γ-Oxocarboxylic Acids in Heterocyclic Synthesis IV. Synthesis of Some Pyridazines Containing Phthalyl- and Tosylamino Acids Using Dicyclohexylcarbodiimide as the Condensing Agent

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3(2*H*)-Oxo-, 3(2*H*)-thioxo- or 3-aminopyridazine derivatives were coupled with *N*-phthalyl- or *N*-tosylamino acids in one-step room-temperature reaction using *N*,*N*′-dicyclohexylcarbodiimide as the condensing agent to furnish the corresponding 3-*N*-(phthalyl- or tosylamino acids) pyridazine derivatives. Hydrazinolysis of the *N*-phthalyl derivatives in methanol yielded the corresponding unprotected derivatives. The antibacterial activities of the prepared compounds were tested.

The pyridazine ring plays an essential role in several biological processes [1, 2]. Likewise, phenoxathiines are found to be associated with significant industrial uses [3], potential bioresponses and physiological activities [4, 5]. Moreover, the presence of D-amino acid residues in antibiotics, such as the gramicidins [6], tyrocidine [7], penicillins [8], and aerosporin [9] has aroused interest in the inhibitory potentialities of various nitrogen heterocycles containing amino acids. In an earlier report [10], we described the preparation of 2-[*N*-(phthalyl- or tosylaminoacyl)thio- or -amino]pyrimidine derivatives.

Accordingly a massive research effort has been expended to synthesis of the novel congeners bearing these biologically active structural moieties within a molecular framework likely to constitute potent antimicrobial agents. An attempt has also been made to take an insight into the structure—activity relationship. The various steps involved in the synthesis of the key intermediate compounds *IV, VI,* and *VII* and their reactions with amino acid residues are shown in Scheme 1.

The required 6-(phenoxathiin-2-yl)-2,3,4,5-tetrahydropyridazin-3-one (*II*) [11] was successively synthesized by the condensation of 4-(phenoxathiin-2-yl)-4-oxobutanoic acid (*I*) [12] with hydrazine hydrate in boiling ethanol. Claisen condensation of *II* with benzaldehyde in ethanolic sodium ethoxide gave 4-benzyl-6-(phenoxathiin-2-yl)pyridazin-3(2*H*)-one (*IV*) through a prototropic rearrangement of the originally formed intermediate *III*. The IR data showed an absorption band around 1665 cm^{-1} characteristic of the carbonyl group of cyclic amide thereby indicating the lactam form *IVA*. They also showed broad band around 2980—3270 cm^{-1} indicating the lactim form *IVB* in a polymeric association. The prepared pyridazinone *IV* can react either in the lactam or lactim form according to the reagent used. Thus, it reacted in the lactim form when heated with $POCl_3/PCl_5$ on steam bath to yield the corresponding 4-benzyl-3-chloro-6-(phenoxathiin-2-yl)pyridazine (*V*) in fairly good yield, which upon subsequent reaction with thiourea in refluxing ethanol or ammonium acetate by fusion furnished the target compounds 3(2*H*)-thioxo- (*VI*) or 3-amino-4-benzyl-6-(phenoxathiin-2-yl)pyridazines (*VII*). Compounds *IV*, *VI,* and *VII* were coupled with phthalyl and tosyl derivatives of the amino acids (glycine, DL-alanine, DL-phenylalanine, and L-valine) in a one-step room-temperature reaction using *N*,*N*′-dicyclohexylcarbodiimide as the condensing agent to furnish the 4-benzyl-6-(phenoxathiin-2-yl)-3-(*N*-phthalyl- or -tosylglycyl-, -DL-alanyl-, -DL-phenylalanyl- or -L-valyloxy)-, -thio)- or -amino)pyridazines *a*—*h* of *VIII*—*X*. Hydrazinolysis of the *N*-phthalyl derivatives *a*—*d* of *VIII*—*X* with hydrazine hydrate in methanol under mild conditions yielded the corresponding 4-benzyl-6-(phenoxathiin-2-yl)-3-(glycyl-, -DL-alanyl-, -DL-phenylalanyl- or -L-valyloxy-, -thio)- or -amino)pyridazines *i*—*l* of *VIII*—*X*. The structures of all prepared compounds were confirmed from their analytical data, ^{1}H NMR and mass spectra (Tables 1 and 2).

