Synthesis and Antimicrobial Activity of Pyridines Bearing Thiazoline and Thiazolidinone Moieties

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Two series of new pyridines bearing thiazoline (3a—n) and thiazolidinone (5a—e) moieties were prepared *via* the cyclization of the corresponding substituted pyridyl thiourea (2a—g) with an appropriately substituted phenacyl bromide or chloroacetic acid, respectively. The antimicrobial activity was determined for representative compounds and most of them showed moderate activity against Gram-positive bacteria.

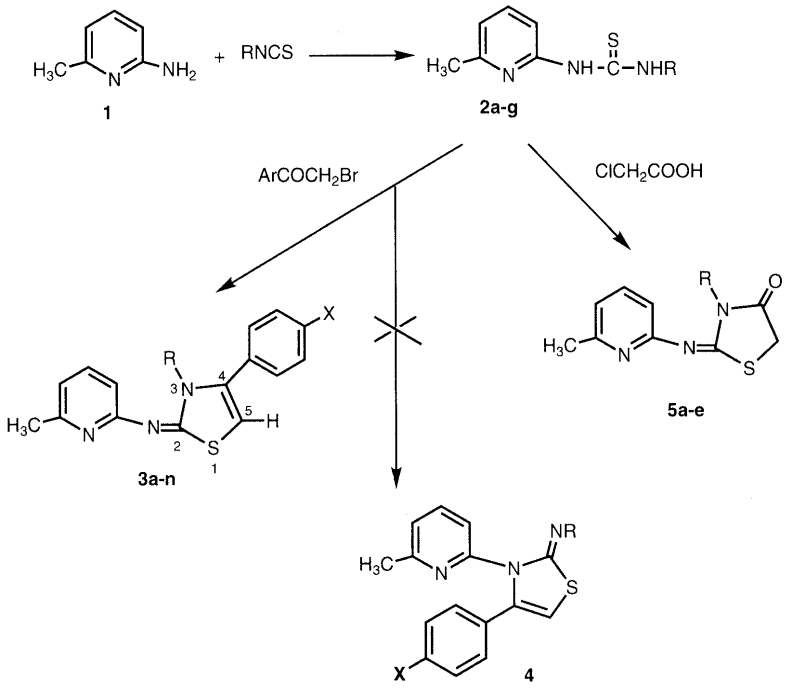
Key words pyridine; thiourea; thiazoline; thiazolidinone; antimicrobial activity

Pyridine derivatives possess a broad spectrum of biological activity.[1] In addition, many thiazoline[2] and thiazolidinone derivatives,[3] exhibit a wide variety of biological activities, such as antimicrobial,[4-7] antiinflammatory,[8] antihistaminic,[9] antihypertensive,[10] hypnotic,[11] and anticonvulsant.[10,12] Therefore, it seemed of interest to prepare new pyridines bearing thiazoline and thiazolidinone moieties, for evaluation of their antimicrobial activity.

Results and Discussion

Chemistry The sequence of reactions adopted for the synthesis of the designed compounds is illustrated in Chart 1.

Reaction of 2-amino-6-methylpyridine (**1**) with alkyl, benzyl and aryl isothiocyanates in ethanol yielded the target compounds 1-(6-methyl-2-pyridyl)-3-(substituted)-thioureas (**2a—g**).[13] The structures of compounds **2** were confirmed on the bases of elemental analyses and spectral data. The IR spectra showed NH and CS stretching bands at 3215—3230 and 1309—1348 cm^{-1}, respectively. The ^{1}H-NMR spectra showed downfield signals at δ 11.6—14.23 attributed to 3-substituted NH and NH of 2-pyridyl appeared as a singlet signal at δ 10.25—10.8. These two signals disappeared with D_2O. The other protons appeared at the expected chemical shifts (Table 1). Condensation of **2** with the appropriate phenacyl bromide in boiling ethanol containing anhydrous sodium acetate may lead to the formation of 6-methyl-2-(3,4-disubstituted-2,3-dihydrothiazol-2-ylidene)aminopyridines (**3a—n**) and/or 6-methyl-2-(2-alkyl(aryl)imino-4-aryl-2,3-dihydrothiazol-3-yl)pyridines (**4**). In fact only one product was obtained as confirmed by TLC. The representation of the structures of the products as **3** and not **4** was based on previous



