Synthesis of Some New Piperazine-N,N'-bis-substituted Derivatives As Potential Biologically Active Agents

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In a search for new bactericidal and fungicidal agents some new piperazine-N,N'-bis-substituted derivatives have been prepared and characterized by their elemental analysis, IR, ^{1}H NMR, and mass spectral data. The antibacterial and antifungal activities of all prepared compounds have been determined using Gentamycin as standard antibiotic. Some compounds showed a high activity equivalent to that of the standard towards *Escherichia coli, Serratia marcescens, Bacillus cereus, Staphylococcus aureus,* and *Candida albicans.*

In recent years, much attention has been focussed on the synthesis of some interesting, variously disubstituted piperazines, which possess a broad spectrum of pharmacological properties [1—6]. This observation prompted us to synthesize some piperazine-N,N'-bis-substituted derivatives containing various heterocyclic moieties. Such compounds are likely to show enhanced biological activities.

The starting compounds *Ia—Ie* were prepared by an acylation of piperazine with *p*-chlorobenzoyl, *p*-nitrobenzoyl, and 2,4-dichlorobenzoyl chlorides or by addition of phenyl or allyl isothiocyanate in the presence of DMF (Scheme 1).

For the synthesis of some new 1,4-disubstituted piperazines which contain some heterocyclic moieties, characterized in Table 1, the compounds *Ia, Ic* underwent condensation with ethanolamine or thiosemicarbazide in hot glacial acetic acid to give 1,4-di(iminoaryl)piperazines *II—IV*, respectively. The structures of the above compounds were supported by their IR spectra which showed bands at $\tilde{\nu}/\mathrm{cm}^{-1}$ 1200, 1620, and 1650 due to C—S, NH_2, and C=N groups. Moreover, ^{1}H NMR spectrum of *IV* exhibited resonance signals due to SH, CH_2, aromatic and NH protons at δ = 3.20—3.80, 3.90—4.40, 7.44—7.49, 7.54—7.56, 12.00, and 13.00. Furthermore, thiosemicarbazone *III* was reacted with malonic acid and acetyl chloride [7] to give 2,3-dihydro-2-thioxo-1*H*, 5*H*-pyrimidine-4,6-dione derivative *V* Similarly, compound *IV* under the same conditions furnished 2-thioxopyrimidine-4,6-dione derivative *VI*, while treatment of compound *IV* with monochloroacetic acid and fused NaOAc in the presence of ethanol [8] afforded thiazolidin-4-one derivative *VII* (Scheme 1).

The structure of compounds *V—VII* was confirmed by elemental analysis, IR, ^{1}H NMR, and mass spectral data. The IR spectra of these compounds showed stretching bands at $\tilde{\nu}/\mathrm{cm}^{-1}$ 1100 (C—S), 1440, 1480 (deformation of CH_2), 1600 (C=N), 1650, 1690 (C=O), and 3100—3500 (b, OH, NH). The ^{1}H NMR resonance signals of *VI* were observed in the range of δ = 3.40—3.90, 7.45—7.49, and 7.52—7.56 due to CH_2, aromatic and NH protons.

The mass spectra of thiazolidin-4-one *VII* showed the molecular ion peak at m/z = 659.9 and the base peak at m/z (I_r/%) = 172.80 (100) and were found to be in conformity with the assigned structure (Scheme 2).

Structure of *Id* was supported by its reaction with formaldehyde in the presence of methanol giving the desired hydroxymethyl derivative *VIII*. The structure of *VIII* was supported by spectral studies. The IR spectrum of compound *VIII* exhibited absorptions due to CH_2, C=C, C=O, and OH functions at $\tilde{\nu}/\mathrm{cm}^{-1}$ 1480, 1650, 1680, and 3380, respectively. Its ^{1}H NMR spectrum displayed signals at δ = 3.37—3.39, 3.45—3.65, 6.92—7.35, and 8.30—8.59 accounted for methylene, piperazine, aromatic and hydroxy protons. Mass spectrum of *VIII* showed the molecular ion peak at m/z = 384, it underwent fragmentation pattern which supported the structure.

