SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF CONDENSED AND UNCONDENSED QUINOXALINES

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Abstract : Cyclocondensation of 2-chloro-3-substituted quinoxalines **4** with semicarbazide or phenylacetylhydrazine gave the corresponding 1,2,4-triazolo[4,3-*a*]quinoxalines **5** and **6** . Reaction of **4** with sodium azide afforded tetrazolo[1,5-*a*]quinoxalines **7**. Heating of 2-hydrazino-3-substituted quinoxalines **9** with diethyl oxalate or acetic anhydride gave the corresponding 3-substituted-1,2,4-triazolo[4,3-*a*]quinoxalines **12** and **13** respectively. The 2-pyrazolylquinoxaline derivatives **14** were also obtained when **9** was heated with acetylacetone. 3-Benzyl-4-oxo-11-substituted-1,2,4-triazino[4,3-*a*]quinoxalines **16** were obtained upon cyclization of hydrazones **15** with phosphoryl chloride. The prepared compounds were evaluated for antibacterial and antifungal activity.

Introduction

It has been reported that 1,2,4-triazolo[4,3-*a*]quinoxaline were found to possess antiallergic (1), antiviral (2,3), anxiolytic (4), inhibition of passive cutaneous anaphylaxis (5) and selective adenosine antagonist (6-11) activities. Tetrazolo[1,5-*a*]quinoxalines were also showed fungicidal (12) activities. In the course of our investigations towards the synthesis of different heterocyclic derivatives from α-keto acids (13-15), we have carried out the preparation of the title compounds.

Results and Discussion

Heating of equimolar amounts of *o*-phenylenediamine **1** with pyruvic acid derivatives, namely: phenylpyruvic acid **2a** or benzylpyruvic acid **2b** gave the corresponding 3-substituted quinoxalin-2-ones **3**, which underwent chlorination with phosphoryl chloride to give the 2-chloroquinoxaline derivatives **4**.

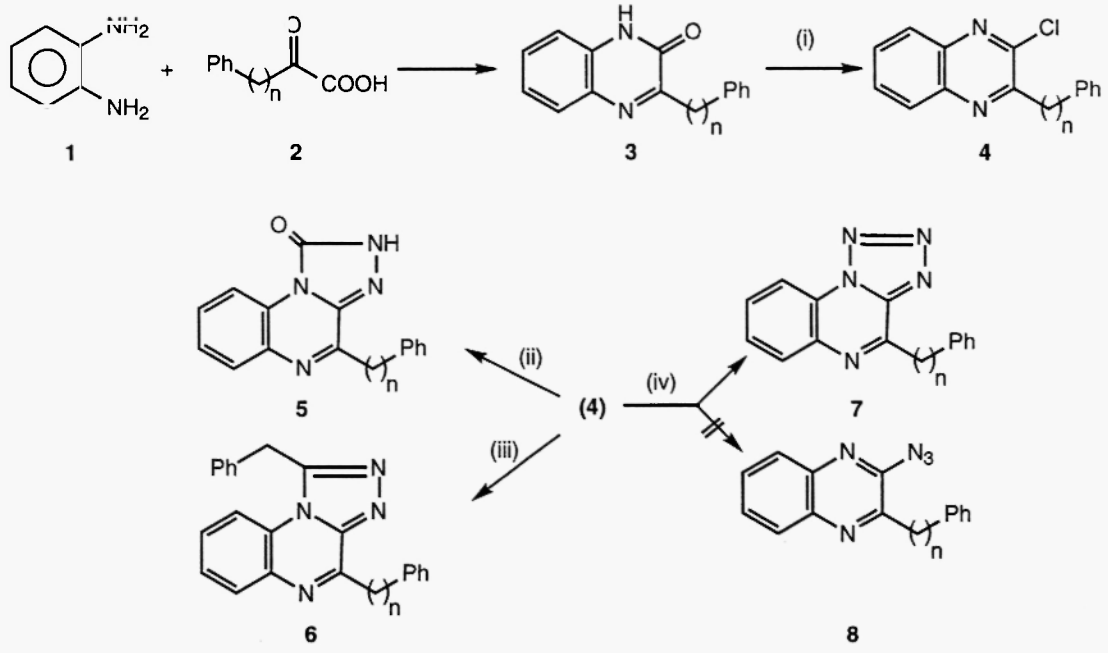
Heating of **4a** or **4b** with semicarbazide hydrochloride in the presence of hydrochloric acid gave products showed C=N, CON and NH IR absorptions. The products were assigned the structure of 3-oxo-10-substituted-1,2,4-triazolo[4,3-*a*]quinoxalines **5a** and **5b**. Reaction of **4a** or **4b** with phenylacetylhydrazine gave the 3-benzyl-10-substituted-1,2,4-triazolo[4,3-*a*] quinoxalines **6a** and **6b** respectively, their MS showed the molecular ion peak at *m/z* 350 and 364 respectively.

