SYNTHESIS AND ANTIMICROBIAL ACTIVITIES OF CONDENSED AND UNCONDENSED 1,2,4-TRIAZINES

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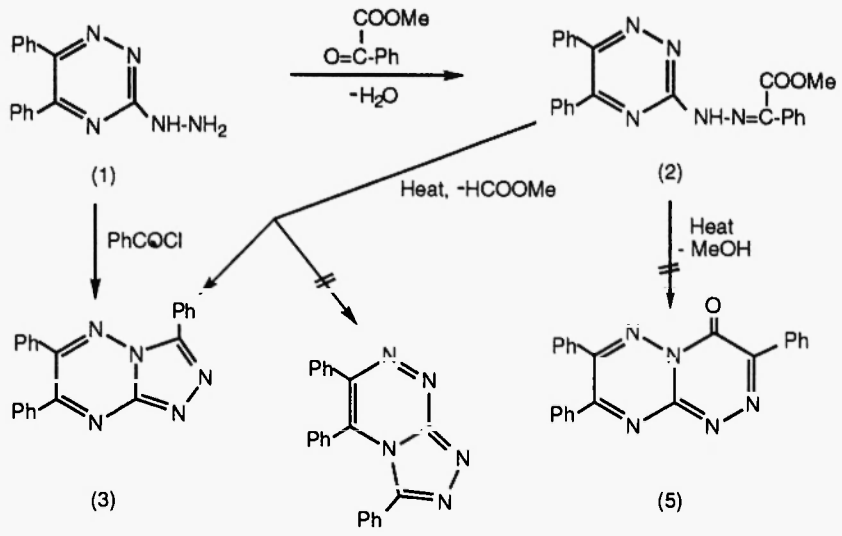
Abstract: Reaction of 3-hydrazino-5,6-diphenyl-1,2,4-triazine **1** with methyl phenylglyoxylate gave 3,6,7-triphenyl-1,2,4-triazolo[4,3-*b*]1,2,4-triazine **3**. Cyclocondensation with pyruvic acid, ethyl pyruvate or diethyl oxalate afforded the corresponding 3-substituted-4-oxo-7,8-diphenyl-1,2,4-triazino[4,3-*b*]1,2,4-triazines **8a,b**. Several 3-(pyrazol-1-yl)-5,6-diphenyl-1,2,4-triazines **10a-c** were prepared by reaction with 1,3-dicarbonyl compounds or acetylenic esters. The hydrazone intermediates of some of these reactions were isolated and characterized. Compounds **2**, **6a,b**, **7**, **9a,b**, and **10a,c** showed no antibacterial activity against *Escherichia coli* and weak to moderate inhibitory activity against *Bacillus subtilis* and *Staphylococcus aureus*. Only compound **6a** which showed weak antifungal activity against *Candida albicans*.

Introduction :

Pertinent to academic interests (1) as well as biological activities (1-4) and applications (1), the synthesis of a large number of compounds belonging to the various types of condensed 1,2,4-triazolo-1,2,4-triazine systems has been reported (2,3,5). Of the fourteen theoretically possible condensed 1,2,4-triazino-1,2,4-triazine systems, we are aware of the synthesis of a relatively few derivatives belonging to only five of these systems namely: 1,2,4-triazino[1,2-*a*] (6), [2,1-*a*] (6), [4,3-*b*] (7-11), [3,4-*c*] (12), and [6,5-*e*] 1,2,4-triazines (13,14). Some 3-(pyrazol-l-yl)-1,2,4-triazine derivatives have also been synthesized (15,16) and found to possess antimicrobial activity (15). As a part of our studies on the utilization of cyclic amidrazones as heterocyclic synthones (17-22), we report in the present investigation on the utilization of 3-hydrazino-5,6-diphenyl-1,2,4-triazine (23) **1** in the synthesis of 3,6,7-triphenyl-1,2,4-triazolo[4,3-*b*]1,2,4-triazine, 3-substituted-4-oxo-7,8-diphenyl-1,2,4-triazino[4,3-*b*]1,2,4-triazines and 3-(pyrazol-1-yl)-5,6-diphenyl-1,2,4-triazines.