The antimicrobial activity of synthesized derivatives was tested against several strains of gram-

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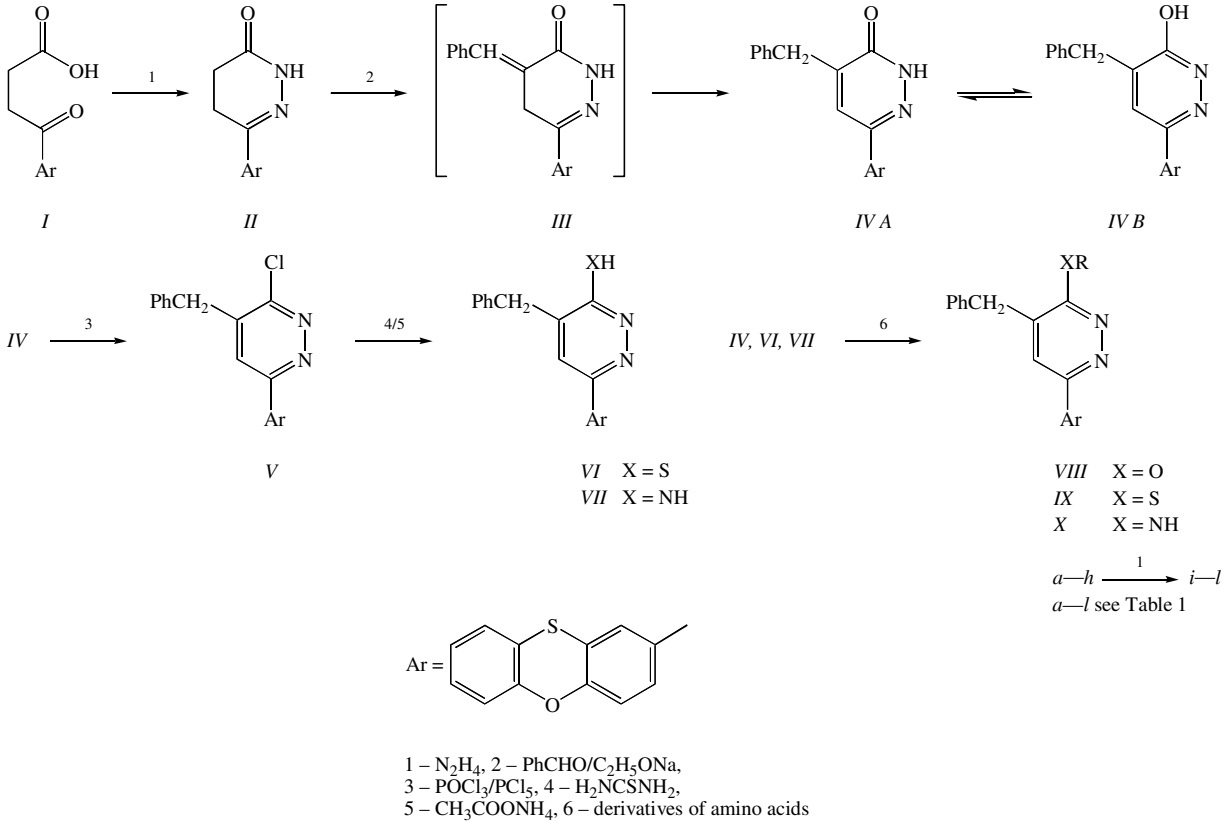

Scheme 1

positive and gram-negative bacteria using sulfadiazine and streptomycin sulfate as a reference standard. According to the solubility of the tested compounds, different polar and nonpolar solvents were used; good solubility was found in 10 vol. % acetone for all the tested compounds. The results are summarized in Table 3.

Structure—activity relationship (SAR) showed that the presence of the tosyl group in the amino acid moiety of the studied compounds enhances their activities compared with the phthalyl group. Also, it was found that the removal of the phthalyl group from the compounds decreases the activities. Compounds *VIII*—*Xe* have activity nearly comparable to the used commercial antibacterial agents.

EXPERIMENTAL

The starting compounds phthalyl- or tosylamino acids were prepared according to the published procedure.

Phthalylglycine (yield 92 %), m.p. = 192—194 °C (from methanol—ether), Ref. [13] gives m.p. = 193—195 °C; phthalyl-DL-alanine (yield 90 %), m.p. = 160—162 °C (from ethanol—water), Ref. [14] gives m.p. = 160—161 °C; phthalyl-DL-phenylalanine (yield 78 %), m.p. = 173—175 °C (from methanol—water), Ref. [15] gives m.p. = 174—175 °C; phthalyl-L-valine (yield 69 %), m.p. = 113—115 °C (from cyclohexane), Ref. [15] gives m.p. = 114—115 °C, $[\alpha]_D^{27} = (-68.5 \pm 1.0)°$ in absolute EtOH; tosylglycine (yield 68 %), m.p. = 148—149 °C (from methanol—ether), Ref. [16] gives m.p. = 148 °C; tosyl-DL-alanine (yield 70 %), m.p. = 137—139 °C (from methanol—ether), Ref. [16] gives m.p. = 139 °C; tosyl-DL-phenylalanine (yield 65 %), m.p. = 124—126 °C (from methanol—water), Ref. [17] gives m.p. = 125—127 °C; tosyl-L-valine (yield 66 %), m.p. = 147—149 °C (from methanol—water), Ref. [17] gives m.p. = 148 °C.