Heating of **4a** or **4b** with sodium azide in the presence of DMF at 100°C gave 4-substituted tetrazolo[1,5-*a*]quinoxalines **7a** and **7b**. The alternative acyclic 2-azidoquinoxaline structure **8** was excluded because of the absence of the characteristic azido group around 2200 cm^{-1} (16) Scheme (1) .

Substitution of the chloro atom of **4a** or **4b** with hydrazine moiety resulted in the hydrazino derivatives **9a** and **9b**.

Heating of **9a** or **9b** with diethyl oxalate gave a single product in each case which showed ester carbonyl and C=N absorptions at 1720, 1617 cm^{-1} and 1720, 1615 cm^{-1} respectively. These spectral data together with the elemental analyses ruled out the probability

of the hydrazide **10** or the 3,4-dioxo-1,2,4-triazino[4,3-*a*]quinoxaline structures **11**, and therefore the assigned structures 3-carboethoxy-10-substituted-1,2,4-triazolo[4,3-*a*]quinoxalines **12a** and **12b**. (Scheme 2). The mass spectra of **12a** and **12b** showed the $M^{+\bullet}$ peak at *m/z* 332 and 346 respectively.



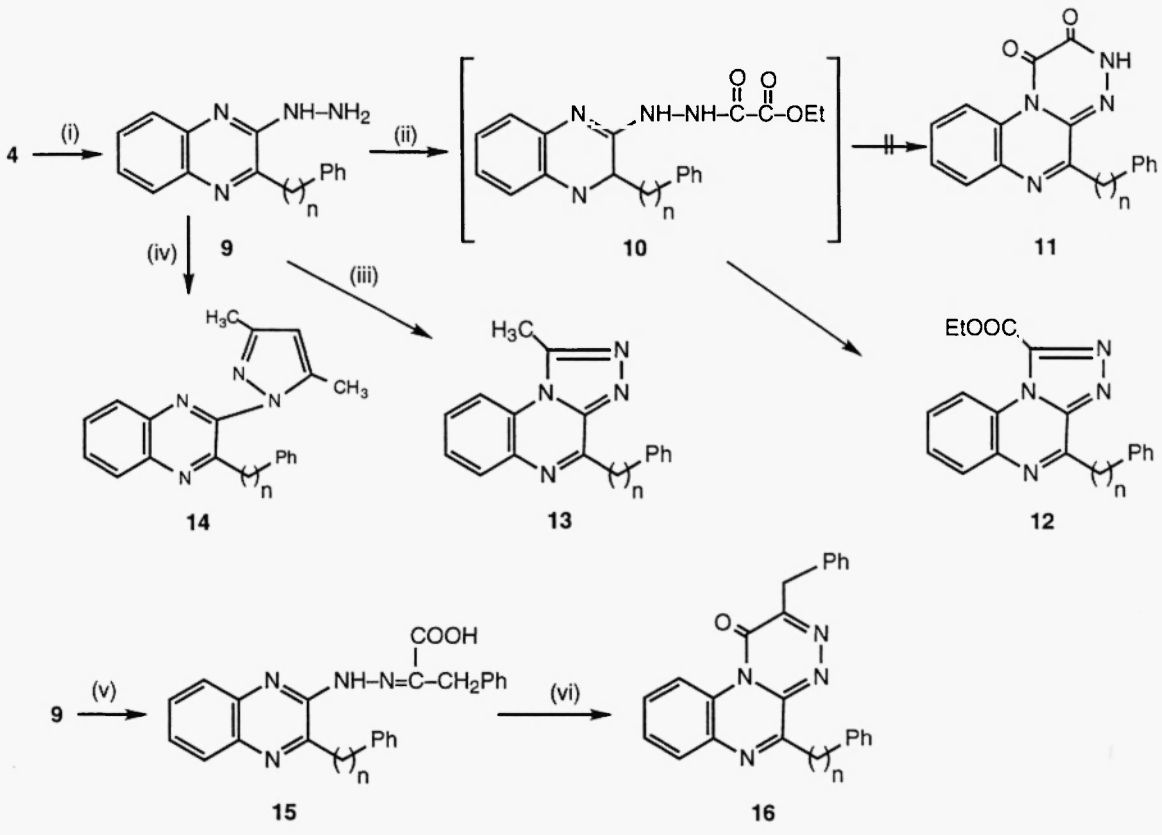
Scheme (1)