R = CH_3, C_2H_5, c-C_6H_{11}, CH_2-C_6H_5, C_6H_5, *p*-Cl-C_6H_4, *p*-CH_3-C_6H_4,
X = Br, Cl, OCH_3, NO_2

Chart 1

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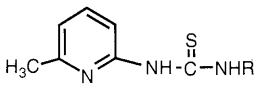
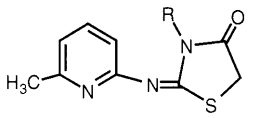
Table 1. Physical Constants and ^{1}H-NMR Spectral Data of 1-(6-Methyl-2-pyridyl)-3-(substituted)thioureas (**2a—g**)



Compd. No.	R	mp (°C) Cryst. sol.	Yield (%)	Mol. formula (M.W.)	Microanalysis % Calcd./Found			^{1}H-NMR (δ ppm, DMSO-d^6)
					C	H	N	
2a	CH_3	210—212 (ethanol)	90	$C_8H_{11}N_3S$ (181.25)	—	—	—	11.6 (1H, brs, $NHCH_3$)[a], 10.4 (1H, s, NH)[a], 7.6 (1H, t, H4 of pyridine), 6.9 (2H, t, H3, H5 of pyridine), 3.2 (3H, d, CH_3NH), 2.45 (3H, s, 6-CH_3)
2b	C_2H_5	205—207 (ethanol)	92	$C_9H_{13}N_3S$ (195.27)	—	—	—	11.8 (1H, t, $NHCH_2$)[a], 10.35 (1H, s, NH)[a], 7.6 (1H, t, H4 of pyridine), 6.8 (2H, t, H3, H5 of pyridine), 3.6 (2H, p, CH_2CH_3), 2.3 (3H, s, 6-CH_3), 1.2 (3H, t, CH_2CH_3)
2c	c-C_6H_{11}	175—178 (ethanol)	85	$C_{13}H_{19}N_3S$ (249.38)	62.61 62.82	7.68 7.80	16.85 16.52	12.1 (1H, d, NH cyclohexyl)[a], 10.25 (1H, s, NH)[a], 7.6 (1H, t, H4 of pyridine), 6.8 (2H, t, H3, H5 of pyridine), 4.3 (hump, 1H of cyclohexyl), 2.33 (3H, s, 6-CH_3), 1.9—1.2 (10H, m, cyclohexyl)
2d	$CH_2C_6H_5$	138—140 (ethanol)	89	$C_{14}H_{15}N_3S$ (257.36)	65.34 65.60	5.88 5.90	16.33 16.40	12.3 (1H, t, $NHCH_3$)[a], 10.59 (1H, s, NH)[a], 7.6 (1H, t, H4 of pyridine), 7.43 (5H, s, ArH), 6.87 (2H, t, H3, H5 of pyridine), 4.9 (2H, d, CH_2Ph), 2.3 (3H, s, 6-CH_3)
2e	C_6H_5	181—183 (DMF–ehanol)	90	$C_{13}H_{13}N_3S$ (243.31)	—	—	—	14.2 (1H, s, NHPh)[a], 10.7 (1H, s, NH)[a], 7.8—7.2 (6H, m, 5ArH, H4 of pyridine), 6.96 (2H, t, H3, H5 of pyridine), 2.46 (3H, s, 6-CH_3)
2f	*p*-Cl-C_6H_4	200—202 (ethanol–acetonitrile)	87	$C_{13}H_{12}ClN_3S$ (277.78)	56.21 56.12	4.35 4.28	15.3 14.87	14.23 (1H, s, NHAr)[a], 10.8 (1H, s, NH)[a], 7.9—7.2 (5H, m, 4ArH, H4 of pyridine), 7.0 (2H, t, H3, H5 of pyridine), 2.43 (3H, s, 6-CH_3)
2g	*p*-$CH_3C_6H_4$	205—206 (ethanol–acetonitrile)	89	$C_{14}H_{15}N_3S$ (257.36)	65.34 65.05	5.87 5.74	16.33 15.88	14.18 (1H, s, NHAr)[a], 10.65 (1H, s, NH)[a], 7.8—6.8 (7H, m, 4ArH, H3, H4, H5 of pyridine), 2.43 (3H, s, 6-CH_3) 2.3 (3H, s, CH_3Ph)

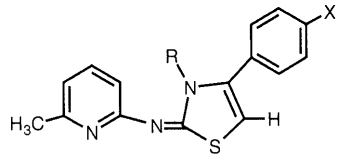
a) Exchangeable in D_2O.