Melting points were taken in open capillary tubes and are uncorrected. IR spectra in KBr were recorded on a Shimadzu 470 spectrophotometer and ^{1}H NMR spectra were recorded on a Varian Gemini, 200 MHz instrument using TMS as internal reference (chemical shifts are expressed as δ). Mass spectra were determined on a Shimadzu, GCMS QP 1000 EX mass spectrometer (70 eV EI mode).

6-(Phenoxathiin-2-yl)-2,3,4,5-tetrahydropyridazin-3-one (*II*)

A solution of *I* (27 g; 0.09 mol) in ethanol (200 cm^3) was treated with hydrazine hydrate (6.8 cm^3, 0.14 mol) and the mixture was refluxed for 6 h. The solid that separated after concentration and cooling was crystallized from ethanol, yield 21 g (79 %), m.p. = 230—232 °C. IR spectrum, $\tilde{\nu}$/cm^{-1}: 2950—3280 (br, OH, NH), 1665 (amidic CO), 1600 (C=N). ^{1}H NMR

Table 1. Analytical Data of Compounds *Ia*—*l* of *VIII*—*X*

Compound	R*	Formula M_r	w_i(calc.)/% w_i(found)/% C	H	N	Yield %	M.p.** °C
VIIIa	Pht.Gly	$C_{33}H_{21}N_3O_5S$	69.34	3.70	7.35	71	185—187[e]
		571.61	69.46	3.79	7.42		
VIIIb	Pht.DL-Ala	$C_{34}H_{23}N_3O_5S$	69.73	3.96	7.18	64	176—178[a]
		585.63	69.84	3.84	7.26		
VIIIc	Pht.DL-Phe	$C_{40}H_{27}N_3O_5S$	72.60	4.11	6.35	62	190—192[a]
		661.73	72.71	4.19	6.42		
VIIId	Pht.L-Val	$C_{36}H_{27}N_3O_5S$	70.46	4.43	6.85	58	222—224[e]
		613.69	70.56	4.35	6.72		
VIIIe	Tos.Gly	$C_{32}H_{25}N_3O_5S_2$	64.52	4.23	7.05	62	237—239[a]
		595.69	64.63	4.11	7.13		
VIIIf	Tos.DL-Ala	$C_{33}H_{27}N_3O_5S_2$	65.01	4.46	6.89	65	251—253[b]
		609.72	65.13	4.35	6.76		
VIIIg	Tos.DL-Phe	$C_{39}H_{31}N_3O_5S_2$	68.30	4.56	6.13	63	197—199[b]
		685.82	68.39	4.47	6.19		
VIIIh	Tos.DL-Val	$C_{35}H_{31}N_3O_5S_2$	65.91	4.90	6.59	70	165—167[e]
		637.77	65.80	4.81	6.44		
VIIIi	Gly	$C_{25}H_{19}N_3O_3S$	68.01	4.34	9.52	72	242—244[a]
		441.50	68.13	4.41	9.43		
VIIIj	DL-Ala	$C_{26}H_{21}N_3O_3S$	68.55	4.65	9.22	65	248—250[b]
		455.53	68.68	4.77	9.31		
VIIIk	DL-Phe	$C_{32}H_{25}N_3O_3S$	72.30	4.74	7.90	62	221—223[b]
		531.63	72.42	4.85	7.79		
VIIIl	L-Val	$C_{28}H_{25}N_3O_3S$	69.54	5.21	8.69	73	261—263[e]
		483.59	69.66	5.10	8.78		
IXa	Pht.Gly	$C_{33}H_{21}N_3O_4S_2$	67.45	3.60	7.15	61	163—165[b]
		587.67	67.57	3.69	7.05		
IXb	Pht.DL-Ala	$C_{34}H_{23}N_3O_4S_2$	67.87	3.85	6.98	59	183—185[b]
		601.70	67.73	3.96	6.86		
IXc	Pht.DL-Phe	$C_{40}H_{27}N_3O_4S_2$	70.88	4.02	6.20	70	200—202[e]
		677.80	70.76	4.12	6.29		
IXd	Pht.L-Val	$C_{36}H_{27}N_3O_4S_2$	68.66	4.32	6.67	66	225—227[e]
		629.75	68.78	4.41	6.56		
IXe	Tos.Gly	$C_{32}H_{25}N_3O_4S_3$	62.83	4.12	6.87	61	151—153[b]
		611.76	62.92	4.21	6.72		
IXf	Tos.DL-Ala	$C_{33}H_{27}N_3O_4S_3$	63.34	4.35	6.71	68	170—172[a]
		625.78	63.42	4.22	6.83		
IXg	Tos.DL-Phe	$C_{39}H_{31}N_3O_4S_3$	66.74	4.45	5.99	73	190—192[a]
		701.88	66.83	4.53	5.87		
IXh	Tos.L-Val	$C_{35}H_{31}N_3O_4S_3$	64.29	4.78	6.43	62	201—203[b]
		653.84	64.39	4.67	6.52		
IXi	Gly	$C_{25}H_{19}N_3O_2S_2$	65.62	4.19	9.18	81	210—212[e]
		457.57	65.74	4.28	9.09		
IXj	DL-Ala	$C_{26}H_{21}N_3O_2S_2$	66.22	4.49	8.91	71	230—232[e]
		471.60	66.31	4.58	8.80		
IXk	DL-Phe	$C_{32}H_{25}N_3O_2S_2$	70.18	4.60	7.67	82	236—238[b]
		547.69	70.26	4.73	7.55		
IXl	L-Val	$C_{28}H_{25}N_3O_2S_2$	67.31	5.04	8.41	69	240—242[b]
		499.65	67.44	5.15	8.54		
Xa	Pht.Gly	$C_{33}H_{22}N_4O_4S$	69.46	3.89	9.82	70	162—164[d]
		570.62	69.54	3.97	9.71		
Xb	Pht.DL-Ala	$C_{34}H_{24}N_4O_4S$	69.85	4.14	9.58	73	153—155[b]
		584.65	69.72	4.22	9.46		
Xc	Pht.DL-Phe	$C_{40}H_{28}N_4O_4S$	72.71	4.27	8.48	68	193—195[c]
		660.75	72.63	4.38	8.59		
Xd	Pht.L-Val	$C_{36}H_{28}N_4O_4S$	70.57	4.61	9.14	71	180—182[e]
		612.70	70.42	4.72	9.26		
Xe	Tos.Gly	$C_{32}H_{26}N_4O_4S_2$	64.63	4.41	9.42	65	207—209[b]
		594.71	64.51	4.54	9.53		
Xf	Tos.DL-Ala	$C_{33}H_{28}N_4O_4S_2$	65.11	4.64	9.20	67	211—213[b]
		608.73	65.21	4.76	9.29		

