

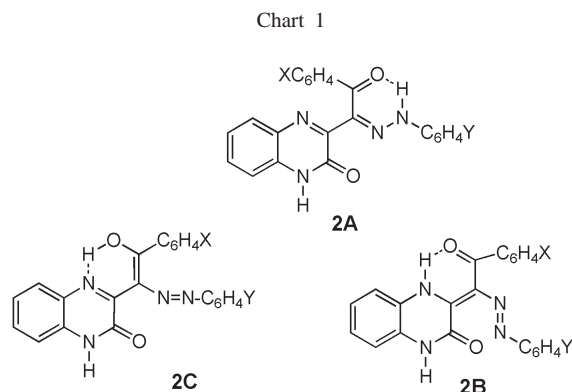
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A novel series of flavazoles **3a-l** were synthesized *via* dehydrative cyclization of a new series of 3-[(α -arylhydrazono)-aroylmethyl]quinoxalin-2(1*H*)-ones **2a-l** and their biological activity has been evaluated. The tautomeric structure of the precursors **2a-l** has also been elucidated.

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In continuation of our recent studies on the effect of substituents on azo-hydrazone tautomerism of arylazo-heterocycles [1,2], we wish to report the results of our investigation of the effect of substituents on the tautomerism of the diazonium coupling products **2** obtained from 3-(aroylmethylene)-3,4-dihydroquinoxalin-2(1*H*)-ones **1** (Chart 1). A literature survey reveals that compounds **2** have not been reported hitherto although their precursors **1** have been known since 1971 [3-5]. As shown in Chart 1, the target diazonium coupling products **2** can exist in one or more of three tautomeric forms namely the hydrazone imine **2A**, azo-enamine **2B** and hydroxyazo-imine **2C** forms.



In addition to the study of tautomerism of **2**, it was thought interesting to explore their utility as precursors for synthesis of functionalized flavazoles namely 3-aryl-1*H*-pyrazolo[3,4-*b*]quinoxaline derivatives **3** (Scheme 1). Our interest in the synthesis of the target compounds **2** and **3** is to explore also their biological activities as some related derivatives have been found to possess antifungal and/or antibacterial activities [6-8].

Results and Discussion.

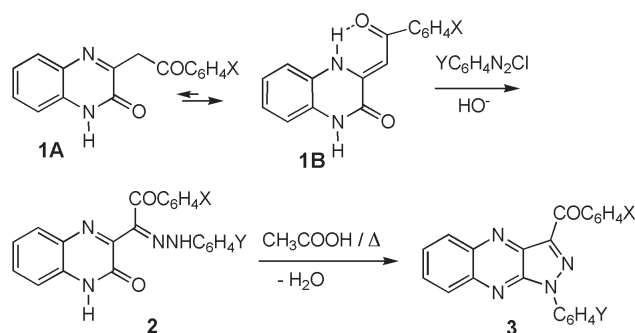
The starting 3-(aroylmethylene)-3,4-dihydroquinoxalin-2(1*H*)-ones **1a-e** were synthesized by the condensation of 1,2-diaminobenzene with the appropriate ethyl 4-aryl-2,4-dioxobutanoate according to literature procedure [3-5] and their ir and ^1H nmr spectra indicate that they exist predom-

inantly in the enamine form **1B** (Scheme 1). The reactions of **1a** with benzenediazonium chloride and its substituted derivatives in ethanol in the presence of sodium hydroxide gave the corresponding 3-[(α -arylhydrazono)-aroylmethyl]-quinoxalin-2(1*H*)-ones **2a-h** (Scheme 1). Similarly benzenediazonium chloride reacted with each of **1b-e** under the same conditions and afforded the coupling products **2i-l**, respectively (Scheme 1). The structures of the products **2a-l** were evident from their spectral (ir, ms and ^1H and ^{13}C nmr) (Table 1) and elemental and analyses (Table 5). The ^1H nmr spectra of **2b,c** and **2l** indicated that each existed in deuteriodimethyl sulfoxide as an equilibrium mixture of the hydrazone imine form **2A** and azoenamine form **2B**. For example, the ^1H nmr spectra of these compounds exhibited the hydrazone NH near δ 13.7 - 13.8 and the $\text{N}_4\text{-H}$ near δ 11.45 - 11.53 due to the tautomers **2A** and **2B**, respectively [9-12]. The integral ratios of hydrazone NH/ $\text{N}_4\text{-H}$ proton signals are 2/3, 2/3 and 1/1 for **2b**, **2c** and **2l**, respectively. The ^1H nmr spectra of the other derivatives **2a** and **2d-k** revealed, however, that each of them existed predominantly in the azoenamine form **2B**. Namely, their ^1H nmr spectra showed only the $\text{N}_4\text{-H}$ proton signal in the region of δ 11.0 - 11.6. In addition to the above signals, all compounds **2a-l** exhibited the $\text{N}_1\text{-H}$ proton signals in the region of δ 12.4 - 12.6 (Table 1). The ^{13}C nmr spectrum of **2d** (Table 1), taken as a typical example of the series, revealed two carbonyl carbon signals at δ 190.6 and 154.4 [13]. The presence of such bands excludes the hydroxyazo tautomeric form **2C** (Chart 1).