Results and Discussion :

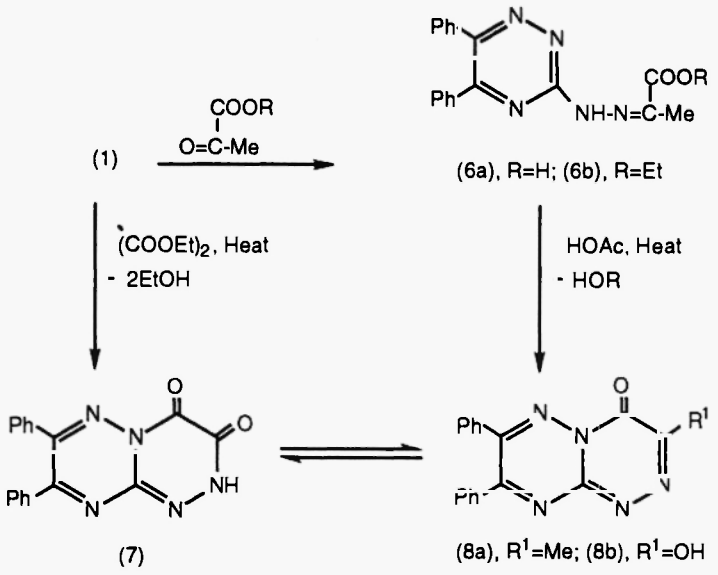
Condensation of **1** with methyl phenylglyoxylate at ambient temperature afforded the corresponding hydrazone **2** (Scheme I) which showed NH, ester-carbonyl and C=N absorptions. In addition to the 15 aromatic proton signals of three phenyl groups, the ^{1}H NMR of **2** showed NH (exchangeable) and methyl proton signals. We have previously reported (18,19) the cyclization of methyl phenylglyoxylate 2-pyridyl- (18), 2-quinolyl- (18), 2-benzothiazolyl- (18), and 4-substituted-1-phthalazinylhydrazones (19) to the corresponding 1,2,4-triazino-heterocycles. Thermal cyclization of **2**, however, gave a single product that showed only C=N, lacked IR amide absorptions, and correctly analyzed for the molecular formula $C_{22}H_{15}N_5$.



Scheme I

These data are incompatible with the expected 3,7,8-triphenyl-1,2,4-triazino[4,3-*b*]1,2,4-triazin-4-one **5** and conform only with either of the isomeric 3,6,7-triphenyl-1,2,4-triazolo[4,3-*b*]1,2,4-triazine **3** or 3,5,6-triphenyl-1,2,4-triazolo[3,4-*c*]1,2,4-triazine **4** structures. Cyclocondensation reactions of 3-hydrazino-1,2,4-triazines with one-carbon inserting reagents may involve N-2 or N-4 of the 1,2,4-triazine ring to give 1,2,4-triazolo[4,3-*b*] (24-28) or [3,4-*c*]1,2,4-triazines (29) respectively. The former mode of cyclization is much more facile due to enhanced nucleophilicity of N-2 as compared to N-4 (29,30). Electronic (31,32) or steric (7) factors, however, may direct the cyclization to take place with N-4. Considering these factors with respect to hydrazone **2**, it can be concluded that: (a) it is devoid of steric factors affecting either N-2 or N-4 and (b) the electron-donating effect of the two phenyl groups is expected to equally affect N-2 and N-4 of the 1,2,4-triazine nucleus; the net result will be the retenion of the enhanced nucleophilicity of N-2. Accordingly, cyclization should take place with N-2 and the product is assigned the 3,5,6-triphenyl-1,2,4-triazolo[4,3-*b*]1,2,4-triazine structure **3**. This conclusion was corroborated by preparing **3** by cyclocondensation of **1** with benzoyl chloride. 1,2,4-Triazolo[3,4-*c*]1,2,4-triazines, such as **4** are known (25,29,31) to undergo facile thermal-, acid- or base-catalyzed Dimroth rearrangement to the thermodynamically more stable 1,2,4-triazolo[5,1-*c*]1,2,4-triazines. 1,2,4-Triazolo[4,3-*b*]1,2,4-triazines, such as **3** are incapable of undergoing this rearrangement. Attempted rearrangement of the obtained 1,2,4-triazolo-1,2,4-triazine by heating with acetic acid or with piperidine, afforded the unchanged starting material; an additional proof for the assigned structure **3**.

Condensation of **1** with pyruvic acid at room temperature gave the corresponding hydrazone **6a** (Scheme II) which showed OH, NH, COOH and C=N IR absorptions. Similarly, ethyl pyruvate reacted with **1** to give the corresponding hydrazone **6b** which showed the triplet-quartet pattern of ^{1}H NMR signals of ethyl groups.



