Synthesis and Biological Evaluation of Some New Fused Heterobicyclic Derivatives Containing 1,2,4-Triazolo/1,2,4-Triazinopyridinone Moieties

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Syntheses of fused heterobicyclic systems containing 1,2,4-triazolo/1,2,4-triazinopyridinone moieties were accomplished by heterocyclization of 4-(4-chlorophenyl)-1,6-diamino-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (*III*) or 6-amino-4-(4-chlorophenyl)-2-oxo-1-(5,6-diphenyl-1,2,4-triazin-3-ylamino)-1,2-dihydropyridine-3,5-dicarbonitrile (*XII*) with α,β-bifunctional oxygen and halooxo compounds in different media in order to establish a relation between structure and their activities. Compounds *III* and *XII* which contain 1,2-biamino group are more favoured to the ring-closure reactions. Structure assignments of new products have been established on the basis of elemental analysis and spectral data. The antimicrobial activity of the products has been also evaluated where some compounds showed a better activity against selected tested microbes in comparison with control.

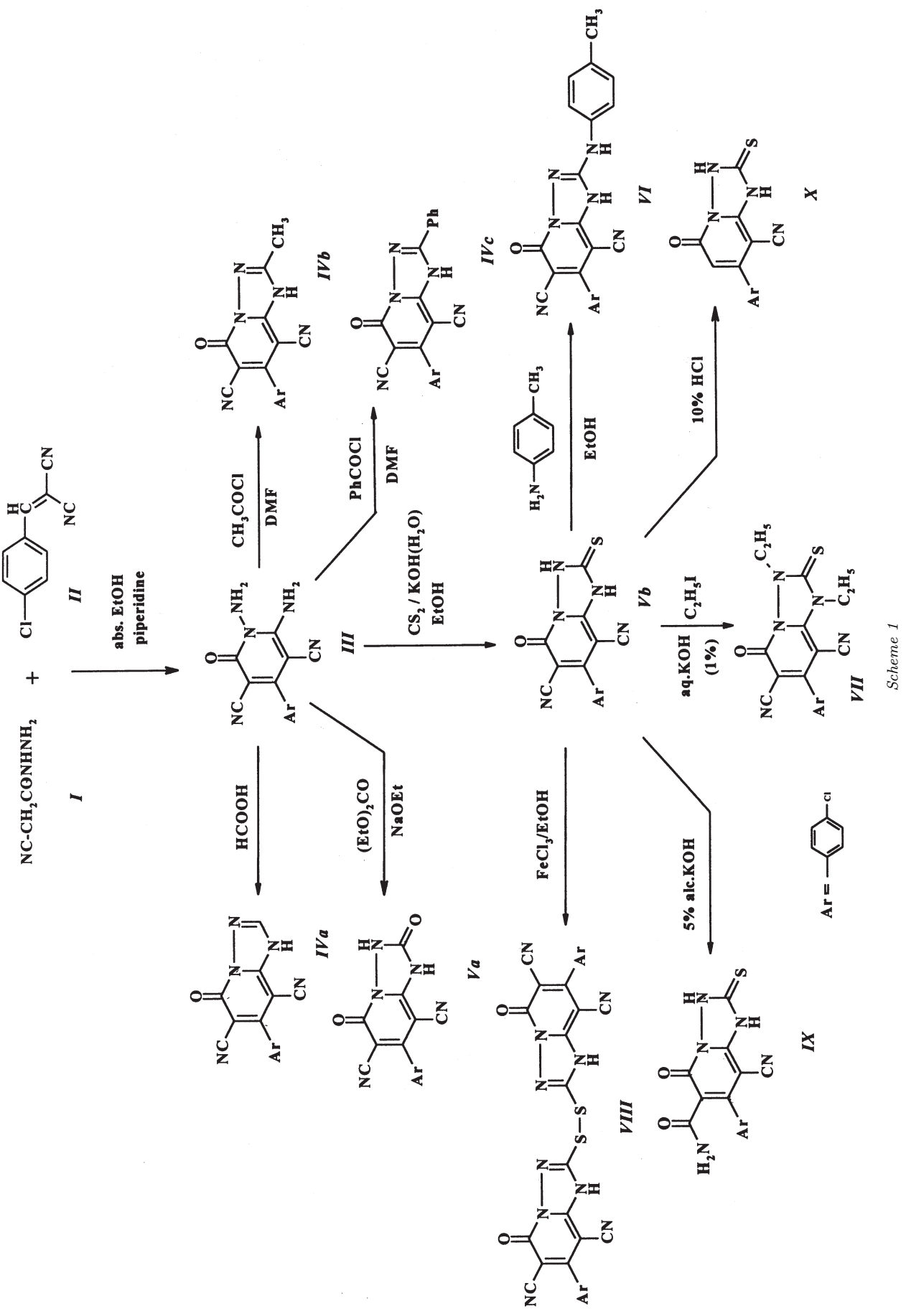
Diverse biological activities are encountered in fused heterocyclic systems containing the pyridine [1], triazole [2], and 1,2,4-triazine [3] moieties. In continuation of our interest in this field [4—7] it was thought worthwhile to incorporate 1,2,4-triazole/triazine to the pyridinone ring using 1,6-diaminopyridinone derivatives [8] as starting material for building of newly fused heterobicyclic systems which are likely to show enhanced biocidal effect.

The starting material 4-(4-chlorophenyl)-1,6-diamino-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (*III*) was obtained [8] from cyclocondensation of cyanoacetohydrazide *I* with *p*-chlorobenzilidenemalononitrile *II* in refluxing absolute ethanol—piperidine.

Treatment of compound *III* with formic acid resulted in the formation of 7-(4-chlorophenyl)-5-oxo-1*H*-4,5-dihydro[1,2,4]triazolo[2,3-*a*]pyridine-6,8-dicarbonitrile (*IVa*), while refluxing *III* with acetyl chloride and benzoyl chloride in DMF produced 7-(4-chlorophenyl)-5-oxo-1*H*-4,5-dihydro-2-(methyl/phenyl)[1,2,4]triazolo[2,3-*a*]pyridine-6,8-dicarbonitrile (*IVb, IVc*), respectively (Scheme 1, Table 1).