A facile synthesis of fully substituted carbamides

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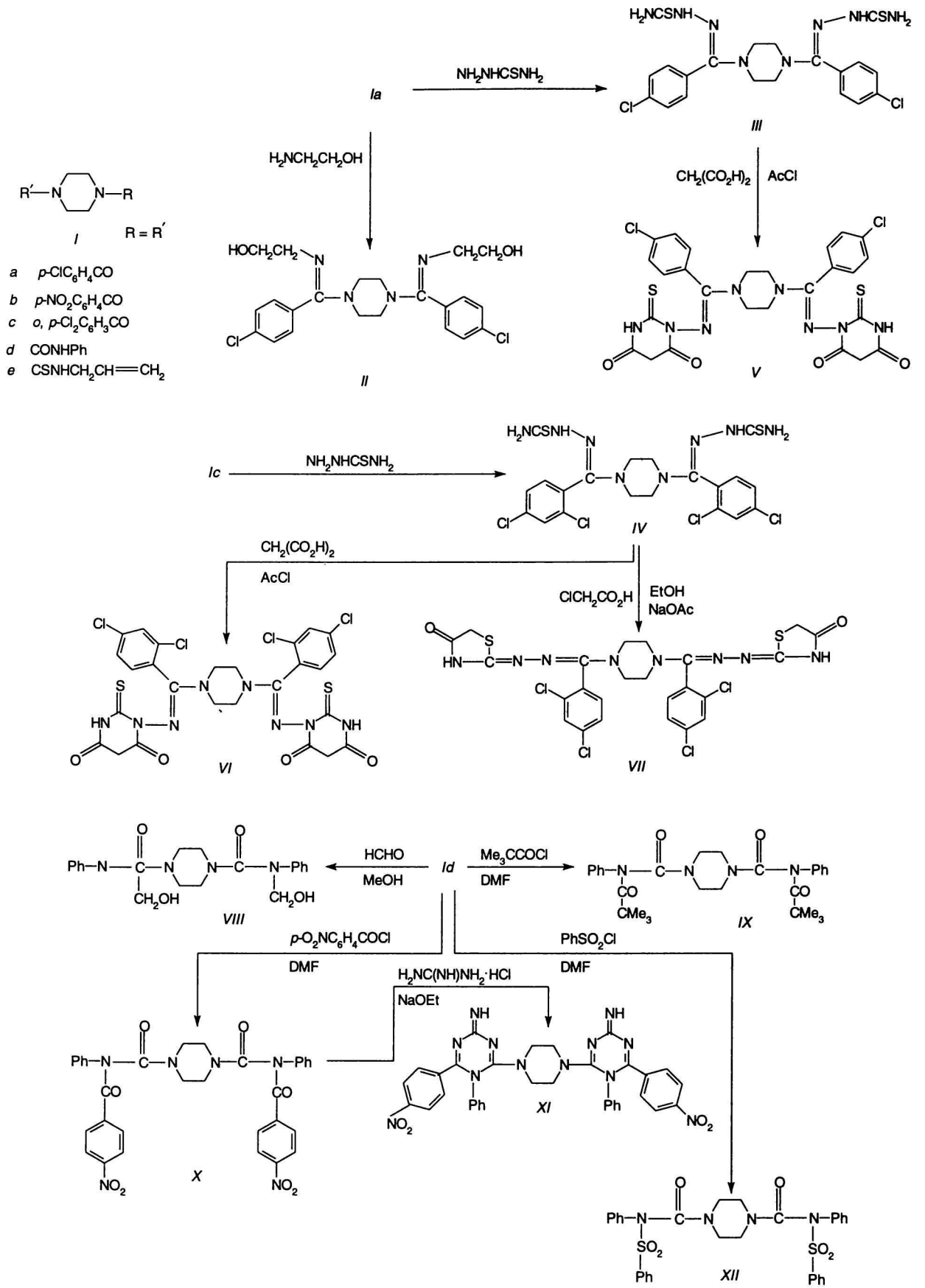
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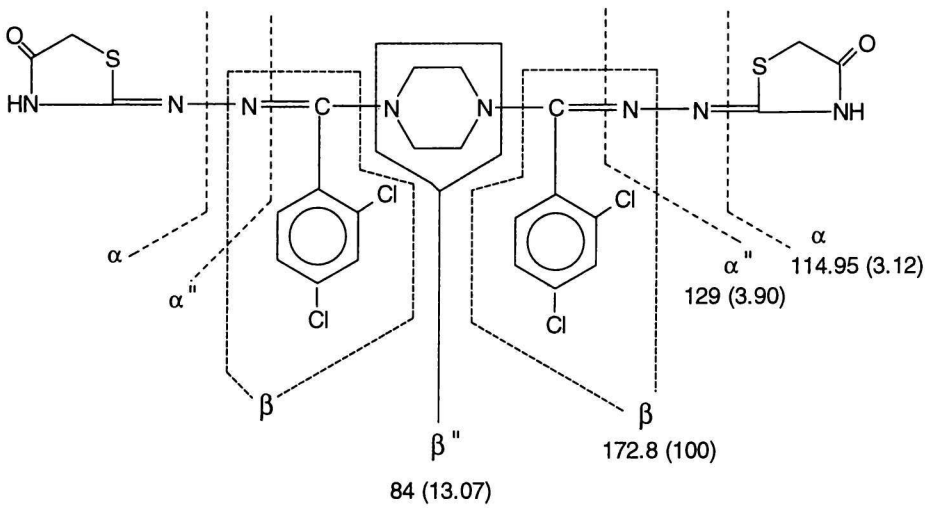
b p-NO2C6H4CO
c o, p-Cl2C6H3CO
d CONHPh
e CSNHCH2CH=CH2
Ia
NH2NHCSNH2
III
H2NCH2CH2OH
II
CH2(CO2H)2
AcCl
V
Ic
NH2NHCSNH2
IV
CH2(CO2H)2
AcCl
ClCH2CO2H
EtOH
NaOAc
VI
VII
Id
HCHO
MeOH
VIII
Me3CCOCl
DMF
IX
p-O2NC6H4COCl
DMF
PhSO2Cl
DMF
H2NC(NH)NH2·HCl
NaOEt
X
XI
XII