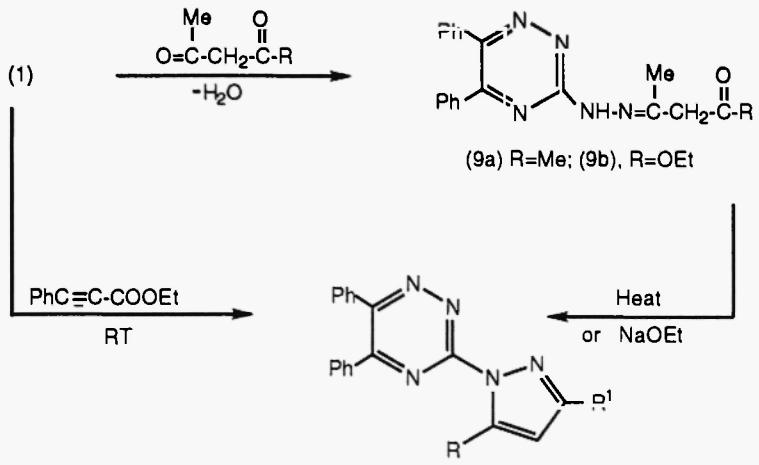
Scheme II

Heating hydrazone **6a** or **6b** with acetic acid gave one and the same product which showed CON and C=N IR absorptions, lacked ^{1}H NMR signals of ethyl group, and analyzed for the molecular formula $C_{18}H_{13}N_5O$. These data are compatible with the 3-methyl-4-oxo-7,8-diphenyl-1,2,4-triazino[4,3-*b*]1,2,4-triazine structure **8a**.

Condensative cyclization of **1** with an equimolar amount of diethyl oxalate gave a product devoid of triplet-quartet pattern of ^{1}H NMR signals characteristic of ethyl groups, showed NH, OH and C=N absorptions and analyzed for $C_{17}H_{11}N_5O_2$. The product was assigned, therefore, the 3,4-dioxo-7,8-diphenyl-1,2,4-triazino[4,3-*b*]1,2,4-triazine structure **7** which probably exists in equilibrium with the-3-hydroxy-4-oxo-7,8-diphenyl-1,2,4-triazine tautomer **8b**.

Reaction of 3-hydrazino-5,6-diphenyl-1,2,4-triazine **1** with acetylacetone at 100 °C afforded the corresponding hydrazone **9a** (Scheme III) that showed IR absorptions characteristic of NH, C=O and C=N. ^{1}H NMR of **9a** showed, in addition to the expected aromatic protons, signals of one NH (exchangeable), two methylene, and two methyl groups. Heating **9a** at 200 °C gave the expected 3-(3,5-dimethylpyrazol-1-yl)-5,6-diphenyl-1,2,4-triazine **10a** which revealed only C=N absorption and lacked NH and C=O absorptions characteristic of the parent hydrazone. Compound **10a** was also prepared in one-step by heating **1** with acetylacetone in boiling methanol for 20 h.

Cyclic amidrazones generally react with ethyl acetoacetate to afford pyrazolyl heterocyclic derivatives (18) or condensed 1,2,4-triazolo-heterocycles (19,20). Heating amidrazone **1** with ethyl acetoacetate for 20 h gave 3-(5-hydroxy-3-methylpyrazol-1-yl)-5,6-diphenyl-1,2,4-triazine **10b**. Carrying out the latter reaction at room temperature gave the hydrazone intermediate **9b** which underwent base-catalyzed cyclization upon heating with sodium ethoxide in ethanol to give **10b**.



(10a), R=R^1=Me; (10b), R=Me, R^1=OH; (10c), R=Ph, R^1=OH

Scheme III

Reaction of **1** with ethyl phenylpropiolate at room temperature gave a product which showed OH and C=N absorptions in the IR region. ^{1}H NMR spectrum of the product revealed pyrazolyl CH and OH proton signals and lacked signals characteristic of ethyl groups. This excluded the possible hydrazone intermediate and the product was assigned, therefore, the 3-(5-hydroxy-3-phenylpyrazol-1-yl)-5,6-diphenyl-1,2,4-triazine structure **10c**.

Compounds **2, 6a,b, 7, 9a,b** and **10a,c** were evaluated for their antibactrial activity *in vitro* against the Gram negative bacterium *E. coli* and the two Gram positive bacteria *B. subtilis* and *S. aureus* as well as for antifungal activity against *C. albicans* using the agar diffusion method (33) (Table I). None of the tested compounds exhibited activity against *E. coli.* However, compounds **6a,b,** and **10a** were found active against *B. subtilis*. Compounds **2, 6a,b,** and **10a,c** were also active against *S. aureus.* Only compound **6a** showed antifungal activity against *C. albicans*.