On the other hand, refluxing compound *III* with diethyl carbonate gave 7-(4-chlorophenyl)-2,5-dioxo-1*H*-2,3,4,5-tetrahydro[1,2,4]triazolo[2,3-*a*]pyridine-6,8-dicarbonitrile (*Va*), while refluxing of *III* with carbon disulfide in ethanolic KOH resulted [9] in the formation of 7-(4-chlorophenyl)-5-oxo-2-thioxo-1*H*-2,3,4,5-tetrahydro[1,2,4]triazolo[2,3-*a*]pyridine-6,8-dicarbonitrile (*Vb*) which on reaction with *p*-toluidine in boiling ethanol produced 7-(4-chlorophenyl)-5-oxo-2-[(*p*-methylphenyl)amino]-1*H*-4,5-dihydro[1,2,4]triazolo[2,3-*a*]pyridine-6,8-dicarbonitrile (*VI*). Formation of compound *Vb* from *III* may occur *via* a nucleophilic addition of NH_2 to electrophilic CS_2 followed by ring-closure reaction through the loss of one mole of H_2S. The structural assignment of the target compound *Vb* was deduced from spectral data. UV absorption spectra exhibited λ_{max} = 330.5 nm, in addition to 279.5 nm due to conjugated both the 3-thioxotriazole and pyridinone rings. ^{1}H NMR spectrum recorded the presence of both NH and SH protons at δ = 3.8 and 5.5 in addition to a and b H of aryl group at 7.54, 7.55 and 7.85, 8.00. Mass spectrum of *Vb* recorded the molecular ion peak (M + 2, 329, I_r = 21.4 %) with a base peak ion at m/z 270 due to 6-amino-4-(*p*-chlorophenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile moiety (Scheme 2).

The original plan of the present work was to synthesize some new 1,2,4-triazolo[2,3-*a*]pyridines. Thus, 7-(4-chlorophenyl)-5-oxo-1,3-diethyl-2-thioxo-1*H*-2,3,4,5-tetrahydro[1,2,4]triazolo[2,3-*a*]pyridine-6,8-dicarbonitrile (*VII*) was obtained from treatment of compound *Vb* with iodoethane in aqueous KOH, while oxidation of *Vb* by treatment with aqueous $FeCl_3$—EtOH [10] gives 7,7′-di(4-chlorophenyl)-5,5′-dioxo-1,1′,5,5′-tetrahydro-2,2′-dithiodi[1,2,4]triazolo[2,3-*a*]-pyridine-6,6′,8,8′-tetracarbonitrile (*VIII*). Midel hy-


NC-CH2CONHNH2
I
II
abs. EtOH
piperidine
III
CH3COCl
DMF
PhCOCl
DMF
CS2 / KOH(H2O)
EtOH
EtOH
10% HCl
aq.KOH
(1%)
C2H5I
HCOOH
(EtO)2CO
NaOEt
FeCl3/EtOH
5% alc.KOH
IVa
IVb
IVc
Va
Vb
VI
VII
VIII
IX
X
Ar =

Scheme 1

Table 1. Characterization of the Prepared Compounds

Compound	Formula*	M_r	Yield %	M.p. °C	Solvent
IVa	$C_{14}H_6N_5OCl$	295.5	60	270	MeOH
IVb	$C_{15}H_8N_5OCl$	309.5	62	275	AcOH
IVc	$C_{20}H_{10}N_5OCl$	371.5	65	260	MeOH
Va	$C_{14}H_6N_5O_2Cl$	311.5	70	265	MeOH
Vb	$C_{14}H_6N_5OClS$	327.5	58	245	EtOH
VI	$C_{21}H_{13}N_6OCl$	400.5	63	225	MeOH
VII	$C_{18}H_{14}N_5OClS$	383.5	69	270	MeOH
VIII	$C_{28}H_{10}N_{10}O_2Cl_2S_2$	653	78	283	MeOH
IX	$C_{14}H_8N_5O_2ClS$	345.5	66	230	EtOH
X	$C_{13}H_7N_4OClS$	302.5	54	210	MeOH
XI	$C_{15}H_{11}N_3S$	265	70	205	MeOH
XII	$C_{28}H_{17}N_8OCl$	516.5	80	238	EtOH
XIII	$C_{30}H_{17}N_8O_2Cl$	556.5	71	170	$(Et)_2O$
XIV	$C_{30}H_{17}N_8O_2Cl$	556.5	55	165	MeOH + MF
XV	$C_{30}H_{19}N_8OCl$	542.5	81	195	MeOH
XVI	$C_{36}H_{21}N_8OCl$	616.5	65	185	MeOH
XVII	$C_{30}H_{15}N_8O_3Cl$	570.5	70	248	$(Et)_2O$
XVIII	$C_{42}H_{25}N_8OCl$	692.5	73	125	MeOH + DMF
XX	$C_{38}H_{20}N_8O_2Cl_2$	691	79	204	EtOH
XXI	$C_{38}H_{22}N_8O_3Cl_2$	709	70	193	EtOH

*Values of the elemental analysis (C, H, N, Cl, and S) are within ± 0.5 % of the theoretical values.

drolysis of *Vb via* refluxing with 5 % alcoholic KOH produced 7-(4-chlorophenyl)-5-oxo-6-carbamoyl-2-thioxo-1*H*-2,3,4,5-tetrahydro[1,2,4]triazolo[2,3-*a*]pyridine-8-carbonitrile (*IX*), while acidic hydrolysis of *Vb* using diluted HCl gave 7-(4-chlorophenyl)-5-oxo-2-thioxo-1*H*-2,3,4,5-tetrahydro[1,2,4]triazolo[2,3-*a*]pyridine-8-carbonitrile (*X*).

The chemical reactivity of the cyano groups as compared with aryl and carbonyl groups in compound *III* was found to depend [11] mainly on the nature of the nucleophile, neighbouring group, basic or acidic medium and also on the reaction conditions. Thus, mechanistic considerations suggested that the cyano group between two powerful electron-withdrawing groups is more probably good-leaving group than other cyano groups.