Scheme 1

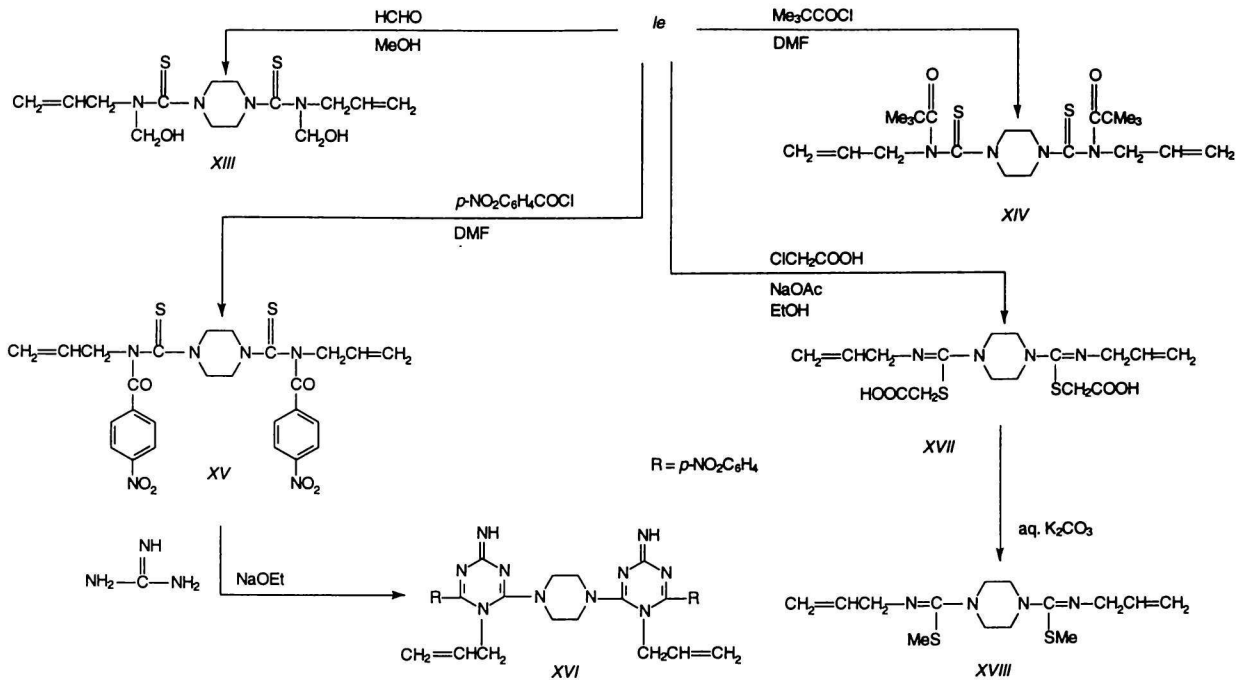
Table 1. Physical Data of the New Synthesized Compounds