Table (I) Results of Antimicrobial Activity

Compd No	Inhibition zones in mm.			
	E.coli	*B.subtilis*	*S. aureus*	*C. albicans*
2	-	-	10.0	-
6a	-	13.0	18.5	11.0
6b	-	12.5	11.5	-
7	-	-	-	-
9a	-	-	-	-
9b	-	-	-	-
10a	-	13.0	11.5	-
10c	-	-	12.0	-

Experimental :

Melting points were obtained on a Mel-Temp II melting point apparatus in open capillaries and are uncorrected. The IR spectra (KBr) were recorded on a Unicam SP-1100 spectrophotometer and ^{1}H NMR [$(CD_3)_2SO$ or $CDCl_3$] on a Varian EM-390 spectrometer. Homogeneity of compounds and follow up of reactions were checked by TLC on silica gel G precoated plates (E. Merck, layer thickness 0.25 mm), used without pretreatment. The spots were detected by I_2 vapour. Elemental microanalyses were performed at the Microanalyses Unit, Cairo University, Cairo, Egypt.

Methyl phenylglyoxylate (5,6-diphenyl-1,2,4-triazin-3-yl)hydrazone 2 :

A solution of 1 (4 mmol) in methanol (20 ml) was added to methyl phenylglyoxylate (4 mmol) and the mixture was kept at room temperature for 24 h. The separated product was filtered and crystallized from chloroform. m.p. 165 °C; yield: 55%. TLC in 19 : 1 chloroform-methanol, R_f = 0.74. (Found : C, 70.6; H, 4.8; N, 16.9. $C_{24}H_{19}N_5O_2$ requires C, 70.4; H, 4.7; N, 17.1%). IR: 3090 (NH), 1710 (ester-carbonyl) and 1575 cm^{-1} (C=N). ^{1}H NMR ($CDCl_3$): δ (ppm) 12.40 (s, 1H, exchangeable, NH), 7.67-7.10 (m, 15 H, aromatic H) and 3.77 (d, 3H, CH_3).

3,6,7-Triphenyl-1,2,4-triazolo[4,3-*b*]1,2,4-triazine 3 :

Method (A): Compound 2 (4 mmol) was heated at 175 °C for 15 min. in an oil bath. After attaining ambient temperature, the melt was triturated with ethyl acetate, filtered and crystallized from methanol. m.p. 270 °C; yield: 50%. TLC in 19 : 1 chloroform-methanol, R_f = 0.41. (Found: C, 75.4; H, 4.2; N, 20.3. $C_{22}H_{15}N_5$ requires C, 75.6; H, 4.3 N, 20.0%). IR: 1565 cm^{-1} (C=N). ^{1}H NMR ($CDCl_3$): δ (ppm) 8.64 - 8.38 (m, 2 H, aromatic H) and 7.69-7.30 (m, 13 H, aromatic H).

Attempted isomerization of compound 3 by heating with acetic acid or piperidine for 6 h. gave unchanged 3.

Method (B): A mixture of 1 (4 mmol) and benzoyl chloride (1 ml) was heated at 100 °C for 8 h. Ice water (50 ml) was added to the reaction mixture and then extracted with chloroform (3 x 15 ml). The chloroform extract was washed with 10% aqueous sodium hydrogencarbonate solution and water, dried and evaporated. The obtained residue was crystallized from methanol to give 3, m.p. 270 °C [ref. (15), m.p. 246 °C]; yield: 38%.

Pyruvic acid (5,6-diphenyl-1,2,4-triazin-3-yl)hydrazone 6a :

The title compound was prepared from 1 (4 mmol) and pyruvic acid (4 mmol) as described for the preparation of 2. It crystallized from methanol. m.p. 150 °C; yield: 55%. TLC in 1 : 1 chloroform-methanol, R_f = 0.53. (Found: C, 64.9; H, 4.6; N, 20.8. $C_{18}H_{15}N_5O_2$ requires C, 64.9; H, 4.5; N, 21.0%). IR: 3600 (OH), 3230 (NH), 1740 (COO) and 1640 cm^{-1} (C=N). ^{1}H NMR [$(CD_3)_2SO$]: δ (ppm) 11.17 (s, 1H, exchangeable, NH), 7.60-7.10 (m, 10 H, aromatic H) and 2.20 (s, 3H, CH_3). The

OH proton was associated with the solvent absorption and appeared as a broad signal at δ 3.48.

