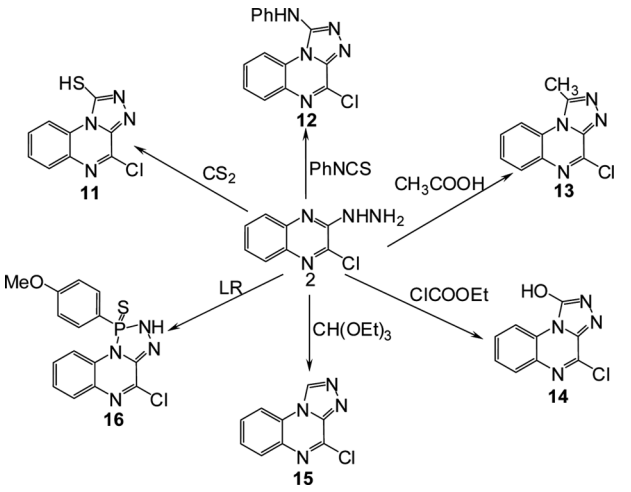
s-triazoloquinoxaline via the reaction of compound **2** with different reagents, namely carbon disulfide, phenyl isothiocyanate, acetic acid, ethylchloroformate, and triethyl orthoformate, to give the corresponding triazoloquinoxaline derivatives **11**–**15**, respectively (Scheme 3). Treatment of compound **2** with Lawesson's reagent (LR) in boiling xylene gave 4-chloro-1-(4-methoxyphenyl)-1,2-dihydro[1,2,4,3]triaza-phospholo-[4,5-a]quinoxaline-1-sulfide (**16**). The IR spectrum of compound **16** did not show the band corresponding to the NH_2 group, while exhibiting the characteristic absorption band at 658 cm^{-1} for P=S. The ^1H NMR spectrum of compound **16** exhibited a singlet signal at 3.7 ppm corresponding to the methoxy group. The mass spectra of compound **16** showed a molecular ion at m/z 362 (83), consistent with formation of the product (Scheme 3).

The o-dihydrazino function in compound **3** was exploited to synthesize some new polyfused heterocyclic compounds. Compound **3** was reacted with carbon disulfide, phenyl isothicyanate, or triethyl orthoformate to give the corresponding di[1,2,4]triazolo[4,3-*a*:3′,4′-*c*]quinoxalines derivatives **17–19**, respectively. IR spectra of compounds **17–19** showed the disappearance of the absorption bands corresponding to the NH_2 group. Compound **3** was allowed to react with LR in boiling xylene to yield 1,6-bis(4-methoxyphenyl)-1,2,5,6-tetrahydrobis[1,2,4,3]triaza-phospholo-[4,5-*a*:4′,5′-*c*]quino-xaline-1,6-disulfide **20** (Scheme 4).

The structures of new compounds were confirmed on the basis of elemental analyses as well as spectral data.

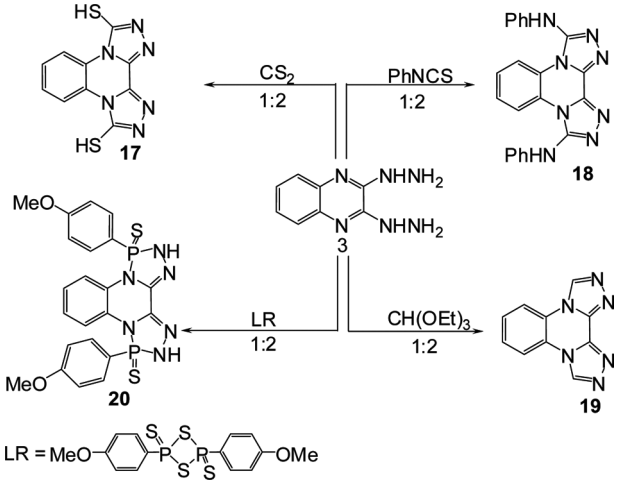
Antimicrobial Evaluation

Newly synthesized compounds were screened for their antifungal activity against *Aspergillus flavus* and *Chrysosporium keratinophilum*, and their antibacterial activities were determined against Gram-positive bacteria (*Staphylococcus aureus*