Compound	Formula M_r	w_i(calc.)/% w_i(found)/%		Yield	M.p.	Solvent
		Cl	S	%	°C	
II	$C_{22}H_{26}N_4Cl_2O_2$ 449.38	15.78 15.20	–	60	230—231	Dil. EtOH
III	$C_{20}H_{22}N_8Cl_2S_2$ 509.48	13.92 13.40	12.59 11.97	70	238—240	Dil. EtOH
IV	$C_{26}H_{22}N_8Cl_2S_2O_4$ 645.55	10.98 10.50	9.93 9.50	55	232—233	EtOH
V	$C_{20}H_{20}N_8Cl_4S_2$ 578.38	24.52 24.00	11.09 10.70	50	235—237	Dil. MeOH
VI	$C_{26}H_{20}N_8Cl_4S_2O_4$ 714.44	19.85 19.05	8.98 8.19	60	241—242	Dil. MeOH
VII	$C_{27}H_{20}N_8Cl_4S_2O_2$ 694.45	20.42 20.00	9.23 8.75	50	230—231	EtOH
VIII	$C_{20}H_{24}N_4O_4$ 384.43	–		75	above 290	EtOH
IX	$C_{28}H_{36}N_4O_4$ 504.63	–	–	80	above 290	AcOH
X	$C_{32}H_{26}N_6O_8$ 622.59		–	70	217—218	AcOH
XI	$C_{34}H_{28}N_{12}O_4$ 668.67	–	–	70	above 290	EtOH
XII	$C_{30}H_{28}N_4S_2O_6$ 604.70	–	10.61 10.01	60	277—278	EtOH
XIII	$C_{14}H_{24}N_4S_2O_2$ 344.50	–	18.62 18.10	50	155—156	Dil. EtOH
XIV	$C_{22}H_{36}N_4S_2O_2$ 452.68	–	14.17 13.90	55	147—148	Dil. EtOH
XV	$C_{26}H_{26}N_6S_2O_6$ 582.66		11.01 10.29	50	173—175	Dil. MeOH
XVI	$C_{28}H_{28}N_{12}O_4$ 596.61	–		65	236—237	EtOH
XVII	$C_{16}H_{24}N_4S_2O_4$ 400.52	–	16.01 15.70	75	155—156	EtOH
XVIII	$C_{14}H_{24}N_4S_2$ 312.50		20.52 20.08	70	152—153	Dil. EtOH

* All the compounds gave satisfactory C, H, and N analysis.



Scheme 2
Mass spectra of the compound *VII* (m/z (I_r/%))



Scheme 3

bearing a piperazine moiety has been described. Thus, compound *Id* underwent acylation in DMF to offer the *N*-pivaloyl and *N*-*p*-nitrobenzoyl derivatives *IX* and *X*, respectively. We now report that these carbamides are convenient for the synthesis of some heterocyclic systems. Thus, compound *X* condensed with guanidine chloride in sodium ethoxide produced the 1,3,5-triazine derivative *XI*. Also, reaction of *Id* with benzenesulfonyl chloride in the presence of DMF yielded the sulfonamide derivative *XII* (Scheme 1).

The absence of NH band in the spectra of compounds *IX*, *X*, and *XII* revealed that the substitution has occurred at NH centre.

In the ^{1}H NMR spectra of the sulfonamide *XII* the signals of piperazine and aromatic protons were observed at $\delta = 3.00$—4.00 and 7.29—7.78. Mass spectra of *XII* gave the molecular ion at $m/z = 604$ and the peak at m/z (I_r/%) = 76.9 (100), from which the fine structure could be deduced.

The original aim of the present work was to synthesize some new piperazine-*N*,*N'*-bis-substituted derivatives and then by cyclocondensation to obtain some new heterocyclic systems. Thus, compound *Ie* was reacted with formaldehyde in methanol *via* the hydroxymethylation reaction to give *XIII* (Scheme 3). Acylation of *Ie* in DMF led to the formation of *N*-pivaloyl and *N*-*p*-nitrobenzoyl derivatives *XIV* and *XV*, respectively. Compound *XV* on cyclocondensation with guanidine chloride in the presence of sodium ethoxide produced 1,3,5-triazine derivative *XVI* (Scheme 3). The latter reaction may occur *via* condensation of carbonyl group of aroyl moiety followed by elimination of H_2S molecule from thiocarbamide under the basic media.

All these compounds *XIII*—*XV* showed the absence of bands due to NH groups. Moreover, resonance signals due to methylene, piperazine, allyl, aromatic and hydroxy protons are also observed in the ^{1}H NMR spectra of compound *XIII*.

Finally, alkylation of compound *Ie* using monochloroacetic acid in the presence of NaOAc—EtOH afforded the mercaptoacetic acid derivative *XVII*. The structure of *XVII* was also supported by the loss of one molecule of CO_2 on boiling with 10 % aqueous K_2CO_3 solution [9] to afford *S*-methyl derivative *XVIII* (Scheme 3).