Table 3. Physical Constants and ^{1}H-NMR Spectral Data of 6-Methyl-2-(3-substituted-4-oxo-thiazolidin-2-ylidene)aminopyridines (**5a—e**)



Compd. No.	R	mp (°C) Cryst. sol.	Yield (%)	Mol. formula (M.W.)	Microanalysis % Calcd./Found			^{1}H-NMR (δ ppm, DMSO-d_6)
					C	H	N	
5a	CH_3	136—137 (ethanol)	95	$C_{10}H_{11}N_3OS$ (221.28)	54.28 54.60	5.01 5.07	18.99 18.60	7.5 (1H, t, H4 of pyridine), 6.85 (2H, t, H3, H5 of pyridine), 3.76 (2H, s, thiazolidine CH_2), 3.35 (3H, s, N–CH_3), 2.55 (3H, s, 6-CH_3)
5b	C_2H_5	116—118 (80% ethanol)	91	$C_{11}H_{13}N_3OS$ (235.31)	56.15 56.73	5.57 5.57	17.86 17.50	7.56 (1H, t, H4 of pyridine), 6.9 (2H, t, H3, H5 of pyridine), 4.0 (2H, q, CH_2CH_3), 3.0 (2H, s, thiazolidine CH_2), 2.55 (3H, s, 6-CH_3), 1.23 (3H, t, CH_2CH_3)
5c	$CH_2C_6H_5$	133—135 (ethanol)	90	$C_{16}H_{15}N_3OS$ (297.38)	64.62 65.30	5.08 4.40	14.13 13.97	7.7 (1H, t, H4 of pyridine), 7.5 (5H, m, ArH), 6.96 (2H, t, H3, H5 of pyridine), 5.1 (2H, s, CH_2Ph), 3.7 (2H, s, thiazolidine CH_2), 2.55 (3H, s, 6-CH_3)
5d	C_6H_5	262—264 (ethanol)	81	$C_{15}H_{13}N_3OS$ (283.35)	63.58 63.30	4.62 4.50	14.83 14.50	7.7—7.33 (6H, m, 5ArH, H4 of pyridine), 6.8 (2H, m, H3, H5 of pyridine), 3.96 (2H, s, thiazolidine CH_2), 2.6 (3H, s, 6-CH_3)
5e	*p*-Cl-C_6H_4	226—228 (ehanol)	80	$C_{15}H_{12}ClN_3OS$ (317.80)	56.63 56.30	3.77 3.90	13.21 13.50	7.6 (1H, s, H4 of pyridine), 7.46 (4H, dd, ArH), 6.89 (2H, t, H3, H5 of pyridine), 4.0 (2H, s, thiazolidine CH_2), 2.63 (3H, s, 6-CH_3)

Table 2. Physical Constants and ^{1}H-NMR Spectral Data of 6-Methyl-2-(3,4-disubstituted-2,3-dihydrothiazol-2-ylidene)aminopyridines (**3a—n**)