Scheme 3. Synthesis of some new triazoloquinoxaline derivatives.

and *Bacillus cereus*) and Gram-negative bacteria (*Pseudomonas aeruginosa* and *Escherichia coli*). The results of antimicrobial testing, as shown in Table 1, revealed that compounds **4, 5**, and **7** have little antimicrobial activity against either Gram-positive and Gram-negative bacteria. Compounds **13** and **16** were comparable to the standard against *P. aeruginosa*, while compound **16** was comparable to the standard against *S. aureus*.[20] Compounds **9–12** possessed little or no activity against Gram-positive and Gram-negative bacteria. Compound **17** showed moderate activity on Gram-negative bacteria, but it was more active on Gram-positive bacteria. As for the antifungal activity, only compound **16** showed strong activity against *A. flavus*, whereas compounds **4, 19**, and **20** showed strong or very strong



Scheme 4. Synthesis of some new ditriazoloquinoxaline derivatives.

Table 1. Antimicrobial activity of compounds **4–20** as indicated by their inhibition zone activity (mm)

	Fungi		Gram-positive bacteria		Gram-negative bacteria	
Comp.	*A. flavus*	*C. keratinophilum*	*S. aureus*	*B. cereus*	*P. aeruginosa*	*E. coli*
4	10	17	13	—	14	—
5	—	10	—	11	14	—
7	—	—	14	13	—	10
9	9	11	10	10	9	—
10	—	10	9	—	—	—
11	—	—	14	9	—	9
12	10	10	—	10	10	10
13	—	10	10	18	20	13
14	9	9	—	12	17	—
15	—	12	8	11	—	12
16	15	13	22	20	21	14
17	—	9	16	15	11	10
18	8	—	17	11	—	10
19	10	16	—	12	16	—
20	12	21	19	14	17	17

activities against *C. keratinophilum*. The other tested compounds showed weak or no activity. Compound **20** can be considered as the most promising antibacterial and antifungal agent (cf. Table 1).

CONCLUSIONS

In conclusion, several fused and polyfused quinoxalines **4–20** were synthesized. Because of the availability of the starting materials, the simplicity of the procedures, and the comparatively reasonable yields of the products, this synthetic approach might be valuable for the synthesis of such ring systems. All the synthesized compounds exhibited good antibacterial activity toward both Gram-positive and Gram-negative bacteria. Some of the synthesized compounds showed good to moderate activity against the tested fungi, especially *C. keratinophilum*, making these compounds very important to treat this dermatophilic fungus.

EXPERIMENTAL

All melting points were determined on a Koffler melting-point apparatus and are uncorrected. IR spectra were obtained on a Nicolet 710 Fourier transform (FT)–IR spectrometer. ^{1}H NMR spectra were recorded on a Varian EM 360 at 60 MHz using tetramethylsilane (TMS) as an internal reference and DMSO-d_6 as a solvent. Elemental analyses were performed on a Perkin-Elmer CHN-2400C analyzer model.

Methods of Synthesis

3-Amino-1,4-dihydropyridazino[3,4-*b*]quinoxaline-4-carbonitrile (4). An equimolar ratio of compound **2** (1.94 g, 0.01 mol), malononitrile (0.66 g, 0.01 mol),

and triethylamine (TEA) (1.20 mL, 0.011 mol) was refluxed in ethanol (20 mL) for 5 h. After cooling, the reaction mixture was poured into ice-cold water containing drops of HCl. The precipitated solid was filtered off, dried, and crystallized from aqueous ethanol as brown crystals, 1.54 g (69%), mp 200 °C; IR: 3555, 3344, 3214 (2NH, NH_2); 2202 (CN) cm^{-1}; ^1H NMR: 8.7 (br, s, 1H, NH), 7.8–6.9 (m, 4H, arom., 1H, NH), 4.2–3.8 (br, 2H, NH_2). Anal. calcd. for $C_{11}H_8N_6$: C, 58.92; H, 3.60; N, 37.48. Found: C, 59.03; H, 3.44; N, 37.36.