Recently, fused heterobicyclic systems containing 1,2,4-triazine moiety have been synthesized [12—15] and showed pharmacological and biocidal activities. Thus, the starting material 6-amino-4-(4-chlorophenyl)-2-oxo-1-(5,6-diphenyl-1,2,4-triazin-3-yl-amino)-1,2-dihydropyridine-3,5-dicarbonitrile (*XII*) was obtained from refluxing compound *III* with 5,6-diphenyl-1,2,4-triazin-3-thiole (*XI*) [16] in boiling ethanol (Scheme 3). Heterocyclization of compound *XII* with monochloroacetic acid or chloroacetyl chloride in boiling DMF led to the direct formation of 8-(4-chlorophenyl)-4-(5,6-diphenyl-1,2,4-triazin-3-yl)-3,6-dioxo-1,2,3,4,5,6-hexahydropyrido[1,2-*b*][1,2,4]triazine-7,9-dicarbonitrile (*XIII*) and the isomeric structure *XIV,* respectively.

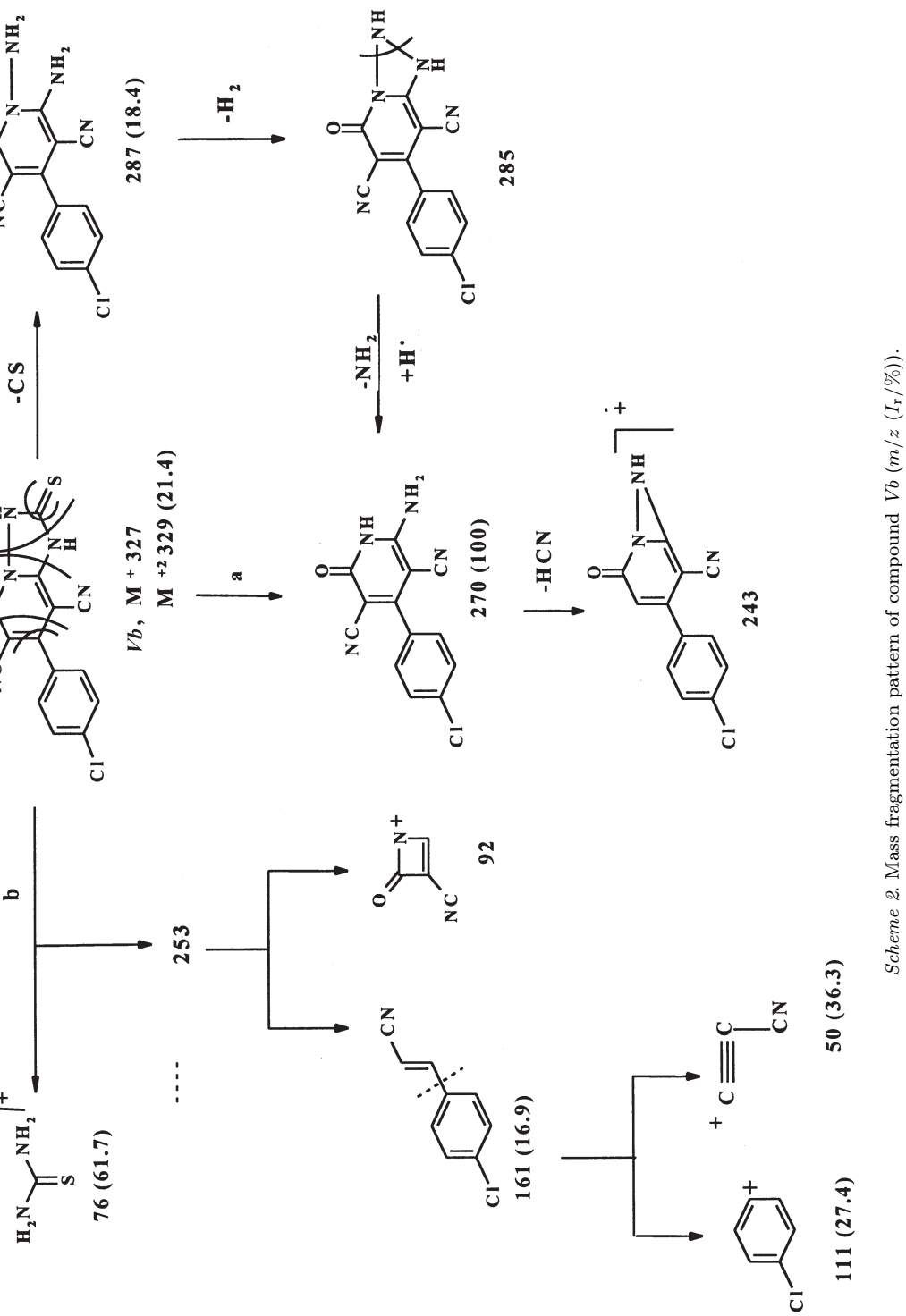
The structural assignments of compounds *XIII* and *XIV*, which may form tautomers, were based on spectral data. We can make a choice between a keto and enol form. The former structure of *XIV* was preferred from appearance of an intense $n \rightarrow \pi^*$ transition in UV spectra at λ_{max} = 311 nm in ethanol indicating the compound *XIV* to be heteroaromatic enol while that in *XIII* appeared at λ_{max} = 404 nm, which confirms that *XIII* is heterocyclic ketone. The low intensity of the absorption band at 311 nm is due to the fact that the attachment of groups containing lone electron pairs (NH) to carbonyl groups (C═O) has marked effect on the $n \rightarrow \pi^*$ transition [17]. ^{1}H NMR spectrum of *XIII* showed the disappearance of hydroxy proton at the positions 5 and 6. On the other hand, solubility of *XIV* and nonsolubility of *XIII* in aqueous NaOH give a good evidence of enolization of *XIV* and ketolization of *XIII* [17].

Alkylation of compound *XII* using 1,2-dibromoethane in ethanolic KOH gave 8-(4-chlorophenyl)-4-(5,6-diphenyl-1,2,4-triazin-3-yl)-6-oxo-1,2,3,4,5,6-hexahydropyrido[1,2-*b*][1,2,4]triazine-7,9-dicarbonitrile (*XV*).

