Synthesis and Antimicrobial Activity of Some Heterocyclic 2,6-Bis(substituted)-1,3,4-thiadiazolo-, Oxadiazolo-, and Oxathiazolidino-Pyridine Derivatives from 2,6-Pyridine Dicarboxylic Acid Dihydrazide

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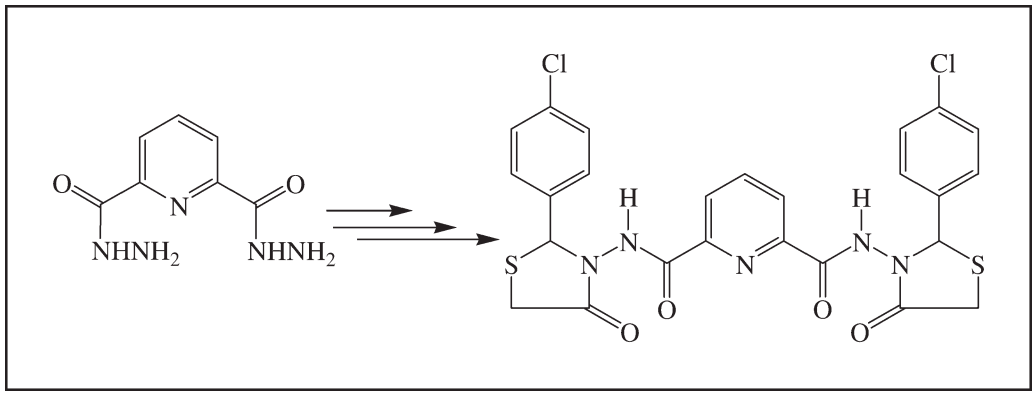

In this work, we report on the synthesis and preliminary biological activity screening of several heterocyclic derivatives **2–15** based on *N*2′,*N*6′-diphenylthiosemi-carbazide pyridine-2,6-dicarbohydrazide **2**, which has been obtained from the corresponding dihydrazide **1**. The biological screening showed that many of these compounds have good antimicrobial activities. The structure of the new compounds has been established on the bases of chemical and spectroscopic evidences.

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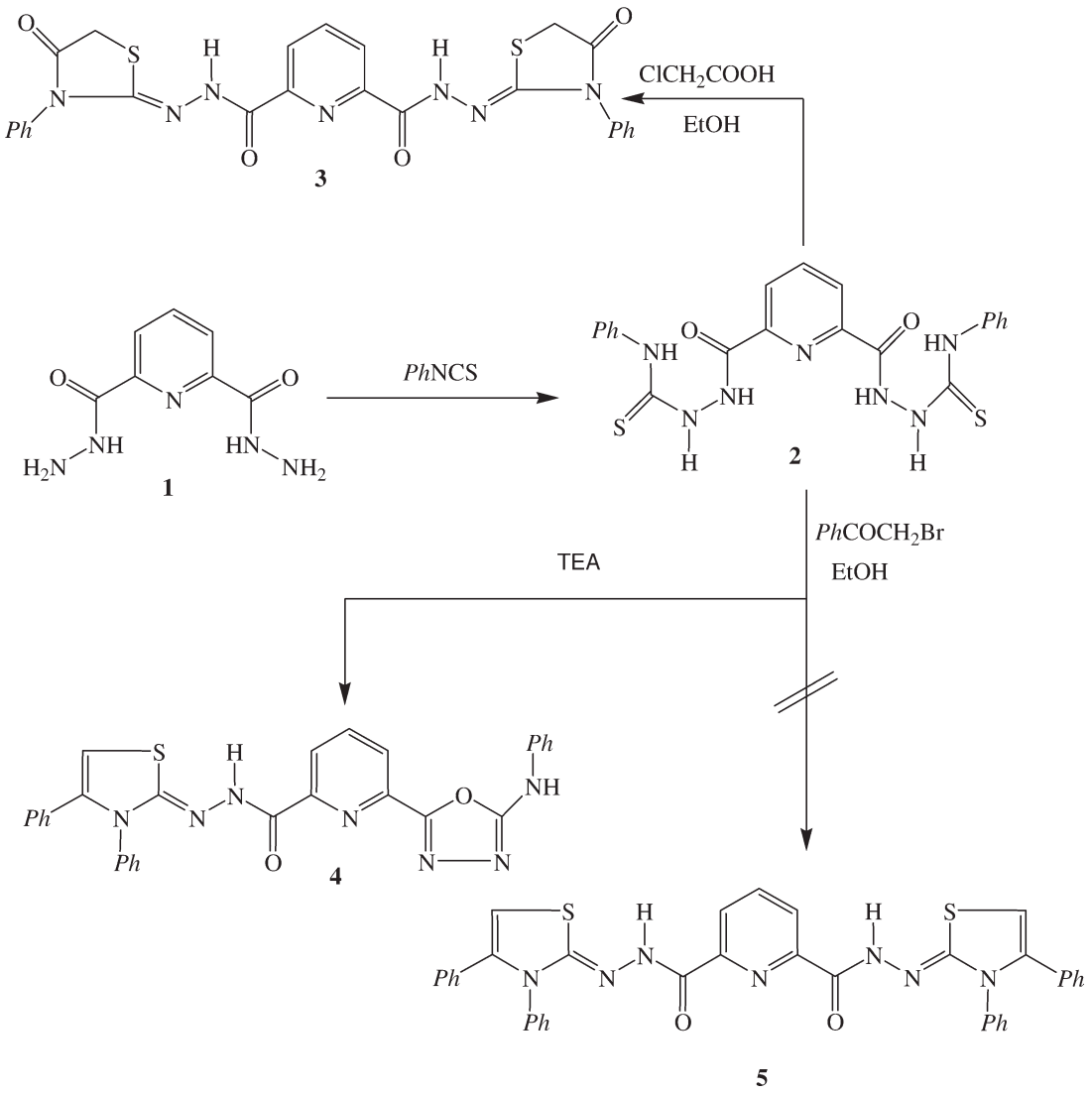
INTRODUCTION