1-(3-Chloroquinoxalin-2-yl)-1H-pyrazole-3,5-diol (5). An equimolar ratio of compound **2** (1.94 g, 0.01 mol), diethylmalonate (1.50 mL, 0.01 mol), and TEA (1.20 mL, 0.011 mol) was refluxed in ethanol (20 mL) for 7 h. After cooling, the reaction mixture was poured into ice-cold water containing drops of HCl. The precipitated solid was filtered, dried, and recrystallized from methanol as brown crystals, 1.34 g (51%), mp 294 °C; IR: 3435 (OH) cm^{-1}; ^1H NMR: 9.8 (br, s, 2H, 2OH), 7.8–6.9 (m, 4H, arom., 1H-pyrazole). Anal. calcd. for $C_{11}H_7ClN_4O_2$: C, 50.30; H, 2.69; N, 21.33. Found: C, 50.25; H, 2.48; N, 21.35.

5-Amino-1-(3-chloroquinoxalin-2-yl)-1,2-dihydro-3H-pyrazol-3-one (7). An equimolar ratio of compound **2** (1.94 g, 0.01 mol), ethylcyanoacetate (1.07 mL, 0.01 mol), and TEA (1.20 mL, 0.011 mol) was refluxed in ethanol (20 mL) for 6 h. After cooling, the reaction mixture was poured into ice-cold water containing drops of HCl. The precipitated solid was filtered, dried, and recrystallized from dioxane as red crystals, 1.54 g (68%), mp 143 °C; IR: 3400 (NH), 3311, 3200 (NH_2), 1673 (CO) cm^{-1}; ^1H NMR: δ 8.1–7.0 (m, 4H, arom., 1H-pyrazole,1H, NH), 5.4–5.0 (br, s, 2H, NH_2). Anal. calcd. for $C_{11}H_8ClN_5O$: C, 50.49; H,3.08; N, 26.76. Found: C, 50.50; H, 2.94; N, 26.80.

3-Hydrazinoquinoxalin-2-yl Thiocyanate (9). To an ethanol solution (30 ml) of compound **2** (1.94 g, 0.01 mol), an equimolar amount of potassium thiocyanate (1.1 g, 0.011 mol) in water was added. After refluxuing for 10 min, a precipitate was formed, which was filtered on hot and washed well with water to give a pure reddish-brown powder, 1.7 g (78%), mp 300 °C; IR 3421 (NH) 3294, 3201 (NH_2), 2178 (SCN) cm^{-1}; ^1H NMR: δ 7.7–7.0 (m, 4H, arom., 1H, NH), 5.3–4.9 (br 2H, NH_2). Anal. calcd. for $C_9H_7N_5S$: C, 49.76; H, 3.25; N, 32.24. Found: C, 49.73; H, 3.21; N, 32.26.

1H-[1,3,4]Thiadiazino[5,6-*b*]quinoxalin-3-amine (10). Compound **9** (1.5 g, 0.007 mol) was refluxed in dimethylformamide (DMF) for 18 h. The precipitated product formed after cooling was filtered off and recrystallized from methanol as brown crystals, 1.0 g (66.7%), charring at 320 °C; IR 3395, 3320, 3198 (NH, NH_2) cm^{-1}; ^1H NMR: δ 9.2 (br, s, 1H, NH), 7.5–7.0 (m, 4H, arom.), 5.1–4.6 (br 2H, NH_2). Anal. calcd. for $C_9H_7N_5S$: C, 49.76; H, 3.25; N, 32.24. Found: C, 49.73; H, 3.21; N, 32.26.

4-Chloro[1,2,4]triazolo[4,3-*a*]quinoxaline-1-thiol (11). A mixture of compound **2** (1.94 g, 0.01 mol) and carbon disulphide (0.9 ml, 0,015 mol) in pyridine (20 mL) was refluxed (until the evolution of H_2S finished). The reaction mixture was then poured onto cold water, and the solid product precipitated was collected by filtration, dried, and recrystallized from dioxane as yellow crystals, 1.8 g (76%),

mp 362 °C; IR: 3112 (NH), 1154 (C=S) cm^{-1}; ^1H NMR: δ 9.9 (br, s, NH), 7.4–6.9 (m, 4H, arom.). Anal. calcd. for $C_9H_5ClN_4S$: C, 45.67; H, 2.13; N, 23.67. Found: C, 45.64; H, 2.10; N, 23.70.

