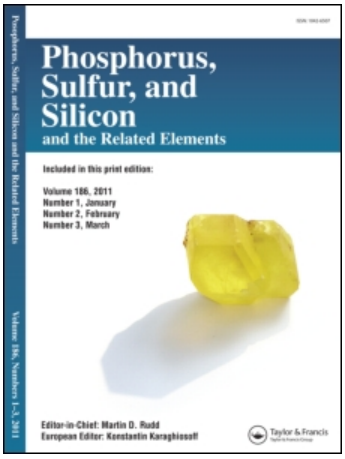

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γ-Oxo Carboxylic Acids in Heterocyclic Synthesis IV. Synthesis of Some Pyridazines Containing Phthalyl and Tosyl Amino Acids Using Dcc as the Condensing Agent

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γ-OXO CARBOXYLIC ACIDS IN HETEROCYCLIC SYNTHESIS IV. SYNTHESIS OF SOME PYRIDAZINES CONTAINING PHTHALYL AND TOSYL AMINO ACIDS USING DCC AS THE CONDENSING AGENT

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*The 3(2*H*)-oxo-, 3(2*H*)-thioxo- or 3-amino-pyridazine derivatives **4**, **6** and **7** were coupled with N-phthalyl- or N-tosyl-amino acids in one-step using N,N′-dicyclohexyl-carbodiimide as the condensing agent to furnish the corresponding 3-(N-phthalyl- or N-tosyl-aminoacyl)pyridazine derivatives **8–10** respectively. Hydrazinolysis of the N-phthalyl derivatives in methanol yielded the corresponding unprotected derivatives **11–13**. The antibacterial activities of the prepared compounds were tested.*

Keywords: Antibacterial activities; 3(2*H*)-oxo-, 3(2*H*)-thioxo- or 3-amino-pyridazine derivatives; pyridazine congeners

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 tosyl-aminoacyl)mercapto- or amino-pyrimidine derivatives. Accordingly, a massive research effort has been expended to synthesize novel congeners bearing these biologically active structural moieties within a molecular framework likely to constitute potent antimicrobial agents. An attempt also has been made to take an insight into the structure-activity relationship.