The IR spectrum of each single product obtained from heating of **9a** or **9b** with excess acetic anhydride, showed only C=N absorptions at 1613 and 1610 cm^{-1} respectively. ^1H NMR spectrum of each product revealed a singlet of three protons intensity at δ 3.10 and 3.14 respectively, due to methyl group protons, therefore, the products were assigned the 3-methyl-1,2,4-triazolo[4,3-*a*]quinoxaline derivatives **13a** and **13b** respectively.

The reaction of **9a** or **9b** with excess acetylacetone afforded a single product in each case, which showed C=N absorptions at 1606 and 1609 cm^{-1} respectively. ^1H NMR spectrum of each product revealed two singlets each of three protons intensity due to two methyl groups protons and a singlet of one proton intensity due to pyrazolyl CH proton. This, beside the elemental analyses and MS spectra excluded the possible alternative products **13** and the products were assigned, therefore, 2-(3,5-dimethylpyrazol-1-yl)-3-substituted quinoxaline structures **14a** and **14b**.

Condensation of **9a** or **9b** with phenylpyruvic acid gave the corresponding hydrazones **15a** and **15b** respectively which showed IR absorptions characteristic of NH, COOH and C=N. Dehydrative cyclization of those hydrozones by heating with phosphoryl chloride gave single

praduct in each case, which revealed IR absorptions of CON and C=N. These data, together with the elemental analysis assigned the structure 3-benzyl-4-oxo-11-substituted-1.2,4-triazine[4,3-*a*]quinoxalines **16a** and **16b**.



a) n = 1 b) n = 2

(i) $NH_2–NH_2$; (ii) $(COOEt)_2$; (iii) Ac_2O; (iv) $CH_3COCH_2COCH_3$; (v) $PhCH_2COCOOH$; (vi) $POCl_3$

Scheme 2

Five test organisms representing different groups of microorganisms were used to evaluate the bioactivity of the tested compounds. Some of the prepared compounds were tested for their antibacterial activity against the Gram positive bacteria (*Bacillus subtilis* DSM 347b, *Sarcina lutea"* local strain", *Staphylococcus aureus* ATCC 25923), and the Gram negative bacterium (*Escherichia coli* ATCC 25922) as well as the antifungal activity against *Candida albicans* DMS 70443 using cup-diffusion technique (17) (Table I).

The effect of the tested compounds on the test organism was variable, compounds **5b** and **14a** were found to be inactive against the five test organisms used. Four compounds only were active only against only one test organism, three of which (**4a, 5a** and **14b**) were active against *S. lutea*, whereas **4b** was active only against *S. aureus*. These four compounds are considered to be of specific or narrow range of antimicrobial activity. Compounds **9b** and **15b** are of less specific activity, the first compound **9b** inhibited growth of the three test organisms *S. aureas, E.*

coli and *C. albicans*, and the second compound **15b** inhibited growth of some of the Gram positive bacteria (*B. Sublilis* and *S. lutea*). Finally, two compounds (**9a** and **15a**) exhibited a wide range of activity against the five test organisms .