Compd. No.	R	X	Yield (%)	mp (°C) Cryst. sol.	Mol. formula (M.W.)	Microanalysis % Calcd./Found C	H	N	^{1}H-NMR (δ ppm, DMSO-d_6)
3a	CH_3	Br	93	162—164 (ethanol)	$C_{16}H_{14}BrN_3S$ (360.27)	53.34 53.76	3.92 4.20	11.66 12.00	7.8 (2H, d, ArH), 7.6 (2H, d, ArH), 7.48 (1H, t, H4 of pyridine), 6.88 (2H, t, H3, H5 of pyridine), 6.6 (1H, s, CH of thiazoline), 3.57 (3H, s, N–CH_3), 2.55 (3H, s, 6-CH_3)
3b	CH_3	Cl	89	147—149 (aq. ethanol)	$C_{16}H_{14}ClN_3S$ (315.82)	60.85 60.54	4.47 4.50	13.31 13.81	7.8—7.4 (5H, m, 4ArH, H4 of pyridine), 6.9 (2H, t, H3, H5 of pyridine), 6.63 (1H, s, CH of thiazoline), 2.63 (3H, s, 6-CH_3)
3c	CH_3	NO_2	85	183—185 (ethanol)	$C_{16}H_{14}N_4O_2S$ (326.37)	58.88 59.15	4.32 4.50	17.17 17.60	8.36 (2H, d, ArH), 7.83 (2H, d, ArH), 7.6 (1H, t, H4 of pyridine), 6.8 (3H, t, 2ArH, CH of thiazoline), 3.6 (3H, s, NCH_3), 2.56 (3H, s, 6-CH_3)
3d	CH_3	OCH_3	83	140—142 (aq. ethanol)	$C_{17}H_{17}N_3OS$ (311.40)	65.57 66.00	5.50 5.48	13.49 13.30	7.6 (1H, t, H4 of pyridine), 7.36 (2H, d, ArH), 7.0 (2H, d, ArH), 6.76 (2H, t, H3, H5 of pyridine), 6.18 (1H, s, CH of thiazoline), 3.9 (3H, s, OCH_3), 3.6 (3H, s, NCH_3), 2.64 (3H, s, 6-CH_3)
3e	C_2H_5	Br	92	110 (aq. ehanol)	$C_{17}H_{16}BrN_3S$ (374.30)	54.55 54.31	4.31 4.33	11.23 10.80	7.37 (2H, d, ArH), 7.43 (3H, m, 2ArH, H4 of pyridine), 6.86 (2H, t, H3, H5 of pyridine), 6.5 (1H, s, CH of thiazoline), 4.1 (2H, q, CH_2CH_3), 2.35 (3H, s, 6-CH_3), 1.2 (3H, t, CH_2CH_3)
3f	C_2H_5	Cl	85	125 (ethanol)	$C_{17}H_{16}ClN_3S$ (329.79)	61.91 62.30	4.98 4.50	12.74 12.40	7.53 (5H, m, 4 ArH, H4 of pyridine), 6.76 (2H, t, H3, H5 of pyridine), 6.46 (1H, s, CH of thiazoline), 4.13 (2H, q, CH_2CH_3), 2.56 (3H, s, 6-CH_3), 1.23 (3H, t, CH_2CH_3)
3g	C_2H_5	NO_2	80	186 (ethanol)	$C_{17}H_{16}N_4O_2S$ (340.40)	59.98 60.40	4.74 4.33	16.46 16.00	8.46 (2H, d, ArH), 7.67 (3H, m, 2ArH, H4 of pyridine), 6.86 (2H, t, H3, H5 of pyridine), 6.7 (1H, s, CH of thiazoline), 4.2 (2H, q, CH_2CH_3), 2.5 (3H, s, 6-CH_3), 1.23 (3H, t, CH_2CH_3)
3h	C_2H_5	OCH_3	83	122—123 (ethanol)	$C_{18}H_{19}N_3OS$ (325.43)	66.43 66.30	5.88 6.10	12.91 13.20	($CDCl_3$) 7.53 (1H, t, H4 of pyridine) 7.36 (2H, d, ArH), 6.96 (2H, d, ArH), 6.73 (2H, t, H3, H5 of pyridine), 6.1 (1H, s, CH of thiazoline), 4.13 (2H, q, CH_2CH_3), 3.9 (3H, s, O-CH_3), 2.63 (3H, s, 6-CH_3), 1.26 (3H, t, CH_2CH_3)
3i	c-C_6H_{11}	Br	75	187—188 (ethanol)	$C_{21}H_{22}BrN_3S$ (428.39)	58.88 59.20	5.18 4.90	9.81 9.50	8.96—7.3 (5H, m, 4 ArH, H4 of pyridine), 6.93 (3H, t, H3, H5 of pyridine, CH of thiazoline), 3.73—3.2 (hump, 1H, cyclohexyl), 2.5 (3H, s, 6-CH_3), 2.2—1.1 (10H, m, cyclohexyl)
3j	c-C_6H_{11}	OCH_3	79	193—195 (ethanol)	$C_{22}H_{25}N_3OS$ (379.52)	69.62 69.68	6.64 6.70	11.07 11.52	($CDCl_3$) 7.46 (3H, t, 2ArH, H4 of pyridine), 7.23—6.73 (5H, m, 2ArH, H3, H5 of pyridine, CH of thiazoline), 3.96 (3H, s, OCH_3), 3.73—3.2 (hump, 1H, CH of cyclohexyl), 2.36 (3H, s, 6-CH_3), 2.4—1.1 (10H, m, cyclohexyl)
3k	$CH_2C_6H_5$	Br	79	196—197 (acetone-$CHCl_3$)	$C_{22}H_{18}BrN_3S$ (436.37)	60.55 60.10	4.16 4.50	9.63 9.40	($CDCl_3$) 7.7—6.4 (12H, m, 9ArH, H3, H4, H5 of pyridine), 6.23 (1H, s, CH of thiazoline), 5.36 (2H, s, CH_2Ph), 2.63 (3H, s, 6-CH_3)
3l	C_6H_5	Br	80	195 (ehanol–acetonitrile)	$C_{21}H_{16}BrN_3S$ (422.35)	59.72 60.06	3.82 3.80	9.95 9.71	7.8—7.06 (10H, m, 9ArH, H4 of pyridine), 6.8 (3H, t, H3, H5 of pyridine, CH of thiazoline), 2.63 (3H, s, 6-CH_3)
3m	C_6H_5	Cl	75	200—202 (ethanol–DMF)	$C_{21}H_{16}ClN_3S$ (377.89)	66.75 66.41	4.27 4.41	11.12 11.30	7.73—7.06 (10H, m, 9ArH, H4 of pyridine), 6.73 (3H, t, H3, H5 of pyridine, CH of thiazoline), 2.56 (3H, s, 6-CH_3)
3n	C_6H_5	OCH_3	79	215 (ethanol–acetonitrile)	$C_{22}H_{19}N_3OS$ (373.12)	70.75 70.50	5.13 5.40	11.26 11.50	7.86—7.33 (10H, m, 9ArH, H4 of pyridine), 7.0 (3H, t, H3, H5 of pyridine, CH of thiazoline), 3.86 (3H, s, OCH_3), 2.56 (3H, s, 6-CH_3)