The ir spectra of the compounds **2a-l** revealed two carbonyl absorption bands in the regions of 1684-1658 and 1625-1615 cm^{-1} assignable to the cyclic amide $\text{C}=\text{O}$ and α,β -unsaturated $\text{C}=\text{O}$ groups, respectively. The lower frequency of the latter group seems to indicate that it is involved in intramolecular hydrogen bond (Chart 1).

The assignment of the tautomeric form **2B** was further evidenced by the electronic absorption spectra. The data are summarized in Table 2. As shown, each of the compounds **2a-l** in dioxane exhibits two characteristic absorption bands in the regions of 460-420 and 415-329 nm. This absorption pattern is similar to that of typical azo chromophore [14]. Furthermore, the spectra of **2d**, taken as a typical example of the two series studied, were recorded in

Scheme 1



For 1, X: **a**, H; **b**, 4-CH₃O; **c**, 4-CH₃; **d**, 4-Br; **e**, 4-NO₂
 For 2-3, X/Y: **a**, H/4-CH₃O; **b**, H/4-CH₃; **c**, H/3-CH₃;
d, H/H; **e**, H/4-Cl; **f**, H/3-Cl; **g**, H/3-NO₂;
h, H/4-NO₂; **i**, 4-CH₃O/H; **j**, 4-CH₃/H;
k, 4-Br/H; **l**, 4-NO₂/H

solvents of different polarities. The spectra obtained showed little shift (Table 2). The small shifts in λ_{\max} of **2d** in different solvents are due to solute-solvent interaction. This finding indicates that the studied compounds exist predominantly in the tautomeric form **2B** excluding the hydroxyazo-enamine form **2C**. In agreement with this conclusion is the observation that the spectra of the arylhydrazones derived from the reaction of quinones with *N*-alkyl-*N*-phenylhydrazine, unlike those of *o*- and *p*-hydroxyphenylazo compounds are largely independent of the solvent polarity [15 - 17].

Next, cyclization of the coupling products **2a-l** was examined. In our hands, refluxing each of such compounds in glacial acetic acid resulted in its dehydrative cyclization to afford the respective 3-aryloxy-1-aryl-1*H*-pyrazolo[3,4-*b*]quinoxalines (flavazoles) **3a-l** (Scheme 1). The structures of these products were established on the basis of their spectra (ir, ms and ¹H and ¹³C nmr) (Table 3) and elemental analyses (Table 6). For example, their ir spectra showed one characteristic carbonyl band in the region of ν 1685 – 1645 cm⁻¹ assignable to the aryl group. Their ¹³C nmr spectra revealed the side-chain carbonyl carbon signal near δ 186.6 and their mass spectra revealed the expected molecular ion peaks together with aryl ion peaks.

Antimicrobial Activity.

Compounds **3a-k** were tested for their antimicrobial activities against four fungal species namely *Aspergillus fumigatus* AF, *Penicillium italicum* PI, *Syncephalastrum racemosum* SR and *Candida albicans* CA as well as four bacteria species namely *Staphylococcus aureus* SA, *Pseudomonas aeruginosa* PA, *Bacillus subtilis* BS and *Escherichia coli* EC. The organisms were tested against the activity in 1.0 μ g/ml for each compound and using inhibition zone diameter in cm (IZD) as criterion for the

antimicrobial activity. Terbinafin as an antifungal agent and chloramphenicol as an antibacterial agent were used as references to evaluate the potency of the test compounds under the same conditions. The results are depicted in Table 4. The results revealed that compounds **3d** and **3k** exhibited the highest degree of inhibition against the tested organism PA, whereas compounds **3f** and **3i** exhibited maximum inhibition against EC. Their activity is similar to that of the standard antifungal and antibacterial agents used. All other compounds either exhibit no activity or being less active against the tested species AF, PI, SR, CA and BS.