Table 1 (Continued)

Compound	R*	Formula M_r	w_i(calc.)/% w_i(found)/% C	H	N	Yield %	M.p.** ℃
Xg	Tos.DL-Phe	$C_{39}H_{32}N_4O_4S_2$	68.40	4.71	8.18	73	170—172[a]
		684.83	68.52	4.83	8.30		
Xh	Tos.DL-Val	$C_{35}H_{32}N_4O_4S_2$	66.02	5.07	8.80	68	190—192[a]
		636.79	66.19	5.13	8.91		
Xi	Gly	$C_{25}H_{20}N_4O_2S$	68.16	4.58	12.72	70	250—252[a]
		440.52	68.26	4.70	12.61		
Xj	DL-Ala	$C_{26}H_{22}N_4O_2S$	68.70	4.88	12.33	65	271—273[a]
		454.55	68.61	4.97	12.42		
Xk	DL-Phe	$C_{32}H_{26}N_4O_2S$	72.43	4.94	10.56	67	231—233[e]
		530.65	72.31	4.81	10.69		
Xl	L-Val	$C_{28}H_{26}N_4O_2S$	69.69	5.43	11.61	59	217—219[a]
		482.60	69.54	5.56	11.73		

*Pht = phthalyl, Tos = tosyl, Gly = glycine, Ala = alanine, Phe = phenylalanine, Val = valine.
** Solvent for crystallization *a*) ethanol, *b*) methanol, *c*) benzene, *d*) cyclohexane, *e*) ethyl acetate.

spectrum (DMSO-d_6), δ_H: 2.51 (t, 2H, CH_2), 3.04 (t, 2H, CH_2), 6.88—8.24 (m, 7H, H_{arom}), 8.94 (br s, 1H, NH, exchangeable). For $C_{16}H_{12}N_2O_2S$ w_i(calc.): 64.85 % C, 4.08 % H, 9.45 % N; w_i(found): 64.72 % C, 4.17 % H, 9.33 % N.