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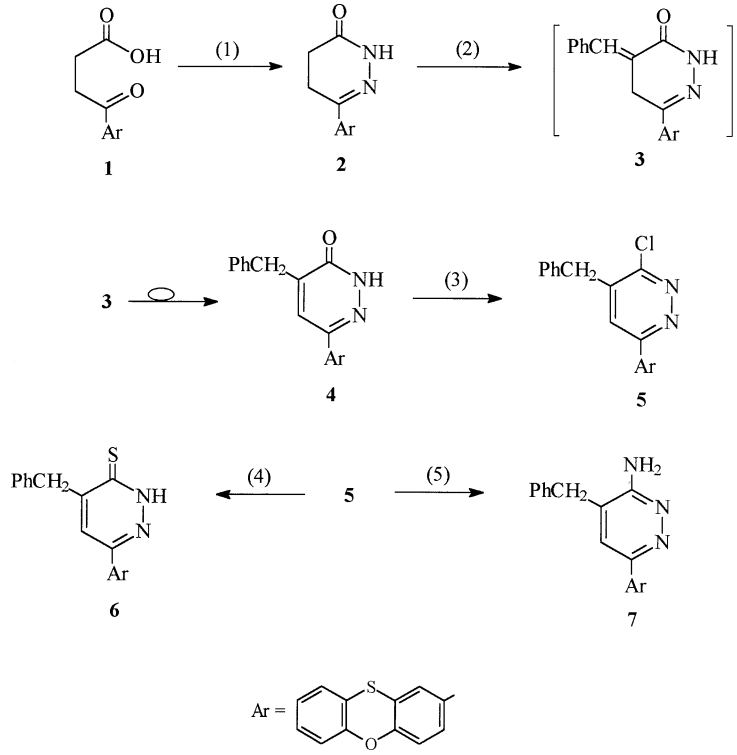
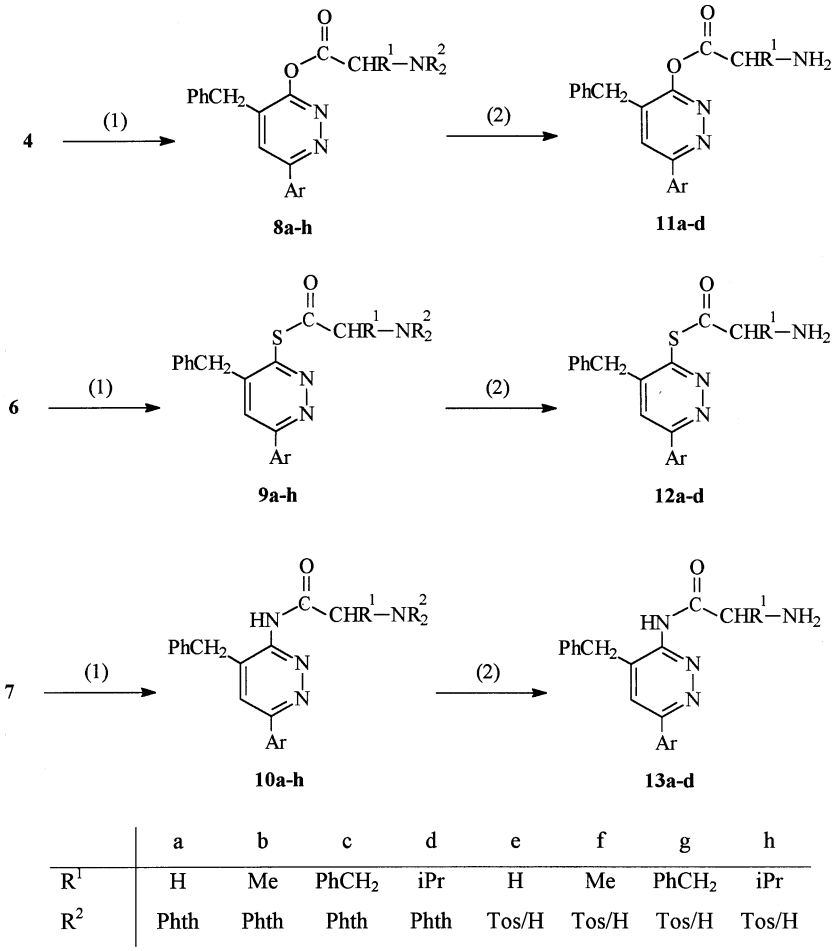


SCHEME 1 (1): N_2H_4; (2): PhCHO/EtONa; (3): $POCl_3/PCl_5$; (4): H_2NCSNH_2; (5): $AcONH_4$.

The various steps involved in the synthesis of the key intermediate compounds **6** and **7** and their reaction with amino acid residues are shown in Schemes 1 and 2.

The required 6-(phenoxathiin-2-yl)-2,3,4,5-tetrahydro-pyridazin-3-one[11] (**2**) was synthesized by the condensation of 4-(phenoxathiin-2-yl)-4-oxobutanoic acid[12] (**1**) with hydrazine hydrate in boiling ethanol. Claisen condensation of **2** with benzaldehyde in ethanolic sodium ethoxide gave 4-benzyl-6-(phenoxathiin-2-yl)pyridazin-3(2*H*)-one (**4**) through a prototropic rearrangement of the originally formed product **3** (Scheme 1). The IR data showed an absorption band around 1665 cm^{-1} characteristic of the carbonyl group of a cyclic amide thereby indicating the lactam form. It reacted when heated with $POCl_3/PCl_5$ on a steam bath to yield the corresponding 4-benzyl-3-chloro-6-(phenoxathiin-2-yl)pyridazine (**5**) with a fairly good yield. Subsequent reaction with thiourea in refluxing ethanol and/or ammonium acetate by fusion



	a	b	c	d	e	f	g	h
R^1	H	Me	$PhCH_2$	iPr	H	Me	$PhCH_2$	iPr
R^2	Phth	Phth	Phth	Phth	Tos/H	Tos/H	Tos/H	Tos/H