EXPERIMENTAL

Melting points were determined on a Gallenkamp apparatus and are uncorrected. IR spectra were recorded in potassium bromide using Perkin Elmer FTIR 1650 and Pye-Unicam SP300 infrared spectrophotometers. ¹H and ¹³C nmr spectra were recorded in deuteriodimethyl sulfoxide using a Varian Gemini 300 spectrometer. Mass spectra were recorded on a GCMS-QP 1000 EX Shimadzu and GCMS 5988-A HP spectrometers. Electronic absorption spectra were recorded on Perkin-Elmer Lambda 40 spectrophotometer. Elemental analyses were carried out at the Microanalytical Laboratory of Cairo University, Giza, Egypt. Ethyl 4-aryl-2,4-dioxobutanoates [18] and 3-(arylmethylene)-3,4-dihydroquinoxalin-2(1*H*)-ones **1** [3-5] were prepared as previously described.

3-[(α -Arylhydrazono)-arylmethyl]quinoxalin-2(1*H*)-ones (2).

General Procedure.

A solution of compound **1** (5 mmoles) and sodium hydroxide (0.5 g, 12.5 mmoles) in ethanol (25 ml) was stirred for 15 minutes, and the resulting mixture was chilled in an ice bath at 0-5 °C. To the stirring cold mixture was added dropwise a solution of aryl diazonium chloride, prepared by diazotizing the appropriate aniline derivative (5 mmoles) dissolved in hydrochloric acid (3 ml, 6 molar solution) with sodium nitrite (0.35 g, 5 mmoles) in a usual way. After the addition of the diazonium salt solution was completed, the whole reaction mixture was left in an ice-box for 1 hour. The precipitated solid was collected by filtration, washed with water and finally recrystallized from the appropriate solvent to give the respective azo derivatives **2**. The physical constants of compounds **2a-l** are listed in Table 5.

1-Aryl-3-aryloxy-1*H*-pyrazolo[3,4-*b*]quinoxalines (3).

General Procedure.

A solution of the appropriate **2** (2 mmoles) in glacial acetic acid (25 ml) was refluxed for 10 hours and the solvent was then evaporated. The solid that remained was triturated with water. The precipitated solid was collected by filtration, washed with water and crystallized from a suitable solvent to yield the respective pyrazolo[3,4-*b*]quinoxaline derivatives **3**. The physical constants of compounds **3a-l** are listed in Table 6.

Antimicrobial Assay.

Cultures of four fungal species *Aspergillus fumigatus* AF, *Penicillium italicum* PI, *Syncephalastrum racemosum* SR and