4-Benzyl-6-(phenoxathiin-2-yl)pyridazin-3(2*H*)-one (*IV*)

To a mixture of *II* (20.7 g; 0.07 mol) and benzaldehyde (7.3 cm^3, 0.072 mol) in ethanol (150 cm^3) an ethanolic sodium ethoxide solution prepared from sodium (1.66 g; 0.072 mol) and dry ethanol (≈ 80 cm^3) was added and the reaction mixture was left overnight at room temperature, diluted with water and rendered just acidic with concentrated HCl. The solid thus obtained was filtered and crystallized from methanol, yield 23.4 g (87 %), m.p. = 203—205 ℃. IR spectrum, $\tilde{\nu}/cm^{-1}$: 2980—3270 (br, OH, NH), 1665 (amidic CO), 1605 (C═N). ^{1}H NMR spectrum (DMSO-d_6), δ_H: 3.64 (s, 2H, CH_2Ph), 6.85—8.33 (m, 13H, H_{arom}), 8.99 (br s, 1H, NH, exchangeable). For $C_{23}H_{16}N_2O_2S$ w_i(calc.): 71.85 % C, 4.19 % H, 7.29 % N; w_i(found): 71.72 % C, 4.26 % H, 7.36 % N.

4-Benzyl-3-chloro-6-(phenoxathiin-2-yl)pyridazine (*V*)

A mixture of pyridazinone *IV* (34 g; 0.088 mol), $POCl_3$ (137 cm^3, 1.5 mol), and PCl_5 (31 g; 0.15 mol) was refluxed on a steam bath for 5 h. The reaction mixture was poured gradually on crushed ice and the solid that separated was filtered off and crystallized from ethanol, yield 27.3 g (77 %), m.p. = 191—193 ℃. IR spectrum, $\tilde{\nu}/cm^{-1}$: 2840—2920 (H_{alkyl}), 1619 (C═C), 1588 (C═N). ^{1}H NMR spectrum ($CDCl_3$), δ_H: 3.68 (s, 2H, CH_2Ph), 6.92—8.44 (m, 13H, H_{arom}). For $C_{23}H_{15}ClN_2OS$ w_i(calc.): 68.56 % C, 3.75 % H, 6.95 % N; w_i(found): 68.66 % C, 3.68 % H, 6.82 % N.

4-Benzyl-6-(phenoxathiin-2-yl)pyridazin-3(2*H*)-thione (*VI*)

A solution of *V* (12.5 g; 0.031 mol) and thiourea (5.3 g; 0.07 mol) in anhydrous ethanol (100 cm^3) was refluxed for 5 h. After cooling, the precipitate was filtered and recrystallized from methanol, yield 10.5 g (85 %), m.p. = 208—210 ℃. IR spectrum, $\tilde{\nu}/cm^{-1}$: 3100—3260 br (NH), 2285 (SH), 1628 (C═N), 1255 (C═S), such IR data explain that the thione *VI* really exists in the thioamide (—NH—C═S) ⇌ iminothiol (—N═C—SH) dynamic equilibrium. ^{1}H NMR spectrum (DMSO-d_6), δ_H: 3.62 (s, 2H, CH_2Ph), 6.88—8.32 (m, 13H, H_{arom}), 9.18 (br s, 1H, —NHC═S ratio 55.8), 11.57 (br s, 1H, SH ratio 44.2). For $C_{23}H_{16}N_2OS_2$ w_i(calc.): 68.97 % C, 4.03 % H, 6.99 % N; w_i(found): 68.85 % C, 4.12 % H, 6.83 % N.

3-Amino-4-benzyl-6-(phenoxathiin-2-yl)-pyridazine (*VII*)

A mixture of *V* (14.5 g; 0.036 mol) and ammonium acetate (12.3 g; 0.16 mol) was heated in an oil bath at 180 ℃ for 4 h. Then the reaction mixture was poured into water and the solid separated was filtered and crystallized from ethanol, yield 10 g (73 %), m.p.= 216—218 ℃. IR spectrum, $\tilde{\nu}/cm^{-1}$: 3175—3360 (multiple bands, NH_2), 2830—2940 (H_{alkyl}), 1620 (C═C), 1592 (C═N). ^{1}H NMR spectrum ($CDCl_3$), δ_H: 3.74 (s, 2H, CH_2Ph), 5.46 (br s, 2H, NH_2, exchangeable), 6.94—8.31 (m, 13H, H_{arom}). For $C_{23}H_{17}N_3OS$ w_i(calc.): 72.04 % C, 4.47 % H, 10.96 % N; w_i(found): 72.12 % C, 4.58 % H, 10.85 % N.