SCHEME 2 Ar: cf. Scheme 1; (1): Phthalyl- or tosyl aminoacid; (2): N_2H_4.

furnished the target compounds 3(2*H*)-thioxo- or 3-amino-4-benzyl-6-(phen-oxathiin-2-yl)pyridazines (**6**) and (**7**) respectively. Compounds **4**, **6**, and **7** 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′-dicyclohex-ylcarbodiimide as the condensing agent to furnish the 4-benzyl-6-(phenoxathiin-2-yl)-3-(N-phthalyl- or N-tosyl-glycyl, -DL-alanyl, -DL-phenylalanyl, or -L-valyl)oxy-, mercapto- or amino-pyridazines **8–10** respectively. Hydrazinolysis of the N-phthalyl derivatives 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-valyl)oxy-, mercapto-, or amino-pyridazines **11–13** respectively. The structures of all prepared compounds were confirmed from their physical and spectral data. The analytical data, ^{1}H NMR and mass spectra are compiled in Tables II and III.

SCREENING FOR AN ANTIMICROBIAL ACTIVITY

The antimicrobial activity of the synthesised derivatives was examined in vitro by the hole plate and filter-paper disc methods.[13] All compounds were tested for activity against several strains of Gram-positive and Gram-negative bacteria using sulfadiazine and streptomycin sulfate as a reference standard. The culture medium was normal nutrient agar supplemented with 1 g of yeast per ml. According to the solubility of the tested compounds, different polar and nonpolar solvents were used; good solubility was found in 10% (V/V) acetone for all the tested compounds. Based on the previous preliminary test, closely spaced test concentrations were selected; they are 500, 250, 125 μg/L. Sulfadiazine and streptomycin sulfate were dissolved in filter sterilized 10 ml of 10% actone (V/V) and employed in similar concentration as control. A qualitative screen was performed on all compounds while quantitative assays were done on active compounds only. The results are summarized in Table I.

Structure-activity relationship (SAR) studied showed that the presence of the tosyl group in the amino acid moiety of our 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 **8e**, **9e**, and **10e** exhibit activities which are nearly comparable to commercial antibacterial agents, such as sulfadiazine and streptomycin sulfate.

EXPERIMENTAL

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, ppm). Mass spectra were determined on a Shimadzu, GCMS QP 1000 EX mass spectrometer (70 eV EI mode).

The starting compounds phthalyl- or tosyl-amino acids were prepared according to the published procedures.

TABLE I Antimicrobial Activity (A) and Minimum Inhibitory Concentration (MIC, mmol/L) for Compounds (**8a–13a**)*,†

	Bacillus subtilis		*Rhadococcus equii*		*Escherichia coli*		*Salmonella typhimurium*		*Pseudomonas aeruginosa*	
Compounds	A	MIC	A	MIC	A	MIC	A	MIC	A	MIC
8a	++	0.44	++	0.44	++	0.44	++	1.13	++	1.13
8e	++	0.21	++	0.21	++	0.21	++	0.21	++	0.21
9a	++	0.21	++	0.85	++	0.21	++	0.21	++	0.21
9e	+++	0.20	+++	0.20	+++	0.20	+++	0.20	+++	0.20
10a	+	0.44	+	0.44	++	0.44	++	1.14	+	1.14
10e	++	0.21	++	0.21	++	0.21	++	0.21	++	0.21
11a	+	1.13	+	0.44	+	1.13	+	1.13	+	1.13
12a	++	1.10	++	0.85	++	1.10	++	1.10	++	1.10
13a	+	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

*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.

†Origin of cultures: Botany Department, Faculty of Science, Benha University, Benha (Egypt).

[a]Sulfadiazine.

[b]Streptomycin sulfate.

[c]Not tested.