4-Chloro-N-phenyl[1,2,4]triazolo[4,3-*a*]quinoxalin-1-amine (12). Compound **2** (1.94 g, 0.01 mol) and phenyl isothiocyanate (1.25 mL, 0.01 mol) in pyridine was allowed to reflux until the evolution of H_2S finished. The reaction mixture was cooled and diluted with water, and the resulting solid was recrystallized from ethanol as yellow crystals, 2.4 g (81%), mp 176 °C; IR: 3389 (NH) cm^{-1}; ^1H NMR: δ 9.7 (br, s, 1H, NH), 7.5–6.7 (m, 9H, arom.). Anal. calcd. for $C_{15}H_{10}ClN_5$: C, 60.92; H, 3.41; N, 23.68. Found: C, 60.90; H, 3.39; N, 23.61.

4-Chloro-1-methyl[1,2,4]triazolo[4,3-*a*]quinoxaline (13). A mixture of compound **2** (1.94 g, 0.01 mol) and acetic acid (10 mL) was heated under reflux for 4 h. After cooling, the precipitate was filtered and recrystallized from dioxane as a yellow powder, 1.7 g (78%), mp 340 °C; IR: 2910 (CH aliph.) cm^{-1}; ^1H NMR: δ 7.2–6.9 (m, 4H arom.), 2.3 (s, 3H, CH_3). Anal. calcd. for $C_{10}H_7ClN_4$: C, 54.93; H, 3.23; N, 25.62. Found: C, 55.08; H, 3.20; N, 25.65.

4-Chloro[1,2,4]triazolo[4,3-*a*]quinoxalin-1-ol (14). Compound **2** (1.94 g, 0.01 mol) and ethylchloroformate (3 mL) was allowed to reflux in pyridine (20 mL) for 3 h. After cooling, the precipitated solid was filtered, washed well with water, dried, and recrystallized from methanol as a dark brown powder, 1.2 g (54%), mp 355 °C; IR: 3420 (OH) cm^{-1}; ^1H NMR: δ 9.2 (s, 1H, OH) 7.6–7.0 (m, 4H, arom.). Anal. calcd. for $C_9H_5ClN_4O$: C, 49.00; H, 2.28; N, 25.40. Found: C, 49.02; H, 2.25; N, 25.37.

4-Chloro[1,2,4]triazolo[4,3-*a*]quinoxaline (15). Compound **2** (1.94 g, 0.01 mol) was allowed to reflux in excess of triethyl orthoformate (15 mL) for 2 h and left to cool to room temperature. The resulting precipitated solid was filtered, dried, and recrystallized from ethanol as yellow crystals, 1.5 g (61%), mp 292 °C; IR: 1613, (C=N) cm^{-1}; ^1H NMR: 8.5 (s, 1H, CH-triazole), δ 8.0–7.5 (m, 4H, arom.). Anal. calcd. for $C_9H_5ClN_4$: C, 52.83; H, 2.46; N, 27.38. Found: C, 52.85; H, 2.43, N, 27.35.

4-Chloro-1-(4-methoxyphenyl)-1,2-dihydro[1,2,4,3]triazaphospholo-[4,5-*a*]quinoxaline-1-sulfide (16). A mixture of 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide (LR) (2.02 g, 0.005 mol) and compound **2** (1.94 g, 0.01 mole) in dry xylene (50 ml) was refluxed until no more of the reactants could be detected by thin-layer chromatography (TLC) (5 h). The reaction mixture was concentrated and left to cool to room temperature. The resultant precipitate was collected by filtration and recrystallized from dioxane as a red powder, mp 215–217 °C; IR: 3308 (NH), 658 (P=S) cm^{-1}; ^1H NMR: δ 9.4 (br, s, 1H, NH), 7.6–7.0 (m, 8H, arom.) 3.7 (s, 3H, CH_3). Anal. calcd. for $C_{15}H_{12}ClN_4OPS$: C, 49.66; H, 3.33; N, 15.44. Found: C, 49.68; H, 3.31; N, 15.41.