discussion of the structures of similar compounds.[12,14] The structures of the reaction products were confirmed by elemental analyses, IR, NMR, and MS analyses. IR spectra revealed the disappearance of NH bands at 3215—3230 cm^{-1}. The ^{1}H-NMR spectra also lacked the NH signals and showed a new singlet signal at δ 6.1—6.8 integrated for one proton, attributed to the C_5-H of the thiazoline ring (Table 2).

Further, reaction of **2** with chloroacetic acid in boiling ethanol containing fused sodium acetate afforded the corresponding 6-methyl-2-(3-substituted-4-oxo-thiazolidin-2-ylidene)aminopyridines (**5a—e**) and not the isomeric 6-methyl-2-(2-alkyl(aryl)imino-4-oxo-thiazolidin-3-yl)-pyridines as expected from our previous discussion.[14] Achary *et al.*[15] obtained similar results and suggested that a heterocyclic moiety, such as 2-benzothiazolyl, 4-ethyl-2-thiazolyl and 2-pyridyl, always occupied the 2-imino position of the 4-thiazolidinone ring.

Table 4. Antimicrobial Activity of the Test Compounds (Diameter of Inhibition Zones in mm)

Compd. No.	*S. aureus*	*B. cereus*	*E. coli*	*S. marescens*	*C. albicans*
2a	10	15	—	13	—
2b	20	—	—	14	—
2c	20	—	—	—	—
2d	20	—	—	—	—
2e[a]	30	—	11	—	—
3a	20	—	—	—	—
3c[a]	15	—	11	13	—
3d	30	28	—	—	—
3e	22	18	—	—	—
3g	20	25	—	—	—
3h	18	—	—	—	—
3l[a]	17	15	—	12	—
5a	12	15	—	—	—
5b	21	—	—	—	—
5c	17	15	12	—	—
Clotrimazole	—	—	—	—	25
Streptomycin	4[b]		3[b]		

a) Concentration of compounds **2e** and **3c** was 2.5 mg/disc, and that of **3l** was 1.66 mg/disc, (clotrimazole, 2.5 mg/disc). *b*) MIC (μg/ml).

The IR spectra of the thiazolidinones **5** showed a carbonyl group absorption at 1709—1712 cm^{-1}. The ^{1}H-NMR spectra lacked the NH signals and showed a new singlet signal at δ 3.7—4 integrated for two protons, which was assigned to the methylene protons of the thiazolidinone ring (Table 3). Electron impact mass spectrum (EI-MS) of three representative compounds were consistent with the expected structure (Experimental section).