The considerable pharmacological importance of pyridine derivatives has attracted a great deal of attention. On the other hand, attachment of other heterocyclic moieties, which are known to possess pharmacological activity, to pyridine ring may enhance their biological activity. In our previous work, we have reported that certain of heterocyclic compounds exhibited antitumor [1], antiparkinsonian [2–4], anti-microbial [5,6], and anti-inflammatory [7–10] activities. Another an interesting group of compounds were found to exhibit pharmacological properties such as analgesic [11,12] and antiarihythmic [13] activities. On the other hand, some synthetic thiazoles exhibit a wide range of biological activities, such as antitumor, antibiotic, antibacterial, antifungal, and antiinflammatory activities [14–17]. Recent studies have shown some new thiazole cand idates as antimicrobial and anticancer agents [18–21]. In addition, we have reported a newly substituted heterocyclic compounds as antitumor [22–24], antimicrobial [25], and anti-inflammatory [26] activities. In particular, 2,6-peptidopyridines exhibited a general ionophoric potency [27] and were used for inventing novel thiocyanate-selective membrane sensors [28]. In view of these observations and in continuation of our previous work in heterocyclic pyridine chemistry, we have herein synthesized of some new derivatives containing pyridine moiety.

RESULTS AND DISCUSSION

In this work, we report on the synthesis and preliminary biological activity screening of several heterocyclic derivatives based on compound **2**, which has been obtained from the corresponding hydrazide **1** according to the published procedure in the previous work [29]. Treatment of compound **2** with chloroacetic acid in absolute ethanol afforded the corresponding derivative **3**. On the other hand, when **2** treated with phenacyl bromide in the presence of catalytic amount of triethylamine gave unexpected product **4** and the expected compound **5** not

Scheme 1



formed (Scheme 1). Structure of **4** was identified by analytical and spectral data. EI-MS spectrum of **4** showed the molecular ion peak at *m/z* 531 (43%) corresponding to the molecular formula $C_{29}H_{21}N_7O_2S$ instead of $C_{37}H_{27}N_7O_2S_2$ (665). As well as, a fragment ion peak at 160 (18%) was supported to the substituted oxadiazole ring. Further confirmation for the unsymmetrical structure **4** was explained by ^{1}H-NMR. It displayed an ABM spin coupling system, each one proton, for the pyridine ring protons at δ 7.90 and 7.95 ppm (dd) and 8.30 (t). Additionally, only one CH proton was appeared at 6.21 along with two singlet signals were assigned at δ 8.90 and 10.35 ppm characteristic for two unequivalent NH protons. Accordingly, for the above spectral data, the structure **4** has been established.

The reasonable suggested mechanism that explains formation of compound **4** was illustrated in Figure 1.

The dihydrazide **1** was reacted with carbon disulfide in ethanolic potassium hydroxide with stirring at room temperature to afford the corresponding potassium salt **6**, which was cyclized by refluxing with alcoholic potassium hydroxide for 3 h, via elimination of two molecule of potassium hydrogen sulfide to compound **7**. The same product **7** has been obtained by carrying the reaction under reflux with carbon disulphide in alcoholic potassium hydroxide in one step. Treatment of the potassium salt **6** with hydrazine hydrate under reflux afforded the corresponding compound **8**, which was also obtained by treating compound **7** with hydrazine hydrate. In addition, treatment of the potassium salt **6** with sulfuric acid under reflux afforded thiadiazole derivative **9** (Scheme 2).

The compound **1** was treated with acid chloride derivatives, namely, benzoyl or 4-chlorobenzoyl chlorides under stirring in dry pyridine to give the corresponding

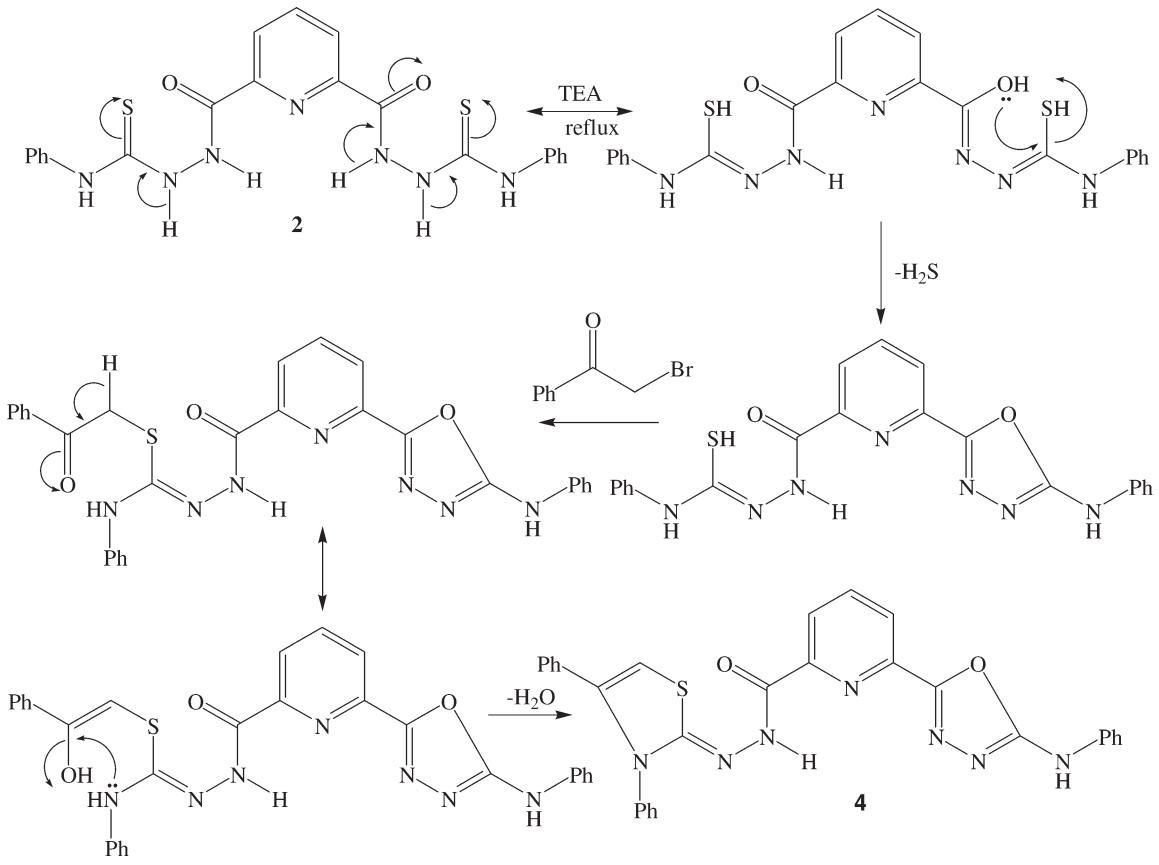


Figure 1. The suggested mechanism that explains formation of compound **4**.