Compound *XVII* showed characteristic IR absorption bands in the region of C=N, C=O, and OH functions. Its resonance signals in the ^{1}H NMR spectra are observed in the range of $\delta = 3.30$—3.40, 3.80—4.10, 4.20—4.40, 5.05—5.18, 5.77—5.99, 7.79, and 7.94 due to the methylene, piperazine, allyl, and hydroxy protons. The mass spectra of *XVII* showed the molecular ion peak at $m/z = 400$, and the peak of molecularly stabilized ions at m/z (I_r/%) = 98.9 (100) was also recorded and found to be in conformity with the assigned structure.

All the new compounds *II*—*XVIII* showed a fulgent effect in comparison with the parent piperazine derivatives *Ia*—*Ie* (Table 2). Compounds *II*, *IV*, *VII*,

Table 2. Diameter of Inhibition Zones (ø) as Criterion of Antimicrobial Acitivity of Some Synthesized Compounds at the Concentration of 3 mg cm^{-3} in DMF (Gentamycin at 0.2 mg cm^{-3} in Distilled Water)

Compound	*Escherichia coli*	*Serratia marcescens*	*Candida albicans*	*Staphylococcus aureus*	*Bacillus cereus*
			ø/nm		
Ia	–	13	–	–	–
Ib	–	15	–	–	
Ic	–	14	–		
Id	–	18	–	–	
Ie	–	13	–	–	–
II	–	22		25	
III	16	21		14	18
IV	19	24	–	18	19
V	16	20		15	16
VI	20	21		19	16
VII	23	20	–	14	20
VIII		–		19	
IX	14	23		16	15
X	18	23	–	14	13
XI	20	24		16	15
XII		21	–	24	
XIII	–	–	–	19	
XIV	13	21		13	16
XV	17	23		18	
XVI	20	18	–	20	16
XVII	–	22	–	22	–
Gentamycin	28	27	22	28	24

XI, and *XII* show a very promising activity of varying degrees on all the tested strains compared with Gentamycin drug.

On the other hand, compounds *V*, *VI*, *XI*, and *XVI* showed a moderate activity against most of the tested organisms. Only one compound, *VII*, revealed higher antimicrobial activity, almost equal to that of Gentamycin.

In order to understand the relationship between the structure and activity, we found that the replacement of the thiocarbamido and/or carbamido group by interesting heterocyclic systems as 2-thioxopyrimidinone and/or 2-iminotriazine as in *V*, *VI*, *XI*, and *XVI* had a marked effect on the spectrum of biological activity, while introduction of thiazolidin-4-one moiety at thiocarbamido group as in *VII* resulted in a much higher order in both tested strains and Gentamycin. Furthermore, substitution at 4- and/or 2,4-positions of the phenyl ring with chlorine atom as in *II*—*VII* gave compounds possessing mainly antifungal activity.

EXPERIMENTAL

Melting points were determined in open glass capillaries and are uncorrected. Microanalyses of C, H, N, S, and Cl were determined at the Microanalytical Unit, Faculty of Science, Cairo University. IR spectra in KBr were recorded on a Pye—Unicam SP 1200 spectrophotometer, ^{1}H NMR spectra were determined in DMSO-d_6 on Bruker WM 90 instrument using TMS as internal standard. Mass spectra were taken on Varian MAT 711 (70 eV, direct inlet recording).

All the synthesized compounds were screened for their antimicrobial activity in DMF at a concentration of 3 mg cm^{-3} followed by the method of diffusion techniques using Gentamycin as standard compound [10]. Strains used were *Escherichia coli, Serratia marcescens, Bacillus cereus, Staphylococcus aureus,* and *Candida albicans.*

Imino Derivatives *II*—*IV*

A suspension of compounds *Ia* or *Ic* (0.01 mol) in ethanol (50 cm^3) was treated with appropriate primary amines (0.02 mol) containing a few drops of glacial acetic acid, then it was refluxed for 2 h, cooled and poured onto ice. The solids thus obtained were filtered and crystallized from the proper solvent to give the imine derivatives *II*—*IV*, respectively (Table 1). IR spectrum of *III*, $\tilde{\nu}$/cm^{-1}: 700 (C—Cl), 780, 850, 910, 1000 (aryl, phenyl groups), 1180 (C—S), 1300 (NCSN), 1440, 1470 (deformation CH_2), 1590—1600 (C=N), 1610—1660 (b, C=N), 2700 (SH), 2900—2980 (b, CH_{aliph}), 3050 (H_{arom}), 3150 (NH), 3300—3550 (b, NH_2); *IV*: 700 (C—Cl), 780, 850—870, 920, 1000 (aryl, phenyl groups), 1190 (C—S), 1300 (NCSN), 1440, 1480 (deformation CH_2), 1590, 1600—1620, 1640—1670 (C=N), 2900—2990 (b, CH_{aliph}), 3060 (H_{arom}), 3150 (NH), 3400—3550 (b, NH_2). ^{1}H NMR spectrum of *IV*, δ: 3.20—3.80 (m, 2H, SH), 3.90—4.40 (m, 8H, CH_2—N piperazine), 7.44—7.49 (m, 3H, H_{arom}), 7.54—7.56 (m, 3H, H_{arom}), 12.00, 13.00 (each s, 2H, NH).