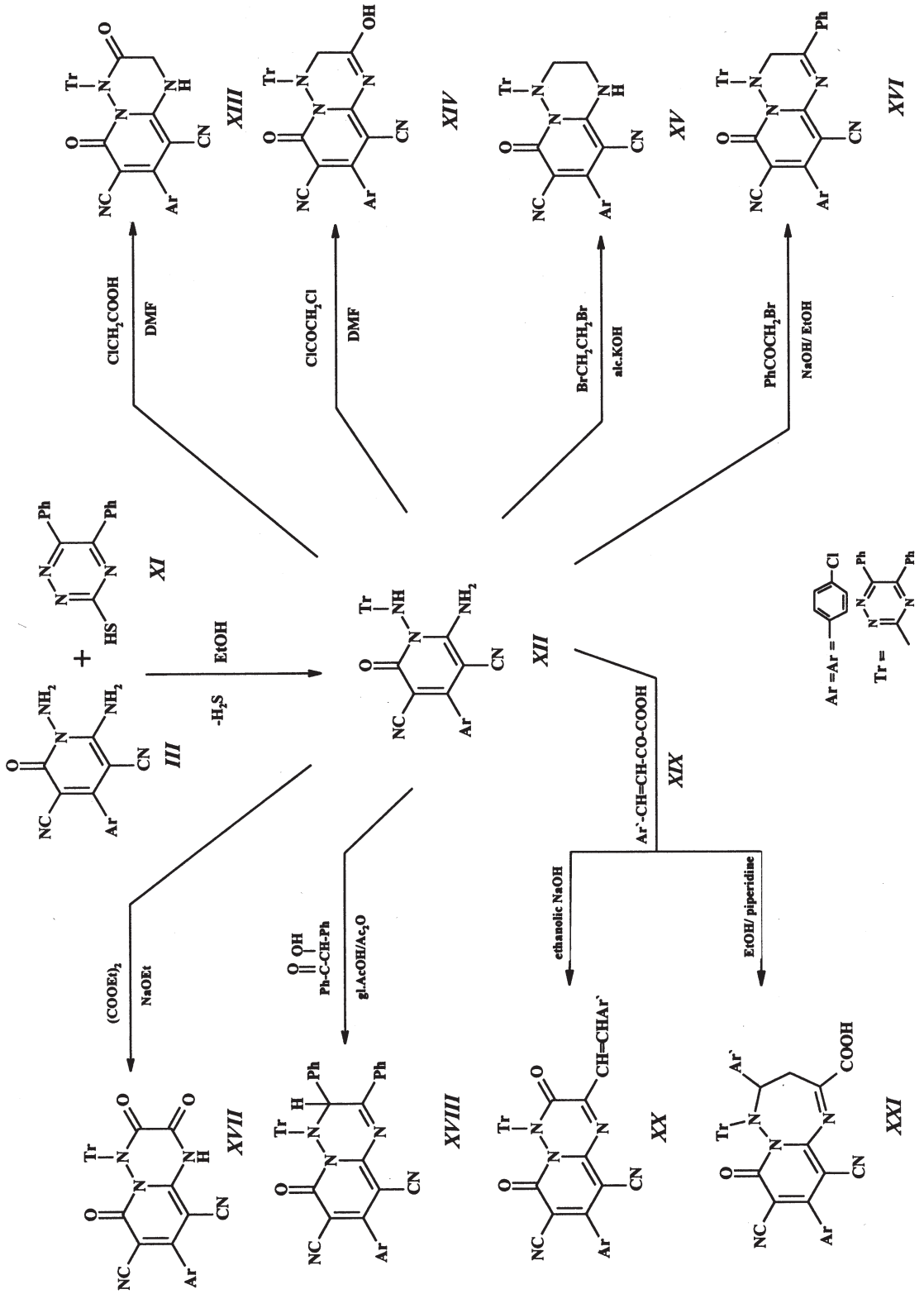
Similarly, compound *XII* when refluxed with 2-bromo-1-phenylethanone in ethanolic NaOH afforded 8-(4-chlorophenyl)-4-(5,6-diphenyl-1,2,4-triazin-3-yl)-6-oxo-2-phenyl-3,4,5,6-tetrahydropyrido[1,2-*b*][1,2,4]-triazine-7,9-dicarbonitrile (*XVI*).

The interaction between *XII* and diethyl oxalate in boiling sodium ethoxide furnished 8-(4-chlorophenyl)-4-(5,6-diphenyl-1,2,4-triazin-3-yl)-2,3,6-trioxo-1,2,3,4,5,6-hexahydropyrido[1,2-*b*][1,2,4]triazine-7,9-dicarbonitrile (*XVII*).

Also, condensation of *XII* with benzoin in glacial acetic acid with fused sodium acetate [18] furnished 8-



Scheme 2. Mass fragmentation pattern of compound *Vb* (m/z (I_r/%)).



Scheme 3

(4-chlorophenyl)-4-(5,6-diphenyl-1,2,4-triazin-3-yl)-6-oxo-2,3-diphenyl-3,4,5,6-tetrahydropyrido[1,2-*b*][1,2,4]-triazine-7,9-dicarbonitrile (*XVIII*).

The greater reactivity of ethylenic groups of *XIX* is presumably due to their favourable location between two carbonyl functions. Thus, treatment of *XII* with α,β-unsaturated oxo acid *XIX* in boiling ethanolic NaOH or ethanol with a few drops of piperidine [19] led to the direct formation of 8-(4-chlorophenyl)-4-(5,6-diphenyl-1,2,4-triazin-3-yl)-3,6-dioxo-2-(2-phenylvinyl)-3,4,5,6-tetrahydropyrido[1,2-*b*][1,2,4]triazine-7,9-dicarbonitrile (*XX*) and 4,9-di(4-chlorophenyl)-8,10-dicyano-7-oxo-5-(5,6-diphenyl-1,2,4-triazin-3-yl)-5*H*-3,4,6,7-tetrahydropyrido[1,2-*b*][1,2,4]triazepine-2-carboxylic acid (*XXI*), respectively.

Formation of compounds *XX* and *XXI* where a nucleophilic attack of NH_2 on carbonyl group of *XIX* was followed by the loss of one mole of H_2O from carboxylic group and/or a nucleophilic attack of NH_2 on arylidine moiety was followed by heterocyclization process.

Structures of the obtained compounds were deduced from both the elemental and spectral analyses.

Careful inspection of the mass spectra of some prepared compounds showed that in all the cases where triazole ring was fused with pyridine moiety, the dominant process was the fragmentation of the molecular ion into a highly delocalized 2-amino-3,5-dicarbonitrile-4-(*p*-chlorophenyl)pyridin-6(1*H*)-one radical ion at *m/z* 270 as base peak (Scheme 2). With compounds bearing 5,6-diphenyl-1,2,4-triazin-3-yl moiety (*XVI* and *XIX*) the splitting off two heterocyclic moieties *via* fragmentation giving a highly delocalized diphenylacetylene radical ion at *m/z* 178 as base peak (Scheme 4) [20] was recorded.