compounds **10a,b**. Also, **1** was condensed with aromatic aldehydes, namely, 4-chloro- or 4-methoxy-benzaldhyde in ethanol to give the corresponding Schiff bases **11a,b**. The carbohydrazide derivatives **10a,b** were heated with sulfuric acid at 120°C to afford the corresponding oxadiazolyl derivative **12a,b**. Also, compounds **10a,b** were treated with phosphorus pentasulphide in dry benzene to afford the corresponding thiadizolylpyridine derivatives **13a,b**. The reaction of the hydrazone derivative **11a** with mercaptoacetic acid in dry benzene, it afforded oxothiazolidin-pyridine-dicarboxamide **14**. Treatment of **11a** with acetic anhydride under reflux afforded oxadiazolylpyridine derivative **15** (Scheme 3).

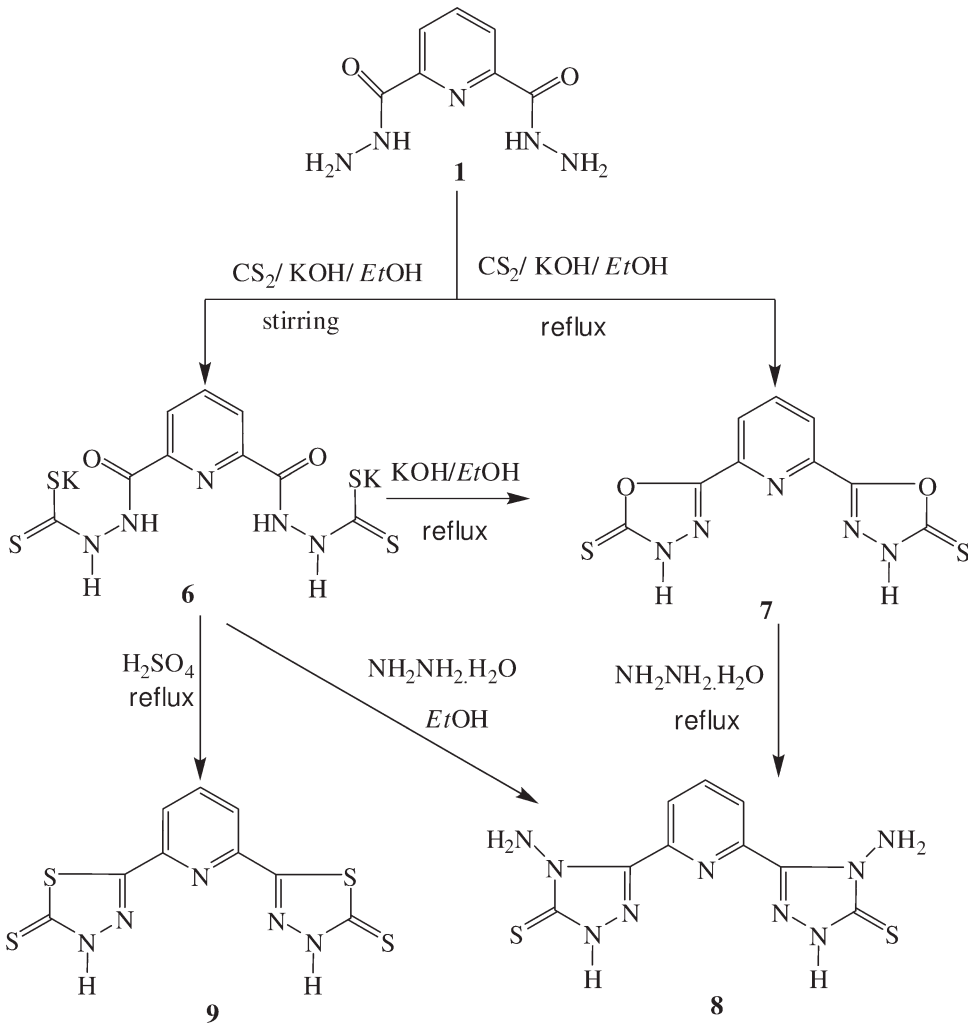
Antimicrobial activity. The newly synthesized compounds were tested for their preliminary antimicrobial activity against different microorganisms representing Gram-positive bacteria (*Bacillus subtilis*, *Bacillus au*reus, and *Staphylococcus aureus*), Gram-negative bacteria (*Escherichia coli*), yeast (*Candida albican*), and fungi (*Aspergillus niger*). The most active compounds were: **4**, **6**, **8**, **10b**, **11a**, **12b**, and **13b** (all organisms), **3**, **9**, and **12a** (*B. aureus*), **5**, **10a**, **14**, and **15** (*Staph. aureus*), **7** and **11b** (*E. coli*), **10b** and **15** (C. *albicans*), and **9**, **14**, and **15** (*A. niger*). The results are summarized in Table 1.

EXPERIMENTAL

Melting points were determined on open glass capillaries using a Electrothermal IA 9000 digital melting point apparatus and corrected. Elemental analyses were performed on Elementar, Vario EL, Microanalytical Unit, National Research Center, Cairo Egypt and were found within ±0.4% of the theoretical values. Infrared spectra were recorded on Carlzeise Spectrophotometer model ''UR 10'' spectrophotometer using the KBr disk technique. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Varian Gemini 270 MHz spectrometer (DMSO-d_6) and the chemical shifts are given in δ (ppm) downfield from tetramethylsilane (TMS) as an internal standard. The mass spectra were measured using a Finnigan SSQ 7000 mass spectrometer. Follow-up of the reactions and checking the purity of the compounds was made by TLC on silica gel-aluminum sheets (Type 60 F_{254}, Merck, Darmstadt, Germany).