2,3-Dihydro-2-thioxo-1*H*,5*H*-pyrimidine-4,6-dione Derivatives *V* and *VI*

A mixture of *III* or *IV* (0.01 mol) and malonic acid (0.02 mol) in acetyl chloride (7 cm^3) was refluxed for 6 h on a steam bath. It was then poured onto crushed ice. The resultant solid was crystallized to give *V* or *VI* (Table 1). IR spectrum of *V*, $\tilde{\nu}/cm^{-1}$: 730 (C—Cl), 800, 880, 920, 1000 (aryl groups), 1170 (C—S), 1300 (NCSN), 1440, 1480 (deformation CH_2), 1590—1600 (C=N), 1650—1700 (C=O), 2900 (CH_{aliph}), 3020 (H_{arom}), 3300—3550 (b, OH ⇌ NH); *VI*: 700 (C—Cl), 750, 850, 900, 1000 (aryl groups), 1180 (C—S), 1300 (NCSN), 1420, 1470 (deformation CH_2), 1600, 1620 (C=N), 1660—1710 (C=O), 2900—2990 (CH_{aliph}), 3050 (H_{arom}), 3150 (NH), 3350—3550 (b, OH ⇌ NH). ^1H NMR spectrum of *VI*, δ: 3.40 (s, 2H, CH_2 of pyrimidine), 3.41 (s, 2H, CH_2 of pyrimidine), 3.41—3.90 (m, 8H, CH_2—N piperazine), 7.45, 7.49 (each m, 3H, H_{arom}), 7.52, 7.56 (each s, 1H, NH).

Thiazolidin-4-one *VII*

A mixture of *IV* (0.01 mol), monochloroacetic acid (0.025 mol), and fused sodium acetate (5 g) in absolute ethanol (100 cm^3) was refluxed for 4 h, cooled, then poured onto cold water. The solid thus obtained was filtered and recrystallized to give compound *VII* (Table 1). IR spectrum, $\tilde{\nu}/cm^{-1}$: 700—730 (C—Cl), 800, 850, 870, 920, 980 (phenyl groups), 1150—1180 (C—S), 1300 (NCSN), 1440—1470, 1500 (deformation CH_2), 1580 (C=N), 1610—1620 (C=N), 1690 (C=O), 2930, 2980 (CH_{aliph}), 3050 (H_{arom}), 3150 (NH), 3300—3550 (b, OH ⇌ NH). Mass spectrum, m/z (I_r/%; molecular formula): 659.9 (0.12; $C_{27}H_{20}N_8Cl_4S_2O_4$), 287 (1.01; $C_{10}H_6N_3Cl_2SO$), 172.8 (100; $C_7H_3NCl_2$), 129 (3.90; $C_3H_3N_3SO$), 114.95 (3.12; $C_3H_3N_2SO$), 84 (13.87; $C_4H_8N_2$).

N-Hydroxymethyl Derivative *VIII*

Equimolar amounts of *Id* (0.01 mol) and HCHO (0.02 mol) in methanol (100 cm^3) were refluxed for 4 h, cooled and poured onto ice. The product was crystallized to give *VIII* (Table 1). IR spectrum, $\tilde{\nu}/cm^{-1}$: 780, 880, 920 (phenyl groups), 1250 (NCON), 1440, 1480 (deformation CH_2), 1630—1650 (C=C), 1670—1690 (C=O), 2900, 2940 (CH_{aliph}), 3050 (H_{arom}), 3380 (OH). ^1H NMR spectrum, δ: 3.37—3.39 (s, 4H, CH_2—O), 3.45—3.65 (m, 8H, CH_2—N), 6.92—7.00 (m, 5H, H_{arom}), 7.20—7.35 (m, 5H, H_{arom}), 8.30, 8.59 (each s, 1H, OH). Mass spectrum, m/z (I_r/%; molecular formula): 384.65 (0.28; $C_{20}H_{24}N_4O_4$), 366 (2.0; $C_{20}H_{22}N_4O_3$), 224.95 (62.29; $C_8H_8N_4O_4$), 140 (30.09; $C_6H_8O_2$), 83.95 (4.59; $C_4H_8N_2$), 76.95 (100; C_6H_5).