Table 2. Spectral Data of Selected Compounds

Compound	^{1}H NMR (DMSO-d_6), δ^a	MS (70 eV) m/z (I_r/%)
VIIIa	3.74 (s, 2H, CH_2Ph), 4.88 (s, 2H, $COCH_2$), 6.89—8.24 (m, 17H, H_{arom})	571 (M^+, 58)
VIIIb	1.18^b (d, 3H, J = 6.8 Hz, $CHCH_3$), 3.67 (s, 2H, CH_2Ph), 5.58 (q, 1H, J = 6.8 Hz, COCH), 6.98—8.32 (m, 17H, H_{arom})	585 (M^+, 67)
VIIIc	2.88^b (d, 2H, J = 6.2 Hz, $CHCH_2$), 3.84 (s, 2H, CH_2Ph), 5.48 (t, 1H, J = 6.2 Hz, COCH), 6.88—8.34 (m, 22H, H_{arom})	661 (M^+, 34)
VIIId	1.15 (d, 6H, J = 6.5 Hz, 2 × CH_3), 2.37 (m, 1H, $CH(CH_3)_2$), 3.81 (s, 2H, CH_2Ph), 5.61 (d, 1H, J = 6.1 Hz, COCH), 6.81—8.27 (m, 17H, H_{arom})	613 (M^+, 70)
VIIIe	2.34 (s, 1H, CH_{3arom}), 3.78 (s, 2H, CH_2Ph), 4.76 (s, 2H, $COCH_2$), 6.83—8.21 (m, 17H, H_{arom}), 10.18 (br s, 1H, NH)	595 (M^+, 76)
VIIIf	1.21^b (d, 3H, J = 6.8 Hz, $CHCH_3$), 2.28 (s, 3H, CH_{3arom}), 3.68 (s, 2H, CH_2Ph), 5.44 (q, 1H, J = 6.8 Hz, COCH), 6.85—8.26 (m, 17H, H_{arom}), 10.09 (br s, 1H, NH)	609 (M^+, 83)
VIIIh	1.10^b (d, 6H, J = 6.5 Hz, 2 × CH_3), 2.34 (s, 3H, CH_{3arom}), 2.32 (m, 1H, $CH(CH_3)_2$), 3.78 (s, 2H, CH_2Ph), 5.53 (d, 1H, J = 6.1 Hz, COCH), 6.90—8.31 (m, 17H, H_{arom}), 10.30 (br s, 1H, NH)	637 (M^+, 66)
VIIIi	3.64^b (s, 2H, CH_2Ph), 4.82 (s, 2H, $COCH_2$), 6.02 (br s, 2H, NH_2), 6.90—8.28 (m, 13H, H_{arom})	441 (M^+, 80)
VIIIj	1.09 (d, 3H, J = 6.4 Hz, $CHCH_3$), 3.84 (s, 2H, CH_2Ph), 5.42 (q, 1H, J = 6.4 Hz, COCH), 5.99 (br s, 2H, NH_2), 6.88—8.31 (m, 13H, H_{arom})	455 (M^+, 62)
VIIIk	2.81 (d, 2H, J = 6.0 Hz, $CHCH_2$), 3.71 (s, 2H, CH_2Ph), 5.38 (t, 1H, J = 6.0 Hz, COCH), 5.92 (br s, 2H, NH_2), 6.80—8.22 (m, 18H, H_{arom})	531 (M^+, 52)
IXa	3.68 (s, 2H, CH_2Ph), 4.91 (s, 2H, $COCH_2$), 6.80—8.14 (m, 17H, H_{arom})	587 (M^+, 67)
IXc	2.79^b (d, 2H, J = 6.1 Hz, $CHCH_2$), 3.75 (s, 2H, CH_2Ph), 5.36 (t, 1H, J = 6.1 Hz, COCH), 6.90—8.20 (m, 22H, H_{arom})	677 (M^+, 48)
IXf	1.08 (d, 3H, J = 6.7 Hz, $CHCH_3$), 2.37 (s, 3H, CH_{3arom}), 3.70 (s, 2H, CH_2Ph), 5.38 (q, 1H, J = 6.7 Hz, COCH), 6.92—8.24 (m, 17H, H_{arom}), 10.32 (br s, 1H, NH)	625 (M^+, 55)
IXi	3.74 (s, 2H, CH_2Ph), 4.86 (s, 2H, $COCH_2$), 5.88 (br s, 2H, NH_2), 6.85—8.30 (m, 13H, H_{arom})	457 (M^+, 51)
IXj	1.18^b (d, 3H, J = 6.8 Hz, $CHCH_3$), 3.77 (s, 2H, CH_2Ph), 5.40 (q, 1H, J = 6.8 Hz, COCH), 5.95 (br s, 2H, NH_2), 6.89—8.33 (m, 13H, H_{arom})	471 (M^+, 60)
IXk	2.88 (d, 2H, J = 6.2 Hz, $CHCH_2$) 3.68 (s, 2H, CH_2Ph), 5.41 (t, 1H,J = 6.2 Hz, COCH), 6.02 (br s, 2H, NH_2), 6.78—8.20 (m, 18H, H_{arom})	547 (M^+, 71)
Xa	3.6^b (s, 2H, CH_2Ph), 4.92 (s, 2H, $COCH_2$), 6.88—8.25 (m, 17H, H_{arom}), 9.99 (br s, 1H, NH)	570 (M^+, 70)
Xb	0.98 (d, 3H, J = 6.8 Hz, $CHCH_3$), 3.75 (s, 2H, CH_2Ph), 5.52 (q, 1H, J = 6.8 Hz, COCH), 6.98—8.41 (m, 17H, H_{arom}), 9.95 (br s, 1H, NH)	584 (M^+, 86)
Xg	2.77 (d, 2H, J = 6.2 Hz, $CHCH_2$), 2.31 (s, 3H, CH_{3arom}), 3.74 (s, 2H, CH_2Ph), 5.46 (t, 1H, J = 6.2 Hz, COCH), 6.88—8.27 (m, 22H, H_{arom}), 9.88—10.60 (br s, 2H, 2 × NH)	684 (M^+, 66)
Xi	3.82 (s, 2H, CH_2Ph), 4.80 (s, 2H, $COCH_2$), 6.12 (br s, 2H, NH_2), 6.91—8.35 (m, 13H, H_{arom}), 10.22 (br s, 1H, NH)	440 (M^+, 48)