Table (I) Results of Antimicrobial Activity

Compd. No.	Inhibition Zones in mm				
	B. Subtilis	*S. lutea*	*S. aureus*	*E. coli*	*C.albicans*
4a	-	17	-	-	-
4b	-	-	10	-	-
5a	-	16	-	-	-
5b	-	-	-	-	-
9a	19	23	14	18	21
9b	-	-	12	10	12
14a	-	-	-	-	-
14b	-	12	-	-	-
15a	15	17	12	14	14
15b	12	13	-	-	14

Experimental

Melting points were determined on Melt-Temp II melting point apparatus and are uncorrected. The IR spectra were recorded as KBr discs on a Perkin-Elmer-599 Spectrometer. ^{1}H NMR spectra were obtained on a Brucher AC 250 MHz Spectrometer using TMS as internal standard. MS were performed on a Hewlett-Packard 5995 gas chromotograph/mass spectrometer (at 70 eV). Microanalyses were carried out at the microanalytical unit, Faculty of Science, Cairo University; the experimental values were in good accordance with the calculated ones.

3-Benzylquinoxalin-2-one 3a :

A solution of **1a** (20 mmol) in ethanol (10 ml) was treated with a solution of **2** (20 mmol) in ethanol (50 ml) and refluxed for 15 min. The solid mass which separated out on cooling was crystallized from ethanol to give **3a** in 53% yield; M.p. 198-199°C Lit (18) 196°C. IR: 1610 (C=N), 1658 cm^{-1} (CON) .

3-(Phenylethyl)quinoxalin-2-one 3b :

A solution of **1b** (20 mmol) in ethanol (10 ml) was acidified with acetic acid (0.5 ml) and the mixture was treated with a solution of **2** (20 mmol) in ethanol (50 ml) and refluxed for 20 min. It was then concentrated and the solid mass which spearated out on cooling was crystallized from ethanol to give **3b** in 51% yield; M.p. 207-209°C. IR: 1607(C=N), 1659 (CON) cm^{-1}. MS (*m/z*,%): 250 (100) , 145 (7), 117 (2). ^{1}H NMR ($CDCl_3$): δ (ppm) 3.07 (m, 4H, CH_2-CH_2), 7.28-7.76 (m, 9H, ArH), 12.37 (s, 1H, NH).

2-Chloro-3-benzylquinoxaline 4a :

A mixture of **3a** (10 mmol) and phosphoryl chloride (30 ml) was refluxed for 2h, cooled and continuously poured into crushed ice. The mixture was neutralized with a saturated solution of sodium bicarbonate and the resulting precipitate was filtered off, washed with water and crytallized from ethanol to give **4a** in 87% yield, M.p. 84-85°C; IR: 1605 cm^{-1} (C=N). MS (*m/z*,%): 256 (19), 254 (56), 219 (100), 91 (100). ^1H NMR (DMSO-d_6): δ (ppm) 4.48(s, 2H, CH_2), 7.32 (m, 5H, ArH), 7.86-8.14 (m, 4H, ArH).

2-Chloro-3-(2-phenylethyl)quinoxaline 4b :

Compound **4b** was prepared from **3b** (10 mmol) and phosphoryl chloride (30 ml) as described for the preparation of **4a**. It was crystallized from ethanol to give **4b** in 85% yield, M.p. 56-58°C; IR: 1597 cm^{-1} (C=N) ; MS (*m/z*,%): 270 (13), 268 (42), 233 (44), 128 (1), 91 (100). ^1H NMR (DMSO-d_6) : δ (ppm) 3.14 (m, 2H, CH_2), 3.37 (m, 2H, CH_2Ph), 7.20-7.32 (m, 5H, ArH), 7.85-8.11 (m, 4H, ArH).

10-Benzyl-3-oxo-1,2,4-triazolo[4,3-*a*]quinoxaline 5a :

A mixture of **4a** (2.5 mmol) and semicarbazide hydrochloride (2.5 mmol) in 75% ethanol (30 ml) in presence of 12 N hydrochloric acid (0.5 ml) was refluxed for 18 h. The mixture was then concentrated and the solid product was filtered, washed with water, and crystallized from ethanol to give **5a** in 51% yield, M.p. 256-258% (dec.). IR: 1607 (C=N), 1701 (CON) and 3140 cm^{-1} (NH). ^1H NMR (DMSO-d_6): δ (ppm) 4.26 (s, 2H, CH_2), 7.20-7.69 (m, 9H, ArH), 8.67 (s, 1H, exchangeable NH).