Bis[1,2,4]triazolo[4,3-*a*:3′,4′-*c*]quinoxaline-3,10-dithiol (17). A mixture of **3** (1.90 g, 0.01 mol) and carbon disulfide (1.8 mL, 0.03 mol) in pyridine (20 mL) was heated under reflux until the evolution of H_2S finished. The reaction mixture was then poured onto cold water, whereby the precipitated solid product was collected by filtration, dried, and recrystallized from acetone as yellow crystals, 1.8 g (66%),

mp > 300 °C; IR: 3216 (NH), 1146 (C=S) cm^{-1}; ^1H NMR: δ 14.9 (s, 1H, SH), 10.5 (s, 1H, NH), 7.9–7.5 (m, 4H, arom.). Anal. calcd. for $C_{10}H_6N_6S_2$: C, 43.78; H, 2.20; N, 30.64. Found: C, 43.76; H, 2.18; N, 30.66.

N^3, N^{10}-Diphenylbis[1,2,4]triazolo[4,3-*a*:3′,4′-*c*]quinoxalin-3,10-diamine (18). Compound **3** (1.90 g, 0.01 mol) and phenyl isothiocyanate (2.60 mL, 0.02 mol) in pyridine was allowed to reflux until the evolution of H_2S finished. The reaction mixture was cooled and diluted with water, and the resulting solid was recrystallized from methanol as yellow powder, 2.1 g (54%), mp > 300 °C; IR: 3230 (NH) cm^{-1}; ^1H NMR: δ 10.2 (br, s, 2H, 2NH), 7.7–6.8 (m, 14H, arom.). Anal. calcd. for $C_{22}H_{16}N_8$: C, 67.34; H, 4.11; N, 28.55. Found: C, 67.41; H, 4.08; N, 28.58.

Bis[1,2,4]triazolo[4,3-*a*:3′,4′-*c*]quinoxaline (19). Compound **3** (1.90 g, 0.01 mol) was allowed to reflux in excess of triethyl orthoformate (20 mL) for 5 h and left to cool to room temperature. The resulting precipitated solid was filtered, dried, and recrystallized from ethanol as a yellow powder, 1.6 g (76%), mp 321 °C; IR: 1631, (C=N) cm^{-1}; ^1H NMR: 8.3–7.4 (m, 4H, arom, 2H, 2CH, triazole). Anal. calcd. for $C_{10}H_6ClN_6$: C, 57.14; H, 2.88; N, 39.98. Found: C, 57.23; H, 2.73; N, 39.87.

1,6-Di(4-methoxyphenyl)-1,2,5,6-tetrahydrobis[1,2,4,5]triazaphospholo [4,5-*a*:4′,5′-*c*]quinoxaline-1,6-disulfide (20). A mixture of 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide LR (4.04 g, 0.01 mol) and compound **3** (1.90 g, 0.01 mol) in dry xylene (70 ml) was refluxed until no more of the reactants could be detected (TLC) (7 h). The reaction mixture was concentrated and left to cool to room temperature. The resultant precipitate was collected by filtration and recrystallized from acetonitrile as-reddish-brown powder, 3.9 g (74%), mp 160 °C; IR: 3244 (NH), 661 (P=S) cm^{-1}; ^1H NMR: δ 9.7 (br, s, 2H, 2NH), 7.7–7.0 (m, 12H, arom.), 3.88–3.85 (d, 6H, $2CH_3$). Anal. calcd. for $C_{22}H_{20}N_6O_2P_2S_2$: C, 50.19; H, 3.83; N, 15.96; S, 12.18. Found: C, 50.21; H, 3.81; N, 15.99; S, 12.20.

Biological Method

The agar plate disc-diffusion method was applied.[21,22] Sterilized filter papers (6 mm in diameter) were wetted with 10 μL of a solution of each compound to be tested, containing 10 mg/mL in DMSO, and the discs were allowed to air dry. The discs were then placed onto the surface of agar plates (nutrient agar for bacteria and Sabouraud's dextrose agar for fungi) seeded with the test organism. Each plate contained 15 mL of the agar medium, previously seeded with 0.2 mL of the broth culture of each organism pregrown for 18 h. The plates were incubated at 37 °C for 48 h for bacteria and 72 h for fungi. The inhibition zones was measured in millimeters. Discs impregnated with DMSO were used as a control, and its inhibition zone was subtracted from the tested compound actual inhibition zone.

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