The bioactivity of pyridine [21], 1,2,4-triazole [22], and 1,2,4-triazine [23] derivatives is well established. In the present work the pyridine ring was combined with 1,2,4-triazole/triazine moieties, which may lead to the products of systems with altered/enhanced bioactivity.

The tested compounds (Table 2) showed variable degrees of inhibition in comparison with control, where compound *XIV* showed the highest antifungal activities against both of used fungi, followed by compounds *X* and *Vb*. This may be due to the presence of 5-hydroxy-1,2,4-triazino (*XIV*) or 3-thioxo-1,2,4-triazolo (*X*, *Vb*) moieties.

Compounds *VI, VIII*, and *XVIII* showed high antifungal activity against *Alternaria alternata* but not against *Aspergillus fumigatus*. This may be due to the presence of 3-aminotriazole moiety (*VI*), disulfide (*VIII*) and 5,6-diphenyl-1,2,4-triazino moiety (*XVIII*), while compound *IX* showed higher antifungal activity against *Aspergillus fumigatus* but not against *Alternaria alternata*. This may be due to the presence of carbamoyl and sulfanyl groups in *IX*.

Compounds *III* and *XII* exhibited moderate antifungal activities. On the other hand, most of all tested compounds showed high antibacterial activities against *Bacillus cereus*. This may be due mainly to the presence of 1,2,4-triazolo/triazino pyridine moieties. From the above observation, we concluded that biological activities of compounds *XIV, XIII*, and *IX* are more effective than that of the control used as special higher antimicrobial agents as well.

Table 2. Antimicrobial Activities of the Compounds* *III*—*XVIII*

Compound	*A. fumigatus*	*A. alternata*	*B. cereus*
III	7	8	22
Vb	8	17	15
VI	2	25	17
VIII	9	12	29
IX	20	8	15
X	11	24	0.0
XII	8	5	25
XIII	3	15	31
XIV	15	35	22
XVIII	2	12	19
DMF (control)	5	7	14

*Diameter of inhibition zones/mm. Values presented are subtraction of the control.

EXPERIMENTAL

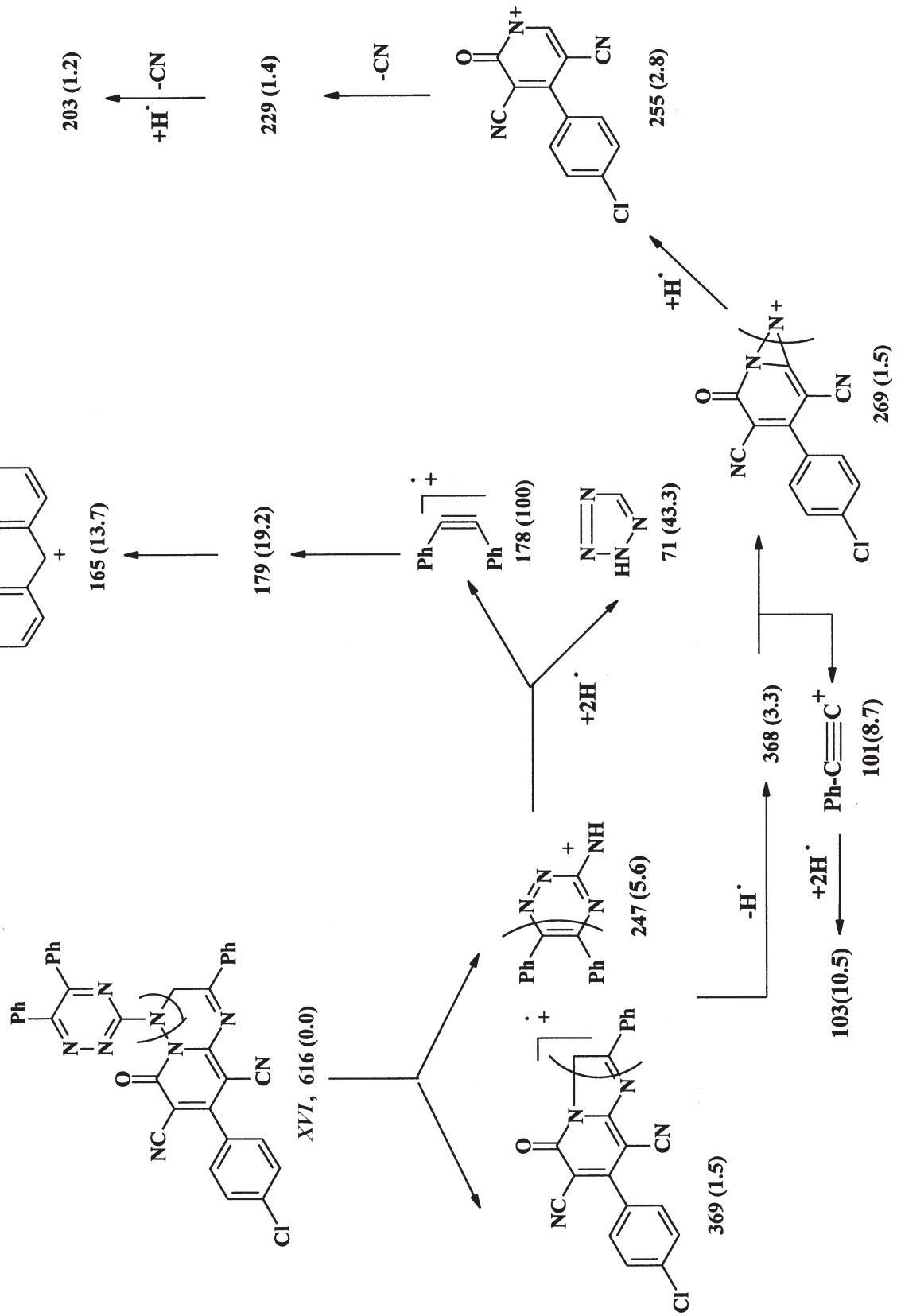
Melting points are uncorrected. UV spectra were recorded in pure DMF on a Perkin—Elmer, Lambda 4B controller Accessory Interface, UV VIS spectrophotometer (λ_{max}/nm (log ε)). IR spectra (KBr) were recorded on a Perkin—Elmer, 1430 ratio recording spectrophotometer ($\tilde{\nu}$/cm^{-1}). ^{1}H NMR spectra were taken on Bruker 200 MHz/52MM spectrometer using DMSO-d_6 as a solvent and TMS as an internal reference (δ). Mass spectra were taken on a Hewlett—Packard model MS 5988 spectrophotometer (70 eV). Compound *XI* was prepared according to the method reported earlier [16].