***N*2′,*N*6′-Bis(4-oxo-3-phenylthiazolidin-2-ylidene)pyridine-2,6-dicarbohydrazide (3).** A mixture of **2** (0.46g, 1 mmol) and chloroacetic acid (0.19 g, 2 mmol) in 20 mL absolute ethanol was refluxed for 20 h. The solvent was concentrated under reduced pressure and the residue was poured onto water, the separated solid was filtered off, washed with water, dried, and crystallized from dioxane to give the title compound **3** in 70% yield as red crystals, mp 306–308°C; IR (KBr): ν = 3332–3240 (NH), 1710 (C=O), 1685 (C=O), 1660 (C=C) cm^{-1}; ^{1}H-NMR (270 MHz, DMSO-d_6): δ = 3.60 (s, 4H, 2CH_2), 7.25–7.75 (m, 10H, Ar—H), 8.14 (d, 2H, J = 8.0 Hz,

Scheme 2



pyrid-H), 8.51 (t, 1H, J = 8.0 Hz, pyrid-H), 12.50 (bs, 2H, 2NH, exchangeable with D_2O); ^{13}C-NMR (67.5 MHz, DMSO-d_6): δ = 29.82 ($2CH_2$), 121.05, 124.01, 128.32, 134.84 (12C, 2Ph), 124.32, 138.56, 148.60 (5C, pyrid-C), 147.76 (2C=N), 156.74 (2C=O, amides), 172.45 (2C=O, thiazole); ms: *m/z* 545 (62), 399 (24), 320 (12), 192 (100), 60 (78); Anal. Calcd. for $C_{25}H_{19}N_7O_4S_2$: C, 55.04; H, 3.51; N, 17.97; S, 11.75. Found: C, 54.95; H, 3.45; N, 17.93; S, 11.70.

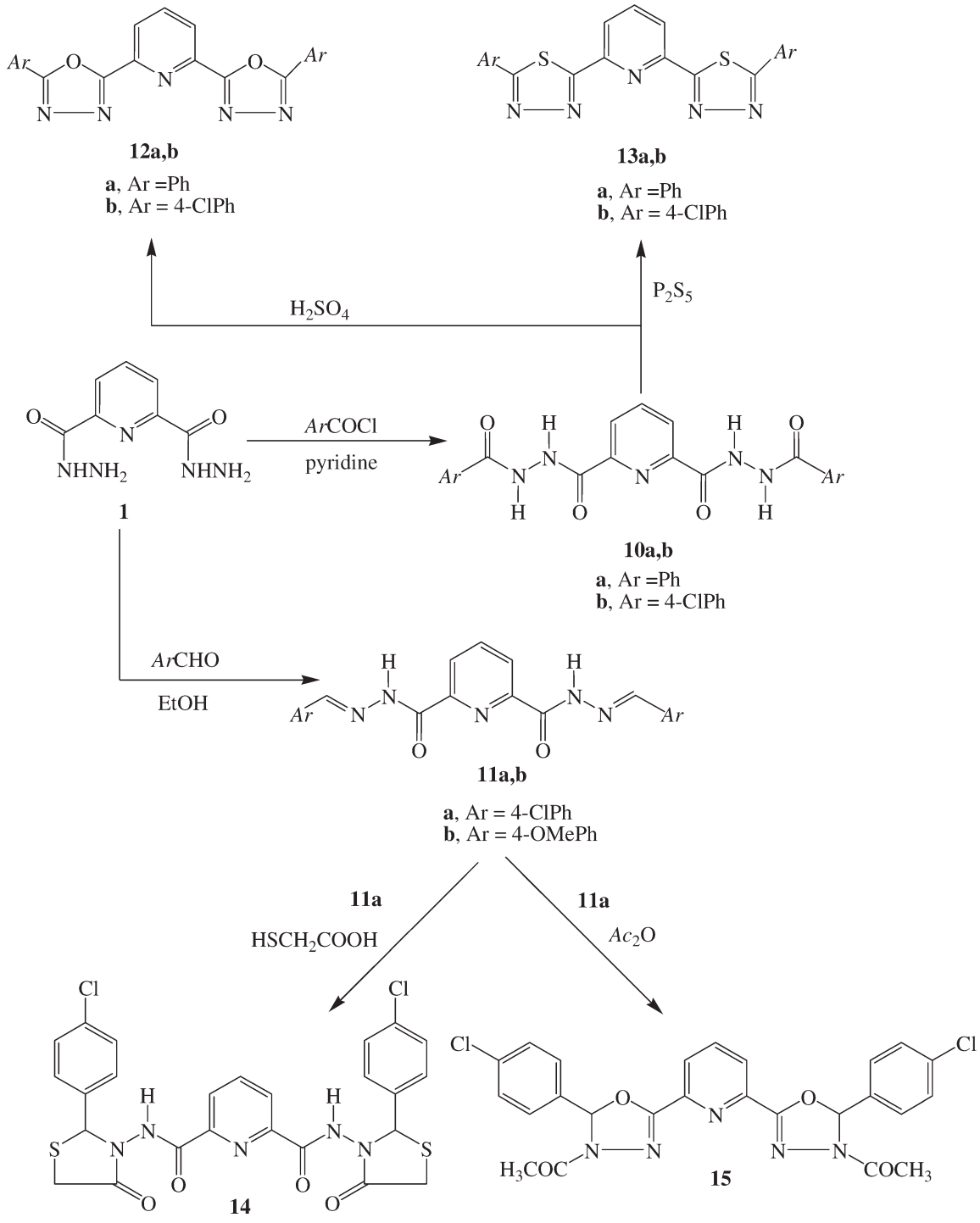
6-(5-(Phenylamino)-1,3,4-oxadiazol-2-yl)-*N*′-(3,4-diphenylthiazol-2(3H)-ylidene) pyridine-2-carbohydrazide (4). To a mixture of **2** (1.40 g, 3 mmol) and phenacyl bromide (0.60 g, 3 mmol) in 50 mL absolute ethanol, a catalytic amount of TEA was added. The reaction mixture was heated under reflux for 3 h, the obtained precipitate was filtered off, and crystallized from ethanol to give the title compound **4** in 60% yield as yellow crystals; mp 298–300°C; IR (KBr): ν = 3334–3220 (NH), 1680 (C=O), 1665 (C=N), 1660 (C=C) cm^{-1}; ^{1}H-NMR (270 MHz, DMSO-d_6): δ = 6.21 (s, 1H, thiazole-H), 7.30–7.80 (m, 15H, Ar—H), 7.90 (dd, 2H, J = 8.0, 2.5 Hz, pyrid-H), 7.95 (t, 2H, J = 8.0 Hz, pyrid-H), 8.30 (dd, 1H, J = 8.0, 2.5 Hz, pyrid-H), 8.90, 10.35 (2s, 2H, 2NH, exchangeable with D_2O); ^{13}C-NMR (67.5 MHz, DMSO-d_6): δ = 118.38, 126.48, 138.24, 150.88, 155.72 (5C, pyrid-C), 115.56, 116.05, 117.92, 118.16, 125.86, 127.36, 128.15, 128.96, 129.18, 133.68, 140.26, 142.90 (18C, 3Ph), 105.78, 147.05, 153.90 (3C, thiazole ring), 150.70, 151.36 (2C, oxadiazole ring), 156.84 (C=O, amide); ms: *m/z* 531 (15), 440 (42), 288 (22), 220 (100), 160 (18), 135 (65); Anal. Calcd. for $C_{29}H_{21}N_7O_2S$: C, 65.52; H, 3.98; N, 18.44; S, 6.03. Found: C, 65.44; H, 3.92; N, 18.38; S, 5.95.