Table 1
Infrared, ¹H nmr and Mass Spectra of the Products **2a-h**

Compound No.	Infrared spectrum ν (cm ⁻¹) (KBr) / ¹ H nmr spectrum (δ , DMSO- <i>d</i> ₆) / Mass spectrum (m/z (relative intensity %)).
2a	3400, 3010, 1666; / 3.71 (s, 3H, ArOCH ₃), 6.89 (d, J = 9 Hz, 2H, ArH), 7.1-7.56, 7.9-7.95 (m, 9H, ArH), 7.6 (d, J = 9 Hz, 2H, ArH), 11.49 (s, 1H, N ₄ -H), 12.52 (s, 1H, N ₁ -H) / 399 (M ⁺ +1, 5), 398 (M ⁺ , 23), 264 (13), 245 (21), 187 (15), 122 (26), 105 (100), 77 (71).
2b	3250, 3109, 1659, 1612 / 2.24 (s, 3H, ArCH ₃), 7.06 (d, J = 9 Hz, 2H, ArH), 7.10-7.64 (m, 9H, ArH), 7.66 (d, J = 9 Hz, 2H, ArH), form 2A : 12.0 (s, 0.4H, N ₁ -H), 13.70 (s, 0.4H, =N-NH), form 2B : 11.50 (s, 0.6H, N ₄ -H), 12.54 (s, 0.6H, N ₁ -H) / 382 (M ⁺ , 28), 245 (18), 183 (33), 105 (100), 91 (41), 77 (83).
2c	3440, 3055, 1666, 1612 / 2.25 (s, 3H, ArCH ₃), 6.81-8.09 (m, 13H, ArH), form 2A : 12.0 (s, 0.4H, N ₁ -H), 13.70 (s, 0.4H, =N-NH), form 2B : 11.45 (s, 0.6H, N ₄ -H), 12.55 (s, 0.6H, N ₁ -H) / 383 (M ⁺ +1, 8), 382 (M ⁺ , 32), 364 (14), 245 (14), 183 (35), 105 (86), 91 (44), 77 (100).
2d[a]	3317, 3101, 1666 / 6.98-7.98 (m, 14 H, ArH), 11.47 (s, 1H, N ₄ -H), 12.56 (s, 1H, N ₁ -H) / 369 (M ⁺ +1, 13), 368 (M ⁺ , 17), 235 (11), 169 (25), 105 (75), 92 (26), 77 (100).
2e	3186, 3109, 1666 / 7.15 (d, J = 7 Hz, 2H, ArH), 7.13-7.75 (m, 9H, ArH), 7.60 (d, J = 7 Hz, 2H, ArH), 11.48 (s, 1H, N ₄ -H), 12.59 (s, 1H, N ₁ -H) / 404 (M ⁺ +2, 7), 403 (M ⁺ +1, 8), 402 (M ⁺ , 18), 245 (12), 203 (21), 172 (26), 126 (14), 105 (100), 90 (17), 77 (85).
2f	3324, 3109, 1666, 1620 / 7.02-7.98 (m, 13H, ArH), 11.45 (s, 1H, N ₄ -H), 12.39 (s, 1H, N ₁ -H) / 404 (M ⁺ +2, 7), 403 (M ⁺ +1, 8), 402 (M ⁺ , 16), 245 (12), 235 (16), 172 (30), 126 (11), 105 (100), 90 (22), 77 (85).
2g	3448, 3109, 1658, 1612 / 7.38-8.00 (m, 13H, ArH), 11.52 (s, 1H, N ₄ -H), 12.67 (s, 1H, N ₁ -H) / 414 (M ⁺ +1, 1), 413 (M ⁺ , 5), 245 (4), 235 (8), 214 (16), 172 (22), 105 (100), 91 (8), 77 (76).
2h	3440, 3101, 1666 / 7.28 (d, J = 7 Hz, 2H, ArH), 7.31-8.01 (m, 9H, ArH), 8.19 (d, J = 7 Hz, 2H, ArH), 11.74 (s, 1H, N ₄ -H), 12.70 (s, 1H, N ₁ -H) / 414 (M ⁺ +1, 3), 413 (M ⁺ , 15), 245 (2), 235 (11), 214 (17), 172 (24), 105 (100), 90 (10), 77 (74).
2i	3300, 3150, 1666 / 3.88 (s, 3H, ArOCH ₃), 6.98 (d, J = 9 Hz, 2H, ArH), 7.08-7.94 (m, 9H, ArH), 7.99 (d, J = 9 Hz, 2H, ArH), 11.49 (s, 1H, N ₄ -H), 12.54 (s, 1H, N ₁ -H) / 398 (M ⁺ , 3), 199 (38), 135 (100), 107 (13), 92 (39), 77 (55).
2j	3400, 3200, 1666 / 2.39 (s, 3H, ArCH ₃), 7.15 (d, J = 8 Hz, 2H, ArH), 7.20-7.64 (m, 9H, ArH), 7.89 (d, J = 8 Hz, 2H, ArH), 11.50 (s, 1H, N ₄ -H), 12.49 (s, 1H, N ₁ -H) / 382 (M ⁺ , 8), 364 (9), 259 (25), 183 (49), 172 (15), 119 (100), 91 (79), 77 (43).
2k	3417, 3100, 1666 / 7.09-7.94 (m, 13 H, ArH), 11.53 (s, 1H, N ₄ -H), 12.54 (s, 1H, N ₁ -H) / 448 (M ⁺ +1, 14), 447 (M ⁺ , 8), 247 (28), 234 (24), 185 (67), 155 (46), 105 (19), 92 (81), 77 (100).
2l	3420, 3113, 1684, 1612 / 7.16 (d, J = 8 Hz, 2H, ArH), 7.2-8.32 (m, 9H, ArH), 8.30 (d, J=8 Hz, 2H, ArH), form 2A : 12.0 (s, 0.5H, N ₄ -H), 13.8 (s, 0.5H, =NNH), form 2B : 11.53 (s, 0.5H, N ₄ -H), 12.54 (s, 0.5H, N ₁ -H) / 413 (M ⁺ , 13), 214 (24), 172 (52), 150 (44), 105 (28), 92 (84), 77 (100).