a) All NH_2 and NH signals were exchangeable with deuterium oxide, *b*) in $CDCl_3$.

4-Benzyl-6-(phenoxathiin-2-yl)-3-(*N*-phthalyl- or -tosylglycyl-, -DL-alanyl-, -DL-phenylalanyl- or -L-valyloxy)-, -thio)- or -amino)pyrimidines *a*—*h* of *VIII*—*X*

N-phthalyl- or *N*-tosylamino acids (0.0031 mol), namely glycine, DL-alanine, DL-phenylalanine or L-valine and pyridazine derivatives *IV*, *VI* or *VII* (0.0031 mol) were dissolved in tetrahydrofuran (30 cm^3). The reaction mixture was cooled to 0 °C, then *N*,*N*′-dicyclohexylcarbodiimide (0.68 g; 0.0033 mol) was added and the mixture was stirred for 2 h at 0 °C, and for another 15 h at room temperature. The precipitated dicyclohexylurea was filtered off and the filtrate was washed successively with 1 M-HCl, 1 M-$NaHCO_3$ and a saturated solution of 1 M-NaCl and dried on anhydrous sodium sulfate and left to stand overnight. It was then filtered and excess of solvent was removed. The residue thus obtained was dissolved in benzene and kept aside for 2 h. The dicyclohexylurea which again precipitated out was filtered off. The solvent was removed at reduced pressure and the residue was crystallized from a proper solvent (Table 1). IR spectrum of *a*—*d* of *VIII*—*X*, $\tilde{\nu}$/cm^{-1}: 2820—2975 (H_{alkyl}), 1750—1785 (imidic CO). In addition to the above bands *a*—*d* of *VIII, IX* exhibited bands at

Table 3. Antimicrobial* Activity** (A) and Minimum Inhibitory Concentration (MIC/(mmol dm^{-3})) for Selected Compounds

Compound	*Bacillus subtilis*		*Rhadococcus equii*		*Escherichia coli*		*Salmonella typhimurium*		*Pseudomonas aeruginosa*	
	A	{MIC}	A	{MIC}	A	{MIC}	A	{MIC}	A	{MIC}
VIIIa	++	0.44	++	0.44	++	0.44	++	1.13	++	1.13
VIIIe	++	0.21	++	0.21	++	0.21	++	0.21	++	0.21
VIIIi	+	1.13	+	0.44	+	1.13	+	1.13	+	1.13
IXa	++	0.21	++	0.85	++	0.21	++	0.21	++	0.21
IXe	+++	0.20	+++	0.20	+++	0.20	+++	0.20	+++	0.20
IXi	++	1.10	++	0.85	++	1.10	++	1.10	++	1.10
Xa	+	0.44	+	0.44	++	0.44	++	1.14	+	1.14
Xe	++	0.21	++	0.21	++	0.21	++	0.21	++	0.21
X_i	+	1.14	+	1.14	+	1.14	+	1.14	+	1.14
S^a	–	NT[c]	+++	0.50	+++	0.50	++	0.50	++	0.50
S^b	–	NT[c]	+++	0.09	+++	0.09	++	0.09	++	0.09

*Origin of cultures: Department of Botany, Faculty of Science, Benha University, Benha, Egypt. *a*) Sulfadiazine, *b*) streptomycin sulfate, *c*) not tested.

** The width of the inhibition zone indicates the potency of activity (diameter of the zone, mm): + mild (1–7), ++ moderate (8–13), +++ marked (14–17).

The results of control samples (showing negative response) are not included.

1730—1740 (—O—C═O, —S—C═O) and *Xa—d* exhibited bands at 3180—3340 (NH, CONH), 1645—1680 (amidic CO). IR spectrum of *e—h* of *VIII—X*, $\tilde{\nu}/cm^{-1}$: 3080—3220 (NH, SO_2NH), 2840—2970 (H_{alkyl}), 1458, 1370 and 1090 (SO_2NH). In addition to the above bands *e—h* of *VIII, IX* exhibited bands at 1735—1750 (—O—C═O, —S—C═O) and *Xe—h* exhibited bands at 3140—3332 (NH, CONH), 1655—1670 (amidic CO).