Phthalylglycine (92%), m.p. 192–194°C (from methanolether), lit.,[14] m.p. 193–195°C; phthalyl-DL-alanine (90%), m.p. 160–162°C (from ethanol-water), lit.,[15] m.p. 160–161°C; phthalyl-DL-phenylalanine (78%), m.p. 173–175°C (from methanol-water), lit.,[16] m.p. 174–175°C; phthalyl-L-valine (69%), 113–115°C (from cyclohexane), lit.,[16] m.p. 114–115°C, $[\alpha]_D^{27}$ −68.5 ± 1.0° in abs. EtOH; tosylglycine (68%), m.p. 148–149°C (from methanol-ether), lit.,[17] m.p. 148°C; tosyl-DL-alanine (70%), m.p. 137–139°C (from methanol-ether), lit.,[17] m.p. 139°C; tosyl-DL-phenylalanine (65%), m.p. 124–126°C from (methanol-water), lit.,[18] m.p. 125–127°C; tosyl-L-valine (66%), m.p. 147–149°C (from methanol-water), lit.,[18] m.p. 148°C.

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

A solution of **1**[12] (27 g, 0.09 mmol) in ethanol (200 ml) was treated with hydrazine hydrate (6.8 ml, 99%, 0.14 mmol) and the mixture was refluxed for 6 h. The solid that separated after concentration and cooling was crystallised from ethanol to furnish the desired compound **2**, 21 g

(79%), m.p. 230–232°C; IR (cm^{-1}): 3280–2950 broad (NH), 1665 (amidic CO), 1600 (C=N); ^1H NMR (DMSO-d_6) δ_H: 2.51 (t, 2H, CH_2, H-4), 3.04 (t, 2H, CH_2 H-5), 6.88–8.24 (m, 7H, Ar-H), 8.94 (br s, 1H, NH, exchangeable). Found: C, 64.72; H, 4.17; N, 9.33%. Calcd for $C_{16}H_{12}N_2O_2S$: C, 64.85; H, 4.08; N, 9.45%.

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

To a mixture of **2** (20.7 g, 0.07 mmol) and benzaldehyde (7.3 ml, 0.072 mmol) in ethanol (150 ml) was added an ethanolic sodium ethoxide solution prepared from sodium (1.66 g, 0.072 mmol) and dry ethanol (~80 ml). The reaction mixture was left overnight at room temperature, diluted with water, and rendered just acidic with conc. HCl. The solid thus obtained was filtered and crystallized from methanol to give **4**, 23.4 g (87%), m.p. 203–205°C; IR (cm^{-1}): 3270–2980 broad (NH), 1665 (amidic CO), 1605 (C=N); ^1H NMR (DMSO-d_6) δ_H: 3.64 (s, 2H, CH_2Ph), 6.85–8.33 (m, 13H, Ar-H), 8.99 (br s, 1H, NH, exchangeable). Found: C, 71.72; H, 4.26; N, 7.36%. Calcd for $C_{23}H_{16}N_2O_2S$: C, 71.85; H, 4.19; N, 7.29%.

4-Benzyl-3-chloro-6-(phenoxathiin-2-yl)pyridazine (5)

A mixture of pyridazinone **4** (34 g, 0.088 mmol), $POCl_3$ (137 ml, 1.5 mmol) and PCl_5 (31 g, 0.15 mmol) 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 to afford **5**, 27.3 g (77%), m.p. 191–193°C; IR (cm^{-1}): 2920–2840 (alkyl-H), 1619 (C=C), 1588 (C=N); ^1H NMR ($CDCl_3$) δ_H: 3.68 (s, 2H, CH_2Ph), 6.92–8.44 (m, 13H, Ar-H). Found: C, 68.66; H, 3.68; N, 6.82%. Calcd for $C_{23}H_{15}ClN_2OS$: C, 68.56; H, 3.75; N, 6.95%.