[a] ¹³C NMR (Me₂SO-*d*₆): δ 190.6, 154.4, 154.2, 143.8, 138.2, 136.6, 133.1, 132.6, 131.8, 130.6, 130.0, 129.7, 128.6, 124.1, 123.1, 116.2, 115.0.

Candida albicans CA as well as four bacterial species *Staphylococcus aureus* SA, *Pseudomonas aeruginosa* PA, *Bacillus subtilis* BS and *Escherichia coli* EC were used to investigate the antimicrobial activity of the compounds **3a-i**. The antimicrobial activity was assayed using the diffusion plate technique. The technique was carried out by pouring a spore suspension of the fungal species (one ml of sterile water contains approximately 10⁸ conidia) or by spreading bacterial suspension over a solidified malt agar medium. The layer is allowed to set for 30 min. A solution of the test compound **3** (1.0 μ g/ml) in dimethylformamide was placed onto sterile 5 mm filter paper

discs and allowed to dry, then the discs were placed on the centre of the malt agar plate and incubated at optimum incubation temperature 28 \pm 2 °C. Test organism growth may be affected by the inhibitory action of the test compound, and so a clear zone around the disc appears as an indication of the inhibition of test organism growth. The size of the clearing zone is proportional to the inhibitory action of the compound. The fungicide Terbinafin and the bactericide chloramphenicol were used as standards under the same conditions. Measurements were carried out after 72 h for fungi and 24 h for bacteria. The results are summarized in Table 4.

Table 2

Electronic Absorption Spectra of the Coupling Products 2a-l in Dioxane

Compound No.	λ_{\max} (Log ϵ)
2a	453 (3.88), 357 (2.69)
2b	434 (3.81), 329 (3.70)
2c	436 (4.16), 413 (4.18)
2d [a]	434 (3.77), 345 (2.50)
2e	437 (3.90), 342 (2.26)
2f	430 (4.10), 370 (3.33)
2g	420 (4.00), 348 (2.65)
2h	430 (3.85), 359 (3.70)
2i	438 (3.82), 415 (3.79)
2j	436 (4.08), 413 (4.10)
2k	433 (3.89), 350 (3.80)
2l	434 (4.00), 343 (3.70)

[a] Solvent: λ_{\max} (Log ϵ): acetic acid: 429 (4.84), 354 (4.77); chloroform: 437 (4.84), 341 (3.74); ethanol: 430 (4.86), 351 (4.15); cyclohexane: 434 (4.82), 338 (5.0).

REFERENCES AND NOTES

- [1] A. S. Shawali, M. H. Abdelkader and F. A. Eltalbawy, *Tetrahedron* **58**, 2875 (2002).
- [2] A. S. Shawali, M. A. N. Mosslihi and Y. F. Mohamed, *Z. Naturforsch.*, **57b**, 552 (2002).
- [3] Y. Iwanami, T. Seki and T. Inajaki, *Bull. Chem. Soc. Jpn.* **44**, 1316 (1971).
- [4] Yu. S. Andreichikov, S. G. Pitirmova, R. F. Saraeva, G. D. Plakhina and L. A. Voronova, *Khim. Geterotsikl. Soedin.*, 407 (1978); *Chem. Abstr.*, **89**, 43329u (1978).
- [5] Yu. S. Andreichikov, S. G. Pitirmova, R. F. Saraeva and A. F. Goleneva, *Khim. Farm. Zh.* **13**, 42 (1979); *Chem. Abstr.*, **92**, 128860x (1980).
- [6] Y. Kurasawa, M. Muramatsu, K. Yamazaki, S. Tajima, Y. Okamoto and A. Takada, *J. Heterocyclic Chem.* **23**, 1379 (1986).
- [7] H. S. Kim, Y. Kurasawa and A. Takada, *J. Heterocyclic Chem.* **26**, 1129 (1989).
- [8] Y. Kurasawa, M. Muramatsu, Y. Okamoto and A. Takada, *J. Heterocyclic Chem.*, **23**, 637 (1986).
- [9] Y. Kurasawa, K. Yamazaki, S. Tajima, Y. Okamoto and A. Takada, *J. Heterocyclic Chem.*, **23**, 957 (1986).