4-Benzyl-6-(phenoxathiin-2-yl)-3-(glycyl- (*i*), -DL-alanyl- (*j*), -DL-phenylalanyl- (*k*) or -L-valyloxy- (*l*) of *VIII*, -thio)- of *IX* or -amino)pyridazines of *X*

0.0014 mol of *N*-phthalyl derivatives *a—d* of *VIII—X* were suspended in 30 cm^3 of methanol. The suspension was brought to reflux, a clear solution resulted, 0.15 cm^3 (0.003 mol) of hydrazine hydrate was added, and the solution was stored for 20 h at 30 °C. The solvent was removed *in vacuo*. 10 cm^3 of 0.5 M-HCl was added to the dry residue, the suspension was kept in an ice bath for 2 h, and the insoluble phthalylhydrazide was removed by filtration. The filtrate was evaporated to dryness *in vacuo*. 10 cm^3 of acetone was added to the oily residue, followed by 30 cm^3 of ether, and the solution was stored for 8 h at 0 °C. The product was collected by filtration, which, upon crystallization from a proper solvent yielded the product. IR spectrum of *i—l* of *VIII, IX*, $\tilde{\nu}/cm^{-1}$: 3290—3480 (multiple bands, NH_2), 2860—2974 (H_{alkyl}), 1740—1755 (—O—C═O, —S—C═O), IR spectrum of *Xi—l*, $\tilde{\nu}/cm^{-1}$ showed bands at 3188—3472 (multiple bands, NH_2 and NH), 2840—2950 (H_{alkyl}), 1655—1670 (amidic CO).

Antimicrobial Activity

The above activity was examined *in vitro* by hole plate and filter-paper disc method [18].

The culture medium was normal nutrient agar supplemented with 1 g of microorganism per cm^{-3}.

Based on the previous preliminary test, closely spaced test concentrations were selected; they are 500 μg dm^{-3}, 250 μg dm^{-3}, 125 μg dm^{-3}. Sulfadiazine and streptomycin sulfate were dissolved in filter sterilized by 10 cm^3 of 10 vol. % acetone and employed in similar concentration as control. A qualitative screen was performed on all compounds while quantitative assays were done on active compounds only.

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REFERENCES

1. Heinisch, G. and Frank, H., *Prog. Med. Chem. 27*, 1 (1990).
2. Heinisch, G. and Kopelent-Frank, H., *Prog. Med. Chem. 29*, 141 (1992).
3. Burns, E. G., Evans, S., Lawrence, K. B., and Vanhanehem, R. C., *U.S. 5*,945,374 (1999); *Chem. Abstr. 131*, 186364*i* (1999).
4. Deopoortere, H., *Pct. Int. Appl. Wo. 13*, 879 (1999); *Chem. Abstr. 130*, 247053*n* (1999).
5. Wolfe, H. R., *Pct. Int. Appl. Wo. 9*, 416 (1999); *Chem. Abstr. 130*, 205105*m* (1999).
6. Synge, R. L. M., *Biochem. J. 39*, 363 (1945).
7. Fox, S. W., Fling, M., and Bollenback, N., *J. Biol. Chem. 155*, 465 (1944).
8. Committee on Medical Research, *O. S. R. D., Washington*, and The Medical Research Council, London, *Science 102*, 627 (1945).

9. Jones, T. S. G., *Biochem. J. 42*, 111 (1948).
10. Wasfy, A. A. F., Amine, M. S., Arief, M. M. H., and Aly, A. A., *Sulfur Lett. 19*, 45 (1995).
11. Wasfy, A. A. F., *Indian J. Chem. 33B*, 1098 (1994).
12. Lescot, E., Buu-Hoi, N. P., and Xuong, D. N., *J. Chem. Soc. 1956*, 2048.
13. Kidd, D. A. and King, F. E., *Nature 162*, 776 (1948).
14. Turner, R. A., *J. Am. Chem. Soc. 75*, 2388 (1955).
15. Fling, M., Minard, F. N., and Fox, S. W., *J. Am. Chem. Soc. 69*, 2466 (1947).
16. Bgibson, C. S. and Simonson, J. I., *J. Chem. Soc. 107*, 798 (1915).
17. Harris, T. S., *J. Biochem. 46*, 582 (1950).
18. Lefert, C., Sirri Pumchidbouree, H., Hampson, S., Workman, S., Sigee, D., Epton, H. A. S., and Harbour, A., *J. Appl. Bacteriol. 78*, 97 (1995).