Potassium salt of thiosemicarbazid derivative (6). To a stirred solution of **1** (1.95 g, 10 mmol) in absolute ethanol 10 mL containing potassium hydroxide (1.68 g, 30 mmol), carbon disulfide (2.28 g, 30 mmol) was added. The reaction mixture was stirred at room temperature for 8 h. After cooling, the product was precipitated with dry ether, filtered off, washed with ether to give the corresponding potassium salt **6** in pure form (86% yield) as white powder; IR (KBr): ν = 3350–3280 (NH), 1688 (C=O), 1259 (C=S) cm^{-1}; Anal. Calcd. for $C_9H_7K_2N_5O_2S_4$: C, 25.52; H, 1.67; N, 16.53; S, 30.28. Found C, 25.46; H, 1.62; N, 16.48; S, 30.24.

2,6-Bis(4,5-dihydro-5-thioxo-1H-1,2,4-oxadiazole-3-yl)pyridine (7)

Method A. To a mixture of **1** (1.95 g, 10 mmol) and potassium hydroxide (1.68 g, 30 mmol) in absolute ethanol 100 mL,

Scheme 3



carbon disulfide (2.28 g, 30 mmol) was added. The reaction mixture was refluxed for 5 h. then diluted with water and acidified with hydrochloric acid pH ~ 3–4. The precipitated solid was filtered off, washed with water, dried, and crystallized from ethanol to give compound **7** in 70% yield as yellow crystals.

Method B. A mixture of **6** (4.23 g, 10 mmol) and potassium hydroxide (1.68 g, 30 mmol) in absolute ethanol 100 mL was refluxed for 4 h. The reaction mixture was diluted with water and acidified with hydrochloric acid pH ~ 3–4. The formed solid was collected by filtration, washed with water, dried, and crystallized from ethanol to give the title compound **7** in 90% yield as yellow crystals; mp 211–213°C; IR (KBr): ν = 3393 (NH), 1665 (C=N), 1660 (C=C) cm^{-1}; ^{1}H-NMR (270 MHz, DMSO-d_6): δ = 7.85–8.25 (m, 3H, pyrid-H), 10.85 (bs, 2H,

Table 1

Antimicrobial activities of newly synthesized compounds **2–15**.

	Inhibition zones (cm)					
	Gram-positive bacteria			Gram-negative bacteria	Yeast	Fungi
Comp. No.	*B. subtilis*	*B. aureus*	*S. aureus*	*E. coli*	*C. albicans*	*A. niger*
2	1.65	1.78	1.77	0.50	–	1.50
3	1.65	1.92	1.62	0.48	–	1.45
4	1.98	1.86	1.94	0.86	0.65	1.95
5	1.62	1.60	1.96	–	–	1.65
6	1.85	1.96	1.88	0.88	0.64	1.99
7	1.55	1.61	1.56	0.91	–	1.75
8	1.84	1.86	1.94	0.87	0.55	1.85
9	1.66	1.95	1.46	0.57	–	2.05
10a	1.70	1.64	1.98	0.54	–	1.46
10b	1.88	1.94	1.95	0.84	0.75	1.89
11a	1.95	1.96	1.88	0.87	0.55	1.96
11b	1.54	1.64	1.52	0.90	–	1.48
12a	1.56	1.98	1.66	0.74	–	1.54
12b	1.85	1.88	1.90	0.86	0.60	1.95
13b	1.96	1.94	1.92	0.90	0.52	1.92
14	1.66	1.72	1.95	0.67	–	2.0
15	1.71	1.66	1.94	1.56	0.86	2.04
Chloramphinicol®	2.0	2.10	2.0	0.95	–	2.10

2NH, exchangeable with D_2O); ^{13}C-NMR (67.5 MHz, DMSO-d_6): δ = 125.48, 135.76, 146.90 (5C, pyrid-C), 149.36, 156.42 (4C, oxadiazole ring); ms: *m/z* 279 (8), 171 (32), 122 (14), 64 (100); Anal. Calcd. for $C_9H_5N_5O_2S_2$: C, 38.70; H, 1.80; N, 25.07; S, 22.96. Found C, 38.64; H, 1.75; N, 24.98; S, 22.90.

2,6-Bis(4-amino-4,5-dihydro-5-thioxo-1H-1,2,4-triazole-3-yl)pyridine (8)

Method A. A solution of 6 (4.23 g, 10 mmol) in hydrazine hydrate (5 mL, 70%) was refluxed for 3 h. After cooling, the white solid formed was filtered off, dried, and crystallized from DMF/EtOH to afford compound 8 in 75% yield as brown crystals.