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

A solution of **5** (12.5 g, 0.031 mmol) and thiourea (5.3 g, 0.07 mmol) in anhydrous ethanol (100 ml) was refluxed for 5 h. After cooling, the precipitate was filtered, and recrystallized from methanol to obtain **6**, 10.5 g (85%), m.p. 208–210°C; IR (cm^{-1}): 3260–3100 broad (NH), 2285 (SH), 1628 (C=N), 1255 (C=S), such IR data explain that the thione **6** really exists in the thioamide (–NH–C=S) ⇌ iminothiol (–N=C–SH) dynamic equilibrium; ^1H NMR (DMSO-d_6) δ_H: 3.62 (s, 2H, CH_2Ph), 6.88–8.32 (m, 13H, Ar-H), 9.18 (br s, 1H, –NHC=S ratio 55.8), 11.57 (br s, 1H, SH ratio 44.2). Found: C, 68.85, H, 4.12; N, 6.83%. Calcd for $C_{23}H_{16}N_2OS_2$: C, 68.97; H, 4.03; N, 6.99%.

3-Amino-4-benzyl-6-(phenoxathiin-2-yl)pyridazine (7)

A mixture of **5** (14.5 g, 0.036 mmol) and ammonium acetate (12.3 g, 0.16 mmol) was heated in an oil bath at 180°C for 4 h. Then the reaction mixture was poured into water and the solid separated was filtered and crystallized from ethanol to give the target compound **7**, 10 g (73%), m.p. 216–218°C; IR (cm^{-1}): 3360–3175 (multiple bands, NH_2), 2940–2830 (alkyl-H), 1620 (C=C), 1592 (C=N); ^1H NMR ($CDCl_3$) δ_H: 3.74 (s, 2H, CH_2Ph), 5.46 (br s, 2H, NH_2, exchangeable), 6.94–8.31 (m, 13H, Ar-H). Found: C, 72.12; H, 4.58; N, 10.85%. Calcd for $C_{23}H_{17}N_3OS$: C, 72.04; H, 4.47; N, 10.96%.

4-Benzyl-6-(phenoxathiin-2-yl)-3-(N-phthalyl- or N-tosyl-glycyl, -DL-alanyl, -DL-phenylalanyl or -L-valyl)oxy-, mercapto- or amino-pyrimidines 8–10

An N-phthalyl- or N-tosyl-amino acids (0.0031 mmol), namely, glycine, DL-alanine, DL-phenylalanine, or L-valine and the pyridazine derivatives **4**, **6**, and/or **7** (0.0031 mmol) were dissolved in tetrahydrofuran (30 ml). The reaction mixture was cooled to 0°C, then N,N′-dicyclohexylcarbodiimide, DCC (0.68 g, 0.0033 mmol) 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 N HCl, 1N $NaHCO_3$, and a saturated solution of 1 N NaCl and dried on anhydrous sodium sulfate and left overnight. It was then filtered and the 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 to furnish compounds **8–10** (Tables II and III). IR (cm^{-1}) of (**8–10**)**a–d**: 2975–2820 (alkyl-H), 1785–1750 (imidic CO). In addition to the above bands (**8**, **9**)**a–d** exhibited bands at 1740–1730 (–O–C=O, –S–C=O) and **10a–d** exhibited bands at 3340–3180 (NH, CONH), 1680–1645 (amidic CO). IR (cm^{-1}) of (**8–10**)**e–h**: 3220–3080 (NH, SO_2NH), 2970–2840 (alkyl-H), 1458, 1370, and 1090 (SO_2NH). In addition to the above bands (**8**, **9**)**e–h** exhibited bands at 1750–1735 (–O–C=O, –S–C=O) and **10e–h** exhibited bands at 3332–3140 (NH, CONH), 1670–1655 (amidic CO).

4-Benzyl-6-(phenoxathiin-2-yl)-3-(glycyl-, DL-alanyl-, DL-phenyl-alanyl-, or L-valyl)oxy-, mercapto-, or amino-pyridazines 11–13

The N-phthalyl derivatives (**8–10**)**a–d** (0.0014 mmol) were suspended in (30 ml) of methanol. The suspension was brought to reflux.