3-Oxo-10-(2-phenylethyl)-1,2,4-triazolo[4,3-*a*]quinoxaline 5b :

Compound **5b** was prepared from **4b** (2.5 mmol) and semicarbazide hydrochloride (2.5 mmol) as decribed for the preparation of **5a**. It was crystallized from ethanol to give **5b** in 55% yield, M. P. 215-217°C (dec.). IR: 1603 (C=N), 1735 (CON), 3026 cm^{-1}(NH) ; MS(*m/z*,%): 290 (64), 246 (24), 199 (1), 91 (100).

3,10-Dibenzyl-1,2,4-triazolo[4,3-*a*]quinoxaline 6a :

A mixture of **4a** (2.5 mmol) and phenylacetylhydrazine (2.5 mmol) in n-butanol (10 ml) was refluxed for 8h. Evaporation of the solvent under reduced pressure gave a residue which was treated with water. The solid product was filtered, washed with water, and crystallized from ethanol to give **6a** in 50% yield, M.p. 157-159°C, IR: 1601 cm^{-1} (C=N) ; MS (*m/z*,%): 350 (83), 349 (100), 259 (2), 231 (4), 91(32). ^1H NMR (DMSO-d_6): δ (ppm) 4.58, 4.94 (2s, 2H each, $2CH_2$), 7.22-8.10 (m, 14H, Ar-H).

3-Benzyl-10-(2-phenylethyl)-1,2,4-triazolo[4,3-*a*]quinoxaline 6b :

Compound **6b** was prepared from **4b** (2.5 mmol) and phenylacetylhydrazine (2.5 mmol) as described for the preparation of **6a**. It was crystallized from ethanol to give **6b** in 60% yield, M.p. 155-157°C. IR: 1611 cm^{-1} (C=N); MS (*m/z*,%): 364 (100), 273 (3), 245 (4), 140 (1).

4-Benzyltetrazolo[1,5-*a*]quinoxaline 7a :

A mixture of **4a** (1.2 mmol) and sodium azide (1.2 mmol) in dimethylforamide (10 ml) was heated on a water bath for 3h. After cooling the mixture was pourd into cold water, and the solid which separated out was filtered, washed with water, and cystallized from ethanol to give **7a** in 86% yield, M.p. 154-155°C. IR: 1591 cm^{-1} (C=N); MS (*m/z*,%): 261 (25), 232 (100), 156 (1), 91 (88).

4-(2-phenylethyl)-tetrazolo[1,5-a]quinoxaline 7b :

Compound **7b** was prepared from **4b** (1.2 mmol) and sodium azide (1.2 mmol) as described for the preparation of **7a**. It was crystallized from ethanol to give **7b** in 92 % yield, M.p. 110-112°C. IR: 1588 cm^{-1} (C=N); MS (*m/z*,%): 275 (25), 170 (10), 142 (1), 91 (100); ^1H NMR ($CDCl_3$): δ (ppm) 3.38 (t, 2H, CH_2), 3.78 (t, 2H, CH_2Ph), 7.20-7.36 (m, 5H, ArH), 7.82-7.85 (m, 2H, ArH), 8.22-8.26, 8.56-8.60 (2m, 1H each, ArH).

2-Hydrazino-3-benzylquinoxaline 9a :

A solution of **4a** (3.0 mmol) in ethanol (24 ml) was refluxed with 90% hydrazine hydrate (2 ml) for 2h. The mixture was concentrated, left to cool and the separated brown needles were filtered, washed with water then with ethanol, and dried to give **9a** in 77% yield, M.p. 155-157°C. IR: 1618 (C=N), 3281 cm^{-1} (NH) ; ^1H NMR (DMSO-d_6): δ (ppm) 4.25 (s, 2H, CH_2), 4.54 (s, 2H, NH_2), 7.19-7.80 (m, 9H, ArH), 8.56 (s, 1H, NH).