Method B. A solution of **7** (2.80 g, 10 mmol) in absolute ethanol 20 mL and hydrazine hydrate (5 mL, 70%) was refluxed for 3 h. The reaction mixture was diluted with water and acidified with diluted hydrochloric acid pH ∼ 6. The precipitated solid was filtered off, dried, and crystallized from DMF/EtOH to give compound **8** in 60% yield as brown crystals; mp 240–242°C; IR (KBr): ν = 3399–3224 (NH_2, NH), 1664 (C=N), 1658 (C=C), 1258 (C=S) cm^{-1}; ^{1}H-NMR (270 MHz, DMSO-d_6): δ = 6.30 (bs, 2H, $2NH_2$ exchangeable with D_2O), 7.70 (d, 2H, *J* = 8.0 Hz, pyrid-H), 8.10 (t, 1H, *J* = 8.0 Hz, pyrid-H), 8.60 (bs, 2H, 2NH, exchangeable with D_2O); ^{13}C-NMR (67.5 MHz, DMSO-d_6): δ = 121.68, 135.56, 153.86 (5C, pyrid-C), 154.15, 178.10 (4C, triazole ring); ms: *m/z* 307 (9), 274 (18), 213 (12), 146 (100), 56 (76); Anal. Calcd. for $C_9H_9N_9S_2$: C, 35.17; H, 2.95; N, 41.01; S, 20.86. Found: C, 35.08; H, 2.88; N, 40.97; S, 20.80.

2,6-Bis(4,5-dihydro-5-thioxo-1H-1,2,4-thiadiazole-3-yl)-pyridine (9). To a stirred ice-cold concentrated sulfuric acid 10 mL, compound 6 (4.23, 10 mmol) was added. The reaction mixture was left over night and then gradually added to crush ice. The separated precipitate was filtered off, washed with water, dried, and crystallized from ethanol to give compound 9 in 78% yield as colorless powder; mp 196–198°C; IR (KBr): ν = 3345–3302 (NH), 1662 (C=N), 1660 (C=C), 1242 (C=S) cm^{-1}; ^{1}H-NMR (270 MHz, DMSO-d_6): δ = 7.97 (d, 2H, *J* = 8.0 Hz, pyrid-H), 8.01 (t, 1H, *J* = 8.0 Hz, pyrid-H), 12.10 (s, 2H, 2NH, exchangeable with D_2O); ^{13}C-NMR (67.5 MHz, DMSO-d_6): δ = 125.24, 135.48 145.75 (5C, pyrid-C), 148.85, 179.66 (4C, thiadiazole ring); ms: *m/z* 311 (45), 204 (100), 144 (32), 103 (16), 75 (85); Anal. Calcd. for $C_9H_5N_5S_4$: C, 34.71; H, 1.62; N, 22.49; S, 41.18. Found: C, 34.65; H, 1.58; N, 22.43; S, 41.09.

***N2′,N6′*-Diaroylpyridine-2,6-dicarbohydrazides (10a) and (10b).** A mixture of **1** (1.95 g, 10 mmol) and benzoyl chloride or 4-chlorobenzoyl chloride (4 mmol) in dry pyridine 15 mL was stirred for 24 h at room temperature. The reaction mixture was poured onto crushed ice, the separated solid was filtered off, washed with water, dried, and crystallized from ethanol to give the title compounds **10a** in 98% yield as colorless powder and **10b** in 93% yield as yellow solid.

***N2′,N6′*-Dibenzoylpyridine-2,6-dicarbohydrazide (10a).** mp 268–270°C; IR (KBr): ν = 3344–3243 (NH), 1690 (C=O), 1680 (C=O), 1660 (C=C) cm^{-1}; ^{1}H-NMR (270 MHz, DMSO-d_6): δ = 7.15–7.70 (m, 10H, Ar—H), 8.10 (d, 2H, *J* = 8.0 Hz, pyrid-H), 8.40 (t, 1H, *J* = 8.0 Hz, pyrid-H), 10.10, 10.90 (2s, 4H, 4NH, exchangeable with D_2O); ^{13}C-NMR (67.5 MHz, DMSO-d_6): δ = 124.52, 138.48, 148.86 (5C, pyrid-C), 126.72, 127.98, 131.78, 133.86 (12C, 2Ph), 160.68, 163.92 (4C, 4C=O, amides); ms: *m/z* 403 (100), 281 (44), 223 (22), 105 (43), 77 (68); Anal. Calcd. for $C_{21}H_{17}N_5O_4$: C, 62.53; H, 4.25; N, 17.36. Found: C, 62.46; H, 4.20; N, 17.30.

***N2′,N6′*-Bis(4-chlorobenzoyl)pyridine-2,6-dicarbohydrazide (10b).** mp 293–295°C; IR (KBr): ν = 3359–3289 (NH), 1700 (C=O), 1670 (C=O), 1660 (C=C) cm^{-1}; ^{1}H-NMR (270 MHz, DMSO-d_6): δ = 7.50, 7.80 (2d, *J* = 8.4 Hz, 8H, Ar—H), 7.95 (d, 2H, *J* = 8.0 Hz, pyrid-H), 8.30 (t, 1H, *J* = 8.0 Hz, pyrid-H), 10.80, 11.30 (2s, 4H, 4NH, exchangeable with D_2O); ^{13}C-NMR (67.5 MHz, DMSO-d_6): δ = 124.55, 138.36, 148.88 (5C, pyrid-C), 128.05, 128.86, 131.78, 137.24

(12C, 2Ph), 160.55, 164.02 (4C, 4C=O, amides); ms: *m/z* 471 (16), 473 (5%), 331 (100), 308 (18), 139 (7), 75 (48); Anal. Calcd. for $C_{21}H_{15}Cl_2N_5O_4$: C, 53.41; H, 3.20; Cl, 15.01; N, 14.83. Found: C, 53.36; H, 3.14; Cl, 14.88; N, 14.76.

***N2′,N6′*-Bis(4-substituted-benzylidene)pyridine-2,6-dicarbohydrazide (11a) and (11b).** A mixture of **1** (1.95 g, 10 mmol) and 4-chloro- or 4-methoxy-benzaldhyde (20 mmol) in absolute ethanol 50 mL was refluxed for 7 h. After cooling, the solid precipitate was filtered off, washed with ethanol, dried, and crystallized from ethanol to give compounds **11a** in 95% yield as yellow solid and **11b** in 90% yield as red solid.