TABLE II Analytical Data of Compounds **8–13**

Compd. No.	R[a]	m.p. [b] θ m/°C	Yield (%)	Mol. Formula (mol. wt.)	Calcd (found) (%) C	H	N
8a	Pht. Gly	185–187[e]	71	$C_{33}H_{21}N_3O_5S$ (571.61)	69.34 (69.46)	3.70 (3.79)	7.35 (7.42)
b	Pht.DL-Ala	176–178[a]	64	$C_{34}H_{23}N_3O_5S$ (585.63)	69.73 (69.84)	3.96 (3.84)	7.18 (7.26)
c	Pht.DL-Phe	190–192[a]	62	$C_{40}H_{27}N_3O_5S$ (661.73)	72.60 (72.71)	4.11 (4.19)	6.35 (6.42)
d	Pht.L-Val	222–224[e]	58	$C_{36}H_{27}N_3O_5S$ (613.69)	70.46 (70.56)	4.43 (4.35)	6.85 (6.72)
e	Tos. Gly	237–239[a]	62	$C_{32}H_{25}N_3O_5S_2$ (595.69)	64.52 (64.63)	4.23 (4.11)	7.05 (7.13)
f	Tos.DL-Ala	251–253[b]	65	$C_{33}H_{27}N_3O_5S_2$ (609.72)	65.01 (65.13)	4.46 (4.35)	6.89 (6.76)
g	Tos.DL-Phe	197–199[b]	63	$C_{39}H_{31}N_3O_5S_2$ (685.82)	68.30 (68.39)	4.56 (4.47)	6.13 (6.19)
h	Tos.DL-Val	165–167[e]	70	$C_{35}H_{31}N_3O_5S_2$ (637.77)	65.91 (65.80)	4.90 (4.81)	6.59 (6.44)
9a	Pht. Gly	163–165[b]	61	$C_{33}H_{21}N_3O_4S_2$ (587.67)	67.45 (67.57)	3.60 (3.69)	7.15 (7.05)
b	Pht.DL-Ala	183–185[b]	59	$C_{34}H_{23}N_3O_4S_2$ (601.70)	67.87 (67.73)	3.85 (3.96)	6.98 (6.86)
c	Pht.DL-Phe	200–202[e]	70	$C_{40}H_{27}N_3O_4S_2$ (677.80)	70.88 (70.76)	4.02 (4.12)	6.20 (6.29)
d	Pht.L-Val	225–227[e]	66	$C_{36}H_{27}N_3O_4S_2$ (629.75)	68.66 (68.78)	4.32 (4.41)	6.67 (6.56)
e	Tos. Gly	151–153[b]	61	$C_{32}H_{25}N_3O_4S_3$ (611.76)	62.83 (62.92)	4.12 (4.21)	6.87 (6.72)
f	Tos. DL-Ala	170–172[a]	68	$C_{33}H_{27}N_3O_4S_3$ (625.78)	63.34 (63.42)	4.35 (4.22)	6.71 (6.83)
g	Tos.DL-Phe	190–192[a]	73	$C_{39}H_{31}N_3O_4S_3$ (701.88)	66.74 (66.83)	4.45 (4.53)	5.99 (5.87)
h	Tos.L-Val	201–203[b]	62	$C_{35}H_{31}N_3O_4S_3$ (653.84)	64.29 (64.39)	4.78 (4.67)	6.43 (6.52)
10a	Pht. Gly	162–164[a]	70	$C_{33}H_{22}N_4O_4S$ (570.62)	69.46 (69.54)	3.89 (3.97)	9.82 (9.71)
b	Pht.DL-Ala	153–155[b]	73	$C_{34}H_{24}N_4O_4S$ (584.65)	69.85 (69.72)	4.14 (4.22)	9.58 (9.46)
c	Pht.DL-Phe	193–195[c]	68	$C_{40}H_{28}N_4O_4S$ (660.75)	72.71 (72.63)	4.27 (4.38)	8.48 (8.59)
d	Pht.L-Val	180–182[e]	71	$C_{36}H_{28}N_4O_4S$ (612.70)	70.57 (70.42)	4.61 (4.72)	9.14 (9.26)
e	Tos. Gly	207–209[b]	65	$C_{32}H_{26}N_4O_4S_2$ (594.71)	64.63 (64.51)	4.41 (4.54)	9.42 (9.53)
f	Tos. DL-Ala	211–213[b]	67	$C_{33}H_{28}N_4O_4S_2$ (608.73)	65.11 (65.21)	4.64 (4.76)	9.20 (9.29)
g	Tos. DL-Phe	170–172[a]	73	$C_{39}H_{32}N_4O_4S_2$ (684.83)	68.40 (68.52)	4.71 (4.83)	8.18 (8.30)