4-(4-Chlorophenyl)-1,6-diamino-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (*III*)

A mixture of *I* (0.01 mol) and *II* (0.01mol) in absolute EtOH (15 cm^3) and piperidine (2 drops) was refluxed for 3 h. The solid thus formed was collected by filtration and crystallized from an appropriate solvent. UV: 330 (2.27), 275.5 (2.60). IR: 3452, 3398 (2NH_2), 2259, 2218 (2CN), 1674 (C═O), 1624 (def. NH_2), 1597 (C═N), 831, 768 (phenyl group), 768 (C—Cl).

7-(4-Chlorophenyl)-5-oxo-1*H*-4,5-dihydro-[1,2,4]triazolo[2,3-*a*]pyridine-6,8-dicarbonitrile (*IVa*)

A mixture of *III* (0.01 mol) and formic acid (0.01 mol) in absolute EtOH (5 cm^3) was heated under re-



Scheme 4. Mass fragmentation pattern of compound *XVI* (m/z (I_r/%)).

flux for 4 h, cooled and poured onto ice. The solid obtained was filtered off and recrystallized. IR: 3224 (NH), 2218 (CN), 1774 (C═O), 1597 (C═N), 768 (aryl group), 721 (C—Cl).

7-(4-Chlorophenyl)-5-oxo-1*H*-4,5-dihydro-2-(methyl/phenyl)[1,2,4]triazolo[2,3-*a*]pyridine-6,8-dicarbonitrile (*IVb*, *IVc*)

A mixture of *III* (0.01 mol) and acetyl chloride or benzoyl chloride (0.01 mol) in DMF (10 cm^3) was heated under reflux for 8 h, cooled and poured onto ice. The solid obtained was filtered off and recrystallized. *IVb*, *m*/*z* (I_r/%): 337.3 (89.8), 229 (16.5), 169 (27.7), 125 (68.1), 91 (26.3), 63 (24.6), 59.3 (21.4), 58 (100), 50 (25.3). ^{1}H NMR: 2.02 (s, 3H, CH_3), 3.5 (s, 1H, NH), 7.3—8.2 (s, 4H, aryl protons). *IVc*, UV: 430 (2.8), 410 (3.75), 329.5 (3.20), 276.5 (3.35). IR: 3209 (NH), 2214 (CN), 1740 (C═O), 1625, 1554 (C═C), 802, 769 (phenyl and aryl groups), 711 (C—Cl).

7-(4-Chlorophenyl)-2,5-dioxo-1*H*-2,3,4,5-tetrahydro[1,2,4]triazolo[2,3-*a*]pyridine-6,8-dicarbonitrile (*Va*)

A mixture of *III* (0.01 mol) and diethyl carbonate (0.01 mol) in sodium ethoxide (20 cm^3, 0.02 mol Na in 100 cm^3 of absolute EtOH) was refluxed for 4 h, cooled and poured onto ice—HCl. The solid obtained was filtered off and recrystallized. IR: 3250—3426 (b, OH, NH), 2220 (CN), 1750, 1659 (2C═O), 801, 766 (aryl group), 642.8 (C—Cl).

7-(4-Chlorophenyl)-5-oxo-2-thioxo-1*H*-2,3,4,5-tetrahydro[1,2,4]triazolo[2,3-*a*]pyridine-6,8-dicarbonitrile (*Vb*)

A mixture of *III* (0.01 mol) and carbon disulfide (0.01 mol) in ethanolic KOH (10 %, 20 cm^3) was refluxed for 6 h, cooled and poured onto ice—HCl. The solid obtained was filtered off and crystallized. UV: 330.5 (1.66), 279.5 (4.12). IR: 3318, 3200 (NH, NH), 2216 (CN), 1639.5 (C═O), 1591 (C═N), 1237 (C═S), 829, 770 (aryl group), 721 (C—Cl). ^{1}H NMR: 3.8 (s, 1H, NH), 5.5 (s, 1H, SH), 7.54, 7.55, 7.55, 8.0 (each s, 4H, aryl protons). *m*/*z* (I_r/%): 329 (21.4), 287 (18.4), 270 (100), 243 (38.3), 207 (25.4), 180 (32.8), 137 (32.3), 102 (33.8), 76 (61.7), 51 (38.8).

7-(4-Chlorophenyl)-5-oxo-2-[(*p*-methylphenyl)-amino]-1*H*-4,5-dihydro[1,2,4]triazolo[2,3-*a*]pyridine-6,8-dicarbonitrile (*VI*)

A mixture of *Vb* (0.01 mol) and *p*-toluidine (0.01 mol) in EtOH (20 cm^3) was refluxed for 6 h, cooled and poured onto ice—HCl. The solid obtained was filtered off and crystallized. IR: 3313 (NH), 3206 (NH), 3095 (CH_{aryl}), 2945 (CH_{aliph}), 2213 (CN), 1666.5 (C═O), 1637 (C═C), 1580 (C═N), 829, 769 (C═C), 726 (C—Cl). *m*/*z* (I_r/%): 329 (8.6), 286 (4.5), 272 (38.8), 270 (100), 243 (24.5), 214 (11.8), 207 (22.9), 190 (42.9), 178 (11), 138 (53.5), 100 (39.6), 76 (51.4), 64 (20.8), 50 (35.5).

7-(4-Chlorophenyl)-5-oxo-1,3-diethyl-2-thioxo-1*H*-2,3,4,5-tetrahydro[1,2,4]triazolo-[2,3-*a*]pyridine-6,8-dicarbonitrile (*VII*)

A mixture of *Vb* (0.01 mol) and iodoethane (0.01 mol) in aqueous KOH (1 %, 100 cm^3) was stirred for 1 h at room temperature. The solid separated was washed with dilute acetic acid, then recrystallized. ^{1}H NMR: 1.284—1.381 (m, 6H, $2CH_3$), 3.10, 3.18, 3.6, 3.8 (s, 4H, $2CH_2$), 7.4—8.1 (m, 4H, aryl protons). *m*/*z* (I_r/%): 285 (17.9), 272 (39.4), 270 (100), 243 (19.5), 232 (23.1), 207 (14.3), 180 (23.9), 165 (19.5), 153 (14.7), 125 (17.1), 100 (15.9), 75 (22.7), 63 (15), 50 (24).