Table 3

Infrared, ^1H nmr and Mass Spectra of the Products 3a-h

Compound No.	Infrared spectrum ν (cm^{-1}) (KBr) / ^1H nmr spectrum (δ , $\text{DMSO}-d_6$) / Mass spectrum (m/z (relative intensity %)).
3a	1650 / 3.88 (s, 3H, ArOCH_3), 7.24 (d, $J = 9$ Hz, 2H, ArH), 7.65-8.00, 8.25-8.28 (m, 9H, ArH), 8.19 (d, $J = 9$ Hz, 2H, ArH) / 381 ($M^+ + 1$, 4), 380 ($M^+ + 12$), 106 (9), 105 (100), 92 (2), 90 (2), 78 (5), 77 (47).
3b [a]	1652 / 2.42 (s, 3H, ArCH_3), 7.46 (d, $J = 8$ Hz, 2H, ArH), 7.60 (d, $J = 8$ Hz, 2H, ArH), 7.73-8.36 (m, 9H, ArH) / 365 ($M^+ + 1$, 3), 364 (M^+ , 11), 106 (8), 105 (100), 91 (3), 90 (2), 77 (51).
3c	1661 / 2.48 (s, 3H, ArCH_3), 6.81-8.37 (m, 13H, ArH) / 365 ($M^+ + 1$, 2), 364 (M^+ , 10), 264 (11), 235 (7), 106 (8), 105 (100), 91 (4), 90 (3), 77 (53).
3d	1686 / 7.48-8.37 (m, ArH) / 351 ($M^+ + 1$, 3), 350 (M^+ , 10), 106 (8), 105 (100), 77 (68).
3e	1662 / 7.43 (d, $J = 8$ Hz, 2H, ArH), 7.52-8.32 (m, 9H, ArH), 8.36 (d, $J = 8$ Hz, 2H, ArH) / 387 ($M^+ + 2$, 3), 386 ($M^+ + 1$, 6), 385 (M^+ , 6), 384 (18), 111 (4), 106 (9), 105 (100), 77 (47).
3f	1662 / 7.43-8.39 (m, ArH) / 387 ($M^+ + 2$, 3), 386 ($M^+ + 1$, 6), 385 (M^+ , 6), 384 (18), 111 (4), 106 (9), 105 (100), 77 (47).
3g	1659 / 7.64-8.42 (m, ArH) / 396 ($M^+ + 1$, 4), 395 (M^+ , 13), 321 (3), 320 (2), 244 (2), 106 (8), 105 (100), 90 (3), 77 (61).
3h	1659 / 7.53 (d, $J = 8$ Hz, 2H, ArH), 6.82-7.40, 8.10-8.80 (m, 9H, ArH), 8.0 (d, $J = 8$ Hz, 2H, ArH) / 396 ($M^+ + 1$, 4), 395 (M^+ , 13), 321 (3), 320 (2), 244 (2), 106 (8), 105 (100), 90 (3), 77 (61).
3i	1643 / 3.88 (s, 3H, ArOCH_3), 7.16 (d, $J = 8$ Hz, 2H, ArH), 7.49-8.33 (m, 9H, ArH), 8.37 (d, $J = 8$ Hz, 2H, ArH) / 381 ($M^+ + 1$, 3), 380 (M^+ , 11), 176 (3), 135 (100), 107 (11), 92 (13), 77 (34).
3j	1654 / 2.11 (s, 3H, ArCH_3), 7.44 (d, $J = 8$ Hz, 2H, ArH), 7.53-8.35 (m, 9H, ArH), 8.39 (d, $J = 8$ Hz, 2H, ArH) / 365 ($M^+ + 1$, 3), 364 (M^+ , 12), 120 (9), 119 (100), 91 (50), 77 (12).
3k	1663 / 7.17 (d, $J = 8$ Hz, 2H, ArH), 7.52-8.29 (m, 9H, ArH), 8.38 (d, $J = 8$ Hz, 2H, ArH) / 431 ($M^+ + 2$, 7), 430 ($M^+ + 1$, 30), 429 (M^+ , 13), 428 (33), 185 (95), 183 (100), 157 (79), 155 (33), 77 (35).
3l	1684 / 6.85-7.59 (m, 9H, ArH), 8.19 (d, $J = 9$ Hz, 2H, ArH), 8.32 (d, $J = 9$ Hz, 2H, ArH) / 395 (M^+ , 2), 309 (100), 234 (11), 187 (21), 150 (26), 104 (18), 90 (12), 77 (15).