(Continued on next page)

TABLE II Analytical Data of Compounds **8–13** *(Continued)*

Compd. No.	R[a]	m.p. [b] θ m/°C	Yield (%)	Mol. Formula (mol. wt.)	Calcd (found) (%) C	H	N
h	Tos. DL-Val	190–192[a]	68	$C_{35}H_{32}N_4O_4S_2$ (636.79)	66.02 (66.19)	5.07 (5.13)	8.80 (8.91)
11a	Gly	242–244[a]	72	$C_{25}H_{19}N_3O_3S$ (441.50)	68.01 (68.13)	4.34 (4.41)	9.52 (9.43)
b	DL-Ala	248–250[b]	65	$C_{26}H_{21}N_3O_3S$ (455.53)	68.55 (68.68)	4.65 (4.77)	9.22 (9.31)
c	DL-Phe	221–223[b]	62	$C_{32}H_{25}N_3O_3S$ (531.63)	72.30 (72.42)	4.74 (4.85)	7.90 (7.79)
d	L-Val	261–263[e]	73	$C_{28}H_{25}N_3O_3S$ (483.59)	69.54 (69.66)	5.21 (5.10)	8.69 (8.78)
12a	Gly	210–212[e]	81	$C_{25}H_{19}N_3O_2S_2$ (457.57)	65.62 (65.74)	4.19 (4.28)	9.18 (9.09)
b	DL-Ala	230–232[e]	71	$C_{26}H_{21}N_3O_2S_2$ (471.60)	66.22 (66.31)	4.49 (4.58)	8.91 (8.80)
c	DL-Phe	236–238[b]	82	$C_{32}H_{25}N_3O_2S_2$ (547.69)	70.18 (70.26)	4.60 (4.73)	7.67 (7.55)
d	L-Val	240–242[b]	69	$C_{28}H_{25}N_3O_2S_2$ (499.65)	67.31 (67.44)	5.04 (5.15)	8.41 (8.54)
13a	Gly	250–252[a]	70	$C_{25}H_{20}N_4O_2S$ (440.52)	68.16 (68.26)	4.58 (4.70)	12.72 (12.61)
b	DL-Ala	271–273[a]	65	$C_{26}H_{22}N_4O_2S$ (454.55)	68.70 (68.61)	4.88 (4.97)	12.33 (12.42)
c	DL-Phe	231–233[e]	67	$C_{32}H_{26}N_4O_2S$ (530.65)	72.43 (72.31)	4.94 (4.81)	10.56 (10.69)
d	L-Val	217–219[a]	59	$C_{28}H_{26}N_4O_2S$ (482.60)	69.69 (69.54)	5.43 (5.56)	11.61 (11.73)

[a] Pht = phthalyl, Tos = tosyl, Gly = glycine, Ala = alanine, Phe = phenylalanine, Val = valine.
[b] solvent for crystallization.
[a] Ethanol.
[b] Methanol.
[c] Benzene.
[d] Cyclohexane.
[e] Ethyl acetate.

A clear solution resulted, hydrazine hydrate (0.15 ml, 0.003 mmol) was added, and the solution was stored for 20 h at 30°C. The solvent was removed in vacuo. To the dry residue there was added (10 ml) of 0.5 N hydrochloric acid, 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. To the oily residue was added acetone (10 ml), followed by ether (30 ml), and the solution was stored for 8 h at 0°C. The product was collected by filtration. Crystallization from