7,7′-Di(4-chlorophenyl)-5,5′-dioxo-1,1′,5,5′-tetrahydro-2,2′-dithiodi[1,2,4]triazolo[2,3-*a*]-pyridine-6,6′,8,8′-tetracarbonitrile (*VIII*)

A mixture of *Vb* (0.01 mol) and $FeCl_3$ (0.01 mol) in EtOH (20 cm^3) was refluxed for 4 h, cooled and poured onto ice. The solid obtained was filtered off and crystallized. UV: 4.32 (1.76), 410 (2.20), 337.5 (2.04), 268.5 (2.8). IR: 3324, 3209 (NH, NH), 2218 (CN), 1655, 1640 (2C═O), 1592 (C═N), 1092 (S—S), 772 (CH_{aryl}), 725 (C—Cl).

7-(4-Chlorophenyl)-5-oxo-6-carbamoyl-2-thioxo-1*H*-2,3,4,5-tetrahydro[1,2,4]triazolo[2,3-*a*]pyridine-8-carbonitrile (*IX*)

A mixture of *Vb* (0.01 mol) and ethanolic KOH (5 %, 20 cm^3) was refluxed for 6 h, cooled and poured onto acetic acid—ice. The solid obtained was filtered off and crystallized. IR: 3385 (NH_2), 3208 (NH), 2217 (CN), 1685, 1641 (C═O), 1592 (C═N), 1176 (C—S), 830, 775 (CH_{aryl}), 727 (C—Cl).

7-(4-Chlorophenyl)-5-oxo-2-thioxo-1*H*-2,3,4,5-tetrahydro[1,2,4]triazolo[2,3-*a*]pyridine-8-carbonitrile (*X*)

A mixture of *Vb* (0.01 mol) and HCl (10 %, 20 cm^3) was refluxed for 4 h, cooled and poured onto ice. The solid obtained was filtered off, washed with aqueous Na_2CO_3 (5 %) and crystallized. IR: 3321, 3183 (NH, NH), 2215 (CN), 1630 (C═O), 1599 (C═N), 833, 770 (CH_{aryl}), 718 (C—Cl).

6-Amino-4-(4-chlorophenyl)-2-oxo-1-(5,6-diphenyl-1,2,4-triazin-3-ylamino)-1,2-dihydropyridine-3,5-dicarbonitrile (*XII*)

A mixture of *III* (0.01 mol) and *XI* (0.01 mol) in EtOH (20 cm^3) was refluxed for 4 h, cooled and collected by filtration and then crystallized. UV: 320.4 (2.41), 286 (2.93). IR: 3452 (NH_2), 3122 (NH), 3057 (CH_{aryl}), 2215 (CN), 1626 (C═O), 1594 (C═N), 881, 802, 762 (aryl groups), 695.7 (C—Cl). ^{1}H NMR: 3.28 (s, 2H, NH_2), 5.8 (s, 1H, NH_{Tr}), 7.37—7.67 (m, 10H, 2Ph), 8.14, 8.43, 8.45 (m, 4H, aryl protons). m/z (I_r/%): 285 (100), 270 (25), 243 (12), 214 (15.5), 178 (18), 161 (15), 138 (12), 111 (10), 75 (25), 50 (28).

8-(4-Chlorophenyl)-4-(5,6-diphenyl-1,2,4-triazin-3-yl)-3,6-dioxo-1,2,3,4,5,6-hexahydropyrido[1,2-*b*][1,2,4]triazine-7,9-dicarbonitrile (*XIII*)

A mixture of *XII* (0.01 mol) and monochloroacetic acid (0.01 mol) in DMF (10 cm^3) was refluxed for 4 h, cooled and poured onto ice. The solid obtained was filtered off and crystallized. UV: 446 (3.4), 404 (2.97), 281 (2.01). IR: 3320 (OH), 3191 (NH), 2928 (CH_{aliph}), 2214 (CN), 1657 (C═O), 1628 (C═O), 1559 (C═N), 1491, 1442 (def. CH_2), 831, 802, 771 (aryl groups), 698 (C—Cl). ^{1}H NMR: 2.5—2.7 (m, 2H, CH_2), 3.8—3.9 (s, 1H, NH), 7.3—7.96 (m, 10H, aromatic protons), 8.0—8.25 (m, 4H, aryl protons).

8-(4-Chlorophenyl)-4-(5,6-diphenyl-1,2,4-triazin-3-yl)-2,6-dioxo-1,2,3,4,5,6-hexahydropyrido[1,2-*b*][1,2,4]triazine-7,9-dicarbonitrile (*XIV*)

A mixture of *XII* (0.01 mol) and chloroacetyl chloride (0.01 mol) in DMF (10 cm^3) was refluxed for 4 h, cooled and poured onto ice. The solid obtained was filtered off and crystallized. UV: 434.5 (0.75), 311 (0.98), 279 (1.03).

8-(4-Chlorophenyl)-4-(5,6-diphenyl-1,2,4-triazin-3-yl)-6-oxo-1,2,3,4,5,6-hexahydropyrido[1,2-*b*][1,2,4]triazine-7,9-dicarbonitrile (*XV*)

A mixture of *XII* (0.01 mol) and 1,2-dibromoethane (0.01 mol) in ethanolic KOH (5 %, 20 cm^3) was refluxed for 6 h, cooled and poured onto ice—HCl. The solid obtained was filtered off and crystallized. IR: 3176 (NH), 3010 (CH_{aryl}), 2979, 2901 (CH_{aliph}), 2211 (CN), 1640 (C═O), 1596 (C═N), 1498, 1443 (def. CH_2), 829, 767 (aryl groups), 696 (C—Cl). ^{1}H NMR: 2.77—2.89 (m, 2H, CH_2), 3.2—3.4 (m, 2H, CH_2), 5.8 (s, 1H, NH), 7.28—7.67 (m, 10H, phenyl protons), 8.24—8.62 (m, 4H, aryl protons).