[a] ^{13}C NMR ($\text{Me}_2\text{SO}-d_6$): δ 186.6, 142.6, 142.5, 141.4, 141.2, 137.5, 137.4, 136.9, 136.5, 134.0, 132.6, 130.9, 130.7, 130.4, 130.1, 129.4, 129.1, 121.7, 21.2.

Table 4
Antimicrobial Activity of the Products **3**

Compound	Microorganism / Inhibition zone diameter (cm) [a]							
	AF	PI	SR	CA	SA	PA	BS	EC
3a	0	0	+	0	0	0	0	+
3b	0	0	+	+	0	0	0	+
3c	0	+	0	0	0	0	0	+
3d	0	+	+	0	+	++	+	0
3e	0	+	0	0	0	+	0	0
3f	0	+	+	0	0	0	+	++
3h	0	+	0	0	+	+	+	0
3i	0	0	+	0	0	+	0	++
3j	0	+	+	0	0	0	0	+
3k	+	0	+	+	0	++	0	0
CA [b]						++	++	++
TE [c]	++	++	++	++	++			

[a] 50 ml of solution in dimethylformamide whose concentration 1.0 µg / ml was tested; [b] Chloramphenicol as standard antibacterial agent; [c] Terbinafin as standard antifungal agent. ++, inhibition value 0.6 – 1.0 cm; +, inhibition value 0.1 – 0.5 cm beyond control; 0, no inhibition detected.

Table 5
Synthesized Compounds **2a-l**

Compound No.	Yield (%)	Mp. (°C) [a]	Molecular formula (mol. wt.)	Analysis Calcd. (Found)		
				C	H	N
2a	85	260-261 (i)	C ₂₃ H ₁₈ N ₄ O ₃ (398.4)	69.34 (69.20)	4.55 (4.30)	14.06 (14.00)
2b	90	256-257 (ii)	C ₂₃ H ₁₈ N ₄ O ₂ (382.4)	72.24 (72.10)	4.74 (4.60)	14.65 (14.50)
2c	84	250-251 (i)	C ₂₃ H ₁₈ N ₄ O ₂ (382.4)	72.24 (72.10)	4.74 (4.50)	14.65 (14.30)
2d	89	245-246 (iii)	C ₂₂ H ₁₆ N ₄ O ₂ (368.4)	71.73 (71.50)	4.38 (4.60)	15.21 (15.00)
2e	95	265-266 (ii)	C ₂₂ H ₁₅ ClN ₄ O ₂ (402.8)	65.60 (65.60)	3.75 (3.70)	13.91 (13.90)
2f	80	258-259 (ii)	C ₂₂ H ₁₅ ClN ₄ O ₂ (402.8)	65.60 (65.40)	3.75 (3.70)	13.91 (14.10)
2g	85	298-299 (i)	C ₂₂ H ₁₅ N ₅ O ₄ (413.4)	63.92 (63.65)	3.66 (3.60)	16.94 (16.73)
2h	90	290-292 (ii)	C ₂₂ H ₁₅ N ₅ O ₄ (413.4)	63.92 (63.80)	3.66 (3.52)	16.94 (16.80)
2i	85	280-281 (ii)	C ₂₃ H ₁₈ N ₄ O ₃ (398.4)	69.34 (69.62)	4.55 (4.64)	14.06 (13.92)
2j	88	274-275 (i)	C ₂₃ H ₁₈ N ₄ O ₂ (382.4)	72.24 (72.09)	4.74 (4.40)	14.65 (14.62)
2k	90	245-246 (i)	C ₂₂ H ₁₅ BrN ₄ O ₂ (447)	59.06 (59.11)	3.36 (3.44)	12.53 (12.61)
2l	75	270-271 (i)	C ₂₂ H ₁₅ N ₅ O ₄ (413.4)	63.92 (63.61)	3.66 (3.52)	16.94 (16.90)