N-Pivaloyl and *N*-*p*-Nitrobenzoyl Derivatives *IX* and *X*

A solution of *Id* (0.01 mol) in DMF (20 cm^3) was treated with pivaloyl or *p*-nitrobenzoyl chloride (each 0.02 mol). The reaction was refluxed for 15 min. Yellow needles which precipitated on cooling were collected by filtration and recrystallized to give *IX* or *X* (Table 1). IR spectrum of *IX*, $\tilde{\nu}/cm^{-1}$: 770, 900 (phenyl groups), 1250—1270 (NCON), 1430, 1470 (deformation CH_2), 1620 (C=C), 1650—1700, 1740 (C=O), 2900—3000 (CH_{aliph}), 3070 (H_{arom}); *X*: 800, 850, 880, 950 (phenyl groups), 1250 (NCON), 1440, 1480 (deformation CH_2), 1650—1680, 1700—1750 (C=O), 2900—2950 (CH_{aliph}), 3050 (H_{arom}).

1,3,5-Triazine Derivative *XI*

A mixture of *X* (0.01 mol) in sodium ethoxide (100 cm^3, 0.02 mol) and guanidine chloride (0.02 mol, in a least volume of H_2O) was stirred for 10 min, then refluxed for 4 h, cooled and poured onto ice. The separated solid was filtered, dried and crystallized to give *XI* (Table 1). IR spectrum, $\tilde{\nu}/cm^{-1}$: 720, 750, 1000 (aryl and phenyl groups), 1250 (NCN), 1350, 1530 $\nu_{as}(NO_2)$, $\nu_s(NO_2)$, 1430, 1460 (deformation CH_2), 1580 (C=N), 1620 (*endo* C=N), 1640 (*exo* C=N), 3350—3380 (b, NH).

Sulfonamide Derivative *XII*

A suspension of *Id* (0.01 mol) in DMF (20 cm^3) and benzenesulfonyl chloride (0.02 mol) was added and refluxed for 1 h, cooled and poured onto crushed ice. The solid thus obtained was filtered and crystallized to give *XII* (Table 1). IR spectrum, $\tilde{\nu}/cm^{-1}$: 750—780, 950, 1000 (phenyl groups), 1180 (C—S), 1280 (NCN), 1350 (SO_2), 1440, 1480 (deformation CH_2), 1600 (C=C), 1680—1700 (C=O), 2900—2950 (CH_{aliph}), 3050 (H_{arom}). ^1H NMR spectrum, δ: 3.00—3.20 (m, 4H, CH_2—N piperazine), 3.40—4.00 (m, 4H, CH_2—N piperazine), 7.29—7.39, 7.45—7.47, 7.49—7.55, 7.59—7.78 (each m, 5H, H_{arom}). Mass spectrum, m/z (I_r/%; molecular formula): 604 (0.01; $C_{30}H_{28}N_4S_2O_6$), 225 (45.28; $C_{12}H_{10}NSO_2$), 140.95 (27.60; $C_6H_5SO_2$), 84.0 (8.86; $C_4H_8N_2$), 76.90 (100; C_6H_5), 55.90 (21.30; 2CO).

N-Hydroxymethyl Derivative *XIII*

A mixture of *Ie* (0.01 mol) and HCHO (0.02 mol) in methanol (50 cm^3) was refluxed for 1 h. The excess of solvent was removed and the precipitate formed was crystallized to give *XIII* (Table 1). IR spectrum, $\tilde{\nu}/cm^{-1}$: 1180 (C—S), 1350 (NCSN), 1430, 1490 (deformation CH_2), 1570—1600 (C=C), 1660 (allyl groups), 2900, 2980 (CH_{aliph}), 3050 (H_{arom}), 3200—3400 (b, OH). ^1H NMR spectrum, δ: 2.30 (s, 4H,

CH_2—O), 3.40 (s, 4H, CH_2—N piperazine), 3.80, 4.20 (each s, 2H, CH_2—N piperazine), 5.00—5.20, 5.80—6.10 (each m, 5H, allyl protons), 7.80, 7.85 (each s, 1H, OH).