2-Hydrazino-3-(2-phenylethyl)quinoxaline 9b :

Compound **9b** was prepared from **4b** (3.0 mmol) and 90% hydrazine hydrate (2 ml) as described for the preparation of **9a**. It was crystallized from ethanol to give **9b** in 71% yield, M.p. 146-148°. IR: 1625 (C=N), 3431 cm^{-1} (NH); ^1H NMR (DMSO-d_6): δ (ppm) 3.11 (s, 4H, CH_2-CH_2), 4.53 (bs, 2H, NH_2), 7.18-7.78 (m, 9H, ArH), 8.56 (s, 1H, NH).

10-Benzyl-3-carboethoxy-1,2,4-triazolo[4,3-*a*] quinoxaline 12a :

A solution of **9a** (2.5 mmol) in diethyl oxalate (10 ml) was refluxed for 1h, cooled and poured into crushed ice. The sticky product was washed with water several times and left overnight then filtered, and crystallized from ethanol to give **12a** in 52% yield, M.p. 120-122°C. IR: 1617 (C=N), 1720 cm^{-1} (COOEt); MS(*m/z*,%): 332 (100), 259 (32), 231 (6) .

3-Carboethoxy-10-(2-phenylethyl)-1,2,4-triazolo[4,3-*a*]quinoxaline 12b :

The title compound was prepared from **9b** (2.5 mmol) and diethyl oxalate (10 ml) as described for the preparation of **12a** . It was crystallized from ethanol to give **12b** in 56% yield, M.p. 103-105°C. IR: 1615 (C=N), 1720 cm^{-1} (COOEt); MS(*m/z*,%): 346 (100), 273 (9), 245 (1) .

10-Benzyl-3-methyl-1,2,4-triazolo[4,3-*a*]quinoxaline 13a :

A solution of **9a** (2.5 mmol) in acetic anhydride (6 ml) was refluxed for 1h, cooled and poured into crushed ice. The resulting precipitate was filtered, washed with water, and crystallized from ethanol to give **13a** in 92% yield, M.p. 176-178°C. IR: 1613 cm^{-1} (C=N); MS

(*m/z*,%): 274 (71), 273 (100), 232 (24), 91 (14). ^{1}H NMR ($CDCl_3$): δ (ppm) 3.10 (s, 3H, CH_3), 4.63 (s, 2H, CH_2), 7.19-7.31 (m, 5H, ArH), 7.51-7.63, 8.00-8.06 (2m, 2H each, ArH).

3-Methyl-10-(2-phenylethyl)-1,2,4-triazolo[4,3-*a*]quinoxaline 13b :

The title compound was prepared from **9b** (2.5 mmol) and acetic anhydride (6 ml) as described for the preparation of **13a**. It was crystallized from ethanol to give **13b** in 92% yield. M.p. 145-147°C. IR: 1610 cm^{-1} (C=N); MS (*m/z*,%): 288 (100), 273 (3), 183 (15); ^{1}H NMR ($CDCl_3$): δ (ppm) 3.14 (s, 3H, CH_3), 3.32, 3.65 (2t, 2H each, $2CH_2$), 7.18-7.38 (m, 5H, ArH), 7.57-7.61, 8.06-8.11 (2m, 2H each, ArH).

3-Benzyl-2-(3,5-dimethylpyrazol-1-yl)quinoxaline 14a :

A solution of **9a** (2.5 mmol) in acetylacetone (10 ml) was refluxed for 1h, cooled and poured into crushed ice to give an oily product, which solidified after a while. It was filtered, washed with water and crystallized from methanol to give **14a** in 80% yield, M.p. 78-80°C. IR: 1606 cm^{-1} (C=N); MS (*m/z*,%): 314 (100), 299 (19), 114 (1), ^{1}H NMR ($CDCl_3$): δ (ppm) 1.83, 2.37 (2s, 3H each, $2CH_3$), 4.60 (s, 2H, CH_2Ph), 5.92(s, 1H, pyrazolyl H), 6.86-7.12 (m, 5H, ArH), 7.74-7.80 (m, 2H, ArH), 8.00, 8.18 (2d, 1H each, ArH).