[a] Solvent: (i) ethanol, (ii) ethanol-dioxane, (iii) dioxane

Table 6
Synthesized Compounds **3a-l**

Compound No.	Yield (%)	Mp. (°C) [a]	Molecular formula (mol. wt.)	Analysis Calcd. (Found)		
				C	H	N
3a	60	153-155 (iv)	C ₂₃ H ₁₆ N ₄ O ₂ (380.4)	72.53 (72.40)	4.21 (4.11)	14.74 (14.42)
3b	60	180-181 (ii)	C ₂₃ H ₁₆ N ₄ O (364.4)	75.82 (75.54)	4.40 (4.10)	15.38 (15.33)
3c	84	250-251 (i)	C ₂₃ H ₁₆ N ₄ O (364.4)	75.82 (75.65)	4.40 (4.11)	15.38 (15.10)
3d	66	220-221 (ii)	C ₂₂ H ₁₄ N ₄ O (350.4)	75.43 (75.20)	4.00 (4.20)	16.00 (15.70)
3e	59	150-151 (i)	C ₂₂ H ₁₃ ClN ₄ O (384.5)	68.66 (68.35)	3.38 (3.20)	14.56 (14.20)
3f	70	144-145 (iv)	C ₂₂ H ₁₃ ClN ₄ O (384.5)	68.66 (68.42)	3.38 (3.09)	14.56 (14.23)
3g	58	200-201 (i)	C ₂₂ H ₁₃ N ₅ O ₃ (395.4)	66.84 (66.62)	3.29 (3.05)	17.72 (17.55)
3h	62	290-292 (i)	C ₂₂ H ₁₃ N ₅ O ₃ (395.4)	66.84 (66.55)	3.29 (3.15)	17.72 (17.44)
3i	54	220-221 (ii)	C ₂₃ H ₁₆ N ₄ O ₂ (380.4)	72.53 (72.34)	4.21 (4.01)	14.74 (14.50)
3j	60	190-191 (i)	C ₂₃ H ₁₆ N ₄ O (364.4)	75.82 (75.65)	4.40 (4.21)	15.38 (15.10)
3k	52	180-181 (i)	C ₂₂ H ₁₃ BrN ₄ O (429)	61.54 (61.53)	3.03 (3.15)	13.05 (13.32)
3l	60	160-162 (i)	C ₂₂ H ₁₃ N ₅ O ₃ (395.4)	66.84 (66.66)	3.29 (3.10)	17.72 (17.70)

[a] Solvent: (i) ethanol, (ii) ethanol-dioxane, (iii) dioxane, (iv) methanol

- [10] Y. Kurasawa, T. Hosaka, A. Takada, H. S. Kim and Y. Okamoto, *J. Heterocyclic Chem.*, **31**, 1661 (1994).
 [11] Y. Kurasawa, T. Hosaka, A. Takada, H. S. Kim and Y. Okamoto, *J. Heterocyclic Chem.*, **32**, 445 (1995).
 [12] Y. Kurasawa, T. Hosaka, A. Takada, H. S. Kim and Y. Okamoto, *J. Heterocyclic Chem.*, **32**, 531 (1995).
 [13] Y. Kurasawa, H. S. Kim, R. Futatsukawa, C. Watanabe, A. Takada and Y. Okamoto, *J. Heterocyclic Chem.*, **26**, 1159 (1989).
 [14] R. Jones, A. J. Ryan, S. Sternhell and S. E. Wright, *Tetrahedron*, **19**, 1497 (1963).
 [15] J. Daunis, M. Follet and C. Marzin; *Org. Magn. Reson.*, **13**, 330 (1980).
 [16] A. S. Shawali and S. M. Gomha, *J. Prakt. Chem.* **342**, 599 (2000); A. S. Shawali and T. A. Farghaly, *Tetrahedron*, **60**, 3051 (2004).
 [17] J. Elguero, P. Goya, A. Martinez and I. Rozas, *Chem. Ber.*, **122**, 919 (1989).
 [18] M. Freri, *Gazz. Chim. Ital.* **68**, 612 (1939).