N-Pivaloyl and *N*-*p*-Nitrobenzoyl Derivatives *XIV* and *XV*

Compounds *XIV* and *XV* were prepared according to the above method for the preparation of *IX* and *X* (Table 1). IR spectrum of *XIV*, $\tilde{\nu}/cm^{-1}$: 1180 (C—S), 1220 (NCSN), 1350 (NCSN), 1430, 1480 (deformation CH_2), 1550—1570 (C=C), 1640 (C=C), 1700 (C=O), 2950 (CH_{aliph}); *XV*: 800, 850, 880, 930 (phenyl groups), 1180 (C—S), 1220 (NCSN), 1320 (NCSN), 1350, 1560 $\nu_{as}(NO_2)$, $\nu_s(NO_2)$, 1440, 1480 (deformation CH_2), 1630 (C=C), 1700—1750 (C=O), 2900 (CH_{aliph}), 3020 (H_{arom}).

1,3,5-Triazine Derivative *XVI*

Compound *XV* (0.01 mol) was dissolved in sodium ethoxide (100 cm^3, 0.02 mol) and added guanidine chloride (0.02 mol in small volume of H_2O), refluxed for 4 h, cooled and then poured onto ice. The solid thus obtained was filtered and crystallized to give *XVI* (Table 1). IR spectrum, $\tilde{\nu}/cm^{-1}$: 790, 820, 880, 940 (phenyl groups), 1300 (NCN), 1440, 1460 (deformation CH_2), 1350, 1520 $\nu_{as}(NO_2)$, $\nu_s(NO_2)$, 1570 (C=N), 1630 (*exo* C=N), 2850—3200 (b, CH_{aliph}, H_{arom}, NH).

Mercaptoacetic Acid Derivative *XVII*

Compound *XVII* was prepared according to the procedure described for *VII* (Table 1). IR spectrum, $\tilde{\nu}/cm^{-1}$: 1180 (C—S), 1220 (NCN), 1330 (NCSN), 1430, 1470 (deformation CH_2), 1530, 1590 (C=N), 1640, 1650 (C=C), 1710, 1720 (C=O), 2950—2970 (CH_{aliph}), 3290—3380 (OH). ^1H NMR spectrum, δ: 3.30—3.40 (s, 4H, CH_2COO), 3.80—4.10, 4.20—4.40 (each s, 4H, CH_2—N piperazine), 5.05—5.18, 5.77—5.99 (each m, 5H, allyl protons), 7.79, 7.94 (each s, 1H, OH). Mass spectrum, m/z (I_r/%; molecular formula): 400 (0.11; $C_{16}H_{24}N_4S_2O_4$), 184.95 (34.75; $C_{12}H_{20}N_4S_2O_4$), 170 (12.48; $C_7H_{11}N_2SO$), 128.9 (32.47; $C_6H_{11}N_2O$), 116.90 (87.33; $C_5H_{11}N_2O$), 114.9 (15.68; $C_5H_9N_2O$), 98.9 (100; $C_5H_{10}N_2$), 83.95 (9.25; $C_4H_8N_2$).

S-Methyl Derivative *XVIII*

A mixture of *XVII* (1 g) and aqueous potassium carbonate (0.05 g cm^{-3}) was refluxed for 1 h, then cooled. The solid thus produced was crystallized to give *XVIII* (Table 1).

REFERENCES

1. Tewari, S. S., Husain, M. I., and Srivasatva, G. C., *J. Indian Chem. Soc. 57*, 330 (1980).
2. Bahadur, S., Varma, R. S., and Saxena, M., *J. Indian Chem. Soc. 57*, 918 (1980).
3. Sengupta, A. K., Bajaj, O. P., and Agarwal, K. C., *J. Indian Chem. Soc. 57*, 1170 (1980).
4. Abuzar, S., Dubey, R., and Sharma, S., *Indian J. Chem., B 24*, 848 (1985).
5. Abdel-Rahman, R. M., *Farmaco 46*, 379 (1991).
6. Abdel-Rahman, R. M., *Farmaco 47*, 319 (1992).
7. Seada, M., Abdel-Rahman, R. M., and Abdel-Megid, M., *Indian J. Heterocycl. Chem. 3*, 9 (1993).
8. Abdel-Rahman, R. M., *Pak. J. Sci. Ind. Res. 30*, 490 (1987).
9. Abdel-Rahman, R. M., Seada, M., Fawzy, M., and El-Baz, *Farmaco 48*, 397 (1993).
10. Mackie, T. J. and Mac Cartheny, J. E., *Practical Medical Microbiology 2.* 30th Edition. Churchill Livingstone, Edinburgh, London, 1989.