2-(3,5-Dimethylpyrazol-1-yl)-3-(2-phenylethyl)quinoxaline 14b :

The title compound was prepared from **9b** (2.5 mmol) and acetylacetone (10 ml) as described for the preparation of **14a**. It was crystallized from ethanol to give **14b** in 80% yield, M.p. 109-111°C. IR: 1606 cm^{-1} (C=N); MS (*m/z*,%): 328 (100), 313 (60), 223 (5), 208 (2), 128 (4): ^{1}H NMR ($CDCl_3$): δ (ppm) 2.26, 2.35 (2s, 3H each, $2CH_3$), 3.05, 3.43 (2t, 2H each, 2 CH_2), 6.06 (s, 1H, pyrazolyl H), 7.15-7.23 (m, 5H, ArH), 7.73-7.79 (m, 2H, ArH), 8.03, 8.13 (2d, 1H each, ArH).

2-[3-Benzyl-2-quinoxalinylhydrazono]-3-phenylpropanoic acid 15a :

A mixture of **9a** (1.5 mmol) and phenylpyruvic acid (1.5 mmol) in ethanol (25 ml) was refluxed for 30 min. and left to cool. The resulting precipitate was filtered, washed with ethanol, and crystallized from ethanol to give **15a** in 85% yield, M.p. 153-155°C. IR: 1609 (C=N), 1726 (COOH), 3060 cm^{-1} (NH); MS (*m/z*,%): 396 (2), 350 (9), 219 (14), 91 (29), 45 (100). ^{1}H NMR (DMSO-d_6): δ (ppm) 4.12, 4.27 (2s, 2H each, $2CH_2$), 7.17-7.74 (m, 14H, ArH), 11.90 (s, 1H, NH), 12.15 (s, 1H, OH).

2-[3-(2′-phenylethyl)-2-quinoxalinylhydrazono]-3-phenylpropanoic acid 15b :

The title compound was prepared from **9b** (1.5 mmol) and phenylpyruvic acid (1.5 mmol) as described for the preparation of **15a**. It was crystallized from ethanol to give **15b** in 86% yield, M.p. 147-149°C. IR: 1606 (C=N), 1740 (COOH), 3027 cm^{-1} (NH); MS (*m/z*,%): 392 (8), 364 (64), 233 (59), 128 (19), 91 (100).

3,11-Dibenzyl-4-oxo-1,2,4-triazino[4,3-a]quinoxaline 16a :

A solution of **15a** (1.2 mmol) in phosphoryl chloride (10 ml) was refluxed for 2h, cooled and poured into crushed ice. The mixture was neutralized with a saturated solution of sodium bicarbonate and the resulting precipitate was filtered, washed with water, and crystallized from ethanol to give **16a** in 43% yield, M.p. 170°C. IR: 1600 (C=N), 1695 cm^{-1} (CON); MS (*m/z*,%): 378 (100), 349 (42), 232 (31), 91 (33); ^1H NMR (DMSO-d_6): δ (ppm) 4.25, 4.55 (2s, 2H each, $2CH_2$), 7.20-7.43 (m, 10H, ArH), 7.69,7.91, 9.48 (3m, 4H, ArH).

3-Benzyl-4-oxo-11-(2-phenylethyl)-1,2,4-triazino[4,3-*a*]quinoxaline 16b:

The title compound was prepared from **15b** (1.2 mmol) and phosphoryl chloride (10 ml) as described for the preparation of **16a** . It was crystallized from ethanol to give **16b** in 32% yield, M.p. 118-119°C. IR: 1600 (C=N), 1680 cm^{-1} (CON); MS (*m/z*,%): 392 (92), 301 (43), 273 (12), 91 (100).

Antimicrobial Screening

The compounds were dissolved in propylene glycol at a concentration of 1 mg/ml. The suitable medium (nutrient agar for bacteria and Sabouraud agar for fungi) was inoculated with the test organisms. A volume of the solution of each of the test compounds equivalent to 100 μg was placed separately in cups (8 mm in diameter, 5 mm in height), cut in the agar. The plates were incubated at 37°C for 18-24 h for bacteria, and 48 h for yeast fungi (*C. albicans*), and the resulting inhibition zones were measured (Table 1). Propylene glycol, which exhibited no antimicrobial activity against the test organisms, was used as a negative control.

Acknowledgement

The auther is grateful to Prof. Dr. Y. M. Gohar, Division of Microbiology, Facutly of Science, Alexandria University for evaluating microbiological activities.

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Received on August 19, 1999