Ethyl pyruvate (5,6-diphenyl-1,2,4-triazin-3-yl)hydrazone 6b :

The title compound was prepared from 1 (4 mmol) and ethyl pyruvate (4 mmol) as described for the preparation of 2. It crystallized from chloroform. m.p. 190-192 °C; yield: 40%. TLC in 29 : 1 chloroform-methanol, R_f = 0.76. (Found: C, 66.4; H, 5.3; N, 19.6. $C_{20}H_{19}N_5O_2$ requires C, 66.5; H, 5.3; N, 19.4%). IR: 3230 (NH), 1710 (ester carbonyl) and 1600 cm^{-1} (C=N). ^{1}H NMR ($CDCl_3$): δ (ppm) 8.93 (s, 1H, exchangeable, NH), 7.73-7.17 (m, 10 H, aromatic H), 4.10 (q, 2H, CH_2CH_3), 2.60 (s, 3H, CH_3) and 1.37 (t, 3H, CH_2CH_3).

3-Methyl-4-oxo-7,8-diphenyl-1,2,4-triazno[4,3-*b*]1,2,4-triazine 8a :

A mixture of 6a or 6b (3 mmol) and acetic acid (10 ml) was heated at reflux for 1 h. Acetic acid was evaporated under reduced pressure and the obtained residue was crystallized from chloroform. m.p. 145 °C; yield: 64% and 56% respectively. TLC in 1 : 1 chloroform-methanol, R_f = 0.72. (Found: C, 68, 6; H, 4.4; N, 22.5. $C_{18}H_{13}N_5O$ requires C, 68, 6; H, 4.1; N, 22.2%). IR: 1720 (CON) and 1630 cm^{-1} (C=N). ^{1}H NMR [$(CD_3)_2SO$]: δ (ppm) 7.67-7.17 (m, 10 H, aromatic H) and 2.27 (s, 3H, CH_3).

3,4-Dioxo-7,8-diphenyl-1,2,4-triazno[4,3-*b*]1,2,4-triazine 7 :

A mixture of 1 (4 mmol) and diethyl oxalate (4 mmol) was heated at 100 °C for 10 h. and then allowed to attain room temperature The product was crystallized from chloroform-methanol. m.p. 315 °C; yield: 33%. TLC in 9 : 1 chloroform-methanol, R_f = 0.51. (Found: C, 64, 6; H, 3.5; N, 22.3. $C_{17}H_{11}N_5O_2$ requires C, 64.4; H, 3.5; N, 22.1%). IR : 3260 (NH) and 1725 (CON), 1565 cm^{-1} (C=N). ^{1}H NMR [$(CD_3)_2SO$]: δ (ppm) 10.51(s,1H, exchangeable, NH) and 7.67-7.07 (m, 10 H, aromatic H).

Acetylacetone (5,6-diphenyl-1,2,4-triazin-3-yl)hydrazone 9a :

A mixture of 1 (4 mmol) and acetylacetone (4 mmol) was heated at 100 °C for 1 h. and then allowed to attain room temperature. The product was triturated with ethyl acetate, filtered and crystallized from methanol. m.p. 189 °C; yield: 47%. TLC in 9 : 1 chloroform-methanol, R_f = 0.62. (Found: C, 69.7, H, 5.3; N, 20.1. $C_{20}H_{19}N_5O$ requires C, 69.6; H, 5.5; N, 20.3%). IR : 3000 (NH), 1625 (C=O) and 1590 cm^{-1} (C=N). ^{1}H NMR ($CDCl_3$): δ (ppm) 13.02 (s, 1H, exchangeable, NH), 7.80-7.16 (m, 10H, aromatic H), 5.06 (s, 2H, CH_2), 2.36 and 2.00 (2s, 3H each, $2CH_3$).

3-(3,5-Dimethylpyrazol-l-yl)-5,6-diphenyl-1,2,4-triazine 10a :

Method (A): Compound 9a (3 mmol) was heated at 200 °C for 30 min. and then allowed to attain room temperature. The product was crystallized from methanol. m.p. 120 °C [(ref. (15), m.p. 134 °C];

yield: 53%. TLC in 19 : 1 chloroform-methanol, R_f = 0.70. (Found: C, 73.6; H, 5.3; N, 21.6. $C_{20}H_{17}N_5$ requires C, 73.4; H, 5.2; N, 21.4%). IR : 1585 cm^{-1} (C=N). ^1H NMR ($CDCl_3$): δ (ppm) 7.67-7.13 (m, 10 H, aromatic H), 6.03 (s, 1H, pyrazole CH), 2.70 and 2.33 (2s, 3H each, $2CH_3$).