8-(4-Chlorophenyl)-4-(5,6-diphenyl-1,2,4-triazin-3-yl)-6-oxo-2-phenyl-3,4,5,6-tetrahydropyrido[1,2-*b*][1,2,4]triazine-7,9-dicarbonitrile (*XVI*)

A mixture of *XII* (0.01 mol) and 2-bromo-1-phenylethanone (0.01 mol) in ethanolic NaOH (10 %, 20 cm^3) was refluxed for 4 h, cooled and poured onto ice—HCl. The solid was filtered off and crystallized. IR: 3015 (CH_{aryl}), 2946 (CH_{aliph}), 2215 (CN), 1634 (C═O), 1598 (C═N), 1490, 1440 (def. CH_2), 831, 763 (aryl groups), 696 (C—Cl). m/z (I_r/%): 369 (1.5), 368 (3.3), 283 (2), 266 (2.1), 190 (3.5), 178 (99.3), 165 (13.7), 152 (15.4), 123 (12.5), 105 (25.1), 96 (30), 83 (55.3), 76 (29), 67 (40.8), 57 (93), 55 (100).

8-(4-Chlorophenyl)-4-(5,6-diphenyl-1,2,4-triazin-3-yl)-2,3,6-trioxo-1,2,3,4,5,6-hexahydropyrido[1,2-*b*][1,2,4]triazine-7,9-dicarbonitrile (*XVII*)

A mixture of *XII* (0.01 mol) and diethyl oxalate (0.01 mol) in sodium ethoxide (20 cm^3, 0.02 mol Na in 100 cm^3 of absolute EtOH) was refluxed for 4 h, cooled and poured onto ice—HCl. The solid obtained was filtered off and crystallized. IR: 3306 (NH), 2216 (CN), 1640—1750 (b, 3C═O), 1594 (C═N), 831, 775 (phenyl groups), 696 (C—Cl). m/z (I_r/%): 287 (11.5), 270 (100), 243 (25), 207 (18), 180 (22.8), 165 (4.3), 152 (3.3), 138 (13), 111 (10), 90 (6.3), 77 (4.1), 63 (9.5), 50 (16.8).

8-(4-Chlorophenyl)-4-(5,6-diphenyl-1,2,4-triazin-3-yl)-6-oxo-2,3-diphenyl-3,4,5,6-tetrahydropyrido[1,2-*b*][1,2,4]triazine-7,9-dicarbonitrile (*XVIII*)

A mixture of *XII* (0.01 mol) and benzoin (0.01 mol) in glacial acetic acid (20 cm^3), fused sodium acetate (1 g), and acetic anhydride (two drops) was refluxed for 4 h, cooled and poured onto ice. The solid obtained was filtered off and crystallized. UV: 430.5 (2.8), 410 (3.75), 329.5 (3.2), 276.5 (3.35). IR: 3063 (CH_{aryl}), 2214 (CN), 166 (C═O), 1591 (C═N), 841, 795, 762, 719 (aryl and phenyl groups), 691 (C—Cl).

8-(4-Chlorophenyl)-4-(5,6-diphenyl-1,2,4-triazin-3-yl)-3,6-dioxo-2-(2-phenylvinyl)-3,4,5,6-tetrahydropyrido[1,2-*b*][1,2,4]triazine-7,9-dicarbonitrile (*XX*)

A mixture of *XII* (0.01 mol) and α,β-unsaturated oxo acid *XIX* (0.01 mol) (prepared from condensation of pyruvic acid and 4-chlorobenzaldehyde in alkaline medium) in ethanolic NaOH (5 %, 20 cm^3) was refluxed for 4 h, cooled, and poured onto ice and dilute acetic acid. The solid obtained was filtered off and crystallized. UV: 322 (1.38), 282 (1.94). IR: 3010 (CH_{aryl}), 2926 (CH_{aliph}), 2214 (CN), 1639—1750 (b, 2C═O, CH═CH), 1594 (C═N), 1494, 1441 (def. CH), 877, 817, 767, 725 (aryl groups), 697 (C—Cl). ^{1}H NMR: 6.26—6.34 (s, 2H, CH═CH), 7.27—7.64 (m, 10H, phenyl protons), 7.67, 7.68, 8.23, 8.31 (s, 4H,

aryl protons). m/z (I_r/%): 285 (8), 283 (20.2), 265 (2.7), 190 (4.1), 178 (100), 165 (14), 152 (13), 138 (8), 115 (5.8), 104 (14), 89 (22.9), 76 (35.5), 63 (15.9), 51 (22.7), 50 (16.5).

4,9-Di(4-chlorophenyl)-8,10-dicyano-7-oxo-5-(5,6-diphenyl-1,2,4-triazin-3-yl)-5*H*-3,4,6,7-tetrahydropyrido[1,2-*b*][1,2,4]triazepine-2-carboxylic acid (*XXI*)

A mixture of *XII* (0.01 mol) and α,β-unsaturated oxo acid *XIX* (0.01 mol) in EtOH (50 cm^3) and piperidine (1 cm^3) was refluxed for 10 h, cooled and poured onto ice. The solid obtained was filtered off and recrystallized. UV: 453.5 (3.41), 393 (3.06), 287.5 (2.99). IR: 3422 (OH), 3062 (CH_{aryl}), 2936, 2859 (CH_{aliph}), 2213 (CN), 1622—1750 (b, 2C=O), 1489, 1448 (def. CH_2), 832, 766 (aryl groups), 698 (C—Cl). ^{1}H NMR: 3.02—3.2 (m, 2H, CH_2), 4.3 (s, 1H, CH), 6.84—7.6 (m, 10H, phenyls), 7.78—8.23 (m, 4H, aryl protons), 9.65—9.73 (s, 1H, OH).

Biological Evaluation

The screening of antibacterial and antifungal activities for the investigated compounds was performed using the disc diffusion method [24, 25] as follows: Filter paper discs (2.5 mm in diameter) were impregnated with 100 ppm of each compound dissolved in DMF, which was used as a control, then individual discs were placed aseptically on the surface of nutrient agar medium seeded with *Bacillus cereus* and incubated at 37 °C for 48 h in the case of antibacterial tests and on the surface of Waksman's agar medium seeded with *Aspergillus fumigatus* and *Alternaria alternata* and then incubated at 30 °C for seven days in the case of antifungal tests. The diameter of inhibition zone in each case was measured and results are presented in Table 2.

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