***N2′,N6′*-Bis(4-chlorobenzylidene)pyridine-2,6-dicarbohydrazide (11a).** mp 209–211°C; IR (KBr): ν = 3385 (NH), 1695 (C=O), 1658 (C=N), 1655 (C=N) cm^{-1}; ^{1}H-NMR (270 MHz, DMSO-d_6): δ = 7.35 (s, 2H, 2CH=N), 7.44, 7.82 (2d, 8H, *J* = 8.5 Hz, Ar—H), 7.96 (d, 2H, *J* = 8.1 Hz, pyrid-H), 8.25 (t, 1H, *J* = 8.1 Hz, pyrid-H), 11.18 (bs, 2H, 2NH, exchangeable with D_2O); ^{13}C-NMR (67.5 MHz, DMSO-d_6): (= 124.62, 138.44, 148.94 (5C, pyrid-C), 128.15, 129.10, 131.68, 137.04 (12C, 2Ph), 142.66 (2C, 2C=N), 157.12 (2C, 2C=O, amides); ms: *m/z* 440 (15), 442 (5), 321 (42), 218 (100), 190 (32), 77 (56); Anal. Calcd. for $C_{21}H_{15}Cl_2N_5O_2$: C, 57.29; H, 3.43; Cl, 16.10; N, 15.91. Found: C, 57.18; H, 3.34; Cl, 16.00; N, 15.84.

***N2′,N6′*-Bis(4-methoxybenzylidene)pyridine-2,6-dicarbohydrazide (11b).** mp 203–205°C; IR (KBr): ν = 3370 (NH), 1693 (C=O), 1664 (C=N), 1659 (C=N) cm^{-1}; ^{1}H-NMR (270 MHz, DMSO-d_6): δ = 3.30 (s, 6H, $2OCH_3$), 7.18 (s, 2H, 2CH=N), 7.55, 7.65 (2d, 8H, *J* = 8.4 Hz, Ar—H), 7.80 (d, 2H, *J* = 8.0 Hz, pyrid-H), 8.30 (t, 1H, *J* = 8.0 Hz, pyrid-H), 12.30 (bs, 2H, 2NH, exchangeable with D_2O); ^{13}C-NMR (67.5 MHz, DMSO-d_6): δ = 55.55 (2C, OCH_3), 124.58, 138.50, 149.04 (5C, pyrid-C), 114.20, 125.74, 129.38, 163.18 (12C, 2Ph), 142.72 (2C, 2C=N), 157.18 (2C, 2C=O, amides); ms: *m/z* 431 (100), 400 (75), 254 (24), 77 (38); Anal. Calcd. for $C_{23}H_{21}N_5O_4$: C, 64.03; H, 4.91; N, 16.23. Found: C, 63.88; H, 4.85; N, 16.16.

2,6-Bis-(5-aryl-1,3,4-oxadiazol-2-yl)pyridines (12a) and (12b). An appropriate amount of **10a,b** (1 mmol) was dissolved in concentrated sulfuric acid 5 mL and heated at 120°C for 3 h. The reaction mixture was cooled, poured onto crushed ice, and left for 1 h. The formed solid was filtered off, dried, and crystallized from dioxane to give the title compounds **12a** in 90% yield as yellow powder and **12b** in 86% yield as brown powder.

2,6-Bis-(5-phenyl-1,3,4-oxadiazol-2-yl)pyridine (12a). mp 274–276°C; IR (KBr): ν = 1665 (C=N), 1662 (C=N) cm^{-1}; ^{1}H-NMR (270 MHz, DMSO-d_6): δ = 7.36–7.72 (m, 10H, Ar—H), 8.18 (d, 2H, *J* = 7.9 Hz, pyrid-H), 8.68 (t, 1H, *J* = 7.9 Hz, pyrid-H); ^{13}C-NMR (67.5 MHz, DMSO-d_6): δ = 120.66, 137.98, 157.01 (5C, pyrid-C), 125.80, 126.85, 128.24, 129.04 (12C, 2Ph), 163.78, 165.32 (4C, oxadiazoles); ms: *m/z* 367 (12), 186 (28), 139 (100), 111 (15); Anal. Calcd. for $C_{21}H_{13}N_5O_2$: C, 68.66; H, 3.57; N, 19.06. Found: C, 68.58; H, 3.50; N, 18.96.

2,6-Bis-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-y1]pyridine (12b). mp 284–386°C; IR (KBr): ν = 1668 (C=N), 1660 (C=N) cm^{-1}; ^{1}H-NMR (270 MHz, DMSO-d_6): δ = 7.40, 7.75 (2d, 8H, *J* = 8.5 Hz, Ar—H), 8.21 (d, 2H, *J* = 8.0 Hz, pyrid-H), 8.75 (t, 1H, *J* = 8.0 Hz, pyrid-H); ^{13}C-NMR (67.5 MHz, DMSO-d_6): δ = 121.58, 138.18, 156.96 (5C, pyrid-C), 123.98, 128.55, 129.15, 133.56 (12C, 2Ph), 163.82, 165.45 (4C, oxadiazoles); ms: *m/z* 436 (10), 438 (3), 279 (75), 139 (100), 77 (86); Anal. Calcd. for $C_{21}H_{11}Cl_2N_5O_2$: C, 57.82; H, 2.54; Cl, 16.25; N, 16.05. Found: C, 57.75; H, 2.50; Cl, 16.18; N, 15.96.

2,6-Bis-(5-aryl-1,3,4-thiadizol-2-y1)pyridines (13a) and (13b). A mixture of **10a,b** (8 mmol) and phosphorus pentasulfide (1.89 g, 16 mmol) in dry benzene 50 mL was refluxed for 7 h. The reaction mixture was filtered off while hot and then the filtrate was concentrated under reduced pressure. The separated yellow solid was filtered off, dried and crystallized from dioxane to give compounds **13a** in 60% yield as red powder and **13b** in 75% yield as yellow crystals.

2,6-Bis-(5-phenyl-[1,3,4-thiadizol-2-yl)pyridine (13a). mp 304–306°C; IR (KBr): ν = 1663 (C=N), 1658 (C=N) cm^{-1}; ^{1}H-NMR (270 MHz, DMSO-d_6): δ = 7.60–7.80 (m, 10H, Ar—H), 8.14 (d, 2H, *J* = 8.1 Hz, pyrid-H), 8.51 (t, 1H, *J* = 8.1 Hz, pyrid-H); ^{13}C-NMR (67.5 MHz, DMSO-d_6): δ = 121.48, 138.06, 156.88 (5C, pyrid-C), 126.08, 127.14, 128.56, 133.16 (12C, 2Ph), 172.18, 174.05 (4C, thiadiazoles); ms: *m/z* 397 (M^+ −2, 14), 383 (100), 326 (54); Anal. Calcd. for $C_{21}H_{13}N_5S_2$: C, 63.14; H, 3.28; N, 17.53; S, 16.05. Found: C, 63.04; H, 3.18; N, 17.46; S, 15.94.