TABLE III Spectral Data of Compounds **8–13**

Compd. No.	^{1}H NMR (DMSO-d_6) δ/ppm[a]	MS (70 eV) m/z (%)
8a	3.74 (s, 2H, CH_2Ph), 4.88 (s, 2H, $COCH_2$), 6.89–8.24 (m, 17H, Ar-H)	571 (M^+, 58)
8b	[b]1.18 (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, Ar-H)	585 (M^+, 67)
8c	[b]2.88 (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, Ar-H)	661 (M^+, 34)
8d	1.15 (d, 6H, J = 6.5, 2xCH_3), 2.37 (m, 1H, $CH(CH_3)_2$), 3.81 (s, 2H, CH_2Ph), 5.61 (d, 1H, J = 6.1, COCH), 6.81–8.27 (m, 17H, Ar-H)	613 (M^+, 70)
8e	2.34 (s, 1H, $ArCH_3$), 3.78 (s, 2H, CH_2Ph), 4.76 (s, 2H, $COCH_2$), 6.83–8.21 (m, 17H, Ar-H), 10.18 (br s, 1H, NH)	595 (M^+, 76)
8f	[b]1.21 (d, 3H, J = 6.8 Hz, $CHCH_3$), 2.28 (s, 3H, $ArCH_3$), 3.68 (s, 2H, CH_2Ph), 5.44 (q, 1H, J = 6.8 Hz, COCH), 6.85–8.26 (m, 17H, Ar-H), 10.09 (br s, 1H, NH)	609 (M^+, 83)
8h	[b]1.10 (d, 6H, J = 6.5, 2xCH_3), 2.34 (s, 3H, $ArCH_3$), 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, Ar-H), 10.30 (br s, 1H, NH)	637 (M^+, 66)
9a	3.68 (s, 2H, CH_2Ph), 4.91 (s, 1H, $COCH_2$), 6.80–8.14 (m, 17H, Ar-H)	587 (M^+, 67)
9c	[b]2.79 (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, Ar-H)	677 (M^+, 48)
9f	1.08 (d, 3H, J = 6.7 Hz, $CHCH_3$), 2.37 (s, 3H, $ArCH_3$), 3.70 (s, 2H, CH_2Ph), 5.38 (q, 1H, J = 6.7 Hz, COCH), 6.92–8.24 (m, 17H, Ar-H), 10.32 (br s, 1H, NH)	625 (M^+, 55)
10a	[b]3.65 (s, 2H, CH_2Ph), 4.92 (s, 2H, $COCH_2$), 6.88–8.25 (m, 17H, Ar-H), 9.99 (br s, 1H, NH)	570 (M^+, 70)
10b	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, Ar-H), 9.95 (br s, 1H, NH)	584 (M^+, 86)
10g	2.77 (d, 2H, J = 6.2 Hz, $CHCH_2$), 2.31 (s, 3H, $ArCH_3$), 3.74 (s, 2H, CH_2Ph), 5.46 (t, 1H, J = 6.2 Hz, COCH), 6.88–8.27 (m, 22H, Ar-H), 9.88–10.60 (br s, 2H, 2x NH)	684 (M^+, 66)
11a	[b]3.64 (s, 2H, CH_2Ph), 4.82 (s, 2H, $COCH_2$), 6.02 (br s, 2H, NH_2), 6.90–8.28 (m, 13H, Ar-H)	441 (M^+, 80)
11b	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, Ar-H)	455 (M^+, 62)
11c	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, Ar-H)	531 (M^+, 52)
12a	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, Ar-H)	457 (M^+, 51)
12b	[b]1.18 (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, Ar-H)	471 (M^+, 60)
12c	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, Ar-H)	547 (M^+, 71)
13a	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, Ar-H), 10.22 (br s, 1H, NH)	440 (M^+, 48)

[a] All NH_2 and NH signals were exchangeable with deuterium oxide.
[b] In $CDCl_3$.

a proper solvent yielded the unprotected compounds **11–13** (Tables II and III). IR (cm^{-1}) of **11** and **12**: 3480–3290 (multiple bands, NH_2), 2974–2860 (alkyl-H), 1755–1740 (—O—C=O, —S—C=O), IR (cm^{-1}) of **13** showed bands at 3472–3188 (multiple bands, NH_2 and NH), 2950–2840 (alkyl-H), 1670–1655 (amidic CO).

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