Method (B): A solution of **1** (4 mmol) in methanol (20 ml) was added to acetylacetone (4 mmol) and the mixture was heated at 100 °C and allowed to attain room temperature. The product which separated was filtered, washed and crystallized from methanol to give **10a** ; yield: 68% .

Ethyl acetoacetate (5,6-diphenyl-1,2,4-triazin-3-yl)hydrazone 9b :

The title compound was prepared from **1** (4 mmol) and ethyl acetoacetate (4 mmol) as described for the preparation of **2**. It crystallized from methanol. m.p. 115 °C; yield: 36%. TLC in 9 : 1 chloroform-methanol, R_f = 0.51. (Found: C, 67.5; H, 5.4; N, 18.4. $C_{21}H_{21}N_5O_2$ requires C, 67.2; H, 5.6; N, 18.7%). IR : 3310 (NH), 1735 (ester-carbonyl) and 1620 cm^{-1} (C=N). ^1H NMR ($CDCl_3$): δ (ppm) 12.50 (s, 1H, exchangeable, NH), 7.60-7.05 (m, 10 H, aromatic H), 4.15 (q, 2H. CH_2CH_3), 3.45 (s, 2H, CH_2), 2.10 (s, 3H, CH_3) and 1.25 (t, 3H, CH_2CH_3).

3-(5-Hydroxy-3-methylpyrazol-1-yl)-5,6-diphenyl-1,2,4-triazine 10b :

Method (A): A mixture of **1** (4 mmol) and ethyl acetoacetate (4 mmol) was heated at 100 °C for 1 h. The product that separated after attaining room temperature was triturated with ethyl acetate, filtered and crystallized from methanol. m.p. 225 °C; yield: 53%. TLC in 9 : 1 chloroform-methanol, R_f = 0.72. (Found: C, 69.6; H, 4.3; N, 21.5. $C_{19}H_{15}N_5O$ requires C, 69.3; H, 4.6; N, 21.3%). IR : 3330 (OH), 1610 cm^{-1} (C=N). ^1H NMR [$(CD_3)_2SO$] : δ(ppm) 10.12 (s,1H, exchangeable, OH), 7.70-7.00 (m, 10H, aromatic H), 5.62 (s, 1H, pyrazole CH) and 2.25 (s, 3H, CH_3).

Method (B): A solution of **9b** (3 mmol) in freshly prepared ethanolic sodium ethoxide solution (10 ml, 0.1 M) was heated at reflux for 6 h. The reaction mixture was neutralized with acetic acid and the product which separated, was filtered, washed with water and crystallized from methanol to give **10b**: yield: 50%.

3-(5-Hydroxy-3-phenylpyrazol-l-yl)-5,6-diphenyl-1,2,4-triazine 10c :

The title compound was prepared from **1** (4 mmole) and ethyl phenylpropiolate (4 mmol) as described for the prepation of **2**. It crystallized from methanol. m.p. 182 °C, yield: 50%. TLC in 29 : 1 chloroform-methanol, R_f = 0.6. (Found: C, 69.6; H, 4.3; N, 21.5. $C_{19}H_{15}N_5O$ requires C, 69.3; H, 4.6; N, 21.3%). IR : 3240 (OH) and 1615 cm^{-1} (C=N). ^1H NMR [$(CD_3)_2SO$] : δ (ppm) 11.11 (s, 1H, exchangeable, OH) 7.80-7.00 (m, 15H, aromatic H) and 5.70 (s, 1H, pyrazole CH).

Antimicrobial Screening :

Sterile nutrient agar (100 ml) was separately inoculated with a 24 h. broth culture (1 ml) of *E. coli, B. subtilis, S. aureus,* or *C. albicans.* Solutions (30 µl) of the tested compounds (2 mg) in DMF (1 ml)

were placed in wells (6 mm diameter) cut in the agar media and the plates were incubated at 37 °C in the case of bacteria and 25 °C in the case of yeast. The diameter of the resulting inhibition zones obtained were measured after 28 h. for bacteria and 96 h. for yeast (Table I).

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