2,6-Bis[5-(4-chorophenyl)-1,3,4-thiadiazol-2-yl]pyridine (13b). mp 310–312°C; IR (KBr): ν = 1665 (C=N), 1660 (C=N) cm^{-1}; ^{1}H-NMR (270 MHz, DMSO-d_6): δ = 7.72, 7.84 (2d, 8H, *J* = 8.4 Hz, Ar—H), 8.16 (d, 2H, *J* = 8.0 Hz, pyrid-H), 8.48 (t, 1H, *J* = 8.0 Hz, pyrid-H); ^{13}C-NMR (67.5 MHz, DMSO-d_6): δ = 121.50, 138.12, 156.92 (5C, pyrid-C), 128.38, 129.10, 130.86, 133.46 (12C, 2Ph), 172.24, 174.35 (4C, thiadiazoles); ms: *m/z* 467 (M^+ −1, 100), 469 (30), 411 (65), 356 (78), 279 (32); Anal. Calcd. for $C_{21}H_{11}Cl_2N_5S_2$: C, 53.85; H, 2.37; Cl, 15.14; N, 14.95; S, 13.69. Found: C, 53.80; H, 2.30; Cl, 15.10; N, 14.90; S, 13.62.

***N2′,N6′*-Bis(2-(4-chlorophenyl)-4-oxothiazolidin-3-yl)pyridine-2,6-dicarboxamide (14).** To a suspension of **11a** (0.44 g, 1 mmol) in dry benzene 50 mL, mercaptoacetic acid (0.84 g, 2 mmol) in dry benzene 5 mL was added with stirring. The reaction mixture was refluxed for 18 h. Then solvent was evaporated under reduced pressure. The residue was triturated with boiling water and left overnight; the formed solid was filtered off, washed with water, dried, and crystallized from ethanol/dioxane to afford the brown powder of compound **14** in 75% yield; mp 224–226°C; IR (KBr): ν = 3363 (NH), 1720 (C=O), 1680 (C=O) cm^{-1}; ^{1}H-NMR (270 MHz, DMSO-d_6): δ = 3.23, 3.34 (2d, 4H, *J* = 2.5 Hz, AB $2CH_2$), 5.95 (s, 2H, 2CH), 7.35, 7.65 (2d, 8H, *J* = 8.5 Hz, Ar—H), 8.10–8.30 (m, 3H, pyrid-H), 11.20 (bs, 2H, 2NH, exchangeable with D_2O); ^{13}C-NMR (67.5 MHz, DMSO-d_6): δ = 124.50, 138.38, 149.70 (5C, pyrid-C), 128.62, 129.85, 132.05, 136.90 (12C, 2Ph), 35.10, 56.98, 168.36 (6C, thiazoles), 160.92 (2C, 2C=O, amides); ms: *m/z* 588 (34), 590 (11), 334 (85), 212 (100), 176 (54), 105 (62); Anal. Calcd. for $C_{25}H_{19}Cl_2N_5O_4S_2$: C, 51.02; H, 3.25; Cl, 12.05; N, 11.90; S, 10.90. Found: C, 50.95; H, 3.20; Cl, 11.98; N, 11.83; S, 10.85.

2,6-Bis(4-acetyl-5-(4-chlorophenyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl)pyridine (15). A solution of **11a** (0.44 g, 1 mmol) in acetic anhydride 15 mL was refluxed for 6–10 h. The solvent was removed under reduced pressure to dryness and the residue was solidified with ether. The obtained solid was filtered off, washed with ether, dried, and crystallized from dioxane to give yellow crystals of compound **15** in 76% yield; mp

250–252°C; IR (KBr): ν = 1715 (C=O), 1660 (C=N), 1600 (C=C) cm^{-1}; ^{1}H-NMR (270 MHz, DMSO-d_6): δ = 2.55 (s, 6H, $2CH_3$), 5.10 (s, 2H, 2CH), 7.60, 7.80 (2d, 8H, J = 8.5 Hz, Ar—H), 7.95 (d, 2H, pyrid-H), 8.30 (t, 1H, pyrid-H); ^{13}C-NMR (67.5 MHz, DMSO-d_6): δ = 23.08 (2C, $2CH_3$), 125.68, 135.86, 146.78 (5C, pyrid-C), 127.92, 128.15, 132.00, 137.88 (12C, 2Ph), 74.05, 155.18 (4C, oxadiazoles), 168.16 (2C, 2C=O, $COCH_3$); ms: m/z 523 ($M^+ - 1$, 22), 525 (7), 439 (43), 359 (100), 258 (37); Anal. Calcd. for $C_{25}H_{19}Cl_2N_5O_4$: C, 57.26; H, 3.65; Cl, 13.52; N, 13.36. Found: C, 57.20; H, 3.60; Cl, 13.46; N, 13.30.

Antimicrobial assay. The newly synthesized compounds were tested for their preliminary antimicrobial activity against different microorganisms representing Gram-positive bacteria (*Bacillus subtilis*, *Bacillus aureus*, and *Staphylococcus aureus*), Gram-negative bacteria (*Escherichia coli*), yeast (*Candida albican*), and fungi (*Aspergillus niger*).

Agar diffusion medium. Nine compounds were screened *in vitro* for their antimicrobial activity against, by agar diffusion method [30]. A suspension of the organisms were added to sterile nutrient agar media at 45°C and the mixture was transferred to sterile Petri dishes and allowed to solidify. Holes of 10 mm in diameter were made using a cork borer. Amounts of 0.1 mL of the synthesized compounds were poured inside the holes. A hole filled with DMSO was also used as control. The plates were left for 1 h at room temperature as a period of pre-incubation diffusion to minimize the effects to variation in time between the applications of the different solutions. The plates were then incubated at 37°C for 24 h and observed for antibacterial activity. The diameters of zone of inhibition were measured and compared with that of the standard, the values were tabulated. Chloramphinicol® (50 μg/mL) was used as standard for antibiotic drug. The observed zone of inhibition is presented in Table 1.

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