Antimicrobial Activity The antimicrobial activities of seven thiazolines (**3a, c, d, e, g, h, l**) and three thiazolidinones (**5a—c**) as well as five of their precursors thioureas (**2a—e**) were evaluated by means of *in vitro* growth-inhibitory activity assay against a variety of Gram-positive and Gram-negative strain bacteria, namely *Staphylococcus aureus*, *B. cereus*, *E. coli* and *Serratia marcescens*, as well as the yeast *C. albicans*. The disc diffusion method was appleid.[16] The zones of inhibition of the test compounds and the references streptomycin and clotrimazole were measured. All the tested compounds showed activity against *Staphylcoccus aureus* and some of them showed activity against *B. cereus*, while a few also showed weak activity against the Gram-negative bacteria (*E. coli* and *Serratia marescens*). None of the test compounds showed activity against the yeast (*C. albicans*).

Experimental

All melting points were determined in an open capillary tube apparatus and are uncorrected. Elemental microanalysis was performed by the Microanalysis Unit, Faculty of Science, Assiut University and the Microanalysis Unit, Faculty of Science, Cairo University. IR spectra were recorded on a Shimadzu 740 spectrometer as KBr discs. ^{1}H-NMR spectra were recorded on an EM-360 60 MHz Varian NMR spectrometer with tetramethylsilane (TMS) as an internal standard, and the chemical shift values are given in δ ppm. Dimethyl sulfoxide-d_6 (DMSO-d_6) was used as the solvent, unless otherwise noted. The purity of the compounds was confirmed by TLC. Mass spectra (MS) were obtained on a JEOL JMS-HX/HX 110 A spectrometer at the Faculty of Pharmaceutical Sciences, Kyoto University, Japan.

1-(6-Methyl-2-pyridyl)-3-(substituted)thioureas (2a—g) The appropriate isothiocyanate (0.01 mol) was added to a solution of **1** (1.08 g, 0.01 mol) in ethanol (50 ml). The reaction mixture was heated under reflux for 3 h, then evaporated under vacuum, and the residue was allowed to cool. The precipitate was filtered off, washed with ethanol and crystallized from a suitable solvent (Table 1).

6-Methyl-2-(3,4-disubstituted-2,3-dihydrothiazol-2-ylidene)aminopyridines (3a—n) A mixture of **2** (0.002 mol), the appropriate phenacyl bromide (0.002 mol) and freshly fused sodium acetate (0.25 g, 0.003 mol) in ethanol (25 ml) was heated under reflux for 4—6 h. The solvent was evaporated off and the reaction product was allowed to cool. The separated product was filtered off, washed with water and crystallized from a suitable solvent (Table 2). Compound **3a**: MS(EI]) *m/z* (%): 361 ($M^+ + 2$, 99.7), 360 ($M^+ + 1$, 72.87), 359 (M^+, 100), 358 (54), 328 (13.67), 326 (13.92), 242 (9.77), 240 (9.68).

6-Methyl-2-(3-substituted-4-oxo-thiazolin-2-ylidene)aminopyridines (5a—e) A mixture of **2** (0.002 mol), chloroacetic acid (0.25 g, 0.0026 mol) and freshly fused sodium acetate (0.21 g, 0.0026 mol) in ethanol (30 ml) was refluxed for 12 h. The solvent was evaporated and the residue was triturated with water. The separated solid was collected by filtration, dried and crystallized (Table 3). Compound **5b**: MS (EI^+) *m/z* (%): 236 ($M^+ + 1$, 13.97), 235 (M^+, 100), 192 (30.32). Compound **5d**: MS (EI^+) *m/z* (%): 284 ($M^+ + 1$, 18.7), 283 (M^+, 100), 241 (37.79), 192 (24.23). Compound **5e**: MS (EI^+) *m/z* (%): 319 ($M^+ + 2$, 37.18), 318 ($M^+ + 1$, 25.1), 317 (M^+, 100), 275 (57.61), 192 (42.01).

Antimicrobial Activity The antimicrobial activity of the test compounds was determined by the disc diffusion method,[16] against Gram-positive bacteria (*Staphylococcus aureus*, ATCC 25923, *B. cereus* DMS 345), Gram-negative bacteria (*E. coli* ATCC 25922, *Serratia marcescens* DMS 1608) and a yeast *C. albicans* WT-5). Each test compound was dissolved in dimethyl sulfoxide and added at a concentration of 5 mg/disc (Whatman No. 3 filter paper, 0.5 cm diameter). Incubation was carried out at 37±1 °C for 24 h, and the diameter of zones of inhibition was measured in millimeters. Streptomycin and clotrimazole were used as standards for antibacterial and antifungal activity, respectively. The results are listed in Table 4.

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